Tetrahedron Vol. 48, No. 23, pp. 4971-4978, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Aminoalkylbenzotriazoles: Reagents for the Aminoalkylation of Electron Rich Heterocycles

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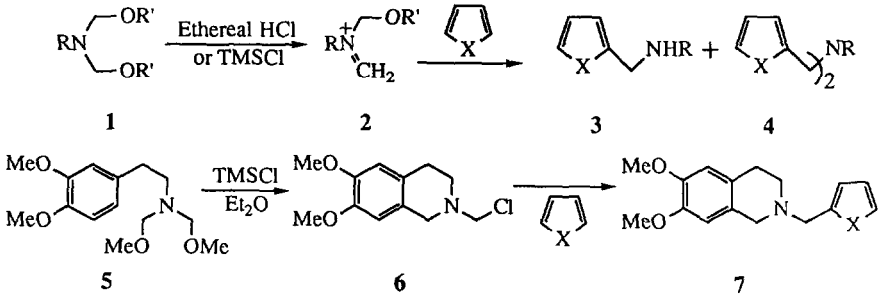
(*Received in UK* 11 *October* 1991)

Key Words: Mannich Reaction/C-Alkylation/Lewis Acid/Indole/Pyrrole/Furan

Abstract: *Secondary and tertiary aminoalkylbenzotriazoles react with pyrrole, indole, their N-methyl analogs and with 2-methylfuran under mild reaction conditions in the presence of a Lewis acid to afford selectively the corresponding secondary or tertiary amines.*

C-Aminoalkylations of electron rich heterocycles generally involve reaction of an amine hydrochloride (or of the amine in acetic acid) and formaldehyde with the heterocycle.[1-4] These Mannich reactions have also been carried out with bis(dialkylamino)methanes or alkoxydialkylaminomethanes activated by acetyl chloride, by sulfur dioxide,[5] or by chlorosilane derivatives.[6] Recently, Heaney and his collaborators[7] used N,N-bis(alkoxymethyl)amines [$RN(CH_2OR')_2$, **1**] as precursors for the synthesis of secondary amines in reactions with pyrroles, indoles and furans, via conversion of **1** to an intermediate iminium salt **2** with ethereal HCl or trimethylsilyl chloride in pentane (Scheme 1). Earlier use of bis(butoxymethyl)-*t*-butylamine in a Grignard-Reformatsky reaction involved a Lewis acid promoted N-alkyl-N-alkoxymethylmethyleneiminium salt.[8]



Scheme 1

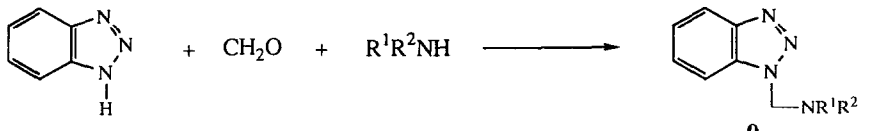
* *This paper is dedicated to the 75th birthday of Professor Gabor Fodor, in appreciation of his science and friendship (ARK).*

As Heaney pointed out, the extensive investigations into the preparation of Mannich bases,[9-12] deal predominantly with the formation of tertiary amines. It has been found that when a primary amine is employed as the starting material in a Mannich reaction, it can react at both amine H-atoms making it difficult to obtain secondary Mannich bases in high yield.[13] The use of oxalate derivatives of primary amines, of sterically hindered primary amines, or the presence of bulky auxiliary groups (which are subsequently removed)[14] does alleviate this problem. However, newer and more general methods for Mannich syntheses of secondary amines are desirable and Heaney's work, in which he has made use of a variety of nucleophiles,[7,15] is a useful step in this direction. Thus the bis ether **5** afforded N-arylmethyl-1,2,3,4-tetrahydroisoquinolines **7** in good yields.[15] However, his aminoalkylations on heterocyclic systems[7] to afford secondary amines **3** were more difficult. In many cases, when the iminium salt **2** was generated using ethereal HCl, mixtures of the secondary **3** and tertiary **4** amines were obtained. Trimethylsilyl chloride gave only the tertiary amine **4**. Furthermore, the yields depended largely on the N-alkyl substituent and were frequently moderate. Bulky substituents (*t*-butyl) inhibited formation of tertiary amines while with isopropyl and *n*-butyl substituents, tertiary amines were also obtained.

