The *N*-Substitution of Aliphatic Primary Amines via 1-[(Alkylamino)methyl]benzotriazoles: Preparation of Secondary Amines

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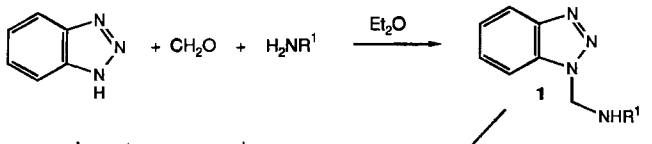
A new method has been developed for the selective conversion of primary aliphatic amines into unsymmetrical secondary amines by Grignard reaction of 1-[(alkylamino)methyl]-benzotriazoles **1**. This method employs simple procedures and mild conditions, and is specific in that only monoalkylation of the primary amines results.

There are few general methods for the efficient and selective monoalkylation of primary amines[1]. Procedures for direct alkylation frequently afford mixtures of amines and are not synthetically useful. The most frequently employed processes involve the preparation and subsequent reduction of the corresponding Schiff bases[2,3]. However, such imines sometimes decompose or polymerize unless at least one aryl group is present at the carbon or the nitrogen atom. Approaches to secondary amines which allow a greater degree of control require the temporary protection of one of the nitrogen positions. Such reactions include the use of arylsulfonyl[4], triflate[5], diethyl phosphite[6], or cyano[7] protecting groups, which undergo monoalkylation under basic conditions and subsequent deprotection to give secondary amines. However, removal of these blocking groups may require vigorous conditions, and the method employing diethyl phosphite is limited to alkylations using primary alkyl halides. Secondary amines can also be prepared by the selective *N*-dealkylation of tertiary amines[8]. We now report a new method for the conversion of primary aliphatic amines into secondary alkyl, or aralkyl amines that is both mild and selective in its application.

Work in this laboratory has led to the development of superior methods for the preparation of a wide range of primary[9], secondary[10], and tertiary[11] amines using the benzotriazole methodology. These methods are based on the ability of 1-(α-aminoalkyl)benzotriazoles, available by Mannich-type condensations, to react smoothly with Grignard reagents and produce amines in high yields. Whereas primary aromatic amines form 1-[(arylamino)methyl]benzotriazoles under standard ethanolic or Dean-Stark conditions[12], the more nucleophilic aliphatic amines usually underwent double Mannich condensations to give the bis[(benzotriazolyl)-methyl]amines[13]. However, recent preliminary studies indicated that the condensation of primary aliphatic amines, benzotriazole, and formaldehyde could be limited to the monoadduct formation of 1-[(alkylamino)methyl]benzotriazoles **1** if the reactions were carried out in either water or ether at room temperature[14]. We have investigated the scope of this selective monoadduct formation from primary aliphatic amines and now report its successful synthetic application for the preparation of secondary amines.



1	R^1	R^2	2
a	*c*-C_6H_{11}	Ph	a
		$PhCH_2$	b
		Et	c
b	*c*-C_5H_9	Ph	d
c	$PhCH(CH_3)$	Ph	e
		$PhCH_2$	f
d	*n*-C_8H_{17}	Ph	g
		$PhCH_2$	h
e	*t*-Bu	Ph	i
		$PhCH_2$	j
f	*s*-Bu	Ph	k

The 1-[(alkylamino)methyl]benzotriazoles **1a–f** were prepared following the procedure recently developed in this laboratory[14]. Mixing equimolar quantities of benzotriazole, the primary aliphatic amine, and aqueous 37% formaldehyde in diethyl ether gave the required monoadducts in high yields (Table 1). NMR analysis of the 1-[(alkylamino)methyl]benzotriazoles in $CDCl_3$ showed the presence of small amounts of the benzotriazol-2-yl isomer due to the known 1,2-isomerization of such compounds in solution[15].

