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Ring expansions of acyloxy nitroso compounds

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ABSTRACT

Treatment of cyclopentanone and cyclobutanone-derived oximes with lead(IV) tetraacetate gives the bright blue acyloxy nitroso compounds, which upon basic hydrolysis yields the ring expansion product cyclic hydroxamic acids in 12–81% yield. Reactions of substituted cyclopentanones provide ring expanded products where the –NOH group regioselectively inserts to the more substituted position and gives a better yield compared to the treatment of the same ketone with a basic solution of Piloty's acid. Reaction of phosphines with acyloxy nitroso compounds generally generates a ring-expanded Beckmann rearrangement product that can be hydrolyzed to the corresponding lactam. Acyloxy nitroso compounds that undergo rapid hydrolysis to HNO do not show this ring expansion reactivity. These results further demonstrate the versatility of acyloxy nitroso compound to yield structurally complex materials.

Introduction

The chemical properties of nitroxyl (HNO) biologically distinguish it from other nitrogen oxides including nitric oxide (NO).[1–4] Nitroxyl readily dimerizes to ultimately form nitrous oxide (N_2O) and condenses with protein thiols to generate disulfides and sulfinamides that mediate much of HNO's distinct biology.[3–5] This electrophilic reactivity demands the use of HNO donors in fundamental studies and such donors form potential therapeutics for congestive heart failure, cancer, alcoholism, and hemolytic disorders.[6–13] Angeli's salt ($Na_2N_2O_3$) and Piloty's acid ($PhSO_2NHOH$, *N*-hydroxy benzenesulfonamide) represent the most widely used HNO donors but numerous structurally and mechanistically diverse HNO donors have appeared, including acyloxy nitroso compounds.[14–19] While stable acyloxy nitroso compounds react as N–O heterodienophiles,[20] relatively little work describing their synthetic potential has appeared and we report two distinct ring expansions of acyloxy nitroso compounds.

Expansion to cyclic hydroxamic acids

Earlier work shows that 1-nitrosocyclohexyl acetate (**1**) hydrolyzes to an unstable α-hydroxy *C*-nitroso species that decomposes to cyclohexanone and HNO (Scheme 1).[21] The reaction of Piloty's acid under basic conditions with four and five-membered ring ketones forms cyclic hydroxamic acids through the intermediacy of the same α-hydroxy *C*-nitroso species.[21] However, the basic hydrolysis of 1-nitroso cyclopentyl acetate (**2a**) yields a six-membered ring cyclic hydroxamic acid (**3a**, 25% yield) with little N_2O (evidence of HNO) formation suggesting a strain-based ring expansion.[21] Given this common α-hydroxy *C*-nitroso intermediate, we pursued the idea that other small (4–5) membered ring acyloxy nitroso compounds would rearrange to cyclic hydroxamic acids under basic conditions.

Condensation of a series of four and five-membered ring ketones (**4a**–**g**) with hydroxylamine gives the corresponding oximes (**5a**–**g**) in good yield (Scheme 2).

Treatment of these oximes with lead(IV) tetraacetate gives the bright blue acyloxy nitroso compounds (**2a**–**g**), which were quickly purified by passage through a short silica column and used without further purification. Slow addition of a methanol solution of **2a**–**g** to a 2 M NaOH solution a 0 °C followed by work up generally produces the corresponding cyclic hydroxamic acid (**3a**–**g**) in good yield (12–81%, Scheme 2, Table 1).

As shown in Table 1, basic hydrolysis of **2a** yields **3a** in 25% yield.[20] Under these conditions, acyloxy nitroso compound (**2a**) disappears and both ketone (**4a**) and oxime (**5a**) form as by-products. Similar treatment of the acyloxy nitroso compound derived from 2-methyl cyclopentanone (**2b**) gives the ring expanded cyclic hydroxamic acid (**3b**) in 77% yield. This result demonstrates two important features of this process: (1) the N-insertion occurs to the more hindered side of the ketone as shown by NMR chemical shift/splitting and integration analysis and (2) the yield vastly

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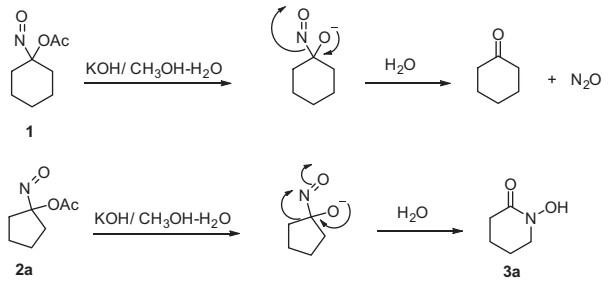


Scheme 1. Pathways of acyloxy nitroso compound hydrolysis.

