A-aryl quaternary centres via asymmetric Vicarious Nucleophilic Substitution

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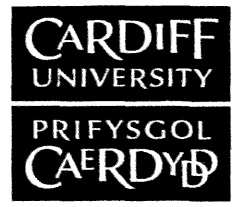

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Acknowledgements

I would like to thank my supervisors Nick Lawrence and Matthew Gray for their help and support during my three years. I would like to thank GlaxoSmithKline and the EPSRC for funding the project and also Cardiff University School of Chemistry for allocating me the project. I would also like to thank Abdul Malik for the X-ray structures and Swansea University Mass Spectrometry department. Finally, I would like to thank Mike Coogan and Dan Pernazza for their help with the project.

Abstract

This dissertation first describes a new method for the formation of α-aryl lactams based on the Vicarious Nucleophilic Substitution reaction. The route involves the three-component coupling of a nitroarene, an α-phenylsulfanyl lactam and an electrophile. The process incorporates various electrophiles and various *N*-substituted cyclic amides and has been developed for the most part using nitrobenzene. The process was also applied to α-phenylsulfanyl pyrazolidinones. The process also includes examples of amides possessing a removable nitrogen protecting group to give access to functionalised amides with a free NH group.

Secondly, an asymmetric version of the VNS reaction is described. The diastereoselectivity of the VNS-alkylation reaction of lactones was studied. For example using an α-phenylsulfanyl-γ-substituted butyrolactone, nitrobenzene and an alkyl halide, diastereoselectivities of greater than 7:1 were observed in some cases. The stereogenic centre at the γ position is clearly able to exert considerable control in the generation of the new stereogenic centre at the α-position.

The third area of research described involves capture of the intermediate VNS anion with aryl electrophiles. Activated electrophiles react in this way *via* an S_NAr process. The VNS and S_NAr reactions were combined to form an efficient one-pot three-component coupling process to give easy access to functionalised diarylmethanes. Reduction of the nitro group of selected products gave a quick and easy route to the oxindole structural motif.

The final chapter describes our attempts to react the intermediate VNS anion with unactivated aryl halides in a transition metal cross-coupling process. Unfortunately, we did not find conditions to effect the coupling of the anion derived from a VNS process with aryl halides. Nevertheless, the anion of nitrophenylacetates prepared *via* deprotonation participates in cross-coupling reactions with ease and provides an alternative way to prepare diarylmethanes. This has the potential to be extremely useful due to the lack of reports of nitroarenes in cross-coupling processes.

Abbreviations

BOC	*tert*-Butyloxycarbonyl
CAN	Ceric Ammonium Nitrate
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-*N,N*-Dimethylaminopyridine
DMD	Dimethyldioxirane
DMF	Dimethylformamide
DMG	Directing Metallating Group
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethyl Sulfoxide
DOE	Design of Experiments
DoM	Directed *ortho* Metalation
EWG	Electron Withdrawing Group
HMPA	Hexamethyl Phosphoramide
HOBt	Hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
IPA	Isopropyl Alcohol
LDA	Lithium Diisopropylamide
LiHMDS	Lithium Hexamethyldisilazide
MOM	Methoxy Methyl
NaHMDS	Sodium Hexamethyldisilazide
NMR	Nuclear Magnetic Resonance Spectroscopy
ONSH	Oxidative Nucleophilic Substitution of Hydrogen
PDT	Photodynamic Therapy
S_NAr	Nucleophilic Aromatic Substitution
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TDA	Tris[2-(methoxyethoxy)ethylamine]
THF	Tetrahydrofuran
TMAI	Trimethylammonium Iodide
TMHI	Trimethylhydrazinium Iodide
TMSCl	Trimethylsilyl Chloride

***p*-TsOH**	***para*-Toluenesulfonic Acid**
VNS	**Vicarious Nucleophilic Substitution**

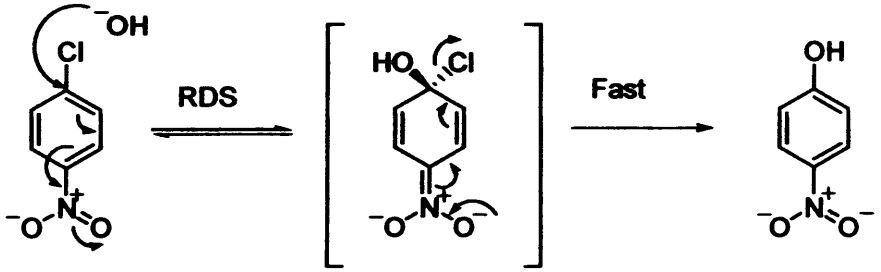
Chapter 1

The study of aromatic reactivity and synthesis has fascinated and occupied chemists since the very early days of the subject. Derivatives of benzene, both simple and complex, form the basis of a multitude of pharmaceuticals, agrochemicals, natural products, petrochemicals, synthetic polymers and materials. Methods designed to control the synthesis of new unexplored aryl derivatives remain as important as ever. This PhD develops one new method for arene synthesis. This introduction summarises some of the important ways by which arenes are prepared.

1.1 Nucleophilic Aromatic substitution (S_NAr)

One of the most important methods is the addition of nucleophiles to the ring to form anionic σ-adducts. There are two ways in which this can happen, firstly addition to the ring in positions occupied with leaving groups such as halogens to form σ^X-adducts and secondly addition in positions occupied with hydrogen to form σ^H-adducts. The case of forming σ^H-adducts will be dealt with later in this Introduction.

The σ^X-adducts formed can undergo rapid elimination of X^-, to give products of nucleophilic aromatic substitution (S_NAr). The mechanism of this reaction is shown in Scheme 1.



Scheme 1

The presence of electron withdrawing groups (such as nitro) *ortho* and *para* to the leaving group substantially enhance the rate of substitution. The reason they can do this is because they stabilize negative charge on adjacent groups at the *ortho* and *para* positions but not at the *meta* position.

The best leaving group in these reactions is fluoride (F^-). Attack at the carbon bearing fluorine is faster than that bearing chlorine or bromine in the rate determining step due to the difference in electronegativity. This process has been known for a long time and has been reviewed extensively.[1-4]

1.2 Oxidative Nucleophilic Substitution of Hydrogen (ONSH)

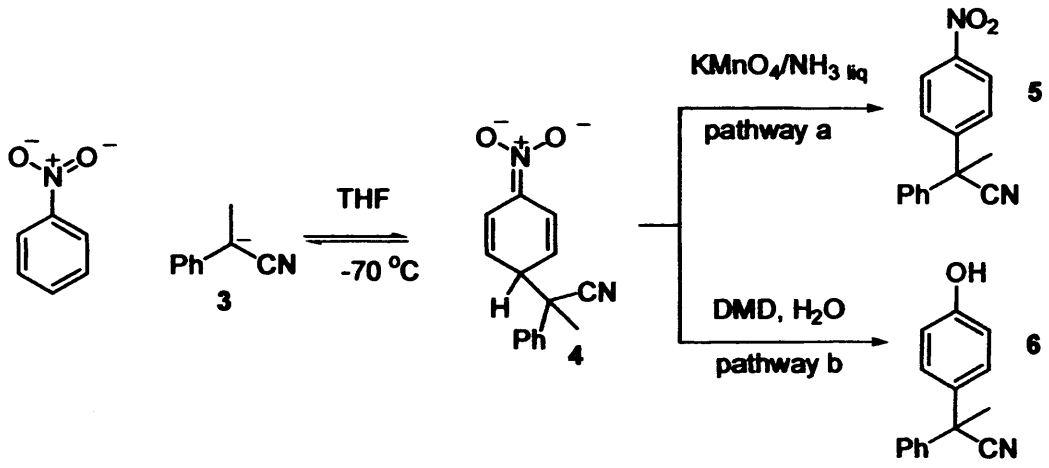
Direct conversion of the σ^H-adducts into products does not occur due to hydride being a very poor leaving group. Without an additional reactant, the σ^H-adducts simply revert to the starting material. Even when the *ortho* or *para* positions are occupied with a good leaving group such as a halogen, it is well known that attack at a carbon-bearing hydrogen is much faster than that bearing halogen.[5-7]

The hydride anion needs to be removed with an additional reactant in a process that is equivalent to oxidation. This process was termed oxidative nucleophilic substitution of hydrogen (ONSH).[8-11]

One of the problems with the ONSH reactions is generally the high sensitivity of C-nucleophilic agents, such as carbanions or Grignard reagents towards oxidation. The introduction of carbon substituents can be carried out provided that the addition of the C-nucleophiles and the formation of the σ^H-adducts proceeds to completion, so amounts of the free nucleophile in the reaction vessel are negligible. Nucleophiles resistant towards oxidation are exemplified by the hydroxide anion and ammonia.

An example of an ONSH reaction is the addition of the 2-phenylpropionitrile carbanion (**3**) to nitrobenzene and its derivatives, carried out in liquid ammonia and THF at –70 °C. The nitroarenes are converted to the σ^H-adducts (**4**) almost quantitatively. These adducts are efficiently oxidized by external oxidants such as $KMnO_4$ in liquid ammonia (pathway a in Scheme 2) and dimethyldioxirane (DMD) in THF-acetone (pathway b in Scheme 2).

Scheme 2

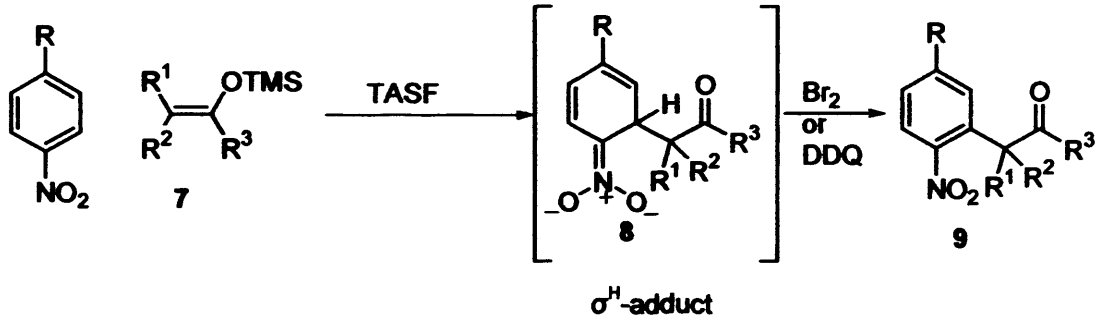


Oxidation with these two oxidants gave two different products leading to the assumption that they react with the σ^H-adducts at different places. Permanganate probably attacks the σ^H-

adduct at the addition site of the nucleophile, producing substituted nitroarene products of oxidative nucleophilic substitution of hydrogen (ONSH) (5).[8-10] Oxidation with DMD proceeds at the carbon with the nitro group to give a substituted phenol **6** in which the nitro group has been replaced by the hydroxy group.[12-13]

An alternative method was developed by RajanBabu and co-workers.[14] This was the fluoride assisted nucleophilic addition of enol silyl ethers to aromatic nitro compounds. It is well established that the stable silyl enol ethers **7** can be activated using a source of fluoride.[15] Oxidation of the resulting σ^H-adducts (**8**) with DDQ or bromine gave α-nitroaryl carbonyl compounds **9** (Scheme 3).

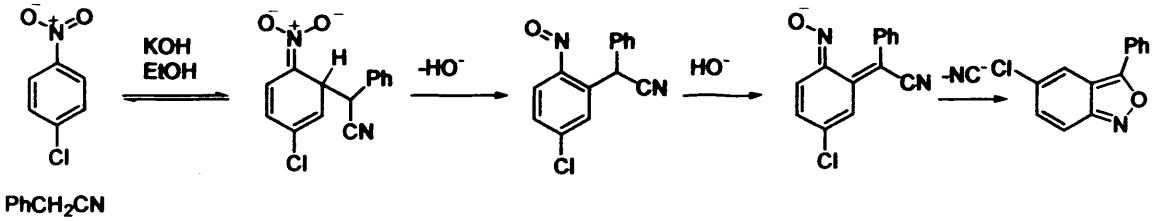
Scheme 3



1.3 Conversion of the σ^H-adducts into Nitroso Compounds

Some σ^H-adducts can undergo spontaneous conversion into substituted nitroso compounds. This reaction can be considered an intramolecular redox process with release of hydroxide ion. This conversion usually takes place in protic solvents *via* protonation of the negatively charged NO_2 group of the σ^H-adducts and elimination of water and is often followed by further transformations of the nitroso compounds[16-21](Scheme 4).

Scheme 4

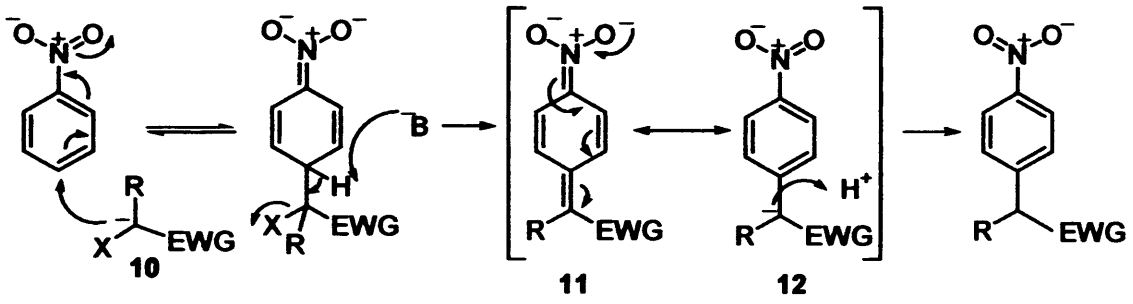


Similar conversion can be promoted by treatment of σ^H-adducts with protic acids, Lewis acids,[22-23] or silylating agents.[24-27]

1.4 Vicarious Nucleophilic Substitution of Hydrogen (VNS)

Perhaps the most general and useful method for transforming σ^H-adducts into products of nucleophilic substitution is the process discovered by Mąkosza[28] and co-workers in the late 1970's. This is a key reaction in this PhD study, so will be reviewed in detail. In this reaction, attack of the nucleophile occurs at carbon bearing hydrogen *ortho* or *para* to the nitro group in the same way as in the ONSH process. Instead of hydrogen, the leaving group connected with the carbanion departs by base induced β-elimination of HX (Scheme 5). Thus the leaving group is acting as a *vicarious* leaving group[29] (in place of) and the reaction was therefore named *Vicarious Nucleophilic Substitution of hydrogen.* We call **11** (and **12**) the post-VNS anion to avoid ambiguity when referring to other anions present in the reaction.

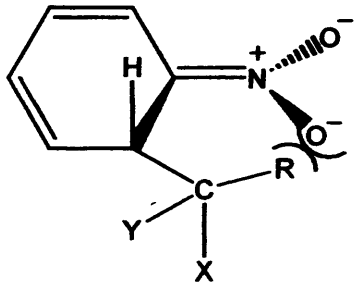
Scheme 5



Due to the fact that attack at carbons bearing hydrogen is significantly faster than at carbons bearing halogens,[5-7] nucleophiles such as chloromethyl phenyl sulfone react with *p*-chloronitrobenzene exclusively at the *ortho* position to the nitro group.[30]

Steric considerations are important in the VNS reaction; if the nucleophile (**10**) is a secondary carbanion, then a mixture of *ortho* and *para* substituted products will occur with nitrobenzene. If **10** is a tertiary carbanion, then exclusive *para* substitution will occur due to a steric clash with the nitro group (Figure 1). If the *para* position is blocked, exclusive *ortho* substitution will occur although with *p*-fluoronitrobenzene, the S_NAr pathway competes with the VNS process.[29]

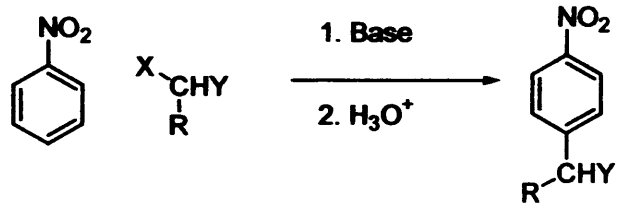
Figure 1



The conditions which favour VNS are sodium or potassium bases in solvents such as DMF, DMSO or liquid ammonia. Under these conditions the *ortho/para* ratio is governed by the kind of carbanion, i.e. the nature of the R group. If the base/solvent system is changed on the other hand to a *t*-BuOK/THF system, there is a unique opportunity with many secondary carbanions to afford selective *ortho* substitution even when there is a vacant *para* position. This effect is observed in the reaction of nitroarenes with chloromethyl phenyl sulfone[31] and acetonitrile[32] derivatives. In this base/solvent system, the carbanions are in the form of tight ion pairs with potassium cations which are attracted by the negatively charged oxygen atoms of the nitro groups. The σ-adducts are then formed *ortho* to the nitro group. To eliminate this effect, one equivalent of a crown ether can be added.[31]

The main requirement for the carbanion is that it should contain a leaving group X connected directly to the carbanion centre. The leaving group must be capable of its elimination as HX from the intermediate σ-adduct. The general structure of the carbanion can be regarded as RC^-XY where X is the leaving group, Y the electron-withdrawing group and R the substituent (Scheme 6).

Scheme 6

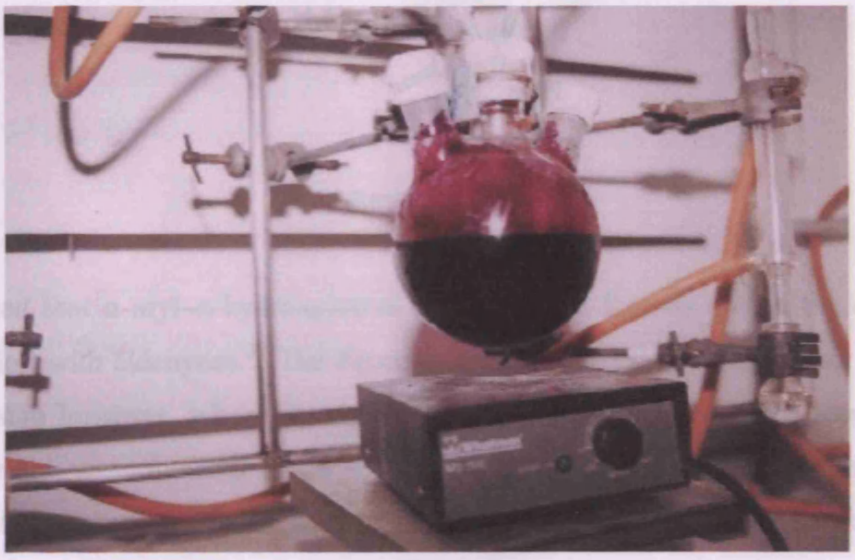


Y = SO_2Ph, $SO_2C(CH_3)_3$, SO_2OPh, $SO_2OCH_2C(CH_3)_3$, $SO_2N(CH_2CH_2)_2O$, SOPh, $POPh_2$, $P(OEt)_2$, CN, COOR', -N=C, PhS, Cl
X = Cl, PhS, Me_2NCCSS, PhO, CH_3O
R = H, alkyl, aryl, PhS, Cl

Almost any combination of the leaving group (X), electron-withdrawing group (Y) and substituent (R) shown will produce a carbanion that will undergo VNS chemistry. However to achieve the best results the combination must be selected meticulously to avoid side reactions that compete with the VNS. One such example is the carbanion derived from methyl chloroacetate which rapidly undergoes self condensation leaving little or no VNS product.

The post VNS anion intermediates are usually highly coloured, a feature which can have some diagnostic value as to whether or not the VNS process has taken place. Below is a typically coloured post VNS anion intermediate (Figure 2).

Figure 2 **A Typical Brightly Coloured Post-VNS anion**

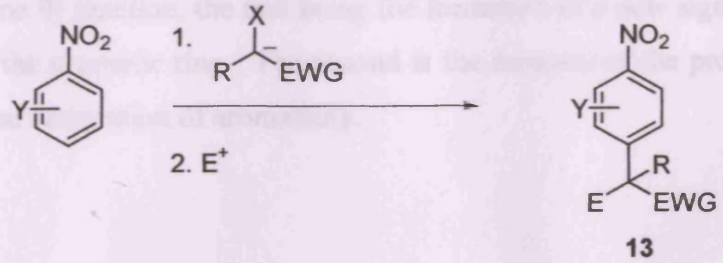


There are a few examples that could be considered early examples of VNS; methylation of nitroarenes and heterocycles with dimsylsodium[33] or with dimethylsulfoxonium methylide[34] and dichloromethylation of *p*-halonitrobenzene with trichloromethyllithium.[35] The mechanistic, synthetic value, and general character of these observed reactions were not, however, recognised.

Aromatic heterocycles bearing a nitro group can also be used in the VNS reaction. The VNS has been performed with 2-and 3-nitrothiophenes, 2-nitrofurans, particularly substituted at C-5, and *N*-alkylated 2- and 3-nitropyrroles.[36]

Previous research in the Lawrence group found that the post VNS anion can not only undergo a proton quench but can also undergo alkylation with electrophiles such as iodomethane. This gave a one-pot three-component coupling VNS/alkylation reaction (Scheme 7) to produce nitroarenes **13** bearing an adjacent quaternary stereogenic centre.[37, 39, 85-6]

Scheme 7



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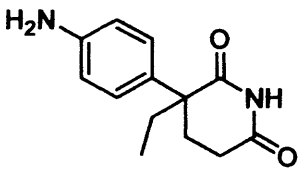
The VNS/alkylation process was used in a racemic synthesis of Aminoglutethimide[37] (Figure 3), an effective anti-cancer drug for the treatment of breast and prostate cancer.[38]

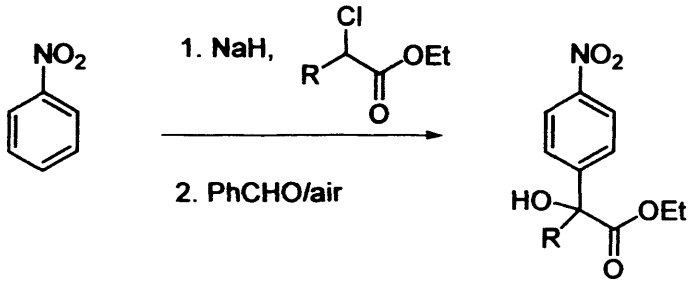
Figure 3



(+/-)-Aminoglutethimide.

It was reported that α-aryl–α-hydroxyesters (**14**) could be formed during the reaction of the post VNS anion with aldehydes.[39] The expected formation of the aldol product did not occur. On one occasion however, when air was inadvertently introduced into the reaction flask, the hydroxy ester **14** was obtained in 50% yield (Scheme 8). It was found that when three equivalents of the ester were used with respect to nitrobenzene the yield can be increased to 66%.

Scheme 8



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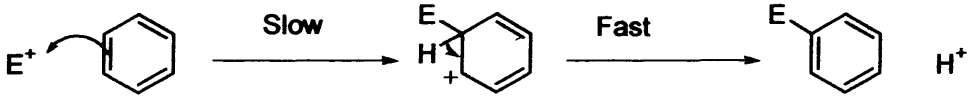
1.5 Electrophilic Aromatic Substitution

This section will briefly discuss electrophilic aromatic substitution, an area of chemistry that has been known for a long time and has been extensively studied and is thoroughly documented.[40] There are two fundamental sequential steps in an electrophilic aromatic substitution (Scheme 9) reaction, the first being the formation of a new sigma bond by attack of an electrophile by the aromatic ring. The second is the removal of the proton by breaking the C-H sigma bond and restoration of aromaticity.

Scheme 9



Substituents affect the reactivity of the aromatic ring. Electron donating substituents such as OH and NH_2 activate the ring making it more reactive than benzene. Electron-withdrawing substituents such as NO_2 deactivate the ring making it less reactive than benzene.

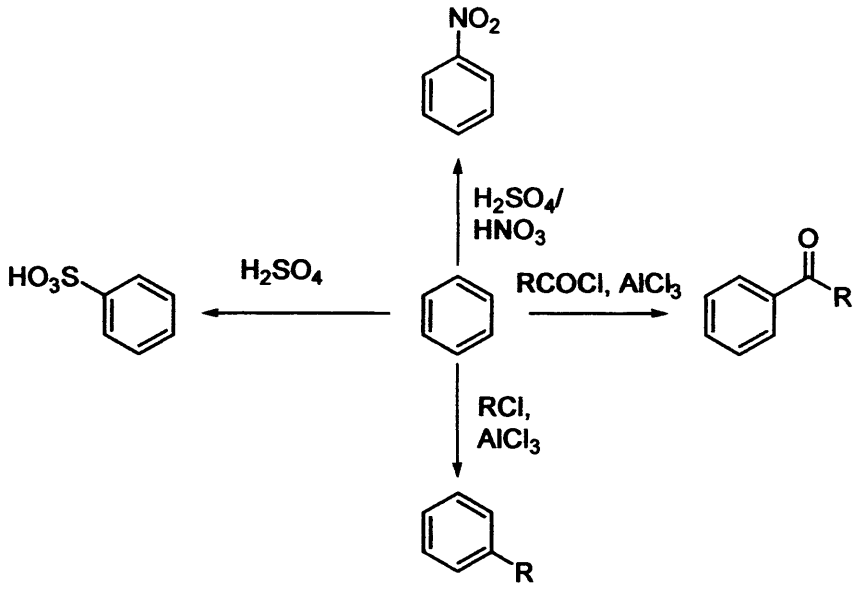
Substituents also affect the orientation of the reaction. The three possible disubstituted products- *ortho, meta* and *para* are not usually formed in equal amounts. The nature of the substituent already present on the benzene ring determines the position of the second substituent. Substituents can be classified into three groups: *ortho/para* directing activators, *ortho/para* directing deactivators and *meta* directing deactivators.

Reactivity and orientation in electrophilic aromatic substitutions are controlled by inductive and resonance effects. Nitration of anisole could occur either *ortho, meta* or *para* to the methoxy group. The intermediates from *ortho* and *para* attack are stabilized. Only in *ortho* and *para* attack are there resonance forms in which the positive charge is stabilized by donation of an electron pair from oxygen. The intermediate from *meta* attack has no such stabilization.

Toluene is *ortho/para* directing because these resonance forms can place the positive charge directly on the methyl substituted carbon, where it is a tertiary carbocation and can be stabilized by the electron donating effect of the methyl group. The halogens are deactivating because their stronger electron withdrawing inductive effect outweighs their weaker electron donating resonance effect. Though weak, that electron donating resonance effect is felt only at the *ortho* and *para* positions. Thus a halogen substituent can stabilize the positive charge of the carbocation intermediates from *ortho* and *para* attack in the same way that hydroxy and amino substituents do.

With electron-withdrawing substituents such as nitro, both *ortho* and *para* intermediates are destabilized because the resonance form places the positive charge on the carbocation intermediate directly on the ring carbon atom that bears the deactivating group. Reaction with an electrophile therefore occurs at the *meta* position. Below are some commonly used transformations (Scheme 10).

Scheme 10

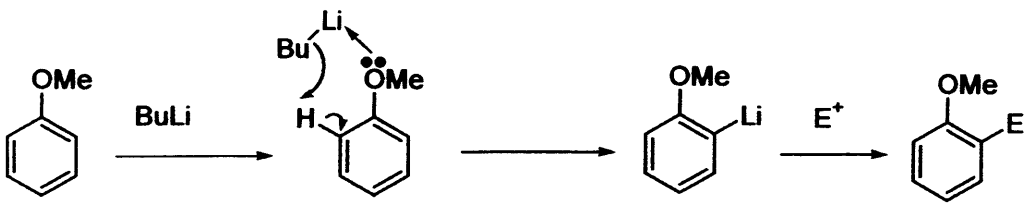


1.6 Directed *ortho*-Metalation (DoM)

This process has a distinct advantage over electrophilic aromatic substitution in that harsh reaction conditions are not required. It can also provide convenient access to 1,2,3- and 1,2,3,4- substituted aromatic systems which can be a daunting task with classical electrophilic aromatic substitution methods. Since its discovery by Gilman[41] and Wittig,[42] DoM took little time to establish itself as a powerful tool available to the organic chemist.

DoM requires the presence of a Directing Metalating Group (DMG) which is an inductively withdrawing atom or group that contains a lone pair of electrons. In the presence of a strong base, usually an alkyllithium, this functional group guides the alkyllithium, so that it attacks the adjacent protons. It does this by forming a complex with the Lewis-acidic metal ions, meaning only protons *ortho* to the functional group can be removed (Scheme 11).

Scheme 11



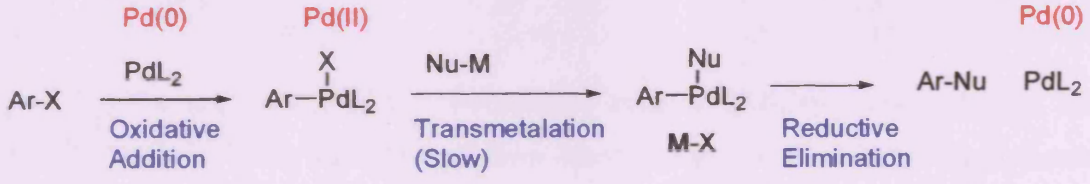
DMG's used include OMe,[41-44] OMOM,[45] and CO_2H[46] among many others.

1.7 Palladium Catalysis.

Palladium-catalysed reactions of aryl halides and triflates with 'hard' organometallic nucleophiles have been widely used over the past 30 years. Variants of these reactions have found widespread applications in modern organic chemistry. Variants include the Suzuki (boron-mediated),[47] Corriu-Kumada-Tamao (magnesium-mediated),[48] Stille (tin-mediated),[49,50] Negishi (zinc-mediated),[51] and Sonogashira (copper-mediated)[52] coupling reactions.

The mechanism of palladium catalysis involves the oxidative addition of the halide or triflate to the initial palladium(0) complex to form a palladium(II) species. The key slow step is a transmetallation, so called because the nucleophile is transferred from the metal in the organometallic reagent to the palladium and the counterion moves in the opposite direction. The new palladium(II) complex with two organic ligands undergoes reductive elimination to give the coupled product and the palladium(0) catalyst ready for another cycle. This process is shown below (Scheme 12).

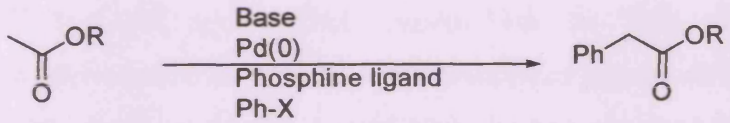
Scheme 12



The palladium catalysed coupling of soft nucleophiles has only been explored in the last 10 years. The studies of Buchwald and Hartwig have proved successful in a wide range of soft organometallic nucleophiles including oxygen-,[53-4] sulfur,[55-60] phosphorus,[61-2] boron[63-4] and silicon based nucleophiles.[65-70]

In recent years the cross-coupling at the α-position of carbonyl compounds such as ketones,[71-9] esters[30, 83] and amides[81-2] with aryl halides has been reported by the groups of Buchwald, Hartwig and Miura (Scheme 13).

Scheme 13



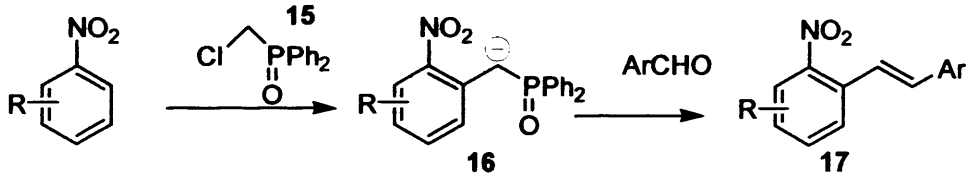
Chapter 2

2.1 Review of VNS for the period 2000-2004

Due to the numerous reviews[30, 83-84] covering VNS before 2000 already available, only VNS after 2000 will be reviewed in this chapter.

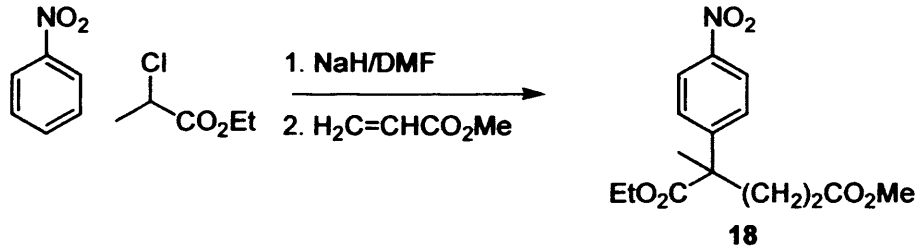
It was found by previous research in the Lawrence group that *E*-stilbenes could be synthesized efficiently *via* a one pot Vicarious Nucleophilic Substitution/ Horner-Wittig reaction. This was achieved by generation of the anion of chloromethyl diphenylphosphinoyl oxide (**15**) with sodium hydride in DMSO and reaction with different nitro-substituted aromatics. The series of VNS products were used in a Horner-Wittig reaction by treatment of base and benzaldehyde derivatives. The desired *E*-stilbenes **17** were produced but only in modest yields. It was thought that the yields of the stilbene might be improved if the anion was used directly. In other words the post-VNS anion **16** was treated with the benzaldehyde derivatives in the same pot (Scheme 14). This approach effectively constitutes a one pot VNS-Horner Wittig reaction. The yields were significantly better than the two step process.[39, 85]

Scheme 14



The post VNS anion undergoes a 1,4-conjugate addition (Michael reaction) with Michael acceptors.[86] The post-VNS anion formed from nitrobenzene and ethyl 2-chloropropionate in a NaH/DMF base/solvent system could be quenched with methyl acrylate to give **18**, which is the product of 1,4-conjugate addition (Scheme 15).

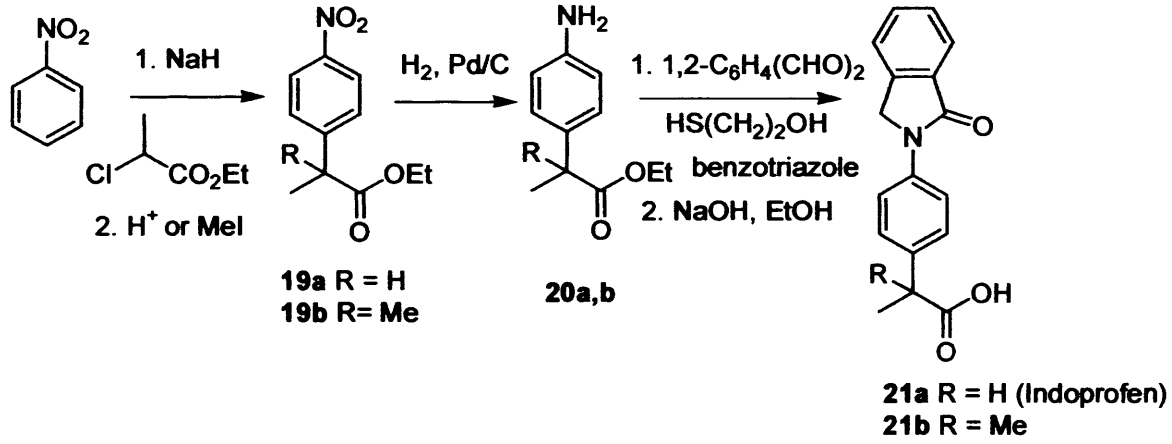
Scheme 15



Derivatives of Indoprofen have been made by a 4-step synthesis that incorporates the VNS process (Scheme 16). Indoprofen (**21a**) is an arylpropionic acid non-steroidal anti-inflammatory drug.[86] The first step in the synthesis was the VNS reaction of ethyl 2-chloropropionate and nitrobenzene in a NaH/DMF base/solvent system with either an acidic or electrophilic quench with methyl iodide to give the VNS products **19a** and **19b**. After the VNS process had been carried out, the product was reduced under hydrogenation conditions to give

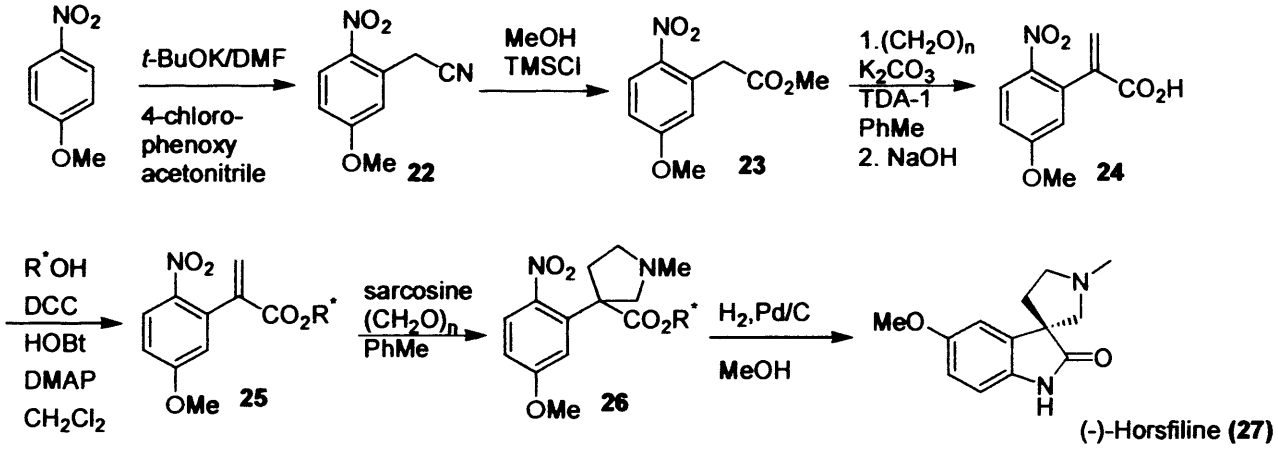
the aniline **20a,b**. The Takahashi protocol [89-90] provided the method for obtaining the phthalimidine derivative from the aniline with 1,2,3-1*H*-benzotriazole, 2-mercaptoethanol and *o*-phthalaldehyde. Saponification of the ester with sodium hydroxide gave Indoprofen **21a** in a 24% overall yield. An α-methyl Indoprofen derivative **21b** was also produced by a VNS/methylation reaction followed by the same condition as the Indoprofen approach.

Scheme 16



Palmisano's synthesis of the natural product (-)-horsfiline (**27**) (Scheme 17) involved a VNS reaction. (-)-Horsfiline (**27**) is a tricyclic alkaloid, first isolated in 1990 from the leaves of *Horsfielda superba*.[89] In the first step of the synthesis 4-nitroanisole and 4-chlorophenoxy acetonitrile were treated with potassium *tert*-butoxide in DMF to give the required VNS product **22** (Scheme 17).[90]

Scheme 17

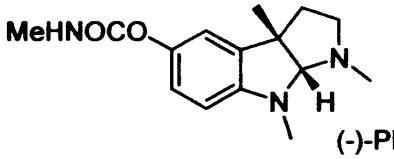


The VNS product **22** was then converted to the ester **23** by methanolysis. On treatment of **23** with *para*-formaldehyde (10 equiv), in the presence of K_2CO_3 and tris[2-(methoxyethoxy)ethyl]amine (TDA-1) as a solid-liquid phase-transfer catalyst in toluene at 85 °C for 3 hours, produced the acrylate product cleanly and in good yield. The ester was then

hydrolysed to the acid **24** which was then coupled to a chiral auxiliary to give **25**. Treatment of this with sarcosine, *p*-formaldehyde, molecular sieves and toluene under reflux produced **26** which after reduction of the nitro group under hydrogenation conditions cyclised onto the ester bearing the chiral auxiliary to give (-)-horsfiline (**27**). Among the chiral auxiliaries tried, only Whitesell's (1*S*,2*R*)-2-phenyl-1-cyclohexanol[90] provided an acceptable level of diastereoselectivity (86% de by HPLC).

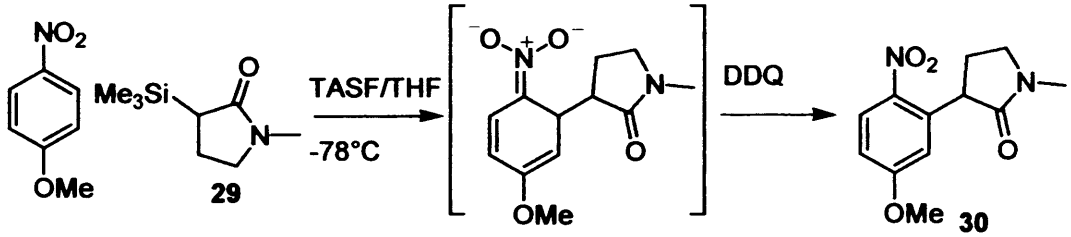
A VNS-type process has also been used in the synthesis of the natural product (-)-Physostigmine (**28**) (Figure 4).[93] The key step in the synthesis the author claimed was a VNS reaction between *p*-nitroanisole and a C-silylated derivative of *N*-methylpyrrolidinone **29** (Scheme 18) followed by oxidation with DDQ to give **30**. This approach however was not strictly VNS but Oxidative Nucleophilic Substitution of Hydrogen (ONSH).

Figure 4



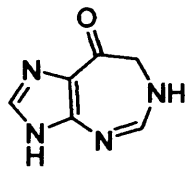
(-)-Physostigmine (**28**)

Scheme 18



Vicarious Nucleophilic Substitution was used in the synthesis of 6,7-dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one (**31**) (Figure 5), which is an important intermediate in organic synthesis.[92] It has been used in the synthesis of natural products pentostatin,[93-5] and coformycin[96] which are both anti-cancer and *anti*-viral nucleosides.

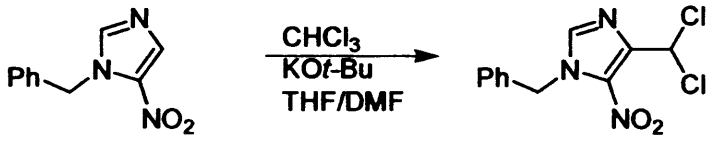
Figure 5



6,7-dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one (**31**)

The synthesis started with the commercially available 4-nitroimidazole. *N*-Benzylation gave a substrate **32** which could undergo the VNS process. It did so with the anion generated from chloroform and potassium *tert*-butoxide (Scheme 19) to give the expected VNS product **33**.

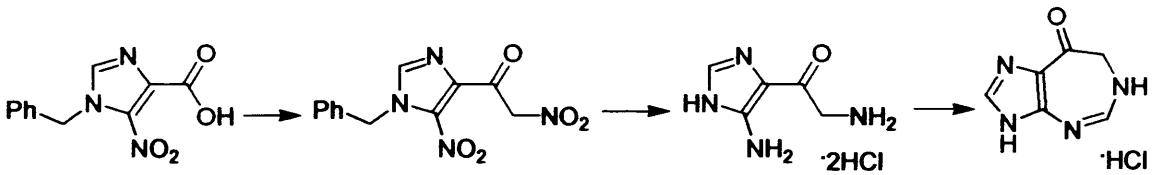
Scheme 19



32 **33**

When the VNS product **33** was treated with formic acid followed by $NaClO_2/NH_2SO_3H$, the carboxylic acid **34** was obtained. This acid was then coupled with nitromethane using CDI to give the dinitroketone **35**. The nitro groups were then reduced with Fe/HCl and the benzyl protecting group removed with Pd/HCO_2NH_4 to give **36**. Treatment of the deprotected product with ethyl formate in DMSO gave the required product **37**, which was isolated as a mono hydrochloride salt (Scheme 20).

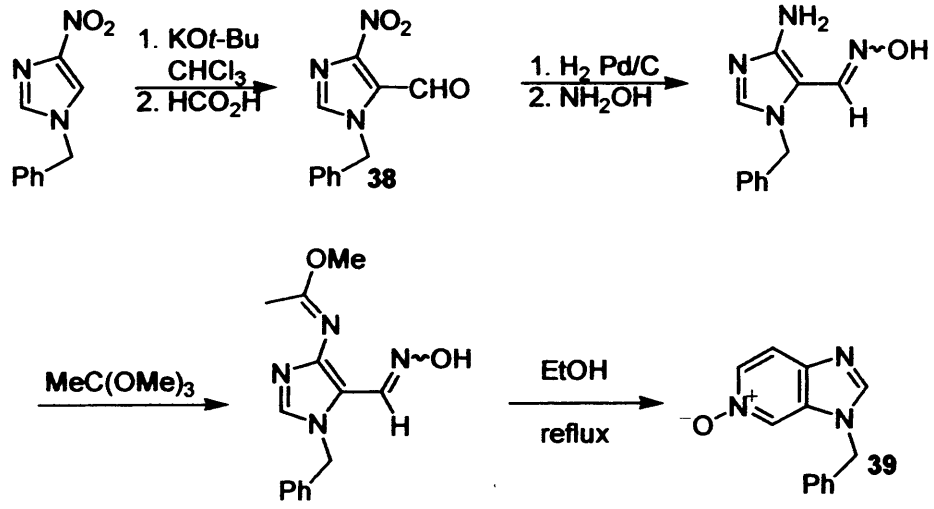
Scheme 20



34 **35** **36** **37**

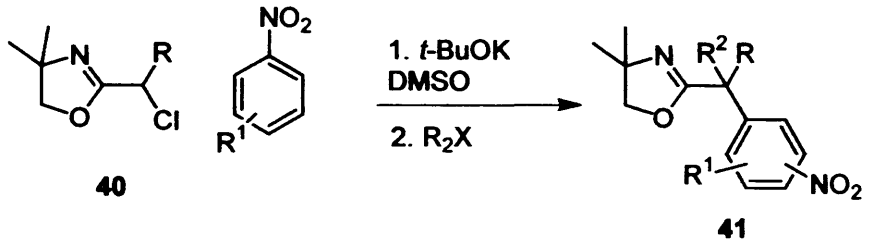
Fused pyrimidines are of particular interest for the synthesis of purine derivatives **39**. The synthesis starts from 4-nitroimidazole-5-carbaldehyde (**38**), readily available from 1-substituted 4-nitroimidazoles *via* VNS dichloromethylation (Scheme 21).[92] This is an example of purine synthesis in which the 6-membered ring is constructed using an existing 5-membered imidazole ring, a strategy not commonly used in the synthesis of purines.

Scheme 21



It has been recently reported that chloralkyloxazolines **40** and other chloroalkyl heterocycles under basic conditions react with nitroarenes to produce VNS products **41** (Scheme 22).[97-8]

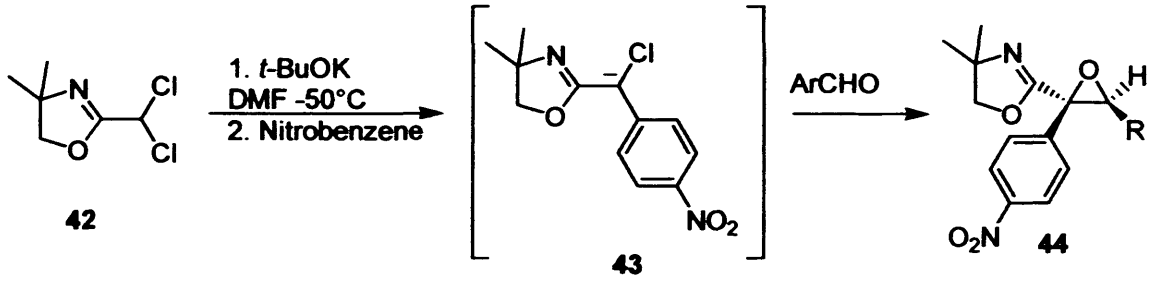
Scheme 22



40 41

No success was achieved when trying to capture the post VNS anion with aldehydes. If instead of using chloromethyloxazolines **40**, dichloromethyloxazoline **42** was used, quenching with benzaldehyde derivatives resulted in oxazolinyldiaryloxirane **44** as a single diastereoisomer (Scheme 23).[99]

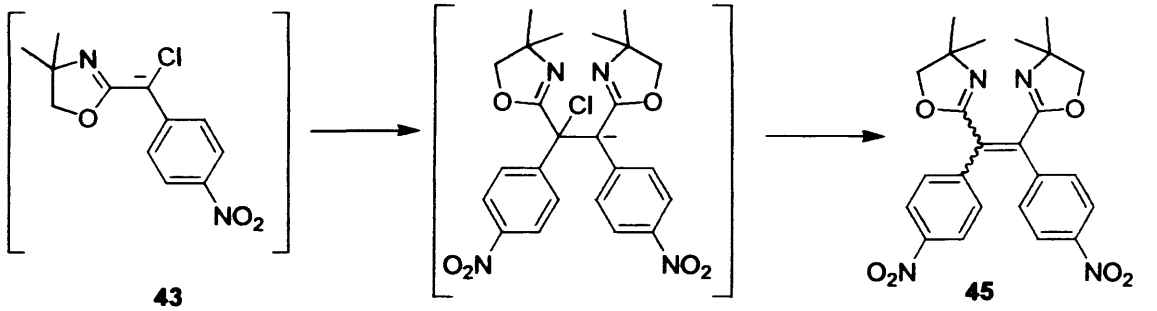
Scheme 23



42 43 44

If the post VNS anion **43** was however left without an electrophilic quench, a mixture of *E* and *Z* 1,2-diaxolinyl-1,2-di-*p*-nitrophenylethene (**45**) (Scheme 24) was formed. In this case, the post VNS anion **43**, which has carbenoid character, undergoes homocoupling, followed by elimination of chloride to generate **45**.

Scheme 24



43 45

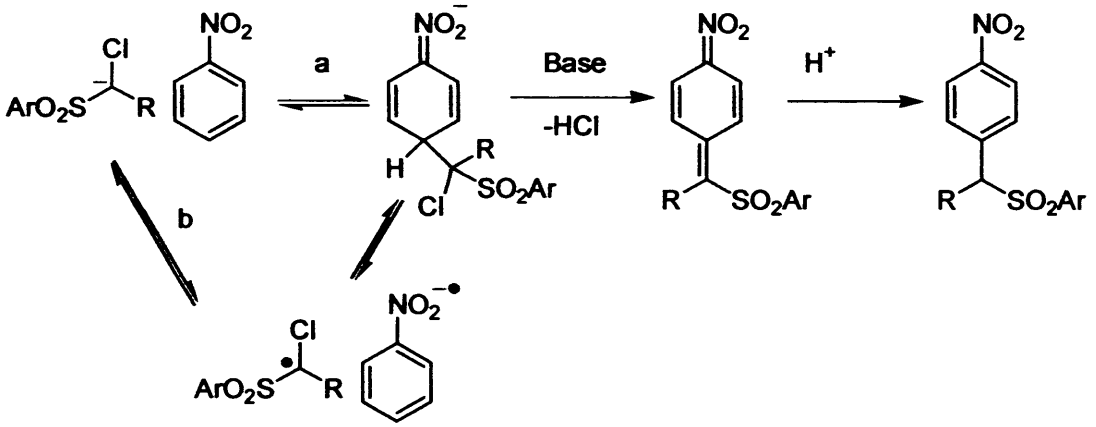
E/*Z* 1:1

Attempts to trap the post VNS anion with ketones and imines resulted in no success with only 1,2-diaxolinyl-1,2-di-*p*-nitrophenylethene (**45**) being formed. If THF was used as the solvent, the VNS reaction occurred exclusively at the carbon *ortho* to the nitro group, which when quenched with benzaldehyde derivatives also gave efficient access to oxiranes.

The mechanistic pathway of the formation of the σ^H-adducts formed in the VNS process was investigated by Mąkosza and Kwast.[100] The two possibilities considered were direct

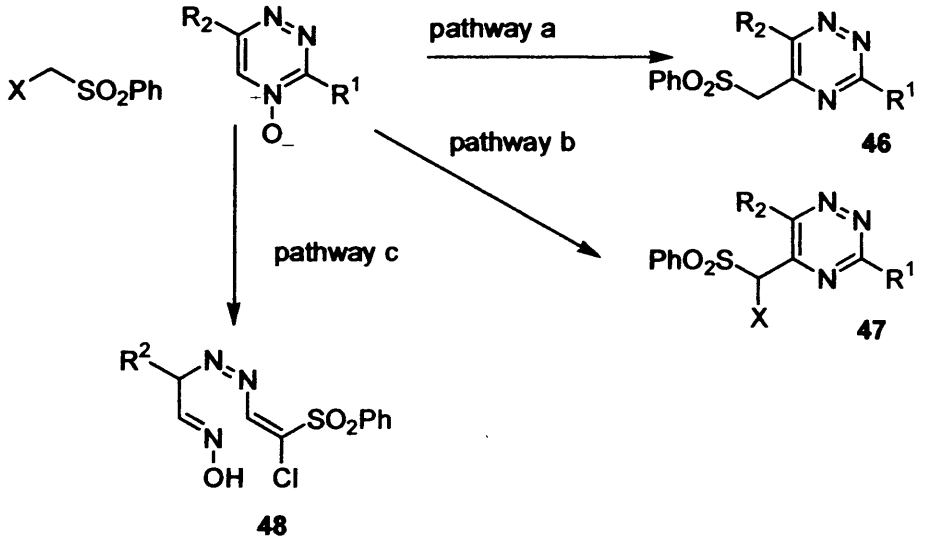
nucleophilic addition of carbanions to nitroarenes *pathway a* (Scheme 24) and a two-step single electron transfer (SET) process *pathway b*. It was concluded on the basis of their observations of typical radical probes (α-halosulfones) with *o*-chloronitrobenzene that the intermediate σ^H-adduct is formed by a one step ionic process and not SET.

Scheme 25



Mąkosza has found that carbanions of halomethyl aryl sulfones react with substituted 1,2,4-triazine-4-oxides by at least three different processes (Scheme 26).[101] Pathways a and b occur when R^1 is not H. Pathway a is the VNS process and Pathway b is deoxygenative replacement of the hydrogen in the 5-position. It was found that using α-haloaryl sulfones as the carbanion resulted predominantly in the products of deoxygenative replacement of hydrogen **47**. Formation of the VNS product **46**, all be it in small amounts, indicated that there are no large differences between the rates of the competing reactions. Changing the reaction conditions had no visible effect on the competition between the two processes.

Scheme 26

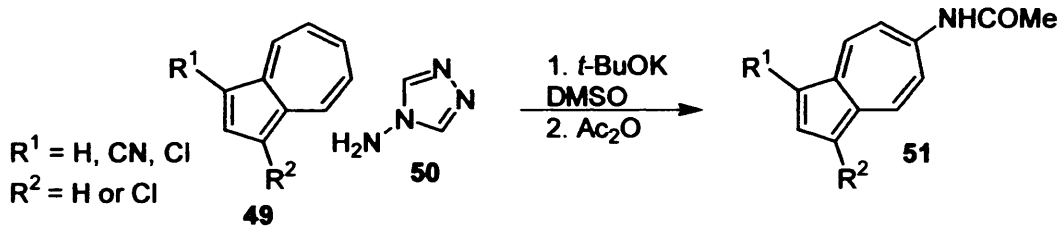


48

It was thought that instead of using an α-bromoaryl sulfone, but an α-chloroaryl sulfone the reaction would proceed *via* the VNS pathway because β-elimination of HBr should proceed much faster than HCl. This proved to be the case and the VNS process (pathway a) occurred predominantly. Pathway c occurs when the R^1 substituent is H which allows nucleophilic attack at this position followed by heterocyclic ring opening in the intermediate σ^H-adduct to produce **48**.

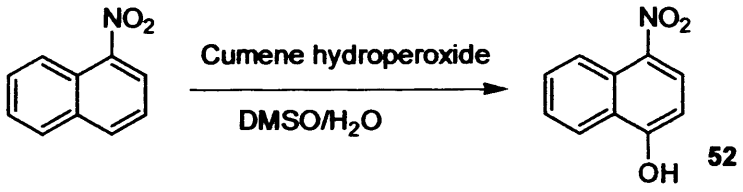
The hydroxylation of nitroarenes proceeds conveniently by the addition of *tert*-butyl or cumyl hydroperoxides in the presence of strong bases.[102-4] These conditions when used with azulenes however provided negative results. It appeared that due to the low nucleophilic activity of the *t*-$BuOO^-$ anion, the σ^H-adduct is not formed. However, reaction with more electrophilic azulenes **49** containing electron-withdrawing substituents in the 5 membered ring proceeded satisfactorily.[105] It was found that 4-aminotriazole **50** is an efficient aminating agent of azulenes when the reaction is carried out in the presence of *t*-BuOK (Scheme 27). The products were of moderate stability so were isolated as the corresponding acetyl derivatives **51**.

Scheme 27



A general method for specific *para*-hydroxylation of nitroarenes has been developed by Zhang. In basic aqueous media, the nucleophilic hydroxylation of nitronaphthalenes with cumene hydroperoxide led to specific *para*-hydroxylation (Scheme 28).[106] The reaction took place very slowly in water due to the insolubility of the starting materials. When the reaction was carried out in anhydrous DMSO, a mixture of *para*- and *ortho*-regioisomers were formed. In a mixture of water (25%) and DMSO (75%), this nucleophilic substitution gave exclusively the product of *para*-hydroxylation **52**.

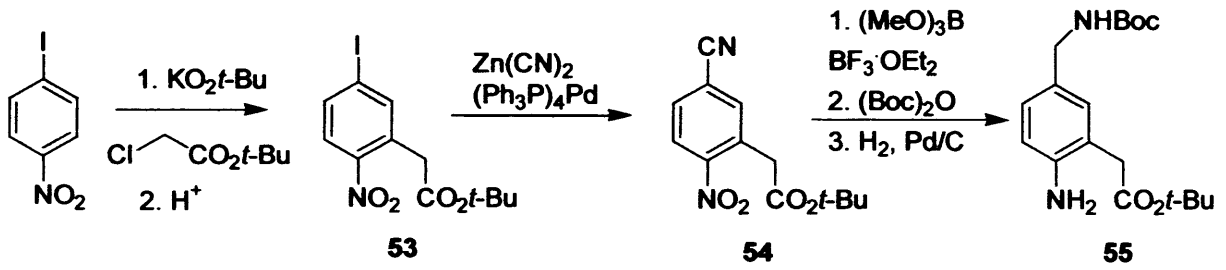
Scheme 28



A series of tricyclic indole-2-carboxylic acid derivatives were synthesized by a route incorporating VNS (Scheme 29). Commercially available 4-iodonitrobenzene was treated with

tert-butyl chloroacetate under VNS conditions to give **53**. Palladium catalysed cyanation was carried out using zinc cyanide to give **54**. Reduction of **54** with $BF_3{\cdot}OEt_2/B(OMe)_3$ in THF followed by Boc protection and then reduction of the nitro group gave the aniline **55**.

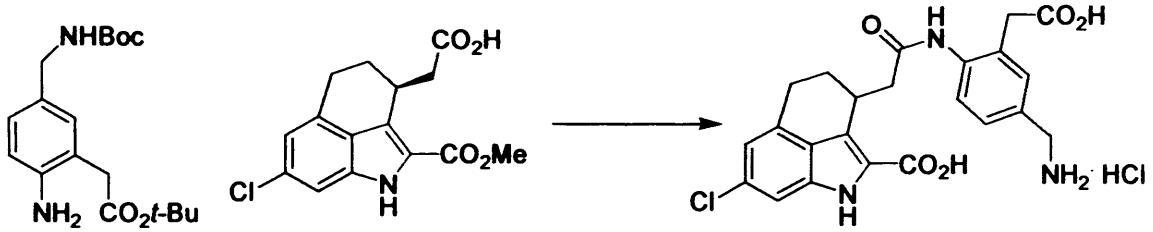
Scheme 29



53 **54** **55**

Condensation of **56** with **57** followed by hydrolysis of the ester gave **58** which was obtained as the hydrochloride salt (Scheme **30**). The tricyclic indole-2-carboxylic acid (**58**) was then evaluated by the radio-ligand binding assay and the anticonvulsant effects investigated in the mouse NMDA-induced seizure model.[107]

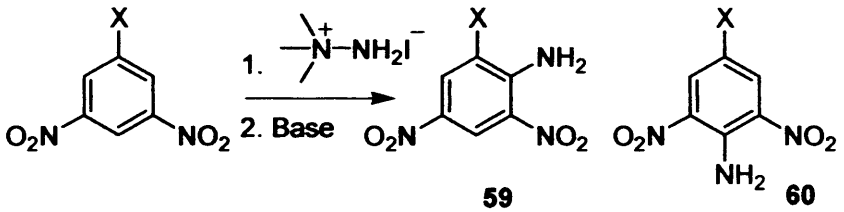
Scheme 30



56 **57** **58**

The direct amination of 1-substituted 3,5-dinitrobenzenes was successfully carried out by the use of 1,1,1-trimethylhydrazinium iodide (TMHI) in the presence of *t*-BuOK or NaOMe in DMSO (Scheme 31).[108]

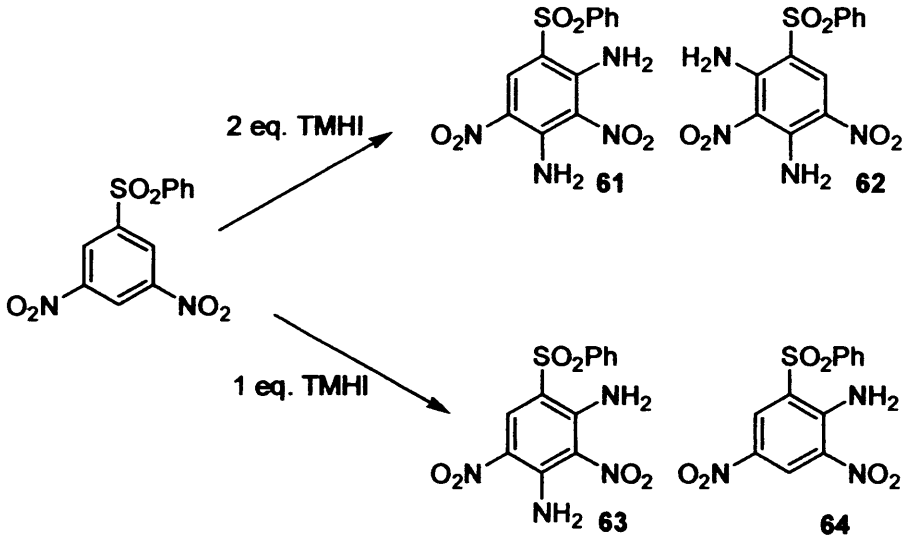
Scheme 31



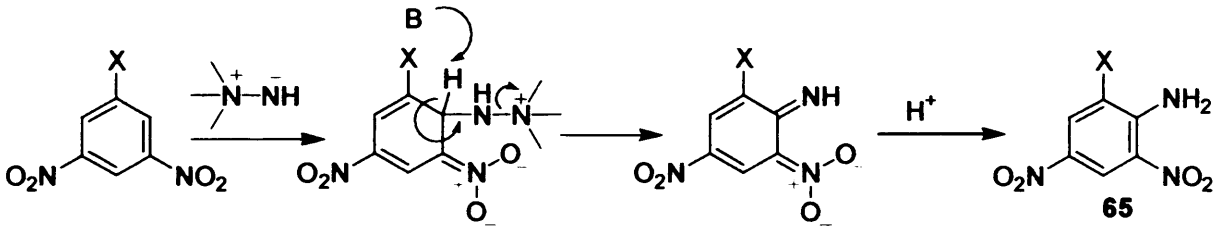
With most substituents, the dinitroanilines **59** and **60** were obtained as a mixture in good yield with the *ortho*-isomer **59** being predominant (*ortho* with respect to the substituent X). When a sulfone was used as the substituent however, two equivalents of TMHI produced a mixture of diamines **62** and **63** (Scheme 32) in a 9:1 ratio. When only one equivalent of TMHI was used in the reaction another mixture of products was formed comprising a monosubstituted product

64, a disubstituted product **63** as well as unreacted starting material was recovered in a 4:1:5 ratio. In the presence of strong base, deprotonation of TMHI occurs resulting in the formation of trimethylammonium iodide (TMAI). The TMAI adds to the nitroaromatic to either the *ortho* or *para* position relative to X to give a σ^H-adduct. Base induced β-elimination of trimethylamine then takes place. Protonation of the post VNS anion then gave the product **65** (Scheme 33).

Scheme 32

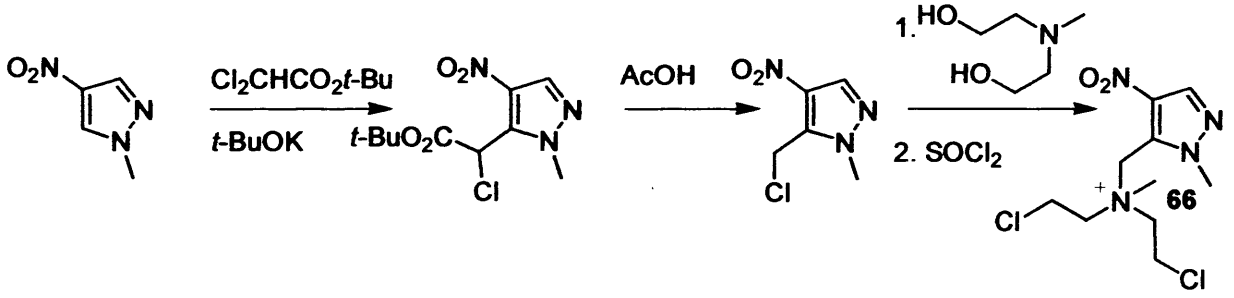


Scheme 33



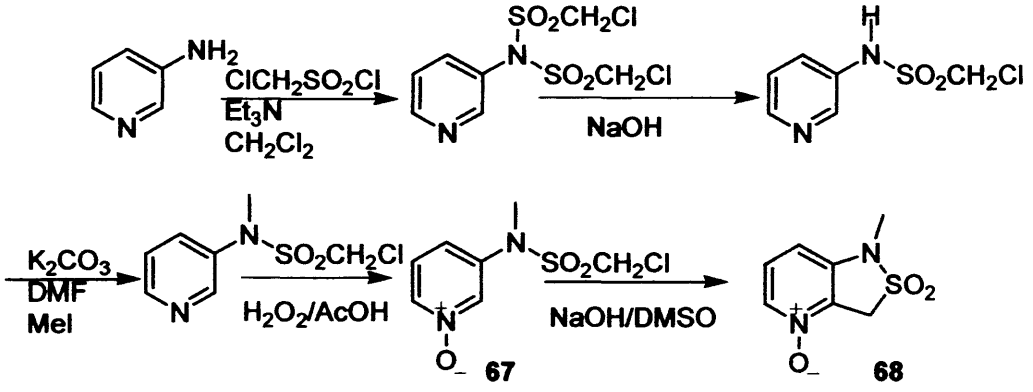
Nitrobenzyl quaternary salts of nitrogen mustards have been reported as hypoxia selective cytotoxins.[109-110] The VNS process was used in the synthesis of a pyrazole analogue **66** that was evaluated as a hypoxia-selective cytotoxin (Scheme 34).[111]

Scheme 34



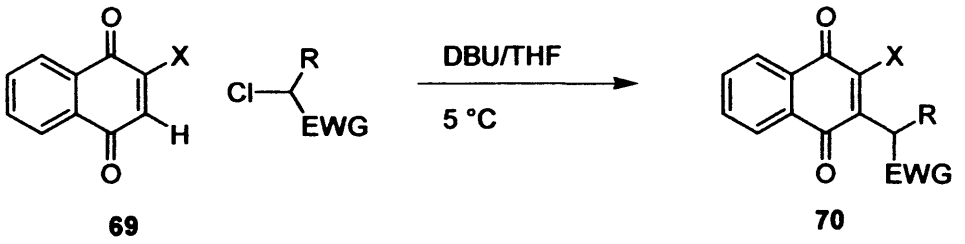
Nitroaromatic compounds are not the only ones to undergo the VNS process. Wojciechowski found that the VNS process could be used in the synthesis of novel isothiazolopyridine and quinoline derivatives **68** (Scheme 35).[112]

Scheme 35



In the final step an intramolecular VNS process takes place. Deprotonation of the sulfone **67** followed by the formation of an intermediate in which base induced β-elimination of HCl takes place. Alternatively, instead of the pyridine *N*-oxide, quaternisation of the nitrogen atom with electrophiles such as methyl iodide produces substrates which undergo the VNS process.

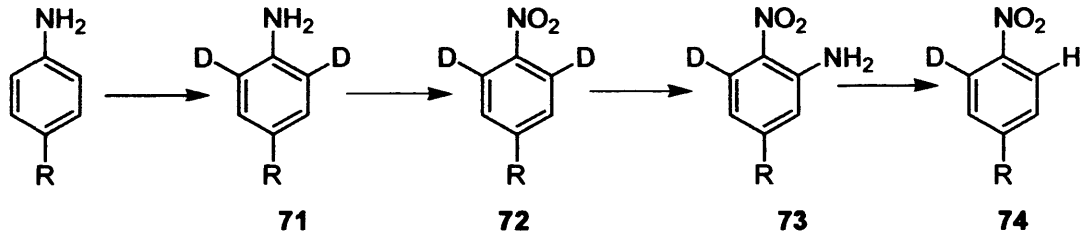
Scheme 36



1,4-Naphthoquinones and derivatives also undergo the VNS process to give **70** (Scheme 36).[113] These VNS reactions in 2-halo substituted naphthoquinones **69** are generally faster processes than Vinylic Nucleophilic Substitution of Halogen (S_NV). The halogen substituent however does result in faster addition of the carbanion to the position occupied by hydrogen due to the increased electrophilic activity. Base induced β-elimination occurs and the expected VNS product **70** formed.

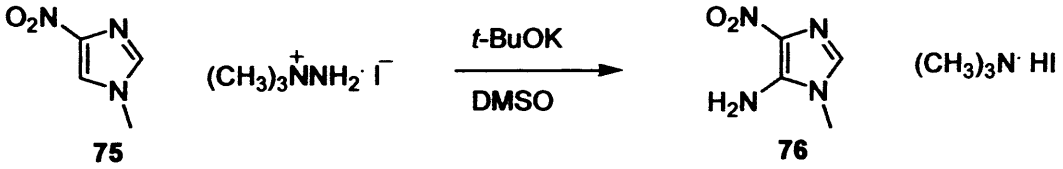
Selectively *ortho*-deuterated nitroarenes can be synthesized in high isotopic purity using a process that involves a VNS step.[114] The method consists of electrophilic aromatic substitution of H for D in *para*-substituted anilines in the *ortho* position to the amino group which was carried out with DCl/D_2O. This was followed by oxidation of the aniline **71** to the nitro-compound **72** followed by a VNS process with *N,N,N*-trimethylhydrazonium iodide to give an *ortho*-nitroaniline **73**. Diazotization and reduction of the diazonium salt gave selectively *ortho*-deuterated nitroarenes **74** in high isotopic purity (Scheme 37).

Scheme 37



It has been found that the VNS process can be carried out upon 1-methyl-4-nitroimidazole (**75**) (Scheme 38), under mild conditions in the presence of sodium methoxide or potassium *tert*-butoxide to give the VNS product (76).[115]

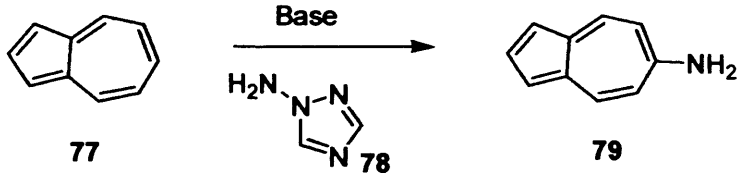
Scheme 38



The VNS C-amination does not occur with 2-methyl-4-nitroimidazole and 1,2-dimethyl-4-nitroimidazole. EPR spectroscopy shows that the VNS C-amination of 1-methyl-4-nitro-imidazole is likely to follow a radical ion mechanism. The EPR signal of the reaction mixture of 1-methyl-4-nitroimidazole with *N,N,N*-trimethylhydrazinium iodide (TMHI) and *t*-BuOK/DMSO can be assigned as the radical ion of 1-methyl-4-nitroimidazole.

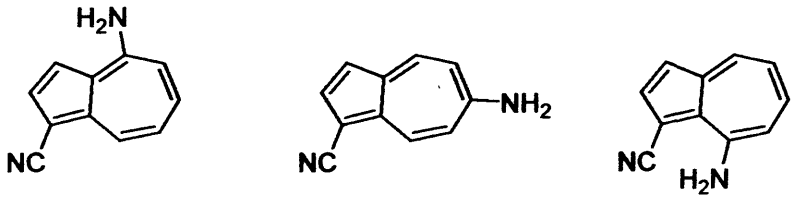
A practical procedure for the synthesis of 6-aminoazulene **79** has been reported using the VNS process. Amination of azulene (**77**) occurs using 4-amino-1,2,4-triazole (**78**) (Scheme 39).[93]

Scheme 39



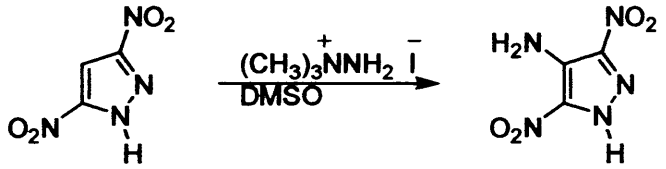
Amination with TMHI of more electrophilic derivatives, substituted at position 1 with CN or COPh, affords mixtures of 4-, 6- and 8-aminoazulenes (Figure 6).

Figure 6



A novel synthesis of 4-amino-3,5-dinitro-*1H*-pyrazole **81** was reported using the VNS process (Scheme 40).[95] Reaction of 1,1,1,-trimethylhydrazinium iodide with 3,5-dinitropyrazole (**80**) in DMSO produced 4-amino-3,5-dinitro-*1H*-pyrazole (**81**).

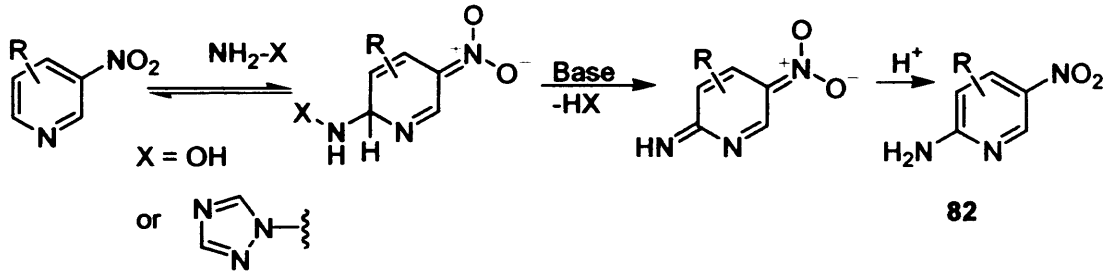
Scheme 40



80 **81**

Two different procedures have been found as a route to 2-amino-5-nitropyridines **82** in moderate to good yields from the VNS process using 3-nitropyridines with either hydroxylamine or 4-amine 1,2,4-triazole as aminating agents (Scheme 41).[96] 2-Amino-5-nitropyridines **82** would be useful starting materials in the synthesis of biologically active compounds. The 2,5-substitution pattern of pyridine is the base for many pharmaceuticals and crop protecting agents. It has proved difficult in the past to obtain this substitution pattern with high regioselectivity.[116] The use of hydroxylamine as the VNS aminating agent provides a simpler and cheaper procedure. In large scale preparations, this procedure would be better because of the easy work up despite the process with 4-amine 1,2,4-triazole giving slightly better yields. The use of 4-amino-1,2,4-triazole demanded an inert atmosphere and DMSO as solvent.

Scheme 41

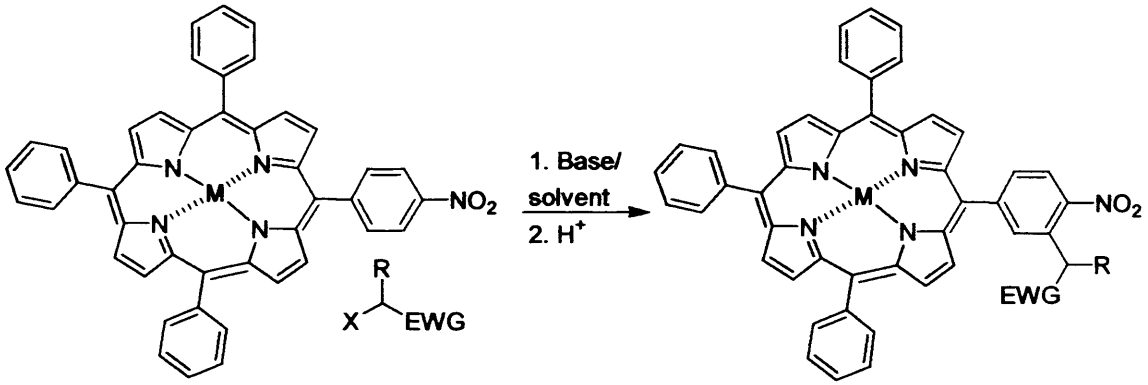


82

Some porphyrin derivatives are used as photosensitizers in photodynamic therapy (PDT).[117-8] PDT is a treatment involving photosensitising drugs and light to kill neoplastic cells. This simple technique is currently being evaluated in multiple clinical trials with promising results.[119-121] Nitration of *meso*-tetraphenyl porphyrin results in mono-nitration in a *para*-position on one of the phenyl rings.[122] The transformation of the two NH centres in the macrocyclic ring into the metal complex **83**, where the central metal cation (Zn^{2+} or Cu^{2+}) is playing the role of a convenient protecting group allowed the VNS process to proceed to **84** in

good yield (Scheme 42). The metal cation offers very labile protection of the NH functions and can easily be removed after reaction if needed.

Scheme 42



A new range of TPP derivatives were synthesized, substituted with α-functionalized alkyl groups *e.g.* arylsulfonyl methyl, cyanomethyl and *N,N*-dimethylsulfonamide. Reactions with tertiary carbanions were unsuccessful due to steric hindrance.

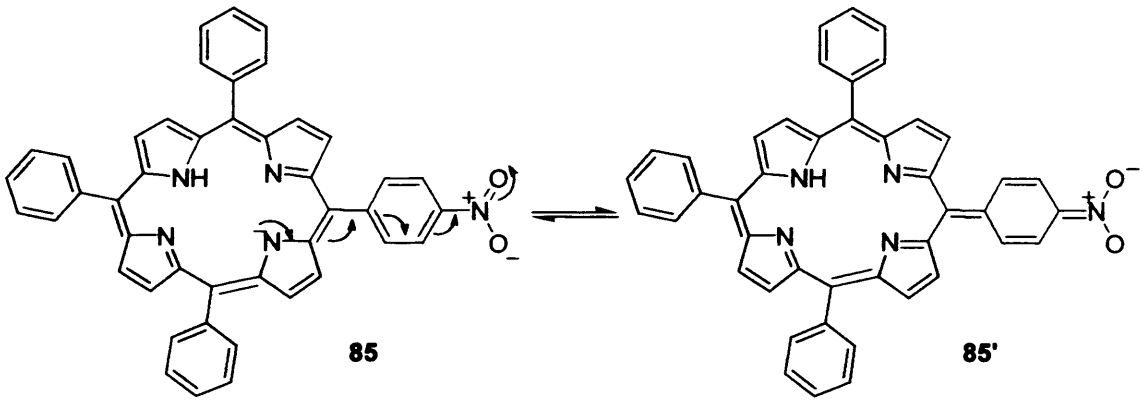


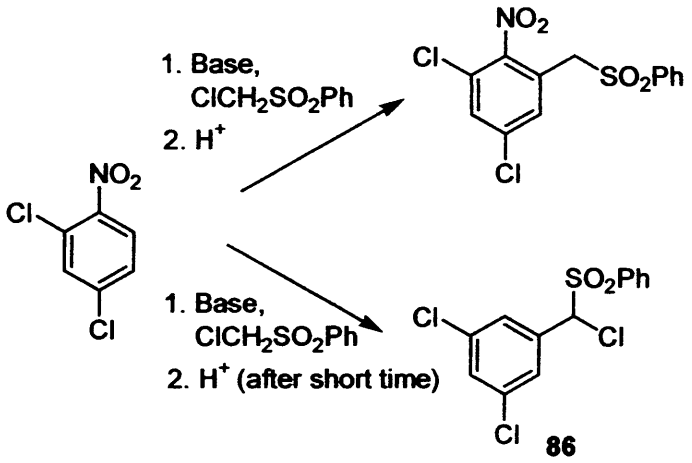
Figure 7

Multiple attempts at utilizing unprotected nitro-*meso*-tetraphenylporphyrin derivatives however proved unsuccessful. Under the strong basic conditions associated with the VNS process deprotonation of the two NH groups occurs so the porphyrin should exist in the *N*-anionic form **85** (Figure 7). At low temperatures the rotation around the C-C bond should be limited, leaving the four *meso* aryl rings orthogonal, thus limiting the conjugation. This would then give the opportunity for VNS to take place on the nitroaromatic as the possibility of increasing the electron density on this ring has been much reduced.[123] This was found to be the case. In *t*-BuOK/THF at –30 °C to –40 °C and *t*-BuOK/DMF at 0 °C the unprotected porphyrins underwent the VNS process to give the desired products in good yield.[119] α-Halomethyl aryl sulfones, α-chloromethyl *N,N*-dialkylsulfonamide and *p*-chlorophenoxyacetonitrile were all

used as the VNS nucleophile. The products obtained gave opportunity for further transformations.

When investigating the effect of halogens on reactions of carbanions with halonitroarenes, Makosza found that under certain conditions, the VNS reaction of chloromethyl phenyl sulfone with 2,4-dinitrochlorobenzene is accompanied by the formation of a considerable amount of (3,5-dichlorophenyl)methyl phenyl sulfone (**86**) (Scheme 43).[124]

Scheme 43

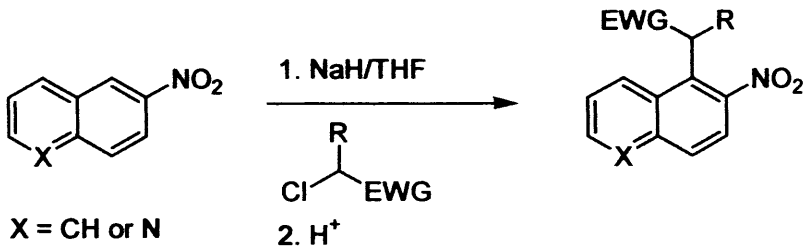


86

The side-product was observed only when the reaction mixture was quenched after a very short time. It was formed by protonation of the intermediate σ^H-adduct followed by elimination of nitrous acid. The essential part of this *cine*-substitution was the acidic quench. When ammonium chloride or acetic acid were used, the starting materials were recovered. However the products of *cine*-substitution **86** were obtained when protonation was performed using dilute strong acids such as HCl or H_2SO_4.

Reaction of 2-nitronaphthalene (**87a**) and 6-nitroquinoline (**87b**) with a secondary carbanion bearing a leaving group and electron withdrawing group such as chloromethyl phenyl sulfone in a NaH/THF base solvent system yielded the conventional products of vicarious nucleophilic substitution of hydrogen **88a** and **88b** (Scheme 44).[94]

Scheme 44



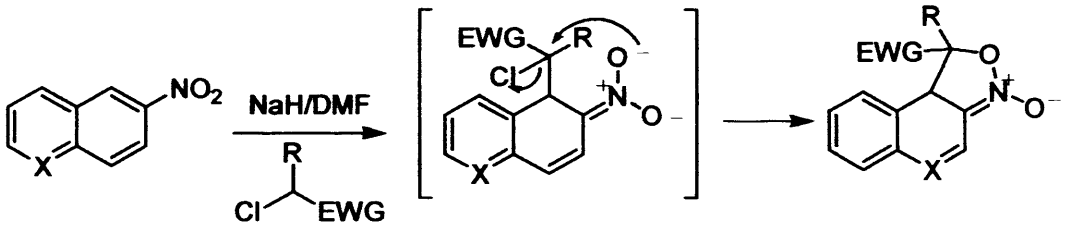
X = CH or N

87a X = CH
87b X = N

88a
88b

However, when secondary and tertiary carbanions were used in a NaH/DMF base solvent system the reactants underwent direct cyclocondensation giving dihydroisoxazolo[4,3-*f*]quinoline *N*-oxides (**89a**) and dihydronapth[2,1-*c*]isoxazole *N*-oxides (**89b**) (Scheme 45).[94]

Scheme 45

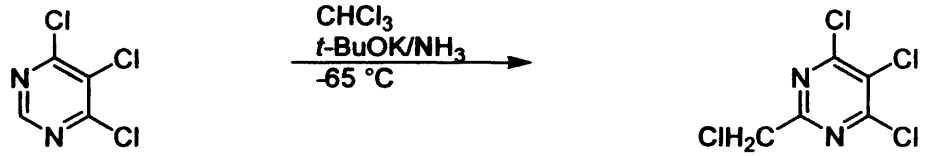


89a X = N
89b X = C

The reaction conditions were tried with *m*-dinitrobenzene as the substrate with secondary and tertiary carbanions but in this case the reaction afforded the VNS products and the desired 2,1-benzisoxazole *N*-oxides were not obtained.

2-Chloropyrimidine and 2,4-dichloropyrimidine react at low temperatures with trihalomethyl carbanions to give covalent σ^H-adducts and the VNS products in low yield. 4,5,6-Trichloropyrimidine in the reactions with carbanions such as $XCHSO_2Tol$ and CBr_3^- and other nucleophiles such as *t*-BuO^- and NH_3 give diverse substituted products of chlorine while in the reaction with CCl_3 anion the VNS process takes place albeit in low yield (Scheme 46).[125]

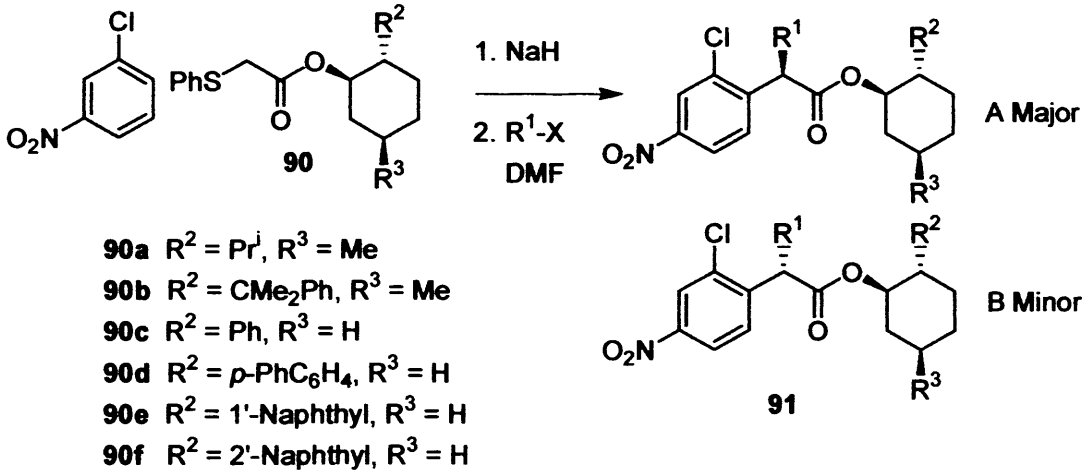
Scheme 46



2.2 Asymmetric Vicarious Nucleophilic Substitution of Hydrogen

The VNS/alkylation process, in which the post-VNS anion was quenched with a variety of electrophiles to produce quaternary stereogenic centres was first reported by Lawrence and co-workers.[38] An unprecedented asymmetric version of the VNS/alkylation reaction was then reported with the use of an appropriate auxiliary incorporated into the nucleophile (Scheme 47).[120]

Scheme 47



90a $R^2 = Pr^i$, R^3 = Me
90b $R^2 = CMe_2Ph$, R^3 = Me
90c R^2 = Ph, R^3 = H
90d $R^2 = p\text{-}PhC_6H_4$, R^3 = H
90e R^2 = 1'-Naphthyl, R^3 = H
90f R^2 = 2'-Naphthyl, R^3 = H

Menthol proved to be a poor auxiliary, since reaction of the VNS nucleophile **90a** with the nitroarene followed by a quench with benzyl bromide gave a 1:1 mixture of diastereoisomers. The reaction of the VNS nucleophile **90b** derived from (-)-8-phenylmenthol however was much more successful. Quenching with methyl iodide gave a 3:1 mixture of diastereoisomers while quenching with benzyl bromide gave a 8:1 mixture. Other auxiliaries were tried such as *trans*-2-phenylcyclohexan-1-ol since both enantiomeric forms are available from a variety of methods, most notably hydroboration[121] or dihydroxylation-reduction[122] of 1-phenyl-cyclohexene. The diastereoselectivity however with this auxiliary was poor.

More sterically demanding auxiliaries were also tried, with quenching of the post-VNS anion with methyl iodide and benzyl bromide, and the results are summarised below (Table 1).

Both products of the VNS reaction of *trans*-2-(2'-naphthyl)cyclohexylphenylsulfonyl acetate **90f** were crystalline. X-ray crystallography showed the major isomer to be the (1*RS*, 2*SR*, α*RS*) diastereosiomer A.

Table 1

Auxiliary		R^1 = Me	R^1 = Bn
			A:B
(-)-Menthol	**91a**	-	1:1 (60)
(-)-8-Phenylmenthol	**91b**	3:1 (67)	8:1 (70)
(-)-*trans*-2-Phenylcyclohexan-1-ol	**91c**	1:1 (55)	2:1 (62)
(+/-)-*trans*-2-(4-Biphenyl)cyclohexan-1-ol	**91d**	1:1 (64)	4:3 (64)
(+/-)-*trans*-2-(1'-Naphthyl)cyclohexan-1-ol	**91e**	3:2 (64)	4:1 (57)
(+/-)-*trans*-2-(2'-Naphthyl)cyclohexan-1-ol	**91f**	3:1 (60)	4:1 (62)

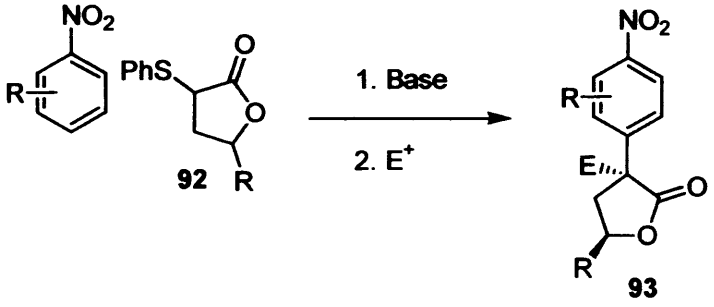
Chapter 3

3.1 Aims

This PhD thesis documents a possibility of applying the VNS process to lactams and thereby developing a new and versatile route to α-aryl lactams. The latter are potentially useful in drug discovery chemistry. They possess several points of structural diversity amenable to convenient derivatization thereby providing an important peptide-like scaffold.

