The Chemistry of Benzotriazole. Part 8.[1] A Novel Two-step Procedure for the *N*-Alkylation of Amides

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Benzotriazole, aldehydes RCHO, and amides R^1CONH_2 react together with elimination of water to form 1 : 1 : 1 adducts which are reduced smoothly by $NaBH_4$ to give the *N*-substituted amides $R^1CONHCH_2R$. Both steps occur in high yields and can be carried out on a large scale, thus comprising a convenient general method for the *N*-alkylation of amides.

The amide moiety is an important constituent of many biologically significant compounds, and the *N*-alkylation of existing amides to give more substituted analogues has attracted much attention. The *N*-alkylation of amides has also been used as an intermediate step in the synthesis of secondary and tertiary amines having different alkyl groups.[2]

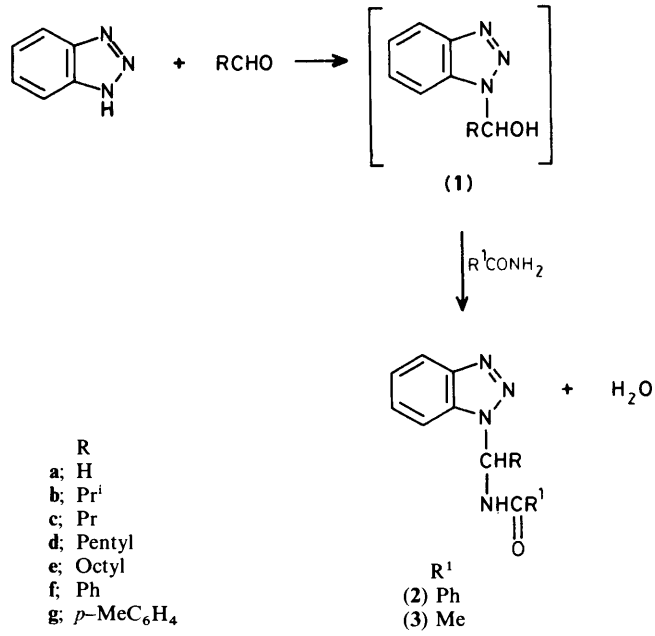
The neutral amide group generally[3] reacts with electrophiles under kinetic control at the carbonyl oxygen atom (see *e.g.* refs. 4 and 5) and indeed amides are protonated at oxygen.[6] Amide anions usually react with electrophiles at the nitrogen atom, and indeed treatment of amide anions with alkyl halides has frequently been used for their *N*-alkylation. However, these methods require the use of a very strong base (often in large excess), such as potassium hydroxide in water,[7] ethanol,[8] or DMSO,[9,10] sodium hydroxide in toluene,[11] sodium in toluene,[12] and have been said[13] 'to produce impure products in indifferent yields under fierce conditions.' Phase-transfer catalysis has been successful using NaOH–benzene for mono-alkylation of both unsubstituted[14] and monosubstituted amides,[13] but perhaps the most successful *N*-alkylation of amides with alkyl halides is that reported by Sukata[15] using KOH on alumina at 60 °C.

Recently Shono and co-workers[16] reported an electro-reductive *N*-alkylation with alkyl halides which gave good yields; however, the method was only applied to secondary amides.

The use of reagents other than alkyl halides to substitute amides is more rare. *N*-Alkylation of amides in variable yields with alcohols at 180 °C was carried out by Watanabe *et al.*, using ruthenium complexes as catalysts.[17] Treatment of amides with formaldehyde gives hydroxymethyl derivatives, and these can be reduced to *N*-methylamides with triethylsilane,[18] but alkylation of amides by other aldehydes has not been reported except for a brief note without experimental detail.[19] Methylation of amides has been reported by treatment with $MeSCH_2Cl$ followed by reduction with Raney nickel,[20] but again no experimental detail was given. The Michael reaction of amides with electrophilic alkenes[21] represents a specialized type of *N*-alkylation.

