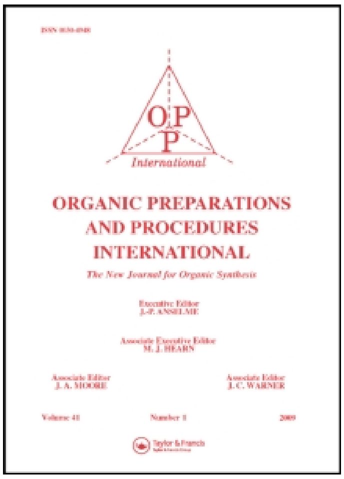

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THE PREPARATION OF 1-(α-AMINOALKYL)-BENZOTRIAZOLES IN AQUEOUS SOLUTION[#]

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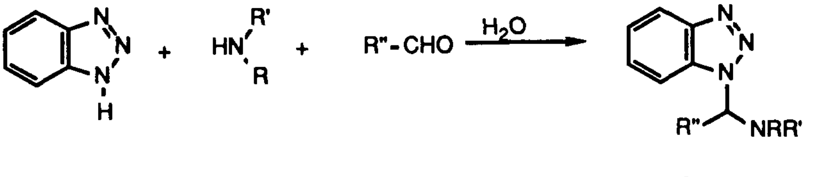
Recent publications from our laboratory have emphasized the synthetic utility of adducts (4) (Scheme 1) formed from benzotriazole (1), amines (2) and aldehydes (3). These adducts have been used as intermediates for the monoalkylation of aromatic and of heteroaromatic amines,[1] for the conversion of secondary aliphatic to tertiary aliphatic amines,[2] and for the preparation of symmetrical secondary and tertiary amines, and of N,N-disubstituted hydroxylamines.[2] The preparation of adducts of these types from formaldehyde (and other aldehydes), benzotriazole, and primary or secondary amines, has usually been carried out in ethanolic solution[3-5] or by the Dean Stark method.[2]



1 2 3 4a-o

Numerous industrial applications,[1] and the diverse biological activity[1,6] of benzotriazole adducts of type (4), prompted us to look for new, facile and inexpensive methods for their preparation. Recently Tychopoulos and co-workers[7] reported that Mannich reactions of phenols or of ketones with secondary amines and formaldehyde were greatly improved using aqueous media compared with alcoholic or hydrocarbon solvents.

TABLE 1. Preparation of 1-(α-Aminoalkyl)benzotriazoles (**4a-o**)[a]

Entry	Amine (RR'NH)			Yield (%)	mp (°C)	Cryst solv.	Literature mp (°C)
No.	R	R'	R"				
4a	H	C_6H_5	H	90	141-143	MeOH	[b]
4b	CH_3	C_6H_5	H	91	75-77	EtOH	76-78[8]
4c	H	4-Cl-C_6H_4	H	80	163-166	EtOH	165-167[1]
4d	H	3-NO_2-C_6H_4	H	97	203-205	EtOH	---
4e	H	4-Bu^n-C_6H_4	H	97	138-139	MeOH	---
4f	H	2,4-$(Pr^i)_2C_6H_3$	H	87	109-111	EtOH/ water	---
4g	H	2-Pyridyl	H	84	136-138	toluene	137-138[1]
4h	H	6-Purinyl	H	86	246-251	water/ AcOH	245-251[1]
4i	H	C_6H_5	CH_3	87	124-130	MeOH	---
4j	H	4-Bu^n-C_6H_4	CH_3	99	117-120	hexane	---
4k	H	2-Pyridyl	CH_3	89	124-126	hexane	---
4l	-$(CH_2)_2$-O-$(CH_2)_2$-		H	91	103-104	Et_2O	104-105[6]
4m	-$(CH_2)_4$-		H	92	79-81	Et_2O	79-81[9]
4n	H	C_6H_5	COOEt	77[c]	105-107	$CHCl_3$/ hexane	---
4o	H	4-CH_3O-C_6H_4	COOEt	93[c]	88-90	EtOH	---

[a] correct analyses (±0.40 % C,H,N) were obtained for all new compounds, see Table 3.

[b] compound reported in ref 3, but no m.p. given

[c] reaction was run in water-EtOH 4:1 mixture

However, Mannich reactions of azoles under these conditions have not previously been reported. We have now found that benzotriazole reacts with various amines and formaldehyde or acetaldehyde (see Table 1) in water at 20° to afford the adducts (4) in high yield. Benzotriazole is first mixed with water and the appropriate amine, whereupon a separate phase is usually formed as an oil or solid. When the aldehyde component is added, a rapid change in the consistency of the mixture can be observed: the oil phase begins to solidify or the solid phase becomes pasty and then resolidifies. The order of the addition seems to be important, as experiments using different addition orders gave lower yields and less pure products. The reaction is usually complete in one hour and the solid product possesses a consistency advantageous for fast filtration. This simple procedure can be carried out on a large scale with no obvious scale-up limitations.

