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Nitrosocarbonyl release from *O*-substituted hydroxamic acids with pyrazolone leaving groups

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This article is dedicated to Professor Gary H. Posner in appreciation of his career contributions to organic chemistry

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ABSTRACT

A new class of nitrosocarbonyl precursors, *O*-substituted hydroxamic acids with pyrazolone leaving groups (OHPY), is described. These compounds generate nitrosocarbonyl intermediates, which upon hydrolysis release nitroxyl (azanone, HNO) under physiologically relevant conditions. Pyrazolones have been used to confirm the generation of nitrosocarbonyls by competitive trapping to form isomeric *N*-substituted hydroxamic acids (NHPY) via an *N*-selective nitrosocarbonyl aldol reaction. The rate of nitrosocarbonyl release from OHPY donors is impacted by donor substituents, including the pyrazolone leaving group.

1. Introduction

Nitroxyl (azanone, HNO), the one-electron reduced and protonated form of nitric oxide, has been shown to improve both vasorelaxation and myocardial contractility, making HNO donors ideal candidates for drug development.[1–9] HNO is a reactive molecule that spontaneously dimerizes to produce hyponitrous acid (HON=NOH), which then dehydrates to give nitrous oxide (N_2O).[10] Due to this inherent reactivity, HNO must be generated in situ through the use of donor compounds.

Angeli's salt ($Na_2N_2O_3$, AS, Fig. 1) is a well-known donor that generates HNO under physiological conditions with a short half-life.[11] Derivatization of this inorganic salt has been unsuccessful to date, thus preventing modification for tunable HNO release. Piloty's acid (PA) derivatives and acyloxy nitroso compounds (AcON) represent other types of HNO donors that have been developed with tunable half-lives.[12–17] Our group has recently reported two new series of HNO donors with half-lives that can be varied from minutes to hours under physiological conditions: (hydroxylamino) pyrazolone (HAPY) and (hydroxylamino)barbituric acid (HABA) derivatives.[18–20] In addition to these examples, the continued development of efficient HNO donors is important to expand the research tools available to understand the potential role of HNO in biological processes.

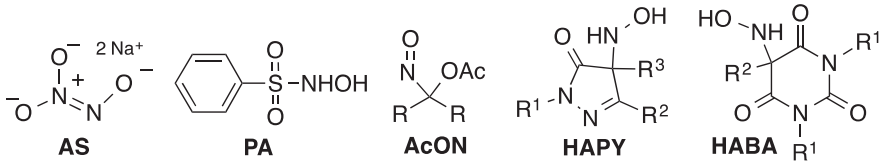

Fig. 1. Some previously reported HNO donors.

Another strategy to release HNO is based on the hydrolysis of nitrosocarbonyl intermediates.[21,22] Nitrosocarbonyls are highly

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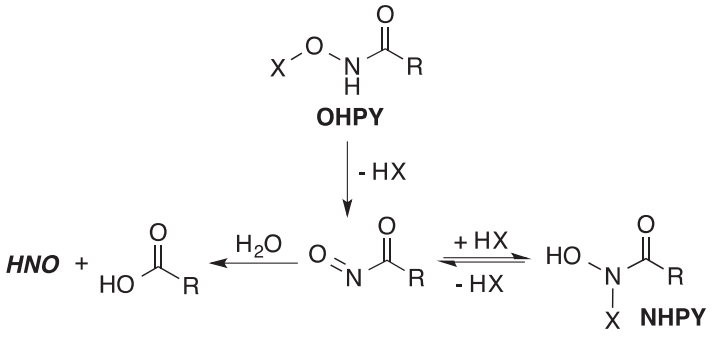
reactive species that can react with nucleophiles including water to generate HNO. Oxidation of hydroxamic acids and thermal decomposition of 9,10-dimethylanthracene adducts represent common approaches to nitrosocarbonyl generation.[23–25] The photolysis of nitrodiazo compounds, nitronates with alpha leaving groups, and 1,2,4-oxadiazole-4-oxides have also been shown to generate nitrosocarbonyls efficiently.[26–28] Recently, the aerobic oxidation of hydroxamic acids by metal catalysts under mild conditions has been developed as an efficient strategy for nitrosocarbonyl generation.[29–46] In general, however, the above methods are not suitable for HNO generation under physiological conditions.

