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A New Synthesis of Alkyl Nitrites: The Reaction of Alkyl Alcohols with Nitric Oxide in Organic Solvents

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In a nonaqueous solvent, alkyl nitrites can be easily achieved through the reaction of alkyl alcohols and gaseous NO. In the presence of air, the nitric oxide can in fact be oxidized to nitrous anhydride, which acts as a nitrosating agent. A quantitative study conducted on cycloalkyl alcohols has shown conversion yields to nitrites within the range 65−90%. This result has been validated by ESR spectroscopy experiments on several alkyl alcohols/NO mixtures, which lead to the detection of the same radical species detectable when a solution of the corresponding nitrites is photolyzed.

Introduction

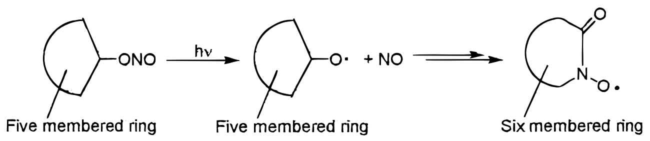
Several methods are available for the preparation of alkyl nitrites, the most important of which is the reaction between the corresponding alcohol and nitrous acid under acidic conditions.[2] We used this method for preparing most of the cyclopentyl-type nitrites previously investigated,[3] whose photolysis leads to the detection of the corresponding δ-valerolactam-1-oxyl-type radicals formed via a ring-expansion process (Scheme 1), but the method fails, for example, in the synthesis of the 3-nitrite-tetrahydrofuran because of the rapid cleavage of the parent alcohol.

An interesting alternative method of synthesis of nitrites is the rapid nitrosyl exchange between an alcohol and *tert*-butyl nitrite:[4] the transfer from the *t*-BuONO to the alcohol takes place very easily at room temperature and leads to a complete nitrosyl exchange within a few minutes. Following this method, the 3-nitrite-tetrahydrofuran was then successfully synthesized.

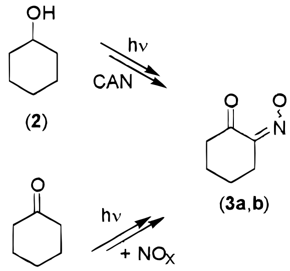
From our previous study[5] conducted on the photoinduced oxidation of alcohols by lanthanide ions (CAN), we were able to hypothesize a further alternative mechanism for the formation of alkyl nitrites starting from the parent alcohol. In particular, the NO itself, or one of its oxidized products, could act directly as the nytrosating agent as suggested for low-molecular-weight alcohols.[6] In this paper we report on the preparation of cycloalkyl nitrites starting from the corresponding cycloalkyl alcohol and nitric oxide, in a solution of acetonitrile and in aerobic conditions.

Results and Discussion

Scheme 1



Scheme 2



The photooxidation of cyclopentanol (**1**) and cyclohexanol (**2**) by CAN (cerium ammonium nitrate)[5] had shown the possibility to detect by ESR spectroscopy radical species that suggested, by their formation, the presence of free NO/NO$_x$ in the medium. For instance, when cyclohexanol was investigated, this led to the detection of two isomer radicals:[7] the 2-oxocyclohexane-1-iminoxyl radical *cis*, (**3a**) [a(N) = 2.675 mT, a(2H$_\beta$) = 0.150 mT; g = 2.0049], and *trans*, (**3b**) [a(N) = 3.275 mT, a(2H$_\epsilon$) = 0.257 mT, a(2H$_\delta$) = 0.150 mT; g = 2.0049]. These radical species are the same that were detectable[8] when the photolysis of an acetonitrile solution of cyclohexanone with NO, in aerobic conditions, was performed directly in the cavity of an ESR spectrometer, Scheme 2. In fact, it is well-known[9] that the cyclohexanone is the main product of the photoinduced oxidation of **2** by CAN, and it could also be anticipated that NO$_x$ would be produced