Nucleophilic displacement of the benzotriazole moiety from the 1-[(alkylamino)methyl]benzotriazoles **1** was achieved by treatment with Grignard reagents at room temperature. The benzotriazole side product was easily removed by alkaline extraction and could be recovered. The resultant secondary amines **2** were purified through formation of their hydrochlorides, followed by recrystallization from ethyl acetate/methanol mixtures (see Table 2).

In conclusion, this alternative process for the monoalkylation of primary aliphatic amines provides a new route employing mild and simple conditions that can be used to prepare a wide variety of secondary alkyl and aralkylamines.

Experimental

Melting points (uncorrected): hot stage microscope. – ^1H, ^{13}C NMR: Varian VXR (300 MHz); $CDCl_3$ with TMS as an internal reference for ^1H NMR and $CDCl_3$ for ^{13}C NMR. – Elemental analyses: Carlo Erba 1106 (under the supervision of Dr. *D. Powell*). – Tetrahydrofuran and diethyl ether were predried and distilled from sodium; commercially available solutions of ethylmagnesium bromide, phenylmagnesium bromide (3.0 M solutions in ether; Aldrich Chem. Co.) and benzylmagnesium chloride (2.0 M solution in THF; Aldrich Chem. Co.) were used.

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General Method for the Preparation of 1-[(Alkylamino)methyl]-benzotriazoles **1**: Benzotriazole (1.18 g, 10 mmol) and the primary amine (10 mmol) were stirred together for 5 min at room temp. in ether (50 ml). Formaldehyde (1.10 ml, 10 mmol), 37% aqueous solution) was then added to the reaction mixture and stirring continued for a further 3 h. The solution was dried with anhydrous $MgSO_4$, filtered, and the ether evaporated under reduced pressure. The products were purified by recrystallization from ether/hexane mixtures (Table 1).

Table 1. Preparation of the *N*-(benzotriazol-1-ylmethyl)amines **1**

1	M.p. (lit. m.p.)[15] [°C]	Yield (%)	Molecular formula	Calcd. (Found) C	H	N
a	59-60 (59-61)	85	$C_{13}H_{18}N_4$	—	—	—
b	57-59 (56-58)	89	$C_{12}H_{16}N_4$	—	—	—
c	92-94	90	$C_{15}H_{16}N_4$	71.40 (71.63)	6.39 (6.34)	22.20 (22.55)
d	82-84	85	$C_{15}H_{24}N_4$	69.19 (69.28)	9.29 (8.96)	21.52 (21.81)
e	62-64 (61-63)	89	$C_{11}H_{16}N_4$	—	—	—
f	oil (oil)	86	$C_{11}H_{16}N_4$	—	—	—

Table 2. Preparation of the secondary amines **2** (hydrochlorides)

2	M.p. (lit. m.p.) [°C]	Yield (%)	Molecular formula	Calcd. (Found) C	H	N
a	281-282 (284)[16]	50	$C_{13}H_{20}ClN$	—	—	—
b	220-222 (199)[16]	64	$C_{14}H_{22}ClN$	70.13 (69.95)	9.25 (9.44)	5.84 (5.71)
c	238-240 (248-250)[17]	56	$C_9H_{20}ClN$	—	—	—
d	219-220 (221-223)[18]	57	$C_{12}H_{18}ClN$	—	—	—
e	168-170 (163-165)[19]	52	$C_{15}H_{18}ClN$	72.72 (72.70)	7.32 (7.43)	5.65 (5.64)
f	232-234	50	$C_{16}H_{20}ClN$	73.41 (73.46)	7.70 (7.89)	5.35 (5.33)
g	199-201	49	$C_{15}H_{26}ClN$	70.42 (70.09)	10.24 (10.42)	5.47 (5.37)
h	212-214	46	$C_{16}H_{28}ClN$	71.21 (71.04)	10.46 (10.68)	5.19 (5.04)
i	252-254 (245-247)[20]	49	$C_{11}H_{18}ClN$	66.15 (65.76)	9.08 (9.21)	7.01 (6.74)
j	246-248	51	$C_{12}H_{20}ClN$	67.43 (67.17)	9.43 (9.54)	6.55 (6.41)
k	139-141 (143-145)[21]	55	$C_{11}H_{18}ClN$	—	—	—