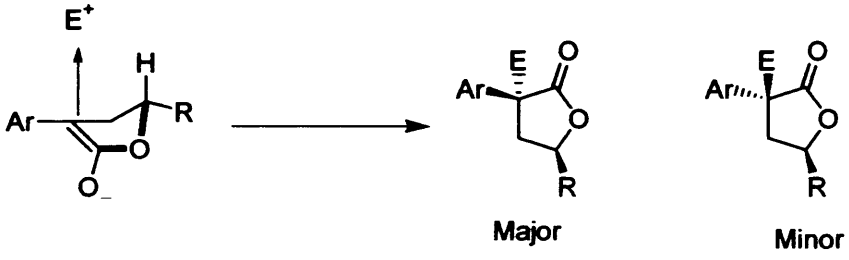
The PhD study also set out to provide further insights into the asymmetric VNS alkylation process. We were keen to investigate the VNS reactions of chiral heterocyclic nucleophiles. The diastereoselectivity of VNS reactions was to be assessed first using an α-thiophenyl lactone possessing a γ-stereogenic centre such as **92** (Scheme 48).

Scheme 48



Reaction of the VNS nucleophile **92** with nitroarenes would generate the post-VNS anion in the usual way. Reaction of this anion with a variety of electrophiles would give the lactone **93** possessing an α-aryl quaternary stereogenic centre. It was expected that the electrophile would approach *anti* to the R group for primarily steric reasons (Scheme 49).

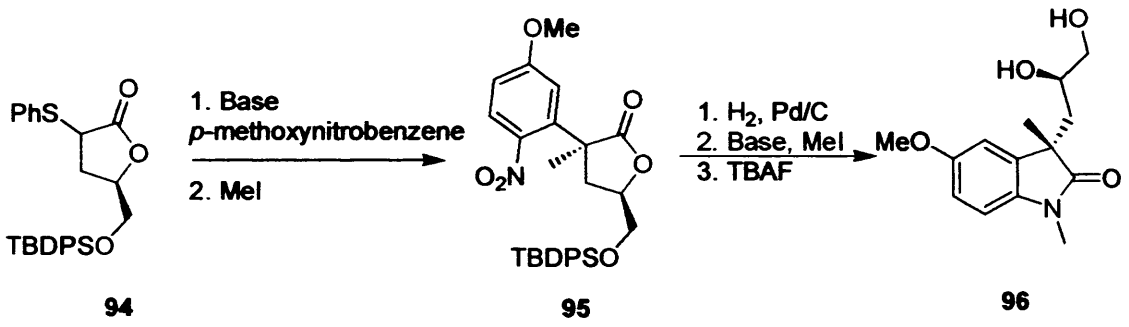
Scheme 49



We hoped to be able to apply this methodology to the total synthesis of Physostigmine, an alkaloid isolated from African Calibar seeds. It possesses interesting biological activity, it is a potent inhibitor of acetylcholinesterase and is used clinically to treat glaucoma and *myasthenia gravis.*[126-7] Physostigmine and analogues[128] are also being evaluated as treatments of Alzheimer's disease and possess morphine-like analgesic properties. The proposed synthesis will commence with a VNS reaction of α-thiophenyl lactone **94** with *p*-methoxynitrobenzene followed by selective reaction of the post-VNS anion with iodomethane (Scheme 50). Catalytic hydrogenation of the nitro compound **95** will provide an aniline derivative, which

will ring-open the lactone, to give, after *N*-methylation an oxindole. Removal of the silyl protecting group will generate the diol **96**.

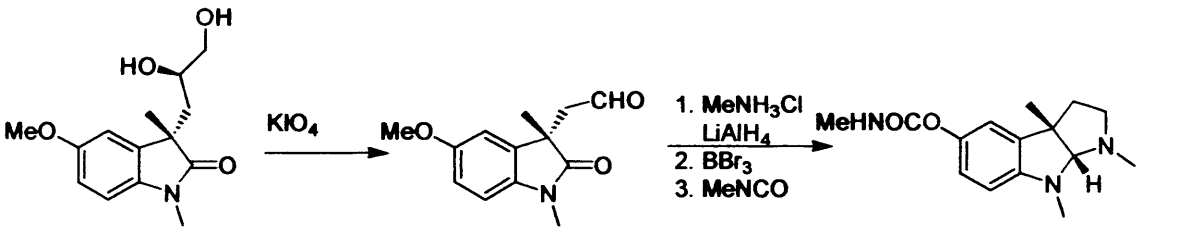
Scheme 50



94 **95** **96**

Treatment of the diol **96** with periodic acid will give the known aldehyde **97**.[129] Physostigmine **98** can be formed from this known aldehyde by sequential reaction with methylamine and $LiAlH_4$ followed by transformation of the methoxyl moiety to the *N*-methyl carbamate group (Scheme 51).

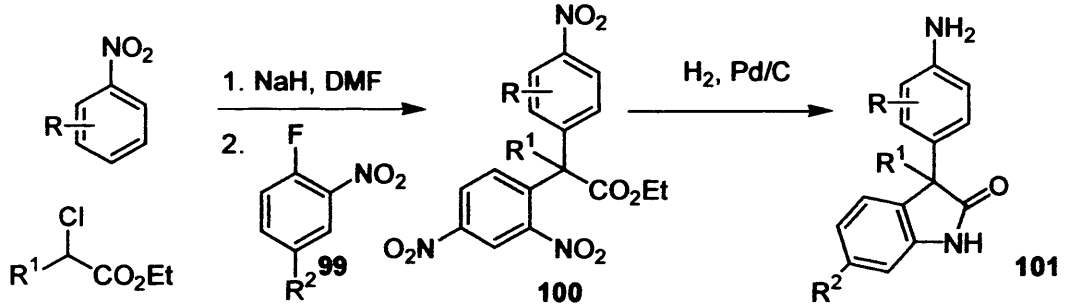
Scheme 51



96 **97** (-)-Physostigmine (**98**)

The following chapters describe the results of my work in attempting to achieve these initial aims. Several additional areas were also studied as the programme of work developed. Most notably the treatment of the post-VNS anion with electron deficient aryl electrophiles **99** such as Sanger's reagent (R^2 = NO_2) was investigated as a possible route to the formation of diarylmethanes **100** and oxindoles **101** (Scheme 52).

Scheme 52

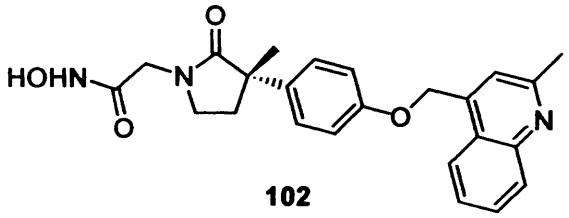


Chapter 4

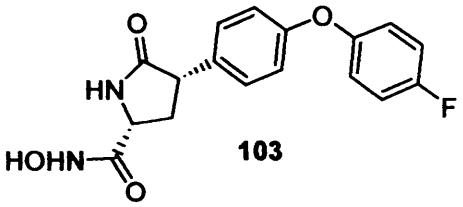
4.1 C-Arylation of Lactams and Pyrazolidinones *via* Vicarious Nucleophilic Substitution of Hydrogen

We have been interested in applying the VNS process to lactams and thereby developing a new and versatile route to α-aryl lactams. The latter are potentially useful in drug discovery chemistry. They possess several points of structural diversity amenable to convenient derivatization thereby providing an important peptide-like scaffold. Such a scaffold has been incorporated into γ-lactam derived inhibitors of tumour necrosis factor α converting enzyme such as **102**,[130] and matrix metalloproteinase-13 inhibitor **103** [131](Figure 8).

Figure 8



102

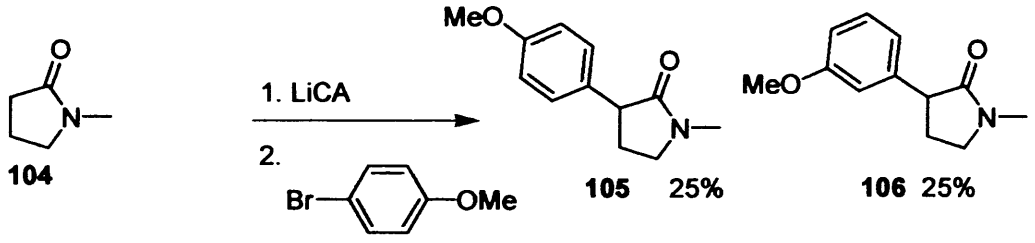


103

It has been shown that the palladium-catalyzed intermolecular coupling of halides and keto enolates is a useful method for synthesizing α-aryl ketones[75] and α-aryl esters.[132] Arylation of other carboxylic acid derivatives such as amides are less common.[132, 133-6]

Few examples of C-arylation of a cyclic amide moiety have been reported in the literature. Stewart and co-workers have utilized an excess of strong base (lithium isopropylcyclohexylamide, 3.2-8 equivalents) in the presence of aryl halides for arylation to proceed at the 3-position (Scheme 53).[137] The reaction of **104** was thought to follow the benzyne mechanism, due to the products **105** and **106** being formed in equal amounts from the reaction of *p*-bromoanisole with NMP and excess LiCA.

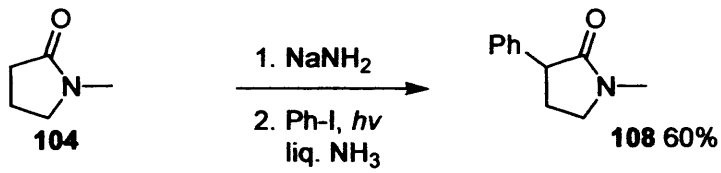
Scheme 53



104 **105** 25% **106** 25%

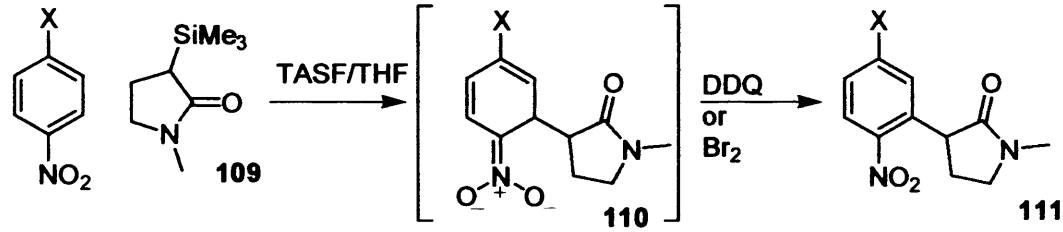
On the other hand, Alonso and co-workers[138] have used 1-alkyl-2-pyrrolidinone enolate ions as nucleophiles to react with aryl halides under *uv* radiation (Scheme 54). The reaction of **104** apparently follows an $S_{RN}1$ mechanism and leads to a single product **108**.

Scheme 54



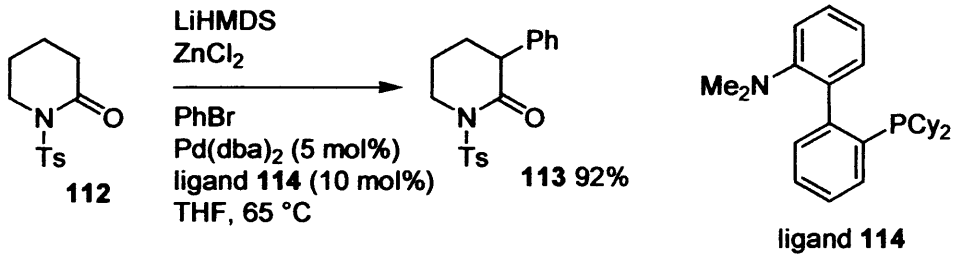
A further example of C-arylation of γ-lactams was reported involving the α-silylated derivative **109** of 1-methyl-2-pyrrolidinone (Scheme 55). The cleavage of the silyl group with fluoride leads to the generation of a stabilized enolate. This can then react reversibly with the electrophilic nitroarene to produce the σ^H-adduct **110** which can then be oxidized to the required product **111** with DDQ or Br_2. Different *para* substituted nitroaromatics were used including *p*-nitroanisole, *p*-nitrotoluene and *p*-bromonitrobenzene.

Scheme 55



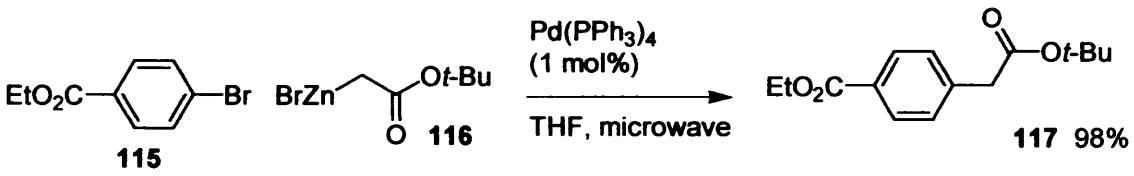
The α-arylation of the zinc enolate of *N*-protected 2-piperidinones with aryl bromides in the presence of a palladium catalyst was reported by Cossy.[139] (Scheme 56). When *N*-tosylpiperidinone **112** was treated under the conditions used for the arylation of esters no arylation occurred. To increase the reactivity, a transmetallation with zinc chloride was carried out. The α-arylation of *N*-tosylpiperidinone **112** and *N*-benzylpiperidinones was achieved in good yields.

Scheme 56



An approach for the α-arylation of esters and amides using Reformatsky reagents under a microwave accelerated reaction and a $Pd(PPh_3)_4$ catalyst has been reported by Moloney[140] (Scheme 57).

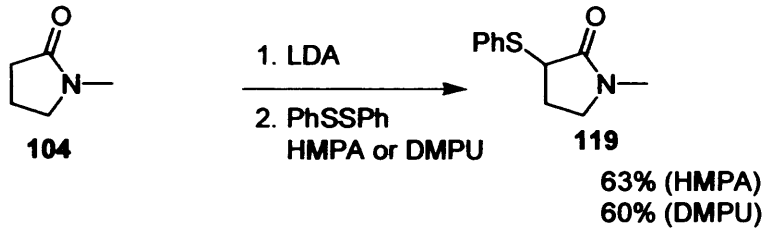
Scheme 57



We thought that a lactam or pyrazolidinone with a vicarious leaving group could undergo the VNS process with nitrobenzene to effect C-3 arylation. If successful this would allow us to develop an asymmetric version of the reaction. We now report that α-sulfanyllactams can be used in the VNS-alkylation reaction without a problem.

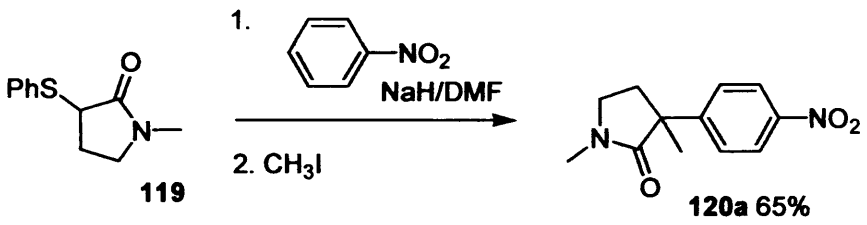
The VNS nucleophile **119** (Scheme 58) was formed by treating *N*-methylpyrrolidinone with 2 equivalents of LDA followed by phenyl disulfide (1 eq.) and HMPA.[141] We found that DMPU could be used as a non-toxic alternative to HMPA without compromising the yield. *N*-Methyl pyrrolidinone was chosen since it is commercially available, cheap and a method of forming the VNS nucleophile with the α-sulfanylphenyl group was already available in the literature.[141]

Scheme 58



The VNS nucleophile **119** dissolved in a solution of DMF with nitrobenzene (1 eq.), was added to a sodium hydride/DMF base solvent system at 0 °C. This produced the normal bright purple intermediate which was quenched with methyl iodide (2 eq.) (Scheme 59). It was found that two equivalents of the electrophile were needed to maximize the yield due to the thiophenolate anion competing with the post-VNS anion for the electrophile. The required product **120** was isolated by column chromatography from the crude reaction mixture which contained unreacted nitrobenzene, mineral oil from the sodium hydride, methylated thiophenol and DMF.

Scheme 59



The two doublets at δ 8.05 and 7.52 (*J* 8.9 Hz) in the ^{1}H-NMR indicated the presence of the *para* substituted nitroaromatic. The *N*-methyl group appears as a singlet at δ 2.86 and the remaining methyl group appears as a singlet at δ 1.48. Multiplets (δ 3.24-3.36), (δ 2.31-2.37) and (δ 2.11-2.19) represent the four protons on the pyrrolidinone ring.

A further series of electrophiles were tried in this VNS/alkylation reaction (Scheme 60). The results are summarised below (Scheme 60, Table 2). The electrophiles were chosen due to them being readily available and highly reactive alkylating agents.

Scheme 60

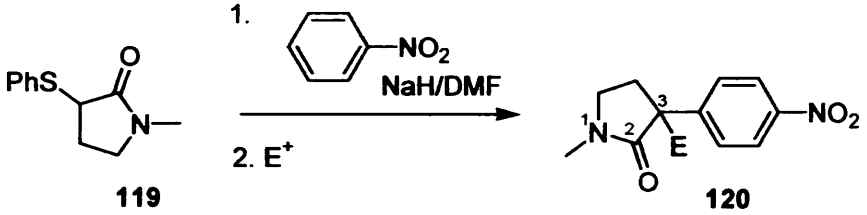


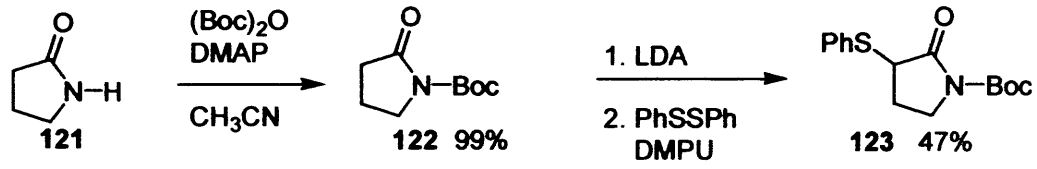
Table 2. Yields of Product Pyrrolidin-2-ones

	Electrophile	E	Yield (%)
120a	Methyl iodide	CH_3	65
120b	HCl	H	66
120c	Allyl bromide	Allyl	66
120d	Benzyl bromide	CH_2Ph	72

The 2 aromatic doublets in the ^{1}H-NMR spectrum representing the *para* substituted nitroaromatic were present in the remaining compounds **120b-d**. The triplet at δ 3.7 (*J* 9.2 Hz) in the ^{1}H-NMR of **120b** indicated a simple proton quench of the post-VNS anion had occurred to give the required product **120b**. The multiplets (δ 5.49-5.56) and (δ 5.00-5.05) along with a doublet at δ 2.57 (*J* 7.2 Hz) in the ^{1}H-NMR spectrum indicated the presence of the allyl group in **120c**. The multiplets at (δ 7.16-7.19) and (δ 7.00-7.02) along with the 2 doublets at δ 3.23 and 2.96 (*J* = 13.3 Hz) indicated the presence of the benzyl group in compound **120d**. For full characterisation details see the experimental section.

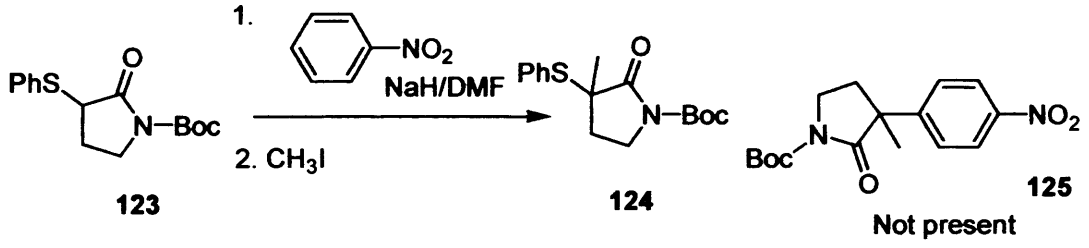
To introduce extra diversity into the reaction, a VNS nucleophile was made from *N*-Boc-pyrrolidinone by the same method as the VNS nucleophile **119** was obtained (Scheme 61). Boc pyrrolidinone (**122**) was obtained by treating pyrrolidinone (**121**) with di-*tert*-butyldicarbonate and DMPA in acetonitrile.[142] The multiplets at (δ 7.22-7.25) and (δ 7.46-7.48) in the ^{1}H-NMR spectrum along with the shift of the singlet representing the Boc group from δ 1.2 in Boc pyrrolidinone to δ 1.4 in the product indicated the required product had been formed. Also the appearance of the ABX system at δ 3.78, (2.30-2.29) and (1.89-1.98) indicated the required product had been formed.

Scheme 61



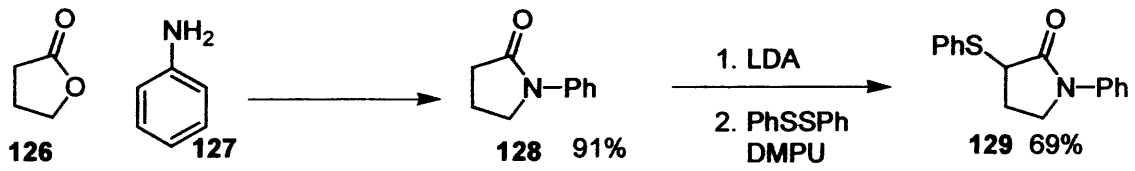
Use of the VNS nucleophile **123** in the VNS/alkylation reaction under the same conditions as those used with the VNS nucleophile **119** was not successful (Scheme 62). The ^{1}H-NMR spectrum of the crude reaction product contained unreacted nitrobenzene, VNS nucleophile **124** that had been methylated at the C-3 position, DMF and mineral oil from the sodium hydride with no trace of the required product **125**. Even though **124** was not isolated, its presence was indicated by the appearance of a singlet at δ 2.71 and the disappearance of the C-3 proton at δ 3.78 in the starting material **123**.

Scheme 62



We explored the scope of the process by using a further series of pyrrolidinones in the VNS/alkylation process. The first of these was based on 1-phenyl-2-pyrrolidinone (**128**). This was prepared by treating γ-butyrolactone (**126**) with aniline (**127**).[143] The VNS nucleophile **129** was then obtained by the usual method (Scheme 63).

Scheme 63



Multiplets (δ 7.81-7.84), (δ 7.59-7.64) and (δ 7.53-7.57) represented the required 10 aromatic protons. The C-3 proton of **129** appeared as a double doublet at δ 4.25 (*J* 6.0 & 8.6 Hz). Elemental analysis also indicated the required product. For full details see the experimental section.

The VNS nucleophile **129** was used in the VNS/alkylation process with a series of electrophiles. The results are summarised below (Scheme 64, Table 3).

Scheme 64

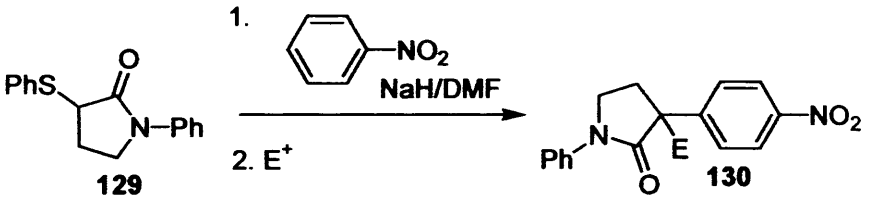


Table 3. Yields of Product Pyrrolidin-2-ones

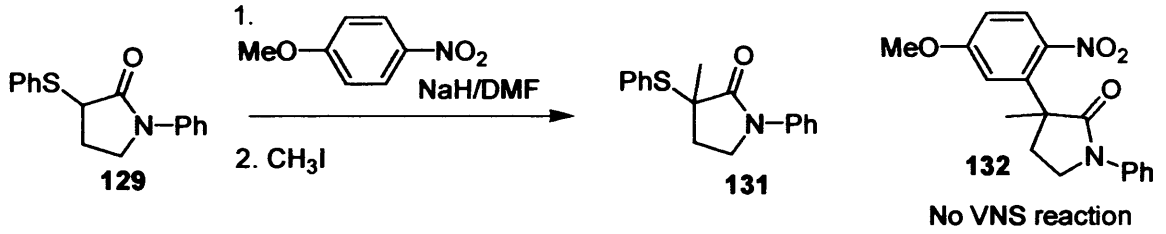
	Electrophile	E	Yield (%)
130a	HCl	H	75
130b	Methyl iodide	CH_3	68
130c	Allyl bromide	Allyl	65
130d	2,4-Dinitrofluorobenzene	2,4-DNB	58

The two aromatic doublets representing the *para*-substituted nitroaromatic were present in compounds **130a-d** indicating VNS had been successful. The *N*-phenyl group was also present in each compound occurring as a doublet and two triplets. Five protons in the non-aromatic region for compound **130a** indicated the correct product.

The presence of the methyl group in **130b** was indicated by a singlet at δ 3.10. The presence of the allyl group in **130c** was indicated by the multiplets at (δ 5.52-5.62), (δ 5.02-5.06) and (δ 2.65-2.67) giving a combined total of 5 protons. The presence of the 2,4-substituted aromatic at the C-3 position of **130d** was indicated by the presence of a doublet at δ 8.55 (*J* 2.4 Hz), double doublet at δ 8.29 (*J* 2.4 & 8.7 Hz) and multiplet at (δ 7.47-7.50) which represented the required 3 protons. The aryl electrophile (2,4-dinitrofluorobenzene) was chosen to show the VNS-S_NAr process mentioned later in this thesis could be extended to lactams with an α-phenylsulfanyl group as the vicarious leaving group.

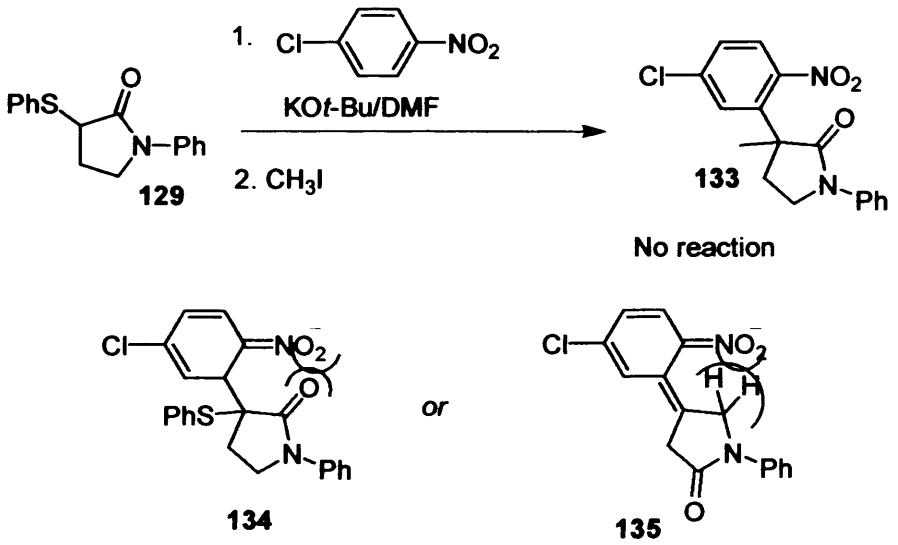
The *ortho* selectivity of the VNS/alkylation process was tested with the VNS nucleophile **129** with *p*-nitroanisole (Scheme 65). The VNS process did not occur under the same conditions as the *para* selective version, since the bright purple intermediate solution, associated with the post-VNS anion not observed.

Scheme 65



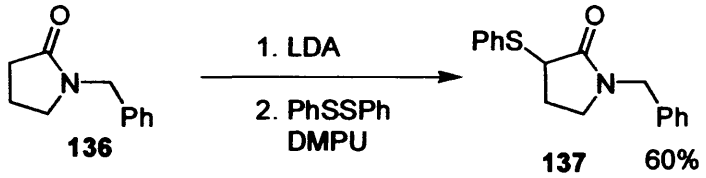
The ^{1}H-NMR spectrum of the crude reaction mixture contained *p*-nitroanisole, the methylated VNS nucleophile **131**, mineral oil and DMF. Although it was not isolated the presence of **131** was indicated by the presence of a singlet at δ 2.69 and the disappearance of the C-3 proton at δ 4.25. The reaction was repeated with a KO*t*-Bu/DMF base solvent system, which also resulted in no success. On this occasion, however, the bright purple colour associated with the post-VNS anion was observed. The problem with using *p*-nitroanisole as a VNS substrate is that it is much less electron-deficient than nitrobenzene, due to the electron-donating nature of the methoxy group. As an alternative to *p*-nitroanisole as the VNS substrate *p*-chloronitrobenzene was tried (Scheme 66) with the same outcome as the *p*-nitroanisole substrate. The steric clash of the tertiary carbanion with the nitro group is the most likely problem with this reaction (Scheme 66). The intermediates **134** and **135** are extremely sterically encumbered, and may therefore not form.

Scheme 66



The next VNS nucleophile studied was based on 1-benzyl-2-pyrrolidinone (**136**). The VNS nucleophile was prepared by the same method as the previous ones (Scheme 67).[144] This was chosen as it offered the opportunity for generating the NH pyrrolidinones that can then be further functionalised.

Scheme 67



The VNS nucleophile **137** was used in the VNS/alkylation reaction with a series of electrophiles (Scheme 68) under identical conditions as discussed previously. The results are summarised below (Scheme 68, Table 4).

Scheme 68

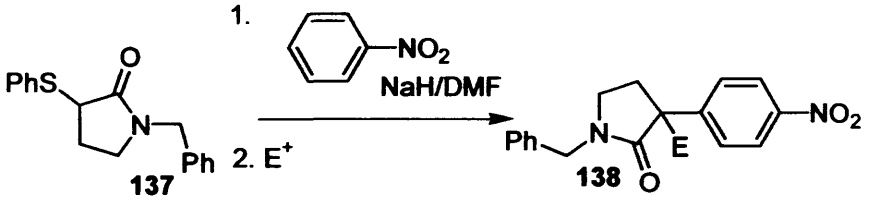


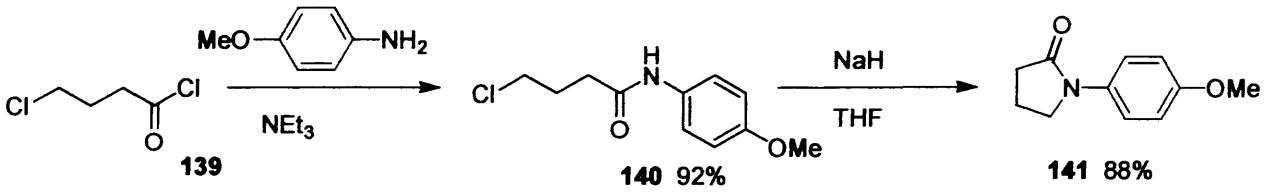
Table 4. Yields of Product Pyrrolidin-2-ones

	Electrophile	E	Yield (%)
138a	HCl	H	62
138b	Methyl iodide	CH_3	66
138c	Ethyl iodide	CH_2CH_3	61

The two aromatic doublets in the ^{1}H-NMR spectrum representing the *para* substituted nitroaromatic were present in compounds **138a-c** indicating that the VNS had been successful. A triplet at δ 3.77 (*J* 9.1 Hz) in the ^{1}H-NMR spectrum of **138a** represents the benzylic proton. A singlet at δ 1.54 indicates that the alkylation with methyl iodide had been successful. A triplet at δ 0.76 (*J* 7.4 Hz) and two double quartets at δ 1.95 (*J* 14.8 & 7.4 Hz) and δ 1.86 (*J* 13.9 & 7.4 Hz) indicated that the quench with ethyl iodide had been successful.

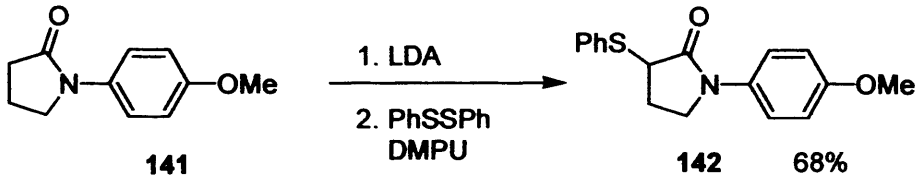
The next VNS nucleophile studied was based on 1-*para*-methoxyphenyl-2-pyrrolidinone (**141**) as this also offered the opportunity for deprotection and further functionalisation. The γ-lactam **141** was formed by treating 4-chlorobutyryl chloride (**139**) with *p*-anisidine and triethylamine (Scheme 69). The product **140** was then treated with sodium hydride to effect cyclization to the pyrrolidinone (Scheme 17).[145]

Scheme 69



The VNS nucleophile was then formed by the usual method (Scheme 70). Treatment of **141** with LDA (2 eq.) followed by phenyl disulfide and DMPU gave **142** in 68% yield

Scheme 70

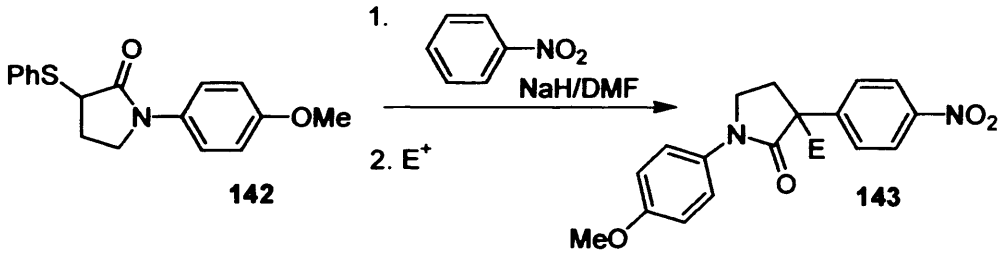


141 **142** 68%

The doublets at δ 7.41 and 6.91 (*J* 9.1 Hz) in the ^{1}H-NMR spectrum of **142** indicates the presence of the *para* substituted anisole. The multiplets at (δ 7.60-7.62) and (δ 7.31-7.37) represents the aromatic group attached to sulfur. A double doublet at δ 4.01 (*J* 5.8 & 8.7) represents the C-3 proton adjacent to the carbonyl. The three remaining protons are represented by multiplets (δ 3.67-3.82), (δ 3.56-3.60) and (δ 2.60-2.65).

The VNS nucleophile **142** was used in the VNS/alkylation process with a series of electrophiles under identical conditions. The results are summarised below (Scheme 71, Table 5). The two aromatic doublets representing the *para*-substituted nitroaromatic were present in compounds **143a-c** indicating that the VNS had been successful.

Scheme 71



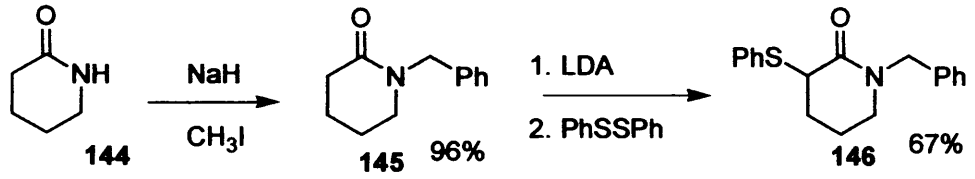
142 **143**

Table 5. Yields of Product Pyrrolidin-2-ones

	Electrophile	E	Yield (%)
143a	HCl	H	73
143b	Methyl iodide	CH_3	83
143c	Benzyl Bromide	$PhCH_2$	66

Having only used γ-lactams so far, we decided to try δ-lactams in the VNS/alkylation process. The VNS nucleophile **146** was prepared in the usual way after *N*-benzylation of commercially available δ-caprolactam (Scheme 72).

Scheme 72



The VNS nucleophile **146** was used in the VNS/alkylation process with nitrobenzene and a series of electrophiles under identical conditions as described earlier.[146] The results are summarised below (Scheme 73, Table 6).

Scheme 73

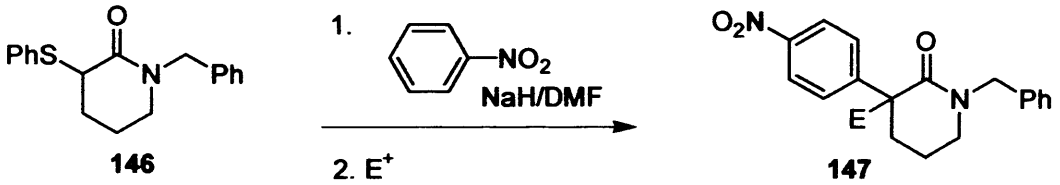


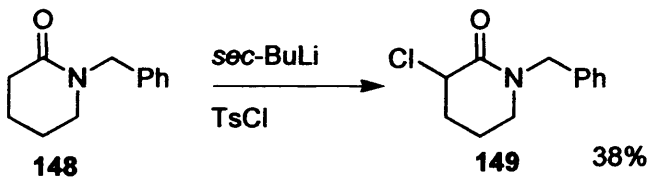
Table 6. Yields of Product Piperidin-2-ones

	Electrophile	E	Yield (%)
147a	HCl	H	64
147b	Methyl iodide	CH_3	61
147c	Ethyl iodide	CH_2CH_3	58

The two aromatic doublets in the ^{1}H-NMR spectrum representing the *para* substituted nitroaromatic were present in **147a-c** indicating that the VNS process had been successful. For full details see the experimental section.

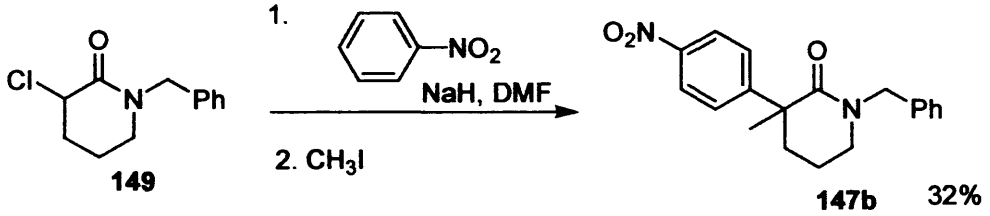
As an alternative to the thiophenolate as the vicarious leaving group, a VNS nucleophile **149** with an α-chloro group was made by treatment of *N*-benzylated δ-valerolactam (**148**) with *sec*-BuLi followed by tosyl chloride (Scheme 74).[147] This was done to give us a method where we could avoid the need for an excess of electrophile due to chloride ion being a poor nucleophile.

Scheme 74



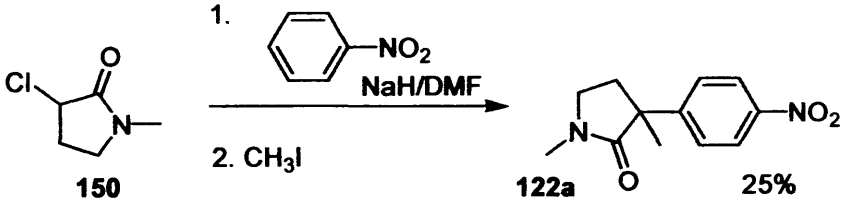
The VNS nucleophile **149** was then used in a VNS/alkylation reaction with nitrobenzene and methyl iodide (1 eq.) under identical conditions as previously described (Scheme 75).

Scheme 75



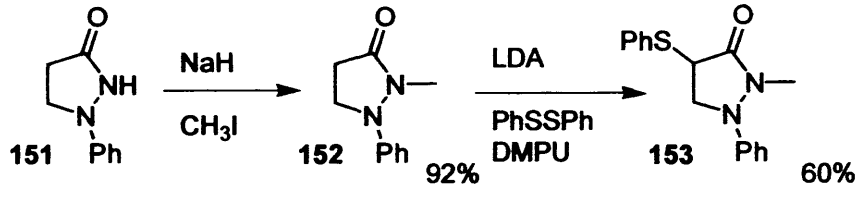
The reaction proceeded, but in much lower yield. The α-chloro-*N*-methylpyrrolidinone (**150**) was made under the same conditions as the α-chloro *N*-benzylpiperidinone (**149**). This was also used in the VNS/alkylation process (Scheme 76). Again, this resulted in a much lower yield of the required VNS product **122a,** as compared to using the equivalent VNS nucleophile **121**.

Scheme 76



We next tried a pyrazolidinone in the VNS/alkylation process. The 2-methylpyrazolidin-3-one **153** was prepared by methylation of the commercially available pyrazolidine[148] followed by the usual method of adding the vicarious leaving group (Scheme 77). A multiplet at (δ 3.89-3.96) and double doublet at δ 3.65 (*J* 11.3 & 14.5 Hz) in the ^{1}H-NMR spectrum of **153** represented the presence of the C-3 and two C-4 protons, indicating the required product. Ten protons were observed in the range δ 6.79-7.33, representing the two phenyl rings. The singlet for the methyl group appears at δ 2.97.

Scheme 77



The VNS nucleophile **153** was then used in the VNS/alkylation process with nitrobenzene and a series of electrophiles, under the usual conditions. The results are summarised (Scheme 78, Table 7). The two aromatic doublets representing the *para*-substituted nitroaromatic were present in compounds **78a-b,** indicating that the VNS process had been successful. For full characterisation details see the experimental section.

Scheme 78

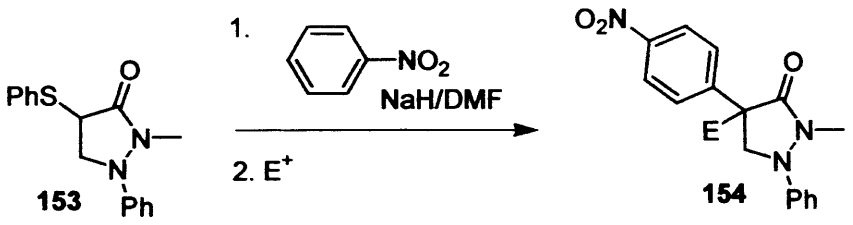
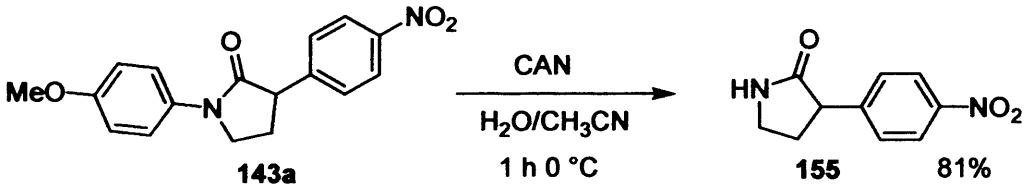


Table 7. Yields of Product Pyrazolidin-3-ones

	Electrophile	E	Yield (%)
154a	HCl	H	69
154b	Methyl iodide	CH_3	47
154c	Benzyl bromide	CH_2Ph	61

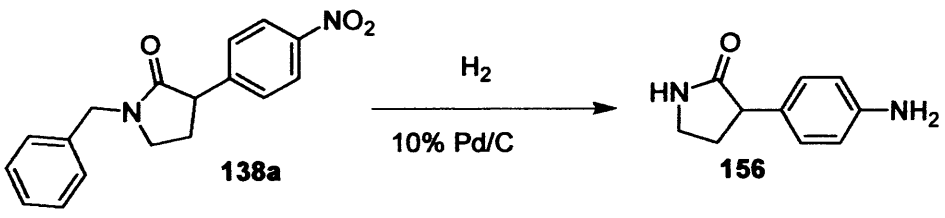
The VNS products (**143a-c**) represent the opportunity for oxidative removal of the *para*-methoxy aromatic making the amide available for further functionalisation. This was achieved with ceric ammonium nitrate (Scheme 79). Treatment with ceric ammonium nitrate, according to the method of Giang[149] gave the amide in quantitative yield. The disappearance of the peaks corresponding to the anisole in the ^{1}H-NMR spectrum indicated that deprotection had occurred successfully, as did the appearance of a singlet at δ 7.0 representing the NH of the amide. Further proof was given by an electrospray accurate mass measurement, which gave a $(M + H)^+$ peak at 207.0699 corresponding to the calculated mass of 207.0691.

Scheme 79



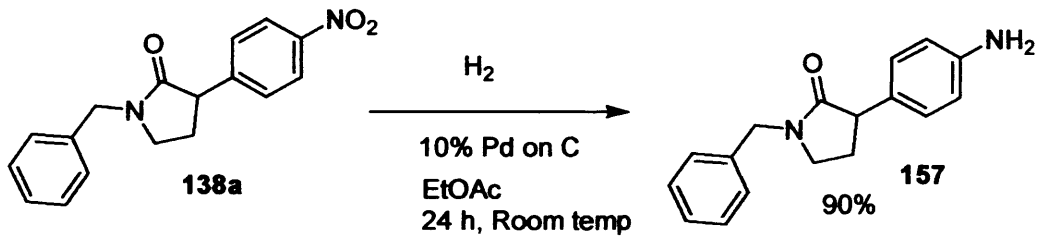
The VNS products (**138a-c** and **147a-c**) can also be deprotected and further functionalised by removal of the benzyl group under hydrogenation conditions (Scheme 80). Under such conditions it was anticipated that the nitro group would also be reduced (*e.g.* **138a→156**).

Scheme 80



Hydrogenation of **138a** in ethyl acetate with activated catalyst (10% Pd on C) under an atmosphere of hydrogen for 24 hours did not proceed as desired. The crude product was checked by ^{1}H-NMR spectroscopy, which showed unfortunately that the benzyl group was still present (Scheme 81) by a singlet at δ 4.44 and multiplet (δ 6.79-7.30). The nitro group was reduced as indicated by the two doublets δ 7.07 and 6.64 (*J* 8.4 Hz). The reaction probably needed to be done under pressure but the required facilities were not available to us.

Scheme 81



Summary and Conclusion

In summary, a useful procedure has been developed that can be used for the α-arylation of pyrrolidinones, piperidinones, and pyrazzolidinones. Even allowing for the limited number of examples of α-arylation of cyclic amides reported, this is potentially of real value. Nitrogen protecting groups have been used successfully which allow for subsequent deprotection and further functionalisation of the amide.

Pyrrolidinones, piperidinones and pyrazolidinones have been incorporated into the VNS/alkylation group by adding an α-phenylsulfanyl VNS leaving group and treating with base and nitrobenzene. Several different *N*-substituted protecting groups such as benzyl and *p*-methoxyphenyl have been incorporated in the VNS nucleophile successfully. The *p*-methoxyphenyl protecting group was successfully removed with ceric ammonium nitrate and although we weren't able to remove the benzyl group we were confident that under hydrogenation conditions above atmospheric pressure we would be able to thus providing the possibility for further functionalistaion of the α-aryl lactam. Unfortunately, however using a *N*-Boc lactam resulted in the VNS/alkylation process not taking place.

Using chloride as the VNS leaving group we were hopeful would lead to a cleaner process due to chloride being a poorer nucleophile than thiophenolate so removing the need for two equivalents of the electrophile. Unfortunately however this resulted in a significant reduction in the yield of the reaction.

All the examples discussed in this chapter have undergone the VNS process at the *para*-position of the nitroarene. When using a *para*-substituted nitroarene to force the VNS

nucleophile onto the *ortho*-position resulted in no success. The most probable reason for this s the clash with the nitro-group (Scheme 66). In the case of the unsuccessful reactions the ^{1}H-NMR spectra of the crude reaction mixtures indicated the presence of the alkylated VNS nucleophile and nitrobenzene.

In conclusion we have developed a simple one pot route to α-aryl cyclic amides. This laid the foundations for the development of an asymmetric process using γ-substituted lactams and lactones as the VNS nucleophile. The lack of success with the *ortho*-selective VNS reaction was worrying as this would be important in the synthesis of Physostigmine (98).

Chapter 5

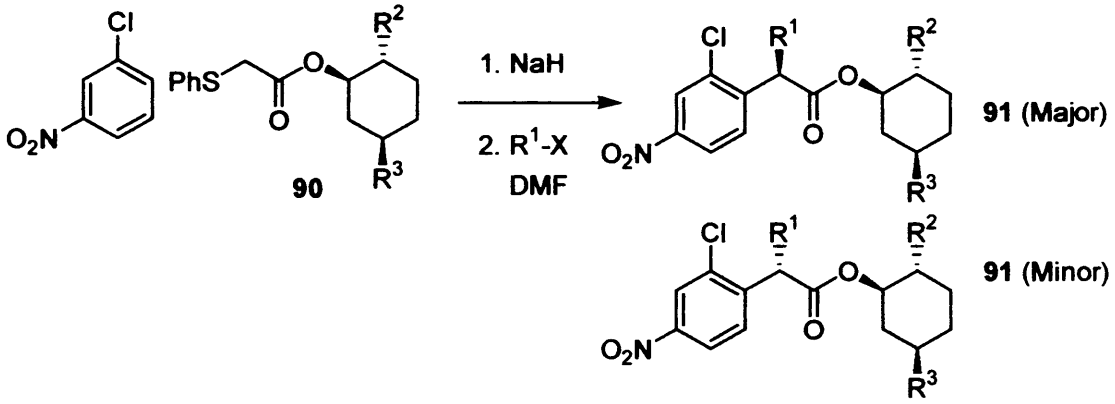
5.1 AsymmetricVicarious Nucleophilic Substitution of Hydrogen

The biological world can be regarded as a chiral world in the chemical sense. It happens often in nature that one enantiomer exhibits biological activity whereas the other enantiomer does not. A number of biologically active natural products contain quaternary carbon atoms.[150-2] Interest in synthesizing them in an optically active form is reflected in the explosive increase in the number of new development for the chiral construction of quaternary carbons that have been published in the last 15 years.

Asymmetric syntheses can be divided into two types, enantioselective syntheses and diastereoselective syntheses. According to Izumi,[153] a reaction is described as enantioselective if the reaction is carried out on an achiral molecule using an enantioselective reagent or catalyst. In the case of diastereoselective synthesis, 'if a molecule contains a centre of chirality and a centre of prochirality and the reaction results in the conversion of the centre of prochirality into a new centre of chirality, the reagent may attack from either face with the result that diastereoisomers are formed.' This definition proposed by Izumi has proven useful for organic and medicinal chemists for classifying asymmetric synthesis.

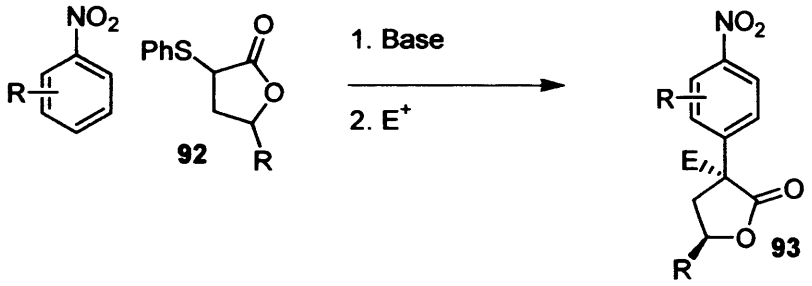
We decided to assess the diastereoselectivity of VNS reactions using an α-thiophenyl-γ-lactone possessing a γ-stereogenic centre to provide a further insight into the asymmetric VNS/alkylation process. As mentioned previously, a diastereoselective version of the VNS/alkylation reaction was reported in the Lawrence group using an auxiliary incorporated into the VNS nucleophile (Scheme 82).[38]

Scheme 82



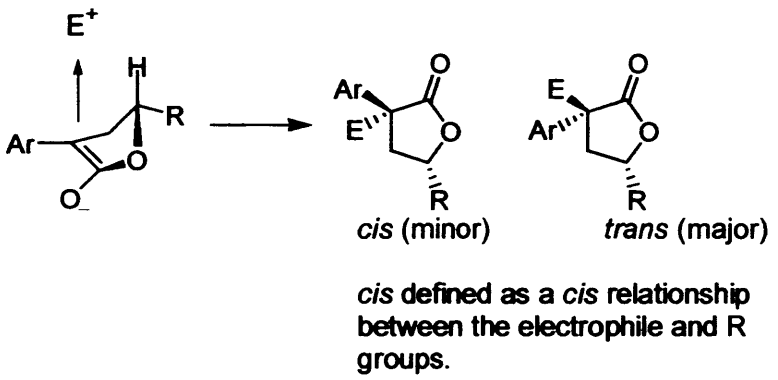
We thought that reaction of the VNS nucleophile **92** with nitroarenes would generate the post-VNS anion in the usual way. Reaction of the post-VNS anion with a variety of electrophiles would hopefully give the lactone **93** possessing an α-aryl quaternary stereogenic centre (Scheme 83).

Scheme 83



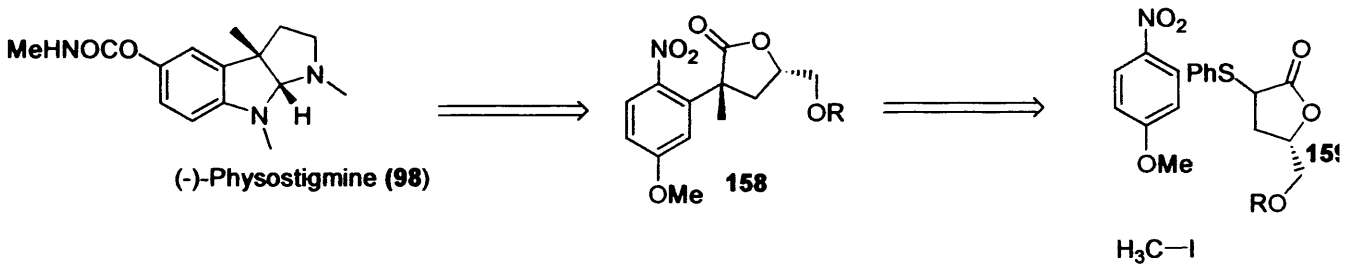
It was expected that the electrophile would approach *anti* to the R group for primarily steric reasons. In other words, the R group is shielding one face of the molecule from the incoming electrophile (Scheme 84). It is known that conventional alkylation of enolates derived from α-aryl-γ-lactones bearing a γ-stereogenic centre results in such 1,3-stereocontrol at acceptable levels.[240]

Scheme 84



The ultimate aim of this section was to develop an efficient synthesis to the natural product physostigmine (**98**) using an asymmetric VNS reaction to produce the required stereochemical arrangement of the molecule (Scheme 85).

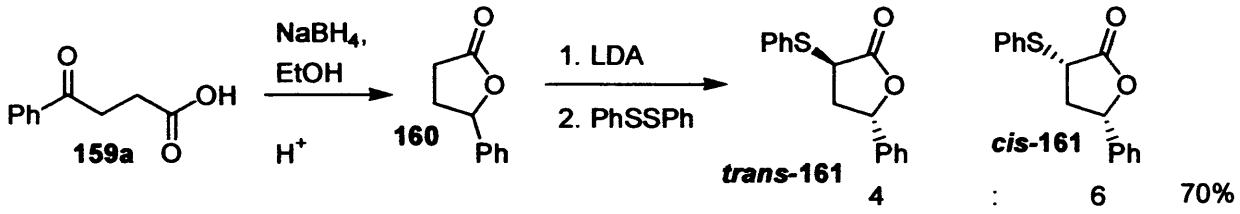
Scheme 85



The first lactone to be studied 'dihydro-5-phenyl(3*H*)furan-2-one (**160**), was formed by reduction of 3-benzoylpropionic acid with sodium borohydride.[222] The α-thiophenyl-γ-butryolactones *cis*-**161** & *trans*-**161** were prepared by a known process from γ-butyrolactone **160**, LDA (1 eq.) and phenyldisulfide (Scheme 86) with a 6:4 ratio of the two diastereoisomers

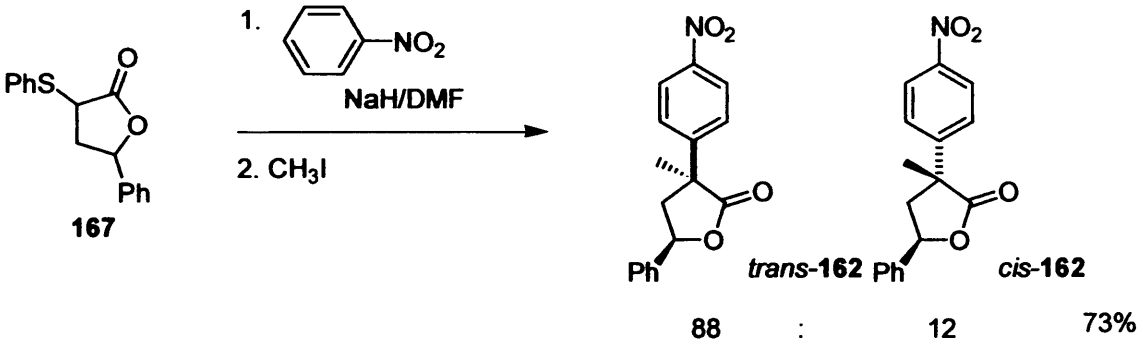
in overall 70% yield.[171] This ratio matched that of the literature procedure. The isomers were separated by column chromatography. The diastereosomers were assigned in the literature procedure by nOe studies.

Scheme 86



The mixture of VNS nucleophiles *trans*-**161** and *cis*-**161** were dissolved in a solution of DMF containing nitrobenzene (1 eq) and added to a sodium hydride/DMF solvent system at 0 °C under nitrogen. After stirring at 0 °C for 2 hours the bright purple solution was quenched with methyl iodide at -78 °C. After work up and purification this left the required product in only 9% yield. It was found that if the post-VNS anion was allowed to warm to room temperature and stirred for 2 hours before the electrophilic quench the yield improved to 73% (Scheme 87) of the *trans*-**162**:*cis*-**162** products (in an 88:12 ratio). The major product was isolated by column chromatography but unfortunately the minor diastereoisomer could not be isolated.

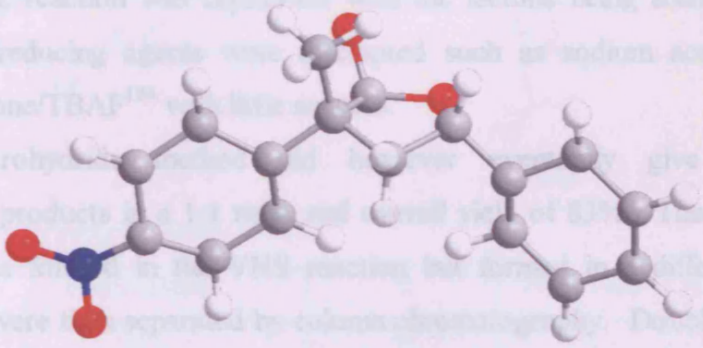
Scheme 87



The presence of the required product was indicated by the presence of doublets at δ 8.21 and 7.71 (*J* 8.9 Hz) in the ^{1}H-NMR spectrum indicating the presence of a *para* substituted nitroaromatic. The double doublets at δ 5.65 (*J* 9.9 & 6.1 Hz), 2.89 (*J* 13.0 & 6.1 Hz) and 2.63 (*J* 13.0 & 9.9 Hz) represent an ABX system consisting of the C-4 and C-5 protons. The phenyl group is represented by a multiplet (δ 7.33-7.41) and the methyl group as a singlet at δ 1.79. Fortunately the major isomer was crystalline. A crystal suitable for X-ray analysis was grown by dissolving a small amount of sample in dichloromethane and then putting this vial into an pot containing hexane. This was then left covered in the dark until crystals were obtained. X-ray crystal structure determination was performed by Abdul Malik of Cardiff University. The

structure clearly reveals the relative stereochemical configuration of the product and shows that the major product is the *trans* isomer, as expected. The lactone **162** adopts an envelope conformation as shown in Figure **9**.

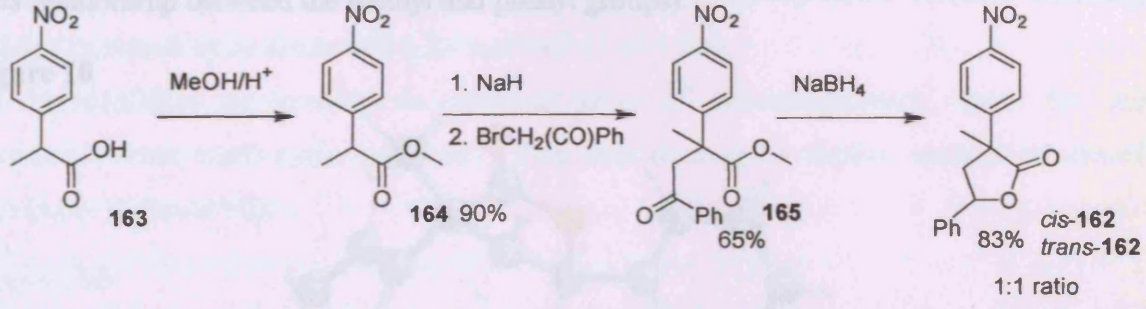
Figure 9



Chem3D representation of the X-ray crystal structure of the *trans*-**162**

The ratio of the major:minor stereoisomers *trans*-**162**:*cis*-**162** is based on analysis of the ^{1}H-NMR spectrum of the crude reaction product. Because the minor isomer was present in only small quantities we were not confident that those peaks we were assigning as corresponding to the minor isomer were indeed those of the *cis*-isomer. A method had to be obtained to make the minor diastereoisomer so that we could accurately assign the peaks in the crude ^{1}H-NMR spectrum and be totally confident of quoting an accurate figure for the diastereoselectivity. The synthetic route chosen is illustrated in Scheme **88**.

Scheme 88

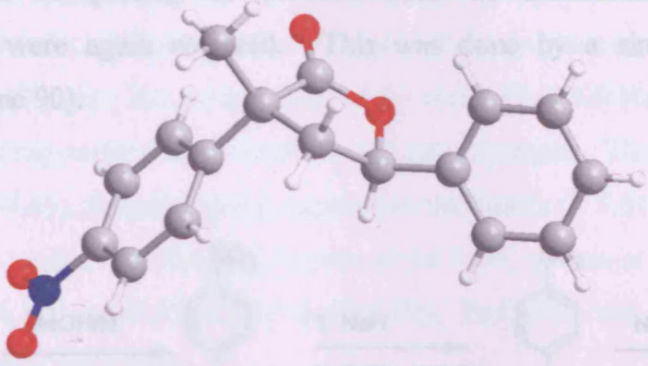


Esterification of the commercially available 4-nitrophenylpropionic acid (**163**) with methanol and sulfuric acid and heating under reflux for 3 hours gave the ester **164** in 90% yield. The ester **164** was then treated with sodium hydride (1 eq.) followed by 2-bromoacetophenone at 0 °C to give **165** in 65% yield. The presence of the required product is indicated by the presence of a singlet at δ 1.85 in the ^{1}H-NMR spectrum representing the methyl group at the quaternary centre. In the starting material **164**, this methyl group appears as a doublet at δ 1.4 (*J* 7.2 Hz). The doublets at δ 3.92 and 3.65 (*J* 17.8 Hz) represent the CH_2 group next to the quaternary

centre. The methyl group of the ester appears as a singlet at δ 3.74. The appearance of singlets at δ 196.3 and 174.7 in the ^{13}C-NMR spectrum indicate the presence of two carbonyl groups. We hoped that reduction of the ketone to the alcohol would cause cyclization onto the ester to give the required lactone **162**. This was achieved using sodium borohydride as the reducing agent although the reaction was capricious with the lactone being sometimes reduced in the process. Other reducing agents were attempted such as sodium acetoxyborohydride and tetramethyldisiloxane/TBAF[154] with little success.

The sodium borohydride method did however eventually give the two required diastereoisomeric products in a 1:1 ratio and overall yield of 83%. These two products were the same products formed in the VNS reaction but formed in a different ratio. The two diastereoisomers were then separated by column chromatography. Doublets at δ 8.15 and 7.67 (*J* 8.8 Hz) in the ^{1}H-NMR spectrum indicated the presence of a *para*-substituted nitroaromatic. The ABX system was represented by double doublets at δ 5.17 (*J* 5.4 & 10.6 Hz), 3.08 (*J* 5.4 & 13.3 Hz) & 2.46 (*J* 10.6 & 13.3 Hz). The phenyl group appeared as a multiplet (δ 7.29-7.37) and the methyl group as a singlet at δ 1.69. Comparing with the ^{1}H-NMR spectrum of the crude reaction product **162** prepared earlier we could deduce which peaks belonged to the minor diastereoisomer *cis*-**162** and the ratio of the two products had therefore been accurately calculated. An X-ray structure was obtained of the minor diastereoisomer (Figure 10): This was done by growing a crystal under the same conditions as mentioned previously for the major product in the VNS reaction. The structure clearly reveals the relative stereochemical configuration of the product and shows that the product is indeed in the *cis* form (*cis* defined as a *cis* relationship between the methyl and phenyl groups).

Figure 10



Chem3D representation of the X-ray crystal structure of the *cis*-**162**

A further series of electrophiles were used in the VNS reaction with nitrobenzene and 5-phenyl-3-phenylsulfanylfuran-2-one (**92**) under identical conditions (Scheme 89). The results are summarised below (Table 8).

Scheme 89

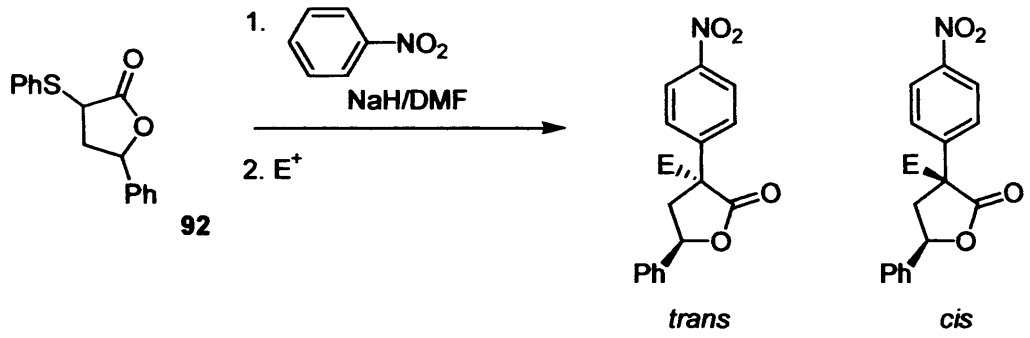


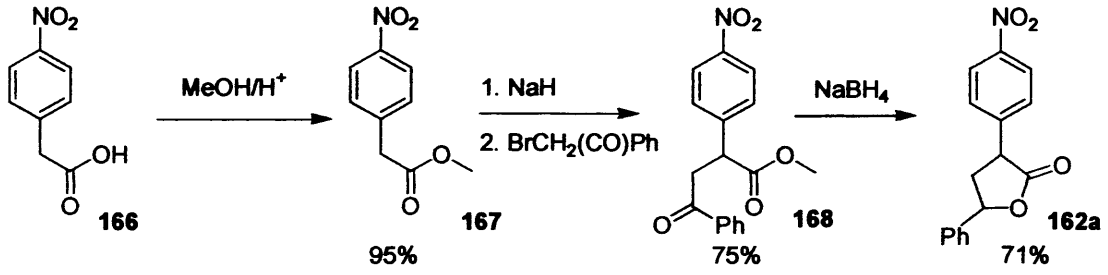
Table 8. Yields of Product Furan-2-ones

	Electrophile	E	Yield (%)	Ratio *trans:cis*
162a	HCl	H	73	73:27
162b	Allyl bromide	CH_2CHCH_2-	67	85:15
162c	Benzyl bromide	$PhCH_2$-	65	>87:13
162d	2-Bromoacetophenone	$PhCH_2(CO)$-	67	>87:13

The doublets representing the 1,4-disubstituted aromatic were present in compounds **162a-d** indicating that the VNS process had been successful. The double doublet at δ 5.50 (*J* 10.7 & 5.5 Hz) in the ^{1}H-NMR spectrum of **162a** indicated a proton quench of the post-VNS anion had taken place. The allyl group in the ^{1}H-NMR spectrum of **162b** is represented by multiplets (δ 5.49-5.68) and (δ 5.09-5.17) and a doublet at δ 2.73 (*J* 7.4 Hz). The benzyl group in the ^{1}H-NMR spectrum of **162c** is represented by doublets at δ 3.63 and 3.16 (*J* 13.2 Hz) along with a multiplet (δ 7.19-7.45). The presence of the acetophenone group in the ^{1}H-NMR spectrum of **162d** is indicated by doublets at δ 3.81 and 3.65 (*J* 18.1 Hz).

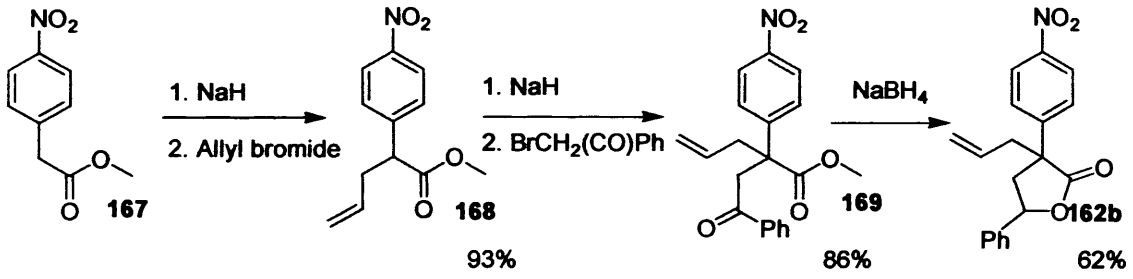
To be confident of quoting an accurate ratio of diastereoisomers again, the minor diastereoisomers were again required. This was done by a similar method as described previously (Scheme 90).

Scheme 90



Again chemoselective reduction of the ketone **168** proved to be capricious, but the required product was eventually isolated, giving a 1:1 mixture of the two diastereoisomers **162a**. However, separation by column chromatography proved to be difficult but the ^{1}H-NMR spectrum of the crude reaction still gave the position of signals of the minor diastereoisomer. From this the accurate ratio of the two diastereoisomers **162a** (*cis*-**162a**: *trans*-**162a** 73:27), obtained from the VNS process of **92** with a proton quench could be quoted.

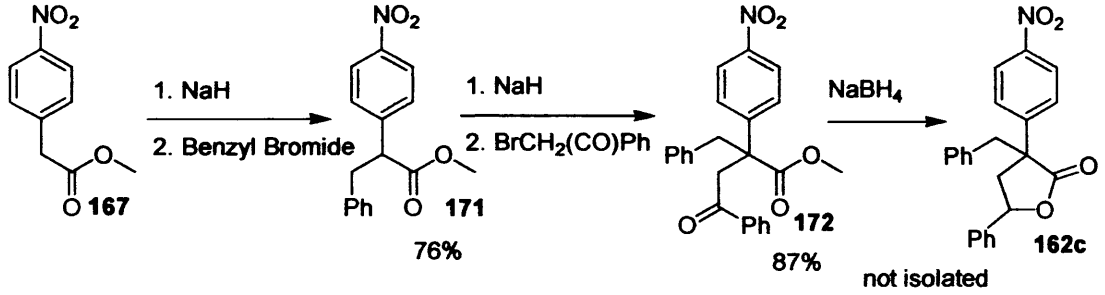
Scheme 91



The minor diastereoisomer of compound **162b** was formed again based on the same method (Scheme 91). Deprotonation of methyl 4-nitrophenylacetate (**167**) with sodium hydride at 0 °C followed by quenching with allyl bromide (1 eq) gave **168** in 93% yield. Treatment of **168** with sodium hydride followed by quenching with 2-bromoacetophenone (1 eq.) gave **169** in 86% yield. The presence of **169** was indicated by the disappearance of the benzylic proton of the starting material at δ 3.78 in the crude ^{1}H-NMR spectrum and the appearance of doublets at δ 3.82 and 3.74 (*J* 18.0 Hz). Doublets at δ 8.16 and 7.89 (*J* 8.9 Hz) represent the *para* substituted nitroaromatic. The phenyl group is represented by a triplet at δ 7.41 (*J* 7.9 Hz) and multiplet (δ 7.49-7.55). The allyl group is represented by multiplets (δ 5.28-5.36 & 4.85-4.93 & 2.94-3.07). The singlet representing the methyl group appeared at δ 3.63.

Reduction of **169** with sodium borohydride gave the two diastereoisomers of **162b** in a 1:1 ratio in 62% overall yield. The doublets at δ 8.28 and 7.72 (*J* 8.9 Hz) in the ^{1}H-NMR spectrum of the *cis* product represent the *para*-substituted nitroaromatic. The phenyl group appears as a multiplet (δ 7.33-7.43), the allyl group appears as multiplets (δ 5.61-5.70 & 5.02-5.18 & 2.68-2.80). The three protons on the ring appear as an ABX system at δ 5.22 (*J* 5.4 & 10.9 Hz), 3.01 (*J* 5.4 & 13.6 Hz) and 2.56 (*J* 10.9 & 13.6 Hz). From this data an accurate ratio of the two diastereoisomers was calculated.

Scheme 92

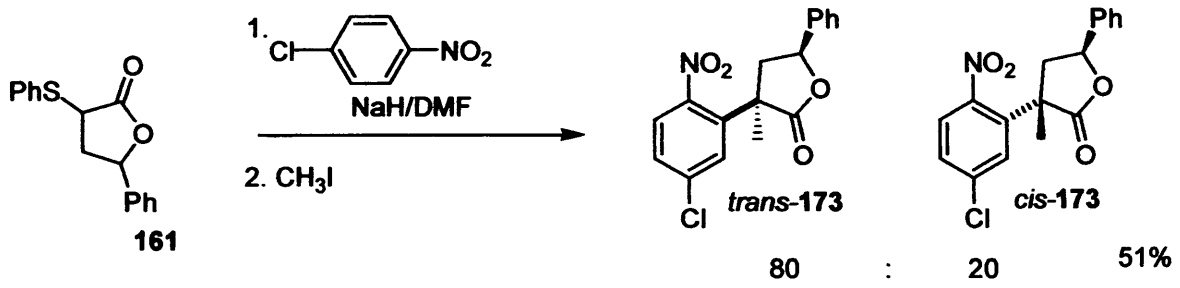


To make the minor diastereoisomer of compound **162c**, the same route was followed (Scheme 92). Deprotonation of methyl 4-nitrophenylacetate (**167**) with sodium hydride at 0 °C followed by an electrophilic quench with benzyl bromide (1 eq) gave **171** in 76% yield. Treatment of **171** with sodium hydride followed by an electrophilic quench with 2-bromoacetophenone (1 eq) gave **172** in 87% yield. The presence of **172** was indicated by the presence of a doublet at δ 8.20 (*J* 8.9 Hz) and multiplet (δ 7.45-7.51) representing the *para*-substituted nitroaromatic. A doublet at δ 3.58 (*J* 13.7 Hz) and multiplet (δ 3.68-3.72) represent the two CH_2 groups. A singlet at δ 3.72 represents the methyl group. The remaining aromatic protons are represented by doublets at δ 7.95 (*J* 7.5 Hz) and 6.52 (*J* 7.4 Hz), triplets at δ 7.62 (*J* 7.5 Hz), 7.14 (*J* 7.4 Hz) and 7.05 (*J* 7.4 Hz) and a multiplet (δ 7.45-7.51). As before the selective reduction of compound **172** proved capricious but this time the required products could not be isolated.

The minor diastereoisomer of compound **162d** was not formed by this method due to the precursor having two identical carbonyl groups of which we only want to reduce the one. Nevertheless in these last two cases, we are not unduly concerned that the ratio we quote in Scheme 89 does not represent the true level of diastereoselectivity.

It was expected that the larger the electrophile, the higher the level of selectivity which would be obtained. The lowest level of selectivity achieved was with a simple proton quench of the post-VNS anion with HCl. Using methyl iodide as the electrophile however produced slightly better stereoselectivity than using allyl bromide as the electrophile. However, all the alkyl halides produced very similar results of stereoselectivity.

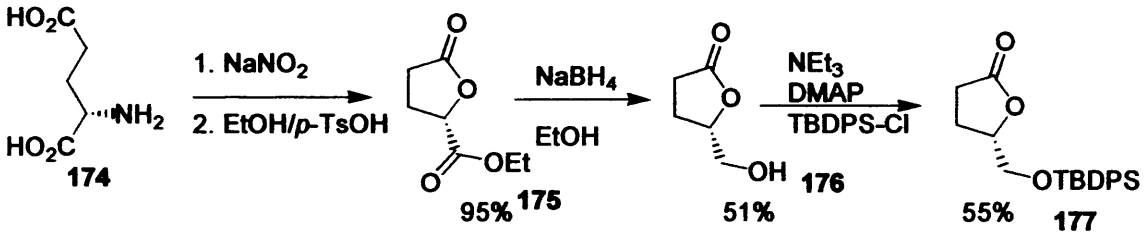
Scheme 93



To study the diastereoselectivity in an *ortho*-selective VNS reaction, *p*-chloronitrobenzene was used as the VNS substrate (Scheme 93). Compound **173** was formed in an overall yield of 51% with a 80:20 ratio of *trans:cis* diastereoisomers. The presence of the required compound **173** was indicated by the presence of a singlet at δ 1.69 in the ^{1}H-NMR spectrum representing the methyl group. An ABX system at δ 5.29 (*J* 9.2 & 6.8 Hz), 2.69 (*J* 13.6 & 6.8 Hz) and 2.49 (*J* 13.6 & 9.2 Hz) represents the three protons on the lactone ring. The three protons on the nitroaromatic ring are represented by doublets at δ 8.35 (*J* 8.9 Hz) & 8.01 (*J* 1.1 Hz) and a double doublet at δ 7.89 (*J* 1.1 & 8.9 Hz). The remaining aromatic protons are represented by a multiplet (δ 7.31-7.45). The major diastereoisomer was isolated by column chromatography. From the results of the previous asymmetric VNS reaction using nitrobenzene, we were confident that the major diastereosiomer could be assigned as the *trans* product.

All the examples of asymmetric VNS discussed so far have produced racemic products. The next stage was to develop the protocol to incorporate a chiral lactone to produce an enantiomerically pure product. The chiral lactone we chose to try was made by the following route (Scheme 94), that has been developed by Herdeis, Tse, Drioh and Hanessian.[155-8]

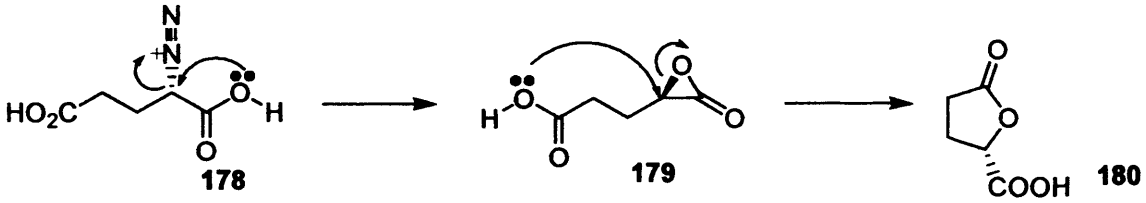
Scheme 94



To check that the lactone **177** was enantiomerically enriched the α_D was measured (+35.3, c = 1.09 in EtOH) and compared to the literature value (+ 35.5 c = 1.09 in EtOH).[172] The first step of the synthesis involves diazotisation of glutamic acid (**174**). The process involves diazotisation of the amine group followed by cyclisation of the adjacent acid that involves an S_N2 inversion. The resulting α-lactone **179** is ring-opened by attack of the other acid to give

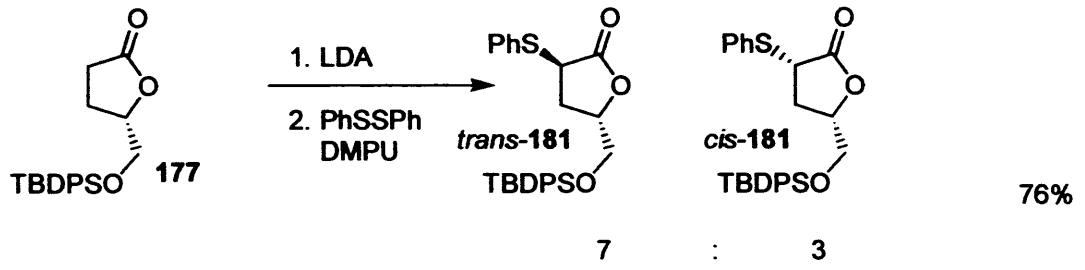
the γ-lactone **180**. Due to the two consecutive S_N2 reactions the reaction takes place in an overall retention of configuration (Scheme 95).

Scheme 95



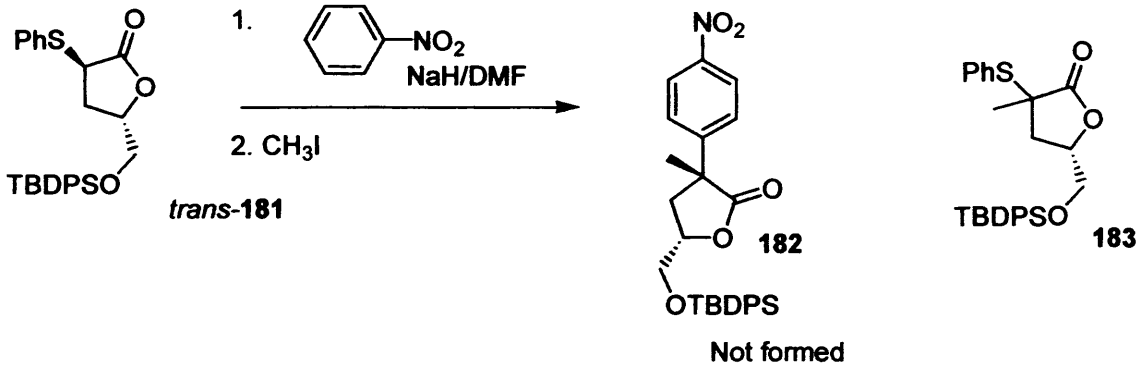
Esterification of **180** with EtOH/*p*-TsOH/benzene gave the ester **175**. Reduction of the ester with sodium borohydride gave the alcohol **176**. Protection of the alcohol with *tert*-butyl diphenylchlorosilane gave the required product **177**. Treatment of **177** with LDA (2 eq.), phenyl disulfide (1 eq.) and DMPU (1 eq.) gave the VNS nucleophiles (*trans*-**181** & *cis*-**181**) (Scheme 96). These were then separated by column chromatography.

Scheme 96



The VNS nucleophiles *trans*-**181** & *cis*-**181** were used in the VNS/alkylation process under the conditions developed previously, namely sodium hydride, nitrobenzene and methyl iodide (Scheme 97).

Scheme 97

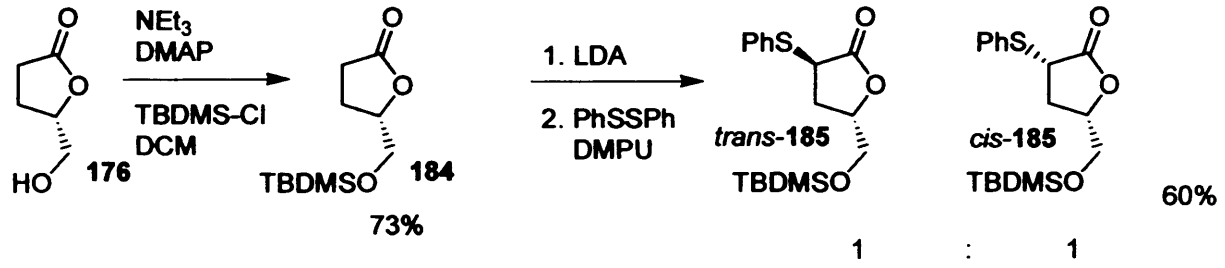


Despite numerous attempts to get this reaction to work, all were unsuccessful. Using sodium hydride as the base resulted in no brightly coloured intermediate being observed. In the ^{1}H-NMR spectrum of the crude reaction mixture nitrobenzene was observed along with the α-

methylated VNS nucleophile **183** although attempts to isolate this compound failed. Changing the base/solvent system to KO*t*-Bu/DMF resulted in the usual bright purple solution. The ^{1}H-NMR spectrum of the crude reaction mixture however showed no sign of the required VNS product. Nitrobenzene was observed as well as a singlet at δ 0.95 along with aromatic protons at (δ 7.41-7.55). There was no indication of the product lactone in the ^{1}H-NMR spectrum, and also no indication of the starting material **181**.

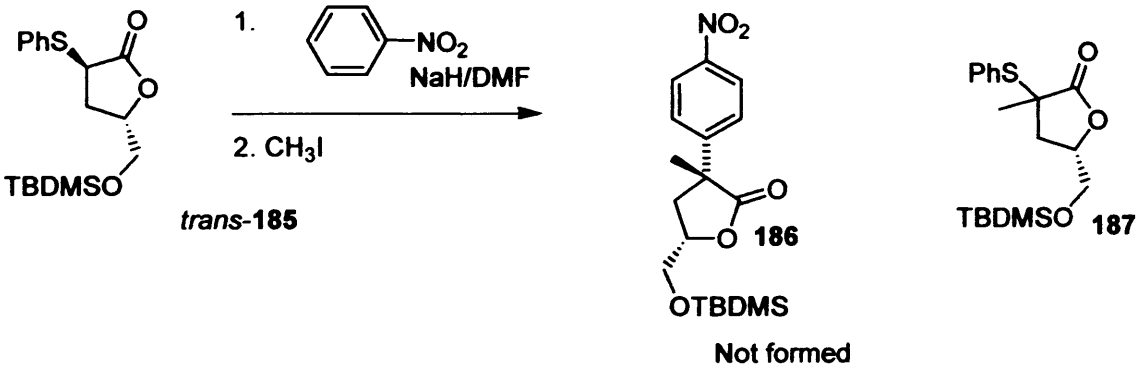
An alternative protecting group was then attempted. This was formed under the same conditions as the previous lactone but using TBDMS-Cl instead of TBDPS-Cl (Scheme 98). The protected lactone **184** was then treated with LDA (2 eq.), DMPU and phenyl disulfide to give the *cis* and *trans* diastereoisomers in a 1:1 ratio (Scheme 98). The two diastereoisomers were separated by column chromatography.

Scheme 98



The presence of the required products was indicated by the presence of a double doublet at δ 4.05 (*J* 7.4 & 9.3 Hz) in one diastereosiomer and a triplet at δ 3.89 (*J* 10.2 Hz) in the other diastereoisomer representing the C-3 protons. The VNS nucleophiles *trans*-**185** & *cis*-**185** were studied in the asymmetric VNS reaction under the previous conditions using both sodium hydride and potassium *tert*-butoxide as the base. Using sodium hydride as the base resulted in no VNS product **186**, but only nitrobenzene and the α-methylated VNS nucleophile **187** present in the ^{1}H-NMR spectrum of the crude reaction mixture (Scheme 99).

Scheme 99

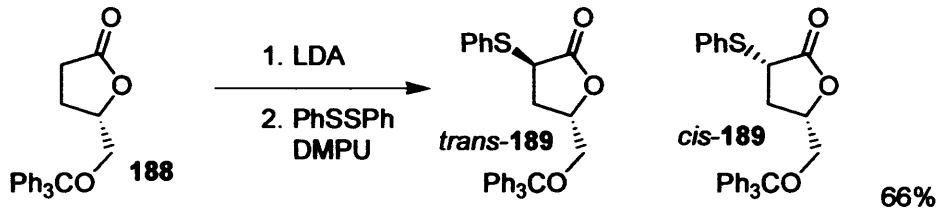


Using potassium *tert*-butoxide as the base again it looked as if the protecting group was being removed by the base as a singlet at δ 0.82 and doublet at 0.00 (*J* 3.7 Hz) was observed in the

^{1}H-NMR of the crude reaction mixture. Nitrobenzene was also present although there was no sign of the peaks associated to a lactone.

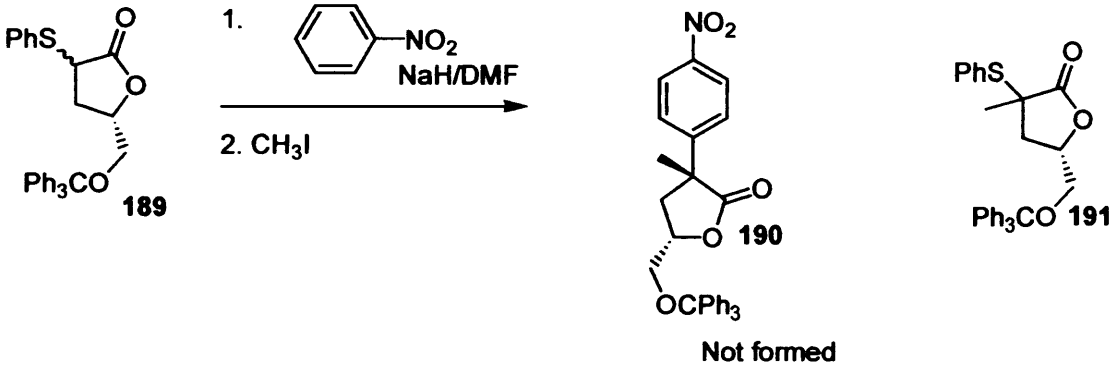
A further VNS nucleophile was studied with a trityl protecting group. This was formed from the commercially available lactone **188** and treatment with LDA (2 eq.), DMPU and phenyl disulfide in THF (Scheme 100) to produce the *cis* and *trans* VNS nucleophiles although these could not be separated by column chromatography.

Scheme 100



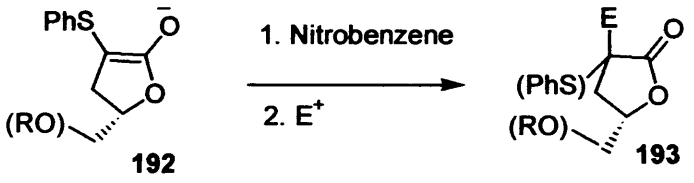
These nucleophiles were studied in the VNS reaction under the same conditions as before. Using sodium hydride as the base resulted in nitrobenzene and the α-methylated VNS nucleophile **191** being observed in the ^{1}H-NMR spectrum of the crude reaction mixture with no trace of the required product **190** (Scheme 101). The same result was observed when potassium *tert*-butoxide was used as the base instead of sodium hydride.

Scheme 101



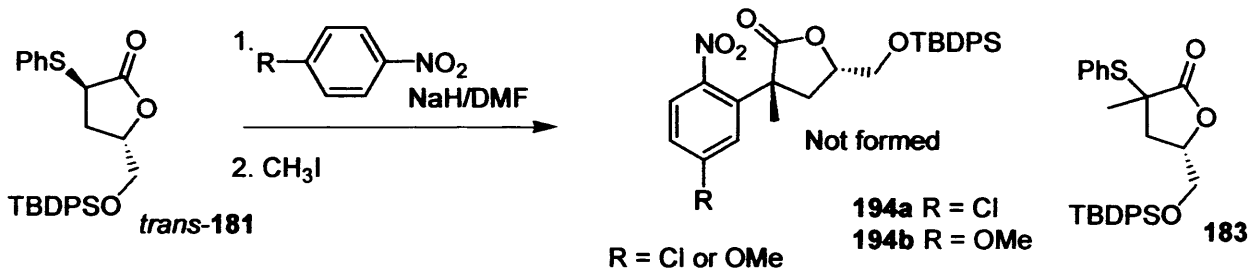
A possible reason as to why these reactions failed is that in formation of the σ_H-adduct causes the large PhS group to be forced *cis* to the large protecting group making the reaction highly unfavourable (Scheme 102). One possible solution is looking for a smaller VNS leaving group.

Scheme 102



Despite the lack of success with nitrobenzene an attempt was made to study the VNS nucleophile **181** in the VNS reaction with *para*-substituted nitroaromatics to obtain the *ortho*-VNS product (Scheme 103) as this would be important in the synthesis of physostigmine (**98**). The same conditions were used as in the earlier attempts with nitrobenzene.

