Reactions of Benzotriazole with Formaldehyde and Aliphatic Primary Amines:[1] Selective Formation of 1:1:1, of 2:2:1, and of 2:3:2 Adducts and a Study of their Reactions with Nucleophiles

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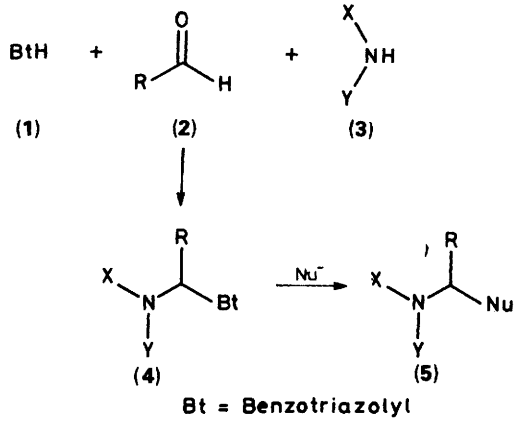
Benzotriazole (BtH) reacts easily with aliphatic primary amines and formaldehyde in aqueous media to give one or more of three types of product: (i) $(BtCH_2)_2NR$ (**5**), (ii) $(BtCH_2NR)_2CH_2$ (**6**), and/or (iii) $BtCH_2NHR$ (**7**). The product formed depends on the molar ratio of the substrates, and on the degree of steric hindrance in the amine, and is also influenced by the nature of the solvent. Primary aliphatic 1,2- or 1,3-diamines yield cyclic aminals which are imidazolidine (**8a**) and hexahydropyrimidine (**8b**) derivatives. Reactions of these aminals with Grignard reagents, and with cyanide anion as nucleophiles, are also described.

Benzotriazole has been developed in our laboratory as an inexpensive and highly efficient synthetic auxiliary group for the *N*-substitution of various nitrogen compounds. Two-step sequences (Scheme 1), consisting of a Mannich type condensation of benzotriazole (**1**) and an aldehyde (**2**) with an NH-compound (**3**), followed by displacement of the benzotriazole moiety in the adduct (**4**) by a nucleophile, have been elaborated as convenient, selective, and usually high-yielding methods for the preparation of many nitrogen-containing-compounds, *e.g.* a wide variety of amines,[1] *N,N*-substituted hydroxylamines,[1b] *N*-substituted amides[2] or thioamides,[3] and amino acid derivatives.[4] Adducts (**4**) derived from aromatic or secondary cyclic amines and formaldehyde or acetaldehyde have also conveniently been obtained in aqueous media.[5]



Scheme 1.

We now disclose results obtained by application of this aqueous technique to aliphatic primary amines. This has led to a convenient new method for the preparation of the previously obtained adducts (**5**) (Scheme 2), and also to the synthesis of novel open-chain (**6**) and cyclic methylene-bridged aminals, (**8**) (Scheme 3) which themselves have considerable synthetic utility. We show that sterically hindered primary aliphatic amines form monosubstituted adducts of type (**7**), previously described only for aromatic and heteroaromatic amines.[5]

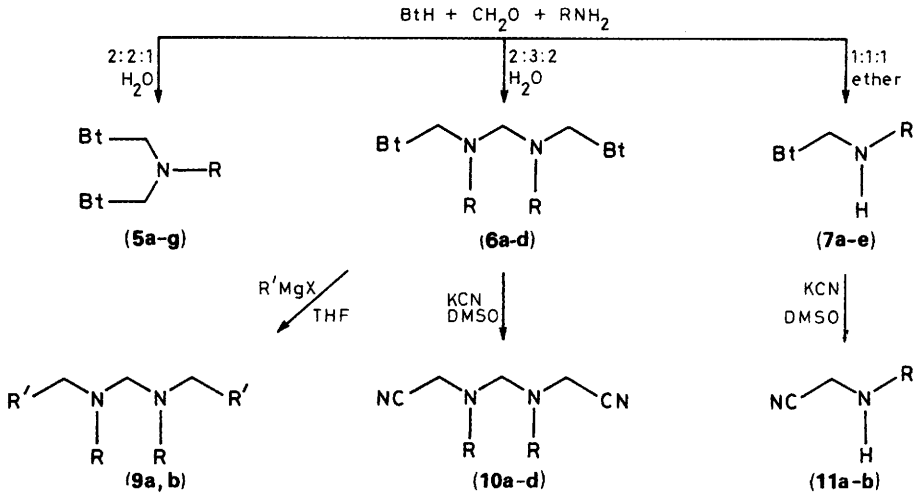
Product Selectivity in Reactions of Benzotriazole, Aliphatic Primary Amines, and Formaldehyde.—Mannich-adducts of type (**5**), derived from 1 mol of an amine, 2 mol of benzotriazole, and 2 mol of formaldehyde were previously obtained by the reactions of 1-hydroxymethylbenzotriazole with primary aliphatic amines; however, simultaneous formation of the corresponding monoadducts [*cf.* (**7**)], and consequent isolation difficulties, were reported.[1a] We now find that the reactions of primary alkyl primary amines ($R'CH_2NH_2$) with benzotriazole and formaldehyde in water at 20 °C, in the correct stoicheiometric ratio (*i.e.* 2:2:1), proceed smoothly to give adducts (**5**) exclusively and in high yield (Table 1). However, an equimolar ratio of the amine, benzotriazole, and formaldehyde gives predominantly aminals of type (**6**); the yield of (**6**) is much increased by using the correct stoicheiometric amount (*i.e.* 1.5 mol) of formaldehyde (Table 2). Similar methylene-bridged adducts (**8a**) and (**8b**) were also prepared from ethane-1,2-diamine and from propane-1,3-diamine (Scheme 3, Table 4).

