New Heteroaromatic Chemistry

A thesis submitted to Cardiff University

By

Chuanjun Song

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School of Chemistry

Cardiff University

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Dedicate to:

My wife, Xuelian Sun

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Finally, I would like to thank my parents and my brothers, who I miss all the time. Special thanks to my wife, Xuelian Sun, for the love, continuous encouragement, cooking, financial support and many more.

Abstract

New Heteroaromatic Chemistry

The current literature for the synthesis of pyrazole derivatives has been reviewed.

A silver nitrate-induced 5-*endo*-dig approach to pyrazolines and pyrazoles is discussed. A brief review of the 5-*endo*-dig cyclisation is included. The propargylic hydrazine precursors are synthesized by four different routes. The key step for the first route is a Mitsunobu reaction of propargylic alcohols with hydrazine derivatives. A short review of the Mitsunobu reaction is also included. The second route applied is a nucleophilic attack onto imines by lithium acetylides followed by electrophilic *N*-amination of the resulting propargylic amine with a oxaziridine. The third route involves *N*-nitrosation of a propargylic amine and subsequent reduction of the nitroso functional group. The final route is a simple nucleophilic substitution of propargyl bromide with hydrazine. Oxidation of pyrazoline to pyrazole and iodination of pyrazole have also been briefly studied. Two examples of 5-*endo*-dig iodocyclisation and one example of palladium-induced 5-*endo*-dig cyclisation are also reported.

Current literature for pyrrole acylation has been reviewed. Representative 2-aryl-*N*-tosylpyrroles were synthesized by Suzuki coupling of 2-bromo-*N*-tosylpyrrole and arylboronic acids. A brief review of Suzuki coupling reaction is included. A new method for the acylation of *N*-tosylpyrroles using carboxylic acids and trifluoroacetic anhydride is discussed. When applied to α,β-unsaturated acids, a *in situ* Nazarov cyclisation follows acylation to give cyclopenta[*b*]pyrrol-6(1*H*)-ones. The Nazarov cyclisation is reviewed. *N*-Detosylation of acylpyrroles has been briefly examined. A study towards the construction of the macrocyclic core of roseophilin by the new pyrrole acylation strategy is discussed.

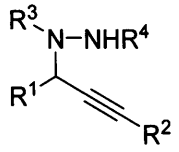
Abbreviations

AIBN	2,2'-azo-*bis*-isobutyrnitrile
APCI	atomospheric pressure chemical ionisation
Bn	benzyl
Boc	*tert*-butoxycarbonyl
CAN	ammonium cerium(IV) nitrate
COSY	correlation spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EI	electron ionisation
eq	equivalents
h	hours
IR	infrared
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazanide
mCPBA	*meta*-chloroperoxybenzoic acid
mp	melting point
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
$Ni(cod)_2$	nickel 1,5-cyclooctadiene
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
py	pyrrole
R_f	retention factor values
Sia	sec-isoamyl (3-methyl-2-butyl)
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Tlc	thin layer chromatography
Ts/tosyl	*para*-toluene sulfonyl

Contents

About this thesis.

The initial idea of the project was to study the syntheses of pyrazole derivatives *via* a 5-*endo*-dig iodocyclization, based on previously successful approaches to iodofurans[1] and iodopyrroles[2] developed by the Knight group. However, it was soon changed to the silver nitrate-induced 5-*endo*-dig cyclization approach to such compounds, due to the finding of the remarkably efficient cyclization of the unprotected propargylic hydrazine **1** (R^4 = H), Figure 1.1, and the catalytic usage of the metal.

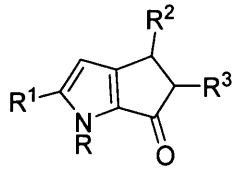


1

R^1 = alkyl, aryl, H; R^2 = alkyl, aryl, H; R^3 = alkyl, allyl, *Ts*, BnOCO; R^4 = H, Boc.

Figure 1.1 ***propargyl hydrazine***

The second part of the thesis, the pyrrole acylation chemistry, was initially planned only to obtain some more data for a publication. However, due to some excellent results, especially the formation of cyclopenta[*b*]pyrrole-6-one **2**, Figure 1.2, when the pyrrole acylation was carried out using α, β-unsaturated acids, this became a central part of the thesis. The chemistry was further developed to construct the macrocyclic core of roseophilin **3**, Figure 1.3.



2

R = H, *Ts*, MeO_2C; R^1 = H, Me, Ph; R^2 = Me, Ph, H; R^3 = Me, H.

Figure 1.2 ***cyclopenta[b]pyrrole-6-one***

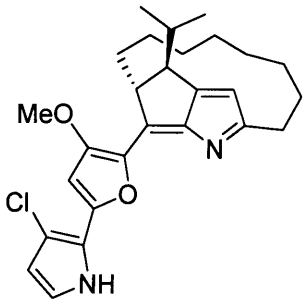


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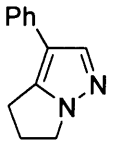
Figure 1.3 ***roseophilin***

Chapter 1

Introduction

1.1 Importance of pyrazole derivatives.

Until now, only very few naturally occurring pyrazole derivatives[3] have been discovered. For example, withasomnine (**4**)[4,5] was isolated from the roots of Indian medicinal plants, *Withania somnifera* and L-β-pyrazolylalanine (**5**)[6] is found in the seeds of many species of cucurbitaceae. It was subsequently demonstrated[6] that pyrazole itself is present in watermelon seeds in a concentration of 280 to 410 $\mu g\ g^{-1}$, depending on the variety.



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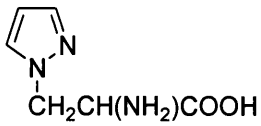

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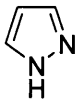

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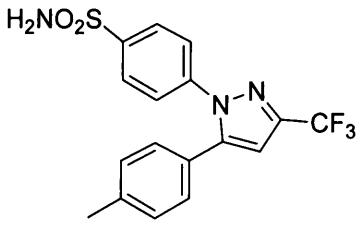
Figure 1.4

It seems that the evolution of organisms has produced few enzymes which can cause formation of an N-N bond. However, many synthetically produced pyrazoles[7] are biologically active. Celecoxib (**7**)[7a,8] is a COX-2 inhibitor for the treatment of chronic inflammatory disease like rheumatoid and osteo-arthritis, while pyrazole **8**[9] was identified as an inhibitor of methionyl-tRNA synthetase. Recently, pyrazole derivatives such as *tris*-(pyrazolyl)methane (TPM) **9** and the isoelectronic *tris*-(pyrazolyl)borate (TPB) **10** have raised a lot of interest in the field of coordination chemistry,[10] especially as useful ligands in the Suzuki reaction.[11]



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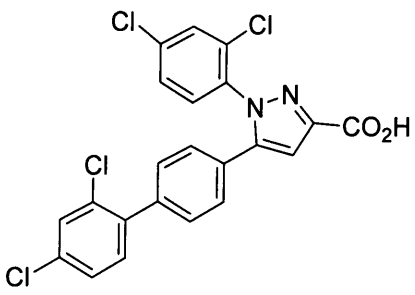

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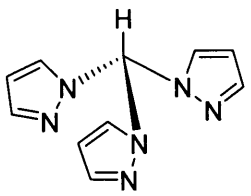

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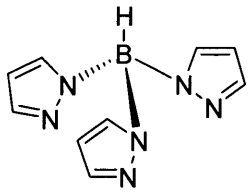

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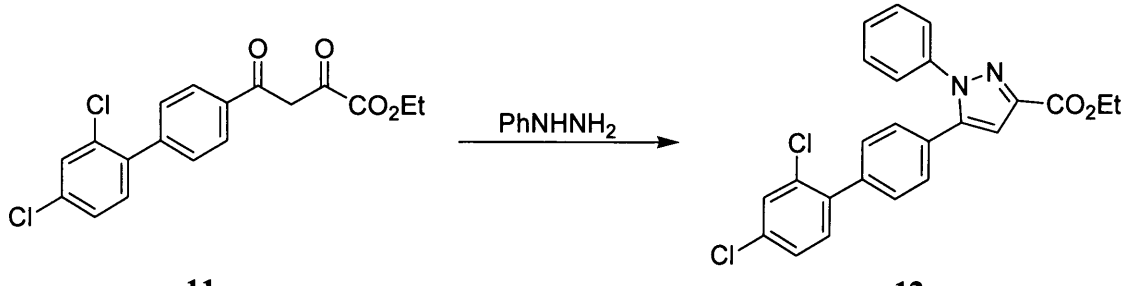
Figure 1.5

1.2 Previous syntheses of pyrazole derivatives.

There have been many reviews on the structure, properties, syntheses and chemistry of pyrazole derivatives,[6a,12] before the appearence of Chapter 3 of Comprehensive Heterocyclic Chemistry in 1996, dealing with pyrazole chemistry. Since then, hundreds of papers have been published about the synthesis of pyrazole derivatives, although only very few of these feature really new chemistry.

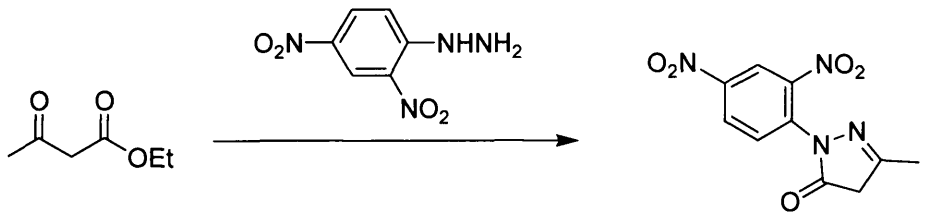
1.2.1 Reaction of hydrazines with β-bifunctional reagents.

This might be the most general approach for the synthesis of pyrazole derivatives. β-Diketones, β-keto-esters and β-ketonitriles have been utilised as starting reagents for the synthesis of pyrazole derivatives,[7-9, 11b, 13-40] as shown in Schemes 1.1 - 1.3.



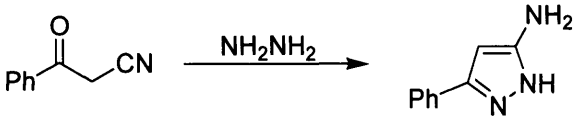
11 12

Scheme 1.1



13 14

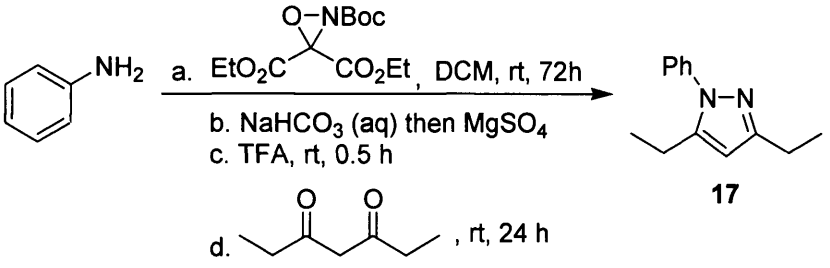
Scheme 1.2



15 16

Scheme 1.3

Armstrong *et al.* reported a one-pot pyrazole synthesis recently (Scheme 1.4).[41] Electrophilic amination of aniline with an oxaziridine afforded the corresponding *N*-Boc hydrazine; the amination reaction mixture was then washed with saturated aqueous sodium bicarbonate and the aqueous layer removed with a pippet before the sequential addition of solid magnesium sulfate, trifluoroacetic acid and the 1,3-diketone. Evaporation of the reaction mixture and filtration on silica then afforded the pyrazole **17** in 59% overall yield.

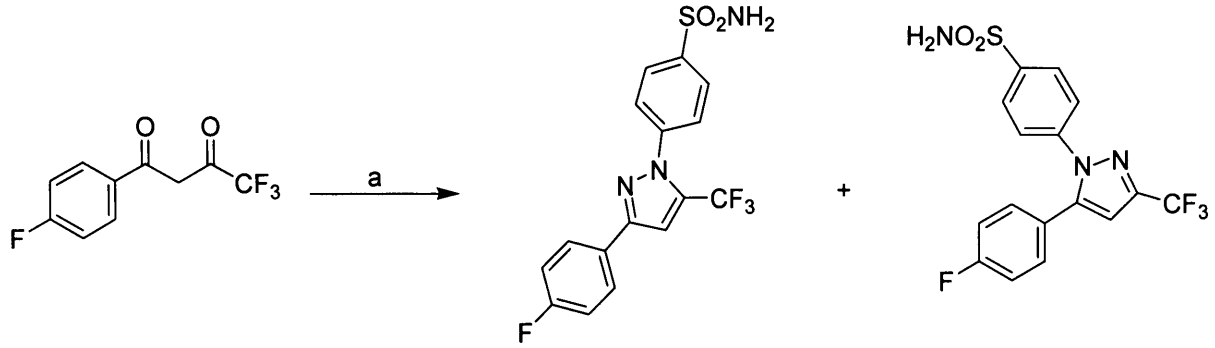


17

Scheme 1.4

The reactions reported above are not always so simple and straightforward as they might first appear. Unless hydrazine itself or symmetrical diketone is used, then more than one isomeric pyrazole derivative is expected to be formed. However, in many cases only one isomer proved to be the reaction product. For example, reaction of the 1,3-diketone **18** with (4-sulfamoyl-

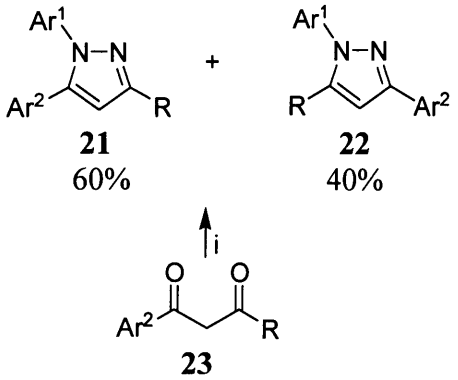
phenyl)hydrazine gave a mixture of the 1,3-diarylpyrazole **19** and 1,5-diarylpyrazole **20**, which could be separated by flash chromatography (Scheme 1.5).[7c]



18 **19** **20**

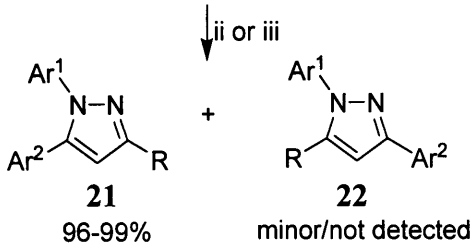
Scheme 1.5 *Reagents and conditions*: (a) (4-sulfamoylphenyl)hydrazine-HCl, EtOH, reflux.

The two component synthesis is generally conducted in acidic medium and the ratio of the two regioisomers is affected by different acids and solvents. Singh *et al.*[8] studied the reaction conditions affecting the regioselectivity during the formation of 1,5-diarylpyrazoles **21** from hydrazines and 1,3-diketones **23** and found that treating the arylhydrazine chlorides with excess triethylamine could improve the regioselectivity greatly (Scheme 1.6). Thus, heating arylhydrazine hydrochlorides with 1-aryl-1,3-diketones **23** in ethanol afforded a ~ 60:40 non-separable mixture of the 1,5-diarylpyrazoles **21** and 1,3-diarylpyrazoles **22**; however, basifying the ethanolic solution of the arylhydrazine hydrochlorides using 3-5 equivalents of triethylamine before heating it together with the 1,3-diketones gave 1,5-diarylpyrazoles **21** with excellent regioselectivity. Improved regioselectivity and yield were obtained by using the arylhydrazine instead of the hydrazine hydrochloride salt.



21 60% **22** 40%

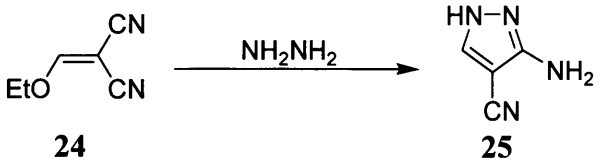
23



Scheme 1.6 *Reagents and conditions*: (i) $Ar^1NHNH_2 \cdot HCl$, absolute ethanol, 50-60 °C, 4-5 h; (ii) $Ar^1NHNH_2 \cdot HCl$, TEA, absolute ethanol, 50-60 °C, 4-5 h; (iii) Ar^1NHNH_2, absolute ethanol, 50-60 °C, 4-5 h.

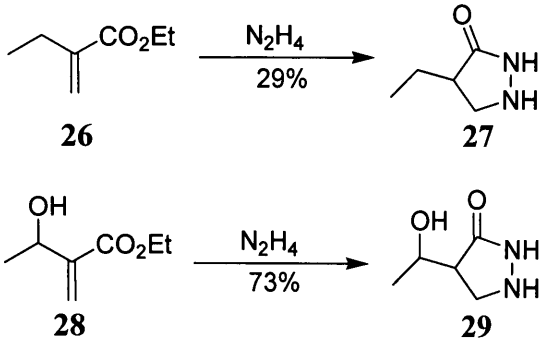
1.2.2 Reactions of hydrazines with Michael acceptor.

A variety of pyrazole derivatives have been synthesized by this method.[42-73] For example, reaction of hydrazine with α,β-unsaturated nitrile **24** leads to the formation of the 3-aminopyrazole **25** very efficiently, as shown in Scheme 1.7.



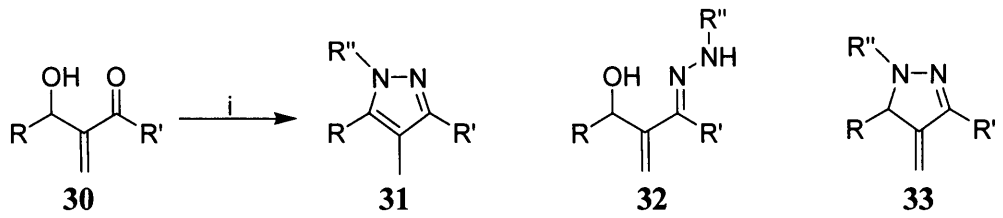
Scheme 1.7

In 1989, Jungheim[74] reported the synthesis of pyrazolidinones **27** and **29** by condensing anhydrous hydrazine with substituted acrylates **26** and **28** (Scheme 1.8).



Scheme 1.8

Later in 2003, Kim *et al.*[75] reported the regioselective synthesis of a series of 1,3,4,5-tetrasubtituted pyrazoles **31** from the reaction of Baylis-Hillman adducts **30** and hydrazine hydrochlorides.



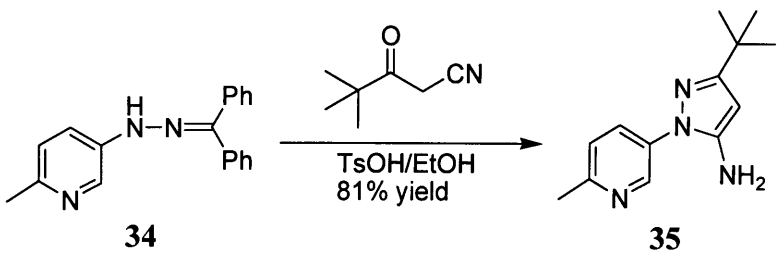
30 **31** **32** **33**

Scheme 1.9 *Reagents and conditions*: (i) R''$NHNH_2$·HCl, $ClCH_2CH_2Cl$, 50-70 °C, 6-72 h, 48-93%.

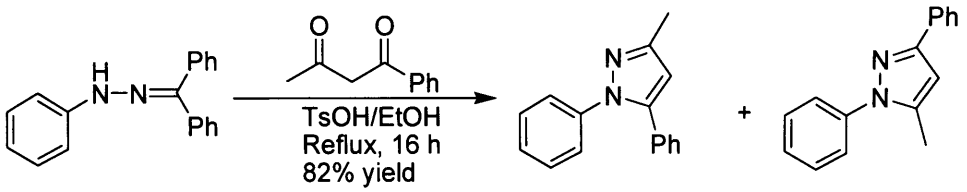
The results obtained are different from those reported by Jungheim above. The authors reasoned that the first step of the mechanism involved the formation of the hydrazone derivatives **32**, which is a well accepted intermediate of one of the two possible mechanistic pathways;[76,77] acid-catalyzed cyclization then gave **33**, and subsequent 1,3-hydrogen transfer gave the pyrazoles **31**.

1.2.3 Syntheses from hydrazones and hydrazonyl halides.

Haddad and co-workers[78,79] have reported the synthesis of pyrazoles from reaction of *N*-arylated benzophenone hydrazones and 1,3-diketones, *β*-ketoester or cyanoketones. Thus, a transhydrazonation reaction between hydrazone **34** and 4,4-dimethyl-3-oxopentanenitrile followed by cyclization lead to the pyrazole **35** (Scheme 1.10). When applied to unsymmetrical diketones, however, this approach also suffered a regioselectivity problem. For example, a mixture of pyrazoles **37** and **38** was obtained in 5 : 1 ratio, respectively in 82% total yield from reaction of hydrazone **36** and 1-phenylbutane-1,3-dione.



34 **35**

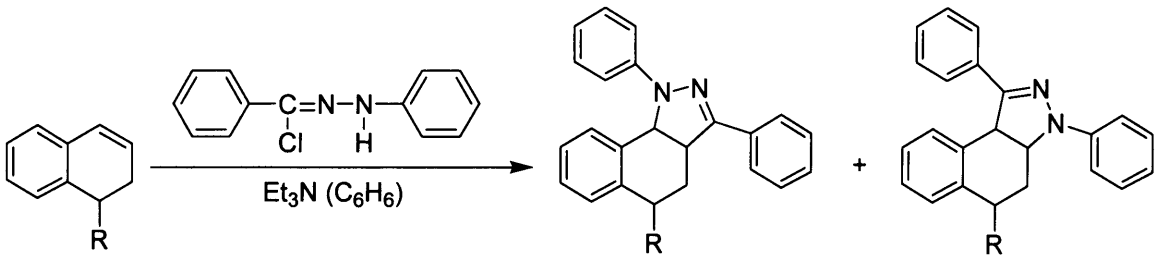


36 **37** **38**

Scheme 1.10

The reaction of hydrazonyl halides with active methylene reagents was reported long ago to yield pyrazole derivatives.[12] Similarly, hydrazonyl halides react with enamines, organomagnesium compounds and acetylenic compounds to yield pyrazoles. These reactions have been reported by Shawali *et al.*.[80-85] Matsumura *et al.*[86] reported the reactions of the 1,4-dianion of acetophenone *N*-ethoxycarbonylhydrazone with carbonyl compounds such as esters, acyl chlorides and amides to give pyrazole and pyrazoline derivatives in good yield.

Kitane *et al.*[87] reported the cycloaddition of diphenylnitrilimine with the 1,2-dihydronaphthalene **39** to give a mixture of compound **40** and **41** (Scheme 1.11).



39 **40** **41**

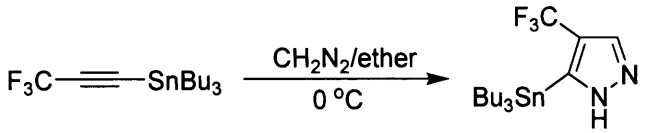
1) R = H, **40a** (80) + **41a** (20), 75% yield;
2) R = Me, **40b** (84) + **41b** (16), 70% yield;
3) R = Ph, **40c** (80) + **41c** (20), 50% yield.

Scheme 1.11

1.2.4 Syntheses from diazo compounds.

The reaction of diazo compounds with olefins and acetylenes is a well established route for the synthesis of pyrazole derivatives.[6,12,88-95] Thus, [1,3]-dipolar cycloaddition of tributyl-(3,3,3-trifluoro-1-propynyl)stannane **42** with diazomethane proceeded smoothly at 0 °C to give the

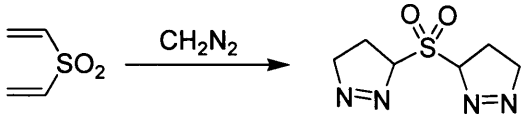
pyrazole **43** in 70% yield, which itself could participate in Stille couplings to introduce a functional group at the 5-position (Scheme 1.12).



42 **43**

Scheme 1.12

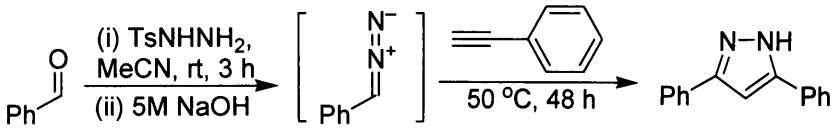
A variety of multiple bond systems have been employed in the same way,[90,96] as shown in Scheme 1.13.



44 **45**

Scheme 1.13

Recently, Aggarwal *et al.*[97] have reported a one-pot method for the preparation of pyrazoles by [1,3]-dipolar cycloaddition of *in situ* generated diazo compounds. Thus, condensation of tosylhydrazine with benzaldehyde followed by treatment with an aqueous solution of sodium hydroxide led to a solution of benzaldehyde tosylhydrazone sodium salt, which upon warming to 50 °C, gave a reddish solution of phenyldiazomethane. Prior to warming the reaction mixture, phenylacetylene was added and the desired 3,5-diphenylpyrazole **46** was obtained in 61% yield as a single regioisomer (Scheme 1.14). Yields were generally between 19% and 67% for the preparation of other pyrazoles from the corresponding aldehydes and alkynes.



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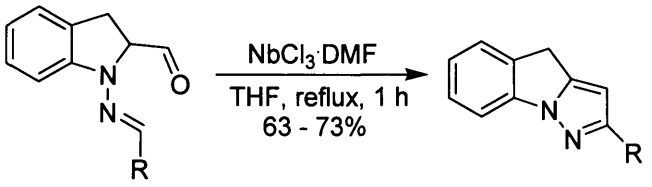
Scheme 1.14

1.2.5 Syntheses *via* intramolecular cyclization.

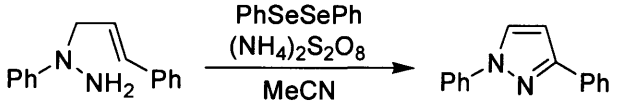
One obvious advantage of intramolecular reactions is to avoid the formation of regioisomers. However, reports of intramolecular approaches to pyrazole derivatives are rare.[98] Shen and Katayama showed that the intramolecular cyclization of aldehyde-hydrazone **47** in the presence of a Lewis acid led to the pyrazole **48** (Scheme 1.15)[99].



47 **48**

Scheme 1.15

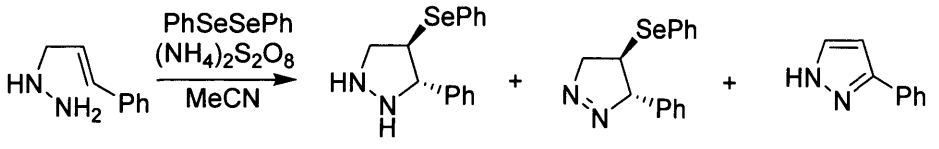
Tiecco *et al.*[100, 101] have studied the phenylselenenyl sulphate-induced 5-*endo*-trig cyclization of allylhydrazines as an approach to pyrazole derivatives. Thus, the reaction of cinnamyl phenylhydrazine **49** with a solution of diphenyl diselenide, ammonium persulfate and trifluoromethanesulfonic acid in acetonitrile at room temperature afforded pyrazole **50** in 62% yield (Scheme 1.16).



49 **50**

Scheme 1.16

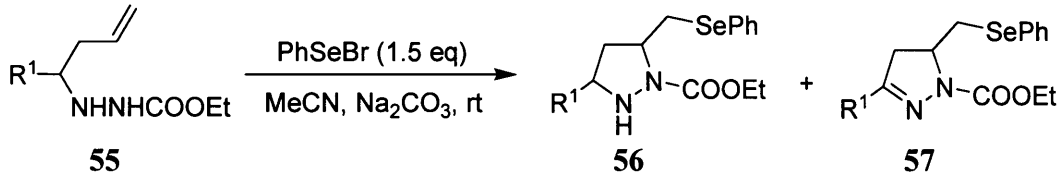
Under the same experimental conditions, however, the reaction of cinnamyl hydrazine **51** gave a mixture of pyrazolidine **52** (10%), pyrazoline **53** (25%) and pyrazole **54** (33%), respectively (Scheme 1.17).



51 **52** **53** **54**

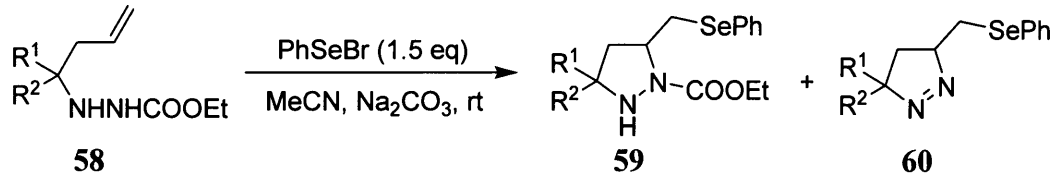
Scheme 1.17

Similarly, in 2001, Paulmier *et al.*[102] reported a selenium-induced 5-*exo*-trig cyclization of homoallylhydrazines for the synthesis of pyrazolidine and pyrazoline derivatives. The homoallylhydrazine substrates were treated with phenylselenenyl bromide (1.5 eq) in acetonitrile in the presence of sodium carbonate. As indicated in Schemes 1.18 - 1.20, the composition of the products depended on the homoallylhydrazine substrates used. In the case of homoallylhydrazines **55** and **58**, a mixture of pyrazolidine **56** or **59**, pyrazoline **57** or **60** and 10-50% of the starting substrates were obtained. When homoallylhydrazine **61** was used, 1-phenyl-2-pyrazoline **62** was the only product obtained, and no trace of the corresponding pyrazolidine was detected. It was also indicated that treatment of substrates **55** or **58** with an excess of selenium reagent (3 eq) produced the corresponding pyrazoline **57** or **60** in good yields.



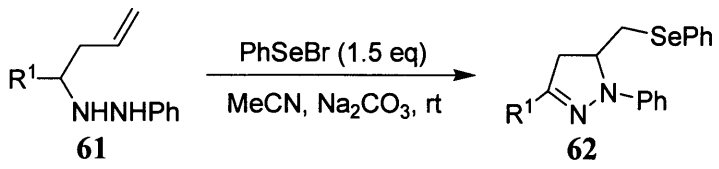
55 **56** **57**

Scheme 1.18



58 **59** **60**

Scheme 1.19 ($R^2 \neq H$)



61 **62**

Scheme 1.20

Chapter 2

Results and Discussion – Silver nitrate-induced 5-*endo*-dig cyclization for the syntheses of pyrazole derivatives.

2.1 Introduction – the 5-*endo*-dig cyclisation.

In 1976, Baldwin[103] reported his empirical rules for predicting the relative facility of ring forming reactions. He used a simple system to classify cyclisation reactions according to: (1) the ring size being formed; (2) whether the bond that breaks as the ring formed is inside (*endo*) or outside (*exo*) the new ring; and (3) whether the electrophile is an sp (digonal), sp^2 (trigonal) or sp^3 (tetrahedral) atom. Thus, a 5-*endo*-dig cyclisation means that the ring being formed has five members; the breaking bond is inside the new ring (*endo*); and the carbon being attacked is a digonal atom (*dig*), as indicated in Figure 2.1.

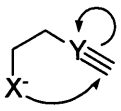
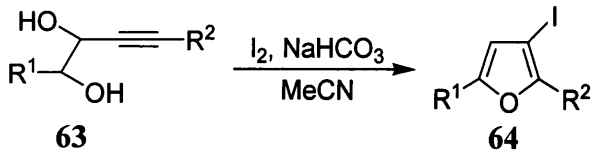


Figure 2.1 5-*endo*-dig cyclisation

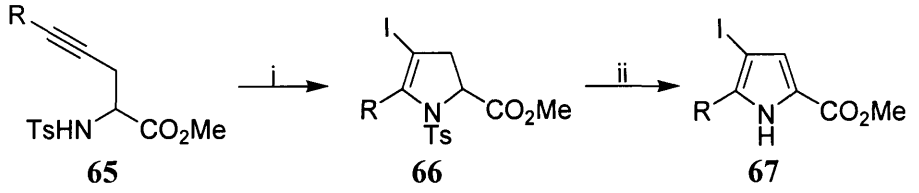
The 5-*endo*-dig cyclisation is favoured according to Baldwin's rules, but has scarely been reported in the literature. In 1996, Bew and Knight[1a] reported that the 5-*endo*-dig iodocyclisation of alk-3-yne-1,2-diols **63**, followed by *in situ* dehydration, gave *β*-iodofurans **64** in good yield (Scheme 2.1). This work was a logical extension to the work on 5-*endo*-trig iodocyclisation of homoallylic alcohols to give iodotetrahydrofurans and of homoallylic sulfonamides to give iodopyrrolidines previously developed within the group.



63 **64**

Scheme 2.1

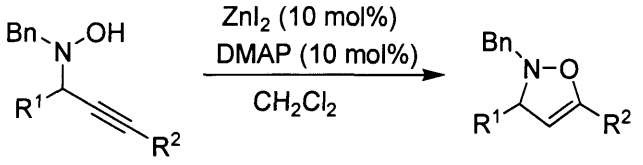
Following on from this, the 5-*endo*-dig methdology was extended to *β*-iodopyrroles. In 1998, Knight and Redfern[2b,2c] reported that homopropargylic sulfonamides **65** undergo 5-*endo*-dig iodocyclisations to give excellent yields of 2,3-dihydropyrroles **66**, using three equivalents of iodine and three equivalents of base (Scheme 2.2). These can then undergo base-induced elimination to the corresponding *β*-iodopyrroles **67**.



65 **66** **67**

Scheme 2.2 *Reagents and conditions*: (i) I_2, K_2CO_3 (3 equiv. Each), dry MeCN, 0-20 °C, 14 h; (ii) DBU (2.1 equiv.), DMF, 20 °C, 14 h.

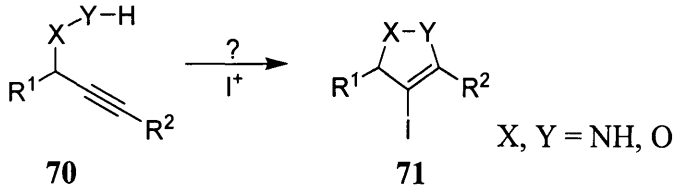
In 2000, Carreira *et al.*[104] reported a 5-*endo*-dig cyclisation of propargylic *N*-hydroxyamines **68** to give 2,3-dihydroisoxazoles **69** (Scheme 2.3). This cyclisation was achieved using 10 mol % each of zinc iodide and 4-dimethylaminopyridine.



68 **69**

Scheme 2.3

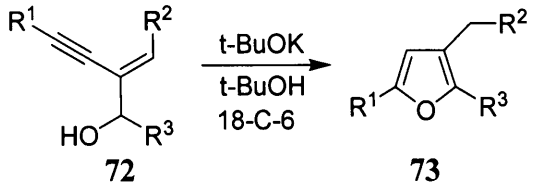
So, can we use a 5-*endo*-dig iodocyclisation on substrates **70** to give compounds **71** as shown in Scheme 2.4?



70 **71**

Scheme 2.4

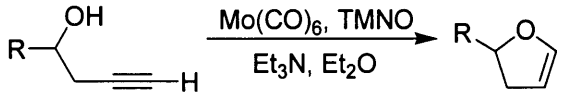
Other groups have used related ring closing reactions and in 1993 Marshall and Dubay[105] reported a base-catalysed cyclisation of *β*-alkynyl allylic alcohols **72**, with subsequent isomerization to form furans **73** (Scheme 2.5).



72 **73**

Scheme 2.5

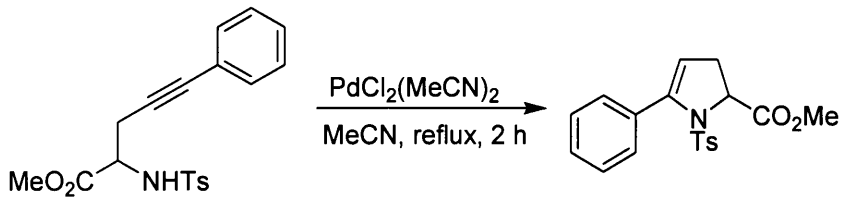
McDonald *et al.*[106] reported a molybdenum pentacarbonyl-trimethylamine promoted cyclisation of 1-alkyn-4-ols **74** to the isomeric 2,3-dihydrofurans **75** in 1993 (Scheme 2.6); the catalyst was formed by reaction of molybdenum hexacarbonyl, triethylamine *N*-oxide (TMNO) and triethylamine.



74 **75**

Scheme 2.6

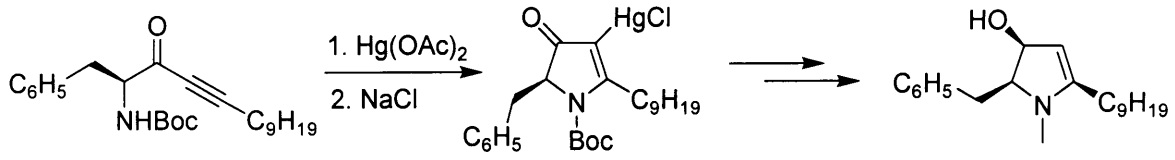
Rutjes *et al.*[107] reported that pyrroline **77** could be obtained in 51% isolated yield, by exposing the cyclisation precursor **76** to bis-(acetonitrile)-dichloropalladium(II) in refluxing acetonitrile for two hours (Scheme 2.7).



76 **77**

Scheme 2.7

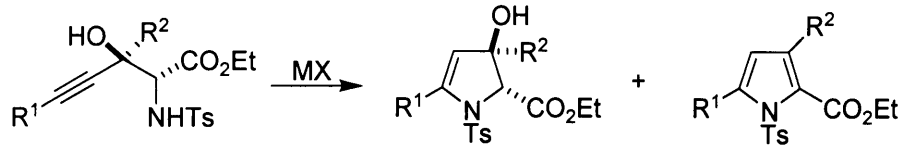
In 1994, Overhand and Hecht[108] reported a 5-*endo*-dig mercury-induced cyclisation to synthesise the natural product (+)-preussin **80** (Scheme 2.8). The cyclisation of the ynone **78** was achieved with mercuric acetate in nitromethane to give a good yield of the intermediate **79**.



78 **79** **80**

Scheme 2.8

Knight and Sharland[109] surveyed a range of transition metal salts for catalysing the cyclisation of ynoates **81** (Scheme 2.9). These were carried out by heating the ynoates **81** with a stoichiometric amount of a metal salt in a 1:1 mixture of ether and pyridine in sealed tubes at 90 °C. Copper(I) acetate, dichloro-*bis*(triphenylphosphine)palladium(II), palladium(II) acetate and mercury(II) acetate had been employed, and copper(I) acetate was found to be the best catalyst for the formation of hydroxyl-dihydropyrroles **82** from ynoates **81** by comparing the efficiency, cost and toxicity. In each case, a small amount of the pyrrole **83** was also formed.

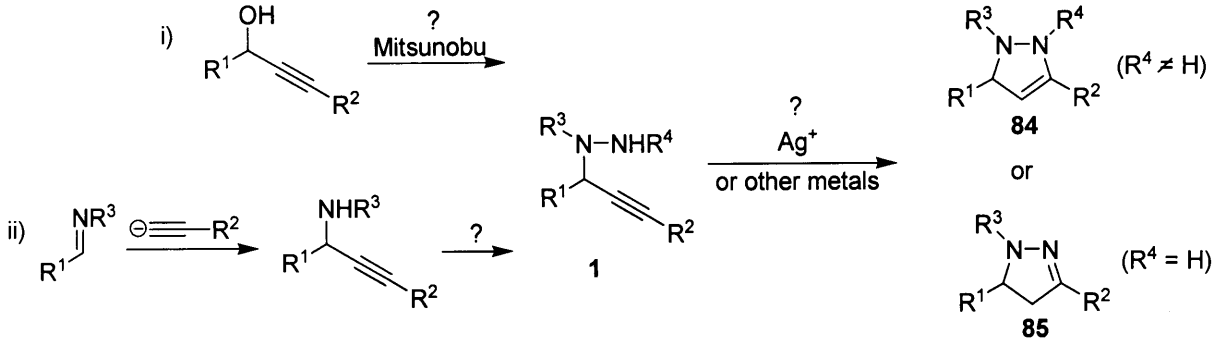


81 **82** **83**

Scheme 2.9

When silver nitrate was applied, the result was amazing - the cyclisation could be carried out at ambient temperature with sub-stoichiometric amounts of the catalyst to give the products **82** in excellent yields.[110] The high efficiency of the silver-catalyst was also reported by Marshall[111] for the synthesis of furan derivatives and Rutjes for the synthesis of proline derivatives.[112]

Inspired by this, we wondered if a metal catalysed 5-*endo*-dig cyclisation of propargylic hydrazine **1** could give dihydropyrazole **84** ($R^4 \neq H$) or **85** ($R^4 = H$) as shown in Scheme 2.10. The remarkable efficiency of these silver-catalysed cyclisations also caused postponement of the planned iodocyclisation research.



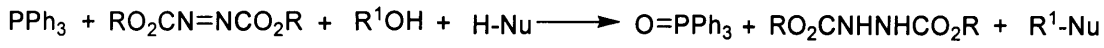
Scheme 2.10

2.2 The use of the Mitsunobu reaction as a key step to form the propargylic hydrazine precursors.

As shown in Scheme 2.10, the propargylic hydrazine precursors **1** could be prepared by a Mitsunobu reaction of the corresponding propargylic alcohol with a suitable acidic component. The acidic component could be an amide, and subsequent *N*-amination of the Mitsunobu products would give the propargylic hydrazine precursors **1**; or it might be a substituted hydrazine derivative, which would give compound **1** directly.

2.2.1 Introduction - The Mitsunobu reaction.

The Mitsunobu reaction refers to the condensation reaction of alcohols using the redox coupling of a triaryl- or trialkylphosphine and a dialkyl azodicarboxylate. [113, 114] The overall reaction is summarized in Scheme 2.11, wherein the alcohol (R^1OH) and an acidic compound (H-Nu) are condensed to form product (R^1-Nu), while triphenylphosphine is oxidized to triphenylphosphine oxide and the azodicarboxylate is reduced to the hydrazine.



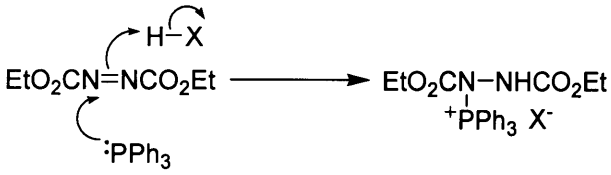
Scheme 2.11

The reaction is generally limited to primary and secondary alcohols, although tertiary alcohols react in a few intramolecular and intermolecular reactions. For secondary alcohols, the reaction

usually proceeds with clean S_N2 inversion of stereochemistry. The acidic component of the reaction generally has an aqueous pK_a < 13, with intramolecular reactions providing the exceptions. Examples of the acidic component include oxygen nucleophiles such as carboxylic acids and phenols, nitrogen nucleophiles such as imides, hydroxamates and heterocycles and sulfur nucleophiles such as thiols and thioamides. Even carbon can act as a nucleophile as in the case of *β*-ketoesters and related structures having 'doubly-activated' C-H bonds.

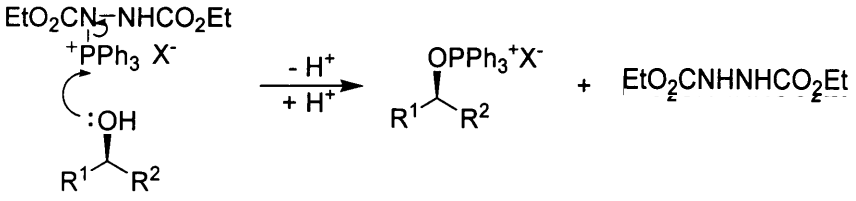
In his 1981 review, Mitsunobu proposed that this overall dehydration reaction using diethyl azodicarboxylate (DEAD) and triphenylphosphine proceeds in three steps: (1) reaction of triphenylphosphine with diethyl azodicarboxylate in the presence of the acidic component to form a salt wherein a phosphorus-nitrogen bond is formed; (2) reaction of the DEAD-triphenylphosphine adduct **86** with the alcohol to form an activated oxyphosphonium ion intermediate **87**; and (3) displacement *via* an S_N2 process to form the inverted product **88** and the phosphine oxide, as shown in Scheme 2.12.

Step 1: Adduct formation.



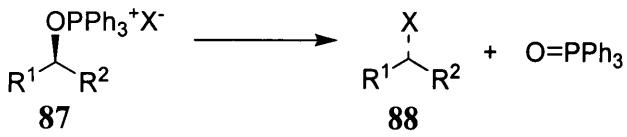
86

Step 2: Alcohol activation.



87

Step 3: S_N2 reaction.



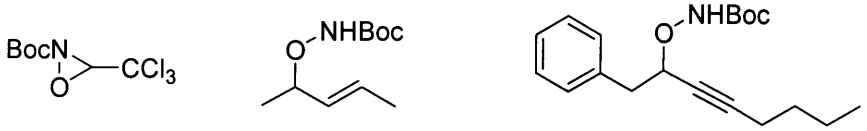
87 **88**

Scheme 2.12

The manipulation of the alcohol functional group is a synthetic goal which has been approached through a wide variety of methods. Most of these rely on activation of the hydroxyl group followed by displacement with an appropriate nucleophile. In the Mitsunobu reaction, the alcohol activation is accomplished *via* an oxyphosphonium salt. In general terms, the advantages of the Mitsunobu method include the following: (1) generally good yields with high stereoselectivity (inversion); (2) experimental ease, since the alcohol activation and displacement reactions take place in one pot, often at room temperature; (3) compatibility with a wide range of functional groups. However, one of the major drawbacks of the Mitsunobu reaction is the difficulty of removing the redox by-products, typically triphenylphosphine oxide and *di*-(ethoxycarbonyl)-hydrazine. This becomes a major concern in large-scale applications, where product purification by chromatography is not feasible.

2.2.2 The use of oxaziridine to form the N-N bond.

In 2000, Foot and Knight[115] reported that the *N*-Boc-3-trichloromethyloxaziridine **89** reacted smoothly with lithium alkoxides, derived from a representative range of alcohols, transferring an NHBoc function to the oxygen to provide *N*-Boc-*O*-alkylhydroxylamines, such as **90** and **91**, as shown in Figure 2.2. This approach is more efficient than the Mitsunobu displacement using *N*-hydroxyphthalimide as the nucleophile, and thus provided a new entry into isoxazolidines and isoxazolines *via* 5-*endo*-trig and 5-*endo*-dig cyclisations of the resulting hydroxylamines [e.g. **91**].

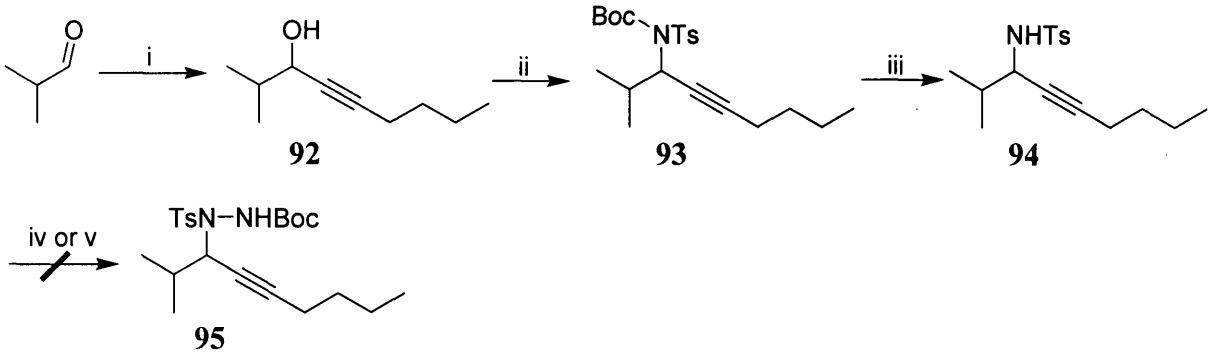


89 **90** **91**

Figure 2.2

Oxaziridines are more widely used for the electrophilic amination of amines, as well as carbon nucleophiles.[116,117] Our first idea of making a propargylic hydrazine precursor was the amination of sulfonamide **94** with oxaziridine **89**; the sulfonamide itself was synthesized by a

Mitsunobu reaction with *N*-Boc-tosylamide as the acidic component, followed by removal of the Boc group (Scheme 2.13). The alcohol **92**, which is a known compound,[118] was synthesized by nucleophilic addition of 1-hexynyl lithium to isobutyraldehyde. Mitsunobu displacement of alcohol **92** with *N*-Boc-tosylamide gave compound **93** in 74% isolated yield, which was deprotected with trifluoroacetic acid (TFA) to give the sulfonamide **94** in 92% isolated yield. The data obtained for compound **94** were in accord with those previously reported by Sisko and Weinreb.[119] The amination reaction was first carried out in a NMR tube. A mixture of the sulfonamide **94** and oxaziridine **89** in $CDCl_3$ was left for 16 hours, but the ^1H NMR spectrum showed no change. Pyridine was then added, and the mixture left for 4 hours. Again, the ^1H NMR spectrum stayed unchanged. The sulfonamide was then treated with *n*-butyllithium, either at 0 °C or -78 °C, before the addition of oxaziridine **89**, and the resulting mixture stirred for 24 hours before working-up. The crude product was purified by column chromatography. However, the desired product **95** was not detected, with some unknown by-products and a small amount of the starting sulfonamide being recovered.

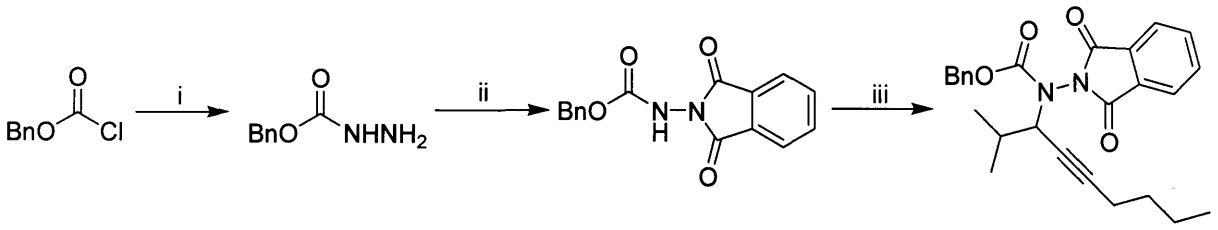


Scheme 2.13 *Reagents and conditions*: (i) 1-hexyne, *n*-BuLi, THF, 0 °C, 0.5 h, then add isobutyraldehyde, 1.5 h, 85%; (ii) **92**, BocNHTs, PPh_3, THF, 0 °C, 10 mins, then add DEAD, r.t., 16 h, 74%; (iii) TFA, DCM, 0 °C, 5 mins, then r.t., 2 h, 92%; (iv) **89**, $CDCl_3$, 16 h; (v) **94**, *n*-BuLi, 0 °C, THF, 15 mins, then add **89**, -78 °C – r.t., 24 h.

Clearly, an alternative strategy was required for introduction of an N-N bond, such as *N*-nitrosation-reduction method, or an alternative version of the Mitsunobu chemistry. Based on a very recent literature precedent, the latter idea was first examined.

2.2.3 The use of Mitsunobu reaction to introduce a hydrazine functional group directly.

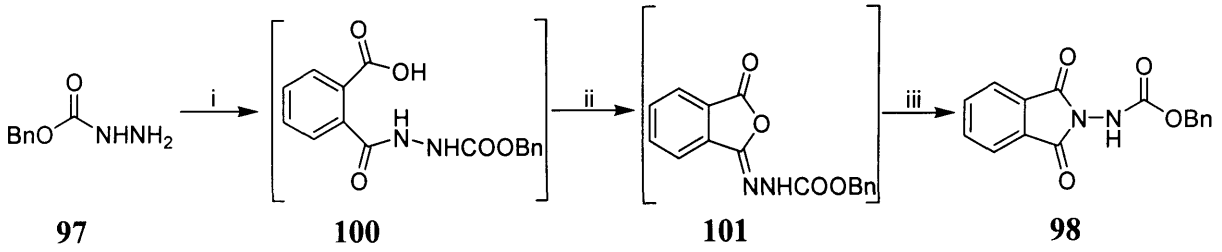
At the stage, when we were studying the *N*-amination using an oxaziridine, we also noticed that Jamart-Grégoire and co-workers reported a synthesis of 1,1-substituted hydrazines by alkylation of *N*-acyl or *N*-alkyloxy-carbonylaminophthalimides using the Mitsunobu protocol.[120] Although these chemists chose only a range of simple primary and secondary alcohols for this Mitsunobu reaction, we wondered if this method could be used with our propargylic alcohols. Fortunately, following the chemistry, we were able obtain the Mitsunobu adduct **99** (Scheme 2.14).



96 **97** **98** **99**

Scheme 2.14 *Reagents and conditions*: (i) hydrazine monohydrate, ether, -2 - -5 °C, adding **96** over 0.5 h, then r.t., 1 h; add H_2O, then etheral hydrogen chloride; then Et_2NH, 50%; (ii) phthalic anhydride, THF, r.t., 10 mins, then add DCC, 1h; then CH_3CO_2H and Et_3N, reflux, 1 h, 85%; (iii) **98**, PPh_3 and **92**, THF, 0 °C, then add DEAD, 0 °C, 2 h, then r.t., 1 h, 73%.

Benzyl carbazate **97** is a known compound. Following a literature procedure,[121] it was obtained in 50% yield as a crystalline solid, following recrystallization from diethyl ether (Scheme 2.14). It was fully characterized by IR, ^1H, ^{13}C NMR, mass spectrometry, microanalysis and melting point, as the only data given in the literature was a melting point and an incorrect microanalysis. Compound **98** is also a known compound, and its preparation involved the formation of two intermediates, compounds **100** and **101**, which have both been isolated and characterized (Scheme 2.15).[120]



97 **100** **101** **98**

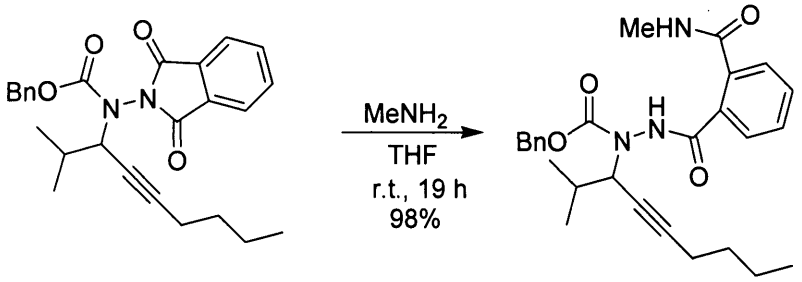
Scheme 2.15 *Reagents and conditions*: (i) phthalic anhydride, THF; (ii) DCC, THF; (iii) CH_3CO_2H, Et_3N, THF, reflux.

In the first step, the reaction of benzyl carbazate **97** with phthalic anhydride at room temperature in THF yielded compound **100**. The addition of DCC to the reaction mixture, upon the completion of the first step, induced cyclization of compound **100** to the corresponding isophthalimide **101**. The final step is the isomerization of compound **101** into the corresponding *N*-substituted aminophthalimide **98**. Thus, following a rapid filtration to remove dicyclohexyl-urea, the filtrate was then refluxed in the presence of two equivalents of triethylammonium acetate to obtain compound **98**. In our hands, we did not separate intermediates **100** and **101**, but instead obtained the phthalimide **98** in a one-pot reaction in 85% isolated yield, directly from benzyl carbazate **97**.

The Mitsunobu reaction was carried out using a typical procedure: 1.5 equivalents of diethyl azodicarboxylate were added to a solution of 1.5 equivalents of the alcohol **92**, 1.0 equivalent of the acidic component **98** and 1.5 equivalents of triphenylphosphine in dry THF, and the resulting mixture stirred at 0 °C for 2 h, then at ambient temperature for 1 h to give compound **99** in 73% yield after chromatography, as an oil (Scheme 2.14). It was characterized by IR, ^1H and ^{13}C NMR, and high resolution mass spectrometry. The IR spectrum showed absorbances characteristic of coupled carbonyl groups at 1799 and 1747 cm^{-1},[122] with the latter broadened, due to overlap with the third carbonyl group. The ^1H NMR signals were all broadened, slightly less so when the spectrum was run at 50 °C, resulting from hindered rotation about the nitrogen to carbonyl bond and the N-N bond, but the chemical shifts and integrations all fitted well with the structure. Some of the ^{13}C NMR signals were also broadened, with the benzyl CH_2 showing

two sets of resonances at 69.5 and 68.7 ppm. Again, the chemical shifts fitted perfectly well with the structure.

Dephthaloylation of compound **99** was first carried out using methylamine. With this reagent, compound **102**, instead of the fully deprotected amine, was formed, resulting from the opening of the phthaloyl ring (Scheme 2.16). Similar results have been reported in the literature.[123]

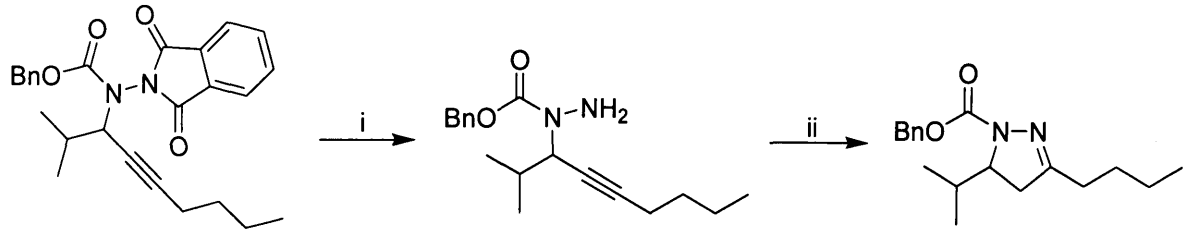


99 **102**

Scheme 2.16

The IR spectrum of the partially deprotected hydrazine **102** showed NH stretching at 3288 cm^{-1}; the ^{1}H and ^{13}C NMR spectra showed the appearance of the new methyl group at 2.66 and 27.3 ppm respectively; the mass spectrum showed a base peak at *m/z* 464 and the high resolution data further confirmed the molecular composition of compound **102**.

However, dephthaloylation of phthalimide **99** with one equivalent of hydrazine hydrate in refluxing ethanol proceeded smoothly to give hydrazine **103** in 68% yield after chromatography (Scheme 2.17). The IR spectrum of compound **103** showed slightly broadened absorption at 3336 cm^{-1}, characteristic for NH_2 stretching, consistent with those reported in the literature[120] and a strong absorption at 1704 cm^{-1}. The ^{1}H NMR spectrum showed a broadened singlet at 3.82 ppm which integrated for two protons, indicating a NH_2 group.



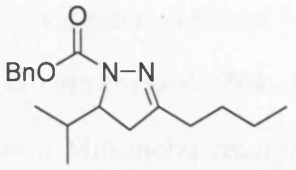
99 **103** **104**

Scheme 2.17 *Reagents and conditions:* (i) $NH_2NH_2{\cdot}H_2O$, C_2H_5OH, reflux, 2 h, 68%; (ii) $AgNO_3/SiO_2$, CH_2Cl_2, 1 h, 57%.

The key cyclisation was carried out as follows: a mixture of hydrazine **103** and 0.1 equivalents of 10% w/w silver nitrate on silica gel in dichloromethane was stirred at ambient temperature in the dark for one hour to give, after filtration, >90% yield of the 4,5-dihydropyrazole **104** (Scheme 2.17). The crude product of the dihydropyrazole **104** was very pure. However, as this was the first time the cyclisation was done, the crude product was further purified by column chromatography, which caused great loss and gave the dihydropyrazole **104** in 57% yield. The spectroscopic data obtained for the dihydropyrazole **104** were consistent with those reported for related compounds in the literature.[96,100,102] The IR spectrum clearly showed the disappearance of the NH_2 stretching. The ^1H NMR spectrum (Figure 2.3) showed two new signals, one at 2.67 ppm as a double doublet with coupling constants of 18.1 and 11.4 Hz, the other one at 2.45 ppm also as a double doublet with coupling constants of 18.1 and 4.9 Hz. These clearly came from the 4-CH_2 ring protons, and formed a nice ABX coupling system with the 5-H ring proton. This 5-H ring proton resonated at 4.18 ppm and appeared as apparent double triplet with coupling constants of 11.4 and 4.4 Hz, due to additional coupling with the isopropyl proton. The two protons of the benzyl CH_2 group were diastereotopic and appeared as two doublets at 5.21 and 5.16 ppm respectively with a coupling constant of 12.4 Hz, with one of them being slightly broadened. Not surprisingly, the two isopropyl methyl groups were clearly distinguished as two doublets at 0.76 and 0.64 ppm respectively, with coupling constants of 6.9 Hz. The evidence for the proposed structure in the ^{13}C NMR spectrum was the disappearance of the C≡C signals and the appearance of the new CH_2 group at 34.0 ppm; it also showed two quaternary carbons at 158.4 and 151.9 ppm, with one of them arising from the new ring C=N bond. The high resolution mass spectrum also indicated it to be the right molecule, in providing agreement between the calculated and found molecular weights for the proposed structure **104**.

^{1}H NMR Spectrum

Benzyl 3-butyl-4,5-dihydro-5-isopropylpyrazole-1-carboxylate (104)



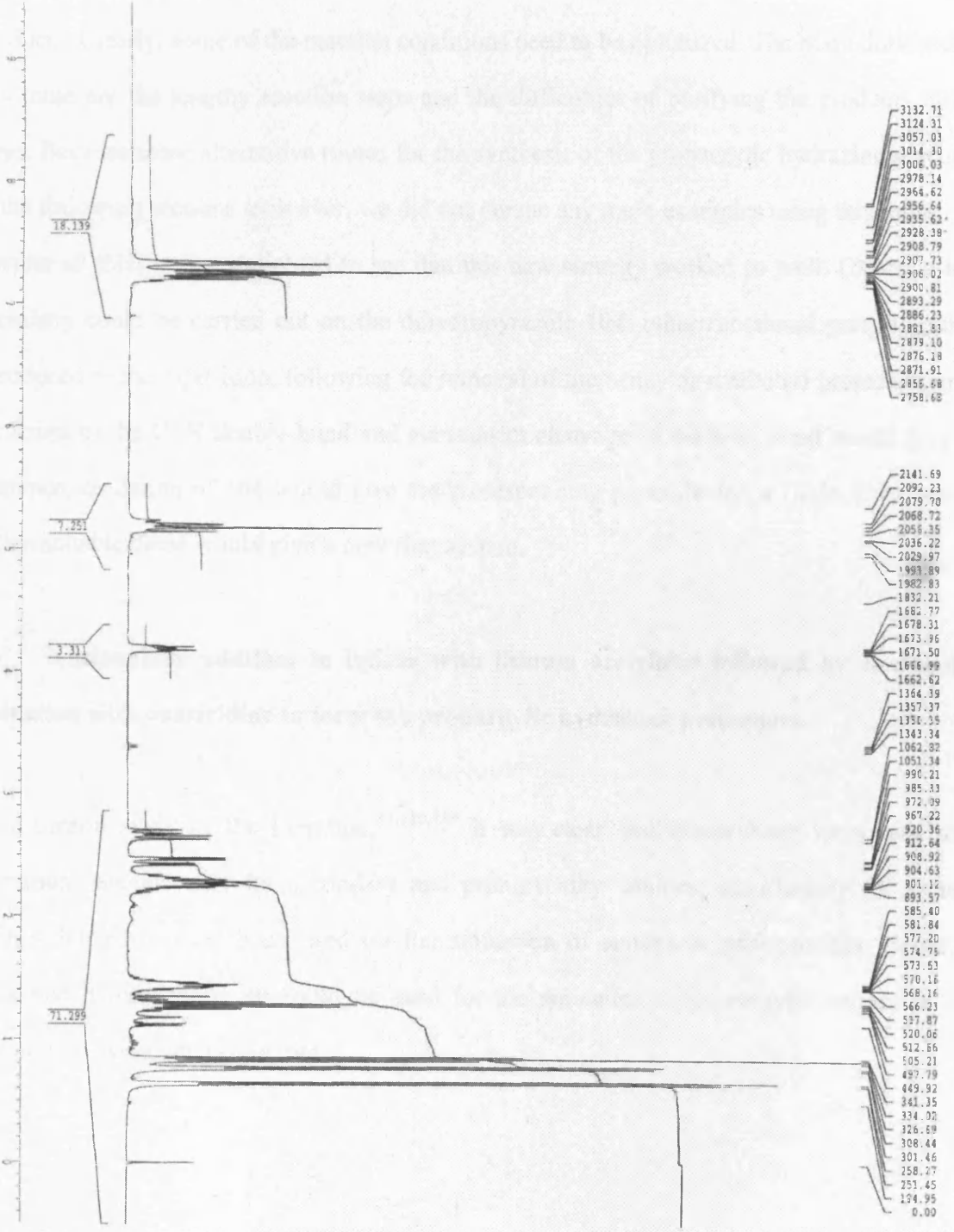


Figure 2.3

2.2.4 Conclusion.

We have shown our first example of silver nitrate-induced 5-*endo*-dig cyclisation of propargylic hydrazine **103** for the synthesis of dihydropyrazole **104**. A key step for the synthesis of the propargylic hydrazine precursor was a Mitsunobu reaction and this route could give chiral products. Clearly, some of the reaction conditions need to be optimized. The main drawbacks of this route are the lengthy reaction steps and the difficulties of purifying the products in most steps. Because some alternative routes for the synthesis of the propargylic hydrazine precursors in the following sections took over, we did not pursue any more examples using this route.

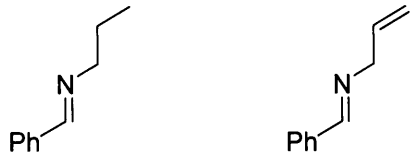
Despite all this, we are delighted to see that this new strategy worked so well. Clearly a lot of chemistry could be carried out on the dihydropyrazole **104**: other functional groups could be introduced to the 1-position, following the removal of the benzyloxycarbonyl protecting group; reduction of the C=N double bond and subsequent cleavage of the N-N bond would give 1,3-diamines; oxidation of **104** would give the corresponding pyrazole and a Diels-Alder reaction with a suitable diene would give a new ring system.

2.3 Nucleophilic addition to imines with lithium acetylides followed by electrophilic amination with oxaziridine to form the propargylic hydrazine precursors.

By a careful study of the literature,[41,116,117] it was clear that oxaziridines were used as *N*-amination reagents only for secondary and primary alkyl amines, occasionally for aromatic amines, but have never been used for the amination of amides or sulfonamides. Hence, we wondered if oxaziridine **89** could be used for the amination of propargylic amines to form propargylic hydrazine precursors.

2.3.1 Syntheses of propargylic amines.

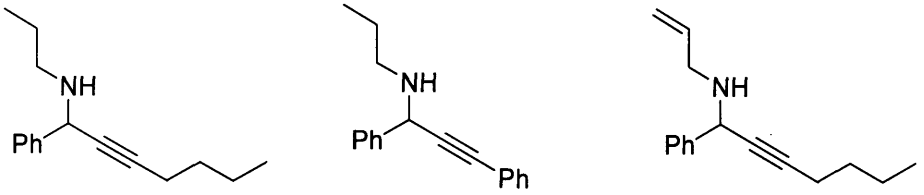
Imines **105**[124a] and **106**[124b] were easily made in excellent yield by condensation of benzaldehyde with the corresponding amines (Figure 2.4).



105 **106**

Figure 2.4

Nucleophilic addition to imines[125-128] **105** and **106** by the corresponding alkynyl or arynyllithium, in the presence of the Lewis acid boron trifluoride diethyl etherate, gave the propargylic amines **107-109** (Figure 2.5). Yields were typically in the range 65% to 75%.

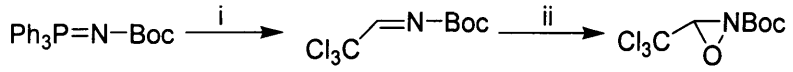


107 **108** **109**

Figure 2.5

2.3.2 Electrophilic amination of the propargylic amines with oxaziridine 89.

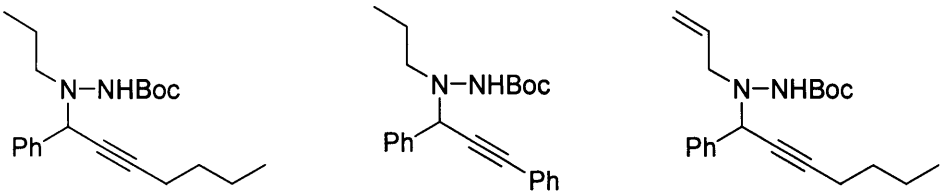
Oxaziridine **89** was synthesized following a literature procedure.[117] Thus, an aza-Wittig reaction of compound **110** with chloral, followed by oxone oxidation of the resulting imine **111**, afforded oxaziridine **89** in almost quantitative yield (Scheme 2.18).



110 **111** **89**

Scheme 2.18 *Reagents and conditions*: (i) Cl_3CCHO, toluene, reflux, 1.5 h, 99%; (ii) oxone, K_2CO_3, $CHCl_3/H_2O$, 0 °C, 99%.

Electrophilic amination of the propargylic amines **107-109** with a slight excess of oxaziridine **89** proceeded very smoothly to give the propargylic hydrazines **112-114** (Figure 2.6). The typical yields were in the range 73% to 80%. The IR spectrums of the propargylic hydrazines **112-114** showed NH absorbances at around 3335 cm^{-1} and absorbances at around 1700 cm^{-1} characteristic of carbonyl groups. The ^{1}H and some of the ^{13}C NMR signals were broadened, but the chemical shifts and integrations all fit well with the structures. The high resolution mass spectra all provided agreement between the calculated and found molecular weights for the proposed structures.

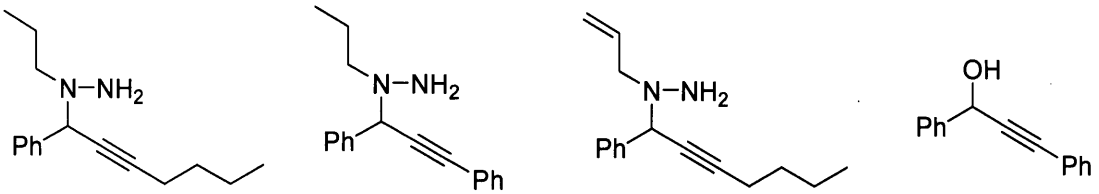


112 **113** **114**

Figure 2.6

2.3.3 Deprotection of Boc group.

Free hydrazines **115-117** could be obtained by simply stirring a solution of compounds **112-114** in formic acid at ambient temperature for 20 hours (Figure 2.7).



115 **116** **117** **118**

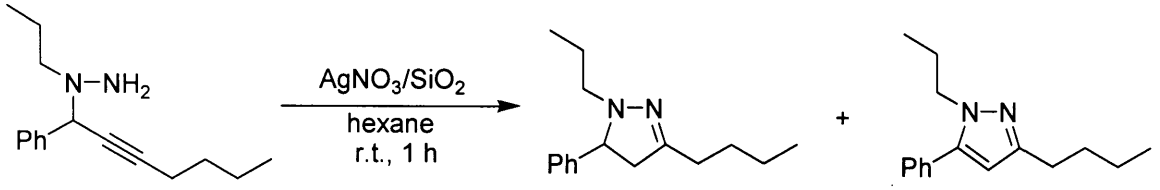
Figure 2.7

These free hydrazines were not stable and attempted purification by column chromatography resulted in the formation of by-products and extensive loss. Hence, they were used directly in the next step without further purification and were characterized by their ^{1}H NMR spectra only. The crude yields for **115** and **117** were excellent, with only around 55% for compound **116**, due

to its sensitive structure, especially given the acidic conditions. The main by-product was the 1,3-diphenylprop-2-yn-1-ol **118**.

2.3.4 Silver nitrate-induced cyclisation.

The silver nitrate-induced cyclisations were carried out as described in Section 2.2.3. Treatment of the crude hydrazine **115** with 0.2 equivalents of 10% w/w silver nitrate on silica gel gave a mixture of the 4,5-dihydropyrazole **119** and the pyrazole **120**, which could be separated by column chromatography (Scheme 2.19). Starting from the Boc protected hydrazine **112**, the isolated yields for dihydropyrazole **119** and **120** were 48% and 9% respectively, which were excellent for two steps. Presumably, the pyrazole **120** resulted from oxidation of the dihydropyrazole **119** by Ag^+. The silver nitrate on silica gel turned black as soon as it was added to the solution of the hydrazine **115** in hexane, indicating the formation of Ag(0). This was not observed for the silver nitrate-induced cyclisation of the hydrazine **103** in Section 2.2.3, probably due to the difference of the benzyloxycarbonyl and propyl substituents on the nitrogen, hence the different electron density of nitrogen. Further investigations of the reasons for oxidation will be discussed later.

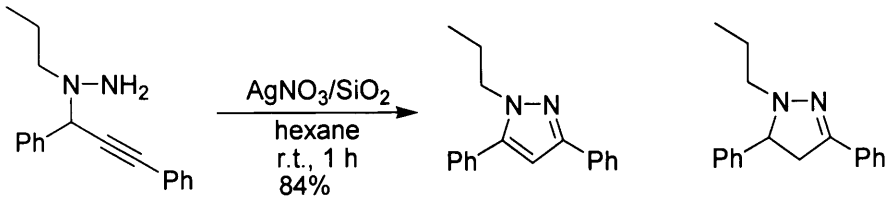


115 **119** **120**

Scheme 2.19

Treatment of the crude hydrazine **116** with 0.1 equivalents of 10% w/w silver nitrate on silica gel gave the pyrazole **121** exclusively; the corresponding 4,5-dihydropyrazole **122** was not detected (Scheme 2.20). The dihydropyrazole **122** might be formed at the initial stage of the cyclisation, but was easily oxidized to the pyrazole **121** because it is highly sensitive to oxidation. From the fact that only 0.1 equivalents of 10% $AgNO_3$-SiO_2 were used, we assume

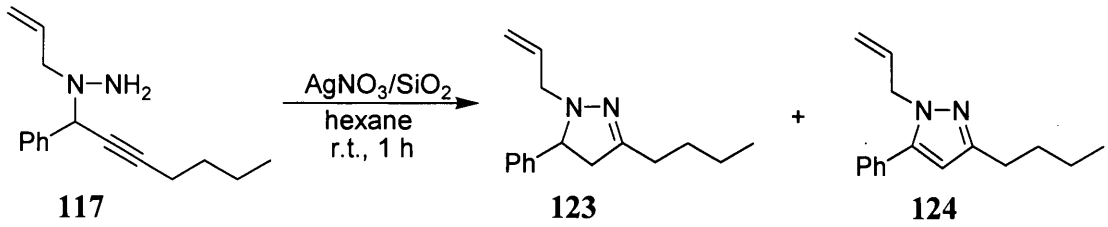
that oxidation of the dihydropyrazoles by Ag^+ was catalytic, although we are not sure about the mechanism.