We now report a novel two-step *N*-monoalkylation of amides of considerable generality using common reagents. Our previous work with benzotriazole has shown[22] that this heterocyclic system reacts easily with amines and aldehydes to form *N*-(aminoalkyl)benzotriazoles. We have demonstrated that benzotriazole, an aliphatic or aromatic aldehyde, and an amide also react to form the corresponding 1 : 1 : 1 adducts in good yields (Scheme 1).

In a one-pot reaction, benzotriazole, the aldehyde, and the amide (in equimolar amounts) are refluxed in dry toluene for 24—48 h. The reaction probably involves the formation of a hydroxyalkylbenzotriazole intermediate (**1**) which subsequently reacts with the amide (Scheme 1). The water formed as a side-product was removed azeotropically with toluene. This procedure was successful for aliphatic and aromatic aldehydes and amides on 0.1 molar scale; details are given in Tables 1 and 2.



Scheme 1.

The structures of the adducts were established on the basis of their spectral properties. In the ^{13}C n.m.r. spectra of adducts (**2**) and (**3**), the chemical shifts of the carbons of the benzotriazole ring (Table 3) corresponded closely to those previously reported for other 1-substituted benzotriazoles.[23] Thus C-7 and C-7a appeared at δ 111.2—109.6 and 132.3—131.0. The chemical shifts for C-3a and C-4 were slightly shielded and occurred at δ 145.4—144.5 and 119.3—118.3, whereas C-5 and C-6 appeared at δ 124.2—122.9 and 127.7—126.2, respectively. The chemical shifts of the carbonyl carbons for compounds (**2**) and (**3**) fall in the region 170.8—166.7 p.p.m. (Table 4).

In addition, the ^{13}C n.m.r. spectra of the adducts (**2**) showed four signals corresponding to the aromatic carbons of benzamide. Compared with the ^{13}C n.m.r. shifts in unsubstituted benzamide, the C-1′ carbon was slightly deshielded (1.6—1.1 p.p.m.); the other carbons were little affected.[24] In the adduct (**3**) the acetamide methyl group resonated at 22.5—21.3 p.p.m.[25] As expected, the absorption peak for the characteristic C-α between the heterocyclic ring and amide nitrogen appeared at δ 69.6—

Table 1. Preparation of the *N*-[1-(benzotriazol-1-yl)alkyl]amides (**2**) and (**3**)

Product	R of RCHO	R^1 of R^1CONH_2	Method[a]	Time (h)	Yield (%)	Recryst. solvent	M.p. (°C)	Crystal form
(2a)	H	Ph	A	24	78	MeOH	177—179	Needles
(2b)	Pr^i	Ph	B	24	52	MeOH	191—193	Prisms
(2c)	Pr	Ph	B	24	59	MeOH	156—159	Prisms
(2d)	Pentyl	Ph	B	48	48	MeOH	110—115	Microcryst.
(2e)	Octyl	Ph	B	48	74	MeOH	102—105	Plates
(2f)	Ph	Ph	B	24	60	MeOH	188—190	Needles
(3b)	Pr^i	Me	B	48	51	Benzene	164—167	Prisms
(3f)	Ph	Me	B	48	45	Benzene	174—177	Needles
(3g)	*p*-MeC_6H_4	Me	B	40	42	Benzene	186—189	Needles

[a] For methods A and B see Experimental section.

Table 2. Elemental analyses of the adducts (**2**) and (**3**)

Product	R of RCHO	R^1 of R^1CONH_2	Required (%)			Molecular formula	Found (%)		
			C	H	N		C	H	N
(2a)	H	Ph	66.7	4.8	22.2	$C_{14}H_{12}N_4O$	66.9	4.8	22.2
(2b)	Pr^i	Ph	69.4	6.2	19.0	$C_{17}H_{18}N_4O$	69.5	6.4	18.9
(2c)	Pr	Ph	69.4	6.2	19.0	$C_{17}H_{18}N_4O$	69.4	6.4	18.9
(2d)	Pentyl	Ph	70.8	6.9	17.4	$C_{19}H_{22}N_4O$	70.3	7.0	17.2
(2e)	Octyl	Ph	72.5	7.7	15.4	$C_{22}H_{28}N_4O$	72.2	7.9	15.2
(2f)	Ph	Ph	73.1	4.9	17.1	$C_{20}H_{16}N_4O$	72.9	4.7	16.9
(3b)	Pr^i	Me	62.0	6.9	24.1	$C_{12}H_{16}N_4O$	61.8	7.1	24.5
(3f)	Ph	Me	67.6	5.3	21.0	$C_{15}H_{14}N_4O$	67.5	5.3	21.0
(3g)	*p*-MeC_6H_4	Me	68.5	5.8	20.0	$C_{16}H_{16}N_4O$	68.0	5.8	19.6

