FIVE-MEMBERED HETEROCYCLES : METALLATION STUDIES AND AZAFULVENES

by

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DEFINITIONS AND ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
Bu	Butyl
DA	Diisopropylamido
DMAD	Dimethylacetylene dicarboxylate
DME	Dimethoxyethane
DMF	Dimethylformamide
DMG	Directed metallation group
E^+	Electrophile
EE	Ethoxyethyl
Et_2O	Diethyl ether
EWG	Electron withdrawing group
F.V.P.	Flash vacuum pyrolysis
LDA	Lithium diisopropylamide
LNMP	Lithium N-methylpiperazide
LTMP	Lithium 2,2,6,6-tetramethylpiperazide
LTMDA	Lithium N,N,N'-trimethylethylenediamine
Me	Methyl
Mes	Mesityl (2,4,6-trimethylphenyl)
Ph	Phenyl
r.t.	Room temperature
SEM	Trimethylsilylethoxymethyl
TBAF	Tetrabutylammonium fluoride
TBDMS	tertiary-Butyldimethylsilyl
TBDMSCl	tertiary-Butyldimethylsilyl chloride
thf	Tetrahydrofuran
THP	Tetrahydropyran
TMEDA	N,N,N',N'-Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride

ABSTRACT

The basic principles and recent developments in directed metallation of aromatic and heteroaromatic systems are reviewed in Chapter 1.

Chapter 2 describes a systematic study of the directed ortho-metallation properties of the imidate functionality. A range of O-methyl N-alkyl and N-aryl imidates were prepared from thiophene- and furan-2-carboxylic acid via their amide and imidochloride derivatives.

Under a wide variety of reaction conditions, lithiation was only observed at the C5-position. The poor directing ability of these imidates is in complete contrast to the oxazolino functionality (a cyclic imidate) which is an efficient ortho director. Reasons for this contrasting behaviour are discussed.

A directed metallation approach to furan analogues of o-xylylene is described in Chapter 3. A 2-secondary amido group allowed introduction of a 3-methyl substituent via directed lithiation, but incorporation of a trimethylsilyl group into this methyl group employing this technique proved unsuccessful. This was accomplished using a 2-oxazolino directing group. However, initial attempts to quaternise the oxazolino functionality failed to give the salt precursor, which should liberate the o-xylylene derivative in the presence of fluoride ion.

Chapter 4 is concerned with the azafulvene system. Flash vacuum pyrolysis of 2-dimethylaminomethylpyrrole led to the parent 1-azafulvene, a highly active species shown to have existence at low temperature by trapping with nucleophiles.

Under more vigorous pyrolytic conditions the 2-dimethylaminomethylpyrrole yielded pyridine, via a ring expansion reaction, possibly involving the azafulvene as an intermediate. 1,3-Dimethyl-2-azafulvene and benzo[b]-2-azafulvene were generated similarly.

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CHAPTER 1

1.1 ORGANOLITHIUM CHEMISTRY

1.1.1 HETEROATOM FACILITATED ORTHO-LITHIATION

In recent years, heteroatom-directed ortho-lithiation has been successfully developed and it quickly appeared as a powerful functionalisation method in the regioselective construction of highly substituted aromatic systems that are difficult to prepare by electrophilic substitution methodology.

This extensive topic will be described only briefly here as a background to the Results and Discussion presented in the thesis. For more detailed accounts the reader is referred to the extensive recent review articles.[1-6]

1.1.2 DEFINITION OF DIRECTED LITHIATION

Directed lithiation may be defined as a process whereby a hydrogen atom in a substrate molecule is replaced regiospecifically by lithium, under the control of one or more atoms or groups already forming part of the substrate.

1.1.3 MECHANISTIC CONSIDERATIONS

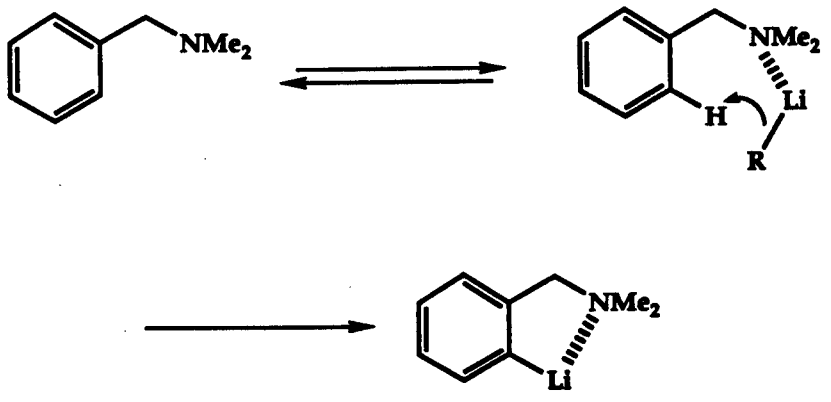
The regioselectivity of lithiation of a substrate molecule can be controlled by the electronic and/or coordinating abilities of its substituents. Lithiating agents can be divided into two classes which correspond to their mechanism of action.

The first type of organolithium reagents are electron-deficient, Lewis acidic oligomers such as ^{n}BuLi in hexane, which exists as hexamers in solution.

The second type of organolithium reagent shows negligible Lewis acid character, due to coordination by solvent or by a complexing agent like TMEDA, and are present in solution as

monomers or dimers. Included in this category are the lithium amide bases such as LDA. For further information concerning the constitution of organolithium reagents in solution, the reader is referred to the books by Wakefield, and the references cited therein.[7]

The "coordination only" mechanism operates when an electron-deficient organolithium reagent is used. An example is the ortho-lithiation of N,N-dimethylbenzylamine (Scheme 1.1). Lith-



SCHEME 1.1

iation occurs at the ortho-position, more rapidly than with benzene, although the inductive effect of the substituent would be expected to decrease the rate of reaction relative to benzene. The mechanism is envisaged as involving coordination of the lithiating agent with the lone pair of electrons on the nitrogen atom of the dimethylamino group (acting as a Lewis base), with the concomitant dissociation of the oligomer. This high effective molarity of activated organolithium reagent in close proximity to the ring leads to protophilic attack on the nearest hydrogen atom, to yield an internally chelated and isolable organolithium species.

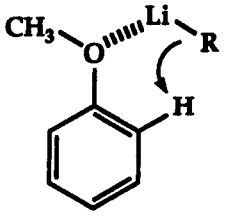
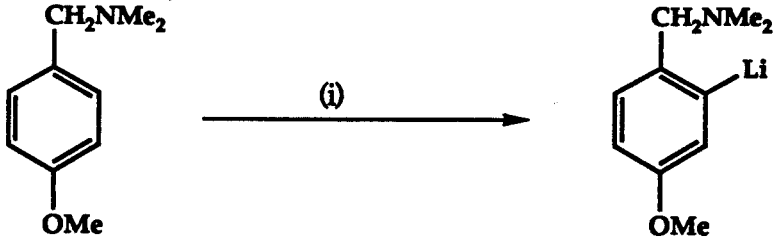


FIGURE 1.1

The "acid-base" mechanism usually operates in conjunction with the "coordination only" mechanism. For example, in the lithiation of anisole (Figure 1.1) there is a rapid coordination of the lithiating agent with the ether group leading to a polarisation of the C-Li and C-H bonds, leaving the ortho-hydrogen atoms more acidic by induction.

Slocum has demonstrated where each type of mechanism can act exclusively.[8] The lithiation of p-methoxy-N,N-dimethylbenzylamine can occur ortho to either substituent depending solely upon the state of coordination of the ^{n}BuLi.

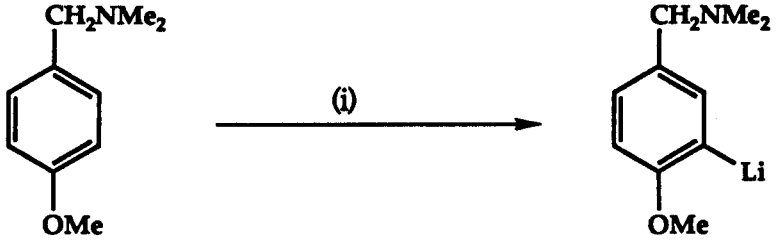
In the first case the ^{n}BuLi is in a high aggregation state, probably existing as a tetramer, and the "coordination only" mechanism predominates: lithiation occurs adjacent to the Lewis basic dimethylaminomethyl group (Scheme 1.2).



Reagents : (i) ^{n}BuLi, Et_2O

SCHEME 1.2

On addition of TMEDA the ^{n}BuLi is transformed into a "co-ordinatively saturated" monomeric state and the "acid-base" mechanism predominates: lithiation occurs adjacent to the methoxy group due to the greater enhancement of the acidity of the adjacent ortho-hydrogen atoms by the inductive effect of the oxygen atom (Scheme 1.3).

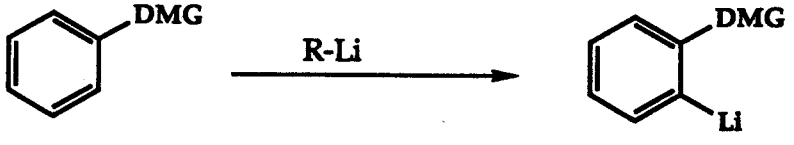


Reagents : (i) ^{n}BuLi, Et_2O, TMEDA

SCHEME 1.3

1.1.4 DIRECTED LITHIATION OF BENZENE DERIVATIVES

An attempt to classify all directing groups, for the reaction shown in Scheme 1.4, based on their inductive electron-



DMG = Directed Metalation Group

SCHEME 1.4

withdrawing or electron-donating and coordinative properties, leads to the following categorisations:

COORDINATION ONLY - Heteroatoms that are attached to a π-system by one or at the most two saturated carbon atoms can lead to ortho-lithiation only via the coordinative

mechanism if the effect of the saturated carbon(s) is considered neutral. The most effective groups are basic amines, for example, $CH_2NR_1R_2$ and $CH_2CH_2NR_1R_2$.

ELECTRON-WITHDRAWING GROUPS - Electron-withdrawing groups with little or no coordinative capacity are effective ortho-directors because of their ability to markedly increase the hydrocarbon acidity of adjacent positions, for example, F, Cl and Br.

ELECTRON-WITHDRAWING GROUPS WITH MODERATE COORDINATION POTENTIAL - A common feature of these functionalities is a moderate capacity for coordination with the lithiating agent. Their inherent effect on the ortho-position is electron-withdrawing by induction. On coordination with the metalating agent this effect is enhanced. Examples include, SO_2-aryl, $SO_2NR_1R_2$ and OR.

ELECTRON-WITHDRAWING GROUPS WITH PRONOUNCED COORDINATION POTENTIAL - These functional groups exhibit the ideal features for facile ortho-lithiations, i.e., a high capacity for effective coordination with the lithiating agent via the non-bonding pair of electrons on a nitrogen atom, and the ability to inductively acidify adjacent hydrogens through their electron-withdrawing properties. Examples include $CONR_1R_2$, 2-oxazolines and 2-pyridines.

Several attempts to provide a "ranking" order for the directing abilities of functional groups have been made. The order given by Gschwend and Rodriguez based upon data gathered from competition experiments, using coordinatively unsaturated lithiating agents is:[1]

$SO_2NR_1R_2$, SO_2-aryl, $CONR_2$ > 2-oxazolines >

CONHR, CSNHR > $CH_2N(CH_3)_2$ > $CR(O^-)$, $CH_2N(CH_3)_2$

> OCH_3 > O-aryl > NH-aryl > S-aryl > NR-aryl > $N(CH_3)_2$ > $CR_1R_2O^-$

Some generalisations upon the published work can be made.

1. The strongest directors of lithiation to an ortho ring position have both an electron-withdrawing effect and the ability to coordinate with the lithiating agent.
2. Where the directing group is separated from the ring by a saturated carbon atom, a basic nitrogen is the most powerful director.
3. In the presence of coordinatively saturated lithiating agents the ranking is determined largely by the acidifying effect of the group.

When two groups capable of directing lithiation are present in a benzene ring the regiochemistry of lithiation becomes dependent upon the relationship of the two groups and the metalating conditions. For example, looking at the benzenoid systems, when a substituent (Y) is present in either a 1,2- or 1,4-relationship to the dominant ortho directing group or atom (X), the general rule is that the higher degree of lithiation occurs ortho to the more powerful directing group (Figures 1.2 and 1.3) The

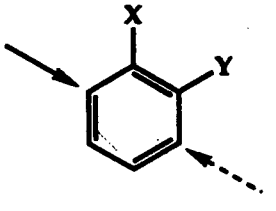


FIGURE 1.2

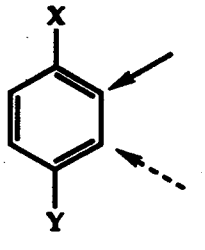


FIGURE 1.3

strength of the director, however, is interdependent on the nature of the lithiating agent utilised.[1] When X and Y are in a 1,3-relationship, even if the directing effect of Y is weak, lithiation occurs predominantly or exclusively in the position ortho to both the beta-directing group X and the substituent Y (Figure 1.4). The degree of regioselectivity depends upon the

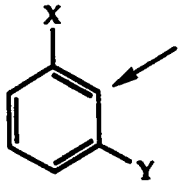
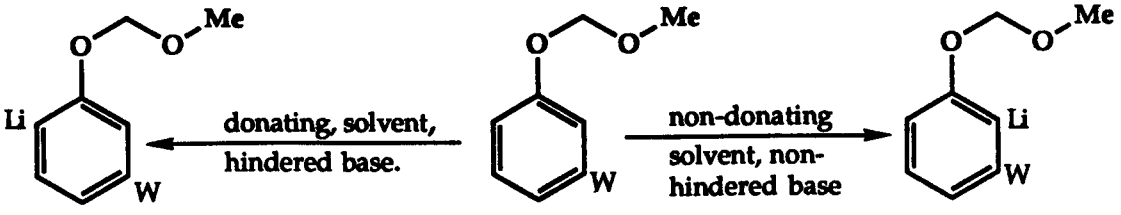


FIGURE 1.4

relative inductive and coordinative capacities of Y. There are some exceptions to this rule. Bhide found that when X = Y = $CONH^tBu$, lithiation occurs in the C4-position of the ring.[9] Winkle and Ronald have similarly found that the site of lithiation of such 1,3-disubstituted benzene derivatives depends upon the nature of the lithiating agent (Scheme 1.5).[10]



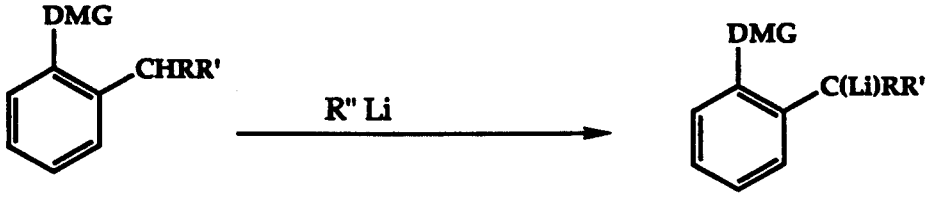
W = Weak directing group

SCHEME 1.5

When W is a weak directing group such as $-OCH_3$, hindered bases in electron-donating solvents lead to lithiation away from

the weak directing group. However, non-hindered bases in non-donating solvents lithiate between the two groups. A balance between coordination of the incoming base and steric hindrance is probably responsible for the change in regioselectivity.

Another aspect of directed lithiation in carbocyclic aromatic systems is the clean lithiation of benzylic hydrogens adjacent to directing groups. If the alkyl group is ortho to a moderate or strong directing group benzylic lithiation will occur (Scheme 1.6).[1]



SCHEME 1.6

1.1.5 DIRECTED LITHIATION OF HETEROAROMATICS

Much of the directed lithiation work in heteroaromatic chemistry has been carried out on thiophene, furan and their derivatives and to a lesser extent pyrrole, imidazole and their derivatives. Much of this work has previously been reviewed and so only the broad conclusions will be outlined here.[11] The presence of ring heteroatoms have a strong influence on the regioselectivity of lithiation reactions.

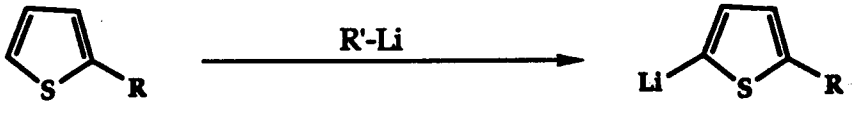
Thiophene and furan themselves are readily mono lithiated and can even be dilithiated under more forcing conditions, using ^{n}BuLi and TMEDA: metalation occurs exclusively adjacent to the heteroatom.[12] Pyrrole and imidazole are themselves deprotonated at nitrogen by lithiating agents and further ring lithiation is

minimal. However, N-protected pyrroles and imidazoles can both be monolithiated easily and also dilithiated in extremely high yields. 2,4- As well as 2,5-dilithiation is observed during dimetallation reactions for N-alkyl pyrroles.

1.1.5.1 2-MONOSUBSTITUTED DERIVATIVES

Because of the great facility with which thiophene itself can be lithiated in its α-position, 2-substituted thiophenes generally undergo lithiation to give a 5-lithio-intermediate in good yields. The strong preference for α-lithiation is a direct consequence of the presence of the ring heteroatom. Even in the presence of "would-be" ortho-directing groups like SO_2R and SO_2NR_2, C5-lithiation is preferred to C3-lithiation (Table 1.1).

TABLE 1.1



R	R'Li	Reference
SO_2Ph	^nBuLi	13
OMe	PhLi	14
SMe	^nBuLi	15
CO_2Li	LDA	16
SO_2NMe_2	^nBuLi	17
CH_2NMe_2	^nBuLi	18

Similar results are achieved for 2-substituted furans and to a lesser extent for 2-substituted N-protected pyrroles and imidazoles.

However, there have been recent reports where 2-monosubstituted thiophenes and furans have been successfully lithiated in the C3-position using a limited number of directing groups. These groups are powerful ortho-directors of lithiation and so under the correct choice of reaction conditions regioselective C3-lithiation is preferred to C5-lithiation (Table 1.2).

TABLE 1.2

R	X	Reference
2-Oxazolines	S, O, NMe	11,19
2-Imidazolines	S, O, NMe	21
-CONHR	S, O	11
$-CO_2Li$	S	11
$-OP(O)(NMe_2)_2$	O	20

ortho-Lithiation (C3) of 1,2-disubstituted pyrroles is less successful. Lithiation of N-methyl pyrrole-2-oxazolinyl derivatives gives a 15:1 ratio of the C3- and C5-lithio species with

considerably reduced levels of lithiation compared to the analogous thiophene and furan derivatives.[19]

1.1.5.2 3-MONOSUBSTITUTED DERIVATIVES

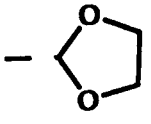
A 3-substituted thiophene whose 3-substituent has any ortho-directing ability (either inductive or coordinative) lithiate at the C2-ring position in a manner analogous to benzene rings disubstituted in a 1,3 pattern with directing groups. Good yields of the 2,3-disubstituted products are achievable. Even weak directors of lithiation such as OMe and SMe lead to good yields of the 2-lithio intermediate (Table 1.3). Not surprisingly, 3-alkyl groups are an exception to this trend.[1] A 3-methyl group leads to an 11:39 mixture of the 2,3- to 2,4-disubstituted products after electrophilic work-up. The methyl group shows no coordinative properties and inductively reduces the acidity of the adjacent protons, and so C5-lithiation is preferred.

3-Monosubstituted furans exhibit similar behaviour to their thiophene analogues. There is little information available on the lithiation of N-protected-3-substituted pyrroles.

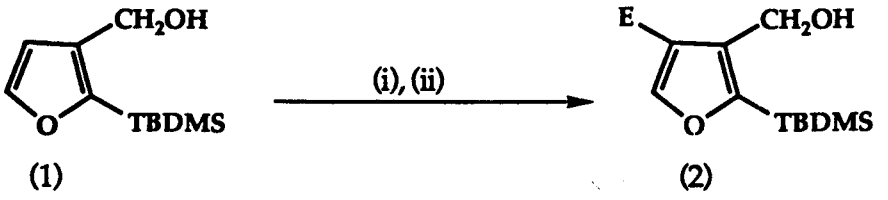
1.1.5.3 DISUBSTITUTED DERIVATIVES

For 2,5- and 3,4-disubstituted thiophenes, lithiation occurs adjacent to the stronger directing group. Lithiation of 2,3-disubstituted thiophenes has been reported for only a very few cases and is found to occur at the α-position of the ring when non-alkyl substituents are present. There are few examples of di- or tri-substituted furans being lithiated with one notable exception. Bures and Keay treated the disubstituted furan (1)

TABLE 1.3

R	R'Li	Reference
CO_2Li	LDA	22, 23
NO_2	LDA	22
SMe	^{n}BuLi	1
CH_2OMe	^{n}BuLi	24
CH_2NMe_2	^{n}BuLi	24
CONHMe	2-^{n}BuLi	18
$O^{t}Bu$	^{n}BuLi	25
OMe	^{n}BuLi	1
Br	Ph-Li	1
	^{n}BuLi	26

with ^{n}BuLi in DME at 0°C and quenched the resulting dianion with electrophiles to give the trisubstituted furan (2) (Scheme 1.7).[27] It is apparent that the C3-hydroxymethyl functionality directs lithiation exclusively into the adjacent C4-position via the coordination only mechanism. This is the first report of a directed lithiation into the C4-position in preference to C5-lithiation.



(1) (2)

Reagents : (i) ^{n}BuLi, DME, 0°C, 0.25h; (ii) LiCl then E^{+}

SCHEME 1.7

1.1.6 SYNTHETIC UTILITY OF THE LITHIATED SPECIES

The lithiated intermediate is a highly reactive species and reacts virtually with any electrophilic centre in a given substrate. Thus, lithiation is a valuable way of introducing functionality into aromatic and heteroaromatic systems. Some of the more widely used electrophiles are collated in Table 1.4 (which is organised according to the nature of bonds formed).

1.1.7 RECENT ADVANCES IN DIRECTED LITHIATION

Although directed metallation is a very useful synthetic tool in aromatic chemistry, there are situations where its use is limited. In this section some of the novel and elegant techniques to overcome a selection of these limitations are demonstrated. Some novel and useful directing groups are also demonstrated and the new technique of ortho magnesiation is introduced.

1.1.7.1 NEW STRATEGIES FOR PROTECTION, ACTIVATION AND DIRECTION IN LITHIATION OF NITROGEN HETEROCYCLES

One of the classical problems of heterocyclic chemistry has been the activation towards proton loss of a CH group adjacent to a heterocyclic NH. In spite of much effort, it is only recently that synthetically useful procedures have been developed.

TABLE 1.4

Bond Type	Electrophile type	Reliability
C-D	D_2O/ROD	Diagnostic
C-C	R-Hal	Usually good
	R-Sulphate	Usually good
	Epoxides	Variable
	RCHO	Usually good
	RCOR'	Usually good
	CO_2	Good
	DMF	Variable
	RCN	Good
	RNCS	Good
	RNCO	Good
C-N	$MeONH_2$	Moderate yields
	TsN_3	Good
C-S	R_2S_2	Good
	S_8	Good
C-Hal	NSC(Cl)	Good
	I_2	Variable
	$BrCH_2CH_2Br$	Variable
C-Si	R_3SiCl	Excellent

1.1.7.1.1 CARBAMATE ANION INTERMEDIATES

Derivatives commonly used to protect NH groups, such as amides and carbamates, are not practical in carbanionic systems because of their great susceptibility to nucleophilic attack.

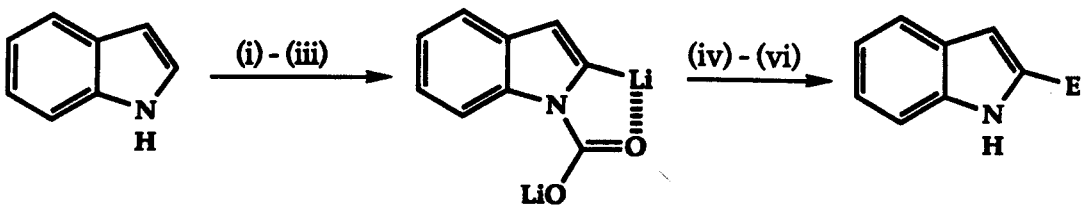
This problem can be partly overcome by the use of more hindered derivatives, but then harsher conditions are usually required for deprotection. As a means of overcoming both of these problems Katritzky has developed a new and elegant approach involving the use of carbon dioxide to protect the nitrogen as its carbamate anion derivative. Because of the presence of the negative charge, these carbamates are much more resistant to nucleophilic displacement of the protecting group but after protonation, they readily undergo decarboxylation on gentle warming to restore the NH functionality.[28-29]

Initial investigations focused on indole where a successful "one-pot" method for the preparation of 2-substituted derivatives was developed.[30]

Indole (**3**) is first converted to its lithium carbamate by sequential treatment with ^{n}BuLi in thf, followed by carbon dioxide (Scheme 1.8). Lithiation of the lithium carbamate at the C2-position was then accomplished with ^{t}BuLi to give (**4**). After an electrophilic quench the reaction was allowed to reach ambient temperature. Treatment of the mixture with aqueous acid, followed by gentle warming to drive off the CO_2 protecting group, gave the product 2-substituted indoles (**5**) in yields ranging from 52 - 86%.

The same technique has also been applied successfully to the conversion of pyrrole (**6**) into 2-substituted pyrroles (**7**) (Scheme 1.9) in yields ranging from 50 - 95%.[31]

The carbon dioxide protection method is also effective for electrophilic substitution of tetrahydroisoquinoline (**8**) at the 1-position, and presently offers the easiest route to compounds of this type (**9**)[32] (Scheme 1.10).

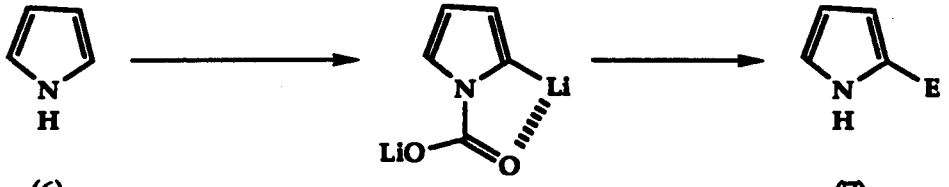


(3) (4) (5)

Reagents : (i) $^{n}BuLi$; (ii) CO_2; (iii) $^{t}BuLi$; (iv) E^+;

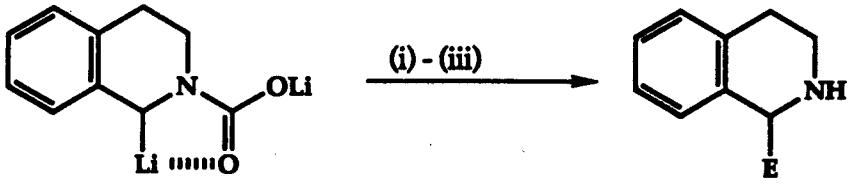
(v) H_3O^+; (vi) Heat

SCHEME 1.8



(6) (7)

SCHEME 1.9



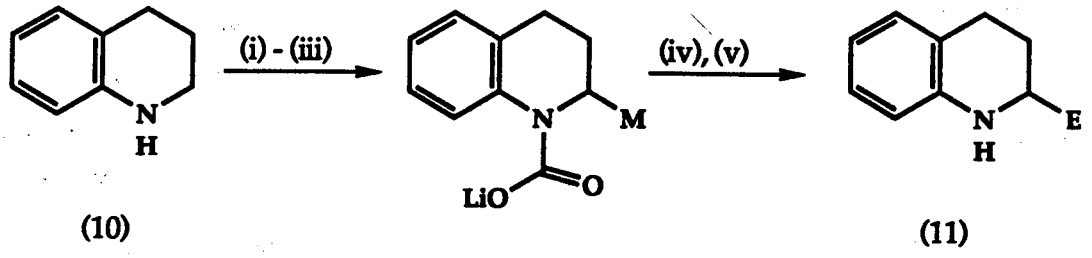
(8) (9)

Reagents : (i) E^+; (ii) H_3O^+; (iii) heat

SCHEME 1.10

For tetrahydroquinoline (**10**), where the α-carbon lacks the activating effect of the adjacent benzene ring, the deprotonation step is much more difficult. However, by using a combination of $KO^{t}Bu$ and $^{t}BuLi$,[33] α-metallation could be accomplished, whereupon

successful reaction with carbonyl electrophiles was achieved. The usual work-up gave α-substituted tetrahydroquinolines (11) in 50 - 70% yield[34] (Scheme 1.11).



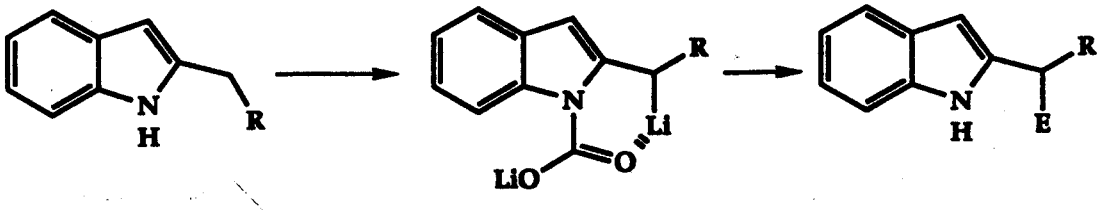
(10) (11)

Reagents : (i) $^{n}BuLi$; (ii) CO_2; (iii) $KO^{t}Bu$, $^{t}BuLi$;

(iv) E^{+}; (v) H_3O^{+}

SCHEME 1.11

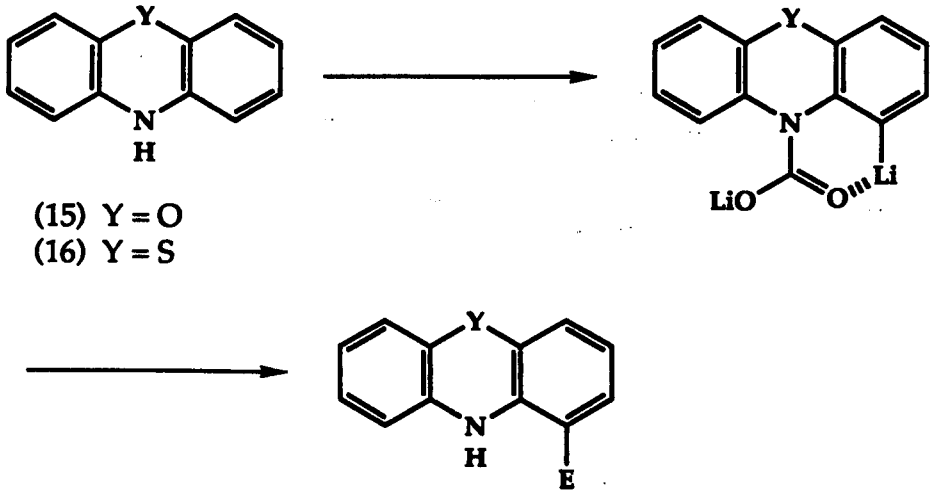
Unlike a number of ortho-lithiation directing methods, the carbamate anion route is not restricted to those systems where the carbanion is located α to the nitrogen atom, and both β-aliphatic and β-aromatic carbons have been successfully lithiated. Thus, when 2-alkyl indoles (12) are protected as their lithium carbamates (13), they readily lithiate on the α-carbon of the alkyl side chain (i.e., β to the nitrogen) to give alkyl substitution products (14) (Scheme 1.12).[35] No aromatic lithiation was observed with any of these alkyl indole derivatives.



(12) (13) (14)

SCHEME 1.12

Both phenoxazine (**15**) and phenothiazine (**16**) were both successfully deprotonated on the adjacent (C-1) aromatic carbon to eventually yield 1-substituted derivatives (**17**) and (**18**) (Scheme 1.13).[36-37]



SCHEME 1.13

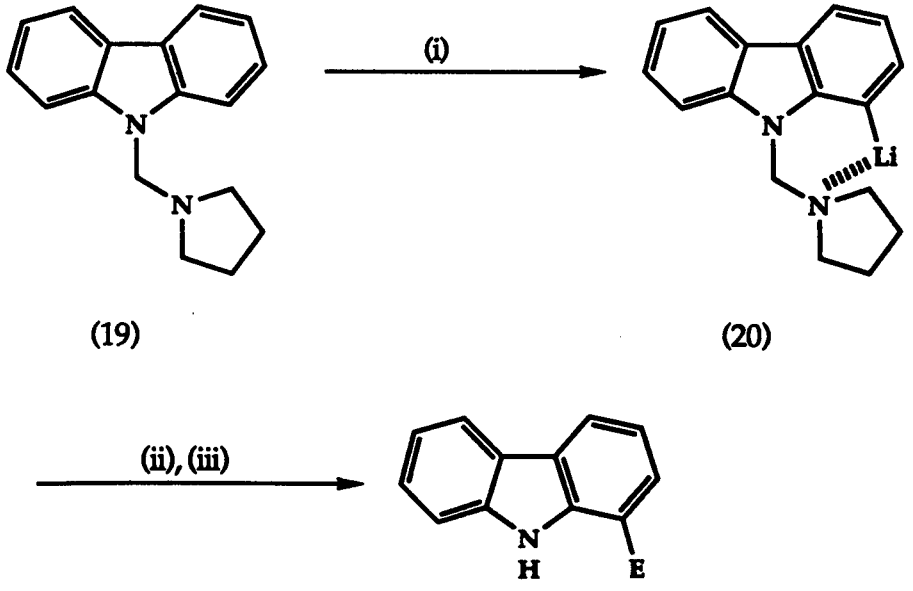
The use of carbon disulphide for the protection of the NH in a number of heterocyclic systems has also been investigated,[38] but the results were not nearly as successful as with carbon dioxide. Similar investigations of SO_2 and SO_3 as potential protecting groups were found equally discouraging.

1.1.7.1.2 AMINAL INTERMEDIATES

The carbon dioxide method is clearly a powerful strategy for protection and activation, although it has definite limitations. It failed in a number of attempted applications with carbazole, dialkylindoles and other heterocycles such as imidazole, benzimidazole and pyrazole. The N-(dialkylamino)methyl (aminal) groups were identified as powerful lithiation directing func-

tions, that were both easy to introduce and subsequently remove.[39] The directing effect of dialkylaminomethyl groups in carbocyclic chemistry is well documented,[1,40-42] and their successful extension to heterocyclic systems represents a valuable addition to their usefulness. Formation of the aminal intermediates is readily achieved by using the Mannich reaction on the heterocycle with the appropriate secondary amine and formaldehyde, while subsequent hydrolysis occurs readily on gentle warming with dilute acid.

Carbazole as its N-pyrrolidinomethyl derivative (**19**), can be effectively and exclusively lithiated at the 4-position adjacent to the nitrogen (Scheme 1.14).[39] The lithio-intermediate (**20**)



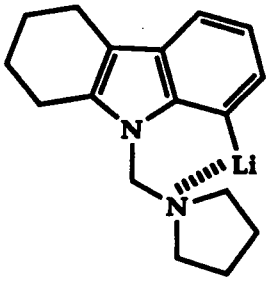
Reagents : (i) ^{t}BuLi; (ii) E^{+}; (iii) H_3O^{+}

SCHEME 1.14

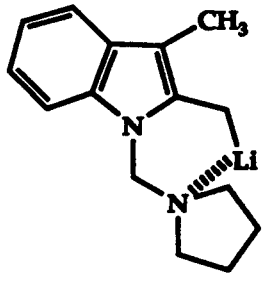
was quenched efficiently with a variety of different electrophiles. The lithiation step was found to be highly solvent dependent, with the best results being obtained in hexane where

direct coordination of the ^{n}BuLi to the dialkylamino group can occur.

Extension of the above lithiation procedure to the N-(pyrrolidinomethyl)derivative of 1,2,3,4-tetrahydrocarbazole showed that lithiation occurred only at the aromatic 8-position to give (21), despite the availability of two different reaction sites. However, when 2,3-dimethylindole was subjected to the same reaction the site of deprotonation was the C2-methyl group, resulting in the lithio-intermediate (22).[39]



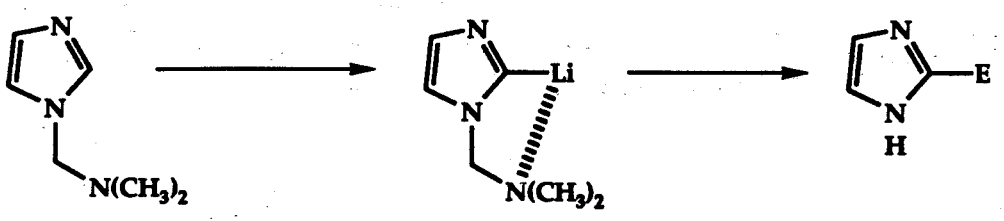
(21)



(22)

The aminal method was successfully extended to other heterocyclic systems, and provided a convenient "two-pot" method for the conversion of imidazoles, benzimidazoles and pyrazoles into their respective 2-, 2-, and 3(5)-substituted derivatives (23), (24) and (25) respectively (Scheme 1.15).[43]

A rather special use of the aminal function has been reported by Muchowski and Hess.[44] These workers investigated the lithiation of the 6-methylamino-1-azafulvene dimer (26), formed by treatment of pyrrole-2-carboxaldehyde with aqueous dimethylamine. Dilithiation occurs readily at the positions α- to the ring nitrogen atoms and after electrophilic addition and subsequent hydrolysis, 5-substituted pyrrole-2-aldehydes (27)



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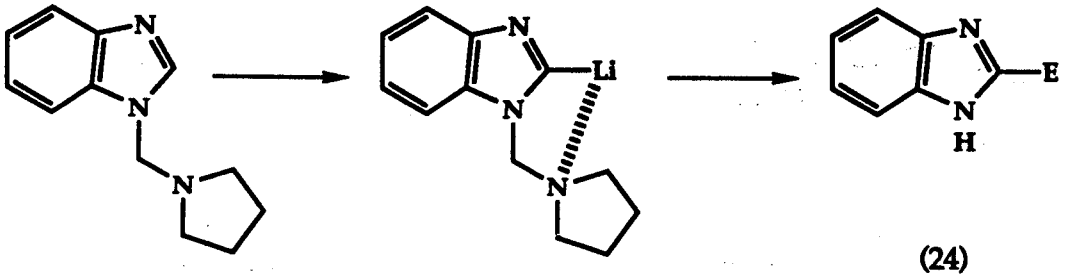
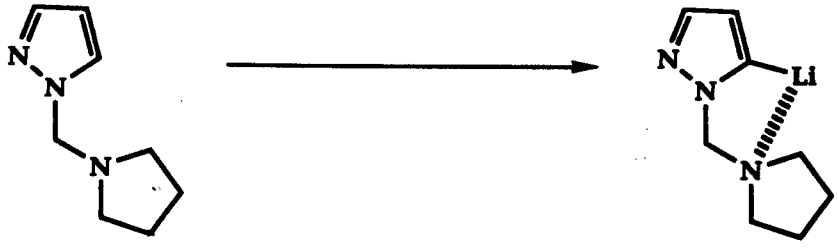
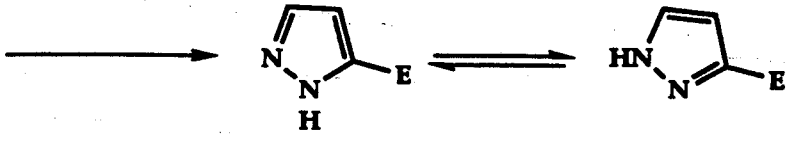


(24)

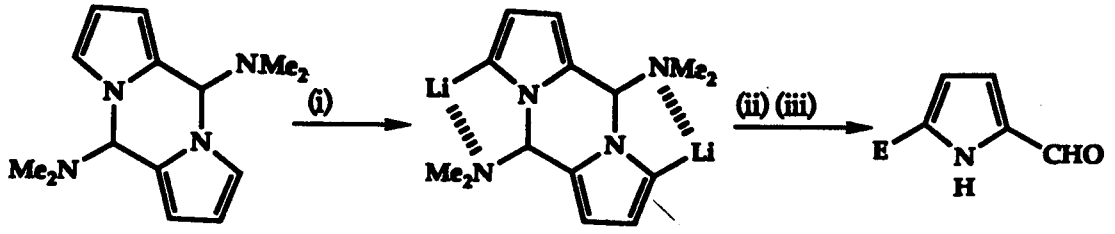




(25)

SCHEME 1.15

were obtained in 54 - 91% yield (Scheme 1.16). This particular example is elegant in that protection of both the ring NH and the carboxaldehyde group are achieved in a "one-pot" strategy. Carboxaldehydes readily undergo nucleophilic attack in the presence of organolithium reagents, and so protection is essential.

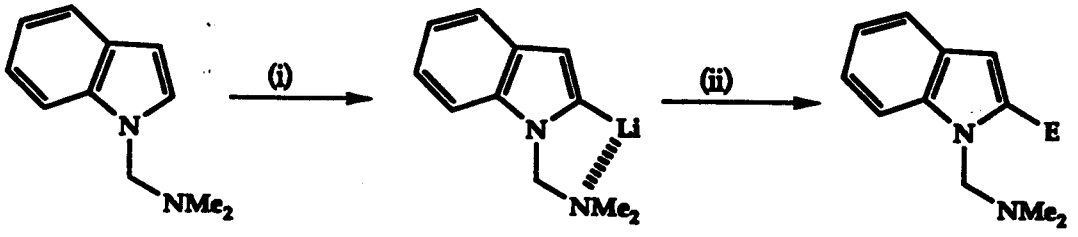


(26) (27)

Reagents : (i) ^{t}BuLi; (ii) E^{+}; (iii) H_3O^{+}

SCHEME 1.16

Recently, Hlasta and Bell reported the use of (dimethylamino)methyl as a directing group for the C2-lithiation of indole.[45] Isogramine (28) undergoes 2-lithiation on reaction with ^{n}BuLi under very practical and straightforward conditions to give the 2-lithio intermediate (29) which was readily quenched with electrophiles (Scheme 1.17). The synthetic utility of this

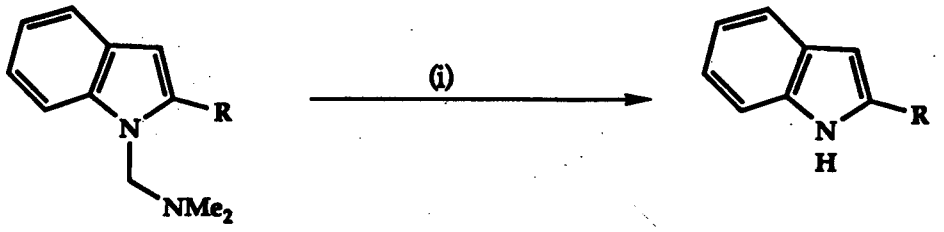


(28) (29)

Reagents : (i) ^{n}BuLi, Et_2O, room temperature; (ii) E^{+}

SCHEME 1.17

reaction was somewhat reduced due to the inability to effect easy removal of the aminal group by acid hydrolysis. Katritzky then reported a reductive elimination method using $NaBH_4$ to successfully deprotect N-aminal indoles which possess substituents not reduced under these conditions (Scheme 1.18).[46]



Reagents : (i) $NaBH_4$, EtOH/thf, reflux, 2h

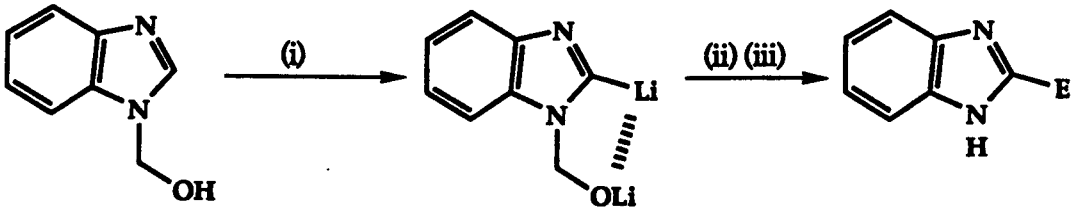
SCHEME 1.18

1.1.7.1.3 HEMIAMINAL ANION INTERMEDIATES

The merits of hemiaminal (α-amino alkoxides) have also been investigated by Katritzky et al., as protecting-directing groups for the lithiation of NH heterocycles. The utility of α-amino alkoxides, in aromatic lithiations,[1,41] and as in situ aldehyde protecting groups[47-48] is well known. Hemiaminals derived from aldehydes and ketones are usually very unstable, but when an electron-withdrawing group is attached to the nitrogen atom they are sometimes stable enough to isolate. Some heterocyclic examples include those derived from benzotriazole, which have been particularly well investigated.[49]

Despite the unfavourable equilibrium in hemiaminal formation, it was envisaged that a heterocycle derived lithium aminal could potentially serve as a protecting-directing group during C-lithiation on the heterocycle. Particularly attractive is the facile deprotection of the heterocycle.

Benzimidazole was lithiated successfully at the C2-position, after conversion to N-hydroxymethyl derivative (30) with formaldehyde. The lithiated species (31) was further converted into a variety of 2-substituted derivatives (24), in an overall "one-pot" procedure (Scheme 1.19).[50] This "one-pot" hemiaminal

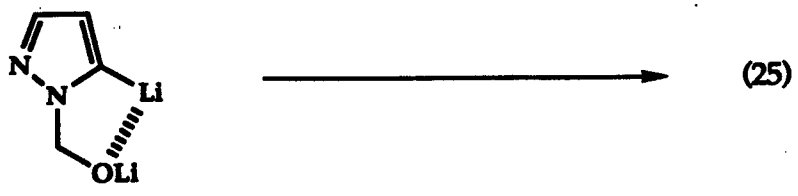


(30) (31) (24)

Reagents : (i) LDA, ^{n}BuLi or ^{t}BuLi; (ii) E^{+}; (iii) NH_4Cl, H_2O

SCHEME 1.19

procedure for benzimidazole is generally not as efficient as the "two-step" aminal method, the reduced yields possibly resulting from solubility problems due to the extra negative charge on the oxygen atom of the hemiaminal. However, the above method has also been applied to pyrazole using dilithio-intermediate (32) and found to be an improvement on the aminal method[51] (Scheme 1.20).

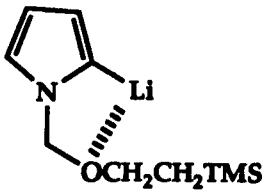


(32) (25)

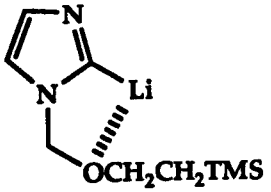
SCHEME 1.20

1.1.7.1.4 TRIMETHYLSILYLETHOXYMETHYL (SEM) FUNCTIONALITY

The SEM group has been utilised by a number of groups for N-protection and C2-activation of the pyrrole, indole and imidazole ring systems.[52-53] It is usually introduced by treatment of the heterocycles with a metal hydride base and subsequent addition of trimethylsilylethoxymethyl chloride. The SEM group facilitates C2-lithiation presumably via the chelated species



(33)



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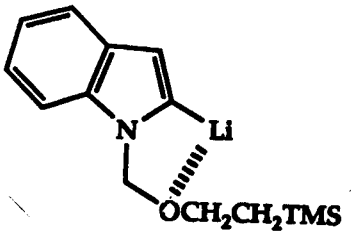
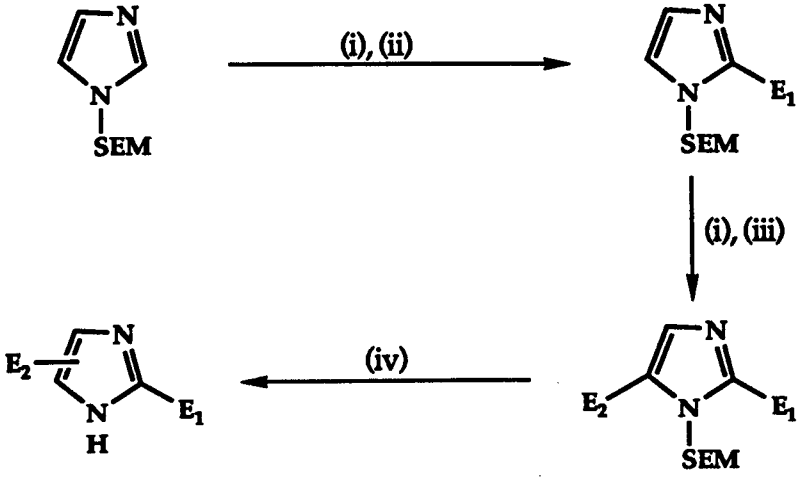


(34)

(33), (34) and (35). Treatment with a variety of electrophiles followed by deprotection under mild conditions by treatment with tetra-n-butylammonium fluoride (TBAF) led to the 2-monosubstituted products in moderate to good yields.

Recently, Lipschutz has demonstrated that N-SEM protected imidazoles can be sequentially derivatised at the C2- and then C5-positions in a "one-pot" operation, using this protection-lithiation methodology (Scheme 1.21).[54] This is an elegant way of achieving 2,4(5)-disubstituted imidazoles.



Reagents : (i) ^{n}BuLi, thf, -78°C; (ii) E_1^+;

(iii) E_2^+; (iv) TBAF

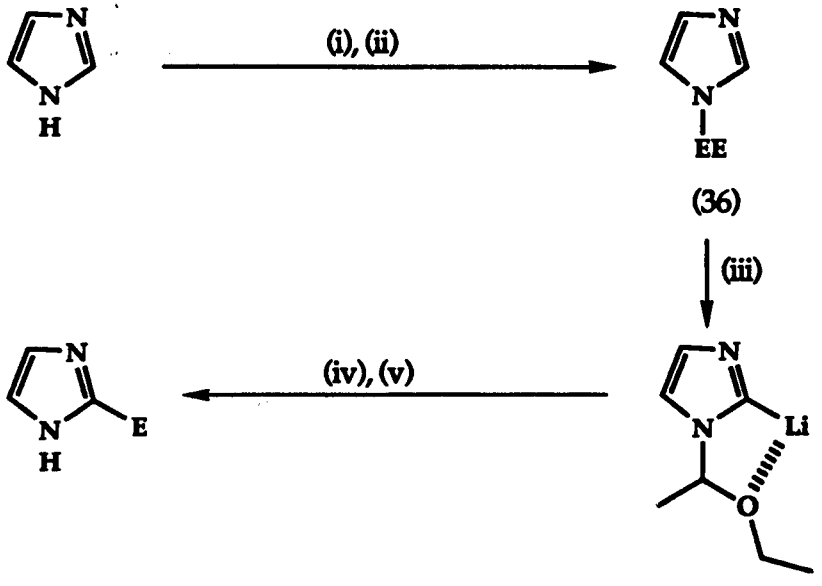
SCHEME 1.21

Although the SEM group is easily introduced and removed and is an effective C2-lithiation director for N-heterocycles, the expense is a serious drawback.

1.1.7.1.5 1-(1-ETHOXYETHYL) : AN EFFECTIVE PROTECTING GROUP FOR IMIDAZOLE NITROGEN

Recently, Brown has demonstrated the synthetic utility of the 1-ethoxyethyl (EE) group for N-protection and C2-lithiation of imidazoles.[55] This is a cheap, easily introduced and removed protecting group and treatment of the lithio-derivative with electrophiles leads to C2- or C5-substituted products in high yields.

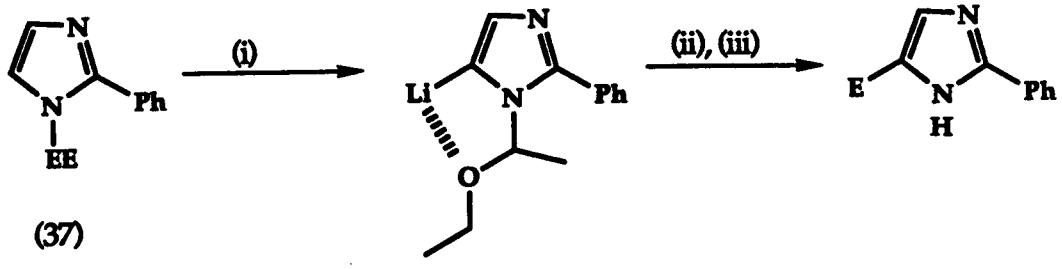
Introduction of the EE group is accomplished by treatment of the imidazole with ^{n}BuLi in thf at 0°C, followed by 1-chloro-1-ethoxyethane (Scheme 1.22). C2-Lithiation of imidazole (36) is



Reagents : (i) ^{n}BuLi, thf, -10°C; (ii) EE–Cl, -20°C, then room temperature; (iii) ^{n}BuLi, thf, -40°C; (iv) E^{+}; (v) H_3O^{+}, heat

SCHEME 1.22

accomplished with ^{n}BuLi in thf at -40°C. After addition of an electrophile the reaction mixture was allowed to reach ambient temperature to give monosubstituted products. C5-Lithiation of imidazole (37) occurred only with ^{s}BuLi at -10°C (Scheme 1.23).