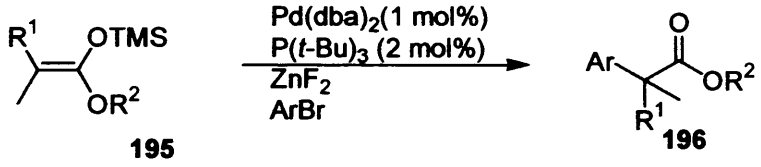
Scheme 103



Unfortunately this also resulted in no success with the *para*-substituted nitroaromatic and only the α-methylated VNS nucleophile **183** was observed in the ^{1}H-NMR spectrum of the crude reaction mixture. A possible problem with the *para*-nitroanisole is the electron-donating nature of the methoxy group.

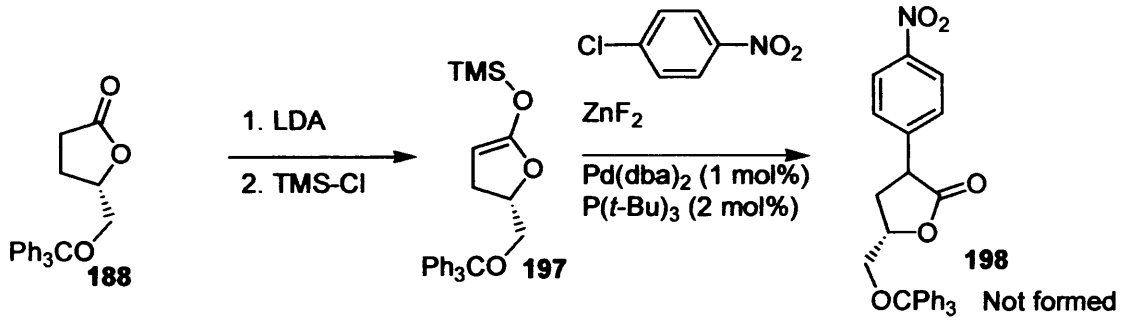
As an alternative to the VNS/alkylation process, we considered Hartwig's palladium-catalysed α-arylation of esters by forming a silyl ketene acetal **195** and then forming the enolate by treatment with a fluoride source (Scheme 104).[82] If we could successfully apply this methodology to effect C-arylation of the lactone, we could obtain the same products as the VNS process which could then be protonated and quenched with electrophiles to carry out a diastereoselective alkylation process. This would hopefully allow us to obtain the substrate required to continue with the proposed synthesis of the natural product physostigmine (**98**).

Scheme 104



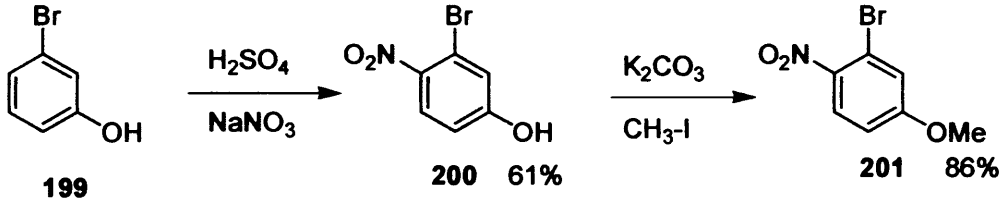
The silyl ketene acetal **197** was formed by treatment of the lactone with LiHMDS followed by chlorotrimethylsilane at –78 °C (Scheme 105). Purification of the product proved to be problematic, so the crude product was used directly in a cross-coupling process with *p*-chloronitrobenzene (Scheme 105).

Scheme 105



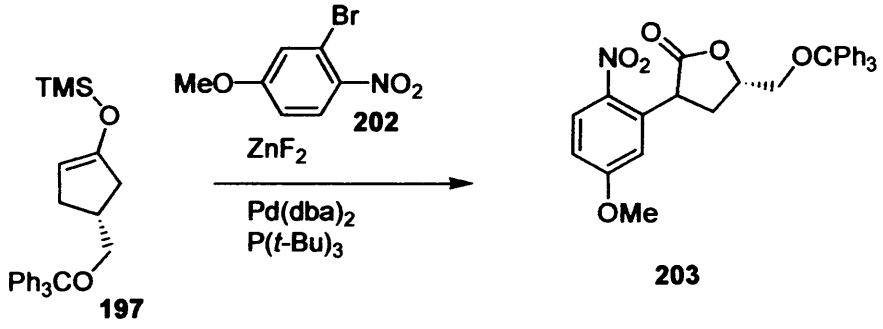
To probe the reactivity of the system, the silyl ketene acetal **197**, P(*t*-Bu)$_3$, $Pd_2(dba)_3$, zinc fluoride and bromobenzene were heated in DMF for 12 hours at 80 °C. The process however also resulted in no success, with the starting materials recovered. 3-Bromo-4-nitroanisole (**201**) was also used in this method as an alternative electrophile. This was prepared by treatment of 3-bromophenol (**199**) with sulphuric acid and sodium nitrate (Scheme 106).[159-160] The product was then methylated with K_2CO_3 and methyl iodide to give the 3-bromo-4-nitroanisole (**201**) in 86% yield.[161]

Scheme 106



The electrophile **201** was then studied in the cross-coupling of the silyl ketene acetal **197** under Hartwig's conditions (Scheme 107). If this proved successful, it would give us the required substrate to continue with the physostigmine synthesis.

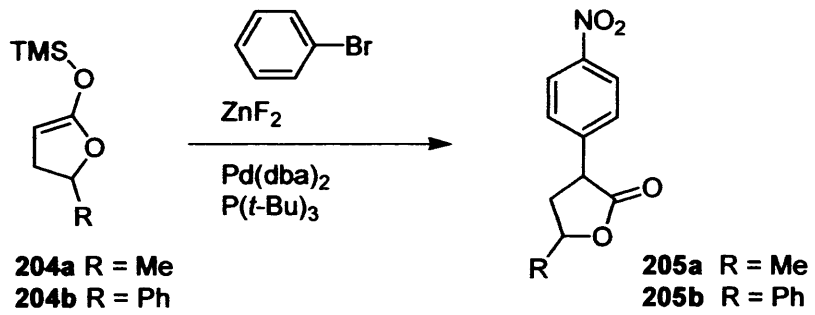
Scheme 107



This attempt also resulted in no success with the starting materials being recovered. Silyl ketene acetals of different lactones were also attempted (Scheme 108) as a test to see if the

problem was with the sterically hindered lactone **188**. Again this resulted in the starting materials being recovered.

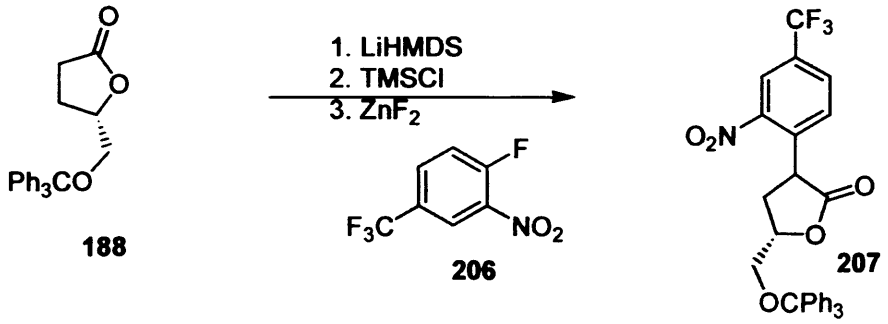
Scheme 108



204a R = Me
204b R = Ph

205a R = Me
205b R = Ph

Scheme 109



188

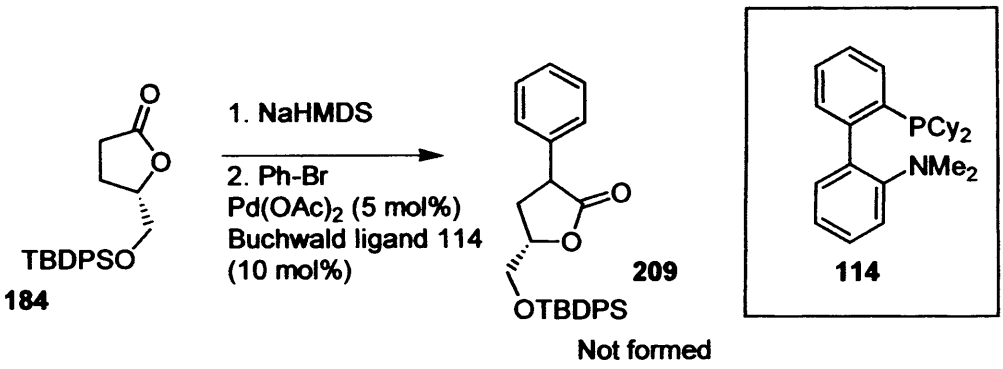
206

207

An attempt was made to use the enolate generated from a silyl ketene acetal in a S_NAr reaction (Scheme 109) as an alternative method to effect C-arylation of the lactone. This again proceeded without success, with the starting materials recovered. 3-Fluoro-4-nitroanisole was also used as an electrophile in this attempted S_NAr reaction (Scheme 109). This also resulted in the starting materials being recovered.

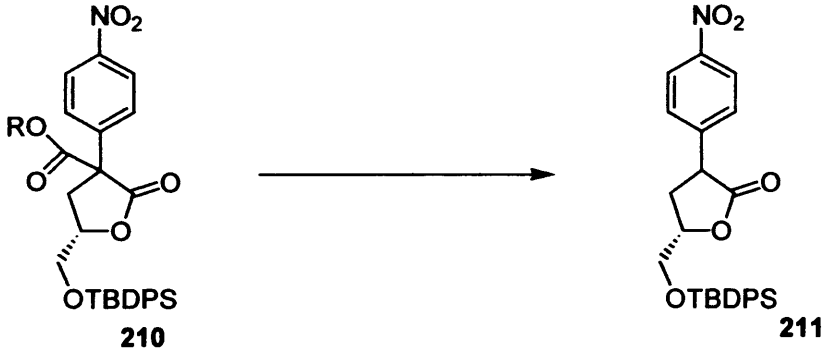
Buchwald's method of cross-coupling esters with aryl bromides was also attempted as a further alternative for forming a C-3 arylation of the lactone. We chose bromobenzene as our electrophile as a test as there was no successful reactions with a nitroaromatic reported by Buchwald (Scheme 110).[162] However this method also resulted in recovery of the starting materials.

Scheme 110



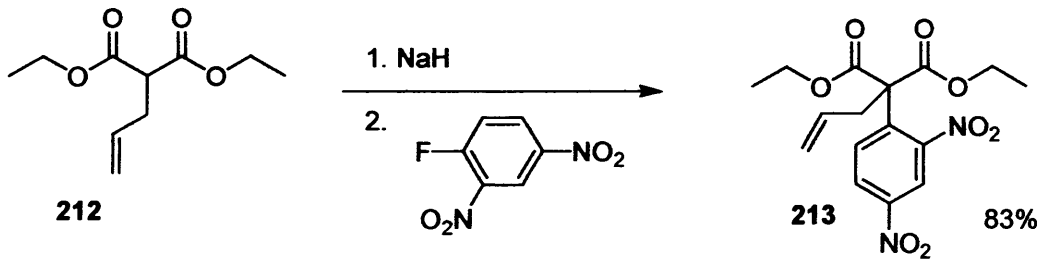
Due to the failure of the cross-coupling and S_NAr approaches, we wondered if we could use an α-carbonyloxylactone **210** and decarboxylate to give the required product **211** (Scheme 111). This again would be an alternative route to get through to the substrate we needed to continue with the synthesis of physostigmine. An α-carbonyloxylactone provides a stabilized enolate similar to that of a malonate which are known to successfully undergo the S_NAr process.

Scheme 111



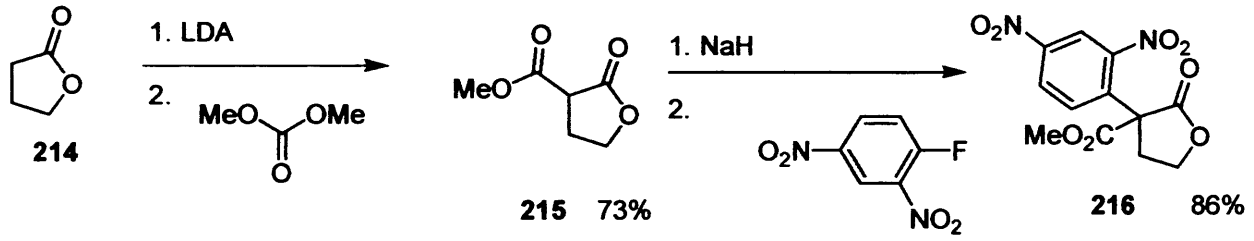
Firstly, we needed to know if a malonate substituted at the carbon between the two carbonyl groups would undergo the S_NAr process. The commercially available malonate **212** was treated with sodium hydride (1 eq.) in DMF at 0 °C and then 2,4-dinitrofluorobenzene before being allowed to warm to room temperature (Scheme 112). This reaction proceeded in 83% yield.

Scheme 112



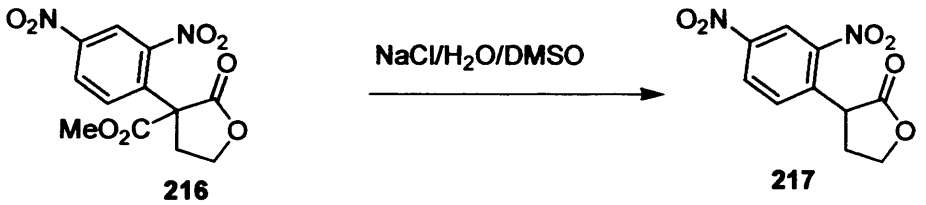
Due to the success of this reaction we decided to form an α-carbonyloxylactone from the lactone. This was done by treating the lactone **214** with LDA followed by dimethyl carbonate (Scheme 113).[163] This reaction proceeded in 73% yield. The product **215** was treated with sodium hydride at 0 °C followed by 2,4-dinitrofluorobenzene and allowed to warm to room temperature (Scheme 113).

Scheme 113



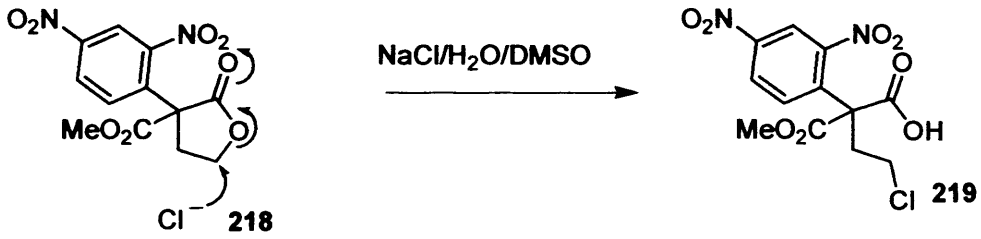
This reaction proceeded in 86% yield. The presence of the required product was indicated by a triplet at δ 3.43 (*J* 8.4 Hz) in the starting material disappearing. Doublets at δ 8.86 (*J* 2.4 Hz) and 7.64 (*J* 8.4 Hz) and a double doublet at δ 8.44 (*J* 2.4 & 8.4 Hz) indicated the presence of the aryl group. We took the product **216** and attempted to decarboxylate using Krapcho conditions (Scheme 114).[164] The product **216** was heated in a flask at 180 °C containing DMSO, sodium chloride and water.

Scheme 114



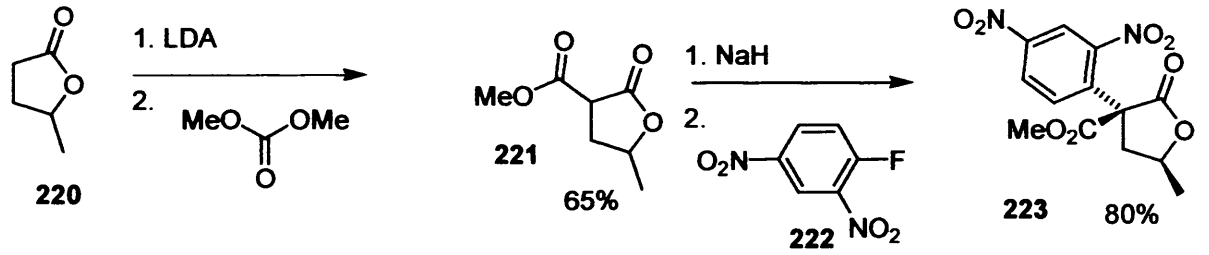
The required product **217** was not formed in this reaction and no starting materials were recovered. The crude ^{1}H-NMR spectrum was no help as it was extremely complicated. We thought that maybe a competing process was taking place as a lactone is a cyclic ester and the C-5 position is unhindered it could be susceptible to attack by the chloride which could then ring open the lactone (eg **218→219**) (Scheme 115). Unfortunately no products could be isolated by column chromatography. Use of LiI instead of water and NaCl resulted in no improvement to the process. We thought that the problem could be avoided, however, if the lactone was substituted at the γ-position which would undergo the competing process more slowly.

Scheme 115



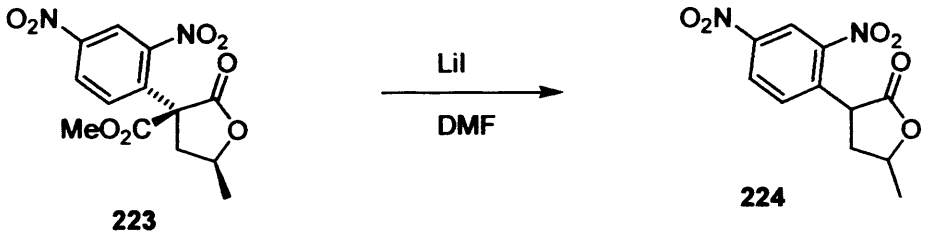
γ-Methyl-γ-butyrolactone **220** was treated with LDA followed by dimethyl carbonate (Scheme 116). This reaction proceeded in 75% yield. A 1:1 mixture of diastereoisomers was observed. This mixture was treated with sodium hydride at 0 °C followed by 2,4-dinitrofluorobenzene to give **223** (Scheme 116). However the stereochemistry of the lactone was not assigned due to the chiral centre being destroyed in the next step. Nevertheless it is highly likely that the aryl group is *trans* to the methyl group.

Scheme 116



The reaction proceeded in 80% yield. Only one product **221** was observed. The product **221** was then treated under Krapcho conditions to undergo decarboxylation (Scheme 117). Unfortunately, however, this process did not occur cleanly, with the ^{1}H-NMR spectrum of the crude reaction product being extremely complex.

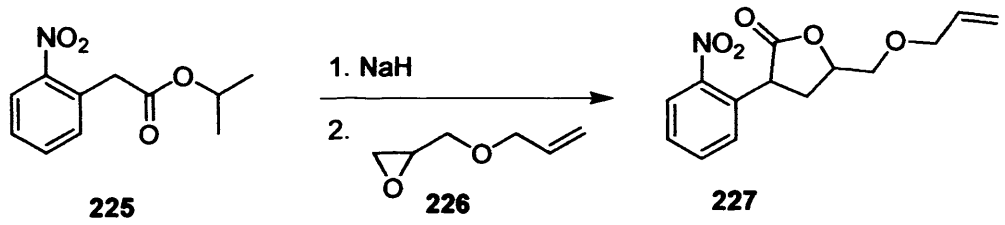
Scheme 117



A further alternative method for forming the required product was treating the enolate of an ester with an epoxide. Despite there being few examples of ester enolates reacting with epoxides in the literature we were hopeful that the nitrophenyl acetates would be more successful due to the similar pK_a of malonates. Malonates readily undergo reactions with epoxides.[165] Isopropyl 2-nitrophenylacetate (**225**) was treated with sodium hydride at 0 °C to

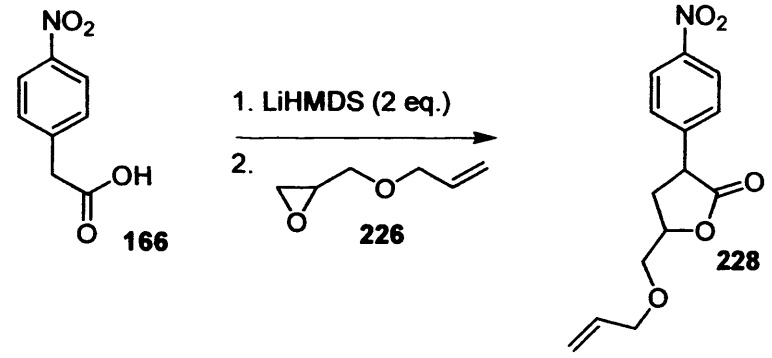
form the enolate followed by an electrophilic quench with allyl glycidyl ether as a simple test. The epoxide was chosen as it was readily available at hand (Scheme 118). Unfortunately, however this resulted in the starting materials being recovered. The reaction was tried several times with heating but all with no success.

Scheme 118



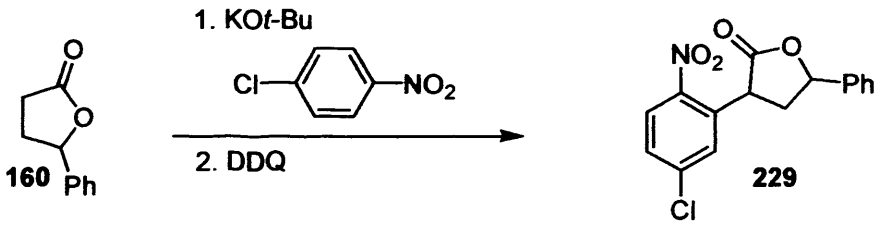
Due to this lack of success we tried treating 4-nitrophenylacetic acid (**166**) with 2 equivalents of base, followed by treatment with the allyl glycidyl ether **226** (Scheme 119) This was tried due to precedent of carboxylic acids reacting with epoxides with 2 equivalents of base to produce a γ-lactone.[166] This however also resulted in the starting materials being recovered.

Scheme 119



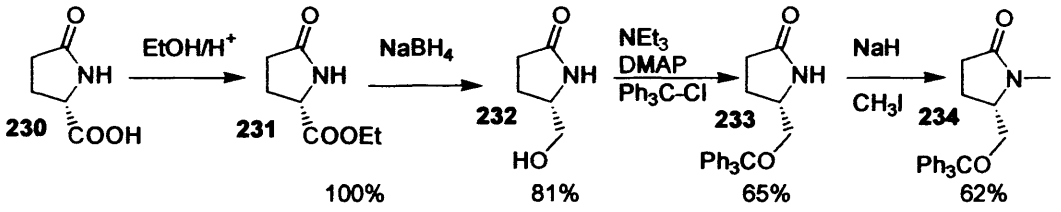
We wondered if oxidative nucleophilic substitution of hydrogen would provide an alternative process to get through to the same products. γ-Phenyl-γ-butyrolactone (**160**) was treated with potassium *tert*-butoxide and 4-chloronitrobenzene followed by DDQ (Scheme 120). ONSH had already been used in the synthesis of physostigmine using the enolate of *N*-methyl pyrrolidinone as mentioned previously. However again this resulted only in the recovery of the starting materials.

Scheme 120



We decided to try a chiral lactam as a VNS nucleophile due to the success with the lactams in the previous chapter. This would hopefully give us a valuable method for forming α-aryl quaternary centres in high selectivity, which as mentioned previously possesses a scaffold with several points of diversity amenable to covenient derivatization thereby providing an important peptide-like scaffold. The chiral lactam was made from commercially available L-pyroglutamic acid (**230**) (Scheme 121) according to the method of Thottathil.[167]

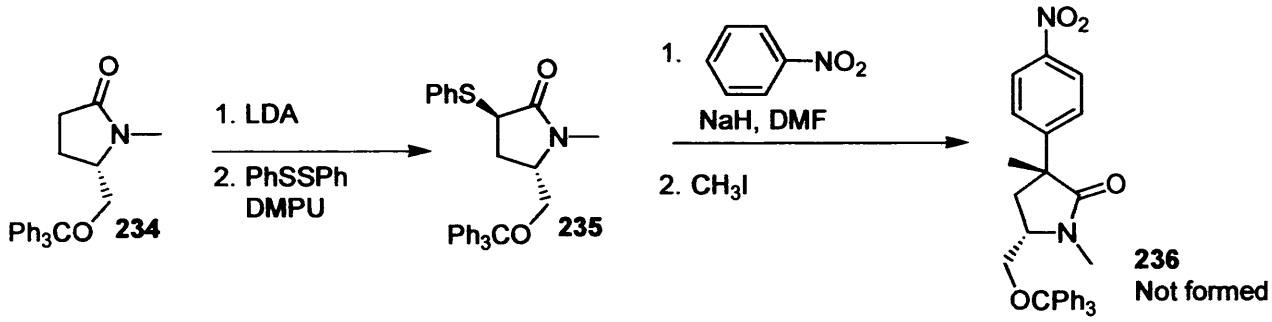
Scheme 121



The pyroglutamic acid **230** was esterified with ethanol and sulphuric acid. The ester **231** was then reduced to the primary alcohol **232** with sodium borohydride. The alcohol **232** was protected with trityl chloride, a bulky group required to shield one side of the lactam in the asymmetric VNS alkylation process. Triethylamine and trityl chloride were added to a solution of 5-hydroxymethylpyrrolidin-2-one (**232**) in dichloromethane. The amide nitrogen was then methylated with sodium hydride and methyl iodide at 0 °C to give the required product **233**. To prove no racemisation had occurred at the chiral centre the α_D was measured (+ 28.4 c = 1.71 in ethanol) and compared with the literature value (+28.9 c = 1.71 in ethanol).[168]

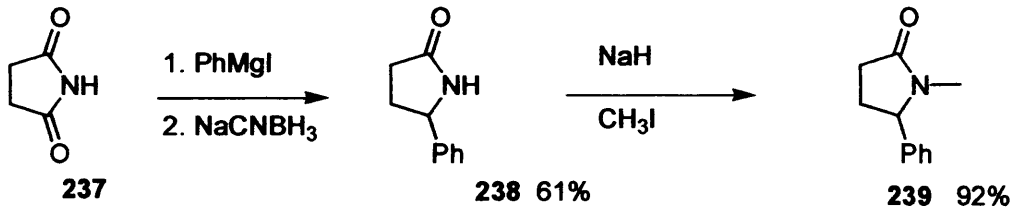
The lactam **234** was then treated with LDA (2 eq) followed by phenyl disulfide (1 eq.) and DMPU (1 eq.) to give the VNS nucleophile **235** (Scheme 122). This process occurred in 55% yield with only the one diastereoisomer observed The stereochemistry of the lactam was not assigned due to the chiral centre being destroyed in the next step. Nevertheless it is highly likely that the thiophenyl group is *trans* to the trityl group. The presence of the desired product was indicated by a presence of a triplet at δ 4.00 (*J* 8.3 Hz). This was then used in the VNS/alkylation process with sodium hydride and nitrobenzene (Scheme 123). The required product was not observed in the crude ^{1}H-NMR spectrum with only nitrobenzene and the α-methylated VNS nucleophile observed. Potassium *tert*-butoxide was tried as a base but also with no success.

Scheme 122



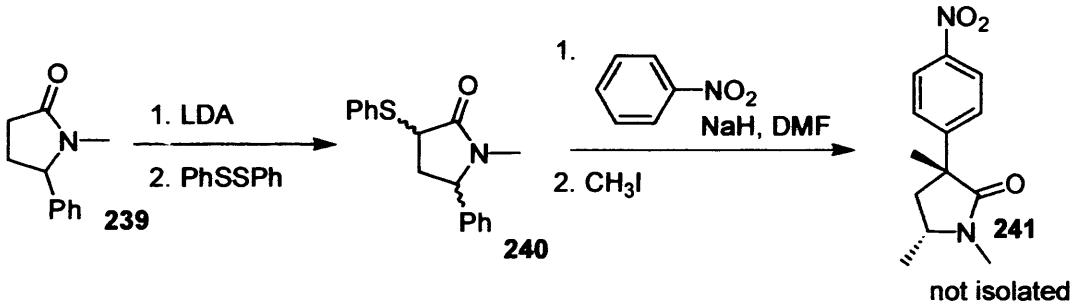
An alternative lactam was also tried in the VNS/alkylation process. This was formed by treatment of succinimide with methylmagnesium iodide followed by treatment of the intermediate with sodium cyanoborohydride (Scheme 123).[169-170]

Scheme 123



N-Methylation of the resulting product **238** with sodium hydride and methyl iodide at 0 °C gave **239**. Treatment of **239** with LDA (2 eq.) followed by phenyl disulfide (1 eq.) and DMPU (1 eq.) at –78 °C gave **240** (Scheme 124). A mixture of the two diastereoisomers were formed which proved difficult to separate by column chromatography. The lactam **240** was used in the VNS/alkylation process (Scheme 124). However this resulted in no VNS product, with nitrobenzene and the α-methylated lactam **241** being recovered.

Scheme 124



Summary and Conclusion

In conclusion, the one pot asymmetric VNS alkylation was developed successfully using Dihydro-5-phenyl-3-(phenylthio)(3H)furan-2-one (**161**) as the VNS nucleophile. Significant diastereoselectivities were observed using **161** as the VNS nucleophile. The method provided

diastereoselectivities of greater than 7:1. The *ortho*-selective VNS reaction was successful using **167** and *p*-chloronitrobenzene, this was important as it gave us hope that the proposed route to physostigmine could be carried out using this method.

Attempting to use a silyl protected lactone resulted in deprotection of the alcohol and loss of the lactone in the work up. Changing to a trityl group also resulted in no success. We considered the possibility that in forming the σ_H-adduct the large PhS group is forced *cis* to the large protecting group making the reaction highly unfavourable (Scheme 102). A possible solution would be to use a smaller VNS leaving group or another solution would be to use a smaller alcohol protecting group although this would probably compromise on the level of diastereoselectivity. The advantage of the PhS VNS leaving group was that it was easy to add to the lactone. An α-chloro lactone is more difficult to form.

We concluded that due to the difficulties associated with getting the conditions right for the VNS reaction an alternative process for the VNS step might be more favourable. We considered Hartwig's cross-coupling of silyl ketene acetals, Buchwald's cross-coupling of esters, the use of an α-carbonyloxylactone followed by decarboxylation and finally treating the enolate of an ester with an epoxide. Hartwig's cross-coupling of silyl ketene acetals and Buchwald's method for cross-coupling of esters both resulted in the recovery of starting materials. The Krapcho decarboxylation of an α-carbonyloxylactone resulted in a complicated ^{1}H-NMR spectrum with a possible competing process occurring (Scheme 115). The asymmetric VNS/alkylation of lactams was also studied but again with no success. Clashes of the large PhS group with the protecting group could again be the problem when the PhS group is forced *cis* on forming the σ_H-adduct.

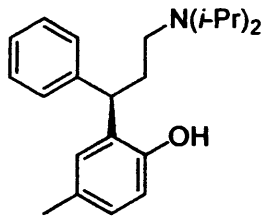
We conclude that in our efforts to obtain high diastereoselectivities that we under estimated the sensitivity of the VNS reaction to steric effects, and should not have used such a bulky directing group. We should have started with a much smaller alcohol protecting group. Future work will be to investigate a smaller VNS leaving group in the reaction to try and avoid the problem of a steric clash between the VNS leaving group and the bulky protecting group (Scheme 102) and also try different alcohol protecting groups in the reaction.

Chapter 6

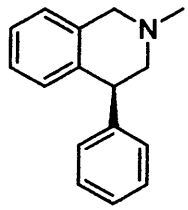
6.1 Synthesis of Diarylmethanes

Diarylmethanes and diarylacetates are extremely useful synthetic intermediates[173-5] and the diarylmethyl motif is found in many pharmacologically important agents[176-9] such as Tolterodine (**242**) and Nomifensine (**243**) (Figure 11). A versatile route to this important scaffold incorporating several points of diversity is potentially useful.

Figure 11



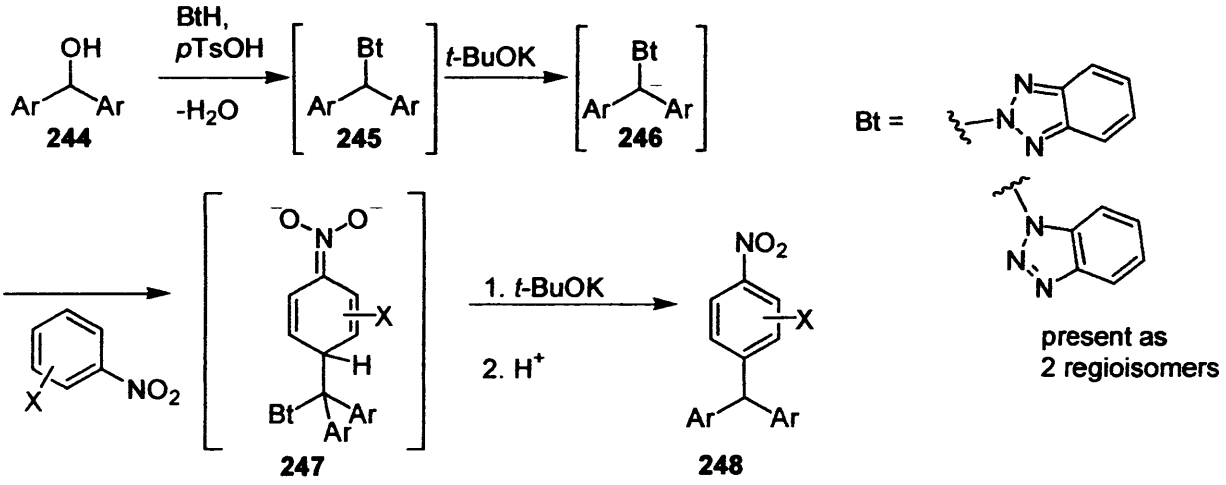
Tolterodine (**242**)



Nomifensine (**243**)

A synthesis of (*p*-nitroaryl)diarylmethanes *via* VNS of hydrogen has been reported by Katritzky (Scheme 125).[180] (Diarylmethyl)benzotriazoles **245** were prepared from benzotriazole and diarylmethanols **244** in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) in benzene with azeotropic removal of water. In these compounds, the benzotriazoyl moiety serves as a carbon-stabilizing and leaving group, in the course of the VNS reaction. (Diarylmethyl)benzotriazoles **245** were reacted with a series of *o*- and *m*-substituted nitrobenzenes. An equimolar mixture of **245** and the nitroarene were added to a solution of potassium *tert*-butoxide in dry THF to give a deep red reaction mixture. Upon quenching with saturated ammonium chloride solution, (nitroaryl)diarylmethanes **248** were obtained.

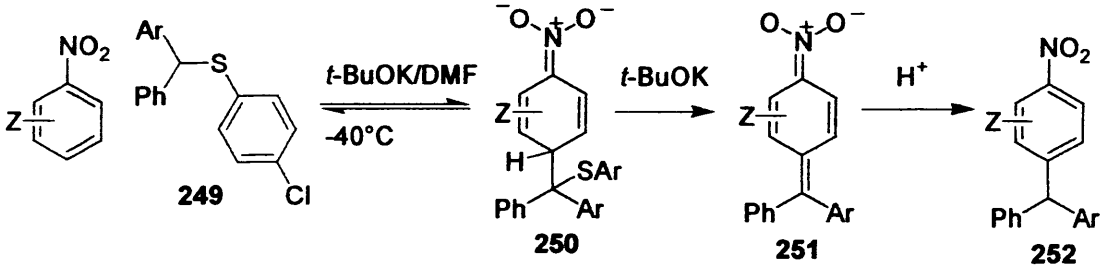
Scheme 125



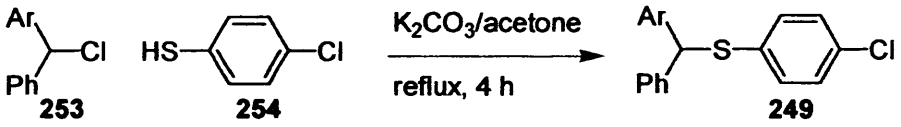
A synthesis of (*p*-nitroaryl)diarylmethanes *via* VNS of hydrogen was also reported by Makosza (Scheme 126).[181] This process used the carbanions of benzhydryl sulfides **249**. These reacted

with nitroarenes in the usual way to produce σ^H-adducts **250** from which base induced β-elimination can take place to give the VNS product **252**. The benzhydryl sulfides **249** were prepared from the reaction of diarylchloromethanes **253** with *p*-chlorothiophenol (**254**) in K_2CO_3/acetone in yields close to quantitative (Scheme 127). The *p*-chlorophenyl sulfides **249** were used as the VNS nucleophile due to *p*-chlorophenylthiolate being a better leaving group than thiophenolate (pK_a (H_2O) is 10 compared to the pK_a *p*-chlorophenylthiolate is 8.1).[182]

Scheme 126



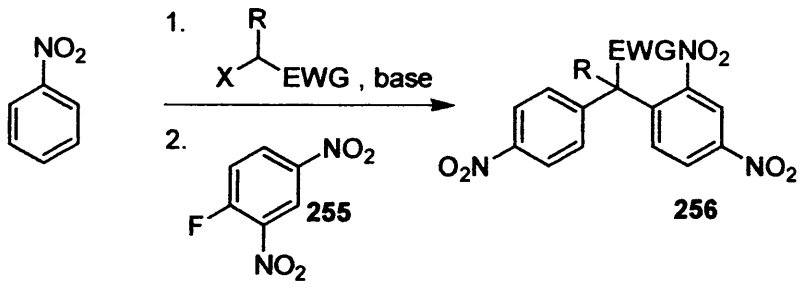
Scheme 127



6.2 The Synthesis of Diarylacetates *via* a Sequential VNS-S_NAr Three Component Coupling Reaction

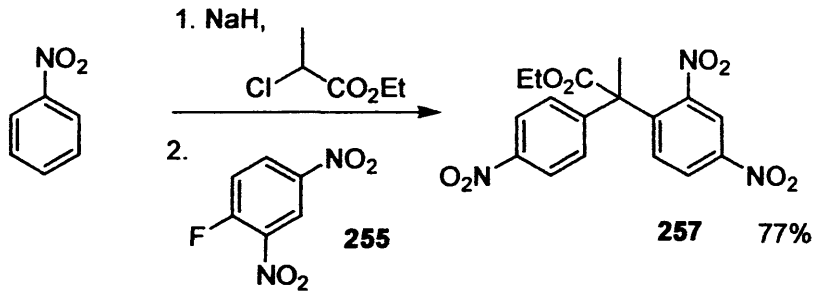
It has been shown that the VNS nucleophiles exhibit reactivity similar to that of the malonate anion. This is not surprising given that other properties such as acidity are similar. For example, the pK_a (DMSO) of ethyl *p*-nitrophenylacetate is 15.1[183] while that of diethyl malonate is 16.4.[184] Malonate is an excellent nucleophile for many S_NAr reactions[185-6] and some examples of the use of nitrophenylacetates in the S_NAr reaction have been reported.[187-9] We were therefore hopeful that the anion derived from the VNS reaction (Scheme 128), would react with activated aryl electrophiles such as **255** to give products such as **256**.

Scheme 128



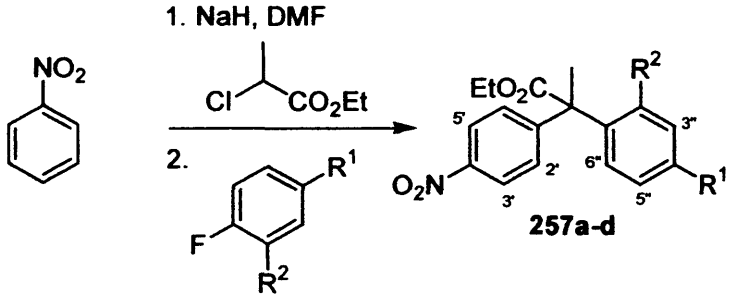
The post VNS anion was generated by addition of nitrobenzene and ethyl 2-chloropropionate in DMF to a suspension of sodium hydride in DMF at –50 °C. This generated the usual brightly coloured intermediate, which after warming to room temperature was cooled back to –50 °C then was quenched with 2,4-dinitrofluorobenzene. The desired diarylacetate **257** was isolated after column chromatography in 77% yield (Scheme 129). The two doublets at δ 8.22 and 7.68 (*J* 9.0 Hz) in the ^{1}H-NMR spectrum indicated the presence of a 1,4-disubstituted aryl group. Doublets at δ 8.80 (*J* 2.4 Hz) and 7.16 (*J* 8.7 Hz) along with a double doublet at δ 8.30 (*J* 2.4 and 8.7 Hz) indicates the presence of a 1,2,4-trisubstituted aryl group. The methyl group appears as a singlet at δ 2.26 indicating that it was attached to a quaternary centre.

Scheme 129



To investigate whether this was a general process the reaction was repeated with several other electrophiles under the same conditions as described. The electrophiles were chosen due to their highly reactive nature and because they were commercially available.

Scheme 130



	R^1	R^2	Yield
257a	CF_3	NO_2	73%
257b	NO_2	NO_2	77%
257c	NO_2	CN	88%
257d	NO_2	CF_3	89%

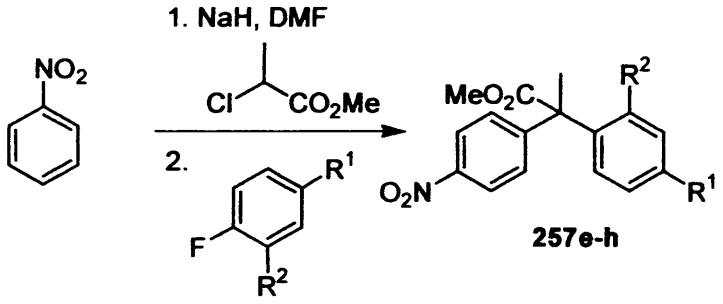
Diarylacetate **257a** was formed using the conditions described above (Scheme 130). The seven aromatic protons representing the two aryl groups appear as a multiplet (δ 8.20-8.23) along with doublets at δ 7.72 (*J* 8.4 Hz) (H-5"), 7.67 (*J* 9.0 Hz) (H-2' & H-6') and 7.06 (*J* 8.4 Hz) (H-6"). The methyl group appears as a singlet at 2.25 indicating the presence of a quaternary centre.

Diarylacetate **257c** was formed in 88% yield using slightly different conditions, instead of using just the one equivalent of ethyl 2-chloropropionate increasing to two equivalents to

increase the yield based on nitrobenzene. This was discovered by previous research in the Lawrence group.[86] The excess nucleophile undergoes self condensation. It was also found that there was no need to cool the reaction mixture to –50 °C for the electrophilic quench. Cooling to 0 °C was sufficient. Diarylacetate **262d** was formed in 89% yield also using two equivalents of ethyl 2-chloropropionate and cooling to 0 °C for the electrophilic quench. The ^{1}H-NMR spectra for both these compounds were consistent with what was observed in diarylacetates **257a** and **257b**. The products were characterized in full (see Experimental section).

It was decided to investigate different nucleophiles in the VNS-S_NAr process. Methyl 2-chloropropionate was investigated as the nucleophile as it was commercially available (Scheme 131).

Scheme 131



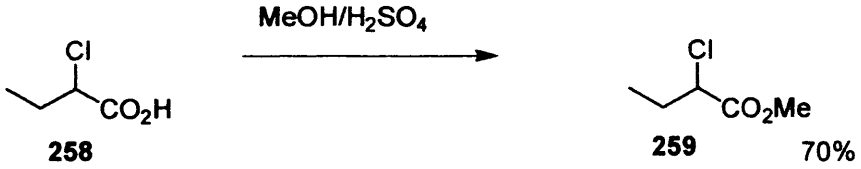
	R^1	R^2	Yield
257e	CF_3	NO_2	69%
257f	NO_2	NO_2	71%
257g	NO_2	CN	86%
257h	NO_2	CF_3	86%

Diarylacetate **257e** was formed in 69% yield using one equivalent of methyl 2-chloropropionate. The reaction was also cooled to –50 °C for the electrophilic quench. One of the two doublets in the ^{1}H-NMR spectrum representing the 1,4-disubstituted aryl group overlaps with one of the signals from the second aryl group to give a multiplet (δ 8.19-8.23). The other doublet of the 1,4-disubstituted aryl group appears at δ 7.68 (*J* 8.9 Hz). Doublets at δ 7.72 (*J* 8.3 Hz) and 7.09 (*J* 8.3 Hz) represent the other two protons on the second aryl group. The methyl group appears as a singlet at δ 2.25 indicating the presence of a quaternary centre.

The process was applied to **257f**, **257g** and **257h**. The products were obtained in good yields (Scheme 7). Diarylacetate **257f** was formed using one equivalent of methyl 2-chloropropionate and the electrophilic quench at –50 °C. Diarylacetates **257g** and **257h** were formed using two equivalents of methyl 2-chloropropionate and the electrophilic quench carried out at 0 °C. The products were characterized in full (see experimental section).

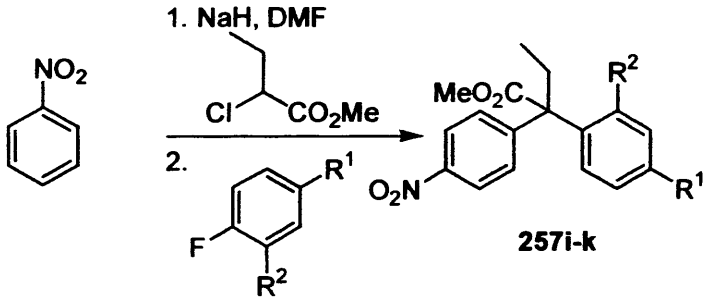
The next nucleophile investigated was methyl 2-chlorobutanoate (**259**) to give us access to butanoates as well as propionates. This was prepared by esterification of chlorobutyric acid (**258**) (Scheme 132).[190]

Scheme 132



Methyl 2-chlorobutanoate was used in the VNS-S_NAr process with a series of electrophiles (Scheme 133). The process was used to make **257i**, **257j** and **257k**. The products were obtained in good yields (Scheme 133). Diarylacetate **257i** was formed using one equivalent of methyl 2-chlorobutanoate and the electrophilic quench at 0 °C. **257j** and **257k** were formed using two equivalents of methyl 2-chlorobutanoate under the same conditions. The products were characterized in full (see Experimental section).

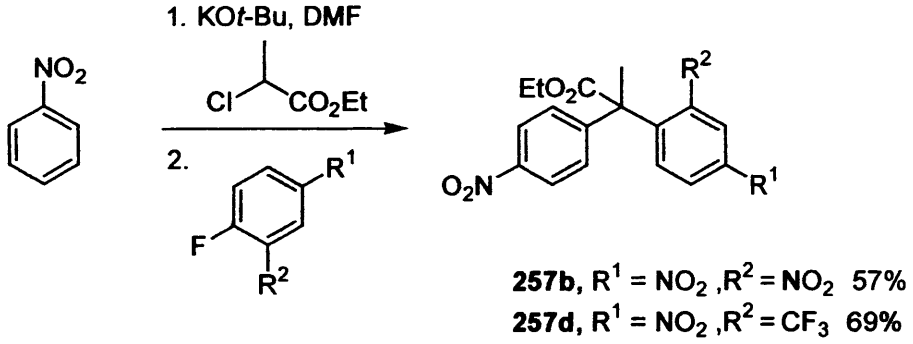
Scheme 133



	R^1	R^2	Yield
257i	CF_3	NO_2	60%
257j	NO_2	NO_2	80%
257k	NO_2	CF_3	69%

The results clearly indicate that the process is general and efficient. The efficiency of the S_NAr process is high, as the yields are close to that expected for protonation of the post-VNS anion.[39] The use of activated arenes allows the S_NAr reaction to proceed conveniently at ambient temperature, avoiding the need for heating. Heating can be problematic for sodium hydride in DMF when the reaction is performed on a large scale.[191] To overcome the problems associated with the NaH/DMF base/solvent system, we next showed the process has potential for scale up using potassium *tert*-butoxide as the base (Scheme 134).

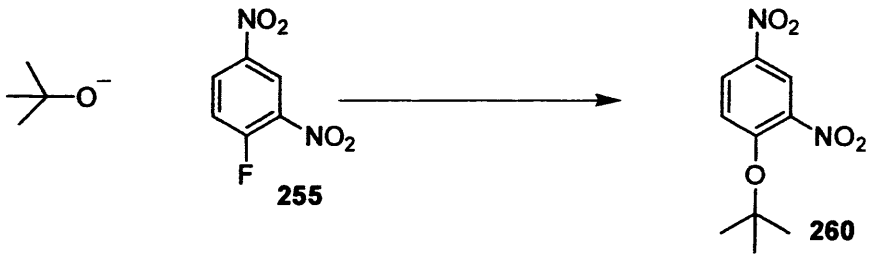
Scheme 134



Diarylacetate **257b** was formed in 57% yield using potassium *tert*-butoxide as the base with one equivalent of ethyl 2-chloropropionate. The reaction was cooled to –50 °C and allowed to warm to –20 °C before cooling back to –50 °C for the electrophilic quench. It was important to

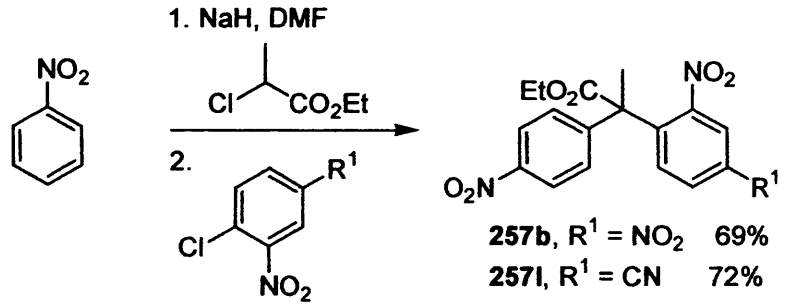
use a maximum of two equivalents of potassium *tert*-butoxide and a slight excess of the electrophile as a side reaction also took place with the *tert*-butoxide anion reacting with the electrophile, as indicated by LC-MS (Scheme 135). Diarylacetate **257d** was formed in 69% yield using the same conditions as described earlier.

Scheme 135



The process is not limited to the use of fluoronitroarenes. 2,4-Dinitrochlorobenzene was used in place of 2,4-dinitrofluorobenzene to give **257b** in 69% yield (Scheme 136). This reaction was carried out with one equivalent of ethyl 2-chloropropionate and cooling to –50 °C. Similarly the VNS-S_NAr reaction with 4-chloro-3-nitrobenzonitrile as the electrophile gave the required product **257l** in 72% yield using one equivalent of ethyl 2-chloropropionate and cooling to –50 °C. The doublets at δ 8.15 and 7.58 (*J* 9.0 Hz) in the ^{1}H-NMR spectrum indicate the presence of a 1,4-disubstituted aryl group. The doublets at δ 8.17 (*J* 1.8 Hz) and 6.97 (*J* 8.7 Hz) along with a double doublet at δ 7.66 (*J* 1.8 & 8.7 Hz) represent the three protons on the second aryl group. The methyl group appears as a singlet at 2.16 indicating the presence of a quaternary centre.

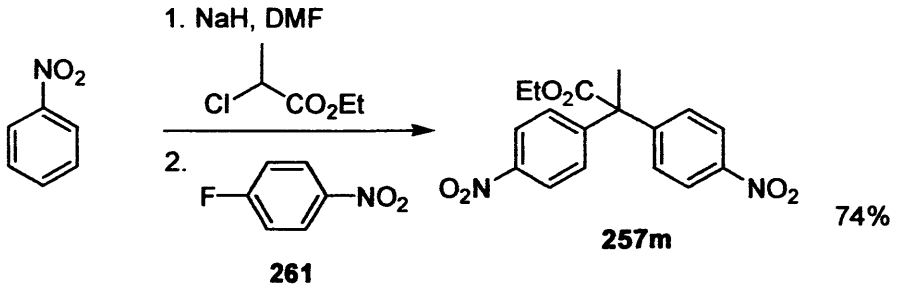
Scheme 136



The less activated 4-fluoronitrobenzene proved sufficiently reactive to enter the VNS-S_NAr process to give **257m** in 74% yield (Scheme 136). This was performed using two equivalents of ethyl 2-chloropropionate and cooling to 0 °C for the electrophilic quench. The two aryl groups were identical so the presence of doublets at δ 8.10 and 7.33 (*J* 8.9 Hz) in the ^{1}H-NMR spectrum when compared to the integration of the methyl group indicates the presence of two

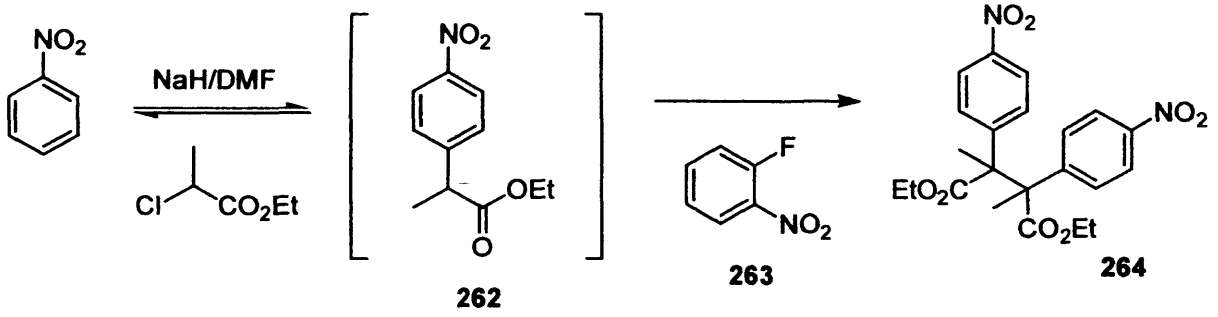
1,4-disubstituted aryl groups. The methyl group appears as a singlet at δ 1.93 indicating that the electrophilic quench had been successful.

Scheme 137



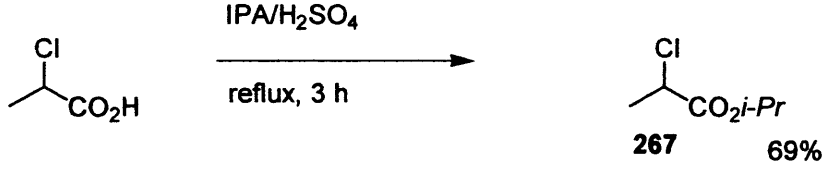
The use of 2-fluoronitrobenzene as the electrophile did not result in the required product. Instead the post VNS anion underwent a coupling reaction with another post VNS anion to give the dimer **264** as a 1:1 mixture of diastereoisomers presumably by a radical pathway (Scheme 138). This process has been observed by previous work in the group.[192] The 2-fluoronitrobenzene (**263**) must be acting as an oxidising agent. The doublets at δ 8.01 7.92, 7.02 and 6.99 (*J* 8.8 Hz) in the ^{1}H-NMR spectrum indicated the presence of two 1,4-disubstituted aryl groups. The multiplet (δ 4.02-4.21) and two triplets at 1.15 and 1.17 (*J* 7.4 Hz) represent the two ethyl groups. Singlets at δ 1.88 and 1.60 represent the other two methyl groups. As far as we can tell this is a novel process.

Scheme 138



Branched esters behaved well in the reaction although the reaction only proceeded with potassium *tert*-butoxide as base and not sodium hydride. The isopropyl ester **266** was prepared by esterification of 2-chloropropionic acid in 69% yield (Scheme 139).

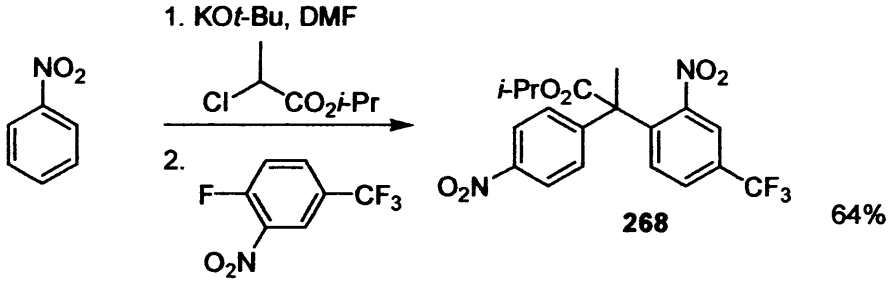
Scheme 139



267 69%

The isopropyl ester was used in the VNS process with nitrobenzene and 4-fluoro-3-nitrobenzotrifluoride as the electrophile (Scheme 140). Using sodium hydride as the base produced no VNS product with nitrobenzene being recovered. Using potassium *tert*-butoxide as the base and keeping the temperature of the reaction mixture between –50 °C and –20 °C gave the VNS product **268** in 64% yield.

Scheme 140

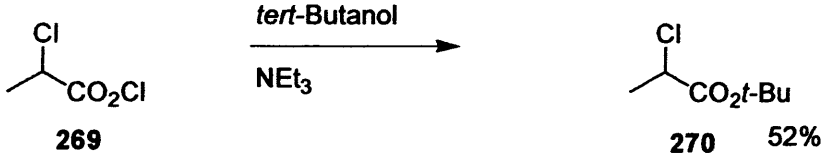


268 64%

One of the two doublets in the ^{1}H-NMR spectrum representing the 1,4-disubstituted aryl group overlaps with one of the signals from the second aryl group to give a multiplet (δ 8.13-8.16). The other doublet of the 1,4-disubstituted aryl group appears at δ 7.60 (*J* 9.0 Hz). A double doublet at δ 7.64 (*J* 1.7 and 8.5 Hz) and a doublet at 7.00 (*J* 8.5 Hz) represent the other two protons on the second aryl group. The methyl group appears as a singlet at δ 2.16 indicating the presence of a quaternary centre.

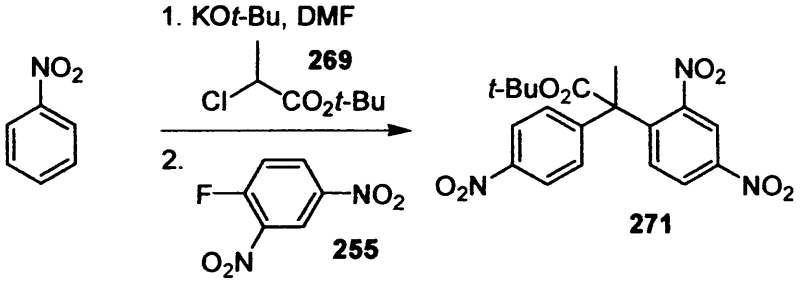
The *tert*-butyl ester **270** was obtained in 52% yield by treatment of 2-chloropropionyl chloride (**269**) with *tert*-butanol and triethylamine (Scheme 141).[193] The *tert*-butyl ester **270** was used in the VNS-S_NAr process (Scheme 142) with potassium *tert*-butoxide as the base and using conditions identical to those used with the isopropyl ester nucleophile. The required VNS product was formed but we had trouble removing excess 2,4-dinitrofluorobenzene from the product.

Scheme 141



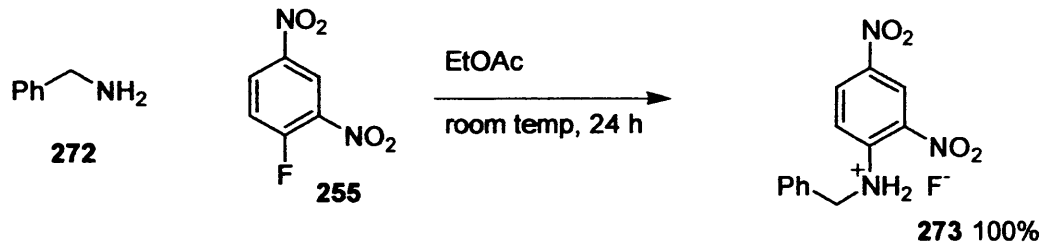
269 **270** 52%

Scheme 142



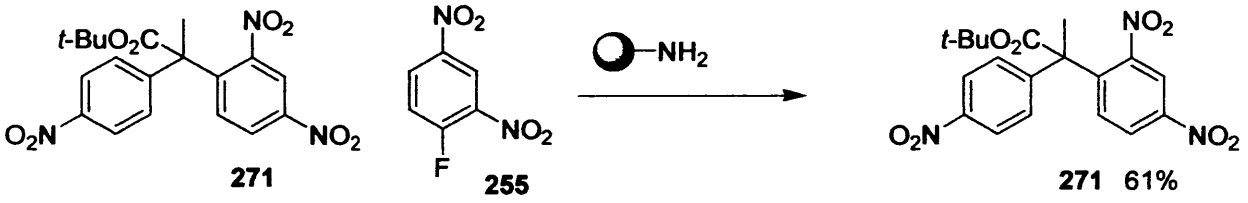
To remove this excess 2,4-dinitrofluorobenzene, we considered the use of a scavenger. We thought that a polymer-supported amine would be successful. As a test, we added benzylamine (1 eq.) to a solution of 2,4-dinitrofluorobenzene in ethyl acetate (Scheme 143) and left the solution to stir overnight. The reaction produced the required product **273** as the HF salt of the amine in quantitative yield.

Scheme 143



As this test was successful, the contaminated VNS product **271** was dissolved in a small amount of ethyl acetate and added to a small filter syringe containing poly(styrene-co divinylbenzene)amino methylated polymer (0.75 g) (2.0-3.5 mmol/g) and the mixture were shaken for 24 hours (Scheme 144). The solution was filtered and the solvent removed on a rotary evaporator to leave the pure product **271** in 61% yield.

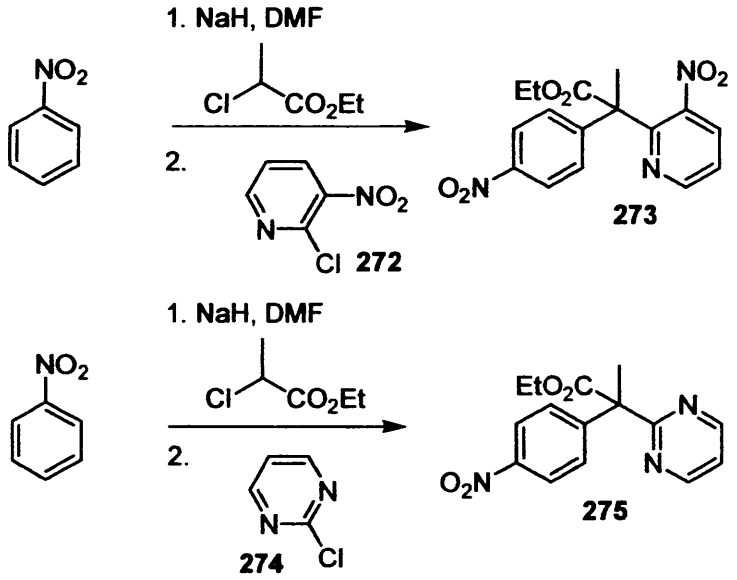
Scheme 144



To further expand the scope of this reaction we attempted to use activated pyridines and pyrimidines in the VNS-S_NAr process (Scheme 145). Pyridines and pyrimidines are important heterocyclic compounds. Several examples of these class of compounds are well known as important biologically active compounds for example 2-(benzylamino)pyrimidine is a antihistaminic agent.[194] 2-Chloro-3-nitropyridine (**272**) and 2-chloropyrimidine (**274**) were

chosen as they were commercially available and known to undergo the S_NAr process. For example 2-chloropyrimidine readily reacts with thiophenolates, phenolates and anilines.[195] These examples were chosen to extend the methodology so that heterocyclic rings could be utilized, which are important in many drugs. There were also literature examples of these electrophiles undergoing C-arylation with enolates.[196-8] The bright purple colour associated with the post VNS anion was observed as expected, but the electrophilic quench with both electrophiles did not occur at room temperature. Careful heating of the reaction mixture to 50 °C also resulted in no success. In both cases the protonated post-VNS anion (ethyl 4-nitrophenylpropionate) was recovered.

Scheme 145



To provide some examples of the *ortho* selectivity of the VNS-S_NAr process, chloromethyl phenyl sulfone was chosen as the VNS nucleophiles, and *p*-chloronitrobenzene as the substrate (Scheme 146 and Table 9).

Scheme 146

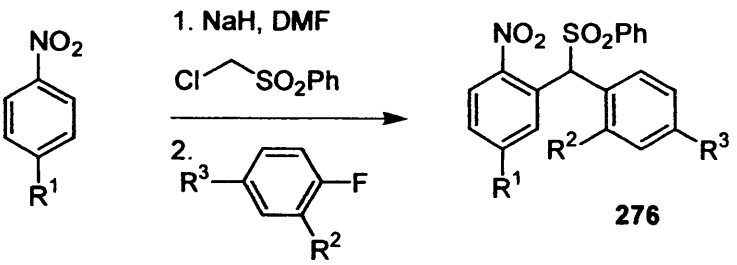


Table 9. Yields of Product Sulfones

	R^1	R^2	R^3	Yield (%)
276a	Cl	NO_2	CF_3	75
276b	Cl	NO_2	NO_2	74
276c	Cl	CN	NO_2	74
276d	Cl	CF_3	NO_2	75
276e	CF_3	NO_2	CF_3	79
276f	CF_3	NO_2	NO_2	81
276g	CF_3	CN	NO_2	78
276h	CF_3	CF_3	NO_2	78

Sulfone **276a** was obtained in 75% yield by adding a mixture of chloromethyl phenyl sulfone (1 eq.) and *p*-chloronitrobenzene in DMF to a suspension of sodium hydride in DMF at 0 °C. This produced a bright purple solution which was allowed to warm to room temperature, stirred for 30 minutes and then cooled back to 0 °C for the electrophilic quench with 4-fluoro-3-nitrobenzotrifluoride. The doublets at δ 8.53 (*J* 8.3 Hz), 8.23 (*J* 1.3 Hz) and double doublet at δ 8.02 (*J* 1.3 and 8.3 Hz) in the ^{1}H-NMR spectrum indicate the presence of a trisubstituted aryl group. The doublets at 8.30 (*J* 2.2 Hz), 7.93 (*J* 8.8 Hz) and double doublet at 7.55 (*J* 2.2 & 8. 8 Hz) indicate the presence of a second trisubstituted aryl group. The mono substituted aryl group was represented by a doublet at δ 7.69 (*J* 7.6 Hz) and triplets at δ 7.64 (*J* 7.6 Hz) and 7.48 (*J* 7.6 Hz). The benzylic proton appears as a singlet at δ 7.40.

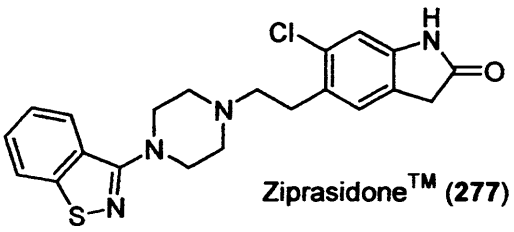
The same process was then applied to a range of electrophiles and nitroarenes, to produce **276b-h** in good yield (see Table 2). The nitroarenes *p*-chloronitrobenzene and *p*-trifluoromethylnitrobenzene were chosen as the VNS substrates as they were both commercially available and it is known that they undergo the VNS process exclusively at the *ortho* position with no competitive S_NAr observed. The products were characterized in full (see Experimental section).

6.3 Formation of Oxindoles

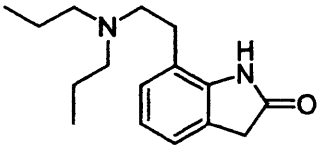
The oxindole moiety is a common motif in many alkaloids and is also found in a number of marketed drugs (Figure 12).[199-200] Ziprasidone (**277**) is a serotonin and dopamine antagonist, and effective as an antipsychotic drug. Many currently available antipsychotropic drugs have the side effect of inducing significant weight gain, which is distressing and stigmatising to

patients and increases the risk of cardiovascular complications,[211] but ziprasidone avoids this side effect.

Figure 12



Ziprasidone™ (277)



Ropinirole™ (278)

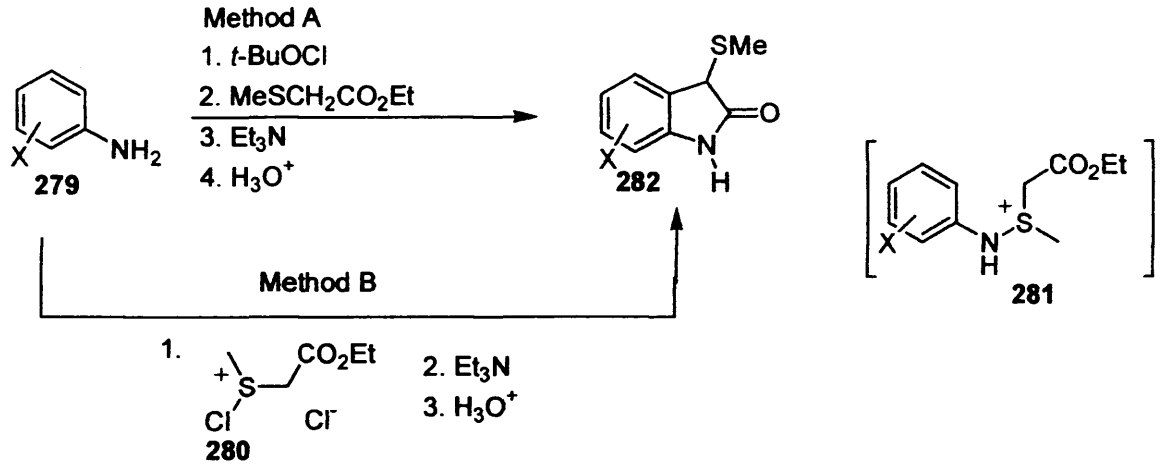
Parkinson's disease causes the brain to lose dopamine, which results in stiffness and rigidity of the muscles, slowness in movement and the tremor of the arms and legs. Levodopa, the main treatment for the disease, is metabolised to the brain as dopamine. The brain's ability to metabolise and store levodopa diminishes after time and it becomes more dependant on the external supply of levodopa. Eventually most patients experience fluctuations when the medication is working and when it is not working in the body.

Ropinirole (**278**) is a direct dopamine receptor agonist that works by minimising the actions of dopamine in the brain and thereby reducing the symptoms of Parkinson's disease.

Because of the very potent and diverse biological activity exhibited by various oxindole derivatives, this heterocyclic system has attracted considerable attention in chemistry, biology and medicine.

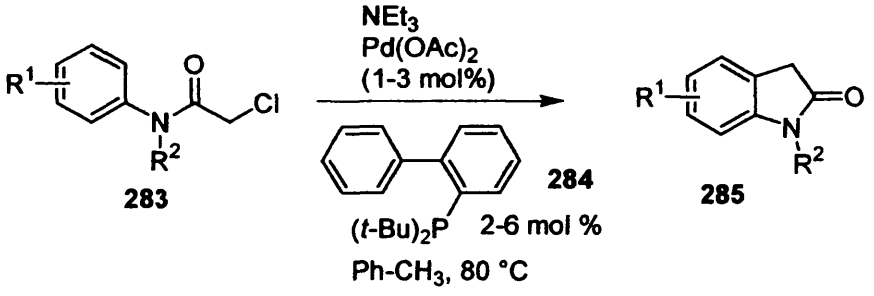
Previous methods for the synthesis of the oxindole motif include Lewis acid mediated cyclization of α-haloacetanilides, cyclization of (*o*-aminophenyl)acetic acid derivatives and the Gassman procedure (Scheme 147). In the Gassman procedure, 3-methylthio-2-oxindoles are produced. The methodology of choice is dependent on the nature of the aromatic ring. When electron withdrawing groups are present, the oxindole can be synthesized by treatment of the aniline with a methylthioacetate ester to furnish an azasulfonium salt (Scheme 147, Method A). Electron-donating groups destabilize the intermediate **281**, and thus give diminished yields of the oxindole **282**. A second method of generation of this salt by reaction of the chlorosulfonium salt **280** with an appropriate aniline (Scheme 147, Method B) gives better yields of the 3-methylthio-2-oxindoles **282**.

Scheme 147



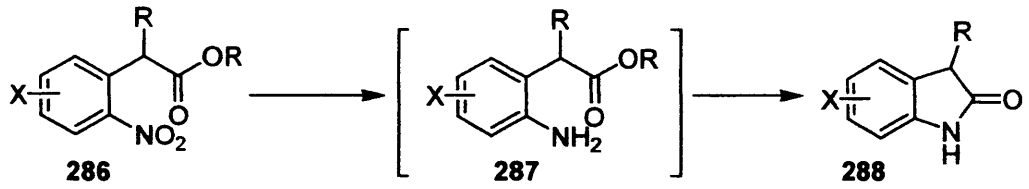
Buchwald reported a novel variant of the Friedel-Crafts procedure using palladium catalysed C-H functionalisation, avoiding the need for harsh reaction conditions (Scheme 148).[202] The combination of catalytic amounts of palladium acetate, 2-(di-*tert*-butylphosphino)biphenyl (**284**) as a ligand, triethylamine as base and α-chloroacetanilides (**283**) can be smoothly converted to oxindoles in good yields with high levels of regioselectivity. The process is most likely initiated by oxidative addition of the α-chloroamide to Pd(0), resulting in a Pd(II) enolate. The formation of the carbon-carbon bond may proceed by an electrophilic aromatic substitution to give a six-membered palladacycle, which undergoes reductive elimination to afford the product oxindole **285** and regenerate the Pd(0) species.

Scheme 148



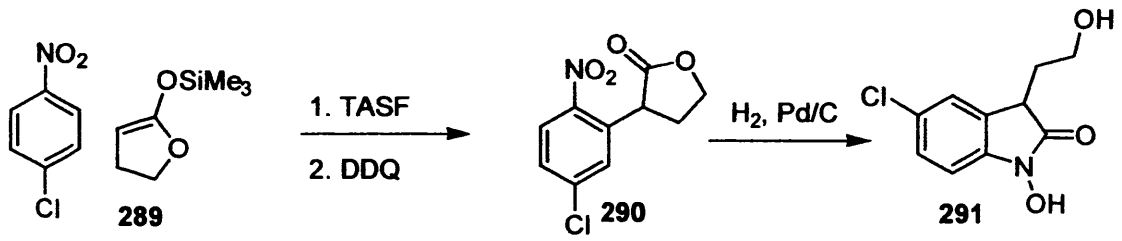
One of the most attractive and general methods for the synthesis of oxindoles is the reductive cyclization of α-nitroaryl carbonyl compounds (Scheme 149). Reduction of the nitroarene **286** to aniline **287** furnishes a nucleophilic nitrogen atom. This can then attack the electrophilic ester to promote cyclization to the oxindole **288**.

Scheme 149



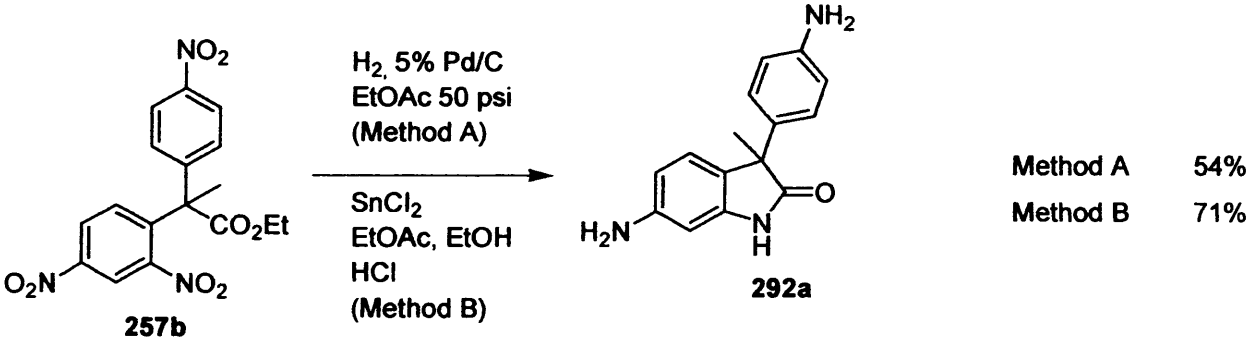
This reaction has been one of the oldest methods for the synthesis of oxindoles even though the availability of the starting materials has been limited. Rajanbabu reported a synthesis of oxindoles based on an oxidative nucleophilic substitution of hydrogen (ONSH) reaction followed by reductive cyclization (Scheme 150).[203] Addition of the silyl ketene acetal **289** to the nitro-aromatic in the presence of tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF) followed by oxidation of the resulting σ^H-adduct gave an α-nitroarylester **290.** Cyclization to the oxindole **291** occurred after hydrogenation of the nitro group of **290.**

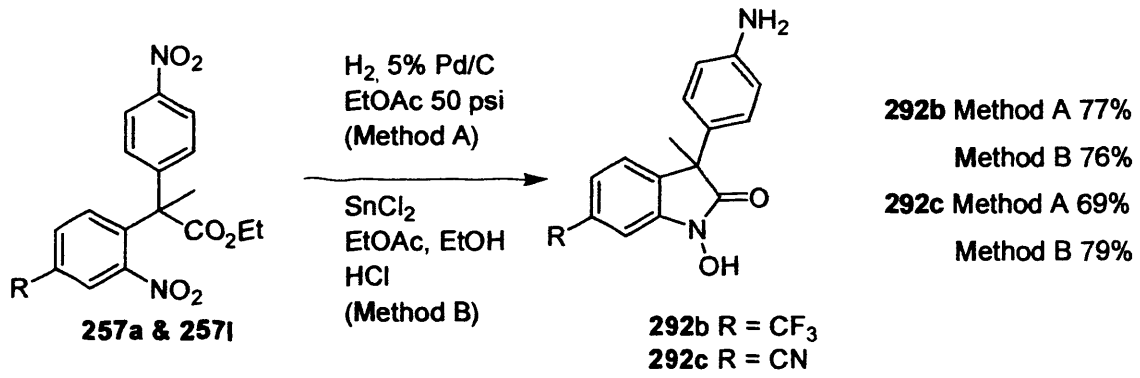
Scheme 150



The diarylacetates **257a-m** synthesized by our VNS-S_NAr process with an *ortho*-nitro group provided the opportunity for formation of 3,3-substituted oxindoles by reduction of the nitro group. This was achieved by hydrogenation (Method A)[204] or Sn(II)-mediated reduction[205] (Scheme 151).

Scheme 151





Oxindole **292a** was formed (method A) by adding 5% Pd/C to a solution of **257b** dissolved in an ethyl acetate/acetic acid mixture in a multi-Parr reaction vessel. While stirring, the mixture was purged with nitrogen and then hydrogen. The reaction mixture was then left stirring under a hydrogen atmosphere (50 psi) for 16 hours. The product was then filtered through a celite plug and the solvent removed on a rotary evaporator to leave the crude product. The crude product was then washed with chloroform to leave the pure product in 54% yield. The doublets at δ 7.05 and 6.70 (*J* 8.6 Hz) in the ^{1}H-NMR spectrum indicate the presence of a 1,4-disubstituted aryl group. The doublets at δ 6.87 (*J* 8.0 Hz) and 6.56 (*J* 2.0 Hz) along with a double doublet at δ 6.46 (*J* 2.0 and 8.0 Hz) indicate the presence of a trisubstituted aryl group. The methyl group appears as a singlet at δ 1.66.

As an alternative method (method B), the ester was dissolved in an ethanol:ethyl acetate 4:1 mixture. Tin(II) chloride dihydrate and a few drops of hydrochloric acid were added and the mixture was heated under reflux for 36 hours. Following an aqueous work up the solvent was removed on a rotary evaporator to leave the crude product. Washing the crude product with chloroform left the pure product **292a** in 71% yield.

Both methods were applied to **257a** and **257l** to give the products **292b** and **292c**. Both methods led to the *N*-hydroxyoxindole being exclusively formed. This was formed because cyclisation of the hydroxylamine was faster than reduction to form the aniline. We found that under the hydrogenation conditions the acid was crucial to forming exclusively the *N*-hydroxyoxindole. Without the acid, a mixture of the oxindole and the *N*-hydroxyoxindole occurred.

Other nitro groups present in the molecules were also reduced under these conditions providing additional points for further functionalization and incorporation of extra diversity. The ester **257b** cleanly gives the oxindole **292a** by both methods of reduction of the nitro group. However, reduction of both **257a** and **257l** gave the 1-hydroxy-oxindoles **292b** and **292c**. It seems that the presence of the electron-withdrawing group impedes reduction of the intermediate hydroxylamine such that cyclization to form the hydroxyoxindole occurs faster.

The formation of the oxindoles involves first reduction of the less hindered nitro group at position 4. Sodium disulfite[179] has been used to reduce similar nitro esters to oxindoles. However when applied to diarylacetates **257a & l** the starting materials remained untouched.

Summary and Conclusion

In conclusion we have therefore shown that intriguing one-pot VNS_{Ar}–S_NAr combination of two types of nucleophilic substitution reaction can be integrated to provide an excellent synthesis of diarylacetate derivatives. The process has been shown to tolerate activated fluoro electrophiles bearing electron withdrawing groups such as cyano, nitro and trifluoromethyl. Chloro electrophiles have also been shown to undergo the S_NAr process with the post VNS anion. The use of 2-fluoronitrobenzene however the post VNS anion underwent a homo coupling reaction to give a dimmer (**264**) as a 1:1 mixture of diastereoisomers presumably by a radical pathway. The 2-fluoronitrobenzene must be acting as an oxidizing agent.

Unfortunately our attempts to use activated pyridines and pyrimidines met with no success with just the VNS product being formed, the post VNS anion did not undergo the S_NAr process.

Due to the problems associated with the sodium hydride/DMF base solvent system a potassium *tert*-butoxide/DMF base solvent system was shown to be acceptable so the process could be conveniently carried out on a large scale. Due to a side with the *tert*-butoxide anion reacting with the electrophile an excess of the electrophile is required. In the case of **271** the excess electrophile could not be separated from the product. We therefore developed a process to scavenge for the excess electrophile using poly(styrene-co-divinylbenzene)amino methylated polymer.

The VNS/S_NAr process was shown to proceed with chloromethyl phenyl sulfone as the VNS nucleophile, *para*-substituted nitroarenes and aryl electrophiles. This provided examples of the *ortho* selectivity of the VNS-S_NAr process.

The diarylacetates **257a-m** provide convenient access to the oxindole motif by reductive cyclization of the nitrogroup. Reduction of the nitro group proceeded of hydrogen (50 psi) over a palladium on carbon catalyst and also using a tin(II)chloride dihydrate and acid. Cyclisation then occurred to produce the required oxindole or the *N*-hydroxy oxindole. The latter being formed because cyclisation of the *N*-hydroxylamine occurred faster than reduction of the *N*-hydroxylamine to the aniline. The only product to go to the required oxindole was **257b** which had a second nitro group present on the second aromatic ring. This would presumably be reduced before the nitro group undergoing the cyclisation due to it being unhindered. As cyclisation the nitro group would be present as the aniline, so therefore an

electron donating group. It seemed that the ring with electron withdrawing groups give the *N*-hydroxyoxindole while those with an electron donating group give the required oxindole.
Future work would be to adapt the conditions of the reductive cyclization so that we could get through to the oxindole without the need to reduce the hydroxyoxindole. Possible options include changing the hydrogenation catalyst or finding an additional method for reduction of nitro groups.

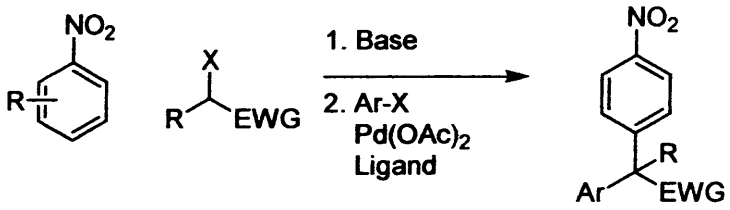
Chapter 7

7.1 Cross-coupling of Nitrophenylacetates

The VNS-S_NAr process covered in Chapter 6 provided a convenient one step process for the formation of diaryl acetates and sulfones. The process is limited to the use of an electron-deficient arene as the electrophile. The least electron-deficient electrophile which was successfully used was *p*-fluoronitrobenzene, which only has one electron-withdrawing group in addition to the leaving group. Electron-rich electrophiles can not be used in this process.

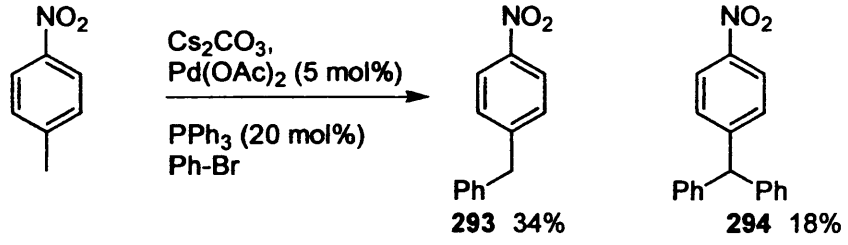
We considered the possibility that the VNS process could be extended to a VNS cross-coupling process (Scheme 152). This would give the opportunity to add electron-rich aromatic rings to the post-VNS anion.

Scheme 152



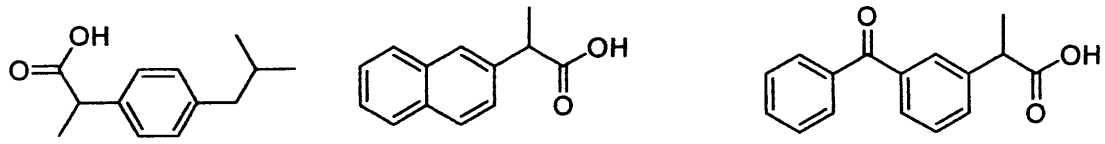
There are very few examples of nitro compounds in transition metal-catalysed cross-coupling reactions. The area of cross-coupling in organic synthesis has been reviewed by Prim[206], Miura[207-8] and Hartwig.[209] One of the few examples was carried out by Miura[210] who reported that *p*-nitrotoluene could effectively react with aryl bromides at its benzylic position in the presence of catalytic amounts of $Pd(OAc)_2$ and PPh_3 with cesium carbonate as a base to give the corresponding mono and/or di-arylated products **293** and **294** (Scheme 153).

Scheme 153



Palladium-catalysed coupling of esters and derivatives was first carried out in the groups of Buchwald[162] and Hartwig.[79] The synthesis of α-aryl esters and their derivatives is extremely important in the synthesis of useful pharmaceutical products. The α-aryl carboxylic acid structure is of particular interest as it forms part of the structure of several marketed drugs such as Ibuprofen, Naproxen and Ketoprofen (Figure 13). These compounds have anti-inflammatory and analgesic properties.

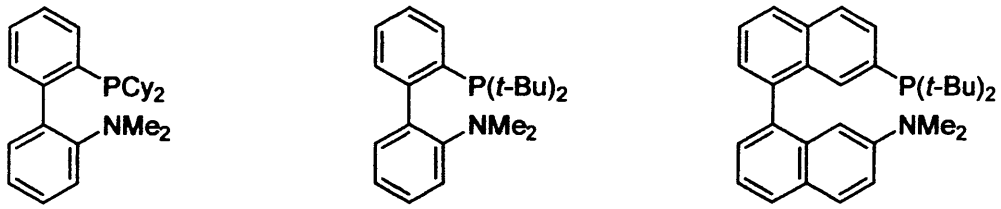
Figure 13



Ibuprofen Naproxen Ketoprofen

The palladium-catalysed α-arylation of ketones was reported in 1997 by the groups of Buchwald,[75] Hartwig[79] and Miura.[211] Buchwald subsequently reported a significant improvement on the initial system based on the use of electron rich, bulky *o*-biphenyl phosphines **114**, **296** and **297** (Figure 14).[78]

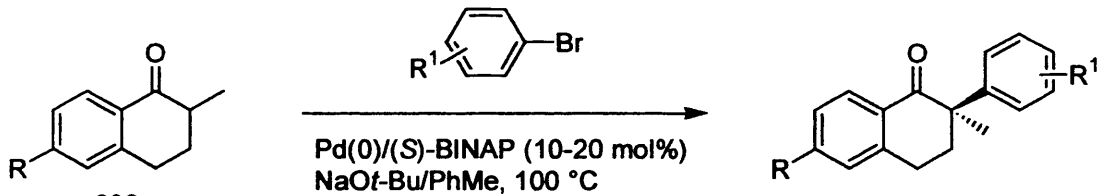
Figure 14



114 **296** **297**

This catalyst system demonstrated a good functional group tolerance and a high selectivity for ketones with two enolizable positions where the less substituted position is arylated. Buchwald also reported an asymmetric version of the ketone arylation system using a Pd/(*S*)-BINAP catalyst (**298**→**299**) (Scheme 154)[76].

Scheme 154

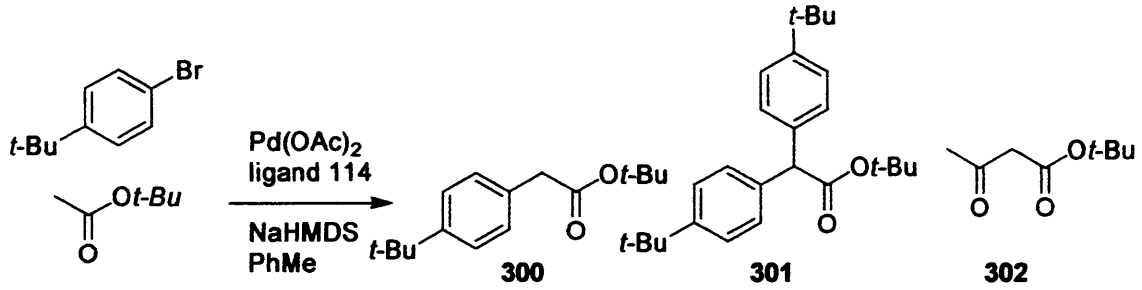


298

299 66% (73% ee) when R & R^1 = H

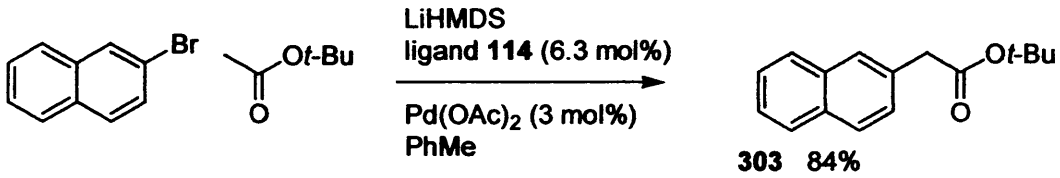
Buchwald took the conditions for the ketone arylation to explore the palladium-catalysed arylation of esters. The initial attempts using 1-bromo-4-*tert*-butylbenzene with *tert*-butyl acetate using NaHMDS and a catalyst derived from **295** and $Pd(OAc)_2$ gave a mixture of mono and di-arylated products **300** and **301** along with significant amounts of the Claisen product **302** (Scheme 155). No nitro-containing substrates were included in this protocol.

