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Synthesis of Cyclic Hydroxamic Acids through −NOH Insertion of Ketones

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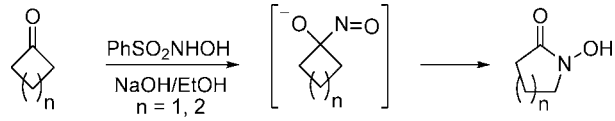
ABSTRACT

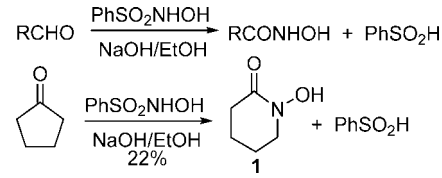


Treatment of cyclobutanone or cyclopentanone with *N*-hydroxybenzenesulfonamide under basic conditions yields the ring-expanded cyclic hydroxamic acid in 18−69% yield. Reactions of substituted cyclobutanones give ring expanded products where the −NOH group regio- and stereoselectively inserts to the more substituted position. This expansion likely proceeds through a mechanism that includes addition of the N-anion of *N*-hydroxybenzenesulfonamide to the ketone and a C-nitroso intermediate that rearranges to the final product.

Recent studies demonstrate the distinct biological character of nitroxyl (HNO) compared to its redox partner nitric oxide (NO) as a signaling agent in the vascular system.[1,2] Nitroxyl exhibits different chemistry from NO by dimerizing and dehydrating to nitrous oxide, by reacting with heme proteins through separate mechanisms to NO, and by rapidly condensing with thiols to yield disulfides and sulfinamides.[3,4] This chemistry requires the use of HNO donors in fundamental chemical and biochemical studies and focuses attention on these donors as potential therapies for various conditions including congestive heart failure, cancer, alcoholism, and hemolytic disorders.[1]

Currently, Angeli's salt ($Na_2N_2O_3$) and Piloty's acid ($PhSO_2NHOH$, *N*-hydroxybenzenesulfonamide) represent the two most widely used HNO sources for routine study. In addition to releasing HNO, Piloty's acid reacts with aldehydes under basic conditions to give the corresponding hydroxamic acid and benzenesulfinic acid, and this reaction forms the basis of the Angeli−Rimini test for the colorimetric identification of aldehydes (Scheme 1).[5,6] Early reports indicate that Piloty's acid reacts with cyclopentanone to yield the correpsonding cyclic hydroxamic acid (**1**, Scheme 1) in low yield.[7] Given our interest in the chemistry of HNO and HNO donors, we further examined this unusual reaction of Piloty's acid with cyclic ketones and showed that under basic conditions *N*-hydroxybenzenesulfonamide reacts with small (four and five-membered) cyclic ketones to give the cyclic hydroxamic acid in moderate yields through a mechanism that includes a *C*-nitroso intermediate.

Scheme 1. Angeli−Rimini Reaction of Aldehydes and Ketones



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Condensation of benzenesulfonyl chloride with hydroxylamine in methanol at room temperature provides *N*-hydroxybenzenesulfonamide required for subsequent reactions.[8] As previously reported,[7] treatment of cyclopentanone with Piloty's acid (0.9 equiv) in ethanol with excess sodium hydroxide at room temperature yields 1-hydroxypiperdin-2-one (**1**, Scheme 1, entry 1, Table 1) in 18% yield. Table 1

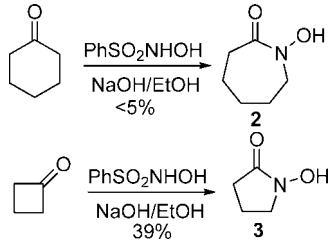
Table 1. Effect of Amount of Piloty's Acid on Yield of **1**

entry	equiv	yield (%)
1	0.9	18
2	2	40
3	4	44
4	6	59
5	10	69

shows that increasing the molar equivalents of Piloty's acid increases the yield of **1** with 2 equiv more than doubling and greater equivalents furthering increasing the isolated yield of **1** (Table 1, entries 2−5). Recrystallization after sublimation of chromatographically purified product gives crystals suitable for X-ray diffraction studies, which confirm the structure of **1** (Supporting Information). The use of sodium methoxide as base or sodium hydride in a polar aprotic solvent (THF) results in product but does not alter the observed yield.