(37)

Reagents : (i) ^{s}BuLi, thf, -10°C, 0.5 h; (ii) E^{+}; (iii) H_3O^{+}

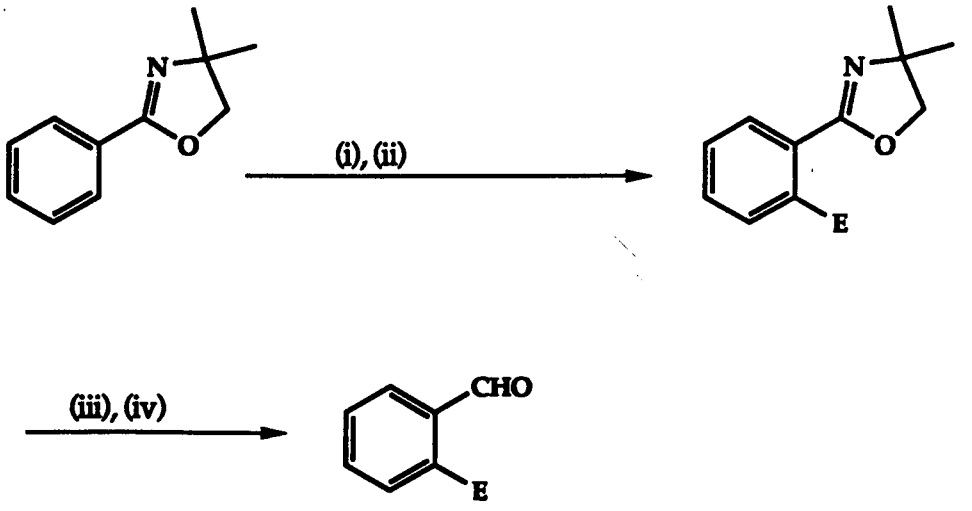
SCHEME 1.23

Deprotection is accomplished by heating (50 - 100°C) a mildly acidic solution of the imidazole-EE derivative for a few hours or by TBAF in thf.

1.1.7.2 α-AMINO ALKOXIDE FUNCTIONALITY : A NEW STRATEGY FOR THE PROTECTION AND DIRECTION OF LITHIATION FOR AROMATIC AND HETEROAROMATIC ALDEHYDES

Aromatic aldehydes are generally not very useful ortho-directors of lithiation as they are susceptible to nucleophilic attack by the organolithium reagent. Previously, oxazolines and N,N-diethylamides have served as functional groups for aromatic ortho-lithiation, and then transformed to aldehydes. However, this conversion requires subsequent chemical steps (Scheme 1.24), and so a more direct route to ortho-substituted aromatic aldehydes is preferred.

Comins has recently derived a "one-pot" synthesis of ortho-substituted aromatic aldehydes via ortho-lithiation utilising an

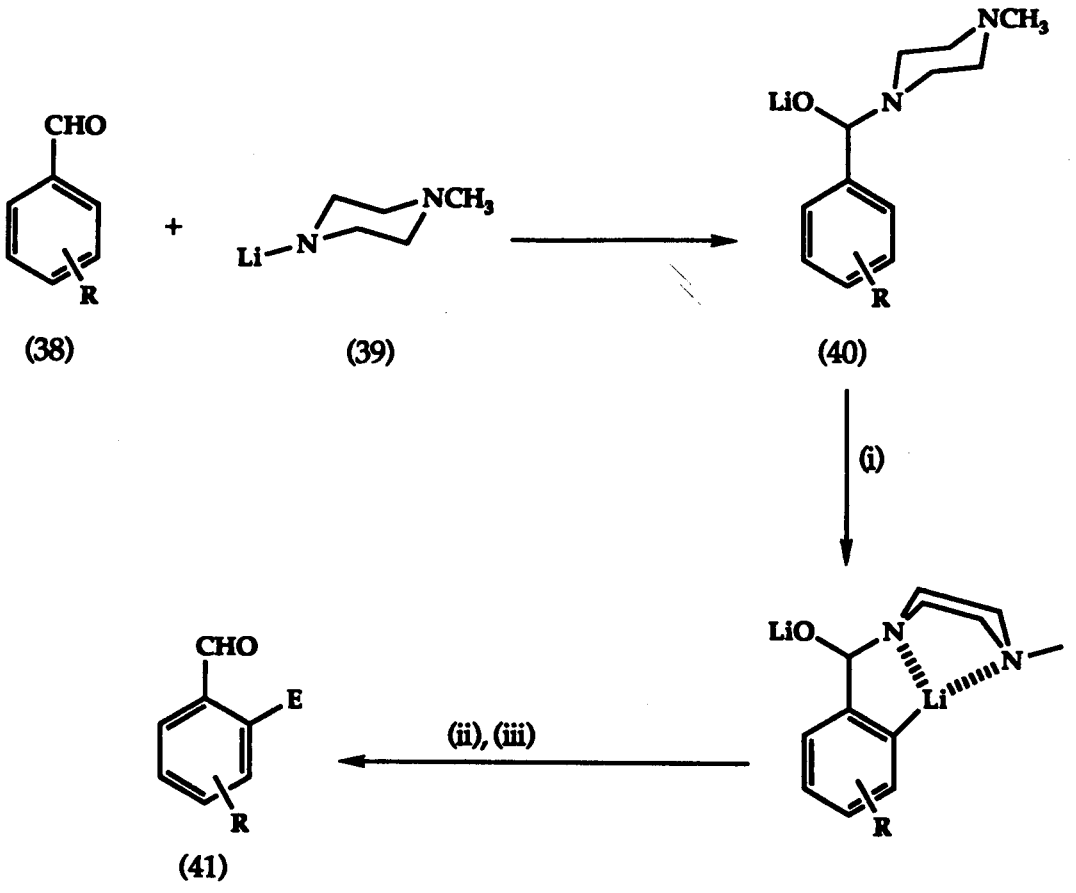


Reagents : (i) RLi; (ii) E^+; (iii) MeI; (iv) $NaBH_4$

SCHEME 1.24

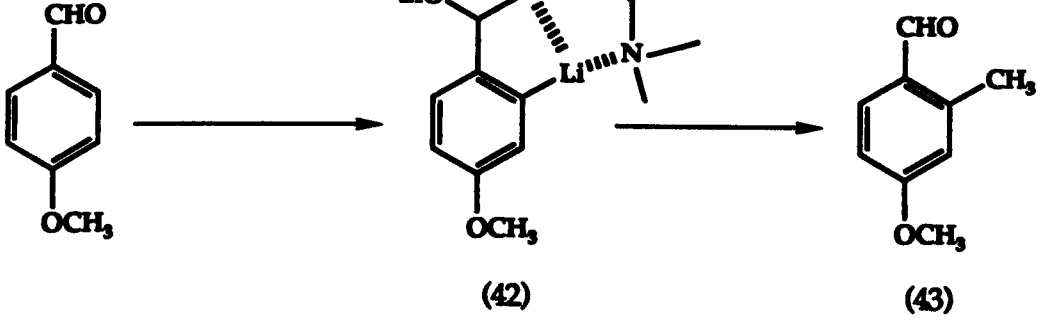
in situ formed α-amino alkoxide as the ortho-activating group.[56-58] These α-amino alkoxides (**40**) are formed via the addition of aromatic aldehydes (**38**) to certain lithium dialkylamides (**39**). These aryl α-amino alkoxides can be ortho-lithiated (by a co-ordination type mechanism), quenched with electrophiles and hydrolysed on work-up to provide ortho-substituted aryl aldehydes (**41**) (Scheme 1.25).

These workers found that the directing power of an α-amino alkoxide could be altered by simply varying the amine component, allowing regioselective control during the lithiation of a deactivated benzene ring. For example, 4-methoxybenzaldehyde was treated with lithiated N,N,N'-trimethylethylenediamine (LTMDA) to form an α-amino alkoxide in situ, and lithiated to give dilithio species (**42**), which was alkylated to give 4-methoxy-2-methylbenzaldehyde (**43**) on aqueous work-up in 90% yield (Scheme 1.26). In this example, lithiation is preferred ortho to the strongly coordinating α-amino alkoxide, via a "coordination only" type mechanism.



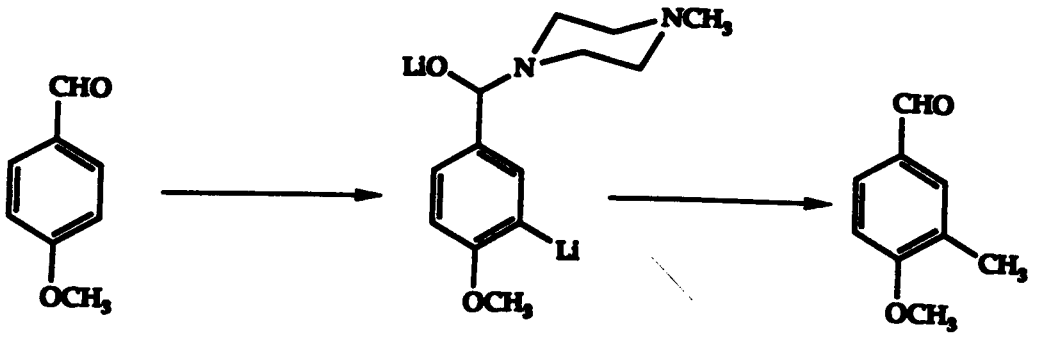
Reagents : (i) 3 ^{n}BuLi, PhH, reflux; (ii) E^{+}; (iii) H_3O^{+}

SCHEME 1.25



SCHEME 1.26

When lithium N-methylpiperazide (LNMP) was utilised as the amine component, lithiation gave the dilithio-intermediate (44) which was methylated, and after work-up provided 4-methoxy-3-methylbenzaldehyde (45) as the sole product in 73% yield[58] (Scheme 1.27). In this example, the coordinating effect of the

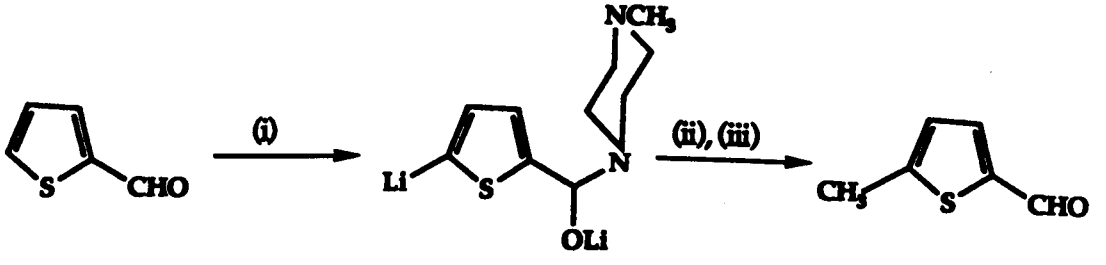


(44) (45)

SCHEME 1.27

α-amino alkoxide is less than the directing effect (inductive) of the methoxy group, and so lithiation is preferred ortho to the methoxy group. Recently, this chemistry has been extended to various aromatic heterocyclic carboxaldehydes.[59]

Thiophene-2-carboxaldehyde (46) was treated with LNMP to form the α-amino alkoxide in situ. Lithiation gave the dilithio species (47), followed by alkylation and aqueous work-up gave 5-methylthiophene-2-carboxaldehyde (48) in 77% yield as the sole product (Scheme 1.28). This result was anticipated since the

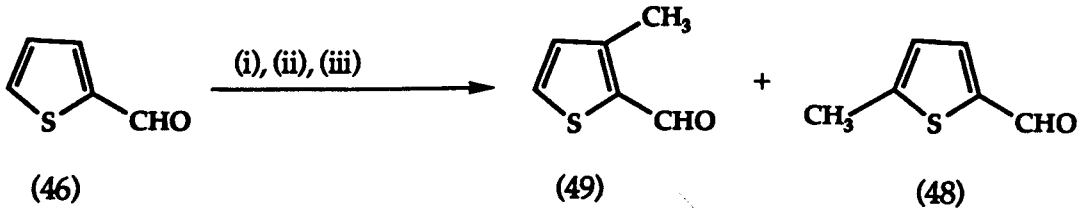


(46) (47) (48)

Reagents : (i) LNMP; (ii) 3^{n}BuLi; (iii) CH_3I, H_2O

SCHEME 1.28

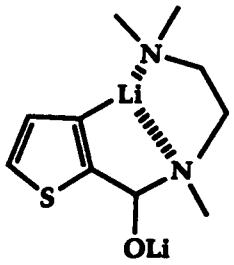
formed α-amino alkoxide group is not a strong directing group. However, attempts to achieve ortho-lithiation using the strongly directing amine component, LTMDA, gave a 69% yield of a mixture of (49) and (48) in a ratio of 2:1 (Scheme 1.29). Product (49)



(46) (49) (48)

Reagents : (i) LTMDA; (ii) 3^{n}BuLi; (iii) CH_3I, H_2O

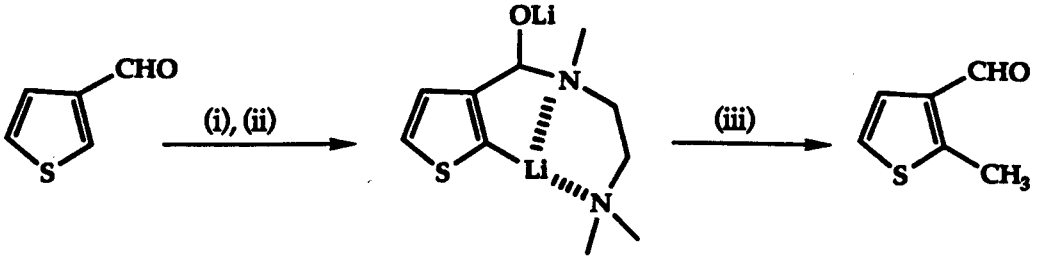
SCHEME 1.29



(50)

is presumably obtained via the dilithio-intermediate (50).

As expected, thiophene-3-carboxaldehyde (51) was successfully lithiated at the C2-position to give the 2,3-disubstituted product (53) (Scheme 1.30), via dilithio-intermediate (52).



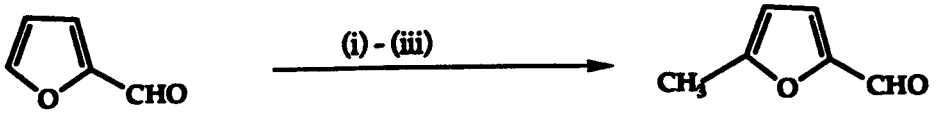
(51) (52) (53)

Reagents : (i) LTMDA; (ii) 1.1 LDA, 0.9 ^{n}BuLi; (iii) CH_3I, H_2O

SCHEME 1.30

For the furan case, 2-furaldehyde (54) was lithiated via an α-amino alkoxide exclusively at the C5-position regardless of

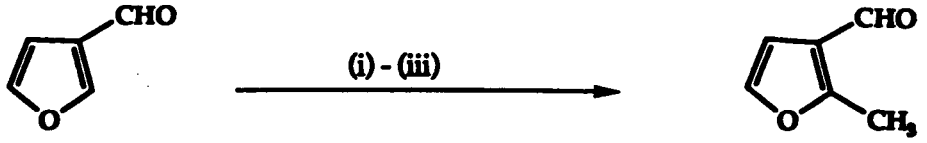
which amine component was used. In these examples, the "acid-base" mechanism is preferred to any "coordination" mechanism by the α-amino alkoxide because of the increased acidity of the C5-proton due to the oxygen heteroatom. With 3-furaldehyde (55) lithiation occurred at the C2-position with high regioselectivity, also regardless of the α-amino alkoxide group utilised (Schemes 1.31 and 1.32).



(54)

Reagents : (i) LNMP; (ii) 1.2 ^{n}BuLi; (iii) CH_3I, H_2O

SCHEME 1.31



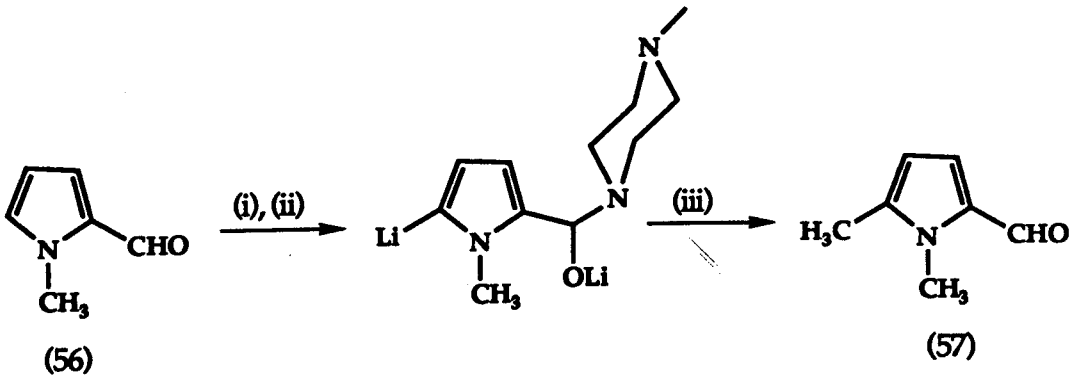
(55)

Reagents : (i) LTMDA; (ii) 2 ^{n}BuLi; (iii) CH_3I, H_2O

SCHEME 1.32

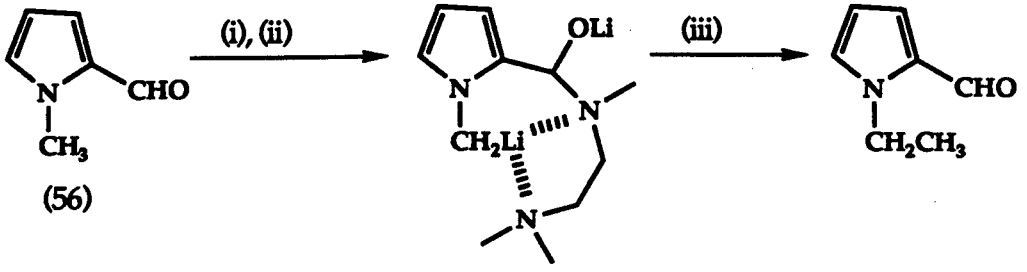
Using this methodology, 1-methyl-2-pyrrolecarboxaldehyde (56) underwent α-lithiation regiospecifically at the C5-position. Methylation and work-up gave 1,5-dimethyl-2-pyrrolecarboxaldehyde (57) as the sole product in 88% yield (Scheme 1.33).

Attempts to achieve ortho-lithiation using LTMDA as the amine component and excess ^{n}BuLi as lithiating base failed, but surprisingly, lithiation occurred exclusively on the N-methyl group. Addition of MeI and aqueous work-up gave N-ethyl-2-pyrrolecarboxaldehyde in 74% yield (Scheme 1.34). Since the acidity



Reagents : (i) LNMP; (ii) 3 ^{n}BuLi, TMEDA; (iii) CH_3I, H_2O

SCHEME 1.33



Reagents : (i) LTMDA; (ii) 3 ^{n}BuLi; (iii) CH_3I, H_2O

SCHEME 1.34

of a pyrrole N-methyl group appears to be relatively low, the authors suggest the reason for this N-methyl lithiation is because of a highly favourable transition state approaching kinetic deprotonation due to an intramolecular TMEDA-like effect (Figure 1.5). This is the first reported example of a directed-lithiation on the N-methyl group of an N-methyl pyrrole.

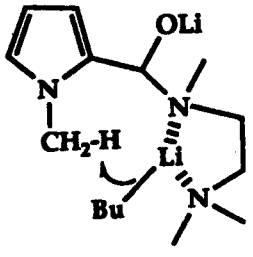
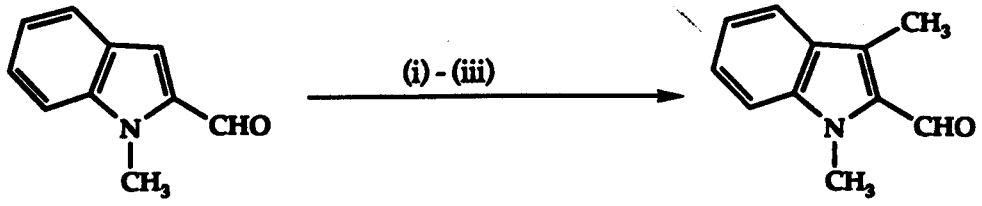


FIGURE 1.5

1-Methylindole-2-carboxaldehyde (58) was regiospecifically lithiated-methylated at the C3-position, using LNMP to form the α-amino alkoxide in 72% yield giving product (59) (Scheme 1.35)

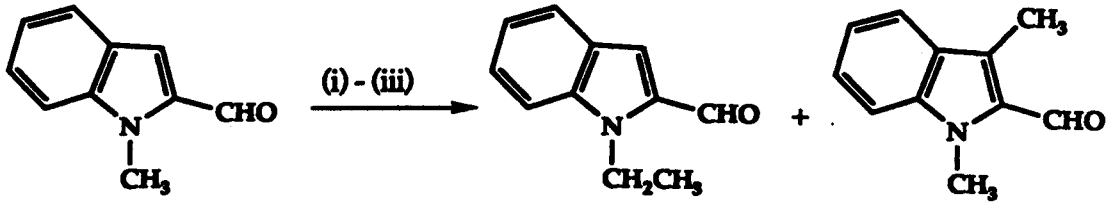


(58) (59)

Reagents : (i) LNMP; (ii) 3 ^{n}BuLi; (iii) CH_3I, H_2O

SCHEME 1.35

However, using LTMDA a mixture of 1-ethyl- (60) and 1,3-dimethylindole-2-carboxaldehydes (59) in a ratio of 42:58 were isolated. The authors claimed this to be the first example of a directed N-methyl lithiation of a 1-methylindole derivative (Scheme 1.36).

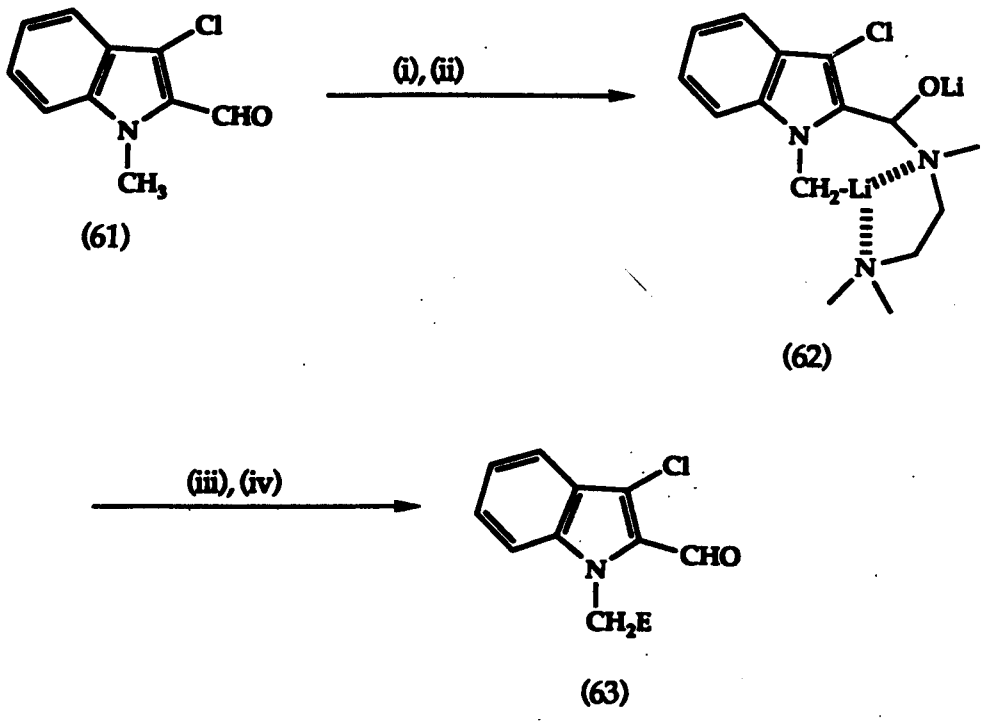


(58) (60) (59)

Reagents : (i) LTMDA; (ii) 2 ^{n}BuLi; (iii) CH_3I, H_2O

SCHEME 1.36

Recently, Comins has achieved the exclusive lithiation-methylation of the N-methyl substitutent of N-methylindole-2-carboxaldehyde by employing a removable blocking group at the C3-position.[60] *In situ* α-amino alkoxide formation and lithiation with ^{n}BuLi gives dianion (62), which on reaction with elec-



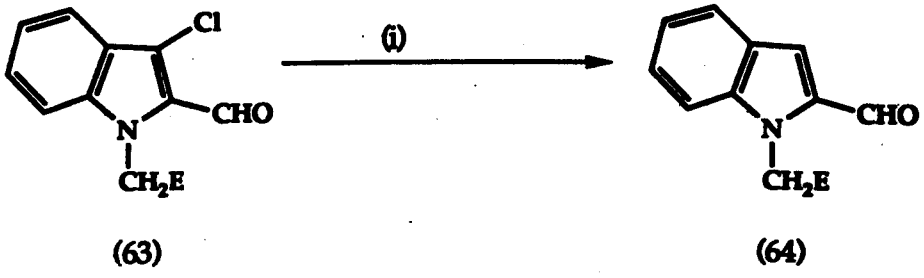
Reagents : (i) LTMDA; (ii) 3 ^{n}BuLi, thf, -40°C, 3h;

(iii) E^{+}; (iv) H_2O

SCHEME 1.37

trophiles and aqueous work-up provides a range of N-methyl substituted indoles in high yields (Scheme 1.37).

The Cl protecting group could then be removed to give an 81% yield of product (64) (Scheme 1.38).

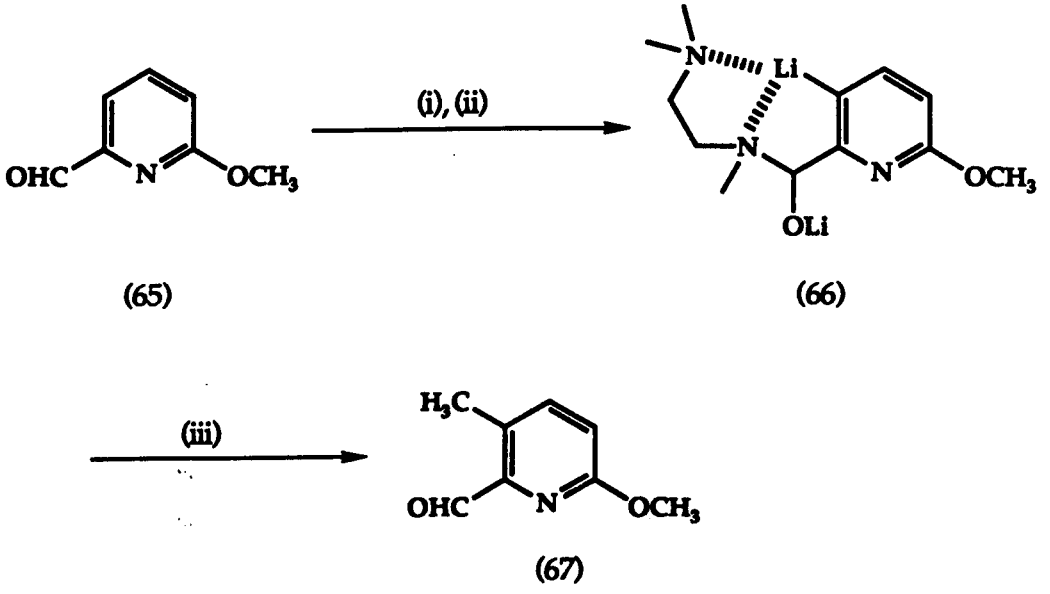


Reagents : (i) 10% Pd/C, EtOH, Et_3N, HCO_2H, reflux, 7h

SCHEME 1.38

Regioselective substitution at C3- or C5- of 6-methoxy-2-pyridinecarboxaldehyde (65) using this directed metallation

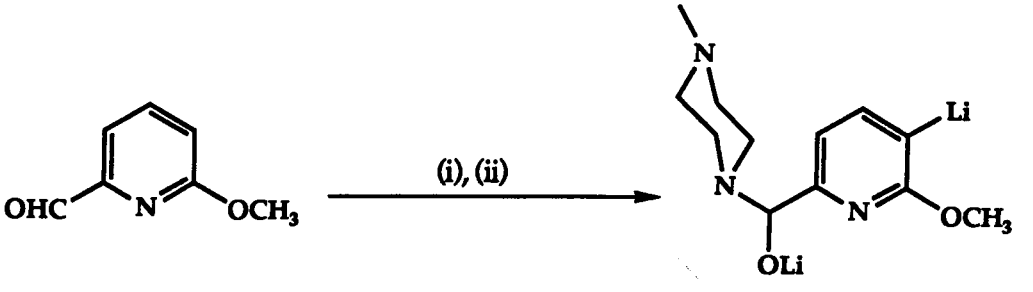
methodology has recently been established.[61] On treatment with LTMDA, pyridinecarboxaldehyde (**65**) is converted into an α-amino alkoxide *in situ*. Lithiation occurs *ortho* to the strongly directing α-amino alkoxide *via* the coordination mechanism, to give dianion (**66**) which on methylation and aqueous work-up provides the trisubstituted pyridine (**67**) in good yield and with high regioselectivity (> 95%) (Scheme 1.39).



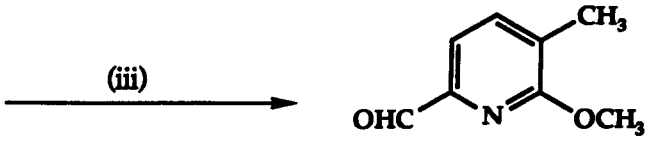
Reagents : (i) LTMDA; (ii) ^{n}BuLi; (iii) MeI, H_2O

SCHEME 1.39

When LNMP is used as the amine component, to give the weaker directing α-amino alkoxide, and ^{t}BuLi is the lithiating agent, lithiation occurs regioselectively at the C5-position *via* the "acid-base" mechanism, to give dianion (**68**). Methylation and aqueous work-up provides the trisubstituted pyridine (**69**) (Scheme 1.40). This "one-pot" lithiation-methylation on various isomeric methoxypyridinecarboxaldehydes was examined, and the regioselectivity of lithiation was found to be dependent on the



(65) (68)



(69)

Reagents : (i) LNMP; (ii) ^{t}BuLi; (iii) CH_3I, H_2O

SCHEME 1.40

aldehyde, the amine component of the α-amino alkoxide, and the metallation conditions. When LTMDA was used as the amine component of the α-amino alkoxide, methylation occurred ortho- to the aldehyde function. The analogous reaction using LNMP as the amine component gave substitution next to the methoxy group.

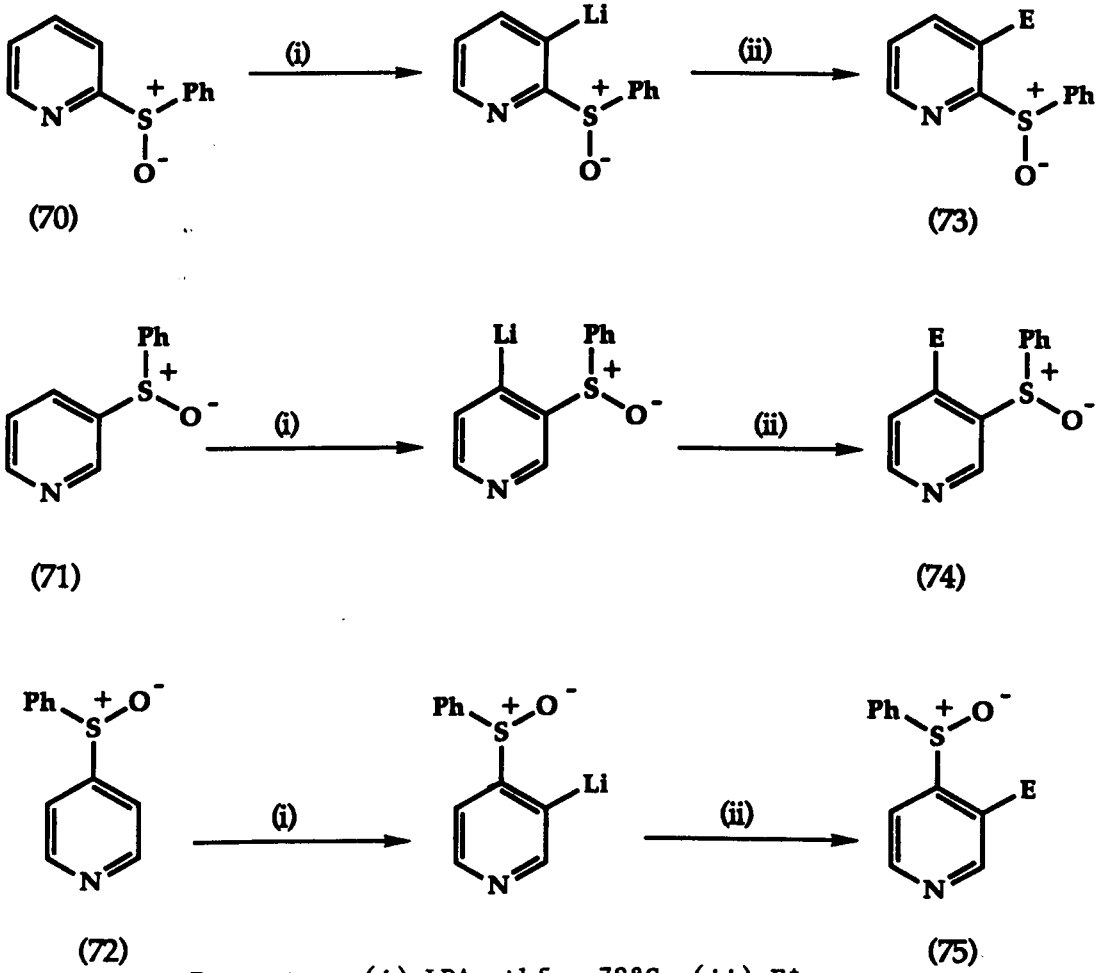
All of these examples demonstrate the synthetic utility of this "one-pot" protection-lithiation-deprotection methodology as a means of introducing substituents into aromatic aldehyde derivatives. This methodology will doubtless find further application in organic synthesis.

1.1.7.3 NEW ADVANCES IN DIRECTED LITHIATION OF PYRIDINE, PYRAZINE, PYRIMIDINES AND PYRIDAZINES

Directed lithiation is not usually a practical method of regioselectively introducing substituents into pyridines and

other six-membered nitrogen heterocycles. This is because of the susceptibility of these compounds to nucleophilic attack by the organolithium reagent. However, recent advances in lithiation methodology overcoming this problem, demonstrates that directed lithiation is becoming a synthetically useful means of introducing substituents into these heterocycles. Some examples are shown below.

Furukawa has recently shown that 2-, 3- and 4-pyridyl phenyl sulphoxides (70) (71) and (72) undergo exclusive ortho-lithiation with LDA and subsequent treatment of the lithio-intermediate with electrophiles gives the corresponding sulphoxides (73), (74) and (75) (Scheme 1.41).[62]

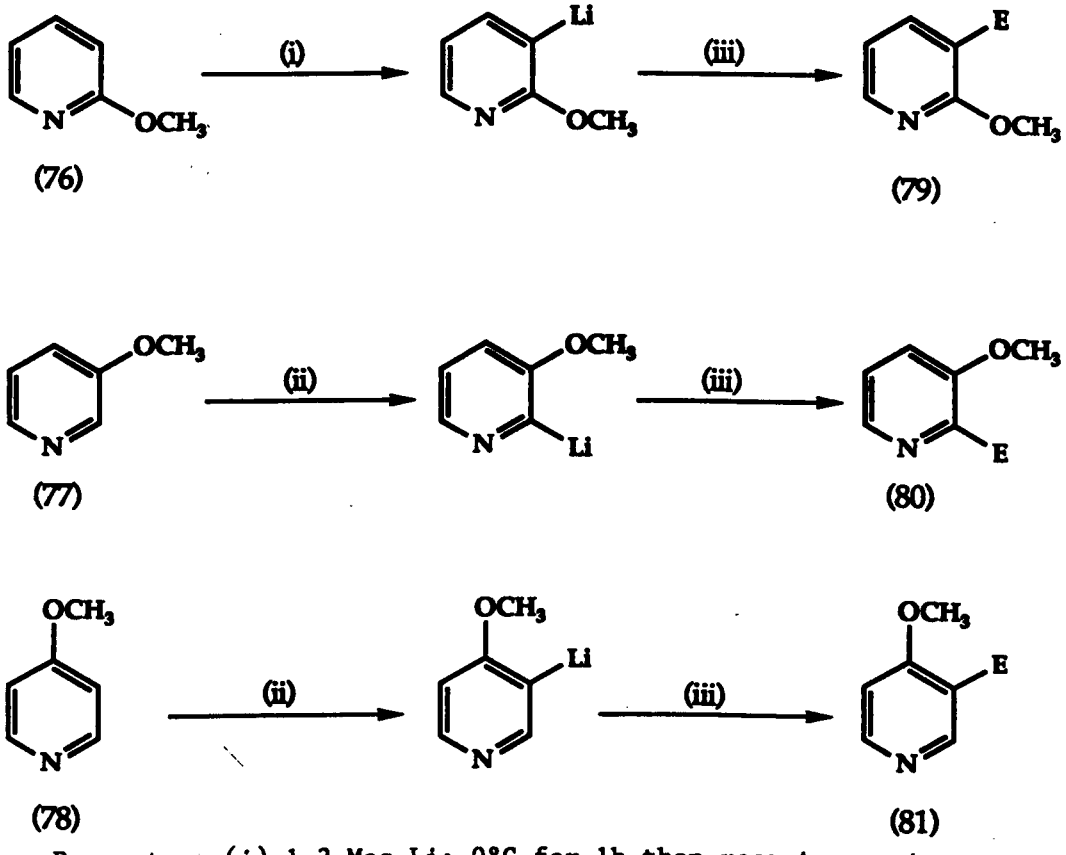


Reagents : (i) LDA, thf, -78°C; (ii) E^+

SCHEME 1.41

The protons ortho to the sulphoxide functionality are presumably the most acidic on the ring and so lithiation occurs by an "acid-base" mechanism. These authors do not suggest any reasoning why lithiation of sulphoxide occurs at the C4-position in preference to the C2-position.

Comins has reported the successful ortho-lithiation of 2-, 3- and 4-methoxypyridines (76), (77) and (78) respectively, using mesityllithium as the lithiating agent.[63] Mesityllithium was found to be the base of choice for it effectively lithiated the methoxypyridine ring without undergoing nucleophilic addition to the pyridine nucleus. Treatment of the lithio-intermediates with a range of electrophiles provides the 2,3- and 3,4-substituted methoxypyridines (79), (80) and (81) respectively, in good yields (Scheme 1.42).



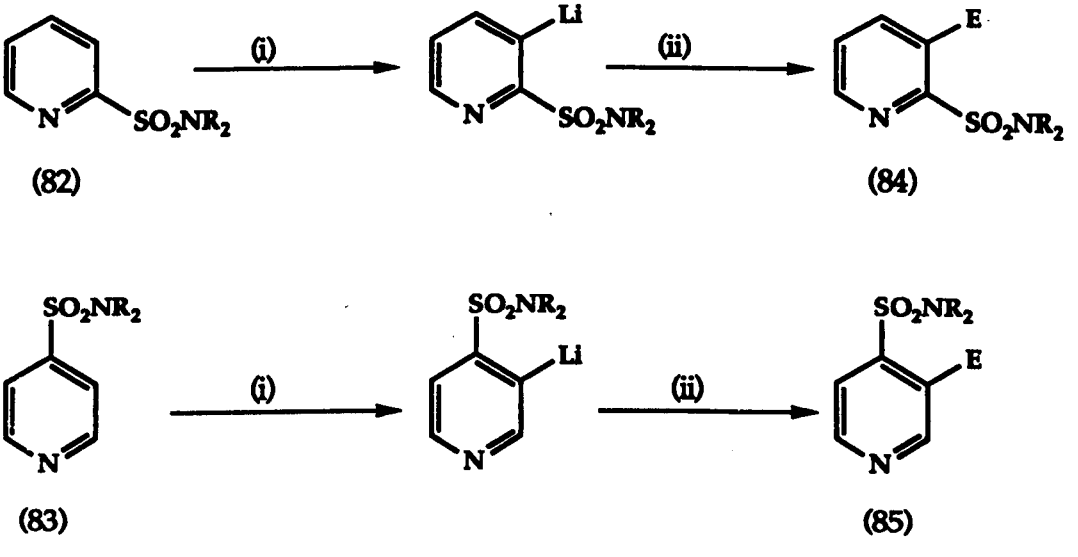
Reagents : (i) 1.3 Mes-Li; 0°C for 1h then room temperature for 1h; (ii) 1.3 Mes-Li, -23°C, 3h; (iii) E^+

SCHEME 1.42

These lithiation reactions also proceed by the "acid-base" mechanism, and it is interesting to observe that lithiation of methoxypyridine (77) occurs exclusively at the C2-position in contrast to the pyridylsulphoxide (71) which lithiates exclusively at the C4-position.

Quéguiner has also demonstrated the successful ortho-lithiation of 2-methoxypyridine by using methyllithium catalysed by a small amount of diisopropylamine.[64] This metallation methodology, called "catalysed metallation" gives good results, allowing the convenient synthesis of various 3-substituted methoxypyridines.

Tertiary 2- and 4-pyridinesulphonamides (82) and (83) have been regioselectively ortho-lithiated at the C3-position using excess LDA, and treated subsequently with various electrophiles to give the corresponding ortho-disubstituted pyridines (84) and (85) respectively (Scheme 1.43).[65] These lithiation reactions

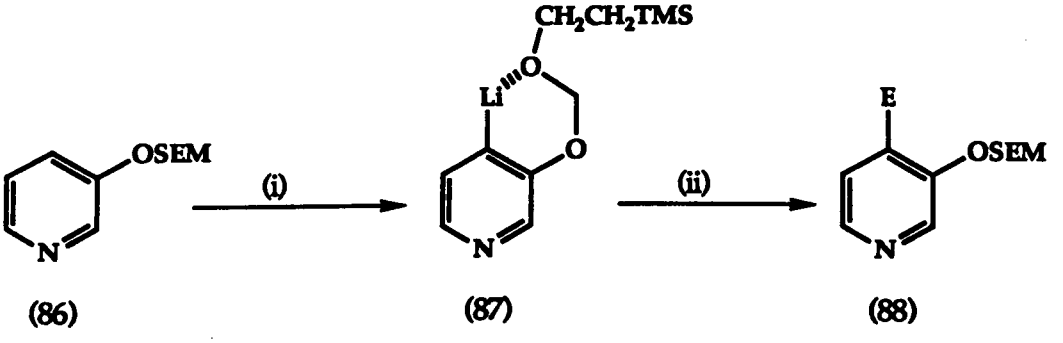


Reagents : (i) 2.0 LDA, Et_2O, -70°C; (ii) E^+

SCHEME 1.43

occur via the "acid base" mechanism, although there might be some "coordination" of the lithiating agent with the sulphonamide functionality.

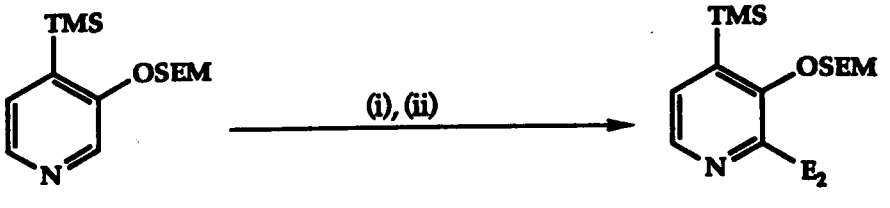
The 2-(trimethylsilyl)ethoxymethoxy (OSEM) functionality has been shown to be a powerful directing group for pyridyl systems.[66] The 3-pyridyl derivative (**86**) was treated with ^{t}BuLi (to avoid competitive nucleophilic attack on the pyridine ring) to give the corresponding ortho-lithiated intermediate (**87**) which reacts with various electrophiles in high yields (Scheme 1.44).



Reagents : (i) ^{t}BuLi, Et_2O, -78°C; (ii) E^+

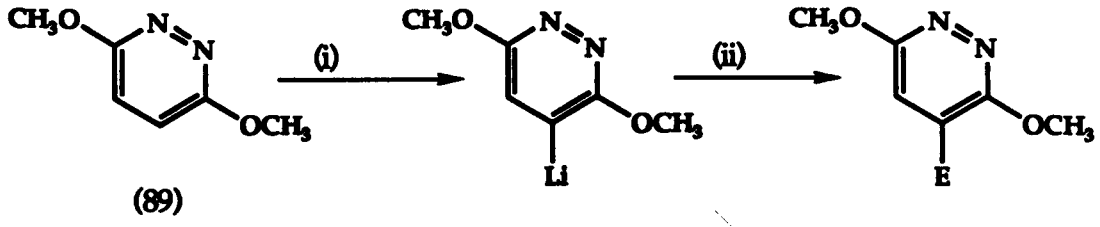
SCHEME 1.44

It is interesting to note that no C2-lithiation is observed. However, if E is a TMS-group it is significant that the pyridyl derivative (**88**) can undergo further lithiation at the C2-position under the same conditions, which upon work-up with electrophiles gives useful 2,3,4-trisubstituted pyridines (Scheme 1.45).

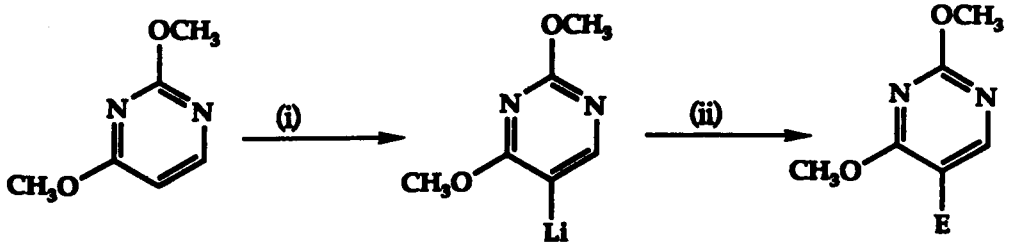


Reagents : (i) ^{t}BuLi, Et_2O, -78°C; (ii) E_2^+

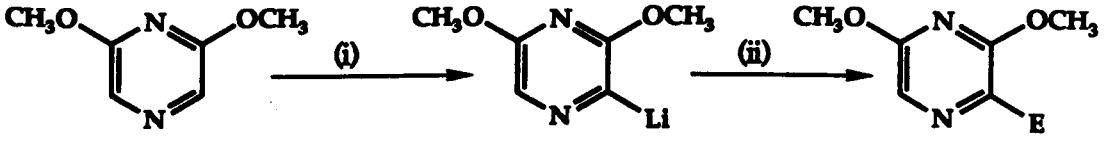
SCHEME 1.45



(89)



(90)



(91)

Reagents : (i) LTMP, thf, -78°C, 0.25h; (ii) E^+

SCHEME 1.46

Regioselective lithiation of the C3- and C5-positions of 6-methoxy-2-pyridinecarboxaldehydes has recently been established by Comins (see Section 1.1.7.2).[61]

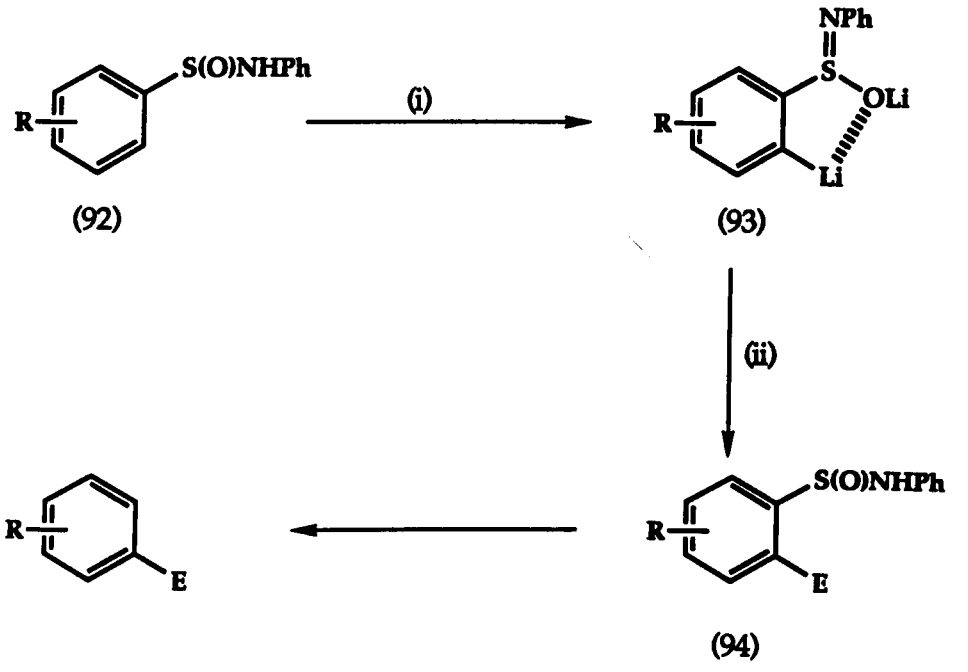
Directed ortho-lithiation of various methoxy pyridazines (89), pyrimidines (90) and pyrazines (91) has recently been investigated by Mattson.[67] These methoxy heterocycles cleanly ortho-lithiate using LTMP, a sterically hindering organolithium reagent. No nucleophilic attack on the heterocycle is observed. Subsequent treatment of the lithio-intermediates with electrophiles occurs in high yield (Scheme 1.46).

These examples demonstrate the synthetic utility of lithiation as a means of introducing substituents into these six-membered heterocyclic systems. The success of these reactions depends on the use of bulky lithiating agents to avoid competing nucleophilic addition reactions.

1.1.7.4 NEW DIRECTING GROUPS FOR ortho-LITHIATION IN AROMATIC CHEMISTRY

The horizons of directed ortho-lithiation continue to broaden owing to the development of new directed metallation groups and the increasing need to construct polysubstituted aromatics devoid of regioisomeric complications. The ideal ortho directing groups are those that direct lithiation regioselectively, and then can be transformed into other functionality or totally removed from the aromatic ring. Some recent examples of new directing groups and their versatility are demonstrated in this Section.

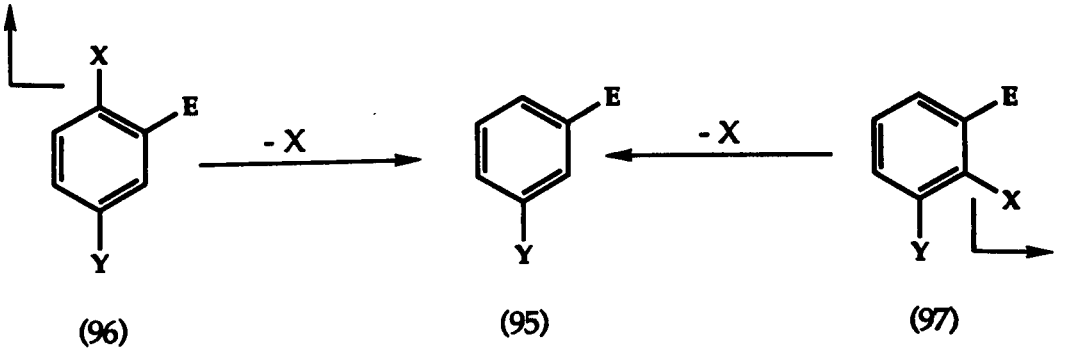
Katritzky has recently reported that the sulphinamide functionality, which is readily removed under mild conditions, acts as a useful directing group in ortho-lithiation.[68] Dilithiation of N-phenylbenzenesulphinamide (92) was readily accomplished using ^{n}BuLi in thf at low temperatures. Addition of appropriate electrophiles to the dilithiated species (93) provided a range of derivatives (94) ortho-substituted to the sulphinamide group in moderate to good yields (Scheme 1.47). Desulphination was readily accomplished by hydrolysis followed by mercuridesulphination. This methodology was fcund to be synthetically useful in the regiospecific construction of diversely functionalised meta-substituted aromatics from precursors consisting of aromatics



Reagents : (i) 2.1 ^{n}BuLi, thf; (ii) E^{+}

SCHEME 1.47

substituted in the ortho or para-position with the sulphinamide directing group. This concept is illustrated in Scheme 1.48 where (95) is obtained either from an aromatic (96), initially substituted in its para-position with the directing group, or from an aromatic (97) initially substituted in its ortho-position.

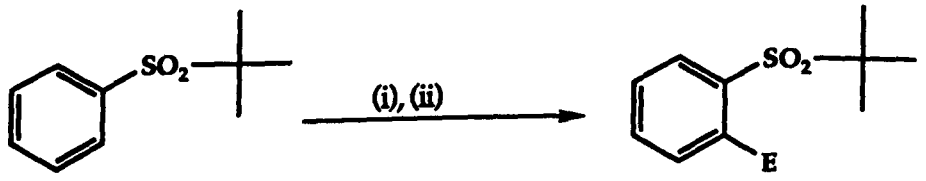


E = New Substituent Introduced

X = Directing Group

SCHEME 1.48

Snieckus and Iwao have recently investigated the ortho directed lithiation capability and synthetic versatility of aryl ^{t}butylsulphones (98).[69] These workers reported that the ^{t}butylsulphone group (a) is an excellent directed ortho-metallation group using the established conditions (Scheme 1.49); (b) is of



(98) (99)

Reagents : (i) ^{n}BuLi, thf, -78°C, 0.5h; (ii) E^{+}

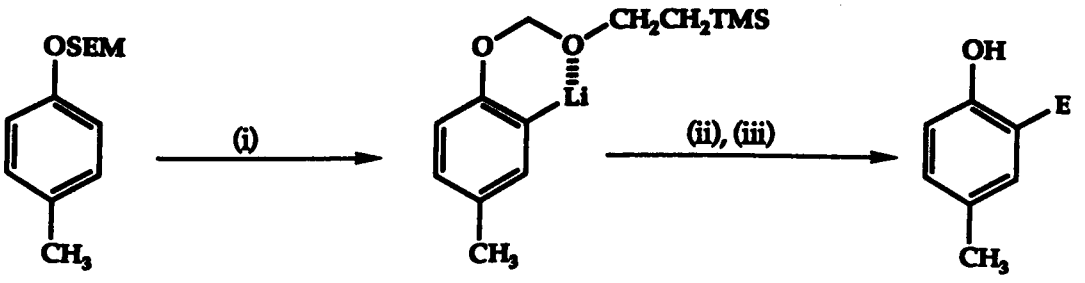
SCHEME 1.49

general utility for the synthesis of a variety of ortho carbon- and heteroatom-substituted arylsulphones (99) that are inaccessible by conventional means; (c) may serve as a latent directed ortho-lithiation group for the synthesis of meta-substituted aromatics and (d) tolerates transition metal catalysed cross-coupling conditions leading to biaryl ^{t}butyl sulphones. Removal of the ^{t}butyl sulphone group is achieved by hydrogenolysis (Raney Ni/EtOH/reflux/15h). These results indicate that the ^{t}butyl sulphone deserves to occupy a prominent position in the repertoire of directed ortho-metallation strategies.