116 **121** **122**

Scheme 2.20

Hydrazine **117** was potentially a tricky one, as competitive 5-*endo*-trig, 4-*exo*-trig, 5-*endo*-dig and 4-*exo*-dig cyclisations might occur. However, treatment of the crude hydrazine **117** with 0.2 equivalents of 10% w/w silver nitrate on silica gel as above gave 5-*endo*-dig cyclisation products, the 4,5-dihydropyrazole **123** and pyrazole **124** (Scheme 2.21). None of the 5-*endo*-trig, 4-*exo*-trig and 4-*exo*-dig cyclisation products were detected. Starting from the Boc protected hydrazine **114**, the isolated yields for dihydropyrazole **123** and pyrazole **124** were 25% and 22% respectively.



117 **123** **124**

Scheme 2.21

The spectroscopic data obtained for dihydropyrazoles **119** and **123** were consistent with those of dihydropyrazole **104**. For example, the ^{1}H NMR spectrum of dihydropyrazole **119** showed the characteristic resonance for the 5-H ring proton at 3.90 ppm and appeared as a double doublet with coupling constants of 14.6 and 9.6 Hz, and formed a typical ABX coupling system with the 4-CH_2 ring protons. One of the 4-CH_2 ring protons resonated at 2.84 ppm and appeared as a double doublet with coupling constants of 16.0 and 9.6 Hz; the other resonated at 2.50 ppm and also appeared as a double doublet with coupling constants of 16.0 and 14.6 Hz. The two protons of the α-CH_2 of the propyl group were inequivalent with one of them resonating at 2.66 ppm

and appearing as a double double doublet with coupling constants of 12.3, 9.2 and 5.2 Hz, and the other resonating at 2.59 ppm and also appearing as a double double doublet with coupling constants of 12.3, 9.2 and 6.7 Hz.

The spectroscopic data obtained for pyrazoles **120**, **121** and **124** were consistent with those reported for related compounds in the literature.[102,129] The ^{1}H NMR spectrum showed the characteristic resonance for the 4-ring protons between 6.0 and 6.5 ppm and appeared as a singlet (Figure 2.8). The chemical shifts of the 4-ring carbons were between 100 and 105 ppm. One of the quaternary carbons resonated at around 145 ppm, while the other resonated between 150 and 155 ppm.

^{1}H NMR Spectrum

1-Allyl-3-butyl-5-phenyl-1*H*-pyrazole (124)

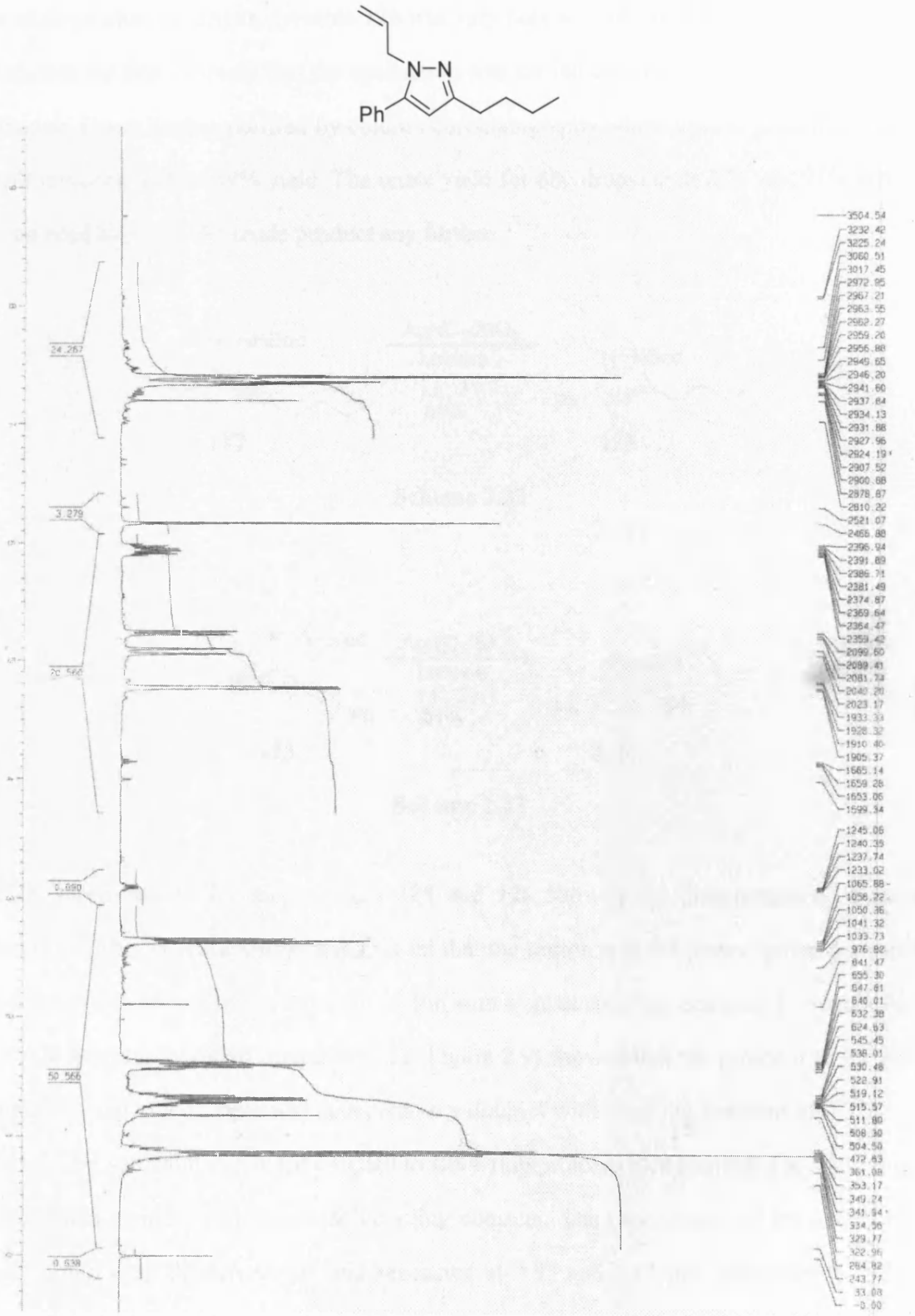
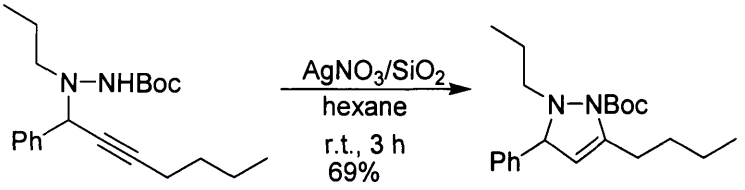


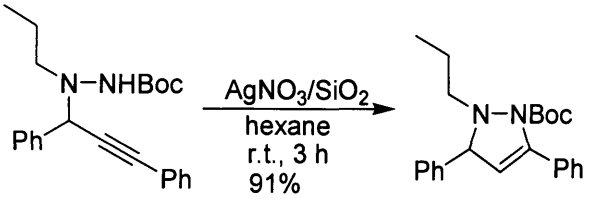
Figure 2.8

Direct cyclisation of hydrazines **112** and **113** was possible, and gave 2,3-dihydropyrazoles **125** and **126** respectively (Scheme 2.22, 2.23). However, slightly longer reaction times were needed. The crude product of dihydropyrazole **125** was very pure and the yield was excellent. However, as this was the first example that the cyclisation was carried out on a Boc protected propargylic hydrazine, it was further purified by column chromatography which caused great loss and gave dihydropyrazole **125** in 69% yield. The crude yield for dihydropyrazole **126** was 91% and there was no need to purify the crude product any further.



112 **125**

Scheme 2.22



113 **126**

Scheme 2.23

The IR spectrums of dihydropyrazoles **125** and **126** showed the disappearance of the NH absorptions. The ^{1}H NMR spectrums showed that the proton α to the phenyl group appeared as a doublet, which coupled to an adjacent proton with a small coupling constant. For example, the ^{1}H NMR spectrum of dihydropyrazole **126** (Figure 2.9) showed that the proton α to the phenyl group resonated at 4.52 ppm and appeared as a doublet with coupling constant of 3.2 Hz. The ^{1}H-^{1}H COSY spectrum showed it coupled to the 4-ring proton which resonated at 5.63 ppm and appeared as a doublet with the same coupling constant. The two protons of the α-CH_2 of the propyl group were diastereotopic, and resonated at 2.92 and 2.83 ppm respectively and both appeared as double double doublets with coupling constants of 11.6, 9.5 and 5.9 Hz. The ^{13}C NMR spectrums showed resonance of the 4-ring tertiary carbon at 108.4 and 112.0 ppm

^{1}H NMR Spectrum

tert-Butyl 2,3-dihydro-3,5-diphenyl-2-propylpyrazole-1-carboxylate (126)

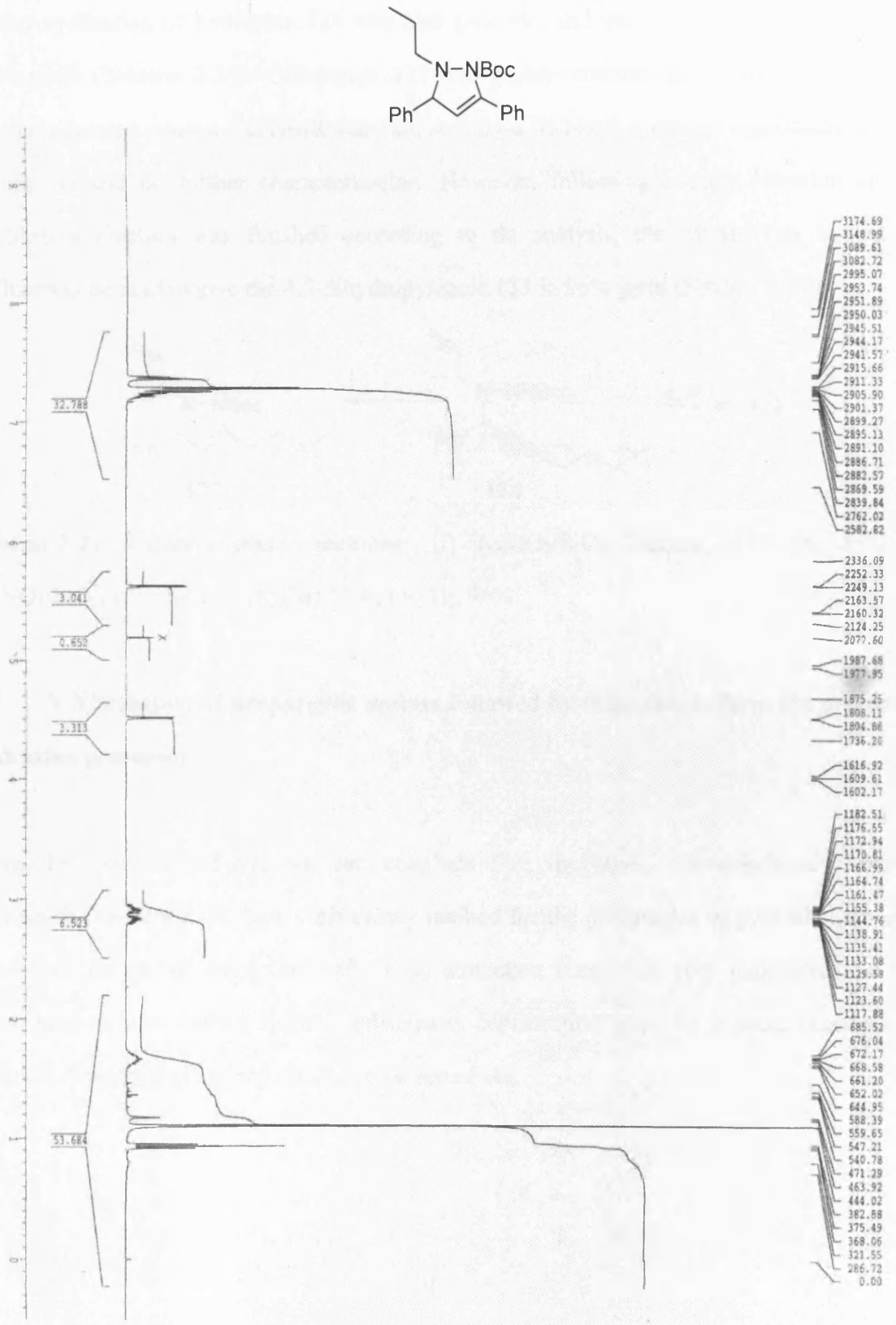
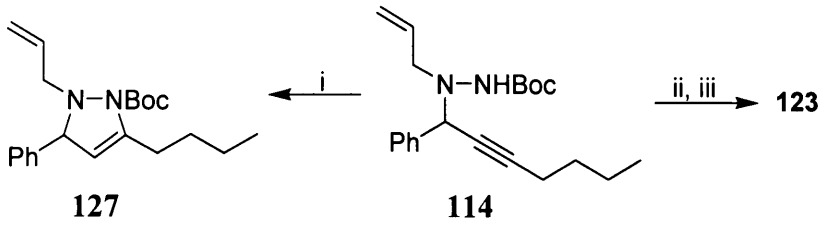


Figure 2.9

respectively for dihydropyrazoles **125** and **126**, while the 5-ring quaternary carbon falled in the region 140-145 ppm.

Direct cyclisation of hydrazine **114** was also possible, and gave 2,3-dihydropyrazole **127** in 85% yield (Scheme 2.24). Compound **127** was highly unstable and large amounts of by-products formed when a ^{13}C NMR was run, so only a ^{1}H NMR spectrum was obtained for this compound and no further characterization. However, following a quick filtration after the cyclisation reaction was finished according to tlc analysis, the filtrate was treated with trifluoroacetic acid to give the 4,5-dihydropyrazole **123** in 96% yield (Scheme 2.24).



127 **114**

Scheme 2.24 *Reagents and conditions*: (i) $AgNO_3/SiO_2$, hexane, r.t., 1h, 85%; (ii) $AgNO_3/SiO_2$, CH_2Cl_2, r.t., 1h; (iii) TFA, r.t., 1h, 96%.

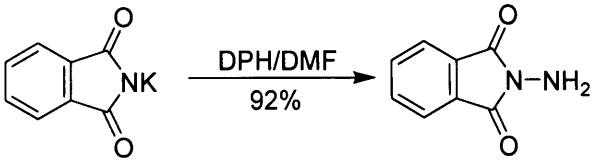
2.4 *N*-Nitrosation of propargylic amines followed by reduction to form the propargylic hydrazine precursor.

From the examples above, we can conclude that the silver nitrate-induced 5-*endo*-dig cyclisation is a very mild, highly efficiency method for the preparation of pyrazole derivatives. However, the use of oxaziridine **89** as an amination reagent is very expensive and time-consuming. It also suffers from a subsequent deprotection step. So a more economic and practical *N*-amination method needed to be sorted out.

2.4.1 Other *N*-amination methods.

a) Direct *N*-amination.

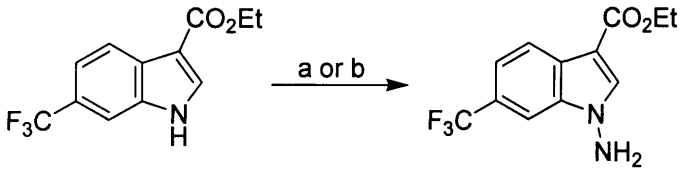
Klötzer[130] reported the use of *O*-(diphenylphosphinyl)hydroxylamine (DPH) as a *N*-amination reagent. Thus, treatment of the potassium salt of phthalimide **128** with DPH in *N,N*-dimethylformamide gave the *N*-aminophthalimide **129** in excellent yield (Scheme 2.25).



128 **129**

Scheme 2.25

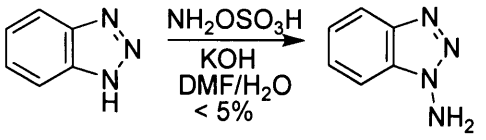
This method, as well as the method of Somei, with hydroxylamine-*O*-sulfonic acid and potassium hydroxide in anhydrous dimethylformamide, was also used for the *N*-amination of indole **130** (Scheme 2.26).[131]



130 **131**

Scheme 2.26 *Reagents and conditions*: (a) NH_2OSO_3H, KOH/K_2CO_3, DMF, r.t., 21%; (b) $Ph_2P(O)ONH_2$, LiHMDS, NMP, -10 °C – r.t., 80%.

Subsequent work by Knight employed these methods in the synthesis of 1-aminobenzotriazole **133**. However, both methods gave very poor yields (Scheme 2.27).



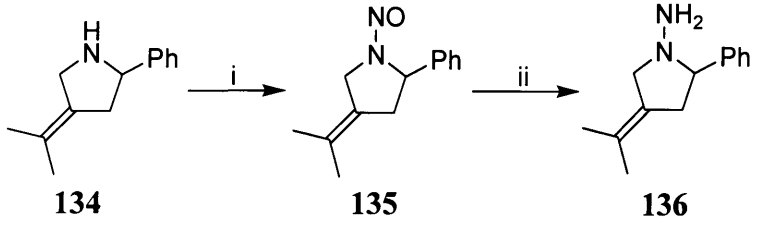
132 **133**

Scheme 2.27

b) *N*-Nitrosation (nitration)-reduction.

N-Nitration of secondary amines with nitrogen dioxide, nitryl chloride, nitrogen pentoxide, nitryl fluoride, nitronium fluoroborate, tetranitromethane and nitrate esters gives the corresponding *N*-nitramines,[132,133] subsequent reduction of which then gives the corresponding hydrazines.[134] However, these methods suffer from the inconvenience of handling, potential explosion hazard of *N*-nitramines and cleavage of the N-N bond during the reduction step.

An alternative and more widely used method is the *N*-nitrosation-reduction approach. The *N*-nitrosation reaction can be carried out by treating secondary amines [e.g. **134**] with sodium nitrite in acidic media.[135-137] Subsequent reduction of the resulting *N*-nitroso compounds [e.g. **135**] then gives the hydrazines [e.g. **136**] (Scheme 2.28). Suitable reducing reagents have been extensively studied; these include zinc in acetic acid,[135] titanium trichloride,[138] sodium dithionite,[136] and lithium aluminum hydride.[137]



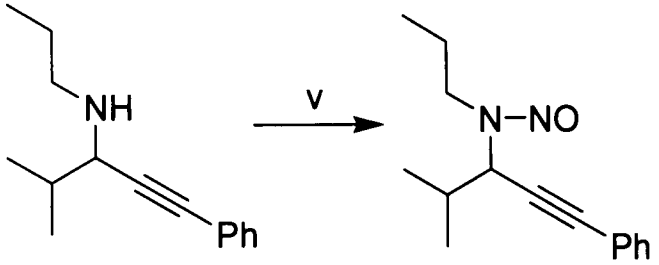
134 **135** **136**

Scheme 2.28 *Reagents and conditions*: (i) $NaNO_2$, 50% aqueous acetic acid; (ii) $LiAlH_4$/ether.

The *N*-nitrosation-reduction method is the most general method for the synthesis of hydrazines. However, it needs to be pointed out that *N*-nitrosamines are extremely toxic, which is the major fault of this method.

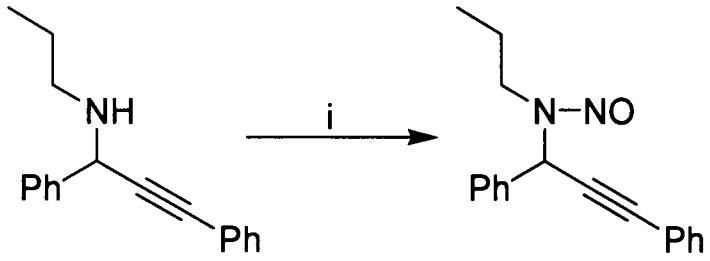
2.4.2 *N*-Nitrosation of propargylic amines.

Nucleophilic addition to the imine **137**[124c], as described in section 2.3.1, gave the propargylic amines **138** and **140**[139] in 64% and 65% isolated yield respectively, *N*-nitrosation of which, following a literature procedure,[135] then gave the *N*-nitrosamines **139** and **141** in 80% and 94% yield respectively (Scheme 2.29). Similarly, the *N*-nitrosamine **142** was obtained in 86% yield by *N*-nitrosation of the propargylic amine **108** (Scheme 2.30).



140 **141**

Scheme 2.29 *Reagents and conditions*: (i) $C_3H_7NH_2$, 0 °C – r.t., 3 h, 84%; (ii) 1-BuLi, THF, 0 °C, 0.5 h, then add **137**, followed by $BF_3{\cdot}Et_2O$, -78 °C - r.t., 19 h, 64% HCl, $NaNO_2$, 0 °C, 1 h, 80%; (iv) PhC≡CH, *n*-BuLi, THF, 0 °C, 0.5 h, then add **137** by $BF_3{\cdot}Et_2O$, -78 °C - r.t., 19 h, 65%; (v) 37% HCl, $NaNO_2$, 0 °C, 7 h, 94%.



108 **142**

Scheme 2.30 *Reagents and conditions*: (i) 37% HCl, $NaNO_2$, 0 °C, 1 h, 86%.

Compared with that of the propargylic amine **140** (Figure 2.10), the ^{1}H NMR spect corresponding *N*-nitrosamine **141** (Figure 2.11) differed significantly. Firstly, the pro CH_2 adjacent to the nitrogen in the propyl group of the *N*-nitrosamine **141** shifted aro downfield than those of the propargylic amine **140**, while the proton adjacent the ni the triple bond shifted around 2 ppm downfield. Secondly, the *N*-nitrosamine **141** ap mixture of two rotamers. The same observation was true with the *N*-nitrosamines **13** The ^{13}C NMR spectrums of these *N*-nitrosamines also showed two sets of rotamers.

^{1}H NMR spectrum

4-Methyl-1-phenyl-*N*-propylpent-1-yn-3-amine (140)

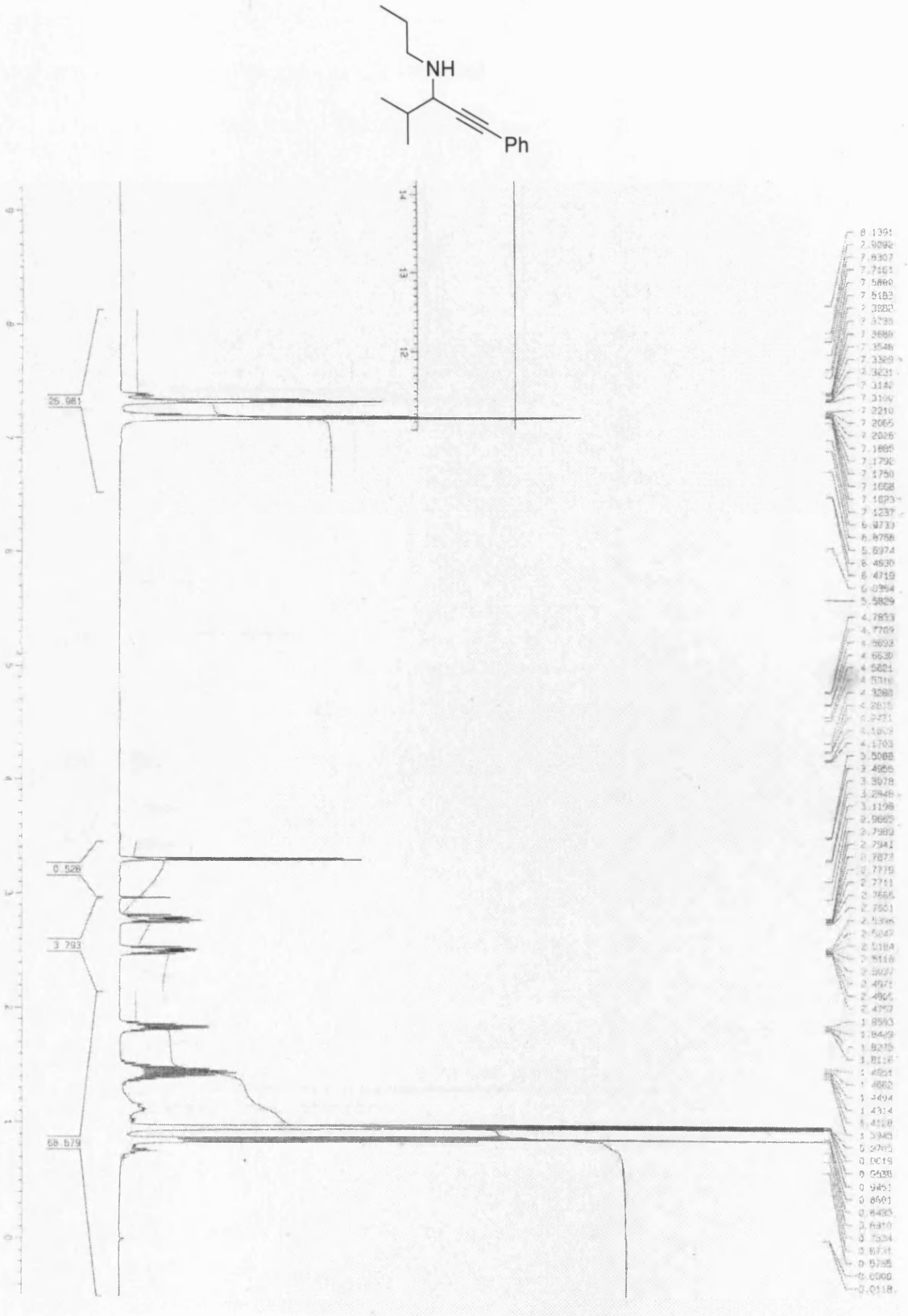


Figure 2.10

^{1}H NMR Spectrum

4-Methyl-*N*-nitroso-1-phenyl-*N*-propylpent-1-yn-3-amine (141)

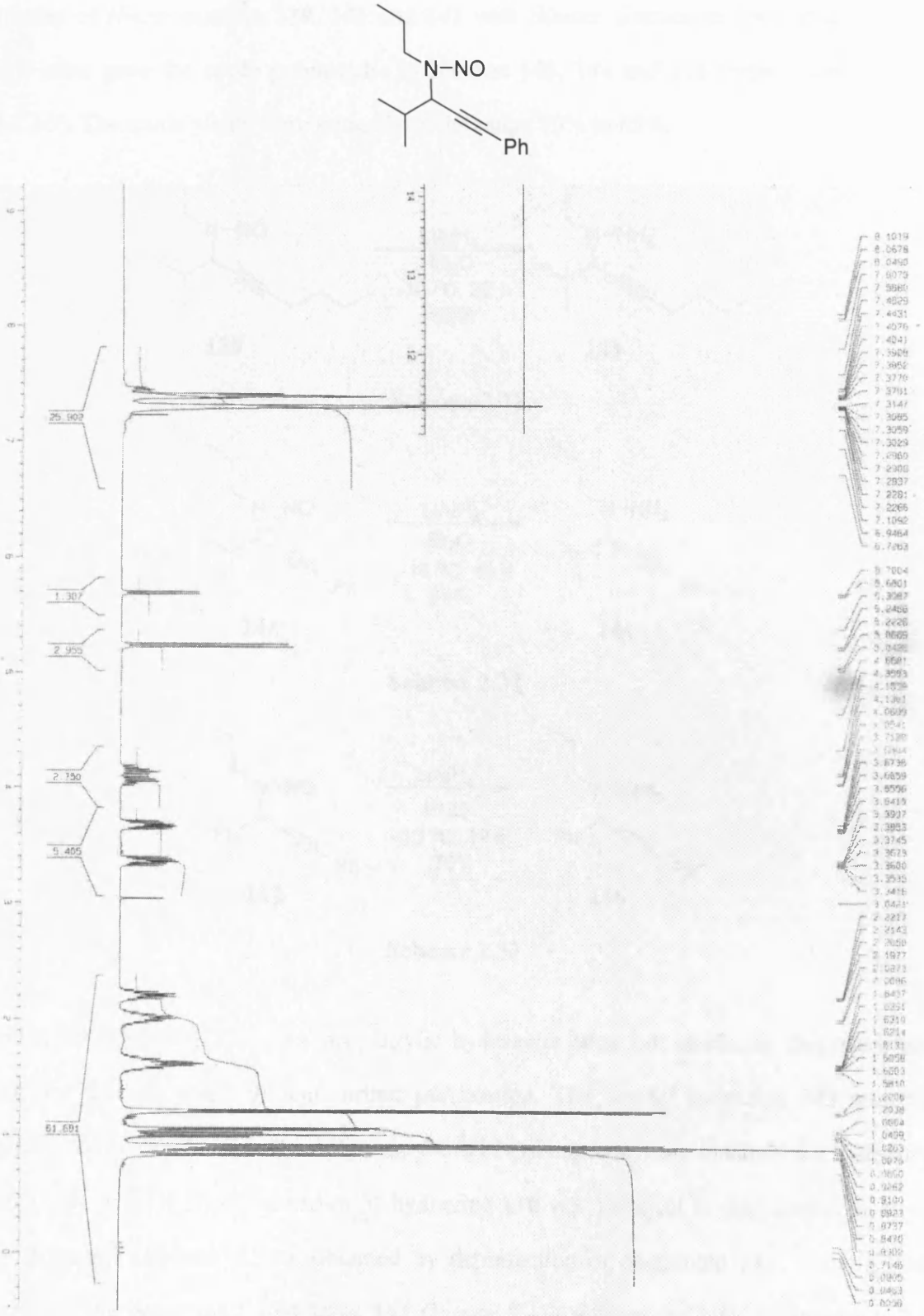
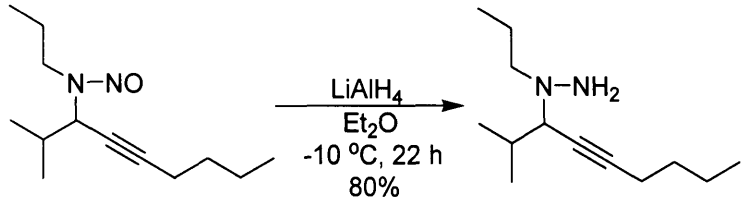


Figure 2.11

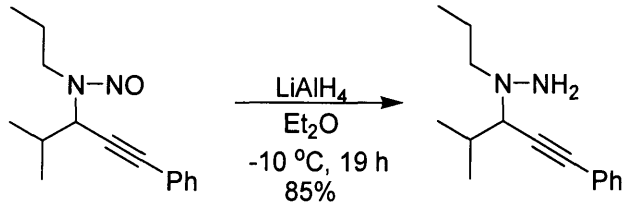
2.4.3 Reduction of *N*-nitrosamines.

Reduction of *N*-nitrosamines **139**, **141** and **142** with lithium aluminium hydride at -10 °C in diethyl ether gave the crude propargylic hydrazines **143**, **144** and **116** respectively (Schemes 2.31-2.33). The crude yields were typically in the range 70% to 85%.



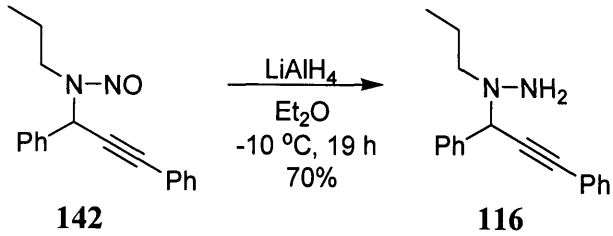
139 **143**

Scheme 2.31



141 **144**

Scheme 2.32



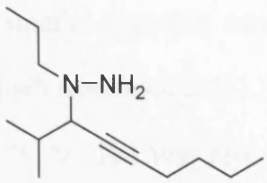
142 **116**

Scheme 2.33

As indicated in section 2.3.3, the propargylic hydrazines were not stable, so they were used directly for the next step, without further purification. The 'crude' hydrazine **143** was pure enough for full characterisation, while only the ^{1}H NMR spectra were obtained for hydrazines **144** and **116**. The ^{1}H NMR spectrum of hydrazine **116** was identical to that displayed by the forgoing sample (Section 2.3.3), obtained by deprotection of compound **113**. The ^{1}H NMR spectrum of the propargylic hydrazine **143** (Figure 2.12) showed the NH_2 resonance at 2.79 ppm and appeared as a broad singlet. The proton adjacent to the nitrogen and the triple bond

^{1}H NMR Spectrum

1-(2'-Methylnon-4'-yn-3'-yl)-1-propylhydrazine (143)



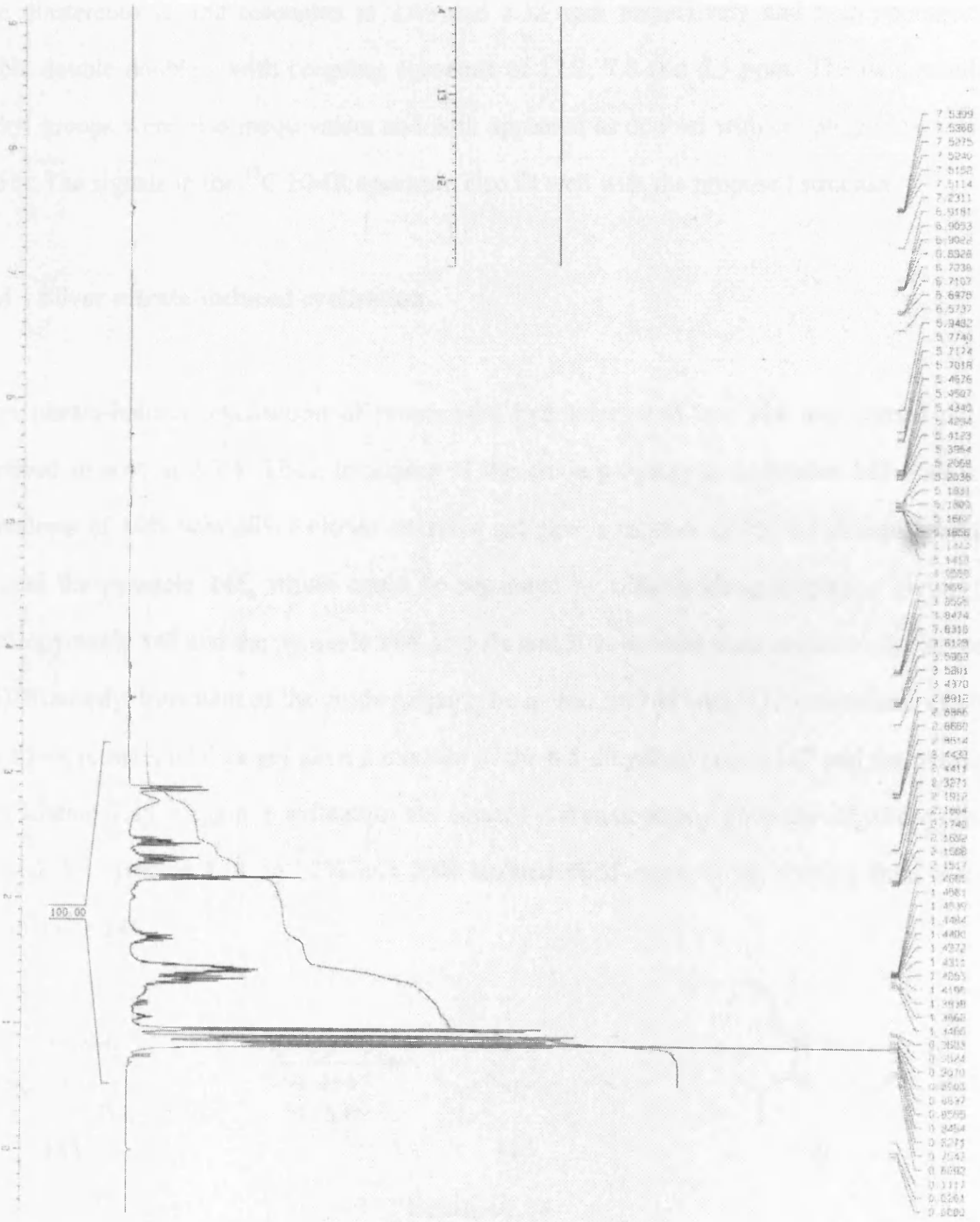
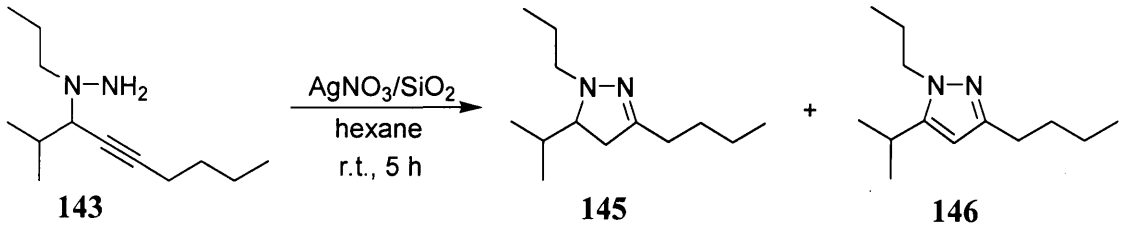


Figure 2.12

resonated at 2.88 ppm and appeared as a double triplet with coupling constants of 10.0 and 1.9 Hz. The larger coupling constant arose from coupling with the isopropyl proton, which fell in the region 1.51-1.31 ppm; while the smaller coupling constant arose from long-range coupling with the α-CH_2 of the butyl group, which resonated at 2.17 ppm and appeared as a triple doublet with coupling constants of 6.9 and 1.9 Hz. The two protons of the α-CH_2 of the propyl group were diastereotopic and resonated at 2.46 and 2.32 ppm respectively and both appeared as double double doublets with coupling constants of 12.2, 7.8 and 6.5 ppm. The two germinal methyl groups were also inequivalent and both appeared as doublet with coupling constants of 6.6 Hz. The signals in the ^{13}C NMR spectrum also fit well with the proposed structure.

2.4.4 Silver nitrate-induced cyclisation.

Silver nitrate-induced cyclisation of propargylic hydrazines **143** and **144** was carried out as described in section 2.3.4. Thus, treatment of the crude propargylic hydrazine **143** with 0.15 equivalents of 10% w/w silver nitrate on silica gel gave a mixture of the 4,5-dihydropyrazole **145** and the pyrazole **146**, which could be separated by column chromatography giving the dihydropyrazole **145** and the pyrazole **146**, in 50% and 30% isolated yield respectively (Scheme 2.34). Similarly, treatment of the crude propargylic hydrazine **144** with 0.12 equivalents of 10% w/w silver nitrate on silica gel gave a mixture of the 4,5-dihydropyrazole **147** and the pyrazole **148** (Scheme 2.35). Again, purification via column chromatography gave the dihydropyrazole **147** and the pyrazole **148**, in 32% and 29% isolated yield respectively, starting from the *N*-nitrosoamine **141**.



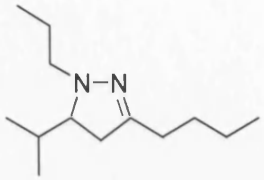
143 **145** **146**

Scheme 2.34

The spectroscopic data obtained for the dihydropyrazoles **145** and **147**, and the py
and **148** were consistent with those reported in section 2.3.4. For example, the
spectrum (Figure 2.13) of the dihydropyrazole **145** showed the 5-ring proton reson
ppm and appeared as a double double doublet with coupling constants of 12.5, 9.9
One of the 4-CH_2 ring protons resonated at 2.37 ppm and appeared as a double d
coupling constants of 16.4 and 9.9 Hz, while the other was obscured by the α-CH_2
group which fell in the same region, 2.30-2.15 ppm. The ^{13}C NMR spectrum (F
showed the quaternary carbon and the 5-CH resonated at 154.8 and 71.8 ppm respe
^{1}H NMR spectrum (Figure 2.15) of the pyrazole **146** showed the 4-ring proton reson
ppm and appeared as a singlet. The ^{13}C NMR spectrum (Figure 2.16) showe
quaternary carbons resonated at 152.1 and 149.5 ppm respectively, and the 4-CH r
99.7 ppm.

^{1}H NMR Spectrum

3-Butyl-4,5-dihydro-5-isopropyl-1-propyl-1*H*-pyrazole (145)



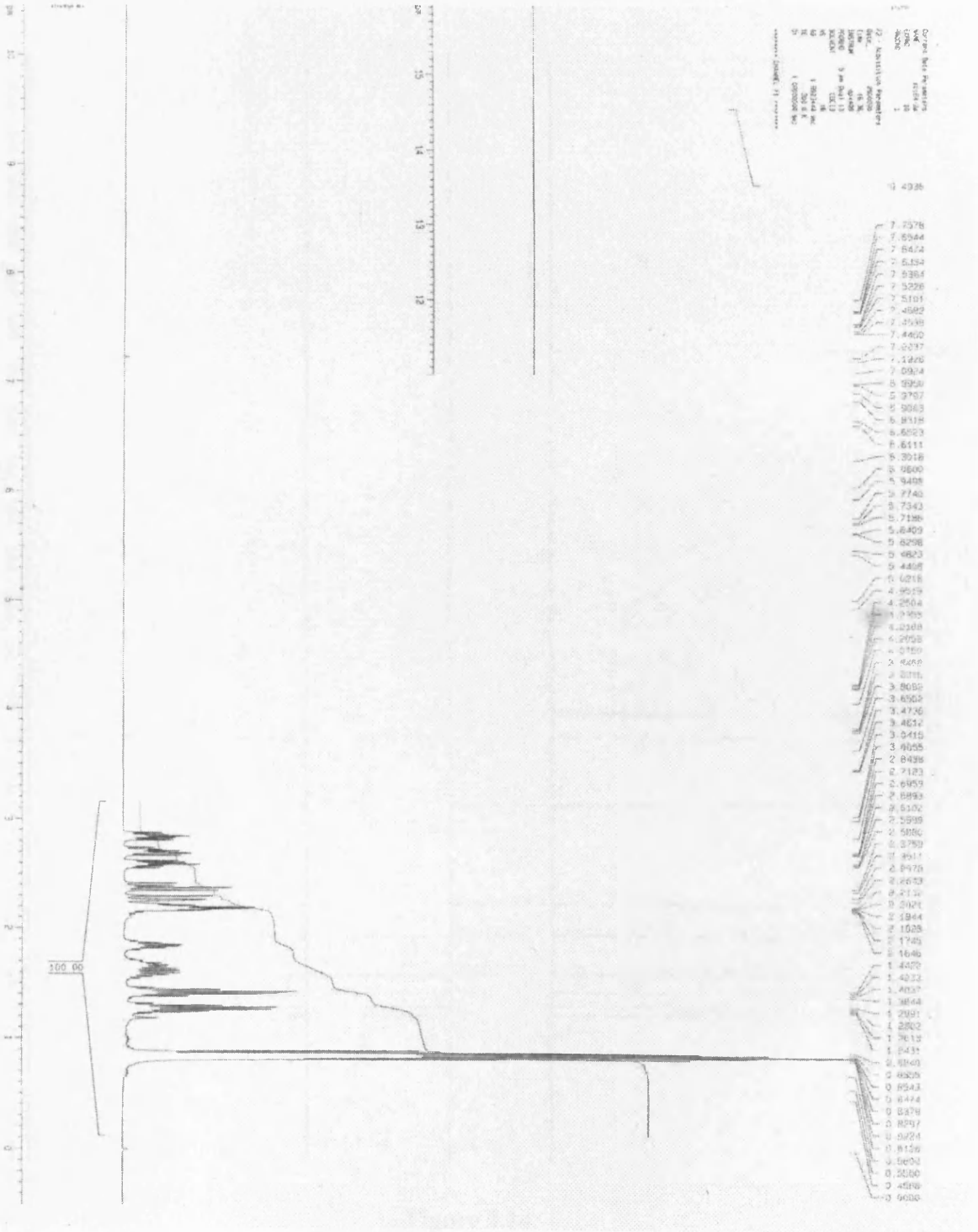
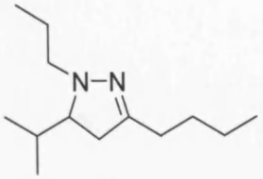


Figure 2.13

^{13}C DEPT NMR Spectrum

3-Butyl-4,5-dihydro-5-isopropyl-1-propyl-1*H*-pyrazole (145)



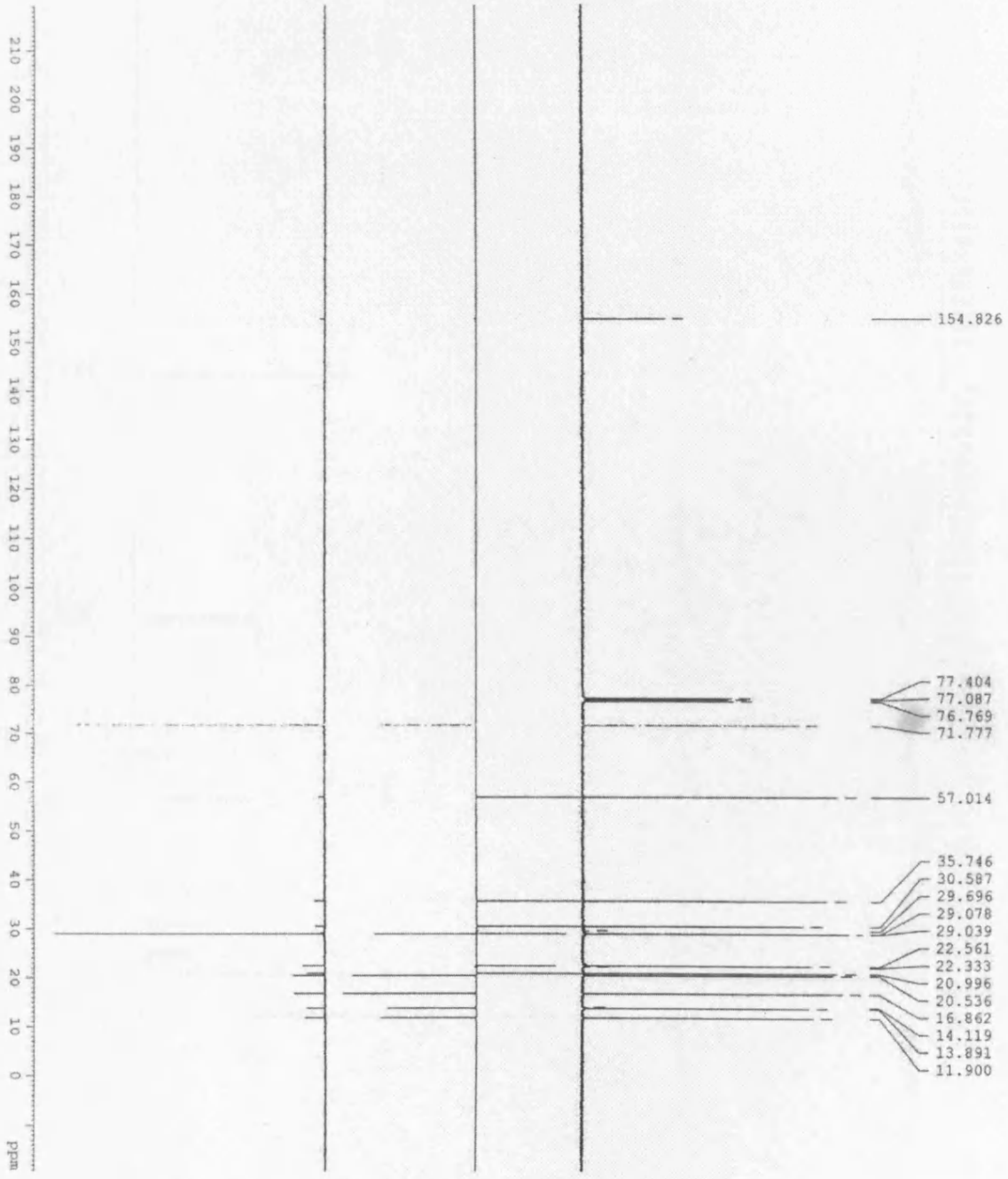
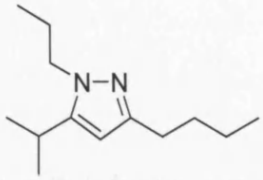


Figure 2.14

^{1}H NMR Spectrum

3-Butyl-5-isopropyl-1-propyl-1*H*-pyrazole (146)



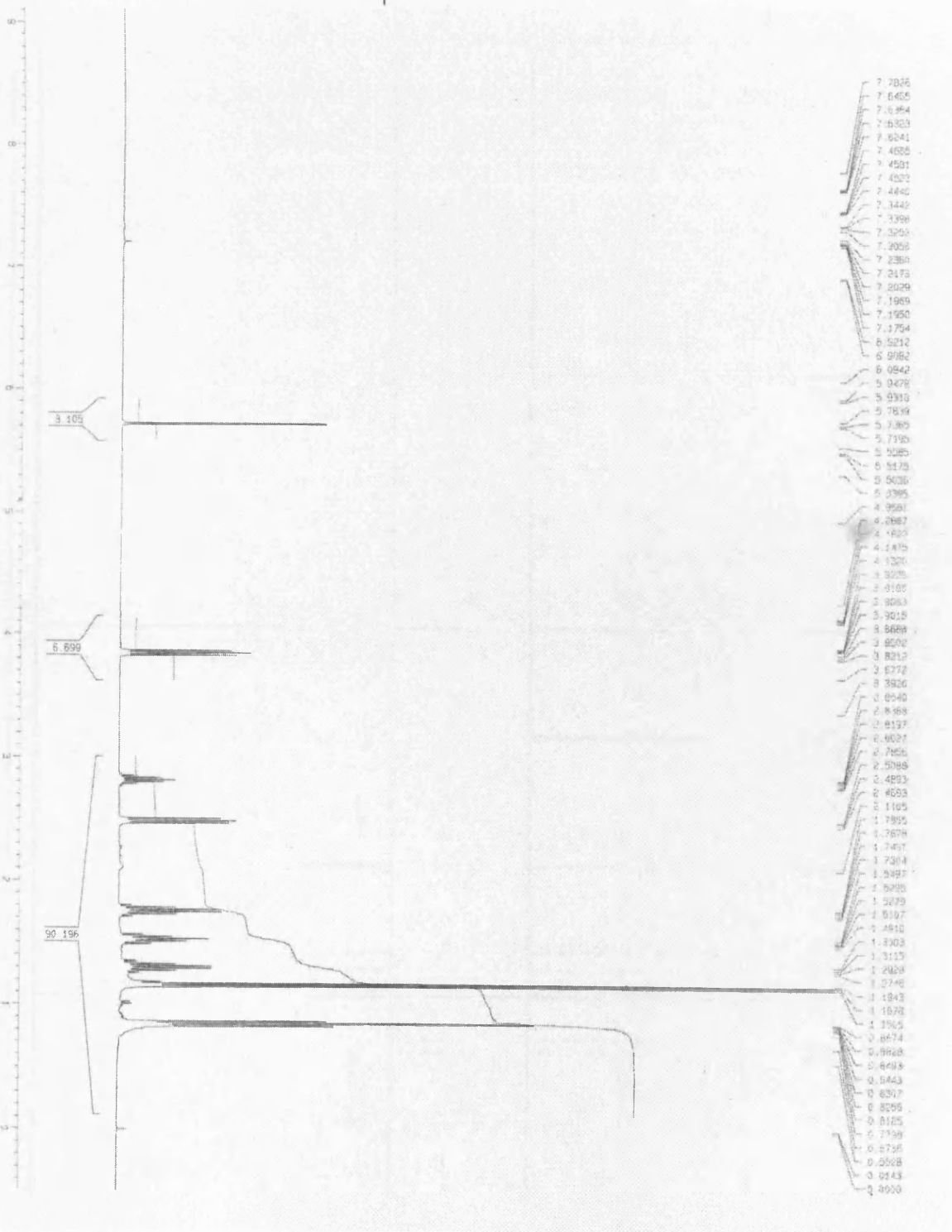


Figure 2.15

^{13}C DEPT NMR Spectrum

3-Butyl-5-isopropyl-1-propyl-1*H*-pyrazole (146)

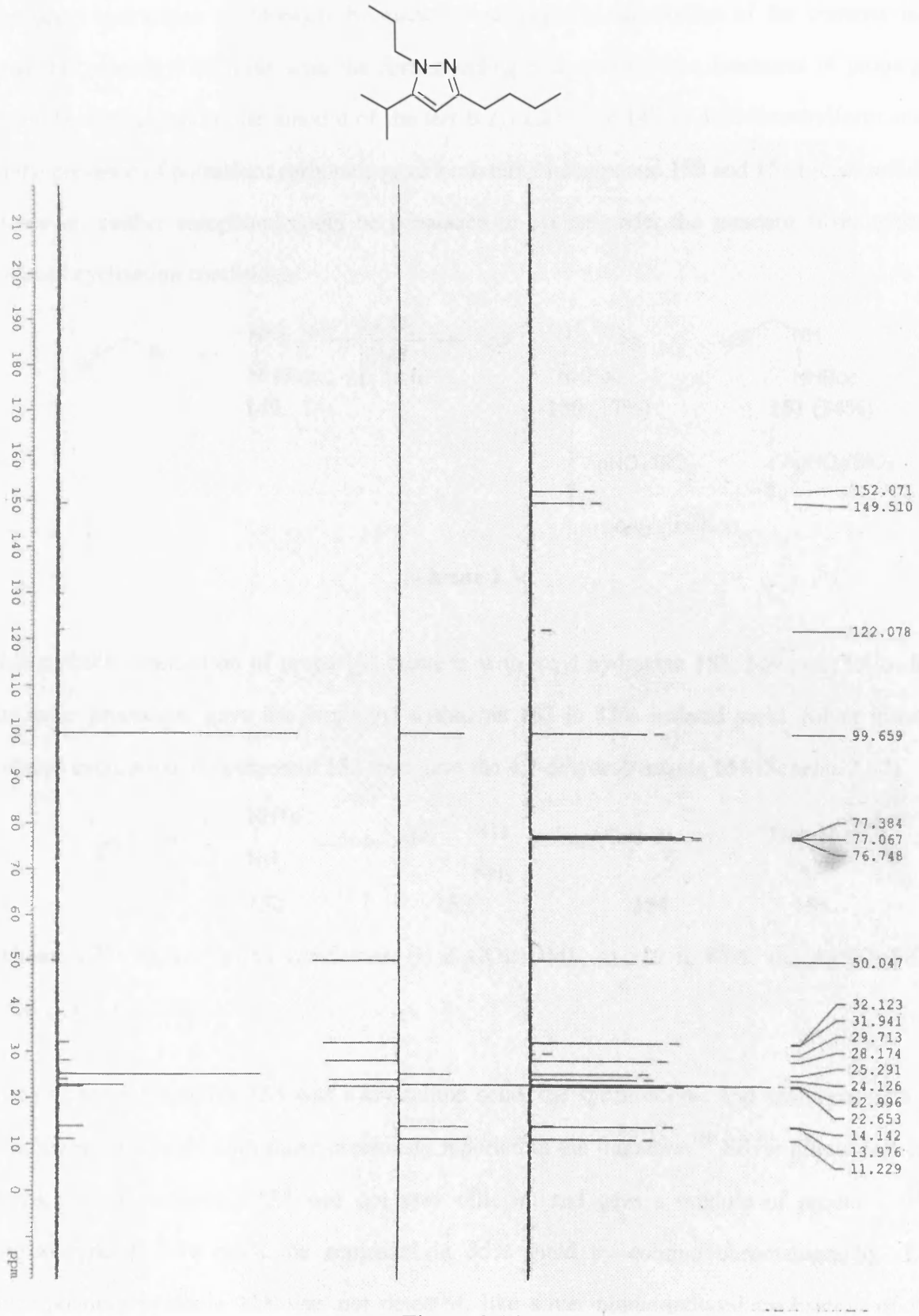
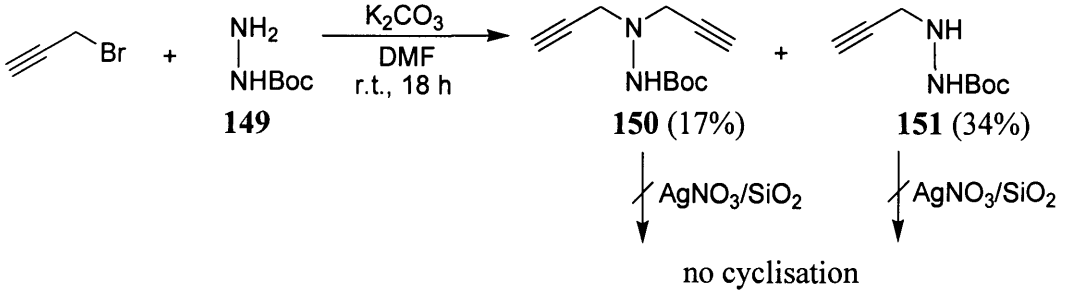


Figure 2.16

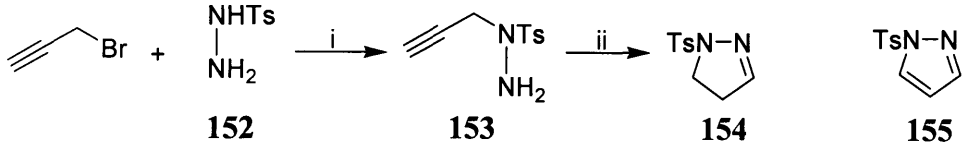
2.5 Cyclisation of propargyl hydrazine.

Propargyl hydrazines could easily be made by nucleophilic substitution of the commercially available propargyl bromide with the corresponding hydrazines. Thus, treatment of propargyl bromide with an equimolar amount of the *tert*-butyl carbazate **149** in *N*,*N*-dimethylformamide in the presence of potassium carbonate gave a mixture of compound **150** and **151** (Scheme 2.36). However, neither compound could be persuaded to cyclise under the standard silver nitrate-induced cyclisation conditions.



Scheme 2.36

Nucleophilic substitution of propargyl bromide with tosyl hydrazine **152**, however, following the same procedure, gave the propargyl hydrazine **153** in 83% isolated yield. Silver nitrate-induced cyclisation of compound **153** then gave the 4,5-dihydropyrazole **154** (Scheme 2.37).



Scheme 2.37 *Reagents and conditions*: (i) K_2CO_3, DMF, r.t., 19 h, 83%; (ii) $AgNO_3/SiO_2$, CH_2Cl_2, r.t., 6 h, 35%.

The propargyl hydrazine **153** was a crystalline solid, the spectroscopic and analytical data of which were in accord with those previously reported in the literature.[140] Silver nitrate-induced cyclisation of compound **153** was not very efficient and gave a mixture of products. The dihydropyrazole **154** could be separated in 35% yield by column chromatography. The corresponding pyrazole **155** was not detected, like silver nitrate-induced cyclisation of the

propargylic benzyloxycarbonylhydrazine **103**, and unlike cyclisation of other propargylic alkyl- or allylhydrazine precursors, where a mixture of dihydropyrazoles and the corresponding pyrazoles were obtained. The ^{1}H NMR spectrum of the dihydropyrazole **154** showed the 3-ring proton resonance at 6.94 ppm and appeared as a triplet with coupling constant of 1.6 Hz. This coupled to the 4-CH_2 ring protons, which resonated at 2.68 ppm and appeared as a triple doublet with coupling constants of 9.6 and 1.6 Hz. The 5-CH_2 ring protons resonated at 3.42 ppm and appeared as a triplet with coupling constant of 9.6 Hz due to coupling to the 4-CH_2. The ^{13}C NMR spectrum showed the characteristic resonance for the 3-CH at 150.2 ppm, and resonance for the 5-CH_2 and 4-CH_2 at 46.5 and 34.2 ppm, respectively.

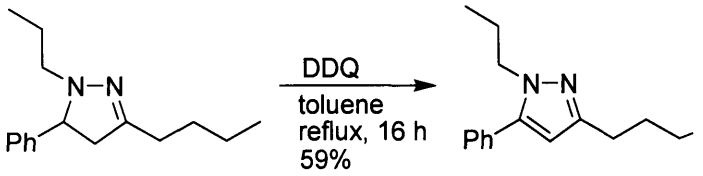
The different regioselectivity for the nucleophilic substitution of propargyl bromide with *tert*-butyl carbazate **149** and tosyl hydrazine **152** suggested that the tosyl group was more electron-withdrawing than the *tert*-butoxycarbonyl group. Even a weak base potassium carbonate could deprotonate the tosyl hydrazine **152**, and the more nucleophilic anion then attacks the propargyl bromide to give the propargyl hydrazine **153**. As for *tert*-butyl carbazate **149**, it was the more nucleophilic NH_2 group that attacked the propargyl bromide, and subsequent de-protonation of the adduct with potassium carbonate then gave the propargyl hydrazine **151**. The nitrogen of compound **151** was even more nucleophilic than that of **149**, though sterically hindered, and a second nucleophilic substitution took place to give compound **150**. Silver nitrate-induced cyclisation did not occur for compounds **150** and **151** maybe because the Boc protected nitrogen was not nucleophilic enough; attempted deprotection was unsuccessful.

2.6 Further study.

2.6.1 Oxidation.

a) Oxidation of 4,5-dihydropyrazoles.

4,5-Dihydropyrazole **119** could be oxidized to the corresponding pyrazole **120** in the presence of three equivalents of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing toluene in 59% isolated yield (Scheme 2.38).



119 **120**

Scheme 2.38

b) Effect of reaction conditions on the ratio of silver nitrate-induced cyclisation products.

Silver nitrate-induced cyclisation of propargylic hydrazine **103** gave 4,5-dihydropyrazole **104** (Scheme 2.17), cyclisation of propargyl hydrazine **153** gave 4,5-dihydropyrazloe **154** (Scheme 2.37), and cyclisation of propargylic hydrazine **116** gave pyrazole **121** (Scheme 2.20), respectively. Cyclisation of all the other propargylic hydrazines gave a mixture of 4,5-dihydropyrazole and pyrazole. Using propargylic hydrazine **144** as an example, the relationship between the reaction conditions and the ratio of the cyclisation products **147** and **148** was studied (Scheme 2.35, Table 2.1, Figure 2.17) to sort out the reasons for dihydropyrazole oxidation. Ratio of the dihydropyrazole **147** and the pyrazole **148** was measured according to the integration of the ^{1}H NMR spectrum of the crude products.

^{1}H NMR Spectrum

Mixture of 4,5-dihydro-5-isopropyl-3-phenyl-1-propyl-1*H*-pyrazole (147) and 5-isopropyl-3-phenyl-1-propyl-1*H*-pyrazole (148).

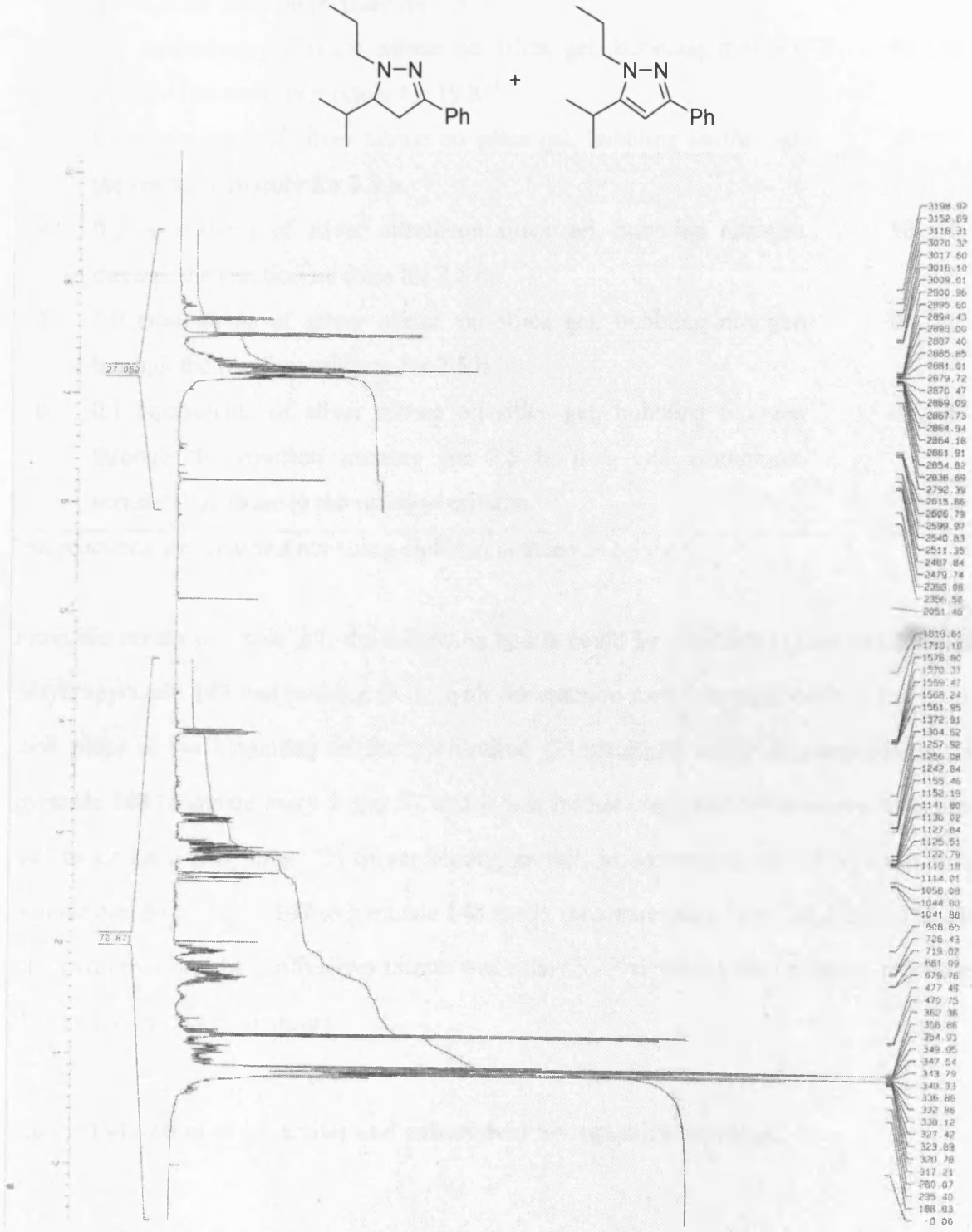


Figure 2.17

Table 2.1 *Ratio of 4,5-dihydropyrazole **147** and pyrazole **148** on different reaction conditions.*

entry	Reaction Conditions[a]	**147 (%): 148(%)**
1	0.1 equivalents of silver nitrate on silica gel, bubbling nitrogen through the reaction mixture for 2.5 h.	67 : 33
2	0.1 equivalents of silver nitrate on silica gel, bubbling nitrogen through the reaction mixture for 19 h.	67 : 33
3	0.1 equivalents of silver nitrate on silica gel, bubbling air through the reaction mixture for 2.5 h.	50 : 50
4	0.3 equivalents of silver nitrate on silica gel, bubbling nitrogen through the reaction mixture for 2.5 h.	50 : 50
5	1.0 equivalents of silver nitrate on silica gel, bubbling nitrogen through the reaction mixture for 2.5 h.	0 : 100
6	0.1 equivalents of silver nitrate on silica gel, bubbling nitrogen through the reaction mixture for 2.5 h, then add ammonium cerium(IV) nitrate to the reaction mixture.	0 : 100

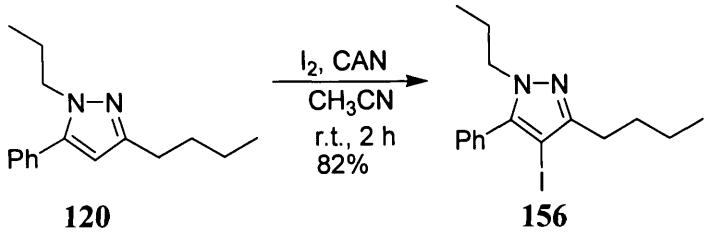
[a] all reactions were carried out using dichloromethane as solvent.

From the results of Table 2.1, the following points could be obtained: (1) the oxidation of the dihydropyrazole **147** had nothing to do with the reaction time (compare entry 1 and 2), and it took place at the beginning of the cyclisation; (2) air could oxide dihydropyrazole **147** to pyrazole **148** (compare entry 1 and 3), and it was further confirmed by exposure of compound **147** to air for a long time; (3) Silver nitrate, as well as ammonium cerium(IV) nitrate could oxidise dihydropyrazole **147** to pyrazole **148** easily (compare entry 1, 4, 5 and 6). (4) Oxidation of dihydropyrazole **147** with silver nitrate was catalytic. Presumably the oxidation proceeded by Ag^+ catalysed loss of hydrogen.

2.6.2 Iodination of pyrazoles and subsequent Sonogashira coupling.

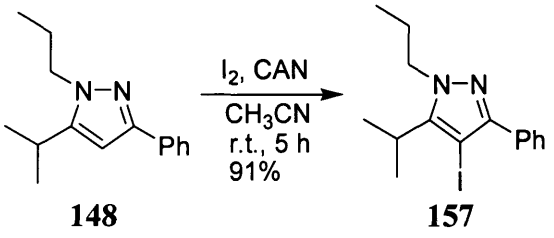
As is mentioned in the beginning, the initial idea of the project was a 5-*endo*-dig iodocyclisation for the synthesis of pyrazole derivatives. We then questioned if it was possible to access iodopyrazoles by iodination of the corresponding pyrazole derivatives? Fortunately, oxidative

iodination[141] of pyrazoles **120** and **148** using elemental iodine in the presence of ammonium cerium(IV) nitrate (CAN) as the *in situ* oxidant gave the iodopyrazoles **156** and **157** in 82% and 91% yield, respectively (Schemes 2.39, 2.40).



120 **156**

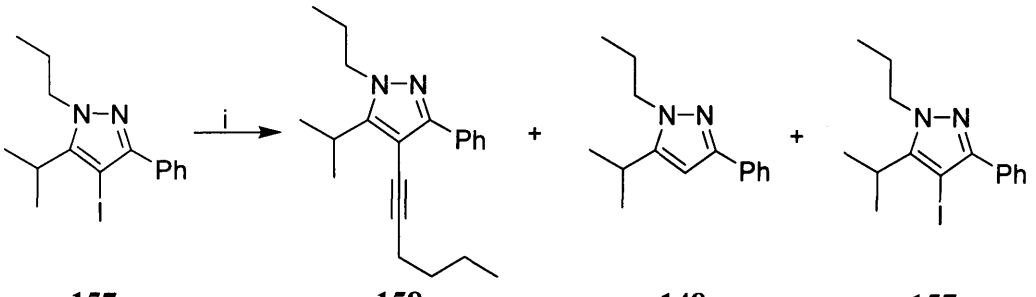
Scheme 2.39



148 **157**

Scheme 2.40

The most convincing evidence of iodination came from the ^{13}C NMR signals. The characteristic pyrazolic C-4 of **156** and **157** appeared at 62.3 and 56.5 ppm respectively, some 42.6 and 42.3 ppm upfield shift than the starting pyrazoles, due to the strong shielding effect of the iodine. Sonogashira coupling[142,143] of iodopyrazole **157** with hexyne gave an inseparable mixture of the desired product **158**, the pyrazole **148** and the starting substrate **157** in a mole ratio of 2:1:1 in > 90% overall yield (Scheme 2.41).



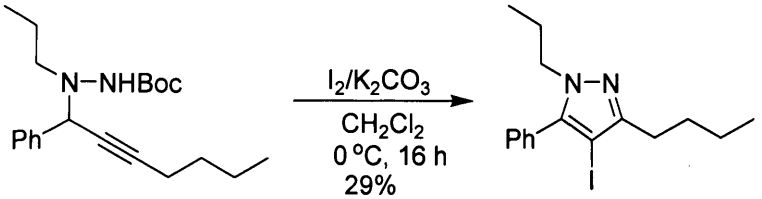
157 **158** **148** **157**

Scheme 2.41 *Reagents and conditions*: (i) 1-hexyne, $PdCl_2(PPh_3)_2$, CuI, Et_3N, reflux, 30 h.

2.7 Other cyclisations.

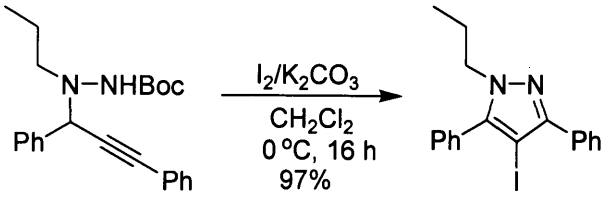
2.7.1 Iodocyclisation: direct formation of iodopyrazoles – the original idea.

5-*Endo*-dig iodocyclisation of propargylic hydrazines **112** and **113** gave iodopyrazoles **156** and **159**, respectively (Schemes 2.42, 2.43). The iodocyclisation was carried out with three equivalents of iodine in the presence of three equivalents of potassium carbonate in dry dichloromethane.



112 **156**

Scheme 2.42



113 **159**

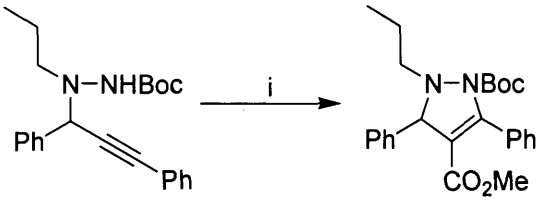
Scheme 2.43

The yield of iodopyrazole **159** was excellent, while the isolated yield of iodopyrazole **156** was only 29%. Another major by-product was separated from the iodocyclisation of the propargylic hydrazine **112**; however, we could not deduce its structure. The spectroscopic and analytical data obtained for iodopyrazole **156** were identical to those displayed by the oxidative iodination product.

We assume that the presence of a base may have caused the decarboxylation, although the mechanism is not yet understood.

2.7.2 Palladium-catalysed cyclisation.

Finally, palladium-catalysed cyclisation[144] of propargylic hydrazine **113** in the presence of carbon monoxide gave 2,3-dihydropyrazole **160** in 15% isolated yield (Scheme 2.44).