While treatment of cyclohexanone with Piloty's acid in basic ethanol yields less than 5% of the corresponding cyclic hydroxamic acid (**2**, *N*-hydroxycaprolactam, Scheme 2),

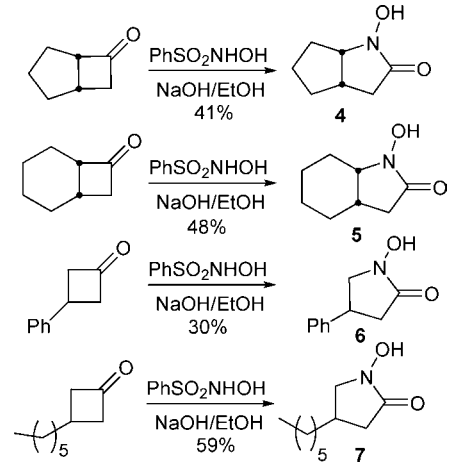
Scheme 2. Reaction of Piloty's Acid with Various Ketones



exposure of cyclobutanone to these conditions gives the five-membered ring hydroxamic acid in 39% yield (**3**, Scheme 2). Slow addition of Piloty's acid to the reaction mixture does not improve yield. The volatiltiy of cyclobutanone and the water solubility of **3** hinders its isolation and purification, which account for the limited yield of **3**, but these results suggest a relationship between ring size and yield. Attempts to convert 2-hexanone to the corresponding hydroxamic acid under identical conditions gives less than 5% of the desired product.

This success with cyclobutanone encouraged the application of this sequence to more substituted, less volatile cyclobutanones (Scheme 3). A standard two-step sequence

Scheme 3. Reaction of Piloty's Acid with Substituted Cylobutanones



of a 2 + 2 cycloaddition between an alkene and dichloroketene followed by Zn/AcOH reduction of the α,α-dichloro ketone intermediate generates various substituted cyclobutanone substrates (Scheme 3).[9,10] Treatment of these cyclobutanones with Piloty's acid (2 equiv) in base forms the corresponding cyclic hydroxamic acids in 30−59% yield (**4**−**7**, Scheme 3). The decreased volatility of the substituted cyclobutanone substrates (compared to cyclobutanone) and the decreased water solubility of the products likely improve the isolated yields and facilitate purification. This sequence yields cyclic five-membered ring hydroxamic acids derived from two unsymmetric bicyclic cyclobutanones (**4** and **5**) and from two symmetric substituted cyclobutanones (**6** and **7**). ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry support the structures of **4**−**7**, and X-ray diffraction studies on crystals of **4** confirms the structure of this bicyclic hydroxamic acid (Figure 1). In addition to

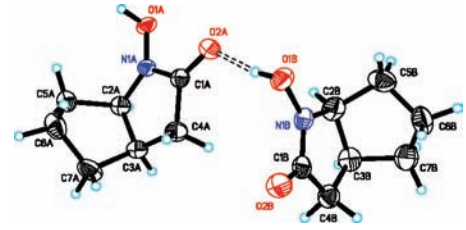


Figure 1. X-ray diffraction structure of **4**.

structural confirmation, the crystallography studies also reveal two important features of this reaction: (1) the −NOH inserts

(8) While commercially available, freshly prepared *N*-hydroxybenzene sulfonamide produces higher yields. Scholz, J. N.; Engel, P. S.; Glidewell, C.; Whitmire, K. H. *Tetrahedron* **1989**, *45*, 7695–7708.

(9) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879–2882.