Directed lithiation is used increasingly in the regioselective construction of highly substituted phenolic compounds. Phenol only undergoes ortho-lithiation using harsh conditions due to the OLi group being a poor director of lithiation.[70] Usually phenols are masked and activated as THP, MOM and $OCONEt_2$ groups, which undergo ortho-lithiation more readily. However, deprotec-

tion of all these systems to phenols normally requires moderately strong acidic or basic conditions.

Snieckus has recently reported the value of the 2-(trimethylsilyl)ethoxymethoxy (OSEM) functionality as an efficient directing group for ortho-lithiation of phenols.[71] Lithiation was achieved using ^{n}BuLi in Et_2O to give the lithio-intermediate (**100**) which reacted with a range of electrophiles. Deprotection of the group was readily achieved under virtually neutral conditions (fluoride ion) to give the substituted products (**101**) in good yields (Scheme 1.50).

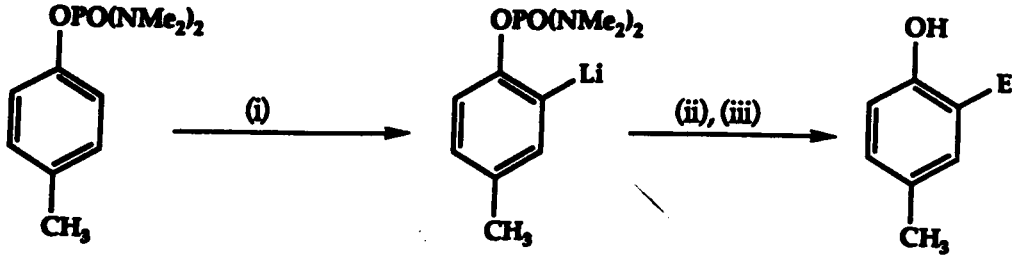


(100) (101)

Reagents : (i) ^{n}BuLi, Et_2O, room temperature; (ii) E^{+};
(iii) TBAF, thf, HMPA, 40°C, 2h

SCHEME 1.50

Watanabe has reported the bis(dimethylamino)phosphoryl group as a new and powerful ortho-directing group for phenols.[72] Treatment of phenyl tetramethylphosphorodiamidate (**102**) with ^{s}BuLi gave the lithio-intermediate (**103**) which was quenched with electrophiles at -105°C (to prevent aryl O → C 1,3-bis(dimethylamino)phosphoryl group migration to the lithiated species), followed by deprotection of the bis(dimethylamino)phosphoryl group under mildly acidic conditions, afforded a range of ortho-substituted phenols (**104**) (Scheme 1.51).



(102) (103) (104)

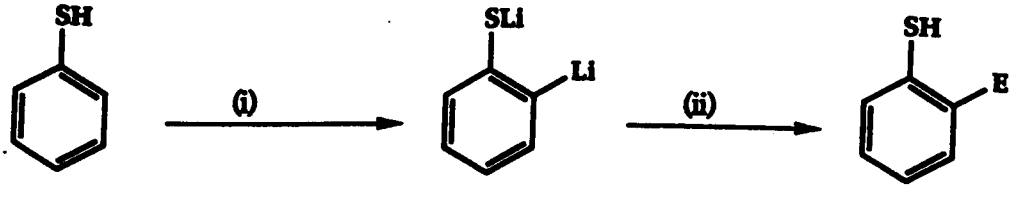
Reagents : (i) ^{s}BuLi, thf, -105°C; (ii) E^{+}, -105°C;

(iii) HCO_2H reflux

SCHEME 1.51

Several research groups have demonstrated that directed ortho-lithiation of arenethiols is a convenient approach to desirable ortho-substituted arenethiol derivatives. Previous attempts at the lithiation of thiophenol gave very low yields of lithiation.[73]

Martin et al., reported that the directed ortho-lithiation of thiophenol (105) using ^{n}BuLi/TMEDA in cyclohexane at room temperature gives an almost quantitative conversion to lithium 2-lithiobenzenethiolate (106). Electrophile quench provides the arenethiol derivatives in moderate to good yields (107) (Scheme 1.52).



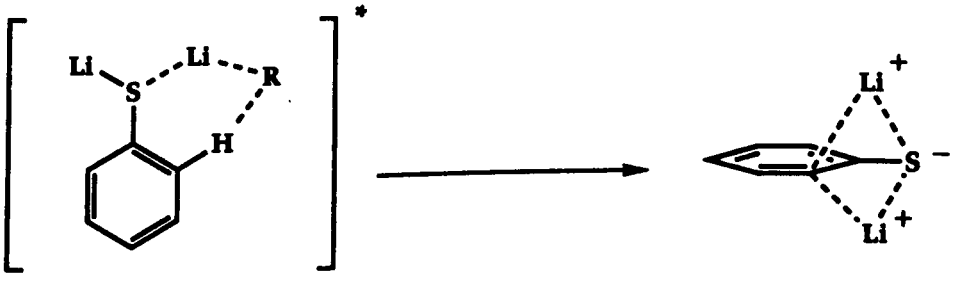
(105) (106) (107)

Reagents : (i) 2.0 ^{n}BuLi, 2.0 TMEDA, cyclohexane,

room temperature; (ii) E^{+}

SCHEME 1.52

The authors suggest that the success of direct ortho-lithiation of lithium benzenethiolate is partly attributable to the choice of cyclohexane as solvent. The non-polar, unreactive cyclohexane solvent may favour coordination of the lithium cations, already coordinated to TMEDA, to the benzenethiolate anionic sulphur. The dilithiated species (**109**) could be formed via a transition state similar to (**108**). The Coulomb inter-

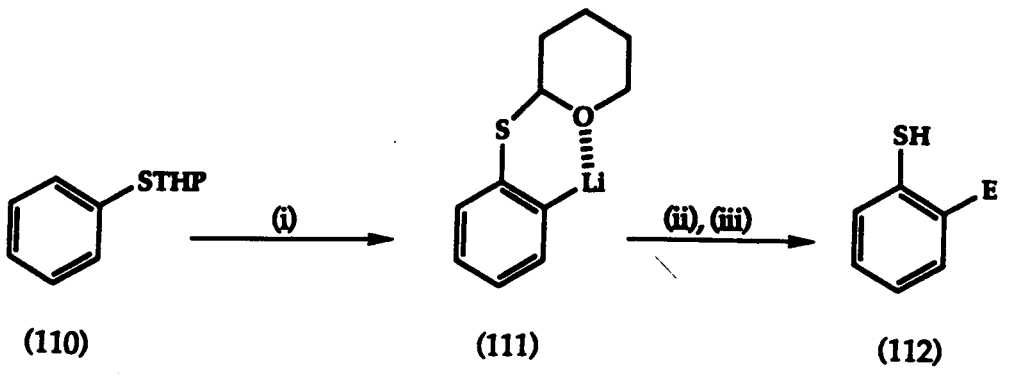


(**108**) (**109**)

actions of two cations and a dicarbanion are favourable in such a geometry. (The lithium cations are also coordinated to the bidentate TMEDA ligands.)

The weak C-S bond of (**109**) provides an antibonding σ^* orbital low enough in energy to provide a stabilising interaction with the adjacent carbanion lone pair of electrons in the plane of the benzene ring. This may significantly contribute to the efficiency of this reaction.

Smith also reported the ortho-lithiation of arenethiols using similar conditions.[75] Block also established similar results too,[76] as well as determining that 2-(phenylthio)tetrahydropyran (**110**) (a protected thiophenol) undergoes ortho-lithiation using ^{t}BuLi in thf/HMPA to yield lithio-intermediate (**111**), which was readily quenched with electrophiles (Scheme 1.53). The



(110) (111) (112)

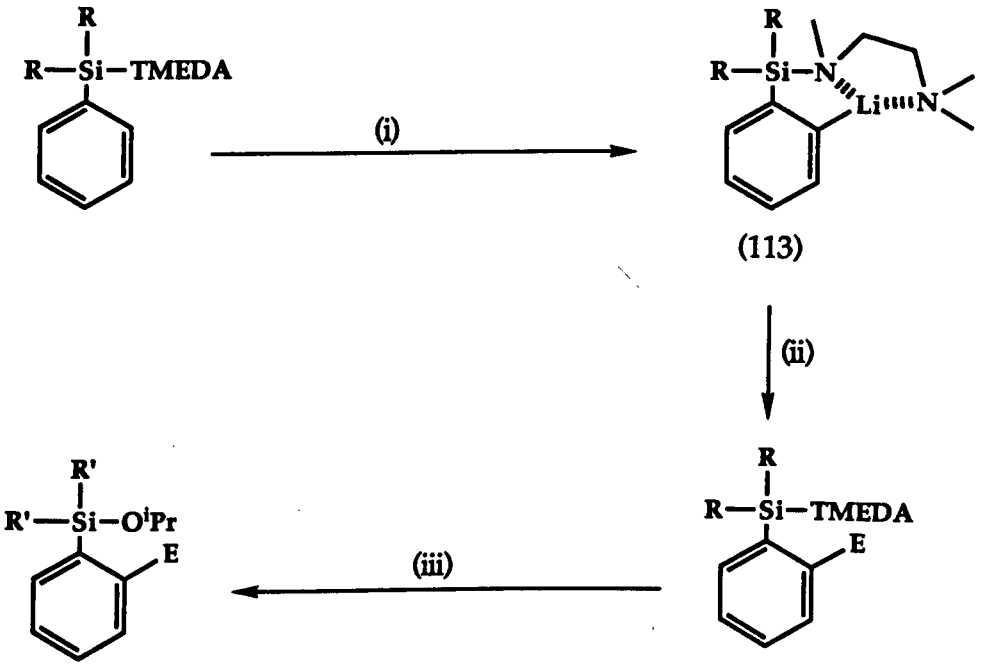
Reagents : (i) ^{t}BuLi, thf/HMPA, -90°C;

(ii) E^{+}; (iii) $HgCl_2$, H_2S

SCHEME 1.53

THP group is readily removed with mercuric chloride followed by hydrogen sulfide to yield the ortho-substituted arenethiol derivative (112).

Ito and Tamao have reported the first ortho-lithiation by amino groups on silicon in phenylsilane derivatives.[77] It was shown that the N,N,N'-trimethylethylene diamino group (TMEDA-) on silicon exhibits a strong directing effect for specific ortho-lithiation (Scheme 1.54) to give the chelated lithio-intermediate (113) which undergoes reaction with electrophiles followed by treatment with ^{i}PrOH/HCl (to convert the amino group into more stable, isolable isopropxysilane derivatives) to yield some hitherto hardy accessible ortho-substituted arylsilanes (114). Deprotection of the silane functionality can be achieved with hydrogen peroxide and TBAF to give some ortho-substituted phenol derivatives.



when R = Ph, R' = Ph

when R = TMEDA, R' = O^{i}Pr

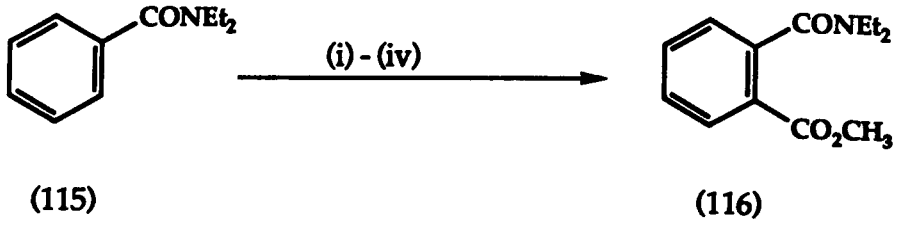
Reagents : (i) 2.8 ^{t}BuLi, pentane, 0°C → room temperature, 2h; (ii) E$^+$, 50°C; (iii) ^{i}PrOH/HCl

SCHEME 1.54

1.1.4.7 DIRECTED ortho MAGNESIATION

Eaton has recently introduced a novel and synthetically valuable strategy of directed ortho-magnesiation in aromatic chemistry, and highlighted some of the advantages of this methodology over ortho-lithiation.[78]

These workers demonstrated this ortho-magnesiation, by reacting N,N-diethylbenzamide (115) at room temperature for several hours in thf with an excess of bis(2,2,6,6-tetramethylpiperidino)magnesium, $(TMP)_2Mg$, or bis(diisopropylamido)magnesium, $(DA)_2Mg$, followed by quenching with carbon dioxide and diazomethane esterification, which gave o-carbomethoxy-N-N-diethylbenzamide (116) in 90% yield (Scheme 1.55).

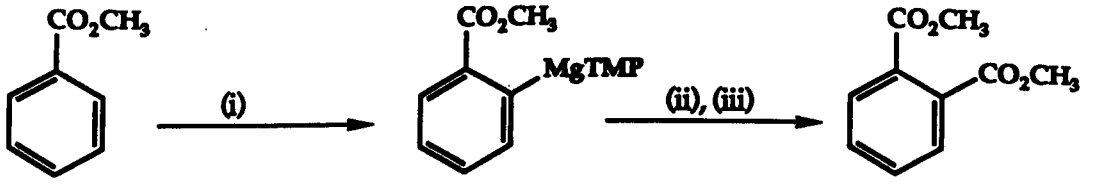


(115) (116)

Reagents : (i) $(TMP)_2Mg$, thf, room temperature; (ii) CO_2; (iii) H_3O^+; (iv) CH_2N_2

SCHEME 1.55

In classic ortho - lithiation reactions, esters are not usually suitable substrates due to their susceptibility to nucleophilic attack. However, methyl and ethyl esters are found to be quite appropriate substrates in ortho-magnesiation using $(TMP)_2Mg$. Treatment of methyl benzoate (117) with excess $(TMP)_2Mg$ in thf at room temperature followed by quenching with carbon dioxide, acidification and esterification gave dimethyl o-phthalate (118) in 81% yield (Scheme 1.56). Apparently, the



(117) (118)

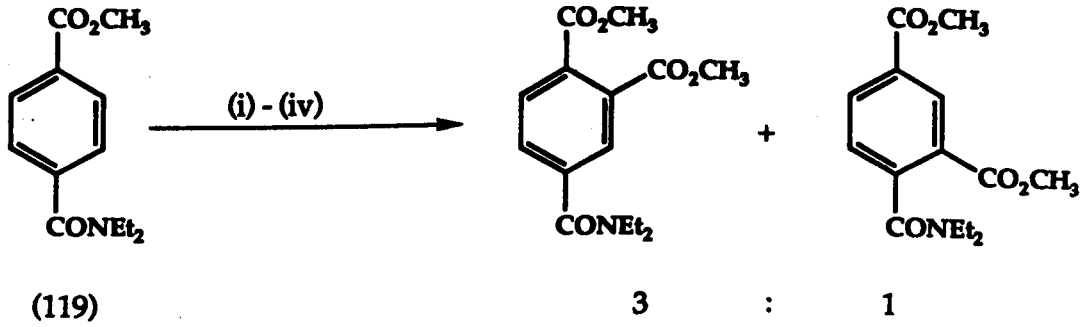
Reagents : (i) $(TMP)_2Mg$, thf, room temperature; (ii) CO_2; (iii) CH_2N_2

SCHEME 1.56

intermediate organometallic, formulated (without regard to aggregation or complexation) as R^1MgTMP is not very reactive; an ester group can coexist with it for some time. The authors refer to such R^1MgNR_2 species as "amido-Grignards". The amine substituent moderates the Grignard reactivity of such compounds by

decreasing nucleophilicity and/or lessening ability to complex with substrate. Electronic and/or steric reasons could also be involved.

Ester activation was found to be superior to amide activation. Reaction of p-carbomethoxy-N,N-diethylbenzamide (**119**) with $(TMP)_2Mg$ followed by carboxylation and esterification gave primarily a 3:1 reaction ortho to the carbomethoxy group (Scheme 1.57). The use of esters rather than amides as activating



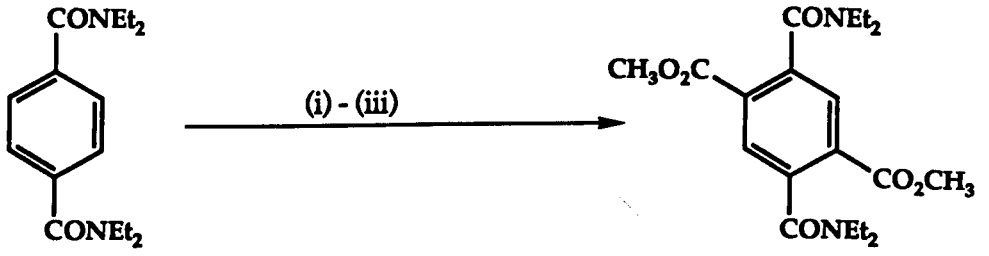
(**119**) 3 : 1

Reagents : (i) $(TMP)_2Mg$; (ii) CO_2; (iii) H_3O^+; (iv) CH_2N_2

SCHEME 1.57

groups in ortho-metallation eases the frustrating problem of how to convert an amide, subsequent to its use as an activator, to a group more amenable to transformation.

ortho-Lithiation twice over on a doubly activated aromatic ring is usually very difficult, presumably due to the change of one C-H bond to a very polar C-Li bond, deactivating the remaining C-H bonds towards lithiation. Carbon-magnesium bonds are not as polarised. Reaction of N,N-diethylterephthalamide (**120**) with excess $(TMP)_2Mg$ in refluxing thf for two hours resulted in double substitution and, after carboxylation and esterification, the pyromellitic acid derivative (**121**) in 87% yield (Scheme 1.58).



(120) (121)

Reagents : (i) $(TMP)_2Mg$; (ii) CO_2; (iii) CH_2N_2

SCHEME 1.58

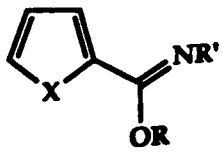
ortho-Magnesiation has the potential to, and undoubtedly will, develop into a synthetically useful technique for the introduction of substituents into aromatic and non-aromatic substrates which possess functionality, susceptible to reaction with lithiating agents.

CHAPTER 2

2.0 INVESTIGATIONS INTO THE DIRECTED LITHIATION OF HETEROAROMATIC IMIDATES

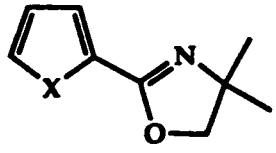
2.1 INTRODUCTION

In continuance of the search for functional groups capable of directing lithiation into the C3-position of thiophenes, furans and pyrroles, the imidate functionality (Figure 2.1) has been thoroughly investigated. In previous work the oxazolinyl functionality (a cyclic imidate) (Figure 2.2) has been shown to



X = O, S

FIGURE 2.1



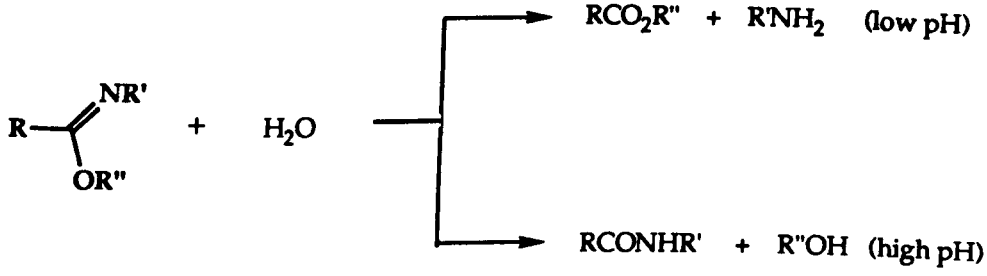
X = O, S, NMe

FIGURE 2.2

successfully direct ortho-lithiation in these five-membered heteroaromatic systems.[19,79-80] The imidate functionality theoretically possesses two important properties which make it a potential ortho-director of lithiation. These are a ligating (Lewis basic) centre, and an ability to interact electronically to reduce the electron density of an attached, heteroaromatic ring.

Some functional groups which have been found to be excellent in directing ortho-lithiation, for example, the secondary amido function, are to some extent vitiated by transformation difficulties.[81] Hydrolysis of secondary amides by aqueous base is exceedingly slow and removal under acidic conditions requires extended heating under reflux. Such vigorous conditions are incompatible with certain functional groups and, in general, with

the furan and pyrrole ring systems. The imidate functionality has the potential to be readily transformed to an ester group under mildly acidic conditions and subsequently hydrolysed to the carboxylic acid. Hydrolysis under basic conditions gives the secondary amide derivative (Scheme 2.1).[82-89] Imidates also



SCHEME 2.1

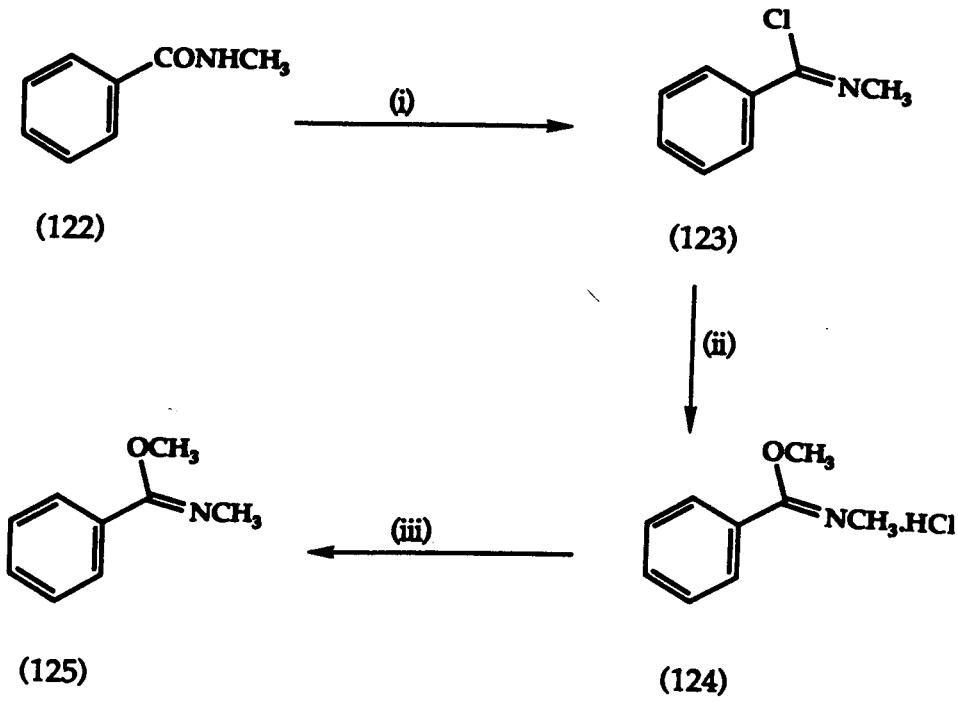
have the potential to undergo catalysed rearrangement reactions to yield tertiary amides.[90-93]

2.2 LITHIATION OF METHYL N-METHYLTHIOPHENE-2-CARBOXIMIDATE

Challis and Frenkel have prepared methyl N-methylbenzimidate (125) in three steps from N-methylbenzamide (122) in good yield (Scheme 2.2).[94]

Treatment of the secondary amide (122) with thionyl chloride under reflux gave the imidoyl chloride (123) which on treatment with anhydrous methanol yielded the hydrochloride salt (124). Treatment of a dilute solution of the hydrochloride salt in an equimolar amount of triethylamine yielded the corresponding imidate (125).

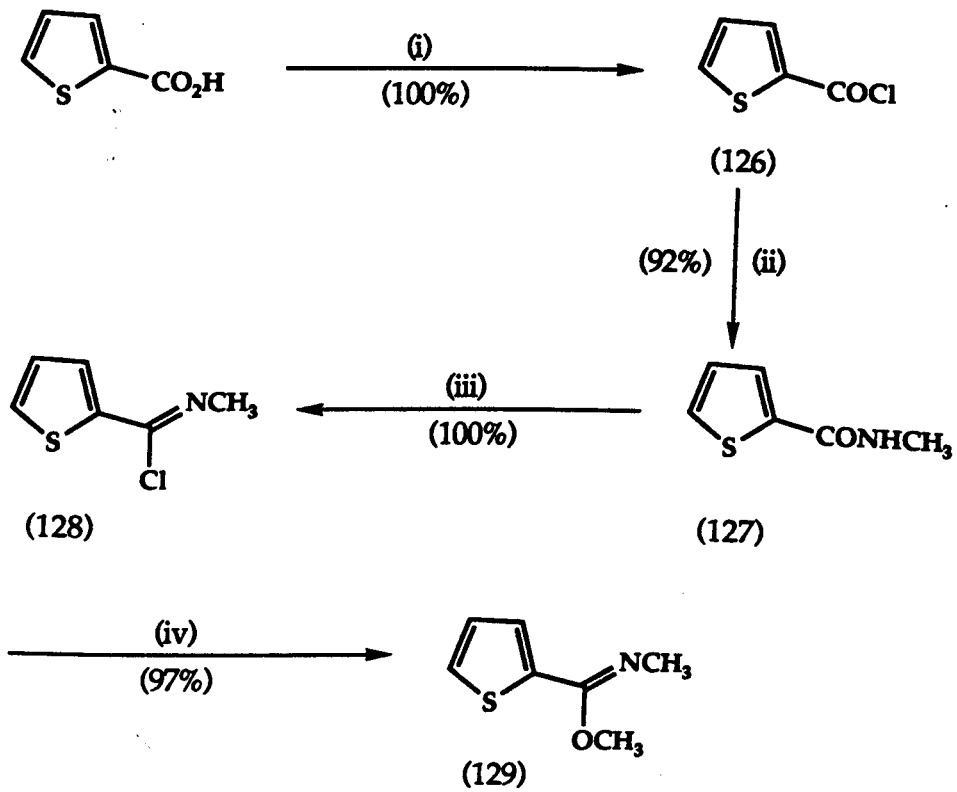
Application of this methodology to the thiophene case allows a convenient approach to the hitherto unknown imidate (129) (Scheme 2.3). Treatment of thiophene-2-carboxylic acid with thionyl chloride under reflux yielded the carbonyl chloride (126)



Reagents : (i) $SOCl_2$, reflux; (ii) MeOH, Et_2O, 0°C;

(iii) Et_3N, Et_2O, 0°C

SCHEME 2.2



Reagents : (i) $SOCl_2$, reflux, 3h; (ii) $MeNH_2$, NaOH (10%),

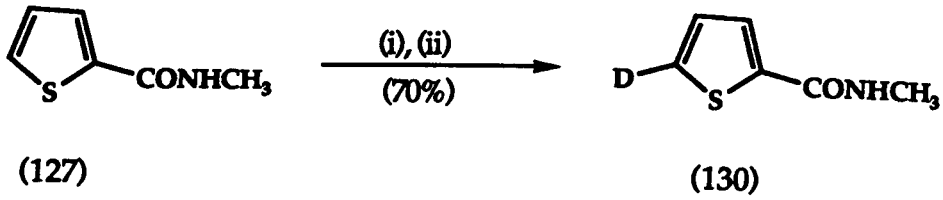
25°C, 12h; (iii) $SOCl_2$, reflux, 18h;

(iv) NaOMe, MeOH, thf, 0°C, 1h

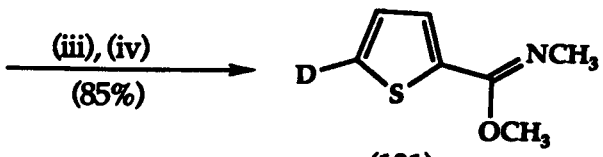
SCHEME 2.3

which was distilled and treated with an aqueous solution of methylamine to give a high yield (83%) of secondary amide (**127**) in this Schotten-Baumann type reaction. The amide (**127**) was converted quantitatively into imidoyl chloride (**128**) by refluxing in thionyl chloride. However, an extended reflux time (eighteen hours) was required for the reaction to go to completion. Addition of a catalytic amount of DMF (two drops) was found to increase the reaction rate. The imidoyl chloride is a moisture-sensitive compound (hydrolysed readily upon exposure to the atmosphere) and must be stored under an inert atmosphere and used quickly. Treatment of imidoyl chloride (**128**) with an excess of sodium methoxide in anhydrous methanol and thf at 0°C gave imidate (**129**) as a pale yellow oil. This is a high yielding (97%) and very clean reaction. Using sodium methoxide instead of methanol is advantageous in that the imidate is formed directly from the imidoyl chloride, rather than having to isolate the hydrochloride salt which is unstable, hygroscopic and generally difficult to handle. Despite the presence of an excess of sodium methoxide, no further nucleophilic attack on the imidate was observed under the conditions used. Imidate (**129**) is stable and easily handled at room temperature and is purified readily by distillation.

Before lithiation studies on imidate (**129**) were undertaken, an unambiguous assignment of the nmr shifts for the C3- and C5-protons of (**129**) was required. Synthesis of the 5-deuterio-isomer of (**129**) was therefore carried out (Scheme 2.4). C5-Lithiation of N-methylthiophene-2-carboxamide (**127**) using LDA in thf at -78°C followed by D_2O quench gave the 5-deuterio compound (**130**) in good yield.[11] Imidate formation as for (**129**) gave the 5-deuterio-imidate (**131**) in high overall yield (85%).



(127) (130)



(131)

Reagents : (i) 2.2 LDA, thf, -78°C, 0.5h; (ii) D_2O; (iii) $SOCl_2$, reflux, 18h; (iv) NaOMe, MeOH, thf, 0°C for 1h then room temperature

SCHEME 2.4

Disappearance of the proton resonance at δ 7.43 confirms that the nmr assignment of (**129**) is H-3 (δ 7.48), H-5 (δ 7.43) and H-4 (δ 7.09). During lithiation studies, the extent of anion formation was monitored by quenching the reaction mixture with either MeOD or D_2O and integration of the aromatic ring ^1H nmr signals, the decrease in the integral for H-3 or H-5 relative to the H-4 integral being proportional to the amount of anion formed. For example, if after addition of excess MeOD and work-up the integrals are:

H-4 = 100 mm

H-3 = 80 mm

H-5 = 30 mm

then the percentage formation of the 3-anion is (100 - 80/100 x 100) = 20%, likewise the percentage formation of the 5-anion is

(100 - 30/100 x 100) = 70%. Therefore, of the recovered material 20% is derived from the 3-lithiated species and 70% from the 5-lithiated species, the remainder being derived from unreacted starting material. Similar analyses have been used successfully in previous work.[11,19,95] Reactions with other electrophiles such as TMSCl and MeI were similarly analysed by nmr, ring proton integration giving very good agreement with glc analysis.

The results of a range of experiments designed to elucidate the factors affecting regioselectivity of lithiation, and to determine the compatibility of the imidate functionality to organolithium reagents, are given in Table 2.1.

It is evident from these results that exclusive, and virtually quantitative α-lithiation is observed with DME and thf as solvent, under the conditions stated (c.f. entries 2.1 - 2.9), presumably via an acid-base mechanism.[1] Even the use of an excess of lithiating agent gave no indication of any C3-lithiation (entry 2.4). One possible reason for this could be the greater solvation of the organolithium reagent by the solvent ligands than by the imidate functionality. This would effectively remove the only directing force that the imidate group exerts. In a non-polar solvent like hexane, where the imidate functionality could be expected to coordinate with the lithiating agent, giving a lower-order oligomer capable of initiating protophilic attack at the C3-position, negligible levels of C3-lithiation were observed. In diethyl ether there was only a limited amount of C5-lithiation. It was significant, and somewhat surprising, to observe the virtual absence of any β-lithiation. In contrast, the oxazoline functionality has been shown to be a

TABLE 2.1

Expt.	Solvent[a]	Temp. (°C)	RLi[b]	Time (h)	E^+	Product Comp. (%)[c] derived from 5-Lith	3-Lith	Total recovered yield (%)[d]
2.1	A	-78	X(1.1)	1	MeOD	100	0	97
2.2	A	-78	X(1.1)	0.25	MeOD	90	0	96
2.3	A	-20	X(1.1)	1	MeOD	100	0	90
2.4	A	-78	X(2.2)	1	MeOD	100	0	98
2.5[e]	A	-78	X(1.1)	1	MeOD	0	0	98
2.6	A	-78	Y(1.1)	1	MeOD	100	0	98
2.7	A	-78	X(1.1)	1	D_2O	100	0	100
2.9	B	-78	Y(1.1)	1	D_2O	90	0	94
2.10	C	-78	X(1.1)	0.5	MeOD	3	3	96
2.11	C	-20	X(1.1)	0.5	MeOD	34	4	100
2.12	D	-78	X(1.1)	0.5	MeOD	15	0	94

a A - thf, B - DME, C = hexane, D = diethylether.

b X = ^{n}BuLi, Y = ^{s}BuLi, Z = LDA. The figures in parenthesis refer to the number of equivalents of organolithium reagent with respect to substrate.

c Estimated by nmr analysis (see text) and expressed as a percentage of recovered yield. Starting imidate (**129**) constitutes balance to 100%.

d With respect to starting material.

e TMEDA was present in equimolar ratio to the base.

highly effective directing group for β-lithiation.[19,79-80] The oxazolines have a rigid conformation and configuration, termed Z-anti-periplanar . Z - refers to the configuration about the carbon-nitrogen double bond; anti-periplanar refers to the OCH_2-/thiophene ring arrangement about the carbon-oxygen single bond. The lone electron-pair on the nitrogen, which are required to coordinate and deoligomerise the organolithium reagent, are exposed in the vicinity of the C3-position (Figure 2.3). This creates a high molarity of "activated" lithiating agent in near proximity to the C3-proton, effecting protophilic attack. Literature evidence suggests that the simple acyclic imidate may predominate in the E (ap) conformation (Figure 2.4).

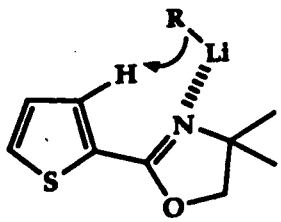


FIGURE 2.3

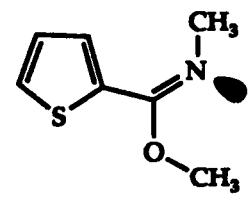
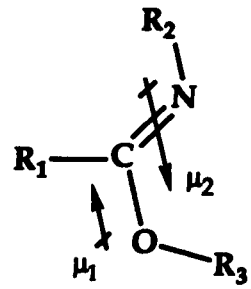


FIGURE 2.4

Exner and Schindler have carried out a complete dipole moment and molecular refraction study on some N-unsubstituted and N-substituted imidates.[96] Measurements were made in benzene, with the rigid cyclic oxazoline, serving as reference. They found the E-configuration to be generally valid for simple N-substituted alkyl and aryl imidates (Figure 2.5) including **(132)** which is analogous to the thiophene derivative. The preference for the E-configuration was attributed to the conformation at the R^3-O bond. Walters et al., confirmed these findings using nmr techniques.[97] However, it must be noted that neither



(132) When $R_1 = Ph$, $R_2 = R_3 = CH_3$

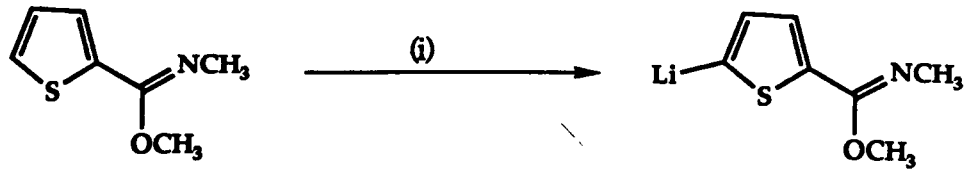
FIGURE 2.5

dipole moment nor nmr studies on imidate groups containing sterically bulky substituents for R^3 or R^2 have been investigated and it is probable that steric effects as well as dipole interactions (themselves being solvent-dependent), influence the E/Z diastereomer ratio of imidates.

If this E(ap) configuration is indeed predominant for the thiophene imidate under the reaction conditions used for lithiation, it can be imagined that the lone pair on the nitrogen of the imidate functionality (essential for coordination of the organolithium reagent) are directed away from the ring, and so exert no directing force (via a "coordinative" mechanism) for ortho-lithiation. Therefore, since there is no competition from the "coordination only" mechanism, the acid-base mechanism is preferred and exclusive α-lithiation is observed.

2.3 SYNTHETICAL APPLICATIONS OF THE LITHIATED THIOPHENE IMIDATE

Although no significant levels of β-lithiation are obtainable by employing the imidate functionality as a directing group, high levels of α-lithiation are achieved. The 5-lithio-inter-



(129) (133)

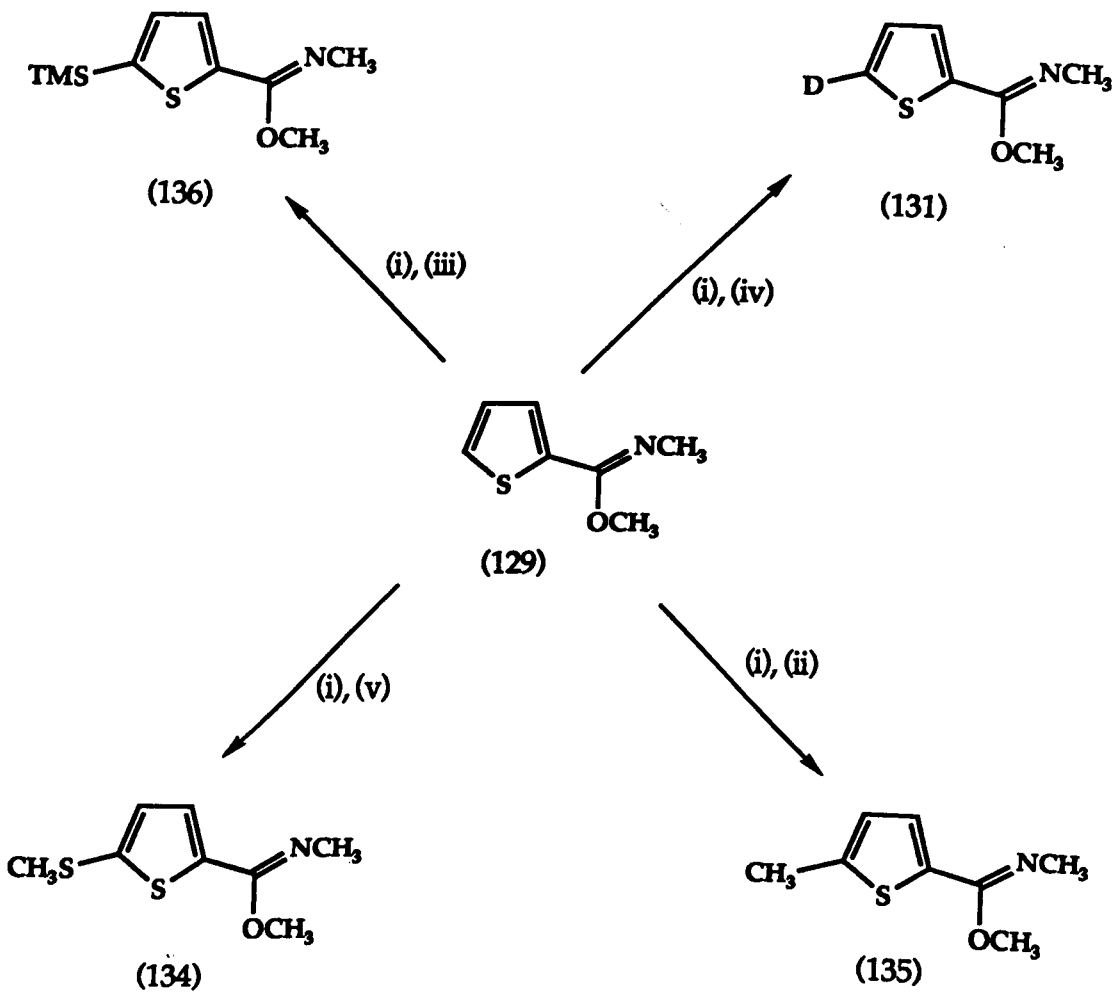
Reagents : (i) ^{n}BuLi, thf, -78°C, 1h

SCHEME 2.5

mediate (133) can be generated (100% yield) by using, for example, ^{n}BuLi in thf at -78°C for one hour (Scheme 2.5). Work-up of the thiophene anion (133) with a range of electrophiles at 20°C yields the 5-substituted imidates (Scheme 2.6). Use of five equivalents of Me_2S_2 gives the methylthio-imidate (134) in good yield (98%). Use of the five equivalents of MeI yields the 5-methyl imidate (135) in high yield (96%), with no sign of any competing N-quaternisation reaction. Addition of 1.1 equivalents of TMSCl gives a reasonable yield (68%) of the 5-silylated imidate (136). The anion also reacts readily with excess MeOD to give quantitative yields of the 5-deuterio-imidate (131).

2.4 LITHIATION OF METHYL N-METHYL-5-TRIMETHYLSILYLTHIOPHENE-2-CARBOXIMIDATE : THE USE OF SILICON BLOCKING GROUPS

It was of interest to determine whether any β-lithiation could be seen when the C5-position of imidate (129) is blocked with a removable blocking group. If lithiation is successful, removal of the blocking group would yield 2,3-disubstituted imidate derivatives of thiophene. A short lithiation study undertaken on imidate (136) revealed that an excess of ^{s}BuLi was



Reagents : (i) ^{n}BuLi, thf, -78°C, 1h; (ii) MeI;

(iii) TMSCl; (iv) MeOD; (v) Me_2S_2

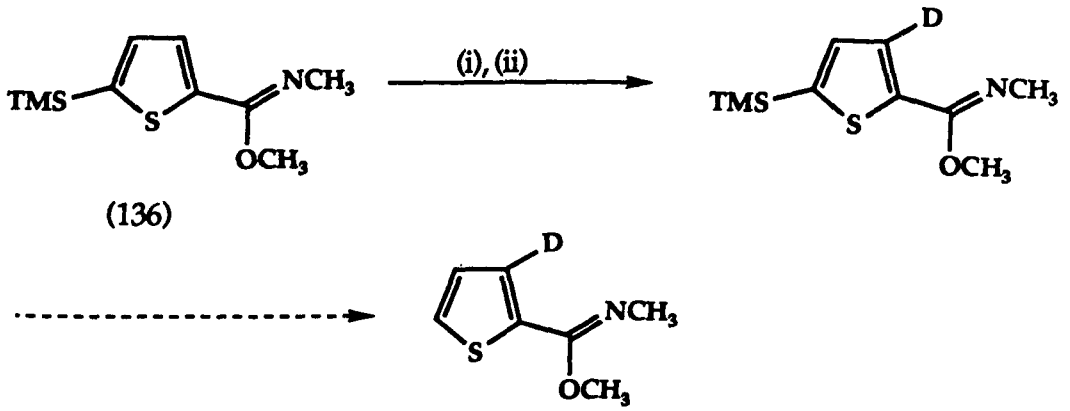
SCHEME 2.6

required for complete β-lithiation (Table 2.2). Thus, when the C5-position is blocked, lithiation becomes favourable at the C3-position, but the stronger base, ^{s}BuLi is required.

2.5 TRANSFORMATION OF THE IMIDATE MOIETY

The imidate group is potentially synthetically equivalent to the carboxylate functionality. Treatment of imidate (129) with aqueous HCl at room temperature yielded the ester (137) as a

TABLE 2.2



Reagents : (i) 2.5 ^{s}BuLi, thf, -78°C, 1h; (ii) D_2O

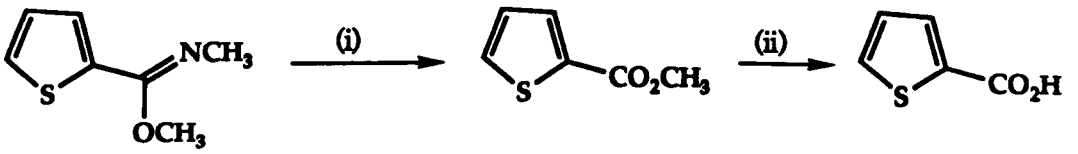
Expt.[a]	Solvent	Temp. (°C)	RLi	Time (h)	E^+	Product Comp. (%) derived from C3-lithiation	Total Recovered Yield (%)
2.13	A	-78	X(1.1)	1	D_2O	0	100
2.14	A	-78	Y(1.1)	1	D_2O	50	96
2.15	A	-78	Y(2.5)	1	D_2O	100	98

a The conventions of Table 2.1 apply.

colourless oil in good yield (76%), which was then readily hydrolysed to thiophene-2-carboxylic acid (97%) (Scheme 2.7).

2.6 ATTEMPTED SYNTHESIS OF N-^{t}BUTYL AND N-ADAMANTYLTHIOPHENE-2-CARBOXIMIDATES

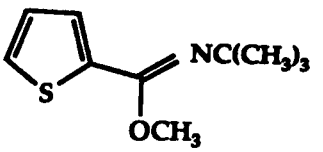
It was of interest to investigate the ortho-directed lithiation properties (if any) of imidate derivatives of thiophene with



(129) (137)

Reagents : (i) H_3O^+, room temperature, 0.5h; (ii) reflux, 3h

SCHEME 2.7



(138)

a "bulky" alkyl group on the nitrogen, and compare the results with those obtained for the N-methyl imidate. Methyl N-^{t}butyl thiophene-2-carboximidate (**138**) was the initial choice for investigation. The E-configuration for this acyclic imidate, assuming it is in a planar arrangement with the thiopene ring, would appear to be unfavourable due to the steric interference of the "bulky" ^{t}butyl group and the C3-proton (Figure 2.6). If this steric influence is strong, the imidate functionality might preferentially adopt a Z-configuration, thus exposing the lone electron pair on the nitrogen in the vicinity of the C3-position (Figure 2.7).

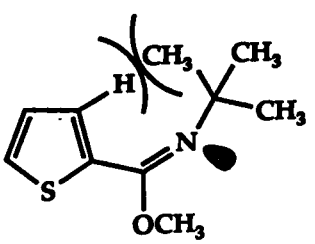


FIGURE 2.6

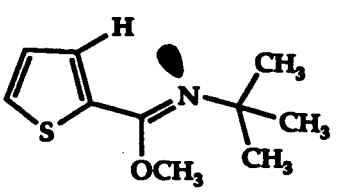
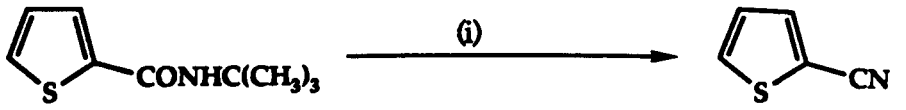


FIGURE 2.7

However, synthesis of imidate (**138**) proved unsuccessful due to the inability to synthesise the intermediate imidoyl chloride. Treatment of N-^{t}butylthiophene-2-carboxamide (**139**) with thionyl chloride under reflux yielded a clean and quantitative amount of thiophene-2-carbonitrile (**140**) (Scheme 2.8). This is the known



(**139**) (**140**)

Reagents : (i) $SOCl_2$, reflux, 3h

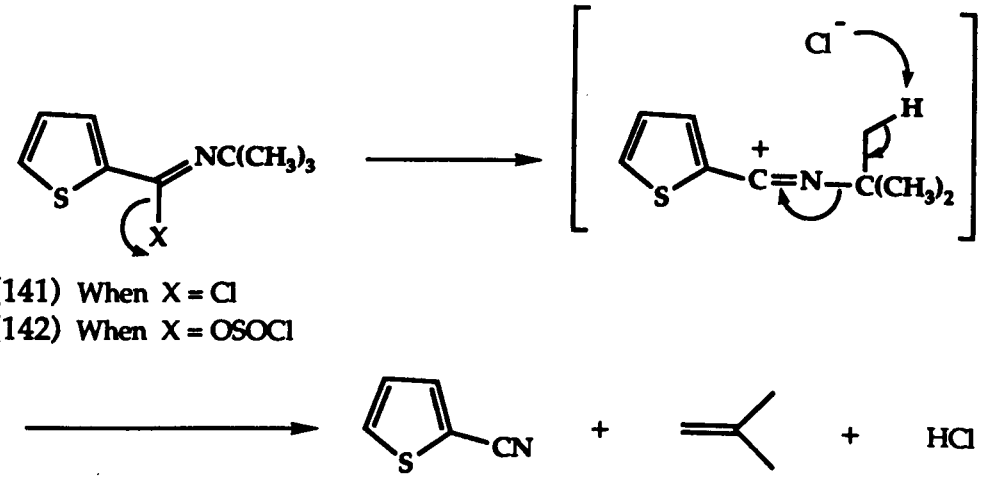
SCHEME 2.8

von Braun reaction (the conversion of an N-alkyl amide to an alkyl halide and nitrile).[98-102] Vaughan and Carlson have investigated the scope and limitations of this reaction on various N-alkylbenzamides and suggest the "probability" of an imidoyl chloride as an intermediate.[103]

However, failure to isolate, or even detect (by ^{1}H nmr) imidoyl chloride (**141**), suggests that the ^{t}butyl group is especially labile in imidoyl chloride (**141**), or even as the chlorosulphite precursor (**142**), leading to it.

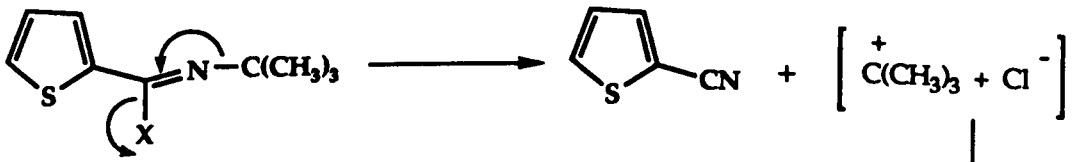
Two limiting mechanistic paths are postulated for this von Braun reaction; one requires dissociation of either (**141**) or (**142**) followed by formation of the nitrile (**140**) from the imidonium cation by the elimination of iso-butene and HCl (path 2.1); and the other may proceed by a "fragmentation" of either (**141**) or (**142**) followed by union of the resultant chloride and the tertiary carbonium ion (Path 2.2).

Due to the inability to isolate imidoyl chloride (**141**), a new functional group was sought that would not decompose under these reaction conditions ($SOCl_2$, heat).



(141) When X = Cl
(142) When X = OSOCl

PATH 2.1

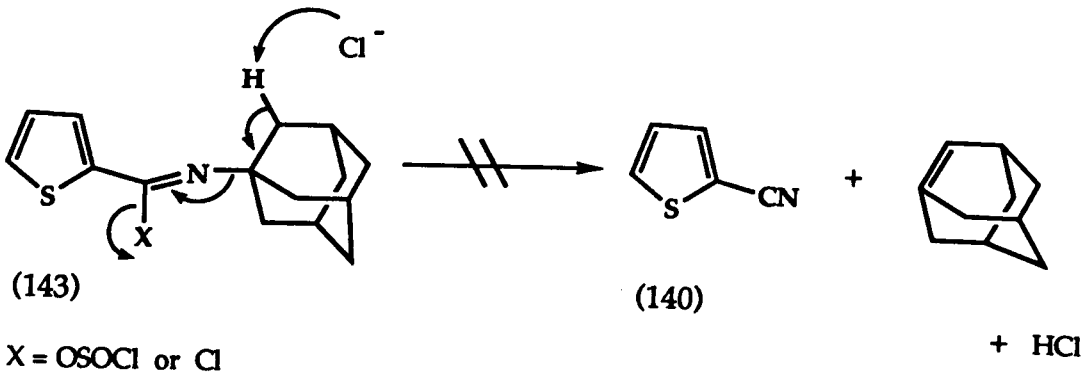


(141) When X = Cl
(142) When X = OSOCl

PATH 2.2

With the characteristics of the ^{t}butyl group in mind (i.e., a sterically bulky group) the adamantyl group was selected as a candidate. If the mechanism of elimination of the ^{t}butyl group in Path 2.1 is correct, then such a pathway should be denied the corresponding N-adamantyl derivative (**143**) due to the geometrical requirements of bonding ("Bredts' rule")[104] (Scheme 2.9). It was also considered unlikely that adamantane would readily accommodate a bridgehead carbonium ion under these conditions, suggesting a mechanism similar to that in Path 2.2, to be unlikely.

However, reaction of N-adamantylthiophene-2-carboxamide (**144**) with $SOCl_2$ under gentle reflux yielded thiophene-2-carbonitrile (**140**) and 1-chloroadamantane (**145**) (Scheme 2.10).

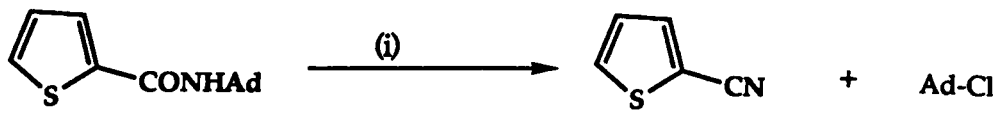


(143)

X = OSOCl or Cl

(140)

SCHEME 2.9



(143) (140) (145)

Reagents : (i) $SOCl_2$, reflux, 2h

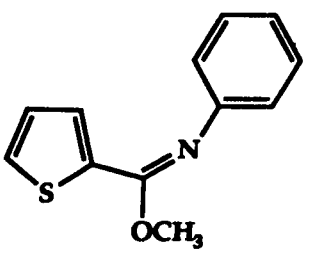
SCHEME 2.10

As with the N-^{t}butyl derivative, all attempts to isolate the imidoyl chloride (or other intermediate) failed suggesting that it is a highly unstable species. Elimination of the adamantyl group must proceed via a carbonium bridgehead intermediate. Further investigation of the literature, revealed that bridgehead carbonium ions can actually adopt a "comfortably flattened" configuration, intermediate between planar and tetrahedral (either extreme being prohibitively strained).[105-106] A figure of only 3.5 Kcal has been calculated for the strain difference between ^{t}butyl and 1-adamantyl carbonium ions.[105] This suggests that Path 2.2 is probably the common route for both the ^{t}butyl and adamantyl derivatives. Because of the difficulties involved no further investigations into the synthesis of these imidates were pursued.

