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A Novel, General Method for the Synthesis of Nitrile Oxides: Dehydration of *O*-Silylated Hydroxamic Acids

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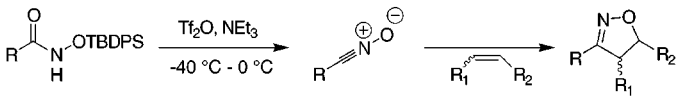
ABSTRACT



***O*-Silylated hydroxamic acids serve as stable, readily accessible, crystalline precursors to nitrile oxides when treated with trifluoromethanesulfonic anhydride and triethylamine. Under these mild conditions in the presence of olefins *O*-silylated hydroxamic acids afford isoxazoline cycloadducts. This procedure represents a novel, general method for the one-step generation of nitrile oxides, which complements existing protocols.**

The [3 + 2] dipolar cycloaddition reaction of olefins and nitrile oxides to give isoxazolines has long been valued as an important transformation for chemical synthesis. These heterocyclic products are not only themselves of interest but are also valuable because they may be readily elaborated to a variety of highly functionalized compounds.[1] Thus, for example, as elegantly exemplified by the recent synthesis of amphotericin,[2] the isoxazoline adducts of a nitrile oxide/olefin cycloaddition reaction can be utilized as masked β-hydroxy carbonyl aldolate equivalents. We have previously reported the dipolar cycloaddition of Me_3SiCHN_2 with chiral acrylates to give optically active pyrazolines, which in turn serve as useful starting materials for the rapid assembly of building blocks for asymmetric synthesis.[3] In our continuing interest in this area, we have sought to develop new methods for the generation and elaboration of similarly functionalized heterocycles. In this regard, although nitrile oxides represent a highly valuable class of dipoles for dipolar cycloaddition reactions, methods for their in situ generation are limited. Thus, there has been interest in the discovery and development of alternative methods for their formation from stable, readily accessible precursors.[4] In this letter, we now report the use of *O*-*tert*-butyldiphenylsilyl hydroxamates as stable, crystalline precursors to nitrile oxides, which in the presence of triflic anhydride and base (Tf_2O, Et_3N, 0 °C, CH_2Cl_2) lead to the formation of nitrile oxides that participate in dipolar cycloaddition reactions with olefins.

There are currently two well-established, widely used methods for the in situ formation of nitrile oxides. The most common approach, base-induced elimination of HCl from hydroximinoyl chlorides, has seen numerous applications in a vast range of cycloadditions.[5] The requisite hydroximinoyl chlorides are prepared from the corresponding oxime, derived from an aldehyde, and an electrophilic chlorine source (NCS, NaOCl, Cl_2). This method is not amenable, however, for substrates highly sensitive to oxidation or halogenation, including electron-rich aromatics, olefins, and sulfides.[6] The second approach, known as the Mukaiyama method, involves the dehydration of nitroalkanes by the action of phenyl isocyanate, DCC, or similar reagents in the presence of base.[7]

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(4) For examples, see: (a) Curran, D. P.; Fenk, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 5310. (b) Nishiwaki, N.; Uehara, T.; Asaka, N.; Tohda, Y.; Ariga, M.; Kanemasa, S. *Tetrahedron Lett.* **1998**, *39*, 4851.

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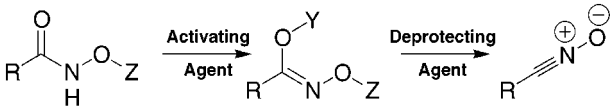
This procedure has been widely utilized and is limited only by the occasional difficulty in obtaining the necessary nitro precursors. Moreover, as a functional group nitroalkanes can display relatively high reactivity toward commonly employed organic and inorganic reagents in a multistep synthesis.