Scheme 155



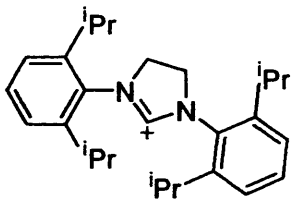
To search for better conditions, a number of reaction variables were tried including temperature, base and ligands. It was found that with a combination of **114** as the ligand, LiHMDS as base and toluene as the solvent it was possible to carry out the reaction at room temperature which suppressed the formation of the diarylated product (Scheme 156). The limitation with this method is the necessity to use 2.3 equivalents of ester and 2.5 equivalents of base to affect complete conversion of the aryl bromide.[162]

Scheme 156



Hartwig also reported a procedure for the palladium-catalysed α-arylation of esters[212] using palladium catalysts ligated by P(*t*-Bu)$_3$ or the hindered carbene precursor SiPr (**304**) (Figure 15) in the presence of 2 equivalents of LiHMDS or NaHMDS. Reactions of *tert*-butyl acetate or *tert*-butyl propionate with a range of aryl bromides proceeded at room temperature with fast rates and high selectivity for monoarylation. No nitro groups were included in this protocol however.

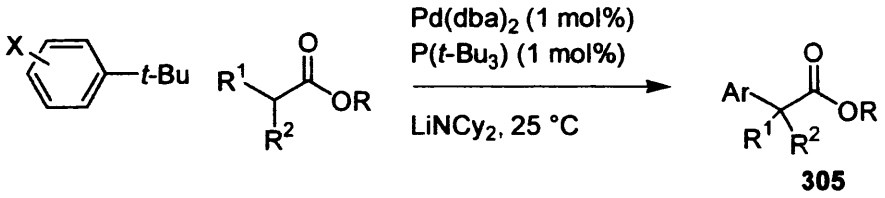
Figure 15



SiPr (**304**)

Use of the stronger hindered amide base LiNCy$_2$ and generation of the enolate prior to the addition of the palladium catalyst and aryl halide provided even more efficient couplings of *tert*-butyl acetate and α,α-disubstituted esters (Scheme 157).[213] Lower catalyst loadings and only a slight excess of ester and base were required.

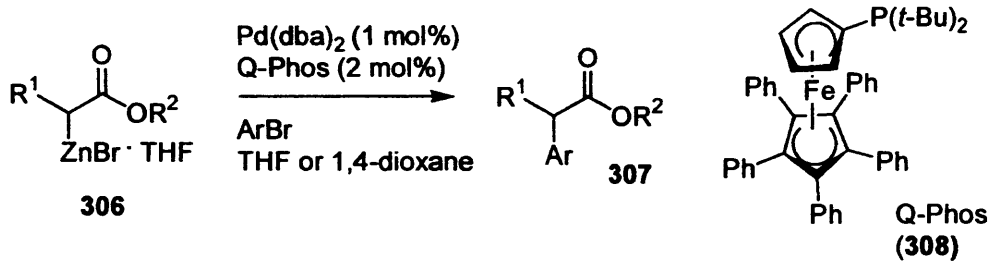
Scheme 157



Hartwig also reported two procedures for the α-arylation of esters and amides under more neutral conditions. The first procedure involved the use of zinc enolates and rests upon the development of catalysts bearing the hindered pentaphenyl ferrocenyldi-*tert*-butylphosphine (Qphos) (**308**) or the highly reactive dimeric Pd(I) complex $[P(t\text{-Bu})_3(PdBr)_2]$. No nitro groups were included in this protocol.

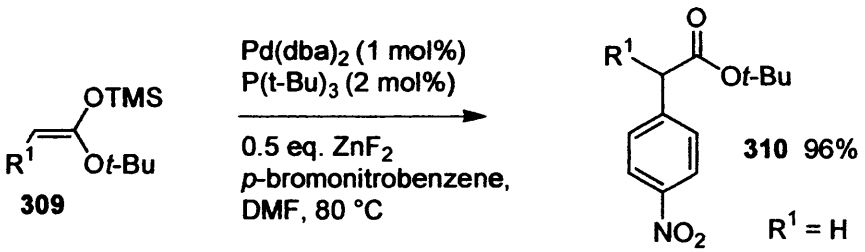
The catalysts above also catalysed the coupling of Reformatsky reagents prepared from activated zinc and α-bromo esters with a variety of base sensitive substrates (Scheme 158). *ortho*-nitrobromobenzene and *para*-nitrobromobenzene were successfully used as electrophiles in this process.

Scheme 158



Hartwig also reported the palladium-catalysed arylation of trimethylsilyl enolates of esters (or silyl ketene acetals) with zinc fluoride as a co-catalyst (Scheme 159). This protocol incorporated nitro groups in the electrophile. *p*-Bromonitrobenzene and *p*-chloronitrobenzene were successfully cross-coupled with esters using this procedure.[214]

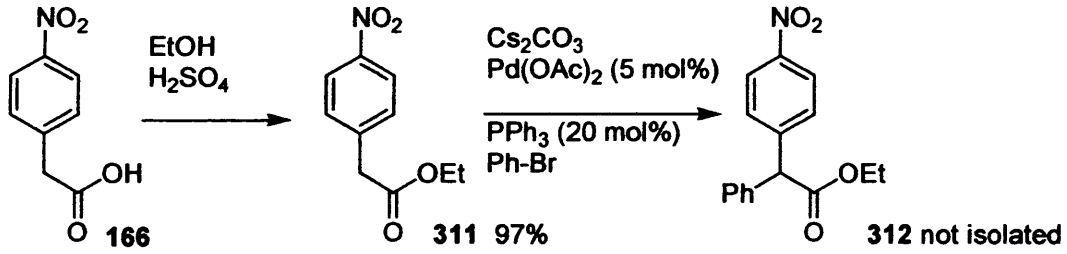
Scheme 159



It was therefore clear that a general method for the cross-coupling of haloarenes and arylacetates possessing nitro substituents would be valuable. Modification of such a process to allow the direct cross-coupling of a nitroarylacetate anion derived from a VNS reaction would

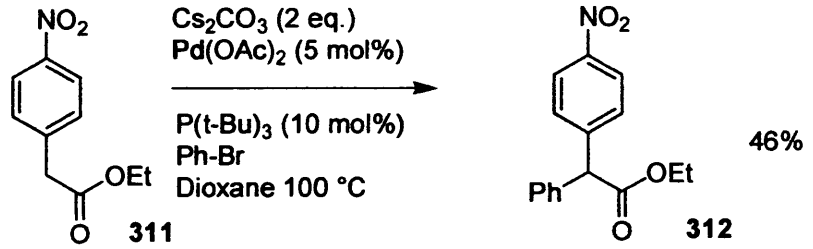
be a second aim. To find suitable conditions for a VNS cross-coupling process, we first attempted to cross-couple the preformed VNS product **311** with bromobenzene (Scheme 160) under the same conditions as used by Miura in the cross-coupling of 4-nitrotoluene with bromobenzene which were heating at 140 °C for 1 hour in DMF.[210] The preformed VNS substrate **311** was formed from commercially available *p*-nitrophenylacetic acid (**166**) by heating under reflux in ethanol with 3 drops of H_2SO_4. The cross-coupling reaction however was unsuccessful, with the starting materials being recovered and no trace of **312**. An attempt to repeat the same reaction carried out by Miura's group to validate the procedure also proved unsuccessful with the starting materials being recovered and a tiny trace of product observed by LC-MS.

Scheme 160



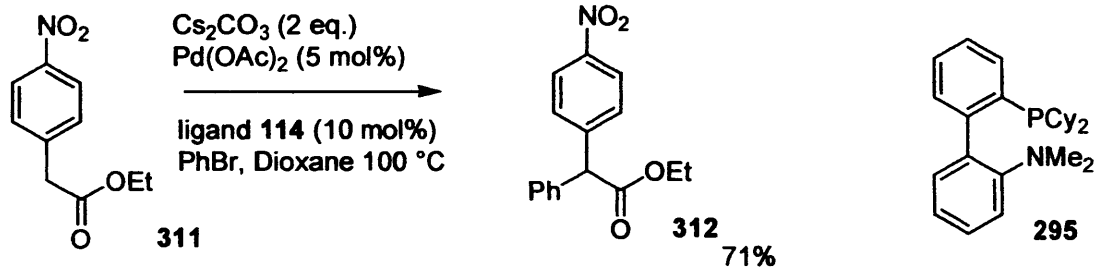
As an alternative approach cesium carbonate (dried) was added to a two necked round bottom flask fitted with a condenser and nitrogen bubbler. This approach was adapted from a method used by Buchwald who cross-coupled ethyl phenyl acetate with aryl bromides.[162] Anhydrous 1,4-dioxane was added to the cesium carbonate. A solution of ethyl 4-nitrophenylacetate in dioxane was then added followed by bromobenzene, palladium acetate and tri(*t*-butyl)phosphine. The mixture was then heated at 100 °C for 24 hours. After cooling to room temperature ethyl acetate was added to the reaction mixture which was then filtered through a silica gel plug. Removal of the solvent on a rotary evaporator gave the crude product which was purified by column chromatography to leave the pure product in 46% yield (Scheme 161). The benzylic proton appears as a singlet at δ 5.10 compared to 3.73 in the starting material. The mono substituted aryl group is represented by a multiplet (δ 7.28-7.37). Using an Electron Ionisation mass-spectrometry technique a molecular ion was found at 285.1014 which corresponds to the calculated molecular ion at 285.1001 indicating that the required product had been formed.

Scheme 161



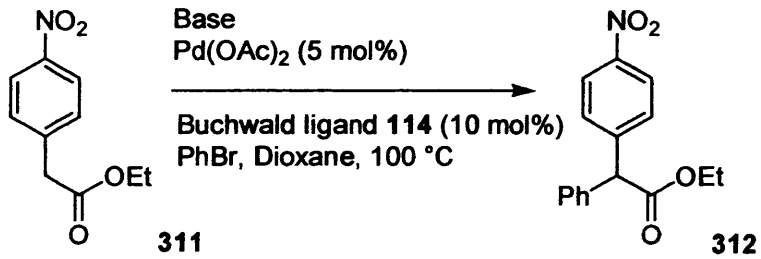
Using potassium phosphate as the base under identical conditions resulted in a slight improvement with the required product being formed in 56% yield. In order to make the process more efficient a different ligand was tried. This was the sterically hindered biphenyl **295** (Figure 14) which was used in the Buchwald group in the cross coupling of the enolates of esters with aryl halides.[162] This was first attempted using the previous conditions (Scheme 162) to produce the required product **312** in 71% yield.

Scheme 162



It was important, if we were to establish methodology for the one-pot VNS cross-coupling reaction, that this process could be performed with typical bases that are used in the VNS reaction such as sodium hydride and potassium *tert*-butoxide. The experiments we carried out with this aim provided very encouraging results. The yields were better than anything encountered previously when potassium *tert*-butoxide was employed as the base. (Scheme 163).

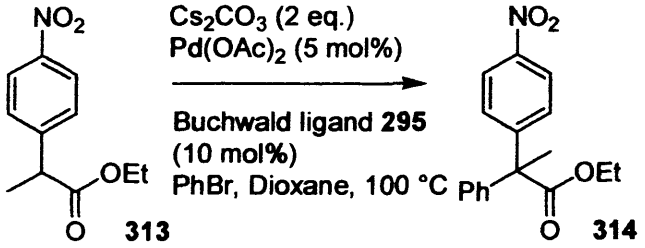
Scheme 163



Base	Yield
Sodium hydride	59%
Potassium *tert*-butoxide	90%

As we had found good conditions for the cross coupling of the nitrophenylacetate, we then needed to find out if these conditions could be transferred to the cross coupling of nitrophenyl propionates. The parent ester **311** cannot be prepared exclusively in a VNS reaction. The use of a secondary carbanion would result in a mixture of *ortho* and *para* phenylacetates.[215-6] Different conditions were tried to cross-couple the nitrophenylpropionate **313** with aryl halides as summarised (Scheme 164), but all without success. The starting materials were recovered after the reaction every time.

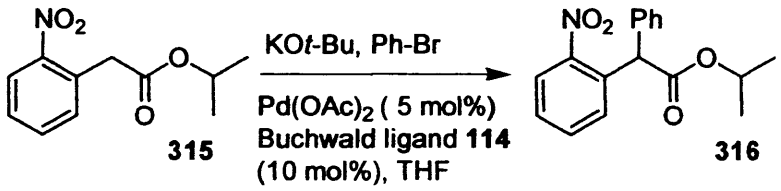
Scheme 164



Solvent	Base	ArX	Yield
Dioxane	KO*t*-Bu	PhBr	0
Dioxane	Cs_2CO_3	PhBr	0
DMF	KO*t*-Bu	PhI	0
THF	KO*t*-Bu	PhBr	0

Since the nitrophenylpropionates could not be cross-coupled with aryl halides, an attempt to cross-couple the preformed *ortho*-VNS product **315** with aryl halides was made (Scheme 165).

Scheme 165

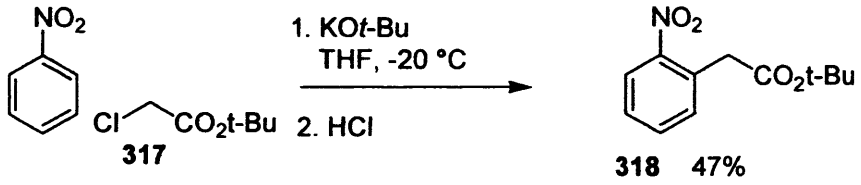


The reaction failed with the starting materials being recovered. The reaction was repeated changing the solvent to 1,4-dioxane, DMF and acetonitrile, all resulting in no success. The reaction time was increased to 48 hours and the reaction temperature increased to the boiling point of the individual solvents. After continuous heating the starting materials decomposed when using THF and 1,4-dioxane as the solvent. The crown ether 18-crown-6 was tried in the reaction due to a literature precedent in which it was used in the alkylation with methyl iodide, but this also resulted in no success.[217] Different bases were also tried: potassium carbonate, potassium phosphate, sodium *tert*-butoxide, sodium hydride and cesium carbonate but all with no success. Iodobenzene was tried instead of bromobenzene also with the same result. A transmetallation with $ZnCl_2$ was also tried with no success.

Despite the lack of success in the cross-coupling of the preformed VNS substrate **313**, the one-pot VNS cross-coupling reaction was attempted. Using a KO*t*-Bu/THF base/solvent system we expected the VNS process to proceed exclusively at the *ortho* position due to tight ion pairs

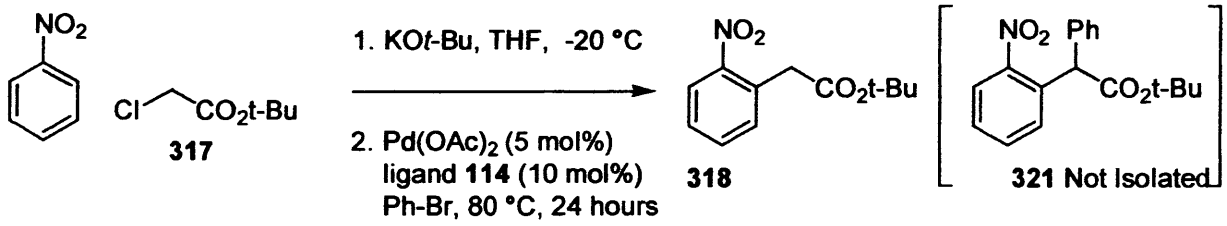
being formed.[31] This reaction was carried out and the required product **318** isolated in 47% yield.

Scheme 166



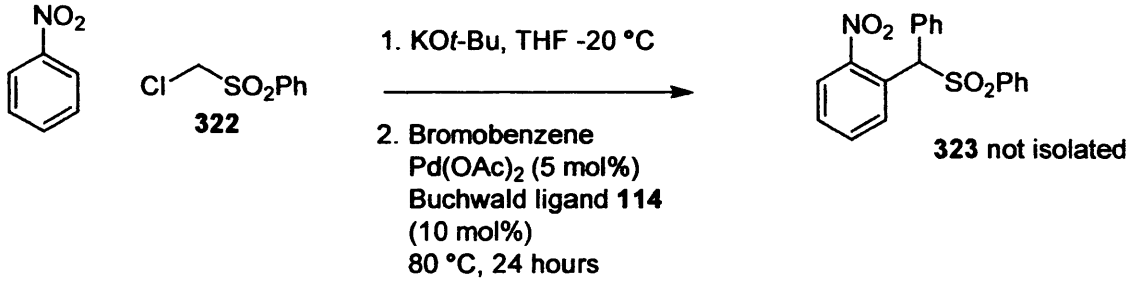
The one-pot VNS cross-coupling process was then attempted but without success with the VNS product **323** being isolated in 43% yield and no sign of the required product **321**. Nitrobenzene and bromobenzene were also present in the crude reaction mixture.

Scheme 167



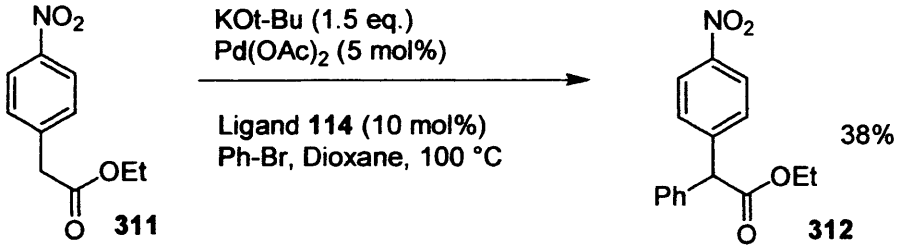
The process was repeated but using chloromethyl phenyl sulfone (**322**) as the VNS nucleophile (Scheme 168). This reaction also resulted in no success. The ^{1}H-NMR showed the VNS product, bromobenzene and nitrobenzene. A very small amount of the VNS cross coupling product **323** was observed by LC-MS. Different bases and solvents were also used in this reaction, however none gave a positive result.

Scheme 168



In the VNS reaction the base is normally present in a slight excess. To determine whether this excess of the base would be a problem in the cross-coupling part of the reaction a cross-coupling reaction of ethyl 4-nitrophenylacetate with bromobenzene was carried out using 1.5 equivalents of potassium *tert*-butoxide (Scheme 169).

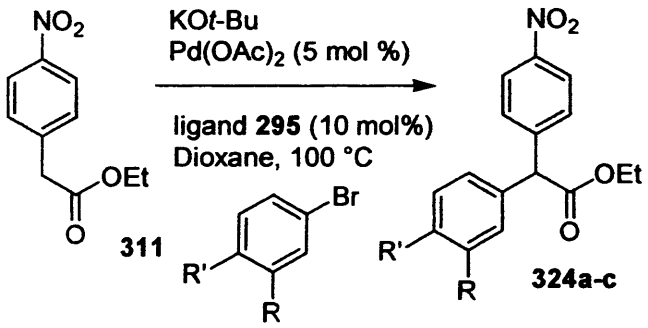
Scheme 169



When the same reaction was carried out with 1 equivalent of base the product **312** was obtained in 90% yield. Using 1.5 equivalents of potassium *tert*-butoxide however resulted in the yield for the reaction dropping to 38%. This was a problem for any possible one-pot VNS cross-coupling process as at least 2 equivalents of base are required for the VNS reaction but the reaction never runs to completion so there would always be excess potassium *tert*-butoxide around to lower the yield for the cross-coupling part of the process.

Different aryl electrophiles were also used in the cross-coupling with nitrophenylacetates under identical conditions (Scheme 170).

Scheme 170



	Solvent	R	R'	Yield
324a	Dioxane	H	OMe	47%
324a	DMF	H	OMe	59%
324b	Dioxane	CF_3	H	69%
324c	Dioxane	CN	H	74%

Changing the solvent to DMF improved the yield of **324a** to 59%. Doublets at δ 8.16 and 7.48 (*J* 8.8 Hz) in the ^{1}H-NMR spectrum indicated the presence of a 1,4-disubstituted aryl group. Accurate mass data for **324a** was also consistent with the assigned structure.

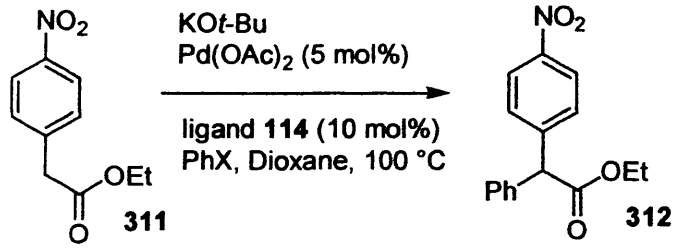
The next electrophile attempted was 3-bromobenzotrifluoride, as it was much more electron deficient. This produced the required product **324b**, which was shown by a doublet at δ 8.21 (*J* 8.8 Hz) and multiplets (δ 7.57-7.60 & 7.48-7.51) representing the required number of aromatic protons. The benzylic proton appears as a singlet at δ 5.15. Accurate mass spectrometry was consistent with the assigned structure.

A further example **324c** was found with the use of 3-bromobenzonitrile. The ^{1}H-NMR spectrum was consistent with what was expected, as was the accurate mass data.

Using 1-iodo-2-nitrobenzene as the electrophile, the reaction did not proceed with the nitrophenylacetate and nitrobenzene being recovered. Presumably, the catalyst undergoes oxidative insertion into the C-I bond but cannot react with the enolate so the electrophile is

reduced to nitrobenzene. Using 1-bromo-2-nitrobenzene as the electrophile also resulted in no success this time with both starting materials being recovered although a trace amount of the desired product was observed by LC-MS.

Scheme 171

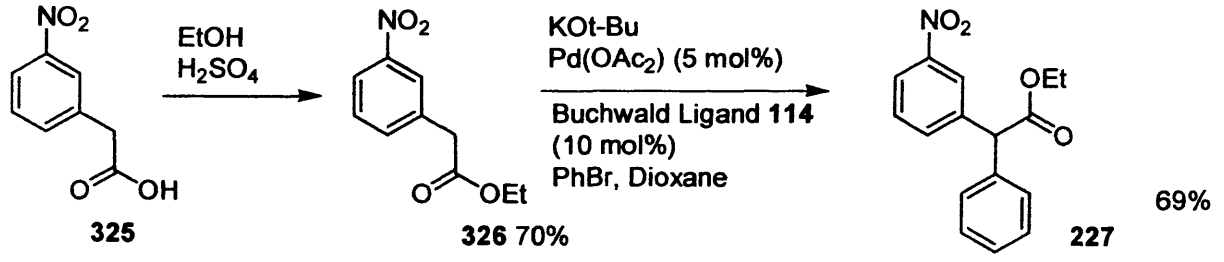


X	Yield (%)
Cl	71
Br	90
I	86

The effect of bromo electrophiles was then compared with the chloro and iodo equivalents under identical conditions (Scheme 171). As can be seen, bromobenzene was the most efficient with the iodo equivalent being only slightly less efficient. Even chlorobenzene gave the required product in good yield.

We attempted to cross-couple the *meta*-nitrophenylacetate **326** with an aryl halide, even though these products could not be formed by a VNS reaction. The *meta*-nitrophenylacetate **326** was formed by esterification of the commercially available acid **325**. The cross-coupling of the nitrophenylacetate **326** with bromobenzene proceeded in 69% yield (Scheme 172) to give the desired product **327**.

Scheme 172

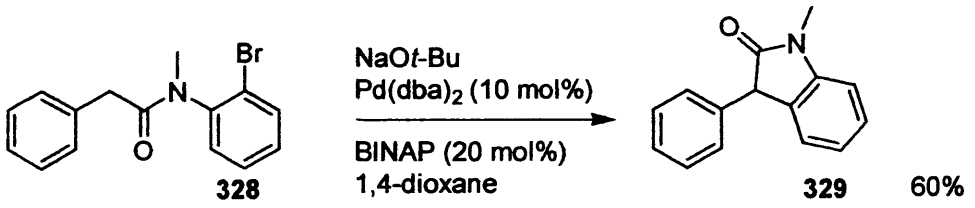


Doublets at δ 8.12 and 7.48 (*J* 8.3 Hz) along with a triplet at δ 7.67 (*J* 8.3 Hz) and a singlet at δ 8.21 in the ^{1}H-NMR spectrum indicate the presence of a 1.3-disubstituted aryl group. The mono substituted aryl group is represented by a multiplet (δ 7.28-7.36). The benzylic proton occurs as a singlet at δ 5.11. Using an electron spray mass-spec technique a $(M + H)^+$ peak was found at 303.1342 which corresponded to the calculated $(M + H)^+$ peak of 303.1339 indicating the correct product had been obtained.

We thought that since the cross-coupling of *ortho* substituted nitrophenylacetates with aryl halides did not proceed (Scheme 165), an intramolecular process might be more favourable.

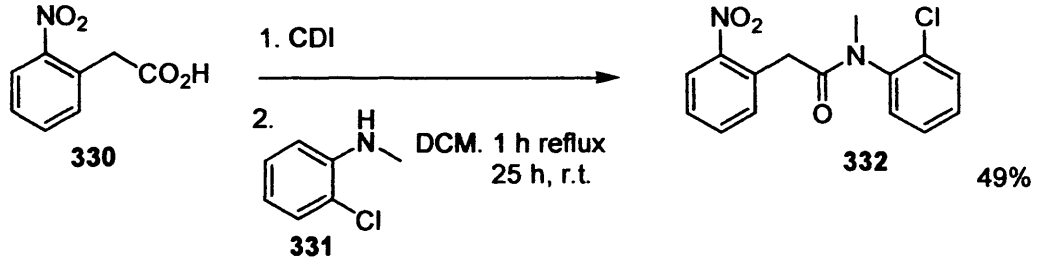
This is based on Hartwig's report of an intramolecular method for the formation of *N*-substituted oxindoles (Scheme 173).[132]

Scheme 173



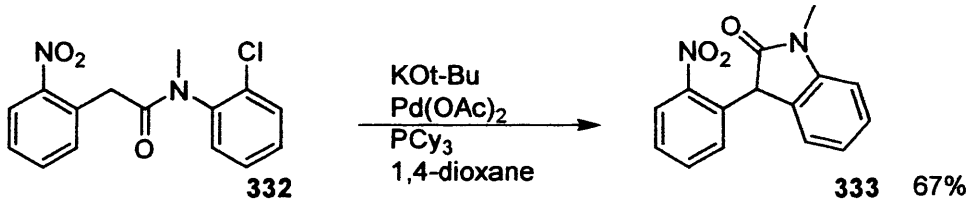
The substrate **332** was formed by addition of 2-nitrophenylacetic acid (**330**), dichloromethane, carbonyldiimidazole (CDI) and 2-chloro-*N*-methylaniline (**331**) to a two neck round bottom flask fitted with a condenser and nitrogen bubbler. The mixture was heated under reflux to give the required product in 49% yield after column chromatography (Scheme 174). Doublets at δ 8.07 (*J* 8.1 Hz) assigned to the proton adjacent to the nitro group and 7.29 (*J* 8.4 Hz) along with multiplets (δ 7.53-7.57 and 7.38-7.42) in the ^{1}H-NMR spectrum indicate the presence of two disubstituted aryl groups. Doublets at δ 3.97 and 3.45 (*J* 16.6 Hz) show the presence of the two benzylic protons, while the methyl group appears as a singlet at δ 3.25.

Scheme 174



The substrate **332** was added to a solution of potassium *tert*-butoxide in 1,4-dioxane followed by palladium acetate and tricyclohexylphosphine (Scheme 175). The reaction mixture was then heated at 100 °C for 2 hours. After cooling to room temperature, the reaction mixture was filtered through a silica gel plug to remove the palladium and then purified by column chromatography to give the required oxindole **333** in 67% yield. Doublets at δ 8.09 (*J* 8.3 Hz) assigned to the proton adjacent to the nitro group and 7.27 (*J* 8.3 Hz) along with multiplets (δ 7.52-7.57 and 7.40-7.45) indicate the presence of the two disubstituted aryl groups. A singlet at δ 5.19 represents the benzylic proton and the methyl group is observed as a singlet at δ 3.22.

Scheme 175



332 **333** 67%

Summary and Conclusion

To conclude, a method for the cross coupling of nitrophenylacetates with aryl halides has been developed. This is potentially very useful due to the lack of palladium cross-coupling reactions for compounds containing a nitro group. Aryl electrophiles with electron withdrawing groups and electron donating groups have been shown to proceed in the reaction. Attempts to extend the process to nitrophenylpropionates met with no success with the starting materials being recovered. Presumably this failed due to the propionates being more sterically hindered than the acetated.

Unfortunately the reaction only proceeded with *para* and *meta*-nitrophenylacetates, and the method for the cross-coupling of *ortho*-nitrophenylacetates remains elusive. Different reaction conditions were tried to get the cross-coupling of *ortho* nitrophenylacetates to proceed such as different solvents, ligands and bases but all with no success. Presumably the problem is due to a steric clash with the nitro group but could also be due to the electronic nature of the nitrogroup. This is unfortunate as this process would provide convenient access to the oxindole structural motif.

An intramolecular cross-coupling process to form *N*-methyloxindoles was successfully carried out. The intramolecular process is more thermodynamically favourable than the intermolecular equivalent but due to the success with the intramolecular process we were hopeful that conditions could be found to get the intermolecular process to proceed.

The one-pot VNS cross-coupling process however proved more difficult, and remains a challenge. The problems we encountered were the lack of success with the nitrophenylpropionates in the cross-coupling process. If we used a secondary carbanion to generate the equivalent post VNS anion a mixture of *ortho* and *para*-substituted VNS products would be formed. We therefore needed a tertiary carbanion to get exclusively the *para*-substituted product. The post VNS anion would then be too hindered to undergo the cross-coupling process.

With an excess of potassium *tert*-butoxide present in the reaction mixture, this produced lower yields, presumably because the *tert*-butoxide anion is adding to the catalyst by oxidative addition. This was a problem as an excess of base is always present in the VNS reaction due to

the reaction never going to completion. Suitable conditions would have to be found to minimize this excess.

Even if we used a *para*-substituted nitroaromatic and secondary carbanion to generate the *ortho* VNS product exclusively we had no success in getting the preformed product to undergo the cross-coupling process.

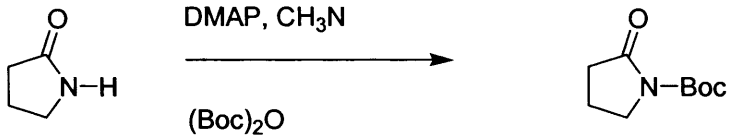
We conclude that it is going to be very difficult to get the one-pot VNS/cross-coupling process to work. The excess of base in the VNS reactions is a serious problem. Possible future work would be to find conditions to cross-couple the *ortho*-nitrophenylacetates with aryl halides and possibly get the one-pot VNS cross-coupling reaction to proceed. This could perhaps be achieved by a different catalyst/ligand system or maybe a base/solvent system we have not tested. A DoE (Design of Experiments) test could perhaps provide the answer in which different catalysts, ligands and bases are screened against each other to attempt to find the ideal conditions.

Chapter 8

8.1 Experimental

General Considerations: Anhydrous *N,N*-dimethylformamide was purchased from Aldrich in a Sure/Seal^{TM} bottle. All other reagents were purchased from commercial suppliers except those described below and used without further purification.

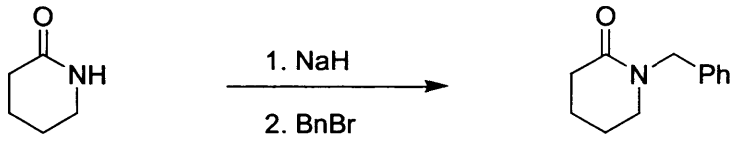
Thin layer chromatography was performed using Merck silica gel 60 F_{254} plates. Column chromatography was performed using silica gel 60 (220-440 mesh). Melting points were obtained using an Electrothermal digital melting point apparatus model 9100. IR spectra was obtained for all previously unreported compounds using a Perkin Elmer 1600 series FTIR instrument. Elemental analyses were performed by the Analytical Department of the School of Chemistry; ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker 400 MHz spectrometer; chemical shifts for ^{1}H NMR are referenced to tetramethylsilane (TMS) as an internal standard while chemical shifts for ^{13}C NMR are referenced to the solvent used. Low resolution mass spectra were determined using a Fisons VG Platform II Quadrupole instrument. High resolution mass spectroscopy was carried out by the EPSRC National Mass Spectrometry Service Centre at Swansea University.



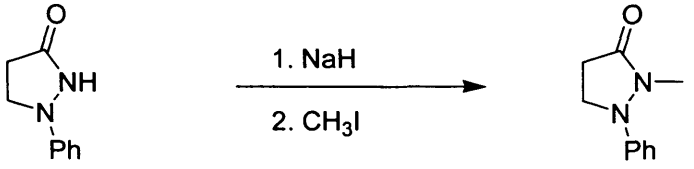
1-tert-Butyloxycarbonyl-pyrrolidin-2-one[142] **(122)**—To a solution of 2-pyrrolidinone (5.0 g, 58.74 mmol) in acetonitrile (100 ml) at 0 °C was added 4-dimethylaminopyridine (0.72 g, 58.74 mmol) and di-*tert*-butyldicarbonate (25.64 g, 117 mmol) with stirring. The reaction was slowly allowed to warm to room temperature overnight. The solvent was removed on a rotary evaporator to give the crude product (12.41 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.4 (silica, hexane:ethyl acetate; 1:1) to give the pure product (10.75 g, 99%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3619 (s), 3544 (s), 2980 (s), 2880 (m), 1786 (s) (C=O), 1560 (w), 1478 (s); δ_H(400 MHz; $CDCl_3$) 3.46 (2H, t, *J* 7.1 Hz, H-5) 2.22 (2H, t, *J* 8.1 Hz, H-3), 1.68-1.76 (2H, m, H-4), 1.23 (9H, s, Boc); δ_C(100 MHz; $CDCl_3$) 174.8 (s) (C=O), 150.3 (s) (C=O), 82.7 (s) (C-$(CH_3)_3$), 46.7 (s) (C-5), 33.1 (s) (C-3), 28.2 (s) (3 × CH_3), 17.6 (s) (C-4); *m/z* (APCI) 186.0 [$(M + H)^+$, 100%].

General Method for *N*-Alkylation—To a slurry of sodium hydride (60% dispersion in oil) (100 mmol) in anhydrous DMF (50 ml) under an inert atmosphere at 0 °C was added the cyclic amide (100 mmol) dropwise. The solution was slowly allowed to warm to room temperature

and stirred for 1 hour. After cooling to 0 °C the electrophile (100 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was then poured onto ice/HCl (1M solution). The product was extracted with dichloromethane (3 × 100 ml). The organic solution was then washed with water (5 × 100 ml) and dried over Na_2SO_4. The drying agent was filtered off and the solvent removed on a rotary evaporator to give the crude product.

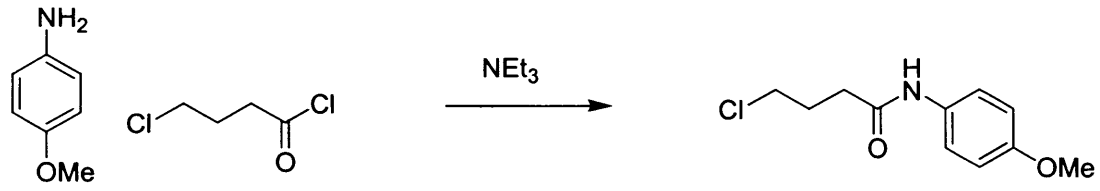


1-Benzyl-piperidin-2-one[147] **(145)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (4.04 g, 100 mmol), DMF (50 ml), piperidin-2-one (10.0 g, 100 mmol) and benzyl bromide (12.0 ml, 100 mmol) to give the crude product (20.9 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.4 (silica, hexane:ethyl acetate; 1:1) to give the pure product (18.1 g, 96%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3483 (s), 2946 (s), 2967 (m), 2356 (m), 1618 (s), 1495 (s), 1451 (s), 1418 (s), 1353 (s), 1263 (s), 1177 (s), 1073 (m), 993 (m); δ_H(400 MHz; $CDCl_3$) 7.10-7.20 (5H, m, Ph) 4.43 (2H, s, CH_2-Ph), 3.04 (2H, t, *J* 5.7 Hz, H-6), 2.32 (2H, t, *J* 6.3 Hz, H-3), 1.55-1.68 (4H,m, H-4 & H-5); δ_C(100 MHz; $CDCl_3$) 170.0 (s) (C=O), 137.5 (s) (C, Ar), 128.8 (s) (2 × CH, Ar), 128.4 (s) (2 × CH, Ar), 127.5 (s) (CH, Ar), 50.2 (s) (CH_2), 47.4 (s) (CH_2), 32.6 (s) (CH_2), 23.3 (s) (CH_2), 21.6 (s) (CH_2); *m/z* (APCI) 190.0 [$(M+H)^+$, 100%].

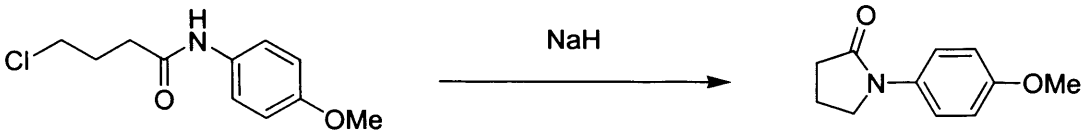


1-Phenyl-2-methylpyrazolidin-3-one[148] **(152)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (2.0 g, 49.6 mmol), 1-phenyl-pyrazolidin-3-one (**151**) (8.0 g, 49.6 mmol) and methyl iodide (6.24 ml, 99.2 mmol) to give the crude product (9.84 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.3 (silica, hexane:ethyl acetate; 1:1) to give the pure product **152** (8.01 g, 92%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 2981 (s), 1691 (s), 1401 (m); δ_H(400 MHz; $CDCl_3$) 7.30 (2H, app. t, *J* 7.6 Hz, Ph) 7.08 (1H, app. t, *J* 7.6 Hz, Ph), 6.95 (2H, app. t, *J* 7.6 Hz, Ph), 3.79 (2H, t, *J* 7.5 Hz, H-4), 3.03 (3H, s, CH_3), 2.50 (2H, t, *J* 7.5 Hz, H-3); δ_C(100 MHz; $CDCl_3$)

172.6 (s) (C=O), 149.7 (s) (C, Ar), 129.4 (s) (2 × CH, Ar), 124.0 (s) (CH, Ar), 119.0 (s) (2 × CH, Ar), 55.6 (s) (CH_2), 30.6 (s) (CH_3), 29.4 (s) (CH_2); *m/z* (APCI) 177.0 [$(M+H)^+$, 100%].



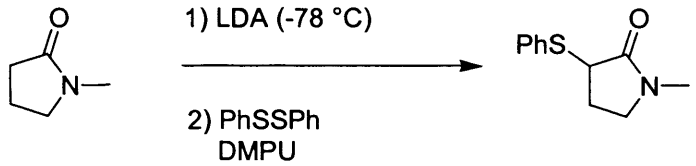
4-Chloro-N-(4-methoxyphenyl)butyramide[145] **(140)**—Triethylamine (20.4 ml) was added to a solution of *p*-anisidine in dry THF (150 ml) at 0 °C. The solution was then stirred at 0 °C for 30 minutes. The acid chloride (10.2 ml, 122 mmol) was then added dropwise at 0 °C over a 10 minute period. The solution was then stirred at 0 °C for 1 hour. The solution was then allowed to warm to room temperature and stirred for a further 2 hours. Water (150 ml) was then added to the reaction mixture and the crude product was extracted with ethyl acetate (3 × 100 ml). The combined organic extracts were then washed with sodium bicarbonate. The solution was then dried over $MgSO_4$ and the solvent removed on a rotary evaporator to give the crude product as a brown crystalline solid. M.p. 83-85 °C (lit. 85 °C)[145]; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2981 (s), 1665 (s), 1625 (m), 1517 (s); δ_H(400 MHz; $CDCl_3$) 8.10 (1H, s, NH), 7.39 (2H, d, *J* 8.3 Hz, H-2 & H-6), 6.81 (2H, d, *J* 8.3 Hz, H-3 & H-5), 3.76 (3H, s, OCH_3), 3.58 (2H, t, *J* 6.2 Hz, $C\underline{H}_2CONH$) 2.48 (2H, t, *J* 7.2 Hz, CH_2Cl), 2.13 (2H, tt, *J* 7.2 & 6.2 Hz, $C\underline{H}_2CH_2Cl$); δ_C(100 MHz; $CDCl_3$) 169.9 (s) (C=O), 156.4 (s) (C, Ar), 130.7 (s) (C, Ar), 121.8 (s) (2 × CH, Ar), 114.1 (s) (2 × CH, Ar), 55.4 (s) (O-CH_3), 44.5 (s) (CH_2), 33.9 (s) (CH_2), 27.9 (s) (CH_2); *m/z* (APCI) 228.0 [$(M+H)^+$, 100%].



1-(4-Methoxyphenyl)pyrrolidin-2-one[145] **(141)**—A solution of 4-chloro-*N*-(4'-methoxyphenyl)butyramide **(140)** (5.0 g, 21.98 mmol) dissolved in anhydrous THF (20 ml) was slowly added to a suspension of sodium hydride (60% dispersion in oil) (0.87 g, 21.98, mmol) in anhydrous THF (20 ml) at 0 °C. The solution was then stirred at room temperature for 24 hours. The solution was then poured into saturated ammonium chloride (100 ml) and extracted with ethyl acetate (3 × 75 ml). The combined organic extracts were then dried over Na_2SO_4. The drying agent was filtered off and the solvent removed on a rotary evaporator to give the crude product (4.26 g) as a brown crystalline solid. The crude product was the

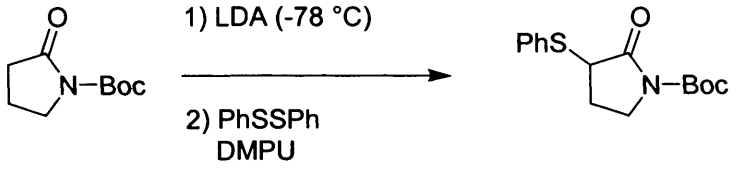
recrystallised from ethanol to give the pure product **141** (3.7 g, 88%) as a brown crystalline solid. M.p. 107-109 °C (lit. 108 °C)[145]; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2980 (s), 1678 (s), 1612 (m), 1514 (s); δ_H(400 MHz; $CDCl_3$) 7.48 (2H, d, *J* 8.4 Hz, H-2 & H-6), 6.81 (2H, d, *J* 8.4 Hz, H-3 & H-5), 3.80 (2H, t, *J* 8.1 Hz, H-5), 3.78 (3H, s, OCH_3), 2.56 (2H, t, *J* 8.1 Hz, H-3) 2.12 (2H, tt, *J* 8.1 & 7.0 Hz, H-4); δ_C(100 MHz; $CDCl_3$) 173.8 (s) (C=O), 156.4 (s) (C, Ar), 132.5 (s) (C, Ar), 121.7 (s) (2 × CH, Ar), 114.0 (s) (2 × CH, Ar), 55.4 (s) (O-CH_3), 49.1 (s) (CH_2), 33.4 (s) (CH_2), 18.0 (s) (CH_2); *m/z* (APCI) 192.0 [$(M+H)^+$, 100%].

General Method for α-phenylsulfanylation—To a solution of diisopropylamine (54 mmol), in dry THF (25 ml) was added *n*-butyllithium (2.5 M in hexanes) (54 mmol) at 0°C. The reaction was allowed to stir at this temperature for 10 minutes before cooling to -78°C with an acetone/dry ice cooling bath. The cyclic amide (26 mmol) dissolved in dry THF (10 ml) was added dropwise to the reaction mixture. The mixture was then stirred at –78 °C for 35 minutes. Phenyl disulfide (26 mmol) dissolved in dry THF (20 ml) containing DMPU (26 mmol) was then added dropwise to the reaction mixture over a 20 minute period. The mixture was then left to stir at –78 °C for another 35 minutes. The mixture was then slowly left to warm to room temperature over an hour and a half. The reaction mixture was then poured into water (200 ml) and then extracted with diethyl ether (3 × 150 ml). The ether extracts were combined and washed consecutively with 10% sodium hydroxide (100 ml), water (100 ml), 10% hydrochloric acid (100 ml) and finally water (100 ml). The solvent was then dried over sodium sulfate. The drying agent was filtered off and the solvent was removed on a rotary evaporator to give the crude product

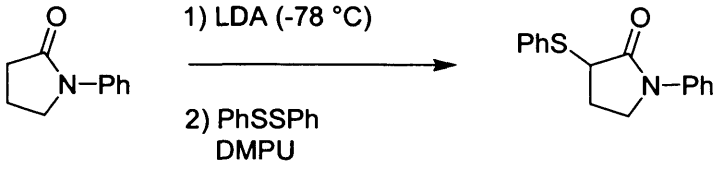


1-Methyl-3-phenylsulfanyl-pyrrolidin-2-one[218] **(119)**—This was prepared by the General Method using diisopropylamine (7.6 ml, 54 mmol, *n*-butyllithium (2.5 M in hexanes) (21.6 ml, 54 mmol), 1-methyl-2-pyrrolidinone (**104**) (5.0 g, 27 mmol), phenyl disulfide (5.7 g, 26 mmol) and DMPU (3.14 ml, 26 mmol) to give the crude product (2.63 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.42 (silica, diethyl ether) to give the pure product (2.63 g, 60%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3549 (br, st), 3055 (w), 2933 (s), 2880 (m), 1706 (s) (C=O), 1582 (m), 1488 (m), 1437 (s), 1402 (m), 1300 (s), 1273 (s), 1107 (m), 1026 (w), 984 (w); δ_H(400 MHz; $CDCl_3$) 7.26-7.31 (2H, m, Ph), 7.04-7.08

(3H, m, Ph), 3.56 (1H, dd, *J* 5.8 & 8.8 Hz, H-3), 2.93-2.99 (1H, m, H-5α), 2.76-2.82 (1H, m, H-5β), 2.18-2.27 (1H, m, H-4α), 1.74-1.82 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 172.2 (s) (C=O), 133.4 (s) (C, Ar), 133.0 (s) (2 × CH, Ar), 129.2 (s) (2 × CH, Ar), 128.1 (s) (CH, Ar), 47.9 (s) (N-CH_3), 47.5 (s) (C-3), 30.4 (s) (CH_2), 26.8 (s) (CH_2); *m/z* (APCI) 209.0 [$(M+H)^+$, 100%].

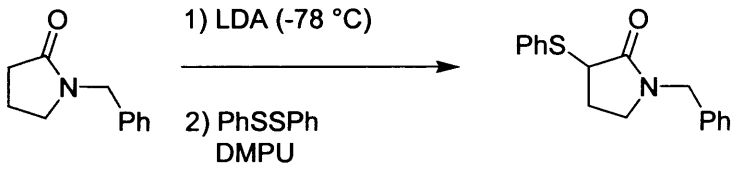


1-Butyloxycarbonyl-3-phenylsulfanylpyrrolidin-2-one **(123)**—This was prepared by the General Method using diisopropylamine (7.9 ml, 56 mmol), *n*-butyllithium (2.5M in hexanes) (22.4 ml, 56 mmol), 1-boc-2-pyrrolidinone (**122**) (5.0 g, 27 mmol), phenyl disulfide (5.9 g, 27 mmol), DMPU (3.26 ml, 27 mmol) to give the crude product (4.15 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.20 (silica, ethyl acetate:hexane; 1:3) to give the pure product (3.7 g, 47%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 2979 (s), 2251 (w), 2933 (s), 1783 (s), 1748 (s), 1717 (s), 1583 (m), 1477 (m), 1437 (m), 1368 (s), 1301 (s), 1257 (s), 1151 (s), 1088 (m), 1041 (w), 1014 (s), 909 (s), 849 (s), 779 (s); δ_H(400 MHz; $CDCl_3$) 7.46-7.48 (2H, m, Ph), 7.22-7.25 (3H, m, Ph), 3.78 (1H, dd, *J* 6.3 & 8.4 Hz, H-3), 3.46-3.58 (2H, m, H-5), 2.30-2.39 (1H, m, H-4α), 1.89-1.98 (1H, m, H-4β), 1.44 (9H, s, H-Boc); δ_C(100 MHz; $CDCl_3$) 171.9 (s) (C=O), 150.4 (s) (C=O), 133.6 (s) (2 × CH, Ar), 132.8 (s) (C, Ar), 129.5 (s) (2 × CH, Ar), 128.6 (s) (CH, Ar), 83.6 (s) (C-$(CH_3)_3$), 49.7 (s) (CH-S), 44.7 (s) (C-5), 28.4 (s) (3 × CH_3), 25.9 (s) (C-4); *m/z* (APCI) 209.0 [$(M+H)^+$, 100%].

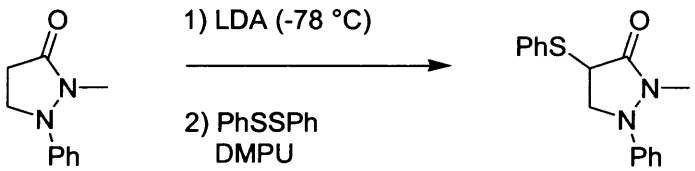


1-Phenyl-3-phenylsulfanylpyrrolidin-2-one **(129)**—This was prepared by the General Method using diisopropylamine (8.72 ml, 62.2 mmol, *n*-butyllithium (2.5 M in hexanes) (24.88 ml, 62.2 mmol), 1-phenyl-2-pyrrolidinone (5.0 g, 31.1 mmol), phenyl disulfide (6.79 g, 31.1 mmol), DMPU (3.75 ml, 31.1 mmol) to give the crude product (5.59 g) as an orange powder. The crude product was then recrystallized from ethanol to give the pure product (5.8 g, 69%) as a slightly brown powder. M.p. 82.5-83.5 °C; (Found C, 71.31; H, 5.63; N 5.20. $C_{16}H_{15}NOS$ requires C, 71.35; H, 5.61; N, 5.20%); υ_{max} (nujol, NaCl plates/ cm^{-1}) 2912 (s), 1682 (s), 1599

(w), 1457 (s), 1379 (s), 1302 (s), 1115 (w), 1091 (w), 895 (m); δ_H(400 MHz; $CDCl_3$) 7.81-7.84 (4H, m, Ph), 7.59-7.64 (2H, m, Ph), 7.53-7.57 (3H, m, Ph), 7.42 (1H, t, *J* 7.4 Hz, Ph), 4.25 (1H, dd, *J* 6.0 & 8.6 Hz, H-3), 3.95-4.01 (1H, m, H-5α), 3.84-3.90 (1H, m, H-5β), 2.81-2.91 (1H, m, H-4α), 2.40-2.49 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 171.8 (s) (C=O), 139.5 (s) (C, Ar), 133.7 (s) (2 x CH, Ar), 133.2 (s) (C, Ar), 129.4 (s) (2 × CH, Ar), 129.3 (s) (2 × CH, Ar), 128.5 (s) (CH, Ar), 125.3 (s) (CH, Ar), 120.4 (s) (CH, Ar), 49.7 (s) (C-3), 46.9 (s) (C-5), 26.7 (s) (C-4); *m/z* (APCI) 270.1 [$(M+H)^+$, 100%] 203.2 (14); (Found: $(M + H)^+$ (ES+), 270.0953 $C_{16}H_{15}NOS$ requires $(M + H)^+$ 220.0947).

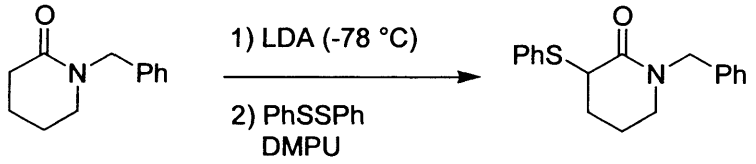


1-Benzyl-3-phenylsulfanylpyrrolidin-2-one[144] **(137)**—This was prepared by the General Method using diisopropylamine (8.97 ml, 64.0 mmol, *n*-butyllithium (2.5 M in hexanes) (25.60 ml, 64.0 mmol), 1-benzyl-2-pyrrolidinone (5.0 ml, 32.0 mmol), phenyl disulfide (6.99 g, 32.0 mmol), DMPU (3.83 ml, 32.0 mmol) to give the crude product (7.46 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.20 (silica, ethylacetate:hexane; 1:3) to give the pure product (5.4 g, 60%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 2901 (s), 1684 (s), 1600 (w); δ_H(400 MHz; $CDCl_3$) 7.51 (2H, d, *J* 7.9 Hz, Ph), 7.19-7.35 (8H, m, Ph), 4.56 (1H, d, *J* 14.5 Hz, HCH), 4.45 (1H, d, *J* 14.5 Hz, HCH), 4.21 (1H, dd, *J* 5.9 & 8.1 Hz, H-3), 3.93-3.99 (1H, m, H-5α), 3.83-3.89 (1H, m, H-5β), 2.77-2.89 (1H, m, H-4α), 2.39-2.46 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 173.9 (s) (C=O), 135.3 (s) (C, Ar), 133.4 (s) (C, Ar), 133.0 (s) (2 × CH, Ar), 131.1 (s) (2 × CH, Ar), 129.2 (s) (2 × CH, Ar), 128.6 (s) (2 × CH, Ar), 128.1 (s) (CH, Ar), 127.5 (s) CH, Ar), 50.9 (s) (CH_2), 47.4 (s) (C-3), 30.1 (s) (CH_2), 26.7 (s) (CH_2); *m/z* (APCI) 284.0 [$(M+H)^+$, 100%].

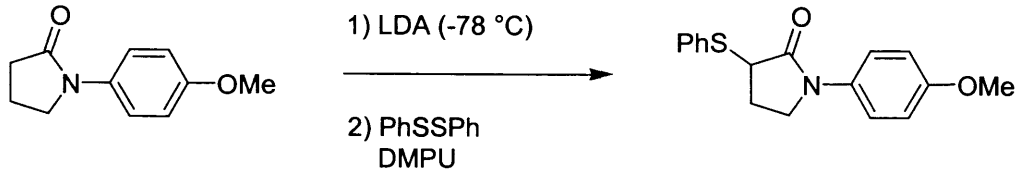


2-Methyl-1-Phenyl-4-pyrazolidin-3-one **(153)**—This was prepared by the General Method using diisopropylamine (3.18 ml, 22.72 mmol, *n*-butyllithium (2.5 M in hexanes) (9.1 ml, 22.72 mmol), 2-methyl-1-phenyl pyrazolidin-3-one (2.0 g, 11.36 mmol), phenyl disulfide (2.48 g, 11.36 mmol), DMPU (1.37 ml, 11.36 mmol) to give the crude product (2.54 g) as a yellow

oil. The crude product was then purified by column chromatography Rf 0.45 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (1.59 g, 49%) as a yellow oil; υ_{max} (neat, NaCl plates/ cm^{-1}) 3058 (s), 2922 (s), 2244 (w), 1951 (w), 1875 (w), 1690 (s) (C=O), 1597 (s), 1490 (s), 1388 (s), 1284 (m), 1112 (m); δ_H(400 MHz; $CDCl_3$) 7.31-7.33 (2H, m, Ph), 7.19 (2H, app. t, *J* 7.8 Hz, Ph), 7.11-7.12 (2H, m, Ph), 6.97 (1H, app. t, *J* 7.3 Hz, Ph), 6.79 (2H, app. d, *J* 7.8 Hz, Ph), 3.89-3.96 (2H, m, H-4 or H-5), 3.65 (1H, dd, *J* 11.3 & 14.5 Hz, H-4 or H-5), 2.97 (3H, s, N-CH_3); δ_C(100 MHz; $CDCl_3$) 170.1 (s) (C=O), 149.4 (s) (C, Ar), 132.9 (s) (C, Ar), 132.8 (s) (2 × CH, Ar), 129.8 (s) (2 × CH, Ar), 128.9 (s) (2 × CH, Ar), 127.4 (s) (CH, Ar), 124.2 (s) (CH, Ar), 118.7 (s) (2 × CH, Ar), 61.7 (s) (C-5), 47.0 (s) (C-5), 31.8 (s) (N-CH_3); *m/z* (APCI) 285.5 [$(M+H)^+$, 100%] 112.7 (33) (Found: $(M + H)^+$ (ES+), 285.1056 $C_{16}H_{16}N_2OS$ requires $(M + H)^+$ 285.1056).

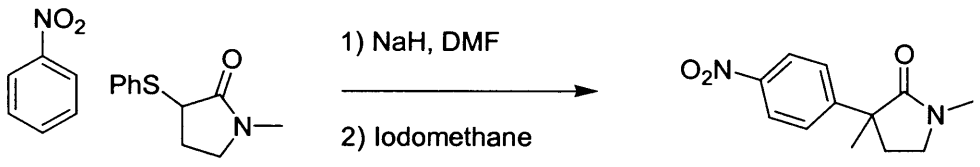


1-Benzyl-3-Phenylsulfanyl-piperidin-2-one[219] **(146)**—This was prepared by the General Method using diisopropylamine (4.45 ml, 31.72 mmol, *n*-butyllithium (2.5M in hexanes) (12.69 ml, 31.72 mmol), 1-benzylpiperidin-2-one (**145**) (3.0 g, 15.86 mmol), phenyl disulfide (3.46 g, 15.86 mmol), DMPU (1.92 ml, 15.86 mmol) to give the crude product (3.81 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.25 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (3.15 g, 67%) as a yellow oil; υ_{max} (neat, NaCl plates/ cm^{-1}) 3059 (m), 2948 (s), 2862 (m), 1952 (w), 1650 (s) (C=O), 1582 (m), 1488 (s), 1438 (s), 1350 (s), 1255 (s), 1177 (s); δ_H(400 MHz; $CDCl_3$) 7.55 (2H, app. d, *J* 7.8 Hz Ph), 7.21-7.31 (8H, m, Ph), 4.7 (1H, d, *J* 14.6 Hz, CH_2-Ph), 4.46 (1H, d, *J* 14.6 Hz, CH_2-Ph), 3.93 (1H, t, *J* 5.6 Hz, H-3), 3.13-3.18 (2H, m, H-6), 1.88-2.11 (3H, m, H-4α, 2 x H-5), 1.61 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 168.7 (s) (C=O), 137.3 (s) (C, Ar), 134.9 (s) (C, Ar), 133.0 (s) (2 × CH, Ar), 129.4 (s) (2 × CH, Ar), 128.8 (s) (2 × CH, Ar), 128.5 (s) (2 × CH, Ar), 128.0 (s) (CH, Ar), 127.9 (s) (CH, Ar), 51.0 (s) (CH_2), 49.4 (s) (CH), 47.6 (s) (CH_2), 28.8 (s) (CH_2), 20.7 (s) (CH_2); *m/z* (APCI) 298 [$(M+H)^+$, 100%].

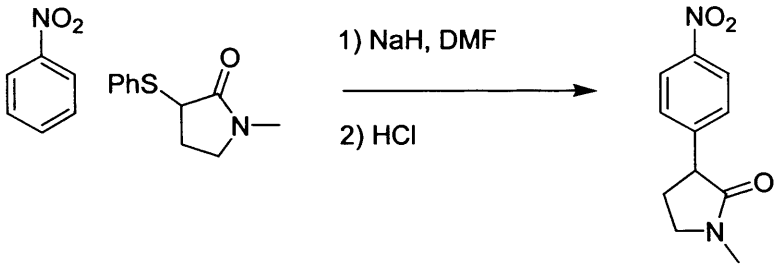


1-(4-Methoxyphenyl)-3-pyrrolidin-2-one **(142)**—This was prepared by the general method using diisopropylamine (4.40 ml, 31.42 mmol, *n*-butyllithium (2.5 M in hexanes) (12.58 ml, 31.42 mmol), 1-(4-methoxyphenyl)-pyrrolidin-2-one (**141**) (3.0 g, 15.71 mmol), phenyl disulfide (3.43 g, 15.71 mmol), DMPU (1.89 ml, 15.71 mmol) to give the crude product (4.3 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.45 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (3.21 g, 68%) as a yellow crystalline solid. M.p. °C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2912 (s), 1677 (s) (C=O), 1514 (m), 1417 (s), 1350 (s); δ_H(400 MHz; $CDCl_3$) 7.60-7.62 (2H, m, Ph), 7.47 (2H, d, *J* 9.1 Hz, Ph), 7.31-7.33 (3H, m, Ph), 6.91 (2H, d, *J* 9.1 Hz, Ph), 4.01 (1H, dd, *J* 5.8 & 8.7 Hz, H-3), 3.67-3.82 (1H, m, H-5α), 3.56-3.60 (1H, m, H-5β), 2.60-2.65 (1H, m, H-4α), 2.18-2.24 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 171.1 (s) (C=O), 156.8 (s) (C, Ar), 133.3 (s) (2 × CH, Ar), 132.9 (s) (C, Ar), 132.3 (s) (C, Ar), 129.0 (s) (2 × CH, Ar), 128.1 (s) (CH, Ar), 121.9 (s) (2 × CH, Ar), 114.0 (s) (2 × CH, Ar), 55.5 (s) ($O\text{-}CH_3$), 49.2 (s) (C-3), 47.0 (s) (C-5), 26.4 (s) (C-4); *m/z* (APCI) 300 [$(M+H)^+$, 100%] 191 (10); (Found: $(M + H)^+$ (ES+), 300.1057 $C_{17}H_{17}NO_2S$ requires $(M + H)^+$ 300.1053).

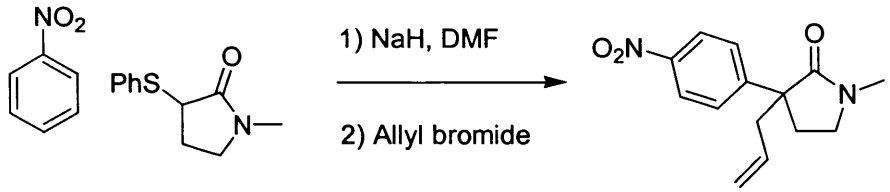
General Method for VNS-Alkylation of Lactams—Sodium hydride (60% dispersion in oil) (14.4 mmol) in anhydrous DMF (5 ml) was flushed with nitrogen and cooled to 0 °C. Nitrobenzene (4.8 mmol) and the VNS nucleophile (4.8 mmol) dissolved in anhydrous DMF (5 ml) was added dropwise to the sodium hydride slurry. The mixture was left to stir at 0 °C for 30 minutes before being allowed to warm to room temperature. The purple reaction mixture was left to stir at room temperature for 2 hours before cooling back down to 0 °C. The electrophile (9.6 mmol) was then added drop-wise to the reaction mixture. The mixture was then allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was then poured onto ice/hydrochloric acid (1M solution). The product was then extracted with dichloromethane (3 × 100 ml), washed with water (5 × 100 ml), sodium bicarbonate (3 × 100 ml) and dried over sodium sulfate. The drying agent was then filtered off and the solvent removed on a rotary evaporator to give the crude product.



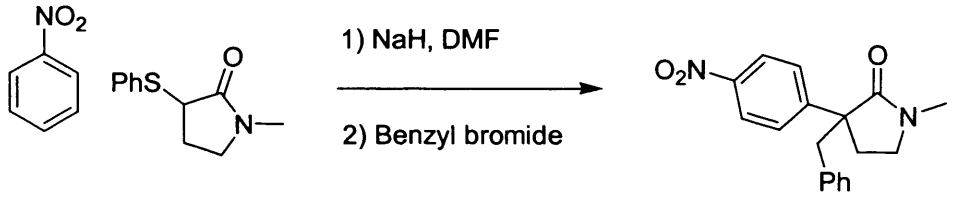
1,3-Dimethyl-3-(4'-nitrophenyl)pyrrolidin-2-one **(120b)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.58 g, 14.4 mmol), 1-methyl-3-phenylsulfanyl-pyrrolidin-2-one (**119**) (1.0 g, 4.8 mmol), nitrobenzene (0.50 ml, 4.8 mmol) and iodomethane (0.45 ml, 7.2 mmol) to give 2.2 g of crude product as a brown oil. The crude product was then purified by column chromatography Rf 0.30 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.73 g, 65%) as a brown oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3463 (br, st), 3077 (m), 2910 (s), 2455 (w), 1689 (s) (C=O); δ_H(400 MHz; $CDCl_3$) 8.05 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.52 (2H, d, *J* 8.9 Hz, H-2' & H-5'), 3.24-3.36 (2H, m, H-5), 2.86 (3H, s, N-CH_3), 2.31-2.37 (1H, m, H-4α), 2.11-2.19 (1H, m, H-4β), 1.48 (3H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 176.5 (s) (C=O), 152.1 (s) (C, Ar), 146.8 (s) (C, Ar), 127.7 (s) (2 × CH, Ar), 123.9 (s) (2 × CH, Ar), 49.1 (s) (C, quaternary), 46.3 (s) (N-CH_2), 35.2 (s) (CH_2), 30.5 (s) (N-CH_3), 25.1 (s) (CH_3); *m/z* (APCI) 235.0[$(M+H)^+$, 100%]; (Found: $(M + H)^+$, 235.1078. $C_{12}H_{14}N_2O_3$ requires $(M + H)^+$ 235.1077).



1-Methyl-3-(4'-nitrophenyl)pyrrolidin-2-one **(120a)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.29 g, 7.2 mmol), 1-methyl-3-phenylsulfanyl-pyrrolidin-2-one (**119**) (0.50 g, 2.4 mmol), nitrobenzene (0.25 ml, 2.4 mmol). No electrophile was added and the mixture was poured onto a mixture of ice and hydrochloric acid (1M) to give the crude product (2.2 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.34 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.37 g, 66%) as a orange crystalline solid. M.p. 74-76 °C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2917 (s), 1672 (m), 1599 (w), 1518 (w), 1461 (s), 1376 (s), 1092 (w), 850 (w); δ_H(400 MHz; $CDCl_3$) 8.10 (2H, d, *J* 8.7 Hz, H-3' & H-5'), 7.38 (2H, d, *J* 8.7 Hz, H-2' & H-5'), 3.71 (1H, t, *J* 9.2 Hz, H-3), 3.40-3.44 (2H, m, H-5), 2.87 (3H, s, N-CH_3), 2.48-2.56 (1H, m, H-4α), 2.02-2.12 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 173.8 (s) (C=O), 147.9 (s) (C, Ar), 147.2 (s) (C, Ar), 129.4 (s) (2 × CH, Ar), 124.2 (s) (2 × CH, Ar), 48.2 (s) (C-3), 47.9 (s) (C-5), 30.5 (s) (N-CH_3), 28.0 (s) (C-4); *m/z* (APCI) 220.8[$(M+H)^+$, 100%]; (Found: $(M + NH_4)^+$, 238.1186. $C_{11}H_{12}N_2O_3$ requires $(M + NH_4)^+$ 238.1186).

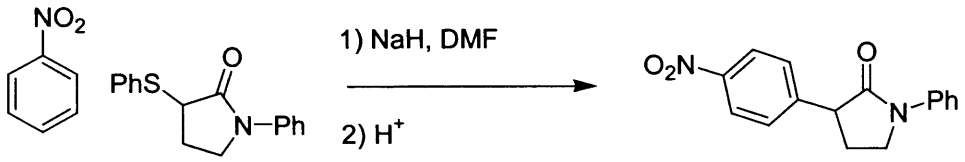


3-Allyl-1-methyl-3-(4'-nitrophenyl)pyrrolidin-2-one **(120c)**—This was prepared by the general method used in the previous compound using sodium hydride (60% dispersion in oil) (0.29 g, 7.2 mmol), 1-methyl-3-phenylsulfanyl-pyrrolidin-2-one (**119**) (0.50 g, 2.4 mmol), nitrobenzene (0.25 ml, 2.4 mmol) and allyl bromide (0.41 ml, 4.8 mmol) to give the crude product (1.46 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.38 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.37 g, 66%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3075 (m), 2922 (s), 1682 (s), 1640 (w), 1602 (s), 1514 (s), 1435 (s), 1403 (s), 1346 (s), 1304 (s), 1101 (s) 1014 (s), 922 (s), 853 (s), 729 (s); δ_H(400 MHz; $CDCl_3$) 8.10 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.63 (2H, d, *J* 8.9 Hz, H-2' & H-5'), 5.49-5.56 (1H, m, CH), 5.00-5.05 (2H, m, $=CH_2$), 3.21-3.31 (2H, m, H-5), 2.84 (3H, s, N-CH_3) 2.57 (2H, d, *J* 7.2 Hz, H_2C=CH-$\underline{CH_2}$-), 2.28-2.39 (2H, m, H-4); δ_C(100 MHz; $CDCl_3$) 175.1 (s) (C=O), 150.3 (s) (C, Ar), 146.9 (s) (C, Ar), 133.3 (s) (H_2C=$\underline{CH}$-), 128.1 (s) (2 × CH, Ar), 123.8 (s) (2 × CH, Ar), 119.8 (s) (H_2C=) 52.4 (s) (C, quaternary), 47.0 (s) (CH_2), 43.8 (s) (C-5), 30.5 (s) (C-4), 30.4 (s) (N-CH_3); *m/z* (APCI) 260.9[$(M+H)^+$, 100%], 205.8 (14); (Found: $(M + H)^+$, 261.1234. $C_{14}H_{16}N_2O_3$ requires $(M + H)^+$ 261.1236).

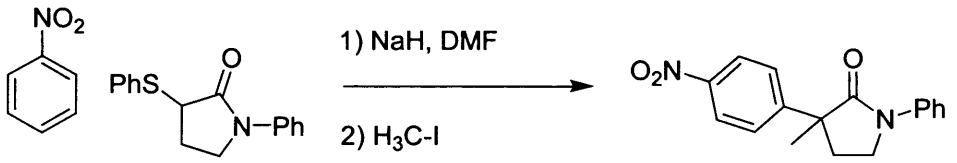


3-Benzyl-1-methyl-3-(4'-nitrophenyl)pyrrolidin-2-one **(120d)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.29 g, 7.2 mmol), 1-methyl-3-phenylsulfanyl-pyrrolidin-2-one (**119**) (0.50 g, 2.4 mmol), nitrobenzene (0.25 ml, 2.4 mmol) and benzyl bromide (0.57 ml, 4.8 mmol) to give the crude product (2.0 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.38 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.55g, 72%) as an orange crystalline solid. M.p. 113-115°C; υ_{max} (nujolt, NaCl plates/ cm^{-1}) 2852 (s), 1668 (s), 1598 (m), 1515 (m), 1377 (m), 1347 (m), 1312 (m); δ_H(400 MHz; $CDCl_3$) 8.11 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.68 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.16-7.19 (3H, m Ph), 7.00-7.02 (2H, m, Ph), 3.23 (1H, d, *J* 13.3 Hz, $\underline{H}$CH-Ph), 2.99-3.03 (1H, m, H-4α), 2.96 (1H, d, *J* 13.3 Hz, HC$\underline{H}$-Ph), 2.70 (3H, s, N-CH_3), 2.47-

2.53 (1H, m, H-4β), 2.25-2.40 (2H, m, H-5); δ_C(100 MHz; $CDCl_3$) 175.2 (s) (C=O), 150.9 (s) (C, Ar), 147.1 (s) (C, Ar), 136.6 (s) (C, Ar), 130.5 (s) (2 × CH, Ar), 128.6 (s) (2 × CH, Ar), 128.2 (s) (2 × CH, Ar), 127.5 (s) (CH, Ar), 123.8 (s) (2 × CH, Ar), 53.8 (s) (C, qaurternary), 46.4 (s) (CH_2), 46.1 (s) (CH_2), 30.1 (s) (N-CH_3), 30.5 (s) (CH_2); *m/z* (APCI) 311.3 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$, 311.1390 $C_{18}H_{18}N_2O_3$ requires $(M + H)^+$ 311.1390).

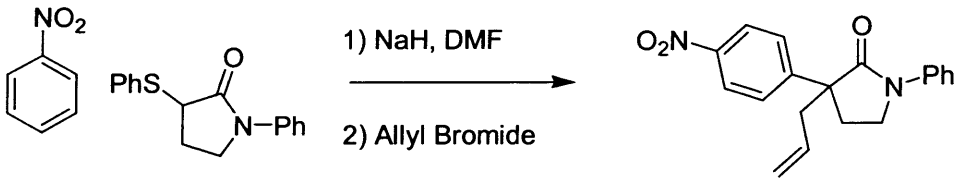


1-Phenyl-3-(4'-nitrophenyl)pyrrolidin-2-one **(130a)**—This was prepared by the general method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (**129**) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) to give the crude product (0.70 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.38 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.39 g, 75%) as an orange crystalline solid. M.p. 117-119 °C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2916 (s), 1690 (s), 1596 (m), 1513 (w), 1463 (s), 1377 (s), 1303 (m); δ_H(400 MHz; $CDCl_3$) 8.08 (2H, d, *J* 8.7 Hz, H-3' & H-5'), 7.56 (2H, app. d, *J* 8.0 Hz, Ph), 7.42 (2H, d, *J* 8.7 Hz, H-2' & H-6'), 7.28 (2H, app. t, *J* 8.0 Hz, Ph), 7.08 (1H, app. t, *J* 8.0 Hz, Ph), 3.79-3.90 (3H, m, H-3 & H-4), 2.53-2.61 (1H, m, H-5α), 2.13-2.23 (1H, m, H-5β), δ_C(100 MHz; $CDCl_3$) 173.0 (s) (C=O), 147.4 (s) (C, Ar), 147.0 (s) (C, Ar), 139.5 (s) (C,Ar), 129.6 (s) (2 × CH, Ar), 129.4 (s) (2 × CH, Ar), 125.4 (s) (CH, Ar), 124.3 (s) (2 × CH, Ar), 120.3 (s) (2 × CH, Ar), 49.7 (s) (CH), 47.1 (s) (CH_2), 27.7 (s) (CH_2); *m/z* (APCI) 283.5 [$(M+H)^+$, 16 %]; (Found: $(M + H)^+$, 283.1079 $C_{16}H_{14}N_2O_3$ requires $(M + H)^+$ 283.1077).

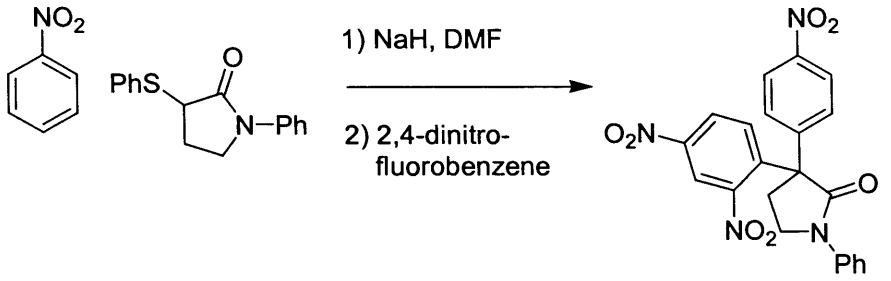


3-Methyl-3-(4'-nitrophenyl)-1-phenylpyrrolidin-2-one **(130b)**—This was prepared by the general method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (**129**) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and iodomethane (0.23 ml, 3.72 mmol) to give the crude product (0.8 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.61 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.38 g, 68%) as a yellow crystalline solid. (Found C,

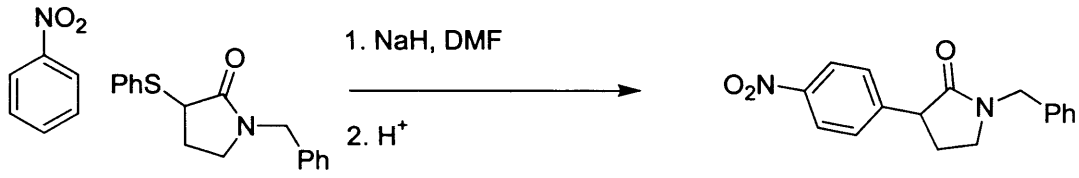
68.81; H, 5.39; N 9.57. $C_{17}H_{16}N_2O_3$ requires C, 68.91; H, 5.44; N, 9.45%); M.p. 160-162°C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2921 (s), 1686 (s) (C=O), 1592 (m), 1456 (s), 1378 (s); δ_H(400 MHz; $CDCl_3$) 8.12 (2H, d, *J* 8.7 Hz, H-3' & H-5'), 7.31-7.35 (4H, m, Ar), 7.10 (2H, app. d, *J* 7.4 Hz, Ph), 6.95 (2H, app. d, *J* 7.6 Hz, Ar), 3.29-3.39 (2H, m, H-5), 2.93 (3H, s, N-CH_3), 2.38 (1H, tdd, *J* 13.7 Hz & 11.9 Hz & 2.01 Hz, H-4α), 2.19 (1H, tdd, *J* 13.7 Hz & 11.9 Hz & 2.01 Hz, H-4β); δ_C(100 MHz; $CDCl_3$) 171.6.(s) (C=O), 149.3 (s) (C, Ar), 147.7 (s) (C, Ar), 143.9 (s) (C, Ar), 130.1 (s) (2 × CH, Ar), 129.9 (s) (2 × CH, Ar), 125.0 (s) (CH, Ar), 124.3 (s) (2 × CH, Ar), 119.3 (s) (2 × CH, Ar), 77.7 (s) (C, q), 63.6 (s) (C-5), 45.9 (s) (C-4), 31.6 (s) (CH_3); *m/z* (APCI) 297.3 [$(M+H)^+$, 100 %]; (Found: $(M + H)^+$, 297.1235. $C_{17}H_{16}N_2O_3$ requires $(M + H)^+$ 297.1234).



3-Allyl-3-(4'-nitrophenyl)-1-phenylpyrrolidin-2-one **(130c)**—This was prepared by the general method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (**129**) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and allyl bromide (0.32 ml, 3.72 mmol) to give the crude product (1.40 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.5 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.39 g, 65%) as a yellow crystalline solid. M.p. 62-63 °C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 3076 (m), 2979 (m), 2892 (m), 2249 (w), 1943 (w), 1861 (w), 1686 (s) 1596 (s) 1502 (s), 1394 (s) 1346 (s); δ_H(400 MHz; $CDCl_3$) 8.09 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.65 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.55 (2H, app. d, *J* 8.0 Hz, Ph), 7.29 (2H, app. t, *J* 8.0 Hz, Ph), 7.08 (1H, app. t, *J* 8.0 Hz, Ph), 5.52-5.62 (1H, m, H_2C=C<u>H</u>-), 5.02-5.06 (2H, m, <u>H_2</u>C=), 3.72-3.78 (1H, m, H-5α), 3.66 (1H, dd, *J* 7.4 & 17.1 Hz, H-5β), 2.65-2.67 (2H, m, =CH-C<u>H_2</u>), 2.39-2.53 (2H, m, 2 × H-4); δ_C(100 MHz; $CDCl_3$) 174.5.(s) (C=O), 149.2 (s) (C, Ar), 147.3 (s) (C, Ar), 139.5 (s) (C,Ar), 133.1 (s) (CH, Ar), 129.4 (s) (2 × CH, Ar), 128.2 (s) (2 × CH, Ar), 125.4 (s) (CH, Ar), 124.0 (s) (2 × CH, Ar), 120.4 (s) (2 × CH, Ar), 120.2 (s) (CH, Ar), 54.0 (s) (C, q), 45.7 (s) (CH_2), 44.0 (s) (CH_2), 30.0 (s) (CH_2); *m/z* (APCI) 323.3 [$(M+H)^+$, 100 %]; (Found: $(M + H)^+$, 323.1390. $C_{19}H_{18}N_2O_3$ requires $(M + H)^+$ 323.1390).

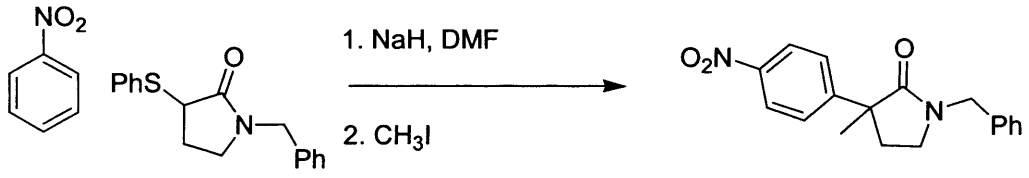


3-(2",4"-dinitrophenyl)-3-(4'-nitrophenyl)-1-phenylpyrrolidin2-one **(130d)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (**129**) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and 2,4-dinitrofluorobenzene (0.47 ml, 3.72 mmol) to give the crude product (1.42 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.19 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.48 g, 58%) as an orange oil. υ_{max} (nujol, NaCl plates/ cm^{-1}) 3071 (m), 2892 (m), 1681 (s), 1487 (s); δ_H(400 MHz; $CDCl_3$) 8.55 (1H, d, *J* 2.4 Hz, H-3"), 8.29 (1H, dd, *J* 2.4 & 8.7 Hz, H-5"), 8.14 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.60 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.47-7.50 (3H, m, H-6" & Ph), 7.3 (2H, app. t, *J* 7.6 Hz, Ph), 7.13 (1H, t, *J* 7.6 Hz, Ph), 3.98-4.09 (2H. m, H-4α & H-4β), 3.38 (1H, ddd, *J* 2 & 6.5 & 13.9 Hz, H-5 α), 2.98 (1H, m, 2.94-3.02, H-5β); δ_C(100 MHz; $CDCl_3$) 170.8.(s) (C=O), 150.6 (s) (C, Ar), 148.1 (s) (C, Ar), 147.3 (s) (C, Ar), 144.4 (s) (C, Ar), 144.1 (s) (C, Ar), 138.8 (s) (C, Ar), 133.8 (s) (CH, Ar), 129.5 (s) (2 × CH, Ar), 129.0 (s) (CH, Ar), 126.8 (s) (CH, Ar), 126.3 (s) (CH, Ar), 124.4 (s) (2 × CH, Ar), 121.2 (s) (CH, Ar), 120.8 (CH, Ar), 58.9 (s) (C, q), 46.3 (s) (CH_2), 31.9 (s) (CH_2); *m/z* (APCI) 449 $[(M+H)^+$, 65 %]; (Found: $(M + NH_4)^+$, 466.1358 $C_{22}H_{16}N_4O_7$ requires $(M + NH_4)^+$ 466.1357).

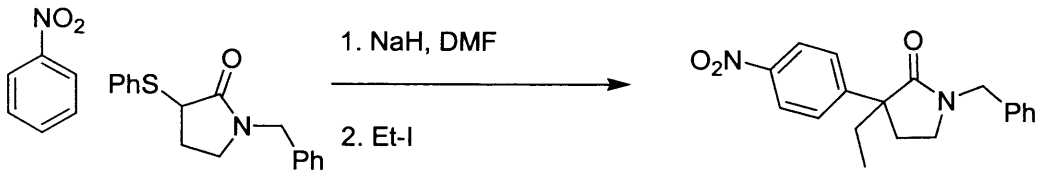


1-Benzyl-3-(4'-nitrophenyl)pyrrolidin-2-one **(138a)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (**137**) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and hydrochloric acid (1 M) (2 ml) to give the crude product (3.34 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.40 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.34 g, 62%) as a white crystalline solid M.p. 91-93°C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2907 (s), 1675 (s), 1601 (m), 1514 (m), 1456 (s), 1377 (w),

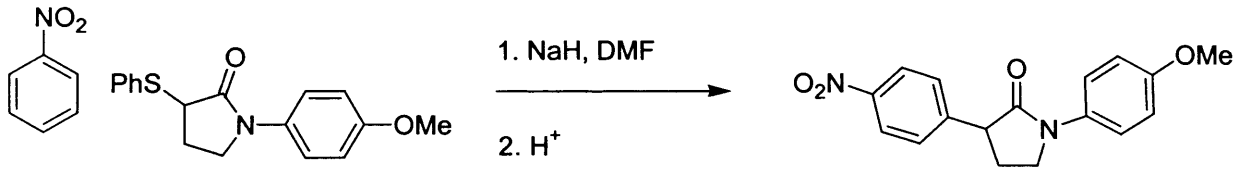
1347 (s), 1285 (m); δ_H(400 MHz; $CDCl_3$) 8.12 (2H, d, *J* 8.7 Hz, H-3' & H-5'), 7.38 (1H, d, *J* 8.7 Hz, H-2' & H-6'), 7.19-7.31 (5H, m, Ph), 4.51 (1H, d, *J* 14.6 Hz, HCH), 4.41 (1H, d, *J* 14.6 Hz, HCH), 3.77 (1H, t, *J* 9.1 Hz, H-3), 3.25-3.31 (2H, m, H-5), 2.44-2.52 (1H. m, H-4α), 2.04 (1H, ddd, *J* 8.6 & 13.0 & 17.1 Hz, H-4β); δ_C(100 MHz; $CDCl_3$) 173.7 (s) (C=O), 147.6 (s) (C, Ar), 147.4 (s) (C, Ar), 136.5 (s) (C,Ar), 129.4 (s) (2 × CH, Ar), 129.3 (s) (2 × CH, Ar), 128.6 (s) (2 × CH, Ar), 128.3 (s) (CH, Ar), 124.3 (s) (2 × CH, Ar), 48.3 (s) (CH), 47.6 (s) (CH_2), 45.2 (s) (CH_2), 27.9 (s) (CH_2); *m/z* (APCI) 297 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+), 297.1238. $C_{17}H_{16}N_2O_3$ requires $M + H)^+$ 297.1234).



3-Methyl-1-benzyl-3-(4'-nitrophenyl)pyrrolidin-2-one **(138b)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (**137**) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and methyl iodide (0.23 ml, 3.72 mmol) to give the crude product (2.21 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.21 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.34 g, 66%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3506 (w), 3064 (s), 2967 (m), 2967 (m), 2927 (w), 2872 (w), 1686 (s) (C=O), 1603 (m), 1520 (s), 1495 (m), 1454 (m), 1429 (m), 1348 (s), 1270 (s); δ_H(400 MHz; $CDCl_3$) 8.09 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.53 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 6.70-7.27 (5H, m, Ph), 4.45 (2H, s, CH_2-Ph), 3.10-3.22 (2H, m, H-5), 2.28-2.34 (1H, m, H-4α), 2.08-2.16 (1H, m, H-4β), 1.54 (3H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 176.5.(s) (C=O), 151.9 (s) (C, Ar), 147.0 (s) (C, Ar), 136.5 (s) (C, Ar), 129.8 (s) (2 × CH, Ar), 129.2 (s) (2 × CH, Ar), 128.6 (s) (CH, Ar), 128.2 (s) (2 × CH, Ar), 124.0 (s) (2 × CH, Ar), 49.3 (s) (C, quaternary), 47.5 (s) (CH_2), 43.6 (s) (CH_2), 35.2 (s) (CH_2), 24.9 (s) (CH_3); *m/z* (APCI) 311 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+), 311.1392 $C_{18}H_{18}N_2O_3$ requires $(M + H)^+$ 311.1390).

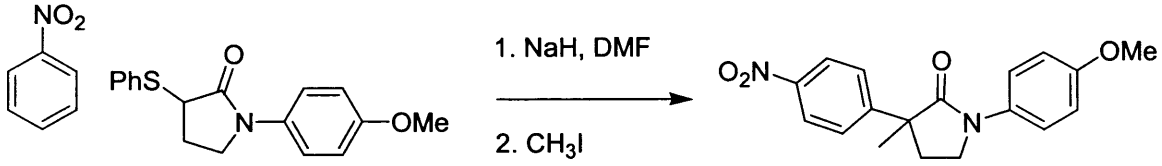


3-Ethyl-1-benzyl-3-(4'-nitrophenyl)pyrrolidin-2-one **(138c)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.23 g, 5.72 mmol), 1-phenyl-3-phenylsulfanyl-pyrrolidin-2-one (**137**) (0.50 g, 1.86 mmol), nitrobenzene (0.19 ml, 1.86 mmol) and ethyl iodide (0.28 ml, 3.50 mmol) to give the crude product (1.04 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.21 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.35 g, 61%) as a yellow crystalline solid. M.p. 110-111 °C; υ_{max} (neat, NaCl plates/ cm^{-1}) 3480 (s), 2932 (s), 1666 (s), 1602 (m), 1515 (m), 1454 (s), 1378 (s), 1106 (m), 855 (m); δ_H(400 MHz; $CDCl_3$) 8.10 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.63 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.19-7.24 (3H, m, Ph), 7.12 (2H, app. d, *J* 7.8 Hz, Ph), 4.48 (1H, d, *J* 14.6 Hz, HCH), 4.37 (1H, d, *J* 14.6 Hz, HCH), 3.08-3.19 (2H, m, H-5), 2.35 (1H, dt, *J* 7.4 & 12.9 Hz, H-4α), 2.20 (1H, dt, *J* 7.4 & 12.9 Hz, H-4β), 1.95 (1H, dq, *J* 14.8 & 7.4 Hz, HCH-CH_3), 1.86 (1H, dq, *J* 13.9 & 7.4 Hz, HCH-CH_3), 0.76 (3H. t, *J* 7.4 Hz, CH_3); δ_C(100 MHz; $CDCl_3$) 175.6.(s) (C=O), 150.3 (s) (C, Ar), 147.1 (s) (C, Ar), 136.6 (s) (C,Ar), 129.2 (s) (2 × CH, Ar), 128.5 (s) (2 × CH, Ar), 128.1 (s) (2 × CH, Ar), 123.9 (s) (2 × CH, Ar), 53.2 (s) (C, quaternary), 47.4 (s) (CH_2), 43.7 (s) (CH_2), 32.3 (s) (CH_2), 30.7 (s) (CH_2), 9.4 (s) (CH_3); *m/z* (APCI) 325 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+), 325.1553 $C_{19}H_{20}N_2O_3$ requires $(M + H)^+$ 325.1547).

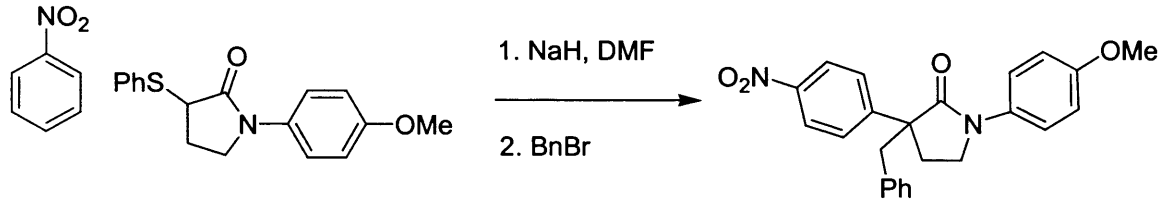


1-(4'-methoxyphenyl)-3-(4"-nitrophenyl)pyrrolidin-2-one **(143a)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.01 mmol), 1-(4-methoxyphenyl)-3-phenylsulfanyl-pyrrolidin-2-one (**142**) (0.50 g, 1.67 mmol), nitrobenzene (0.17 ml, 1.67 mmol) and saturated ammonium chloride (0.50 ml) to give the crude product (1.85 g) as brown oil. The crude product was then purified by column chromatography Rf 0.20 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.38 g, 73%) as a yellow crystalline solid. M.p. 157-159 °C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2909 (s), 2360 (s), 1694 (s), 1603 (m), 1514 (m), 1492 (s), 1377 (s), 1346 (m), 1252 (m); δ_H(400 MHz; $CDCl_3$) 8.14 (2H, d, *J* 8.6 Hz, H-3' & H-5'), 7.48 (2H, d, *J* 9.0 Hz, H-2" & H-6"), 7.44 (2H, d, *J* 8.6 Hz, H-2' & H-6'), 6.85 (2H, d, *J* 9.0 Hz, H-3" & H-5"), 3.80-3.95 (3H, m, H-3 & H-5), 3.73 (3H, s, O-CH_3), 2.57-2.67 (1H, m, H-4α), 2.17-2.27 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 172.6.(s) (C=O), 157.3 (s) (C, Ar), 147.5 (s) (C, Ar), 147.1 (s) (C, Ar), 132.6 (s) (C, Ar), 129.5 (s) (2 × CH, Ar), 124.3 (s) (2

× CH, Ar), 122.1 (s) (CH, Ar), 114.5 (s) (2 × CH, Ar), 55.9 (s) (O-CH_3), 49.5 (s) (CH), 47.5 (s) (CH_2), 27.8 (s) (CH_2); *m/z* (APCI) 313 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+) 313.1184. $C_{17}H_{16}N_2O_4$ requires $(M + H)^+$ 313.1183).