113 **160**

Scheme 2.44 *Reagents and conditions*: (i) CO, $PdCl_2$, $CuCl_2$, K_2CO_3, NaOAc, MeOH, r.t., 48 h, 15%.

The structure of dihydropyrazole **160** could be confirmed by comparing its spectrum with those of dihydropyrazole **126** (Figure 2.9). A strong absorption at 1730 cm^{-1} characteristic for carbonyl group appeared in the IR spectrum. The ^1H NMR spectrum of dihydropyrazole **160** (Figure 2.18) showed that the doublet at 5.63 ppm for the 4-ring proton of the dihydropyrazole **126** disappeared; the 3-ring proton changed from a doublet to singlet. The new methyl group resonated at 3.50 ppm and appeared as a singlet. The tertiary carbon at 112.0 ppm disappeared; two quaternary carbons at 165.1 and 113.4 ppm and one primary carbon at 51.7 ppm appeared in the ^{13}C NMR spectrum.

^{1}H NMR spectrum

1-*tert*-Butyl, 4-methyl 2,3-dihydro-3,5-diphenyl-2-propylpyrazole-1,4-dicarboxylate (160)

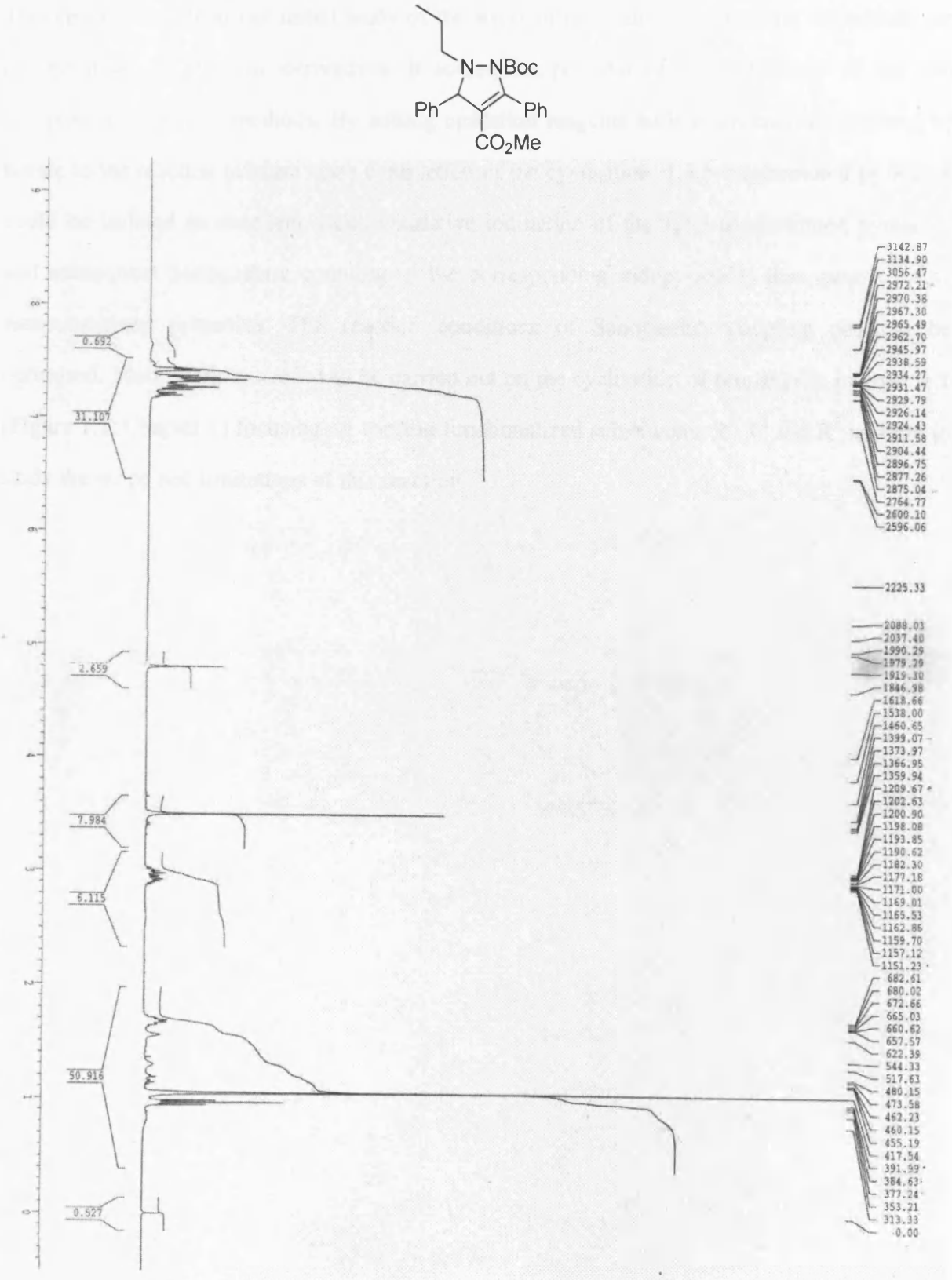


Figure 2.18

2.8 Conclusion.

This chapter described our initial study of the silver nitrate-induced 5-*endo*-dig cyclisation for the syntheses of pyrazole derivatives. It solved the problem of regioselectivity of the two components synthesis methods. By adding oxidation reagents such as ammonium cerium(IV) nitrate to the reaction mixture upon completion of the cyclisation, 1,3,5-trisubstituted pyrazoles could be isolated in excellent yield. Oxidative iodination of the 1,3,5-trisubstituted pyrazoles and subsequent Sonogashira coupling of the corresponding iodopyrazoles then gave 1,3,4,5-tetrasubstituted pyrazoles. The reaction conditions of Sonogashira coupling need to be optimised. More work is needed to be carried out on the cyclisation of propargylic hydrazine **1** (Figure 1.1, Chapter 1) focusing on varying functionalized substituents R^1 R^2 and R^3 in order to study the scope and limitations of this reaction.

Chapter 3

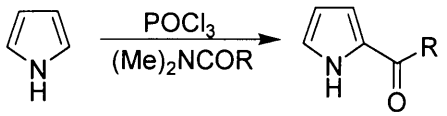
Results and Discussion – Pyrrole acylation towards the construction of the macrocyclic core of roseophilin.

This chapter describes a new method for the acylation of *N*-tosylpyrroles using carboxylic acids and trifluoroacetic anhydride (TFAA), which gives the corresponding 2-acyl-*N*-tosylpyrroles regioselectively. When applied to *α,β*-unsaturated acids, an *in situ* Nazarov cyclisation following the acylation gives annulated pyrroles **2** (Figure 1.2, Chapter 1), thus providing a very efficient method for the construction of the macrocyclic core of roseophilin **3** (Figure 1.3, Chapter 1).

3.1 Introduction - Previous methods for pyrrole acylation.

3.1.1 By Vilsmeier reaction.

Because of their very high reactivity towards electrophilic substitution and general sensitivity to acid-catalysed polymerisation, there are few very efficient methods available for the selective acylation of pyrroles; mixtures of 2- and 3-acylated products are often obtained. The Vilsmeier reaction, with phosphorus oxychloride and *N,N*-dimethyl carboxamides, is perhaps the most proven method for the synthesis of 2-acylpyrroles **162**, uncontaminated by significant amounts of the corresponding 3-acyl isomers or *bis*-acyl derivatives (Scheme 3.1).[145,146]

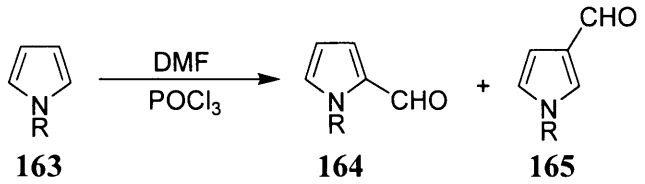


161 **162**

R = H, Me, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_9H_{19}, *n*-$C_{11}H_{23}$, Ph.

Scheme 3.1

For *N*-substituted pyrroles **163**, however, if the R group is a very large one, such as iso-propyl or *tert*-butyl, the acylation can occur at the normally unfavoured 3-position (Scheme 3.2).[147]



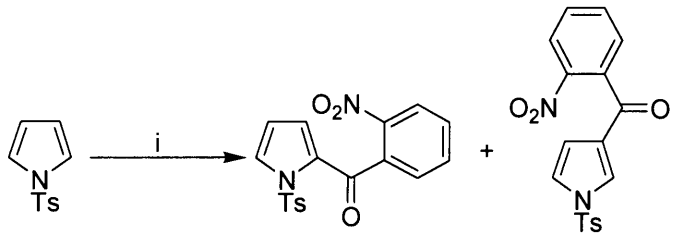
163 **164** **165**

1) R = Me, 95% for 164a, 0% for 165a;
2) R = *i*-Pr, 8% for 164b, 71% for 165b;
3) R = *t*-Bu, 5% for 164c, 64% for 165c.

Scheme 3.2

3.1.2 Direct electrophilic substitution of pyrroles.

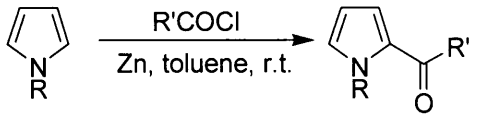
This is usually carried out with acyl chlorides or acid anhydrides in the presence of a Lewis acid.[148-150] Normally, a mixture of 2- and 3-acylpyrroles is obtained and the ratio of the products depend greatly on the Lewis acids used. As shown in Scheme 3.3, if stannic chloride is used as the catalyst, compound **167** and **168** were isolated in 56% and 11% yields, respectively; however, the use of aluminium trichloride gave the same compounds **167** and **168** but in 13% and 52% yields, respectively.



166 **167** **168**

Scheme 3.3 *Reagents and conditions*: i) 2-$NO_2C_6H_4COCl$, $ClCH_2CH_2Cl$, catalyst, 22 °C.

A more recent report[151] has outlined a general method for the selective 2-acylation of a range of pyrrole derivatives **163** (R ≠ H), as well as of pyrrole itself, by exposure to an acid chloride and zinc powder in toluene. Yields are generally 80% or better from these highly regioselective acylations (Scheme 3.4).

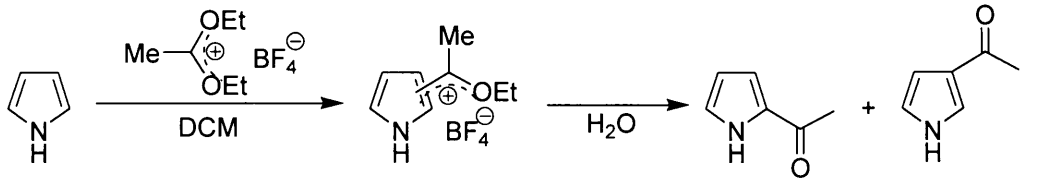


163 **169**

R = H, Bn, Boc, Ts; R' = alkyl, aryl.

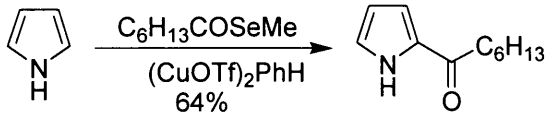
Scheme 3.4

Other acylation methods include condensation of pyrrole **161** with dialkoxycarbenium tetrafluoroborates, followed by hydrolysis of the product **170** to give a mixture of acylpyrroles **171** and **172** (Scheme 3.5),[152] or with selenol esters in the presence of a complex of copper(I) triflate and benzene to give 2-acylpyrrole **173** (Scheme 3.6).[153]



161 **170** **171** (3%) **172** (14%)

Scheme 3.5

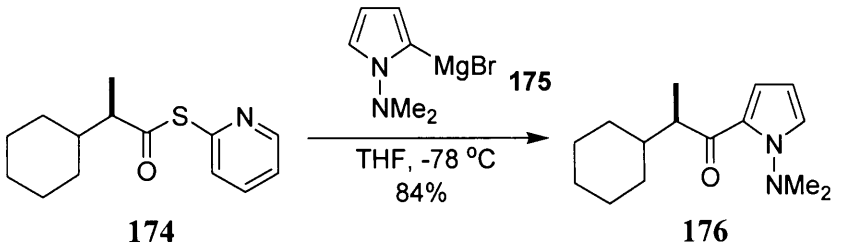


161 **173**

Scheme 3.6

3.1.3 Acylation of pyrryl Grignard reagents or 2-lithiated pyrroles.

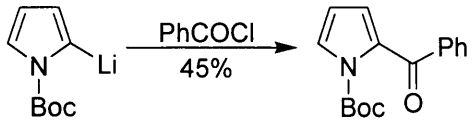
Condensation of pyrryl Grignard reagent **175** with pyridinethiol ester **174** produced the 2-acylpyrrole **176** exclusively in 84% isolated yield (Scheme 3.7). This route was reported by Martinez *et al.*.[154] The same method was also applied by Nicolaou *et al.*[155] during their total synthesis of the ionophore antibiotic X-14547A.



174 176

Scheme 3.7

A less efficient route was reported by Hasan *et al.*.[156] In this, 2-lithiated pyrrole **177**, obtained by treatment of the corrresponding *N*-protected pyrrole with lithium 2,2,6,6-tetramethylpiperidide, was trapped with benzoyl chloride to give the 2-acylpyrrole **178** in 45% isolated yield (Scheme 3.8).

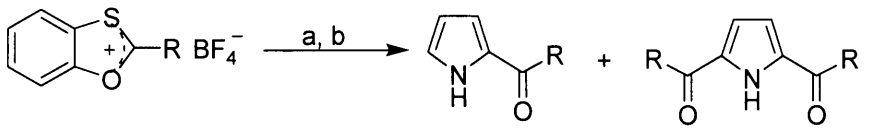


177 **178**

Scheme 3.8

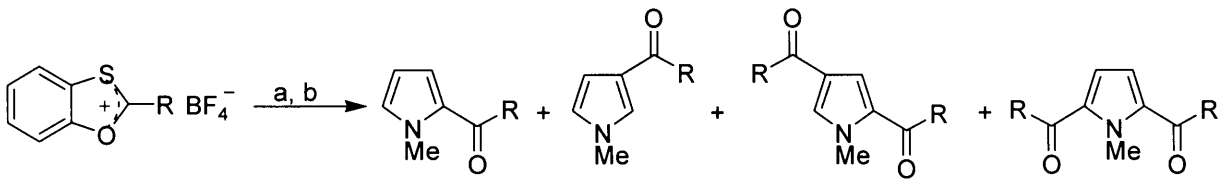
3.1.4 Other methods.

Barbero *et al.*[157] have reported 1,3-benzoxathiolium tetrafluoroborates **179** as masked acylating reagents, and studied the acylation of pyrrole and *N*-methylpyrrole with these. The reactions on pyrrole were regiospecific. 2-Acylpyrroles **162** (R= aryl, alkyl) or 2,5-diacyl-pyrroles **180** (R = aryl, alkyl) and a mixture of both were obtained according to the molar ratio of the reagents (Scheme 3.9). The reactions on *N*-methylpyrrole were not regioselective, and both α- and β-positions were attacked. So, depending on the molar ratio of the reagents, 2-acyl-*N*-methylpyrroles **181**, 3-acyl-*N*-methylpyrroles **182**, 2,4-diacyl-*N*-methylpyrroles **183** and/or 2,5-diacyl-*N*-methylpyrroles **184** were obtained (Scheme 3.10).



179 **162** **180**

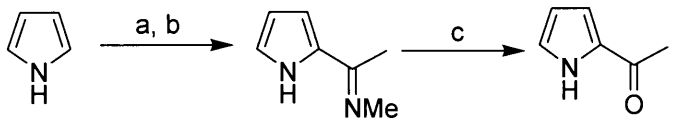
Scheme 3.9 *Reagents and conditions*: (a) pyrrole, pyridine, CH_3CN, r.t.; (b) HgO/35% aqueous HBF_4, THF.



179 **181** **182** **183** **184**

Scheme 3.10 *Reagents and conditions*: (a) *N*-methylpyrrole, pyridine, CH_3CN, r.t.; (b) HgO/ 35% aqueous HBF_4, THF.

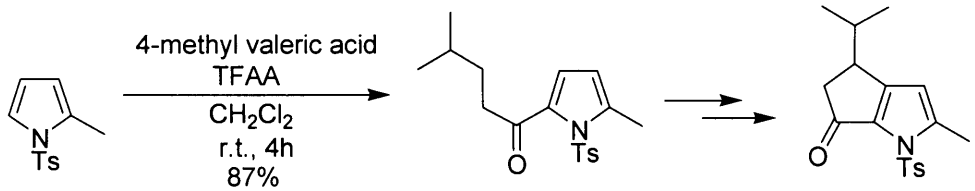
N-Methylacetonitrilium tetrafluoroborate has also been used as an acylating reagent.[158] Thus, treatment of pyrrole with this reagent produced a mixture of imine **185** and the corresponding tetrafluoroborate salt, which could be converted into the imine **185** in almost quantitative yield using 2M aqueous sodium hydroxide. When the imine **185** was heated under reflux with aqueous sodium acetate, 2-acetylpyrrole **171** was isolated in 92% yield (Scheme 3.11).



161 **185** **171**

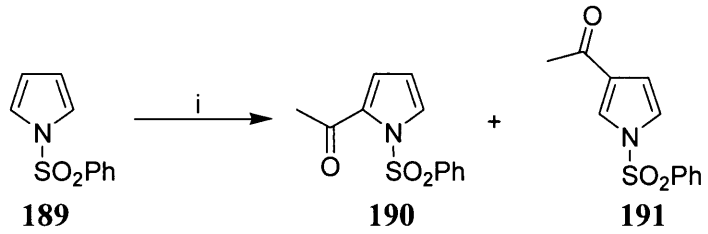
Scheme 3.11 *Reagents and conditions*: (a) $MeCN^+MeBF_4^-$, DCM, -30 °C - -20 °C, 16h; (b) 2M NaOH, 0 °C, 94%; (c) aqueous NaOAc, reflux, 92%.

Clearly, an obvious way to moderate the excessive reactivity of a 'free' pyrrole is to derivatise it by placing an electron withdrawing group on the nitrogen. During her studies on the synthesis of the bicyclic ring system **188** of roseophilin **3**, Fagan[159] synthesized the 2-acylpyrrole **187** in 87% yield by acylation of *N*-tosyl-2-methylpyrrole **186** using 4-methylvaleric acid and trifluoroacetic anhydride (Scheme 3.12).



Scheme 3.12

This method was first applied by Kakushima *et al.*[150] for the regioselective synthesis of 2-acetylpyrrole **190**. Thus, treatment of 1-phenylsulfonylpyrrole **189** with a large excess of acetic acid and trifluoroacetic anhydride gave a mixture of the 2-acetylpyrrole **190** and the 3-isomer **191** in a ratio of 97.6:2.4; no trifluoroacylation product was detected (Scheme 3.13). This was the only reaction of the type ever reported by the authors and no other examples had been tried.

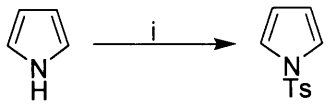


Scheme 3.13 *Reagents and conditions*: (i) $MeCO_2H$, TFAA, CH_2Cl_2, r.t., 2h, 100% combined yield.

Although unexplored by the above authors, this method could potentially be a much better general method for 2-acylation of deactivated pyrroles, as it avoids the necessity to preform the acid chloride, amide or anhydride of the acylating species. To investigate this method in more detail, we chose to use *N*-tosylpyrrole, 2-methyl-*N*-tosylpyrrole and a series of 2-aryl-*N*-tosylpyrroles as representative examples.

3.2 Synthesis of *N*-tosylpyrroles.

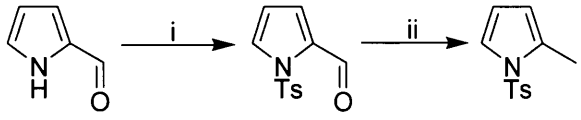
N-Tosylpyrrole **166** was obtained in 90% yield by treating the sodium salt of pyrrole with tosyl chloride (Scheme 3.14).



161 **166**

Scheme 3.14 *Reagents and conditions*: (i) Na, THF, reflux, 24 h, then add *Ts*Cl, r.t., 24 h, 90%.

2-Methyl-*N*-tosylpyrrole **186** was synthesized in two steps starting from commercially available pyrrole-2-carboxaldehyde **192**. Thus, protection of compound **192** with tosyl chloride gave 1-tosylpyrrole-2-carboxaldehyde **193** in 63% isolated yield, subsequent reductive deoxygenation[160] of which, using borane *tert*-butylamine complex and aluminium chloride, then gave compound **186** in 60% isolated yield (Scheme 3.15).

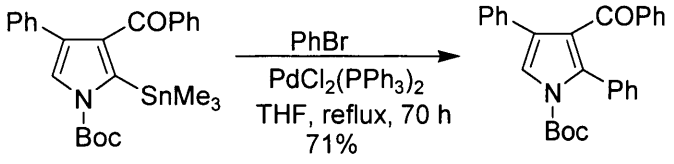


192 **193** **186**

Scheme 3.15 *Reagents and conditions*: (i) NaH, THF, r.t., 15 mins, then add TsCl, 1.5 h, 63%; (ii) $AlCl_3$, $(CH_3)_3CNH_2{\cdot}BH_3$, CH_2Cl_2, r.t., 15 mins, then add **193**, 3 h, 60%.

The synthesis of 2-arylpyrrole derivatives has been extensively reported in the literature.[161-167] Amongst these, palladium-catalysed cross-coupling reactions seemed to be most straight-forward and efficient.

The Stille[168] cross-coupling of the trimethylstannylpyrrole **194** with bromobenzene gave the corresponding 2-phenylpyrrole **195** in 71% yield (Scheme 3.16).[169]

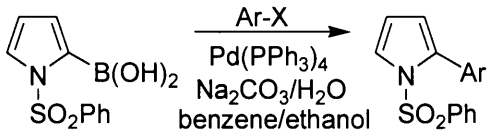


194 **195**

Scheme 3.16

Grieb and Ketcha[170] reported a synthesis of 2-aryl-*N*-(phenylsulfonyl)pyrroles **197** by a Suzuki cross-coupling of *N*-(phenylsulfonyl)pyrrole-2-boronic acid **196** with a variety of aryl halides

(Ar-X = PhBr, 4-$MeOC_6H_4I$, 4- $CH_3COC_6H_4Br$, 4-$NO_2C_6H_4I$, 1-Br-Naphth), which gave the 2-aryl derivatives **197a-e** in 39 - 91% yields (Scheme 3.17).

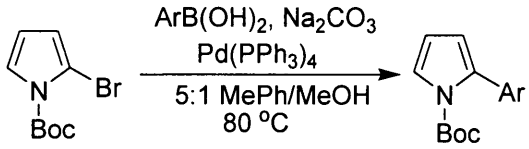


196 **197**

197a: Ar = Ph, 39%
197b: Ar = 1-Naph, 52%
197c: Ar = 4-$NO_2C_6H_4$, 91%
197d: Ar = 4-AcC_6H_4, 67%
197e: Ar = 4-$MeOC_6H_4$, 39%

Scheme 3.17

Good yields were obtained only with electron-poor aryl halides from the above Suzuki cross-coupling. In 1998, Burgess *et al.*[171] reported their Suzuki cross-coupling of bromopyrrole **198** with aryl boronic acids to give the corresponding 2-arylpyrroles **199a-d** in excellent yields (Scheme 3.18).



198 **199**

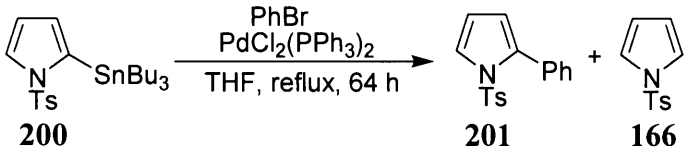
199a: Ar = Ph, 99%
199b: Ar = 1-Naphth, 93%
199c: Ar = 4-$MeOC_6H_4$, 90%
199d: Ar = 4-FC_6H_4, 99%

Scheme 3.18

This method was later applied by Knight *et al.*[172] for the cross-coupling of 2-bromo-*N*-tosylpyrrole. The yields were generally moderate.

In our hands, the Stille cross-coupling of 2-tributylstannyl-*N*-tosylpyrrole **200** with bromobenzene gave an inseparable mixture of the desired 2-phenyl-*N*-tosylpyrrole **201** and *N*-tosylpyrrole **166** in a 1:1 ratio (Scheme 3.19). However, Suzuki cross-coupling of 2-bromo-*N*-

tosylpyrrole **204** with arylboronic acids gave good to excellent yields of the corresponding 2-aryl-*N*-tosylpyrroles (see Scheme 3.22 in section 3.2.2).



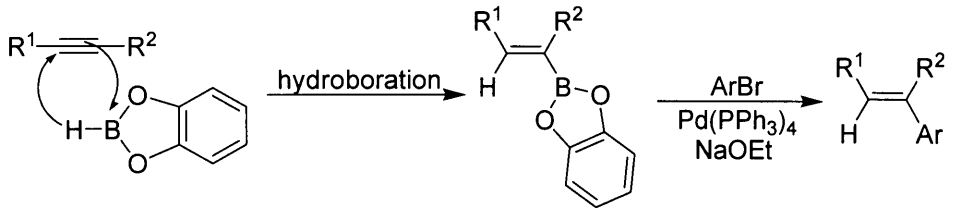
200 **201** **166**

Scheme 3.19

3.2.1 Introduction – The Suzuki cross-coupling reaction.

Since first being published in 1979, the palladium-catalysed Suzuki coupling[144] of a boronic acid with a halide or triflate has developed into one of the most important cross-coupling reactions. A very wide range of palladium(0) catalysts or precursors can be used for the cross-coupling reaction. $Pd(PPh_3)_4$ is most commonly used, but $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ with PPh_3 or other phosphine ligands are also efficient, since these combinations are stable to air and readily reduced to the active Pd(0) complexes with organometallics or the phosphines used in the cross-coupling.

The original version consisted of hydroboration of an alkyne with catecholborane, followed by palladium(0)-catalysed coupling of the resulting vinyl boronate with an aromatic iodide or bromide (Scheme 3.20). The hydroboration is generally regioselective for the less hindered position.



Scheme 3.20

Like many other coupling reactions, the mechanism of the Suzuki cross-coupling reaction involves oxidative addition-transmetalation-reductive elimination sequences. Oxidative addition of 1-alkenyl, 1-alkynyl, allyl, benzyl or aryl halides to a palladium(0) complex affords a stable

trans-σ-palladium(II) complex **S-1**. Transmetalation then affords intermediate **S-2** and reductive elimination of organic partners from **S-2** finally reproduces the palladium(0) complex (Figure 3.1).

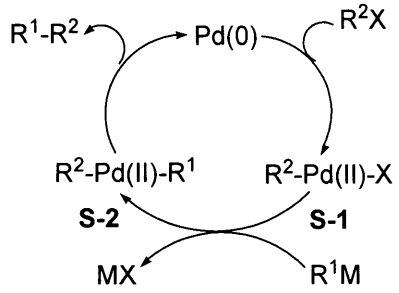
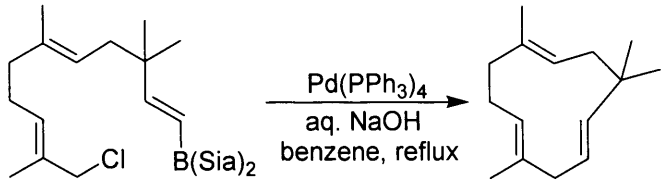


Figure 3.1 *A general catalytic cyclic for cross-coupling.*

Oxidative addition is often the rate-determining step in the catalytic cycle. The relative reactivity decreases in the order of I > OTf > Br >> Cl. Aryl and 1-alkenyl halides activated by the proximity of electron-withdrawing groups are more reactive to the oxidative addition than those with donating groups, thus allowing the use of chlorides such as 3-chloroenones for the cross-coupling reaction.

An additional base, such as sodium or potassium carbonate, phosphate, hydroxide or alkoxide is usually needed in the Suzuki coupling, which accelerates the transmetallation step by quaternization of organoboron compounds to give a more nucleophilic 'ate' complex.

The Suzuki cross-coupling reaction of organoboron reagents with organic halides or triflates represents one of the most straightforward methods for carbon-carbon bond formation. The reaction proceeds under mild conditions, being unaffected by the presence of water which is often used as a co-solvent, tolerating a broad range of functionality, and yielding non-toxic by-products. Conjugated dienes, biaryls and even vinylic sulfides have been synthesized using this method. Intramolecular coupling is also possible and can be used to make large rings such as humulene **203** (Scheme 3.21).

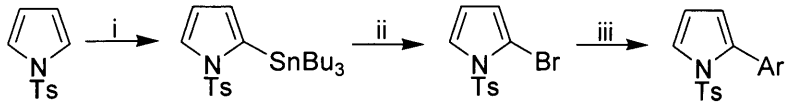


202 **203**

Scheme 3.21

3.2.2 Synthesis of 2-aryl-*N*-tosylpyrroles by Suzuki cross-coupling reaction.

As described above, 2-aryl-*N*-tosylpyrroles **201**, **205-207** were synthesized by the Suzuki cross-coupling of 2-bromo-*N*-tosylpyrrole **204** with the corresponding arylboronic acids. Unfortunately, direct bromination of *N*-tosylpyrrole **166** to give the required 2-bromopyrrole derivative **204**, while possible, gave very low yields. In 1995, Meijer *et al.*[173] reported that *N*-Boc-2-bromopyrrole **198** could be obtained in excellent yield by treating *N*-Boc-2-trimethylstannylpyrrole with *N*-bromosuccinimide. Accordingly, in the present study, the 2-bromopyrrole derivative **204** was obtained in two steps starting from *N*-tosylpyrrole **166** (Scheme 3.22). Thus, tributylstannylation of *N*-tosylpyrrole **166**, using *tert*-butyllithium and tributylstannyl chloride, occurred at the 2-position only to give the tributylstannylpyrrole derivative **200** in 70% isolated yield. The bromide-tin exchange of compound **200** was carried out with *N*-bromosuccinimide to give the bromopyrrole derivative **204** in 85% isolated yield. Suzuki coupling of compound **204** with the corresponding boronic acids then gave 2-aryl-*N*-tosylpyrroles **201**, **205**, **206** and **207** respectively. The spectroscopic data obtained for compounds **201**, **205** and **206** were in accord with those previously reported in the literature.[172]

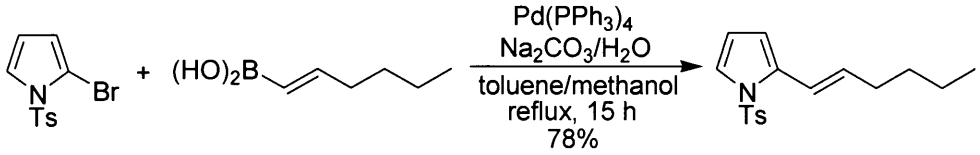


166 **200** **204**

201: Ar = Ph, 78%
205: Ar = 4-$MeOC_6H_4$, 78%
206: Ar = 3-$O_2NC_6H_4$, 96%
207: Ar = 2-Naphth, 74%

Scheme 3.22 *Reagents and conditions*: (i) *t*-BuLi, THF, -78 °C – r.t., 0.5 h, then add Bu_3SnCl, -78 °C, 0.5 h, then r.t., 18 h, 70%; (ii) NBS, THF, -78 °C, 40 mins, then 0 °C, 19 h, 85%; (iii) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3/H_2O, toluene/methanol, 80 °C 15 h.

Accordingly, 2-hexenyl-*N*-tosylpyrrole **209** was synthesized in 78% isolated yield by Suzuki cross-coupling under the above conditions (Scheme 3.23). The ^{1}H NMR spectrum of the 2-hexenylpyrrole derivative **209** showed the pyrrole-3 proton resonance at 6.31 ppm and appeared as a double doublet with coupling constants of 3.3 and 1.8 Hz. The pyrrole-4 proton resonated at 6.22 ppm and appeared as a triplet with coupling constant of 3.3 Hz. Unfortunately, the pyrrole-5 proton was obscured by the tosyl-2 and tosyl-6 protons which fell in the same region, 7.29-7.26 ppm. The α-proton of the hexenyl group resonated at 6.78 ppm and appeared as a double triplet with coupling constants of 15.7 and 1.2 Hz, the latter due to allylic coupling with the CH_2 adjactent to the double bond. The β-proton of the hexenyl group, resonated at 5.94 ppm, also appeared as a double triplet with coupling constants of 15.7 and 7.1 Hz.



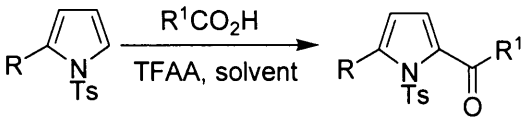
204 **208** **209**

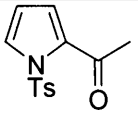
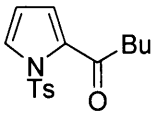
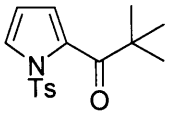
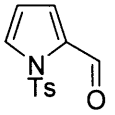
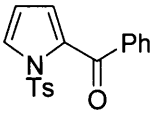
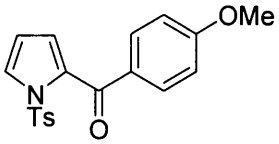
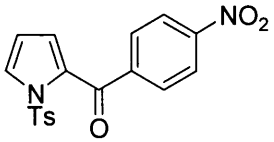
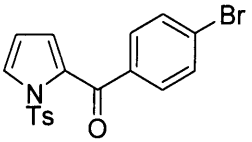
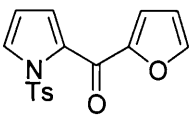
Scheme 3.23

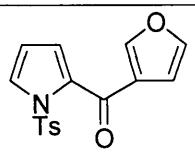
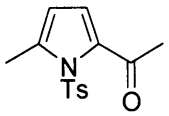
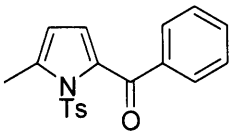
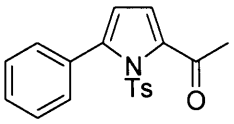
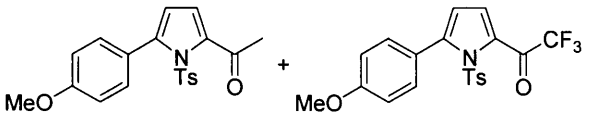
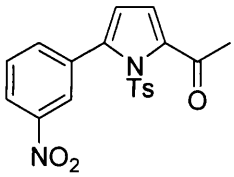
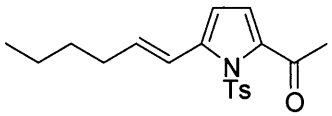
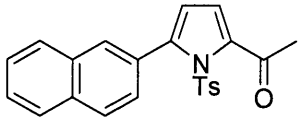
3.3 Acylation of *N*-tosylpyrroles.

As mentioned in Section 3.1.4 and shown in Scheme 3.13, acylation of 1-phenylsulfonylpyrrole **189** with a large excess of acetic acid and trifluoroacetic anhydride gave the 2-acetylpyrrole **190** together with a small amount of the 3-isomer **191** (2.4%). Our initial study showed that *N*-tosylpyrrole **166** could be acetylated using four equivalents of acetic acid in a mixture of trifluoroacetic anhydride and dichloromethane at ambient temperature to give the 2-acetylpyrrole **210** in 94% yield, while no corresponding 3-acetyl isomer was detected. Further studies showed that the acylation could be carried out using less carboxylic acid and trifluoroacetic anhydride. In some cases, when acylation proceeded slowly or did not work at ambient temperature, it was necessary to carry out the reaction under reflux in dichloromethane, or even 1,2-dichloroethane, with a higher boiling point (83 °C). The results using this method with a range of *N*-tosylpyrroles and carboxylic acids are collected in Table 3.1.

Table 3.1 *Acylation of N-tosylpyrroles by carboxylic acids and trifluoroacetic anhydride.*



Entry	Reagents and conditions	Products	Yield (%)[a]
1	R = H, CH_3CO_2H (4.0 eq), CH_2Cl_2, r.t., 29 h.	 **210**	94
2	R = H, $BuCO_2H$ (4.0 eq), CH_2Cl_2, r.t., 16 h, then reflux 7 h.	 **211**	82
3	R = H, *t*-$BuCO_2H$ (4.0 eq), $Cl(CH_2)_2Cl$, reflux, 119 h.	 **212**	72
4	R = H, HCO_2H (2.0 eq), CH_2Cl_2, reflux, 48 h.	 **193**	0[b]
5	R = H, $PhCO_2H$ (2.0 eq), $Cl(CH_2)_2Cl$, reflux, 70 h.	 **213**	84
6	R = H, 4-$MeOC_6H_4CO_2H$ (2.0 eq), CH_2Cl_2, r.t., 48 h.	 **214**	84
7	R = H, 4-$NO_2C_6H_4CO_2H$ (2.0 eq), $Cl(CH_2)_2Cl$, reflux, 19 h.	 **215**	0[b]
8	R = H, 4-$BrC_6H_4CO_2H$ (2.0 eq), $Cl(CH_2)_2Cl$, reflux, 19 h.	 **216**	0[b]
9	R = H, 2-furoic acid (2.0 eq), CH_2Cl_2, reflux, 48 h.	 **217**	0[b]

10	R = H, 3-furoic acid (2.0 eq), CH_2Cl_2, reflux, 48 h.	 **218**	0[b]
11	R = Me, CH_3CO_2H (3.6 eq), CH_2Cl_2, 0 °C, 2 h.	 **219**	83
12	R = Me, $PhCO_2H$ (4.0 eq), CH_2Cl_2, r.t., 42 h.	 **220**	96
13	R = Ph, CH_3CO_2H (2.0 eq), CH_2Cl_2, r.t., 43 h.	 **221**	74
14	R = 4-$MeOC_6H_4$, CH_3CO_2H (2.0 eq), CH_2Cl_2, r.t., 35 h.	 **222** + **223**	**222**: 40 **223**: 11
15	R = 3-$O_2NC_6H_4$, CH_3CO_2H (2.0 eq), $Cl(CH_2)_2Cl$, reflux, 48 h.	 **224**	58
16	R = 1-hexenyl, CH_3CO_2H (2.0 eq), CH_2Cl_2, r.t., 45 h.	 **225**	0[c]
17	R = 2-naphthyl, CH_3CO_2H (2.0 eq), CH_2Cl_2, r.t., 95 h.	 **226**	79

[a] Isolated yield. [b] Starting material recovered. [c] Polymers and a variety of decomposition products formed.

The regioselectivity of the acylation could be decided by comparison of the ^1H NMR spectra with similar compounds in the literature.[148c,150] For 3-acylpyrroles, the 2-Hs resonate in the region 7.5-8.0 ppm and appear as double doublets with coupling constants between 1.5 and 2.5 Hz, or as an apparent triplet with coupling constants of around 2.0 Hz; the 4-Hs resonate in the region 6.5-7.0 ppm and also appear as double doublets with one coupling constant of around 3.5

Hz, with the other between 1.5 and 2.0 Hz. The 5-Hs resonate in the region 7.0-7.5 ppm and appear as double doublets with one coupling constant of around 3.5 Hz, and the other between 2.0 and 2.5 Hz. For 2-acylpyrroles, the 3-Hs resonate in the region 6.5-7.2 ppm, the 5-Hs resonate in the region 7.5-8.0 ppm, and both appear as double doublets, with one coupling constant between 3.0 and 4.0 Hz, while the other is between 1.5 and 2.0 Hz. The 4-Hs resonate in the region 6.0-6.5 ppm and appear as an apparent triplet with a coupling constant of around 3.5 Hz (Figure 3.2).

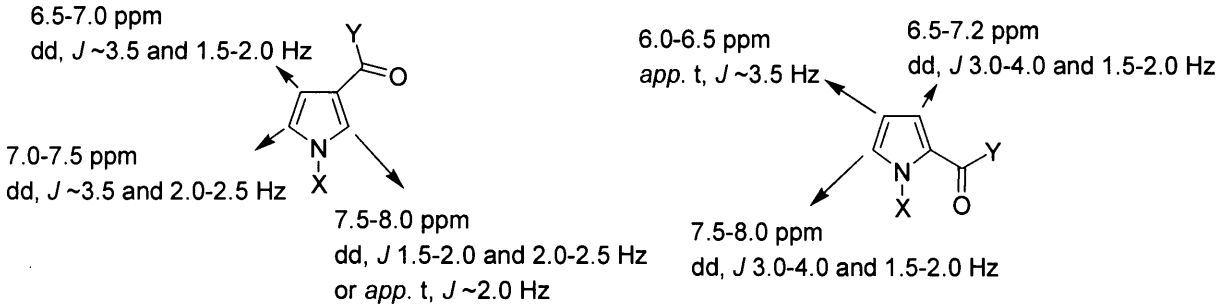
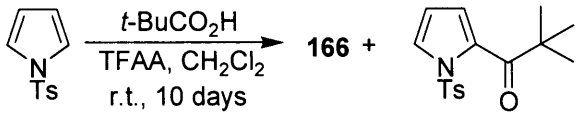


Figure 3.2

The ^{1}H NMR data of all our acylation products were consistent with that of the reported 2-acylpyrroles, not the 3-acylpyrroles. Besides the regioselective outcome of 2-acylpyrroles, no acylation occurred at the phenyl rings (entries 13-15, 17).

The reactivity of the acids depended on both their steric and electronic properties. The more sterically hindered an acid is, the slower the reaction (entries 1-3). While acetic acid reacted smoothly in dichloromethane at ambient temperature, it was necessary to reflux the reaction mixture for pentanoic acid. Acylation with the much more hindered pivalic acid even required prolonged reflux (119 h) in dichloroethane for completion. In a separate reaction, a mixture of *N*-tosylpyrrole **166**, pivalic acid, and trifluoroacetic anhydride in dichloromethane was stirred at ambient temperature for 10 days before work-up, and the 2-acylpyrrole **212** was isolated only in 39% yield, together with 46% starting material recovered (Scheme 3.24).



166 **212**

Scheme 3.24

The ^{1}H NMR spectrum of the 2-acylpyrrole **212** (Figure 3.3) showed that the pyrrole-3 proton resonated at 6.64 ppm and appeared as double doublets with coupling constants of 3.7 and 1.5 Hz; the pyrrole-4 proton resonated at 6.17 ppm and appeared as an apparent triplet with a coupling constant of 3.4 Hz; and the pyrrole-5 proton resonated at 7.45 ppm and appeared as a double doublet with coupling constants of 3.3 and 1.5 Hz, consistent with those discussed above. While acylation of *N*-tosylpyrrole **166** with benzoic acid (entry 5) required reflux in dichloroethane for 70 hours to reach completion, acylation with *para*-methoxybenzoic acid (entry 6) proceeded smoothly at ambient temperature in dichloromethane and the reaction was complete after 48 hours. When there was an electron-withdrawing group on the phenyl ring, such as 4-nitrobenzoic acid (entry 7) and 4-bromobenzoic acid (entry 8), acylation did not occur at all even after prolonged reflux in dichloroethane.

As expected, the presence of an α-methyl substituent provided significant additional activation towards acylation, which was shown by the relatively milder reaction conditions required to acylate 2-methyl-*N*-tosylpyrrole **186** (entries 11, 12). Despite this, no 3-acyl isomers were evident in ^{1}H NMR spectra of the crude products.

^{1}H NMR Spectrum

2-(2'',2''-Dimethylpropanoyl)-1-(4'-methylphenylsulfonyl)pyrrole (212)

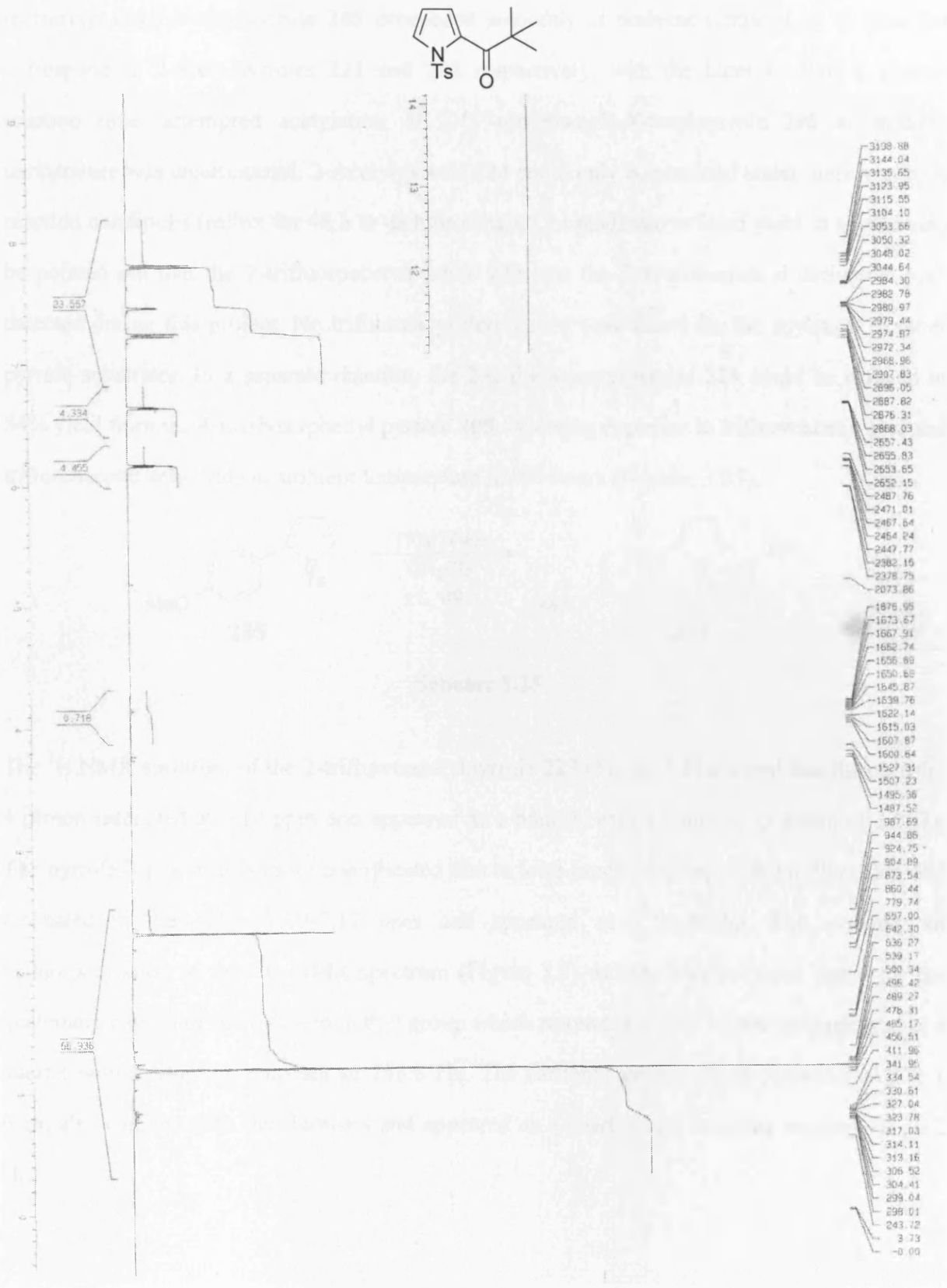
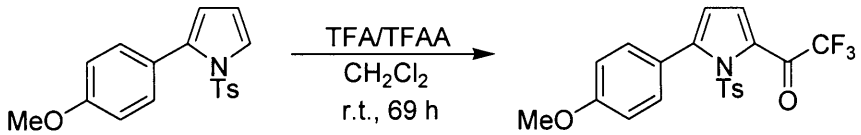


Figure 3.3

Acylations of representative 2-aryl-*N*-tosylpyrroles were also similarly selective for the α-pyrryl positions (entries 13-15, 17). While acetylation of 2-phenyl-*N*-tosylpyrrole **201** and 2-(4'-methoxyphenyl)-*N*-tosylpyrrole **205** proceeded smoothly at ambient temperature to give the corresponding 2-acetylpyrroles **221** and **222** respectively, with the latter needing a shorter reaction time, attempted acetylation of 2-(3'-nitrophenyl)-*N*-tosylpyrrole **206** at ambient temperature was unsuccessful. 2-Acetylpyrrole **224** could only be obtained under more vigorous reaction conditions (reflux for 48 h in dichloroethane), in moderate isolated yield. It should also be pointed out that the 2-trifluoroacetylpyrrole **223** was the first trifluoroacyl derivative ever detected during this project. No trifluoroacyl derivatives were found for the acylation of other pyrrole substrates. In a separate reaction, the 2-trifluoroacetylpyrrole **223** could be isolated in 84% yield from the 4-methoxyphenyl pyrrole **205** following exposure to trifluoroacetic acid and trifluoroacetic anhydride at ambient temperature for 69 hours (Scheme 3.25).



205 **223**

Scheme 3.25

The ^{1}H NMR spectrum of the 2-trifluoroacetylpyrrole **223** (Figure 3.4) showed that the pyrrole-4 proton resonated at 6.12 ppm and appeared as a doublet with a coupling constant of 3.9 Hz. The pyrrole-3 proton was more complicated due to long-range coupling with the fluorides, and resonated in the range 7.19-7.17 ppm and appeared as a multiplet. The evidence of trifluoroacylation in the ^{13}C NMR spectrum (Figure 3.5) was the characteristic signal for the quaternary carbon of the trifluoromethyl group which resonated at 116.5 ppm and appeared as a quartet with a coupling constant of 288.8 Hz. The carbonyl group, which resonated at 171.2 ppm, also coupled with the fluorides and appeared as a quartet with coupling constant of 36.2 Hz.

^{1}H NMR Spectrum

5-(4''-methoxyphenyl)-1-(4'-methylphenylsulfonyl)-2-trifluoroacetylpyrrole (223)

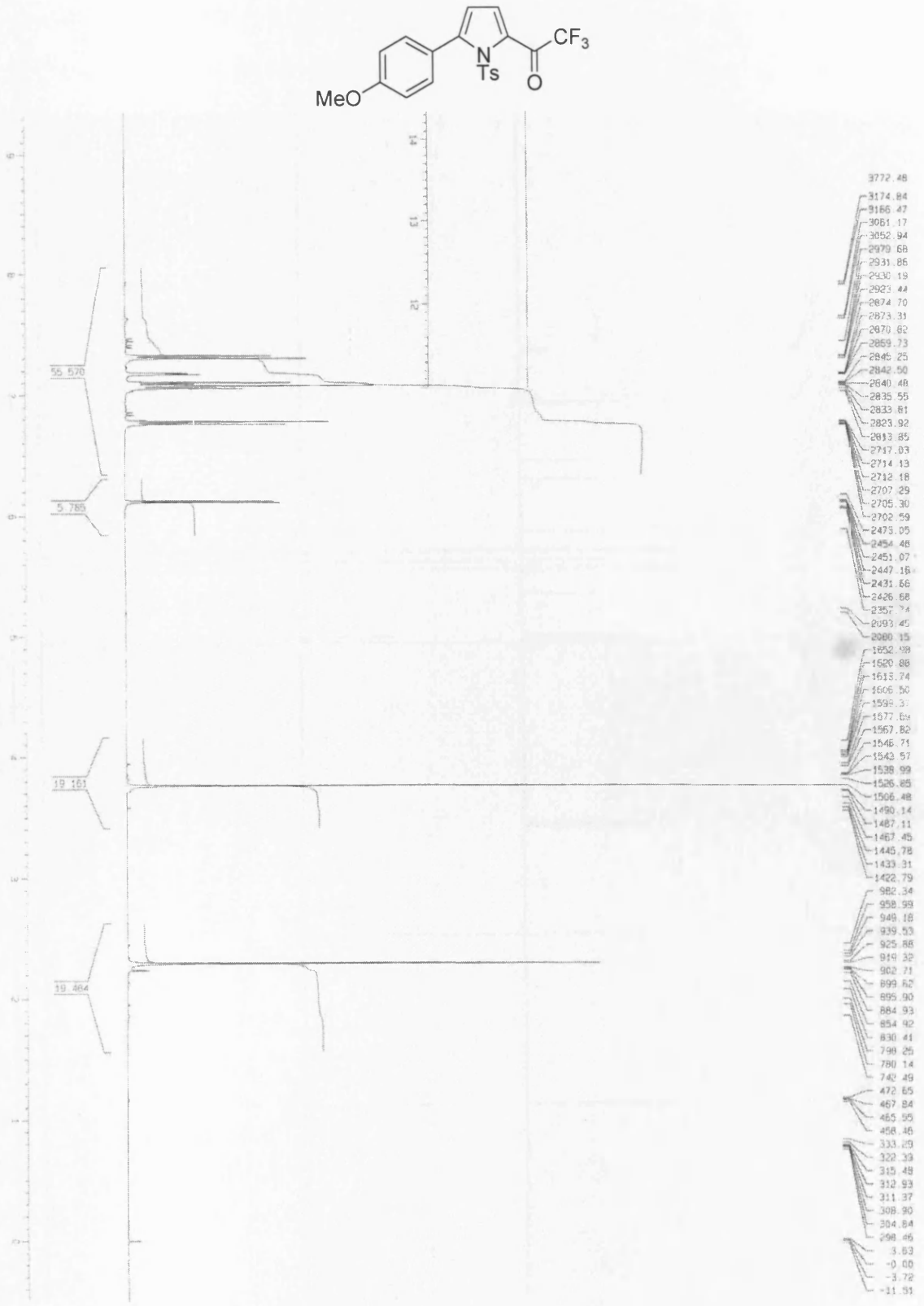


Figure 3.4

^{13}C NMR Spectrum

5-(4''-methoxyphenyl)-1-(4'-methylphenylsulfonyl)-2-trifluoroacetylpyrrole (223)

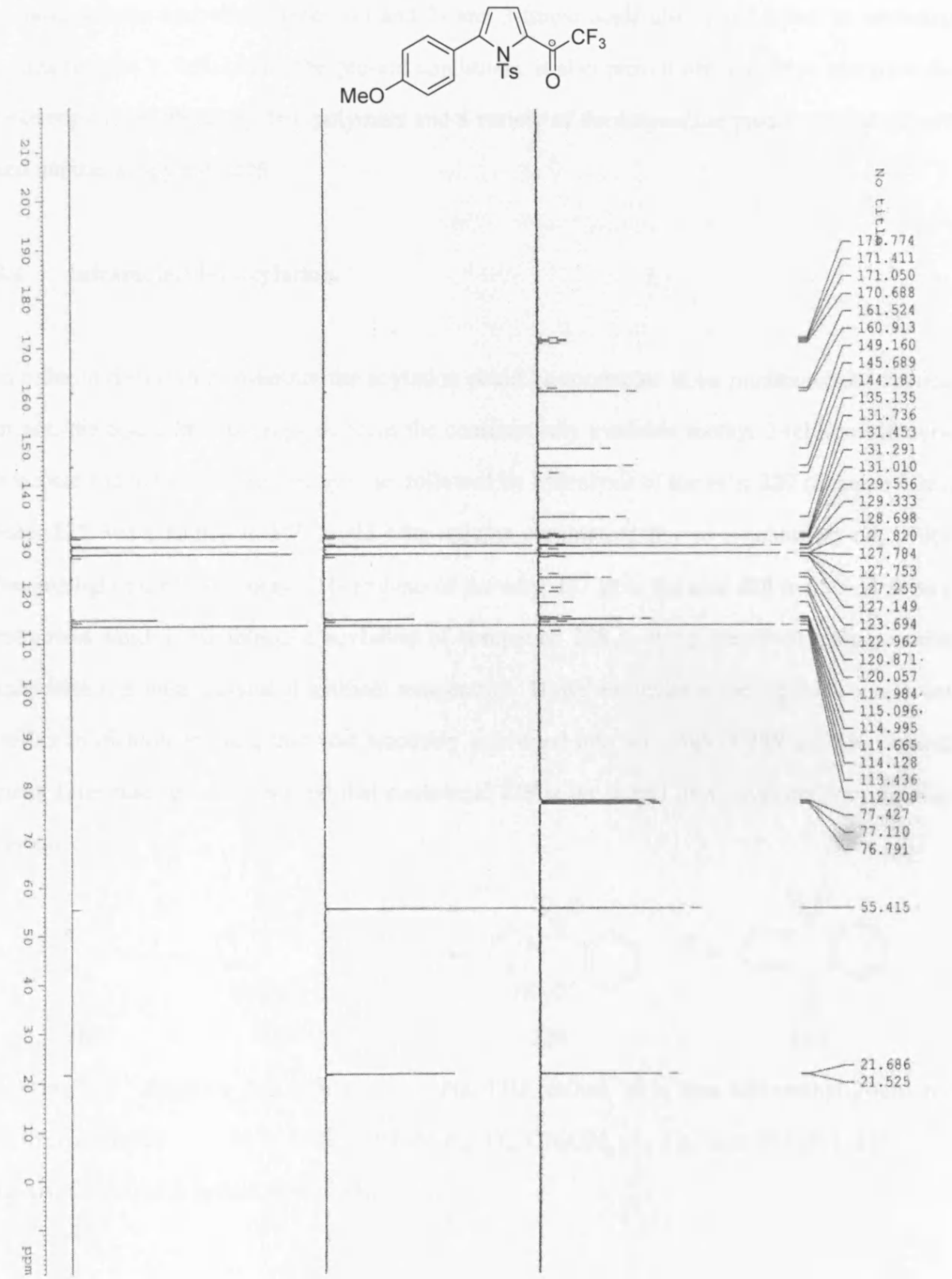
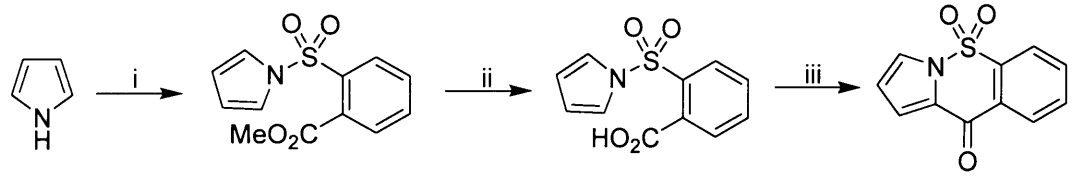


Figure 3.5

Besides the high regioselectivity and chemoselectivity of this method, some limitations were also discovered: direct formylation using formic acid failed to deliver any pyrrole-2-carboxaldehyde derivatives (entry 4) and 2- and 3-furoic acids also failed to act as acylating agents (entries 9, 10). Under the present conditions, it also proved impossible to acetylate the hexenylpyrrole **209** (entry 16); polymers and a variety of decomposition products were formed and not the acylpyrrole **225**.

3.4 Intramolecular acylation.

In order to demonstrate whether the acylation could be conducted in an intramolecular fashion or not, the acid **228** was prepared from the commercially available methyl 2-(chlorosulfonyl)-benzoate and the sodium salt of pyrrole, followed by hydrolysis of the ester **227** (Scheme 3.26). Ester **227** was obtained in 55% yield after column chromatography as a colourless oil, which became light purple on storage. Hydrolysis of the ester **227** gave the acid **228** in 85% yield as a colourless solid. Intramolecular acylation of compound **228** in the presence of trifluoroacetic anhydride was unsuccessful at ambient temperature. However, under more vigorous conditions (reflux in dichloroethane), this was smoothly converted into the product **229** in 78% isolated yield. Literature searches showed that compound **229** is the parent of a novel heterocyclic ring system.



161 **227** **228** **229**

Scheme 3.26 *Reagents and conditions*: (i) Na, THF, reflux, 20 h, then add methyl 2-(chloro-sulfonyl)benzoate, r.t., 24 h, 55%; (ii) 12M K_2CO_3, CH_3OH, r.t., 3 h, then 2M HCl, 85%; (iii) TFAA, $Cl(CH_2)_2Cl$, reflux, 50 h, 78%.

The ^{1}H NMR spectrum of compound **229** (Figure 3.6) clearly showed the disappearance of the pyrrole-2 proton. The pyrrole-3 proton resonated at 7.40 ppm and appeared as a double doublet with coupling constants of 3.6 and 1.1 Hz; the pyrrole-4 proton resonated at 6.55 ppm and appeared as an apparent triplet with a coupling constant of 3.3 Hz; the pyrrole-5 proton resonated at 7.57 ppm and appeared as a double doublet with coupling constants of 2.7 and 1.1 Hz, which all fits with the structure being a 2-acylated pyrrole, as mentioned above. The ^{13}C NMR spectrum (Figure 3.7) showed the resonance of the carbonyl group at 170.7 ppm, together with signals of the other three quaternary carbons at 138.5, 132.5 and 131.3 ppm, respectively. The number of tertiary carbons all fit well for the proposed structure. The high resolution mass spectrum also provided agreement between the calculated and found molecular weights for the proposed structure **229**.

^{1}H NMR Spectrum

10*H*-Pyrrolo[1,2-*b*][1,2]benzothiazin-10-one, 5,5-dioxide (229)

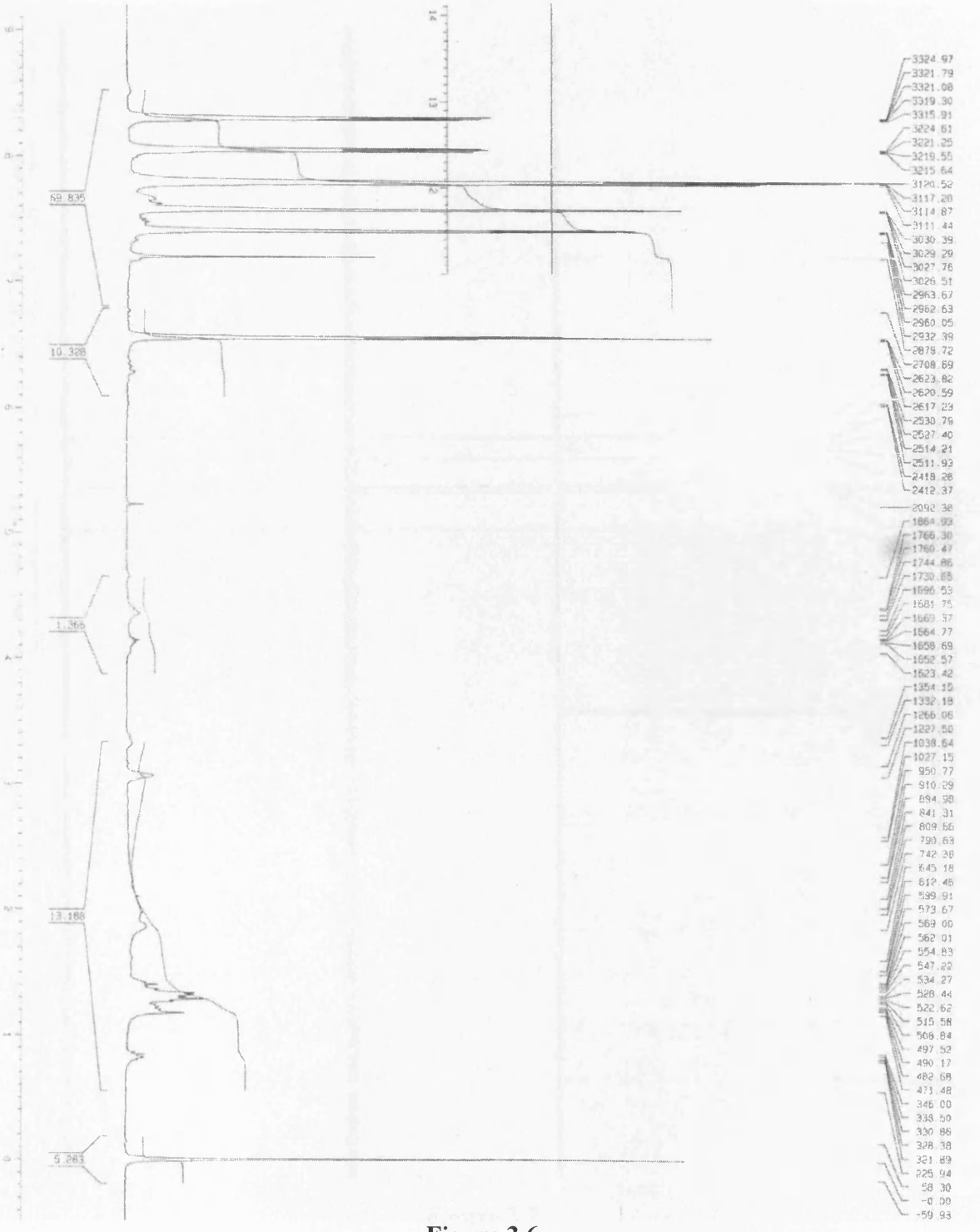
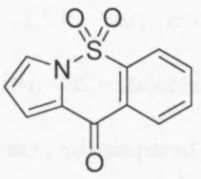


Figure 3.6

^{13}C DEPT NMR Spectrum

10*H*-Pyrrolo[1,2-*b*][1,2]benzothiazin-10-one, 5,5-dioxide (229)



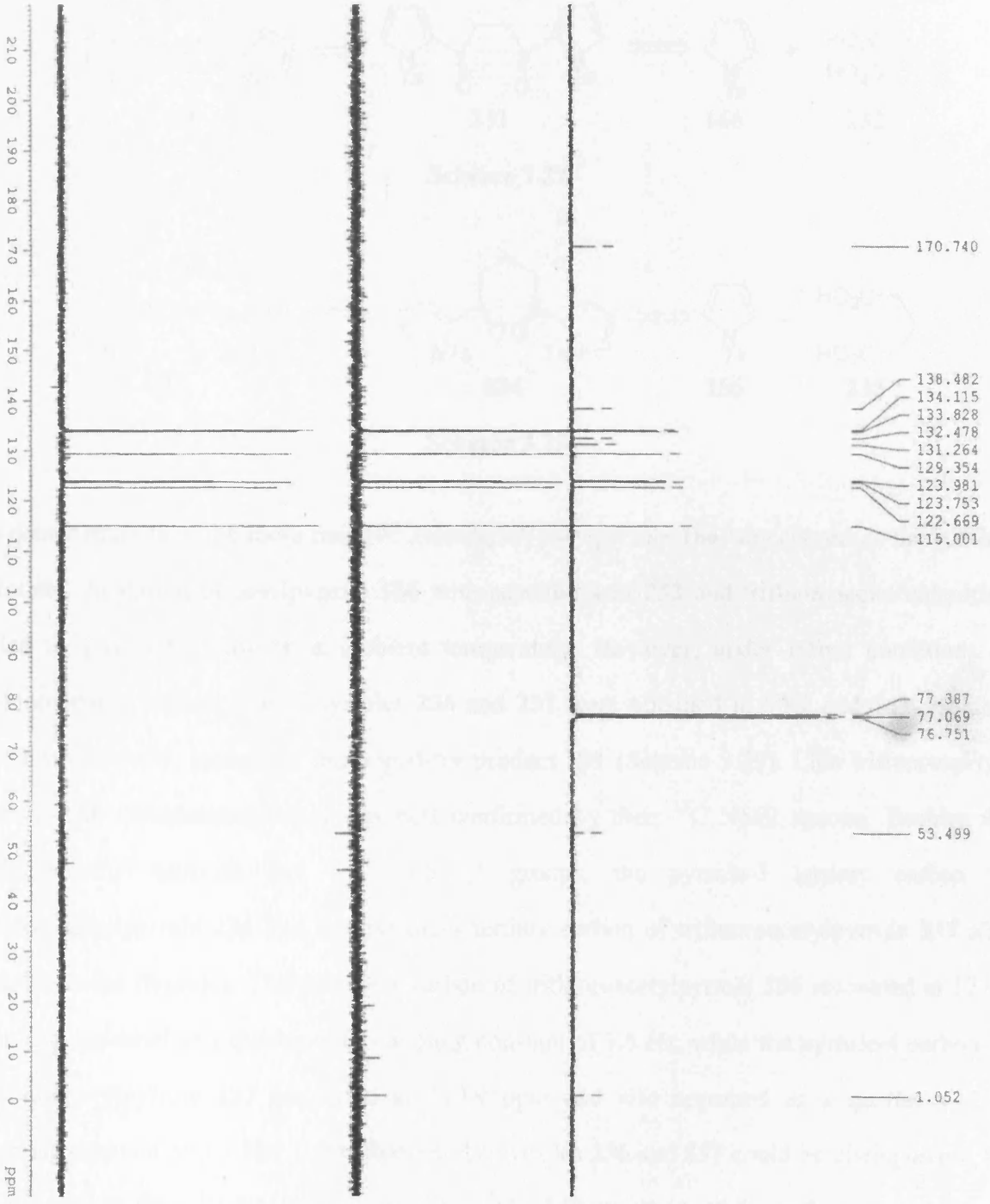
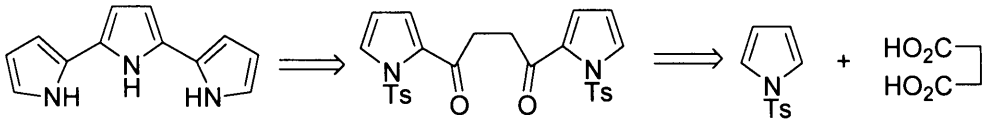


Figure 3.7

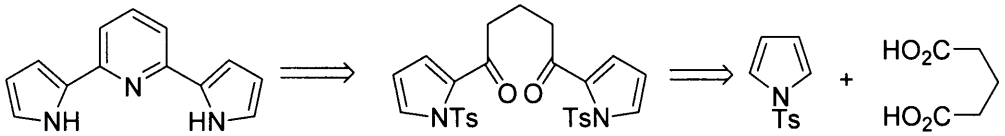
3.5 Acylation with diacids.

Compounds containing units **230**[174] or **233**[175] are excellent ligands, which could easily be obtained, if successful, by pyrrole acylation with succinic acid **232** or glutaric acid **235** followed by amination of the products **231** or **234** and subsequent deprotection (Schemes 3.27 and 3.28).



230 **231** **166** **232**

Scheme 3.27

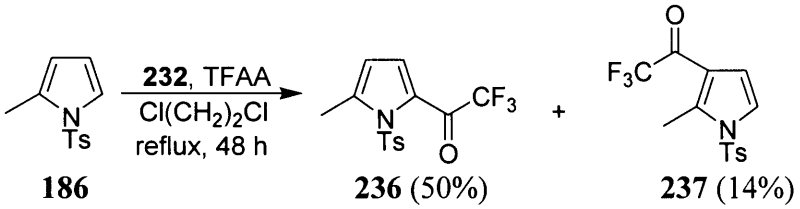


233 **234** **166** **235**

Scheme 3.28

To demonstrate this, the more reactive 2-methyl-*N*-tosylpyrrole **186** was chosen as the starting substrate. Acylation of tosylpyrrole **186** with succinic acid **232** and trifluoroacetic anhydride failed to give any products at ambient temperature. However, under reflux conditions in dichloroethane, trifluoroacetyl pyrroles **236** and **237** were obtained in 50% and 14% isolated yields respectively, instead of the hoped-for product **231** (Scheme 3.29). Like trifluoroacetyl-pyrrole **223**, trifluoroacetylation was best confirmed by their ^{13}C NMR spectra. Besides the trifluoromethyl carbons and the carbonyl groups, the pyrrole-3 tertiary carbon of trifluoroacetylpyrrole **236** and the pyrrole-4 tertiary carbon of trifluoroacetylpyrrole **237** also coupled to the fluorides. The pyrrole-3 carbon of trifluoroacetylpyrrole **236** resonated at 127.5 ppm and appeared as a quartet with coupling constant of 3.8 Hz, while the pyrrole-4 carbon of trifluoroacetylpyrrole **237** resonated at 110.9 ppm and also appeared as a quartet with a coupling constant of 3.7 Hz. The trifluoroacetylpyrroles **236** and **237** could be distinguished by comparison of their ^{1}H NMR spectrums. The ^{1}H NMR spectrum of the trifluoroacetylpyrrole **236** showed that the pyrrole-4 proton resonated at 6.09 ppm and appeared as a doublet with a

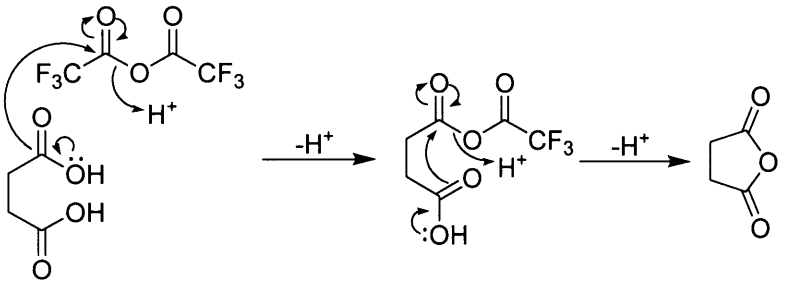
coupling constant of 4.0 Hz, while the pyrrole-3 proton was more complicated due to coupling with the fluorides and appeared as a multiplet in the region 7.14-7.13 ppm. The pyrrole-5 proton of trifluoroacetylpyrrole **237** was expected to appear as a doublet; however it was obscured by the tosyl-3 and -5 protons which fell in the same region 7.31-7.29 ppm. Not surprisingly, the pyrrole-4 proton appeared as a multiplet in the region 6.60-6.58 ppm.



186 **236** (50%) **237** (14%)

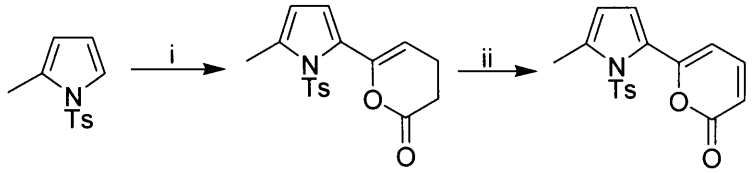
Scheme 3.29

The reason for trifluoroacetylation might be that, under the reaction conditions, the 'unreactive' succinic anhydride was formed (Scheme 3.30), thus the normally uncompetitive trifluoroacetylation took place to give trifluoroacetylpyrrole **236** and **237** (the mechanism of acylation will be discussed later). The high reactivity of tosylpyrrole **186** towards acylation and the vigorous reaction conditions resulted in poor regioselectivity. Both trifluoroacetylpyrrole **236** and **237** were formed. A similar result was obtained when refluxing a mixture of tosylpyrrole **186** with trifluoroacetic anhydride in dichloroethane.



