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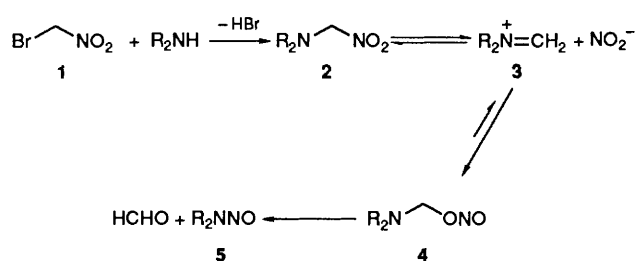
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Bromonitromethane readily converts secondary amines to N-nitrosamines in aqueous and organic solvents at room temperature *via* reaction of an iminium ion intermediate with nitrite ion.

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

$$Br\text{-}NO_2 + R_2NH \xrightarrow{-HBr} R_2N\text{-}NO_2 \rightleftharpoons \overset{+}{R_2N}=CH_2 + NO_2^-$$

$$\mathbf{1} \qquad\qquad\qquad\qquad \mathbf{2} \qquad\qquad \mathbf{3}$$

$$HCHO + R_2NNO \longleftarrow R_2N\text{-}ONO$$

$$\mathbf{5} \qquad\qquad\qquad \mathbf{4}$$

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$_3$CN (δ in ppm relative to SiMe$_4$)

	δ(^{13}C)							
	syn				*anti*			
N-Nitrosamine	a	b	c	d	a'	b'	c'	d'
(morpholine structure)	44.0	68.0	—	—	53.0	69.4	—	—
(diethanolamine structure)	48.2	58.7	—	—	56.6	60.3	—	—[a]
(dibutylamine structure)	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$_3$CN as solvents, when followed by ^{13}C NMR spectroscopy. In D$_2$O, 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 correspond-

ing 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$_3$CN. 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$_2$O 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 ($\mathbf{1} \rightarrow \mathbf{2}$) 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, $\mathbf{1} \rightarrow \mathbf{2}$, 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]

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