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The Use of Bis(Aminol) Ethers Derived from Aliphatic Primary Amines in the Synthesis of Secondary and Tertiary Amines

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Abstract: A series of bis(aminol) ethers were prepared from primary aliphatic amines and benzylamine together with formaldehyde and either ethanol or methanol ; they were reacted with electrophiles to give *N*-alkyl-*N*-alkoxymethyl-methyleneiminium salts which gave mixtures of secondary and tertiary amines in reactions with electron rich aromatic compounds: sequential reactions with two different nucleophiles gave the expected tertiary amines.

Introduction

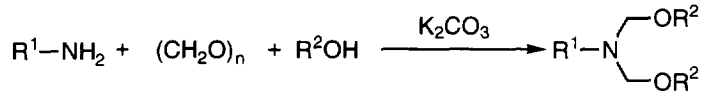
Secondary amines are frequently used in Mannich reactions for the preparation of tertiary amines whereas primary amines are rarely employed.[1] The latter produce secondary amines as the initial products which can participate further in the reaction leading to mixtures of products. The classical Mannich reactions of pyrroles afford much lower yields of aminoalkylation products using primary amines than those obtained using secondary amines.[2] A limited success was reported in the condensation of pyrroles with formalin and an excess of primary amine hydrochlorides that possess a bulky substituent on the nitrogen atom.[3]

The development of new methods for the preparation of secondary amines is a desirable objective.[4] A systematic study of the methods of preparation of secondary amines has been undertaken by Katritzky and his collaborators by employing *N*-substituted benzotriazoles as synthetic auxiliaries.[5] The condensation of benzotriazole, formaldehyde, and primary amines affords 1-[(alkylamino)methyl]benzotriazoles which in the presence of Grignard reagents, undergo nucleophilic displacement of the benzotriazole moiety to give a variety of secondary amines.[6] Furthermore, 1-(trimethylsilyl)benzotriazole facilitates additions of Grignard reagents to imines to give the corresponding secondary aliphatic amines.[7]

As a part of our investigation of Mannich reactions using non-aqueous conditions and silicon reagents to generate the electrophile we made a preliminary report of a new route to secondary amines from *N,N*-bis(alkoxymethyl)alkylamines [bis(aminol) ethers].[8] We concentrated on the use of these reagents as precursors for the synthesis of secondary and tertiary amines in reactions with aromatic compounds. Katritzky and his co-workers have recently reported the preparation of secondary and tertiary amines by their aminoalkylbenzotriazole methodology involving reactions of furans, pyrroles, and indoles.[9] The present paper describes our new methodology for the preparation of secondary amines; it is also demonstrated that bis(aminol) ethers can be used as bis-aminoalkylating agents for use in the formation of tertiary amines.

Results and Discussion

Our interest in Mannich reactions[10] has previously been concentrated on the use of secondary amines. As a development from these studies we undertook an investigation of the use of primary amines in the synthesis of secondary amines. The formation of benzoxazines[11] by the interaction of phenols with bis(aminol) ethers and their use in the preparation of tertiary amines bearing three different groups[11d] suggested the use of the potentially interesting bis(aminol) ethers as precursors to protected secondary amines as well as bis-aminoalkylating reagents. We have recently reported the synthesis of 2-arylmethyltetrahydroisoquinolines from *N,N*-bis(methoxymethyl)-3,4-dimethoxy-β-phenylethylamine and secondary amine formation by the interaction of either *N,N*-bis(ethoxymethyl)- or *N,N*-bis(ethoxymethyl)-4-methoxy-β-phenylethylamine with 2-methylfuran.[12] In the course of our investigations we prepared a number of other bis(aminol) ethers (**1a-e**), in reasonable yields, by the condensation of anhydrous primary alkylamines or benzylamine with paraformaldehyde in an excess of methanol or ethanol in the presence of potassium carbonate.



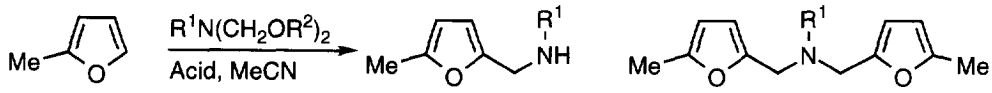
(**1**)

(**a**, R^1 = i-Pr; R^2 = Et) (**b**, R^1 = n-Bu; R^2 = Et)

(**c**, R^1 = t-Bu; R^2 = Me) (**d**, $R^1 = R^2$ = Et)

(**e**, R^1 = $PhCH_2$; R^2 = Et)

In order to evaluate the reactivity of bis(aminol) ethers we studied a series of reactions with 2-methylfuran in the presence of various acidic reagents. It was envisaged that it should be possible to generate methyleneiminium ions and to protect simultaneously the product of the reactions. The purpose was to devise conditions such that a protected secondary amine could be intercepted giving rise to the possibility of having sequential reactions with two different nucleophiles. Alternatively, bis(aminol) ethers could be used as bis-aminoalkylating agents for the formation of tertiary amines having two identical substituents. In most cases we isolated both secondary (**3a-e**) and tertiary (**4a-e**) amines (**Table 1**).



(**3a-e**) (**4a-e**)

Higher yields of secondary amines (**3a-e**) were isolated when hydrogen chloride was the only acid present in the reaction mixture. The chlorosilane derivatives promoted the formation of tertiary amines (**4a-e**). As the *in situ* reactions gave a mixture of secondary and tertiary amines it was envisaged that would be more profitable to carry out these reactions with preformed iminium salts. The transient existence of *N*-alkyl-*N*-alkoxymethylmethyleneiminium salts has been suggested in a proposed mechanism of the reaction of phenols with bis(aminol) ethers as used for the preparation of 3,4-dihydro-1,3-benzoxazines.[13] The participation of such electrophilic species in the Grignard-Reformatsky reaction of bis(*n*-butoxymethyl)-*t*-butylamine is another example where *N*-alkyl-*N*-alkoxy(methylene) iminium salt has been a suggested intermediate.[14] In that case it

was postulated that magnesium bromide functions as the Lewis acid that is involved in the formation of the reactive intermediate. Treatment of bis(aminol) ethers with acidic reagents such as acetyl chloride, chlorosilane derivatives, or ethereal hydrogen chloride, in petroleum ether, gave the alkoxymethylmethyleneiminium salts as hygroscopic solids in essentially quantitative yield.

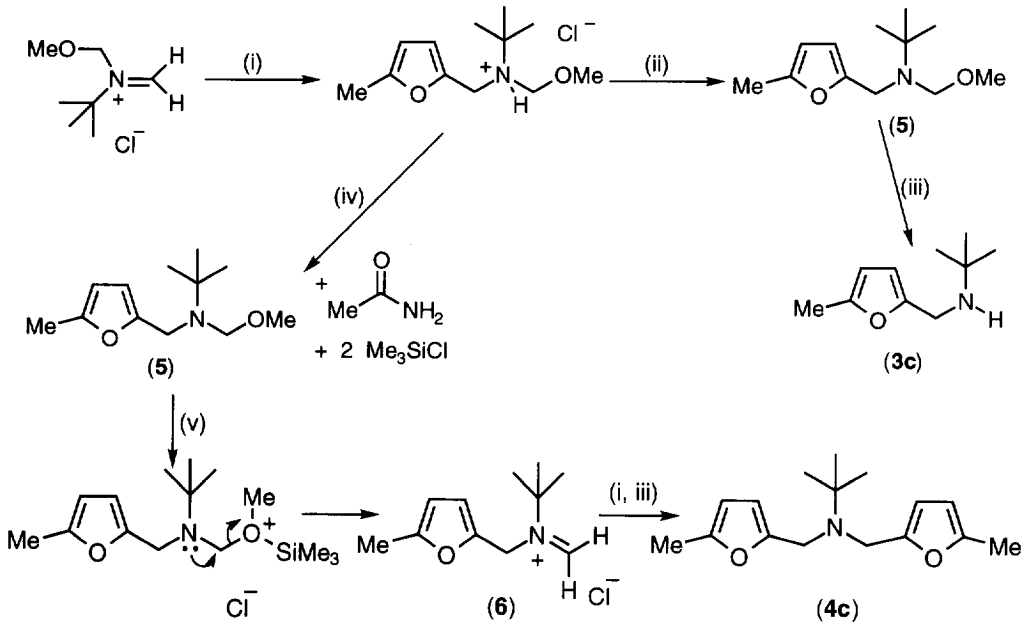
TABLE 1
***In Situ* Reactions of 2-Methylfuran with Bis(aminol) Ethers**

