JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Metal Nitrite: A Powerful Oxidizing Reagent

Mahiuddin Baidya and Hisashi Yamamoto*

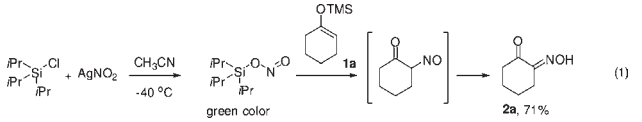
Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637, United States

Supporting Information

ABSTRACT: An efficient and simple source of nitroso reagents and their oxidation reactions are described. The combination of a Lewis acid and a metal nitrite was applied to the oxidation of silyl enol ethers. Amino acid and peptide derivatives were easily accessed through in situ C−C bond cleavage of fully substituted silyl enol ethers upon oxidation.

During the last three decades, new classes of nitroso compounds have emerged and found numerous applications in organic synthesis.[1−4] Since most of these compounds are toxic and explosive and require several steps to prepare, their scopes of application are limited. The development of new practical, safe sources of nitroso compounds for oxidation reactions remains a challenge.

The combination of metal nitrite and Lewis acid could be a convenient route: triisopropylsilylchloride (TIPSCl) was exposed to silver nitrite in acetonitrile to generate silyl nitrite (eq 1).[5] A pale-green color immediately appeared with the precipitation of silver chloride, clearly indicating the generation of the nitroso compound.[6a] Indeed, addition of silyl enol ether **1a** into the reaction mixture exclusively afforded keto oxime **2a** in 71% isolated yield.



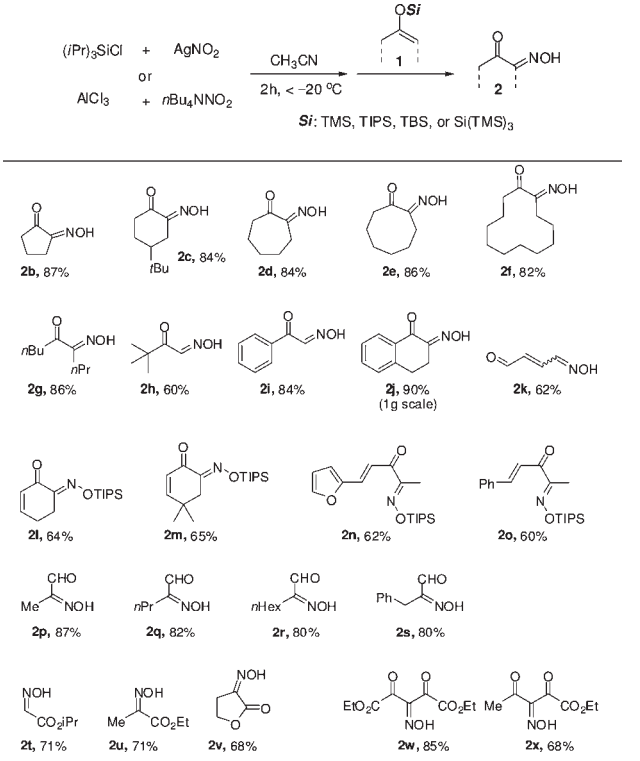
(1)

The reaction seemed to be general, and several Lewis acids could be used with silver nitrite: $TiCl_4$ (40%), $InCl_3$ (41%), $FeCl_3$ (47%), and $AlCl_3$ (45%). Furthermore, other commercially available nitrite salts, including $NaNO_2$/15-crown-5 (74%) and nBu_4NNO_2 (60%), could also be employed. Thus, this route appears to be a simple, easily accessible, and relatively safe source of nitroso reagents.[6b]

The oxygen bridge between the Lewis acid (LA) and the nitroso moiety (LA−O−NO) plays a crucial role. The activation of the oxophilic Lewis acid overcompensates for the resonance stabilization of the nitroso moiety.

