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Versatile New Reagent for Nitrosation under Mild Conditions

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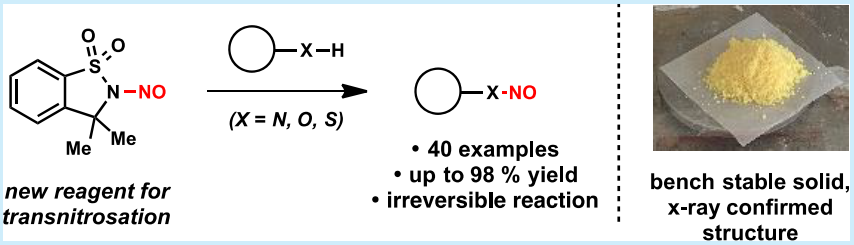

ABSTRACT: Here we report a new chemical reagent for transnitrosation under mild experimental conditions. This new reagent is stable to air and moisture across a broad range of temperatures and is effective for transnitrosation in multiple solvents. Compared with traditional nitrosation methods, our reagent shows high functional group tolerance for substrates that are susceptible to oxidation or reversible transnitrosation. Several challenging nitroso compounds are accessed here for the first time, including ^{15}N isotopologues. X-ray data confirm that two rotational isomers of the reagent are configurationally stable at room temperature, although only one isomer is effective for transnitrosation. Computational analysis describes the energetics of rotamer interconversion, including interesting geometry-dependent hybridization effects.

Nitric oxide (NO) is a small molecule of extreme biological importance. It has been implicated in a range of biological processes including vasodilation,[1] immune regulation,[2] neurotransmission,[3] and the inhibition of platelet aggregation.[4] Because NO is a gaseous molecule with low water solubility, medicinal applications targeting NO pathways predominately involve organic molecules capable of generating NO *in situ* via direct bond cleavage, enzymatic processes, or both.[1b,5] As shown in Figure 1, several small molecules possessing heteroatom–NO or $-NO_2$ bonds are effective NO donors used to treat multiple medical conditions. Whereas alkyl nitrites and nitrates are most often used as vasodilators, several *N*-nitroso compounds are potent DNA alkylators that effectively halt tumor growth in certain cancers.[6] Interestingly, whereas the *N*-nitrosourea lomustine has been used to treat brain tumors and Hodgkin's lymphoma,[7] the structurally similar semustine has been removed from the market and is rated as a Group I carcinogen by the IARC.[8] This dramatic difference from just a single remote methyl group suggests a sensitive structure–activity relationship for *N*-nitrosoureas acting as chemotherapeutics. In addition, *N*-nitrosoamines are valuable synthetic intermediates but are also found as potentially toxic contaminants throughout our environment that require detection and remediation.[9] The ability to easily access a variety of structurally diverse nitroso compounds is critical to both fully exploiting potential synthetic and medicinal benefits and developing tools to address toxicity concerns that affect public health.

Traditional methods for nitrosation have involved the use of inorganic nitrites, such as $NaNO_2$, under strongly acidic conditions to generate electrophilic sources of NO.[10] These methods can be effective for the nitrosation of amides, secondary amines, and certain alcohols but lead to rapid diazotization when reacting with primary amines.[11] In addition, $NaNO_2$ decomposes under basic conditions, and the requirement for nitrosation at low pH limits the scope of substrates that can effectively participate. Because of this observed limitation, recent synthetic efforts have shifted to using the commercially available *tert*-butyl nitrite (TBN) as an electrophilic transnitrosation reagent.[12] Unlike inorganic nitrites, TBN does not require strong acidic conditions for transnitrosation, although some nucleophiles require excess TBN to minimize reversible transnitrosation with *tert*-butanol.[13] TBN has been effective for nitrosating amides, secondary amines, and certain alcohols but is known to oxidize primary alcohols under atmospheric conditions.[14,15] Because TBN has been known to undergo both homolytic thermolysis and air-mediated oxidation at room temperature, cryogenic storage under an inert atmosphere is required. As detailed later, we have developed a new organic reagent that serves as an attractive alternative to TBN for the transnitrosation of nucleophiles under mild conditions. *N*-Nitrososulfonamide