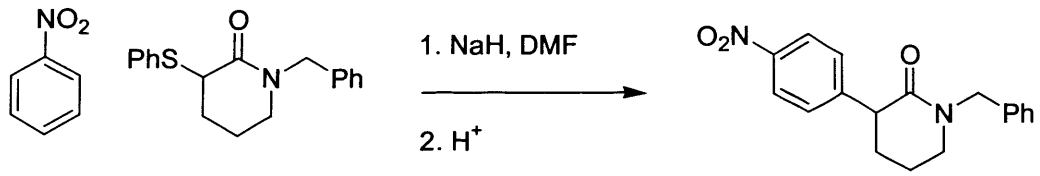


3-Methyl-1-(4'-methoxyphenyl)-3-(4"-nitrophenyl)pyrrolidin-2-one (**143b**)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.01 mmol), 1-(4-methoxyphenyl)-3-phenylsulfanyl-pyrrolidin-2-one (**142**) (0.50 g, 1.67 mmol), nitrobenzene (0.17 ml, 1.67 mmol) and methyl Iodide (0.21 ml, 3.34 mmol) to give the crude product (1.41 g) as brown oil. The crude product was then purified by column chromatography Rf 0.19 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.45 g, 83%) as a yellow crystalline solid. M.p. 84-85 °C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2922 (s), 1688 (s), 1603 (m), 1463 (s), 1377 (m), 1296 (w), 1244 (w), 1024 (w), 840 (m); δ_H(400 MHz; $CDCl_3$) 8.10 (2H, d, *J* 8.7 Hz, H-3' & H-5'), 7.58 (2H, d, *J* 8.7 Hz, H-2' & H-6'), 7.48 (2H, d, *J* 8.9 Hz, H-2" & H-6"), 6.84 (2H, d, *J* 8.9 Hz, H-3" & H-5"), 3.73-3.78 (1H, m, H-5α), 3.72 (3H, s, O-CH_3), 3.62-3.68 (1H, m, H-5β), 2.47-2.57 (1H, m, H-4α), 2.25-2.31 (1H, m, H-4β), 1.58 (3H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 175.4.(s) (C=O), 157.2 (s) (C, Ar), 151.4 (s) (C, Ar), 147.1 (s) (C, Ar), 132.8 (s) (C, Ar), 127.8 (s) (2 × CH, Ar), 124.1 (s) (2 × CH, Ar), 122.1 (s) (2 × CH, Ar), 114.5 (s) (2 × CH, Ar), 55.9 (s) (O-CH_3), 50.5 (s) (C, quaternary), 45.9 (s) (CH_2), 34.8 (s) (CH_2), 25.6 (s) (CH_3); *m/z* (APCI) 327 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+) 327.1337 $C_{18}H_{18}N_2O_4$ requires $(M + H)^+$ 327.1339).

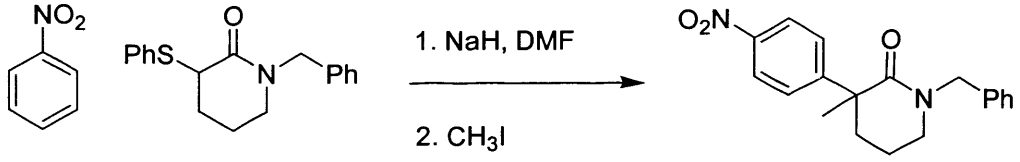


3-Benzyl-1-(4'-methoxyphenyl)-3-(4"-nitrophenyl)-pyrrolidin-2-one (**143c**)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.01 mmol), 1-(4-methoxyphenyl)-3-phenylsulfanyl-pyrrolidin-2-one (**142**) (0.50 g, 1.67 mmol), nitrobenzene (0.17 ml, 1.67 mmol) and benzyl bromide (0.40 ml, 3.34 mmol) to give the crude product (2.60 g) as brown oil. The crude product was then purified by column chromatography Rf 0.41 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.44 g, 66%) as an orange

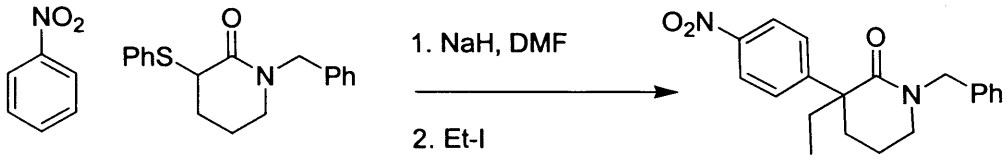
oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 2956 (s), 1681 (s), 1453 (s), 1110 (s); δ_H(400 MHz; $CDCl_3$) 8.20 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.80 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.40 (2H, d, *J* 9.0 Hz, H-2" & H-6"), 7.24-7.28 (3H, m, Ph), 7.10-7.12 (2H, m, Ph), 6.91 (2H, d, *J* 9.0 Hz, H-3" & H-5"), 3.81 (3H, s, O-CH_3), 3.50 (1H, dt, *J* 7.0 & 9.5 Hz, H-5α), 3.43 (1H, d, *J* 13.4 Hz, HCH-Ph), 3.21-3.27 (1H, m, H-5β), 3.15 (1H, d, *J* 13.4 Hz, HCH-Ph), 2.51-2.57 (2H, m, H-4); δ_C(100 MHz; $CDCl_3$) 174.1 (s) (C=O), 157.3 (s) (C, Ar), 150.0 (s) (C, Ar), 147.2 (s) (C, Ar), 136.6 (s) (C, Ar), 132.5 (s) (C, Ar), 130.6 (s) (2 × CH, Ar), 128.7 (s) (2 × CH, Ar), 127.6 (s) (CH, Ar), 123.9 (s) (2 × CH, Ar), 122.5 (s) (2 × CH, Ar), 114.4 (s) (2 × CH, Ar), 55.9 (s) (O-CH_3), 55.0 (s) (C, quaternary), 46.1 (s) (CH_2), 46.0 (s) (CH_2), 30.0 (s) (CH_3); *m/z* (APCI) 403 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+) 403.1581 $C_{18}H_{18}N_2O_4$ requires $(M + H)^+$ 403.1580).



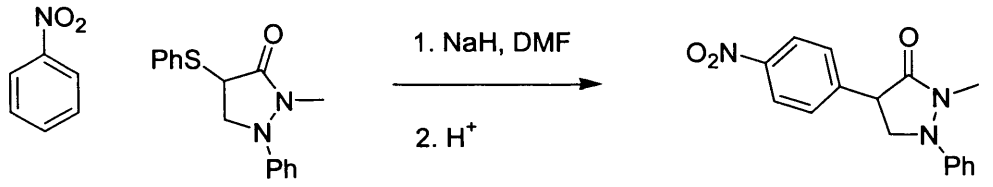
1-Benzyl-3-(4"-nitrophenyl)piperidin-2-one **(147a)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.01 mmol), 1-benzyl-3-phenylsulfanyl-piperidin-2-one (**146**) (0.50 g, 1.67 mmol), nitrobenzene (0.17 ml, 1.67 mmol) and saturated ammonium chloride (2.0 ml) to give the crude product (1.80 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.41 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.33 g, 64%) as a yellow crystalline solid. M.p. 104-105 °C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 3458 (s), 3029 (s), 2940 (s), 2240 (m), 1710 (s), 1627 (s), 1518 (s), 1452 (s), 1348 (s), 1249 (m), 1195 (m), 1108 (m), 1015 (m); δ_H(400 MHz; $CDCl_3$) 8.11 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 7.31 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 7.21-7.29 (5H, m, Ph), 4.59 (3H, s, CH_2), 3.76 (1H, dd, *J* 6.1 & 9.2 Hz, H-3), 3.24-3.36 (2H, m, H-6), 2.09-2.17 (1H, m, H-4α), 1.73-1.93 (3H, m, H-4β & H-5); δ_C(100 MHz; $CDCl_3$) 169.8.(s) (C=O), 149.7 (s) (C, Ar), 147.1 (s) (C, Ar), 137.4 (s) (C, Ar), 129.8 (s) (2 × CH, Ar), 129.1 (s) (2 × CH, Ar), 128.7 (s) (2 × CH, Ar), 128.1 (s) (CH, Ar), 124.1 (s) (2 × CH, Ar), 51.0 (s) (CH_2), 49.2 (s) (CH), 47.6 (s) (CH_2), 30.3 (s) (CH_2), 21.4 (s) (CH_2); *m/z* (APCI) 311 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+) 311.1388 $C_{18}H_{18}N_2O_3$ requires $(M + H)^+$ 311.1390).



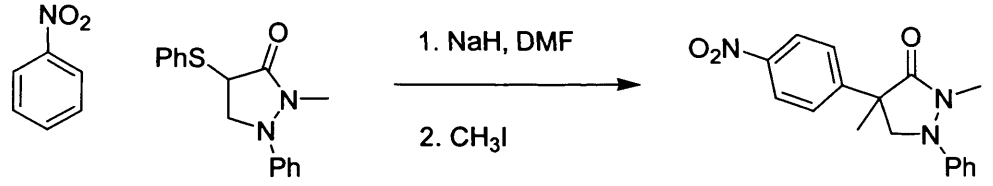
3-Methyl-1-benzyl-3-(4"-nitrophenyl)piperidin-2-one **(147b)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.16 g, 4.05 mmol), 1-Benzyl-3-phenylsulfanyl-piperidin-2-one (**146**) (0.40 g, 1.35 mmol), nitrobenzene (0.14 ml, 1.35 mmol) and methyl iodide (0.17 ml, 2.70 mmol) to give the crude product (1.30 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.10 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.27 g, 61%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3460 (s), 3027 (s), 2938 (s), 1701 (s), 1637 (s), 1518 (s), 1453 (s), 1350 (s), 1249 (m), 1199 (m), 1101 (m), 1012 (m); δ_H(400 MHz; $CDCl_3$) 8.08 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.41 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.19-7.30 (5H, m, Ph), 4.73 (1H, d, *J* 14.4 Hz, HCH-Ph), 4.45 (1H, d, *J* 14.4 Hz, HCH-Ph) 3.19-3.27 (2H, m, H-6), 2.11-2.18 (1H, m, H-4α), 1.87-1.96 (1H, m, H-4β), 1.63-1.71 (1H, m, H-5α), 1.44-1.55 (1H, m, H-5β), 1.58 (3H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 173.0.(s) (C=O), 153.9 (s) (C, Ar), 146.8 (s) (C, Ar), 137.6 (s) (C, Ar), 129.1 (s) (2 × CH, Ar), 128.7 (s) (2 × CH, Ar), 128.0 (s) (2 × CH, Ar), 127.8 (s) (2 × CH, Ar), 124.0 (s) (2 × CH, Ar), 51.2 (s) (CH_2), 48.5 (s) (C, quaternary), 48.1 (s) (CH_2), 37.0 (s) (CH_2), 27.9 (s) (CH_3), 19.6 (s) (CH_2); *m/z* (APCI) 325 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+) 325.1551. $C_{19}H_{20}N_2O_3$ requires $(M + H)^+$ 325.1547).



3-Ethyl-1-benzyl-3-(4"-nitrophenyl)piperidin-2-**one** **(147c)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.04 mmol), 1-benzyl-3-phenylsulfanyl-piperidin-2-one (**146**) (0.50 g, 1.68 mmol), nitrobenzene (0.18 ml, 1.68 mmol) and ethyl iodide (0.52g, 3.36 mmol) to give the crude product (1.43 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.27 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.33 g, 58%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 2929 (s), 1618 (s), 2938 (s), 1494 (s), 1377 (m), 1194 (m); δ_H(400 MHz; $CDCl_3$) 8.07 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.47 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.19-7.27 (5H, m, Ph); δ_C(100 MHz; $CDCl_3$) 172.0.(s) (C=O), 152.7 (s) (C, Ar), 146.8 (s) (C, Ar), 137.6 (s) (C, Ar), 129.7 (s) (2 × CH, Ar), 129.1 (s) (2 × CH, Ar), 128.6 (s) (2 × CH, Ar), 128.0 (s) (CH, Ar), 123.9 (s) (2 × CH, Ar), 52.4 (s) (C, quaternary), 51.2 (s) (CH_2), 48.0 (s) (CH_2), 34.3 (s) (CH_2), 31.3 (s) (CH_2), 19.0 (s) (CH_2), 9.6 (s) (CH_3); *m/z* (APCI) 339 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+) 339.1708. $C_{20}H_{22}N_2O_3$ requires $(M + H)^+$ 339.1703).

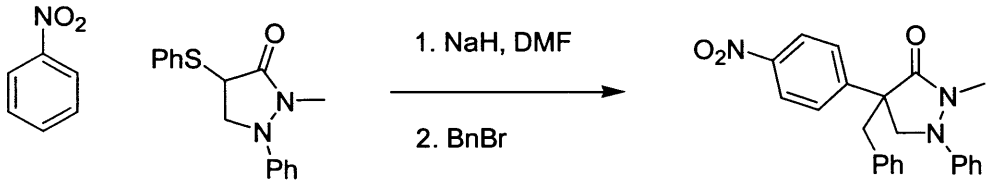


***1-Phenyl-2-methyl-4-(4"-nitrophenyl)pyrazolidin-3-one* (154a)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.21 g, 5.28 mmol), 1-phenyl-2-methyl-4-phenylsulfanyl-pyrazolidin-3-one (**153**) (0.50 g, 1.76 mmol), nitrobenzene (0.18 ml, 1.76 mmol) and saturated ammonium chloride (2.0 ml) to give the crude product (1.01 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.14 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.36 g, 69%) as a yellow crystalline solid. M.p. 170-172 °C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2918 (s), 1699 (s), 1595 (m), 1513 (m), 1462 (s), 1377 (m); δ_H(400 MHz; $CDCl_3$) 7.97 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 7.17-7.23 (4H, m, H-2', H-6', H-3" & H-5"), 6.96 (1H, app. t, *J* 7.5 Hz, H-4"), 6.81 (2H, d, *J* 7.5 Hz, H-2" & H-6"), 3.76-3.96 (3H, m, H-3 & H-4), 2.96 (3H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 171.6.(s) (C=O), 149.3 (s) (C, Ar), 147.6 (s) (C, Ar), 143.9 (s) (C, Ar), 130.1 (s) (2 × CH, Ar), 129.9 (s) (2 × CH, Ar), 125.0 (s) (CH, Ar), 124.3 (s) (2 × CH, Ar), 119.2 (s) (2 × CH, Ar), 63.6 (s) (CH_2), 45.9 (s) (CH_3 or CH), 31.6 (s) (CH_3 or CH); *m/z* (APCI) 298 $[(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+) 298.1181. $C_{16}H_{15}N_3O_3$ requires $(M + H)^+$ 298.1186).

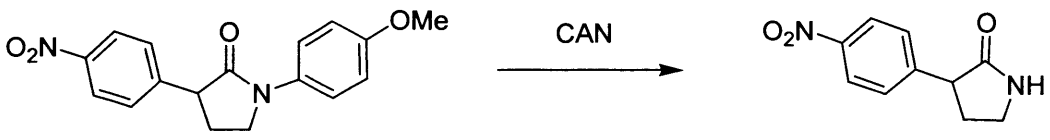


***4-Methyl-1-phenyl-2-methyl-4-(4"-nitrophenyl)pyrazolidin-3-one* (154b)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.21 g, 5.28 mmol), 1-phenyl-2-methyl-4-phenylsulfanyl-pyrazolidin-3-one (**153**) (0.50 g, 1.76 mmol), nitrobenzene (0.18 ml, 1.76 mmol) and methyl iodide (0.22 ml, 3.52 mmol) to give the crude product (1.22 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.50 (silica, hexane:ethyl acetate; 1:1) to give the pure product (0.26 g, 47%) as a yellow crystalline solid. M.p. 200 °C *dec*; υ_{max} (nujol, NaCl plates/ cm^{-1}) 3383 (s), 2923 (s), 2455 (w), 1939 (m), 1462 (m), 1376 (m); δ_H(400 MHz; $CDCl_3$) 7.96 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 7.42 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 7.13 (2H, app. t, *J* 8.1 Hz, Ph), 6.89 (1H, app. t, *J* 8.1 Hz, Ph), 6.73 (2H, app. d, *J* 8.1 Hz, Ph), 4.20 (1H, d, *J* 11.7 Hz, HCH), 3.95 (1H, d, *J* 11.7 Hz, HCH), 3.07 (3H, s, N-CH_3), 1.44 (3H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 174.3.(s) (C=O), 149.7 (s) (C, Ar), 149.6 (s)

(C, Ar), 147.0 (s) (C, Ar), 129.7 (s) (2 × CH, Ar), 128.6 (s) (2 × CH, Ar), 124.0 (s) (CH, Ar), 123.9 (s) (2 × CH, Ar), 118.1 (s) (2 × CH, Ar), 67.8 (s) (CH_2), 49.4 (s) (C, quaternary), 32.1 (s) (CH_3), 25.4 (s) (CH_3); *m/z* (APCI) 312.0 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+) 312.1340 $C_{17}H_{17}N_3O_3$ requires $(M + H)^+$ 312.1343).



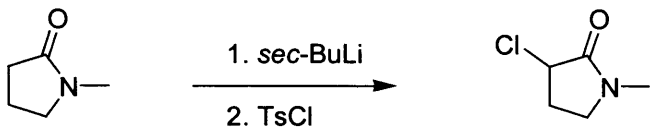
4-Benzyl-1-phenyl-2-methyl-4-(4"-nitrophenyl)pyrazolidin-3-one **(154c)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.01 mmol), 1-phenyl-2-methyl-4-phenylsulfanyl-pyrazolidin-3-one (**153**) (0.50 g, 1.76 mmol), nitrobenzene (0.18 ml, 1.76 mmol) and benzyl bromide (0.40 ml, 3.34 mmol) to give the crude product (2.60 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.41 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.41 g, 61%) as a yellow crystalline solid. υ_{max} (nujol, NaCl plates/ cm^{-1}) 2920 (s), 2440 (w), 1921 (w), 1690 (s), 1595 (m), 1507 (m), 1462 (s) (s); δ_H(400 MHz; $CDCl_3$) 7.97 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 7.39 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 7.21-7-29 (3H, m, Ph), 7.15 (2H, app. t, *J* 8.0 Hz, Ph), 7.10-7.13 (2H, m, Ph), 6.91 (1H, t, *J* 8.0 Hz, Ph), 6.70 (2H, app. d, *J* 8.0 Hz, Ph), 4.19 (1H, d, *J* 11.9 Hz, HCH), 3.93 (1H, d, *J* 11.9 Hz, HCH), 3.41 (1H, d, *J* 13.1 Hz, HCH-Ph), 3.13 (1H, d, *J* 13.1 Hz, HCH-Ph), 3.10 (3H, s, N-CH_3); δ_C(100 MHz; $CDCl_3$) 173.7 (s) (C=O), 149.9 (s) (C, Ar), 149.7 (s) (C, Ar), 146.9 (s) (C, Ar), 130.0 (s) (2 × CH, Ar), 128.5 (s) (2 × CH, Ar), 127.9 (s) (CH, Ar), 127.0 (s) (2 × CH, Ar), 126.7 (s) (2 × CH, Ar), 123.9 (s) (CH, Ar), 123.7 (s) (2 × CH, Ar), 117.9 (s) (2 × CH, Ar), 67.9 (s) (CH_2), 49.9 (s) (C, quaternary), 43.0 (s) (CH_2), 32.2 (s) (CH_3); *m/z* (APCI) 388.0 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+) 388.1586 $C_{17}H_{17}N_3O_3$ requires $(M + H)^+$ 388.1583).



3-(4"-Nitrophenyl)-pyrrolidin-2-one **(155)**—Cerium ammonium nitrate (0.53 g, 0.96 mmol) was dissolved in water (6.0 ml) and added to a solution of 1-(4'-methoxyphenyl)-3-(4"-nitrophenyl)-pyrrolidin-2-one (**143a**) (200 mg, 0.32 mmol) in acetonitrile (12.0 ml) at 0 °C. After stirring for 1 hour excess solid sodium sulfite was added. The solvent was then removed

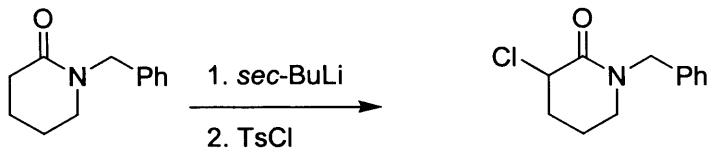
on a rotary evaporator. Ethyl acetate (20.0 ml) was then added to the organic residue. The solution was then washed with brine, dried over magnesium sulfate and the solvent removed on a rotary evaporator to leave the crude product (0.21 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.10 (silica, hexane:ethyl acetate; 1:1) to give the pure product (98 mg, 81%) as a yellow crystalline solid. M.p. 168-170 °C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2922 (s), 1676 (s), 1598 (m), 1528 (m), 1464 (s), 1377 (m), 1346 (s); δ_H(400 MHz; $CDCl_3$) 8.15 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 7.41 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 7.0 (1H, s, NH), 3.73 (1H, t, *J* 9.4 Hz, H-3), 3.41-3.46 (2H, m, H-5), 2.55-2.64 (1H, m, H-4α), 2.15-2.25 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 177.9.(s) (C=O), 147.5 (s) (C, Ar), 147.0 (s) (C, Ar), 129.5 (s) (2 × CH, Ar), 124.4 (s) (2 × CH, Ar), 47.7 (s) (CH), 41.0 (s) (CH_2), 30.8 (s) (CH_2); *m/z* (APCI) 207 [$(M+H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+) 207.0699 $C_{10}H_{10}N_2O_3$ requires $(M + H)^+$ 207.0691).

General Method for α-chlorination of Lactams—To a stirred solution of the lactam (31.26 mmol) in dry THF (30 ml) at –78 °C under an inert atmosphere was added *sec*-Buli (34.3 mmol) (1.4 M in cyclohexanes) and the reaction mixture was stirred for 30 minutes. *p*-Toluenesulfonyl chloride (50 mmol) dissolved in dry THF (25 ml) was added dropwise to the reaction mixture, which was then allowed to warm to room temperature. After stirring for 16 hours the resulting suspension was quenched with saturated ammonium chloride (100 ml) and the aqueous layer was washed with ethyl acetate (3 x 50 ml). The organic layers were combined, washed with water (50 ml), dried over Na_2SO_4, the solvent removed on a rotary evaporator to give the crude product.

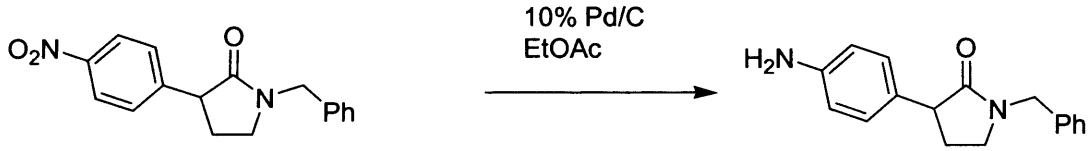


1-Methyl-3-chloro-pyrrolidin-2-one[220] **(150)**—This was prepared by the General Method using 1-methyl-2-pyrrolidinone (**104**) (3.0 ml, 31.26 mmol), *sec*-BuLi (25.0 ml, 35 mmol) (1.4 M in cyclohexanes), and *p*-toluenesulfonyl chloride (9.1 g, 50.1 mmol) to give the crude product as an orange oil. The crude product was then purified by column chromatography Rf 0.0.37 (silica, dichloromethane:ethyl acetate; 1:1) to give the pure product (2.09 g, 50%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 1698 (s), 1513 (m), 1344 (m); δ_H(400 MHz; $CDCl_3$) 4.29 (1H, dd, *J* 4.6 & 7.7 Hz, H-3), 3.40-3.51 (1H, m, H-5α), 3.22-3.33 (1H, m, H-5β), 2.81 (3H, s, CH_3), 2.42-2.60 (1H, m, H-4α), 2.06-2.21 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$)

169.1.(s) (C=O), 56.9 (s) (C-3), 48.4 (s) (N-CH_3), 47.8 (s) (C-5), 32.1 (s) (C-4); *m/z* (APCI) 134.0 [$(M+H)^+$, 100%].

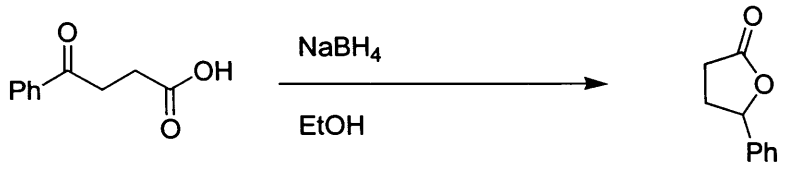


1-Benzyl-3-chloro-piperidin-2-one[142] **(149)**—This was prepared by the General Method using 1-benzyl-piperidin-2-one (**145**) (1.3 g, 6.87 mmol), *sec*-Buli (5.5 ml, 7.7 mmol) (1.4 M in cyclohexanes), and *p*-toluenesulfonyl chloride (2.0g, 11.0 mmol) to give the crude product as a yellow oil. The crude product was then purified by column chromatography Rf 0.10 (silica, hexane:ethyl acetate; 3:2) to give the pure product (0.58 g, 38%) as a yellow crystalline solid. M.p. 71-73 °C (lit. 72-73 °C)[142]; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2956 (s), 2240 (w), 1657 (s), 1493 (s), 1452 (s), 1353 (s), 1173 (s), 1079 (m), 951 (m); δ_H(400 MHz; $CDCl_3$) 7.12-7.24 (5H, m, Ph), 4.61 (1H, d, *J* 14.6 Hz, HCH-Ph), 4.40 (1H, t, *J* 4.4 Hz, H-3), 4.33 (1H, d, *J* 14.6 Hz, HCH-Ph), 3.08-3.19 (2H, m, H-6), 1.99-2.14 (3H, m, H-5 & H-4 α), 1.62-1.67 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 173.6.(s) (C=O), 136.9 (s) (C, Ar), 130.3 (s) (2 × CH, Ar), 129.0 (s) (2 × CH, Ar), 127.9 (s) (CH, Ar), 55.6 (s) (CH), 50.8 (s) (CH_2), 47.4 (s) (CH_2), 31.4 (s) (CH_2), 19.0 (s) (CH_2); *m/z* (APCI) 224.0 [$(M+H)^+$, 100%].

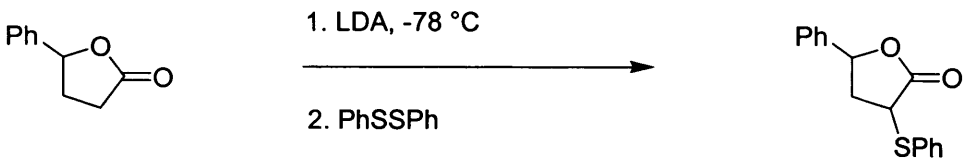


3-Methyl-1-benzyl-3-(4'-aminophenyl)pyrrolidin-2-one **(156)**—In a two necked round bottom flask was added 10% palladium on carbon (25 mg) and ethyl acetate (2 ml). The catalyst was activated by flushing with hydrogen 3 times. 3-Methyl-1-benzyl-3-(4'-nitrophenyl)-pyrroldinin-2-one (**138a**) was added to the flask. The mixture was flushed with hydrogen and then left to stir under hydrogen at atmospheric pressure for 24 hours. The reaction mixture was then filtered through celite and then reduced on a rotary evaporator to give the crude product (210 mg) as a brown oil. The crude product was then purified by column chromatography Rf 0.20 (silica, hexane: ethyl acetate 1:3) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3489 (s), 3410 (s), 2981 (s), 1691 (s); δ_H(400 MHz; $CDCl_3$) 7.07 (2H, d, *J* 8.4 Hz, H-2' & H-6'), 6.79-7.30 (5H, m, Ph), 6.64 (2H, d, *J* 8.4 Hz, H-3' & H-5'), 4.44 (2H, s, CH_2-Ph), 3.49 (2H, s, CH_3), 3.09-3.21 (2H, m, H-5), 2.23-2.29 (1H, m, H-4α), 2.03-2.11 (1H, m, H-4β), 1.52 (3H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 177.1 (s) (C=O), 149.2 (s) (C, Ar), 146.3 (s) (C, Ar), 135.7 (s) (C, Ar),

129.5 (s) (2 × CH, Ar), 128.3 (s) (CH, Ar), 128.0 (s) (2 × CH, Ar), 123.5 (s) (2 × CH, Ar), 119.8 (s) (2 × CH, Ar), 49.7 (s) (C, quaternary), 47.4 (s) (CH_2), 43.2 (s) (CH_2), 35.1 (s) (CH_2), 24.8 (s) (CH_3); *m/z* (APCI) 281.0 [$(M+H)^+$, 100%].



Dihydro-5-phenyl(3H)furan-2-one[221] **(160)**—3-Benzoylpropionic acid (2.0 g, 11.2 mmol) was dissolved in ethanol (50 ml). A solution of sodium borohydride (0.85 g, 22.4 mmol) in ethanol (25 ml) was slowly added at 0 °C. Following the addition the reaction mixture was stirred at room temperature for four hours. The reaction was followed by TLC. After acidification with 10% HCl most of the ethanol was removed on a rotary evaporator. The resulting mixture was cooled to room temperature and extracted with dichloromethane (3 × 50 ml). The dichloromethane was removed on a rotary evaporator to give the crude product (1.70 g) as a white solid. The product was then purified by column chromatography Rf 0.25 (silica, hexane:ethyl acetate 3:1) to give the pure product (1.39 g, 51%) as a white crystalline solid. M.p.35-37 °C (lit. 37-38 °C).[221] υ_{max} (nujol on NaCl plates/ cm^{-1}) 2921 (s), 1794 (s) (C=O), 1459 (s), 1376 (s), 1170 (m), 939 (w), 698 (w), δ_H(400 MHz; $CDCl_3$) 7.25-7.45 (5H, m, aromatic), 5.5, (1H, m, C<u>H</u>-O), 2.80 (3H, m, C<u>H</u>$_2$-C=O + HC<u>H</u>), 2.25 (1H, m, <u>H</u>CH), δ_C(400 MHz; $CDCl_3$) 177.0 (s) (C=O), 139.4 (s) (C, Ar), 128.8 (s) (2 × CH, Ar), 128.5 (s) (CH, Ar), 125.3 (s) (2 × CH, Ar), 81.2 (s) (Ph-<u>C</u>-O), 31.0 (s) (<u>C</u>-C=O), 29.0 (s) (CH_2-<u>C</u>H_2-CH) *m/z* (APCI) 162.9 [$(M + H)^+$, 100%].

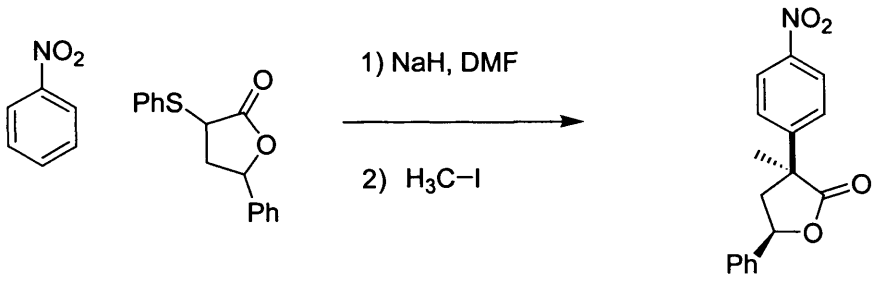


(3SR,5RS) & (3RS,5RS)-Dihydro-5-phenyl-3-(phenylthio)(3H)furan-2-one [171] **(161)**—To a solution of di-isopropylamine (0.33 ml, 2.35 mmol) in dry THF (10 ml) was added *n*-butyllithium (0.67 ml, 2.35 mmol) at –78 °C under nitrogen. The mixture was stirred for half an hour at this temperature. The lactone **166** (0.35 g, 2.35 mmol) was dissolved in dry THF (5 ml), cooled to –78 °C and added to the LDA solution. The reaction mixture was stirred at –78 °C for a further half hour. Phenyl disulfide (0.55 g, 2.56 mmol) was dissolved in dry THF (5

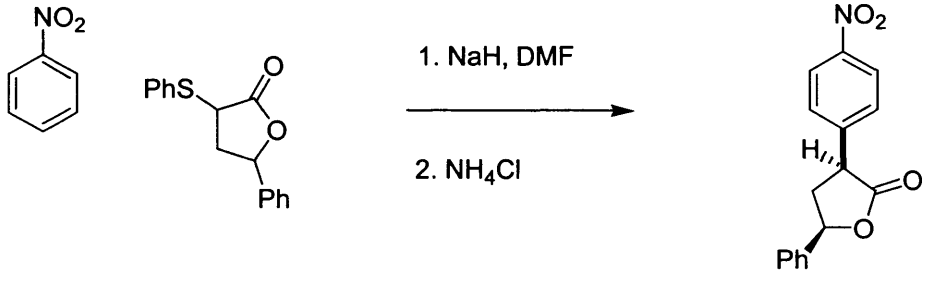
ml) at –78 °C and added dropwise to the reaction mixture. The mixture was stirred at –78 °C for three hours. The reaction was then quenched with saturated aqueous ammonium chloride (2 ml). The organic product was extracted with chloroform (3 × 25 ml) and washed with water (3 × 25 ml), sodium, bicarbonate (25 ml) and the solvent was dried (magnesium sulfate) and removed to give the crude product (0.63 g) as a yellow crystalline solid. The product was then purified by column chromatography (silica, hexane:ethyl acetate 3:1) to give the *cis* and *trans* products (0.40 g, 70% overall yield). *Cis*-**161** (0.24 g) as a white crystalline solid: Rf (Hexane:Ethyl acetate 3:1) 0.28, M.p. 92-94 °C (lit. 94 °C)[171] ; υ_{max} (nujol; NaCl plates/ cm^{-1}) 2926 (s), 1772 (s), 1457 (m), 1376 (w), 1176 (m), 1017 (m), 940 (m), 756 (m); δ_H(400 MHz; $CDCl_3$) 7.48-7.51 (2H, m. aromatic), 7.26-7.35 (6H, m, aromatic), 7.05-7.08 (2H, m, aromatic), 5.30 (1H, dd, *J* 10.0 & 6.1 Hz, H-5), 4.08 (1H, dd, *J* 11.5 & 8.7 Hz, H-3), 2.97 (1H, ddd, *J* 13.4, 8.9 & 6.3 Hz, H-4α), 2.20 (1H, ddd, *J* 13.4, 11.5 & 10.1 Hz, H-4β); δ_C(400 MHz; $CDCl_3$) 174.5 (s) (C=O), 138.5 (s) (C, Ar), 134.5 (s)(C, Ar), 132.0 (s) (C, Ar), 129.5 (s) (C, Ar), 129.0 (s) (C, Ar), 128.5 (s) (C, Ar), 126.5 (s) (C, Ar) 126.0 (s) (C, Ar), 79.0 (s) (C-O), 47.0 (s) (C-S), 39.0 (s) (CH_2) *m/z* (APCI) 271.0 [$(M+H)^+$, 100%]; *Trans*-**161** (0.16 g) as a white crystalline solid: Rf (Hexane:ethyl acetate) 0.32, M.p. 80-81 °C (lit. 81-82 °C)[250]; υ_{max} (nujol; NaCl plates/ cm^{-1}) 2928 (s), 1769 (s), 1460 (m), 1372 (w), 1177 (m), 1020 (m), 755 (m); δ_H(400 MHz; $CDCl_3$) 7.49-7.51 (2H, m, aromatic), 7.20-7.35 (8H, m, aromatic), 5.39 (1H, t, *J* 7.6 Hz, H-5), 3.96 (1H, dd, *J* 8.0 & 4.2 Hz, H-3), 2.56 (2H, m, H-4α & H-4β); δ_C(400 MHz; $CDCl_3$) 174.0 (s) (C=O), 137.5 (s) (C, Ar), 133.0 (s) (C, Ar), 131.0 (s) (C, Ar), 129.0 (s) (C, Ar), 128.0 (s) (C, Ar), 127.5 (s) (C, Ar), 124.5 (s) (C, Ar), 78.5 (s) (C-O), 44.0 (s) (C-S), 37.5 (s) (CH_2); *m/z* (APCI) 271 [$(M+H)^+$, 100%].

General Method for Asymmetric VNS—Sodium hydride (60% dispersion in oil) (4.6 mmol) was added to anhydrous DMF (3 ml) and the mixture flushed with nitrogen and cooled to 0 °C. The thiophenylated lactone 167 (4.6 mmol) and nitrobenzene (4.6 mmol) were dissolved in anhydrous DMF (5 ml) and added dropwise to the sodium hydride slurry. The reaction was stirred at 0 °C for thirty minutes before being allowed to warm to room temperature and stirred at this temperature for two hours. The reaction was then cooled to –50 °C using a methanol/cardice cooling bath. The electrophile (9.2 mmol) was added to the solution. The solution was then allowed to warm to room temperature and stirred at this temperature for two hours. The reaction mixture was poured onto ice/hydrochloric acid (1 M solution) (50 ml). The product was then extracted with dichloromethane (5 × 50 ml) and then washed with water

(5 × 50 ml), sodium bicarbonate (3 × 50 ml) and dried (sodium sulfate). The solvent was removed on a rotary evaporator to give the crude product.

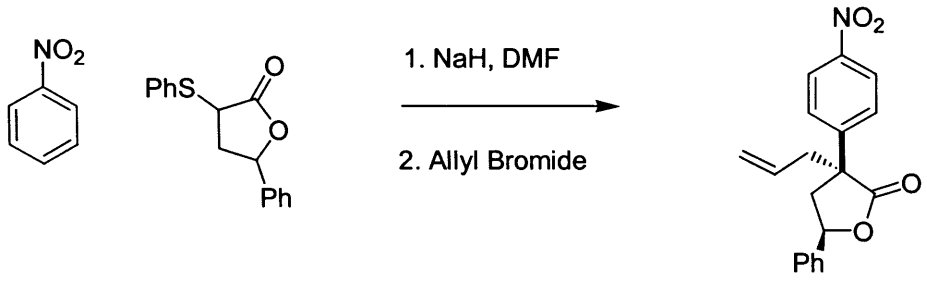


(3SR,5RS)-3-Methyl-3-(4'-nitrophenyl)-5-phenyldihydro(3H)furan-2-one **(162)**—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone **161** (0.50 g, 1.85 mmol), nitrobenzene (0.20 ml, 1.85 mmol) and iodomethane (0.24 ml, 3.7 mmol) to give the crude product (0.62 g) an orange oil. The crude product was purified using column chromatography (silica, hexane:ethyl acetate 3:1 Rf 0.20) to give the pure product (0.41g, 73%) as a white crystalline solid. M.p. 122-124 °C; (Found C, 68.8; H, 4.9; N 4.8% $C_{17}H_{15}NO_4$ requires C, 68.7; H, 5.1; N, 4.7%); υ_{max} (nujol on NaCl plates/ cm^{-1}) 2918 (m), 1758 (s) (C=O), 1344 (m), 1177 (m), 848 (m), 732 (m), 694 (m), δ_H (400 MHz; $CDCl_3$), 8.21 (2H, d, *J* 8.9 Hz, H-3' and H-5'), 7.71 (2H, d, *J* 8.9 Hz, H-2' and H-6'), 7.33-7.41 (5H, m, Ph), 5.65 (1H, dd, *J* 9.9 & 6.1 Hz, H-5), 2.89 (1H, dd, *J* 13.0 & 6.1 Hz, H-4α), 2.63 (1H, dd, *J* 13.0 & 9.9 Hz, H-4β), 1.79 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$), 178.5 (s) (C=O), 149.5 (s) N(C, Ar), 147.4 (s) (C, Ar), 138.7 (s) (C, Ar), 129.3 (s) (2 × CH, Ar), 129.2 (s) (CH, Ar), 127.8 (s) (2 × CH, Ar), 125.8 (s) (2 × CH, Ar), 124.2 (s) (2 × CH, Ar), 78.4 (s) (C-5), 49.0 (s) (C-3), 46.6 (s) (CH_2), 25.6 (s) (CH_3); *m/z* (APCI) 298.0 [$(M + H)^+$, 100 %], 282.0 (24), 252.0 (24), 220.9 (7), 219.9 (62), 192.0 (8), 79.2 (9); (Found: $(M + NH_4)^+$ (ES^+), 315.1348. $C_{17}H_{15}NO_4$ requires $(M + NH_4)^+$ 315.1345).



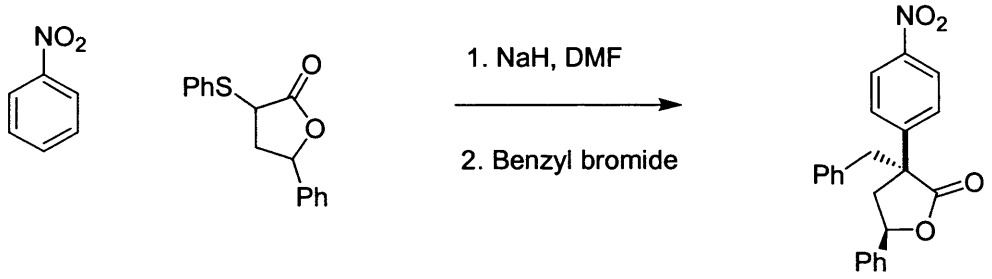
(3SR,5RS)-Dihydro-3-(4'-nitrophenyl)-5-phenyl(3H)furan-2-one **(162a)**—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone

161 (0.50 g, 1.85 mmol), nitrobenzene (0.20 ml, 1.85 mmol) and saturated aqueous ammonium chloride (2.0 ml) to give the crude product (0.94 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.28 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.41 g, 73%) as a white crystalline solid. M.p. 117-119 °C; (Found C, 67.93; H, 4.87; N 4.86%. $C_{16}H_{13}NO_4$ requires C, 67.8; H, 4.6; N, 4.9%); υ_{max} (nujol on NaCl plates/ cm^{-1}) 2917 (m), 1759 (s) (C=O), 1367 (m), 1321 (w), 1172 (m), 907 (m), 848 (m), 732 (m); δ_H(400 MHz; $CDCl_3$) 8.16 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 7.46 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 7.27-7.38 (5H, m, Ph), 5.50 (1H, dd, *J* 10.7 & 5.5 Hz, H-5), 4.11 (1H, dd, *J* 12.8 & 8.4 Hz, H-3), 3.03-3.10 (1H, m, H-4α), 2.30-2.39 (1H, m, H-4β); δ_C (100 MHz; $CDCl_3$), 177.7 (s) (C=O), 149.2 (s) (C, Ar), 147.7 (s) (C, Ar), 138.9 (s) (C, Ar), 129.3 (s) (2 × CH, Ar), 129.0 (s) (CH, Ar), 127.9 (s) (2 × CH, Ar), 125.7 (s) (2 × CH, Ar), 124.3 (s) (2 × CH, Ar), 78.7 (s) (C-5), 50.9 (s) (C-3), 46.4 (s) (C-4); *m/z* (APCI) 284.0 [$(M + H)^+$, 100 %]; (Found: $(M + H)^+$ (APCI) 283.0846 $C_{16}H_{13}NO_4$ requires $(M + H)^+$ 283.0845.

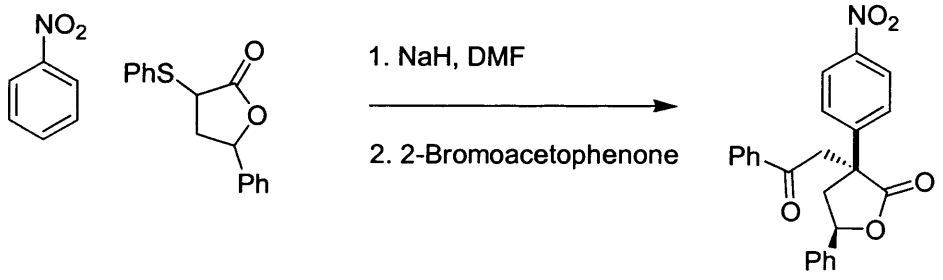


(3SR,5RS)-3-Allyl-3-(4'-nitrophenyl)-5-phenyldihydro(3H)furan-2-one **(162b)**—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone **161** (0.50 g, 1.85 mmol), nitrobenzene (0.20 ml, 1.85 mmol) and allyl bromide (0.16 ml, 1.85 mmol) to give the crude product (1.0 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.28 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.41 g, 67%) as a white crystalline solid. M.p. 124-126 °C; (Found C, 70.71; H, 5.22; N 4.03. $C_{19}H_{17}NO_4$ requires C, 70.6; H, 5.3; N, 4.3%); υ_{max} (nujol on NaCl plates/ cm^{-1}) 2919 (m), 1760 (s) (C=O), 1341 (m), 1173 (m), 840 (m); δ_H (400 MHz; $CDCl_3$) 8.12 (2H, d, *J* 9.0 Hz, H-3' & H-5'), 7.67 (2H, d, *J* 9.0 Hz, H-2' & H-6'), 7.21 (5H, m, Ph), 5.49-5.68 (2H, m, H-4 & -C<u>H</u>=CH_2), 5.09-5.17 (2H, m, $C\underline{H}_2$=CH-), 2.98 (1H, dd, *J* 6.7 & 13.2 Hz, H-3α), 2.73 (2H, d, *J* 7.40 Hz, -$C\underline{H}_2$-CH=CH_2), 2.55 (1H, dd, *J* 9.2 & 13.2 Hz, H-3β); δ_C (100 MHz; $CDCl_3$) 177.0 (s) (C=O), 147.4 (s) (C, Ar), 147.0 (s) (C, Ar), 138.6 (s) (C, Ar), 128.9 (s) (CH), 128.8 (s) (2 × CH, Ar), 127.8 (s) (2 × CH, Ar), 125.9 (s) (C, Ar), 125.3 (s) (2 × CH, Ar), 123.5 (s) (2 × CH, Ar), 121.1 (s) (CH_2), 77.8 (s) (C-5), 51.9 (s) (C, quaternary), 43.7 (s) (CH_2), 42.0 (s)

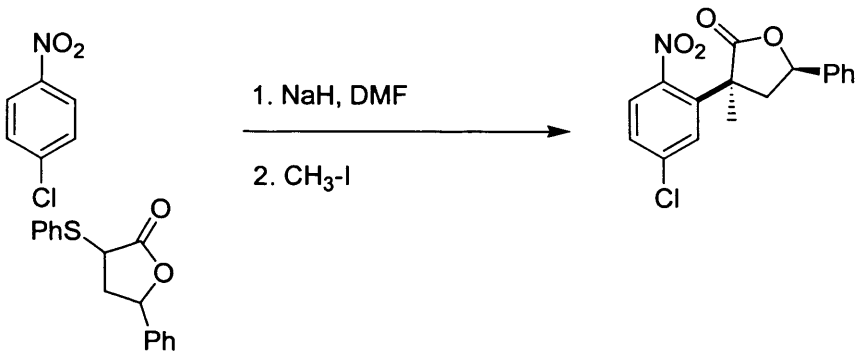
(CH_2); *m/z* (APCI) 324.0 [$(M + H)^+$, 100%], 296.0 (19), 279.0 (9), 105.1 (5), 71.4 (4); (Found: $(M + H)^+$ (APCI), 324.1236 $C_{19}H_{17}NO_4$ requires $(M + H)^+$ 324.1236).



(3SR,5RS)-3-Benzyl-3-(4'-nitrophenyl)-5-phenyldihydro(3H)furan-2-one **(162c)**—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone **161** (0.50 g, 1.85 mmol), nitrobenzene (0.20 ml, 1.85 mmol) and benzyl bromide (0.32 g, 1.85 mmol) to give the crude product (0.95 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.46 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.34 g, 65%) as a white crystalline solid. M.p. 139-141 °C; (Found C, 74.17; H, 5.23; N 3.60%. $C_{23}H_{19}NO_4$ requires C, 74.0; H, 5.1; N, 3.75%); υ_{max} (nujol on NaCl plates/ cm^{-1}) 2918 (s), 1759 (s) (C=O), 1671 (w), 1595 (m), 1501 (w), 1462 (s), 1373 (m), 1353 (m); δ_H (400 MHz; $CDCl_3$) 8.19 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 7.69 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 7.19-7.45 (10H, m, Ph), 5.58 (1H, dd, *J* 10.0 & 6.2 Hz, H-5), 3.63 (1H, d, *J* 13.2 Hz, HCH-Ph), 3.16 (1H, d, *J* 13.2 Hz, HCH-Ph), 2.94 (1H, dd, *J* 7.4 & 14.1 Hz, H-4α), 2.48 (1H, dd, *J* 9.0 & 14.1 Hz, H-4β); δ_C (100 MHz; $CDCl_3$) 178.1 (s) (C=O), 149.0 (s) (C, Ar), 147.6 (s) (C, Ar), 140.2 (s) (C, Ar), 138.9 (s) (C, Ar), 129.7 (s) (2 × CH, Ar), 129.3 (s) (CH, Ar), 127.7 (s) (2 × CH, Ar), 125.5 (s) (2 × CH, Ar), 125.3 (s) (CH, Ar), 125.0 (s) (2 × CH, Ar), 124.3 (s) (2 × CH, Ar), 123.6 (s) (2 × CH, Ar), 78.0 (s) (C-5), 48.7 (s) (C-3), 46.1 (s) (CH_2), 44.7 (s) (CH_2); *m/z* (APCI) 374.0 [$(M + H)^+$, 100 %]; (Found: $(M + H)^+$ (APCI) 373.1316 $C_{23}H_{19}NO_4$ requires $(M + H)^+$ 373.1314).



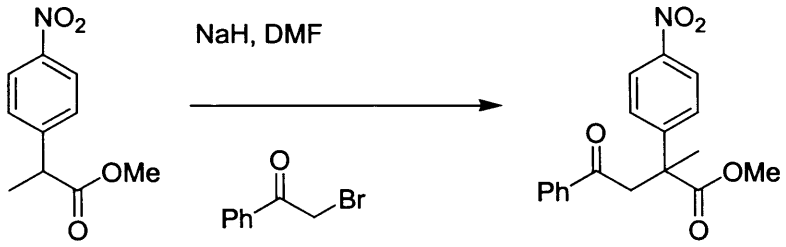
(3SR,5RS)-3-(2-oxo-2-phenylethyl)-3-(4'-nitrophenyl)-5-phenyldihydro(3H)furan-2-one (**162d**)—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone **161** (0.50 g, 1.85 mmol), nitrobenzene (0.20 ml, 1.85 mmol) and 2-bromoacetophenone (0.37 g, 1.85 mmol) to give the crude product (1.2 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.42 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.41 g, 67%) as a white crystalline solid. M.p. 152-154 °C; υ_{max} (nujol on NaCl plates/ cm^{-1}) 2918 (s), 1765 (s) (C=O), 1673 (m), 1596 (m), 1510 (m), 1462 (s), 1377 (m), 1348 (m), 1203 (w); δ_H(400 MHz; $CDCl_3$) 8.05 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.84 (2H, app. d, *J* 8.0 Hz, Ph), 7.61 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.53 (1H, app. t, *J* 7.3 Hz, Ph), 7.39 (2H, app. t, *J* 7.8 Hz, Ph), 7.17-7.24 (3H, m, Ph), 7.08-7.14 (2H, m, Ph), 5.83 (1H, dd, *J* 5.8 & 8.4 Hz, H-5), 3.81 (1H, d, *J* 18.1 Hz, HCH), 3.65 (1H, d, *J* 18.1 Hz, HCH), 3.29 (1H, dd, *J* 8.5 & 13.6 Hz, H-4α), 2.81 (1H, dd, *J* 5.8 & 13.6 Hz, H-4β); δ_C (100 MHz; $CDCl_3$) 196.4 (s) (C=O), 178.0 (s) (C=O), 148.5 (s) (C, Ar), 147.4 (s) (C, Ar), 140.0 (s) (C, Ar), 136.2 (s) (C, Ar), 134.5 (s) (CH, Ar), 129.3 (s) (2 × CH, Ar), 129.1 (s) (2 × CH, Ar), 128.7 (s) (CH, Ar), 128.5 (s) (2 × CH, Ar), 128.1 (s) (2 × CH, Ar), 125.5 (s) (2 × CH, Ar), 124.2 (s) (2 × CH, Ar), 78.8 (s) (C-5), 50.1 (s) (C, quaternary), 48.5 (s) (CH_2), 42.1 (s) (CH_2); *m/z* (ES^+) 402.0 [$(M + H)^+$, 100%]; (Found: $(M + H)^+$ (ES^+), 402.1337. $C_{24}H_{19}NO_5$ requires $(M + H)^+$ 402.1335).



(3SR,5RS)-3-Methyl-3-(5'-chloro-2'-nitrophenyl)-5-phenyldihydro(3H)furan-2-one (**173**)—This was prepared by the General Method using sodium hydride (0.19 g, 4.6 mmol), the thiophenylated lactone **161** (0.50 g, 1.85 mmol), 4-chloronitrobenzene (0.29 g, 1.85 mmol) and methyl iodide (0.25 ml, 1.85 mmol) to give the crude product (1.2 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.37 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.28 g, 51%) as a white crystalline solid. M.p. 179-181 °C; (Found C, 61.65; H, 4.30; N 4.19%. $C_{17}H_{14}ClNO_4$ requires C, 61.55; H, 4.25; N, 4.22%); υ_{max} (nujol on NaCl plates/ cm^{-1}) 2918 (s), 1762 (s) (C=O), 1666 (w), 1592 (m), 1496 (w);

δ_H(400 MHz; $CDCl_3$) 8.35 (1H, d, *J* 8.9 Hz, H-3'), 8.01 (1H, d, *J* 1.1 Hz, H-6'), 7.89 (1H, dd, *J* 1.1 & 8.9Hz, H-4'), 7.31-7.45 (5H, m, Ph), 5.29 (1H, dd, *J* 9.2 & 6.8 Hz, H-5), 2.69 (1H, dd, *J* 13.6 & 6.8 Hz, H-4α), 2.49 (1H, dd, *J* 13.6 & 9.2 Hz, H-4β), 1.69 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$), 174.6 (s) (C=O), 148.1 (s) (C, Ar), 139.9 (s) (C, Ar), 138.2 (s) (C, Ar), 136.9 (s) (C, Ar), 129.9 (s) (CH, Ar), 129.1 (s) (CH, Ar), 127.9 (s) (CH, Ar), 125.3 (s) (2 × CH, Ar), 124.0 (s) (2 × CH, Ar), 122.8 (s) (CH, Ar), 80.4 (s) (C-5), 49.8 (s) (C-3), 44.6 (s) (CH_2), 23.6 (s) (CH_3); *m/z* (APCI) 332.0 [$(M + H)^+$, 100%]; (Found: $(M + H)^+$ (APCI), 336.0614. $C_{17}H_{14}ClNO_4$ requires $(M + H)^+$ 331.0611).

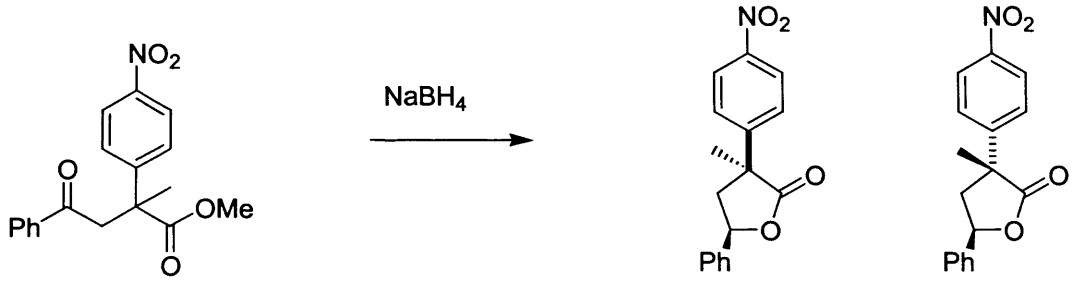
General Method for Alkylation of Nitrophenylacetates/propionates—Sodium hydride (60% dispersion in oil) (1 eq.) was added to anhydrous DMF and the mixture flushed with nitrogen and cooled to 0 °C. Methyl 4-nitrophenyl propionate (**173**) (24.4 mmol) dissolved in DMF (20 ml) was then added and the solution was stirred at 0 °C for one hour. The electrophile (24.4 mmol) dissolved in DMF (10 ml) was added dropwise to the solution at –50 °C. The solution was then allowed to warm to room temperature and stirred for a further two hours. The reaction mixture was then poured onto ice/hydrochloric acid (1M solution) and extracted with dichloromethane (3 × 50 ml). The combined organic extracts were washed well with water (5 × 50 ml), sodium bicarbonate (3 × 50 ml), dried (sodium sulfate) and the solvent removed on a rotary evaporator to give the crude product.



Methyl (2-methyl-2-(4'-nitrophenyl)-4-oxo-4-pheny)butyrate (**165**)—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.98 g, 24.4 mmol, methyl 4-nitrophenylpropionate (**164**) (5.1 g, 24.4 mmol) and 2-bromoacetophenone (4.86 g, 24.4 mmol) to give the crude product (5.6 g) as an orange crystalline solid. The crude product was recrystallized from ethanol to give the pure product (5.2 g, 65%) as a yellow crystalline solid. R.f. 0.40 (silica, 3:1 hexane:ethyl acetate). M.p.134-136 °C; (Found C, 66.61; H, 4.5.32; N 4.11%. $C_{18}H_{17}NO_5$ requires C, 66.1; H, 5.2; N, 4.3%); υ_{max} (nujol, NaCl plates/ cm^{-1}) 2974 (s), 1726 (C=O) (m), 1684 (C=O) (m), 1596 (m), 1460, 1377 (m), 854 (m). δ_H(400 MHz; $CDCl_3$) 8.19 (2H, d, *J* 9.0 Hz, H-3' & H-5'), 7.95 (2H, app. d, *J* 7.6 Hz, aromatic), 7.57-7.63 (3H, m,

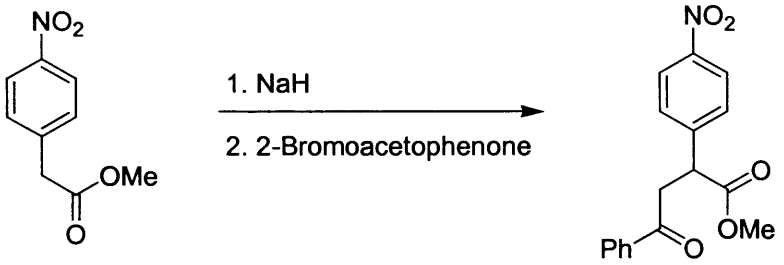
aromatic), 7.45 (2H, app. t, *J* 7.6 Hz, aromatic), 3.92 (1H, d, *J* 17.8 Hz, HCH), 3.74 (3H, s, OCH_3) 3.65 (1H, d, *J* 17.8 Hz, HCH), 1.85 (3H, s, CH_3). δ_C(400 MHz; $CDCl_3$) 196.3 (s) (C=O), 174.7 (s) (C=O), 150.4 (s) (C, Ar), 146.9 (s) (C, Ar), 136.5 (s) (C, Ar), 133.6 (s) (CH, Ar), 128.7 (s) (2 × CH, Ar), 128.0 (s) (2 × CH, Ar), 127.1 (s) (2 × CH, Ar), 123.8 (s) (2 × CH, Ar), 52.7 (s) (O-CH_3), 48.3 (s) (C, quaternary), 47.7 (s) (CH_2), 23.6 (s) (CH_3). *m/z* (APCI) 328.0 [$(M + H)^+$, 100 %], 296.0 (58), 279.0 (11), 263.0 (3), 105.1 (18); (Found: $(M + H)^+$ (ES^+), 328.1187. $C_{18}H_{17}NO_5$ requires $(M + H)^+$ 328.1185).

General Method for Reduction of Ketones—The ester (1.53 mmol) was dissolved in chloroform (10 ml). A solution of sodium borohydride (3.06 mmol) in methanol (10 ml) was slowly added to the solution at 0 °C. Following the addition the reaction mixture was stirred at room temperature for four hours. The reaction was monitored by TLC. After acidification with 10% hydrochloric acid most of the methanol was removed on a rotary evaporator. The resulting mixture was cooled to room temperature and extracted with dichloromethane (3 × 25 ml). The dichloromethane was washed with water (3 × 20 ml), sodium bicarbonate (20 ml) and dried (sodium sulfate) to give the crude product.

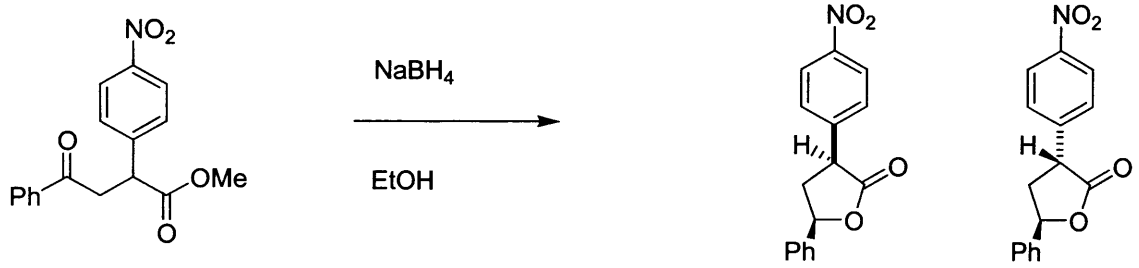


(3SR,5RS) & (3RS,5RS)-3-Methyl-3-(4'-nitrophenyl)-5-phenyldihydro(3H)furan-2-one (**162**)—This was prepared by the General Method using methyl (2-methyl-2-(4'-nitrophenyl)-4-oxo-4-pheny)butyrate (**165**) (1.00 g, 3.06 mmol) and sodium borohydride (232 mg, 6.12 mmol) to give the crude product (0.83 g, 83%) as a 1:1 mixture of the two diastereoisomers. The two diastereoisomers were then separated by column chromatography (silica, 3:1, hexane: ethyl acetate, v/v).*Cis* isomer (0.41 g): Rf 0.28 (silica, hexane:ethyl acetate 3:1); M.p. 129-132 °C; (Found C, 68.55; H, 4.99; N 4.88, $C_{17}H_{15}NO_4$ requires C, 68.7; H, 5.1; N, 4.7%); υ_{max} (nujol on NaCl plates/ cm^{-1}) 2920 (m), 1761 (s) (C=O), 1343(m), 1178 (m), 848 (m), 731 (m); δ_H(400 MHz; $CDCl_3$) 8.15 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 7.67 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 7.31-7.41 (5H, m, aromatic), 5.17 (1H, dd, *J* 5.4 & 10.6 Hz, H-5), 3.08 (1H, dd, *J* 5.4 & 13.3 Hz, H-4α), 2.46 (2H, dd, *J* 10.7 & 13.3 Hz, H-4β), 1.69 (3H, s, CH_3); δ_C (400 MHz;

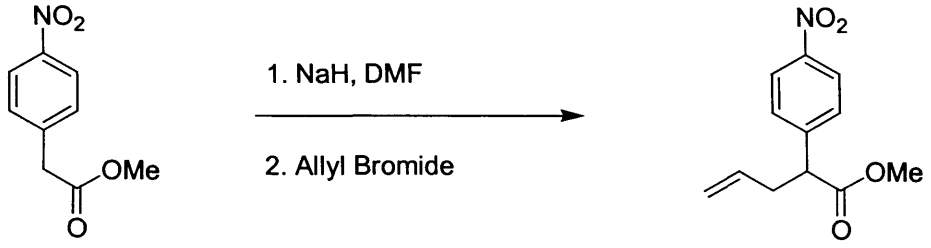
$CDCl_3$) 178.0 (s) (C=O), 149.1 (s) (C, Ar), 146.9 (s) (C, Ar), 138.2 (s) (C, Ar), 128.9 (s) (2 × CH, Ar), 128.8 (s) (CH, Ar), 127.1 (s) (2 × CH, Ar), 125.5 (s) (2 × CH, Ar), 124.3 (s) (2 × CH, Ar), 78.0 (s) (HC-O), 50.5 (s) (C, quaternary), 46.4 (s) (CH_2), 26.4 (s) (CH_3); *m/z* (APCI) 298.0 [$(M + H)^+$, 100 %], (Found: $(M + NH_4)^+$ (ES^+), 315.1348. $C_{17}H_{15}NO_4$ requires $(M + NH_4)^+$ 315.1345).



Methyl (2-(4'-nitrophenyl)-4-oxo-4-phenyl)butyrate **(168)**—This was prepared by the General Method using sodium hydride (1.03 g, 25.62 mmol), methyl 4-nitrophenylacetate (**167**) (5.0 g, 25.62 mmol) and 2-bromoacetophenone (5.10 g, 25.62 mmol) to give the crude product (7.9 g) as a yellow crystalline solid. The crude product recrystallised from hot ethanol to give the pure product as a yellow crystalline solid (6.05 g, 75%). M.p. 161-163 °C; υ_{max} (nujol on NaCl plates/ cm^{-1}) 2926 (s), 1725 (s) (C=O), 1681 (s) (C=O), 1594 (m), 1519 (s), 1462 (s), 1377 (m), 1348 (m), 1259 (m), 1234 (m), 1205 (m), 1163 (m), 1110 (m), 997 (m), 964 (m), 866 (m), 834 (m), 762 (m), 736 (m), 690 (m); δ_H(400 MHz; $CDCl_3$) 8.22 (2H, d, *J* 8.7 Hz, H-3' & H-5'), 7.97 (2H, d, *J* 8.7 Hz, H-2' & H-6'), 7.41-7.61 (5H, m, Ph), 4.44 (1H, dd, *J* 5.0 & 9.4 Hz, CH), 3.95 (1H, dd, *J* 9.4 & 18.0 Hz, HCH), 3.72 (3H, s, OCH_3), 3.36 (1H, dd, *J* 5.0 & 18.0 Hz, HCH); δ_C(400 MHz; $CDCl_3$) 196.7 (s) (C=O), 172.7 (s) (O-C=O), 148.0 (s) (C, Ar), 145.6 (s) (C, Ar), 136.0 (s) (C, Ar) 133.7 (s) (CH, Ar), 129.0 (s) (2 × CH, Ar), 128.7 (s) (2 × CH, Ar), 128.1 (s) (2 × CH, Ar), 124.1 (s) (2 × CH, Ar), 52.8 (s) (C-O), 46.2 (s) (Ph-CH), 42.2 (s) (CH_2); *m/z* (APCI) 314.0 [$(M + H)^+$, 100 %], 283.0 (2), 282.0 (42), 60.4 (8) (Found: $(M + H)^+$ (ES^+), 314.0953. $C_{17}H_{15}NO_5$ requires $(M + H)^+$ 314.0950).

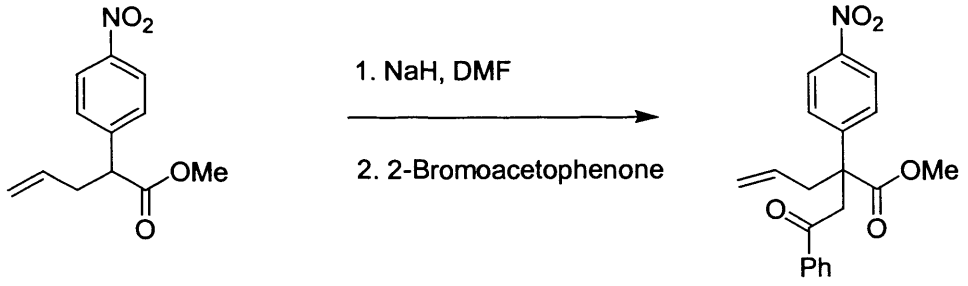


(3SR,5RS) & (3RS,5RS)-3-(4'-Nitrophenyl)-5-phenyldihydro(3H)furan-2-one **(162a)**—This was prepared by the General Method using sodium borohydride (60 mg, 1.60 mmol), 2-(4'-nitrophenyl)-4-oxo-4-phenyl butyric acid methyl ester (**168**) (0.50 g, 1.60 mmol), ethanol (20 ml) and chloroform (10 ml) to give the crude product as a 1:1 mixture of diastereoisomers (0.63 g) as a yellow oil. *Trans*-**162a**: M.p. 117-119 °C; (Found C, 67.93; H, 4.87; N 4.86%. $C_{16}H_{13}NO_4$ requires C, 67.8; H, 4.6; N, 4.9%); υ_{max} (nujol on NaCl plates/ cm^{-1}) 2917 (m), 1759 (s) (C=O), 1367 (m), 1321 (w), 1172 (m), 907 (m), 848 (m), 732 (m); δ_H(400 MHz; $CDCl_3$) 8.16 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 7.46 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 7.27- 7.38 (5H, m, Ph), 5.50 (1H, dd, *J* 10.7 & 5.5 Hz, H-5), 4.11 (1H, dd, *J* 12.8 & 8.4 Hz, H-3), 3.03-3.10 (1H, m, H-4α), 2.30-2.39 (1H, m, H-4β); δ_C (100 MHz; $CDCl_3$), 177.7 (s) (C=O), 149.2 (s) (C, Ar), 147.7 (s) (C, Ar), 138.9 (s) (C, Ar), 129.3 (s) (2 × CH, Ar), 129.0 (s) (CH, Ar), 127.9 (s) (2 × CH, Ar), 125.7 (s) (2 × CH, Ar), 124.3 (s) (2 × CH, Ar), 78.7 (s) (C-5), 50.9 (s) (C-3), 46.4 (s) (C-4); *m/z* (APCI) 284.0 [$(M + H)^+$, 100 %]; (Found: $(M + H)^+$ (APCI) 283.0846 $C_{16}H_{13}NO_4$ requires $(M + H)^+$ 283.0845. It was not possible to isolate the *cis* diastereoisomer from the crude products.

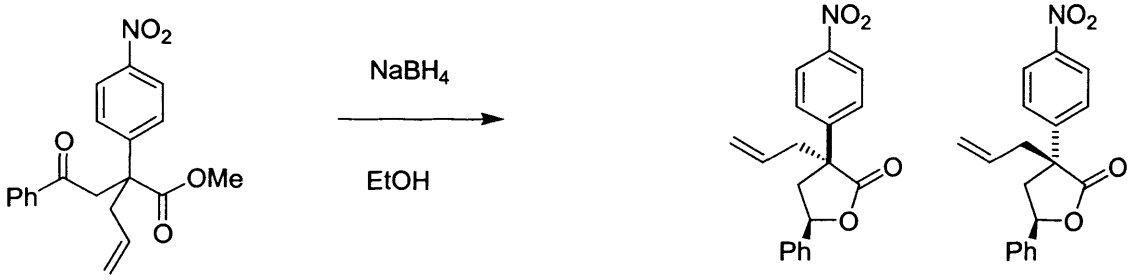


Methyl (2-(4'-nitrophenyl)pent-4-enoate[222] **(168)**—This was prepared by the General Method using sodium hydride (0.14 g, 10.3 mmol), methyl 4-nitrophenylacetate (**167**) (2.0 g, 10.3 mmol) and allyl bromide (0.89 ml, 10.3 mmol) to give the crude product (2.98 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.30 (silica, hexane:ethyl acetate; 3:1) to give the pure product (2.25 g, 93%) as a yellow oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 2925 (s), 1736 (s) (C=O), 1685 (s) (C=C), 1596 (s), 1518 (s), 1461 (s), 1376 (s), 1344 (s), 1254 (m), 1168 (s), 1110 (m), 1053 (m); δ_H(400 MHz; $CDCl_3$) 8.18 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.49 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 5.63-5.73 (1H, m, H_2C=C<u>H</u>-), 5.01-5.09 (2H, m, H_2C=C), 3.78 (1H, t, *J* 7.7 Hz, C<u>H</u>-Ar), 3.69 (3H, s, OC<u>H</u>$_3$), 2.82-2.90 (1H, m, HC<u>H</u>-C-Ar), 2.51-2.58 (1H, m, <u>H</u>CH-C-Ar); δ_C (100 MHz; $CDCl_3$) 173.0 (s) (C=O), 147.6 (s) (C, Ar), 146.1 (s) (C, Ar), 134.5 (s) (CH), 129.4 (s) (2 × CH, Ar), 124.2 (s) (2 × CH, Ar), 118.3

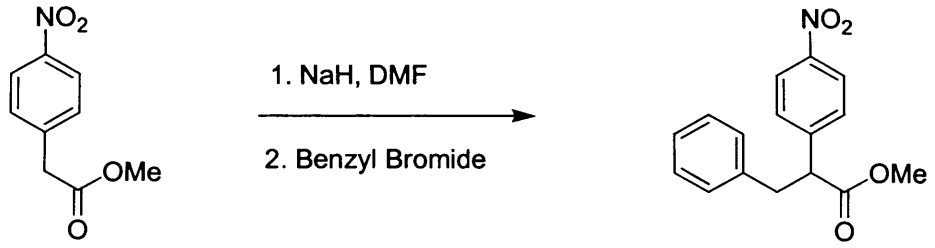
(s) (CH_2), 52.7 (s) (CH, Ar), 51.5 (s) (O-CH_3), 37.8 (s) (CH_2); *m/z* (APCI) 236.0 [$(M + H)^+$, 100 %], 209.9 (8), 175.9 (16), 73.3 (7).



Methyl (2-(4-nitrophenyl)-2-(2-oxo-2-phenyl-ethyl)pent-4-enoate **(169)**—This was prepared by the General Method using sodium hydride (0.08 g, 2.13 mmol), methyl ester **168** (0.5 g, 2.13 mmol) and 2-bromoacetophenone (0.42 g, 2.13 mmol) to give the crude product (0.74 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.30 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.65 g, 86%) as a yellow crystalline solid. M.p. 152-154 °C; υ_{max} (nujol on NaCl plates/ cm^{-1}) 3080 (s), 2952 (s), 2854 (m), 2455 (m), 1931 (m), 1737 (s), 1642 (s), 1604 (s), 1517 (s), 1435 (s), 1435 (s), 1109 (s), 995 (s); δ_H(400 MHz; $CDCl_3$) 8.16 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.89 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.49-7.55 (3H, m, Ph), 7.41 (2H, app. t, *J* 7.9 Hz, Ph), 5.28-5.36 (1H, m, H_2C=C<u>H</u>-), 4.85-4.93 (2H, m, <u>H_2</u>C=), 3.82 (1H, d, *J* 18.0 Hz, O=C-<u>H</u>CH), 3.74 (1H, d, *J* 18.0 Hz, O=C-HC<u>H</u>), 3.63 (3H, s, OCH_3), 2.94-3.07 (2H, m, H_2C=CH-C<u>H_2</u>-); δ_C(100 MHz; $CDCl_3$) 196.5 (s) (C=O), 174.1 (s) (C=O), 148.5 (s) (C, Ar), 146.9 (s) (C, Ar), 136.6 (s) (C, Ar) 134.0 (s) (CH), 132.6 (s) (CH), 128.9 (s) (2 × CH, Ar) 128.2 (s) (2 × CH, Ar) 127.6 (s) (2 × CH, Ar), 123.7 (s) (2 × CH, Ar), 120.0 (s) (CH_2), 54.1 (s) (O-CH_3), 51.6 (s) (C, quaternary), 42.5 (s) (CH_2), 40.5 (s) (CH_2); *m/z* (APCI) 354.0 [$(M + H)^+$, 100 %], 322 (88); (Found: $(M + NH_4)^+$ (ES^+) 371.1611 $C_{20}H_{19}NO_5$ requires $(M + NH_4)^+$ 371.1607).

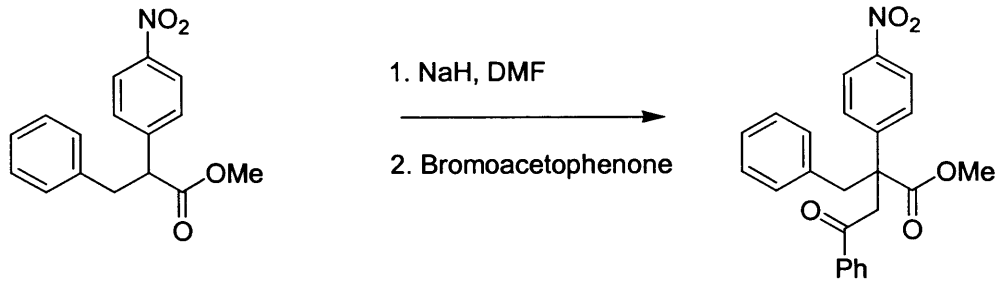


(3SR,5RS) & (3RS,5RS)-3-Allyl-3-(4'-nitrophenyl)-5-phenyldihydro(3H)furan-2-one (**162b**)—This was prepared by the General Method using sodium borohydride (80 mg, 2.17 mmol), methyl (2-(4-nitrophenyl)-2-(2-oxo-2-phenylethyl))pent-4-enoate (**169**) (0.64 g, 2.17 mmol), ethanol (10 ml) and chloroform (5 ml) to give the crude product as a 1:1 mixture of diastereoisomers (0.60 g) as an orange oil. The two diastereoisomers were then separated by column chromatography (silica, 3:1, hexane: ethyl acetate, v/v) (62% overall yield). *Cis* isomer (0.30 g) Rf 0.34 (silica, hexane:ethyl acetate; 3:1) M.p. 127-130 °C; υ_{max} (nujol on NaCl plates/ cm^{-1}) 2918 (m), 1758 (s) (C=O), 1339 (m), 1172 (m), 843 (m); δ_H (400 MH_Z; $CDCl_3$) 8.28 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.72 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.33-7.43 (5H, m, Ph), 5.61-5.70 (1H, m, -C<u>H</u>=CH_2), 5.22 (1H, dd, *J* 5.4 & 10.9 Hz, H-5), 5.02-5.18 (2H, m, $C\underline{H}_2$=CH-), 3.01 (1H, dd, *J* 5.4 & 13.6 Hz, H-3α), 2.68-2.80 (2H, m, -$C\underline{H}_2$-CH=CH_2), 2.56 (1H, dd, *J* 10.9 & 13.6 Hz, H-3β); δ_C (100 MHz; $CDCl_3$) 176.9 (s) (C=O), 147.5 (s) (C, Ar), 146.9 (s) (C, Ar), 138.0 (s) (C, Ar), 131.8 (s) (CH), 128.9 (s) (2 × CH, Ar), 128.8 (s) CH), 127.6 (s) (2 × CH, Ar), 125.6 (s) (C, Ar), 124.2 (s) (2 × CH, Ar), 120.7 (s) (CH_2), 77.3 (s) (C-5), 54.0 (s) (C, quaternary), 43.7 (s) (CH_2), 41.8 (s) (CH_2); *m/z* (APCI) 324 [$(M + H)^+$, 100%]; (Found: $(M + H)^+$ (APCI) 324.1236. $C_{19}H_{17}NO_4$ requires $(M + H)^+$ 324.1236).

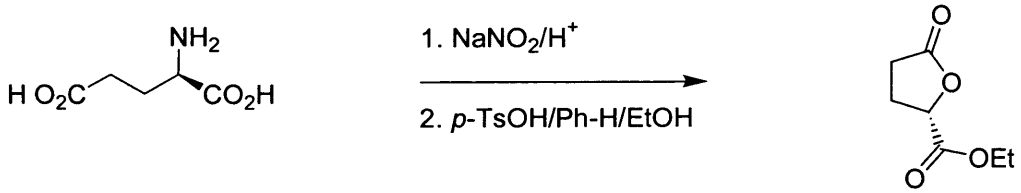


Methyl (2-(4-nitrophenyl)-3-phenyl)propionate[223] (**171**)—This was prepared by the General Method using sodium hydride (0.14 g, 10.3 mmol), methyl 4-nitrophenylacetate (**167**) (2.0 g, 10.3 mmol) and benzyl bromide (1.22 ml, 10.3 mmol) to give the crude product (2.80 g) as an orange crystalline solid. The crude product was then recrystallized from ethanol to give the pure product (2.22 g, 76%) as a yellow crystalline solid. M.p. 59-60 °C (lit. 60-61 °C)[223]; υ_{max} (nujol on NaCl plates/ cm^{-1}) 2921 (s), 1741 (s) (C=O), 1596 (m), 1458 (s), 1346 (m); δ_H(400 MHz; $CDCl_3$) 8.15 (2H. d, *J* 8.8 Hz, H-3' & H-5'), 7.44 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 7.17-7.26 (3H, m, Ph), 7.06 (2H, app. d, *J* 8.3 Hz, Ph), 3.97 (1H, t, *J* 7.8 Hz, CH), 3.64 (3H, s, OCH_3), 3.44 (1H, dd, *J* 13.8 & 7.8 Hz, HC<u>H</u>), 3.04 (1H, dd, *J* 13.8 & 7.8 Hz, <u>H</u>CH); δ_C(100 MHz; $CDCl_3$) 172.7 (s) (C=O), 147.2 (s) (C, Ar), 145.6 (s) (C, Ar), 137.8 (s) (C, Ar), 129.1 (s)

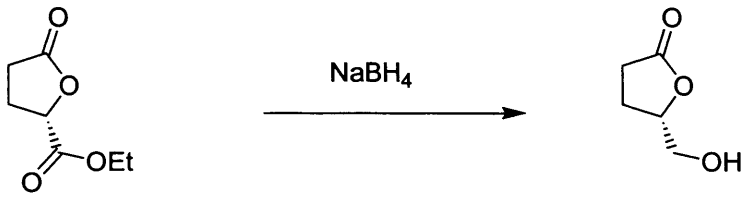
(2 × CH, Ar), 128.8 (s) (2 × CH, Ar), 128.5 (s) (2 × CH, Ar), 126.8 (s) (CH, Ar), 123.8 (s) (2 × CH, Ar), 53.4 (s) (O-CH_3), 52.4 (s) (CH,Ar), 39.6 (CH_2); *m/z* (APCI) 286.0 [$(M + H)^+$, 100%].



Methyl (2-benzyl-2-(4-nitrophenyl)-4-oxo-4-phenylbutyrate **(172)**—This was prepared by the General Method using sodium hydride (67 mg, 1.79 mmol), methyl (2-(4-nitrophenyl)-3-phenyl)propionate (**171**) (0.5 g, 1.79 mmol) and 2-bromoacetophenone (0.36g, 1.79 mmol) to give the crude product (0.74 g) as a yellow crystalline solid. The crude product was then purified by column chromatography Rf 0.41 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.63 g, 87%) as a yellow crystalline solid. M.p. 170-171 υ_{max} (nujol on NaCl plates/ cm^{-1}) 2929 (s), 1716 (s), 1687 (m), 1595 (m), 1521 (m), 1464 (s), 1376 (m), 1349 (m), 1219 (m), 1062 (m), 860 (m); δ_H(400 MHz; $CDCl_3$) 8.20 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.95 (2H, app. d, *J* 7.5 Hz, Ph), 7.62 (1H, app. t, *J* 7.5 Hz, Ph), 7.45-7.51 (4H, m, Ph), 7.14 (1H, app. t, *J* 7.4 Hz, Ph), 7.05 (2H, app. t, *J* 7.4 Hz, Ph), 6.52 (2H, d, *J* 7.4 Hz, Ph), 3.72 (3H, s, O-CH_3), 3.68-3.72 (3H, m, CH_2 & HCH), 3.58 (1H, d, *J* 13.7 Hz, HCH); δ_C(100 MHz; $CDCl_3$) 197.2 (s) (C=O), 174.7 (s) (C=O), 149.2 (s) (C, Ar), 147.3 (s) (C, Ar), 137.0 (s) (C, Ar) 136.4 (s) (C, Ar), 134.0 (s) (CH, Ar), 130.5 (s) (2 × CH, Ar), 129.2 (s) (2 × CH, Ar) 128.6 (s) (2 × CH, Ar), 128.4 (s) (2 × CH, Ar), 128.1 (s) (2 × CH, Ar), 127.4 (s) (CH, Ar), 124.0 (s) (2 × CH, Ar), 53.1 (s) (O-CH_3), 53.0 (s) (C, quaternary), 42.5 (s) (CH_2), 42.0 (s) (CH_2); *m/z* (APCI) 404.0 [$(M + H)^+$, 100 %], 372 (40); (Found: $(M + H)^+$ (APCI), 404.1500. $C_{24}H_{21}NO_5$ requires $(M + H)^+$ 404.1498).



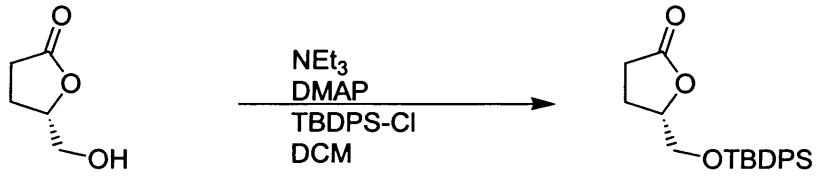
(S)-Dihydro-5-carboethoxy(3H)furan-2-one [156] **(175)**—To a solution of L-glutamic acid (**174**) (90.0 g, 0.61 mol) in water (240 ml) and conc. hydrochloric acid (126 ml) was added slowly over a period of 6 hours at 0 °C a solution of sodium nitrite (63.0 g, 0.91 mol) in water (135 ml). The clear solution was then stirred at room temperature overnight. Evaporation to dryness gave a pale yellow oil. Ethyl acetate (300 ml) was added to the oil, the insoluble material was filtered off and the organic solution dried over Na_2SO_4. The solvent was then removed on a rotary evaporator to leave a pale yellow syrup (80.6 g). Ethanol (130 ml), benzene (300 ml) and *p*-TsOH (2.0 g) were added to the yellow syrup. The solution was then heated under reflux for 5 hours using a Dean-stark apparatus. The solvents were removed under reduced pressure. Benzene (100 ml) was added and the solution was washed with water (100 ml), Na_2CO_3 (100 ml) and water (100 ml) before drying over Na_2SO_4. Removal of the solvent left the crude product as a colourless oil (92.3 g, 95%). υ_{max} (neat, NaCl plates/ cm^{-1}) 1784 (s) (C=O), 1747 (s) (C=O); δ_H(400 MHz; $CDCl_3$) 4.91-4.97 (1H, m, H-5), 4.31 (2H, q, *J* 7.0 Hz, O-CH_2), 2.20-2.80 (4H, m, H-3 & H-4), 1.34 (3H, t, *J* 7.0 Hz, CH_3); δ_C(100 MHz; $CDCl_3$) 177.9 (s) (C=O), 88.9 (s) (C-5), 59.5 (s) (CH_2), 35.2 (s) (C-3), 17.7 (s) (C-4), 13.6 (s) (CH_3); *m/z* (APCI) 159.0 [$(M + H)^+$, 100%].



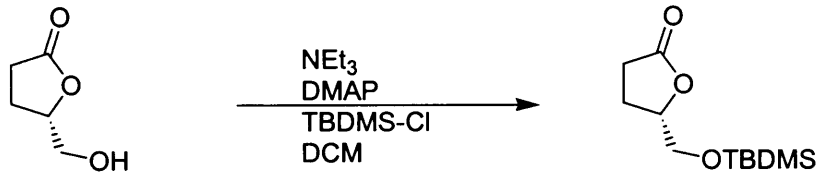
(S)-(+)-5-Hydroxymethyldihydro(3H)furan-2-one [224] **(176)**—A solution of dihydro-5-carboethoxy(3H)furan-2-one (**175**) (53.12 g, 0.34 mol) in ethanol (300 ml) was added dropwise to a stirred suspension of sodium borohydride (8.3 g, 0.22 mol) in ethanol (180 ml). The solution was stirred at room temperature for 90 minutes before being acidified to pH 3 with 10% aq. HCl at 0 °C. The resulting white precipitate was filtered off and the filtrate was evaporated under vacuum. Methanol (100 ml) was added to the residue and evaporated under vacuum (4 times) to give the crude product (28.8 g) as a clear oil. The crude product was then purified by column chromatography Rf 0.35 (silica, ethanol:chloroform; 7:93) to give the pure product (19.8 g, 51%) as a clear oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3403 (s) (O-H), 1767 (s) (C=O), 1190 (s); δ_H(400 MHz; $CDCl_3$) 4.58-4.62 (1H, m, H-5), 3.84 (1H, dd, *J* 3.2 & 12.8 Hz, O-HCH), 3.61 (1H, dd, *J* 4.4 & 12.8 Hz, O-HCH), 3.53 (1H, s, O-H), 2.46-2.63 (2H, m, H-3),

2.19-2.28 (1H, m, H-4α), 2.10-2.15 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 178.3 (s) (C=O), 81.1 (s) (CH_2), 63.9 (s) (CH), 28.5 (s) (CH_2), 23.1 (s) (CH_2); *m/z* (APCI) 117.0 [$(M + H)^+$, 100%].

General Method for Silyl protection of Alcohols—A mixture of alcohol (155 mmol), triethylamine (43.0 ml), silyl chloride (155 mmol), DMAP (15.5 mmol) and dichloromethane (200 ml) were stirred together for 24 hours. The reaction mixture was then poured into water (200 ml) and extracted with dichloromethane (3 × 100 ml). The combined organic extracts were then dried over sodium sulfate. The drying agent was filtered off and the solvent removed on a rotary evaporator to give the crude product.

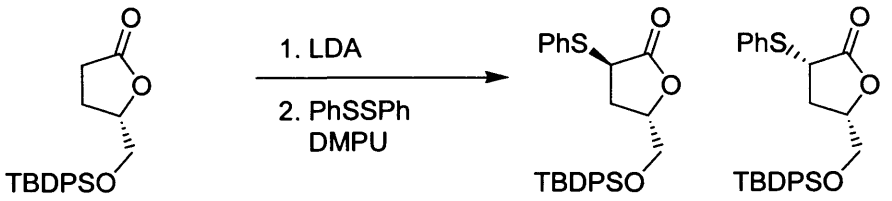


(S)-(+)-5-(tert-Butyldiphenylsilanyloxymethyl)-dihydro(3H)furan-2-one[158] (**177**)—This was prepared by the General Method using (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone (**176**) (18.0 g, 155 mmol), DMAP (1.89 g, 15.5 mmol), TBDPS-Cl (40.35 g, 155 mmol), triethylamine (43 ml, 313 mmol) and dichloromethane to give the crude product (51.9 g) as a black oil. The crude product was then purified by column chromatography Rf 0.18 (silica, ethyl acetate:hexane; 1:3) to give the pure product (30.2 g, 55%) as a white crystalline solid. $[\alpha]_D$ +35.3° $[\alpha]_D$ (c 1.09 in ethanol) (lit. +35.5° c 1.09 in ethanol)[158]; M.p. 74-75 °C (lit. 75-77 °C)[255]; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2966 (s), 1769 (s) (C=O), 1457 (s), 1377 (s), 1266 (m), 1170 (s); δ_H(400 MHz; $CDCl_3$) 7.56 (2H, app. d, *J* 7.5 Hz, Ph), 7.26-7.32 (3H, m, Ph), 4.46 (1H, ddd, *J* 3.1 & 5.7 & 8.3 Hz, H-5), 3.76 (1H, dd, *J* 3.1 & 11.4 Hz, O-HCH), 3.55 (1H, dd, *J* 3.1 & 11.4 Hz, H-5), 2.54 (1H, ddd, *J* 7.2 & 10.1 & 17.5 Hz, H-3α), 2.36 (1H, ddd, *J* 6.7 & 9.9 & 16.7 Hz, H-3β), 2.02-2.19 (2H, m, H-4), 0.95 (9H, s, $(CH_3)_3$); δ_C(100 MHz; $CDCl_3$) 178.0 (s) (C=O), 136.1 (s) (CH, Ar), 136.0 (s) (CH, Ar), 133.3 (s) (C, Ar), 132.9 (s) (C, Ar), 130.4 (s) (CH, Ar), 128.3 (s) (CH, Ar), 80.4 (s) (CH), 65.9 (s) (CH_2), 29.1 (s) (CH_2), 27.2 (s) (CH_3), 24.0 (s) (CH_2), 19.6 (s) C, quaternary); *m/z* (APCI) 355.0 [$(M + H)^+$, 100%].

