Pergamon

Tetrahedron Letters 41 (2000) 8421–8424

TETRAHEDRON
LETTERS

Reaction of nitric oxide with benzyl cyanide to yield a bis-diazeniumdiolated imidate

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Received 24 August 2000; revised 7 September 2000; accepted 11 September 2000

Abstract

The reaction of nitric oxide with benzyl cyanide in the presence of sodium methoxide forms the bis-diazeniumdiolated imidate, $PhC[C(OMe){=}NH][N(O)NO^{-}Na^{+}]_2$. This compound decomposes in acidic media to yield nitric oxide, nitrous oxide and 2-oximino-2-phenylacetic acid methyl ester. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: nitrogen oxides; nitriles; imidic acids and derivatives; diazenes.

Despite the widely growing use of diazeniumdiolates (compounds containing the $–[N(O)NO]^{-}$ functional group) as selective nitric oxide donor compounds for biological research,[1–4] the fundamental chemistry of this functional group is not as yet fully understood. Recently, several reports on the decomposition of mono substituted carbon-bound diazeniumdiolates have demonstrated the contradictory behavior of these compounds. On the one hand, the 2-adamantyl derivative was shown to decompose in a stepwise manner to liberate nitrous oxide as the sole nitrogenous gas.[5,6] On the other hand, the acidic decomposition of *N*-nitrosohydroxyguanidines produces both nitric oxide (NO) and nitrous oxide (N_2O) in a ratio which is pH dependent[7] and certain enamine diazeniumdiolates produce only NO on decomposition.[8] The factors which control the ratio of NO to N_2O are of great interest for the design and synthesis of novel NO donor carbon based diazeniumdiolates.

The pioneering work of Wilhelm Traube demonstrated that nitroalkanes, alcohols, ketones, certain esters and benzyl cyanide react with NO in the presence of strong base to form compounds in which either one or two of the acidic protons have been replaced by a diazeniumdiolate group.[9] As an extension to the simple hydrogen replacement reaction, we

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PII: S0040-4039(00)01535-5

would like to report our observation that the reaction of nitric oxide with benzyl cyanide in a solution of methanolic sodium methoxide yields the bis-diazeniumdiolated imidate, which decomposes in acidic media to produce NO, N_2O and 2-oximino-2-phenylacetic acid methyl ester, as illustrated in Fig. 1.

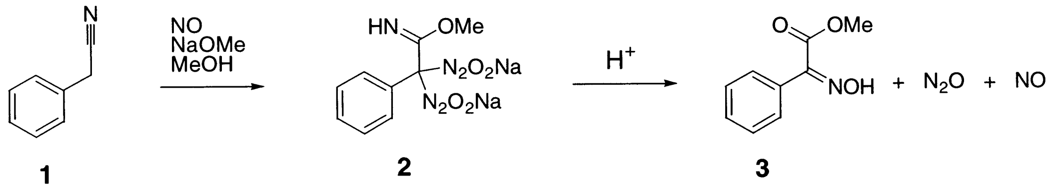

Figure 1. Synthesis of **2** and its decomposition to yield nitric oxide and nitrous oxide

In a typical procedure, benzyl cyanide (Compound **1**; 5 mL; 0.043 mol) was dissolved in 50 mL methanol in a pressure bottle and 2 equivalents of sodium methoxide (0.086 mol) were slowly added. After 10 cycles of nitrogen/vacuum degassing, the solution was exposed to 40 psi NO for 24 h with stirring at room temperature. During this time, copious amounts of a cream colored precipitate formed. After removing the excess nitric oxide gas, the precipitate was filtered, dissolved in a minimum of water and immediately precipitated with an excess of methanol. The resulting snow white material was the bis-diazeniumdiolated imidate, compound **2**: 35% yield, $\lambda_{\max}=264$ nm, $\varepsilon=14.0$ mM^{-1} cm^{-1} (0.1 M NaOH); chars above 250°C; ^{1}H NMR (300 MHz, D_2O) 3.8 ppm (s, 3H), 7.2–7.6 ppm (m, 5H). Anal. calcd for $C_9H_9N_5O_5Na_2{\cdot}2H_2O$: C, 30.95; H, 3.75; N, 20.05. Found: C, 30.65; H, 3.85; N, 19.79. There is no nitrile absorption in the infrared spectrum but rather a strong absorption at 1665 cm^{-1} corresponding to the C=N(H) stretch of the imidate.[10]

