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THE NITROSATION OF IMIDAZOLINES AND OXAZOLINES

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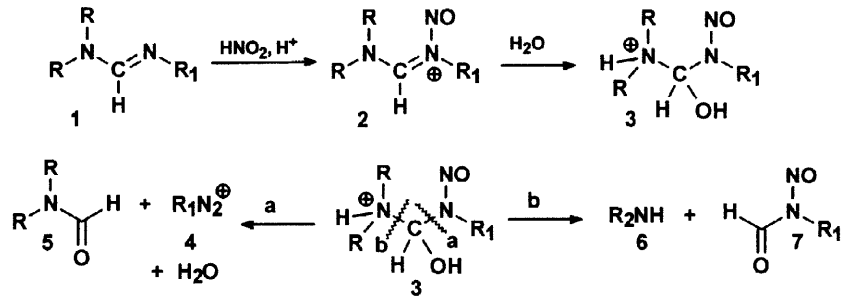
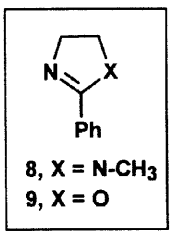
Abstract: Nitrosation (HOAc / $NaNO_2$) of 1-methyl-2-phenyl-2-imidazoline **8** results in cleavage of only the C-N single bond and production of *N*-(2-methylnitrosaminoethyl)-*N*-nitrosobenzamide **10**. In contrast, 2-phenyl-2-oxazoline **9** nitrosates very rapidly to give products (**13-16**) derived from a diazonium ion arising from the exclusive cleavage of the C=N.

While much attention has been given to processes which generate trace, but significant qualities of nitrosamines, little attention has been paid to other transformations of diet derived or biosynthesized nitrosating agents which may yield highly reactive cell damaging electrophiles in vivo. A goal of our research is to identify structural features of consumed or natural compounds which may render them highly reactive toward nitrosating agents.[1,2]

We have demonstrated that the nitrosation of open-chain tertiary amidines not only produces nitrosamines rapidly, as hypothesized, but generates reactive diazonium ions and unstable *N*-nitrosoamides as major products.[2] Although more than one pathway to the product manifold was considered to be operative, our attention focused on the decomposition of the tetrahedral intermediate **3** of Scheme 1, a reactive α-hydroxynitrosamine. Cleavage of bond **a** produces a diazonium ion **4**, whereas scission of bond **b** generates a nitrosoamide. Evidence in support of reaction by both pathways was produced, but the yield of products arising from the diazonium ion **4** exceeded the yield of the amide **5**, suggesting other paths to **4**. Because α-hydroxynitrosamines are known to have short half-lives and produce even more reactive diazonium ions, the formation of products by pathway **a** was anticipated, whereas the competitive formation of **7** was not.

Scheme 1





In order to investigate the factors controlling the decomposition of intermediates structurally like **3**, where the amidine or related imidate moieties are constrained within a ring, we have compared the nitrosation products and rates of two related heterocycles, an imidazoline **8**, an amidine, and a 2-oxazoline **9**, an imidate. Re-

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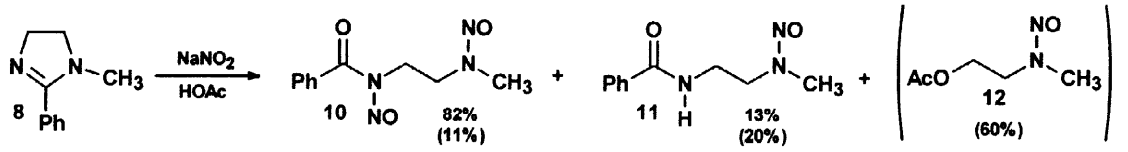
markably, the compounds react by completely different pathways and the imidazoline produces no products expected of an α-hydroxynitrosamine. Only products arising from cleavage by pathway **b** of Scheme 1 are observed.

1-Methyl-2-phenyl-2-imidazoline[3] **8** was prepared (90% yield) by the lithiation (nBuLi/THF/ -78 °C) of commercially available 2-phenylimidazoline, followed by alkylation with methyl iodide. Nitrosation of **8** (0.17M) with an 8-fold excess of $NaNO_2$ (4 M in H_2O) in glacial acetic (25 °C) acid led

Scheme 2



to 65% consumption (HPLC) of the starting material within 40 min. Within 3 h all of the NO_2^- and 90% of the substrate had been consumed. Neutralization, extraction, and chromatography of the product mixture on silica (hexane/EtOAc) permitted the isolation and characterization of the products shown in Scheme 2.