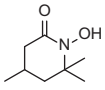
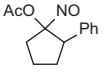
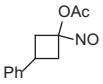
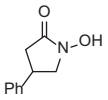
improves from the direct treatment of the ketone with basic solutions of Piloty's acid (77% vs 5%).[21] Examination of the crude reaction mixture by NMR spectroscopy shows the formation of only a single regioisomer. The yield improvement likely results from the lack of a requirement to generate the N-anion of Piloty's acid under these reaction conditions in the presence of acidic ketone α-hydrogens. Other substituted acyloxy nitroso compounds (**2c**–**f**) smoothly rearrange to form the more hindered cyclic hydroxamic acids (**3c**–**f**). Single crystal X-ray crystallographic analysis clearly defines the structure of **3c** and **3e** and confirms that rearrangement occurs to the most hindered side (Fig. 1). Exposure of the cyclobutanone-derived acyloxy nitroso compound (**2g**) to basic conditions yields the five-membered ring hydroxamic acid (**3g**) in 81% yield (Scheme 2, Table 1).

Scheme 1 depicts a likely mechanism for these transformations. Basic hydrolysis of the acetate group would give the unstable α-hydroxy *C*-nitroso species that undergoes ring expansion to the cyclic hydroxamic acid as previously demonstrated suggesting that the electrophilic nitroso group coupled with the strain within the smaller rings induces rearrangement to the cyclic hydroxamic acid.[21] These results show this pathway operates in four and five membered ring acyloxy nitroso compounds but not in the larger non-strained six membered ring compound. The reaction of substituted acyloxy nitroso compounds-derived from substituted cyclopentanones affords ring expanded products where the –NOH group regioselectively inserts to the more substituted position similar to other well-known ring expansion rearrangements (Baeyer–Villiger).[21] This methodology provides a direct and rapid method to generate structurally diverse cyclic hydroxamic acids from four and five membered ring ketones that are not easily accessible other methods (including the reaction of *N*-hydroxybenzenesulfonamide with the ketone under basic conditions).[22]

Phosphine-mediated Beckmann rearrangement

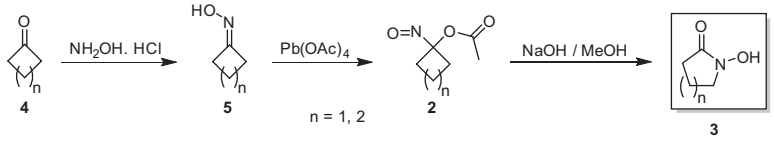
During the investigation of acyloxy nitroso compounds as potential HNO donors, our group also examined the reactions of phosphines as new HNO traps through their formation of unique aza-ylide products.[23,24] Phosphines react as nucleophiles with a variety of electrophilic nitroso compounds (*C*-nitroso, *S*-nitroso, and H-NO) to yield numerous products depending on the structure of the phosphine and the nitroso substrate.[25,26] Given the known reactivity and the potential of acyloxy nitroso compounds to release HNO,[14,16,27] the reaction of acyloxy nitroso compounds and triaryl phosphines was explored.

Table 1
The ring expansion products (**3a**–**g**) from the corresponding ketones (**4a**–**g**)

Entry	Starting ketone (**4**)	Acyloxy nitroso compound (**2**)	Product (**3**)	% yield
a				25
b				77
c				71
d				12
e				63
f				67
g				81

Treatment of 1-nitrosocyclohexyl acetate (**1**) with triphenylphosphine (TPP) in benzene or toluene at room temperature results in an exothermic reaction with the disappearance of the deep blue color. After 60 min, analysis of the reaction mixture by ^{31}P NMR spectroscopy and mass spectrometry shows the generation of triphenyl phosphine oxide (δ = 26.09 ppm, m/z = 279.1, 95% yield, Scheme 3), which was identical to a standard. In addition to phosphine oxide, a seven membered ring Beckmann rearrangement product (**6**, Scheme 3) forms in 55% yield that was identified by GC–MS (m/z = 156) and both 1D and 2D NMR spectroscopy (Supporting information). Acid-catalyzed hydrolysis of **6** (1 M HCl) yields caprolactam (**7**, Scheme 3), which was also identical to a known standard by both MS and NMR analysis.

