New synthetic reactions, involving the use of solids

THIS THESIS IS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

By

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ABBREVIATIONS

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Ac	acetate
Anal	Analysis
app	Apparent
n-Bu	*n*-Butyl
sec-Bu	*sec*-Butyl
t-Bu	*tert*-Butyl
calcd	Calculated
$CDCl_3$	Deuteriated chloroform
d	Doublet
DCM	Dichloromethane
dd	Double doublet
DEPT	Distortionless Enhancement by Polarization Transfer
DMAE	Dimethylaminoethanol
DMF	*N*,*N*-Dimethylformamide
DMG	Directing metallating group
DMSO-d_6	Deuteriated dimethylsulfoxide
dt	Double triplet
EI-MS	Electron impact - mass spectra
ES	Electrospray - mass spectra
IR	Infra red
LDA	Lithium diisopropyl amide
LiCKOR	Alkyllithiums /potassium *tert*-butoxide
LTMP	Lithium 2,2,6,6-Tetramethylpiperidide
Mp	Melting point
^{13}C NMR	Carbon nuclear magnetic resonance
^{1}H NMR	Proton nuclear magnetic resonance
o-	*ortho*-
PMDTA	*N*, *N*, *N'*, *N''*, *N''*-pentamethyldiethylenetriamine
s	Singlet
TEA	Triethylamine
TFA	Trifluoroacetic acid

TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	Tetramethylsilane
J	coupling constants
δ	Chemical shifts

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SUMMARY

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Directed lithiation and substitution of various *N*-benzyl pivalamides and various *N'*-benzyl-*N,N*-dimethylureas could be achieved using *t*-BuLi in THF at low temperature followed by reactions with various electrophiles to give ring substitution *ortho* to the pivaloylaminomethyl side-chain and urea containing group respectively. Trifluoroacetic anhydride induced dehydration of substituted 2-(pivaloylaminomethyl)phenyl- and 2 (dimethylaminocarbonylmethyl)phenylmethanols gives the corresponding isoindolines in excellent yields.

Lithiation of 2- and 4-substituted pyridines, namely *N*-(pyridinylmethyl)pivalamides, *N'*-(pyridinylmethyl)-*N,N*-dimethylureas and pyridinylmethyl *tert*-butylcarbamates, with two mole equivalents of *t*-BuLi in anhydrous THF at -78 °C takes place on the nitrogen and on the methylene group of the side-chain. The lithium reagents thus obtained react with a variety of electrophiles to give the corresponding side-chain substituted derivatives in high yields. While the lithiation and substitution of *N*-(pyridin-3-ylmethyl)pivalamide, *N'*-(pyridin-3-ylmethyl)-*N,N*-dimethylurea and pyridin-3-ylmethyl *tert*-butylcarbamate with two mole equivalents of alkyllithium in anhydrous THF at -78 °C takes place on the nitrogen and on the *ortho*-position or on the side-chain depending on the type of lithium reagent. Treatment of one of the ring substituted products with trifluoroacetic anhydride in dichloromethane under reflux conditions led to formation of the corresponding 1*H*-pyrrolo[3,4-*c*]pyridine.

A convenient method for Knoevenagel condensation of aromatic aldehydes with active methylene compounds to synthesize arylidene compounds was developed using inexpensive and environmentally friendly reagents such as K_2CO_3. The method is simple and the conditions are mild to provide high product yields.

A boron reaction, which produces an alkyl ester *via* migration without any by-product, has been developed using $HBCl_2$ on a solid-support.

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CHAPTER ONE

DIRECTED LITHIATION OF AROMATIC COMPOUNDS

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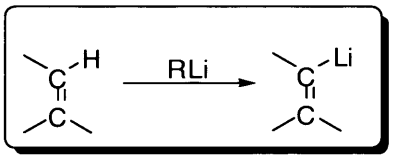
DIRECTED LITHIATION OF AROMATIC COMPOUNDS

1.1 Introduction

Electrophilic aromatic substitution reactions are important in the preparation of aromatic compounds as well as in industrial chemistry. The reactions often take place under harsh conditions, involve tedious work up procedures or use of large amounts of acids which may induce environmental pollution, and often lead to positional isomers.[1a] In the past decade, many efforts have been made to develop these reactions. It is notable that organolithium reagents have become key intermediates for regioselective construction of polysubstituted aromatic and heteroaromatic compounds.

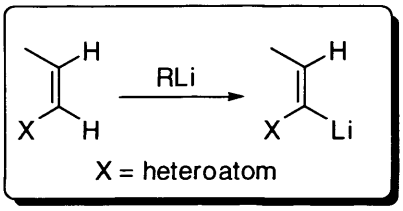
As defined by Gilman and Morton, the terms "metalation" in general and "lithiation" in particular refer to replacement of a hydrogen atom by a metal such as lithium to form a covalent metal/lithium-carbon bond (Eq. 1.1).[1b]



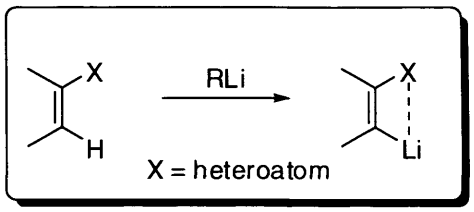
(Eq. 1.1)

After the discovery that some functional groups can help lithiation reactions, the process termed "heteroatom-facilitated lithiation" has become recognized as an important tool.[1c,1d] In the presence of certain heteroatoms, the rate of lithiation process is enhanced and occurs more regioselectively on the carbon atom closest to the heteroatom. Such lithiations are classified into alpha and beta (*ortho*) lithiations. In alpha lithiation the metalating agent deprotonates the atom alpha to the heteroatom to form a carbon-lithium bond (Eq. 1.2). In beta lithiation the metalating agent is directed to deprotonate the carbon atom beta to the heteroatom containing substituent

(Eq. 1.3), while the term "*ortho*-lithiation" is only used in case of beta lithiation of aromatic systems.



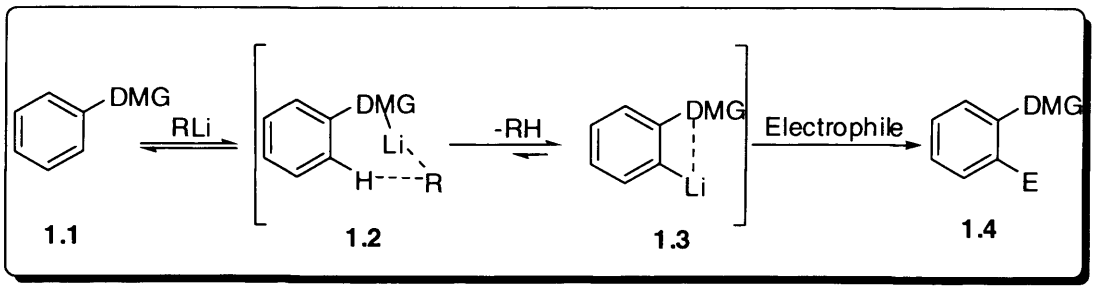
(Eq. 1.2)



(Eq. 1.3)

1.2 Directed lithiation of aromatic compounds

Organolithiums are central to many aspects of synthetic organic chemistry. One of these is the regioselective synthesis of *ortho*-disubstituted aromatics. The directed *ortho*-metallation reaction of aromatic compounds comprises deprotonation of a site *ortho* to a substituent that possesses a heteroatom (oxygen, nitrogen or sulfur). Such a substituent is known as a directing metallating group (DMG). The lithiation reaction of an aromatic compound **1.1** by a base, normally an alkyllithium reagent, gives an *ortho*-lithiated species **1.3** (Scheme 1.1). Treatment of **1.3** with electrophilic reagents produces *ortho*-disubstituted products **1.4**.[2-20] Apparently, complexation occurs between the substituent group and the lithium reagent prior to lithiation, and this serves to bring the lithiating agent into closer proximity with the *ortho* proton, which is then selectively removed.[21]



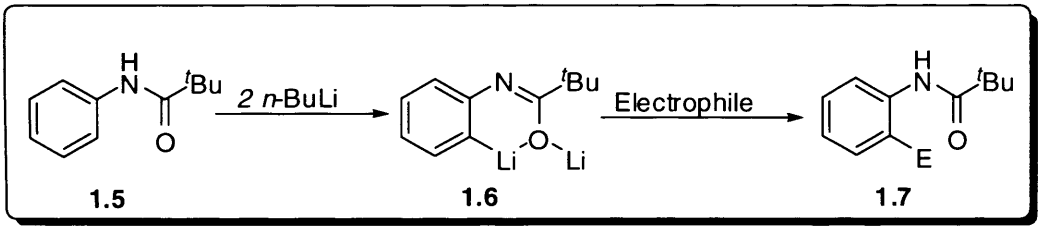
Scheme 1.1

The DMG could be a strong activator, such as SO_2NR_2, NHCOR, $CONR_2$, CSNHR, CONHR, $OCONR_2$, CO_2R, CH_2NHR, OCH_2OMe; a moderate activator, such as OR, NR_2, SR, CF_3, F; or a weak activator, such as CH_2OH and $CH(OR)_2$.

1.2.1 Nitrogen as an *ortho*-directing atom

The lithiation of *N,N*-disubstituted aniline requires the use of extreme forcing conditions; for example, *N,N*-disubstituted aniline is lithiated in refluxing hexane overnight in 55% yield.[22,23] This may be due to the poor acidity of the adjacent hydrogen atoms.

The dilithiated pyridine **1.6** formed after the reaction of *N*-pivaloylaniline (**1.5**) with two mole equivalents of *n*-BuLi, which has been reacted with electrophiles to give 2-substituted derivatives **1.7** (Scheme 1.2) in yields of 53-78%,[24] shows that the oxygen atom of a monodeprotonated amide can serve as a ligand for the metalating agent.

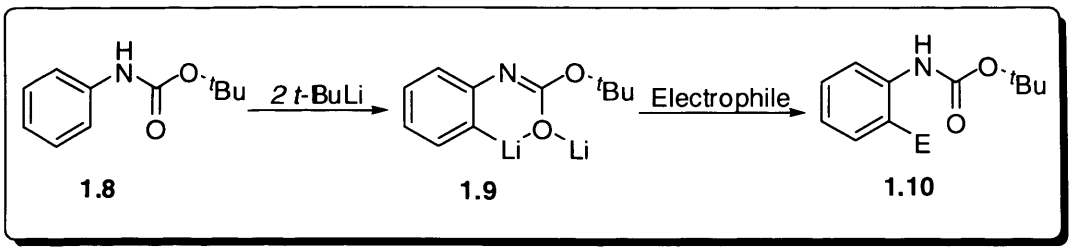


1.5 **1.6** **1.7**

Scheme 1.2

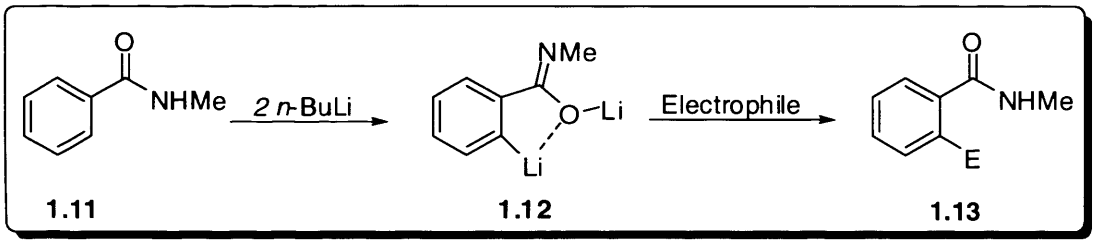
The methodology of heteroatom facilitated lithiation has received considerable attention. Use of *N*-related DMG's such as carbamates,[25,26] secondary amides,[27] tertiary amides[28-33]and dialkylamino groups[34] has become an extremely powerful tool in the field of organic synthesis. Although the pivaloylamino group is a good *ortho*-directing group, it is difficult to remove the pivaloyl group if the unsubstituted aniline is required. In order to find an easily removable group, *ortho*-lithiation of *N*-(*tert*-butoxycarbonyl)aniline **1.8** was developed. It takes place with 2.4 equivalents

of *tert*-butyllithium at -20 °C. The intermediate **1.9** reacts with electrophiles to give compounds **1.10** (Scheme 1.3) in yields of 59-91%.[25]



Scheme 1.3

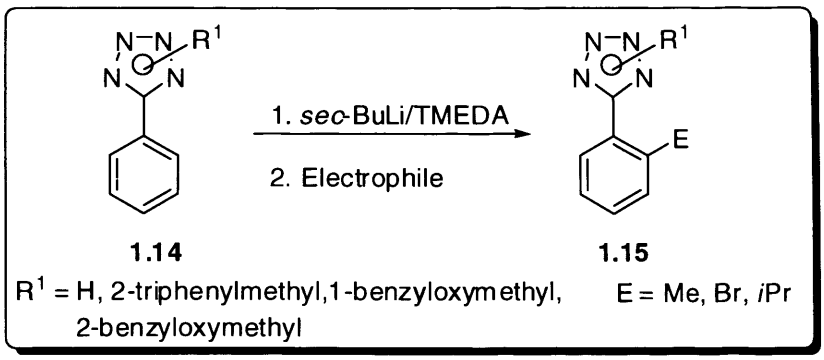
Secondary benzamides are useful in directed metalation. For example, *N*-methylbenzamide (**1.11**) has been lithaited by *n*-BuLi producing the dilithioamide **1.12**. Reactions with electrophiles give compounds **1.13** (Scheme 1.4) in yields of 43-81%; such compounds have been further elaborated to produce isocoumarin derivatives.[35,36]



Scheme 1.4

The tertiary amide group is a more powerful directing group for *ortho*-lithiation than other known directing groups, because it is relatively resistant to attack by nucleophiles and is easily introduced.[28,37] The disadvantage of using tertiary amides as *ortho*-directing groups, however, is their resistance to hydrolysis.[2]

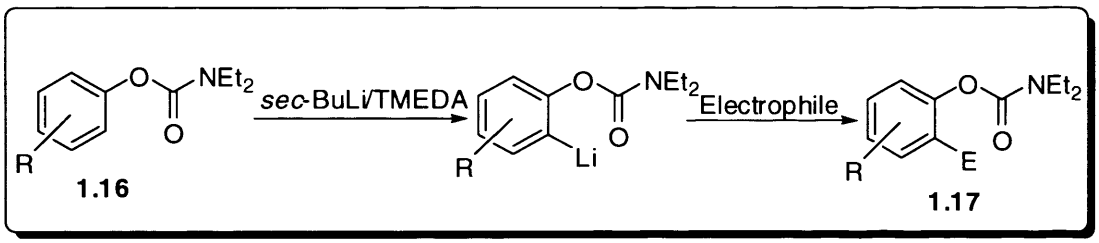
Lithiation followed by electrophilic trapping of aryltetrazole derivatives **1.14**, resulted in the formation of *ortho*-disubstituted derivatives **1.15** in yields of 38-88% using 3 equivalents of *sec*-BuLi/TMEDA in THF at -78 °C for 1 h (Scheme 1.5).[38]



Scheme 1.5

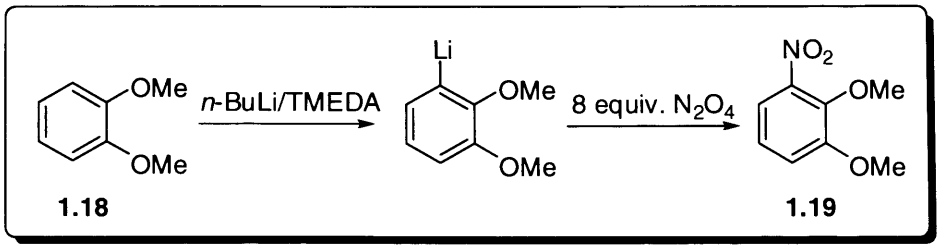
1.2.2 Oxygen as an *ortho*-directing atom

Directed metalation of *O*-arylcarbamates allows the regiospecific synthesis of *ortho*-substituted carbamates. Thus, treatment of compound **1.16** by 1.1 equivalents of *sec*-BuLi/TMEDA in THF at -78 °C for 1 h followed by reaction with electrophiles afforded compounds **1.17** (Scheme 1.6) in yields of 62-88%.[39]



Scheme 1.6

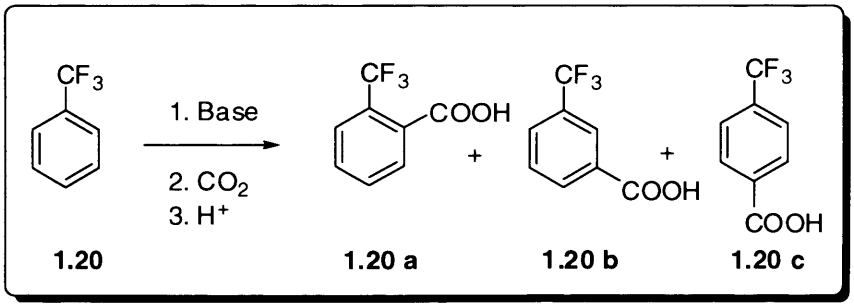
Also, 1,2-dimethoxybenzene (**1.18**) has been lithiated by *n*-BuLi/TMEDA in THF at -78 °C to -108 °C followed by low temperature N_2O_4 nitration to give nitrobenzene derivative **1.19** (Scheme 1.7) in 67 % yield.[40] The authors followed the procedure of McMurry et al.,[41] except that 2.5 equivalents of *n*-BuLi was used to complete the *ortho*-lithiation.



Scheme 1.7

1.2.3 Halogen as an *ortho*-directing atom

The metalation of (trifluoromethyl)benzene has been accomplished with butyllithium in refluxing diethyl ether to afford 24%, 9% and 0.2% of 2-, 3-, and 4-(trifluoromethyl)benzoic acid (**1.20 a**, **1.20 b** and **1.20 c**), respectively (Scheme 1.8). On repetition of this work by Schlosser et al. in 1998 by the use of *N*, *N*, *N'*, *N''*, *N''*-pentamethyldiethylenetriamine (PMDTA)/*sec*-butyllithium in THF at -75 °C (Scheme 1.8) they were able to improve the yields (47% **1.20 a** contaminated with 25% **1.20 b** and 6% **1.20 c**). Selectivity, in the sense of clean *ortho*-metalation, was only achieved with butyllithium in the presence of potassium *tert*-butoxide (LIC-KOR) (**1.20 a**: 67% crystallized).[42,43]

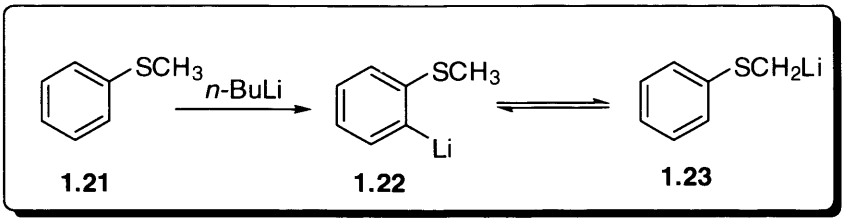


Scheme 1.8

1.2.4 Sulfur as an *ortho*-directing atom

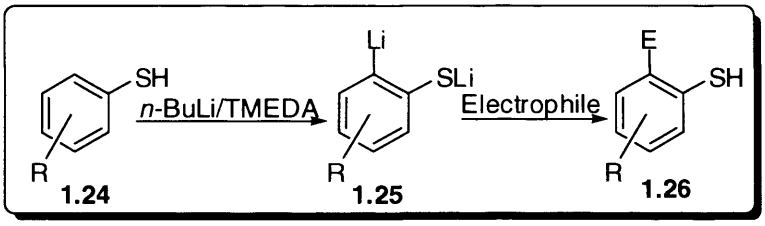
The thioethers fall between ethers and anilines in *ortho*-lithiation directing ability. Lithiation of thioanisole (**1.21**) gives either the kinetic ring-metalation product **1.22** or the thermodynamic side-chain-metalated species **1.23** (Scheme 1.9). The

side-chain deprotonation product is more stable due to stabilization of the anion by *d* shells of sulfur, which is not available in anisole.[44,45]



Scheme 1.9

Directed lithiation of thiophenols **1.24** using *n*-BuLi/TMEDA in cyclohexane or hexane at 0-20 °C gives lithium 2-lithiobenzenethiolates **1.25,** which have been reacted with a variety of electrophiles (deuterium oxide, carbon dioxide, acetone, diphenyl disulfide, chlorotrimethylsilane and methyl iodide) to give 2-substituted derivatives **1.26** (Scheme 1.10) in good yields.[46-48]



Scheme 1.10

The strategy of using a wide range of functional groups in directing lithiation has great importance in the synthesis of various regiospecifically substituted benzenes and heterocycles.[49-55]

1.3 Directed lithiation of heterocycles

Heterocyclic compounds are at the heart of many biologically active compounds and therefore their elaboration is of great importance. Electron-deficient six-membered aromatic heterocycles can be deprotonated with sterically hindered LDA[56-61] or LTMP,[62-66] but not by simple alkyllithiums due to nucleophilic attack on the azomethine bond by the alkyllithiums. However, pyridine can be deprontonated at

C-2 using what is called "super base", which is an association of *n*-butyllithium and lithium 2-(dimethylamino)ethoxide (LiDMAE) in a polar solvent (Figure 1.1); this type of association enhances the basicity/nucleophilicity ratio of *n*-butyllithium and successfully converts the nucleophilic alkyllithium compound into a metalating agent.

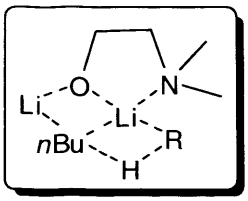
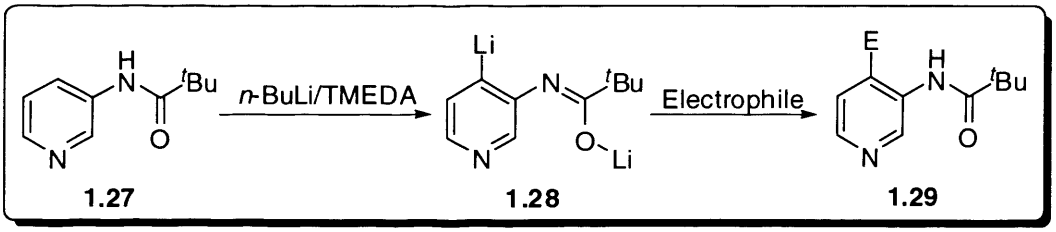


Figure 1.1

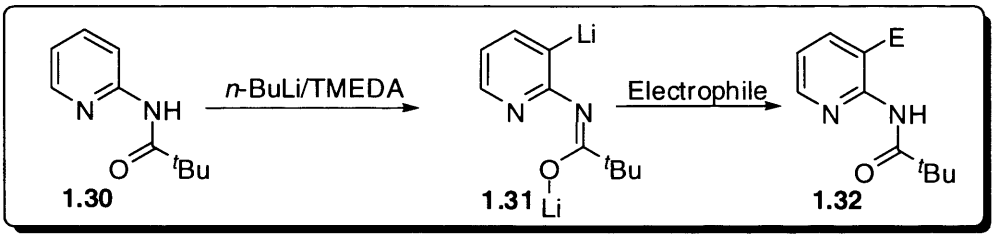
Substituted aminopyridines are important starting materials for metalation reactions. For example, the metalation of 3-pivaloylaminopyridine (**1.27**) has been carried out in diethyl ether at -10 °C in the presence of 2.5-3 equivalents of *n*-BuLi/TMEDA. Lithiated pyridine derivative **1.28** was reacted with electrophiles leading to the corresponding 4-substituted 3-pivaloylaminopyridines **1.29** (Scheme 1.11) in yields of 50-85 %.[67] By contrast, as reported by Turner,[68] metalation of compound **1.27** cannot be achieved using *n*-BuLi in THF at 0 °C for 3 h due to nucleophilic attack by the lithiating agent on the pyridine ring. However, use of *n*-BuLi/TMEDA instead of *n*-BuLi in diethyl ether instead of THF prevents the addition reaction in most cases.



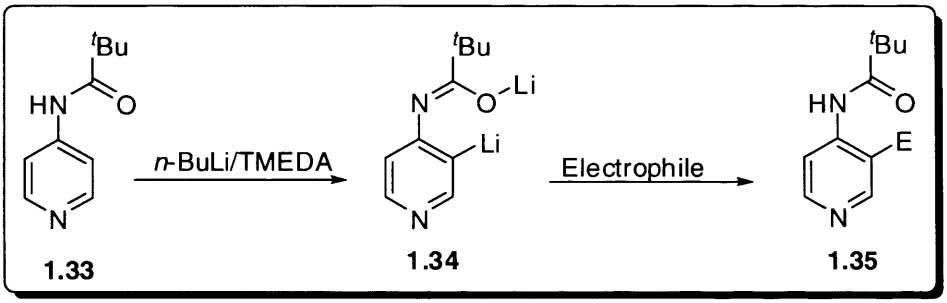
Scheme 1.11

Regioselective *ortho*-lithiations of 2- and 4-pivaloylaminopyridines take place much more readily than for the 3-isomer and are selective for deprotonation at C-3.

Thus, on treatment of 2-pivaloylaminopyridine (**1.30**) and 4-pivaloylaminopyridine (**1.33**) with *n*-BuLi/TMEDA or *n*-BuLi in diethyl ether or THF the *ortho*-lithiated species **1.31** and **1.34**, respectively, are obtained. The lithiated intermediates have been reacted with a range of electrophiles to give the corresponding 2,3-disubstituted pyridines **1.32** and 3,4-disubstituted pyridines **1.35,** respectively (Scheme 1.12 and 1.13) in a good to excellent yields.[67,68]

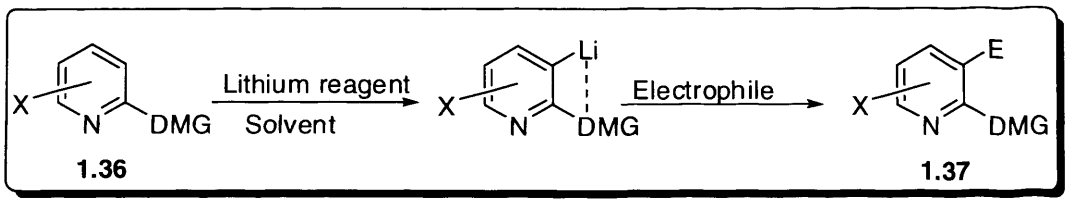


Scheme 1.12



Scheme 1.13

In general, according to the position of the DMG, lithiation occurs next to it to give the appropriately substituted product. For example, the directed lithiation of pyridines **1.36**, having a DMG at C-2, takes place at C-3 (Scheme 1.14). Table 1.1 shows some other examples of the lithiation of 2-substituted pyridines using different organolithium reagents at various reaction temperatures.



1.36 1.37

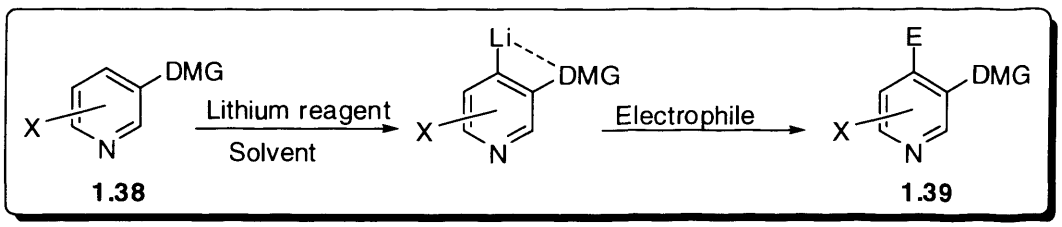
Scheme 1.14

Table 1.1 Directed lithiation of various 2-substituted pyridines **1.36** according to Scheme 1.14 under various reaction conditions

DMG	Lithium reagent	Solvent	T (°C)	Yield (%)[a]
$CONEt_2$[69]	*Sec*-BuLi	THF	-78	50-53
CON^iPr_2[70]	LDA	Et_2O	-78	35-81
CONHPh[71]	*n*-BuLi	THF	-78	48-65
SO^tBu[72]	LDA	THF	-78	74-82
COOH[73,74]	*n*-BuLi/LTMP	THF	-75 to 0	65-85
F[75]	LDA	THF	-78	61-96
Cl[76]	LDA	THF	-85	69-85

[a] Yield of isolated product **1.37** after purification by column chromatography in most cases.

The directed lithiation of pyridines **1.38** having a DMG at C-3 using different organolithium reagents takes place at C-4 (Scheme 1.13). Table 1.2 shows some examples of directed lithiation of 3-substituted pyridines.



1.38 1.39

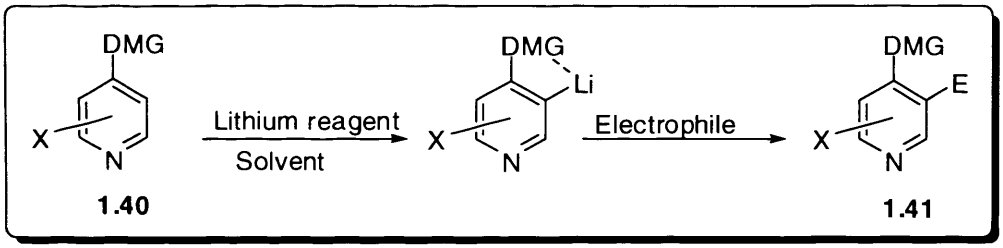
Scheme 1.15

Table 1.2 Directed lithiation of various 3-substituted pyridines **1.38** according to Scheme 1.15 under various reaction conditions

DMG	Lithium reagent	Solvent	T (°C)	Yield (%)[a]
$NHCO_2{}^tBu$[77]	*n*-BuLi/TMEDA	Et_2O	-78 to 10	59-84
$CONEt_2$[78]	LDA	THF	-78	80
CON^iPr_2[79,80]	LTMP/TMEDA	THF	-70	55-68
OMe[81]	*n*-BuLi	THF	0	71-99
Br[82]	LDA	THF	-78	59-94
F[83]	*n*-BuLi/^{t}BuOK	THF	-75	51

[a] Yield of isolated product **1.39** after purification by column chromatography in most cases.

Also, the presence of a DMG at C-4 of the pyridine derivatives **1.40** directed the lithiating reagent towards C-3; the lithium reagent was reacted with electrophiles to give the corresponding 3,4-disubstituted pyridines (Scheme 1.16). Table 1.3 shows some examples of directed lithiation of 4-substituted pyridines.



1.40 **1.41**

Scheme 1.16

Table 1.3 Directed lithiation of various 4-substituted pyridines **1.40** according to Scheme 1.16 under various reaction conditions

DMG	Lithium reagent	Solvent	T (°C)	Yield (%)[a]
CON^iPr_2[70]	LDA	Et_2O	-78	37-55
CONHPh[71]	*n*-BuLi	THF	-78	61
OMe[84]	PhLi	THF	0	67-90
COOH[73,74]	*n*-BuLi/LTMP	THF	-75 to-25	53-78

[a] Yield of isolated product **1.41** after purification by column chromatography in most cases.

1.4 Some experimental considerations

1.4.1 The lithiating agent

Many organolithium reagents are now commercially available. Hydrocarbon solutions of *n*, *s* and *t*-BuLi are the source of most organolithiums. A list of the most common commercially available organolithium reagents is shown in Table 1.4

Table 1.4 The most common commercially available organolithium reagents[a]

Organolithium reagent	Solvent	Concentration (M)
n-Butyllithium	Hexanes	1.6, 2.5 and 10.0
	Cyclohexane	2.0
	Pentane	2.0
sec-Butyllithium	Cyclohexane	1.3
	Diethyl ether	1.4
tert-Butyllithium	Pentane	1.5 and 1.7
Methyllithium	Cumene/tetrahydrofuran	1.0
Phenyllithium	Cyclohexane/diethyl ether	1.8

[a] Available from Sigma-Aldrich Chemical Company. Also, some such reagents are available from Fluka and Alfa Aesar.

The electron-deficient lithium atom of an organolithium compound requires substantial stabilisation, so that in hydrocarbon solution organolithiums are aggregated as hexamers, tetramers or dimers.[85] The degree of aggregation depends on steric hindrance. Primary organolithiums are hexamers in hydrocarbon solution. Secondary and tertiary organolithiums are tetramers, while benzyllithiums and very bulky alkyllithiums are dimers.[86] The presence of ether or THF reduces the degree of aggregation, because these coordinating ligands provide an alternative source of electron density for the electron-deficient lithium atoms. The best established methods

for estimating the actual strength of organolithium reagents are the Watson[87] and Gilman[88] double titration methods.

Most commercial organolithium reagents are prepared by the reaction of organic halides with lithium metal; these are then used in halogen-lithium exchange and lithiation reactions to generate other more complex organolithiums.

1.4.1.1 Preparation of organolithium compounds by reaction with lithium metal

Organolithium reagents are industrially prepared by the reaction of an organic halide with lithium metal (Eq. 1.4).[89] However, a side reaction of this synthesis is, for example, the organolithium produced (RLi) could react with alkyl halide (RX) to produce a coupled product (R-R) *via* Wurtz coupling.

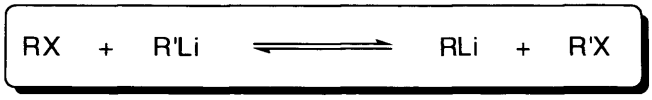
(Eq. 1.4)

1.4.1.2 Preparation of organolithium compounds by reaction with lithium salts of radical anions

The reactions of organic halides with lithium metal leads to organolithium compounds *via* electron transfer.[90] As, an alternative to lithium metal, radical anions formed by reduction of an aromatic system such as naphthalene with metallic lithium can provide electron transfer to an organic halide, to give organolithium compounds. With lithium naphthalene yields are variable, but with lithium 4,4'-di-*tert*-butylbiphenyl high yields are reported,[91] and this reagent gives some organolithiums that are unobtainable by other methods.[92]

1.4.1.3 Preparation of organolithium compounds by halogen-lithium exchange

The general halogen-lithium exchange reaction (Eq. 1.5) has been used for preparing organolithium compounds.

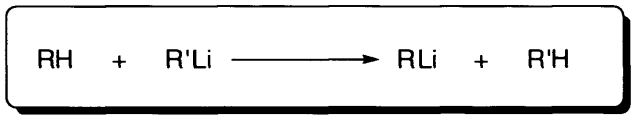


(Eq. 1.5)

As this is an equilibrium reaction, the reaction is successful only if the formed lithium reagent has a more stable carbanion than the starting lithium reagent. The reaction of butyllithium with aryl halides leads to aryllithium compounds. With iodo and bromo compounds the reaction is general and often proceeds remarkably rapidly even at low temperatures.[89]

1.4.1.4 Preparation of organolithium compounds by lithiation

The replacement of hydrogen by lithium in an organic compound (Eq. 1.6), is perhaps the most versatile method for preparing organolithium compounds.[89]



(Eq. 1.6)

1.4.2 The solvent

The most commonly used solvents for lithiation reactions are diethyl ether, tetrahydrofuran, and hexane. As with other reactions involving organometallic reagents, all solvents should be dry. Solvents used in lithiation reactions have low-enough freezing points which allow them not to be frozen at low temperature. Tetrahydrofuran, although it is the most commonly used alternative solvent to diethyl ether, is more readily attacked by organolithium reagents than diethyl ether and much more hygroscopic than diethyl ether.

1.4.3 Reactions at low temperature and under inert atmosphere

Lithiation reactions are carried out under inert atmosphere (nitrogen or argon) and at low temperature, which is often -78 °C because of the convenience of solid

carbon dioxide-acetone cooling baths. Various other temperatures can be achieved by using an appropriate liquid and forming a slush from it by stirring with liquid nitrogen or CO_2 in a Dewar-type container (Table 1.4).

Table 1.5 Cooling bath compositions

System	Temperature of slush bath (°C)
Tetrachloromethane/N_2	-23
Acetonitrile/CO_2	-42
t-Butyl amine/N_2	-68
Acetone/ CO_2	-78
Ethyl acetate/N_2	-84
Methanol/N_2	-98
Methylcyclohexane/ N_2	-126
Pentane/ N_2	-131

1.5 Conclusion

Directed lithiation of aromatic compounds by organolithium reagents under various reaction conditions followed by reaction with electrophiles is used to produce *ortho*-disubstituted derivatives. The process has been applied widely to various aromatics and heterocycles, giving the corresponding *ortho*-disubstituted derivatives that might be difficult to prepare by other means.

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CHAPTER TWO

DIRECTED LITHIATION OF VARIOUS *N*-BENZYLPIVALAMIDES AND *N'*-BENZYL-*N,N*-DIMETHYLUREAS

CHAPTER TWO

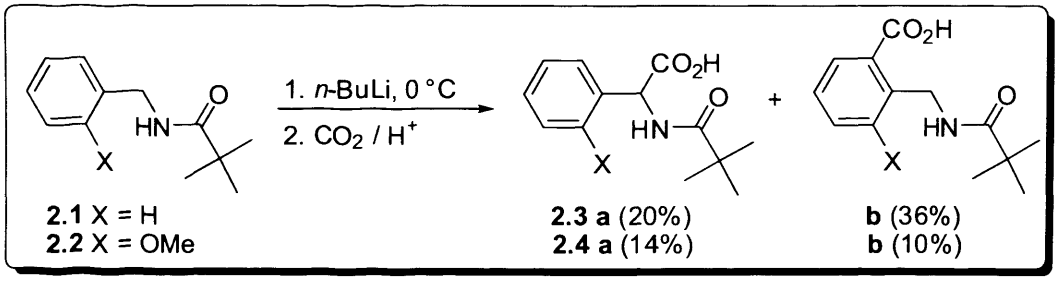
DIRECTED LITHIATION OF VARIOUS *N*-BENZYLPIVALAMIDES AND *N'*-BENZYL-*N,N*-DIMETHYLUREAS

2.1 Directed lithiation of various *N*-benzylpivalamides

2.1.1 Background

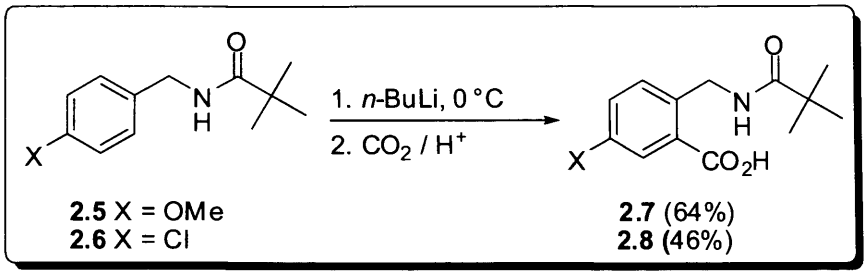
Organolithiums are central to many applications of organic synthesis. One of these is the regioselective synthesis of *ortho*-disubstituted aromatics. Lithiation of aromatics followed by electrophilic substitution is one of the most efficient approaches for synthesis of substituted derivatives.[1-7]

Schlosser has shown that the lithiation reaction of *N*-benzylpivalamide **(2.1)** and *N*-(2-methoxybenzyl)pivalamide **(2.2)** gave a mixture of substituted products **2.3** and **2.4** respectively when treated with *n*-BuLi in THF at 0 °C.[8] Reaction of the lithium intermediates with carbon dioxide gave a mixture of the α-substituted and *o*-substituted products in low yields (Scheme 2.1).[8]



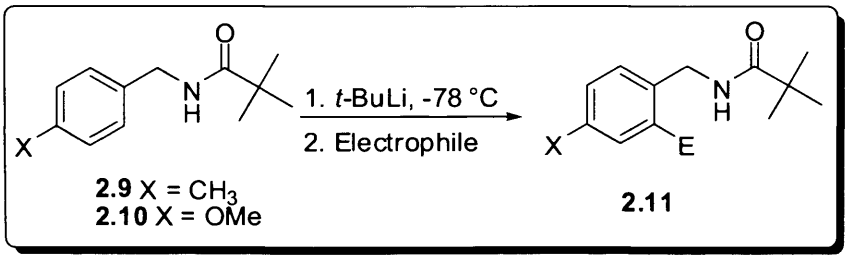
Scheme 2.1

Under the same conditions the lithiation reaction of *N*-(4-methoxybenzyl)pivalamide **(2.5)** and *N*-(4-chlorobenzyl)pivalamide **(2.6)** took place selectivity *ortho* to the pivaloylaminomethyl group to give **2.7** (64%) and **2.8** (46%) respectively (Scheme 2.2).[8] However the generality of the reaction has never been tested.



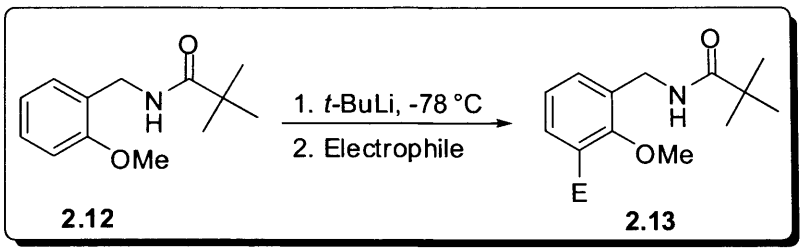
Scheme 2.2

Very recently, Smith's group has developed simple and convenient procedures for directed lithiation and substitution of various *N*-benzylpivalamides to produce various substituted derivatives in high yields.[9] For example the directed lithiation of *N*-(4-methybenzyl)pivalamide **(2.9)** and *N*-(4-methoxybenzyl)pivalamide **(2.10)** using *t*-BuLi in THF at -78 °C for 4 h took place selectivity *ortho* to the pivaloylaminomethyl group. The reactions of the lithium reagents obtained with electrophiles produce the corresponding 2-substituted compounds **2.11** in yields of 77-88% (Scheme 2.3).[9]



Scheme 2.3

Also, lithiation of *N*-(2-methoxybenzyl)pivalamide **(2.12)** using *t*-BuLi at -78 °C in THF for 4 h followed by reaction with electrophiles gave the corresponding *N*-(3-subsitituted 2-methoxybenzyl)pivalamides **2.13** (Scheme 2.4) in high yields (73-86%).[10] It is clear that lithiation and substitution took place *ortho* to the methoxy group rather than *ortho* to the pivaloylaminomethyl group.[10] By contrast, Schlosser had reported different products following lithiation of the same substrate.[8]



Scheme 2.4

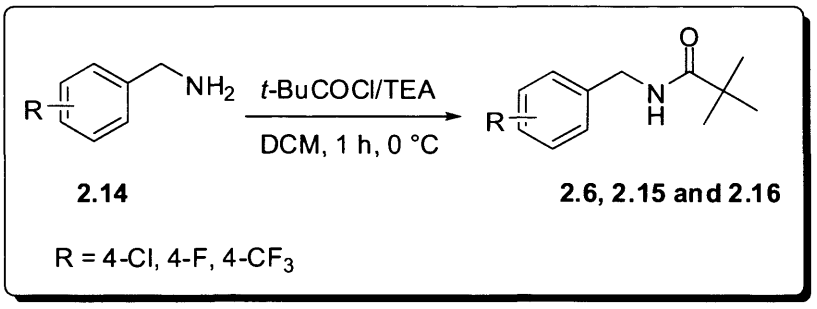
In continuation of these studies, it was of interest to see if the corresponding halo derivatives could be lithiated and substituted selectively in a similar manner and also to examine the applicability and generality of the process. Therefore, the first aim of the work represented in this chapter was to synthesize other *N*-(substituted benzyl)pivalamides and investigate their lithiation reactions, to enable convenient syntheses of the corresponding substituted derivatives. We have selected *N*-benzylpivalamides carrying chloro, fluoro and trifluoromethyl substituents.

Smith's group had been able to establish conditions for a high yielding and general ring substitution. It was planned to extend the range of substrates by applying their conditions to the halo derivatives. The results, which we now report in this chapter, show that the lithiation of *N*-(4-chlorobenzyl)pivalamide took place *ortho* to the pivaloylaminomethyl group, which is consistent with Schlosser's finding with *n*-BuLi at 0 °C.[8] We also found that lithiation of *N*-(4-fluorobenzyl)pivalamide and *N*-(4-trifluoromethylbenzyl)pivalamide took place smoothly at the 2-position *ortho* to the pivaloylaminomethyl group in good yields.

2.1.2 Syntheses of various *N*-benzylpivalamides

The first task was to synthesize various *N*-benzyl pivalamides, namely *N*-(4-chlorobenzyl)pivalamide **(2.6)**, *N*-(4-fluorobenzyl)pivalamide **(2.15)** and *N*-(4-trifluoromethylbenzyl)pivalamide **(2.16)** and investigate their lithiation. These compounds were prepared according to a literature procedure.[11] Reactions of pivaloyl

chloride with benzylamine derivatives **2.14** in dichloromethane (DCM) and in the presence of triethylamine (TEA) at 0 °C gave compounds **2.6**, **2.15** and **2.16** (Scheme-2.5). The solids obtained after work-up were purified by crystallization from Et_2O or EtOAc/Et_2O mixture (1/3) to give pure products as colourless crystals in high yields (Table 2.1). The structures of compounds **2.6**, **2.15** and **2.16** were confirmed by various spectroscopic techniques (Section 2.4).



Scheme 2.5

Table 2.1 Syntheses of *N*-(substitutedbenzyl)pivalamides according to Scheme 2.5

Product	R	Yield (%)[a]
2.6	4-Cl	94
2.15	4-F	95
2.16	4-CF_3	75

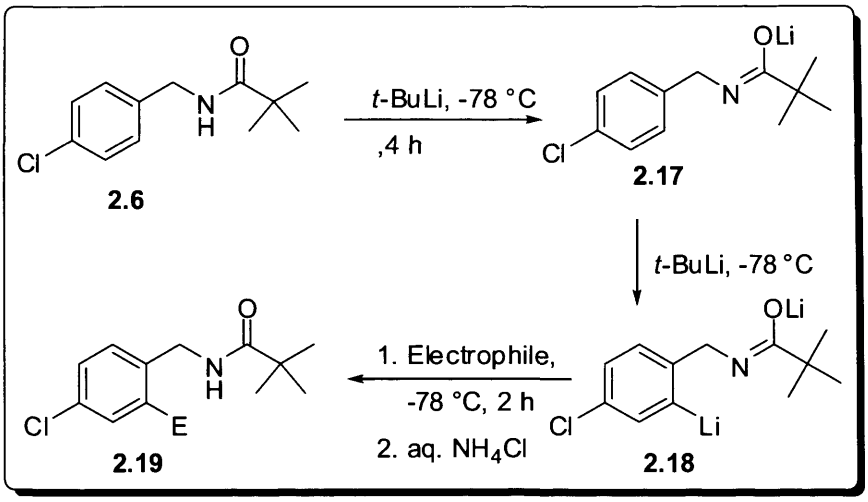
[a] Yield of isolated product after crystallization.