Table 3. ^{13}C N.m.r. chemical shifts (δ) of the benzotriazole carbons in compounds (**2**) and (**3**)[a]

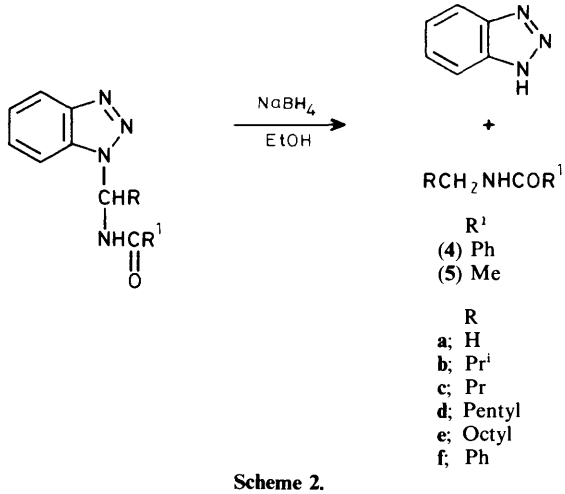
Product	C-3a	C-4	C-5	C-6	C-7	C-7a
(2a)	145.4	118.9	123.8	127.2	111.2	132.2
(2b)	145.0	119.0	123.7	127.1	111.0	132.0
(2c)	145.2	119.1	123.9	127.1	111.1	132.0
(2d)	145.3	119.2	124.2	127.7	110.5	132.0
(2e)	145.4	119.3	124.2	127.7	110.5	132.8
(2f)	145.3	119.2	123.9	127.3	111.0	132.0
(3b)	145.0	119.2	124.1	127.6	110.2	133.2
(3f)	145.3	119.1	123.9	127.2	110.8	131.8
(3g)	144.5	118.3	122.9	126.2	109.6	131.1

[a] All spectra were run on Varian XL 200 (50 MHz, FT mode) and in $(CD_3)_2SO$ except those for compounds (**2d**), (**2e**), (**3b**), and (**3g**) were run in $CDCl_3$.

51.7. In the ^{13}C n.m.r. spectra (Table 5a), the aliphatic carbons of the R substituents of the adducts (**2**) displayed a similar pattern as for the aliphatic amines published elsewhere,[24] whereas the aromatic carbons of phenyl substitutents in compounds (**2f**), **3f**), and (**3g**) gave rise to the signals in the region 137.4—125.4 (Table 5b). The quaternary carbons could be easily assigned; in addition to C-4′, however, the assignments of the chemical shifts for C-2′ and C-3′ are interchangeable.

In the ^1H n.m.r. spectra of compounds (**2**) and (**3**) (Table 6), the most deshielded aromatic proton has been assigned to C-4 of the benzotriazole.[23] The other aromatic protons of benzotriazole and phenyl substitutents appeared as a complex multiplet between 8.15 and 7.13 p.p.m. The NH protons resonated at δ 10.25—9.79 as a doublet with a coupling constant in the range 8—9 Hz. The methine proton was significantly deshielded to δ 7.04—6.26 due to the effect exerted by the benzotriazole ring and appeared as a well resolved signal with a coupling constant in the range 6—8 Hz. Protons attached to C-β gave rise to the obscure multiplet in the region 3.49—2.45 p.p.m. The other aliphatic protons of the acyclic substitutent R appeared upfield as complex multiplets. The exception was observed for the methyl groups in compounds (**2b**) and (**3b**). The chemical shifts of those two non-equivalent methyl groups in the isopropyl substituent differed by about 0.5 p.p.m. and appeared as sharp doublets with a coupling constant of 6 and 7 Hz, respectively.