Hindered primary amines in which the amino group is attached to a tertiary or elaborated secondary carbon atom, as exemplified by t-butylamine and by cyclohexylamine, form adducts of type (**7**), in water with either an equimolar quantity or with an excess of formaldehyde (Table 3). Using less sterically hindered amines (iso-propylamine, s-butylamine, neopentylamine), and a benzotriazole–amine–formaldehyde molar ratio of 1:1:1, formation of a mixture of all the three types of adducts, (**5**), (**6**), and (**7**), was observed. In the reaction with neopentylamine, the product of type (**5**) predominates and after work up (**5b**) was isolated in 50% yield. However, when diethyl ether was used as solvent, reactions of all these amines (iso-propylamine, s-butylamine, t-butylamine, cyclohexylamine, and neopentylamine) with benzotriazole and formaldehyde (in a stoicheiometric ratio 1:1:1), give adducts of type (**7**) in good yield and high purity.

The adducts (**5a–g**) are recorded in Table 1, the novel polyaminals (**6a–d**) in Table 2, monoadducts (**7a–d**) in Table 3, and cyclic aminals (**8a–b**) in Table 4. The data for (**5c–e**) and (**5g**) are in good correlation with those previously reported;[1a] all new compounds were characterised by C,H,N analysis and by their NMR spectra.

NMR Spectra and Isomerisation of the Adducts (**5**), (**6**), (**7**), *and* (**8**).—The ^{13}C and ^1H NMR spectra for the new adducts (**5b,e,f**) are listed in Tables 5 and 6. The spectra clearly demonstrate that all these compounds exist both in $CDCl_3$ and in DMSO solution exclusively in the benzotriazol-1-yl isomeric forms (see below).

In contrast, the methylene-bridged aminals (**6**) and (**8**), as

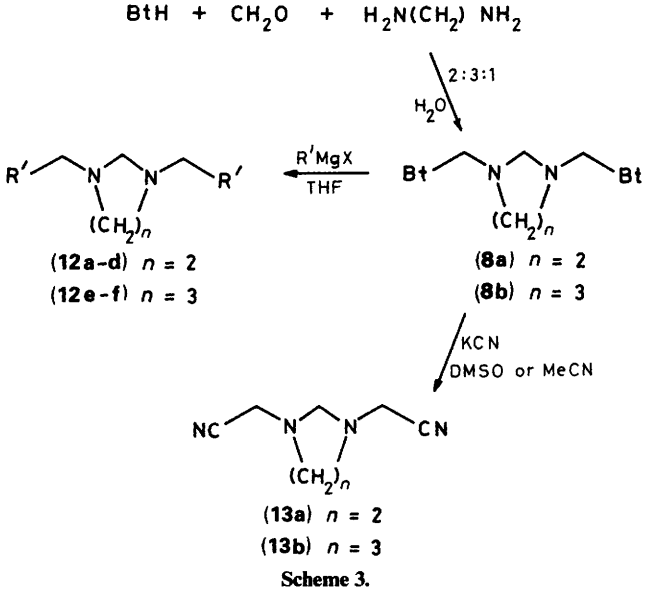


Scheme 2.

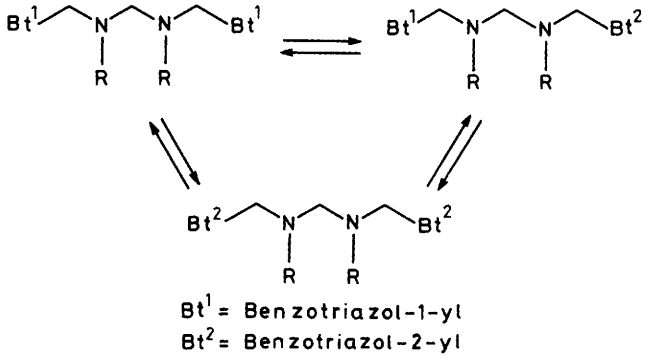
Table 1. Preparation of *N,N*-bis(benzotriazol-1-ylmethyl)amines (**5a–g**).

Compd. no.	R	Yield[a] (%)	M.p. (°C) Found	M.p. (°C) Lit.	Molecular formula	Found (Required) (%) C	H	N
(**5a**)	Bu	85	111–114[b]		$C_{18}H_{21}N_7$	64.2 (64.5)	6.1 (6.3)	28.9 (29.2)
(**5b**)[c]	Neopentyl	50[b]	132–134[b]		$C_{19}H_{23}N_7$	65.5 (65.3)	6.7 (6.6)	28.4 (28.1)
(**5c**)	n-Octyl	90	88–89[b]	88–89[1a]	$C_{22}H_{29}N_7$			
(**5d**)	Cyclohexyl	89	118–119[d]	118–119[1a]	$C_{20}H_{23}N_7$			
(**5e**)	$PhCH_2$	87	113–115[b]	108–109[1a]	$C_{21}H_{19}N_7$	(68.5 (68.3)	5.2 (5.2)	26.2 (26.5)
(**5f**)	$(CH_2)_2NMe_2$	92	92–94		$C_{18}H_{22}N_8$	61.6 (61.7)	6.3 (6.3)	32.05[b] (32.0)
(**5g**)	OH	94	174–175[b]	173–174[1a]	$C_{14}H_{13}N_7O$			

[a] Yields of crude, NMR pure products. [b] Recrystallised from EtOH. [c] Molar ratio of benzotriazole–amine–formaldehyde for the preparation = 2:2:3 (see Discussion). [d] Recrystallised from hexanes.