Our attention was next turned to investigation of the directed lithiation of *N*-(4-chlorobenzyl)pivalamide with *t*-BuLi at -78 °C followed by reactions with a range of electrophiles.

2.1.3 Directed lithiation of *N*-(4-chlorobenzyl)pivalamide (2.6)

Double lithiation of *N*-(4-chlorobenzyl)pivalamide **(2.6)** with *n*-BuLi in dry THF at 0 °C followed by reaction with carbon dioxide as an electrophile has been previously reported by Schlosser (scheme 2.2).[8] However, the corresponding carboxylic acid was obtained in only 46% yield and carbon dioxide was the only electrophile used.[8] Therefore, it was of interest to test the generality of the process and to attempt to increase the yield of the product. Previous experience in the group showed that *t*-BuLi is more efficient than *n*-BuLi and *sec*-BuLi as a lithiating agent.[9] Therefore, lithiation of **2.6** with *t*-BuLi (2.2 mole equivalents) in THF at -78 °C was carried out.

Initial addition of *t*-BuLi provided a yellow solution, presumably because of formation of the monolithium reagent **2.17**, until one equivalent had been added, then gave a brownish solution after the remaining *t*-BuLi was added, presumably because of formation of the dilithium reagent **2.18;** the mixture was then stirred for 4 h at -78 °C. An electrophile (1.1 mole equivalents) was added and the mixture was stirred for another 2 h (Scheme 2.6) at -78 °C. The reaction mixture was allowed to warm to room temperature and quenched by the addition of saturated aqueous NH_4Cl solution. The product mixtures were examined by TLC and showed the formation of new products. The crude products obtained were purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure compounds that were shown (see below) to be the corresponding substituted products **2.19** (Scheme 2.6) in high yields (Table 2.2).



Scheme 2.6

Table 2.2 Syntheses of *N*-(2-substituted-4-chlorobenzyl)pivalamides according to Scheme 2.6

Product	**Electrophile**	**E**	**Yield (%)**[a]
2.20	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	83
2.21	PhCHO	PhCH(OH)	82
2.22	Ph_2CO	$Ph_2C(OH)$	79
2.23	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	73
2.24	EtI	Et	79
2.25	D_2O	D	88

[a] Yield of isolated product after purification by column chromatography.

As can be seen from Table 2.2, the yields in all cases were high and the process was general to produce various 2-substituted products.

The structures of compounds **2.20-2.25** were confirmed by ^1H NMR and ^{13}C NMR spectrscopy. The ^1H NMR spectra showed the presence of CH_2 signals, indicating that lithiation took place on the ring and not on the side-chain. It was difficult from simple ^1H NMR spectra of the products to be certain whether lithiation had taken place *ortho* to the CH_2NHCO^tBu group or *ortho* to the Cl group. However,

an X-ray crystal structure (Figure 2.1) of compound **2.21** confirmed that the electrophile had been introduced *ortho* to the pivaloylaminomethyl group. Moreover, lithiation next to the CH_2NHCO^tBu group was expected based on Schlosser's results following lithiation of the same substrate.[8] The ^{13}C NMR spectra of compounds **2.20-2.25** showed a highly downfield singlet signal around δ = 177 - 178 ppm for the carbonyl groups and also showed all the other appropriate carbon resonances.

The ^1H NMR spectra of **2.20** and **2.21** showed that the signals of the two hydrogens of their CH_2 groups appeared separately, as two separated double doublets (*e.g.* Figure 2.2), verifying that they are diasterotopic. The diasterotopicity arises from the creation of a stereogenic carbon centre, on reactions of lithium intermediates **2.18** with aldehydes. Compounds **2.20** and **2.21** were, of course, present as racemic mixtures.

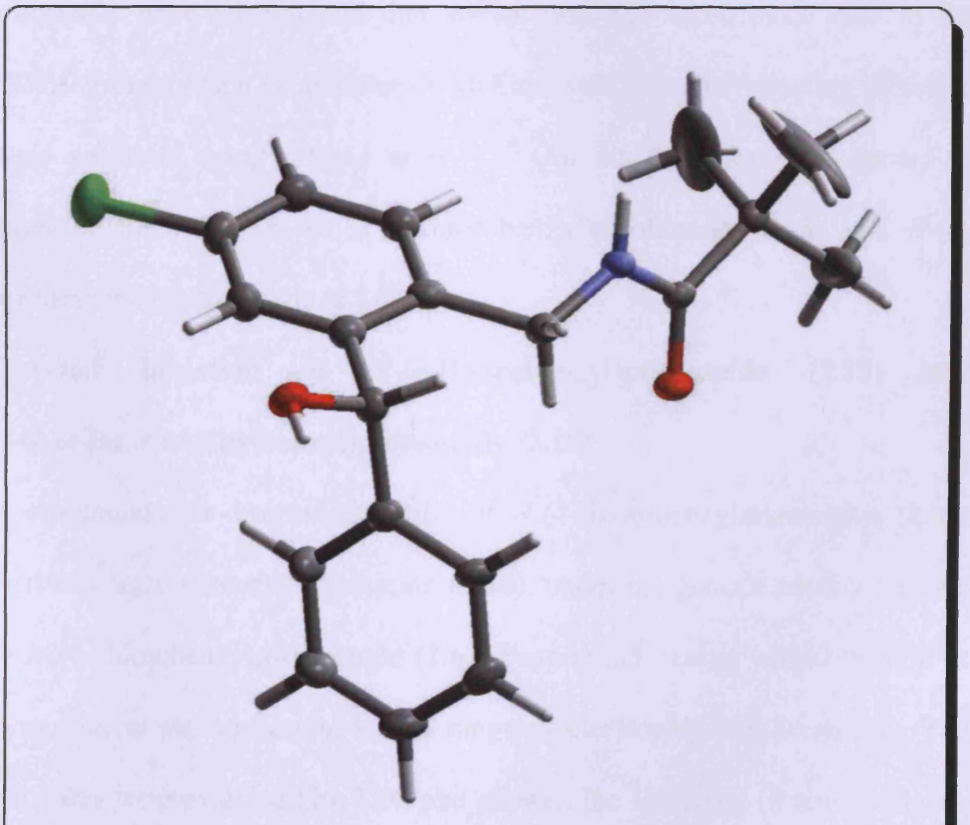


Figure 2.1 X-ray crystal structure of compound **2.21**

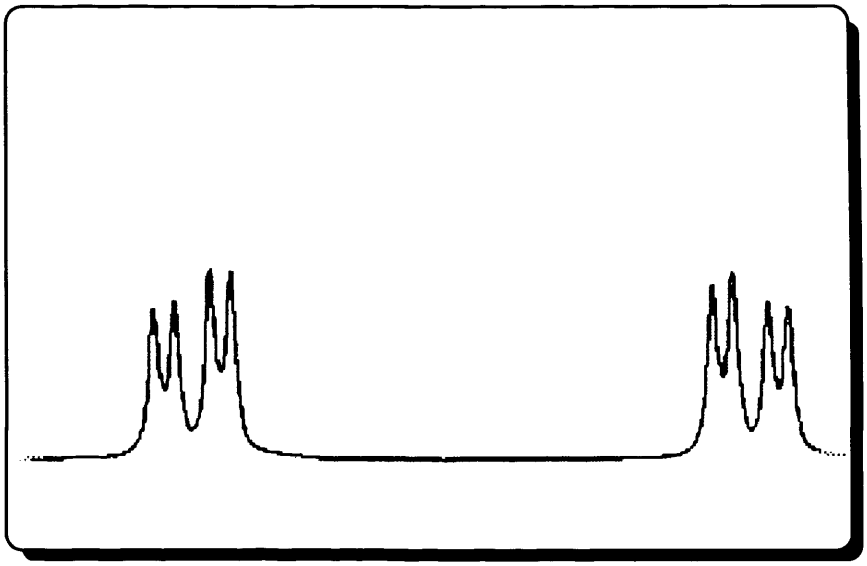


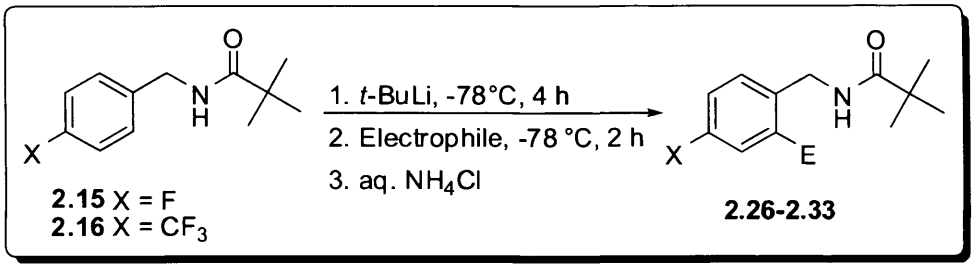
Figure 2.2 part of the ^{1}H NMR spectrum of compound 2.20, showing the presence of two double doublets at 4.30-3.95 ppm

The results obtained clearly indicated that the reactions of the lithium reagent with electrophiles were general and that substitution had taken place next to the CH_2NHCO^tBu group, which is consistent with Schlosser's results following lithiation of the same substrate using *n*-BuLi at 0 °C.[8] Our attention was next turned to investigation of the lithiation of *N*-(4-fluorobenzyl)pivalamide (**2.15**) and *N*-(4-trifluoromethylbenzyl)pivalamide (**2.16**).

2.1.4 Directed lithiation of *N*-(4-fluorobenzyl)pivalamide (2.15) and *N*-(4-trifluoromethylbenzyl)pivalamide (2.16)

It was found that directed lithiation of *N*-(4-fluorobenzyl)pivalamide (**2.15**) and *N*-(4-trifluoromethylbenzyl)pivalamide (**2.16**), under the general conditions used to lithiate *N*-(4-chlorobenzyl)pivalamide (**2.6**) (Section 2.3), using *t*-BuLi in THF at -78 °C, was general and successful with a range of electrophiles (Scheme 2.7). The product mixtures were examined by TLC and showed the formation of new products. The crude products obtained were purified by column chromatography (silica gel;

Et_2O-hexane, 1:3) to give the corresponding substituted products **2.26-2.33** (Scheme 2.7) in high yields (Table 2.3). The products were all characterised by standard spectroscopic methods (Section 2.4).



Scheme 2.7

Table 2.3 Yields of **2.26-2.33** according to Scheme 2.7

Product	X	Electrophile	E	Yield (%)[a]
2.26	F	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	78
2.27	F	PhCHO	PhCH(OH)	79
2.28	F	Ph_2CO	$Ph_2C(OH)$	77
2.29	F	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	81
2.30	F	EtI	Et	82
2.31	F	D_2O	D	86
2.32	CF_3	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	84
2.33	CF_3	Ph_2CO	$Ph_2C(OH)$	79

[a] Yield of isolated product after purification by column chromatography.

The structures of compounds **2.26-2.33** were confirmed by ^1H NMR and ^{13}C NMR spectroscopy. The ^1H NMR spectra showed the presence of CH_2 signals, indicating again that lithiation took place on the ring. In addition, the X-ray crystal structure (Figure 2.3) of compound **2.28** confirmed that the electrophile had again been introduced *ortho* to the pivaloylaminomethyl group. The ^{13}C NMR spectra of compounds **2.26-2.33** also showed all the other appropriate carbon resonances.

The ^{1}H NMR spectra of **2.26, 2.27** and **2.32** showed that the signals of the two hydrogens of their CH_2 groups appeared separately, as two separated double doublets, verifying that they are diasterotopic. Compounds **2.26, 2.27** and **2.32** were of course present as racemic mixtures.

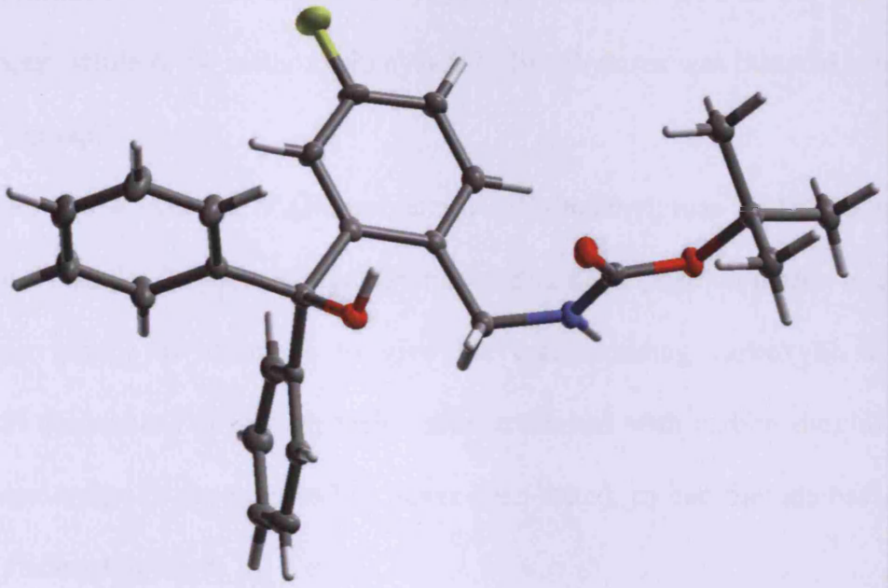


Figure 2.3 X-ray crystal structure of compound **2.28**

The results obtained clearly indicated that reactions of the lithium reagents derived from **2.15** and **2.16** with electrophiles are general and substitution had taken place next to the CH_2NHCO^tBu group.

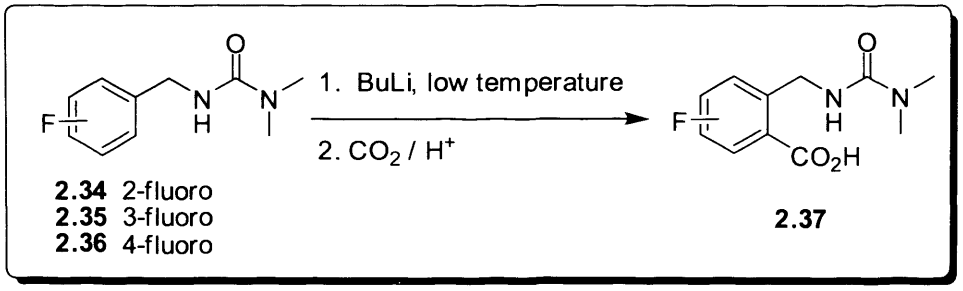
2.2 Directed lithiation of various *N'*-benzyl-*N,N*-dimethylureas

2.2.1 Background

Smith showed that lithiation of *N'*-aryl-*N,N*-dimethylureas was highly dependent on the nature of substituents on the aryl ring. In favourable cases, ring-lithiated intermediates were generated in high yield *via* directed lithiation.[12] In other cases, lithiation took place on the *N*-methyl groups of the urea moiety or

elsewhere on the aryl ring.[12] For example, lithiation of *N'*-(4-chlorophenyl)- and *N'*-(4-trifluoromethylphenyl)-*N,N*-dimethylureas took place *ortho* to the urea containing group, using *n*-BuLi at 0 °C.[12] However, *n*-BuLi failed to lithiate *N'*-(4-fluorophenyl)-*N,N*-dimethylurea under similar conditions, but the use of *t*-BuLi did effect lithiation on the ring next to the urea unit.[12] By contrast, *N'*-(4-methylphenyl)-*N,N*-dimethylurea was lithiated primarily on one of the *N*-methyl groups under using *t*-BuLi at -20 °C similar conditions, while *N'*-(4-methoxyphenyl)-*N,N*-dimethylurea was lithiated *ortho* to the methoxy group.[12]

Schlosser has shown that *N'*-(fluorobenzyl)-*N,N*-dimethylureas **2.34**, **2.35** and **2.36** (2-,3- and 4- isomers) were successfully lithiated at the 2-position (*ortho* to the urea containing group) in all cases to give the corresponding carboxylic acid derivatives **2.37** (Scheme 2.8) in high yields after treatment with carbon dioxide.[13] However, the generality of the process has never been tested, carbon dioxide having been the only electrophile used.



Scheme 2.8

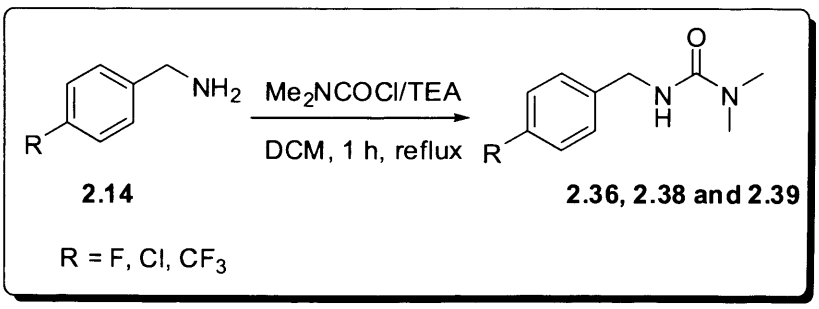
Therefore, it was of interest to investigate the lithiation and substitution of various *N'*-(substituted benzyl)-*N,N*-dimethylureas. We decided to try conditions similar to those used for directed lithiation of substituted *N*-benzylpivalamides (Sections 2.1.3 and 2.1.4). In order to examine the products formed and the generality of the process, we selected *N'*-(4-chlorobenzyl)-*N,N*-dimethylurea,

N'-(4-fluorobenzyl)-*N,N*-dimethylurea and *N'*-(4-trifluoromethylbenzyl)-*N,N*-dimethylurea as substrates for this study.

In the following sections, we report the successful syntheses of these *N'*-(substituted benzyl)-*N,N*-dimethylureas and their lithiation reactions, with *t*-BuLi (2.2 equivalents) in dry THF, followed by reactions of the lithium intermediates generated *in-situ* with various electrophiles to produce the corresponding substituted products in high yields.

2.2.2 Syntheses of *N'*-(4-substituted benzyl)-*N,N*-dimethylureas 2.36, 2.38 and 2.39

The chosen substituted ureas were prepared according to a procedure reported by Smith's group.[9] A mixture of **2.14** and dimethylcarbamoyl chloride in DCM, in the presence of triethylamine as a base, was heated under reflux conditions for 1 h (Scheme 2.9). The solids obtained after work-up were purified by crystallization from Et_2O or EtOAc/Et_2O mixture (1/3) to give compounds **2.36, 2.38** and **2.39** as white crystals in yields of 66-71% (Table 2.4). The structures of compounds **2.36, 2.38** and **2.39** were confirmed by various spectroscopic techniques (Section 2.4).



Scheme 2.9

Table 2.4 Syntheses of *N'*-(4-substituted benzyl)-*N,N*-dimethylureas according to Scheme 2.9

Product	R	Yield (%)[a]
2.36	F	68
2.38	Cl	71
2.39	CF_3	66

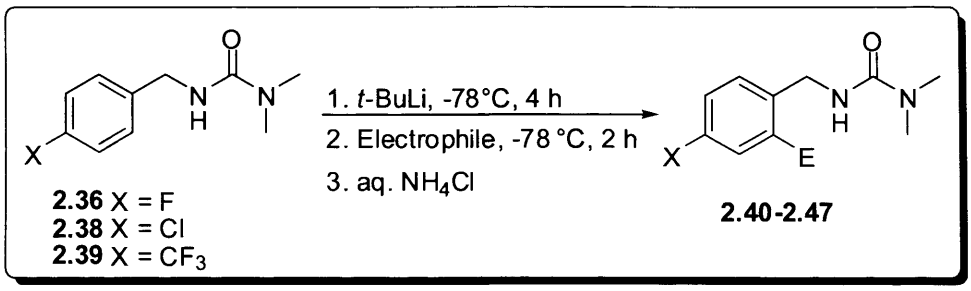
[a] Yield of isolated product after crystallization.

Having successfully synthesized various *N'*-(4-substituted benzyl)-*N,N*-dimethylureas, our attention was next turned to investigation of their lithiation reactions, under the general conditions used for *N*-(4-substituted benzyl)pivalamides (Section 2.1.3 and 2.1.4) using *t*-BuLi at -78 °C, followed by reactions with a range of electrophiles to give the corresponding substituted derivatives.

2.2.3 Directed lithiation of *N'*-(4-substituted benzyl)-*N,N*-dimethylureas 2.36, 2.38 and 2.39

Previous experience with *N*-(4-substituted benzyl)pivalamides suggested that *t*-BuLi might provide higher yields of lithiation products than *sec*- or *n*-BuLi. Therefore, double lithiation of *N'*-(4-fluorobenzyl)-*N,N*-dimethylurea **(2.36)**, *N'*-(4-chlorobenzyl)-*N,N*-dimethylurea **(2.38)** and *N'*-(4-trifluoromethylbenzyl)-*N,N*-dimethylurea **(2.39)** were attempted under identical conditions using *t*-BuLi (2.2 mole equivalents) at -78 °C in dry THF for 4 h (Scheme 2.10). Two mole equivalents of *t*- BuLi were required, the first one to deprotonate the NH proton and the second one, it was hoped, to deprotonate the ring at the 2-position. The dilithium reagents were reacted with a range of electrophiles (benzaldehyde, 4-anisaldehyde, iodoethane or deuterium oxide) for 2 h at -78 °C (Scheme 2.10). The mixtures were allowed to warm to room temperature and quenched by the addition of aqueous NH_4Cl solution.

Following work-up, the residues obtained were purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give the corresponding substituted products (Table 2.5) in high yields. The products were all characterised by standard spectroscopic methods (Section 2.4).



Scheme 2.10

The NMR spectra of all compounds showed the presence of CH_2 signals and NMe_2 signals, indicating that lithiation took place on the ring; the position of substitution was expected to be next to the $CH_2NHCOMe_2$ group based on Schlosser's results.[13] Also, the products **2.40-2.47** have very similar NMR spectra to those of corresponding pivaloyl derivatives, except for the signal due to NMe_2 instead of the *tert*-butyl group. For example, the ^{13}C NMR chemical shift for the newly formed quaternary aromatic carbon atoms were at 133.8-136.3, compared to values of 135.8-145.7 for C-2 of the pivaloyl derivatives, this confirmed that the substitution was next to the $CH_2NHCONMe_2$ group. The ^{13}C NMR spectra of compounds **2.40-2.47** showed all the appropriate carbon resonances. The ^1H NMR spectra of compounds **2.40**, **2.41**, **2.43**, **2.44** and **2.47** showed that the signals of the two hydrogens of their CH_2 groups appeared separately, as two separated double doublets, which converted to two doublets after addition of D_2O (*e.g.* Figure 2.4), verifying that they are diastereotopic. Such compounds would obviously be formed as racemic mixtures.

Table 2.5 Yields of **2.40-2.47** according to Scheme 2.10

Product	X	Electrophile	E	Yield (%)[a]
2.40	F	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	83
2.41	F	PhCHO	PhCH(OH)	83
2.42	F	D_2O	D	86
2.43	Cl	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	79
2.44	Cl	PhCHO	PhCH(OH)	79
2.45	Cl	EtI	Et	77
2.46	Cl	D_2O	D	89
2.47	CF_3	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	83

[a] Yield of isolated product after purification by column chromatography.

As can be seen from Table 2.5, the yields in all cases were high and the process was general to produce various 2-substituted products. The lithiation of *N'*-(4-substituted benzyl)-*N,N*-dimethylureas **2.36**, **2.38** and **2.39** took place selectively *ortho* to the urea containing group using *t*-BuLi at -78 °C.

Figure 2.4 part of the ^1H NMR spectrum of compound 2.42, showing the presence of a simple doublet at 4.25 ppm

2.3 Conclusion

A simple, efficient and high yielding lithiation procedure that allows electrophilic substitution of various *N*-(4-substituted benzyl)pivalamides and various *N'*-(4-substituted benzyl)-*N,N*-dimethylureas has been demonstrated to provide various substituted derivatives. Lithiation of *N*-(4-substituted benzyl)pivalamides and *N'*-(4-substituted benzyl)-*N,N*-dimethylureas using *t*-BuLi at -78 °C in THF, followed by reaction with various electrophiles, gives ring substitution *ortho* to the pivaloylaminomethyl side-chain and urea containing group respectively, which acted as directed metalating groups (DMG's). This work has been published.[15]

2.4 Experimental

2.4.1 General experimental

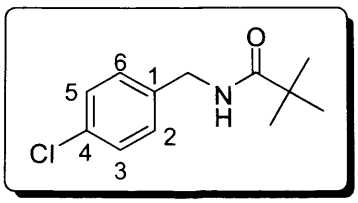
Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance spectrometers operating at 400 and 500 MHz for ^{1}H and 100 and 125 MHz for ^{13}C measurements, respectively. Chemical shifts δ are reported in parts per million (ppm) relative to TMS and coupling constants *J* are in Hz and have been rounded to the nearest whole number. ^{13}C multiplicities are based on DEPT signals. Assignments of signals are based on coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. Low-resolution mass spectra, high-resolution mass spectra and electron impact (EI) at 70 eV were recorded on a Waters GCT Premier spectrometer. Accurate mass data and low-resolution mass spectra were also obtained on a Waters LCT Premier XE instrument. Electrospray (ES) and atmospheric pressure chemical ionization (APCI) analyses were also

performed on the Waters LCT Premier XE instrument. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer and were measured either as thin films (for liquids) or as KBr discs (for solids). Microanalyses were performed by Warwick analytical service at the University of Warwick. X-ray analyses were obtained from the X-Ray Crystallography Service, School of Chemistry, Cardiff University, Cardiff, UK. Column chromatography was carried out using Fischer Scientific silica 60A (35-70 micron). Alkyllithiums were obtained from Aldrich Chemical Company and were estimated prior to use by the method of Watson and Eastham.[14] Other chemicals were obtained from Aldrich Chemical Company and used without further purification. THF was distilled from sodium benzophenone ketyl. Other solvents were purified by standard procedures.[16,17]

2.4.2 Syntheses of various *N*-benzylpivalamides

To a cooled solution (0 °C) of the appropriate benzylamine (**2.14**; 40.0 mmol) and triethylamine (8.0 mL) in CH_2Cl_2 (100 mL) pivaloyl chloride (5.3 g, 44.3 mmol) was slowly added in a drop-wise manner over 30 min. The reaction mixture was stirred at 0 °C for an extra 1 h. The mixture was poured onto H_2O (100 mL) and the organic layer was separated, washed with H_2O (2 x 50 mL) and dried ($MgSO_4$) and the solvent was then removed under reduced pressure. The solids obtained were purified by crystallization from Et_2O–hexane (2:1) to give the pure *N*-(4-substituted benzyl)pivalamides **2.6, 2.15** and **2.16** as white crystals. The yields obtained are reported in Table 2.1.

_N_-(4-Chlorobenzyl)pivalamide (2.6)



Yield: 8.50 g (37.8 mmol; 94%).

MP: 114-116 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, J = 8 Hz, 2 H, H-3/H-5), 7.19 (d, J = 8 Hz, 2 H, H-2/H-6) 6.05 (br, 1 H, NH), 4.35 (d, J = 6 Hz, 2 H, CH_2), 1.20 [s, 9 H, $C(CH_3)_3$].

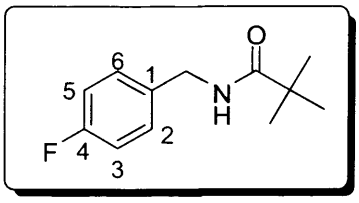
^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 137.3 (s, C-1), 133.2 (s, C-4), 128.9 (d, C-3/C-5), 128.8 (d, C-2/C-6), 42.8 (t, CH_2), 38.7 [s, $C(CH_3)_3$], 27.6 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 227 (32) [$M^{\bullet+}$ ^{37}Cl], 225 (98) [$M^{\bullet+}$ ^{35}Cl], 183 (15), 125 (100), 89 (10), 57 (19).

HRMS: *m/z* calcd for $C_{12}H_{16}NO^{35}Cl$ $[M]^+$, 225.0920; found, 225.0920.

FT–IR: ν_{max} = 3377 (NH), 2966 (CH), 1652 (C=O), 1514 (aromatic C=C), 1427, 1366, 1285, 1215 cm^{-1}.

_N_-(4-Fluorobenzyl)pivalamide (2.15)



Yield: 7.95 g (38.0 mmol; 95%).

Mp: 97-99 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (m, 2 H, H-2/H-6), 7.00 (m, 2 H, H-3/H-5) 6.10 (br, 1 H, NH), 4.35 (d, J = 6 Hz, 2 H, CH_2), 1.22 [s, 9 H, $C(CH_3)_3$].

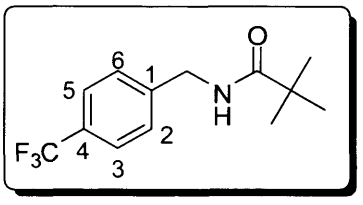
^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 162.5 (d, $^1J_{C\text{-}F}$ = 245 Hz, C-4), 134.6 (d, $^4J_{C\text{-}F}$ = 3 Hz, C-1), 129.3 (d, $^3J_{C\text{-}F}$ = 8 Hz, C-2/C-6), 115.5 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-3/C-5), 42.8 (t, CH_2), 38.7 [s, $C(CH_3)_3$], 27.6 [q, $C(CH_3)_3$].

ES–MS: *m/z* (%) = 210 (100) [MH^+], 150 (8).

HRMS: *m/z* calcd for $C_{12}H_{17}NOF$ $[MH]^+$, 210.1294; found, 210.1300.

FT–IR: ν_{max} = 3371 (NH), 2966 (CH), 1656 (C=O), 1510 (aromatic C=C), 1429, 1366, 1214, 1157 cm^{-1}.

_N_-(4-Trifluoromethylbenzyl)pivalamide (2.16)



Yield: 7.80 g (30.1 mmol; 75%).

Mp: 127-129 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60 (m, 2H, H-3/H-5), 7.39 (m, 2H, H-2/H-6) 6.18 (br, 1H, NH), 4.30 (d, J = 6 Hz, 2H, CH_2), 1.27 [s, 9H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.6 (s, C=O), 142.9 (s, C-1), 129.6 (q, $^2J_{C\text{-}F}$ = 33 Hz, C-4) 127.7 (d, C-2/C-6), 125.6 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-3/C-5), 124.2 (q, $^1J_{C\text{-}F}$ = 269 Hz, CF_3), 43.0 (t, CH_2), 38.8 [s, $C(CH_3)_3$], 27.6 [q, $C(CH_3)_3$].

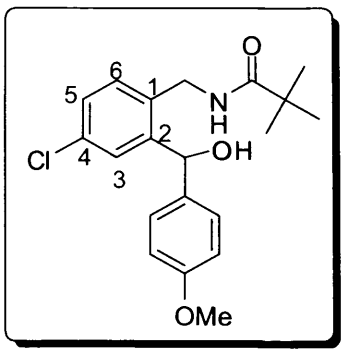
APCI–MS: *m/z* (%) = 536 (27) [2M + NH_4^+], 519 (12) [2M + H^+], 301 (100) [M + $MeCNH^+$], 277 (29) [M + NH_4^+], 260 (42).

HRMS: *m/z* calcd for $C_{13}H_{17}NOF_3$ $[MH]^+$, 260.1262; found, 260.1265.

2.4.3 Synthesis of *N*-(2-substituted 4-chlorobenzyl)pivalamides 2.20-2.25 *via* directed lithiation of *N*-(4-chlorobenzyl)pivalamide (2.6)

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-78 °C), stirred solution of *N*-(4-chlorobenzyl)pivalamide (**2.6**; 0.45 g, 2.0 mmol) in anhydrous THF (20 mL) under nitrogen. Formation of the monolithium reagent **2.17** was observed as a yellow solution and the dilithium reagent **2.18** was observed as a brownish solution. The mixture was stirred at -78 °C for 4 h, to ensure the complete formation of the dilithium reagent **2.18**, after which electrophile (2.2 mmol), in anhydrous THF (8 ml) if solid, otherwise neat, was added. The mixture was stirred for 2 h at -78 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was then diluted with Et_2O (10 mL) and quenched with aq. sat. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; Et_2O-hexane, 1:3) to give pure *N*-(2-substituted 4-chlorobenzyl)pivalamides **2.20-2.25**. The yields obtained are reported in Table 2.2.

_N_-(4-Chloro-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)pivalamide (2.20)



Yield: 0.60 g (1.66 mmol, 83%).

Mp: 212–214 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.93 (br, exch., 1 H, NH), 7.50 (s, 1 H, H-3), 7.30 (d, J = 8 Hz, 1 H, H-5), 7.20 (d, 2 H, J = 9 Hz, H-2/H-6 of 4-methoxyphenyl), 7.12 (d, J = 8 Hz, 1 H, H-6), 6.88 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.93 (d, J = 3 Hz, exch., 1 H, OH), 5.89 (d, J = 3 Hz, 1 H, CH), 4.30 (dd, J = 6, 14 Hz, 1 H, CH_aH$_b$), 3.95 (dd, J = 6, 14 Hz, 1 H, CH$_a$$H_b$), 3.70 (s, 3 H, OCH_3), 1.10 [s, 9H, $C(CH_3)_3$].

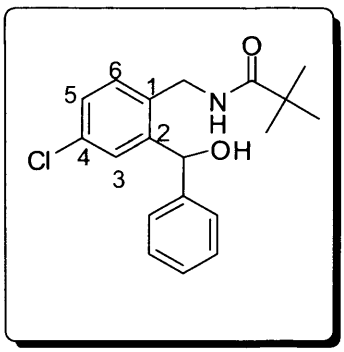
^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.9 (C=O), 158.8 (C-4 of 4-methoxyphenyl), 145.3 (C-1), 136.0 (C-1 of 4-methoxyphenyl), 135.8 (C-2), 131.6 (C-4), 129.0 (C-6), 128.8 (C-2/C-6 of 4-methoxyphenyl), 127.0 (C-3), 126.5 (C-5), 114.1 (C-3/C-5 of 4-methoxyphenyl), 70.4 (CH), 55.5 (OCH_3), 40.0 [$C(CH_3)_3$], 38.5 (CH_2), 27.9 [$C(CH_3)_3$].

EI-MS: *m/z* (%) = 361 (1) [$M^{\bullet+}$], 343 (57), 328 (7), 312 (26), 286 (100), 258 (29), 243 (45), 242 (46), 208 (50), 149 (65), 135(20), 57 (40).

HRMS: *m/z* calcd for $C_{20}H_{24}NO_3{}^{35}Cl$ $[M]^+$: 361.1445; found: 361.1447.

FT–IR: ν_{max} = 3326 (NH and OH), 2963 (CH), 1634 (C=O), 1539 (aromatic C=C), 1509, 1293, 1246, 1195 cm^{-1}.

N-(4-Chloro-2-(hydroxyphenylmethylbenzyl)pivalamide (2.21)



Yield: 0.54 g (1.63 mmol, 82%).

Mp: 180–182 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.90 (app. t, J = 6 Hz, exch., 1 H, NH), 7.85-7.70 (m, 5 H, Ph), 7.70 (s, 1 H, H-3), 7.67 (d, J = 8 Hz, 1 H, H-5), 7.62 (d, J = 8 Hz, 1 H, H-6), 6.60 (s, exch., 1 H, OH), 5.85 (s, 1 H, CH), 4.90 (dd, J = 6, 14 Hz, 1 H, CH_aH$_b$), 4.65 (dd, J = 6, 14 Hz, 1 H, CH$_a$$H_b$), 1.50 [s, 9 H, C(CH$_3$)$_3$].

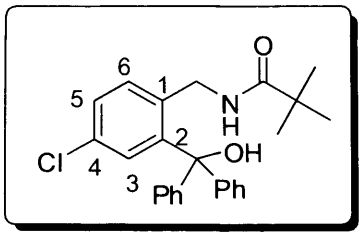
^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.9 (C=O), 158.8 (C-2), 145.3 (C-1), 136.0 (C-4), 135.8 (C-1 of Ph), 130.7 (C-4 of Ph), 128.7 (C-3/C-5 of Ph), 127.7 (C-6), 127.6 (C-5), 127.5 (C-3), 127.4 (C-2/C-6 of Ph), 72.1 (CH), 39.9 (CH$_2$), 38.7 [C(CH$_3$)$_3$], 27.4 [C(CH$_3$)$_3$].

EI-MS: *m/z* (%) = 331 (1) [M$^{\bullet+}$], 313 (35) [M$^{\bullet+}$ – H$_2$O], 256 (29) [M$^{\bullet+}$ – H$_2$O – ^{t}Bu], 225 (59), 173 (39), 125 (100), 89 (65), 57 (95).

HRMS: *m/z* calcd for C$_{19}$H$_{22}$NO$_2$^{35}Cl [M]$^+$: 331.1339; found: 331.1345.

FT–IR: ν_{max} = 3431 (NH and OH), 2968 (CH), 1590 (C=O), 1571 (aromatic C=C), 1474, 1360, 1228, 1167 cm^{-1}.

_N_-(4-Chloro-2-(hydroxydiphenylmethyl)benzyl)pivalamide (2.22)



Yield: 0.64 g (1.57 mmol, 79%).

Mp: 240–242 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.83 (br, exch., 1 H, NH), 7.38-7.36 (m, 10 H, 2 Ph), 7.30 (d, J = 8 Hz, 1 H, H-5), 7.20 (d, J = 8 Hz, 1 H, H-6), 7.10 (s, exch., 1 H, OH), 6.50 (s, 1 H, H-3), 3.90 (d, J = 6 Hz, 2 H, CH_2), 1.07 [s, 9 H, $C(CH_3)_3$].

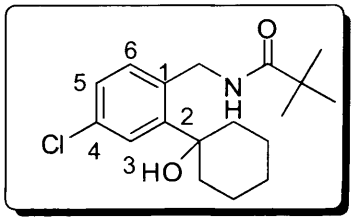
^{13}C NMR (125 MHz, DMSO-d_6): δ = 178.2 (C=O), 147.3 (C-1 of 2 Ph), 147.2 (C-2), 138.9 (C-1), 132.3 (C-4), 130.6 (C-6), 128.9 (C-3), 128.4 (C-3/C-5 of 2 Ph), 127.8 (C-2/C-6 of 2 Ph), 127.5 (C-4 of 2 Ph), 127.5 (C-5), 81.6 (C-OH), 41.0 (CH_2), 38.4 [$C(CH_3)_3$], 27.8 [$C(CH_3)_3$].

APCI-MS: *m/z* (%) = 471 (60) [$M^{\bullet+}$ + $MeCNNa^+$], 446 (100) [$M^{\bullet+}$ + K^+], 390 (80), 289 (40).

HRMS: *m/z* calcd for $C_{25}H_{26}NO_2{}^{35}ClK$ $[M + K]^+$: 446.1289; found: 446.1304.

FT–IR: ν_{max} = 3357 (NH and OH), 2969 (CH), 1643 (C=O), 1527 (aromatic C=C), 1480, 1348, 1214, 1163 cm^{-1}.

_N_-(4-Chloro-2-(1-hydroxycyclohexyl)benzyl)pivalamide (2.23)



Yield: 0.47 g (1.45 mmol, 73%).

Mp: 166–168 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.91 (s, 1 H, H-3), 7.83 (t, J = 6 Hz, 1 H, NH), 7.80 (d, J = 8 Hz, 1 H, H-5), 7.63 (d, J = 8 Hz, 1 H, H-6), 5.22 (s, exch., 1 H, OH), 5.20 (d, J = 6 Hz, 2 H, CH_2N), 2.40–2.05 [m, 10 H, $(CH_2)_5$], 1. 60 [s, 9 H, $C(CH_3)_3$].

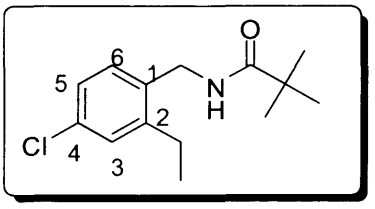
^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.8 (C=O), 150.2 (C-2), 138.4 (C-1), 132.4 (C-4), 132.4 (C-6), 126.8 (C-3), 126.0 (C-5), 73.9 (C-OH), 41.7 (CH_2NH), 38.8 (C-2/C-6 of cyclohexyl), 29.7 [$C(CH_3)_3$], 27.4 [$C(CH_3)_3$], 25.8 (C-4 of cyclohexyl), 22.2 (C-3/C-5 of cyclohexyl).

EI-MS: *m/z* (%) = 323 (1) [$M^{\bullet+}$], 305 (33), 225 (100), 176 (95), 125 (100), 102 (90), 89 (83), 77 (55), 57 (99).

HRMS: *m/z* calcd for $C_{18}H_{26}NO_2{}^{35}Cl$ $[M]^+$: 323.1652; found: 323.1656

FT–IR: ν_{max} = 3372 (NH and OH), 2922 (CH), 1644 (C=O), 1556 (aromatic C=C), 1456, 1298, 1158, 1105 cm^{-1}.

_N_-(4-Chloro-2-ethylbenzyl)pivalamide (2.24)



Yield: 0.40 g (1.58 mmol, 79%).

Mp: 117–119 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (s, 1 H, H-3), 7.20 (d, J = 8 Hz, 1 H, H-5), 7.15 (d, J = 8 Hz, 1 H, H-6), 5.80 (br, exch., 1 H, NH), 4.40 (d, J = 6 Hz, 2 H, CH_2N), 2.65 (q, J = 7 Hz, 2 H, CH_2CH_3), 1.20 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.20 [s, 9 H, $C(CH_3)_3$].

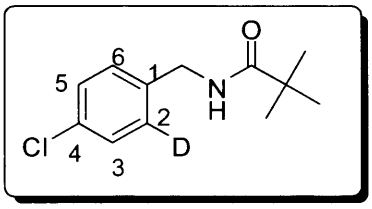
^{13}C NMR (125 MHZ, $CDCl_3$): δ = 178.1 (C=O), 144.3 (C-2), 134.1 (C-1), 133.5 (C-4), 130.0 (C-6), 128.7 (C-3), 126.2 (C-5), 40.7 (CH_2NH), 38.7 [$C(CH_3)_3$], 27.6 [$C(CH_3)_3$], 25.2 (CH_2CH_3), 15.5 (CH_2CH_3).

EI-MS: *m/z* (%) = 255 (19) [$M^{\bullet+}$ ^{37}Cl], 253 (60) [$M^{\bullet+}$ ^{35}Cl], 152 (100), 117 (50).

HRMS: *m/z* calcd for $C_{14}H_{20}NO^{35}Cl$ $[M]^+$: 253.1233; found: 253.1234.

FT–IR: ν_{max} = 3440 (NH), 2934 (CH), 1636 (C=O), 1571 (aromatic C=C), 1445, 1210, 1151, 1065 cm^{-1}.

_N_-(4-Chloro-2-deuteriobenzyl)pivalamide (2.25)



Yield: 0.40 g (1.76 mmol, 88%).

Mp: 114–116 °C (Mp of undeuteriated analogue 114–116 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8 Hz, 1 H, H-5), 7.20 (s, 1 H, H-3), 7.18 (d, *J* = 8 Hz, 1 H, H-6), 6.09 (br t, exch., 1 H, NH), 4.40 (d, *J* = 6 Hz, 2 H, CH_2), 1.22 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4 (C=O), 137.2 (C-1), 133.1 (C-4), 128.9 (C-3), 128.8 (C-5), 128.7 (C-6), 128.6 (seen as three lines, 1:1:1, because of coupling to D, C-2), 42.8 (CH_2), 38.7 [$C(CH_3)_3$], 27.6 [$C(CH_3)_3$].

APCI-MS: *m/z* (%) = 229 (33) [MH^+ ^{37}Cl], 227 (100) [MH^+ ^{35}Cl], 181 (5).

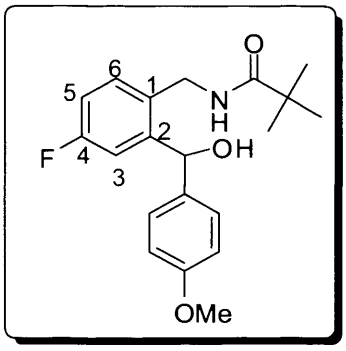
HRMS: *m/z* calcd for $C_{12}H_{16}DNO^{35}Cl$ $[MH]^+$: 227.1061; found: 227.1059.

FT–IR: ν_{max} = 3284 (NH), 2921 (CH), 1646 (C=O), 1538 (aromatic C=C), 1481, 1273, 1119, 1035 cm^{-1}.

2.4.4 Synthesis of 2.26-2.33 *via* directed lithiation of *N*-(4-fluorobenzyl)pivalamide (2.15) and *N*-(4-trifluoromethylbenzyl)pivalamide (2.16)

The procedure was identical with that described in Section 2.4.3 except that the appropriate *N*-(4-substituted benzyl)pivalamide was used. The reaction was worked-up as usual and the residues obtained were purified by column chromatography (silica gel; Et_2O-hexane, 1:3) to give pure products **2.26-2.33**. The yields obtained are reported in Table 2.3.

_N_-(4-Fluoro-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)pivalamide (2.26)



Yield: 0.54 g (1.56 mmol, 78%).

Mp: 200–202 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.93 (app. t, J = 6 Hz, exch., 1 H, NH), 7.30 (m, 1 H, H-6), 7.20 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.12 (m, 1 H, H-5), 7.05 (m, 1 H, H-3), 6.89 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.93 (s, exch., 1 H, OH), 5.89 (s, 1 H, CH), 4.30 (dd, J = 6, 14 Hz, 1 H, CH_aH_b), 3.95 (dd, J = 6, 14 Hz, 1 H, CH_aH_b), 3.71 (s, 3 H, OCH_3), 1.10 [s, 9H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.8 (C=O), 161.6 (d, $^1J_{C\text{-}F}$ = 241 Hz, C-4), 158.8 (C-4 of 4-methoxyphenyl), 145.7 (d, $^3J_{C\text{-}F}$ = 8 Hz, C-2), 136.2 (C-1 of 4-methoxyphenyl), 132.7 (d, $^4J_{C\text{-}F}$ = 2 Hz, C-1), 129.1 (d, $^3J_{C\text{-}F}$ = 8 Hz, C-6), 128.8

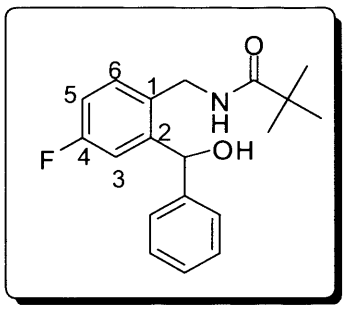
(C-2/C-6 of 4-methoxyphenyl), 114.0 (C-3/C-5 of 4-methoxyphenyl), 113.6 (d, $^2J_{C\text{-}F}$ = 21 Hz, C-3), 113.3 (d, $^2J_{C\text{-}F}$ = 21 Hz, C-5), 70.4 (CH), 55.5 (OCH_3), 40.0 [$C(CH_3)_3$], 38.5 (CH_2), 27.9 [$C(CH_3)_3$].