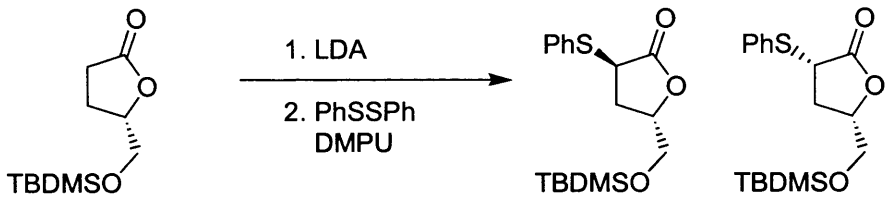


(S)-(+)-5-(tert-Butyl-dimethylsilyloxymethyl)dihydro(3H)furan-2-one [225] **(184)**—This was prepared by the General Method using (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone (**176**) (2.53 g, 21.78 mmol), DMAP (0.27 g, 21.7 mmol), TBDMS-Cl (3.28 g, 21.78 mmol), triethylamine (6.04 ml, 44.0 mmol) and dichloromethane (50 ml) to give the crude product (4.89 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.20 (silica, ethyl acetate:hexane; 1:3) to give the pure product (3.62 g, 73%) as a colourless oil. $[\alpha]_D$ – 10.7° (c 0.5 in $CHCl_3$) (lit. –11.0° c 0.5 in ethanol)[225]; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2931 (s), 2857 (s), 1778 (s), 1462 (s), 1361 (m), 1257 (s); δ_H(400 MHz; $CDCl_3$) 4.52 (1H, ddd, *J* 3.2 & 5.2 & 8.0 Hz, Ph), 3.79 (1H, dd, *J* 3.2 & 11.2 Hz, O-HCH), 3.55 (1H, dd, *J* 3.2 & 11.2, HCH), 2.52 (1H, ddd, *J* 7.2 & 9.9 & 17.5 Hz, H-3α), 2.37 (1H, ddd, *J* 6.7 & 9.9 & 16.7 Hz, H-3β), 2.05-2.25 (2H, m, H-4), 0.81 (9H, s, $(CH_3)_3$), 0.00 (6H, d, *J* 3.6 Hz, 2 × (CH_3)); δ_C(100 MHz; $CDCl_3$) 178.0 (s) (C=O), 80.5 (s) (CH, Ar), 65.2 (s) (CH_2), 28.9 (s) (CH_2), 26.1 (s) (CH_3), 23.9 (s) (CH_2), 18.6 (s) (C, quaternary); *m/z* (APCI) 231.0 [$(M + H)^+$, 100%].

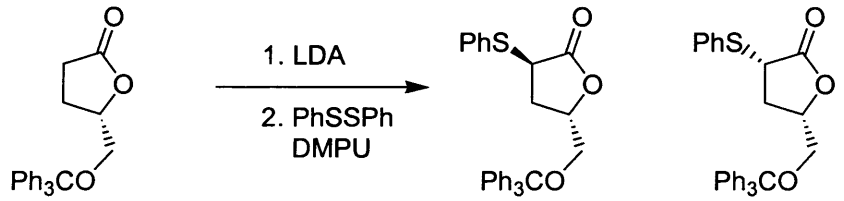
General Method for α-phenylsulfanylation of lactones—A solution of diisopropylamine (28.2 mmol) in dry THF (5 ml) was cooled to 0 °C and flushed with nitrogen. *n*-Butyllithium (28.2 mmol) (2.5 M in hexanes) was added dropwise to the reaction mixture. The mixture was stirred at 0 °C for 10 minutes before cooling to –78 °C in a dry ice/acetone cooling bath. The lactone (14.1 mmol.) dissolved in dry THF (5 ml) was added dropwise to the solution. The mixture was stirred at –78 °C for 35 minutes. Phenyl disulfide (14.12 mmol) and DMPU (14.12 mmol) dissolved in dry THF (5 ml) was added dropwise to the reaction mixture. The mixture was stirred at –78 °C for a further 35 minutes before being allowed to warm to room temperature. The reaction mixture was then poured into water (100 ml) and extracted with ether (3 × 100 ml). The combined organic extracts were then washed successively with 10% NaOH (100 ml), water (100 ml), 10% HCl (100 ml) and water (100 ml). The organic solution was then dried over Na_2SO_4. The drying agent was filtered off and the solvent removed on a rotary evaporator to give the crude product.



(3R,5S) & (3S,5S)-5-(tert-Butyldiphenylsilyloxymethyl)-3-phenylsulfanyldihydro(3H)furan-2-one [226](**181**)—This was prepared by the General Method using diisopropylamine (3.96 ml, 28.2 mmol, *n*-butyllithium (2.5 M in hexanes) (11.3 ml, 28.24 mmol), the lactone **178** (5.0 g, 14.12 mmol), phenyl disulfide (3.08 g, 14.12 mmol), DMPU (1.71 ml, 14.12 mmol) to give the crude product (6.40 g) as an orange oil. The crude product was then purified by column chromatography (silica, ethyl acetate:hexane; 1:3) to give the two diastereoisomers (4.96 g, 76%) in a *cis:trans* ratio of 3:7 as colourless oils. *Cis* product (1.49 g): Rf 0.28 (ethyl acetate: hexane 1:3) υ_{max} (neat, NaCl plates/ cm^{-1}) 2928 (s), 1771 (s), 1457 (m), 1376 (m), 1180 (m), 1020 (m); δ_H(400 MHz; $CDCl_3$) 7.51-7.55 (4H, m, Ph), 7.44-7.47 (2H, m, Ph), 7.28-7.35 (6H, m, Ph), 7.21-7.25 (3H, m, Ph), 4.35 (1H, ddd, *J* 2.9 & 4.9 & 7.6 Hz, H-5), 4.04 (1H, dd, *J* 7.4 & 9.3Hz, H-3), 3.78 (1H, dd, *J* 2.8 & 11.5 Hz, HCH-O), 3.53 (1H, dd, *J* 2.8 & 11.5 Hz, HCH-O), 2.55-2.63 (1H, m, H-4α), 2.17-2.26 (1H, m, H-4β), 0.94 (9H, s, $(CH_3)_3$; δ_C(100 MHz; $CDCl_3$) 175.1 (s) (C=O), 136.1 (s) (CH, Ar), 136.0 (s) (CH, Ar), 135.3 (s) (CH, Ar), 133.7 (s) (C, Ar), 133.6 (s) (C, Ar), 133.3 (s) (C, Ar), 130.5 (s) (CH, Ar), 129.7 (s) (CH, Ar), 128.8 (s) (CH, Ar), 128.4 (s) (CH, Ar), 78.6 (s) (C-5), 64.8 (s) (CH_2), 46.3 (s) (CH), 31.6 (s) (CH_2), 27.2 (s) (CH_3), 19.7 (s) (C); *m/z* (APCI) 463.0 [$(M + H)^+$, 100%]; *trans* product (3.47 g): Rf 0.32 (ethyl acetate: hexane 1:3) υ_{max} (neat, NaCl plates/ cm^{-1}) 2928 (s), 1769 (s), 1458 (m), 1376 (m), 1179 (m), 1017 (m); δ_H(400 MHz; $CDCl_3$) 7.51-7.56 (4H, m, Ph), 7.39-7.44 (2H, m, Ph), 7.25-7.35 (6H, m, Ph), 7.15-7.19 (3H, m, Ph), 4.38 (1H, ddd, *J* 4.5 & 6.4 & 8.9 Hz, H-5), 3.88 (1H, t, *J* 10.2 Hz, H-3), 3.65 (1H, dd, *J* 3.9 & 11.5 Hz, HCH-O), 3.53 (1H, dd, *J* 4.6 & 11.5 Hz, HCH-O), 2.49 (1H, ddd, *J* 6.6 & 9.3 & 15.9 Hz, H-4α), 2.07-2.16 (1H, m, H-4β), 0.93 (9H, s, $(CH_3)_3$; δ_C(100 MHz; $CDCl_3$) 174.6 (s) (C=O), 135.7 (s) (CH, Ar), 135.6 (s) (CH, Ar), 133.2 (s) (CH, Ar), 132.9 (s) (C, Ar), 132.7 (s) (C, Ar), 132.5 (s) (C, Ar), 129.9 (s) (CH, Ar), 129.2 (s) (CH, Ar), 128.4 (s) (CH, Ar), 127.8 (s) (CH, Ar), 78.1 (s) (C-5), 64.4 (s) (CH_2), 45.9 (s) (CH), 31.3 (s) (CH_2), 26.7 (s) (CH_3), 19.2 (s) (C); *m/z* (APCI) 463.0 [$(M + H)^+$, 100%].

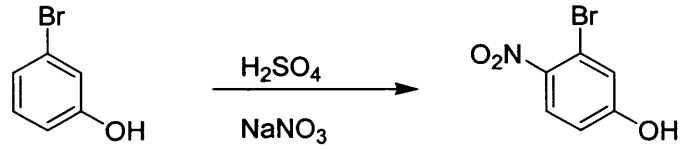


(3R,5S) & (3S,5S)-5-(tert-Butyldimethylsilyloxymethyl)-3-phenylsulfanyldihydro(3H)furan-2-one (**185**)—This was prepared by the gGeneral Method using diisopropylamine (1.23 ml, 8.68 mmol, *n*-butyllithium (2.5 M in hexanes) (3.47 ml, 8.68 mmol), the lactone **177** (1.0 g, 4.34 mmol), phenyl disulfide (0.95 g, 4.34 mmol), DMPU (0.52 ml, 4.34 mmol) to give the crude product (1.19 g) as a yellow oil. The crude product was then purified by column chromatography (silica, ethyl acetate:hexane; 1:3) to give the two diastereo isomers (0.88 g, 60%) in a *cis:trans* ration of 1:1 as colourless oils. *cis* product (0.44 g): υ_{max} (neat, NaCl plates/ cm^{-1}) 2927 (s), 1772 (s), 1457 (m), 1377 (m), 1183 (m), 1021 (m); δ_H(400 MHz; $CDCl_3$) 7.27-7.30 (2H, m, Ph), 7.03-7.09 (3H, m, Ph), 4.36 (1H, ddd, *J* 3.0 & 4.9 & 7.6 Hz, H-5), 4.05 (1H, dd, *J* 7.4 & 9.3Hz, H-3), 3.78 (1H, dd, *J* 2.9 & 11.5 Hz, HCH-O), 3.53 (1H, dd, *J* 2.9 & 11.5 Hz, HCH-O), 2.54-2.62 (1H, m, H-4α), 2.16-2.25 (1H, m, H-4β), 0.80 (9H, s, $(CH_3)_3$), 0.00 (6H, d, *J* 3.6 Hz, 2 × (CH_3)); δ_C(100 MHz; $CDCl_3$) 175.0 (s) (C=O), 133.7 (s) (C, Ar), 133.1 (s) (2 × CH, Ar), 129.3 (s) (2 × CH, Ar), 128.0 (s) (CH, Ar), 78.5 (s) (C-5), 64.7 (s) (CH_2), 46.2 (s) (CH), 31.6 (s) (CH_2), 27.2 (s) (CH_3), 19.7 (s) (C); *m/z* (APCI) 339.0 $[(M + H)^+$, 100%]; *trans* product (0.44 g): υ_{max} (neat, NaCl plates/ cm^{-1}) 2928 (s), 1774 (s), 1458 (m), 1376 (m), 1181 (m), 1020 (m); δ_H(400 MHz; $CDCl_3$) 7.26-7.29 (2H, m, Ph), 7.04-7.10 (3H, m, Ph), 4.39 (1H, ddd, *J* 4.5 & 6.4 & 9.0 Hz, H-5), 3.89 (1H, t, *J* 10.2 Hz, H-3), 3.66 (1H, dd, *J* 3.9 & 11.5 Hz, HCH-O), 3.53 (1H, dd, *J* 4.6 & 11.5 Hz, HCH-O), 2.50 (1H, ddd, J 6.6 & 9.3 & 16.0 Hz, H-4α), 2.06-2.15 (1H, m, H-4β), 0.93 (9H, s, $(CH_3)_3$), 0.00 (6H, d, *J* 3.6 Hz, 2 × (CH_3)); δ_C(100 MHz; $CDCl_3$) 174.9 (s) (C=O), 133.8 (s) (C, Ar), 133.0 (s) (2 × CH, Ar), 129.4 (s) (2 × CH, Ar), 127.9 (s) (CH, Ar), 78.0 (s) (C-5), 64.3 (s) (CH_2), 45.9 (s) (CH), 31.4 (s) (CH_2), 26.7 (s) (CH_3), 19.1 (s) (C); *m/z* (APCI) 339.0 $[(M + H)^+$, 100%].

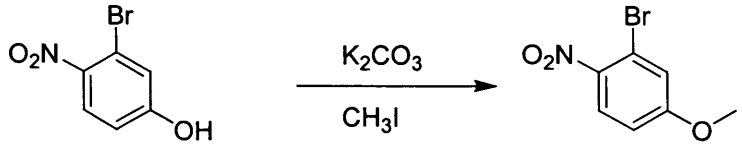


(3R,5S) & (3S,5S)-5-(trityloxymethyl)-3-phenylsulfanyldihydro(3H)furan-2-one (**189**)—This was prepared by the General Method using diisopropylamine (3.96 ml, 28.2 mmol, *n*-butyllithium (2.5 M in hexanes) (11.3 ml, 28.24 mmol), the lactone **188** (5.0 g, 14.12 mmol),

phenyl disulfide (3.08 g, 14.12 mmol), DMPU (1.71 ml, 14.12 mmol) to give the crude product (6.40 g) as an orange oil. The product was purified by column chromatography (ethyl acetate:hexane 1:3) to give the two diastereoisomers (4.34 g, 66%) in a 7:3 ratio. The two diastereoisomers were not able to be separated by column chromatography.

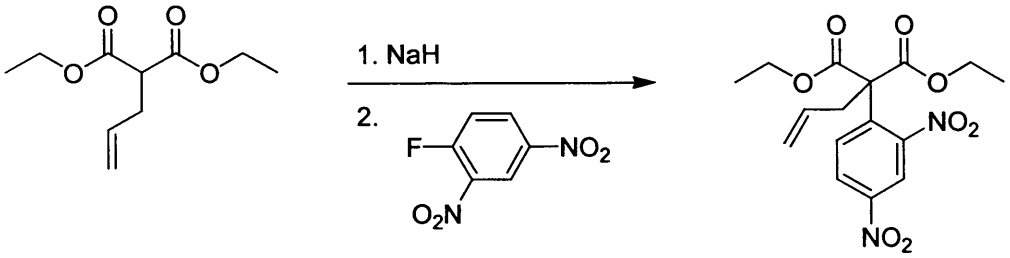


3-Bromo-4-nitrophenol[159] **(200)**—In a 3 necked (500 ml) round bottom flask fitted with a condenser and nitrogen bubbler was added sodium nitrate (22.6 g, 266 mmol), sulphuric acid (31.4 g) and water (60 ml). *m*-Bromophenol (25.0 g, 144.5 mmol) in ethanol (20 ml) was slowly added keeping the temperature below 25 °C. After stirring at room temperature for two hours, the mixture was diluted with water (150 ml). The product was then extracted with ether (3 × 100 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent removed on a rotary evaporator to give the crude product (29.71 g) as an orange solid. The crude product was then purified by column chromatography Rf 0.20 (silica, ethyl acetate:hexane; 1:3) to give the pure product (19.3 g, 61%) as white needles. M.p. 129-131 °C (lit. 131 °C)[159]; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2926 (s), 1556 (s), 1460 (s), 1376 (m), 1297 (m), 1194 (m); δ_H(400 MHz; $CDCl_3$) 7.93 (1H, d, *J* 8.8 Hz, H-5), 7.17 (1H, d, *J* 2.4 Hz, H-2), 6.88 (1H, dd, *J* 2.4 & 8.8 Hz, H-6); δ_C(100 MHz; $CDCl_3$) 163.7 (s) (C, Ar), 143.2 (s) (C, Ar), 129.7 (s) (CH, Ar), 122.7 (s) (CH, Ar), 117.6 (s) (C, Ar), 116.4 (s) (CH, Ar); *m/z* (APCI) 218.0 [$(M + H)^+$, 50%], 220.0 (50%)

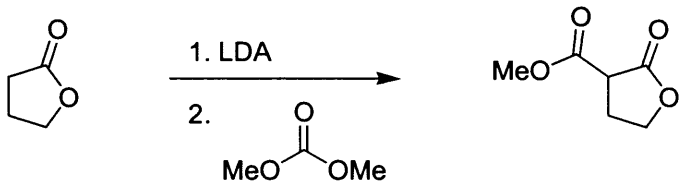


3-Bromo-4-nitroanisole[161] **(201)**—3-Bromo-4-nitrophenol (**200**) (10.0 g, 45.66 mmol) was dissolved in acetone (75 ml) and treated with potassium carbonate (12.63 g, 90 mmol) at 40 °C for 10 minutes. The resulting suspension was then cooled to 0 °C. Methyl iodide (5.63 ml, 90 mmol) was added dropwise. The solution was stirred at 40 °C for 3 hours. The solvent was removed on a rotary evaporator and dichloromethane (50 ml) was added to the residue. The insoluble material was filtered off and the solvent removed on a rotary evaporator to leave the product (9.1 g, 86%) as yellow needles. M.p. 44-46 °C (lit. 44-45 °C)[161]; υ_{max} (nujol, NaCl

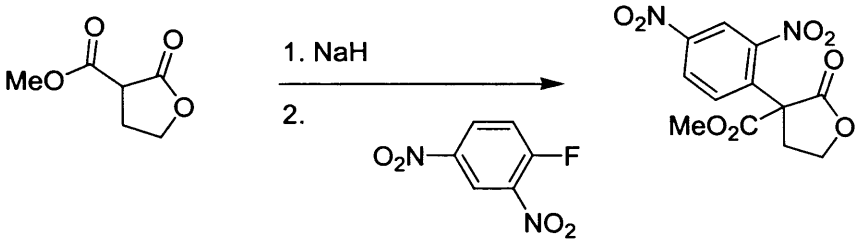
plates/ cm^{-1}) 2926 (s), 1554 (s), 1459 (s), 1371 (m), 1296 (m), 1190 (m); δ_H(400 MHz; $CDCl_3$) 7.91 (1H, d, *J* 8.9 Hz, H-5), 7.18 (1H, d, *J* 2.4 Hz, H-2), 6.89 (1H, dd, *J* 2.4 & 8.9 Hz, H-6), 3.73 (3H, s, OCH_3); δ_C(100 MHz; $CDCl_3$) 163.5 (s) (C, Ar), 143.0 (s) (C, Ar), 129.5 (s) (CH, Ar), 122.4 (s) (CH, Ar), 117.3 (s) (C, Ar), 116.2 (s) (CH, Ar), 56.3 (s) (OCH_3); *m/z* (APCI) 232.0 [$(M + H)^+$, 50%], 234 (50%)



Diethyl 2-allyl-2-(2,4-dinitrophenyl)malonate **(213)**—In a two necked round bottom flask fitted with a condenser and nitrogen bubbler was added sodium hydride (60% dispersion in oil (0.11 g, 2.75 mmol) followed by dry THF (5 ml). The flask was then cooled to 0 °C. Diethyl allyl malonate (0.50 ml, 2.54 mmol) in dry THF (5 ml) was then added dropwise. The reaction mixture was stirred at 0 °C for 20 minutes. 2,4-Dinitrofluorobenzene (0.47 g, 2.54 mmol) was then added dropwise to the reaction mixture. The solution was stirred at 0 °C for a further 30 minutes. The solution was then allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was then poured into an ice/HCl solution (1M) and then extracted with dichloromethane (3 × 25 ml). The organic solution was then washed with water (3 × 25 ml) and then dried over Na_2SO_4. The solvent was then removed on a rotary evaporator to give the crude product (0.84 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.33 (silica, ethyl acetate:hexane; 1:3) to give the pure product (0.77 g, 83%) as a clear oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3098 (s), 1554 (s), 2982 (s), 1733 (s), 1639 (w), 1606 (m), 1539 (s), 1466 (s), 1351 (s), 1202 (s), 1028 (s); δ_H(400 MHz; $CDCl_3$) 8.78 (1H, d, *J* 2.4 Hz, H-3'), 8.34 (1H, dd, *J* 2.4 & 8.8 Hz, H-5'), 7.53 (1H, d, *J* 8.8 Hz, H-6'), 5.60-5.70 (1H, m, H_2C=C<u>H</u>-), 4.97-5.02 (2H, m, H_2C=), 4.08-4.20 (4H, m, CH_2-O), 3.25 (2H, d, *J* 7.2 Hz, CH_2-C-Ar), 1.16 (6H, t, *J* 7.2 Hz, C<u>H</u>$_3$-CH_2); δ_C(100 MHz; $CDCl_3$) 168.1 (s) (C=O), 150.0 (s) (C, Ar), 147.2 (s) (C, Ar), 139.1 (s) (C, Ar), 133.1 (s) (CH), 132.5 (s) (CH), 126.8 (s) (CH), 121.2 (s) (CH), 120.6 (s) (CH_2), 63.5 (s) (C, quaternary), 62.8 (s) (CH_2), 40.1 (s) (CH_2), 14.4 (s) (CH_3); *m/z* (APCI) 367.0 [$(M + H)^+$, 100%]. (Found: $(M + H)^+$ (APCI), 367.1068. $C_{16}H_{18}N_2O_8$ requires $(M + H)^+$ 367.1063).

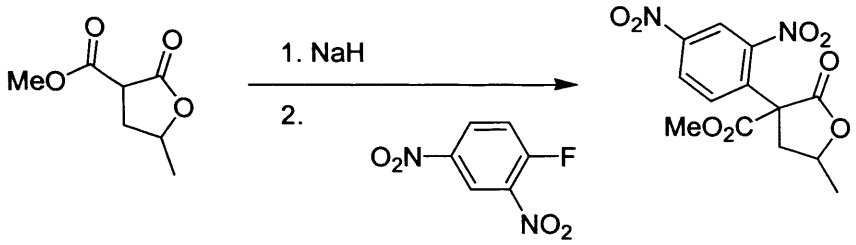


Dihydro-3-carbomethoxy(3H)furan-2-one [163] **(215)**—To a solution of diisopropylamine (3.65 ml, 26.0 mmol) and dry THF (10 ml) was added at 0 °C *n*-butyllithium (2.5 M in hexanes) (10.42 ml, 26.0 mmol). The solution was stirred at 0 °C for 10 minutes before being cooled to –78 °C. γ-Butyrolactone (1.0 ml, 13.0 mmol) was added dropwise to the stirred solution. The solution was stirred for a further 20 minutes at –78 °C before dimethyl carbonate (6.57 ml, 78.0 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. Saturated NH_4Cl (5 ml) was then added slowly to the solution. The product was then extracted with ether (3 × 50 ml). The combined extracts were dried over Na_2SO_4 and the solvent removed on a rotary evaporator to give the crude product (2.06 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.38 (silica, ethyl acetate:hexane; 1:1) to give the pure product (1.36 g, 73%) as a clear oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3098 (s), 1740 (s), 1538 (s), 1465 (s), 1351 (s), 1028 (s); δ_H(400 MHz; $CDCl_3$) 4.24 (1H, dt, *J* 5.2 & 8.4 Hz, H-5α), 4.13 (1H, dt, *J* 5.2 & 8.8 Hz, H-5β), 3.57 (3H, s, O-CH_3), 3.43 (1H, t, *J* 8.4 Hz, H-3), 2.30-2.45 (2H, m, H-4); δ_C(100 MHz; $CDCl_3$) 172.0 (s) (C=O), 167.7 (s) (C=O), 66.6 (s) (CH_2), 51.9 (s) (CH_3), 44.8 (s) (CH), 25.5 (s) (CH_2); *m/z* (APCI) 145.0 [$(M + H)^+$, 100%].

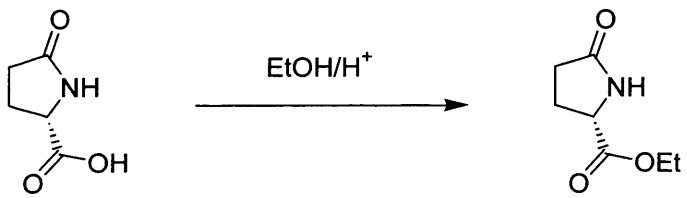


Dihydro-3-(2'-4'-Dinitrophenyl)-3-carbomethoxy(3H)furan-2-one **(216)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (167 mg, 4.16 mmol), dihydro-3-carbomethoxy*(3H)*furan-2-one **(215)** (0.50 g, 3.47 mmol) and 2,4-dinitrofluorobenzene (0.65 g, 3.47 mmol) to give the crude product (1.11 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.19 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.93 g, 86%) as an orange oil. υ_{max} (neat, NaCl plates/ cm^{-1}) 3028 (s), 1733 (s), 1539 (s), 1465 (s), 1348 (s); δ_H(400 MHz; $CDCl_3$) 8.86 (1H, d, *J* 2.4

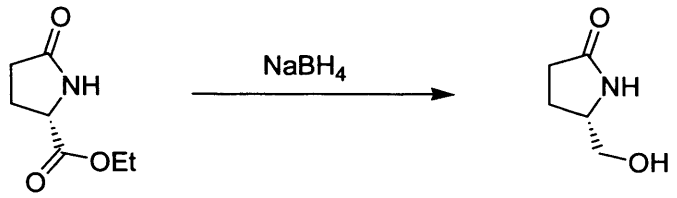
Hz, H-3'), 8.44 (1H, dd, *J* 2.4 & 8.4Hz, H-5'), 7.64 (1H, d, *J* 8.4 Hz, H-6'), 4.60 (1H, ddd, *J* 6.0 & 8.0 & 8.8 Hz, H-5α), 4.30 (1H, ddd, *J* 6.4 & 8.0 & 8.8 Hz, H-5β), 3.69 (3H, s, OCH_3), 3.57 (1H, ddd, *J* 6.4 & 8.0 & 14.0 Hz, H-4α), 2.55 (1H, ddd, *J* 5.6 & 8.0 & 14.0 Hz); δ_C(100 MHz; $CDCl_3$) 172.4 (s) (C=O), 167.3 (s) (C=O), 148.9 (s) (C, Ar), 147.9 (s) (C, Ar), 138.6 (s) (C, Ar), 131.9 (s) (CH, Ar), 128.3 (s) (CH, Ar), 121.9 (s) (CH, Ar), 67.1 (s) (CH_2), 60.7 (s) (C, quaternary), 54.4 (s) (CH_3), 36.3 (s) (CH_2); *m/z* (APCI) 311.0 [$(M + H)^+$, 100%].



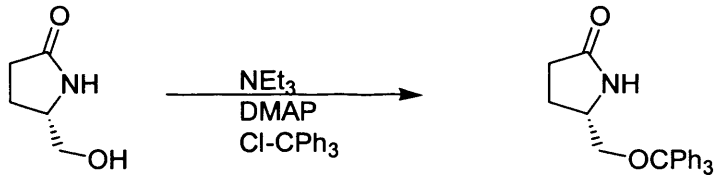
Dihydro-3-(2'-4'-dinitrophenyl)-3-carbomethoxy-5-methyl(3H)furan-2-one **(223)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.38 g, 9.49 mmol), 5-methyldihydro-3-carbomethoxy*(3H)*furan-2-one (**221**) (1.50 g, 9.49 mmol) and 2,4-dinitrofluorobenzene (1.76 g, 9.49 mmol) to give the crude product (2.76 g) as an orange oil (only the *trans* product was observed). The crude product was then purified by column chromatography Rf 0.20 (silica, hexane:ethyl acetate; 3:1) to give the pure product (2.44 g, 80%) as a yellow crystalline solid. M.p. 120-121 °C; υ_{max} (nujol, NaCl plates/ cm^{-1}) 2922 (s), 2853 (s), 1668 (s), 1538 (m), 1462 (s), 1376 (s), 1158 (w); δ_H(400 MHz; $CDCl_3$) 8.99 (1H, d, *J* 2.4 Hz, H-3'), 8.51 (1H, dd, *J* 2.4 & 8.6 Hz, H-5'), 7.63 (1H, d, *J* 8.6 Hz, H-6'), 4.54 (1H, ddd, *J* 6.1 & 12.1 & 16.2 Hz, H-5), 3.73 (3H, s, OCH_3), 3.30 (1H, dd, *J* 10.1 & 14.1 Hz, H-4α), 2.69 (1H, dd, *J* 6.1 & 14.1 Hz, H-4β), 1.55 (3H, d, *J* 6.1 Hz, CH_3), 2.55 (1H, ddd, *J* 5.6 & 8.0 & 14.0 Hz); δ_C(100 MHz; $CDCl_3$) 172.3 (s) (C=O), 167.4 (s) (C=O), 148.4 (s) (C, Ar), 148.1 (s) (C, Ar), 138.7 (s) (C, Ar), 131.7 (s) (CH, Ar), 128.5 (s) (CH, Ar), 122.4 (s) (CH, Ar), 76.1 (s) (O-CH_3), 63.5 (s) (C, quaternary), 54.3 (s) (CH), 43.6 (s) (CH_2), 20.6 (CH_3); *m/z* (APCI) 325.0 [$(M + H)^+$, 100%]. (Found: $(M + H)^+$ (APCI), 325.0591 $C_{13}H_{12}N_2O_8$ requires $(M + H)^+$ 325.0594).



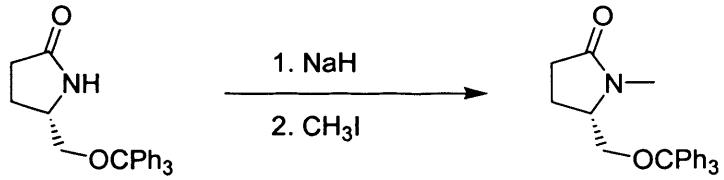
(S)-5-Carboethoxypyrrolidin-2-one [227] **(231)**—To a stirred suspension of L-pyroglutamic acid **(230)** (52.0 g, 403 mmol) in dry toluene (260 ml) was added ethanol (50 ml) and sulphuric acid (1 ml). The reaction vessel was fitted with a Dean-Stark apparatus and the mixture was heated under reflux with azeotropic removal of water for six hours. After cooling the reaction mixture was diluted with chloroform (250 ml) and then treated with potassium carbonate (20.0 g, 145 mmol). After effervesence ceased the reaction mixture was filtered through celite and concentrated *in vacuo* to afford the product (63.3 g, 100%) as a white crystalline solid. M.p. 53-54 °C (lit. 54-55 °C)[227]; υ_{max} (neat, NaCl plates/ cm^{-1}) 2985 (s), 1700 (s), 1404 (s), 1377 (s), 1203 (s), 1111 (m), 1021 (s), 918 (m); δ_H(400 MHz; $CDCl_3$) 4.14 (1H, dd, *J* 4.9 & 8.7 Hz, H-5), 4.07 (2H, q, *J* 7.1 Hz, O-CH_3), 2.20-2.38 (3H, m, H-3 & H-4α), 2.02-2.06 (1H, m, H-4β), 1.14 (3H, t, *J* 7.1 Hz, CH_3); δ_C(100 MHz; $CDCl_3$) 179.3 (s) (C=O), 172.6 (s) (C=O), 61.7 (s) (CH), 56.0 (s) (CH_2), 29.7 (s) (CH_2), 25.0 (s) (CH_3), 14.3 (s) (CH_2); *m/z* (APCI) 158.0 [$(M + H)^+$, 100%].



(S)-5-Hydroxymethyl pyrrolidin-2-one[228] **(232)**—The ester **231** (5.0 g, 31.85 mmol) dissolved in ethanol (30 ml) was treated at 0 °C with sodium borohydride (1.25 g, 33.0 mmol) portionwise over 10 minutes. The reaction mixture was slowly allowed to warm to room temperature and stirred for a further 90 minutes. The reaction was then cooled to 0 °C hydrochloric acid (2 ml) was cautiously added to quench the reaction mixture. Filtration of the precipitated salts through celite and concentration of the resultant liquor afforded the crude product (4.6 g) as a colourless oil. The crude product was then purified by column chromatography Rf 0.20 (silica, hexane:ethyl acetate; 2:1) to give the pure product (2.97 g, 81%) as a white solid. M.p. 85-87 °C (lit. 86-67 °C)[228]; υ_{max} (neat, NaCl plates/ cm^{-1}) 2926 (s), 1680 (s), 1460 (s), 1377 (s), 1081 (w), 1017 (w), 722 (m); δ_H(400 MHz; $CDCl_3$), 7.54 (1H, s, O-H), 4.89 (1H, s, NH), 3.70-3.74 (1H, m, H-5), 3.65 (1H, dd, *J* 3.7 & 11.6 Hz, HC<u>H</u>-O), 3.48 (1H, dd, *J* 4.7 & 11.6 Hz, HC<u>H</u>-O), 2.25-2.34 (1H, m, H-4), 2.08-2.12 (1H, m, H-3α), 1.70-1.74 (1H, m, H-3β); δ_C(100 MHz; $CDCl_3$) 179.8 (s) (C=O), 65.8 (s) (CH_2), 56.8 (s) (CH), 30.5 (s) (CH_2), 22.8 (s) (CH_2); *m/z* (APCI) 116.0 [$(M+H)^+$, 100%].

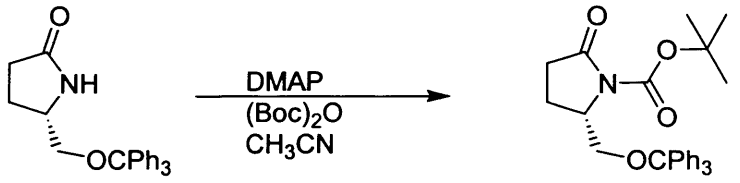


(S)-5-Trityloxymethyl pyrrolidin-2-one[168] **(233)**—To a solution of the alcohol **232** (2.37 g, 20.61 mmol) in dichloromethane (50 ml) was added triethylamine (5.60 ml, 40.0 mmol) and triphenylchloromethane (7.75 g, 28 mmol) and the reaction mixture was stirred at room temperature for 20 hours. Water (30 ml) was then added and the product was extracted with dichloromethane (3 × 50 ml). The combined extracts were dried over Na_2SO_4 and the solvent removed on a rotary evaporator to give the crude product (9.1 g) as an orange powder. The crude product was then purified by column chromatography Rf 0.43 (silica, hexane:ethyl acetate; 1:3) to give the pure product (4.81 g, 65%) as a white powder. $[\alpha]_D$ +28.4° (c 1.71 in ethanol) (lit. +28.9° c 1.71 in ethanol)[168]; M.p. 164-166 °C (lit. 165.5-166 °C)[168]; υ_{max} (nujol on NaCl plates/cm^{-1}) 2922 (s), 1668 (s) (C=O), 1462 (s), 1377 (s); δ_H(400 MHz; $CDCl_3$) 7.27-7.44 (15H, m, Ph), 3.84-3.94 (1H, m, H-5), 3.22 (1H, dd, *J* 4.0 & 9.3 Hz, HCH-O), 3.02 (1H, dd, *J* 8.3 & 9.3 Hz, HCH-O), 2.33 (2H, t, *J* 8.1 Hz, H-3), 2.12-2.21 (1H, m, H-5α), 1.63-1.74 (1H, m, H-5β); δ_C(100 MHz; $CDCl_3$) 178.5 (s) (C=O), 144.0 (s) (C, Ar), 129.0 (s) (2 × CH, Ar), 128.3 (s) (2 × CH, Ar), 127.6 (s) (CH, Ar) 87.2 (s) (C-Ph), 67.5 (s) (CH_2), 54.5 (s) (CH), 30.1 (s) (CH_2), 23.7 (s) (CH_2); *m/z* (APCI) 358.0 [$(M+H)^+$, 100%].

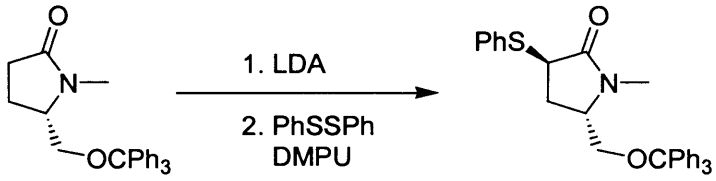


(S)-1-Methyl-5-trityloxymethylpyrrolidin-2-one **(234)**—5-Trityloxymethyl pyrrolidin-2-one **(233)** (1.5 g, 4.2 mmol) in dry THF (5 ml) was added dropwise at 0 °C to a suspension of sodium hydride (60% dispersion in oil) (0.50 g, 12.6 mmol). The mixture was then stirred at 0 °C for 20 minutes. Methyl iodide (1.26 ml, 20.3 mmol) was slowly added and the mixture was stirred overnight at room temperature. The mixture was filtered through a celite plug and which was washed several times with THF. The filtrate and the washings were pooled together and evaporated to dryness. The residue was partitioned between chloroform (50 ml) and water (50 ml). The water layer was washed with chloroform (3 × 25 ml). The combined extracts were pooled together and dried over $MgSO_4$. The solvent was removed on a rotary evaporator

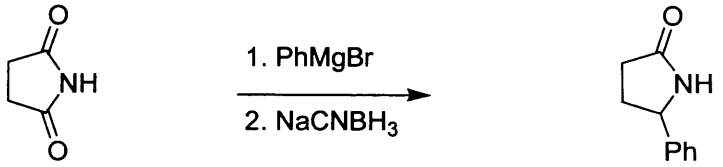
to give the crude product (2.3 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.43 (silica, hexane:ethyl acetate; 1:3) to give the pure product (0.97 g, 62%) as a yellow oil. υ_{max} (nujol on NaCl plates/cm^{-1}) 2936 (s), 2235 (w), 1963 (w), 1681 (s), 1449 (s); δ_H(400 MHz; $CDCl_3$) 7.27 (6H, app. d, *J* 7.3 Hz, Ph), 7.15 (6H, app. t, *J* 7.3 Hz, Ph), 7.10 (3H, app. t, *J* 7.3 Hz, Ph), 3.59 (1H, dd, *J* 3.6 & 10.0 Hz, HCH-O), 2.99 (1H, dd, *J* 4.5 & 10.0 Hz, HCH-O), 2.61 (3H, s, N-CH_3), 2.33-2.43 (1H, m, H-3α), 2.11-2.22 (1H, m, H-3β), 1.86-1.97 (1H, m, H-4α), 1.64-1.72 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 175.8 (s) (C=O), 144.0 (s) (C, Ar), 129.3 (s) (2 × CH, Ar), 128.8 (s) (2 × CH, Ar), 127.8 (s) (CH, Ar) 87.3 (s) (C-Ph), 64.5 (s) (CH_2), 60.4 (s) (CH), 30.7 (s) (CH_2), 28.8 (s) (CH_3), 22.0 (s) (CH_2); *m/z* (APCI) 372.0 [$(M+H)^+$, 100%].



(S)-1-Boc-5-trityloxymethylpyrrolidin-2-one[30] **(234a)**—To a solution of 5-Trityloxymethyl pyrrolidin-2-one (**238**) (1.5 g, 4.20 mmol) in acetonitrile (50 ml) at 0 °C was added DMAP (52 mg, 0.42 mmol) and di-*tert*-butyldicarbonate (1.83 g, 8.4 mmol) with stirring. The reaction was allowed to slowly warm to room temperature and stirred overnight. The solvent was then removed on a rotary evaporator to give the crude product (2.56 g) as a brown solid. The crude product was then purified by column chromatography Rf 0.12 (silica, hexane:ethyl acetate; 3:1) to give the pure product (1.24 g, 65%) as a white solid. M.p. 107-108 °C (lit. 108 °C)[230]; υ_{max} (nujol on NaCl plates/cm^{-1}) 2928 (s), 1685 (s), 1449 (s) 1376 (s); δ_H(400 MHz; $CDCl_3$) 7.30 (6H, app. d, *J* 7.6 Hz, Ph), 7.13 (6H, app. t, *J* 7.6 Hz, Ph), 7.06 (3H, app. t, *J* 7.6 Hz, Ph), 4.13-4.16 (1H, m, H-5), 3.41 (1H, dd, *J* 4.3 & 13.7 Hz, HCH-O), 2.87 (1H, dd, *J* 2.5 & 9.4 Hz, HCH-O), 2.67-2.74 (1H, m, H-3α), 2.27-2.34 (1H, m, H-3β), 1.91-1.98 (1H, m, H-4α), 1.78-1.83 (1H, m, H-4β) 1.34 (9H, s, $(CH_3)_3$); δ_C(100 MHz; $CDCl_3$) 175.7 (s) (C=O), 150.1 (s) (C, Ar), 144.0 (s) (2 × CH, Ar), 129.0 (s) (2 × CH, Ar), 128.4 (s) (CH, Ar) 127.3 (s) (C-Ar), 87.3 (s) (C-Ph), 83.1 (s) (C), 64.6 (s) (CH), 58.0 (s) (CH_2), 32.7 (s) (CH_2), 28.3 (s) (3 × CH_3), 21.8 (s) (CH_2); *m/z* (APCI) 458.0 [$(M+H)^+$, 100%].

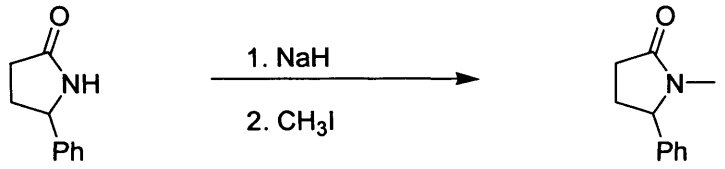


(5S,3R)-3-Phenylsulfanyl-1-methyl-5-trityloxymethylpyrrolidin-2-one **(235)**—To a solution of diisopropylamine (0.38 ml, 2.70 mmol) in dry THF (5 ml) was added at 0 °C *n*-butyllithium (2.5 M in hexanes) (1.08 ml, 2.31 mmol). The solution was stirred at 0 °C for 20 minutes before cooling to –78 °C. 1-Methyl-5-trityloxymethyl pyrrolidin-2-one (**234**) (0.50 g, 1.35 mmol) dissolved in dry THF (5 ml) was added dropwise to the solution which was then stirred at –78 °C for 35 minutes. Phenyl disulfide (0.30 g, 1.35 mmol) and DMPU (1.08 ml, 1.35 mmol) in dry THF (5 ml) was added dropwise to the reaction mixture. The solution was then stirred for a further 35 minutes at –78 °C and then allowed to warm to room temperature. The reaction mixture was then poured into water (20 ml) and extracted with ether (3 × 20 ml). The combined extracts were washed successively with 10% NaOH (25 ml), Water (25 ml), 10% HCl (25 ml) and water (25 ml) and then dried over Na_2SO_4. The solvent was removed on the rotary evaporator to give the crude product (0.80 g) as a yellow oil. The crude product was then purified by column chromatography Rf 0.43 (silica, hexane:ethyl acetate; 3:1) to give the pure product (0.36 g, 55%) as a yellow oil. υ_{max} (neat, NaCl plates/cm^{-1}) 2929 (s), 1689 (s); δ_H(400 MHz; $CDCl_3$) 7.41-7.49 (2H, m, Ph), 7.17-7.31 (18H, m, Ph), 4.00 (1H, t, *J* 8.3 Hz, H-3), 3.27-3.30 (1H, m, H-5), 3.22 (1H, dd, *J* 3.3 & 10.2 Hz, HC<u>H</u>-O), 3.02 (1H, dd, *J* 3.9 & 10.2 Hz, <u>H</u>CH-O), 2.65 (3H, s, CH_3), 2.24-2.28 (1H, m, H-4α), 2.01-2.10 (1H, m, H-4β); δ_C(100 MHz; $CDCl_3$) 172.7 (s) (C=O), 143.4 (s) (C, Ar), 133.6 (s) (C, Ar), 132.6 (s) (CH, Ar), 128.9 (s) (2 × CH, Ar) 128.6 (s) (2 × CH-Ar), 128.0 (s) (CH, Ar), 127.9 (s) (2 × CH, Ar), 127.7 (s) (CH, Ar), 127.3 (s) (2 × CH, Ar), 87.0 (s) (C), 63.1 (s) (CH_2), 58.1 (s) (CH), 47.5 (s) (CH), 30.5 (s) (CH2), 28.8 (s) (CH); *m/z* (APCI) 480.0 [$(M+H)^+$, 100%]. (Found: $(M + H)^+$ (APCI), 480.1924 $C_{31}H_{29}NO_2S$ requires $(M + H)^+$ 480.1919).



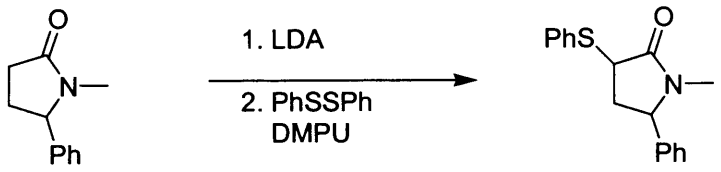
5-Phenyl-pyrrolidin-2-**one**[169] **(238)**—In a 500 ml round bottom flask was added magnesium turnings (4.75 g, 200 mmol) followed by dry ether (100 ml). Bromobenzene (7.9 g, 51.4 mmol) was slowly added to the flask over a period of 30 minutes. The reaction mixture was

then cooled to 0 °C. Succinimide (5.0 g, 50.4 mmol) dissolved in dichloromethane (200 ml) was then added to the solution which was then allowed to warm to room temperature and stirred for 18 hours. Sodium cyanoborohydride (3.8 g, 60.55 mmol) was added to the solution followed by slow addition of a 6 M HCl solution to keep the pH 3-4. After stirring for 30 minutes the solution was neutralised with 10% NaOH and extracted with dichloromethane (3 × 100 ml). The solvent was removed on a rotary evaporator to give the crude product (9.14 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.42 (ethyl acetate) to give the pure product (4.95 g, 61%) as a white solid. M.p. 105-107 °C (lit. 107 °C)[169]; υ_{max} (nujol on NaCl plates/cm^{-1}) 3451 (s), 2938 (s), 1663 (s), 1458 (s), 1395 (s), 1351 (s); δ_H(400 MHz; $CDCl_3$) 7.21-7.41 (5H, m, Ph), 6.72 (1H, s, N-H), 4.76 (1H, t, *J* 7.1 Hz, H-5), 2.31-2.72 (3H, m, H-3 & H-4α), 1.92-1.97 (1H, m, H-4 β); δ_C(100 MHz; $CDCl_3$) 178.9 (s) (C=O), 142.5 (s) (C, Ar), 128.9 (s) (2 × CH, Ar), 127.9 (s) (CH, Ar), 125.6 (s) (2 × CH, Ar) 58.2 (s) (CH), 31.3 (s) (CH_2), 30.4 (s) (CH_2); *m/z* (APCI) 162.0 [$(M+H)^+$, 100%].



1-Methyl-5-phenyl-pyrrolidin-2-one[170] **(239)**—To a suspension of sodium hydride (60% dispersion in oil) (0.37 g, 9.32 mmol) in dry THF (10 ml) was added dropwise at 0 °C a solution of 5-phenyl-2-pyrrolidinone **(238)** (1.5 g, 9.32 mmol) in dry THF (5 ml). The mixture was stirred at 0 °C for 10 minutes before being allowed to warm to room temperature and stirred for a further 30 minutes. The reaction mixture was then cooled to 0 °C and iodomethane (0.58 ml, 9.32 mmol) was added dropwise to the reaction mixture which was then allowed to warm to room temperature and stirred overnight. The reaction mixture was then poured onto ice/HCl (1 M solution) and extracted with dichloromethane (3 × 50 ml). The combined extracts were then washed with water (3 × 50 ml) and dried over $MgSO_4$. The solvent was then removed on a rotary evaporator to give the crude product (1.45 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.34 (silica, hexane:ethyl acetate; 3:1) to give the pure product (1.51 g, 92%) as a yellow oil. υ_{max} (neat, NaCl plates/cm^{-1}) 1692 (s), 1377 (m), 1134 (s); δ_H(400 MHz; $CDCl_3$) 7.06-7.54 (5H, m, Ph), 4.52 (1H, dt, *J* 2.1 & 6.5, H-5), 2.66 (3H, s, N-CH_3), 1.48-2.94 (4H, m, H-3 & H-4); δ_C(100 MHz; $CDCl_3$) 176.0 (s) (C=O), 141.5 (s) (C, Ar), 129.4 (s) (2 × CH, Ar), 128.5 (s) (CH, Ar),

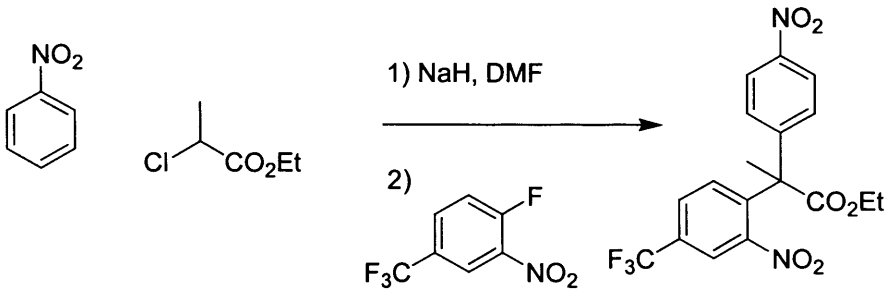
126.7 (s) (2 × CH, Ar) 65.0 (s) (CH), 30.6 (s) (CH_2), 28.8 (s) (CH_3), 28.6 (s) (CH_2); *m/z* (APCI) 176.0 [$(M+H)^+$, 100%].



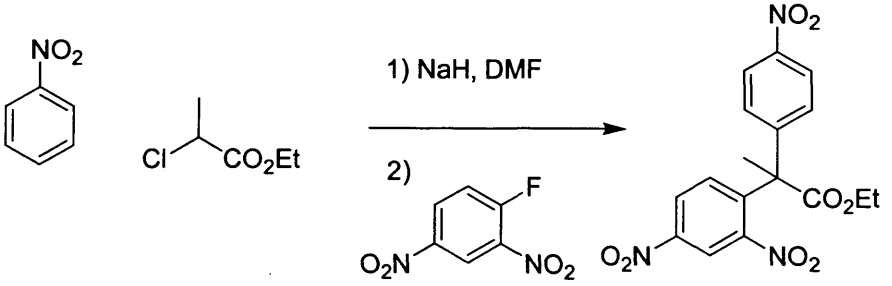
1-Methyl-5-phenyl-3-phenylsulfanylpyrrolidin-2-one **(240)**—This was prepared by the General Method using diisopropylamine (1.52 ml, 10.8 mmol) *n*-butyllithium (2.5 M in hexanes) (4.32 ml, 9.24 mmol), 1-methyl-5-phenyl-pyrroldin-2-one (**239**) (0.94g, 5.40 mmol), DMPU (4.32 ml, 5.4 mmol) and phenyl disulfide (1.2 g, 5.4 mmol) to give the crude product as a yellow oil (0.31 g). The crude product was then purified by column chromatography Rf 0.31 (hexane: ethyl acetate 3:1) to give a mixture of diastereoisomers (0.56 g, 37%) that could not be separated by column chromatography.

General Method for the VNS-S_NAr Process

Sodium hydride (60% dispersion in oil) (20.3 mmol) was added to anhydrous DMF (5 ml) and the mixture flushed with nitrogen and cooled to 0 °C. The VNS nucleophile (8.13 mmol) and the nitroarene (8.13 mmol) were dissolved in anhydrous DMF (5 ml) and added dropwise to the sodium hydride slurry. The reaction mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature. The reaction mixture was then cooled to -50 °C using CO_2/methanol cooling bath. The electrophile (8.13 mmol) in anhydrous DMF (2 ml) was then added and the resulting mixture was allowed to warm to room temperature and stirred for a further two hours. The reaction mixture was poured onto ice/hydrochloric acid (50 ml, 1 M solution) and extracted with dichloromethane (3 × 30 ml). The combined organic extracts were washed well with distilled water (5 × 50 ml), saturated aqueous sodium bicarbonate solution (3 × 50 ml), dried (magnesium sulfate) and the solvent removed under reduced pressure to give the crude product.

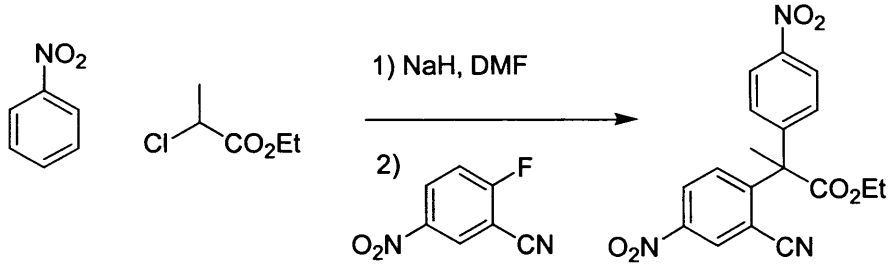


Ethyl 2-(4'-nitrophenyl)-2-(2"-nitro-4"-trifluoromethylphenyl)propionate **(257a)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.81 g, 20.3 mmol), ethyl 2-chloropropionate (1.11 g, 8.13 mmol), nitrobenzene (0.84 ml, 8.13 mmol) and 4-fluoro-3-nitrobenzotrifluoride (1.14 ml, 8.13 mmol) to give the crude product (3.09 g) as a brown oil. The crude product was then purified by column chromatography R_f 0.21 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (2.42 g, 73%) as a yellow crystalline powder. M.p. 114-115.5 °C; (Found C, 52.40; H, 3.72; N 6.82. $C_{18}H_{15}F_3N_2O_6$ requires C, 52.43; H, 3.67; N, 6.79%); υ_{max} (nujol on NaCl plates/cm^{-1}) 2924 (s), 1708 (s) (C=O), 1626 (m), 1604 (m), 1571 (m), 1518 (m), 1462 (s), 1349 (s), 1129 (s), 905 (m), 857 (s), 796 (m), 729 (s), 706 (m); δ_H(400 MHz; $CDCl_3$) 8.20-8.23 (3H, m, H-3' & H-5' & H-3"), 7.72 (1H, d, *J* 8.4 Hz, H-5"), 7.67 (2H, d, *J* 9.0 Hz, H-2' & H-6'), 7.06 (1H, d, *J* 8.4 Hz, H-6"), 4.13-4.16 (1H, m, HC<u>H</u>), 4.01-4.08 (1H, m, <u>H</u>CH), 2.25 (3H, s, CH_3), 1.18 (3H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3$); δ_C(100 MHz; $CDCl_3$) 170.8 (s) (C=O), 149.2 (s) (C, Ar), 148.6 (s) (C, Ar), 147.4 (s) (C, Ar), 143.3 (s) (C, Ar), 132.5 (s) (CH, Ar), 130.8 (q) (<u>C</u>-CF_3, *J* 34.3 Hz), 129.2 (s) (2 × CH, Ar) 124.0 (s) (2 × CH, Ar), 122.6 (s) (CH, Ar), 122.6 (q) (CF_3, *J* 271.1 Hz), 62.4 (s) (CH_2), 56.0 (s) (C, quaternary), 25.6 (s) (C-<u>C</u>H_3), 13.6 ($CH_2\underline{C}H_3$); *m/z* (APCI) 413.1 [$(M+H)^+$, 100%] 412.5 (49); (Found (ES+): $(M + NH_4)^+$ 430.1224 $C_{18}H_{15}N_2O_6F_3$ requires $(M + NH_4)^+$ 430.1226).

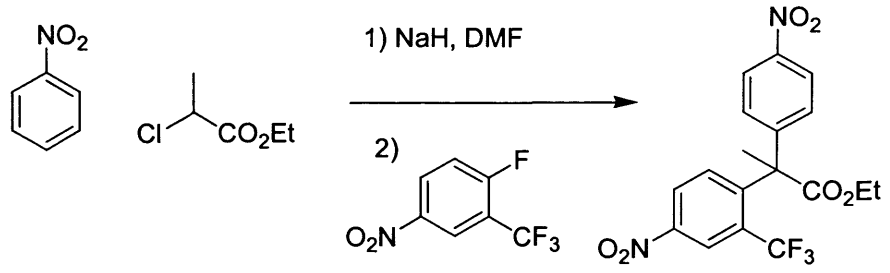


Ethyl 2-(2',4'-dinitrophenyl)-2-(4"-nitrophenyl)propionate **(257b)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.81 g, 20.3 mmol), ethyl 2-chloropropionate (1.11 g, 8.13 mmol), nitrobenzene (0.84 ml, 8.13 mmol) and 2,4-dinitrofluorobenzene (1.02 ml, 8.13 mmol) to give the crude product (2.85 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.17 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (2.41 g, 77%) as a brown oil. υ_{max} (liquid film on NaCl plates/ cm^{-1}) 2984 (m), 1738 (s) (C=O), 1604 (s), 1521 (s), 1349 (s), 909 (m), 835 (m), 650 (m); δ_H (400 MHz; $CDCl_3$) 8.80 (1H, d, *J* 2.4 Hz, H-3'), 8.30 (1H, dd, *J* 2.4 & 8.7 Hz, H-5'), 8.22 (2H, d, *J* 9.0 Hz, H-3" & H-5"), 7.68 (2H, d, *J* 9.0 Hz, H-2" & H-6"), 7.16 (1H, d, *J* 8.7 Hz, H-6'), 4.15-4.22 (1H, m, O-HC<u>H</u>-CH_3), 4.01-4.09 (1H, m, O-<u>H</u>CH-CH_3), 2.26

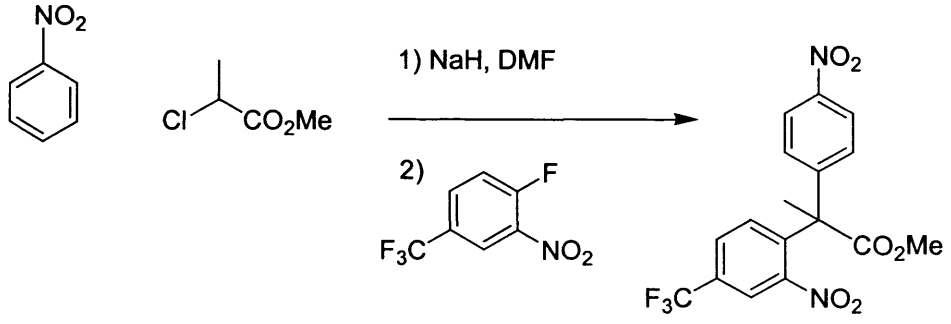
(3H, s, CH_3), 1.18 (3H, t, *J* 7.2 Hz, $C\underline{H}_3$-CH_2); δ_C (100 MHz; $CDCl_3$) 170.5 (s) (C=O), 149.4 (s) (C, Ar), 148.0 (s) (C, Ar), 147.6 (s) (C, Ar), 146.7 (s) (C, Ar), 146.0 (s) (C, Ar), 132.9 (s) (CH, Ar), 129.3 (s) (2 × CH, Ar), 126.8 (s) (CH, Ar), 123.8 (s) (2 × CH, Ar), 120.9 (s) (CH, Ar), 62.6 (s) (CH_2), 56.2 (s) (C, quaternary), 25.6 (s) (CH_3), 13.7 (s) ($\underline{C}H_3$-CH_2); *m/z* (APCI) 389.9 $[(M+H)^+$, 100%], 345.1 (36); (Found (APCI) $(M + H)^+$, 390.0943 $C_{17}H_{15}N_3O_8$ requires $(M + H)^+$ 390.0937).



Ethyl 2-(2'-cyano-4'-nitrophenyl)-2-(4"-nitrophenyl)propionate **(257c)**—This was prepared by the General Method, but cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.25 g, 6.09 mmol), ethyl 2-chloropropionate (0.52 ml, 4.07 mmol), nitrobenzene (0.21 ml , 2.03 mmol) and 2-fluoro-5-nitrobenzonitrile (0.34 g, 2.03 mmol) to give the crude product (1.08 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.18 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.66 g, 88%) as a yellow crystalline powder. M.p. 115-117 °C; υ_{max} (nujol on NaCl plates/ cm^{-1}) 2954 (s), 2853 (s), 1715(s), 1606 (m), 1527 (s), 1463 (s), 1377 (m), 1355 (s), 1257 (m), 1217 (m), 1089 (m), 1046 (m), 906 (w), 864 (m), 736 (m); δ_H (400 MHz; $CDCl_3$) 8.56 (1H, d, *J* 1.9 Hz, H-3'), 8.33 (1H, dd, *J* 1.9 & 8.8 Hz, H-5'), 8.28 (2H, d, *J* 8.6 Hz, H-3" & 5"), 7.63 (2H, d, *J* 8.6 Hz, H-2" & 6"), 7.21 (1H, d, *J* 8.8 Hz, H-6'), 4.31-4.41 (1H, m, HC$\underline{H}$-CH_3), 4.23-4.29 (1H, m, $\underline{H}$CH-CH_3), 2.17 (3H, s, CH_3), 1.28 (3H, t, *J* 7.1 Hz, $C\underline{H}_3$-CH_2); δ_C (100 MHz; $CDCl_3$) 171.4 (s) (C=O), 154.0 (s) (C, Ar), 147.7 (s) (C, Ar), 146.8 (s) (C, Ar), 146.5 (s) (C, Ar), 129.9 (s) (CH, Ar), 129.6 (s) (CH, Ar), 129.1 (s) (2 × CH, Ar), 127.2 (s) (CH, Ar), 124.0 (s) (2 × CH, Ar), 115.8 (s) (CN or $\underline{C}$-CN), 114.5 (s) (CN or $\underline{C}$-CN), 63.1 (s) (CH_2), 56.9 (s) (C, quaternary), 25.3 (s) (CH_3), 13.8 (s) ($\underline{C}H_3$-CH_2); *m/z* (APCI) 369.8 $[(M+H)^+$, 100%], 341.8 (18), 295.8 (42); (Found (ES+) $(M + NH_4)^+$, 387.1306 $C_{18}H_{15}N_3O_6$ requires $(M + NH_4)^+$ 387.1305).

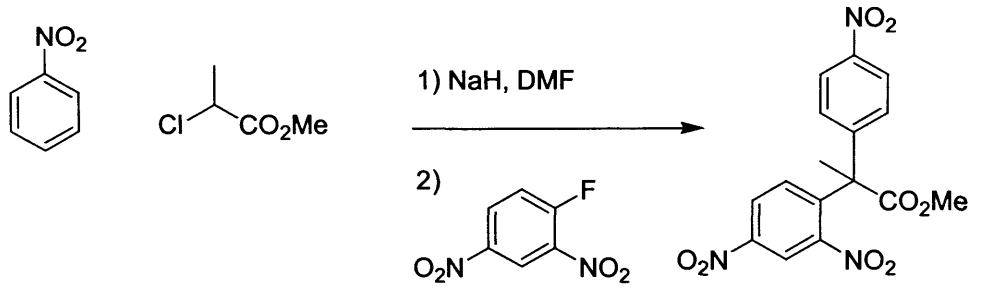


Ethyl 2-(4'-nitrophenyl)-2-(4"-nitro-2"-trifluoromethylphenyl)propionate **(257d)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.25 g, 6.09 mmol), ethyl 2-chloropropionate (0.52 ml, 4.07 mmol), nitrobenzene (0.21 ml, 2.03 mmol) and 2-fluoro-5-nitrobenzotrifluoride (0.43 g, 2.03 mmol) to give the crude product (1.20 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.26 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.75 g, 89%) as a yellow crystalline powder. M.p. 117-118.2 °C; (Found C, 51.74; H, 3.64; N 6.83. $C_{18}H_{15}F_3N_2O_6$ requires C, 52.43; H, 3.67; N, 6.79%); υ_{max} (nujol on NaCl plates/cm^{-1}) 1737 (s) (C=O), 1591 (m), 1527 (s), 1462 (s), 1349 (m), 1309 (m), 1117 (w), 910 (w), 857 (w), 737 (w); δ_H (400 MHz; $CDCl_3$) 8.58 (1H, d, *J* 2.4 Hz, H-3"), 8.32 (1H, dd, *J* 2.4 & 8.9 Hz, H-5"), 8.20 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.64 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.41 (1H, d, *J* 8.9 Hz, H-6"), 4.23-4.29 (1H, m, HC<u>H</u>-CH_3), 4.11-4.20 (1H, m, <u>H</u>CH-CH_3), 2.10 (3H, s, CH_3), 1.19 (3H, t, *J* 7.1 Hz, C<u>H</u>$_3$-CH_2) ; δ_C (100 MHz; $CDCl_3$) 172.1 (s) (C=O), 149.4 (s) (C, Ar), 148.3 (s) (C, Ar), 147.1 (s) (C, Ar), 146.8 (s) (C, Ar), 131.2 (s) (CH, Ar), 130.9 (q) (<u>C</u>-CF_3, *J* 32.6 Hz), 128.8 (s) (2 × CH, Ar), 126.1 (s) (CH, Ar), 124.4 (s) (CH, Ar), 123.6 (s) (2 × CH, Ar), 122.7 (q) (CF_3, *J* 273 Hz), 62.4 (s) (CH_2), 56.2 (s) (C, quaternary), 28.4 (s) (CH_3), 13.7 (s) (CH_3-CH_2); *m/z* (APCI) 369.8 [$(M+H)^+$, 100%], 341.8 (17.5), 295.8 (42); *m/z* (APCI) 412.9 [$(M+H)^+$, 100%], 370.1 (65), 364.9 (14); (Found (APCI) $(M + H)^+$, 413.0960. $C_{17}H_{15}N_3O_8$ requires $(M + H)^+$ 413.0953).



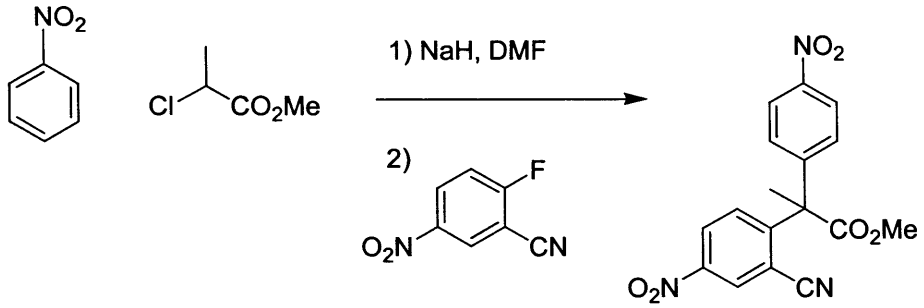
Methyl 2-(4'-nitrophenyl)-2-(2"-nitro-4"-trifluoromethylphenyl)propionate **(257e)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.81 g, 20.3 mmol), methyl 2-chloropropionate (1.0 g, 8.13 mmol), nitrobenzene (0.84 ml, 8.13 mmol)

and 4-fluoro-3-nitrobenzotrifluoride (1.14 ml, 2.03 mmol) to give the crude product (3.59 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.30 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (2.21 g, 69%) as a yellow crystalline solid. M.p. 125.5-127.5 °C; υ_{max} (nujol on NaCl plates/cm^{-1}) 2925 (s), 1974 (w), 1722 (s), 1626 (m), 1572 (m), 1518 (s), 1464 (s), 1321 (s), 1136 (s) 1048 (m), 1013 (w), 974 (m), 899 (m), 882 (m); δ_H (400 MHZ; $CDCl_3$) 8.19-8.23 (3H, m, H-3' & H-5' & H-3"), 7.72 (1H, d, *J* 8.3 Hz, H-5"), 7.68 (2H, d, *J* 8.9 Hz, H-2' & H-5'), 7.09 (1H, d, *J* 8.3 Hz, H-6"), 3.66 (3H, s, O-CH_3), 2.25 (3H, s, CH_3); δ_C (400 MHz; $CDCl_3$) 171.5 (s) (C=O), 149.3 (s) (C, Ar), 148.3 (s) (C, Ar), 147.5 (s) (C, Ar), 143.2 (s) (C, Ar), 132.3 (s) (CH, Ar), 131.0 (q) (C-CF_3, *J* 34.5 Hz), 129.3 (s) (2 × CH, Ar), 129.3 (s) (CH, Ar), 123.7 (s) (2 × CH, Ar), 122.8 (s) (C, Ar), 122.3 (q) (CF_3, *J* 271.1 Hz), 55.9 (s) (C, quaternary), 52.9 (s) (H_3C-O-), 25.8 (s) (CH_3); *m/z* (EI) 398.1 [(MI), 100%] (Found (EI) M^+ 398.0723 $C_{17}H_{13}F_3N_2O_6$ requires M^+ 398.0720).

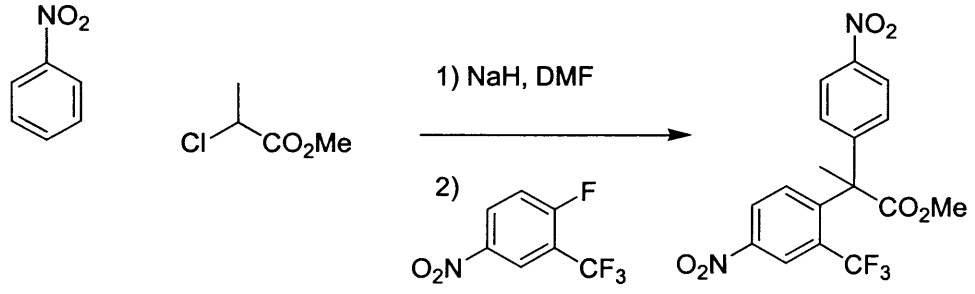


Methyl 2-(2',4'-dinitrophenyl)-2-(4"-nitrophenyl)propionate **(257f)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.20 g, 5.10 mmol), methyl 2-chloropropionate (0.25 g, 2.03 mmol), nitrobenzene (0.21 ml, 2.03 mmol) and 2,4-dinitrofluorobenzene (0.26 ml, 2.03 mmol) to give the crude product (0.79 g) as a brown oil. The crude product was then purified by column chromatography, Rf 0.45 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.53 g, 71%) as a yellow crystalline solid. M.p. 153-155 °C; υ_{max} (nujol on NaCl plates/cm^{-1}) 2925 (s), 1731 (s), 1600 (s), 1463 (s), 1349 (s), 1204 (m), 1125 (w), 1093 (m), 1046 (w), 1012 (w), 981 (m), 919 (m), 900 (w), 869 (w), 834 (m), 737 (m); δ_H (400 MHz; $CDCl_3$) 8.80 (1H, d, *J* 2.4 Hz, H-3'), 8.30 (1H, dd, *J* 2.4 & 8.8 Hz, H-5'), 8.23 (2H, d, *J* 9.0 Hz, H-3" & H-5"), 7.66 (2H, d, *J* 9.0 Hz, H-2" & H-6"), 7.14 (1H, d, *J* 8.8 Hz, H-6'), 3.72 (3H, s, O-CH_3), 2.26 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 171.1 (s) (C=O), 149.4 (s) (C, Ar), 147.8 (s) (C, Ar), 147.7 (s) (C, Ar), 146.7 (s) (C, Ar), 145.8 (s) (C, Ar), 132.8 (s) (CH, Ar), 129.3 (s) (2 × CH, Ar), 126.8 (s) (CH, Ar), 123.9 (s) (CH, Ar), 120.9 (s) (CH, Ar), 56.1 (s) (C, quaternary), 53.1 (s) (O-CH_3), 25.7 (s) (CH_3); *m/z* (APCI) 375.9

[$(M+H)^+$, 100%], 343.8 (44), 315.8 (13),; (Found (ES+) $(M + NH_4)^+$, 393.1041, $C_{16}H_{13}N_3O_8$ requires $(M + NH_4)^+$ 393.1046).

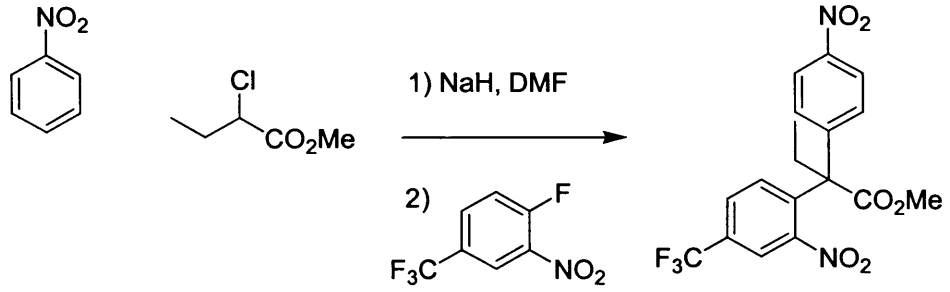


Methyl 2-(2'-cyano-4'-nitrophenyl)-2-(4"-nitrophenyl)propionate **(257g)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.25 g, 6.09 mmol), methyl 2-chloropropionate (0.47 ml, 4.07 mmol), nitrobenzene (0.21 ml, 2.03 mmol) and 2-fluoro-5-nitrobenzonitrile (0.34 g, 2.04 mmol) to give the crude product (1.0 g) as a brown oil. The crude product was then purified by column chromatography, Rf 0.19 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.62 g, 86%) as a yellow crystalline solid. M.p. 163-164.4 °C; (Found C, 58.04; H, 3.85; N 11.93. $C_{18}H_{15}F_3N_2O_6$ requires C, 57.47; H, 3.69; N, 11.82%); υ_{max} (nujol on NaCl plates/ cm^{-1}) 2922 (s), 2852 (s), 2225 (w), 1724 (s), 1607 (m), 1520. (s), 1464 (s), 1377 (w) 1356 (s), 1256 (m), 1217 (m), 1088 (m), 1046 (m), 905 (m), 836 (m), 736 (m); δ_H (400 MHz; $CDCl_3$) 8.57 (1H, d, *J* 2.4 Hz, H-3'), 8.32 (1H, dd, *J* 2.4 & 8.8 Hz, H-5'), 8.30 (2H, d, *J* 8.9 Hz, H-3" & H-5"), 7.63 (2H, d, *J* 8.9 Hz, H-2" & H-6"), 7.18 (1H, d, *J* 8.8 Hz, H-6'), 3.86 (3H, s, O-CH_3), 2.26 (3H, s, CH_3); δ_C (100 MH_Z; $CDCl_3$) 171.9 (s) (C=O), 153.9 (s) (C, Ar), 147.7 (s) (C, Ar), 146.6 (s) (C, Ar), 129.9 (s) (CH, Ar), 129.6 (s) (CH, Ar), 129.1 (s) (2 × CH, Ar), 127.2 (s) (CH, Ar), 124.1 (s) (2 × CH, Ar), 115.7 (s) (CN or C-CN), 114.4 (s) (CN or C-CN), 56.9 (s) (C, quaternary), 53.7 (s) (O-CH_3), 25.3 (s) (CH_3); *m/z* (APCI) 355.9 [$(M+H)^+$, 100%], 335.7 (10), 295.9 (12); (Found (ES+) $(M + NH_4)^+$, 373.1147, $C_{17}H_{13}N_3O_6$ requires $(M + NH_4)^+$ 373.1148).



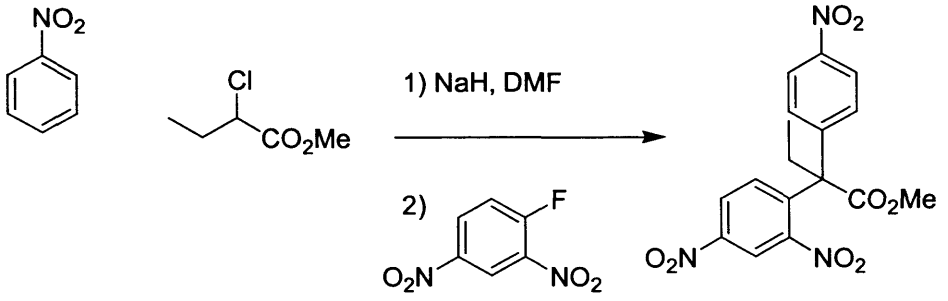
Methyl 2-(4'-nitrophenyl)-2-(4"-nitro-2"-trifluoromethyl)phenylpropionate **(257h)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride

(60% dispersion in oil) (0.25 g, 6.09 mmol), methyl 2-chloropropionate (0.47 ml, 4.07 mmol), nitrobenzene (0.21 ml , 2.03 mmol) and 2-fluoro-5-nitrobenzotrifluoride (0.45 ml, 2.04 mmol) to give the crude product (1.27 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.24 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.70 g, 86%) as a yellow crystalline solid. M.p. 135.5-137.5 °C; (Found C, 51.43; H, 3.27; N 6.92. $C_{18}H_{15}F_3N_2O_6$ requires C, 51.27; H, 3.29; N, 7.03%); υ_{max} (nujol on NaCl plates/cm^{-1}) 2922 (s), 1742 (m), 1594 (w), 1512 (m), 1461 (s), 1377 (s), 1170 (m), 1124 (m), 1071 (w), 920 (w), 854 (m); δ_H (400 MHz; $CDCl_3$) 8.59 (1H, d, *J* 2.4 Hz, H-3"), 8.34 (1H, dd, *J* 2.4 & 8.9 Hz, H-5"), 8.13 (2H, d, *J* 9.0 Hz, H-3' & H-5'), 7.64 (2H, d, *J* 9.0 Hz, H-2' & H-6'), 7.44 (1H, d, *J* 8.9 Hz, H-6"), 3.74 (3H, s, O-CH_3), 2.12 (3H, s, CH_3); δ_C (100 MH_Z; $CDCl_3$) 173.0 (s) (C=O), 149.6 (s) (C, Ar), 148.6 (s) (C, Ar), 147.6 (s) (C, Ar), 147.3 (s) 131.6 (s) (CH, Ar), 131.2 (q) (C-CF_3, *J* 32.1 Hz), 130.3 (s) (CH, Ar), 129.1 (s) (2 × CH, Ar), 126.5 (s) (CH, Ar), 124.8 (s) (C, Ar), 124.0 (s) (2 × CH, Ar)123.6 (q) (CF_3, *J* 273.5 Hz), 123.0 (C, Ar), 56.5 (s) (C, quaternary), 53.5 (s) (O-CH_3), 28.8 (s) (CH_3); *m/z* (APCI) 399.0 [$(M+H)^+$, 100%]; (Found (CI) $(M + NH_4)^+$, 416.1067, $C_{17}H_{13}N_3O_6$ requires $(M + NH_4)^+$ 416.1069).

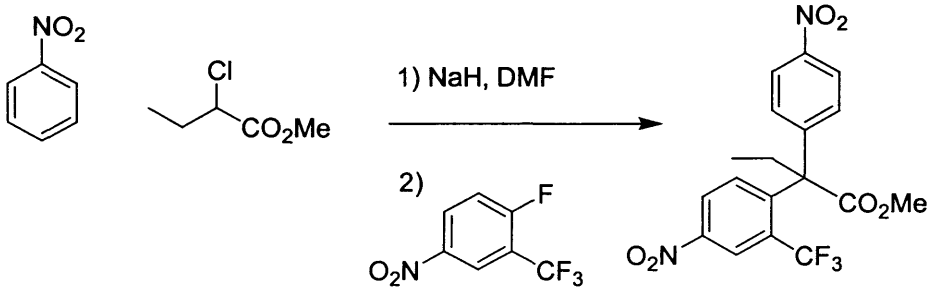


Methyl 2-(4'-nitrophenyl)-2-(2"-nitro-4"-trifluoromethyl)butanoate **(257i)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.19 g, 4.60 mmol), methyl 2-chlorobutanoate (0.25 g, 1.83 mmol), nitrobenzene (0.19 ml, 1.83 mmol) and 4-fluoro-3-nitrobenzotrifluoride (0.26 ml, 1.83 mmol) to give the crude product (0.78 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.38 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.45 g, 60%) as a yellow oil. υ_{max} (liquid film on NaCl plates/cm^{-1}) 3090 (m), 2955 (s), 1739 (s), 1629 (s), 1606 (m), 1538 (s), 1462 (m), 1327 (s), 1127 (s) 1014 (s), 903 (s), 883 (w), 851 (s), 798 (m), 752 (m); δ_H (400 MHz; $CDCl_3$) 8.21 (1H, d, *J* 1.3 Hz, H-3"), 8.16 (2H, d, *J* 9.0 Hz, H-3' & H-5'), 7.85 (1H, dd, *J* 1.3 & 8.4 Hz, H-5"), 7.63 (2H, d, *J* 9.0 Hz, H-2' & H-6'), 7.46 (1H, d, *J* 8.4 Hz, H-6"), 3.65 (3H, s, O-CH_3), 2.74-2.83 (1H, m, HC<u>H</u>-CH_3), 2.64-2.72 (1H, m, <u>H</u>CH-CH_3), 0.90 (3H, t, *J* 7.4 Hz, CH_3); δ_C (100 MH_Z; $CDCl_3$) 171.0 (s) (C=O), 150.0 (s) (C, Ar), 147.4 (s) (C, Ar), 147.0 (s) (C, Ar), 140.1 (s) (C, Ar), 132.6 (s) 131.1 (q) (C-CF_3, *J*

34.7 Hz), 129.6 (s) (2 × CH, Ar), 128.6 (s) (CH, Ar), 123.4 (s) (2 × CH, Ar), 123.1 (s) (CH, Ar), 59.5 (s) (C, quaternary), 52.7 (s) (O-CH_3), 30.6 (s) (CH_2), 9.7 (s) (CH_3); *m/z* (APCI) [$(M + H)^+$, 100%], (Found: $(M + NH_4)^+$ (ES+): 430.1221 $C_{18}H_{15}F_3N_2O_6$ requires $(M + NH_4)^+$ 430.1226).



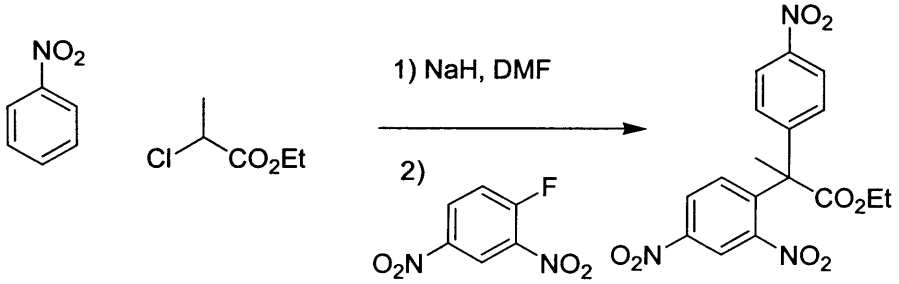
Methyl 2-(2',4'-dinitrophenyl)-2-(4"-nitrophenyl)butanoate **(257j)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.23 g, 5.75 mmol), methyl 2-chlorobutanoate (0.50 g, 3.66 mmol), nitrobenzene (0.19 ml, 1.83 mmol) and 2,4-dinitrofluorobenzene (0.23 ml, 1.90 mmol) to give the crude product (0.85 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.12 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.57 g, 80%) as a yellow crystalline solid. M.p. 59.1-61.7 °C; υ_{max} (nujol on NaCl plates/ cm^{-1}) 2922 (s), 1738 (s), 1462 (s), 1376 (m); δ_H (400 MH_Z; $CDCl_3$) 8.78 (1H, d, *J* 2.4 Hz, H-3'), 8.45 (1H, dd, *J* 2.4 & 8.9 Hz, H-5'), 8.16 (2H, d, *J* 9.0 Hz, H-3" & H-5"), 7.64 (2H, d, *J* 9.0 Hz, H-2" & H-6"), 7.59 (1H, d, *J* 8.9 Hz, H-6'), 3.66 (3H, s, O-CH_3), 2.79-2.89 (1H, m, HC<u>H</u>), 2.67-2.77 (1H, m, <u>H</u>CH), 0.92 (3H, t, *J* 7.4 Hz, C<u>H</u>$_3$-CH_2); δ_C (100 MH_Z; $CDCl_3$) 170.7 (s) (C=O), 150.1 (s) (C, Ar), 147.1 (s) (C, Ar), 146.9 (s) (C, Ar), 142.9 (s) (C, Ar), 133.1 (s) (CH, Ar), 129.7 (s) (2 × CH, Ar), 126.3 (s) (CH, Ar), 123.5 (s) (2 × CH, Ar), 121.2 (s) (CH, Ar), 59.7 (s) (C, quaternary), 52.8 (s) (O-CH_3), 30.8 (s) (CH_2), 9.7 (s) (CH_3); *m/z* (APCI) [$(M + H)^+$, 100%], (Found: $(M + NH_4)^+$ (ES+): 407.1198 $C_{17}H_{15}N_3O_8$ requires $(M + NH_4)^+$ 407.1203).



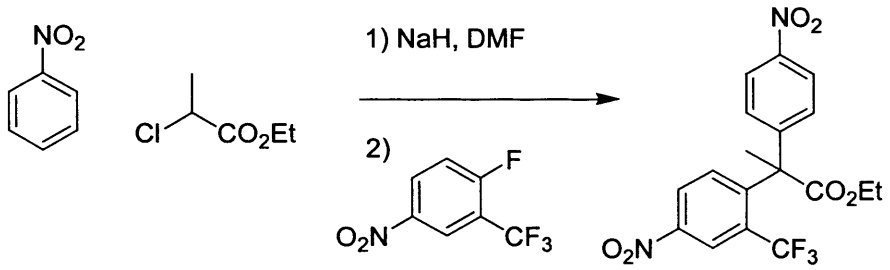
Methyl 2-(4'-nitrophenyl)-2-(4"-nitro-2"-trifluoromethylphenyl)butanoate **(257k)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60%

dispersion in oil) (0.18 g, 4.50 mmol), methyl 2-chlorobutanoate (0.25 g 1.83 mmol), nitrobenzene (0.19 ml, 1.83 mmol) and 2-fluoro-5-nitrobenzotrifluoride (0.38 g, 1.83 mmol) to give the crude product (0.72 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.23 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.52 g, 69%) as a yellow crystalline solid. M.p. 119-121 °C; υ_{max} (nujol on NaCl plates/cm^{-1}) 2966 (s), 1737 (s), 1618 (m), 1591 (m), 1529 (m), 1376 (s), 1173 (m), 1122 (m), 1051 (m), 998 (m), 909 (m), 854 (m), 740 (m); δ_H (400 MH_Z; $CDCl_3$) 8.50 (1H, d, *J* 2.5 Hz, H-3"), 8.38 (1H, dd, *J* 2.5 & 8.8 Hz, H-5"), 8.06 (2H, d, *J* 9.0 Hz, H-3' & H-5'), 7.73 (1H, d, *J* 8.8 Hz, H-6"), 7.57 (2H, d, *J* 9.0 Hz, H-2' & H-6'), 3.62 (3H, s, O-CH_3), 2.53-2.62 (1H, m, HCH), 2.28-2.37 (1H, m, HCH), 0.84 (3H, t, *J* 7.3 Hz, CH_2CH_3); δ_C (100 MH_Z; $CDCl_3$) 171.9 (s) (C=O), 149.0 (s) (C, Ar), 147.3 (s) (C, Ar), 147.1 (s) (C, Ar), 147.0 (s) (C, Ar), 131.8 (q) (C-CF_3 *J* 32 Hz), 131.2 (s) (CH, Ar), 129.4 (s) (2 × CH, Ar), 126.4 (s) (CH, Ar), 124.9 (s) (CH, Ar), 123.6 (s) (2 × CH, Ar), 59.4 (s) (C, quaternary), 53.0 (s) (O-CH_3), 34.8 (s) (CH_2), 10.2 (s) (CH_3CH_2); *m/z* (APCI) 412.9 [$(M+H)^+$, 100%], (Found: $(M + NH_4)^+$ (Ammonia CI) 430.1228, $C_{18}H_{15}F_3N_2O_6$ requires $(M + NH_4)^+$ 430.1226).

General Method for VNS-S_NAr with KO*t*-Bu—In a three necked round bottomed flask fitted with a condenser and nitrogen bubbler was added potassium *tert*-butoxide (7.2 mmol) followed by anhydrous DMF (5 ml). Nitrobenzene (2.39 mmol) the VNS nucleophile (4.8 mmol) dissolved in anhydrous DMF (2 ml) were added at –40 °C. The reaction mixture was stirred for 30 minutes allowing the temperature to warm to –20 °C. The reaction mixture was then checked by LC. The electrophile (3.59 mmol) was then added dropwise to the reaction mixture. The solution was then allowed to warm to room temperature and stirred for 4 hours. The reaction mixture was then poured onto ice/HCl (1M solution) and then extracted with dichloromethane (3 × 50 ml). The organic solution was then washed with water (3 × 50 ml) and then dried over Na_2SO_4. The solvent was removed to give the crude product.