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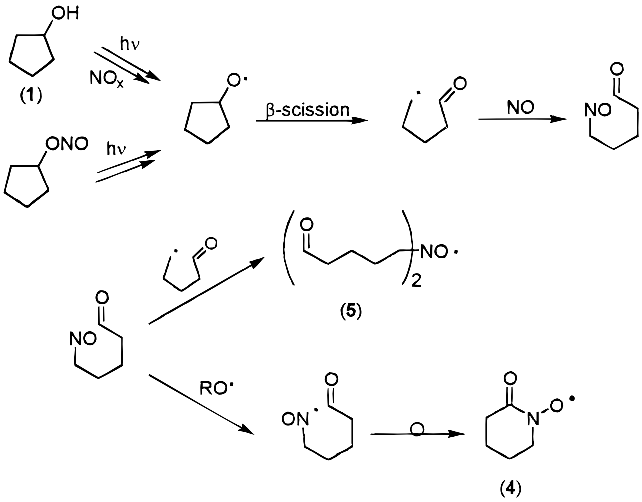
Table 1. ESR Hyperfine Splitting Constants (*a*, mT)[a] of Nitroxide Radicals Generated by Photolysis of Acetonitrile Solutions of Alkyl Alcohols and NO

substrate	radical	*a*	*g*[b]
1	**4**	a(N) = 0.760 $a(2H_\epsilon)$ = 1.160[c] $a(2H_\beta)$ = 0.180	2.0064
	5	a(N) = 1.500 a(4H) = 1.000	2.0054
6	**8**	a(N) = 0.650 $a(H_\epsilon)$ = 0.710 $a(2H_\beta)$ = 0.125	2.0064
	9[d]	a(N) = 1.450 a(2H) = 0.912 a(H) = 0.575	2.0053
7	**10**	a(N) = 0.737 $a(H_\epsilon)$ = 1.238 $a(H_{\beta'})$ = 0.212 $a(H_\beta)$ = 0.150	2.0064
	11[d]	a(N) = 1.475 a(2H) = 0.375	2.0054

[a] Typically at −30 °C. [b] Values are ± 0.0002; the *g* factors have been determined by comparison with the *g* factor of the DPPH (2.0037 ± 0.0001). [c] The numbering starts from the carbonyl group next to the nitrogen atom. [d] At 0 °C.

Scheme 3



in this reaction because the primary photochemical process which is believed[10,11] to occur during the photolysis of CAN is the transfer of an electron from one nitrate ligand to the central Ce(IV) atom to yield the nitrate radical:

$$Ce(IV)NO_3^- \xrightarrow{h\nu} Ce(III) + NO_3^\bullet$$

Even more remarkable was the result achieved when cyclopentanol (**1**) was investigated: the δ-valerolactam-1-oxyl radical (**4**) and the dialkyl nitroxide (**5**), i.e., the same radical species resulting in the photolysis of the cyclopentyl nitrite,[3] Table 1, were detected (see Scheme 3). To account for these findings, the interaction between unreacted alcohol and free NO/NO_x yielding to the corresponding nitrite had to be invoked. Thus, in principle, the photolysis of a solution of an alkyl alcohol and NO could lead to the detection, by ESR spectroscopy, of the same radical species obtained from the corresponding nitrite. At this point, experiments on acetonitrile solutions of alcohols/NO_x, whose behavior of the corresponding nitrites toward photolysis is well known,[3,12] were then conducted. For instance, the cyclopentanol/NO mixture led to the detection of the hypothesized radicals **4** and **5**,[3,13] Scheme 3.

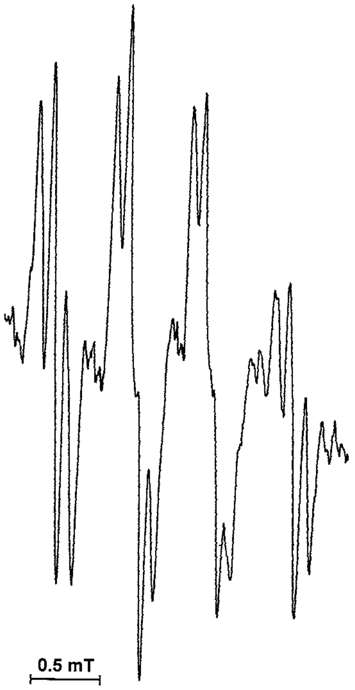


Figure 1. ESR spectrum obtained in the photolysis of an acetonitrile solution of **6** (10^{-3} M), into which gaseous NO has been bubbled for 2 min, showing radical **8** at −30 °C.