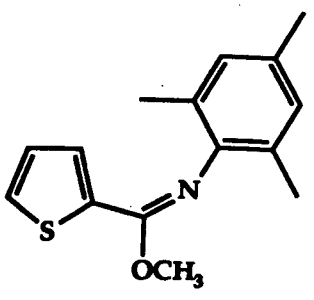
2.7 LITHIATION OF METHYL N-(2,4,6-TRIMETHYLPHENYL)THIOPHENE-2-CARBOXIMIDATE

It was still our interest to synthesise an imidate derivative of thiophene with a sterically "bulky" group on the nitrogen. Attention was turned to the N-aryl imidates. Methyl N-(2,4,6-trimethylphenyl)thiophene-2-carboximidate (**150**) was chosen as an ideal candidate. The trimethylphenyl group is bulky and could be expected to interfere sterically with the C3-proton of thiophene if the E-configuration is adopted (provided the imidate group and the thiophene ring are in the same plane). As postulated for the ^{t}butyl and adamantyl derivatives, this imidate might be expected to adopt an alternative conformation/configuration in order to relieve the steric strain, and so might have a significant effect on the directing properties (coordinative) of the imidate functionality.

N-Phenylthiophene-2-carboximidate (**146**) was synthesised to establish conditions for the general synthesis of N-aryl imidate derivatives. This imidate (**146**) was prepared in excellent yields, using similar methodology as for the N-methyl derivative (**129**). Imidate (**150**) was prepared in excellent yield (92%) as a



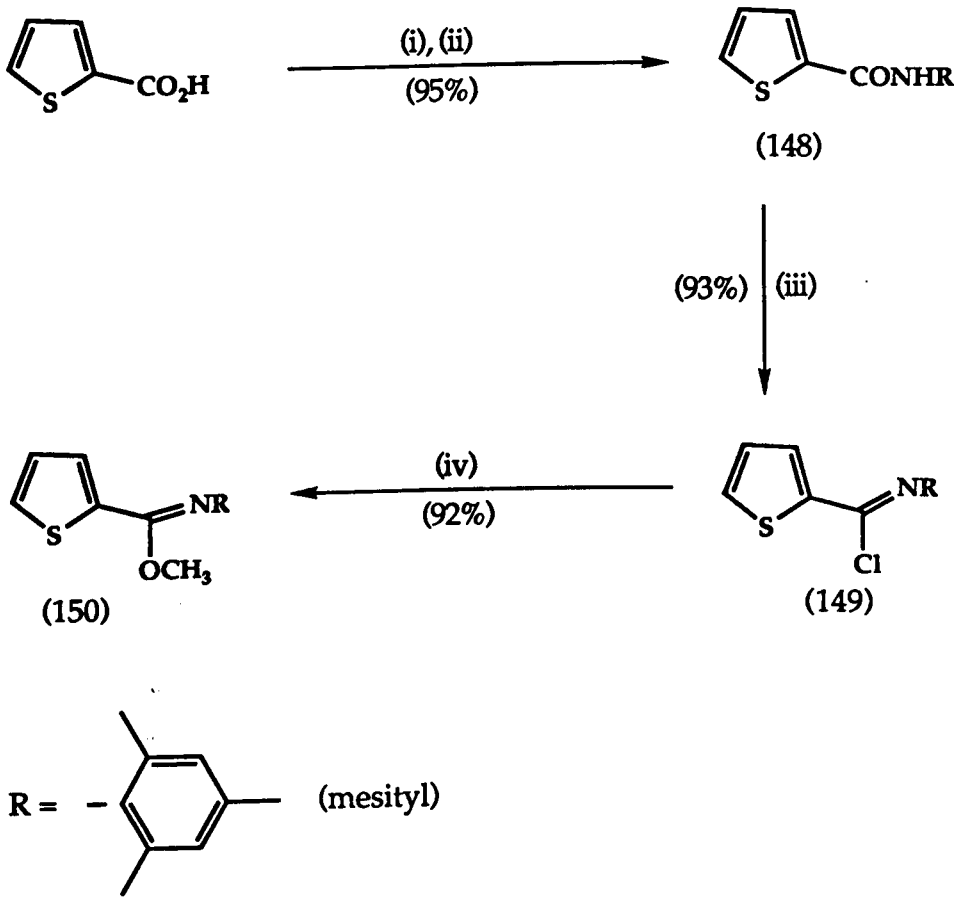
(146)



(150)

pale yellow solid via imidoyl chloride (**149**) which was formed in high yields (93%) by reacting the secondary amide (**148**) in neat

thionyl chloride under reflux for three hours. Treatment of imidoyl chloride (**149**) with sodium methoxide in methanol at 0°C gave the required imidate (Scheme 2.11).



Reagents : (i) $SOCl_2$, reflux, 3h; (ii) RNH_2, CH_2Cl_2, <10°C; (iii) $SOCl_2$, reflux, 3h; (iv) NaOMe, MeOH, thf, 0°C

SCHEME 2.11

The results of a range of experiments designed to elucidate the factors affecting regioselectivity of lithiation are given in Table 2.3. From these results it is evident that exclusive and virtually quantitative α-lithiation occurred in thf solution with either ^{n}BuLi, ^{s}BuLi or LDA, via an acid-base mechanism.[1] When the solvent is DME (entry 2.21), C5-lithiation was also observed,

TABLE 2.3

Expt.	Solvent	Temp. (°C)	RLi	Time (h)	E^+	Product Comp. (%) derived from 5-Lith	3-Lith	Recovered Yield (%)
2.16	A	-78	X(1.1)	1	MeOD	90	0	94
2.17	A	-78	Z(1.1)	1	MeOD	90	0	90
2.18	A	-78	Y(1.1)	1	MeOD	93	0	100
2.19	A	-78	Y(2.2)	1	D_2O	95	0	96
2.20[b]	A	-78	X(1.1)	1	MeOD	0	0	99
2.21	B	-78	X(1.1)	1	MeOD	70	0	98
2.22[b]	B	-78	X(1.1)	1	MeOD	0	0	98
2.23	C	-78	X(1.1)	1	MeOD	0	3	96
2.24	C	-20	X(1.1)	0.5	MeOD	9	14	98
2.25	C	r.t.	X(1.1)	0.5	MeOD	8	11	96
2.26	C	-20	Y(1.1)	0.5	MeOD	0	3	96
2.27	C	r.t.	X(3.0)	0.5	MeOD	6	10	100

a The conventions of Table 2.1 apply.

b TMEDA was present in equimolar ratio to the base.

but the overall level of lithiation was reduced due to the insolubility of the lithio-intermediate in this solvent.

The use of excess ^{s}BuLi (entry 2.19) still did not lead to C3-lithiation, but increased the level of C5-lithiation.

In hexane at -78°C, there was virtually no lithiation at all, due to the insolubility of the substrate at this temperature (entry 2.23). Repeating this reaction at increased temperatures

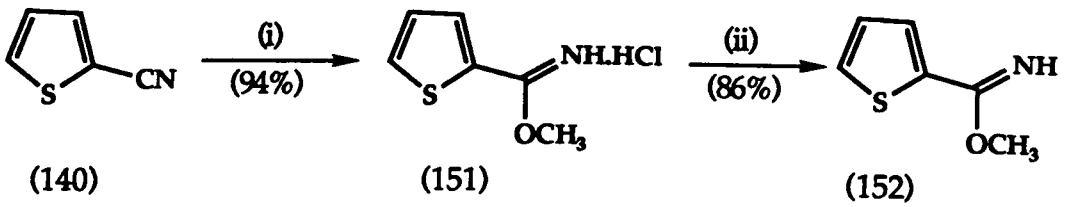
(entries 2.24 and 2.25) increased the solubility of the substrate, yet the regioselectivity and overall level of lithiation was poor. Using ^{s}BuLi instead of ^{n}BuLi in hexane, did not improve the levels of lithiation (entry 2.26). Nor did the use of excess ^{n}BuLi in hexane (entry 2.27). On addition of TMEDA (entries 2.20 and 2.22), surprisingly no lithiation was observed. TMEDA is a complexing agent, that deoligomerises the lithiating agent making it more coordinatively saturated, so C5-lithiation *via* the acid-base mechanism would be anticipated.

It can be concluded that the methyl *N*-(2,4,6-trimethylphenyl)imidate functionality will not effectively direct *ortho*-lithiation into the C3-position of the thiophene ring. It is clear that the directing force (coordinative and/or inductive) of this functionality is poor, compared to that of the ring heteroatom.

2.8 LITHIATION OF METHYL THIOPHENE-2-CARBOXIMIDATE

The lithiation of a simple *N*-unsubstituted imidate was briefly investigated. Imidate (**152**) was obtained *via* the Pinner synthesis.[107-108] Thiophene-2-carbonitrile (**140**) was treated with an equimolar amount of anhydrous methanol under acidic conditions at 0°C. It was important to control the temperature of the reaction at 0°C to prevent decomposition of the imidate hydrochloride salt (**151**). Treatment of (**151**) with sodium bicarbonate solution (10% w/w) in ether at 0°C provided the imidate base (**152**) in high yield (86%) as a mobile oil (Scheme 2.12).

Treatment of imidate (**152**) with 2.0 equivalents of ^{n}BuLi in thf at -78°C for half an hour, followed by electrophilic quench,



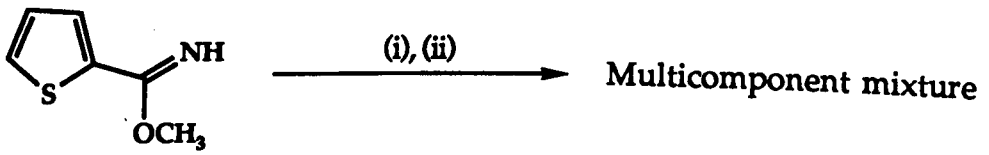
(140) (151) (152)

Reagents : (i) MeOH, HCl (g), 0°C;

(ii) $NaHCO_3$ (10% w/w), Et_2O, 0°C

SCHEME 2.12

yielded a mixture of products by tlc analysis. Infrared analysis indicated the presence of a nitrile functionality and the ^1H nmr spectrum showed the presence of thiophene-2-carbonitrile and its 5-deuterio-isomer along with products resulting from nucleophilic addition of the organolithium reagent to these nitrile derivatives (Scheme 2.13).

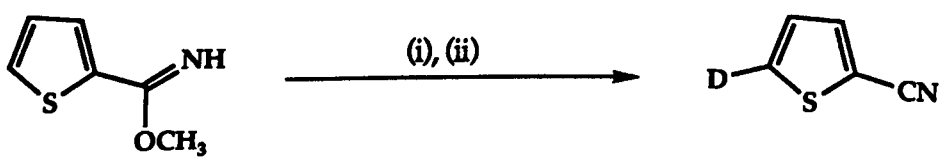


(152)

Reagents : (i) ^nBuLi, thf, -78°C, 0.5h; (ii) MeOD

SCHEME 2.13

Treatment of the imidate (152) with 2.0 equivalents of the sterically hindered organolithium reagent, LDA, gave an excellent yield of 5-deutero-thiophene-2-carbonitrile (153) (80%, by ^1H nmr analysis). No products resulting from nucleophilic addition reactions of the organolithium reagent to the nitrile were observed (Scheme 2.14).



(152) (153)

Reagents : (i) 2.0 LDA, thf, -78°C, 0.5h; (ii) MeOD

SCHEME 2.14

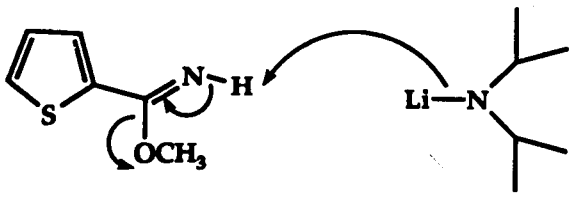


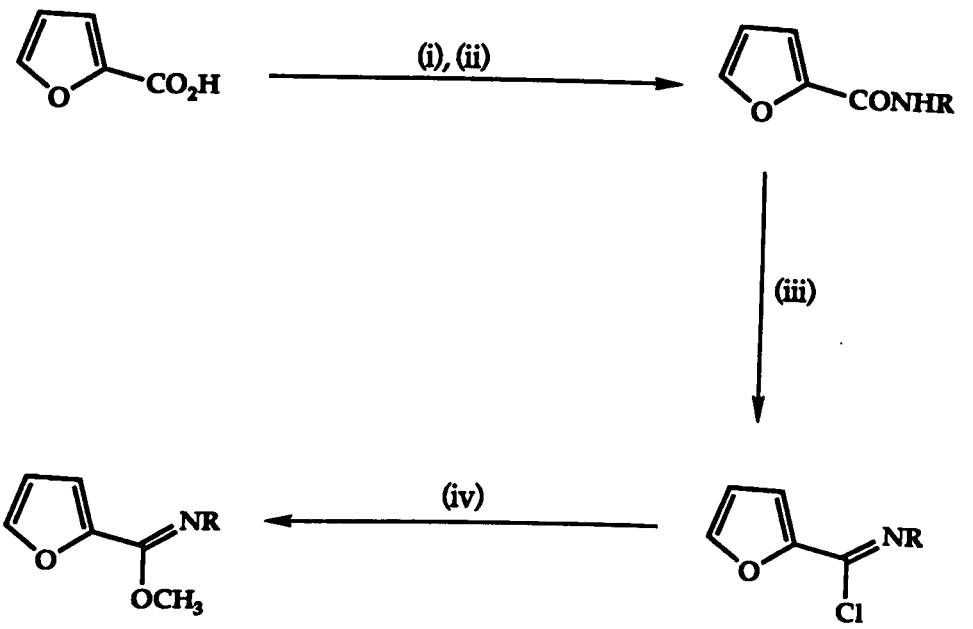
FIGURE 2.8

In this reaction, the first equivalent of LDA removes the more acidic NH proton with the concomitant elimination of methoxide to form the nitrile (Figure 2.8). The acidic α-proton is removed with the second equivalent of LDA by an acid-base mechanism.

2.9 LITHIATION OF N-METHYL AND N-ARYLFURAN-2-CARBOXIMIDATES

Lithiation studies on some imidate derivatives of furan were investigated and the results compared with those obtained for thiophene. Methyl N-methylfuran-2-carboximidate (**156**), methyl N-phenylfuran-2-carboximidate (**159**) and methyl N-(2,4,6-trimethylphenyl)furan-2-carboximidate (**162**) were synthesised in excellent yields (94%, 97% and 94% respectively) using the same procedure as for the thiophene analogues (Scheme 2.15).

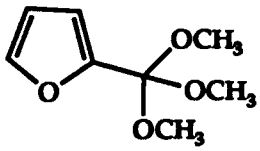
Imidoyl chloride (**155**) when purified is an unstable, lachrymatory colourless oil, which rapidly decolourises at low temperatures (0 - 5°C) under an inert atmosphere. Consequently, (**155**) was prepared and used immediately. Preparation of imidate (**156**) was successfully achieved by the very slow addition of sodium methoxide in methanol at 0°C. Too rapid an addition always yielded small amounts (< 20%) of a side product, which showed a



R	Amide	Yield (%)	Imidoyl Chloride	Yield (%)	Imidate	Yield (%)
Methyl	**(154)**	73	**(155)**	79	**(156)**	94
Phenyl	**(157)**	94	**(158)**	100	**(159)**	97
Mesityl	**(160)**	94	**(161)**	99	**(162)**	94

Reagents : (i) $SOCl_2$, reflux, 3h; (ii) $MeNH_2$, NaOH (10% w/w) for **(154)**; RNH_2, CH_2Cl_2, <10°C for **(157)** and **(160)**; (iii) $SOCl_2$, reflux; (iv) NaOMe, MeOH, thf, 0°C for 1h.

SCHEME 2.15



(163)

characteristic singlet at δ 3.21 ppm in the ^{1}H nmr, suggesting the presence of ortho formate ester (**163**). (It is noteworthy that no similar product was observed in the synthesis of the thiophene analogue.) No side-products were encountered in the preparation of (**159**) and (**162**).

A short lithiation study on imidate (**156**) (Table 2.4) showed exclusive and high yielding amounts of C5-lithiation when thf is

TABLE 2.4

Expt.	Solvent	Temp. (°C)	RLi	Time (h)	E^+	Product Comp. (%) derived from 5-Lith	3-Lith	Recovered Yield (%)
2.28	A	-78	Z(1.1)	0.5	MeOD	91	0	94
2.29	A	-78	X(1.1)	0.5	MeOD	100	0	87
2.30	A	-78	Y(1.1)	0.5	MeOD	91	0	94
2.31	A[b]	-78	X(1.1)	0.5	MeOD	0	0	96
2.32	A[b]	-78	Y(1.1)	0.5	MeOD	0	0	100
2.33	C	-78	X(1.1)	0.5	MeOD	11	0	98

a The conventions of Table 2.1 apply.

b TMEDA was present in equimolar ratio to the base.

used as solvent (entries 2.28 - 2.30). Addition of TMEDA prevents any ring lithiation (entries 2.31 and 2.32). Using hexane as solvent, a very poor level of lithiation was observed (entry 2.33).

A lithiation study on imidate (**159**) (Table 2.5) also showed exclusive, yet virtually quantitative C5-lithiation with ^{n}BuLi, ^{s}BuLi and LDA. An exception to this was when using ^{s}BuLi in DME (entry 2.43), due to the insolubility of the lithio-intermediate at this temperature. Once again, addition of TMEDA seems to

TABLE 2.5

Expt.	Solvent	Temp. (°C)	RLi	Time (h)	E^+	Product Comp. (%) derived from 5-Lith	3-Lith	Recovered Yield (%)
2.34	A	-78	X(1.1)	0.5	MeOD	100	0	100
2.35	A	-78	Z(1.1)	0.5	MeOD	84	0	100
2.36[b]	A	-78	X(1.1)	0.5	MeOD	0	0	100
2.37	A	-78	X(2.2)	0.5	MeOD	100	0	100
2.38	A	-20	X(1.1)	0.5	MeOD	95	0	85
2.39	A	-78	Y(1.1)	0.5	MeOD	100	0	100
2.40	A	-78	Y(2.2)	0.5	MeOD	100	0	88
2.41[b]	A	-78	Y(1.1)	0.5	MeOD	0	0	98
2.42	B	-78	X(1.1)	0.5	D_2O	100	0	96
2.43	B	-78	Y(1.1)	0.5	D_2O	75	0	96

a The conventions of Table 2.1 apply.

b TMEDA was present in equimolar ratio to the base.

render ring lithiation unfavourable (entries 2.36 and 2.41). Addition of excess lithiating agent only ensures quantitative C5-lithiation, with no sign of any C3-lithiation (entries 2.37 and 2.40).

The results of the lithiation experiments on imidate (**162**) (Table 2.6), not surprisingly, were similar to those obtained for (**159**), with a disappointing lack of β-selectivity.

It is clear from these results (Tables 2.4, 2.5 and 2.6) that β-lithiation of the furan ring cannot be successfully accomplished using the imidate functionality as an ortho-directing group. Only C5-lithiation is observed. These results follow

TABLE 2.6

Expt.	Solvent	Temp. (°C)	RLi	Time (h)	E^+	Product (%) derived from 5-Lith	Comp. 3-Lith	Recovered Yield (%)
2.44	A	-78	X(1.1)	0.5	MeOD	86	0	96
2.45	A	-78	X(2.2)	0.5	MeOD	96	0	100
2.46	A	-78	Y(1.1)	0.5	D_2O	90	0	94
2.47	A	-78	Z(1.1)	0.5	MeOD	77	0	92
2.48	A	-78	Y(2.2)	0.5	MeOD	100	0	100
2.49	A	-78	X(1.1)	0.5	MeOD	100	0	98
2.50[b]	A	-78	X(1.1)	0.5	MeOD	0	0	98
2.51	B	-78	X(1.1)	0.5	MeOD	97	0	98

a The conventions of Table 2.1 apply.

b TMEDA was present in equimolar ratio to the base.

the same trend and support those obtained for the corresponding imidate derivatives of thiophene. Presumably the reasoning why the imidate functionality is such an ineffective ortho-directing group for thiophene applies to furan.

Further studies on the imidate functionality were, therefore, not considered to be worthwhile.

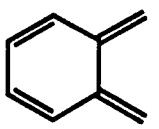
CHAPTER 3

3.0 THE APPLICATION OF DIRECTED LITHIATION IN THE SYNTHESIS OF PRECURSORS TO HETEROCYCLIC ANALOGUES OF o-XYLYLENE

3.1 APPROACHES TO THE FURAN ANALOGUES OF o-XYLYLENE

3.1.1 INTRODUCTION

There are many reports in the literature concerned with o-xylylene (**164**) (also known as o-quinodimethane and o-quinodi-

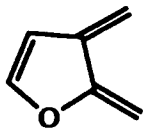


(164)

methide) and its derivatives. o-Xylylene has great potential in organic synthesis as a Diels-Alder diene and has found wide application in the synthesis of natural products including steroids,[109-112] alkaloids[113] and anthracyclinones.[114]

The heterocyclic analogues of o-xylylene are of considerable interest for their potential in organic synthesis. Indole-2,3-xylylenes have been extensively applied in the alkaloid field,[115] otherwise studies of the five-membered heterocyclic analogues have been limited largely to the furan (**165**),[116-121] thiophene (**166**)[122-126] and their benzo derivatives. Very recently the oxazole (**167**), thiazole (**168**) and imidazole (**169**) analogues have been reported.[127]

The furan xylylene (**165**) has previously been generated flash pyrolytically by retro Diels-Alder fragmentation of (**170**)[119] and elimination of benzoic acid from ester (**171**).[116] It is remarkably stable, can be isolated at low temperature and treatment of



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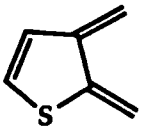

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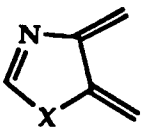
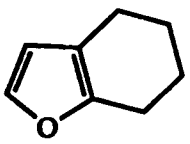


(167) when x = O
(168) when x = S
(169) when x = NH



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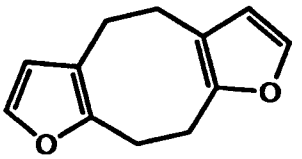

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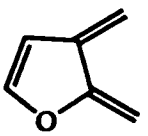

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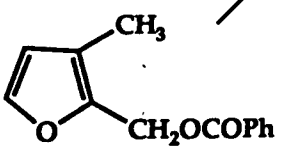

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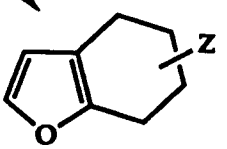
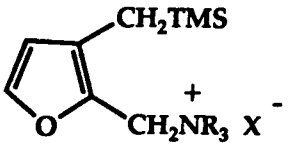


(172)

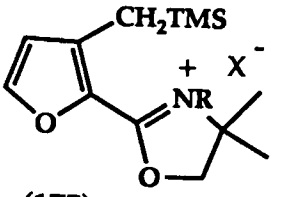
SCHEME 3.1

the cold pyrolysate with dienophiles in solution gives Diels-Alder adducts (172). In the absence of dienophiles the [4+4] head-to-head dimer is isolated (173) (Scheme 3.1).

There has been no literature report on the generation of o-xylylene (165) in solution and subsequent trapping with dienophiles in situ. It was our aim to incorporate directed lithiation methodology in the synthesis of precursors (174) and (175) to furan analogues of o-xylylene. It was anticipated that a fluoride ion-induced desilylation would lead to the furan

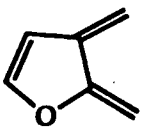


(174)

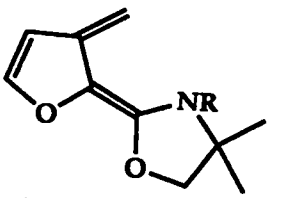


(175)

xylylene (**165**) and the substituted furan xylylene (**176**) respectively. This 1,4-elimination reaction has previously been demonstrated to be an efficient and versatile method for the generation of o-xylylene (**164**)[128-129] and the thiophene analogue (**166**).[123-124,130]



(165)

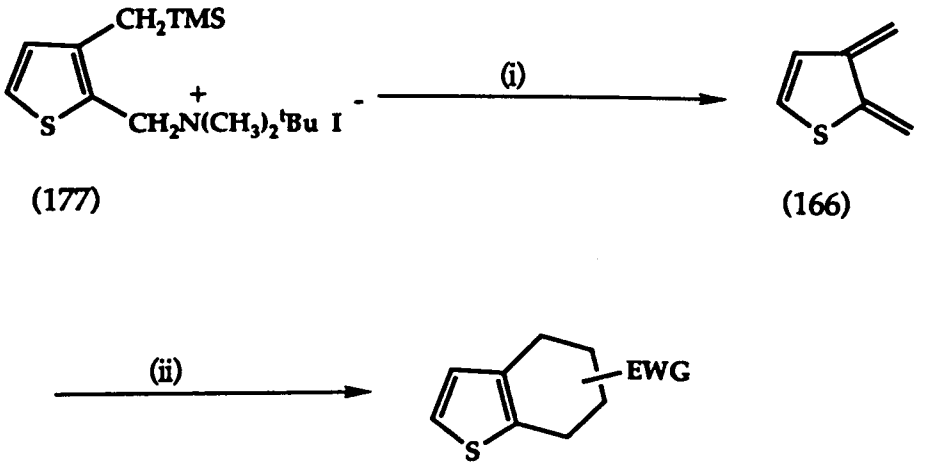


(176)

3.1.2 ATTEMPTED AMIDE MEDIATED SYNTHESIS OF A PRECURSOR TO THE FURAN ANALOGUE OF o-XYLYLENE

Chadwick and Plant have successfully synthesised salt (**177**), and treated it with a source of fluoride ion to give the thiophene o-xylylene (**166**) which was successfully trapped in high yields with a variety of dienophiles (Scheme 3.2).[130]

These workers used a directed ortho-lithiation strategy to introduce a trimethylsilylmethyl functionality into the C3-position of the thiophene ring. Carpenter and Chadwick have previously demonstrated the N-^{t}butyl secondary amido functional-

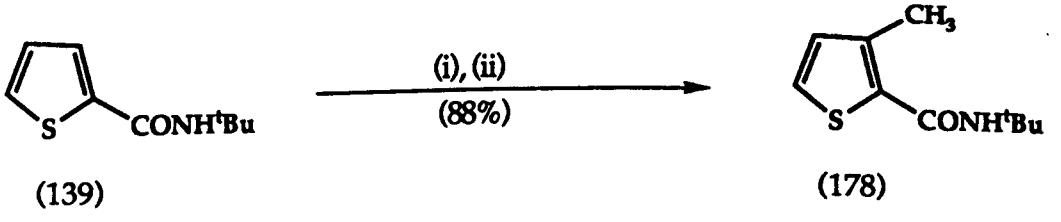


(177) (166)

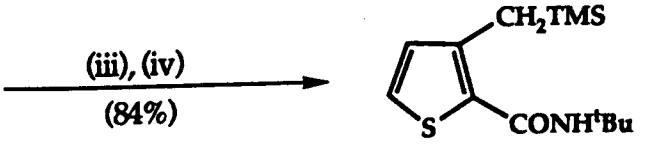
Reagents : (i) CsF; (ii) CH_2=CH-EWG

SCHEME 3.2

ity to be an excellent director of ortho-lithiation in hetero-aromatics.[11,81] Lithiation of N-^{t}butylthiophene-2-carboxamide (**139**), followed by reaction with one equivalent of MeI gave N-^{t}butyl-3-methylthiophene-2-carboxamide (**178**) in excellent yield (88%). A second directed lithiation and subsequent silylation into the C3-methyl group gave excellent yields of the silylated amide (**179**) (Scheme 3.3). These two lithiation reactions are



(139) (178)



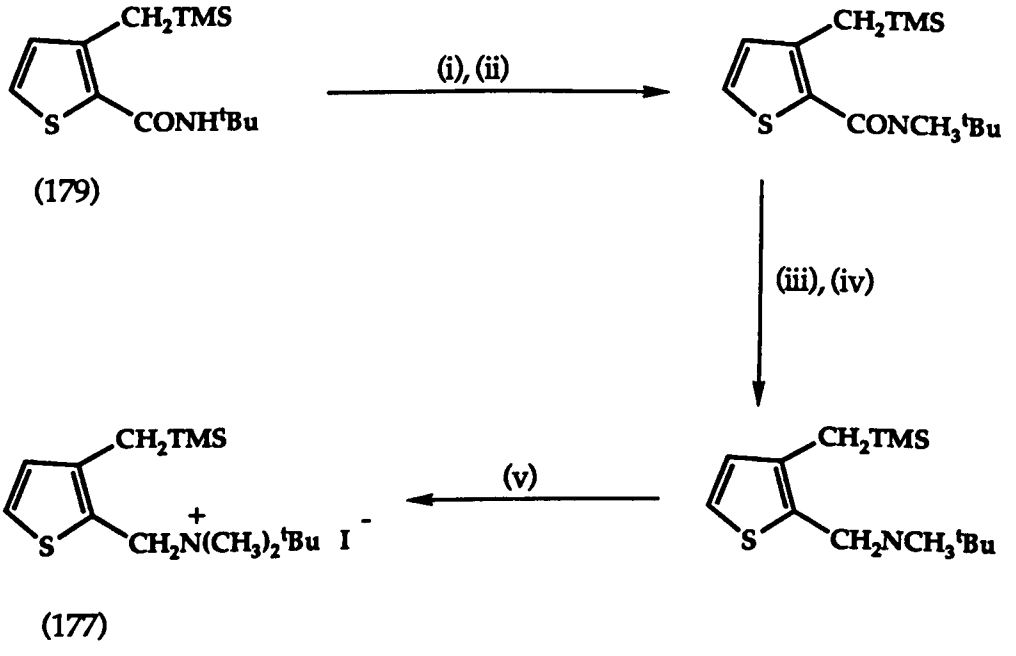
(179)

Reagents : (i) ^{n}BuLi, DME, -78°C, 2h; (ii) MeI;

(iii) ^{s}BuLi, thf, -78°C, 0.5 h; (iv) TMSCl, -78°C, 0.25h

SCHEME 3.3

the important steps in the synthesis of precursor (**177**), because it gives rise to the 2,3-disubstituted thiophene, which is difficult to obtain by other methodology. Silylated amide (**179**) is then successfully converted into salt (**177**) in three steps, using straight forward reactions (Scheme 3.4).



(179)

(177)

Reagents : (i) ^{n}BuLi, thf, -78°C, 0.5h; (ii) MeI;

(iii) $LiAlH_4$, Et_2O, reflux, 24h; (iv) H_2O;

(v) MeI, room temperature, 12h

SCHEME 3.4

Application of this chemistry to the construction of a precursor to the furan analogue has been investigated. The approach is outlined in Figure 3.1. The key step being the

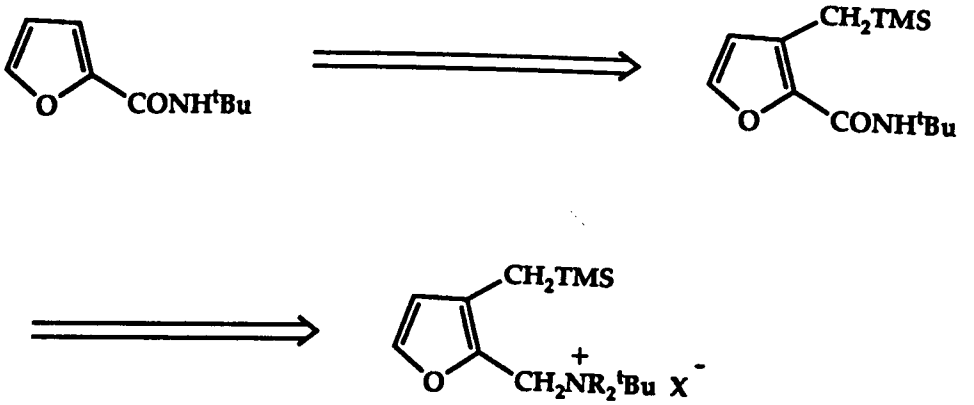
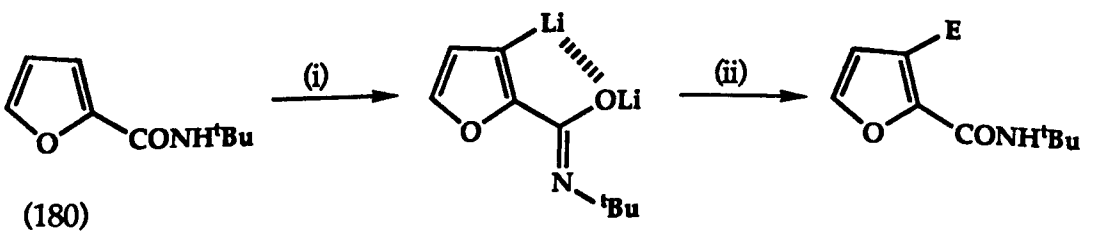


FIGURE 3.1

introduction of a trimethylsilyl methyl- group by two successive lithiation reactions, with subsequent transformation of the secondary amide into the quaternary ammonium salt.

3.1.2.1 ATTEMPTED SYNTHESIS OF N-^{t}BUTYL-3-TRIMETHYLSILYL-METHYLFURAN-2-CARBOXAMIDE

The first step was to synthesise N-^{t}butyl-3-methylfuran-2-carboxamide (**181**) from N-^{t}butylfuran-2-carboxamide (**180**) via a directed lithiation-methylation approach. Carpenter and Chadwick have reported the preparation of the dilithio-intermediate (**182**) and reacted it with a wide range of electrophiles to give excellent yields of 2,3-disubstituted furan amides (Scheme 3.5).[11,81] However, they did not report any attempts on



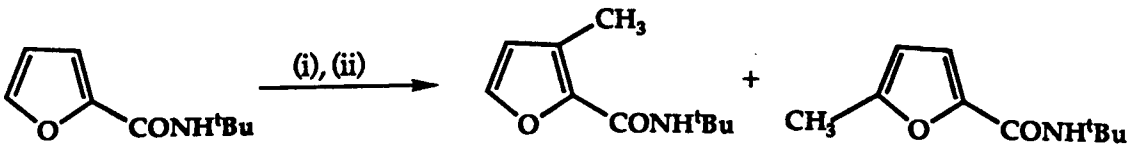
(180) (182)

Reagents : (i) ^{s}BuLi, DME, -78°C, 1h; (ii) E$^+$

SCHEME 3.5

reacting the dilithio species with an equimolar amount of MeI to give (**181**).

The dilithio intermediate (**182**) was prepared as outlined in Scheme 3.5 and treated with one equivalent of MeI. This reaction gave a poor yield of product (**181**) as judged by nmr and tlc analysis. The best yield of the C3-methylated amide (**181**), (82%), was achieved using ^{n}BuLi in DME at -78°C. However, some of the C5-methylated amide (**183**) (18%), was also present (Scheme 3.6). These two isomers proved difficult to separate by chromatographic methods.



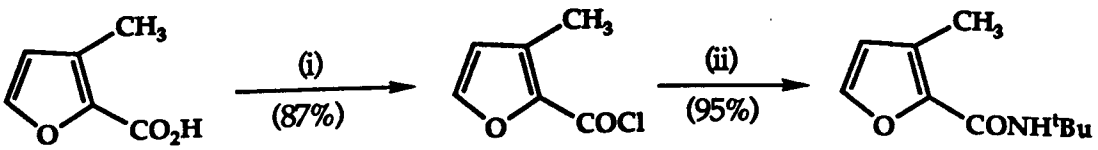
(180) (181) (183)

Reagents : (i) ^{n}BuLi, DME, -78°C, 2h;

(ii) MeI, -78°C for 0.5h, then room temperature

SCHEME 3.6

Alternatively, amide (**181**) could be prepared on a larger scale from 3-methylfuran-2-carboxylic acid (**184**) via acid chloride (**185**). The reaction is clean and high yielding (95%) to give the product as a white crystalline solid (Scheme 3.7).

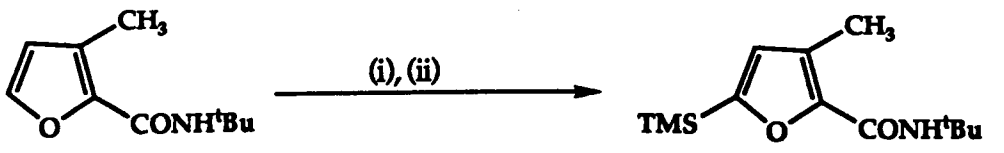


(184) (185) (181)

Reagents : (i) $SOCl_2$, reflux; (ii) $^{t}BuNH_2$, CH_2Cl_2, < 10°C

SCHEME 3.7

In an attempt to achieve lithiation and silylation into the C3-methyl group, the 3-methylamide (**181**) was treated with ^{n}BuLi in thf at 0°C for half an hour, followed by subsequent treatment with TMSCl (Scheme 3.8). These conditions have been shown to



(181) (186)

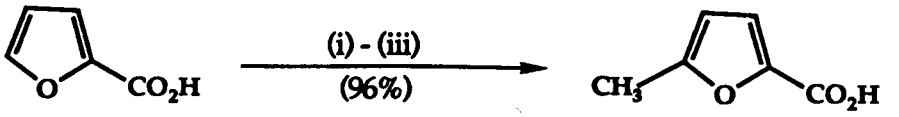
Reagents : (i) ^{n}BuLi, thf, 0°C, 0.5h; (ii) TMSCl

SCHEME 3.8

lead to high levels of benzylic substitution in the corresponding thiophene. Unfortunately, even under these conditions only C5-silylated product (**186**) was observed by nmr analysis. The inherently faster lithiation of the furan nucleus by the acid-base mechanism, and a possibly less stable benzylic anion, may be responsible for this change in regioselectivity between ring systems.

The problem of α-lithiation in this instance can be overcome by employing a methyl blocking group. However, attempts at introducing the methyl group into the C5-position of amide (**181**) using the conditions outlined in Scheme 3.8 gave a mixture of products, including starting material, presumably due to the poor reactivity of the C5-anion with the less reactive alkylating agent in this solvent.

This problem was overcome by introducing the C5-methyl group into furan-2-carboxylic acid (**187**) by the general procedure of Knight and Nott[131] (Scheme 3.9) to give 5-methylfuran-2-carboxy-



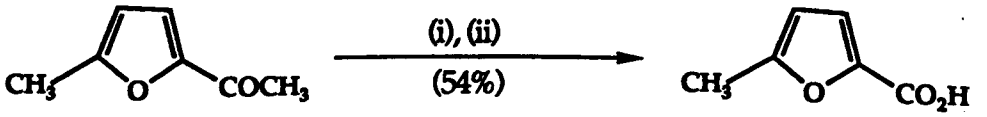
(187) (188)

Reagents : (i) 2.1 LDA, thf, -78°C, 1h; (ii) MeI; (iii) H_3O^+

SCHEME 3.9

lic acid (**188**) in excellent yield (96%). Attempts at repeating this reaction on a larger scale (> 5.00g) gave lower levels of C5-methylation presumably due to the insolubility of the dilithio-intermediate at this temperature, despite scaling up the quantity of solvent. This "scaling-up" problem limits the synthetic utility of this reaction.

Alternatively, acid (**188**) could be prepared on a multigram scale from 2-acetyl-5-methylfuran (**189**) in reasonable yield (54%) (Scheme 3.10).



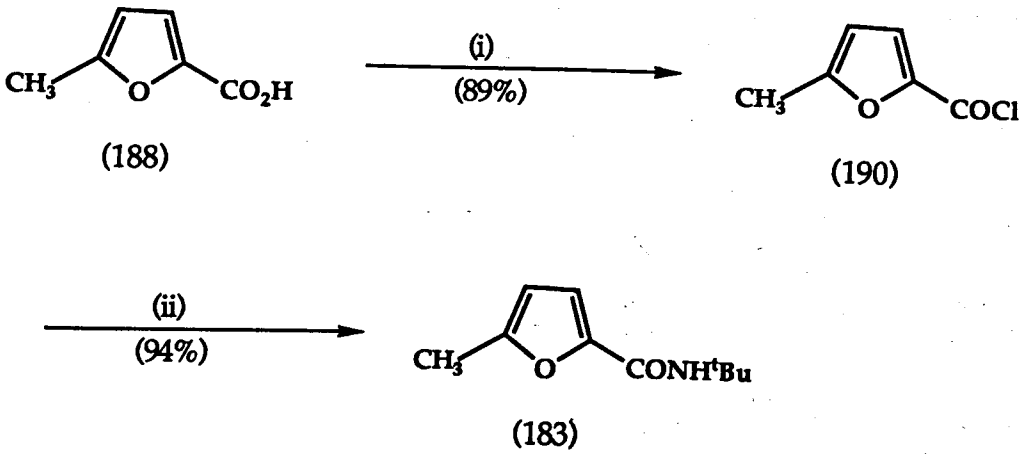
(189) (188)

Reagents : (i) NaOCl, heat; (ii) H_3O^+

SCHEME 3.10

Amide (**183**) was then readily prepared from 5-methylfuran-2-carboxylic acid (**188**) via acid chloride (**190**) (Scheme 3.11). This reaction proceeded cleanly to give the amide in excellent overall yield (84%).

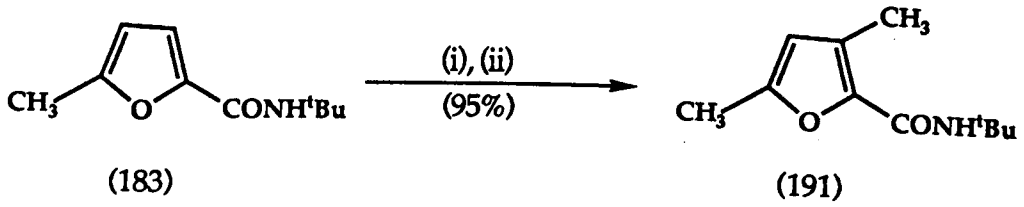
Treatment of amide (**183**) with ^nBuLi in DME at -78°C for half an hour followed by subsequent reaction with one equivalent of



(188) (190) (183)

Reagents : (i) $SOCl_2$, reflux; (ii) $^tBuNH_2$, CH_2Cl_2, < 10°C

SCHEME 3.11



(183) (191)

Reagents : (i) ^nBuLi, DME, -78°C, 0.5h; (ii) MeI

SCHEME 3.12

MeI gave the dimethylated product as a waxy solid in excellent yield (95%) (Scheme 3.12).

At this point conditions needed to be established for regiospecific lithiation-silylation into the C3-methyl group. The results of a range of experiments designed to elucidate the factors affecting regioselectivity of lithiation of N-^{t}butyl-3,5-dimethylfuran-2-carboxamide (**191**) are given in Table 3.1. The results show that incorporation of a TMS group regioselectively into the C3-methyl group *via* directed lithiation is an inefficient process. The highest yield of exclusive C3-silylation was only 17% (entry 3.2) (Scheme 3.13). The yield of C3-

TABLE 3.1

Expt.[a]	Solvent[b]	Temp. (°C)	R-Li[c]	Time (h)	TMS-incorp. into C3-methyl group (%)[d]
3.1	A	-78	Y(2.1)	0.5	0
3.2	A	0	X(2.1)	0.5	17
3.3	A	-20	Y(2.05)	0.5	8
3.4	A	r.t.	X(2.05)	1	0
3.5	A	-78	Y(2.1)	0.5	0
3.6[e]	A	-78	Y(2.5)	0.5	40[f]
3.7	B	0	Y(2.05)	0.5	0
3.8	B	0	Y(2.05)	0.5	0
3.9	B	-78	Y(2.1)	0.5	0
3.10[e]	B	-78	X(2.2)	0.5	18[f]

a All reactions were quenched with TMSCl.

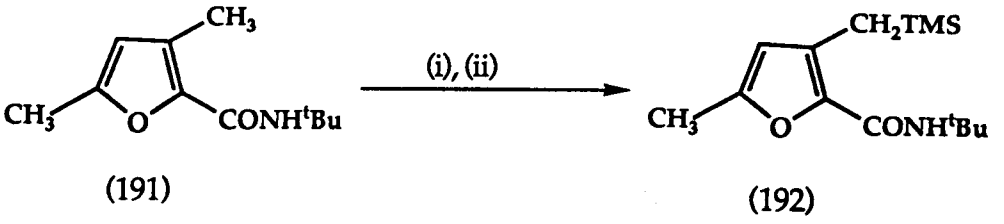
b A = thf, B = DME.

c X = ^{n}BuLi, Y = ^{s}BuLi. The figures in parenthesis refer to the number of equivalents of organolithium reagent with respect to substrate.

d Estimated by nmr analysis and expressed as a percentage of recovered yield. Starting material constitutes balance to 100%.

e After addition of organolithium reagent, the reaction was left at -78°C for half an hour and then warmed quickly to room temperature.

f Some C5-methyl silylated and disilylated product observed.



(191) (192)

Reagents : (i) 2.1 ^{n}BuLi, thf, 0°C, 0.5h; (ii) TMSCl

SCHEME 3.13

methyl silylation increased to 40% (entry 3.6), when the reaction mixture was quickly brought to room temperature, before being quenched with TMSCl. However, levels of C5-methyl silylation were observed. The C5- and C3-silylated isomers proved difficult to separate by chromatographic techniques.

It is evident that the C3-methyl protons for amide (**191**) are less readily deprotonated by lithiating agents than those for the thiophene derivative. The ^{t}butyl secondary amido functionality has been well established as an excellent ortho-directing group for the furan ring,[11,81] the reasoning postulated is that the bulky ^{t}butyl group helps predispose the amidate anion to a conformation allowing maximum stabilisation of the dilithiated intermediate. Such a conformation may also permit efficient delivery of the second equivalent of organolithium reagent to the β-position by the intermediate anion (Figure 3.2). This direct-

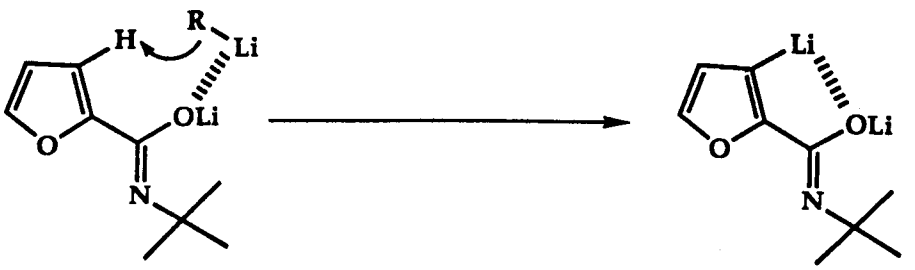
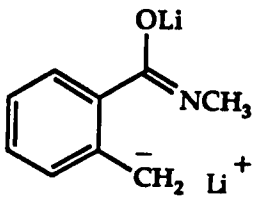


FIGURE 3.2

ing force is present for C3-methyl deprotonation of the thiophene derivative, and it is reasonable to assume it is present for the furan derivative. Presumably, the benzylic anion formed for this furan derivative is unstable. Furan is less aromatic in character than thiophene because of the reduction in the extent of mesomerism due to the electronegativity of the oxygen hetero-atom. Therefore, the benzylic anion is less delocalised in furan than it is for the thiophene case. It is noteworthy that the benzylic anion (**193**) of N-methyl-o-toluamide is known to be



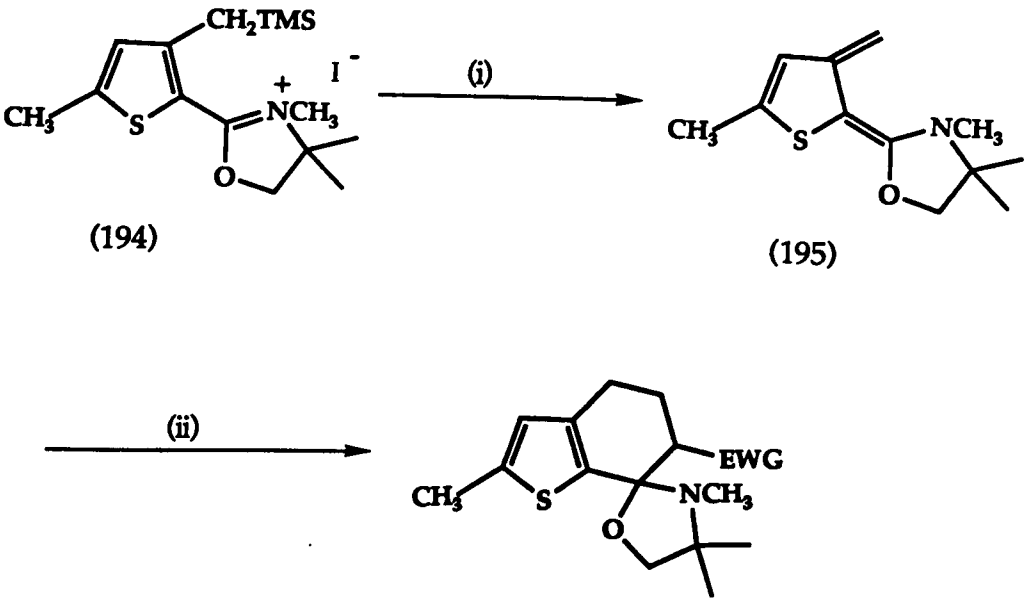
(193)

formed readily (2 ^{n}BuLi, thf, reflux, 0.25h),[132] presumably because the negative charge can be effectively delocalised around the aromatic ring.

Due to the the lack of success in introducing a TMS-group efficiently into the C3-methyl group, the pathway to this particular precursor of the furan analogue of o-xylylene was abandoned.

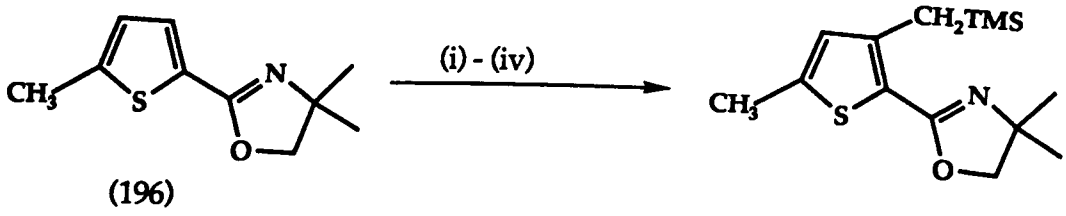
3.1.3 OXAZOLINE MEDIATED SYNTHESIS OF A PRECURSOR TO THE FURAN ANALOGUE OF o-XYLYLENE

Chadwick and Plant successfully synthesised salt (**194**) and treated it with a source of fluoride ion to give the thiophene



Reagents : (i) CsF; (ii) CH_2=CH-EWG

SCHEME 3.14



Reagents : (i) ^{n}BuLi, Et_2O, -78°C, 0.25h, then 0°C for 0.5h;
(ii) MeI; (iii) ^{s}BuLi, Et_2O, -78°C for 0.5h
then warm quickly to room temperature; (iv) TMSCl

SCHEME 3.15

o-xylylene derivative (**195**) which was trapped with a variety of dienophiles in excellent yields (Scheme 3.14).[123]

The oxazoline functionality was used to good effect as an ortho-directed lithiation group, to introduce a trimethylsilylmethyl functionality into the β-position of (**196**) (Scheme 3.15). Quaternisation with methyl iodide yielded the oxazolinium salt (**194**).

Preliminary attempts to apply this route to the furan analogue have now been extended.[130] The key reactions are the introduction of the trimethylsilylmethyl functionality by two successive directed lithiations, followed by quaternisation of the oxazoline (Figure 3.3).

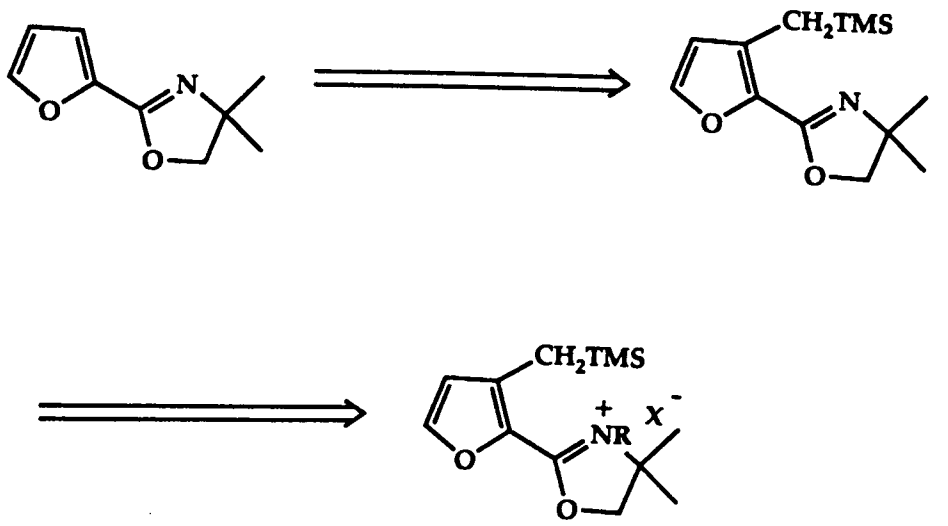
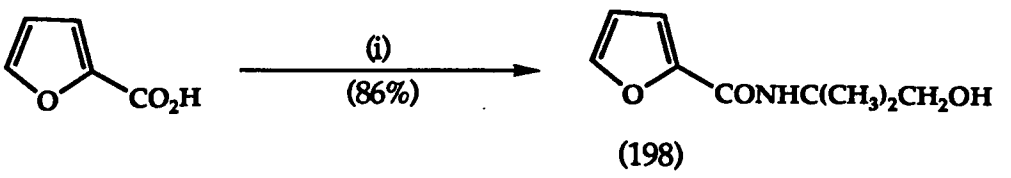


FIGURE 3.3

3.1.3.1 SYNTHESIS OF 4,4-DIMETHYL-2-(3-TRIMETHYLSILYLMETHYL-5-METHYL-2-FURYL)OXAZOLINE

4,4-Dimethyl-2-(2-furyl)oxazoline (**197**) was synthesised in high overall yield (77%) using the general method of Meyers,[133] from furan-2-carboxylic acid *via* conversion to the acid chloride, formation of the intermediate amide (**198**) and ring closure with thionyl chloride (Scheme 3.16).