Bis(aminol) Ether	Solvent	Acid	Time (h)	Temp.	Products Yield (%) 3	4
i-PrN(CH_2OEt)$_2$	MeCN	Me_3SiCl	16	RT	**a** (38)	**a** (56)
	MeCN	CH_3COCl	19	RT	**a** (44)	**a** (37
	MeCN	$TiCl_4$ (25mol%)	18	-55°C – RT	**a** (31)	**a** (49)
	CH_2Cl_2	$TiCl_4$ (25mol%)	4	RT	**a** (58)	**a** (15)
	MeCN	$MeSiCl_3$	19	RT	**a** (53)	**a** (24)
	MeCN	$(CF_3CO)_2O$	3	RT	**a** (24)	**a** (17)
	MeCN	SO_2	3	RT	**a** (22)	**a** (21)
	MeCN	Et_2O·HCl	16	RT	**a** (63)	**a** (9)
i-PrN(CH_2OEt)CH_2OCH_2OEt	MeCN	$MeSiCl_3$	72	RT	**a** (20)	**a** (43)
n-BuN(CH_2OEt)$_2$ /2mol	MeCN	$MeSiCl_3$ /2mol	18	RT	**b** (0)	**b** (87)
t-BuN(CH_2OMe)$_2$	MeCN	Et_2O·HCl	2	RT	**c** (72)	**c** (22)
EtN(CH_2OEt)$_2$	MeCN	Et_2O·HCl	2	RT	**d** (41)	**d** (23)
$PhCH_2N(CH_2OEt)_2$	MeCN	$MeSiCl_3$	21	RT	**e** (33)	-

As in the case of *in situ* reactions, the best yields of secondary amines (**3a-e**) were obtained from iminium salts prepared using hydrogen chloride. Attempts to duplicate the yields obtained in the reactions where the iminium species were generated by chlorosilane derivatives were unsuccessful. It is possible that in some cases the silanes were occluded in the precipitated salt promoting the formation of a second iminium species and hence the tertiary amines (**4a-e**). The yields of secondary amines depended on the structure of the *N*-alkyl residue; more sterically demanding alkyl groups reduce the formation of tertiary amine possibly due to inhibition of the silylation of the aminol ether that precedes the formation of the second iminium salt.

A series of experiments was carried out in which a non-nucleophilic base such as di-*iso*-propylethylamine, dicyclohexylmethylamine, 2,6-lutidine, propylene oxide, or potassium carbonate was added initially. They all resulted in complete or partial inhibition of the potential reactions. Two key experiments provided strong evidence about the reaction pathway and the effect of chlorosilane derivatives in the reaction mixture. Duplicate reactions of *N*-methoxymethyl-*N*-*t*-butylmethyleneiminium chloride with 2-methylfuran were carried out in which the iminium salt was prepared using hydrogen chloride. In one, a half-mole equivalent of bis(trimethylsilyl)acetamide was also added. In the control experiment (entry 14, **Table 2**) the yields of secondary (**3c**) and tertiary (**4c**) amines were 80% and 13% respectively. In the presence of the HCl scavenger a complete reversal occurred yielding the secondary amine (**3c**) in 12% and the tertiary amine (**4c**) in 80%. This evidence supports the view that the strongly azophilic hydrogen chloride protonates the nitrogen in the intermediate aminol ether (**5**), ***Scheme 1***, which therefore survives until the end of the reaction. On the other hand the HCl scavenger is able to generate 2 mole equivalents of chlorotrimethylsilane in the reaction mixture. The silicon reagent, being oxophilic, silylates the intermediate aminol ether (**5**) at the oxygen and leads to the generation of the second

iminium salt (**6**) and ultimately to the tertiary amine. The intermediacy of the aminol ether (**5**) was further substantiated by its isolation in 47% yield from a reaction which worked-up by adding Hunig's base to the reaction mixture after 24 h.



Scheme 1

(i)2-methylfuran, MeCN; (ii) Hunig's base; (iii) water;
(iv) bis(trimethylsilyl)acetamide; (v) chlorotrimethylsilane

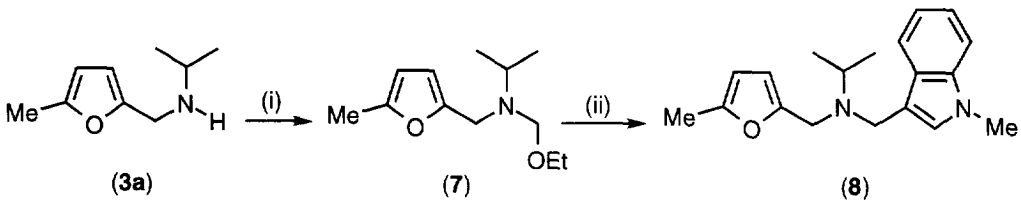
Further evidence in favour of the proposed reaction pathway was provided by the preparation of the equivalent intermediate aminol ether (**7**) from the secondary amine (**3a**), by the usual procedure[16] in 74% yield. Subsequent reaction of the compound (**7**) with *N*-methylindole, in the presence of trichloromethylsilane, afforded the mixed tertiary amine (**8**) in 71% (***Scheme 2***.) This reaction shows that sequential reactions can be carried out with two different nucleophiles and hence allows the preparation of tertiary amines with three different substituents on the nitrogen atom.

The methodology was also applied to other aromatic compounds, namely 1,3-dimethoxybenzene, *N*-methylpyrrole, *N*-methylindole, and furan. A qualitative indication of the greater reactivity of these iminium salts as compared to *N,N*-dialkylmethyleneiminium salts is evident from the results obtained. Notably, that *N,N*-dimethylmethyleneiminium chloride in a reaction with the least nucleophilic substrate, 1,3-dimethoxybenzene, gave only 4% of the expected Mannich base, whereas in reactions with the bis(aminol) ether (**1c**) afforded reasonable yields of the secondary amine (**9**) under the same reaction conditions.

TABLE 2

Reactions of 2-Methylfuran with Preformed Iminium Salts

Iminium Salt		Acid	Time	Temp. (°C)	Products Yield (%)	
Entry	R				3	4
1	i-Pr	$MeSiCl_3$	24 h	RT	**a** (65)	**a** (17)
2	i-Pr	$MeSiCl_3$	41 h	RT	**a** (9)	**a** (70)
3	i-Pr (2 mol)	$MeSiCl_3$	2 h	RT	**a** (48)	**a** (20)
4	i-Pr	CH_3COCl	3 h	RT	**a** (23)	**a** (45)
5	i-Pr	CH_3COCl	10 days	-40 to -20	**a** (55)	**a** (31)
6	^{i}Pr	HCl (gas)	2 h	RT	**a** (77)	**a** (15)
7	n-Bu	$MeSiCl_3$	24 h	RT	**b** (57)	**b** (11)
8	n-Bu	Me_3SiCl	2 h	-40	**b** (59)	**b** (6)
9	n-Bu	CH_3COCl	24 h	RT	**b** (18)	**b** (24)
10	t-Bu	$MeSiCl_3$	24 h	RT	**c** (68)	**c** (20)
11	t-Bu	$MeSiCl_3$	72 h	RT	**c** (35)	**c** (51)
12	t-Bu	Me_3SiCl	42 h	RT	**c** (62)	**c** (33)
13	t-Bu	Me_3SiCl	3 h	RT	**c** (74)	**c** (19)
14	t-Bu	$Et_2O{\cdot}HCl$	3 h	RT	**c** (80)	**c** (13)
15	Et	$MeSiCl_3$	18 h	RT	**d** (13)	**d** (42)
16	$PhCH_2$	$MeSiCl_3$	21 h	RT	**e** (41)	-

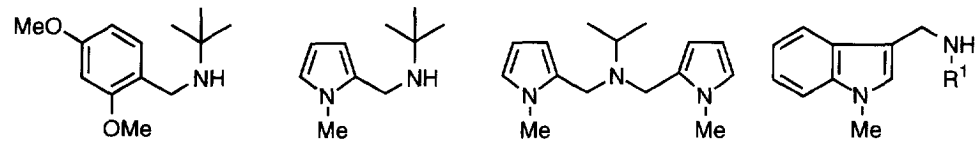


(**3a**) (**7**) (**8**)

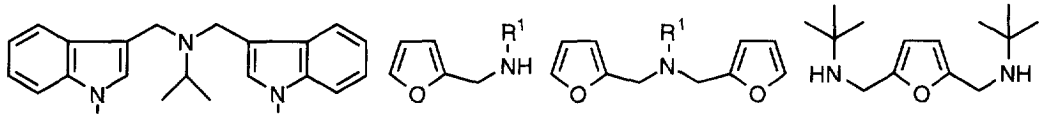
Scheme 2

(i) $(CH_2O)_n$, EtOH, K_2CO_3; (ii) *N*-methylindole, $MeSiCl_3$, MeCN, RT

Furan gave 2,5-di-*N*-t-butylaminomethylfuran (**18**) when the reaction was performed at room temperature. Increasing the amount of furan used resulted, as expected, in the predominance of tertiary amine (**19**) after a long interval of time. *N*-methylpyrrole gave reasonable yields of secondary amine (**10**) only when the reaction was conducted at low temperature. *N*-methylindole, having only one position activated towards aminoalkylation, gave reasonable yields of the secondary amine (**12**) in the absence of chlorosilane derivatives. The secondary amine (**14**) was obtained exclusively when the reaction was performed at low temperature using a sterically demanding alkyl group on nitrogen.