Reduction of Adducts to N-*Alkylamides.*—The adducts described above are readily reduced by sodium borohydride in absolute ethanol to the *N*-alkylated amides (with elimination of benzotriazole) in excellent yields (Scheme 2). The *N*-alkylamides



Scheme 2.

were identified by comparison of m.p.s with literature values (Table 7), and by their spectral data.

The ^{13}C n.m.r. spectra of the *N*-alkylated amides (**4**) and (**5**) (Tables 4 and 5) resembled, in many respects, those of the parent

Table 4. ^{13}C N.m.r. chemical shifts (δ) for the substituent R^1 in compounds (**2**)—(**7**)[a–c]

Product	C=O	$NHCH_2R^1$	C-1′	C-2′	C-3′	C-4′	$NHCH_nR$
(**2a**)	166.9		132.8	127.4	128.2	131.7	51.7
(**2b**)	166.9		133.1	127.6	128.1	131.6	69.6
(**2c**)	166.7		133.1	127.6	128.2	131.7	63.8
(**2d**)	167.4		133.1	127.4	128.3	131.9	62.7
(**2e**)	167.3		133.1	127.4	128.4	132.0	62.7
(**2f**)	166.9		132.9	127.8	128.4	131.7	66.0
(**3b**)	170.8		22.5				67.8
(**3f**)	169.8		22.2				65.1
(**3g**)	169.3		21.3				64.0
(**4a**)	168.4		134.3	126.8	128.2	131.0	26.6
(**4b**)	167.7		134.8	126.8	128.4	131.1	47.3
(**4c**)	167.6		134.7	126.8	128.3	131.1	39.7
(**4d**)	167.5		134.5	126.8	128.0	130.8	39.9
(**4e**)	167.5		134.7	126.8	128.3	131.1	40.0
(**4f**)	167.5		134.2	126.9	128.4	131.4	43.9
(**5f**)	170.3		22.5				43.1
(**6a**)		55.6	139.7	127.8	128.0	126.6	35.6
(**6b**)		57.2	140.4	127.7	128.0	126.5	53.7
(**6c**)		53.7	140.3	127.9	128.2	126.7	48.9
(**6d**)		53.9	140.3	127.9	128.0	126.6	49.3
(**6e**)		54.0	140.4	127.9	128.2	126.7	49.4
(**6f**)		53.0	140.2	127.9	128.2	126.7	53.0
(**7f**)		*d*	43.3	14.9			53.6

[a] All spectra were run on Varian XL 200 (50 MHz, FT mode). [b] Spectra of compounds (**2a**—**c**), (**2f**), and (**3f**) were run in $(CD_3)_2SO$. [c] Spectra of compounds (**2d**—**e**), (**3b**), (**3g**), (**4**), and (**5**) were run in $CDCl_3$. [d] See C-1′.

Table 5a. ^{13}C N.m.r. of the selected substituents R in compounds (**2**)—(**6**)[a,b]

	b; Pr^i			**c**; Pr			**d**; Pentyl				
Product	CH	Me	Me	C-1	C-2	Me	C-1	C-2	C-3	C-4	Me
(**2**)	31.0	19.2	18.4	34.8	18.4	13.2	33.9	31.0	25.0	22.2	13.5
(**3**)	32.4	18.9	18.5								
(**4**)	28.1	20.1	20.1	31.5	20.0	13.7	31.2	29.3	26.4	22.3	13.7
(**6**)	28.1	20.4	20.4	32.0	20.3	13.9	31.6	29.9	26.8	22.4	13.8

	e; Octyl							
Product	C-1	C-2	C-3	C-4	C-5	C-6	C-7	Me
(**2**)	34.0	25.4	29.1	29.0	28.8	31.6	22.5	14.0
(**4**)	31.7	26.9	29.4	29.2	29.1	29.5	22.5	14.0
(**6**)	31.8	27.3	29.5	29.5	29.2	30.0	22.6	14.0

