Pergamon

Tetrahedron Letters 39 (1998) 5933–5936

TETRAHEDRON
LETTERS

Reaction of nitric oxide with the imine double bond of certain Schiff bases

Joseph A. Hrabie[a*], Aloka Srinivasan[b], Clifford George[c] and Larry K. Keefer[b]

[a]*Chemical Synthesis and Analysis Laboratory, SAIC Frederick, NCI-Frederick Cancer Research and Development Center, Frederick, Maryland 21702 USA*
[b]*Chemistry Section, Laboratory of Comparative Carcinogenesis, National Cancer Institute, FCRDC, Frederick, Maryland 21702 USA*
[c]*Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375 USA*

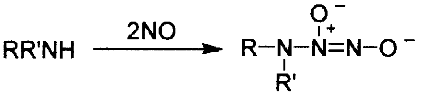
Received 13 May 1998; accepted 9 June 1998

Abstract

Reaction of nitric oxide with N-benzylidene-4-methoxyaniline produced 4-methoxybenzenediazonium nitrate and benzaldehyde. This may represent an example of the electrophilic reaction of NO with a double bond.

Keywords: Nitrogen oxides; Imines; Fragmentation reactions; Diazenes

Despite the longstanding importance of nitric oxide in atmospheric processes [1] and the recent revelation of its ubiquitous role in biology [2], the chemistry of this deceptively simple looking diatomic molecule remains largely an enigma. While most research has been directed towards an understanding of reactions in which NO behaves as a free radical, we have utilized the reaction of NO as an electrophile with amines to produce numerous diazenium-1,2-diolates (**1**) for use as nitric oxide donors in biological studies [3]. Although electrophilic reactions of NO are rare, they have been known since the last century. Traube [4] reported that the reaction of enolate anions with NO produces compounds analogous to **1** with the N_2O_2 functional group bound to carbon.



$$\mathrm{RR'NH} \xrightarrow{2\mathrm{NO}} \mathrm{R{-}\underset{R'}{N}{-}\overset{O^-}{N^+}{=}N{-}O^-}$$

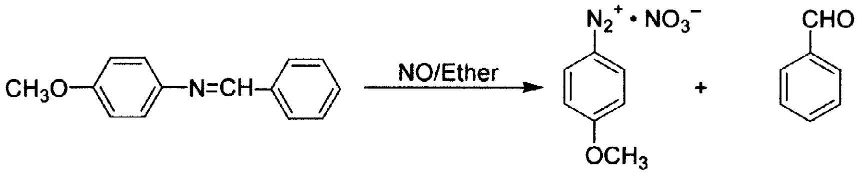
1

The reaction of NO with simple olefins has been the subject of considerable controversy for some time [5] due to the complex mixture of products formed. Nevertheless, the reaction is acknowledged to be radical in character, initiated either by nitrogen dioxide impurity [5] or photochemically [6]. This fact has recently been exploited through the use of ortho-

PII: S0040-4039(98)01218-0

quinodimethanes [7] as spin traps although reactions of other dienes with NO produce nitroalkanes via multi-step radical processes [8].

We would like to report our observation that NO gas reacts directly with Schiff bases derived from p-methoxyaniline and that the product ultimately isolated in good yield is **3**, a stable crystalline diazonium nitrate.