Recent work in our laboratory has utilized benzotriazole extensively as a synthetic auxiliary. We have demonstrated that benzotriazole is a good leaving group by displacing it with a variety of nucleophiles.[16] Such displacement of benzotriazole from aminoalkylbenzotriazoles occur via iminium intermediates. These derivatives thus have potential as aminoalkylating agents for electron rich heterocyclic systems and we present here some of our results in this direction.

Synthesis of Secondary and Tertiary Aminoalkylbenzotriazoles

Aminoalkylbenzotriazoles have been prepared by a variety of methods in our laboratory.[16] The method employed here was developed recently for the synthesis of secondary amines.[17] Thus, equimolar ratios of benzotriazole, formaldehyde, and the appropriate amine were stirred at ambient temperature in diethyl ether (Scheme 2) to give the corresponding Mannich bases **9a-e** as mixtures of the 1- and 2-substituted derivatives in yields of over 90%. Four known compounds show spectral properties in agreement with the literature data and the new one (**9e**) was characterized by its ^1H and ^{13}C NMR spectra and used without further purification. Compounds **9** are formed as 1-substituted benzotriazole derivatives; in solution they exist in equilibrium with their 2-substituted isomer. This behavior is known and has been reported in the literature.[16]



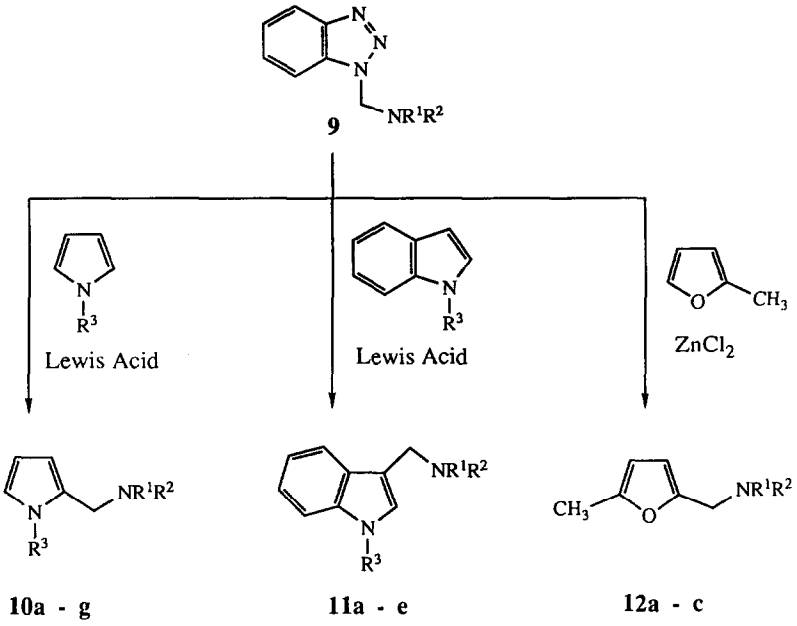
8 **9**

a) R^1R^2 = -$(CH_2)_4$-
b) R^1R^2 = -$(CH_2)_5$-
c) R^1 = H; R^2 = *c*-C_6H_{11}
d) R^1 = H; R^2 = *c*-C_5H_9
e) R^1 = H; R^2 = Bu

Scheme 2

C-Alkylation of NH-Heterocycles

Tertiary Amines. The tertiary amines **9a,b** were heated under reflux in methylene chloride for 3 h with pyrrole or N-methylpyrrole in the presence of aluminium(III) chloride (Scheme 3) to afford the aminoalkylated products (**10a-c**) in yields of 70-96% (Table 1). With indole and N-methylindole, the reaction occurred at the more reactive 3-position to afford **11a** (84%) and **11b** (91%) respectively. The products were all characterized by their NMR spectral data (Tables 2 and 3). In particular, the methylene protons appeared as singlets between 3.36 and 3.81 ppm. The upfield shift (ca 2 ppm) of these protons from those observed for the starting materials indicated C-alkylation had occurred on the aromatic ring of the heterocycle. The methylene signals for the pyrrole derivatives were about 0.2 ppm upfield from those of the indole derivatives. Compounds **10a-c** and **11a,b** have been reported in the literature. These compounds have previously been synthesized by reacting the heterocycle with the amine hydrochloride and formaldehyde[3,4] or with aminals activated by trimethylsilyl chloride.[6] As can be seen in Table 1, with the exception of one case, our yields are much higher than those previously reported.