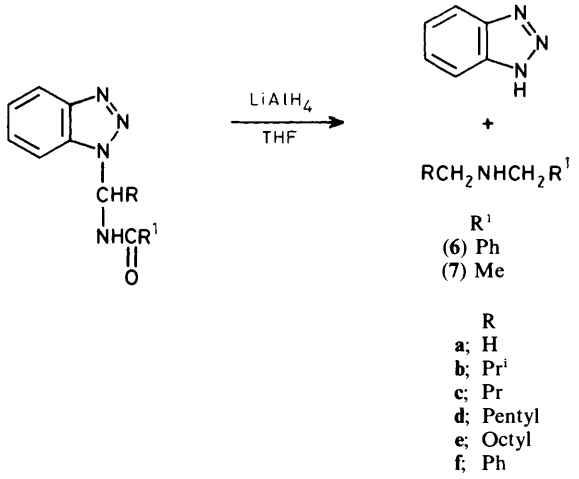
[a] All spectra were run on Varian XL 200 (50 MHz, FT mode). [b] All spectra were run in $CDCl_3$ except those for compounds (**2a**—**c**) which were run in $(CD_3)_2SO$.

Table 5b. ^{13}C N.m.r. of the aromatic substituents R in compounds (**2**)—(**7**)[a,b]

Product	C-1	C-2	C-3	C-4	Others
(**2f**)	136.2	128.6	128.0	126.8	
(**3g**)	136.3	132.2	127.2	126.5	19.8 (Me)
(**3f**)	132.2	128.1	125.4	137.4	
(**5f**)	138.2	128.4	127.7	127.4	
(**6f**)	140.2	127.9	128.2	126.7	
(**7f**)	140.1	128.0	128.2	126.7	

[a] All spectra were run on Varian XL 200 (50 MHz, FT mode). [b] All spectra were run in $CDCl_3$ except those for compounds (**2f**) and (**3f**) which were run in $(CD_3)_2SO$.

adducts: no significant changes were observed in the chemical shifts of C=O or the carbons of the substitutents R and R^1. The principal differences were in the chemical shifts of the characteristic C-α which, in the absence of the benzotriazole residue, has been shifted upfield into the δ 47.3—26.6 region (Table 4). The



Scheme 3.

Table 6. ^{1}H N.m.r. chemical shifts of compounds (**2**) and (**3**)[a,b]

	Benzotriazole and R^1				CHNH			NH		Substituent R								
Product	4-H (1 H) d(Hz)	7-H (1 H) (d)	Other Ar (m)	H		H	M[c]		M		H (m)			H	M		Me (3 H)	M
(**2a**)	8.09 (9)	*d*	7.96—7.13	8	6.26	2	d[e]	9.79	d[g]	3.49—3.01	1	CH	1.27	3	d	Me	0.67	d[e]
(**2b**)	8.19 (7)	8.05[h]	7.78—7.40	7	6.60	1	d[g]	9.79	d[g]	2.48—2.45	2	CH_2	1.50—1.21	2	m	CH_2	0.95	t[h]
(**2c**)	8.17 (7)	8.07[h]	7.99—7.37	7	6.98	1	q[g]	9.80	d[g]	2.51—2.48	2	CH_2	1.60—1.02	6	m	$(CH_2)_3$	0.83—0.60	m
(**2d**)	8.17 (7)	*i*	8.14—7.41	8	6.92	1	d[g]	9.80	d[g]	2.70—2.36	2	CH_2	1.40—1.90	12	m	$(CH_2)_6$	0.90—0.80	m
(**2e**)	8.19 (9)	*i*	7.97—7.27	9	6.96	1	q[f]	*i*					*d*					
(**2f**)	8.25 (7)	*i*	8.08—7.36	14	*i*			10.25	d[g]									
(**3b**)	8.07 (8)	8.87[g]	7.54—7.37	2	6.44	1	t[j]	8.58	d[k]	2.91—2.73	1	CH	1.23	3	d[h]	Me	0.77	d[h]
(**3f**)	8.04—7.33 (10 H, m)																	
	2.04 (3 H, s, Me)				*i*			*9.8*	*d*[k]				*i*					
(**3g**)	8.00 (8)	7.93[k]	7.48—7.31	6	7.04	1	d[g]	9.66	d[k]				7.17	4	q[g]	(4 × CH)	2.31	s
	2.04 (3 H, s, Me)																	