ES-MS: *m/z* (%) = 346 (1) [MH^+], 328 (100) 227 (24).

HRMS: *m/z* calcd for $C_{20}H_{25}NO_3F$ [$MH]^+$: 346.1818; found: 346.1830.

FT–IR: ν_{max} = 3316 (NH and OH), 2963 (CH), 1632 (C=O), 1542 (aromatic C=C), 1438, 1250, 1173, 1097 cm^{-1}.

_N_-(4-Fluoro-2-(hydroxyphenylmethylbenzyl)pivalamide (2.27)



Yield: 0.50 g (1.58 mmol, 79%).

Mp: 157–159 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.93 (app. t, *J* = 6 Hz, exch., 1H, NH), 7.32-7.23 (m, 6 H, Ph and H-6), 7.15 (m, 1 H, H-5), 7.05 (m, 1 H, H-3), 6.05 (s, exch., 1 H, OH), 5.95 (s, 1 H, CH), 4.30 (dd, *J* = 6, 14 Hz, 1 H, CH_aH_b), 4.02 (dd, *J* = 6, 14 Hz, 1 H, CH_aH_b), 1.10 [s, 9 H, $C(CH_3)_3$].

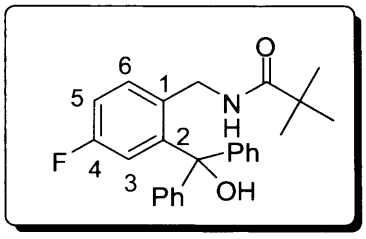
^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.6 (d, $^1J_{C\text{-}F}$ = 241 Hz, C-4), 158.5 (C=O), 145.4 (d, $^3J_{C\text{-}F}$ = 8 Hz, C-2), 144.1 (C-1 of Ph), 132.9 (d, $^4J_{C\text{-}F}$ = 3 Hz, C-1), 132.9 (C-4 of Ph), 129.3 (d, $^3J_{C\text{-}F}$ = 8 Hz, C-6), 128.6 (C-3/C-5 of Ph), 127.5 (C-2/C-6 of Ph), 113.8 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-3), 113.6 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-5), 70.8 (CH), 40.0 [$C(CH_3)_3$], 38.5 (CH_2), 27.9 [$C(CH_3)_3$].

ES-MS: *m/z* (%) = 316 (15) [MH^+], 298 (100), 237 (8).

HRMS: *m/z* calcd for $C_{19}H_{23}NO_2F$ $[MH]^+$: 316.1713; found: 316.1715.

FT–IR: ν_{max} = 3454 (NH and OH), 2962 (CH), 1600 (C=O), 1468 (aromatic C=C), 1380, 1261, 1097 cm^{-1}.

_N_-(4-Fluoro-2-(hydroxydiphenylmethyl)benzyl)pivalamide (2.28)



Yield: 0.60 g (1.53 mmol, 77%).

Mp: 216–218 °C.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.85 (t, *J* = 6 Hz, exch., 1 H, NH), 7.29-7.22 (m, 11 H, 2 Ph and H-6), 7.13-710 (m, 2 H, H-3 and H-5), 6.22 (s, exch., 1 H, OH), 4.95 (d, *J* = 6 Hz, 2 H, CH_2), 1.10 [s, 9 H, $C(CH_3)_3$].

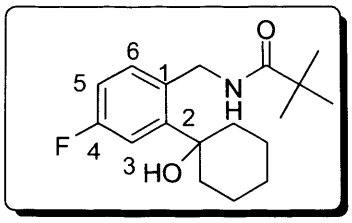
^{13}C NMR (125 MHz, DMSO-d_6): δ = 178.1 (C=O), 160.3 (d, $^1J_{C\text{-}F}$ = 240 Hz, C-4), 147.4 (d, $^3J_{C\text{-}F}$ = 7 Hz, C-2), 135.8 (C-1 of 2 Ph), 132.9 (d, $^4J_{C\text{-}F}$ = 3 Hz, C-1), 130.8 (d, $^3J_{C\text{-}F}$ = 7 Hz, C-6), 128.4 (C-3/C-5 of 2 Ph), 127.8 (C-2/C-6 of 2 Ph), 127.5 (C-4 of 2 Ph), 116.1 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-3), 114.4 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-5), 81.6 (C-OH), 40.2 (CH_2), 38.4 [$C(CH_3)_3$], 27.8 [$C(CH_3)_3$].

EI-MS: *m/z* (%) = 374 (100) [$MH^+ - H_2O$], 273(5).

HRMS: *m/z* calcd for $C_{25}H_{25}NOF$ $[MH - H_2O]^+$: 374.1920; found: 374.1925.

FT–IR: ν_{max} = 3398 (NH and OH), 2991 (CH), 1667 (C=O), 1582 (aromatic C=C), 1433, 1307, 1114, 1068 cm^{-1}.

_N_-(4-Fluoro-2-(1-hydroxycyclohexylbenzyl)pivalamide (2.29)



Yield: 0.50 g (1.63 mmol, 81%).

Mp: 140–142 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.88 (br, exch., 1 H, NH), 7.22-6.98 (m, 3 H, H-3, H-5 and H-6), 5.0 (s, exch., 1 H, OH), 4.55 (d, J = 6 Hz, 2 H, CH_2N), 1.93–1.50 [m, 10 H, $(CH_2)_5$], 1.10 [s, 9 H, $C(CH_3)_3$].

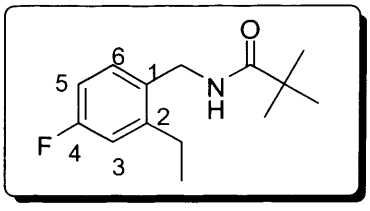
^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.8 (C=O), 162.2 (d, $^{1}J_{C\text{-}F}$ = 240 Hz, C-4), 150.4 (d, $^{3}J_{C\text{-}F}$ = 8 Hz, C-2), 134.8 (d, $^{4}J_{C\text{-}F}$ = 2 Hz, C-1), 129.9 (d, $^{3}J_{C\text{-}F}$ = 8 Hz, C-6), 113.1 (d, $^{2}J_{C\text{-}F}$ = 20 Hz, C-3), 112.5 (d, $^{2}J_{C\text{-}F}$ = 20 Hz, C-5), 73.0 (C-OH), 41.2 (CH_2NH), 38.5 [$C(CH_3)_3$], 37.7 (C-2/C-6 of cyclohexyl), 27.9 [$C(CH_3)_3$], 25.6 (C-4 of cyclohexyl), 22.3 (C-3/C-5 of cyclohexyl).

ES-MS: *m/z* (%) = 308 (100) [MH^+], 290 (25).

HRMS: *m/z* calcd for $C_{18}H_{27}NO_2F$ [$MH]^+$: 308.2026; found: 308.2039.

FT–IR: ν_{max} = 3419 (NH and OH), 2956 (CH), 1671 (C=O), 1530 (aromatic C=C), 1462, 1321, 1239, 1095 cm^{-1}.

_N_-(4-Fluoro-2-ethylbenzyl)pivalamide (2.30)



Yield: 0.39 g (1.64 mmol, 82%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.05 (m, 1 H, H-6), 6.72-6.61 (m, 2 H, H-3 and H-5), 6.49 (br, exch., 1 H, NH), 4.20 (d, J = 6 Hz, 2 H, CH_2N), 2.49 (q, J = 7 Hz, 2 H, CH_2CH_3), 1.10 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.10 [s, 9 H, $C(CH_3)_3$].

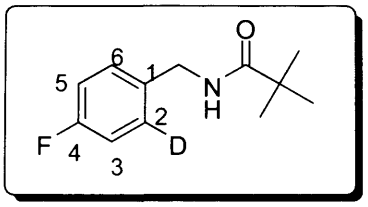
^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.3 (C=O), 162.1 (d, $^{1}J_{C-F}$ = 246 Hz, C-4), 144.3 (d, $^{3}J_{C-F}$ = 7 Hz, C-2), 131.6 (d, $^{4}J_{C-F}$ = 2 Hz, C-1), 129.6 (d, $^{3}J_{C-F}$ = 7 Hz, C-6), 114.9 (d, $^{2}J_{C-F}$ = 21 Hz, C-3), 112.4 (d, $^{2}J_{C-F}$ = 21 Hz, C-5), 40.3 (CH_2N), 38.5 [$C(CH_3)_3$], 27.4 [$C(CH_3)_3$], 25.1 (CH_2), 14.6 (CH_3).

EI-MS: *m/z* (%) = 237 (100) [$M^{\bullet+}$], 219 (28), 194 (15), 135 (82), 115 (32), 85 (15), 57 (20).

HRMS: *m/z* calcd for $C_{14}H_{20}NOF$ $[M]^+$: 237.1529; found: 237.1522.

FT–IR: ν_{max} = 3438 (NH), 2962 (CH), 1639 (C=O), 1491 (aromatic C=C), 1388, 1261, 1093 cm^{-1}.

_N_-(2-Deuterio-4-fluorobenzyl)pivalamide (2.31)



Yield: 0.36 g (1.71 mmol, 86%).

Mp: 97–99 °C (Mp of undeuteriated analogue 97–99 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12 (m, 1 H, H-6), 6.93-6.89 (m, 2 H, H-3 and H-5), 6.10 (br, exch., 1 H, NH), 4.29 (d, J = 6 Hz, 2 H, CH_2), 1.15 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4 (C=O), 162.1 (d, $^{1}J_{C-F}$ = 244 Hz, C-4), 134.5 (d, $^{4}J_{C-F}$ = 3 Hz, C-1), 129.2 (d, $^{3}J_{C-F}$ = 8 Hz, C-6), 128.9 (seen as six lines, because of

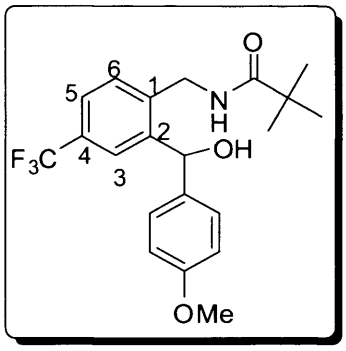
coupling to F and D, J = 8, 25 Hz, C-2), 115.5 (d, $^2J_{C\text{-}F}$ = 12 Hz, C-3), 115.3 (d, $^2J_{C\text{-}F}$ = 12 Hz, C-5), 42.7 (CH_2), 38.7 [$C(CH_3)_3$], 27.6 [$C(CH_3)_3$].

ES-MS: *m/z* (%) = 210 (58) [$M^{\bullet+}$], 167 (10), 110 (100), 57 (20).

HRMS: *m/z* calcd for $C_{12}H_{15}DNOF$ $[M]^+$: 210.1279; found: 210.1279.

FT–IR: ν_{max} = 3381 (NH), 2934 (CH), 1600 (C=O), 1524 (aromatic C=C), 1440, 1214, 1026 cm^{-1}.

_N_-(4-Trifluoromethyl-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)pivalamide (2.32)



Yield: 0.66 g (1.67 mmol, 84%).

Mp: 197-199 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.05 (br, 1 H, NH), 7.90 (s, 1 H, H-3), 7.61 (d, J = 8 Hz, 1 H, H-5), 7.30 (d, J = 8 Hz, 1 H, H-6), 7.20 (d, J = 8 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 6.89 (d, J = 8 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.05 (s, 1 H, OH), 5.95 (s, 1 H, CH), 4.40 (dd, J = 5, 16 Hz, 1 H, CH_aH_b), 4.0 (dd, J = 5, 16 Hz, 1 H, CH_aH_b), 3.75 (s, 3 H, OCH_3), 1.15 [s, 9 H, $C(CH_3)_3$].

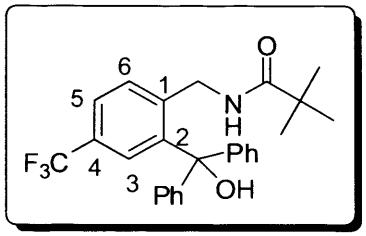
^{13}C NMR (125 MHz, DMSO-d_6): δ = 178.0 (s, C=O), 158.9 (s, C-4 of 4-methoxyphenyl), 144.0 (s, C-1) 141.6 (s, C-1 of 4-methoxyphenyl), 135.8 (s, C-2), 128.9 (d, C-2/C-6 of 4-methoxyphenyl), 127.6 (q, $^2J_{C\text{-}F}$ = 30 Hz, C-4) , 127.5 (d, C-6), 126.1 (m, CF_3), 123.9 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-3), 123.0 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-5), 114.1 (d, C-

3/C-5 of 4-methoxyphenyl) 70.4 (d, CH), 55.5 (q, OCH_3), 40.2 [s, $C(CH_3)_3$], 38.6 (t, CH_2), 27.9 [q, $C(CH_3)_3$],.

APCI–MS: *m/z* (%) = 378 (100) [$MH^+ - H_2O$], 290 (100).

HRMS: *m/z* calcd for $C_{21}H_{23}NO_2F_3$ [$MH - H_2O]^+$, 378.1681; found, 378.1682.

_N_-(4-Trifluoromethyl-2-(hydroxydiphenylmethyl)benzyl)pivalamide (2.33)



Yield: 0.70 g (1.58 mmol, 79%).

Mp: 216-218 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.55 (s, 1 H, H-3) 7.39-7.27 (m, 11 H, 2 Ph, H-5), 6.98 (d, 1 H, J = 8 Hz, H-6), 6.41 (t, J = 6 Hz, 1 H, NH), 5.32 (br, 1 H, OH), 4.20 (d, J = 6, 2 H, CH_2), 1.1 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.7 (s, C=O), 146.6 (s, C-1 of 2 Ph), 145.7 (s, C-2), 142.9 (s, C-1), 131.4 (d, C-6), 128.7 (q, $^2J_{C\text{-}F}$ = 32 Hz, C-4), 128.3 (d, C-3/C-5 of 2 Ph), 127.7 (d, C-2/C-6 of 2 Ph), 127.6 (d, C-4 of 2 Ph), 126.3 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-3), 125.6 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-5), 124.0 (q, $^1J_{C\text{-}F}$ = 269 Hz, CF_3), 82.4 (s, C-OH), 41.8 (t, CH_2), 38.4 [s, $C(CH_3)_3$], 27.4 [q, $C(CH_3)_3$].

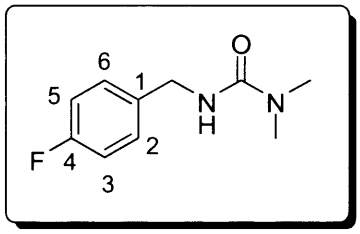
ES–MS: *m/z* (%) = 424 (100) [$MH^+ - H_2O$], 290 (5).

HRMS: *m/z* calcd for $C_{26}H_{25}NOF_3$ [$MH - H_2O]^+$, 424.1888; found, 424.1876.

2.4.5 Synthesis of *N'*-(4-substituted benzyl)-*N,N*-dimethylureas 2.36, 2.38 and 2.39

A stirred mixture of the appropriate benzylamine (**2.14**; 40.0 mmol), dimethylcarbamoyl chloride (4.83 g, 45 mmol) and triethylamine (5.05 g, 55.0 mmol) in CH_2Cl_2 (60 mL) was heated under reflux for 1 h. The mixture was poured onto H_2O (50 mL) and the organic layer was separated, washed with H_2O (2 x 25 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The solids obtained were purified by crystallization from EtOAc/Et_2O (1/3) to give pure products **2.36**, **2.38** and **2.39** as white crystalline solids. The yields obtained are reported in Table 2.4.

N'-(4-Fluorobenzyl)-N,N-dimethylurea (2.36)



Yield: 5.30 g (27.0 mmol, 68%).

Mp: 112-114 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (m, 2 H, H-2/H-6), 7.0 (m, 2 H, H-3/H-5), 4.90 (br, 1 H, NH), 4.35 (d, J =6 Hz, 2 H, CH_2), 2.93 (s, 6 H, NMe_2).

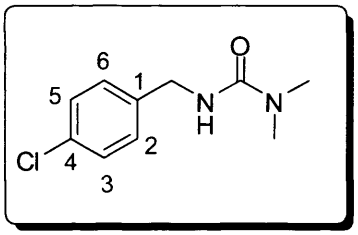
^{13}C NMR (500 MHz, $CDCl_3$): δ= 161.5 (d, $^1J_{C\text{-}F}$ = 246 Hz, C-4), 158.3 (s, C=O), 135.7 (d, $^4J_{C\text{-}F}$ = 3 Hz, C-1), 129.3 (d, $^3J_{C\text{-}F}$ = 8 Hz, C-2/C-6), 115.4 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-3/C-5), 44.2 (t, CH_2), 36.2 (q, NMe_2).

AP–MS: *m/z* (%) = 197 (100) [MH^+, 100], 150 (10), 109 (15).

HRMS: *m/z* calcd for $C_{10}H_{14}N_2OF$ $[MH]^+$, 197.1090; found, 197.1091.

FT–IR: ν_{max} = 3332 (NH), 2931 (CH), 1634 (C=O), 1537 (aromatic C=C), 1509, 1428, 1377, 1221, 1156 cm^{-1}.

_N'_-(4-Chlorobenzyl)-_N,N_-dimethylurea (2.38)



Yield: 6.0 g (28.3 mmol, 71%).

Mp: 133-135 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, J = 8 Hz, 2 H, H-3/H-5), 7.28 (d, J = 8 Hz, 2 H, H-2/H-6), 5.0-4.85 (br, 1 H, NH), 4.40 (d, J = 6 Hz, 2 H, CH_2), 2.93 (s, 6H, NMe_2).

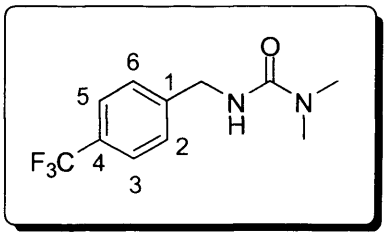
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C=O), 138.4 (s, C-1), 132.9 (s, C-4), 129.0 (d, C-2/C-6), 128.6 (d, C-3/C-5), 44.3 (t, CH_2), 36.3 (q, NMe_2).

EI–MS: *m/z* (%) = 214 (33) [$M^{\bullet+}$ ^{37}Cl], 212 (100) [$M^{\bullet+}$ ^{35}Cl], 133 (12), 72 (25).

HRMS: *m/z* calcd for $C_{10}H_{13}N_2O^{35}Cl$ $[M]^+$, 212.0716; found, 212.0713.

FT–IR: ν_{max} = 3367 (NH), 2930 (CH), 1644 (C=O), 1522 (aromatic C=C), 1491, 1372, 1215, 1092 cm^{-1}.

_N'_-(4-Trifluoromethylbenzyl)-_N,N_-dimethylurea (2.39)



Yield: 6.50 g (26.4 mmol, 66%).

Mp: 143-145 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58 (m, 2 H, H-3/H-5), 7.40 (m, 2 H, H-2/H-6), 5.03 (br, 1 H, NH), 4.43 (d, J=6 Hz, 2 H, CH_2), 2.92 (s, 6 H, NMe_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ= 158.3 (s, C=O), 144.1 (s, C-1), 129.3 (q, $^2J_{C-F}$ = 32 Hz, C-4), 127.7 (d, C-2/C-6), 125.4 (q, $^3J_{C-F}$ = 3 Hz, C-3/C-5), 124.2 (q, $^1J_{C-F}$ = 272 Hz, CF_3), 44.4 (t, CH_2), 36.2 (q, NMe_2).

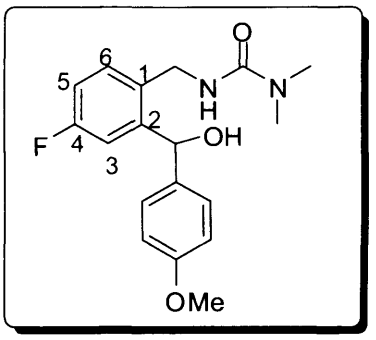
ES–MS: *m/z* (%) = 493 (39) [2M + H^+], 288 (62) [M + $MeCNH^+$], 247 (100) [MH^+].

HRMS: *m/z* calcd for $C_{11}H_{14}N_2OF_3$ [$MH]^+$, 247.1058; found, 247.1046.

2.4.6 Synthesis of 2.40-2.47 *via* directed lithiation of *N'*-(4-fluorobenzyl)-*N,N*-dimethylurea (2.36), *N'*-(4-chlorobenzyl)-*N,N*-dimethylurea (2.38) and *N'*-(4-trifluoromethylbenzyl)-*N,N*-dimethylurea (2.39)

The procedure was identical with that described in Section 2.4.3 except that the appropriate *N'*-(substituted benzyl)-*N,N*-dimethylurea was used. The reaction was worked-up as usual and the residues obtained were purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure products **2.40-2.47**. The yields obtained are reported in Table 2.5.

N'-(4-Fluoro-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)-*N,N*-dimethylurea (2.40)



Yield: 0.55 g (1.65 mmol, 83%).

Mp: 197–199 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.20-7.10 (m, 3 H, H-3, H-5 and H-6), 7.10 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.05 (app. t, J = 6 Hz, exch., 1 H, NH), 6.85 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.65 (s, exch., 1 H, OH), 5.91 (s, 1 H, CH), 4.29 (dd, J = 6, 16 Hz, 1 H, CH_aH$_b$), 3.95 (dd, J = 6, 16 Hz, 1 H, CH$_a$$H_b$), 3.72 (s, 3 H, OCH_3), 2.80 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.6 (d, $^1J_{C\text{-}F}$ = 241 Hz, C-4), 158.8 (C=O), 158.5 (C-4 of 4-methoxyphenyl), 145.7 (d, $^4J_{C\text{-}F}$ = 3 Hz, C-1), 136.3 (C-1 of 4-methoxyphenyl), 133.8 (d, $^3J_{C\text{-}F}$ = 7 Hz, C-2), 129.8 (d, $^3J_{C\text{-}F}$ = 7 Hz, C-6), 128.8 (C-2/C-6 of 4-methoxyphenyl), 114.0 (C-3/C-5 of 4-methoxyphenyl), 113.5 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-3), 113.2 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-5), 70.3 (CH), 55.5 (OCH_3), 40.2 (CH_2), 36.3 [$N(CH_3)_2$].

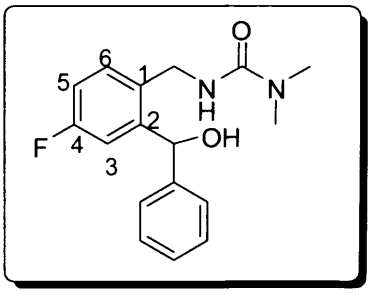
ES-MS: *m/z* (%) = 333 (33) [MH^+], 315 (100) [$MH^+ - H_2O$], 227 (15).

HRMS: *m/z* calcd for $C_{18}H_{22}N_2O_3F$ [MH]$^+$: 333.1614; found: 333.1601.

FT–IR: ν_{max} = 3314 (NH and OH), 2976 (CH), 1637 (C=O), 1518 (aromatic C=C), 1437, 1302, 1209, 1027 cm^{-1}.

Anal. Calc. For $C_{18}H_{21}N_2O_3F$: C, 65.05; H, 6.37; N, 8.43. Found: C, 65.19; H, 6.42; N, 8.45.

_N'_-(4-Fluoro-2-(hydroxyphenylmethyl)benzyl)-_N,N_-dimethylurea (2.41)



Yield: 0.50 g (1.65 mmol, 83%).

Mp: 165–167 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.38-7.21 (m, 7 H, Ph, H-5 and H-6), 7.05 (m, 1 H, H-3), 6.7 (app. t, J = 6 Hz, exch., 1 H, NH), 6.05 (d, J = 4 Hz, exch., 1 H, OH), 6.0 (d, J = 4 Hz, 1 H, CH), 4.30 (dd, J = 6, 14 Hz, 1 H, CH_aH$_b$), 4.05 (dd, J = 6, 14 Hz, 1 H, CH$_a$$H_b$), 2.80 [s, 6 H, N(CH$_3$)$_2$].

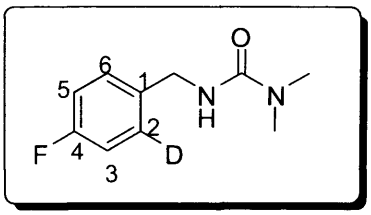
^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.6 (d, $^1J_{C\text{-}F}$ = 247 Hz, C-4), 158.5 (C=O), 145.4 (d, $^4J_{C\text{-}F}$ = 3 Hz, C-1), 144.3 (C-1 of Ph), 134.0 (d, $^3J_{C\text{-}F}$ = 8 Hz, C-2), 130.0 (d, $^3J_{C\text{-}F}$ = 8 Hz, C-6), 130.0 (C-4 of Ph), 128.6 (C-3/C-5 of Ph), 127.5 (C-2/C-6 of Ph), 113.7 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-3), 113.4 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-5), 70.7 (CH), 40.2 (CH$_2$), 36.3 [N(CH$_3$)$_2$].

AP-MS: *m/z* (%) = 303 (85) [MH$^+$], 285 (100) [MH$^+$ – H$_2$O], 197 (13).

HRMS: *m/z* calcd for C$_{17}$H$_{20}$N$_2$O$_2$F [MH]$^+$: 303.1509; found: 303.1497.

FT–IR: ν_{max} = 3434 (NH and OH), 2929 (CH), 1630 (C=O), 1573 (aromatic C=C), 1437, 1283, 1057 cm^{-1}.

_N'_-(2-Deuterio-4-fluorobenzyl)-_N,N_-dimethylurea (2.42)



Yield: 0.34 g (1.72 mmol, 86%).

Mp: 112–114 °C (Mp of undeuteriated analogue 112–114 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18 (m, 1 H, H-6), 6.90-6.85 (m, 2 H, H-3 and H-5), 5.05 (s, exch., 1 H, NH), 4.25 (d, J = 6 Hz, 2 H, CH_2), 2.80 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.9 (d, $^1J_{C\text{-}F}$ = 246 Hz, C-4), 158.4 (C=O), 135.7 (q, $^4J_{C\text{-}F}$ = 3 Hz, C-1), 129.1 (d, $^3J_{C\text{-}F}$ = 8 Hz, C-6), 128.8 (seen as six lines because of coupling to F and D, J = 8, 24 Hz, C-2), 115.2 (d, $^2J_{C\text{-}F}$ = 12 Hz, C-3), 115.0 (d, $^2J_{C\text{-}F}$ = 12 Hz, C-5), 44.1 (CH_2), 36.2 [$N(CH_3)_2$].

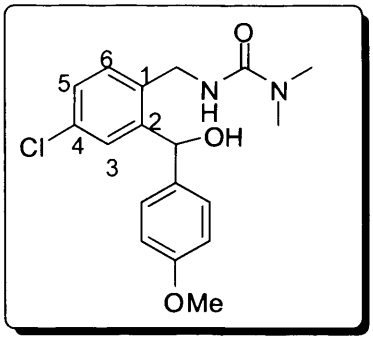
AP-MS: *m/z* (%) = 395 (63) [2 M + H^+], 261 (10) [M + $MeCNNa^+$], 239 (17) [M + $MeCNH^+$], 198 (100) [MH^+].

HRMS: *m/z* calcd for $C_{10}H_{13}DN_2OF$ $[MH]^+$: 198.1153; found: 198.1147.

FT–IR: ν_{max} = 3387 (NH), 2962 (CH), 1598 (C=O), 1489 (aromatic C=C), 1443, 1261, 1097 cm^{-1}.

_N'_-(4-Chloro-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)-_N,N_-dimethylurea

(2.43)



Yield: 0.55 g (1.58 mmol, 79%).

Mp: 186–188 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.50 (s, 1 H, H-3), 7.30 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.25 (d, J = 8 Hz, 1 H, H-5), 7.22 (d, J = 8 Hz, 1 H, H-6), 6.90 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.65 (app. t, J = 6 Hz, exch., 1 H, NH), 5.95 (s, exch., 1 H, OH), 5.90 (s, 1 H, CH), 4.30 (dd, J = 6, 14 Hz, 1 H, CH_aH$_b$), 4.00 (dd, J = 6, 14 Hz, 1 H, CH$_a$$H_b$), 3.75 (s, 3 H, OCH_3), 2.80 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.8 (C=O), 158.5 (C-4 of 4-methoxyphenyl), 145.3 (C-1), 137.0 (C-1 of 4-methoxyphenyl), 136.3 (C-2), 131.5 (C-4), 129.8 (C-5), 128.6 (C-2/C-6 of 4-methoxyphenyl), 126.7 (C-3), 126.5 (C-6), 113.8 (C-3/C-5 of 4-methoxyphenyl), 70.4 (CH), 55.3 (OCH_3), 36.1 (CH_2), 29.5 [$N(CH_3)_2$].

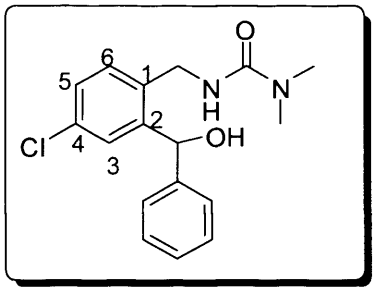
EI-MS: *m/z* (%) = 351 (3) [MH^+ ^{37}Cl], 349 (10) [MH^+ ^{35}Cl], 333 (33), (100), 287 (3), 245 (3), 243 (3).

HRMS: *m/z* calcd for $C_{18}H_{22}N_2O_3{}^{35}Cl$ $[MH]^+$: 349.1319; found: 349.1334.

FT–IR: ν_{max} = 3351 (NH and OH), 2957 (CH), 1632 (C=O), 1544 (aromatic C=C), 1477, 1248, 1172, 1024 cm^{-1}.

Anal. Calc. For $C_{18}H_{21}N_2O_3Cl$: C, 61.98; H, 6.07; N, 8.03. Found: C, 61.99; H, 6.09; N, 7.87.

_N'_-(4-Chloro-2-(hydroxyphenylmethyl)benzyl)-_N,N_-dimethylurea (2.44)



Yield: 0.50 g (1.57 mmol, 79%).

Mp: 190–192 °C.

^{1}H NMR (500MHz, DMSO-d_6): δ = 7.45 (s, 1 H, H-3), 7.35-7.28 (m, 5 H, Ph), 7.22 (d, J = 8 Hz, 1 H, H-5), 7.20 (d, J = 8 Hz, 1 H, H-6), 6.72 (app. t, J = 6 Hz, exch., 1 H, NH), 6.05 (s. exch., 1 H, OH), 5.95 (s, 1 H, CH), 4.30 (dd, J = 6, 14 Hz, 1 H, CH_aH$_b$), 4.05 (dd, J = 6, 14 Hz, 1 H, CH$_a$$H_b$), 2.79 [s, 6 H, N(CH$_3$)$_2$].

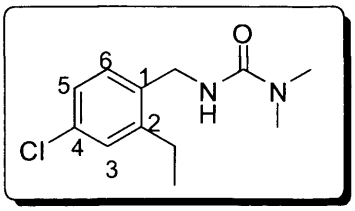
^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.5 (C=O), 145.0 (C-1 of Ph), 144.2 (C-1), 137.1 (C-2), 131.5 (C-4), 129.8 (C-6), 128.6 (C-3/C-5 of Ph), 127.5 (C-2/C-6 of Ph), 127.4 (C-3), 127.0 (C-4 of Ph), 126.7 (C-5), 70.7 (CH), 40.8 (CH$_2$), 36.3 [N(CH$_3$)$_2$].

ES-MS: *m/z* (%) = 300 (38) [M$^{\bullet+}$ – H$_2$O], 214 (15), 227 (100), 152 (70), 117 (20), 72 (98).

HRMS: *m/z* calcd for $C_{17}H_{17}N_2O^{35}Cl$ [M – H$_2$O]$^+$: 300.1029; found: 300.1026.

FT–IR: ν_{max} = 3432 (NH and OH), 2963 (CH), 1658 (C=O), 1564 (aromatic C=C), 1456, 1262, 1152, 1090 cm^{-1}.

_N'_-(4-Chloro-2-ethylbenzyl)-_N,N_-dimethylurea (2.45)



Yield: 0.37 g (1.54 mmol, 77%).

Mp 102–104 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.25 (s, 1 H, H-3), 7.20 (d, J = 8 Hz, 1 H, H-5), 7.18 (d, J = 8 Hz, 1 H, H-6), 6.80 (t, J = 6 Hz, exch., 1 H, NH), 4.22 (d, J = 6 Hz, 2 H, CH_2N), 2.82 [s, 6 H, $N(CH_3)_2$], 2.62 (q, J = 7 Hz, 2 H, CH_2CH_3), 1.15 (t, J = 7 Hz, 3 H, CH_2CH_3).

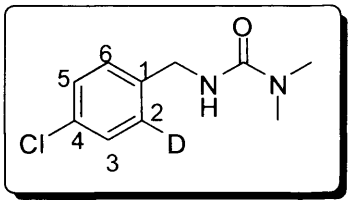
^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.6 (C=O), 144.0 (C-2), 137.8 (C-1), 131.4 (C-4), 129.7 (C-6), 128.0 (C-3), 125.8 (C-5), 40.8 (CH_2NH), 36.4 [$N(CH_3)_2$], 24.9 (CH_2CH_3), 15.1 (CH_2CH_3).

AP-MS: *m/z* (%) = 503 (15) [2 M + Na^+], 304 (100) [^{35}Cl M + $MeCNNa^+$], 306 (33) [^{37}Cl M + $MeCNNa^+$], 279 (10) [M + K^+], 243 (32) [^{37}Cl MH^+], 241 (95) [^{35}Cl MH^+], 153 (10).

HRMS: *m/z* calcd for $C_{12}H_{18}N_2O^{35}Cl$ $[MH]^+$: 241.1108; found: 241.1106.

FT–IR: ν_{max} = 3387 (NH), 2934 (CH), 1633 (C=O), 1571 (aromatic C=C), 1443, 1361, 1171, 1045 cm^{-1}.

_N'_-(4-Chloro-2-deuteriobenzyl)-_N,N_-dimethylurea (2.46)



Yield: 0.38 g (1.78 mmol, 89%).

Mp 133-135 °C (Mp of undeuteriated analogue 133-135 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8 Hz, 1 H, H-5), 7.20 (s, 1 H, H-3), 7.17 (d, *J* = 8 Hz, 1 H, H-6), 4.92 (br, exch., 1 H, NH), 4.35 (d, *J* = 6 Hz, 2 H, CH_2), 2.90 [s, 6 H, $N(CH_3)_2$].

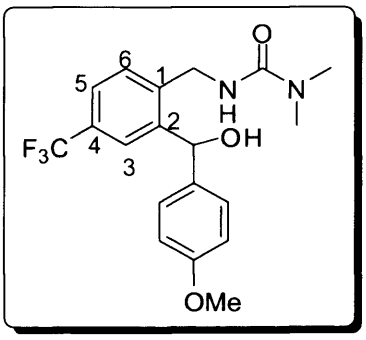
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (C=O), 138.4 (C-1), 132.8 (C-4), 128.9 (seen as three lines, 1:1:1, because of coupling to D, C-2), 128.7 (C-3), 128.6 (C-5), 128.5 (C-6), 44.2 (CH_2), 36.2 [$N(CH_3)_2$].

AP-MS: *m/z* (%) = 216 (33) [MH^+ ^{37}Cl], 214 (100) [MH^+ ^{35}Cl], 124 (15).

HRMS: *m/z* calcd for $C_{10}H_{13}DN_2O^{35}Cl$ $[MH]^+$: 241.0857; found: 214.0851.

FT–IR: ν_{max} = 3395 (NH), 2958 (CH), 1598 (C=O), 1572 (aromatic C=C), 1496, 1444, 1260, 1091 cm^{-1}.

_N'_-(4-Trifluoromethyl-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)-_N,N_-dimethylurea (2.47)



Yield: 0.63 g (1.65 mmol, 83%).

Mp: 188-190 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.85 (s, 1 H, H-3), 7.60 (d, *J* = 8 Hz, 1 H, H-5), 7.40 (d, *J* = 8 Hz, 1 H, H-6), 7.20 (d, *J* = 8 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 6.90 (d, *J* = 8 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.80 (t, *J* = 6 Hz, 1 H, NH),

6.05 (s, 1 H, OH), 5.98 (s, 1 H, CH), 4.38 (dd, J = 6, 14 Hz, 1 H, CH_aH_b), 4.00 (dd, J = 6, 14 Hz, 1 H, CH_aH_b), 3.72 (s, 3H, OCH_3), 2.80 (s, 6H, NMe_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.8 (s, C-4 of 4-methoxyphenyl), 158.5 (s, C=O), 144.0 (s, C-1), 142.8 (s, C-1 of 4-methoxyphenyl), 136.0 (s, C-2), 128.8 (d, C-2/C-6 of 4-methoxyphenyl), 128.2 (s, C-6), 127.5 (q, $^2J_{C\text{-}F}$ = 31 Hz, C-4), 125.6 (m, CF_3), 123.8 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-3), 122.9 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-5), 114.0 (d, C-3/C-5 of 4-methoxyphenyl), , 70.3 (d, C-OH), 55.5 (q, OCH_3), 46.5 (t, CH_2), 36.3 (q, NMe_2).

ES–MS: *m/z* (%) = 446 (100) [M + $MeCNNa^+$], 365 (20) [$MH^+ - H_2O$], 187 (17), 105 (15).

HRMS: *m/z* calcd for $C_{19}H_{20}N_2O_2F_3$ [$MH - H_2O$]$^+$, 365.1477; found, 365.1489.

2.5 References

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CHAPTER THREE

SYNTHESIS OF SUBSTITUTED ISOINDOLINES

CHAPTER THREE

SYNTHESIS OF SUBSTITUTED ISOINDOLINES

3.1 Introduction

Isoindole derivatives have been reported in natural products and synthetic pharmaceuticals.[1-3] The methods commonly used to synthesize these compounds involve condensation of 1,4-dicarbonyl compounds and amines, reaction of *o*-phthaldehyde with potassium cyanide and methylamine hydrochloride, cyclization of α-enamino acids and Diels–Alder reactions.[4-10] However, such methods often involve several steps and/or produce low yields. The lithiation of tertiary amides followed by a dearomatising cyclisation reaction to give dihydroisoindolones has been reported by Clayden, who has used such an approach to produce some natural products such as kainic acid.[11-15] Very recently, Smith's research group reported the successful synthesis of a range of substituted isoindolines (both substituted in the benzene and the pyrrolidine rings) *via* cyclization of hydroxyalkyl-substituted benzylamines on treatment with TFAA.[16] The reaction proved to be simple and high yielding, but had been applied to only a limited number of examples.[16] It was of interest to test the possibility of extending the range by cyclising the compounds of general formula **3.2**, which were prepared from **3.1** as reported in Chapter 2, to the corresponding isoindolines of the general formula **3.3** (Figure 3.1).

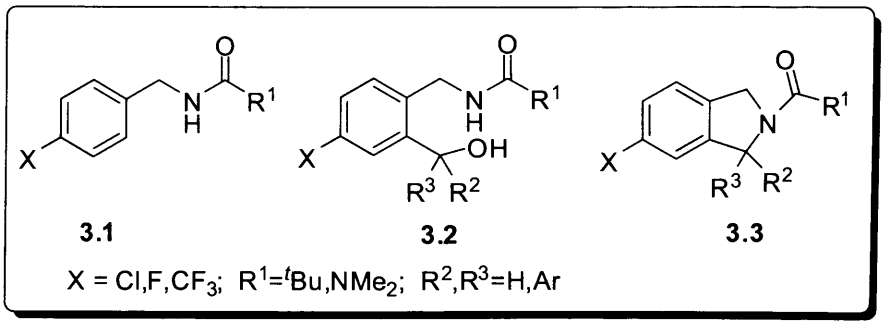
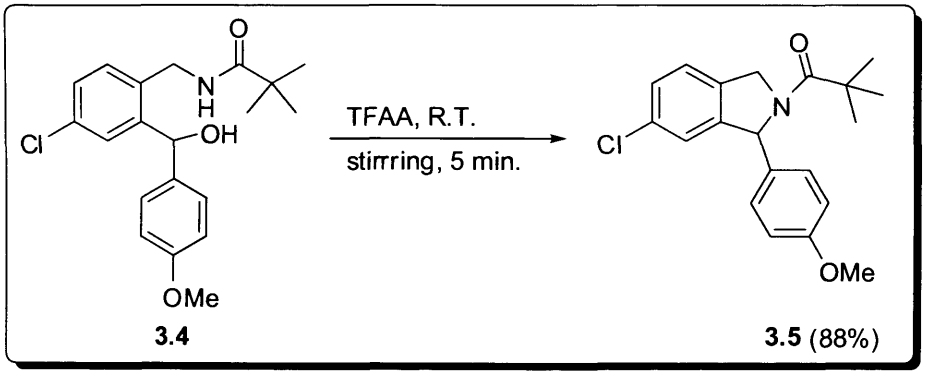


Figure 3.1

The aim of the work presented in this chapter was therefore to investigate if cyclization of **3.2** could be achieved by treatment with TFAA in DCM at room temperature.

3.2 Synthesis of 6-chloro-1-(4-methoxyphenyl)-2-pivaloylisoindoline 3.5

As a test, compound **3.4** was dissolved in DCM at room temperature and few drops of trifluoroacetic anhydride (TFAA) were added (Scheme 3.1). The mixture was stirred and examined by TLC and showed the formation of a new product. The reaction was complete within 5 minutes, at which time no starting material was left. The mixture was quenched by the addition of water and worked up. The residue obtained was subjected to flash column chromatography (silica gel; Et_2O-hexane, 1:2) to give the pure product as colourless crystals. The product was identified as **3.5** and was obtained in 88% yield.



Scheme 3.1

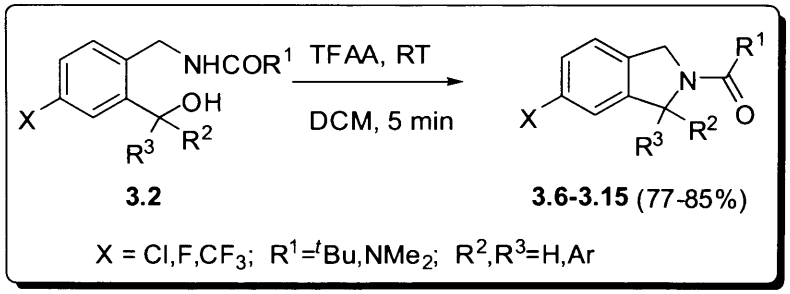
The structure of compound **3.5** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry. In the ^{1}H NMR spectrum of compound **3.5** there were no exchangeable hydrogens. Also, NMR showed all appropriate hydrogen and carbon resonances. The EI-mass spectrum of compound **3.5** showed molecular ion peaks at *m/z* = 345 and 343 due to $M^{\bullet+}$ (^{37}Cl) and $M^{\bullet+}$ (^{35}Cl). The accurate mass of the molecular ion peak at *m/z* = 343 confirmed the formula as $C_{20}H_{22}{}^{35}ClNO_2$, indicating the loss of 18 from the molecular weight of the starting material **3.4**. The IR spectrum

of compound **3.5** showed no absorption band corresponding to stretching vibrations of the NH or OH group. Clearly, cyclization of **3.5** *via* dehydration had taken place.

The ^{1}H NMR spectra of compound **3.5** also showed diastereotopicity for the two hydrogens of the CH_2 group at position 3 of the isoindoline ring. Compound **3.5** was obviously a racemic mixture, since no chiral reagents were used in its production.

3.3 Synthesis of substituted isoindolines 3.6-3.15

Having, produced compound **3.5** successfully, we attempted cyclization of other compounds of the general formula **3.2** with TFAA at room temperature in DCM (Scheme 3.2). The reaction mixtures were examined by TLC and when the TLC showed that the starting material had disappeared they were quenched by the addition of water. The crude products were subjected to flash column chromatography (silica gel; Et_2O-hexane, 1:2) to give the corresponding isoindolines **3.6-3.15** (Scheme 3.2) in good yields (Table 3.1). The products were all characterized by standard spectroscopic methods (Section 3.7).



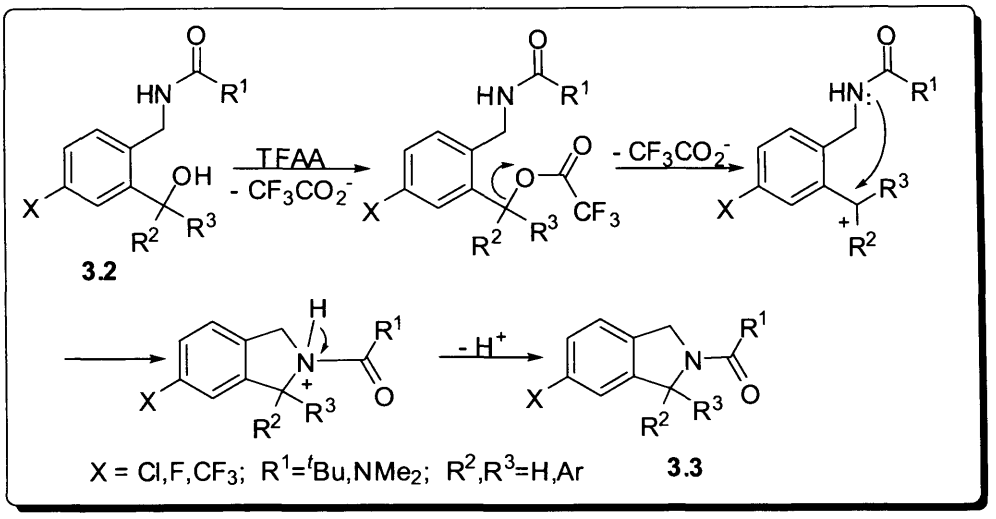
Scheme 3.2

Table 3.1: Synthesis of 1-substituted *N*- substituted lisoindolines according to Scheme 3.2

Product	X	R^1	R^2	R^3	Yield (%)[a]
3.6	Cl	^{t}Bu	Ph	Ph	77
3.7	F	^{t}Bu	H	4-$MeOC_6H_4$	83
3.8	F	^{t}Bu	Ph	Ph	83
3.9	Cl	NMe_2	H	4-$MeOC_6H_4$	77
3.10	Cl	NMe_2	H	Ph	77
3.11	F	NMe_2	H	4-$MeOC_6H_4$	83
3.12	F	NMe_2	H	Ph	85
3.13	CF_3	^{t}Bu	H	4-$MeOC_6H_4$	85
3.14	CF_3	^{t}Bu	Ph	Ph	81
3.15	CF_3	NMe_2	H	4-$MeOC_6H_4$	85

[a] Yield of isolated product after purification by column chromatography.

