The Chemistry of *N*-Substituted Benzotriazoles. Part 20.[1] Mono-*N*-t-Butylation of Aromatic and Heteroaromatic Amines

Alan R. Katritzky* and Jean-Jacques Vanden Eynde
Department of Chemistry, University of Florida, Gainesville, Florida 32611, U.S.A.

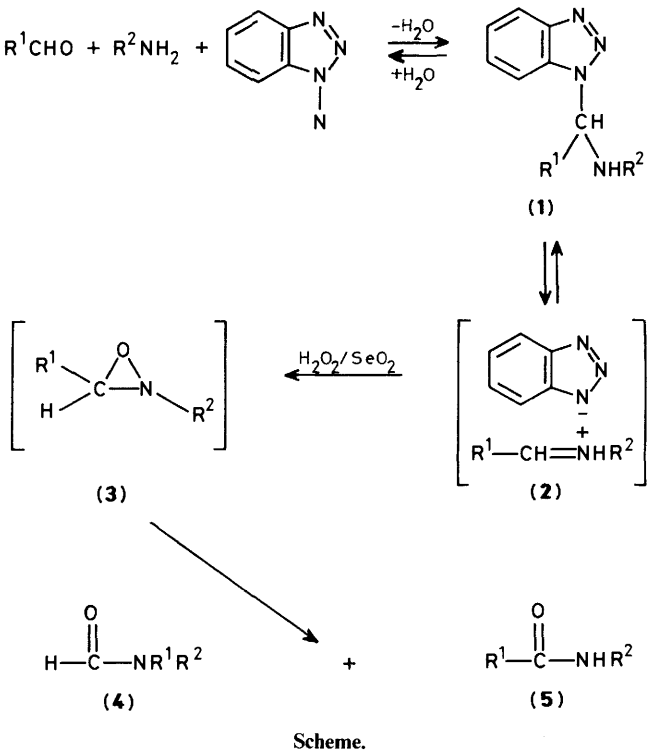
Adducts $R^1CH(Bt)NHAr$, readily available from aldehydes, primary aromatic or heteroaromatic amines, and benzotriazole are converted by H_2O_2–SeO_2 into mixtures of $R^1CONHAr$ and $HCONR^1Ar$ in proportions which depend rationally on the nature of the R^1 group. For R^1 = Bu^t, the formamide $HCON(Bu^t)Ar$ is formed in satisfactory yields thus enabling the title reaction to be achieved.

We have recently applied benzotriazole chemistry to the mono-*N*-alkylation of aromatic and heteroaromatic primary amines.[2] In this procedure, which was shown to possess considerable advantages over others available, an aldehyde R^1CHO, the amine $ArNH_2$, and benzotriazole form an adduct, $R^1CH(Bt)NHAr$ [*cf.* (**1**); Scheme], which is then treated with a Grignard reagent RMgBr to form the alkylated amine $R^1R^2CHNHAr$. In this sequence, R^1 can be hydrogen, so primary or secondary alkyl groups can be introduced: however, the scope of the analogous reaction to form compounds of the type $R'NHAr$ where R′ is a tertiary group is very limited.[3] We now report a method for the mono-*N*-t-butylation of aromatic and heteroaromatic amines which is potentially extendible to the introduction of tertiary alkyl groups in general. Our method is based on the oxidation and subsequent rearrangement of the benzotriazole adducts (**1**) in which R^1 is a t-butyl group.

A series of adducts (**1**) (Table 1) were prepared from an aldehyde, an amine, and benzotriazole by one of the standard procedures,[4] and their oxidation studied under various conditions. We observed that these adducts (**1**) are readily converted by hydrogen peroxide in the presence of selenium dioxide[5] into mixtures of formamide (**4**) and amide (**5**) (Scheme). Aqueous hydrogen peroxide was found to be the best oxidant, despite the fact that under these conditions hydrolysis of (**1**) occurs to a significant extent. For example, (**1a**) reacted neither with potassium permanganate in the presence of dicyclohexano-18-crown-6[6] nor with pyridinium dichromate;[7] with *m*-chloroperbenzoic acid,[8] reaction was very slow and yielded, beside the expected amides, a complex mixture of by-products.