[a] All spectra were run on Varian XL 200 (200 MHz, FT mode). [b] All spectra were run in $(CD_3)_2SO$ except those for compounds (**2d**), (**2e**), (**3b**), and (**3g**) which were run in $CDCl_3$. [c] Multiplicity: m = multiplet, q = quartet, t = triplet, d = doublet, s = singlet. [d] Signals appeared with other aromatics. [e] J = 6 Hz. [f] NH appeared as a broad signal. [g] J = 8 Hz. [h] J = 7 Hz. [i] NH signal appeared together with aromatic protons, non-distinguishable. [j] J = 10 Hz. [k] J = 9 Hz. [l] J = 9 Hz.

Table 7. Preparation of the *N*-monoalkylated amides (**4**) and (**5**) RCH_2NHCOR^1

Product	R	R^1	Yield (%)	Recryst. solvent	M.p. (°C)	Lit. m.p. (°C)
(**4a**)	H	Ph	96	Light petroleum	75—77	78[26]
(**4b**)	Pr^i	Ph	96	Benzene	55—57	55—58[27]
(**4c**)	Pr	Ph	96	EtOH	69—71	68—70[28]
(**4d**)	Pentyl	Ph	97	MeOH	55—58	56.5—57[29]
(**4e**)	Octyl	Ph	99	EtOH	48—50	49[30]
(**4f**)	Ph	Ph	94	MeOH	104—105	105—106[31]
(**5f**)	Ph	Me	98	Benzene	58—60	61[32]

Table 8. ^{1}H N.m.r. chemical shifts of the *N*-alkylated amides (**4**) and (**5**)[a]

	R^1			NH	RCH_nNH			R									
Product	2-H (2 H, m)	3-, 4-H (m)	H	(1 H)		H	M[b]	H (m)			H	M			H	M	
(**4a**)	7.82—7.77	7.43—7.30	4	*c*	2.93	3	d[d]										
(**4b**)	7.80—7.76	7.47—7.35	3	6.63[e]	3.26	2	t[f]	2.00—1.79	1	CH	0.95	6	d[f]	2 × Me			
(**4c**)	7.81—7.61	7.45—7.32	3	6.83[e]	3.45—3.35	2	m	1.61—1.31	4	$(CH_2)_2$	0.91	3	t[f]	Me			
(**4d**)	7.85—7.80	7.45—7.27	4	*e*	3.41—3.31	2	m	1.59—1.53	2	CH_2	1.26—1.25	6	m	$(CH_2)_3$	0.85—0.82	3	m	Me
(**4e**)	7.81—7.76	7.45—7.28	3	6.78[e]	3.45—3.35	2	m	1.61—1.55	2	CH_2	1.54—1.25	12	m	$(CH_2)_6$	0.90—0.84	3	m	Me
(**4f**)	7.81—7.79[g]	7.60—7.24	6	7.01[e]	4.55	4	d[h]			*c*							
(**5f**)	7.27—7.16 (m)		6	*c*	4.28—4.25	2	m	1.86	3	Me							

[a] All spectra were run on Varian XL 200 (200 MHz, FT mode), in $CDCl_3$. [b] Multiplicity: m = multiplet, t = triplet, d = doublet, s = singlet. [c] See aromatics. [d] J = 5 Hz. [e] NH signal was very broad. [f] J = 7 Hz. [g] 4 H. [h] J = 6 Hz.

Table 9. Preparation of the *N*-monoalkylated amines (**6**) and (**7**) $RCH_2NHCH_2R^1$

Product	R	R^1	Yield (%)	G.c.–m.s. Calculated	G.c.–m.s. Obtained
(**6a**)	R	Ph	76	121.089 1(4)	121.088 2(6)
(**6b**)	Pr^i	Ph	75	163.136 0(9)	163.136 7(6)
(**6c**)	Pr	Ph	58	163.136 0(9)	163.136 1(5)
(**6d**)	Pentyl	Ph	66	192.167 3(4)	191.166 8(2)
(**6e**)	Octyl	Ph	64	233.214 3(4)	233.215 4(1)
(**6f**)	Ph	Ph	65	197.120 4(4)	198.119 3(5)
(**7f**)	Me	Me	83	135.104 7(9)	135.104 5(9)

^{1}H n.m.r. data of the amides (**4**) and (**5**) are shown in Table 8. The absorption peaks for the protons attached to C-α are now shifted upfield to δ 4.55—2.96.