From the results in Table 3.1, it is clear that the cyclization is a general process, producing various substituted isoindolines in good yields. The ^{1}H NMR spectra of compounds **3.7, 3.9-3.13** and **3.15** all showed the expected diastereotopicity for the two hydrogens of the CH_2 group at position 3 of the isoindoline ring. A possible mechanism for the formation of compounds of the general formula **3.3** is shown in Scheme 3.3.



Scheme 3.3

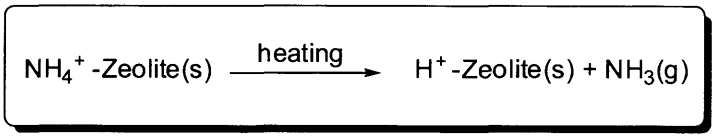
3.4 Synthesis of substituted isoindolines involving use of acidic solid catalysts

The use of traditional reagents such as mineral acids or strong bases has many disadvantages including handling difficulties and the formation of large volumes of toxic waste. These problems can often be overcome by use of alternative catalysts, which are environmentally friendly. Thus, alumina, silica, clays, synclysts and zeolites have been shown to have many useful applications in organic reactions. The important physical properties of these materials are that they often have very large surface areas, that they are usually stable to quite high temperatures, and that they are typically activated (for example by calcination) before use. It was of interest to see whether solid acid catalysts could bring about the same kinds of cyclisations that had been successful with TFAA.

Aluminosilicate zeolites can be classified according to their cage and pore structures into small (*e.g.* zeolite A), medium (*e.g.* zeolite ZSM-5) and large (*e.g.* zeolite β) pore zeolites. The structural units of zeolites are $[SiO_4]^{4-}$ and $[AlO_4]^{5-}$ tetrahedra (T) that are linked together through oxygen atoms to form a three-dimensional network. The active Brønsted sites in zeolites can be increased by first replacing the sodium cation of a zeolite by an ammonium cation by treatment with an

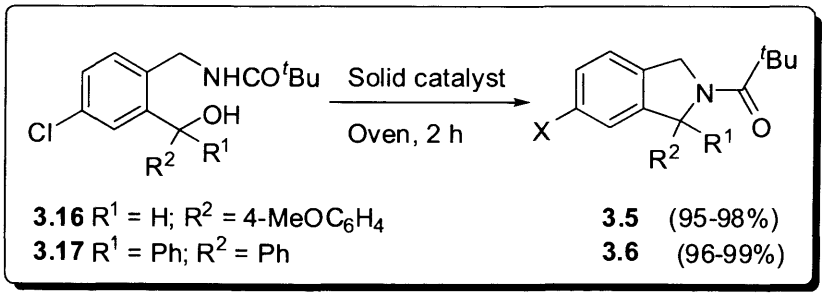
ammonium salt and then heating the NH_4^+ zeolite, during which loss of NH_3 takes place to leave the H^+ zeolite (Scheme 3.4).[17,18] The protons are attached to oxygen atoms of the aluminosilicate framework and during calcination of the zeolite (*e.g.* heating it to a high temperature in air) water is removed and converts some of the Brønsted acid sites into Lewis acid centres.

We decided to investigate the cyclisation of two substrates, **3.16** and **3.17**, with a large pore zeolite (zeolite β), a fairly strongly acidic amorphous catalyst (Synclyst), and a weakly acidic solid catalyst (silica).



Scheme 3.4

Compounds **3.16** and **3.17** were ground together with the selected acidic solid catalysts at room temperature and then heated to 100 °C in a vacuum oven for 2 h. In each case work-up of the reaction mixture by extraction of the product from the solid with dichloromethane gave the cyclised product (**3.5** or **3.6**, respectively, Scheme 3.5) in excellent yield (Table 3.2).



Scheme 3.5

Table 3.2 Yields of **3.5** and **3.6** using various solid catalysts according to Scheme 3.5

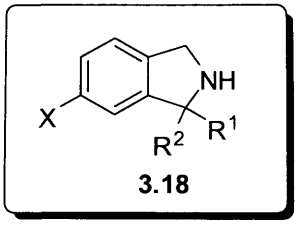
Solid catalyst	S.M[a]	Product	Yield (%)
Zeolite β	3.16	3.5	98
Silica gel	3.16	3.5	95
Synclysts	3.16	3.5	96
Zeolite β	3.17	3.6	99
Silica gel	3.17	3.6	96
Synclysts	3.17	3.6	98

[a] Starting material used according to Scheme 3.5

The products were found to be identical in all respects with the ones produced according to Schemes 3.1 and 3.2 using TFAA. As can be seen from Table 3.2 the yields were high with all of the acidic solids. Therefore either of the two methods can be used for synthesis of such compounds. However the method involving use of solid catalysts gave better yields, involved an easier work-up and utilised a catalyst rather than consuming TFAA as a reagent.

3.5 Attempted synthesis of *N*-unsubstituted 1-substituted isoindolines

In order to render the synthetic approach described in Sections 3.2 and 3.3 even more valuable, it would be useful if the pivaloyl group in compounds of the general formula **3.3** (R^1 = ^{t}Bu; Figure 3.1) could be removed to reveal a free NH without the isoindole ring system itself being damaged. We therefore decided to attempt to remove the pivaloyl group in compounds **3.6** to provide products of the general formula **3.18** (Figure 3.2).



3.18

Figure 3.2

Using compound **3.6** as the model, the compound was treated with a few drops of trifluoroacetic acid at room temperature in DCM for 2 h. The reaction mixture was quenched with water then worked–up. Following work-up, the reaction mixture was subjected to TLC, which showed that no new product was present. The quantitative recovery of **3.6** indicated that no reaction took place under the conditions tried. Therefore, we decided to carry out the reaction of **3.6** with trifluoroacetic acid in DCM under reflux conditions for 20 minutes, at which time TLC indicated the presence of a complex mixture of products. Purification of the product mixture by column chromatography on silica gel proved to be difficult and no pure products were separated. No further attempts were made to try to find conditions under which removal of the pivaloyl group from compound **3.6** could be successful.

In order to see whether the dimethylaminocarbonyl group in compound **3.11** could be hydrolyzed, it was treated with few drops of TFAA at room temperature in DCM for 2 h. The reaction mixture was quenched with water and the reaction mixture was subjected to TLC, which showed that no new product was present. The quantitative recovery of **3.11** indicated that again no reaction took place under the conditions tried. Therefore, the reaction was carried out under reflux conditions for 2 h, but again, TLC and NMR indicated the presence of mainly starting material in the reaction mixture. No further attempts were made to try to find conditions under which removal of the dimethylaminocarbonyl group from compound **3.11** could be successful.

3.6 Conclusion

Dehydration of various substituted benzylamines with trifluoroacetic anhydride gave the corresponding isoindolines in excellent yields. The process was general, simple and convenient for the compounds tried. This work has been published.[19] An alternative approach involved heating the products with a solid acid catalyst, which gave high yields and a convenient work-up for the two cases tried.

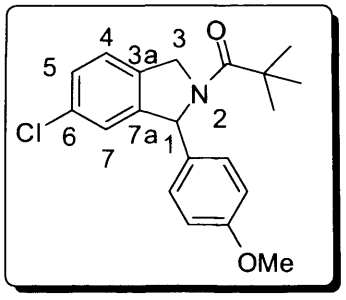
3.7 Experimental

3.7.1 General experimental

See Chapter 2; Section 2.4.1

3.7.2 Synthesis of 6-chloro-1-(4-methoxyphenyl)-2-pivaloylisoindoline (3.5) *via* cyclization of *N*-(4-chloro-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)pivalamide (3.4)

Trifluoroacetic anhydride (0.5 mL) was added to a stirred solution of *N*-(4-chloro-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)pivalamide (**3.4**; 0.48 g, 1.34 mmol) in DCM (10 mL) at room temperature. The mixture was stirred for 5 min at room temperature, after which TLC showed the formation of a pure product. The reaction mixture was quenched with H_2O (10 mL). The organic layer was separated, washed with aq. sat. $NaHCO_3$ (10 mL), H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure **3.5** (0.42 g, 1.22 mmol, 88%) as a white solid.



Yield: 0.42 g (1.22 mmol, 88%).

Mp: 137–139 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (s, 1 H, H-7), 7.20 (d, J = 8 Hz, 1 H, H-5), 7.10 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.0 (d, J = 8 Hz, 1 H, H-4), 6.75 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.20 (s, 1 H, H-1), 5.14-5.10 (m, 2 H, H-3a and H-3b), 3.70 (s, 3 H, OCH_3), 1.25 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 162.7 (s, C-4 of 4-methoxyphenyl), 159.0 (s, C-7a), 142.1 (s, C-3a), 134.1 (s, C-1 of 4-methoxyphenyl), 133.7 (s, C-6), 128.2 (d, C-2/C-6 of 4-methoxyphenyl), 127.9 (d, C-4), 123.8 (d, C-7), 123.5 (d, C-5), 114.1 (d, C-3/C-5 of 4-methoxyphenyl), 68.9 (d, C-1), 55.2 (q, OCH_3), 53.3 (t, C-3), 39.5 [s, $C(CH_3)_3$], 27.3 [q, $C(CH_3)_3$].

EI-MS: *m/z* (%) = 345 (22) [$M^{\bullet+}$ ^{37}Cl], 343 (67) [$M^{\bullet+}$ ^{35}Cl], 312 (28), 286 (100), 258 (29), 243 (45), 208 (50), 165 (18), 116 (16), 57 (40).

HRMS: *m/z* calcd. for $C_{20}H_{22}NO_2{}^{35}Cl$ $[M]^+$ 343.1339; found 343.1340.

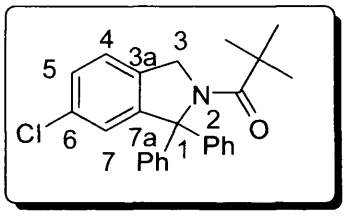
IR (FT): ν = 2921 (CH), 1635 (C=O), 1460, 1383, 1260, 1154, 1106 cm^{-1}.

3.7.3 Synthesis of substituted isoindolines 3.6-3.15

The procedure was identical to that described in Section 3.7.2 except that compounds of the general formula **3.2** (0.48 g) were used as starting materials instead of **3.4**. The reaction mixture was worked-up as described in Section 3.7.2 and the

residue obtained subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure products **3.6-3.15**.

6-Chloro-1,1-diphenyl-2-pivaloylisoindoline (3.6)



Yield: 0.37 g (0.95 mmol, 77%).

Mp: 166–168 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24-7.18 (m, 10 H, 2 Ph), 7.15 (s, 1 H, H-7), 7.10 (d, J = 8 Hz, 1 H, H-5), 6.85 (d, J = 8 Hz, 1 H, H-4), 5.14 (s, 2 H, H-3), 1.18 [s, 9H, $C(CH_3)_3$].

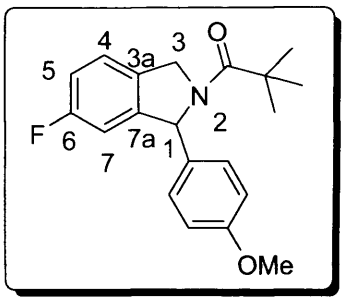
^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.4 (s, C=O), 147.9 (s, C-7a), 142.0 (s, C-1 of 2 Ph), 133.9 (s, C-3a), 133.8 (s, C-6), 128.3 (d, C-3/C-5 of 2 Ph), 128.1 (d, C-4), 127.7 (d, C-2/C-6 of 2 Ph), 126.9 (d, C-4 of 2 Ph), 124.9 (d, C-7), 123.2 (d, C-5), 80.5 (s, C-1), 53.0 (t, C-3), 39.7 [s, $C(CH_3)_3$], 27.6 [q, $C(CH_3)_3$].

ES-MS: *m/z* (%) = 392 (33) [MH^+ ^{37}Cl], 390 (100) [MH^+ ^{35}Cl].

HRMS: *m/z* calcd. for $C_{25}H_{25}NO^{35}Cl$ $[MH]^+$ 390.1625; found 390.1630.

IR (FT): ν = 2921 (CH), 1632 (C=O), 1420, 1310, 1291, 1113, 1023 cm^{-1}.

6-Fluoro-1-(4-methoxyphenyl)-2-pivaloylisoindoline (3.7)



Yield: 0.40 g (1.22 mmol, 83%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (m, 1 H, H-4), 7.09 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl) 6.92 (m, 1 H, H-5), 6.72 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.61 (m, 1 H, H-7), 6.21 (s, 1 H, H-1), 5.12-5.07 (m, 2 H, H-3a and H-3b), 3.70 (s, 3 H, OCH_3), 1.23 [s, 9 H, $C(CH_3)_3$].

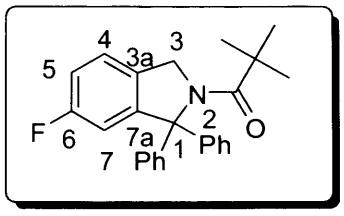
^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.6 (s, C=O), 162.8 (d, $^1J_{C\text{-}F}$ = 247 Hz, C-6), 158.9 (s, C-4 of 4-methoxyphenyl), 142.7 (s, C-7a), 134.5 (s, C-3a), 130.9 (s, C-1 of 4-methoxyphenyl), 127.9 (d, C-2/C-6 of 4-methoxyphenyl), 123.7 (d, $^3J_{C\text{-}F}$ = 9 Hz, C-4), 115.3 (d, $^2J_{C\text{-}F}$ = 23 Hz, C-7), 114.1 (d, C-3/C-5 of 4-methoxyphenyl), 110.6 (d, $^2J_{C\text{-}F}$ = 23 Hz, C-5), 69.0 (d, C-1), 55.2 (q, CH_3), 53.1 (t, C-3), 39.4 [s, $C(CH_3)_3$], 27.4 [q, $C(CH_3)_3$].

ES-MS: *m/z* (%) = 328 (100) [MH^+] 146 (12), 130 (8).

HRMS: *m/z* calcd. for $C_{20}H_{23}NO_2F$ $[MH]^+$ 328.1713; found 328.1709.

IR (FT): ν = 2963 (CH), 1722 (C=O), 1440, 1311, 1199, 1161, 1011 cm^{-1}.

6-Fluoro-1,1-diphenyl-2-pivaloylisoindoline (3.8)



Yield: 0.40 g (1.07 mmol, 83%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20-7.09 (m, 11 H, 2 Ph and H-7), 6.85 (m, 1 H, H-4), 6.58 (m, 1 H, H-5), 5.18 (s, 2 H, H-3), 1.20 [s, 9 H, $C(CH_3)_3$].

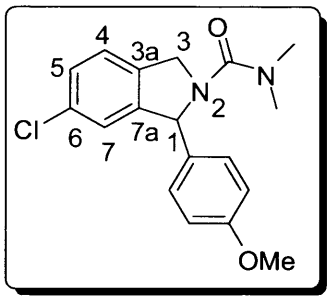
^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.1 (s, C=O), 163.4 (d, $^1J_{C\text{-}F}$ = 245 Hz, C-6), 147.6 (s, C-7a), 141.1 (s, C-1 of 2 Ph), 129.8 (s, C-3a), 128.2 (d, C-3/C-5 of 2 Ph), 127.9 (d, C-2/C-6 of 2 Ph), 127.3 (s, C-4 of 2 Ph), 123.3 (d, $^3J_{C\text{-}F}$ = 9 Hz, C-4), 115.6 (d, $^2J_{C\text{-}F}$ = 23 Hz, C-7), 111.7 (d, $^2J_{C\text{-}F}$ = 23 Hz, C-5), 81.5 (d, C-1), 53.2 (t, C-3), 40.1 [s, $C(CH_3)_3$], 27.2 [q, $C(CH_3)_3$].

ES-MS: *m/z* (%) = 374 (100) [MH^+], 273 (6).

HRMS: *m/z* calcd. for $C_{25}H_{25}NOF$ $[MH]^+$ 374.1920; found 374.1914.

IR (FT): ν = 2931 (CH), 1612 (C=O), 1496, 1454, 1411, 1289, 1072 cm^{-1}.

6-Chloro-2-dimethylaminocarbonyl-1-(4-methoxyphenyl)isoindoline (3.9)



Yield: 0.37 g (1.12 mmol, 77%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (s, 1 H, H-7), 7.20 (d, J = 8 Hz, 1 H, H-5), 7.10 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 6.90 (d, J = 8 Hz, 1 H, H-4), 6.75 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.25 (d, J = 3 Hz, 1 H, H-1), 4.95 (dd, J = 3, 14 Hz, 1 H, H-3a), 4.50 (d, J = 14 Hz, 1 H, H-3b), 3.65 (s, 3 H, OCH_3), 2.75 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8 (s, C=O), 159.1 (s, C-4 of 4-methoxyphenyl), 143.8 (s, C-7a), 135.1 (s, C-3a), 134.7 (s, C-6), 133.4 (s, C-1 of 4-methoxyphenyl) 128.3 (d, C-2/C-6 of 4-methoxyphenyl), 127.8 (d, C-4), 123.8 (d, C-7), 123.3 (d, C-5),

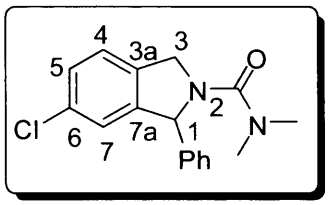
114.0 (d, C-3/C-5 of 4-methoxyphenyl), 67.2 (d, C-1), 55.2 (q, OCH_3), 54.6 (t, C-3), 38.3 [q, $N(CH_3)_2$].

APCI-MS: *m/z* (%) = 333 (33) [MH^+ ^{37}Cl], 331 (100) [MH^+ ^{35}Cl], 243 (10), 223 (22).

HRMS: *m/z* calcd. for $C_{18}H_{20}N_2O_2{}^{35}Cl$ $[MH]^+$ 331.1213; found 331.1215.

IR (FT): ν = 2963 (CH), 1644 (C=O), 1485, 1438, 1261, 1098 cm-^{1}.

6-Chloro-2-dimethylaminocarbonyl-1-phenylisoindoline (3.10)



Yield: 0.37 g (1.23 mmol, 77%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (s, 1 H, H-7), 7.20-7.10 (m, 5 H, Ph), 7.09 (d, *J* = 8 Hz, 1 H, H-5), 6.90 (d, *J* = 8 Hz, 1 H, H-4), 6.25 (d, *J* = 3 Hz, 1 H, H-1), 4.95 (dd, *J* = 3, 14 Hz, 1 H, H-3a), 4.53 (d, *J* = 14 Hz, 1 H, H-3b), 2.80 [s, 6 H, $N(CH_3)_2$].

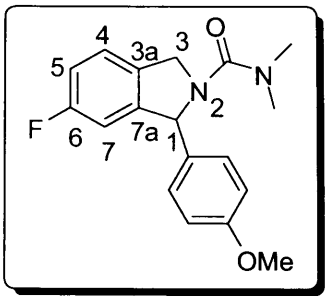
^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8 (s, C=O), 143.5 (s, C-7a), 142.8 (s, C-3a), 134.6 (s, C-1 of Ph), 133.5 (s, C-6), 128.7 (d, C-3/C-5 of Ph), 127.9 (d, C-4), 127.7 (d, C-7), 127.0 (d, C-2/C-6 of Ph), 123.7 (d, C-5), 123.4 (d, C-4 of Ph), 67.8 (d, C-1), 54.9 (t, C-3), 38.3 [q, $N(CH_3)_2$].

APCI-MS: *m/z* (%) = 303 (33) [MH^+ ^{37}Cl], 301 (100) [MH^+ ^{37}Cl], 256 (10), 213 (13).

HRMS: *m/z* calcd. for $C_{17}H_{18}N_2O^{35}Cl$ $[MH]^+$ 301.1108; found 301.1096.

IR (FT): ν = 2971 (CH), 1698 (C=O), 1540, 1466, 1427, 1368, 1156, 1087 cm^{-1}.

2-Dimethylaminocarbonyl-6-fluoro-1-(4-methoxyphenyl)isoindoline (3.11)



Yield: 0.40 g (1.27 mmol, 83%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.15 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.10 (m, 1 H, H-4), 6.90 (m, 1 H, H-5), 6.75 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.60 (m, 1 H, H-7), 6.28 (s, 1 H, H-1), 4.92 (d, J = 13 Hz, 1 H, H-3a), 4.50 (d, J = 13 Hz, 1 H, H-3b), 3.70 (s, 3 H, OCH_3), 2.80 [s, 6 H, $N(CH_3)_2$].

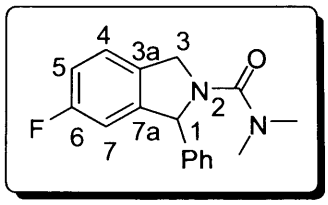
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.7 (s, C=O), 162.3 (d, $^1J_{C\text{-}F}$ = 247 Hz, C-6), 159.1 (s, C-4 of 4-methoxyphenyl), 143.9 (s, C-7a), 135.2 (s, C-3a), 131.6 (s, C-1 of 4-methoxyphenyl), 128.3 (d, C-2/C-6 of 4-methoxyphenyl), 123.4 (d, $^3J_{C\text{-}F}$ = 8 Hz, C-4), 114.9 (d, $^2J_{C\text{-}F}$ = 24 Hz, C-7), 114.0 (d, C-3/C-5 of 4-methoxyphenyl), 110.5 (d, $^2J_{C\text{-}F}$ = 24 Hz, C-5), 67.4 (d, C-1), 55.2 (q, CH_3), 54.5 (t, C-3), 38.3 [q, $N(CH_3)_2$].

ES-MS: *m/z* (%) = 315 (100) [MH^+], 146 (15), 130 (8).

HRMS: *m/z* calcd. for $C_{18}H_{20}N_2O_2F$ $[MH]^+$ 315.1509; found 315.1501.

IR (FT): ν = 2960 (CH), 1639 (C=O), 1465, 1423, 1367, 1321, 1251, 1133, 1072 cm^{-1}.

2-Dimethylaminocarbonyl-6-fluoro-1-phenylisoindoline (3.12)



Yield: 0.41 g (1.44 mmol, 85%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25-7.10 (m, 6 H, Ph, H-7), 6.85 (m, 1 H, H-4), 6.63 (m, 1 H, H-5), 6.30 (s, 1 H, H-1), 5.00 (d, J = 13 Hz, 1 H, H-3a), 4.55 (d, J = 13 Hz, 1 H, H-3b), 2.82 [s, 6 H, $N(CH_3)_2$].

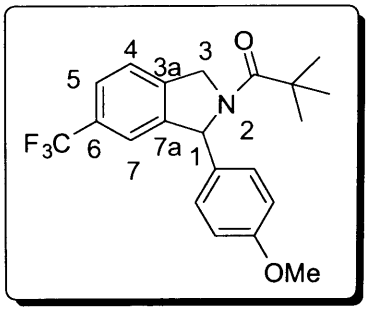
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.7 (s, C=O), 162.5 (d, $^1J_{C\text{-}F}$ = 246 Hz, C-6), 143.2 (s, C-7a), 142.4 (s, C-1 of Ph), 131.2 (s, C-3a), 129.0 (d, C-3/C-5 of Ph), 127.9 (d, C-4 of Ph), 126.9 (d, C-2/C-6 of Ph), 123.5 (d, $^3J_{C\text{-}F}$ = 9 Hz, C-4), 115.2 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-7), 110.6 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-5), 68.2 (d, C-1), 54.8 (t, C-3), 38.5 [q, $N(CH_3)_2$].

ES-MS: *m/z* (%) = 285 (100) [MH^+], 197 (8).

HRMS: *m/z* calcd. for $C_{17}H_{18}N_2OF$ $[MH]^+$ 285.1403; found 285.1392.

IR (FT): ν = 2951 (CH), 1632 (C=O), 1586, 1517, 1486, 1376, 1285, 1178, 1038 cm^{-1}.

6-Trifluoromethyl-1-(4-methoxyphenyl)-2-pivaloylisoindoline (3.13)



Yield: 0.41 g (1.09 mmol, 85%).

Oil.

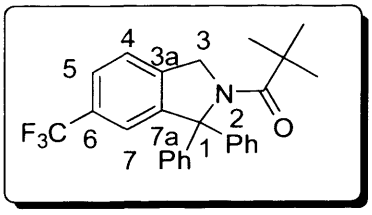
^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.49 (s, 1 H, H-7), 7.35 (d, J = 8 Hz, 1 H, H-5), 7.23 (d, J = 8 Hz, 1 H, H-4), 7.09 (d, J = 8 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 6.72 (d, J = 8 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.25 (s, 1 H, H-1), 5.15-5.12 (m, 2 H, H-3a and H-3b), 3.70 (s, 3 H, OCH_3), 1.21[s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.5 (s, C=O), 159.0 (s, C-4 of 4-methoxyphenyl), 142.0 (s, C-3a) 139.8 (s, C-7a), 134.8 (d, C-4), 130.6 (q, $^2J_{C\text{-}F}$ = 33 Hz, C-6), 128.2 (s, C-1 of 4-methoxyphenyl), 127.7 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-7), 124.9 (m, CF_3), 122.9 (d, C-2/C-6 of 4-methoxyphenyl), 120.6 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-5), 114.2 (d, C-3/C-5 of 4-methoxyphenyl), 68.4 (d, C-1), 55.2 (q, OCH_3), 53.4 (s, C-3), 39.4 [s, $C(CH_3)_3$], 27.1 [q, $C(CH_3)_3$].

ES–MS: *m/z* (%) = 378 (100) [MH^+], 353 (19), 337 (17), 290 (45).

HRMS: *m/z* calcd for $C_{21}H_{23}NO_2F_3$ [$MH]^+$, 378.1681; found, 378.1675.

6-Trifluoromethyl-1,1-diphenyl-2-pivaloylisoindoline (3.14)



Yield: 0.39 g (0.92 mmol, 81%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (m, 1 H, H-7), 7.35 (m, 1 H, H-5), 7.28-7.13 (m, 11 H, 2 Ph, H-4), 5.25 (s, 2 H, H-3), 1.22 [s, 9 H, $C(CH_3)_3$].

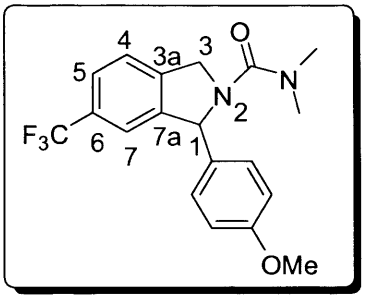
^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.4 (s, C=O), 162.5 (s, C-3a), 146.6 (s, C-7a), 141.2 (s, C-1 of 2 Ph), 138.5 (d, C-4), 131.3 (q, $^2J_{C\text{-}F}$ = 33 Hz, C-6), 128.2 (d, C-3/C-5

of 2 Ph), 127.9 (d, C-2/C-6 of 2 Ph), 127.3 (m, CF_3), 125.0 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-7), 122.5 (d, C-4 of 2 Ph), 121.7 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-5), 81.2 (s, C-1), 53.3 (t, CH_2), 40.0 [s, $C(CH_3)_3$], 27.2 [q, $C(CH_3)_3$].

ES–MS: *m/z* (%) = 424 (100) [MH^+].

HRMS: *m/z* calcd for $C_{26}H_{25}NOF_3$ [$MH]^+$, 424.1888; found, 424.1901.

2-Dimethylaminocarbonyl-6-trifluoromethyl-1-(4-methoxyphenyl)isoindoline (3.15)



Yield: 0.41 g (1.13 mmol, 85%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (s, 1 H, H-7), 7.30 (d, *J* = 8, 1 H, H-5), 7.18 (d, *J* = 8 Hz, 1 H, H-6), 7.11 (d, *J* = 8 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 6.72 (d, *J* = 8 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.30 (s, 1 H, CH), 5.00 (d, *J* = 14 Hz, 1 H, H-3a), 4.60 (d, *J* = 14 Hz, 1 H, H-3b), 3.70 (s, 3 H, OCH_3), 2.80 (s, 6 H, NMe_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8 (s, C=O), 159.2 (s, C-4 of 4-methoxyphenyl), 142.7 (s, C-3a), 140.2 (s, C-7a), 134.8 (d, C-4), 130.4 (q, $^2J_{C\text{-}F}$ = 32 Hz, C-6), 128.3 (d, C-2/C-6 of 4-methoxyphenyl), 124.8 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-7), 123.8 (q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 122.6 (s, C-1 of 4-methoxyphenyl), 120.7 (seen as four lines because of coupling to F, *J* = 4 Hz, C-5), 114.1 (d, C-3/C-5 of 4-methoxyphenyl), 67.3 (d, C-1), 55.2 (q, OCH_3), 54.8 (t, C-3), 38.3 (q, NMe_2).

ES–MS: *m/z* (%) = 365 (100) [MH^+], 146 (10), 105 (5).

HRMS: *m/z* calcd for $C_{19}H_{20}N_2O_2F_3$ $[MH]^+$, 365.1477; found, 365.1461.

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CHAPTER FOUR

INVESTIGATION OF THE LITHIATION OF VARIOUS SUBSTITUTED PYRIDINES

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INVESTIGATION OF THE LITHIATION OF VARIOUS SUBSTITUTED PYRIDINES

4.1 Introduction

Heterocyclic compounds are of great importance to life because such ring structures exist in many products such as vitamins, hormones, antibiotics and alkaloids as well as pharmaceuticals, herbicides, dyes and many more compounds.[1] Regioselective lithiation is an efficient route to these compounds. However metalation of many pyridines is not a practical reaction, largely because the π deficient pyridine ring is attacked on the azomethine bond by alkyllithiums. Some alternatives such as LDA[2-7] and LTMP[8-12] have been used to overcome these nucleophilic attacks. Mixtures of alkyllithium reagents and coordinating ligands, such as diamines (*e.g.* TMED)[13,14] or aminoalchols (*e.g.* DMAE)[15,16] or even metal alkoxides (such mixtures are known as superbases or LiCKOR reagents),[17-21] have been designed to enhance the basicity and prevent the nucleophilicity through the formation of sterically hindered complexes.

The chlorine atom in 2-chloropyridine was known to direct metallation at C-3 with LDA as the basic reagent,[22] while 2-fluoropyridine has been lithiated successfully at C-6 by treatment with *n*-BuLi/LiDMAE.[23] 2,3-Dibromopyridine was subjected to bromine-lithium exchange at 0 °C by using $TMSCH_2Li$/LiDMAE (2:1) in toluene to give 3-bromopyridine.[24]

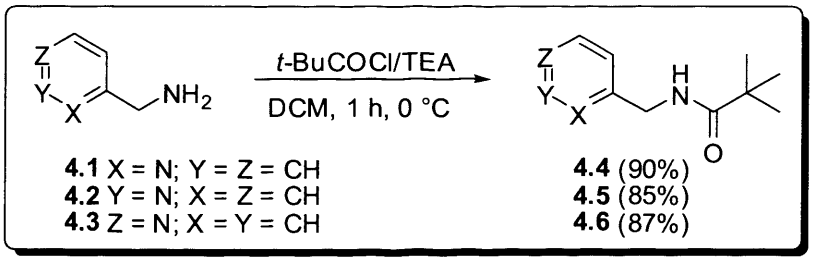
Having successfully lithiated and substituted various *N*-(substituted benzyl)pivalamides and various *N'*-(substituted benzyl)-*N*-*N*-dimethylureas selectivity using *t*-BuLi at -78 °C in THF, it was a challenge to study analogous heteroaromatic compounds to see if these compounds could be lithiated and substituted selectively in

similar manner. Therefore, the aim of the work in this chapter was to synthesise various substituted pyridines such as *N*-(pyridinylmethyl)pivalamides, *tert*-butyl pyridinylmethyl carbamates and *N'*-(pyridinylmethyl)-*N*,*N*-dimethylureas and investigate their lithiation reactions, to enable convenient syntheses of the corresponding substituted derivatives.

The first tasks of the work were to synthesize 2-, 3- and 4-pivaloylaminomethylpyridines and investigate their lithiation reactions under various reaction conditions

4.2 Synthesis of 2-, 3- and 4-pivaloylaminomethylpyridines

The reaction of compound **4.1** or **4.2** or **4.3** with pivaloyl chloride in dichloromethane (DCM) and in the presence of triethylamine (TEA) at 0 °C for 1 h gave *N*-(pyridine-2-ylmethyl)pivalamide **(4.4)**, *N*-(pyridine-3-ylmethyl)pivalamide **(4.5)** and *N*-(pyridine-4-ylmethyl)pivalamide **(4.6)** respectively in high yields (Scheme 4.1). The structures of **4.4**, **4.5**and **4.6** were confirmed by various spectroscopic techniques (Section 4.14).

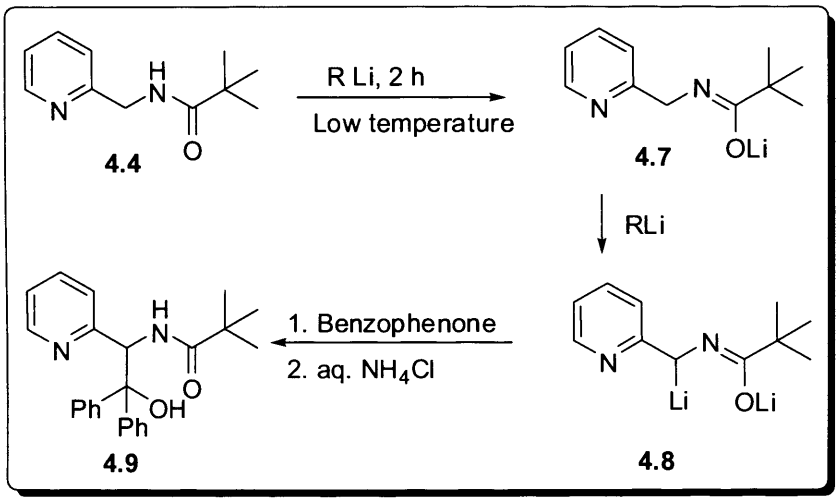


Scheme 4.1

4.3 Lithaition of *N*-(pyridine-2-ylmethyl)pivalamide (4.4)

Double lithiation of compound **4.4** was investigated under various reaction conditions in order to see the effect of those conditions on the reaction selectivity and yield of products. Initially the reaction of **4.4** with *n*-BuLi (2.2 mol equivalents) was carried out in THF at -78 °C for 2 h. Two mole equivalents of *n*- BuLi were used, the

first one to deprotonate the NH proton to produce the monolithium reagent **4.7** and the second one to deprotonate on carbon, perhaps on the CH_2 on the side-chain to produce the dilithium reagent **4.8**. Benzophenone (1.1 mole equivalents) was added as a solution in THF and the mixture was stirred for another 2 h (Scheme 4.2) at -78 °C. The reaction mixture was allowed to warm to room temperature and quenched with the addition of saturated aqueous NH_4Cl solution. The product mixture was examined by TLC and showed the formation of a new product. The crude product obtained was purified by column chromatography (silica gel; AcOEt–hexane) and was identified (see below) as *N*-(2-hydroxy-2,2-diphenyl-1-(pyridin-2-yl)ethyl)pivalamide **(4.9)** in 79% yield (Scheme 4.2).



Scheme 4.2

The only pure isolated product was **4.9** and no other products were isolated from the residue. Compound **4.9** was isolated from the reaction of the dilithium reagent **4.8** with benzophenone (side-chain substitution). The ^1H and ^{13}C NMR spectra of **4.9** showed the absence of CH_2 signals, indicating that lithiation took place at CH_2 of the CH_2NHCO^tBu group. The ^{13}C NMR signals of the two phenyl groups of benzophenone appeared separately, verifying that they were diastereotopic. The diastereotopicity arises from creation of a stereogenic carbon during lithiation at the

side-chain, followed by reaction with benzophenone. Compound **4.9** would be present as a racemic mixture.

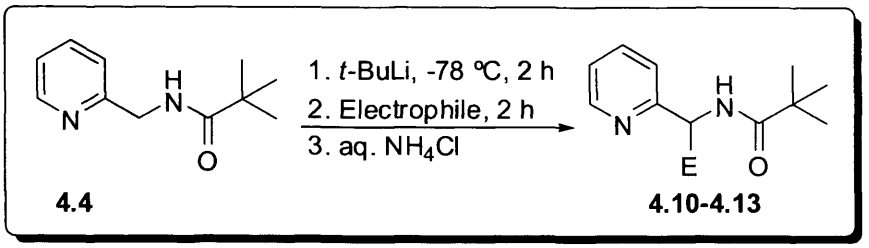
It was possible that other lithiating reagents might have an effect on the site of the lithiation and it was of interest to see if the reaction would proceed differently with such reagents. We therefore attempted double lithiation of **4.4** using *t*-BuLi and LDA. It was found that lithiation of **4.4** with *t*-BuLi and LDA (2.2 mole equivalents) under similar reaction conditions to those used in the case of *n*-BuLi, followed by reaction with benzophenone, gave **4.9** in slightly better yields (87% and 81% respectively) after separation by column chromatography (Table 4.1). Also, we attempted to lithiate **4.4** using *t*-BuLi in THF at 0 °C; however, the yield of **4.9** was marginally less than the one obtained at -78 °C.

Table 4.1 Yields of **4.9** formed by lithiation of **4.4** using RLi, followed by reaction with benzophenone according to Scheme 4.2

Entry	RLi	Temperature (°C)	Yield (%)[a]
1	*t*-BuLi	-78	87
2	*t*-BuLi	0	84
3	*n*-BuLi	-78	79
4	LDA	-78	81

[a] Yield of isolated product after purification by column chromatography.

Our attention was next turned to test the generality of that lithiation by lithiating compound **4.4** with *t*-BuLi in THF at -78 °C, followed by reaction with electrophiles, which gave compounds **4.10-4.13** (Scheme 4.3) in yields of 75-86% (Table 4.2). The structures of compounds **4.10-4.13** were confirmed by various spectroscopic techniques (Section 4.14).



Scheme 4.3

Table 4.2 Yields of **4.10-4.13** according to Scheme 4.3

Product	Electrophile	E	Yield (%)[a]
4.10	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	75
4.11	Me_2CO	$Me_2C(OH)$	84
4.12	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	86
4.13	EtI	Et	86

[a] Yield of isolated product after purification by column chromatography.

As for **4.9**, the ^1H and ^{13}C NMR spectra of **4.10-4.13** showed the absence of CH_2 signals, indicating that lithiation took place on CH_2 of the CH_2NHCO^tBu group. The ^{13}C NMR signals of compound **4.11** showed that the two methyl groups of the acetone-derived product appeared separately, verifying that they were diastereotopic. Also, The ^1H NMR signals of compound **4.13** showed that the signals of the two hydrogens of the CH_2 unit of the ethyl group appeared separately, as two separated multiplets (Figure 4.1), verifying that they were also diastereotopic. The ^1H and ^{13}C NMR spectra of compound **4.10** showed that it was a mixture of two diastereoisomers.(62:38) (Figure 4.2) due to the creation of two stereogenic carbon centres during lithiation at the side-chain followed by reaction with 4-anisaldehyde. The results obtained clearly indicated that reactions of lithium reagent **4.8** with electrophiles are general.

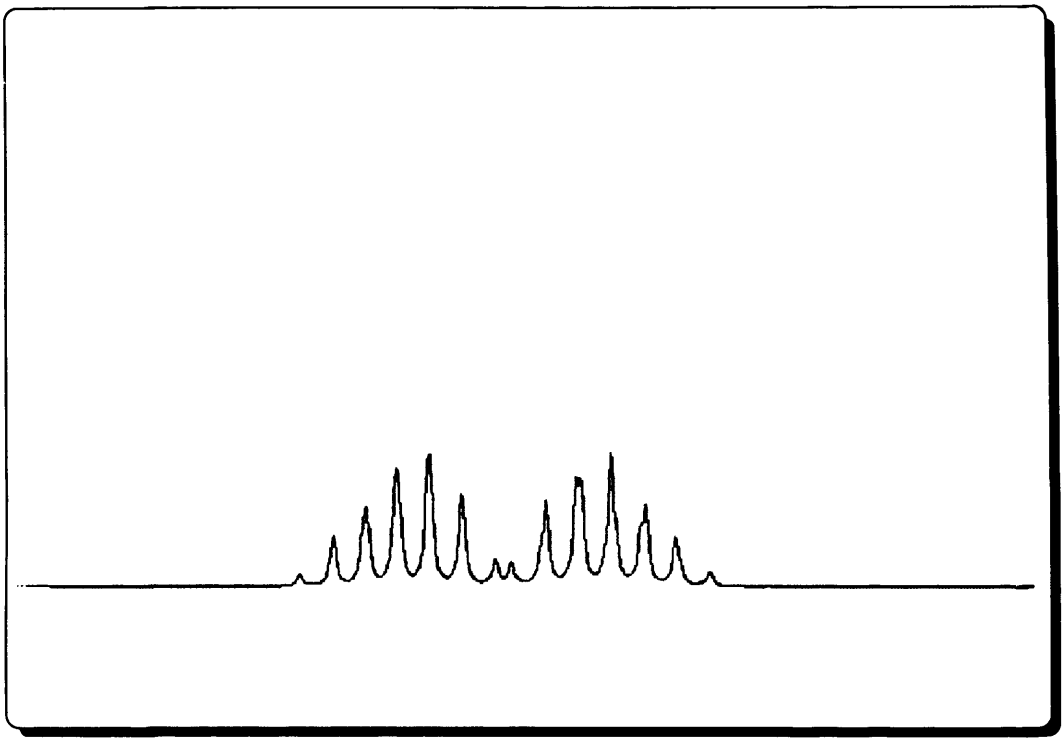


Figure 4.1 Part of the ^{1}H NMR spectrum of compound 2.13, showing the presence of two multiplets at 1.81-1.72 ppm

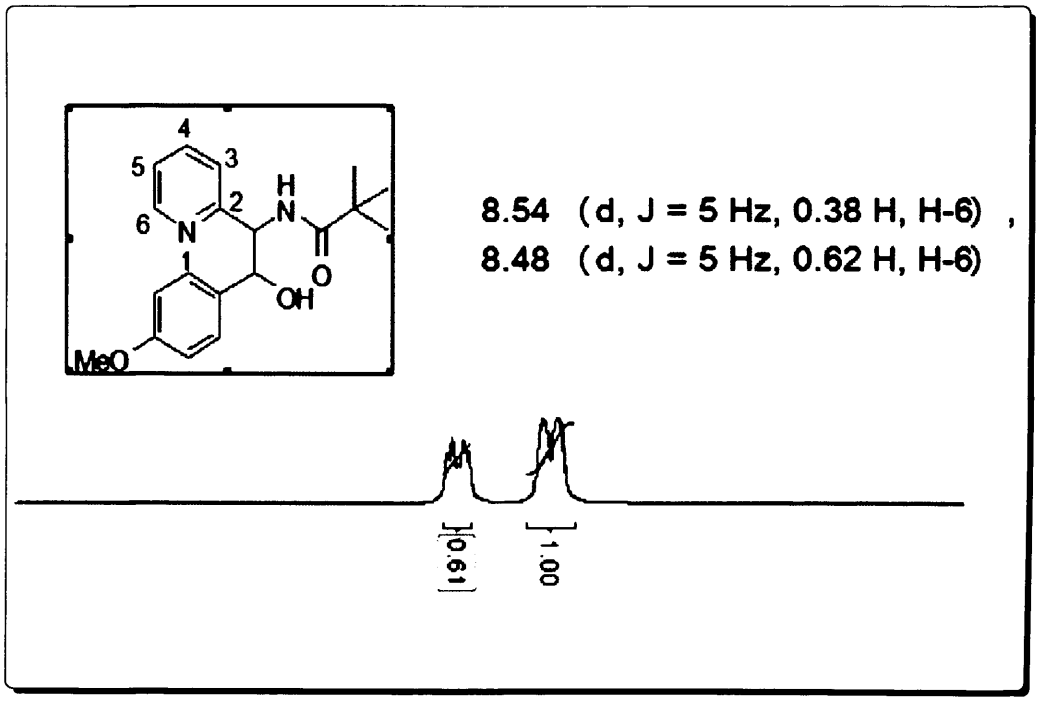
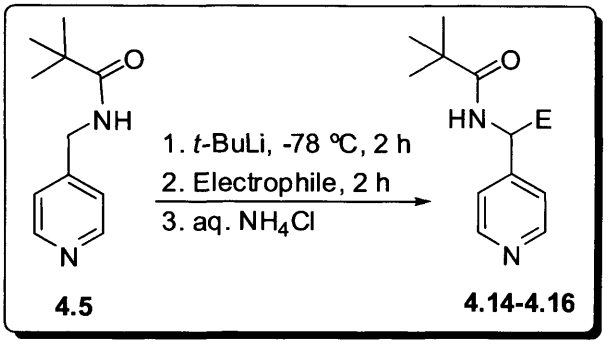


Figure 4.2 Part of the ^{1}H NMR spectrum of compound 4.10, showing signals for two diastereoisomers a, b (38:62)

4.4 Lithiation of *N*-(pyridine-4-ylmethyl)pivalamide (4.5)

Previous experience of the lithiation of *N*-(pyridine-2-ylmethyl)pivalamide **(4.4)** suggested that *t*-BuLi might provide good yields of substitution products from lithiation of **4.5** followed by treatment with electrophiles. Therefore, several reactions were carried out with *t*-BuLi in THF at -78 °C (Scheme 4.4). The directed lithiation of *N*-(pyridine-4-ylmethyl)pivalamide **(4.5)** took place smoothly at the side-chain to give compounds **4.14-4.16** (Scheme 4.4) in high yields (Table 4.3). The structures of compounds **4.14-4.16** were confirmed by various spectroscopic techniques (Section 4.14).