The mechanism of the reaction probably involves the known[9] reversible ionic dissociation of (**1**) into (**2**) followed by oxidation to an oxaziridine [(**3**); Scheme]. As in other three-membered ring systems, relief of ring strain provides the driving force for bond cleavage. In the oxaziridine series, N–O bond cleavage is preferred when there are alkyl group(s) on the carbon atom and an aryl group on the nitrogen atom; the bond fission is accompanied by the 1,2 shift of a group from the carbon atom to the nitrogen atom so that a mixture of two isomeric amides can be obtained.[10]

The results of the hydrogen peroxide oxidation experiments are summarized in Table 2 (analytical data in Table 3). The two types of products (**4**) and (**5**) are easily distinguished by n.m.r. spectroscopy. Indeed, in the ^{13}C n.m.r. spectra, the carbon atom of the carbonyl function in the formamide (**4**) appears around 160 p.p.m. whereas for the amide (**5**) that signal is shifted downfield to around 175 p.p.m. Furthermore, in the ^1H n.m.r. spectra, the chemical shift of the proton(s) of the methylene or methine group adjacent either to the nitrogen atom [around 4.5 p.p.m. for the formamides (**4**)] or to the carbonyl function [around 2 p.p.m. for the amides (**5**)] also affords unambiguous proof of the formation of the isomeric derivatives. The integrated intensity of these signals was used to determine the ratio (**4**):(**5**) (see Table 2).



Scheme.

The relative proportion of (**4**) and (**5**) formed depends dramatically on the nature of the R^1 group and this dependency can be compared to that observed during the pinacol rearrangement[11] with the migration aptitude being the same as the order of increasing bulk. That parallelism is not surprising as the rearrangement of certain 1,2-diols was proved[12] to proceed *via* epoxides, the structures of which are closely related to those of the oxaziridines postulated in the mechanism outlined in the Scheme. In particular, when R^1 = Bu^t the formamides (**4**) are formed in moderate yield, but practically exclusively. Our method then provides a useful synthetic route to the non-symmetrically disubstituted formamides (**4a**—**k**) of which to date, the sole example reported in the literature is (**4h**).

As emphasized in a previous paper[2] in this series, the mono-*N*-alkylation of aromatic amines with alkyl halides is frequently a tedious process because for most methods *N*,*N*-(dialkyl)arylamines are invariably by-products.[13] Moreover, with most branched alkyl halides, yields fall dramatically because of competing amine-induced elimination: yields as low as 12%

Table 1. Preparation and analytical data of the benzotriazole precursors (**1**)

Compound	R^1	R^2	Formula	Yield (%)	Crystal form	M.p. (°C)	Found (%) (Required) C	H	N	^{13}C n.m.r. δ N–*C*–N (p.p.m.)
(**1a**)	Pr	2-Pyridyl	$C_{15}H_{17}N_5$	80	Needles	128—129[a]	67.3 (67.3	6.4 6.4	26.4 26.2)	66.9[b]
(**1b**)	Pr^i	2-Pyridyl	$C_{15}H_{17}N_5$	95	Prisms	168—169[a]	67.2 (67.4	6.4 6.4	26.3 26.2)	71.9[c]
(**1c**)	Bu^t	2-Pyridyl	$C_{16}H_{19}N_5$	85	Prisms	210—211[a]	68.6 (68.3	6.9 6.8	24.9 24.9)	74.6[c]
(**1d**)	Pr^i	3-Pyridyl	$C_{15}H_{17}N_5$	80	Needles	146—148	67.4 (67.4	6.4 6.4	26.5 26.2)	76.5[c]
(**1e**)	Bu^t	3-Pyridyl	$C_{16}H_{19}N_5$	85	Needles	157—159	68.5 (68.3	6.9 6.8	25.1 24.9)	*d*
(**1f**)	Bu^t	4-Methyl-2-pyridyl	$C_{17}H_{21}N_5$	90	Prisms	201—203	69.0 (69.1	6.9 7.2	23.7 23.7)	73.5[c]
(**1g**)	Bu^t	5-Chloro-2-pyridyl	$C_{15}H_{18}ClN_5$	95	Needles	184—186	61.0 (60.85	5.7 5.75	22.35 22.2)	*d*
(**1h**)	Bu^t	Ph	$C_{17}H_{20}N_4$	95	Needles	160—162	73.1 (72.8	7.3 7.2	20.3 20.0)	76.2[c]
(**1i**)	Bu^t	3-Chlorophenyl	$C_{17}H_{19}ClN_4$	90	Needles	170—172	64.7 (64.9	6.1 6.1	17.8 17.8)	76.6[c]
(**1j**)	Bu^t	3-Nitrophenyl	$C_{17}H_{19}N_5O_2$	85	Needles	168—169	62.6 (62.8	5.9 5.9	21.5 21.5)	76.0[c]
(**1k**)	Bu^t	4-Nitrophenyl	$C_{17}H_{19}N_5O_2$	90	Prisms	172—173	62.8 (62.8	5.9 5.9	21.55 21.5)	

