Novel aminoalkylation reactions of electron-rich aromatic compounds

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NOVEL AMINOALKYLATION REACTIONS OF ELECTRON-RICH AROMATIC COMPOUNDS.

by

Robert F. Wilkins

A thesis submitted in partial fulfilment of the requirements for the award of:

Doctor of Philosophy
of the Loughborough University of Technology.

Supervisor: Professor H. Heaney.

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To Mum, Dad and Jo, with love.
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ABSTRACT

It has been shown that preformed methyleneiminium salts react readily with N-substituted pyrroles, and both furan and 2-methylfuran, to give Mannich bases in good yields. Furan itself has previously been reported not to undergo the Mannich reaction. Thus furan reacts with \( N,N\)-dimethyl(methylene)iminium chloride to give 2-(\( N,N\)-dimethylaminomethyl)furan.

Modification of these experimental methods has enabled Mannich reactions to be carried out in non-protic solvents whilst avoiding high concentrations of acid. Thus bis-(dialkylamino)methanes (aminals) and alkoxydialkylaminomethanes (aminol ethers) were interacted with sulphur dioxide or chlorosilanes to generate reactive aminoalkylating species "in situ". Such species were then used to functionalise aromatic substrates.

It has been demonstrated that a number of cyclic aminals and aminol ethers will function as Mannich reagents in "in situ" reactions. This type of reaction enables two functional groups to be simultaneously introduced into nucleophilic substrates. Thus 2-methylfuran will react with 1,3-dimethylimidazolidine in the presence of trichloromethylsilane to give \( N,N'\)-dimethyl-\( N'\)-(5'-methyl-2'-furylmethyl)ethylene diamine which contains both secondary and tertiary amine groups. Similarly interaction of \( N\)-methylindole with 3-methyl-1,3-oxazolidine and a chlorosilane yields 3-(\( N'\)-2'-hydroxyethyl-\( N'\)-methylaminomethyl)-\( N\)-methylindole, which has a tertiary amine substituent and a terminal alcohol functionality. The use of \( t\)-butylchlorodimethylsilane as the activating agent enables the said hydroxyl group to be simultaneously protected as its \( t\)-butyl-dimethylsilyl ether.

5-methyl-2-(\( N\)-methy1aminomethyl)furan was prepared by the removal of the hydroxyethyl substituent from 2-(\( N\)-2'-hydroxyethyl-\( N\)-methylaminomethyl)-5-methylfuran.
The use of thionyl chloride as an activating reagent has enabled us to prepare methyl 2-(5'-methyl-2'-furyl)-2-(N-2''-chloroethyl-N-methylamino)-acetate, a racemic aryl glycine derivative, from 2-methoxycarbonyl-3-methyl-1,3-oxazolidine, in a reaction with 2-methylfuran.
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ABBREVIATIONS.

Ac    Acyl
Ar    Aryl
b.p.  Boiling point
Bu, Bu'  n-Butyl
Bu'  iso-Butyl
tBu'  tert-Butyl
CBz  Benzyloxycarbonyl
DBU  1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM  Dichloromethane
DIBAL-H  Di-iso-butylaluminium hydride
DMAP  4-N,N-Dimethylaminopyridine
DMF  Dimethylformamide
DMSO  Dimethyl sulfoxide
Et  Ethyl
HMPT  Hexamethylphosphorus triamide
hrs.  Hours
LA  Lewis acid
LDA  Lithium di-iso-propylamide
L.U.T.  Loughborough University of Technology
Me  Methyl
m.p.  Melting point
n.m.r.  Nuclear magnetic resonance
Pr'  iso-Propyl
Ph  Phenyl
p.p.m.  Parts per million
TBDMS  tert-Butyldimethylsilyl
THF  Tetrahydrofuran
TMS  Tetramethysilane
p-TSA  para-Toluenesulphonic acid
CHAPTER ONE

Introduction

For many years, α-aminoalkylation has been recognised as an excellent method for introducing a single carbon atom into compounds containing an acidic hydrogen. The true potential of the reaction was first recognised by Mannich in the early 1900s, and hence this synthetic process bears his name.

The widespread interest in the Mannich reaction stems from several aspects of the chemistry. In the reaction, a basic amine functionality is introduced, which, upon protonation or alkylation, yields a quaternary ammonium species, and thus confers solubility in hydroxylic solvents. Secondly, the Mannich bases thus formed have been shown to be quite reactive, and hence the amine may be readily converted into a wide variety of other functional groups. These processes may be performed chemically or biologically, and it is the latter area which has led to a thorough investigation of the pharmacological properties of Mannich bases.

The Mannich reaction essentially consists of a condensation between an amine (or ammonia), an aldehyde and a compound possessing one or more acidic hydrogens. Classically, this type of reaction is carried out in water, alcohol or acetic acid, with the amine present in the form of its hydrochloride salt or free base. Formaldehyde (other aldehydes are rarely used) is introduced as an aqueous solution or in one of its polymeric forms. A typical condensation is shown in Scheme 1.

However, this type of methodology has serious drawbacks. A combination of long reaction times, high temperatures and high acid concentration often leads to reduced yields and unwanted side reactions. In recent years
such problems have largely been overcome by the use of preformed iminium salts as aminoalkylating agents under relatively mild conditions. Reactions at lower temperatures in aprotic solvents have enabled highly functionalised substrates to undergo the Mannich reaction (Scheme 2). The increased selectivity of iminium salts as Mannich reagents has allowed certain transformations to be carried out regio– or stereo–specifically.

1.1 Scope of the Mannich Reaction

The particular reaction which is reported to have led to Mannich's great interest in the aminoalkylation process is that between antipyrine salicylate (1), formaldehyde and ammonium chloride (Equation 1) 8.

Since that time, a wide range of publications has given comprehensive coverage of the Mannich reaction, notably books by Reichert 8 and by Hellmann and Opitz 5, and a number of reviews by Blicke 8, Hellmann and Opitz 7, Thompson 8 and Tramontini 9. An overview of some of the more interesting work in this area since 1970 will appear in forthcoming reviews 10.

\[
\begin{align*}
\text{Me-CO-Me} & + (\text{CH}_2\text{O})_3 + \text{EI}_2\text{NH}_2\text{Cl}^- \\
\xrightarrow{i} & \xrightarrow{ii} \text{Me-CO-CH}_2\text{-CH}_2\text{-NEI}_2 \\
\text{62–70%}^1
\end{align*}
\]

i. HCl, MeOH, reflux; ii. NaOH, H2O.

SCHEME 1
In view of the considerable coverage which this work has enjoyed, this introduction will concentrate on giving a broad insight into the scope and mechanism of the reaction.

**SCHEME 2**
1.1.1 Mannich Reactions of Carbonyl Compounds

The most widely documented substrates involved in Mannich reactions are carbonyl compounds, especially ketones. Reactions are generally carried out under conditions favouring enolisation, or in which the enol form may be “trapped” before reaction as its silyl enol ether.

One of the earliest examples of a Mannich condensation of a ketone was in the synthesis of tropinone (4), a precursor to a number of important bases in the atropine family of alkaloids. The reaction involves a two-fold condensation between succindialdehyde (2), methylamine and the calcium salt of acetonedicarboxylic acid (3), followed by hydrolysis to give (4) (Scheme 3).

Mannich reactions of unsymmetrical ketones under classical conditions have generally led to mixtures of isomeric α-aminoketones. The ratio of isomer formation has been shown to depend on the structure of the starting
ketone\textsuperscript{12}, with a tendency for the more highly branched $\beta$-aminoketone to predominate, due to the greater thermodynamic stability of the related enol.

Recent improvements brought about by the use of preformed iminium salts have given higher yields and enabled a greater selectivity of reaction to be obtained. Kinast and Tietze have shown that Mannich reactions of a range of ketones and aldehydes proceed to greater conversion when the substrate is treated with $N,N$-dimethyl(methylene)iminium chloride in acetonitrile, compared with reactions under classical conditions\textsuperscript{13}. It is noted that aminoalkylation occurred almost exclusively at the most substituted position.
The work of Jasor and his co-workers suggested that by varying the counter-ion of the iminium salt and the reaction solvent, regiospecific $\alpha$-aminoalkylation could be obtained. Thus the use of $N,N$-dimethyl(methylene)iminium trifluoracetate in trifluoroacetic acid yields mainly the more substituted isomeric aminoketone, whilst using the bulkier $N,N$-di-iso-propyl(methylene)iminium perchlorate in acetonitrile gives predominantly the less substituted isomer.

Hooz and Bridson reported the regiospecific generation of Mannich bases via the reaction of enolborinates (5) with $N,N$-dimethyl(methylene)iminium iodide (Eschenmoser's salt) (6), as shown in Equation 2.

$$R_2B\text{-}O\text{-}C\text{=}\text{CHR} + \text{Me}_2\text{N}\text{=}\text{CH}_2\text{I}^- \rightarrow R'\text{C}\text{=}\text{CHR} \text{CH}_2\text{NMe}_2$$

Equation 2

The use of enolates in the aminoalkylation of the carbonyl function has enabled normally unreactive species to undergo the Mannich reaction. Danishefsky and his collaborators treated the enolate derived from the lactone (7) with (6) to give the $\alpha$-aminoalkylated product (8). Subsequent quaternisation and elimination gave the biologically active natural product $dl$-vernolepin (9) (Scheme 4).

A similar approach was adopted during the total syntheses of $dl$-vernolepin and $dl$-vernomenin.
Poulter's group has also reported the introduction of $\alpha$-methylen substituents to carbonyl functions in ketones, esters and lactones using such methods\textsuperscript{18}.

The regiospecific generation of $\alpha$-aminoalkyl derivatives of unsymmetrical ketones has also been investigated by Holy and Wang\textsuperscript{19}. Using the procedure recommended by House\textsuperscript{20} the appropriate silyl enol ether was generated, followed by quenching with $N,N$-dimethyl(methylene)iminium trifluoracetate, to give the required isomeric ketone in good yield. The method was also extended to include esters, lactones, aldehydes and carboxylic acids.
Several of the above-mentioned works were reviewed, and their scope broadened in a communication by Holy's group\textsuperscript{21}. These authors concluded that the best reagent for work of this type was the freshly-distilled iminium trifluoracetate in dichloromethane.

More recently a regioselective procedure for the synthesis of $\alpha$-aminoalkyl ketones has been proposed, in which the required silyl enol ether and the iminium salt were generated separately, without isolation, and combined. Workup in the usual way gave the expected products, with unsymmetrical ketones yielding the regioisomeric aminoketones in predictable proportions\textsuperscript{22}.

A further improvement on this methodology, in work carried out in these laboratories by Robin Fairhurst, has enabled similar reactions to be carried out in a "one-pot" procedure\textsuperscript{23}. Treatment of the appropriate ketone with chlorotrimethylsilane and triethylamine, followed by sodium iodide in acetonitrile. Addition of an alkoxydialkylaminomethane (aminol ether) then gives the corresponding Mannich base in good yield (Scheme 5).

\begin{center}
\begin{tikzpicture}
  \node[draw, ellipse, text width=2cm] (k) at (0,0) {\textbf{SCHEME 5}}; \\

  \node[draw, ellipse, text width=2cm] (k1) at (0,-1) {\textbf{i, ii, iii}}; \\

  \node[draw, ellipse, text width=2cm] (k2) at (0,-2) {71\%}; \\

  \node[draw, ellipse, text width=2cm] (k3) at (0,-3) {i. $\text{Me}_3\text{SiCl}$, $\text{Et}_3\text{N}$, 0°C; \ ii. NaI, MeCN, 35°C, 1hr; \ iii. $\text{Me}_2\text{NCH}_2\text{OPr}^\text{t}$, 2hr.}; \\

\end{tikzpicture}
\end{center}
A further interesting piece of work in this field reports the reaction of \( t\)-butyldimethylsilyl(TBDMS) enol ethers (10) with \( N,N\)-dimethyl-(methylene)iminium iodide (6) to give the corresponding Mannich base (11) in which the TBDMS enol residue is retained (Equation 3)\(^\text{24}\).

\[
\begin{array}{c}
\text{Bu}^t \\
\text{Me-Si-Me} \\
\text{O} \\
R^1 = R^2 + \text{Me}_2^+ \text{N} = \text{CH}_2 \text{I}^{-} \xrightarrow{\text{CH}_2\text{Cl}_2} \text{R}^1 \text{R}^2 \text{NMe}_2 \\
\text{Bu}^t \\
\text{Me-Si-Me} \\
\text{O} \\
\end{array}
\]

\[\text{EQUATION 3}\]

The position of the enol double bond is shown to be dependent on the nature of \( R^1 \) and whether the parent ketone has a cyclic structure.

The utility of the Mannich reaction in synthesising natural products and their derivatives was exemplified in the preparation of 16\( \alpha \)-methyl-8\( \alpha \)-estradiol (14)\(^\text{25}\), whose 16\( \alpha \)-ethyl analogue was reported to show antiestrogenic activity in the treatment of breast tumours. The keto-steroid (12) was aminoalkylated as shown in Scheme 6. Subsequent elimination of the amine function using acetic anhydride, followed by catalytic reduction, gave (13), which was converted to (14) by reduction with lithium aluminium hydride and ether cleavage using \( \text{di-iso-butyllaluminium hydride (DIBAL-H)} \).
i. $\text{Me}_2\text{N}=\text{CH}_2\text{Li}^-\text{MeCN}$;  
ii. $\text{Ac}_2\text{O}$;  
iii. $\text{H}_2$, Pd, C, EtOH;  
iv. LiAlH$_4$;  
v. DIBAL-H.

**SCHEME 6**
1.1.2 Mannich Reactions of Aliphatic Nitro–Compounds

The high degree of reactivity of aliphatic nitro–compounds towards electrophiles is widely known. The Mannich reactions of such substrates with formaldehyde and ammonia or a primary or secondary amine is well documented. It was shown that nitroethane will undergo condensation with formaldehyde and diethylamine to give the expected nitroamine in good yield (Equation 4).26

\[
\begin{align*}
\text{MeCH}_2\text{NO}_2 + \text{CH}_2\text{O} + \text{Et}_2\text{NH} & \rightarrow \text{MeCH} - \text{NO}_2 \\
& \quad \text{CH}_2\text{NEt}_2 \\
& \quad 69\%
\end{align*}
\]

Equation 4

By varying the molar ratios of reagents, nitrodiamines were readily formed. In several cases nitroamines were reduced to the corresponding polyamines.27

A number of studies by Fernandez and his collaborators involved the reactions of nitro–compounds with bis–(dialkylaminomethanes (aminals) in a range of aprotic solvents.28 Treatment with di–(N–piperidyl)methane under anhydrous conditions yielded the first reported example of a mono–alkylated derivative of nitromethane.28c

More recently the first examples of Mannich reactions in which two equivalents of a primary nitroalkane undergo condensation with formaldehyde and a primary amine have been reported, the Mannich bases thus formed being used in radical cyclisation reactions. Thus treatment
of iso-butylamine with a large excess of nitroethane and paraformaldehyde yields the Mannich base (15), which readily cyclises to give the pyrrolidine derivative (16) (Scheme 7).

\[
\text{MeCH}_2\text{NO}_2 + (\text{CH}_2\text{O})_n + \text{Bu'}\text{NH}_2 \rightarrow \begin{array}{c}
\text{Me} \\
\text{Bu'}
\end{array}
\begin{array}{c}
\text{NCH}_2\text{CH-NO}_2 \\
\text{Me}
\end{array}
\]

\[
\begin{array}{c}
\text{Me} \\
\text{Bu'}
\end{array}
\begin{array}{c}
\text{NCH}_2\text{CH-NO}_2 \\
\text{Me}
\end{array} \quad \text{i, ii}
\]

\[
\begin{array}{c}
\text{Me} \\
\text{Bu'} \\
\text{NO}_2
\end{array}
\begin{array}{c}
\text{NO}_2 \\
\text{Me}
\end{array}
\]

i. NaOMe, MeOH, Et_2O; ii. K_3Fe(CN)_6, H_2O.

**SCHEME 7**

**1.1.3 Mannich Reactions of Acetylenes**

The Mannich reaction has been successfully accomplished with a number of acetylenic substrates. Such reactions have often been carried out in the presence of copper salts in order to render the triple bonds more nucleophilic. Propargyl alcohol (17) is reported to give a Mannich reaction with a number of secondary amines in the presence of copper (II) sulphate, and affords the expected products in good to excellent yields (Equation 5).
More recently, a novel method of ring formation has involved attack of acetylenes on iminium ions, promoted by the addition of nucleophiles such as bromide, iodide and azide\(^{31}\). This method has led to the stereospecific formation of an exocyclic double bond as the key step in the synthesis of the pumilotoxin A alkaloids (Equation 6).

1.1.4 Mannich Reactions of Cyclopropanes

Investigations have been carried out into the interaction of 2-siloxycyclopropanecarboxylates with iminium salts in the presence of Lewis acids\(^{32}\). Thus treatment of (18) with an equimolar quantity of titanium...
tetrachloride (LA) generates the intermediate (19), which is then trapped by \( N,N\text{-dimethyl(methylene)iminium trifluoromethanesulphonate} \) to yield the Mannich base (20) (Scheme 8).

\[
\begin{align*}
\text{(18)} & \quad \overset{\text{i}}{\leftrightarrow} \quad \text{(19)} \\
\text{(20)} & \quad \overset{\text{ii}}{\rightarrow} \\
i & \text{LA; } \text{ii. } \text{Me}_2\text{N}=\text{CH}_2\text{OSO}_2\text{CF}_3^-, \text{CH}_2\text{Cl}_2.
\end{align*}
\]

**SCHEME 8**

Such Mannich bases may be subsequently deaminated to yield the \( \alpha\text{-methylene} \) ester, or readily transformed to \( \alpha\text{-methylene-\( \gamma\text{-butyrolactones}} \).
1.1.5 Mannich Reactions of Organometallic Substrates

A further approach to the synthesis of compounds containing a terminal methylene residue is that of Roberts\textsuperscript{33}. Preparation of the corresponding Grignard or organolithium reagent from the alkyl halide is followed by reaction with N,N-dimethyl(methylene)iminium iodide. Subsequent oxidation and thermal decomposition yields the desired terminal olefin (21) in good overall yield (Scheme 9).

\[
\begin{align*}
\text{H-C-X} & \xrightarrow{\text{i, ii}} \text{H-C-CH}_2\text{NMMe}_2 \xrightarrow{\text{iii, iv}} \text{R}^1\text{C} = \text{CH}_2 \\
& \text{i. Mg or Li; ii. Me}_2\text{N}=\text{CH}_2 \Gamma; \text{ iii. H}_2\text{O}_2; \text{ iv. 160°C.}
\end{align*}
\]

**SCHEME 9**

1.1.6 Mannich Reactions of Phenols

The Mannich condensation of phenols under classical aqueous conditions is widely reported to give ortho-- rather than para--substitution\textsuperscript{4–8}. Under conditions of excess aminoalkylating agents, polysubstitution of the phenol nucleus often occurs, the reactivity of the ring presumably being enhanced by each addition of an electron–releasing aminoalkyl residue.

There are many examples quoted in the literature of the Mannich reaction of binuclear phenols, in which reaction again tends to occur ortho-- to the hydroxyl group. Thus 2–naphthol is reported to undergo condensation with
a range of aminals\textsuperscript{34} and aminol ethers\textsuperscript{35} to give the corresponding 1-dialkylaminomethyl-2-naphthol.

A range of 2-hydroxy-3-aminomethylnaphthaquinones has also been synthesised for testing as potential anti-malarial\textsuperscript{36} and anti-cancer agents\textsuperscript{37}.

The Mannich reaction has often been utilised in the nuclear methylation of phenols. Typically, 4-methoxyphenol undergoes condensation with dimethylamine and formaldehyde to yield the corresponding disubstituted Mannich base. Hydrogenolysis using a copper chromite catalyst gives 4-methoxy-2,6-dimethylphenol in high yield\textsuperscript{38}. A more recent method for deamination of such Mannich bases involves treatment with tri-\textit{n-}butyltin hydride at elevated temperatures\textsuperscript{39}.

More recently the regioselective formation of \textit{ortho}-substitution products using preformed iminium salts under solid-liquid phase transfer conditions has been reported (Scheme 10)\textsuperscript{40}.

\begin{center}
\textbf{SCHEME 10}
\end{center}
However, the work of George Papageorgiou, in these laboratories, has failed to duplicate the high yields or selectivity claimed. Studies of the reactions of phenols with aminals and aminol ethers in the presence of sulphur dioxide have been carried out by the same worker. The most interesting and informative results were obtained from reactions using 2,5-dimethylphenol. A relatively high degree of regioselectivity was obtained by using the reagents in specific molar ratios (Equation 7).

\[
\begin{align*}
\text{Me} & \quad \text{CH}_2\text{N}2\text{Et} \quad \text{Me} \\
\text{Me} & \quad \text{CH}_2\text{N}2\text{Et} \\
\text{Et}_2\text{NCH}_2\text{OEt} & \quad \text{Me} \\
(2 \text{ equiv.}) & \quad \text{SO}_2 \\
\text{MeCN, reflux} & \quad 2\text{hrs} \\
\rightarrow & \quad \text{Me} \\
\text{Et}_2\text{NH}_2\text{C} & \quad \text{Me} \\
\text{Et}_2\text{NH}_2\text{C} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

EQUATION 7

The work of Böhme and Eichler reported the formation of Mannich bases from resorcinol dimethylether and phloroglucinol trimethylether. These reactions, using \textit{N}-pyrrolidinyl- and \textit{N}-morpholinyl-(methylene)iminium chloride, were the first example of Mannich reactions using preformed iminium salts. Thus \textit{N}-pyrrolidinyl(methylene)iminium chloride (22d) and phloroglucinol trimethylether (23) were heated together in acetonitrile to yield the Mannich base, which was isolated as its hydrochloride salt (24) (Equation 8).
1.1.7 Mannich Reactions of Arylamines

Mannich reactions of $N,N$-dialkylarylamines give rise to products substituted at the para-position. Detailed studies of such reactions in the presence of dilute acetic acid suggested that yields are dependent on acid concentration. Typically, $N,N$-dimethylaniline reacts with formaldehyde and piperidine in the presence of acetic acid to give 4-dimethylaminobenzylamine (25) in good yield (Equation 9).

For substrates in which the 4-position is substituted, aminoalkylation occurs in the ortho-position.

The reactivity sequence of secondary arylamines is further complicated. Thus in the presence of high concentrations of acid, ring-substitution occurs, whereas at low acid concentration the $N$-alkylated product is obtained (Scheme 11).
\[
\text{Me}_2\text{N-} + \text{CH}_2\text{O} + \text{NH}_2
\]

\[
\xrightarrow{\text{CH}_3\text{CO}_2\text{H}} \quad \text{Me}_2\text{N-CH}_2\text{NH}
\]

\text{(25), 69%}

\text{EQUATION 9}

\text{SCHEME 11}
Tseou and Yang have shown the orientation of attack in Mannich reactions of naphthylamines to be in the 4-position for 1-naphthylamine and the 1-position for the 2-isomer, in condensations with aminol ethers.

1.1.8 Mannich Reactions of Ferrocene

Ferrocene (25) is reported to undergo the Mannich reaction, in low yield, using bis-(N,N-dimethylamino)methane in glacial acetic acid, in the presence of phosphoric acid. The reaction yields a mixture of the products of substitution in one or both rings. The latter (27) in the form of its dimethiodide, has proved useful in the preparation of a range of symmetrically disubstituted ferrocenes (Scheme 12).

1.1.9 Mannich Reactions of Heterocyclic Substrates

The Mannich reaction of thiophene has been known for several years. In a number of studies in this area, Hartough and his co-workers were able to isolate moderate yields of 2-thienylamine and several of its derivatives from the corresponding thiophene, ammonium chloride and formaldehyde, though attempted reactions using primary and secondary amines were less successful.

Under classical conditions the more electron-rich 2-methoxy-, 3-methoxy- and 3,4-dimethoxy-thiophenes were reported to yield 2-substituted Mannich bases with a range of secondary amines and formaldehyde.

Thiophene itself yields 2-(N,N-dimethylaminomethyl)thiophene in 55% yield upon heating under reflux in acetonitrile with N,N-dimethyl(methylene)iminium chloride.
A recent modification of this procedure allowed the regiospecific formation of the unfavoured 3-substituted derivative of thiophene. Thus 3-thienyltrimethylstannane (28) was stirred in dichloromethane with N,N-dimethyl(methylene)iminium chloride (22a) to yield the 3-substituted product (29) (Equation 10).

In the search for new therapeutic agents, a series of Mannich derivatives of indolizines was synthesised by Harrell's group, on the strength of the
known biological activity of certain aminoalkylindoles. Several of these showed a marked effect in depressing the central nervous system activity of mice and rabbits.

Other workers found difficulty in purifying the products from the Mannich reaction of 8-acetindolizine (30) under classical conditions. However, the use of preformed iminium salts enabled the 3-substituted products to be isolated as their hydrochloride salts (31) (Equation 11).
Imidazoles were initially reported to be unreactive under normal Mannich conditions, with the exception of benzimidazole. However, it was subsequently reported that imidazoles unsubstituted in the 1-position readily undergo the Mannich reaction under such conditions. In acidic media reaction occurs at the 1-position, giving N-aminoalkylated products in good to excellent yields. Under basic conditions a complex mixture of products is obtained, arising from the Mannich reaction at nitrogen, and C-substitution at the 2-, 4- and 5-positions.

A series of 4-substituted 4H-[1,2,4] triazolo[4,3-a][1,4] benzodiazepines were prepared as potential cholecystokinin antagonists. The 4-N,N-dimethylaminomethyl-derivative (33) was synthesised via a Mannich reaction on the triazole ring of (32) at the unsubstituted carbon using N,N-dimethyl(methylene)iminium chloride in dry, degassed dimethylformamide (Equation 12).

\[
\text{Equation 12}
\]

It was reported that two additional by-products were detected during the course of the reaction, one of which rearranged to the desired compound...
during work-up. The authors tentatively suggested that such products may arise from initial attack of the iminium salt on the triazole nitrogen atoms.

Whilst thiazole itself is reported not to undergo the Mannich reaction, the addition of electron-releasing groups to the parent ring system is shown to enhance its reactivity. Thus 2-acetamido-4-methylthiazole (34) reacts with formaldehyde and dimethylamine, in aqueous acetic acid, to afford the Mannich base (35) in excellent yield (Equation 13)\textsuperscript{58}.

\begin{equation}
\begin{array}{c}
\text{Me} \\
\text{NHCOCMe} \\
\text{NH} \\
\text{S} \\
\text{Me} \\
\text{NHCOCMe} \\
\end{array} \xrightarrow{\text{Me}_2\text{NH, CH}_2\text{O, CH}_3\text{CO}_2\text{H}} \quad \text{Me} \\
\text{S} \\
\text{NHCOCMe} \\
\text{CH}_2\text{NMMe}_2 \\
\end{array}
100^\circ \text{C, 5hrs.}
\end{equation}

\textbf{EQUATION 13}

In order to determine whether nicotinic acid is incorporated into nicotine via the 1,4-dihydro-species (36), a biomimetic route was established\textsuperscript{57}. Accordingly, glutaraldehyde, ammonia and \textsuperscript{14}C radiolabelled 1-methyl-\Delta^1-pyrrolinium acetate were stirred in aqueous solution at various pHs. After addition of inactive nicotine, reisolated material was found to be partially radiolabelled. Thus it was suggested that the biosynthesis of nicotine (38) may involve a Mannich reaction between dihydronicotinic acid (36) and a pyrrolinium salt (37), with subsequent oxidative decarboxylation (Scheme 13).
The Mannich reactions of pyrroles, indoles and furans will be discussed to a greater depth in subsequent chapters.
1.2 Mechanism of the Mannich Reaction

At the present time, almost all mechanistic studies of the Mannich reaction have been carried out in aqueous media. The results obtained have helped to establish a general mechanistic pattern which fits most observations.

In acidic media the formation of iminium salts is suggested, which may then undergo reaction with suitable substrates via an $S_N1$-type mechanism. Under basic conditions, the intermediate hydroxymethylamine (39), formed by the condensation of formaldehyde and amine, may be the reactive intermediate, though in the presence of excess amine or an alcoholic solvent (39) is probably converted to the aminal or the aminol ether respectively. Such intermediates may then give substitution products through an $S_N2$-type process. These equilibria are summarised in Scheme 14.

The possibility of Mannich reactions occurring by the initial condensation of the active hydrogen component with formaldehyde, followed by reaction with an amine, was suggested but then subsequently discounted on the basis of strong experimental evidence. In reactions where the intermediate methylol has given a Mannich base on treatment with an amine, a mechanism was proposed whereby an active methylol dissociates under the reaction conditions to liberate formaldehyde, which then reacts by the usual pathway$^{27a}$.

It was proposed that iminium ions were present as intermediates in Mannich reactions carried out using classical reagents, or aminals under acidic conditions$^{58}$. Experimental evidence strongly supported this suggestion. An intermediate iminium cation was also postulated in the kinetic studies of the Mannich reaction of ethylmalonic acid$^{59}$.
Although the experimental evidence of later authors\textsuperscript{60} contradicted, in part, earlier mechanistic suggestions\textsuperscript{58}, it was observed that such proposals would be acceptable if they were modified to take into account the probable effect of changing the pH of the reaction medium.
The work of Burckhalter and his collaborators provided an insight into the mechanism of the Mannich reaction of phenols. The preponderance of ortho- versus para-substitution observed was explained in terms of reaction via a quasi 6-membered transition state (41), as shown in Scheme 15. Hydrogen-bonding between the phenolic hydrogen and the basic nitrogen of the Mannich reagent was thought to precede the formation of the chelated intermediate (40). The reactive methylene group is then brought into position for the electrophilic attack in the ortho- position in the aromatic ring.

\[ \text{SCHEME 15} \]

Kinetic studies of the reactions of aliphatic nitro-compounds with aminals in aprotic solvents led to the suggestion that reaction occurs via a hydrogen-bonded complex (42) of the aci-nitro form of, for example, 2-nitropropane with the aminal, in low dielectric media (Scheme 16).
In solvents of higher dielectric constant, the hydroxyl proton is co-ordinated to the solvent shell of 2-nitropropane.

The Mannich reaction of 2,4,6-trinitrotoluene with di-(N-piperidyl)methane is proposed to occur via an 8-membered transition state involving the aci-form of the nitro-compound.

On treatment of nitromethane with di-(N-piperidyl)methane the monosubstitution product was formed. However, on addition of water or ethoxy-N-piperidylmethane disubstitution resulted, suggesting that a hydroxymethylamine or alkoxy methylamine intermediate is necessary for this to occur.
Di-\((N\text{-piperidy})\)methane was reported to react faster with nitrocompounds than di-\((N\text{-morpholiny})\)methane\(^{27a}\), a fact that may only be attributed to a difference in basicity since the steric demands of the two compounds are similar. Two unsymmetrical aminals were synthesised, and Mannich bases formed from these were shown to have incorporated the more basic amine function into the aminoalkyl residue\(^{63}\). Thus the condensation of acetophenone with 5-bromo-1-piperidylmethylisatin (43) gave \(N\text{-(2-benzoylethyl)piperidine}\) (Equation 14).

The same workers also showed steric factors to be of great importance in the Mannich reaction.

The co-enzyme tetrahydrofolate (44) was reported to undergo cyclisation with formaldehyde to yield 5,10-methylenetetrahydrofolate\(^{64}\).
The reaction has been shown to occur most readily under acidic conditions, with rate enhancement observed in the presence of secondary amine catalysts. The evidence provided suggested initial condensation of secondary amine with formaldehyde, with subsequent dehydration to yield an iminium ion. Nucleophilic attack by $N_5$, followed by elimination of secondary amine yields a second iminium ion, which then undergoes rapid attack by $N_{10}$ (Scheme 17).

\[
\begin{align*}
R_2NH & + CH_2O & \rightleftharpoons & HO-CH_2-NR_2 \\
\downarrow i & H_2O & + H_2C=NR_2 & \rightleftharpoons \uparrow ii \\
\downarrow & +H_2O & + HNR_2 & \rightleftharpoons \\
\uparrow & +H^+ & \\
\end{align*}
\]

i. $H^+$; ii. tetrahydrofolate.

**SCHEME 17**

Further kinetic evidence for the presence of an iminium cation intermediate was provided by studies of the condensation of a tetrahydroquinoline derivative with formaldehyde$^{65}$. 
From the overview presented it can be seen that the Mannich reaction, in its many forms, has prompted a great deal of synthetic and mechanistic interest. However, there obviously still remains much scope for both improvement of experimental methods and increasing the range of substrates and reagents that may be used in this highly versatile reaction.
CHAPTER TWO

Mannich Reactions Using Preformed Iminium Salts.

2.1 Pyrroles

Much of the interest in the substitution of the pyrrole nucleus arises from the fact that its structure, in both its aromatic and reduced forms, is incorporated into a number of important natural products. The pyrrole ring system itself contains six $\pi$-electrons, which are delocalised over five atoms, and hence is said to be "$\pi$-excessive". As such, it is susceptible to attack by a wide range of electrophiles under relatively mild conditions.$^{66}$

The attack of an electrophile will give the resonance-stabilised cationic intermediates (45) and (46), en route to 2- and 3-substitution.

\[ \text{(45)} \]
\[ \text{(46)} \]

The greater degree of delocalisation of the positive charge observed in (45), and hence the lower energy of the system, explains the predominance of electrophilic substitution of pyrrole at the 2-position.

Since 2-substitution of pyrroles generally occurs in good yields, recent work in this field has centred around the use of bulky substituents on the nitrogen atom to promote electrophilic attack at the 3-position. The results obtained by several groups of workers have been summarised in a recent review.$^{67}$
Early studies of the effect of a variety of 1-substituents on a single reaction concentrated on the Vilsmeier–Haack formylation of pyrroles\textsuperscript{68}. The greatest 3-directing effect came from the t-butyl group, with iso-propyl and benzyl showing some influence. Other workers showed that the extremely bulky 1-triphenylmethyl group gave generally high proportions of 3-substitution products, though in the majority of reactions isolated yields were poor\textsuperscript{69}. Recent investigations into the interaction of a range of pyrroles with nitrilium salts have also shown a trend towards a greater degree of 3-substitution in the presence of bulkier 1-substituents\textsuperscript{70}. Several groups have reported that 1-benzenesulphonylpyrrole undergoes Friedel–Crafts acylation exclusively at the 8-position in the presence of aluminium chloride\textsuperscript{71,72}, though other reactions using this substrate have shown little selectivity\textsuperscript{72}. This N-substituent can later be removed by base hydrolysis.

Further advances in this field of study have included the use of 1-tri-iso-propylsilyl\textsuperscript{73} and 1-TBDMS-pyrrole\textsuperscript{74}. Once again, electrophilic substitution was observed to occur almost exclusively at the 3-position. Subsequent cleavage of the silyl residue was carried out under mild conditions using fluoride anion, ensuring the survival of the functional groups involved.

2.1.1 Mannich Reactions of Pyrroles

The Mannich reaction of pyrroles has been widely studied, often with a view to obtaining novel physiologically active alkylating species. The first such functionalisation of pyrroles utilised aqueous formaldehyde and secondary amines, with the addition of acetic acid to the reaction mixture improving yields in some cases\textsuperscript{63}. The products obtained were derived from substitution at the 2- or 2,5-positions. It was reported that Mannich reactions under these conditions failed using N-substituted pyrroles.
At a similar time, other workers obtained solely the 2-substituted derivatives of pyrrole by employing secondary and primary amine hydrochlorides in Mannich reactions, the latter giving poorer yields. Significantly higher yields of such Mannich bases were later reported using the same experimental procedures followed by chromatographic separation.

Further investigation of Mannich reactions of N-substituted pyrroles enabled the preparation of the corresponding 2- and 2,5-derivatives to be achieved. These reactions were carried out using secondary amine hydrochlorides at 60°C, and the mono- and di-substituted Mannich bases (47) and (48), could be isolated exclusively by varying the molar ratios of reagents (Scheme 18).

Further studies by Herz’s group involved reactions of 2,5-disubstituted pyrroles. Thus it was found that treatment of 1,2,5-trimethylpyrrole with dimethylamine hydrochloride and aqueous formaldehyde gave 3-(N,N-dimethylaminomethyl)-1,2,5-trimethylpyrrole in 69% yield. Further substitution at the 4-position was obtained by using two molar...
equivalents, though no $N$-aminoalkylation was observed when using a large excess of the reagents in the presence of 2,5-disubstituted-1H-pyrroles.

A number of 3,4,5-tri- and 1,3,4,5-tetra-substituted 2-methylpyrroles were shown to give side-chain substitution products when treated with secondary amine hydrochloride in acetic acid (Equation 15).79

\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \begin{array}{c} \text{N} \\ \text{Me} \\ \text{Me} \end{array} \quad \text{CO}_2\text{Et} \xrightarrow{\text{Me}_2\text{NH_2Cl, CH}_2\text{O}} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} \quad \text{Me_2NCH_2CH_2} \quad \text{Me} \quad \text{CO}_2\text{Et} \quad \text{CH}_3\text{CO}_2\text{H, 2hrs}} \quad 95\% 

EQUATION 15

Other interesting aspects of the Mannich chemistry of pyrroles have emerged. The formation of pyrrole trimer is thought to proceed via a series of Mannich reactions preceded by protonation at $C-3$.80

More recently, quaternisation of 1-($N,N$-dimethylamino)pyrrole (49) followed by treatment with sodium methoxide in DMSO gave the nitrogen ylide (50). This intermediate undergoes a Stevens-type rearrangement to give a mixture of 1- and 2-($N,N$-dimethylaminomethyl)pyrrole, (52) and (53), the former being a novel type of compound. Various studies have led to a mechanistic proposal involving rearrangement via a contact ion pair (51) (Scheme 19).81

It was predicted that preformed iminium salts could be used in Mannich reactions with aromatic systems.82 Since pyrrole is a strong nucleophile,
showing general reactivity comparable with that of phenols, it was envisaged that a series of \(N\)-alkylpyrroles would undergo the Mannich reaction with iminium salts. Thus in the absence of high concentrations of acid, and at relatively low temperatures, the problems of side reactions and the formation of polymeric materials could be avoided. It was the aim of our initial work to devise such reaction conditions.

Iminium salts have been widely used in carrying out Mannich reactions during the past twenty-five years. However, the first reported isolation of an iminium salt occurred almost sixty years ago when Stewart and Bradley obtained \(N,N\)-di-\(iso\)-butyl(methylene)iminium chloroplatinate (56) by treatment of \(n\)-butoxy-\(N,N\)-di-\(iso\)-butylaminomethane (54) in aqueous hydrochloric acid with chloroplatinic acid (55) (Equation 16).

SCHEME 19
However, it is only in more modern times that such reagents have been used in synthesis. Several methods of forming iminium salts from aminals and aminol ethers were published by Bohme and Hartke. Treatment of di-(N-piperidyl)methane (56e) with an acyl halide gave N-piperidyl(methylene)iminium halide (22e) or (57), in essentially quantitative yield (Equation 17).

The iminium fluoborate may be isolated on treatment of the aminal with boron trifluoride in the presence of butyryl fluoride. The iminium chlorides were later used in reactions with phenol ethers.

Since that time a number of new methods of iminium salt formation have been published. Treatment of trimethylamine N-oxide with a dichloromethane solution of trifluoroacetic anhydride yielded N,N-dimethyl(methylene)iminium trifluoroacetate.
A novel and elegant route to $N,N$-dimethyl(methylene)iminium iodide was reported by Eschenmoser's group\textsuperscript{86}. Reaction of di-iodomethane with trimethylamine gives the ammonium salt (58), which, when heated at 150°C in tetrahydrothiophene dioxide, thermally decomposes to eliminate methyl iodide, leaving Eschenmoser's salt (6) as a crystalline precipitate (Scheme 20).

$$
\begin{align*}
\text{Me} - \text{N} & \quad \text{Me} + \text{CH}_2\text{I}_2 \quad \text{i} \quad \rightarrow \quad \text{Me} - \text{N}^+\text{CH}_2\text{I}^- \\
\text{Me} & \quad \text{Me}
\end{align*}
$$

(58)

$$
\begin{align*}
\text{Me} - \text{N} & \quad \text{Me} \quad \text{i} \quad \rightarrow \quad \text{Me} - \text{N}^+\text{CH}_2\text{I}^- + \text{MeI} \\
\text{Me} & \quad \text{Me}
\end{align*}
$$

(6)

i. dioxane, EtOH, 100hrs.; ii. (CH\textsubscript{2})\textsubscript{4}SO\textsubscript{2}, 150°C, 15min.

**SCHEME 20**

A more straightforward preparation of Eschenmoser's salt, and other iminium iodides, involves treatment of the appropriate aminal with iodotrimethylsilane in anhydrous ether\textsuperscript{87}.