Scheme 3.30

When the acylation was carried out with glutaric acid **235**, again, instead of the hoped-for product **234**, the dihydropyranone derivative **238** was obtained in 59% isolated yield. DDQ oxidation of this dihydropyranone **238** gave the pyranone **239** in 39% isolated yield (Scheme 3.31).



186 **238** **239**

Scheme 3.31 *Reagents and conditions*: (i) **235**, TFAA, $Cl(CH_2)_2Cl$, r.t., 48 h, then reflux 24 h, 59%; (ii) DDQ, toluene, reflux, 17 h, 39%.

Evidently, a second acylation of 2-methyl-*N*-tosylpyrrole **186** by the remaining carboxylic acid group does not occur as fast as intramolecular cyclisation onto the new ketone function, followed by dehydration.

The spectroscopic data obtained for the dihydropyranone **238** were consistent with those reported for related compounds in the literature.[176-179] The IR spectrum showed the carbonyl absorption at 1765 cm^{-1}, characteristic for such a lactone. The ^1H NMR spectrum (Figure 3.8) showed the resonance of the pyrrole-3 and pyrrole-4 protons at 6.16 ppm and 5.81 ppm respectively, and both appeared as a doublet with coupling constants of 3.4 Hz. The 5-proton of the dihydropyranone resonated at 5.46 ppm, and appeared as a triplet with a coupling constant of 4.7 Hz, due to coupling with the 4-CH_2. The latter, which also coupled with the 3-CH_2, resonated at 2.36 ppm and appeared as a triple doublet with coupling constants of 7.4 and 4.7 Hz. The 3-CH_2 resonated at 2.62 ppm and appeared as a triplet with a coupling constant of 7.4 Hz. The ^{13}C DEPT NMR spectrum (Figure 3.9) showed the resonance of the carbonyl group at 169.1 ppm; the 5-tertiary carbon resonance at 106.9 ppm. The 3-CH_2 and 4-CH_2 resonated at 28.0 and 19.1 ppm respectively.

The spectroscopic data obtained for the pyranone **239** were also consistent with those reported in the literature for related compounds.[180,181] The IR spectrum showed the carbonyl absorption at 1723 cm^{-1}. The ^1H NMR spectrum (Figure 3.10) showed that the pyranone-4 proton resonated at 7.32 ppm and appeared as a double doublet with coupling constants of 9.4 and 6.6 Hz, due to coupling with the pyranone-3 and pyranone-5 protons, one of which resonated at 6.31 ppm and appeared as a doublet with a coupling constant of 6.6 Hz, and the other resonated at 6.22 ppm and also appeared as a doublet with a coupling constant of 9.4 Hz. The ^{13}C DEPT

NMR spectrum (Figure 3.11) showed the carbonyl resonance at 161.9 ppm. The 4- and 5-pyranone tertiary carbons resonated at 143.6 and 105.8 ppm respectively. The numbers, chemical shifts and multiplicities of other carbons all fit well with the proposed structure **239**.

^{1}H NMR Spectrum

3,4-Dihydro-6-[5'-methyl-1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]pyran-2-one (238)

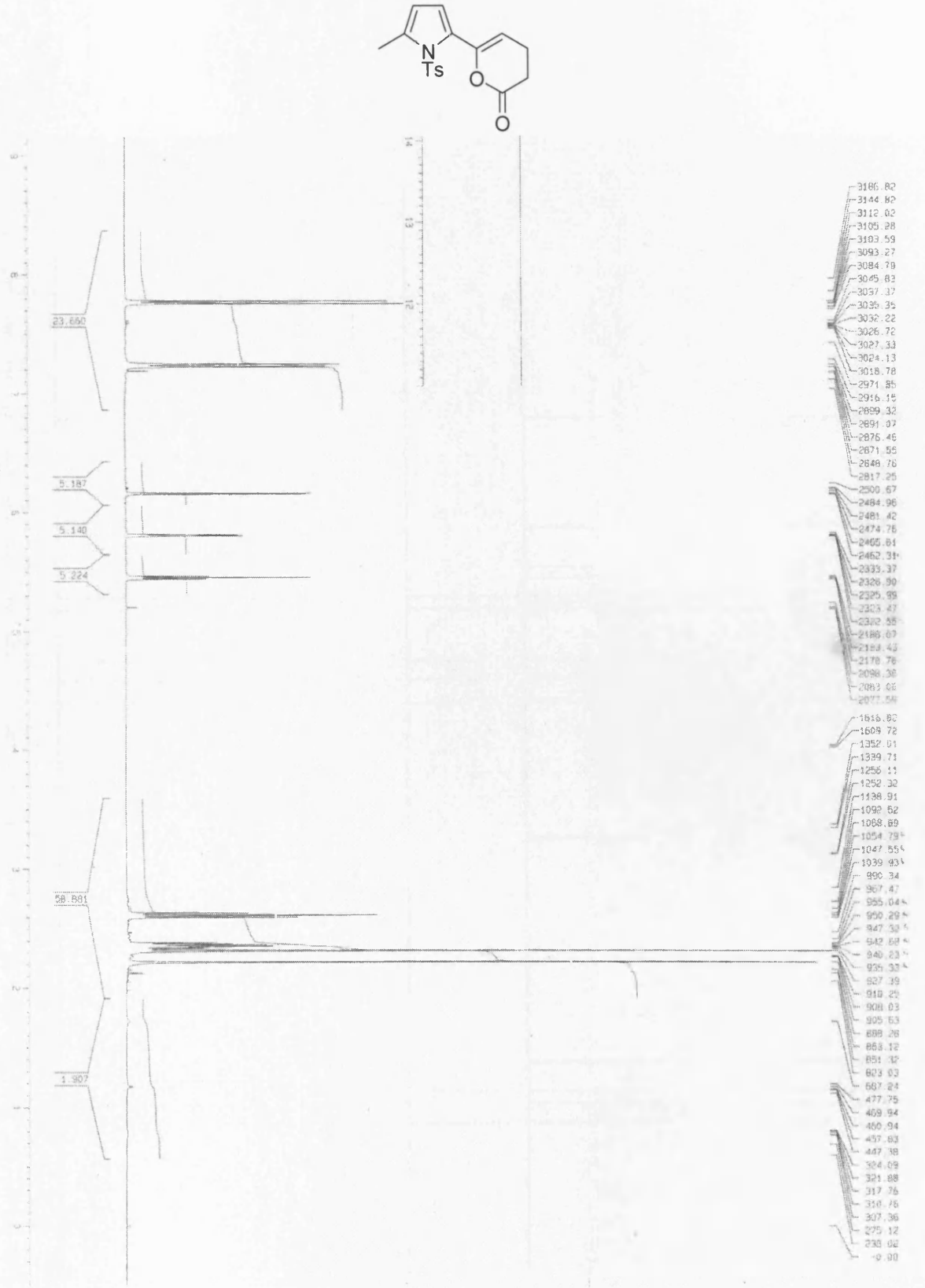
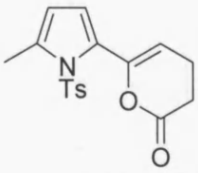


Figure 3.8

^{13}C DEPT NMR Spectrum

3,4-Dihydro-6-[5'-methyl-1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]pyran-2-one (238)



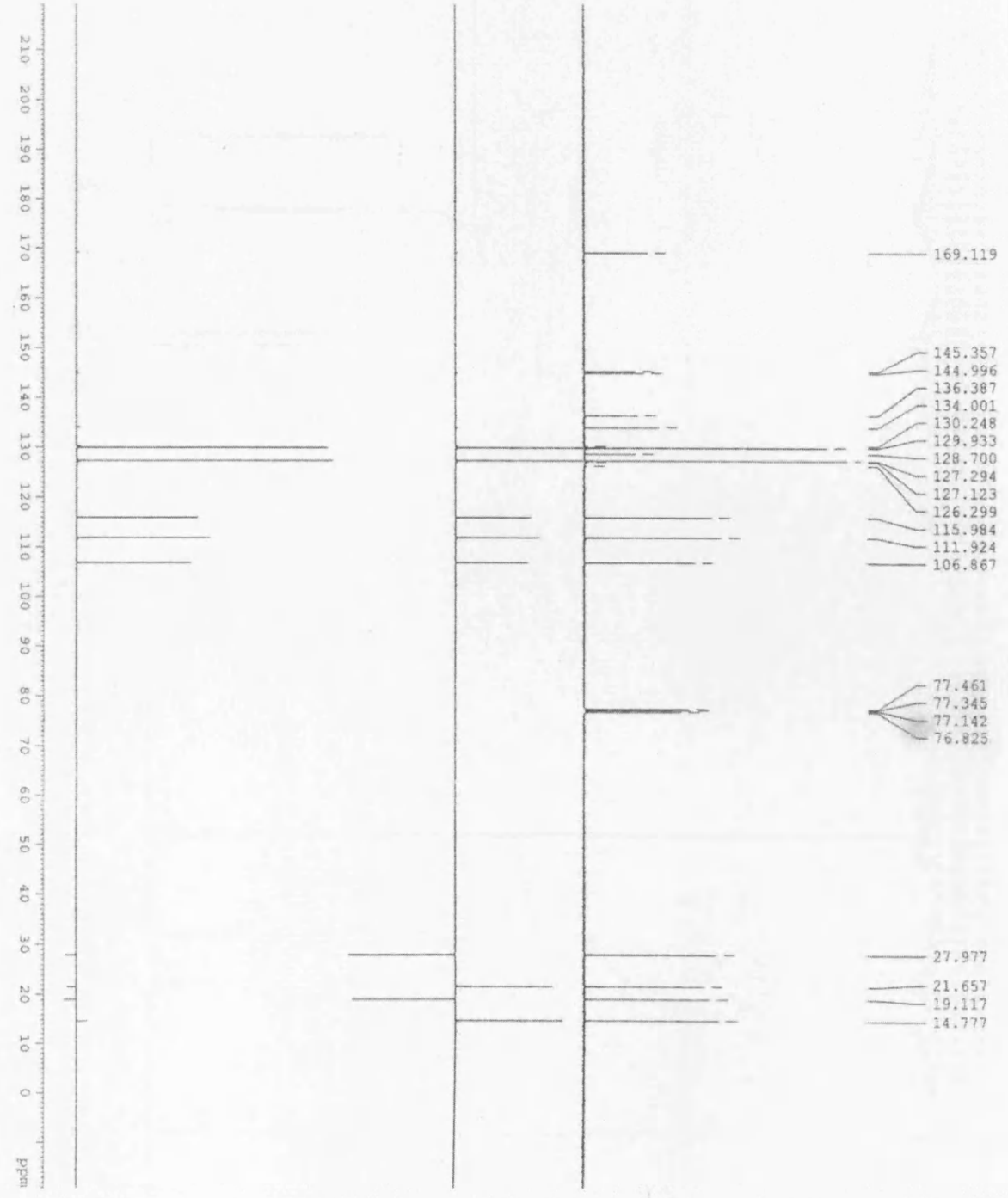


Figure 3.9

^{1}H NMR Spectrum

6-[5'-Methyl-1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]pyran-2-one (239)

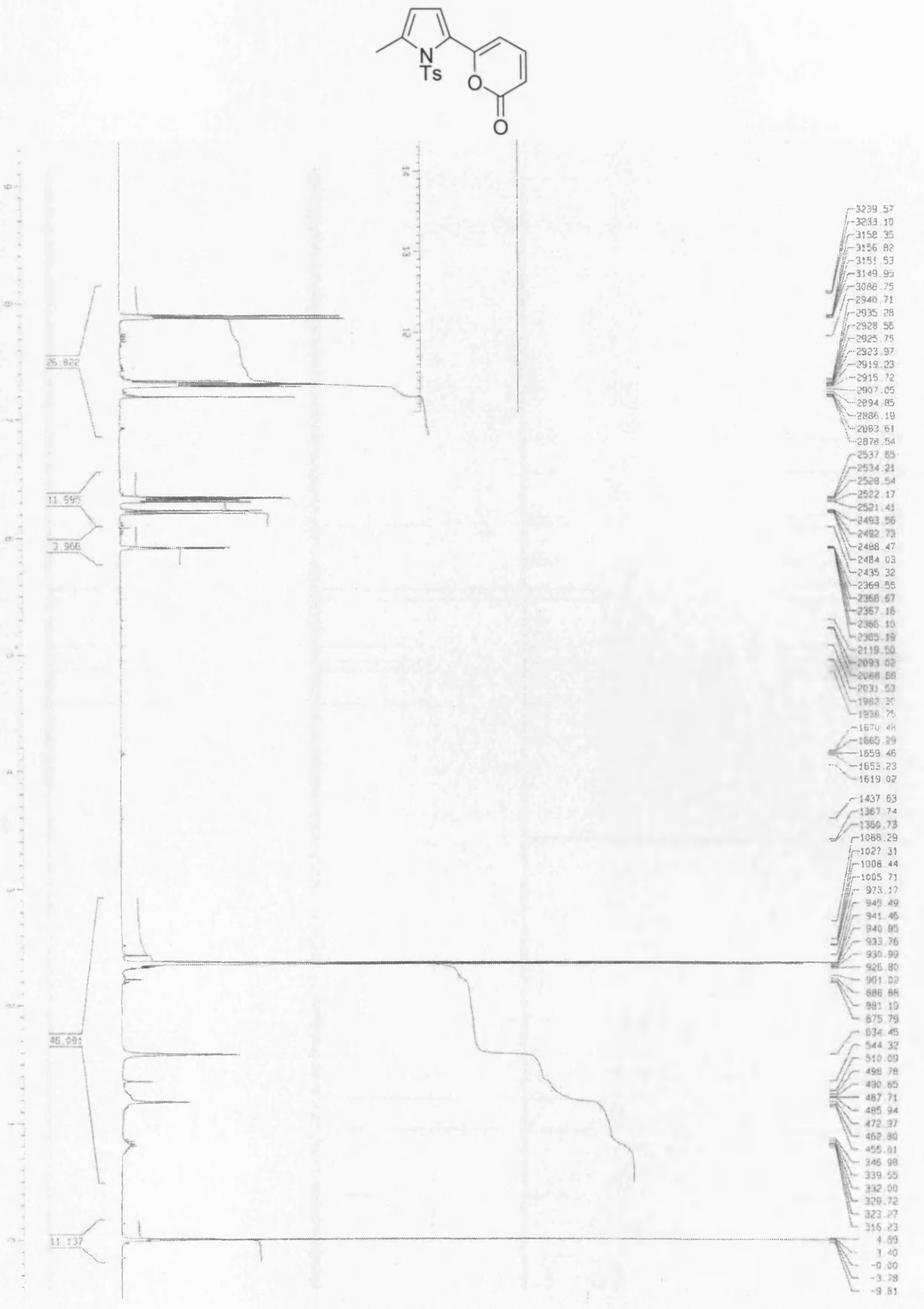
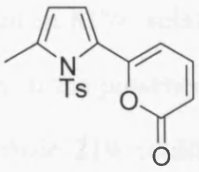


Figure 3.10

^{13}C DEPT NMR Spectrum

6-[5'-Methyl-1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]pyran-2-one (239)



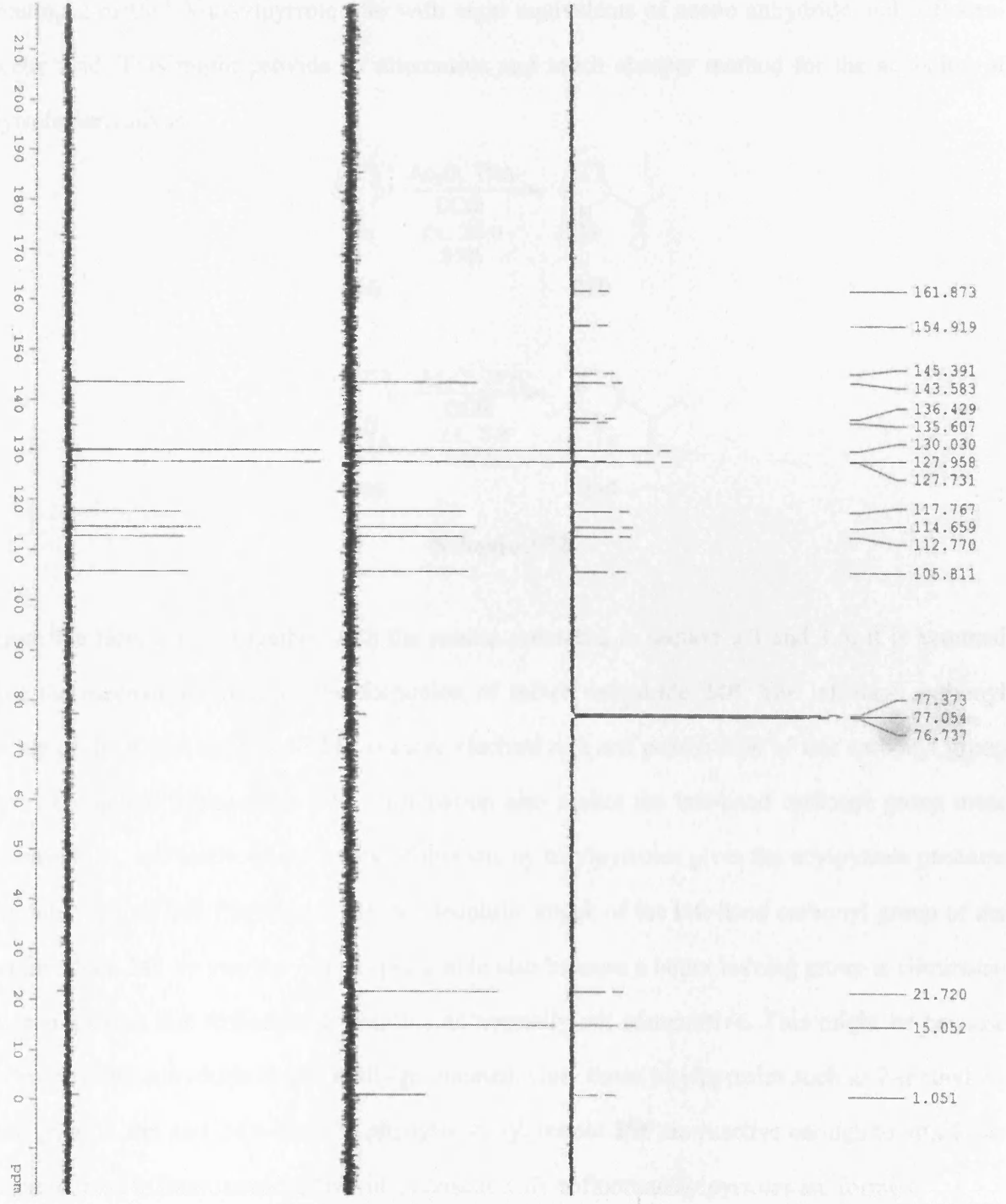
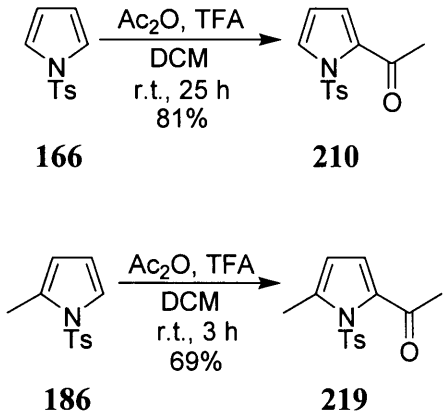


Figure 3.11

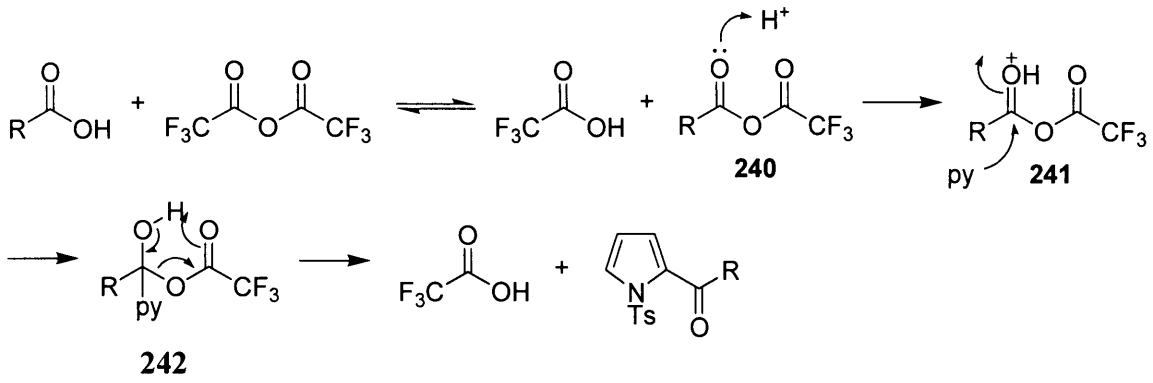
3.6 Acylation mechanism.

Acetylpyrrole **210** could also be obtained in 81% isolated yield by treating *N*-tosylpyrrole **166** with four equivalents of acetic anhydride in the presence of a large excess of trifluoroacetic acid (Scheme 3.32). Similarly, the acetylpyrrole **219** could be obtained in 69% isolated yield by treating 2-methyl-*N*-tosylpyrrole **186** with eight equivalents of acetic anhydride and trifluoro-acetic acid. This might provide an alternative and much cheaper method for the acylation of pyrrole derivatives.



Scheme 3.32

From the facts above, together with the results presented in section 3.3 and 3.5, it is assumed that the mechanism involves the formation of mixed anhydride **240**. The left-hand carbonyl group of the mixed anhydride **240** is more electron rich and protonation of this carbonyl group gives the active intermediate **241**. Protonation also makes the left-hand carbonyl group more electrophilic, and nucleophilic attack of this site by tosylpyrroles gives the acylpyrrole products *via* intermediate **242** (Scheme 3.33). Nucleophilic attack of the left-hand carbonyl group of the intermediate **241** by tosylpyrroles is preferable also because a better leaving group is eliminated. It is surprising that trifluoroacetylation was normally not competitive. This might be because trifluoroacetic anhydride is less easily protonated. Only those tosylpyrroles such as 2-methyl-*N*-tosylpyrrole **186** and 2-(*p*-methoxyphenyl)-1-tosylpyrrole **205** are reactive enough to attack the unprotonated trifluoroacetic anhydride, consequently trifluoroacetylpyrroles are formed.



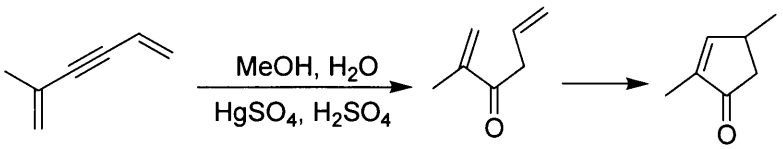
240 **241** **242**

Scheme 3.33

3.7 Acylation with α, β-unsaturated acids.

3.7.1 Introduction – The Nazarov cyclisation.

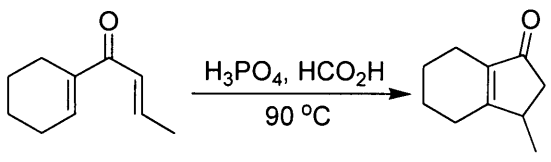
Nazarov and co-workers explored the acid-catalysed ring closure of allyl vinyl ketone **244** to give the corresponding 2-cyclopentanone **245** during the 1940s and 1950s (Scheme 3.34). This general method for the construction of cyclopentenones and in particular ring-fused systems has been extensively reviewed.[182]



243 **244** **245**

Scheme 3.34

Nazarov initially formulated a direct acid-catalyzed closure of the allyl vinyl ketones to explain product formation. However in 1952, Braude and Coles illustrated that the reaction proceeded *via* α,α'-divinylketones, such as substrate **246**, and suggested that the reaction went through a carbocationic intermediate to give product **247** (Scheme 3.35).

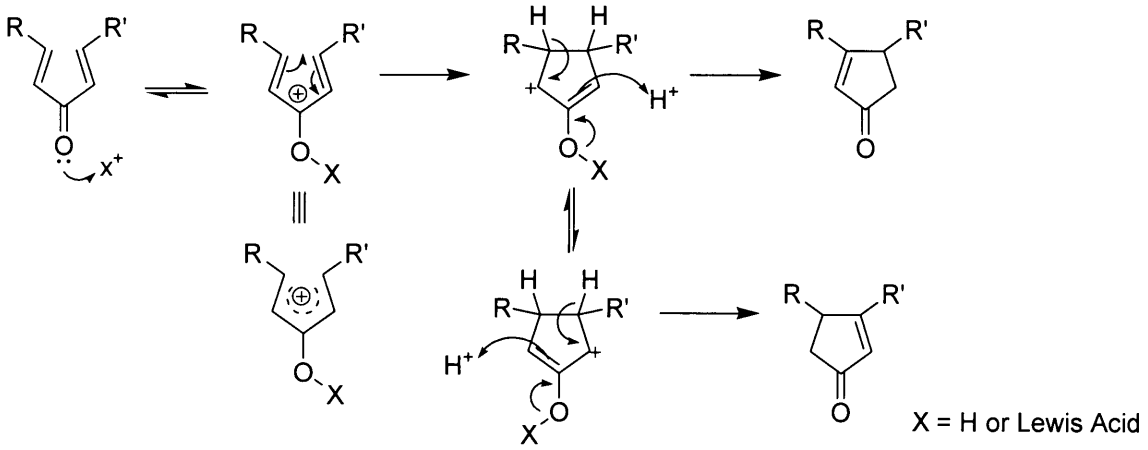


246 **247**

Scheme 3.35

Further mechanistic work lead to the definition of the Nazarov cyclisation being revised to specifically mean the acid-catalysed closure of divinyl ketones to 2-cyclopentenones. All of the starting materials for the reaction are operational equivalents in that they are all transformed into divinyl ketones under conditions that induce cyclisation. Identification of divinyl ketones as key intermediates led to the exploration of precursors other than dienynes (Scheme 3.34), for example the use of propargylic amines as precursor to divinyl ketones. Another advance was the realisation that Lewis acids could be used to effect cyclisation, which can often be a more efficient and convenient tactic than the classical reagent, 90% polyphosphoric acid.

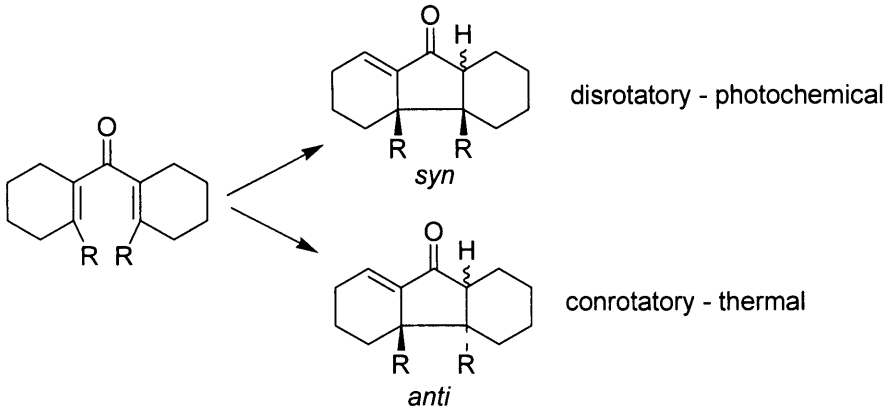
Eventually, it was realised that the Nazarov reaction belonged to the general class of cationic electrocyclic reactions, which meant that it could include the use of pentadienyl cations or equivalents. This again widened the range of substrates that could be used. The Nazarov cyclisation is now well established as a pericyclic reaction, and more specifically is a 4π-electrocyclic ring closure reaction of a pentadienyl cation. The mechanism for the reaction is shown in Scheme 3.36. As shown here in the case of an unsymmetrical starting material, a mixture of products that differ in the position of the double bond can be obtained, due to the delocalisation of the cationic charge.



Scheme 3.36

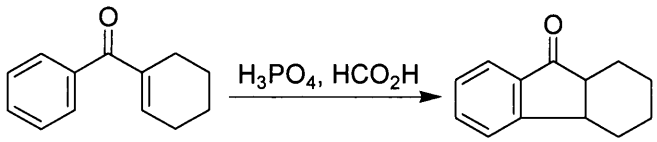
The most convincing evidence for a pericyclic mechanism was the demonstration of complementary rotatory pathways for the thermal (conrotatory) and photochemical (disrotatory) cyclisations of bis(1-cyclohexenyl)ketones, as predicted by the conservation of orbital

symmetry (Scheme 3.37) .The stereochemical outcome of the reaction can thus be accurately predicted and this feature has significantly enhanced its utility.



Scheme 3.37

As mentioned above, the original substrates for these reactions were divinyl and allyl vinyl ketones. Monocyclic substrates require one of the vinyl groups to be embedded in the existing ring, which may vary in size from 5 to 12 atoms. Bicyclic precursors can also be used, where both vinyl groups are embedded within different rings, again of varying size. In general, the final position of the double bond will be in a position that is the more highly substituted. If the conditions are vigorous enough, aromatic substrates [e.g. **248**] can also be used (Scheme 3.38). The driving force for aromaticity will mean the double bond will return to the aromatic ring [e.g. **249**].

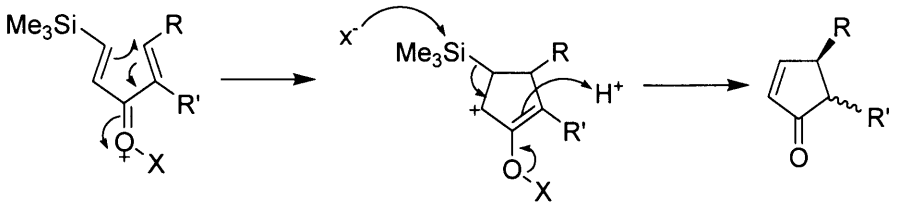


248 **249**

Scheme 3.38

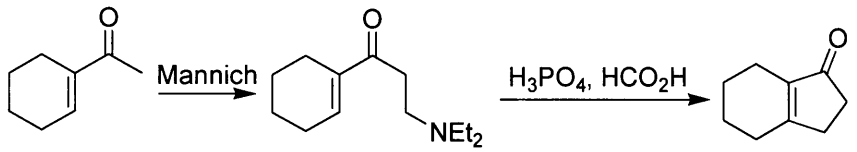
One of the major deficiencies of the Nazarov cyclisation as a cationic electrocyclisation is the non-selective placement of the double bond in many of the products. The β-cation stabilising effect of a strategically placed organosilicon group has been used to overcome this. The silicon group remains a spectator until the crucial collapse of the cation, when it directs the double bond to the thermodynamically less stable position; its bulk can also control the relative

stereochemistry upon ring closure (Scheme 3.39). Similarly, tin substituents can be used to direct the position of the double bond to the less substituted position. This is complementary to the silicon-directing cyclisation as it allows a different method for the construction of the divinyl ketone.



Scheme 3.39

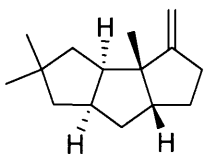
The cyclisation can also be achieved by the *in situ* generation of a divinyl ketone by the elimination of a β-heterosubstituent. An example of this is the β-amino enone **251**, prepared from a Mannich condensation of ketone **250**, as shown in Scheme 3.40.[182] There are many other methods for the *in situ* generation of suitable divinyl ketones including starting from dienynes, alkynic alcohols, enynols, yne-diols and α-vinylcyclobutanones.



250 **251** **252**

Scheme 3.40

The Nazarov cyclisation has been successfully used in the synthesis of many natural products, including (±)-hirsutene **253**, of the polyquinane series of natural products (Figure 3.12).[182]



253

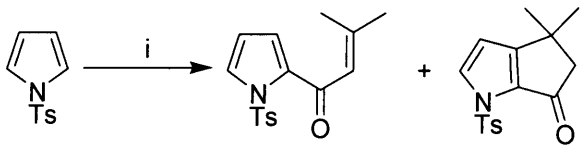
Figure 3.12

The reaction is a simple one to achieve experimentally, usually involving a Brønsted or a Lewis acid. The classical reagent is polyphosphoric acid, usually in formic acid or sulphuric acid.

Modern applications of Lewis acids include the use of tin tetrachloride, boron trifluoride, aluminium trichloride or ferric chloride in a chlorinated solvent.

3.7.2 Acylation.

Acylation of *N*-tosylpyrrole **166** with 3,3-dimethylacrylic acid and trifluoroacetic anhydride gave the 'normal' ketone **254** in 63% isolated yield, together with another product (Scheme 3.41). The IR spectrum of the latter showed a strong absorption at 1694 cm^{-1}, characteristic for a carbonyl group. The mass spectrum suggested it was a mono-acylated product of tosylpyrrole **166**. Compared with compound **254**, the ^{1}H NMR spectrum of the new product (Figure 3.13) showed clearly the disappearance of the double bond from the 3,3-dimethylacrylic acid and the appearance of a new CH_2 signal at 2.64 ppm as a singlet; it also showed this compound to be a 2,3-disubstituted pyrrole, due to the presence of two pyrrylic protons at 6.14 and 7.53 ppm with a coupling constant of 3.1 Hz. The new CH_2 appeared at 57.5 ppm in the ^{13}C NMR spectrum (Figure 3.14). This evidence, together with the quaternary carbon signal at 34.5 ppm all indicated the new compound to be the annulated pyrrole **255**, which came from intramolecular cyclisation of compound **254**. Subsequently, it was found that if the reaction was carried out in dichloroethane under reflux, compound **255** could be isolated as the only product in 51% yield.



166 **254** **255**

Scheme 3.41 *Reagents and conditions*: (i) 3,3-dimethylacrylic acid, TFAA, CH_2Cl_2, r.t., 48 h, 63% for **254**, 13% for **255**.

^{1}H NMR Spectrum

4,5-Dihydro-4,4-dimethyl-1-(4'-methylphenylsulfonyl)cyclopenta[*b*]pyrrol-6(1*H*)-one (255)

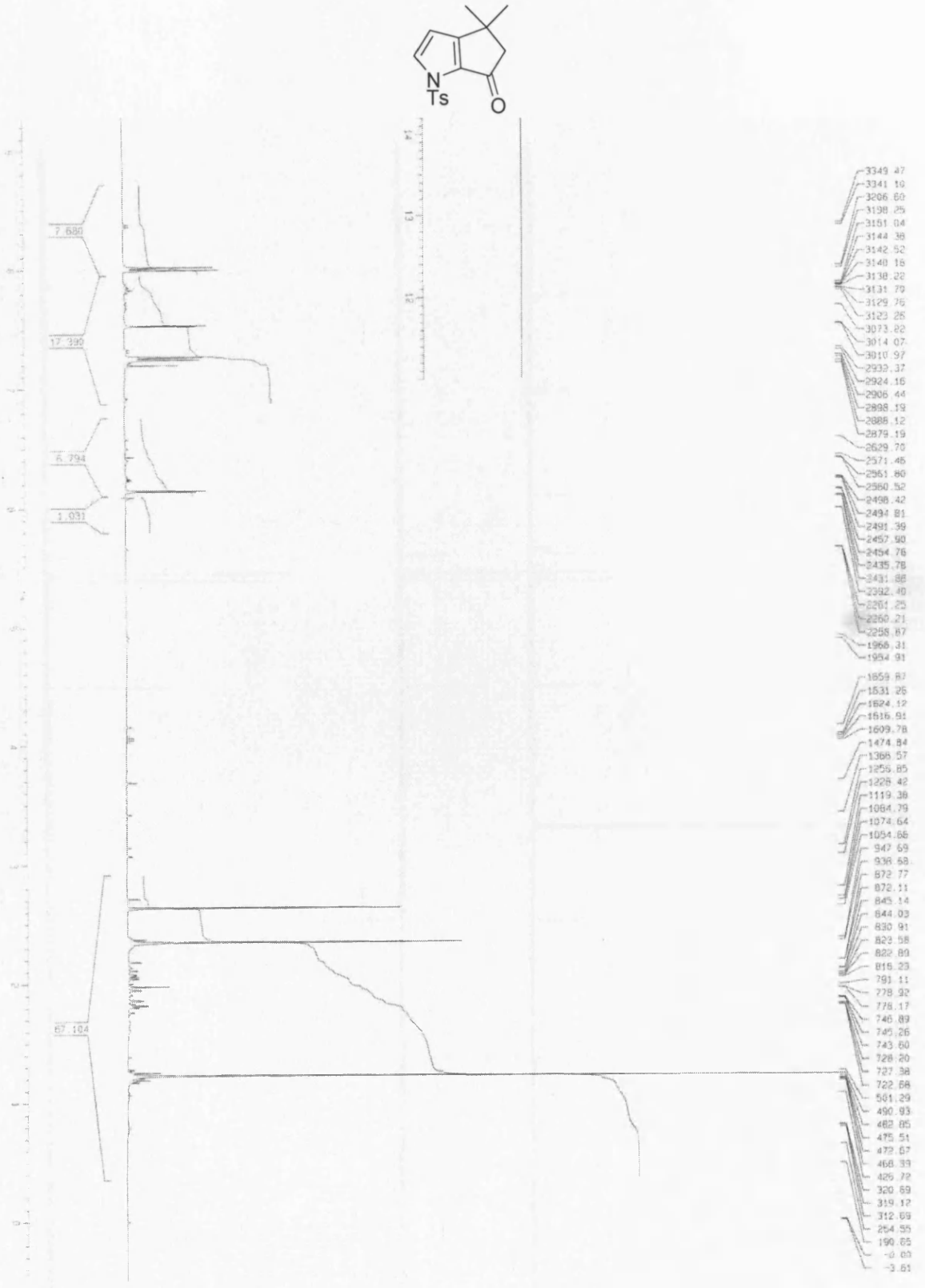


Figure 3.13

^{13}C DEPT NMR Spectrum

4,5-Dihydro-4,4-dimethyl-1-(4'-methylphenylsulfonyl)cyclopenta[*b*]pyrrol-6(1*H*)-one (255)

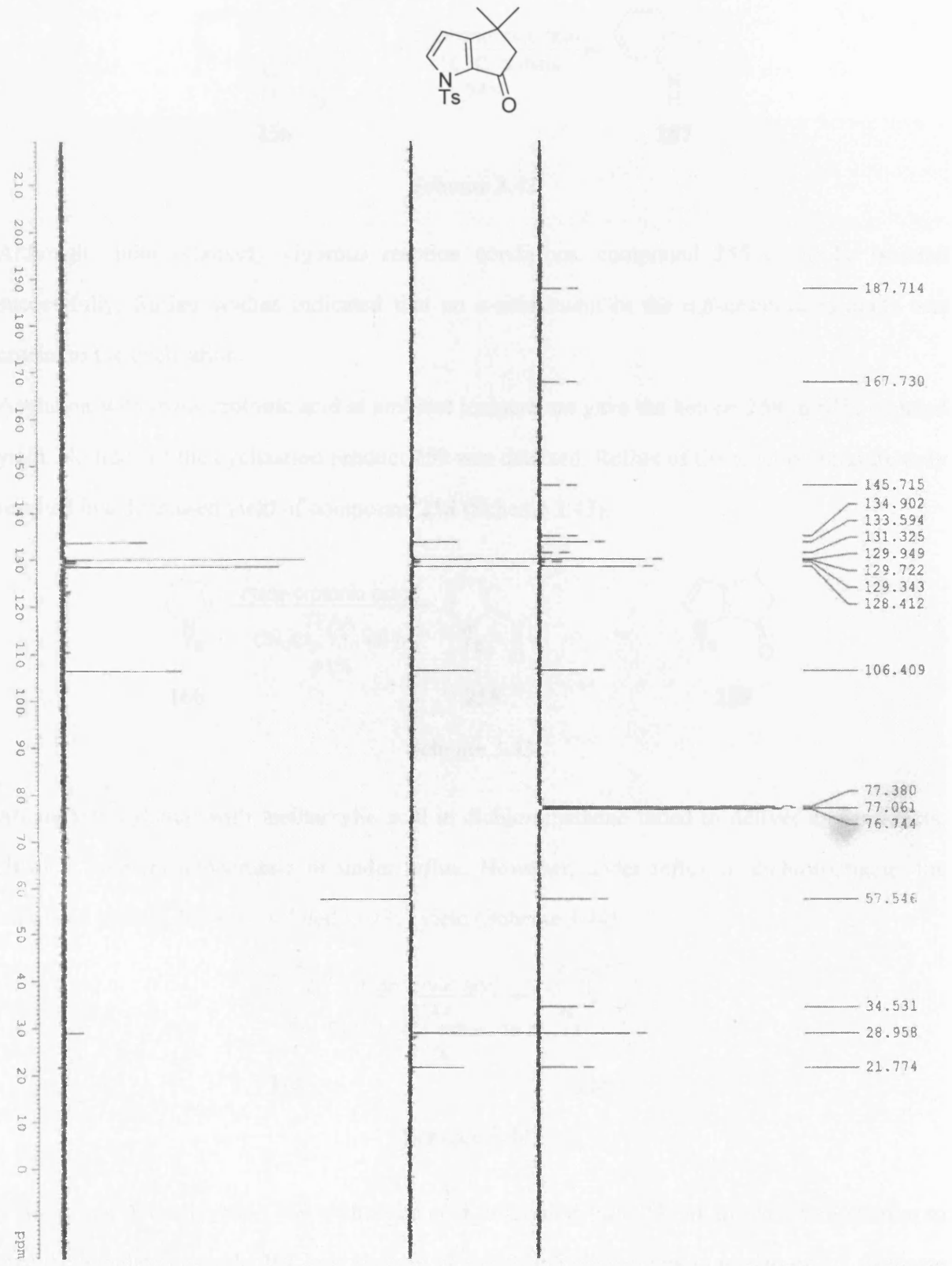
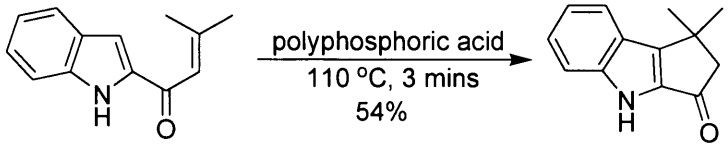


Figure 3.14

Although there is no literature precedent for this kind of reaction next to a pyrrole ring, there are some reports with a related indole ring system (Scheme 3.42).[183,184]

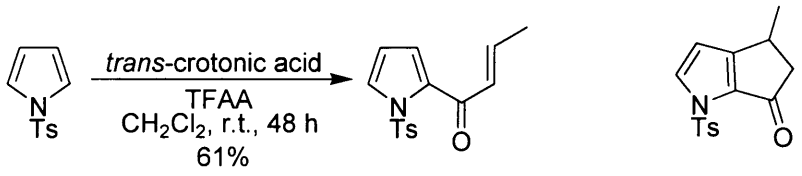


256 **257**

Scheme 3.42

Although under relatively vigorous reaction conditions, compound **255** could be isolated successfully, further studies indicated that an α-substituent in the α,β-unsaturated acids was crucial to the cyclisation.

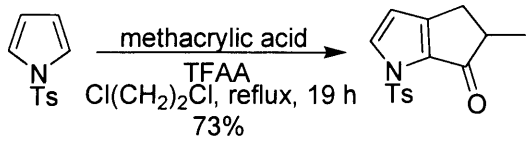
Acylation with *trans*-crotonic acid at ambient temperature gave the ketone **258** in 61% isolated yield. No trace of the cyclisation product **259** was detected. Reflux of the reaction mixture only resulted in a decreased yield of compound **258** (Scheme 3.43).



166 **258** **259**

Scheme 3.43

Attempted acylation with methacrylic acid in dichloromethane failed to deliver any products, either at ambient temperature or under reflux. However, under reflux in dichloroethane, the annulated pyrrole **260** was isolated in 73% yield (Scheme 3.44).

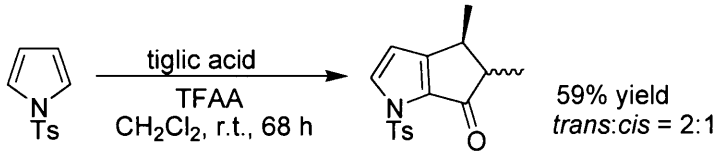


166 **260**

Scheme 3.44

Acylation of *N*-tosylpyrrole **166** with tiglic acid proceeded smoothly at ambient temperature to give the annulated pyrrole **261** as a mixture of *trans*- and *cis*-isomers in a ratio of 2:1 (Scheme 3.45). The *trans*- and *cis*-isomers of the annulated pyrrole **261** could be distinguished by the

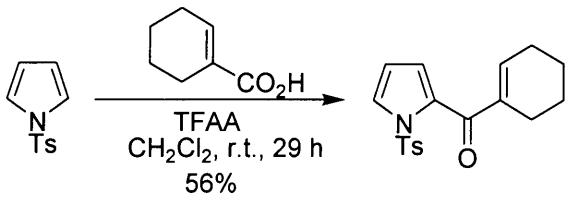
upfield shift[185] and relatively smaller coupling constant[186] of the ring-juncture protons in the *trans* side chain configuration. The ^{1}H NMR spectrum of the annulated pyrrole **261** (Figure 3.15) showed that the 5-ring proton of the *cis*-isomer resonated at 3.12 ppm and appeared as an apparent quintet with a coupling constant of 7.0 Hz; the 4-ring proton resonated at 2.89 ppm and also appeared as an apparent quintet with a coupling constant of 7.2 Hz. The 5-ring proton of the *trans*-isomer resonated at 2.58 ppm and appeared as double quartet with coupling constants of 2.7 and 7.0 Hz; the 4-ring proton was obscured by the Me of the tosyl group, which fell in the same region, 2.32-2.35 ppm.



166 **261**

Scheme 3.45

It is perhaps surprising that acylation of *N*-tosylpyrrole **166** with cyclohexene-1-carboxylic acid failed to deliver any cyclisation products and the ketone **262** was isolated in 56% yield, perhaps because of a steric effect or the conformational constraints of the cyclohexene ring (Scheme 3.46). Refluxing a mixture of compound **262** with trifluoroacetic anhydride or trifluoroacetic acid resulted in decomposition.



166 **262**

Scheme 3.46

^{1}H NMR Spectrum

***trans*- and *cis*-4,5-Dihydro-4,5-dimethyl-1-(4'-methylphenylsulfonyl)cyclopenta[*b*]pyrrol-6(1*H*)-one (261)**

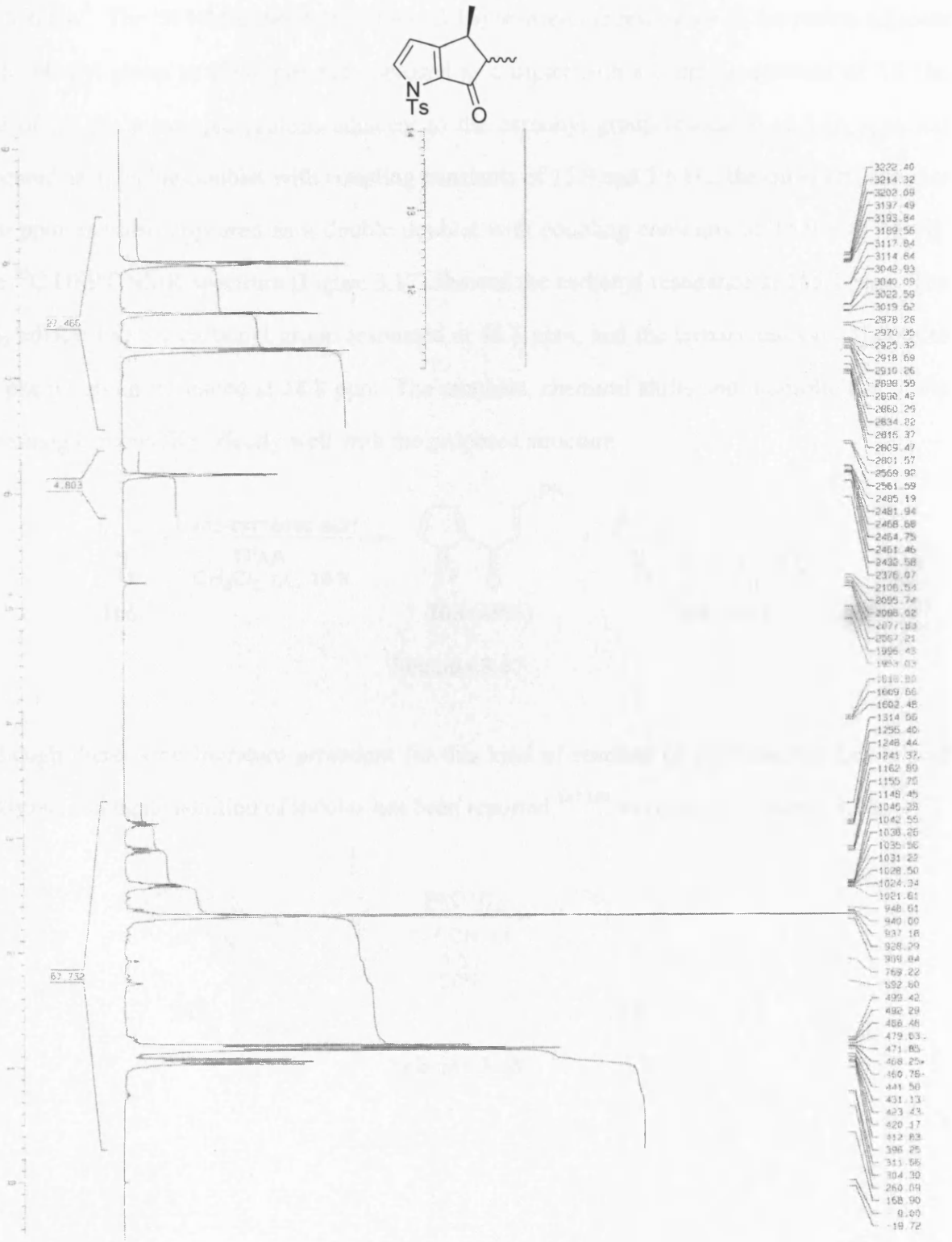
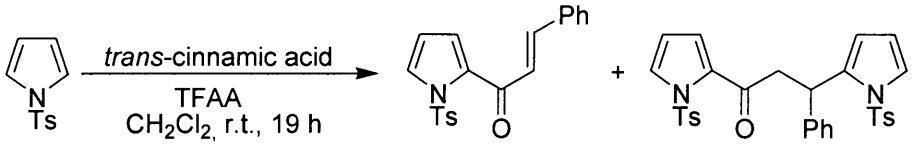


Figure 3.15

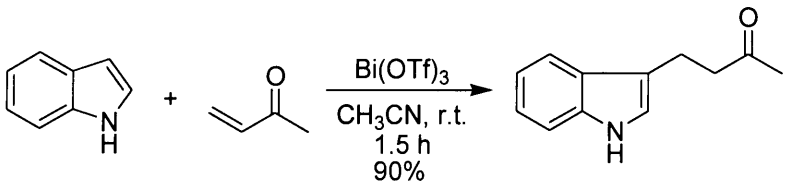
Acylation of *N*-tosylpyrrole **166** with *trans*-cinnamic acid gave a mixture of the ketone **263** and its conjugate addition product **264** with *N*-tosylpyrrole **166** in 49% and 9% isolated yield, respectively (Scheme 3.47). The IR spectrum of compound **264** showed the carbonyl absorption at 1676 cm^{-1}. The ^{1}H NMR spectrum (Figure 3.16) showed the resonance of the proton adjacent to the phenyl group at 5.08 ppm and appeared as a triplet with a coupling constant of 7.5 Hz. One of the diastereotopic protons adjacent to the carbonyl group resonated at 3.16 ppm and appeared as a double doublet with coupling constants of 15.9 and 7.5 Hz; the other resonated at 3.06 ppm and also appeared as a double doublet with coupling constants of 15.9 and 7.5 Hz. The ^{13}C DEPT NMR spectrum (Figure 3.17) showed the carbonyl resonance at 185.1 ppm. The CH_2 adjacent to the carbonyl group resonated at 46.6 ppm, and the tertiary carbon adjacent to the phenyl group resonated at 38.8 ppm. The numbers, chemical shifts and multiplicities of the remaining carbons fit perfectly well with the proposed structure.



166 **263** (49%) **264** (9%)

Scheme 3.47

Although there is no literature precedent for this kind of reaction of pyrroles, the Lewis acid catalyzed conjugate addition of indoles has been reported,[187,188] as shown in Scheme 3.48.



265 **266**

Scheme 3.48

^{1}H NMR Spectrum

3-Phenyl-1,3-bis[1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]propan-1-one (264)

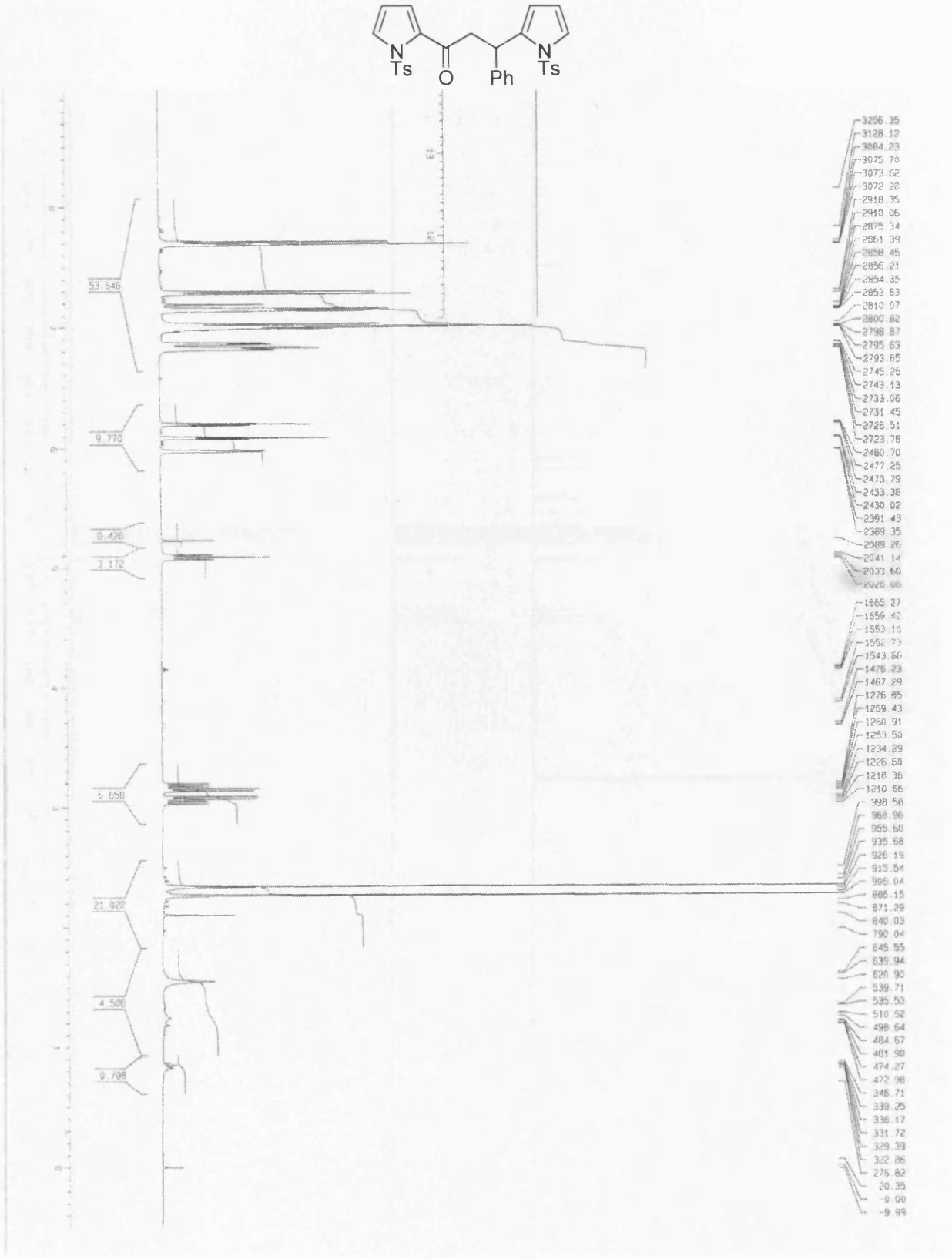
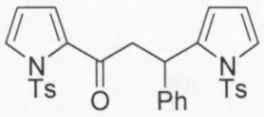


Figure 3.16

^{13}C NMR Spectrum

3-Phenyl-1,3-bis[1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]propan-1-one (264)



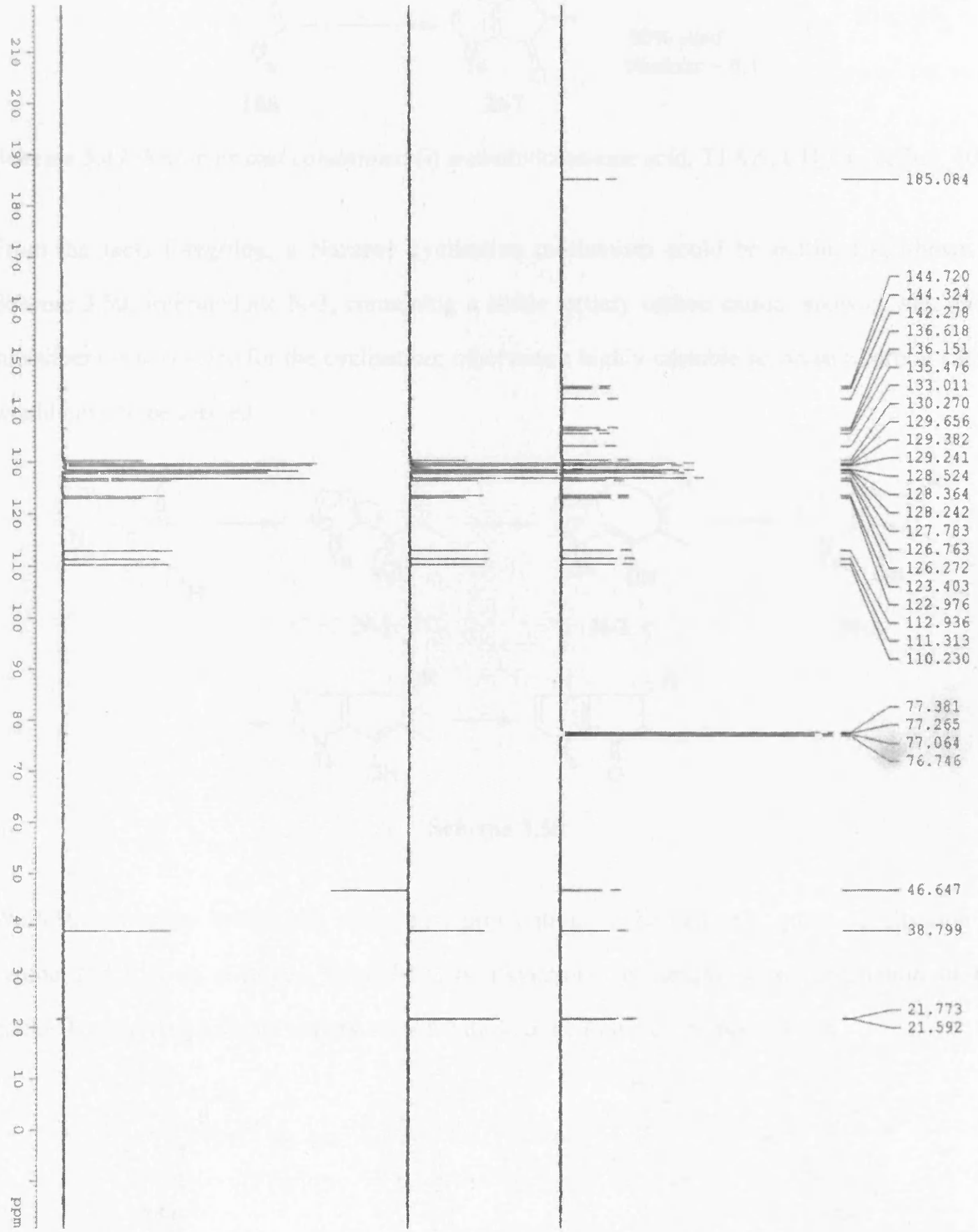
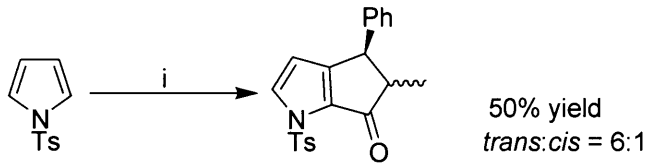


Figure 3.17

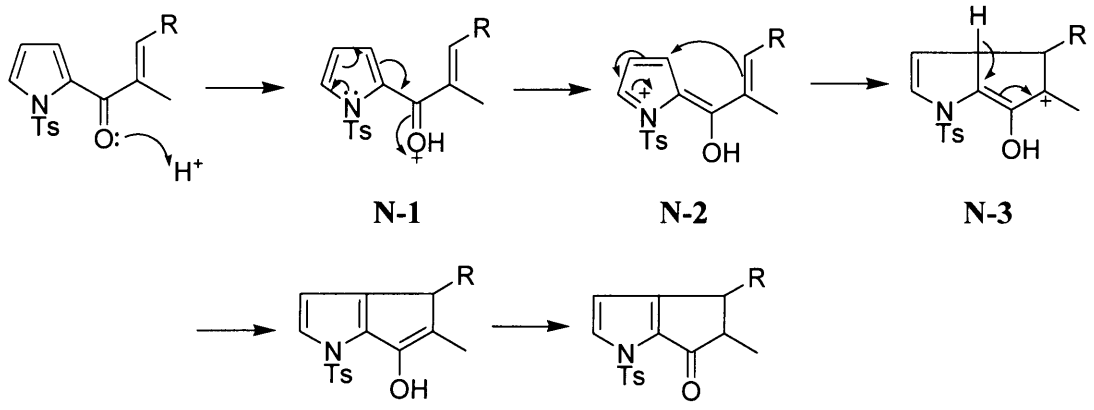
With an α-methyl substituent, that is, acylation of *N*-tosylpyrrole **166** with α-methylcinnamic acid gave the annulated pyrrole **267** in moderate yield, as a mixture of *trans*- and *cis*-isomers in a ratio of 6 : 1 (Scheme 3.49).



166 **267**

Scheme 3.49 *Reagents and conditions*: (i) α-methylcinnamic acid, TFAA, CH_2Cl_2, reflux, 40 h.

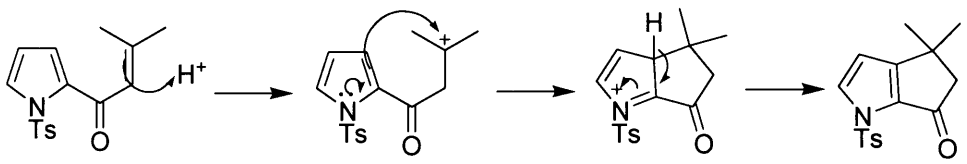
From the facts foregoing, a Nazarov cyclisation mechanism could be outlined as shown in Scheme 3.50. Intermediate N-3, containing a stable tertiary carbon cation, showed why an α-substituent is necessary for the cyclisation; otherwise a highly unstable secondary carbon cation would have to be formed.



N-1 **N-2** **N-3**

Scheme 3.50

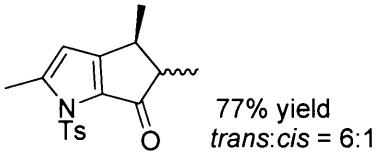
While the Nazarov cyclisation starts with protonation of the carbonyl group, cyclisation of ketone **254** follows a typical Friedel-Crafts alkylation mechanism, with protonation of the double bond giving a stable tertiary carbon cation in the first step (Scheme 3.51).



254 **255**

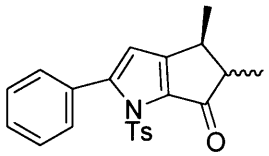
Scheme 3.51

Following a typical acylation procedure, annulated pyrrole **268** could be isolated in 77% yield as a mixture of *trans*- and *cis*-isomers in a ratio of 6:1 from 2-methyl-*N*-tosylpyrrole **186** following exposure to tiglic acid and trifluoroacetic anhydride in dichloromethane at ambient temperature for 48 hours (Figure 3.18). Similarly, annulated pyrrole **269** could be isolated in 51% yield as a mixture of *trans*- and *cis*-isomers in a ratio of 6:1 from 2-phenyl-*N*-tosylpyrrole **201**, after being refluxed with tiglic acid and trifluoroacetic anhydride in dichloromethane for 96 hours.



77% yield
trans:*cis* = 6:1

268

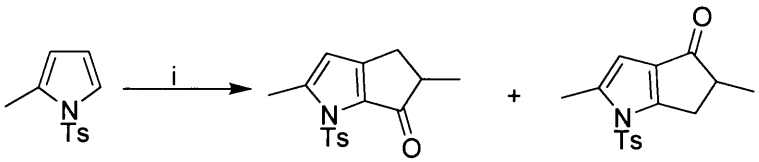


51% yield
trans:*cis* = 6:1

269

Figure 3.18

Acylation of 2-methyl-*N*-tosylpyrrole **186** with methacrylic acid and trifluoroacetic anhydride in refluxing dichloroethane was less regioselective and gave a mixture of annulated pyrroles **270** and **271** in excellent combined yield (Scheme 3.52), while acylation with *trans*-crotonic acid failed to give any separable products. The reason for the poor regioselectivity might be because of the severe reaction conditions and the relatively high reactivity of 2-methyl-*N*-tosylpyrrole **186** towards acylation.

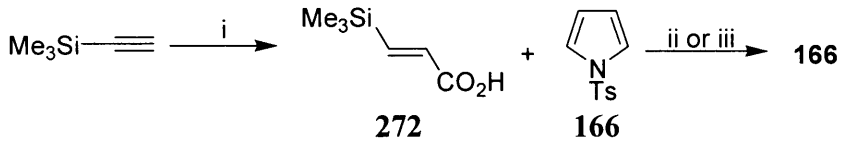


186 **270** **271**

Scheme 3.52 *Reagents and conditions*: (i) methacrylic acid, TFAA, $Cl(CH_2)_2Cl$, reflux, 21 h; 82% for **270**, 9% for **271**.

As indicated in section 3.7.1, a β-organosilicon group would benefit the Nazarov cyclisation for its β-cation stabilising property. If the above proposed mechanism for Nazarov cyclisation (Scheme 3.50) was correct, then a β-trialkylsilyl group would help by stabilising the carbon cation of intermediate **N-3**. In order to prove this, we synthesized the *E*-3-trimethylsilyl acrylic

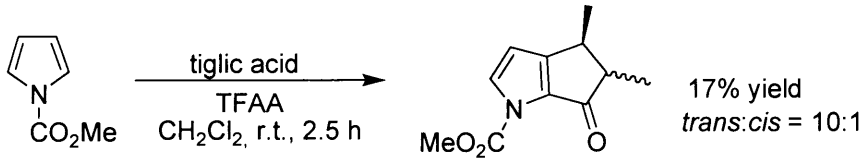
acid **272** in 59% from trimethylsilylacetylene, following a literature procedure.[189] Unfortunately, exposure of *N*-tosylpyrrole **166** to a mixture of the acid **272** and trifluoroacetic anhydride failed to deliver any product, either at ambient temperature in dichloromethane or under reflux in 1,2-dichloroethane (Scheme 3.53). In each case, the *N*-tosylpyrrole **166** was recovered.



272 **166**

Scheme 3.53 *Reagents and conditions*: (i) CO_2 (1 atm), $Ni(cod)_2$, DBU, THF, 0 °C, 2 h, 59%; (ii) TFAA, DCM, r.t., 3 days; (iii) TFAA, $Cl(CH_2)_2Cl$, reflux, 16 h.

Finally, acylation of methyl 1-pyrrolecarboxylate **273** with tiglic acid and trifluoroacetic anhydride in dichloromethane at ambient temperature gave annulated pyrrole **274** in 17% isolated yield as a mixture of *trans*- and *cis*-isomers in a ratio of 10:1 (Scheme 3.54). Another product was largely formed; however, we were unable to determine its structure.

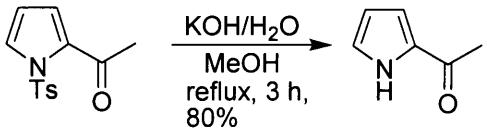


273 **274**

Scheme 3.54

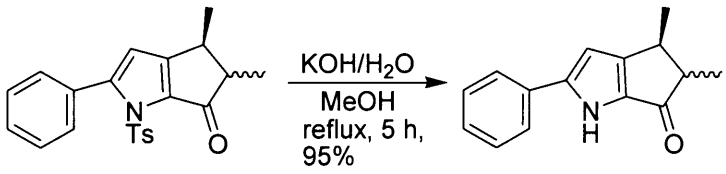
3.8 *N*-Detosylation.

'Free' 2-acetylpyrrole **171**[149] could be obtained in 80% yield by simply exposing the corresponding 2-acetyl-*N*-tosylpyrrole **210** to potassium hydroxide in aqueous methanol (Scheme 3.55). Similarly, 'free' annulated pyrrole **275** could also be obtained in 95% yield by detosylation of the corresponding *N*-tosyl derivative **269**, without a change in the ratio of the *trans*- and *cis*-isomers (Scheme 3.56).



210 **171**

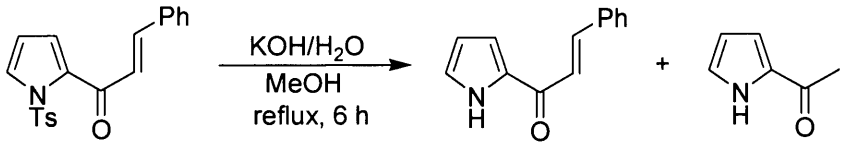
Scheme 3.55



269 **275**

Scheme 3.56

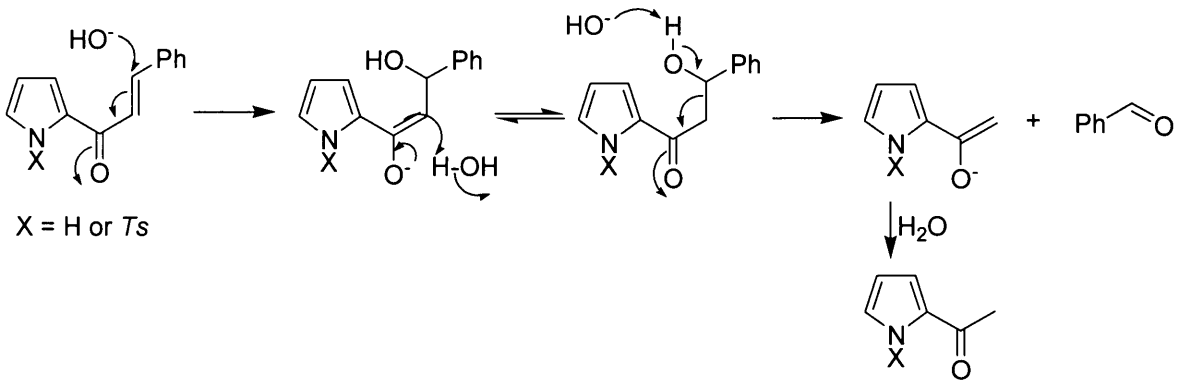
When this method was applied to ketone **263**, the corresponding detosylation derivative **276**[190] was isolated in 32% yield, accompanied by 2-acetylpyrrole **171**, which was isolated in 59% yield (Scheme 3.57)



263 **276** (32%) **171** (59%)

Scheme 3.57

Under the reaction conditions, a retro-aldol reaction occurred either on compound **263** or **276** to eventually yield the acetylpyrrole **171** (Scheme 3.58).



Scheme 3.58

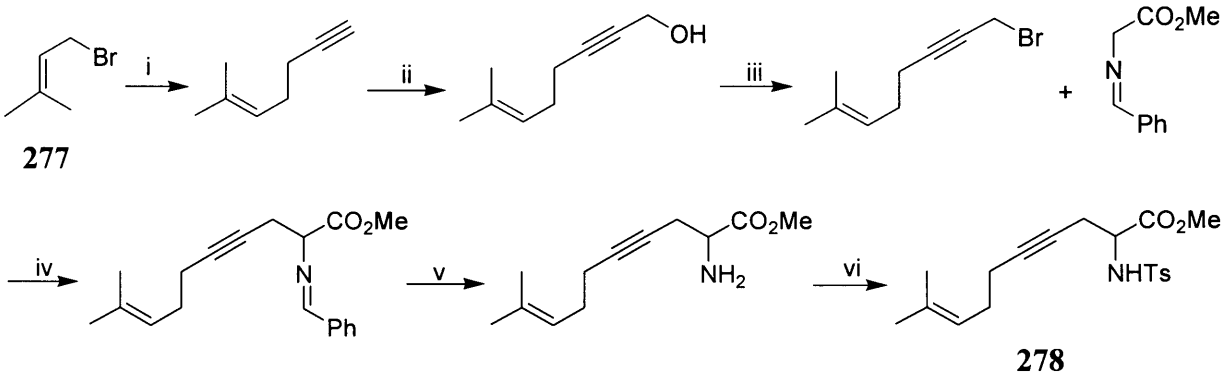
Although we have not examined any alternatives, clearly, another method for the detosylation of compound **263** needs to be defined.

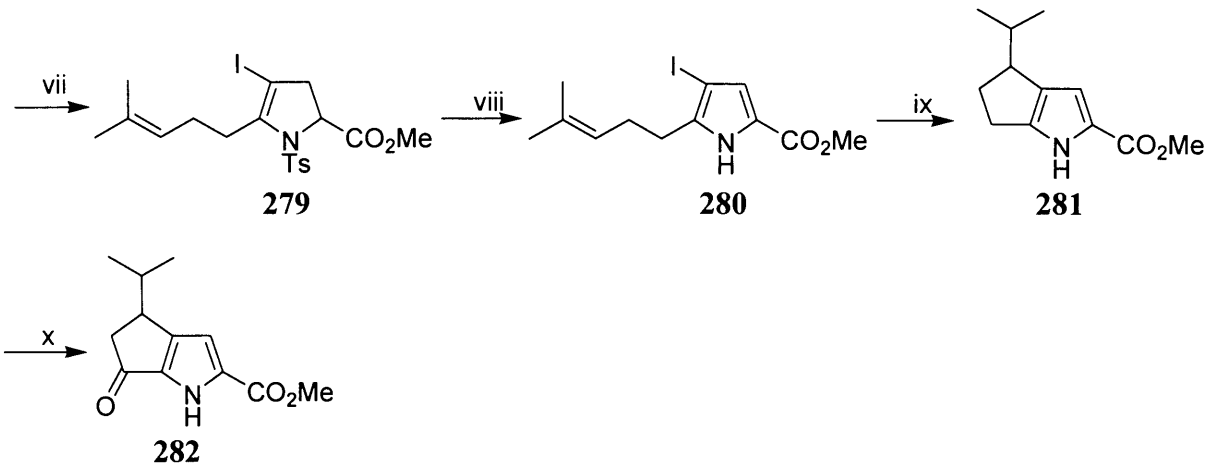
The Nazarov cyclisation for the preparation of annulated pyrroles in Section 3.7, together with the work of detosylation of this section leads us nicely to Section 3.9.