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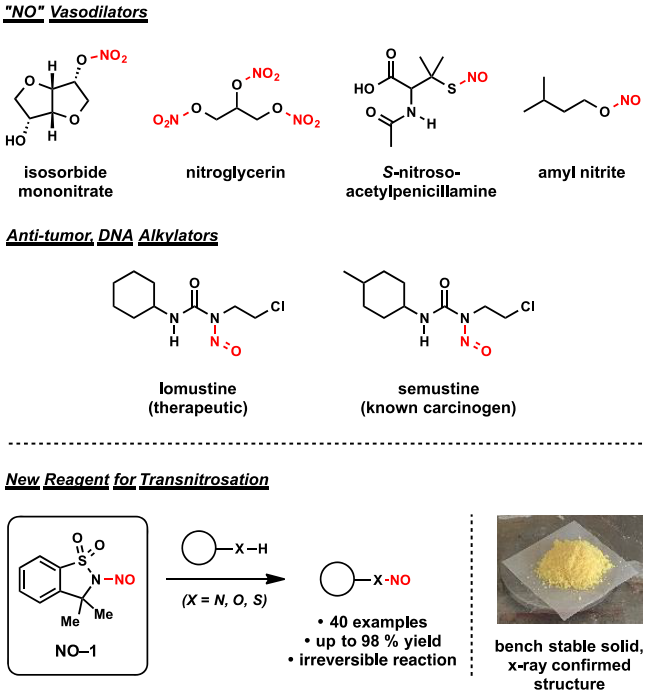

Figure 1. Biologically active "NO" molecules (top), and a new bench-stable reagent for transnitrosation (bottom).

reagent, **NO−1**, is a an easily synthesized crystalline material that maintains long-term integrity under ambient storage conditions (Figure 1).[16] Upon irreversible transnitrosation with a variety of nucleophiles, the sulfonamide byproduct of **NO−1** is easily recovered to regenerate **NO−1** with high fidelity. Alkyl alcohols, amines, amides, ureas, and thiols are all effectively irreversibly nitrosated by **NO−1** under mild conditions, resulting in several nitroso compounds that are reported here for the first time.

Our interest in transnitrosation came from our work on C−H functionalizations involving radical hydrogen atom abstractions. On the basis of work from our lab and others, the diazobicyclo radical cation produced via the single-electron reduction of Selectfluor has been shown to be an effective C−H abstractor.[17] We sought to explore alternative sources of N-centered radicals for C−H abstraction, and became interested in nitrosoamines and nitrosoamides as potential radical precursors. A large body of work by Chow involves the generation of N-centered radicals via the light-mediated cleavage of N−NO bonds.[18] Several N-centered radicals derived from simple cyclic nitrosoamides were capable of C−H abstraction in our hands but with limited synthetic efficiency. In an effort to generate more electron-deficient N-centered radicals, we explored *N*-nitrososulfonamides as radical precursors. de Boer had previously shown sulfonamidyl radicals capable of abstracting hydrogens from solvent under thermal conditions, and recent reports describe related intramolecular and intermolecular hydrogen-atom abstractions.[19]

During the course of our studies, we found limited success for intermolecular C−H abstraction using *N*-nitrososulfonamides as radical precursors but found them to be effective transnitrosating reagents. Although this type of reactivity has been reported, a well known limitation of *N*-nitrososulfonamides as transnitrosating reagents is their propensity for thermal decomposition.[20] In fact, *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) is a well-known commercial reagent that requires only mild heating under basic conditions to generate an equivalent of diazomethane. Several Diazald analogues were explored as alternatives but were found to be thermally unstable under ambient conditions (Figure 2). In an

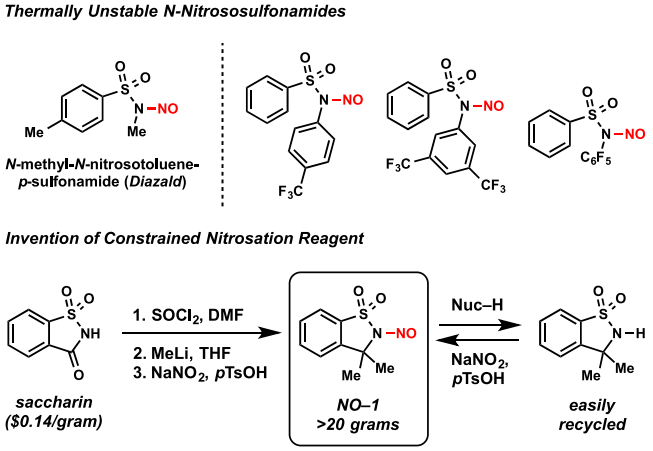

Figure 2. *N*-nitrososulfonamides prone to thermal decomposition (top) and the invention of geometrically constrained **NO−1** (bottom).