All of the analyzed alcohols led to the detection of the forecasted radical species, i.e., those observed when the corresponding nitrites[3,12,14] are photolyzed. Unexpectedly, the 1,4-anhydroerithritol (tetrahydro-3,4-furandiol) (**6**) and the 2-methylcyclopentanol (**7**) enabled us to detect[15] (see Table 1) the corresponding δ-valerolactam-1-oxyl-type radicals, respectively **8** (see Figure 1) and **10** (see Figure 2). Detection had failed when the pure nitrites were investigated. Most likely, this alternative pathway established more favorable conditions for the formation of the 5-nitroso-pentanal-type (**12**) intermediate, precursor of the δ-valerolactam-1-oxyl-type radical (see Scheme 4).

Hence, the interaction between an alkyl alcohol and NO to form the corresponding alkyl nitrite seemed likely, even though no direct evidence or information on its nature has been reported. The UV spectroscopy could in principle fulfill this request. Thus, the UV−visible absorption spectra of an acetonitrile solution of cyclopentanol/NO and of pure cyclopentyl nitrite were compared. The two solutions showed an identical spectrum, with

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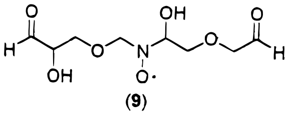
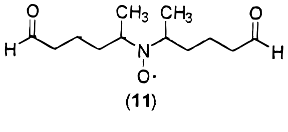
(15) Besides radicals **8** and **10**, it was possible to identify, at higher temperature (0 °C) and higher flow rates (0.8 mL/min) the nitroxides **9** and **11**, respectively, deriving from the competitive β-scission processes.



(9)



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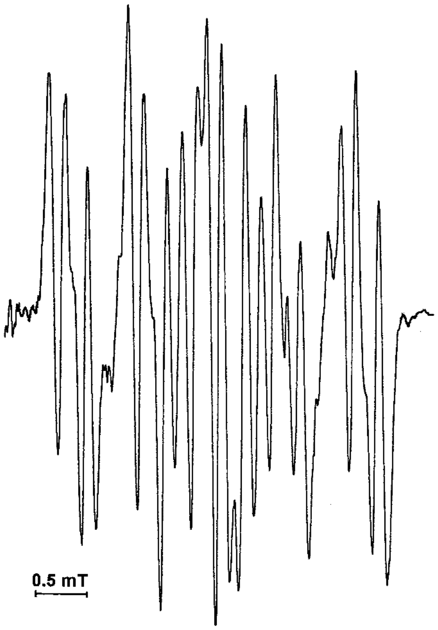
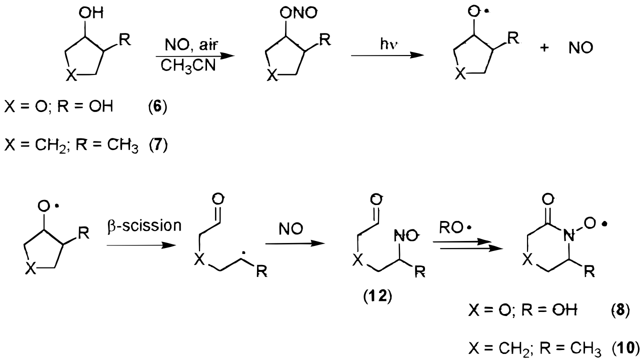


Figure 2. ESR spectrum obtained in the photolysis of an acetonitrile solution of **7** (10^{-3} M), into which gaseous NO has been bubbled for 2 min, showing radical **10** at −30 °C.

Scheme 4



absorption bands in the region between 320 and 410 nm (see the Experimental Section), i.e., those characteristic of the cyclopentyl nitrite.[16]

Although these results support the formation of the nitrite, they do not give any information about the yield of the reaction. In fact, because ESR spectroscopy is a very sensitive technique of investigation, detecting ca. $10^{-4}/10^{-5}$ M, the yield could be very low, and thus the process may be not suitable for synthetic purposes.