Anodic oxidation has proved to be a useful tool for the generation of iminium ion intermediates. Shono's group has developed a method whereby such ions are trapped with methanol prior to treatment with a range of nucleophiles in the presence of Lewis acid catalysts\textsuperscript{88}. This methodology avoids the problems associated with the instability of such nucleophiles under the conditions required for anodic oxidation.
2.1.2 Preparation of Iminium Salts

2.1.2.1 From the Aminal

Of the wide variety of routes to iminium salts available, the method of choice took into account ease of the preparation and the cost of reagents. Thus the method of Kinast and Tietze\textsuperscript{13}, itself a variation of Bohme's procedure\textsuperscript{84}, was used in our study. This involved treatment of the appropriate aminal with acetyl chloride in anhydrous ether, the salt (22) precipitating out as a white solid. The procedure to form the aminals from which the iminium salts were generated was that developed by Knoevenagel\textsuperscript{88,89}. Aqueous secondary amine was added to a stirred solution of formaldehyde to give the aminal (56) in good yield. The reactions are summarised in Scheme 21 and Table 1.

\[
\text{R}_2\text{NH} + \text{CH}_2\text{O} \xrightarrow{\text{i}} \text{R}_2\text{N}^-\text{CH}_2^-\text{NR}_2
\]

\[
(56) + \text{MeCOCI} \xrightarrow{\text{ii}} \text{R}_2\text{N}^+\text{CH}_2\text{Cl}^- (\text{+ MeCONR}_2)
\]

\(\text{i. H}_2\text{O, 25°C; ii. Et}_2\text{O, N}_2, 0\text{°C.}\)

**SCHEME 21**

It was also desirable to isolate an iminium salt with an alkyl substituent on the methylene carbon in order to determine whether bulky residues on carbon would adversely affect reaction with pyrroles. Hence the aminal
Table 1
Preparation of Aminals and Iminium Salts

<table>
<thead>
<tr>
<th>Amine</th>
<th>Aminal Structure</th>
<th>Yield / %</th>
<th>Iminium Salt Structure</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂NH</td>
<td>56a</td>
<td>84</td>
<td>22a</td>
<td>91</td>
</tr>
<tr>
<td>Et₂NH</td>
<td>56b</td>
<td>90</td>
<td>22b</td>
<td>99</td>
</tr>
<tr>
<td>Pr₂NH</td>
<td>56c</td>
<td>37⁴</td>
<td>22c</td>
<td>0</td>
</tr>
<tr>
<td>(CH₂)₄NH</td>
<td>56d</td>
<td>84</td>
<td>22d</td>
<td>95</td>
</tr>
<tr>
<td>(CH₂)₅NH</td>
<td>56e</td>
<td>79</td>
<td>22e</td>
<td>92</td>
</tr>
<tr>
<td>O(CH₂CH₂)₂NH</td>
<td>56f</td>
<td>66</td>
<td>22f</td>
<td>98</td>
</tr>
</tbody>
</table>

a. Impure material. Reaction did not work at all until K₂CO₃ was added to the reaction mixture.

(59) from piperidine and acetaldehyde was formed⁹¹, and converted to the iminium salt (60) in the usual way.

![N=N=CH-CH₂-N](image_url)

(59)

![N=CH₂-CHO](image_url)

(60)

2.1.2.2 From the Aminol Ether

The failure to isolate a pure sample of bis-(N,N-di-iso-propylamino)methane was previously documented by Fernandez, who was unable to prepare aminals from a number of bulky amines³⁴. Thus it was decided to prepare a sample of N,N-di-iso-propyl(methylene)iminium chloride via the aminol ether,
according to the procedure of Duboudin and her co-workers\textsuperscript{92}. Di-iso-propylamine, ethanol and potassium carbonate were stirred with paraformaldehyde, and gave, after distillation, ethoxy-\(-N,N-\text{di-iso-}\)propylaminomethane. This was then treated with trichloromethylsilane, under nitrogen, to yield the iminium salt (22c) (Scheme 22).

\[
\text{Pr}_2\text{NH} + (\text{CH}_2\text{O})_n \xrightarrow{\text{i}} \text{Pr}_2\text{NCH}_2\text{OEt} \\
(61b)
\]

\[
(61b) + \text{MeSiCl}_3 \xrightarrow{\text{ii}} \text{Pr}_2\text{N}^+\text{CH}_2\text{Cl}^- ( + \text{MeCl}_2\text{SiOEt}) \\
(22c)
\]

i. K\textsubscript{2}CO\textsubscript{3}, EtOH, 25\textdegree C; ii. Et\textsubscript{2}O, N\textsubscript{2}, 0\textdegree C.

\section*{SCHEME 22}

It would appear that the driving force for the reaction to form the salt is the formation of the relatively strong silicon-oxygen bond.

\subsection*{2.1.2.3 From the Amine Salt}

A general method was sought for the preparation of iminium salts with substituents at the methylene carbon. By the procedure of Leonard and Paukstelis pyrrolidinium perchlorate and fluoborate (62) were formed, and reacted with a series of carbonyl compounds to yield iminium salts (63) (Scheme 23)\textsuperscript{93}.
The results of these preparations are given in Table 2.

Table 2
Preparation of Iminium Salts from Amine Salts

<table>
<thead>
<tr>
<th>Amine salt</th>
<th>Structure</th>
<th>Iminium Salt $R^1$ =</th>
<th>Iminium Salt $R^2$ =</th>
<th>Yield (63) /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>62a</td>
<td>63a</td>
<td>Me</td>
<td>Me</td>
<td>79</td>
</tr>
<tr>
<td>62a</td>
<td>63b</td>
<td>H</td>
<td>Pr$^i$</td>
<td>73</td>
</tr>
<tr>
<td>62b</td>
<td>63c</td>
<td>H</td>
<td>Pr$^i$</td>
<td>50</td>
</tr>
<tr>
<td>62a</td>
<td>63d</td>
<td>H</td>
<td>2-furyl</td>
<td>67</td>
</tr>
</tbody>
</table>
2.1.3 Mannich Reactions of N-Methylpyrrole with Preformed Iminium Salts

It was envisaged that allowing a small excess of N-methylpyrrole to react with the iminium salt, under anhydrous conditions and in a suitable solvent, would yield the 2-aminoalkylated pyrrole. Initial reactions were carried out in dichloromethane or acetonitrile, using $N,N$-dimethyl(methylene)-iminium chloride ($22a, R_2=\text{Me}_2$) (Equation 18 and Table 3).

![Chemical structure](Image)

**EQUATION 18**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Reaction time</th>
<th>Yield (47a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>20 mins.</td>
<td>31</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>40 mins.</td>
<td>47</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>2 hrs.</td>
<td>51</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>24 hrs.</td>
<td>72</td>
</tr>
<tr>
<td>MeCN</td>
<td>2 hrs.</td>
<td>79</td>
</tr>
</tbody>
</table>
It would appear from these results, and from observations made during the reactions, that the difference in reactivity between the two systems lies in the increased solubility of the iminium salt in acetonitrile as compared with dichloromethane. Thus, having chosen acetonitrile as a suitable solvent, similar reactions were carried out using N-methylpyrrole and a range of iminium salts. The results are shown in Table 4.

\[
\begin{align*}
R_2^+N=CH_2 & \quad \text{Cl}^- \\
(22) & \\
R_2^+C=CR^1 & \quad R^2^- \\
(60) \text{ or } (63)
\end{align*}
\]

Table 4
Reactions of N-Methylpyrrole with Iminium Salts

<table>
<thead>
<tr>
<th>Structure</th>
<th>Iminium Salt</th>
<th>Reaction time /hrs.</th>
<th>Mannich base yield /%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R_2^-</td>
<td>R^1^-</td>
<td>R^2^-</td>
</tr>
<tr>
<td>(22a)</td>
<td>Me_2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(22b)</td>
<td>Et_2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(22c)</td>
<td>Pr^-i</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(22d)</td>
<td>Pr^-i</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(22e)</td>
<td>(CH_2)_5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(22f)</td>
<td>O(CH_2CH_2)_2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(60) X=Cl</td>
<td>(CH_2)_5</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>(63) X=ClO_4</td>
<td>(CH_2)_4</td>
<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>(63) X=ClO_4</td>
<td>(CH_2)_4</td>
<td>Pr^-i</td>
<td>H</td>
</tr>
<tr>
<td>(63) X=BF_4</td>
<td>(CH_2)_4</td>
<td>Pr^-i</td>
<td>H</td>
</tr>
<tr>
<td>(63) X=ClO_4</td>
<td>(CH_2)_4</td>
<td>2-furyl</td>
<td>H</td>
</tr>
</tbody>
</table>

a. Yields not optimised.
b. Also gave 1.4% 2,5-disubstituted material.
c. Also gave 4.7% 2,5-disubstituted material.
d. Also gave 10% 2,5-disubstituted material.
As can be seen from the results, N-methylpyrrole reacts with a range of methyleneiminium salts to give 2-substituted products in good yields (Equation 18). The steric demand of the nitrogen substituents appears to have little effect on the yields observed. In the case of N-morpholinylmethyleneiminium chloride, the low yield after a short time may be due to the relative insolubility of this salt compared with others. The yields may be reduced in some cases due to the partial hydrolysis of the iminium salt on handling. Casual observations made while conducting the experiments suggest that such hydrolysis occurs more rapidly along the series:

(22), $R_2 = \text{morpholinyl} \sim \text{piperidyl} < \text{dimethyl} \sim \text{diethyl} \sim \text{di-iso-propyl}.$

It was noted that in certain cases a small amount of disubstituted product was also obtained. This is probably due to the fact that the energy requirements for reaction of the pyrrole and the iminium salt, and for reaction of the monosubstituted product and the salt are of similar magnitude.

All attempted reactions between the C-alkylated iminium salts and N-methylpyrrole failed, even on prolonged heating under reflux. These results are not entirely surprising in view of the general inability of previous workers to carry out successful Mannich reactions using aldehydes other than formaldehyde. The reaction of pyrrole, acetaldehyde and a secondary amine is reported to give the corresponding Mannich base in 0–5% yield, together with a large amount of tarry residues$^{53,94}$. More nucleophilic substrates such as 2-hydroxy-1,4-naphthaquinones$^{37}$ and 2-naphthol$^{95}$, however, are reported to undergo such reactions. Thus the reaction of 2-naphthol, benzaldehyde and dimethylamine in ethanol gave a good yield of the expected Mannich base (Equation 19).
The condensation product of cyclohexanone with morpholine and glyoxylic acid (64) was reported to yield the lactone (65) following treatment with dilute hydrochloric acid (Scheme 24). In all the attempted reactions with C-alkylated iminium salts, the reagents appeared to be insoluble in refluxing acetonitrile, and seemed very resistant to hydrolysis by atmospheric moisture. This may reflect the stabilising
effect of electron-releasing alkyl substituents on the positively charged iminium species. This lack of reactivity observed was mirrored by results obtained by Heathcock, who found that iminium perchlorates prepared by Leonard's procedure were not sufficiently electrophilic to react with allylsilanes or silyl enol ethers. However these salts did react smoothly with allylstannanes and metal enolates (Equation 20).

\[
\begin{align*}
\text{N}^{+} \text{CH-Pr}^{t} & \quad \text{ClO}_{4}^{-} + \quad \text{MeOBut}^{t} \\
& \quad \xrightarrow{\text{OLi}} \\
& \quad \text{Pr}^{t} \quad \text{Me} \quad \text{CO}_{2} \text{-Bu}^{t} \\
\end{align*}
\]

80%, (66) : (67) = 67:33

EQUATION 20

Other authors have suggested the possibility of deprotonation and subsequent enamine formation in the case of aminals with methylene carbon substituents possessing an \(\alpha\)-proton. Duhamel reported that the addition of 2-lithio-1,3-dithiane to preformed iminium salts yielded aminoalkyldithianes. However, it was suggested that when the iminium salt bears an \(\alpha\)-hydrogen the reaction is in competition with elimination leading to the formation of enamines.
2.1.4 Bis-aminoalkylation of \( N \)-Methylpyrrole

Since it was observed that the use of a two-fold excess of amine hydrochloride and formaldehyde under aqueous conditions yielded the 2,5-disubstituted Mannich base with \( N \)-methylpyrrole\(^{77} \), it was felt that treatment with an excess of preformed iminium salt would afford similar results. Hence \( N \)-methylpyrrole and a two-and-a-half-fold excess of the methyleneiminium salt were stirred together, as shown in Equation 21, to give solely the disubstituted product (48) in high yield, after a prolonged reaction period.

\[
\text{Equation 21}
\]

The results of these reactions are given in Table 5.

It is interesting to observe that in all cases the yields quoted are in excess of those for the monosubstitution reactions, despite the fact that the monosubstituted pyrrole must act as an intermediate to disubstitution. It is assumed that a better conversion to the monosubstituted product is achieved because of the presence of the large excess of iminium salt. It is also noted that if the reaction time is reduced to the same order as for the monosubstitution reactions, a mixture of 2- and 2,5-substituted products
results. This is probably because the 2–substitution product exists mainly in the form of its hydrochloride, which is presumably less nucleophilic than the free base. However attempted competition reactions to deduce the relative reactivities did not yield conclusive results, probably because of inefficient mixing of the reagents and the consequent inhomogeneity of the system.

2.1.5 The Effect of Bulky N–Substituents on the Aminoalkylation of Pyrrole

As previously mentioned, recent studies of electrophilic substitution reactions of pyrroles have included attempts to introduce functionality in the 3–position. It was decided to obtain a series of pyrroles with bulky nitrogen substituents to see whether substitution was driven to the 3–position by steric factors. The pyrroles studied were functionalised at nitrogen by methyl, t–butyl, benzyl (68a) and triphenylmethyl (68b) groups.
respectively. The latter two pyrroles were not commercially available and therefore had to be synthesised. \( N \)-Benzylpyrrole (68a) was prepared according to the method of Heaney and Ley, as shown in Scheme 25\(^9\).

\[
\begin{array}{c}
\text{Pyrole} \quad \overset{\text{i}}{\longrightarrow} \quad \left[ \text{Pyrole K}^+ \right] \quad \overset{\text{ii}}{\longrightarrow} \quad \text{Pyrole} \\
\text{CH}_2 \text{Ph} \\
\end{array}
\]

i. KOH, DMSO; ii. PhCH\(_2\)Br.

**SCHEME 25**

\( N \)-Triphenylmethylpyrrole (68b) was formed in the reaction between triphenylmethylamine and 2,5-dimethoxytetrahydrofuran using the procedure devised by Elming and Clauson-Kaas\(^{100}\). Triphenylmethylamine was prepared in good yield by stirring triphenylmethyl chloride in liquid ammonia (Scheme 26).

\[
\begin{array}{c}
\text{Ph}_3\text{C-Cl} \quad \overset{\text{i}}{\longrightarrow} \quad \text{Ph}_3\text{C-NH}_2 \\
\text{75\%} \\
\text{CPh}_3 \\
\end{array}
\]

i. \( \text{NH}_3 \); ii. 2,5-dimethoxytetrahydrofuran, \( \text{CH}_3\text{CO}_2\text{H} \), benzene, reflux.

**SCHEME 26**

Each of the aforementioned pyrroles (68) was subjected to treatment with iminium salts under conditions designed to give monosubstitution of the pyrrole nucleus, as shown in Equation 22 and Table 6.
\[
\begin{align*}
&\text{Pyrrrole} \quad \text{Iminium salt} \\
&\text{RI} = \text{R2} = \text{Me}_2 \\
&\text{PhCH}_2 \text{Me}_2 \\
&\text{Bu}^+ \text{Me}_2 \\
&\text{Ph}_3 \text{CMe}_2 \\
&\text{Ph}_3 \text{CMe}_2 \\
&\text{Me(CH}_2)_5 \\
&\text{PhCH}_2 \text{(CH}_2)_5 \\
&\text{Ph}_3 \text{C(CH}_2)_5 \\
\end{align*}
\]

Equation 22

Table 6
Reactions of N-Substituted Pyrroles with Iminium Salts

<table>
<thead>
<tr>
<th>Pyrrrole (68), R1 =</th>
<th>Iminium salt (22), R2 =</th>
<th>Reaction time /hrs</th>
<th>Mannich base</th>
<th>Yield /%a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me2</td>
<td>2</td>
<td>(47a)</td>
<td>79</td>
</tr>
<tr>
<td>PhCH2</td>
<td>Me2</td>
<td>2</td>
<td>(69a)</td>
<td>79</td>
</tr>
<tr>
<td>Bu</td>
<td>Me2</td>
<td>2</td>
<td>(69b)</td>
<td>39</td>
</tr>
<tr>
<td>Ph3C</td>
<td>Me2</td>
<td>48</td>
<td>—</td>
<td>8b</td>
</tr>
<tr>
<td>Ph3C</td>
<td>Me2</td>
<td>168</td>
<td>—</td>
<td>c</td>
</tr>
<tr>
<td>Me</td>
<td>(CH2)5</td>
<td>2</td>
<td>(47d)</td>
<td>66</td>
</tr>
<tr>
<td>PhCH2</td>
<td>(CH2)5</td>
<td>2</td>
<td>(69c)</td>
<td>35</td>
</tr>
<tr>
<td>Ph3C</td>
<td>(CH2)5</td>
<td>48</td>
<td>—</td>
<td>0</td>
</tr>
</tbody>
</table>

a. Yields not optimised.
b. Reaction gave only 3-substituted product.
c. Increasing reaction time and heating under reflux gave only the 3,4-disubstituted product in 11% yield.

Several interesting points become evident on analysis of these results. It can be seen that whilst only 3-substitution is observed for N-triphenylmethylpyrrole, the yield is extremely poor and this is reflected in decreasing yields of 2-substitution along the series.
Increasing the bulk of the amine substituent also led to a marked decrease in yield using $N$-benzylpyrrole and a complete lack of reaction with $N$-triphenylmethylpyrrole, even under forcing conditions. These results are consistent with those obtained by Herz and Rogers\textsuperscript{77}, who found that yields obtained in classical Mannich reactions with $N$-phenylpyrrole were considerably lower than with $N$-methylpyrrole. This fact was attributed to deactivation of the aromatic ring by the electron-withdrawing phenyl group. However, similar results were observed in the reaction using $N$-t-butylpyrrole, in which electron density on the ring will be similar to that observed for $N$-methylpyrrole. Thus it is concluded that steric repulsion is, in fact, the overriding reason for such observations. That iminium salts unable to react at the 2-position of $N$-substituted pyrroles due to steric factors give little or no 3-substitution demonstrates their relatively low electrophilicity.

2.2 Furans

Furan, like pyrrole, is an electron-rich heterocycle, and its reactions with electrophiles are generally similar. However, furan is considerably less reactive than pyrrole towards electrophiles, and its tendency to give 2-substitution rather than 3-substitution is much more pronounced.

2.2.1 Mannich Reactions of Furans

In contrast to pyrrole, the Mannich chemistry of furans has not been widely explored. Treatment of 2-methylfuran with aqueous formaldehyde and a range of secondary and primary amine hydrochlorides furnished a number of novel furfurylamines, the yields being higher using secondary amines\textsuperscript{101}. An improved preparation of 2-($N,N$-dimethylaminomethyl)-5-methyl-
furan (70) involved heating 2-methylfuran, aqueous formaldehyde and aqueous dimethylamine in acetic acid at elevated temperature to give the product in good yield on work-up (Equation 23):\(^\text{102}\).

\[
\begin{align*}
\text{Me} & \quad \text{CH}_2\text{O} & & \text{Me}_2\text{NH} \\
\text{Furan} & & & \text{CH}_3\text{CO}_2\text{H} \\
& & & 100^\circ\text{C} \\
\rightarrow & & & \text{Me} \quad \text{NMe}_2 \\
\text{Product (70), 69–86%}
\end{align*}
\]

**EQUATION 23**

Attempted Mannich reactions of furans with deactivating ring substituents were reported to fail. Thus no Mannich base was obtained on treating 2-furoic acid (71, \(R=\text{CO}_2\text{H}\)) or ethyl 2-furoate (71, \(R=\text{CO}_2\text{Et}\)) with ethylamine hydrochloride and aqueous formaldehyde:\(^\text{103}\).

\[
\begin{align*}
\text{R} & \quad \text{CH}_2\text{O} \\
(71) & & & \\
\text{Furan}
\end{align*}
\]

However, the same author reports condensation of furfuryl alcohol (71, \(R=\text{CH}_2\text{OH}\)) with formaldehyde and both dimethylamine hydrochloride and morpholine hydrochloride to give the corresponding 5-aminomethylated products in 12 and 42% yields respectively.

Higher yields of aminomethylated derivatives of furfuryl alcohol were obtained by heating the substrate under reflux with the appropriate secondary amine hydrochloride and paraformaldehyde. These products
were required in the first stage of the synthesis of a range of 2,5-bis-(dialkylaminomethyl)furan quaternary salts with potential activity as ganglion-blocking agents\textsuperscript{104}.

The reaction of the fufural-\textit{N}-pyrrolidinylhydrazone (72) with \textit{N}-piperidyl(methylene)iminium chloride (22e) in warm DMF gave the disubstituted furan derivative (73) in excellent yield (Equation 24)\textsuperscript{105}.

\begin{equation}
\begin{array}{c}
\text{\includegraphics[width=0.5\textwidth]{reaction_diagram.png}} \\
(72) + (22e) \xrightarrow{\text{DMF, 40°C}} (73), 86\
\end{array}
\end{equation}

**EQUATION 24**

A number of Mannich bases were prepared from bicyclic furans in order to study their pharmacological activity. Thus 6-(4H)cyclopenta[b]furanone (74) was treated with paraformaldehyde and morpholine hydrochloride in ethanol to yield the Mannich base (75), which is substituted \(\alpha\) to the ketone function\textsuperscript{106}.

\begin{equation}
\begin{array}{c}
\text{\includegraphics[width=0.5\textwidth]{reaction_diagram2.png}} \\
(74) + (\text{CH}_2\text{O})_n + \text{Cl}^- \xrightarrow{\text{EtOH}} (75) \\
\end{array}
\end{equation}

**EQUATION 25**
2.2.3 Mannich Reactions of Furans with Preformed Iminium Salts

It has been reported that furan itself fails to yield a Mannich base under classical conditions\textsuperscript{102a}. A review has suggested that only alkyl-substituted furans will undergo the Mannich reaction\textsuperscript{107}, and this has been further interpreted as a demonstration of the marked effect of alkyl substituents on electrophilic attack\textsuperscript{66b}.

A number of studies have been carried out into the relative rates of electrophilic substitution in five-membered heterocyclic systems\textsuperscript{108-110}. From a series of competition experiments the following rates of trifluoroacetylation were determined: thiophene (1.0), furan (1.4 x 10\textsuperscript{5}), 2-methylfuran (1.2 x 10\textsuperscript{5}) and pyrrole (5.3 x 10\textsuperscript{5})\textsuperscript{109}. These results are of the same order as those observed on treatment with the cationic metal diene complex [C\textsubscript{6}H\textsubscript{5}Fe(CO)\textsubscript{3}]\textsuperscript{+}: thiophene (1.0), furan (3 x 10\textsuperscript{3}) and pyrrole (5 x 10\textsuperscript{5})\textsuperscript{110}. Thus, despite the relatively low nucleophilicity of furan compared with its 2-methyl analogue, it can be seen that its reactivity is greater than that of thiophene by a factor of 10\textsuperscript{2}-10\textsuperscript{3}. Consequently, since thiophene itself yields a Mannich base with a preformed methyleneiminium salt\textsuperscript{49}, it was envisaged that such a reaction would also be applicable to furan and 2-methylfuran.

In view of the success observed in reactions using N-alkylpyrroles, it was decided to attempt a series of reactions of furan and 2-methylfuran with preformed iminium salts. It can now be reported that both substrates give Mannich bases in good to excellent yields on stirring with such iminium salts in acetonitrile at ambient temperature\textsuperscript{111}. The reactions of furan itself are summarised in Equation 26 and Table 7. Reaction times and conditions are not optimised, though it is suggested that the duration of these reactions may be reduced without adversely affecting the yields.
\[
\text{EQUATION 26}
\]

Table 7
Reactions of Furan with Iminium Salts

<table>
<thead>
<tr>
<th>Iminium salt (22), ( R_2 = )</th>
<th>Reaction time /hrs.</th>
<th>Mannich base Structure</th>
<th>Yield /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Me}_2 )</td>
<td>52</td>
<td>(76a)</td>
<td>41</td>
</tr>
<tr>
<td>( \text{Me}_2 )</td>
<td>52(^a)</td>
<td>(76a)</td>
<td>39</td>
</tr>
<tr>
<td>( \text{Me}_2 )</td>
<td>72</td>
<td>(76a)</td>
<td>66</td>
</tr>
<tr>
<td>( \text{Pr}^i_2 )</td>
<td>120</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>( \text{O(CH}_2)_4 )</td>
<td>120</td>
<td>(76b)</td>
<td>74(^b)</td>
</tr>
<tr>
<td>( \text{O(CH}_2)_5 )</td>
<td>31</td>
<td>(76c)</td>
<td>66(^b)</td>
</tr>
<tr>
<td>( \text{O(CH}_2)_5 )</td>
<td>120</td>
<td>(76c)</td>
<td>74</td>
</tr>
<tr>
<td>( \text{O(CH}_2)_5 )</td>
<td>120(^a)</td>
<td>(76c)</td>
<td>60</td>
</tr>
<tr>
<td>( \text{O(CH}_2\text{CH}_2)_2 )</td>
<td>120</td>
<td>(76d)</td>
<td>67</td>
</tr>
<tr>
<td>( \text{O(CH}_2\text{CH}_2)_2 )</td>
<td>120(^a)</td>
<td>(76d)</td>
<td>52</td>
</tr>
</tbody>
</table>

\(^a\) Reactions carried out under reflux.

\(^b\) Slight traces of the corresponding aminal were discovered in the distilled material.
It is interesting to note that no reaction was observed with \( N,N\text{-di-iso-propylamino(methylene)iminium chloride} \). This is perhaps due to the fact that furan is not sufficiently nucleophilic to overcome the steric requirements for reaction to occur. Only di-iso-propylamine was isolated upon basic extraction of the reaction mixture, presumably as a result of hydrolysis of unreacted iminium salt.

In certain reactions, relatively small amounts of 2,5-disubstituted material (77) were isolated along with the major 2-aminoalkylated product (76). Once again this is probably due to the similar energetic requirements for each of the reaction steps involving an iminium salt.

It is also noteworthy that traces of aminal (56d) were detected in reactions with \( N\text{-piperidiny} \text{(methylene)iminium chloride} \). This may also have been present in reactions using the \( N,N\text{-dimethyl} \) analogue, but would have been removed under vacuum along with the solvent during work-up. Further investigation into the interaction of furan and \( N\text{-pyrrolidinyl(methylene)iminium chloride} \) showed a tendency for large amounts of aminal relative to Mannich base to be isolated when reactions were quenched after a relatively short time, though this decreased as the reaction progressed. The results of this study are shown in Table 8.

**Table 8**

<table>
<thead>
<tr>
<th>Reaction time /hrs.</th>
<th>Yield Mannich base (76b) /%</th>
<th>Yield dipyrrolidinylmethane (56d) /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>17</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>56</td>
</tr>
<tr>
<td>11.5</td>
<td>46</td>
<td>48</td>
</tr>
<tr>
<td>120</td>
<td>74</td>
<td>5</td>
</tr>
</tbody>
</table>
It was felt that the recovery of large amounts of aminal was due to the hydrolysis of unreacted iminium salt during work-up to give secondary amine and formaldehyde, which then recombined to form the aminal (56) (Scheme 27).

\[
\begin{align*}
R_2^+ \equiv CH_2 \text{Cl}^- & \xrightarrow{i} \quad R_2NH + CH_2O \\
& \xrightarrow{(22)} \quad R_2NCH_2NR_2
\end{align*}
\]

(22)

1. Acid-base work-up.

**SCHEME 27**

This was confirmed by subjecting a portion of N-pyrrolidinyl-(methylene)iminium chloride to acid-base extraction, upon which large quantities of aminal were isolated.

The reason for the failure of previous workers\textsuperscript{102a} to isolate a Mannich base from furan is not apparent. The possibility of a rearrangement or disproportionation reaction taking place has been discounted, since 2-(\(N,N\)-dimethylaminomethyl)furan is recovered quantitatively following treatment with methanolic hydrogen chloride, conditions under which furyl alcohol is reported to rearrange to laevulinic acid upon acid work-up\textsuperscript{112}. The same Mannich base was also reisolated after being subjected to the conditions under which its 5-methyl analogue was successfully aminoalkylated\textsuperscript{102a}. It is possible, however, that the unexpectedly high volatility of this material led to the problems of isolation experienced by early workers.

The reaction of 2-methylfuran with the iminium salts previously prepared provided some interesting results upon isolation of the basic extracts during
work-up. When the basic aqueous media was extracted with diethyl ether, the expected Mannich base (78) was isolated in good to excellent yield. However, on extraction with dichloromethane, as was the normal practice in early investigations, varying amounts of the amine hydrochloride (79) and the quaternary ammonium salt (80) were also isolated in some experiments, together with the expected liquid Mannich base (Scheme 28).

\[
\begin{align*}
\text{Me}^+ & \quad \text{O} & \quad \text{R}_2^+ \equiv \text{CH}_2 \quad \text{Cl}^- \\
\text{(22)} &
\end{align*}
\]

\[
\text{(78)} \quad + \quad \text{Me}^- & \quad \text{O} & \quad \text{R}_2^+ \equiv \text{NR}_2 \quad \text{Cl}^- \\
\text{(79)} &
\]

\[
\text{Me}^- & \quad \text{O} & \quad \text{R} \quad \equiv \quad \text{NR}_2 \quad \text{Cl}^- \\
\text{(80)} &
\]

i. MeCN, N₂, 25°C; ii. extraction with ether; iii. extraction with DCM.

**SCHEME 28**

The results obtained on treatment of 2-methylfuran with iminium salts are given in Table 9.

In order to confirm the structures of the amine hydrochloride (79a) and the quaternary salt (80a) from the reactions using \( N,N \)-dimethyl(methylene)iminium chloride, each was independently synthesised. The amine hydrochloride (79a) was prepared by treatment of an ethereal solution of the Mannich base (78a) with concentrated
Table 9
Reactions of 2-Methylfuran with Iminium Salts

<table>
<thead>
<tr>
<th>Iminium salt (22), R₂ =</th>
<th>Reaction time /hrs.</th>
<th>Extraction solvent</th>
<th>Mannich base Structure</th>
<th>Yield /% a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂</td>
<td>72</td>
<td>DCM</td>
<td>(78a)</td>
<td>29–46 b</td>
</tr>
<tr>
<td>Me₂</td>
<td>2</td>
<td>Et₂O</td>
<td>(78a)</td>
<td>78</td>
</tr>
<tr>
<td>Me₂</td>
<td>24</td>
<td>Et₂O</td>
<td>(78a)</td>
<td>84</td>
</tr>
<tr>
<td>Me₂</td>
<td>72</td>
<td>Et₂O</td>
<td>(78a)</td>
<td>83</td>
</tr>
<tr>
<td>Pr₁₂</td>
<td>72</td>
<td>DCM</td>
<td>(78b)</td>
<td>65</td>
</tr>
<tr>
<td>(CH₂)₄</td>
<td>72</td>
<td>DCM</td>
<td>(78c)</td>
<td>28–74 b</td>
</tr>
<tr>
<td>(CH₂)₄</td>
<td>72</td>
<td>Et₂O</td>
<td>(78c)</td>
<td>94</td>
</tr>
<tr>
<td>(CH₂)₅</td>
<td>72</td>
<td>DCM</td>
<td>(78d)</td>
<td>67</td>
</tr>
<tr>
<td>O(CH₂CH₂)₂</td>
<td>72</td>
<td>DCM</td>
<td>(78e)</td>
<td>85</td>
</tr>
</tbody>
</table>

a. Yields not optimised.
b. (79) and (80) also isolated.

hydrochloric acid to yield a material whose melting point compared favourably with that quoted in the literature⁰¹.

The quaternary salt (80a) was prepared in essentially quantitative yield from (78a) by reaction with acetyl chloride in dichloromethane (Equation 27).

Although high-field ¹H and ¹³C n.m.r. spectroscopy and elemental analysis indicated the structure of (80a), we were unable to observe the molecular ion by electron impact mass spectrometry. The mass spectrum obtained was almost identical to that observed for the Mannich base (78a). However, the molecular ion was observed using chemical ionisation and fast atom bombardment (FAB) techniques.
Further confirmation of the structure of (80a) was provided by x-ray crystallographic studies carried out by Cathy Burns at this University. The crystal structure of the quaternary salt is shown in Figure 1.

The extraction with dichloromethane of the basic aqueous media during work-up of the reaction between 2-methylfuran and N-pyrrolidinyl(methylene)iminium chloride also led to a mixture of products. $^1$H n.m.r. of the crude extracts showed resonances at chemical shifts similar to those observed for (79a) and (80a), and hence could be attributed to the N-pyrrolidinyl analogues.

Though no solid materials were isolated from reactions using $N,N$-di-iso-propyl-,$N$-piperidyl- and $N$-morpholinyi-(methylene)-iminium chlorides, it is not certain that the corresponding salts are not formed since these reactions were only carried out once.

Such results prompted further investigation into the mode of formation of these salts. It was found that allowing a mixture of
Figure 1
X-ray Crystallographic Structure of $N,N'$-Dimethyl-$N,N'$-di-(5-methyl-2-furylmethyl)ammonium Chloride
2-(N,N-dimethylaminomethyl)-5-methylfuran (78a) and its hydrochloride (79a) to stand in dichloromethane for 72 hours resulted in the formation of the quaternary salt (80a) and increased amounts of (79a) at the expense of the Mannich base. A further experiment involved allowing a dichloromethane solution of the free base (78a) to stand for one week. A mixture of (78a), (79a) and (80a) was isolated on removal of the solvent.

The reaction of amines with dichloromethane is well documented. Interaction of trimethylamine with dichloromethane was reported to yield the N-chloromethylammonium salt (81)\textsuperscript{114}. Kinetic studies of the reactivity of dichloromethane towards amines showed that tertiary amines without bulky substituents undergo fairly rapid reaction\textsuperscript{115}.

\[
\text{Me}_3\text{N}^+\text{CH}_2\text{Cl} \quad \text{Cl}^- \\
(81)
\]

Following discussions with Mills\textsuperscript{116}, it is proposed that the amine hydrochloride (79a) and the quaternary ammonium salt (80a) are formed via reaction of the Mannich base (78a) with the dichloromethane solvent. Such interaction yields the N-chloromethylammonium salt (82), which then eliminates tertiary amine to give a benzylic–type cation (83). This may then capture a second molecule of (78a) to yield the quaternary salt (80a). The tertiary chloromethylamine exists mainly in its ionic form (22a) which will rapidly undergo hydrolysis by adventitious moisture during transferring and evaporation to give formaldehyde and dimethylamine hydrochloride. The latter undergoes exchange of hydrogen chloride with (78a) to give (79a) and liberate dimethylamine (Scheme 29).

In view of the high yields of Mannich bases generally obtained in reactions using methyleneiminium chlorides, it is difficult to understand the dissatisfaction with these reagents communicated by some authors. Holy's
SCHEME 29

i. 2-(N,N-dimethylaminomethyl)-5-methylfuran; ii, H₂O.
i. 2-((N,N-dimethylaminomethyl)-5-methylfuran; ii, H₂O.

SCHEME 29
group\textsuperscript{21} suggested that the iminium trifluoroacetate and iodide are both superior reagents due to their greater solubility in low polarity solvents, though we have demonstrated that no such problem exists when reactions are carried out in acetonitrile. The same authors also professed a preference for the iminium iodide over the chloride due to the latter being more hygroscopic. This observation contradicts the findings of our group, since the iminium chlorides appear to us to be easier to handle than the corresponding iodides. Indeed, Eschenmoser's salt rapidly turns brown in the presence of light.

Reissig and Lorey reported that Mannich bases of 2-siloxycyclopropanecarboxylates are formed more readily, and with greater reproducibility, using the iminium trifluoromethanesulphonate than with the corresponding chloride\textsuperscript{31a}. Once again the heterogeneous character of the reaction mixture is cited as a possible cause of this problem. It is felt that a further contributing factor may be that the iminium chloride (22a) has been shown by \textsuperscript{13}C n.m.r. experiments to exist partially in the covalent form (84) in dichloromethane solution. (Equation 28)\textsuperscript{111}.

\begin{equation}
\text{Me}_2\text{N}^+\text{CH}_2\text{Cl}^-
\quad \leftrightarrow \quad \text{Me}_2\text{N}-\text{CH}_2\text{Cl}
\end{equation}

\textbf{EQUATION 28}

Indeed, Bohme's early studies suggested such compounds to be covalent. The tendency to form a covalent bond is probably a reflection of the greater nucleophilicity of chloride ion compared with that of the trifluoromethanesulphonate anion.
"In Situ" Mannich Reactions

The Mannich reaction may proceed via a number of mechanisms, as exemplified in Chapter 1, depending on the conditions used and the type of reactive intermediate generated. A number of authors have described the interaction of both aminals and aminol ethers with highly nucleophilic substrates to yield Mannich bases\textsuperscript{118-122}. Examples of this type of reaction are given in Equations 29 and 30.

\[
\begin{align*}
\text{Equation 29} \\
\text{PhCH}_2\text{MgBr} & + \text{EI(CH}_2\text{)}_2\text{N} \xrightarrow{\text{EtOH, reflux}} \text{PhCH}_2\text{CH}_2\text{N} & = 66\%\text{ }^{119}
\end{align*}
\]
However, less nucleophilic substrates do not yield Mannich bases under similar conditions. Thus treatment of \(N\)-methylpyrrole with bis-(\(N,N\)-dimethylaminomethane or ethoxy-\(N,N\)-diethylaminomethane in acetonitrile gives no condensation product.

Our interest in the possibility of carrying out "one-pot" Mannich reactions using aminals and aminol ethers was prompted by the observation that iminium salts were generated by the interaction of acetyl chloride with an aminal, or of trifluoroacetic anhydride with an amine. Initial investigations of "one-pot" Mannich reactions of \(N\)-methylpyrrole were carried out by George Papageorgiou in these laboratories, using aminals and aminol ethers, with acetyl chloride and sulphur dioxide as acidic reagents. Despite the limited success with acetyl chloride, reactions using sulphur dioxide gave good yields of the desired Mannich bases.

3.1 Preparation of Aminol Ethers

In order that such "one-pot" Mannich reactions could be further studied, it was necessary to synthesise other aminol ethers to supplement the range of aminals and the aminol ether already prepared. Two new aminol ethers, (61a) and (61c), were made, in the yields shown.

\[
\begin{align*}
\text{Et}_2\text{NCH}_2\text{OEt} & \quad \text{(61a), 54\%} \\
\text{NCH}_2\text{OEt} & \quad \text{(61c), 66\%}
\end{align*}
\]

The preparation of the aminol ethers was complicated by the formation of both the corresponding aminal and a higher-boiling material. It has been suggested that aminol ethers can react further with formaldehyde
to give alkoxymethoxydialkylaminomethanes. This may be seen formally as the incorporation of a second molecule of formaldehyde into the aminol ether structure. A pure sample of the high-boiling product from the reaction of diethylamine, paraformaldehyde and ethanol was isolated in 19% yield by George Papageorgiou, its structure being confirmed by $^1$H and $^{13}$C n.m.r. spectroscopy.

$$\text{Et}_2\text{N} - \text{CH}_2\text{O} - \text{CH}_2\text{OEt}$$

(85)

It is likely that the yields quoted for the aminol ethers could be improved by a careful choice of the reagent ratios. Presumably the yield of the high-boiling compound could be reduced by using a smaller amount of paraformaldehyde in the reaction mixture. It was reported by some workers that excess alcohol was used to increase the yield of aminol ether compared with the aminal. The same group also suggested that increasing the molecular weight of the alkoxy residue would give a greater proportion of aminol ether.

3.2 "In Situ" Mannich Reactions Using Sulphur Dioxide

Following our initial successful isolation of furan Mannich bases, it was decided to attempt "one-pot" reactions with furan and 2-methylfuran and sulphur dioxide (Equation 31). Thus it was hoped to widen the scope of our methodology, and to gain potentially valuable information concerning the reaction mechanisms and intermediates involved.

The results of these reactions are given in Table 10.
Reactions of Furans with Aminals and Aminol Ethers Using Sulphur Dioxide

Furan (71). Reagent Reaction time Mannich base Yield

<table>
<thead>
<tr>
<th>Furan (71), R=</th>
<th>Reagent</th>
<th>Reaction time /hrs.</th>
<th>Mannich base Structure</th>
<th>Yield /%&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield aminal (56d) /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>(56d)</td>
<td>48</td>
<td>(78c)</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>Me</td>
<td>(61c)</td>
<td>48</td>
<td>(78c)</td>
<td>68</td>
<td>19&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>H</td>
<td>(61c)</td>
<td>48</td>
<td>(76b)</td>
<td>0</td>
<td>44&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields not optimised.

<sup>b</sup> Based on 2 moles aminol ether give 1 mole amina.

It can be seen that a good yield of Mannich base from 2-methylfuran was obtained using an aminol ether, which proved to be the more reactive of the two reagents under these conditions, though no reaction was observed using furan itself. Thus it can be concluded that iminium salts are not...
intermediates in this type of reaction. This is confirmed by $^{13}$C n.m.r. spectroscopic studies, which showed no evidence for iminium salt formation when sulphur dioxide was added to a solution of bis-(N,N-dimethylamino)methane in deuteroacetonitrile at low temperatures. It is thought that intermediates of the types (86) and (87) are involved, which are not sufficiently electrophilic to give a reaction with furan.

\[ \text{(86)} \]

\[ \text{(87)} \]

The formation of aminal as a by-product of the reaction was once again attributed to hydrolysis of unreacted Mannich reagent and subsequent recombination of the hydrolysis products. This was confirmed by the isolation of aminal following acid-base extraction of ethoxy-N-pyrrolidinyl-methane.

3.3. "In Situ" Mannich Reactions Using Silicon Reagents

Silicon reagents have been used recently in reactions with both aminals and aminol ethers for the preparation of iminium chlorides. In view of the promising results obtained in Mannich reactions with aminals and aminol ethers activated by sulphur dioxide, it was envisaged that similar "in situ" reactions could be carried out using chlorosilanes (89) as the acidic reagents. Thus a number of reactions of both furan and 2-methylfuran were attempted under such conditions, yielding the expected Mannich bases (76) or (78) in most cases, together with variable amounts of aminal (Equation 32).
The results for the reactions of furan are given in Table 11.