(9) (10) (11) (12; R^1 = i-Pr) (14; R^1 = t-Bu)



(13) (15; R^1 = ^{i}Pr) (16; R^1 = ^{i}Pr) (18)

(17; R^1 = ^{t}Bu) (19; R^1 = ^{t}Bu)

In conclusion this investigation furnished useful information about the mechanistic aspects of the reactions of bis(aminol) ethers with electron rich aromatic compounds. It has been shown that interception of the reaction after the first stage can be achieved when hydrogen chloride is the only acid present in the reaction mixture, thereby providing a new method for the preparation of secondary amines. The use of chlorosilane derivatives is important if the preparation of tertiary amines is desired.

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Experimental

Infrared spectra were recorded on a Perkin-Elmer 257 spectro-photometer. ^{1}H n.m.r. Spectra were recorded on Varian EM 360 A (60 MHz) or Bruker AC-250 (250 MHz) spectrometers. ^{13}C n.m.r. Spectra in $CDCl_3$ were recorded on Bruker WP 80 (20.1 MHz), together with off resonance decoupling, or Bruker ACF-250 (62.9 MHz) spectrometers. Multiplicities are reported as broad singlet (br.s), singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Mass Spectra were recorded by electron impact using a Kratos (M.S.80) spectrometer or by fast atom bombardment (FAB) using a V.G.70-250 S spectrometer. Melting Points were recorded using a Kofler hot stage apparatus and are uncorrected. Microanalyses were carried out by the former Fisons plc, (Pharmaceutical Division, Loughborough).

Preparation of Bis(aminol) Ethers (1)—General Procedure

Paraformaldehyde (2 equiv.) was added to a stirred mixture of anhydrous primary amine (1 equiv.), ethanol or methanol and potassium carbonate (1 equiv.) at 0 °C. The mixture was then stirred vigorously for 2 days at room temperature. The solid was filtered and washed with dried ether. The filtrate was fractionally distilled through an 18" Vigreux column to remove the ether and excess alcohol and the residue was distilled under reduced pressure.

The following bis(aminol) ethers were prepared:

***N,N*-Bis(ethoxymethyl)isopropylamine (1a)** was isolated by fractional distillation. The first fraction *N,N-bis(ethoxymethyl)-isopropylamine* (**1a**) (39.44g, 45%), b.p. 66-72 °C /12 mmHg; δ_H (60 MHz)

1.12 (6H, d, J = 6 Hz, NCH[CH_3]$_2$), 1.18 (6H, t, J = 7.5 Hz, OCH$_2$CH_3), 3.27 (1H, sept., J = 6 Hz, C*H* Me$_2$), 3.37 (4H, q, J = 7.5 Hz, CH_2 CH$_3$), and 4.30 (4H, s, NCH$_2$O) ppm; δ_C (20.1 MHz), 15.3 (q, CH$_2$*C* H$_3$), 21.8 (q, CH[*C* H$_3$]$_2$), 50.1 (d, *C* HMe$_2$), 62.0 (t, O*C* H$_2$CH$_3$), and 82.7 (t, NCH$_2$O) ppm; (m/z) 175 (M$^+$, 13.4%), 59 (100), M$^+$ measured 175.1566; $C_9H_{21}NO_2$ requires 175.1572. The second fraction *N-ethoxymethyl-N-ethoxymethoxymethylisopropylamine* **(2)** (17.45g, 17%), b.p. 85-95 °C/12 mmHg; δ_H (60 MHz), 1.06-1.40 (6H, d, CH[CH_3]$_2$), and (6H, t, OCH$_2$CH_3), 3.10-3.80 (1H, sept., C*H* Me$_2$, and 4H, t, OCH_2 CH$_3$), 4.37 (2H, s, NCH$_2$OEt), 4.53 (2H, s, NCH_2 OCH$_2$), and 4.73 (2H, s, OCH$_2$OEt) ppm; (m/z); 205 (M$^+$, 0.9%), 59 (62.5), 31 (100), M$^+$ measured 205.1670; $C_{10}H_{23}NO_3$ requires 205.1678.

***N,N*-Bis(ethoxymethyl)-*n*-butylamine (1b):** *n*-butylamine yielded *N,N-bis(ethoxymethyl)-n-butylamine* (**1b**) (104.41g, 55%), b.p. 66-68 °C/4 mmHg, (lit.[17], no physical data given). i.r. (film) ν_{max} 2960, 2928, 2856, 1456, 1376 cm^{-1}; δ_H (60 MHz), 1.20 (6H, t, J = 7.5 Hz, OCH$_2$CH_3), 0.76-1.67 (7H, m, CH$_3$CH$_2$CH$_2$), 2.13 (2H, t, CH$_2$N), 3.45 (4H, q, J = 7.5 Hz, OCH_2 CH$_3$), and 4.27 (4H, s, NCH$_2$O) ppm; δ_C (20.1 MHz), 14.0 (q, *C* H$_3$[CH$_2$]$_3$N), 15.2 (q, OCH$_2$*C* H$_3$), 20.5 (t, CH$_3$*C* H$_2$[CH$_2$]$_2$N), 31.1 (t, CH$_3$CH$_2$*C* H$_2$CH$_2$N), 49.6 (t, CH$_3$[CH$_2$]$_2$*C* H$_2$N), 62.6 (t, O*C* H$_2$CH$_3$), and 84.8 (t, NCH$_2$O) ppm; (m/z); 189 (M$^+$, 7.4%), 59 (100), M$^+$ measured 189.1725; $C_{10}H_{23}NO_2$ requires 189.1729.

***N,N*-Bis(methoxymethyl)-*t*-butylamine (1c)**:*t*-butylamine yielded *N,N-bis(methoxymethyl)-t-butylamine* (**1c**) (52.57g, 33%), b.p. 72 °C/12 mmHg. i.r. (film) ν_{max} 3484, 2976, 2804, 2760, 1558, 1538, 1470 cm^{-1}; δ_H (60 MHz) 1.27 (9H, s, C[CH$_3$]$_3$), 3.27 (6H, s, OCH$_3$), and 4.40 (4H, s, NCH$_2$O) ppm; δ_C (62.9 MHz), 29.5 (C[*C* H$_3$]$_3$), 53.5 (CMe$_3$), 53.9 (OCH$_3$), and 83.6 (NCH$_2$O) ppm; (m/z); 161 (M$^+$, 4.7%), 70 (100), M$^+$ measured 161.1418; $C_8H_{19}NO_2$ requires 161.1416.

***N,N*-Bis(ethoxymethyl)ethylamine (1d)**: ethylamine yielded *N,N-bis(ethoxymethyl)ethylamine* (**1d**) (96.76g, 40%), b.p. 90-92 °C/150 mmHg; δ_H (60 MHz) 1.10 (3H, t, J = 7.5 Hz, NCH$_2$CH_3), 1.18 (6H, t, J = 7.5 Hz, OCH$_2$CH_3), 2.90 (2H, q, J = 7.5 Hz, NCH_2 CH$_3$), 3.46 (4H, q, J = 7.5 Hz, OCH_2 CH$_3$), and 4.30 (4H, s, NCH$_2$O) ppm; δ_C (20.1 MHz) 14.0 (q, NCH$_2$*C* H$_3$), 15.3 (q, OCH$_2$*C* H$_3$), 43.9 (t, NC H$_2$CH$_3$), 62.6 (t, O*C* H$_2$CH$_3$), and 84.3 (t, NCH$_2$O) ppm; (m/z); 161 (M$^+$, 7.8%), 116 (5.5), 59 (95.5), 31 (100), M$^+$ measured 161.1410; $C_8H_{19}NO_2$ requires 161.1416.

