Metal Nitrite: A Powerful Oxidizing Reagent

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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 is 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 have found numerous applications in organic synthesis.[1-4] Since most of these compounds are toxic, explosive, and require several steps to prepare, their scopes of application are limited. The development of new practical and 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] Immediately, a pale green color appeared with the precipitation of silver chloride, which clearly indicates the generation of the nitroso compound.[6a] Indeed, addition of silyl enol ether **1a** into the reaction mixture exclusively resulted in the keto oxime **2a** in 71% isolated yield.
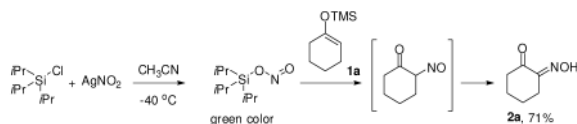
$$\tag{1}$$

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%). Further, other commercially available nitrite salts NaNO$_2$/15-crown-5 (74%) and nBu$_4$NNO$_2$ (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 nitroso moiety (*LA*-O-NO) plays a crucial role. The resonance stabilization of the nitroso moiety is overcompensated by the activation of oxophilic Lewis acid.

Experiments that probed the scope of this process under optimized conditions are summarized in Chart 1. A broad spectrum of silyl enol ethers, cyclic and acyclic, was

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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**,**e**). The scale-up was also compatible: the reaction of silyl enol ether derived from α-tetralone was performed on gram scale and the desired product was isolated in 90% yield (Chart 1, **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 isolated as TIPS-protected (**2l**–**o**). Acid sensitive heterocyclic furan substitution was also tolerated (**2n**).

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 the α-hydroxyimino aldehydes **2p**–**s** could be obtained in high yields. In contrast, conventional procedures to prepare these compounds require multistep transformations. Exposure of silyl ketene acetals and the sodium-enolates of active methylene derivatives furnished desired products in good yields (**2t**–**x**).

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 4,6). The ratio of **2/3** did not change even after the reaction times were prolonged. Surprisingly, no double oxidation product was observed for twelve-membered **1f** (entry 5).

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

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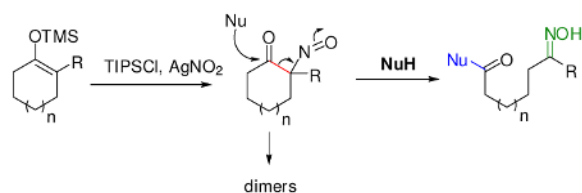
(2)

Gratifyingly, switching the solvent from CH_3CN to DMF retarded the dimerization process significantly and the successive treatment of external nucleophiles caused the carbon-carbon bond cleavage reaction (eq 2).[7] Sodium methoxide produced the expected carbon-carbon cleavage products in high yields (Chart 3, **5a**–**c**). Amazingly, both primary and secondary amines can also efficiently cleave the C-C bond to render amides (Chart 3, **6a**–**l**). Importantly, free amino acid esters are also effective. L-valine, L-alanine, and L-proline methyl esters gave the expected peptides in good yields (**6m**–**r**). Various hetero atoms such as oxygen, sulfur, and nitrogen-containing derivatives 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 the amide synthesis methods are relatively rare.

These substituted oximes **5**,**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 by short synthesis of the peptidoglycan mimetic peptide analogue.[9] Scheme 3 demonstrates the power of this process by the remarkably short step 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 which 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 smoothly cleaved under O- and N-nucleophiles to generate polyfunctional amides. This methodology can be used for the rapid synthesis of amino acid and peptide derivatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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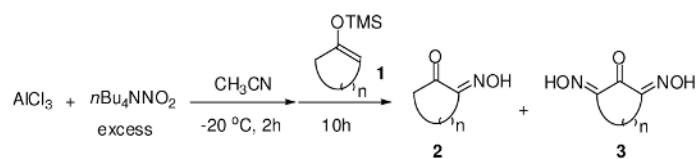
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(6). (a) More intense color was observed for the reaction with Ph_3SiCl and $(EtO)_3SiCl$. (b) $(iPr)_3SiONO$ is not volatile. Its boiling point is 40.5– 41.5 °C/1.9 mbar (from reference 5), which is much higher compared to commonly used isobutyl nitrite (*b.p.* = 66 °C at atmospheric pressure).

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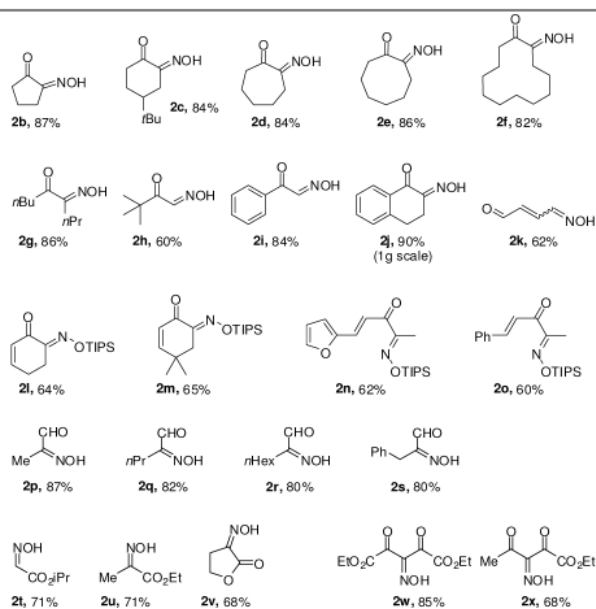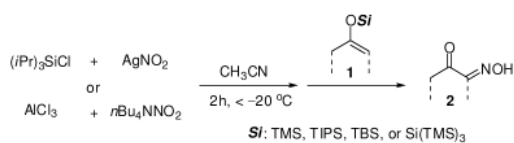
Chart 1.