Formation of the 5-methyloxazoline (**199**) was accomplished in excellent yield by treating the oxazoline (**197**) with LDA in the presence of TMEDA, followed by low temperature methylation with an excess of MeI. The use of an excess of MeI (5.0 equivalents) did not lead to any quaternisation of the oxazoline functionality (Scheme 3.17).



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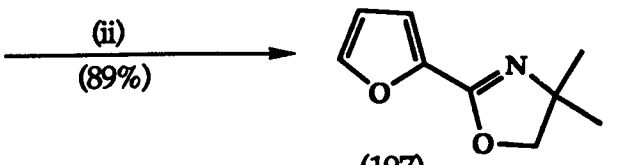
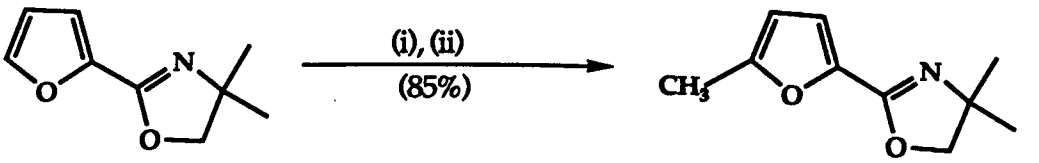


(197)

Reagents : (i) $SOCl_2$, $NH_2C(CH_3)_2CH_2OH$, CH_2Cl_2;

(ii) $SOCl_2$, $Ph\text{-}CH_3$

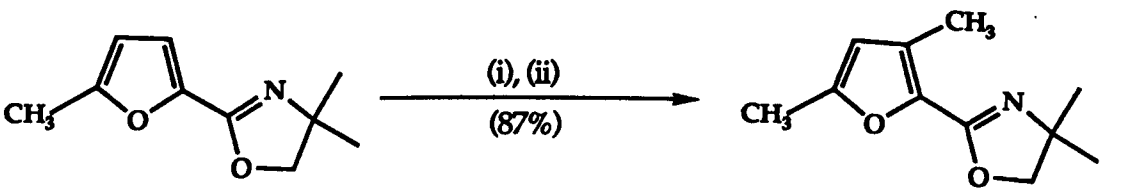
SCHEME 3.16



(197) (199)

Reagents : (i) 1.5 LDA, TMEDA, thf, -78°C, 1h; (ii) MeI

SCHEME 3.17



(199) (200)

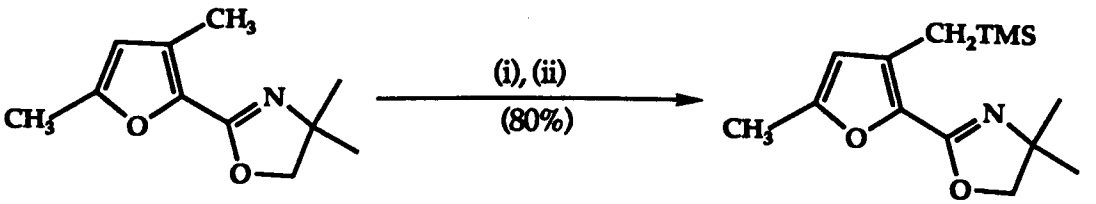
Reagents : (i) 1.5m $^{n}BuLi$, thf, -78°C, 0.5h;

(ii) MeI, -78°C for 0.5h, then room temperature

SCHEME 3.18

Treatment of the C5-methyl oxazoline (**199**) with $^{n}BuLi$ in thf followed by alkylation with MeI gave an excellent yield (87%) of the 3,5-dimethyloxazoline (**200**) (Scheme 3.18).

Conditions have been established for the regioselective lithiation and silylation into the C3-methyl group. Treatment of the dimethyl oxazoline (**200**) with ^{s}BuLi in thf at -78°C for half an hour, then warming the solution quickly to room temperature with subsequent TMSCl quench, gave an excellent yield (80%) of the silylated oxazoline (**201**) (Scheme 3.19). This lithiation



(200) (201)

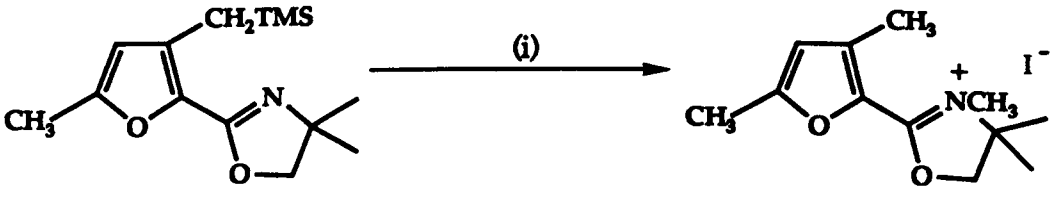
Reagents : (i) ^{s}BuLi, thf, -78°C, 0.5 h then warm quickly to room temperature; (ii) TMSCl (1.0 equivalent)

SCHEME 3.19

reaction is presumably via the "coordination-only" mechanism (the pK_a's of the C3- and C5-methyl protons would be expected to be similar). It was essential to warm the reaction mixture quickly to room temperature from -78°C before quenching with TMSCl, in order to achieve high levels of TMS-incorporation. Addition of this electrophile at -78°C led to poor levels of TMS incorporation (24% by ^{1}H nmr analysis).

It is interesting to note that for this furan derivative, benzylic deprotonation does occur. It is possible that the electron-withdrawing effect of the oxazoline functionality helps reduce the negative charge, thus stabilising the intermediate anion. In the case of the amido functionality, its electron-withdrawing capabilities are somewhat diminished due to it already containing a negative charge.

Treatment of the silylated oxazoline (**201**) with neat MeI at room temperature, showed no signs of quaternisation. Addition of acetonitrile as solvent, followed by refluxing for twenty-four hours led to quaternisation of the oxazoline functionality, but virtually total desilylation occurred yielding salt (**202**) (Scheme 3.20). These same reaction conditions have been applied prev-

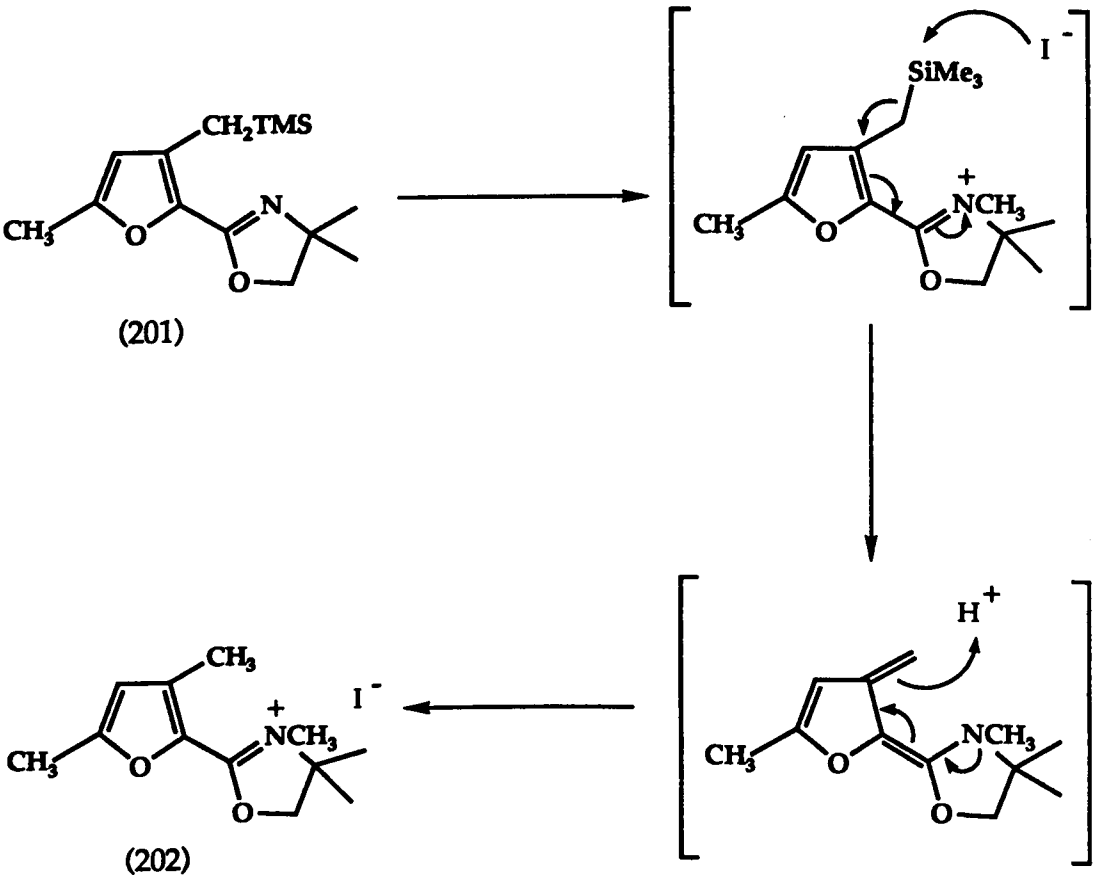


(201) (202)

Reagents : (i) MeI, CH_3CN, reflux 24h

SCHEME 3.20

iously to give excellent yields of the oxazolinium salt for the thiophene derivative, with no report of any desilylation.[130] It is possible that quaternisation of the silylated oxazoline (**201**) does occur, and that the TMS-group is displaced *via* nucleophilic attack by iodide ions with formation of an *o*-xylylene, which being highly reactive, abstracts a proton from the solvent (Scheme 3.21). Due to a shortage of time, no other alkylating agents (especially those with a less nucleophilic counter ion) were investigated. When a successful alkylating agent has been found, then a thorough study into *o*-xylylene generation can take place.



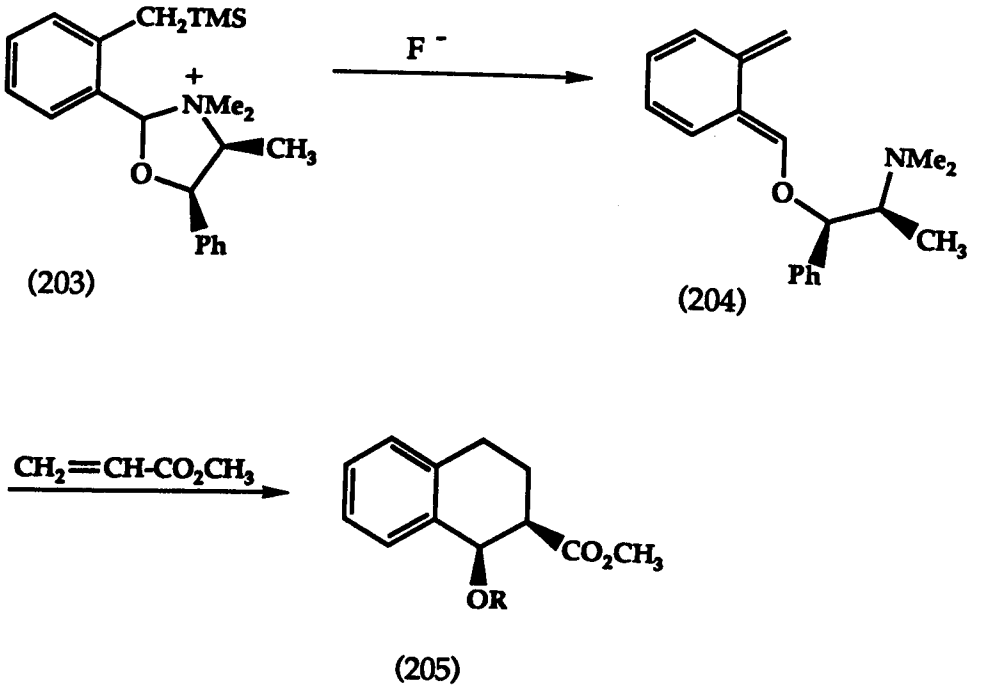
SCHEME 3.21

3.2 AN APPROACH TO A THIOPHENE ANALOGUE OF o-XYLYLENE

3.2.1 INTRODUCTION

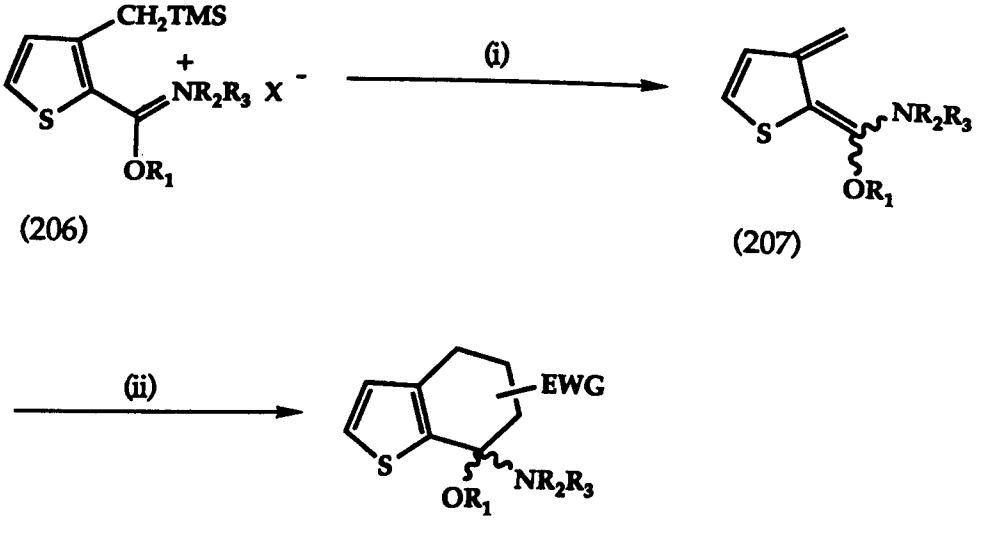
There have been no literature reports of asymmetric induction in Diels-Alder reactions involving thiophene analogues of o-xylylene bearing chiral auxiliaries. There has been limited studies carried out in the benzene series.

For example, Ito et al., have treated the oxazolidinium system (**203**) with fluoride ion to give o-xylylene (**204**) bearing a chiral auxiliary that partially controlled the stereochemistry of the subsequent addition of methyl acrylate.[134] Adduct (**205**) was formed with 33% diastereomeric excess (Scheme 3.22). The asymmetric induction was attributed to the ability of the chiral auxiliary to block one face of the o-xylylene or to specifically direct the dienophile to one face of the o-xylylene.



(203) (204) (205)

SCHEME 3.22



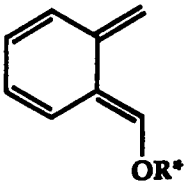
(206) (207)

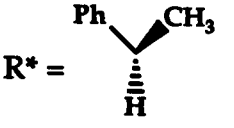
Reagents : (i) CsF; (ii) CH_2=CH-EWG

SCHEME 3.23

It was our aim to synthesise the o-xylylene precursor (**206**), and then to investigate the reactions of the o-xylylene (**207**) with various dienophiles (Scheme 3.23). If these reactions proved successful introduction of various chiral alkoxy groups

into the substrate (**206**, R_1 = chiral group) would open up the possibility of asymmetric induction in the Diels-Alder reaction involving o-xylylene (**207**). Charlton has previously demonstrated the usefulness of chiral alkoxy groups in controlling the stereochemistry in reactions of o-xylylene (**208**) with various dienophiles.[135]





(208)

The substrate (**206**) was to be synthesised using directed lithiation methodology. The approach is outlined in Figure 3.4, and involves the introduction of the trimethylsilyl group via a directed lithiation-silylation followed by transformation of the amide into an imidate salt via an imidoyl chloride intermediate.

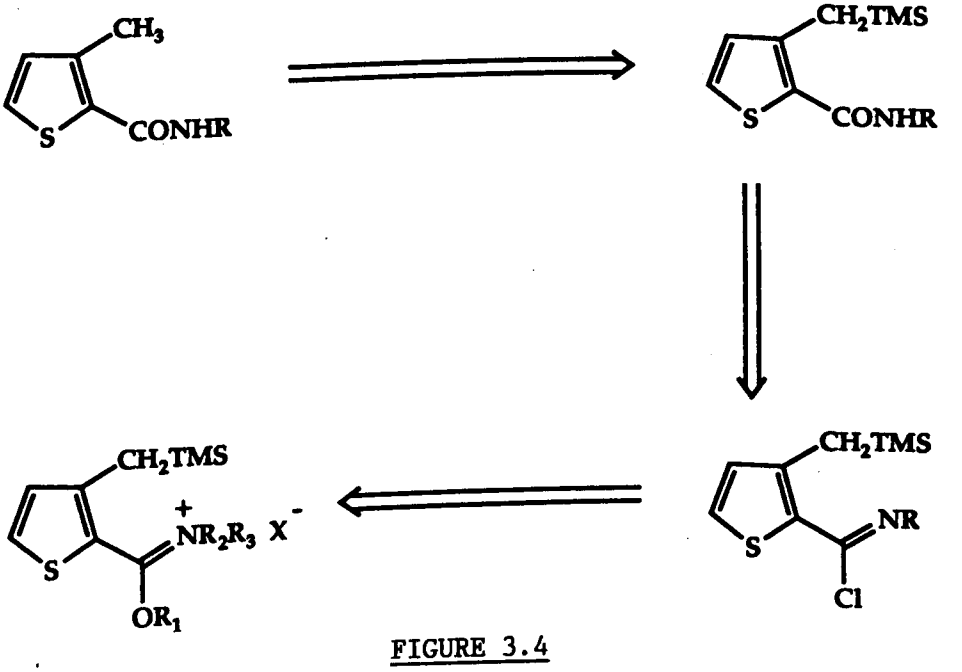


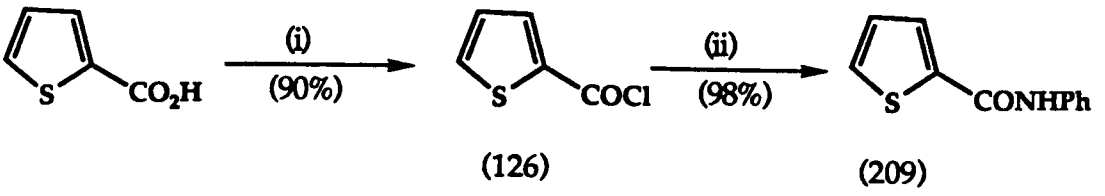
FIGURE 3.4

3.2.2 SYNTHESIS OF METHYL N-PHENYL-5-METHYL-3-^{t}BUTYLDIMETHYL SILYLMETHYL-5-METHYLTHIOPHENE-2-CARBOXIMIDATE (221)

The trimethylsilyl functionality was to be introduced into the C3-methyl group by means of a directed lithiation-silylation approach using a secondary amido moiety as the directing group. However, we have previously demonstrated that it is not viable to use the N-^{t}butyl or N-1-adamantyl derivatives (proven ortho-directed lithiation groups) as they undergo the von Braun reaction on heating in thionyl chloride in preference to forming their respective imidoyl chlorides (see Section 2.6), which are required for the next stage of the reaction pathway. Nor was it viable to use the N-methyl derivative as this secondary amide requires extending refluxing times in $SOCl_2$ to form its imidoyl chloride. Such vigorous conditions were deemed incompatible with the incorporated trialkylsilyl group. Therefore, an alternative secondary amido functionality was sought. The N-phenyl secondary amide group was chosen as an ideal candidate. Although, not a proven ortho-directed lithiation group in the thiophene case, it has previously been demonstrated to be excellent in the benzene series.[1] This secondary amido functionality also can be transformed readily into its imidoyl chloride derivative.

Firstly, it was necessary to establish the ortho-directing capabilities of N-phenylthiophene-2-carboxamide (**209**). This amide was prepared in excellent overall yield (88%) from thiophene-2-carboxylic acid via its acid chloride (**126**) (Scheme 3.24).

ortho-Lithiation was effected quantitatively by treating the amide with ^{n}BuLi in thf followed by D_2O quench (Scheme 3.25).

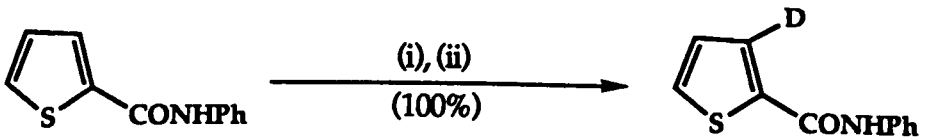


(126) (209)

Reagents : (i) $SOCl_2$, reflux, 5h;

(ii) $PhNH_2$, CH_2Cl_2, room temperature, 12h

SCHEME 3.24



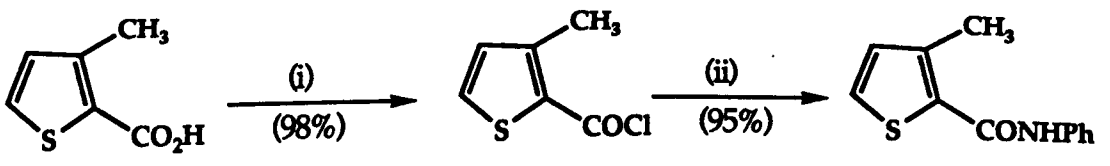
(209) (210)

Reagents : (i) 2.2 $^{n}BuLi$, thf, -78°C, 1h; (ii) D_2O

SCHEME 3.25

This reaction demonstrates this particular secondary amido group (strictly the amidate anion) to be an effective directing group.

It was then important to establish whether or not this functionality would direct lithiation regioselectively into a C3-methyl group. N-Phenyl-3-methylthiophene-2-carboxamide (213) was synthesised from 3-methylthiophene-2-carboxylic acid (211) in excellent overall yield (93%) via acid chloride (212) (Scheme 3.26).



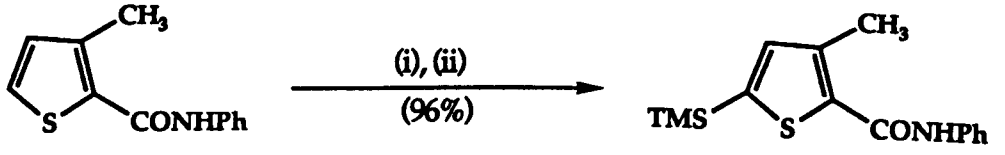
(211) (212) (213)

Reagents : (i) $SOCl_2$, reflux, 4h;

(ii) $PhNH_2$, CH_2Cl_2, Et_3N, room temperature, 12 h

SCHEME 3.26

Treatment of amide (**213**) with ^{n}BuLi in thf at 0°C for half an hour, followed by quenching with TMSCl yielded only C5-silylated product (**214**) (Scheme 3.27). These exact reaction



(213) (214)

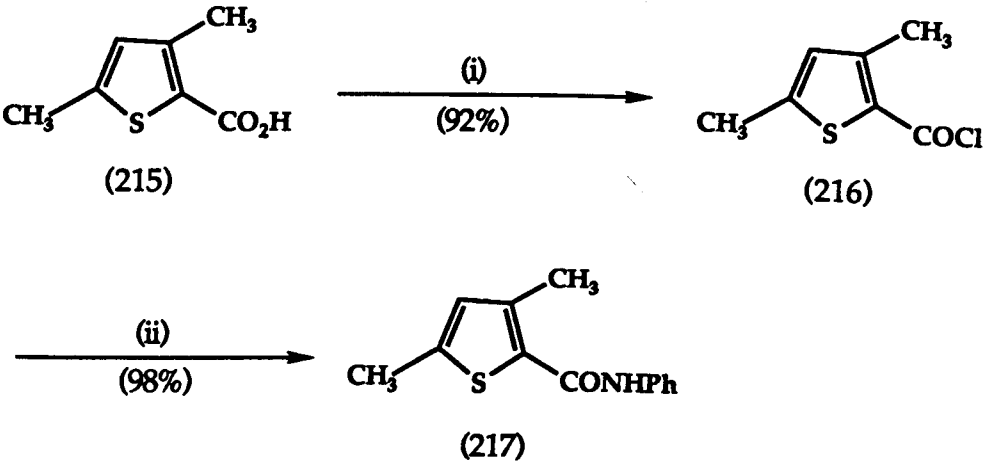
Reagents : (i) 2.2 ^{n}BuLi, thf, 0°C, 0.5h; (ii) TMSCl

SCHEME 3.27

conditions have been shown to lead to high levels of benzylic substitution for the corresponding N-^{t}butyl secondary amido derivative of thiophene. Therefore, the N-phenyl secondary amido functionality is not as effective a director of lithiation as the N-^{t}butyl secondary amido group.

The problem of α-lithiation was circumvented by employing a methyl blocking group into the C5-position. N-Phenyl-3,5-dimethylthiophene-2-carboxamide (**217**) was prepared in excellent overall yield (90%) from 3,5-dimethylthiophene-2-carboxylic acid (**215**) via acid chloride (**216**) (Scheme 3.28).

Treatment of amide (**217**) with ^{n}BuLi in thf at -20°C for half an hour, followed by quenching with TMSCl, gave the silylated secondary amide (**218**) as a stable, yellow immobile oil (80%) (Scheme 3.29). However, all attempts at forming an imidoyl chloride from amide (**218**) proved unsuccessful, yielding intractable products, which showed appreciable desilylation by ^{1}H nmr (Scheme 3.30).

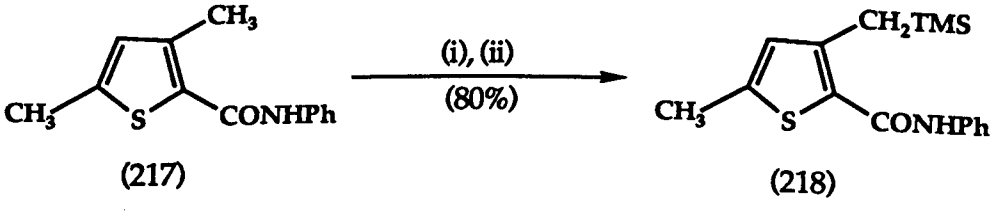


(215) (216) (217)

Reagents : (i) $SOCl_2$, reflux, 6h;

(ii) $PhNH_2$, CH_2Cl_2, room temperature, 12h

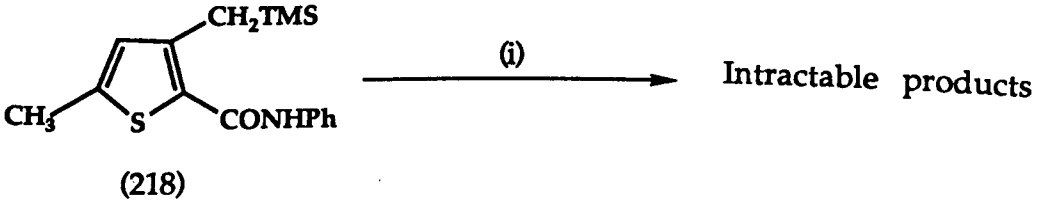
SCHEME 3.28



(217) (218)

Reagents : (i) 2.0 $^{n}BuLi$, thf, -20°C, 0.5h; (ii) TMSCl

SCHEME 3.29

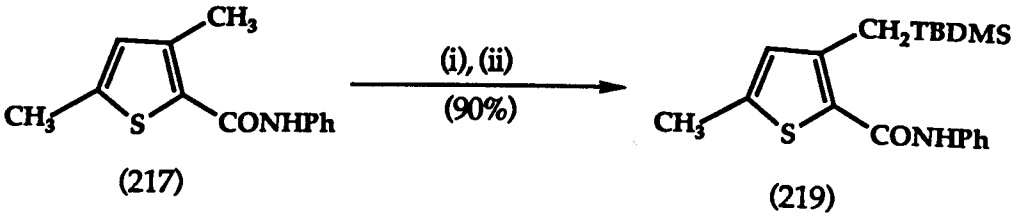


(218)

Reagents : (i) $SOCl_2$, heat, 3h

SCHEME 3.30

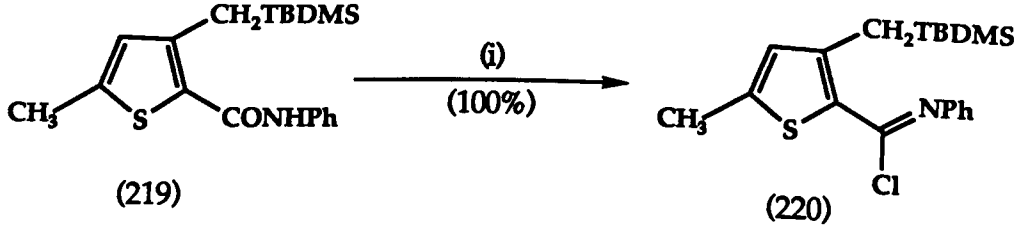
This problem was overcome by using the ^{t}butyldimethylsilyl-derivative (**219**) obtained in high yield (90%) by quenching the dianion with TBDMSCl (Scheme 3.31).



(217) (219)

Reagents : (i) 2.1 ^{n}BuLi, thf, -20°C, 0.5h; (ii) TBDMSCl

SCHEME 3.31



(219) (220)

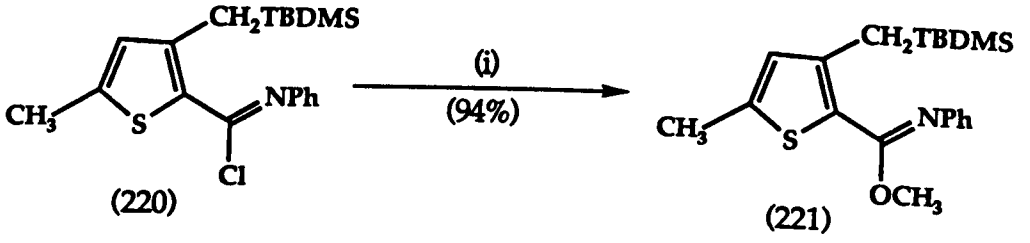
Reagents : (i) $SOCl_2$, reflux, 3h

SCHEME 3.32

Treatment of the silylated amide (**219**) with thionyl chloride under reflux for three hours gave the silylated imidoyl chloride (**220**) quantitatively, as a lachrymatory, red immobile oil (Scheme 3.32). This was a very clean reaction and no desilylation was observed.

This imidoyl chloride (**220**) is a highly reactive species, and conversion to the imidate (**221**) (94%) with sodium methoxide in methanol (Scheme 3.33) was encouraging for the proposed introduction of chiral alkoxides.

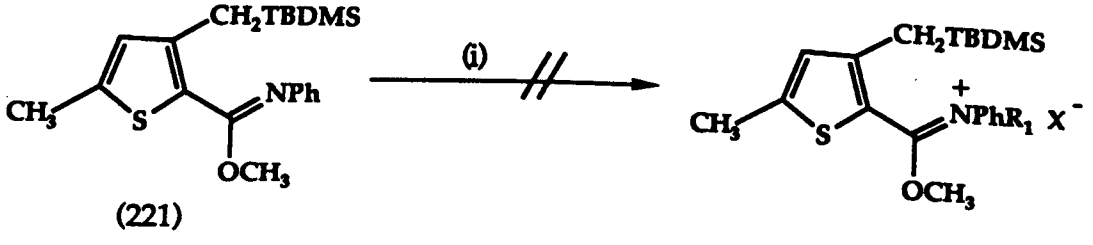
However, the final step, quaternisation of the silylated imidate (**221**) with a variety of alkylating agents including MeI, ^{n}BuBr, $ClCO_2CH_3$ and $Et_3O^{+}BF_4^{-}$ proved unsuccessful and starting material was recovered each time (Scheme 3.34). Imidate (**221**) cannot be effectively quaternised, presumably due to the electron



Reagents : (i) NaOMe, MeOH, thf,

0°C for 1h then room temperature

SCHEME 3.33



Reagents : (i) R_1-X

R_1X = MeI, ^nBuBr, $Et_3O^+BF_4^-$ and $ClCO_2CH_3$

SCHEME 3.34

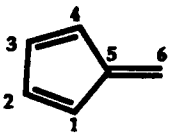
density on the nitrogen atom being somewhat reduced by the inductive effect of the phenyl ring. Because of this failure to quaternise the imidate functionality all further attempts on forming o-xylylene precursor (**206**) were discontinued.

CHAPTER 4

4.0 AZAFULVENES

4.1 INTRODUCTION

Azafulvenes are formally derived by replacement of one or more of the C-atoms, 1 - 4 of the fulvene nucleus (222) with N atoms.



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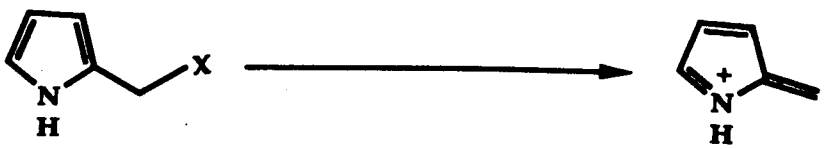
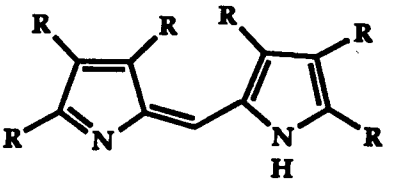


(223)

SCHEME 4.1

Azafulvenes and azafulvenium salts are widely implicated as intermediates in the substitution reactions of compounds of the type (223), possessing a leaving group (Scheme 4.1). Relatively few derivatives have been isolated and these are limited to those systems which are stabilised by substituents (usually phenyl groups). Some of the best characterised examples of the azafulvene system are the highly coloured 2,2'-dipyrromethenes (224),[136] which are important intermediates in the synthesis of porphyrins.

The objective of this particular work was to produce some simple azafulvenes, under conditions where their reactivity could be investigated systematically. The existing literature on azafulvene and azafulvenones are briefly reviewed in Sections 4.1.1 - 4.1.3.

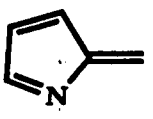


(224)

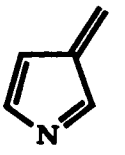
4.1.1 MONOAZAFULVENES

4.1.1.1 STRUCTURE AND REACTIVITY

The parent 1- and 2-azafulvenes (225) and (226) respectively are hitherto unknown, presumably because of their high reactivity.

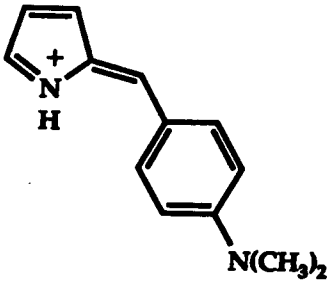


(225)



(226)

The stability of these systems and their salts depends greatly on the types of substituents on the five-membered ring or at the C6-position. For example, the 6-aryl-azafulvenium salt (227) (formed in the well established Ehrlich test for pyrroles[137-139]) is found to be reasonably stable. The stability of its corresponding free base, however, is extremely pH dependent and attempts towards its isolation generally result in polymerisation.[138-139] 6,6-Diphenyl-1-azafulvene (228) is stable and the 2,4-diphenylazafulvenes (229) - (231) are stable solids, in contrast to the corresponding 2,4-dimethyl compounds which are



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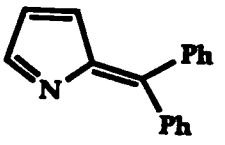
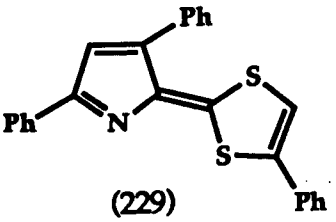
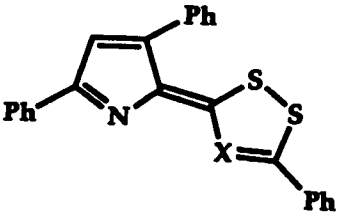


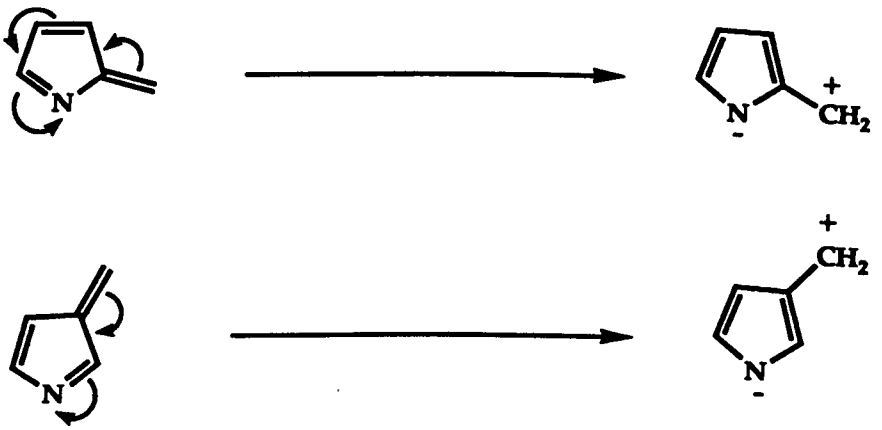
(228)



(229)



(230) when x = CH
(231) when x = N

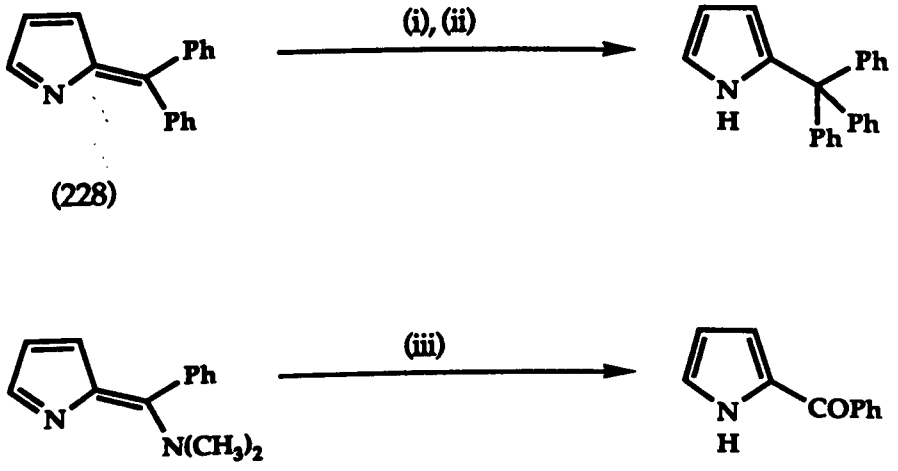


SCHEME 4.2

only stable in solution.[140-141] The stabilities of the analogous 2-azafulvenes are low. Resonance stabilisation of the type outlined in Scheme 4.2 should be important in the azafulvene systems and this is supported by spectroscopic data (mainly

ultraviolet absorption maxima). The high dipole moment of 2.06D for 6,6-diphenyl-1-azafulvene (**228**)[142] is good evidence that the contributions of the dipolar canonical forms to the ground state structure of the 1-azafulvene system are significant. The generally high reactivity of these systems towards nucleophilic attack at the C6-position supports this picture.

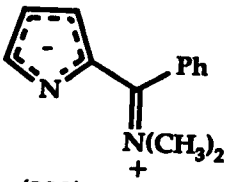
Substituents at the C6-position greatly influence the reactivity of the azafulvenes. For example, 6,6-diphenyl-1-azafulvene (**228**) is stable (due to conjugation) and reacts comparatively slowly with strong nucleophiles. However, 6-(N,N-dimethylamino)-6-phenyl-1-azafulvene (**232**) has been shown to be highly susceptible to nucleophilic attack at the C6-position (Scheme 4.3).[143] This result seems surprising because the



Reagents : (i) PhLi; (ii) H_2O; (iii) OH^-/H_2O

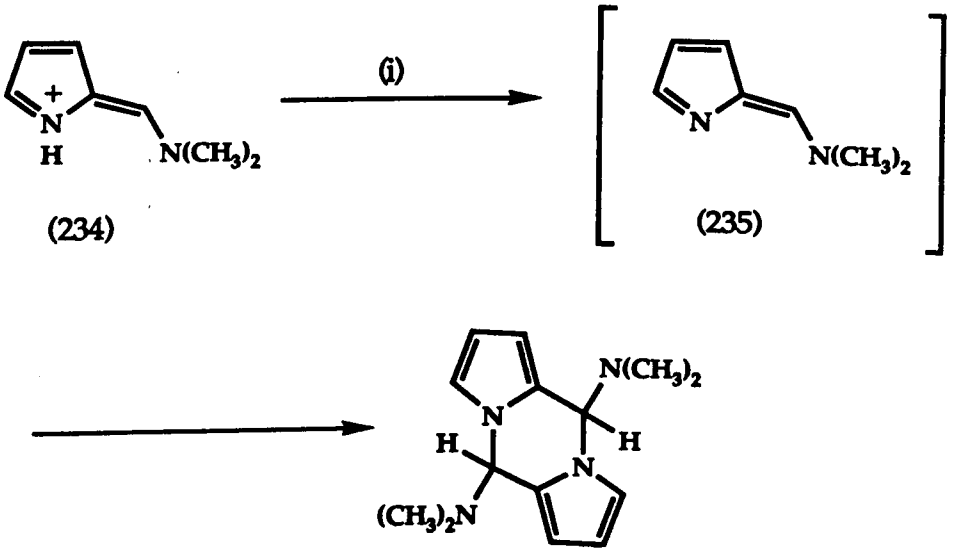
SCHEME 4.3

electron-donating $-NMe_2$ group would be expected to stabilise the azafulvene system via the extra dipolar canonical structure (**233**), and no explanation was given for this apparent anomalous behaviour.



(233)

In the absence of a C6-phenyl group, the reactivity of the azafulvene system appears to be extremely high. For example, the 1-protonated salt (**234**) is an intermediate of the Vilsmaier-Haack formylation of pyrrole and although formation of the base (**235**) can be observed in solution when the salt is treated with triethylamine, attempts at its isolation result in a 1,3-dipolar dimerisation to give (**236**) (Scheme 4.4).[143-145]



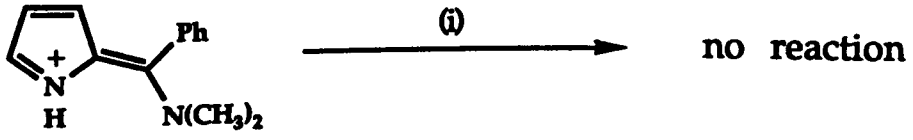
(234) (235) (236)

Reagents : (i) Et_3N

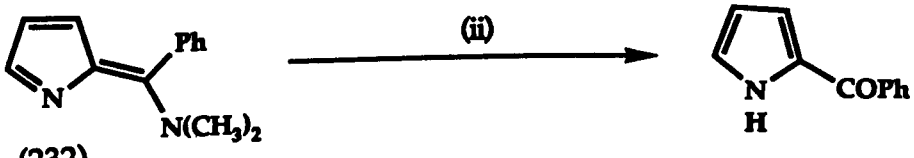
SCHEME 4.4

Protonation of the azafulvenes occurs on the heteroatom to give their corresponding salts, which are generally more stable than the bases. Jones has reported that, somewhat surprisingly,

the salts appear to be less susceptible than their bases towards nucleophilic attack at the C6-position. He quotes as evidence, the fact that 6-(N,N-dialkylamino)-6-phenyl-1-azafulvenium salts (237) are soluble in water without decomposition, whereas the conversion of the corresponding base (232) into 2-benzoylpyrrole occurs at room temperature in "wet" dichloromethane (Scheme 4.5).[143] The author does not give any explanation for this



(237)



(232)

Reagents : (i) H_2O; (ii) "wet" CH_2Cl_2

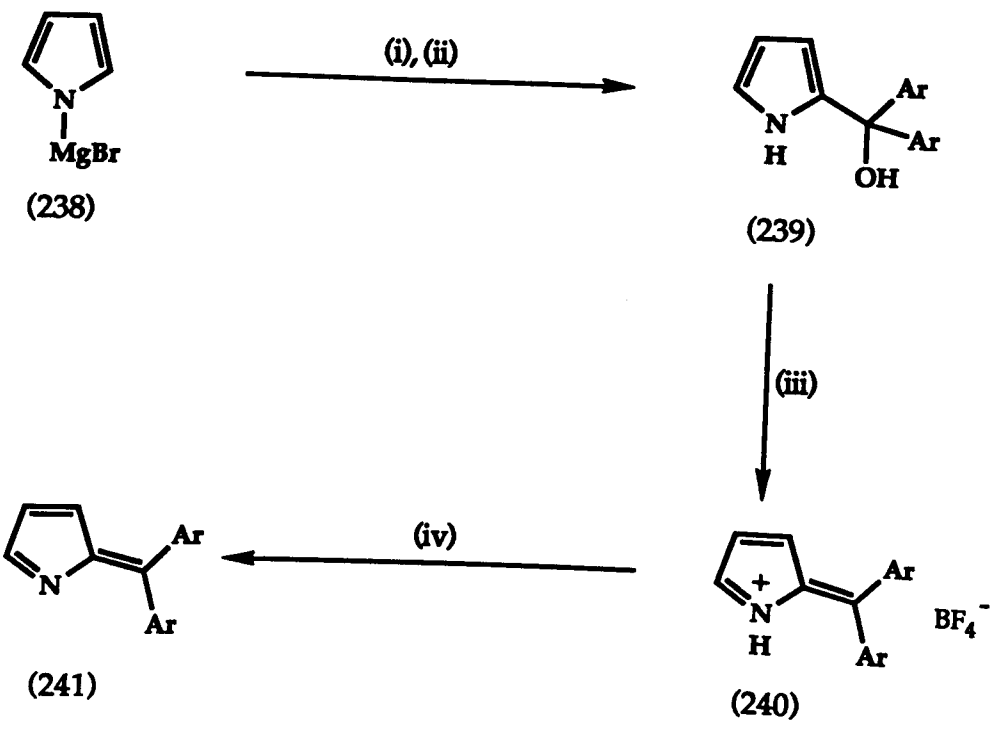
SCHEME 4.5

"apparent" anomaly and insufficient experimental details were given to warrant further speculation here.

4.1.1.2 SYNTHESIS OF MONOAZAFULVENE SYSTEMS

In this section, the syntheses of some of the more common azafulvene derivatives are described.

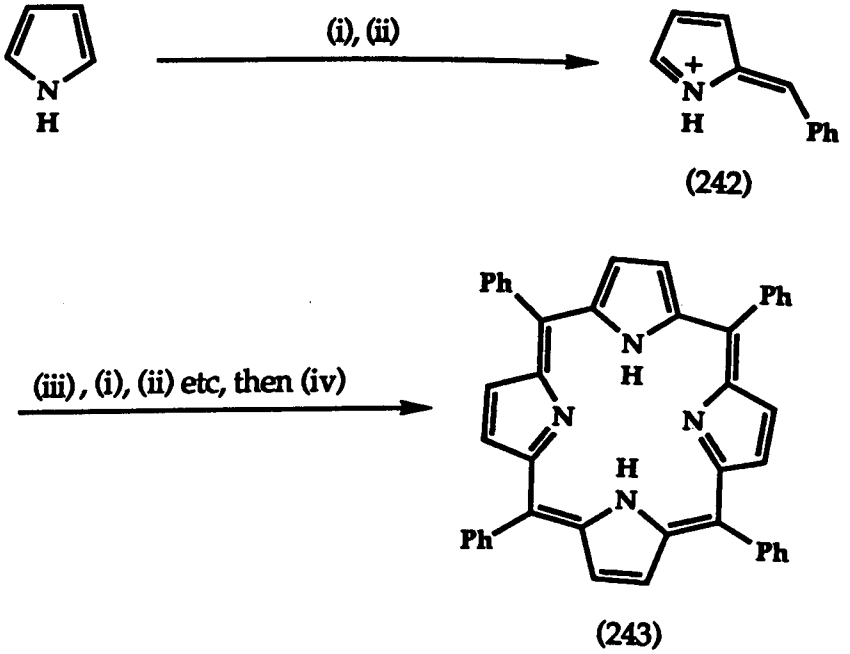
6,6-Diaryl-1-azafulvenium salts (240) are obtained *via* the diaryl-2-pyrrylcarbinols (239), by the reaction of pyrrylmagnesium bromide (238) with the appropriately substituted benzophenones. Conversion of the salts into the bases (241) is effected on reaction with triethylamine (Scheme 4.6).[142-143]



Reagents : (i) ArCOAr; (ii) H_2O; (iii) HBF_4; (iv) Et_3N

SCHEME 4.6

Treatment of pyrrole with benzaldehyde and acid initially gives the azafulvenium salt (242), which reacts readily with more pyrrole and benzaldehyde to eventually give, on oxidation, the tetraphenylporphyrin (243) in low yield (Scheme 4.7).[152]



Reagents : (i) PhCHO; (ii) H_3O^+; (iii) Pyrrole; (iv) air

SCHEME 4.7

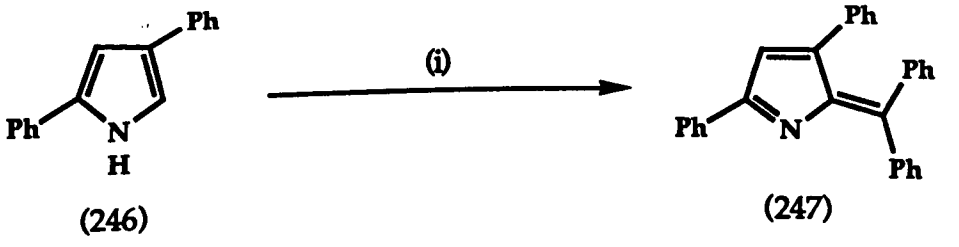
Treatment of 2-lithio-1-methylpyrrole (**244**) with various substituted benzophenones yielded the corresponding 1-methyl-1-azafulvenium salts (**245**) (Scheme 4.8).[143]

(244) (245)

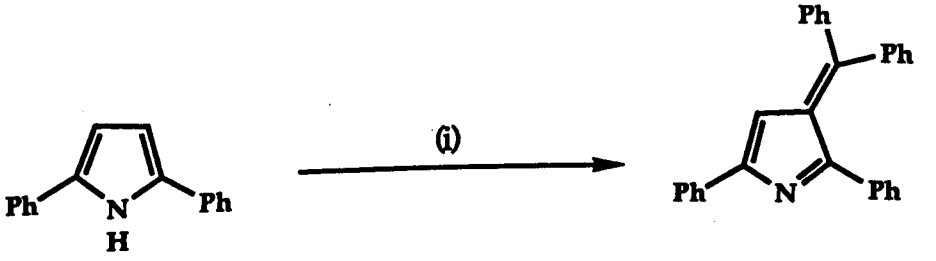
Reagents : (i) ArCOAr; (ii) HBF_4

SCHEME 4.8

The isomeric 6,6-diphenylazafulvenes (**247**) and (**249**) have also been synthesised, by heating diphenyldichloromethane under reflux with 2,4- and 2,5-diphenylpyrrole (**246**) and (**248**) respectively (Scheme 4.9).[140]



(246) (247)



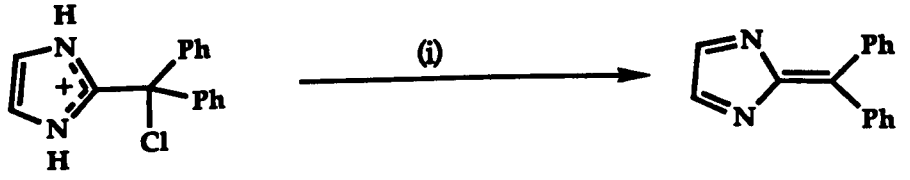
(248) (249)

Reagents : (i) Ph_2CCl_2, reflux

SCHEME 4.9

4.1.2 DI- AND TRIAZAFULVENES

There have been few reports in the literature concerning the chemistry of di- and triazafulvenes. Rohr and Staab reported 6,6-diphenyl-1,4-diazafulvene (**251**), a stable crystalline solid, to be the first diazafulvene.[146] This was produced by the elimination of hydrogen chloride from the salt (**250**) (Scheme 4.10).

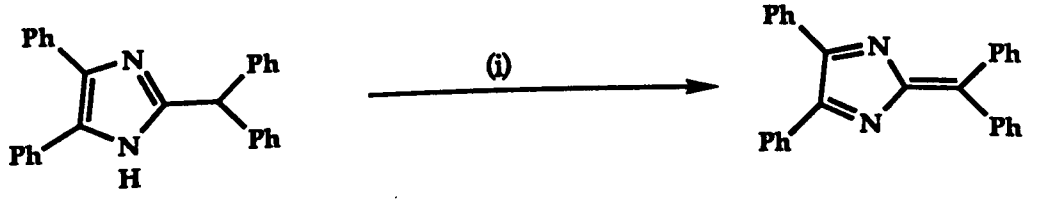


(250) (251)

Reagents : (i) Et_3N

SCHEME 4.10

Hill later reported the synthesis of various substituted 1,4-diazafulvenes and investigated their spectroscopical properties.[147] For example, diazafulvene (**253**) was prepared readily from (**252**) *via* an oxidation reaction using lead dioxide (Scheme 4.11).