Scheme 4.4

Table 4.3 Yields of **4.14-4.16** according to Scheme 4.4

Product	Electrophile	E	Yield (%)[a]
4.14	C_6H_4CHO	$C_6H_4CH(OH)$	79
4.15	Ph_2CO	$Ph_2C(OH)$	76
4.16	EtI	Et	80

[a] Yield of isolated product after purification by column chromatography.

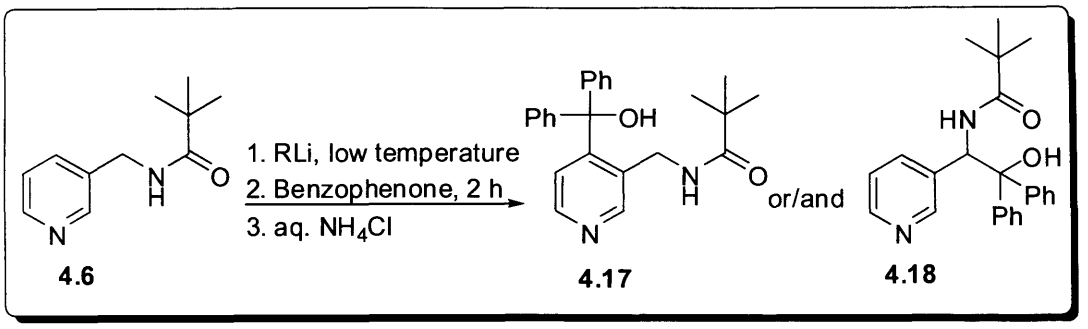
Compounds **4.15** and **4.16** would be formed as racemic mixtures. The ^1H and ^{13}C NMR spectra of compound **4.14** showed that it was a mixture of two diastereoisomers (78:22) due to the creation of two stereogenic carbon centres during

lithiation at the side-chain, followed by reaction with benzaldehyde. As can be seen from Table 4.3, the yields in all cases tried were high and the process appeared to be general to produce various side-chain substituted products.

4.5 Lithiation of *N*-(pyridine-3-ylmethyl)pivalamide (4.6)

It was found that directed lithiation of *N*-(pyridine-3-ylmethyl)pivalamide **(4.6)**, under the general conditions used to lithiate 2- and 4-pivaloylaminomethylpyridines **4.4** and **4.5** respectively, was not selective and gave a mixture of *o*- and side-chain substituted products. Double lithiation of compound **4.6** using *t*-BuLi in THF at -78 °C, followed by reaction with benzophenone gave compound **4.17** (*o*-substitution) and compound **4.18** (side-chain substitution) (Scheme 4.5) in a very poor yields (combined yield 13%) and the starting material **4.6** was recovered in 65% yield. It seems likely that other lithiating reagent might have an effect on the site of lithiation. We therefore attempted double lithiation of **4.6** using LDA and *n*-BuLi. It was found that lithiation of **4.6** with *n*-BuLi (2.2 mole equivalents) in THF at -78 °C, followed by reaction with benzophenone gave **4.17** (*o*-substitution) in 21% yield after separation by column chromatography. The rest of the mixture consisted of starting material **4.6** and a new product **4.19** (Figure 4.3). The ^{1}H NMR spectrum showed the presence of signals corresponding to a butyl group, which could be attributed to nucleophilic attack by butyllithium on the pyridine ring, perhaps at the C-6 position. By contrast, reaction of compound **4.6** with LDA under the same conditions, followed by reaction with benzophenone, gave **4.18** (side-chain substitution) in 44% yield with 30% recovered starting material. Therefore a series of experiments was conducted to try to improve the yields of **4.17** (Table 4.4) and **4.18** (Table 4.5).

Double lithiation of compound **4.6** using *n*-BuLi or *n*-BuLi/TMEDA in THF for 2 or 4 h at different reaction temperatures was attempted (Table 4.4).



Scheme 4.5

Table 4.4 Conditions screening for lithiation of **4.6** to produce **4.17** according to Scheme 4.5

Entry	RLi	RLi (equiv)	Temp (°C)	Time[a] (h)	S.M.[b] (%)[c]	4.17 (%)[d]
1	*n*-BuLi	2	0	2	65	6
2	*n*-BuLi	2	-78	2	54	21
3	*n*-BuLi	2	-78	4	52	21
4	*n*-BuLi	3	-78	2	42	32
5	*n*-BuLi	3	-78	4	40	40
6	*n*-BuLi	4	-78	2	38	32
7	*n*-BuLi/TMEDA	2.5	-10	2	85[e,f]	—
8	*n*-BuLi/TMEDA	2.5	-78	2	43	22
9	*n*-BuLi/TMEDA	2.5	-78	4	53	23
10	*n*-BuLi/TMEDA	2.5	-100	2	48[f]	22

[a] Time of the lithiation step.

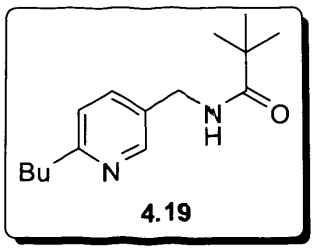
[b] Compound **4.19** was present along with the S.M., S.M. = starting material.

[c] GC yield.

[d] Yield of isolated product after purification by column chromatography.

[e] The reaction was performed in Et_2O

[f] Compound **4.19** was not seen in this reaction



4.19

Figure 4.3

As can be seen from Table 4.4, entry 5 showed that compound **4.17** was obtained in 40% yield when compound **4.6** was lithiated at -78 °C using *n*-BuLi in THF for 4 h followed by reaction with benzophenone. In all of the reactions with *n*-BuLi there was evidence for formation of some product **4.19** from nucleophilic attack by *n*-BuLi on the pyridine nucleus. It was felt that perhaps clean lithiation of compound **4.6** could not be achieved with *n*-BuLi in THF due to this process. However, it has previously been reported that lithiation of 3-(pivaloylamino)pyridine took place at C-4 in 50-60% yield using *n*-BuLi/TMEDA.[25] Therefore, lithiation of **4.6** was also investigated using *n*-BuLi/TMEDA under various reaction conditions in an attempt to improve the yield. It can be seen from Table 4.4, entry 7 that lithiation of compound **4.6** did not take place in diethyl ether while in THF at -78 °C for 2 or 4 h the product of lithiation was obtained in quite low yield (22% and 23% respectively). Interestingly, compound **4.19,** derived from the nucleophilic attack by *n*-BuLi on the pyridine ring, was not obtained when the lithiation took place at -100 °C, but the yield of lithiation product was still low and less starting material was recovered, so it is clear that some other process must have taken place.

From the data obtained, lithiation of **4.6** by butyllithium was complicated with nucleophilic attack by *n*-BuLi on the pyridine ring. All attempts to improve the yields of *ortho*-metalation by finding suitable reaction conditions proved unsuccessful. Therefore, attention was next turned to lithiation of compound **4.6** using

LDA in an attempt to improve the yield of product **4.18** (side-chain substitution). Double lithiation of compound **4.6** using LDA in THF for 2 or 4 h at different reaction temperatures was attempted (Table 4.5).

Table 4.5 Conditions screening for lithiation of **4.6** to produce **4.18** according to Scheme 4.5

Entry	RLi	RLi (equiv)	Temp (°C)	Time[a] (h)	S.M[b]. (%)	4.18 (%)[c]
1	LDA	2	0	2	52	13
2	LDA	2	-35	2	55	16
3	LDA	2	-78	2	59	18
4	LDA	2	-78	4	30	44
5	LDA	3	-78	2	22	52
6	LDA	3	-78	4	33	35
7	LDA	4	-78	2	38	33
8	LDA	3	-100	2	52	19
9	LDA	3	-100	4	57	16

[a] Time of the lithiation step.

[b] S.M. = starting material.

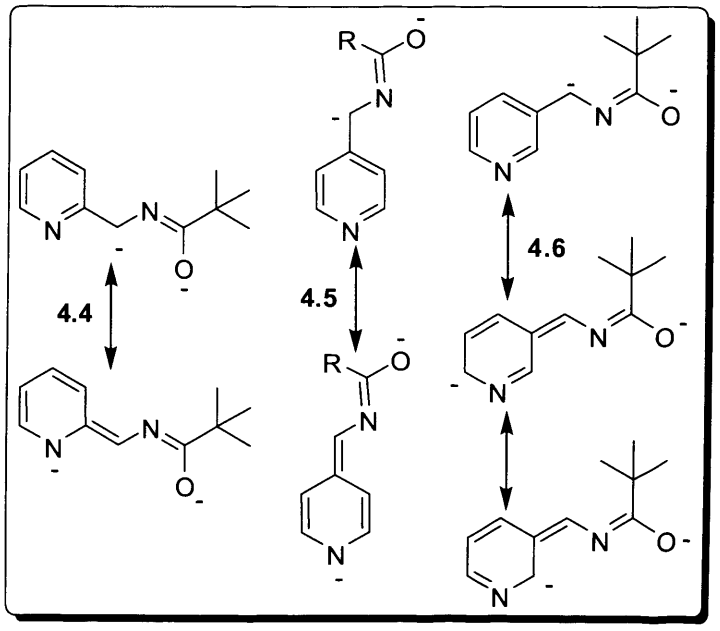
[c] Yield of isolated product after purification by column chromatography.

As can be seen from Table 4.5, the best conditions to produce compound **4.18** in a maximum yield 52% involved use of three equivalents of LDA at -78 °C for 2 h.

The structures of **4.17** and **4.18** were confirmed by various spectroscopic techniques (Section 4.14). As shown previously with compound **4.9**, the ^{1}H and ^{13}C NMR spectra of **4.18** also showed the absence of CH_2 signals, indicating that lithiation took place on CH_2 of the CH_2NHCO^tBu group, and the ^{13}C NMR signals showed that the two phenyl groups appeared separately, verifying that they were diastereotopic. By contrast, the ^{1}H and ^{13}C NMR spectra of compound **4.17** showed

the presence of CH_2 signals, indicating that lithiation took place on the ring. The ^{13}C NMR spectrum of **4.17** also showed a signal somewhat downfield in the region of 148.0 ppm, attributed to C-4, which had been somewhat upfield at δ = 134.5 ppm region before the electrophile was introduced into the ring. This pattern indicated that electrophile was introduced at the 4-posistion *ortho* to the CH_2NHCO^tBu group.

The difference in the reaction behaviour between 3-pivaloylaminomethylpyridine and 2- and 4-pivaloylaminopyridines under identical lithiation conditions can be explained on the basis of increasing the acidity in the latter. Resonance forms that place a negative charge on the pyridine nitrogen are the most significant contributors in the resonance structures of **4.4** and **4.5** (Scheme 4.6), while no similar resonance forms exist for **4.6** (Scheme 4.6). The presence of negative charge on N renders the anion more stable, so the acidity of the CH_2 protons in compounds **4.4** and **4.5** is higher than for those in compound **4.6**. As a result, the lithiation on CH_2 in the 2- and 4- isomers is favourable, while in case of the 3- isomer there is a competition between the CH_2 protons at the side-chain and the ring protons.

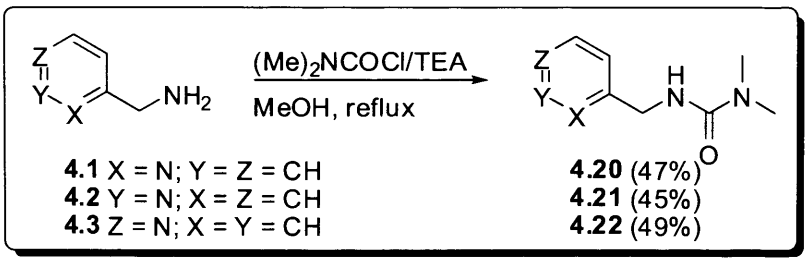


Scheme 4.6

It was suggested to change the DMG, which might have an effect on the site of lithiation. The second task reported in this chapter was therefore to investigate directed lithiation and substitution of the three isomers of *N'*-(pyridinylmethyl)-*N,N*-dimethylureas under various reaction conditions and test the generality of the process.

4.6 Synthesis of various *N'*-(pyridinylmethyl)-*N,N*-dimethylureas

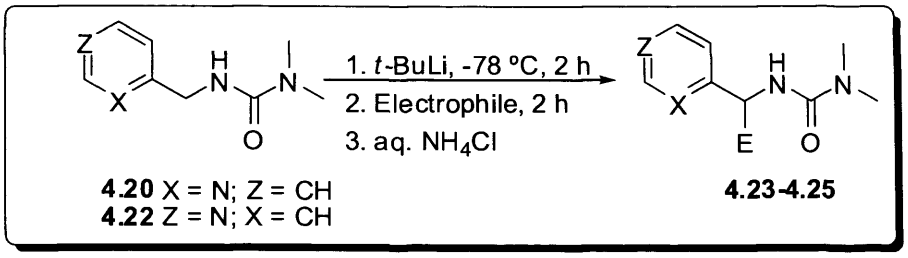
A stirred mixture of compound **4.1** or **4.2** or **4.3**, dimethylcarbamoyl chloride and triethylamine in methanol was heated under reflux for 1 h. The mixture was poured onto H_2O. The solids obtained in modest yields after work-up were identified as *N'*-(pyridine-2-ylmethyl)-*N,N*-dimethylurea **(4.20)**, *N'*-(pyridine-3-ylmethyl)-*N,N*-dimethylurea **(4.21)** and *N'*-(pyridine-4-ylmethyl)-*N,N*-dimethylurea **(4.22)** respectively (Scheme 4.7). The structures of **4.20**, **4.21**and **4.22** were confirmed by various spectroscopic techniques (Section 4.14).



Scheme 4.7

4.7 Lithiation of the 2- and 4- isomers of *N'*-(pyridinylmethyl)-*N,N*-dimethylureas

Double lithiation of compounds **4.20** and **4.22** with *t*-BuLi in THF at -78 °C for 2 h, followed by reactions with electrophiles (Scheme 4.8) gave products **4.23-4.25** in reasonable yields (Table 4.6). The structures of compounds **4.23-4.25** were confirmed by various spectroscopic techniques (Section 4.14).



Scheme 4.8

Table 4.6 Yields of **4.23-4.25** according to Scheme 4.8

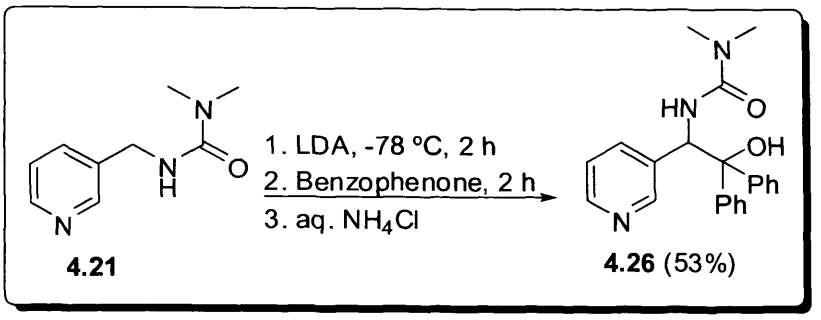
Product	X	Z	Electrophile	E	Yield (%)[a]
4.23	N	CH	Ph_2CO	$Ph_2C(OH)$	65
4.24	N	CH	EtI	Et	68
4.25	CH	N	Ph_2CO	$Ph_2C(OH)$	62

[a] Yield of isolated product after purification by column chromatography.

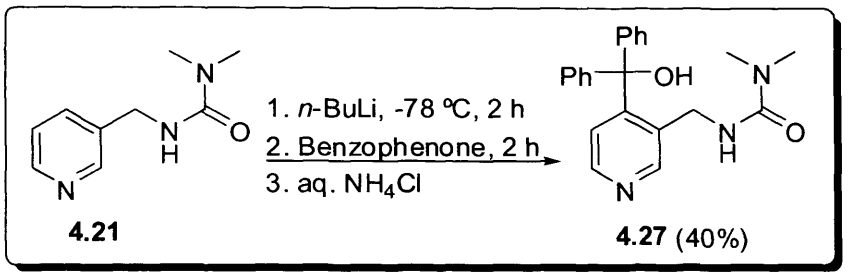
The compounds **4.23-4.25** showed similar features in their NMR spectra as previously observed for compound **4.9** and others, which confirmed that substitution, had taken place at the side-chain position.

4.8 Lithiation of *N'*-(pyridine-3-ylmethyl)-*N,N*-dimethylurea (4.21)

The lithiation reaction of compound **4.21** under similar conditions used to lithiate *N*-(pyridine-3-ylmethyl)pivalamide (Section 4.5), using LDA or *n*-BuLi in THF at -78 °C, followed by reaction with benzophenone, gave compound **4.26** (side-chain substitution; 53%) or compound **4.27** (*o*-substitution; 40%) respectively (Scheme 4.9 and 4.10). No other compounds were identified in the product mixtures.



Scheme 4.9



Scheme 4.10

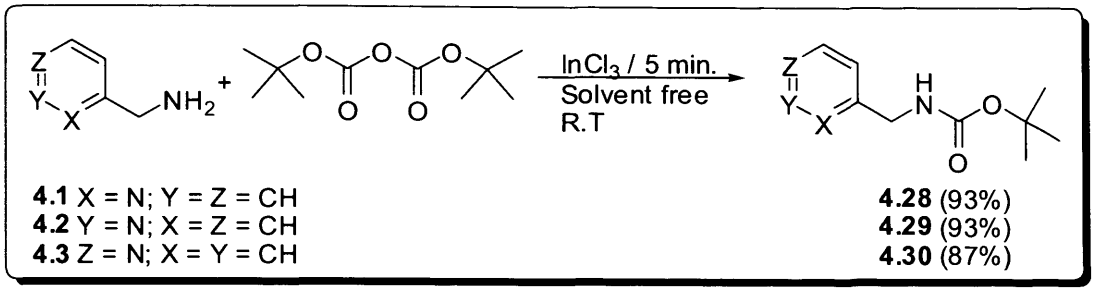
The ^{1}H and ^{13}C NMR spectra of **4.26** showed the absence of CH_2 signals, indicating that lithiation took place on CH_2 of the CH_2NHCO^tBu group, while the ^{1}H and ^{13}C NMR spectra of **4.27** showed the presence of CH_2 signals, indicating that lithiation took place on the ring. The structures of compounds **4.26** and **4.27** were confirmed by a range of spectroscopic techniques (Section 4.14).

The third task reported in this chapter was use of a carbamate group as a DMG group for directed lithiation and substitution of the 2-, 3- and 4- isomers of *tert*-butyl pyridinylmethyl carbamates under various reaction conditions.

4.9 Synthesis of various *tert*-butyl pyridinylmethyl carbamates

Di-*tert*-butyl dicarbonate [$(Boc)_2O$] was added to a magnetically stirred solution of compound **4.1** or **4.2** or **4.3** and $InCl_3$ at room temperature. Vigorous effervescing was observed. The reaction mixture was stirred and monitored by TLC until completion. The solids obtained, in excellent yields, were identified as *tert*-butyl pyridine-2-ylmethylcarbamate **(4.28)**, *tert*-butyl pyridine-3-ylmethylcarbamate **(4.29)**

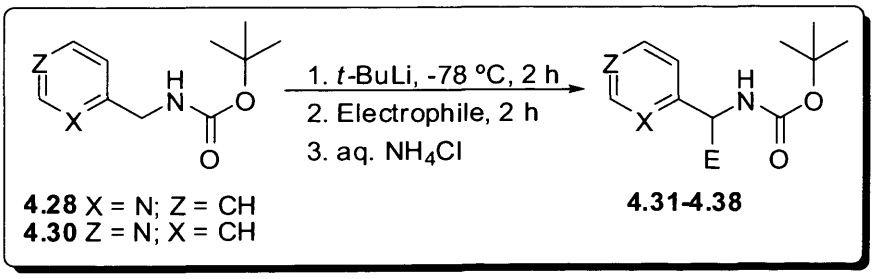
and *tert*-butyl pyridine-4-ylmethylcarbamate **(4.30)** respectively (Scheme 4.11). The structures of **4.28**, **4.29**and **4.30** were confirmed by various spectroscopic techniques (Section 4.14).



Scheme 4.11

4.10 Lithiation of the 2- and 4- isomers of *tert*-butyl pyridinylmethyl carbamates

Double lithiation of compounds **4.28** and **4.30** with *t*-BuLi in THF at -78 °C for 2 h, followed by reactions with electrophiles (Scheme 4.12), gave products **4.31-4.38** in high yields (Table 4.7). The structures of compounds **4.31-4.38** were confirmed by standard spectroscopic methods (see experimental section for details). EI-mass spectra showed molecular ion peaks for all products and NMR spectra showed all appropriate carbon resonances.



Scheme 4.12

Table 4.7 Yields of **4.31-4.38** according to Scheme 4.12

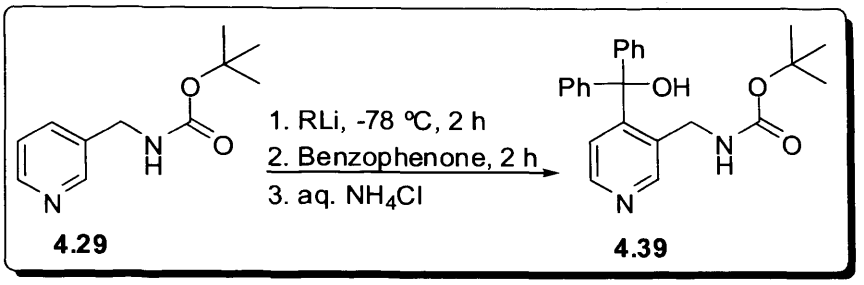
Product	X	Z	Electrophile	E	Yield (%)[a]
4.31	N	CH	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	71
4.32	N	CH	Ph_2CO	$Ph_2C(OH)$	85
4.33	N	CH	$PhCOCH_3$	$PhC(OH)CH_3$	76
4.34	N	CH	Me_2CO	$Me_2C(OH)$	79
4.35	N	CH	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	80
4.36	CH	N	Ph_2CO	$Ph_2C(OH)$	77
4.37	CH	N	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	74
4.38	CH	N	EtI	Et	74

[a] Yield of isolated product after purification by column chromatography.

The ^1H and ^{13}C NMR spectra of compound **4.31** (after column chromatography) showed that it was a mixture of two diastereoisomers (55:45). due to the creation of two stereogenic carbon centres during the reaction. In the case of **4.33** the material obtained following column chromatography showed signals in NMR spectra that indicated it to be a single diastereoisomer. No attempt was made to identify which diasteroisomer was obtained. It is likely that a small amount of the other diastereoisomer was formed in the reaction but removed during the purification process.

4.11 Lithiation of *tert*-butyl pyridine-3-ylmethyl carbamate (4.29)

Double lithiation of compound **4.29** was investigated under various reaction conditions in an attempt to enable a convenient lithiation procedure that would allow synthesis of various substituted *tert*-butyl pyridine-3-ylmethyl carbamates. The lithiation of compound **4.29** using various alkyl lithium reagents at -78 °C for 2 h, followed by reaction with benzophenone was attempted (Scheme 4.13; Table 4.8).



Scheme 4.13

Table 4.8 Conditions screening for lithiation of **4.29** to produce **4.39** according to Scheme 4.13

Entry	RLi	S.M.[a] (%)	Yield (%)[b]
1	*n*-BuLi	72[c]	12
2	LDA	87	—
3	*t*-BuLi	18	60

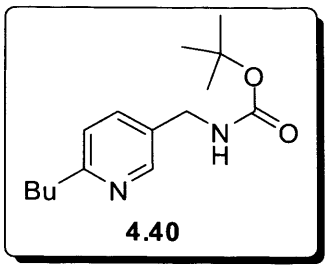
[a] S.M. = starting material.

[b] Yield of isolated product after purification by column chromatography.

[c] Compound **4.40** was present along with the S.M.

As can be seen, lithiation of compound **4.29** gave 12% of compound **4.39** using *n*-BuLi. The rest of the mixture consisted of starting material **4.29** and a new product thought to be **4.40** (Figure 4.4), as a result of its ^{1}H NMR spectrum showing the presence of signals corresponding to a butyl group, which could be attributed to nucleophilic attack by butyllithium on the pyridine ring, perhaps at the C-6 position. No reaction took place using LDA as the lithiating agent and 87% of the starting material was recovered. By contrast lithiation of compound **4.29** took place selectively on the ring at C-4, *ortho* to the CH_2NHCO^tBu group, using *t*-BuLi in THF at -78 °C (Scheme 4.13), and no product corresponding to lithiation at any position other than C-4 was identified. The ^{1}H and ^{13}C NMR spectra of **4.39** showed the presence of CH_2 signals, indicating that lithiation had indeed taken place on the ring.

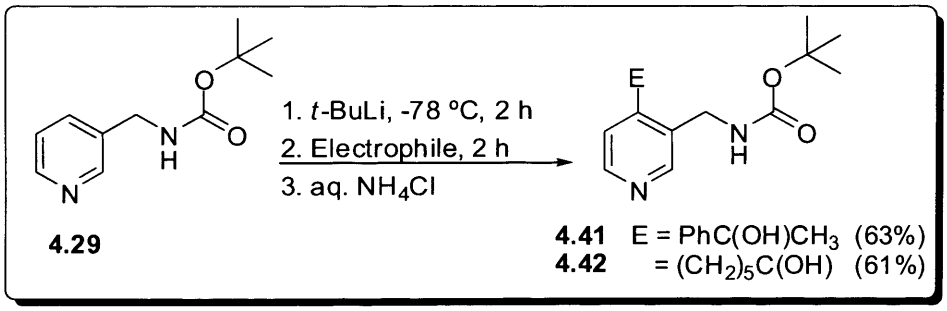
The structure of compound **4.39** was confirmed by various spectroscopic techniques (Section 4.14).



4.40

Figure 4.4

Our attention was next turned to test the generality of that lithiation by lithiating compound **4.29** with *t*-BuLi in THF at -78 °C, followed by reaction with acetophenone and cyclohexanone, which gave compounds *tert*-butyl (4-(1-hydroxy-1-phenylethyl)pyridin-3-yl)methylcarbamate (**4.41**; 63%) and *tert*-butyl(4-(1-hydroxycyclohexyl)pyridine-3-yl)methylcarbamate (**4.42**; 61%) respectively (Scheme 4.14). The structures of compounds **4.41** and **4.42** were confirmed by various spectroscopic techniques (Section 4.14).

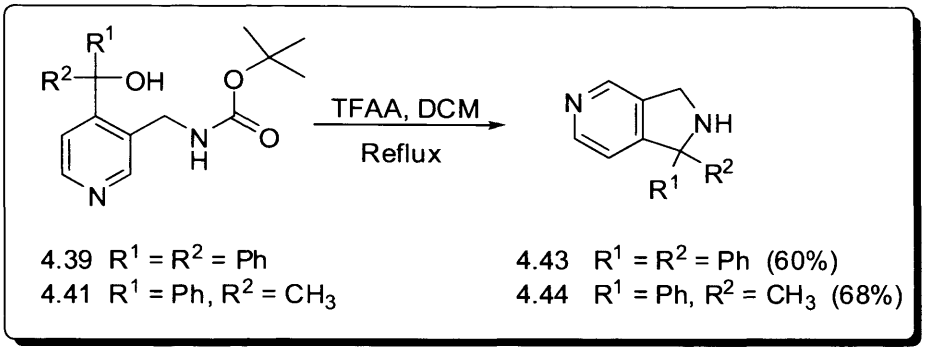


Scheme 4.14

4.12 Synthesis of 1,1-diphenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (4.43) and 1-methyl-1-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (4.44)

It was of interest to test the possibility of cyclising compound **4.39** and **4.41**. Therefore, as tests, compound **4.39** and **4.41** were dissolved in DCM, a few drops of trifluoroacetic anhydride (TFAA) were added and the reaction mixtures were heated

under reflux for 12 h (Scheme 4.15). The mixtures were examined by TLC and showed the formation of new products. The reactions were complete within 12 hour, at which time no starting materials were left. The mixtures were quenched by the addition of water and worked up. The residues obtained were subjected to flash column chromatography (silica gel; AcOEt–hexane) to give the pure products. The products were identified as **4.43** and **4.44** in yields of 60% and 68% respectively.



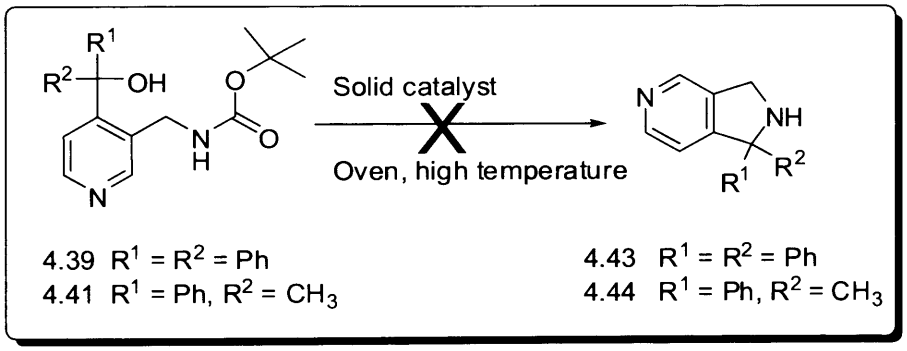
Scheme 4.15

The structures of compounds **4.43** and **4.44** were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry. In the ^{1}H NMR spectrum of compounds **4.43** and **4.44** showed all appropriate hydrogen and carbon resonances. The EI-mass spectrum of compound **4.43** showed a pseudo molecular ion peak at *m/z* = 273 (MH^{+}), while **4.44** showed a molecular ion peak at *m/z* = 210 ($M^{\bullet+}$). The accurate masses of these peaks at *m/z* = 273 and *m/z* = 210 confirmed the formulas as $C_{19}H_{17}N_2$ and $C_{14}H_{14}N_2$ respectively, indicating the loss of 17 (HO) and 101 [$CO_2C(CH_3)_3$] from the molecular weights of the starting materials **4.39** and **4.41**, respectively. Clearly, cyclization of **4.39** and **4.41** *via* dehydration had taken place followed by hydrolysis to produce *N*-unsubstituted azaisoindole derivatives **4.43** and **4.44**.

4.13 Attempted synthesis of *N*-unsubstituted azaisoindole derivatives 4.43 and 4.44 involving use of acidic solid catalysts

We decided to investigate the cyclisation of **4.39** and **4.41** with a large pore zeolite (zeolite β), a fairly strongly acidic amorphous catalyst (Synclyst), and a weakly acidic solid catalyst (silica).

Compounds **4.39** and **4.41** were ground together with the selected acidic solid catalysts at room temperature and then heated to high temperatures in a vacuum oven for 2 h to 12 h. The reaction mixtures were subjected to TLC, which showed that no new products were present. In each case the reaction mixture was worked up by extraction of the product from the solid with dichloromethane (Scheme 4.16). The quantitative recovery of **4.39** and **4.41** indicated that no reactions took place under the conditions tried.



Scheme 4.16

All attempts to achieve such cyclization using acidic solid catalysts were unsuccessful.

4.14 Conclusion

A simple, efficient and fairly high yielding lithiation procedure that allows electrophilic substitution of various substituted pyridines has been demonstrated to provide various substituted derivatives. Lithiation of 2- and 4- isomers of

N-(pyridinylmethyl)pivalamides, *N'*-(pyridinylmethyl)-*N*,*N*-dimethylureas and *tert*-butyl pyridinylmethyl carbamates using *t*-BuLi at -78 °C in THF, followed by reaction with various electrophiles, takes place on the CH_2 group in good yields, while the lithiation of the 3- isomers of *N*-(pyridinylmethyl)pivalamide and *N'*-(pyridinylmethyl)-*N*,*N*-dimethylurea using *n*-BuLi at -78 °C in THF, give predominantly ring substitution at the 4-position *ortho* to the pivaloylaminomethyl side-chain and urea-containing groups, respectively, but in poor yields. The lithiation of the *tert*-butyl pyridine-3-ylmethyl carbamate, using *t*-BuLi at -78 °C in THF, followed by reaction with various electrophiles, takes place selectivity at the 4-position (on the ring) *ortho* to the directed metalating group in modest yields.

4.15 Experimental

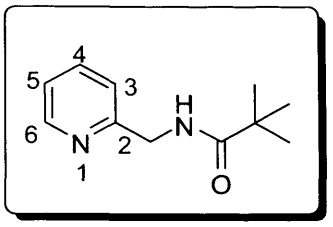
4.15.1 General experimental

See Chapter 2; Section 2.4.1

4.15.2 Synthesis of 2-, 3- and 4-pivaloylaminomethylpyridines

To a cooled solution (0 °C) of pyridinylmethylamine derivative (4.32 g, 40.0 mmol) and triethylamine (8.0 mL) in CH_2Cl_2 (100 mL) pivaloyl chloride (5.3 g, 44.3 mmol) was slowly added in a drop-wise manner over 30 min. The reaction mixture was stirred at 0 °C for an extra 1 h. The mixture was poured onto H_2O (100 mL) and the organic layer was separated, washed with H_2O (2 x 50 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The products obtained were identified as *N*-(pyridine-2-ylmethyl)pivalamide **4.4**, *N*-(pyridine-3-ylmethyl)pivalamide **4.5** and *N*-(pyridine-4-ylmethyl)pivalamide **4.6**.

_N_-(Pyridine-2-ylmethyl)pivalamide (4.4)



Yield: 6.89 g (35.9 mmol, 90%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45 (d, J = 5 Hz, 1 H, H-6), 7.59-7.56 (m, 1 H, H-4), 7.16 (d, J = 8 Hz, 1H, H-3), 7.12-7.10 (m, 1 H, H-5), 7.04 (br., exch., 1 H, NH), 4.45 (d, J = 6 Hz, 2 H, CH_2), 1.18 [s, 9 H, $C(CH_3)_3$] ppm.

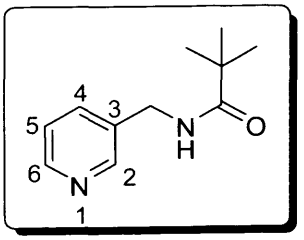
^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.5 (s, C=O), 156.7 (s, C-2), 148.9 (d, C-6), 136.7 (d, C-4), 122.2 (d, C-3), 122.0 (d, C-5), 44.4 (t, CH_2), 38.7 [s, $C(CH_3)_3$], 27.6 [s, $C(CH_3)_3$] ppm.

EI–MS: *m/z* (%) = 192 (10) [$M^{\bullet+}$], 135 (100) [$M^{\bullet+}$ – ^{t}Bu], 107 (30) [$M^{\bullet+}$ – CO^{t}Bu], 92 (85), 79 (13), 65 (20), 57 (^{t}Bu, 13).

HRMS: *m/z* calcd. for $C_{11}H_{16}N_2O$ $[M]^+$ 192.1263; found 192.1256.

IR (FT): ν = 3347 (NH and OH), 2965 (CH), 1652 (C=O), 1531 (aromatic C=C), 1479, 1253, 1226, 1149 cm^{-1}.

_N_-(Pyridine-3-ylmethyl)pivalamide (4.5)



Yield: 6.50 g (33.9 mmol, 85%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41-8.39 (m, 2 H, H-2/H-6), 7.52 (d, *J* = 8 Hz, 1 H, H-4), 7.17 (dd, *J* = 5, 8 Hz, 1 H, H-5), 6.37 (br., exch., 1 H, NH), 4.36 (d, *J* = 6 Hz, 2 H, CH_2), 1.15 [s, 9 H, $C(CH_3)_3$] ppm.

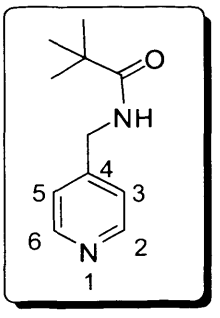
^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.6 (s, C=O), 148.9 (s, C-2), 148.7 (d, C-6), 135.3 (s, C-3), 134.5 (d, C-4), 123.6 (d, C-5), 40.9 (t, CH_2), 38.7 [s, $C(CH_3)_3$], 27.6 [s, $C(CH_3)_3$] ppm.

APCI–MS: *m/z* (%) = 193 (100) [MH^+].

HRMS: *m/z* calcd. for $C_{11}H_{17}N_2O$ [$MH]^+$ 193.1341; found 193.1332.

IR (FT): ν = 3340 (NH and OH), 2966 (CH), 1651 (C=O), 1593 (aromatic C=C), 1481, 1324, 1259, 1207, 1121 cm^{-1}.

_N_-(Pyridine-4-ylmethyl)pivalamide (4.6)



Yield: 6.70 g (34.9 mmol, 87%).

M.p: 88-90 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 5 Hz, 2 H, H-2/H-6), 7.03 (d, *J* = 5, 2 H, H-3/H-5), 6.91 (br., exch., 1 H, NH), 4.30 (d, *J* = 6 Hz, 2 H, CH_2), 1.14 [s, 9 H, $C(CH_3)_3$] ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.9 (s, C=O), 149.6 (d, C-2/C-6), 148.4 (s, C-4), 122.0 (d, C-3/C-5), 42.1 (t, CH_2), 38.7 [s, $C(CH_3)_3$], 27.5 [s, $C(CH_3)_3$] ppm.

EI–MS: *m/z* (%) = 192 (100) [$M^{\bullet+}$], 150 (20), 93 (55).

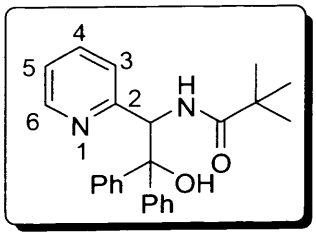
HRMS: *m/z* calcd. for $C_{11}H_{16}N_2O$ [$M]^+$ 192.1263; found 192.1254.

IR (FT): ν = 3370 (NH and OH), 2968 (CH), 1660 (C=O), 1563 (aromatic C=C), 1480, 1366, 1216, 1068 cm^{-1}.

4.15.3 Synthesis of substituted (pyridine-2-yl)(pivaloylamino)methanes 4.9-4.13 *via* directed lithiation of *N*-(pyridine-2-ylmethyl)pivalamide (4.4)

A solution of *t*-BuLi in pentane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-78 °C), stirred solution of *N*-(pyridin-2-ylmethyl)pivalamide (**4.4**; 0.38 g, 2.0 mmol) in anhydrous THF (20 mL) under N_2. Formation of the monolithium reagent was observed as a brown solution and the dilithium reagent was observed as a reddish brown solution. The mixture was stirred at -78 °C for 2 h, to ensure the complete formation of the dilithium reagent, after which electrophile (2.2 mmol), in anhydrous THF (8 ml) if solid, otherwise neat, was added. The mixture was stirred for 2 h at -78 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was then diluted with Et_2O (10 mL) and quenched with aq. sat. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product obtained was purified by column chromatography (silica gel; AcOEt–hexane) to give pure products.

N-(2-Hydroxy-2,2-diphenyl-1-(pyridin-2-yl)ethyl)pivalamide (4.9)



Yield: 0.65 g (1.74 mmol, 87%).

M.p: 183-185 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 5 Hz, 1 H, H-6), 7.73 (br., exch., 1 H, OH), 7.55 (d, *J* = 8 Hz, 4 H, H-2/H-6 of 2 Ph), 7.51-7.48 (m, 1 H, H-4), 7.37 (d, *J* = 8 Hz, 1H, H-3), 7.22 (t, *J* = 8 Hz, 2 H, H-4 of 2 Ph), 7.05 (t, *J* = 8 Hz, 4 H, H-3/H-5 of 2 Ph), 6.93-6.90 (m, 1 H, H-5), 6.77 (d, *J* = 8 Hz, exch., 1 H, NH), 6.00 (d, *J* = 8 Hz, 1 H, CHNH), 1.28 [s, 9 H, $C(CH_3)_3$] ppm.

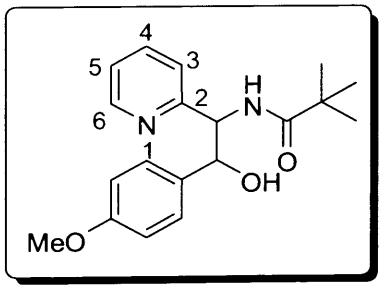
^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8 (s, C=O), 159.8 (s, C-2), 147.9 (d, C-6), 145.7 (s, C-1 of Ph), 144.5 (s, C-1 of Ph), 137.5 (d, C-4), 128.2 (d, C-3/C-5 of Ph), 128.0 (d, C-3/C-5 of Ph), 126.8 (d, C-3), 126.4 (d, C-5), 125.5 (d, C-2/C-6 of Ph), 125.3 (d, C-2/C-6 of Ph), 122.7 (d, C-4 of Ph), 122.7 (d, C-4 of Ph), 80.8 (s, COH), 56.7 (d, CHNH), 38.5 [s, $C(CH_3)_3$], 27.1 [s, $C(CH_3)_3$] ppm.

APCI–MS: *m/z* (%) = 375 (100) [MH^+], 357 (50) [$MH^+ - H_2O$].

HRMS: *m/z* calcd. for $C_{24}H_{27}N_2O_2$ $[MH]^+$ 375.2073; found 375.2062.

IR (FT): ν = 3447 (NH and OH), 2967 (CH), 1650 (C=O), 1573 (aromatic C=C), 1423, 1366, 1215, 1061 cm^{-1}.

_N_-(2-Hydroxy-2-(4-methoxyphenyl)-1-(pyridin-2-yl)ethyl)pivalamide (4.10)



Yield: 0.49 g (1.49 mmol, 75%).

M.p: 149-151 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 5 Hz, 0.38 H, H-6 of isomer **a**), 8.48 (d, *J* = 5 Hz, 0.62 H, H-6 of isomer **b**), 7.66-7.62 (m, 1 H, H-4 of **a** + **b**), 7.40 (br., exch., 1 H, NH of **a** + **b**), 7.25-7.23 (m, 1 H, H-3 of **a** + **b**), 7.20-718 (m, 1 H, H-5 of **a** + **b**),

6.93 (d, J = 9 Hz, 0.76 H, H-2/H-6 of 4-methoxyphenyl of **a**), 6.85 (d, J = 9 Hz, 1.24 H, H-2/H-6 of 4-methoxyphenyl of **b**), 6.74-6.72 (m, 2 H, H-3/H-5 of 4-methoxyphenyl of **a** + **b**), 5.22-5.21 (m, 1 H, CHOH of **a** + **b**), 5.20-5.19 (m, 1 H, CHNH of **a** + **b**), 5.14 (br., exch., 1 H, OH of **a** + **b**), 3.80 (s, 1.14 H, OCH_3 of **a**), 3.76 (s, 1.86 H, OCH_3 of **b**), 1.21 [s, 3.42 H, $C(CH_3)_3$ of **a**], 1.12 [s, 5.58 H, $C(CH_3)_3$ of **b**] ppm.

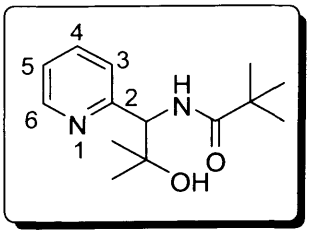
^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.4, 178.9 (2 s, C=O of **a**, **b**), 159.2, 159.0 (2 s, C-4 of 4-methoxyphenyl of **a**, **b**), 158.8 (s, C-2 of **a** + **b**), 156.9 (s, C-1 of 4-methoxyphenyl of **a** + **b**), 148.4, 148.2 (2 d, C-6 of **a**, **b**), 137.1, 137.0 (2 d, C-4 of **a**, **b**), 127.3, 127.2 (2 d, C-2/C-6 of 4-methoxyphenyl of **a**, **b**), 124.1, 124.0 (2 d, C-3 of **a**, **b**), 122.9, 122.8 (2 d, C-5 of **a**, **b**), 113.5, 113.2 (2 d, C-3/C-5 of 4-methoxyphenyl of **a**, **b**), 77.8, 75.4 (2 d, CHOH of **a**, **b**) 58.7, 58.1 (2 d, CHNH of **a**, **b**) 55.3, 55.2 (2 s, OCH_3 of **a**, **b**), 38.79, 38.75 [2 s, $C(CH_3)_3$ of **a**, **b**], 27.5, 27.4 [2 s, $C(CH_3)_3$ of **a**, **b**] ppm.

APCI–MS: *m/z* (%) = 329 (100) [MH^+], 311 (95) [$MH^+ - H_2O$], 115 (8).

HRMS: *m/z* calcd. for $C_{19}H_{25}N_2O_3$ $[MH]^+$ 329.1865; found 329.1857.

IR (FT): ν = 3370 (NH and OH), 2965 (CH), 1651 (C=O), 1571 (aromatic C=C), 1473, 1248, 1215, 1173 cm^{-1}.

_N_-(2-Hydroxy-2-methyl-1-(pyridin-2-yl)propyl)pivalamide (4.11)



Yield: 0.42 g (1.68 mmol, 84%).

M.p: 112-114 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 5 Hz, 1 H, H-6), 7.69-7.67 (m, 1 H, H-4), 7.37 (d, *J* = 8 Hz, 1H, H-3), 7.25-7.23 (m, 1 H, H-5), 6.91 (d, *J* = 6 Hz, exch., 1 H, NH), 5.42 (br., exch., 1 H, OH), 4.85 (d, *J* = 6 Hz, 1 H, CHNH), 1.28 (s, 3 H, CH_3), 1.18 [s, 9 H, $C(CH_3)_3$], 1.05 (s, 3 H, CH_3) ppm.

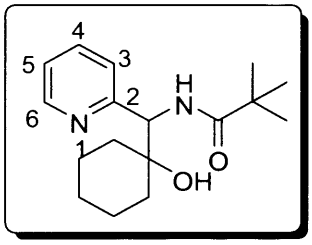
^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2 (s, C=O), 159.8 (s, C-2), 148.7 (d, C-6), 137.2 (d, C-4), 124.7 (d, C-3), 122.8 (d, C-5), 73.0 (s, COH), 59.2 (d, CHNH), 38.8 [s, $C(CH_3)_3$], 27.8 (q, CH_3), 27.5 [s, $C(CH_3)_3$], 26.7 (q, CH_3) ppm.

APCI–MS: *m/z* (%) = 251 (100) [MH^+], 233 (20) [$MH^+ - H_2O$].

HRMS: *m/z* calcd. for $C_{14}H_{23}N_2O_2$ [MH]$^+$ 251.1760; found 251.1762.

IR (FT): ν = 3446 (NH and OH), 2982 (CH), 1648 (C=O), 1572 (aromatic C=C), 1438, 1278, 1212, 1145 cm^{-1}.