effort to overcome this limitation, we sought to develop a class of geometrically constrained *N*-nitrososulfonamides that resisted thermal degradation. Beginning with the artificial sweetener saccharin as a starting material, a series of straightforward transformations yield **NO−1** in high yield. This synthetic sequence is amenable to scaling with no appreciable loss in efficiency. (See the Supporting Information (SI) for details.) In our hands, **NO−1** has been shown to be indefinitely bench-stable under ambient conditions with no significant decrease in activity upon standing for several months. Upon successful transnitrosation, the sulfonamide byproduct can be recovered to regenerate **NO−1** in a one-step synthesis. With the new reagent in hand, we explored the scope of nucleophiles that efficiently transnitrosate with **NO−1**.

Cyclic and acyclic amines are effectively nitrosated by **NO−1** (Scheme 1, entries **1**−**5**). Free alcohols are tolerated (**6**), although it is likely that transnitrosation initially occurs at oxygen prior to intramolecular transnitrosation to the amine. Carboxylic acids are well tolerated, allowing for the direct nitrosation of amino acids (entries **7**−**10**). Finally, cyclic amides are efficiently nitrosated in high yields (entries **11**−**14**). To the best of our knowledge nitroso compounds **9**, **11**, and **13** are reported here for the first time.

Although reagent **NO−1** is effective for the synthesis of nitrosoamines and nitrosoamides, many of the structures shown in Scheme 1 may be directly accessed by reaction with TBN. Conversely, alkyl alcohols often require excess TBN to promote transnitrosation or suffer from unwanted oxidation under ambient conditions. Scheme 2 shows that **NO−1** efficiently nitrosates a variety of alcohol structures. Primary (**15**−**25**), secondary (**26**−**33**), and tertiary (**34** and **35**) alcohols are all effectively nitrosated in good to excellent yields. Activated benzylic or allylic alcohols are not susceptible to oxidation, although no effort is made to exclude oxygen from solvents or reaction flasks. In addition, **NO−1** tolerates elevated temperature in the presence of alkynes (**21**) and alkenes (**20**, **23**−**25**, **31**, **32**, and **34**) without evidence of byproducts resulting from homolytic N−N cleavage of **NO−1**.

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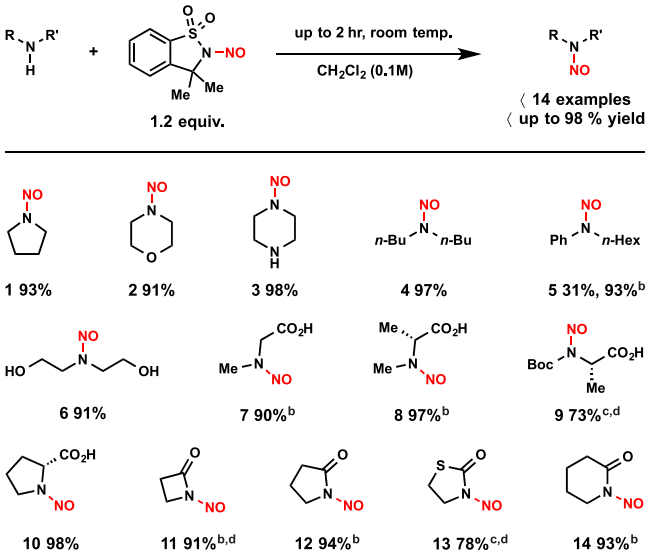
Scheme 1. Amine and Amide Nitrosation with NO−1[a]