[a] Ref. 4*a*. [b] Spectrum in $CDCl_3$. [c] Spectrum in [$^2H_6$]DMSO. [d] Insoluble.

Table 2. Oxidation of the adducts (**1a**—**k**)

Starting material No	R^1	R^2	$HCONR^1R^2$ (**4**) No	Yield (%) isolated	Ratio (**4**):(**5**) Yield determined by n.m.r.	R^1CONHR^2 (**5**)[a] No	^{13}C n.m.r. ($CDCl_3$) δ *C*=O (p.p.m.)	Yield (%) determined by n.m.r.	Calc. total yield (%)
(**1a**)	Pr	2-Pyridyl	(**4a**)	20	1	(**5a**)[c]	171.9	20	40
(**1b**)	Pr^i	2-Pyridyl	(**4b**)	20	4	(**5b**)	176.0	5	25
(**1c**)	Bu^t	2-Pyridyl	(**4c**)	29	>10	(**5c**)[d]	176.6	<2	30
(**1d**)	Pr^i	3-Pyridyl	(**4d**)	20	4	(**5d**)[e]	*b*	5	25
(**1e**)	Bu^t	3-Pyridyl	(**4e**)	34	>10	(**5e**)[f]	*b*	<2	35
(**1f**)	Bu^t	4-Methyl-2-pyridyl	(**4f**)	29	>10	(**5f**)[d]	176.3	<2	30
(**1g**)	Bu^t	5-Chloro-2-pyridyl	(**4g**)	39	>10	(**5g**)[d]	176.9	<2	40
(**1h**)	Bu^t	Ph	(**4h**)	24	>10	(**5h**)[g]	*b*	<2	25
(**1i**)	Bu^t	3-Chlorophenyl	(**4i**)	34	>10	(**5i**)[h]	*b*	<2	35
(**1j**)	Bu^t	3-Nitrophenyl	(**4j**)	29	>10	(**5j**)[h]	*b*	<2	30
(**1k**)	Bu^t	4-Nitrophenyl	(**4k**)	34	>10	(**5k**)[i]	*b*	<2	35

[a] Not isolated. [b] Not detected. [c] A. Mndzhoyan and V. Afrikyan, *Izv. Akad. Nauk. Armyan. SSSR, Ser. Khim. Nauk.*, 1957, **10**, 143 (*Chem. Abstr.*, **52**, 4641b). [d] J. Turner, *J. Org. Chem.*, 1983, **48**, 3401. [e] H. Rapoport, M. Look, and G. Kelly, *J. Am. Chem. Soc.*, 1952, **74**, 6293. [f] F. El-Zahraa, S. El-Basil, M. El-Sayed, K. M. Ghoneim, and M. Khalifa, *Pharmazie*, 1979, **34**, 12. [g] M. Nojima, F. Shiba, M. Yoshimura, and N. Tokura, *Chem. Lett.*, 1972, 1133. [h] H. Freund, H. Arndt, and R. Rusch, G. P. 1,166,647/1962 (*Chem. Abstr.*, **60**, 16438e). [i] P. Verkade, B. Wepster, and P. Witjens, *Recl. Trav. Chim. Pays-Bas*, 1951, **70**, 127.