Experiments that probed the scope of this process under the optimized conditions are summarized in Chart 1. A broad spectrum of silyl enol ethers, both cyclic and acyclic, were employed to afford the desired products in good to excellent yields. Generally, (*E*)-oximes were observed, except for the seven- and eight-membered rings (**2d** and **2e**). The scaleup was also compatible: the reaction of the silyl enol ether derived from α-tetralone was performed on a gram scale, and the desired product was isolated in 90% yield (**2j**). Oxidation proceeded smoothly with silyl dienol ether to generate the 1,4-adduct (**2k**) exclusively. When triisopropyl silyl enol ethers were used, the desired oximes were TIPS-protected upon isolation (**2l**−**o**). Acid-sensitive heterocyclic furan substitution was also tolerated (**2n**).

Chart 1. Oxidation of Silyl Enol Ethers with Metal Nitrites[a−d]



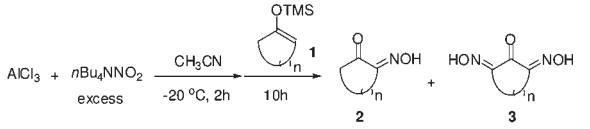
[a]*Si* = TMS for **2b**−**k**, **2u**, and **2v**; TIPS for **2l**−**o**; TBS for **2t**; and $Si(TMS)_3$ for **2p**−**s** [(*Z*)-silyl enol ethers were used]. [b] Instead of silyl enol ethers, sodium enolates were used for **2w** and **2x**. [c]Isolated yields are reported. [d]DMF was used as the solvent for **2l**−**o**.

While the reactions of silyl nitrite with aldehyde-derived silyl enol ethers were sluggish under the optimized conditions, oxidation with aluminum nitrite proceeded cleanly, and α-hydroxyimino aldehydes **2p**−**s** were obtained in high yields. In contrast, conventional procedures for preparing these compounds require multistep transformations. Exposure of silyl ketene acetals to the sodium enolates of active methylene derivatives furnished the desired products in good yields (**2t**−**x**).

Received: July 19, 2011
Published: August 10, 2011

dx.doi.org/10.1021/ja206736q | *J. Am. Chem. Soc.* 2011, 133, 13880–13882

Chart 2. Double Oxidation of Silyl Enol Ethers 1



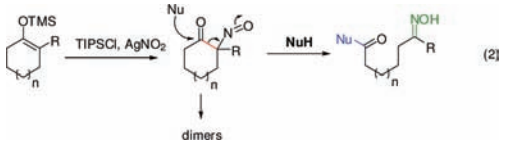
Entry	1	n	2, % yields [a]	3, % yields [a]
1	**1a**	3	**2a** [b]	**3a**, 83
2	**1b**	2	**2b** [b]	**3b**, 81
3	**1d**	4	**2d** [b]	**3d**, 83
4	**1e**	5	**2e**, 41	**3e**, 46
5	**1f**	9	**2f**, 67	**3f** [b]
6	**1g**		**2g**, 40	**3g**, 30

[a]Isolated yields. [b]Not observed.

When excess aluminum nitrite derived from $AlCl_3$ and $(nBu)_4NNO_2$ was used, the silyl enol ethers **1** produced the doubly oxidized products **3** as the major products (Chart 2). On the other hand, mixtures of **2** and **3** were isolated for **1e** and **1g** (entries 4 and 6). The **2**/**3** ratio did not change even when the reaction time was prolonged. Surprisingly, no double oxidation product was observed for 12-membered ring **1f** (entry 5).

On the basis of these observations, a possible path for the formation of **3** is depicted in Scheme 1. After the first monooxidation, oxime **2** complexes with the Lewis acid, which induces further enolization of the ketone. The enol thus obtained is further oxidized to generate dioxime **3**. We hypothesize that a syn alignment of the C═O and C═N bonds in **2** is required for double coordination with the aluminum ion. Such a preferred alignment, which was observed in the crystal structure of **2b** (five-membered ring **A** in Scheme 1), induced the enolization process required for further oxidation. In contrast, the anti alignment of the C═O and C═N bonds of the 12-membered ring **2f** (**B** in Scheme 1) impedes the required coordination with aluminum, and thus, no further oxidation proceeds. A mixed situation can be considered for the formation of mixtures of **2** and **3** from eight-membered-ring and acyclic silyl enol ethers (**1e** and **1g**, respectively).

