Formation of $[^{15}N]_3$ *N*-(4-Phenyl-furazan-3-yl)-benzamide by a Furoxan to Furazan Rearrangement during the Attempted Synthesis of $[^{15}N]_3$ 2-Oxy-4-phenylfurazan-3-carbonitrile

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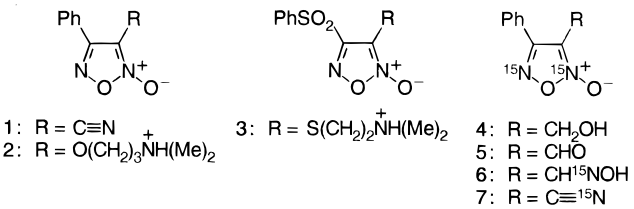
Received July 15, 1999

Introduction

During the past decade, recognition of the importance of nitric oxide (NO) as a biomolecular signaling molecule has brought about escalating interest in compounds which can release it under in vivo conditions. Several classes of compounds have been investigated as potential treatments for disorders characterized by defects in the NO biosynthetic pathway including nitrate esters,[1] *S*-nitrosothiols (thionitrites),[2−5] and heterocyclic furazan 2-oxides (furoxans). A large number of derivatives of this latter category were first prepared and assayed for NO-release by Gasco and co-workers.[6−10] Our interest focused on carbonitrile **1** and the oxalate salts of **2** and **3** since they displayed the most potent activity, but the decomposition mechanism(s) and nitrogen-containing products released under physiological conditions were unclear.

Results and Discussion

We had previously used ^{15}N NMR spectroscopy to study radical mechanisms in some reactions of peroxynitrite,[11] where decomposition times of the order of a few minutes and low sensitivity preclude acquisition at natural abundance. These same factors coupled with the availability of ^{15}N-labeled materials also made the technique propitious for examining furoxan decomposition. However, only **1** could be realistically prepared with two ^{15}N atoms in the furoxan ring (introduced simply by using $Na^{15}NO_2$ in the reported synthesis of unlabeled **4**). Furthermore, the procedure of Capdevielle et al.,[12] although somewhat unorthodox, promised easy conversion of $[^{15}N]_2$ carbaldehyde **5** to $[^{15}N]_3$ carbonitrile **7** in high yield without the need to prepare $[^{15}N]_3$ oxime **6** required by the original method of Gasco et al.[7] The Capdevielle synthesis



1: R = C≡N
2: R = $O(CH_2)_3\overset{+}{N}H(Me)_2$
3: R = $S(CH_2)_2\overset{+}{N}H(Me)_2$
4: R = CH_2OH
5: R = CHO
6: R = $CH^{15}NOH$
7: R = $C{\equiv}{}^{15}N$

involves in situ oxidation of an intermediate aldimine using $^{15}NH_4Cl$, metallic copper powder and pyridine under an oxygen atmosphere according to the equation

$$Cu + 2^{15}NH_4Cl + {}^1/_2O_2 \rightarrow CuCl_2 + 2^{15}NH_3 + H_2O$$

On performing the reaction with aldehyde **5**, the expected carbonitrile **7** was not formed. Instead, the product isolated was $[^{15}N]_3$ *N*-(4-phenyl-furazan-3-yl)-benzamide (**12**). There is no immediately obvious rationalization as to how, under these conditions, a benzamide could have formed with the observed configuration since Capdevielle et al. note only two possible limitations of their synthesis, neither of which are applicable in this case. These are: (a) enolizable aliphatic aldehydes do not react due to their high instability toward oxidation and aldol condensation and (b) some aromatic nitriles cannot be prepared if they are readily oxidizable or contain halogen atoms which can exchange with copper halogen ligands. We do not have sufficient evidence from this isolated observation to draw direct conclusions regarding the mechanism of formation of **12**. However, a meaningful comparison can be drawn with the classical studies on furoxan to furazan rearrangements described in a comprehensive and authoritative review by Gasco and Boulton.[13] The work of Bertelson et al.[14] on the reaction of aniline with dibenzoyl furoxan is of particular relevance and Scheme 1 illustrates the analogous mechanism with $^{15}NH_3$ and **5** as the substrate.

Nucleophilic attack by $^{15}NH_3$ on carbaldehyde **5** followed by release of formamide from the amino-methanolate ion **8** would yield the intermediate hydroxyimino-phenyl-acetonitrile *N*-oxide **9**. Nitrile oxides are common intermediates in reactions involving furoxans, and in certain cases, they can be trapped as a dipolar cycloadduct. Re-attack of $HCO^{15}NH_2$ on the nitrile oxide to form *N*-(1,2-bis-hydroxyimino-2-phenyl-ethyl)-formamide **10** is evidently more favorable than addition of a further molecule of $^{15}NH_3$. In the case of dibenzoylfuroxan, one of the oxime nitrogen atoms can attack the benzoyl carbonyl group to give an unstable nitrosoisoxazole[15] which rearranges, spontaneously or on heating, to the colorless furazan.[14,16] It does appear more likely that their