***N,N*-Bis(ethoxymethyl)benzylamine (1e)**: benzylamine yielded *N,N-bis(ethoxymethyl)benzylamine* (**1e**) (124.51g, 56%), b.p. 84-86 °C/0.2 mmHg, (lit.[11a], b.p. 80 °C/0.1 mmHg). i.r. (film) ν_{max} 3084, 3060, 3028, 2968, 1948, 1806, 1602, 1584, 1494 cm^{-1}; δ_H (60 MHz), 1.17 (6H, t, J = 7.5 Hz, CH$_2$CH_3), 3.47 (4H, q, J = 7.5 Hz, CH_2 CH$_3$), 3.97 (2H, s, PhCH$_2$N), 4.27 (4H, s, NCH$_2$O), and 7.27 (5H, br.s, PhH) ppm; δ_C (62.9 MHz), δ = 15.2 (CH$_2$*C* H$_3$), 52.8 (PhCH$_2$), 62.8 (O*C* H$_2$CH$_3$), 83.7 (NCH$_2$O), 126.9 (C-4], 128.2 (C-3 and C-5), 128.8 (C-2 and C-6), and 139.2 (C-1) ppm; (m/z); 223 (M$^+$, 2.2%), 91 (100), M$^+$ measured 223.1557; calc. for $C_{13}H_{21}NO_2$ 223.1572.

***In Situ* Reactions of Bis(aminol) Ethers with 2-Methylfuran**

An acidic reagent (1.1 equiv.) was added to a mixture of 2-methylfuran (1.0 equiv.) and a bis(aminol ether) (1.1 equiv.) in acetonitrile under nitrogen. The mixture was then stirred at room temperature. Water (20 ml) was added and the solvent removed in *vacuo*. The residue was washed with ether (3x30 ml) and then basified to pH 14 with 2 M sodium hydroxide solution and extracted with ether (3x40 ml). The combined organic extracts from the basic solution were dried and concentrated in *vacuo* and distilled (Kugelrohr).

Reaction of 2-Methylfuran and *N,N*-Bis(ethoxymethyl)isopropylamine (1a)

2-Methylfuran (1.23g, 15 mmol), (**1a**) (2.89g, 16.5 mmol), and chlorotrimethylsilane (1.79g, 16.5 mmol) in acetonitrile (60 ml) were stirred at room temperature for 16 h. Kugelrohr distillation of the crude product afforded two fractions. The first fraction was shown to be *N-(5-methylfurfuryl)isopropylamine* (**3a**) (0.88g, 38%), b.p. 70 °C / 1.5 mmHg, (lit.[18], 82-3 °C/20 mmHg); i.r. (film) ν_{max} 3324 (NH), 2964, 2924, 1616, 1566, and 1446 cm^{-1}; δ_H (60 MHz) 1.10 (6H, d, J = 6 Hz, CH[CH_3] $_2$), 1.73 (1H, br.s, D_2O ex., NH), 2.27 (3H, s, CH_3), 2.87 (1H, sept. J = 6 Hz, $CHMe_2$), 3.73 (2H, s, CH_2N), 5.77-5.93 (1H, m, 4-H), and 6.00 (1H, d, J = 3 Hz, 3-H) ppm; δ_C (20.1 MHz), 13.5 (q, CH_3), 22.8 (q, CH[C H_3]$_2$), 44.1 (t, CH_2N), 47.7 (d, $CHMe_2$), 106.0 (d, C-4), 107.3 (d, C-3), 151.1 (s, C-2), and 152.6 (s, C-5] ppm; (m/z); 153 (M^+, 9.8%), 95 (100), M^+ measured 153.1158; calc for $C_9H_{15}NO$ 153.1154. The second fraction was shown to be *N,N-di(5-methylfurfuryl)isopropylamine* (**4a**) (1.04g, 56%), b.p. 120 °C/0.2 mmHg; i.r. (film) ν_{max} 2964, 2924, 1614, 1566, 1450 cm^{-1}; δ_H (60 MHz), 1.07 (6H, d, J = 6 Hz, CH[CH_3]$_2$), 2.20 (6H, s, CH_3), 3.03 (1H, sept. J = 6 Hz, CH Me_2), 3.63 (4H, CH_2N), 5.83-5.97 (2H, m, 4-H), and, 6.08 (2H, d, J = 3 Hz, 3-H) ppm; δ_C (20.1 MHz), δ = 13.6 (q, CH_3), 18.6 (q, CH[C H_3]$_2$), 46.3 (t, CH_2N), 50.5 (d, C HMe_2), 106.0 (d, C-4], 108.9 (d, C-3], 151.3 (s, C-2), and 152.7 (s, C-5) ppm; (m/z); 247 (M^+, 6.2%), 95 (100), M^+ measured 247.1561; $C_{15}H_{21}NO_2$ requires 247.1572.

Reaction of *N,N*- Bis(ethoxymethyl)-*n*-butylamine (1b) with Two Equivalents of 2-Methylfuran

2-Methylfuran (3.28g, 40 mmol), (**1b**) (3.79g, 20 mmol) and trichloromethylsilane (5.80g, 40 mmol) in acetonitrile (80 ml) at room temperature for 18 h gave, after work-up, *N,N-di(5-methylfurfuryl)-n-butylamine* (**4b**) (4.56g, 87%), b.p. 100 °C /0.2 mmHg. i.r. (film) ν_{max} 2952, 2924, 2816, 1612, 1566, 1452, 1382 cm^{-1}; δ_H (60 MHz), δ = 0.67-1.80 (7H, m, $CH_3CH_2CH_2$), 2.27 (6H, s, CH_3), 2.43 (2H, t, $CH_3(CH_2)_2CH_2$ N), 3.60 (4H, s, NCH_2), 5.80-5.97 (2H, m, 4-H), and 6.07 (2H, d, J = 3 Hz, 3-H) ppm; δ_C (20.1 MHz) 13.6 (q, $ArCH_3$), 14.0 (q, C $H_3[CH_2]_3$), 20.6 (t, CH_3C $H_2[CH_2]_2$), 29.4 (t, CH_3CH_2C H_2CH_2), 49.8 (t, $ArCH_2N$), 52.8 (t, NC $H_2[CH_2]_2CH_3$), 106.0 (d, C-4), 109.5 (d, C-3), 150.7 (s, C-2), and 151.4 (s, C-5) ppm; (m/z); 261 (M^+, 67.2%), 218 (100), M^+ measured 261.1778; $C_{16}H_{23}NO_2$ requires 261.1729.

Reaction of 2-Methylfuran and *N,N*-Bis(methoxymethyl)-*t*-butylamine (1c)

Ethereal hydrogen chloride (1.07 M, 15.4 ml, 16.5 mmol) was added to a mixture of 2-methylfuran (15 mmol, 1.23g) and (**1c**) (2.76g, 16.5 mmol) in acetonitrile (45 ml). The mixture was stirred at room temperature for 2 h giving after work-up and Kugelrohr distillation two fractions. The first fraction was shown to be *N-(5-methylfurfuryl)-t-butylamine* (**3c**) (1.82g, 72%), b.p. 75 °C/1.5 mmHg; i.r. (film) ν_{max} 3316 (NH), 3104, 2964, 2924, 2836, 1650, 1618, 1568, 1478 cm^{-1}; δ_H (60 MHz) 1.17 (9H, s, C[CH_3]$_3$), 1.00-1.30 (1H, br.s, D_2O ex., NH), 2.27 (3H, s, $ArCH_3$), 3.70 (2H, s, NCH_2), 5.80-5.93 (1H, m, 4-H), and 6.07 (1H, d, J = 3 Hz, 3-H) ppm; δ_C (100.4 MHz) 13.6 (Ar-CH_3), 28.9 (C[C H_3]$_3$), 40.0 (NCH_2), 50.6 (C(CH_3)$_3$), 106.0 (C-4), 107.1 (C-3), 151.3 (C-2), and 152.6 (C-5) ppm; (m/z); 167 (M^+, 5.9%), 95 (100), M^+ measured 167.1296; $C_{10}H_{17}NO$ requires 167.1310. The second fraction was shown to be *N,N-di(5-methylfurfuryl)-t-butylamine* (**4c**) (0.44g, 22%), b.p. 110 °C/0.01 mmHg. i.r. (film) ν_{max} 2966, 2920, 2838, 1652, 1616, 1570, 1476 cm^{-1}; δ_H (60 MHz) 1.17 (9H, s, C[CH_3]$_3$), 2.27 (6H, s, $ArCH_3$), 3.77 (4H, s, NCH_2), 5.80-5.93 (2H, m, 4-H), 6.03 (2H, d, J = 3 Hz, 3-H) ppm; δ_C (20.1 MHz) 13.6 (q, $ArCH_3$), 27.5 (q, C[C H_3]$_3$), 44.3 (t, NCH_2), 54.5 (s, C[CH_3]$_3$), 106.0 (d, C-4), 108.7 (d, C-3), 150.7 (s, C-2), and 152.7 (s, C-5) ppm; (m/z); 261 (M^+, 53.4%), 152 (100), M^+ measured 261.1721; $C_{16}H_{23}NO_2$ requires 261.1729.