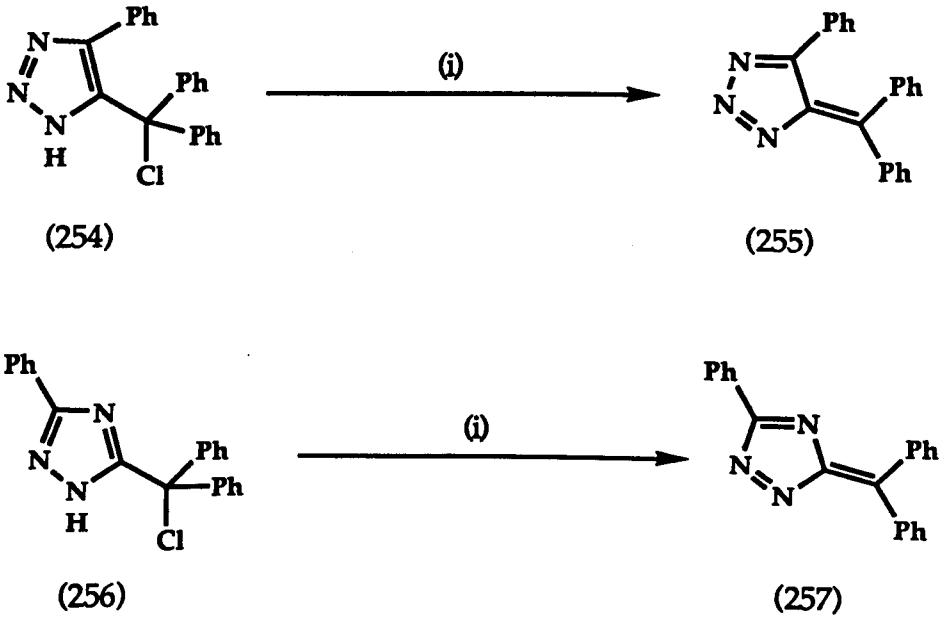


(252) (253)

Reagents : (i) PbO_2

SCHEME 4.11

Burgess and Sanchez have synthesised and briefly investigated the chemistry of some triazafulvenes.[148] These workers synthesised the 1,2,3-triazafulvene (**255**) and the 1,2,4-triaza-



Reagents : (i) Et_3N, thf/benzene, -78°C

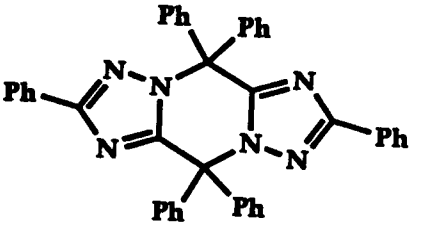
SCHEME 4.12

fulvene (257) via the dehydrohalogenation of (254) and (256) respectively, in the presence of triethylamine in thf/benzene at -78°C (Scheme 4.12). These triazafulvenes were stable in this solvent combination for up to eight hours at -78°C. The ring phenyl group was crucial to improving their stability, without it they rapidly decomposed.

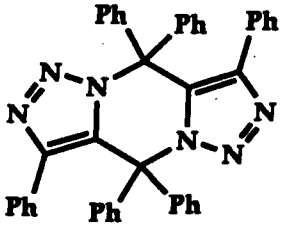
Treatment of (255) and (257) with methanol occurred slowly to yield their respective (methoxydiphenylmethyl)phenylazoles (258) and (259).

(258) (259)

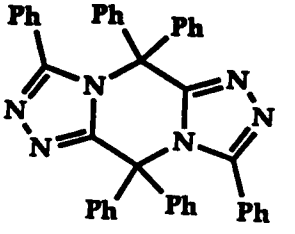
If allowed to warm to 30°C in solution, fulvenes (255) and (257) dimerised giving the products (260) and either (261) or (262) respectively (the latter two products being indistinguishable with the available spectral data).



(261)



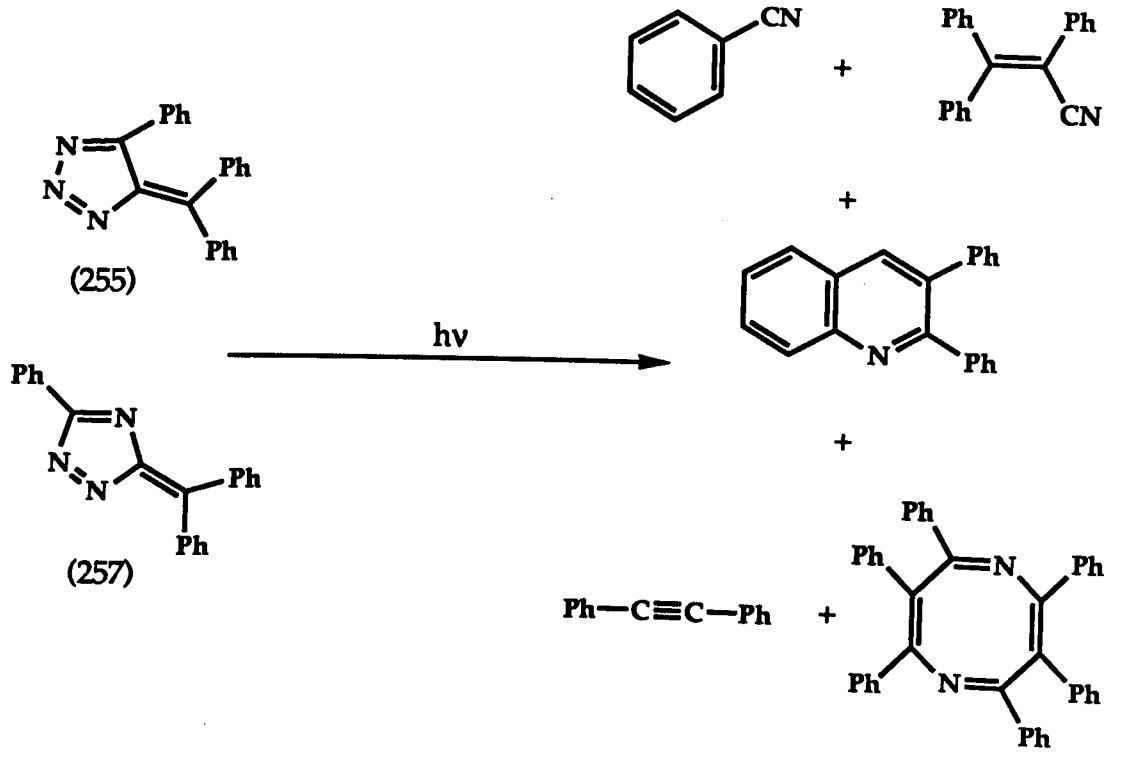
(260)



(262)

It was found that the 1,2,4-triazafulvene system (257) was more stable than its 1,2,3-isomer (255). HMO theory reveals a greater π-charge density at position 1,4 relative to 2,3 in the highest occupied molecular orbital of the reference hydrocarbon, fulvene. Thus, the authors suggest that heteroatom replacement at 1,4 is more effective than at 2,3 in increasing resonance energy, and therefore the 1,2,4 congener is more stable.

Irradiation of thf-benzene solutions of the triazafulvenes (255) or (257) at -78°C, led to the elimination of nitrogen and the formation of a mixture of isolable products, which involved azete and azatriafulvene as possible unstable precursors (Scheme 4.13).

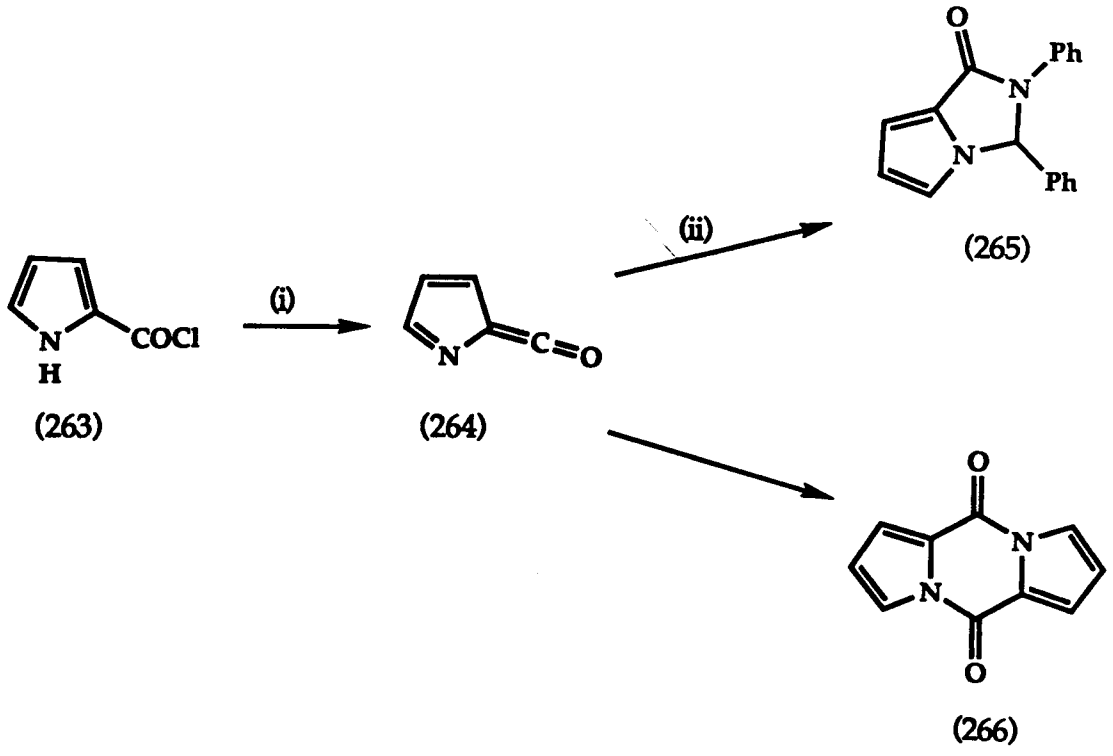


SCHEME 4.13

4.1.3 AZAFULVENONES

There have been some preliminary investigations into the chemistry and reactivity of azafulvenones. Whitlock first postulated the generation of the 1-azafulven-6-one (**264**), in the base-induced elimination reaction of pyrrole-2-carbonyl chloride (**263**).[149] In the absence of a trapping agent, the ketene dimer (**266**) was obtained. Repeating the reaction in the presence of benzalaniline, adduct (**265**) was formed in 62% yield (Scheme 4.14).

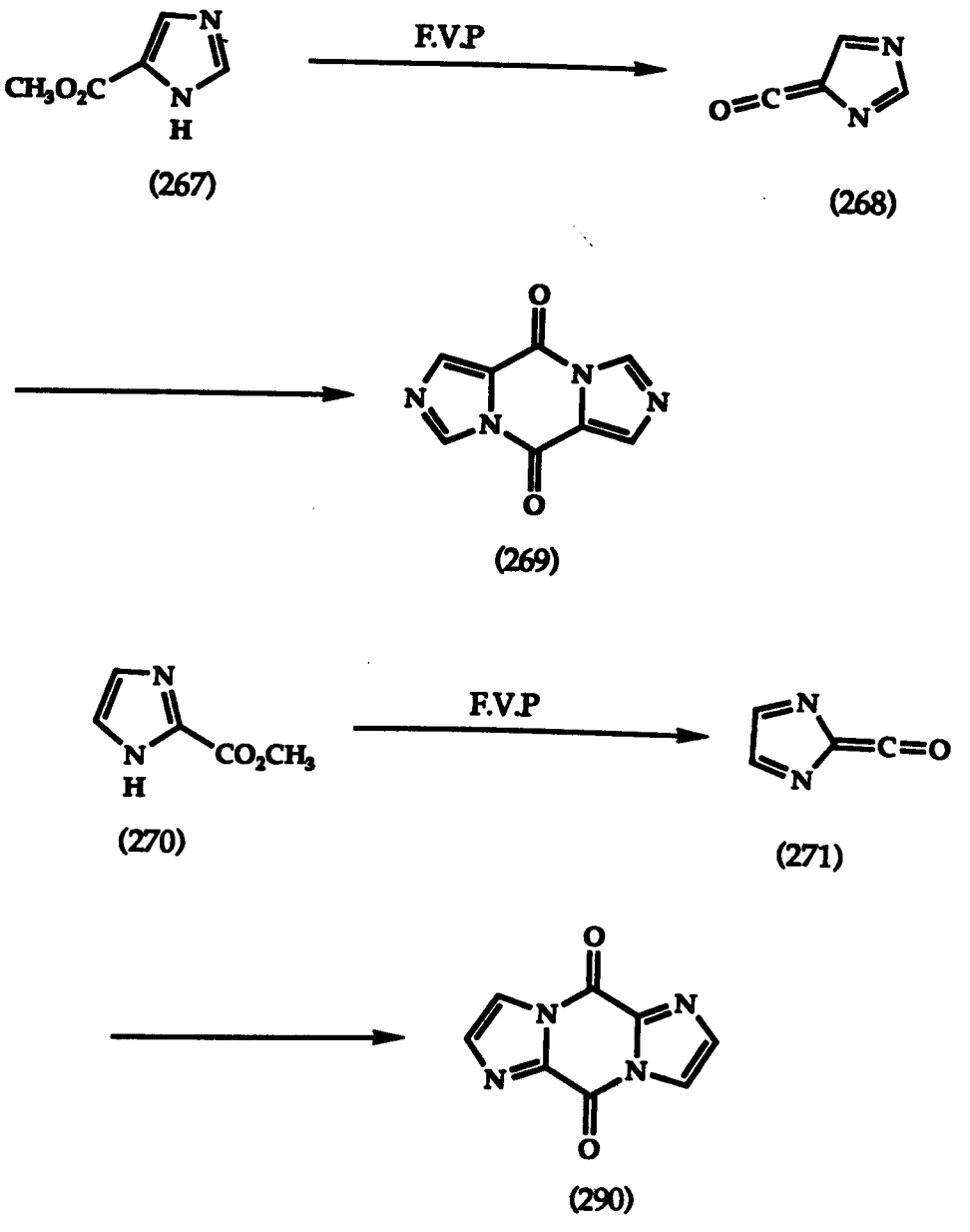
Wentrup also generated the 1-azafulven-6-one *via* the flash vacuum pyrolysis of pyrrole-2-carboxylic acid and its methyl ester.[150] The azafulvenone (**264**) was directly observed by infrared and mass spectrometry (providing evidence for its existence), trapped with methanol which regenerated the starting material and isolated in the form of dimer (**266**). Wentrup *et*



Reagents : (i) Et_3N; (ii) PhCH=NPh

SCHEME 4.14

al., have also generated the 1,3- and 1,4-diazafulvenones (**268**) and (**271**), via the FVP of methyl 4- and 2-imidazolecarboxylates (**267**) and (**270**) respectively, and monitored these pyrolyses with low-temperature infrared and high-temperature mass spectrometry.[151] They found that (**268**) and (**271**) dimerised to the diketopiperazines (**269**) and (**290**) respectively (Scheme 4.15).



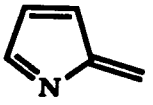
(267) (268) (269) (270) (271) (290)

SCHEME 4.15

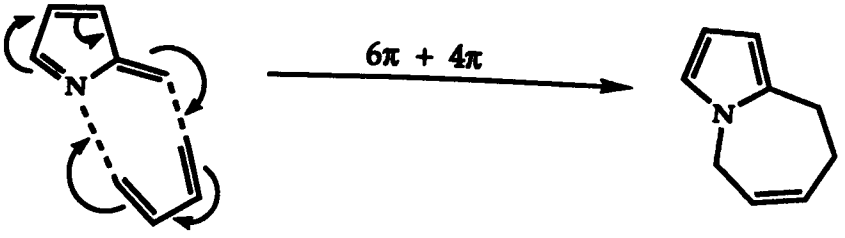
4.2 FLASH VACUUM PYROLYTIC GENERATION OF AZAFULVENES

4.2.1 1-AZAFULVENES

Our initial aim was to generate the parent 1-azafulvene (**225**) under conditions such that it could be isolated and subjected to various reactions. Flash vacuum pyrolytic elimination with isolation at low temperatures was therefore our preferred approach. In particular, we hoped to explore its reactivity in cycloaddition reactions. In principle, the



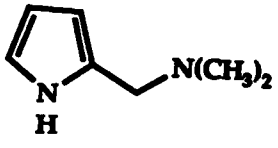
(225)



SCHEME 4.16

heterofulvenes can function as 2π, 4π or 6π systems. For example, the addition of a 4π-diene or a 1,3-dipole across the 1,6-position is allowed and geometrically feasible, has precedent in the case of fulvenes, and would provide a simple route to a wide variety of fused heterocycles (Scheme 4.16).

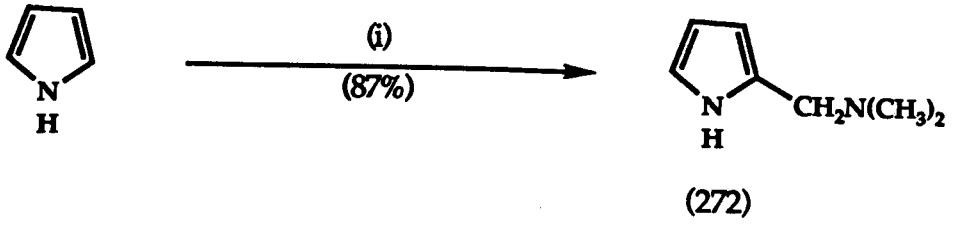
The 2-dimethylaminomethylpyrrole (272) was chosen for our initial investigations. This compound (272) was synthesised in



(272)

excellent yield (87%) from pyrrole <u>via</u> a Mannich type reaction, employing the conditions reported by Herz, Dittmer and Cristol (Scheme 4.17).[153]

2-Dimethylaminomethylpyrrole (272) was pyrolysed at 650°C/2 x 10^{-3} torr and the products were condensed on to a cold finger

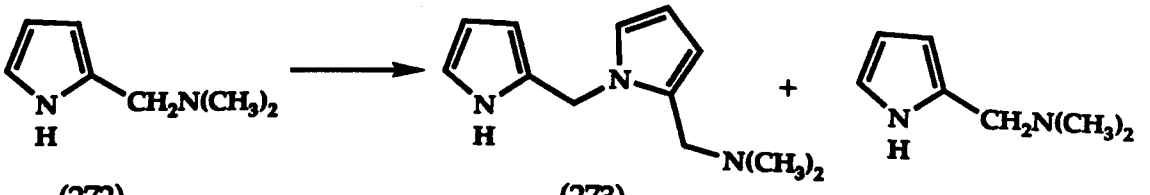


(272)

Reagents : (i) CH_2O (40% solution), $Me_2NH \cdot HCl$, < 60°C

SCHEME 4.17

at -78°C. The pyrolysate was then allowed to warm to room temperature. ^1H Nmr analysis indicated the presence of recovered starting material (272) together with another product (in a ratio of 1:1) which was assigned as the "dimer" (273).[154] Repeating this pyrolysis onto a cold finger at -196°C, yielded predominantly starting material (272) together with a trace of the "dimer" (273) (in a ratio of ~ 5.8:1) (Scheme 4.18).

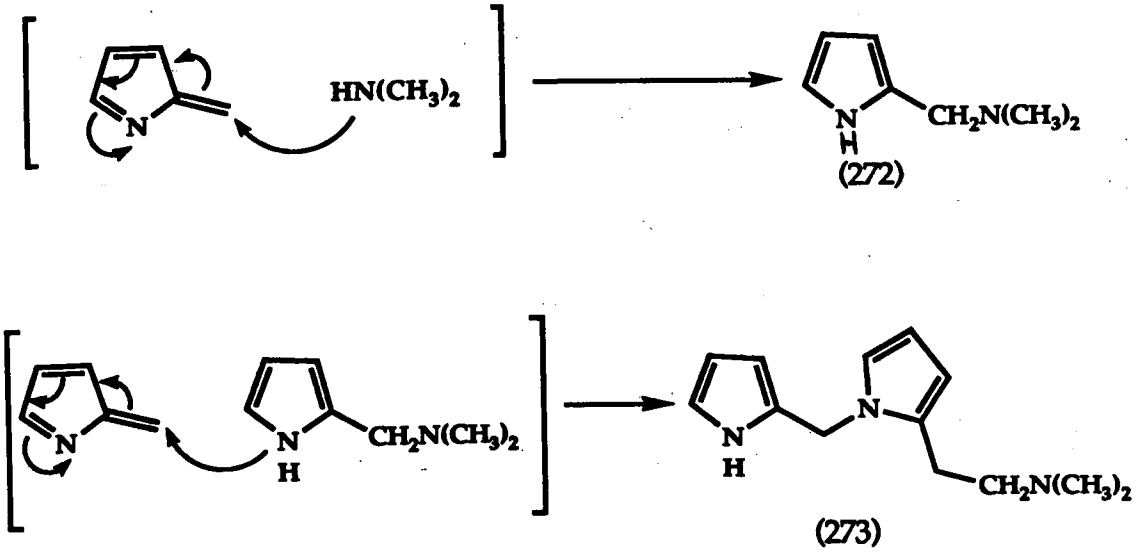


(272) (273) (272)

SCHEME 4.18

Initially, it was presumed that the majority of the Mannich base (272) had passed unchanged along the pyrolysis tube, the origins of the "dimer" was not clear.

However, after further consideration of these results we speculated that elimination of dimethylamine to produce the azafulvene might have occurred followed by readdition of dimethylamine to regenerate (272) as the cold finger warmed to room temperature. This would also explain the formation of the "dimer" (273), which could be due to the reaction of the azaful-



SCHEME 4.19

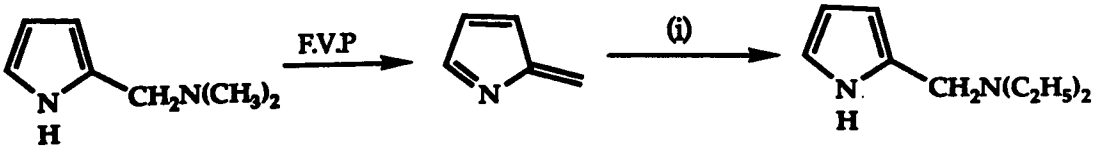
vene with starting material regenerated on the cold finger (Scheme 4.19).

When the cold finger is at -196°C it can be assumed that the majority of the eliminated dimethylamine is retained on the cold surface, which re-adds to the azafulvene on warming to room temperature. When the cold finger is at -78°C, some of the dimethylamine (m.p., -93°C) "escapes" from the cold surface and so on warming to room temperature, the reaction of the azafulvene with starting material, forming "dimer" (273), becomes more competitive.

To confirm this, the pyrolysis procedure was repeated employing a highly reactive nucleophile (to compete with the dimethylamine for nucleophilic addition to the azafulvene) as a co-condensate.

2-Dimethylaminomethylpyrrole (272) was pyrolysed (650°C/2 x 10^{-3} torr) and co-condensed with a large excess of diethylamine on to the cold surface (-78°C), the nucleophile being introduced after the pyrolysis zone just prior to the condensation surface.

The pyrolysate was allowed to warm to room temperature and the diethylamine was removed in vacuo. ^{1}H Nmr analysis indicated the formation of 2-diethylaminomethylpyrrole (274) in excellent yield (94%) along with a trace of starting material (272) (6%) (Scheme 4.20). This result provides more evidence for the formation of the parent 1-azafulvene.



(272) (225) (274)

Reagents : (i) Et_2NH

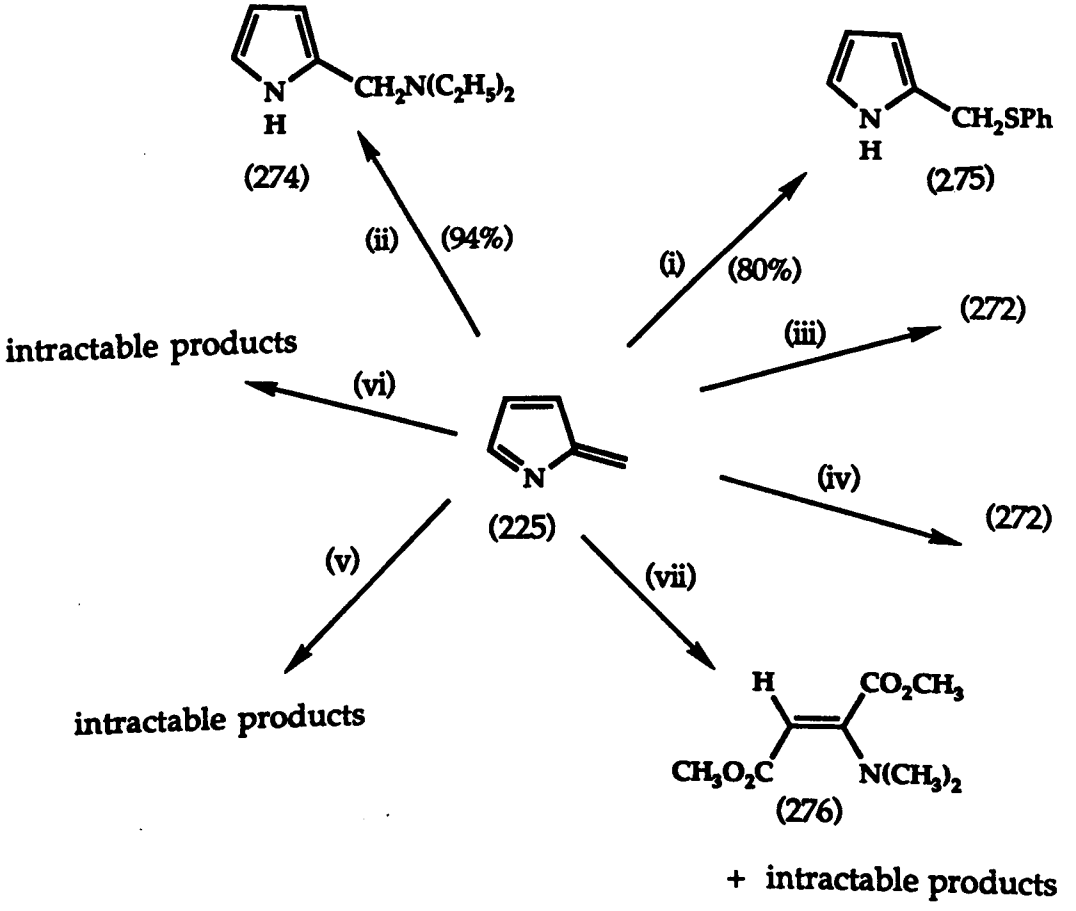
SCHEME 4.20

To prove this reaction was not just a nucleophilic substitution reaction (272) was stirred with an excess of diethylamine for three hours at room temperature (conditions more severe to those reached on the cold finger). No 2-diethylaminomethylpyrrole (274) was obtained.

Further evidence that the 1-azafulvene is an intermediate, with an appreciable lifetime was obtained by pyrolysing (272) on to a cold finger (-196°C) with co-condensation of dichloromethane. After pyrolysis, the dichloromethane (containing pyrolysate) was allowed to melt (~ 97°C) and to run off the cold finger into a solution of diethylamine (20 ml) and dichloromethane (20 ml) at -78°C. The reaction was stirred for half an hour and allowed to reach room temperature. ^{1}H Nmr analysis indicated the presence of 2-diethylaminomethylpyrrole (274) and 2-dimethylaminomethylpyrrole (272) in a ratio of 1:1. In this

instance, the yield of (274) is somewhat reduced, due to the eliminated dimethylamine re-adding on to the azafulvene as the pyrolysate dripped off the cold finger.

With the pyrolysis conditions (650°C/2 x 10^{-3} torr) established for the formation of 1-azafulvene, various nucleophiles, electrophiles, a diene and a dienophile were employed as co-condensates (Scheme 4.21). The yields reported are as judged by ^{1}H nmr analysis.



Reagents : (i) PhSH; (ii) Et_2NH; (iii) MeOH;

(iv) cyclopentadiene; (v) CH_3CO_2H; (vi) $(CH_3CO)_2O$;

(vii) DMAD

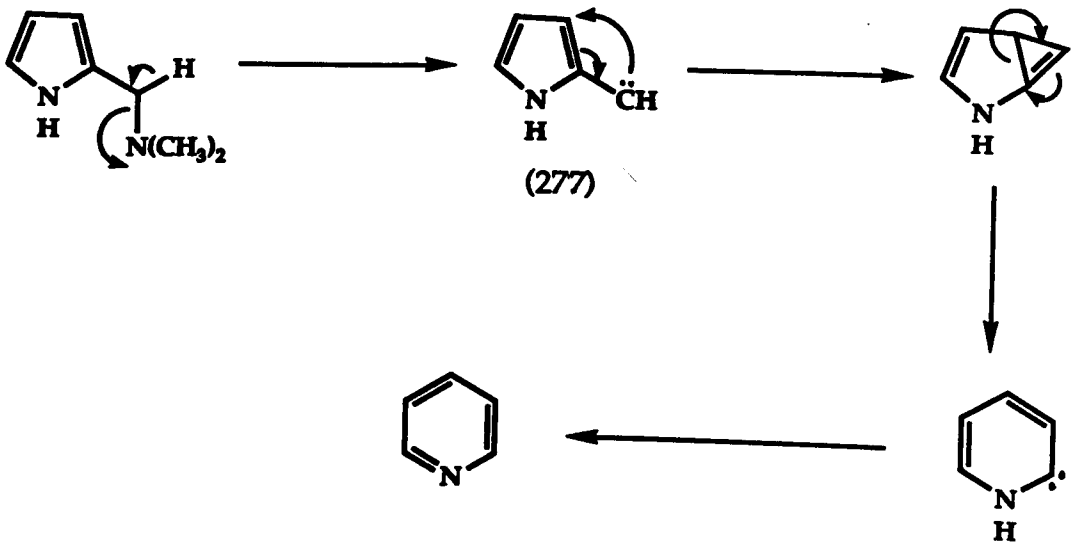
SCHEME 4.21

Co-condensation of 1-azafulvene with thiophenol gave 2-phenylthiomethylpyrrole (275) in good yield (80%). With an excess of diethylamine, 2-diethylaminomethylpyrrole (274) was obtained in excellent yield (94%). Treatment of (225) with an excess of anhydrous methanol yielded only starting material (272). In this case, dimethylamine re-added in preference to the less nucleophilic methanol. Co-condensation with dimethylacetylene dicarboxylate (DMAD) yielded (276) via a nucleophilic addition reaction of dimethylamine to the acetylene. Some intractable product was also produced and it was uncertain as to whether this was due simply to polymerisation of the azafulvene or from decomposition of an unstable adduct formed from its reaction with DMAD.

Treatment of (225) with the electrophiles acetic acid and acetic anhydride led to intractable products.

Attempts at trapping (225) in a cycloaddition reaction with the "slightly" electron-rich cyclopentadiene proved unsuccessful, regenerated starting material being recovered.

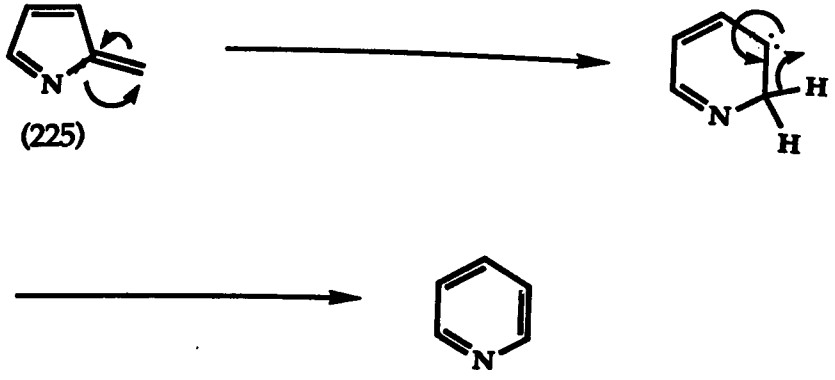
Although dimethylamine is readily eliminated from (272) to generate the 1-azafulvene, its high tendency towards readdition is a problem. In an effort to minimise re-attack of dimethylamine, we attempted to remove it by adsorption using SiO_2 covered glass tubes along the pyrolysis tube. This failed, but gave rise to a ring expansion reaction. The pyrolysate was found to contain a mixture of products including pyrrole, regenerated starting material and pyridine (as identified by gc/ms) in a ratio of 1:1.9:1.7 respectively. The ring expansion reaction giving pyridine is interesting and its mechanism of formation is worth speculation. One possible mechanism involves a carbene



SCHEME 4.22

intermediate such as (277) generated by the 1,2-elimination of dimethylamine (Scheme 4.22).

Alternatively, the reaction could involve the 1-azafulvene (225) as an intermediate (Scheme 4.23).

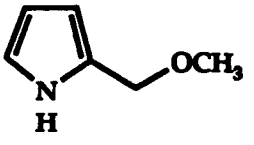


SCHEME 4.23

There are isolated reports in the literature of similar ring expansion reactions. Fulvene and benzofulvene have been shown to undergo ring expansion reactions to benzene and naphthalene respectively.[165-166] Brown has shown that pyrolysis of 2- and

3-dimethylaminomethylindole leads to the formation of a small quantity of quinoline, and he actually speculated that azafulvenes might be involved as intermediates.[155] Although interesting and potentially useful, no further investigations into this ring expansion reaction were carried out.

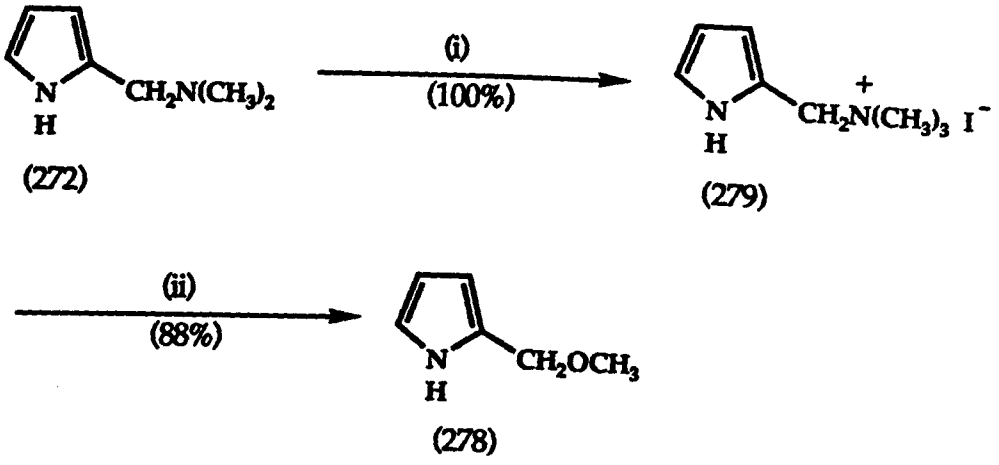
Because readdition of dimethylamine is such a "problem" in these reactions, we required an alternative 2-substituted pyrrole possessing a leaving group that would eliminate but not re-add. 2-Methoxymethylpyrrole (278) was therefore investigated; it is



(278)

easily synthesised and we know from our previous work that methanol is much less reactive than dimethylamine towards the azafulvene.

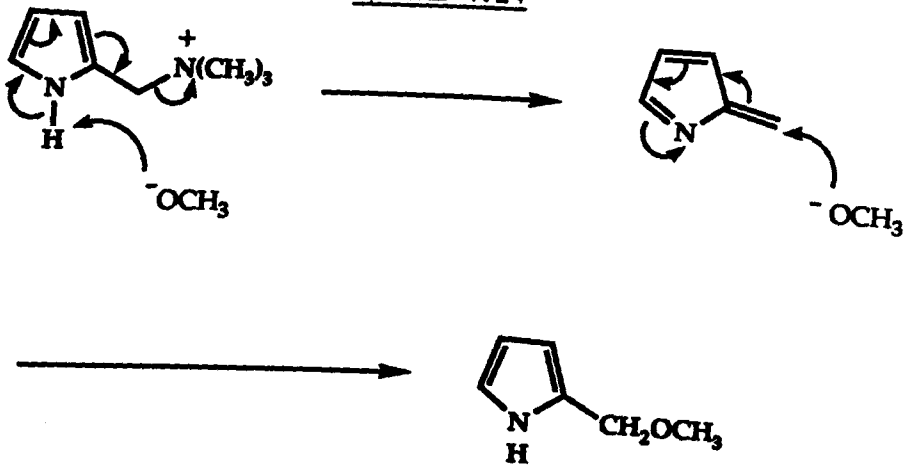
Treatment of 2-dimethylaminomethylpyrrole (272) with MeI in thf at 0°C yielded the quaternised salt (279) which underwent reaction with sodium methoxide in methanol to give the product (278) in excellent yield (88%) (Scheme 4.24). It is noteworthy that this reaction possibly involves an azafulvene intermediate (as suggested by Kenner[156]). Removal of the acidic proton on the pyrrole nitrogen by sodium methoxide with concomitant elimination of trimethylamine, would lead to the azafulvene, which would undergo reaction with the methoxide ions (Path 4.1). It is possible that this reaction pathway probably works in conjunction with that involving a straightforward nucleophilic displacement of trimethylamine (Path 4.2).



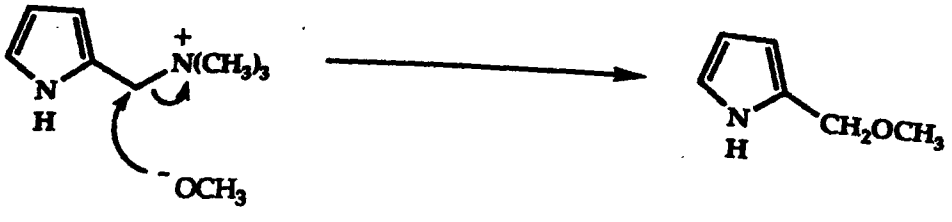
(272) (279) (278)

Reagents : (i) MeI, thf, 0°C, $^3/_4$h; (ii) NaOMe, MeOH, reflux, 3h

SCHEME 4.24

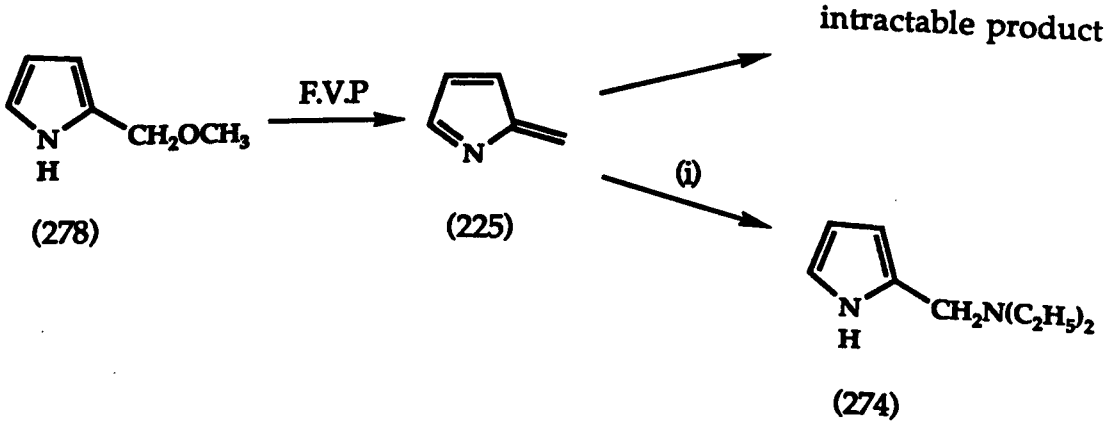


PATH 4.1



PATH 4.2

Pyrolysis of (278) at temperatures less than 800°C/2 x 10^{-3} torr led to the recovery of starting material. Repeating the pyrolysis and co-condensing with diethylamine also led to the total recovery of starting material, indicating no elimination of methanol. However, pyrolysis of (278) at 900°C/2 x 10^{-3} torr on to a cold finger (-196°C) yielded a brown intractable product, suggesting the generation of the azafulvene which underwent polymerisation in preference to re-addition of methanol. Repetition of this pyrolysis with co-condensation of diethylamine, gave 2-diethylaminomethylpyrrole (274) in 80% yield as judged by ^1H nmr analysis (Scheme 4.25). thus confirming the formation of 1-azafulvene.



Reagents : (i) Et_2NH

SCHEME 4.25

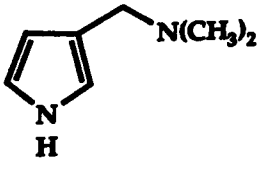
However, treatment of (225) with an excess of 2,3-dimethyl-1,3-butadiene, cyclopentadiene and tetraphenylcyclopentadienone yielded mainly intractable products in each case. One explanation for this is that the reactive azafulvene is generated in very high concentrations, even when diluted by an excess of diene, and that at such high concentrations polymerisation is

rapid (diffusion controlled) when compared to the rate of cycloaddition. Due to the lack of success in isolating a cycloadduct and because of the general difficulties in handling and pyrolysing the 2-methoxy precursor (**278**), further investigations into the chemistry of the parent 1-azafulvene were abandoned.

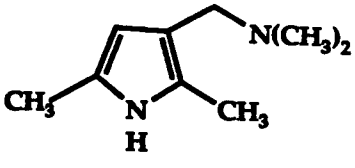
4.2.2 2-AZAFULVENES

Failure to trap 1-azafulvene in cycloadditions led us to consider 2-azafulvenes. It is noteworthy that 2-azadienes are generally easier to trap in cycloaddition reactions than their 1-azadiene isomers.

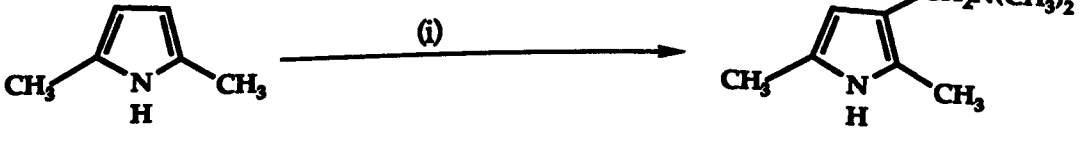
3-Dimethylaminomethylpyrrole (**280**) is not readily available but its dimethylated analogue (**281**) is easily synthesised in high yield (87%) by treating 2,5-dimethylpyrrole (**282**) with a solution of dimethylamine hydrochloride in formalin at room temperature (Scheme 4.26).



(280)



(281)

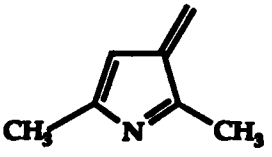


(282) (281)

Reagents : (i) CH_2O (40% solution), $Me_2NH{\cdot}HCl$, < 60°C

SCHEME 4.26

Pyrolysis of (281) at 700°C/2 x 10^{-3} torr with co-condensation of diethylamine yielded an approximate 1:1 mixture of 3-diethylaminomethyl-2,5-dimethylpyrrole (283) and regenerated starting material (281). This result is good evidence for the generation of the 2-azafulvene (284). Confirmation that this

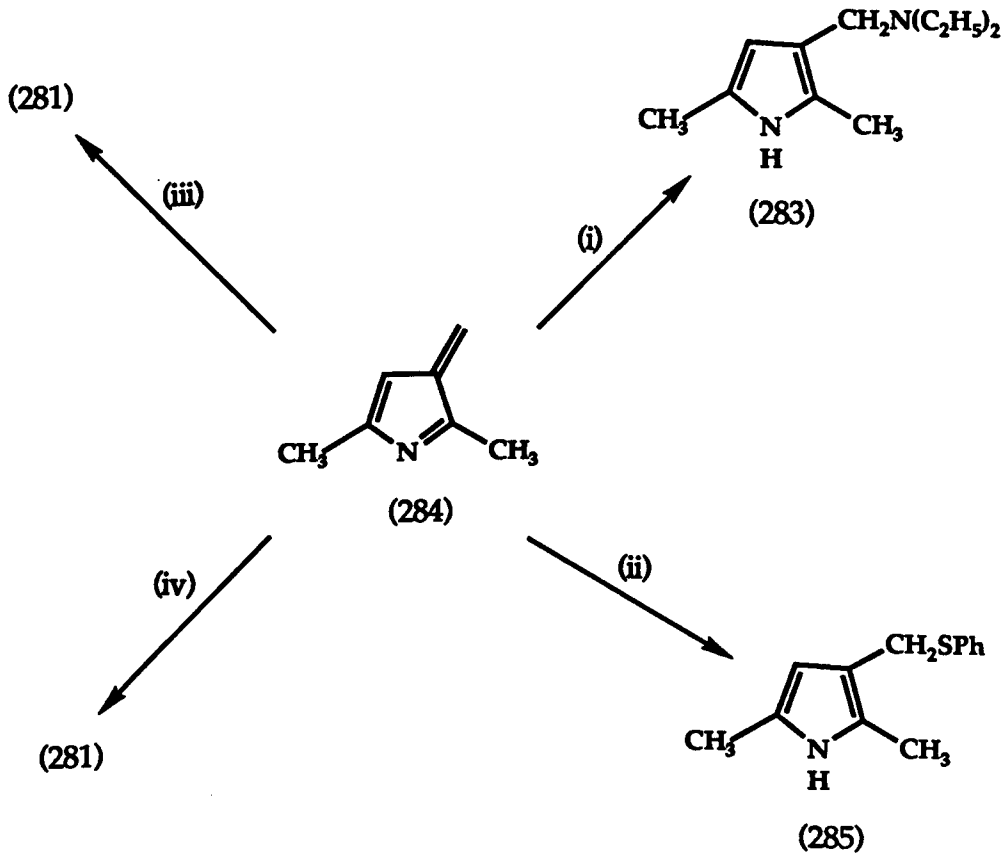


(284)

reaction was not just a straightforward nucleophilic displacement reaction was obtained by treating (281) with diethylamine at room temperature. As expected, no reaction was observed. With the pyrolysis conditions established for the generation of the 2-azafulvene, its reactivity with certain co-condensates was investigated (Scheme 4.27).

Treatment of (284) with thiophenol gave the 3-phenylthiomethyl derivative (285) in high yield (74%). Total recovery of regenerated starting material (281) was obtained when methanol and 2,3-dimethyl-1,3-butadiene were employed as co-condensates. As seen for the 1-azafulvene case these reagents cannot compete with the readdition of dimethylamine.

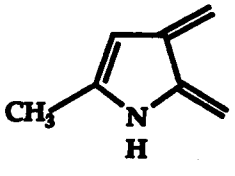
It is noteworthy that (281) is a potential precursor to the o-xylylene (286), via a 1,4-elimination reaction. However, we saw no evidence for the formation of (286). Trapping with thiophenol only led to the isolation of the 3-phenylthiomethyl derivative (285). The formation of a mixture of the 2- and 3-isomers would be expected if an o-xylylene had been involved.



Reagents : (i) $HNEt_2$; (ii) PhSH; (iii) MeOH;

(iv) 2,3-dimethyl-1,3-butadiene

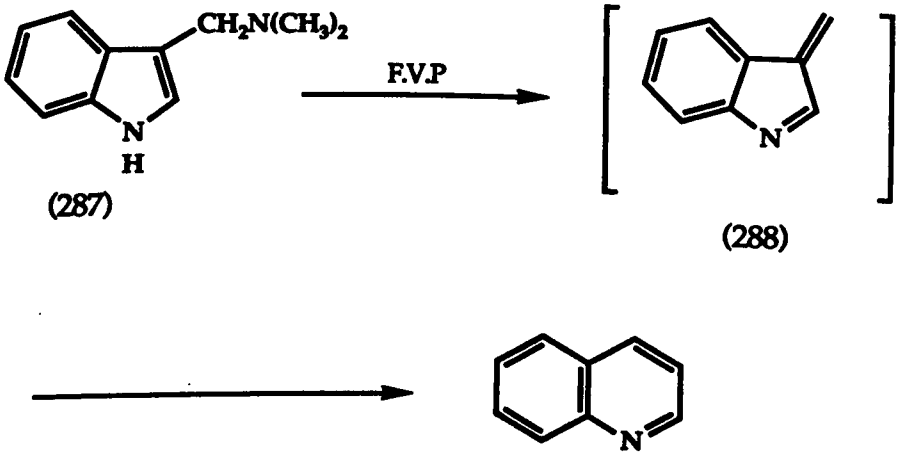
SCHEME 4.27



(286)

In conclusion, the 2-azafulvene system can be generated from (281) and trapped with reactive nucleophiles. A full study of its reaction with a whole range of dienes and dienophiles (electron-rich and deficient) needs to be undertaken to establish its readiness to undergo cycloadditions.

Continuing our investigations into azafulvenes we briefly looked into a benzoazafulvene. Brown has previously shown that the products resulting from the pyrolysis of 3-dimethylaminomethylindole (gramine) (287) at 820°C/1 x 10^{-2} torr over silica packing included dimethylaminoacetonitrile, methylaminoacetonitrile, quinoline, indole, o-vinylbenzonitrile and recovered starting material (287). He speculated upon the involvement of the azafulvene (288) as an intermediate, especially in the ring expansion reaction leading to quinoline (Scheme 4.28). Further

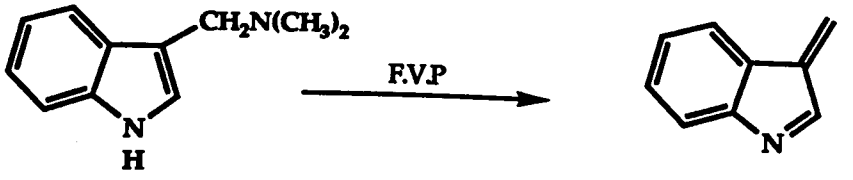


SCHEME 4.28

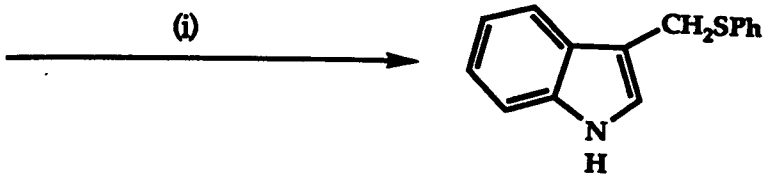
evidence comes from the recovery of significant amounts of starting material (287), possibly due to the readdition of dimethylamine to the azafulvene.

We were interested in determining whether or not an azafulvene is generated in this pyrolysis. Firstly, we repeated this pyrolysis employing the same conditions adopted by Brown, but without the silica packing. The four major products isolated were o-vinylbenzonitrile, indole, quinoline and regenerated starting material as identified by tlc and ^{1}H nmr analysis, thus confirming Brown's results.

Pyrolysing (**287**) at 700°C/2 x 10^{-3} torr with co-condensation of thiophenol led to a high isolated yield (70%) of 3-phenylthiomethylindole (**289**) (Scheme 4.29). The result is good evidence



(287) (288)



(289)

Reagents : (i) PhSH

SCHEME 4.29

for the generation of the benzoazafulvene (**288**). Repeating the pyrolysis using methanol did not give rise to any 3-methoxymethylindole. As before, the dimethylamine presumably re-added to the benzoazafulvene in preference over methanol.

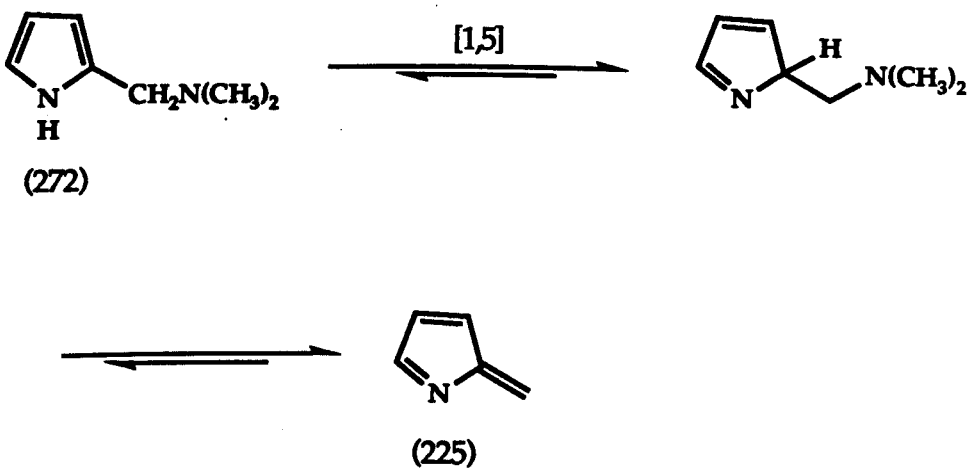
Employing 2,3-dimethyl-1,3-butadiene as a co-condensate did not yield any cycloadduct.

Therefore, the benzoazafulvene (**288**) can be generated effectively *via* the thermal elimination of dimethylamine and undergoes reaction with reactive nucleophiles.

4.3 MECHANISMS FOR THE FORMATION OF AZAFULVENES

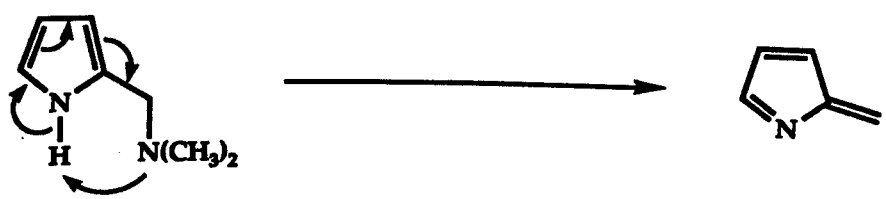
The mechanisms involved in the formation of these azafulvenes are unclear, but are worthy of speculation.

The 1-azafulvene (**225**) could, in principle, be generated from (**272**) via a thermally allowed 1,5-sigmatropic shift of the proton on the pyrrole nitrogen, followed by a 1,2-elimination of dimethylamine (Scheme 4.30).