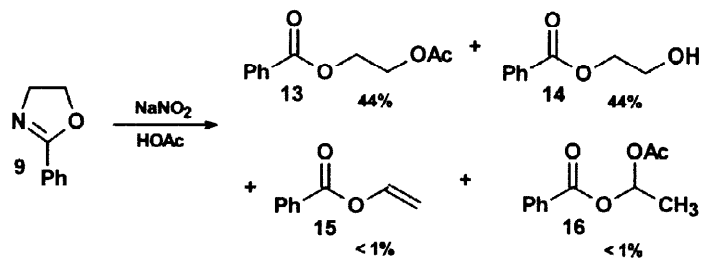
Compound **11**,[4] $C_{10}H_{13}N_3O_2$ showed bands (cm^{-1}) in its IR spectrum characteristic of an amide (NH, 3350, C=O, 1640) and a nitrosamine (1580, 1540). Both the ^1H and the ^{13}C NMR spectra of **11** exhibited sets signals of unequal intensity characteristic of nitrosamine *Z* and *E* isomers (e.g. (^1H NMR) CH_3 at δ 3.13 (*E*), major isomer; and δ 3.84 (*Z*)). On the basis of these data and the NMR spectra, structure **11** (86% *E*) was assigned to this compound. The major product of the transformation is unstable and decomposes over the course of several hours at r.t. It was assigned the structure of the *N*-nitrosoamide **10** on the basis of the following data: IR, no NH, C=O at 1707, NNO bands at 1580 and 1509; ^1H NMR peak intensities were consistent with the presence of two isomers (79% *E*, ArH δ 7.43-7.72, CH_2CH_2 δ 4.31 (4H, m), CH_3 δ 3.02 (s, 3H); 21% *Z*, ArH δ 7.43-7.72, CH_2 δ 4.07 (2H t J = 6 Hz), CH_2 δ 3.73 (2H t J = 6 Hz), CH_3 δ 3.74): ^{13}C NMR showed two C=O at δ 172.67 (*E*) and 172.53 (*Z*) and other peaks consistent with the assigned structure.[5,6] While the amide **11** could not be converted to the *N*-nitrosoamide **10** under the reaction conditions, the conversion was accomplished with $NaNO_2$ in acetic anhydride.[6] Nitrosation of **8** at 37 °C led to the isolation of a new product, 2-acetoxyethylmethylnitrosamine **12.**[7]

Yield data given in parentheses in Scheme 2 for the nitrosation products of **8** are for the reaction at 37 °C (24 h) and the others were produced at 25 °C (3 h). Addition of the *N*-nitrosoamide **10** to HOAc at 37 °C resulted in the formation of the acetate **12** after several hours. These data are consisted with the known ability of *N*-nitrosoamides to generate diazonium derived products through rearrangement to diazonium carboxylates.[6] Several conclusions can be made on the basis of the data in hand: 1) Nitrosation of **8** produces diazonium ions only through the decomposition of the *N*-nitroso amide and not through reaction intermediates generated prior to its formation; 2) The excess of diazonium derived products observed in our prior work on amidine nitrosation likely came from the thermal decomposition of *N*-nitrosoamides; 3) The *N*-nitrosoamide **10** is not formed from the nitrosation of the amide **11** under our nitrosation conditions: 4) The amide **11** could be formed either from nitrosation of on the amino N followed by hydrolytic opening of the C=N-,[2] or by the denitrosa-

tion of **10** under the reaction conditions. The operation of the latter pathway is supported by the known, relatively facile, denitrosation of *N*-nitrosoamides,[8] and the fact that the yield of **11** is greater when the reaction is conducted at the higher temperature.

Nitrosation of commercially available 2-phenyl-2-oxazoline (0.18 M) with a 6-fold excess of $NaNO_2$ (4 M in H_2O) at 25 °C led to the complete consumption of the substrate within two minutes and the production of the products shown in Scheme 3. Separation was accomplished by flash chromatography after neutralization of the reaction mixture and extraction. Each of the four esters **13-16** produced in this transformation are known, well characterized compounds[9] and our spectral data are in complete agreement with those published for each.

Scheme 3

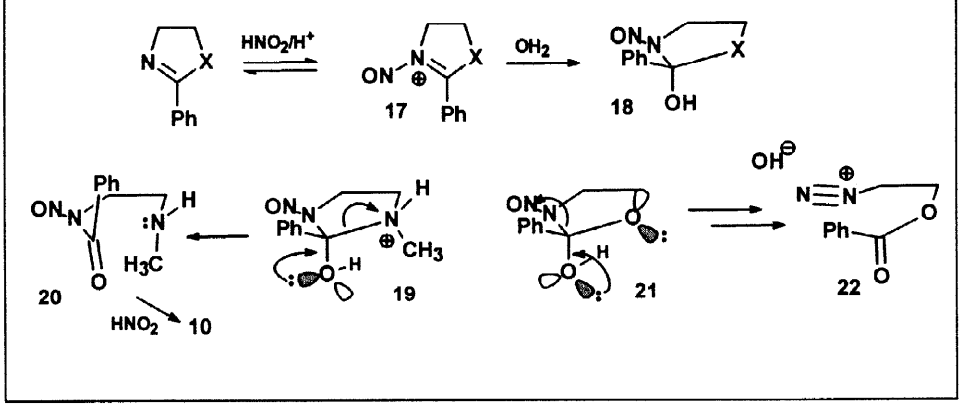


The products shown in Scheme 3 are typical of those derived from a diazonium ion precursor. The trace products **15-16** can be explained by the elimination of, or rearrangement of a carbocation, while the major compounds, **13-14** arise from nucleophilic substitution of acetic acid or water, respectively, on the diazonium ion. None of these products are consistent with the formation of *N*-(2-hydroxyethyl)-*N*-nitrosobenzamide. The decomposition of this *N*-nitrosoamide through a diazonium ion would produce acetates as major products rather than benzoates. Thus, the products from the nitrosation **8** and **9** are arising by significantly different pathways.