When fully substituted silyl enol ethers were used, clean formation of the nitroso derivative was observed (eq 2). However, the nitroso compound easily dimerized (for the crystal structure, see p S26 in the Supporting Information) and precipitated from the reaction mixture.



Gratifyingly, switching the solvent from CH_3CN to *N*,*N*-dimethylformamide (DMF) retarded the dimerization process significantly, and subsequent treatment with external nucleophiles caused the carbon−carbon bond cleavage reaction (eq 2).[7] Sodium methoxide produced the expected carbon−carbon bond cleavage products in high yields (**5a**−**c** in Chart 3). Amazingly, both primary and secondary amines could also efficiently cleave the C−C bond to render amides (**6a**−**l**). Importantly, free amino acid esters were also effective. L-Valine, L-alanine, and L-proline

Scheme 1. Plausible Mechanism for the Formation of 3

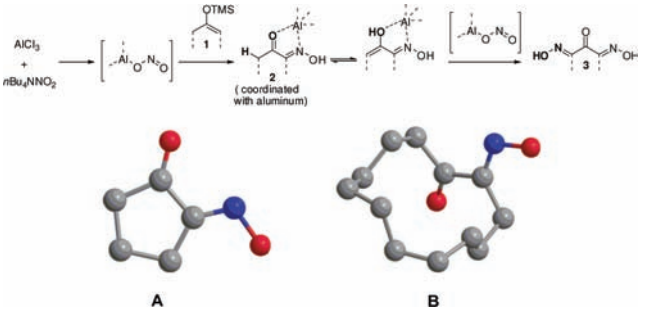
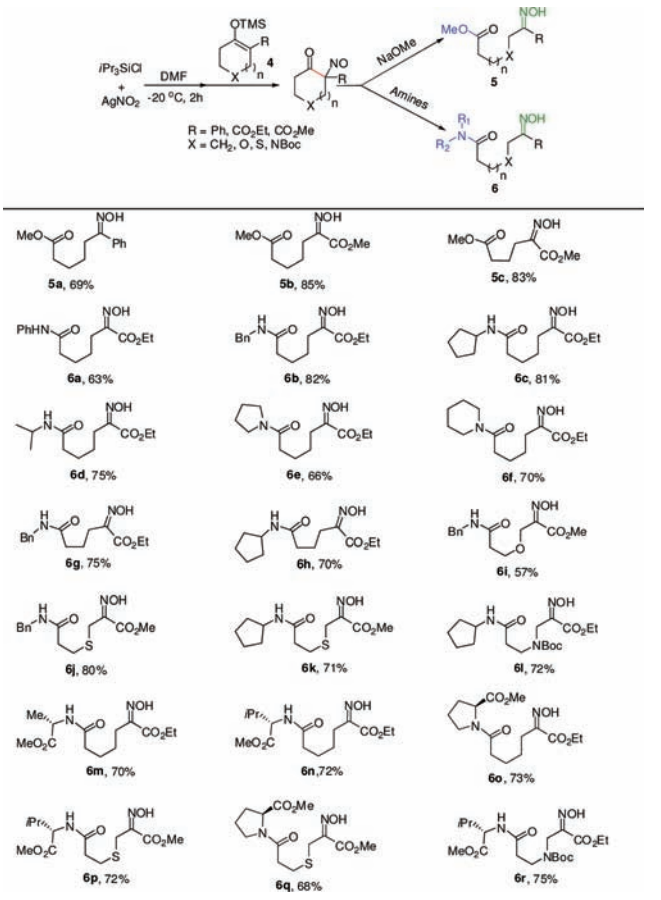