Table 11
Reactions of Furan with Aminals and Aminol Ethers Using Silicon Reagents

<table>
<thead>
<tr>
<th>Reagent (88)</th>
<th>Silane (89)</th>
<th>Reaction time /hrs.</th>
<th>Mannich base Structure</th>
<th>Yield /%&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield aminal (56) /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Me₂N)₂CH₂</td>
<td>Me₃SiCl</td>
<td>48</td>
<td>(76a)</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>[(CH₂)₄N]₂CH₂</td>
<td>Me₃SiCl</td>
<td>48</td>
<td>(76b)</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>[(CH₂)₅N]₂CH₂</td>
<td>MeSiCl₃</td>
<td>48</td>
<td>(76b)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>[(CH₂)₅N]₂CH₂</td>
<td>Me₃SiCl</td>
<td>72</td>
<td>(76c)</td>
<td>0</td>
<td>74</td>
</tr>
<tr>
<td>[(CH₂)₅N]₂CH₂</td>
<td>MeSiCl₃</td>
<td>72</td>
<td>(76c)</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>(CH₂)₄NCH₂OEt</td>
<td>Me₃SiCl</td>
<td>48</td>
<td>(76b)</td>
<td>52</td>
<td>19</td>
</tr>
<tr>
<td>(CH₂)₄NCH₂OEt</td>
<td>Me₂SiCl₂</td>
<td>48</td>
<td>(76b)</td>
<td>67</td>
<td>24</td>
</tr>
<tr>
<td>(CH₂)₄NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>48</td>
<td>(76b)</td>
<td>62</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields not optimised.
The reactions of 2-methylfuran are summarised in Table 12.

Table 12
Reactions of 2-Methylfuran with Aminals and Aminol Ethers Using Silicon Reagents

<table>
<thead>
<tr>
<th>Reagent (88)</th>
<th>Silane (89)</th>
<th>Reaction time /hrs.</th>
<th>Mannich base Structure</th>
<th>Mannich base Yield /%</th>
<th>Yield aminal (56) /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>[(CH₄)₄N]₂CH₂</td>
<td>Me₃SiCl</td>
<td>48</td>
<td>(78c)</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>[(CH₄)₄N]₂CH₂</td>
<td>Me₂SiCl₂</td>
<td>48</td>
<td>(78c)</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>[(CH₄)₄N]₂CH₂</td>
<td>MeSiCl₃</td>
<td>48</td>
<td>(78c)</td>
<td>64</td>
<td>0</td>
</tr>
<tr>
<td>[(CH₂)₅N]₂CH₂</td>
<td>Me₃SiCl</td>
<td>72</td>
<td>(78d)</td>
<td>6</td>
<td>61</td>
</tr>
<tr>
<td>[(CH₂)₅N]₂CH₂</td>
<td>MeSiCl₃</td>
<td>72</td>
<td>(78d)</td>
<td>65</td>
<td>14</td>
</tr>
<tr>
<td>(CH₂)₄NCH₂OEt</td>
<td>Me₃SiCl</td>
<td>48</td>
<td>(78c)</td>
<td>86</td>
<td>0</td>
</tr>
<tr>
<td>(CH₂)₄NCH₂OEt</td>
<td>Me₂SiCl₂</td>
<td>48</td>
<td>(78c)</td>
<td>84</td>
<td>0</td>
</tr>
<tr>
<td>(CH₂)₄NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>48</td>
<td>(78c)</td>
<td>84</td>
<td>0</td>
</tr>
</tbody>
</table>

a. Yields not optimised.

Once again, a comparison of the results quoted in Tables 11 and 12 suggests that 2-methylfuran is considerably more reactive than the unactivated ring, with better yields of Mannich bases observed for all systems. Generally speaking, the best results were obtained using an aminol ether activated by dichlorodimethylsilane or trichloromethylsilane. It is particularly significant that the reactions of 2-methylfuran with aminals and chlorotrimethylsilane yield little or no Mannich base.

¹³C N.m.r. spectroscopy indicated that methyleneiminium salts are formed when solutions of aminol ethers in deuteroacetonitrile-sulphur dioxide are treated with dichlorodimethylsilane or trichloromethylsilane. Thus when
a solution of ethoxy-\(N,N\)-diethylaminomethane in deuterioacetonitrile-
sulphur dioxide was shaken with one mole equivalent of
dichlorodimethylsilane, the broad-band \(^1\)H-decoupled \(^{13}\)C n.m.r. spectrum
immediately showed three peaks at \(\delta_c=12.5\) (s), 55.0 (t, \(J=3.5\)Hz) and 165.4
(t, \(J=13.5\)Hz) p.p.m.. The latter signal is typical of that observed for the
methylene carbon of an iminium salt\(^{128}\), and appears as a triplet due to
coupling with \(^{14}\)N. Contrary to these findings we were unable to detect
the presence of iminium salts when aminals were treated with
chlorotrimethylsilane. Thus, since good yields of Mannich bases from
2-methylfuran, and indeed furan itself, were only obtained in reactions
using reagent systems that are known to give iminium salts, one may
tentatively conclude that aminals (56) do not interact with
chlorotrimethylsilane to generate these intermediates (Scheme 30).

\[
\begin{align*}
R_2\text{N}-\text{CH}_2-\text{NR}_2 + \text{Me}_3\text{SiCl} & \rightleftharpoons R_2\text{N}-\text{CH}_2-\text{NR}_2 ^+ \text{Cl}^- \\
(56) & \quad (90) \quad \text{SiMe}_3
\end{align*}
\]

**SCHEME 30**

The reason for lower yields of Mannich bases from furan, in systems in
which iminium salts are generated, compared with results obtained with
preformed iminium salts, remains obscure. It can only be concluded that
the product is partially destroyed by the silicon reagent.
Once again, it is observed that "in situ" reactions involving aminol ethers often yield the corresponding aminal as a by-product, especially in lower energy systems. It is thought that this process occurs via the breakdown of the unreacted Mannich intermediate, as previously described.

From the results obtained it can be seen that a number of mechanisms may operate in "one-pot" Mannich reactions of chlorosilanes, depending on the substrates and reagents used. For systems in which iminium salts are known to be generated, reaction is thought to occur in the manner shown, for the interaction of an aminol ether (61) with trichloromethylsilane (Scheme 31).

\[
R_2N-CH_2-OEt + MeSiCl_3 \rightleftharpoons R_2N-CH_2-OEt Cl^- \quad \text{(61)}
\]

\[
\rightarrow R_2N=CH_2 Cl^- \quad (+ \text{MeCl}_2\text{SiOEt})
\]

\[
\text{i. ArH; ii. work-up.}
\]

**SCHEME 31**

In order to establish the generality of this type of reaction, further studies were carried out in collaboration with George Papageorgiou, using other heterocyclic substrates\(^{125}\). The writer's contribution yielded the compounds (47a), (48a), (91) and (92), as described in Table 13.
Reactions of Pyrroles and Indoles with Aminals and Aminol Ethers Using Silicon Reagents

<table>
<thead>
<tr>
<th>Heterocyclic substrate</th>
<th>Aminal or aminol ether</th>
<th>Silane (89)</th>
<th>Reaction time /hrs.</th>
<th>Yield Mannich base (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Methylpyrrole</td>
<td>(Me₂N)₂CH₂</td>
<td>Me₂SiCl₂</td>
<td>24</td>
<td>(47a), 59</td>
</tr>
<tr>
<td>Indole</td>
<td>(Me₂N)₂CH₂</td>
<td>Me₃SiCl</td>
<td>48</td>
<td>(91), 63</td>
</tr>
<tr>
<td>N-Methylindole b</td>
<td>Et₂NCH₂OEt</td>
<td>Me₃SiCl</td>
<td>48</td>
<td>(92), 76</td>
</tr>
</tbody>
</table>

a. Yields not optimised.
b. For preparation, see Chapter 4.

It can be seen that good yields of Mannich bases were obtained. It is noted that the strongly nucleophilic substrates react readily with the quaternary silylammonium species (90) which, it is proposed, is generated in reactions using aminals with chlorotrimethylsilane.
3.4 "In Situ" Reactions of Aminol Ethers Derived from Acetic Acid

We have suggested that one possible reason for the failure of Mannich reactions involving C-substituted iminium salts is that of electron-release leading to a stable low energy cationic species (Chapter 2). Gross and Freiberg have prepared iminium salts with the methoxycarbonyl group as the carbon substituent\textsuperscript{127}. The iminium salts (94) were generated by the treatment of C-methoxycarbonyl aminol ethers (93) with thionyl chloride or acetyl chloride (Equation 33).

\[ R_2NCH-\text{CO}_2\text{Me} + \text{SOCl}_2 \rightarrow R_2N=\text{CH-CO}_2\text{Me}^+ \]  
\[
\text{or (MeCOCI)} \\
\text{EQUATION 33}
\]

We may anticipate that these salts will be more electrophilic, and presumably more reactive, than the C-alkylated iminium species. This was borne out by their use in Mannich reactions with a wide range of active methylene compounds\textsuperscript{128}. Thus acetophenone and N-piperidyl(methoxycarbonylmethylene) iminium chloride (95) were shown to undergo condensation to give the Mannich base (96) in good yield (Equation 34).

\[ R_2N=\text{CH} \rightarrow \text{Cl}^- \]  

The only other reported use of these iminium salts is in the functionalisation of 8-acetoxyindolizines\textsuperscript{52}.
It was felt that further insight could be gained into the feasibility of preparing $C$-substituted Mannich bases by attempting a series of reactions with $C$-methoxycarbonyl aminol ethers (99) using the technology we have previously developed for the "in situ" generation of Mannich intermediates.

Thus two aminol ethers (99) were prepared as shown in Scheme 32.

$$\text{Scheme 32}$$
Methyl dimethoxyacetate (97) was prepared by the method of Gross and Freiberg\textsuperscript{129}. Thus dichloroacetic acid was added to freshly prepared sodium methoxide in methanol. The resulting sodium salt of the acid (100) was treated with thionyl chloride, with esterification of the acid chloride occurring "in situ" (Scheme 33).

\[
\begin{align*}
\text{Na}^{+}\text{OMe}^{-} & + \text{Cl}_2\text{CHCO}_2\text{H} \xrightarrow{\text{i}} (\text{MeO})_2\text{CHCO}_2^{-}\text{Na}^{+} \\
& \xrightarrow{\text{ii, iii}} (\text{MeO})_2\text{CHCO}_2\text{Me}
\end{align*}
\]

\text{i. MeOH; ii. SOCl}_2; \text{ iii. HCl, MeOH.}

\text{SCHEME 33}

Conversion of (97) to methyl $\alpha$-chloro-$\alpha$-methoxyacetate (98) occurred readily on heating with phosphorus pentachloride\textsuperscript{130}. The chloroester (98) was then treated with two equivalents of a secondary amine to yield the corresponding aminol ether (99), together with the amine hydrochloride, which was easily removed by filtration\textsuperscript{127}. However, difficulties were encountered in obtaining pure samples of the aminol ethers. Distillation of these compounds under high vacuum gave the desired aminol ether in low yield, together with an unidentified material of similar boiling point, as well as polymeric residues. After several attempts to obtain pure samples of these compounds it was decided that the best method lay in careful distillation using a Kugelrohr apparatus. Since the undistilled aminol ethers appeared to be $\geq 90\%$ pure by $^1\text{H}$ n.m.r. spectroscopy, it is possible that the
somewhat higher yields recorded by earlier workers\textsuperscript{52,127,128} were of crude material, which could then be converted almost quantitatively into the required iminium salts. Attempted "in situ" reactions of unpurified aminol ethers gave reduced yields of Mannich bases in these laboratories.

Thus a number of reactions were carried out with these aminol ethers (99), activated by trichloromethylsilane, and a range of aromatic heterocyclic substrates (101), to yield the expected C–substituted Mannich bases (102). The results obtained are summarised in Equation 35 and Table 14.

\[
\begin{align*}
\text{ArH} + \text{MeO}_2\text{CH-CO}_2\text{Me} + \text{MeSiCl}_3 & \xrightarrow{\text{MeCN, N}_2, 25^\circ\text{C}} \text{Ar-CH-NR}_2 \text{CO}_2\text{Me} \\
(101) + (99) & \Rightarrow (102)
\end{align*}
\]

EQUATION 35

As can be seen, the yields of Mannich bases were generally high. The products from furan and 2–methylfuran were readily purified by distillation. The Mannich bases from N–methylindole were viscous oils which proved to be homogenous by \textsuperscript{1}H n.m.r. spectroscopy and t.l.c.. The products from indole itself were amorphous solids, which is not unexpected since the indole derivative (103) is also reported to exist in this state\textsuperscript{128}.

The derivatives of indole proved to be single substances by \textsuperscript{1}H n.m.r. and t.l.c. and the structures of all four compounds were confirmed by electron impact mass spectrometry.
Table 14
Reactions of Furans and Indoles with C-Methoxycarbonyl Aminol Ethers Using Trichloromethylsilane

<table>
<thead>
<tr>
<th>Heterocyclic substrate (101)</th>
<th>Aminol ether (99), R₂ =</th>
<th>Reaction time /hrs.</th>
<th>Mannich base Structure</th>
<th>Yield /%&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furan</td>
<td>(CH₂)₄</td>
<td>48</td>
<td>(102a)</td>
<td>47</td>
</tr>
<tr>
<td>Furan</td>
<td>(CH₂)₅</td>
<td>39</td>
<td>(102b)</td>
<td>58</td>
</tr>
<tr>
<td>2-Methylfuran</td>
<td>(CH₂)₄</td>
<td>48</td>
<td>(102c)</td>
<td>64</td>
</tr>
<tr>
<td>2-Methylfuran</td>
<td>(CH₂)₅</td>
<td>48</td>
<td>(102d)</td>
<td>91</td>
</tr>
<tr>
<td>Indole</td>
<td>(CH₂)₄</td>
<td>48</td>
<td>(102e)</td>
<td>80</td>
</tr>
<tr>
<td>Indole</td>
<td>(CH₂)₅</td>
<td>48</td>
<td>(102f)</td>
<td>97</td>
</tr>
<tr>
<td>N-Methylindole&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(CH₂)₄</td>
<td>20</td>
<td>(102g)</td>
<td>88</td>
</tr>
<tr>
<td>N-Methylindole&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(CH₂)₅</td>
<td>39</td>
<td>(102h)</td>
<td>86</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields not optimised.

<sup>b</sup> For preparation, see Chapter 4.

It is felt that the methodology described for "one-pot" syntheses of Mannich bases is superior to that of Duboudin<sup>22</sup>, since it does not suffer the handling complications involved in generating and mixing two reactive species.
Mannich Reactions of Oxazolidines

It was envisaged that the scope of the Mannich reaction could be increased by using a wider range of reagents from which iminium ions could be generated. The ring-chain tautomerism of 3-methyl-1,3-oxazolidine (104a) has been studied by $^1$H n.m.r. spectroscopy (Equation 36).\textsuperscript{131}

\[ \text{O\hspace{5pt}N\hspace{5pt}Me} \quad \overset{\text{H}^+}{\leftrightarrow} \quad \text{H}_2\text{C} \quad \overset{\text{N\hspace{5pt}Me}}{\text{HO}} \]

EQUATION 36

It was determined that under strongly acidic conditions the open-chain form (105) exists as 10–20% of the equilibrium mixture. This apparent breakdown of Baldwin's rules has been discussed further elsewhere.\textsuperscript{132} Thus it was anticipated that these reagents would react with chlorosilanes to generate Mannich intermediates "in situ", which could then be used to functionalise a suitable range of nucleophilic heterocycles.

1,3-Oxazolidines were first synthesised by Knorr and Matthes.\textsuperscript{133} A comprehensive review covers oxazolidine chemistry to 1953.\textsuperscript{134} A number of oxazolidines have been used synthetically in reactions with Grignard reagents.\textsuperscript{135}

A series of studies by Griengl's group utilised 1,3-oxazolidines in synthetic routes to 7- and 8-membered heterocyclic compounds. Early work involved the reaction of enol ethers or 5-methyl-2,3-dihydrofuran with
1,3-oxazolidines in dimethyl sulphoxide, in the presence of Lewis acids, to yield a range of monocyclic and bicyclic 1,4-oxazepines\textsuperscript{136}. Latterly, 1,3-oxazolidines (106) were treated with trifluoroacetic acid in order to generate iminium ions (107), which were then trapped with cyclic alkenes to give bicyclic 1,4-oxazepines\textsuperscript{137}. Reaction of (107) with enamines (108) gave 7-dialkylaminoperhydro-1,4-oxazepines (109), as shown in Scheme 34\textsuperscript{138}.

\begin{equation}
\begin{array}{c}
\text{R}^2 \quad \text{R}^1 \\
\text{O} \\
\text{N} \quad \text{R}
\end{array}
\quad \xrightarrow{i} \quad
\begin{array}{c}
\text{R}^2 \quad \text{R}^1 \\
\text{HO} \\
\text{N}^+ \quad \text{CF}_3 \text{CO}_2^-
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{R}^2 \quad \text{R}^1 \\
\text{HO} \\
\text{N}^+ \quad \text{CF}_3 \text{CO}_2^-
\end{array}
\quad \xrightarrow{(107)} \quad
\begin{array}{c}
\text{R}^2 \quad \text{R}^1 \\
\text{R}^3 \quad \text{N} \\
\text{CH} \\
\text{R}^4 \quad \text{Me}
\end{array}
\quad \xrightarrow{\text{i. CF}_3\text{CO}_2\text{H.}}
\begin{array}{c}
\text{R}^2 \quad \text{R}^1 \\
\text{R}^3 \quad \text{N} \\
\text{N} \\
\text{R}
\end{array}
\end{equation}

\textbf{SCHEME 34}

The examples given are the only known synthetic uses to date of iminium salts derived from oxazolidines.

4.1 Preparation of 3-Substituted-1,3-oxazolidines

In order to test our hypothesis that 1,3-oxazolidines could be activated by chlorosilanes, we set ourselves the target of preparing a range of 3-substituted-1,3-oxazolidines (104). The procedure used was that of Jones\textsuperscript{139}, as suggested by Lambert\textsuperscript{131}, which involved heating the appropriate \textit{N}-substituted ethanolamine (110) and paraformaldehyde in benzene under
reflux, with continuous removal of water by a Dean and Stark apparatus (Equation 37).

\[ \begin{align*}
R^1 \text{NH} & \quad \text{OH} \quad \text{(110)} \\
+ \quad (\text{CH}_2\text{O})_n & \xrightarrow{\text{PhH, reflux} \atop \text{Dean and Stark}} \quad R^1 \text{N} \quad \text{O} \quad \text{(104)}
\end{align*} \]

**EQUATION 37**

This method worked well for the high-boiling 1,3-oxazolidines, but in the case of 3-methyl- and 3-ethyl-1,3-oxazolidine, yields were reduced due to co-distillation of benzene with the product. Two superior methods for the synthesis of 3-methyl-1,3-oxazolidine were devised. The first involved stirring \(N\)-methylethanolamine and aqueous formaldehyde overnight, followed by continuous extraction with diethyl ether. The highest-yielding procedure adopted required heating \(N\)-methylethanolamine and paraformaldehyde under reflux in the absence of a solvent, using anhydrous potassium carbonate as a dehydrating agent. The results of these preparations are given in Table 15.

4.2 Furans

It was decided to carry out a series of reactions of 3-substituted-1,3-oxazolidines with furan and 2-methylfuran, using chlorosilanes as activating agents. A typical synthetic route, which allows the introduction of two functional groups simultaneously into the side chain of the Mannich base (111), is outlined in Equation 38.
Table 15
Preparation of 3-Substituted-1,3-oxazolidines

<table>
<thead>
<tr>
<th>1,3-Oxazolidine (104), Structure</th>
<th>$R^1$</th>
<th>Method of preparation</th>
<th>Yield /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(104a)</td>
<td>Me</td>
<td>Benzene, Dean and Stark</td>
<td>30-33</td>
</tr>
<tr>
<td>(104a)</td>
<td>Me</td>
<td>Aqueous</td>
<td>51</td>
</tr>
<tr>
<td>(104a)</td>
<td>Me</td>
<td>Solvent-free</td>
<td>61-70</td>
</tr>
<tr>
<td>(104b)</td>
<td>Et</td>
<td>Benzene, Dean and Stark</td>
<td>62</td>
</tr>
<tr>
<td>(104b)</td>
<td>Et</td>
<td>Solvent-free</td>
<td>62</td>
</tr>
<tr>
<td>(104c)</td>
<td>Bu</td>
<td>Benzene, Dean and Stark</td>
<td>80</td>
</tr>
<tr>
<td>(104d)</td>
<td>PhCH$_2$</td>
<td>Benzene, Dean and Stark</td>
<td>92</td>
</tr>
<tr>
<td>(104e)</td>
<td>Ph</td>
<td>Benzene, Dean and Stark</td>
<td>87</td>
</tr>
</tbody>
</table>

\[
\text{EQUATION 38}
\]

The results of these experiments are given in Table 16.
Table 16
Reactions of Furans with 3-Substituted-1,3-oxazolidines Using Silicon Reagents

<table>
<thead>
<tr>
<th>Furan (71), R=</th>
<th>1,3-Oxazolidine (104), R¹=</th>
<th>Silane (89)</th>
<th>Reaction time /hrs.</th>
<th>Mannich base Structure</th>
<th>Yield /%a</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Me</td>
<td>Me₂SiCl</td>
<td>48</td>
<td>(111a)</td>
<td>30</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>MeSiCl₃</td>
<td>48</td>
<td>(111a)</td>
<td>75</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me₂SiCl</td>
<td>48</td>
<td>(111b)</td>
<td>79</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>MeSiCl₃</td>
<td>48</td>
<td>(111b)</td>
<td>87</td>
</tr>
<tr>
<td>Me</td>
<td>Et</td>
<td>Me₂SiCl</td>
<td>44</td>
<td>(111c)</td>
<td>79</td>
</tr>
<tr>
<td>Me</td>
<td>Et</td>
<td>MeSiCl₃</td>
<td>44</td>
<td>(111c)</td>
<td>89</td>
</tr>
<tr>
<td>Me</td>
<td>Bu⁺</td>
<td>Me₂SiCl</td>
<td>75</td>
<td>(111d)</td>
<td>53</td>
</tr>
<tr>
<td>Me</td>
<td>Bu⁺</td>
<td>MeSiCl₃</td>
<td>44</td>
<td>(111d)</td>
<td>85</td>
</tr>
<tr>
<td>Me</td>
<td>PhCH₂</td>
<td>Me₂SiCl</td>
<td>20</td>
<td>(111e)</td>
<td>73</td>
</tr>
<tr>
<td>Me</td>
<td>PhCH₂</td>
<td>MeSiCl₃</td>
<td>20</td>
<td>(111e)</td>
<td>82</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>Me₂SiCl</td>
<td>7–24</td>
<td>(111f)</td>
<td>32–55</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>MeSiCl₃</td>
<td>15</td>
<td>(111f)</td>
<td>36</td>
</tr>
</tbody>
</table>

a. Yields not optimised.

It can be seen that good yields of the hydroxyethyl Mannich bases (111) were obtained in all the reactions of 2-methylfuran. As expected the yield of (111a) from the reaction of furan, 3-methyl-1,3-oxazolidine and chlorotrimethylsilane was low, but was significantly improved when trichloromethylsilane was used.
The product (111f) derived from the reactions of 3-phenyl-1,3-oxazolidine proved difficult to isolate in reproducible yields.

There is less disparity between the yields from reactions involving chlorotrimethylsilane and trichloromethylsilane than is observed with aminals and acyclic aminol ethers. This suggests a higher degree of reactivity for the intermediates involved in reactions of 3-substituted-1,3-oxazolidines.

### 4.3 N-Methylpyrrole

The successful introduction of a side chain containing both tertiary amine and primary alcohol groups into the 2-methylfuran nucleus, via Mannich reactions with 3-substituted-1,3-oxazolidines, suggested that further investigation of other electron-rich heterocycles would be profitable. Thus reactions between 3-methyl-1,3-oxazolidine and N-methylpyrrole yielded a mixture of the 2-substituted (112) and 2,5-disubstituted (113) Mannich bases on treatment with trichloromethylsilane, but only the monosubstituted derivative using chlorotrimethylsilane (Scheme 35).

Treatment of 3-methyl-1,3-oxazolidine with trichloromethylsilane in diethyl ether yielded a white sticky solid whose structure could not be clarified by low-field $^1$H n.m.r. spectroscopy. However, it is assumed that the material was the silyloxyiminium chloride (114). Subsequent dissolution in acetonitrile and treatment with N-methylpyrrole gave (112) in 62\% yield.

It is interesting to note that a reaction in which we attempted to activate 3-methyl-1,3-oxazolidine with acetyl chloride failed to yield a Mannich base.
4.4 Indoles

Indole, like pyrrole, is a highly nucleophilic aromatic system. It undergoes electrophilic attack most readily at the 3-position, via the resonance-stabilised cation (115).
In view of the presence of the indole sub-unit in many natural product structures, it was felt that investigation of the Mannich reactions of indoles with 3-substituted-1,3-oxazolidines would prove interesting.

4.4.1 Mannich Reactions of Indoles

The Mannich reaction of indoles under classical conditions has enjoyed widespread coverage in the literature. Kuhn and Stein reported the reaction of indole, formaldehyde and dimethylamine in the presence of glacial acetic acid to yield gramine (116). This is a very useful intermediate in the routes to important 3-substituted indoles, such as tryptophan (117), an essential amino acid (Scheme 36).

![Scheme 36](image)

SCHEME 36

More recently the Mannich chemistry of indoles has centred around the synthesis of natural products, notably the ergot alkaloids. This group of
biologically active indole alkaloids comprises of an indole skeleton with an α-substituted C₆-isoprene unit at the 4-position. Thus, as part of a long-term project to synthesise various members of the ergot alkaloid family, a range of 4-substituted indoles were shown to undergo the Mannich reaction with N,N-dimethyl(methylene)iminium chloride (22a) in excellent yields, as exemplified by Equation 39.

\[
\text{HC=CH-O\textsubscript{Me} } + \text{ Me}_2^\text{+} \text{N}=\text{CH}_2 \text{Cl}^- \rightarrow \text{HC=CH-O\textsubscript{Me} } \text{NMe}_2
\]

EQUATION 39

Other groups have reported functionalisation of indoles at the 3-position in the preparation of ergot alkaloids. The total synthesis of (±)-6,7-secoagroclavine includes the reaction of a 4-substituted indole with the iminium chloride (22a)\textsuperscript{142}. Similarly, functionality has been introduced at the 3-position en route to the clavicipatic acids\textsuperscript{143}.

A novel approach to the synthesis of the ergot alkaloids involved functionalisation of 1,4-bis-(trimethylsilyl)indole (118) at the 3-position using a range of electrophiles. Hence 4-trimethylsilylgramine, a useful intermediate to the further modification of indole at the 3-position, was prepared by the reaction of (118) with N,N-dimethyl(methylene)iminium chloride\textsuperscript{144}.

An intramolecular Mannich condensation is involved in the generation of the A and F rings of an advanced synthetic intermediate in the formation of penitrem D, a member of the tremorgenic indole alkaloid family\textsuperscript{145}.
Thus the Mannich reaction of (119), employing dimethylamine in acetic acid-THF is thought to yield the intermediate gramine analogue (120), which subsequently undergoes cyclisation with loss of amine to give (121) (Scheme 37).

\[
\text{MPM = } p-\text{MeO-}
\]

\[
\text{C}_6\text{H}_4-\text{CH}_2
\]

(121), 87%

i. Me\textsubscript{2}NH, CH\textsubscript{3}CO\textsubscript{2}H, THF; ii. H\textsuperscript{+}, -Me\textsubscript{2}NH.

**SCHEME 37**

4.4.2 Reactions of Indoles Using 3-Substituted-1,3-oxazolidines

A number of reactions of indole and N-methylindole (prepared by the method of Heaney and Ley\textsuperscript{99}) with 3-substituted-1,3-oxazolidines (104) and chlorosilanes (89) yielded the expected N-hydroxyethyl Mannich bases (123), as shown in Equation 40 and Table 17.
Table 17  
Reactions of Indoles with 3-Substituted-1,3-oxazolidines Using Silicon Reagents

<table>
<thead>
<tr>
<th>Indole (122), R=</th>
<th>1,3-Oxazolidine, (104), R'=</th>
<th>Silane (89)</th>
<th>Reaction time /hrs.</th>
<th>Mannich base Structure</th>
<th>Yield /% a</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>PhCH₂</td>
<td>MeSiCl₃</td>
<td>20</td>
<td>(123a)</td>
<td>84</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me₃SiCl</td>
<td>48</td>
<td>(123b)</td>
<td>67</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>MeSiCl₃</td>
<td>48</td>
<td>(123b)</td>
<td>91</td>
</tr>
<tr>
<td>Me</td>
<td>Et</td>
<td>Me₃SiCl</td>
<td>44</td>
<td>(123c)</td>
<td>62</td>
</tr>
<tr>
<td>Me</td>
<td>Et</td>
<td>MeSiCl₃</td>
<td>44</td>
<td>(123c)</td>
<td>94</td>
</tr>
<tr>
<td>Me</td>
<td>PhCH₂</td>
<td>Me₃SiCl</td>
<td>24</td>
<td>(123d)</td>
<td>95</td>
</tr>
<tr>
<td>Me</td>
<td>PhCH₂</td>
<td>MeSiCl₃</td>
<td>24</td>
<td>(123d)</td>
<td>96</td>
</tr>
</tbody>
</table>

a. Yields not optimised.

Once again yields are generally high, especially when using trichloromethylsilane as an activating agent. The Mannich base derived from indole itself proved to be stable, highly crystalline solids. However, in all cases the products from reactions using N-methylindole were involatile.
oils, which were shown to be homogeneous by $^1$H n.m.r. spectroscopy. The Mannich bases were then treated with ethereal hydrogen chloride to yield their respective hydrochloride salts, which gave satisfactory micro-analyses.

4.5 3-Substituted-1,3-oxazolidine from Ephedrine

As part of a long-term aim to synthesise Mannich bases with pharmacological activity$^{61}$, Harrell discovered that a reaction of 1,2-diphenyldiazepine (124) with ephedrine (125) and aqueous formaldehyde gave the Mannich base (126), which proved to be a strong central nervous system depressant (Equation 41).

It is interesting to speculate whether such a reaction involved the intermediacy of a 1,3-oxazolidine.

Numerous 1,3-oxazolidines have been prepared from ephedrine, although these appear only to have been used synthetically as co-reactants with Grignard reagents$^{148}$. 

EQUATION 41
Thus it was decided to prepare the corresponding oxazolidine (128) from (1R,2S)-ephedrine (127) and paraformaldehyde, in the usual way (Equation 42).

\[
\text{MeNH H H} + (\text{CH}_2\text{O})_n \xrightarrow{\text{K}_2\text{CO}_3, \text{PhH}_2, \text{Dean and Stark, reflux.}} \text{MePh} \xrightarrow{\text{Dean and Stark, reflux.}} (128), 93\%
\]

EQUATION 42

The reaction of furan with 3,4-dimethyl-5-phenyloxazolidine (128) gave recovered starting material in the presence of chlorotrimethylsilane, though using trichloromethylsilane the Mannich base (129a, R=H) was obtained in 18% yield together with starting material. A similar reaction with 2-methylfuran gave (129b, R=Me) in 25% yield using chlorotrimethylsilane. However, activation of (128) with trichloromethylsilane led to the isolation of (129b) in 80% yield.

4.6 Protection of the Alcohol Function

The greater stability of TBDMS ethers as compared with trimethylsilyl ethers suggested that reactions of t-butylchlorodimethylsilane with 3-methyl-1,3-oxazolidine, in the presence of a suitable aromatic substrate, would permit the isolation of Mannich bases containing an alcohol
functionality protected as its silyl ether. A precedent for this type of reaction involves the cleavage of tetrahydrofuran with \( t\)-butylchlorodimethylsilane (130) in the presence of sodium iodide to yield \( 1\-t\-butyl\-dimethylsiloxy\-4\-iodobutane \) (131) (Scheme 38).47

\[
\begin{align*}
\text{Me} & \quad \text{Bu}^1\text{-Si-Cl} \quad \overset{\text{i}}{\longrightarrow} \quad \left[ \begin{array}{c}
\text{Me} \\
\text{Bu}^1\text{-Si-I} \\
\text{Me}
\end{array} \right] \quad \overset{\text{ii}}{\longrightarrow} \\
\text{Bu}^1\text{-Si-O-} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\( \text{Me} \quad \text{Bu}^1\text{-Si-I} \quad \text{Me} \)

\( \text{Bu}^1\text{-Si-O-} \quad \text{Me} \\
\text{Me} \quad \text{Me} \)

i. NaI, MeCN; ii. THF, \( N_2 \), 55°C, 10hrs.

**SCHEME 38**

Thus, the reaction of 3-methyl-1,3-oxazolidine (104a), 2-methylfuran and \( t\)-butylchlorodimethylsilane led to the formation of the protected alcohol (132) in 32% yield after 48 hours. Neither the addition of sodium iodide to the reaction mixture, nor heating at 55°C for 16 hours improved this yield. However a prolonged reaction period (14 days) gave (132) in 66% yield.

\[
\begin{array}{c}
\text{Me}\quad \text{Me} \\
\text{Me} \quad \text{Me}
\end{array}
\]

\( \text{Me} \quad \text{Me} \)

\( \text{Me} \quad \text{Me} \)

In view of the impractical timescale of this reaction it was felt necessary to increase the reactivity of the silylating agent.
The most frequently employed method of t-butyldimethylsilylation involves the use of t-butylchlorodimethylsilane (130) together with a base. The earliest procedure used imidazole as a basic catalyst in the protection of hydroxyl groups\textsuperscript{148}, though more recent methods recommend the use of 4-\textit{N},\textit{N}-dimethylaminopyridine (DMAP) in the presence of another base, such as triethylamine\textsuperscript{149}. The use of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) is suggested\textsuperscript{150}, and 1,2,4-triazole (133) is reported to be the reagent of choice in the silylation of tribenzoylated ribofuranose\textsuperscript{151}.

Initial attempts to improve the yield in our silylation reaction involving 2-methylfuran used imidazole and DMAP without success, the former giving mixtures of products. However the use of one equivalent of 1,2,4-triazole in conjunction with the silane gave the desired product in 61\% yield in 72 hours. In similar reactions using \textit{N}-methylindole the addition of (133) or DMAP gave the corresponding Mannich base (134) in 51\% and 53\% yields respectively (Scheme 39).

\begin{tikzpicture}

\node at (0,0) {\textbf{SCHEME 39}};
\end{tikzpicture}
The increased electrophilicity of the silylating agent is thought to be due to the formation of the silylammonium complex (135) (Equation 43).

![Equation 43]

The higher yields reported for reactions using 1,2,4-triazole over imidazole may be explained in terms of the greater positive charge accumulated on the substituted nitrogen as more CH groups in the ring are replaced by electronegative nitrogen atoms\(^{152}\).

It is possible that the reactions could have been carried out more efficiently using the highly reactive \(t\)-butyldimethylsilyl trifluoromethanesulphonate\(^{153}\) or perchlorate\(^{154}\). However, trace amounts of moisture would lead to the formation of the corresponding trifluoromethanesulphonic and perchloric acids, which would rapidly destroy the furan nucleus. The silyl perchlorate was also rejected due to its potentially explosive nature.

### 4.7 Conversion to the Secondary Amine

In order to extend the synthetic utility of Mannich reactions of 3-substituted-1,3-oxazolidines, it was decided to attempt the overall dehydroxyalkylation of the Mannich base (111b) to yield the corresponding secondary amine (136) (Scheme 40).
The first stage of the planned synthetic route used a known literature procedure, involving the interaction of hexamethylphosphorus triamide (HMPT) and carbon tetrachloride in the presence of the alcohol. Chloride ion is ultimately involved in nucleophilic attack on the phosphonium salt to give the chloroalkyl compound (Scheme 41).

Thus HMPT was added to a mixture of the Mannich base alcohol and carbon tetrachloride in ether at -40°C. Warming to room temperature yielded the β-chloroethylamine. A superior yield was realised when the mixture was stirred overnight, though gentle reflux in DMF diminished this (Scheme 42).
The Boord reaction involves the elimination of alkoxide and halogen from \( \beta \)-haloethers using zinc, sodium or magnesium. This reaction is of fairly broad scope, and has been carried out using \( \beta \)-chloroamines\textsuperscript{156}, though a secondary amine does not appear to have been isolated.

Initial attempts to carry out dechloroethylation of (141) by heating under reflux with zinc or magnesium failed to yield the corresponding secondary amine (136), giving instead a large recovery of starting material. Ultrasonic activation of the metal, or entrainment of magnesium using 1,2-dibromoethane also failed to give a reaction. It was felt that protonation of the amine would increase its potential as a leaving group, and that the addition of iodide ion to the reaction mixture may give exchange with chloride to furnish a more electrophilic centre for metal co-ordination.

Hence the chloroamine (141) was treated with zinc and sodium iodide in acetic acid, and the reaction mixture was subjected to ultrasonication to clean the metal surface. Heating the mixture under reflux then gave the secondary amine (136) in good yield (Scheme 43).

Prolonging the period of reflux tended to decrease the yield of (136), whilst leading to larger amounts of resinous material. The role of the iodide ion in the reaction is not clear. It is possible that ion exchange with chloride occurs, as has previously been suggested, though formation of zinc iodide
cannot be ruled out. This would probably act as a Lewis acid catalyst in enhancing the leaving group effect of the amine, hence facilitating attack of zinc on the halogen. Removing sodium iodide from the reaction mixture caused the yield to fall from 53% to 15% after 3 hours. However, addition of zinc iodide in its place gave 42% of the secondary amine (136). A number of possible mechanistic pathways are shown in Scheme 44.

\[
\text{ArCH}_2\text{NHMe} + \text{CH}_2=\text{CH}_2\text{I} + \text{ZnX}_2
\]

\(\text{ArCH}_2\text{NMe} \quad X = \text{Cl or I}\)

i. NaI, CH\(_3\)CO\(_2\)H, Zn; ii. ZnI\(_2\), CH\(_3\)CO\(_2\)H, Zn or NaI, CH\(_3\)CO\(_2\)H, Zn.

**SCHEME 43**

**SCHEME 44**
4.8 Mannich Reactions of 2-Substituted-3-methyl-1,3-oxazolidines

In the continued pursuit of Mannich bases with substituents on the α-carbon to the nucleophile, it was decided to synthesise several 2-substituted-3-methyl-1,3-oxazolidines. Thus, using the methods previously described, such oxazolidines (142) were prepared in the yields shown from the reaction of N-methylethanolamine with the appropriate aldehydes (Table 18).

![Mannich Reaction Structure](image)

Table 18

Preparation of the 2-Substituted-3-methyl-1,3-oxazolidines

<table>
<thead>
<tr>
<th>Structure</th>
<th>Oxazolidine</th>
<th>Yield /% a</th>
</tr>
</thead>
<tbody>
<tr>
<td>(142a)</td>
<td>Me H H</td>
<td>50</td>
</tr>
<tr>
<td>(142b)</td>
<td>Bu H H</td>
<td>53</td>
</tr>
<tr>
<td>(142c)</td>
<td>Ph H H</td>
<td>58</td>
</tr>
<tr>
<td>(142d)</td>
<td>Me Me Ph</td>
<td>84</td>
</tr>
</tbody>
</table>

a. Yields not optimised.

However, a number of reactions of 2-methylfuran and N-methylpyrrole, using these reagents and chlorosilanes, failed to yield Mannich bases, giving instead polymeric materials. Since 2- t-butyl-3-methyl-1,3-oxazolidine
does not afford a Mannich base, it would appear that deprotonation and subsequent enamine formation is not the sole cause of the failure of these reactions. It was felt that the most likely reason for the lack of reaction was probably stabilisation of the iminium species, as described in Chapter 2.

Since acyclic aminol ethers derived from acetic acid have been shown to react readily with a number of heteroaromatic nucleophiles, we set ourselves the target of synthesising a 2-alkoxycarbonyl-3-methyl-1,3-oxazolidine. It was envisaged that such a compound could be prepared from a glyoxylic acid ester and \( N \)-methylethanolamine. Ethyl glyoxylate was thus prepared by the method of Kelly\textsuperscript{157}, in which diethyl tartrate (143) underwent oxidative cleavage on treatment with periodic acid (144) in dry ether (Equation 44). Distillation gave a pale yellow mobile liquid, which was redistilled from phosphorus pentoxide to yield pure ethyl glyoxylate (145), which polymerised rapidly on standing.

\[
\begin{align*}
\text{HO-CH-} & \text{CO}_2\text{Et} \\
\text{HO-CH-} & \text{CO}_2\text{Et} \\
(143) & \\
+ & \text{HJO}_6 \\
(144) & \xrightarrow{\text{Et}_2\text{O}} \text{2 OH-CO}_2\text{Et} \\
(145) & , 52\%
\end{align*}
\]

\textbf{EQUATION 44}

A superior method was used in the preparation of methyl glyoxylate, involving the acid-catalysed exchange of an alcohol equivalent between an acetal ester and a carboxylic acid\textsuperscript{158}. Thus methyl dimethoxyacetate (97) and glyoxylic acid monohydrate (146) were heated together in the presence of a catalytic amount of \textit{para}-toluenesulphonic acid. Dehydration
with phosphorus pentoxide, followed by distillation, gave methyl glyoxylate (147) (Scheme 45).

\[
\begin{align*}
\text{MeO} & \quad \text{CH-CO}_2\text{Me} + \text{OHC-CO}_2\text{H} \cdot \text{H}_2\text{O} \xrightarrow{i, \text{ii}} 2 \text{OHC-CO}_2\text{Me} \\
(97) & \quad (146) & (147), 64%
\end{align*}
\]

\(i. p-TSA, 80^\circ\text{C}, 18\text{hrs}; \ ii. P_2\text{O}_5, 80^\circ\text{C}, 4\text{hrs.}\)

**SCHEME 45**

Freshly prepared methyl glyoxylate (147) and \(N\)-methylethanolamine (110a) were heated under reflux for one hour in benzene, using the method previously described, to yield 2-methoxycarbonyl-3-methyl-1,3-oxazolidine (148) (Equation 45).

\[
(147) + \text{MeNH} \xrightarrow{\text{PhH, reflux, Dean and Stark, 1hr.}} \text{MeN} \quad \tilde{\text{C}} \quad \text{O}
\]

\(148\), 51%

**EQUATION 45**

The ethoxycarbonyl analogue was prepared by a similar method in 58% yield.