Scheme 3.



Scheme 4.

well as the monoadducts (**7**), each exist in $CDCl_3$ solution as a mixture of isomers, resulting from the known[6] 1,2-isomerisation of *N*-(aminomethyl)benzotriazole derivatives. The isomeric compositions of the three-component mixtures of the adducts (**6**) and (**8**) (Scheme 4) were investigated by ^1H NMR. spectroscopy. The singlets of the central methylene protons appear in the region of 3.5—3.8 ppm and are sufficiently separated to allow quantitative evaluation. The ratios of the isomers were calculated (i) for compounds (**6a,b,d**) as *ca.* 9:6:1 for the 1,1′-1,2′-, and 2,2′-isomers [only a trace of 2-yl isomers detected for (**6c**)] and (ii) for compounds (**8**) as *ca.* 9:3 for the 1′1′-1,2′, and only a trace of the 2,2′ isomers. In the ^{13}C NMR spectra, a multiplicity of the central methylene bridge signals (δ 70–72 ppm.), as well as of the benzotriazole ring signals, was observed due to the above mentioned isomerisation. Similar

Table 2. Preparation of *N,N'*-bis(benzotriazol-1-ylmethyl)-*N,N'*-dialkylmethanediamines (**6a—d**).

Compd. no.	R	Yield[a] (%)	M.p. (°C)	Molecular formula	Found (%) C	H	N	Required (%) C	H	N
(6a)	Bu	87	87–89[b]	$C_{23}H_{32}N_8$	65.4	7.55	27.0	65.7	7.6	26.7
(6b)	n-Octyl	91	62–64[c]	$C_{31}H_{48}N_8$	69.8	9.3	21.35	69.9	9.1	21.0
(6c)	$PhCH_2$	65[b]	133–135[c]	$C_{29}H_{28}N_8$	71.3	5.8	22.9	71.2	5.8	23.2
(6d)	Bu[i]	99	85–87[c]	$C_{23}H_{32}N_8$	65.6	7.5	27.0	65.7	7.7	26.6

[a] Yields of crude, n.m.r. pure products. [b] Recrystallised from EtOH. [c] Recrystallised from hexanes.

Table 3. Preparation of *N*-(benzotriazol-1-ylmethyl)amines (**7**) and aminoacetonitriles (**11**).

Compd. no.	R	Yield[a] (%)	M.p. or b.p. (°C)	Molecular formula	Found (%) (Required %) C	H	N
(7a)	Bu[t]	89	61–63[b]	$C_{11}H_{16}N_4$	64.4 (64.7)	8.1 (7.9)	27.4 (27.4)
(7b)	Cyclohexyl	100	59–61[c]	$C_{13}H_{38}N_4$	67.5 (67.8)	7.9 (7.9)	24.5 (24.3)
(7c)	Pr[i]	96[d]	Oil	$C_{10}H_{14}N_4$			
(7d)	Bu[s]	86[d]	Oil	$C_{11}H_{16}N_4$			
(7e)	Neopentyl	98	64–66[c]	$C_{12}H_{18}N_4$	65.9 (66.0)	8.3 (8.3)	26.0 (25.7)
(11a)	Bu[t]	70	*e*	$C_6H_{12}N_2$			
(11b)	Cyclohexyl	87	82–86/1[f]	$C_8H_{14}N_2$			

[a] Yields of crude, NMR pure products, except for (**7b**), (**7e**), see below. [b] Recrystallised from EtOH. [c] Recrystallised from hexanes. [d] The products are identified by ^1H and ^{13}C NMR; both (**7c**) and (**7d**) are contaminated with 10–15% of compounds of type (**5**) (they are insufficiently stable to purify for CHN analysis and do not form molecular ions in MS). [e] Lit.,[17] b.p. 90–99 °C at 22 mmHg. The product was characterised by high resolution MS (Found: M^+, 112.0990. $C_6H_{12}N_2$ requires 112.1000). [f] Lit.,[17] b.p. 77–82 °C at 1 mmHg.

Table 4. Preparation of 1,3-disubstituted imidazolidine and hexahydropyrimidine derivatives (**8**), (**12**), and (**13**) $RCH_2N(CH_2)_nN(CH_2R)CH_2$.

Compd. no.	*n*	R	Yield[a] (%)	M.p. or b.p. (°C)	Molecular formula	Found (Required) (%) C	H	N
(8a)	2	Bt	85	97–99[b]	$C_{17}H_{18}N_8$	61.1 (61.1)	5.4 (5.4)	34.0 (33.5)
(8b)	3	Bt	93	63–65[b]	$C_{18}H_{20}N_8$	62.5 (62.05)	5.9 (5.8)	32.2 (32.2)
(12a)	2	Et	72	152–154[c]	$C_9H_{20}N_2$	41.2 (41.2)	4.5 (3.95)	18.35[c] (18.0)
(12b)	2	Bu	68	158–160[c]	$C_{13}H_{28}N_2$	44.5 (44.8)	5.1 (5.1)	17.0[c,d] (16.7)
(12c)	2	n-Octyl	75	168–170 (decomp.)[c]	$C_{21}H_{44}N_2$	59.2 (59.1)	7.2 (7.5)	16.3[c,e] (16.7)
(12d)	2	Vinyl	74	Oil	$C_9H_{16}N_2$	*f*		
(12e)	3	Et	77	Oil	$C_{10}H_{22}N_2$	*g*		
(12f)	3	Vinyl	87	Oil	$C_{10}H_{18}N_2$	*h*		
(13a)	2	CN	85[k]	Oil	$C_7H_{10}N_4$	*i*		
(13b)	3	CN	87[k]	99–101[b]	$C_8H_{12}N_4$	*j*		