Compounds **1a–b** and **1e–f** were previously reported by our group[14]. To illustrate the generality of this method, two additional novel benzotriazole adducts were prepared: *N*-[(benzotriazol-1-yl)-methyl](1-phenylethyl)amine (**1c**) and *N*-[(benzotriazol-1-yl)methyl]octylamine (**1d**).

1c: ^1H NMR: δ = 1.2–1.4 (d, 3H, CH_3), 2.6–2.7 (br. s, 1H, NH), 3.55–3.65 (q, 1H, CH), 5.2–5.6 (dd, 2H, CH_2), 7.2–8.1 (m, 9H, ArH). – ^{13}C NMR: δ = 24.3 (CH_3); 54.0 (CH); 59.9 (CH_2); 109.3 (C-7), 119.6 (C-4), 123.7 (C-5), 127.0 (C-6), 132.9 (C-7a), 145.6 (C-3a) (benzotriazol-1-yl); 126.8, 128.3, 128.4, 143.5 (phenyl).

1d: ^1H NMR: δ = 0.75 (t, *J* = 6 Hz, 3H, CH_3), 1.1–1.45 (m, 12H, $6CH_2$), 2.45 (m, 2H, CH_2), 5.5–5.8 (m, 2H, NCH_2NH), 7.2–8.0 (m, 4H, ArH). – ^{13}C NMR: δ = 13.8 (CH_3); 22.4, 26.8, 29.0, 29.1, 29.5, 31.5, 46.3 ($7\,CH_2$), 62.5 (NCH_2NH), 109.2 (C-7), 119.7 (C-4), 123.8 (C-5), 126.2 (C-6), 132.8 (C-7), 145.8 (C-3a) (benzotriazol-1-yl).

General Procedure for the Preparation of the Secondary Amines **2**: To a stirred solution of the 1-[(alkylamino)methyl]benzotriazole **1** (10 mmol) in THF under nitrogen was added dropwise benzyl-

Table 3. ^1H-NMR data for the secondary amines **2** (hydrochlorides)

2	Alkyl	$[CH_2]_n$ (n=1,2)	Ph (m,5H,ArH)	NH_2 (br.s,2H)
a	1.05-1.3 (m, 3H), 1.5-1.9 (m, 5H), 2.1-2.25 (m, 2H)(cyclohexyl); 2.7-2.9 (m, 1H, CH)	4.05 (s, 2H)	7.30-7.70	9.8
b	1.15-1.3 (m, 3H), 1.6-1.9 (m, 5H), 2.2-2.35 (m, 2H)(cyclohexyl); 2.95-3.1 (m, 1H, CH)	3.1-3.4 (m, 4H)	7.20-7.35	9.2
c	0.9-0.95 (t, J=7Hz, 3H, CH_3); 1.16-1.96 (m, 10H),(cyclohexyl); 2.8-2.94 (m, 3H, CH, CH_2)	2.16-2.20 (m,2H)	—	9.2
d	1.43-1.54 (m, 2H), 1.78-1.90 (m, 3H), 1.94-1.99 (m, 3H),(cyclopentyl); 3.1-3.2 (m, 1H, CH)	4.06 (s, 2H)	7.29-7.56	8.2
e	1.77-1.79 (d, J=7Hz, 3H, CH_3); 4.0-4.06 (m, 1H, CH);	3.60-3.9 (s, 2H)	7.28-7.60 (m, 10H)	10
f	1.92-1.95 (d, J=7Hz, 3H, CH_3); 4.26-4.28 (q, J=7Hz, 1H, CH);	2.84-3.40 (m, 4H)	7.12-7.64 (m, 10H)	10
g	0.85 (t, J=7Hz, 3H, CH_3); 1.2-1.4 (m, 10H, $5CH_2$); 1.8-1.9 (m, 2H, CH_2); 2.7-2.85 (m, 2H, CH_2)	4.05-4.15 (m, 2H)	7.30-7.70	9.8
h	0.85 (t, J=7Hz, 3H, CH_3); 1.1-1.4 (m, 10H, $5CH_2$); 1.8-2.0 (m, 2H, CH_2); 2.9-3.0 (m, 2H, CH_2)	3.1-3.3 (s, 4H)	7.20-7.30	9.6
i	1.36 (s, 9H, CH_3)	3.84-3.88 (t, J=6Hz, 2H)	7.20-7.65	9.5
j	1.49 (s, 9H, CH_3)	3.08-3.39 (m, 4H)	7.13-7.28	9.4
k	0.92 (t, J=7Hz, 3H, CH_3); 1.38 (d, J=6Hz, 3H, CH_3); 1.6-2.0 (m, 2H, CH_2); 2.8-2.9 (m, 1H, CH)	4.00-4.13 (m, 2H)	7.3-7.7	9.7