3.9 Studies towards the construction of the macrocyclic core of Roseophilin using Nazarov cyclisation.

3.9.1 Introduction - Previous work of the Knight group towards the construction of the mocrocyclic core of Roseophilin.

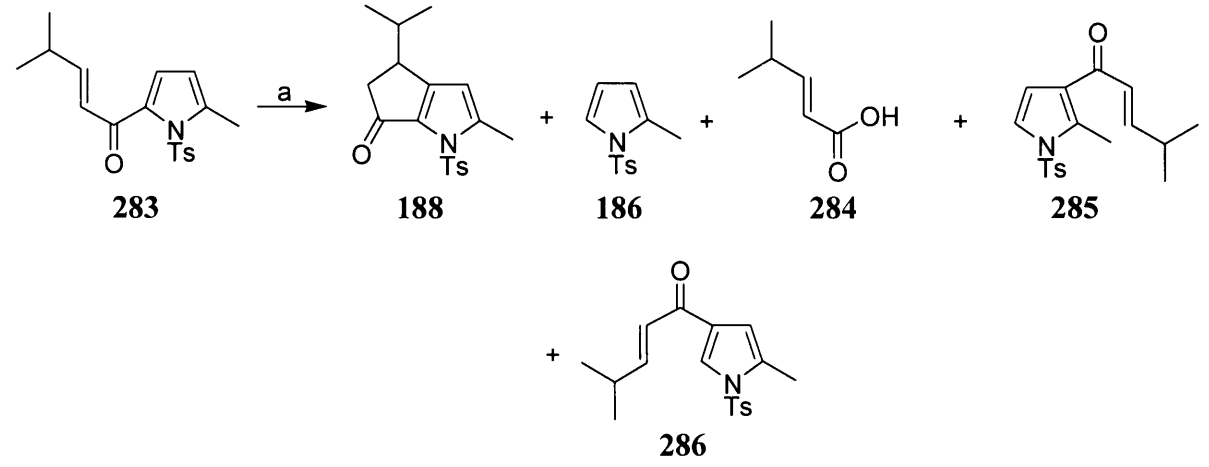
In 1999, Fagan and Knight[191] reported a 5-*endo*-dig iodocyclisation followed by radical cyclisation strategy to form the bicyclic core **282** of Roseophilin **3**, as shown in Scheme 3.59. Starting from commercially available prenyl bromide **277**, the key starting material **278** was synthesized in six steps, in good overall yield. Treatment of the enynoate **278** with iodine in dry acetonitrile in the presence of potassium carbonate gave 50 - 60% isolated yields of the iodo-dihydropyrrole **279**, which underwent smooth elimination of toluene-*p*-sulphinic acid upon exposure to 2.1 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dimethyl-formamide at ambient temperature, to provide the *β*-iodopyrrole **280** in 90% isolated yield. Radical cyclisation by slow addition of tributyltin hydride and azo-*bis*-isobutyronitrile (AIBN) to a refluxing benzene solution of iodopyrrole **280** gave the annulated pyrrole **281** in 65% isolated yield. Finally, the required ketone function was introduced by a very efficient oxidation using lead(IV) acetate in refluxing chloroform to give an intermediate *bis*-acetoxy species, which was readily hydrolysed to the target bicycle **282**.





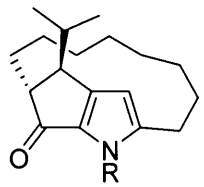
Scheme 3.59 *Reagents and conditions*: (i) $BrMgCH_2C{\equiv}CH$, $HgCl_2$, CuCl, Et_2O, 20 °C, 16 h; (ii) *n*-BuLi, THF, -78 °C then add $(CH_2O)_n$, warm to 20 °C, 16 h; (iii) NBS, PPh_3, DCM, -30 °C; (iv) glycine ester, LDA, THF, -78 °C then added alkynyl bromide and slowly warm to 20 °C, 16 h; (v) 1M HCl, Et_2O, 20 °C, 1 h, then K_2CO_3; (vi) TsCl, DMAP, Et_3N, DCM, 20 °C, 16 h; (vii) I_2, K_2CO_3, dry MeCN, 20 °C, 16 h, 50 – 60%; (viii) DBU, DMF, 20 °C, 24 h, 90%; (ix) Bu_3SnH, AIBN, C_6H_6, added during 8 h, 80 °C, 65%; (x) $Pb(OAc)_4$, $CHCl_3$, reflux, 24 h, then 1M HCl, 4h, 90%.

An alternative idea investigated by Fagan for construction of the cyclopentenone ring of the macrotricyclic core of roseophilin was to use a Nazarov cyclisation.[192] Thus, the precursor **283** was treated with a variety of Lewis or Brønsted acids, either at ambient temperature or under reflux conditions. These included zinc chloride, aluminium trichloride, boron trifluoride diethyl etherate, trifluoroacetic acid, ferric trichloride and tin tetrachloride. Among these, the use of tin tetrachloride gave the best results, but only in a disappointing 16% isolated yield of the hoped-for bicyclic ring **188**, together with the retro-Friedel-Crafts reaction products **186** and **284**, and the re-acylation products **285** and **286**, as shown in Scheme 3.60.



Scheme 3.60 *Reagents and conditions*: (a) $SnCl_4$, $CHCl_3$, 20 °C, 16 h.

By using α,β-unsaturated acids as acylation reagents as described in Section 3.7, the cyclopentenone ring of the macrocyclic core **287** (Figure 3.19) could be easily constructed in a one-pot reaction.

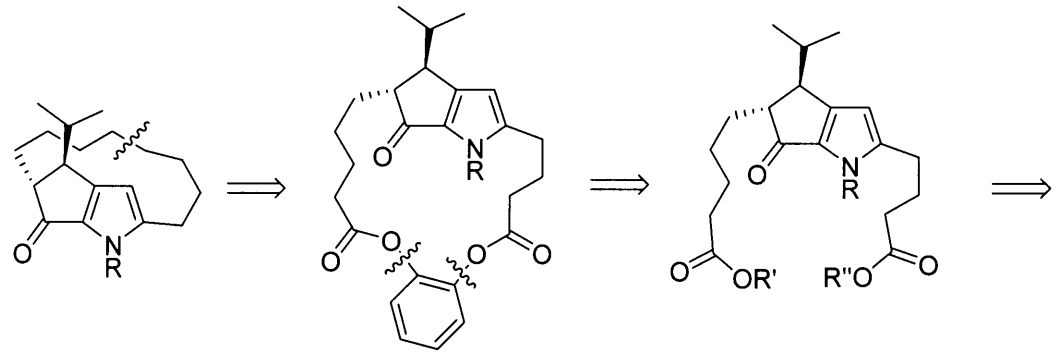


287

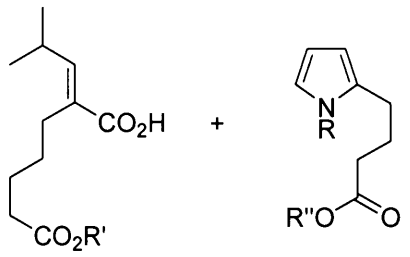
Figure 3.19 *Macrocyclic core of roseophilin.*

3.9.2 Retrosynthetic analysis.

The approach taken to the macrocyclic core **287** is outlined in retrosynthetic Scheme 3.61. The key step is an acylation of a pyrrole derivative **291** with an α,β-unsaturated acid **290** followed by Nazarov cyclisation to give the annulated pyrrole derivative **289**. If successful, ring closure of compound **289** by ester exchange with catechol could then give compound **288**. If R' or R'' is a 2-hydroxyphenoxyl group, then the ring closure reaction becomes intramolecular. Hopefully, Dieckmann reaction of compound **288** followed by decarboxylation and ketone reduction could then give the macrocyclic core **287**.



287 **288** **289**

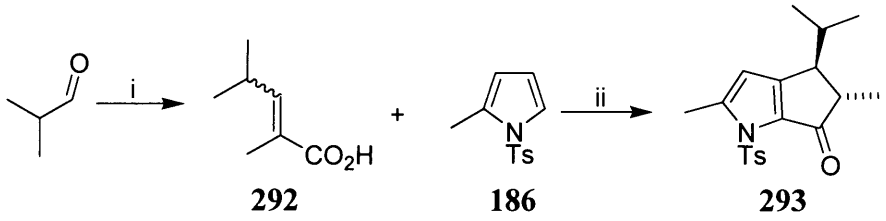


290 **291**

Scheme 3.61

3.9.3 A model system.

Due to the novel nature of this work, a model system was required. 2,4-Dimethylpent-2-enoic acid **292** and 2-methyl-*N*-tosylpyrrole **186** were chosen as the acylation components because of their structure similarity to compound **290** and **291**. Acid **292** was prepared by a Horner-Emmons reaction as a mixture of *E*- and *Z*-isomers in a ratio of 6:1 as a colourless oil.[193,194] It was used directly for the acylation of 2-methyl-*N*-tosylpyrrole **186** without further purification. Acylation of 2-methyl-*N*-tosylpyrrole **186** with acid **292** and trifluoroacetic anhydride proceeded smoothly at ambient temperature to give the annulated pyrrole **293** in 64% isolated yield as *trans*-isomer only, due to the bulk of the isopropyl group (Scheme 3.62).

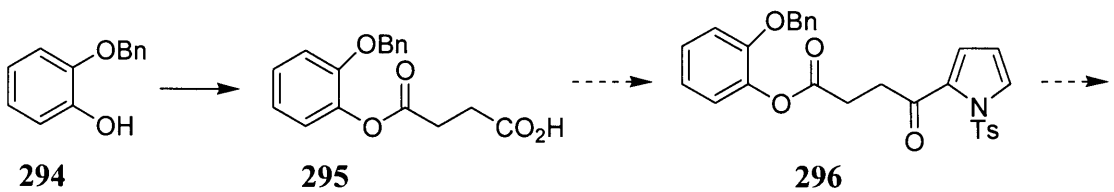


292 **186** **293**

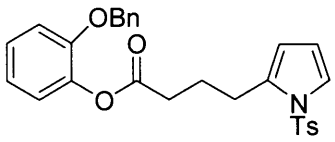
Scheme 3.62 *Reagents and conditions*: (i) NaH, $(EtO)_2PH(O)$, $CH_3CHBrCO_2H$, THF, r.t., 48 h, 58%; (ii) TFAA, CH_2Cl_2, r.t., 48 h, 64%.

3.9.4 Synthesis of substituted pyrrole component.

Because a catechol substitutent was needed in the ring closure step of compound **289**, we chose to synthesize the substituted pyrrole component where R'' in compound **291** was a 2-hydroxyphenoxyl group. As shown in Scheme 3.63, if acylation of *N*-tosylpyrrole **166** with the acid **295** was successful, selective reduction of the product **296** then gave the hoped-for pyrrole derivative **297**.



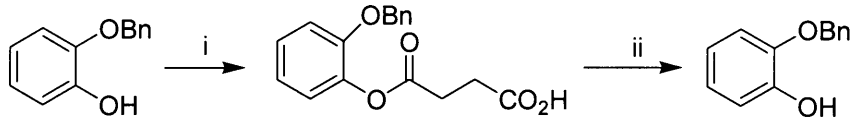
294 **295** **296**



297

Scheme 3.63

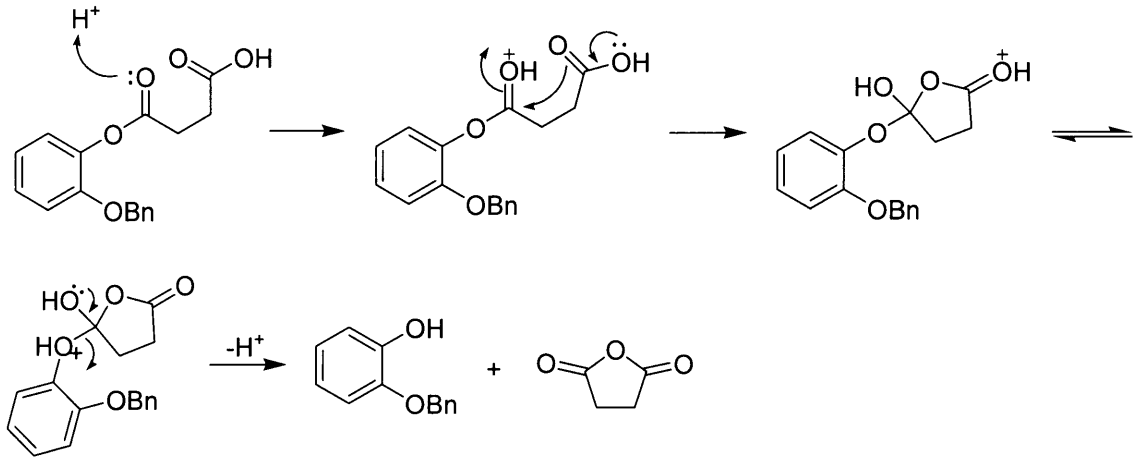
However, acylation of *N*-tosylpyrrole **166** with acid **295** in the presence of trifluoroacetic anhydride, after base work-up, gave compound **294** instead of **297** (Scheme 3.64).



294 **295** **294**

Scheme 3.64 *Reagents and conditions*: (i) succinic anhydride, DMAP, pyridine, r.t., 48 h, then 2M HCl, 96%; (ii) **166**, TFAA, CH_2Cl_2, r.t., 6 days.

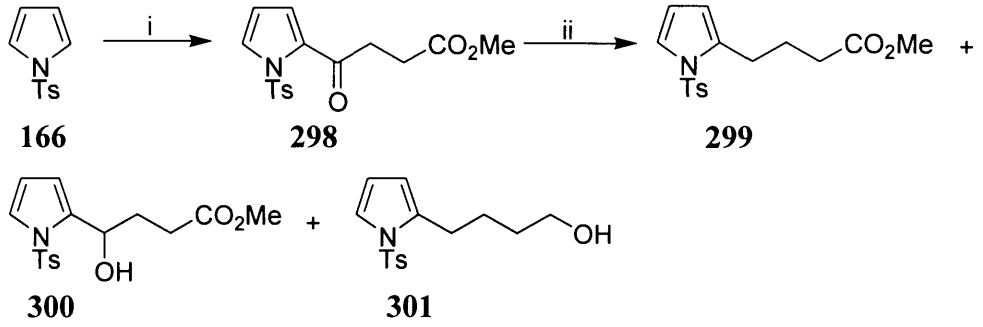
The 2-benzyloxyphenoxyl is a good leaving group. Under the reaction conditions, presumably an intramolecular cyclisation of compound **295** gave 2-benzyloxyphenol **294** and succinic anhydride (Scheme 3.65).



Scheme 3.65

Fortunately, acylation of *N*-tosylpyrrole **166** with mono-methyl succinate and trifluoroacetic anhydride under reflux in dichloroethane gave the acylpyrrole derivative **298** in almost quantitative yield as a solid (Scheme 3.66). Subsequent reduction of compound **298** with

borane-*tert*-butylamine complex in the presence of aluminium chloride was not very chemoselective, and gave compound **299** in 30% isolated yield only, together with compounds **300** and **301** in 9% and 29% yield respectively.

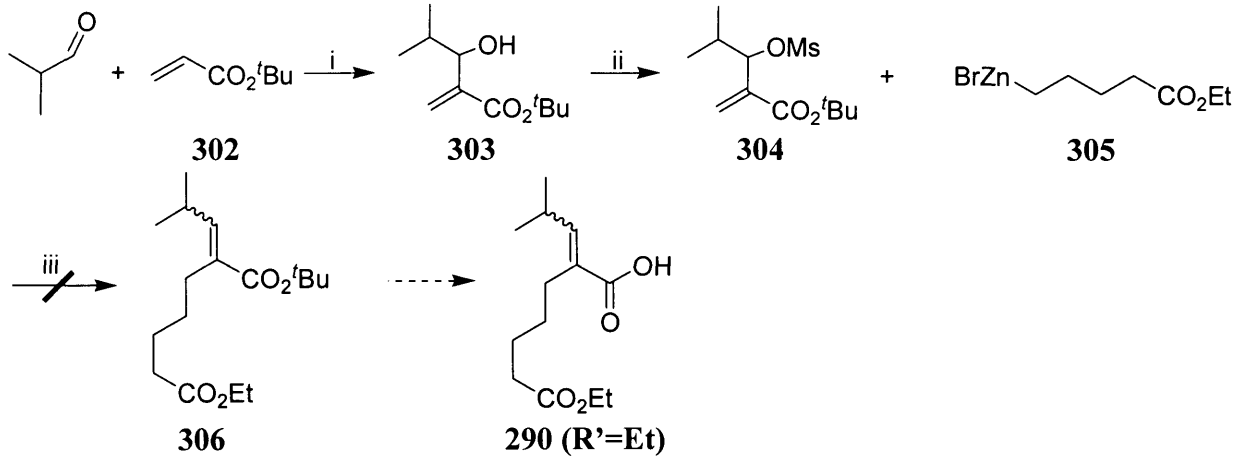


Scheme 3.66 *Reagents and conditions*: (i) mono-methyl succinate, TFAA, $Cl(CH_2)_2Cl$, reflux, 24 h, 99%; (ii) borane-*tert*-butylamine complex, $AlCl_3$, CH_2Cl_2, r.t., 2 h, 30% for **299**, 9% for **300**, 29% for **301**.

3.9.5 Synthesis of *α*, *β*-unsaturated acid component.

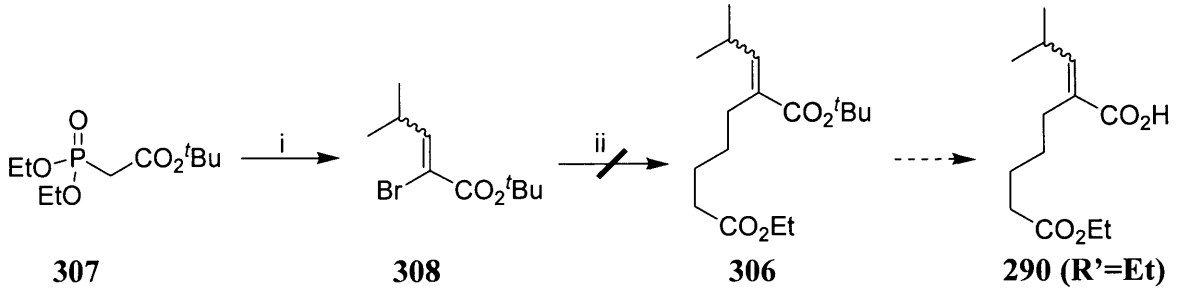
Having successfully synthesized the substituted pyrrole component **299**, we then needed to synthesize the *α*,*β*-unsaturated acid component **290**.

The first idea was a S_N2' displacement of the allylic mesylate **304** with 5-ethoxy-5-oxo-pentylzinc bromide **305**.[195] Baylis-Hillman reaction[196] between *iso*butyraldehyde and *tert*-butyl acrylate **302** for a prolonged reaction time gave compound **303** in 39% isolated yield. Mesylation of compound **303** then gave the allylic mesylate **304** in 82% isolated yield as a colourless oil. Unfortunately, attempted S_N2' displacement of compound **304** with 5-ethoxy-5-oxopentylzinc bromide **305** was unsuccessful. Treatment of compound **305** with copper cyanide before mixing it with allylic mesylate **304** also failed to deliver any S_N2' displacement product **306**, and in each case compound **304** was recovered (Scheme 3.67).



Scheme 3.67 *Reagents and conditions*: (i) quinuclidine, r.t., 28 days, 39%; (ii) MsCl, Et_3N, THF, 0 °C, 1 h, 82%; (iii) THF, -78 °C - r.t., 20 h.

A second idea for synthesizing the α,β-unsaturated acid component **290** was a coupling reaction between the bromopentenoate **308**[197] and 5-ethoxy-5-oxopentylzinc bromide **305**.[198] The bromopentenoate **308** was synthesized, according to a literature procedure *via* a Horner-Emmons reaction, in 53% isolated yield from compound **307**, as a mixture a *E*- and *Z*-isomers in a ratio of 5:4 as a colourless oil.[199] However, coupling between compound **308** and 5-ethoxy-5-oxopentylzinc bromide **305** catalysed by tris(dibenzylideneacetone)dipalladium(0) failed to deliver any product **306** (Scheme 3.68).



Scheme 3.68 *Reagents and condition*: (i) NaH, **307**, Et_2O, 0 °C, 1 h, then add Br_2, 2 h, then add NaH, 1 h, then add *iso*butyraldehyde, 0 °C - r.t., 17 h, 53%; (ii) $(C_6H_5CH{=}CHCO\text{-}CH{=}CHC_6H_5)_3Pd_2$, PPh_3, **305**, THF, r.t., 5 days.

3.10 Conclusion.

This chapter described a new method for the regioselective synthesis of 2-acylpyrroles by acylation of *N*-tosylpyrroles with carboxylic acids and trifluoroacetic anhydride, together with the first examples of Nazarov cyclisation using pyrroles. Because of the lack of time, the work in Section 3.9 for the construction of the macrocyclic core **287** of roseophilin was not pursued any further. But clearly there is a lot of scope for further investigation. Besides altering reactants and reaction conditions for the two routes introduced in Section 3.9.5, there are many alternative methods for the synthesis of the α, β-unsaturated acids component **290** such as a Suzuki coupling reaction between compound **308** and the corresponding organo-borane.

Chapter 4

Experimental

4.1 General details.

All non-aqueous reactions, unless otherwise stated, were conducted in oven or flame-dried apparatus under an atmosphere of dry nitrogen with magnetic stirring. Low temperatures were obtained using solid carbon dioxide and an acetone bath (-78 °C) or an ice-water bath (0 °C) or an ice-acetone bath (-10–0 °C). Heated reactions were conducted in a stirred oil bath heated on a magnetically stirred hotplate.

Solvents were dried and purified prior to use, where necessary. Tetrahydrofuran was distilled from sodium. *N*, *N*-Dimethylformamide, dichloromethane and acetonitrile were distilled from calcium hydride. Toluene was dried over sodium wire prior to use. Pyridine and triethylamine were dried over and distilled from potassium hydroxide. Ether was distilled from sodium benzophenone ketyl. All solutions of crude products were dried by brief exposure to anhydrous magnesium sulphate ($MgSO_4$), unless otherwise stated, then filtered and evaporated under reduced pressure (Buchi rotary evaporator under water pump pressure and a warm water bath). Column chromatography was carried out on Fisher silica gel 60A (particle size 35-70 micron) as the stationary phase, and the solvent petroleum ether referred to the fraction boiling in the range of 40–60 °C. All reactions were monitored by Thin Layer Chromatography (tlc) using Merck silica gel 60 F_{254} precoated aluminium backed plates that were visualised with ultraviolet light, and then with either potassium permanganate or ammonium molybdate as the appropriate. Retention factor values (R_f) were reported in the appropriate solvent system.

All melting points (mp °C) were determined on a Kofler hot-stage apparatus and were uncorrected. Infrared spectra were obtained using a Perkin Elmer 1600 series Fourier Transform Infrared Spectrometer, as liquid films on sodium chloride plates [film] or pressed into a transparent disc with dry powdered solid potassium bromide [KBr].

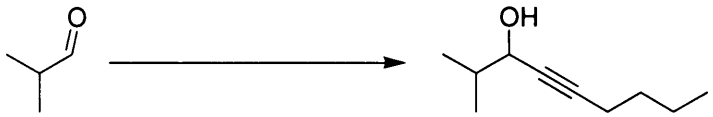
Proton (^{1}H) NMR spectra were recorded on a Bruker DPX 400 instrument at 400 MHz, as dilute solutions in deuteriochloroform at 298 K, unless otherwise stated. The chemical shifts were recorded relative to residual chloroform (7.27 ppm) as an internal standard. Abbreviations used for the multiplicities were: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), br. (broad), m (unresolved multiplet), app. (apparent) or as a combination of multiplicities. All coupling constants (*J*) were recorded in Hertz (Hz). Carbon (^{13}C) NMR spectra were recorded on the same instrument and conditions, but operating at 100.6 MHz. Chemical shifts were reported relative to residual chloroform (77.0 ppm) as an internal standard in a broad band decoupled mode. Assignments were made on the basis of chemical shift and coupling constant data using DEPT-135 and COSY experiments where required.

Mass spectra were recorded on a FisonsVG Platform Quadrapole Mass Spectrometer using atmospheric pressure chemical ionisation [APCI]. m/z Values were reported with the percentage abundance in parentheses. Accurate high resolution mass spectral data were determined by the EPSRC Mass Spectrometry Service Centre at University of Wales Swansea and the molecular formula corresponds to the observed signal using the most abundant isotopes of each element. All molecular formula were given for value quoted either molecular + hydrogen (M^+ + H) or molecular + ammonium ion ($M^+ + NH_4$). Microanalytical data were determined by Warwick Analytical Service Ltd at University of Warwick and were quoted as atom percentages.

4.2 Experimental procedures.

All compounds described in this thesis, where relevant, are racemates unless indicated otherwise.

2-Methylnon-4-yn-3-ol (92)[118]

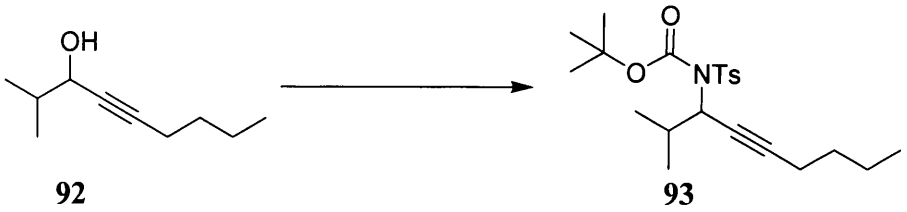


92

To an ice-cold solution of 1-hexyne (2.17 g, 26.3 mmol, 1.2 eq) in dry tetrahydrofuran (50 ml) was added *n*-butyllithium (9.6 ml of a 2.5 M solution in hexane, 24 mmol, 1.1 eq). The reaction mixture was stirred at 0 °C for 0.5 h. Isobutyraldehyde (1.58 g, 21.9 mmol, 1.0 eq) was added dropwise and the resulting mixture stirred for a further 1.5 h at 0 °C, before the addition of water (3 ml). The tetrahydrofuran was evaporated. The residue was partitioned between saturated aqueous ammonium chloride (50 ml) and diethyl ether (50 ml), and the separated aqueous phase extracted with diethyl ether (2 x 50 ml). The combined organic solutions were washed with brine, then dried, filtered and evaporated to give the *propargylic alcohol* **92** (2.86 g, 85%) as an orange oil. The spectroscopic data obtained were in accord with those previously reported in the literature:[118] R_f 0.49 (petroleum ether-diethyl ether 3:1); ν_{max}/cm^{-1} [film] 3363 (OH), 1468, 1381, 1149 and 1024; δ_H 4.00 (1H, dt, *J* 6.1 and 2.2, 3-H), 2.40 (1H, *br. s.*, OH), 2.07 (2H, td, *J* 7.6 and 2.2, 6-CH_2), 1.73-1.64 (1H, m, 2-H), 1.42-1.21 (4H, m, 7- and 8-CH_2) and 0.85-0.72 (9H, m, 3 x Me); δ_C 86.3, 80.2 (both C), 68.3 (3-CH), 35.1 (2-CH), 31.1(6-CH_2), 22.2 (7-CH_2), 18.7 (Me), 18.5 (Me), 17.7 (8-CH_2) and 13.9 (9-Me); m/z (APCI) 155 (M^+ + H, 2%), 137 (M^+ - H_2O, 98), 115 (39), 95 (25), 83 (61), 81 (100) and 71 (76).

(The sample was pure enough for use in the next step. Attempted vacuum distillation resulted in extensive loss.)

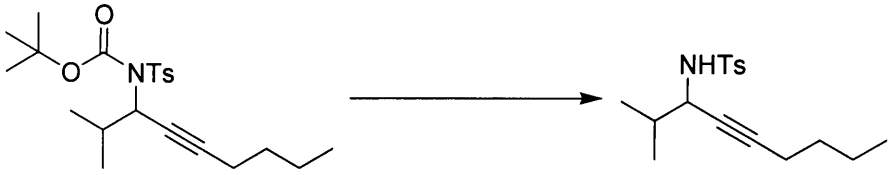
N-(*tert*-Butoxycarbonyl)-2-methyl-N-(4'-methylphenylsulfonyl)-non-4-yn-3-amine (93)



92 **93**

A solution of the propargylic alcohol **92** (0.90 g, 5.83 mmol, 1.0 eq), *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulphonamide (1.58 g, 5.83 mmol, 1.0 eq) and triphenylphosphine (1.68 g, 6.41mmol, 1.1 eq) in dry tetrahydrofuran (50 ml) was stirred at 0 °C under nitrogen for 10 minutes. Diethyl azodicarboxylate (1.12 g, 6.41mmol, 1.1 eq) was then added dropwise. The resulting mixture was then allowed to warm to room temperature and stirred for 16 hours, and the bulk of the tetrahydrofuran was evaporated. The residue was partitioned between dichloromethane (50 ml) and water (50 ml) and the separated aqueous layer extracted with dichloromethane (2 x 50 ml). The combined organic extracts were dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 9 : 1) to give the *non-4-yn-3-amine derivative* **93** (1.77 g, 74%) as an orange oil: R_f 0.89 (dichloromethane); ν_{max}/cm^{-1} [film] 1732 (C=O), 1599, 1468, 1356, 1280, 1249 and 1153; δ_H 7.82 (2H, d, *J* 8.3, 2'- and 6'-H), 7.21 (2H, d, *J* 8.3, 3'- and 5'-H), 4.71 (1H, dt, *J* 10.5 and 2.2, 3-H), 2.42 (1H, dsept, *J* 10.5 and 6.7, 2-H), 2.35 (3H, s, *Ts*-Me), 2.13 (2H, td, *J* 7.0 and 2.2, 6-CH_2), 1.41-1.28 (4H, m, 7- and 8-CH_2), 1.26 (9H, s, ^{t}Bu), 1.04 (3H, d, *J* 6.7, Me), 0.95 (3H, d, *J* 6.7, Me) and 0.80 (3H, t, *J* 7.2, 9-Me); δ_C 150.2 (C=O), 143.8, 137.6 (both C), 129.1 (2'- and 6'-CH), 127.8 (3'- and 5'-CH), 84.4, 84.2, 77.7 (all C), 57.3 (3-CH), 32.4 (2-CH), 30.7 (6-CH_2), 27.9 (^{t}Bu), 21.8 (7-CH_2), 21.6, 20.8, 19.4 (all Me), 19.2 (8-CH_2) and 13.6 (9-Me); m/z (APCI) 352 (M^+ - ^{t}Bu, 15%), 137 (100), 81 (30); m/z (NH_4-CI) 425 (M^+ + NH_4, 10%), 369 (50), 325 (100) [Found: M^+ + NH_4, 425.2475. $C_{22}H_{37}N_2O_4S$ requires 425.2469].

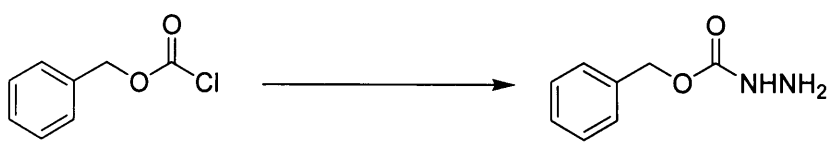
2-Methyl-*N*-(4'-methylphenylsulfonyl)-non-4-yn-3-amine (94)[119]



93 **94**

A solution of the non-4-yn-3-amine derivative **93** (843 mg, 2.1 mmol) in trifluoroacetic acid (1 ml) and dichloromethane (4 ml) was stirred at 0 °C for 5 minutes, then at room temperature for 2 h, before being partitioned between saturated aqueous sodium carbonate (20 ml) and dichloromethane (20 ml). The separated aqueous phase was extracted with dichloromethane (2 x 20 ml). The combined organic solutions were dried, filtered, and evaporated to give the *N-tosylnon-4-yn-3-amine* **94** (585 mg, 92%) as an orange solid. An analytical sample was obtained by recrystallization from hexane to give a colourless solid. The spectroscopic and analytical data obtained were in accord with those previously reported in the literature[119] and showed: R_f 0.10 (petroleum ether-diethyl ether 5 : 1); mp: 79.5-80.5 °C [lit.[119] mp 76-77 °C]; ν_{max}/cm^{-1} [KBr] 3270 (NH), 2220, 1462, 1377 and 1162; δ_H 7.72 (2H, d, *J* 8.2, 2_{Ts}- and 6_{Ts}-H), 7.21 (2H, d, *J* 8.2, 3_{Ts}- and 5_{Ts}-H), 4.88 (1H, *br.* d, *J* 5.2, NH), 3.78 (1H, ddt, *J* 9.5, 5.2 and 2.1, 3-H), 2.34 (3H, s, *Ts*-Me), 1.81-1.75 (3H, m, 2-H and 6-CH_2), 1.15-1.11 (4H, m, 7- and 8-CH_2), 0.87 (6H, d, *J* 6.8, 2 x Me) and 0.75 (3H, t, *J* 7.0, 9-Me); δ_C 143.5, 138.0 (both C), 129.7 (2_{Ts}- and 6_{Ts}-CH), 127.8 (3_{Ts}- and 5_{Ts}-CH), 86.0, 76.9 (both C), 52.2 (3-CH), 34.2 (2-CH), 30.8 (6-CH_2), 22.2 (*Ts*-Me), 21.9 (7-CH_2), 19.1 (Me), 18.4 (Me), 17.9 (8-CH_2) and 13.9 (9-Me); m/z (APCI) 308 ($M^+ + 1$, 100%), 137 (68) and 81 (72).

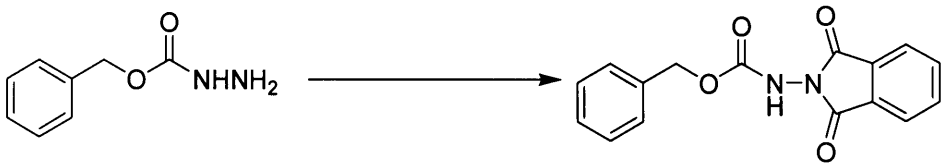
Benzyl carbazate (97)[121]



96 **97**

To a vigorously stirred solution of hydrazine monohydrate (10.0 g, 0.2 mol, 1.0 eq) in diethyl ether (50 ml) was added dropwise benzyl chloroformate **96** (6.9 g, 0.04 mol, 0.2 eq) over 0.5 h, keeping the temperature of the reaction mixture between –5 °C and –2 °C. After the addition, the reaction mixture was stirred for a further 1 h without cooling, during which time a precipitate formed. Water (20 ml) was then added and the two clear phases separated. The ethereal solution was washed with water (5 ml), then dried and treated with ethereal hydrogen chloride [Preparation procedure: To an ice-cold solution of dry methanol (12.8 g, 0.4 mol, 1.0 eq) in diethyl ether (30 ml) was added dropwise acetyl chloride (31.4 g, 0.4 mol, 1.0 eq). The resulting reaction mixture was stirred for 0.5 h to give the ethereal solution of hydrogen chloride]. The resulting precipitate was filtered and dried under reduced pressure to give *benzyl carbazate hydrochloride* (4.7 g, mp 155~155.5 °C [lit.[121] mp 170-170.5 °C]) as a colorless solid, which was suspended in ice-cold chloroform (30 ml). Diethylamine was added until a clear solution was obtained. Diethyl ether (120 ml) was then added and the resulting precipitate of diethylamine hydrochloride was filtered off. The filtrate was evaporated. The residue was recrystallised from ether to give the *benzyl carbazate* **97** (3.3 g, 50%) as a colourless solid, which showed: mp 65-67 °C; [lit.[121] mp 67-69 °C]; [found: C, 57.94; H, 6.05; N 16.82. $C_8H_{10}N_2O_2$ requires C, 57.82; H, 6.07; N, 16.86%]; ν_{max}/cm^{-1} [KBr] 3303 (NH), 3190 (NH), 1688 (C=O), 1650, 1524, 1464, 1377, 1296 and 1086; δ_H 7.17 (5H, *br. res.*, Ar-H), 6.37 (1H, *br.* s, NH), 4.96 (2H, s, CH_2) and 3.57 (2H, *br.* s, NH_2); δ_C 159.1 (C=O), 136.4 (C), 129.0 (2 x CH), 128.7 (CH), 128.6 (2 x CH) and 67.7 (CH_2); m/z (APCI) 167 (M^+ + H, 5%) and 91 (100).

_N_-Benzyloxycarbonylaminophthalimide (98)[120]

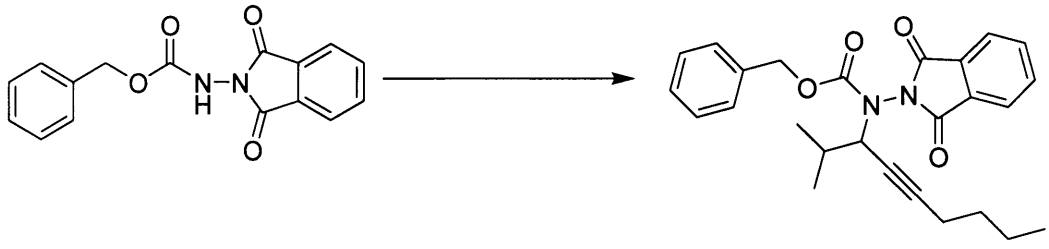


97 **98**

A solution of phthalic anhydride (446 mg, 3.0 mmol, 1.0 eq) and benzyl carbazate **97** (500 mg, 3.0 mmol, 1.0 eq) in dry tetrahydrofuran (40 ml) was stirred at room temperature for 10

minutes, before the addition of *N,N*-dicyclohexylcarbodiimide (745 mg, 3.6 mmol, 1.2 eq). The resulting reaction mixture was stirred for 1 h. The white precipitate of dicyclohexylurea was removed by filtration. Acetic acid (362 mg, 6.0 mmol, 2 eq) and triethylamine (609 mg, 6.0 mmol, 2.0 eq) were then added to the filtrate and the resulting reaction mixture was refluxed for 1 h. The bulk of the volatiles was evaporated and the residue partitioned between diethyl ether (100 ml) and water (50 ml). The separated aqueous layer was extracted with diethyl ether (2 x 50 ml). The combined organic solutions were dried, filtered and evaporated to give a solid, which was purified by column chromatography (petroleum ether-diethyl ether 3 : 1) to give the *phthalimide* **98** (759 mg, 85%) as a colourless solid. The data obtained were in accord with those previously reported in the literature:[120] mp 131-132 °C [lit.[120] mp 140 °C]; ν_{max}/cm^{-1} [KBr] 3252 (NH), 1797 (C=O), 1729 (C=O), 1463, 1377, 1252 and 1115; δ_H 7.83 (2H, dd, *J* 5.2 and 3.1, Ar-H), 7.71 (2H, dd, *J* 5.2 and 3.1, Ar-H), 7.29 (5H, *br.* s, Ar-H), 7.05 (1H, s, NH) and 5.13 (2H, s, Ph*CH*$_2$); δ_C 168.0 (C=O), 157.4 (C=O), 138.3 (C), 137.5 (2 x CH), 132.6 (CH), 131.3 (2 x CH), 131.0 (2 x CH), 128.6 (C), 126.8 (2 x CH) and 71.3 (Ph*CH*$_2$); m/z (APCI) 297 (M^+ + H, 75%), 151 (20) and 91 (100).

_N_-Benzyloxycarbonyl-_N_-(2-methylnon-4-yn-3-yl)aminophthalimide (99)

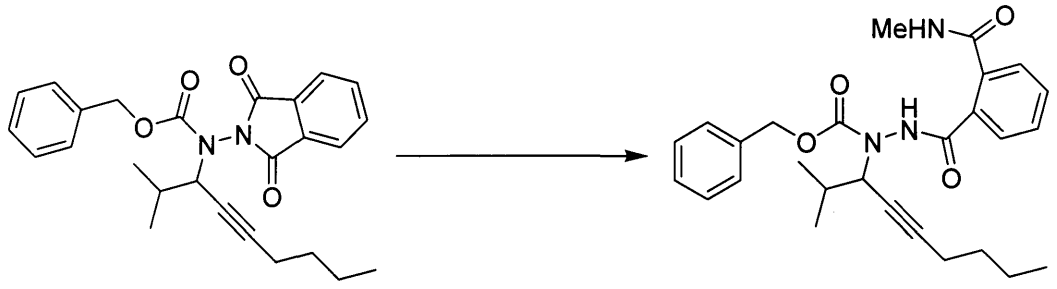


98 **99**

To an ice-cold solution of *N*-benzyloxycarbonylaminophthalimide **98** (260 mg, 0.88 mmol, 1.0 eq), triphenylphosphine (346 mg, 1.32 mmol, 1.5 eq) and 2-methylnon-4-yn-3-ol **92** (204 mg, 1.32 mmol, 1.5 eq) in dry tetrahydrofuran (40 ml) was added diethyl azodicarboxylate (230 mg, 1.32 mmol, 1.5 eq). The resulting mixture was stirred at 0 °C for 2 h, then allowed to warm to ambient temperature and stirred for a further 1 h. The solvent was evaporated and the residue partitioned between ethyl acetate (50 ml) and water (50 ml). The separated aqueous phase was

extracted with ethyl acetate (2 x 50 ml) and the combined organic extracts dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 4 : 1) to give the *phthalimide* **99** (279 mg, 73%) as a colourless oil: R_f 0.31 (petroleum ether-diethyl ether 3 : 1); ν_{max}/cm^{-1} [film] 1799 (C=O), 1747 (C=O), 1468, 1412, 1382, 1288, 1215 and 1078; δ_H 7.93-7.79 (4H, m, Ar-H), 7.60-7.18 (5H, m, Ar-H), 5.27-4.82 (3H, m, *br. res.*, Ph*CH*$_2$ and 3-H), 2.05 (3H, *br. res.*, 2-H and 6-CH_2), 1.28-1.07 (10H, m, 7- and 8-CH_2, 2 x Me) and 0.76-0.73 (3H, *br. res.*, 9-Me); δ_C 166.1, 165.5, 154.7 (all C=O), 136.0, 135.0, 130.4, 130.2, 128.8, 128.3, 127.6, 124.2, 124.1, 88.4 (C, *br. res.*), 74.8 (C, *br. res.*), 69.5 and 68.7 (Ph*CH*$_2$), 60.0 (3-CH, *br. res.*), 33.7 (2-CH, *br. res.*), 30.8 (6-CH_2), 22.2 (7-CH_2), 20.2 (Me, *br. res.*), 19.3 (Me, *br. res.*), 18.6 (8-CH_2) and 13.9 (9-Me); m/z (APCI) 433 (M^+ + H, 100%) and 377 (22) [Found: M^+ + H, 433.2124. $C_{26}H_{29}N_2O_4$ requires 433.2122].

1-Benzyloxycarbonyl-2-[(2''-methylcarbamoyl)benzoyl]-1-(2'-methylnon-4'-yn-3'-yl)-hydrazine (102)

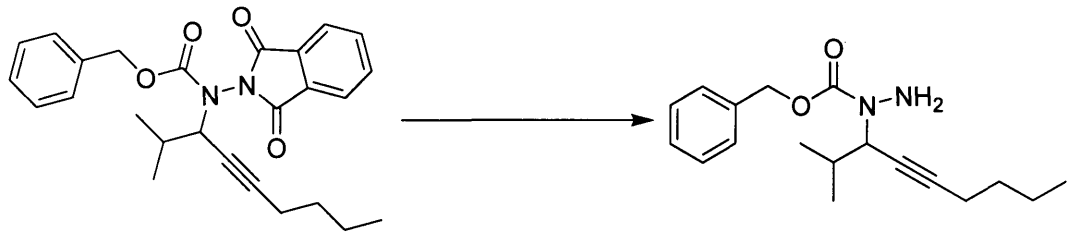


99 **102**

To an ice-cold solution of the phthalimide **99** (200 mg, 0.46 mmol, 1.0 eq) in tetrahydrofuran was added methylamine (40% solution in water, 75 mg, 0.97 mmol, 2.1 eq). The resulting mixture was then allowed to warm to ambient temperature and stirred for 19 h, before being evaporated. The residue was dissolved in ethyl acetate (20 ml), then the solution dried and evaporated to give the *hydrazine* **102** (208 mg, 98%) as a viscous oil: ν_{max}/cm^{-1} [film] 3288 (NH), 2229, 1714 (C=O), 1693 (C=O), 1641 (C=O) and 1597; δ_H 8.59 (1H, *br. s*, NH), 7.46-7.23 (9H, m, Ar-H), 6.84 (1H, *br.* s, NH), 5.06 (2H, *br.* s, Ph*CH*$_2$), 4.69 (1H, *br. res.*, 3'-H), 2.66 (3H, *br.* s, *Me*NH), 2.09 (2H, td, *J* 6.9 and 1.7, 6'-CH_2), 1.90-1.82 (1H, m, 2'-H), 1.38-1.23

(4H, m, 7'- and 8'-CH_2), 0.98 (6H, d, *J* 6.7, 2 x Me) and 0.75 (3H, t, *J* 7.2, 9'-Me); δ_C 168.6 (C=O), 155.6 (C=O), 136.2, 135.2, 132.4 (all C), 131.3 (2 x CH), 130.5 (2 x CH), 128.9 (2 x CH), 128.6 (CH), 128.2 (2 x CH), 87.2, 75.7 (both C), 68.8 (Ph*CH*$_2$), 60.8 (3'-CH), 32.5 (2'-CH), 31.0 (6'-CH_2), 27.3 (MeNH), 22.4 (7'-CH_2), 20.1, 19.9 (both Me), 18.8 (8'-CH_2) and 14.0 (9'-Me); m/z (APCI) 464 (M^+ + H, 100%), 433 (5), 83 (20) and 71 (54) [Found: M^+ + H, 464.2545. $C_{27}H_{34}N_3O_4$ requires 464.2544].

1-Benzyloxycarbonyl-1-(2'-methylnon-4'-yn-3'-yl)hydrazine (103)



99 **103**

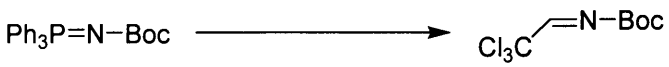
A solution of the phthalimide **99** (910 mg, 2.1 mmol, 1.0 eq) and hydrazine hydrate (107 mg, 2.1 mmol, 1.0 eq) in ethanol (20 ml) was refluxed for 2 h and then cooled. Concentrated hydrochloric acid (32%) was added until the solution was strongly acidic. The precipitate was filtered off and the filtrate evaporated. The residue was basified with 1M aqueous sodium hydroxide (50 ml) then extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 3 : 1, then 2 : 1) to give the *hydrazine* **103** (429 mg, 68%) as a colourless oil: R_f 0.56 (petroleum ether-diethyl ether 1 : 1); ν_{max}/cm^{-1} [film] 3336, 1704 (C=O), 1404, 1296 and 1093; δ_H 7.43-7.33 (5H, m, Ar-H), 5.19 (2H, s, Ph*CH*$_2$), 4.45 (1H, *br. res.*, 3'-H), 3.82 (2H, *br.* s, NH_2), 2.21 (2H, td, *J* 6.9 and 1.9, 6'-CH_2), 2.07 (1H, *br. res.*, 2'-H), 1.51-1.38 (4H, m, 7'- and 8'-CH_2), 1.07 (3H, d, *J* 6.7, Me), 0.91 (3H, t, *J* 7.2, 9'-Me) and 0.87 (3H, d, *J* 6.7, Me); δ_C 136.1 (C), 128.2 (2 x CH), 127.9 (2 x CH), 127.6 (CH), 84.7, 76.7 (both C), 67.5 (Ph*CH*$_2$), 57.0 (3'-CH), 31.0 (2'-CH), 30.5 (6'-CH_2), 21.7 (7'-CH_2), 19.4, 18.9 (both Me), 18.1 (8'-CH_2) and 13.3 (9'-Me); m/z (APCI) 303 (M^+ + H, 100%) and 91 (40).

Benzyl 3-butyl-4,5-dihydro-5-isopropylpyrazole-1-carboxylate (104)

103 **104**

To a solution of the hydrazine **103** (30 mg, 0.1 mmol, 1.0 eq) in dry dichloromethane (5 ml) was added silver nitrate (~10 wt % on silica gel, 20 mg, 0.01 mmol, 0.1 eq). The resulting mixture was stirred in the dark for 1 h, then filtered through a pad of celite, and the combined filtrate and washings (CH_2Cl_2) were evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 3 : 1) to give the *dihydropyrazole-1-carboxylate* **104** (17 mg, 57%) as a colourless oil, which showed: ν_{max}/cm^{-1} [film] 1696 (C=O), 1455, 1316 and 1117; δ_H 7.34-7.18 (5H, m, Ar-H), 5.21 (1H, d, *J* 12.4, $H_{\alpha\text{-Bn}}$), 5.16 (1H, d, *J* 12.4, $H_{\beta\text{-Bn}}$), 4.18 (1H, *app.* dt, *J* 11.4 and 4.4, 5-H), 2.67 (1H, dd, *J* 18.1 and 11.4, 4-H_α), 2.45 (1H, dd, *J* 18.1 and 4.9, 4-H_β), 2.34-2.21 (3H, m, 1'-CH_2 and 1''-H), 1.48-1.40 (2H, m, 2'-CH_2), 1.27 (2H, sext, *J* 7.3, 3'-CH_2), 0.84 (3H, t, *J* 7.3, 4'-Me), 0.76 (3H, d, *J* 6.9, Me) and 0.64 (3H, d, *J* 6.9, Me); δ_C 158.4 (C=O), 151.9 (C=N), 135.7 (C), 127.2 (2 x CH), 126.9 (2 x CH), 126.7 (CH), 65.9 (Ph*CH*$_2$), 61.4 (5-CH), 34.0 (4-CH_2), 28.8 (1'-CH_2), 28.1 (1''-CH), 27.6 (2'-CH_2), 21.4 (3'-CH_2), 17.1 (4'-Me), 13.6 (Me) and 12.5 (Me); m/z (APCI) 303 (M^+ + H, 60%), 83 (20) and 71 (100) [Found: M^+ + H, 303.2069. $C_{18}H_{27}N_2O_2$ requires 303.2072].

***tert*-Butyl 2,2,2-trichloroethylidenecarbamate (111)**[117]

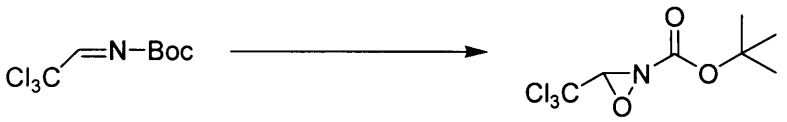


110 **111**

A solution of anhydrous chloral (6.1 g, 0.041 mol, 1.2 eq) and the *N*-Boc iminophosphorane **110**[116] (13.0 g, 0.034 mmol, 1.0 eq) in dry toluene (50 ml) was refluxed for 1.5 h, then cooled. After evaporation of the toluene, triphenylphosphine oxide was precipitated by the addition of hexane and filtered off. The filtrate was evaporated to give the *carbamate* **111** (8.4 g, 99%) as a

colourless solid. The data obtained were in accord with those previously reported in the literature:[117] mp 50-53 °C [lit.[117] mp 58 °C]; δ_H 8.00 (1H, s, *H*C=N), 1.44 (9H, s, ^{t}Bu); δ_C 161.6, 159.5 (both C), 93.3 (Cl_3C), 85.1 (C) and 28.2 (^{t}Bu).

tert-Butyl 3-trichloromethyl-2-oxaziridinecarboxylate (89)[117]



111 **89**

OXONE (Potassium monopersulfate triple salt, active oxygen *ca.* 4.7%, 13 g) was added to a vigorously stirred, ice-cold mixture of the carbamate **111** (7.9 g, 32 mmol) and potassium carbonate (10 g) in chloroform (100 ml) and water (300 ml). After stirring for 1 hour, the aqueous phase was discarded and replaced by a fresh solution of potassium carbonate and OXONE. A total of 8 such cycles was carried out. The organic phase was then washed with water (3 x 200 ml), dried and evaporated (bath temp. < 20 °C) to give a pungent orange oil, which was purified by column chromatography (dichloromethane) to give the *oxaziridine* **89** (8.3 g, 99%) as a colourless, reeking oil. The data obtained were in accord with those previously reported in the literature:[117] δ_H 4.90 (1H, s, 3-H) and 1.48 (9H, s, ^{t}Bu); δ_C 157.9 (C=O), 93.6 (Cl_3C), 86.9 (C), 81.0 (3-CH) and 27.6 (^{t}Bu).

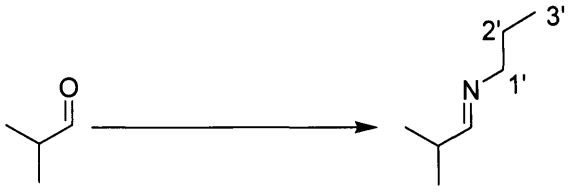
_N_-Propyl phenylmethanimine (105)[124a]

105

A mixture of benzaldehyde (2.08 g, 19.7 mmol, 1.0 eq) and propylamine (1.40 g, 23.6 mmol, 1.2 eq) was stirred at 0 °C for 4 h. Diethyl ether (20 ml) was then added and the water layer removed. The ethereal solution was then dried, filtered and evaporated to give the *imine* **105** (2.68 g, 92%) as a colourless oil. The spectroscopic data obtained were in accord with those previously reported in the literature:[124a] ν_{max}/cm^{-1} [film] 1646 (C=N), 1580, 1451, 1380, 1338

and 1310; δ_H 8.26 (1H, *app.* s, *H*C=N), 7.78-7.75 (2H, m, Ar-H), 7.42-7.40 (3H, m, Ar-H), 3.59 (2H, td, *J* 6.9 and 1.2, 1-CH_2), 1.77 (2H, *app.* sext, *J* 7.2, 2-CH_2) and 0.99 (3H, t, *J* 7.4, 3-Me); δ_C 160.3 (CH=N), 136.1 (C), 130.1 (Ar-CH), 128.0 (2 x Ar-CH), 127.7 (2 x Ar-CH), 63.3 (1-CH_2), 23.8 (2-CH_2) and 11.6 (3-Me); m/z (APCI) 148 (M^+ + H, 100%) and 106 (26).

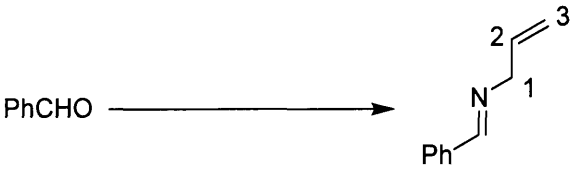
2-Methyl-*N*-propylpropanimine (137)[124c]



137

Propylamine (8.63 g, 0.15 mol, 1.4 eq) was added dropwise to isobutyraldehyde (7.94 g, 0.11 mol, 1.0 eq) at 0 °C. The reaction mixture was then allowed to warm to ambient temperature and stirred for 3 h. Diethyl ether (50 ml) was then added and the water layer removed. The ethereal solution was dried, filtered and carefully evaporated to afford the *imine* **137** (10.4 g, 84%) as a colourless oil: δ_H 7.42 (1H, d, *J* 5.1, HC=N), 3.24 (2H, t, *J* 6.9, 1'-CH_2), 2.40-2.31 (1H, m, 2-H), 1.53 (2H, *app.* sext, *J* 7.2, 2'-CH_2), 0.99 (6H, d, *J* 6.9, 2 x Me) and 0.80 (3H, t, *J* 7.4, 3'-Me); δ_C 169.8 (CH=N), 63.4 (1'-CH_2), 34.3 (2-CH), 24.1 (2'-CH_2), 19.7 (2 x Me) and 11.9 (3'-Me).

***N*-Allyl phenylmethanimine (106)**[124b]

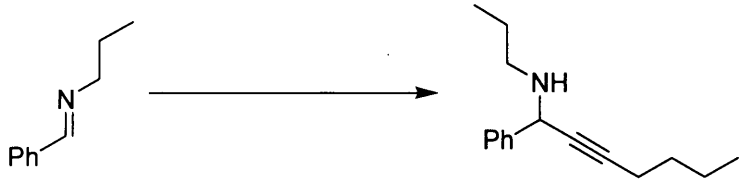


106

A mixture of benzaldehyde (2.09 g, 19.7 mmol, 1.0 eq) and allylamine (1.69 g, 29.6 mmol, 1.5eq) was stirred at room temperature for 3 h. Diethyl ether (20 ml) was then added and the water layer removed. The ethereal solution was dried, filtered and evaporated to give the *imine* **106** (2.33 g, 81%) as a colourless oil. The spectroscopic data obtained were in accord with those

previously reported in the literature:[124b]: ν_{max}/cm^{-1} [film] 1648 (C=N), 1580, 1451, 1308, 1219 and 1024; δ_H 8.17 (1H, *app.* s, HC=N), 7.66-7.64 (2H, m, Ar-H), 7.31-7.28 (3H, m, Ar-H), 5.98 (1H, ddt, *J* 17.2, 10.3 and 5.6, 2-H), 5.14 (1H, *app.* ddd, *J* 17.2, 3.2 and 1.4, 3-H_E), 5.06 (1H, *app.* dt, *J* 10.3 and 1.4, 3-H_Z) and 4.16-4.14 (2H, m, 1-CH_2); δ_C 162.4 (CH=N), 136.6 (C), 136.3 (Ar-CH), 131.1 (2-CH), 129.0 (2 x Ar-CH), 128.6 (2 x Ar-CH), 116.5 (3-CH_2) and 64.0 (1-CH_2); m/z (APCI) 146 (M^+ + 1, 100%).

1-Phenyl-*N*-propylhept-2-yn-1-amine (107)

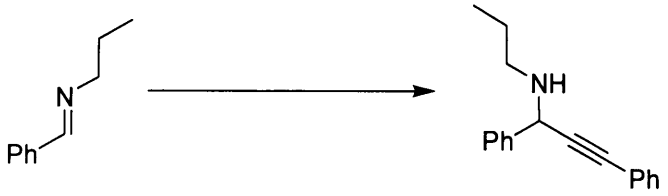


105 **107**

To an ice-cold solution of 1-hexyne (5.0 g, 61.2 mmol, 3 eq) in dry tetrahydrofuran (150 ml) was added *n*-butyllithium (2.5 M solution in hexane, 23.7 ml, 59 mmol, 2.9 eq). The resulting reaction mixture was stirred for 40 minutes, before being cooled to -78 °C. A solution of the imine **105** (3.0 g, 20.4 mmol, 1.0 eq) in dry tetrahydrofuran (20 ml) was then added dropwise, followed by boron trifluoride diethyl etherate (7.2 g, 51.0 mmol, 2.5 eq). The resulting mixture was then allowed to warm to ambient temperature and stirred for 19 h, before the addition of water (10 ml). The bulk of the tetrahydrofuran was evaporated. The residue was partitioned between dichloromethane (100 ml) and water (100 ml) and the separated aqueous phase extracted with dichloromethane (2 x 100 ml). The combined organic solutions were washed with brine, then dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 5 : 1, then 3 : 1) to give the *hept-2-yn-1-amine* **107** (3.0 g, 64%) as an orange oil, which showed: R_f 0.36 (petroleum ether-diethyl ether 3 : 1); ν_{max}/cm^{-1} [film] 2360, 1452 and 1093; δ_H 7.53 (2H, *app.* d, *J* 7.2, Ar-H), 7.39-7.28 (3H, m, Ar-H), 4.57 (1H, *br. res.*, 1-H), 2.74 (1H, ddd, *J* 11.1, 7.9 and 6.6, 1'-H_α), 2.62 (1H, ddd, *J* 11.1, 7.9 and 6.6, 1'-H_β), 2.29 (2H, td, *J* 7.0 and 2.0, 4-CH_2), 1.58-1.42 (6H, m, 2'-, 5- and 6-CH_2), 0.95 (3H, t, *J* 7.4, Me) and 0.94 (3H, t, *J* 7.4, Me); δ_C 141.3 (C), 128.4 (2 x Ar-CH), 127.5 (2 x

Ar-CH), 127.4 (Ar-CH), 85.6, 80.1 (both C), 54.3 (1-CH), 49.2 (1'-CH_2), 31.0 (4-CH_2), 23.1 (CH_2), 22.0 (CH_2), 18.6 (CH_2), 13.6 (Me) and 11.9 (Me); m/z (APCI) 230 (M^+ + H, 100%) and 171 (45) [Found: M^+ + H, 230.1909. $C_{16}H_{24}N$ requires 230.1903].

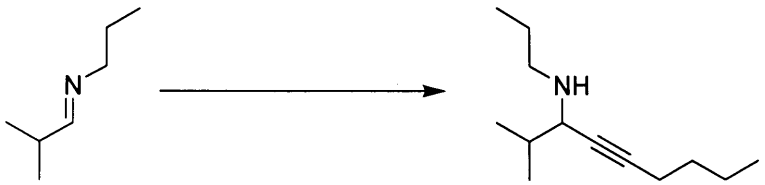
1,3-Diphenyl-*N*-propylprop-2-yn-1-amine (108)



105 **108**

To an ice-cold solution of phenyl acetylene (2.1 g, 20.4 mmol, 3 eq) in dry tetrahydrofuran (20 ml) was added *n*-butyllithium (2.5 M solution in hexane, 7.6 ml, 19 mmol, 2.8 eq). The resulting reaction mixture was stirred for 0.5 h at 0 °C, then cooled to -78 °C. A solution of the imine **105** (1.0 g, 6.8 mmol, 1.0 eq) in dry tetrahydrofuran (5 ml) was added dropwise, followed by boron trifluoride diethyl etherate (2.5 g, 17.7 mmol, 2.6 eq). The resulting reaction mixture was then allowed to warm to ambient temperature and stirred for 16 h, before the addition of water (2 ml). The bulk of the tetrahydrofuran was evaporated. The residue was partitioned between dichloromethane (50 ml) and water (50 ml). The separated aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined organic solutions were washed with brine, then dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 3 : 1) to give the *prop-2-yn-1-amine* **108** (1.28 g, 75%) as a colourless oil, which showed: R_f 0.45 (petroleum ether-diethyl ether 3 : 1); ν_{max}/cm^{-1} [film] 3311 (NH), 1598, 1490, 1453, 1281 and 1114; δ_H 7.48-7.18 (10H, m, Ar-H), 4.68 (1H, s, 1-H), 2.69 (1H, ddd, *J* 11.2, 8.0 and 6.8, 1'-H_α), 2.57 (1H, ddd, *J* 11.2, 8.0 and 6.4, 1'-H_β), 1.49-1.39 (3H, m, NH and 2'-CH_2), 0.82 (3H, t, *J* 7.4, 3'-Me); δ_C 141.1 (C), 132.1 (2 x Ar-CH), 129.0 (2 x Ar-CH), 128.8 (2 x Ar-CH), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.1 (2 x Ar-CH), 123.7 (C), 90.1 (C), 85.8 (C), 55.2 (1-CH), 49.8 (1'-CH_2), 23.7 (2'-CH_2) and 12.4 (3'-Me); m/z (APCI) 250 (M^+ + H, 2%), 191 (100) and 113 (28).

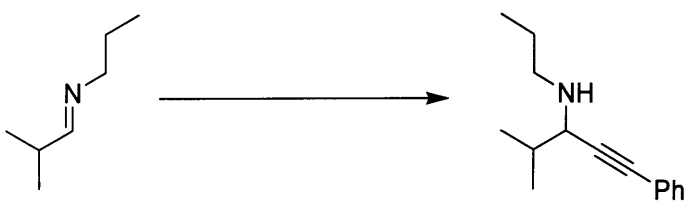
2-Methyl-*N*-propylnon-4-yn-3-amine (138)



137 **138**

To an ice-cold solution of 1-hexyne (1.70 g, 20.3 mmol, 3 eq) in dry tetrahydrofuran (10 ml) was added *n*-butyllithium (2.5 M solution in hexane, 7.6 ml, 19 mmol, 2.8 eq). The resulting solution was stirred for 0.5 h, before being cooled to -78 °C. A solution of the imine **137** (0.77 g, 6.8 mmol, 1.0 eq) in dry tetrahydrofuran (3 ml) was added dropwise, followed by boron trifluoride diethyl etherate (2.5 g, 17.6 mmol, 2.6 eq). The resulting mixture was then allowed to warm to ambient temperature and stirred for 19 h, before the addition of water (2 ml). The bulk of the tetrahydrofuran was evaporated. The residue was partitioned between diethyl ether (50 ml) and water (50 ml) and the separated aqueous phase was extracted with diethyl ether (2 x 50 ml). The combined organic solutions were washed with brine, then dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 3 : 1) to give the *non-4-yn-3-amine* **138** (0.85 g, 64%) as a colourless oil, which showed: ν_{max}/cm^{-1} [film] 1463, 1381 and 1112; δ_H 3.12-3.11 (1H, m, 3-H), 2.75 (1H, ddd, *J* 11.0, 8.5 and 6.6, 1'-H$_\alpha$), 2.48 (1H, ddd, *J* 11.0, 8.5 and 5.9, 1'-H$_\beta$), 2.16 (2H, td, *J* 7.0 and 1.2, 6-CH_2), 1.82-1.71 (1H, m, 2-H), 1.54-1.32 (6H, m, 2'-, 7- and 8-CH_2) and 0.94-0.85 (12H, m, 4 x Me); δ_C 84.5, 80.2 (both C), 56.9 (3-CH), 50.2 (1'-CH_2), 33.0 (2-CH), 31.5 (6-CH_2), 23.5, 22.2 (both CH_2), 20.2 (Me), 18.7 (CH_2), 17.8, 13.9 and 12.2 (all Me); m/z (APCI) 196 (M^+ + H, 100%) [Found: M^+ + H, 196.2061. $C_{13}H_{26}N$ requires 196.2060].

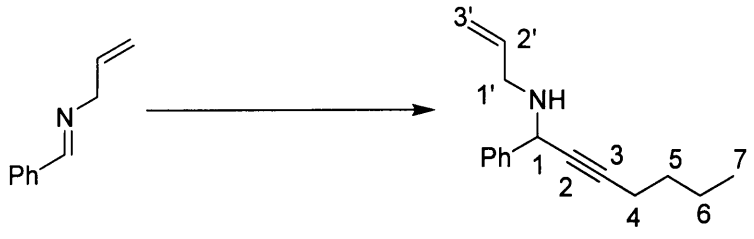
4-Methyl-1-phenyl-*N*-propylpent-1-yn-3-amine (140)[139]



137 **140**

To an ice-cold solution of phenyl acetylene (3.90 g, 38.7 mmol, 3 eq) in dry tetrahydrofuran (20 ml) was added *n*-butyllithium (2.5 M solution in hexane, 14.4 ml, 36 mmol, 2.8 eq). The resulting solution was stirred at 0 °C for 0.5 h, before being cooled to -78 °C. A solution of the imine **137** (1.50 g, 12.9 mmol, 1.0 eq) in dry tetrahydrofuran (3 ml) was added dropwise, followed by boron trifluoride diethyl etherate (3.7 g, 25.8 mmol, 2.0 eq). The resulting mixture was then allowed to warm to ambient temperature and stirred for 19 h, before the addition of water (2 ml). Most of the tetrahydrofuran was evaporated. The residue was partitioned between diethyl ether (50 ml) and water (50 ml). The separated aqueous phase was extracted with diethyl ether (2 x 50 ml). The combined organic solutions were washed with brine, then dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 3 : 1) to give the *pent-1-yn-3-amine* **140** (1.80 g, 65%) as an orange oil. The spectroscopic data obtained were in accord with those previously reported in the literature[139] and showed: ν_{max}/cm^{-1} [film] 1598, 1489, 1465, 1382 and 1113; δ_H 7.33-7.16 (5H, m, Ar-H), 3.30 (1H, d, *J* 5.3, 3-H), 2.78 (1H, ddd, *J* 11.1, 8.4 and 6.5, 1'-H_α), 2.51 (1H, ddd, *J* 11.1, 8.4 and 5.9, 1'-H_β), 1.89-1.78 (1H, m, 4-H), 1.54-1.34 (2H, m, 2'-CH_2), 0.96 (3H, d, *J* 6.7, Me), 0.95 (3H, d, *J* 6.7, Me) and 0.85 (3H, t, *J* 7.4, 3'-Me); δ_C 131.7 (2 x Ar-CH), 128.2 (2 x Ar-CH), 127.8 (Ar-CH), 123.6, 90.0, 84.3 (all C), 57.1 (3-CH), 50.0 (1'-CH_2), 32.9 (4-CH), 23.3 (2'-CH_2), 20.0 (Me), 17.8 (Me) and 11.9 (3'-Me); m/z (APCI) 216 (M^+ + H, 100%) and 157 (44) [Found: M^+ + H, 216.1748. $C_{15}H_{22}N$ requires 216.1747].

N-Allyl-1-phenylhept-2-yn-1-amine (109)

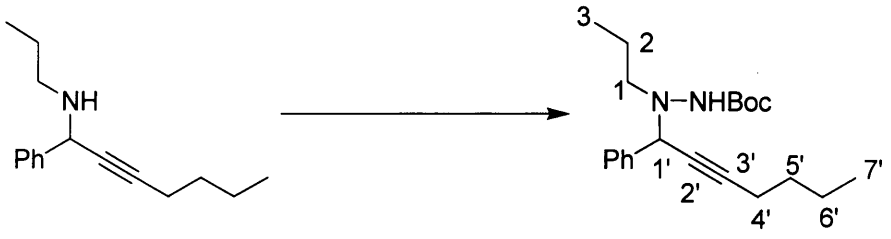


106 **109**

To an ice-cold solution of 1-hexyne (3.7 g, 0.045 mol, 3 eq) in dry tetrahydrofuran (20 ml) was added *n*-butyllithium (2.5 M solution in hexane, 15.0 ml, 0.04 mol, 2.5 eq). The resulting

solution was stirred for 0.5 h, before being cooled to -78 °C. A solution of the imine **106** (2.18 g, 0.015 mol, 1.0 eq) in dry tetrahydrofuran (5 ml) was added dropwise, followed by boron trifluoride diethyl etherate (4.3 g, 0.03 mol, 2.0 eq). The resulting mixture was then allowed to warm to ambient temperature and stirred for 20 h, before the addition of water (5 ml). The bulk of the tetrahydrofuran was evaporated. The residue was partitioned between diethyl ether (100 ml) and water (70 ml) and the separated aqueous phase extracted with diethyl ether (2 x 100 ml). The combined organic solutions were washed with brine, then dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 3 : 1) to give the *hept-2-yn-1-amine* **109** (2.4 g, 70%) as a colourless oil, which showed: ν_{max}/cm^{-1} [film] 1601, 1494, 1455 and 1088; δ_H 7.43 (2H, *app.* d, *J* 7.2, Ar-H), 7.27-7.16 (3H, m, Ar-H), 5.84 (1H, ddt, *J* 17.1, 10.3 and 5.9, 2'-H), 5.14 (1H, *app.* dq, *J* 17.1 and 1.4, 3'-H_E), 5.02 (1H, *app.* dd, *J* 10.3 and 1.4, 3'-H_Z), 4.48 (1H, *br. res.*, 1-H), 3.30 (1H, ddt, *J* 13.8, 5.9 and 1.4, 1'-H_α), 3.23 (1H, ddt, *J* 13.8, 5.9 and 1.4, 1'-H_β), 2.18 (2H, td, *J* 7.0 and 2.0, 4-CH_2), 1.46-1.32 (4H, m, 5- and 6-CH_2) and 0.83 (3H, t, *J* 7.2, 7-Me); δ_C 141.1 (C), 136.5 (Ar-CH), 128.4 (2 x Ar-CH), 127.6 (2 x Ar-CH), 127.6 (2'-CH), 116.4 (3'-CH_2), 85.9, 79.8 (both C), 53.5 (1-CH), 49.8 (1'-CH_2), 31.0 (4-CH_2), 22.0 (5-CH_2), 18.6 (6-CH_2) and 13.7 (7-Me); m/z (APCI) 228 (M^+ + H, 92%) and 171 (100).

2-(*tert*-Butoxycarbonyl)-1-(1'-phenylhept-2'-yn-1'-yl)-1-propylhydrazine (112)

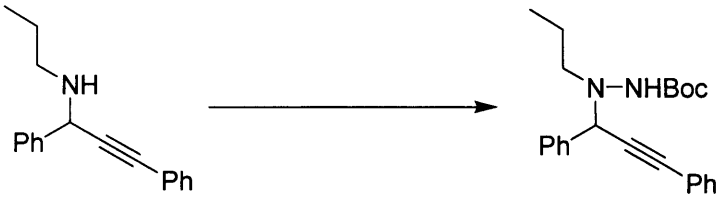


107 **112**

To a solution of the propargylic amine **107** (2.3 g, 10.0 mmol, 1.0 eq) in dry dichloromethane (40 ml) at -78 °C was added dropwise a solution of the oxaziridine **89** (2.7 g, 10.3 mmol, 1.03 eq) in dichloromethane (10 ml). The resulting mixture was then allowed to warm to ambient temperature and stirred for 15 h. The solvent was evaporated. The residue was purified by

column chromatography (petroleum ether-diethyl ether 5 : 1) to give the *hydrazine* **112** (2.70 g, 78%) as a colourless oil, which showed: R_f 0.70 (petroleum ether-diethyl ether 3 : 1); ν_{max}/cm^{-1} [film] 3338 (NH), 2248, 1698 (C=O), 1494, 1366, 1237, 1167, 1072 and 1017; δ_H 7.57-7.16 (5H, m, Ar-H), 5.47-4.71 (2H, m, *br. res.*, 1'-H and NH), 2.47-2.45 (2H, *br. res.*, 1-CH_2), 2.27 (2H, td, *J* 7.0 and 1.8, 4'-CH_2), 1.56-1.36 (6H, m, 5'-, 6'- and 2-CH_2), 1.28 (9H, s, ^{t}Bu), 0.88 (3H, t, *J* 7.3, Me) and 0.84-0.82 (3H, *br. res.*, Me); δ_C 154.8 (C=O), 137.5 (C), 128.6 (Ar-CH), 127.9 (2 x Ar-CH), 127.6 (2 x Ar-CH), 89.5, 81.5, 79.6 (all C), 62.6 (1'-CH), 53.4 (1-CH_2), 31.0 (4'-CH_2), 28.2 (^{t}Bu), 22.1, 20.4, 18.5 (all CH_2), 13.6 (Me) and 11.7 (Me); m/z (APCI) 345 (M^+ + H, 100%) [Found: M^+ + H, 345.2538. $C_{21}H_{33}N_2O_2$ requires 345.2537].