The \(^1\text{H}\) n.m.r. spectrum of 2-methoxycarbonyl-3-methyl-1,3-oxazolidine (148) proved to be interesting, in common with that of the other 2-substituted oxazolidines prepared.
FIGURE 2

The complexity of the spectrum can be attributed to diastereotopicity effects due to the introduction of a chiral centre at the 2-position. The high-field $^1$H n.m.r. spectrum shows resonances at $\delta=2.72$ (dt, 1H) and $\delta=3.17$ (dt,1H) for protons $H_a$ and $H_b$ (Figure 2), and $\delta=3.69-4.01$ (m,2H) which may be assigned to $H_c$ and $H_d$. Thus it can be seen that on each of the methylene carbons, the two protons are in different magnetic environments. The structure of (148) was confirmed from spectral data and high resolution electron impact mass spectrometry. The high-field $^1$H and $^1$H-$^{13}$C correlation n.m.r. spectra of (148) are shown in Figures 3 and 4.

A number of reactions of both 2-methoxycarbonyl- and 2-ethoxycarbonyl-3-methyl-1,3-oxazolidine were carried out using 2-methylfuran in the presence of chlorosilanes. However, no Mannich base was isolated from such reactions. The use of stronger Lewis acids (boron trifluoride etherate and titanium tetrachloride), or even a protic acid (trifluoroacetic acid) also failed to give the required product, presumably due to the higher energy of formation of the required iminium salt.

The known cleavage of tetrahydrofuran by $t$-butylchlorodimethylsilane and iodide ion suggested that $S_N2$ cleavage of a carbon-oxygen bond on the side remote from the nitrogen and the electron-withdrawing group was possible. Reaction with thionyl chloride, a reagent well known for
Figure 3

$^1$H N.m.r. Spectrum of 2-Methoxycarbonyl-3-methyl-1,3-oxazolidine
Figure 4

$^1$H–$^{13}$C Correlation N.m.r. Spectrum of 2–Methoxycarbonyl–3–methyl–1,3–oxazolidine
the conversion of alcohols into the related alkyl chlorides, could cause cleavage of the ring in such a manner, and simultaneously provide an additional driving force for the generation of an iminium salt by the liberation of sulphur dioxide. Thus the treatment of 2-methoxy carbonyl-3-methyl-1,3-oxazolidine (148) with thionyl chloride gave the expected N-chloroethyl Mannich base (149) (Equation 46).

\[
\begin{align*}
\text{MeCN, } \text{N}_2 \quad 25^\circ\text{C}, \quad 72\text{hrs.} \\
\text{MeCN, } \text{N}_2 \quad 25^\circ\text{C}, \quad 72\text{hrs.}
\end{align*}
\]

\[148\]

\[149, \text{42}\%\]

A plausible mechanism for this reaction is shown in Scheme 46. Reaction of (148) with thionyl chloride gives the oxonium species (150), which undergoes nucleophilic attack by chloride ion at the 5-position. Elimination of sulphur dioxide then yields the iminium species (151) which may then interact with the aromatic ring in the usual way.

The reactions of 2-alkoxycarbonyl-1,3-oxazolidines are of great importance since they allow the simultaneous introduction of a number of functional groups into the aminoalkyl residue. However, more significantly, the formation of a new chiral centre opens the door to the possibility of stereoselective Mannich reactions using chiral oxazolidines.
A number of reactions in this chapter have been reported in a preliminary communication, which also discusses the Mannich reactions of oxazolidines with phenols and silyl enol ethers.\textsuperscript{159}
CHAPTER 5

Miscellaneous Mannich Reactions of Aromatic Species

5.1 Imidazolidines

In view of the success that had been achieved using 1,3-oxazolidines, which are nominally cyclic aminol ethers, in Mannich reactions, it was envisaged that cyclic aminals would also prove to be useful reagents. The $^1$H n.m.r. of 1,3-dimethylimidazolidine (152a), a cyclic aminal, has been studied in trifluoroacetic acid, and ring-chain tautomerism similar to that reported for 1,3-oxazolidines was observed (Equation 47)\(^{180}\).

\[
\begin{align*}
\text{Me}-\text{N}-\text{Me} & \quad \overset{\text{Me}-\text{NH}}{\underset{\text{Me}}{\rightleftharpoons}} \text{Me}\text{H}_2\text{C}\text{N}^+\text{Me} \\
(152a) & \quad (153)
\end{align*}
\]

EQUATION 47

The proportion of the open-chain form (153) is found to be increased from 15–20% to about 28% if the 2-position is substituted by a phenyl group, probably due to resonance stabilisation of the cation\(^{181}\).

A precedent for the use of an iminium species analogous to (153) in a Mannich-type reaction was given in a mechanistic postulation for the intramolecular cyclisation of the co-enzyme tetrahydrofolate with formaldehyde (Chapter 1)\(^{64}\).

In order to test our predictions it was necessary to prepare 1,3-dimethylimidazolidine (152a). Initial attempts involved the
condensation of aqueous formaldehyde with $N$, $N'$-dimethylethylene-diamine (154), according to the method of Riddell\textsuperscript{162}. However, it proved difficult to isolate a pure product under these conditions, probably due to contaminants in the starting material. Thus the reaction of the diamine with paraformaldehyde was carried out in benzene, using potassium carbonate as a dehydrating agent, giving (152a) in low yield on careful distillation (Equation 48).

\[
\begin{align*}
\text{MeNH} & \quad \text{HNMe} \\
\text{(154)}
\end{align*}
\begin{align*}
+ \quad (\text{CH}_2\text{O})_n \quad \xrightarrow{\text{PhH, reflux, 6hrs, Dean and Stark}}
\text{MeN} & \quad \text{NMe} \\
\text{(152a)}
\end{align*}
\]

EQUATION 48

Carrying out the reaction in DMF at 80°C is reported to give (152a) in good yield\textsuperscript{163}, but on the one attempt using this method we failed to isolate the product.

A second reagent, 1,3-dibenzylimidazolidine (152b), was prepared by Robin Fairhurst, in these laboratories, using the method described in Equation 48.

A short series of reactions using 1,3-imidazolidines (152) was carried out with furan substrates (71), using chlorosilanes (89) as activating agents. Thus it was deemed possible to form Mannich bases (155) containing both secondary and tertiary amine functionalities (Equation 49).
The results of these experiments are given in Table 19.

Table 19
Reactions of Furans with Imidazolidines Using Silicon Reagents

<table>
<thead>
<tr>
<th>Furan (71), R</th>
<th>Imidazolidine (152), R¹</th>
<th>Silane (89)</th>
<th>Reaction time /hrs.</th>
<th>Yield Mannich base /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Me</td>
<td>MeSiCl₃</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me₃SiCl</td>
<td>48</td>
<td>&lt;11&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>MeSiCl₃</td>
<td>48</td>
<td>71</td>
</tr>
<tr>
<td>Me</td>
<td>PhCH₂</td>
<td>MeSiCl₃</td>
<td>168</td>
<td>0</td>
</tr>
</tbody>
</table>

a. Yields not optimised.
b. Total yield of basic material =11%. Mannich base was not separated from recovered imidazolidine.

There are few conclusions which may be drawn from the results at such an early stage of investigation. It can be seen that the intermediate formed by the interaction of 1,3-dimethylimidazolidine and trichloromethylsilane
is not sufficiently electrophilic to yield a Mannich base with furan, though reaction with 2-methylfuran proceeds smoothly to give the novel Mannich base (155a).

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{OSSa} & \\
\text{Me} & \quad \text{N} \quad \text{NHMe}
\end{align*}
\]

(155a)

Once again it is observed that trichloromethylsilane is generally a more reactive acidic reagent than its monochloro- analogue.

We have so far failed to isolate a Mannich base using 1,3-dibenzylimidazolidine, despite the fact that this compound undergoes ring-chain tautomerism\(^{161}\) in the manner described for its 1,3-dimethyl analogue. It is suggested that steric interaction with the bulky benzyl substituent inhibits the formation of a reactive intermediate with trichloromethylsilane.

It can thus be concluded that 1,3-dimethylimidazolidines are less versatile Mannich reagents than 1,3-oxazolidines, under the reaction conditions we have used. This was further exemplified by Robin Fairhurst, in these laboratories, who failed to isolate Mannich bases from reactions of imidazolidines with a range of silyl enol ethers, using trichloromethylsilane and trimethylsilyl trifluoromethanesulphonate as co-reagents. It may well be necessary to resort to other Lewis acids such as thionyl chloride.
It was felt that the scope of "in situ" Mannich reactions could also be increased by an investigation of the chemistry of dihydro-1,3-benzoxazines.

The reaction of substituted phenols with primary amines and formaldehyde was shown to give the corresponding 2-aminomethylphenol (156), the 3-substituted benzoxazine (157) or the bis-(2-hydroxybenzyl)amine (158) in high yield, depending on the molar ratios of reagents used and the amine and phenol substituents.

\[
\begin{align*}
\text{(156)} & : R^1 \text{OH} \quad R^2 \text{NHR} \\
\text{(157)} & : R^1 \text{O} \quad R^2 \text{N} \quad R \\
\text{(158)} & : R^1 \text{OH} \quad \text{R} \quad \text{HO} \quad \text{R}^2
\end{align*}
\]

Mannich reactions of dihydro-1,3-benzoxazines have previously been reported, using phenols as co-reactants, with electronic effects proving to affect the type of reactions observed in condensations of halophenols. However, the promised extension of this work to include other systems did not materialise.

The condensation of hydroquinone (159) with formaldehyde and primary amines can give two possible bis-oxazine derivatives, (160) and (161) (Equation 50).

\[
\text{R}^1 \text{OH} \quad \text{R} \quad \text{HO} \quad \text{R}^2
\]

Latterly, similar compounds have been prepared from 2-methylhydroquinone using a bis-aminol ether. The ring-chain tautomerism of 2-aryl-1,3-benzoxazines has been investigated, showing
the expected equilibrium between the benzoxazine and the ring-opened Schiff base. 

It was decided to synthesise representative dihydro-1,3-benzoxazines in order that Mannich reactions of heteroaromatic substrates with these reagents could be studied in the presence of chlorosilanes. Two benzoxazines were prepared by the reaction of ortho- and para-cresol with aqueous formaldehyde and dimethylamine in dioxane, according to Burke's procedure (Equation 51).

Since dihydro-1,3-benzoxazines have been shown to undergo cleavage in hot ethanol, it was envisaged that treatment of such reagents with chlorosilanes would readily generate reactive Mannich intermediates. Hence,
a series of reactions of these systems with electron-rich heterocycles was shown to yield the appropriate Mannich bases (163), as described in Equation 52 and Table 20.

\[
\text{ArH} + \text{162} + \text{163} \xrightarrow{\text{MeCN, N}_2, 25^\circ\text{C}} \text{EQUATION 52}
\]

**Table 20**

Reactions of 2-Methylfuran and N-Methylindole with Dihydro-1,3-benzoxazines Using Silicon Reagents

<table>
<thead>
<tr>
<th>Heterocyclic substrate (101)</th>
<th>Benoxazine (162)</th>
<th>Silane (89)</th>
<th>Reaction time /hrs.</th>
<th>Mannich base Structure</th>
<th>Yield /%&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Methylfuran</td>
<td>Me</td>
<td>H</td>
<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
<td>48</td>
<td>(163a) 24&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2-Methylfuran</td>
<td>Me</td>
<td>H</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;SiCl</td>
<td>48</td>
<td>(163a) 29&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2-Methylfuran</td>
<td>Me</td>
<td>H</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>48</td>
<td>(163a) 84</td>
</tr>
<tr>
<td>2-Methylfuran</td>
<td>H</td>
<td>Me</td>
<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
<td>48</td>
<td>(163b) 49&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2-Methylfuran</td>
<td>H</td>
<td>Me</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;SiCl</td>
<td>48</td>
<td>(163b) 72</td>
</tr>
<tr>
<td>2-Methylfuran</td>
<td>H</td>
<td>Me</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>48</td>
<td>(163b) 78</td>
</tr>
<tr>
<td>N-Methylindole</td>
<td>Me</td>
<td>H</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>22</td>
<td>(163c) 83</td>
</tr>
<tr>
<td>N-Methylindole</td>
<td>H</td>
<td>Me</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>22</td>
<td>(163d) 72</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields not optimised.
<sup>b</sup> 48% benzoxazine recovered.
<sup>c</sup> 53% benzoxazine recovered.
<sup>d</sup> 24% benzoxazine recovered.
Thus it can be seen that dihydro-1,3-benzoxazines will function readily as Mannich reagents under the conditions described, yielding Mannich bases with phenol substituents. Once again the best yields and cleanest reactions were achieved using trichloromethylsilane as the acidic reagent. It would appear that the equilibrium towards formation of the Mannich intermediate between chlorotrimethylsilane and the dihydro-1,3-benzoxazines lies towards starting materials, and hence benzoxazine is recovered in these reactions. The effectiveness of dichlorodimethylsilane as a co-reagent seems to be intermediate to that of its mono- and tri-chloro- analogues, as would be expected.

It is possible that the failure of previous authors to report further Mannich reactions of systems other than phenols relates to problems experienced in controlling the formation of bis-aryl systems under aqueous conditions. Alternatively, such reactions simply may not have worked, as in the case of Mannich condensations of N-alkylpyrroles using secondary amines and aqueous formaldehyde.

It would be interesting at a later stage to investigate the effect on the reactions described of varying the N-substituent and introducing halogen groups to the aromatic ring of the benzoxazines.

5.3 Mannich Reactions of Aryltrialkylstannanes

Aryltrialkylstannanes are known to yield aromatic species with predetermined regiochemistry on treatment with electrophiles via an *ipso*-addition–with–elimination mechanism\(^{169}\). This reactivity is due to the high polarisability of the carbon–tin bond, and a number of electrophiles have been reported to undergo such reactions. The use of aryltrialkylsilanes is the more common method in reactions with strong electrophiles\(^{170}\).
Previous studies by Mark Cooper, in these laboratories, have shown that aryltrialkylstannanes (164) will react with $N,N$-dimethyl-(methylene)iminium chloride (22a) in dichloromethane to give the corresponding Mannich bases (165) in good yield (Equation 53)\textsuperscript{50}.

\[
\text{ArSnR}_3 + \text{Me}_2\text{N}=\text{CH}_2\text{Cl}^- \xrightarrow{\text{CH}_2\text{Cl}_2, \text{N}_2 \text{ reflux}} \text{ArCH}_2\text{NMe}_2
\]

\text{EQUATION 53}

More recently, the treatment of the tropolone derivative (166) with (22a) was found to result in *ipso*-substitution (Equation 54)\textsuperscript{171}.

\[
\begin{array}{c}
\text{MeO} \\
\text{O} \\
\text{SnMe}_3 \\
\text{MeO}
\end{array} + (22a) \rightarrow \begin{array}{c}
\text{MeO} \\
\text{O} \\
\text{CH}_2\text{NMe}_2
\end{array}
\]

\text{EQUATION 54}

However, Mark Cooper was unable to isolate a Mannich base on prolonged stirring of 4-trimethylsilylanisole with (22a) in dichloromethane, and the corresponding reaction with 2-trimethylsilylanisole gave a yield of less than 5%. We felt that it would be interesting to study the reaction of
2,4-dimethoxyphenyltrimethylsilane (168) with \( N \)-morpholinyl-(methylene)iminium chloride (22f), in view of the proven reactivity of the same salt with 1,3-dimethoxybenzene\(^{42} \). Hence (168) was prepared by formation of the Grignard reagent (167) from 2,4-dimethoxybromobenzene, which was quenched with chlorotrimethylsilane in a "one-pot" procedure (Scheme 47).

\[
\text{Br} \quad \text{OMe} \quad \text{OMe} \\
\text{OMe} \quad \text{OMe} \\
\text{MgBr} \quad \text{SiMe}_3
\]

\( \xrightarrow{i} \)

\[
\begin{array}{c}
\text{OMe} \quad \text{OMe} \\
\text{OMe} \\
(167)
\end{array}
\xrightarrow{ii}
\]

\[
\begin{array}{c}
\text{OMe} \\
\text{OMe} \\
\text{OMe}
\end{array}
\]

i. Mg, THF, reflux; ii. Me\(_3\)SiCl.

**SCHEME 47**

Treatment of (168) with the iminium salt (22f) gave the Mannich base (169) in a similar yield to that observed by Böhme (Equation 55).

\[
(168) + \text{O} \quad \text{N} = \text{CH}_2 \\
\xrightarrow{\text{MeCN, 25°C}} \\
(22f)
\]

\[
\text{OMe} \quad \text{OMe} \\
\text{OMe}
\]

**EQUATION 55**
Thus it would appear that for electron-rich benzenoid systems the carbon-silicon bond is sufficiently polarisable to direct \textit{ipso} attack, since no product from non-\textit{ipso} substitution was detected. In order to ensure that the trimethylsilyl residue was not lost on work-up, a portion of (168) was subjected to acid washing, but no evidence for carbon-silicon bond cleavage was observed.

It is interesting to note, however, that \textit{a}-substitution was favoured over \textit{ipso}-attack in the functionalisation of 1,4-bis-(trimethylsilyl)indole with \textit{N,N}-dimethyl(methylene)iminium chloride\textsuperscript{44}.

It was felt that it would be desirable to broaden the scope of Mannich reactions with aryltrialkylstannanes by increasing the range of iminium salts used, and by carrying out reactions using Mannich intermediates generated "in situ". The results reported are the writer’s contribution to an extension of the previous work, and were obtained in close collaboration with George Papageorgiou\textsuperscript{72}.

The required aryltin compounds (170) were prepared by an analogous procedure to that shown in Scheme 47. The results of these preparations are shown in Table 21.

\begin{equation}
\begin{array}{c}
\text{SnR}_1^1 \\
\text{SnR}_3^3 \\
\text{SnR}_2^2
\end{array}
\end{equation}

(170)
Table 21

Preparation of Aryltrialkylstannanes

<table>
<thead>
<tr>
<th>Structure</th>
<th>Aryltrialkylstannane</th>
<th>Yield /%&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(170a)</td>
<td>Bu&lt;sup&gt;a&lt;/sup&gt; H H H</td>
<td>83</td>
</tr>
<tr>
<td>(170b)</td>
<td>Bu&lt;sup&gt;a&lt;/sup&gt; Me H</td>
<td>78</td>
</tr>
<tr>
<td>(170c)</td>
<td>Bu&lt;sup&gt;a&lt;/sup&gt; H OMe</td>
<td>81</td>
</tr>
<tr>
<td>(170d)</td>
<td>Me H OMe</td>
<td>59</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields not optimised.

A number of reactions of such reagents with preformed methyleneiminium salts (22) were carried out, as shown in Equation 56 and Table 22. In view of the generally higher yields obtained by Mark Cooper at elevated temperatures, and our own findings that acetonitrile is a superior solvent, reactions were carried out in this solvent under reflux.

\[
\text{SnR}_3^+ + R_2^+ N=CH_2 Cl^- \xrightarrow{\text{MeCN, N}_2, \text{reflux}} CH_2NR_2^+ R^2 R^3 \]

EQUATION 56
It can be seen from these results that reactions of aryltrialkylstannanes with iminium salts other than N,N-dimethyl(methylene)iminium chloride gave generally poor yields of Mannich bases (171). The exception to this involves reactions of the more activated 4-anisylstannanes with N-morpholino(methylene)iminium chloride. The low reactivity of these systems is demonstrated by the recovery of the unreacted arylstannane from the non-basic extracts of the reactions. The low yields are thought to be due to complex steric factors which are not clearly understood, and are, perhaps, exemplified by the extremely poor recovery of the expected Mannich base from the reaction of 4-anisytrimethylstannane with N,N-di-iso-propyl(methylene)iminium chloride.
There appears little difference in yields observed in reactions involving trimethyl- and the bulkier tributyl-stannanes, in accordance with previous observations. This has been explained in terms of the increase in steric interaction caused by the bulk of the tributyltin group being offset by greater relief of steric strain in reactions using this substituent.

In order to simplify procedures, reactions were carried out using the "in situ" methods we had devised, with chlorosilanes being used to activate aminals and aminol ethers, as shown in Equation 57 and Table 23.

\[
\begin{align*}
\text{(170)} & \\
\text{(172)} & \\
\text{(89)} & \\
\text{(171)} & \\
\end{align*}
\]

\text{EQUATION 57}

Once again, yields for these reactions are generally poor, with the better results being obtained using electron-rich stannanes. This is in agreement with the observations of George Papageorgiou, who found that good yields were obtained in reactions with 3-thienyltrimethylstannane. We would normally expect to see similar yields for "in situ" reactions and those using preformed iminium salts. However, yields of Mannich bases quoted in Table 23 are often significantly lower than those for the corresponding reactions.
Table 23

Reactions of Aryltrialkylstannanes with Aminals and Aminol Ethers Using Silicon Reagents

<table>
<thead>
<tr>
<th>Aryltrialkylstannane (170)</th>
<th>Reagent (172)</th>
<th>Silane (89)</th>
<th>Reaction time /hrs.</th>
<th>Mannich base Structure</th>
<th>Yield /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu&lt;sup&gt;n&lt;/sup&gt; H H H</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;NCH&lt;sub&gt;2&lt;/sub&gt;OEt</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>26</td>
<td>(171b)</td>
<td>20</td>
</tr>
<tr>
<td>Bu&lt;sup&gt;n&lt;/sup&gt; H H H</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;NCH&lt;sub&gt;2&lt;/sub&gt;OEt</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>26</td>
<td>(171b)</td>
<td>29</td>
</tr>
<tr>
<td>Bu&lt;sup&gt;n&lt;/sup&gt; Me H H</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;NCH&lt;sub&gt;2&lt;/sub&gt;OEt</td>
<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
<td>25</td>
<td>(171d)</td>
<td>19</td>
</tr>
<tr>
<td>Bu&lt;sup&gt;n&lt;/sup&gt; Me H H</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;NCH&lt;sub&gt;2&lt;/sub&gt;OEt</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>25</td>
<td>(171d)</td>
<td>13</td>
</tr>
<tr>
<td>Bu&lt;sup&gt;n&lt;/sup&gt; Me H H</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;NCH&lt;sub&gt;2&lt;/sub&gt;OEt</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>25</td>
<td>(171d)</td>
<td>18</td>
</tr>
<tr>
<td>Bu&lt;sup&gt;n&lt;/sup&gt; H OMe</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;NCH&lt;sub&gt;2&lt;/sub&gt;H</td>
<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
<td>42</td>
<td>(171j)</td>
<td>45</td>
</tr>
<tr>
<td>Bu&lt;sup&gt;n&lt;/sup&gt; H OMe</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;NCH&lt;sub&gt;2&lt;/sub&gt;H</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>68</td>
<td>(171j)</td>
<td>65</td>
</tr>
<tr>
<td>Me H OMe</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;NCH&lt;sub&gt;2&lt;/sub&gt;OEt</td>
<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
<td>24</td>
<td>(171j)</td>
<td>62</td>
</tr>
<tr>
<td>Bu&lt;sup&gt;n&lt;/sup&gt; H OMe</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;NCH&lt;sub&gt;2&lt;/sub&gt;OEt</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>42</td>
<td>(171e)</td>
<td>20</td>
</tr>
<tr>
<td>Bu&lt;sup&gt;n&lt;/sup&gt; H OMe</td>
<td>(Clh&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>42</td>
<td>(171g)</td>
<td>38</td>
</tr>
<tr>
<td>Bu&lt;sup&gt;n&lt;/sup&gt; H OMe</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;NCH&lt;sub&gt;2&lt;/sub&gt;OEt</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>28</td>
<td>(171h)</td>
<td>53</td>
</tr>
<tr>
<td>Me H OMe</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;NCH&lt;sub&gt;2&lt;/sub&gt;OEt</td>
<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
<td>24</td>
<td>(171h)</td>
<td>38</td>
</tr>
</tbody>
</table>

a. Yields not optimised.

using iminium salts. It is presumed that the Mannich bases formed may be destroyed, in part, by the chlorosilane present in these reactions. An exchange reaction of the trialkyltin with a trialkylsilyl residue could give an unreactive aryltrialkylsilane, together with trialkyltin chloride, which was shown not to activate ethoxy-N,N-diethylaminomethane to reaction with 2-methylfuran. However, this possibility was discounted since no trimethylsilylbenzene was isolated on treatment of phenyltributylstannane with chlorotrimethylsilane in acetonitrile.
5.4 Mannich Reactions Using Imines

In view of our difficulty in forming Mannich bases substituted at the α-carbon to the heterocyclic substrate, we turned our attention briefly to the use of imines in Mannich reactions.

A large number of Mannich reactions using imines and aliphatic substrates are reported in the literature, and are reviewed in three works\textsuperscript{10a,173,174}. However, few examples of reactions with aromatic species are reported.

The reaction of indole with ethyldene-\textit{iso}-propylamine (173a) in acetic acid–benzene was reported to yield the corresponding Mannich base (174) (Equation 58)\textsuperscript{175}.

\[
\text{Indole} + \text{MeCH}=\text{N–Pr}^1 \xrightarrow{\text{CH}_3\text{CO}_2\text{H, PhH}} \text{Me–NH–Pr}^1
\]

\text{(173a)}

\text{(174), 60%}

\text{EQUATION 58}

However, the yield fell to 39% when indole, acetaldehyde and \textit{iso}-propylamine were combined in the same solvent system. The corresponding reaction with ethyldene–\textit{t}-butylamine gave poor yields, presumably due to steric interactions.
Indole was reported to react with the cyclic 1-piperideine (175) in a citrate buffer to give the Mannich base (176) in moderate yield (Equation 59)\textsuperscript{176}.

\[
\text{Indole} + \text{1-piperideine} \rightarrow \text{Mannich base (176), 40–55\%}
\]

EQUATION 59

Thus ethylidene-\textit{iso}-propylamine (173a) and \textit{iso}-butylidene-\textit{iso}-propylamine (173b) were prepared by the method of Tiollais (Equation 60)\textsuperscript{177}. Equimolar quantities of the appropriate aldehyde and \textit{iso}-propylamine were carefully mixed, followed by workup to give the imines (173).

\[
R-\text{CHO} + \text{Pr}^1-\text{NH}_2 \rightarrow R-\text{CH}=\text{N}-\text{Pr}^1
\]

(173\textit{a}), $R=\text{Me}$, 76%

(173\textit{b}), $R=\text{Pr}^1$, 61%

EQUATION 60

A short series of reactions using these reagents in conjunction with electron-rich heterocyclic substrates (101) was carried out. Condensation occurred readily under the conditions previously described\textsuperscript{175} to yield a number of novel Mannich bases (177), as shown in Equation 61 and Table 24.
\[
\begin{array}{cccc}
\text{ArH} & + & R-\text{CH}=\text{N-Pr}^1 & \xrightarrow{\text{CH}_2\text{CO}_2\text{H}, \text{PhH}, 0^\circ\text{C}, 96\text{hrs.}} \text{Ar}-\text{CH}-\text{NH-Pr}^1 \\
(101) & (173) & & (177)
\end{array}
\]

**EQUATION 61**

**Table 24**
Reactions of Pyrroles and Indole with Imines

<table>
<thead>
<tr>
<th>Heterocyclic substrate (101)</th>
<th>Imine (173), R=</th>
<th>Mannich base Structure</th>
<th>Yield /% a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrrole</td>
<td>Me</td>
<td>(177a)</td>
<td>64</td>
</tr>
<tr>
<td>N-Methylpyrrole</td>
<td>Me</td>
<td>(177b)</td>
<td>43</td>
</tr>
<tr>
<td>Pyrrole</td>
<td>Pr i</td>
<td>(177c)</td>
<td>69</td>
</tr>
<tr>
<td>N-Methylpyrrole</td>
<td>Pr i</td>
<td>(177d)</td>
<td>43</td>
</tr>
<tr>
<td>Indole</td>
<td>Pr i</td>
<td>(177e)</td>
<td>65</td>
</tr>
</tbody>
</table>

a. Yields not optimised.

It can thus be seen that Mannich bases can successfully be isolated from imines when similar reactions using iminium salts fail. It is felt at this stage that this may be attributed to the increased reactivity of protonated imines (178) compared with iminium salts (179). This in turn may be due to the increased stability of the iminium salt via electron donation by two, rather than one, alkyl groups.
EXPERIMENTAL

General Procedures

Dry, distilled solvents were obtained as follows:

**Acetic acid:** fractionally crystallised three times under nitrogen and used immediately.

**Acetonitrile:** distilled from phosphorus pentoxide then anhydrous potassium carbonate. Stored over 3A molecular sieves.

**Benzene:** fractionally distilled and stored over 3A molecular sieves.

**Dichloromethane:** distilled from phosphorus pentoxide and stored over 3A molecular sieves.

**Diethyl ether:** distilled from calcium chloride and, if necessary, lithium aluminium hydride–triphenylmethane, then stored over 3A molecular sieves.

**DMSO:** stirred with barium oxide overnight, fractionally distilled under reduced pressure and stored over 4A molecular sieves under nitrogen.

**1,4-Dioxane:** distilled from sodium and used immediately.

**Ethanol:** distilled from magnesium ethoxide and stored over 4A molecular sieves.

**Methanol:** distilled from magnesium methoxide and stored over 4A molecular sieves.
Petroleum ether, pentane and 2,2,4-trimethylpentane: fractionally distilled.

Propan-2-ol: distilled from magnesium propoxide and stored over 4A molecular sieves.

Tetrahydrofuran: distilled from lithium aluminium hydride-triphenylmethane and used immediately.

Unless otherwise stated, solutions of products in organic solvents were routinely dried over magnesium sulphate.

Nitrogen: oxygen-free nitrogen was dried by passing successively through concentrated sulphuric acid, sodium hydroxide pellets and silica gel.

NMR spectra: all spectra were recorded in CDCl₃ unless otherwise stated, and referenced to TMS. ¹H n.m.r. spectra were recorded on Varian CW-60 (60MHz), Perkin-Elmer R32 (90MHz), Jeol GSX-270/54 (270MHz) or Bruker AMX 360 (360MHz) spectrometers. ¹³C n.m.r. spectra were recorded on Bruker WP80 (20.1MHz), Jeol GSX-270/54 (67.8MHz) or Bruker AMX 360 (90.6MHz) spectrometers. Multiplicities are reported as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and double doublet (dd), etc.

Infra-red spectra: spectra were recorded on a Perkin-Elmer 257 spectrophotometer; only selected absorbances are reported. Spectra were recorded as thin films (film), potassium bromide discs (KBr) or nujol mulls (nujol).
**Optical rotations**: rotations were measured at ambient temperature using an Optical Activity AA–10 polarimeter.

**Mass spectra**: mass spectra were recorded by electron impact using a Kratos M.S.80 spectrometer or by fast atom bombardment using a VG 70- 250S spectrometer.

**Melting points**: melting points were obtained using a Kofler hot stage apparatus and are uncorrected.

**Analyses**: microanalyses were carried out by Manchester University and Fison's p.l.c. (Loughborough).
Method A

Reaction of Aromatic Substrates with Iminium Salts

Freshly distilled aromatic compound (22 mmol) and iminium salt (20 mmol or 55 mmol) were stirred together at room temperature under nitrogen in acetonitrile (150 ml). After the required time the mixture was concentrated in vacuo, quenched with water (50 ml) and acidified to pH 1 with 2N hydrochloric acid. The aqueous layer was washed with dichloromethane (3 x 25 ml) and then basified to pH 14 with 4M sodium hydroxide. The cloudy suspension was extracted with dichloromethane (3 x 25 ml), and the combined extracts were dried and concentrated in vacuo. The residue was then distilled under vacuum using a Kugelröhr apparatus, or recrystallised.

Method B

In a variation of Method A, the aqueous media was extracted with diethyl ether.

Method C

Reaction of Aromatic Substrates with Aminals and Aminol Ethers using Silicon Reagents

Freshly distilled aromatic compound (1.1 equiv.) and aminal or aminol ether (1 equiv.) were stirred together in acetonitrile at 0°C, under a still head of nitrogen. Chlorosilane (1.1 equiv.) in acetonitrile was added dropwise and the reaction mixture was allowed to warm to room temperature.
Stirring was continued for the required time, followed by work-up as described in Method A.

**Method D**

In a variation of Method C, the aqueous media was extracted with diethyl ether.

**Method E**

**Reaction of Arylttrialkylstannanes with Iminium Salts**

Arylttrialkylstannane (1 equiv.) and iminium salt (1.1 equiv.) in acetonitrile were heated together under gentle reflux, under a still head of nitrogen, followed by work-up as described in Method C.

**Method F**

**Reaction of Arylttrialkylstannanes with Aminals and Aminol Ethers using Silicon Reagents**

Arylttrialkylstannane (1 equiv.) and aminal or aminol ether (1.1 equiv.) were stirred together in acetonitrile at 0°C, under a still head of nitrogen. Chlorosilane (1.1 equiv.) in acetonitrile was added dropwise and then the reaction mixture was heated under gentle reflux, followed by work-up as described in Method C.
2.1.1 Preparation of Bis-(N,N-dimethylamino)methane

Dimethylamine (90.2g, 2 mol, 40% aqueous solution) was added dropwise to stirred ice-cooled formaldehyde (30.0g, 1 mol, 36% aqueous solution). The mixture was allowed to stand overnight, and then saturated with solid potassium hydroxide. The upper layer was separated and dried over potassium hydroxide pellets, which were then removed. The residual liquid was fractionally distilled to yield the aminal (56a) (86.2g, 84%), b.p. 82–83°C at 178 torr, 82–84°C at 82–84°C, 1H n.m.r. (60 MHz), δ = 2.19 (12H, s, CH3), and 2.66 (2H, s, CH2) p.p.m..

2.1.2 Preparation of Bis-(N,N-diethylamino)methane

Diethylamine (53.5g, 0.73 mol) and formaldehyde (11.0g, 0.365 mol, 36% aqueous solution) were treated as described in 2.1.1 to yield the aminal (56b) (51.9g, 90%), b.p. 47–48°C/7.5 mmHg, (lit.83, 166–67°C/757 mmHg), 1H n.m.r. (60 MHz), δ = 1.00 (12H, t, J = 7 Hz, CH2CH3), 2.62 (8H, q, J = 7 Hz, CH2CH3), and 3.05 (2H, s, N–CH2–N) p.p.m..

2.1.3 Preparation of Di-(N-pyrrolidinyl)methane

Pyrrolidine (35.1g, 0.2 mol) and formaldehyde (3.0g, 0.1 mol, 36% aqueous solution) were treated as described in 2.1.1 to yield the aminal (56d) (32.3g, 84%), b.p. 65–66°C/5 mmHg (lit.78, 60°C/3.5 mmHg), 1H n.m.r. (60 MHz), δ = 1.57–1.98 (8H, m, C(3 and 4)H), 2.38–2.81 (8H, m, C(2 and 5)H), and 3.23 (2H, s, CH2) p.p.m..
2.1.4 Preparation of Di-\((\text{N-piperidy})\text{methane}\)

Piperidine \((170.3\text{g}, 2 \text{ mol})\) and formaldehyde \((30.0\text{g}, 1 \text{ mol}, 36\% \text{ aqueous solution})\) were treated as described in 2.1.1 to yield the aminal \((56\text{e})\) \((144.2\text{g}, 79\%)\), b.p. \(100^\circ\text{C}/10 \text{ mmHg}\) \((\text{lit.}^{89}, 103-104^\circ\text{C}/14 \text{ mmHg})\), \(^1\text{H n.m.r.} \quad \delta = 1.39-1.73 \quad (12\text{H, m, C}(3,4 \text{ and } 5)\text{H}), \quad 2.23-2.53 \quad (8\text{H, m, C}(2 \text{ and } 6)\text{H}), \quad \text{and } 2.77 \quad (2\text{H, s, CH}_2) \text{ p.p.m.}

2.1.5 Preparation of Di-\((\text{N-morpholiny})\text{methane}\)

Morpholine \((43.6\text{g}, 0.5 \text{ mol})\) and formaldehyde \((7.5\text{g}, 0.25 \text{ mol}, 36\% \text{ aqueous solution})\) were treated as described in 2.1.1 to yield the aminal \((56\text{f})\) \((28.0\text{g}, 66\%)\), b.p. \(116^\circ\text{C}/10 \text{ mmHg}\) \((\text{lit.}^{120}, 99-107^\circ\text{C}/2 \text{ mmHg})\), \(^1\text{H n.m.r.} \quad \delta = 2.40-2.60 \quad (8\text{H, m, C}(2 \text{ and } 6)\text{H}), \quad 2.87 \quad (2\text{H, s, CH}_2), \quad \text{and } 3.58-3.80 \quad (8\text{H, m, C}(3 \text{ and } 5)\text{H}) \text{ p.p.m.}

2.1.6 Preparation of \(1,1\text{-Di-}(\text{N-piperidy})\text{ethane}\)

Piperidine \((42.5\text{g}, 0.5 \text{ mol})\), acetaldehyde \((12.1\text{g}, 0.275 \text{ mol})\) and anhydrous potassium carbonate \((10\text{g}, 0.07 \text{ mol})\) were stirred together at \(-5^\circ\text{C}\) for 15 minutes. The reaction mixture was filtered and concentrated \textit{in vacuo}, followed by distillation to yield the aminal \((59)\), b.p. \(69-70^\circ\text{C}/2.5 \text{ mmHg}\) \((\text{lit.}^{91}, 58-60^\circ\text{C}/3 \text{ mmHg})\), \(^1\text{H n.m.r.} \quad \delta = 0.98 \quad (3\text{H, d, J = 6 Hz, CH}_3), \quad 1.24-1.74 \quad (12\text{H, m, C}(3,4 \text{ and } 5)\text{H}) \quad \text{and } 2.25 \quad (9\text{H, m, CH and C}(2 \text{ and } 6)\text{H}) \text{ p.p.m.}

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2.2.1 Preparation of Ethoxy-\(N,N\)-di-\(iso\)-propylaminomethane

Di-\(iso\)-propylamine (20.2 g, 0.2 mol), ethanol (18.8 g, 0.4 mol) and anhydrous potassium carbonate (33.2 g, 0.24 mol) were stirred at 0°C for 10 minutes. Paraformaldehyde (4.8 g, 0.16 mol equiv.) was added in one portion and the resulting suspension was stirred overnight. The reaction mixture was filtered and the solid residue was washed with dry ether. The combined filtrates were concentrated \textit{in vacuo} followed by fractional distillation to yield ethoxy-\(N,N\)-di-\(iso\)-propylaminomethane (61b) (22.3 g, 87%), b.p. 42°C/5 mmHg, \(^1\)H n.m.r. (60 MHz), \(\delta = 1.11\) (12H, d, \(J = 7\) Hz, CH(CH\(_3\))\(_2\)), 1.17 (3H, t, \(J = 7\) Hz, CH\(_2\)CH\(_3\)), 3.15 (2H, sept., \(J = 7\) Hz, CH), 3.37 (2H, q, \(J = 7\) Hz, CH\(_2\)CH\(_3\)) and 4.22 (2H, s, OCH\(_2\)) p.p.m., \(^{13}\)C n.m.r. (20.1 MHz), \(\delta = 15.5\) (q, CH\(_2\)CH\(_3\)), 22.3 (q, CH(CH\(_3\))\(_2\)), 48.7 (d, CH), 61.4 (t, CH\(_2\)CH\(_3\)), and 79.6 (t, OCH\(_2\)) p.p.m.; m/z (M*) 159.1612, C\(_9\)H\(_{21}\)NO requires 159.1623.

2.2.2 Preparation of Ethoxy-\(N,N\)-diethylaminomethane

Diethylamine (18.3 g, 0.25 mol), ethanol (23.0 g, 0.5 mol), anhydrous potassium carbonate (41.5 g, 0.3 mol) and paraformaldehyde (6.0 g, 0.2 mol equiv.) were treated as described in 2.2.1 to yield ethoxy-\(N,N\)-diethylaminomethane (61a) (17.7 g, 54%), b.p. 132–33°C (lit.\(^{83}\), 132–34°C), \(^1\)H n.m.r. (60 MHz), \(\delta = 1.10\) (6H, t, \(J = 7\) Hz, NCH\(_2\)CH\(_3\)), 1.25 (3H, t, \(J = 7\) Hz, OCH\(_2\)CH\(_3\)), 2.74 (4H, q, \(J = 7\) Hz, NCH\(_2\)CH\(_3\)), 3.43 (2H, q, \(J = 7\) Hz, OCH\(_2\)CH\(_3\)), and 4.21 (2H, s, OCH\(_2\)) p.p.m., \(^{13}\)C n.m.r. (20.1 MHz), \(\delta = 13.4\) (q, NCH\(_2\)CH\(_3\)), 15.5 (q, OCH\(_2\)CH\(_3\)), 46.6 (t, NCH\(_2\)CH\(_3\)), 63.3 (t, OCH\(_2\)CH\(_3\)), and 84.4 (t, NCH\(_2\)O) p.p.m.
2.2.3 Preparation of Ethoxy-N-pyrrolidinylmethane

Pyrrolidine (14.2g, 0.2 mol), ethanol (18.8g, 0.4 mol), anhydrous potassium carbonate (33.2g, 0.24 mol) and paraformaldehyde (4.8g, 0.16 mol equiv.) were treated as described in 2.2.1 to yield ethoxy-N-pyrrolidinylmethane (61c) (13.6g, 66%), b.p. 64-65°C/12 mmHg, 1H n.m.r. (60 MHz), δ = 1.23 (3H, t, J = 7 Hz, CH₃), 1.55-1.92 (4H, m, C(2) and 5)H, 2.56-2.94 (4H, m, C(3) and 4)H, 3.53 (2H, q, J = 7 Hz, CH₂CH₃), and 4.24 (2H, s, OCH₂) p.p.m.