A quantitative product analysis of the reactions between **1**, **2**, cycloheptanol (**13**), and cyclooctanol (**14**) and NO in acetonitrile was then conducted (see the Experimental Section). The yield of conversion into the corresponding nitrites was, in each case, very high, which validated this new method of synthesis of alkyl nitrites (see Table 2).

Table 2. Product Distribution from Reactions of Gaseous NO and Several Cycloalkyl Alcohols in the Presence of Oxygen in CH_3CN at 0 °C

substrate	nitrite (%)[a]	recovered alcohol (%)[a]
1	89.1	10.9
2	82.2	17.8
13	87.6	12.4
14[b]	64.3	35.7

[a] Values calculated by GC−MS analysis using an internal standard. [b] If the cyclooctyl nitrite is not recovered rapidly from the solution, in the presence of an excess of NO the yield in the product becomes lower and correspondingly the formation of a byproduct, the 4-nitrosocyclooctanol, is observed as a result of the occurrence of a 1,5-H shift process.

The reaction mechanism, however, was still completely unknown. The real nitrosating agent could be either NO or a product of its oxidation. In fact, in the presence of oxygen the nitric oxide is readily oxidized to NO_2 and then converted to N_2O_3 (eqs 1 and 2),[6,17,18] which is

$$2\ NO + O_2 \rightarrow 2\ NO_2 \tag{1}$$

claimed to be an active nitrosating species[18,19] even in organic solvent solutions.[20,21]

$$NO_2 + NO \rightleftharpoons N_2O_3 \tag{2}$$

In particular, at 0 °C in the presence of air and with an excess of NO, the equilibrium in reaction 2 is shifted[6] toward the formation of N_2O_3, as confirmed by the appearance of a pale blue color due to the solvation of the N_2O_3.[17] To discriminate between NO and N_2O_3 as the actual nitrosating agent, two experiments, one with and one without the presence of air, were performed. The experiment conducted in anaerobic condition showed the formation of only traces of cyclopentyl nitrite, thus suggesting N_2O_3 as the real active species in the nitrosating process.[18]

Conclusions

Cycloalkyl alcohols combine with oxides of nitrogen to form the corresponding nitrites. NO does not react directly with alcohols, but must undergo oxidation to form N_2O_3, a likely candidate as nitrosating species[19−21] in this reaction sequence:[6,18]

$$2\ NO + O_2 \rightarrow 2\ NO_2$$

$$NO + NO_2 \rightleftharpoons N_2O_3$$

$$ROH + N_2O_3 \rightarrow RONO + HNO_2$$

This method of synthesis seems to be very promising for preparing directly, in organic solvent, alkyl nitrites in very good yields, thus avoiding many restrictions caused by the low solubility of organic compounds in aqueous medium, as well as damage caused by the acidic medium. Even more interesting seems the possibility, shown by preliminary results obtained by ESR experiments, to consider this procedure a very promising method for converting polyalcohols, such as ribose or glucose, or other substrates of biological interest, such as testosterone, into the corresponding nitrites.

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Nitrous anhydride, produced from the reaction of NO with molecular oxygen, is likely to be a potent nitrosating agent in vivo at physiological pH.[22,23] In fact, N_2O_3 may damage DNA directly through nitrosation of primary amines on DNA bases or indirectly via nitrosation of various secondary amines to form *N*-nitrosamines, which can then be metabolized to strongly alkylating electrophiles capable of reacting with DNA.[22,23] N_2O_3 may also react with the sulfhydryl groups of various proteins.[18,23,24] On the basis of our findings, it can be suggested that this nitrosating agent could also be capable of damaging DNA through direct interaction with the hydroxyl functions of the sugar framework.

Experimental Section

Materials. All alcohols were commercial products and used as received unless the purity was less than 98%, in which case they were distilled. The alkyl nitrites were prepared through the standard procedure[2] or by bubbling of gaseous NO in the solution of the corresponding alcohols.