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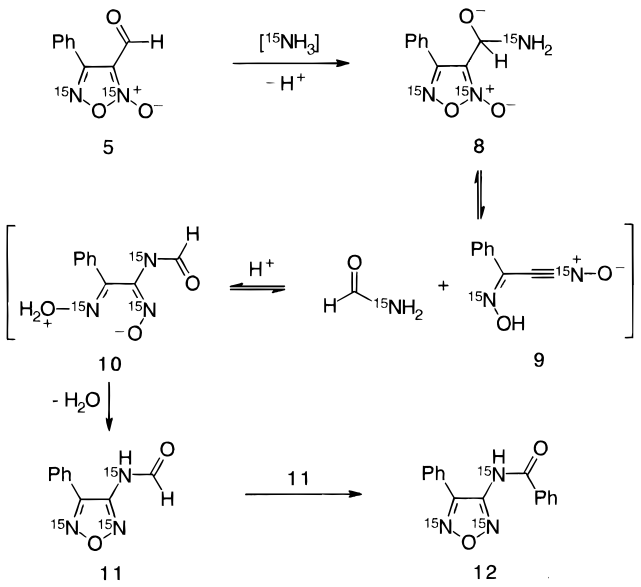
10.1021/jo991133+ CCC: $18.00
Published on Web 10/21/1999

Scheme 1



proposed open-chain amidoxime structure was actually a 5-hydroxy-3-amino-isoxazol-4-one oxime. However, since a second carbonyl group is unavailable on **10**, the only option is for one of the oxime oxygen atoms to attack the other oxime nitrogen atom followed by condensation to generate furazan **11** directly without going via an intermediate isoxazole. A similarly detailed discussion of the mechanism of formation of **12** from **11** would be unsound, but one explanation may be that a carbamoyl radical cation forms and then abstracts a phenyl residue from a further molecule of **11**. Although it may be fortuitous, an overall yield close to 50% supports this conclusion, and there is no reasonable alternative source of a phenyl group. Bidentate chelation of copper salts by amino furazans has been reported,[17] and there are many examples of Cu^{2+} complexes participating in $1e^-$ catalytic cycles. The best illustrations of this are Cu-containing enzymes such as superoxide dismutase.

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In summary, it is apparent that although the Capdevielle reaction for one-pot conversion of aldehydes to nitriles is a very convenient and widely applicable synthetic procedure, 3-substituted furoxans appear to be susceptible to rearrangement when substitutions with amine nucleophiles are attempted even under relatively mild conditions.

Experimental Section

General. Approximately 98% AtomN technical grade $Na^{15}NO_2$ and ~90% AtomN $^{15}NH_4Cl$ were used. Commercially available starting materials were used without further purification. Preparation of **1** by reaction of cinnamyl alcohol with $NaNO_2$ in acetic acid and oxidation with activated MnO_2 in $CHCl_3$ has been reported in full elsewhere.[6−8] $[^{15}N]_2$−labeled derivatives were obtained by following the same synthetic procedures, but using $Na^{15}NO_2$ in the first step. NMR spectra were recorded in $CDCl_3$; ^1H at 200 MHz, ^{13}C at 50.3 MHz and ^{15}N at 50.7 MHz referenced to liquid ammonia at 25 °C.

$[^{15}N]_3$ *N*-(4-phenyl-furazan-3-yl)-benzamide 12 (attempted preparation of $[^{15}N]_3$ 2-oxy-4-phenyl-furazan-3 carbonitrile 7). The method of Capdevielle et al.[12] was followed using **5** (152 mg, 0.8 mmol), copper powder (76 mg, 1.2 mmol, 1.5 equiv) and $^{15}NH_4Cl$ (85 mg, 1.6 mmol, 2 equiv) in pyridine (25 cm^3). Flash chromatography (petroleum ether-ethyl acetate, 3:2) afforded **12** as straw-colored plates (109 mg, 51%): mp 146−148 °C (lit. [unlabeled compound][18] 148 °C). ^1H 8.64 (~0.5H, s), 8.18 (~0.5H, s), 7.47−7.90 (10H, m, J = 7.7 and 3.9 Hz). ^{13}C 165.7 (d, J = 12.9 Hz), 150.4, 149.4, 133.7, 132.5 (d, J = 10.0 Hz), 131.3, 129.9, 129.5, 128.0, 125.7. ^{15}N 412.4, 394.5, 102.1, 100.3. *m*/*z* (EI+) 268 (17), 105 (100), 77 (37). HRMS: calcd for $C_{15}H_{11}{}^{15}N_3O_2$ 268.0975 (assumes 2 × 97.5% atomN and 1 × 90% atomN), found 268.0969. Anal. Calcd for $C_{15}H_{11}{}^{15}N_3O_2$: C, 67.16; H, 4.13; ^{15}N, 16.78. Found: C, 67.25; H, 4.21; N, 16.64.

Acknowledgment. We thank the Wellcome Trust for NMR facilities, the BBSRC and the Rollo Trust for financial support of the work and Professor Alberto Gasco for helpful suggestions.

Supporting Information Available: ^{15}N NMR spectrum of compound **12**. ORTEP representation of the X-ray structure of compound **12** with experimental details and tables listing the refined coordinates, bond lengths, bond angles and anisotropic thermal parameters with esd's. This material is available free of charge via the Internet at http://pubs.acs.org.

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