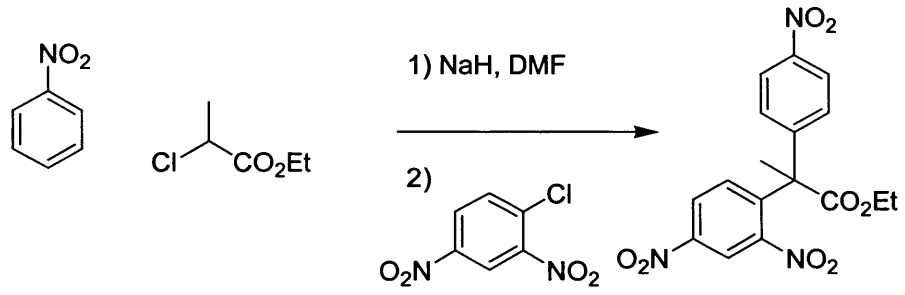


Ethyl 2-(2',4'-dinitrophenyl)-2-(4"-nitrophenyl)propionate (**257b**)—This was prepared by the method above using potassium *tert*-butoxide (0.80 g, 7.2 mmol), ethyl 2-chloropropionate (0.61 ml, 4.8 mmol), nitrobenzene (0.25 ml, 2.39 mmol) and 2,4-dinitrofluorobenzene (0.45 ml, 3.59 mmol) to give the crude product as an orange oil (2.02 g). The crude product was then purified by column chromatography Rf 0.17 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.53 g , 57%) as an orange oil. υ_{max} (liquid film on NaCl plates/ cm^{-1}) 2984 (m), 1738 (s) (C=O), 1604 (s), 1521 (s), 1349 (s), 909 (m), 835 (m), 650 (m); δ_H (400 MHz; $CDCl_3$) 8.80 (1H, d, *J* 2.4 Hz, H-3'), 8.30 (1H, dd, *J* 2.4 & 8.7 Hz, H-5'), 8.22 (2H, d, *J* 9.0 Hz, H-3" & H-5"), 7.68 (2H, d, *J* 9.0 Hz, H-2" & H-6"), 7.16 (1H, d, *J* 8.7 Hz, H-6'), 4.15-4.22 (1H, m, O-HC<u>H</u>-CH_3), 4.01-4.09 (1H, m, O-<u>H</u>CH-CH_3), 2.26 (3H, s, CH_3), 1.18 (3H, t, *J* 7.2 Hz, <u>CH_3</u>-CH_2); δ_C (100 MHz; $CDCl_3$) 170.5 (s) (C=O), 149.4 (s) (C, Ar), 148.0 (s) (C, Ar), 147.6 (s) (C, Ar), 146.7 (s) (C, Ar), 146.0 (s) (C, Ar), 132.9 (s) (CH, Ar), 129.3 (s) (2 × CH, Ar), 126.8 (s) (CH, Ar), 123.8 (s) (2 × CH, Ar), 120.9 (s) (CH, Ar), 62.6 (s) (CH_2), 56.2 (s) (C, quaternary), 25.6 (s) (CH_3), 13.7 (s) (<u>CH_3</u>-CH_2); *m/z* (APCI) 389.9 [$(M+H)^+$, 100%], 345.1 (36); (Found (APCI) $(M + H)^+$ 390.0943. $C_{17}H_{15}N_3O_8$ requires $(M + H)^+$ 390.0937).

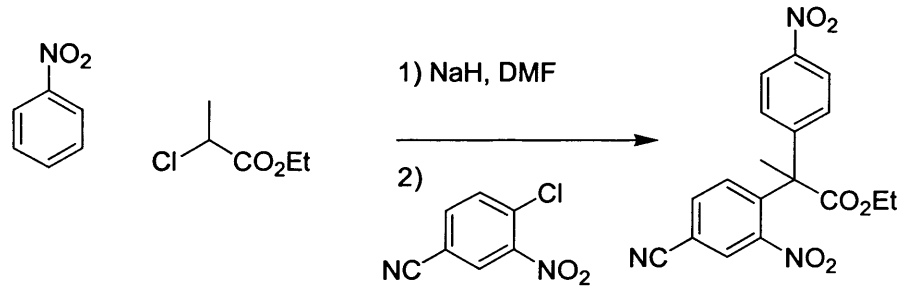


Ethyl 2-(4'-nitrophenyl)2-(4"-nitro-2"- trifluoromethylphenyl)propionate (**257d**)—This was prepared by the General Method using potassium *tert*-butoxide (0.80 g, 7.2 mmol), ethyl 2-chloropropionate (0.61 ml, 4.8 mmol), nitrobenzene (0.25 ml, 2.39 mmol) and 2-fluoro-5-nitrobenzotrifluoride (0.44 ml, 3.1 mmol) to give the crude product (1.10 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.26 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.68 g, 69%) as a yellow crystalline powder. M.p. 117-118.2 °C; (Found C, 51.74; H, 3.64; N 6.83. $C_{18}H_{15}F_3N_2O_6$ requires C, 52.43; H, 3.67; N, 6.79%); υ_{max} (nujol on NaCl plates/cm^{-1}) 1737 (s) (C=O), 1591 (m), 1527 (s), 1462 (s), 1349 (m), 1309 (m), 1117 (w), 910 (w), 857 (w), 737 (w); δ_H (400 MHz; $CDCl_3$) 8.58 (1H, d, *J* 2.4 Hz, H-3"), 8.32 (1H, dd, *J* 2.4 & 8.9 Hz, H-5"), 8.20 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.64 (2H, d, *J* 8.9 Hz, H-2' & H-6'), 7.41 (1H, d, *J* 8.9 Hz, H-6"), 4.23-4.29 (1H, m, HC<u>H</u>-CH_3), 4.11-4.20 (1H, m, <u>H</u>CH-CH_3), 2.10 (3H, s, CH_3), 1.19 (3H, t, *J* 7.1 Hz, <u>CH_3</u>-CH_2) ; δ_C (100 MHz; $CDCl_3$) 172.1 (s) (C=O), 149.4 (s) (C, Ar), 148.3 (s) (C, Ar), 147.1 (s) (C, Ar),

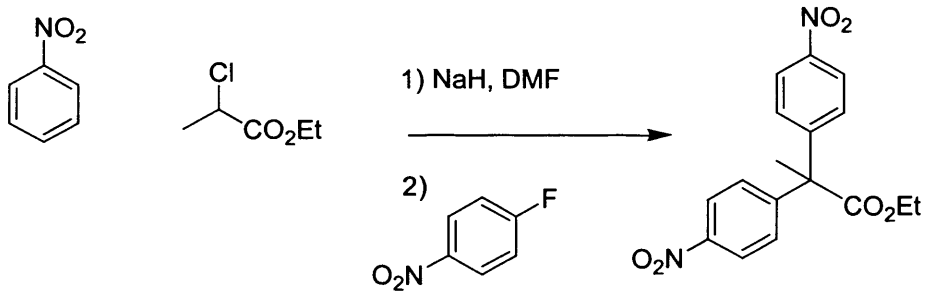
146.8 (s) (C, Ar), 131.2 (s) (CH, Ar), 130.9 (q) (C-CF_3, *J* 32.6 Hz), 128.8 (s) (2 × CH, Ar), 126.1 (s) (CH, Ar), 124.4 (s) (CH, Ar), 123.6 (s) (2 × CH, Ar), 122.7 (q) (CF_3, *J* 273 Hz), 62.4 (s) (CH_2), 56.2 (s) (C, quaternary), 28.4 (s) (CH_3), 13.7 (s) (CH_3-CH_2); *m/z* (APCI) 369.8 $[(M+H)^+$, 100%], 341.8 (17.5), 295.8 (42); *m/z* (APCI) 412.9 $[(M+H)^+$, 100%], 370.1 (65), 364.9 (14); (Found (APCI) $(M + H)^+$ 413.0960. $C_{17}H_{15}N_3O_8$ requires $(M + H)^+$ 413.0953).



Ethyl 2-(2',4'-dinitrophenyl)-2-(4"-nitrophenyl)propionate **(257b)**—This was prepared by the General Method used in the previous compound using sodium hydride (60% dispersion in oil) (0.81 g, 20.3 mmol), ethyl 2-chloropropionate (1.11g, 8.13 mmol), nitrobenzene (0.84 ml, 8.13 mmol) and 2,4-dinitrochlorobenzene (1.64 g, 8.13 mmol) to give the crude product (2.85 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.17 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (2.16 g, 69%) as a brown oil. υ_{max} (liquid film on NaCl plates/ cm^{-1}) 2984 (m), 1738 (s) (C=O), 1604 (s), 1521 (s), 1349 (s), 909 (m), 835 (m), 650 (m); δ_H (400 MHz; $CDCl_3$) 8.80 (1H, d, *J* 2.4 Hz, H-3'), 8.30 (1H, dd, *J* 2.4 & 8.7 Hz, H-5'), 8.22 (2H, d, *J* 9.0 Hz, H-3" & H-5"), 7.68 (2H, d, *J* 9.0 Hz, H-2" & H-6"), 7.16 (1H, d, *J* 8.7 Hz, H-6'), 4.15-4.22 (1H, m, O-HC<u>H</u>-CH_3), 4.01-4.09 (1H, m, O-<u>H</u>CH-CH_3), 2.26 (3H, s, CH_3), 1.18 (3H, t, *J* 7.2 Hz, <u>C</u>H_3-CH_2); δ_C (100 MHz; $CDCl_3$) 170.5 (s) (C=O), 149.4 (s) (C, Ar), 148.0 (s) (C, Ar), 147.6 (s) (C, Ar), 146.7 (s) (C, Ar), 146.0 (s) (C, Ar), 132.9 (s) (CH, Ar), 129.3 (s) (2 × CH, Ar), 126.8 (s) (CH, Ar), 123.8 (s) (2 × CH, Ar), 120.9 (s) (CH, Ar), 62.6 (s) (CH_2), 56.2 (s) (C, quaternary), 25.6 (s) (CH_3), 13.7 (s) (<u>C</u>H_3-CH_2); *m/z* (APCI) 389.9 $[(M+H)^+$, 100%], 345.1 (36); (Found (APCI) $(M + H)^+$ 390.0943 $C_{17}H_{15}N_3O_8$ requires $(M + H)^+$ 390.0937).

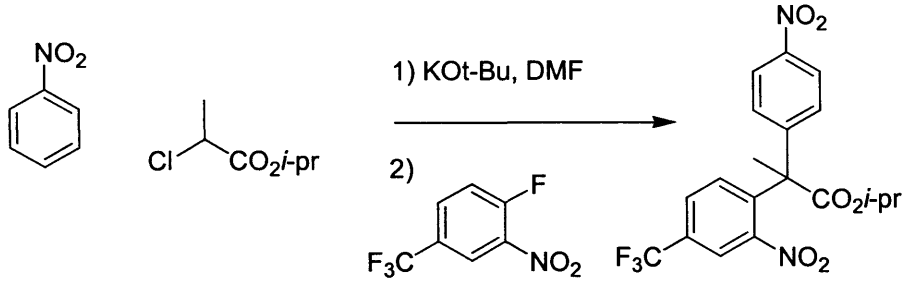


Ethyl 2-(4'-cyano-2'-nitro)-2-(4"-nitrophenyl)propionate **(257l)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.68 g, 17.01 mmol), ethyl 2-chloropropionate (1.24 ml, 9.72 mmol), nitrobenzene (0.5 ml, 4.86 mmol) and 4-chloro-3-nitrobenzonitrile (0.89 g, 4.86 mmol) to give the crude product (4.02 g) as a brown oil. The crude product was then purified by column chromatography Rf 0.12 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (1.29 g, 72%) as a brown crystalline solid. M.p. 129-131 °C υ_{max} (nujol NaCl plates/ cm^{-1}) 2919 (s), 2234 (w), 1721 (s), (C=O), 1603 (w) 1464 (s), 1347 (s), 1265 (m); δ_H (400 MHz; $CDCl_3$) 8.17 (1H, d, *J* 1.8 Hz, H-3'), 8.15 (2H, d, *J* 9.0 Hz, H-3" & H-5"), 7.66 (1H, dd, *J* 1.7 & 8.2 Hz, H-5'), 7.58 (2H, d, *J* 9.0 Hz, H-2" & H-6"), 6.97 (1H, d, *J* 8.7 Hz, H-6'), 4.10 (1H, dq, *J* 3.7 & 7.2 Hz, HCH-CH_3), 3.97 (1H, dq, *J* 3.7 & 7.2 Hz, HCH-CH_3), 2.16 (3H, s, CH_3), 1.11 (3H, t, J 7.2 Hz, CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 171.0 (s) (C=O), 149.8 (s) (C, Ar), 148.5 (s) (C, Ar), 147.9 (s) (C, Ar), 144.8 (s) (C, Ar), 136.0 (s) (CH, Ar), 133.0 (s) (CH, Ar), 129.7 (s) (2 × CH, Ar), 129.4 (s) (CH, Ar), 124.2 (s) (2 × CH, Ar), 116.5 (s) (C, Ar), 113.2 (s) (C, Ar), 62.0 (s) (CH_2), 56.5 (s) (C, quaternary), 25.9 (s) (CH_3), 14.1 (s) (CH_3-CH_2); *m/z* (APCI) 370.1 [$(M+H)^+$, 100%]; (Found (APCI) $(M + NH_4)^+$, 387.1308 $C_{17}H_{15}N_3O_8$ requires $(M + NH_4)^+$ 387.1305).

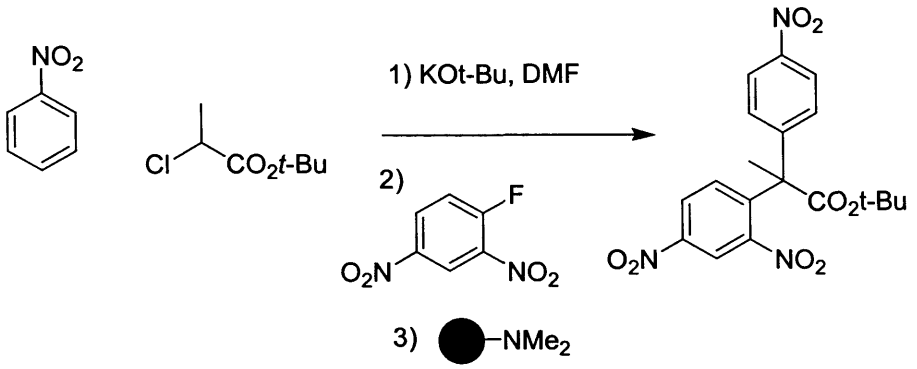


Ethyl 2,2-bis(4'-nitrophenyl)propionate[230] **(257m)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (1.3 g, 32.54 mmol), ethyl 2-chloro-propionate (2.07 ml, 16.26mmol), nitrobenzene (0.84 ml, 8.13 mmol) and 4-fluoronitrobenzene (0.86 ml, 8.13 mmol) to give the crude product (3.68 g) as an orange oil. The crude product was then purified by column chromatography Rf 0.24 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (2.07 g, 74%) as an orange oil; υ_{max} (nujol on NaCl plates/cm^{-1}) 3081 (w), 2989 (s), 2457(w), 1928 (w), 1721 (s), 1596 (s), 1530 (s), 1463 (s) 1342 (s), 1248 (s), 1094 (s), 1014 (s), 858 (m); δ_H (400 MHz; $CDCl_3$) 8.10 (4H, d, *J* 8.9 Hz, H-3'& H-5'), 7.33 (4H, d, *J* 8.9 Hz, H-2' & H-6'),4.19 (2H, q, *J* 7.1 Hz, CH_2), 1.93 (3H, s, CH_3), 1.16 (3H, t, *J* 7.1 Hz, CH_2CH_3), δ_C (100 MHz; $CDCl_3$) 173.2 (s) (C=O), 150.9 (s) (C, Ar), 147.3 (s) (C, Ar), 129.4 (s) (4 × CH, Ar), 123.9 (s) (4 × CH, Ar), 62.8 (s) (CH_2), 57.2

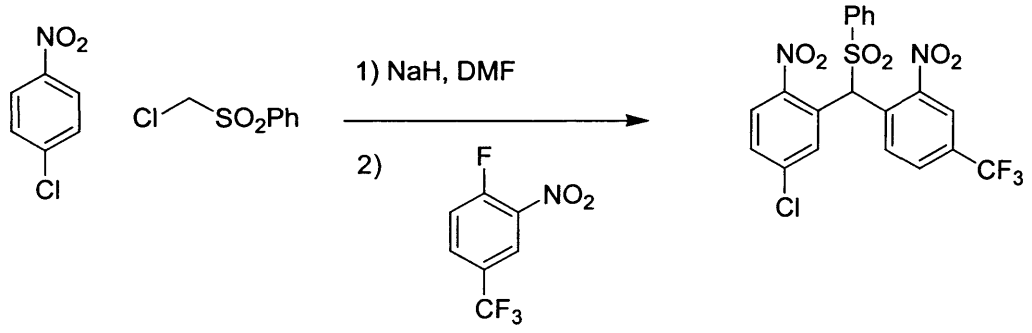
(s) (C, quaternary), 27.0 (s) (CH_3), 14.3 (s) (CH_3); *m/z* (APCI) 345.1 [$(M+H)^+$, 100%], (Found: MI (EI) 344.1004 $C_{17}H_{16}N_2O_6$ requires MI 344.1003).



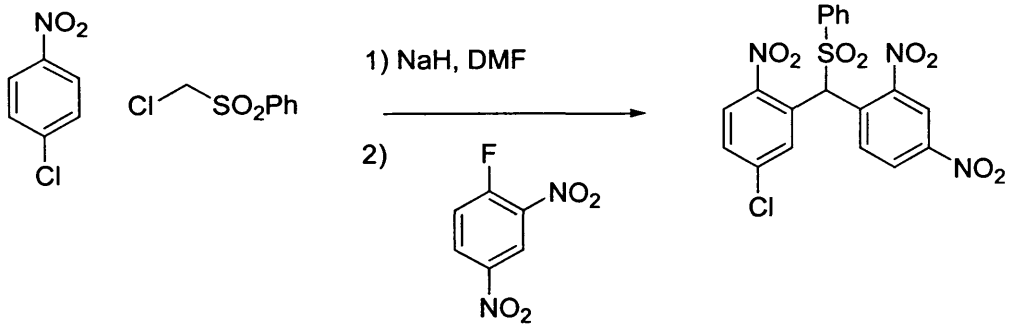
Isopropyl 2-(4'-nitrophenyl)-2-(2"-nitro-4"-trifluoromethylphenyl)propionate **(268)**—In a 100 ml round bottom flask was added potassium *tert*-butoxide (0.75 g, 6.64 mmol) and DMF (5 ml). The mixture was flushed with nitrogen and cooled to –50 °C in a CO_2/methanol cooling bath. Nitrobenzene (0.34 ml, 3.32 mmol) and isopropyl 2-chloropropionate (0.50 g, 3.32 mmol) dissolved in anhydrous DMF (5 ml) was added dropwise to the reaction mixture. The bright purple solution was stirred at –50 °C for 10 minutes and then slowly warmed to –20 °C before cooling back to –50 °C. 4-Fluoro-3-nitrobenzotrifluoride (0.47 ml, 3.32 mmol) was added dropwise to the reaction mixture, which was then slowly warmed to room temperature. The reaction mixture was stirred at room temperature for 2 hours and then poured onto a ice/HCl (1M) solution. The product was extracted with dichloromethane (3 × 30 ml), then washed with water (3 × 30 ml), sodium bicarbonate (30 ml) and dried over sodium sulfate. The drying agent was filtered and the solvent removed on a rotary evaporator to give an orange oil (1.7 g). The crude product was then purified by column chromatography R_f 0.25 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.86 g, 61%) as a yellow crystalline powder. M.p. 284-286 °C υ_{max} (nujol NaCl plates/ cm^{-1}) 2922 (s), 1705 (s), (C=O), 1630 (w) 1454 (s), 1376 (m), 1318 (m); δ_H (400 MHz; $CDCl_3$) 8.13-8.16 (3H, m, H-3" & H-3' & H-5'), 7.64 (1H, dd, *J* 1.7 & 8.5 Hz, H-5"), 7.60 (2H, d, *J* 9.0 Hz, H-2' & H-6'), 7.0 (1H, d, *J* 8.5 Hz, H-6"), 4.88 (1H, sept, *J* 6.3 Hz, C<u>H</u>-$(CH_3)_2$), 2.16 (3H, s, CH_3), 1.09 (3H, d, *J* 6.3 Hz, C<u>H</u>$_3$-CH-CH_3), 1.03 (3H, d, *J* 6.3 Hz, CH_3-CH-C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 170.6 (s) (C=O), 149.6 (s) (C, Ar), 149.0 (s) (C, Ar), 147.8 (s) (C, Ar), 143.7 (s) (C, Ar), 132.8 (s) (CH, Ar), 130.9 (q) (*J* 34.3 Hz) (<u>C</u>-CF_3), 129.3 (s) (2 × CH, Ar), 129.2 (s) (CH, Ar), 123.6 (s) (2 × CH, Ar), 122.9 (s) (CH, Ar), 122.6 (q) (*J* 271.2 Hz) (CF_3), 70.7 (s) (C-O), 56.2 (s) (C, quaternary), 25.5 (s) (CH_3), 21.4 (s) (CH_3), 21.1 (s) (CH_3); *m/z* (APCI) 427 [$(M+H)^+$, 100%], 316 (8); (Found (ES+) $(M + NH_4)^+$ 444.1383. $C_{19}H_{17}N_2O_6F_3$ requires $(M + NH_4)^+$ 444.1377).



tert-Butyl 2-(2',4'-dinitrophenyl)-2-(4"-nitrophenyl)propionate **(271)**—This was prepared by the General Method using potassium *tert*-butoxide (0.85 g, 7.6 mmol), *tert*-butyl 2-chloropropionate (0.50 g, 3.04 mmol), nitrobenzene (0.31 ml, 3.04 mmol), 2,4-dinitrofluorobenzene (0.57 ml, 4.56 mmol) and anhydrous DMF (10 ml) to give the crude product as an orange oil (2.51 g). The crude product was then purified by column chromatography Rf 0.29 (silica, 7:3. hexane:acetone; v/v) to give the product as an orange oil (1.0 g). To remove the excess 2,4-dinitrofluorobenzene still present the product was dissolved in ethyl acetate (5 ml) and added to a plastic filter syringe containing poly(styrene-co divinylbenzene)amino methylated (0.75 g). The column was fitted with a cap and shaken vigorously for 24 hours. The filtrate was then collected and the solvent removed on a rotary evaporator to give the pure product as an orange oil (0.88 g, 69%). υ_{max} (oil, NaCl plates/ cm^{-1}) 2918 (s), 1731 (s), 1603 (s), 1524 (s), 1463 (s), 1375 (s); δ_H (400 MHz; $CDCl_3$) 8.72 (1H, d, *J* 2.4 Hz, H-3'), 8.20 (1H, dd, *J* 2.4 & 8.6 Hz, H-5'), 8.16 (2H, d, *J* 9.0 Hz, H-3" & H-5"), 7.58 (2H, d, *J* 9.0 Hz, H-2" & H-6"), 7.04 (1H, d, *J* 8.6 Hz, H-6'), 2.16 (3H, s, CH_3), 1.25 (9H, s, $(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 169.4 (s) (C=O), 149.9 (s) (C, Ar), 148.9 (s) (C, Ar), 147.9 (s) (C, Ar), 146.9 (s) (C, Ar), 146.6 (s) (C, Ar), 133.4 (s) (CH,Ar), 129.6 (s) (2 × CH, Ar), 127.0 (s) (CH, Ar), 124.0 (s) (2 × CH, Ar), 121.2 (s) (CH, Ar), 84.7 (s) (C-0), 57.5 (s) (C,quaternary), 27.8 (s) ($(CH_3)_3$), 25.9 (s) (CH_3); *m/z* (ES+) 435.2 $[(M+NH_4)^+$, 100%]; (Found (ES+) $(M + NH_4)^+$ 435.1505. $C_{19}H_{19}N_3O_8$ requires $(M + NH_4)^+$ 435.1510).

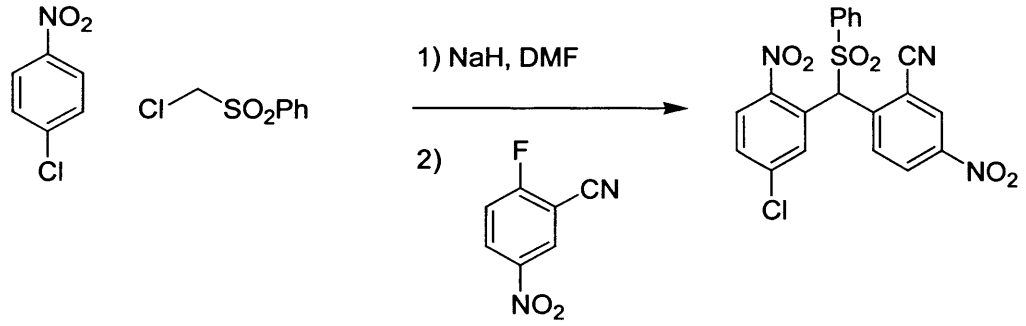


Phenyl (5'-chloro-2'-nitrophenyl)(4"-trifluoromethyl-2"-nitrophenyl)methyl sulfone **(276a)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.26 g, 6.55 mmol), chloromethyl phenyl sulfone (0.42 g, 2.22 mmol), *p*-chloronitrobenzene (0.50 g, 2.62 mmol) and 4-fluoro-3-nitrobenzotrifluoride (0.38 ml, 2.64 mmol) to give the crude product (1.12 g) as a yellow oil. The crude product was then purified by column chromatography, Rf 0.38 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.98 g, 75%) as a yellow crystalline solid. M.p. 178-179.8 °C; υ_{max} (nujol on NaCl plates/cm^{-1}) 2922 (s), 1627 (w), 1602 (w), 1546 (m), 1462 (s), 1326 (s), 1154, (m), 912 (w), 892 (w), 847 (w), 784 (w), 720 (w); δ_H (400 MHz; $CDCl_3$) 8.53 (1H, d, *J* 8.3 Hz, H-3'), 8.30 (1H, d, *J* 2.2 Hz, H-3"), 8.23 (1H, d, *J* 1.3 Hz, H-6'), 8.02 (1H, dd, *J* 1.3 & 8.3 Hz, H-4'), 7.93 (1H, d, *J* 8.8 Hz, H-6"), 7.69 (2H, d, *J* 7.6 Hz, -SO_2-Ph), 7.64 (1H, t, *J* 7.6 Hz, -SO_2-Ph), 7.55 (1H, dd, *J* 2.2 & 8.8 Hz, H-5"), 7.48 (2H, t, *J* 7.6 Hz, -SO_2-Ph), 7.40 (1H, s, CH); δ_C (100 MHz; $CDCl_3$), 149.8 (s) (C, Ar), 147.8 (s) (C, Ar), 140.1 (s) (C, Ar), 136.8 (s) (C, Ar), 135.1 (s) (CH, Ar), 132.7 (q) (C-CF_3, *J* 32 Hz), 132.6 (s) (CH, Ar), 131.6 (s) (CH, Ar), 130.6 (s) (CH, Ar), 129.9 (s), (CH, Ar), 129.8 (s), (C, Ar), 129.5 (s) (2 × CH, Ar), 129.1 (s) (2 × CH, Ar), 127.8, (s) (C, Ar), 127.3 (s) (CH, Ar), 123.1 (s) (CH, Ar), 122.06 (q) (CF_3, *J* 271 Hz), 121.0 (s) (CH, Ar), 61.3 (s) (CH); *m/z* (APCI) 501.1 [$(M+H)^+$, 100%], 500.4 (57), 360.9 (26), 358.7 (81) (Found (ES+) $(M + H)^+$ 501.0136. $C_{20}H_{12}ClF_3N_2O_6S$ requires $(M + H)^+$ 501.0135).

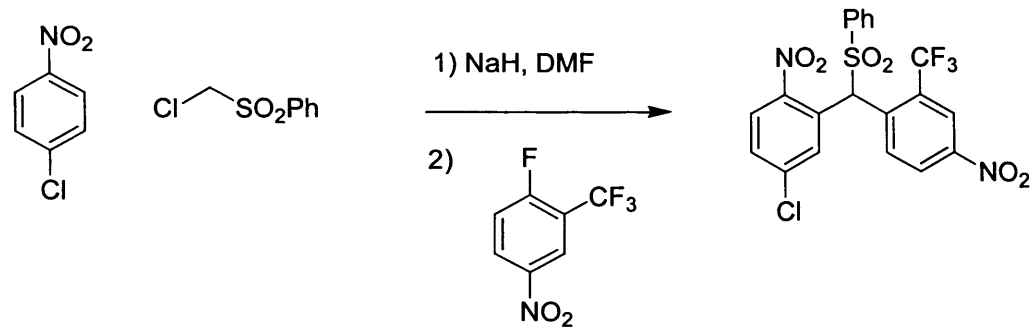


Phenyl (5'-chloro-2'-nitrophenyl)(2",4"-dinitrophenyl)methyl sulfone **(276b)**—This was prepared by the General Method using sodium hydride (60% dispersion in oil) (0.23 g, 5.75 mmol), chloromethyl phenyl sulfone (0.42 g, 2.22 mmol), *p*-chloronitrobenzene (0.35 g, 2.22 mmol) and 2,4-dinitrofluorobenzene (0.28 ml, 2.62 mmol) to give the crude product (1.20 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.41 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.78 g, 74%) as a yellow crystalline solid. M.p. 178.1-179.7 °C; (Found C, 47.74; H, 2.57; N 8.71. $C_{18}H_{15}F_3N_2O_6$ requires C, 47.76; H, 2.53; N, 8.79%); υ_{max} (nujol on NaCl plates/cm^{-1}) 2925 (s), 2360 (w),

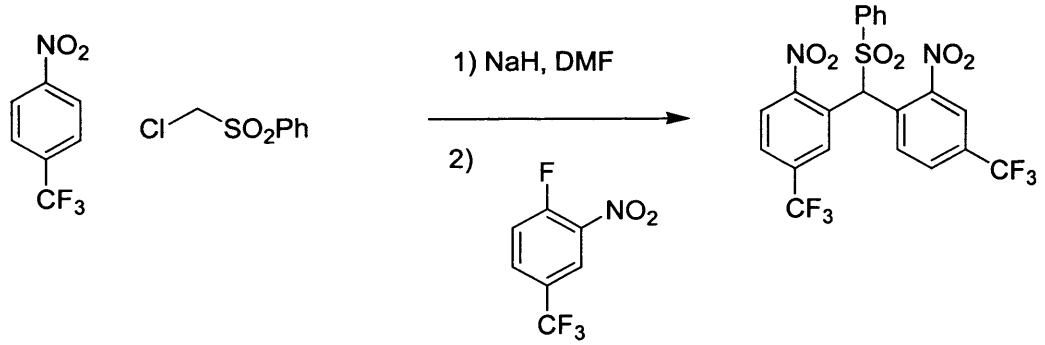
1601 (m), 1570 (w), 1529 (m), 1465 (s), 1377 (w), 1339 (m), 1183 (w), 1152 (m), 1085 (w), 914 (m), 848 (m), 723 (m); δ_H (400 MHz; $CDCl_3$) 8.74 (1H, d, *J* 2.2 Hz, H-3"), 8.46-8.53 (2H, m, H-3' & H-5"), 8.26 (1H, d, *J* 2.2 Hz, H-6'), 7.88 (1H, d, *J* 8.8 Hz, H-4'), 7.63 (2H, d, *J* 8.2 Hz, $PhSO_2$), 7.59 (1H, t, *J* 8.2 Hz, -$PhSO_2$), 7.50 (1H, dd, *J* 2.2 & 8.7 Hz, H-6"), 7.42 (2H, t, *J* 8.2 Hz, $PhSO_2$), 7.35 (1H, s, CH); δ_C (100 MHz; $CDCl_3$), 149.9 (s) (C, Ar), 147.9 (s) (C, Ar), 147.7 (s) (C, Ar), 140.3 (s) (C, Ar), 136.6 (s) (C, Ar), 135.2 (s) (CH, Ar), 133.1 (s) (CH, Ar), 132.4 (s) (C, Ar), 131.5 (s) (CH, Ar), 130.7 (s) (CH, Ar), 129.6 (s) (2 × CH, Ar), 129.1, (s) (2 × CH, Ar), 127.5 (s) (C, Ar), 127.4 (s) (CH, Ar), 127.3 (s) (CH, Ar), 121.1 (s) (CH, Ar) 61.4 (s) (CH); *m/z* (APCI) 477.9 [$(M+H)^+$, 100 %]; (Found: (Ammonia CI): $(M + NH_4)^+$, 495.0379, $C_{17}H_{13}N_3O_6$ requires $(M + NH_4)^+$ 495.0377).



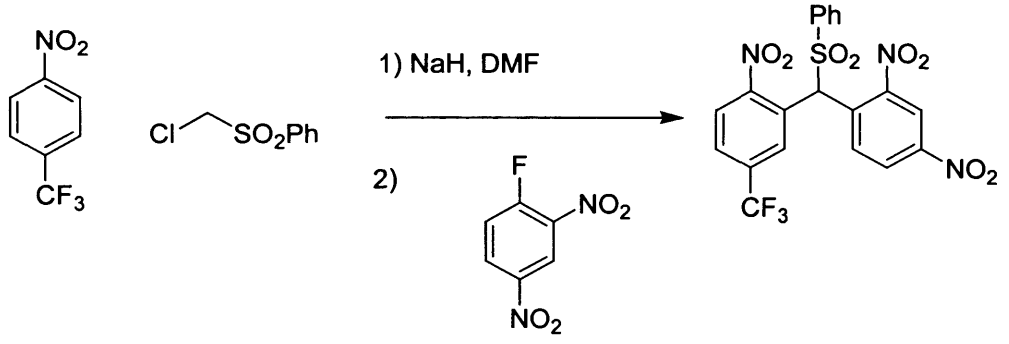
Phenyl (5'-chloro-2'-nitrophenyl)(2"-nitrile-4"-nitrophenyl)methyl sulfone (**276c**)—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.23 g, 5.75 mmol), chloromethyl phenyl sulfone (0.50 g, 2.62 mmol), *p*-chloronitrobenzene (0.42 g, 2.62 mmol) and 2-fluoro-5-benzonitrile (0.44 g, 2.64 mmol) to give the crude product (1.20 g) as an orange solid. The crude product was then purified by column chromatography, Rf 0.18 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.78 g, 74%) as a yellow crystalline solid. M.p. 196-198 °C; (Found C, 52.49; H, 2.64; N 9.23. $C_{18}H_{15}F_3N_2O_6$ requires C, 52.47; H, 2.64; N, 9.23%); υ_{max} (nujol on NaCl plates/cm^{-1}) 2933 (s), 1608.0 (w), 1533.8 (m), 1460.0 (m), 1342.9 (m), 1152.7 (m); δ_H (400 MHz; $CDCl_3$) 8.53 (1H, dd, *J* 2.4 Hz & 8.8 Hz, H-5"), 8.47 (1H, d, *J* 2.4 Hz, H-3"), 8.41 (1H, d, *J* 2.4 Hz, H-6'), 8.29 (1H, d, *J* 8.8 Hz, H-4'), 8.02 (1H, d, *J* 8.8 Hz, H-6"), 7.71 (3H, m, -SO_2-Ph), 7.60 (1H, dd, *J* 2.2 Hz & 8.8 Hz, H-3'), 7.54 (1H, t, *J* 7.8 Hz, -SO_2Ph), 6.90 (1H, s, HC-SO_2-Ph); δ_C (100 MHz; $CDCl_3$), 147.7 (s) (C, Ar), 147.3 (s) (C, Ar), 140.8 (s) (C, Ar), 140.6 (s) (C, Ar), 136.1 (s) (C, Ar), 135.5 (s) (CH, Ar), 131.9 (s) (CH, Ar), 131.1 (s) (CH, Ar), 130.9 (s) (CH, Ar), 129.8 (s) (2 × CH, Ar), 129.3 (s) (2 × CH, Ar), 128.1 (s) (CH, Ar), 127.6 (s) (CH, Ar), 127.5 (s) (C, Ar), 127.4 (s) (CH, Ar), 117.1 (s) (CN or C, Ar), 114.4 (s) (CN or C, Ar), 65.6 (s) (CH); *m/z* (APCI) 458.0 [$(M+H)^+$, 100 %], 457.4 (31), 318.9 (50); (Found: $(M+NH_4)^+$, 457.0491. $C_{20}H_{12}ClN_3O_6S$ requires($M + NH_4)^+$ 475.0479).



Phenyl (5'-chloro-2'-nitrophenyl)(2"-trifluoromethyl-4"-nitrophenyl)methyl sulfone (**276d**)—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.23 g, 5.75 mmol), chloromethyl phenyl sulfone (0.42 g, 2.22 mmol), *p*-chloronitrobenzene (0.35 g , 2.22 mmol) and 2-fluoro-5-benzotrifluoride (0.54 g, 2.64 mmol) to give the crude product (1.48 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.41 (silica, 3:1. hexane:ethyl acetate; v/v to give the pure product (0.98 g, 75%) as a yellow crystalline solid. M.p. 178.2-180.0 °C; (Found C, 48.12; H, 2.39; N 5.60. $C_{18}H_{15}F_3N_2O_6$ requires C, 47.96; H, 2.41; N, 5.59%); υ_{max} (nujol on NaCl plates/cm^{-1}) 2925 (s), 2360 (w), 1734 (w), 1618 (w), 1597 (m), 1532 (m), 1466 (s), 1376 (s), 1309 (s), 1154 (s), 1084 (w), 1051 (m), 917 (m), 842 (m), 757 (w), 728 (m); δ_H (400 MHz; $CDCl_3$) 9.10 (1H, d, *J* 8.8 Hz, H-3'), 8.65 (1H, dd, *J* 2.3 & 8.8 Hz, H-5"), 8.50 (1H, d, *J* 2.2 Hz, H-3"), 8.10 (1H, d, *J* 8.7 Hz, H-4'), 7.75 (2H, d, *J* 8.1 Hz, $PhSO_2$), 7.62-7.65 (3H, m, H-6' & $PhSO_2$ & CH), 7.57 (1H, dd, *J* 2.1 & 8.7 Hz, H-6"), 7.49 (2H, t, *J* 8.1 Hz, $PhSO_2$); δ_C (100 MHz; $CDCl_3$), 148.4 (s) (C, Ar), 148.1 (s) (C, Ar), 140.4 (s) (C, Ar), 137.0 (s) (C, Ar), 137.0 (s) (C, Ar), 135.4 (s) (CH, Ar), 133.6 (s) (CH, Ar), 132.4 (q) (C-CF_3, *J* 32 Hz), 131.8 (s) (CH, Ar), 131.0 (s) (CH, Ar), 129.9 (s) (2 × CH, Ar), 129.3 (s) (2 × CH, Ar), 128.3 (s) (CH, Ar), 127.3 (s) (CH, Ar), 126.6 (s) (C, Ar), 122.8 (q) (CH, Ar, *J* 6.1 Hz), 122.6 (q) (CF_3, *J* 266 Hz), 61.5 (s) (CH); *m/z* (APCI) 501.0 $[(M + H)^+$, 100 %]; (Found (ES+): $(M + NH_4)^+$, 518.0393, $C_{20}H_{12}ClF_3N_2O_6$ requires $(M + NH_4)^+$ 518.0400).

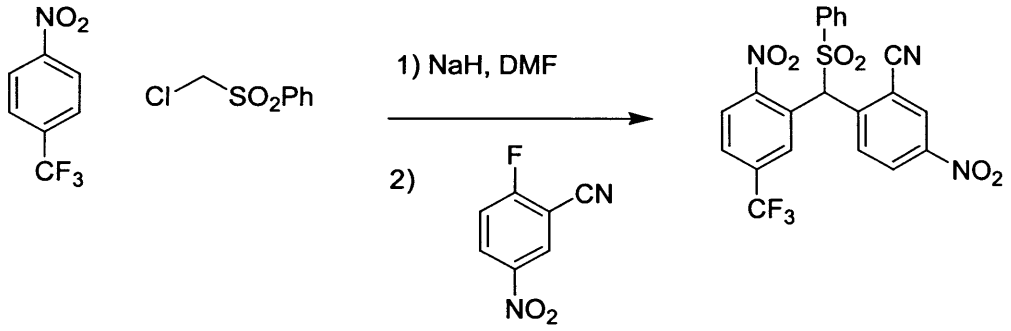


***Phenyl (5'-trifluoromethyl-2'-nitrophenyl)(2"-trifluoromethyl-4"-nitrophenyl)methyl sulfone* (276e)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.13 g, 3.30 mmol), chloromethyl phenyl sulfone (0.25 g, 1.31 mmol), 4-nitro-α,α,α-trifluoro toluene (0.25 g , 1.31 mmol) and 4-fluoro-3-benzotrifluoride (0.19 ml, 1.35 mmol) to give the crude product (0.80 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.38 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.57 g, 81%) as a yellow crystalline solid. M.p. 158-159.8 °C; υ_{max} (nujol on NaCl plates/cm^{-1}) 2925 (s), 2852 (s), 1628 (w), 1538 (s), 1462 (s), 1375 (w), 1330 (s), 1248 (w), 1184 (m), 1155 (m), 1131 (m), 1094 (m), 935 (w), 854 (m), 727 (m); δ_H (400 MHz; $CDCl_3$) 8.63 (1H, s, H-3"), 8.46 (1H, d, *J* 8.4 Hz, H-3'), 8.25 (1H, s, H-6'), 8.04 (2H, d, *J* 8.3 Hz, H-4' & H-5"), 7.86 (1H, d, *J* 8.5 Hz, H-6"), 7.68 (2H, d, *J* 7.8 Hz, $PhSO_2$), 7.64 (1H, t, J 7.50 Hz, $PhSO_2$), 7.48 (2H, t, *J* 7.8 Hz, $PhSO_2$), 7.38 (1H, s, CH); δ_C (100 MHz; $CDCl_3$), 151.7 (s) (C, Ar), 149.9 (s) (C, Ar), 136.6 (s) (C, Ar), 135.2 (s) (CH, Ar), 134.9 (q) (C-CF_3, *J* 34 Hz), 132.9 (q) (C-CF_3, *J* 34 Hz), 132.4 (s) (CH, Ar), 130.0 (s) (CH, Ar), 129.6 (s) (2 × CH, Ar), 129.5 (s) (C, Ar), 128.6 (2 × CH, Ar), 128.6, (s) (CH, Ar), 127.7 (s) (CH, Ar), 126.9 (s) (C, Ar), 126.4 (s) (CH, Ar), 123.2 (s) (CH, Ar), 122.51 (q) (CF_3, *J* 272 Hz), 122.31 (q) (CF_3, *J* 272 Hz), 61.2 (s) (CH); *m/z* (APCI) 535.2 [$(M+H)^+$, 100%], 534.5 (65); Found (ES+): $(M + NH_4)^+$, 552.0663. $C_{21}H_{12}F_6N_2O_6$ requires $(M + NH_4)^+$ 552.0664.



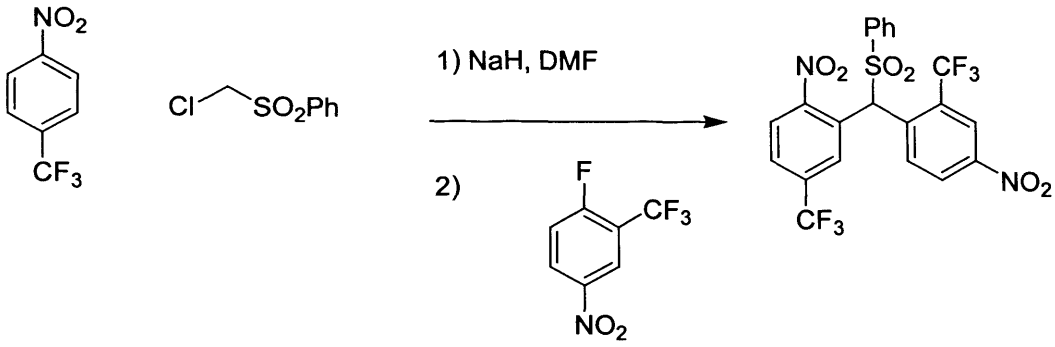
***Phenyl (5'-trifluoromethyl-2'-nitrophenyl)(2",4"-dinitrophenyl)methyl sulfone* (276f)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.13 g, 3.30 mmol), chloromethyl phenyl sulfone (0.25 g, 1.31 mmol), 4-nitro-α,α,α-trifluorotoluene (0.25 g , 1.31 mmol) and 2,4-dinitrofluorobenzene (0.17 ml, 1.31 mmol) to give the crude product (0.68 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.41 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.53 g, 79%) as a yellow crystalline solid. M.p. 215.1-217.3 °C; (Found C, 46.67; H, 2.39; N 8.25. $C_{18}H_{15}F_3N_2O_6$ requires C, 46.98; H, 2.37; N, 8.20%); υ_{max} (nujol on NaCl plates/cm^{-1}) 2918 (s), 2852 (s), 1604 (s), 1539 (s), 1465 (s), 1400 (s), 1180 (m), 1154 (m),

1127 (m), 1095 (m), 913 (m), 852 (m), 756 (m); δ_H (400 MHz; $CDCl_3$) 8.84 (1H, d, *J* 2.4 Hz, H-3"), 8.65 (1H, s, H-6'), 8.6 (1H, dd, *J* 2.4 & 8.7 Hz, H-5"), 8.48 (1H, d, *J* 8.8 Hz, H-6"), 8.06 (1H, d, *J* 8.4 Hz, H-4'), 7.88 (1H, d, *J* 8.5 Hz,, H-3'), 7.65-7.71 (3H, m, $PhSO_2$), 7.50 (2H, t, *J* 7.8 Hz, $PhSO_2$), 7.40 (1H, s, CH); δ_C (100 MHz; $CDCl_3$), 151.7 (s) (C, Ar), 150.0 (s) (C, Ar), 148.0 (s) (C, Ar), 136.5 (s) (C, Ar), 135.3 (s) (CH, Ar), 133.0 (s) (CH, Ar), 132.0 (s) (C, Ar), 129.7 (s) (2 × CH, Ar), 129.0 (s) (2 × CH, Ar), 128.50 (s) (CH, Ar), 127.9 (s) (CH, Ar), 127.4, (s) (CH, Ar), 126.6 (s) (C, Ar), 126.5 (s) (CH, Ar), 121.3 (s) (CH, Ar), 61.29 (s) (H<u>C</u>-SO_2Ph); *m/z* (APCI) 512.0 [$(M + H)^+$, 100%], 511.4 (75); Found (ES+): $(M + NH_4)^+$, 529.0636, $C_{20}H_{12}F_3N_3O_8S$ requires $(M + NH_4)^+$ 529.0641.



Phenyl (5'-trifluoromethyl-2'-nitrophenyl)(2"-4"-dinitrophenyl)methyl sulfone **(276g)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.13 g, 3.30 mmol), chloromethyl phenyl sulfone (0.25 g, 1.31 mmol), 4-nitro-α,α,α-trifluorotoluene (0.25 g , 1.31 mmol) and 2-fluoro-5-nitrobenzonitrile (0.22 g, 1.32 mmol) to give the crude product (1.03 g) as an orange oil. The crude product was then purified by column chromatography, Rf 0.26 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.51 g, 78%) as a yellow crystalline solid. M.p. 197.9-200 °C; (Found C, 51.41; H, 2.42; N 8.55. $C_{21}H_{12}F_6NO_6S$ requires C, 51.33; H, 2.46; N, 8.55%) υ_{max} (nujol on NaCl plates/cm^{-1}) 2924 (s), 1610 (w), 1581 (w), 1542 (s), 1464 (s), 1356 (m), 1334 (m), 1253 (w), 1177 (m), 1129 (m), 1092 (m), 976 (w), 932 (m), 858 (s), 788 (m), 730 (m); δ_H (400 MHz; $CDCl_3$) 8.64 (1H, s, H-6'), 8.48 (1H, dd, *J* 2.4 & 8.7 Hz, H-5"), 8.42 (1H, d, *J* 2.4 Hz, H-3"), 8.17 (1H, d, *J* 8.8 Hz, H-6"), 8.06 (1H, d, *J* 8.6 Hz, H-4'), 7.83 (1H, d, *J* 8.5 Hz, H-3'), 7.62-7.66 (3H, m, $PhSO_2$), 7.47 (2H, t, *J* 7.8 Hz, $PhSO_2$), 7.20 (1H, s, CH); δ_C (400 MHz; $CDCl_3$), 151.8 (s) (C, Ar), 147.8 (s) (C, Ar), 140.4 (s) (C, Ar), 136.8 (s) (C, Ar), 136.2 (s) (CH, Ar) 136.0 (s) (C, Ar), 135.3 (q) (<u>C</u>-CF_3, *J* 34 Hz), 133.2 (s) (CH, Ar), 130.6 (s) (2 × CH, Ar), 129.9 (s) (2 × CH, Ar), 128.3 (s) (CH, Ar), 127.6 (s) (CH, Ar), 126.9 (s) (CH, Ar), 126.7 (s) (CH, Ar), 123.8 (s) (CH, Ar), 122.1 (q) (CF_3, *J* 268 Hz), 117.1 (s) (CN or C, Ar), 114.4 (s) (CN or

C, Ar), 61.3 (s) (HC-SO_2Ph); *m/z* (APCI) 491.9 {$(M + H)^+$, 100 %], 349.5 (85); (Found $(M + NH_4)^+$, 509.0748, $C_{21}H_{12}F_3N_3O_6S$ requires $(M + NH_4)^+$ 509.0743).



***Phenyl (5'-trifluoro-2'-nitrophenyl)(2"-trifluoromethyl-4"-nitrophenyl)methyl sulfone* (276h)**—This was prepared by the General Method, cooling to 0 °C instead of –50 °C using sodium hydride (60% dispersion in oil) (0.13 g, 3.30 mmol), chloromethyl phenyl sulfone (0.25 g, 1.31 mmol), 4-nitro-α,α,α-trifluorotoluene (0.25 g , 1.31 mmol) and 2-fluoro-5-nitrobenzotrifluoride (0.28 g, 1.34 mmol) to give the crude product (1.16 g) as an orange solid. The crude product was then purified by column chromatography, Rf 0.42 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.55 g, 78%) as a yellow crystalline solid. M.p. 190-192 °C; (Found C, 47.17; H, 2.26; N 5.34. $C_{21}H_{12}F_6N_2O_6S$ requires C, 47.2; H, 2.26; N, 5.24%) υ_{max} (nujol on NaCl plates/cm^{-1}) 2924 (s), 1621 (m), 1596 (m), 1537 (s), 1462 (s), 1329 (s), 1127 (s), 919 (s), 854 (s), 797 (w), 784 (w); δ_H (400 MHz; $CDCl_3$) 9.00 (1H, d, *J* 8.7 Hz, H-5"), 8.57 (1H, dd, *J* 2.3 & 8.7 Hz, H-6"), 8.43 (1H, d, *J* 2.3 Hz, H-3"), 8.17 (1H, d, *J* 8.5 Hz, H-3'), 7.85 (1H, s, H-6'), 7.80 (1H, d, *J* 8.5 Hz, H-4'), 7.66 (2H, t, *J* 7.7 Hz, $PhSO_2$), 7.56 (1H, t, *J* 7.7 Hz, $PhSO_2$), 7.49 (1H, s, CH), 7.41 (2H, t, *J* 7.7 Hz, $PhSO_2$); δ_C (100 MHz; $CDCl_3$), 149.8 (s) (C, Ar), 147.8 (s) (C, Ar), 140.1 (s) (C, Ar), 136.8 (s) (C, Ar), 135.1 (s) (CH, Ar), 132.9 (s) (CH, Ar), 131.6 (s) (CH, Ar), 130.6 (s) (CH, Ar), 129.9 (s) (CH, Ar), 129.5 (s) (CH, Ar), 129.1 (s) (CH, Ar), 127.8 (s) (C, Ar), 127.3 (s) (CH, Ar), 123.1 (s) (CH, Ar), 121.0 (s) (C, Ar), 61.3 (s) (HC-SO_2Ph); *m/z* (APCI) 535.4 [$(M+H)^+$, 100%)], 511.4 (75), 370.9 (25).

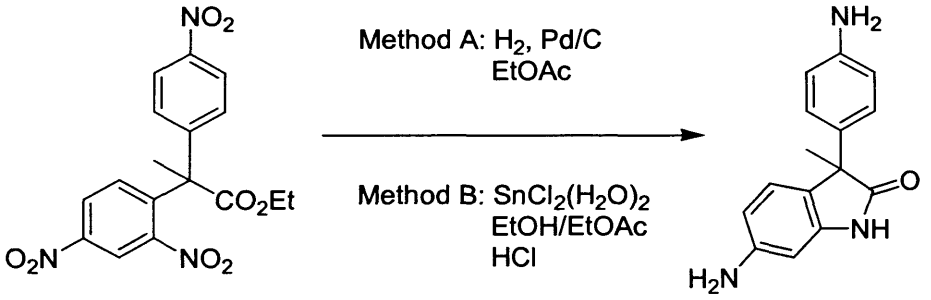
General Methods for the Formation of Oxindoles

Method A

In a Multi-Parr reaction vessel the ester (0.51 mmol) was added followed by 5% Pd/C (25 mg) (Johnson Mattey type 58 paste) (47.5% H_2O), ethyl acetate (2.5 ml) and acetic acid (0.25 ml). The mixture was stirred, purged with nitrogen (5 times) and then hydrogen (5 times) and left under hydrogen (50 psi). Continual checking by LC led to complete conversion of the starting material after 16 hours. The product was then filtered through a celite plug and then the solvent removed on a rotary evaporator to give the crude product.

Method B

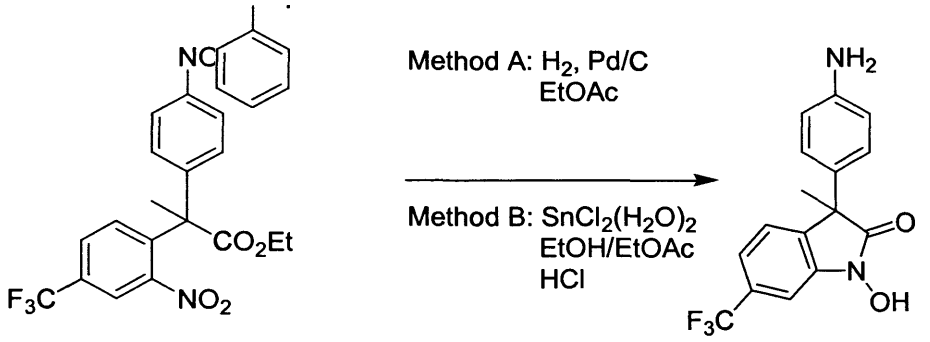
In a 2-necked round bottom flask fitted with a condenser and nitrogen bubbler was added tin(II) chloride dihydrate (25.7 mmol), the ester (2.57 mmol), ethanol (40 ml), ethyl acetate (10 ml) and conc. HCl (3 drops). The solution was heated under reflux for 36 hours and then cooled to room temperature. The solution was reduced on a rotary evaporator to give a pale yellow oil. Ethyl acetate (50 ml) was added followed by sodium hydrogen carbonate (50 ml). The product was extracted with ethyl acetate (3 × 25 ml) and then washed with water (50 ml) and saturated sodium chloride (50 ml). The solution was then dried over magnesium sulfate and reduced on a rotary evaporator to give the crude product.



***3-Methyl-3-(4'-aminophenyl)-6-aminooxindole* (292a)** *Method A*:—This was performed by the General Method using the ester **257b** (200 mg, 0.51 mmol), 5% Pd/C (25 mg), ethyl acetate (2.5 ml) and acetic acid (0.25 ml). The product was left in the vessel for 16 hours, checking by LC until complete conversion had occurred. The crude product (115 mg) was obtained as an orange crystalline solid after being filtered through celite. The crude product was then washed with chloroform on a filter, dried and collected leaving a slightly brown crystalline solid (70 mg, 54%).

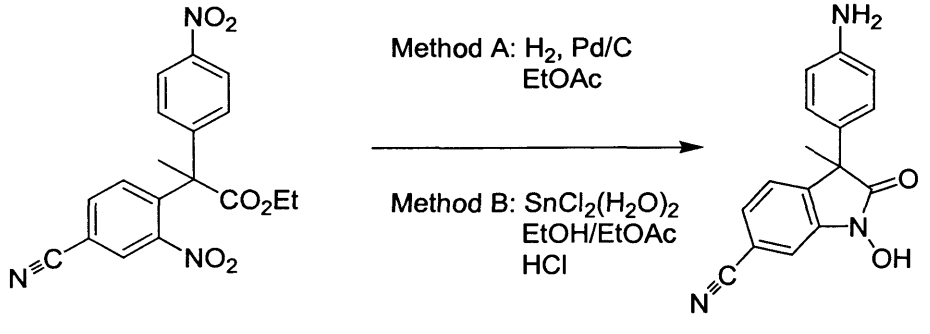
Method B:—This was prepared by the General Method using the ester **257b** (1.0 g, 2.57 mmol), tin(II) chloride dihydrate (5.81 g, 25.7 mmol), ethanol (40 ml), ethyl acetate (10 ml) and conc. hydrochloric acid (3 drops) and heating under reflux for 36 hours, to give the crude product as a brown crystalline solid (0.82 g). The crude product was then washed with chloroform on a filter, dried and collected leaving a slightly brown crystalline solid (0.46 g, 71%). M.p. 149-151 °C; υ_{max} (nujol NaCl plates/ cm^{-1}) 3350 (wk, br) (O-H), 1698 (s) (C=O); δ_H (400 MHz; MeOD) 7.05 (2H, d, J 8.6 Hz, H-2' & H-6'), 6.87 (1H, d, J 8.0 Hz, H-4), 6.70 (2H, d, J 8.6 Hz, H-3' & H-5'), 6.56 (1H, d, J 2.0 Hz, H-7), 6.46 (1H, dd, J 2.0 & 8.0 Hz, H-5"); 1.66 (3H, s, CH_3); δ_C (100 MHz; MeOD) 178.3 (s) (C=O), 150.6 (s) (C, Ar), 146.7 (s) (C, Ar), 144.0 (s) (C, Ar), 132.9 (s) (C, Ar), 128.9 (s) (2 × CH, Ar), 125.7 (s) (CH, Ar), 123.0 (s)

(C, Ar), 115.7 (s) (2 × CH, Ar), 111.0 (s) (CH, Ar), 97.3 (s) (CH, Ar), 51.6 (s) (C, q), 24.0 (s) (CH_3); m/z (CI+) 271.2 [$(M+NH_4)^+$, 100%], Found (ES+) $(M + NH_4)^+$, 271.1557 $C_{15}H_{15}N_3O$ requires $(M + NH_4)^+$ 271.1553.



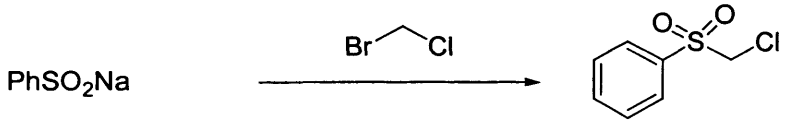
1-Hydroxy-3-methyl-3-(4'-aminophenyl)-6-trifluoromethyloxindole **(292b)** *Method A:*—This was prepared by the General Method using the ester **257a** (100 mg, 0.24 mmol), 5% Pd/C (25 mg), ethyl acetate (2.5 ml) and acetic acid (0.25 ml). The product was left in the vessel for 17 hours, checking by LC until complete conversion had occurred. The crude product (130 mg) was obtained as a brown crystalline solid after being filtered through celite. This was then washed with chloroform to leave a white crystalline solid (60 mg, 77%).

Method B:—This was prepared by the General Method using the ester **257a** (0.35 g, 0.85 mmol), tin(II) chloride dihydrate (1.95 g, 8.5 mmol), ethanol (9 ml), ethyl acetate (3 ml) and conc. hydrochloric acid (3 drops). The reaction mixture was heated under reflux for 24 hours, and then worked up as before to give a brown crystalline solid (0.31 g). This solid was then washed with chloroform as before to leave a white crystalline solid (0.23 g, 76%). M.p. 219-221 °C; υ_{max} (nujol NaCl plates/ cm^{-1}) 3420 (Br, s) (N-OH),1666 (s) (C=O) (s);.δ_H (400 MHz; MeOD) 7.44 (1H, d, *J* 3.6 Hz, H-7), 7.34-7.38 (2H, m, H-4 & H-5), 7.01 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 6.68 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 1.76 (3H, s, CH_3); δ_C (100 MHz; MeOD) 175.6 (s) (C=O), 147.1 (s) (C, Ar), 142.3 (s) (C, Ar), 136.7 (s) (C, Ar), 130.2 (q, *J* 32 Hz), (C-CF_3) 128.0 (s) (C, Ar), 126.8 (s) (2 × CH, Ar), 124.1 (s) (CH, Ar), 119.9 (s) (CH, Ar), 115.1 (s) (2 × CH, Ar), 103.8 (s) (CH, Ar), 50.4 (s) (C, q), 21.5 (s) (CH_3); *m/z* (ES+) 323.1 [$(M+H)^+$, 100%], (Found (ES+) $(M + NH_4)^+$ 340.1266 $C_{16}H_{13}N_2O_2F_3$ requires $(M + NH_4)^+$ 340.1266.

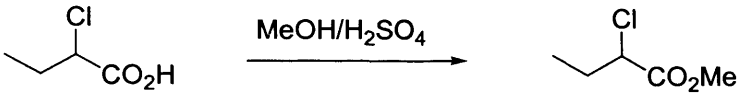


1-Hydroxy-3-methyl-3-(4'-aminophenyl)-6-cyanooxindole **(292c)** *Method A*:—This was prepared by the General Method using the ester **2571** (200 mg, 0.54 mmol), 5% Pd/C (25 mg), ethyl acetate (2.5 ml) and acetic acid (0.25 ml). The product was left in the vessel for 20 hours, checking by LC until complete conversion had occurred. The crude product (124 mg) was obtained as a yellow crystalline solid after being filtered through celite. This was then washed with chloroform to leave a white crystalline solid (104 mg, 69%).

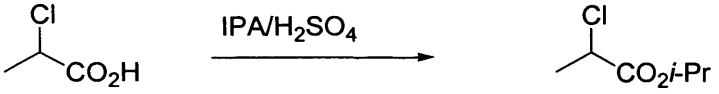
Method B:—This was prepared by the General Method using the ester **2571** (1.0 g, 2.71 mmol), tin(II) chloride dihydrate (6.12 g, 27.1 mmol), ethanol (40 ml), ethyl acetate (10 ml) and conc. hydrochloric acid (3 drops). The reaction mixture was heated under reflux for 36 hours, and then worked up as before to give a brown crystalline solid (0.80 g). This solid was then washed with chloroform as before to leave a white crystalline solid (0.60 g, 79%). M.p. 254-256 °C υ_{max} (nujol NaCl plates/ cm^{-1}) 3350 (wk, br) (O-H), 1712 (s) (C=O); δ_H (400 MHz; DMSO) 11.10 (1H, s, O-H), 7.54 (1H, dd, *J* 1.6 & 7.6 Hz, H-5), 7.40-7.42 (2H, m, H-4 & H-7), 6.86 (2H, d, *J* 8.4 Hz, H-2' & H-6'), 6.49 (2H, d, *J* 8.4 Hz, H-3' & H-5'), 1.63 (3H, s, CH_3); δ_C (100 MHz; DMSO).174.2 (s) (C=O), 148.5 (s) (C, Ar), 142.9 (s) (C, Ar), 138.0 (s) (C, Ar), 127.8 (s) (CH, Ar), 127.2 (s) (2 × CH, Ar), 126.2 (s) (C, Ar), 125.1 (s) (CH, Ar), 119.1 (s) (C, Ar), 114.1 (s) (2 × CH, Ar), 110.9 (s) (CN), 109.9 (s) (CH, Ar), 50.1 (s) (C, quaternary), 22.4 (s) (CH_3); *m/z* (ES+) 280.2 [$(M+H)^+$, 100%], Found (ES+) $(M + NH_4)^+$ 297.1348. $C_{16}H_{13}N_3O_2$ requires $(M + NH_4)^+$ 297.1346.



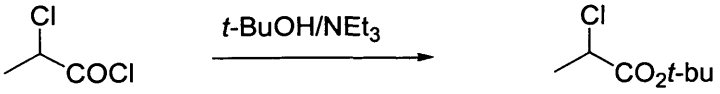
Chloromethyl phenyl sulfone[231] **(322)**—Sodium benzenesulfinate dihydrate (15 g, 75 mmol) and bromochloromethane (11.63 g, 90 mmol) in DMSO (40 ml) was heated at 100 °C for 4 hours. The mixture was cooled, poured into water and extracted with dichloromethane (3 × 100 ml). The combined extracts were washed with water (3 × 100 ml) and dried over magnesium sulfate. The solvent was removed to leave an orange crystalline solid (14.6 g). Recrystallisation from carbon tetrachloride provided white crystals of the sulfone (10.25 g, 72 %). M.p. 52-54 °C (lit. M.p. 52-53 °C)[231], υ_{max} (nujol on NaCl plates/cm^{-1}) 3055 (s), 3016 (s), 2942 (s), 1584 (m), 1444 (m), 1376 (w), 1322 (s), 1309 (s), 1240 (s), 1161 (s), 1140 (s), 1079 (s), 1015 (m), 866 (m); δ_H(400 MHz; $CDCl_3$) 7.96 (2H, dd, *J* 1.1 & 7.9 Hz, *ortho* CH), 7.73 (1H, dd, *J* 1.1 & 7.9 Hz, *para* CH), 7.61 (2H, t, *J* 7.9 Hz, *meta* CH), 4.55 (2H, s, CH_2); δ_C(100 MHz; $CDCl_3$) 135.5 (s) (C, Ar), 134.7 (s) (2 × CH, Ar), 129.3 (s) (CH, Ar), 129.2 (s) (2 × CH, Ar), 58.4 (s) (CH_2); *m/z* (APCI) 191.2 [$(M+H)^+$, 100%].



Methyl 2-chlorobutanoate[190] **(259)**—Chlorobutyric acid (10.59 g, 8.17 mmol) and methanol (100 ml) were added to a 250 ml 2-necked round bottomed flask fitted with a condenser and nitrogen bubbler. Sulfuric acid (0.5 ml) was added and the mixture was heated under reflux for 3 hours. The mixture was then cooled and most of the methanol was removed on a rotary evaporator. The product was then extracted with ether (3 × 50 ml), dried followed by removal of the ether on a rotary evaporator to give the product as a clear oil (7.77 g, 70%). υ_{max} (liquid film on NaCl plates/ cm^{-1}) 2995 (m), 2975 (m, br), 2955 (w), 2886 (w), 1750 (s) (C=O), 1460 (w), 1440 (w), 1380 (m), 1355 (m), 1170 (w); δ_H (400 MHz; $CDCl_3$) 3.68 (3H, t, *J* 7.0 Hz, OCH_3), 4.20 (1H, t, *J* 7.0 Hz, CH-Cl), 1.92 (2H, quintet, *J* 7.0 Hz, CH_2), 1.00 (3H, t, *J* 7.0 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 169.6 (s) (C=O), 58.7 (s) (C-O), 52.5 (s) (C-Cl), 28.7 (s) (CH_2), 10.5 (s) (CH_3); *m/z* (APCI) 138 [(M (^{37}Cl)+ H)$^+$, 33%], 136 [(M (^{35}Cl) + H)$^+$, 100%].



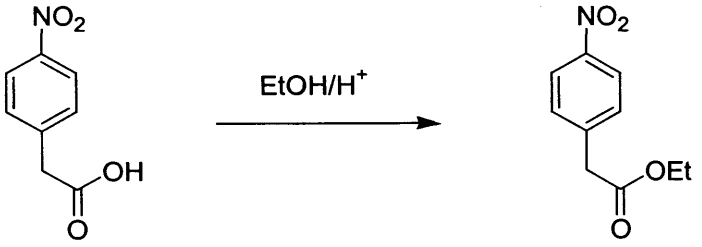
Isopropyl 2-chloropropionate[232] **(267)**—This was achieved using the General Method above as a yellow oil (69%). υ_{max} (liquid film on NaCl plates/ cm^{-1}) 3478 (wk, br), 2984 (m), 2936 (w), 2360 (w), 1744 (s) (C=O), 1452 (m), 1379 (m), 1326 (m), 1278 (m), 1248 (m); δ_H (400 MHz; $CDCl_3$) 5.0 (1H, septet, *J* 6.2 Hz, H_3C-C<u>H</u>-CH_3), 4.33 (1H, q, *J* 6.8 Hz, CH-Cl), 1.67 (3H, d, *J* 6.8 Hz, CH_3), 1.27 (6H, dd, *J* 6.2 & 2.1 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 170.1 (s) (C=O), 70.1 (s) (C-O), 53.2 (s) (C-Cl), 21.8 (s) (2 × CH_3); *m/z* (APCI) 152 [(M (^{37}Cl) +H)$^+$, 33%], 150 [(M (^{35}Cl) +H)$^+$, 100%]



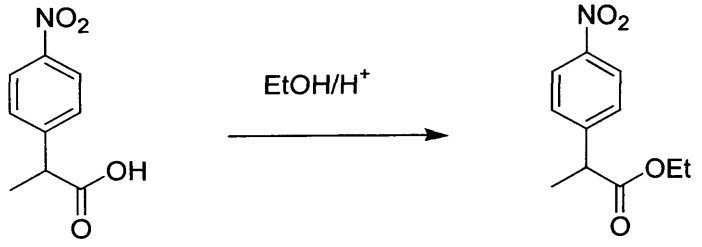
tert-Butyl 2-chloropropionate[193] **(269)**—To a solution of 2-chloropropionyl chloride (10 ml, 108.5 mmol) and *tert*-butanol (28.0 g, 0.35 mol) in toluene (100 ml) was added dropwise over an hour a triethylamine (15.8 ml, 115 mmol) at room temperature. The solution was then stirred for 20 minutes before heated to 90 °C for 6 hours. Water (50 ml was added after cooling. The organic layer was separated and washed successively with water (50 ml), aqueous sodium bicarbonate (50 ml) and water (50 ml). The organic layer was then dried over

magnesium sulfate. Removal of the solvent on a rotary evaporator gave a clear oil (53%). υ_{max} (liquid film on NaCl plates/ cm^{-1}) 2981 (s), 2936 (m), 1739 (s) (C=O), 1480 (w), 1454 (m), 1252 (m), 1157 (s), 1074 (m), 993 (m), 846 (m); δ_H (400 MHz; $CDCl_3$) 4.22 (1H, q, *J* 7.0 Hz, Cl-CH), 1.58 (3H, d, *J* 7.0 Hz, CH_3), 1.42 (9H, s, 3 × CH_3); δ_C (100 MHz; $CDCl_3$) 169.6 (s) (C=O), 82.8 (s) (C-O), 54.1 (s) (C-Cl), 28.2 (s) (3 × CH_3), 21.9 (s) (CH_3); *m/z* (APCI) 166.0 [(M (^{37}Cl) + H)$^+$, 33%], 164 [(M (^{35}Cl) + H)$^+$, 100%].

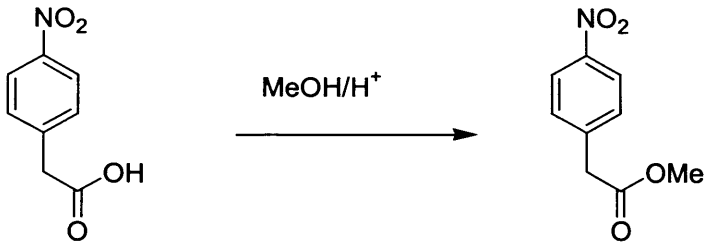
General Procedure for esterification of nitrophenylacetic/propionic acids—The acid (55.24 mmol) in ethanol (100 ml) and sulfuric acid (1 ml) was heated under reflux for 3 hours. Most of the ethanol was then removed on a rotary evaporator. Ether (50 ml) and sodium bicarbonate (sat. aq. 50 ml) was added and the organic product was extracted with ether (3 × 50 ml). The solvent was then dried over Na_2SO_4 and then removed on a rotary evaporator to give the pure product



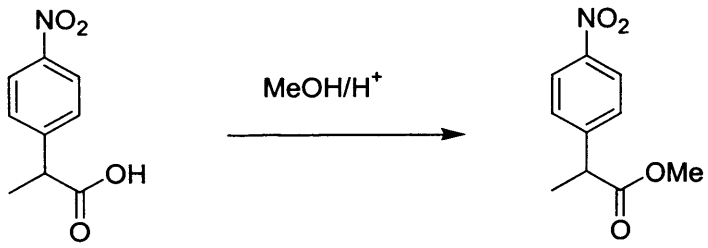
***Ethyl 4-nitrophenylacetate*[233] (311)**—This was prepared by the General Method using 4-nitrophenylacetic acid (10 g, 51.28 mmol), ethanol (100 ml) and sulfuric acid (1 ml) to give the pure product as a yellow crystalline solid (11.24 g, 97%). M.p. 65-67 °C (65-66 °C)[233]; ν_{max} (nujol on NaCl plates/cm^{-1}) 1725 (s), 1601 (m), 1465 (s), 1375 (s); δ_H(400 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* 8.8 Hz, H-3 & H-5), 7.46 (2H, d, *J* 8.8 Hz, H-2 & H-6), 4.18 (2H, q, *J* 7.2 Hz, CH_2), 3.73 (2H, s, CH_2), 1.27 (3H, t, *J* 7.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 171.9 (s) (C=O), 148.7 (s) (C, Ar), 141.9 (s) (C, Ar), 131.5 (s) (2 × CH, Ar), 124.8 (s) (2 × CH, Ar), 57.1 (s) (CH_2), 41.3 (s) (CH_2), 14.8 (s) (CH_3);. *m/z* (APCI) 210.0 [(M + H)$^+$, 100%].



Ethyl 2-(4'-nitrophenyl)propionate[86] **(313)**—This was prepared by the General Method using 2-(4'-nitrophenyl)propionic acid (**169**) (10 g, 51.28 mmol), ethanol (100 ml) and sulfuric acid (1 ml) to give the product (10.38 g, 91%) as a yellow oil. %). ν_{max} (liq. film on NaCl plates/cm^{-1}) 1736 (s) (C=O), 1601 (m), 1521 (s), 1478 (s), 1210 (s), δ_H(400 MHz, $CDCl_3$) 8.19 (2H, d, *J* 8.8 Hz, H-3 & H-5), 7.50 (2H, d, *J* 8.8 Hz, H-2 & H-6), 4.09-4.21 (2H, m, CH_2), 3.84 (1H, q, J 7.2 Hz, CH_3), 1.55 (3H, d, *J* 7.2 Hz, $C\underline{H}_3$), 1.24 (3H, q, *J* 7.4 Hz, CH_3); δ_C(100 MHz, $CDCl_3$), 174.1 (s) (C=O), 147.7 (s) (C, Ar), 146.3 (s) (C, Ar), 129.3 (s) (2 × CH, Ar), 124.5 (s) (2 × CH, Ar), 57.3 (s) (O-CH_2), 41.9 (s) (CH), 19.8 (s) (CH_3), 14.9 (s) (CH_3). *m/z* (APCI) 224.0 [(M + H)$^+$, 100 %].

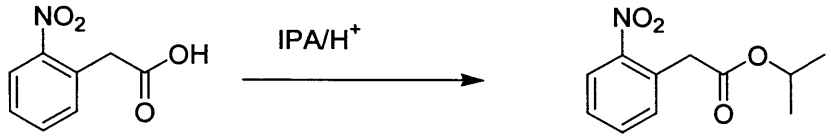


Methyl 4-nitrophenylacetate[234] **(167)**—This was prepared by the General Method using 4-nitrophenyl acetic acid (**166**) (10 g, 55.24 mmol), methanol (100 ml) and sulfuric acid (1 ml) to give the pure product as a yellow crystalline solid (10.3 g, 95%). M.p. 53-55 °C (53-54 °C)[234]; ν_{max} (nujol on NaCl plates/cm^{-1}) 1724 (s), 1600 (m), 1464 (s), 1377 (s) 1347 (m), 1108 (w), 1014 (w), 854 (w); δ_H(400 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* 8.7 Hz, H-3 & H-5), 7.46 (2H, d, *J* 8.7 Hz, H-2 & H-6), 3.75 (3H, s, OCH_3), 3.70 (3H, s, CH_2), δ_C (100 MHz, $CDCl_3$) 172.1 (s) (C=O), 148.9 (s) (C, Ar), 141.7 (s) (C, Ar), 131.5 (s) (2 × CH, Ar), 124.7 (s) (2 × CH, Ar), 53.0 (s) (O-CH_3), 41.2 (s) (CH_2); *m/z* (APCI) 196.0[(M + H)$^+$, 100%], 89.2 (8), 61.3 (7.4), 60.5 (16.7).

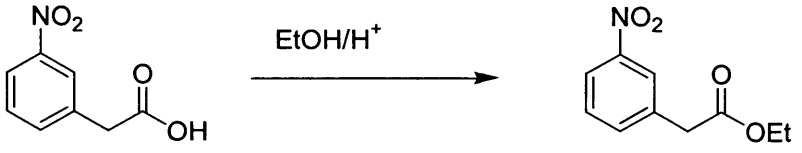


Methyl 2-(4'-nitrophenyl)propionate[235] **(164)**—This was prepared by the General Method using 2-(4'-nitrophenyl)propionic acid (**163**) (10 g, 51.28 mmol), methanol (100 ml) and sulfuric acid (1 ml) to give the pure product as a yellow oil (9.57 g, 90%). ν_{max} (liq. film on

NaCl plates/cm^{-1}) 1738 (s) (C=O), 1606 (m), 1522 (s), 1211 (s), 859 (s), δ_H(400 MHz, $CDCl_3$) 8.17 (2H, d, *J* 8.7 Hz, H-3 & H-5), 7.4 (2H, d, *J* 8.7 Hz, H-2 & H-6), 3.84 (1H, q, *J* 7.2 Hz, C<u>H</u>), 3.55 (3H, s, OC<u>H</u>$_3$), 1.40 (3H, d, *J* 7.2 Hz, CH_3), δ_c(100 MHz, $CDCl_3$) 174.2 (s) (C=O), 147.9 (s) (C, Ar), 146.5 (s) (C, Ar), 129.4 (s) (2 × CH, Ar), 124.6 (s) (2 × CH, Ar), 53.9 (s) (O-CH_3), 45.1 (s) (-<u>C</u>-C=O), 19.8 (s) (CH_3). *m/z* (APCI) 209.9 [$(M + H)^+$, 100 %], 192.9 (7), 177.9 (14), 163.9 (3), 150.9 (6), 149.9 (13).

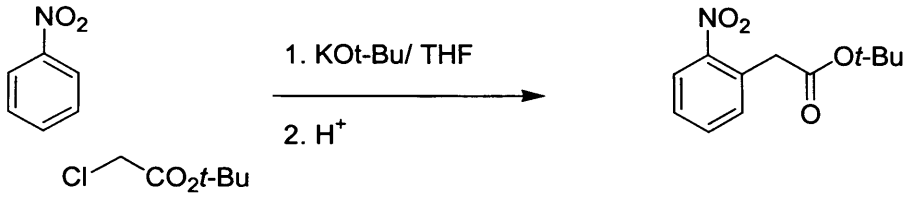


Isopropyl 2-nitrophenylacetate[236] **(315)**—This was prepared by the General Method using 2-nitrophenylacetic acid (8.0 g, 44.2 mmol), IPA (100 ml) and sulfuric acid (1 ml) to give the pure product as a pale yellow oil (7.90 g, 80%). ν_{max} (liq. film on NaCl plates/cm^{-1}) 3444 (w), 3070 (w), 2981 (m), 2936 (m), 2878 (w), 2363 (w), 1949 (w), 1729 (s) (C=O), 1613 (m), 1580 (m), 1526 (s), 1467 (m), 1414 (m), 1348 (s), 1222 (s), 1105 (s), 1047 (w), 957 (s); δ_H(400 MHz, $CDCl_3$) 8.11 (1H, d, *J* 8.5 Hz, H-3), 7.60 (1H, t, *J* 8.5 Hz, H-5), 7.47 (1H, t, *J* 8.5 Hz, H-4), 7.36 (1H, d, *J* 8.5 Hz, H-6), 5.04 (1H, *septet*, *J* 6.4 Hz, <u>H</u>C(CH_3)$_2$), 3.99 (2H, s, CH_2), 1.24 (6H, d, *J* 6.4 Hz, 2 × CH_3), δ_C(100 MHz, $CDCl_3$) 169.9 (s) (C=O), 149.2 (s) (C, Ar), 133.9 (s) (CH, Ar), 133.7 (s) (CH, Ar), 130.4 (s) (C, Ar), 128.9 (s) (CH, Ar), 125.6 (s) (CH, Ar), 69.3 (s) (CH) 40.6 (s) (CH_2), 22.1 (s) (2 × CH_3); *m/z* (APCI) 224.1 [$(M+H)^+$, 100%].



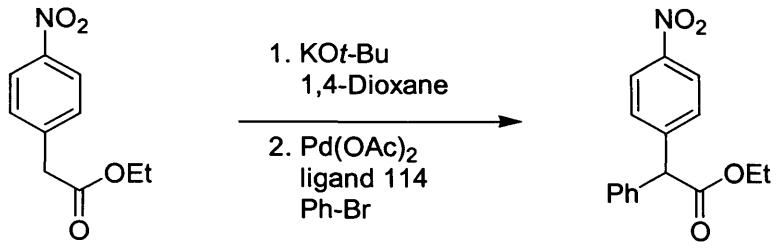
Ethyl 3-nitrophenylacetate[237] **(326)**—This was prepared by the General Method using 3-nitrophenylacetic acid (**325**) (5 g, 27.7 mmol), ethanol (50 ml) and sulfuric acid (0.5 ml) to give the pure product as a pale yellow oil (4.04 g, 70%). ν_{max} (liq. film on NaCl plates/cm^{-1}) 3091 (w), 2983 (m), 2938 (w), 2360 (w), 1737 (s) (C=O), 1619 (w), 1583 (w), 1531 (s), 1480 (w), 1445 (w), 1417 (w), 1352 (s), 1253 (m), 1227 (m), 1162 (s), 1098 (m), 1030 (s); δ_H(400 MHz, $CDCl_3$) 8.17 (1H, s, H-2), 8.14 (1H, d, *J* 8.4 Hz, H-6), 7.64 (1H, d, *J* 8.4 Hz, H-4), 7.52 (1H, t, *J* 8.4 Hz, H-5), 4.19 (2H, q, *J* 7.2 Hz, O-CH_2-), 3.74 (2H, s, Ar-CH_2), 1.28 (3H, t, *J* 7.2 Hz, CH_3), δ_C(100 MHz, $CDCl_3$) 170.8 (s) (C=O), 148.6 (s) (C, Ar), 136.4 (s) (C, Ar), 136.1 (s)

(CH, Ar), 129.8 (s) (CH, Ar), 124.7 (s) (CH, Ar), 122.6 (s) (CH, Ar), 61.7 (s) (CH_2) 41.0 (s) (CH_2), 14.5 (s) (CH_3); *m/z* (APCI) 216.1 [$(M+H)^+$, 100%].

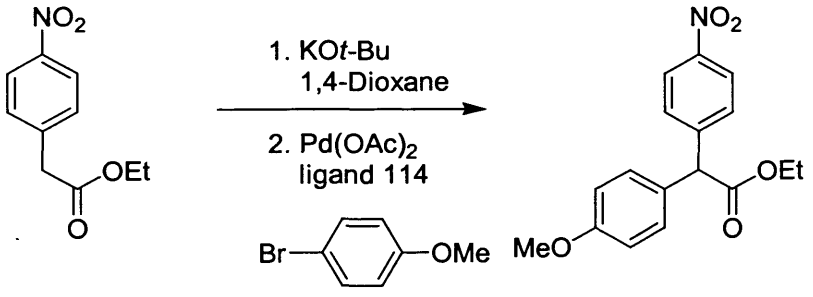


***tert-Butyl 2-nitrophenylacetate*[238] (318)**—Potassium *tert*-butoxide (0.6 g, 6.1 mmol) was dissolved in anhydrous THF (5 ml) under nitrogen, then cooled to –70 °C (bath temp). Nitrobenzene (0.25 ml, 2.43 mmol) and *tert*-butyl chloroacetate (0.35 ml, 2.43 mmol) dissolved in THF (2 ml) were slowly added to the basic solution. The solution was then stirred while slowly warming to around –20 °C for an hour. The reaction was then quenched with HCl (1M) (2 ml), then allowed to warm to room temperature. The product was then extracted with dichloromethane (3 × 20 ml), washed with water (3 × 20 ml), sodium bicarbonate (sat. aq. 20 ml) and dried over Na_2SO_4. The solvent was then removed on a rotary evaporator to give an orange oil (0.75 g). The crude product was then purified by column chromatography R_f 0.21 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.27 g, 47%) as a yellow oil. δ_H(400 MHz, $CDCl_3$) 8.10 (1H, d, *J* 8.3 Hz, H-6), 7.58 (1H, t, *J* 8.3 Hz, H-4), 7.46 (1H, t, *J* 8.3 Hz, H-5), 7.34 (1H, d, *J* 8.3 Hz, H-3), 3.94 (2H, s, CH_2), 1.44 (9H, s, 3 × CH_3); δ_C(100 MHz; $CDCl_3$) 169.3 (s) (C=O), 149.0 (s) (C, Ar), 133.6 (s) (C, Ar), 133.5 (s) (CH, Ar), 128.5 (s) (CH, Ar), 127.1 (s) (CH, Ar), 125.3 (s) (CH, Ar), 81.9 (s) (O-C), 41.2 (s) CH_2), 28.1 (s) (3 × CH_3); $[(M+H)^+$ 100%].

General Method for cross-coupling nitrophenylacetates with aryl halides—In a 100 ml two-necked round bottom flask fitted with a condenser which was attached to a schlenk line, under a flow of nitrogen was added the base (2.39 mmol), and solvent (3 ml). The flask was cooled to 0 °C in an ice bath and the ester (2.39 mmol) dissolved in solvent (2 ml) was then added dropwise to the basic solution. The solution was allowed to warm to room temperature and a mixture of palladium acetate (5 mol %), the ligand (10 mol %) and electrophile (2.39 mmol) dissolved in solvent were added to the bright purple solution. The mixture was heated in an oil bath while monitoring the reaction progress by HPLC. The mixture was then cooled to room temperature where ethyl acetate (20 ml) was added and the mixture was filtered through a silica gel plug to remove the palladium. The filtrate was collected and the solvent was removed on a rotary evaporator to give the crude product.

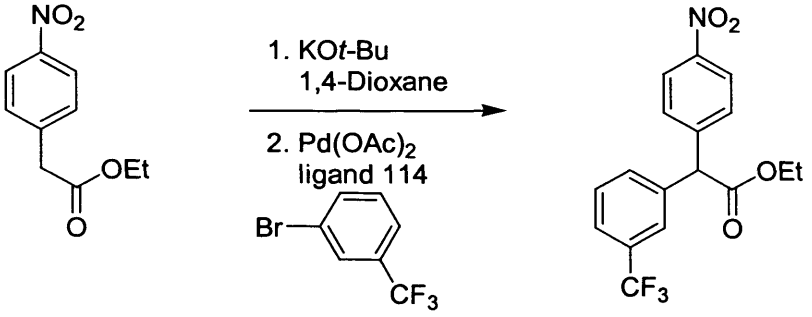


Ethyl 2-(4'-nitrophenyl)-2-phenylacetate **(312)**—This was prepared by the General Method using potassium *tert*-butoxide (268 mg, 2.39 mmol), 1,4-dioxane (8 ml), ethyl 4-nitrophenylacetate (**311**) (0.50 g, 2.39 mmol), palladium acetate (26.8 mg, 0.12 mmol), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (**114**) (94.5 mg, 0.24 mmol) and bromobenzene (0.26 ml, 2.39 mmol). The mixture was heated in an oil bath (110 °C) (bath temp) for 2 hours while monitoring the reaction progress by HPLC to give the crude product as a brown oil (0.76 g). The crude product was then purified by column chromatography R_f 0.3 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.61 g, 90%) as a yellow oil. ν_{max} (liq. film on NaCl plates/cm^{-1}) 3064 (w), 3030 (w), 2983 (m), 2937 (m), 2455 (w), 2364 (w), 1931 (w), 1732 (s), 1606 (s), 1522 (s), 1494 (m), 1453 (m), 1349 (s), 1194 (s), 1154 (s), 1111 (m); δ_H(400 MHz, $CDCl_3$) 8.16 (2H, d, *J* 8.6 Hz, H-3' & H-5'), 7.50 (2H, d, *J* 8.6 Hz, H-2' & H-6'), 7.28-7.37 (5H, m, Ph), 5.10 (1H, s, CH-Ph), 4.24 (2H, q, *J* 7.0 Hz, CH_2), 1.26 (3H, t, *J* 7.0 Hz, CH_3); δ_C(100 MHz, $CDCl_3$) 171.8 (s) (C=O), 147.5 (s) (C, Ar), 146.4 (s) (C, Ar), 131.7 (s) (C, Ar), 130.0 (s) (2 × CH, Ar), 129.4 (s) (2 × CH, Ar), 128.8 (s) (2 × CH, Ar), 128.3 (s) (CH, Ar) 124.1 (s) (2 × CH, Ar), 62.1 (s) (CH), 57.1 (s) (CH_2), 14.5 (s) (CH_3); *m/z* (APCI) 286.0 [$(M+H)^+$, 100%]; (Found (EI+): M^+ 285.1014. $C_{16}H_{15}NO_4$ requires M^+ 285.1001).

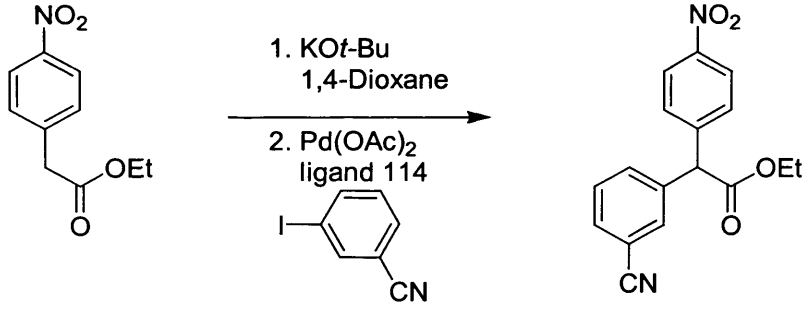


Ethyl 2-(4'-nitrophenyl)-2-(4"-methoxyphenyl)acetate **(324a)**—This was prepared by the General Method using 4-bromoanisole (0.30 ml, 2.39 mmol) instead of bromobenzene to give the pure product as a pale yellow oil after chromatography R_f 0.5 (silica, 1:1. hexane:ethyl acetate; v/v) (0.35 g, 47%). ν_{max} (liq. film on NaCl plates/cm^{-1}) 3051 (w), 3049 (m), 1901 (w), 1735 (s) (C=O), 1549 (m), 1416 (m), 1361 (s), 1209 (m); δ_H(400 MHz, $CDCl_3$) 8.16 (2H, d, *J*

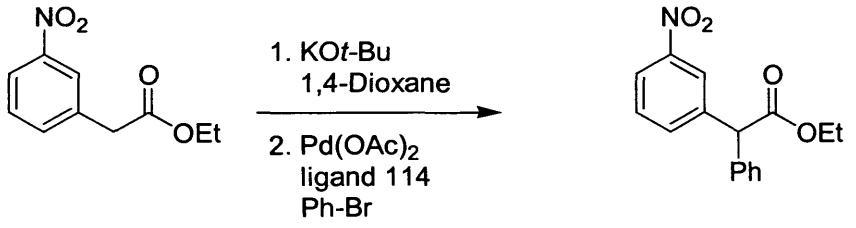
8.8 Hz, H-3' & H-5'), 7.48 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 7.23 (2H, d, *J* 8.2 Hz, H-2" & H-6"), 6.88 (2H, d, *J* 8.2 Hz, H-3" & H-5"), 5.05 (1H, s, CH), 4.24 (2H, q, *J* 6.8 Hz, CH_2), 1.26 (3H, t, *J* 6.8 Hz, CH_3); δ_C(100 MHz, $CDCl_3$) 171.7 (s) (C=O), 149.1 (s) (C, Ar), 148.2 (s) (C, Ar), 131.1 (s) (2 x CH, Ar), 129.6 (s) (C, Ar), 128.3 (s) (2 × CH, Ar), 123.9 (s) (2 × CH, Ar), 119.1 (s) (C, Ar), 109.1 (s) (2 × CH, Ar), 79.7 (s) (CH), 63.9 (s) (CH2), 56.7 (s) (O-CH_3), 14.7 (s) (CH3); *m/z* (APCI) 316.3 [$(M+H)^+$, 100%]; (Found (EI+): M^+ 315.1110. $C_{17}H_{17}NO_5$ requires M^+ 315.1107).



