ORGANIC LETTERS

2003
Vol. 5, No. 25
4907−4909

New Approach for the Synthesis of Isoxazoline-*N*-oxides

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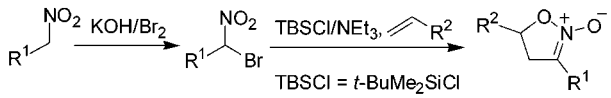
Received October 21, 2003

ABSTRACT

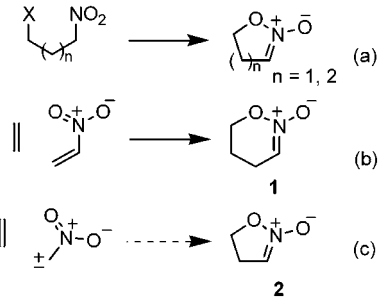


A strategy for the synthesis of isoxazoline-*N*-oxides (cyclic five-membered nitronates) from primary nitro compounds and olefins is described. The key step of the process involves 1,3-dipolar cycloaddition of corresponding 1-bromosilyl nitronates with alkenes.

In recent years cyclic six-membered alkyl nitronates **1** (oxazine-*N*-oxides) have been extensively investigated.[1] This is primarily associated with their employment as intermediates in natural product synthesis.[1a] At the same time, five-membered nitronates **2** (isoxazoline-*N*-oxides), though discovered much earlier than six-membered analogues, are seldom used.[2] The conventional strategy for the preparation of cyclic five- and six-membered nitronates implies intramolecular O-alkylation of properly functionalized aliphatic nitro compounds (Scheme 1, eq a).[3] However, no general method for the synthesis of such starting nitro compounds is available, and each particular substrate requires special approach.

A [4 + 2] cycloaddition between conjugate nitro alkenes and olefins represents a more advanced and efficient way to access oxazine-*N*-oxides **1** (Scheme 1, eq b).[1]

Scheme 1. Synthesis of Cyclic Nitronates



Similarly, isoxazoline-*N*-oxides **2** could be retrosynthetically disconnected by means of 1,3-dipolar cycloaddition. The forward reaction would require nitrocarbenes as 1,3-dipoles (Scheme 1, eq c).

Along these lines, 40 years ago several isoxazoline-*N*-oxides were obtained (Scheme 2).[4] However, mechanistic

(1) (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (b) Seebach, D.; Lyapkalo, I. M.; Dahinden, R. *Helv. Chim. Acta* **1999**, *82*, 1829.

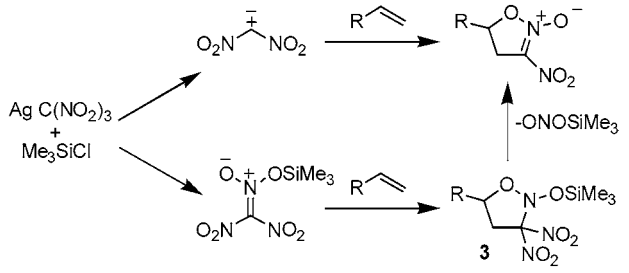
(2) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; pp 267−274.

(3) (a) Kohler, E. P.; Barrett, G. R. *J. Am. Chem. Soc.* **1924**, *46*, 2105. (b) Tartakovsky, V. A.; Gribov, B. G.; Savostianova, I. A.; Novikov, S. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1965**, *14*, 1602. (c) Clagett, M.; Gooch, A.; Graham, P.; Holy, N.; Mains, B.; Strunk, J. *J. Org. Chem.* **1976**, *41*, 4033. (d) Kaji, E.; Zen, S. *Chem. Pharm. Bull.* **1980**, *28*, 479. (e) Arai, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2525. (f) Scardovi, N.; Casalini, A.; Peri, F.; Righi, P. *Org. Lett.* **2002**, *4*, 965. (g) Kanemasa, S.; Yoshimiya, T.; Wada, E. *Tetrahedron Lett.* **1998**, *39*, 8869. (h) Rosini, G.; Marotta, E.; Righi, P.; Seerden, J.-P. *J. Org. Chem.* **1991**, *56*, 6258. (i) Marotta, E.; Baravelli, M.; Maini, L.; Righi, P.; Rosini, G. *J. Org. Chem.* **1998**, *63*, 8235. (j) Rosini, G.; Galarini, R.; Marotta, E.; Righi, P. *J. Org. Chem.* **1990**, *55*, 781. (k) Galli, C.; Marotta, E.; Righi, P.; Rosini, G. *J. Org. Chem.* **1995**, *60*, 6624. (l) Gil, M. V.; Roman, E.; Serrano, J. A. *Tetrahedron Lett.* **2000**, *41*, 3221.

(4) Chlenov, I. E.; Kashutina, M. V.; Ioffe, S. L.; Novikov, S. S.; Tartakovsky, V. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1969**, *18*, 1948.