The rates of decomposition of **8** and **9** have been estimated under similar conditions (0.22 M substrate, 0.44 M NO_2^-, glacial acetic acid) by HPLC. At a reaction time of 10 min, 89% of the imidazoline **8** remains, whereas only 22% of the oxazoline **9** is left, demonstrating its much greater reactivity. Amidines consume more NO_2^- than the imidate moiety of the oxazoline. The formation of the *N*-nitrosoamide-nitrosamine **10** requires at least two molar equivalents of NO_2^- whereas the diazonium ion products derived from **9** would appear to only require a single equivalent. The slower reaction of the imidazoline, is anticipated, in part, from its higher basicity. Protonation of one of the nitrogens will reduce its nitrosation rate. Stereoelectronic factors may also contribute to the more rapid reaction of **9** as we discuss below.

The nitrosation of either **8** or **9** should produce the nitrosimminium ion **17**. In either case the positive charge can be delocalized to the other ring heteroatom. Reaction of **17** with water will generate the tetrahedral intermediate **18**. Specific depiction of this intermediate is

Scheme 4



shown for each substrate as **19** and **21**. The different reaction pathways are seen to arise in response to two effects; 1) the nature of the leaving group, and 2) stereoelectronic factors. In **19** the CH_3 bearing N will protonate making it a better leaving group. There are two stereoelectronic interactions in **19** which could facilitate the heterolytic scission of either C-N bond. The darker orbital on the OH is anti-periplanar to the C-N(CH_3) bond and facilitates its cleavage through overlap with the σ^* MO of the bond being broken.[10] But a similar arrangement exists with the lighter colored of the two orbitals and the C-N(NO) bond. Since these effects must be nearly equivalent, it follows that the methyl ammonium ion must be a better leaving group that the diazotate and this factor controls the reaction course. The secondary amine in the *N*-nitrosoamide will be rapidly nitrosated to give **10** under the reaction conditions.

In the case of the intermediate produced from the oxazoline, **21**, unshared pairs from both the ring O and the OH can be oriented anti-periplanar to the C-N bond and facilitate its breaking.[10] As is the case in **19** the cleavage of the other bond is facilitated by an OH lone pair (the lighter). Either the ring O or the NO O could be transiently protonated to provide for much better leaving groups but regardless of such catalysis, the stereoelectronic factors which favor C-N cleavage appear to prevail.

In this paper we have focused our attention on the different modes of reactivity of these related heterocycles toward nitrous acid. The nitrosating conditions, glacial acetic acid, were chosen so as to force reaction compared to aqueous buffer solutions where the concentrations active of the nitrosating agent are much lower. Preliminary experiments show that the oxazoline **10** nitrosates rapidly in aqueous buffer at pH 3.8 at 25 °C. While data on the imidazoline are forthcoming, we know that its reactivity is significantly less. Molecules containing the oxazoline moiety should be suspected as being capable of producing reactive electrophiles upon gastric nitrosation.

References and Notes

(1) Loeppky, R. N.; Bao, Y. T.; Bae, J. Y.; Yu, L.; Shevlin, G. In *Nitrosamines and Related N-Nitroso Compounds: Chemistry and Biochemistry*; Loeppky, R. N.; Michejda, C. J., Eds.; American Chemical Society: Washington, DC, **1994**; pp. 52-65.

(2) Loeppky, R. N.; Yu, L. *Tetrahedron Lett.* **1990**, *31*, 3263-3266.

(3) Piskov, V. B.; Kasperovich, V. P.; Yakovleva, L. M. *Khim. Geterotsikl. Soedin.* **1976**, 1112-1118.

(4) Anal: Calcd. for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.27. Found: C, 57.93; H, 6.31; N, 20.07.

(5) For typical spectral data see ref. 6 and Garcia, J.; Gonzalez, J.; Segura, R.; Urpi, F.; Vilarrasa, J. *J. Org. Chem.* **1984**, *49*, 3322-3327.

(6) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6608.

(7) Koepke, S. R.; Kupper, R.; Michejda, C. J. *J. Org. Chem.* **1979**, *44*, 2718-2722.

(8) Llewellyn, J. W.; Williams, J. M. *J. Chem. Soc. D* **1971**, 1386-1387.

(9) for **16**, see: Bhat, S.; Ramesha, A. R.; Chandrasekaran, S. *Synlett* **1995**, *4*, 329-30.

(10) Deslongchamps, P.; Dube, S.; Lebreaux, C.; Patterson, D. R.; Taillefer, R. J. *Can. J. Chem.* **1975**, *53*, 2791-2807.