Table 4. ^{13}C-NMR data for the secondary amines **2** (hydrochlorides)

2	Alkyl	$[CH_2]_n$ (n=1,2)	Aryl
a	24.3, 24.6, 28.7, 55.1	47.0	128.9, 129.0, 130.1, 130.4
b	24.4, 24.7, 29.1, 57.3	32.3, 45.8	126.8, 128.5, 128.6, 136.8
c	11.1, 24.3, 24.6, 28.7, 56.9	19.2, 45.8	—
d	23.6, 31.1, 52.5	49.5	128.9, 129.2, 130.2, 130.3
e	24.4, 57.4	51.5	129.1, 129.2, 130.6, 135.9, 128.0, 128.7, 129.0, 129.9
f	19.7, 58.1	31.4, 46.3	127.8, 128.6, 129.4, 136.7, 126.9, 128.6, 129.3, 135.8
g	14.0, 22.5, 25.8, 26.7, 28.9, 29.0, 31.6, 46.0	50.4	129.0, 129.3, 130.1, 130.3
h	13.9, 22.4, 25.9, 26.7, 28.9, 29.0, 31.6, 47.9	32.2, 49.0	126.9, 128.6, 128.7, 136.4
i	26.0, 45.9	57.9	128.6, 128.8, 130.6, 130.9
j	25.3, 42.7	32.1, 56.6	126.3, 128.1, 128.2, 136.6
k	9.6, 14.8, 25.3, 53.3	47.0	128.5, 128.7, 129.9, 130.0

magnesium chloride (7.5 ml, 15 mmol, 2.0 M THF solution). The reaction mixture was stirred at room temp. for 12 h, after which the solution was quenched with 20% aqueous ammonium chloride solution (20 ml). The aqueous phase was extracted with ether (2 × 20 ml), and the combined organic phases were washed with 5% aqueous sodium hydroxide solution (2 × 20 ml) and then water, until the aqueous layer remained at pH = 7. The ether solution was dried with anhydrous $MgSO_4$ and evaporated to give the crude product as an oil. To a solution of the crude amine (5 mmol) in dry ether (50 ml) was added an ether solution (50 ml) saturated with hydrogen chloride. The resulting precipitate was filtered and recrystallized from ethyl acetate/methanol mixtures to give the pure hydrochloride (Tables 2–4).