10.1021/ol0360602 CCC: $25.00
Published on Web 11/20/2003

Scheme 2. Formation of 3-Nitroisoxazoline-*N*-oxides

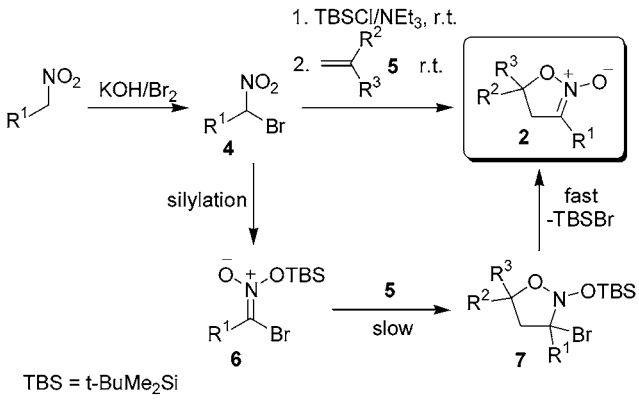


studies demonstrated that reaction proceeded not via dinitrocarbene but through the intermediacy of silyl nitronate and isoxazolidines **3**, which underwent elimination of silyl nitrite.[5]

Because of the low yields of the products, the approach shown in Scheme 2 does not have preparative value, and no other reports on construction of isoxazoline-*N*-oxides by means of nitrocarbenes (or their equivalents) have been published.[6]

Herein we present a new convenient method for the synthesis of nitronates **2** from primary aliphatic nitro compounds (Scheme 3). The starting nitro compounds are

Scheme 3. Synthesis of Isoxazoline-*N*-oxides



first brominated according to literature procedures.[7] Treatment of 1-bromonitroalkanes **4** in dichloromethane with *tert*-butyldimethylchlorosilane and triethylamine followed by addition of alkene **5** gives rise to the desired products **2**.

Apparently, the formation of nitronates **2** from **4** occurs through silyl nitronates **6** rather than through corresponding nitrocarbenes.[8] Under the reaction conditions the silyl nitronates **6** are initially produced and undergo 1,3-dipolar cycloaddition with the alkene to form *N*-silyloxyisoxazolidines **7**.[9,10] Rapid elimination of *tert*-butyldimethylbromosilane from **7** finally affords nitronates **2**.

The cycloaddition of silyl nitronates **6** to alkenes is the rate-determining step of the process. Thus, monitoring the reaction between 1-bromonitroethane and methyl acrylate, the intermediate isoxasolidine **7** (R^1 = Me, R^2 = CO_2Me, R^3 = H) was not detected at any time.

The main results of the synthesis of isoxazoline-*N*-oxides are collected in Table 1.

Table 1. Synthesis of Isoxazoline-*N*-oxides[a]

entry	**4**	R^1	**5**	R^2	R^3	**2**	time, days	yield[b] **2**, %
1[c]	**4a**	Me	**5a**	COOMe	H	**2a**	4	67
2	**4a**	Me	**5b**	COOMe	Me	**2b**	8	78
3[c]	**4a**	Me	**5c**	COMe	H	**2c**	4	77[d]
4	**4a**	Me	**5d**	Ph	H	**2d**	7	73
5	**4a**	Me	**5e**	2-Py	H	**2e**	3	91
6	**4a**	Me	**5f**	OEt	H	**2f**	14	78
7	**4b**	Et	**5b**	COOMe	Me	**2g**	8	77
8	**4b**	Et	**5d**	Ph	H	**2h**	7	67
9	**4b**	Et	**5e**	2-Py	H	**2i**	3	81
10	**4c**	Ph	**5a**	COOMe	H	**2j**	31	57
11	**4d**	Bn	**5b**	COOMe	Me	**2k**	8	62
12	**4d**	Bn	**5e**	2-Py	H	**2l**	3	79
13	**4d**	Bn	**5g**	$Me(CH_2)_4$	H	**2m**	30	40
14	**4d**	Bn	**5h**	$SiEt_3$	H	**2n**	14	56
15[c]	**4e**	H	**5d**	Ph	H	**2o**	3	17

[a] All reactions were carried out in CH_2Cl_2 with reagent ratio **4**:TBSCl:NEt_3 = 1:1.1:1.1. The ratio **4**:**5** = 1:5 unless mentioned otherwise. [b] Isolated yield unless mentioned otherwise. [c] The ratio **4**:**5** = 1:1.05. [d] The yield was determined by ^{1}H NMR spectrum with internal standard (*trans*-stilbene) because **2c** partially decomposes upon isolation.