2-(*tert*-Butoxycarbonyl)-1-(1',3'-diphenylprop-2'-ynyl)-1-propylhydrazine (113)



108 **113**

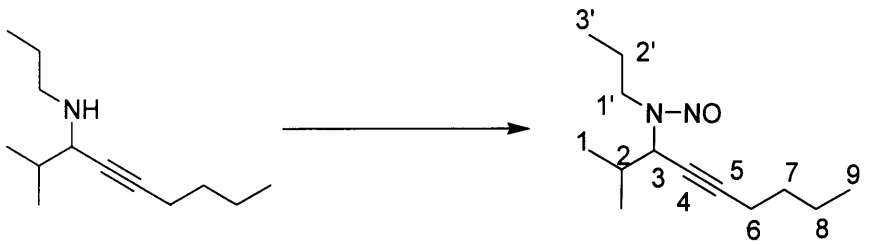
To a solution of the propargylic amine **108** (180 mg, 0.72 mmol, 1.0 eq) in dry dichloromethane (15 ml) at -78 °C was added dropwise a solution of the oxaziridine **89** (210 mg, 0.80 mmol, 1.1 eq) in dichloromethane (3 ml). The resulting mixture was then allowed to warm to ambient temperature and stirred for 15 h. The solvent was evaporated and the residue purified by column chromatography (petroleum ether-diethyl ether 10 : 1, then 5 : 1) to give the *hydrazine* **113** (193 mg, 73%) as an orange oil, which showed: R_f 0.52 (petroleum ether-diethyl ether 3 : 1); ν_{max}/cm^{-1} [film] 3334 (NH), 2248, 1698 (C=O), 1599, 1490, 1453, 1355, 1243, 1167, 1071 and 1028; δ_H 7.67-7.21 (10H, m, Ar-H), 5.50 (1H, *br.* s, 1'-H), 5.07 (1H, *br.* s, NH), 2.64-2.62 (2H, m, *br. res.*, 1-CH_2), 1.55-1.44 (2H, m, 2-CH_2), 1.31 (9H, s, ^{t}Bu) and 0.89 (3H, t, *J* 7.0, 3-Me); δ_C 155.2 (C=O), 137.4 (C), 132.3, 129.0, 128.8, 128.5, 128.3 (all Ar-CH), 122.9, 89.3, 84.3, 80.1 (all C), 63.4 (1'-CH), 56.5 (1-CH_2), 28.6 (^{t}Bu), 20.8 (2-CH_2) and 12.1 (3-Me); m/z (APCI) 365 (M^+ + H, 20%), 309 (15) and 191 (100).

1-Allyl-2-(*tert*-butoxycarbonyl)-1-(1'-phenylhept-2'-yn-1'-yl)-hydrazine (114)

109 **114**

To a solution of the propargylic amine **109** (1.5 g, 6.6 mmol, 1.0 eq) in dry dichloromethane (30 ml) at -78 °C was added dropwise a solution of the oxaziridine **89** (2.1 g, 8.0 mmol, 1.2 eq) in dichloromethane (5 ml). The resulting reaction mixture was then allowed to warm to ambient temperature and stirred for 18 h. The solvent was evaporated and the residue purified by column chromatography (petroleum ether-ethyl acetate 10 : 1) to give the *hydrazine* **114** (1.8 g, 80%) as a colourless oil, which showed: ν_{max}/cm^{-1} [film] 1715 (C=O), 1493, 1367, 1248, 1163, 1050 and 1021; δ_H 7.56-7.17 (5H, m, Ar-H), 5.86-5.76 (1H, *br. res.*, 2-H), 5.54-5.42 (1H, *br. res.*, NH), 5.22-5.15 (1H, *br. res.*, 3-H_α), 5.08-5.05 (1H, *br. res.*, 3-H_β), 4.88-4.78 (1H, *br. res.*, 1'-H), 3.25 (2H, *br. res.*, 1-CH_2), 2.29 (2H, td, *J* 6.9 and 1.6, 4'-CH_2), 1.56-1.37 (4H, m, 5'- and 6'-CH_2), 1.25 (9H, s, ^{t}Bu) and 0.89 (3H, t, *J* 7.2, 7'-Me); δ_C 154.7 (C=O), 137.4 (C), 134.5, 128.6, 128.0, 127.7 (all CH), 118.3 (3-CH_2), 89.6, 79.7, 74.0 (all C), 61.4 (1'-CH), 58.1 (1-CH_2), 31.0 (4'-CH_2), 28.1 (^{t}Bu), 22.1 (5'-CH_2), 18.5 (6'-CH_2) and 13.6 (7'-Me); m/z (APCI) 343 (M^+ + H, 100%) and 287 (5) [Found: M^+ + H, 343.2385. $C_{21}H_{31}N_2O_2$ requires 343.2380].

2-Methyl-*N*-nitroso-*N*-propylnon-4-yn-3-amine (139)

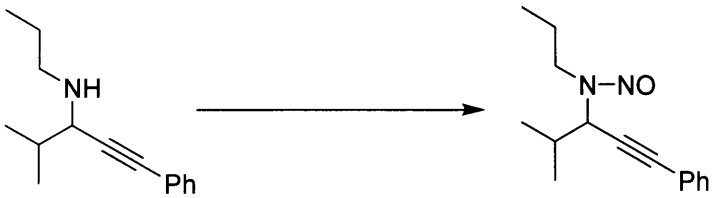


138 **139**

To an ice-cold solution of the propargylic amine **138** (0.52 g, 2.66 mmol, 1.0 eq) in 32% hydrochloric acid (0.61 g, 0.5 ml, 5.3 mmol, 2.0 eq) was added dropwise a solution of sodium nitrite (0.22 g, 3.19 mmol, 1.2 eq) in water (1 ml). The resulting mixture was stirred at 0 °C for 1 h, before being extracted with diethyl ether (30 ml). The organic extract was washed with

water (50 ml), and then dried, filtered and evaporated to give the *N-nitrosoamine* **139** (0.48 g, 80%) as an orange oil, which showed a mixture of two rotamers: ν_{max}/cm^{-1} [film] 1458, 1344, 1189 and 1062; δ_H (5.38 (0.33H, dt, *J* 8.0 and 1.4) and 4.93 (0.67H, dt, *J* 9.6 and 1.1), 3-H), (4.06-3.90 (0.67H, m), 3.60-3.50 (0.67H, m) and 3.30-3.20 (0.67H, m), 1'-CH_2), 2.18-1.30 (9H, m, 2-H, 2'-, 6-, 7- and 8-CH_2) and (1.07 (2H, d, *J* 6.6), 0.96-0.79 (9H, m) and 0.72 (1H, d, *J* 6.6), 4 x Me); δ_C 87.8, 86.4, 75.2, 74.3 (all C), 62.2 (3-CH), 51.9 (1'-CH_2), 51.0 (3-CH), 45.1 (1'-CH_2), 33.1 and 31.5 (2-CH), 30.5, 30.4, 23.6, 21.8, 19.9 (all CH_2), 19.5, 19.3, 19.2, 18.6 (all Me), 18.2 (CH_2), 13.4, 11.7 and 11.4 (all Me); m/z (APCI) 225 (M^+ + H, 100%) and 137 (27) [Found: M^+ + H, 225.1963. $C_{13}H_{25}N_2O$ requires 225.1961].

4-Methyl-*N*-nitroso-1-phenyl-*N*-propylpent-1-yn-3-amine (141)

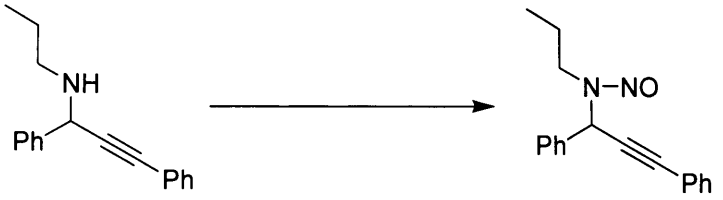


140 **141**

To an ice-cold solution of the propargylic amine **140** (6.5 g, 30.2 mmol, 1.0 eq) in 37% hydrochloric acid (6.0 g, 60.8 mmol, 2.0 eq) was added dropwise a solution of sodium nitrite (2.5 g, 36.2 mmol, 1.2 eq) in water (5 ml). The resulting mixture was stirred at 0 °C for 7 h, before being extracted with diethyl ether (100 ml). The organic extract was washed with water (2 x 100 ml), then dried, filtered and evaporated to give the *N-nitrosoamine* **141** (6.90 g, 94%) as an orange oil, which showed a mixture of two rotamers: δ_H 7.41-7.23 (5H, m, Ar-H), (5.69 (0.3H, d, *J* 8.1) and 5.23 (0.7H, d, *J* 9.7), 3-H), (4.19-4.02 (0.6H, m), 3.68 (0.7H, ddd, *J* 13.0, 10.2 and 5.7) and 3.37 (0.7H, ddd, *J* 13.0, 10.2 and 5.7), 1'-CH_2), (2.27-2.15 (0.7H, m), 2.07-1.94 (1H, m) and 1.71-1.54 (1.3H, m), 4-H and 2'-CH_2) and (1.21 (2.1H, d, *J* 6.7), 1.06 (0.9H, d, *J* 6.7), 1.01 (0.9H, t, *J* 7.5), 0.93-0.87 (4.2H, m) and 0.84 (0.9H, d, *J* 6.7), 3 x Me); δ_C 132.5, 132.0, 129.2, 129.1, 128.8, 128.7 (all Ar-CH), 122.6, 122.5, 87.5, 86.1, 84.9, 84.2 (all C), 62.8 (3-CH), 52.5 (1'-CH_2), 51.5 (3-CH), 45.7 (1'-CH_2), 33.5 and 32.1 (4-CH), 24.0 and 20.5 (2'-

CH_2), 20.1, 19.9, 19.7, 19.3 (all Me), 12.3 and 11.9 (3'-Me); m/z (APCI) 245 (M^+ + H, 100%) and 157 (98) [Found: M^+ + H, 245.1646. $C_{15}H_{21}N_2O$ requires 245.1648].

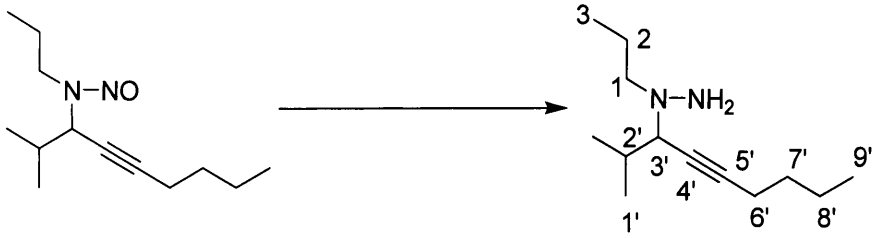
1,3-Diphenyl-*N*-nitroso-*N*-propylprop-2-yn-1-amine (142)



108 **142**

To an ice-cold solution of the propargylic amine **108** (270 mg, 1.08 mmol, 1.0 eq) in 32% hydrochloric acid (0.25 g, 2.16 mmol, 2.0 eq) was added dropwise a solution of sodium nitrite (90 mg, 1.30 mmol, 1.2 eq) in water (1 ml). The resulting mixture was stirred at 0 °C for 1 h, before being extracted with diethyl ether (20 ml). The organic extract was washed with water (2 x 20 ml), then dried, filtered and evaporated to give the *N-nitrosoamine* **142** (260 mg, 86%) as an orange oil, which showed a mixture of two rotamers: δ_H (7.48-7.15 (10.38 H, m) and 6.89 (0.62H, s), Ar-H and 1-H), (3.96-3.80 (0.76H, m), 3.39 (0.62H, ddd, *J* 13.2, 10.2 and 5.6) and 3.16 (0.62H, ddd, *J* 13.2, 10.2 and 5.3), 1'-CH_2), (1.63 (0.76H, *app.* sext, *J* 7.4) and 1.38-1.12 (1.24H, m), 2'-CH_2) and (0.74 (1.14H, t, *J* 7.4) and 0.61 (1.86H, t, *J* 7.5), 3'-Me); δ_C 135.7, 135.5 (both C), 132.2, 132.2, 129.6, 129.5, 129.4, 129.3, 129.0, 128.9, 128.1, 128.0 (all Ar-CH), 122.4, 122.2, 89.6, 86.8, 83.5, 83.5 (all C), 59.2 and 51.7 (1-CH), 46.7 and 45.0 (1'-CH_2), 23.3 and 20.7 (2'-CH_2), 12.2 and 11.7 (3'-Me); m/z (APCI) 279 (M^+ + H, 100%).

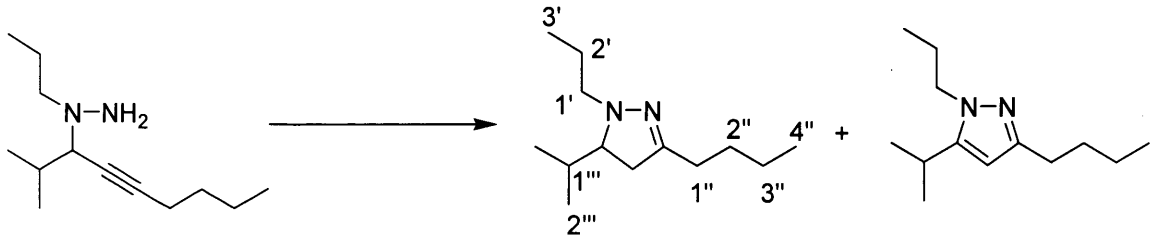
1-(2'-Methylnon-4'-yn-3'-yl)-1-propylhydrazine (143)



139 **143**

To a cold (-10 °C) solution of the *N*-nitrosoamine **139** (0.35 g, 1.56 mmol, 1.0 eq) in dry diethyl ether (20 ml) was added lithium aluminium hydride (0.12 g, 3.16 mmol, 2.0 eq). The resulting mixture was stirred at -10 °C for 22 h, before the dropwise addition of wet ether (10 ml), followed by 2M aqueous sodium hydroxide (15 ml). The separated organic phase was washed with water (50 ml) and brine (30 ml) and then dried, filtered and evaporated to give the *hydrazine* **143** (0.27 g, 82%) as an orange oil, which showed: ν_{max}/cm^{-1} [film] 2958, 2873, 1467 and 1381; δ_H 2.88 (1H, dt, *J* 10.0 and 1.9, 3'-H), 2.79 (2H, *br.* s, NH_2), 2.46 (1H, ddd, *J* 12.2, 7.8 and 6.5, 1-H$_\alpha$), 2.32 (1H, ddd, J 12.2, 7.8 and 6.5, 1-H$_\beta$), 2.17 (2H, td, *J* 6.9 and 1.9, 6'-CH_2), 1.75-1.63 (1H, m, 2'-H), 1.51-1.31 (6H, m, 2-, 7'- and 8'-CH_2), 0.96 (3H, d, *J* 6.6, Me), 0.90 (3H, d, *J* 6.6, Me) and 0.84 (6H, t, *J* 7.3, 9'- and 3-Me); δ_C 87.2, 75.6 (both C), 66.7 (3'-CH), 60.0 (1-CH_2), 31.2 (6'-CH_2), 31.1 (2'-CH), 21.9, 20.8 (both CH_2), 20.6, 19.7 (both Me), 18.3 (CH_2), 13.6 and 11.7 (both Me); m/z (APCI) 211 (M^+ + H, 15%), 209 (M^+ - H, 30), 129 (32) and 71 (100).

3-Butyl-4,5-dihydro-5-isopropyl-1-propyl-1*H*-pyrazole (145) and 3-butyl-5-isopropyl-1-propyl-1*H*-pyrazole (146)



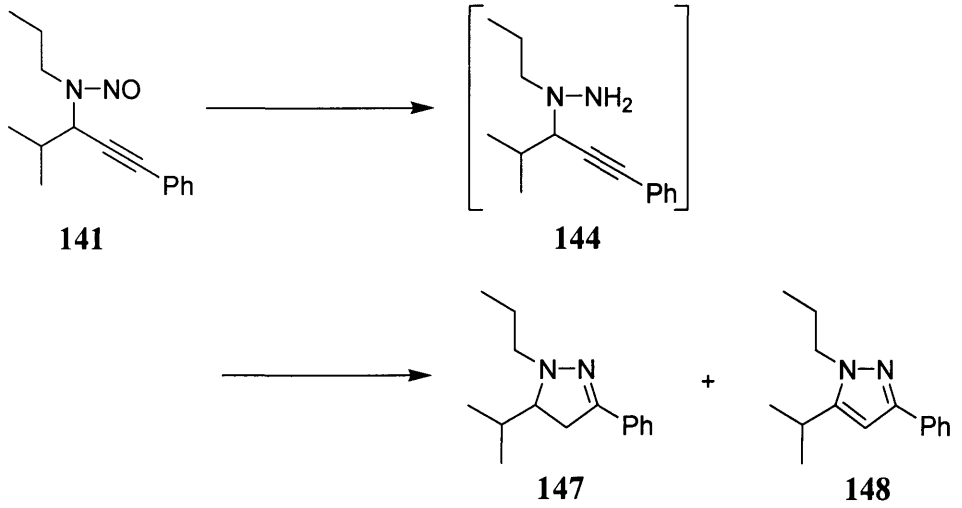
143 **145** **146**

To a solution of the propargylic hydrazine **143** (250 mg, 1.19 mmol, 1.0 eq) in hexane (30 ml) was added silver nitrate (~10 wt % on silica gel, 300 mg, 0.18 mmol, 0.15 eq). The resulting mixture was stirred at ambient temperature in the dark for 5 h, then filtered through a pad of celite and the filtrate evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 10 : 1, then 5 : 1) to give the *4,5-dihydropyrazole* **145** (126 mg, 50%) and the *pyrazole* **146** (75 mg, 30%) both as orange oils.

The *4,5-dihydropyrazole* **145** showed: R_f 0.51 (petroleum ether-diethyl ether 3 : 1); ν_{max}/cm^{-1} [film] 1465 and 1384; δ_H 2.88-2.81 (1H, m, 1'-H_α), 2.71 (1H, ddd, *J* 12.5, 9.9 and 6.8, 5-H), 2.62-2.56 (1H, m, 1'-H_β), 2.37 (1H, dd, *J* J 16.4 and 9.9, 4-H_α), 2.30-2.15 (3H, 4-H_β and 1''-CH_2), 1.90-1.79 (1H, m, 1'''-H), 1.74-1.53 (2H, m, 2'-CH_2), 1.46-1.39 (2H, m, 2''-CH_2), 1.32-1.23 (2H, m, 3''-CH_2) and 0.89-0.81 (12H, m, 4 x Me); δ_C 154.8 (C=N), 71.8 (5-CH), 57.0 (1'-CH_2), 35.7, 30.6, 29.1 (all CH_2), 29.0 (1'''-CH), 22.6, 21.0 (both CH_2), 20.5, 16.9, 13.9 and 11.9 (all Me); m/z (APCI) 211 (M^+ + H, 100%) [Found: M^+ + H, 211.2172. $C_{13}H_{27}N_2$ requires 211.2169].

The *pyrazole* **146** showed: R_f 0.29 (petroleum ether-diethyl ether 3 : 1); ν_{max}/cm^{-1} [film] 1543, 1465 and 1383; δ_H 5.72 (1H, s, 4-H), 3.85 (2H, t, *J* 7.5, 1'-CH_2), 2.87-2.77 (1H, m, 1'''-H), 2.49 (2H, t, *J* 7.9, 1''-CH_2), 1.81-1.71 (2H, m, 2'-CH_2), 1.57-1.49 (2H, m, 2''-CH_2), 1.35-1.25 (2H, m, 3''-CH_2), 1.16 (6H, d, *J* 6.9, 2 x Me), 0.85 (3H, t, *J* 7.4, Me) and 0.84 (3H, t, *J* 7.4, Me); δ_C 152.1, 149.5 (both C), 99.7 (4-CH), 50.0 (1'-CH_2), 32.1, 28.2 (both CH_2), 25.3 (1'''-CH), 24.1 (CH_2), 23.0 (2 x Me), 22.7 (CH_2), 14.0 and 11.2 (both Me); m/z (APCI) 209 (M^+ + H, 100%) [Found: M^+ + H, 209.2006. $C_{13}H_{25}N_2$ requires 209.2012].

4,5-Dihydro-5-isopropyl-3-phenyl-1-propyl-1*H*-pyrazole (147) and 5-isopropyl-3-phenyl-1-propyl-1*H*-pyrzazloe (148)



141 **144** **147** **148**

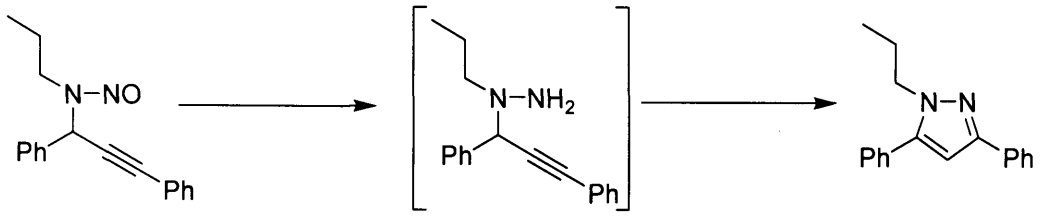
To a cold (-10 °C) solution of the *N*-nitrosoamine **141** (484 mg, 1.98 mmol, 1.0 eq) in dry diethyl ether (40 ml) was added lithium aluminium hydride (90 mg, 2.38 mmol, 1.2 eq). The

resulting mixture was stirred at -10 °C for 19 h, before the dropwise addition of wet ether (10 ml), followed by 2M aqueous sodium hydroxide (20 ml). The separated organic phase was washed with water (50 ml) and brine (50 ml), and then dried, filtered and evaporated to give the crude *hydrazine* **144** (δ_H 7.42-7.24 (5H, m, Ar-H), 3.18 (1H, d, *J* 10.1, 3'-H), 2.62-2.46 (2H, m, 1-CH_2), 1.95-1.82 (1H, m, 4'-H), 1.56-1.50 (2H, m, 2-CH_2), 1.08 (3H, d, *J* 6.6, Me), 1.00 (3H, d, *J* 6.6, Me) and 0.90 (3H, t, *J* 7.5, 3-Me)], which was dissolved directly in dry hexane (20 ml). To this solution was added silver nitrate (~10 wt % on silica gel, 408 mg, 0.24 mmol, 0.12 eq). The resulting mixture was stirred at ambient temperature in the dark for 3 h, then filtered through a pad of celite. Evaporation of the filtrate left a residue which was purified by column chromatography (petroleum ether-diethyl ether 10 : 1, the 5 : 1) to give the *4,5-dihydropyrazole* **147** (147 mg, 32%) and the *pyrazole* **148** (130 mg, 29%) both as orange oils.

The *4,5-dihydropyrazole* **147** showed: R_f 0.54 (petroleum ether-diethyl ether 5 : 1); ν_{max}/cm^{-1} [film] 1586, 1465, 1385, 1363 and 1144; δ_H 7.57-7.54 (2H, m, Ar-H), 7.28-7.17 (3H, m, Ar-H), 3.17 (1H, ddd, *J* 13.5, 10.5 and 4.6, 5-H), 2.96-2.84 (2H, m, 4-H_α and 1'-H_α), 2.81 (1H, ddd, *J* 12.6, 8.9 and 5.0, 1'-H_β), 2.63 (1H, dd, *J* 16.2 and 13.5, 4-H_β), 2.00-1.92 (1H, m, $HC(Me)_2$), 1.81-1.63 (2H, m, 2'-CH_2) and 0.93-0.82 (9H, m, 3 x Me); δ_C 149.2 (C=N), 134.0 (C), 128.6 (2 x Ar-CH), 128.4 (Ar-CH), 126.1 (2 x Ar-CH), 72.0 (5-CH), 56.4 (1'-CH_2), 33.6 (4-CH_2), 29.1 ($CH(Me)_2$), 21.4 (2'-CH_2), 20.8, 17.0 and 12.4 (all Me); m/z (APCI) 231 (M^+ + H, 100%) and 187 (10) [Found: M^+ + H, 231.1851. $C_{15}H_{23}N_2$ requires 231.1856].

The *pyrazole* **148** showed: R_f 0.43 (petroleum ether-diethyl ether 5 : 1); ν_{max}/cm^{-1} [film] 1605, 1543, 1509, 1462, 1384, 1309, 1202 and 1061; δ_H 7.69 (2H, *app.* d, *J* 7.6, Ar-H), 7.27 (2H, *app.* t, *J* 7.6, Ar-H), 7.16 (1H, *app.* t, *J* 7.6, Ar-H), 6.23 (1H, s, 4-H), 3.93 (2H, t, *J* 7.5, 1'-CH_2), 2.91-2.81 (1H, m, $HC(Me)_2$), 1.87-1.77 (2H, m, 2'-CH_2), 1.20 (6H, d, *J* 6.8, 2 x Me) and 0.87 (3H, t, *J* 7.5, 3'-Me); δ_C 150.5, 150.1, 134.0 (all C), 128.5 (2 x Ar-CH), 127.3 (Ar-CH), 125.5 (2 x Ar-CH), 98.8 (4-CH), 50.5 (1'-CH_2), 25.4 ($CH(Me)_2$), 24.1 (2'-CH_2), 23.0 (2 x Me) and 11.3 (Me); m/z (APCI) 229 (M^+ + H, 100%) [Found M^+ + H, 229.1699. $C_{15}H_{21}N_2$ requires 229.1695].

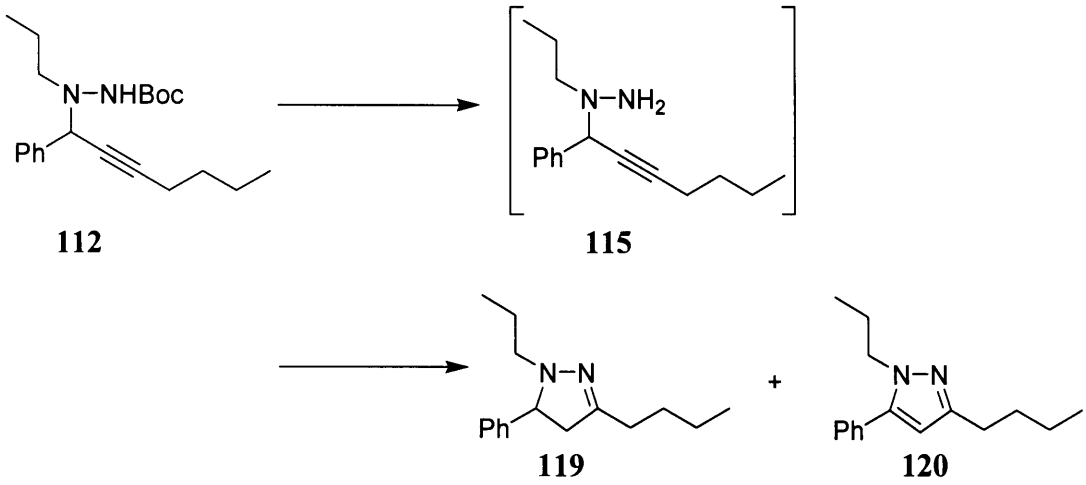
3,5-Diphenyl-1-propyl-1*H*-pyrazole (121)



142 **116** **121**

To a cold (-10 °C) solution of the *N*-nitrosoamine **142** (300 mg, 1.08 mmol, 1.0 eq) in dry diethyl ether (20 ml) was added lithium aluminium hydride (50 mg, 1.30 mmol, 1.2 eq). The resulting mixture was stirred at -10 °C for 19 h, before the dropwise addition of wet ether (10 ml), followed by 2M aqueous sodium hydroxide (10 ml). The separated organic phase was washed with water (50 ml) and brine (50 ml), and then dried, filtered and evaporated to give the crude *hydrazine* **116** as a mixture of two rotamers (δ_H 7.57-7.21 (10H, Ar-H), (5.01 (0.5H, s) and 4.70 (0.5H, s), 1'-H), (2.76-2.70 (1H, m) and 2.62-2.58 (1H, m), 1-CH_2), (1.87 (1H, s) and 1.80 (1H, s), NH_2), (1.63-1.53 (1H, m) and 1.28-1.21 (1H, m), 2-CH_2) and (0.89 (1.5H, t, *J* 7.4) and 0.76 (1.5H, t, *J* 7.4), 3-Me)), which was dissolved directly in dry dichloromethane (20 ml). To this solution was added silver nitrate (~10 wt % on silica gel, 187 mg, 0.11 mmol, 0.1 eq). The resulting mixture was stirred at ambient temperature in the dark for 2 h, then filtered through a pad of celite, the filtrate evaporated and the residue purified by column chromatography (petroleum ether-diethyl ether 10 : 1, the 5 : 1) to give the *pyrazole* **121** (167 mg, 59%) as an orange oil, which showed: R_f 0.32 (petroleum ether-diethyl ether 5 : 1); ν_{max}/cm^{-1} [film] 1643, 1606, 1484, 1462, 1316, 1208 and 1073; δ_H 7.78-7.18 (10H, m, Ar-H), 6.50 (1H, s, 4-H), 4.04 (2H, t, *J* 7.4, 1'-CH_2), 1.81 (2H, sext, *J* 7.4, 2'-CH_2) and 0.78 (3H, t, *J* 7.4, 3'-Me); δ_C 150.5, 145.0, 133.6, 131.0 (all C), 129.0, 128.7, 128.6, 128.5, 127.6, 125.6 (all Ar-CH), 103.3 (4-CH), 51.3 (1'-CH_2), 24.0 (2'-CH_2) and 11.1 (3'-Me); m/z (APCI) 263 (M^+ + H, 100%) [Found: M^+ + H, 263.1541. $C_{18}H_{19}N_2$ requires 263.1543].

3-Butyl-4,5-dihydro-5-phenyl-1-propyl-1*H*-pyrazole (119) and 3-butyl-5-phenyl-1-propyl-1*H*-pyrazole (120)



112 **115** **119** **120**

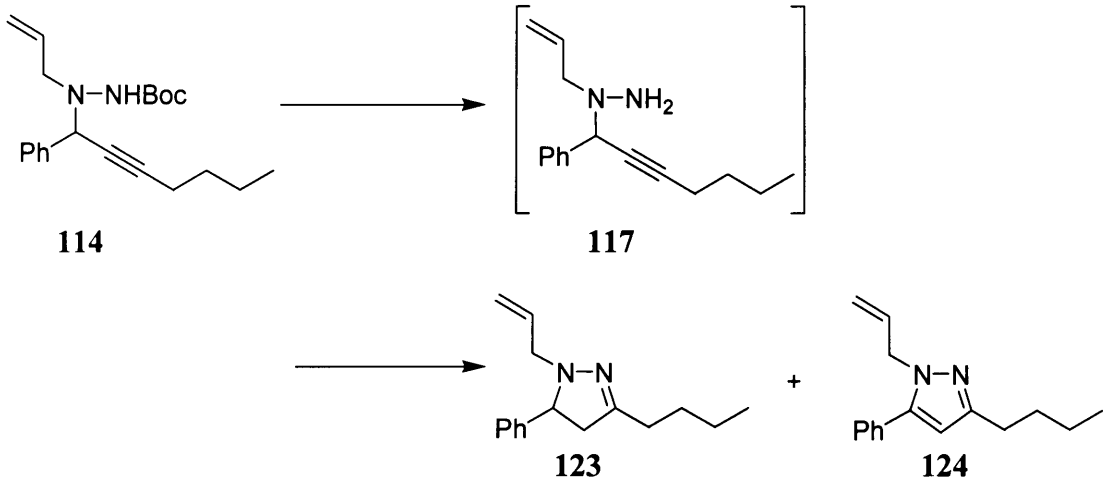
A solution of the propargylic hydrazine **112** (165 mg, 0.48 mmol, 1.0 eq) in formic acid (2 ml) was stirred at ambient temperature for 20 h, then basified with 2M aqueous sodium hydroxide and extracted with diethyl ether (2 x 20 ml). The combined organic extracts were dried, filtered and evaporated to give the crude *hydrazine* **115** (δ_H 7.49-7.14 (5H, m, Ar-H), 4.70 (1H, *br. res.*, 1'-H), 2.93 (2H, *br.* s, NH_2), 2.50-2.42 (2H, m, 1-CH_2), 2.26 (2H, td, *J* 7.0 and 2.0, 4'-CH_2), 1.54-1.33 (6H, m, 5'-, 6'- and 2-CH_2) and 0.87-0.81 (6H, m, 3 x Me)), which was dissolved directly in dry hexane (10 ml). To this solution was added silver nitrate (~10 wt % on silica gel, 170 mg, 0.1 mmol, 0.2 eq). The resulting mixture was stirred at ambient temperature in the dark for 1 h, then filtered through a pad of celite. Evaporation of the filtrate left a residue which was purified by column chromatography (petroleum ether-diethyl ether 10:1) to give the *4,5-dihydropyrazole* **119** (56 mg, 48%) and the *pyrazole* **120** (10 mg, 9%), both as colourless oils.

The *4,5-dihydropyrazole* **119** showed: R_f 0.40 (petroleum ether-diethyl ether 3 : 1); ν_{max}/cm^{-1} [film] 1603, 1494, 1455, 1383, 1134 and 1011; δ_H 7.36-7.17 (5H, m, Ar-H), 3.90 (1H, dd, *J* 14.6 and 9.6, 5-H), 2.84 (1H, dd, *J* 16.0 and 9.6, 4-H_α), 2.66 (1H, ddd, *J* 12.3, 9.2 and 5.2, 1'-H_α), 2.59 (1H, ddd, *J* 12.3, 9.2 and 6.7, 1'-H_β), 2.50 (1H, dd, *J* 16.0 and 14.6, 4-H_β), 2.26-2.22 (2H. m, 1''-CH_2), 1.65-1.27 (6H, m, 2'-, 2''- and 3''-CH_2), 0.85 (3H, t, *J* 7.3, Me) and 0.77 (3H, t, *J* 7.4, Me); δ_C 155.0, 141.9 (both C), 128.9 (2 x Ar-CH), 127.9 (2 x Ar-CH), 127.8 (Ar-

CH), 72.2 (5-CH), 57.3, 45.7, 30.0, 29.4, 23.0, 21.5 (all CH_2), 14.3 and 12.2 (both Me); m/z (APCI) 245 (M^+ + H, 100%).

The *pyrazole* **120** showed: R_f 0.22 (petroleum ether-diethyl ether 3 : 1); ν_{max}/cm^{-1} [film] 1495 and 1459; δ_H 7.39-7.30 (5H, m, Ar-H), 5.99 (1H, s, 4-H), 3.94 (2H, t, *J* 7.5, 1'-CH_2), 2.58 (2H, t, *J* 7.8, 1''-CH_2), 1.75-1.32 (6H, m, 2'-, 2''- and 3''-CH_2), 0.87 (3H, t, *J* 7.4, Me) and 0.73 (3H, t, *J* 7.4, Me); δ_C 152.9, 144.4, 131.8 (all C), 129.2 (2 x Ar-CH), 128.9 (2 x Ar-CH), 128.6 (Ar-CH), 104.9 (4-CH), 51.2 (1'-CH_2), 32.5, 28.4, 24.4, 23.0 (all CH_2), 14.4 and 11.5 (both Me); m/z (APCI) 243 (M^+ + H, 100%) [Found: M^+ + H, 243.1853. $C_{16}H_{23}N_2$ requires 243.1856].

1-Allyl-3-butyl-4,5-dihydro-5-phenyl-1*H*-pyrazole (123) and 1-allyl-3-butyl-5-phenyl-1*H*-pyrazole (124)



114 **117** **123** **124**

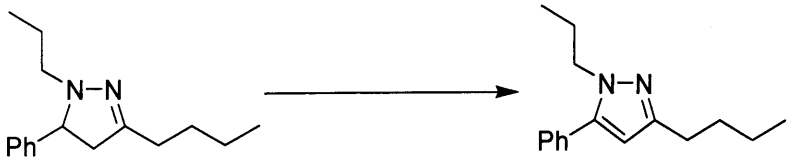
A solution of the propargylic hydrazine **114** (200 mg, 0.58 mmol, 1.0 eq) in formic acid (3 ml) was stirred at ambient temperature for 20 h, then basified with 2M aqueous sodium hydroxide and extracted with diethyl ether (2 x 30 ml). The combined organic extracts were dried, filtered and evaporated to give the crude *hydrazine* **117** (δ_H 7.54-7.12 (5H, m, Ar-H), 5.87 (1H, dddd, *J* 17.4, 10.2, 7.4 and 5.5, 2-H), 5.20 (1H, *app.* dd, *J* 17.4 and 1.2, 3-H_E), 5.10 (1H, *app.* d, *J* 10.2, 3-H_Z), 4.81 (1H, *br. res.*, 1'-H), 3.27 (1H, *app.* dd, *J* 13.3 and 5.5, 1-H_α), 3.16 (1H, *app.* dd, *J* 13.3 and 7.4, 1-H_β), 2.29 (2H, td, *J* 7.0 and 2.0, 4'-CH_2), 1.54-1.30 (4H, m, 5'- and 6'-CH_2) and 0.87 (3H, t, *J* 7.3, 7'-Me)), which was dissolved directly in dry hexane (10 ml). To this solution was added silver nitrate (~10 wt % on silica gel, 190 mg, 0.11 mmol, 0.2 eq). The resulting

mixture was stirred at ambient temperature in the dark for 1 h, then filtered through a pad of celite, the filtrate evaporated and the residue purified by column chromatography (petroleum ether-diethyl ether 10 : 1) to give the *4,5-dihydropyrazole* **123** (35 mg, 25%) and the *pyrazole* **124** (30 mg, 22%), both as orange oils.

The *4,5-dihydropyrazole* **123** showed: R_f 0.29 (petroleum ether-ethyl acetate 5 : 1); ν_{max}/cm^{-1} [film] 1603 and 1454; δ_H 7.38-7.19 (5H, m, Ar-H), 5.85-5.79 (1H, m, 2'-H), 5.09-5.04 (2H, m, 3'-CH_2), 4.04 (1H, dd, *J* 14.2 and 9.7, 5-H), 3.62-3.57 (1H, m, 1'-H_α), 3.26 (1H, *app.* dd, *J* 14.3 and 7.8, 1'-H_β), 2.86 (1H, dd, *J* 16.3 and 9.7, 4-H_α), 2.55 (1H, dd, *J* 16.3 and 14.2, 4-H_β), 2.27-2.21 (2H, m, 1''-CH_2), 1.47-1.27 (4H, m, 2''- and 3''-CH_2) and 0.86 (3H, t, *J* 7.3, 4''-Me); δ_C 155.0, 141.0 (both C), 134.4 (Ar-CH), 128.5 (2 x Ar-CH), 127.6 (2 x Ar-CH), 127.5 (2'-CH), 117.9 (3'-CH_2), 69.9 (5-CH), 56.5, 45.2, 30.4, 29.0, 22.5 (all CH_2) and 13.9 (Me); m/z (APCI) 243 (M^+ + H, 60%), 83 (40) and 71 (100) [Found: M^+ + H, 243.1856. $C_{16}H_{23}N_2$ requires 243.1856].

The *pyrazole* **124** showed: R_f 0.18 (petroleum ether-ethyl acetate 5 : 1); ν_{max}/cm^{-1} [film] 1551, 1496, 1384 and 1303; δ_H 7.43-7.31 (5H, m, Ar-H), 6.17 (1H, s, 4-H), 5.95 (1H, ddt, *J* 17.0, 10.2 and 5.0, 2'-H), 5.24 (1H, *app.* d, *J* 10.2, 3'-H_Z), 5.10 (1H, *app.* d, *J* 17.0, 3'-H_E), 4.77 (2H, d, *J* 5.0, 1'-CH_2), 2.65 (2H, t, *J* 7.7, 1''-CH_2), 1.60 (2H, quint, *J* 7.7, 2''-CH_2), 1.36-1.26 (2H, m, 3''-CH_2) and 0.85 (3H, t, *J* 7.3, 4''-Me); δ_C 153.8, 146.3 (both C), 133.0 (Ar-CH), 129.5 (2'-CH), 129.3 (C), 129.0 (2 x Ar-CH), 128.7 (2 x Ar-CH), 118.3 (3'-CH_2), 105.4 (4-CH), 51.8 (1'-CH_2), 31.6 (1''-CH_2), 28.6 (2''-CH_2), 22.5 (3''-CH_2) and 13.9 (4''-Me); m/z (APCI) 241 (M^+ + H, 100%) and 107 (10) [Found: M^+ + H, 241.1699. $C_{16}H_{21}N_2$ requires 241.1699].

3-Butyl-5-phenyl-1-propyl-1*H*-pyrazole (120)

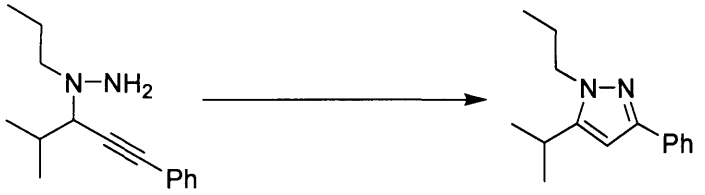


119 **120**

To a solution of the 4,5-dihydropyrazole **119** (35 mg, 0.14 mmol, 1.0 eq) in toluene (20 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (95 mg, 0.42 mmol, 3.0 eq). The resulting

mixture was refluxed for 16 h and cooled. The undissolved material was filtered off and the filtrate evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 5:1) to give the *pyrazole* **120** (20 mg, 59%) as a colourless oil, the spectroscopic and analytical data of which were identical to those displayed by the forgoing sample.

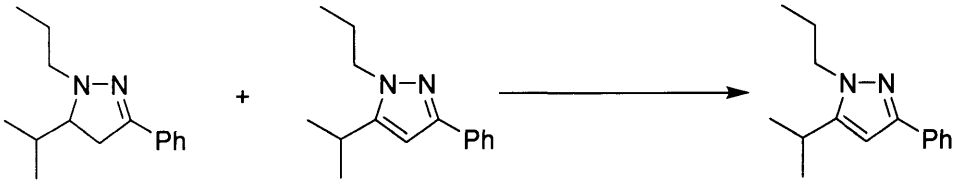
5-Isopropyl-3-phenyl-1-propyl-1*H*-pyrazole (148)



144 **148**

To a solution of crude propargylic hydrazine **144** (200 mg, 0.87 mmol, 1.0 eq) in dry dichloromethane (10 ml) was added silver nitrate (~10 wt % on silica gel, 1.5 g, 0.87 mmol, 1.0 eq). The resulting mixture was stirred at ambient temperature in the dark for 2.5 h, then filtered through a pad of celite. The filtrate was evaporated to give the *pyrazole* **148** (198 mg, 100%) as an orange oil with no need for further purification. The spectroscopic and analytical data obtained were identical to those displayed by the forgoing sample.

5-Isopropyl-3-phenyl-1-propyl-1*H*-pyrazole (148)

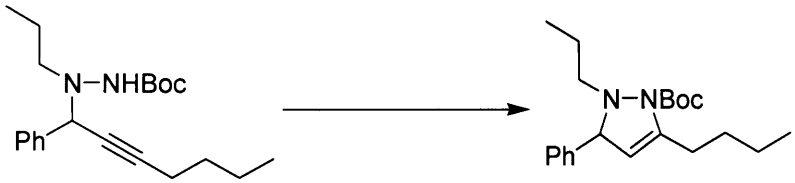


147 **148** **148**

To a 2:1 mixture of the 4,5-dihydropyrazole **147** and the pyrazole **148** (500 mg, 2.17 mmol) in acetonitrile (10 ml) was added ammonium cerium(IV) nitrate (600 mg, 1.09 mmol). The resulting mixture was stirred at ambient temperature for 26 h., and then the solvent was evaporated. The residue was dissolved in dichloromethane (50 ml) and the resulting solution washed with saturated aqueous sodium thiosulfate (50 ml) and brine (50 ml), then dried and

evaporated to give the *pyrazole* **148** (440 mg, 88%) as an orange oil, the spectroscopic and analytical data of which were identical to those displayed by the forgoing sample.

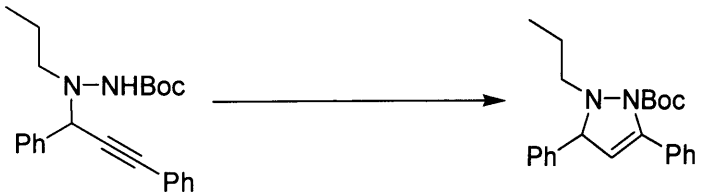
tert-Butyl 5-butyl-2,3-dihydro-3-phenyl-2-propylpyrazole-1-carboxylate (125)



112 **125**

To a solution of the *N*-Boc hydrazine **112** (450 mg, 1.3 mmol, 1.0 eq) in dry hexane (20 ml) was added silver nitrate (~10 wt % on silica gel, 440 mg, 0.3 mmol, 0.2 eq). The resulting mixture was stirred at ambient temperature in the dark for 3 h, then filtered through a pad of celite and the filtrate evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 20 : 1) to give the *2,3-dihydropyrazole-1-carboxylate* **125** (310 mg, 69%) as a colourless oil, which showed: R_f 0.78 (petroleum ether-diethyl ether 5 : 1); ν_{max}/cm^{-1} [film] 1706 (C=O), 1655, 1455, 1367, 1252, 1161 and 1127; δ_H 7.21-7.09 (5H, m, Ar-H), 5.02 (1H, *app.* t, *J* 1.5, 4-H), 4.32 (1H, *br. res.*, 3-H), 2.78 (1H, *app.* dt, *J* 11.6 and 7.8, 1'-H_α), 2.69 (1H, *app.* dt, *J* 11.6 and 6.8, 1'-H_β), 2.55-2.38 (2H, m, 1''-CH_2), 1.57-1.44 (4H, m, 2'- and 2''-CH_2), 1.41 (9H, s, ^{t}Bu), 1.35-1.25 (2H, m, 3''-CH_2), 0.89 (3H, t, *J* 7.3, Me) and 0.84 (3H, t, *J* 7.3, Me); δ_C 153.8 (C=O), 142.6, 142.0 (both C), 128.5 (2 x Ar-CH), 126.8 (Ar-CH), 126.0 (2 x Ar-CH), 108.4 (4-CH), 80.6 (C), 70.4 (3-CH), 60.5 (1'-CH_2), 29.9, 28.7 (both CH_2), 28.4 (^{t}Bu), 22.3, 20.0 (both CH_2), 14.0 and 12.0 (both Me); m/z (APCI) 345 (M^+ + H, 100%) and 289 (30) [Found: M^+ + H, 345.2538. $C_{21}H_{33}N_2O_2$ requires 345.2537].

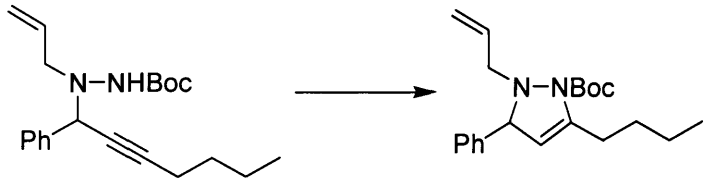
tert-Butyl 2,3-dihydro-3,5-diphenyl-2-propylpyrazole-1-carboxylate (126)



113 **126**

To a solution of the *N*-Boc hydrazine **113** (0.11 g, 0.3 mmol, 1.0 eq) in dry hexane (10 ml) was added silver nitrate (~10 wt % on silica gel, 0.3 g, 0.2 mmol, 0.6 eq). The resulting mixture was stirred at ambient temperature in the dark for 3 h, then filtered through a pad of celite. The filtrate was evaporated to give the *2,3-dihydropyrazole-1-carboxylate* **126** (0.10 g, 91%) as a colourless oil, which showed: R_f 0.51 (petroleum ether-diethyl ether 3 : 1); ν_{max}/cm^{-1} [film] 1714 (C=O), 1454, 1366, 1252, 1160 and 1127; δ_H 7.38-7.21 (10H, m, Ar-H), 5.63 (1H, d, *J* 3.2, 4-H), 4.52 (1H, d, *J* 3.2, 3-H), 2.92 (1H, ddd, *J* 11.6, 9.5 and 5.9, 1'-H_α), 2.83 (1H, ddd, *J* 11.6, 9.5 and 5.9, 1'-H_β), 1.72-1.61 (2H, m, 2'-CH_2), 1.11 (9H, s, ^{t}Bu) and 0.94 (3H, t, *J* 7.4, 3'-Me); δ_C 156.2 (C=O), 142.9, 141.2, 133.4 (all C), 129.5, 128.8, 128.4, 127.2, 126.9 (all Ar-CH), 112.0 (4-CH), 82.4 (C), 73.2 (3-CH), 62.3 (1'-CH_2), 28.2 (^{t}Bu), 21.5 (2'-CH_2) and 12.2 (3'-Me); m/z (APCI) 263 (M^+ - $C_5H_9O_2$, 100%); m/z (EI) 364 (M^+, 100%) and 308 (50); m/z (NH_4-CI) 365 (M^+ + H, 100%) and 263 (70) [Found: M^+ + H, 365.2229. $C_{23}H_{29}N_2O_2$ requires 365.2229].

tert-Butyl 2-allyl-5-butyl-2,3-dihydro-3-phenylpyrazole-1-carboxylate (127)

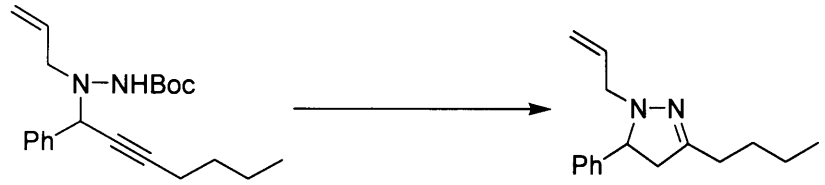


114 **127**

To a solution of the *N*-Boc hydrazine **114** (100 mg, 0.29 mmol, 1.0 eq) in dry hexane (20 ml) was added silver nitrate (~10 wt % on silica gel, 98 mg, 0.06 mmol, 0.2 eq). The resulting mixture was stirred at ambient temperature in the dark for 1 h and then filtered through a pad of celite. The filtrate was evaporated to give the *2,3-dihydropyrazole-1-carboxylate* 127 (85 mg, 85%) as a colourless oil: δ_H 7.26-7.15 (5H, m, Ar-H), 5.93 (1H, dddd, *J* 17.2, 10.2, 7.4 and 6.1, 2'-H), 5.17 (1H, *app.* dd, *J* 17.2 and 1.2, 3'-H_E), 5.12 (1H, *app.* d, *J* 10.2, 3'-H_Z), 5.02 (1H, *app.* t, *J* 1.3, 4-H), 4.41 (1H, *br. res.*, 3-H), 3.48 (1H, *app.* dd, *J* 12.8 and 6.1, 1'-H_α), 3.41 (1H, *app.* dd, *J* 12.8 and 7.4, 1'-H_β), 2.53-2.42 (2H, m, 1''-CH_2), 1.42-1.28 (13H, m, 2''-, 3''-CH_2 and ^{t}Bu) and 0.87 (3H, t, *J* 7.3, 4''-Me).

(This compound was highly unstable, so it was not characterized any further with other spectroscopic method.)

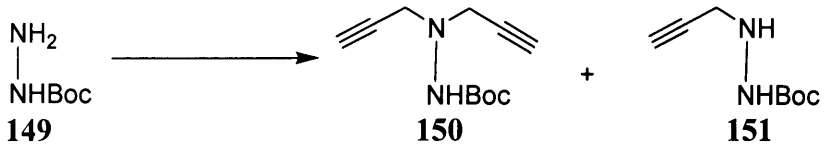
1-Allyl-3-butyl-4,5-dihydro-5-phenyl-1*H*-pyrazole (123)



114 **123**

To a solution of the *N*-Boc hydrazine **114** (50 mg, 0.15 mmol, 1.0 eq) in dry dichloromethane (10 ml) was added silver nitrate (~10 wt % on silica gel, 50 mg, 0.03 mmol, 0.2 eq). The resulting mixture was stirred at ambient temperature in the dark for 1 h and then filtered through a pad of celite. Trifluoroacetic acid (1 ml) was then added to the filtrate and the resulting solution stirred for 1 h, before the addition of saturated aqueous sodium carbonate (20 ml). The separated aqueous phase was extracted with dichloromethane (50 ml). The combined organic extracts were dried, filtered and evaporated to give the *4,5-dihydropyrazole* **123** (35 mg, 96%) as an orange oil, the spectroscopic and analytical data of which were identical to those displayed by the forgoing sample.

1-(*tert*-Butoxycarbonyl)-2,2-di(prop-2'-ynyl)-hydrazine (150) and 1-(*tert*-Butoxycarbonyl)-2-(prop-2'-ynyl)-hydrazine (151)



149 **150** **151**

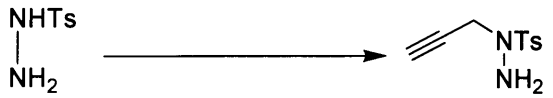
To a solution of *tert*-butyl carbazate **149** (1.0 g, 7.6 mmol, 1.0 eq) and potassium carbonate (1.5 g, 10.9 mmol, 1.4 eq) in *N,N*-dimethylformamide (5 ml) was added propargyl bromide (0.93 g, 0.7 ml, 8 mmol, 1.03 eq). The resulting mixture was stirred at ambient temperature for 18 h and filtered. The filtrate was diluted with dichloromethane (50 ml) and washed with water (5 x 50 ml). The separated organic phase was dried, filtered and evaporated. The residue was separated by column chromatography (petroleum ether-ethyl acetate 3:1) to give the *dipropargyl-*

hydrazine **150** (0.26 g, 17%) and the *propargylhydrazine* **151** (0.44 g, 34%), both as colourless solid.

The *dipropargylhydrazine* **150** showed: R_f 0.70 (petroleum ether-ethyl acetate 1:1); mp 76-82 °C; ν_{max}/cm^{-1} [KBr] 3326, 3278, 3210, 2110, 1735, 1508, 1370, 1237 and 1157; δ_H 5.84 (1H, *br.* s, NH), 3.63 (4H, d, *J* 2.3, 2 x 1'-CH_2), 2.26 (2H, t, *J* 2.3, 2 x 3'-H) and 1.40 (9H, s, ^{t}Bu); δ_C 154.3 (C=O), 80.6, 77.1 (both C), 74.4 (2 x 3'-CH), 45.5 (2 x 1'-CH_2) and 28.3 (^{t}Bu); m/z (APCI) 209 (M^+ + H, 5%), 153 (100), 135 (8) and 107 (12) [Found: M^+ + H, 209.1285. $C_{11}H_{17}N_2O_2$ requires 209.1285].

The *propargylhydrazine* **151** showed: R_f 0.58 (petroleum ether-ethyl acetate 1:1); mp 157 °C; ν_{max}/cm^{-1} [KBr] 3322, 3274, 1700, 1547, 1487, 1369, 1250 and 1164; δ_H 6.46 (1H, *br.* s, NH), 3.99 (1H, *br.* s, NH), 3.62 (2H, d, *J* 2.5, 1'-CH_2), 2.24 (1H, t, *J* 2.5, 3'-H) and 1.45 (9H, s, ^{t}Bu); δ_C 156.4 (C=O), 80.6, 80.0 (both C), 72.3 (3'-CH), 41.0 (1'-CH_2) and 28.2 (^{t}Bu); m/z (APCI) 114 (M^+ - ^{t}Bu, 20%), 97 (15), 57 (100) and 41 (94).

1-(Prop-2'-ynyl)-1-(4''-methylphenylsulfonyl)-hydrazine (153)[140]



152 **153**

To a solution of *p*-toluenesulfonyl hydrazine **152** (1.0 g, 5.4 mmol, 1.0 eq) and potassium carbonate (1.1 g, 8.0 mmol, 1.5 eq) in *N,N*-dimethylformamide (6 ml) was added propargyl bromide (0.68 g, 0.5 ml, 5.7 mmol, 1.06 eq). The resulting mixture was stirred at ambient temperature for 19 h and filtered. The filtrate was diluted with dichloromethane (50 ml) and washed with water (4 x 50 ml). The separated organic phase was dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-ethyl acetate 3:1) to give the *propargylhydrazine* **153** (1.00 g, 83%) as a colourless solid, the spectroscopic and analytical data obtained were in accord which those previously reported in the literature[140] and showed: mp 77-81 °C; [lit.[140] mp 77-79 °C]; ν_{max}/cm^{-1} [KBr] 3359, 3273, 1596, 1337, 1164 and 1090; δ_H 7.75 (2H, d, *J* 8.2, 2''- and 6''-H), 7.31 (2H, d, *J* 8.2, 3''- and 5''-H), 4.16 (2H, d, *J* 2.4, 1'-CH_2), 3.77 (2H, *br.* s, NH_2), 2.40 (3H, s, *Ts*-Me) and 2.07 (1H, t, *J* 2.4, 3'-H); δ_C 144.7, 131.6

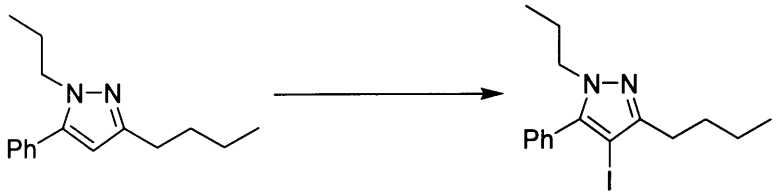
(both C), 129.6 (2''- and 6''-CH), 129.0 (3''- and 5''-CH), 75.6 (2'-C), 74.9 (3'-CH), 42.4 (1'-CH_2) and 21.6 (*Ts*-Me); m/z (APCI) 225 (M^+ + H, 100%), 157 (80) and 139 (40).

4,5-Dihydro-1-(4'-methylphenylsulfonyl)-1*H*-pyrazole (154)

153 **154**

To a solution of the propargylhydrazine **153** (2.2 g, 9.8 mmol, 1.0 eq) in dry dichloromethane (50 ml) was added silver nitrate (~10 wt % on silica gel, 1.7 g, 1.0 mmol, 0.1 eq). The resulting mixture was stirred at ambient temperature in the dark for 6 h and then filtered through a pad of celite. The filtrate was evaporated and the residue purified by column chromatography (petroleum ether-ethyl acetate 1 : 1) to give the *4,5-dihydropyrazole* **154** (0.78 g, 35%) as a colourless solid, which showed: R_f 0.19 (petroleum ether-ethyl acetate 1 : 1); mp 147-154 °C; ν_{max}/cm^{-1} [KBr]1594, 1348, 1290, 1164, and 1097; δ_H 7.69 (2H, d, *J* 8.2, 2'- and 6'-H), 7.26 (2H, d, *J* 8.2, 3'- and 5'-H), 6.94 (1H, t, *J* 1.6, 3-H), 3.42 (2H, t, *J* 9.6, 5-CH_2), 2.68 (2H, td, *J* 9.6 and 1.6, 4-CH_2) and 2.36 (3H, s, *Ts*-Me); δ_C 150.2 (C=N), 144.5, 131.0 (both C), 129.6 (2'- and 6'-CH), 128.9 (3'- and 5'-CH), 46.5 (5-CH_2), 34.2 (4-CH_2) and 21.7 (*Ts*-Me); m/z (APCI) 225 (M^+ + H, 100%), 155 (80) and 139 (25) [Found: M^+ + H, 225.0694. $C_{10}H_{13}N_2O_2S$ requires 225.0692].

3-Butyl-4-iodo-5-phenyl-1-propyl-1*H*-pyrazole (156)

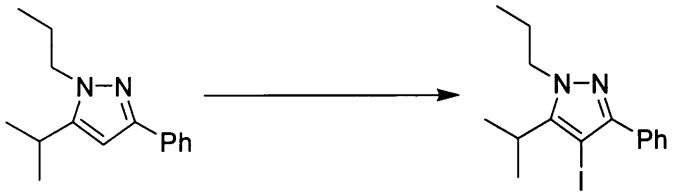


120 **156**

To a solution of pyrazole **120** (12 mg, 0.05 mmol, 1.0 eq) in acetonitrile (10 ml) was added iodine (8 mg, 0.03 mmol, 0.6 eq), followed by ammonium cerium(IV) nitrate (16 mg, 0.03 mmol, 0.6 eq). The resulting mixture was stirred at ambient temperature for 2 h. The solvent was evaporated. The residue was dissolved in ethyl acetate (50 ml) and the resulting solution

washed with ice-cold saturated aqueous sodium thiosulfate (30 ml) and then brine (30 ml). The separated organic phase was dried, filtered and evaporated to give the *iodopyrazole* **156** (15 mg, 82%) as an orange oil, which showed: R_f 0.44 (petroleum ether-ethyl acetate 5 : 1); ν_{max}/cm^{-1} [film] 1460 and 1378; δ_H 7.44-7.26 (5H, m, Ar-H), 3.89 (2H, t, *J* 7.3, 1'-CH_2), 2.57 (2H, t, *J* 7.9, 1''-CH_2), 1.69-1.57 (4H, m, 2'- and 2''-CH_2), 1.36 (2H, sext, *J* 7.4, 3''-CH_2), 0.90 (3H, t, *J* 7.4, 4''-Me) and 0.69 (3H, t, *J* 7.4, 3'-Me); δ_C 153.5, 144.8, 130.4 (all C), 130.1 (2 x Ar-CH), 129.0 (Ar-CH), 128.6 (2 x Ar-CH), 62.3 (4-C), 52.0 (1'-CH_2), 31.4, 28.3, 23.9, 22.6 (all CH_2), 14.0 and 11.0 (both Me); m/z (APCI) 369 (M^+ + H, 100%) [Found: M^+ + H, 369.0824. $C_{16}H_{22}IN_2$ requires 369.0828].

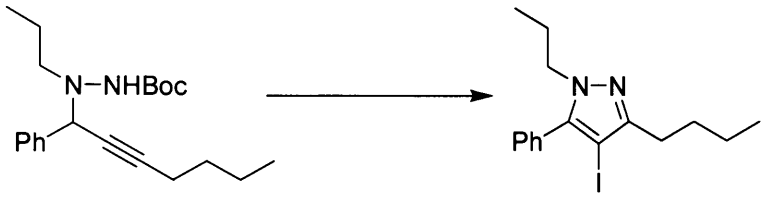
4-Iodo-5-isopropyl-3-phenyl-1-propyl-1*H*-pyrazole (157)



148 **157**

To a solution of pyrazole **148** (64 mg, 0.28 mmol, 1.0 eq) in acetonitrile (10 ml) was added iodine (43 mg, 0.17 mmol, 0.6 eq), followed by ammonium cerium(IV) nitrate (93 mg, 0.17 mmol, 0.6 eq). The resulting mixture was stirred at ambient temperature for 5 h. The solvent was evaporated. The residue was dissolved in dichloromethane (50 ml) and the resulting solution washed with saturated aqueous sodium thiosulfate (40 ml) and then brine (40 ml). The organic phase was then dried, filtered and evaporated to give the *iodopyrazole* **157** (90 mg, 91%) as an orange oil, which showed: ν_{max}/cm^{-1} [film] 1497, 1454, 1365, 1308, 1157 and 1096; δ_H 7.68-7.26 (5H, m, Ar-H), 4.08 (2H, t, *J* 7.5, 1'-CH_2), 3.20 (1H, sept, *J* 7.2, $HC(Me)_2$), 1.86-1.77 (2H, m, 2'-CH_2), 1.37 (6H, d, *J* 7.2, 2 x Me) and 0.92 (3H, t, *J* 7.5, 3'-Me); δ_C 151.7, 147.4, 133.4 (all C), 128.6 (2 x Ar-CH), 128.1 (2 x Ar-CH), 127.9 (Ar-CH), 56.5 (4-C), 52.3 (1'-CH_2), 26.8 ($CH(Me)_2$), 24.3 (2'-CH_2), 20.7 (2 x Me) and 11.2 (3'-Me); m/z (APCI) 355 (M^+ + H, 100%) [Found: M^+ + H, 355.0661. $C_{15}H_{20}N_2I$ requires 355.0666].

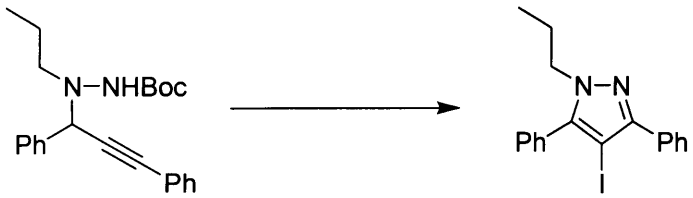
3-Butyl-4-iodo-5-phenyl-1-propyl-1*H*-pyrazole (156)



112 **156**

To an ice-cold solution of the *N*-Boc hydrazine **112** (115 mg, 0.33 mmol, 1.0 eq) in dry dichloromethane (20 ml) was added potassium carbonate (140 mg, 1.01 mmol, 3.0 eq), followed by the dropwise addition of a solution of iodine (258 mg, 1.02 mmol, 3.0 eq) in dry dichloromethane (10 ml). The resulting mixture was stirred at 0 °C for 16 h before the addition of saturated aqueous sodium thiosulfate until the excess of iodine decoloured. The separated aqueous phase was extracted with dichloromethane (2 x 40 ml). The combined organic extracts were washed with brine (50 ml), then dried and evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 5 : 1) to give the *iodopyrazole* **156** (35 mg, 29%) as an orange oil, the spectroscopic and analytical data of which were identical to those displayed by the forgoing sample.

3,5-Diphenyl-4-iodo-1-propyl-1*H*-pyrazole (159)

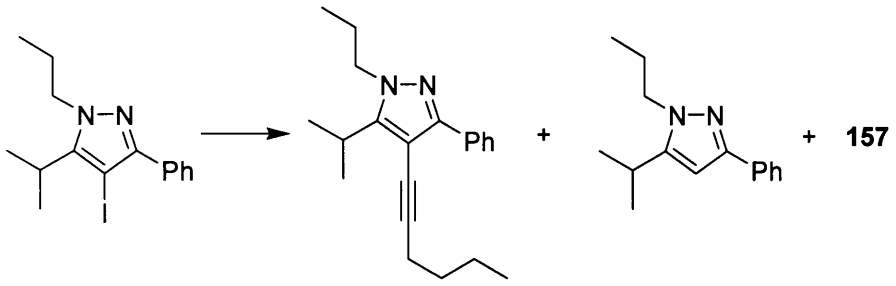


113 **159**

To an ice-cold solution of the *N*-Boc hydrazine **113** (130 mg, 0.36 mmol, 1.0 eq) in dry dichloromethane (10 ml) was added potassium carbonate (149 mg, 1.08 mmol, 3.0 eq), followed by the dropwise addition of a solution of iodine (274 mg, 1.08 mmol, 3.0 eq) in dry dichloromethane (5 ml). The resulting mixture was stirred at 0 °C for 16 h before the addition of saturated aqueous sodium thiosulfate until the excess of iodine decoloured. The separated aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined organic extracts

were dried and evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 10:1) to give the *iodopyrazole* **159** (136 mg, 97%) as an orange oil, which showed: R_f 0.48 (petroleum ether-diethyl ether 5 : 1); ν_{max}/cm^{-1} [film] 1475, 1453 and 1156; δ_H 7.81-7.28 (10H, m, Ar-H), 3.95 (2H, t, *J* 7.4, 1'-CH_2), 1.71 (2H, sext, *J* 7.4, 2'-CH_2) and 0.72 (3H, t, *J* 7.4, 3'-Me); δ_C 151.8, 146.7, 133.6 (all C), 130.7 (2 x Ar-CH), 129.7 (Ar-CH), 129.2 (2 x Ar-CH), 128.8 (2 x Ar-CH), 128.7 (2 x Ar-CH), 128.5 (Ar-CH), 60.9 (4-C), 52.8 (1'-CH_2), 24.2 (2'-CH_2) and 11.5 (3'-Me); m/z (APCI) 389 (M^+ + H, 100%) [Found: M^+ + H, 389.0510. $C_{18}H_{18}IN_2$ requires 389.0509].

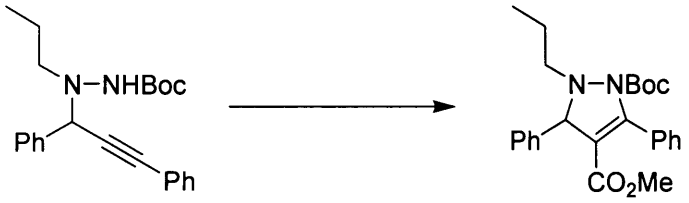
4-(Hexyn-1'-yl)-5-isopropyl-3-phenyl-1-propyl-1*H*-pyrazole (158)



157 **158** **148**

A mixture of the iodopyrazole **157** (20 mg, 0.06 mmol, 1.0 eq), hexyne (7.4 mg, 0.01 ml, 0.1 mmol, 1.5 eq), *bis*(triphenylphosphine)-palladium(II) chloride (2.1 mg, 0.05 eq), copper(I) iodide (1.1 mg, 0.1 eq) and triethylamine (1 ml) was refluxed for 1 h and cooled. The volatile was evaporated. The residue was dissolved in diethyl ether. The resulting solution was filtered and then evaporated. The residue was purified by flash chromatography (petroleum ether-diethyl ether 10:1 then 5:1) to give an inseparable mixture of the *hexynylpyrazole* **158**, the *pyrazole* **148** and the *iodopyrazole* **157** (15 mg) in a ratio of 2:1:1 as a colourless oil. In addition to the resonances showed by *pyrazole* **148** and *iodopyrazole* **157**, the *hexynylpyrazole* **158** was characterised by: δ_H 7.99 (2H, m, Ar-H), 7.29-7.21 (3H, m, Ar-H), 3.98 (2H, t, *J* 7.4, $CH_2C_2H_5$), 3.09-2.98 (1H, m, $CHMe_2$), 2.38 (2H, t, *J* 6.9, 3'-CH_2), 1.56-0.86 (18H, m). m/z (APCI) 309 (M^+ + H, 100%).

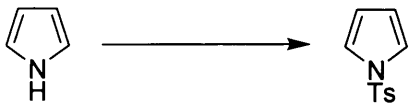
1-*tert*-Butyl 4-methyl 2,3-dihydro-3,5-diphenyl-2-propylpyrazole-1,4-dicarboxylate (160)



113 **160**

A solution of *N*-Boc hydrazine **113** (180 mg, 0.49 mmol, 1.0 eq) in dry methanol (15 ml) was flushed thoroughly with carbon monoxide. To this solution was added potassium carbonate (135 mg, 0.98 mmol, 2.0 eq), sodium acetate (80 mg, 0.98 mmol, 2.0 eq), copper chloride (198 mg, 1.47 mmol, 3.0 eq) and palladium chloride (5 mg, 0.03 mmol, 0.06 eq). The resulting mixture was stirred at ambient temperature under a carbon monoxide balloon for 2 days. The bulk of the methanol was evaporated. The residue was purified by column chromatography (petroleum ether-diethyl ether 6:1) to give the *dicarboxylate* **160** (30 mg, 15%) as an orange oil, which showed: R_f 0.30 (petroleum ether-diethyl ether 5 : 1); ν_{max}/cm^{-1} [film] 1730, 1710, 1694, 1626, 1494, 1447, 1368, 1234, 1156 and 1076; δ_H 7.43-7.19 (10H, m, Ar-H), 4.80 (1H, s, 3-H), 3.50 (3H, s, MeO), 3.02-2.88 (2H, m, 1'-CH_2), 1.71-1.64 (2H, m, 2'-CH_2), 1.04 (9H, s, ^{t}Bu) and 0.96 (3H, t, *J* 7.4, 3'-Me); δ_C 165.1, 152.8, 150.5, 141.5, 132.0 (all C), 129.8, 128.9, 127.8, 127.1, 126.3 (all Ar-CH), 113.4 (C), 82.4 (C), 71.6 (3-CH), 60.9 (1'-CH_2), 51.7 (OMe), 28.0 (^{t}Bu), 20.5 (2'-CH_2) and 12.2 (3'-Me); m/z (APCI) 423 (M^+ + H, 1%), 93 (100) and 75 (30) [Found: M^+ + H, 423.2281. $C_{25}H_{31}N_2O_4$ requires 423.2278].

1-(4'-Methylphenylsulfonyl)pyrrole (166)[200]

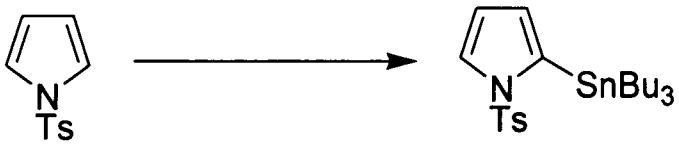


161 **166**

To a solution of pyrrole **161** (10 ml, 9.67 g, 144 mmol, 1.5 eq) in dry tetrahydrofuran (50 ml) was added sodium (2.87 g, 125 mmol, 1.3 eq). The mixture was refluxed until all the metal had reacted (*ca.* 24 h), then cooled to ambient temperature. A solution of tosyl chloride (18.90 g, 96 mmol, 1.0 eq) in dry tetrahydrofuran (50 ml) was added dropwise and the resulting mixture

1059 and 1034; δ_H 7.76 (2H, d, *J* 8.3, 2'- and 6'-H), 7.28 (2H, d, *J* 8.3, 3'- and 5'-H), *app.* t, *J* 2.3, 2- and 5-H), 6.30 (2H, *app.* t, *J* 2.3, 3- and 4-H) and 2.40 (3H, s, *Ts*-Me); 136.5 (both C), 130.4 (2'- and 6'-CH), 127.3 (3'- and 5'-CH), 121.1 (2- and 5-CH), and 4-CH) and 22.0 (*Ts*-Me); m/z (APCI) 222 (M^+ + H, 100%) and 155 (78).