TABLE 2. ^{13}C-NMR Spectroscopic Data for the New 1-(α-Aminoalkyl) benzotriazoles (4); Benzotriazole signals

Entry		Carbon of Benzotriazole Ring					
No	solvent	3a	4	5	6	7	7a
4a	$CDCl_3$+d_6-DMSO	145.7	119.0	123.9	127.1	110.9	132.2
4d	$CDCl_3$+d_6-DMSO	145.4	119.1	124.1	127.3	110.9	132.1
4e	d_6-DMSO	145.3	118.3	122.9	126.1	109.8	131.5
4f	d_6-DMSO	145.5	118.9	122.9	126.8	110.8	132.2
4i[a]	$CDCl_3$	144.1	118.3	122.6	125.8	110.2	131.9
4j	$CDCl_3$	145.8	119.0	123.3	126.4	110.8	132.2
4k[a]	$CDCl_3$	146.0	119.6	123.9	127.1	110.9	131.9
4n	$CDCl_3$	144.7	118.2	122.9	126.3	109.8	130.2
4o	$CDCl_3$	146.4	120.0	124.3	127.8	110.3	131.5

[a] Weak additional signals, due to the known isomerisation of aminoalkyl benzotriazoles[9] (i.e. 4 signals of 2-substituted benzotriazole ring and duplication of the Cα and the R"(Me) signals) are observed.

TABLE 3. ^{13}C-NMR Data for the New 1-(α-Aminoalkyl) benzotriazoles (4): Substituent signals

Entry			Carbon Atom of R' Group[b]				
No	C(α)	R''	i	o	m	p	substituent
4a	57.5	--	145.5	112.9	129.0	118.2	----
4d	56.1	--	148.6	106.6 119.1	147.0 112.1	130.1	----
4e	57.2	--	142.3	128.0	131.8	112.2	12.9,21.2 32.8,33.5
4f	57.6	--	139.9	137.7 111.3	123.8 123.5	132.2	22.5,24.9 26.1,32.6
4i[a]	20.4	65.9	145.2	112.4	128.0	117.8	----
4j	21.2	65.9	142.5	128.4	130.5	113.1	13.0,21.2 32.8,33.6
4k[a]	21.6	63.4	156.1	108.2	137.8 147.7	114.8	----
4n	68.1	12.5 61.5 164.8	142.8	112.3	127.8	117.9	----
4o	70.4	13.7 63.3 166.5	147.9	114.8	115.3	153.7	55.4

[a] see under Table 2

[b] i, o, m, p refer to the position of the carbon relative to the NH group; non-identical o and m signals are given in the order of the ring-numbering.

EXPERIMENTAL SECTION

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM 360L (60 MHz) spectrometer using tetramethylsilane (TMS) as the internal reference; ^{13}C-NMR spectra were registered on a Varian XL-200 spectrometer (FT mode, 50 MHz) in $CDCl_3$ or d_6-DMSO using the solvent signal as the reference.

General Procedure for the Preparation of Benzotriazole Adducts (4a-o).

Benzotriazole (10 mmol), the appropriate amine (10 mmol) and distilled water (10 ml) were stirred vigorously for 5 min. at 20-25°C. An equimolar amount of formaldehyde (0.75 ml 37% aq. soln.) or acetaldehyde (0.56 ml) was added to the reaction mixture and the stirring was continued for 60 minutes at room temperature. The products were filtered and washed with water. Analytical samples were obtained by recrystallization from solvents given in Table 1 and were identified by spectroscopic methods.

TABLE 4. Elemental Analyses of new 1-(α-Aminoalkyl)benzotriazoles

Entry	Calculated(%)			Formula	Found(%)		
No	C	H	N		C	H	N
4a	69.64	5.36	25.00	$C_{13}H_{12}N_4$	69.79	5.40	25.01
4d	57.35	5.14	25.00	$C_{13}H_{11}N_5O_2$	57.52	5.01	25.49
4e	72.82	7.19	19.99	$C_{16}H_{20}N_4$	72.73	7.44	19.97
4f	73.99	7.84	18.17	$C_{19}H_{24}N_4$	73.91	7.95	18.13
4i	70.58	5.88	23.52	$C_{14}H_{14}N_4$	70.24	5.71	23.22
4j	73.46	7.48	19.04	$C_{18}H_{22}N_4$	73.72	7.63	19.33
4k	65.50	5.04	29.41	$C_{13}H_{13}N_5$	65.61	5.41	29.49
4n	64.85	5.44	18.91	$C_{16}H_{16}N_4O_2$	64.98	5.43	19.02
4o	62.57	5.66	17.17	$C_{17}H_{18}N_4O_3$	62.98	5.31	17.37

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