A wide variety of 3,5-substituted cyclic nitronates **2** can be readily obtained. Starting bromonitro compounds **4** may contain alkyl, benzyl, or phenyl groups. Terminal alkenes with either donor or acceptor substituents, as well as with alkyl and phenyl groups, are suitable substrates for the reaction. The successful utilization of ethyl vinyl ether is of special interest, because the cycloaddition of electron-rich olefins is not typical for silyl nitronates.[11] Even an example

(5) Ioffe, S. L.; Makarenkova, L. M.; Kashutina, M. V.; Tartakovsky, V. A.; Rozhdestvenskaya, N. N.; Kovalenko, L. I.; Isagulianz, G. V. *J. Org. Chem. USSR (Engl. Transl.)* **1973**, *9*, 931.

(6) Recently Charette demonstrated that some equivalents of nitrocarbenes react with alkenes upon catalysis by transition metals, affording not isoxazoline-*N*-oxides but nitrocyclopropanes. The rearrangement of nitrocyclopropanes into isoxazoline-*N*-oxides promoted by Lewis acids was occasionaly observed. See: (a) Charette, A. B.; Wurz, R. P.; Ollevier, T. *Helv. Chim. Acta* **2002**, *85*, 4468. (b) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327.

(7) (a) Erickson, A. S.; Kornblum, N. *J. Org. Chem.* **1977**, *42*, 3764. (b) Fishwick, B. R.; Rowles, D. K.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1171.

(8) Attempts to generate and trap nitrocarbene from **4a** by deprotonation and bromide abstraction with silver salts failed.

(9) Silyl nitronates **6** can be isolated and characterized as air-sensitive species (see Supporting Information for details). Probably because of the hydrolytic sensitivity of **6** it is better to use *tert*-butyldimethylsilyl rather than trimethylsilyl derivatives. In contrast to other types of silyl nitronates, 1-bromosilyl nitronates have not been studied. Only silylation of bromonitromethane was briefly mentioned; see: Kashutina, M. V. Ph.D. Dissertation, Zelinsky Institute of organic chemistry, Moscow, 1974.

(10) 1,3-Dipolar cycloaddition with alkenes is the most typical reaction of silylnitronates. See: (a) Ioffe, S. L.; Kashutina, M. V.; Shitkin, V. M.; Jankelevich, A. Z.; Levin, A. A.; Tartakovsky, V. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1972**, *21*, 1292. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988.

(11) Only intramolecular cycloaddition of silyl nitronate with a vinyl ether fragment was reported. See: Hassner, A.; Friedman, O.; Dehaen, W. *Liebigs Ann./Recueil* **1997**, 587.

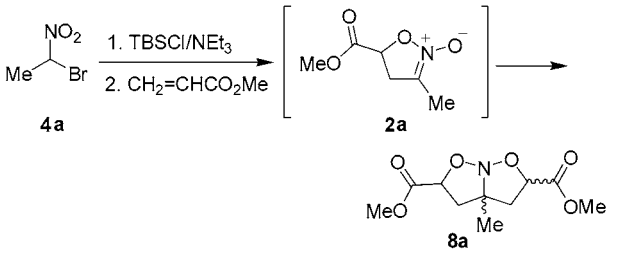
of selective trapping of another intermediate on ethyl vinyl ether in the presence of silyl nitronate was described.[12] Surprisingly, internal alkenes such as dimethyl maleate, *trans*-stilbene, indene, and norbornene do not react with silyl nitronates **6**, presumably owing to steric reasons.

For complete conversion of silyl nitronates **6** to the products reaction time from several days to 1 month at room temperature is required. At elevated temperature the yield of isoxazoline-*N*-oxides decreases, which can be associated with their thermal instability.

1,3-Dipoles isoxazoline-*N*-oxides could also cycloadd to the alkenes. However, the diminished reactivity of five-membered nitronates in 1,3-dipolar cycloaddition was noted in earlier reports.[13] As a result, even when active dipolarophiles are employed, the contribution of double addition does not exceed 10%. Nevertheless, using 50 equiv of methyl acrylate in reaction with **4a** during 5 days allows isolation of bicyclic adduct **8a** (Scheme 4).

In summary, we developed a convenient method for the construction of 3,5-substituted isoxazoline-*N*-oxides **2** from simple precursors, primary nitro compounds and terminal alkenes. We believe that 1,3-cycloaddition strategy will broaden the scope of available nitronates. Our further efforts will involve elaboration of this new methodology, as well as investigation of transformations of obtained isoxazoline-*N*-oxides.

Scheme 4. Double Cycloaddition Process



Acknowledgment. This work was performed at the Scientific Educational Center for young chemists and supported by the Russian Foundation for Basic Research (grants 03-03-33350, 03-03-04001), Federal Target Program Integration (project B-0062), and Scientific School (1442.2003.3).

Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0360602

(12) Ioffe, S. L.; Lyapkalo, I. M.; Tishkov, A. A.; Strelenko, Yu. A.; Tartakovsky, V. A. *Tetrahedron* **1997**, *53*, 13085.

(13) Chlenov, I. E.; Khudak, V. I.; Tartakovsky, V. A.; Novikov, S. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1969**, *18*, 2113.