[a] Yields of crude, NMR pure products (**12a–c**) contain 10–15% impurities. [b] Recrystallised from EtOH. [c] Oil: m.p. and C,H,N analysis is given for picrate obtained and recrystallised from EtOH. [d] MS: M^+ (212, 17.98%), $M^+ - 1$ (211, 100%). [e] MS: M^+ (324, 16.48%), $M^+ - 1$ (323, 100%). [f] Characterised by high-resolution MS (Found: $M^+ - 1$, 151.1235, $C_9H_{15}N_2$ requires 151.1241). [g] Characterised by high-resolution MS (Found: $M^+ - 1$, 169.1705, $C_{10}H_{11}N_2$ requires 169.1704). [h] Characterised by high-resolution MS (Found: $M^+ - 1$, 165.1383, $C_{10}H_{17}N_2$ requires 165.1391). [i] Characterised by high-resolution MS (Found: $M^+ - 1$, 149.0824, $C_7H_9N_4$ requires 149.0827). [j] Characterised by high-resolution MS (Found: $M^+ - 1$, 163.0990, $C_8H_{11}N_4$ requires 163.0983. [k] Obtained according to general procedure D.

isomerisations of the monoadducts (**7**) are observed in their ^{13}C NMR spectra (Table 7), however, in the ^1H NMR spectra the signals are not sufficiently separated for quantitative evaluations. The ^{13}C NMR and ^1H NMR spectra of the new derivatives of type (**6**), (**7**), and (**8**), are listed in Tables 9–10, 7–8, 11–12, respectively.

Reactions of the Adducts (**6**) *and* (**8**) *with Grignard Reagents.*—The simultaneous nucleophilic displacement of both the benzotriazole moieties in adducts of type (**5**) to give tertiary amines with two identical *N*-substitutents was previously reported.[1b] We now find that Grignard reagents similarly convert the adducts (**6**) and (**8**) into the diamines (**9**) and (**12**), respectively, in good yields (Schemes 2, 3 and Tables 4, 13).

The open-chain aminals (**6**) are less reactive and require considerably longer times for complete reaction than their

Table 5. ^{13}C NMR spectra[a] of the new *N,N*-bis(benzotriazol-1-ylmethyl)amines (**5a, e, f**).

Compd. no.	Benzotriazole signals						NCH_2N	R
	C-3a	C-4	C-5	C-6	C-7	C-7a		
(5a)	145.96	119.89	124.08	127.72	109.76	133.16	64.33	13.52, 19.82, 29.41, 50.12
(5b)	145.68	119.81	123.91	127.65	109.51	133.23	66.88	27.41, 33.08, 62.58
(5e)	145.81	119.80	124.08	127.66	109.81	133.16	63.38	54.45, 127.95, 128.60, 129.06, 136.26
(5f)	145.88	119.73	124.04	127.63	109.99	133.11	64.56	45.33, 48.11, 57.84

[a] Spectra were registered in $CDCl_3$.

Table 6. ^1H NMR spectra[a] of the new *N,N*-bis(benzotriazol-1-ylmethyl)amines (**5b,e,f**)

Compd. no.	Benzotriazole signals				NCH_2N	R
	4H	5H	6H	7H		
(5a)[b]	8.12 (2 H, d)	7.60 (2 H, t)	7.45 (2 H, t)	8.05 (2 H, d)	5.9 (2 H, s)	2.70 (2 H, t), 1.20–1.40 (2 H, m) 0.95–1.05 (2 H, m), 0.60 (3 H, t)
(5b)	8.05 (2 H, d)	7.48 (2 H, t)	7.35 (2 H, t)	7.60 (2 H, d)	5.7 (4 H, s)	2.75 (2 H, s), 0.75 (9 H, s)
(5e)	8.05 (2 H, d)	7.2–7.5 (6 H, m)[c]			5.6 (4 H, s)	3.95 (2 H, s), 7.2–7.5 (5 H, m)[c]
(5f)	7.95 (2 H, d)	7.44 (2 H, t)	7.36 (2 H, t)	7.75 (2 H, d)	5.6 (4 H, s)	2.08 (6 H, s), 2.35 (2 H, t) 2.95 (2 H, t)

[a] Spectra were registered in $CDCl_3$. [b] Spectrum was registered in [$^2H_6$]-DMSO. [c] Overlapping signals.

Table 7. ^{13}C NMR spectra[a] of *N*-(benzotriazolylmethyl)amines (**7a–e**) and aminoacetonotriles (**11a,b**) XCH_2NHR.