2.3.1 Preparation of Pyrrolidinium Perchlorate

Perchloric acid (5.02g, 50 mmol, 70% aqueous solution) was added dropwise to stirred ice-cooled pyrrolidine (3.56g, 50 mmol) until just acidic to Congo Red. A few drops of the amine were added, and the water removed under high vacuum. The soft, white solid was recrystallised to give pyrrolidinium perchlorate (62a) (8.32g, 97%) as white crystals, m.p. 239-40°C (from propan-2-ol-diethyl ether) (lit., 240-42°C).

2.3.2 Preparation of Pyrrolidinium Fluoborate

Fluoboric acid (4.39g, 50 mmol, 40% aqueous solution) and pyrrolidine (3.56g, 50 mmol) were treated as described in 2.3.1 to give pyrrolidinium fluoborate (62b) (5.97g, 75%) as a soft yellow solid, m.p. 228-29°C (from propan-2-ol-diethyl ether).
2.4.1 Preparation of $N,N$-Dimethyl(methylene)iminium Chloride

Bis-($N,N$-dimethylamino)methane ($56a$) (20.4g, 0.20 mol) in dry ether (100 ml) was stirred rapidly and cooled to 0 to $-10^\circ\text{C}$, under a still head of nitrogen. To this was added, dropwise, a solution of freshly distilled acetyl chloride (17.3g, 0.22 mol) in dry ether (100 ml). The resulting white solid was rapidly filtered, and washed with dry ether (3 x 200 ml), whilst keeping damp. The solid was transferred to a round bottomed flask and dried in vacuo to yield the iminium salt ($22a$) (17.0g, 91%), which was stored under dry nitrogen.

2.4.2 Preparation of $N,N$-Diethyl(methylene)iminium Chloride

Bis-($N,N$-diethylamino)methane ($56b$) (31.7 g, 0.20 mol) and acetyl chloride (17.3g, 0.22 mol) were treated as described in 2.4.1 to yield the iminium salt ($22b$) (24.0g, 99%) as a white solid.

2.4.3 Preparation of $N$-Pyrrolidinyl(methylene)iminium Chloride

Di-($N$-pyrrolidinyl)methane ($56d$) (30.9g, 0.20 mol) and acetyl chloride (17.3g, 0.22 mol) were treated as described in 2.4.1 to yield the iminium salt ($22d$) (22.7g, 95%) as a white solid.

2.4.4 Preparation of $N$-Piperidyl(methylene)iminium Chloride

Di-($N$-piperidyl)methane ($56e$) (36.5g, 0.20 mol) and acetyl chloride (17.3g, 0.22 mol) were treated as described in 2.4.1 to yield the iminium salt ($22e$) (24.6g, 92%) as a white solid.
2.4.5 Preparation of \( N\)-Morpholinyldimethyleneiminium Chloride

Di-(\( N\)-morpholinyldimethane (56f) (23.2g, 0.125 mol) and acetyl chloride (10.8g, 0.138 mol) were treated as described in 2.4.1 to yield the iminium salt (22f) (16.6g, 98%) as a white solid.

2.4.6 Preparation of \( N\)-Ethylideneperidinium Chloride

1,1-Di-(\( N\)-piperidyl)ethane (59) (10.0g 51 mmol) and acetyl chloride (4.4g, 56 mmol) were treated as described in 2.4.1 to yield the iminium salt (60) (6.30g, 84%) as a brown solid.

2.4.7 Preparation of \( N,N\)-Di-\( iso\)-propyl(dimethylene)iminium Chloride

Ethoxy-\( N,N\)-di-\( iso\)-propylaminomethane (61b) (9.0g, 57 mmol) was added dropwise to an ice-cooled stirring solution of trichloromethylsilane in acetonitrile (25 ml), under a still head of nitrogen. After addition the mixture was stirred for 10 minutes at room temperature, then the solvent was removed in vacuo. The residue was washed with dry ether (25 mol) and dried in vacuo to give the iminium salt (22c) (7.90g, 93%) as a white solid, which was stored under nitrogen.\( ^1\)H n.m.r. (20.1 MHz, CD₃CN), \( \delta = 21.3 \) (q, CH₃), 60.5 (d, CH₂), and 163.1 (t, J = 1.25 Hz, CH₂) p.p.m..

2.4.8 Preparation of \( N\)-\( iso\)-Propylideneperyrolidinium Perchlorate

Pyrrolidinium perchlorate (62a) (7.92g, 46 mmol) and freshly distilled acetone (5.34g, 92 mmol) were placed in a round-bottomed flask and the
contents were swirled, or gently warmed, until an exothermic reaction occurred. The white crystals formed were filtered, washed with ether and dried to yield the iminium salt (63a) (7.70g, 79%), m.p. 231–32°C (from propan-2-ol) (lit.93, 232–33°C).

2.4.9 Preparation of N-iso-Butyldene.pyrrolidinium Perchlorate

Pyrrolidinium perchlorate (62a) (7.92g, 46 mmol) and iso-butyraldehyde (6.64g, 92 mmol) were treated as described in 2.4.8 to yield the iminium salt (63b) (7.56g, 73%) as white crystals, m.p. 237–38°C (from propan-2-ol-diethyl ether) (lit.93, 238–40°C).

2.4.10 Preparation of N-iso-Butyldene.pyrrolidinium Fluoroborate

Pyrrolidinium fluoroborate (62b) (5.97g, 37.3 mmol) and iso-butyraldehyde (5.38g, 74.6 mmol) were treated as described in 2.4.8 to yield the iminium salt (63c) (3.98g, 50%), m.p. 223–24°C (from propan-2-ol-diethyl ether).

2.4.11 Preparation of N-Furfurylidene.pyrrolidinium Perchlorate

Pyrrolidinium perchlorate (62a) (7.92g, 46 mmol) and furfuraldehyde (8.83g, 92 mmol) were treated as described in 2.4.8. Standing overnight at -22°C gave the iminium salt (63d) (7.69g, 67%) as a yellow solid, m.p. 98–99°C (from ethanol) (lit.93, 99–100°C).
2.5.1 Reaction of N-Methylpyrrole with N,N-Dimethyl(methylene)iminium Chloride

N-Methylpyrrole (2.23g, 27.5 mmol) and the iminium salt (22a) (2.35g, 25 mmol) in acetonitrile (150 mL) were treated as described in Method A, for 2 hours, to yield 2-(N',N'-dimethylaminomethyl)-N-methylpyrrole (47a) (2.72g, 79%), b.p. 54–56°C/5 mmHg (lit.77, 53–54°C/6 mmHg), \(^1\)H n.m.r. (60 MHz), \(\delta = 2.16 \,(6\text{H}, \text{s}, \text{NCH}_3), 3.29 \,(2\text{H}, \text{s}, \text{CH}_2), 3.57 \,(3\text{H}, \text{s}, \text{ArCH}_3), 5.96–6.07 \,(2\text{H}, \text{m}, \text{C}(3 \text{ and } 4)\text{H}), \text{and } 6.45–6.56 \,(1\text{H}, \text{m, C}(5)\text{H}) \text{ p.p.m.}, \,^{13}\text{C n.m.r.} \,(20.1 \text{ MHz}), \delta = 33.5 \,(q, \text{ ArCH}_3), 44.7 \,(q, \text{ NCH}_3), 55.7 \,(t, \text{ CH}_2), 106.4 \,(d, \text{ C}(4)), 109.3 \,(d, \text{ C}(3)), 122.4 \,(d, \text{ C}(5)), \text{and } 129.8 \,(s, \text{ C}(2)) \text{ p.p.m.; m/z (M\textsuperscript{+}) 138.1149, C\textsubscript{8}H\textsubscript{14}N\textsubscript{2} requires 138.1157.}

2.5.2 Reaction of N-Methylpyrrole with N,N-Diethyl(methylene)iminium Chloride

N-Methylpyrrole (1.78g, 22 mmol) and the iminium salt (22b) (2.43g, 20 mmol) in acetonitrile (120 mL) were treated as described in Method A, for 2 hours, to yield 2-(N',N'-diethylaminomethyl)-N-methylpyrrole (47b) (2.16g, 65%), b.p. 55–60°C/2.5 mmHg (lit.77, 75–77°C/6 mmHg), \(^1\)H n.m.r. (60 MHz), \(\delta = 0.98 \,(6\text{H}, \text{t, } J = 7.5 \text{ Hz, CH}_2\text{CH}_3), 2.49 \,(4\text{H}, \text{q, } J = 7.5 \text{ Hz, CH}_2\text{CH}_3), 3.47 \,(2\text{H}, \text{s, ArCH}_2), 3.62 \,(3\text{H}, \text{s, NCH}_3), 5.93–6.08 \,(2\text{H}, \text{m, C}(3 \text{ and } 4)\text{H}), \text{and } 6.44–6.56 \,(1\text{H}, \text{m, C}(5)\text{H}) \text{ p.p.m.}, \,^{13}\text{C n.m.r.} \,(20.1 \text{ MHz}), \delta = 11.8 \,(q, \text{ CH}_2\text{CH}_3), 33.7 \,(q, \text{ NCH}_3), 46.5 \,(t, \text{ CH}_2\text{CH}_3), 50.0 \,(t, \text{ ArCH}_2), 106.3 \,(d, \text{ C}(4)), 109.3 \,(d, \text{ C}(3)), 122.2 \,(d, \text{ C}(5)), \text{and } 130.1 \,(s, \text{ C}(2)) \text{ p.p.m.; found: C, 72.15; H, 11.1; N, 17.1. C\textsubscript{10}H\textsubscript{16}N\textsubscript{2} requires C, 72.2; H, 10.9; N, 16.85%; m/z (M\textsuperscript{+}) 166.1462, requires 166.1470.
A second fraction obtained proved to be \(2,5\)-bis-\(-(N',N'-diethylaminomethyl)-N'-methylpyrrole\) (48b) (0.08g, 1.4%), b.p. 125°C/0.01 mmHg (see 2.6.2).

### 2.5.3 Reaction of \(N\)-Methylpyrrole with \(N,N\)-Di-\(iso\)-propyl-(methylene)iminium Chloride

\(N\)-Methylpyrrole (1.08g, 13.2 mmol) and the iminium salt (22c) (1.80g, 12 mmol) in acetonitrile (72 ml) were treated as described in Method A, for 2.5 hours, to yield \(2-(N',N'-di-\(iso\)-propylaninomethyl)-N'-methylpyrrole\) (47c) (0.63g, 70%), b.p. 67-70°C/0.7 mmHg, \(^1\)H n.m.r. (360 MHz), \(\delta = 1.00\ (12H, d, J = 6.7\ Hz, CHCH_3), 2.99\ (2H, sept., J = 6.7\ Hz, CH), 3.62\ (2H, s, CH), 3.64\ (3H, s, NCH_3), 5.96-6.01\ (2H, m, C(3 and 4)H), and 6.53-6.55\ (1H, m, C(5)H) p.p.m., \(^13\)C n.m.r. (90.6 MHz), \(\delta = 20.2\ (q, CHCH_3), 33.9\ (q, NCH_3), 41.2\ (t, CH_2), 46.8\ (d, CH), 105.9\ (d, C(4)), 109.0\ (d, C(3)), 122.1\ (d, C(5)) and 130.9\ (s, C(2)) p.p.m.; found: C, 74.1; H, 11.6; N, 14.7. C_{12}H_{22}N_2 requires C, 74.15; H, 11.4; N, 14.4%; m/z (M*) 194.1765, requires 194.1783.

### 2.5.4 Reaction of \(N\)-Methylpyrrole with \(N\)-Piperidyl(methylene)-iminium Chloride

\(N\)-Methylpyrrole (1.78g, 22 mmol) and iminium salt (22e) (2.67g, 20 mmol) in acetonitrile (120 ml) were treated as described in Method A, for 2 hours, to yield \(2-(N'-piperidylmethyl)-N'-methylpyrrole\) (47d) (2.37g, 66%), b.p. 115-20°C/5.5 mmHg (lit\(^\text{77}\), 97°C/5 mmHg), \(^1\)H n.m.r. (90 MHz), \(\delta =\)
1.29–1.70 (6H, m, C(3’, 4’ and 5’)H), 2.22–2.42 (4H, m, C(2’ and 6’)H), 3.32 (2H, s, CH₂), 3.58 (3H, s, NCH₃), 5.86–6.01 (2H, m, C(3 and 4)H), and 6.42–6.52 (1H, m, C(5)H) p.p.m.; ¹³C n.m.r. (20.1 MHz), δ = 24.7 (t, C(4’)), 26.2 (t, C(3’ and 5’)), 33.6 (q, NCH₃), 54.3 (t, C(2’ and 6’)), 55.3 (t, CH₂), 106.2 (d, C(4)), 109.3 (d, C(3)), 122.2 (d, C(5)) and 129.4 (s, C(2)) p.p.m.; found: C, 73.9; H, 10.3; N, 15.55. C₁₀H₁₉N₂ requires C, 74.1; H, 10.2; N, 15.7%; m/z (M⁺) 178.1473, requires 178.1470.

2.5.5 Reaction of N-Methylpyrrole with N-Morpholinyl(methylene)-iminium Chloride

N-Methylpyrrole (1.34 g, 16.5 mmol) and iminium salt (22f) (2.03 g, 15 mmol) in acetonitrile (90 ml) were treated as described in Method A, for 24 hours, to yield 2-(N’-morpholinylmethyl)-N-methylpyrrole (47e) (1.48 g, 55%), b.p. 105–108°C/3.5 mmHg (lit.²⁷, 113–14°C/5 mmHg), 'H n.m.r. (60 MHz), δ = 2.17–2.46 (4H, m, C(3’ and 5’)H), 3.37 (2H, s, CH₂), 3.60 (3H, s, CH₃), 3.44–3.73 (4H, m, C(2’ and 6’)H), 5.87–6.02 (2H, m, C(3 and 4)H), and 6.40–6.55 (1H, m, C(5)H) p.p.m.; ¹³C n.m.r. (20.1 MHz), δ = 33.8 (q, NCH₃), 53.4 (t, C(3’ and 5’)), 54.8 (t, CH₂), 67.1 (t, C(2’ and 6’)), 106.3 (d, C(4)), 109.8 (d, C(3)), 122.1 (d, C(5)), and 128.4 (s, C(2)) p.p.m.; m/z (M⁺) 180.1258, C₁₀H₁₆N₂O requires 180.1263.

A second fraction obtained proved to be 2,5-di-(N’-morpholinylmethyl)-N-methylpyrrole (48e) (0.48 g, 10%), b.p. 140–50°C/0.1 mmHg (see 2.6.5).
2.6.1 Preparation of \(2,5\)-Bis-(\(N'\,N'\)-dimethylaminomethyl)-\(N\)-methylpyrrole

\(N\)-Methylpyrrole (1.62 g, 20 mmol) and \(N,N\)-dimethyl(methylene)iminium chloride (22a) in acetonitrile (220 ml) were treated as described in Method A, for 72 hours, to yield the Mannich base (48a) (3.08 g, 79%), b.p. 87°C/3.5 mmHg (lit. 77, 87-88°C/3.5 mmHg). \(^1\)H n.m.r. (60 MHz), \(\delta = 2.18\) (12H, s, NCH\(_3\)), 3.31 (4H, s, CH\(_2\)), 3.61 (3H, s, ArCH\(_3\)), and 5.89 (2H, s, C(3 and 4)H) p.p.m., \(^1^3\)C n.m.r. (20.1 MHz), \(\delta = 30.2\) (q, ArCH\(_3\)), 44.8 (q, NCH\(_3\)), 56.1 (t, CH\(_2\)), 107.7 (d, C(3 and 4)), and 130.3 (s, C(2 and 5)) p.p.m.; m/z (M\(^+\)) 195.1731, C\(_{11}\)H\(_{21}\)N\(_3\) requires 195.1735.

2.6.2 Preparation of \(2,5\)-Bis-(\(N'\,N'\)-diethylaminomethyl)-\(N\)-methylpyrrole

\(N\)-Methylpyrrole (1.22 g, 15 mmol) and \(N,N\)-diethyl(methylene)iminium chloride (22b) (4.56 g, 37.5 mmol) in acetonitrile (200 ml) were treated as described in Method A, for 96 hours, to yield the Mannich base (48b) (3.28 g, 87%), b.p. 128-33°C/0.3 mmHg. \(^1\)H n.m.r. (60 MHz), \(\delta = 0.98\) (12H, t, J = 7 Hz, CH\(_2\)CH\(_3\)), 2.47 (8H, q, J = 7 Hz, CH\(_2\)CH\(_3\)), 3.47 (4H, s, ArCH\(_2\)), 3.66 (3H, s, NCH\(_3\)), and 5.87 (2H, s, C(3 and 4)H) p.p.m., \(^1^3\)C n.m.r. (20.1 MHz), \(\delta = 11.8\) (q, CH\(_2\)CH\(_3\)), 30.7 (q, NCH\(_3\)), 46.6 (t, CH\(_2\)CH\(_3\)), 50.4 (t, ArCH\(_2\)), 107.6 (d, C(3 and 4)), and 130.6 (s, C(2 and 5)) p.p.m.; m/z (M\(^+\)) 251.2355, C\(_{15}\)H\(_{29}\)N\(_3\) requires 251.2361.
2.6.3 Preparation of 2,5-Bis-(N',N'-di-iso-propylaminomethyl)-N-methylpyrrole

N-Methylpyrrole (0.65 g, 8 mmol) and N,N-di-iso-propyl(methylene)-iminium chloride (22c) (2.99 g, 20 mmol) in acetonitrile (120 ml) were treated as described in Method A, for 72 hours, to yield the Mannich base (48c) (1.84 g, 75%), which crystallised on standing, b.p. 130°C/0.5 mmHg, m.p. 61°C; ¹H n.m.r. (60 MHz), δ = 1.00 (24H, d, J = 7 Hz, CHCH₃), 3.01 (4H, sept., J = 7 Hz, CHḍ), 3.63 (4H, s, CH₂), 3.67 (3H, s, NCH₃), and 5.87 (2H, s, CH and 4) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 20.3 (q, CHCH₃), 41.8 (t, CH₂), 47.0 (d, CHḍ), 107.3 (d, CH₂ and 4'), and 131.4 (s, CH and 5') p.p.m.; found: C, 73.9; H, 12.5; N, 13.55. C₁₉H₃₇N₃ requires C, 74.2; H, 12.15; N, 13.7%; m/z (M⁺) 307.2973, requires 307.2987.

2.6.4 Preparation of 2,5-Di-(N-piperidyl)methyl)-N-methylpyrrole

N-Methylpyrrole (1.22 g, 15 mmol) and N-piperidyl(methylene)iminium chloride (22e) (5.09 g, 38 mmol) in acetonitrile (170 ml) were treated as described in Method A, for 120 hours, to yield the Mannich base (48d) (4.04 g, 98%), b.p. 120°C/0.5 mmHg (lit.⁷⁷, 165–67°C/3 mmHg); ¹H n.m.r. (60 MHz), δ = 1.29–1.75 (12H, m, CH₃, 4' and 5') H, 2.15–2.52 (8H, m, CH₂ and 6') H, 3.37 (4H, s, CH₂), 3.65 (3H, s, NCH₃), and 5.88 (2H, s, CH₃ and 4) H p.p.m.

2.6.5 Preparation of 2,5-Di-(N-morpholinybmethyl)-N-methylpyrrole

N-Methylpyrrole (0.81 g, 10 mmol) and N-morpholinybmethylene-iminium chloride (22f) (3.39 g, 25 mmol) in acetonitrile (150 ml) were treated as described in Method A, for 120 hours, to give the Mannich base (48e)
(1.87g, 67%) as a white solid, m.p. 71–72°C (from ethyl acetate), \( ^1H \) n.m.r. (60 MHz), \( \delta = 2.24–2.60 \) (8H, m, C(3’ and 5’))H, 3.41 (4H, s, CH\(_2\)), 3.52–3.86 (8H, m, C(2’ and 6’))H, 3.64 (3H, s, NCH\(_3\)), and 5.90 (2H, s, C(3 and 4))H p.p.m., \( ^{13}C \) n.m.r. (20.1 MHz), \( \delta = 30.7 \) (q, NCH\(_3\)), 53.4 (t, C(3’ and 5’)), 55.2 (t, CH\(_2\)), 67.2 (t, C(2’ and 6’)), 108.2 (d, C(3 and 4)), and 129.3 (s, C(2 and 5)) p.p.m.; m/z (M\(^+\)) 279.1951, C\(_{18}\)H\(_{25}\)N\(_3\)O\(_2\) requires 279.1947.

2.7.1 Preparation of \( N \)-Benzylpyrrole

Potassium hydroxide pellets (32g, 0.6 mol) were stirred in DMSO (200 ml) for 10 minutes at room temperature. Pyrrole (10g, 0.15 mol) was then added and stirring was continued for a further 45 minutes. Benzyl bromide (33g, 0.19 mol) was added gradually over 10 minutes, and stirring was maintained for a further 45 minutes. The reaction mixture was quenched with water (200 ml) and extracted with ether (3 x 100 ml), washing each extract with water (3 x 50 ml). The ether layers were combined, dried and concentrated in vacuo, followed by vacuum distillation to give \( N \)-benzylpyrrole (68a) (17.0g, 72%), b.p. 80°C/1 mm Hg (lit.\(^{180}\), 67–68°C/0.35 mmHg), \( ^1H \) n.m.r. (90 MHz), \( \delta = 4.87 \) (2H, s, CH\(_2\)), 6.03 (2H, t, J\(_{AB}\) = 2 Hz, C(3 and 4))H, 6.45 (2H, t, J\(_{AB}\) = 2 Hz, C(2 and 5))H, and 6.82–7.24 (5H, m, PhH) p.p.m., \( ^{13}C \) n.m.r.(20.1 MHz), \( \delta = 53.0 \) (t, CH\(_2\)), 108.7 (d, C(3 and 4)), 121.1 (d, C(2 and 5)), 127.0 (d, C(4’)), 127.6 (d, C(2’ and 6’)), 128.7 (d, C(3’ and 5’)), and 138.4 (s, C(1’)) p.p.m..
2.7.2 Preparation of $N$-Triphenylmethylpyrrole

Triphenylmethyl chloride (25g, 90 mmol) was stirred in liquid ammonia (600 ml) for 5 hours. After evaporation of the excess ammonia, the residue was suspended in ether (350 ml) and washed with saturated sodium carbonate solution (150 ml). The organic layer was removed, dried and concentrated *in vacuo* to yield triphenylmethylamine (17.6g, 75%) as a yellow solid, m.p. 102-104°C (from ethyl acetate–petroleum ether 40-60) (lit.69, 102–104°C). $^1$H n.m.r. (90 MHz), $\delta$ = 2.28 (2H, br.s, NID, and 7.12 (l5H, s, PhID p.p.m..

Triphenylmethylamine (15g, 58 mmol), 2,5-dimethoxytetrahydrofuran (9g, 69 mmol), glacial acetic acid (42 ml) and benzene (90 ml) were stirred and heated under reflux for 16 hours. The black solid obtained on concentration of the reaction mixture was recrystallised with activated charcoal to yield $N$-triphenylmethylpyrrole (68b) (10.4g, 58%) as white needles, m.p. 244–46°C (from benzene) (lit.69, 245–46°C). $^1$H n.m.r. (90 MHz), 6.10 (2H, t, $J_{AB}$ = 2 Hz, C(3 and 4)ID, 6.51 (2H, t, $J_{AB}$ = 2 Hz, C(2 and 5)ID, and 6.98-7.30 (15H, m, PhID p.p.m..

2.8.1 Reaction of $N$-Benzylpyrrole with $N,N$-Dimethyl(methylene)-iminium Chloride

$N$-Benzylpyrrole (68a) (2.59g, 16.5 mmol) and iminium salt (22a) (1.41g, 15 mmol) in acetonitrile (90 ml) were treated as described in Method A, for 2 hours, to yield 2-($N',N'$-dimethylaminomethyl)$-N$-benzylpyrrole (69a) (2.53g, 79%), b.p. 120°C/0.2 mmHg, $^1$H n.m.r. (90 MHz), $\delta$ = 2.15 (6H, s, NCH$_3$), 3.20 (2H, s, ArCH$_2$), 5.18 (2H, s, PhCH$_2$), 5.95–6.10 (2H, m, C(3 and 4)ID), 6.53–6.62 (1H, m, C(5)ID, and 6.89–7.37 (5H, m, PhID p.p.m.,
\(^{13}\text{C n.m.r. (20.1 MHz)}\), \(\delta = 44.9 \text{ (q, NCH}_3\text{), 50.2 \text{ (t, PhCH}_2\text{), 55.8 \text{ (t, ArCH}_2\text{),}
106.9 \text{ (d, C(4)), 109.7 \text{ (d, C(3)), 122.2 \text{ (d, C(5)), 126.7 \text{ (d, C(3') and 5')}, 127.1
(d, C(4')), 128.5 \text{ (d, C(2' and 6'), 129.7 \text{ (s, C(2))}, and 139.1 \text{ (s, C(1')) p.p.m.;}
\text{m/z (M}^+\text{) 214.1468, C}_{14}\text{H}_{18}\text{N}_2 \text{requires 214.1470.}

2.8.2 Reaction of \(N-t\)-Butylpyrrole with \(N,N\)-Dimethyl(methylene)iminium Chloride

\(N-t\)-Butylpyrrole (1.35g, 11 mmol) and iminium salt (22a) (0.94g, 10 mmol) in acetonitrile (60 ml) were treated as described in Method A, for 2 hours. The crude residue from extraction and concentration was chromatographed on grade 3 alumina with ethyl acetate–petroleum ether 40–60 (2:3) and yielded 2-(\(N,N\)-dimethylaminomethyl)\(N\)-t-butylpyrrole (69b) (0.71g, 39%), \(^1\text{H n.m.r. (90 MHz)}, \delta = 1.61 \text{ (9H, s, CCH}_3\text{)}, 2.17 \text{ (6H, s, NCH}_3\text{), 3.40
(2H, s, CH}_2\text{), 5.97–6.10 \text{ (2H, m, C(2 and 5))}, and 6.72–6.83 \text{ (1H, m, C(4)) p.p.m.; m/z (M}^+\text{) 180.1619, C}_{11}\text{H}_{20}\text{N}_2 \text{requires 180.1626.}

2.8.3 Reaction of \(N\)-Triphenylmethylpyrrole with \(N,N\)-Dimethyl-(methylene)iminium Chloride

\(N\)-Triphenylmethylpyrrole (68b) (1.70g, 5.5 mmol) and iminium salt (22a) (0.47g, 5 mmol) in acetonitrile (150 ml) were treated as described in Method A, for 48 hours. Recrystallisation of the crude material from extraction and concentration gave 3-(\(N,N\)-dimethylaminomethyl)\(N\)-triphenylmethylpyrrole (0.15g, 8%) (from ethyl acetate), \(^1\text{H n.m.r. (60 MHz)}, \delta = 2.20 \text{ (6H, s, NCH}_3\text{), 3.30 \text{ (2H, s, CH}_2\text{), 6.04–6.17 \text{ (1H, m, C(4))}, 6.50–6.67 \text{ (2H, m, C(2 and 5))}, and 7.25 \text{ (15H, br.s, Ph) p.p.m.}
Repeating the reaction with heating under reflux, for 168 hours, gave 3,4-bis-(N',N'-dimethylaminomethyl)-N-triphenylmethylpyrrole (0.24g, 11%) (from ethyl acetate). 'H n.m.r. (60 MHz), δ = 2.20 (12H, s, NCH₃), 3.30 (4H, s, CH₂), 6.51 (2H, s, C(2 and 5)H), and 7.25 (15H, br.s, PhH) p.p.m.

2.8.4 Reaction of N-Benzylpyrrole with N-Piperidyl(methylene)-iminium Chloride

N-Benzylpyrrole (68a) (2.59g, 16.5 mmol) and iminium salt (22e) (2.01g, 15 mmol) in acetonitrile (90 ml) were treated as described in Method A, for 2 hours, to yield, after careful fractional distillation, 2-(N'-piperidylmethyl)-N-benzylpyrrole (69c) (1.34g, 35%), b.p. 130°C/0.1 mm Hg, 'H n.m.r. (60 MHz), δ = 1.24–1.60 (6H, m, C(3', 4' and 5')H), 2.11–2.43 (4H, m, C(2' and 6')H), 3.27 (2H, s, ArCH₂), 5.25 (2H, s, PhCH₂), 5.96–6.18 (2H, m, C(3 and 4)H), 6.57–6.72 (1H, m, C(5)H), and 6.94–7.39 (5H, m, PhH) p.p.m., 13C n.m.r. (20.1 MHz), δ = 24.6 (t, C(4')), 26.0 (t, C(3' and 5')), 50.4 (t, PhCH₂), 54.2 (t, C(2' and 6')), 55.4 (t, ArCH₂), 106.8 (d, C(4)), 109.8 (d, C(3)), 122.1 (d, C(5)), 126.8 (d, C(3'' and 5''))), 127.0 (d, C(4'')), 128.4 (d, C(2'' and 6'')), 129.3 (s, C(2)), and 139.3 (s, C(1'')) p.p.m.; m/z (M⁺) 254.1784, C₁₇H₂₂N₂ requires 254.1783.

2.9.1 Reaction of Furan with N,N-Dimethyl(methylene)iminium Chloride

Furan (2.25g, 33 mmol) and iminium salt (22a) (2.81g, 30 mmol) in acetonitrile (150 ml) were treated as described in Method A, for 72 hours, to yield 2-(N,N-dimethylaminomethyl)furan (76a) (2.76g, 66%), b.p.
64-66°C/15 mmHg, \(^1\)H n.m.r. (60 MHz), \(\delta = 2.27\) (6H, s, CH\(_3\)), 3.48 (2H, s, CH\(_2\)), 6.14-6.43 (2H, m, C(3 and 4)H), and 7.33-7.46 (1H, m, C(5)H) p.p.m., \(^{13}\)C n.m.r. (20.1 MHz), \(\delta = 44.0\) (q, CH\(_3\)), 54.9 (t, CH\(_2\)), 107.5 (d, C(3)), 109.3 (d, C(4)), 141.2 (d, C(5)), and 151.8 (s, C(2)) p.p.m.; m/z (M\(^+\)) 125.0831, C\(_7\)H\(_{11}\)NO requires 125.0841.

2.9.2. Reaction of Furan with N–Pyrrolidinyl(methylene)iminium Chloride

Furan (1.50g 22 mmol) and iminium salt (22d) (2.39g, 20 mmol) in acetonitrile (125 ml) were treated as described in Method A, for 120 hours, to yield 2-(N-pyrrolidinylmethyl)furan (76b) (2.24g, 74%), b.p. 67-68°C/ 3.5 mmHg, which was slightly contaminated with di–N–pyrrolidinymethane (56d) (0.09g, 5%, based on iminium salt) (determined by \(^1\)H n.m.r.), \(^1\)H n.m.r. (60 MHz), \(\delta = 1.61-1.96\) (4H, m, C(3' and 4')H), 2.34-2.71 (4H, m, C(2' and 5')H), 3.63 (2H, s, CH\(_2\)), 6.07-6.35 (2H, m, C(3 and 4)H), and 7.27-7.41 (1H, m, C(5)H) p.p.m., \(^{13}\)C n.m.r. (20.1 MHz), \(\delta = 23.4\) (t, C(3' and 4')), 52.1 (t, CH\(_2\)), 53.9 (t, C(2' and 5')), 107.5 (d, C(3)), 110.0 (d, C(4)), 141.8 (d, C(5)), and 153.1 (s, C(2)) p.p.m.

2.9.3 Reaction of Furan with N–Piperidyl(methylene)iminium Chloride

Furan (1.26g, 18.4 mmol) and iminium salt (22e) (2.24g, 16.8 mmol) in acetonitrile (70 ml) were treated as described in Method A, for 120 hours, to yield 2–(N-piperidylmethyl)furan (76c) (2.06g, 74%), b.p. 67–68°C/ 1 mmHg, \(^1\)H n.m.r. (60 MHz), \(\delta = 1.25–1.79\) (6H, m, C(3', 4' and 5')H), 2.25–2.56 (4H, m, C(2' and 6')H), 3.49 (2H, s, CH\(_2\)), 6.08–6.38 (2H, m, C(3 and 4)H), and 7.26–7.45 (1H, m, C(5)H) p.p.m., \(^{13}\)C n.m.r. (20.1 MHz), \(\delta =\)
24.3 (t, C(4'), 25.9 (t, C(3' and 5')), 54.2 (t, C(2' and 6')), 55.7 (t, CH₂), 108.5 (d, C(3)), 110.0 (d, C(4)), 141.9 (d, C(5)), and 152.2 (s, C(2)) p.p.m.; m/z (M⁺) 165.1145. C₁₀H₁₅NO requires 165.1154.

Repeating the reaction with heating under reflux, for 120 hours, gave (76c) (1.67g, 60%), together with 2,5-di-(N-piperidylmethyl)furan (77c) (0.15g, 7%), b.p. 103–106°C/1 mmHg, ¹H n.m.r. (60 MHz), δ = 1.30–1.87 (12H, m, C(3', 4' and 5')H), 2.26–2.64 (8H, m, C(2' and 6')H), 3.51 (4H, s, CH₂), and 6.09 (2H, s, C(3 and 4)H) p.p.m.; m/z (M⁺) 262.2026, C₁₅H₂₈N₂O requires 262.2045.

2.9.4 Reaction of Furan with N-Morpholinyl(methylene)iminium Chloride

Furan (1.50g, 22 mmol) and iminium salt (2.71g, 20 mmol) in acetonitrile (80 ml) were treated as described in Method A, for 120 hours, to yield 2-(N-morpholinylmethyl)furan (76d) (2.23g, 67%), b.p. 55–58°C/1 mmHg, ¹H n.m.r. (60 MHz), δ = 2.32–2.58 (4H, m, C(3' and 5')H), 3.52 (2H, s, CH₂), 3.58–3.84 (4H, m, C(2' and 6')H), 6.11–6.37 (2H, m, C(3 and 4)H), and 7.28–7.41 (1H, m, C(5)H) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 54.7 (t, C(3' and 5')), 56.5 (t, CH₂), 68.0 (t, C(2' and 6')), 109.0 (d, C(3)), 110.1 (d, C(4)), 148.7 (d, C(5)), and 152.7 (s, C(2)) p.p.m.; m/z (M⁺) 167.0936, C₉H₁₃NO₂ requires 167.0946, together with 2,5-di-(N-morpholinylmethyl)furan (77d) (0.13g, 5%) b.p. 100–105°C/1 mmHg, ¹H n.m.r. (60 MHz), δ = 2.33–2.64 (8H, m, C(2' and 6')H), 3.54 (4H, s, CH₂), 3.58–3.84 (8H, m, C(3' and 5')H), and 6.13 (2H, s, C(3 and 4)H) p.p.m.; m/z (M⁺) 266.1626, C₁₄H₂₂N₂O₅ requires 266.1630.
Repeating the reaction with heating under reflux, for 120 hours, gave (76d) (1.74g, 52%), together with (77d) (0.68g, 25%).

2.10.1 Reaction of 2-Methylfuran with N,N-Dimethyl(methylene)iminium Chloride

2-Methylfuran (2.87g, 35 mmol) and iminium salt (22a) (3.00g, 32 mmol) in acetonitrile (110 ml) were treated as described in Method A, for 72 hours, to yield 5-methyl-2-(N,N-dimethylaminomethyl)furan (78a) (1.29–2.04g, 29–46%), b.p. 54–55°C/17 mmHg (lit. 68–70°C/ 25 mmHg), 1H n.m.r. (60 MHz), δ = 2.26 (9H, br.s., NCH 3 and ArCH 3 ), 3.39 (2H, s, CH 2 ), 5.81–6.01 (1H, m, C(4)H), and 6.08 (1H, d, J AB = 3 Hz, C(3)H) p.p.m., 13C n.m.r. (20.1 MHz), δ = 13.5 (q, ArCH 3 ), 45.0 (q, NCH 3 ), 56.1 (t, CH 2 ), 106.1 (d, C(3)), 109.3 (d, C(4)), and 150.7 and 151.7 (s, C(2) and s, C(5)) p.p.m.; m/z (M+) 139.0994, C 9 H 13 NO requires 139.0997; together with varying amounts of solid material. The solid proved to be a mixture of 5-methyl-2-(N,N-dimethylaminomethyl)furan hydrochloride (79a) and N,N-dimethyl-N,N-di-(5-methyl-2-furylmethyl)ammonium chloride (80a) by 1H n.m.r., and a small amount of (80a) was isolated by fractional crystallisation, m.p. 188°C (from dichloromethane–petroleum ether 40–60). The 1H n.m.r. of the mixture showed resonances identical to those for valid samples of (79a) and (80a), which were independently prepared (see 2.10.2 and 2.10.3).

Repeating the reaction using Method B, for 24 hours, yielded (78a) (3.74g, 84%).
2.10.2 Preparation of 5-Methyl-2-\(\text{N},\text{N}\)-dimethylaminomethyl\)-furan Hydrochloride

5-Methyl-2-\(\text{N},\text{N}\)-dimethylaminomethyl\)furan (78a) (3.00 g, 21.5 mmol) was stirred in diethyl ether (15 ml) at 0°C, and hydrochloric acid (0.80 g, 21.9 mmol, 36% aqueous solution) was added dropwise. The solvent was removed \emph{in vacuo}, and the residue recrystallised to yield the hydrochloride (79a) (3.72 g, 98%) as white crystals, m.p. 158.5-159°C (from acetone-ethyl acetate-petroleum ether 40-60) (lit.\textsuperscript{10}, 158-158.5°C), \textsuperscript{1}H n.m.r. (90 MHz), \(\delta\) = 2.27 (3H, s, ArCH\(_3\)), 2.66 (6H, s, NCH\(_3\)), 4.04 (2H, s, CH\(_2\)), 5.90-6.01 (1H, m, C(4)H), and 6.41 to 6.51 (1H, m, C(3)H) p.p.m.

2.10.3 Preparation of \(\text{N},\text{N}\)-Dimethyl-\(\text{N},\text{N}\)-di-(5-methyl-2-furyl-methyl)ammonium Chloride

5-Methyl-2-\(\text{N},\text{N}\)-dimethylaminomethyl\)furan (78a) (3.19 g, 22.9 mmol) was stirred in dry dichloromethane (15 ml) at -10 - 0°C. Freshly distilled acetyl chloride (0.90 g, 11.5 mmol) in dichloromethane (15 ml) was added dropwise over 30 minutes. The mixture was stirred for a further 1 hour at room temperature, and the solvent was removed \emph{in vacuo}. The residue was recrystallised several times to yield the ammonium salt (80a) (3.01 g, 97%) as white crystals, m.p. 188°C (from dichloromethane-petroleum ether 40-60), \textsuperscript{1}H n.m.r. (360 MHz), \(\delta\) = 2.31 (6H, s, ArCH\(_3\)), 3.28 (6H, s, NCH\(_3\)), 4.99 (4H, s, CH\(_2\)), 6.05 (2H, d, J\(_{AB}\) = 2.5 Hz, C(4)H), and 6.63 (2H, d, J\(_{AB}\) = 2.5 Hz, C(3)H) p.p.m., \textsuperscript{13}C n.m.r. (90.6 MHz), \(\delta\) = 13.5 (ArCH\(_3\)), 49.3 (NCH\(_3\)), 59.4 (CH\(_2\)), 107.4 (C(4)), 118.4 (C(3)), 140.7 (C(5)), and 155.4 (C(2)) p.p.m.; found: C, 62.15; H, 7.2; N, 5.25. \(\text{C}_{44}\text{H}_{26}\text{ClNO}_2\) requires C, 62.35; H, 7.45; N, 5.2%; m/z (M\textsuperscript{+}-35) 234.160, requires 234.194.
2.10.4 Reaction of 2-Methylfuran with N,N-Di-iso-propyl-(methylene)iminium Chloride

2-Methylfuran (1.35g, 16.5 mmol) and iminium salt (22c) (2.25g, 15 mmol) in acetonitrile (75 ml) were treated as described in Method A, for 72 hours, to yield 5-methyl-2-(N,N-di-iso-propylaminomethyl)furan (78b) (1.89, 65%), b.p. 94–96°C/4.5 mmHg. ¹H n.m.r. (60 MHz), δ = 1.04 (12H, d, J= 7 Hz, CHCH₃), 2.25 (3H, s, ArCH₃), 3.08 (2H, sept., J= 7 Hz, CH), 3.60 (2H, s, CH₂), 5.77–5.93 (1H, m, C(4)H), and 6.00 (1H, d, JAB = 3 Hz, C(3)H) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 13.5 (q, CH₃), 20.8 (q, CHCH₃), 42.5 (t, CH₂), 48.6 (d, CH), 106.1 (d, C(3)), 107.2 (d, C(4)), 150.5 and 154.7 (s, C(2) and s, C(5)) p.p.m.; m/z (M⁺) 195.1610, C₁₂H₂₁NO requires 195.1623.