Chart 3. Oxidation of Quaternary Silyl Enol Ethers and One-Pot C−C Bond Cleavage Reactions[a]

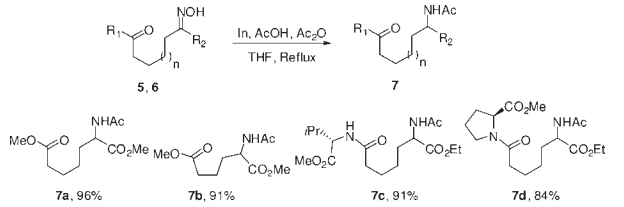


[a]Isolated yields are given.

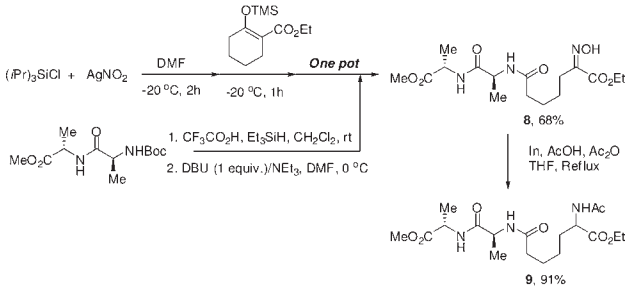
methyl esters gave the expected peptides in good yields (**6m**−**r**). Various derivatives containing heteroatoms such as oxygen, sulfur, and nitrogen were also effective for this cleavage process. It should be emphasized that secondary amines can also be reacted with high efficiency under very mild reaction conditions to generate tertiary amides, for which amide synthesis methods are relatively rare.

These substituted oximes **5** and **6** were chemoselectively reduced with indium metal to access protected amino acids and dipeptides **7** in excellent yields (Scheme 2).[8] The synthetic utility of this new oxidation/cleavage strategy was further verified

Scheme 2. Synthesis of Protected Amino Acids and Dipeptides by Indium-Mediated Reduction of Oximes



Scheme 3. Synthesis of a Protected Peptidoglycan Mimetic Peptide Analogue



by the short synthesis of a peptidoglycan mimetic peptide analogue.[9] Scheme 3 demonstrates the power of this process by the remarkably short synthesis of aminopimelyl-L-alanyl-L-alanine (**9**), a biologically important peptide analogue.

In conclusion, we have developed a new and flexible route to metal nitrite that is useful for α- and/or α,α′-oxidation of carbonyl compounds under very mild conditions. For α,α-disubstituted ketones, the resultant nitroso compounds can be smoothly cleaved by treatment with O- and N-nucleophiles to generate polyfunctional amides. This methodology can be used for the rapid synthesis of amino acid and peptide derivatives.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures, characterization data for prepared compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
yamamoto@uchicago.edu

■ ACKNOWLEDGMENT

We gratefully acknowledge NIH for a grant supporting this research (Asymmetric Oxidation: 2R01GM068433-05). We also thank Dr. Antoni Jurkiewicz, Dr. Ian Steele, and Dr. Jin Qin for sharing their expertise in NMR spectroscopy, X-ray crystallography, and mass spectrometry, respectively.

■ REFERENCES

(1) Reviews: (a) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1. (b) Iwasa, S.; Fakhruddin, A.; Nishiyama, H. *Mini-Rev. Org. Chem.* **2005**, *2*, 157. (c) Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5630.

