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N-NITROSAMINES *via* THE PHASE-TRANSFER MEDIATED NITROSATION OF SECONDARY AMINES WITH SODIUM NITRITE AND N-HALOAMIDES

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Secondary amines are cleanly and readily converted to the corresponding N-nitrosamines in high yields under phase-transfer conditions by means of sodium nitrite and N-haloamides; the active nitrosating agent is presumed to be dinitrogen tetroxide.

The recently reported conversion of N-chlorodialkylamines (1) to N-nitrosamines with *two* equivalents of sodium nitrite (Eq. 1),[1] has been postulated to proceed *via* nucleophilic displacement of nitrite ion on *chlorine* and the eventual *in situ* generation of dinitrogen tetroxide, which acts as a very efficient nitrosating agent.[2] The evolution of a brown gas (NO_2)

$$R_2N{-}Cl + 2NaNO_2 \xrightarrow[CH_3CN]{\Delta} R_2N{-}NO + NaNO_3 + NaCl \qquad (1)$$

observed in some of these reactions became particularly noticeable with N-chlorosuccinimide as the substrate. These observations led us to consider this combination of reagents as a novel, convenient and *neutral* method for the nitrosation of amines.

The reaction of dibenzylamine with N-chlorosuccinimide (NCS) and excess sodium nitrite in dry acetonitrile at reflux gave N-nitrosodibenzylamine (2a) in 69% yield. In view of the limited solubility of sodium nitrite in acetonitrile, a phase-transfer agent was utilized in conjunction with NCS and sodium nitrite. N-Nitrosodibenzylamine was formed immediately um salts were also investigated (Table 2). The importance of the presence of the nitrite ion in the organic phase was underscored by the effect of the lipophilicity of the phase-transfer agent.[7] Thus a more hydrophilic ammonium salt such as tetramethylammonium bromide, led mainly to the formation of N-chlorodibenzylamine whereas tetra-n-hexylammonium bromide afforded N-nitrosodibenzylamine in excellent yields. Without a catalyst, N-chlorination was the major process, providing N-chlorodibenzylamine in excellent yield. The nitrosation of other functional groups by this new technique is currently under investigation in our laboratories.

TABLE 1. Yield of 2a with Various Halogen Sources[a]

NCS	NBS	$PyH^+ Br_3^-$	Br_2[b]	NCP[c]
89%	92%	97%	quant.	nearly quant.

a) Benzyltriethylammonium chloride used as PTC agent; traces of benzaldehyde were detected (by nmr) in the crude products. b) Formation of benzaldehyde was nearly completely repressed by the addition of one equivalent of triethylamine; without triethylamine, the reaction was not as clean and the presence of several by-products was detected (by tlc). c) N-Chlorophthalimide.

TABLE 2. Nitrosation of 1a with NCS in the Presence of Various PTC Agents

$R_4N^+ X^-$	Yields of 2a	Other Products
$(n\text{-Hexyl})_4N^+ Br^-$	90%	PhCHO(traces)[a]
$PhCH_2\overset{+}{N}Et_3$	89%	PhCHO(traces)[a]
$Me_4N^+ Br^-$	traces(tlc)	$(PhCH_2)_2N\text{-}Cl$(92%)
No Catalyst	0%	$(PhCH_2)_2N\text{-}Cl$(91%)

a) Probably arising from dehydrohalogenation of N-chlorodibenzylamine followed by in situ hydrolysis of the resulting aldimine (see Ref. 1) in nearly quantitative yield upon addition of an aqueous solution of two equivalents each of sodium nitrite and of a quaternary ammonium salt to a solution of NCS and dibenzylamine (1a). Similarly, dicyclohexylamine (1b)

$$\underset{\mathbf{1}}{R_2NH} + NCS + 2NaNO_2 \xrightarrow[HO_2-CH_2Cl_2]{C_6H_5CH_2\overset{+}{N}Et_3Cl^-} \underset{\mathbf{2}}{R_2N-NO} \qquad (2)$$

a) R = $PhCH_2$ b) R = Cyclohexyl c) R = o-Biphenylyl

Yields : 2a, 89%; 2b, 92%; 2c, 90%

and carbazole (1c) were converted to the corresponding N-nitrosamines (2b and 2c) in excellent yields. Scheme 1 summarizes a possible path for the generation of dinitrogen tetroxide. The report that nitryl chloride reacts with silver nitrite to afford nitrogen dioxide,[3] led us to believe the reaction of NCS with nitrite ion to be the key step rather than a mechanism

$$\begin{aligned} NCS + NO_2^- &\longrightarrow NO_2Cl + \text{succinimide ion} \\ NO_2Cl + NO_2^- &\longrightarrow Cl^- + ON-ONO_2 \rightleftharpoons 2\,NO_2 \\ R_2NH + N_2O_4 &\longrightarrow R_2N-NO + HNO_3 \\ \text{succinimide ion} + HNO_3 &\longrightarrow \text{succinimide} + NO_3^- \end{aligned}$$

Scheme 1

involving the initial formation of the N-haloamines.[4] In spite of the fact that nitryl chloride has long been known, the most efficient synthesis involves the reaction of chlorosulfonic acid and anhydrous nitric acid;[5] no precendent could be found for the direct action of nitrite ion on NCS. It was thus decided to examine other halogen sources, such as N-bromosuccinamide (NBS), pyridinium bromide perbromide, elemental bromine and N-chlorophthalimide under PTC conditions; the results of the nitrosation of dibenzylamine under these conditions are summarized in Table 1. Much to our surprise, elemental bromine proved to be very effective in the presence of an added base,[6] as was pyridinium bromide perbromide. These results are consistent with the mechanism shown in Scheme 1. Other quaternary ammoni-

REFERENCES

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1. M. Nakajima, J. C. Warner and J.-P. Anselme, Chem. Comm., 000 (1984).
2. E. H. White, J. Am. Chem. Soc., 77, 6008 (1955).
3. A. Exner, Ber. Wien. Akad., 65, 120 (1872); Gmelin, "Handbuch der Anorganischen Chemie," Deutschen Chemischen Gesellshaft, 8th Ed., Vol. 8, p. 782ff (1936).
4. The formation of N-nitrosocarbazole under these conditions provides support for the initial generation of dinitrogen tetroxide since the reaction of NCS with carbazole in dichloromethane failed to yield N-chlorocarbazole (see Ref. 1).
5. R. C. Paul, D. Singh and K. C. Malhotra, J. Chem. Soc. (A), 1936 (1968); nitryl chloride decomposes in water to nitric and hydrochloric acids.
6. W. Manchot and F. Oberhauser, Z. Anorg. Chem., 139, 45 (1924); nitrite ion is reported to be oxidized by elemental bromine in aqueous solution to sodium nitrate and two equivalents of hydrogen bromide.
7. See E. V. Dehmlow and S. S. Dehmlow, "Phase-Transfer Catalysis", Second Ed., Verlag Chemie, Weinheim, FRG, 1983; C. M. Starks and C. Liotta, "Phase-Transfer Catalysis. Principles and Techniques", Academic Press, London and New York, 1978; W. P. Weber and G. W. Gokel, "Phase-Transfer Catalysis in Organic Synthesis" in "Reactivity and Structure", K. Hafner Ed., Vo. 4, Springer-Verlag, Berlin-Heidelberg, 1977; A. Brändstrom, "Preparative Ion-Pair Extraction. An Introduction to Theory and Practice", Apotekarsocieten/Hässle, Läkemedel, Stockholm, 1974.

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