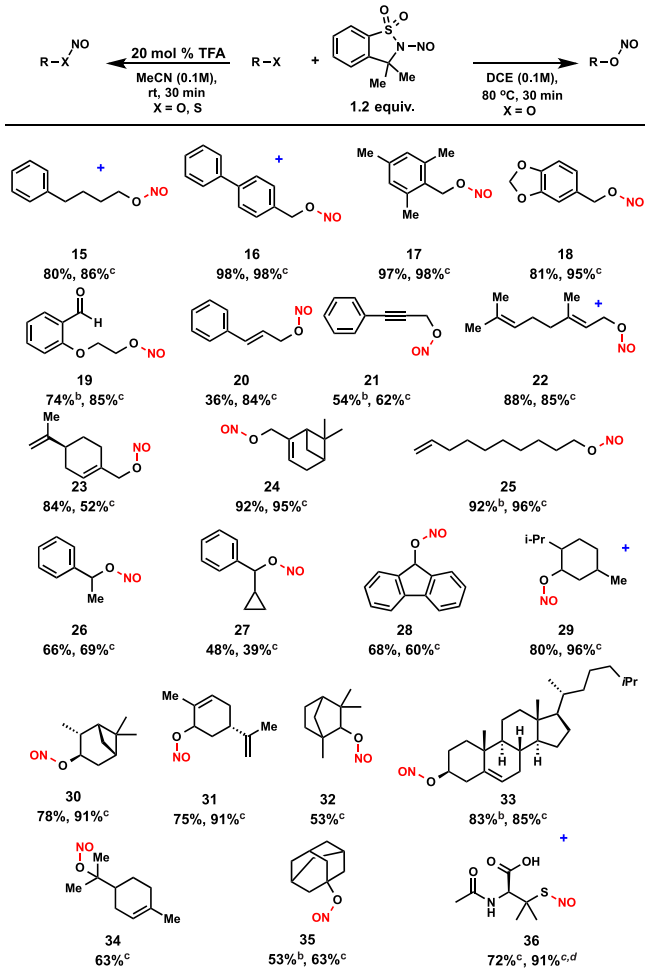
[a]General reaction conditions: Amine/amide (0.2 mmol) and **NO−1** (0.24 mmol) in 2 mL of CH_2Cl stirred at room temperature. Yields refer to chromatographically pure material. [b]Reaction was heated to 80 °C in 1,2-dichloroethane. [c]Reaction was run at room temperature in CH_3CN with trifluoroacetic acid added (0.04 mmol). [d]First known report of structure.

N-Acetylpenicillamine is also successfully nitrosated to produce *S*-nitroso-*N*-acetylpenicillamine (**36**), a molecule implicated in signaling pathways associated with vasodilation.[21,22] For substrates that do not tolerate elevated temperatures, an alternative experimental procedure involving catalytic trifluoroacetic acid is generally effective. Isolated yields for both procedures are given for the majority of substrates shown in Scheme 2. In many cases, transnitrosation is effective in multiple organic solvents.

One of the strengths of our transnitrosation method is the ability to easily incorporate isotopically labeled ^{15}NO into target molecules. Because enriched $Na^{15}NO_2$ is commercially available, we produced **^{15}NO−1** to explore its efficacy in transnitrosation (Scheme 3). To our satisfaction, this reagent behaved analogously to **NO−1** with no loss of stability or reactivity. A secondary amine (**37**), alcohol (**38**), and thiol (**39**) were all successfully nitrosated in high yields to produce enriched materials.

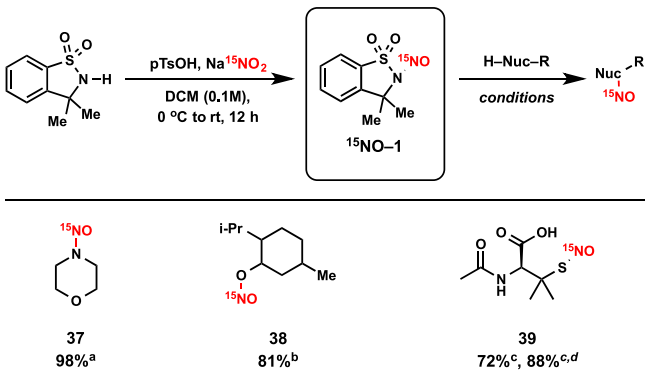
Although the efficiency of transnitrosation with **NO−1** is established, early efforts were plagued by batch-to-batch variability and irreproducible yields under certain conditions. A comparison of crystallographic data from multiple synthetic batches of **NO−1** suggested that the rotational configuration of the nitroso group affected the efficiency of transnitrosation. Data from a batch of **NO−1** that produced low yields for transnitrosation were especially informative (~35% conversion for **15**, Scheme 2). As shown in Figure 3, a poorly performing batch of **NO−1** exists as a mixture of stable rotational isomers centered around the N−N−O bond. Superimposed structures show that the molecular geometry is nearly identical throughout both isomers, beyond the orientation of the nitroso N−O bond. Interestingly, while ineffective at room temperature, this batch of **NO−1** was still capable of transnitrosation to produce **15** in high yields at an elevated temperature. This suggested either that both isomers were