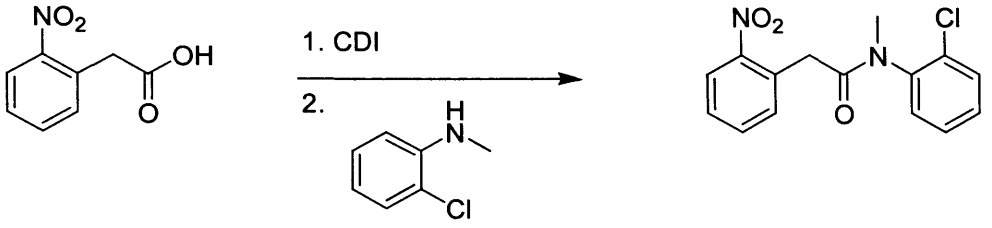
Ethyl 2-(4'-nitrophenyl)-2-(3"-trifluoromethylphenyl)acetate **(324b)**—This was prepared by the General Method using 3-bromonitrobenzotrifluoride (0.34 ml, 2.39 mmol) instead of bromobenzene to give the pure product as a pale yellow oil after chromatography R_f 0.5 (silica, 3:1. hexane:ethyl acetate; v/v) (0.55 g, 65%). ν_{max} (liq. film on NaCl plates/cm^{-1}) 3049 (w), 2981 (s), 1733 (s) (C=O), 1608 (s), 1521 (s), 1487 (m), 1350 (s), 1196 (s), 1160 (s), 1028 (s); δ_H(400 MHz, $CDCl_3$) 8.21 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 7.57-7.60 (2H, m, H-Ar), 7.48-7.51 (5H, m, H-Ar), 5.15 (1H, s, CH), 4.26 (2H, q, *J* 7.2 Hz, CH_2), 1.28 (3H, t, *J* 7.2 Hz, CH_3); δ_C(100 MHz, $CDCl_3$) 171.8 (s) (C=O), 145.4 (s) (C, Ar), 138.6 (s) (C, Ar), 132.3 (s) (C, Ar), 130.8 (q) (C-CF_3, *J* 34.2 Hz) 129.9 (s) (2 × CH, Ar), 129.8 (s) (CH, Ar), 125.7 (s) (CH, Ar), 125.2 (s) (CH, Ar), 124.4 (s) (2 × CH, Ar), 123.9 (s) (CH, Ar), 122.7 (q) (CF_3, *J* 271 Hz), 62.4 (s) (CH_2), 56.8 (s) (O-CH_3), 14.4 (s) (CH_3); *m/z* (APCI) 354.1 [$(M+H)^+$, 100%]; (Found (EI+): M^+ 353.0863. $C_{17}H_{14}NO_4F_3$ requires M^+ 353.0875).



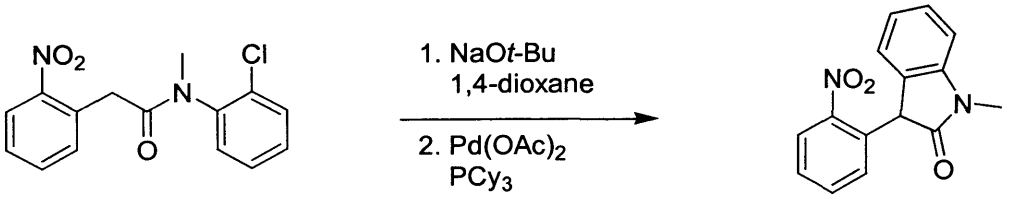
Ethyl 2-(4'-nitrophenyl)-2-(3"-cyanophenyl)acetate (**324c**)—This was prepared by the General Method using 3-iodobenzonitrile (0.55 g, 2.39 mmol) instead of bromobenzene and DMF as the solvent to give the pure product as a pale yellow oil after chromatography R_f 0.3 (silica, 1:1. hexane:ethyl acetate; v/v) (0.55 g, 74%). ν_{max} (liq. film on NaCl plates/cm^{-1}) 3057 (w), 3049 (w), 1941 (w), 1729 (s) (C=O), 1611 (m), 1594 (w), 1517 (s), 1479 (s), 1345 (s); δ_H(400 MHz, $CDCl_3$) 8.23 (2H, d, *J* 8.9 Hz, H-3' & H-5'), 7.76 (1H, s, H-2"), 7.62-7.70 (4H, m, H-2', H-6', H-4" & H-6"), 7.50 (1H, t, *J* 8.2 Hz, H-5"), 4.50 (1H, s, CH-Ar), 4.40 (2H, q, *J* 7.8 Hz, CH_2), 1.32 (3H, t, *J* 7.8 Hz, CH_3); δ_C(100 MHz, $CDCl_3$) 172.6 (s) (C=O), 148.2 (s) (C, Ar), 148.1 (s) (C, Ar), 142.9 (s) (C, Ar), 132.6 (s) (CH, Ar) 132.0 (s) (CH, Ar), 131.1 (s) (CH, Ar), 129.8 (s) (CH, Ar), 128.6 (s) (2 × CH, Ar), 124.0 (s) (2 × CH, Ar), 118.8 (s) (C, Ar), 113.1 (s) (CN), 80.1 (s) (CH), 64.6 (s) (CH_2), 14.4 (s) (CH_3); *m/z* (APCI) 311.1 [$(M+H)^+$, 100%]; (Found (EI+): M^+ 310.0956. $C_{17}H_{14}N_2O_4$ requires M^+ 310.0954).



Ethyl 2-(3'-nitrophenyl)-2-phenyacetate (**327**)—This was prepared by the General Method using ethyl 3-nitrophenylacetate (**326**) (0.50 g, 2.39 mmol) instead of ethyl 4-nitrophenylacetate (**316**) and DMF as the solvent to give the pure product as a pale yellow oil after chromatography R_f 0.3 (silica, 3:1. hexane:ethyl acetate; v/v) (0.47 g, 69%). ν_{max} (liq. film on NaCl plates/cm^{-1}) 2924 (s), 1770 (s) (C=O), 1681 (s), 1604 (m), 1537 (m), 1401 (s), 1354 (m), 1107 (m); δ_H(400 MHz, $CDCl_3$) 8.21 (1H, s, H-2'), 8.12 (1H, d, *J* 8.3 Hz, H-4'), 7.67 (1H, d, *J* 8.3 Hz, H-6'), 7.48 (1H, t, *J* 8.3 Hz, H-5'), 7.28-7.36 (5H, m, Ph), 5.11 (1H, s, CH-Ar), 4.24 (2H, q, *J* 7.4 Hz, CH_2), 1.26 (3H, t, *J* 7.4 Hz, CH_3); δ_C(100 MHz, $CDCl_3$) 171.9 (s) (C=O), 148.7 (s) (C, Ar), 141.3 (s) (C, Ar), 137.8 (s) (C, Ar), 135.3 (s) (CH, Ar) 129.9 (s) (CH, Ar), 129.4 (s) (2 x CH, Ar), 128.8 (s) (2 x CH, Ar), 128.3 (s) (CH, Ar), 124.1 (s) (CH, Ar), 122.8 (s) (CH, Ar), 62.2 (s) (CH), 57.0 (s) (CH_2), 14.5 (s) (CH_3); *m/z* (APCI) 286.3 [$(M+H)^+$, 100%]; (Found (ES+): $(M + NH_4)^+$, 303.1342. $C_{16}H_{19}N_2O_4$ requires $(M + NH_4)^+$ 303.1345).



N-(2'-Chlorophenyl)-N-methyl-2-(2"-nitrophenyl)acetamide **(332)**—This was prepared according to the general method developed by Jones.[240] In a 2-necked round bottom flask fitted with a condenser connected to a Schlenk line was added, under nitrogen, 2-nitrophenylacetic acid (1.0 g, 5.52 mmol), dichloromethane (10 ml) and carbonyldiimidazole (0.96 g, 5.52 mmol). The mixture was heated under reflux for 1 hour. 2-Chloro-*N*-methylaniline (0.68 ml, 5.52 mmol) was then added dropwise to the reaction mixture after cooling. The mixture was then heated under reflux for 1 hour. After checking the progress of the reaction by HPLC the mixture was left to stir at room temperature for 24 hours. The mixture was then diluted with ethyl acetate then washed with 1M HCl (20 ml), water (20 ml) and brine (20 ml). The solution was then dried over $MgSO_4$ and the solvent removed on a rotary evaporator to give an orange oil (2.18 g). The crude product was then purified by column chromatography R_f 0.10 (silica, 3:1. hexane:ethyl acetate; v/v) to give the pure product (0.69 g, 49%) as a white crystalline powder. M.p. 154-156 °C. Found C, 59.17; H, 4.26; N 9.45. $C_{15}H_{13}N_2O_3Cl$ requires C, 59.12; H, 4.30; N, 9.19%); ν_{max} (nujol on NaCl plates/cm^{-1}) 3058 (w), 2991 (s), 1691 (s) (C=O), 1613 (m), 1518 (s), 1479 (s), 1360 (s); δ_H(400 MHz, $CDCl_3$) 8.07 (1H, app. d, *J* 8.1 Hz, H-3"), 7.53-7.57 (3H, m, H-Ar), 7.38-7.42 (3H, m, H-Ar), 7.29 (1H, app. d, *J* 8.4 Hz, H-6'), 3.97 (1H, d, *J* 16.6 Hz, HCH), 3.45 (1H, d, *J* 16.6 Hz, HCH), 3.25 (3H, s, CH_3), δ_C(100 MHz; $CDCl_3$) 169.5 (s) (C=O), 149.3 (s) (C, Ar), 141.1 (s) (C, Ar), 134.0 (s) (CH, Ar), 133.7 (s) (CH, Ar), 133.5 (s) (C, Ar), 131.5 (s) (C, Ar), 131.2 (s) (CH, Ar) 130.7 (s) (CH, Ar), 130.3 (s) (CH, Ar), 129.1 (s) (CH, Ar), 128.5 (s) (CH, Ar), 125.5 (s) (CH, Ar), 39.9 (s) (CH_3), 36.8 (s) (CH_2); *m/z* (APCI) 305.4 [$(M+H)^+$, 100%]; 307.1 (34%); (Found (ES+): $(M + H)^+$, 305.0686. $C_{15}H_{14}N_2O_3Cl$ requires $(M + H)^+$ 305.0693).



3-(2'-Nitrophenyl)oxindole (**333**)—This was prepared by the General Method using *N*-(2'-chlorophenyl)-*N*-methyl-2-(2"-nitrophenyl)acetamide (**332**) (187 mg, 0.58 mmol) instead of ethyl 4-nitrophenylacetate and tricyclohexyphosphine (8.2 mg, 0.058mmol) instead of 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl with no bromobenzene present and 1,4-dioxane (4 ml) in total to give the pure product as a white crystalline solid after chromatography R_f 0.3 (silica, 1:1. hexane:ethyl acetate; v/v) (104 mg, 67%). M.p. 145-157 °C. (Found C, 67.41; H, 4.45; N 10.32. $C_{15}H_{12}N_2O_3$ requires C, 67.16; H, 4.51; N, 10.44%); ν_{max} (nujol on NaCl plates/cm^{-1}) 3057 (w), 2990 (s), 1689 (s) (C=O), 1645 (m), 1609 (s), 1517 (s), 1495 (s), 1375 (s), 1209 (m), 1173 (m); δ_H(400 MHz, $CDCl_3$) 8.09 (1H, d, *J* 8.3 Hz, H-3'), 7.52-7.57 (3H, m, H-Ar), 7.40-7.45 (3H, m, H-Ar), 7.27 (1H, d, *J* 8.3 Hz, H-Ar), 5.19 (1H, s, CH), 3.22 (3H, s, CH_3), δ_C(100 MHz; $CDCl_3$) 169.9 (s) (C=O), 149.2 (s) (C, Ar), 141.2 (s) (C, Ar), 133.7 (s) (CH, Ar), 133.5 (s) (CH, Ar), 133.2 (s) (C, Ar), 131.0 (s) (C, Ar), 130.7 (s) (CH, Ar) 130.4(s) (CH, Ar), 129.7 (CH, Ar), 128.4 (s) (CH, Ar), 128.0 (s) (CH, Ar), 124.9 (s) (CH, Ar), 99.7 (s) (CH), 38.7 (s) (CH_3); *m/z* (APCI) 269.1 [$(M+H)^+$, 100%]; (Found (ES+): $(M + H)^+$, 269.0928. $C_{15}H_{13}N_2O_3$ requires $(M + H)^+$ 269.0927).

References

References

1. Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* **1951**, 49, 273.
2. Miller, J. *Aromatic Nucleophilic Substitution;* Elsevier: Amsterdam. **1968**.
3. Buncel, E.; Crampton, M.R; Strauss, M.J; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions;* Elsevier: Amsterdam. **1984.**
4. Terrier, F. *Nucleophilic Aromatic Displacement;* Verlag Chemie: Weinheim, 1991.
5. Strauss, M.J. *Chem. Rev.* **1970**, 70, 667.
6. Terrier, A. *Chem. Rev.* **1982**, 82, 87.
7. Artamkina, O.A.; Egorov, M.P.; Beletskaya, I.P. *Chem. Rev.* **1982**, 82, 4.
8. Mąkosza, M.; Staliński, K. *Chem.-Eur. J.* **1997**, 3, 2025.
9. Mąkosza, M.; Staliński, K. *Synthesis* **1998**, 1631.
10. Mąkosza, M.; Staliński, K. *Tetrahedron* **1998**, 54, 8797.
11. Mąkosza, M.; Staliński, K. *Pol. J. Chem.* **1999**, 73, 151.
12. Mąkosza, M.; Staliński, K.; Zhao, C-G. *J. Org. Chem.* **1998**, 63, 4390.
13. Adam, W.; Mąkosza, M.; Zhao, C-G; Surowiec, M. *J. Org. Chem.* **2000**, 65, 1099.
14. RajanBabu, T.V.; Reddy, G.S.; Fukunaga, T. *J. Am. Chem. Soc.* **1985**, 107, 5473.
15. Kramarova, E.P.; Anisomova, N.A.; Baukov, Y. *Zh. Obshch. Khim.* **1991**, 61, 1406.
16. Davis, R.B.; Pizzini, L.C. *J. Org. Chem.* **1960**, 25, 1884.
17. Davis, R.B.; Pizzini, L.C; Benigni, J.D. *J. Am. Chem. Soc.* **1960**, 82, 2913.
18. Davis, R.B.; Pizzini, L.C.; Bara, E.J. *J. Org. Chem.* **1961**, 26, 4270.
19. Davis, R.B.; Benigni, J.D. *J. Org. Chem.* **1962**, 27, 1605.
20. Davis, R.B.; Benigni, J.D. *J. Chem. Eng. Data* **1963**, 8, 578.
21. Davis, R.B; Weber, J.D. *J. Chem. Eng. Data.* **1963**, 8, 580.
22. Wróbel, Z. *Pol. J. Chem.* **1998**, 72, 2384.
23. Wróbel, Z. *Eur. J. Org. Chem.* **2000**, 521.
24. Wróbel, Z.; Mąkosza, M. *Synlett* **1993**, 597.
25. Wróbel, Z. *Tetrahedron Lett.* **1997**, 38, 4913.
26. Wróbel, Z. *Synthesis* **1997**, 753.
27. Wróbel, Z. *Synthesis* **2001**, 1927.
28. Golifiński, J; Mąkosza, M. *Tetrahedron Lett.* **1978**, 29, 3495.
29. Mąkosza, M; Glinka, T. *J. Org. Chem.* **1983**, 48, 3860.
30. Mąkosza, M; Winiarski, J. *Acc. Chem. Res.* **1987**, 20, 282.
31. Mąkosza, M; Glinka, T; Kinowski, A. *Tetrahedron* **1984**, 40, 1863.

32. Mąkosza, M; Wenäll, M; Goliński, M; Kinowski, A. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1985**, 32, 427.
33. Russell, G.A; Weiner, S.A. *J. Org. Chem.* **1966**, 31, 248.
34. Traynelis, V. J; McSweeney, J.V. *J. Org. Chem.* **1966**, 31, 243.
35. McBee, E.T; Wesseler, E.P; Hodgins, T. *J. Org. Chem.* **1971**, 36, 2907.
36. Mąkosza, M; Slomka, E. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1984**, 32, 69.
37. Bushell, S.M.; Crump, P.; Lawrence, N.J.; Pineau, G. *Tetrahedron*, **1998**, 54, 2269.
38. Lonning, P.E.; Kvinnsland, S. *Drugs*, **1988**, 685; Shaw, M.A.; Nicholls, P.J.; Smith, H.J. *J. Steroid Biochem.*, **1989**, 31, 137.
39. Lawrence, N.J.; Lamarche, O.; Thurrab, N. *J. Chem. Soc. Chem. Commun.* **1999**, 689.
40. Taylor, R. *Electrophilic Aromatic Substitution, Wiley, Chichester.* **1990**.
41. Gilman, H.; Bebb, R. *J. Am. Chem. Soc.* **1939**, 61, 109.
42. Wittig, G.; Fuhrman, F. *Chem.Ber.* **1940**, 73, 1139.
43. Tahara, N.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* **2002**, 43, 9069.
44. Slocum, D.W.; Moon, R.; Thomson, J.; Coffey, D.S.; Hi, J.D.; Slocum , G.; Siegal, A.; Gayton-Garcia, R. *Tetrahedron Lett.* **1994**, 35, 385.
45. Winkle, M.R.; Ronald, R.C. *J. Org. Chem.* **1982**, 47, 2101.
46. Wakefield, B.J. *The Chemistry of Organolithium compounds, Pergamon, Oxford.* **1974**.
47. Suzuki, A. *J. Organomet. Chem.* **1999**, 576, 147.
48. Tamao, K. *Comprehensive Organic Synthesis;* Trost, B.M., Ed.; *Pergamon: Oxford,* **1991**, 3, 435.
49. Farina, V.; Krishnamurthy, V.; Scott, W.J. *Org. React.* **1997**, 50, 1.
50. Gallagher, W.P.; Terstiege, I.; Maleckza, Jr., R.E. *J. Am. Chem. Soc.* **2001**, 123, 3194.
51. Edrik, E. *Tetrahedron* **1992**, 48, 9577.
52. Kraft, P.; Bajgrowitcz, J.A.; Denis, C.; Frater, G. *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 2980.
53. Palucki, M.; Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1996**, 118, 10333.
54. Mann.G.; Hartwig, J.F. *J. Am. Chem. Soc.* **1996**, 118, 13109.
55. Hartwig, J.F. *Acc. Chem. Res.* **1998**, 31, 852.
56. Li, G.Y. *Angew. Chem., Int. Ed. Engl.* **2001**, 40, 1513.
57. Baranano, D.; Hartwig, J.F. *J. Am. Chem. Soc.* **1995**, 117, 2937.
58. Zheng,N.; McWilliams, J.C.; Fleitz, F.J.; Armstrong, J.D.; Volante, R.P. *J. Org. Chem.* **1998**, 63, 9606.
59. Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, 57, 3069.

60. Mann, G.; Baranano, D.; Hartwig, J.F.; Rheingold, A.L.; Guzei, I.A. *J. Am. Chem. Soc.* **1998**, 120, 9205.
61. Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Synthesis* **1981**, 56.
62. Hirao, T.; Masunaga, T. Yamada, N.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn* **1982**, 55, 909.
63. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, 60, 7508.
64. Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *Synthesis* **2000**, 778.
65. Grushi, V.V.; Alper, H. *Chem. Rev.* **1994**, 94, 1047.
66. Horn, K.A. *Chem. Rev.* **1995**, 95, 1317.
67. Matsumoto, H.; Yoshihiro, K.; Nagashima, S.; Watanabe, H.; Nagai, Y. *J. Org. Chem.* **1977**, 128, 409.
68. Eaborn, C.; Griffiths, R.W.; Pidcock, A. *J. Organomet. Chem.* **1982**, 225, 331.
69. Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1987**, 28, 4715.
70. Shirakawa, E.; Kurahashi, T.; Yoshida, H.; Hiyama, T. *J. Chem. Soc. Chem. Commun.* **2000**, 1895.
71. Satoh, T.; Kawamura, Y.; Nomura, M. *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1740.
72. Satoh, T.; Inoh, J.I.; Kawamura, Y.; Kawamura, M. Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, 71, 2239.
73. Terao, Y.; Satoh, T, Miura, M.; Nomura, M. *Bull. Chem.Soc. Jpn.* **1999**, 72, 2345.
74. Terao, Y.; Satoh, T. Miura, M. Nomura, M. *Tetrahedron* **2000**, 56, 1315.
75. Palucki, M. Buchwald, S.L. *J. Am. Chem. Soc.* **1997**, 119, 11108.
76. Ahman, J.; Wolfe, J.P.; Troutman, M.V.; Palucki, M.; Buchwald, S.L. *J. Am. Chem. Soc.* **1998**, 120, 1918.
77. Old, D.W.; Wolfe, J.P.; Buchwald, S.L.; *J. Am. Chem.Soc.* **1998**, 120, 9722.
78. Fox, J.M.; Huang, X.; Chieffi, A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2000**, 122, 1360.
79. Hamann, B.C.; Hartwig, J.F. *J. Am. Chem. Soc.* **1997**, 119, 12382.
80. Kawatsura, M.; Hartwig, J.F.; *J. Am. Chem. Soc.* **1999**, 121, 1473.
81. Shaughnessy, K.H.; Hamann, B.C.; Hartwig, J.F.; *J. Org. Chem.* **1998**, 63, 6456.
82. Hama, T.; Liu, X.; Culkin, D.A.; Hartwig, J.F. *J. Am. Chem. Soc.* **2003**, 125, 11176.
83. Mąkosza, M.; Wojciechowski, K. *Liebigs. Ann.* **1997**, 1805.
84. Mąkosza, M.; Kwast, A. *J. Phys. Org. Chem.* **1998**, 11, 341.
85. Lawrence, N.J.; Liddle, J.; Jackson, D. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2260.
86. Lawrence, N.J.; Liddle, J.; Bushell, S.M.; Jackson, D.A. *J. Org. Chem.* **2002**, 67, 457.
87. Takahashi, I.; Kawakami, E.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett.* **1996**, 353.
88. Takahashi, I.; Hirano, E.; Kawakami, T.; Kitajima, H. *Heterocycles* **1996**, 43, 2343.

89. Jossang, A.; Jossang, P.; Hadi, H.A.; Sevonat, T.; Bodo, B. *J. Org. Chem.* **1991**, 56, 6527.

90. Cravatto, G.; Giovenzana, G.B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, 66, 8447.

91. Rege, P.; Johnson, F. *J. Org. Chem.* **2003**, 68, 6133.

92. Ostrowski, S. *Polish. J. Chem.* **2001**, 75, 1661.

93. Mąkosza, M.; Osinski, P.W.; Ostrowski, S. *Polish J. Chem.* **2001**, 75, 275.

94. Makuoka, H.; Tomioka, Y. *J. Heterocyclic Chem.* **2003**, 40, 1051.

95. Schmidt, R.D.; Lee, G.S.; Pagoria, P.F.; Mitchell, A.R.; Gilardi, R. *J. Heterocyclic Chem.* **2001**, 38, 1227.

96. Bakke, J.M.; Svensen, H.; Trevison, R. *J. Chem. Soc. Perkin Trans. 1* **2001**, 376.

97. Floria, S.; Lorusso, P.; Granito, C.; Ronzini, L/; Troisi, L. *Eur. J. Org. Chem.* **2003**, 4053.

98. Florio, S.; Lorusso, P.; Luisi, R.; Granito, C.; Ronzini, L.; Triosi, L. *Eur. J. Org. Chem.* **2004**, 2118.

99. Floria, S.; Lorusso, P.; Granito, C.; Luisi, R.; Troisi, L. *J. Org. Chem.* **2004**, 2343.

100. Mąkosza, M.; Kwast, A. *Eur. J. Org. Chem.* **2004**, 2125.

101. Kozhevnikov, D.N.; Rusinov, V.L.; Chupakhin, O.N.; Mąkosza, M.; Rykowski, A.; Wolinska, E. *Eur. J. Org. Chem.* **2002**, 1412.

102. Mąkosza, M.; Sienkiewicz, K.; *J. Org. Chem.* **1990**, 55, 4979.

103. Mąkosza, M.; Sienkiewicz, K.; *J. Org. Chem.* **1998**, 63, 4199.

104. Mathersteig, G.; Prizkov, w.; Voerckel. *J. Prakt. Chem.* **1990**, 332, 569

105. Mąkosza, M.; Podraza, R. *Eur. J. Org. Chem.* **2000**, 193.

106. Zhu, L.; Zhang, L. *Tetrahedron Lett.* **2000**, 41, 3519.

107. Katayama, S.; Ae, N.; Kodo, T.; Masumoto, S.; Hourai, S.; Tamamura, C.; Tanaka, H.; Nagata, R. *J. Med. Chem.* **2003**, 46, 691.

108. Rozhkov, V.V.; Sherelev, S.; *J. Org. Chem.* **2003**, 68, 2498.

109. Brown, J.M. *Cancer Res.* **1999**, 59, 5863.

110. Brown, J.M. *Mol. Med. Today.* **2000**, 6, 157.

111. Tercel, M.; Lee, A.E.; Hogg. A.; Anderson, R.F.; Lee, H.H.; Slim, B.G.; Denny, W.A.; Wilson, W.R. *J. Med. Chem.* **2001**, 44, 3511.

112. Wojciechowski, K.; Koniński, S. *Tetrahedron* **2001**, 57, 5009.

113. Mąkosza, M.; Koniński, S. *Tetrahedron* **2001**, 57, 9615.

114. Lemek, T.; Mąkosza, M.; Golinski, J. *Tetrahedron* **2001**, 57, 4753.

115. Donskaya, O.V.; Elokhina, V.N.; Nakhmonovich, A.S.' Vakul'skaya, T.I.; Larina, L.I.; Vokin, A.I.; Albanov, A.I.; Lopyrev, V.A. *Tetrahedron Lett.* **2002**, 43, 6613.
116. Scriven, E.F.V. *17th International Congress of Heterocyclic Chemistry, IL-33, Vienna* **1999**
117. Sternberg, E.D.; Dolphin, D. *Tetrahedron* **1998**, 54, 4151.
118. Hsi, R.A.; Rosenthal, D.I.; Eletstein, E. *Drugs* **1999**, 57, 725.
119. Dougherty, T.J.; Kaufman, J.E.; Goldfarb, A. *Cancer Res.* **1985**, 38, 2628.
120. Delaney, T.F.; Glabslein, E. *Compr. Ther.* **1988**, 14, 43.
121. Schweitzer, V.G. *Otolaryngol. Head Neck Surg.* **1990**, 102, 225.
122. Kruper *Jr,* W.J.; Chamberlin, T.A.; Kochanny, M. *J. Org. Chem.* **1989**, 54, 2753.
123. Ostrowski, S.; Urbanska, N.; Mikus, A. *Tetrahedron Lett.* **2003**, 44, 4373.
124. Mąkosza, M.; Lobonova, O.; Kwast, A. *Tetrahedron* **2004**, 60, 2577.
125. Mąkosza, M.; Ostrowski, S. *Polish J. Chem.* **2000**, 74, 1355.
126. Brossi, A. *J. Med. Chem.* **1990**, 33, 2311.
127. Sano, M.; Bell, K.; Marder, K.; Stricks, L. *Clinical Pharm.* **1993**, 16, 6.
128. Pei, X-F.; Greig, N.H.; Bi, S.; Brossi, A. *Med. Chem. Res.* **1995**, 6, 455.
129. Ashimari, A.; Matsoura, T.; Overman, L.E.; Poon, D.J. *J. Org. Chem.* **1993**, 58, 6849.
130. Duan, J.J.W.; Chen, L.H.; Wasserman, Z.R.; Lu, Z.H.; Liu, R.Q.; Covington, M.B.; Qian, M.X.; Hardman, K.D.; Magolda, R.L.; Newton, R.C.; Christ, D.D.; Wexler, R.R.; Decicco, C.P. *J. Med. Chem.* **2002**, 45, 4954.
131. Robinson, R.P.; Laird, E.R.; Blake, J.F.; Bordner, J.; Donahue, K.M.; Lopresti-Morrow, L.L.; Mitchell, P.G.; reese, M.R.; Reeves, L.M.; Stam, E.J.; Yocum, S.A. *J. Med. Chem.* **2000**, 43, 2293.
132. Shaugnnessy, H.H.; Hamaan, B.C.; Hartwig, J.F. *J. Org. Chem.* **1998**, 63, 6546.
133. Freund, R.; Mederski, W.W.K.R. *Helv. Chim. Acta* **2000**, 83, 1247.
134. Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, 3, 631.
135. Lee, S.; Hartwig, J.F. *J. Org. Chem.* **2001**, 66, 3402.
136. Zhang, J.Y.; Zhang, H. *Tetrahedron Lett.* **2002**, 43, 193.
137. Stewart, J.D.; Fields, S.C.; Kochhar, K.S.; Pinnick, H.W. *J. Org. Chem.* **1987**, 52, 2110.
138. Alonso, R.A.; Rodriguez, C.H.; Rossi, R.A. *J. Org. Chem.* **1989**, 54, 5983.
139. Cossy, J.; De Filippis, A.; Pardo, D.G. *Org. Lett.* **2003**, 5, 3037.
140. Bentz, E.; Moloney, M.G.; Westaway, S.M. *Tetrahedron Lett.* **2004**, 45, 7395.
141. Zoretic, P.A.; Soja, P. *J. Org. Chem.* **1976**, 41, 3587.
142. Williams, G.D.; Pike, R.A.; Wade, C.E.; Willis, M. *Org. Lett.* **2003**, 5, 4227.

143. Meyer, W.L.; Vaughan, W.Y. *J. Org. Chem.* **1957**, 22, 1554.
144. Guzman, A. *Chem. Ind. (London)* **1977**, 357.
145. Easton, C.J.; Pitt, M.J.; Ward, C.M. *Tetrahedron* **1995**, 51, 12781.
146. Nokagana, M.; Torisawa, Y.; Hosaka, T.; Tanabe, K.; Alkawa, M.; Hino, T. *Heterocycles* **1993**, 36, 1157.
147. Dyer, J.; King, A.; Keeling, S.; Moloney, M.G. *J. Chem. Soc. Perkin Trans. 1* **2000**, 2793.
148. Bellamy, A.J.; Inneb, D.I.; Hillson, P.J. *J. Chem. Soc. Perkin Trans. 2.* **1983**, 179.
149. Giang, L,T.; Fetter, J.; Lempert, K.; Kajtar-Pereby, M.; Gomory, A. *Tetrahedron* **1996**, 52, 10169.
150. Fuji, K. *Chem. Rev.* **1993**, 2037.
151. Christoffers, A.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, 40, 4591.
152. Corey, E.J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl* **1998**, 37, 385.
153. Izumi, Y. *Angew. Chem., Int. Ed. Engl.* **1971**, 10, 871.
154. Lawrence, N.J.; Bushell, S.M. *Tetrahedron Lett.* **2000**, 41, 4507.
155. Herdeis, C. *Synthesis* **1986**, 232.
156. Tse, A.; Mansour, T.S. *Tetrahedron Lett.* **1995**, 36, 7807.
157. Drioh, S.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron Asymmetry* **2000**, 56, 1353.
158. Hanessian, S.; Murray, P.J. *Tetrahedron*, **1987**, 43, 5055.
159. Hodgson, H.H.; Moore, F.H. *J. Chem. Soc.* **1926**, 159.
160. Hodgson, H.H.; Moore, F.H. *J. Chem. Soc.* **1925**, 1602.
161. Wright, C.; Shulkind, M.; Jones, K.; Thompson, M. *Tetrahedron Lett.* **1987**, 260, 6389.
162. Moradi, W.A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2001**, 123, 7996.
163. Bukowska, M.; Prejner, J. *Pol. J. Chem.* **1986**, 957.
164. Krapcho, P.; Glynn, G.A.; Grenon, B.J. *Tetrahedron Lett.* **1967**, 8, 215.
165. Federici, I.C.; Righi, G.; Leucio, R.B.; Chiummiento, L.; Funicello, M. *Tetrahedron Lett.* **1994**, 35, 793.
166. Iwai, K. *Bull. Chem. Soc. Jpn.* **1977**, 50, 242.
167. Thottathil, J.K.; Przybyla, C.; Malley, M.; Gougoutas, J.Z. *Tetrahedron Lett.* **1986**, 27, 1533.
168. Tomioka, K.; Svenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, 27, 369.
169. Maldaner, A.O.; Pilli, R.A. *Tetrahedron* **1999**, 55, 13321.
170. Lley. J.; Tolando, R.; Constantino, L. *J. Chem. Soc. Perkin Trans. 2.* **2001**, 1299.

171. Flores-parra, A.; Gutierrez-avell, D.M.; Guzman-vazquez, Z.Y.L.; Ariza-castolo, A.; Contreras, R. *J. Org. Chem.* **1992**, 57, 6067.

172. Blackwell, C.M.; Davidson, A.H.; Launchbury, S.B.; Lewsis, C.N.; Morrice, E.M.; Reeve, M.M.; Roffey, J.A.R.; Tipping, A.S.; Todd, R.S. *J. Org. Chem.* **1992**, 57, 5596.

173. Itami, K.; Mineno, M.; Kamei, T.; Yoshida, J. *Org. Lett.* **2002**, 4, 3635.

174. Hermanns, N.; Dohmen, S.; Bolm, C.; Brase, S. *Angew. Chem. Int. Ed.* **2002**, 41, 3692.

175. Vanier, C.; Large, F.; Wagner, A.; Mioskowski, C. Angew. Chem. Int. Ed. **2000**, 39, 1679.

176. Plobeck, N.; Delarme, D.; Wei, Z.Y.; Yang, H.; Zhou, S.Y.; Walpole, C.; Brown, W.; Zhou, E.; Laborre, M.; Payza, K/; St-onge, S.; Kamassch, A.; Marin, P.E.; Projean, D.; Ducharme, J.; Roberts, E. *J. Med. Chem.* **2000**, 43, 3878.

177. Hsin, L.W.; Dersch, C.M.; Baumann, M.H.; Stafford, D.; Glowa, J.R.; Rothman, R.B.; Jacobsen, A.E.; Rice, K-C. *J. Med. Chem.* **2002**, 45, 1321.

178. Wai, J.S.; Egbertson, M.S.; Payne, L.S.; Fisher, T.E.; Embrey, M.W.; Tran, L.O.; Melamed, J.Y.; Langford, H.M.; Guare, J.P.; Zhuang, L.G.; Grey, V.E.; Vacca, J.P.; Holloway, M.K.; Naylor-olsen, A.M.; Hazuda, A.M.; Felock, D.J.; Felock, P.J.; Wolfe, A.L.; Stillmock, K.A.; Schleif, W.A.; Gabryelski, L.J.; Youngs, D. *J. Med. Chem.* **2000**, 43, 4923.

179. Heuwasam, P.; Gribkoff, V.K.; Pendri, Y.; Dworetsky. S.I.; Meanwell, N.A.; Martinez, E.; Bassard, C.G.; Post-Munson, D.J.; Trojinacki, J.T.; Yeleswaram, K.; Pajar, L.M.; Knipe, J.; Gao, Q.; Perrone, R.; Slarreth, J.E. *Biorg. Med. Chem. Lett.* **2002**, 12, 1023.

180. Katritzky, A.R.; Toader, D. *J. Org. Chem.* **1997**, 62, 4137.

181. Mąkosza, M.; Voskresensky, S. *Synthesis* **2000**, 9, 1237.

182. Overman, L.E.; Matzinger, D.; O'Conner, E.M.; Overman, J.D. *J. Am. Chem. Soc.* **1974**, 96, 6081.

183. Kabochnik, M.L.; Lobonov, D.I.; Matveeva, A.G.; Kovsheva, O.E.; Terekhova, M.I. *Izv. Akad. Nauk SSSR Ser. Khim.* **1991**, 1598.

184. Olstead, W.N.; Bardwell, F.G. *J. Org. Chem.* **1980**, 45, 3299.

185. Gurjar, M.; Ready, D.S.; Murugaich, A.; Murugaiah, S. *Synthesis* **2000**, 1659.

186. Selevakumar, N.; Reddy, B.Y.; Kumar, G.S.; Iqbal, J. *Tetrahedron Lett.* **2001**, 42, 8395.

187. Bluhm, A.L.; Souse, J.A.; Weinstein, J. *J. Org. Chem.* **1964**, 29, 636.

188. Borsche, W.; Fedler, A. *Chem. Ber.* **1913**, 46, 2125.

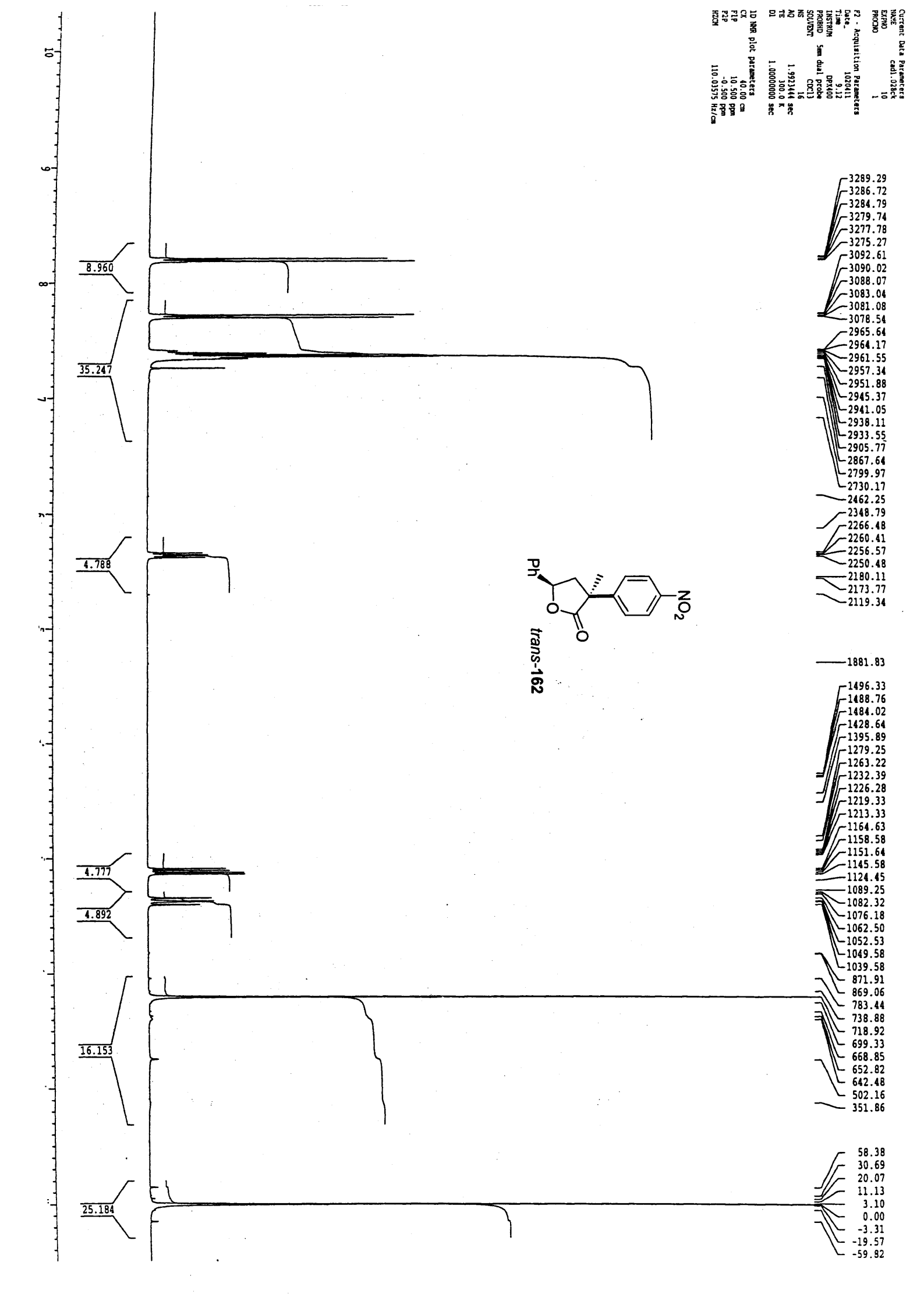
189. Wrobel, Z.; Wojciechowski, K. *Pol. J. Chem.* **1992**, 66, 1125.

190. Pitkanen, M.T.; Korhonen, I.O.O.; Korvola, J.N.J. *Tetrahedron* **1981**, 37, 529.

191. Ende, D.J.; Vogt, D.F. *Org. Proc. Res. Dev.* **2003**, 7, 1029.
192. Liddle, J. PhD thesis, UMIST, Manchester, **1997**.
193. Rolla, F. *J. Org. Chem.* **1982**, 47, 4327.
194. Matsukawa, T.; Shirakawa, K.; Kawasaki, H. *J. Pharm. Soc. Jpn* **1951**, 46, 895.
195. Cherng, Y-J. *Tetrahedron* **2002**, 58, 887.
196. Katz, R.B.; Voyle, M. *Synthesis* **1989**, 314.
197. Liu, M.C.; Tai-shun, S.; Sarsorelli, A-C. *Synth. Commun.* **1990**, 20, 2965.
198. Bordel, P.; Bolanos, A.; Kohn, H. *J. Med. Chem.* **1994**, 4567.
199. Gunasekara, N.S.' Spencer, C.M.; Keating, G.M. *Drugs* **2002**, 62, 1217.
200. Gallagher, G. Jr.; Lavanchy, P.G.; Wilson, J.W.; Hieble, J.P.; DeManinis, R.M. *J. Med. Chem.* **1985**, 28, 1533.
201. Howard, H.R.; Seeger, T.F. *Novel Antipsychotics. Annu. Rep. Med. Chem.* **1993**, 28, 39.
202. Hennessy, E.J.; Buchwald, S.L. *J. Am. Chem. Soc.* **2003**, 125, 12084.
203. Rajanbabu, T.V.; Chernard, B.L.; Petti, M.A. *J. Org. Chem.* **1986**, 51, 1704.
204. Kraus, G.A.; Frazier, K. *Tetrahedron Lett.* **1978**, 19, 3195.
205. Kraynack, E.A.; Dalgard, J.E.; Gaeta, F.C.A. *Tetrahedron Lett.* **1998**, 39, 7679.
206. Prim, D.; Campagne, J-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, 58, 2041.
207. Satoh, T.; Miura, M.; Nomura, M. *J. Organometallic Chem.* **2002**, 661, 161.
208. Miura, M.; Nomura, M. *Topics in Current Chemistry (Cross-coupling)* **2002**, 211.
209. Culkin, D.A.; Hartwig, J.F. *Acc. Chem. Res.* **2003**, 36, 234.
210. Inoh, J.; Satoh, T.; Pivsa-Art, S.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, 39, 4673.
211. Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 1470.
212. Lee, S.; Beare, N.A.; Hartwig, J.F. *J. Am. Chem. Soc.* **2001**, 123, 8410.
213. Jorgensen, M.; Lee, S.; Liu, X.; Wolkowski, J.P.; Hartwig, J.F. *J. Am. Chem. Soc.* **2002**, 124, 12557.
214. Liu, X.; Hartwig, J.F. *J. Am. Chem. Soc.* **2004**, 126, 5182.
215. Golinski, J.; Makosza, M. *Tetrahedron Lett.* **1978**, 19, 3495.
216. Makosza, M.; Golinski, J.; Baran, J. *J. Org. Chem.* **1984**, 49, 1488.
217. Prasad, G.; Hanna, P.E.; Noland, W.E.; Venkatraman, W. *J. Org. Chem.* **1991**, 56, 7188.
218. Zoretic, P.A.; Soja, P. *J. Org. Chem.* **1976**, 3587.
219. Nokagana, M.; Torisawa, Y.; Hosaka, T.; Tanabe, K.; Alkawa, M.; Hino, T. *Heterocycles* **1993**, 1157.

220. Vedejs, E.; Galante, R.J.; Goekjian, P.G. *J. Am. Chem. Soc.*. **1998**, 3613.
221. Brown, J.F.; Slusarczuk, G.M.J. *J. Org. Chem.* **1964**, 29, 2810.
222. Pour, M.; Spulak, M.; Buchta, V.; Waisser, K. *Biorg. Med. Chem. Lett.* **2000**, 16, 1893.
223. Schauble, J.H.; Walter, G.J.; Morin, J.G. *J. Org. Chem.* **1974**, 39, 755.
224. Drioh, S.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron Asymmetry* **2000**, 10, 1353.
225. Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, 62, 168.
226. Wilson, L.J.;. Liotta, D.C. *J. Org. Chem.* **1992**, 57, 1948.
227. Khim, S.; Cederstrom, E.; Ferri, D.C.; Mariano, P.S. *Tetrahedron* **1996**, 52, 3195.
228. Davies, S.G.; Dixon, D.J.; Doisneau, G.J.; Prodger, J.C.; Sanganee, H.J. *Tetrahedron Asymmetry* **2002**, 13, 647.
229. *Chem. Pharm. Bull.* **1989**, 1087.
230. Zinic.M.; Blazevic, N.; Kajfez, F.; Sunjic, V. *J. Heterocyclic Chem* **1977**, 14, 1225..
231. Hojo, M.; Yoshida, Z. *J. Am. Chem. Soc.* **1968**, 90, 4496.
232. Concellón, J.M.; Rodríguez-Solla, H.; Méjica, C. *Tetrahedron Lett.* **2004**, 45, 2977.
233. Selling, H.A. *Tetrahedron.* **1975**, 31, 2387.
234. Ford, J.A.; Wilson, C.V.; Young, W.R. *J. Org. Chem.* **1967**, 32, 173.
235. Hino, K.; Nakamura, H.; Nagai, Y.; Uno, H.; Nishimura, H. *J. Med. Chem.* **1983**, 67, 222.
236. Strazzolini, P.; Giumanini, A.G.; Runco, A.; Scuccato, M. *J. Org. Chem.* **1998**, 63, 952.
237. Ginsburg, D.*J. Org. Chem.* **1950**, 15, 1003.
238. Hodges, J.C.; Wang, W.; Riley, F. *J. Org. Chem.* **2004**, 69, 2504.
239. Jones, K.; McCarthy, C. *Tetrahedron Lett.* **1989**, 30, 2657.
240. Takahashi, M.; Shioura, Y.; Murakami, T.; Ogasawara, K. *Tetrahedro: Asymmetry,* **1997**, 8, 1235.

Appendix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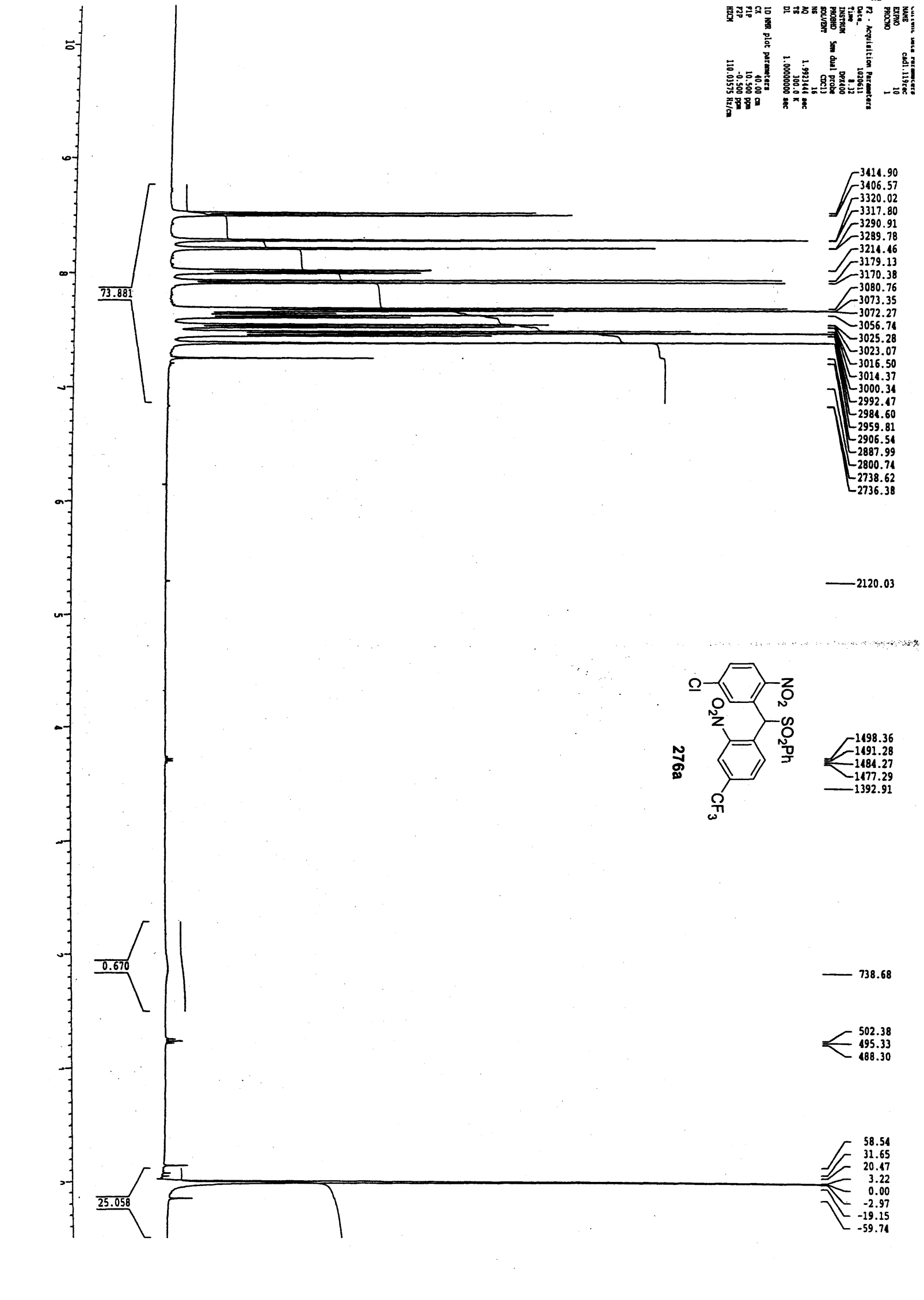
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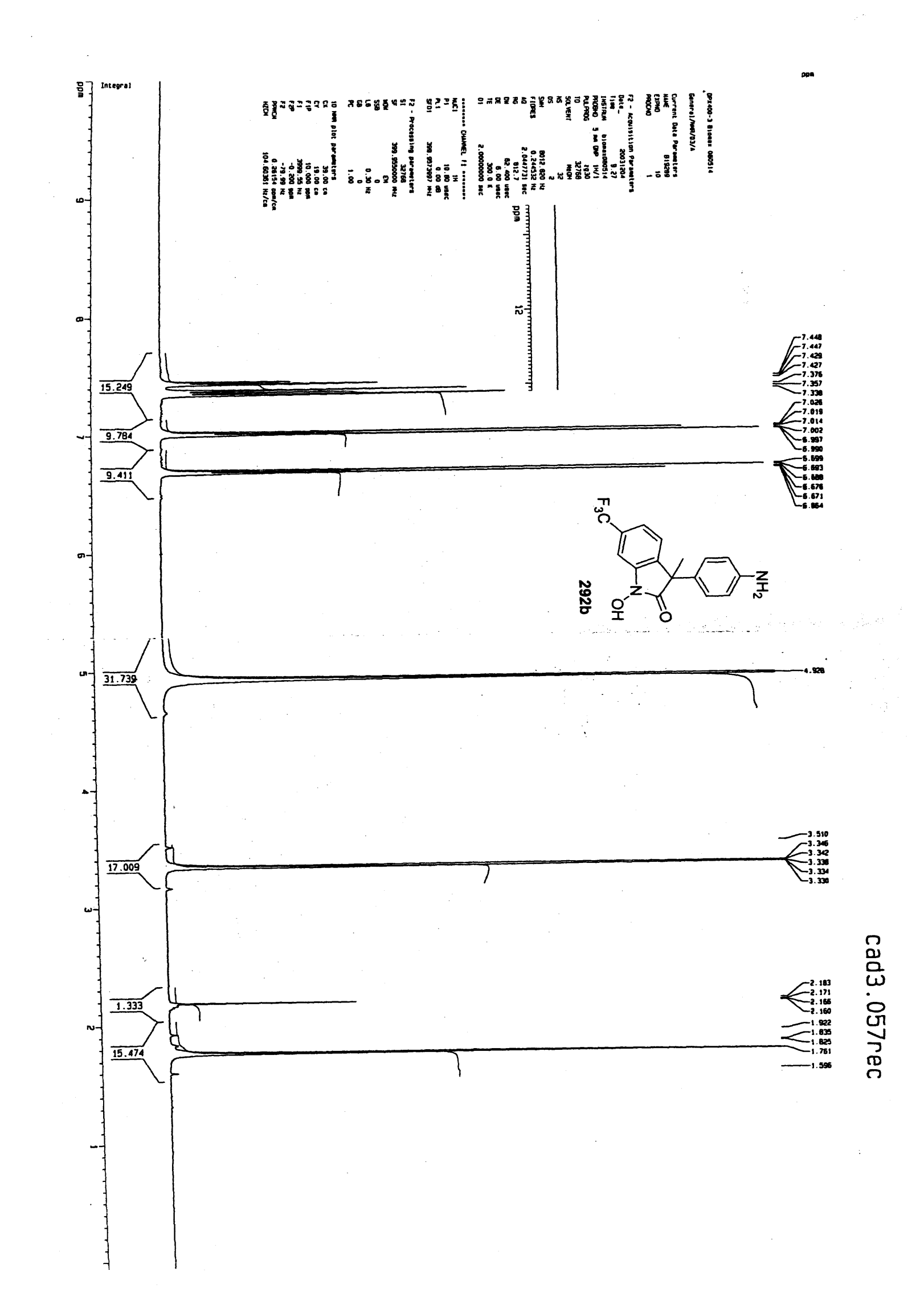
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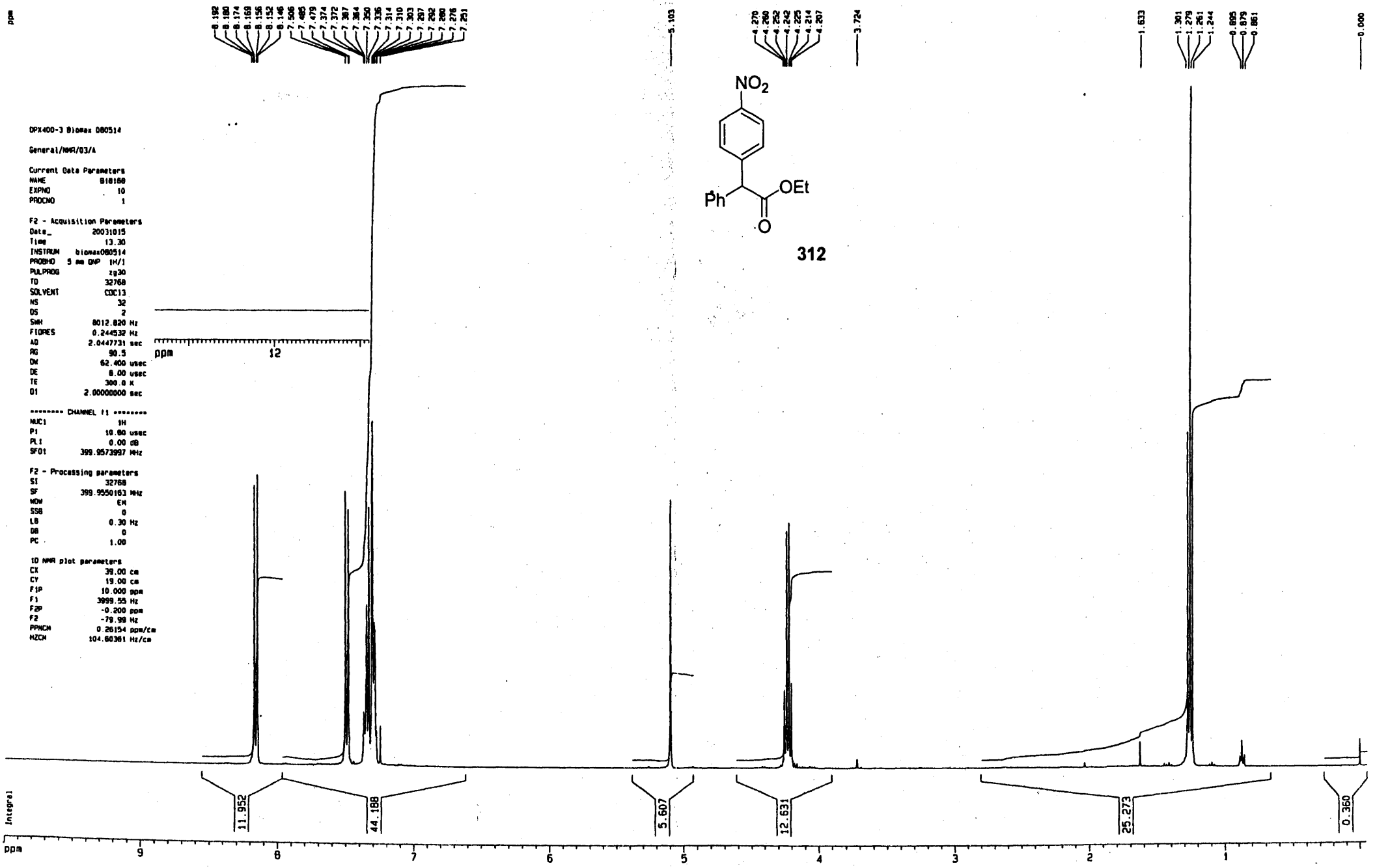

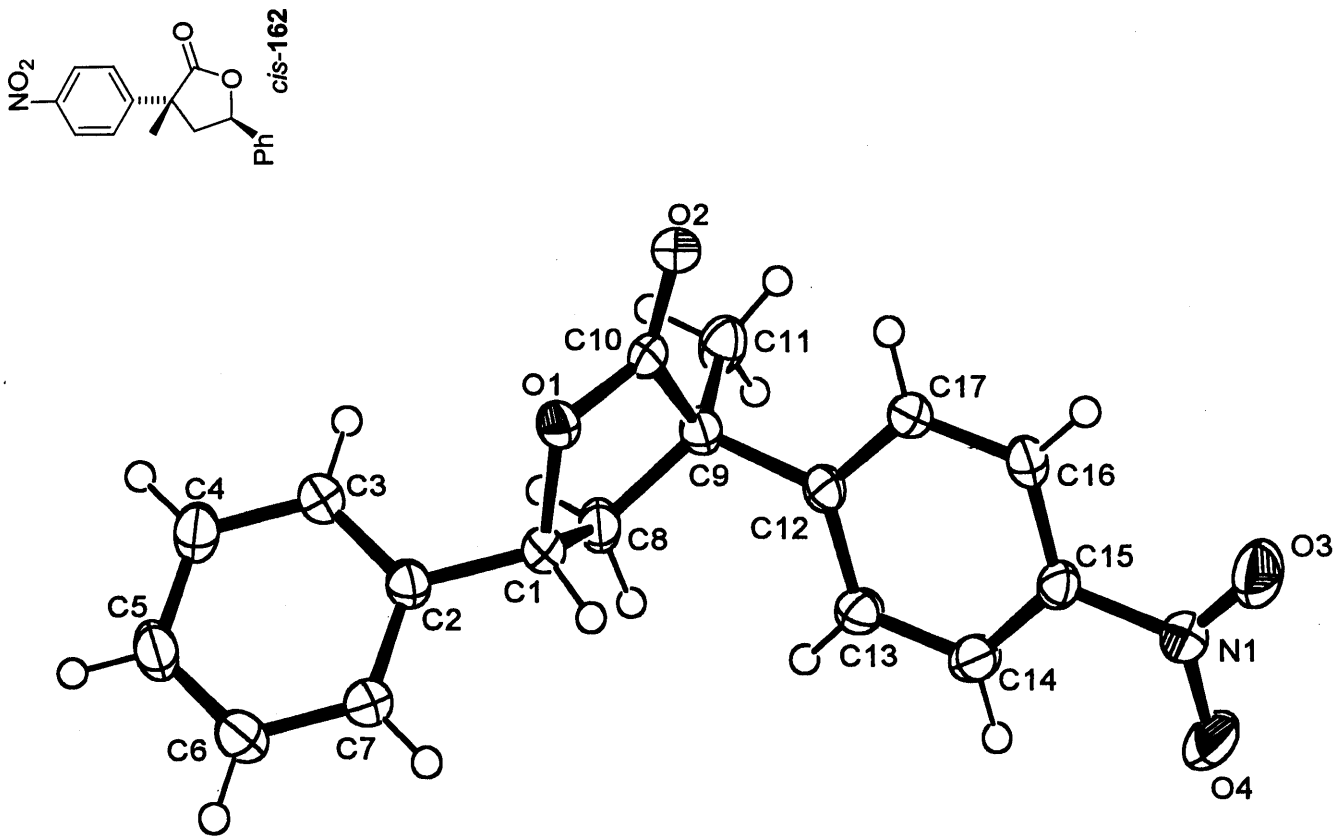
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O3
C5
C2
C1
C13
C14
N1
C6
C7
O4

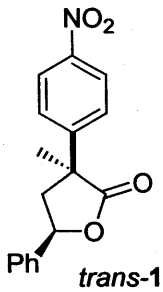
Table 1. Crystal data and structure refinement for 02LAWRENCE2.

Empirical formula	C17 H15 N O4
Formula weight	297.30
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 6.9801(2) A alpha = 90 deg. b = 12.4598(4) A beta = 95.2175(14) deg. c = 16.6818(6) A gamma = 90 deg.
Volume	1444.82(8) A^3
Z	4
Density (calculated)	1.367 Mg/m^3
Absorption coefficient	0.098 mm^-1
F(000)	624
Crystal size	0.25 x 0.20 x 0.20 mm
Theta range for data collection	2.95 to 27.51 deg.
Index ranges	-9<=h<=9, -16<=k<=16, -21<=l<=21
Reflections collected	14145
Independent reflections	3310 [R(int) = 0.1146]
Max. and min. transmission	0.9806 and 0.9759
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3310 / 0 / 200
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R1 = 0.0541, wR2 = 0.1285
R indices (all data)	R1 = 0.0887, wR2 = 0.1451
Largest diff. peak and hole	0.220 and -0.331 e.A^-3

Table 3. Bond lengths [A] and angles [deg] for 02LAWRENCE2.

O(1)-C(10)	1.348(2)	O(1)-C(1)	1.471(2)
O(2)-C(10)	1.205(2)	O(3)-N(1)	1.218(2)
O(4)-N(1)	1.217(2)	N(1)-C(15)	1.468(2)
C(1)-C(2)	1.506(2)	C(1)-C(8)	1.525(2)
C(2)-C(7)	1.385(2)	C(2)-C(3)	1.390(2)
C(3)-C(4)	1.391(2)	C(4)-C(5)	1.380(3)
C(5)-C(6)	1.385(3)	C(6)-C(7)	1.389(3)
C(8)-C(9)	1.533(2)	C(9)-C(10)	1.529(2)
C(9)-C(11)	1.535(2)	C(9)-C(12)	1.536(2)
C(12)-C(17)	1.390(2)	C(12)-C(13)	1.394(2)
C(13)-C(14)	1.382(2)	C(14)-C(15)	1.378(3)
C(15)-C(16)	1.381(2)	C(16)-C(17)	1.381(2)

C(10)-O(1)-C(1)	110.26(12)	O(4)-N(1)-O(3)	122.79(16)
O(4)-N(1)-C(15)	118.45(15)	O(3)-N(1)-C(15)	118.75(14)
O(1)-C(1)-C(2)	108.12(13)	O(1)-C(1)-C(8)	103.38(12)
C(2)-C(1)-C(8)	115.83(15)	C(7)-C(2)-C(3)	119.23(16)
C(7)-C(2)-C(1)	119.83(15)	C(3)-C(2)-C(1)	120.93(15)
C(2)-C(3)-C(4)	120.20(17)	C(5)-C(4)-C(3)	120.15(17)
C(4)-C(5)-C(6)	119.94(17)	C(5)-C(6)-C(7)	119.94(17)
C(2)-C(7)-C(6)	120.54(17)	C(1)-C(8)-C(9)	103.63(14)
C(10)-C(9)-C(8)	100.41(13)	C(10)-C(9)-C(11)	110.61(14)
C(8)-C(9)-C(11)	113.30(15)	C(10)-C(9)-C(12)	108.72(14)
C(8)-C(9)-C(12)	115.19(13)	C(11)-C(9)-C(12)	108.32(13)
O(2)-C(10)-O(1)	120.94(15)	O(2)-C(10)-C(9)	128.16(15)
O(1)-C(10)-C(9)	110.89(13)	C(17)-C(12)-C(13)	118.16(15)
C(17)-C(12)-C(9)	119.46(14)	C(13)-C(12)-C(9)	122.26(15)
C(14)-C(13)-C(12)	120.94(16)	C(15)-C(14)-C(13)	119.16(16)
C(14)-C(15)-C(16)	121.49(15)	C(14)-C(15)-N(1)	119.20(15)
C(16)-C(15)-N(1)	119.30(16)	C(17)-C(16)-C(15)	118.58(16)
C(16)-C(17)-C(12)	121.63(15)		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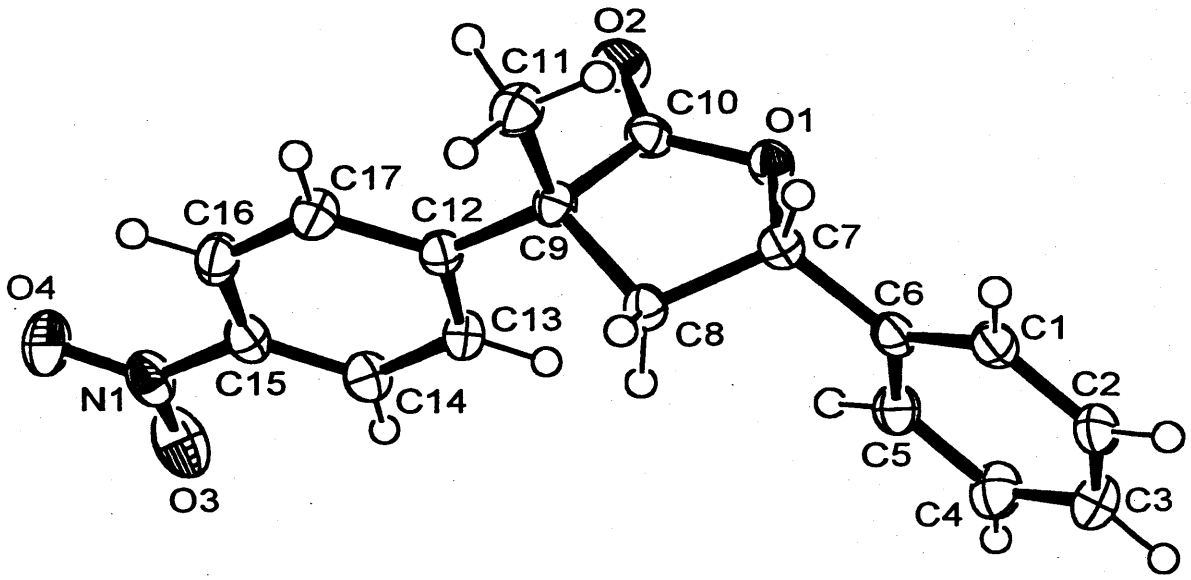
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N1
C14
C5
O3
C4
C3

Table 1. Crystal data and structure refinement for Lawrencel.

Empirical formula	C17 H15 N O4
Formula weight	297.30
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 8.1290(3) A alpha = 83.7880(11) deg. b = 9.1740(3) A beta = 79.0930(11) deg. c = 10.2670(4) A gamma = 72.8210(13) deg.
Volume	717.18(5) A^3
Z	2
Density (calculated)	1.377 Mg/m^3
Absorption coefficient	0.099 mm^-1
F(000)	312
Crystal size	0.15 x 0.12 x 0.12 mm
Theta range for data collection	3.00 to 27.46 deg.
Index ranges	-10<=h<=10, -11<=k<=11, -13<=l<=13
Reflections collected	12481
Independent reflections	3257 [R(int) = 0.0584]
Max. and min. transmission	0.9882 and 0.9853
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3257 / 0 / 200
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0450, wR2 = 0.1063
R indices (all data)	R1 = 0.0589, wR2 = 0.1142
Largest diff. peak and hole	0.303 and -0.277 e.A^-3

Table 3. Bond lengths [A] and angles [deg] for Lawrence1.

O(1)-C(10)	1.3491(16)	O(1)-C(7)	1.4749(15)
O(2)-C(10)	1.2044(16)	O(3)-N(1)	1.2280(17)
O(4)-N(1)	1.2261(17)	N(1)-C(15)	1.4734(17)
C(1)-C(2)	1.390(2)	C(1)-C(6)	1.3923(18)
C(2)-C(3)	1.381(2)	C(3)-C(4)	1.390(2)
C(4)-C(5)	1.384(2)	C(5)-C(6)	1.3926(18)
C(6)-C(7)	1.4974(18)	C(7)-C(8)	1.5297(17)
C(8)-C(9)	1.5407(18)	C(9)-C(12)	1.5238(18)
C(9)-C(10)	1.5320(18)	C(9)-C(11)	1.5397(18)
C(12)-C(17)	1.3922(19)	C(12)-C(13)	1.3946(18)
C(13)-C(14)	1.3846(18)	C(14)-C(15)	1.381(2)
C(15)-C(16)	1.376(2)	C(16)-C(17)	1.3902(19)

C(10)-O(1)-C(7)	110.49(10)	O(4)-N(1)-O(3)	123.76(12)
O(4)-N(1)-C(15)	118.04(13)	O(3)-N(1)-C(15)	118.19(12)
C(2)-C(1)-C(6)	120.45(13)	C(3)-C(2)-C(1)	120.11(13)
C(2)-C(3)-C(4)	119.68(13)	C(5)-C(4)-C(3)	120.42(13)
C(4)-C(5)-C(6)	120.25(13)	C(1)-C(6)-C(5)	119.10(12)
C(1)-C(6)-C(7)	119.64(12)	C(5)-C(6)-C(7)	121.22(11)
O(1)-C(7)-C(6)	109.30(10)	O(1)-C(7)-C(8)	103.81(9)
C(6)-C(7)-C(8)	116.11(11)	C(7)-C(8)-C(9)	103.31(10)
C(12)-C(9)-C(10)	109.90(10)	C(12)-C(9)-C(11)	113.85(11)
C(10)-C(9)-C(11)	106.80(11)	C(12)-C(9)-C(8)	114.17(11)
C(10)-C(9)-C(8)	101.56(10)	C(11)-C(9)-C(8)	109.61(10)
O(2)-C(10)-O(1)	121.48(12)	O(2)-C(10)-C(9)	127.83(12)
O(1)-C(10)-C(9)	110.67(10)	C(17)-C(12)-C(13)	118.27(12)
C(17)-C(12)-C(9)	122.38(12)	C(13)-C(12)-C(9)	119.34(11)
C(14)-C(13)-C(12)	121.56(12)	C(15)-C(14)-C(13)	118.31(13)
C(16)-C(15)-C(14)	122.09(12)	C(16)-C(15)-N(1)	119.18(13)
C(14)-C(15)-N(1)	118.70(13)	C(15)-C(16)-C(17)	118.74(13)
C(16)-C(17)-C(12)	121.02(13)		

ORGANIC LETTERS

2004
Vol. 6, No. 26
4957−4960

Synthesis of Diaryl Acetates and Oxindoles via a Sequential VNS_{Ar}–S_NAr Three-Component Coupling Reaction

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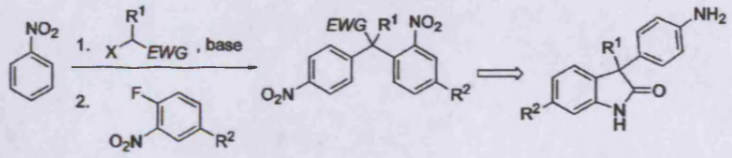
Received October 12, 2004

ABSTRACT

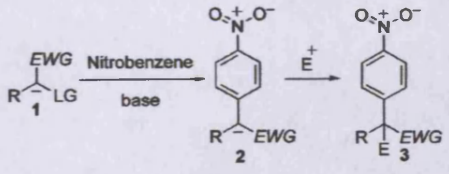


The VNS and S_NAr reactions combine to form an efficient three-component one-pot route to diarylmethanes. The products of selected diaryl acetates provide modular 3-aryloxindole derivatives.

The vicarious nucleophilic substitution (VNS_{Ar}) of hydrogen in aromatic systems provides a direct and efficient route to functionalized aromatics. The reaction, pioneered by Makosza and co-workers,[1] is most often encountered with nitroarenes, as illustrated in Scheme 1. In contrast to conventional nucleophilic aromatic substitution reactions, a good nucleofugal group is not required. We have shown that the anion **2** produced by addition of the nucleophile **1** to nitrobenzene, and elimination of HX from the σ-adduct, can react with a range of electrophiles.[2] This aspect of VNS chemistry provides a powerful process in which simple precursors can be elaborated in a three-component coupling reaction.

We have shown that **2** exhibits reactivity similar to that of the malonate ion. This is not too surprising given that other properties such as acidity are similar. For example the pK_a (DMSO) of ethyl *p*-nitrophenylacetate is 15.1,[3] while that of diethyl malonate is 16.4.[4] Malonate is an excellent nucleophile for many S_NAr reactions,[5] and some examples[6] of the use of nitrophenylacetates in the S_NAr reaction have been reported. We were therefore hopeful that the anion **2**, derived from the VNS reaction, would react in the S_NAr reaction.

Scheme 1. One-Pot VNS−Electrophilic Quench Process[a]



[a] LG = leaving group (e.g., Cl or PhS); EWG = electron-withdrawing group.

† Cardiff University and H. Lee Moffitt Cancer Center & Research Institute.

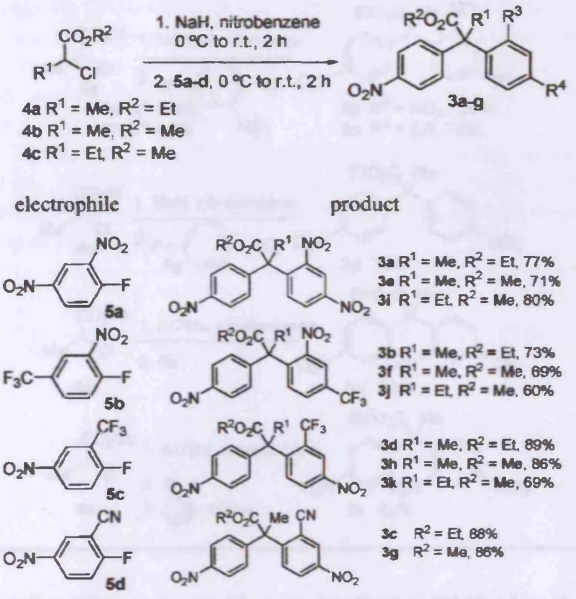
‡ GlaxoSmithKline.

(1) (a) Mąkosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631−2666. (b) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282−289. (c) Mąkosza, M.; Wojciechowski K. *Heterocycles* **2001**, *54*, 445−474.

(2) Lawrence, N. J.; Lamarche, O.; Thurrab, N. *Chem. Commun.* **1999**, 689−690. Bushell, S. M.; Crump, J. P.; Lawrence, N. J.; Pineau, G. *Tetrahedron* **1998**, *54*, 2269−2274. Lawrence, N. J.; Liddle, J.; Jackson, D. A. *Tetrahedron Lett.* **1995**, *36*, 8477−8480. Lawrence, N. J.; Liddle, J.; Jackson, D. A. *Synlett* **1996**, 55−56. Drew, M. D.; Jackson, D. A.; Lawrence, N. J.; Liddle, J.; Pritchard, R. G. *Chem. Commun.* **1997**, 189−190. Lawrence, N. J.; Liddle, J.; Bushell, S. M.; Jackson, D. A. *J. Org. Chem.* **2002**, *67*, 457−464.

10.1021/ol047890y CCC: $27.50
Published on Web 11/24/2004

Scheme 2. Three-Component VNS_{Ar}–S_NAr Coupling Reaction



Diarylmethanes are extremely useful synthetic intermediates,[7] and the diarylmethyl motif is found in many pharmacologically important agents.[8] A versatile route to this important scaffold incorporating several points of diversity is potentially useful. The diarylmethyl group is also embedded within many important drugs, e.g., 3-arylindole derivatives. Makosza[9] and Katritzky[10] have described the synthesis of diarylmethanes via VNS reaction of nucleophiles of type **1** in which the electron-withdrawing group comprises one of the aryl groups. The new method described below is ideally suited for the synthesis of functionalized diarylmethanes in which only one of the aryl groups is introduced in the VNS reaction.

We now report that the anion **2** can be arylated by the reaction with substituted *ortho*-halonitroarenes. The process not only is efficient but also uniquely combines two different sequential modes of aromatic nucleophilic substitution.

Reaction of ethyl 2-chloropropionate (**4a**) with nitrobenzene in the presence of NaH gave the usual dark blue-colored solution of the intermediate anion **2** (Scheme 1). Addition of 2,4-dinitrofluorobenzene (**5a**) in DMF resulted in rapid decolorization of the solution. The desired diarylmethane **3a** was isolated in 77% yield (Scheme 2).[11] The ^1H NMR spectrum clearly indicated the presence of both a 1,4-disubstituted and 1,2,4-trisubstituted aryl group.[12] This is consistent with the expected para-selective VNS reaction followed by S_NAr process.

To explore the scope of the reaction, a number of simple esters **4a**–**c** were combined with nitrobenzene and different S_NAr electrophiles **5a**–**d** under the reaction conditions described above. The results shown in Table 1 clearly indicate that the process is general and efficient. The efficiency of the S_NAr process is high, as the yields are close to that expected for the protonation of the anion **2**.[2] The use of activated arenes **5a**–**d** allows the S_NAr reaction to proceed conveniently at ambient temperature, avoiding the need for

Table 1. Yields of Product Diarylmethyl Sulfones **8a**–**h**

	R^1	R^3	R^4	yield (%)
a	Cl	NO_2	NO_2	74
b	Cl	NO_2	CF_3	75
c	Cl	CN	NO_2	74
d	Cl	CF_3	NO_2	75
e	CF_3	NO_2	NO_2	79
f	CF_3	NO_2	CF_3	81
g	CF_3	CN	NO_2	78
h	CF_3	CF_3	NO_2	78

(3) Kabachnik, M. I.; Lobanov, D. I.; Matveeva, A. G.; Kovsheva, O. E.; Terekhova, M. I.; Petrov, E. S.; Petrovskii, P. V.; Matrosov, E. I. *Izv. Akad. Nauk SSSR. Ser. Khim.* **1991**, 1598–1604.

(4) Olstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299–3305.

(5) Gurjar, M.; Reddy, D. S.; Murugaiah, A.; Murugaiah, S. *Synthesis* **2000**, 1659–1661. Selvakumar, N.; Reddy, B. Y.; Kumar, G. S.; Iqbal, J. *Tetrahedron Lett.* **2001**, *42*, 8395–8398.

(6) Bluhm, A. L.; Sousa, J. A.; Weinstein, J. *J. Org. Chem.* **1964**, *29*, 636–640. Borsche, W.; Fiedler, A. *Chem. Ber.* **1913**, *46*, 2117–2131. Wrobel, Z.; Wojciechowski, K. *Pol. J. Chem.* **1992**, *66*, 1125–1129. Cheng, X.-M.; Lee, C.; Klutchko, S.; Winters, T.; Reynolds, E. E.; Welch, K. M.; Flynn, M. A.; Doherty, A. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2999–3002.

(7) For examples: (a) Itami, K.; Mineno, M.; Kamei, T.; Yoshida, J. *Org. Lett.* **2002**, *4*, 3635–3638. (b) Hermanns, N.; Dahmen, S.; Bolm, C.; Brase, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692–3694. (c) Vanier, C.; Lorge, F.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1679–1683.

(8) For examples: (a) Plobeck, N.; Delorme, D.; Wei, Z. Y.; Yang, H.; Zhou, F.; Schwarz, P.; Gawell, L.; Gagnon, H.; Pelcman, B.; Schmidt, R.; Yue, S. Y.; Walpole, C.; Brown, W.; Zhou, E.; Labarre, M.; Payza, K.; St-Onge, S.; Kamassah, A.; Morin, P. E.; Projean, D.; Ducharme, J.; Roberts, E. *J. Med. Chem.* **2000**, *43*, 3878–3894. (b) Hsin, L. W.; Dersch, C. M.; Baumann, M. H.; Stafford, D.; Glowa, J. R.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2002**, *45*, 1321–1329. (c) Wai, J. S.; Egbertson, M. S.; Payne, L. S.; Fisher, T. E.; Embrey, M. W.; Tran, L. O.; Melamed, J. Y.; Langford, H. M.; Guare, J. P.; Zhuang, L. G.; Grey, V. E.; Vacca, J. P.; Holloway, M. K.; Naylor-Olsen, A. M.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Schleif, W. A.; Gabryelski, L. J.; Young, S. D. *J. Med. Chem.* **2000**, *43*, 4923–4926. (d) Hewawasam, P.; Gribkoff, V. K.; Pendri, Y.; Dworetzky, S. I.; Meanwell, N. A.; Martinez, E.; Boissard, C. G.; Post-Munson, D. J.; Trojnacki, J. T.; Yeleswaram, K.; Pajor, L. M.; Knipe, J.; Gao, Q.; Perrone, R.; Starrett, J. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1023–1026.

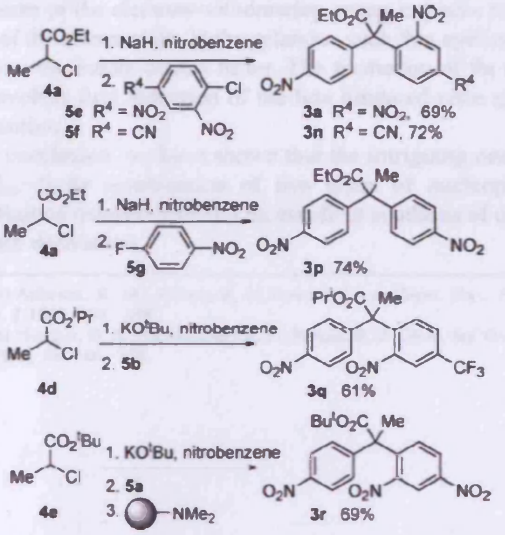
(9) Makosza, M.; Surowiec, M.; Voskresensky, S. *Synthesis* **2000**, 1237–1240.

(10) Katritzky, A. R.; Toader, D. *J. Org. Chem.* **1997**, *62*, 4137–4141.

(11) **General Procedure for the VNS_{Ar}–S_NAr Reaction.** Sodium hydride (60% dispersion in oil) (0.813 g, 20.3 mmol) was added to anhydrous DMF (5 mL) and the mixture flushed with nitrogen and cooled to 0 °C. Chloroester **4** (8.13 mmol) and nitrobenzene (0.84 mL, 8.13 mmol) were dissolved in anhydrous DMF (5 mL) and added dropwise to the sodium hydride slurry. The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. The reaction mixture was then cooled back to 0 °C using an ice-cooling bath. Aryl halide **5** (8.13 mmol) in anhydrous DMF (2 mL) was then added, and the resulting mixture was allowed to warm to room temperature and stirred for a further 2 h. The reaction mixture was poured onto ice/hydrochloric acid (50 mL, 1 M solution) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed well with distilled water (5 × 50 mL) and then saturated aqueous sodium bicarbonate solution (3 × 50 mL) and dried (magnesium sulfate), and the solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography

(12) Other characterization data (e.g., ^{13}C NMR, MS, IR) support the product assignment.

Scheme 3. Further Examples of the $VNS_{Ar}-S_NAr$ Reaction



heating. This can be problematic for NaH in DMF when the reaction is performed on a large scale.[13] We have therefore shown that the process has potential for scale-up by using *tert*-BuOK as the base. In these cases, the VNS reaction between nitrobenzene (1 equiv) and **4a** (2 equiv) was performed with *tert*-BuOK (3 equiv) while carefully maintaining the temperature between −40 and −50 °C. The solution of the post-VNS anion was warmed to −20 °C before addition of **5a** or **5d** to give **3a** and **3d** in 57 and 69% yields, respectively.

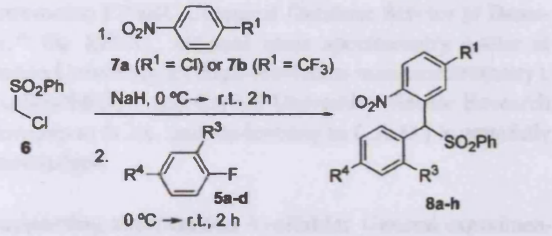
The process is not limited to the use of fluoronitroarenes (Scheme 3). 2,4-Dinitrochloronitrobenzene (**5e**) was used in place of 2,4-dinitrofluorobenzene (**5a**) to give **3a** from **4a** in 69% yield. Similarly, the VNS−S_NAr reaction of 4-chloro-3-nitrobenzonitrile (**5f**) and **4a** gives the nitrile **3n** (Scheme 3). The use of the less activated 4-fluoronitrobenzene (**5g**) is still sufficiently reactive to engage ion the $VNS_{Ar}-S_NAr$ process to give **3p** in 74% yield.

Branched esters behave well in the reaction. The isopropyl ester **4d** gave ester **3q** when aryl fluoride **5b** was used as the electrophile. The *tert*-butyl ester **3r** was obtained in the same way from the VNS nucleophile **4e**. In the synthesis of **3r**, we were unable to separate the product from unreacted **5a** by chromatography. The unreacted aryl fluoride was scavenged using dimethylamino-functionalized polystyrene. Simply shaking the mixture of **5b** and **3r** with the resin in EtOAc cleanly removed the aryl fluoride, leaving the product ester pure.

The $VNS_{Ar}-S_NAr$ reaction was used for the synthesis of diarylmethyl sulfones, to provide examples of the process with ortho selectivity. Reaction of chloromethyl phenyl sulfone (**6**) with *p*-chloronitrobenzene (**7a**) and **5a** gave the

(13) For a summary of the safety hazards associated with the large-scale use of sodium hydride in DMF, see: am Ende, D. J.; Vogt, P. F. *Org. Proc. Res. Dev.* **2003**, *7*, 1029−1033.

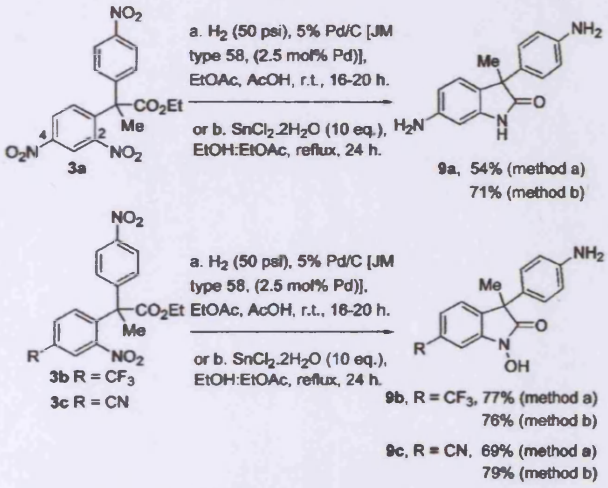
Scheme 4. $VNS_{Ar}-S_NAr$ Reaction of Sulfones



sulfone **8a** (Scheme 4). Other examples (Table 1) indicate that the arylation of the *ortho*-nitrobenzyl sulfonyl anion is not problematic.

The synthetic utility of the method is illustrated in Scheme 5, by the synthesis of oxindole derivatives. This class of

Scheme 5. Use of $VNS_{Ar}-S_NAr$ Products for Oxindole Synthesis



heterocycle is an important synthetic building block and also includes members with important biological activity.[8d,14] Those products **3** possessing an ortho nitro group ($R^3 = NO_2$), are converted into their corresponding 3,3-disubstituted oxindole, by hydrogenation (method a), or Sn(II)-mediated reduction (method b). The presence of other nitro groups that are also reduced under these conditions provides additional points for further functionalization and incorporation of extra diversity. The ester **3a** cleanly gave the oxindole

(14) (a) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084−12085. (b) Gunesekara, N. S.; Spencer, C. M.; Keating, G. M. *Drugs* **2002**, *62*, 1217−1251. (c) Bromidge, S. M.; Dabbs, S.; Davies, D. T.; Duckworth, D. M.; Forbes, I. T.; Ham, P.; Jones, G. E.; King, F. D.; Saunders: D. V.; Starr, S.; Thewlis, K. M.; Wyman, P. A.; Blaney, F. E.; Naylor, C. B.; Bailey, F.; Blackburn, T. P.; Holland, V.; Kennett, G. A.; Riley, G. J.; Wood, M. D. *J. Med. Chem.* **1998**, *41*, 1598−1612. (d) Gallagher, G. J.; Lavanchy, P. G.; Wilson, J. W.; Hieble, J. P.; DeMarinis, R. M. *J. Med. Chem.* **1985**, *28*, 1533−1536. (e) Natarajan, A.; Fan, Y. H.; Chen, H.; Guo, Y. H.; Iyasere, J.; Harbinski, F.; Christ, W. J.; Aktas, H.; Halperin, J. A. *J. Med. Chem.* **2004**, *47*, 1882−1885.

9a by both methods. However, reduction of both **3b** and **3c** gave the 1-hydroxyoxindoles **9b** and **9c**.[15] It seems that the presence of the electron-withdrawing group impedes reduction of the intermediate hydroxylamine such that cyclization to form the indole occurs faster. The formation of **9a** from **3a** involves first reduction of the less hindered nitro group at position 4.

In conclusion, we have shown that the intriguing one-pot VNS_{Ar}–S_NAr combination of two types of nucleophilic substitution reaction provides an excellent synthesis of diaryl acetate derivatives.

(15) Acheson, R. M.; Prince, R. J.; Proctor, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 595–598.

(16) Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746–749.

Acknowledgment. The support of our work by the EPSRC (Research Grant GR/S25456/01: 500 MHz NMR spectrometer; EPSRC Chemical Database Service at Daresbury;[16] the EPSRC national mass spectrometry center at Swansea University for high-resolution mass spectrometry), GlaxoSmithKline, and Cardiff University (Senior Research Fellowship to N.J.L. and studentship to C.A.D.) is gratefully acknowledged.

Supporting Information Available: General experimental procedures and characterization data and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047890Y