Reaction of Cycloalkyl Alcohols with Gaseous NO. Approximately 0.015 mol of the appropriate cycloalkyl alcohol was dissolved in 20 mL of CH_3CN. The solution was then kept at 0 °C, and gaseous NO was bubbled gently for 1 h in the presence of a stream of air. Once quantitative GC−MS analyses were performed on the solutions, the solvent was removed under reduced pressure, and the nitrites were obtained by distillation under vacuum. All products gave analytical and spectral data in agreement with literature values and with the structural assignment.[3,12,25]

Cyclopentyl nitrite: bp 102−103 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.54−1.91 (6H, m), 1.87−2.22 (2H, m), 5.78 (1H, m, CH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 24.0 (CH_2), 33.1 (CH_2), 81.9 (CH). Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.09; H, 7.93; N, 12.11.

Cyclohexyl nitrite: bp 40 °C at 23 mbar; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.14−1.73 (6H, m), 1.68−1.88 (2H, m), 1.86−2.08 (2H, m), 5.35, (1H, m, CH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 24.7 (CH_2), 26.0 (CH_2), 33.1 (CH_2), 79.0 (CH). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.84; H, 8.66; N, 10.75.

Cycloheptyl nitrite: bp 74 °C at 23 mbar; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.42−1.93 (10H, m), 1.92−2.17 (2H, m), 5.54 (1H, m, CH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 23.6 (CH_2), 29.1 (CH_2), 35.1 (CH_2), 81.4 (CH). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.65; H, 9.22; N, 9.70.

Cyclooctyl nitrite: bp 86−87 °C at 23 mbar; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.43−1.80 (10H, m), 1.77−2.04 (4H, m), 5.51 (1H, m, CH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 23.6 (CH_2), 26.0 (CH_2), 27.7 (CH_2), 32.6 (CH_2), 81.2 (CH). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.15; H, 9.56; N, 8.84.

2-Methylcyclopentyl nitrite: 1.53 g, 79.3%, bp 118−120 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (3H, d, CH_3), 1.19−1.42 (2H, m), 1.67−1.82 (2H, m), 1.87−2.36 (3H, m), 5.29 (1H, m, CH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 18.8 (CH_3), 23.3 (CH_2), 32.1 (CH_2), 32.8 (CH_2), 40.6 (CH), 88.2 (CH). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.76; H, 8.63; N, 10.80.

4-Hydroxytetrahydro-3-furanyl nitrite: 1.91 g, 95.6%; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.24 (1H, bs, OH), 3.73 (2H, m), 3.92 (2H, m), 4.29 (1H, bs, C*H*-OH), 6.14 (1H, bs, CH−ONO); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 71.9 ($2CH_2$), 72.4 (CH−OH), 73.5 (CH−ONO). Anal. Calcd for $C_4H_7NO_4$: C, 36.09; H, 5.30; N, 10.52. Found: C, 36.04; H, 5.36; N, 10.49.

GC−MS Studies. Quantitative GC−MS analyses were performed using as internal standards 1,4-dioxane for the cyclohexanol and *n*-butyl ether for the other alcohols, with a gas chromatograph equipped with a methyl silicone plus 5% phenyl silicone capillary column and fid integration. All compounds were identified by comparison of their retention times with those of authentic samples and by their mass spectra.

UV−Visible Experiments. The UV−vis absorption spectrum of an acetonitrile solution of the pure cyclopentyl nitrite was recorded in the range between 300 and 440 nm and compared to that obtained from an acetonitrile solution of cyclopentanol into which gaseous NO had been bubbled for 1 h at 0 °C. The two solutions showed identical spectra with clear absorption bands at $\lambda_{max} = 338.1$, 349.0, 360.3, and 373.3 nm.

ESR Experiments. Acetonitrile solutions of the alkyl alcohol (10^{-3} M), in which pure gaseous NO was bubbled for 1−2 min, were prepared.[26] The solutions were then continuously flowed by a syringe pump (at flow rates in the range 0.1−0.6 mL/min) through a flat cell arrangement (0.3 mm optical path length) and directly photolyzed in the cavity of a Varian E−104 ESR spectrometer equipped with a variable temperature control system. The irradiation was performed with a 500 W high-pressure mercury lamp. The acetonitrile was deoxygenated before being used, by purging with N_2 gas for 50−60 min.

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[26] Because of the high sensitivity of the ESR spectroscopy, the samples were prepared by bubbling NO into an acetonitrile solution of the appropriate alcohol for only a short lapse of time. In these conditions, a small amount of the nitrite is formed, which is enough to allow the detection of the related radical species.