Scheme 2. Alcohol Nitrosation with NO−1[a]



[a]General reaction conditions: Alcohol (0.2 mmol) and **NO−1** (0.24 mmol) in 2 mL 1,2-dichloroethane (DCE) stirred at 80 °C for 30 min. Yields refer to chromatographically pure material. [b]Reaction was run in CH_3CN at 80 °C. [c]Reaction was run at room temperature in CH_3CN with trifluoroacetic acid added (0.04 mmol). [d]NMR yield using 1,2,4,5-tetramethylbenzene as a standard.

Scheme 3. Nitrosation with ^{15}NO−1



[a]Reaction conditions: Nucleophile (0.2 mmol) and **^{15}NO−1** (0.24 mmol) in 2 mL of dichloromethane stirred at room temperature for 30 min. [b]1,2-Dichloroethane (DCE) stirred at 80 °C for 30 min. [c]CH_3CN with trifluoroacetic acid (0.04 mmol) at room temperature for 30 min. [d]NMR yield using 1,2,3,4,5-tetramethylbenzene as an internal standard.

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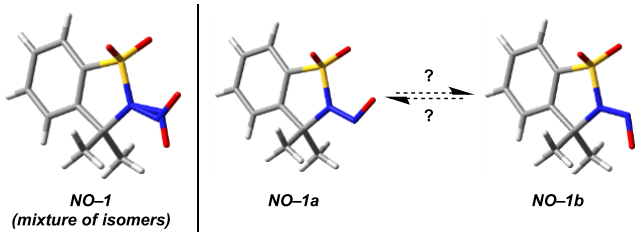

Figure 3. Crystallographic data for **NO−1** as a mixture of rotational isomers (left) and the individual structures (right) found within the crystal lattice.

sufficiently reactive at an elevated temperature or that thermally induced conversion to a single active rotamer was occurring.

To better understand the possibility of thermal interconversion between stable rotational isomers, we computed a potential energy scan of **NO−1** along the S−N−N−O dihedral angle (Figure 4, red data). Initial results confirmed that structure **NO−1a** was lower in energy than **NO−1b** by approximately −1.2 kcal/mol (0 and 180° dihedral angles, respectively). Interestingly, different rotational barriers were calculated rotating between 0 and 90° than from 180 to 360°. Discontinuities in the potential energy scan were also noted between 130 and 140° and 290 and 300°, which suggested a change in the ground-state electronic structure and warranted further investigation. Indeed, upon analyzing the geometries of **NO−1** at each data point along the potential energy scan, we noted geometry/hybridization changes of the nitrogen atom within the ring.

To further investigate this hybridization change along the scan coordinate, we computed two additional potential energy scans with geometric constraints that imposed either sp^2 or sp^3 hybridization at the nitrogen in the ring (Figure 4, green and blue data, respectively). As shown in Figure 4, the observed discontinuities in the initial scan (Figure 4, top panel) were confirmed to result from changes in electronic states. Specifically, the different electronic states correspond to different hybridizations, sp^2 and sp^3, of the nitrogen in the ring that are induced by geometric changes of **NO−1**. Overlap of the red data with either the blue or green curves indicates the hybridization of the energy-minimized structure at a particular dihedral angle. Lack of overlap, coinciding with discontinuities in the unrestricted data (red), indicates a geometry that does not fit neatly into the limiting definitions of sp^2 or sp^3 hybridization.