Reaction of 2-Methylfuran and *N,N*-Bis(ethoxymethyl)ethylamine (1d)

Ethereal hydrogen chloride (1.07 M, 15.4 ml, 16.5 mmol) was added to a mixture of 2-methylfuran (1.23g, 15 mmol) and (**1d**) (2.66g, 16.5 mmol) in acetonitrile (45 ml) at room temperature. The mixture was stirred for 2 h giving, after work-up and Kugelrohr distillation, two fractions. The first fraction was shown to be *N-(5-methylfurfuryl)ethylamine* (**3d**) (0.85g, 41%), b.p. 85 °C/2.5 mmHg, (lit.[18], 71-6 °C/ mmHg); i.r. (film) ν_{max} 3308 (NH), 2964, 1682, 1568, 1456, 1388 cm^{-1}; δ_H (60 MHz) 1.10 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.43 (1H, s, D_2O ex., NH), 2.27 (3H, s, $ArCH_3$), 2.67 (2H, q, J = 7.5 Hz, CH_2 CH_3), 3.70 (2H, s, NCH_2), 5.77-5.93 (1H, m, 4-H), and 6.00 (1H, d, J = 3 Hz, 3-H) ppm; δ_C (20.1 MHz) 13.6 (q, 5-CH_3), 15.2 (q, CH_2C H_3), 43.4 (t, C H_2CH_3), 46.3 (t, $ArCH_2N$), 106.0 (d, C-4), 107.6 (d, C-3), 151.3 (s, C-2), and 152.4 (s, C-5) ppm; (m/z); 139 (M^+, 27.9%), 95 (100), M^+ measured 139.0989; $C_8H_{13}NO$ requires 139.0997. The second fraction was shown to be *N,N-di(5-methylfurfuryl)ethylamine* (**4d**) (0.41g, 23%), b.p. 95 °C/0.02 mmHg, (lit.[19], 127-30 °C/6mmHg); i.r. (film) ν_{max} 2966, 2928, 1612, 1566, 1452, 1380 cm^{-1}; δ_H (60 MHz) 1.10 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.27 (6H, s, $ArCH_3$), 2.53 (2H, q, J = 7.5 Hz, CH_2 CH_3), 3.60 (4H, s, $ArCH_2$), 5.77-5.93 (2H, m, 4-H), and 6.06 (2H, d, J = 3 Hz, 3-H) ppm; δ_C (20.1 MHz) 12.4 (q, CH_2C H_3), 13.6 (q, 5-CH_3), 47.0 (t, C H_2CH_3), 49.3 (t, $ArCH_2N$), 106.0 (d, C-4), 109.7 (d, C-3), 150.5 (s, C-2), and 151.5 (s, C-5) ppm; (m/z); 233 (M^+, 100%), M^+ measured 233.1397; calc. for $C_{14}H_{19}NO_2$ 233.1416.

***N*-(5-methylfurfuryl)benzylamine (3e)**

Ethereal hydrogen chloride (15.4 ml, 16.5 mmol) was added to a mixture of 2-methylfuran (1.23g, 15mmol) and (**1e**) (3.68g, 16.5 mmol) in acetonitrile (45 ml). The mixture was stirred at room temperature for 2 h affording after work-up and Kugelrohr distillation, *N-(5-methylfurfuryl)benzylamine* (**3e**) (1.35g, 45%), b.p. 150 °C/0.02 mmHg, (lit.[18], 104-8 °C/1 mmHg); i.r. (film) ν_{max} 3228 (NH), 3060, 3024, 2920, 2830, 2828, 2220, 1602, 1564, 1492, 1382 cm^{-1}; δ_H (60 MHz) 2.90 (1H, br.s. D_2O ex., NH), 2.27 (3H, s, CH_3), 3.63 (2H, s, CH_2N), 3.80 (2H, s, $PhCH_2N$), 5.83-6.00 (1H, m, 4'-H), 6.10 (1H, d, J = 3 Hz, 3'-H), and 7.33 (5H, br.s, PhH) ppm; δ_C (20.1 MHz) 13.5 (q, CH_3), 49.5 (t, CH_2N), 57.0 (t, $PhCH_2N$), 106.0 (d, C-4'), 109.5 (C-3'), 126.9 (d, C-4), 128.2 (d, C-3 and C-5), 129.0 (d, C-2 and C-6), 139.3 (s, C-1), 151.0 (s, C-2'), and (s, C-5') ppm; (m/z); 201 (M^+, 15.7%), 91 (100) M^+ measured 201.1144; calc. for $C_{13}H_{15}NO$ 201.1154.

Reaction of 2-Methylfuran with *N-n*-Butyl-*N*-ethoxymethyl(methylene)iminium Chloride

2-Methylfuran (0.66g, 8 mmol) was added to a solution of the iminium salt (1.65g, 9.2 mmol), (prepared from (**1b**) and trichloromethylsilane), in acetonitrile (40 ml). The mixture was then stirred at room temperature for 22 h. After work-up and Kugelrohr distillation two products were isolated: *N-(5-methylfurfuryl)-n-butylamine* (**3b**) (0.71g, 54%), b.p. 90 °C/1 mmHg, (lit.[18], 110-15 °C/22 mmHg). i.r. (film) ν_{max} 3328 (NH), 3104, 2956, 2924, 2872, 1680, 1614, 1566, 1454 cm^{-1}; δ_H (400 MHz) 0.93 (3H, t, J = 7.5 Hz, $N[CH_2]_3CH_3$), 1.27-1.40 (2H, m, $N[CH_2]_2CH_2$ CH_3), 1.43-1.53 (2H, m, NCH_2CH_2 CH_2CH_3), 1.92 (1H, br.s, D_2O ex., NH), 2.30 (3H, s, $ArCH_3$), 2.63 (2H, t, J = 7.5 Hz, $NCH_2[$ $CH_2]_2CH_3$), 3.73 (2H, s, $ArCH_2N$), 5.83-5.90 (1H, m, 4-H), and 6.05 (1H, d, J = 1.5 Hz, 3-H) ppm; δ_C (100.4 MHz) 13.6 ($ArCH_3$), 14.0 ($[CH_2]_3C$ H_3), 20.5 ($N[CH_2]_2C$ H_2CH_3), 31.9 (NCH_2C $H_2CH_2CH_3$), 46.3 ($ArCH_2N$), 48.8 (NC $H_2[CH_2]_2CH_3$), 105.9 (C-4), and 107.8 (C-3), 151.4 (C-2), 151.9 (C-5 ppm; (m/z); 167 (M^+, 100%), M+ measured 167.1308; $C_{10}H_{17}NO$ requires 167.1310. The second product was *N,N-di(5-methylfurfuryl)-n-butylamine* (**4b**) (0.14g, 13%), b.p. 150 °C/0.01 mmHg.

_N_-(5-Methylfurfuryl)-_N_-methoxymethyl-_t_-butylamine (5)

2-Methylfuran (1.15g, 14 mmol) was added to a solution of _N_-methoxymethyl-_N_-t-butyl(methylene)iminium chloride (2.48g, 15 mmol) (prepared from **1c** and $Et_2O.HCl$) in acetonitrile (40 ml) under nitrogen. The mixture was stirred at room temperature for 17 h followed by the addition of di-isopropylethylamine (2.07g, 16 mmol). Stirring was continued for 10 minutes and the solvent was removed in *vacuo*. The residue, a crystalline solid, was washed with light petroleum ether (3x40 ml). The combined organic washings were concentrated in *vacuo* and the residue, a pale yellow oil (2.20g), was purified by Kugelrohr distillation affording *N-(5-methylfurfuryl)-N-methoxymethyl-t-butylamine* (**5**) (1.38g, 47%), b.p. 80 °C/0.1 mmHg. i.r. (film) ν_{max} 2972, 2804, 1568, 1468, 1394, 1362 cm^{-1}; δ_H (250 MHz) 1.21 (9H, s, $C[CH_3]_3$), 2.26 (3H, s, $ArCH_3$), 3.37 (3H, s, OCH_3), 3.85 (2H, s, $ArCH_2N$), 4.18 (2H, s, NCH_2OMe), 5.85-5.86 (1H, m, 4-H), and 6.03 (1H, δ, J = 2.9 Hz, 3-H) ppm; δ_C (62.1 MHz) 13.6 (5-CH_3), 28.6 ($C[C\ H_3]_3$), 42.6 ($ArCH_2N$), 54.3 (CMe_3), 54.4 (OCH_3), 82.5 (NCH_2OMe), 105.9 (C-4), 108.4 (C-3), 151.1 (C-2), and 152.7 (C-5) ppm; (m/z); 211(M^+, 2.6%), 95 (100), M^+ measured 211.1579; $C_{12}H_{21}NO_2$ requires 211.1572.