In principle, in the presence of an activating agent, suitably *O*-substituted hydroxamic acids should be amenable to a dehydration reaction to yield the corresponding nitrile oxides (Scheme 1). Surprisingly, this sequence has not been

Scheme 1. Conversion of Hydroxamates to Nitrile Oxides

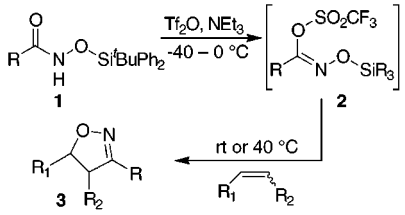


previously exploited for the preparation of nitrile oxides.[8] Likely precluding its development is the tendency of hydroxamates to form isocynates, via the Lossen rearrangement, under the conditions that would be required for their dehydration.[9] We speculated, however, that proper selection of the hydroxamate protecting group (Z) and activating agent (Y) would lead to cleavage of the C−O bond, via dehydration, in preference to the N−O bond (Lossen rearrangement).

In preliminary studies, treatment of *O*-protected benzhydroxamic acids (Scheme 1, Z = SiR_3, Boc, or ^{t}Bu) with acylating or sulfonylating reagents (MsCl, Tf_2O, perfluorobutanesulfonyl fluoride, oxalyl chloride) occurred predominantly at the carbonyl oxygen, as expected from the literature precedent with amides and *O*-alkyl hydroxamates.[10] Treatment of these intermediates with various deprotection reagents (TBAT ($[Bu_4N]Ph_3SiF_2$), pyridinium acetate, NEt_3, Hünig's base) resulted in either formation of a nitrile oxide, as detected by trapping with norbornene, or decomposition. The *O*-Boc and *O*-*tert*-butyl derivatives gave primarily the products of Lossen rearrangement; however, *O*-silyl derivatives proved successful. In particular, the *O*-*tert*-butyldiphenylsilylated hydroxamate was identified as optimal in terms of ease of preparation, reactivity, stability of the precursor, and crystallinity. In contrast, the *O*-$SiMe_3$ and *O*-Si^{t}BuMe$_2$ hydroxamates proved too labile for general use.

In comparison to procedures employing other activating agents such as mesic anhydride, the use of triflic anhydride offers distinct advantages. Thus, when triflic anhydride was employed in the activation step we noted that use of a desilylation agent was unnecessary for nitrile oxide formation (Scheme 2). This observation led to the development of an

Scheme 2. Conversion of Silyl Hydroxamates to Nitrile Oxides



experimentally straightforward procedure for the generation of nitrile oxides: treatment of the *O*-Si^{t}BuPh$_2$-protected hydroxamate with 1.1 equiv of triflic anhydride in the presence of 3 equiv of triethylamine at −40 °C, followed by warming to room temperature.

As shown in Table 1, the use of *O*-Si^{t}BuPh$_2$-protected hydroxamates as precursors permits the preparation of a wide range of nitrile oxides. In particular, aromatic (entries 1−3), unsaturated (entry 4), and saturated hydroxamates (entries 5 and 6) all participated in the dipolar cycloaddition reaction with the range of alkenes representative of those normally employed.

Intramolecular nitrile oxides cycloadditions are also readily achieved with this method.[11] The cycloadduct yields are comparable to those previously reported employing existing, complementary methods.

Although the requisite hydroxamates may be prepared simply by the silylation of the corresponding hydroxamic acid (NaH, ClSi^{t}BuPh$_2$),[12] they are also conveniently synthesized by the coupling of carboxylic acids and *O*-Si^{t}BuPh$_2$ hydroxylamine, a stable, crystalline, and easily prepared reagent.[13] In contrast to chlorinated aldoxamines and some nitroalkanes, we have found these precursors amenable to a number of synthetic transformations and common chromatographic techniques, while still allowing for a single step generation of the nitrile oxide.