Herein, we report a novel class of nitrosocarbonyl donors that upon deprotonation and loss of the leaving group (Scheme 1, HX=pyrazolone) generate nitrosocarbonyl intermediates that can hydrolyze to release HNO under physiological conditions. As has been demonstrated in recent reports,[33,35,36,40–42,45] nitrosocarbonyls can react with nucleophiles through an *N*-selective nitrosocarbonyl aldol reaction to produce *N*-substituted hydroxamic acid adducts. We have recently found that pyrazolones are efficient traps for nitrosocarbonyl intermediates to generate *N*-substituted hydroxamic acid derivatives with pyrazolone leaving groups (NHPY) in a reversible manner.[47] In the current work, we observe OHPY decomposition to generate nitrosocarbonyls which further react with pyrazolones to produce isomeric NHPY compounds (Scheme 1). We have synthesized and studied NHPY compounds independently, and have recently demonstrated the efficient formation of nitrosocarbonyl intermediates upon decomposition of these compounds.[47]

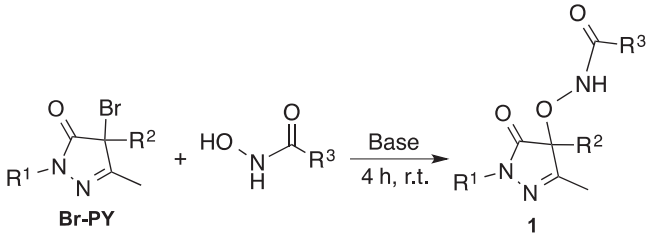


Scheme 1. Reactivity of OHPY nitrosocarbonyl precursors.

2. Results and discussion

2.1. Synthesis

OHPY compounds **1** have been synthesized by formation of the corresponding bromide (Br-PY) followed by reaction with hydroxamic acids (Scheme 2). Initially, OHPY **1a** was synthesized without the need for chromatographic purification, and its structure was confirmed by X-ray crystallography (Supplementary data). The other precursors were purified using column chromatography.



Scheme 2. Synthesis of OHPY derivatives.

The OHPY and NHPY isomers can obviously be distinguished by X-ray crystallography. An analysis of ^{13}C NMR data and available crystal structures (Supplementary data), reveal that OHPY and NHPY compounds have distinctive chemical shifts for their quaternary carbons (δ=87.6–90.2 ppm for OHPY vs δ=68.4–76.5 ppm for NHPY). Thus, ^{13}C NMR spectroscopy conveniently allows the two isomers to be distinguished if crystal structures cannot be obtained.

2.2. Decomposition of OHPY compounds

Nitrosocarbonyl formation following OHPY decomposition under physiological conditions was studied. As described above, the reaction of nitrosocarbonyls and pyrazolones to produce NHPY compounds can be efficient. Upon nitrosocarbonyl generation from OHPY precursors **1**, therefore, a competition exits between hydrolysis to generate HNO and carboxylic acid **4** (Scheme 3, *Path A*) and trapping by the pyrazolone byproduct **2** to produce NHPY compounds **3** (Scheme 3, *Path B*). NHPY compounds subsequently can also release nitrosocarbonyl intermediates with half-lives that depend on R^1, R^2, and R^3 (Scheme 3, *Path C*).[47]

^1H NMR spectroscopy was used to examine the decomposition of OHPY donors and measure relative product yields in aqueous solution (Table 1).[19,20] Pyrazolone **2**, NHPY **3**, and carboxylic acid **4** are cleanly formed as the only observable organic products. Because NHPY compounds **3a**, **3c**, and **3d** all have half-lives on the order of days,[47] *Path C* in Scheme 3 does not contribute to the observed chemistry for OHPY donors **1a**, **1c**, and **1d**. Thus, the relative yields of pyrazolone **2** and carboxylic acid **4** compared with that for NHPY compound **3** in Table 1 reflect the competition between *Path A* and *Path B* for these donors.

OHPY decomposition was also monitored by UV–vis spectroscopy to measure donor half-lives at pH 7.4 and 37 °C (Table 1). Based on the chemistry of related HNO donors,[19,20] we propose that the first step of decomposition is deprotonation which leads to release of nitrosocarbonyl plus pyrazolone. If the barrier to dissociation from anionic OHPY is very small, observed half-lives should correlate with donor pK_a and the pyrazolone leaving group.[19,20] Pyrazolone **2a** (R^1=Ph, R^2=(C(=NOMe)Me, pK_a=6) is a better leaving group than pyrazolone **2b** (R^1=Ph, R^2=Me, pK_a=7.6),[19] consistent with the much shorter half-life for OHPY **1a** ($t_{1/2}$=25 min) compared with **1b** (stable). Exchanging the R^1 group from phenyl to methyl (OHPY **1c** vs **1d**) increases the half-life by a factor of two, consistent with that previously reported for analogous HAPY and NHPY donors.[19,47] A comparison of the known pK_a values of the related