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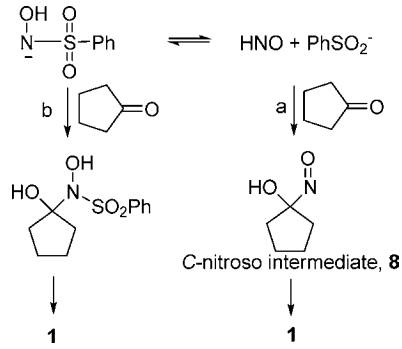
to the more substituted side of the ketone demonstrating regioselectivity and (2) the −NOH group adds stereoselectively with the overall ring juncture relative stereochemistry remaining cis. NMR and chromatographic analysis of the crude reaction mixture do not reveal the presence of any other hydroxamic acids. These results appear similar to the Baeyer−Villiger oxidation of ketones with migration of the more electron-donating branch with retention of configuration.[11]

Early work proposes two mechanistic possibilities for this unusual transformation. The first includes the direct addition of HNO or $^{-}$NO to the ketone to form a *C*-nitroso intermediate that rearranges to the observed product (**8**, Scheme 4, path a).[7] Further experiments argue against this

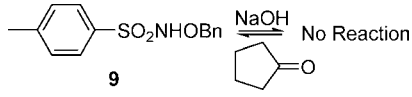
Scheme 4. Proposed Mechanisms for Formation of **1**



route and suggest instead that a nucleophilic addition of the N-anion of Piloty's acid to the cyclic ketone gives a tetrahedral intermediate that rearranges to the ring-expanded hydroxamic acid with the loss of benzenesulfinic acid (Scheme 4, path b).[12,13] Such a mechanism finds direct precedence in the known reaction of aldehydes with Piloty's acid to form hydroxamic acids (the Angeli−Rimini reaction, Scheme 1).[13]

Experiments with *O*-benzyl *p*-toluene *N*-hydroxysulfonamide (**9**), prepared by the treatment of *p*-tosyl chloride with *O*-benzylhydroxylamine, provide insight into the mechanism (Scheme 5). This compound cannot decompose to HNO

Scheme 5. Reaction with O-Protected Piloty's Acid



(Scheme 4, path a) but can form an N-anion that should react to give an *O*-alkyl cyclic hydroxamate (Scheme 4, path b).

(11) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, *73*, 7–750.
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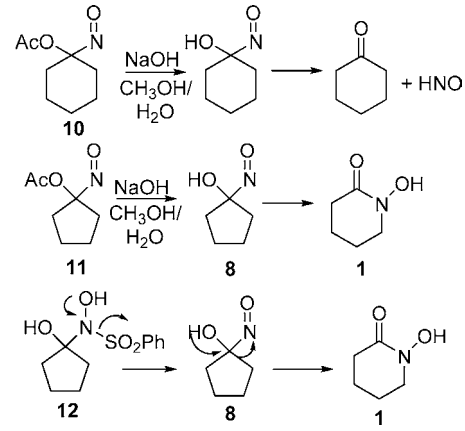
Reaction of **9** with cyclobutanone or cyclopentanone fails to yield any insertion product arguing against both path a and b (Schemes 4 and 5) as the mechanism of product formation. Treatment of **9** with NaH in THF followed by methyl iodide produces the N-methylated product verifying the nucleophilic abiltiy of the anion of **9** (Supporting Information). This result also eliminates the potential invovlement of O-nitrene intermediates that could form through the dissociatoin of the N-anion of Piloty's acid. In addition, incubation of cyclopentanone with Angeli's salt in a methanol/buffer mixture, conditions that clearly generate HNO as judged by gas chromatographic identification of nitrous oxide, fail to produce **1** arguing against path a. Previous pK_a calculations also disfavor the direct reaction of $^{-}$NO with cyclic ketones to form a *C*-nitroso intermediate and product (Scheme 4, path a).[14]