_N_-((1-Hydroxycyclohexyl)(pyridin-2-yl)methyl)pivalamide (4.12)



Yield: 0.50 g (1.72 mmol, 86%).

M.p: 170-172 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 5 Hz, 1 H, H-6), 7.68-7.66 (m, 1 H, H-4), 7.38 (d, *J* = 8 Hz, 1H, H-3), 7.23-7.21 (m, 1 H, H-5), 6.85 (d, *J* = 8 Hz, exch., 1 H, NH), 5.27 (br., exch., 1 H, OH), 4.94 (d, *J* = 8 Hz, 1 H, CHNH), 1.86-1.38 (m, 10 H, cyclohexyl), 1.17 [s, 9 H, $C(CH_3)_3$] ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.1 (s, C=O), 159.8 (s, C-2), 148.8 (d, C-6), 137.2 (d, C-4), 124.8 (d, C-3), 122.7 (d, C-5), 73.8 (s, COH), 57.8 (d, CHNH), 38.8

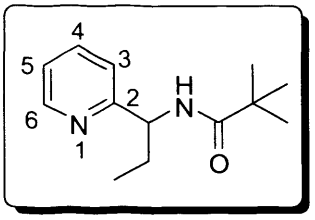
[s, $C(CH_3)_3$], 36.2 (t, C-2/C-6 of cyclohexyl), 27.5 [s, $C(CH_3)_3$], 25.6 (t, C-4 of cyclohexyl), 21.8 (t, C-3/C-5 of cyclohexyl) ppm.

EI–MS: *m/z* (%) = 290 (10) [$M^{\bullet+}$], 272 (35) [$M^{\bullet+} - H_2O$], 239 (55), 205 (25), 192 (100), 159 (100), 107 (100), 92 (93), 57 (50).

HRMS: *m/z* calcd. for $C_{17}H_{26}N_2O_2$ $[M]^+$ 290.1994; found 290.1995.

IR (FT): ν = 3447 (NH and OH), 2938 (CH), 1652 (C=O), 1572 (aromatic C=C), 1458, 1366, 1215, 1105 cm^{-1}.

_N_-(1- (Pyridin-2-yl)propyl))pivalamide (4.13)



Yield: 0.38 g (1.73 mmol, 86%).

M.p: 58-60 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 5 Hz, 1 H, H-6), 7.57-7.55 (m, 1 H, H-4), 7.14 (d, *J* = 8, 1H, 3-H), 7.12-7.10 (m, 1 H, H-5), 6.99 (br., exch., 1 H, NH), 4.90 (q, *J* = 6 Hz, 1 H, CHNH), 1.81 (m, 1 H, CH_aCH_b), 1.72 (m, 1 H, CH_aCH_b), 1.16 [s, 9 H, $C(CH_3)_3$], 0.74 (t, *J* = 7 Hz, 3 H, CH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.9 (s, C=O), 160.1 (s, C-2), 149.1 (d, C-6), 136.5 (d, C-4), 122.4 (d, C-3), 122.2 (d, C-5), 54.7 (d, CH), 38.8 [s, $C(CH_3)_3$], 29.4 (t, CH_2), 27.6 [s, $C(CH_3)_3$], 9.8 (q, CH_3) ppm.

EI–MS: *m/z* (%) = 220 (12) [$M^{\bullet+}$], 191 (30) [$M^{\bullet+}$ – Et], 163 (65) [$M^{\bullet+}$ – ^{t}Bu]), 135 (20) [$M^{\bullet+}$, CO^{t}Bu], 120 (100), 107 (43), 92 (20), 57 (35).

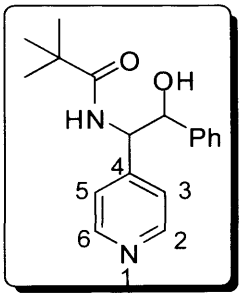
HRMS: *m/z* calcd. for $C_{13}H_{20}N_2O$ $[M]^+$ 220.1576; found 220.1574.

IR (FT): ν = 3433 (NH and OH), 2968 (CH), 1649 (C=O), 1571 (aromatic C=C), 1507, 1304, 1215, 1150 cm^{-1}.

4.15.4 Synthesis of substituted (pyridine-4-yl)(pivaloylamino)methanes 4.14-4.16 *via* directed lithiation of *N*-(pyridine-4-ylmethyl)pivalamide (4.5)

The procedure was identical with that described in Section 4.14.3 except that *N*-(pyridine-4-ylmethyl)pivalamide **4.5** was used instead of *N*-(pyridine-2-ylmethyl)pivalamide **4.4**. After work-up the residues obtained were purified by column chromatography (silica gel; AcOEt–hexane) to give pure products. **4.14-4.16** The yields obtained are reported in Table 4.3.

N-(2-Hydroxy-2-phenyl-1-(pyridin-4-yl)ethyl)pivalamide (4.14)



Yield: 0.47 g (1.58 mmol, 79%).

M.p: 133-135 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 5 Hz, 2 H, H-2/H-6 of **a** + **b**), 8.26 (d, *J* = 5 Hz, 2 H, H-3/H-5 of **a** + **b**), 7.36-7.10 (m, 5 H, Ph of **a** + **b**), 6.72 (br., exch., 1 H, NH of **a** + **b**), 5.11-5.08 (m, 1 H, CHOH of **a** + **b**), 5.09-5.07 (m, 1 H, CHNH of **a** + **b**), 5.02 (br., exch., 1 H, OH of **a** + **b**), 1.18 [s, 1.98 H, $C(CH_3)_3$ of **a**], 1.09 [s, 7.02 H, $C(CH_3)_3$ of **b**] ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4, 178.2 (2 s, C=O of **a**, **b**), 150.2 (s, C-4 of **a** + **b**), 149.3, 148.8 (2 d, C-2/C-6 of **a**, **b**), 147.5 (s, C-4 of **a** + **b**), 140.9, 139.8 (2 s, C-1 of Ph of **a**, **b**), 128.4, 128.3 (2 d, C-3/C-5 of Ph of **a**, **b**), 128.1, 127.9 (2 d, C-4 of Ph of **a**, **b**), 126.2, 125.8 (2 d, C-2/C-6 of Ph of **a**, **b**), 123.2, 122.2 (2 d, C-3/C-5 of

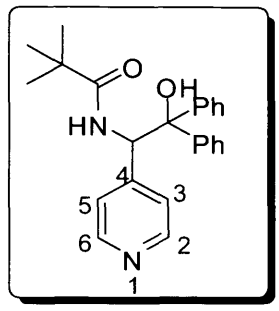
a, b), 75.6, 75.2 (2 d, CHOH of **a**, **b**), 58.2, 58.1 (2 d, CHNH of **a**, **b**), 38.8 [s, $C(CH_3)_3$ of **a** + **b**], 27.41, 27.37 [2 s, $C(CH_3)_3$ of **a**, **b**] ppm.

EI–MS: *m/z* (%) = 280 (15) [$M^{\bullet+} - H_2O$], 192 (100), 174 (90), 107 (90).

HRMS: *m/z* calcd. for $C_{18}H_{20}N_2O$ [$M - H_2O$]$^+$ 280.1576; found 280.1569.

IR (FT): ν = 3451 (NH and OH), 2967 (CH), 1657 (C=O), 1562 (aromatic C=C), 1417, 1365, 1214, 1061 cm^{-1}.

N-(2-Hydroxy-2,2-diphenyl-1-(pyridin-4-yl)ethyl)pivalamide (4.15)



Yield: 0.57 g (1.52 mmol, 76%).

M.p: 218-220 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 5 Hz, 2 H, H-2/H-6), 7.53 (d, *J* = 8 Hz, 4 H, H-2/H-6 of 2 Ph), 7.37 (t, *J* = 8 Hz, 2 H, H-4 of 2 Ph), 7.30-7.17 (m, 4 H, H-3/H-5 of 2 Ph), 6.95 (d, *J* = 5 Hz, 2 H, H-3/H-5), 6.76 (d, *J* = 8 Hz, exch., 1 H, NH), 5.93 (d, *J* = 8 Hz, 1 H, CHNH), 3.96 (br., exch., 1 H, OH), 1.00 [s, 9 H, $C(CH_3)_3$] ppm.

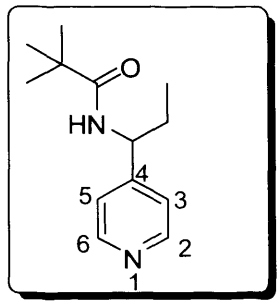
^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.6 (s, C=O), 148.8 (d, C-2/C-6), 147.8 (s, C-4), 144.1 (s, C-1 of Ph), 143.7 (s, C-1 of Ph), 128.5 (d, C-3/C-5 of Ph), 128.2 (d, C-3/C-5 of Ph), 127.53 (d, C-4 of Ph), 127.46 (d, C-4 of Ph), 125.9 (d, C-2/C-6 of Ph), 125.7 (d, C-2/C-6 of Ph), 124.0 (d, C-3/C-5), 80.9 (s, COH), 58.42 (d, CHNH), 38.6 [s, $C(CH_3)_3$], 27.1 [s, $C(CH_3)_3$] ppm.

ES–MS: *m/z* (%) = 438 (20) [$M^{\bullet+}MeCNNa^+$], 375 (40) [$M^{\bullet+}MeCNH^+$], 375 (100) [MH^+], 357 (5) [$MH^+ - H_2O$], 234 (60), 193 (100).

HRMS: *m/z* calcd. for $C_{24}H_{27}N_2O_2$ $[MH]^+$ 375.2073; found 375.2075.

IR (FT): ν = 3455 (NH and OH), 2967 (CH), 1658 (C=O), 1510 (aromatic C=C), 1419, 1367, 1214, 1059 cm^{-1}.

_N_-(1-(Pyridin-4-yl)propyl))pivalamide (4.16)



Yield: 0.35 g (1.59 mmol, 80%).

M.p: 111-113 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 5 Hz, 2 H, H-2/H-6), 7.03 (d, *J* = 5 Hz, 2 H, H-3/H-5), 5.78 (d, *J* = 7 Hz, exch., 1 H, NH), 4.70 (q, *J* = 7 Hz, 1 H, CHNH), 1.70 (m, 1 H, CH_aCH_b), 1.61 (m, 1 H, CH_aCH_b), 1.08 [s, 9 H, $C(CH_3)_3$], 0.80 (t, *J* = 7 Hz, 3 H, CH_2CH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.0 (s, C=O), 151.7 (s, C-4), 149.9 (d, C-2/C-6), 121.5 (d, C-3/C-5), 53.7 (d, CH), 38.7 [s, $C(CH_3)_3$], 28.7 (t, CH_2), 27.6 [s, $C(CH_3)_3$], 10.5 (q, CH_3) ppm.

EI–MS: *m/z* (%) = 220 (35) [$M^{\bullet+}$], 191 (80) [$M^{\bullet+}$ – Et], 120 (100) [$M^{\bullet+}$ – NHCO^{t}Bu], 106 (65), 65 (15).

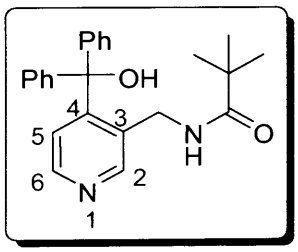
HRMS: *m/z* calcd. for $C_{13}H_{20}N_2O$ $[M]^+$ 220.1576; found 220.1577.

IR (FT): ν = 3458 (NH and OH), 2969 (CH), 1663 (C=O), 1601 (aromatic C=C), 1475, 1367, 1214, 1022 cm^{-1}.

4.15.5 Synthesis of *N*-((4-(hydroxydiphenylmethyl)pyridin-3-yl)methyl)pivalamide (4.17) and *N*-(2-hydroxy-2,2-diphenyl-1-(pyridin-3-yl)ethyl)pivalamide (4.18) *via* directed lithiation of *N*-(pyridine-3-ylmethyl)pivalamide (4.5)

The procedure was identical with that described in Section 4.14.3 except that the *N*-(pyridine-3-ylmethyl)pivalamide **4.6** was used instead of *N*-(pyridine-2-ylmethyl)pivalamide **4.4** and the appropriate organolithium reagent was used.In particular, a solution of *n*-BuLi in pentane (2.6 mL, 2.5 M, 6.6 mmol) was used to produce compound **4.17** and a solution of LDA in THF/heptane/ethylbenzene (3.3 mL, 2.0 M, 6.6 mmol) was used to produce compound **4.18**. Benzophenone (1.20 g, 6.6 mmol, 3.3 mole equivalents) was used as the elctrophile. The reactions were worked-up as usual and the residues obtained were purified by column chromatography (silica gel; AcOEt–hexane) to give pure products.

N-((4-(Hydroxydiphenylmethyl)pyridin-3-yl)methyl)pivalamide (4.17)



Yield: 0.30 g (0.80 mmol, 40%).

M.p: 211-213 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.37 (s, 1 H, H-2), 8.33 (d, J = 5 Hz, 1 H, H-6), 7.87 (br., exch., 1 H, NH) 7.15-7.38 (m, 11H, 10 H of 2 Ph and OH), 6.53 (d, J = 5 Hz, 1 H, H-5), 4.10 (d, J = 6 Hz, 2 H, CH_2), 1.09 [s, 9 H, $C(CH_3)_3$] ppm.

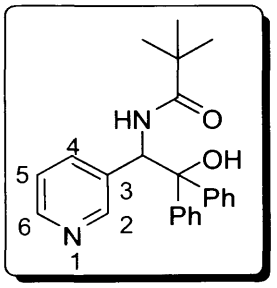
^{13}C NMR (125 MHz, DMSO-d_6): δ = 178.2 (s, C=O), 152.8 (d, C-2), 150.0 (d, C-6), 148.0 (s, C-4), 146.40 (s, C-1 of Ph), 134.3 (s, C-3), 128.5 (d, C-3/C-5 of 2 Ph), 127.8 (d, C-2/C-6 of 2 Ph), 127.6 (d, C-4 of 2 Ph), 123.3 (d, C-5), 81.5 (s, COH), 39.7 (t, CH_2), 38.5 [s, $C(CH_3)_3$], 27.8 [s, $C(CH_3)_3$] ppm.

EI–MS: *m/z* (%) = 374 (10) [$M^{\bullet+}$], 358 (50), 255 (100), 179 (100)

HRMS: *m/z* calcd. for $C_{24}H_{26}N_2O_2$ $[M]^+$ 374.1994; found 374.1989.

IR (FT): ν = 3581 (NH and OH), 2984 (CH), 1596 (C=O), 1425 (aromatic C=C), 1240, 1017 cm^{-1}.

_N_-(2-Hydroxy-2,2-diphenyl-1-(pyridin-3-yl)ethyl)pivalamide (4.18)



Yield: 0.39 g (1.04 mmol, 52%).

M.p: 222-224 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.47 (s, 1 H, H-2), 7.88 (d, *J* = 5 Hz, 1 H, H-6), 7.57 (d, *J* = 8 Hz, 1 H, H-4), 7.38-6.99 (m, 10 H, 2 Ph), 6.90 (dd, *J* = 5, 8 Hz, 1 H, H-5), 5.96 (d, *J* = 6 Hz, 1 H, CHNH), 5.22 (br., exch., 1 H, OH), 4.43 (d, *J* = 6 Hz, 1 H, NH), 0.99 [s, 9 H, $C(CH_3)_3$] ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7 (s, C=O), 149.4 (d, C-2), 147.4 (d, C-6), 144.6 (s, C-1 of Ph), 144.1 (s, C-1 of Ph), 137.2 (d, C-4), 135.0 (s, C-3), 128.4 (d, C-3/C-5 of Ph), 128.1 (d, C-3/C-5 of Ph), 127.4 (d, C-4 of Ph), 127.2 (d, C-4 of Ph), 126.2 (d, C-2/C-6 of Ph), 125.9 (d, C-2/C-6 of Ph), 122.5 (d, C-5), 80.8 (s, COH), 57.7 (d, CHNH), 38.6 [s, $C(CH_3)_3$], 27.2 [s, $C(CH_3)_3$] ppm.

APCI–MS: *m/z* (%) = 416 (40) [$M^{\bullet+}MeCNH^+$], 375 (100) [MH^+], 234 (30), 193 (35), 126 (30).

HRMS: *m/z* calcd. for $C_{24}H_{27}N_2O_2$ $[MH]^+$ 375.2073; found 375.2079.

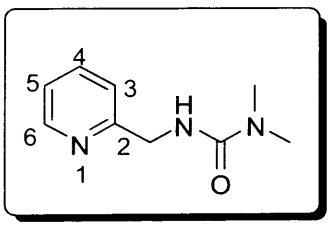
IR (FT): ν = 3434 (NH and OH), 2432 (CH), 1652 (C=O), 1558 (aromatic C=C), 1423, 1336, 1213, 1025 cm^{-1}.

Anal. Calc. For $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.81; H, 7.03; N, 6.35.

4.15.6 Synthesis of various *N'*-(pyridinylmethyl)-*N,N*-dimethylureas

A stirred mixture of the appropriate pyridinylmethylamine derivative (4.32 g, 40.0 mmol), dimethylcarbamoyl chloride (4.83 g, 45 mmol) and triethylamine (5.05 g, 55.0 mmol) in methanol (20 mL) was heated under reflux for 1 h. The mixture was poured onto H_2O (50 mL) and the organic layer was separated, washed with H_2O (2 x 25 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give **4.20**, **4.21** and **4.22**.

N'-(Pyridine-2-ylmethyl)-*N,N*-dimethylurea (4.20)



Yield: 3.36 g (18.8 mmol, 47%).

Oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 5 Hz, 1 H, H-6), 7.55-7.53 (m, 1 H, H-4), 7.21 (d, *J* = 8 Hz, 1H, H-3), 7.07-7.04 (m, 1 H, H-5), 5.82 (br., exch., 1 H, NH), 4.43 (d, *J* = 5 Hz, 2 H, CH_2), 2.86 (s, 6 H, NMe_2) ppm.

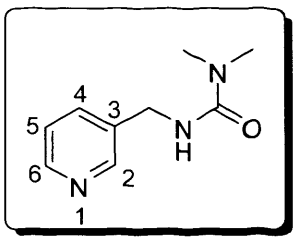
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5 (s, C=O), 158.0 (s, C-2), 148.8 (d, C-6), 136.6 (d, C-4), 122.0 (d, C-3), 121.9 (d, C-5), 45.9 (t, CH_2), 36.2 (q, NMe_2) ppm.

APCI–MS: *m/z* (%) = 180 (100) [MH^+], 135 (85).

HRMS: *m/z* calcd. for $C_9H_{14}N_3O$ [MH]$^+$ 180.1137; found 180.1139.

IR (FT): ν = 3343 (NH and OH), 2925 (CH), 1635 (C=O), 1534 (aromatic C=C), 1474, 1232, 1049 cm^{-1}.

_N'_-(Pyridine-3-ylmethyl)-_N,N_-dimethylurea (4.21)



Yield: 3.22 g (18.0 mmol, 45%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.48-8.42 (m, 2 H, H-2/H-6), 7.70 (d, *J* = 8 Hz, 1 H, H-4), 7.21 (dd, , *J* = 5, 8 Hz, 1 H, H-5), 5.07 (br., exch., 1 H, NH), 4.36 (d, *J* = 6 Hz, 2 H, CH_2), 2.85 (s, 6 H, NMe_2) ppm.

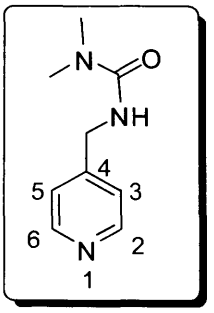
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C=O), 148.7 (d, C-2), 148.0 (d, C-6), 136.1 (s, C-3), 136.0 (d, C-4), 123.7 (d, C-5), 42.4 (t, CH_2), 36.3 (q, NMe_2) ppm.

EI–MS: *m/z* (%) = 179 (100) [$M^{\bullet+}$], 135 (40), 107 (45).

HRMS: *m/z* calcd. for $C_9H_{13}N_3O$ [M]$^+$ 179.1059; found 179.1057.

IR (FT): ν = 3335 (NH and OH), 2929 (CH), 1633 (C=O), 1537 (aromatic C=C), 1427, 1378, 1234, 1033 cm^{-1}.

_N'_-(Pyridime-4-ylmethyl)-_N,N_-dimethylurea (4.22)



Yield: 3.50 g (19.5 mmol, 49%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 5 Hz, 2 H, H-2/H-6), 7.16 (d, *J* = 5 Hz, 2 H, H-3/H-5), 4.80 (br., exch., 1 H, NH), 4.38 (d, *J* = 6 Hz, 2 H, CH_2), 2.89 (s, 6 H, NMe_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.2 (s, C=O), 149.8 (d, C-2/C-6), 149.1 (s, C-4), 122.2 (d, C-3/C-5), 43.8 (t, CH_2), 36.3 (q, NMe_2) ppm.

APCI–MS: *m/z* (%) = 180 (100) [MH^+], 131 (20).

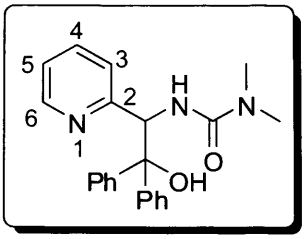
HRMS: *m/z* calcd. for $C_9H_{14}N_3O$ [$M]^+$ 180.1137; found 180.1145.

IR (FT): ν = 3337 (NH and OH), 2929 (CH), 1635 (C=O), 1537 (aromatic C=C), 1417, 1359, 1233, 1066 cm^{-1}.

4.15.7 Syntheses of various substituted (dimethylaminocarbonylamino)(pyridine-2-yl)methanes 4.23-4.25 *via* directed lithiation of *N'*-(pyridine-2-ylmethyl)-*N*,*N*-dimethylurea (4.20) and *N'*-(pyridine-4-ylmethyl)-*N*,*N*-dimethylurea (4.22)

The procedure was identical with that described in Section 4.14.3 except that *N'*-(pyridine-2-ylmethyl)-*N*,*N*-dimethylurea **4.20** and *N'*-(pyridine-4-ylmethyl)-*N*,*N*-dimethylurea **4.22** were used instead of *N*-(pyridine-2-ylmethyl)pivalamide **4.4**. The reaction was worked-up as usual and the residue obtained was purified by column chromatography (silica gel; AcOEt–hexane) to give pure product. The yields obtained are reported in Table 4.6

N'-(2-Hydroxy-2,2-diphenyl-1-(pyridine-2-yl)ethyl)-N,N-dimethylurea (4.23)



Yield: 0.47 g (1.30 mmol, 65%).

M.p: 197-199 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37 (d, J = 5 Hz, 1 H, H-6), 7.67-6.99 (m, 14 H, 10H of 2 Ph, H-4/H-3/H-5 and OH), 5.98 (d, J = 8 Hz, 1 H, NH), 5.79 (d, J = 8 Hz, exch., 1 H, CHNH), 2.74 (s, 6 H, NMe_2) ppm.

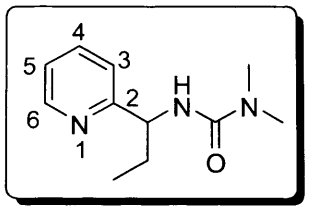
^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.5 (s, C=O), 157.6 (s, C-2), 147.6 (d, C-6), 145.8 (s, C-1 of Ph), 144.7 (s, C-1 of Ph), 137.5 (d, C-4), 128.2 (d, C-3/C-5 of Ph), 127.9 (d, C-3/C-5 of Ph), 126.7 (d, C-3), 126.3 (s, C-4 of Ph), 126.3 (s, C-4 of Ph), 125.6 (d, C-2/C-6 of Ph), 125.5 (d, C-2/C-6 of Ph), 122.5 (d, C-5), 80.9 (s, COH), 58.4 (d, CHNH), 36.0 (q, NMe_2) ppm.

APCI–MS: m/z (%) = 362 (100) [MH^+], 344 (50) [$MH^+ - H_2O$].

HRMS: m/z calcd. for $C_{22}H_{24}N_3O_2$ [MH]$^+$ 362.1869; found 362.1879

IR (FT): ν = 3459 (NH and OH), 2924 (CH), 1652 (C=O), 1569 (aromatic C=C), 1450, 1371, 1267, 1094 cm^{-1}.

_N,N_-Dimethyl- _N'_-(1- (pyridin-2-yl)propyl))urea (4.24)



Yield: 0.28 g (1.35 mmol, 68%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (d, J = 5 Hz, 1 H, H-6), 7.36-7.34 (m, 1 H, H-4), 6.96 (d, J = 8 Hz, 1 H, H-3), 6.88-6.86 (m, 1 H, H-5), 5.50 (br., exch., 1 H, NH), 4.64 (q, J = 7 Hz, 1 H, CHNH), 2.66 (s, 6 H, NMe_2), 1.58 (m, 1 H, CH_aCH_b), 1.42 (m,1 H, CH_aCH_b), 0.57 (t, J = 7 Hz, 3 H, CH_2CH_3) ppm.

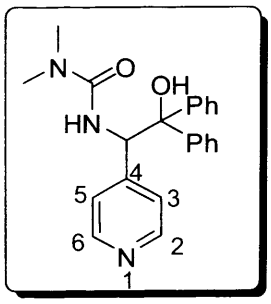
^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1 (s, C=O), 158.0 (s, C-2), 149.0 (d, C-6), 136.4 (d, C-4), 122.4 (d, C-3), 122.0 (d, C-5), 56.3 (d, CH), 36.1 (q, NMe_2), 29.9 (t, CH_2), 9.9 (q, CH_3) ppm.

APCI–MS: m/z (%) = 208 (100) [MH^+], 163 (60).

HRMS: m/z calcd. for $C_{11}H_{18}N_3O$ [$MH]^+$ 208.1450; found 208.1455.

IR (FT): ν = 3419 (NH and OH), 2986 (CH), 1642 (C=O), 1594 (aromatic C=C), 1472, 1381, 1265, 1150 cm^{-1}.

_N'_-(2-Hydroxy-2,2-diphenyl-1-(pyridine-4-yl)ethyl)-_N,N_-dimethylurea (4.25)



Yield: 0.45 g (1.25 mmol, 62%).

M.p: 204-206 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 5 Hz, 2 H, H-2/H-6), 7.56-6.89 (m, 12 H, 10 H of 2 Ph and H-3/H-5), 6.52 (d, *J* = 8 Hz, exch., 1 H, NH), 6.38 (br., exch., 1 H, OH), 5.77 (d, *J* = 8 Hz, 1 H, CHNH), 2.70 (s, 6 H, NMe_2) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.8 (s, C=O), 150.1 (s, C-4), 148.5 (d, C-2/C-6), 145.4 (s, C-1 of Ph), 145.2 (s, C-1 of Ph), 128.4 (d, C-3/C-5 of Ph), 127.9 (d, C-3/C-5 of Ph), 127.1 (d, C-4 of Ph), 126.8 (d, C-2/C-6 of Ph), 126.7 (d, C-2/C-6 of Ph), 124.8 (d, C-3/C-5), 80.0 (s, COH), 60.7 (d, CHNH), 36.4 (q, NMe_2) ppm.

APCI–MS: *m/z* (%) = 362 (20) [MH^+], 344 (50) [$MH^+ - H_2O$], 262 (60), 180 (100)

HRMS: *m/z* calcd. for $C_{22}H_{24}N_3O_2$ $[MH]^+$ 362.1869; found 362.1875.

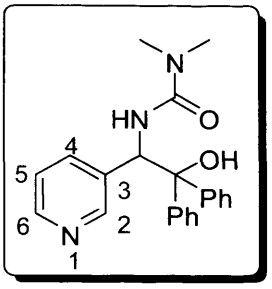
IR (FT): ν = 3329 (NH and OH), 2917 (CH), 1630 (C=O), 1510 (aromatic C=C), 1419, 1367, 1275, 1059 cm^{-1}.

4.15.8 Synthesis of *N'*-(2-hydroxy-2,2-diphenyl-1-(pyridine-3-yl)ethyl)-*N*,*N*-dimethylurea (4.26) and *N'*-((4-(hydroxydiphenymethyl)pyridine-3-yl)methyl)-*N*,*N*-dimethylurea (4.27) *via* directed lithiation of *N'*-(pyridine-3-ylmethyl)-*N*,*N*-dimethylurea (4.21)

The procedure was identical with that described in Section 4.14.3 except that *N'*-(pyridine-3-ylmethyl)-*N*,*N*-dimethylurea **4.21** was used instead of *N*-(pyridine-2-ylmethyl)pivalamide **4.4** and the appropriate organolithium reagent was used.In particular, a solution of *n*-BuLi in pentane (2.6 mL, 2.5 M, 6.6 mmol) was used to produce compound **4.17** and a solution of LDA in THF/heptane/ethylbenzene (3.3 mL, 2.0 M, 6.6 mmol) was used to produce compound **4.18**. Benzophenone (1.20 g, 6.6 mmol, 3.3 mole equivalents) was used as the elctrophile. The reactions were

worked-up as usual and the residues obtained were purified by column chromatography (silica gel; AcOEt–hexane) to give pure products.

_N'_-(2-Hydroxy-2,2-diphenyl-1-(pyridine-3-yl)ethyl)-_N,N_-dimethylurea (4.26)



Yield: 0.38 g (1.05 mmol, 53%).

M.p: 203-205 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (s, 1 H, H-2), 7.96 (d, J = 5 Hz, 1 H, H-6), 7.52 (d, J = 8 Hz, 1 H, H-4), 7.31 -6.86 (m, 11 H, 10 H of 2 Ph and OH), 7.01 (dd, J = 5, 8 Hz, 1 H, H-5), 5.82 (br., exch., 1 H, NH), 5.76 (d, J = 6 Hz, 1 H, CHNH), , 2.64 (s, 6 H, NMe_2) ppm.

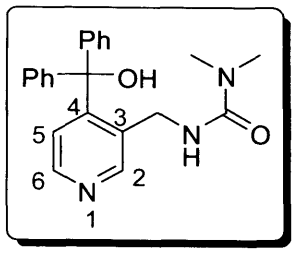
^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.4 (s, C=O), 149.2 (d, C-2), 146.6 (d, C-6), 144.7 (s, C-1 of Ph), 144.4 (s, C-1 of Ph), 137.8 (s, C-3), 136.4 (d, C-4), , 128.5 (d, C-3/C-5 of Ph), 128.0 (d, C-3/C-5 of Ph), 127.3 (d, C-4 of Ph), 127.1 (d, C-4 of Ph), 126.5 (d, C-2/C-6 of Ph), 125.8 (d, C-2/C-6 of Ph), 122.6 (d, C-5), 80.9 (s, COH), 59.4 (d, CHNH), 36.1 (q, NMe_2) ppm.

APCI–MS: *m/z* (%) = 362 (100) [MH^+], 120 (65).

HRMS: *m/z* calcd. for $C_{22}H_{24}N_3O_2$ [$MH]^+$ 362.1869; found 362.1874.

IR (FT): ν = 3366 (NH and OH), 2927 (CH), 1623 (C=O), 1522 (aromatic C=C), 1448, 1380, 1214, 1064 cm^{-1}.

_N'_-((4-(Hydroxydiphenymethyl)pyridine-3-yl)methyl)-_N,N_-dimethylurea (4.27)



Yield: 0.29 g (0.80 mmol, 40%).

M.p: 219-221 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (s, 1 H, H-2), 8.26 (d, J = 5 Hz, 1 H, H-6), 7.33-7.28 (m, 11 H, 10 H of 2 Ph and OH), 6.59 (d, J = 5 Hz, 1 H, H-5), 5.38 (t, J = 6 Hz, exch., 1 H, NH), 4.12 (d, J = 6 Hz, 1 H, CH_2), 2.82 (s, 6 H, NMe_2) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 153.6 (s, C-4), 152.1 (d, C-2), 147.8 (s, C-6), 146.7 (d, C-1 of 2 Ph), 134.6 (s, C-3), 128.1 (d, C-3/C-5 of Ph), 127.6 (d, C-2/C-6 of Ph), 127.2 (d, C-4 of Ph), 124.0 (d, C-5), 81.3 (s, COH), 41.1 (d, CH_2), 36.2 (q, NMe_2) ppm.

EI–MS: *m/z* (%) = 361 (10) [$M^{\bullet+}$], 343 (70).

HRMS: *m/z* calcd. for $C_{22}H_{23}N_3O_2$ $[M]^+$ 361.1790; found 361.1790.

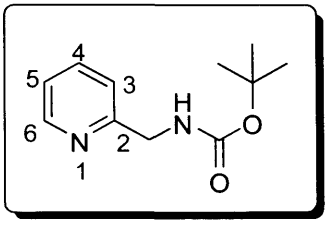
IR (FT): ν = 3583 (NH and OH), 2965 (CH), 1638 (C=O), 1524 (aromatic C=C), 1476, 1376, 1218, 1028 cm^{-1}.

4.15.9 Syntheses of various *tert*-butyl pyridinylmethyl carbamates

Di-*tert*-butyl dicarbonate [$(Boc)_2O$] (8.72 g, 40.0 mmol) was added to a magnetically stirred solution of the appropriate pyridinylmethylamine derivative (4.32 g, 40.0 mmol) and $InCl_3$ (0.11 g, 0.05 mmol) at room temperature. Vigorous effervescing was observed. The reaction was stirred and monitored by TLC until completion. The mixture was diluted in ethyl acetate (20ml). The organic layer was

washed with H_2O (2×10ml), $NaHCO_3$ (2×10ml), and H_2O (2×10ml) respectively, dried with $MgSO_4$ and concentrated under reduced pressure to give *tert*-butyl pyridine-2-ylmethylcarbamate **4.28**, *tert*-butyl pyridine-3-ylmethylcarbamate **4.29** or *tert*-butyl pyridine-4-ylmethylcarbamate **4.30**.

tert-Butyl pyridine-2-ylmethylcarbamate (4.28)



Yield: 7.74 g (37.2 mmol, 93%).

Oil.

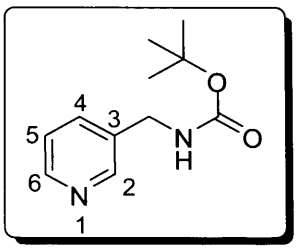
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 5 Hz, 1 H, H-6), 7.60-7.58 (m, 1 H, H-4), 7.23 (d, *J* = 8 Hz, 1 H, H-3), 7.12-7.10 (m, 1 H, 5-H), 5.82 (br., exch., 1 H, NH), 4.40 (d, *J* = 5 Hz, 2 H, CH_2), 1.41 [s, 9 H, $C(CH_3)_3$] ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.6 (s, C=O), 156.0 (s, C-2), 149.0 (d, C-6), 136.6 (d, C-4), 122.1 (d, C-3), 121.6 (d, C-5), 79.3 [s, $C(CH_3)_3$], 45.7 (t, CH_2), 28.4 [s, $C(CH_3)_3$] ppm. EI–MS: *m/z* (%) = 209 (5) [MH^+], 153 (100) [$M^{\bullet+}$ – ^{t}Bu], 135 (95) [$M^{\bullet+}$- O^{t}Bu], 109 (98), 92 (95), 80 (83), 57 (93).

HRMS: *m/z* calcd. for $C_{11}H_{17}N_2O_2$ $[MH]^+$ 209.1290; found 209.1293.

IR (FT): ν = 3343 (NH and OH), 2977 (CH), 1712 (C=O), 1571 (aromatic C=C), 1477, 1275, 1249, 1171 cm^{-1}.

tert-Butyl pyridine-3-ylmethylcarbamate (4.29)



Yield: 7.70 g (37.0 mmol, 93%).

Oil.

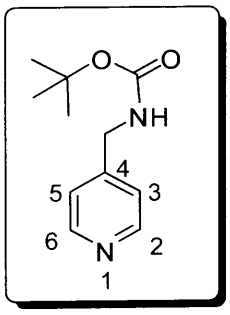
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.19 (s, 1 H, H-2), 8.13 (d, J = 5 Hz, 1 H, H-6), 7.34 (d, J = 8 Hz, 1 H, H-4), 6.93 (dd, J = 5, 8 Hz, 1 H, H-5), 6.45 (br., exch., 1 H, NH), 4.01 (d, J = 6 Hz, 2 H, CH_2), 1.16 [s, 9 H, $C(CH_3)_3$] ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.2 (s, C=O), 148.5 (d, C-2), 148.0 (d, C-6), 135.0 (s, C-3), 134.9 (d, C-4), 123.2 (d, C-5), 79.0 [s, $C(CH_3)_3$], 41.8 (t, CH_2), 28.2 [s, $C(CH_3)_3$] ppm. EI–MS: *m/z* (%) = 208 (5) [$M^{\bullet+}$], 152 (30), 135 (20), 107 (68), 80 (100).

HRMS: *m/z* calcd. for $C_{11}H_{16}N_2O_2$ $[M]^+$ 208.1212; found 208.1207.

IR (FT): ν = 3352 (NH and OH), 2980 (CH), 1707 (C=O), 1579 (aromatic C=C), 1431, 1367, 1249, 1218, 1165 cm^{-1}.

tert-Butyl pyridine-4-ylmethylcarbamate (4.30)



Yield: 7.24 g (34.8 mmol, 87%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 5 Hz, 2 H, H-2/H-6), 7.18 (d, *J* = 5 Hz, 2 H, H-3/H-5), 5.44 (br., exch., 1 H, NH), 4.30 (d, *J* = 6 Hz, 2 H, CH_2), 1.45 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0 (s, C=O), 149.8 (d, C-2/C-6), 148.4 (s, C-4), 122.0 (d, C-3/C-5), 79.9 [s, $C(CH_3)_3$], 43.4 (t, CH_2), 28.3 [s, $C(CH_3)_3$] ppm.

EI–MS: *m/z* (%) = 208 (10) [$M^{\bullet+}$], 152 (90), 134 (70), 107 (85), 92 (38), 80 (100), 57 (90).

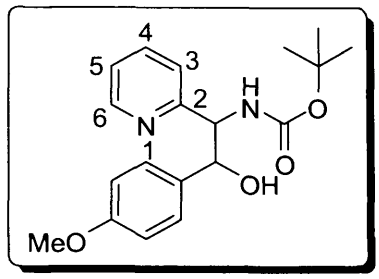
HRMS: *m/z* calcd. for $C_{11}H_{16}N_2O_2$ $[M]^+$ 208.1212; found 208.1209.

IR (FT): ν = 3219 (NH and OH), 2971 (CH), 1707 (C=O), 1565 (aromatic C=C), 1454, 1278, 1217, 1167 cm^{-1}.

4.15.10 Syntheses of various substituted (*tert*-butoxy carbonyl amino)(pyridine-2-yl)methanes 4.31-4.38 *via* directed lithiation of *tert*-butyl pyridine-2-ylmethylcarbamate (4.28) and *tert*-butyl pyridine-4-ylmethylcarbamate (4.30)

The procedure was identical with that described in Section 4.14.3 except that the *tert*-butylpyridine-2-ylmethylcarbamate **4.28** or *tert*-butyl pyridine-4-ylmethylcarbamate **4.30** were used instead of *N*-(pyridine-2-ylmethyl)pivalamide **4.4**. The reaction was worked-up as usual and the residues obtained were purified by column chromatography (silica gel; AcOEt–hexane) to give pure products. The yields obtained are reported in Table 4.7.

tert-Butyl 2-hydroxy-2-(4-methoxyphenyl)-1-(pyridin-2-yl)ethylcarbamate (4.31)



Yield: 0.49 g (1.42 mmol, 71%).

M.p: 99-101 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, J = 5 Hz, 0.45 H, H-6 of isomer **a**), 8.51 (d, J = 5 Hz, 0.55 H, H-6 of isomer **b**), 7.64-7.60 (m, 1 H, H-4 of **a** + **b**), 7.25-7.23 (m, 1 H, H-3 of **a** + **b**), 7.20-7.18 (m, 1 H, H-5 of **a** + **b**), 7.04-7.01 (m, 2 H, H-2/H-6 of 4-methoxyphenyl of **a** + **b**), 6.86 (d, J = 8 Hz, 0.90 H, H-3/H-5 of 4-methoxyphenyl of **a**), 6.75 (d, J = 8 Hz, 1.1 H, H-3/H-5 of 4-methoxyphenyl of **b**), 6.00 (br., exch., 1 H, NH of **a** + **b**), 5.79-5.77 (m, 1 H, CHOH of **a** + **b**), 5.16-5.12 (m, 1 H, CHNH of **a** + **b**), 4.92 (br., exch., 1 H, OH of **a** + **b**), 3.80 (s, 1.35 H, OCH_3 of **a**), 3.76 (s, 1.65 H, OCH_3 of **b**), 1.44 [s, 4.05 H, $C(CH_3)_3$ of **a**], 1.37 [s, 4.95 H, $C(CH_3)_3$ of **b**] ppm.

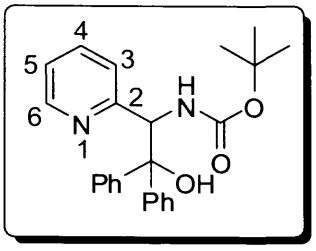
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.5, 159.0 (2 s, C-4 of 4-methoxyphenyl of **a**, **b**), 158.7 (s, C-2 of **a** + **b**), 157.8 (s, C=O of **a** + **b**), 156.8, 156.1 (2 s, C-1 of 4-methoxyphenyl of **a**, **b**), 148.7, 148.4 (2 d, C-6 of **a**, **b**), 137.0, 136.9 (2 d, C-4 of **a**, **b**), 127.5, 127.1 (2 d, C-2/C-6 of 4-methoxyphenyl of **a**, **b**), 124.0, 123.6 (2 d, C-3 of **a**, **b**), 122.8 (d, C-5 of **a** + **b**), 113.6, 113.3 (2 d, C-3/C-5 of 4-methoxyphenyl of **a**, **b**), 79.8, 79.7 (2 d, CHOH of **a**, **b**), 75.5 [s, $C(CH_3)_3$ of **a** + **b**], 59.6, 59.2 (2 d, CHNH of **a**, **b**), 55.24, 55.16 (2 s, OCH_3 of **a**, **b**), 28.34, 28.29 [2 s, $C(CH_3)_3$ of **a**, **b**] ppm.

APCI–MS: *m/z* (%) = 345 (100) [MH^+], 289 (10), 271 (10).

HRMS: *m/z* calcd. for $C_{19}H_{25}N_2O_4$ $[MH]^+$ 345.1814; found 345.1809.

IR (FT): ν = 3436 (NH and OH), 2981 (CH), 1704 (C=O), 1572 (aromatic C=C), 1438, 1365, 1216, 1171 cm^{-1}.

tert-Butyl 2-hydroxy-2,2-diphenyl-1-(pyridin-2-yl)ethylcarbamate (3.32)



Yield: 0.66 g (1.69 mmol, 85%).

M.p:155-157 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 5 Hz, 1 H, H-6), 7.58 (d, *J* = 8 Hz, 4 H, H-2/H-6 of 2 Ph), 7.41-7.38 (m, 1 H, H-4), 7.31 (d, *J* = 8 Hz, 1 H, H-3), 7.22 (t, *J* = 8 Hz, 4 H, H-3/H-5 of 2 Ph), 7.09 (t, *J* = 8 Hz, 2 H, H-4 of 2 Ph), 6.99-6.95 (m, 1 H, H-5), 5.75 (br., exch., 1 H, NH), 5.72 (s, 1 H, CHNH), 5.70 (br., exch., 1 H, OH), 1.19 [s, 9 H, $C(CH_3)_3$] ppm.

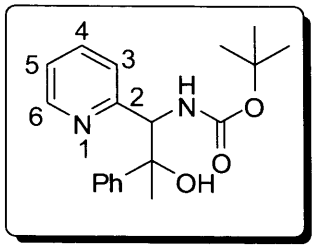
^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0 (s, C-2), 155.5 (s, C=O), 148.0 (d, C-6), 145.9 (s, C-1 of Ph), 144.5 (s, C-1 of Ph), 137.3 (d, C-4), 128.1 (d, C-3/C-5 of Ph), 127.9 (d, C-3/C-5 of Ph), 126.7 (d, C-4 of Ph), 126.3 (d, C-4 of Ph), 125.7 (d, C-2/C-6 of Ph), 125.5 (d, C-2/C-6 of Ph), 125.1 (d, C-3), 122.6 (d, C-5), 80.9 (s, COH), 79.5 [s, $C(CH_3)_3$], 58.1 (d, CHNH), 28.2 [s, $C(CH_3)_3$] ppm.

APCI–MS: *m/z* (%) = 391 (100) [MH^+].

HRMS: *m/z* calcd. for $C_{24}H_{27}N_2O_3$ [$MH]^+$ 391.2022; found 391.2032.

IR (FT): ν = 3273 (NH and OH), 2981 (CH), 1701 (C=O), 1573 (aromatic C=C), 1449, 1304, 1216, 1160 cm^{-1}.

tert-Butyl 2-hydroxy-2-phenyl-1-(pyridin-2-yl)propylcarbamate (3.33)



Yield: 0.50 g (1.52 mmol, 76%).

M.p: 150-152 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 5 Hz, 1 H, H-6), 7.71-7.68 (m, 1 H, H-4),7.57 (d, *J* = 8 Hz, 2 H, H-2/H-6 of Ph), 7.38-7.34 (m, 3 H, H-3/H-5 and H-4 of Ph), 7.30-7.24 (m, 2 H, H-3, H-5), 6.38 (br., exch., 1 H, NH), 5.65 (br., exch., 1 H, OH), 4.99 (d, *J* = 6 Hz, 1 H, CHNH), 1.37 (s, 3 H, CH_3), 1.23 [s, 9 H, $C(CH_3)_3$] ppm.

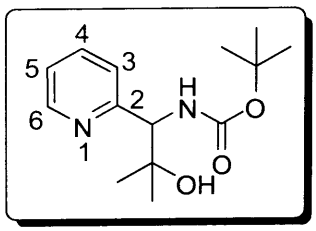
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.8 (s, C-2), 156.4 (s, C=O), 148.6 (d, C-6), 145.2 (s, C-1 of Ph), 137.3 (d, C-4), 128.0 (d, C-3/C-5 of Ph), 126.7 (d, C-3), 125.2 (d, C-2/C-6 of Ph), 124.8 (d, C-4 of Ph), 122.9 (d, C-5), 79.3 (s, COH), 77.1 [s, $C(CH_3)_3$], 61.0 (d, CHNH), , 28.1 [s, $C(CH_3)_3$] ppm.