Compd. no.	X[b]	CH_2	R
(7a)	145.97, 119.38, 123.52, 126.74, 110.06, 132.02 (143.92; 125.97; 117.87)	58.62 (66.29)	28.97, 50.36 (28.94; 50.51)
(7b)	145.40, 118.88, 123.70, 126.75, 111.12, 132.40 (144.07; 126.07; 119.05)	60.22 (67.57)	23.92, 25.54, 32.34, 52.07 (–; –; 32.53; 52.21)
(7c)	145.86, 119.79, 123.77, 127.21, 109.26, 132.67) (144.50; 126.28; 118.15)	60.09 (68.06)	22.23, 44.61 (22.23; 44.54)
(7d)	145.77, 119.59, 123.56, 126.97, 109.23, 132.52 (143.95; 125.95; 117.91)	60.19 (67.99)	9.51, 19.15, 28.95, 50.35 (9.44; 18.79; 28.86; 50.10)
(7e)	145.90, 119.74, 123.68, 127.10, 109.34, 132.70 (144.10; 126.07; 118.06)	63.70 (71.83)	27.18, 31.07, 58.65
(11a)	119.59	30.74	28.44, 51.03
(11b)	117.96	34.02	24.14, 25.60, 32.28, 54.85

[a] ^{13}C NMR spectra were registered in $CDCl_3$ and for (**7b**) in [$^2H_6$]-DMSO solutions. Benzotriazol-2-yl isomer signals in parentheses. [b] The order of the benzotriazole signals: 3a-4-5-6-7-7a for 1-yl, and 3a(7a)-4(7)-5(6) for 2-yl isomers.

Table 8. ^1H NMR spectra[a] of *N*-(benzotriazolylmethyl)amines (**7a–e**) and aminoacetonitriles (**11a,b**) XCH_2NHR.

Compd. no.	X	CH_2	R
(7a)	8.00–7.30 (1 H, m)	5.60 (2 H, s)	1.00 (9 H, s)
(7b)	8.10–7.30 (4 H, m)	5.55 (2 H, s)	2.15 (1 H, m), 1.00 (5 H, m), 1.60 (5 H, m)
(7c)	8.00–7.30 (4 H, m)	5.55 (2 H, s)	1.00 (6 H, d), 2.55 (1 H, m)
(7d)	8.00–7.30 (4 H, m)	5.50 (2 H, t)	0.65 (3 H, t), 0.90 (3 H, d), 1.30 (2 H, m), 2.4 (1 H, m)
(7e)	8.00–7.30 (4 H, m)	5.50 (2 H, s)	0.90 (9 H, s), 2.30 (2 H, s)
(11a)		3.60 (2 H, s)	1.2 (9 H, s)
(11b)		3.65 (2 H, s)	(2.65 (1 H, m) 1.80–0.8 (10 H, m)

[a] ^1H NMR spectra were registered in $CDCl_3$ and for (**7b**) in [$^2H_6$]-DMSO solution; the CH_2 and R signals of the benzotriazol-1-yl and -2-yl isomers are not separated.

cyclic analogues (**8**) (see Experimental section). The reactions were performed in dry tetrahydrofuran at room temperature. The side-product benzotriazole was easily removed by alkaline extraction during the work-up, and the products were pure as isolated as indicated by their carbon and proton spectra. The analytical samples were purified by column chromatography or by transformation to picrates.

The synthesis of open-chain aminals of type (**9**) has not been previously achieved by C–C bond formation reactions. Such aminals are generally obtained from secondary amines and formaldehyde.[7–11] Primary aliphatic amines react with formaldehyde to give hexahydrotriazines.[12,13]

N,N-Disubstituted cyclic aminals of type (**12**) (*i.e.* imidazolidines and hexahydropyrimidines) were previously prepared from *N,N'*-disubstituted ethane-1,2- or propane-1,3-diamines with aliphatic aldehydes.[14,15]

Reaction of the Adducts (**6**), (**7**), *and* (**8**) *with Cyanide*

Table 9. ^{13}C NMR spectra[a] of *N,N'*-bis(benzotriazolylmethyl)-*N,N'*-dialkylmethanediamines (**6a–d**).

Compd. no.	Benzotriazole signals C-3	C-4	C-5	C-6	C-7	C-7a	$BtCH_2N$	NCH_2N	R
(6a)	144.81	188.97	123.75	127.23	110.54	133.59	63.08	71.08	13.60, 19.81, 28.72, 48.28
(6b)	145.45	119.78	123.70	127.35	109.40	133.89	62.68	70.93	13.99, 22.54, 27.14, 27.19, 29.19, 29.28, 31.71, 49.54
(6c)	145.38	119.78	123.78	127.37	109.48	133.86	61.99	70.97	53.29[b]
(6d)	144.77	119.04	123.81	127.39	110.47	133.72	63.34	72.39	20.49, 25.34, 57.03

[a] The spectra were registered in $CDCl_3$ solutions for (**6b–c**) and in [$^2H_6$]-DMSO solution for (**6a**) and (**6d**). Signals given for the predominate 1,1[1] isomers. [b] Phenyl signals: 127.52, 128.56. 128.84, 137.52

Table 10. ^1H NMR spectra[a] of *N,N'*-bis(benzotriazolylmethyl)*N,N'*-dialkylmethanediamines (**6a–d**).