Reduction of Adducts to Secondary Amines.—Some of the adducts were also reduced by $LiAlH_4$ (Scheme 3) to give the expected secondary amines (**6**) and (**7**) (Table 9). The identity of these secondary amines were confirmed by their ^{1}H n.m.r. spectra.

In the ^{1}H n.m.r. spectra of the amine (**6**), the characteristic methylene protons attached to the aromatic ring appeared as a singlet at δ 3.75—3.69, whereas the doublet at δ 2.61—2.40 p.p.m. corresponds to the protons attached to C-α for the amines (**6b**—**e**) (Table 10). The ^{13}C n.m.r. spectra of the *N*-alkylated amines (**6**) and (**7**) (Tables 4 and 5) showed some similarities to those of the corresponding adducts. The reduced carbonyl carbon appeared as methylene carbon at δ 57.2—53.0 and C-α resonated at δ 53.8—35.6 p.p.m. (Table 4).

Table 11 records some of the most characteristic i.r. bands for compounds (**2**)—(**7**). All exhibit the expected absorptions in the regions 3 310—3 265 and 1 600—1 525 cm^{-1}, respectively,

Table 10. ^{1}H N.m.r. chemical shifts of the *N*-alkylated amines (**6**) and (**7**)[a–c]

Product	R^1, 2-, 3-, 4-H (5 H, m)	NH (1 H, s)	R^1CH_2 (2 H, s)	$NHCH_n$ (2 H, t, *J* 7 Hz)	R (m)	H			H	m	
(**6a**)	7.2[d]	1.89	3.69	2.40[e]							
(**6b**)	7.28—7.26	*f*	3.73	2.40	1.84—1.64	1	CH	0.88	6	d[g]	2Me
(**6c**)	7.31—7.23	*f*	3.78	2.61	1.83—1.24	4	$(CH_2)_2$	0.90	3	t[g]	Me
(**6d**)	7.30—7.20	*h*	3.75	2.60	1.56—1.28	9	$(CH_2)_4$, NH	0.91—0.84	3	m	Me
(**6e**)	7.31—7.23	*h*	3.76	2.60	1.60—1.02	15	$(CH_2)_7$, NH	0.98—0.78	3	m	Me
(**6f**)	7.30—7.20[i]	1.67	3.75[j]				(R = R^1)				
(**7f**)	8.32—8.19	2.47	4.66	3.62—3.51[k]	2.07—1.99	3	Me				

[a] All spectra were run on XL 200 (200 MHz, FT mode). [b] All spectra were run in $CDCl_3$. [c] Reference was Me_4Si. [d] Singlet. [e] 3 H, s. [f] NH signal was broad. [g] *J* = 7 Hz. [h]NH signal was in aliphatic region. [i] 10 H. [j] 4 H. [k] Multiplet.

Table 11. I.r. characteristic bands for compounds (**2**)—(**7**)[a,b]

Product	NH stretching	C=O stretching	NH bending
(**2a**)	3 300m	1 650s	1 560m
(**2b**)	3 300m	1 665m	1 575w
(**2c**)	3 300w	1 670m	1 525m
(**2d**)	3 290w	1 665m	1 530m
(**2e**)	3 300m	1 660s	1 580w
(**2f**)	3 280w	1 650m	1 525m
(**3b**)	3 265s	1 675s	1 535m
(**3f**)	3 280m	1 645s	1 520m
(**3g**)	3 280w	1 690s	1 515w
(**4a**)	3 300s	1 640m	1 540m
(**4b**)	3 290m	1 640s	1 540m
(**4c**)	3 300s	1 640s	1 535m
(**4d**)	3 310m	1 640m	1 535m
(**4e**)	3 310s	1 640s	1 540s
(**4f**)	3 310w	1 640w	1 570m
(**5f**)	3 290m	1 635m	1 540m
(**6a**)	3 310w		1 600w
(**6b**)	3 300w		1 600w
(**6c**)	3 300w		1 600w
(**6d**)	3 300w		1 600w
(**6e**)	3 300w		1 600w
(**6f**)	3 310w		1 600w
(**7f**)	3 290w		1 600w