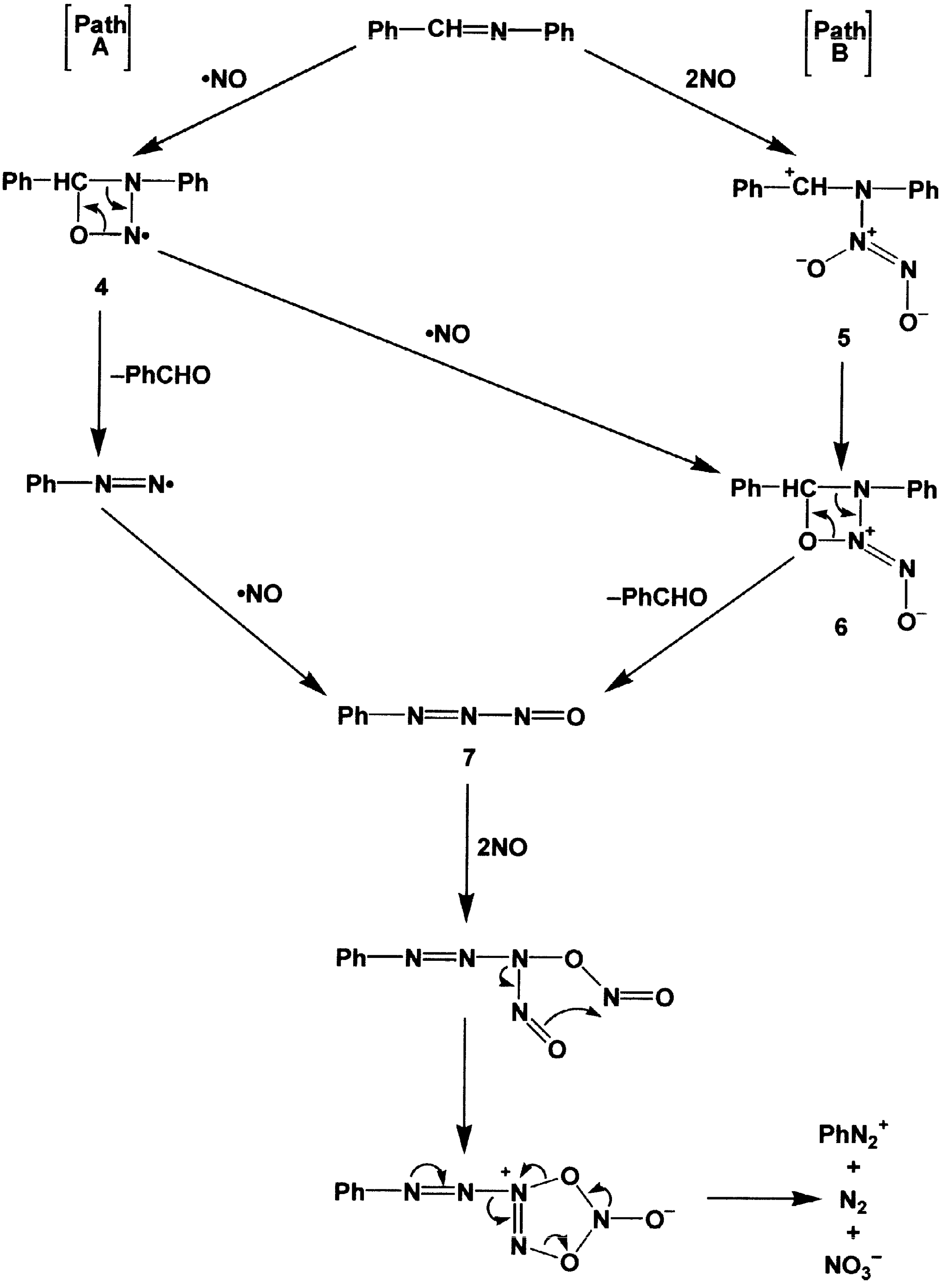
2 **3**

In a typical procedure, N-benzylidene-4-methoxyaniline (**2**; 3.60 g; 0.017 mole) was dissolved in ether (100 mL); the solution was placed in a standard Parr hydrogenation bottle and deoxygenated with nitrogen. A home-built all stainless steel substitute for the standard Parr 3911 hydrogenation apparatus [9] was used to place the solution under NO at a pressure of 80 psig and the reaction was stirred 15 h whilst an orange precipitate formed. The total net gas uptake was estimated to be roughly 3 equivalents (0.05 mole) using the reduction in pressure, the volume of the system and the ideal gas law. The excess gas was swept away with nitrogen; the peach colored solid was filtered and recrystallized from methanol/ether to yield **3** (2.10 g; 65%) as off-white (pinkish) needles (Compound **3**: mp 129°C dec. ^{1}H NMR (200 MHz, D_2O) δ 4.09 (s, 3H), 7.36-7.45 (m, 2H), 8.46-8.54 (m, 2H); ^{13}C NMR (D_2O) δ 60.2, 103.9, 120.7 (2C), 138.4 (2C), 173.2. Anal. Calcd for $C_7H_7N_3O_4$: C, 42.65; H, 3.58; N, 21.31; NO_3^-, 31.5. Found: C, 42.71; H, 3.60; N, 21.34; NO_3^-, 31.9.). Analysis of the initial mother liquor from this reaction by HPLC employing an internal standard revealed the formation of one equivalent of benzaldehyde (identity confirmed by GC-MS and NMR). No nitrite was found in either the crystalline solid or the mother liquor. The pressure apparatus currently in use does not allow for the sampling of any gaseous products.