APCI–MS: *m/z* (%) = 329 (100) [MH^+], 273 (13), 255 (5).

HRMS: *m/z* calcd. for $C_{19}H_{25}N_2O_3$ $[MH]^+$ 329.1865; found 329.1863.

IR (FT): ν = 3437 (NH and OH), 2982 (CH), 1704 (C=O), 1570 (aromatic C=C), 1434, 1369, 1214, 1169 cm^{-1}.

tert-Butyl 2-hydroxy-2-methyl-1-(pyridin-2-yl)propylcarbamate (3.34)



Yield: 0.42 g (1.58 mmol, 79%).

M.p. 156-158 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 5 Hz, 1 H, H-6), 7.62-7.60 (m, 1 H, H-4), 7.27 (d, *J* = 8 Hz, 1 H, H-3), 7.17-7.14 (m, 1 H, H-5), 5.67 (d, *J* = 8 Hz, exch., 1 H, NH), 5.25 (br., exch., 1 H, OH), 4.47 (d, *J* = 8 Hz, 1 H, CHNH), 1.33 [s, 9 H, $C(CH_3)_3$], 1.25 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3) ppm.

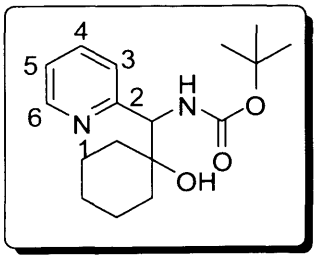
^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.2 (s, C-2), 155.8 (s, C=O), 148.8 (d, C-6), 137.2 (d, C-4), 124.4 (d, C-3), 122.8 (d, C-5), 79.4 [s, $C(CH_3)_3$], 73.0 (s, COH), 60.7 (d, CHNH), 28.4 [s, $C(CH_3)_3$], 27.9 (q, CH_3), 26.5 (q, CH_3) ppm.

APCI–MS: *m/z* (%) = 267 (100) [MH^+], 211 (65), 193 (17).

HRMS: *m/z* calcd. for $C_{14}H_{23}N_2O_3$ $[MH]^+$ 267.1709; found 267.1696.

IR (FT): ν = 3437 (NH and OH), 2981 (CH), 1704 (C=O), 1570 (aromatic C=C), 1367, 1274, 1216, 1164 cm^{-1}.

tert-Butyl (1-hydroxycyclohexyl)(pyridin-2-yl)methylcarbamate (4.35)



Yield: 0.49 g (1.60 mmol, 80%).

M.p: 178-180 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 5 Hz, 1 H, H-6), 7.69-7.66 (m, 1 H, H-4), 7.34 (d, *J* = 8 Hz, 1 H, H-3), 7.25-7.23 (m, 1 H, H-5), 5.72 (d, *J* = 8 Hz, exch., 1 H, NH), 5.18 (s, exch., 1 H, OH), 4.64 (d, *J* = 8 Hz, 1 H, CHNH), 1.83-1.31 (m, 10 H, cyclohexyl), 1.40 [s, 9 H, $C(CH_3)_3$] ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.2 (s, C-2), 155.8 (s, C=O), 148.9 (d, C-6), 137.2 (d, C-4), 124.5 (d, C-3), 122.7 (d, C-5), 79.3 [s, $C(CH_3)_3$], 73.9 (s, COH), 59.3 (d, CHNH), 36.2 (t, C-2/C-6 of cyclohexyl), 28.4 [s, $C(CH_3)_3$], 25.7 (t, C-4 of cyclohexyl), 21.8 (t, C-3/C-5 of cyclohexyl) ppm.

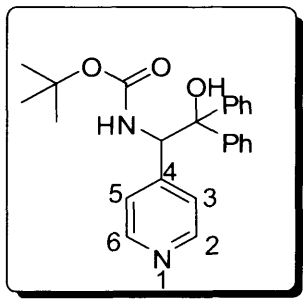
APCI–MS: *m/z* (%) = 307 (100) [MH^+], 251 (20).

HRMS: *m/z* calcd. for $C_{17}H_{27}N_2O_3$ $[MH]^+$ 307.2022; found 307.2025.

IR (FT): ν = 3438 (NH and OH), 2981 (CH), 1704 (C=O), 1572 (aromatic C=C), 1440, 1309, 1214, 1166 cm^{-1}.

Anal. Calc. For $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.39; H, 8.48; N, 9.14.

tert-Butyl 2-hydroxy-2,2-diphenyl-1-(pyridin-4-yl)ethylcarbamate (4.36)



Yield: 0.60 g (1.54 mmol, 77%).

M.p: 178-180 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.25 (d, *J* = 5 Hz, 2 H, H-2/H-6), 7.60-7.06 (m, 10 H, 2 Ph), 7.06 (d, *J* = 5 Hz, 2 H, H-3/H-5), 6.00 (br., exch., 1 H, NH), 5.61 (d, *J* = 8 Hz, 1 H, CHNH), 1.32 [s, 9 H, $C(CH_3)_3$] ppm.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.4 (s, C=O), 149.1 (s, C-4), 148.6 (d, C-2/C-6), 146.8 (s, C-1 of Ph), 144.8 (s, C-1 of Ph), 128.5 (d, C-3/C-5 of Ph), 128.0 (d, C-3/C-5 of Ph), 127.3 (d, C-4 of Ph), 126.8 (d, C-4 of Ph), 126.7 (d, C-2/C-6 of

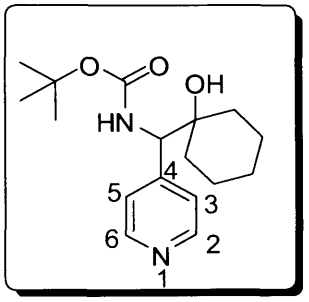
Ph), 126.1 (d, C-2/C-6 of Ph), 124.7 (d, C-3/C-5), 80.2 (s, COH), 79.0 [s, $C(CH_3)_3$], 60.6 (d, CHNH), , 28.6 [s, $C(CH_3)_3$] ppm.

ES–MS: *m/z* (%) = 432 (13) [$M^{\bullet+}MeCNH^+$], 391 (100) [MH^+], 250(40), 209(60), 153(10).

HRMS: *m/z* calcd. for $C_{24}H_{27}N_2O_3$ $[MH]^+$ 391.2022; found 391.2034.

IR (FT): ν = 3583 (NH and OH), 2399 (CH), 1709 (C=O), 1523 (aromatic C=C), 1475, 1363, 1212, 1063 cm^{-1}.

tert-Butyl (1-hydroxycyclohexyl)(pyridin-4-yl)methylcarbamate (4.37)



Yield: 0.45 g (1.47 mmol, 74%).

Oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 5 Hz, 2 H, H-2/H-6), 7.19 (d, *J* = 5 Hz, 2 H, H-3/H-5), 5.79 (d, *J* = 6 Hz, exch., 1 H, NH), 4.44 (d, *J* = 6 Hz, 1 H, CHNH), 3.14 (br., exch., 1H, OH), 1.82-1.07 (m, 10 H, cyclohexyl), 1.31 [s, 9 H, $C(CH_3)_3$] ppm.

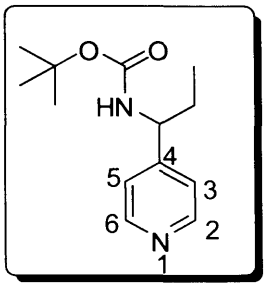
^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.6 (s, C=O), 149.3 (s, C-4), , 149.0 (d, C-2/C-6), 123.8 (d, C-3/C-5), 79.7 [s, $C(CH_3)_3$], 72.8 (s, COH), 61.3 (d, CHNH), 35.6 (t, C-2/C-6 of cyclohexyl), 28.3 [s, $C(CH_3)_3$], 25.4 (t, C-4 of cyclohexyl), 21.8 (t, C-3/C-5 of cyclohexyl) ppm.

APCI–MS: *m/z* (%) = 348 (40) [$M^{\bullet+}MeCNH^+$], 307 (100) [MH^+], 209 (5).

HRMS: *m/z* calcd. for $C_{17}H_{27}N_2O_3$ $[MH]^+$ 307.2022; found 307.2027.

IR (FT): ν = 3438 (NH and OH), 2979 (CH), 1699 (C=O), 1560 (aromatic C=C), 1449, 1321, 1274, 1216, 1166 cm^{-1}.

tert-Butyl 1-(pyridin-4-yl)propylcarbamate (4.38)



Yield: 0.35 g (1.48 mmol, 74%).

M.p: 124-126 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 5 Hz, 2 H, H-2/H-6), 7.20 (d, *J* = 5 Hz, 2 H, H-3/H-5), 5.13 (d, *J* = 6 Hz, exch., 1 H, NH), 4.55 (m, 1 H, CHNH), 1.74 (m, 1 H, CH_aCH_b), 1.46 (m, 1 H, CH_aCH_b), 1.43 [s, 9 H, $C(CH_3)_3$], 0.92 (t, *J* = 7 Hz, 3 H, CH_2CH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3 (s, C=O), 152.1 (s, C-4), 149.9 (d, C-2/C-6), 121.5 (d, C-3/C-5), 79.8 [s, $C(CH_3)_3$], 55.5 (d, CHNH), 29.3 (t, CH_2), 28.3 [s, $C(CH_3)_3$], 10.4 (q, CH_3) ppm.

EI–MS: *m/z* (%) = 237 (5) [MH^+], 207 (100) [$M^{\bullet+}$ – Et], 163 (80) [$M^{\bullet+}$ – O^{t}Bu], 151 (100), 133 (100), 120 (50), 107 (100), 78 (90), 57 (35).

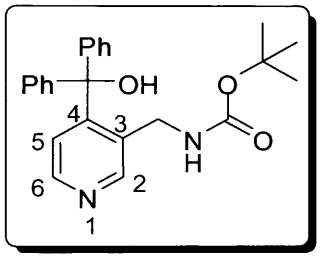
HRMS: *m/z* calcd. for $C_{13}H_{21}N_2O_2$ $[MH]^+$ 237.1603; found 237.1614.

IR (FT): ν = 3447 (NH and OH), 2977 (CH), 1710 (C=O), 1563 (aromatic C=C), 1417, 1367, 1216, 1167 cm^{-1}.

4.15.11 Syntheses of various 4-substituted-3-(*tert*-butoxy carbonylaminomethyl)pyridines 4.39-4.42 *via* directed lithiation of *tert*-butyl pyridine-3-ylmethylcarbamate (4.29)

The procedure was identical with that described in Section 4.14.3 except that *tert*-butyl pyridine-3-ylmethylcarbamate **4.29** was used instead of *N*-(pyridine-2-ylmethyl)pivalamide **4.4**. The reaction was worked-up as usual and the residue obtained was purified by column chromatography (silica gel; AcOEt–hexane) to give pure product.

tert-Butyl (4-(hydroxydiphenylmethyl)pyridin-3-yl)methylcarbamate (4.39)



Yield: 0.47 g (1.20 mmol, 60%).

M.p: 215-217 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.45 (s, 1 H, H-2), 8.34 (d, J = 5 Hz, 1 H, H-6), 7.36 (t, J = 8 Hz, 4 H, H-3/H-5 of 2 Ph), 7.31 (t, J = 8 Hz, 2 H, H-4 of 2 Ph), 7.19 (d, J = 8 Hz, 4 H, H-2/H-6 of 2 Ph), 6.89 (br., exch., 1 H, NH), 6.54 (d, J = 5 Hz, 1 H, H-5), 4.07 (d, J = 6 Hz, 2 H, CH_2), 1.38 [s, 9 H, $C(CH_3)_3$] ppm.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 156.2 (s, C=O), 152.9 (s, C-1 of Ph), 150.0 (d, C-2), 148.1 (d, C-6), 146.2 (s, C-4), 134.4 (s, C-3), 128.4 (d, C-3/C-5 of 2 Ph), 127.9 (d, C-2/C-6 of 2 Ph), 127.7 (d, C-4 of 2 Ph), 123.4 (d, C-5), 81.7 (s, COH), 78.5 [s, $C(CH_3)_3$], 40.6 (t, CH_2), 28.7 [s, $C(CH_3)_3$] ppm.

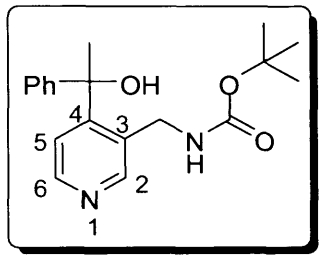
APCI–MS: *m/z* (%) = 432 (5) [$M^{\bullet+}$MeCNH$^+$], 391 (100) [MH^+], 115 (8).

HRMS: *m/z* calcd. for $C_{24}H_{27}N_2O_3$ $[MH]^+$ 391.2022; found 391.2017.

IR (FT): ν = 3447 (NH and OH), 2980 (CH), 1692 (C=O), 1591 (aromatic C=C), 1445, 1369, 1214, 1076 cm^{-1}.

Anal. Calc. For $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17. Found: C, 73.69; H, 6.84; N, 6.80.

tert-Butyl (4-(1-hydroxy-1-phenylethyl)pyridin-3-yl)methylcarbamate (4.41)



Yield: 0.41 g (1.25 mmol, 63%).

Oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, H-2), 8.30 (d, *J* = 5 Hz, 1 H, H-6), 7.79 (d, *J* = 8 Hz, 2 H, H-2/H-6 of Ph), 7.49-7.27 (m, 3 H, H-3/H-5 and H-4 of Ph), 7.07 (d, *J* = 5 Hz, 1 H, H-5), 6.20 (br., exch., 1 H, NH), 4.17 (d, *J* = 6 Hz, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 1.31 [s, 9 H, $C(CH_3)_3$] ppm.

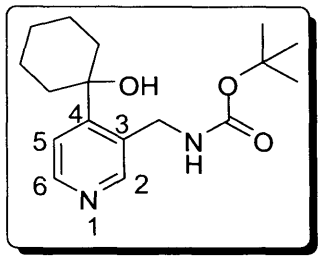
^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1 (s, C=O), 148.7 (d, C-2), 148.1 (d, C-6), 136.9 (s, C-4), 135.1 (s, C-1 of Ph), 134.9 (s, C-3), 132.9 (d, C-4 of Ph), 128.4 (d, C-3/C-5 of Ph), 128.1 (d, C-2/C-6 of Ph), 123.3 (d, C-5), 79.1 (s, COH), 77.4 [s, $C(CH_3)_3$], 41.9 (t, CH_2), 28.2 [s, $C(CH_3)_3$], 26.3 (q, CH_3) ppm.

EI–MS: *m/z* (%) = 313 (5) $[M^{\bullet+} - CH_3]$, 271 (10) $[M^{\bullet+} - {}^tBu]$, 210 (60), 195 (100), 180 (60), 133 (85), 83 (95).

HRMS: *m/z* calcd. for $C_{18}H_{21}N_2O_3$ $[M - CH_3]^+$ 313.1552; found 313.1555.

IR (FT): ν = 3352 (NH and OH), 2979 (CH), 1686 (C=O), 1581 (aromatic C=C), 1449, 1391, 1267, 1166 cm^{-1}.

tert-Butyl (4-(1-hydroxycyclohexyl)pyridine-3-yl)methylcarbamate (4.42)



Yield: 0.37 g (1.21 mmol, 61%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, H-2), 8.32 (d, *J* = 5 Hz, 1 H, H-6), 7.11 (d, *J* = 5 Hz, 1 H, H-5), 5.98 (br., exch., 1 H, NH), 5.98 (br., exch., 1 H, OH), 4.18 (d, *J* = 6 Hz, 2 H, CH_2), 2.25-144 (m, 10 H, cyclohexyl), 1.32 [s, 9 H, $C(CH_3)_3$] ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1 (s, C=O), 148.7 (d, C-2), 148.2 (d, C-6), 135.2 (s, C-4), 134.9 (s, C-3), 123.4 (d, C-5), 79.4 [s, $C(CH_3)_3$], 71.9 (s, COH), 43.7 (t, CH_2), 38.0(t, C-2/C-6 of cyclohexyl), 28.2 [s, $C(CH_3)_3$], 25.8 (t, C-4 of cyclohexyl), 21.5 (t, C-3/C-5 of cyclohexyl) ppm.

ES–MS: *m/z* (%) = 307 (100) [MH^+], 250 (43) [MH^+ – ^{t}Bu], 209 (68), 194 (35), 153 (20).

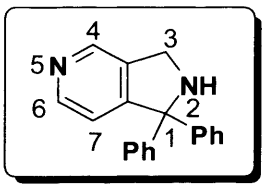
HRMS: *m/z* calcd. for $C_{17}H_{27}N_2O_3$ $[MH]^+$ 307.2022; found 307.2014.

IR (FT): ν = 3347 (NH and OH), 2979 (CH), 1700 (C=O), 1579 (aromatic C=C), 1449, 1367, 1280, 1252, 1167 cm^{-1}.

4.15.12 Synthesis of 1,1-diphenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (4.43) and 1-methyl-1-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (4.44)

Trifluoroacetic anhydride (a few drops) was added to a stirred solution of *tert*-butyl (4-(hydroxydiphenylmethyl)pyridin-3-yl)methylcarbamate (**4.39**) or *tert*-butyl (4-(1-hydroxy-1-phenylethyl)pyridin-3-yl)methylcarbamate (**4.41**) (0.5 g) in DCM (10 mL). The mixtures were refluxed for 12 h, after which TLC showed the formation of a pure products. The reaction mixtures were quenched with H_2O (10 mL). The organic layers were separated, washed with aq. sat. $NaHCO_3$ (10 mL) and H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residues obtained were subjected to flash column chromatography (silica gel; AcOEt–hexane) to give the pure products. The products were identified as1,1-diphenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (**4.43**) and 1-methyl-1-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (**4.44**).

1,1-Diphenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (4.43)



Yield: 0.30 g (1.10 mmol, 60%).

M.p: 206-208 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.48 (s, 1 H, H-4), 8.39 (d, J = 5 Hz, 1 H, H-6), 7.36-7.18 (m, 10 H, 2 Ph), 6.47 (d, J = 5 Hz, 1 H, H-7), 5.0 (br., exch., 1 H, NH), 3.43 (d, J = 6 Hz, 2 H, CH_2) ppm.

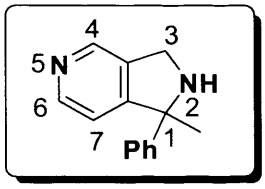
^{13}C NMR (125 MHz, DMSO-d_6): δ = 156.1 (s, C-1a), 152.7 (d, C-4), 149.5 (d, C-6), 146.7 (s, C-3a), 134.2 (s, C-1 of 2 Ph), 128.4 (d, C-3/C-5 of 2 Ph), 127.8 (d, C-2/C-6 of 2 Ph), 127.5 (d, C-4 of 2 Ph), 123.7 (d, C-7), 81.5 (s, C-1), 41.9 (t, CH_2) ppm.

APCI–MS: *m/z* (%) = 314 (25) [$M^{\bullet+}$ + MeCNH], 273 (100) [MH^+], 256 (13).

HRMS: *m/z* calcd. for $C_{19}H_{17}N_2$ [MH]$^+$ 273.1392; found 273.1393.

IR (FT): ν = 3054 (NH), 2985 (CH), 1589 (aromatic C=C), 1422, 1265 cm^{-1}.

1-Methyl-1-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (4.44)



Yield: 0.34 g (1.61 mmol, 68%).

Oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.55 (s, 1 H, H-4), 8.27 (br., exch., 1 H, NH), 7.53 (d, *J* = 5 Hz, 1 H, H-6), 7.25-7.15 (m, 6 H, 5 H of Ph and H-7), 3.50 (d, *J* = 13 Hz, 1 H, CH_aH$_b$), 3.03 (d, *J* = 13 Hz, 1 H, CH$_a$$H_b$) 1.77 (s, 3 H, CH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1 (s, C-7a), 152.0 (d, C-4), 150.2 (d, C-6), 148.7 (s, C-3a), 133.5 (s, C-1 of Ph), 128.2 (d, C-3/C-5 of Ph), 126.8 (d, C-4 of Ph), 124.9 (d, C-2/C-6 of Ph), 121.6 (d, C-7), 75.7 (s, C-1), 42.4 (t, CH_2), 31.8 (q, CH_3) ppm.

EI–MS: *m/z* (%) = 210 (25) [$M^{\bullet+}$], 195 (100), 133 (30).

HRMS: *m/z* calcd. for $C_{14}H_{14}N_2$ [M]$^+$ 210.1157; found 210.1151.

IR (FT): ν = 3054 (NH), 2986 (CH), 1570 (aromatic C=C), 1421, 1265 cm^{-1}.

4.16 References

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CHAPTER FIVE

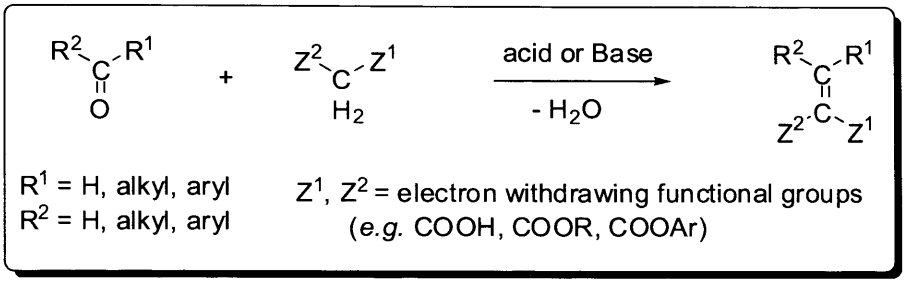
A KNOEVENAGEL REACTION INVOLVING USE OF SOLIDS

CHAPTER FIVE

A KNOEVENAGEL REACTION INVOLVING USE OF SOLIDS

5.1 Introduction

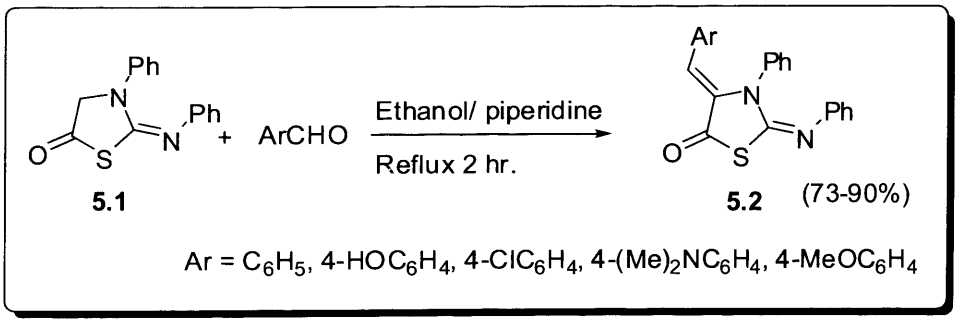
A Knoevenagel reaction is the condensation of aldehydes or ketones with active methylene compounds in the presence of acidic or basic catalysts (Scheme 5.1).



Scheme 5.1

Not only is the Knoevenagel condensation reaction important to produce C-C bonds, but it is also considered as one of the most environmentally friendly methods, having water as its only *co*-product. The reaction is carried out using acidic or basic catalysts. For example, ethylenediamine, piperidine, alkyl ammonium salts, $ZnCl_2$, Al_2O_3, KF-Al_2O_3 silica-gel and amino-substituted resins have all been used in such reactions.[1-7] A range of benzaldehydes has been reacted with a diverse set of active methylene substrates, typically by refluxing in ethanol in the presence of a catalytic amount of piperidine.[7] Most products are generally free of impurities after washing with organic solvents. Some products, however, have given some problems in the removal of both piperidine and piperidine-based by-products. In such cases, reactions performed in deoxygenated solvents under argon gave the same by-products.[7] Because the reaction is very dependent on the efficient removal of water, finding a suitable catalyst has attracted chemists' interests. It was noted that the Knoevenagel condensation reaction could take place in absence of any solvent and also under thermal heating conditions or microwave irradiation-assisted conditions.

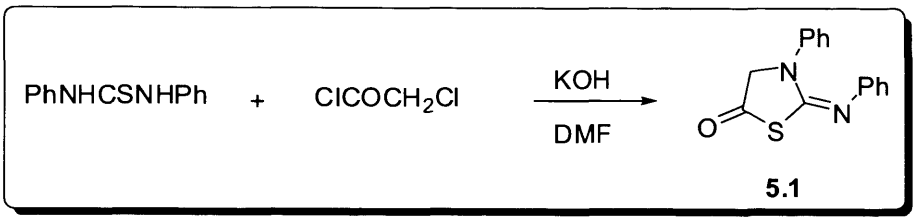
The aim of the work reported in this chapter was to investigate the microwave irradiation-assisted and thermal solvent-free Knoevenagel condensation of aromatic aldehydes with compounds possessing active methylene groups either without a catalyst or catalysed by a simple base such as K_2CO_3. We thought that if the reaction could be accomplished using potassium carbonate, the product would be more easily isolated (simple water washing) than from the traditional method using an organic base. As the substrates for study we chose **5.1**. According to the literature compound **5.1** reacts with a variety of aromatic aldehydes in ethanol containing a catalytic amount of piperdine to give a series of arylidene compounds **5.2** in high yield (Scheme 5.2).[8] We wished to see if we could conduct simple reactions in the solid state using a solid phase catalyst. 3-Phenyl-2-phenyliminothiazolidin-5-one (**5.1**) was selected as substrate for the study. The results, which we now report in this chapter, showed that a convenient method for Knoevenagel condensation of 4-nitrobenzaldeyde with thiazolidine-5-one to synthesise the corresponding arylidene compound was indeed possible using inexpensive and environmentally friendly reagents such as K_2CO_3.



Scheme 5.2

5.2 Attempted Knoevenagel condensation of 3-phenyl-2-phenyliminothiazolidine-5-one with aromatic aldehydes in the solid state

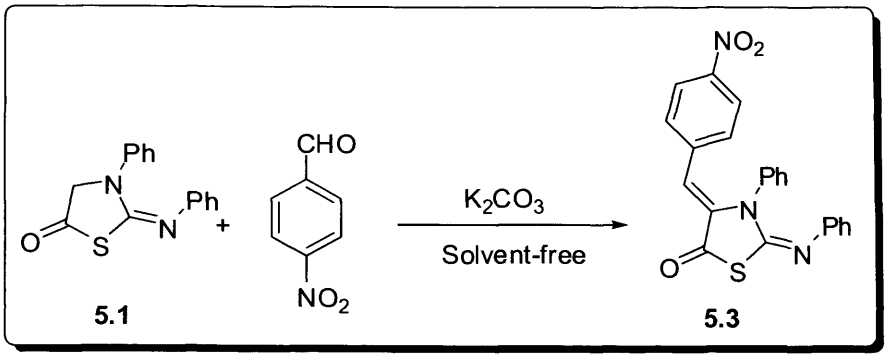
3-Phenyl-2-phenyliminothiazolidin-5-one (**5.1**) was prepared according to a literature procedure.[8] Reaction of *N,N'*-diphenylthiourea with chloroacetyl chloride in DMF containing a quantitative amount of KOH gave compound **5.1** in 89% yield (Scheme 5.3).



Scheme 5.3

The ^{1}H and ^{13}C NMR spectra confirmed the chemical structure of compound **5.1**. The ^{1}H NMR spectrum of **5.1** showed a singlet signal at δ = 3.85 corresponding to the methylene protons and a multiplet signal at δ = 6.85-7.50 due to the aromatic protons. The ES-mass spectrum of compound **5.1** showed a pseudo molecular ion peak at *m/z* = 269 $[MH]^{+}$. The accurate mass of the molecular ion peak at *m/z* = 269 confirmed the formula as $C_{15}H_{13}N_2OS$.

From the view point of green chemistry it was of interest to investigate the condensation reaction using anhydrous K_2CO_3 in the solid state, without solvent. Therefore, a solvent-free mixture of **5.1**, 4-nitrobenzaldehyde and K_2CO_3 was ground with a pestle in a mortar and then subjected to microwave irradiation (power = 300 W, irradiation time 30 min.). Afterwards, the mixture was placed in a soxhlet and extracted with ethanol; evaporation of the solvent and crystallisation from ethanol gave the corresponding arylidine compound **5.3** in 48% yield (Scheme 5.4).



Scheme 5.4

The ^{1}H and ^{13}C NMR confirmed the chemical structure of compound **5.3**. The ^{1}H NMR spectrum showed the absence of the methylene proton signals, indicating that the condensation took place at CH_2. The EI-mass spectrum of compound **5.3** showed a molecular ion peak at *m/z* = 401 $[M]^+$. The accurate mass of the molecular ion peak at *m/z* = 401 confirmed the formula as $C_{22}H_{15}N_3O_3S$.

A similar solid-state reaction between compound **5.1** and 4-nitrobenzaldehyde in the presence of K_2CO_3 was conducted in a sealed tube, which was placed in an oil bath preheated to 120 °C for two hours, in order to provide a comparison with the microwave conditions. Subsequent extraction gave compound **5.3** in 50% yield (Scheme 5.4).

The spectra of the product were identical in all respects to those obtained from the product of the previous reaction. A series of experiments was conducted in a sealed tube, which was placed in an oil bath, to study the role of K_2CO_3 and temperature on the reaction yield (Table 5.1). In most cases the mixture was placed in a soxhlet and extracted with ethanol; evaporation of the solvent and crystallisation from ethanol gave the corresponding arylidine compound **5.3** (Scheme 5.4).

Table 5.1 Conditions screening for Knoevenagel condensation of **5.1** to produce **5.3** according to Scheme 5.4

Entry	Equivalents of base	Temperature	Time (hour)	Yield (%)[a]
1	0	120	2	—[b,c]
2	1	25	24	—[b,c]
3	1	80	2	50
4	0.25	80	12	44
5	0.25	80	9	46

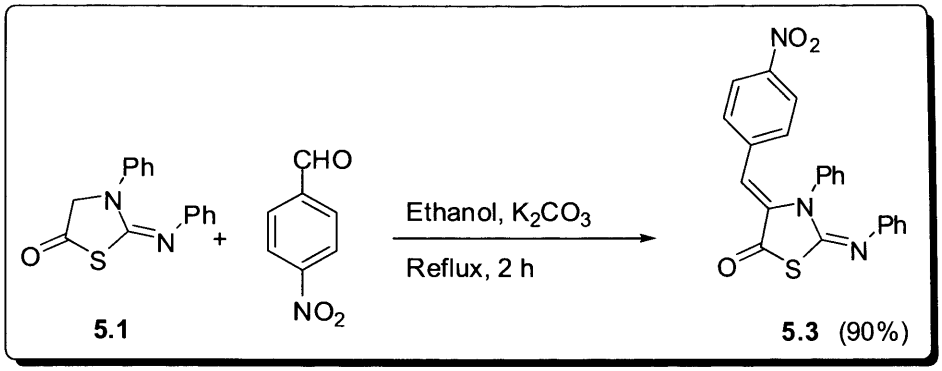
[a] Yield of isolated product after crystallization

[b] The mixture was not subjected to soxhlet extraction because no product was indicated by TLC

[c] The yield was not determined

As can be seen from Table 5.1, the Knoevenagel condensation reaction took place under thermal conditions to give around 50% of compound **5.3** even at 80 °C instead of 120 °C and also showed the catalytic role of K_2CO_3 in the rate of the reaction to completion. It should be noted that in the absence of any catalyst the condensation reaction failed to give the desired product. Also, prolonging the reaction period beyond 2 hours did not produce any improvement in the yield. As a result, it was decided to repeat the reaction in the liquid phase using ethanol as a solvent to see whether the low yield in the solid state reactions was due to any intrinsic problem with this particular reaction rather than just a problem with the solid-state conditions.

A mixture of compound **5.1** and 4-nitrobenzaldehyde in ethanol containing a catalytic amount of K_2CO_3 was refluxed for two hours. After work-up compound **5.3** was obtained in 90% yield (Scheme 5.5).



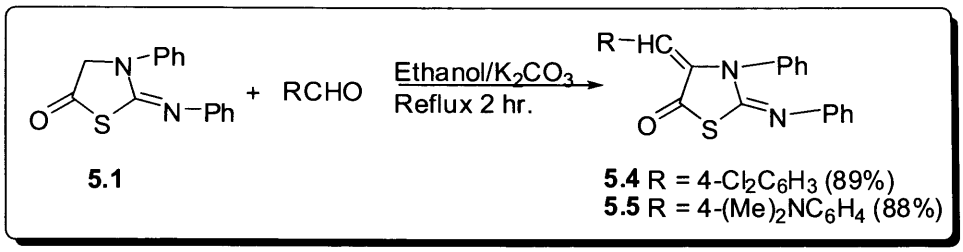
Scheme 5.5

Indeed, when the reaction was repeated using a nitrogen atmosphere it produced compound **5.3** in even higher yield (97%), possibly suggesting that some of the 4-nitrobenzaldehyde was oxidised by air during the previous reaction. These results clearly showed that there was no intrinsic problem with the reaction, which could give very high yields in liquid phase reactions and so it seemed that the low yields obtained in the solid state reactions must result from some issue relating to the reaction conditions. Given that the reaction worked well in the liquid phase and that all the same ingredients were present during the soxhlet extraction process, it was even possible that the original solid state reaction had not produced as much of the product as had been isolated, but that some reaction had taken place during the soxhlet extraction process.

In order to test this possibility a mixture of compound **5.1** and 4-nitrobenzaldehyde in the presence of K_2CO_3 was ground together and immediately placed in a soxhlet and extracted with ethanol, a yellow product was observed and was indicated by TLC but the yield wasn't determined.

It was of interest to see if the conditions relating to Scheme 5.4 were general. Therefore, reaction of **5.1** with various aldehydes [2,4-dichlorobenzaldehyde, 4-(*N*,*N*-dimethylamino)benzaldehyde] were attempted (Scheme 5.5) under conditions similar to those reported in Scheme 5.5. The reaction mixtures were worked-up as described

before. The solid products that formed were filtered off, dried and crystallized from ethanol to afford crystals of compounds **5.4** and **5.5** (Scheme 5.6) in high yield.

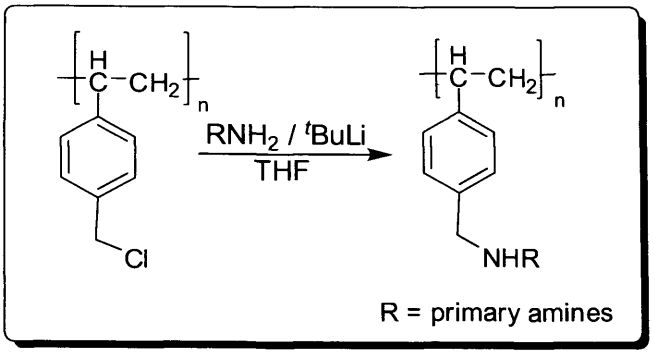


Scheme 5.6

As can be seen from Scheme 5.6, the yields in all cases were high and the process was general to produce various arylidene compounds.

The structures of compounds **5.4** and **5.5** were confirmed by standard spectroscopic methods (see experimental section for details). EI-mass spectra showed molecular ion peaks for all products and NMR spectra showed all appropriate carbon resonances.

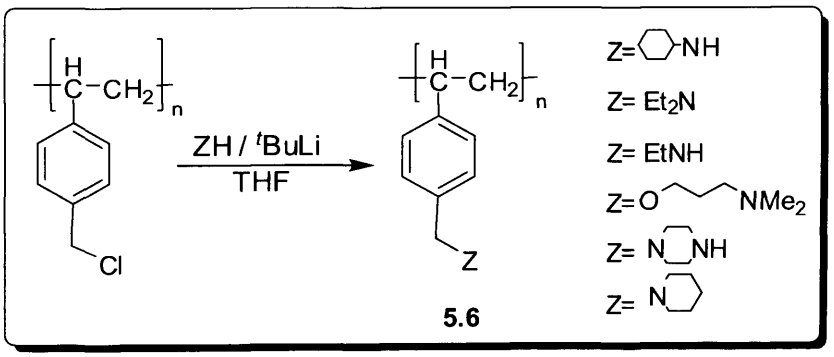
Since potassium carbonate had not been a very successful catalyst in the solid-state process we decided to attempt the reaction with a solid base that resembled the more traditional amine catalysts, yet could in principle be recycled easily and reused. We thought that a modified Merrifield resin might be suitable for such reactions. Fortunately, the Smith group had already reported the synthesis and use of various Merrifield resins possessing alkylaminomethyl units (Scheme 5.7).[9] We therefore attempted to prepare and use such basic catalysts in the reaction represented in Scheme 5.5.



Scheme 5.7

5.3 Synthesis of basic Merrifield resins

These types of catalysts were prepared according to a literature procedure.[9] A solution of *t*-BuLi in pentane was added to a cooled solution (-78 °C) of the appropriate amine. The mixture was slowly warmed to room temperature, then transferred via double ended needle to a chilled (-78 °C) suspension of Merrifield's resin (chloromethylated polystyrene, 1% cross-linked, 200–400 mesh, extent of labeling: 1.0-1.3 mmol g^{-1} Cl, *ex* Aldrich) in THF. The mixture was stirred for a further 30 minutes at -78 °C and then left overnight at room temperature. Following work-up the corresponding alkylamino-substituted Merrifield resins were obtained (Scheme 5.8).



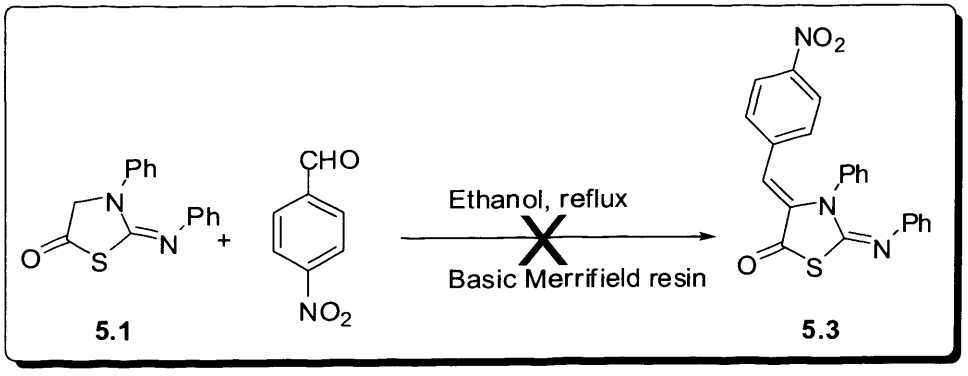
Scheme 5.8

The degree of amino group functionalization was determined by acid-base titration. A sample of the dried polymer was treated with a mixture of methanolic HCl

and 1,4-dioxane containing a known quantity of HCl. The mixture was stirred magnetically for 3 h and then filtered at the pump. The supernatant solution, diluted with water, was titrated with standard 0.01M aqueous NaOH. The difference between the amount of HCl determined by titration and the amount of HCl originally added indicated the amount of amino group present in the resins. The results indicated that the functional yield was around 92% in each case, which may indicate that the extent of Cl substitution in the original resin was a little less than the figure given on the label.

5.4 Use of basic Merrifield resins as catalysts in a Knoevenagel condensation reaction

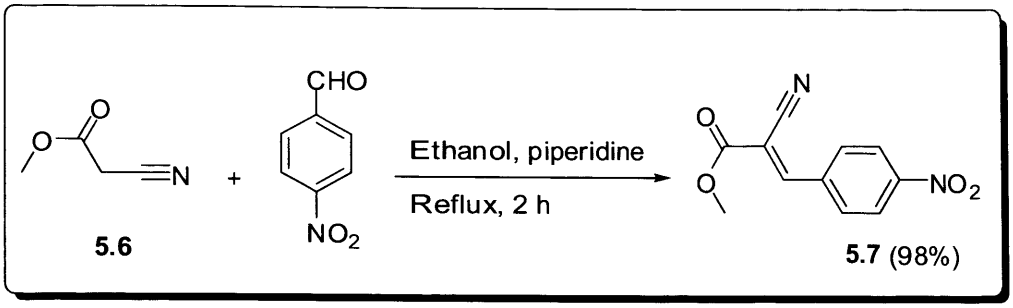
Mixtures of compound **5.1** and 4-nitrobenzaldehyde in ethanol containing a catalytic or stoichiometric amount of various basic Merrifield resins of type **5.6** were refluxed and the product mixtures were examined by TLC. Unfortunately, the mixtures showed the presence of only the starting materials (5.1 and 4-nitrobenzaldehyde) and no new products were formed (Scheme 5.9).



Scheme 5.9

It was of interest to see if the reaction would proceed differently with another active methylene compound, for example, methyl cyanoacetate. First, a mixture of compound **5.6** and 4-nitrobenzaldehyde in ethanol containing a catalytic amount of

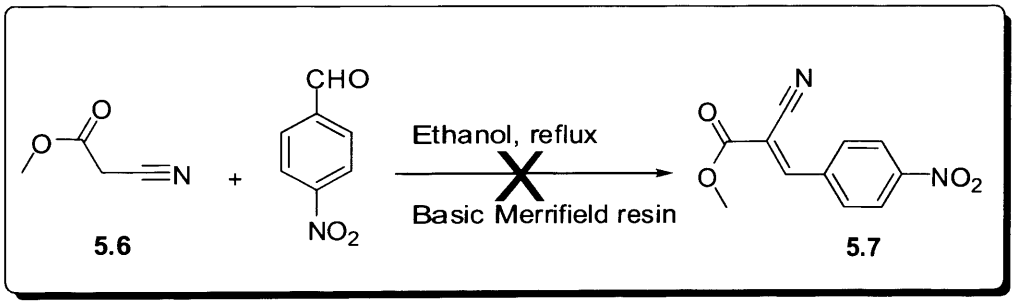
piperidine was refluxed for two hours. After work-up compound **5.7** was obtained in 98% yield (Scheme 5.10).



Scheme 5.10

We therefore attempted reaction of **5.6** with 4-nitrobenzaldehyde in ethanol containing a catalytic or stoichiometric amount of various basic Merrifield resins of type **5.6**.

The reaction mixtures were heated at reflux in ethanol and the product mixtures were examined by TLC. Unfortunately, the mixtures showed the presence of only the starting materials (**5.6** and 4-nitrobenzaldehyde) and no new products were formed (Scheme 5.11).



Scheme 5.11

Since no reaction took place in any of the attempts, it seems that, unfortunately, such catalysts are not suitable for Knoevenagel condensation reactions.

5.5 Conclusion

A convenient method for Knoevenagel condensation of aromatic aldehydes

with active methylene compounds to synthesize arylidene compounds was developed using inexpensive and environmentally friendly reagents such as K_2CO_3. The method is simple and the condition is mild to provide high product yield.

5.6 Experimental details

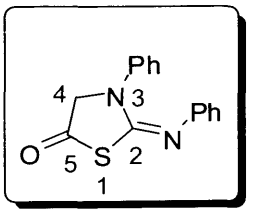
5.6.1 General experimental

See Chapter 2; Section 2.4.1

5.6.2 Synthesis of 3-phenyl-2-phenylimino-thiazolidin-5-one (5.1)

A mixture of *N,N'*-diphenylthiourea (2.29 g, 10 mmol) and chloroacetyl chloride (2.27 g, 20 mmol) was stirred in DMF (25 ml) containing KOH (0.56 g, 10 mmol) for 10 h. The reaction mixture was poured onto crushed ice. The precipitate which formed was filtered off, dried and crystallized from ethanol to give buff crystals of compound **5.1**.

3-Phenyl-2-phenylimino-thiazolidin-5-one



Yield: 2.39 g (8.91 mmol; 89%).

MP: 183-185 °C (lit.[8] 172-173 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.50-6.85 (m, 10 H, 2 Ph), 3.85 (s, 2 H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ= 171.4 (s, C=O), 154.9 (s, C-2), 148.1 (s, C-1 of Ph), 134.8 (s, C-1 of Ph), 129.4 (d, C-3/C-5 of Ph), 129.2 (d, C-3/C-5 of Ph), 129.0 (d, C-4 of Ph), 128.0 (d, C-2/C-6 of Ph), 124.7 (d, C-4 of Ph), 120.9 (d, C-2/C-6 of Ph), 32.9 (t, CH_2).

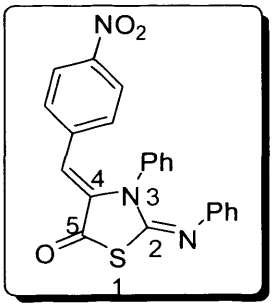
ES–MS: *m/z* (%) = 269 (100) [MH^+].

HRMS: *m/z* calcd for $C_{15}H_{13}N_2OS$ [MH]$^+$, 269.0749; found, 269.0742.

5.6.3 Synthesis of 4-(4-nitrobenzylidene)-3-phenyl-2-phenyliminothiazolidin-5-one (5.3)

A mixture of compound **5.1** (2.68 g, 10 mmol) and 4-nitrobenzaldehyde (1.51, 10 mmol) in ethanol (20 ml) containing a catalytic amount of K_2CO_3 (0.06 g) was refluxed under nitrogen for 2 h. The reaction mixture was cooled; the solid product that formed was filtered off, dried and crystallized from ethanol to afford yellow crystals of compound **5.3**.

4-(4-Nitrobenzylidene)-3-phenyl-2-phenyliminothiazolidin-5-one (5.3)



Yield: 3.89 g (9.70 mmol; 97%).

MP: 398-400 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-nitrobenzylidene), 7.75 (s, 1 H, olefinic CH), 7.54-6.90 (m, 12 H, H-2/H-6 of 4-nitrobenzylidene and 10 H of 2 Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ= 165.8 (s, C=O), 149.6 (s, C-2), 147.9 (s, C-1 of Ph), 147.6 (s, C-4 of 4-nitrobenzylidene), 139.9 (s, C-4), 134.4 (s, C-1 of Ph), 130.4 (d, C-2/C-6 of 4-nitrobenzylidene), 129.4 (d, C-3/C-5 of Ph), 129.2 (d, C-3/C-5 of Ph),

128.2 (d, C-4 of Ph), 128.0 (d, C-3/C-5 of 4-nitrobenzylidene), 126.2 (s, C-1 of 4-nitrobenzylidene), 125.4 (d, CH), 124.3 (d, C-2/C-6 of Ph), 124.2 (d, C-4 of Ph), 120.9 (d, C-2/C-6 of Ph).

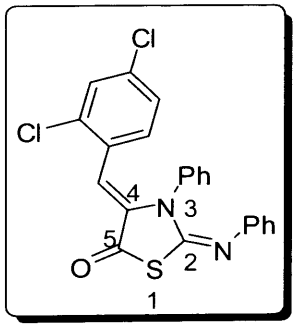
EI–MS: *m/z* (%) = 401 (30) [$M^{\bullet+}$], 371 (90), 149 (100).