_N_-(5-Methylfurfuryl)-_N_-ethoxymethylisopropylamine (7)

Paraformaldehyde (1.5g, 50 mmol equiv.) was added to a mixture of _N_-(5-methylfurfuryl)isopropylamine (**3a**) (7.66g, 50 mmol), ethanol (46.08g, 1 mol) and potassium carbonate (6.91g, 50 mmol). The mixture was vigorously stirred for 36 h at room temperature. The solid was filtered off and washed with dry ethanol (30 ml). The ethanol was removed by distillation through an 18" Vigreux column and the residue was distilled under reduced pressure, (Kugelrohr), yielding *N-(5-methylfurfuryl)-N-ethoxymethyl-isopropylamine* (**7**) (7.85g, 74%), b.p. 65 °C /0.03 mmHg. i.r. (film) ν_{max} 2968, 1680, 1566, 1454, 1384 cm^{-1}; δ_H (60 MHz) 0.97-1.30 (9H, t, CH_2CH_3, and d, $CH[CH_3]_2$), 2.27 (3H, s, 5-CH_3), 3.10 (1H, sept., J = 6 Hz, $CHMe_2$), 3.40 (2H, q, J = 7.5 Hz, NCH_2CH_3), 3.80 (2H, s, $ArCH_2N$), 4.20 (2H, s, NCH_2OEt), 5.77-5.93 (1H, m, 4-H), and 6.03 (1H, d, J = 3 Hz, 3-H) ppm; δ_C (20.1 MHz) 13.5 (q, 5-CH_3), 15.3 (q, CH_2CH_3), 20.7 (q, $CH[C\ H_3]_2$), 44.8 (t, $ArCH_2N$), 51.1 (d, $CHMe_2$), 62.5 (t, $OC\ H_2CH_3$), 82.3 (t, NCH_2O), 106.0 (d, C-4), 108.5 (d, C-3), 151.2 (s, C-2), and 152.0 (s, C-5) ppm; (m/z); 211 (M^+, 11.9%), 166 (100), M^+ measured 211.1536; $C_{12}H_{21}NO_2$ requires 211.1572.

_N_-Isopropyl-_N_-(5'-methylfurfuryl)-1-methyl-3-indolylmethylamine (8)

Chlorotrimethylsilane (1.64g, 11 mmol) was added dropwise to a mixture of _N_-methylindole (1.31g, 10 mmol) and _N_-(5-methylfurfuryl)-_N_- ethoxymethylisopropylamine (**7**) (2.32g, 11 mmol) in acetonitrile (40 ml) at 0 °C under nitrogen. After 4 h water (20 ml) was added and the solvent was removed in *vacuo*. The residue was washed with ether (3x20 ml) and then basified to pH 14 with 4M sodium hydroxide and extracted with ether (3x30 ml). The combined organic extracts from the basic solution were dried and concentrated in *vacuo* to a brown viscous oil which was triturated with ether / petroleum ether (40-60 °C) and cooled at – 20 °C, crystallising as a brown solid. Recrystallisation from 20% aqueous ethanol afforded *N-isopropyl-N-(5'-methylfurfuryl)-1-methyl-3-indolylmethylamine* (**8**) as a white solid (2.09g, 71%), m.p. 46-48 °C. Found: C, 77.29; H, 7.98; N, 9.58. $C_{19}H_{24}N_2O$ requires C, 76.99; H, 8.16; N, 9.45%; i.r. (KBr) ν_{max} 2964, 1652, 1566, 1556, 1470, 1424, 1384, 1360 cm^{-1}; δ_H (250 MHz) 1.07 (6H, d, J = 6.5 Hz, $CH[CH_3]_2$), 2.27 (3H, s, 5'-CH_3), 3.08 (1H, sept. J = 6.5 Hz, $CHMe_2$), 3.60 (2H, s, 2'-CH_2N), 3.74 (3H, s, NCH_3), 3.79 (2H, s, 3-CH_2N), 5.86-5.87 (1H, m, 4'-H), 6.04 (1H, d, J = 2.9 Hz, 3'-H), 7.00 (1H, s, 2-H), 7.08-7.26 (3H, m, 4-H, 5-H, and 6-H), and 7.74-7.77 (1H, m, 7-H) ppm; δ_C (62.9 MHz) 13.6 (5'-CH_3), 18.2 ($CH[C\ H_3]_2$), 32.4 (NCH_3), 44.6 (2'-CH_2N), 46.1 (3-CH_2N), 49.3 ($CHMe_2$), 105.9 (C-4'), 108.1 (C-3'), 108.9 (C-7), 113.2 (C-3), 118.6 (C-4), 120.0 (C-5), 121.4 (C-6), 127.8 (C-2), 128.2 (C-3a), 137.2 (C-7a), 150.7 (C-2'), and

152.7 (C-5']-) ppm; (m/z); 296 (M^+, 5.9%), 144 (100), M^+ measured 296.1878; $C_{19}H_{24}N_2O$ requires 296.1888.

2,4-Dimethoxy-*N*-*t*-butylbenzylamine (9)

1,3-Dimethoxybenzene (10.36g, 75 mmol) was added to the iminium salt (2.48g, 15 mmol) (prepared from (**1c**) and Et_2O.HCl) in acetonitrile (75 ml). The mixture was stirred at room temperature for 5 days, affording after work-up, unreacted 1,3-dimethoxybenzene (8.21g, 79%) and *2,4-dimethoxy-N-t-butylbenzylamine* (**9**) (2.20g, 66%), b.p. 115 °C/0.01 mmHg. i.r. (film) ν_{max} 3320 (NH), 2960, 2832, 1614, 1588, 1508, 1466 cm^{-1}; δ_H (60 MHz) 1.18 (9H, s, $C[CH_3]_3$), 1.25 (1H, br.s, D_2O ex., NH), 3.63 (2H, s, CH_2N), 3.77 (6H, s, OCH_3), 6.27-6.60 (2H, m, 5-H and 6-H), and 7.17 (1H, d, J_{AB} = 9 Hz, 3-H) ppm; δ_C (20.1 MHz) 29.1 (q, $C[CH_3]_3$), 41.9 (t, CH_2N), 50.5 (s, CMe_3), 55.1 (q, OCH_3), 98.5 (d, C-3), 104.0 (d, C-5), 122.1 (s, C-1), 130.2 (d, C-6), 158.4 (s, C-4), and 160.0 (s, C-2) ppm; (m/z); 223 (M^+, 3.8%), 151 (100), M^+ measured 223.1572; $C_{13}H_{21}NO_2$ requires 223.1572.

2-(*N*-*t*-Butylaminomethyl)-1-methylpyrrole (10)

N-methylpyrrole (1.22g, 15 mmol) in dichloromethane (25 ml) cooled to -78 °C was added to a solution of the iminium salt (2.73g, 16.5 mmol) (prepared from **1c** and Et_2O·HCl) in dichloromethane (25 ml) at -78 °C and gave after 8 h, *2-(N-t-butylaminomethyl)-1-methylpyrrole* (**10**) (1.22g, 59%), b.p. 80 °C /0.5 mmHg; i.r. (film) ν_{max} 3300 (NH), 3100, 2962, 1658, 1497, 1473, 1362 cm^{-1}; δ_H (60 MHz) 0.77 (1H, br.s, D_2O ex., NH), 1.17 (9H, s, $C[CH_3]_3$), 3.60 (3H, s, NCH_3), 3.63 (2H, s, NCH_2), 5.87-6.03 (2H, m, 3-H and 4-H), 6.37-5.53 (1H, m, 5-H) ppm; δ_C (20.1 MHz) 28.9 (q, $C[CH_3]_3$), 33.4 (q, NCH_3), 38.7 (t, CH_2N), 50.2 (s, CMe_3), 106.4 (d, C-3), 107.3 (d, C-4), 122.0 (d, C-5), and 131.9 (s, C-2) ppm; (m/z); 166 (M^+, 16.7%), 94 (100), M^+ measured 166.1448; $C_{10}H_{18}N_2$ requires 166.1470.