Compd. no.	Benzotriazole signals	$BtCH_2N$	NCH_2N	R
(6a)	8.10–7.25 (8 H, m)	5.80–5.60 (4 H, m)	3.55 (1.1 H, s),[b] 3.65 (0.75 H, s), 3.82 (0.15 H, s)	0.95 (6 H, t), 1.35 (4 H, m), 1.65 (4 H, m), 2.70 (4 H, m)
(6b)	8.06–7.25 (8 H, m)	6.00–5.60 (4 H, m)	3.53 (1.1 H, s),[b] 3.67 (0.75 H, s), 3.84 (0.15 N, s	0.90 (6 H, t), 1.20 (20 H, bs), 1.56 (4 H, m), 2.63 (4 H, m)
(6c)[c]	8.12–8.03 (2 H, m), 7.5–7.25 (6 H, m)[d]	5.70 (4 H, m)	3.85 (2 H, s)	3.85 (4 H, s), 7.5–7.25 (10 H, m)[d]
(6d)	8.10–7.20 (8 H, m)	5.95–5.55 (4 H, m)	3.50 (1.1 H, s),[b] 3.65 (0.75 H, s), 3.80 (0.15 H, s)	0.95 (12 H, d), 2.6–1.95 (6 H, m)

[a] The spectra were registered in $CDCl_3$ solutions for (**6b–d**) and in [$^2H_6$]-DMSO solution for (**6a**). [b] Signals for 1,1'-1,2' and 2,2' isomer (see Discussion). [c] Only trace of 2-yl isomer detected. [d] Overlapping signals.

Table 11. ^{13}C NMR spectra[a] of imidazolidine and hexahydropyrimidine derivatives (**8**), (**12**), and (**13**) $R\overline{CH_2N(CH_2)_nN(CH_2R)CH_2}$.

Compd. no.	R	RCH_2N	Ring carbons C-2	C-4	C-5
(8a)[b]	145.67, 119.63, 123.89, 127.48, 109.42, 133.20	64.56	70.00	48.82	
(8b)[b]	145.65, 119.56, 123.87, 127.46, 109.77, 133.18	66.47	69.98	48.97	22.07
(12a)	11.57, 22.01	52.15	76.56	57.26	
(12b)	13.48, 22.41, 28.61, 29.86	52.20	76.52	56.24	
(12c)	13.84, 22.45, 27.26, 28.84, 29.08, 29.35, 29.50, 31.61	52.21	76.54	55.45	
(12d)	116.69, 135.62	52.00	75.69	58.08	
(12e)	11.79, 20.16	52.34	76.34	57.21	23.49
(12f)	117.22, 135.45	52.11	75.45	58.41	23.47
(13a)	115.26	40.77	72.69	50.62	
(13b)	114.76	42.31	72.37	49.99	21.76

[a] Spectra were registered in $CDCl_3$. [b] Signals for the predominate 1,1'-isomers.

Anion.—The synthetic potential of the new adducts (**6**) and (**8**) extends to the preparation of the substituted α-aminoacetonitriles (**10**) and (**13**), respectively, by using the CN^- anion as nucleophile in the benzotriazole displacement reaction (Schemes 2, 4 and Tables 4, 13). The difference in the reactivity of the open-chain (**6**) and the cyclic (**8**) derivatives, noted above, is again observed. Reactions of the cyclic adducts (**8**) with potassium cyanide in refluxing acetonitrile for 24 h gave compounds (**13**) in good yields, but the conversion of the open-chain analogues (**6**) under similar conditions were incomplete even after a reaction time of 30 h. However, dimethyl sulphoxide as a solvent greatly increased the rate so that the reactions were completed (i) with adducts (**6**) at 60–70 °C in 6 h, or (ii) with adducts (**8**) at 20 °C in 12 h. The products in both cases are easily isolated in a practically pure state (see Experimental section). The preparation of 1,3-bisacetonitriles of type (**13**) can also be performed as a one-pot reaction from ethane-1,2-diamine or propane-1,3-diamine, benzotriazole, formaldehyde, and potassium cyanide, using dimethyl sulphoxide as a solvent (see Experimental section).

The ^{13}C and ^1H n.m.r. spectra of the novel α-aminoacetonitriles of type (**10**) are listed in Tables 14 and 15. Cyclic 1,3-bisacetonitrile (**13a**) is new, (**13b**) was previously obtained by cyclocondensation of propane-1,3-diamine, formaldehyde, and hydroxyacetonitrile.[16]

Adducts of type (**7**) can similarly be transformed to known aminoacetonitriles (**11a**) and (**11b**).[17] The reactions of adducts (**7a**) and (**7b**) with potassium cyanide in dimethyl sulphoxide were completed at 60–70 °C in 6 h to give the nitriles (**11a**) and (**11b**) respectively, in good yields (Table 3).

Conclusions

In these reactions of benzotriazole, primary amines, and formaldehyde, selective methods for the preparation of three types of adduct [*i.e* (**5**), (**6**), and (**7**)] have been elaborated. The synthetic utility of adducts of type (**5**) has previously been demonstrated.[1b] The results described in this paper extend the synthetic application of the adducts of type (**6**), (**7**), and (**8**) to the preparation of the open-chain aminals (**9**), to the cyclic

Table 12. ^{1}H NMR spectra[a] of imidazolidine and hexahydropyrimidine derivatives (**8**), (**12**), and (**13**) $RCH_2N(CH_2)_nN(CH_2R)CH_2$.