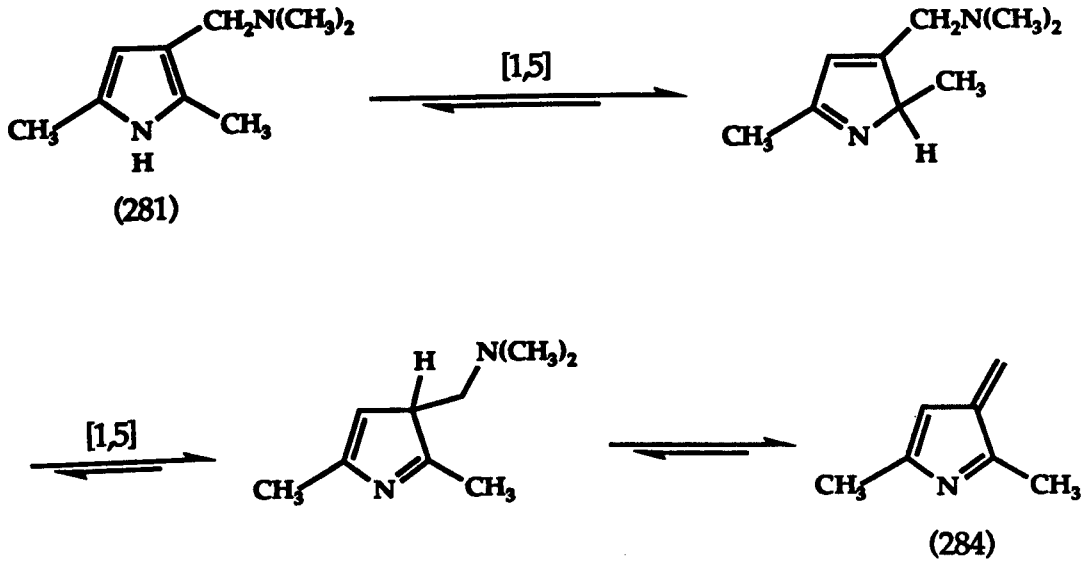
SCHEME 4.30

However, a concerted elimination resulting from the direct attack of the basic nitrogen on the 1-NH is plausible (Scheme 4.31).



SCHEME 4.31

The 2-azafulvene (**284**) could be generated via two successive 1,5-sigmatropic shifts followed by a 1,2-elimination of dimethylamine (Scheme 4.32). Obviously, the concerted process outlined in Scheme 4.31 is not possible for this case.


CH2N(CH3)2
CH3
N
H
CH3
[1,5]
CH2N(CH3)2
CH3
CH3
N
H
(281)
[1,5]
H
N(CH3)2
CH3
N
CH3
CH3
N
CH3
(284)

SCHEME 4.32

CHAPTER 5

5.0 EXPERIMENTAL

Product purity was checked by thin layer chromatography (tlc) on Merck 10 x 2 cm aluminium-backed plates with an 0.2 mm layer of Kieselgel 60 F_{254}.

Flash column chromatography was carried out using Mackerey Nagel MN-Kieselgel 60, and dry flash column chromatography was carried out using Merck Kieselgel 60 Hz.

Melting points (m.p.) were determined on a Köfler block and are uncorrected. Melting points are expressed in degrees Celsius (°C).

Microanalyses were performed in the University of Liverpool Microanalyses Laboratory.

^1H Nmr spectra were recorded, either on a Perkin Elmer R34 (220 MHz) or a Bruker AC200 (200 MHz) spectrometer. Solvents are indicated in the text, and tetramethylsilane or dichloromethane were used as internal references. For signals other than singlets (s), doublets (d), doublet of doublets (dd), triplets (t), quartets (q) and multiplets (m), the number of lines are indicated.

Ir spectra were recorded on an A.E.I. MS902 VG Analytical 7070E, or a Mattson Centauri Spectrometer.

Solvents were dried and distilled prior to use: diethylether (Et_2O), dimethoxyethane (DME) and tetrahydrofuran (thf) from sodium benzophenone; hexane, acetonitrile, diisopropylamine, N,N,N',N'-tetramethylethylenediamine (TMEDA), and dimethylformamide (DMF) from CaH_2. Methanol was distilled from magnesium methoxide.

Unless impractical, commercial argon gas was used to provide an inert atmosphere in all reactions.

The concentrations of solutions of commercial ^{n}BuLi and ^{s}BuLi were determined by titration against diphenylacetic acid in thf.[158]

The temperature reported for certain reactions, e.g., -78°C, refers to the temperature of the cooling medium rather than the internal temperature of the reaction itself.

5.1 N-METHYLTHIOPHENE-2-CARBOXAMIDE (127)

Thiophene-2-carboxylic acid (40.0 g, 0.31 mol), and thionyl chloride (112.44 ml, 1.55 mol) were heated under reflux for five hours. The excess of thionyl chloride was removed under reduced pressure and the crude acid chloride (**126**) added dropwise to a solution of commercial aqueous $MeNH_2$ (41.33 ml, 0.31 mol) in dilute aqueous sodium hydroxide (10%, w/w, 100 ml). After addition of the acid chloride the mixture was stirred for a further twelve hours and extracted with ethyl acetate (5 x 30 ml) and washed with dilute aqueous HCl (5% v/v, 30 ml), water (2 x 30 ml) and brine (30 ml). The organic layer was dried ($MgSO_4$) and evaporated to give the crude product which was recrystallised (ethyl acetate - light petroleum) to give the pure amide (**127**) (36.28 g, 83%) as colourless crystals; m.p., 111 - 113°C (lit.,[159] 110 - 112°C). (Found: C, 51.08; H, 4.98; N, 9.89. Calculated for C_6H_7NOS, C, 51.04; H, 5.00; N, 9.92%); δ ($CDCl_3$), 7.64 (1H, dd, J 3.92, 1.12 Hz, thiophene 3-H), 7.43 (1H,dd, J 5.04, 1.12 Hz, thiophene 5-H), 7.15 (1H, br., NH), 7.03 (1H, dd, J 5.04, 3.92 Hz, thiophene 4-H), 3.18 (3H, s, NCH_3); $\nu_{max.}$ (mull), 3285, 1610, 1560, 1350, 1300, 1245 and 855 cm^{-1}. m/z 141 (M^+, 44%), 111 (100), 83 (15), 57(10) and 39(30).

5.2 N-METHYL-5-DEUTERIOTHIOPHENE-2-CARBOXAMIDE (130)

N-Methylthiophene-2-carboxamide (127) (0.50 g, 3.55 mmol) in thf (10 ml) was added to a solution of ^{n}BuLi (5.65 ml, 7.80 mmol) and diisopropylamine (1.10 ml, 7.80 mmol) in thf (30 ml) at -78°C, and the reaction mixture stirred for half an hour. After this period of time the reaction mixture was quenched with MeOD (2 ml) and allowed to reach room temperature. The bulk of the solvent was removed in vacuo and the residue suspended in water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with water (2 x 10 ml), brine (1 x 10 ml) and dried ($MgSO_4$). Evaporation of the solvent yielded a colourless solid (0.45 g). Analysis by ^{1}H nmr indicated a 70% deuterium incorporation at the C5-position of the starting material (127).

5.3 N-(2,4,6-TRIMETHYL)PHENYLTHIOPHENE-2-CARBOXAMIDE (148)

Thiophene-2-carbonyl chloride (126) (22.34 g, 0.152 mol) in dichloromethane (50 ml) was added dropwise to a solution of 2,4,6-trimethylaniline (20.62 g, 0.152 mol), triethylamine (31.80 ml, 0.229 mol) and dichloromethane (100 ml) at room temperature (25°C). The mixture was then refluxed for twelve hours, washed with water (2 x 50 ml), and dried ($MgSO_4$). The combined organic solutions were evaporated under reduced pressure to yield the crude amide. Recrystallisation (ethyl acetate - light petroleum) gave the pure amide (148) (33.58 g, 95%) as a colourless crystalline solid; m.p., 180 - 181°C (lit.,[160] 164 - 165°C). (Found: C, 68.50; H, 6.16; N, 5.57. Calculated for $C_{14}H_{15}NOS$, C, 68.54; H, 6.16; N, 5.17%); δ ($CDCl_3$), 7.84 (1H, br., NH), 7.63 (1H, dd, J 3.92, 1.12 Hz, thiophene 3-H), 7.45 (1H, dd, J 4.76,

1.12 Hz, thiophene 5-H), 7.02 (1H, dd, J 4.76, 3.92 Hz, thiophene 4-H), 6.85 (2H, s, aryl 3-H), 2.27 (3H, s, aryl CH_3), 2.13 (6H, s, aryl CH_3); $\nu_{max.}$ (mull), 3230, 3080, 2900, 1630, 1605, 1535, 1310 and 850 cm^{-1}; m/z 245.08769 (M^+, 35%, calculated for $C_{14}H_{15}NOS$ 245.08744), 134(38) and 111(100).

5.4 N-METHYLFURAN-2-CARBOXAMIDE (154)

2-Furoic acid (10.19 g, 0.091 mol) and thionyl chloride (19.81 ml, 0.273 mol) were heated under reflux for five hours. The excess of thionyl chloride was removed under reduced pressure and the crude acid chloride added dropwise to a solution of commercial aqueous $MeNH_2$ (10.22 ml, 0.091 mol) in dilute aqueous sodium hydroxide (10%, w/w, 50 ml). The mixture was stirred for a further twelve hours and extracted with ethyl acetate (2 x 60 ml) and washed with dilute aqueous HCl (5% v/v, 20 ml), water (2 x 20 ml) and brine (20 ml). The organic layer was dried ($MgSO_4$) and evaporated to give the crude product which was purified by bulb-to-bulb distillation to give the pure amide (**154**) as a colourless oil (7.00 g, 73%), b.p., 142°C at 3 mmHg. On cooling a colourless crystalline solid was obtained; m.p., 59 - 61°C (lit.,[161] 62 - 64.5°C); δ ($CDCl_3$), 7.40 (1H, d, J 1.68 Hz, furan 5-H), 7.09 (1H, d, J 3.36 Hz, furan 3-H), 6.44 (1H, dd, J 3.36, 1.68 Hz, furan 4-H), 2.96 (3H, d, N-CH_3); $\nu_{max.}$ (mull), 3300, 3100, 2950, 1660, 1570, 1400, 1340 and 830 cm^{-1}; m/z 125.0479 (M^+, 61%, calculated for $C_6H_7NO_2$ 125.0477), 95(100), 82(5) and 58(8).

5.5 N-PHENYLFURAN-2-CARBOXAMIDE (157)

Furan-2-carbonyl chloride (15.0 g, 0.115 mol) in dichloromethane (40 ml) was added dropwise to a solution of aniline (10.69 g, 0.115 mol), triethylamine (24 ml, 0.172 mol) and dichloromethane (80 ml) at room temperature (25°C). The reaction vessel became warm and was cooled with an ice-bath. The resulting solution was stirred for twelve hours, washed with water (2 x 50 ml) and brine (40 ml) and dried ($MgSO_4$). The organic solvent was evaporated to yield the crude product. Recrystallisation (ethyl acetate - light petroleum) gave the pure amide (**157**) (20.31 g, 94%) as a colourless crystalline solid; m.p., 124 - 125°C, (lit.,[162] 124 - 125°C). (Found: C, 70.63; H, 4.81; N, 7.41. Calculated for $C_{11}H_9NO_2$, C, 70.58; H, 4.85; N, 7.48%); δ ($CDCl_3$), 8.26 (1H, br., N-H), 7.66 (2H, d, phenyl 2-H), 7.44 (1H, dd, J 2.23, 0.67 Hz, furan 5-H), 7.32 (2H, t, phenyl 3-H), 7.19 (1H, dd, J 3.34, 0.67 Hz, furan 3-H), 7.11 (1H, t, phenyl 4-H), 6.49 (1H, dd, J 3.34, 2.23 Hz, furan 4-H); $\nu_{max.}$ (mull), 3300, 3150, 2950, 1660, 1600, 1450, 1330 and 760 cm^{-1}; m/z 187.0632 (M^+, 42%, calculated for $C_{11}H_9NO_2$ 187.0633) and 95(100).

5.6 N-(2,4,6-TRIMETHYL)PHENYLFURAN-2-CARBOXAMIDE (160)

Furan-2-carbonyl chloride (15.0 g, 0.115 mol) in dichloromethane (50 ml) was added dropwise to a solution of 2,4,6-trimethylaniline (15.54 g, 0.115 mol), triethylamine (24 ml, 0.172 mol) and dichloromethane (80 ml). The reaction vessel became warm. The resulting solution was refluxed for twelve hours, washed with water (3 x 30 ml), and dried ($MgSO_4$). The combined washings were basified to pH 11 (KOH aq., 40% w/w) and extracted

with CH_2Cl_2 (3 x 30 ml) and the extracts dried ($MgSO_4$). The combined organic solutions were evaporated under reduced pressure to give the crude product. Recrystallisation (ethyl acetate - light petroleum) gave the pure amide (**160**) (24.86 g, 94%) as a colourless crystalline solid; m.p., 162 - 163°C. (Found: C, 73.24; H, 6.57; N, 6.00. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11%); δ ($CDCl_3$), 7.64 (1H, br., NH), 7.48 (1H, d, J 1.68 Hz, furan 5-H), 7.17 (1H, d, J 3.92 Hz, furan 3-H), 6.90 (2H, s, aryl 3-H), 6.50 (1H, dd, J 3.92, 1.68 Hz, furan 4-H), 2.27 (3H, s, aryl CH_3), 2.21 (6H, s, aryl CH_3); $\nu_{max.}$ (mull), 3280, 2950, 1660, 1590, 1490, 1340, 1040 and 870 cm^{-1}; m/z 229.1108 (M^+, 37%, $C_{14}H_{15}NO_2$ requires 229.1103), 200(7), 134(100), 95(74), 77(8) and 65(7).

5.7 N-METHYLTHIOPHENE-2-CARBOXIMIDOYL CHLORIDE (128)

N-Methylthiophene-2-carboxamide (**127**) (5.50 g, 0.039 mol) was heated under reflux with thionyl chloride (15 ml, 0.21 mol) for eighteen hours. Excess of thionyl chloride was removed *in vacuo* and the residue was distilled under reduced pressure to give the pure imidoyl chloride (**128**) (6.00 g, 96%) as a colourless oil, b.p., 88°C at 15 mmHg. (Found: C, 44.79; H, 3.70; N, 8.66. C_6H_6NSCl requires C, 45.14; H, 3.79; N, 8.77%); δ ($CDCl_3$), 7.71 (1H, dd, J 3.80, 1.01 Hz, thiophene 3-H), 7.43 (1H, dd, J 4.92, 1.01 Hz, thiophene 5-H), 7.03 (1H, dd, J 4.92, 3.80 Hz, thiophene 4-H), 3.40 (3H, s, NCH_3); $\nu_{max.}$ (film), 3090, 2950, 1665, 1420, 1235, 990 and 800 cm^{-1}; m/z 159 (M^+, 19%), 143(20), 124(54), 109(100), 102(22), 75(31) and 45(40).

5.8 N-PHENYLTHIOPHENE-2-CARBOXIMIDOYL CHLORIDE

N-Phenylthiophene-2-carboxamide (**209**) (10.0 g, 0.49 mol) was heated under reflux with thionyl chloride (70 ml, 0.96 mol) for two hours. Excess of thionyl chloride was removed *in vacuo* and the residue was distilled under reduced pressure to give the pure N-phenylthiophene-2-carboximidoyl chloride (10.47 g, 96%) as a pale yellow viscous oil, b.p., 128°C at 0.7 mmHg. On cooling a waxy yellow solid was obtained; m.p., 28 - 29°C. (Found: C, 59.57; H, 3.60; N, 6.17. $C_{11}H_8NSCl$ requires C, 59.59; H, 3.64; N, 6.32%); δ ($CDCl_3$), 7.74 (1H, dd, *J* 3.92, 1.12 Hz, thiophene 3-H), 7.44 (1H, dd, *J* 5.04, 3.92 Hz, thiophene 4-H), 7.33 (2H, t, phenyl 3-H), 7.13 (1H, t, phenyl 4-H), 7.02 (1H, dd, *J* 5.04, 1.12 Hz, thiophene 5-H), 6.97 (2H, d, phenyl 2-H); $\nu_{max.}$ (film), 3060, 1630, 1580, 1470, 1230, 1150, 1040 and 820 cm^{-1}; *m/z* 221.0062 (M^+, 33%, $C_{11}H_8NS^{35}Cl$ requires 221.0066), 203(13), 111(36), 77(39), 51(18) and 39(11).

5.9 N-(2,4,6-TRIMETHYLPHENYL)THIOPHENE-2-CARBOXIMIDOYL CHLORIDE (149)

N-2,4,6-Trimethylphenylthiophene-2-carboxamide (**148**) (5.00 g, 20 mmol) was heated under reflux with thionyl chloride (25 ml, 0.35 mol) for three hours. Excess of thionyl chloride was removed *in vacuo* and the residue was distilled under reduced pressure to give the pure imidoyl chloride (**149**) (5.00 g, 93%) as a viscous oil, b.p., 138°C at 3 mmHg. On cooling a light yellow solid was obtained; m.p., 63 - 65°C. (Found: C, 63.70; H, 5.29; N, 5.18. $C_{14}N_{14}NSCl$ requires C, 63.75; H, 5.53; N, 5.31%); δ ($CDCl_3$), 7.78 (1H, dd, *J* 3.92, 1.12 Hz, thiophene 3-H), 7.50 (1H, dd, *J* 5.16, 1.22 Hz, thiophene 5-H), 7.10 (1H, dd, *J* 5.16, 3.92

Hz, thiophene 4-H), 6.88 (2H, d, aryl 3-H), 2.27 (3H, s, aryl CH_3), 2.07 (6H, s, aryl CH_3); $\nu_{max.}$ (mull), 3080, 2900, 1655, 1630, 1480, 1140, 1050 and 850 cm^{-1}; m/z 263.0531 (M^+, 8%, $C_{14}H_{14}NOS^{35}Cl$ requires 263.0535), 228(24), 110(28), 91(36), 77(38), 44(58) and 36(100).

5.10 N-METHYLFURAN-2-CARBOXIMIDOYL CHLORIDE (155)

N-Methylfuran-2-carboxamide (154) (5.0 g, 40 mmol) was heated under reflux with thionyl chloride (25 ml, 0.34 mol) for twelve hours. Excess of thionyl chloride was removed in vacuo and the residue was distilled under reduced pressure to give the pure imidoyl chloride (155) (4.53 g, 79%) as a pale yellow oil, b.p., 37°C at 0.06 mmHg. (Found: C, 50.06; H, 4.23; N, 9.67. C_6H_6NOCl requires C, 50.20; H, 4.21; N, 9.76%); δ ($CDCl_3$), 7.52 (1H, d, J 1.68 Hz, furan 5-H), 7.00 (1H, d, J 3.36 Hz, furan 3-H), 5.46 (1H, dd, J 3.36, 1.68 Hz, furan 4-H), 3.44 (3H, s, NCH_3); $\nu_{max.}$ (film), 3180, 2950, 1705, 1500, 1180 and 850 cm^{-1}; m/z 145 (M^+, 3%), 143(9), 108(100), 93(82) and 64(41).

5.11 N-PHENYLFURAN-2-CARBOXIMIDOYL CHLORIDE (158)

N-Phenylfuran-2-carboxamide (157) (2.0 g, 11 mmol) was heated under reflux with thionyl chloride (15 ml, 0.21 mol) for three hours. Excess of thionyl chloride was removed in vacuo and the residue was purified by Kugelröhr distillation to give the pure imidoyl chloride (158) (2.20 g, 100%) as a pale yellow oil. (Found: C, 64.14; H, 3.85; N, 6.74. $C_{11}H_8NOCl$ requires C, 64.25; H, 3.92; N, 6.81%); δ ($CDCl_3$), 7.60(1H, d, J 1.68 Hz, furan 5-H), 7.37 (2H, t, phenyl 3-H), 7.23 (1H, d, J 3.92 Hz, furan 3-H), 7.19 (1H, t, phenyl 4-H), 7.05 (2H, d, phenyl 2-H),

6.52 (1H, dd, J 3.92, 1.68 Hz, furan 4-H); $\nu_{max.}$ (film), 3200, 3100, 1680, 1610, 1500, 1410, 1220, 1180, 1040 and 970 cm^{-1}; m/z 205.0292 (M^+, 25%, $C_{11}H_8NO^{35}Cl$ requires 205.0294), 170(100), 115(6) and 77(77).

5.12 N-(2,4,6-TRIMETHYLPHENYL)FURAN-2-CARBOXIMIDOYL CHLORIDE (161)

N-(2,4,6-Trimethylphenyl)furan-2-carboxamide (**160**) (1.00 g, 4.04 mmol) was heated under reflux with thionyl chloride (15 ml, 0.21 mol) for three hours. Excess of thionyl chloride was removed in vacuo and the residue was distilled under reduced pressure to give the pure imidoyl chloride (**161**) (1.07 g, 99%) as a viscous yellow oil, b.p., 115°C at 0.1 mmHg. On cooling a waxy yellow solid was obtained; m.p., 46 - 47°C. (Found: C, 67.52; H, 5.63; N, 5.64. $C_{14}H_{14}NOCl$ requires C, 67.88; H, 5.70; N, 5.65%); δ ($CDCl_3$), 7.65 (1H, d, J 1.60 Hz, furan 5-H), 7.25 (1H, d, J 3.92 Hz, furan 3-H), 6.90 (2H, s, aryl 3-H), 6.59 (1H, dd, J 3.92, 1.60 Hz, furan 4-H), 2.30 (3H, s, aryl CH_3), 2.10 (6H, s, aryl CH_3); $\nu_{max.}$ (film), 3180, 2950, 1680, 1490, 1220, 1040, 970 and 870 cm^{-1}; m/z 247.0767 (M^+, 38%, $C_{14}H_{14}NO^{35}Cl$ requires 247.0764), 212(100), 197(21), 168(6), 134(9), 119(11), 91(24), 77(19) and 65(10).

5.13 METHYL N-METHYLTHIOPHENE-2-CARBOXIMIDATE (129)

A solution of sodium methoxide (1.0 g, 18.52 mmol) in methanol (15 ml) was added dropwise to N-methylthiophene-2-carboximidoyl chloride (**128**) (1.02 g, 6.39 mmol) in thf (10 ml) at 0°C. The solution was stirred at 0°C for half an hour and allowed to reach room temperature (25°C) and stirred for twelve

hours. The bulk of the methanol and thf was removed in vacuo and the residue was diluted with diethyl ether (40 ml) and washed with sodium bicarbonate (2 x 20 ml), water (1 x 20 ml) and brine (1 x 20 ml). The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo to give a pale yellow oil which was purified by distillation under reduced pressure to give the pure imidate (**129**) (0.93 g, 97%) as a colourless oil, b.p., 60°C at 1.0 mmHg. (Found: C, 53.93; H, 5.86; N, 8.82. C_7H_9NOS requires C, 54.17; H, 5.84; N, 9.02%); δ ($CDCl_3$), 7.48 (1H, dd, J 3.79, 1.12 Hz, thiophene 3-H), 7.43 (1H, dd, J 5.02, 1.12 Hz, thiophene 5-H), 7.09 (1H, dd, J 5.02, 3.79 Hz, thiophene 4-H), 3.78 (3H, s, OCH_3), 3.34 (3H, s, NCH_3); $\nu_{max.}$ (film), 3090, 2950, 1665, 1440, 1365, 1270, 1220, 1025 and 860 cm^{-1}; m/z 155.0402 (M^+, 40%, C_7H_9NOS requires 155.0405), 154(41), 141(9), 124(86), 111(100), 97(44), 83(14), 72(10) and 57(11).

5.14 METHYL N-METHYL-5-DEUTERIOTHIOPHENE-2-CARBOXIMIDATE (131)

^nBuLi (2.43 ml, 3.55 mmol) was added to imidate (**129**) (0.50 g, 3.23 mmol) in thf (30 ml) at -78°C and the mixture stirred for one hour, after which MeOD (1 ml, excess) was added and the reaction mixture allowed to reach room temperature. The solvents were removed under reduced pressure and the residue suspended in distilled water (10 ml) and extracted with diethyl ether (2 x 30 ml). The combined organic extracts were washed with water (1 x 10 ml) and brine (1 x 10 ml), dried ($MgSO_4$) and the solvent removed in vacuo to yield the 5-deuterio-imidate (**131**) as a pale yellow oil (0.50 g, 100%); δ ($CDCl_3$), 7.48 (1H, d, J 3.92 Hz, thiophene 3-H), 7.09 (1H, d, J 3.92 Hz, thiophene 4-H), 3.78 (3H, s, OCH_3), 3.34 (3H, s, NCH_3).

5.15 METHYL N-METHYL-5-METHYLTHIOTHIOPHENE-2-CARBOXIMIDATE (134)

^{n}BuLi (2.43 ml, 3.55 mmol) was added to imidate (**129**) (0.50 g, 3.23 mmol) in thf (30 ml) at -78°C and the mixture stirred for one hour, after which Me_2S_2 (1.45 ml, 16.15 mmol) was added and the reaction mixture was allowed to reach room temperature over seven hours. The solvents were removed under reduced pressure and the residue suspended in distilled water (15 ml) and extracted with diethyl ether (3 x 40 ml). The combined extracts were washed with water (1 x 10 ml) and brine (1 x 15 ml), dried ($MgSO_4$) and the solvent removed in vacuo to give the product (134) as a yellow oil (0.64 g, 98%); δ ($CDCl_3$), 7.34 (1H, d, J 3.84 Hz, thiophene 3-H), 6.99 (1H, d, J 3.84 Hz, thiophene 4-H), 3.75 (3H, s, OCH_3), 3.33 (3H, s, NCH_3), 2.54 (3H, s, SCH_3); $\nu_{max.}$ (film), 2945, 1665, 1435, 1330, 1310, 1085, 1045, 805, 710 and 690 cm^{-1}; m/z 201.02804 (M^+, 80%, $C_8H_{11}NOS$ requires 201.02821), 186(9), 170(100), 155(56), 143(41), 114(32) and 94(8).

5.16 METHYL N-METHYL-5-METHYLTHIOPHENE-2-CARBOXIMIDATE (135)

^{n}BuLi (2.43 ml, 3.55 mmol) was added to imidate (**129**) (0.50 g, 3.23 mmol) in thf (30 ml) at -78°C and the mixture stirred for one hour, after which MeI (1.01 ml, 16.15 mmol) was added and the reaction mixture was allowed to reach room temperature over seven hours. The solvents were removed under reduced pressure and the residue suspended in distilled water (15 ml) and extracted with diethyl ether (3 x 40 ml). The combined extracts were washed with water (1 x 15 ml) and brine (1 x 15 ml), dried ($MgSO_4$) and the solvent removed in vacuo to give the spectroscopically pure product (135) as a pale yellow oil (0.52 g, 96%); δ ($CDCl_3$), 7.28

(1H, d, J 3.70 Hz, thiophene 3-H), 6.75 (1H, d, J 3.70 Hz, thiophene 4-H), 3.74 (3H, s, OCH_3), 3.32 (3H, s, NCH_3), 2.49 (3H, s, thiophene CH_3); $\nu_{max.}$ (film), 3050, 2930, 2850, 1650, 1455, 1390, 1250, 1208, 1060, 1018 and 805 cm^{-1}; m/z 169.05627 (M^+, 45%, $C_8H_{11}NOS$ requires 169.05614), 138(100), 124(70), 111(55) and 97(14).

5.17 METHYL N-METHYL-5-TRIMETHYLSILYLTHIOPHENE-2-CARBOXIMIDATE (136)

^nBuLi (2.57 ml, 3.55 mmol) was added to imidate (**129**) (0.50 g, 3.23 mmol) in thf (30 ml) at -78°C and the mixture stirred for one hour, after which TMSCl (0.45 ml, 3.55 mmol) was added and the reaction mixture was allowed to reach room temperature over eight hours. The solvents were removed under reduced pressure and the solids suspended in distilled water (15 ml) and extracted with ethyl acetate (3 x 20 ml). The combined extracts were washed with water (1 x 10 ml) and brine (1 x 15 ml) and dried ($MgSO_4$). The solvent was removed in vacuo to give a brown oil which was purified by Kugelröhr distillation to yield the pure product (**136**) (0.50 g, 68%) as a pale yellow oil; δ ($CDCl_3$), 7.49 (1H, d, J 3.92 Hz, thiophene 3-H), 7.20 (1H, d, J 3.92 Hz, thiophene 4-H), 3.74 (3H, s, OCH_3), 3.32 (3H, s, NCH_3), 0.33 (9H, s, TMS); $\nu_{max.}$ (film), 2950, 1650, 1430, 1390, 1300, 1190, 1065, 970, 740 and 680 cm^{-1}; m/z 227 (M^+, 58%), 212(92), 183(100), 166(25), 115(15), 73(60) and 59(14).

5.18 METHYL N-PHENYLTHIOPHENE-2-CARBOXIMIDATE (146)

A solution of sodium methoxide (5.0 g, 90.0 mmol) in methanol (25 ml) was added dropwise to N-phenylthiophene-2-

carboximidoyl chloride (6.01 g, 27.0 mmol) in thf (30 ml) at 0°C. The solution was stirred at 0°C for half an hour and allowed to reach room temperature (22°C) and stirred for a further twelve hours. A white solid precipitated out. Work-up as for (**129**) gave a yellow oil which was purified by distillation under reduced pressure to give the pure imidate (**146**) (5.30 g, 91%) as a colourless oil, b.p., 121°C at 3.0 mmHg. On cooling a colourless solid was obtained; m.p., 48 - 49°C. (Found: C, 66.37; H, 5.07; N, 6.41. $C_{12}H_{11}NOS$ requires C, 66.33; H, 5.10; N, 6.45%); δ (d_6-DMSO), 7.63 (1H, dd, J 5.04, 1.12 Hz, thiophene 5-H), 7.32 (2H, t, phenyl 3-H), 7.10 (1H, t, phenyl 4-H), 6.93 (1H, dd, J 5.04, 3.92 Hz, thiophene 4-H), 6.90 (1H, dd, J 3.92, 1.12 Hz, thiophene 3-H), 6.80 (2H, dd, phenyl 2-H), 3.88 (3H, s, OCH_3); $\nu_{max.}$ (mull), 3080, 2860, 1650, 1590, 1450, 1350, 1260 and 760 cm^{-1}; m/z 217.0557 (M^+, 16%, $C_{12}H_{11}NOS$ requires 217.0561), 186(24), 111(100), 77(91), 62(51) and 39(79).

5.19 METHYL N-(2,4,6-TRIMETHYLPHENYL)THIOPHENE-2-CARBOXIMIDATE (150)

A solution of sodium methoxide (4.0 g, 74.10 mmol) in methanol (20 ml) was added to N-(2,4,6-trimethylphenyl)thiophene-2-carboximidoyl chloride (**149**) (4.0 g, 15.20 mmol) in thf (25 ml) at 0°C. The solution was stirred at 0°C for one hour and allowed to reach room temperature (23°C) and stirred for a further twelve hours. Work-up as for (**129**) yielded a yellow oil which was purified by distillation under reduced pressure to give the pure imidate (**150**) (3.61 g, 92%) as a viscous, yellow oil, b.p., 133°C at 2.0 mmHg. On cooling a pale yellow solid was obtained; m.p., 70.5 - 71.5°C. (Found: C, 69.19; H, 6.52; N,

5.28. $C_{15}H_{17}NOS$ requires C, 69.46; H, 6.61; N, 5.40%); δ ($CDCl_3$), 7.22 (1H, dd, J 3.92, 1.12 Hz, thiophene 5-H), 7.02 (1H, dd, J 5.04, 1.12 Hz, thiophene 3-H), 6.86 (2H, s, aryl 3-H), 6.83 (1H, dd, J 5.04, 3.92 Hz, thiophene 4-H), 4.00 (3H, s, OCH_3), 2.29 (3H, s, aryl CH_3), 1.98 (6H, s, aryl CH_3); $\nu_{max.}$ (mull), 3050, 2900, 1655, 1455, 1355, 1260, 1100, 1070, 980 and 850 cm^{-1}; m/z 259.1026 (M^+, 23%, $C_{15}H_{17}NOS$ requires 259.1031), 228(28), 160(18), 119(22), 111(100), 91(60), 77(51), 65(29), 51(28), 45(26) and 41(46).

5.20 METHYL THIOPHENE-2-CARBOXIMIDATE (152)

Excess hydrogen chloride gas (dry) was passed for one hour through a solution of thiophene-2-carbonitrile (**140**) (1.00 g, 9.16 mmol) and methanol (0.37 ml, 9.16 mmol) in diethyl ether (15 ml) at 0°C. A colourless crystalline solid precipitated out. After standing for forty-eight hours at room temperature, the product hydrochloride salt was shaken vigorously with a saturated solution of sodium bicarbonate (20 ml) and dichloromethane (40 ml) at 0°C. The organic layer was separated and dried ($MgSO_4$) and the solvent removed in vacuo to yield a brown oil, which was purified by distillation under reduced pressure to give the pure imidate (**152**) (0.87 g, 67%) as a pale yellow oil, b.p., 90°C at ~15 mmHg; δ ($CDCl_3$), 7.45 (1H, dd, J 3.64, 1.12 Hz, thiophene 3-H), 7.35 (1H, dd, J 5.04, 1.12 Hz, thiophene 5-H), 7.01 (1H, dd, J 5.04, 3.64 Hz, thiophene 4-H), 3.87 (3H, s, OCH_3); $\nu_{max.}$ (film), 3280, 3060, 2920, 1625 and 1065 cm^{-1}; m/z 141 (M^+, 36%), 110(100), 97(21), 84(77), 69(24) and 58(24).

5.21 METHYL N-METHYLFURAN-2-CARBOXIMIDATE (156)

A solution of sodium methoxide (3.50 g, 24.39 mmol) in methanol (20 ml) was slowly added dropwise to N-methylfuran-2-carboximidoyl chloride (155) (0.50 g, 3.48 ml) in thf (30 ml) at 0°C. The solution was stirred at 0°C for two hours and allowed to reach room temperature (22°C) and stirred for a further five hours. Work-up as for (129) yielded a pale yellow oil which was purified by distillation under reduced pressure to give the pure imidate (156) (0.42 g, 94%) as a colourless oil, b.p., 70°C at ~20 mmHg. (Found: C, 60.22; H, 6.57; N, 10.03. $C_7H_9NO_2$ requires C, 60.42; H, 6.52; N, 10.07%); δ ($CDCl_3$), 7.50 (1H, d, J 1.68 Hz, furan 5-H), 6.82 (1H, d, J 3.64 Hz, furan 3-H), 6.46 (1H, dd, J 3.64, 1.68 Hz, furan 4-H), 3.75 (3H, s, OCH_3), 3.36 (3H, s, NCH_3); $\nu_{max.}$ (film), 3150, 2950, 1690, 1500, 1300, 1220, 1050, 990, 900 and 760 cm^{-1}; m/z 139.0631 (M^+, 23%, $C_7H_9NO_2$ requires 139.0633), 125(25), 108(17), 95(100) and 82(13).

5.22 METHYL N-PHENYLFURAN-2-CARBOXIMIDATE (159)

A solution of sodium methoxide (11.0 g, 0.204 mol) in methanol (30 ml) was added dropwise to a solution of N-phenylfuran-2-carboximidoyl chloride (158) (10.83 g, 0.053 mol) at 0°C. The solution was stirred at 0°C for a further five hours and allowed to reach room temperature (21°C) and stirred for two hours. Work- up as for (129) yielded a pale brown oil which was purified by distillation under reduced pressure to give the pure imidate (159) (10.26 g, 97%) as a colourless oil, b.p., 94°C at 0.1 mmHg. On cooling a colourless solid was obtained; m.p., 39 - 40°C. (Found: C, 71.54; H, 5.45; N, 6.88. $C_{12}H_{11}NO_2$ requires C, 71.63; H, 5.51; N, 6.96%); δ (d_6-DMSO), 7.69 (1H, d,

J 1.67 Hz, furan 5-H), 7.31 (2H, t, phenyl 3-H), 7.07 (1H, t, phenyl 4-H), 6.78 (2H, d, phenyl 2-H), 6.45 (1H, dd, J 3.90, 1.67 Hz, furan 4-H), 6.05 (1H, d, J 3.90 Hz, furan 3-H), 3.86 (3H, s, OCH_3); $\nu_{max.}$ (film), 3200, 3050, 1680, 1615, 1505, 1250, 1140 and 780 cm^{-1}; m/z 201.0787 (M^+, 100%, $C_{12}H_{11}NO_2$ requires 201.0789), 187(6), 170(58), 143(16), 95(17) and 77(14).

5.23 METHYL N-(2,4,6-TRIMETHYLPHENYL)FURAN-2-CARBOXIMIDATE (162)

A solution of sodium methoxide (12.00 g, 0.22 mol) in methanol (25 ml) was added dropwise to N-(2,4,6-trimethylphenyl)-furan-2-carboximidoyl chloride (**161**) (10.84 g, 43.80 mmol) in thf (30 ml) at 0°C. The solution was stirred at 0°C for two hours and allowed to reach room temperature (23°C) overnight. A white precipitate appeared after this period of time. Work-up as for (**129**) yielded a pale yellow oil which was purified by distillation under reduced pressure to give the pure imidate (**162**) (10.01 g, 94%) as a colourless oil, b.p., 115°C at 0.3 mmHg. On cooling a colourless solid was obtained; m.p., 46 - 47°C. (Found: C, 73.42; H, 7.03; N, 5.58. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%); δ ($CDCl_3$), 7.36 (1H, d, J 1.67 Hz, furan 5-H), 6.89 (2H, s, aryl 3-H), 6.22 (1H, dd, J 3.90, 1.67 Hz, furan 4-H), 5.88 (1H, d, J 3.90 Hz, furan 3-H), 4.05 (3H, s, OCH_3), 2.28 (3H, s, aryl CH_3), 1.99 (6H, s, 2 x aryl CH_3); $\nu_{max.}$ (mull), 3150, 2950, 1660, 1470, 1290, 1240, 1180, 1030, 860 and 760 cm^{-1}; m/z 243.1263 (M^+, 4%, $C_{15}H_{17}NO_2$ requires 243.1259), 229(48), 194(12), 149(34), 134(100) and 95(53).

5.24 GENERAL METHODS FOR LITHIATION AND DEUTERATION STUDIES OF THE THIOPHENE- AND FURAN-2-CARBOXIMIDATES

METHOD A

^{n}BuLi or ^{s}BuLi, hexane or diethyl ether as solvent. To the imidate (0.50 g) in hexane or diethyl ether was added commercial ^{n}BuLi in hexane or ^{s}BuLi in cyclohexane at the required temperature. The mixture was stirred under an inert atmosphere for the requisite time. The electrophile (MeOD or D_2O) was added, the mixture allowed to warm to room temperature, and then stirred for a further twelve hours unless otherwise stated. Water (10 ml) and then diethyl ether (60 ml) were added. The organic solution was separated, washed with water (2 x 10 ml) and brine (1 x 10 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the products which were analysed by nmr, the results of which are shown in their respective Tables.

METHOD B

DME or thf as solvent. The procedure was the same as for Method A, except that the solvent was removed under reduced pressure prior to the addition of water. Solids were then suspended in diethyl ether (60 ml).

METHOD C

Lithiations with LDA. To diisopropylamine in the required solvent was added an equimolar quantity of ^{n}BuLi at the requisite temperature. The imidate derivatives, in the required solvent (10 ml) were then added and the experiment continued as in Methods A or B.

5.25 N-^{t}BUTYL-3-METHYLFURAN-2-CARBOXAMIDE (**181**)

^{t}Butylamine (5.82 ml, 55.36 mmol) was added dropwise to 3-methylfuran-2-carbonyl chloride (**185**) (4.00 g, 27.68 mmol) dissolved in dichloromethane (50 ml) with the reaction temperature maintained below 10°C. When the amine had been added the reaction mixture was stirred at room temperature for twelve hours. The solution was then washed with water (2 x 40 ml) and separated. The aqueous washings were basified to pH 11 (KOH aqueous, 40% w/w) and extracted with dichloromethane (2 x 40 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to give the amide (**181**) as a colourless crystalline solid (4.78 g, 95%) which was pure by tlc analysis. A small sample was recrystallised for analysis (light petroleum) to yield colourless needles; m.p., 87 - 89°C. (Found: C, 66.06; H, 8.37; N, 7.29. $C_{10}H_{15}NO_2$ requires C, 66.27; H, 8.34; N, 7.73%); δ ($CDCl_3$), 7.15 (1H, d, *J* 1.61 Hz, furan 5-H), 6.20 (1H, d, *J* 1.61 Hz, furan 4-H), 6.10 (1H, br., NH), 2.29 (3H, s, CH_3), 1.36 (9H, s, ^{t}Bu); $\nu_{max.}$ (mull), 3350, 2910, 1645, 1615, 1540, 1455, 1310, 1280, 1205, 860 and 760 cm^{-1}; *m/z* 181.1099 (M^{+}, 7%, $C_{10}H_{15}NO_2$ requires 181.1103), 109(46), 57(39), 53(100) and 51(27).

5.26 5-METHYLFURAN-2-CARBOXYLIC ACID (**188**)

Furan-2-carboxylic acid (**187**) (0.50 g, 4.46 mmol) was added to LDA (9.15 mmol) in thf (30 ml) at -78°C and the mixture was stirred at -78°C for half an hour, after which time MeI was added (0.83 ml, 13.38 mmol). The mixture was stirred at -78°C for a further half an hour and allowed to reach room temperature. The thf was removed *in vacuo* and ethyl acetate (80 ml) and water (15 ml) were added to the residue. The organic phase was washed

with water (2 x 10 ml), brine (1 x 10 ml) and dried ($MgSO_4$) and the solvent was removed in vacuo to give the crude product (**188**) (0.40 g, 71%). A small sample was purified by sublimation to yield colourless needles; m.p., 106 - 108°C (lit.,[131] 108 - 109°C). (Found: C, 57.19; H, 4.64. Calculated for $C_6H_6O_3$, C, 57.14; H, 4.80%); δ (d_6-acetone), 9.92 (1H, br., OH), 7.13 (1H, d, J 3.35 Hz, furan 3-H), 6.23 (1H, d, J 3.35 Hz, furan 4-H), 2.35 (3H, s, CH_3), m/z 126.0316 (M^+, 100%, calculated for $C_6H_6O_3$ 126.0317), 109(38), 81(36), 69(18) and 57(27).

5.27 N-^{t}BUTYL-5-METHYLFURAN-2-CARBOXAMIDE (183)

^{t}Butylamine (6.78 ml, 64.50 mmol) was added dropwise to 5-methylfuran-2-carbonyl chloride (**190**) (4.66 g, 32.25 mmol) dissolved in dichloromethane (50 ml) with the reaction temperature maintained below 10°C. On completion of the addition, the mixture was stirred at room temperature for twelve hours. Work-up as for (**181**) yielded the amide (**183**) as a yellow waxy solid (5.50 g, 94%) which was pure by tlc analysis. A small sample was recrystallised for analysis (light petroleum) to yield a pale yellow solid; m.p., 64 - 66°C. (Found: C, 66.15; H, 8.51; N, 7.39. $C_{10}H_{15}NO_2$ requires C, 66.27; H, 8.34; N, 7.73%); δ ($CDCl_3$), 6.83 (1H, d, J 3.24 Hz, furan 3-H), 6.08 (1H, br., NH), 5.96 (1H, d, J 3.24 Hz, furan 4-H), 2.23 (3H, s, CH_3), 1.36 (9H, s, ^{t}Bu); $\nu_{max.}$ (mull), 3350, 2900, 1670, 1610, 1555, 1450, 1210, 1020, 845 and 765 cm^{-1}; m/z 181.1101 (M^+, 15%, $C_{10}H_{15}NO_2$ requires 181.1103), 166(15), 125(21), 109(100), 57(14) and 53(10).

5.28 N-^{t}BUTYL-3,5-DIMETHYLFURAN-2-CARBOXAMIDE (191)

To the amide (**183**) (4.50 g, 24.90 mmol) in DME (200 ml) at -78°C was added ^{n}BuLi (35.74 ml, 52.20 mmol) and the mixture stirred at -78°C for half an hour to give a yellow dianion. After which, MeI (1.63 ml, 26.10 mmol) was added and the mixture stirred at -78°C for a further half an hour and then allowed to warm to room temperature. The DME was removed *in vacuo* and ethyl acetate (150 ml) and water (30 ml) were added to the residue. The organic phase was washed with water (3 x 15 ml), brine (1 x 20 ml) and dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude product. Purification by flash chromatography (ethyl acetate - light petroleum, 1:1 as eluant) yielded the pure amide (**191**) as a waxy solid (4.61 g, 95%); δ ($CDCl_3$), 6.02 (1H, br., NH), 5.83 (1H, s, furan 4-H), 2.24 (3H, s, CH_3), 2.18 (3H, s, CH_3), 1.37 (9H, s, ^{t}Bu); $\nu_{max.}$ (mull), 3350, 2950, 1665, 1560, 1505, 1455, 1365, 1295 and 810 cm^{-1}; *m/z* 195.1261 (M^{+}, 24%, $C_{11}H_{17}NO_2$ requires 195.1259), 180(10), 139(26), 123(100), 109(9) and 41(12).

5.29 4,4-DIMETHYL-2-(2-FURYL)OXAZOLINE (197)

Meyers' general approach to oxazoline synthesis was followed. Furan-2-carboxylic acid (20.0 g, 0.18 mol) and distilled thionyl chloride (100 ml, 1.38 mol) were heated under reflux for four hours. The excess of thionyl chloride was removed *in vacuo* and the residue distilled under reduced pressure to give the acid chloride (16.63 g, 71%), b.p., 68°C at ~15 mmHg.

A solution of 2-amino-2-methyl-propan-1-ol (22.72 g, 0.25 mol) in dichloromethane (60 ml) was added to a solution of the acid chloride (16.63 g, 0.13 mol) in dichloromethane (60 ml),

with the reaction temperature held below 10°C. The mixture was stirred for twelve hours, washed with water (2 x 40 ml), brine (1 x 30 ml), dried ($MgSO_4$) and evaporated to give the crude amide, N-(2-hydroxy-1,1-dimethylethyl)furan-2-carboxamide (**198**) as a pale yellow, viscous oil which was used without further purification.

The amide (**198**) (20.11 g, 0.11 mol) was dissolved in toluene and thionyl chloride (31.89 ml, 0.44 mol) was added dropwise keeping the reaction temperature below 30°C. Stirring was continued for twelve hours at 25°C, after which the toluene was removed in vacuo and the residue taken up into water (100 ml). The solution was basified to pH 12 (NaOH, 40% w/w) and extracted with diethyl eher (3 x 40 ml). The organic extracts were combined and dried ($MgSO_4$). Evaporation of the solvent gave the crude product as a yellow oil which was purified by distillation under reduced pressure to give the pure product (**197**) (16.15 g, 89%) as a colourless oil, b.p., 75°C at 0.15 mmHg. On cooling a colourless crystalline solid was obtained; m.p., 36 - 37°C (lit.,[19] 36.5 - 37.5°C); δ ($CDCl_3$), 7.52 (1H, dd, J 1.68, 0.67 Hz, furan 5-H), 6.92 (1H, dd, J 3.36, 0.67 Hz, furan 3-H), 6.45 (1H, dd, J 3.36, 1.68 Hz, furan 4-H), 4.04 (2H, s, OCH_2), 1.34 (6H, s, 2 x CH_3); $\nu_{max.}$ (film), 3100, 2950, 1660, 1470, 1305, 1180, 1075 and 960 cm^{-1}; m/z 165.0784 (M^+, 50%, calculated for $C_9H_{11}NO_2$ 165.0790), 150(100), 135(15), 122(26), 95(100) and 72(12).

5.30 4,4-DIMETHYL-2-(5-METHYL-2-FURYL)OXAZOLINE (**199**)

Furyl-oxazoline (**197**) (4.00 g, 24.00 mmol) dissolved in thf (15 ml) was added to a solution of LDA (27.40 mmol) and TMEDA (27.40 mmol) in thf (100 ml) at -78°C. The mixture was stirred

at -78°C for one hour and then MeI (7.55 ml, 0.12 mol) was added. The mixture was allowed to warm to room temperature and stirred for a further four hours. The solvent was removed in vacuo and the residue taken up into ethyl acetate (100 ml) and water (20 ml). The organic phase was washed with water (2 x 15 ml) and brine (1 x 20 ml) and dried ($MgSO_4$). The solvent was evaporated to yield the crude product (**199**) (3.69 g, 85%) as a brown oil, which was spectroscopically pure; δ ($CDCl_3$), 6.82 (1H, d, J 1.61 Hz, furan 3-H), 6.08 (1H, d, J 1.61 Hz, furan 4-H), 4.08 (2H, s, OCH_2), 2.38 (3H, s, furan CH_3), 1.36 (6H, s, 2 x oxazoline CH_3); $\nu_{max.}$ (film), 2920, 1675, 1600, 1630, 1460, 1320, 1110 and 800 cm^{-1}; m/z 179.0948 (M^+, 27%, calculated for $C_{10}H_{13}NO_2$ 179.0946), 164(100), 152(24), 136(30), 109(77), 95(40) and 57(52).

5.31 4,4-DIMETHYL-2-(3,5-DIMETHYL-2-FURYL)OXAZOLINE (**200**)

To 5-methylfuryl-oxazoline (**199**) (3.47 g, 19.40 mmol) dissolved in thf (150 ml) at -78°C was added ^nBuLi (19.92 ml, 29.08 mmol), and the mixture stirred at -78°C for half an hour, after which time, MeI (6.09 ml, 96.93 mmol) was added. The mixture was stirred at -78°C for half an hour and then allowed to warm to room temperature. The solvent was removed in vacuo and the residue taken up in ethyl acetate (100 ml) and water (20 ml). The organic phase was washed with water (2 x 15 ml) and brine (1 x 15 ml) and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product (**200**) as a mobile oil (3.27 g, 87%) which was chromatographically pure; δ ($CDCl_3$), 5.92 (1H, s, furan 4-H), 4.05 (2H, s, OCH_2), 2.32 (3H, s, furan CH_3), 2.23 (3H, s, furan CH_3), 1.38 (6H, s, 2 x oxazoline CH_3); $\nu_{max.}$ (film), 2950, 1655, 1625, 1550, 1410, 1320, 1190, 1145, 1060, 970 and 810 cm^{-1}; m/z 193 (M^+, 53%), 178(100), 150(35) and 122(43).

5.32 4,4-DIMETHYL-2-(3-TRIMETHYLSILYLMETHYL-5-METHYL-2-FURYL)OXAZOLINE (201)

To the 3,5-dimethylfuryl-oxazoline (**200**) (0.30 g, 1.55 mmol) dissolved in thf (30 ml) at -78°C was added ^{s}BuLi (2.03 ml, 2.18 mmol) and the mixture stirred at -78°C for half an hour. The solution was quickly warmed to room temperature and TMSCl (0.20 ml, 1.55 mmol) was added. The solution was stirred for half an hour and then MeOH (5 ml) was added. The solvent was removed *in vacuo* and the residue taken up in diethyl ether (80 ml) and water (20 ml). The organic phase was washed with water (2 x 10 ml) and brine (1 x 10 ml) and then dried ($MgSO_4$). Evaporation of the solvent yielded (**201**) as a viscous yellow oil (0.33 g, 80%) which was spectroscopically pure; δ ($CDCl_3$), 5.78 (1H, s, furan 4-H), 4.33 (2H, s, OCH_2), 2.55 (3H, s, furan CH_3), 2.43 (2H, s, CH_2TMS), 1.67 (6H, s, 2 x oxazoline CH_3), 0.37 (9H, s, TMS); $\nu_{max.}$ (film), 2940, 1655, 1620, 1545, 1420, 1320, 1255, 1190, 1060 and 970 cm^{-1}; *m/z* 265.1503 (M^+, 31%, $C_{14}H_{23}NO_2$ requires 265.1498), 250(29), 195(10) and 73(100).

5.33 N-PHENYLTHIOPHENE-2-CARBOXAMIDE (209)

Thiophene-2-carbonyl chloride (**126**) (20.0 g, 0.137 mol) in dichloromethane (50 ml) was added dropwise to a solution of aniline (12.70 g, 0.137 mol), triethylamine (28.50 ml, 0.21 mol) and dichloromethane (100 ml), keeping the reaction temperature below 25°C. The resulting solution was stirred for twelve hours, washed with water (3 x 30 ml), and dried ($MgSO_4$). The combined washings were basified to pH 11 (KOH aqueous, 40% w/w) and extracted with CH_2Cl_2 (3 x 30 ml) and the extracts dried

($MgSO_4$). The combined organic solutions were evaporated under reduced pressure to give the crude product. Recrystallisation (ethyl acetate - light petroleum) gave the pure amide (**209**) (25.90 g, 93%) as a colourless crystalline solid; m.p., 148 - 149°C (lit.,[163] 144 - 145°C). (Found: C, 65.05; H, 4.45; N, 6.85. Calculated for $C_{11}H_9NOS$ C, 65.00; H, 4.46; N, 6.89%); δ (d_6- DMSO), 8.09 (1H, dd, J 3.92, 1.12 Hz, thiophene 3-H), 7.89 (1H, dd, J 5.04, 1.12 Hz, thiophene 5-H), 7.77 (2H, d, phenyl 2-H), 7.40 (2H, t, phenyl 3-H), 7.27 (1H, dd, J 5.04, 3.92 Hz, thiophene 4-H), 7.15 (1H, t, phenyl 4-H); $\nu_{max.}$ (mull), 3310, 2900, 1635, 1600, 1535, 1450 and 760 cm^{-1}; m/z 203 (M^+, 27%), 111 (100) and 83(9).