2.10.5 Reaction of 2-Methylfuran with N-Pyrrolidinyl-(methylene)iminium Chloride

2-Methylfuran (1.81g, 22 mmol) and iminium salt (22d) (2.39g, 20 mmol) in acetonitrile (100 ml) were treated as described in Method A, for 72 hours, to yield 5-methyl-2-(N-pyrrolidinylmethyl)furan (78c) (0.92–2.44g, 28–74%), b.p. 72–74°C/2.8 mmHg, ¹H n.m.r. (60 MHz), δ = 1.63–1.95 (4H, m, C(3’ and 4’)H), 2.24 (3H, s, CH₃), 2.33–2.71 (4H, m, C(2’ and 5’)H), 3.53 (2H, s, CH₂), 5.71–5.91 (1H, m, C(4)H), and 6.00 (1H, d, JAB = 3 Hz, C(3)H) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 13.5 (q, CH₃), 23.5 (t, C(3’ and 4’)), 52.3 (t, CH₂), 53.9 (t, C(2’ and 5’)), 105.9 (d, C(3)), 108.4 (d, C(4)), and 151.3 (s, C(2 and 5)) p.p.m.; m/z (M⁺) 165.1145, C₁₀H₁₅NO requires 165.1154, together with varying amounts of solid material. The solid appeared, by ¹H n.m.r., to be a mixture of 5-methyl-2-(N-pyrrolidinylmethyl)furan hydrochloride (79b) and N,N-di-(5-methyl-2-furylmethyl)-N-pyrrolidinylammonium chloride (80b), which were not separated.
Repeating the reaction using Method B, for 72 hours, yielded \(78\text{c}\) (3.10g, 94%).

2.10.6 Reaction of 2-Methylfuran with \(N\)-Piperidyl(methylene)iminium Chloride

2-Methylfuran (1.81g, 22 mmol) and iminium salt \(22\text{e}\) (2.67g, 20 mmol) in acetonitrile (100 ml) were treated as described in Method A, for 72 hours, to yield 5-methyl-2-(\(N\)-piperidyl)methylfuran \(78\text{d}\) (2.39g, 67%), b.p. 126–29°C/4 mmHg (lit.\textsuperscript{10}, 88–89°C/6 mmHg), \(^1\text{H}\) n.m.r. (60 MHz), \(\delta = 1.27–1.78\) (6H, m, C(3'), 4' and 5'H), 2.30 (3H, s, CH\(_3\)), 2.30–2.57 (4H, m, C(2' and 6')H), 3.42 (2H, s, CH\(_2\)), 5.79–5.96 (1H, m, C(4'H), and 6.01 (1H, d, \(J_{AB} = 3\) Hz, C(3'H) p.p.m., \(^{13}\text{C}\) n.m.r. (20.1 MHz), \(\delta = 13.6\) (q, CH\(_3\)), 24.3 (t, C(3')), 25.9 (t, C(3' and 5')), 54.2 (t, C(2' and 6')), 55.9 (t, CH\(_2\)), 106.0 (d, C(3)), 109.5 (d, C(4)), and 150.4 and 151.6 (s, C(2) and s, C(5)) p.p.m.; m/z (M\(^+\)) 179.1298, \(C_{11}H_{17}NO\) requires 179.1310.

2.10.7 Reaction of 2-Methylfuran with \(N\)-Morpholinyl(methylene)-iminium Chloride

2-Methylfuran (1.81g, 22 mmol) and iminium salt \(22\text{f}\) (2.71g, 20 mmol) in acetonitrile (100 ml) were treated as described in Method A, for 72 hours, to yield 5-methyl-2-(\(N\)-morpholinyl)methylfuran \(78\text{e}\) (3.09g, 85%), b.p. 139–40°C/4.3 mmHg (lit.\textsuperscript{10}, 133°C/20 mmHg), \(^1\text{H}\) n.m.r. (60 MHz), \(\delta = 2.26\) (3H, s, CH\(_3\)), 2.27–2.56 (4H, m, C(3' and 5'H)), 3.44 (2H, s, CH\(_2\)), 3.52–3.83 (4H, m, C(2' and 6')H), 5.76–5.97 (1H, m, C(4'H), and 6.04 (1H, d, \(J_{AB} = 3\) Hz, C(3'H) p.p.m., \(^{13}\text{C}\) n.m.r. (20.1 MHz), \(\delta = 13.6\) (q, CH\(_3\)), 53.4 (t, C(3' and
5'), 55.5 (t, CH₂), 66.9 (t, C(2' and 6')), 106.1 (d, C(3)), 110.0 (d, C(4)), and
149.5 and 152.0 (s, C(2) and s, C(5)) p.p.m.; m/z (M⁺) 181.1086, C₁₀H₁₅NO₂
requires 181.1102.
3.1.1 Reaction of 2-Methylfuran with Di-(N-pyrrolidinyl)methane using Sulphur Dioxide

2-Methylfuran (1.81g, 22 mmol) and di-(N-pyrrolidinyl)methane (56d) (2.58g, 20 mmol) in acetonitrile (70 ml) were treated with sulphur dioxide (20 ml, 0.45 mol) as described in 3.1.1, for 48 hours, to yield 5-methyl-2-(N-pyrrolidinyl)methylfuran (78c) (2.25g, 68%), b.p. 65-70°C/2.5 mmHg, which was contaminated with di-(N-pyrrolidinyl)methane (56d) (0.30g, 19%, based on aminol ether) (determined by ¹H n.m.r.).

3.1.2 Reaction of 2-Methylfuran with Ethoxy-N-pyrrolidinylmethylene using Sulphur Dioxide

2-Methylfuran (1.81g, 22 mmol) and ethoxy-N-pyrrolidinylmethylene (61c) (2.58g, 20 mmol) in acetonitrile (70 ml) were treated with sulphur dioxide (20 ml, 0.45 mol) as described in 3.1.1, for 48 hours, to yield 5-methyl-2-(N-pyrrolidinyl)methylfuran (78c) (2.25g, 68%), b.p. 65-70°C/2.5 mmHg, which was contaminated with di-(N-pyrrolidinyl)methane (56d) (0.30g, 19%, based on aminol ether) (determined by ¹H n.m.r.).

3.2.1 Reaction of Furan with Di-(N-pyrrolidinyl)methane using Trichloromethylsilane

Furan (2.25g, 33 mmol) and di-(N-pyrrolidinyl)methane (56d) (4.63g, 30 mmol) in acetonitrile (100 ml) were treated with trichloromethylsilane...
(4.93g, 33 mmol) in acetonitrile (100 ml), as described in Method C, for 48 hours, to yield 2-\((N\text{-pyrrolidinylmethyl})\)furan (76b) (0.47g, 10%), b.p. 60-62°C/2.5 mmHg.

### 3.2.2 Reaction of Furan with Di-\((N\text{-piperidyl})\)methane using Trichloromethylsilane

Furan (1.87g, 27.5 mmol) and di-\((N\text{-piperidyl})\)methane (56e) (4.56g, 25 mmol) in acetonitrile (60 ml) were treated with trichloromethylsilane (4.11g, 27.5 mmol) in acetonitrile (60 ml), as described in Method C, for 72 hours, to yield 2-\((N\text{-piperidylmethyl})\)furan (76c) (0.74g, 18%), b.p. 65-71°C/1 mmHg, which was contaminated with (56e) (1.37g, 30% recovered) (determined by \(^1\)H n.m.r.).

### 3.2.3 Reaction of Furan with Ethoxy-\(N\text{-pyrrolidinylmethyl}\)methane using Chlorotrimethylsilane

Furan (2.25g, 33 mmol) and ethoxy-\(N\text{-pyrrolidinylmethyl}\)methane (61c) (4.26g, 30 mmol) in acetonitrile (100 ml) were treated with chlorotrimethylsilane (3.59g, 33 mmol) in acetonitrile (100 ml), as described in Method C, for 48 hours, to yield 2-\((N\text{-pyrrolidinylmethyl})\)furan (76b) (2.37g, 52%), b.p. 68-70°C/3.5 mmHg, which was contaminated with di-\((N\text{-pyrrolidinylmethyl})\)methane (56d) (0.43g, 19%, based on aminol ether) (determined by \(^1\)H n.m.r.).

Repeating the reaction using dichlorodimethylsilane (4.26g, 33 mmol) gave (76b) (3.03g, 67%), which was contaminated with (56d) (0.19g, 8%, based on aminol ether) (determined by \(^1\)H n.m.r.).
Repeating the reaction using trichloromethylsilane (4.93g, 33 mmol) gave (76b) (2.81g, 62%), which was contaminated with (56d) (0.56g, 24%, based on aminol ether) (determined by $^1$H n.m.r.).

### 3.3.1 Reaction of 2-Methylfuran with Di-(N-pyrrolidinyl)methane using Dichlorodimethylsilane

2-Methylfuran (2.71g, 33 mmol) and di-(N-pyrrolidinyl)methane (56d) (4.63g, 30 mmol) in acetonitrile (100 ml) were treated with dichlorodimethylsilane (4.26g, 33 mmol) in acetonitrile (100 ml), as described in Method C, for 48 hours, to yield 5-methyl-2-(N-pyrrolidinyl)methylfuran (78c) (2.88g, 58%), b.p. 70-72°C/2 mmHg.

Repeating the reaction using trichloromethylsilane (4.93g, 33 mmol) gave (78c) (3.19g, 64%).

### 3.3.2 Reaction of 2-Methylfuran with Di-(N-piperidyl)methane using Chlorotrimethylsilane

2-Methylfuran (2.26g, 27.5 mmol) and di-(N-piperidyl)methane (56e) (4.56g, 25 mmol) in acetonitrile (100 ml) were treated with chlorotrimethylsilane (2.99g, 27.5 mmol) in acetonitrile (100 ml), as described in Method C, for 72 hours, to yield 5-methyl-2-(N-piperidyl)methylfuran (78d) (0.28g, 6%) b.p. 120-25°C/3 mmHg, which was contaminated with (56e) (2.80g, 61% recovered) (determined by $^1$H n.m.r.).

Repeating the reaction using trichloromethylsilane (4.11g, 27.5 mmol) gave (78d) (2.93g, 65%), which was contaminated with (56e) (0.66g, 14% recovered) (determined by $^1$H n.m.r.).
3.3.3 Reaction of 2-Methylfuran with Ethoxy-N-pyrrolidinylmethane using Chlorotrimethylsilane

2-Methylfuran (2.71 g, 33 mmol) and ethoxy-N-pyrrolidinylmethane (61c) (4.26 g, 30 mmol) in acetonitrile (100 ml) were treated with chlorotrimethylsilane (3.59 g, 33 mmol) in acetonitrile (100 ml) as described in Method C, for 48 hours, to yield 5-methyl-2-(N-pyrrolidinylmethy)furan (78c) (4.27 g, 86%), b.p. 102–104°C/4 mmHg.

Repeating the reaction using dichlorodimethylsilane (4.26 g, 33 mmol) gave (78c) (4.20 g, 84%).

Repeating the reaction using trichloromethylsilane (4.93 g, 33 mmol) gave (78c) (4.71 g, 95%).

3.4.1 Reaction of N-Methylpyrrole with Bis-(N,N-dimethylamino)methane using Dichlorodimethylsilane

N-Methylpyrrole (2.81 g, 27.5 mmol) and bis-(N,N-dimethylamino)methane (56a) (2.56 g, 25 mmol) in acetonitrile (65 ml) were treated with dichlorodimethylsilane (3.55 g, 27.5 mmol) in acetonitrile (60 ml), as described in Method C, for 24 hours, to yield 2-(N',N'-dimethylaminomethyl)-N-methylpyrrole (47a) (1.83 g, 53%), b.p. 56°C/5 mmHg, together with a mixture of (47a) (0.22 g, 6%) and 2,5-bis-(N',N'-dimethylaminomethyl)-N-methylpyrrole (48a) (0.61 g, 25%) b.p. 60–95°C/5 mmHg (determined by ¹H n.m.r.).
3.4.2 Reaction of Indole with Bis-\((N,N\text{-dimethylamine})\)methane using Chlorotrimethylsilane

Indole (3.22g, 27.5 mmol) and bis-\((N,N\text{-dimethylamino})\)methane (56a) (2.56g, 25 mmol) in acetonitrile (75 ml) were treated with chlorotrimethylsilane (2.99g, 27.5 mmol) in acetonitrile (50 ml), as described in Method C, for 48 hours, to yield a crude mixture of a solid and an oil. Trituration with diethyl ether–petroleum ether 40–60 (1:4) followed by recrystallisation gave 3-\((N,N\text{-dimethylaminomethyl})\)indole (92a) (2.77g, 63%) as white crystals, m.p. 134–35°C (from cyclohexane) (lit.\(^{140}\), 134°C), \(^1\)H n.m.r. (60 MHz), \(\delta = 2.32\) (6H, s, CH\(_3\)), 3.67 (2H, s, CH\(_2\)), 6.90–7.36 (4H, m, C(2, 5, 6 and 7)H), 7.58–7.84 (1H, m, C(4)H), and 8.99 (1H, br.s, D\(_2\)O ex., NH) p.p.m.; \(v_{\text{max}}\) (KBr), 3196 (NH) cm\(^{-1}\); m/z (M\(^+\)) 174.1148, C\(_{11}\)H\(_{14}\)N\(_2\) requires 174.1157.

3.4.3 Reaction of N-Methylindole with Ethoxy-\(N,N\text{-diethylaminomethane}\) using Chlorotrimethylsilane

\(N\text{-Methylindole}\) (0.44g, 11 mmol) and ethoxy-\(N,N\text{-diethylaminomethane}\) (61a) (0.31g, 10 mmol) in acetonitrile (35 ml) were treated with chlorotrimethylsilane (1.20g, 11 mmol) in acetonitrile (35 ml), as described in Method C, for 48 hours, to yield 3-(\(N',N'\text{-diethylaminomethyl}\))-\(N\text{-methylindole}\) (92b) (2.16g, 76%) as a pale yellow oil, b.p. 145°C/0.25 mmHg (lit.\(^{181}\), (hydrochloride, m.p.174°C), \(^1\)H n.m.r. (60 MHz), \(\delta = 1.02\) (6H, t, J = 7.5 Hz, CH\(_2\)CH\(_3\)), 2.54 (4H, q, J = 7.5 Hz, CH\(_2\)CH\(_3\)), 3.53 (3H, s, NCH\(_3\)), 3.71 (2H, s, ArCH\(_2\)), 6.83 (1H, br.s, C(2)H), 6.94–7.36 (3H, m, C(5, 6 and 7)H), and 7.57–7.85 (1H, m, C(4)H) p.p.m.; m/z (M\(^+\)) 216.1626, C\(_{14}\)H\(_{20}\)N\(_2\) requires 216.1626.
3.5.1 Preparation of Methyl Dimethoxyacetate

Sodium (80.5 g, 3.0 mol) was carefully dissolved in dry methanol (750 ml) in an apparatus protected from moisture with a calcium chloride drying tube. Dichloroacetic acid (129 g, 1.0 mol) was then added to the stirred solution at 40°C over 40 minutes, and then the reaction mixture was heated under reflux for 5 hours. The solution was cooled with an ice bath and neutralised to phenolphthalein with methanolic hydrogen chloride. The stirred mixture was cooled to -25°C (acetone–dry ice), and treated dropwise with thionyl chloride (59.5 g, 0.5 mol). The mixture was allowed to stand overnight, filtered to remove sodium chloride and the methanol was distilled away at atmospheric pressure. The residue was fractionally distilled to yield methyl dimethoxyacetate (97) (93.1 g, 69%) as the major component, b.p. 58–61°C/12 mmHg (lit. 129, 54–55°C/10 mmHg), 1H n.m.r. (60 MHz), δ = 3.55 (6H, s, CHOCH₃), 3.94 (OH, s, CO₂CH₃), and 4.95 (1H, s, CH) p.p.m., ν_max. (film), 1757 (C=O), and 2836 (OCH) cm⁻¹.

3.5.2 Preparation of Methyl α-Chloro–α-methoxyacetate

Methyl dimethoxyacetate (97) (30.2 g, 0.225 mol) was added over 15 minutes to phosphorus pentachloride (46.9 g, 0.225 mol) in an apparatus protected from moisture. The mixture was stirred and warmed to 40°C until all the solid had dissolved, and then heated to 80°C for approximately 30 minutes. When no further gas was evolved, the solution was heated to 140°C for 80 minutes to complete the reaction. The reaction mixture was fractionally distilled to give a fore-run of phosphorus oxychloride, b.p. 28°C/12 mmHg, and methyl α–chloro–α–methoxyacetate (98) (28.3 g, 91%) as the major fraction, b.p. 65–66°C/12 mmHg (lit. 129, 60–61°C/10 mmHg, 1H n.m.r. (60 MHz), δ = 3.66 (3H, s, CHOCH₃), 3.90 (3H, s, CO₂CH₃), and 5.83 (1H, s, CH) p.p.m., ν_max. (film), 1754 (C=O), and
3.5.3 Preparation of Methyl α-Methoxy-α-pyrrolidinylacetate

Methyl α-chloro-α-methoxyacetate (98) (5.54g, 40 mmol) was added dropwise to a stirred ice-cooled solution of freshly distilled pyrrolidine (5.83g, 82 mmol) in dry ether (50 ml), in an apparatus protected from moisture. After addition, stirring was continued for 1 hour at 0°C and then 1 hour at room temperature. The pyrrolidine hydrochloride was removed by filtration and washed with a small amount of cold ether. The combined filtrates were washed with cold 1M sodium carbonate solution (2 x 50 ml), dried over sodium sulphate and concentrated in vacuo to give a pale yellow liquid (4.92g). Careful Kugelrohr distillation gave methyl α-methoxy-α-pyrrolidinylacetate (99a) (2.44g, 35%), b.p. 51-55°C/0.01 mmHg, ¹H n.m.r. (60 MHz, δ = 1.58-1.96 (4H, m, C(3 and 4)H), 2.49-3.04 (4H, m, C(2 and 5)H), 3.35 (3H, s, CHOCH₃), 3.74 (3H, s, CO₂CH₃), and 4.48 (1H, s, CH₃) p.p.m., ν_max. (film), 1752 (C=O), and 2824 (OCH) cm⁻¹, together with a second, unidentified fraction, b.p. 56-70°C/0.01 mmHg.

3.5.4 Preparation of Methyl α-Methoxy-α-piperidylacetate

Methyl α-chloro-α-methoxyacetate (98) (20.78g, 0.15 mol) and freshly distilled piperidine (26.83g, 0.315 mol) in dry ether (180 ml) were treated as described in 3.5.3 to yield methyl α-methoxy-α-piperidylacetate (99b) (11.40g, 41%), b.p. 55-62°C/0.02 mmHg (lit.²⁷, 55-56°C/0.01 mmHg), ¹H n.m.r. (60 MHz, δ = 1.45-1.86 (6H, m, C(3, 4 and 5)H), 2.30-2.94 (4H, m, C(2 and 6)H), 3.43 (3H, s, CHOCH₃), 3.78 (3H, s, CO₂CH₃), and 4.23 (1H, s, CH₃) p.p.m., ν_max. (film), 1748 (C=O), and 2820 (OCH) cm⁻¹.
3.6.1 Reaction of Furan with Methyl α-Methoxy-α-pyrrolidinylacetate using Trichloromethylsilane

Furan (0.37g, 5.5 mmol) and methyl α-methoxy-α-pyrrolidinylacetate (99a) (0.87g, 5 mmol) in acetonitrile (20 ml) were treated with trichloromethylsilane (0.82g, 5.5 mmol) in acetonitrile (10 ml), as described in Method D, for 48 hours, to yield methyl 2-(2'-furyl)-2-(N-pyrrolidinyl)acetate (102a) (0.49g, 47%), b.p. 70–73°C/0.01 mmHg, ¹H n.m.r. (60 MHz), δ = 1.44–2.02 (4H, m, C(3’ and 4’))H), 2.30–2.88 (4H, m, C(2’ and 5’))H), 3.75 (3H, s, CH₃), 4.31 (1H, s, CH), 6.24–6.46 (2H, m, C(3) and 4’)H), and 7.31–7.47 (1H, m, C(5’)H) p.p.m., ν max. (film), 1752 (C=O), and 2808 (OCH) cm⁻¹; m/z (M⁺) 209.1059, C₁₃H₁₉NO₃ requires 209.1052.

3.6.2 Reaction of Furan with Methyl α-Methoxy-α-piperidylacetate using Trichloromethylsilane

Furan (0.52g, 7.7 mmol) and methyl α-methoxy-α-piperidylacetate (99b) (1.31g, 7 mmol) in acetonitrile (25 ml) were treated with trichloromethylsilane (1.15g, 7.7 mmol) in acetonitrile (15 ml), as described in Method D, for 39 hours, to yield methyl 2-(2'-furyl)-2-(N-piperidyl)acetate (102b) (0.92g, 58%), b.p. 82–85°C/0.01 mmHg, ¹H n.m.r. (60 MHz), δ = 1.19–1.83 (6H, m, C(3), 4” and 5”)H), 2.28–2.65 (4H, m, C(2” and 6”)H), 3.72 (3H, s, CH₃), 4.28 (1H, s, CH), 6.24–6.42 (2H, m, C(3’ and 4’)H), and 7.29–7.46 (1H, m, C(5’)H) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 24.4 (t, C(4”)), 26.2 (t, C(3” and 5”)), 51.7 (m, CH₃ and C(2” and 6”)), 67.0 (d, CH), 109.7 and 110.3 (d, C(3) and d, C(4’)), 142.6 (d, C(5’)), 149.7 (s, C(2’)), and 169.8 (s, CO₂CH₃) p.p.m., ν max. (film),
1738 (C=O), and 2808 (OCH) cm⁻¹; m/z (M⁺) 223.1212, C₁₂H₁₇NO₃ requires 223.1208.

3.6.3 Reaction of 2-Methylfuran with Methyl α-Methoxy-α-pyrrolidinylacetate using Trichloromethylsilane

2-Methylfuran (0.45g, 5.5 mmol) and methyl α-methoxy-α-pyrrolidinylacetate (99a) (0.87g, 5 mmol) in acetonitrile (20 ml) were treated with trichloromethylsilane (0.82g, 5.5 mmol) in acetonitrile (10 ml), as described in Method D, for 48 hours, to yield methyl 2-(5'-methyl-2'-furyl)-2-(N-pyrrolidinyl)acetate (102c), (0.72g, 64%), b.p. 98-100°C/0.01 mmHg, ¹H n.m.r. (60 MHz), δ = 1.58-1.96 (4H, m, C(3" and 4")H), 2.27 (3H, s, ArCH₃), 2.36-2.78 (4H, m, C(2" and 5")H), 3.70 (3H, s, CO₂CH₃), 4.18 (1H, s, CH), 5.80-5.99 (1H, m, C(4")H), and 6.22 (1H, d, Jₐₙ = 3 Hz, C(3")H) p.p.m., vₑₓₐₓ (film), 1752 (C=O), and 2800 (OCH) cm⁻¹; m/z (M⁺) 223.1210, C₁₂H₁₇NO₃ requires 223.1208.

3.6.4 Reaction of 2-Methylfuran with Methyl α-Methoxy-α-piperidylacetate using Trichloromethylsilane

2-Methylfuran (0.54g, 6.6 mmol) and methyl α-methoxy-α-piperidylacetate (99b) (1.12g, 6 mmol) in acetonitrile (20 ml) were treated with trichloromethylsilane (0.99g, 6.6 mmol) in acetonitrile (10 ml), as described in Method D, for 48 hours, to yield methyl 2-(5'-methyl-2'-furyl)-2-(N-piperidyl)acetate (102d) (1.29g, 91%), b.p. 112-15°C/0.2 mmHg, ¹H n.m.r. (60 MHz), δ = 1.13-1.87 (6H, m, C(3",4" and 5")H), 2.24-2.64 (4H, m, C(2" and 6")H), 2.26 (3H, s, ArCH₃), 3.71 (3H, s, CO₂CH₃), 4.17 (1H, s, CH), 5.77-5.96 (1H, m, C(4")H), and 6.19 (1H, d,
J_{AB} = 3 \text{ Hz}, \text{ C(3')} \text{ p.p.m., } ^{13}\text{C n.m.r. (20.1 MHz), } \delta = 13.5 \text{ (q, ArCH}_3\text{), 24.5 (t, C(4'')), 26.1 (t, C(3'' and 5'')), 51.7 (m, CH}_3\text{ and C(2' and 6'')), 67.3 (d, CH), 106.4 (d, C(3')), 110.7 (d, C(4')), and 147.5 and 152.4 (s, C(2) and s, C(5)), and 170.0 (s, CO}_2\text{CH}_3\text{) p.p.m., } \nu_{\text{max}} \text{(film), 1740 (C=O), and 2808 (OCH) cm}^{-1}; \text{ m/z (M}^+) \text{ 237.1367, C}_{13}\text{H}_{19}\text{N}_2\text{O}_3 \text{ requires 237.1365.}

**3.6.5 Reaction of Indole with Methyl α-Methoxy-α-pyrrolidinylacetate using Trichloromethylsilane**

Indole (0.64g, 5.5 mmol) and methyl α-methoxy-α-pyrrolidinylacetate (99a) (0.87g, 5 mmol) in acetonitrile (20 ml) were treated with trichloromethylsilane (0.82g, 5.5 mmol) in acetonitrile (10 ml), as described in Method D, for 48 hours to yield methyl 2-(3'-indolyl)-2-(N-pyrrolidinyl)acetate (102e) (1.03g, 80%) as an amorphous pale yellow solid, which gave one spot by t.l.c., R_t = 0.44 (ethyl acetate–petroleum ether 40–60 (1:4)), and R_f = 0.54 (ethyl acetate–petroleum ether 40–60 (2:3)).

^1\text{H n.m.r. (60 MHz), } \delta = 1.49–1.91 (4H, m, C(3'' and 4''))H), 2.34–2.83 (4H, m, C(2'' and 5''))H), 3.64 (3H, s, CH}_3\text{), 4.42 (1H, s, CH), 6.88–7.45 (4H, m, C(2', 5', 6' and 7')H), 7.58–7.92 (1H, m, C(4')H), and 9.41 (1H, br.s., D}_2\text{O ex., NH), p.p.m., } ^{13}\text{C n.m.r. (20.1 MHz), } \delta = 23.5 (t, C(3'' and 4''))H), 51.9 (q, CH}_3\text{), 52.4 (t, C(2' and 5'))H), 64.9 (d, CH), 111.4 (s, C(3')), 111.6 (d, C(7')), 119.2 (d, C(6')), 119.7 (d, C(4')), 122.0 (d, C(5')), 124.4 (d, C(2')), 125.3 (s, C(3'a'l)), 136.2 (s, C(7'a'l)), and 173.1 (s, CO}_2\text{CH}_3\text{) p.p.m., } \nu_{\text{max}} \text{(nujol) 1734 (C=O), 2852 (OCH), and 3404 (NH) cm}^{-1}; \text{ m/z (M}^+) \text{ 258.1372, C}_{15}\text{H}_{18}\text{N}_2\text{O}_2 \text{ requires 258.1368.
3.6.6 Reaction of Indole with Methyl α-Methoxy-α-piperidylacetate using Trichloromethylsilane

Indole (0.77g, 6.6 mmol) and methyl α-methoxy-α-piperidylacetate (99b) (1.12g, 6 mmol) in acetonitrile (20 ml) were treated with trichloromethylsilane (0.99g, 6.6 mmol) in acetonitrile (10 ml), as described in Method D, for 48 hours, to yield methyl 2-(3'-indoly)-2-(N-piperidyl)acetate (102f) (1.67g, 97%), as an amorphous white solid, which gave one spot by t.l.c., Rf = 0.22 (ethyl acetate–petroleum ether 40–60 (1:4)), and Rf = 0.67 (ethyl acetate–petroleum ether 40–60 (2:3)). 1H n.m.r. (60 MHz), δ = 1.09-1.78 (6H, m, C(3′), 4″ and 5″H), 2.21-2.77 (4H, m, C(2″ and 6″H)), 3.63 (3H, s, CH3), 4.41 (1H, s, CH), 6.87-7.45 (4H, m, C(2′, 5′, 6′ and 7′H), 7.60-7.95 (1H, m, C(4′)H), and 9.19 (1H, br.s, D2O ex., NH) p.p.m., 13C n.m.r. (20.1 MHz), δ = 24.4 (t, C(4″)H), 25.8 (t, C(3″ and 5″)), 51.7 (q, CH3), 52.3 (t, C(2″ and 6″)), 66.6 (d, CH), 110.1 (s, C(3′)), 111.6 (d, C(7′)), 119.5 (d, C(6′)), 119.7 (d, C(4′)), 122.0 (d, C(5′)), 124.7 (d, C(2′)), 127.4 (s, C(3′a)), 136.2 (s, C(7′a)), and 173.1 (s, CO2CH3) p.p.m., v max. (nujol), 1732 (C=O), 2852 (OCH), and 3396 (NH) cm⁻¹; m/z (M+) 272.1500, C16H20N2O2 requires 272.1525.

3.6.7 Reaction of N-Methylindole with Methyl α-Methoxy-α-pyrrolidinylacetate using Trichloromethylsilane

N-Methylindole (0.83g, 6.3 mmol) and methyl α-methoxy-α-pyrrolidinylacetate (99a) (1.00g, 5.77 mmol) in acetonitrile (25 ml) were treated with trichloromethylsilane (0.95g, 6.3 mmol) in acetonitrile (15 ml), as described in Method D, for 20 hours, to yield methyl 2-(N-methyl-3'-indoly)-2-(N-pyrrolidinyl)acetate (102g) (1.38g, 88%), as a viscous pale yellow oil, which gave one spot by t.l.c., Rf = 0.38 (ethyl acetate–petroleum ether 40–60 (1:4)), and Rf = 0.67 (ethyl acetate–
petroleum ether 40–60 (2:3)), $^1$H n.m.r. (60 MHz), $\delta = 1.53–1.97$ (4H, m, C(3" and 4")H), 2.30–2.78 (4H, m, C(2" and 5")H), 3.55 (3H, s, NCH$_3$), 3.59 (3H, s, CO$_2$CH$_3$), 4.37 (1H, s, CH), 6.93–7.27 (4H, m, C(2', 5', 6' and 7')H), and 7.63–7.94 (1H, m, C(4')H) p.p.m., $^{13}$C n.m.r. (20.1 MHz), $\delta = 23.4$ (t, C(3" and 4")), 32.6 (q, NCH$_3$), 51.7 (q, CO$_2$CH$_3$), 52.2 (t, C(2" and 5")), 64.7 (d, CH), 109.3 (d, C(7")), 110.5 (s, C(3")), 119.5 (d, C(6")), 119.6 (d, C(4")), 121.8 (d, C(5")), 127.4 (s, C(3'a)), 128.3 (d, C(2")), 136.9 (s, C(7'a)), and 172.7 (s, CO$_2$CH$_3$) p.p.m., $\nu_{\text{max}}$ (film), 1744 (C=O), and 2876 (OCH) cm$^{-1}$; m/z (M$^+$) 272.1514, C$_{10}$H$_{20}$N$_2$O$_2$ requires 272.1525.

3.6.8 Reaction of $N$-Methylindole with Methyl $\alpha$-Methoxy-$\alpha$-piperidylacetate using Trichloromethylsilane

$N$-Methylindole (1.01g, 7.7 mmol) and methyl $\alpha$-methoxy-$\alpha$-piperidylacetate (99b) (1.31g, 7 mmol) in acetonitrile (25 ml) were treated with trichloromethylsilane (1.15g, 7.7 mmol) in acetonitrile (15 ml), as described in Method D, for 39 hours, to yield methyl 2-($N$-methyl-3'-indolyO-2-($N$-piperidyOacetate (102h) (1.72g, 86%) as a viscous pale yellow oil, which gave one spot by t.l.c., $R_t = 0.62$ (ethyl acetate–petroleum ether 40–60 (1:4)), and $R_t = 0.81$ (ethyl acetate–petroleum ether 40–60 (2:3)), $^1$H n.m.r. (60 MHz), $\delta = 1.21–1.82$ (6H, m, C(3", 4" and 5")H), 2.27–2.75 (4H, m, C(2" and 6")H), 3.59 (3H, s, NCH$_3$), 3.63 (3H, s, CO$_2$CH$_3$), 4.39 (1H, s, CH), 6.92–7.28 (4H, m, C(2', 5', 6' and 7')H), and 7.64–7.93 (1H, m, C(4')H) p.p.m., $^{13}$C n.m.r. (20.1 MHz), $\delta = 24.5$ (t, C(4")), 26.1 (t, C(3" and 5")), 32.5 (q, NCH$_3$), 51.4 (q, CO$_2$CH$_3$), 52.0 (t, C(2" and 6")), 66.5 (d, CH), 109.2 (s, C(3")), 109.2 (d, C(7")), 119.4 (d, C(6")), 120.0 (d, C(4")), 121.8 (d, C(5")), 127.9 (s, C(3'a)), 128.7 (d, C(2")), 137.0 (s, C(7'a)), and 172.6 (s, CO$_2$CH$_3$) p.p.m., $\nu_{\text{max}}$ (film), 1734 (C=O), and 2852 (OCH) cm$^{-1}$; m/z (M$^+$) 286.1673, C$_{17}$H$_{22}$N$_2$O$_2$ requires 286.1681.
4.1.1 Preparation of 3-Methyl-1,3-oxazolidine (Aqueous Method)

Formaldehyde (33.03g, 1.1 mol, 36% aqueous solution) was added dropwise to a stirred solution of \( N \)-methylethanolamine (75.11g, 1 mol) at 0°C. The resulting solution was allowed to come to room temperature, stirred overnight and basified with solid sodium hydroxide. The oxazolidine did not separate, and thus the solution was continuously extracted with diethyl ether (600 ml) for 24 hours. The ether solution was fractionally distilled to yield 3-methyl-1,3-oxazolidine (104a) (44.4g, 51%), b.p. 98–99°C [lit.\(^{131}\), 97–99°C], \(^1\)H n.m.r. (60 MHz), \( \delta = 2.43 \) (3H, s, CH\(_3\)), 2.94 (2H, t, J = 7 Hz, NCH\(_2\)CH\(_2\)), 3.78 (2H, t, J = 7 Hz, OCH\(_2\)CH\(_2\)), and 4.24 (2H, s, NCH\(_2\)O) p.p.m., \(^{13}\)C n.m.r. (20.1 MHz, CD\(_2\)Cl\(_2\)), \( \delta = 41.8 \) (CH\(_3\)), 55.1 (NCH\(_2\)CH\(_2\)), 64.2 (OCH\(_2\)CH\(_2\)), and 89.3 (NCH\(_2\)O) p.p.m.; m/z (M\(^+\)) 87.0672, C\(_4\)H\(_9\)NO requires 87.0684.

4.1.2 Preparation of 3-Methyl-1,3-oxazolidine (Solvent-free Method)

\( N \)-Methylethanolamine (15.02g, 0.2 mol), paraformaldehyde (10.01g, 0.33 mol equiv.) and anhydrous potassium carbonate (11.06g, 0.08 mol) were heated under gentle reflux in an oil bath for 6 hours. The mixture was filtered, the solid residue was washed with 150 ml diethyl ether and the combined filtrates were dried. The ether solution was fractionally distilled to yield 3-methyl-1,3-oxazolidine (104a) (10.63–12.15g, 61–70%), b.p. 97–100°C.

4.1.3 Preparation of 3-Ethyl-1,3-oxazolidine

\( N \)-Ethylethanolamine (89.2g, 1 mol) and paraformaldehyde (33.0g, 1.1 mol equiv.) were heated together under gentle reflux in benzene (500 ml). Water
was azeotropically removed using a Dean and Stark trap. When the reaction was complete, the mixture was cooled and the benzene solution was fractionally distilled to give a mixture of 3-ethyl-1,3-oxazolidine (104b) and benzene (27.6g), b.p. 81–118°C, together with pure (104b) (62.6g, 62%), b.p. 118–19°C (lit., 122°C). 'H n.m.r. (60 MHz), δ = 1.12 (3H, t, J = 8.5 Hz, CH₃), 2.58 (2H, q, J = 8.5 Hz, CH₂CH₃), 2.93 (2H, t, J = 6.5 Hz, NCH₂CH₂), 3.79 (2H, t, J = 6.5 Hz, OCH₂CH₂), and 4.28 (2H, s, NCH₂O) p.p.m.; m/z (M⁺) 101.0828, C₆H₁₁NO requires 101.0841.

4.1.4 Preparation of 3-Ethyl-1,3-oxazolidine (Solvent-free Method)

N-Ethylethanolamine (35.6g, 0.4 mol), paraformaldehyde (18.0g, 0.6 mol equiv.) and anhydrous potassium carbonate (22.1g, 0.16 mol) were treated as described in 4.1.2, for 4.5 hours, to yield 3-ethyl-1,3-oxazolidine (104b) (25.0g, 62%), b.p. 119–21°C.

4.1.5 Preparation of 3-t-Butyl-1,3-oxazolidine

N-t-Butylethanolamine (58.6g, 0.5 mol) and paraformaldehyde (16.5g, 0.55 mol equiv.) in benzene (250 ml) were treated as described in 4.1.3, for 20 hours. Concentration in vacuo and fractional distillation gave a mixture of 3-t-butyl-1,3-oxazolidine (104c) and benzene (6.7g), b.p. 25–43°C/12 mmHg, together with pure (104c) (51.8g, 80%), b.p. 43°C/12 mmHg (lit., 63–64°C/32 mmHg), 'H n.m.r. (60 MHz), δ = 1.12 (9H, s, CH₃), 2.92 (2H, t, J = 6.5 Hz, NCH₂CH₂), 3.82 (2H, t, J = 6.5 Hz, OCH₂CH₂), and 4.40 (2H, s, NCH₂O) p.p.m.; ¹³C n.m.r. (67.8 MHz), δ = 27.0 (CH₃), 45.2 (NCH₂CH₂), 52.5 (CCH₃), 66.2 (OCH₂CH₂), and 81.0 (NCH₂O) p.p.m.; m/z (M⁺) 129.1142, C₇H₁₅NO requires 129.1154.
4.1.6 Preparation of 3-Benzyl-1,3-oxazolidine

N-Benzylethanolamine (75.6 g, 0.5 mol) and paraformaldehyde (16.5 g, 0.55 mol equiv.) in benzene (250 ml) were treated as described in 4.1.3, overnight. Concentration and distillation gave 3-benzyl-1,3-oxazolidine (104d) (74.7 g, 92%), b.p. 66–69°C/0.1 mmHg (lit. 184, 90–95°C/1.5 mmHg), \(^1\)H n.m.r (60 MHz), \(\delta = 2.89\) (2H, t, J = 7 Hz, NCH\(_2\)CH\(_2\)), 3.67 (2H, s, PhCH\(_2\)), 3.77 (2H, s, OCH\(_2\)CH\(_2\)), 4.30 (2H, s, NCH\(_2\)O), and 7.35 (5H, s, PhH) p.p.m., \(^{13}\)C n.m.r. (67.8 MHz), \(\delta = 51.7\) (NCH\(_2\)CH\(_2\)), 57.8 (PhCH\(_2\)), 63.1 (OCH\(_2\)CH\(_2\)), 86.4 (NCH\(_2\)O), 127.1 (C(4')), 128.2 (C(2' and 6')), 128.6 (C(3' and 5')), and 138.7 (C(1')) p.p.m.; m/z (M\(^+\)) 163.0972, C\(_{10}\)H\(_{13}\)NO requires 163.0997.

4.1.7 Preparation of 3-Phenyl-1,3-oxazolidine

2-Anilinoethanol (68.6 g, 0.5 mol) and paraformaldehyde (16.5 g, 0.55 mol equiv.) in benzene (250 ml) were treated as described in 4.1.3, overnight. Concentration and distillation gave 3-phenyl-1,3-oxazolidine (104e) (65.0 g, 87%), b.p. 68–72°C/0.1 mmHg (lit. 185, 94°C/1.5 mmHg), which solidified on cooling, m.p. 28°C (from pentane) (lit. 186, 28°C), \(^1\)H n.m.r. (270 MHz), \(\delta = 3.36\) (2H, t, J = 6 Hz, NCH\(_2\)CH\(_2\)), 4.11 (2H, t, J = 6 Hz, OCH\(_2\)CH\(_2\)), 4.82 (2H, s, NCH\(_2\)O), 6.48 (2H, d, J\(_{AC} = 8\) Hz, C(2' and 6')H), 6.75 (1H, t, J\(_{AB} = 8\) Hz, C(4'H), and 7.22 (2H, m, C(3' and 5')H) p.p.m., \(^{13}\)C n.m.r. (67.8 MHz), \(\delta = 46.0\) (NCH\(_2\)CH\(_2\)), 67.3 (OCH\(_2\)CH\(_2\)), 81.1 (NCH\(_2\)O), 112.5 (C(2' and 6')), 117.5 (C(4')), 129.3 (C(3' and 5')), and 145.6 (C(1')) p.p.m., m/z (M\(^+\)) 149.0837, C\(_9\)H\(_{11}\)NO requires 149.0841.
4.2.1 Reaction of Furan with 3-Methyl-1,3-oxazolidine using Chlorotrimethylsilane

Furan (0.75g, 11 mmol) and 3-methyl-1,3-oxazolidine (104a) (0.87g, 10 mmol) in acetonitrile (50 ml) were treated with chlorotrimethylsilane (1.20g, 11 mmol) in acetonitrile (25 ml), as described in Method D, for 48 hours, to yield 2-(N-2'-hydroxyethyl-N-methylaminomethyl)furan (111a) (0.47g, 30%), b.p. 52°C/0.35 mmHg, ¹H n.m.r. (60 MHz), δ = 2.27 (3H, s, CH₃), 2.57 (2H, t, J = 6 Hz, NCH₂CH₂), 3.63 (2H, s, ArCH₂), 3.64 (2H, t, J = 6 Hz, OCH₂), 4.59 (1H, s, D₂O ex.,OH), 6.12–6.40 (2H, m, C(3) and 4)H, and 7.30–7.44 (1H, m, C(5)H) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 41.8 (q, CH₂), 53.8 (t, NCH₂CH₂), 58.3 (t, ArCH₂), 59.0 (t, OCH₂), 108.1 and 110.1 (d, C(3) and d, C(4)), 142.1 (d, C(5)), and 152.0 (s, C(2)) p.p.m.; m/z (M⁺) 155.0947, C₈H₁₃NO₂ requires 155.0946.