Although stable in 0.01 M NaOH solution, compound **2** decomposes vigorously in acidic media to produce NO and N_2O. The amount of N_2O generated as detected by gas chromatography was independent of pH. Whether in 1.0 M HCl or in pH 7.4 phosphate buffer, 1.5 molecules of N_2O were evolved for each molecule of diazeniumdiolated imidate that decomposed. The amount of NO produced, as detected by chemiluminescence and confirmed by the Griess assay,[11] varied slightly from a maximum of 0.5 molecules in 10% H_2SO_4 to a minimum of 0.3 molecules in pH 7.4 buffer per molecule of compound **2**. The rate of decomposition of compound **2**, followed spectrophotometrically by the decay of the peak at 264 nm, shows linear dependence upon pH in the range 4.0–7.4. The pseudo first-order rate constant at 37°C and pH 7.4, 0.1 M phosphate buffer, was found to be $3.35\pm0.27\times10^{-3}$ s^{-1} ($t_{1/2}=3.4$ minutes).

The organic product, isolated from the acidic decomposition of **2** as fine colorless needles, is compound **3**: mp = 146–147°C (lit.[12] 145–148°C with 142–143°C reported for the purified (*E*)-configured oxime[13]); ^{1}H NMR (300 MHz, $CDCl_3$) 3.81 ppm (s, 3H), 7.2–7.6 ppm (m, 5H). Anal. calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.20; H, 5.10; N, 7.80. In the infrared spectrum, the carbonyl appears as a strong, sharp absorption at 1725 cm^{-1}. While formation of the ester is not surprising since imidates are known to undergo hydrolysis in dilute acid,[14] isolation and characterization of **3** represents an important confirmation of Traube's speculation that bis-diazeniumdiolates might release NO via decomposition to oximes.[9]

It is worthwhile to note that the diazeniumdiolated imidate has been isolated from the reaction under a variety of conditions. These include the use of sodium hydroxide as the base, as well as using only 1 atmosphere of nitric oxide in the headspace. Interruption of the reaction in NaOH after only 2 h yielded a product with an infrared spectrum identical to that obtained from the methoxide method. This was somewhat surprising since it is known that the conversion of benzyl cyanide to the imidate proceeds only to the extent of 12% in 24 h at room temperature.[15] However, the presence of a strongly electron withdrawing group would be expected to facilitate this conversion, and the diazeniumdiolate group is capable of activating by electron withdrawal.[16] Therefore, in the case presented here, we speculate that the bis-diazeniumdiolated nitrile is transiently formed but rapidly undergoes conversion to the imidate under these reaction conditions (Fig. 2).

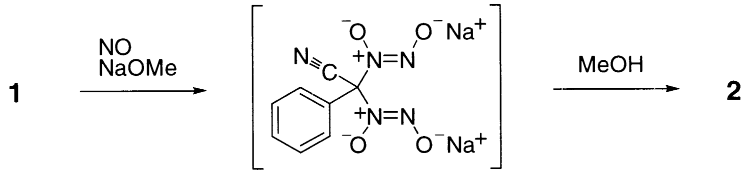

Figure 2. Intermediate in the proposed stepwise reaction pathway

An alert reader might then ask if acetonitrile would react with NO in the presence of base since acetonitrile has been shown to be an excellent solvent for the synthesis of various polyamine diazeniumdiolates.[17] Apparently, the polyamines lack the basicity to abstract protons from acetonitrile and in those reaction mixtures only the polyamines combine with NO in the above syntheses. However, we have found that in the presence of the stronger base sodium methoxide, acetonitrile does react with NO to produce a fine, light yellow precipitate. This material not only produces gases upon acidification but also turns blue, suggesting the formation of a C-nitroso compound. Further investigations into the reaction chemistry of NO and nitriles are underway.

Traube reacted benzyl cyanide with nitric oxide in EtOH/EtONa solution under seemingly similar conditions but obtained the nitrile instead of the imidate as the ultimate product. Our results represent yet another manifestation of the relatively great solvent sensitivity noted in previous diazeniumdiolation reactions.[17] Acetonitrile has emerged as a popular solvent for these reactions and this report also represents an important cautionary note concerning its use under highly basic conditions. Finally, the demonstration of nitric oxide release from this type of C-diazeniumdiolate may also be of significance in the realm of drug discovery since it serves to further clarify the structural requirements for NO release from this type of compound.[8]

Acknowledgements

We thank Mr. Michael Citro for the nitric oxide analysis, Mr. Stephen Fox for the nitrous oxide analysis and Mr. John Klose for the NMR data. This project was funded in part by the National Cancer Institute under Contract NO1-CO-56000.

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