Compd. no.	R	RCH_2N	Cyclic protons		
			2-CH_2	4-CH_2	5-CH_2
(**8a**)	8.05–7.50 (8 H, m)	5.40–5.60 (4 H, s)	3.75 (1.5 H, s),[b] 4.00 (0.5 H, s), 4.15 (trace, s)	2.80 (4 H, s)	
(**8b**)	8.00–7.35 (8 H, m)	5.45–5.65 (4 H, s)	3.60 (1.5 H, s),[b] 3.70 (0.5 H, s), 3.80 (trace, s)	2.55 (4 H, t)	1.55 (2 H, m)
(**12a**)	0.90 (6 H, t), 1.45 (4 H, q)	2.35 (4 H, m)	3.45 (2 H, s)	2.75 (4 H, s)	
(**12b**)	0.90 (6 H, t), 1.40 (8 H, m)	2.50 (4 H, m)	3.40 (2 H, s)	2.70 (4 H, s)	
(**12c**)	0.90 (6 H, t), 1.40 (24 H, m)	2.55 (4 H, m)	3.40 (2 H, s)	2.75 (4 H, s)	
(**12d**)	5.90–5.70 (2 H, m), 5.20–5.00 (4 H, m)	3.15 (4 H, 2 × t)	3.25 (2 H, s)	2.65 (4 H, s)	
(**12e**)	0.95 (6 H, t), 1.50 (4 H, q)	2.30 (4 H, t)	3.10 (2 H, s)	2.45 (4 H, t)	1.70 (2 H, m)
(**12f**)	5.90—5.70 (2 H, m), 5.20–5.00 (4 H, m)	2.95 (4 H, 2 × t)	3.10 (2 H, s)	2.45 (4 H, t)	1.65 (2 H, m)
(**13a**)		3.73 (4 H, s)	3.65 (2 H, s)	3.05 (4 H, s)	
(**13b**)		3.70 (4 H, s)	3.60 (2 H, s)	2.75 (4 H, t)	1.75 (2 H, m)

[a] Spectra were registered in $CDCl_3$. [b] Signals for 1,1′-1,2′ and 2,2′ isomers (see Discussion).

Table 13. Preparation of methanediamine derivatives (**9a,b**) and (**10a–d**) $R'CH_2N(R)CH_2N(R)CH_2R'$.

Compd. no.	R	R′	Yield[a] (%)	M.p. (°C)	Molecular formula	Found (%) (Required)		
						C	H	N
(**9a**)	n-Octyl	Et	83	Oil[b]	$C_{23}H_{50}N_2$	77.7 (77.9)	14.0 (14.2)	7.6 (7.9)
(**9b**)	n-Octyl	Bu^n	67	Oil[b]	$C_{27}H_{58}N_2$	79.0 (78.95)	13.8 (14.2)	7.0 (6.8)
(**10a**)	Bu^n	CN	80	Oil[b]	$C_{13}H_{24}N_4$	65.9 (66.1)	10.3 (10.2)	23.6 (23.7)
(**10b**)	n-Octyl	CN	89	78–80[c]	$C_{21}H_{40}N_4$	72.1 (72.4)	11.9 (11.6)	15.5[e] (16.0)
(**10c**)	$PhCH_2$	CN	85	62–64[d]	$C_{19}H_{20}N_4$	74.7 (75.0)	6.5 (6.6)	18.6[f] (18.4)
(**10d**)	Bu^i	CN	72	Oil[b]	$C_{13}H_{24}N_4$	65.7 (66.1)	10.0 (10.2)	23.9 (23.7)

[a] Yields of crude, NMR pure products. [b] For C,H,N analysis purified by column chromatography on silica gel using CH_2Cl_2 as eluant. [c] Recrystallised from EtOH. [d] Recrystallised from hexanes. [e] Characterised by high-resolution MS (Found: M^+, 348.3259. $C_{21}H_{40}N_4$ requires 348.3252). [f] MS: (CI) $M^+ + 1$ (305, 48.19%).

Table 14. ^{13}C NMR spectra[a] of *N,N′*-dialkyl(*N,N′*-disubstituted)methanediamine derivatives (**9a,b**) and (**10a,d**) $R'CH_2N(R)CH_2N(R)CH_2R'$.

Compd. no.	R	R′	$R'CH_2(N)$	NCH_2N
(**9a**)	14.05, 22.63, 27.52, 27.65, 29.27, 29.50, 31.83, 54.15	11.96, 19.92	52.86	74.69
(**9b**)	13.99, 22.58, 27.46, 27.56, 29.21, 29.46, 31.77, 54.15	13.99, 22.58, 26.63, 29.80	52.79	74.63
(**10a**)	13.57, 20.00, 29.03, 51.14	114.84(CN)	39.01	72.71
(**10b**)	13.89, 22.45, 26.86, 27.00, 29.06, 29.12, 31.62, 51.48	114.83(CN)	39.06	72.82
(**10c**)	127.92, 128.71, 128.78, 136.21, 55.77	114.49(CN)	38.79	72.56
(**10d**)	20.19, 25.71, 59.52	114.72(CN)	39.37	73.39

[a] Spectra were recorded in $CDCl_3$.

Table 15. ^{1}H NMR spectra[a] of methanediamine derivatives (**9a,b**) and (**10a–d**) $R'CH_2N(R)CH_2N(R)CH_2R'$.

Compd. no.	R and $R'CH_2$ signals	NCH_2N
(**9a**)	0.90–0.80 (12 H, m, 4 × CH_3), 1.25–1.40 (28 H, m, 14 × CH_2), 2.45—2.20 (8 H, m, 4 × NCH_2)	3.30 (2 H, br s)
(**9b**)	0.90–0.80 (12 H, m, 4 × CH_3), 1.20–1.45 (36 H, m, 18 × CH_2), 2.40–2.30 (8 H, m, 4 × NCH_2)	3.30 (2 H, br s)
(**10a**)	0.85 (6 H, t), 1.50–1.25 (8 H, m), 2.55 (4 H, t), 3.55 (4 H, s, CH_2CN)	3.20 (2 H, s)
(**10b**)	0.90 (6 H, t), 1.50–1.10 (24 H, m), 2.55 (4 H, t), 3.60 (4 H, s, CH_2CN)	3.15 (2 H, s)
(**10c**)	3.58 (4 H, s), 7.35 (10 H, s), 3.8 (4 H, s, CH_2CN)	3.50 (2 H, s)
(**10d**)	0.90 (12 H, d), 1.80 (2 H, m), 2.35 (4 H, d), 3.65 (4 H, s, CH_2CN)	3.25 (2 H, s)

[a] Spectra were recorded in $CDCl_3$.

aminals (**12**), and to aminoacetonitriles (**10**), (**11**), and (**13**). The present methods possess several advantages: simplicity of procedure, easily available starting materials, and a large variety of possible products. Further synthetic applications of adducts of type (**7**) will be the subject of future investigations.