For structures of R^1 - R^3 see Table 1

Scheme 3

Secondary Amines. Using Aluminium(III) chloride, the secondary aminoalkylbenzotriazoles **9c-e** afforded uncharacterizable tars. However, the milder Lewis acid zinc(II) chloride gave the secondary amines **10d-g** and **11c-e** in yields of 62-93% (Table 1). The isolated yields for the pyrrole adducts were lower than for the indoles. However, the problem was not incomplete reaction or formation of tertiary amines but one of purification. The yields of the crude amines isolated from the reaction mixtures were about 85-95% (as

determined by GC). Of special interest are the N-butyl analogs **10e** and **11d**. Here, without the presence of a bulky N-substituted group, there was no indication of the corresponding tertiary amine being formed. This is in contrast to Heaney's work[7] where even with the more bulky isopropyl group, tertiary amines were obtained. With indole and **9e**, the corresponding secondary amine was obtained along with a small amount (ca 10%) of the tertiary amine N-butyl-bis(indol-3-ylmethyl)amine (as evidenced by the NMR of the crude mixture). However, with N-methylindole, the secondary amine **11d** was isolated in 89% yield. In the ^1H spectra of the secondary amines, the methylene protons showed similar patterns to those observed for the tertiary amines but were about 0.2 ppm further downfield. On the other hand, in the ^{13}C NMR, the methylene carbon signal appeared between 5 and 10 ppm upfield from the corresponding tertiary amine signal.

None of the secondary amines **10d-g** and **11c-e** has previously been reported. Analogous compounds (N-methyl, N-ethyl and N-isopropyl) have previously been obtained in yields of 15-40% by reaction of the amine hydrochloride and formaldehyde with pyrrole.[2,3]

Table 1. Preparation of Secondary and Tertiary Amines.[a]

Compd	R^1	R^2	R^3	Lewis Acid	Yield[b] (%)	Molecular Formula	HRMS Found	HRMS Reqd.
10a		$-(CH_2)_4-$	H	$AlCl_3$	92(71)[4]	$C_9H_{14}N_2$		
10b		$-(CH_2)_4-$	Me	$AlCl_3$	96(75)[6]	$C_{10}H_{16}N_2$		
10c		$-(CH_2)_5-$	Me	$AlCl_3$	70(86)[3](38)[6]	$C_{11}H_{18}N_2$		
10d	H	*c*-C_6H_{11}	H	$ZnCl_2$	64	$C_{11}H_{18}N_2$	178.1459	178.1469
10e	H	Bu	Me	$ZnCl_2$	62	$C_{10}H_{18}N_2$	166.1470	166.1470
10f	H	*c*-C_5H_9	Me	$ZnCl_2$	71	$C_{11}H_{18}N_2$	178.1460	178.1469
10g	H	*c*-C_6H_{11}	Me	$ZnCl_2$	82	$C_{12}H_{20}N_2$	192.1620	192.1626
11a		$-(CH_2)_5-$	H	$AlCl_3$	84(75)[4,c]	$C_{14}H_{18}N_2$		
11b		$-(CH_2)_4-$	Me	$AlCl_3$	91(71)[4]	$C_{14}H_{18}N_2$		
11c	H	*c*-C_6H_{11}	H	$ZnCl_2$	87	$C_{15}H_{20}N_2$	228.1626	228.1626
11d	H	Bu	Me	$ZnCl_2$	89	$C_{14}H_{20}N_2$	216.1628	216.1626
11e	H	*c*-C_6H_{11}	Me	$ZnCl_2$	93	$C_{16}H_{22}N_2$	242.1785	242.1783
12a		$-(CH_2)_5-$	-	$ZnCl_2$	87(77)[1]	$C_{11}H_{17}NO$	179.1310	179.1310
12b	H	Bu	-	$ZnCl_2$	58(53)[7]	$C_{10}H_{17}NO$	167.1317	167.1310
12c	H	*c*-C_5H_9	-	$ZnCl_2$	47	$C_{11}H_{17}NO$	179.1317	179.1310

[a] Except for **11a**, all compounds were obtained as oils. [b] Yields in parenthesis are yields from the literature references cited. [c] Colorless plates, m.p. 158-160 °C, (lit.[4] m.p. 160-161 °C).