The following reaction of *O*-*tert*-butyldiphenylsilyl benhydroxamate with norbornene is representative for the conversion of hydroxamates to nitrile oxides and their susequent cycloaddition with alkenes. To a stirred solution of *O*-Si^{t}BuPh$_2$ benzhydoxamate (50 mg, 0.13 mmol, 1.0 equiv) and NEt_3 (540 uL, 0.39 mmol, 3.0 equiv) in 2.0 mL of CH_2Cl_2 at −40 °C was added triflic anhydride (0.63 M solution in CH_2Cl_2, 0.24 mL, 0.15 mmol, 1.1 equiv)

(8) (a) To our knowledge, there has been only one report of a similar transformation, namely, the thermolysis of 1,3,2,4-dioxathiazole 2-oxides to give apparent generation of nitrile oxides, albeit with competing isocyanate formation. In contrast, cyclic hydroxamate esters give exclusively isocynates via Lossen rearrangement; see: Frantz, J. E.; Pearl, H. K. *J. Org. Chem.* **1975**, *41*, 1296. (b) *O*-Trimethylsilyl hydroximinoyl chlorides have been used to prepare nitrile oxides. However, the necessary intermediates must be prepared from nitrile oxides themselves, and the method is therefore not, in itself, a preparative method for nitrile oxides. Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1983**, *48*, 2780.

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(11) In preliminary work, we have documented that **3a**, 6-dihydro-3*H*-cyclopenta[*c*]isoxazoline can be prepared by intramolecular nitrile oxide cycloaddition reaction of the corresponding silylated hydroxamic acid. This result along with an accompanying study of intramolecular cycloadditions utilizing the method described herein is part of ongoing investigations in our group and will be reported as results become available.

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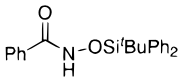
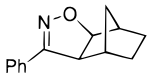
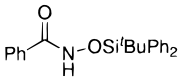
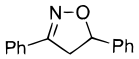
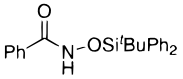
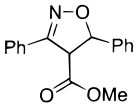
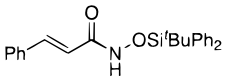
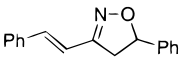
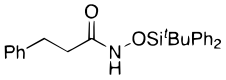
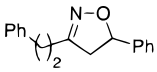
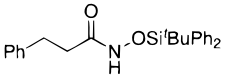
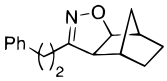
Table 1. Dipolar Cycloaddition Reactions of Alkenes and Nitrile Oxides Generated from *O*-Si^{t}BuPh$_2$Si Hydroxamates[a]

Entry	Hydroxamate	Alkene	Cycloadduct	Cmpd	Time	Yield
1		A[b]		**3a**	5 h	85 %
2		B		**3b**	5 h	88 %
3		C		**3c**	5 h	60 %
4		B		**3d**	10 h	55 %
5		B		**3e**	15 h	62 %
6		A		**3f**	15 h	54 %

[a] Conditions: Tf_2O, NEt_3, CH_2Cl_2, −40 to 0 °C, then olefin, rt or 40 °C. [b] **A** = norbornene, **B** = styrene, **C** = methyl cinnamate.

dropwise. After the addition was complete, the solution was allowed to warm to 0 °C for 1 h before norbenene (0.025 g, 0.27 mmol, 2.0 equiv) was added. The reaction was warmed to room temperature and stirred for 5 h. Aqueous workup and purification by flash chromatography (silica gel, hexane/EtOAc 20:1) provided the isoxazoline **3a** as a white solid (24 mg, 86% yield). This material was identical spectroscopically (^{1}H and ^{13}C NMR) and by melting point (mp 99−100 °C) to an authentic sample prepared as previously described.[14]

In summary, we have found *O*-Si^{t}BuPh$_2$-protected hydroxamates to be stable, readily accessible precursors to nitrile oxides, which in a single step under mild conditions lead to cycloadducts.

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Supporting Information Available: Full characterization and experimental procedures for the synthesis of the silylated hydroxaminates. This material is available free of charge via the Internet at http://pubs.acs.org.

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