Diazonium nitrate **3** was also isolated in good yield from the reaction of NO with the analogous Schiff bases derived from anisaldehyde and p-tolualdehyde. In view of the novel nature of this reaction the structure of **3** was verified via X-ray crystallography (Orthorhombic, space group Pbca, a = 3.636(2), b = 9.892(1), c = 20.707(3) A, Z = 8, FW = 197.2 g/mol, D_c = 1.48 g/cm^3. Clear plate 0.05 x 0.12 x 0.52 mm. Siemens SHELX-97. Full matrix least squares refinement on F^2 to final R1(F) = 6.52%, wR(F^2) = 13.23% for all data).

It is possible to postulate two mechanisms for this reaction as shown in Scheme 1. Both mechanisms lead to the common intermediate **7**, a nitrosodiazene which undergoes the radical addition of two molecules of NO across the nitroso group and subsequent extrusion of nitrogen forming the diazonium nitrate. These steps have literature precedent in the reaction of nitrosobenzene with NO to yield benzenediazonium nitrate [10] and their possible role in a variety of other

Scheme 1


Path A
Path B
Ph—CH=N—Ph
•NO
2NO
4
5
•NO
−PhCHO
Ph—N=N•
6
•NO
−PhCHO
Ph—N=N—N=O
7
2NO
PhN2+
+
N2
+
NO3−

reactions has been discussed [5]. In path A, the initial reaction between NO and the imine is a 2+2 cycloaddition reaction which has precedent in the reaction of nitrosobenzene with diphenylketene [11], substituted ethylenes [12] and Schiff bases [13] although no precedent exists for NO itself. In path B, the initial step is the electrophilic reaction of NO with the imine nitrogen which has ample precedent in our own preparations of diazeniumdiolates [3,9]. The formation and subsequent opening of the four-membered ring of both intermediates **4** and **6** have precedent in the decomposition of N-nitroso imines [14]. The two mechanisms are both consistent with the net uptake of three molar volumes of gas since they utilize four equivalents of NO and produce one equivalent of nitrogen. Since N_2 is used in our equipment to remove O_2, we could not easily verify its generation but this seems consistent with all of the above referenced reactions of NO.

We believe that path B represents the likely mechanism for this reaction since the intermediate radicals of path A would not likely result in such a clean reaction (our analysis of the mother liquor showed only unreacted imine and benzaldehyde, with no other side-products). We know of no precedent for NO itself to undergo this type of cycloaddition. The electrophilic reaction is probably favored over the radical reactions reported to occur with olefins because the higher electronegativity of nitrogen imparts the imine with considerable polar character.

ACKNOWLEDGMENT: This work was supported in part by the Office of Naval Research. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

References

[1] Heicklen J, Cohen N. The role of nitric oxide in photochemistry. In:Noyes WA Jr., Hammond GS, Pitts JN Jr., editors. Advances in photochemistry. Volume 5. New York:John Wiley, 1968:157-328.
[2] Butler AR, Williams DLH. Chem. Soc. Rev. 1993; 22:233-241.
[3] Keefer LK, Nims RW, Davies KM, Wink DA. Methods Enzymol. 1996; 268:281-293.
[4] Traube W. Liebigs Ann. Chem. 1898; 300:81-128.
[5] Brown JF Jr. J. Am. Chem. Soc. 1957; 79:2480-2488.
[6] Tuaillon J, Perrot R. Helv. Chim. Acta 1978; 61:558-566.
[7] Korth H-G, Sustmann R, Lommes P, Paul T, Ernst A, de Groot H, Hughes L, Ingold KU. J. Am. Chem. Soc. 1994; 116:2767-2777.
[8] Kelly DR, Jones S, Adigun JO, Koh KSV, Hibbs DE, Hursthouse MB, Jackson SK. Tetrahedron 1997; 53:17221-17234.
[9] Hrabie JA, Klose JR, Wink DA, Keefer LK. J. Org. Chem. 1993; 58:1472-1476.
[10] Bamberger E. Ber. 1897; 30:506-513.
[11] Kerber RC, Cann MC. J. Org. Chem. 1974; 39:2552-2558.
[12] Ingold CK, Weaver SD. J. Chem. Soc. 1924; 125:1456-1462.
[13] Ingold CK. J. Chem. Soc. 1924; 125:87-102.
[14] White EH, Wilson AA, Anhalt JP, Baumgarten RJ, Choca JI. J. Org. Chem. 1982; 47:2892-2896.