***N,N*- Di(1-methyl-2-pyrrolylmethyl)isopropylamine (11)**

N-methylpyrrole and the iminium salt (prepared from **1a** and trichloromethylsilane) yielded *N,N- di(1-methyl-2-pyrrolylmethyl)isopropylamine* (**11**) (67%) as pale yellow crystals, m.p. 86-88 °C. i.r. (KBr) ν_{max} 3100, 2964, 2928, 2804, 1684, 1634, 1558, 1494 cm^{-1}; δ_H (60 MHz) 1.03 (6H, d, J = 6 Hz, $CH[CH_3]_2$), 2.97 (1H, sept., J = 6 Hz, $CHMe_2$), 3.40 (6H, s, NCH_3), 3.47 (4H, s, NCH_2), 5.93-6.03 (4H, m, 3-H and 4-H), and 6.43-6.57 (2H, m, 5-H) ppm; δ_C (20.1 MHz) 16.7 (q, $CH[CH_3]_2$), 33.2 (q, NCH_3), 44.4 (t, CH_2N), 47.6 (d, $CHMe_2$), 106.3 (d, C-3), 109.7 (d, C-4), 122.2 (d, C-5), and 130.0 (s, C-2) ppm; (m/z); 245 (M^+, 4.6%), 94 (100), M^+ measured 245.1866; $C_{15}H_{23}N_3$ requires 245.1892.

***N,N*-Di(1-methyl-3-indolylmethyl)isopropylamine (13)**

N-methylindole (2.36g, 18 mmol) and the iminium salt prepared from (**1a**) afforded *N,N-di(1-methyl-3-indolylmethyl)isopropylamine* (**13**) (2.10g, 67.5%) m.p. 119-120 °C. Found: C, 80.25; H, 8.18; N, 12.20 $C_{23}H_{27}N_3$ requires C, 79.96; H, 7.88; N, 12.16%; i.r. (KBr) ν_{max} 3052, 2960, 2868, 2808, 1872, 1756, 1656, 1616, 1574 cm^{-1}; δ_H (60 MHz) 1.10 (6H, d, J = 6 Hz, $CH[CH_3]_2$), 3.20 (1H, sept., J = 6 Hz, $CHMe_2$), 3.55 (6H, s, NCH_3), 3.77 (4H, s, CH_2N), 6.83 (2H, s, 2-H), 6.93-7.23 (6H, m, 4-H, 5-H, and 6-H), 7.57-7.83 (2H, m, 7-H) ppm; δ_C (20.1 MHz) 17.3 (q, $CH[CH_3]_3$), 32.0 (q, NCH_3), 44.6 (t, CH_2N), 48.0 (d, $CHMe_2$), 108.9 (d, C-7), 113.7 (s, C-3), 118.5 (d, C-5), 120.1 (d, C-4), 121.3 (d, C-6), 127.8 (d, C-2), 128.2 (s, C-3a), and 137.3 (s, C-7a) ppm; (m/z); 345 (M^+, 6.7%), 144 (100), M^+ measured 345.2188; $C_{23}H_{27}N_3$ requires 345.2205.

Reaction of *N*-methylindole with *N,N*- Bis(ethoxymethyl)isopropylamine (1a)

Ethereal hydrogen chloride (1.07M, 15.4 ml, 16.5 mmol) was added to a mixture of *N*-methylindole (1.97g, 15 mmol) and (**1a**) (2.89g, 16.5 mmol) in acetonitrile (45 ml). The mixture was stirred at room temperature for 2 h and the crude product was isolated as a viscous oil. Kugelrohr distillation gave *3-(N- isopropylaminomethyl)-1-methylindole* (**12**) as a pale yellow oil (1.94g, 64%), b.p. 115 °C/0.05 mmHg. i.r. (film) ν_{max} 3376 (NH), 3052, 2960, 2824, 1660, 1614, 1574 cm^{-1}; δ_H (60 MHz) 1.10 (6H, d, J = 6 Hz, CH[CH_3]$_2$), 1.63 (1H, s, D_2O ex., NH), 2.90 (1H, sept., J = 6 Hz, $CHMe_2$), 3.60 (3H, s, NCH_3), 3.93 (2H, s, CH_2N), 6.92 (1H, s, 2-H), 6.97-7.30 (3H, m, 4-H, 5-H, and 6-H), and 7.53-7.73 (1H, m, 7-H) ppm; δ_C (20.1 MHz) 23.0 (q, CH[*C* H_3]$_2$), 32.2 (q, NCH_3), 42.4 (t, CH_2N), 48.8 (d, $CHMe_2$), 109.1 (d, C-7), 114.0 (s, C-3), 118.9 (d, C-4 and C-5]), 121.5 (d, C-6), 126.9 (d, C-2), 127.6 (s, C-3a), and 137.2 (s, C-7a) ppm; (m/z); 202 (M^+, 14.4%), 144 (100), M^+ measured 202.1420; $C_{13}H_{18}N_2$ requires 202.1470. The residue after distillation was recrystallised from aqueous ethanol to give *N,N-di(1-methyl-3-indolylmethyl)isopropylamine* (**13**) (0.79g, 30%), m.p. 119-121 °C.

3-(*N-t*-Butylaminomethyl)-1-methylindole (14)

A solution of *N*-methylindole and the iminium salt (prepared from **1c** and Et_2O·HCl) in dichloromethane (25 ml) at -78 °C gave *3-(N-t-butylaminomethyl)-1-methylindole* (**14**) as a pale yellow oil (80%), b.p. 110-120 °C/0.01 mmHg. i.r. (film) ν_{max} 3304 (NH), 3052, 2960, 2876, 2820, 1614, 1556, 1474 cm^{-1}; δ_H(60 MHz) 0.93 (1H, br.s, D_2O ex., NH), 1.20 (9H, s, C[CH_3]$_3$), 3.50 (3H, s, NCH_3), 3.87 (2H, s, CH_2N), 6.87 (1H, s, 2-H), 6.97-7.27 (3H, m, 4-H, 5-H, and 6-H), 7.47-7.73 (1H, m, 7-H) ppm; δ_C (20.1 MHz) 29.1 (q, C[*C* H_3]$_3$), 32.3 (q, NCH_3), 37.8 (t, NCH_2), 50.4 (s, CMe_3), 109.2 (d, C-7), 114.3 (s, C-3), 118.8 (d, C-4 and C-5), 121.6 (d, C-6), 127.0 (d, C-2), 127.5 (s, C-3a), and 137.2 (s, C-7a) ppm; (m/z); 216 (M^+, 16.0%), 144 (100), M^+ measured 216.1618; $C_{14}H_{20}N_2$ requires 216.1626.

Reaction of Furan with *N*-Ethoxymethyl-*N-n*-isopropyl(methylene)iminium Chloride

Furan was added to the iminium salt (prepared from **1a** and trichloromethylsilane) in acetonitrile and gave after distillation (Kugelrohr) two products: *N- furfurylisopropylamine* (**15**) (40%), b.p. 90 °C/15 mmHg, (lit.[19], 82-5 °C/19 mmHg); i.r. (film) ν_{max} 3320 (NH), 3112, 2968, 2868, 2828, 2636, 1632, 1600, 1502, 1466, 1442 cm^{-1}; δ_H (60 MHz) 1.07 (6H, d, J = 6 Hz, CH[CH_3]$_2$), 1.50 (1H, br.s, D_2O ex., NH), 2.80 (1H, sept., J = 6 Hz, $CHMe_2$), 3.77 (2H, s, NCH_2), 6.07-6.37 (2H, m, 3-H and 4-H), and 7.23-7.37 (1H, m, 5-H) ppm; δ_C (20.1 MHz) 18.8 (q, CH[*C* H_3]$_2$), 46.3 (t, CH_2N), 50.7 (d, $CHMe_2$), 107.9 (d, C-3), 110.1 (d, C-4), 141.6 (d, C-5) and 153.7 (s, C-2) ppm; (m/z); 139 (M^+, 8.7%), 81 (100), M^+ measured 139.0973; $C_8H_{13}NO$ requires 139.0997. The second product was *N,N-di(furfuryl)isopropylamine* (**16**) (30%), b.p. 75 °C/0.05 mmHg. i.r. (film)ν_{max} 2964, 1598, 1500, 1460, 1382 cm^{-1}; δ_H (60 MHz) 1.03 (6H, d, J = 6 Hz, CH[CH_3]$_2$), 2.93 (1H, sept., J = 6 Hz, $CHMe_2$), 2.63 (4H, s, CH_2N), 6.00-6.30 (4H, m, 3-H and 4-H), and 7.20-7.33 (2H, m, 5-H) ppm; δ_C (20.1 MHz) 22.8 (q, CH[*C* H_3]$_2$), 43.9 (t, NCH_2), 47.7 (d, $CHMe_2$), 106.6 (d, C-3), 110.2 (d, C-4), 141.7 (d, C-5), and 154.5 (s, C-2) ppm; (m/z); 219 (M^+, 5.6%), 81 (100), M^+ measured 219.1254; $C_{13}H_{17}NO_2$ requires 219.1259.