have been reported [14] for the mono-*N*-t-butylation of aniline. *N*-t-Butylaniline is somewhat more conveniently prepared by the action of t-butylamine on bromobenzene in the presence of sodium (30%),[15] by reaction of nitrobenzene with t-butylmagnesium chloride (40%),[16] by oxidative coupling of lithium di-t-butylcuprate with aniline (46%),[17] by vapour-phase alkylation of aniline with 2-methylpropan-2-ol (55%),[18] or by methylation of acetone anil with methyl-lithium (61%).[19] However, none of these routes is especially attractive as a general method. Moreover, for heterocyclic amines containing one (or more) nitrogen atom(s) in the ring, the problem of t-alkylation is intensified because alkylation with an alkyl halide usually occurs on the ring nitrogen atom to a greater extent than on the exocyclic amino function.[20] To our knowledge, only one paper [21] has reported the preparation of a (mono-t-butylamino)pyridine: the 2-isomer was obtained in poor yield (<5%) by the irradiation of 2-fluoropyridine in the presence of t-butylamine. 2-(t-Butylamino)pyridine, previously described as a brown oil, was obtained by us as a white crystalline solid.

As the deformylation of formamides is routine, hydrolysis of compounds (**4**) should yield secondary amines. This assumption is confirmed by the conversion of three examples, (**4c**), (**4g**), and (**4j**) into 2-(t-butylamino)pyridine, 2-(t-butylamino)-5-chloropyridine, and *N*-t-butyl-3-nitroaniline respectively. Thus, the sequence described in this paper represents a novel route to secondary non-symmetrical amines and, more particularly, to mono-*N*-t-butyl (hetero)arylamines, previously accessible only with difficulty, if at all.

Table 3. Analytical data for the formamides (**4a**—**k**)

Compound	R^1	R^2	Formula	Crystal Form	M.p. (°C)	Found (%) (Required) C	H	N	^{13}C n.m.r. ($CDCl_3$) δ C=O (p.p.m.)
(**4a**)	Pr	2-Pyridyl	$C_9H_{12}N_2O$	Oil		65.9	7.4		162.0
						(65.8	7.4	17.1)	
(**4b**)	Pr^i	2-Pyridyl	$C_9H_{12}N_2O$	Oil		65.75	7.4		162.3
						(65.8	7.4	17.1)	
(**4c**)	Bu^t	2-Pyridyl	$C_{10}H_{14}N_2O$	Oil		67.4	7.9		162.3, 162.1
						(67.4	7.9	15.7)	
(**4d**)	Pr^i	3-Pyridyl	$C_9H_{12}N_2O$	Oil		65.7	7.4		162.1, 161.4
						(65.8	7.4	17.6)	
(**4e**)	Bu^t	3-Pyridyl	$C_{10}H_{14}N_2O$	Prisms[b]	52—53	67.6	8.0	15.8	162.5, 162.2
						(67.4	7.9	15.7)	
(**4f**)	Bu^t	4-Methyl-2-pyridyl	$C_{11}H_{16}N_2O$	Oil		68.65	8.4	14.95	162.0, 161.8
						(68.7	8.4	14.6)	
(**4g**)	Bu^t	5-Chloro-2-pyridyl	$C_{10}H_{13}ClN_2O$	Needles[c]	80—81	56.3	6.1	13.6	162.2
						(56.5	6.2	13.2)	
(**4h**)[a]	Bu^t	Ph	$C_{11}H_{15}NO$	Oil					162.7, 161.9
(**4i**)	Bu^t	3-Chlorophenyl	$C_{11}H_{14}ClNO$	Needles[b]	89—90	62.3	6.7	6.6	162.7, 162.2
						(62.4	6.7	6.6)	
(**4j**)	Bu^t	3-Nitrophenyl	$C_{11}H_{14}N_2O_3$	Needles[d]	133—134	59.5	6.4	12.7	162.3, 162.2
						(59.45	6.35	12.6)	
(**4k**)	Bu^t	4-Nitrophenyl	$C_{11}H_{14}N_2O_3$	Needles[d]	116—117	59.4	6.4	12.6	162.1
						(59.45	6.35	12.6)	

[a] C. Yoder, J. Sandberg, and W. Moore, *J. Am. Chem. Soc.*, 1974, **96**, 2260. [b] From ether. [c] From light petroleum (b.p. 38—56 °C). [d] From ethanol.

Experimental

M.p.s were determined on a hot-stage microscope and are uncorrected. ^1H n.m.r. spectra were recorded on a Varian EM-360L (60 MHz) or on a Varian XL-200 (200 MHz) and ^{13}C n.m.r. spectra were recorded on a Varian XL-200 (50 MHz) spectrometer; tetramethylsilane was used as internal reference. Elemental analyses were carried out under the supervision of Dr. R. W. King, University of Florida (solids), or by the Atlantic Microlab, Inc., Atlanta, Georgia (liquids).