[a] All spectra were run on a Perkin-Elmer 285B spectrophotometer. [b] Solids were run as mulls in Nujol, the oils (amines) were run as films. [c] Intensity: s = strong, m = medium, w = weak.

corresponding to the N—H stretching and bending vibrations. Compounds (**2**)—(**5**) also showed the characteristic medium to strong absorption for the amide carbonyl group at 1 670—1 635 cm^{-1}.

Conclusion

The easy formation of acyl- and aroyl-aminobenzotriazole derivatives thus allows the exclusive *N*-monoalkylation of aliphatic and aromatic amides by reduction of these adducts using sodium borohydride in absolute ethanol. Additionally, *N*-alkylated amines were prepared from the adducts with an excess of lithium aluminium hydride in THF. The sequences each proceed with good overall yields for both aliphatic and aromatic aldehydes.

This new method thus allows the *N*-monoalkylation of amides in a two-step procedure, applicable on a large scale, and using readily accessible reagents.

Experimental

M.p.s were determined on a Kofler hot-stage microscope, and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 283B spectrophotometer. ^{1}H N.m.r. spectra were obtained on Varian XL200 (200 MHz, FT mode) spectrometer, with Me_4Si as an internal standard. ^{13}C N.m.r. spectra were obtained on a Varian XL200 (50 MHz) spectrometer.

General Procedure for the Preparation of Adducts (**2**) *and* (**3**).—*Method A. N*-Hydroxymethylbenzotriazole (14.9 g, 0.1 mol), the amide (0.1 mol), and dry toluene (40 ml) were refluxed in a Dean-Stark apparatus for the appropriate length of time and the water collected was removed azeotropically. The toluene was removed at 60 °C/30 mmHg. The residue was treated with diethyl ether (200 ml) and the resulting solid recrystallized from the appropriate solvent to give compound (**2**) or (**3**) (see Table 1).

Method B. Benzotriazole (11.9 g, 0.1 mol), the aldehyde (0.1 mol), and the amide (0.1 mol) were refluxed for 24—48 h in dry toluene (40 ml) in a Dean-Stark apparatus. Water (*ca.* 1.5 ml) was formed and removed azeotropically. Toluene was then removed at 60 °C/30 mmHg and the residue was treated with diethyl ether (200 ml) and the resulting solid was recrystallized from the appropriate solvent to give compound (**2**) or (**3**) (see Table 1).

General Procedure for Preparation of N-*Alkylated Amides* (**4**) *and* (**5**).—Compound (**2**) or (**3**) (3 mmol) was dissolved in absolute ethanol (30 ml). Solid sodium borohydride (0.33 g, 9 mmol) was added in one portion to the stirred solution. The clear solution was refluxed for 3 h and the solvent was evaporated at 30 °C. The residue was diluted with water (30 ml) and extracted with chloroform (3 × 30 ml). The organic layer was washed with 2M NaOH (30 ml), water (30 ml), and dried with $MgSO_4$ (10 g). The solvent was evaporated at 20 °C, to afford the amides which were pure by t.l.c., ^{1}H n.m.r., and m.p.s (Table 7).

General Procedure for Preparation of N-*Alkylated Amines* (**6**) *and* (**7**).—Compound (**2**) or (**3**) (3 mmol) was dissolved in dry THF (30 ml). Solid lithium aluminium hydride (0.30 g, excess) was slowly added in three portions to the stirred solution. The resulted suspension was heated for 30 min. Ice (1 g) was added to decompose the unchanged lithium aluminium hydride. The solvent was evaporated at 30 °C. The residue was treated with 2M NaOH (30 ml) and extracted with chloroform (3 × 30 ml). The organic layer was washed with 2M NaOH (30 ml) and water (30 ml) and dried with $MgSO_4$ (10 g). The solvent was evaporated at 20 °C to afford benzylamines pure by t.l.c., ^{1}H n.m.r., and g.c.–m.s. (Table 9).

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