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Reactions of Acyl Nitroso Compounds with Amines: Production of Nitroxyl (HNO) with the Preparation of Amides

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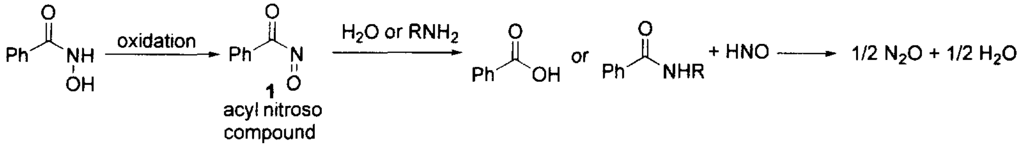
Abstract: *Oxidation of hydroxamic acids in the presence of amines generates nitrous oxide (N_2O) and the corresponding amide. The identification of N_2O suggests the intermediacy of nitroxyl (HNO). Retro-Diels Alder dissociation of cyclopentadiene-acyl nitroso compound cycloadducts releases N_2O with amide formation.* Copyright © 1996 Elsevier Science Ltd

Nitric oxide (NO), produced in a variety of mammalian cells by the nitric oxide synthase catalyzed oxidation of L-arginine, is now known to have numerous important functions in many physiological systems.[1] Nitroxyl (HNO or NO^-), the one-electron reduction product of NO, has been implicated in the wide variety of biological effects attributed to NO.[2] Indeed, a number of nitroxyl releasing compounds mimic the vasodilatory effects of NO by relaxing pre-constricted rabbit aortic rings in vitro.[3] Antibody catalyzed nitroxyl production in the presence of superoxide dismutase, an enzyme capable of oxidizing NO^- to NO, produces NO indicating that sources of nitroxyl can be considered as sources of nitric oxide.[4]

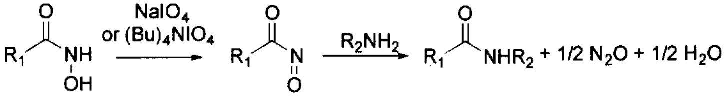
Acyl nitroso compounds (**1**, Scheme 1) have found much use as N-O heterodienophiles in the total synthesis of nitrogen containing natural products.[5] Prior evidence indicates that acyl nitroso compounds may represent reliable sources of nitroxyl. Oxidation of benzohydroxamic acid in water produces benzoic acid and nitrous oxide (N_2O), presumably by the nucleophilic substitution or solvolysis of the acyl nitroso compound with water (Scheme 1).[6] Identification of N_2O indicates the formation of nitroxyl which dimerizes and dehydrates to form N_2O in aqueous solution (Scheme 1).[7] Acyl nitroso species have also been implicated in the decomposition of various N,O-diacylated 4-chlorobenzenesulfohydroxamates (Piloty's acid derivatives), known sources of nitroxyl.[8] Formation of amides from the oxidation of hydroxamic acids in the presence of amines (Scheme 1) has been noted without evidence of nitroxyl formation.[9] We wish to report results concerning nitroxyl formation from acyl nitroso compounds generated in the presence of amines.

Scheme 1



Syringe pump addition of various hydroxamic acids to an aqueous solution of sodium periodate and an amine produced the corresponding amides with the simultaneous release of N_2O (Table 1).[10] Gas chromatographic analysis of the reaction headspace indicated that 45-70% of the theoretical yield of N_2O was generated.[11] Nitrous oxide production occurred to a similar extent in the oxidation of structurally varied hydroxamic acids in the presence of the same amine (Entry 1). Likewise, the yield of nitrous oxide remained within this range when various amines were utilized as nucleophiles (Entries 2-4). Similar yields of N_2O were obtained when tetra-*n*-butylammonium periodate was employed as the oxidant (Entries 5-8) in methylene chloride (CH_2Cl_2). The identification of nitrous oxide from these reactions provides evidence for nitroxyl production during the reaction.

