Tetrahedron Letters No. 40, pp 3831 - 3834. **0040-4039/79/1001-3831$02.00/0**
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N-NITROSAMINES FROM CARBAMOYL CHLORIDES

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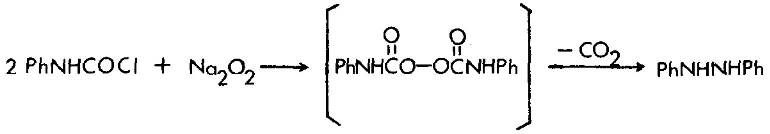
Summary. The action of sodium nitrite on disubstituted carbamoyl chlorides provides the corresponding N-nitrosamines in excellent yields.

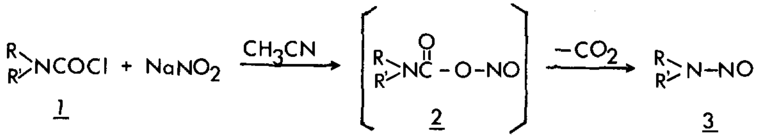
With the current renewed interest in N-nitrosamines, came the realization that a great deal of the basic organic chemistry of this class of compounds remains unexplored. Even the synthesis of nitrosamines has consisted essentially of one reaction with several variants, namely the reaction of secondary amines with a source of nitrosonium ion.[1] The reaction of anions of secondary amines with nitrosyl chloride has been reported recently[2] while the interesting description of the nitrosation of diethylamine with nitroprusside in aqueous alkaline solution has not been amplified further.[3] Since the nitrosation of secondary amines is usually carried out under acidic conditions,[1] it was felt that alternate methods for the synthesis of N-nitrosamines were needed, particularly in view of the sensitive groups present in many N-nitrosamines of interest in cancer research.

The reaction of phenylcarbamoyl chloride with sodium peroxide has been reported to give a 70% yield of hydrazobenzene (Eq. 1).[4] Presumably,



$$2\,PhNHCOCl + Na_2O_2 \longrightarrow \left[PhNH\overset{\overset{O}{\|}}{C}O-O\overset{\overset{O}{\|}}{C}NHPh\right] \xrightarrow{-CO_2} PhNHNHPh \qquad (1)$$

homolytic scission of the oxygen-oxygen bond of the intermediate carbamoyl peroxides followed by the loss of carbon dioxide gave the anilinyl radicals which coupled to yield hydrazobenzene. This suggested to us that the reaction of carbamoyl chlorides with nitrite ion might constitute a novel albeit indirect route to N-nitrosamines under *neutral* conditions. Indeed, it was felt that the nitrogen-oxygen bond of the putative carbamoyl nitrites (2) might also suffer homolytic cleavage to give the aminyl radicals and nitric oxide. Recombination of these two radicals could then afford the N-nitrosamines in acceptable yields. The results of the experiments exceeded our expectations.

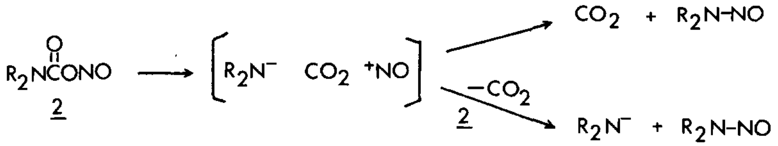


(2)

The reaction of dibenzylcarbamoyl chloride [1, R = R' = PhCH$_2$][5] with sodium nitrite in acetonitrile resulted in evolution of carbon dioxide and formation of N-nitrosodibenzylamine [3, R = R' = PhCH$_2$] in nearly quantitative yield after overnight reflux. Similarly, diphenylcarbamoyl chloride [1, R = R' = Ph] and di-*n*-hexylcarbamoyl chloride[6] [1, R = R' = *n*-C$_6$H$_{11}$] gave the corresponding N-nitrosamines 3 in 100% and 92% yields respectively. Under the same conditions, N-chlorocarbonyl carbazole [1, R = R' = bifluorenyl][7] and N-chlorocarbonyl N'-methylpiperazine [1, R = R' = CH$_3$N(CH$_2$)$_2$][8] gave only trace amounts of the desired N-nitrosamines (tlc) and extensive decomposition products; however, N-nitrosocarbazole and N-nitroso-N'-methylpiperazine were obtained in 78% and 76% yields respectively when the same reaction was carried out at room temperature. All the nitrosamines were characterized by their physical constants, spectral data and/or comparison with authentic samples or by conversion to the amine hydrochlorides.

Although the rationale for attempting the reaction depicted in Eq. 2 was predicated on the anticipated *radical* cleavage of the N-O bond of 2, it is now felt the current data militate against a radical mechanism.[9]

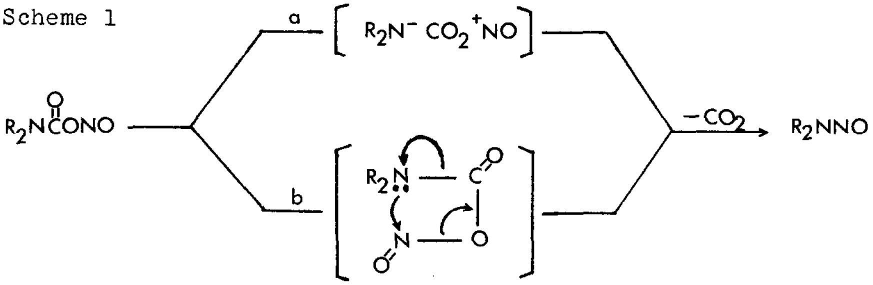
It seems unlikely that had nitric oxide and the aminyl radicals been generated, such high yields of pure products would have been obtained. Other possible mechanisms involve the dissociation of 2 into an ion-pair followed by recombination or nitrosation of R_2N^- by the carbamoyl nitrite 2 in a chain-type reaction. Alternatively, intramolecular self-nitrosa-



(3)

tion *via* a four-membered ring transition state could lead directly to the N-nitrosamines. However, further work will be required before a definite mechanism can be proposed.

Scheme 1



We are currently investigating the action of nitrite ion on systems related to carbamoyl chlorides, namely thiocarbamoyl [$R_2NC(S)$], sulfamoyl [R_2NSO_2] and sulfinyl [R_2NSO] chlorides in order to ascertain to the feasibility of generating N-nitrosamines from such precursors.

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9. The same conclusion was reached by Norris [J. Am. Chem. Soc., 81, 3346 (1959)]. After our initial results, we became aware of this work which describes the formation of dimethylnitrosamine (66% yield) from the reaction of dimethylcarbamoyl chloride with silver nitrite in acetonitrile. N-Nitrosamines were also by-products of the reaction of carbamoyl chlorides with silver nitrate. Possible mechanisms for this unusual reaction will be the subject of a future publication.

(Received in USA 30 March 1979)