Repeating the reaction using trichloromethylsilane (1.64g, 11 mmol) gave (111a) (1.17g, 75%).

4.2.2 Reaction of 2-Methylfuran with 3-Methyl-1,3-oxazolidine using Chlorotrimethylsilane

2-Methylfuran (0.90g, 11 mmol) and 3-methyl-1,3-oxazolidine (104a) (0.87g, 10 mmol) in acetonitrile (50 ml) were treated with chlorotrimethylsilane (1.20g, 11 mmol) in acetonitrile (25 ml), as described in Method D, for 48 hours, to yield 2-(N-2'-hydroxyethyl-N-methylaminomethyl)-5-methylfuran (111b) (1.33g, 79%), b.p. 63°C/0.45 mmHg, ¹H n.m.r. (60 MHz), δ = 2.25 (6H, s, NCH₃ and ArCH₃), 2.56 (2H, t, J = 6 Hz, NCH₂CH₂), 3.55 (2H, s, ArCH₂), 3.63 (2H, t, J = 6 Hz, OCH₂), 4.06 (1H, s, D₂O ex.,OH), 5.80–5.98 (1H, m, C(4)H), and 6.07 (1H, d, J₉₋₋₈ = 3 Hz, C(3)H) p.p.m.; νₘₐₓ (film), 3412 (OH) cm⁻¹; m/z (M⁺) 155.0947, C₈H₁₅NO₂ requires 155.0946.
169.1093, C9H15NO2 requires 169.1103.

Repeating the reaction using trichloromethylsilane (1.64g, 11 mmol) gave (111b) (1.47g, 87%).

4.2.3 Reaction of 2-Methylfuran with 3-Ethyl-1,3-oxazolidine using Chlorotrimethylsilane

2-Methylfuran (1.35g, 16.5 mmol) and 3-ethyl-1,3-oxazolidine (104b) (1.52g, 15 mmol) in acetonitrile (50 ml) were treated with chlorotrimethylsilane (1.79g, 16.5 mmol) in acetonitrile (25 ml), as described in Method D, for 44 hours, to yield 2-(N-ethyl-N-2'-hydroxyethylaminomethyl)-5-methylfuran (111c) (2.17g, 79%), b.p. 63–64°C/0.1 mmHg, 1H n.m.r. (60 MHz), δ = 1.03 (3H, t, J = 7 Hz, CH2CH3), 2.29 (3H, s, ArCH3), 2.57 (2H, q, J = 7 Hz, CH2CH3), 2.65 (2H, t, J = 5.5 Hz, NCH2CH2), 3.49 (1H, s, D2O ex., OH), 3.58 (2H, t, J = 5.5 Hz, OCH2), 3.65 (2H, s, ArCH2), 5.80–5.95 (1H, m, C(4)H), and 6.06 (1H, d, JAB = 3 Hz, C(3)H) p.p.m.; νmax (film), 3392 (OH) cm⁻¹; found: C, 65.15; H, 9.5; N, 7.7. C10H17NO2 requires C, 65.5; H, 9.35; N, 7.6%; m/z (M⁺) 183.1256, requires 183.1259.

Repeating the reaction using trichloromethylsilane (2.47g, 16.5 mmol) gave (111c) (2.44g, 89%).

4.2.4 Reaction of 2-Methylfuran with 3–t–Butyl-1,3-oxazolidine using Chlorotrimethylsilane

2-Methylfuran (1.35g, 16.5 mmol) and 3–t–butyl-1,3-oxazolidine (104c) (1.94g, 15 mmol) in acetonitrile (50 ml) were treated with chlorotrimethylsilane (1.79g, 16.5 mmol) in acetonitrile (25 ml), as
described in Method D, for 75 hours, to yield a mixture of 2-(N-t-butyl-N-2'-hydroxyethylaminomethyl)-S-methylfuran (111d) and (104c), b.p.<75°C/0.1 mmHg, together with pure (111d) (1.41g, 53%), b.p. 75-76°C/0.1 mmHg. H n.m.r. (60 MHz), δ = 1.16 (9H, s, CCH₃), 2.26 (3H, s, ArCH₃), 2.79 (2H, t, J = 5.5 Hz, NCH₂CH₂), 3.06 (1H, s, D₂O ex., OH), 3.39 (2H, t, J = 5.5 Hz, OCH₂), 3.69 (2H, s, ArCH₂), 5.83-5.98 (1H, m, C(4)H), and 6.07 (1H, d, J_AB = 3 Hz, C(3)H). ¹³C n.m.r. (20.1 MHz), δ = 13.5 (q, ArCH₃), 27.4 (q, CCH₃), 46.4 (t, NCH₂CH₂), 51.1 (t, ArCH₂), 54.9 (s, CCH₃), 60.3 (t, OCH₂), 106.3 and 108.1 (d, C(3) and d, C(4)), and 150.9 and 153.3 (d, C(2) and d, C(5)) p.p.m., ν max. (film), 3428 (OH) cm⁻¹; found: C, 68.0; H, 10.0; N, 6.6. C₁₂H₁₉NO₂ requires C, 68.2; H, 10.0; N, 6.6%; m/z (M⁺) 211.1557, requires 211.1572.

Repeating the reaction using trichloromethylsilane (2.47g, 16.5 mmol), for 44 hours, gave (111d) (2.70g, 85%).

4.2.5 Reaction of 2-Methylfuran with 3-Benzyl-1,3-oxazolidine and Chlorotrimethylsilane

2-Methylfuran (1.35g, 16.5 mmol) and 3-benzyl-1,3-oxazolidine (104d) (2.45g, 15 mmol) in acetonitrile (50 ml) were treated with chlorotrimethylsilane (1.79g, 16.5 mmol) in acetonitrile (25 ml), as described in Method D, for 20 hours, to yield 2-(N-benzyl-N-2'-hydroxyethylaminomethyl)-S-methylfuran (111e) (2.67g, 73%), b.p. 115-16°C/0.05 mmHg, ¹H n.m.r. (60 MHz), δ = 2.28 (3H, s, CH₃), 2.70 (2H, t, J = 5.5 Hz, NCH₂CH₂), 2.93 (1H, s, D₂O ex., OH), 3.59 (2H, t, J = 5.5 Hz, OCH₂), 3.63 (2H, s, ArCH₂), 3.66 (2H, s, PhCH₂), 5.85-6.01 (1H, m, C(4)H), 6.09 (1H, d, J_AB = 3 Hz, C(3)H), and 7.31 (5H, s, PhH) p.p.m., ν max. (film), 3420 (OH) cm⁻¹; m/z (M⁺) 245.1412, C₁₅H₁₉NO₂ requires 245.1416.
Repeating the reaction using trichloromethylsilane (2.47 g, 16.5 mmol) gave (111e) (3.02 g, 82%).

4.2.6 Reaction of 2-Methylfuran with 3-Phenyl-1,3-oxazolidine using Chlorotrimethylsilane

2-Methylfuran (1.35 g, 16.5 mmol) and 3-phenyl-1,3-oxazolidine (104e) (2.24 g, 15 mmol) in acetonitrile (50 ml) were treated with chlorotrimethylsilane (1.79 g, 16.5 mmol) in acetonitrile (25 ml), as described in Method D, for 24 hours, to give a crude brown oil. Fractional distillation using the Kugelröhre apparatus gave a fore-run of recovered (104e), b.p. 90–95°C/0.1 mmHg, together with 2-(N'-2'-hydroxyethyl-N'-phenylaminomethyl)-5-methylfuran (111f) (1.92 g, 55%), b.p. 125–28°C/0.05 mmHg, ¹H n.m.r. (60 MHz), δ = 2.20 (3H, s, CH₃), 2.68 (1H, s, D₂O ex., OH), 3.29–3.82 (4H, m, CH₂CH₂), 4.39 (2H, s, ArCH₂), 5.78–5.96 (1H, m, C(4)H), 6.03 (1H, d, Jₐₕ = 3 Hz, C(3)H), and 6.54–7.39 (5H, m, PhH) p.p.m., ν max. (film), 3376 (OH) cm⁻¹; m/z (M⁺) 231.1258, C₁₄H₁₇N₀₂ requires 231.1259.

Repeating the reaction using trichloromethylsilane (2.47 g, 16.5 mmol), for 15 hours, gave recovered (104e), together with (111f) (1.26 g, 36%).

4.3 Reaction of N-Methylpyrrole with 3-Methyl-1,3-oxazolidine using Chlorotrimethylsilane

N-Methylpyrrole (1.62 g, 22 mmol) and 3-methyl-1,3-oxazolidine (104a) (1.74 g, 20 mmol) in acetonitrile (50 ml) were treated at room temperature with chlorotrimethylsilane (2.17 g, 22 mmol) in acetonitrile (50 ml), as described in Method C, for 72 hours, to yield 2-(N'-2'-hydroxyethyl-N'-methylaminomethyl)-N-methylpyrrole (112) (2.47 g, 73%),
b.p. 69–70°C/0.12 mmHg, ¹H n.m.r. (60 MHz), δ = 2.18 (3H, s, NCH₃) 2.51 (2H, t, J = 5.5 Hz, NCH₂CH₂), 3.02 (1H, br.s, D₂O ex., OH), 3.45 (2H, s, ArCH₂), 3.54 (2H, t, J = 5.5 Hz, OCH₂), 3.60 (3H, s, ArCH₃), 5.99 (2H, d, J_ab = 2.5 Hz, C(3 and 4)D), and 6.46–6.63 (1H, m, C(5)H) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 33.6 (q, ArCH₃), 41.5 (q, NCH₃), 53.9 (t, NCH₂CH₂), 58.4 and 58.9 (t, ArCH₂ and t, OCH₂), 106.4 (d, C(4)), 109.7 (d, C(3)), 122.5 (d, C(5)), and 129.0 (s, C(2)) p.p.m., ν_max (film), 3404 (OH) cm⁻¹; m/z (M⁺) 168.1247, C₉H₁₆N₂O requires 168.1263.

Repeating the reaction using trichloromethylsilane (2.99g, 22 mmol) gave a crude brown oil. Fractional distillation using the Kugelrohr apparatus gave (112) (1.98g, 54%), b.p. 68–70°C/0.13 mmHg, together with impure 2,5-di-(N'-2'-hydroxyethyl-N'-methylaminomethyl)-N-methylpyrrole (113) (0.69g, 12%), b.p. 115–20°C/0.13 mmHg, ¹H n.m.r. (60 MHz), δ = 2.21 (6H, s, NCH₃), 2.50 (4H, t, J = 5.5 Hz, NCH₂CH₂), 3.47 (4H, s, ArCH₂), 3.55 (4H, t, J = 5.5 Hz, OCH₂), 3.61 (3H, s, ArCH₃), and 5.90 (2H, s, C(3 and 4)D) p.p.m., ν_max (film), 3416 (OH) cm⁻¹.

4.4.1 Reaction of Indole with 3-Benzyl-1,3-oxazolidine using Trichloromethylsilane

Indole (1.93g, 16.5 mmol) and 3-benzyl-1,3-oxazolidine (104d) (2.45g, 15 mmol) in acetonitrile (50 ml) were treated with trichloromethylsilane (2.47g, 16.5 mmol) in acetonitrile (25 ml), as described in Method D, for 20 hours, to give a pale orange solid. Recrystallisation using activated charcoal gave 3-(N'-benzyl-N'-2'-hydroxyethylaminomethyl)indole (123a) (3.52g, 84%) as colourless plates, m.p. 104–105°C (from diethyl ether–petroleum ether 40–60), ¹H n.m.r. (60 MHz), δ = 2.63 (2H, t, J = 5.3 Hz, NCH₂CH₂), 2.65 (1H, s, D₂O ex., OH), 3.55 (2H, t, J = 5.3 Hz, OCH₂), 3.62 (3H, s, ArCH₂),
3.78 (2H, s, PhCH₂), 6.82–7.38 (4H, m, C(2, 5, 6 and 7)H), 7.27 (5H, s, PhH), 7.42–7.70 (1H, m, C(4)H), and 8.22 (1H, br.s, D₂O ex., NH) p.p.m., ν max. (KBr), 3288 (NH), and 3412 (OH) cm⁻¹; found: C, 77.5; H, 7.3; N, 9.7. C₁₈H₂₀N₂O requires C, 77.1; H, 7.2; N, 10.0%; m/z (M⁺) 280.1598, requires 280.1576.

4.4.2 Reaction of N-Methylindole with 3-Methyl-1,3-oxazolidine using Chlorotrimethylsilane

N-Methylindole (1.44g, 11 mmol) and 3-methyl-1,3-oxazolidine (104a) (0.87g, 10 mmol) in acetonitrile (35 ml) were treated with chlorotrimethylsilane (1.20g, 11 mmol) in acetonitrile (15 ml), as described in Method D, for 20 hours, to give a viscous yellow liquid. Column chromatography on alumina (grade 3) with methanol–chloroform (1:9) gave 3-(N'-2'-hydroxyethyl-N'-methylaminomethyl)-N-methylindole (123b) (1.45g, 67%) as a very pale yellow oil, ¹H n.m.r. (60 MHz), δ = 2.22 (3H, s, NCH₃), 2.53 (2H, t, J = 5.5 Hz, NCH₂CH₂), 3.38 (1H, s, D₂O ex., OH), 3.58 (2H, t, J = 5.5 Hz, OCH₂), 3.61 (3H, s, ArCH₃), 3.69 (2H, s, ArCH₂), 6.83 (1H, s, C(2)H), 6.95–7.31 (3H, m, C(5,6 and 7)H), and 7.52–7.82 (1H, m, C(4)H) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 32.0 (q, CH₃), 41.7 (q, NCH₃), 52.6 (t, NCH₂CH₂), 58.4 and 58.9 (t, ArCH₂ and t, OCH₂), 109.1 (d, C(7)), 110.8 (s, C(3)), 119.0 (d, C(6)), 119.2 (d, C(4)), 121.4 (d, C(5)), 128.4 (d, C(2)), 128.4 (s, C(3a)), and 137.0 (s, C(7a)) p.p.m., ν max (film), 3388 (OH) cm⁻¹; m/z (M⁺) 218.1408, C₁₃H₁₈N₂O requires 218.1419.

Repeating the reaction on a 25 mmol scale using trichloromethylsilane (4.10g, 27.5 mmol) gave (123b) (4.92g, 91%), b.p. 137–39°C/0.02 mmHg, after Kugelröhr distillation.
The Mannich base (123b) was further characterised as its hydrochloride salt. Thus dry ethereal hydrogen chloride was added in fine droplets to a solution of (123b) (2.00g, 9.2 mmol) in dry ether (200 ml) until no further precipitation occurred. The solid was filtered and washed with dry ether. Recrystallisation using activated charcoal gave the amine hydrochloride (2.28g, 98%) as white crystals, m.p. 126.5–27.5°C (decomp.) (from dichloromethane–petroleum ether 40–60; found: C, 61.3; H, 7.7; N, 10.7. C_{13}H_{19}ClN_{2}O requires C, 61.3; H, 7.7; N, 11.0%.

4.4.3 Reaction of N-Methylindole with 3-Ethyl-1,3-oxazolidine using Chlorotrimethylsilane

N-Methylindole (2.16g, 16.5 mmol) and 3-ethyl-1,3-oxazolidine (104b) (1.52g, 15 mmol) in acetonitrile (50 ml) were treated with chlorotrimethylsilane (1.79g, 16.5 mmol) in acetonitrile (25 ml), as described in Method D, for 44 hours, to give 3-((N'-ethyl-N'-2'-hydroxyethylaminomethyl)-N-methylindole (123c) (2.15g, 62%) as a yellow oil, \( ^1\)H n.m.r. (60 MHz), \( \delta = 1.05 \) (3H, t, J = 7.5 Hz, CH\(_2\)CH\(_3\)), 2.28–2.78 (4H, m, CH\(_2\)CH\(_3\) and NCH\(_2\)CH\(_2\)), 3.05 (1H, s, D\(_2\)O ex., OH), 3.49 (2H, t, J = 5.5 Hz, OCH\(_2\)), 3.63 (3H, s, NCH\(_3\)), 3.77 (2H, s, ArCH\(_2\)), 6.86 (1H, s, C(2)H), 6.90–7.47 (3H, m, C(5, 6 and 7)H), and 7.51–7.75 (1H, m, C(4)H) p.p.m., \( v_{\text{max}} \) (film), 3408 (OH) cm\(^{-1}\); m/z (M\(^+\)) 232.1590, C\(_{14}\)H\(_{20}\)N\(_2\)O requires 232.1576.

Repeating the reaction using trichloromethylsilane (2.47g, 16.5 mmol) gave (123c) (3.26g, 94%).

The corresponding hydrochloride salt was prepared from the Mannich base (123c) (1.80g, 7.7 mmol), as described in 4.4.2. Recrystallisation using activated charcoal gave the amine hydrochloride (2.03g, 97%) as white
crystals, m.p. 156.5–57.5°C (from dichloromethane–petroleum ether 40–60); found: C, 62.5; H, 8.1; N, 10.4. \( \text{C}_{14}\text{H}_{2}\text{ClN}_{2}\text{O} \) requires C, 62.5; H, 7.9; N, 10.4%.

4.4.4 Reaction of \( N \)-Methylindole with 3-Benzyl-1,3-oxazolidine using Chlorotrimethylsilane

\( N \)-Methylindole (2.16g, 16.5 mmol) and 3-benzyl-1,3-oxazolidine (104d) (2.45g, 15 mmol) in acetonitrile (50 ml) were treated with chlorotrimethylsilane (0.79g, 16.5 mmol) in acetonitrile (25 ml), as described in Method D, for 24 hours, to yield a viscous pale yellow oil. Dry flash chromatography on t.l.c. grade silica with ethyl acetate–petroleum ether 40–60 (100% – 0%) gave 3-(\( N' \)-benzyl-\( N' \)-2'-hydroxyethylamino-methyl)-\( N \)-methylindole (123d) (4.2180 95%) as a viscous colourless oil which would not crystallise, \( ^1\text{H} \) n.m.r. (60 MHz), \( \delta = 2.56 \) (2H, t, \( J = 5.5 \) Hz, NCH\textsubscript{2}CH\textsubscript{2}), 2.77 (1H, s, D\textsubscript{2}O ex., OH), 3.40 (3H, s, NCH\textsubscript{3}), 3.49 (2H, t, OCH\textsubscript{2}), 3.53 (2H, s, ArCH\textsubscript{2}), 3.70 (2H, s, PhCH\textsubscript{2}), 6.75 (1H, m, C(2)\textsubscript{H}), 6.80–7.38 (3H, m, C(5, 6 and 7)\textsubscript{H}), and 7.47–7.68 (1H, m, C(2)\textsubscript{H}) p.p.m., \( \nu \text{max.} \) (film), 3428 (OH) cm\textsuperscript{-1}; m/z (M\textsuperscript{+}) 294.1726, \( \text{C}_{19}\text{H}_{22}\text{N}_{2}\text{O} \) requires 294.1732.

Repeating the reaction using trichloromethylsilane (2.47g, 16.5 mmol) gave (123d) (3.82g, 86%).

The corresponding hydrochloride salt was prepared from the Mannich base (123d) (2.37g, 8.05 mmol), as described in 4.4.2. Recrystallisation using activated charcoal gave the amine hydrochloride (2.63g, 99%) as white needles, m.p. 135.5–36.5°C (from dichloromethane–petroleum ether 40–60); found: C, 68.9; H, 7.2; N, 8.15. \( \text{C}_{19}\text{H}_{22}\text{ClN}_{2}\text{O} \) requires C, 68.95; H, 7.0; N, 8.5%.
4.5.1 Preparation of 3,4-Dimethyl-5-phenyloxazolidine

\( (1R,2S) \)-Ephedrine (125) (33.05 g, 0.2 mol), paraformaldehyde (6.61 g, 0.22 mol equiv.) and potassium carbonate (30.41 g, 0.22 mol) in benzene (300 ml) were heated under gentle reflux for 6 hours. The mixture was filtered, washed with diethyl ether and the combined filtrates were dried. The solution was concentrated \textit{in vacuo} and distilled to give 3,4-dimethyl-5-phenyloxazolidine (128) (33.10 g, 93%), b.p. 70°C/0.1 mmHg \textit{lit.}^48, 80°C/0.5 mmHg, \( \delta \) H n.m.r. (60 MHz), \( \delta = 0.67 \) (3H, d, J = 6.5 Hz, \( \text{CH}_3 \)), 2.29 (3H, s, NCH\(_3\)), 2.53–3.05 (1H, m, \( \text{CH}_3\text{CH} \)), 4.01 and 4.81 (1H, d, J = 3 Hz and 1H, d, J = 3 Hz, \( \text{CH}_2 \)), 5.06 (1H, d, J = 7.5 Hz, \( \text{PhCH} \)), and 7.27 (5H, s, PhH) p.p.m., \( \delta \) C n.m.r. (20.1 MHz), \( \delta = 14.2 \) (q, \( \text{CH}_3 \)), 37.5 (q, \( \text{NCH}_3 \)), 63.4 (d, \( \text{CH}_3\text{CH} \)), 82.0 (d, \( \text{PhCH} \)), 88.2 (t, \( \text{CH}_2 \)), 127.1 (d, C(2' and 6')), 127.3 (d, C(4')), 127.9 (d, C(3' and 5')), and 140.2 (s, C(1')) p.p.m., \([\alpha]_2^{27} + 10.8^\circ \) (CHCl\(_3\); m/z (M\(^+\)) 177.1126, \( \text{C}_{11}\text{H}_{15}\text{NO} \) requires 177.1153.

4.5.2 Reaction of 2-Methylfuran with 3,4-Dimethyl-5-phenyloxazolidine using Chlorotrimethylsilane

2-Methylfuran (0.90 g, 11 mmol) and 3,4-dimethyl-5-phenyloxazolidine (128) (1.77 g, 10 mmol) in acetonitrile (50 ml) were treated with chlorotrimethylsilane (1.20 g, 11 mmol) in acetonitrile (25 ml), as described in Method D, for 48 hours. Fractional distillation using the Kugelröhr apparatus gave (128) (1.11 g, 63% recovered), b.p. 60–63°C/0.04 mmHg, together with 2-(N-methyl-N-(5′-methyl-2′-furylmethyl)amino)-1-phenyl-1-propanol (129b) (0.64 g, 25%), b.p. 100–10°C/0.04 mmHg, \( \delta \) H n.m.r. (60 MHz), \( \delta = 0.89 \) (3H, d, J = 6.5 Hz, \( \text{CCH}_3 \)), 2.26 (3H, s, \text{ArCH}_3), 2.28 (3H, s, NCH\(_3\)), 2.61–3.12 (1H, m, \( \text{CH}_3\text{CH} \)), 3.64 (2H, s, \( \text{CH}_2 \)), 3.82 (1H, s, \( \text{D}_2\text{O ex. OH} \)), 4.91 (1H, d, J = 4 Hz, \( \text{PhCH} \)), 5.82–6.00 (1H, m, C(4')H),
6.04 (1H, d, $J_{AB} = 3$ Hz, C(3′)H), and 7.33 (5H, s, PH) p.p.m., $^{13}$C n.m.r. (20.1 MHz), $\delta = 9.8$ (q, CCH$_3$), 13.5 (q, ArCH$_3$), 39.1 (q, NCH$_3$), 51.1 (t, CH$_2$), 62.4 (d, CH$_3$CH), 72.9 (d, PhCH), 106.0 (d, C(3′)), 109.4 (d, C(4′)), 126.2 (d, C(2′ and 6′)), 126.8 (d, C(4′)), 127.9 (d, C(3′ and 5′)), 142.9 (s, C(1′)), and 150.8 and 151.5 (s, C(2′) and s, C(5′)) p.p.m., which was contaminated with (128) (0.08g, 5% recovered) (determined by $^1$H n.m.r.).

Repeating the reaction using trichloromethylsilane (1.64g, 11 mmol) gave (128) (0.19g, 11% recovered), together with pure 2-(N-methyl-N-(5′-methyl-2′-furylmethylamino)-1-phenyl-1-propanol (2.08g, 80%), b.p. 105–108°C/0.03 mmHg, $\nu_{max}$ (film), 3432 (OH) cm$^{-1}$, $[\alpha]_D^{20} = 1.9^\circ$ (CHCl$_3$); found: C, 74.05; H, 8.0; N, 5.5. C$_{15}$H$_{21}$N$_2$O$_2$ requires C, 74.1; H, 8.15; N, 5.4%.

4.6.1 Reaction of 2-Methylfuran with 3-Methyl-1,3-oxazolidine using $t$-Butylchlorodimethylsilane

2-Methylfuran (0.90g, 11 mmol) and 3-methyl-1,3-oxazolidine (104a) (0.87g, 10 mmol) in acetonitrile (75 ml) were stirred at 0°C under a still head of nitrogen. $t$-Butylchlorodimethylsilane (130) (1.66g, 11 mmol) was added in one portion, and stirring was continued for 48 hours. The solvent was removed in vacuo and the residue was partitioned between pentane-diethyl ether (9:1) (50 ml) and saturated sodium bicarbonate solution (50 ml). The organic layer was removed and the aqueous layer was extracted with pentane-ether (50 ml). The combined organic layers were extracted with bicarbonate solution (50 ml), dried over sodium sulphate and concentrated in vacuo. The residue was distilled using the Kugelröhr apparatus to yield 2-(N-2′-$t$-butoxyethyl-N-methylaminomethyl)-5-methylfuran (132) (0.91g, 32%), b.p. 78°C/0.03 mmHg, $^1$H n.m.r. (60 MHz), $\delta = 0.06$ (6H, s, SiCH$_3$), 0.90 (9H, s, CCH$_3$), 2.26 (3H, s, ArCH$_3$),
2.30 (3H, s, NCH₃), 2.56 (2H, t, J = 6 Hz, NCH₂CH₂), 3.54 (2H, s, ArCH₂), 3.76 (2H, t, J = 6 Hz, OCH₂), 5.80–5.98 (1H, m, C(4)H), and 6.07 (1H, d, J_AB = 3 Hz, C(3)H) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = -5.8 (q, SiCH₃), 13.1 (q, ArCH₃), 17.8 (s, CCH₃), 25.5 (q, CCH₂), 42.4 (q, NCH₃), 54.1 (t, NCH₂CH₂), 58.2 (t, ArCH₂), 61.4 (t, OCH₂), 105.5 (d, C(3)), 108.9 (d, C(4)), and 150.2 and 151.0 (s, C(2) and s, C(5)) p.p.m., ν_max (film) 1106 (SiO) cm⁻¹; found: C, 63.5; H, 10.0; N, 4.95. C₁₅H₂₉N₂O₂Si requires C, 63.55; H, 10.0; N, 5.3%; m/z (M⁺) 283.1964, requires 283.1967.

Repeating the reaction, for 14 days, gave (132) (1.86g, 66%).

Repeating the reaction, with the addition of 1,2,4-triazole (133) (0.76g, 11 mmol), for 72 hours, gave (132) (1.72g, 61%).

4.6.2 Reaction of N-Methylindole with 3-Methyl-1,3-oxazolidine using t-Butylchlorodimethylsilane

N-Methylindole (1.15g, 8.8 mmol) and 3-methyl-1,3-oxazolidine (104a) (0.70g, 8 mmol) in acetonitrile (40 ml) were treated with t- butylchlorodimethylsilane (130) (1.33g, 8.8 mmol) and 1,2,4-triazole (133) (0.61g, 8.8 mmol), as described in 4.6.1, for 72 hours, to give a pale yellow liquid. Fractional distillation using the Kugelröhr apparatus gave 3-(N'-2'-t-butoxyethyl-N'-methylaminomethyl)-N-methylindole (134) (1.36g, 51%), b.p. 133–34°C/0.007 mmHg, ¹H n.m.r. (60 MHz), δ = 0.04 (6H, s, SiCH₃), 0.90 (9H, s, CCH₃), 2.28 (3H, s, NCH₃), 2.59 (2H, t, J = 6 Hz, NCH₂CH₂), 3.61 (3H, s, ArCH₃), 3.73 (2H, s, ArCH₂), 3.78 (2H, t, J = 6 Hz, OCH₂), 6.82–7.32 (4H, m, C(2), 5, 6 and 7)H, and 7.57–7.90 (1H, m, C(4)H) p.p.m., ν_max (film) 1102 (SiO) cm⁻¹; m/z (M⁺) 332.2295, C₁₉H₃₂N₂O₂Si requires 332.2284.
Repeating the reaction on a 10 mmol scale using 4-N,N-dimethylaminopyridine (1.34g, 10 mmol) gave (134) (1.76g, 53%), b.p. 138°C/0.005 mmHg.

4.7.1 Preparation of 2-(N-2'-chloroethyl-N-methylaminomethyl)-5-methylfuran

The alcohol (111b) (5.43g, 32 mmol) and carbon tetrachloride (5.38g, 35 mmol) in dry ether (25 ml) were stirred at -40°C (dry ice-acetone) under a still head of nitrogen. Hexamethylphosphorus triamide (137) (6.36 ml, 35 mmol) in dry ether (25 ml) was added dropwise by syringe. The resulting mixture was allowed to warm to room temperature and stirred for 1.5 hours during which time two layers separated. Water (25 ml) was added and the ethereal layer was separated, washed with water (25 ml), dried, and concentrated in vacuo. The resulting yellow liquid was distilled using the Kugelrohr apparatus to yield 2-(N-2'-chloroethyl-N-methylaminomethyl)-5-methylfuran (141) (3.36g, 54%), b.p. 75-76°C/0.5 mmHg, ¹H n.m.r. (60 MHz), δ = 2.27 (3H, s, ArCH₃), 2.33 (3H, s, NCH₃), 2.74 (2H, t, J = 7 Hz, NCH₂CH₂), 3.55 (2H, t, J = 7 Hz, OCH₂), 3.58 (2H, s, ArCH₂), 5.82-6.06 (1H, m, C(4)H), and 6.13 (1H, d, Jₐₙ = 3 Hz, C(3)H) p.p.m.; m/z (M⁺) 187.0738 and 189.0737, C₉H₁₄ClNO requires 187.0734 and 189.0734.

4.7.2 Preparation of 5-Methyl-2-(N-methylaminomethyl)furan

The β-chloroamine (141) (0.62g, 3.3 mmol), anhydrous sodium iodide (0.49g, 3.3 mmol) and zinc powder (0.43g, 0.0066g atom) in glacial acetic acid (10 ml) were subjected to ultrasonication for 1 hour, and then heated under gentle reflux for 1.75 hours in an apparatus protected from moisture.
The resulting mixture was added to 2M hydrochloric acid (25 ml) and extracted with ether (2 x 15 ml). The aqueous layer was basified with 4M sodium hydroxide, extracted with ether (3 x 30 ml), and the combined ether extracts were washed with water (2 x 30 ml), dried, and concentrated in vacuo using a cold water bath. The residual brown liquid was distilled using the Kugelröhr apparatus to yield 5-methyl-2-(N-methylaminomethyl)furan (136) (0.32g, 61%), b.p. 76-78°C/13 mmHg, 1H n.m.r. (60 MHz), δ = 1.67 (1H, s, D₂O ex., NH), 2.28 (3H, s, ArCH₃), 2.43 (3H, s, NCH₃), 3.69 (2H, s, CH₂), 5.83-6.01 (1H, m, C(4)H), and 6.09 (1H, d, Jₐₕ = 3 Hz, C(3)H) p.p.m., ν max. (film) 3328 (NH) cm⁻¹; m/z (M⁺) 125.0836, C₇H₁₁NO requires 125.0841.

4.8.1 Preparation of Ethyl Glyoxylate

Diethyl tartrate (143) (41.24g, 0.2 mol) was stirred in dry ether (360 ml) under nitrogen, and cooled with a cold water bath. Periodic acid (144) (45.60g, 0.2 mol) was added in portions over a period of 1 hour and the milky reaction mixture was stirred for a few minutes longer until the ether was almost clear and the white solid had separated. The ether phase was decanted, dried over 4Å molecular sieves (7.5g) and concentrated in vacuo. The residue was distilled from phosphorus pentoxide (7g) and decanted onto fresh phosphorus pentoxide (5g). Redistillation gave ethyl glyoxylate (145) (21.79g, 52%) as a mobile pale yellow liquid which became colourless and viscous on standing, b.p. 46-48°C/20 mmHg (lit. 40-45°C/22 mmHg), 1H n.m.r. (60 MHz), δ = 1.37 (3H, t, J = 7 Hz, CH₃), 4.30 (2H, q, J = 7 Hz, CH₂), and 9.31 (1H, s, CHO) p.p.m.
4.8.2 Preparation of Methyl Glyoxylate

Methyl dimethoxyacetate (97) (31.5 g, 236 mmol), glyoxylic acid monohydrate (146) (21.0 g, 228 mmol) and para-toluenesulphonic acid monohydrate (0.15 g) were heated together at 80°C for 18 hours. The resulting syrup was cooled in ice-methanol and phosphorus pentoxide (24 g) was added in portions. The mixture was distilled, and redistillation from phosphorus pentoxide (10 g) gave methyl glyoxylate (147) (25.8 g, 64%) as a pale yellow liquid, b.p. 49-51°C/20 mmHg (lit. 50-59°C/25 mmHg).

\[ ^1H \text{n.m.r.} (60 \text{ MHz}), \delta = 4.95 (3H, s, CH}_3 \text{), and 9.41 (1H, s, CHO) p.p.m. \]

4.8.3 Preparation of 2-Methoxycarbonyl-3-methyl-1,3-oxazolidine

Freshly distilled methyl glyoxylate (147) (21.0 g, 238 mmol) and N-methylethanolamine (110a) (17.9 g, 238 mmol) in benzene (250 ml) were treated as described in 4.1.3, for 3 hours. The residue was filtered to remove solid, concentrated \textit{in vacuo} and distilled to yield 2-methoxycarbonyl-3-methyl-1,3-oxazolidine (148) (17.6 g, 51%), b.p. 38-40°C/1 mmHg, \(^1H\) n.m.r. (360 MHz), 2.45 (3H, s, NCH)_3, 2.72 (1H, dt, NCH), 3.17 (1H, dt, NCH), 3.68 (3H, s, CO_2CH)_3, 3.69-4.01 (2H, m, OCH_2), and 4.48 (1H, s, CH) p.p.m., \(^13C\) n.m.r. (90.6 MHz), \( \delta = 41.2 (\text{NCH}_3), 51.9 (\text{CO}_2\text{CH}_3), 53.3 (\text{NCH}_2), 65.5 (\text{OCH}_2), 93.5 (\text{CH}), \text{and 170.3 (CO}_2\text{CH}_3) \text{ p.p.m.}, \nu_{\text{max.}} \text{ (film)} 1750 (\text{C=O}) \text{ cm}^{-1}. \]

4.8.4 Preparation of 2-Ethoxycarbonyl-3-methyl-1,3-oxazolidine

Freshly distilled ethyl glyoxylate (145) (6.61 g, 65 mmol) and N-methylethanolamine (110a) (4.86 g, 65 mmol) in benzene (200 ml) were treated as described in 4.1.3, for 1 hour, to yield
2-ethoxycarbonyl-3-methyl-1,3-oxazolidine (8.03 g, 58%), b.p. 40–42°C/0.7 mmHg. 1H n.m.r. (360 MHz), δ = 1.31 (3H, t, J = 7.2 Hz, CH₂CH₃), 2.54 (3H, s, NCH₃), 2.81 (1H, dt, NCH), 3.27 (1H, dt, NCH), 3.98–4.10 (2H, m, OCH₂), 4.16–4.25 (2H, m, CH₂CH₃), and 4.54 (1H, s, CH) p.p.m., 13C n.m.r. (90.6 MHz), δ = 13.8 (CH₂CH₃), 41.0 (NCH₃), 53.2 (NCH₂), 60.7 (CH₂CH₃), 65.3 (OCH₂), 93.3 (CH), and 169.7 (CO₂CH₂) p.p.m., ν max. (film) 1748 (C=O) cm⁻¹; m/z (M⁺) 159.0886, C₇H₁₃NO₃ requires 159.0895.

4.8.5 Reaction of 2-Methylfuran with 2-Methoxycarbonyl-3-methyl-1,3-oxazolidine using Thionyl Chloride

2-Methylfuran (1.07 g, 13 mmol) and 2-methoxycarbonyl-3-methyl-1,3-oxazolidine (148) (1.70, 11.7 mmol) in acetonitrile (40 ml) were treated with thionyl chloride (1.55 g, 13 mmol) (freshly distilled from quinoline) in acetonitrile (20 ml), as described in Method D, for 64 hours. The black reaction mixture gave a pale yellow liquid on acid-base extraction, which was distilled using the Kugelrohr apparatus to yield methyl 2-(5'-methyl-2'-furyl)-2-(N-2''-chloroethyl-N-methylamino)acetate (149) (1.20 g, 42%), b.p. 96–98°C/0.01 mmHg. 1H n.m.r. (60 MHz), δ = 2.29 (3H, s, ArCH₃), 2.44 (3H, s, NCH₃), 2.68–3.12 (2H, m, NCH₂), 3.28–3.67 (2H, m, CH₂CH₂), 3.75 (3H, s, CO₂CH₂), 4.52 (1H, s, CH), 5.87–6.05 (1H, m, C(4)H), and 6.22 (1H, d, JAB = 3 Hz, C(3)H) p.p.m., ν max. 1740 (C=O) cm⁻¹; found: C, 53.5; H, 6.5; N, 5.7; Cl, 14.7. C₁₄H₁₈ClNO₃ requires C, 53.8; H, 6.6; N, 5.7; Cl, 14.4%; m/z (M⁺) 245.0834 and 247.0836, requires 245.0819 and 247.0789.
5.1.1 Preparation of 1,3-Dimethylimidazolidine

\(N,N'\)-dimethylethylenediamine (154) (16.68 g, 189 mmol), paraformaldehyde (6.25 g, 208 mmol equiv.) and anhydrous potassium carbonate (28.76 g, 208 mmol) were heated under reflux in benzene (300 ml) for 6 hours. The reaction mixture was filtered and most of the benzene was removed by distillation through a 15 cm Vigreux column. The residue was carefully fractionated using a 38 cm Vigreux column to yield 1,3-dimethylimidazolidine (152) (7.17 g, 38%), b.p. 108-111°C (lit. \(^{163}\) 114°C), \(^1\)H n.m.r. (60 MHz), \(\delta = 2.39\) (6H, s, NCH\(_3\)), \(2.79\) (4H, NCH\(_2\)CH\(_2\)), and \(3.32\) (2H, s, NCH\(_2\)N) p.p.m., \(^{13}\)C n.m.r. (20.1 MHz), \(\delta = 41.6\) (q, NCH\(_3\)), 54.9 (t, NCH\(_2\)CH\(_2\)), and 80.2 (t, NCH\(_2\)N) p.p.m.

5.1.2 Reaction of 2-Methylfuran with 1,3-Dimethylimidazolidine using Trichloromethylsilane

2-Methylfuran (0.72 g, 8.8 mmol) and 1,3-dimethylimidazolidine (152) (0.80 g, 8 mmol) in acetonitrile (40 ml) were treated with trichloromethylsilane (0.32 g, 8.8 mmol) in acetonitrile (20 ml), as described in Method D, for 48 hours, to yield \(N,N'\)-dimethyl-N-(5'-methyl-2'-furylmethyl)ethylene diamine (155a) (1.28 g, 71%), b.p. 66°C/ 0.05 mmHg, \(^1\)H n.m.r. (60 MHz), \(\delta = 1.58\) (1H, s, D\(_2\)O ex., NH), 2.24 (6H, ArCH\(_3\) and NCH\(_3\)), 2.43 (3H, s, NHCH\(_2\)) 2.46-2.77 (4H, m, CH\(_2\)CH\(_2\)), 3.48 (2H, s, ArCH\(_2\)), 5.76-5.95 (1H, m, C(4)H), and 6.01 (1H, d, J\(_{AB}\) = 3 Hz, C(3)H) p.p.m., \(^{13}\)C n.m.r. (20.1 MHz), \(\delta = 13.5\) (q, ArCH\(_3\)), 36.5 (q, NHCH\(_3\)), 42.1 (q, NCH\(_3\)), 49.6 (t, CH\(_2\)NCH\(_2\)), 54.3 (t, ArCH\(_2\)), 56.0 (t, NHCH\(_2\)), 106.6 (d, C(3)), 109.3 (d, C(4)), and 150.7 and 151.4 (s, C(2) and s, C(5)) p.p.m.; found: C, 65.5; H, 9.7; N, 15.5. \(C_{10}H_{18}N_2O\) requires C, 65.8; H, 9.95; N, 15.4%; m/z (M\(^+\)) 182.1412, requires 182.1419.
5.2.1 Preparation of 3,4-Dihydro-3,8-dimethyl-2H-1,3-benzoxazine

Methylamine (12.4g, 0.4 mol, 25% aqueous solution) was added slowly to a stirred ice-cooled solution of formaldehyde (24.0g, 0.8 mol, 36% aqueous solution) in 1,4-dioxane (150 ml). *ortho*-Cresol (43.2g, 0.4 mol) in 1,4-dioxane (50 ml) was added dropwise and the mixture was heated under reflux for 3 hours. The reaction mixture was concentrated in vacuo, and 6M sodium hydroxide (35 ml) was added to the residue. The mixture was partitioned between diethyl ether (100 ml) and saturated sodium sulphate (100 ml), and the aqueous layer was then washed with ether (2 x 50 ml). The combined ether extracts were washed with saturated sodium sulphate (50 ml), dried and concentrated in vacuo. The residue was distilled to yield 3,4-dihydro-3,8-dimethyl-2H-1,3-benzoxazine (162a) (26.3g, 40%), b.p. 80–82°C/0.1 mmHg (lit. 80–90°C/0.3 mmHg), ¹H n.m.r. (60 MHz), δ = 2.18 (3H, s, PhCH₃), 2.54 (3H, s, NCH₃), 3.57 (2H, s, PhCH₂), 4.74 (2H, s, NCH₂O), and 6.62–7.18 (3H, m, PhH) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 15.5 (q, PhCH₃), 39.6 (q, NCH₃), 52.4 (t, PhCH₂), 83.9 (t, NCH₂O), 119.3 (s, C(6)), 120.0 (d, C(4a)), 125.1 (d, C(8)), 125.4 (s, C(5)), 128.9 (d, C(7)), and 152.1 (s, C(8a)) p.p.m.; m/z (M⁺) 163.0987, C₁₀H₁₃NO requires 163.0997.