Table 1. Production of N_2O and Amides from Oxidatively Generated Acyl Nitroso Compounds in the Presence of Amines

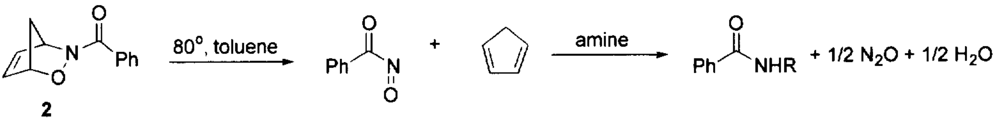


			% Yield Amide (% Yield N_2O)		
Entry	Amine (R_2 =)	Conditions	R_1 = Ph	R_1 = CH_2Ph	R_1 = CH_3
1	benzyl	H_2O, rt	65(68)	70(47)	70(52)
2	isobutyl	H_2O, rt	52(42)	46	43
3	cyclohexyl	H_2O, rt	35(69)	40	33
4	diethyl	H_2O, rt	16(48)	16	17
5	benzyl	CH_2Cl_2, rt	40(59)	65	70
6	isobutyl	CH_2Cl_2, rt	56(36)	49	46
7	cyclohexyl	CH_2Cl_2, rt	40(43)	40	31
8	diethyl	CH_2Cl_2, rt	40(42)	17	20

The isolated yields of amides were similar for the oxidation of structurally varied hydroxamic acids in the presence of the same amine (Table 1). The yield of amide was highest when non-hindered primary amines were employed and decreased as the steric size of the amine increased (Entries 2-4). Amide formation occurred to a similar extent using both aqueous (Entries 1-4) and organic oxidation systems (Entries 5-8). The identification of the corresponding O-acylhydroxamates and carboxylic acids (5 and 10% respectively, Entry 1 R = Ph) from these reactions accounts for the remainder of the organic products and supports the proposed mechanism of amide formation by nucleophilic substitution of the electrophilic acyl nitroso species.[9]

Retro-Diels Alder dissociation of cyclopentadiene or 9,10-dimethylanthracene-acyl nitroso compound cycloadducts provides an alternative method of acyl nitroso compound preparation.[12] Thermolysis of cycloadduct **2**, prepared from benzohydroxamic acid and cyclopentadiene,[13] in the presence of benzylamine gave N-benzylbenzamide in 88% yield with the formation of N_2O (Table 2, Entry 1). Thermal decomposition of **2** in the presence of other amines gave the corresponding amides in yields superior to those from oxidative acyl nitroso compound generation with the production of N_2O (Entries 2-4).[14] While the production of nitrous oxide from these reactions was clearly evident by gas chromatographic analysis of the reaction headspace, only 8-12% of the theoretical yield of N_2O was detected in each case. The diminished yields of N_2O may possibly be due to the generation of nitroxyl, an inherently unstable molecule, at an elevated temperature perhaps leading to the formation of other nitrogen oxides.

Table 2. Production of N_2O and Amides from Acyl Nitroso Compounds Generated by Retro-Diels Alder Dissociation and Amines.



2

Entry	Amine	% Yield Amide (N_2O Generation)
1	benzylamine	88 (+)
2	isobutylamine	70 (+)
3	cyclohexylamine	84 (+)
4	diethylamine	48 (+)

In conclusion, the results indicate that acyl nitroso compounds (**1**) generated through the oxidation of hydroxamic acids or retro-Diels Alder dissociation are good sources of nitroxyl (HNO or NO^-). The retro-Diels Alder dissociation of cycloadducts such as **2** in the presence of nucleophiles represents a mechanistically new method of nitroxyl generation. Efforts toward nitroxyl generation under more biological conditions in addition to experiments directed towards defining the scope of this reaction are currently underway.