These results led to the examination of acyloxy nitroso compounds as precursors to the *C*-nitroso intermediate (**8**, Scheme 4) and cyclic hydroxamic acids. Our previous work shows that hydrolysis of the cyclohexyl-derived acetoxy nitroso compound (**10**, Scheme 6) forms cyclohexanone and

Scheme 6. Modified Reaction Mechanism



HNO (as judged by nitrous oxide generation) through a *C*-nitroso intermediate and highlights these compounds as new HNO donors.[15] Hydrolysis of the cyclopentyl-derived acetoxy nitroso compound (**11**), generated by the lead tetraacetate oxidation of cyclopentanone oxime,[15] yields cyclic hydroxamate (**1**, Scheme 6) in 75% yield and only trace amounts of nitrous oxide (indicating little HNO formation). These results provide evidence of a *C*-nitroso intermediate during the formation of **1** from cyclopentanone and Piloty's acid in basic conditions and also show a ring size dependency on the reaction pathway. Scheme 6 depicts

(14) Bartberger, M. D.; Liu, W.; Ford, E.; Miranda, K. M.; Switzer, C.; Fukuto, J. M.; Farmer, P. J.; Wink, D. A.; Houk, K. N. *Proc. Natl. Acad. of Sci. U. S. A.* **2002**, *99*, 10958–10963. This work suggests a pK_a of 11.4 for HNO as well as a kinetic barrier of deprotonation between the singlet acid (HNO) and the predicted triplet conjugate base $^{-}$NO (isoelectronic with oxygen).
(15) Sha, X.; Isbell, T. S.; Patel, R. P.; Day, C. S.; King, S. B. *J. Am. Chem. Soc.* **2006**, *128*, 9687–9692.

a mechanism where addition of the N-anion of Piloty's acid generates a tetrahedral intermediate (**12**) that eliminates benzenesulfinic acid to give the *C*-nitroso intermediate (**8**, Scheme 6). This mechanism produces the orignially proposed *C*-nitroso intermediate (**8**) through this tetrahedral intermediate. This *C*-nitroso intermediate either eliminates HNO to give the ketone (cyclohexyl) or rearranges to the cyclic hydroxamic acid (cyclobutyl, cyclopentyl). Increasing the amount of Piloty's acid would increase the amount of the reactive N-anion under equilibrium conditions and result in an increased yield of the observed product (Table 1). The *C*-nitroso interemediate (**8**) shows structural similarity to the accepted peroxy intermediates in the Baeyer−Villiger reaction and the observed regiochemistry and stereochemistry appears consistent.[11] Obviously, the ring strain of the *C*-nitroso intermediate plays a major determinant in product outcome. Unfavorable elicpsing interactions leading to ring strain likely drive rearrangement of the smaller membered rings to larger rings that relieve these interactions.

In summary, these results show that the N-anion of Piloty's acid reacts with four- and five-membered ring cyclic ketones to form tetrahedral intermediates that rearrange to *C*-nitroso species and ulimately a cyclic hydroxamic acid (depending on ring size) in moderate yields. These experiments suggest a regio- and stereoselective rearrangement similar to the Baeyer−Villiger reaction. This chemistry shows the complexity of the reactions of *N*-hydroxysulfonamides and may prove useful for the synthesis of various cyclic hydroxamic acid containing compounds, such as siderophores,[16−19] natural iron-chelating compounds that show promise as new antibiotics.[16,17] As such, these studies also compliment other methods for the direct conversion of ketones to the corresponding N−OH amides.[20−23] This work aids in the structural development of new HNO (both Piloty's acid and acyloxy nitroso-based) donors as the reactivity of the N-anion must be considered for Piloty's acid-based donors and the structures, particularly ring size, must be taken into account for new acyloxyl nitroso compounds.

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Supporting Information Available: Experimental details for the synthesis and characterization of **1**−**7** and **9**−**11**, including X-ray data for **1** and **4** This material is available free of charge via the Internet at http://pubs.acs.org.

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