C-Alkylation of 2-Methylfuran

2-Methylfuran, with **9b, 9d,** or **9e** in the presence of zinc(II) chloride, gave the corresponding amines **12a-c.** While the yield of the tertiary amine **12a** was good (87%), the yields of the secondary amines **12b,c** were lower (58 and 47% respectively). Heaney[7] obtained 53% of **12b** in addition to 13% of the tertiary amine while we only obtained the secondary amine **12b** for the N-butyl case. The compounds were characterized by their ^1H and ^{13}C NMR spectra (Tables 2 and 3) and by HRMS. As in the case of the nitrogen heterocycles, the methylene protons for the tertiary amines were upfield (ca 0.25 ppm) as compared to those of the secondary amines.

Table 2. ^1H NMR data of Secondary and Tertiary Amines

Product	Heterocycle	CH_2N^a	NR^1R^2
10a	10.9-10.7(bs,1H), 6.64[b], 6.1-6.0[c]	3.61	2.54[d], 1.78[d]
10b	6.55[b], 6.1-5.95[c], 3.62[e]	3.53	2.45[d], 1.73[d]
10c	6.56[b], 6.02-5.95[c], 3.63[e]	3.36	2.36[d], 1.51[d], 1.455-1.35[c]
10d	9.6-9.5(bs,1H), 6.65[b], 6.1-6.0[c]	3.80	2.49[b], 2.0-1.5(m,6H), 1.3-1.0[d] [f]
10e	6.55[b], 6.05-5.95[c], 3.61[e]	3.70	2.62(t,2H,*J*=7 Hz), 1.55-1.3[d], 1.20(bs,1H), 0.91(t,3H,*J*=7.3 Hz)
10f	6.54[b], 6.03-5.98[c], 3.61[e]	3.68	3.15-3.05[b], 1.85-1.25(m,9H)
10g	6.55[b], 6.03-5.95[c], 3.61[e]	3.72	2.48[b], 1.9-1.5(m,5H), 1.35-1.05(m,5H), [f]
11a	8.9-8.8(bs,1H),7.70[g], 7.3-7.05[h], 6.99(s,1H)	3.72	2.50[d], 1.56[d], 1.4-1.3[c]
11b	7.7-7.6[b], 7.3-7.05[h], 6.99(s,1H), 3.70[e]	3.81	2.6-2.5[d], 1.8-1.7[d]
11c	9.25(bs,1H), 7.60[g], 7.2-7.1[h], 6.87(s,1H)	4.00	2.60[b], 2.0-1.0(m,10H), [f]
11d	7.63[g], 7.3-7.05[h], 6.97(s,1H), 3.70[e]	3.95	2.69(t,2H,*J*=7.1 Hz), 1.6-1.3(m,5H) 0.91(t,3H,*J*=7.2 Hz)
11e	7.61[g], 7.25-7.10[h], 6.93(s,1H), 3.63[e]	3.96	2.55[b], 2.0-1.0(m,10H) [f]
12a	6.1-6.0[b], 5.9-5.8[b], 2.26[e]	3.43	2.38[d], 1.7-1.55[d], 1.45-1.35[c]
12b	6.05-6.0[b], 5.9-5.85[b], 2.26[e]	3.70	2.60(t,2H,*J*=7.0 Hz), 1.5-1.3[d], 0.90(t,3H,*J*=7.2 Hz), [f]
12c	6.05-6.0[b], 5.9-5.85[b], 2.26[e]	3.69	3.08(quintet,1H,*J*=6.8 Hz), 1.9-1.3(m,8H), [f]

[a] (s, 2H). [b] (m, 1H). [c] (m, 2H). [d] (m, 4H). [e] (s, 3H). [f] aliphatic N*H* not observed. [g] (d, *J*=7.8 Hz). [h] (m, 3H).

Conclusions

Tertiary amines have been prepared by a variety of Mannich reactions in the literature. However, secondary amines are more difficult to prepare by Mannich type reactions are usually obtained in low yields and have usually been accompanied by the formation of the corresponding tertiary amines. The methodology

described herein presents a new and convenient route for the selective preparation of either secondary or of tertiary amines under mild reaction conditions and in yields mostly higher than those previously reported.