5.2.2 Preparation of 3,4-Dihydro-3,6-dimethyl-2H-1,3-benzoxazine

Methylamine (12.4g, 0.4 mol, 25% aqueous solution), formaldehyde (24.0g, 0.8 mol, 36% aqueous solution) and *para*-cresol (43.2g, 0.4 mol) in 1,4-dioxane (200 ml) were treated as described in 5.2.1, except that the product was extracted between diethyl ether and 0.1M potassium hydroxide. The crude oily solid was crystallised from propan-2-ol, and a small amount was sublimed for spectral analysis, to give 3,4-dihydro-3,6-dimethyl-2H-1,3-benzoxazine (162b) (54.1g, 83%), m.p. 49°C (sublimed) (lit. 165, 47–50°C).
49–49.5°C, $^1$H n.m.r. (60 MHz), $\delta$ = 2.24 (3H, s, PhCH$_3$), 2.59 (3H, s, NCH$_3$), 3.90 (2H, s, PhCH$_2$), 4.74 (2H, s, NCH$_2$O), and 6.54–7.06 (3H, m, PhH) p.p.m., $^{13}$C n.m.r. (20.1 MHz), $\delta$ = 20.6 (q, PhCH$_3$), 39.8 (q, NCH$_3$), 52.3 (t, PhCH$_2$), 83.8 (t, NCH$_2$O), 116.2 (d, C(8)), 119.7 (s, C(4a)), 128.0 (d, C(5)), 128.4 (d, C(7)), 129.9 (s, C(6)), and 151.6 (s, C(3a)) p.p.m.; m/z (M$^+$) 163.0986, C$_{16}$H$_{13}$NO requires 163.0997.

5.2.3 Reaction of 2-Methylfuran with 3,4-Dihydro-3,8-dimethyl-2H-1,3-benzoxazine using Chlorotrimethylsilane

2-Methylfuran (0.90g, 11 mmol) and the benzoxazine (162a) (1.63g, 10 mmol) in acetonitrile (50 ml) were treated with chlorotrimethylsilane (1.20g, 11 mmol) in acetonitrile (25 ml), as described in Method D, for 48 hours, to yield 6-methyl-2-(N-methyl-N-(5'-methyl-2'-furylmethyl)aminomethyl)phenol (163a) (0.60g, 24%), b.p. 90–100°C/0.02 mmHg, $^1$H n.m.r. (60 MHz), $\delta$ = 2.26 (9H, s, ArCH$_3$, PhCH$_3$ and NCH$_3$), 3.56 (2H, s, ArCH$_2$), 3.66 (2H, s, PhCH$_2$), 5.82–5.98 (1H, m, C(4')H), 6.11 (1H, d, $J_{AB}$ = 3 Hz, C(3')H), and 6.51–7.20 (3H, m, PhH) p.p.m., $^{13}$C n.m.r. (20.1 MHz), $\delta$ = 13.5 (q, ArCH$_3$), 15.7 (q, PhCH$_3$), 40.9 (q, NCH$_3$), 52.6 (t, ArCH$_2$), 59.8 (t, PhCH$_2$), 106.3 (d, C(3)), 110.3 (d, C(4)), 118.6 (d, C(5)), 121.2 (s, C(6)), 124.8 (s, C(2)), 125.1 (d, C(5)), 126.3 (d, C(3)), and 148.8 and 152.1 (s, C(2) and s, C(3)), and 156.3 (s, C(1)) p.p.m., which was contaminated with (162a) (0.79g, 48% recovered) (determined by $^1$H n.m.r.).

Repeating the reaction using dichlorodimethylsilane (1.42g, 11 mmol) gave (163a) (0.71g, 29%), which was contaminated with (162a) (0.86g, 53% recovered) (determined by $^1$H n.m.r.).
Repeating the reaction using trichloromethylsilane gave pure (163a) (2.07 g, 84%), b.p. 97-100°C/0.02 mmHg, $\nu_{\text{max}}$ 3428 (OH) cm$^{-1}$; m/z (M$^+$) 245.1417. $C_{15}H_{19}NO_2$ requires 245.1416.

5.2.4 Reaction of 2-Methylfuran with 3,4-Dihydro-3,6-dimethyl-2H-1,3-benzoazaine using Chlorotrimethylsilane

2-Methylfuran (0.90 g, 11 mmol) and the benzoxazine (162b) (1.63 g, 10 mmol) in acetonitrile (50 ml) were treated with chlorotrimethylsilane (1.20 g, 11 mmol) in acetonitrile (25 ml), as described in Method D, for 48 hours, to yield 4-methyl-2-(N-methyl-N-(5'-methyl-2'-furylmethyldiaminomethyl)phenol (163b) (1.20 g, 49%), b.p. 100-107°C/0.03 mmHg. $^1$H n.m.r. (60 MHz), $\delta$ = 2.22 (3H, s, PhCH$_3$), 2.25 (6H, s, ArCH$_3$ and NCH$_3$), 3.55 (2H, s, ArCH$_2$), 3.63 (2H, s, PhCH$_2$), 5.78-5.94 (1H, m, C(4')H), 6.08 (1H, d, $J_{AB}$ = 3 Hz, C(3')H), 6.60-7.07 (3H, m, PhH), and 10.23 (1H, br.s, D$_2$O ex., OH) p.p.m. $^{13}$C n.m.r. (20.1 MHz), $\delta$ = 13.4 (q, ArCH$_3$), 20.4 (q, PhCH$_3$), 41.0 (q, NCH$_3$), 52.7 (t, ArCH$_2$), 59.8 (t, PhCH$_2$), 106.3 (d, C(3)), 110.3 (d, C(4')), 116.0 (d, C(6)), 121.7 (s, C(4)), 127.8 (s, C(2)), 129.2 (d, C(3) and d, C(5)), and 148.9 and 152.1 (s, C(2) and s, C(5')), and 155.8 (s, C(1)) p.p.m., which was contaminated with (162b) (0.39, 24% recovered) (determined by $^1$H n.m.r.).

Repeating the reaction using dichlorodimethylsilane (1.42 g, 11 mmol) gave pure (163b) (1.72 g, 72%), b.p. 105-107°C/0.03 mmHg.

Repeating the reaction using trichloromethylsilane (1.42 g, 11 mmol) gave pure (163b) (1.92 g, 78%), $\nu_{\text{max}}$ 3104 (OH) cm$^{-1}$; found: C, 73.2; H, 7.7; N, 6.0. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%; m/z (M$^+$) 245.1402, requires 245.1416.
5.2.5 Reaction of N-Methylindole with 3,4-Dihydro-3,8-dimethyl-2H-1,3-benzoxazine using Trichloromethylsilane

N-Methylindole (2.16g, 16.5 mmol) and the benzoxazine (162a) (2.45g, 15 mmol) in acetonitrile (50 ml) were treated with trichloromethylsilane (2.47g, 16.5 mmol) in acetonitrile (25 ml), as described in Method D, for 22 hours. The crude solid obtained from extraction was dissolved in diethyl ether and treated with activated charcoal. Crystallisation at -22°C gave 6-methyl-2-((N-methyl-N-(N'-methyl-3'-indolylmethyl)aminomethyl)phenol (163c) (3.68g, 83%), as white needles, m.p. 91.5–92°C (from diethyl ether–petroleum ether 40–60). 1H n.m.r. (60 MHz), δ = 2.19 (3H, s, PhCH₃), 2.23 (3H, s, NCH₃), 3.60 (3H, s, ArCH₃), 3.66 and 3.69 (2H, s, PhCH₂ and 2H, s, ArCH₂), 6.46–7.32 (7H, m, PhH and C(2', 5', 6' and 7)H), 7.45–7.75 (1H, m, C(4)H), and 11.16 (1H, br.s, D₂O ex., OH p.p.m., ν max. (KBr) 3415 (OH) cm⁻¹; found: C, 77.5; H, 7.5; N, 9.4. C₁₅H₂₂N₂O requires C, 77.5; H, 7.5; N, 9.5%; m/z (M⁺) 294.1729, requires 294.1732.

5.2.6 Reaction of N-Methylindole with 3,4-Dihydro-3,6-dimethyl-2H-1,3-benzoxazine using Trichloromethylsilane

N-Methylindole (4.32g, 33 mmol) and the benzoxazine (162b) (4.90g, 30 mmol) in acetonitrile (100 ml) were treated with trichloromethylsilane (4.94g, 33 mmol) in acetonitrile (50 ml), as described in Method D, for 22 hours. The crude solid obtained from extraction was dissolved in diethyl ether and treated with activated charcoal. Crystallisation at -22°C gave 4-methyl-2-((N-methyl-N-(N'-methyl-3'-indolylmethyl)aminomethyl)phenol (163d) (6.62g, 72%), as white crystals, m.p. 111–12°C (from diethyl ether–petroleum ether 40–60). 1H n.m.r. (60 MHz), δ = 2.20 (6H, s, PhCH₃ and NCH₃), 3.62 (3H, s, ArCH₃), 3.65 and 3.71 (2H, s, PhCH₂ and 2H, s, ArCH₂), 6.59–7.34 (7H, m, PhH and C(2', 5', 6' and 7)H), 7.44–7.76
(1H, m, C(4')H), and 10.82 (1H, br.s, D$_2$O ex., OH) p.p.m. $\nu$$_{max}$ (KBr), 3420 (OH) cm$^{-1}$; m/z (M$^+$) 294.1728, C$_{19}$H$_{22}$N$_2$O requires 294.1732.

5.3.1 Preparation of 2,4-Dimethoxyphenyltrimethylsilane

1-Bromo-2,4-dimethoxybenzene (9.15g, 43.6 mmol) in dry THF (25 ml) was added dropwise to a stirred mixture of chlorotrimethylsilane (4.89g, 45 mmol) and magnesium turnings (1.22g, 0.05g atom) in THF (50 ml). The mixture was heated under reflux for 4 hours and then added to ice. The mixture was acidified with 2M sulphuric acid, and the organic layer was separated. The aqueous layer was extracted with ether (2 x 50 ml) and the combined organic layers were washed with saturated sodium bicarbonate (50 ml) and water (2 x 50 ml). The ether solution was dried, concentrated $in$ $vacuo$ and distilled to yield 2,4-dimethoxyphenyltrimethylsilane (168) (6.31g, 69%), b.p. 92-93°C/2.5 mmHg, $^1$H n.m.r. (60 MHz), $\delta$ = 0.23 (9H, s, SiCH$_3$), 3.78 (6H, s, OCH$_3$), 6.40-6.61 (2H, m, C(3)H and C(6)H), and 7.26 (1H, d, J = 7.5 Hz, C(5)H) p.p.m.; m/z (M$^+$) 210.1067, C$_{11}$H$_{18}$O$_2$Si requires 210.1076.

5.3.2 Reaction of 2,4-Dimethoxyphenyltrimethylsilane with N-Morpholinyl(methyleneliminium Chloride

Arylsilane (168) (2.52g, 12 mmol) and iminium salt (22f) (1.63g, 12 mmol) in acetonitrile (50 ml) were treated as described in Method F, for 2 hours, to yield N-(2,4-dimethoxybenzyl)morpholine (169) (1.42g, 60%), b.p. 100-10°C/0.01 mmHg, $^1$H n.m.r. (90 MHz), $\delta$ = 2.30-2.63 (4H, m, C(2 and 6)H), 3.47 (2H, s, CH$_2$), 3.49-3.81 (4H, m, C(3 and 5)H), 3.77 (6H, s, OCH$_3$), 6.33-6.63 (2H, m, C(5' and 6')H), and 7.20 (1H, d, J$_{AB}$ = 8.5 Hz, C(3')H) p.p.m.; m/z (M$^+$) 237.1359, C$_{19}$H$_{19}$NO$_3$ requires 237.1365.
5.4.1 Preparation of Phenyltri-n-butylstannane

Bromobenzene (34.54g, 0.22 mol) was added to dry magnesium turnings (4.86g, 0.2g atom) in dry THF (100 ml) under a still head of nitrogen, with the addition of a crystal of iodine to initiate reaction. The reaction was completed by heating under gentle reflux for 2 hours. Tri-n-butyltin chloride (32.55g, 0.1 mol) in THF (25 ml) was then added dropwise to maintain gentle reflux, and the reaction was heated under gentle reflux overnight. The mixture was cooled, poured onto ice–ammonium chloride, and acidified with 2M sulphuric acid. The solution was extracted with ether (3 x 100 ml) and the combined ethereal extracts were washed with saturated sodium bicarbonate (100 ml) and water (2 x 100 ml). The ether solution was stirred with saturated ethanolic potassium fluoride (100 ml) for 2 hours, filtered, dried and concentrated in vacuo. The residue was fractionally distilled to yield phenyltri-n-butylstannane (170a) (30.34g, 83%), b.p. 119ºC/0.4 mmHg (lit.186, 139ºC/0.6 mmHg), ¹H n.m.r. (60 MHz), δ = 0.53–1.83 (27H, m, BuH), and 7.10–7.61 (5H, m, PhH) p.p.m.

5.4.2 Preparation of o-Tolyltri-n-butylstannane

o-Bromotoluene (37.63g, 0.22 mol), magnesium (4.86g, 0.2g atom) and tri-n-butyltin chloride (32.55g, 0.1 mol) were treated as described in 5.4.1 to yield o-tolyltri-n-butylstannane (170b) (29.84g, 78%), b.p. 143–45ºC/0.45 mmHg , ¹H n.m.r. (60 MHz), δ = 0.60–1.87 (27H, m, BuH), 2.39 (3H, s, PhCH₃), and 7.00–7.57 (4H, m, PhH) p.p.m.
5.4.3 Preparation of 4-Methoxyphenyltri-n-butylstannane

4-Bromoanisole (174.5g, 0.97 mol), magnesium (21.4g, 0.88g atom) and tri-n-butyltin chloride (130.2g, 0.40 mol) were treated as described in 5.4.1 to yield 4-methoxyphenyltri-n-butylstannane (170c) (129.3g, 81%), b.p. 160–62°C/0.8 mmHg (lit.\(^{188}\), 158–60°C/0.5 mmHg), \(^1H\) n.m.r. (60 MHz), \(\delta = 0.57–1.84\) (27H, m, Bu\(\text{H}\)), 3.74 (3H, s, OCH\(_3\)), and 6.69–7.51 (2H, AA'BB'q, J\(_{AB}\) = 8.5 Hz, Ph\(\text{H}\)) p.p.m.,

5.4.4 Preparation of 4-Methoxyphenyltrimethylstannane

4-Bromoanisole (26.97g, 0.15 mol), magnesium (3.40g, 0.14g atom) and trimethyltin chloride (19.93g, 0.10 mol) were treated as described in 5.4.1 to yield 4-methoxyphenyltrimethylstannane (170d), (15.89g, 59%), b.p. 96°C/2.4 mmHg (lit.\(^{189}\), 102°C/3.5 mmHg), \(^1H\) n.m.r. (60 MHz), \(\delta = 0.27\) (9H, s, SnCH\(_3\)), 3.74 (3H, s, OCH\(_3\)), and 6.80–7.58 (4H, AA'BB'q, J\(_{AB}\) = 8 Hz, Ph\(\text{H}\)) p.p.m.,

5.5.1 Preparation of N-Benzylpyrrolidine

Phenyltri-n-butylstannane (170a) (1.84g, 5 mmol) and N-pyrrolidinyl-(methylene)iminium chloride (22d) (0.66g, 5.5 mmol) in acetonitrile (50 ml) were treated as described in Method E, for 20 hours, to yield N-benzylpyrrolidine (171a) (0.09g, 11%), b.p. 55°C/1.5 mmHg (lit.\(^{190}\), 116–22°C/22 mmHg), \(^1H\) n.m.r. (60 MHz), \(\delta = 1.67–1.97\) (4H, m, C(3 and 4)\(\text{H}\)), 2.38–2.77 (4H, m, C(2 and 5)\(\text{H}\)), 3.64 (2H, s, CH\(_2\)), and 7.30 (5H, br.s, Ph\(\text{H}\)) p.p.m.; m/z (M\(^+\)) 161.1198, C\(_{11}\)H\(_{15}\)N requires 161.1204.
5.5.2 Preparation of *N*-Benzylmorpholine

Phenyltri-*n*-butylstannane (170a) (1.84g, 5 mmol) and *N*-morpholinyl-(methylene)iminium chloride (22f) (0.75g, 5.5 mmol) in acetonitrile (50 ml) were treated as described in Method E, for 20 hours, to yield *N*-benzylmorpholine (171b) (0.13g, 15%), b.p. 62-64°C/1.5 mmHg (lit.¹⁹¹, 128-29°C/13 mmHg), ¹H n.m.r. (60 MHz), δ = 2.27-2.58 (4H, m, C(3 and 5)H), 3.47 (2H, s, CH₂), 3.55-3.84 (4H, m, C(2 and 6)H, and 7.28 (5H, br.s, PhH) p.p.m.; m/z (M⁺) 177.1151, C₁₇H₂₅NO requires 177.1154.

5.5.3 Preparation of *N*-(2-Methylbenzyl)pyrrolidine

o-Tolyltrin-*n*-butylstannane (170b) (1.91g, 5 mmol) and *N*-pyrrolidinyl(methylene)iminium chloride (22d) (0.66g, 5.5 mmol) in acetonitrile (50 ml) were treated as described in Method E, for 20 hours, to yield *N*-(2-methylbenzyl)pyrrolidine (171c) (0.11g, 13%), b.p. 90°C/0.7 mmHg (lit.¹⁹², 113-15°C/12 mmHg), ¹H n.m.r. (60 MHz), δ = 1.60-1.92 (4H, m, C(3 and 4)H), 2.34-2.70 (4H, m, C(2 and 5)H), 2.35 (3H, s, PhCH₃), 3.59 (2H, s, CH₂), and 7.20 (4H, br.s, PhH) p.p.m.; m/z (M⁺) 175.1349, C₁₂H₁₇N requires 175.1361.

5.5.4 Preparation of *N*-(2-Methylbenzyl)morpholine

o-Tolyltrin-*n*-butylstannane (170b) (1.91g, 5 mmol) and *N*-morpholinyl(methylene)iminium chloride (22f) (0.75g, 5.5 mmol) in acetonitrile (50 ml) were treated as described in Method E, for 20 hours, to yield *N*-(2-methylbenzyl)morpholine (171d) (0.11g, 12%), b.p. 106°C/0.9 mmHg (lit.¹⁹³, 149-51°C/10 mmHg), ¹H n.m.r. (60 MHz), δ = 2.30-2.57.
(4H, m, C(3 and 5)H), 2.35 (3H, s, PhCH₃), 3.45 (2H, s, CH₂), 3.57–3.83 (4H, m, C(2 and 6)H), and 7.17 (4H, br.s, PhH) p.p.m.; m/z (M⁺) 191.1307; C₁₂H₁₉NO requires 191.1310.

5.5.5 Preparation of 4-Methoxy-N,N-diethylbenzylamine

4-Methoxyphenyltrimethylstannane (170d) (1.35g, 5 mmol) and N,N-diethyl(methylene)iminium chloride (22b) (0.67g, 5.5 mmol) in acetonitrile (50 ml) were treated as described in Method E, for 20 hours, to yield 4-methoxy-N,N-diethylbenzylamine (171e) (0.22g, 23%), b.p. 99°C/1 mmHg (lit.¹⁹, 126°C/15 mmHg); ¹H n.m.r. (60 MHz), δ = 1.03 (6H, t, J = 7 Hz, CH₂CH₃), 3.68 (3H, s, OCH₃), and 6.64–7.31 (4H, AA'BB'q, Jₐₙ = 8.5 Hz, PhH) p.p.m.; m/z (M⁺) 193.1447; C₁₂H₁₉NO requires 193.1467.

Repeating the reaction using 4-methoxyphenyltri-n-butylstannane (170c) (1.98g, 5 mmol), for 28 hours, gave (171e) (0.25g, 26%).

5.5.6 Preparation of N-(4-Methoxybenzyl)pyrrolidine

4-Methoxyphenyltrimethylstannane (170d) (1.35g, 5 mmol) and N-pyrrolidinyl(methylene)iminium chloride (22d) (0.66g, 5.5 mmol) in acetonitrile (50 ml) were treated as described in Method E, for 20 hours, to yield N-(4-methoxybenzyl)pyrrolidine (171g) (0.31g, 33%), b.p. 120°C/3 mmHg; ¹H n.m.r. (60 MHz), δ = 1.62–1.96 (4H, m, C(3 and 4)H), 2.29–2.70 (4H, m, C(2 and 5)H), 3.53 (2H, s, CH₂), 3.76 (3H, s, CH₃), and 6.63–7.47 (4H, AA'BB'q, Jₐₙ = 8 Hz, PhH) p.p.m.; ¹³C n.m.r. (20.1 MHz), δ = 23.5 (t, C(3 and 4)), 54.1 (t, C(2 and 5)), 55.2 (q, CH₃), 60.1 (t, CH₂), 113.7 (d, C(2' and 6')), 130.1 (d, C(3' and 5')), 131.7 (s, C(1)), and 158.8 (s,
C(4') p.p.m.; m/z (M⁺) 191.1305, C₁₂H₁₇NO requires 191.1310.

Repeating the reaction using 4-methoxyphenyltri-n-butylstannane (170c) (1.98g, 5 mmol), for 68 hours, gave (171g) (0.22g, 23%).

5.5.7 Preparation of N-(4-Methoxybenzyl)morpholine

4-Methoxyphenyltrimethylstannane (170d) (1.35g, 5 mmol) and N-morpholinylmethyleneiminium chloride (22f) (0.75g, 5.5 mmol) in acetonitrile (50 ml) were treated as described in Method E, for 20 hours, to yield N-(4-methoxybenzyl)morpholine (171h) (0.63g, 59%), b.p. 122°C/0.8 mmHg (lit.195, 136–39°C/1 mmHg), ¹H n.m.r. (60 MHz), δ = 2.23–2.60 (4H, m, C(3 and 5)H), 3.40 (2H, s, CH₂), 3.53–3.90 (4H, m, C(2 and 6)H), 3.77 (3H, s, CH₃), and 6.70–7.40 (4H, AA'BB'q, JAB = 10 Hz, PhH) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 53.6 (t, C(3 and 5)), 55.0 (q, CH₃), 62.8 (t, CH₂), 66.9 (t, C(2 and 6)), 113.7 (d, C(2' and 6')), 129.9 (s, C(1')), 130.3 (d, C(3' and 5')), and 158.9 (s, C(4')) p.p.m.; m/z (M⁺) 207.1256, C₁₂H₁₇NO₂ requires 207.1259.

Repeating the reaction using 4-methoxyphenyltri-n-butylstannane (170c) (3.97g, 10 mmol), for 43 hours, gave (171h) (1.11g, 53%).

5.6.1 "In Situ" Preparation of N-Benzylimorpholine

Phenyltri-n-butylstannane (170a) (1.84g, 5 mmol) and di-(N-morpholinylmethylene)methane (56f) (1.02g, 5.5 mmol) in acetonitrile (35 ml) were treated with trichloromethylsilane (0.82g, 5.5 mmol) in acetonitrile (15 ml), as described in Method F, for 26 hours, to yield N-benzylimorpholine (171b) (0.18g, 20%).
Repeating the reaction using ethoxy-N-morpholinylmethane (0.80g, 5.5 mmol) gave (171b) (0.26g, 29%).

5.6.2 "In Situ" Preparation of \(N,N-2\)-Trimethylbenzylamine

\(\sigma\)-Tolyltri-n-butylstannane (170b) (1.91g, 5 mmol) and \(N,N\)-dimethylamino-iso-propyloxymethane (0.64g, 5.5 mmol) in acetonitrile (35 ml) were treated with chlorotrimethylsilane (0.60g, 5.5 mmol) in acetonitrile (15 ml), as described in Method F, for 25 hours, to yield \(N,N-2\)-trimethylbenzylamine (171i) (0.14g, 19%), b.p. 65°C/1 mmHg (lit.\(^{196}\), 73–75°C/10 mmHg), \(^1\)H n.m.r. (60 MHz), \(\delta = 2.15 (6H, s, NCH\_3), 2.30 (3H, s, PhCH\_3), 3.22 (2H, s, CH\_2), and 7.20 (4H, br.s, PhH) p.p.m..

Repeating the reaction using trichloromethylsilane (0.82g, 5.5 mmol) gave (171i) (0.10g, 13%).

5.6.3 "In Situ" Preparation of \(N-(2\)-Methylbenzyl)morpholine

\(\sigma\)-Tolyltri-n-butylstannane (170b) (1.91g, 5 mmol) and di-(N-morpholinylmethane (56f) (1.02g, 5.5 mmol) in acetonitrile (35 ml) were treated with trichloromethylsilane (0.82g, 5.5 mmol) in acetonitrile (15 ml), as described in Method F, for 25 hours, to yield \(N-(2\)-methylbenzyl)morpholine (171d) (0.17g, 18%).

5.6.4 "In Situ" Preparation of 4-Methoxy-\(N,N\)-dimethylbenzylamine

4-Methoxyphenyltri-n-butylstannane (170c) (1.99g, 5 mmol) and bis-(\(N,N\)-dimethylamino)methane (56a) (0.56g, 5.5 mmol) in acetonitrile
(35 ml) were treated with chlorotrimethylsilane (0.60 g, 5.5 mmol) in acetonitrile (15 ml), as described in Method F, for 42 hours, to yield 4-methoxy-\(N,N\)-dimethylbenzylamine (171) (0.37 g, 45%), b.p. 122–24°C/18 mmHg (lit. \(^{187}\), 104–106°C/12 mmHg), \(^1H\) n.m.r. (60 MHz), \(\delta = 2.20\) (6 H, s, NCH\(_3\)), 3.35 (2 H, s, CH\(_2\)), 3.80 (3 H, s, CH\(_3\)), and 6.75–7.25 (4 H, AA'BB'q, \(J_{AB} = 9\) Hz, PhH) p.p.m., \(^{13}C\) n.m.r. (20.1 MHz), \(\delta = 45.2\) (q, NCH\(_3\)), 55.0 (q, OCH\(_3\)), 63.8 (t, CH\(_2\)), 113.7 (d, C(2 and 6)), 130.2 (d, C(3 and 5)), 131.1 (s, C(1)), and 158.9 (s, C(4)) p.p.m.; m/z (M\(^+\)) 165.1146, C\(_{10}\)H\(_{15}\)NO requires 165.1153.

Repeating the reaction using trichloromethylsilane (0.82 g, 5.5 mmol), for 68 hours, gave (171) (0.53 g, 65%).

Repeating the reaction using 4-methoxyphenyltrimethylstannane (170c) (0.85 g, 3.1 mmol) and \(N,N\)-dimethylamino-iso-propyloxymethane (0.43 g, 3.7 mmol), for 24 hours, gave (171) (0.32 g, 62%).

5.6.5 "In Situ" Preparation of 4-Methoxy-\(N,N\)-diethylbenzylamine

4-Methoxyphenyltri-\(n\)-butylstannane (170c) (3.98 g, 10 mmol) and ethoxy-\(N,N\)-diethylaminomethane (61a) (1.44 g, 11 mmol) in acetonitrile (70 ml) were treated with trichloromethylsilane (1.64 g, 11 mmol) in acetonitrile (30 ml), as described in Method F, for 42 hours, to yield 4-methoxy-\(N,N\)-diethylbenzylamine (171e) (0.38 g, 20%).

5.6.6 "In Situ" Preparation of \(N\)-(4-Methoxybenzyl)pyrrolidine

4-Methoxyphenyltri-\(n\)-butylstannane (170c) (3.98 g, 10 mmol) and di-(\(N\)-pyrrolidinyl)methane (56d) (1.70 g, 11 mmol) in acetonitrile (70 ml)
were treated with trichloromethylsilane (1.64 g, 11 mmol) in acetonitrile (30 ml), as described in Method F, for 42 hours, to yield N-(4-methoxybenzyl)pyrrolidine (171g) (0.72 g, 38%).

5.6.7 "In Situ" Preparation of N-(4-Methoxybenzyl)morpholine

4-Methoxyphenyltri-n-butylstannane (170c) (3.98 g, 10 mmol) and di-(N-morpholinyl)methane (56f) (2.05 g, 11 mmol) in acetonitrile (70 ml) were treated with trichloromethylsilane (1.64 g, 11 mmol) in acetonitrile (30 ml), as described in Method F, for 28 hours, to yield N-(4-methoxybenzyl)morpholine (171h) (1.12 g, 53%).

Repeating the reaction using 4-methoxyphenyltrimethylstannane (170d) (0.85 g, 3.1 mmol), ethoxy-N-morpholinylmethane (0.54 g, 3.7 mmol) and chlorotrimethylsilane (0.40 g, 3.7 mmol) gave (171h) 0.25 g, 38%.

5.7.1 Preparation of Ethylidene-iso-propylamine

Acetaldehyde (17.62 g, 0.4 mol) was added dropwise to stirred, ice-cooled iso-propylamine (23.64 g, 0.4 mol). Potassium hydroxide pellets were then added and the organic layer was separated and dried over fresh pellets overnight. The liquid was distilled, firstly from potassium hydroxide, and then from barium oxide, under nitrogen, to yield ethylidene-iso-propylamine (173a) (25.88 g, 76%), b.p. 61–63°C (lit.177, 58–59°C/754 mmHg), 1H n.m.r. (60 MHz), δ = 1.11 (6H, d, J = 6 Hz, CHCH₃), 1.89 (d, J = 5 Hz, N=CHCH₃), 3.27 (1H, sept., J = 6 Hz, N–CH), and 7.67 (1H, q, J = 5 Hz, N=CH) p.p.m., 13C n.m.r. (20.1 MHz), δ = 22.2 (q, CHCH₃), 24.2 (q, N=CHCH₃), 61.2 (d, CHCH₃), and 157.8 (d, N=CH) p.p.m., v max (film) 1672 (C=N) cm⁻¹.
5.7.2 Preparation of *iso*-Butylidene-*iso*-propylamine

*iso*-Butyraldehyde (28.85g, 0.4 mol) and *iso*-propylamine (23.64g, 0.4 mol) were treated as described in 5.7.2 to yield *iso*-butylidene-*iso*-propylamine (173b) (27.65g, 61%), b.p. 98–101°C (lit.77, 100°C), \(^1\)H n.m.r. (60 MHz), \(\delta = 0.87–1.33 (12\text{H}, \text{m, CHCH}_3), 2.07–2.80 (1\text{H, m, NCH=CH}), 3.30 (1\text{H, sept., J = 6.5 Hz, C=NCH}), \text{and 7.46 (1H, d, J = 5.5 Hz, N=CH)} \text{p.p.m.}.

5.8.1 Reaction of Ethylidene-*iso*-propylamine with Pyrrole

Ethylidene-*iso*-propylamine (173a) (1.87g, 22 mmol) in benzene (4 ml) was added dropwise to a stirred solution of pyrrole (1.34g, 20 mmol) in acetic acid (12 ml), with the temperature maintained below 15°C. The reaction mixture was kept at 4°C for 96 hours, and then poured into ice-water (50 ml) and ether (10 ml). The ether layer was separated and washed with 2M potassium bisulphite solution (2 x 10 ml). The aqueous layers were combined and washed with ether (2 x 5 ml), basified to pH 14 with 10M sodium hydroxide solution and extracted with ether (3 x 20 ml). The ethereal extracts were dried, concentrated *in vacuo* and chromatographed on grade 3 alumina with ethyl acetate. The solid obtained was recrystallised three times to yield 2-(*iso*-propylaminoethylidene)pyrrole (174a) (1.96g, 64%) as a white solid, m.p. 54–55°C (from 2,2,4-trimethylpentane), \(^1\)H n.m.r. (60 MHz), \(\delta = 0.84–1.23 (7\text{H, m, CH(CH}_3)_2 \text{and D}_2\text{O ex., NH}), 1.35 (3\text{H, d, J = 7 Hz, CHCH}_3), 2.79 (1\text{H, sept., J = 6 Hz, CH(CH}_3)_2), 3.97 (1\text{H, q, J = 7 Hz, ArCH}), 5.89–6.22 (2\text{H, m, C(3 and 4)}\text{H}), 6.57–6.76 (1\text{H, m, C(5)}\text{H}), \text{and 8.80 (1H, brs, D}_2\text{O ex., pyrrole NH) p.p.m.}, ^{13}\text{C n.m.r. (20.1 MHz),}\delta = 22.7, 23.3 \text{and 23.5 (m, CH(CH}_3)_2 \text{and CHCH}_3), 46.0 (d, CH(CH}_3)_2), 48.7 (d, ArCH), 104.3 (d, C(4)), 108.1 (d, C(3)), 116.3 (d, C(5)), \text{and 136.5 (s, C(2)) p.p.m.; m/z (M+) 152.1313, C}_9\text{H}_{16}\text{N}_2 \text{requires 152.1313.}
5.8.2. Reaction of Ethylidene-iso-propylamine with N-Methylpyrrole

Ethylidene-iso-propylamine (173a) (1.70g, 20 mmol) and N-methylpyrrole (1.78g, 22 mmol) were treated as described in 5.8.1. The crude brown oil obtained was distilled using the Kugelröhr apparatus to yield 2-(iso-propylaminoethylidene)-N-methylpyrrole (174b) (1.43g, 43%), b.p. 45°C/0.1 mmHg, ¹H n.m.r. (60 MHz), δ = 0.83 (1H, s, NH), 1.01 (6H, d, J = 6 Hz, CH(CH₃)₂), 1.36 (3H, d, J = 7H, CHCH₃), 2.84 (1H, sept., J = 6 Hz, CH(CH₃)₂), 3.61 (3H, s, NCH₃), 3.93 (1H, q, J = 7 Hz, ArCH), 5.90–6.10 (2H, m, C(3 and 4)H), and 6.38–6.53 (1H, m, C(5)H) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 21.2, 23.1 and 23.5 (m, CH(CH₃)₂ and CHCH₃), 33.7 (q, NCH₃), 45.3 (d, CH(CH₃)₂), 47.2 (d, ArCH), 105.2 (d, C(4)), 106.4 (d, C(3)), 121.9 (d, C(5)), and 136.4 (s, C(2)) p.p.m., νmax (film) 3308 (NH) cm⁻¹; found: C, 72.2; H, 10.9; N, 16.7. C₁₀H₁⁵N₂ requires C, 72.2; H, 10.9; N, 16.85%; m/z (M⁺) 166.1463, requires 166.1470.

5.8.3 Reaction of iso-Butylidene-iso-propylamine with Pyrrole

iso-Butylidene-iso-propylamine (173b) (2.27g, 20 mmol) and pyrrole (1.48g, 22 mmol) were treated as described in 5.8.1. The crude solid obtained was recrystallised twice to yield 2-(iso-propylamino-iso-butylidene)pyrrole (174c) (2.46g, 69%) as white crystals, m.p. 61°C (from 2,2,4-trimethylpentane), ¹H n.m.r. (60 MHz), δ = 0.60–1.17 (13H, m, CH(CH₃)₂, CH(CH₃)₂ and NH), 1.74 (1H, br.sept., J = 6 Hz, CHCH(CH₃)₂), 2.64 (1H, sept., J = 6 Hz, NHCH(CH₃)₂), 3.57 (1H, d, J = 6 Hz, ArCH), 5.83–6.23 (2H, m, C(3 and 4)H), 6.54–6.77 (1H, m, C(5)H), and 8.70 (1H, br.s, pyrrole NH) p.p.m., ¹³C n.m.r. (20.1 MHz), δ = 19.0, 19.7, 22.8 and 24.2 (m, CH(CH₃)₂ and CH(CH₃)₂), 34.3 (d, CHCH(CH₃)₂), 46.8 (d, NHCH(CH₃)₂), 60.4 (d, ArCH), 106.0 (d, C(4)), 107.8 (d, C(3)), 116.0 (d, C(5)),
and 133.4 (s, C(2)) p.p.m., \( v_{\text{max}} \) (KBr), 3292 (NH), and 3464 (pyrrole NH) cm\(^{-1}\); found: C, 73.3; H, 11.3; N, 15.85. \( \text{C}_{11}\text{H}_{20}\text{N}_{2} \) requires C, 73.3; H, 11.2; N, 15.5%; m/z (M\(^{+}\)) 180.1625, requires 180.1626.

5.8.4 Reaction of \( \text{iso-Butylidene-iso-propylamine} \) with \( \text{N-Methylpyrrole} \)

\( \text{iso-Butylidene-iso-propylamine} \) (173b) (2.27g, 20 mmol) and \( \text{N-methylpyrrole} \) (1.78g, 22 mmol) were treated as described in 5.8.1. The crude oil was chromatographed on grade 3 alumina with ethyl acetate-petroleum ether 40-60 (gradient elution, 0 \( \rightarrow \) 100%), and the required fractions were concentrated, and distilled using the Kugelröhr apparatus to yield 2-(\( \text{iso-propylamino-iso-butylidene} \))-\( \text{N-methylpyrrole} \) (174d) (1.66g, 43%), b.p. 70\(^{\circ}\)/7 mmHg, \(^{1}\)H n.m.r. (60 MHz), \( \delta = 0.67-1.13 \) (13H, m, CH(CH\(_{3}\))\(_{2}\), CH(CH\(_{3}\))\(_{2}\) and NH), 1.80 (1H, br.sept., J = 7 Hz, CHCH(CH\(_{3}\))\(_{2}\)), 2.61 (1H, sept., J = 6 Hz, NHCH(CH\(_{3}\))\(_{2}\)), 3.46 (1H, d, J = 7 Hz, ArCH), 3.58 (3H, s, NCH\(_{3}\)), 5.83-6.07 (2H, m, C(3 and 4)H), and 6.37-6.52 (1H, m, C(5)H) p.p.m., \(^{13}\)C n.m.r. (20.1 MHz), \( \delta = 19.6, 22.3 \) and 24.3 (m, CH(CH\(_{3}\))\(_{2}\) and CH(CH\(_{3}\))\(_{2}\)), 33.8 (q, NCH\(_{3}\)), 34.0 (d, CHCH(CH\(_{3}\))\(_{2}\)), 45.8 (d, NHCH(CH\(_{3}\))\(_{2}\)), 59.2 (d, ArCH), 106.6 (d, C(4)), 106.7 (d, C(3)), 121.5 (d, C(5)), and 134.7 (s, C(2)) p.p.m., \( v_{\text{max}} \) (film) 3416 (NH) cm\(^{-1}\); found: C, 74.3; H, 11.2; N, 14.7. \( \text{C}_{12}\text{H}_{22}\text{N}_{2} \) requires C, 74.15; H, 11.4; N, 14.4%; m/z (M\(^{+}\)) 194.1760 requires 194.1783.

5.8.5 Reaction of \( \text{iso-Butylidene-iso-propylamine} \) with Indole

\( \text{iso-Butylidene-iso-propylamine} \) (173b)(2.49g, 22 mmol) and indole(2.34g, 20 mmol) were treated as described in 5.8.1. The crude solid obtained was
recrystallised to yield 3-(iso-propylamino-iso-butylidene)indole (174e) (2.96 g, 65%) as a white solid, m.p. 86°C (from 2,2,4-trimethylpentane), 

\( \text{'H n.m.r. (60 MHz), } \delta = 0.67-1.27 \text{ (12H, m, CH(CH}_3)_2 \text{ and CH(CH}_3)_2 \text{)}, \ 1.36 \text{ (1H, s, D}_2\text{O ex., NH), 2.03 (1H, br.sept., J = 6.5 Hz, CHCH(CH}_3)_2 \text{), 2.71 (1H, sept., J = 6 Hz, NHCH(CH}_3)_2 \text{)}, 3.81 (1H, d, J = 6.5 Hz, ArCH), 7.13-7.34 \text{ (4H, m, C(2,5,6 and 7)H), 7.53-7.81 (1H, m, C(4)H), and 8.41 (1H, br.s, D}_2\text{O ex., indole NH p.p.m.}, \ \text{'C n.m.r. (20.1 MHz), } \delta = 19.5, 20.2, 22.4 \text{ and 24.2 (m, CH(CH}_3)_2 \text{ and CH(CH}_3)_2 \text{), 34.1 (d, CHCH(CH}_3)_2 \text{), 46.1 (d, NHCH(CH}_3)_2 \text{), 59.2 (d, ArCH), 111.4 (d, C(7)), 117.8 (s, C(3)), 119.1 (d, C(6)), 119.8 (d, C(4)), 121.6 (d, C(5)), 122.5 (d, C(2)), 127.6 (s, C(3a)), and 136.6 (s, C(7a)) p.p.m.; found: C, 78.1; H, 9.7; N, 12.1. C_{15}H_{22}N_2 \text{ requires C, 78.2; H, 9.6; N, 12.2%}. \)
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