5.34 N-PHENYL-3-DEUTERIOTHIOPHENE-2-CARBOXAMIDE (210)

^nBuLi (3.93 ml, 5.41 mmol) was added to N-phenylthiophene-2-carboxamide (**209**) (0.50 g, 2.46 mmol) in thf (30 ml) at -78°C and the mixture stirred at -78°C for one hour. After which, D_2O (1 ml) was added and the mixture was allowed to reach room temperature. The solvent was removed *in vacuo* and the residue suspended in distilled water and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with water (1 x 20 ml), brine (1 x 20 ml) and dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield a colourless crystalline solid (0.48 g). Recrystallisation (ethyl acetate - light petroleum, 40 - 60°C) gave the pure amide (**210**) as a colourless crystalline solid; m.p., 149 - 150°C; δ (d_6-DMSO), 7.89 (1H, d, J 5.04 Hz, thiophene 5-H), 7.77 (2H, d, phenyl 2-H), 7.40 (2H, t, phenyl 3-H), 7.27 (1H, d, J 5.04 Hz, thiophene 4-H), 7.15 (1H, t, phenyl 4-H).

5.35 N-PHENYL-3-METHYLTHIOPHENE-2-CARBOXAMIDE (213)

3-Methylthiophene-2-carbonyl chloride (**212**) (20.0 g, 0.125 mol) in dichloromethane (50 ml) was added dropwise to a solution of aniline (11.59 g, 0.125 mol), triethylamine (25.86 ml, 0.187 mol) and dichloromethane (100 ml) at room temperature (25°C). The resulting solution was stirred for twelve hours, washed with water (3 x 30 ml) and dried ($MgSO_4$). The combined washings were basified to pH 11 (KOH aqueous, 40% w/w) and extracted with CH_2Cl_2 (3 x 40 ml) and the extracts dried ($MgSO_4$). The combined organic extracts were evaporated under reduced pressure to give the crude product. Recrystallisation (ethyl acetate - light petroleum) gave the pure amide (**213**) (26.50 g, 98%) as colourless needles; m.p., 130 - 131°C (lit.,[164] 126°C). (Found: C, 66.43; H, 5.10; N, 6.38. Calculated for $C_{12}H_{11}NOS$ C, 66.33; H, 5.10; N, 6.45%); δ ($CDCl_3$), 7.63 (2H, d, phenyl 2-H), 7.57 (1H, br., NH), 7.41 (2H, t, phenyl 3-H), 7.37 (1H, d, J 5.03 Hz, thiophene 5-H), 7.19 (1H, t, phenyl 4-H), 6.98 (1H, d, J 5.03 Hz, thiophene 4-H), 2.63 (3H, s, CH_3); $\nu_{max.}$ (mull), 3295, 2900, 1645, 1600, 1520, 1320, 1260 and 760 cm^{-1}; m/z 217.0560 (M^+, 17%, calculated for $C_{12}H_{11}NOS$ 217.0561), 125(100) and 97(19).

5.36 N-PHENYL-3,5-DIMETHYLTHIOPHENE-2-CARBOXAMIDE (217)

Aniline (10.50 ml, 0.12 mol) was added dropwise to 3,5-dimethylthiophene-2-carbonyl chloride (**216**) (10.05 g, 0.06 mol) dissolved in dichloromethane (60 ml) with the reaction temperature maintained below 10°C. On completion of the addition, the mixture was stirred at room temperature for twelve hours. Work-up as for (**213**) gave the spectroscopically pure product (12.98 g, 98%). A small sample was purified by recrystallisation (light

petroleum - ethyl acetate) to give the pure amide (217) as colourless crystals; m.p., 102 - 103°C; δ ($CDCl_3$), 7.54 (2H, d, phenyl 2-H), 7.29 (2H, t, phenyl 3-H), 7.08 (1H, t, phenyl 4-H), 6.57 (1H, s, thiophene 4-H), 2.47 (3H, s, thiophene CH_3), 2.42 (3H, s, thiophene CH_3); $\nu_{max.}$ (mull), 3250, 3050, 2920, 1645, 1600, 1535, 1445, 1325 and 1270 cm^{-1}; m/z 231.0715 (M^+, 41%, $C_{13}H_{13}NOS$ requires 231.0718), 173(20), 139(100) and 67(8).

5.37 N-PHENYL-3-TRIMETHYLSILYLMETHYL-5-METHYLTHIOPHENE-2-CARBOXAMIDE (218)

^nBuLi (18.24 ml, 26.63 ml) was added to the amide (217) (3.00 g, 26.63 ml) in thf (180 ml) at -20°C and the mixture stirred at -20°C for half an hour to give a brown dianion. After which, TMSCl (1.68 ml, 13.25 mmol) was added and the mixture left at -20°C for quarter of an hour and then allowed to reach room temperature. The solvent was removed in vacuo and ethyl acetate (150 ml) and water were added to the residue. The organic phase was washed with water (2 x 20 ml), brine (1 x 20 ml) and dried ($MgSO_4$) and the solvent was removed in vacuo to give the crude product which was purified by Kugelröhr distillation to yield the pure amide (218) as a pale yellow viscous oil (3.15 g, 80%); δ ($CDCl_3$), 7.62 (2H, d, phenyl 2-H), 7.42 (2H, t, phenyl 3-H), 7.24 (1H, t, phenyl 4-H), 6.56 (1H, s, thiophene 4-H), 2.72 (2H, s, CH_2TMS), 2.56 (3H, s, thiophene CH_3), 0.25 (9H, s, TMS); $\nu_{max.}$ (film), 3330, 3060, 2940, 1655, 1520, 1450, 1320, 1250 and 850 cm^{-1}; m/z 303.1111 (M^+, 56%, $C_{16}H_{21}NOSSi$ requires 303.1113), 288(74), 211(64), 169(11), 139(16), 73(100) and 45(23).

5.38 N-PHENYL-3-^{t}BUTYLDIMETHYLSILYLMETHYL-5-METHYLTHIOPHENE-2-CARBOXAMIDE (219)

^{n}BuLi (6.22 ml, 9.09 ml) was added to the amide (**217**) (1.00 g, 4.33 mmol) in thf (60 ml) at -20°C and the mixture stirred for half an hour to form a brown dianion. After which, TBDMSCl (0.67 g, 4.42 mmol) was added and the reaction mixture allowed to reach room temperature. Work-up as for (**218**) gave the amide (**219**) as a viscous yellow oil (1.35 g, 90%) which was pure by tlc analysis; δ ($CDCl_3$), 7.60 (2H, d, phenyl 2-H), 7.38 (2H, t, phenyl 3-H), 7.18 (1H, t, phenyl 4-H), 6.55 (1H, s, thiophene 4-H), 2.70 (2H, s, $C\underline{H}_2$TBDMS), 2.53 (3H, s, thiophene CH_3), 1.01 (9H, s, $Si(CH_3)_2{}^{t}\underline{Bu}$), 0.22 (6H, s, $Si\underline{(CH_3)_2}{}^{t}Bu$); $\nu_{max.}$ (film), 3310, 3050, 2930, 1650, 1595, 1515, 1455, 1315, 1250 and 1155 cm^{-1}; m/z 345.1575 ($\underline{M}^{+}$, 1%, $C_{19}H_{27}NOSSi$ requires 345.1583), 288(100), 214(7) and 73(19).

5.39 N-PHENYL-3-^{t}BUTYLDIMETHYLSILYLMETHYL-5-METHYLTHIOPHENE-2-CARBOXIMIDOYL CHLORIDE (220)

Amide (**219**) (1.19 g, 3.45 mmol) was heated under reflux with thionyl chloride (25 ml, 0.34 mol) for three hours. Excess of thionyl chloride was removed in vacuo to yield the product (**220**) as a viscous oil (1.26 g, 100%) which was spectroscopically pure; δ ($CDCl_3$), 7.44 (2H, t, phenyl 3-H), 7.25 (1H, t, phenyl 4-H), 7.03 (2H, d, phenyl 2-H), 6.61 (1H, s, thiophene 4-H), 2.81 (2H, s, $C\underline{H}_2$TBDMS), 2.57 (3H, s, thiophene CH_3), 1.96 (9H, s, $Si(CH_3)_2{}^{t}\underline{Bu}$), 0.15 (6H, s, $Si\underline{(CH_3)_2}{}^{t}Bu$); $\nu_{max.}$ (film), 3060, 2900, 1640, 1590, 1440, 1250, 1145, 900 and 820 cm^{-1}.

5.40 METHYL N-PHENYL-3-^{t}BUTYLDIMETHYLSILYLMETHYL-5-METHYL-THIOPHENE-2-CARBOXIMIDATE (221)

A solution of sodium methoxide (0.10 g, 4.09 mmol) in methanol (20 ml) was added dropwise to the imidoyl chloride (220) (1.35 g, 3.71 mmol) in thf (30 ml) at 0°C. The solution was stirred at 0°C for one hour and allowed to warm to room temperature. The bulk of the methanol and thf were removed *in vacuo* and the residue suspended in water (30 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organic layers were washed with brine (1 x 20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the required imidate (221) as a yellow viscous oil (1.25 g, 94%) which was pure by nmr analysis; δ ($CDCl_3$), 7.33 (2H, t, phenyl 3-H), 7.11 (1H, t, phenyl 4-H), 6.91 (2H, d, phenyl 2-H), 6.35 (1H, s, thiophene 4-H), 4.01 (3H, s, OCH_3), 2.41 (3H, s, thiophene CH_3), 2.15 (2H, s, CH_2TBDMS), 1.03 (9H, s, $Si(CH_3)_2{}^{t}Bu$), 0.10 (6H, s, $Si(CH_3)_2{}^{t}Bu$); $\nu_{max.}$ (film), 3020, 2910, 1640, 1590, 1460, 1365, 1075 and 825 cm^{-1}; m/z 359.1739 (M^{+}, 3%, $C_{20}H_{29}NOS$ requires 359.1739), 302(100), 213(7) and 73(24).

5.41 2-DIMETHYLAMINOMETHYLPYRROLE (272)[153]

A solution of dimethylamine hydrochloride (24.00 g, 0.30 mol) in formalin (24.04 g, 0.30 mol of a 40% solution) was added slowly with stirring to pyrrole (18.92 g, 0.28 mol) at such a rate that the temperature did not exceed 60°C. Stirring was continued for one hour after the addition was completed and the mixture was left for twelve hours at room temperature. The reaction mixture was poured on to sodium hydroxide solution (20%, w/w, 100 ml) and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were washed with water (2 x 20 ml),

brine (1 x 20 ml) and dried ($MgSO_4$) and the solvent was removed in vacuo to yield the spectroscopically pure product (**272**) (30.37 g, 87%). A small sample was purified for analysis by Kugelröhr distillation to yield a colourless oil which crystallised in the receiver in the form of colourless needles; m.p., 60 - 62°C (lit.,[153] 64°C); δ ($CDCl_3$), 6.99 (1H, m, pyrrole 5-H), 6.42 (2H, m, pyrrole 4-H, 3-H), 3.80 (2H, s, $\underline{CH_2}NMe_2$), 2.61 (6H, s, $N(CH_3)_2$); $\nu_{max.}$ (mull), 3370, 3100, 2850, 1455, 1345, 1240, 1005 and 830 cm^{-1}; m/z 124.1002 ($\underline{M}^+$, 38%, calculated for $C_7H_{12}N_2$ 124.001), 80(100), 53(14) and 44(26).

5.42 2-DIETHYLAMINOMETHYLPYRROLE (274)

MeI (0.18 ml, 2.96 mmol) was added to a solution of 2-dimethylaminomethylpyrrole (0.35 g, 2.82 mmol) in dry thf (2.5 ml) at 0°C and the reaction stirred for one hour at 0°C. A white precipitate developed. Diethylamine (20 ml, 0.19 mol) was then added and the reaction mixture was refluxed for two hours. The bulk of the solvents were then removed in vacuo and the residue was suspended in water and extracted with diethyl ether (3 x 30 ml). The combined organic extracts were washed with water (2 x 10 ml), brine (1 x 10 ml) and dried ($MgSO_4$) and the solvent was removed in vacuo to yield the product as a brown oil (0.15 g, 35%) which was spectroscopically pure (by ^1H nmr); δ ($CDCl_3$), 8.80 (1H, br., NH), 6.62 (1H, m, pyrrole 5-H), 6.03 (1H, m, pyrrole 4-H), 5.94 (1H, m, pyrrole 3-H), 3.50 (2H, s, $\underline{CH_2}$-NEt_2), 2.46 (4H, q, J 8.91 Hz, $C\underline{H_2}CH_3$), 0.94 (6H, t, J 8.91 Hz, $CH_2C\underline{H_3}$); $\nu_{max.}$ (film), 3360, 3200, 2950, 2800, 1475, 1370, 1120, 1030, 800 and 720 cm^{-1}; m/z 152.13103 ($\underline{M}^+$, 15%, calculated for $C_9H_{16}N$ 152.13135), 80(100), 72(40) and 58(63).

5.43 2-METHOXYMETHYLPYRROLE (278)

MeI (1.10 ml, 0.018 mol) was added dropwise to a solution of 2-dimethylaminomethylpyrrole (2.00 g, 0.16 mol) in thf (6 ml) at 0°C and the reaction mixture stirred for one hour at this temperature. A white precipitate developed. Acetonitrile (2 ml) was then added and the precipitate virtually dissolved. Sodium methoxide (1.31 g, 0.024 mol) in anhydrous methanol was added dropwise, and the reaction mixture was then heated under reflux for two hours. The bulk of the solvents were removed *in vacuo* and the residue suspended in water and extracted with diethyl ether (3 x 40 ml). The combined organic extracts were washed with water (2 x 10 ml), brine (1 x 10 ml) and dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield a brown oil which was purified by Kugelröhr distillation to give the pure product (278) (1.58 g, 88%) as a colourless oil; δ ($CDCl_3$), 6.72 (1H, m, pyrrole 5-H), 6.14 (2H, m, pyrrole 4-H, 3-H), 4.42 (2H, s, $OC\underline{H}_2$), 3.31 (3H, s, OCH_3); $\nu_{max.}$ (film), 3300, 2850, 1455, 1370, 1180, 1050 and 790 cm^{-1}; m/z 111.0683 ($\underline{M}^+$, 19%, C_6H_9NO requires 111.0684), 80(100) and 53(13).

5.44 2,5-DIMETHYL-3-DIMETHYLAMINOMETHYLPYRROLE (281)[157]

A solution of dimethylamine hydrochloride (10.79 g, 0.13 mol) in commercial aqueous formalin (10.75 g, 0.13 mol) was added slowly with stirring to 2,5-dimethylpyrrole (12.00 g, 0.126 mol) at such a rate that the temperature did not exceed 60°C. After the addition was completed the mixture was left for twelve hours at room temperature. The reaction mixture was poured on to a solution of sodium hydroxide (20% w/w, 100 ml) and extracted with diethyl ether (4 x 40 ml). The combined organic extracts were

washed with water (2 x 10 ml), brine (1 x 20 ml) and dried ($MgSO_4$) and the solvent removed in vacuo to yield the spectroscopically pure product (by ^1H nmr) as a yellow solid (16.75 g, 87%); m.p., 96 - 98°C (lit.,[157] 99 - 100°C); δ ($CDCl_3$), 8.75 (1H, br., NH), 5.97 (1H, s, pyrrole 4-H), 3.49 (2H, s, CH_2NMe_2), 2.47 (6H, s, NCH_3), 2.39 (3H, s, CH_3), 2.33 (3H, s, CH_3); $\nu_{max.}$ (mull), 3220, 3150, 2850, 1600, 1450, 1365, 1700, 1005 and 845 cm^{-1}; m/z 152.1311 (M^+, 12%, calculated for $C_9H_{10}N_2$ 152.1314), 107(100), 66(60) and 44(33).

5.45 FLASH VACUUM PYROLYSIS (F.V.P.) INSTRUMENTATION AND EXPERIMENTAL TECHNIQUES

All pyrolyses were conducted in the apparatus shown in Figure 5.1. The apparatus was connected to a broad sweep vacuum

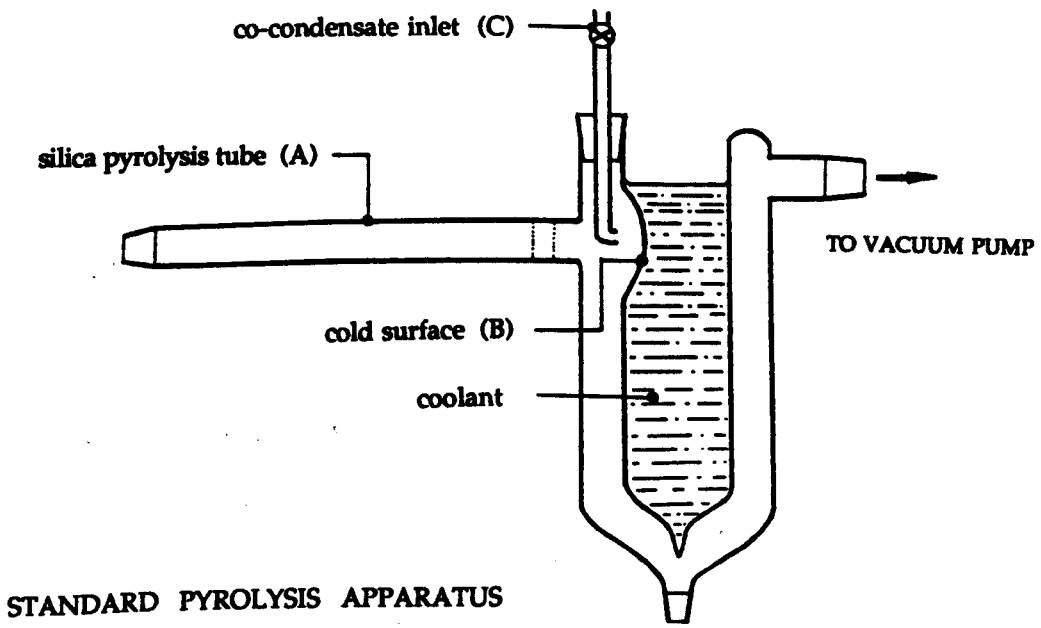


FIGURE 5.1

pump (Edwards rotary pump 8) capable of maintaining a pressure of between 10^{-2} and 10^{-3} torr (measured by an Edwards 1105 digital recorder), and the silicon pyrolyses tube (A) was heated by an external electric oven to the desired pyrolytic temperature as measured by insertion of a thermocouple (0°C - 1000°C).

The material to be pyrolysed was dissolved in a 50 ml B19 round-bottomed flask, and the solvent removed in vacuo so as to deposit the substrate as a thin film or glass on the inner surface of the flask. The flask was then fitted to the end of the silica tube and the system was evacuated, and the cold finger was cooled to -196°C by liquid nitrogen or to -78°C by a solid carbon dioxide/acetone slush. Co-condensates were introduced into the apparatus just before the cold surfaces (B) through the inlets (C). Solids were sublimed in the hot zone by heating in a Kugelröhr oven so that the pyrolysis proceeded at the rate of 0.1 g hr^{-1}.

When the pyrolysis was complete the vacuum pump was isolated and dry nitrogen or argon was introduced through a tap in the pumping arm. The round-bottomed flask and oven were removed and replaced with a drying tube while nitrogen or argon gas were passed through the apparatus. When the oven tube had cooled, the coolant in the cold finger was removed and the pyrolysate allowed to warm to room temperature under the inert atmosphere. The pyrolysate was removed from the cold finger by addition of a suitable solvent (usually dichloromethane).

Pyrolysis involving silica catalysts were carried out by pre-coating five silica glass tubes (50 mm x 8 mm O/D) with the catalyst (SiO_2; Merck type 5717), and introducing them into the pyrolysis tube (A) prior to the pyrolysis.

5.46 PYROLYSIS OF 2-DIMETHYLAMINOMETHYLPYRROLE (272)

2-Dimethylaminomethylpyrrole (**272**) (0.293 g, 2.36 mmol) was pyrolysed at 650°C/2 x 10^{-3} torr over four hours with a sublimation temperature of 20°C to give a pale yellow pyrolysate on the cold finger (-196°C). After warming to room temperature the pyrolysate was removed by dichloromethane (40 ml) and the solvent was then evaporated to yield a pale yellow solid (0.282 g). ^{1}H Nmr analysis indicated the presence of recovered starting material (**272**) (85%) and "dimer" (**273**) (15%). ^{1}H Nmr for "dimer" (**273**); δ ($CDCl_3$), 6.62 (2H, m, 2 x pyrrole 5-H), 6.08 (4H, m, 2 x pyrrole 3-H, 4-H), 4.88(2H, s, $-CH_2-$), 3.40 (2H, s, $\underline{CH_2}NMe_2$), 2.26 (6H, s, $N(CH_3)_2$).

5.46.1 CO-CONDENSATION WITH DIETHYLAMINE

2-Dimethylaminomethylpyrrole (**272**) (0.244 g, 1.97 mmol) was pyrolysed at 650°C/2 x 10^{-3} torr over three hours with co-condensation of diethylamine (20 ml) onto the cold finger (-78°C). After this time, the pyrolysate was allowed to warm to room temperature and the diethylamine was removed <u>in vacuo</u> to give a brown oil. The oil was suspended in water (5 ml) and extracted with diethyl ether (3 x 20 ml). The combined organic extracts were washed with brine (5 ml) and dried ($MgSO_4$) and the solvent was removed <u>in vacuo</u> to yield a pale brown oil (0.22 g). ^{1}H Nmr analysis indicated the presence of 2-diethylaminomethylpyrrole (**274**) and (**272**) in a 16:1 ratio. These two products proved to be inseparable by chromatographic techniques.

5.46.2 CO-CONDENSATION WITH THIOPHENOL

2-Dimethylaminomethylpyrrole (272) (0.229 g, 1.85 mmol) was pyrolysed at 650°C/2 x 10^{-3} torr over four hours with co-condensation of thiophenol (20 ml) onto the cold finger (-196°C). After which, the pyrolysate was allowed to reach room temperature and the thiophenol was removed in vacuo to give a pale brown oil. ^{1}H Nmr analysis indicated the presence of 2-phenylthiomethylpyrrole (275) and (272) in a 4:1 ratio. Separation of the crude pyrolysate by flash column chromatography (Al_2O_3 : light petroleum-ethyl acetate, 9:1 as eluant) yielded the pure product (275) (0.19 g) as a colourless waxy solid; m.p., 54 - 56°C; δ ($CDCl_3$), 8.19 (1H, br., NH), 7.25 - 7.04 (5H, m, phenyl-H), 6.60 (1H, m, pyrrole 5-H), 6.01 (1H, m, pyrrole 3-H), 5.94 (1H, m, pyrrole 4-H), 4.04 (2H, s, CH_2S); $\nu_{max.}$ (mull), 3340, 3020, 2910, 1575, 1460, 1420, 1070 and 730 cm^{-1}; m/z 189.0612 (M^+, 6%, $C_{11}H_{11}NS$ requires 189.0612), 80(100) and 109(17).

5.46.3 CO-CONDENSATION WITH METHANOL

2-Dimethylaminomethylpyrrole (272) (0.156 g, 1.26 mmol) was pyrolysed at 650°C/2 x 10^{-3} torr over four hours with co-condensation of methanol (15 ml) onto the cold finger (-196°C). After which, the pyrolysate was warmed to room temperature and the methanol was removed in vacuo to yield the pale yellow solid (0.152 g). ^{1}H Nmr analysis indicated only the presence of recovered starting material (272).

5.46.4 CO-CONDENSATION WITH ACETIC ANHYDRIDE AND ACETIC ACID

Pyrolysis of (272) at 650°C/2 x 10^{-3} torr with co-condensation of acetic acid or acetic anhydride on to the cold finger (-196°C), only yielded intractable products.

5.46.5 CO-CONDENSATION WITH DIMETHYL ACETYLENEDICARBOXYLATE

2-Dimethylaminomethylpyrrole (**272**) (0.197 g, 1.59 mmol) was pyrolysed at 650°C/2 x 10^{-3} torr over five hours with co-condensation of DMAD (10 ml) on to the cold finger (-196°C). After this time, the pyrolysate was warmed to room temperature and the DMAD was removed *in vacuo* to give a brown oil. The only isolable product after flash column chromatography (Al_2O_3 : light petroleum - ethyl acetate, 2:1 as eluant) was a colourless oil, identified to be (**276**); δ ($CDCl_3$), 4.58 (1H, s, vinylic-H), 3.96 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 2.88 (6H, s, $N(CH_3)_2$); m/z 187.0847 (M^+, 40%, calculated for $C_8H_{13}NO_4$ 187.0845), 156(50), 128(100), 114(16), 82(34), 72(53) and 68(36).

5.46.6 CO-CONDENSATION WITH CYCLOPENTADIENE

Pyrolysis of (**272**) at 650°C/2 x 10^{-3} torr with co-condensation of cyclopentadiene at -196°C failed to give any cycloadduct. Only starting material (**272**) was recovered.

5.46.7 OVER SILICA PACKING

2-Dimethylaminomethylpyrrole (**272**) (0.221 g, 1.78 mmol) was pyrolysed at 650°C/2 x 10^{-3} torr over a silica catalyst for four hours on to a cold finger (-196°C). After warming to room temperature the pyrolysate was removed by dichloromethane (30 ml). Removal of the solvent *in vacuo* yielded a brown oil. G.C. analysis indicated the presence of three major products identified by G.C./M.S. to be pyrrole, pyridine and recovered starting material (**272**), in a ratio of 1:1.7:1.9 respectively as judged by ^1H nmr integration; G.C./M.S. for pyrrole; t_r = 1.22 min, 67 (M^+, 100%) and 41(34); for pyridine; t_r = 1.17 min, 79

($\underline{M}^+$, 100%) and 52(53); for (**272**); t_r = 5.25 min, 124 ($\underline{M}^+$, 24%), 80(100), 52(25) and 44(45).

5.47 PYROLYSIS OF 2-METHOXYMETHYLPYRROLE (278)

2-Methoxymethylpyrrole (**278**) (0.100 g, 0.90 mmol) was pyrolysed at 900°C/2 x 10^{-3} torr over four hours with a sublimation temperature of between 0°C - 5°C to give a pale yellow pyrolysate on the cold finger (-196°C). After warming to room temperature, a black intractable product was formed on the cold finger which was insoluble in organic solvent.

5.47.1 CO-CONDENSATION WITH DIETHYLAMINE

2-Methoxymethylpyrrole (**278**) (0.190 g, 1.71 mmol) was pyrolysed at 900°C/2 x 10^{-3} torr over four hours with co-condensation of diethylamine (15 ml) on to the cold finger at -196°C. After which, the pyrolysate was allowed to warm to room temperature and the diethylamine was removed *in vacuo*. The residue was suspended in water (10 ml) and extracted with diethyl ether (4 x 20 ml). The combined organic extracts were washed with brine (1 x 10 ml) and dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield a brown oil (0.20 g). ^1H Nmr analysis indicated the presence of 2-diethylaminomethylpyrrole (**274**) and (**278**) in a 4:1 ratio.

5.47.2 CO-CONDENSATION WITH DIENES

Pyrolysis of (**278**) at 900°C/2 x 10^{-3} torr with co-condensation of cyclopentadiene, 2,3-dimethyl-1,3-butadiene and tetraphenylcyclopentadienone onto a cold finger at -196°C, failed to give any isolable cycloadducts.

5.48 PYROLYSIS OF 3-DIMETHYLAMINOMETHYL-2,5-DIMETHYLPYRROLE (281)

5.48.1 CO-CONDENSATION WITH DIETHYLAMINE

3-Dimethylaminomethyl-2,5-dimethylpyrrole (**281**) (0.232 g, 1.53 mmol) was pyrolysed at 700°C/2 x 10^{-3} torr over four hours with a sublimation temperature of 35°C and co-condensed with diethylamine (15 ml) on to a cold finger at -196°C. After which, the pyrolysate was allowed to warm to room temperature and the diethylamine was removed *in vacuo* to give a brown oil. The oil was suspended in water (8 ml) and extracted with diethyl ether (3 x 25 ml). The combined organic extracts were washed with brine (5 ml) and dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield a pale brown oil (0.16 g). ^{1}H Nmr analysis indicated the presence of 3-diethylaminomethyl-2,5-dimethylpyrrole (**283**) and recovered starting material (**281**) in a ratio of ~1:1. These two products proved difficult to separate by chromatographic methods. Spectral analysis for (**283**) includes; δ ($CDCl_3$), 7.86 (1H, br., NH), 5.70 (1H, s, pyrrole 4-H), 3.18 (2H, s, $\underline{CH_2}NMe_2$), 2.47(4H, q, *J* 7.12 Hz, $C\underline{H_2}CH_3$), 2.11 (3H, s, CH_3), 2.07 (3H, s, CH_3), 0.99 (6H, t, *J* 7.12 Hz, $CH_2C\underline{H_3}$); *m/z* 180.1624 ($\underline{M}^+$, 2%, calculated for $C_{11}H_{20}N_2$, 180.1627).

5.48.2 CO-CONDENSATION WITH THIOPHENOL

3-Dimethylaminomethyl-2,5-dimethylpyrrole (0.129 g, 1.16 mmol) was pyrolysed at 700°C/2 x 10^{-3} torr over four hours and co-condensed with thiophenol (15 ml) on to a cold finger at -196°C. After which, the pyrolysate was allowed to reach room temperature and the thiophenol was removed *in vacuo* to give a pale brown oil. ^{1}H Nmr analysis indicated the presence of

3-phenylthiomethyl-2,5-dimethylpyrrole (**285**) and recovered starting material (**281**) in a ratio of 2.8:1, as well as a trace of an unidentified product. Separation of the crude pyrolysate by flash column chromatography (Al_2O_3 : light petroleum - ethyl acetate, 19:1 as eluant) gave the pure product (**285**) (0.120 g) as a viscous colourless oil, which rapidly decolourised on standing at room temperature; δ ($CDCl_3$), 7.40 (1H, br., NH), 7.29 - 7.10 (5H, m, phenyl-H), 5.71 (1H, s, pyrrole 4-H), 3.90 (2H, s, CH_2S), 2.10 (3H, s, pyrrole CH_3), 2.02 (3H, s, pyrrole CH_3); $\nu_{max.}$ (film), 3340, 3030, 2900, 1570, 1465, 1420, 1220, 1070, 1005 and 720 cm^{-1}; m/z 217.09059 (M^+, 3%, $C_{13}H_{15}NS$ requires 217.09252), 108(100), 94(8) and 66(14).

5.48.3 CO-CONDENSATION WITH METHANOL

3-Dimethylaminomethyl-2,5-dimethylpyrrole (**281**) (0.262 g, 1.72 mmol) was pyrolysed at 700°C/2 x 10^{-3} torr over five hours and co-condensed with methanol (20 ml) on to a cold finger at -196°C. After which, the pyrolysate was allowed to reach room temperature and the methanol was removed *in vacuo* to yield a yellow solid (0.26 g). ^1H Nmr analysis indicated the total recovery of starting material.

5.48.4 CO-CONDENSATION WITH 2,3-DIMETHYL-1,3-BUTADIENE

Pyrolysis of (**281**) (0.232 g, 2.09 mmol) at 700°C/2 x 10^{-3} torr over three hours with co-condensation of 2,3-dimethyl-1,3-butadiene (10 ml) at -196°C, failed to give any cycloadduct.

5.49 PYROLYSIS OF 3-DIMETHYLAMINOMETHYLINDOLE (GRAMINE)

5.49.1 CO-CONDENSATION WITH DICHLOROMETHANE

3-Dimethylaminomethylindole (**287**) (0.299 g, 1.72 mmol) was pyrolysed at 800°C/2 x 10^{-3} torr over four hours with a sublimation temperature of between 55 - 60°C, and co-condensed with dichloromethane (30 ml) on to a cold finger at -196°C. After which, the pyrolysate was allowed to warm to room temperature, and the solvent was removed in vacuo to yield a brown oil. ^{1}H Nmr analysis and tlc analysis indicated that the pyrolysate contained four major components which were identified to be quinoline, indole, o-vinylbenzonitrile and recovered starting material.

5.49.2 CO-CONDENSATION WITH THIOPHENOL

3-Dimethylaminomethylindole (**287**) (0.169 g, 0.970 mmol) was pyrolysed at 700°C/2 x 10^{-3} torr over four hours with co-condensation of thiophenol (15 ml) on to a cold finger at -196°C. After which, the pyrolysate was warmed to room temperature and the thiophenol was removed in vacuo to yield a brown oil. ^{1}H Nmr analysis of the pyrolysate indicated 3-phenylthiomethylindole (**289**) to be the major component. Purification by flash column chromatography (Al_2O_3 : light petroleum - ethyl acetate, 12:1 as eluant) yielded the pure product (**289**) as a colourless oil (0.162 g, 70%) which rapidly decolourised on standing at room temperature; δ ($CDCl_3$), 7.84 (1H, br., NH), 7.62 (1H, d, indole 7-H), 7.29 - 7.09 (8H, m, indole and phenyl-H), 6.95 (1H, d, indole 2-H), 4.26 (2H, s, CH_2S); $\nu_{max.}$ (film), 3380, 2870, 1580, 1425, 1350, 1065, 995 and 715 cm^{-1}; m/z 239.0736 (M^+, 4%, $C_{15}H_{13}NS$ requires 239.0769) and 130(100).

5.49.3 CO-CONDENSATION WITH METHANOL

3-Dimethylaminomethylindole (**287**) (0.265 g, 1.52 mmol) was pyrolysed at 700°C/2 x 10^{-3} torr over six hours with co-condensation of methanol (15 ml) on to a cold finger at -196°C. After which, the pyrolysate was allowed to reach room temperature, and the methanol was removed *in vacuo* to yield a yellow solid. Analysis by tlc and ^{1}H nmr indicated the presence of mainly regenerated starting material (**287**) along with small quantities of indole, quinoline and *o*-vinylbenzonitrile. There was no evidence for the formation of any 3-methoxymethylindole.

5.49.4 CO-CONDENSATION WITH 2,3-DIMETHYL-1,3-BUTADIENE

Pyrolysis of (**287**) (0.262 g, 1.50 mmol) at 700°C/2 x 10^{-3} torr over four hours with co-condensation of 2,3-dimethyl-1,3-butadiene (10 ml) at -196°C, failed to give any cycloadduct.

BIBLIOGRAPHY

1 H.W. Gschwend and H.R. Rodriguez, Org.React., (N.Y.), 1979, **26**, 1.

2 V. Snieckus, Heterocycles, 1980, **14**, 1649.

3 P. Beak and V. Snieckus, Acc.Chem.Res., 1982, **15**, 306.

4 N.S. Narashimhan and R.S. Mali, Synthesis, 1983, **12**, 957.

5 V. Snieckus, Lect.Heterocycl.Chem., 1984, **7**, 95.

6 V. Snieckus, Bull.Soc.Chim., Fr., 1988, 67.

7 (a) B.J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon, Oxford, 1974.

(b) B.J. Wakefield, "Organolithium Methods", Academic Press, London, 1988.

8 D.W. Slocum and C.A. Jennings, J.Org.Chem., 1976, **41**, 3653.

9 B.H. Bhide, Chem.Ind., (London), 1974, **19**, 75.

10 R. Ronald and M.R. Winkle, Tetrahedron, 1983, **39**, 2031.

11 A.J. Carpenter, Ph.D. Thesis, Liverpool, 1986.

12 D.J. Chadwick and C. Wilbe, J.Chem.Soc., Perkin Trans. 1, 1977, 887.

13 W.E. Truce and M.F. Amos, J.Am.Chem.Soc., 1951, **73**, 3013.

14 J. Sice, J.Am.Chem.Soc., 1953, **75**, 3697.

15 Y.L. Gd'dfarb, M.A. Kalik and M.L. Kirmalova, J.Gen.Chem., U.S.S.R., (Engl.Transl.), 1959, **29**, 3592.

16 D.W. Knight and A.P. Nott, J.Chem.Soc., Perkin Trans. 1, 1983, 791.

17 D.W. Slocum and P.L. Gierer, J.Org.Chem., 1973, **38**, 4189.

18 D.W. Slocum and P.L. Gierer, J.Org.Chem., 1976, **41**, 3668.

19 D.J. Chadwick, M.V. McKnight and R.I. Ngochindo, J.Chem. Soc., Perkin Trans. 1, 1982, 1343.

20 J.H. Nasman, N. Kopola and G. Pensar, Tetrahedron Lett., 1986, 1391.

[21] D.J. Chadwick and D.S. Ennis, unpublished results, 1989.

[22] G.M. Davies and P.S. Davies, Tetrahedron Lett., 1972, 3507.

[23] D.W. Knight and A.P. Nott, Tetrahedron Lett., 1980, 5051.

[24] D.W. Slocum and P.L. Gierer, J.Chem.Soc., Chem.Commun., 1971, 305.

[25] S. Gronowitz, Ark.Kemi., 1960, **16**, 363.

[26] S. Gronowitz and B. Persson, Acta Chem.Scand., Ser.B, 1968, **22**, 1353.

[27] E.J. Bures and B.A. Keay, Tetrahedron Lett., 1988, 1247.

[28] A.R. Katritzky, H. Faid-Allah and C.M. Marson, Heterocycles, 1987, **26**, 1333.

[29] A.R. Katritzky, in "Organic Synthesis : Modern Trends", p. 203, O. Chizhov ed., Blackwell Scientific, 1987.

[30] A.R. Katritzky and K. Akutagawa, Tetrahedron Lett., 1985, **26**, 5935.

[31] A.R. Katritzky and K. Akutagawa, Org.Prep.Proced.Int., 1988, **20**, 585.

[32] A.R. Katritzky and K. Akutagawa, Tetrahedron, 1986, **42**, 2571.

[33] L. Lochmann and J. Trekoval, Collect.Czech.Chem.Commun., 1988, **53**, 76.

[34] A.R. Katritzky and S. Sengupta, J.Chem.Soc., Perkin Trans. 1, 1989, 17.

[35] A.R. Katritzky and K. Akutagawa, J.Am.Chem.Soc., 1986, **108**, 6808.

[36] A.R. Katritzky, L.M. Vazquez de Miguel and G.W. Rewcastle, Heterocycles, 1987, **26**, 3135.

[37] A.R. Katritzky, L.M. Vazquez de Miguel and G.W. Rewcastle, Synthesis, 1988, 215.

38 A.R. Katritzky, C.M. Marson and H. Faid-Allah, Heterocycles, 1987, **26**, 1657.

39 A.R. Katritzky, G.R. Rewcastle and L.M. Vazquez de Miguel, J.Org.Chem., 1988, **53**, 794.

40 I. Omae, Chem.Rev., 1979, **79**, 287.

41 J.L. Wardell, in "The Chemistry of the Metal-Carbon Bond", Vol. 4, p. 1, F.R. Hartley, ed., John Wiley and Sons Limited, 1987.

42 N.S. Narshimhan and R.S. Mali, Topics in CurrentChem., 1987, **138**, 63.

43 A.R. Katritzky, G.R. Rewcastle and W.Q. Fan, J.Org.Chem., 1988, **53**, 5685.

44 J.M. Muchowski and P. Hess, Tetrahedron Lett., 1988, **29**, 777.

45 D.J. Hlasta and M.R. Bell, Heterocycles, 1989, **29**, 849.

46 A.R. Katritzky, P. Lue and Y. Xiong Chen, J.Org.Chem., 1990, **55**, 3688.

47 U. Michael and S. Gronowitz, Acta Chem.Scand., 1968, 1353.

48 D.L. Comins and J.D. Brown, J.Org.Chem., 1984, **49**, 1078.

49 A.R. Katritzky, W.H. Ramer and J.N. Lam, J.Chem.Soc., Perkin Trans. 1, 1987, 775.

50 A.R. Katritzky and K. Akutagawa, J.Org.Chem., 1989, **54**, 2949.

51 A.R. Katritzky, J.N. Lam and S. Sengupta, in "Progress in Heterocyclic Chemistry", **1**, pp. 1 - 29, Pergamon Press, 1989.

52 J.P. Whitten, D.P. Matthews and J.R. McCarthy, J.Org.Chem., 1986, **51**, 1891.

[53] M.P. Edwards, A.M. Doherty, S.V. Ley and H.M. Organ, Tetrahedron, 1986, **42**, 3723.

[54] B.H. Lipschutz, W. Vaccaro and B. Huff, Tetrahedron Lett., 1988, **29**, 3411.

[55] T.S. Manoharan and R.S. Brown, J.Org.Chem., 1988, **53**, 1107.

[56] D.L. Comins, J.D. Brown and N.B. Mantlo, Tetrahedron Lett., 1982, **23**, 3979.

[57] D.L. Comins and J.D. Brown, Tetrahedron Lett., 1983, **24**, 5465.

[58] D.L. Comins and J.D. Brown, J.Org.Chem., 1984, **49**, 1078.

[59] D.L. Comins and M.O. Killpack, J.Org.Chem., 1987, **52**, 104.

[60] D.L. Comins and M.O. Killpack, Tetrahedron Lett., 1989, **30**, 4337.

[61] D.L. Comins and D.H. LaMunyon, Tetrahedron Lett., 1988, **29**, 773.

[62] N. Furukawa, T. Shibutani and H. Fujihara, Tetrahedron Lett., 1989, **30**, 7091.

[63] See reference 61.

[64] F. Trécourt, M. Mallet, F. Marsais and G. Quéguiner, J.Org. Chem., 1988, **53**, 1367.

[65] F. Marsais, A. Cronnier, F. Trécourt and G. Quéguiner, J. Org.Chem., 1987, **52**, 1133.

[66] S. Sengupta and V. Snieckus, Tetrahedron Lett., 1990, **31**, 4267.

[67] R.J. Mattson and C.P. Sloan, J.Org.Chem., 1990, **55**, 3410.

[68] A.R. Katritzky and P. Lue, J.Org.Chem., 1990, **55**, 74.

[69] M. Iwao, T. Iihama, K.K. Mahalanabis, H. Perrier and V. Snieckus, J.Org.Chem., 1989, **54**, 24.

[70] G.H. Posner and K.A. Canella, J.Am.Chem.Soc., 1985, **107**, 2571.

[71] S. Sengupta and V. Snieckus, Tetrahedron Lett., 1990, **31**, 4267.

[72] M. Watanabe, M. Date, K. Kawanishi, M. Tsukazaki and S. Furukawa, Chem.Pharm.Bull., 1989, **37**, 2564.

[73] H. Gilman, C.E. Arntzen and F.J. Webb, J.Org.Chem., 1945, **10**, 374.

[74] G.D. Figuly, C.K. Loop and J.C. Martin, J.Am.Chem.Soc., 1989, **111**, 654.

[75] K. Smith, C.M. Lindsay and G.J. Pritchard, J.Am.Chem.Soc., 1989, **111**, 665.

[76] E. Block, V. Eswarakrishnan, M. Gernon, G. Ofori-Okai, C. Saha, K. Tang and J. Zubieta, J.Am.Chem.Soc., 1989, **111**, 658.

[77] K. Tamao, H. Yao, Y. Tsutsumi, H. Abe, T. Hayashi and Y. Ito, Tetrahedron Lett., 1990, **31**, 2925.

[78] P.E. Eaton, C.H. Lee and Y. Xiong, J.Am.Chem.Soc., 1989, **111**, 8016..

[79] L.D. Vecchia and I. Vlattas, J.Org.Chem., 1977, **42**, 2469.

[80] P. Ribereau and G. Quéguiner, Tetrahedron, 1984, **40**, 2107.

[81] A.J. Carpenter and D.J. Chadwick, J.Org.Chem., 1985, **50**, 4362.

[82] G.L. Schmir and B.A. Cunningham, J.Am.Chem.Soc., 1965, **87**, 5692.

[83] T. Okuyama, D.J. Sahn and G.L. Schmir, J.Am.Chem.Soc., 1973, **95**, 2345.

[84] R.K. Chaturvedi and G.L. Schmir, J.Am.Chem.Soc., 1968, **90**, 4413.

85 T. Okuyama, T.C. Pletcher, D.J. Sahn and G.L. Schmir, J.Am. Chem.Soc., 1973, **95**, 1253.

86 G.M. Blackburn and W.P. Jencks, J.Am.Chem.Soc., 1968, **90**, 2638.

87 T.C. Pletcher, S. Koehler and E.H. Cordes, J.Am.Chem.Soc., 1968, **90**, 7072.

88 W.P. Jenks and M. Gilchrist, J.Am.Chem.Soc., 1968, **90**, 2622.

89 T. Okuyama and G.L. Schmir, J.Am.Chem.Soc., 1972, **94**, 8805.

90 G. Lander, J.Chem.Soc., 1903, **83**, 406.

91 J.W. Schulenberg and S. Archer, Org.React., 1965, **14**, 1.

92 A. Arbuzov and V. Schishkin, Dokl.Akad.Nauk., S.S.S.R., 1961, **141**, 349; Chem.Abstr., 1962, **56**, 11491.

93 A. Arbuzov and V. Shishkin, Dokl.Akad.Nauk., S.S.S.R., 1961, **141**, 611; Chem.Abstr., 1962, **56**, 15424.

94 B. Challis and D.A. Frenkel, J.Chem.Soc., Perkin Trans. 2, 1978, **1**, 193.

95 D.J. Chadwick and R.I. Ngochindo, J.Chem.Soc., Perkin Trans. 1, 1984, 481.

96 O. Exner and O. Schindler, Helv.Chim.Acta, 1972, **55**, 1921.

97 C.O. Meese, W. Walter and M. Berger, J.Am.Chem.Soc., 1974, **96**, 2259.

98 H. von Peckmann, Ber., 1900, **33**, 611.

99 H. Ley and E. Holzweissig, Ber., 1903, **36**, 18.

100 J. von Braun, Ber., 1904, **37**, 2812.

101 J. von Braun and W. Pinkernell, Ber., 1934, **67**, 1218.

102 N.J. Leonard and E.W. Nommensen, J.Am.Chem.Soc., 1949, **71**, 2808.

103 W.R. Vaughan and R.D. Carlson, J.Am.Chem.Soc., 1962, **84**, 769.

[104] For reviews, G. Köbrich, Angew.Chem., Int.Ed.Engl., 1973, **12**, 464; G.L. Buchanan, Chem.Soc.Rev., 1974, **3**, 41.

[105] P. Schleyer and R.D. Nicholas, J.Am.Chem.Soc., 1961, **83**, 2700.

[106] U. Schollkopf, Angew.Chem., 1960, **72**, 147.

[107] R. Roger and D.G. Neilson, Chem.Rev., 1961, **61**, 179.

[108] A. Pinner, "Die Imidoäther und ihre Derivative", Oppenheim, Berlin, 1892.

[109] R.L. Funk and K.P.C. Vollhardt, Chem.Soc.Rev., 1980, **9**, 41.

[110] W. Oppolzer, Synthesis, 1978, 793.

[111] T. Kametani and H. Nemoto, Tetrahedron, 1981, **37**, 3.

[112] S. Djuric, T. Sarkar and P. Magnus, J.Am.Chem.Soc., 1980, **102**, 6885.

[113] W. Oppolzer and K. Keller, J.Am.Chem.Soc., 1971, **93**, 3836.

[114] F.A.J. Kerdesky, R.J. Ardecky, M.V. Lushmikanthon and M.P. Cava, J.Am.Chem.Soc., 1981, **103**, 1992.

[115] K. Cardwell, B. Hewitt, M. Ladlow and P. Magnus, J.Am.Chem. Soc., 1988, **110**, 2242 and references therein.

[116] W.S. Trahanovsky, T.J. Cassady and T.L. Woods, J.Am.Chem. Soc., 1981, **103**, 6691.

[117] C.-H. Chou and W.S. Trahanovsky, J.Am.Chem.Soc., 1986, **108**, 4138.

[118] C.-H. Chou and W.S. Trahanovsky, J.Org.Chem., 1986, **51**, 4208.

[119] J. Jullien, M. Pechine, F. Perez and J.J. Piode, Tetrahedron Lett., 1979, **19**, 3079.

[120] A. Schweig and N. Munzel, Angew.Chem., Int.Ed.Engl., 1987, **26**, 474.

[121] K.J. Stone, M.M. Greenberg, S.C. Blackstock and J.A. Berson, J.Am.Chem.Soc., 1989, **111**, 3659 and 3671.

[122] P.M.S. Chauhan, G. Jenkins, S.M. Walker and R.C. Storr, Tetrahedron Lett., 1988, **29**, 117.

[123] D.J. Chadwick and A. Plant, Tetrahedron Lett., 1987, **28**, 6085.

[124] A.M. Van Leusen and K.J. van den Berg, Tetrahedron Lett., 1989, **29**, 2689.

[125] N. Munzel and A. Schweig, Chem.Ber., 1988, **121**, 791.

[126] A.P.A. Crew, G. Jenkins, R.C. Storr and M. Yelland, Tetrahedron Lett., 1990, **31**, 1491.

[127] P.M.S. Chauhan, A.P.A. Crew, G. Jenkins, R.C. Storr, S.M. Walker and M. Yelland, Tetrahedron Lett., 1990, **31**, 1487.

[128] Y. Ito, M. Nakatsuka and T. Saegusa, J.Am.Chem.Soc., 1980, **102**, 863.

[129] Y. Ito, M. Nakatsuka and T. Saegusa, J.Am.Chem.Soc., 1981, **103**, 476.

[130] A. Plant, Ph.D. Thesis, Liverpool, 1988.

[131] D.W. Knight and A.P. Nott, J.Chem.Soc., Perkin Trans. 1, 1981, 1125.

[132] R.L. Vaux, W.H. Puterbaugh and C.R. Hauser, J.Org.Chem., 1964, **29**, 3514.

[133] A.I. Meyers, D. Temple, D. Haidukewych and E.D. Mihelich, J. Org.Chem., 1974, **39**, 2787.

[134] Y. Ito, Y. Amino, M. Nakatsuka and T. Saegusa, J.Am.Chem. Soc., 1983, **105**, 1586.

[135] J.L. Charlton, Can.J.Chem., 1986, **64**, 720.

[136] H. Fischer and H. Orth, in "Die Chemie des Pyrrols", Vol. II, Akademische Verlag, Leipzig, 1939.

[137] L.R. Morgan and R.Schunior, J.Org.Chem., 1962, **27**, 3696.

[138] A.J Castro, G. Tertzakian, B.T. Nakata and D.A. Bose, Tetrahedron, 1967, **23**, 4499.

[139] A. Treibs and E. Herrman, Z.Physiol.Chem., 1955, **299**, 168.

[140] R. Gomper and R. Weiss, Angew.Chem., Internat.Ed.Engl., 1968, **7**, 296.

[141] R. Gomper and R. Weiss, Tetrahedron Lett., 1970, 481.

[142] K. Hafner and K. Pfeiffer, Tetrahedron Lett., 1968, 4311.

[143] R.A. Jones and G.P. Bean, Org.Chem., 1977, **34**, 426.

[144] W. Herz and J. Brasch, J.Org.Chem., 1958, **23**, 711.

[145] H.R. Hensel, Chem.Ber., 1966, **99**, 868.

[146] W. Rohr and H.A. Staab, Angew.Chem., Internat.Ed.Engl., 1965, **4**, 1073.

[147] J.H.M. Hill, J.Org.Chem., 1967, **32**, 3214.

[148] E.M. Burgess and J.P. Sanchez, J.Org.Chem., 1974, **39**, 940.

[149] R.J. Boatman and H.W. Whitlock, J.Org.Chem., 1976, **41**, 3050.

[150] G. Gross and C. Wentrup, J.Chem.Soc., Chem.Commun., 1982, 360.

[151] A. Maquestiau, A. Tommasetti, C. Pedregal-Freire, J. Elgaro, R. Flammang, U.E. Wiersum, H. Bender and C. Wentrup, J.Org. Chem., 1986, **51**, 306.

[152] A.D. Adler, F.R. Longo, J.D. Finarelli, J. Goldmacher, J. Assour and 1. Korsakoff, J.Org.Chem., 1967, **32**, 476.

[153] W. Herz, K. Dittmer and S.J. Cristol, J.Am.Chem.Soc., 1947, **69**, 1698.

[154] K. Randles and R.C. Storr, unpublished results.

[155] R.F.C. Brown, N. Hooley and F.N. Irvine, Aust.J.Chem., 1974, **27**, 671.

156 A. Hayes, G.W. Kenner and N.R. William, J.Chem.Soc., 1958, 3779.

157 W. Herz and R.L. Settine, J.Org.Chem., 1959, **24**, 201.

158 W. Kotion and L. Baclawski, J.Org.Chem., 1976, **41**, 1871.

159 S.L. Shapiro, V.A. Parrino and L. Freedman, J.Am.Chem.Soc., 1959, **81**, 3728.

160 P. Caramella, G. Cellerino, P. Grünanger, F.M. Albini and M.R. ReCellerino, Tetrahedron, 1978, **34**, 3545.

161 R.I. Meltzer, A.D. Lewis and J.A. King, J.Am.Chem.Soc., 1955, **77**, 4062.

162 U. Farcasan, F. Paiu, A. Donea, C. SArbu and G. Coman, Stud. Univ.Babes Bolyai, (SER) Chem., 1982, **27**, 22.

163 G.M. Badger, R.T. Howard and A. Simons, J.Chem.Soc., 1952, 2849.

164 G. Alberghina and S. Fisichella, J.Chem.Soc., Perkin Trans. 2, 1978, **1**, 81.

165 M.L. Hefferman and A. J. Jones, J.Chem.Soc., Chem.Commun., 1966, 120.

166 R.F.C. Brown, G.E. Gream, D.E. Peters and R.K. Solly, Aust. J.Chem., 1968, **21**, 2233.