Oxidation of silyl enol ethers with metal nitrites[a–d]

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

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

Chart 2.
Double oxidation of silyl enol ethers **1**
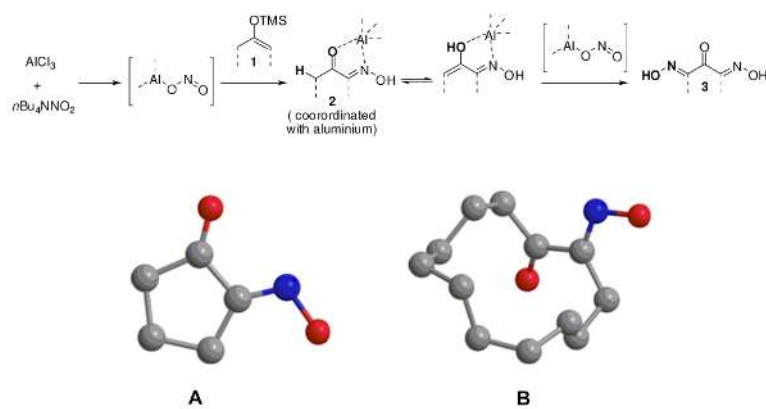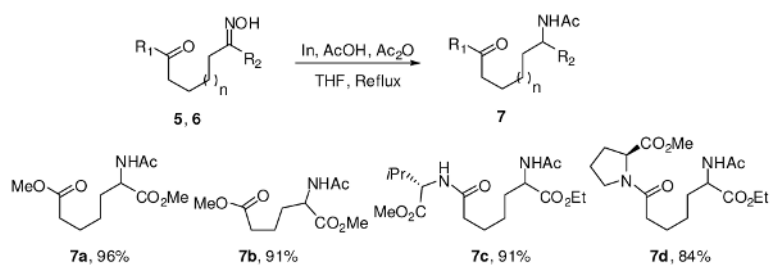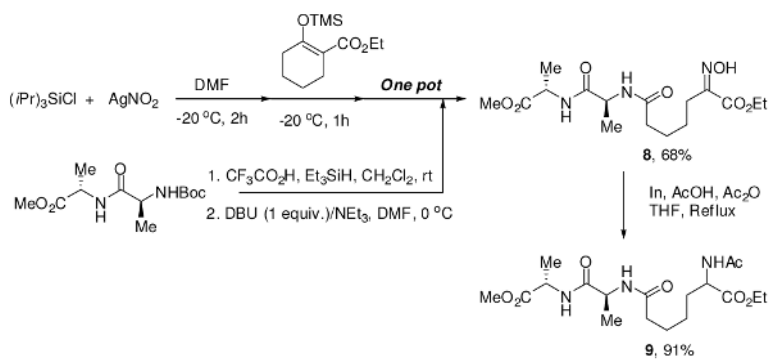[a] Isolated yields. [b] Not observed.
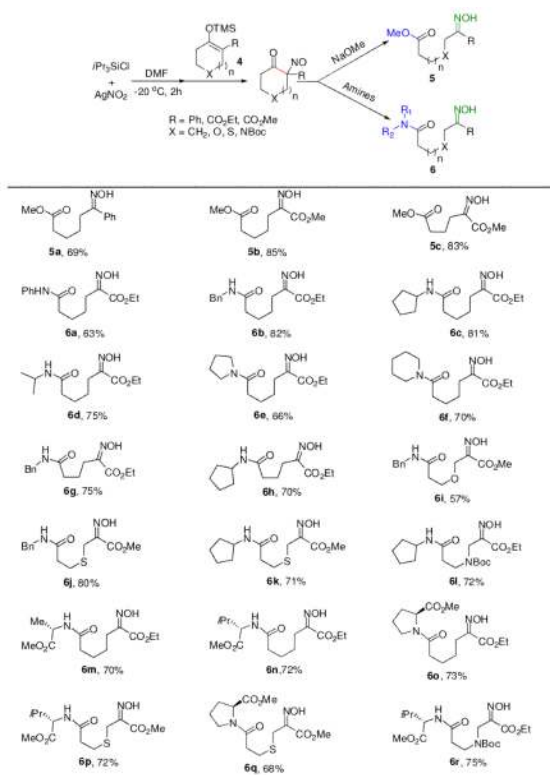
Chart 3.
Oxidation of quaternary silyl enol ethers and one pot C-C bond cleavage reactions[a]
[a] Isolated yields in %.

Scheme 1.
Plausible mechanism for the formation of **3**

Scheme 2.
Synthesis of protected amino acids and dipeptides by indium mediated reduction of oximes

Scheme 3.
Synthesis of protected peptidoglycan mimetic peptide analogue