The reaction of **1** with TPP was monitored using UV–Vis spectrometry following the disappearance of the absorbance at 667 nm corresponding to the nitroso group (Table 2). Incubation of **1** with TPP in benzene or toluene at room temperature shows an exponential decrease of **1** over time and the rate shows a linear dependence on the concentration of phosphine (Table 2) suggesting a bimolecular reaction. Under pseudo-first order conditions (10 equiv of TPP) an observed rate constant of k = 3.5 min^{-1} with a half-life of $t_{1/2}$ = 0.2 min is observed (Table 2). As expected, these results reveal that phosphines react faster with most acyloxy nitroso compounds than these compounds hydrolyze to HNO (for **1**, $t_{1/2}$ = 800 min, pH 7.6 1:1 Tris buffer/MeOH).[27]



Scheme 2. Conversion of ketones to cyclic hydroxamic acids via acyloxy nitroso compounds.

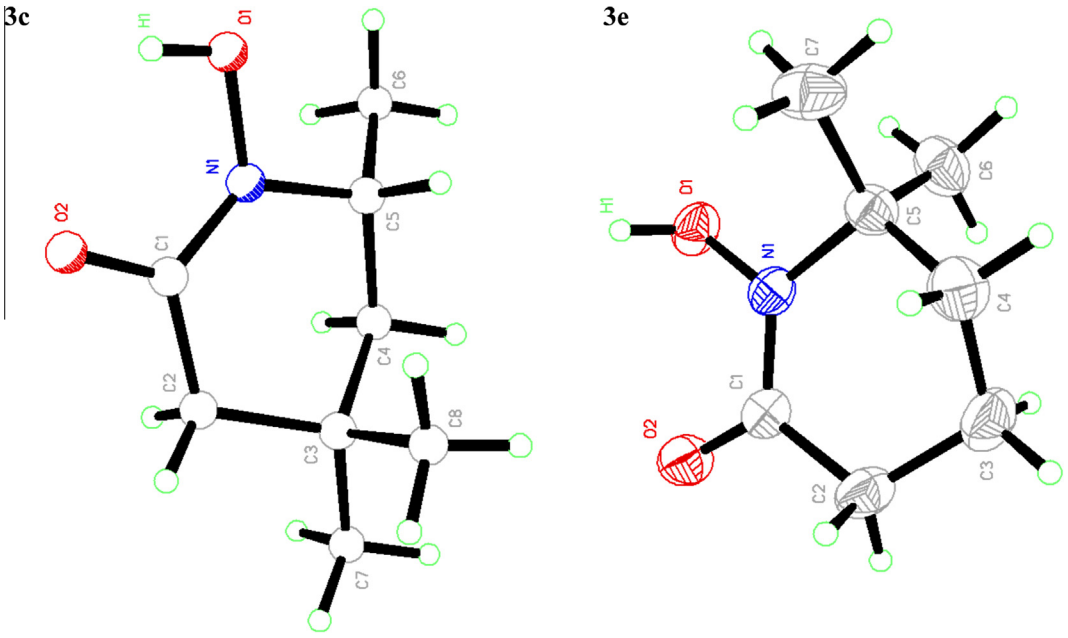
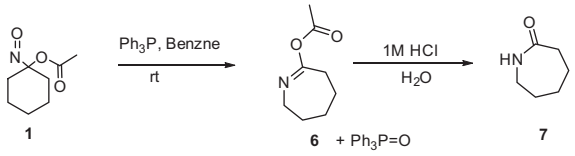


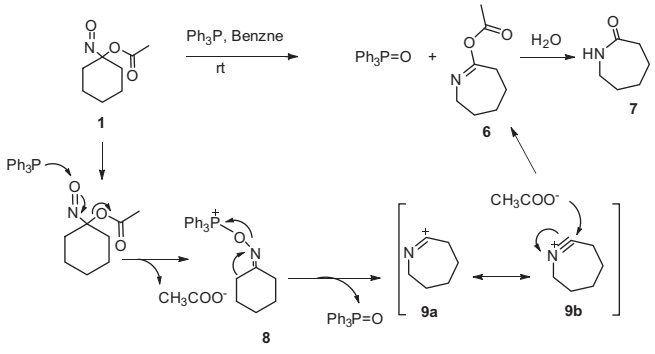
Figure 1. X-ray crystallography data for hydroxamic acids **3c** and **3e**.



Scheme 3. Reaction of 1-nitrosocyclohexyl acetate (**1**) with TPP.