1-(4'-Methylphenylsulfonyl)-2-(tri-*n*-butylstannyl)pyrrole (200)

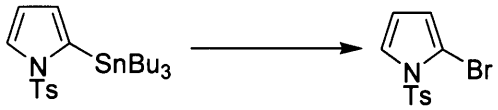


166 **200**

N-Tosylpyrrole **166** (755 mg, 3.4 mmol, 1.0 eq) was dissolved in dry tetrahydrofura under nitrogen and the solution cooled to -78 °C. To this was added dropwise *tert*-bu (1.7 M solution in pentane, 2.3 ml, 3.92 mmol, 1.15 eq). The reaction mixture was the to warm to room temperature and stirred for 30 minutes, cooled to -78 °C again butyltin chloride (1.28 g, 4 mmol, 1.15 eq) was added. After this addition, the mixture at this temperature for another 30 minutes after which the olive solution was stirre temperature for 18 hours. The solvent was removed under reduced pressure and die (50 ml) and water (50 ml) were added. The separated aqueous phase was extracted wi ether (2 x 50 ml). The combined organic extracts were dried, filtered and evapor residue was purified by flash chromatography (petroleum ether-ethyl acetate 12 : 1) t *stannane* **200** (1.34 g, 77%) as a colourless oil, which showed: R_f 0.51 (petroleum e acetate 3:1); ν_{max}/cm^{-1} [film] 2956, 2921, 1597, 1463, 1358, 1201, 1171, 1146 and 7.42 (2H, d, *J* 8.3, 2'- and 6'-H), 7.33 (1H, dd, *J* 2.9 and 1.0, 5-H), 7.16 (2H, d, *J* 8.3 5'-H), 6.36 (1H, dd, *J* 2.9 and 1.0, 3-H), 6.33 (1H, t, *J* 2.9, 4-H), 2.30 (3H, s, *Ts*-Me),

(6H, m, 3 x (2''-CH_2)), 1.21 (6H, sext, *J* 7.3, 3 x (3''-CH_2)), 1.00-0.96 (6H, m, 3 x (1''-CH_2)) and 0.79 (9H, t, *J* 7.3, 3 x (4''-Me)); δ_C 144.4, 137.4, 135.4 (all C), 129.2 (2'- and 6'-CH), 126.0 (3'- and 5'-CH), 125.7 (5-CH), 124.6 (3-CH), 114.4 (4-CH), 29.0 (3 x CH_2), 27.4 (3 x CH_2), 21.6 (*Ts*-Me), 13.8 (3 x (4''-Me)) and 11.5 (3 x (1''-CH_2)); m/z (APCI) 512 [M^+(^{120}Sn) + H, 20%], 510 [M^+(^{118}Sn) + H, 10%], 508 [M^+(^{116}Sn) + H, 5%], 454 (20), 452 (10), 450 (5), 292 (10), 291 (5), 222 (30) and 71 (100) [Found: M^+ + H, 512.1644. $C_{23}H_{38}NO_2S^{120}Sn$ requires 512.1640].

2-Bromo-1-(4'-methylphenylsulfonyl)pyrrole (204)[172]



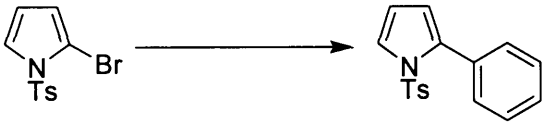
200 **204**

A solution of stannane **200** (745 mg, 1.46 mmol, 1.0 eq) in dry tetrahydrofuran (30 ml) was cooled to -78 °C. *N*-Bromosuccinimide (287 mg, 1.61 mmol, 1.1 eq) was added and the reaction mixture was stirred for another 0.5 hour at -78 °C, then at 0 °C for 19 hours before the addition of saturated aqueous sodium thiosulphate (30 ml). The organic layer was separated, dried and the solvent evaporated. The crude product was purified by flash chromatography (petroleum ether–ethyl acetate 20 :1, then 10 : 1) to give the *bromopyrrole* **204** (371 mg, 85%) as a colourless solid. The spectroscopic and analytical data obtained were in accord with those previously reported in the literature[172] and showed: R_f 0.37 (petroleum ether–ethyl acetate 5:1); mp 91-93 °C [lit.[172] mp 105-106 °C]; ν_{max}/cm^{-1} [KBr] 1594, 1438, 1375, 1264, 1174, 1137, 1085 and 1048; δ_H 7.73 (2H, d, *J* 8.3, 2'- and 6'-H), 7.38 (1H, dd, *J* 3.5 and 2.0, 5-H), 7.23 (2H, d, *J* 8.3, 3'- and 5'-H), 6.19 (1H, dd, *J* 3.5 and 2.0, 3-H), 6.15 (1H, t, *J* 3.5, 4-H) and 2.33 (3H, s, *Ts*-Me); δ_C 145.6, 135.0 (both C), 130.0 (2'- and 6'-CH), 127.9 (3'- and 5'-CH), 124.3 (5-CH), 117.9, 112.6 (both CH), 100.0 (2-C) and 21.7 (*Ts*-Me); m/z (APCI) 302 [M^+ (^{81}Br) + H, 30%], 300 [M^+ (^{79}Br) + H, 20%] and 72 (100) [Found: $M^+ + NH_4$, 316.9955. $C_{11}H_{14}{}^{79}Br\,N_2O_2S$ requires 316.9954].

General procedure for Suzuki coupling reactions

2-Bromo-*N*-tosylpyrrole **204** (300 mg, 1.00 mmol, 1.0 eq) was dissolved in toluene (10 ml) and methanol (2 ml). Dry nitrogen was passed through the solution for 10 minutes. A boronic acid (1.02 mmol, 1.02 eq), *tetrakis*(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol, 0.05 eq) and saturated aqueous sodium carbonate (212 mg, 2.00 mmol, 2.0 eq) were added subsequently while still passing nitrogen through the solution. The reaction mixture was then stirred at 80 °C under nitrogen for 15 hours, then cooled to room temperature and the layers separated. The organic layer was dried, filtered and evaporated. The crude product was purified by column chromatography.

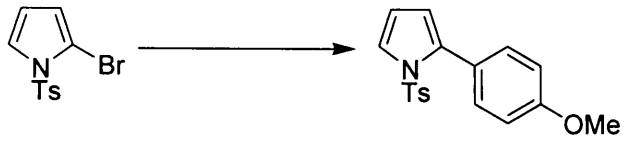
1-(4'-Methylphenylsulfonyl)-2-phenylpyrrole (201)[172]



204 **201**

Phenylboronic acid (42 mg, 0.34 mmol, 1.02 eq; Aldrich) was reacted with 2-bromo-*N*-tosylpyrrole **204** (100 mg, 0.33 mmol, 1.0 eq) as described in the general procedure. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 10 : 1) to afford the *phenylpyrrole* **201** (77 mg, 78%) as a colourless solid (turned purple on storage). The spectroscopic and analytical data obtained were in accord with those previously reported in the literature[172] and showed: R_f 0.33 (petroleum ether-ethyl acetate 5:1); mp 112-115°C [lit.[172] mp 123-124 °C]; ν_{max}/cm^{-1} [KBr] 1654, 1460, 1366, 1176, 1129 and 1056; δ_H 7.35 (1H, dd, *J* 3.3 and 1.7, 5-H), 7.27-7.13 (7H, m, all Ar-H), 7.00 (2H, d, *J* 8.3, 3'- and 5'-H), 6.21 (1H, t, *J* 3.3, 4-H), 6.06 (1H, dd, *J* 3.3 and 1.7, 3-H) and 2.25 (3H, s, *Ts*-Me); δ_C 144.7, 136.0, 135.6, 131.5 (all C), 131.0 (2 x CH), 129.4 (2 x CH), 128.3 (Ar-CH), 127.4 (2 x CH), 127.1 (2 x CH), 124.1 (5-CH), 115.8, 112.1 (both CH), and 21.6 (*Ts*-Me); m/z (APCI) 298 (M^+ + H, 100%) and 108 (30) [Found: M^+ + H, 298.0897. $C_{17}H_{16}NO_2S$ requires 298.0896].

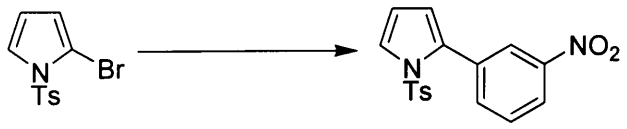
2-(4''-Methoxyphenyl)-1-(4'-methylphenylsulfonyl)pyrrole (205)[172]



204 **205**

4-Methoxybenzeneboronic acid (120 mg, 0.79 mmol, 1.02 eq; Lancaster) was reacted with 2-bromo-*N*-tosylpyrrole **204** (232 mg, 0.77 mmol, 1.0 eq) as described in the general procedure. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 5:1) to afford the *para-methoxyphenylpyrrole* **205** (77 mg, 78%) as a colourless solid. The spectroscopic and analytical data obtained were in accord with those previously reported in the literature[172] and showed: R_f 0.23 (petroleum ether-ethyl acetate 5:1); mp 101-103°C [lit.[172] mp 120-121 °C]; ν_{max}/cm^{-1} [KBr] 1612, 1512, 1466, 1362, 1294, 1247, 1169, 1144 and 1060; δ_H 7.33 (1H, dd, *J* 3.2 and 1.7, 5-H), 7.16 (2H, d, *J* 8.3, 2'- and 6'-H), 7.07 (2H, d, *J* 8.7, 2''- and 6''-H), 7.02 (2H, d, *J* 8.3, 3'- and 5'-H), 6.75 (2H, d, *J* 8.7, 3''- and 5''-H), 6.20 (1H, t, *J* 3.2, 4-H), 6.02 (1H, dd, *J* 3.2 and 1.7, 3-H), 3.76 (3H, s, *Me*O) and 2.26 (3H, s, *Ts*-Me); δ_C 159.7, 144.7, 135.8, 135.6 (all C), 132.2 (2 x CH), 129.4 (2 x CH), 127.1 (2 x CH), 123.8 (C), 123.7 (5-CH), 115.4 (CH), 112.8 (3''- and 5''-CH) 112.0 (CH), 55.3 (*Me*O) and 21.6 (*Ts*-Me); m/z (APCI) 328 (M^+ + H, 20%), 148 (10) and 75 (100) [Found: M^+ + H, 328.1006. $C_{18}H_{18}NO_3S$ requires 328.1002].

1-(4'-Methylphenylsulfonyl)-2-(3''-nitrophenyl)pyrrole (206)[172]

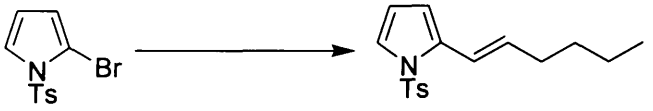


204 **206**

3-Nitrobenzeneboronic acid (170 mg, 1.02 mmol, 1.02 eq; Lancaster) was reacted with 2-bromo-*N*-tosylpyrrole **204** (300 mg, 1.0 mmol, 1.0 eq) as described in the general procedure. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 5 : 1) to afford the *meta-nitrophenylpyrrole* **206** (329 mg, 96%) as a purple solid. The spectroscopic data obtained were in accord with those previously reported in the literature[172] and showed: R_f

0.20 (petroleum ether-ethyl acetate 5:1); mp 70-71°C; ν_{max}/cm^{-1} [KBr] 1595, 1527, 1367, 1394, 1296, 1191, 1170, 1150, 1088 and 1065; δ_H 8.13 (1H, dd, *J* 8.2 and 1.3, 4''-H), 7.84 (1H, d, *J* 1.3, 2''-H), 7.63 (1H, d, *J* 7.5, 6''-H), 7.45 (1H, *app.* dd, *J* 8.2 and 7.5, 5''-H), 7.41 (1H, dd, *J* 3.3 and 1.7, 5-H), 7.17 (2H, d, *J* 8.3, 2'- and 6'-H), 7.07 (2H, d, *J* 8.3, 3' and 5'-H), 6.28 (1H, t, *J* 3.3, 4-H), 6.19 (1H, dd, *J* 3.3 and 1.7, 3-H) and 2.28 (3H, s, *Ts*-Me); δ_C 147.4, 145.5 (both C), 137.1 (CH), 135.3, 133.1, 133.1 (all C), 129.7 (2'- and 6'-CH), 128.4 (CH), 126.9 (3'- and 5'-CH), 125.2, 125.1, 123.0, 117.2, 112.5 (all CH) and 21.6 (*Ts*-Me); m/z (APCI) 343 (M^+ + H, 50%), 122 (5), 88 (40), 86 (45) and 72 (100) [Found: M^+ + H, 343.0744. $C_{17}H_{15}N_2O_4S$ requires 343.0747].

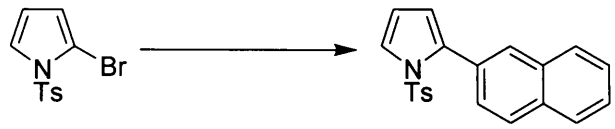
(*E*)-2-(1''-Hexen-1''-yl)-1-(4'-methylphenylsulfonyl)pyrrole (209)



204 **209**

(*E*)-1-Hexen-1-ylboronic acid (131 mg, 1.02 mmol, 1.02 eq; Aldrich) was reacted with 2-bromo-*N*-tosylpyrrole **204** (300 mg, 1.0 mmol. 1.0 eq) as described in the general procedure. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 10:1) to afford the *hexenylpyrrole* **209** (238 mg, 78%) as a colourless oil, which showed: R_f 0.43 (petroleum ether-ethyl acetate 5:1); ν_{max}/cm^{-1} [film] 2958, 2929, 1596, 1466, 1369, 1190, 1154, 1090 and 1054; δ_H 7.70 (2H, d, *J* 8.3, 2'- and 6'-H), 7.29-7.26 (3H, m, 5-, 3'- and 5'-H), 6.78 (1H, dt, *J* 15.7 and 1.2, 1''-H), 6.31 (1H, dd, *J* 3.3 and 1.8, 3-H), 6.22 (1H, t, *J* 3.3, 4-H), 5.94 (1H, dt, *J* 15.7 and 7.1, 2''-H), 2.40 (3H, s, *Ts*-Me), 2.18 (2H, qd, *J* 7.1 and 1.2, 3''-CH_2), 1.45-1.29 (4H, m, 4''- and 5''-CH_2) and 0.94 (3H, t, *J* 7.2, 6''-Me); δ_C 144.8, 136.1, 134.2 (all C), 133.4 (1''-CH), 129.8 (2'- and 6'-CH), 127.0 (3'- and 5'-CH), 122.3 (5-CH), 118.6 (3-CH), 112.1, 110.8 (both CH), 32.6 (3''-CH_2), 31.3 (4''-CH_2), 22.2 (5''-CH_2), 21.6 (*Ts*-Me) and 14.0 (6''-Me); m/z (APCI) 304 (M^+ + H, 100%) [Found: M^+ + H, 304.1366. $C_{17}H_{22}NO_2S$ requires 304.1366].

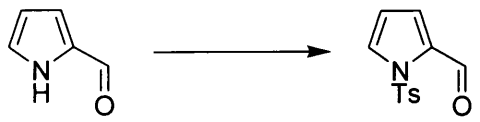
1-(4'-Methylphenylsulfonyl)-2-(naphthalene-2''-yl)pyrrole (207)



204 **207**

2-Naphthaleneboronic acid (175 mg, 1.02 mmol, 1.02 eq; Lancaster) was reacted with 2-bromo-*N*-tosylpyrrole **204** (300 mg, 1.0 mmol. 1.0 eq) for 65 hours as described in the general procedure. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 12:1, then 9:1) to afford the *naphthalenylpyrrole* **207** (256 mg, 74%) as a colourless solid, which showed: R_f 0.30 (petroleum ether-ethyl acetate 10:1); mp 126-129 °C; ν_{max}/cm^{-1} [KBr] 1595, 1488, 1456, 1363, 1173, 1143, 1088 and 1059; δ_H 7.74-7.59 (3H, m, all Ar-H), 7.49 (1H, s, 1''-H), 7.39-7.32 (4H, m, all Ar-H), 7.08 (2H, d, *J* 8.1. 2'- and 6'-H), 6.86 (2H, d, *J* 8.1. 3'- and 5'-H), 6.21 (1H, t, *J* 3.2, 4-H), 6.11 (1H, dd, *J* 3.2 and 1.7, 3-H) and 2.15 (3H, *Ts*-Me); δ_C 144.9, 136.1, 135.6, 133.0, 132.6 (all C), 129.8 (CH), 129.5 (2'- and 6'-CH), 129.2 (C), 128.9, 128.2, 127.8 (all CH), 127.2 (3'- and 5'-CH), 126.8, 126.6, 126.3, 124.4, 116.4, 112.5 (all CH) and 21.6 (*Ts*-Me); m/z (APCI) 348 (M^+ + H, 100%) [Found: M^++H, 348.1055. $C_{21}H_{18}NO_2S$ requires 348.1053].

1-(4'-Methylphenylsulfonyl)pyrrole-2-carboxaldehyde (193)[201]



192 **193**

Sodium hydride (2.3 g of a 60% dispersion in mineral oil, 57 mmol, 1.2 eq) was washed with dry tetrahydrofuran (2 x 30 ml) and suspended in dry tetrahydrofuran (30 ml). Pyrrole-2-carboxaldehyde **192** (4.5 g, 47.3 mmol, 1.0 eq) in dry tetrahydrofuran (10 ml) was added dropwise and stirring continued for 15 minutes. Tosyl chloride (11.7 g, 61.4 mmol, 1.3 eq) in dry tetrahydrofuran (15 ml) was then added dropwise and the resulting mixture stirred for a further 1.5 hours before quenching with water (50 ml). Tetrahydrofuran was removed by evaporation and the residue diluted with dichloromethane (100 ml). The separated aqueous

layer was extracted with dichloromethane (2 x 100 ml) and the combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (2 x 100 ml) and brine (100 ml). The organic solution was then dried, filtered and evaporated. The residue was purified by flash chromatography on silica gel (petroleum ether-ethyl acetate 3:1) to give the *aldehyde* **193** (7.43 g, 63%) as a light brown solid. An analytical sample was recrystallised from ethyl acetate / petroleum ether. The data obtained were in accord with those previously reported in the literature[201] and showed: R_f 0.30 (petroleum ether-ethyl acetate 3:1); mp 94-95 °C [lit.[201] mp 94.6 °C]; δ_H 9.99 (1H, s, HC=O), 7.82 (2H, d, *J* 8.3, 2'- and 6'-H), 7.64 (1H, dd, *J* 3.1 and 1.7, 5-H), 7.34 (2H, d, *J* 8.3, 3'- and 5'-H), 7.17 (1H, dd, *J* 3.7 and 1.7, 3-H), 6.42 (1H, *app.* t, *J ca.* 3.4, 4-H) and 2.43 (3H, s, *Ts*-Me); δ_C 179.0 (C=O), 146.0, 135.1, 133.5 (all C), 130.2 (2'- and 6'-CH), 129.5 (5-CH), 127.5 (3'- and 5'-CH), 124.6 (3-CH), 112.4 (4-CH) and 21.7 (*Ts*-Me).

2-Methyl-1-(4'-methylphenylsulfonyl)pyrrole (186)[202]

193 **186**

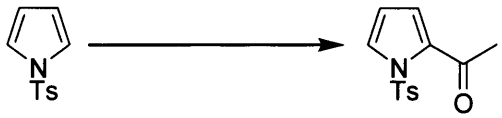
To a suspension of aluminium chloride (2.35 g, 17.6 mmol, 1.0 eq) in dichloromethane (50 ml), was added borane *tert*-butylamine complex (3.06 g, 35.2 mmol, 2.0 eq). The resulting mixture was stirred for 15 minutes and a solution of *N*-tosylpyrrole carboxaldehyde **193** (4.39 g, 17.6 mmol, 1.0 eq) in dichloromethane (20 ml) was added. After 3 hours, the reaction was carefully quenched with ice-cold water (100 ml) and extracted with dichloromethane (2 x 100 ml). The combined organic solutions were washed with 2M hydrochloric acid (100 ml), saturated aqueous sodium hydrogen carbonate (100 ml) and brine (100 ml), then dried, filtered and evaporated. The residue was purified by flash chromatography (petroleum ether-ethyl acetate 9:1) to give the *2-methyl-N-pyrrole* **186** (2.50 g, 60%) as a colourless solid. The spectroscopic and analytical data obtained were in accord with those previously reported in the literature[202] and showed: R_f 0.53 (petroleum ether-ethyl acetate 3:1); mp 86-88 °C [lit.[202] mp 87-88 °C]; δ_H 7.59 (2H, d, *J* 8.4, 2'- and 6'-H), 7.22-7.18 (3H, m, 5-, 3'- and 5'-H), 6.08 (1H, t, *J* 3.3, 4-H),

5.87-5.86 (1H, m, 3-H), 2.32 (3H, s, *Ts*-Me) and 2.21 (3H, s, 2-Me); δ_C 145.2, 136.7, 131.2 (all C), 130.4 (2'- and 6'-CH), 127.2 (3'- and 5'-H), 122.4 (5-CH), 113.5 (4-CH), 111.6 (3-CH), 22.0 (*Ts*-Me) and 14.0 (2-Me); m/z (APCI) 236 (M^+ + H, 100%).

General procedure for pyrrole acylation

To a solution of the pyrrole (1.0 mmol, 1.0 eq) and trifluoroacetic anhydride (see individual experiment) in dichloromethane or 1, 2-dichloroethane, was added the acid (2.0-4.0 mmol, 2.0-4.0 eq). The reaction mixture was stirred either at room temperature or under reflux until completion according to tlc analysis. The (cooled) reaction mixture was then diluted with dichloromethane, basified with saturated aqueous sodium carbonate or 2M aqueous sodium hydroxide, then washed with brine, dried, filtered and evaporated. The residue was either characterised directly or purified by column chromatography.

2-Acetyl-1-(4'-methylphenylsulfonyl)pyrrole (210)[203]



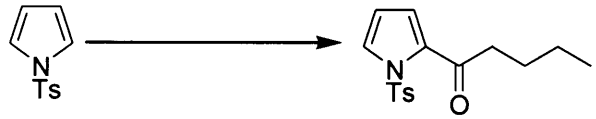
166 **210**

A solution of *N*-tosylpyrrole **166** (0.56 g, 2.55 mmol, 1.0 eq), trifluoroacetic anhydride (6 ml) and glacial acetic acid (0.61 g, 10.20 mmol, 4.0 eq) in dichloromethane (30 ml) was stirred at room temperature for 29 hours. Standard work-up as described in the general procedure give the *acetylpyrrole* **210** (0.63 g, 94%) as a pure, colourless solid without further purification. The spectroscopic and analytical data obtained were in accord with those previously reported for this compound in the literature[203] and showed: R_f 0.46 (petroleum ether-ethyl acetate 1:1); mp 113-115 °C [lit.[203] mp 106-107 °C]; ν_{max}/cm^{-1} [KBr] 1672 (C=O), 1594, 1442,1406, 1367, 1328, 1263, 1174, 1147 and 1088; δ_H 7.82 (2H, d, *J* 8.3, 2'- and 6'-H), 7.74 (1H, dd, *J* 3.1 and 1.7, 5-H), 7.24 (2H, d, *J* 8.3, 3'- and 5'-H), 6.98 (1H, dd, *J* 3.8 and 1.7, 3-H), 6.26 (1H, *app.* t, *J ca.* 3.5, 4-H), 2.32 (3H, s, Me) and 2.27 (3H, s, Me); δ_C 185.9 (C=O), 144.8, 135.8, 133.2 (all C), 130.4 (5-CH), 129.3 (2'- and 6'-CH), 128.3 (3'- and 5'-CH), 124.5 (3-CH), 110.3 (4-CH), 27.0

(*Me*CO) and 21.7 (*Ts*-Me); m/z (APCI) 264 (M^+ + H, 100%), 222 (44) and 155 (14) [Found: M^+ + H, 264.0690. $C_{13}H_{14}NO_3S$ requires 264.0689].

(The product **210** could also be obtained, in 81% yield, by treating *N*-tosylpyrrole **166** (50 mg, 0.23 mmol, 1.0 eq) with acetic anhydride (94 mg, 0.92 mmol, 4.0 eq) and trifluoroacetic acid (0.5 ml) in dichloromethane at ambient temperature for 25 hours.)

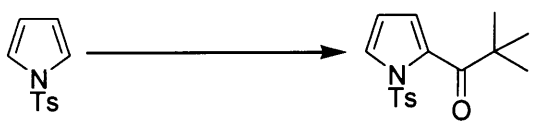
1-(4'-Methylphenylsulfonyl)-2-pentanoylpyrrole (211)



166 **211**

Valeric acid (0.55 g, 5.4 mmol, 4 eq) was added to a solution of *N*-tosylpyrrole **166** (0.30 g, 1.4 mmol, 1.0 eq) and trifluoroacetic anhydride (3 ml) in dichloromethane (20 ml). The resulting mixture was stirred at room temperature for 16 hours, then refluxed for 7 hours. Standard work-up as described in the general procedure give the *acylpyrrole* **211** (0.34 g, 82%) as a colourless solid, which showed: R_f 0.25 (petroleum ether-ethyl acetate 5:1); mp 57-58 °C; ν_{max}/cm^{-1} [KBr] 1679 (C=O), 1594, 1439, 1362, 1306, 1252, 1140 and 1087; δ_H 7.82 (2H, d, *J* 8.3, 2'- and 6'-H), 7.71 (1H, dd, *J* 3.1 and 1.7, 5-H), 7.23 (2H, d, *J* 8.3, 3'- and 5'-H), 6.95 (1H, dd, *J* 3.7 and 1.7, 3-H), 6.24 (1H, *app.* t, *J ca.* 3.4, 4-H), 2.59 (2H, t, *J* 7.6, 2''-CH_2), 2.33 (3H, s, *Ts*-Me) 1.50 (2H, quint, *J* 7.6, 3''-CH_2), 1.20 (2H, sext, *J* 7.6, 4''-CH_2) and 0.79 (3H, t, *J* 7.6, 5''-Me); δ_C 189.2 (C=O), 144.7, 136.0, 133.4 (all C), 130.0 (5-CH), 129.3 (2'- and 6'-CH), 128.3 (3'- and 5'-CH), 123.3 (3-CH), 110.2 (4-CH), 39.2 (2''-CH_2), 27.0 (3''-CH_2), 22.3 (4''-CH_2), 21.7 (*Ts*-Me) and 13.9 (5''-Me); m/z (APCI) 306 (M^+ + H, 100%) [Found: M^+ + H, 306.1157. $C_{16}H_{20}NO_3S$ requires 306.1158].

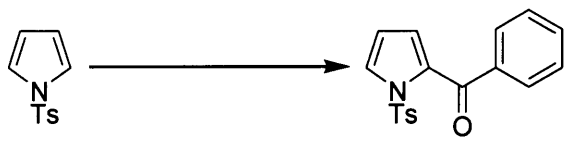
2-(2'',2''-Dimethylpropanoyl)-1-(4'-methylphenylsulfonyl)pyrrole (212)



166 **212**

A solution of *N*-tosylpyrrole **166** (50 mg, 0.23 mmol, 1.0 eq), trifluoroacetic anhydride (1 ml) and pivalic acid (92 mg, 0.90 mmol, 4 eq) in 1, 2-dichloroethane (5 ml) was refluxed for 119 hours. After work-up, the crude product was purified by column chromatography (petroleum ether-dichloromethane 2:1, then 1:1) to give the *acylpyrrole* **212** (50 mg, 72%) as a colourless oil, which showed: R_f 0.35 (petroleum ether-dichloromethane 1:1); ν_{max}/cm^{-1} [film] 1668 (C=O), 1596, 1443, 1368, 1304, 1174, 1145, 1091, 1064, 1042 and 1014; δ_H 7.80 (2H, d, *J* 8.3, 2'- and 6'-H), 7.45 (1H, dd, *J* 3.3 and 1.5, 5-H), 7.23 (2H, d, *J* 8.3, 3'- and 5'-H), 6.64 (1H, dd, *J* 3.7 and 1.5, 3-H), 6.17 (1H, *app.* t, *J ca.* 3.4, 4-H), 2.31 (3H, s, *Ts*-Me) and 1.19 (9H, s, ^{t}Bu); δ_C 199.7 (C=O), 144.8, 136.4, 132.3 (all C), 129.5 (2'- and 6'-CH), 128.0 (3'- and 5'-CH), 126.6 (5-CH), 118.2 (3-CH), 110.4 (4-CH), 44.2 (2''-C), 27.7 (^{t}Bu) and 21.7 (*Ts*-Me); m/z (APCI) 306 (M^+ + H, 100%), 223 (5) and 91 (30) [Found: M^+ + H, 306.1162. $C_{16}H_{20}NO_3S$ requires 306.1158].

2-Benzoyl-1-(4'-methylphenylsulfonyl)pyrrole (213)

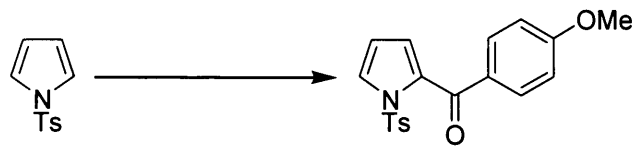


166 **213**

Benzoic acid (110 mg, 0.90 mmol, 2.0 eq) was added to a solution of tosylpyrrole **166** (100 mg, 0.45 mmol, 1.0 eq) and trifluoroacetic anhydride (1 ml) in 1,2-dichloroethane (8 ml). The reaction mixture was refluxed for 70 hours. Standard work-up as described in the general procedure give the *benzoylpyrrole* **213** (123 mg, 84%) as a colourless solid, which showed: R_f 0.31 (petroleum ether-ethyl acetate 3:1); mp 148-151 °C; ν_{max}/cm^{-1} [KBr] 1651 (C=O), 1596, 1452, 1360, 1329, 1258, 1170 and 1149; δ_H 7.93 (2H, d, *J* 8.3, 2'- and 6'-H), 7.71-7.67 (3H, m, 2''-, 6''- and 5-H), 7.47-7.43 (1H, m, 4''-H), 7.32 (2H, t, *J* 7.7, 3''- and 5''-H), 7.26 (2H, d, *J* 8.3, 3'- and 5'-H), 6.60 (1H, dd, *J* 3.5 and 1.6, 3-H), 6.23 (1H, t, *J* 3.5, 4-H) and 2.32 (3H, s, *Ts*-Me); δ_C 184.5 (C=O), 145.1, 137.9, 136.2, 133.1 (all C), 132.8 (4''-CH), 129.8 (2 x CH), 129.5

(2 x CH), 129.5 (5-CH), 128.5 (2 x CH), 128.3 (2 x CH), 125.3 (3-CH), 110.7 (4-CH) and 21.8 (*Ts*-Me); m/z (APCI) 326 (M^+ + H, 100%) and 105 (46) [Found: M^+ + NH_4, 343.1113. $C_{18}H_{19}N_2O_3S$ requires 343.1111].

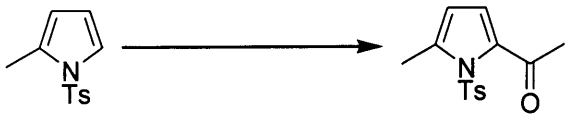
2-(4''-Methoxybenzoyl)-1-(4'-methylphenylsulfonyl)pyrrole (214)



166 **214**

A mixture of *N*-tosylpyrrole **166** (120 mg, 0.54 mmol, 1.0 eq), trifluoroacetic anhydride (1 ml) and *para*-methoxybenzoic acid (164 mg, 1.08 mmol, 2.0 eq) in dichloromethane (15 ml) was stirred at room temperature for 48 hours, before work-up as describe in the general procedure. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 5:1, then 3 : 1) to give the *acylpyrrole* **214** (161 mg, 84%) as a syrup, which showed: R_f 0.17 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1642 (C=O), 1598, 1441, 1372, 1329, 1255, 1171, 1147, 1089, 1057 and 1015; δ_H 7.91 (2H, d, *J* 8.3, 2'- and 6'-H), 7.73 (2H, d, *J* 8.8, 2''- and 6''-H), 7.61 (1H, dd, *J* 3.1 and 1.6, 5-H), 7.25 (2H, d, *J* 8.3, 3'- and 5'-H), 6.81 (2H, d, *J* 8.8, 3''- and 5''-H), 6.56 (1H, dd, *J* 3.6 and 1.6, 3-H), 6.21 (1H, *app.* t, *J ca.* 3.4, 4-H), 3.73 (3H, s, *Me*O) and 2.31 (3H, s, *Ts*-Me); δ_C 183.7 (C=O), 163.5, 145.0, 136.3, 133.2 (all C), 132.2 (2 x CH), 130.5 (C), 129.5 (2 x CH), 128.7 (5-CH), 128.4 (3'- and 5'-CH), 123.9 (3-CH), 113.6 (3''- and 5''-CH), 110.7 (4-CH), 55.5 (*Me*O) and 21.8 (*Ts*-Me); m/z (APCI) 356 (M^+ + H, 100%) [Found: M^+ + H, 356.0956. $C_{19}H_{18}NO_4S$ requires 356.0951].

2-Acetyl-5-methyl-1-(4'-methylphenylsulfonyl)pyrrole (219)

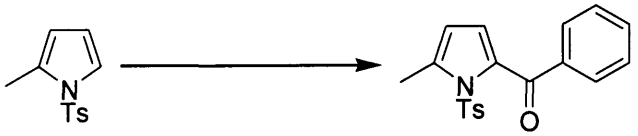


186 **219**

A solution of 2-methyl-*N*-tosylpyrrole **186** (50 mg, 0.21 mmol, 1.0 eq), acetic anhydride (172 mg, 1.68 mmol, 8 eq) and trifluoroacetic acid (0.5 ml) in dichloromethane (10 ml) was stirred at room temperature for 3 hours. Standard work-up as described in the general procedure give a crude product, which was purified by column chromatography (petroleum ether-ethyl acetate 3:1) to obtain the *acetylpyrrole* **219** (40 mg, 69%) as a colourless solid, which showed: R_f 0.30 (petroleum ether-ethyl acetate 3:1); mp 86-88 °C; [Found: C, 60.30; H, 5.42; N, 5.03. $C_{14}H_{15}NO_3S$ requires C, 60.63; H, 5.45; N, 5.05%]; ν_{max}/cm^{-1} [KBr] 1671 (C=O), 1462, 1376, 1319, 1260, 1173, 1128 and 1099; δ_H 7.87 (2H, d, *J* 8.2, 2'- and 6'-H), 7.26 (2H, d, *J* 8.2, 3'- and 5'-H), 6.79 (1H, d, *J* 3.7, 3-H), 5.94 (1H, d, *J* 3.7, 4-H), 2.51 (3H, s, Me), 2.35 (3H, s, Me) and 2.34 (3H, s, Me); δ_C 188.1 (C=O), 145.1, 142.1, 137.4, 136.2 (all C), 129.9 (2'- and 6'-CH), 128.0 (3'- and 5'-CH), 123.0 (3-CH), 112.8 (4-CH), 28.3 (*Me*CO), 22.1 (*Ts*-Me) and 16.6 (5-Me); m/z (APCI) 278 (M^+ + H, 100%) [Found: M^+ + H, 278.0856. $C_{14}H_{16}NO_3S$ requires 278.0851].

(The product **219** could also be obtained, in 80% yield, by treating 2-methyl-*N*-tosylpyrrole **186** (1.21 g, 5.1 mmol, 1.0 eq), as described in the general procedure, with acetic acid (1.11 ml, 8.6 mmol, 3.6 eq) and trifluoroacetic anhydride (12 ml) in dichloromethane (12 ml) at room temperature for 2 hours.)

2-Benzoyl-5-methyl-1-(4'-methylphenylsulfonyl)pyrrole (220)

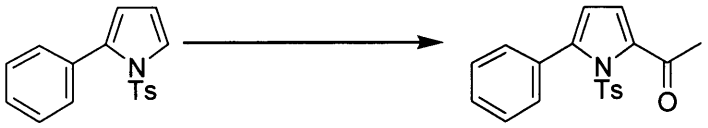


186 **220**

A solution of 2-methyl-*N*-tosylpyrrole **186** (200 mg, 0.85 mmol, 1.0 eq), trifluoroacetic anhydride (1.5 ml) and benzoic acid (415 mg, 3.40 mmol, 4 eq) in dichloromethane (15 ml) was stirred at room temperature for 42 hours, before the addition of 2M aqueous sodium hydroxide (50 ml). Work-up as described in the general procedure gave a crude product, which was

purified by column chromatography (petroleum ether-ethyl acetate 5:1) to afford the *benzoylpyrrole* **220** (276 mg, 96%) as a colourless oil, which showed: R_f 0.36 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1652 (C=O), 1598, 1483, 1361, 1326, 1265, 1174 and 1108; δ_H 8.01 (2H, d, *J* 8.3, 2'- and 6'-H), 7.82 (2H, dd, *J* 7.4 and 1.2, 2''- and 6''-H), 7.45 (1H, tt, *J* 7.4 and 1.2, 4''-H), 7.33 (2H, t, *J* 7.4, 3''- and 5''-H), 7.25 (2H, d, *J* 8.3, 3'- and 5'-H), 6.37 (1H, d, *J* 3.5, 3-H), 5.89 (1H, d, *J* 3.5, 4-H), 2.42 (3H, s, Me) and 2.31 (3H, s, Me); δ_C 185.6 (C=O), 145.1, 139.4, 137.9, 136.4, 135.1 (all C), 132.9 (4''-CH), 130.1 (2 x CH), 129.8 (2 x CH), 128.3 (2 x CH), 128.1 (2 x CH), 122.3 (3-CH), 112.3 (4-CH), 21.7 (*Ts*-Me) and 15.3 (5-Me); m/z (APCI) 340 (M^+ + H, 100%) [Found: M^+ + H, 340.1004. $C_{19}H_{18}NO_3S$ requires 340.1002].

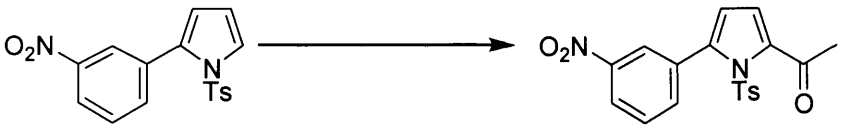
2-Acetyl-1-(4'-methylphenylsulfonyl)-5-phenylpyrrrole (221)



201 **221**

A mixture of 2-phenyl-*N*-tosylpyrrole **201** (70 mg, 0.24 mmol, 1.0 eq), acetic acid (29 mg, 0.48 mmol, 2.0 eq) and trifluoroacetic anhydride (0.5 ml) in dichloromethane (10 ml) was stirred at room temperature for 43 hours, before being quenched with 2M aqueous sodium hydroxide (50 ml). The crude product was purified by column chromatography (petroleum ether-ethyl acetate 3:1) to give the *acetylpyrrole* **221** (60 mg, 74%) as a syrup, which showed: R_f 0.23 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1682 (C=O), 1596, 1470, 1366, 1308, 1225, 1175 and 1092; δ_H 7.33-7.29 (3H, m, 2'-, 6'- and 4''-H), 7.26-7.22 (2H, m, both Ar-H), 7.18-7.14 (2H, m, both Ar-H), 7.05 (2H, d, *J* 8.2, 3'- and 5'-H), 6.79 (1H, d, *J* 3.5, 3-H), 6.05 (1H, d, *J* 3.5, 4-H), 2.52 (3H, s, *Me*CO) and 2.29 (3H, s, *Ts*-Me); δ_C 190.5 (C=O), 145.1, 144.9, 139.9, 135.3, 131.3 (all C), 130.0 (2 x CH), 129.1 (2 x CH), 129.0 (4''-CH), 127.8 (2 x CH), 127.7 (2 x CH), 122.4 (3-CH), 114.9 (4-CH), 29.5 (*Me*CO) and 21.7 (*Ts*-Me); m/z (APCI) 340 (M^+ + H, 100%) and 298 (5) [Found: M^+ + H, 340.1004. $C_{19}H_{18}NO_3S$ requires 340.1002].

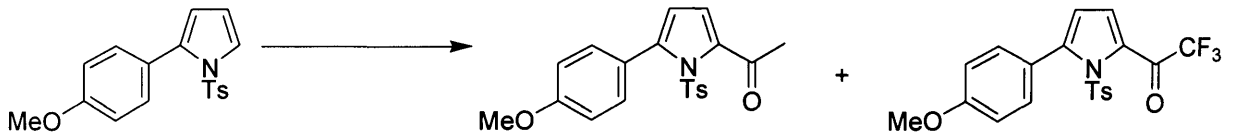
2-Acetyl-1-(4'-methylphenylsulfonyl)-5-(3''-nitrophenyl)pyrrole (224)



206 **224**

A mixture of 2-(3'-nitrophenyl)-1-tosylpyrrole **206** (150 mg, 0.44 mmol, 1.0 eq), acetic acid (53 mg, 0.88 mmol, 2.0 eq) and trifluoroacetic anhydride (1 ml) in 1,2-dichloroethane (10 ml) was refluxed for 48 hours, before work-up as described in the general procedure. The crude product was purified by column chromatography (petroleum ether-dichloromethane 1:3, then 1:6, then petroleum ether-ethyl acetate 1:1) to give the *acetylpyrrole* **224** (98 mg, 58%) as a colourless solid: R_f 0.18 (petroleum ether-ethyl acetate 3:1); mp 130-132 °C; ν_{max}/cm^{-1} [KBr] 1687 (C=O), 1531, 1370, 1346, 1229, 1188 and 1175; δ_H 8.16 (1H, dd, *J* 8.0 and 1.6, 4''-H), 7.88 (1H, t, *J* 1.6, 2''-H), 7.62 (1H, dd, *J* 8.0 and 1.6, 6''-H), 7.49 (1H, t, *J* 8.0, 5''-H), 7.38 (2H, d, *J* 8.2, 2'- and 6'-H), 7.12 (2H, d, *J* 8.2, 3'- and 5'-H), 6.83 (1H, d, *J* 3.5, 3-H), 6.19 (1H, d, *J* 3.5, 4-H), 2.52 (3H, s, *Me*CO) and 2.32 (3H, s, *Ts*-Me); δ_C 190.2 (C=O), 147.5, 145.8, 141.6, 140.3 (all C), 136.0 (CH), 135.1, 133.1 (both C), 129.5 (2'- and 6'-CH), 128.9 (CH), 127.5 (3'- and 5'-CH), 124.3, 123.6, 122.0, 116.1 (all CH), 29.4 (*Me*CO) and 21.7 (*Ts*-Me); m/z (APCI) 385 (M^+ + H, 100%), 343 (10), 90 (10) [Found: M^+ + H, 385.0846. $C_{19}H_{17}N_2O_5S$ requires 385.0853].

2-Acetyl-5-(4''-methoxyphenyl)-1-(4'-methylphenylsulfonyl)pyrrole (222) and 5-(4''-methoxyphenyl)-1-(4'-methylphenylsulfonyl)-2-trifluoroacetylpyrrole (223)



205 **222** **223**

A solution of 2-(*p*-methoxyphenyl)-1-tosylpyrrole **205** (145 mg, 0.44 mmol, 1.0 eq), acetic acid (53 mg, 0.88 mmol, 2.0 eq) and trifluoroacetic anhydride (1 ml) in dichloromethane (20 ml) was stirred at room temperature for 35 hours, before work-up as described in the general procedure.

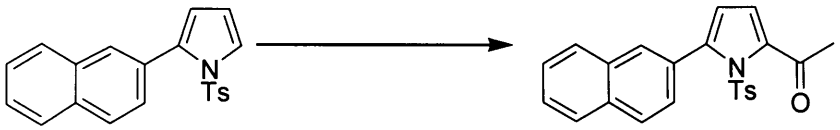
The crude product was separated by column chromatography (petroleum ether-ethyl acetate 3:1) to give the *acetylpyrrole* **222** (65 mg, 40%) and the *trifluoroacetylpyrrole* **223** (21 mg, 11%), both as syrups.

The *acetylpyrrole* **222** showed: R_f 0.23 (petroleum ether-ethyl acetate 3 : 1); ν_{max}/cm^{-1} [film] 1680 (C=O), 1611, 1471, 1367, 1292, 1252, 1175, 1091 and 1031; δ_H 7.27 (2H, d, *J* 8.2, 2'- and 6'-H), 7.10 (2H, d, *J* 8.7, 2''- and 6''-H), 7.05 (2H, d, *J* 8.2, 3'- and 5'-H), 6.79-6.77 (3H, m, 3-, 3''- and 5''-H), 5.98 (1H, d, *J* 3.4, 4-H), 3.78 (3H, s, *Me*O), 2.52 (3H, s, *Me*CO) and 2.30 (3H, s, *Ts*-Me); δ_C 190.8 (C=O), 160.3, 145.0, 144.9, 139.8, 135.1 (all C), 131.5 (2 x CH), 129.1 (2 x CH), 127.6 (2 x CH), 123.7 (C), 122.7 (3-CH), 114.3 (4-CH), 113.2 (3''- and 5''-CH), 55.4 (*Me*O), 29.6 (*Me*CO) and 21.7 (*Ts*-Me); m/z (APCI) 370 (M^+ + H, 100%), 328 (15), 215 (35) and 109 (45) [Found: M^+ + H, 370.1107. $C_{20}H_{20}NO_4S$ requires 370.1108].

The *trifluoroacetylpyrrole* **223** showed: R_f 0.35 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1694 (C=O), 1609, 1463, 1372, 1295, 1255, 1174, 1147, 1089, 1031 and 942; δ_H 7.32 (2H, d, *J* 8.4, 2'- and 6'-H), 7.19-7.17 (1H, m, 3-H), 7.11-7.06 (4H, m, 3'-, 5'-, 2''- and 6''-H), 6.77 (2H, d, *J* 8.8, 3''- and 5''-H), 6.12 (1H, d, *J* 3.9, 4-H), 3.77 (3H, s, *Me*O) and 2.30 (3H, s, *Ts*-Me); δ_C 171.2 (q, J_{FC} 36.2, C=O), 160.9, 149.2, 145.7, 135.1 (all C), 131.5 (2 x CH), 131.3 (C), 129.3 (2 x CH), 127.8 (2 x CH), 127.8 (3-CH), 123.0 (C), 116.5 (q, J_{FC} 288.8, CF_3), 114.7 (4-CH), 113.4 (3''- and 5''-CH), 55.4 (*Me*O) and 21.7 (*Ts*-Me); m/z (APCI) 424 (M^+ + H, 100%), 270 (8), 209 (5) and 173 (20) [Found: M^+ + H, 424.0822. $C_{20}H_{17}F_3NO_4S$ requires 424.0825].

(The *trifluoroacetylpyrrole* **223** was also obtained, in 84% yield, by treating 2-(4'-methoxyphenyl)-1-tosylpyrrole **205** (120 mg, 0.37 mmol, 1.0 eq) with trifluoroacetic acid (0.1 ml) and trifluoroacetic anhydride (1 ml) at room temperature for 69 hours.)

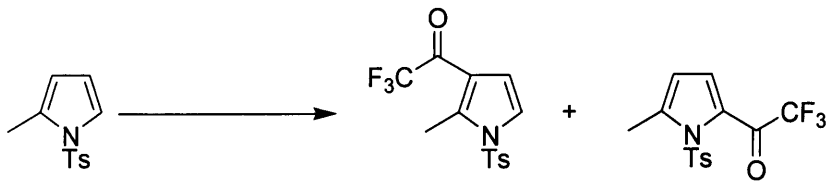
2-Acetyl-1-(4'-methylphenylsulfonyl)-5-(naphthalene-2''-yl)pyrrole (226)



207 **226**

A solution of 2-naphthalen-2-yl-*N*-tosylpyrrole **207** (174 mg, 0.5 mmol, 1.0 eq), acetic acid (60 mg, 1.0 mmol, 2.0 eq) and trifluoroacetic anhydride (1 ml) in dichloromethane (20 ml) was stirred at room temperature for 95 hours, before work-up as described in the general procedure. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 3:1) to give the *acylpyrrole* **226** (154 mg, 79%) as a syrup, which showed: R_f 0.14 (petroleum ether-ethyl acetate 5:1); ν_{max}/cm^{-1} [film] 1681 (C=O), 1596, 1493, 1455, 1367, 1308, 1222, 1189 and 1091; δ_H 7.77-7.75 (1H, m, Ar-H), 7.69 (1H, d, *J* 8.5, Ar-H), 7.66-7.63 (1H, m, Ar-H), 7.54 (1H, s, 1''-H), 7.44-7.41 (2H, m, both Ar-H), 7.32-7.30 (3H, m, all Ar-H), 6.97 (2H, d, *J* 8.2, 3'- and 5'-H), 6.81 (1H, d, *J* 3.4, 3-H), 6.12 (1H, d, *J* 3.4, 4-H), 2.53 (3H, s, *Me*CO) and 2.25 (3H, s, *Ts*-Me); δ_C 190.5 (C=O), 145.2, 145.0, 140.1, 135.3, 133.2, 132.5 (all C), 129.3 (CH), 129.1 (2'- and 6'-CH), 128.9 (C), 128.3 (CH), 127.8 (3'- and 5'-CH), 127.8 127.5, 127.4, 126.9, 126.6 (all CH), 122.6 (3-CH), 115.3 (4-CH), 29.5 (*Me*CO) and 21.7 (*Ts*-Me); m/z (APCI) 390 (M^+ + H, 100%), 348 (10) and 235 (10) [Found: M^+ + H, 390.1163. $C_{23}H_{20}NO_3S$ requires 390.1158].

2-Methyl-1-(4'-methylphenylsulfonyl)-3-trifluoroacetylpyrrole (237) and 5-methyl-1-(4'-methylphenylsulfonyl)-2-trifluoroacetylpyrrole (236)



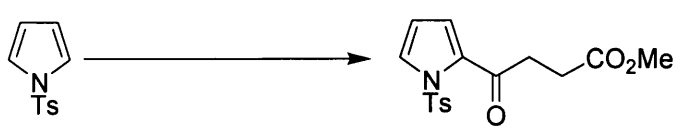
186 **237** **236**

A mixture of trifluoroacetic anhydride (1 ml), 2-methyl-*N*-tosylpyrrole **186** (200mg, 0.85 mmol, 1.0 eq) and 1,2-dichloroethane (5 ml) was refluxed for 48 hours, before work-up as described in the general procedure. The crude product was separated by column chromatography (petroleum ether-ethyl acetate 5:1) to give the *3-trifluoroacetylpyrrole* **237** (40 mg, 14%) and the *2-trifluoroacetyl isomer* **236** (140 mg, 50%), both as colourless solids.

The *3-trifluoroacetylpyrrole* **237** showed: R_f 0.28 (petroleum ether-ethyl acetate 5:1); mp 68-70 °C; ν_{max}/cm^{-1} [KBr] 1693 (C=O), 1596, 1548, 1501, 1368, 1305, 1250, 1174, 1151, 1102 and 1027; δ_H 7.70 (2H, d, *J* 8.4, 2'- and 6'-H), 7.31-7.29 (3H, m, 3'-, 5'- and 5-H), 6.60-6.58 (1H, m, 4-H), 2.62 (3H, s, 2-Me) and 2.38 (3H, s, *Ts*-Me); δ_C 176.9 (q, J_{FC} 35.1, C=O), 146.5, 141.9, 134.6 (all C), 130.5 (2'- and 6'-CH), 127.6 (3'- and 5'-CH), 121.8 (5-CH), 117.5 (C), 116.4 (q, J_{FC} 289.8, CF_3), 110.9 (q, J_{FC} 3.7, 4-CH), 21.8 (*Ts*-Me) and 12.7 (2-Me); m/z (APCI) 332 (M^+ + H, 100%) [Found: M^+ + H, 332.0561. $C_{14}H_{13}F_3NO_3S$ requires 332.0563].

The *2-trifluoroacetylpyrrole* **236** showed: R_f 0.23 (petroleum ether-ethyl acetate 5:1); mp 58-61 °C; ν_{max}/cm^{-1} [KBr] 1702 (C=O), 1596, 1480, 1380, 1275, 1246, 1228, 1176, 1151, 1105 and 1051; δ_H 7.90 (2H, d, *J* 8.4, 2'- and 6'-H), 7.27 (2H, d, *J* 8.4, 3'- and 5'-H), 7.14-7.13 (1H, m, 3-H), 6.09 (1H, d, *J* 4.0, 4-H), 2.58 (3H, s, 5-Me) and 2.34 (3H, s, *Ts*-Me); δ_C 168.5 (q, J_{FC} 35.7, C=O), 146.2, 145.6, 135.9 (all C), 129.7 (2'- and 6'-CH), 128.1 (C), 128.0 (3'- and 5'-CH), 127.5 (q, J_{FC} 3.8, 3-CH), 116.7 (q, J_{FC} 289.2, CF_3), 113.9 (4-CH), 21.7 (*Ts*-Me) and 16.5 (5-Me); m/z (APCI) 332 (M^+ + H, 100%) [Found: M^+ + H, 332.0566. $C_{14}H_{13}F_3NO_3S$ requires 332.0563].

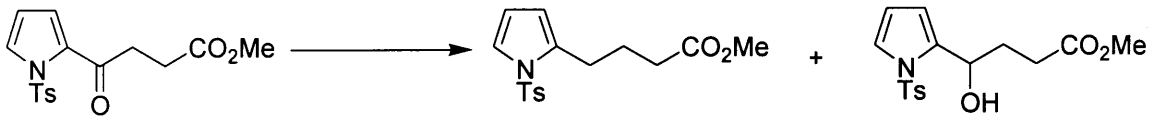
Methyl 4-oxo-4-[1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]butanoate (298)



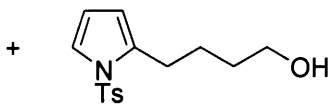
166 **298**

A solution of *N*-tosylpyrrole **166** (1.24 g, 5.6 mmol, 1.0 eq), mono-methyl succinate (3.0 g, 22.7 mmol, 4.0 eq) and trifluoroaectic anhydride (2 ml) in 1,2-dichloroethane (20 ml) was refluxed for 24 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 1:1) to give the *succinate* **298** (1.86 g, 99%) as a colourless solid, which showed: R_f 0.11 (petroleum ether-ethyl acetate 3:1); mp 107-108 °C; ν_{max}/cm^{-1} [KBr] 1734 (C=O), 1686 (C=O), 1440, 1355, 1230, 1168, 1138, 1086, 1062 and 1028; δ_H 7.77 (2H, d, *J* 8.3, 2''- and 6''-H), 7.68 (1H, dd, *J* 3.1 and 1.7, 5'-H), 7.19 (2H, d, *J* 8.3, 3''- and 5''-H), 7.02 (1H, dd, *J* 3.8 and 1.7, 3'-H), 6.23 (1H, *app.* t, *J ca.* 3.5, 4'-H), 3.50 (3H, s, *Me*O), 2.93 (2H, t, *J* 7.0, 2-CH_2), 2.52 (2H, t, *J* 7.0, 3-CH_2) and 2.28 (3H, s, *Ts*-Me); δ_C 186.2 (4-C=O), 173.0 (1-C=O), 144.9, 135.7, 132.6 (all C), 130.2 (5'-CH), 129.3 (2''- and 6''-CH), 128.3 (3''- and 5''-CH), 123.8 (3'-CH), 110.5 (4'-CH), 51.7 (*Me*O), 33.8 (2-CH_2), 27.9 (3-CH_2) and 21.6 (*Ts*-Me); m/z (APCI) 336 (M^+ + H, 100%) [Found: M^+ + H, 336.0898. $C_{16}H_{18}NO_5S$ requires 336.0900].

Methyl 4-[1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]butanoate (299), methyl 4-hydroxy-4-[1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]butanoate (300) and 4-[1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]butan-1-ol (301)



298 **299** **300**



301

To a suspension of aluminium chloride (111 mg, 0.83 mmol, 1.0 eq) in dry dichloromethane (30 ml), was added borane-*tert*-butylamine complex (144 mg, 1.66 mmol, 2.0 eq). The resulting mixture was stirred for 20 minutes and a solution of the succinate **298** (280 mg, 0.83 mmol, 1.0 eq) in dry dichloromethane (20 ml) was added. After stirring for 2 hours, the reaction was

quenched with ice and extracted with dichloromethane (2 x 100 ml). The combined organic extracts were washed with 2M hydrochloric acid (100 ml), saturated aqueous sodium hydrogen carbonate (100 ml), then dried, filtered and evaporated. The crude residue was separated by column chromatography (petroleum ether-ethyl acetate 3:1, then 1:1) to give the *butanoate* **299** (80 mg, 30%) as an orange solid, the *hydroxy-butanoate* **300** (26 mg, 9%) and the *butanol* **301** (70 mg, 29%) both as colourless oils.

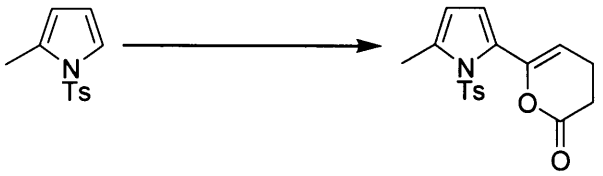
The *butanoate* **299** showed: R_f 0.55 (petroleum ether-ethyl acetate 1:1); mp 68-69 °C; ν_{max}/cm^{-1} [KBr] 1738 (C=O), 1435, 1385, 1173, 1121, 1088 and 1058; δ_H 7.55 (2H, d, *J* 8.4, 2''- and 6''-H), 7.21-7.19 (3H, m, 3''-, 5''- and 5'-H), 6.11 (1H, *app.* t, *J ca.* 3.3, 4'-H), 5.94-5.93 (1H, m, *br. res.*, 3'-H), 3.57 (3H, s, *Me*O), 2.63 (2H, t, *J* 7.5, 2-CH_2), 2.31 (3H, s, *Ts*-Me), 2.24 (2H, t, *J* 7.5, 4-CH_2) and 1.82 (2H, quint, *J* 7.5, 3-CH_2); δ_C 173.7 (C=O), 144.8, 136.4, 134.5 (all C), 130.0 (2''- and 6''-CH), 126.7 (3''- and 5''-CH), 122.5 (5'-CH), 112.4, 111.4 (both CH), 51.6 (*Me*O), 32.9 (2-CH_2), 26.5, 24.0 (both CH_2) and 21.6 (*Ts*-Me); m/z (APCI) 322 (M^+ + H, 100%) [Found: M^+ + H, 322.1112. $C_{16}H_{20}NO_4S$ requires 322.1108].

The *hydroxy-butanoate* **300** showed: R_f 0.33 (petroleum ether-ethyl acetate 1:1); ν_{max}/cm^{-1} [film] 3446 (OH), 1732 (C=O), 1596, 1438, 1365, 1173, 1090 and 1059; δ_H 7.60 (2H, d, *J* 8.3, 2''- and 6''-H), 7.23 (2H, d, *J* 8.3, 3''- and 5''-H), 7.21-7.20 (1H, m, 5'-H), 6.24-6.22 (1H, m, *br. res.*, 3'-H), 6.18 (1H, *app.* t, *J ca.* 3.4, 4'-H), 4.83 (1H, dd, *J* 8.7 and 4.6, 4-H), 3.59 (3H, s, *Me*O), 2.48-2.37 (2H, m, 2-CH_2), 2.34 (3H, s, *Ts*-Me) and 2.14-1.98 (2H, m, 3-CH_2); δ_C 174.1 (C=O), 145.3, 137.5, 136.1 (all C), 130.1 (2''- and 6''-CH), 126.6 (3''- and 5''-CH), 123.5 (5'-CH), 112.4, 111.8 (both CH), 64.7 (4-CH), 51.7 (*Me*O), 30.7, 30.1 (both CH_2) and 21.7 (*Ts*-Me); m/z (APCI) 336 (M^+ - H, 30%), 320 (80), 306 (100) and 288 (50).

The *butanol* **301** showed: R_f 0.24 (petroleum ether-ethyl acetate 1:1); ν_{max}/cm^{-1} [film] 3375 (OH), 1596, 1484, 1364, 1174, 1151, 1090 and 1054; δ_H 7.55 (2H, d, *J* 8.3, 2''- and 6''-H), 7.21-7.19 (3H, m, 3''-, 5''- and 5'-H), 6.11 (1H, *app.* t, *J ca.* 3.3, 4'-H), 5.92-5.91 (1H, *br. res.*, 3'-H), 3.53 (2H, t, *J* 6.1, 1-CH_2), 2.75 (1H, *br. s.*, OH), 2.61-2.58 (2H, m, 4-CH_2), 2.30 (3H, s, *Ts*-Me) and 1.60-1.46 (4H, m, 2- and 3-CH_2); δ_C 144.9, 136.4, 135.5 (all C), 130.0 (2''- and 6''-

CH), 126.7 (3''- and 5''-CH), 122.3 (5'-CH), 112.1, 111.4 (both CH), 62.4 (1-CH_2), 32.1, 26.9, 25.0 (all CH_2) and 21.6 (*Ts*-Me); m/z (APCI) 294 (M^+ + H, 100%) [Found: M^+ + H, 294.1160. $C_{15}H_{20}NO_3S$ requires 294.1158].

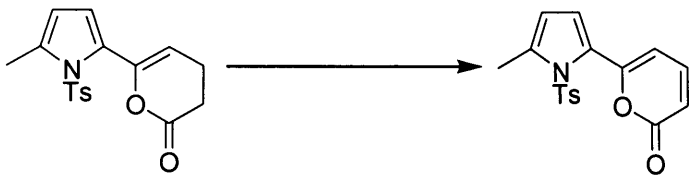
3,4-Dihydro-6-[5'-methyl-1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]pyran-2-one (238)



186 **238**

A solution of 2-methyl-*N*-tosylpyrrole **186** (300 mg, 1.27 mmol, 1.7 eq), glutaric acid (101 mg, 0.76 mmol, 1.0 eq) and trifluoroacetic anhydride (1 ml) in dichloromethane (20 ml) was stirred at room temperature for 48 hours, then refluxed for 24 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 3:1) to give the *dihydropyranone* **238** (149 mg, 59%) as a colourless solid, which showed: R_f 0.22 (petroleum ether-ethyl acetate 3:1); mp 124-127 °C; ν_{max}/cm^{-1} [KBr] 1765 (C=O), 1596, 1365, 1290, 1253, 1187, 1168, 1105 and 1057; δ_H 7.77 (2H, d, *J* 8.3, 2''- and 6''-H), 7.24 (2H, d, *J* 8.3, 3''- and 5''-H), 6.16 (1H, d, *J* 3.4, 3'-H), 5.81 (1H, d, *J* 3.4, 4'-H), 5.46 (1H, t, *J* 4.7, 5-H), 2.62 (2H, t, *J* 7.4, 3-CH_2), 2.36 (2H, td, *J* 7.4 and 4.7, 4-CH_2), 2.32 (3H, s, Me) and 2.22 (3H, s, Me); δ_C 169.1 (C=O), 145.4, 145.0, 136.4, 134.0 (all C), 129.9 (2''- and 6''-CH), 128.7 (C), 127.3 (3''- and 5''-CH), 116.0 (3'-CH), 111.9 (4'-CH), 106.9 (5-CH), 28.0 (3-CH_2), 21.7 (*Ts*-Me), 19.1 (4-CH_2) and 14.8 (5'-Me); m/z (APCI) 332 (M^+ + H, 100%) [Found: M^+ + H, 332.0953. $C_{17}H_{18}NO_4S$ requires 332.0951].

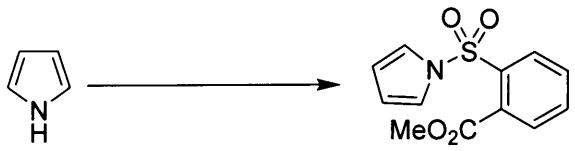
6-[5'-Methyl-1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]pyran-2-one (239)



238 **239**

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (143 mg, 0.63 mmol, 3.0 eq) was added to a solution of the dihydropyranone **238** (69 mg, 0.21 mmol, 1.0 eq) in toluene (10 ml). The reaction mixture was refluxed for 17 hours and cooled. The undissolved material was filtered off. The filtrate was washed with 2M aqueous sodium hydroxide (20 ml) then evaporated. The residue was purified by column chromatography (petroleum ether-ethyl acetate 5:2) to give the *pyranone* **239** (27 mg, 39%) as a soft solid: R_f 0.44 (petroleum ether-ethyl acetate 1:1); mp 126-131 °C; ν_{max}/cm^{-1} [KBr] 1723 (C=O), 1628, 1546, 1366, 1261, 1189, 1169, 1104 and 808; δ_H 7.89 (2H, d, *J* 8.3, 2''- and 6''-H), 7.32 (1H, dd, *J* 9.4 and 6.6, 4-H), 7.30 (2H, d, *J* 8.3, 3''- and 5''-H), 6.34 (1H, d, *J* 3.4, 3'-H), 6.31 (1H, d, *J* 6.6, 3-H), 6.22 (1H, d, *J* 9.4, 5-H), 5.92 (1H, d, *J* 3.4, 4'-H), 2.36 (3H, s, Me) and 2.35 (3H, s, Me); δ_C 161.9 (C=O), 154.9, 145.4 (both C), 143.6 (4-CH), 136.4, 135.6 (both C), 130.0 (2''- and 6''-CH), 128.0 (C), 127.7 (3''- and 5''-CH), 117.8, 114.7, 112.8 (all CH), 105.8 (5-CH), 21.7 (*Ts*-Me) and 15.1 (5'-Me); m/z (APCI) 330 (M^+ + H, 100%) [Found: M^+ + H, 330.0791. $C_{17}H_{16}NO_4S$ requires 330.0795].

Methyl 2-(1'-pyrrol-1'-ylsulfonyl)benzoate (227)

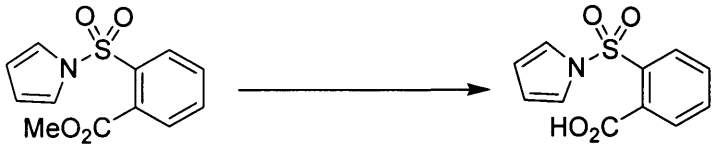


161 **227**

To a solution of pyrrole **161** (0.48 g, 7.2 mmol, 1.3 eq) in dry tetrahydrofuran (40 ml), was added sodium (0.14 g, 6.1 mmol, 1.1 eq). The resulting mixture was refluxed until all the metal had reacted (*ca.* 20 h), then cooled. A solution of methyl 2-(chlorosulfonyl)benzoate (1.29 g,

5.5 mmol, 1.0 eq; ACROS) in dry tetrahydrofuran (10 ml) was added dropwise. The reaction mixture was stirred at room temperature for 24 hours, before quenching with water. The aqueous phase was extracted with ether (50 ml). The combined organic solutions were dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-ethyl acetate 5:1. then 3:1) to give the *benzoate* **227** (0.81 g, 55%) as a colourless oil, which became light purple on storage. It showed: R_f 0.21 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1738 (C=O), 1456, 1433, 1324, 1297, 1262, 1191, 1172, 1120, 1058 and 1032; δ_H 7.53-7.51 (2H, m, both Ar-H), 7.45-7.43 (2H, m, both Ar-H), 7.15 (2H, *app.* t, *J* 2.3, 2'- and 5'-H), 6.24 (2H, *app.* t, *J* 2.3, 3'- and 4'-H), 3.91 (3H, s, Me); δ_C 167.2 (C=O), 137.1 (C), 133.7 (CH), 132.4 (C), 131.2, 129.3, 128.1 (all CH), 121.4 (2'- and 5'-CH), 113.5 (3'- and 4'-CH) and 53.4 (Me); m/z (APCI) 266 (M^+ + H, 100%), 199 (5) and 139 (8).

2-(1'-Pyrrol-1'-ylsulfonyl)benzoic acid (228)

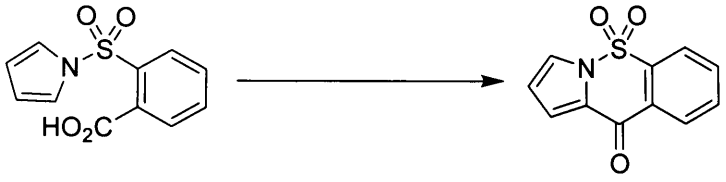


227 **228**

To a solution of methyl 2-pyrrolesulfonyl benzoate **227** (0.48 g, 1.8 mmol) in methanol (7 ml) was added 12M aqueous potassium carbonate (1.5 ml). The reaction mixture was stirred at room temperature for 3 hours, diluted with ethyl acetate (50 ml) and water (50 ml), then acidified with 2M hydrochloric acid to pH 6. The layers were separated and the aqueous layer extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with brine (50 ml), then dried, filtered, and evaporated to give the *acid* **228** (0.38 g, 85%) as a colourless solid, which showed: mp 179-181 °C; ν_{max}/cm^{-1} [KBr] 3422 (OH), 1701 (C=O), 1457, 1419, 1368, 1298, 1176, 1127 and 1057; δ_H (d_6-DMSO) 7.87-7.84 (2H, m, both Ar-H), 7.77-7.73 (2H, m, both Ar-H), 7.42 (2H, *app.* t, *J* 2.3, 2'- and 5'-H) and 6.44 (2H, *app.* t, *J* 2.3, 3'- and 4'-H);

δ_C (d_6-DMSO) 168.5 (C=O), 135.4 (C), 135.1 (CH), 134.6 (C), 131.4, 129.3, 128.7 (all CH), 121.9 (2'- and 5'-CH) and 113.9 (3'- and 4'-CH).

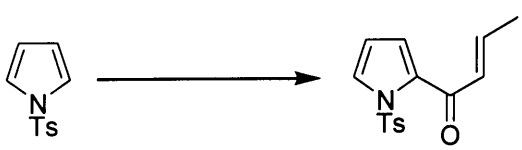
10*H*-Pyrrolo[1,2-*b*][1,2]benzothiazin-10-one, 5,5-dioxide (229)



228 **229**

To a solution of 2-pyrrolesulfonylbenzoic acid **228** (50 mg, 0.2 mmol) in 1,2-dichloroethane (5 ml), was added trifluoroacetic anhydride (1 ml). The reaction mixture was refluxed for 50 hours, then basified with saturated aqueous sodium carbonate to pH 9-10. The layers were separated and the aqueous layer extracted with dichloromethane (50 ml). The combined organic solutions were dried, filtered and evaporated. The residue was triturated with hexane to give the *heterocycle* **229** (36 mg, 78%) as a colourless solid, which showed: mp 114-117 °C; ν_{max}/cm^{-1} [KBr] 1654 (C=O), 1542, 1429, 1342, 1291, 1186, 1162 and 1051; δ_H 8.31-8.28 (1H, m, Ar-H), 8.07-8.03 (1H, m, Ar-H), 7.80-7.77 (2H, m, both Ar-H), 7.57 (1H, dd, *J* 2.7 and 1.1, $5_{pyrrole}$-H), 7.40 (1H, dd, *J* 3.6 and 1.1, $3_{pyrrole}$-H) and 6.55 (1H, *app.* t, *J ca.* 3.3, $4_{pyrrole}$-H); δ_C 170.7 (C=O), 138.5 (C), 134.1, 133.8 (both CH), 132.5, 131.3 (both C), 129.4, 124.0, 123.8, 122.7 and 115.0 (all CH); m/z (APCI) 234 (M^+ + H, 100%) [Found: $M^+ + NH_4$, 251.0487. $C_{11}H_{11}N_2O_3S$ requires 251.0485].

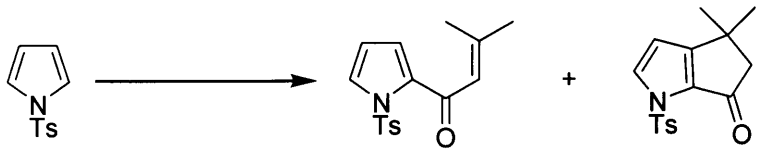
(*E*)-1-[1'-(4''-Methylphenylsulfonyl)pyrrol-2'-yl]but-2-en-1-one (258)



166 **258**

A solution of *N*-tosylpyrrole **166** (100 mg, 0.45 mmol, 1.0 eq), *trans*-crotonic acid (97 mg, 1.13 mmol, 2.5 eq) and trifluoroacetic anhydride (1 ml) in dichloromethane (10 ml) was stirred at room temperature for 48 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 3:1) to give the *enone* **258** (79 mg, 61%) as an orange oil, which showed: R_f 0.29 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1668 (C=O), 1625, 1597, 1541, 1494, 1440, 1401, 1367, 1302, 1245, 1174, 1145, 1091 and 1053; δ_H 7.85 (2H, d, *J* 8.3, 2''- and 6''-H), 7.70 (1H, dd, *J* 3.2 and 1.7, 5'-H), 7.24 (2H, d, *J* 8.3, 3''- and 5''-H), 6.92 (1H, dd, *J* 3.8 and 1.7, 3'-H), 6.86 (1H, dq, *J* 15.4 and 6.9, 3-H), 6.50 (1H, dq, *J* 15.4 and 1.6, 2-H), 6.26 (1H, *app.* t, *J ca.* 3.4, 4'-H), 2.33 (3H, s, *Ts*-Me) and 1.82 (3H, dd, *J* 6.9 and 1.6, 3-Me); δ_C 179.1 (C=O), 144.7 (C), 144.1 (3-CH), 136.2, 133.9 (both C), 130.0 (5'-CH), 129.4 (2''- and 6''-CH), 128.2 (3''- and 5''-CH), 128.1, 123.1 (both CH), 110.4 (4'-CH), 21.7 (*Ts*-Me) and 18.4 (3-Me); m/z (APCI) 290 (M^+ + H, 100%) [Found: M^+ + H, 290.0846. $C_{15}H_{16}NO_3S$ requires 290.0845].