HRMS: *m/z* calcd for $C_{22}H_{15}N_3O_3S$ $[M]^+$, 401.0834; found, 401.0837.

5.6.4 Synthesis of 4-(2,4-dichlorobenzylidene)-3-phenyl-2-phenyliminothiazolidin-5-one (5.4) and 4-(4-(dimethylamino)benzylidene)-3-phenyl-2-phenyliminothiazolidin-5-one (5.5)

The procedure was identical to that described in Section 5.6.3 except that 2,4-dichlorobenzaldehyde (1.75 g, 10 mmol) and 4-(*N*,*N*-dimethylamino)benzaldehyde (1.49 g, 10 mmol) were used as the aldehydes. The reaction mixtures were worked-up as described in Section 5.6.3 and the residues obtained crystallized from ethanol to afford crystals of compounds **5.4** and **5.5**

4-(2,4-Dichlorobenzylidene)-3-phenyl-2-phenyliminothiazolidin-5-one (5.4)



Yield: 3.80 g (8.94 mmol; 89%).

MP: 175-177 °C

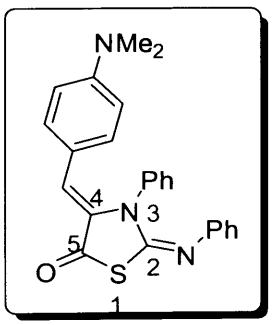
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.0 (s, 1 H, H-3 of 2,4-dichlorobenzylidene), 7.50-6.86 (m, 13 H, H-5/H-6 of 2,4-dichlorobenzylidene and 10 H of 2 Ph).

^{13}C NMR (125 MHz $CDCl_3$): δ= 165.7 (s, C=O), 150.2 (s, C-2), 148.0 (s, C-1 of Ph), 140.4 (s, C-4), 136.2 (s, C-1 of Ph), 134.5 (s, C-2 of 2,4-dichlorobenzylidene), 130.8 (s, C-1 of 2,4-dichlorobenzylidene), 130.2 (d, C-6 of 2,4-dichlorobenzylidene), 129.6 (d, C-3/C-5 of Ph), 129.4 (d, C-3/C-5 of Ph), 129.3 (d, C-4 of Ph), 129.1 (d, C-3 of 2,4-dichlorobenzylidene), 128.0 (d, C-5 of 2,4-dichlorobenzylidene), 127.6 (s, C-4 of 2,4-dichlorobenzylidene), 126.4 (d, CH), 125.1 (d, C-2/C-6 of Ph), 124.2 (d, C-4 of Ph), 121.1 (d, C-2/C-6 of Ph).

EI–MS: *m/z* (%) = 427 (20) [$M^{\bullet+}$ ^{37}Cl], 425 (60) [$M^{\bullet+}$ ^{35}Cl], 389 (70), 268 (25), 194 (100).

HRMS: *m/z* calcd for $C_{22}H_{14}N_2OS^{35}Cl_2$ $[M]^+$, 424.0204; found, 424.0195.

4-(4-(*N*,*N*-Dimethylamino)benzylidene)-3-phenyl-2-phenyliminothiazolidin-5-one (5.5)



Yield: 3.50 g (8.77 mmol; 88%).

MP: 218-220 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (s, 1 H, olefinic CH), 7.56-7.0 (m, 12 H, H-2/H-6 of 4-dimethylaminobenzylidene and 10 H of 2 Ph), 6.72 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-dimethylaminobenzylidene), 3.05 (s, 6 H, NMe_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0 (s, C=O), 152.0 (s, C-2), 151.1 (s, C-4 of 4-dimethylaminobenzylidene), 148.7 (s, C-1 of Ph), 135.1 (s, C-4), 132.4 (s, C-1 of Ph), 132.2 (d, C-2/C-6 of 4-dimethylaminobenzylidene), 129.2 (d, C-3/C-5 of Ph), 128.7 (d, C-3/C-5 of Ph), 128.2 (s, C-1 of 4-dimethylaminobenzylidene), 128.0 (d, C-4 of Ph), 124.6 (d, CH), 124.3 (d, C-2/C-6 of Ph), 121.3 (d, C-2/C-6 of Ph), 115.3 (d, C-4 of Ph), 111.9 (d, C-3/C-5 of 4-dimethylaminobenzylidene).

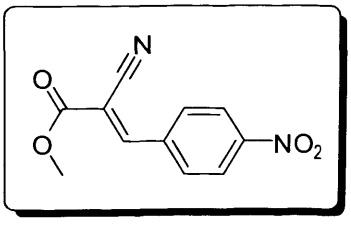
EI–MS: *m/z* (%) = 399 (60) [$M^{\bullet+}$], 177 (100), 149 (30).

HRMS: *m/z* calcd for $C_{24}H_{21}N_3OS$ $[M]^+$, 399.1405; found, 399.1406.

5.6.5 Synthesis of methyl 2-cyano-3-(4-nitrophenyl)acrylate (5.7)

A mixture of compound **5.6** (0.99 g, 10 mmol) and 4-nitrobenzaldehyde (1.51, 10 mmol) in ethanol (20 ml) containing a catalytic amount of piperidine (two drops) was refluxed for 2 h. The reaction mixture was cooled; the solid product that formed was filtered off, dried and crystallized from ethanol to afford crystals of compound **5.7**.

Methyl 2-cyano-3-(4-nitrophenyl)acrylate (5.7)



Yield: 2.27 g (9.78 mmol; 98%).

MP: 180-181 °C (Lit.[10] 177-178 °C)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.15 (s, 1 H, olefinic CH), 8.43 (d, J = 8 Hz, 2 H, H-3/H-5 of 4-nitrobenzylidene), 8.24 (d, J = 8 Hz, 2 H, H-2/H-6 of 4-nitrobenzylidene), 3.82 (s, 3 H, OCH_3).

5.7 References

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CHAPTER SIX

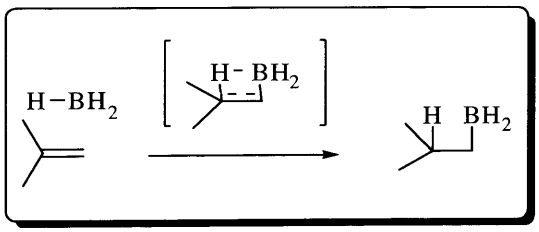
REACTION OF ETHYL DIAZOACETATE WITH BORON COMPOUNDS

CHAPTER SIX

REACTION OF ETHYL DIAZOACETATE WITH BORON COMPOUNDS

6.1 Introduction

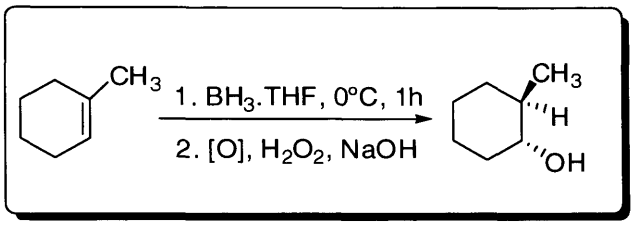
Since the discovery of the hydroboration reaction in the early 1960s by Herbert C. Brown, organoboron chemistry has flourished into an invaluable area of organic chemistry. The facile addition of the boron-hydrogen bond to carbon-carbon multiple bonds of unsaturated organics makes the corresponding organoboranes readily available for application in organic synthesis.[1-3] One of the many interesting reactions that such organoboranes undergo is oxidation with alkaline hydrogen peroxide, which proves to be rapid and affords quantitative yields of products. The most important features of the hydroboration reactions are their regio- and stereoselectivities. The regioselectivity arises from the fact that the boron atom usually adds to the least hindered carbon atom of the unsaturated moiety. In addition to this, the concerted mechanism results in *syn*-addition that leads to the observed stereoselectivity. It appears that the hydroboration reaction involves a simple four-centre transition state, with the direction of addition controlled primarily by the polarization of the boron-hydrogen bond (Scheme 6.1).



Scheme 6.1

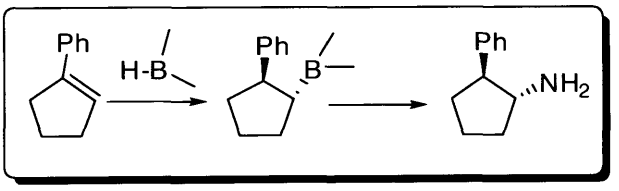
In view of the massive increase of developments in the organoborane area, it is not possible in this chapter to present a reasonably complete survey of the field with individual discussion of the various points of special interest. However, some examples of applications of borane reagents in organic synthesis are mentioned.

The most well known variation of the hydroboration reaction is the hydroboration-oxidation reaction.[4] This remarkable reaction converts an alkene to the corresponding alcohol, while retaining the regio- and stereoselectivities of the initial hydroboration. This means the so called *anti*-Markovnikov alcohols can be prepared from alkenes with high stereoselectivity, *e.g.* the hydroboration-oxidation of 1-methylcyclohexene to give pure *trans*-2-methylcyclhexanol (Scheme 6.2).[5a]



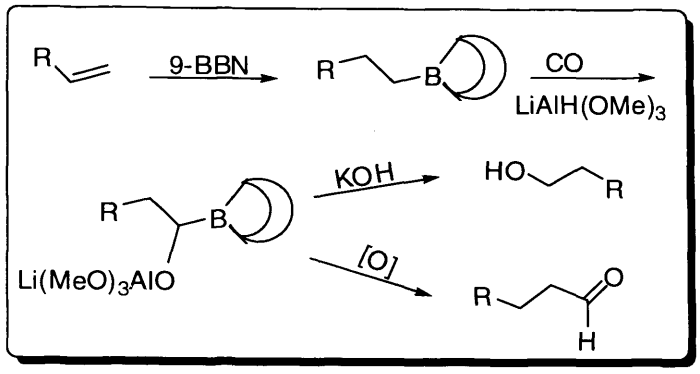
Scheme 6.2

Another useful application is to replace the boron with an amino group to give a route for the formation of primary amines. Organoboranes are converted by chloramine or *O*-hydroxylaminesulfonic acid to primary amines (Scheme 6.3).[5b]



Scheme 6.3

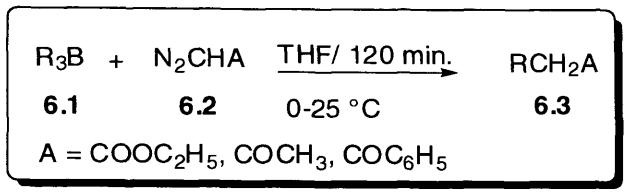
The reactions of organoboranes with carbon monoxide can be controlled to produce aldehydes, ketones and tertiary alcohols. Thus, treatment of organoboranes with carbon monoxide in the presence of certain hydride reagents provides an intermediate which can be oxidized to the corresponding aldehyde or hydrolysed to the alcohol derivatives (Scheme 6.4).



Scheme 6.4

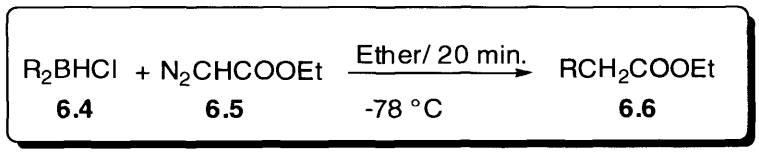
These three examples all illustrate one of the most important types of organoboron reactions, which involve migration of an organic group from boron to an adjacent atom. Typically, such reactions occur readily for trialkylboranes, but get progressively more difficult as the electron deficiency of the boron atom diminishes, for example when the boron atom has OR or NR_2 groups bound to it. In some reactions, such as the oxidation and amination reactions described above, alkyl groups directly bonded to boron are replaced during the reaction by groups attached to boron by oxygen or nitrogen atoms, so that reaction gets progressively slower as each alkyl group of a trialkylborane reacts. Therefore, for some reactions only one or two of the three alkyl groups can be migrated, leading to wastage of alkyl groups. There is a need to find alternative procedures to overcome such difficulties. The aim of the work reported in this chapter was to investigate the migration of the alkyl group from a compound having a single alkyl group attached to the boron atom to the carbon atom of a diazocarbonyl compound. The migration of an alkyl group to the carbon atom of a diazocarbonyl compounds is already known in the literature.[6-13] For example trialkylboranes **6.1** have been reacted with a variety of functionally substituted diazocarbonyl compounds **6.2** (Scheme-6.5).[7,8,10] However, only one of the three possible alkyl groups was transferred and products **6.3** were therefore obtained in poor

(maximum 33%) yields based on alkyl residues, and especially so for organoboranes containing bulky alkyl groups.



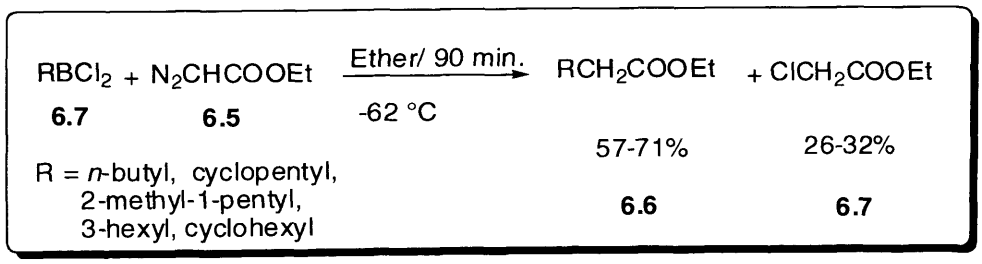
Scheme 6.5

Dialkylchloroboranes **6.4** offer an improvement, since they react readily at -78 °C with ethyl diazoacetate (**6.5**) to give the corresponding esters **6.6** in high yields based on the stoichiometry of the reaction (Scheme 6.6).[11] However, even in these reactions only one of the two available alkyl groups is used, so that the maximum yield based on alkyl groups is 50%.



Scheme 6.6

Alkyldichloroboranes **6.7** offer the possibility to make full use of the only alkyl group and indeed react with ethyl diazoacetate (**6.5**) to give the alkyl-substituted esters **6.6**, but in yields of only 57-71% (Scheme 6.7) because the reactions give mixtures of the desired alkyl-substituted esters **6.6** and ethyl chloroacetate (**6.7**), derived from chlorine transfer, in yields of 26-32% (Scheme 6.7).[12]

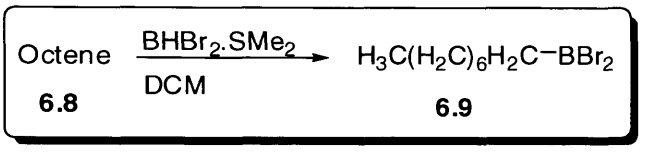


Scheme 6.7

In the present work we proposed to study the analogous reactions of alkyldibromoboranes or alternative conditions for the reactions with alkyldichloroboranes in the hope of developing a reaction in which only the alkyl group would be transferred in high yield.

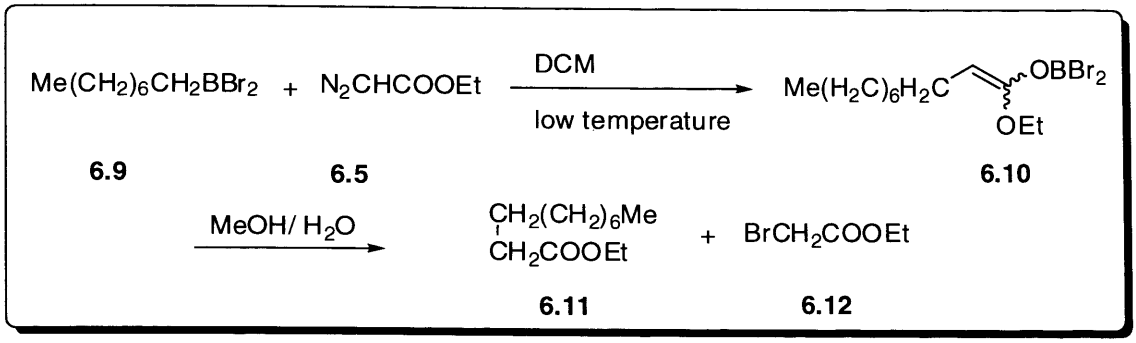
6.2 Preparation of octyldibromoborane followed by reaction with ethyl diazoacetate

Initially, we proposed to synthesise octyldibromoborane (**6.9**), which can be prepared from the reaction of octene (**6.8**) with dibromoborane-dimethylsulfide according to a literature procedure (Scheme 6.8).[14,15]



Scheme 6.8

A sample of the mixture was submitted for ^{11}B NMR, which clearly indicated formation of octyldibromoborane, which resonated at around 58-68 ppm as compared to dibromoborane, which resonated at higher field, around 0-10 ppm. The borane reagent having been successfully prepared, was cooled to -68 °C; ethyl diazoacetate was injected into the reaction mixture containing the octyldibromoborane (**6.9**; Scheme 6.9) and the mixture was stirred for 1.5 hours at that temperature. Following methanolysis and hydrolysis the mixture was worked-up and the crude product mixture was analysed by various techniques to quantify the mixture.



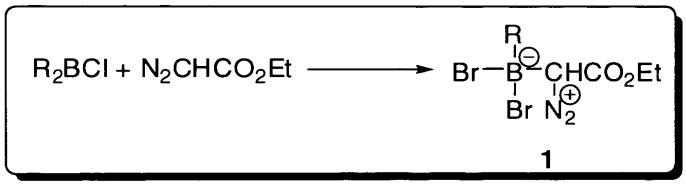
Scheme 6.9

The mechanism

It is believed that the reaction mechanism would proceed by the following steps:

Step 1

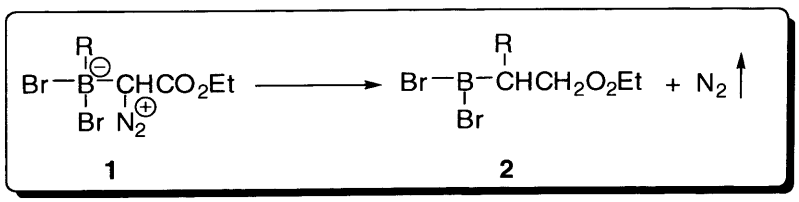
The diazo compound coordinates to the borane reagent to produce the quaternary boron intermediate **1** (Eq. 6.1).



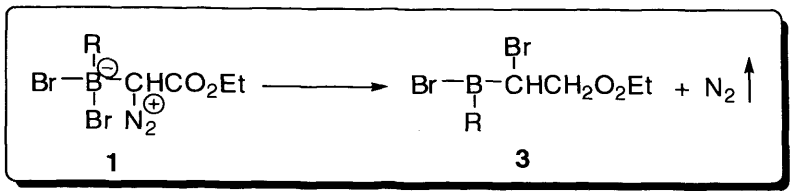
(Eq. 6.1)

Step 2

Loss of nitrogen from **1** with an alkyl group or bromine migration (Eq. 6.2 and Eq. 6.3).



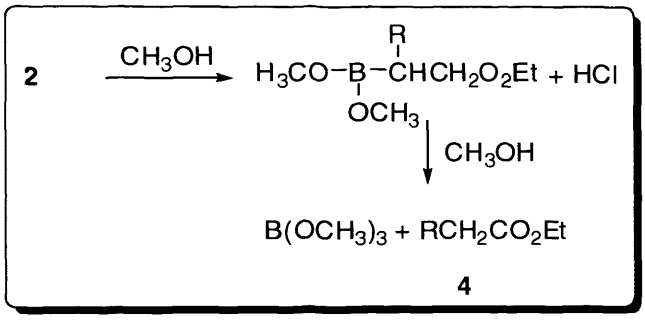
(Eq. 6.2)



(Eq. 6.3)

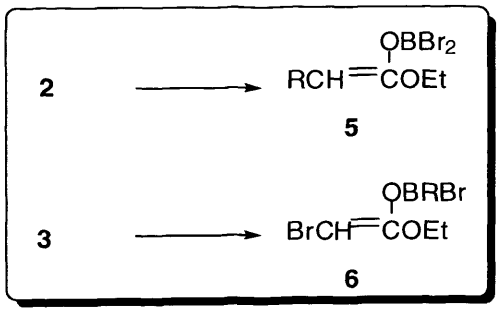
Step 3

Intermediate **2** on methanolysis gives the desired product **4** (Eq. 6.4). (It is possible that intermediate **3** might also lead to **4**, but it is not so clear what the stereochemistry would be in that case)



(Eq. 6.4)

It was suggested by Pasto and Wojtkowski[16] that intermediates such as **2** or **3** exist in the isomeric enol borinate forms **5** or **6** (Eq. 6.5). Such intermediates are rapidly hydrolyzed by water.



(Eq. 6.5)

It seemed from the ^{1}H NMR spectrum of the crude product that the desired product (**6.11**) was obtained, but there were clearly other compounds also present. A flame test (green colour) indicated the presence of boron in the sample. The

complexity of the ^1H NMR signals did not allow quantification of the mixture. It was thought that quantitative GC would be a better technique to gain a clearer picture of what was going on in the reaction. We established GC conditions under which the mixture could be quantified by selecting an appropriate column, temperature program and flow rate (see Section 6.7.1). The response factors for standard samples of starting materials and expected products were calculated by quantitive GC. The GC trace of the product mixture showed the presence of three signals along with a signal for the added standard (hexadecane). The first signal (Rt = 1.78 min under the conditions; 30% yield) was for ethyl bromoacetate (**6.12**). The second signal (Rt = 6.09; 17% yield) was for the desired product, ethyl decanoate (**6.11**). The third signal (Rt = 9.30) was not identified. The mixture was also submitted for GC-MS and high resolution mass spectrometry.

The GC-MS experiment, which utilised a different GC column, provided valuable information. The GC trace of the reaction mixture confirmed the formation of ethyl decanoate (**6.11**) and ethyl bromoacetate (**6.12**) as significant products (Scheme 6.9).[12] In this case, however, two other signals were seen in the GC trace. One was believed to be due to the cyclic boron compound **6.13** since the EI-mass spectrum showed a molecular ion peak at *m/z* = 420 and the accurate mass of this ion confirmed its formula as $C_{24}H_{51}B_3O_3$. Such compounds are common in reactions of alkyldihaloboranes with water and could be produced from unreacted octyldibromoborane (**6.9**) during work-up. The other showed an EI-mass spectral signal at *m/z* = 241, the accurate mass of which confirmed the formula as $C_{14}H_{25}O_3$. This could correspond to any of the three structures shown as **6.14** (Figure 6.1), by loss of OEt, OH or OH, respectively, from their correspnding molecular ions. Such compounds could arise from reaction of intermediate **6.10** with ethyl diazoacetate or

ethyl bromoacetate. Further information would be required in order to distinguish these possibilities.

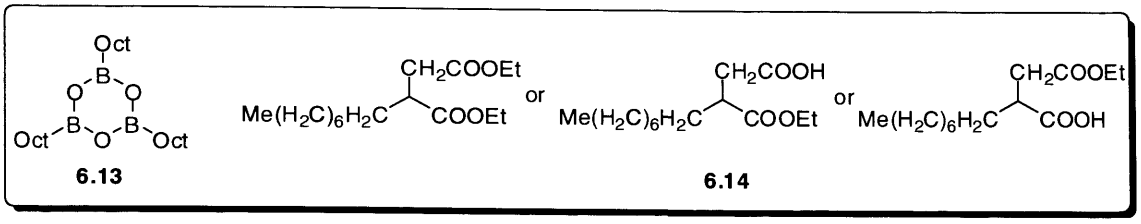


Figure 6.1

Before attempting further characterisation of **6.14**, however, our attention was turned to studying the reaction represented in Scheme 6.9 under different reaction conditions in an attempt to improve the yield of **6.11** and if possible to eliminate the formation of the other products. The most obvious parameter to vary was reaction temperature. Therefore, two similar experiments were attempted except that the reaction temperature was different (Table 6.1).

Table 6.1: Yields from the reaction of **6.9** with ethyl diazoacetate according to Scheme 6.9.

Entry	**Temperature** (°C)	**Yield (%)**		**Total Yield of products accounted for (%)**[a,b]
		6.11	**6.12**	
1	-90	18	56	74
2	-78	22	42	64

[a] Compounds **6.13** and **6.14** were produced in both cases; however, their yields were not calculated because of the lack of the appropriate standards.

[b] Octene was recovered in *ca.* 12% yield in each case.

It seemed likely that the reaction had somehow stopped for whatever reason. We considered the possibility of ethyl diazoacetate had all decomposed and therefore decided to check the amount of nitrogen evolved during the reaction. The amount of

nitrogen evolved during the reactions was determined using a gas burette. The simple gas burette design used is shown in Figure 6.2.[17]

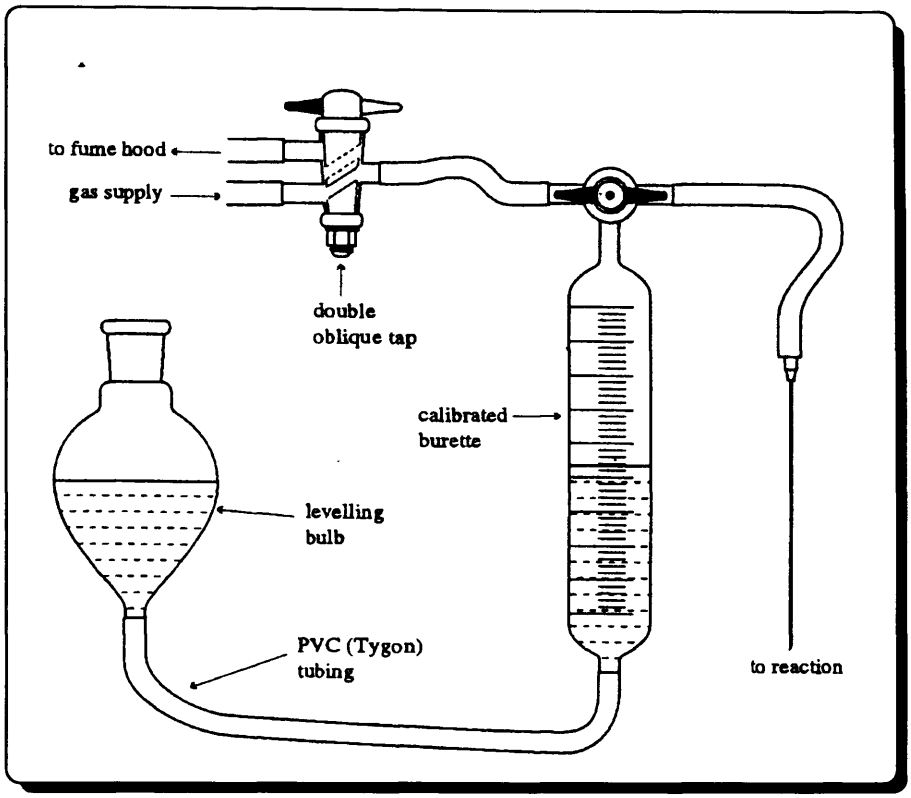


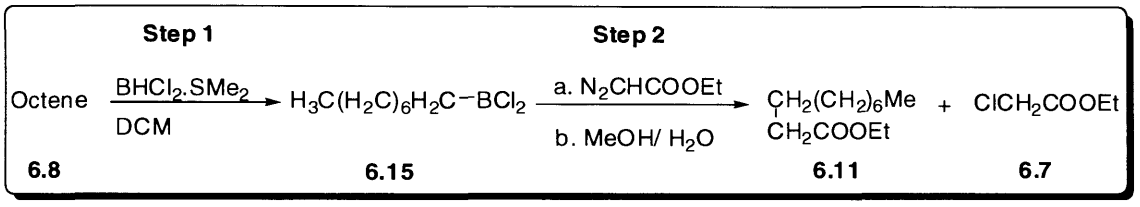
Figure 6.2 the gas burette design

All reactions evolved nitrogen quantitatively (> 95%), indicating that the ethyl diazoacetate had reacted fully.

All of the above reactions were conducted with alkyldibromoborane. It was of interest to know whether the same situation would exist with the chloro analogue. Therefore; our attention was next turned to use the chloroborane reagent instead of bromoborane. Recently it was reported that $HBCl_2.SMe_2$ is 20 times more reactive than $HBBr_2.SMe_2$.[18] This finding is in agreement with the fact that $HBBr_2.SMe_2$ is a more stable complex than $HBCl_2.SMe_2$.[15,19] This follows the fact that BBr_3 is a stronger Lewis acid than BCl_3 and hence bromoboranes are more acidic and form more stable complexes than the corresponding chloroboranes.

6.3 Preparation of octyldichloroborane using dichloroborane followed by reaction with ethyl diazoacetate

The procedure was identical with that described with bromoborane except that $BHCl_2$ was used in the hydroboration step to produce octyldichloroborane (**6.15**), followed by reaction with ethyl diazoacetate (**6.5**) at low temperature (Scheme 6.10). In order to confirm if there was any unreacted octyldichloroborane, the reaction mixture was oxidized. Octanol would be the expected product from oxidation of any unreacted octyldichloroborane. Indeed, octanol was seen to be present, indicating there was unreacted octylboron compound.



Scheme 6.10

A series of similar experiments was conducted except that the reaction times were varied for both steps. The reaction mixtures were quantified and analysed by GC. The results obtained are recorded in Table 6.2. The GC trace of the product mixtures showed that the amount of unreacted octene was in the range of 3-4%. The results clearly showed that the yield of the desired product **6.11** was better than in the case of octyldibromoborane under similar reaction conditions (42% compared with only 17% for reactions carried out with 1:1 boron compound:diazoester at -68 °C). Also, the yield of **6.7** was low compared with the corresponding one **6.12** produced as in Scheme 6.9. This procedure is therefore potentially more attractive than the corresponding one represented in Scheme 6.9. However, the mass balance was still low (*ca.* 70%). The mass balance was improved to 92% and the yield of **6.11** was

improved to 58% when an excess of ethyl diazoacetate (*ca.* 50%) was used. Also, the yield of **6.7** was increased to 34% (Table 6.4, entry 3).

Table 6.2: Yields from the reaction of **6.15** with ethyl diazoacetate (**6.5**) according to Scheme 6.10 at -68 °C

Entry	Reaction time (h)			Yields %[a]	
	Step one	Step two	Octene	6.11	6.7
1	3	1.5	3	32	12
2	24	3	3	42	28
3	24	3	4[b]	58[b]	34[b]

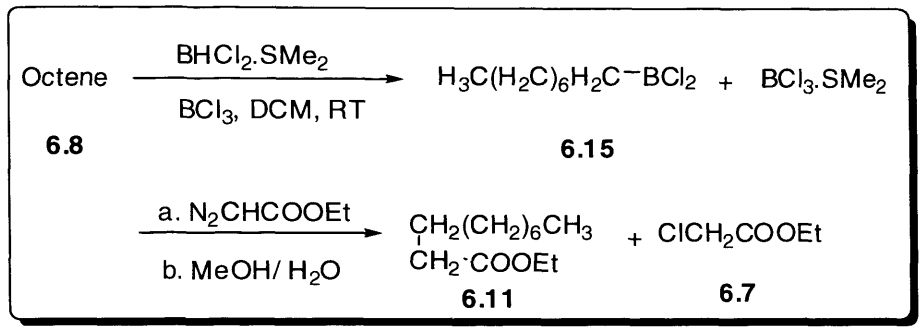
[a] Yield calculated by GC using dodecane as standard.

[b] Yield obtained when an extra 50% of ethyl diazoacetate was added after 1.5 h of the second step and the mixture was then stirred for another 1.5 h.

It was reported that there is an important role of the Me_2S in hydroboration reactions of chloroborane-dimethyl sulfide complex.[18] The rate of hydroboration was decreased when the quantity of Me_2S was increased.[18] This is due to the fact that the reaction is dependent on the dissociation of the Me_2S from the boron atom. Also, it was found that the Lewis base reattached itself back to the boron atom after hydroboration. It was suggested the addition of BCl_3 along with $HBCl_2$ in the hydroboration step could reduce the long reaction time (24h) needed and might also affect the yield of organoboron compound obtained. The presence of trichloborane would also reduce the chance of Me_2S to reattach to the alkyldichloroborane in the second step. Therefore, we decided to investigate the reaction with ethyl diazoacetate of octyldichloroborane prepared in the presence of BCl_3.

6.4 Preparation of octyldichloroborane using dichloroborane and boron trichloride followed by reaction with ethyl diazoacetate

The reaction in Scheme 6.11 was attempted in which the first step (hydroboration) was carried out at room temperature in the presence of BCl_3 for 2 h. The second step (migration and methanolysis) was carried out at -68 °C for 1.5 h.



Scheme 6.11

The GC results of the product mixture showed that **6.11** and **6.7** were formed in 51 and 23% yields, respectively, indicating that the yield of **6.11** was improved by 9% when BCl_3 was used. Also, the yield of **6.7** was reduced by 5% compared with the reaction where no BCl_3 was used (Table 6.2; Entry 2). However, the mass balance was still low (*ca.* 74%).

It was of interest to study the effect of quantity of BCl_3 on the yield of both **6.11** and **6.7** and try to find conditions under which the yield of **6.11** could be maximised and yield of **6.7** could be minimised. Therefore, a series of similar experiments was conducted in which the quantity of BCl_3 was varied. The reaction mixtures were quantified and analysed by GC. The results obtained are recorded in Table 6.3. The GC trace of the product mixtures showed that the amount of unreacted octene was in the range of 3-4%, showing that the hydroboration was essentially complete under these conditions. The yield of the desired product **6.11** was in the range of 38-51%, with an apparent trend to higher yield with increased quantity of

BCl_3 (for 1:1 $RBCl_2$:ethyl diazoacetate reactions). Also, the yield of **6.7** was in the range of 18-25% for such 1:1 reactions. The mass balance was improved when an excess of ethyl diazoacetate (*ca.* 50%) was used, but at the expense of **6.11**, because **6.7** became the major product (52%; Table 6.3; entry 4) when a 50% excess of ethyl diazoacetate was used for a reaction with 0.1 equivalents of BCl_3, while the yield of **6.7** was 25% and the yield of **6.11** was 44% when a 20% excess of ethyl diazoacetate was used (entry 5).

In conclusion, compound **6.11** could be produced in the yield of 51% with no octene recovered along with 23% of **6.7** when BCl_3 was used in equimolar ratio to $BHCl_2$. Variation in the quantity of BCl_3 provides no benefit in terms of yields of the desired product.

Table 6.3: Yields from the reaction of **6.15** with ethyl diazoacetate according to Scheme 6.11 at -68 °C

Entry	Reagent (mole equivalent)	Yields %[a]		
		octene	6.11	6.7
1	$HBCl_2.SMe_2/BCl_3$ (1:1)	–	51	23
2	$HBCl_2.SMe_2/BCl_3$ (1:0.2)	3	44	25
3	$HBCl_2.SMe_2/BCl_3$ (1:0.1)	3	38	18
4	$HBCl_2.SMe_2/BCl_3$ (1:0.1)	4[b]	40[b]	52[b]
5	$HBCl_2.SMe_2/BCl_3$ (1:0.1)	3[c]	44[c]	25[c]

[a] Yield calculated by GC using dodecane as standard.

[b] Yield obtained when an extra 50% of ethyl diazoacetate was added.

[c] Yield obtained when an extra 20% of ethyl diazoacetate was added.

6.5 Application to solid-supported octyldichloroborane

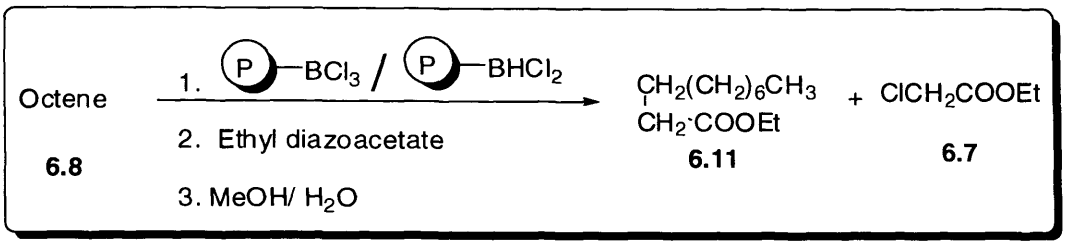
Use of solid-supports in organic reaction has some advantages. For example: solid-supported reagents are easily removed; excess reagents can be used to drive

reactions to completion without introducing difficulties in purification; ease of handling is especially important when dealing with expensive or time-intensive catalysts; toxic and expensive reagents are safely handled when contained on solid-supports; and potentially the most interesting thing is that the solid-supported reagent may react differently, and perhaps more selectively, than their unbound counter parts.

Within our research group another researcher had prepared a polymeric sulfide material, which could be used as a solid-support for borane.[20] It was assumed that the polymer would form similar complexes with $BHCl_2$ and BCl_3, so attempts were made to make separate complexes of the two species. The colleague provided a sample of the polymer, one portion of which was mixed with a dichloromethane solution of BCl_3 for two hours. Another portion was mixed with $HBCl_2$-dimethyl sulfide and left overnight. Solvent was removed from each complex with a syringe and then the solid was washed with fresh dichloromethane. Finally, residual solvent was removed under reduced pressure. The degree of loading for each complex was estimated by treating an aliquot with a mixture of H_2O and MeOH, diluting to an appropriate volume, then titrating with 0.1 M NaOH to estimate the amount of HCl and boric acid generated. The results indicated that the BCl_3-polymer complex contained around 3 mmol g^{-1}, corresponding to around 45% loading of BCl_3, while the other complex contained around 4 mmol g^{-1} of $BHCl_2$, corresponding to around 67% loading of $HBCl_2$.

It was of interest to see how these complexes would behave during hydroboration and subsequent reaction with ethyl diazoacetate. This was tested by reaction of a mixture of the two complexes with 1-octene for preparation of octyldichloroborane, followed by reaction with ethyl diazoacetate at -68 °C (Scheme 6.12), following a procedure similar to that described previously without

solid-supported reagents (Scheme 6.11). Three separate reactions having different stoichiometries were performed and the results obtained are reported in Table 6.4.



Scheme 6.12

Table 6.4: Yields of **6.11** and **6.7** according to Scheme 6.12

Entry	Reagent stoichiometry (mole equivalent)	Yields %[a]		
	P—$BHCl_2$ / P—BCl_3 / N_2CHCO_2Et	**octene**	**6.11**	**6.7**
1	1.0/1.1/1.5	–	24	9
2	1.0/0.75/1.0	–	40	–
3	1.0/0.75/1.2	–	31	26

[a] Yield calculated by GC using dodecane as standard..

Although the reasons are not clear, there appears to be a significant advantage of using the polymeric material as a solid-support in that the yields of the by-product **6.7** were much lower than for the comparable reactions in homogeneous solution. In one case the by-product was not observed at all and it was therefore easy to obtain the product in pure form. However, the yield of 6.11 was very low. This may reflect a rather poor production of octyldichloroborane and such a possibility would be worthy of further investigation. However, time did not permit such further investigation within the confines of this project.

6.6 Conclusion

There does not appear to be any advantage in using alkyldibromoboranes over alkyldichloroboranes in reactions with ethyl diazoacetate, since significant quantities of ethyl bromoacetate are formed in such reactions. We were also not able to find conditions under which ethyl chloroacetate could be eliminated from reactions of ethyl diazoacetate with octyldichloroborane. However, by use of a polymer-complex of octyldichloroborane we have observed a much lower tendency to produce ethyl chloroacetate as a by-product and in one case no by-product at all was seen. This example demonstrates the possibility that a good synthetic method for formation of alkyl esters might be achievable. Studying the solid-supported reagent in greater detail in the future could be worthwhile.

6.7 Experimental

6.7.1 General experimental

For general chemicals see Chapter 2; Section 2.4.1. Many of boron compounds used in the work reported in this chapter (*e.g.* borane, tribromoborane) were highly sensitive to moisture and/or oxygen of the air. Such items are generally handed under atmosphere of dry nitrogen in a glove box (especially for solids) or as solution in dry solvent using syringe techniques. Reaction mixtures were generally worked up by oxidation using basic hydrogen peroxide. The reaction mixtures were analysed and quantified by GC. The GC conditions are recorded in Table 6.5.

Table 6.5 GC conditions

Instrument	SHIMADZU GC-17A
Column	Zebron ZB-5HT Inferno 15 m × 0.25 mm ID × 0.1 μm df
Injection mode	Split ratio (100:1)
Injection Volume	0.5 μL
Injection Temperature	250 °C
Detector Temperature	250 °C
Temperature Programme	35-220 at 20 °C/min
Carrier Gas	Hydrogen UHP
Flow rate	43 ml / min.
Detector type	F.I.D.
Pressure	16 kpa
Auto stop	16.00 min.

6.7.2 Preparation of octyldibromoborane followed by reaction with ethyl diazoacetate at -68°C

A mixture of tribromoborane-dimethyl sulfide (3.12 g, 10.0 mmol) and borane-dimethyl sulfide (0.32 g, 5.0 mmol) was stirred at 40 °C for 12 h under nitrogen. Excess dimethyl sulfide was removed under a nitrogen stream to leave dibromoborane-dimethyl sulfide (3.43 g, *ca.* 100%) as a clear and viscous liquid. A solution of octene (1.68 g, 15 mmol) in DCM (10 ml) was stirred at 25 °C and then dibromoborane-dimethylsulfide (3.43 g, 15 mmol) was added to it *via* a syringe. The reaction mixture was heated under reflux for 3 h. The mixture was cooled to -68 °C (controlled dry ice/acetone bath) and a cold solution (-90 °C) of ethyl diazoacetate (1.7 g, 15 mmol) in DCM (20 ml) was added to the stirred mixture *via* a double ended needle over 20 minutes. The mixture was stirred for an additional 90 minutes at -68 °C and then treated at this temperature with methanol (5 ml) followed by water

(5 ml). The reaction mixture was then warmed up to room temperature. The aqueous layer was saturated with aqueous potassium carbonate and the organic layer was separated and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue obtained was analysed by GC using hexadecane as a GC standard.

6.7.3 Preparation of octyldibromoborane followed by reaction with ethyl diazoacetate at -90 °C

The procedure was identical with that described previously except that the temperature used was -90 °C instead of -68 °C.

6.7.4 Preparation of octyldibromoborane followed by reaction with ethyl diazoacetate at -78 °C

The procedure was identical with that described previously except that the temperature used was -78 °C instead of -68 °C.

6.7.5 Preparation of octyldichloroborane followed by reaction with ethyl diazoacetate at -68 °C

A mixture of dichloroborane (0.72 g, 5.0 mmol) and octene (0.568 g, 5.0 mmol) in DCM (10 ml) was heated under reflux for 3-24 h. The mixture was cooled to -68 °C. A solution of ethyl diazoacetate in DCM (20 ml) was stirred at -68 °C then was transferred through a double ended needle over 20 minutes to the reaction mixture. The mixture was stirred for an additional 1.5-3 h at -68 °C and then treated at this temperature with methanol (5 ml) followed by water (5 ml). The reaction mixture was worked up as usual and analysed by GC.

6.7.6 Preparation of octyldichloroborane in the presence of boron trichloride followed by reaction with ethyl diazoacetate at -68 °C

The procedure was identical with that described in Section 6.7.5 except that BCl_3 was used along with dichloroborane in different molar proportions and that the mixture was stirred at 25 °C for two hours. The reaction mixtures were hydrolysed and analysed as previously reported.

6.7.7 Preparation of solid-supported dichloroborane

A solution of a polythiaalkane polymer (supplied by a colleague; 1.48 g, 20.0 mmol S) in dichloromethane (25 ml) was mixed with $HBCl_2$-dimethyl sulfide (2.89 ml, 20 mmol) and left overnight. Solvent was removed with a syringe and then the solid was washed with fresh DCM. Finally residual solvent was removed under reduced pressure to leave the polymer-supported dichloroborane. The analysis revealed the presence of 4 mmol of $HBCl_2$ g^{-1} of complex, corresponding to 67% loading of S atoms.

6.7.8 Preparation of solid-supported trichloroborane

A solution of a polythiaalkane polymer (supplied by a colleague; 1.48 g, 20.0 mmol S) in dichloromethane (25 ml) was mixed with BCl_3-dimethyl sulfide (20 ml, 1 M, 20 mmol) for 2 hours. Solvent was removed with a syringe and then the solid was washed with fresh DCM. Finally residual solvent was removed under reduced pressure to leave the polymer-supported trichloroborane. The analysis revealed the presence of 3 mmol of BCl_3 g^{-1} of complex, corresponding to 45% loading of S atoms.

6.7.9 Preparation of solid-supported octyldichloroborane in the presence of solid-supported trichloroborane followed by reaction with ethyl diazoacetate at -68 °C

The procedure was identical with that described in Section 6.7.5 except that BCl_3 on the polymeric sulfide material was used along with dichloroborane on the polymeric sulfide material in different mole equivalents and that the mixture was stirred at 25 °C for two hours. The reaction mixtures were hydrolysed and analysed as previously reported.

6.8 References

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FINAL CONCLUSION AND FUTURE WORK

A simple, efficient and high yielding lithiation procedure that allows electrophilic substitution of various *N*-benzyl pivalamides and various *N'*-benzyl-*N*,*N*-dimethylureas has been demonstrated to provide various substituted derivatives. Cyclization reactions of some of the products with TFAA, *via* dehydration from the OH and hydrogen from the NH, takes place to give the corresponding isoindolines in excellent yields. Future work in this part could aim to change the position of halo substituents and see if the corresponding halo derivatives could be lithiated and substituted selectively in similar manner and also examine the applicability and generality of the process.

Also, a simple, efficient lithiation procedure that allows electrophilic substitution of various substituted pyridines has been demonstrated to provide various substituted derivatives. In this case cyclization gives the corresponding 1*H*-pyrrolo[3,4-*c*]pyridines. Future work in this part could aim to try some different substituted pyridines and see if the corresponding derivatives could be lithiated and substituted selectively in similar manner and also examine the applicability and generality of the process.

A boron reaction, which produces an alkyl ester *via* migration with by-product by using $HBCl_2$, has been developed using $HBCl_2$ on a solid-support. However, the yield of the alkyl ester was low and it seems that there is a significant advantage of using the polymeric material as a solid-support in the formation of the by-product. Therefore, future work in this part could aim to do further investigation to understand the role of such polymeric material in the reaction and to find the reason for the disappearance of the by-product as well as improve the yield of alkyl ester.