Experimental

Melting points were determined on a bristoline hot-stage microscope and are uncorrected. ^1H (300 MHz) NMR spectra were recorded on a Varian VXR-300 (FT mode) spectrometer with Me_4Si as internal standard. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument using the solvent peak $CDCl_3$, δ 77.0 as reference. High Resolution Mass Spectromery was carried out on a Finnigan Mat 95. Elemental analyses (C,H,N) were carried out using a Carlo Erba 1106 elemental analyzer. Flash chromatography was run on EM Science silica gel 60 (230-400 mesh).

A General Procedure for Aminomethylbenzotriazoles 9a-e:

A mixture of benzotriazole (1.18 g, 10 mmol) and the corresponding amine (10 mmol) in Et_2O or CH_2Cl_2 (50 mL) was stirred for 5 min at ambient temperature. Formaldehyde (37% aqueous; 1.10 mL, 10 mmol) was added and the reaction mixture stirred for an additional 3 h. The solution was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The solids were purified by crystallization and the oils by column chromatography. Compounds **9a-d** are previously reported in the literature.[17-19]

N-[(Benzotriazolyl)methyl]butylamine (9e): The crude product was obtained as a pale yellow oil (91%) and used without further purification.

A General Procedure for the C-Aminoalkylation of Heterocycles

Preparation of Tertiary Amines: Aluminium(III) chloride (10 mmol) was added to a solution of the aminomethylbenzotriazole (5 mmol) in methylene chloride (20 ml). The corresponding heterocycle (6 mmol) was added and the mixture heated under reflux for 3 h. The product was poured into aqueous NaOH solution (0.2M; 25 ml) and extracted with chloroform (3 x 20 ml). The combined organic extract was washed with aqueous NaOH (1M), water, and dried ($MgSO_4$). The crude materials were purified by column chromatography (chloroform) to afford pale yellow oils (except for **11a** which was isolated as colorless plates).

Preparation of Secondary Amines: As above except zinc(II) chloride was used instead of aluminium(III) chloride.

Table 3. ^{13}C NMR data of Secondary and Tertiary Amines.

Product	Heterocycle	R^3	CH_2N	NR^1R^2
10a	129.2, 117.5, 107.4, 106.9	-	52.8	53.8, 23.3
10b	130.4, 121.8, 108.1, 106.1	33.6	51.4	53.8, 23.4
10c	129.4, 122.2, 109.1, 105.9	33.8	55.0	54.1, 26.0, 24.5
10d	130.6, 117.1, 107.6, 105.9	-	43.7	56.5, 33.3, 26.0, 24.9
10e	131.3, 122.0, 107.4, 106.2	33.5	45.4	49.0, 32.0, 20.4, 13.9
10f	131.7, 122.0, 107.3, 106.3	33.5	44.1	59.2, 33.0, 23.9
10g	131.6, 121.9, 107.2, 106.3	33.5	42.5	56.1, 33.4, 26.1, 24.8
11a	136.0, 128.3, 124.1, 121.6	-	53.8	54.2, 25.8, 24.3
	119.2, 115.2, 111.9, 111.1			
11b	136.7, 127.9, 121.3, 119.2	32.5	50.2	54.0, 23.4
	118.8, 112.2, 109.0, 108.9			
11c	136.2, 126.8, 122.6, 121.6	-	41.7	56.6, 33.3, 26.0, 24.9
	119.0, 118.3, 114.3, 111.3			
11d	136.9, 127.4, 127.0, 121.5	32.5	44.7	49.4, 32.2, 20.5, 14.0
	118.8, 118.7, 113.8, 109.1			
11e	136.6, 127.3, 126.9, 121.4	32.3	41.6	56.2, 33.4, 26.1, 24.8
	118.7, 118.6, 113.8, 109.0			
12a	151.4, 150.0, 109.2, 105.6, 13.5	-	55.6	54.0, 25.6, 24.1
12b	152.0, 151.0, 107.3, 105.6, 13.3	-	46.1	48.6, 31.9, 20.2, 13.8
12c	152.1, 151.1, 107.3, 105.7, 13.4	-	45.0	58.7, 32.9, 24.0

Acknowledgements: We thank Ms. Kristi Chrispell for her help in preparing some of the benzotriazole adducts and for other preliminary work for this paper.

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