Facile Formation of *N*-Nitrosamines from Bromonitromethane and Secondary Amines

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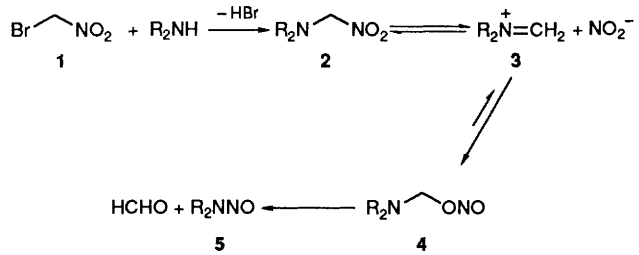
Bromonitromethane readily converts secondary amines to *N*-nitrosamines in aqueous and organic solvents at room temperature *via* reaction of an iminium ion intermediate with nitrite ion.

The reactions of bromonitromethane **1** with a range of nucleophiles have been widely reported. In all but two cases the nucleophile reacts at the bromine atom to displace nitromethane anion,[1,2] *i.e.* the bromine leaves as Br^+. With dimethyl sulphide[2] and nitrite ion,[3] however, nucleophilic attack proceeds exclusively at the carbon atom with displacement of bromine as Br^-.

Surprisingly, the reactions of bromonitromethane with amines have not been reported and we have therefore examined these for examples of primary, secondary and



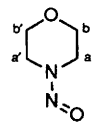
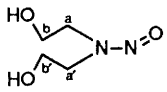
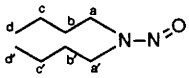
Scheme 1 Formation of *N*-nitrosamines from bromonitromethane and secondary amines

Table 1 Formation of *N*-nitrosamines from bromonitromethane (1 mmol dm^{-3}) and amine (4 mmol dm^{-3}) in MeCN at 70 °C

	Yield[a] of *N*-nitrosamine (%)		
Time/days	Di-n-butylamine	Morpholine	Pyrrolidine
1	35	67	25
2	49	80	31
4	52	80	39
7	54	94	62

[a] Relative to bromonitromethane.

Table 2 ^{13}C NMR chemical shifts of *N*-nitrosamines in CD_3CN (δ in ppm relative to $SiMe_4$)

	δ(^{13}C)							
	syn				*anti*			
N-Nitrosamine	a	b	c	d	a′	b′	c′	d′
	44.0	68.0	—	—	53.0	69.4	—	—
	48.2	58.7	—	—	56.6	60.3	—	—[a]
	43.2	28.4	19.9	13.6	51.9	30.6	20.6	13.6

[a] These values agree with ref. 9.

tertiary amines in both organic and aqueous solvents. The amines investigated were: methylamine (40% aq. sol.), isopropylamine, *O*-methylethanolamine, morpholine, di-n-butylamine, diethanolamine, pyrrolidine, *N*-methylmorpholine and triethanolamine.

For the tertiary amines in both organic and aqueous solvents, there is no reaction other than a small amount of deprotonation to yield the deep red bromonitromethane nitronate anion. For the primary amines likewise, there are no detectable reactions other than deprotonation in $CDCl_3$ and CD_3CN as solvents, when followed by ^{13}C NMR spectroscopy. In D_2O, however, the primary amines catalyse the otherwise slow hydrolysis of bromonitromethane to formaldehyde.[4]

The most interesting findings apply to secondary amines, which react with bromonitromethane to give the corresponding *N*-nitrosamines in substantial yield, as determined by GC analysis (Table 1). Further when bromonitromethane (2 mol dm^{-3}) is treated with morpholine (4.1 mol dm^{-3}), at room temperature, a precipitate of morpholinium bromide is formed immediately with $CDCl_3$ as solvent, and over *ca.* 24 h in CD_3CN. The ^{13}C NMR spectrum of the supernatant solution shows no evidence of bromonitromethane (δ 62.1 ppm), but reveals four new peaks due to *N*-nitrosomorpholine (Table 2). Similar results are obtained with the other secondary amines. In D_2O as solvent, the morpholinium salt remains in solution, and the *N*-nitrosamine is readily extracted into diethyl ether.

A plausible mechanism for the *N*-nitrosamine formation (Scheme 1) involves initial displacement of Br^- by amine to give the geminal nitramine **2**, followed by loss of NO_2^- to give the iminium ion **3**. Nucleophilic attack by NO_2^- (*via* oxygen) on the iminium ion **3** gives the *N*-nitrosamine **5** *via* the geminal amino nitrite ester **4**.

The absence of nitromethane (or its nitronate anion) in detectable amounts implies that nucleophilic attack by the amino N-atom proceeds at carbon (**1** → **2**) with displacement of Br^- rather than at bromine. This was confirmed for the reaction of diethanolamine (7 mmol dm^{-3}) with bromonitromethane (5 mmol dm^{-3}) in water where Br^- (monitored by ion chromatography) was released quantitatively with $t_{\frac{1}{2}}$ *ca.* 20 min at 70 °C. Thus, secondary amines show the same exceptional nucleophilic behaviour as dimethyl sulphide[2] and nitrite ion[3] towards bromonitromethane for reasons which are not fully understood at present.

The absence of peaks in the ^{13}C NMR spectra of the reaction solutions assignable to either the geminal nitramine **2** or the amino nitrite ester **4** suggests that: (*i*) the initial nucleophilic attack, **1** → **2**, is rate-limiting; (*ii*) reaction of **3** with the N-atom of NO_2^- is either difficult or highly reversible in agreement with previous results;[5–7] and (*iii*) conversion of **4** to **5** is irreversible.

The intermediate iminium ion **3** has been implicated previously in the formaldehyde-catalysed formation of *N*-nitrosamines[5–7] on purely kinetic grounds. Its participation in the present reactions is strongly supported by an additional experiment. Thus, addition of $Na^{15}NO_2$ to the reaction solutions produces *N*-nitrosamines labelled at the nitroso N-atom. The ^{15}N chemical shifts are: 146 ppm for *N*-nitrosomorpholine and 154 ppm for *N*-nitrosodiethanolamine, relative to $CH_3{}^{15}NO_2$ as external standard. These shifts have not been reported previously, but they are consistent with values for other *N*-nitrosoamines.[8]

Received, 13th August 1990; Com. 0/03718D

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