Table 2
Kinetics of the reaction of compound **1** with TPP in benzene

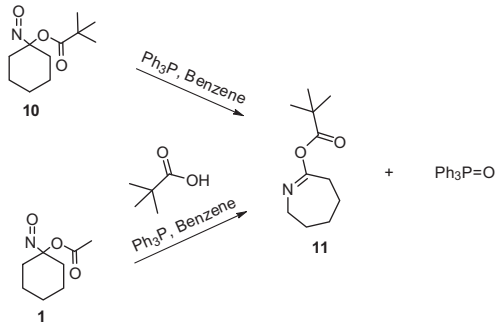
Entry	Compound	TPP (equiv)	Observed rate constant (k_{obs}, min^{-1})	$t_{1/2}$ (min)
1	**1**	1	0.09	8
2	**1**	2	0.18	3.7
3	**1**	5	0.5	1.4
4	**1**	10	3.5	0.2



Scheme 4. Proposed mechanism for the reaction of 1-nitrosocyclohexyl acetate (**1**) with TPP.

Scheme 4 shows the proposed mechanism for the conversion of **1** to caprolactam upon reaction with triphenyl phosphine.

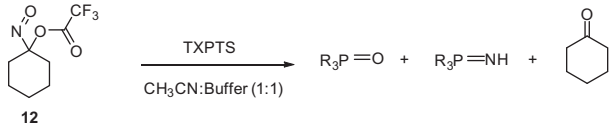
Addition of the phosphine to the nitroso oxygen atom with simultaneous loss of the acetate group would yield the electrophilic phosphonium ion adduct (**8**, Scheme 4). Beckman rearrangement of this phosphonium ion results in ring expansion to **9** with the formation of triphenyl phosphine oxide (Scheme 4). Addition of acetate to **9** gives **6** and hydrolysis produces caprolactam (**7**, Scheme 4). Such a mechanism finds direct precedence in a similar ring expansion during the reaction of 1-chloro-1-nitrosocyclohexane during its reaction with triphenyl phosphine.[28]



Scheme 5. Reaction of NCA and NCP with TPP.

Treatment of 1-nitrosocyclohexyl pivalate (**10**) with TPP in benzene also gives triphenyl phosphine oxide and the corresponding pivalate ester (**11**, Scheme 5). ^{1}H and ^{13}C NMR spectroscopy both confirm the structure of **11**. Further support of Scheme 4 as a plausible rearrangement mechanism comes from the treatment of **1** with triphenyl phosphine in the presence of excess pivalic acid, which also yields **11** suggesting the trapping of **9** by the free carboxylic acid.

Addition of 1-nitroscyclohexyl trifluoroacetate (**12**, Scheme 6), an acyloxy nitroso compound that rapidly hydrolyzes to HNO ($t_{1/2}$ = 121 ms),[5] to a solution of TXPTS (tris(2,4-dimethyl-5-sulfophenyl)phosphine trisodium salt) in 1:1 acetonitrile/Tris buffer (0.1 M, pH 7.6) gives the corresponding phosphine oxide and aza-ylide. GC–MS analysis also reveals the formation of cyclohexanone from the reaction that further supports hydrolysis of **12** to HNO. These results suggest that **12** rapidly hydrolyzes to HNO, which is trapped as the aza-ylide by TXPTS as previously described.[26]



Scheme 6. Reaction of **12** with TXPTS in 1:1 acetonitrile/Tris buffer (0.1 M, pH 7.6).

Overall, these results show that acyloxy nitroso compounds directly react with phosphines to yield ring expanded products unless they first hydrolyze to HNO, which then reacts with the phosphine to give the expected products.

Conclusion

In summary, this work shows that acyloxy nitroso compounds undergo two separate ring expansion reactions. First, acyloxy nitroso compounds-derived from four and five membered ring ketones hydrolyze under basic conditions to give the cyclic hydroxamic acid in 12–81% yield. Reactions of acyloxy nitroso compounds derived from substituted cyclopentanones provide ring expanded products where the –NOH group regioselectively inserts to the more substituted position. These reactions show better yields than an earlier Letter of these products obtained by basic treatment of Piloty's acid.[21] Secondly, we also provide the first Letter of the reaction of acyloxy nitroso compounds with phosphines to yield Beckmann-type rearrangement products. Acyloxy nitroso compounds that rapidly hydrolyze to HNO do not directly react with the phosphine but instead the phosphine traps the nascent HNO to give a unique aza-ylide product. This work shows further versatility of acyloxy nitroso compounds, which are easily accessible from the corresponding oxime and thus ketone, to provide relatively complex products through simple transformations.

Author contributions

The manuscript was written through contributions of all authors. M.B.H., R.M., R.B., and M.E.S. performed all the experiments. S.B.K. and O.M.A. wrote and edited the manuscript. All authors have given approval to the final version of the manuscript.

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Supplementary data

Supplementary data (experimental details of the synthetic procedures and characterization data for all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.002.

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