Benzotriazole Adducts (**1**): *General Procedure.*—The appropriate aldehyde (10 mmol), the appropriate amine (10 mmol), and benzotriazole (1.19 g, 10 mmol) were heated in ethanol (10 ml) under reflux for 4 h. The solvent was evaporated under reduced pressure and the residue was triturated with ether to afford the crude product (**1**). Analytical samples of (**1**) were obtained by recrystallization from ethanol. Yields and physical properties are given in Table 1.

Oxidation with Hydrogen Peroxide: General Procedure.—The benzotriazole adduct (**1**) (10 mmol), aqueous 30% hydrogen peroxide (1.2 ml, 10 mmol), and a catalytic amount of selenium dioxide were heated in methanol (10 ml) under reflux for 6 h. The methanol was removed under reduced pressure and the residue extracted with chloroform (25 ml × 3). An aliquot of the organic solution was dried ($MgSO_4$) and concentrated to afford the crude reaction products which were analysed by n.m.r. spectroscopy. The remaining chloroform solution was washed successively with 1M hydrochloric acid (15 ml), 1M sodium hydroxide (15 ml), and water (15 ml). The organic layer was dried ($MgSO_4$), concentrated, and the residue purified by column chromatography on silica gel with benzene–ether (4:1) as eluant. Yields and physical properties of the formamides (**4**) are given in Tables 2 and 3.

Hydrolysis of the Formamides (**4c**), (**4g**), *and* (**4j**): *General Procedure.*—The formamide (5 mmol) was heated in 1M sodium hydroxide (2 ml) and ethanol (8 ml) under reflux for 6 h. After cooling, the solution was extracted with chloroform (25 ml × 3). The organic layers were collected, dried ($MgSO_4$), concentrated, and the residue was purified by column chromatography on silica gel with benzene-ether (4:1) as eluant.

(a) 2-(*t-Butylamino*)*pyridine*, previously described as a brown oil,[21] was isolated as a white solid (0.68 g, 90%) and recrystallized from light petroleum (b.p. 38—56 °C), m.p. 52—53 °C (Found: C, 71.65; H, 9.4; N, 18.5. $C_9H_{14}N_2$ requires C, 72.0; H, 9.4; N, 18.65%); δ_H(60 MHz; $CDCl_3$) 1.4 (9 H, s, Me), 4.8 (1 H, br s, NH), 6.5 (2 H, m, 3-H and 5-H), 7.2 (1 H, m, 4-H), and 8.2 (1 H, m, 6-H); δ_C(50 MHz, $CDCl_3$) 29.4 (CH_3), 50.5 (CMe_3), 108.5 (3-C), 112.1 (5-C), 136.6 (4-C), 147.9 (6-C), and 158.3 (2-C).

(b) 5-*Chloro*-2-(*t-butylamino*)*pyridine* was isolated as an oil (0.83 g, 90%) (Found: C, 58.6; H, 7.1. $C_9H_{13}ClN_2$ requires C, 58.5; H, 7.1%); δ_H(60 MHz; $CDCl_3$) 1.3 (9 H, s, Me), 4.4 (1 H, br s, NH), 6.2 (1 H, d, 3-H), 7.1 (1 H, dd, 4-H), and 7.9 (1 H, d, 6-H); δ_C(50 MHz; $CDCl_3$) 29.1 (CH_3), 50.7 (CMe_3), 109.5 (3-C), 118.9 (5-C), 136.3 (4-C), 146.0 (6-C), and 156.5 (2-C).

(c) 3-*Nitro*-N-*t-butylaniline* was isolated as an oil (0.78 g, 80%) (Found: C, 62.0; H, 7.3. $C_{10}H_{14}N_2O_2$ requires C, 61.8; H, 7.3); δ_H(60 MHz; $CDCl_3$) 1.4 (9 H, s, Me), 3.9 (1 H, br s, NH), and 6.8—7.5 (4 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 29.6 (CH_3), 51.4 (CMe_3), 109.1 (2-C), 111.7 (4-C), 121.4 (6-C), 129.4 (5-C), 147.7 (1-C or 3-C), and 149.1 (3-C or 1-C).

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