Reference and Notes

1. Kerwin, J.F., Jr.; Lancaster, J.R., Jr.; Feldman, P.L. *J. Med. Chem.* **1995**, 38, 4343-4462.

2. (a) Arnelle, D.R.; Stamler, J.S. *Arch. Biochm. Biophys.* **1995**, *318*, 279-285. (b) Fukuto, J.M.; Hobbs, A.J.; Ignarro, L.J. *Biochem. Biophys. Res. Commun.* **1993**, *196*, 707-713.

3. (a) Fukuto, J. M.; Gulati, P.; Nagasawa, H.T. *Biochem Pharmacol.* **1994**, *47*, 922-924. (b) Fukuto, J.M.; Hszieh, R.; Gulati, P.; Chiang, K.T.; Nagasawa, H.T. *Biochem. Biophys. Res. Commun.* **1992**, *137*, 1367-1373.

4. Bahr, N.; Guller, R.; Reymond, J.L.; Lerner, R.A. *J. Am. Chem. Soc.* **1996**, *118*, 3550-3555.

5. Streith, J.; Defoin, A. *Synthesis* **1994**, 1107-1117.

6. Beckwith, A.L.J.; Evans, G.W. *J. Chem. Soc.* **1962**, 130-137.

7. Bonner, F.T.; Hughes, M.N. *Comments Inorg. Chem.* **1988**, *7*, 215-234.

8. Nagasawa, H. T.; Kawle, S. P.; Elderling, J. A.; DeMaster, E. G.; Fukuto, J. M. *J. Med. Chem.* **1995**, *38*, 1865-1871.

9. Sklarz, B.; Al-Sayab, A.F. *J. Chem. Soc.* **1964**, 1318-1320.

10. General Procedure-A solution of benzohydroxamic acid (0.150 g, 1.09 mmol) in methanol:water (1:4, 10 mL, 0.1 *M*) was added by syringe pump (0.33 mL/min) to a solution of sodium periodate (0.257 g, 1.20 mmol) and benzylamine (0.13 mL, 1.20 mmol) in water (20 mL) at room temperature in a 100 mL round-bottom flask equipped with a rubber septa. Saturated aqueous sodium bisulfite (5 mL) was added when the reaction was judged complete by thin-layer chromatography. The solution was extracted with CH_2Cl_2 (3 x 25 mL), the organic layers combined, dried over sodium sulfate, filtered and concentrated to give a residue which was purified by silica gel flash chromatography to give (0.152 g, 65%) of N-benzylbenzamide.

11. General Procedure for Nitrous Oxide Analysis-N_2O detection and quantification was performed by injecting an aliquot of the reaction headspace (100 μL, 0.11 mmol hydroxamic acid scale) onto a 5890 Hewlett Packard gas chromatograph equipped with a thermal conductivity detector, a 6 ft. X 1/8 in. Porapak Q column at an operating oven temperature of 50 °C with a flow rate of 13.6 mL/min (helium). Retention time of N_2O was 2.20 minutes and was identical to a known sample of N_2O (Aldrich). Quantitation was achieved by comparing injections of known amounts of authentic N_2O.

12. (a) Keck, G.E.; Webb, R.R.; Yates, J.B. *Tetrahedron* **1981**, *37*, 4007-4016. (b) Horsewood, P.; Kirby, G.W.; Sharma, R.P.; Sweeny, J.G. *J. Chem. Soc. Perkin Trans. I* **1981**, 1802-1806.

13. Kirby, G.W.; Sweeny, J.G. *J. Chem. Soc. Perkin Trans. I* **1981**, 3250-3254.

14. General Procedure-In a 4 in. sealed tube, cycloadduct **2** (0.219 g, 1.09 mmol) and benzylamine (0.13 mL, 1.19 mmol) were dissolved in toluene (15 mL) and heated to 80 °C. After 20 h, the solution was cooled to room temperature and concentrated to provide a residue which was purified by flash chromatography to give (0.202 g, 88 %) of N-benzylbenzamide.

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