Experimental

M.p.s were determined on a hot-stage microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL 200 (200 or 50 MHz) instrument in deuteriochloroform and [$^2H_6$]dimethyl sulphoxide using tetramethylsilane

for proton and the solvent signals for carbon spectra, as reference. Combustion analyses were carried out using Carlo Erba 1106 elemental analyser under the supervision of Dr. Dave Powell or by the Atlantic Microlab. Low resolution mass spectra were taken on an AE1 MS30 mass spectrometer. Exact mass measurements were performed on a KRATOS MS-80-RFA double focusing spectrometer using the peak matching technique at nominal resolution of 5 000 (10% valley definition). Tetrahydrofuran and diethyl ether were distilled under nitrogen from sodium/benzophenone immediately before use. Silica gel (230–400 mesh) was obtained from Merck.

Preparation of Adducts (**5**), (**6**), *and* (**8**): *General Procedure A*.—Benzotriazole (20 mmol), the appropriate amine [10 mmol of monoamine for (**5**), 20 mmol of monoamine for (**6**) or 10 mmol of diamine for (**8**)] and distilled water (20 ml) were stirred vigorously for 5 min at 20 °C. Formaldehyde 37% aqueous solution [20 mmol for (**5**) or 30 mmol for (**6**) and (**8**)] was then added to the reaction mixture, and stirring continued for 30 min at 20 °C. The crude products were filtered off and washed with water. Analytical samples were recrystallised from the solvent given in Tables 1, 2, and 4.

Preparation of the Adducts (**7**): *General Procedure B*.—Benzotriazole (10 mmol), dissolved in diethyl ether (50 ml), and primary amine (10 mmol) were stirred for 5 min at 20 °C. Formaldehyde 37% aqueous solution (10 mmol) was then added to the reaction mixture, and the stirring was continued for 3 h at 20 °C. The solution was dried over calcium chloride, and the solvent was evaporated. The solid products were purified by recrystallisation from solvent given in Table 3.

Preparation of the Open-chain Aminals (**9**) *and Cyclic Aminals* (**12**) *with Grignard Reagents: General Procedure C*.—To a Grignard reagent prepared from magnesium turnings (21 mmol) and appropriate alkyl halides (20 mmol) in anhydrous tetrahydrofuran (20 ml), was added the appropriate benzotriazole adduct (**6**) or (**8**) (10 mmol) dissolved in anhydrous tetrahydrofuran (50 ml), over 15 min. The reaction mixture was stirred at room temperature for 15 h [for adducts (**6a–d**)] or 5 h [for cyclic adducts (**8a–b**)] and then 20 ml of 20% ammonium chloride solution was added. The aqueous phase was extracted with ether (3 × 20 ml); the combined organic solutions were washed with 5% aqueous sodium hydroxide (2 × 20 ml) and again with water, and then dried ($MgSO_4$). Evaporation of solvent afforded the crude products (for analytical data see Tables 4 and 13).

Preparation of N,N-*bisacetonitrile Derivatives* (**10**), (**11**), and (**13**): General Procedure D.—Benzotriazole adduct [10 mmol (**6**) or (**8**) or 20 mmol (**7**)] and potassium cyanide (20 mmol) were stirred in dimethyl sulphoxide (10 ml) at 60 °C for 6 h [for adducts (**6**) and (**7**)] or at 20 °C for 12 h [for adducts (**8**)]. After addition of 20 ml of distilled water the mixture was extracted with ether (3 × 20 ml) the ethereal extract was washed with 5% aqueous sodium hydroxide (2 × 20 ml) and with water to pH = 7, and then dried ($MgSO_4$). Evaporation of solvent afforded the crude products (for analytical data see Tables 3, 4, and 13).

Preparation of 1,3-*Bisacetonitrile Derivatives* (**13a,b**) *in Acetonitrile*.—To a solution of the benzotriazole adduct of type (**8**) (10 mmol) in acetonitrile (50 ml), potassium cyanide (20 mmol) was added. The reaction is completed after 24 h under reflux. The solvent was evaporated, and products were isolated as is described in general procedure D [yield 88 and 85% for (**13a**) and (**13b**), respectively; for analytical data see Table 4].

Preparation of 1,3-*Bisacetonitriles* (**13a–b**) (*One-pot Procedure*).—Benzotriazole (10 mmol), dissolved in dimethyl sulphoxide (20 ml), and either ethane-1,2-diamine or propane-1,3-diamine (10 mmol) were stirred at 20 °C for 5 min. Formaldehyde 37% aqueous solution (15 mmol) was then added, and the reaction was continued for 30 min. Next, potassium cyanide (20 mmol) was added, and the reaction mixture was stirred for 12 h at 20 °C. The products were isolated as described in General procedure D [yield 85 and 87% for (**13a**) and (**13b**), respectively].

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