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SYNTHESIS OF N-ALKYL-N-(1-HYDROPEROXYALKYL)NITROSAMINES BY OXYGENATION OF LITHIATED DIALKYLNITROSAMINES

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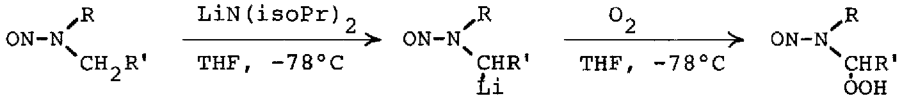
Abstract: N-Alkyl-N-(1-hydroperoxyalkyl)nitrosamines were synthesized from N,N-dialkylnitrosamines by lithiation with lithium diisopropylamide, followed by oxygenation with oxygen in good yields.

The stability and the strong reactivity of α-N-nitroso carbanions toward electrophilic reagents have been well documented recently, however, the products of the reaction between the carbanions and oxygen were not isolated because of their instability.[1] This report describes the isolation and characterization of the products, N-alkyl-N-(1-hydroperoxyalkyl)nitrosamines, obtained by treatment of lithiated dialkylnitrosamines with oxygen.[2] Formation of the hydroperoxides by nucleophilic substitution of the corresponding 1-acetoxyalkylnitrosamines were reported in the previous communication.[3]

In a typical experiment, 20 mmol of N,N-dibutylnitrosamine in 10 ml of dry tetrahydrofurane (THF) was added dropwise to a stirred solution of lithium diisopropylamide, prepared from 20 mmol diisopropylamine in 80 ml THF and 20 mmol n-butyllithium in n-hexane, at -78°C during 15 min period. After stirring for 10 min, oxygen was passed into the solution through a gas dispersion tube at the same temperature until changes in reaction temperature and in color of the solution ceased. To the reaction solution was added 50 ml ethyl acetate and then 20 ml of 2 N hydrochloric acid under vigorous stirring, and the mixture was allowed to warm to room temperature with continuous stirring. The organic layer was separated from the aqueous layer, and was washed with water, dried, and evaporated under reduced pressure. An oily residue was purified by silica gel column chromatography eluted with a mixture of n-hexane, ether, methylene chloride (8 : 3 : 2) to give N-butyl-N-(1-hydroperoxybutyl)nitrosamine in 34% yield with the recovery of the starting material in 17%. The spectral properties of the product are identical with those of authentic sample.[3] Similarly N,N-dipropylnitrosamine, N,N-diethylnitrosamine, N,N-dimethylnitrosamine, and N-butyl-N-methylnitrosamine were converted into the corresponding 1-hydroperoxyalkyl compounds listed in the Table. The structures of these compounds were established by their NMR, UV, and IR spectral data.[4]



(1-5)

Table. Preparation of N-alkyl-N-(1-hydroperoxyalkyl)nitrosamines

Compound	R	R'	Yield(%)
(1)	$CH_2CH_2CH_2CH_3$	$CH_2CH_2CH_3$	34
(2)	$CH_2CH_2CH_3$	CH_2CH_3	32
(3)	CH_2CH_3	CH_3	32
(4)	CH_3	H	44
(5)	$CH_2CH_2CH_2CH_3$	H	21

The reaction was fast, and prolonged oxygenation resulted in poor yield, and sometimes gave explosive by-products. When both primary and secondary hydroperoxides were possible as in the case of 5, only primary hydroperoxide was isolated under the condition examined.

This reaction suggests the possible formation of the hydroperoxides from N,N-dialkylnitrosamines in the presence of base and oxygen. Moreover, the hydroperoxides are good precursors for the preparation of α-hydroxyalkyl nitrosamines, the important intermediates involved in the metabolic activation of carcinogenic N,N-dialkylnitrosamines.[2]

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References and Notes

1. D. Seebach, and D. Enders, Angew. Chem., 87, 1 (1975).
2. Presented in part at the 6th Meeting on Analysis and Formation of N-Nitroso Compounds, Budapest, Hungary, October, 1979.
3. M. Mochizuki, T. Anjo, Y. Wakabayashi, T. Sone, and M. Okada, Tetrahedron Lett., 21, (1980), preceding paper.
4. 1, 4, and 5 were described in reference 3.

   2: NMR ($CDCl_3$, TMS) δ: 10.86(b.s, 1H), 6.00(t, $J = 7Hz$, 1H), 3.47(t, $J = 8Hz$, 2H), 1.7(m, 4H), 1.02(t, $J = 7Hz$, 3H), 0.90(t, $J = 7Hz$, 3H). IR (neat) cm^{-1}: 3250, 1460. UV (EtOH) nm(ε): 231(7000), 363(66).

   3: NMR ($CDCl_3$, TMS) δ: 10.85(b.s, 1H), 6.24(q, $J = 7Hz$, 1H), 3.60(q, $J = 7Hz$, 2H), 1.58(d, $J = 7Hz$, 3H), 1.12(t, $J = 7Hz$, 3H). IR (KBr disk) cm^{-1}: 3250, 1465. UV (EtOH) nm(ε): 229(6700), 357(67). mp. 39 - 40°C.

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