Experimental efforts confirmed that **NO−1a** is the active rotational isomer for transnitrosation at room temperature. Simply heating a crude mixture of **NO−1** to 80 °C as a final step in the synthesis yields a reagent that consistently transnitrosates at room temperature and a crystal structure consistent with **NO-1a**. Efforts to identify the source of disparate reactivity between **NO−1a** and **NO−1b** at room temperature are ongoing.

We have reported the invention of a new reagent for transnitrosation under mild conditions. This reagent requires no special handling for use or storage, nitrosates nucleophiles irreversibly, and is straightforward to regenerate from the byproducts of a successful reaction. High functional group tolerance and efficiency under a variety of reaction conditions make this an ideal reagent to explore nitrosated molecules that are challenging, or impossible, to make via traditional

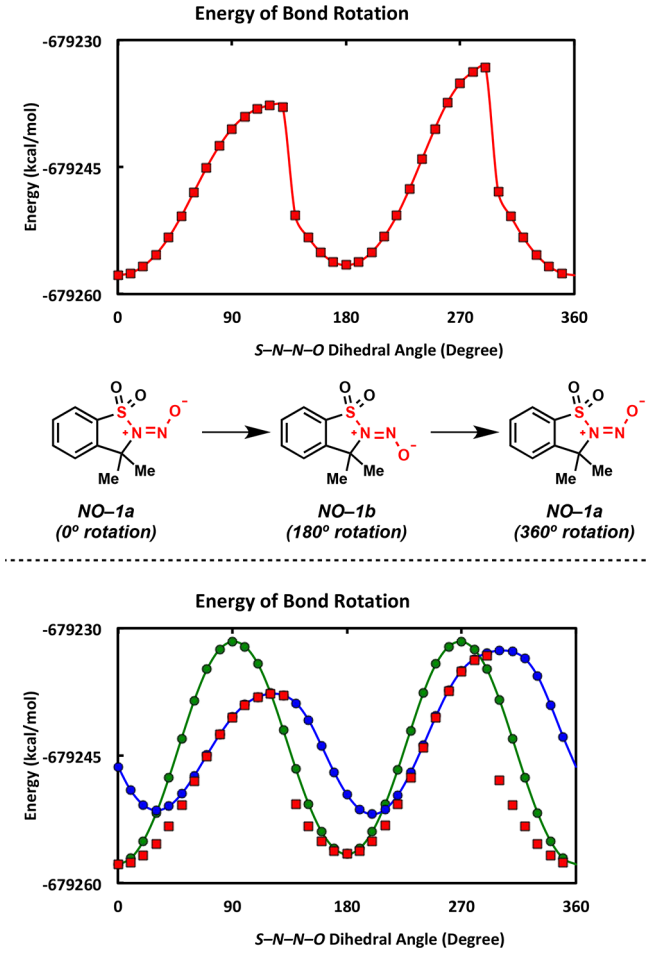

Figure 4. All calculations were run using the B3LYP/6-311+G(2d,p) model chemistry with MeCN using the polarizable continuum model for solvents. Top: Red data represent the potential energy scan of a S−N−N−O dihedral angle while the nitrogen in the ring is unconstrained. Representative rotational isomers **1a** and **1b** are the dominant species where indicated. Bottom: Green data represent a potential energy scan of a S−N−N−O dihedral angle while constraining the nitrogen in the ring to sp^2 hybridization. Blue data represent a potential energy scan of a S−N−N−O dihedral angle while constraining the nitrogen in the ring to sp^3 hybridization. Red data are shown overlaid for reference.

methods.[23] Two rotational isomers of **NO−1** are stable at room temperature, although theoretical and experimental data suggest a single isomer (**NO−1a**) is active for transnitrosation. Future work will involve further exploration of molecules that can be nitrosated by **NO−1** and identification of features that favor reaction from **NO−1a** at room temperature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00637.

Detailed experimental and computational procedures, full characterization, and copies of all spectra (PDF)

Accession Codes

CCDC 2067875−2067876 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by

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Notes

The authors declare no competing financial interest.

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(22) Other less substituted thiols produced *S*-nitrosothiols that decomposed under ambient conditions to yield disulfides.

(23) Several *N*-nitroso compounds are known carcinogens, and the toxicity profile for many of the products shown herein is not established. Care should be taken to avoid direct exposure to any heteroatom−nitroso compounds with unknown toxicity profiles.

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