CAS Registry Numbers

1a: 126541-65-9 / **1b**: 126541-66-0 / **1c**: 126541-67-1 / **1d**: 126541-68-2 / **1e**: 126541-69-3 / **1f**: 126541-70-6 / **2a** · HCl: 126541-71-7 / **2b** · HCl: 126541-72-8 / **2c** · HCl: 126541-73-9 / **2d** · HCl: 126541-74-0 / **2e** · HCl: 126299-15-8 / **2f** · HCl: 126541-75-1 / **2g** · HCl: 126541-76-2 / **2h** · HCl: 126541-77-3 / **2i** · HCl: 75351-09-6 / **2j** · HCl: 126541-78-4 / **2k** · HCl: 126541-79-5 / *c*-$C_6H_{11}NH_2$: 108-91-8 / *c*-$C_5H_9NH_2$: 1003-03-8 / $PhCH(Me)NH_2$: 98-84-0 / $Me[CH_2]_7NH_2$: 111-86-4 / *t*$BuNH_2$: 75-64-9 / *s*$BuNH_2$: 13952-84-6 / 1*H*-benzotriazole: 95-14-7

[1] J. R. Malpass in *Comprehensive Organic Chemistry*, (I. O. Sutherland, Ed.) vol. 2, part 6.1, Pergamon Press, Oxford 1979.
[2] R. W. Layer, *Chem. Rev.* **63** (1963) 489.
[3] W. S. Emerson, *Org. React.* **4** (1948) 174.
[4] J. B. Hendrickson, R. Bergeron, *Tetrahedron Lett.* **1970**, 345.
[5] J. B. Hendrickson, R. Bergeron, *Tetrahedron Lett.* **1973**, 3839.
[6] A. Zwierzak, J. Brylikowska-Piotrowicz, *Angew. Chem.* **89** (1977) 109; *Angew. Chem. Int. Ed. Engl.* **16** (1977) 107.
[7] V. F. Anikin, E. V. Ganin, G. L. Kamalov *Ukr. Khim. Zh. (Russ. Ed.)* **48** (1982) 100 [*Chem. Abstr.* **96** (1982) P 162070g].
[8] E. Yankep, H. Kapnang, G. Charles, *Tetrahedron Lett.* **1989**, 7383.
[9] A. R. Katritzky, J. Jiang, L. Urogdi, *Tetrahedron Lett.* **1989**, 3303.
[10] A. R. Katritzky, S. Rachwal, B. Rachwal, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 805.
[11] A. R. Katritzky, S. Rachwal, J. Wu, *Can. J. Chem.*, in the press.
[12] A. R. Katritzky, S. Rachwal, B. Rachwal, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 799.
[13] A. R. Katritzky, K. Yannakopoulou, P. Lue, D. Rasala, L. Urogdi, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 225.
[14] A. R. Katritzky, B. Pilarski, L. Urogdi, *J. Chem. Soc., Perkin Trans. 1*, in the press.
[15] A. R. Katritzky, K. Yannakopoulou, *Heterocycles* **28** (1989) 1121.
[16] J. von Braun, G. Blessing, F. Zobel, *Ber. Dtsch. Chem. Ges.* **56** (1923) 1988.
[17] A. Skita, F. Keil, *Monatsh. Chem.* **53** (1929) 753.
[18] J. R. Corrigan, N.-J. Sullivan, H. W. Bishop, *J. Am. Chem. Soc.* **75** (1953) 6258.
[19] A. P. Terent'ev, E. G. Rukhadze, V. V. Dunina, E. V. Drobyshevskaya, *Zh. Obshch. Khim.* **38** (1968) 715 [*Chem. Abstr.* **69** (1968) P 51756h].
[20] B. L. Emling, R. J. Horvath, A. J. Saraceno, E. F. Ellermeyer, L. Haile, L. D. Hudac, *J. Org. Chem.* **24** (1959) 657.
[21] R. L. Lutz, P. S. Bailey, R. J. Rowlett, Jr., J. W. Wilson, III, R. K. Allison, M. T. Clark, N. H. Leake, R. H. Jordan, R. J. Keller, III, K. C. Nicodemus, *J. Org. Chem.* **12** (1947) 760.

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