(2) Cyanonitroso compounds: (a) Horsewood, P.; Kirby, G. W. *Chem. Commun.* **1971**, 1139. α-Halonitroso compounds:(b) Wichterle, O. *Collect. Czech. Chem. Commun.* **1947**, *12*, 292. (c) Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991. (d) Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M. *J. Am. Chem. Soc.* **1992**, *114*, 5900. (e) Zhang, D.; Suling, C.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 885. Vinyl nitroso compounds:(f) Faragher, R.; Gilchrist, T. L. *Chem. Commun.* **1976**, 581. (g) Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1283. Nitrosoimines:(h) Gilchrist, T. L.; Peek, M. E.; Rees, C. W. *Chem. Commun.* **1975**, 913. (i) Gilchrist, T. L.; Harris, C. J.; Hawkins, D. G.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2166. Nitrosoamidines:(j) Miller, C. A.; Batey, R. A. *Org. Lett.* **2004**, *6*, 699. *N*-Phosphinoylnitroso compounds:(k) Ware, R. W., Jr.; King, S. B. *J. Am. Chem. Soc.* **1999**, *121*, 6769. (l) Ware, R. W., Jr.; King, S. B. *J. Org. Chem.* **2000**, *65*, 8725. (m) Ware, R. W., Jr.; Day, C. S.; King, S. B. *J. Org. Chem.* **2002**, *67*, 6174. Nitroso formate esters:(n) Kirby, G. W.; McGuigan, H.; Mackinnon, J. W. M.; Mclean, D.; Sharma, R. P. *J. Chem. Soc., Perkin Trans 1* **1985**, 1437.

(3) Nitroso benzene and pyridylnitroso compounds: (a) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995. (b) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514. (c) Yamamoto, H.; Kawasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595. (d) Labaziewicz, H.; Lindfors, K. R.; Kejonen, T, H. *Heterocycles* **1989**, *29*, 2327.

(4) Applications in total synthesis: (a) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *J. Org. Chem.* **1998**, *63*, 8397. (b) Li, J.; Lang, F.; Ganem, B. *J. Org. Chem.* **1998**, *63*, 3403. (c) Faitg, T.; Soulié, J.; Lallemand, J.-Y.; Ricard, L. *Tetrahedron: Asymmetry* **1999**, *10*, 2165. (d) Blakemore, P. R.; Kim, S.-K.; White, J. D.; Yokochi, A. F. T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1831. (e) Ozawa, T.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 3338. (f) Li, F.; Brogan, J. B.; Gage, J. L.; Zhang, D.; Miller, M. J. *J. Org. Chem.* **2004**, *69*, 4538. Microreview:(g) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031.

(5) Weidenbruch, M.; Sabeit, F. *Z. Naturforsch.* **1976**, *31B*, 1212.

(6) (a) More intense color was observed for the reaction with Ph_3SiCl and $(EtO)_3SiCl$. (b) $(iPr)_3SiONO$ is not volatile. Its boiling point is 40.5−41.5 °C at 1.9 mbar (see ref 5), which is much higher than that of commonly used isobutyl nitrite (bp = 66 °C at atmospheric pressure).

(7) C−C bond cleavage reactions using nitrosobenzene and ketones: (a) Payetee, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 12276. (b) Delgado, A.; Garcia, J. M.; Mauleon, D.; Minguillon, C.; Subirats, J. R.; Feliz, M.; Lopez, F.; Velasco, D. *Can. J. Chem.* **1988**, *66*, 517. (c) Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, *1*, 27.

(8) (a) Harrison, J. R.; Moody, C. J.; Pitts, M. R. *Synlett* **2000**, 1601. (b) Pitts, M. R.; Harrison, J. R.; Moody, C. J.; Pitts, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955.

(9) (a) Anderson, J. W; Adediran, S. A.; Charlier, P.; Nguyen-Disteche, M.; Frere, J.-M.; Nicholas, R. A.; Pratt, R. F. *Biochem. J.* **2003**, *373*, 949. (b) Macheboeuf, P.; Contreras-Martel, C.; Job, V.; Dideberg, O.; Dessen, A. *FEMS Microbiol. Rev.* **2006**, *30*, 673. (c) Sauvage, E.; Duez, C.; Herman, R.; Kerff, F.; Petrella, S.; Anderson, J. W.; Adediran, S. A.; Pratt, R. F.; Frere, J.-M.; Charlier, P. *J. Mol. Biol.* **2007**, *371*, 528.