3-Methyl-1-[1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]but-2-en-1-one (254) and 4,5-dihydro-4,4-dimethyl-1-(4'-methylphenylsulfonyl)cyclopenta[*b*]pyrrol-6(1*H*)-one (255)



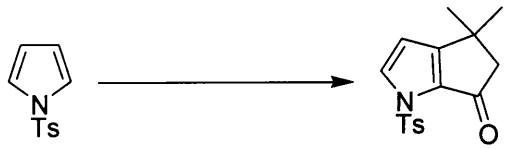
166 **254** **255**

A solution of *N*-tosylpyrrole **166** (100 mg, 0.45 mmol, 1.0 eq), 3,3-dimethylacrylic acid (100 mg, 0.99 mmol, 2.2 eq) and trifluoroacetic anhydride (0.5 ml) in dichloromethane (15 ml) was stirred at room temperature for 48 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 3:1, then 2:1, then 1:1) to give the *enone* **254** (86 mg, 63%) and the *cyclopentapyrrole* **255** (18 mg, 13%), both as brown oils.

The *enone* **254** showed: R_f 0.28 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1660 (C=O), 1621, 1549, 1440, 1368, 1306, 1251, 1174, 1144, 1088, 1064 and 1033; δ_H 7.86 (2H, d, *J* 8.3, 2''- and 6''-H), 7.64 (1H, dd, *J* 3.2 and 1.7, 5'-H), 7.22 (2H, d, *J* 8.3, 3''- and 5''-H), 6.85 (1H, dd, *J* 3.7 and 1.7, 3'-H), 6.33 (1H, *app.* q, *J* 0.6, 2-H), 6.22 (1H, *app.* t, *J ca.* 3.5, 4'-H), 2.33 (3H, s, *Ts*-Me); 1.99 (3H, d, *J* 0.6, 4-Me_E) and 1.82 (3H, s, 4-Me_Z); δ_C 180.0 (C=O), 155.6, 144.6, 136.2, 135.6 (all C), 129.3 (5'-CH), 129.3 (2''- and 6''-CH), 128.4 (3''- and 5''-CH), 122.0, 121.5 (both CH), 110.3 (4'-CH), 27.8 (Me), 21.7 (*Ts*-Me) and 20.9 (Me); m/z (APCI) 304 (M^+ + H, 100%) [Found: M^+ + H, 304.1006. $C_{16}H_{18}NO_3S$ requires 304.1002].

The *cyclopentapyrrole* **255** showed: R_f 0.19 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1694 (C=O), 1596, 1447, 1422, 1370, 1177, 1154 and 1057; δ_H 8.01 (2H, d, *J* 8.3, 2'- and 6'-H), 7.53 (1H, d, *J* 3.1, 2-H), 7.26 (2H, d, *J* 8.3, 3'- and 5'-H), 6.14 (1H, d, *J* 3.1, 3-H), 2.64 (2H, s, 5-CH_2), 2.35 (3H, s, *Ts*-Me) and 1.23 (6H, s, 2 x (4-Me)); δ_C 187.7 (C=O), 167.7, 145.7, 134.9 (all C), 133.6 (2-CH), 131.3 (C), 129.9 (2'- and 6'-CH), 128.4 (3'- and 5'-CH), 106.4 (3-CH), 57.5 (5-CH_2), 34.5 (4-C), 29.0 (2 x (4-Me)) and 21.8 (*Ts*-Me); m/z (APCI) 304 (M^+ + H, 80%), 112 (15), 86 (15) and 72 (100) [Found: M^+ + H, 304.1000. $C_{16}H_{18}NO_3S$ requires 304.1002].

4,5-Dihydro-4,4-dimethyl-1-(4'-methylphenylsulfonyl)cyclopenta[*b*]pyrrol-6(1*H*)-one (255)

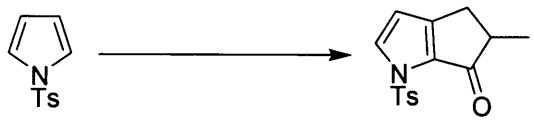


166 **255**

A solution of *N*-tosylpyrrole **166** (200 mg, 0.9 mmol, 1.0 eq), 3,3-dimethylacrylic acid (180 mg, 1.8 mmol, 2.0 eq) and trifluoroacetic anhydride (0.5 ml) in 1,2-dichloroethane (5 ml) was refluxed for 16 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl

acetate 3:1) to give the *cyclopentapyrrole* **255** (140 mg, 51%) as a brown oil, the spectroscopic and analytical data of which were identical to those displayed by the foregoing sample.

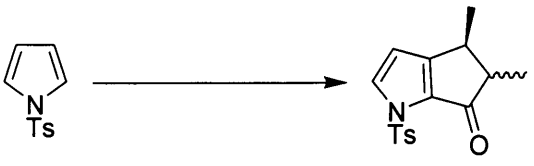
4,5-Dihydro-5-methyl-1-(4'-methylphenylsulfonyl)cyclopenta[*b*]pyrrol-6(1*H*)-one (260)



166 **260**

A solution of *N*-tosylpyrrole **166** (200 mg, 0.9 mmol, 1.0 eq), methacrylic acid (194 mg, 2.3 mmol, 2.5 eq) and trifluoroacetic anhydride (0.5 ml) in 1,2-dichloroethane (5 ml) was refluxed for 19 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 3:1) to give the *cyclopentapyrrole* **260** (190 mg, 73%) as an orange solid, which showed: R_f 0.25 (petroleum ether-ethyl acetate 3:1); mp 126-128 °C; ν_{max}/cm^{-1} [KBr] 1697 (C=O), 1377, 1174 and 1136; δ_H 7.99 (2H, d, *J* 8.3, 2'- and 6'-H), 7.57 (1H, d, *J* 3.1, 2-H), 7.23 (2H, d, *J* 8.3, 3'- and 5'-H), 6.15 (1H, d, *J* 3.1, 3-H), 2.93 (1H, dd, *J* 17.1 and 6.6, 4-H$_\alpha$), 2.84-2.76 (1H, m, 5-H), 2.32 (3H, s, *Ts*-Me), 2.29 (1H, dd, *J* 17.1 and 2.5, 4-H$_\beta$) and 1.18 (3H, d, *J* 7.5, 5-Me); δ_C 191.7 (C=O), 157.2, 145.7, 134.9 (all C), 133.7 (2-CH), 132.8 (C), 129.9 (2'- and 6'-CH), 128.3 (3'- and 5'-CH), 108.9 (3-CH), 47.6 (5-CH), 29.4 (4-CH_2), 21.7 (*Ts*-Me) and 16.9 (5-Me); m/z (APCI) 290 (M^+ + H, 100%) [Found: M^+ + H, 290.0844. $C_{15}H_{16}NO_3S$ requires 290.0845].

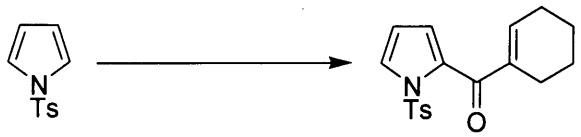
***trans*- and *cis*-4,5-Dihydro-4,5-dimethyl-1-(4'-methylphenylsulfonyl)cyclopenta[*b*]pyrrol-6(1*H*)-one (261)**



166 **261**

A mixture of *N*-tosylpyrrole **166** (100 mg, 0.45 mmol, 1.0 eq), tiglic acid (90 mg, 0.90 mmol, 2.0 eq) and trifluoroacetic anhydride (0.5 ml) in dichloromethane (10 ml) was stirred at room temperature for 68 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-dichloromethane 1:2, then 1:4, then 1:9) to afford the *cyclopentapyrrole* **261** (81 mg, 59%) as a mixture of *cis*- and *trans*-isomers in a ratio of 1:2, as a syrup, which showed: R_f 0.29 (petroleum ether-dichloromethane 1:3); ν_{max}/cm^{-1} [film] 1694 (C=O), 1596, 1447, 1425, 1378, 1227, 1175, 1146, 1130, 1089, 1062, 1018 and 921; δ_H 8.01-7.97 (2H, m, 2'- and 6'-H, both isomers), 7.55 (1H, d, *J* 3.0, 2-H, both isomers), 7.24 (2H, d, *J* 8.2, 3'- and 5'-H, both isomers), 6.17-6.15 (1H, m, 3-H, both isomers), 3.12 (0.33H, *app.* quint, *J ca.* 7.0, 5-H, *cis*-isomer), 2.89 (0.33H, *app.* quint, *J ca.* 7.2, 4-H, *cis*-isomer), 2.58 (0.67H, qd, *J* 7.0 and 2.7, 5-H, *trans*-isomer), 2.35-2.32 (3.67H, m, 4-H for *trans*-isomer and *Ts*-Me for both isomers), 1.19 (2H, d, *J* 7.0, 5-Me, *trans*-isomer), 1.16 (2H, d, *J* 7.5, 4-Me, *trans*-isomer), 1.07 (1H, d, *J* 7.7, 4-Me, *cis*-isomer) and 1.04 (1H, d, *J* 7.3, 5-Me, *cis*-isomer); δ_C 191.6 (C=O, *cis*-isomer), 190.8 (C=O, *trans*-isomer), 163.1 (*cis*-isomer), 161.5 (*trans*-isomer), 145.7 (*trans*-isomer), 145.7 (*cis*-isomer), 134.9 (*cis*-isomer), 134.9 (*trans*-isomer) (all C), 133.6 (2-CH, *trans*-isomer), 133.6 (2-CH, *cis*-isomer), 132.0 (C, *trans*-isomer), 131.9 (C, *cis*-isomer), 129.9 (2'- and 6'-CH, both isomers), 128.3 (3'- and 5'-CH, *trans*-isomer), 128.3 (3'- and 5'-CH, *cis*-isomer), 107.9 (3-CH, *cis*-isomer), 107.7 (3-CH, *trans*-isomer), 56.6 (5-CH, *trans*-isomer), 51.0 (5-CH, *cis*-isomer), 37.0 (4-CH, *trans*-isomer), 31.7 (4-CH, *cis*-isomer), 21.7 (*Ts*-Me, both isomers), 18.7 (5-Me, *trans*-isomer), 16.3 (5-Me, *cis*-isomer), 14.8 (4-Me, *trans*-isomer) and 11.9 (4-Me, *cis*-isomer); m/z (APCI) 304 (M^+ + H, 100%) [Found: M^+ + H, 304.1004. $C_{16}H_{18}NO_3S$ requires 304.1002].

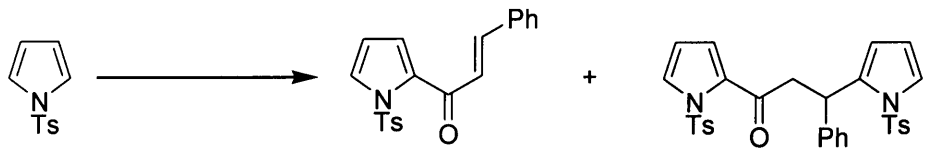
Cyclohex-1''-en-1''-yl-[1-(4'-methylphenylsulfonyl)pyrrol-2-yl]methanone (262)



166 **262**

A solution of *N*-tosylpyrrole **166** (300 mg, 1.36 mmol, 1.0 eq), cyclohexene-1-carboxylic acid (343 mg, 2.72 mmol, 2.0 eq) and trifluoroacetic anhydride (2 ml) in dichloromethane (20 ml) was stirred at room temperature for 29 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 10:1) to give the *enone* **262** (250 mg, 56%) as an orange solid, which showed: R_f 0.32 (petroleum ether-ethyl acetate 5:1); mp 126-128 °C; ν_{max}/cm^{-1} [KBr] 1638 (C=O), 1596, 1448, 1366, 1311, 1249, 1171, 1146, 1088 and 1059; δ_H 7.97 (2H, d, *J* 8.3, 2'- and 6'-H), 7.59 (1H, dd, *J* 3.1 and 1.7, 5-H), 7.34 (2H, d, *J* 8.3, 3'- and 5'-H), 6.81-6.79 (1H, m, 2''-H), 6.60 (1H, dd, *J* 3.5 and 1.7, 3-H), 6.27 (1H, *app.* t, *J ca.* 3.4, 4-H), 2.41 (3H, s, *Ts*-Me), 2.33-2.31 (2H, m, *br. res.*, 6''-CH_2), 2.26-2.24 (2H, m, *br. res.*, 3''-CH_2) and 1.71-1.63 (4H, m, 4''- and 5''-CH_2); δ_C 186.9 (C=O), 144.9 (C), 144.0 (2''-CH), 139.5, 136.3, 133.0 (all C), 129.5 (2'- and 6'-CH), 128.2 (3'- and 5'-CH), 127.6 (5-CH), 122.0 (3-CH), 110.5 (4-CH), 26.1 (6''-CH_2), 23.6 (3''-CH_2), 21.9 (CH_2), 21.7 (*Ts*-Me) and 21.6 (CH_2); m/z (APCI) 330 (M^+ + H, 100%) [Found: M^+ + H, 330.1163. $C_{18}H_{20}NO_3S$ requires 330.1158].

(*E*)-1-[1'-(4''-Methylphenylsulfonyl)pyrrol-2'-yl]-3-phenylprop-2-en-1-one (263) and 3-phenyl-1,3-bis[1'-(4''-methylphenylsulfonyl)pyrrol-2'-yl]propan-1-one (264)



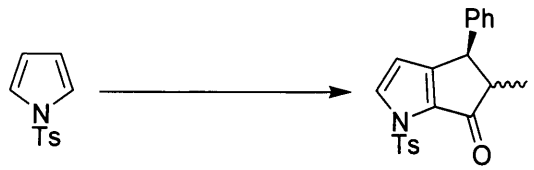
166 **263** **264**

A solution of *N*-tosylpyrrole **166** (300 mg, 1.36 mmol, 1.0 eq), *trans*-cinnamic acid (403 mg, 2.72 mmol, 2.0 eq) and trifluoroacetic anhydride (2 ml) in dichloromethane (20 ml) was stirred at room temperature for 19 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was separated by column chromatography (petroleum ether-ethyl acetate 3:1, then 1:1) to afford the *propenone* **263** (235 mg, 49%) as a colourless solid and the *dipyrrylpropanone* **264** (35 mg, 9%) as a syrup.

The p*ropenone* **263** showed: R_f 0.24 (petroleum ether-ethyl acetate 3:1); mp 111-113 °C; ν_{max}/cm^{-1} [KBr] 1658 (C=O), 1605, 1435, 1401, 1348, 1184, 1146, 1054 and 975; δ_H 7.85 (2H, d, *J* 8.3, 2''- and 6''-H), 7.72 (1H, dd, *J* 3.1 and 1.7, 5'-H), 7.55 (1H, d, *J* 15.8, 3-H), 7.42-7.40 (2H, m, both Ar-H), 7.25-7.23 (3H, m, all Ar-H), 7.20 (2H, d, *J* 8.3, 3''- and 5''-H), 7.09 (1H, d, *J* 15.8, 2-H), 7.03 (1H, dd, *J* 3.7 and 1.7, 3'-H), 6.26 (1H, *app.* t, *J ca.* 3.4, 4'-H) and 2.27 (3H, s, *Ts*-Me); δ_C 178.6 (C=O), 144.9 (C), 143.8 (3-CH), 136.2, 134.6, 134.4 (all C), 130.5, 130.4 (both CH), 129.5 (2 x CH), 129.0 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 123.5, 122.8 (both CH), 110.7 (4'-CH) and 21.8 (*Ts*-Me); m/z (APCI) 352 (M^+ + H, 100%) and 108 (70) [Found: M^+ + H, 352.1003. $C_{20}H_{18}NO_3S$ requires 352.1002].

The *dipyrrylpropanone* **264** showed: R_f 0.19 (petroleum ether-dichloromethane 1:10); ν_{max}/cm^{-1} [film] 1676 (C=O), 1596, 1438, 1365, 1174, 1145, 1091 and 1063; δ_H 7.71-7.68 (3H, m, $5_{\alpha\text{-pyrrole}}$-, $2_{\alpha\text{-}Ts}$- and $6_{\alpha\text{-}Ts}$-H), 7.29 (2H, d, *J* 8.3, $2_{\beta\text{-}Ts}$- and $6_{\beta\text{-}Ts}$-H), 7.15-7.13 (3H, m, $3_{\alpha\text{-}Ts}$-, $5_{\alpha\text{-}Ts}$- and $5_{\beta\text{-pyrrole}}$-H), 7.03-6.96 (5H, m, all Ar-H), 6.86 (1H, dd, *J* 3.6 and 1.6, $3_{\alpha\text{-pyrrole}}$-H), 6.83-6.81 (2H, m, both Ar-H), 6.19 (1H, t, *J* 3.6, $4_{\alpha\text{-pyrrole}}$-H), 6.08 (1H, t, *J* 3.4, $4_{\beta\text{-pyrrole}}$-H), 5.98-5.97 (1H, m, *br.res.*, $3_{\beta\text{-pyrrole}}$-H), 5.08 (1H, t, *J* 7.5, 3-H), 3.16 (1H, dd, *J* 15.9 and 7.5, 2-H_α), 3.06 (1H, dd, *J* 15.9 and 7.5, 2-H_β), 2.34 (3H, s, *Ts*-Me_α) and 2.27 (3H, s, *Ts*-Me_β); δ_C 185.1 (C=O), 144.7, 144.3, 142.3, 136.6, 136.2, 135.5, 133.0 (all C), 130.3 (CH), 129.7 (2 x CH), 129.2 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 127.8 (2 x CH), 126.8 (2 x CH), 126.3, 123.4, 123.0, 112.9 111.3, 110.2 (all CH), 46.6 (2-CH_2), 38.8 (3-CH), 21.8 and 21.6 (both *Ts*-Me); m/z (APCI) 573 (M^+ + H, 25%), 310 (10), 261 (10), 250 (10), 156 (20), 140 (30), 123 (45) and 108 (100) [Found: M^+ + H, 573.1517. $C_{31}H_{29}N_2O_5S_2$ requires 573.1512].

trans- and _cis_-4,5-Dihydro-5-methyl-1-(4'-methylphenylsulfonyl)-4-phenylcyclopenta[_b_]-pyrrol-6(1_H_)-one (267)

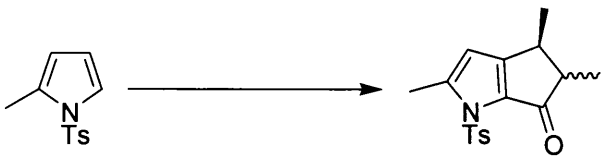


166 **267**

A solution of _N_-tosylpyrrole **166** (210 mg, 0.95 mmol, 1.0 eq), α-methylcinnamic acid (386 mg, 2.38 mmol, 2.5 eq) and trifluoroacetic anhydride (1 ml) in dichloromethane (15 ml) was refluxed for 40 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 5:1) to afford the *cyclopentapyrrole* **267** (173 mg, 50%) as a mixture of *trans*- and *cis*-isomers in a ratio 6:1, as a syrup, which showed: R_f 0.33 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1698 (C=O), 1596, 1494, 1454, 1423, 1376, 1192, 1175, 1139, 1088, 1047 and 1004; δ_H 8.04-8.01 (2H, m, 2'- and 6'-H, both isomers), 7.63 (0.14H, d, *J* 3.1, 2-H, *cis*-isomer), 7.60 (0.86H, d, *J* 3.0, 2-H, *trans*-isomer), 7.29-7.13 (5H, m, all Ar-H, both isomers), 7.04-7.01 (2H, m, Ar-H, both isomers), 6.09 (0.14H, d, *J* 3.1, 3-H, *cis*-isomer), 6.04 (0.86H, d, *J* 3.0, 3-H, *trans*-isomer), 4.32 (0.14H, d, *J* 6.8, 4-H, *cis*-isomer), 3.69 (0.86H, d, *J* 3.3, 4-H, *trans*-isomer), 3.12 (0.14H, *app.* quint, *J ca.* 7.3, 5-H, *cis*-isomer), 2.65 (0.86H, qd, *J* 7.4 and 3.3, 5-H, *trans*-isomer), 2.36 (0.43H, s, *Ts*-Me, *cis*-isomer), 2.34 (2.57H, s, *Ts*-Me, *trans*-isomer), 1.24 (2.57H, d, *J* 7.4, 5-Me, *trans*-isomer) and 0.65 (0.43H, d, *J* 7.7, 5-Me, *cis*-isomer); δ_C 191.2 (C=O, *cis*-isomer), 190.3 (C=O, *trans*-isomer), 159.1 (*cis*-isomer), 158.7 (*trans*-isomer), 145.9 (*trans*-isomer), 141.2 (*trans*-isomer), 134.9 (*trans*-isomer) (all C), 134.1 (CH, *cis*-isomer), 133.9 (CH, *trans*-isomer), 132.9 (C, *trans*-isomer), 130.1 (2 x CH, both isomers), 128.9 (2 x CH, *cis*-isomer), 128.9 (2 x CH, *trans*-isomer), 128.4 (2 x CH, *trans*-isomer), 128.4 (2 x CH, *cis*-isomer), 127.3 (2 x CH, both isomers), 127.1 (CH, both isomers), 109.0 (3-CH, *cis*-isomer), 108.6 (3-CH, *trans*-isomer), 58.5 (4-CH, *trans*-siomer), 52.4 (4-CH, *cis*-isomer), 48.4 (5-CH, *trans*-isomer), 43.9 (5-CH, *cis*-isomer), 21.8 (*Ts*-Me, both isomers), 14.8 (5-Me, *trans*-isomer)

and 13.9 (5-Me, *cis*-isomer); m/z (APCI) 366 (M^+ + H, 100%) [Found: M^+ + H, 366.1161. $C_{21}H_{20}NO_3S$ requires 366.1158].

trans- and _cis_-4,5-Dihydro-1-(4'-methylphenylsulfonyl)-2,4,5-trimethylcyclopenta[_b_]-pyrrol-6(1_H_)-one (268)

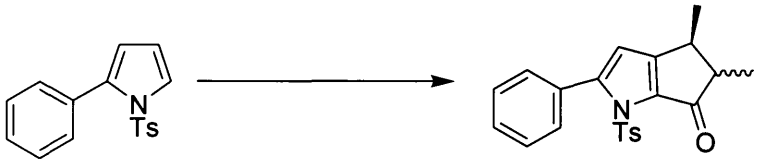


186 **268**

A solution of 2-methyl-*N*-tosylpyrrole **186** (200 mg, 0.85 mmol, 1.0 eq), tiglic acid (213 mg, 2.13 mmol, 2.5 eq) and trifluoroacetic anhydride (1 ml) in dichloromethane (30 ml) was stirred at room temperature for 48 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 3:1) to give the *cyclopentapyrrole* **268** (209 mg, 77%) as a mixture of *trans*- and *cis*-isomers in a ratio 6:1, as a syrup, which showed: R_f 0.22 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1695 (C=O), 1597, 1493, 1459, 1375, 1277, 1239, 1181, 1141, 1091, 1049, 1010, 985, 927 and 816; δ_H 8.00-7.96 (2H, m, 2'- and 6'-H, both isomers), 7.23-7.21 (2H, m, 3'- and 5'-H, both isomers), 5.91 (0.14H, s, 3-H, *cis*-isomer), 5.90 (0.86H, s, 3-H, *trans*-isomer), 3.04 (0.14H, *app.* quint, *J ca.* 7.0, 5-H, *cis*-isomer), 2.86 (0.14H, *app.* quint, *J ca.* 7.6, 4-H, *cis*-isomer), 2.49 (0.86H, qd, *J* 7.2 and 2.9, 5-H, *trans*-isomer), 2.49 (2.57H, s, 2-Me, *trans*-isomer), 2.48 (0.43H, s, 2-Me, *cis*-isomer), 2.31 (2.57H, s, *Ts*-Me, *trans*-isomer), 2.30 (0.43H, s, *Ts*-Me, *cis*-isomer), 2.29 (0.86H, qd, *J* 7.4 and 2.9, 4-H, *trans*-isomer), 1.15 (2.57H, d, *J* 7.4, 4-Me, *trans*-isomer), 1.14 (2.57H, d, *J* 7.2, 5-Me, *trans*-isomer), 1.06 (0.43H, d, *J* 7.6, 4-Me, *cis*-isomer) and 0.99 (0.43H, d, *J* 7.4, 5-Me, *cis*-isomer); δ_C 190.6 (C=O, *cis*-isomer), 189.8 (C=O, *trans*-isomer), 161.7 (*cis*-isomer), 160.1 (*trans*-isomer), 146.2 (*trans*-isomer), 146.1 (*cis*-isomer), 145.4 (*trans*-isomer), 145.3 (*cis*-isomer), 136.0 (*cis*-isomer), 136.0 (*trans*-isomer), 132.6 (*trans*-isomer), 132.5 (*cis*-isomer) (all C), 129.9 (2'- and 6'-CH, both isomers),

127.8 (3'- and 5'-CH, *trans*-isomer), 127.8 (3'- and 5'-CH, *cis*-isomer), 109.1 (3-CH, *cis*-isomer), 109.0 (3-CH, *trans*-isomer), 56.2 (5-CH, *trans*-isomer), 50.7 (5-CH, *cis*-isomer), 36.5 (4-CH, *trans*-isomer), 31.2 (4-CH, *cis*-isomer), 21.7 (*Ts*-Me, both isomers), 18.8 (Me, *trans*-isomer), 16.2 (Me, *cis*-isomer), 15.6 (Me, both isomers), 15.1 (Me, *trans*-isomer) and 12.0 (Me, *cis*-isomer); m/z (APCI) 318 (M^+ + H, 100%) [Found: M^+ + H, 318.1157. $C_{17}H_{20}NO_3S$ requires 318.1158].

trans- and _cis_-4,5-Dihydro-4,5-dimethyl-1-(4'-methylphenylsulfonyl)-2-phenyl-cyclopenta[_b_]pyrrol-6(1_H_)-one (269)

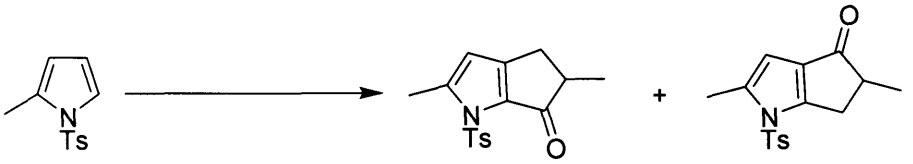


201 **269**

A solution of 2-phenyl-*N*-tosylpyrrole **201** (150 mg, 0.5 mmol, 1.0 eq), tiglic acid (100 mg, 1.0 mmol, 2.0 eq) and trifluoroacetic anhydride (0.9 ml) in dichloromethane (15 ml) was refluxed for 96 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 5:1, then 3:1) to give the *cyclopentapyrrole* **269** (96 mg, 51%) as a mixture of *trans*- and *cis*-isomers in a ratio of 6:1, as a syrup, which showed: R_f 0.17 (petroleum ether-ethyl acetate 5:1); ν_{max}/cm^{-1} [film] 1699 (C=O), 1596, 1464, 1383, 1192, 1180, 1127, 1090 and 1019; δ_H 7.77-7.73 (2H, m, 2'- and 6'-H, both isomers), 7.39-7.22 (5H, m, all Ar-H, both isomers), 7.18 (2H, d, *J* 8.1, 3'- and 5'-H, both isomers), 6.09 (0.14H, s, 3-H, *cis*-isomer), 6.08 (0.86H, s, 3-H, *trans*-isomer), 3.14 (0.14H, *app.* quint, *J ca.* 7.1, 5-H, *cis*-isomer), 2.96 (0.14H, *app.* quint, *J ca.* 7.5, 4-H, *cis*-isomer), 2.59 (0.86H, qd, *J* 7.1 and 2.9, 5-H, *trans*-isomer), 2.40 (0.86H, qd, *J* 7.4 and 2.9, 4-H, *trans*-isomer), 2.32 (3H, s, *Ts*-Me, both isomers), 1.22 (2.57H, d, *J* 7.4, 4-Me, *trans*-isomer), 1.21 (2.57H, d, *J* 7.1, 5-Me, *trans*-isomer), 1.12 (0.43H, d, *J* 7.6, 4-Me, *cis*-isomer) and 1.06 (0.43H, d, *J* 7.4, 5-Me, *cis*-isomer); δ_C 191.8 (C=O, *cis*-isomer), 191.1 (C=O, *trans*-isomer),

162.1 (*cis*-isomer), 160.5 (*trans*-isomer), 149.7 (both isomers), 145.3 (both isomers), 135.9 (both isomers), 134.4 (both isomers), 131.6 (both isomers) (all C), 129.8 (2 x CH, both isomers), 129.7 (2 x CH, both isomers), 129.3 (Ar-CH, both isomers), 128.1 (2 x CH, both isomers), 127.7 (2 x CH, both isomers), 111.3 (3-CH, *cis*-isomer), 111.1 (3-CH, *trans*-isomer), 56.3 (5-CH, *trans*-isomer), 50.9 (5-CH, *cis*-isomer), 36.7 (4-CH, *trans*-isomer), 31.5 (4-CH, cis-*isomer*), 21.8 (*Ts*-Me, both isomers), 18.9 (Me, *trans*-isomer), 16.3 (Me, *cis*-isomer), 15.2 (Me, *trans*-isomer) and 12.1 (Me, *cis*-isomer); m/z (APCI) 380 (M^+ + H, 100%) [Found: M^+ + H, 380.1313. $C_{22}H_{22}NO_3S$ requires 380.1315].

4,5-Dihydro-2,5-dimethyl-1-(4'-methylphenylsulfonyl)cyclopenta[*b*]pyrrol-6(1*H*)-one (270) and 5,6-dihydro-2,5-dimethyl-1-(4'-methylphenylsulfonyl)cyclopenta[*b*]pyrrol-4(1*H*)-one (271)



186 **270** **271**

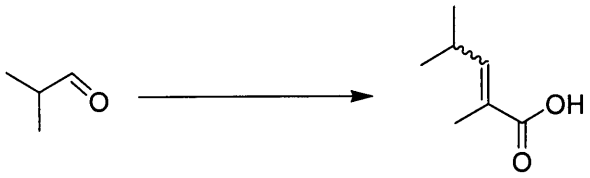
A solution of 2-methyl-*N*-tosylpyrrole **186** (70 mg, 0.3 mmol, 1.0 eq), methacrylic acid (77 mg, 0.9 mmol, 3.0 eq) and trifluoroacetic anhydride (0.5 ml) in 1,2-dichloroethane (5 ml) was refluxed for 21 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was separated by column chromatography (petroleum ether-ethyl acetate 5:2) to give the *cyclopentapyrrole-6-one* **270** (75 mg, 82%) as a colourless solid and the *cyclopentapyrrole-4-one* **271** (8 mg, 9%) as a sticky oil.

The *cyclopentapyrrole-6-one* **270** showed: R_f 0.21 (petroleum ether-ethyl acetate 3:1); mp 106-108 °C; ν_{max}/cm^{-1} [KBr] 1738 (C=O), 1666, 1627, 1444, 1404, 1261, 1049, 998, 922 and 862; δ_H 7.98 (2H, d, *J* 8.3, 2'- and 6'-H), 7.23 (2H, d, *J* 8.3, 3'- and 5'-H), 5.89 (1H, s, 3-H), 2.86 (1H, dd, *J* 16.9 and 6.7, 4-H_α), 2.82-2.75 (1H, m, 5-H), 2.51 (3H, s, 2-Me), 2.33 (3H, s, *Ts*-Me), 2.21 (1H, dd, *J* 16.9 and 2.2, 4-H_β) and 1.19 (3H, d, *J* 7.4, 5-Me); δ_C 190.8 (C=O), 155.9, 146.3,

145.3, 136.1, 133.5 (all C), 129.9 (2'- and 6'-CH), 127.8 (3'- and 5'-CH), 110.1 (3-CH), 47.3 (5-CH), 29.1 (4-CH_2), 21.7 (*Ts*-Me), 17.2 (Me) and 15.7 (Me); m/z (APCI) 304 (M^+ + H, 100%) [Found: M^+ + H, 304.1003. $C_{16}H_{18}NO_3S$ requires 304.1002].

The *cyclopentapyrrole-4-one* **271** showed: R_f 0.13 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1694 (C=O), 1597, 1538, 1493, 1428, 1259, 1164, 1089 and 1026; δ_H 7.66 (2H, d, *J* 8.3, 2'- and 6'-H), 7.30 (2H, d, *J* 8.3, 3'- and 5'-H), 6.00 (1H, s, 3-H), 3.43 (1H, dd, *J* 18.1 and 6.5, 6-H_α), 2.90-2.82 (1H, m, 5-H), 2.77 (1H, dd, *J* 18.1 and 2.2, 6-H_β), 2.39 (3H, s, 2-Me), 2.27 (3H, s, *Ts*-Me) and 1.25 (3H, d, *J* 7.5, 5-Me); δ_C 199.7 (C=O), 159.7, 146.0, 138.1, 135.6 (all C), 130.4 (2'- and 6'-CH), 128.1 (C), 127.1 (3'- and 5'-CH), 105.2 (3-CH), 46.3 (5-CH), 32.8 (6-CH_2), 21.8 (*Ts*-Me), 16.9 (Me) and 14.6 (Me); m/z (APCI) 304 (M^+ + H, 100%) [Found: M^+ + H, 304.1001. $C_{16}H_{18}NO_3S$ requires 304.1002].

_E/Z_-2,4-dimethylpent-2-enoic acid (292)[194]

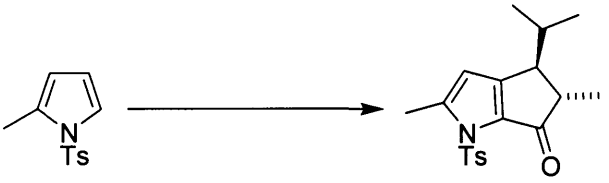


292

Sodium hydride (60% dispersion in mineral oil, 1.2 g, 30 mmol, 3.0 eq) was suspended in dry tetrahydrofuran (50 ml) after washing twice with dry tetrahydrofuran (2 x 50 ml). Diethyl phosphite (1.38 g, 10 mmol, 1.0 eq) in dry tetrahydrofuran (10 ml) was added, followed by α-bromopropionic acid (1.53 g, 10 mmol, 1.0 eq). After hydrogen evolution had ceased, *iso*butyraldehyde (0.72 g, 10 mmol, 1.0 eq) in tetrahydrofuran (10 ml) was added. The reaction mixture was stirred at room temperature for 2 days. After the addition of ethanol (1 ml), the mixture was poured into water (100 ml), which was then washed with diethyl ether (20 ml). The aqueous phase was acidified to pH 2-3 with 2M hydrochloric acid and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried then evaporated to give the *pentenoic acid* **292** (0.74 g, 58%), as a mixture of *E*- and *Z*-isomer in a ratio of 6:1, as a

colourless oil, which could be used for next step without further purification. The spectroscopic data obtained were in accord with those previously reported in the literature:[194]: δ_H 6.71 (0.86H, dd, *J* 9.9 and 1.3, 3-H, *E*-isomer), 5.84 (0.14H, dd, *J* 9.9 and 1.3, 3-H, *Z*-isomer), 2.67-2.61 (0.86H, m, 4-H, *E*-isomer), 1.87 (0.43H, d, *J* 1.3, 2-Me, *Z*-isomer), 1.82 (2.57H, d, *J* 1.3, 2-Me, *E*-isomer), 1.01 (5.14H, d, *J* 6.6, 2 x Me, *E*-isomer) and 0.96 (0.86H, d, *J* 6.7, 2 x Me, *Z*-isomer); m/z (APCI) 129 (M^+ + H, 17%) and 111 (100).

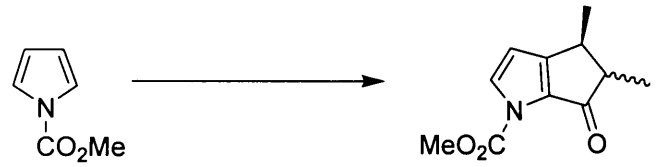
trans-4,5-Dihydro-2,5-dimethyl-4-isopropyl-1-(4'-methylphenylsulfonyl)cyclopenta[_b_]-pyrrol-6(1_H_)-one (293)



186 **293**

A solution of 2-methyl-*N*-tosylpyrrole **186** (55 mg, 0.23 mmol, 1.0 eq), 2,4-dimethylpent-2-enoic acid **292** (118 mg, 0.92 mmol, 4.0 eq) and trifluoroacetic anhydride (0.5 ml) in dichloromethane (10 ml) was stirred at room temperature for 48 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 4:1) to give the *trans-cyclopentapyrrole* **293** (51 mg, 64%) as a syrup, which showed: R_f 0.35 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1694 (C=O), 1597, 1494, 1451, 1377, 1193, 1137, 1089 and 1042; δ_H 8.05 (2H, d, *J* 8.3, 2'- and 6'-H), 7.31 (2H, d, *J* 8.3, 3'- and 5'-H), 6.00 (1H, s, 3-H), 2.59 (3H, s, 2-Me), 2.55 (1H, qd, *J* 7.4 and 2.3, 5-H), 2.43-2.41 (4H, m, 4-H and *Ts*-Me), 1.88-1.19 (1H, m, 1''-H), 1.25 (3H, d, *J* 7.4, 5-Me), 0.91 (3H, d, *J* 6.8, Me) and 0.90 (3H, d, *J* 6.8, Me); δ_C 190.4 (C=O), 158.0, 145.9, 145.3, 136.0, 133.4 (all C), 129.9 (2'- and 6'-CH), 127.8 (3'- and 5'-CH), 110.4 (3-CH), 51.1 (5-CH), 48.8 (4-CH), 31.3 (1''-CH), 21.7 (*Ts*-Me), 20.3, 19.9, 17.3 and 15.7 (all Me); m/z (APCI) 346 (M^+ + H, 100%) [Found: M^+ + H, 346.1474. $C_{19}H_{24}NO_3S$ requires 346.1471].

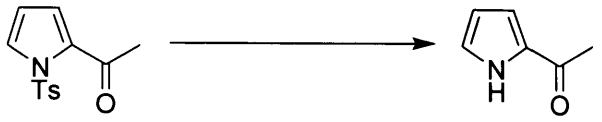
trans- and _cis_-Methyl 4,5-dihydro-4,5-dimethyl-6-oxocyclopenta[_b_]pyrrole-1-carboxylate (274)



273 **274**

A solution of methyl 1-pyrrolecarboxylate **273** (222 mg, 1.77 mmol, 1.0 eq; Aldrich), tiglic acid (356 mg, 3.54 mmol, 2.0 eq) and trifluoroacetic anhydride (1 ml) in dichloromethane (20 ml) was stirred at room temperature for 2.5 hours, before work-up as described in the general procedure for pyrrole acylation. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 5:1, then 3:1) to give the *cyclopentapyrrole* **274** (62 mg, 17%) as a mixture of *trans*- and *cis*-isomers in a ratio of 10:1, as an orange oil, which showed: R_f 0.18 (petroleum ether-ethyl acetate 3:1); ν_{max}/cm^{-1} [film] 1754 (C=O), 1704 (C=O), 1444, 1426, 1353, 1301, 1195 and 1149; δ_H (400) 7.63 (1H, d, *J* 3.1, 2-H, both isomers), 6.19 (1H, d, *J* 3.1, 3-H, both isomers), 3.96 (3H, s, MeO, both isomers), 3.19 (0.09H, *app.* quint, *J ca.* 7.0, 5-H, *cis*-isomer), 2.99 (0.09H, *app.* quint, *J ca.* 6.8, 4-H, *cis*-isomer), 2.64 (0.91H, qd, *J* 7.1 and 2.8, 5-H, *trans*-isomer), 2.40 (0.91H, qd, *J* 7.4 and 2.8, 4-H, *trans*-isomer), 1.25 (2.73H, *d*, *J* 7.1, 5-Me, *trans*-isomer), 1.23 (2.73H, d, *J* 7.4, 4-Me, *trans*-isomer), 1.13 (0.27H, d, *J* 7.7, Me, *cis*-isomer) and 1.10 (0.27H, d, *J* 7.4, Me, *cis*-isomer); δ_C 191.9 (6-C=O, *cis*-isomer), 191.2 (6-C=O, *trans*-isomer), 163.2 (*C*O_2Me, *cis*-isomer), 161.8 (*C*O_2Me, *trans*-isomer), 150.1 (C, both isomers), 133.2 (2-CH, *trans*-isomer), 133.1 (2-CH, *cis*-isomer), 132.3 (C, both isomers), 108.2 (3-CH, *cis*-isomer), 108.1 (3-CH, *trans*-isomer), 56.7 (5-CH, *trans*-isomer), 54.5 (*Me*O_2C-, both isomers), 51.3 (5-CH, *cis*-isomer), 36.7 (4-CH, *trans*-isomer), 31.4 (4-CH, *cis*-isomer), 19.1 (5-Me, *trans*-isomer), 16.3 (5-Me, *cis*-isomer), 15.3 (4-Me, *trans*-isomer) and 12.1 (4-Me, *cis*-isomer); m/z (APCI) 208 (M^+ + H, 100%) [Found: M^+ + H, 208.0966. $C_{11}H_{14}NO_3$ requires 208.0968].

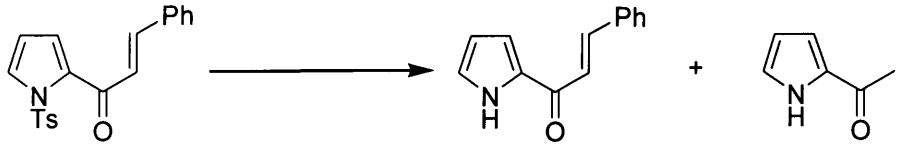
2-Acetylpyrrole (171)[149]



210 **171**

A solution of 2-acetyl-*N*-tosylpyrrole **210** (120 mg, 0.46 mmol) in 7M aqueous potassium hydroxide (5 ml) and methanol (5 ml) was refluxed for 3 hours, then the methanol was evaporated. The aqueous residue was extracted with ether (2 x 50 ml). The combined etheral extracts were dried, filtered and evaporated to give the *acetylpyrrole* **171** (40 mg, 80%) as a colourless solid, the spectroscopic and analytical data obtained were in accord with those previously reported in the literature[149] and showed: R_f 0.48 (petroleum ether-ethyl acetate 1:1); mp 82-86 °C [lit.[149] mp 89-90 °C]; δ_H 10.27 (1H, *br.* s, NH), 7.00-6.99 (1H, m, 5-H), 6.87-6.85 (1H, m, 3-H), 6.20-6.18 (1H, m, 4-H) and 2.37 (3H, s, *Me*CO); δ_C 187.4 (C=O), 131.1 (C), 124.3 (5-CH), 116.3 (3-CH), 109.5 (4-CH) and 24.5 (*Me*CO); m/z (APCI) 110 (M^+ + H, 100%).

(*E*)-3-Phenyl-1-(1'-pyrrol-2'-yl)prop-2-en-1-one (276)[190] and 2-acetylpyrrole (171)



263 **276** **171**

A solution of enone **263** (55 mg, 0.16 mmol) in 10M aqueous potassium hydroxide (5 ml) and methanol (5 ml) was refluxed for 6 hours then the methanol was evaporated. The aqueous residue was extracted with ether (2 x 50 ml). The combined etheral extracts were dried, filtered and evaporated. The residue was separated by column chromatography (dichloromethane-ethyl acetate 30:1) to give the *enone* **276** (10 mg, 32%) and the *acetylpyrrole* **171** (10 mg, 59%), both as colourless solids.

The spectroscopic and analytical data obtained for the *enone* **276** were in accord with those previously reported in the literature[190] and showed: R_f 0.32 (dichloromethane-ethyl acetate

30:1); mp 129-133 °C [lit.[190] mp 140-142 °C]; ν_{max}/cm^{-1} [KBr] 3236 (NH), 1652 (C=O), 1589, 1407, 1137 and 1114; δ_H 9.66 (1H, *br.* s, NH), 7.77 (1H, d, *J* 15.7, 3-H), 7.59-7.57 (2H, m, 2''- and 6''-H), 7.38-7.32 (4H, m, 2-, 3''-, 4''- and 5''-H), 7.06-7.01 (2H, m, 3'- and 5'-H) and 6.31-6.29 (1H, m, 4'-H); δ_C 178.9 (C=O), 142.3 (3-CH), 135.0, 133.2 (both C), 130.3 (CH), 128.9 (2 x CH), 128.4 (2 x CH), 125.3 (CH), 121.9 (CH), 116.3 (3'-CH) and 111.1 (4'-CH); m/z (APCI) 198 (M^+ + H, 40%) and 131 (100) [Found: M^+ + H, 198.0914. $C_{13}H_{12}NO$ requires 198.0913].

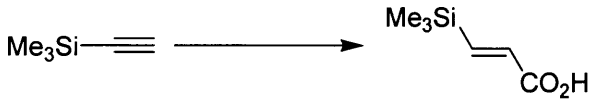
trans- and _cis_-4,5-Dihydro-4,5-dimethyl-2-phenylcyclopenta[_b_]pyrrol-6(1_H_)-one (275)

269 **275**

A solution of cyclopenta[*b*]tosylpyrrole **269** (30 mg, 0.08 mmol) in 10M aqueous potassium hydroxide (5 ml) and methanol (5 ml) was refluxed for 5 hours then the methanol was evaporated. The aqueous residue was acidified with 1M hydrochloric acid to pH 6, then extracted with diethyl ether (2 x 50 ml). The combined organic extracts were dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-ethyl acetate 3:1) to give the *cyclopentapyrrole* **275** (17 mg, 95%) as a mixture of *trans*- and *cis*-isomers in a ratio of 6:1, as a colourless solid, which showed: R_f 0.24 (petroleum ether-ethyl acetate 3:1); mp 168-171 °C; ν_{max}/cm^{-1} [KBr] 3193 (NH), 1653 (C=O), 1465, 1455, 1290 and 1266; δ_H 7.78-7.76 (2H, m, 2'- and 6'-H, both isomers), 7.38-7.34 (2H, m, 3'- and 5'-H, both isomers), 7.28-7.25 (1H, m, 4'-H, both isomers), 6.42-6.41 (1H, m, 3-H, both isomers), 3.31 (0.14H, *app.* quint, *J ca.* 7.0, 5-H, *cis*-isomer), 3.06 (0.14H, *app.* quint, *J ca.* 7.4, 4-H, *cis*-isomer), 2.75 (0.86H, qd, *J* 7.1 and 2.6, 5-H, *trans*-isomer), 2.47 (0.86H, qd, *J* 7.4 and 2.6, 4-H, *trans*-isomer), 1.32 (2.57H, d, *J* 7.1, 5-Me, *trans*-isomer), 1.29 (2.57H, d, *J* 7.4, 4-Me, *trans*-isomer), 1.19 (0.43H, d, *J* 7.8, 4-Me, *cis*-isomer) and 1.16 (0.43H, d, *J* 7.3, 5-Me, *cis*-isomer); δ_C for *trans*-isomer 193.9

(C=O), 157.9, 146.7, 133.1, 131.7 (all C), 128.9 (2 x CH), 128.4 (4'-CH), 125.7 (2 x CH), 102.4 (3-CH), 56.5 (5-CH), 37.7 (4-CH), 19.6 and 15.3 (both Me); the *cis*-isomer could be identified by δ_C 32.1 (4-CH), 16.9 and 12.3 (both Me); m/z (APCI) 226 (M^+ + H, 100%) [Found: M^+ + H, 226.1224. $C_{15}H_{16}NO$ requires 226.1226].

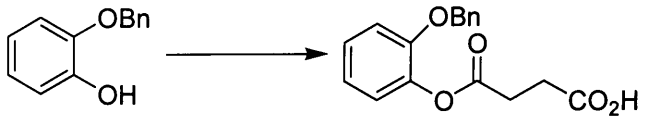
(*E*)-3-(trimethylsilyl)acrylic acid (272)[204]



272

To a mixture of $Ni(cod)_2$ (550 mg, 2.0 mmol, 0.9 eq) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.6 ml, 4 mmol, 1.8 eq) in dry tetrahydrafuran (16 ml) was added slowly a solution of trimethylsilyl acetylene (216 mg, 0.3 ml, 2.2 mmol, 1.0 eq) in tetrahydrafuran (16 ml) under carbon dioxide (1 atm) for 1 h at 0 °C. The resulting mixture was then kept stirring at 0 °C for 2 h. Diluted hydrochloric acid was added, and the mixture was extracted with dichloromethane (3 x 100 ml). The combined organic layer was washed with brine, then dried and evaporated. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 4:1) to give the *trimethylsilylacrylic acid* **272** (230 mg, 59%) as a colourless oil, the ^1H NMR spectrum data of which were in accord with those previously reported in the literature[204] and showed: δ_H 7.25 (1H, d, *J* 18.8, 3-H), 6.10 (1H, d, *J* 18.8, 2-H) and 0.00 (9H, s, $SiMe_3$).

3-(2'-Benzyloxyphenoxycarbonyl)propanoic acid (295)

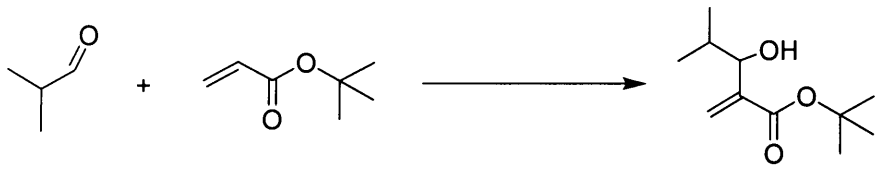


294 **295**

To a solution of 2-benzyloxyphenol **294** (2 ml, 11.4 mmol, 1.0 eq) in pyridine (10 ml) was added 4-(dimethylamino)pyridine (0.28 g, 2.3 mmol, 0.2 eq), followed by succinic anhydride

(2.3 g, 22.8 mmol, 2.0 eq). The resulting mixture was stirred at ambient temperature for 2 days, then diluted with dichloromethane (100 ml) and washed with 2M hydrochloric acid (3 x 50 ml), then brine (50 ml). The organic phase was dried and evaporated. The residue was triturated with hexane to give the *propanoic acid* **295** (3.28 g, 96%) as a white solid, which showed: mp 98-100 °C; ν_{max}/cm^{-1} [KBr] 1759 (C=O), 1714(C=O), 1605, 1502, 1454, 1436, 1403, 1311, 1288, 1257, 1182, 1149 and 1106; δ_H 7.34-6.85 (9H, m, Ar-H), 5.00 (2H, s, Bn-CH_2), 2.78 (2H, t, *J* 6.7, 3-CH_2) and 2.64 (2H, t, *J* 6.7, 2-CH_2); δ_C 178.1 (C=O), 170.4 (C=O), 150.1, 140.1, 136.7 (all C), 128.6 (2 x CH), 128.0 (CH), 127.3 (2 x CH), 127.0 (CH), 122.8 (CH), 120.2 (CH), 114.0 (CH), 70.6 (Bn-CH_2), 29.0 and 28.7 (both CH_2); m/z (APCI) 301 (M^+ + H, 55%), 283 (10) and 201 (100).

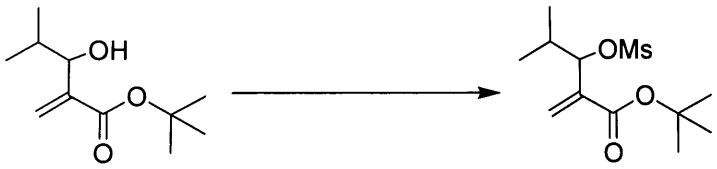
tert-Butyl 3-hydroxy-4-methyl-2-methylenepentanoate (303)



302 **303**

To a stirred mixture of *iso*butyraldehyde (1 ml, 1.0 eq) and *tert*-butyl acrylate **302** (2 ml, 1.2 eq), was added quinuclidine (0.6 g, 0.5 eq). The resulting mixture was stirred at ambient temperature for 28 days. Excess unreacted reagents were evaporated under reduced pressure. The residue was purified by column chromatography (petroleum ether-ethyl acetate 6:1) to give the *pentanoate* **303** (0.87 g, 39%) as a colourless oil, which showed: R_f 0.32 (petroleum ether-ethyl acetate 5:1); ν_{max}/cm^{-1} [film] 3464 (OH), 1709 (C=O), 1628, 1460, 1393, 1368, 1256, 1154 and 1119; δ_H 6.08 (1H, *app.* s, 1'-H_α), 5.58 (1H, *app.* s, 1'-H_β), 3.94 (1H, d, *J* 6.9, 3-H), 2.51 (1H, *br. s*, OH), 1.89-1.77 (1H, m, 4-H), 1.43 (9H, s, ^{t}Bu), 0.90 (3H, d, *J* 6.7, Me) and 0.80 (3H, d, *J* 6.7, Me); δ_C 166.2 (C=O), 142.8 (2-C), 125.0 (1'-CH_2), 81.3 (C), 77.8 (3-CH), 32.9 (4-CH), 28.0 (^{t}Bu), 19.6 and 17.7 (both Me).

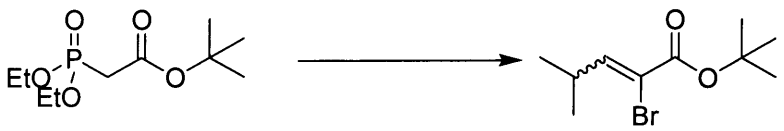
tert-Butyl 3-methanesulfonyloxy-4-methyl-2-methylenepentanoate (304)



303 **304**

To an ice-cold solution of the pentanoate **303** (120 mg, 0.6 mmol, 1.0 eq) in dry tetrahydrofuran (10 ml) were added triethylamine (182 mg, 1.8 mmol, 3 eq) and methanesulphonyl chloride (206 mg, 1.8 mmol, 3 eq). The resulting mixture was stirred for 1 hour after which time the reaction was quenched with saturated aqueous sodium bicarbonate (50 ml) and diluted with diethyl ether (50 ml). The layers were separated. The organic layer was washed with saturated aqueous ammonium chloride (50 ml) and brine (50 ml), then dried, filtered and evaporated to afford the *methanesulphonate* **304** (136 mg, 82%) as a colourless oil, which showed: R_f 0.22 (petroleum ether-ethyl acetate 5:1); ν_{max}/cm^{-1} [film] 1709 (C=O), 1633, 1368, 1300, 1258, 1177, 1154 and 1095; δ_H 6.31 (1H, *app.* s, 1'-H$_\alpha$), 5.80 (1H, *app.* s, 1'-H$_\beta$), 5.17 (1H, d, *J* 5.6, 3-H), 2.89 (3H, s, *Me*SO_2), 2.10-1.98 (1H, m, 4-H), 1.44 (9H, s, ^{t}Bu), 0.92 (3H, d, *J* 6.8, Me) and 0.88 (3H, d, *J* 6.8, Me); δ_C 164.1 (C=O), 139.5 (2-C), 126.9 (1'-CH_2), 84.4 (3-CH), 81.9 (C), 38.5 (*Me*SO_2), 32.4 (4-CH), 28.0 (^{t}Bu), 18.8 and 16.9 (both Me).

***(E)*- and *(Z)-tert*-Butyl 2-bromo-4-methylpent-2-enoate (308)[197]**



307 **308**

To a suspension of sodium hydride (60% dispersion in mineral oil, 0.34 g, 8.5 mmol, 1.0 eq) in dry diethyl ether (50 ml) was added dropwise *tert*-butyl diethylphosphonoacetate **307** (2.15 g, 8.5 mmol, 1.0 eq; Aldrich) at 0 °C. After stirring for 1 hour, bromine (0.44 ml, 8.5 mmol, 1.0 eq) was carefully added. The resulting mixture was stirred for an additional 2 hours. Sodium

hydride (60% dispersion in mineral oil, 0.34 g, 8.5 mmol, 1.0 eq) was added in portions. After 1 hour, *iso*butyraldehyde (0.77 ml, 8.5 mmol, 1.0 eq) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 17 hours. After hydrolysis with brine (50 ml), the separated aqueous layer was extracted with diethyl ether (2 x 50 ml). The combined organic solutions were dried, filtered and evaporated. The residue was purified by column chromatography (petroleum ether-dichloromethane 3:1) to afford the *enoate* **308** (1.12 g, 53%) as a mixture of *E*- and *Z*-isomers in a ratio of 5:4, as a colourless oil. The spectroscopic data obtained were in accord with those previously reported in the literature[197] and showed: R_f 0.54 (petroleum ether-dichloromethane 1:1); ν_{max}/cm^{-1} [film] 1723 (C=O), 1624, 1459, 1369, 1279, 1242, 1165 and 1141; δ_H 6.96 (0.44H, d, *J* 9.3, 3-H, *Z*-isomer), 6.35 (0.56H, d, *J* 10.1, 3-H, *E*-isomer), 3.19-3.10 (0.56H, m, 4-H, *E*-isomer), 2.87-2.78 (0.44H, m, 4-H, *Z*-isomer), 1.52 (5H, s, ^{t}Bu, *E*-isomer), 1.51 (4H, s, ^{t}Bu, *Z*-isomer), 1.07 (2.67H, d, *J* 6.6, 2 x (4-Me), *Z*-isomer) and 1.03 (3.33H, d, *J* 6.8, 2 x (4-Me), *E*-isomer); δ_C 162.2 (C=O, *E*-isomer), 161.6 (C=O, *Z*-isomer), 152.2 (3-CH, *E*-isomer), 150.7 (3-CH, *Z*-isomer), 116.0 (C, *Z*-isomer), 111.5 (C, *E*-isomer), 83.0 (C, *E*-isomer), 82.6 (C, *Z*-isomer), 31.7 (4-CH, *Z*-isomer), 30.8 (4-CH, *E*-isomer), 27.9 (^{t}Bu, both isomers), 22.2 (2 x (4-Me), *E*-isomer) and 20.9 (2 x (4-Me), *Z*-isomer); m/z (APCI) 195 (30), 193 (30), 156(100), 153 (75), 128 (30) and 123(35); m/z (NH_4-CI) 268 ($M^+(^{81}Br)$ + H, 100) and 266 ($M^+(^{79}Br)$ + H, 100) [Found: M^+ + NH_4, 266.0748. $C_{10}H_{21}{}^{79}BrNO_2$ requires 266.0750].

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A new method for the acylation of pyrroles

Chuanjun Song, David W. Knight* and Maria A. Whatton (neé Fagan)

Cardiff School of Chemistry, Cardiff University, PO Box 912, Cardiff CF10 3TB, UK

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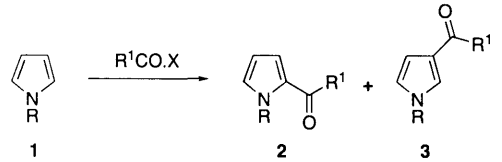
Abstract—*N*-Tosylpyrroles can be very efficiently converted into the corresponding 2-acylpyrroles by reaction with carboxylic acids and trifluoroacetic anhydride; little or none of the isomeric 3-acyl derivatives are formed.

Because of their very high reactivity towards electrophilic substitution and general sensitivity to acid-catalysed polymerisation, there are few very efficient methods available for the selective acylation of pyrroles **1**; mixtures of 2- and 3-acylated product **2** and **3** are often obtained (Scheme 1). Perhaps the best and most proven method is by Vilsmeier reaction with phosphorus oxychloride and *N*,*N*-dimethyl acetamide, which leads to respectable yields of 2-acetylpyrrole.[1] The same method, when applied to the general series of *N*,*N*-dimethylcarboxamides, is also viable and delivers good yields (75–80%) of 2-acylpyrroles, uncontaminated by significant amounts of the corresponding 3-acyl isomers or bis-acyl derivatives.[2] This is certainly not the case with direct acetylation with acetic anhydride, which gives mixtures of 2- and 3-acetylpyrrole in moderate overall yields.[3] A similar but even less efficient result has been obtained using triethyl orthoacetate and $BF_3{\cdot}OEt_2$ as catalyst.[4] The formation of both possible isomers (Scheme 1) also plagues otherwise reasonably efficient methodology based on the thermal rearrangement of *N*-acetylpyrroles[5] or on the acylation of pyrryl Grignard reagents with a variety of electrophiles at the carboxylic acid oxidation level.[6] Less direct but nevertheless efficient alternatives, which do not appear to suffer from formation of 3-acyl isomers, include condensations of pyrrole with a 1,3-benzoxathiolium tetrafluoroborate followed by mercury(II) oxide-induced hydrolysis[7] or an *N*-methylnitrilium salt, obtained by *N*-methylation of the corresponding nitrile using Meerwein's reagent, followed by hydrolysis of the resulting imine.[8] Clearly, an obvious way to moderate the excessive reactivity of a 'free' pyrrole is to derivatise it by placing an electron withdrawing group on the nitrogen. In this respect, sulfonyl derivatives have been the most widely studied. Unfortunately, the problem of mixed product formation (Scheme 1) has been found to persist in acylations of such derivatives (R = SO_2Ar), at least under Friedel–Crafts conditions using aluminium trichloride as the catalyst and various aroyl chlorides,[9] although not when the electrophile is an alkanoyl chloride and the catalyst is $BF_3{\cdot}OEt_2$.[10,11] A more recent report[12] has outlined a general method for the selective 2-acylation of a range of pyrrole derivatives (*N*-Boc; *N*-SO_2Ar) as well as of pyrrole itself, by exposure to an acid chloride and zinc powder in toluene. Yields are generally 80% or better from these highly regioselective acylations. It was against this background that we felt somewhat uncertain as to the best method to use for the preparation of a series of deactivated (i.e., *N*-derivatised; preferably *N*-tosyl) 2-acylpyrroles, which were required for a separate study.[13] Clearly, the use of anhydrides would be rather wasteful, especially when the precursor acid is relatively precious. However, we were intrigued by the contrast between the foregoing results and those reported by Kakushima et al.[14] These authors report that either an acid chloride or the corresponding anhydride, in combination with boron trifluoride etherate, will acylate an *N*-tosylpyrrole slowly and largely in the 2-position



1 2 3

Scheme 1.

* Corresponding author. Tel./fax: +44 2920 874 210; e-mail: knightdw@cf.ac.uk

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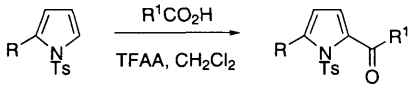
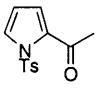
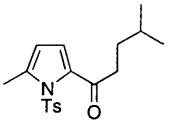
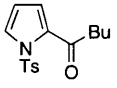
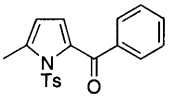
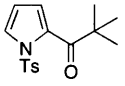
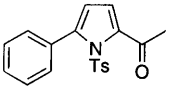
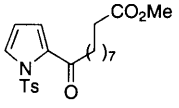
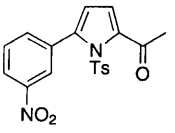
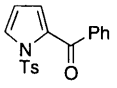
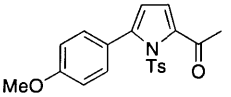
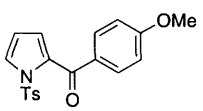
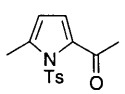
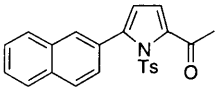
(42–83% yields) with 5–15% of the 3-acyl derivative also being formed. By contrast, the use of the stronger Lewis acid, $AlCl_3$, was reported to give only 3-acyl derivatives (generally >95%) quite rapidly at ambient temperature. In our hands, the former method, when applied to 2-methyl-*N*-tosylpyrrole using $BF_3{\cdot}OEt_2$, gave only moderate yields of the desired 2-acyl-*N*-tosyl-5-methylpyrroles, together with substantial amounts of the 3-acyl isomer from various alkanoyl chlorides. Attempts to secure useful yields using other Lewis acids (e.g., $ZnCl_2$, $SnCl_4$, $TiCl_4$) were also not successful. However, we noted that these authors had commented that 2-acetyl-*N*-tosylpyrrole could also be obtained, but in excellent yield, using a 'large excess'of acetic acid and trifluoroacetic anhydride. The fact that a somewhat related mixture of trifluoroacetic anhydride (TFAA) and phosphoric acid had been used to induce thiophene acylation[15] led us to investigate this method in more detail. We were also attracted by the additional favourable prospect of being able to use carboxylic acids directly, rather than the derived acid chlorides, anhydrides or amides.

Initial experiments established that 2-methyl-*N*-tosylpyrrole could indeed be acetylated using a large excess (>10 equiv) of acetic acid in a 1:1 mixture of TFAA and dichloromethane at ambient temperature. Whilst none of the corresponding 3-acetyl isomer was detected, we were a little surprised to observe that a by-product was rather the 2,4-diacetyl derivative. The large excess of reagents is evidently sufficient to overcome the deactivating effect of the first acetyl group. At least, a 2,4-disubstitution pattern is what would be expected from a second acetylation. Subsequent optimisation experiments defined a more efficient procedure, in which acetylation was achieved using 4 equiv or less of the carboxylic acid. Under these conditions, no 2,4-diacyl products were detected. The results using this method with a range of *N*-tosylpyrroles and carboxylic acids are collected in Table 1.[16]

Table 1. Acylation of *N*-tosylpyrroles by carboxylic acids and trifluoroacetic acid



Entry; acid [equiv] conditions	Yield (%)	Product[16]	Entry; acid [equiv] conditions	Yield (%)	Product[16]
1; R = H. HOAc [4.0]; 20 °C, 30 h, CH_2Cl_2.	94		**8**; R = Me. $Me_2CH(CH_2)_2CO_2H$ [1.5]; 20 °C, 4 h, CH_2Cl_2.	87	
2; R = H. $BuCO_2H$ [4.0]; 20 °C, 16 h then reflux, 7 h CH_2Cl_2.	90		**9**; R = Me. $PhCO_2H$ [4.0]; 20 °C, 42 h, CH_2Cl_2.	96	
3; R = H. *t*-$BuCO_2H$ [4.0]; reflux, 119 h, $Cl(CH_2)_2Cl$.	72		**10**; R = Ph. HOAc [2.0]; 20 °C, 43 h, CH_2Cl_2.	74	
4; R = H. $MeO_2C(CH_2)_8CO_2H$ [1.5] reflux, 48 h, CH_2Cl_2.	73		**11**; R = *m*-$O_2NC_6H_4$ HOAc [2.0]; reflux, 48 h, $Cl(CH_2)_2Cl$.	57	
5; R = H. $PhCO_2H$ [2.0]; reflux, 70 h, $Cl(CH_2)_2Cl$.	84		**12**; R = *p*-$MeOC_6H_4$. HOAc [2.0]; 20 °C, 35 h, CH_2Cl_2.	40[a]	
6; R = H. *p*-$MeOC_6H_4CO_2H$ [2.0]; 20 °C, 48 h, CH_2Cl_2.	84				
7; R = Me. HOAc [3.6]; 0 °C, 2 h, CH_2Cl_2.	83		**13**; R = 2-naphthyl. HOAc [2.0]; 20 °C, 95 h, CH_2Cl_2.	79	

[a] The 5-trifluoroacetyl derivative was also isolated in 11% yield.

As expected (entries 1–6), *N*-tosylpyrrole itself proved to be somewhat less reactive than its 2-methyl derivative used in the initial optimisations. While acetic acid reacted smoothly if slowly in dichloromethane at ambient temperature, in order to secure a similarly excellent yield from pentanoic acid, it was necessary to reflux the reaction mixture (entry 2). The much more hindered and electron-rich pivalic acid required prolonged reflux in dichloroethane before a respectable yield (72%; entry 3) of the corresponding acylpyrrole was obtained. Benzoic acid (entry 5) also only reacted slowly under these more vigorous conditions; despite the lengthy reaction times however, no 3-acylated derivatives were evident in ^{1}H NMR spectra of the crude products. In contrast, 4-methoxybenzoic acid reacted smoothly at ambient temperature (entry 6). That the presence of an α-methyl substituent provides significant additional activation is shown by the relatively milder conditions required to acylate 2-methyl-*N*-tosylpyrrole (entries 7–9). Acylations of representative 2-aryl-*N*-tosylpyrroles[17] (entries 10–13) were also similarly selective for the α-pyrryl position and best carried out at ambient temperature for extended periods. Some limitations which were discovered were perhaps not too surprising: direct formylation using formic acid failed to deliver any pyrrole-2-carboxaldehyde derivatives and 2- and 3-furoic acids also failed to act as acylating agents. Under the present conditions, it is also proved impossible to acetylate the alkenylpyrrole **4**; polymers and a variety of decomposition products were formed and not the ketone **5** (Scheme 2).

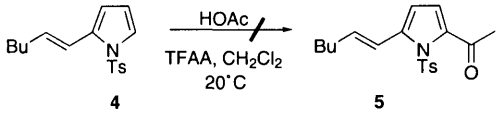
In addition to these limitations there are, however, three additional and positive caveats to this work. Firstly, such acylations can be conducted in an intramolecular fashion. To demonstrate this, we prepared the substituted sulfonamide **6** from 2-methoxycarbonylbenzenesulfonyl chloride and the sodium salt of pyrrole followed by ester saponification. We were delighted to observe that, albeit under relatively vigorous conditions, this was smoothly converted into the hoped-for product **7**, in 78% isolated yield (Scheme 3). To the best of our knowledge, compound **7** represents the parent of a novel heterocyclic ring system.

Secondly, we found that the dihydropyrone **8** was obtained when 2-methyl-*N*-tosylpyrrole was exposed to glutaric acid (0.5 equiv). Further oxidation then gave a moderate but unoptimised return of ca. 40% of the pyrone **9** (Scheme 4). Evidently, a second acylation of *N*-tosylpyrrole does not occur as fast as intramolecular cyclisation of the remaining carboxylic acid group onto the new ketone function, followed by dehydration. Studies of the chemistry of these potentially useful structures are underway.

Thirdly, by reduction of the new carbonyl group, this present method could represent part of an efficient method for overall pyrrole α-alkylation. We initially tried various classical methods for selectively reducing the ketone group in the keto-ester shown in entry 4 of Table 1 (Scheme 5). Unfortunately, both Clemmensen and various versions of the Wolff-Kishner reduction methods failed. However, a more recent method featuring the borane-*t*-butylamine complex as reductant, assisted by aluminium trichloride,[18] did produce the desired product **10** but was somewhat impractical in its original version, due to the claimed requirement for a considerable excess of the reagents. Fortunately, an optimisation study showed this to be unnecessary and delivered cleanly an 85% yield of the ester **10** as shown.

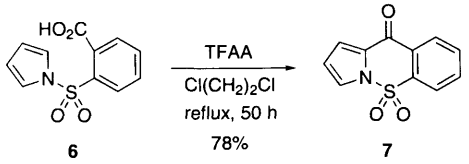
Finally, 'free' pyrroles can also be obtained by this route, followed by subsequent *N*-detosylation. Although we have not examined any alternatives, simply exposing the 2-acyl-*N*-tosylpyrroles to potassium hydroxide in aqueous methanol (3 h, 60 °C) delivers >80% yield of the NH-pyrroles, also uncontaminated by any migration products.[19]

In summary, it would appear that the combination of a carboxylic acid and trifluoroacetic anhydride is a simple and practical method for the selective 2-acylation of *N*-tosylpyrroles. We assume that the mechanism involves mixed anhydride formation between TFAA and the



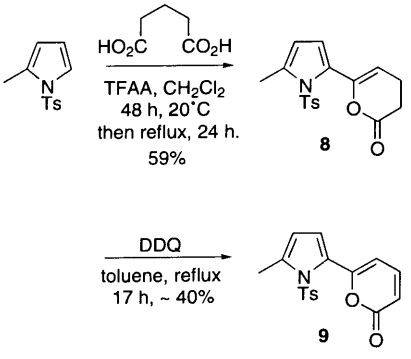
4 5

Scheme 2.

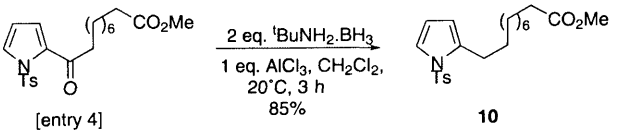


6 7

Scheme 3.



Scheme 4.



Scheme 5.

reacting carboxylic acid. It is perhaps surprising therefore that only in the example involving acetylation of 2-(4-methoxyphenyl)-*N*-tosylpyrrole (entry 12) was an isolable amount of a 2-trifluoroacetyl derivative formed.

Acknowledgements

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16. A typical procedure is as follows: *5-Methyl-2-(4-methylpentanoyl)-N-(4-toluenesulfonyl)-pyrrole.* To a stirred solution of 2-methyl-*N*-tosylpyrrole (7.173 g, 33 mmol), trifluoroacetic anhydride (50 ml) and dichloromethane (75 ml) maintained at 0 °C was added 4-methylpentanoic acid (6.2 ml, 49 mmol). The resulting solution was stirred without further cooling until TLC analysis showed complete conversion (ca. 4 h) and then the volatiles were removed by rotary evaporation. The residue was stirred briefly with dichloromethane (30 ml) and 10% aqueous sodium carbonate (50 ml) then the organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 20 ml). The combined organic solutions were then washed with brine (50 ml), dried ($MgSO_4$), filtered and evaporated. Column chromatography of the residue (SiO_2, 10% EtOAc–40–60° petrol) then separated the acylpyrrole (Table 1, entry 8) (9.56 g, 87%) as a yellow oil, which showed R_f 0.75 (80% Et_2O–40–60° petrol), ν_{max}/cm^{-1} (film) 1679, 1597, 1488, 1366, 1177, 1105 and 812, δ_H (400 MHz, $CDCl_3$) 0.82 (6H, d, *J* 6.3 Hz, 2 × Me), 1.41–1.58 (3H, m, 4′-H and 3-CH_2), 2.34 (3H, s, Ar-Me), 2.46 (3H, s, 5-Me), 2.58–2.69 (2H, m, 2′-CH_2), 5.91 (1H, d, *J* 3.5 Hz, 4-H), 6.69 (1H, d, *J* 3.5 Hz, 3-H), 7.25 (2H, d, *J* 8.2 Hz) and 7.90 (2H, d, *J* 8.2 Hz), δ_C (100 MHz, $CDCl_3$) 16.3 (5-Me), 2.21 (Ar-Me), 22.8 (2 × Me), 28.2 (4′-CH), 34.2 (3′-CH_2), 39.3 (2′-CH_2), 112.6 (4-CH), 121.1 (3-CH), 128.1 (2 × ArCH), 129.9 (2 × ArCH), 136.7, 137.3, 141.0, 145.1 (all ArC) and 192.0 (C=O), *m/z* (APCI) 334 ($M + H^+$ 100%) (Found: $M + H^+$, 334.1474. Calcd for $C_{18}H_{24}NO_3S$, 334.1477).
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