Reaction of Furan with *N*-Methoxymethyl-*N-t*-butyl(methylene)iminium Chloride

Furan was added to the iminium salt (prepared from **1c** and Et_2O·HCl) in acetonitrile and gave after distillation (Kugelrohr) two products: *N- furfuryl-t-butylamine* (**17**) (0.72g, 31%), b.p. 80 °C/8 mmHg; i.r. (film) ν_{max} 3320 (NH), 3130, 2960, 1600, 1505, 1480, 1445, 1390, 1305 cm^{-1}; δ_H (60 MHz) 1.10 (9H, s, C[CH_3]$_3$),

1.17 (1H, br.s. D_2O ex., NH), 3.75 (2H, s, CH_2N), 6.07-6.37 (2H, m, 3-H and 4-H), and 7.27-7.37 (1H, m, 5-H) ppm; δ_C (20.1 MHz) 29.0 (q, C[*C* $H_3]_3$), 40.1 (t, CH_2N), 50.5 (s, CMe_3), 106.1 (d, C-3), 110.2 (d, C-4), 141.5 (d, C[-5), and 154.9 (s, C-2) ppm; (m/z); 153 (M^+, 2.7%), 81 (100), M+ measured 153.1153; $C_9H_{15}NO$ requires 153.1154. The second product was *2,5-di(N-t-butylaminomethyl)furan* (**18**) (21%), b.p. 80 °C/0.01 mmHg; i.r. (film) ν_{max} 3304 (NH), 2964, 2868, 1566, 1478, 1446, 1388, 1362 cm^{-1}; δ_H (60 MHz) 1.17 (18H, s, 2xC[*CH*$_3$]$_3$), 2.33 (2H, br.s, D_2O ex., 2 NH's), 3.73 (4H, s, 2xCH_2N), 6.08 (2H, s, 3-H and 4-H) ppm; δ_C (20.1 MHz) 29.0 (q, C[*C* $H_3]_3$), 40.2 (t, CH_2N), 50.5 (s, CMe_3), 106.9 (d, C-3 and C-4), and 153.9 (s, C-2 and C-5) ppm; (m/z); 238 (M^+, 13.6%), 166 (99), 110 (100), M^+ measured 238.2045; $C_{14}H_{26}N_2O$ requires 238.2045.

Reaction of an Excess of Furan with *N*-Methoxymethyl-*N*-*t*-butyl(methylene)iminium Chloride

Furan was added to the iminium salt (prepared from **1c**) in acetonitrile and yielded after distillation (Kugelrohr) two products: *N- furfuryl-t-butylamine* (**17**) (24%), b.p. 80 °C/8 mmHg. The second product was*N,N-di(furfuryl)-t-butylamine* (**19**) (62%), b.p. 90 °C/0.05 mmHg; i.r. (film) ν_{max} 3112, 2972, 1596, 1504, 1364 cm^{-1}; δ_H (20.1 MHz) 1.13 (9H, s, C[*CH*$_3$]$_3$), 3.80 (4H, s, CH_2N), 6.07-6.33 (4H, m, 3-H and 4-H), and 7.27-7.40 (2H, m, 5-H) ppm; δ_C (20.1 MHz) 27.4 (q, C[*C* $H_3]_3$), 44.4 (t, CH_2N), 54.5 (s, CMe_3), 107.8 (d, C-3), 110.1 (d, C-4), 141.3 (d, C-5), and 154.5 (s, C-2) ppm; (m/z); 233 (M^+, 22.9%), 218 (90), 70 (100), M^+ measured 233.1410; $C_{14}H_{19}NO_2$ requires 233.1416.

REFERENCES

1. Reichert, B. "Die Mannich Reaktion", Springer-Verlag, Berlin, **1959**; Hellman, H; Opitz, G. "α-Aminoalkylierung", Verlag Chemie, Weinheim, **1960**; Tramontini, M. *Synthesis*, **1973**, 703-775; Tramontini, M.; Angiolini, L. *Tetrahedron*, **1990**, *46*, 1791-1837.
2. Hertz, W.; Rogers, J.L. *J. Am. Chem. Soc.*, **1951**, *73*, 4921-4923; Hertz, W.; Ditter, K.; Cristol, S.J. *J. Am. Chem. Soc.*, **1947**, *69*, 1698-1700.
3. Raines, S.; Kovacs, C.A. *J. Heterocycl. Chem.*, **1970**, *7*, 223-225.
4. Danishefsky, S.; Guingant, A.; Prisbylla, M. *Tetrahedron Lett.*, **1980**, 2033-2036.
5. Katritzky, A.R.; Rachwall, S.; Rachwall, B. *J. Chem. Soc., Perkin Trans. 1*, **1987**,791-798; Katritzky, A.R.; Rachwall, S.; Rachwall, B. *ibid.*, **1987**, 799-804; Katritzky, A.R.; Rachwall, S.; Rachwall, B., *ibid.*, **1987**, 805-809; Katritzky, A.R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *ibid.*, **1989**, 225-233; Katritzky, A.R.; Zhao, X.; Hitchings, G.J. *Synthesis*, **1991**, 703-707.
6. Katritzky, A.R.; Noble, G.; Pilarski, B.; Harris, P. *Chem. Ber.*, **1990**, *123*, 1443-1445
7. Katritzky, A.R.; Hong, Q.; Yang, Z. *J. Org. Chem.*, **1994**, *59*, 7947-7948; Katritzky, A.R.; Hong, Q.; Yang, Z. *J. Org. Chem.*, **1995**, *60*, 3405-3408.
8. Earle, M.J.; Fairhurst, R.A.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Tetrahedron Lett.*, **1990**, *31*, 4229-4232.
9. Katritzky, A.R.; Yang, Z.; Lam, J.N. *Tetrahedron*, **1992**, *48*, 4971-4978.

10. Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Tetrahedron Lett.*, **1988**, *29*, 2377-2380-; Eyley, S.C.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *ibid.*, 2997-3000; Fairhurst, R.A.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *ibid.*, 5801-5804; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *J. Chem. Soc., Chem. Commun.*, **1988**, 1161-1163; Cooper, M.S.; Fairhurst, R.A.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Tetrahedron*, **1989**, *45*, 1155-1166; Fairhurst, R.A.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Tetrahedron Lett.*, **1989**, *30*, 1433-1436.
11. (a). Fields, D.L.; Miller, J.B.; Reynolds, D.D. *J. Org. Chem.*, **1962**, *27*, 2749-2753; (b) Reynolds, D.D. *J. Heterocycl.*, **1970**, *7*, 1397-1400; (c) Reynolds, D.D.; Cossar, B.C. *ibid.*, **1971**, *8*, 611-615; (d) Ahn, J.S.; Hahm, D.G.; Heaney, H.; Wilkins, R.F. *Bull. Korean Chem. Soc.*, **1994**, *15*, 617-618; (e) El Gihani, M.T.; Heaney, H.; Slawin, A.M.Z. *Tetrahedron Lett.*, **1995**, *36*, 4905-4908.
12. Cooper, M.S.; Earle, M.J.; Fairhurst, R.A.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Synlett.*, **1990**, 617-618; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Tetrahedron*, **1995**, *51*, 10737-10750.
13. Gaines, J.R.; Swanson, A.W. *J. Heterocycl. Chem.*, **1971**, *8*, 249-251
14. Johnson, P.Y.; Jacobs, I.; Kerkman, D.J. *J. Org. Chem.*, **1975**, *40*, 2710-2720.
15. Böhme, H.; Viehe, H.G. "Iminium Salts in Organic Chemistry", Part 1, in " Advances in Organic Chemistry", Vol. 9, ed. Taylor, E.C. John Wiley and sons, Interscience, New York, 1976 and 1979.
16 Rochin, C.; Babot, O.; Dungues, J.; Duboudin, F. *Synthesis*, **1986**, 228-229.
17. Azerbaev, I.N.; Erzhanov, K.B.; Omarova, T.A.; Konysbaev, Z.K. *Izv. Akad. Nauk. Kaz. SSR, Ser. Khim.*, **1978**, *28*, 70-75; *Chem. Abs.*, **1978**, *88*, 190550s.
18. Holdren, R.F.; Hixon, R.M. *J. Am. Chem. Soc.*, **1946**, *68*, 1198-1200.
19. Grail, G.F.; Tenenbaun, L.E.; Tolstoouhov, A.V.; Duca, C.J.; Reinhard, J.F.; Anderson, F.E.; Scudi, J.V. *J. Am. Chem. Soc.*, **1952**, *74*, 1313-1315.

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