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Unprecedented in Situ Oxidative Ring Cleavage of Isoxazolidines: Diastereoselective Transformation of Nitronic Acids and Derivatives into 3-Hydroxymethyl 4-Nitro Tetrahydrofurans and Pyrrolidines

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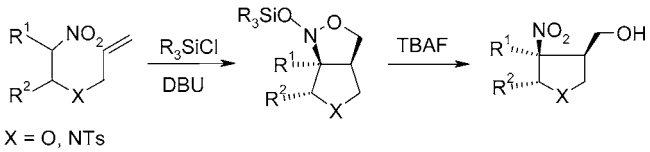
ABSTRACT



Nitronic acids undergo an intramolecular 1,3-dipolar cycloaddition to unactivated double bonds, and the resulting isoxazolidines spontaneously evolve by an unprecedented in situ oxidative ring cleavage. The extension of this transformation to silyl nitronates results in a general diastereoselective construction of hydroxymethyl nitro functionalized tetrahydro-furans and -pyrrolidine having up to four consecutive stereogenic centers.

aci-Nitro anions constitute particularly useful and versatile intermediates, having found many important synthetic applications.[1]

We have a long-standing and continuing interest in this field,[2] and recently we reported the CAN-promoted one-electron oxidation[3] of unsaturated *aci*-nitronates **2**. The corresponding radicals **3** evolve through a stereoselective 5-*exo*-oxidative cyclization giving rise to *exo*-nitronitronates **4** along with a diastereomeric mixture of the corresponding nitro alcohols **5** (Scheme 1). Unfortunately, all attempts to extrapolate this transformation to the pyrrolidine series were unsuccessful as a result of the oxidative degradation of the unsaturated nitroamine intermediate[4] (Scheme 1).

Moreover, the corresponding alkyl or silyl nitronates have been successfully involved in intramolecular 1,3-dipolar cycloadditions with olefins leading to useful isoxazoline and isoxazolidine intermediates.[5] Importantly enough, and to the best of our knowledge, the same behavior of their nitronic acid precursors, easily obtained by protonation of nitronates, has never been reported.[1b]

(1) (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988.

(2) Guillaume, M.; Dumez, E.; Rodriguez, J.; Dulcère, J.-P. *Synlett* **2002**, 1183−1185. Dulcère, J.-P.; Dumez, E. *Chem. Commun.* **1997**, 971−972. Dumez, E.; Rodriguez, J.; Dulcère, J.-P. *Chem. Commun.* **1997**, 1831−1832. Dumez, E.; Faure, R.; Dulcère, J.-P. *Eur. J. Org. Chem.* **2001**, 2577−2588.

(3) Durand, A.-C.; Dumez, E.; Rodriguez, J.; Dulcère, J.-P. *Chem. Commun.* **1999**, 2437−2438.

(4) For a successful related transformation in the pyrrolidine series, see: Jahn, U.; Müller, M.; Aussieker, S. *J. Am. Chem. Soc.* **2000**, *122*, 5212−5213.

(5) (a) Namboothiri, I. N. N.; Hassner, A.; Gottlieb, H. E. *J. Org. Chem.* **1997**, *62*, 485−492. (b) Cheng, Q.; Oritani, T.; Horiguchi, T.; Shi, Q. *Eur. J. Org. Chem.* **1999**, 2689−2693. (c) Namboothiri, I. N. N.; Hassner, A. *Top. Curr. Chem.* **2001**, *216*, 1−49; (d) Duffy, J. L.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 3783−3785.

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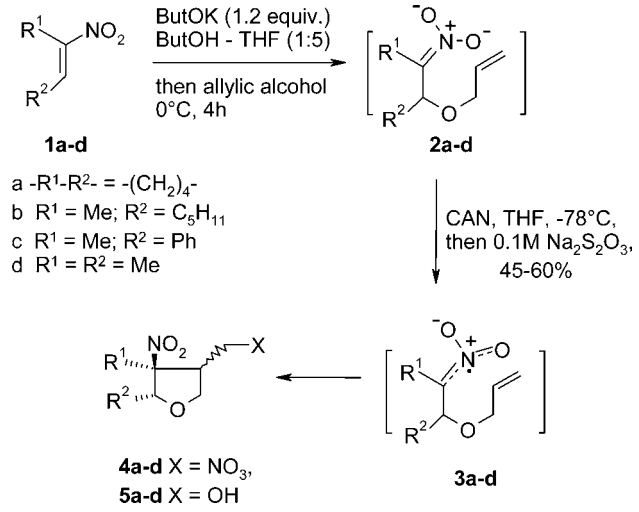
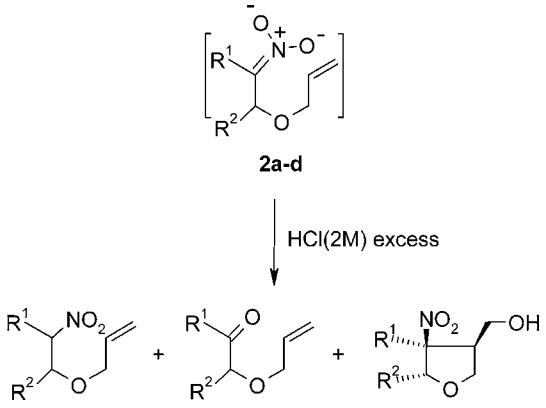
Scheme 1. One-Electron Oxidation of *aci*-Nitronates **2**



We have now found that not only can nitronic acids give an intramolecular 1,3-dipolar cycloaddition to an unactivated double bond but also the resulting isoxazolidines spontaneously evolve by an unprecedented in situ oxidative ring cleavage. The result is the diastereoselective construction of hydroxymethyl nitro functionalized tetrahydro-furans and -pyrrolidine having up to four consecutive stereogenic centers. Both of these five-membered ring heterocyles are highly functionalized scaffolds and have many synthetic as well as biological potentialities.[6]

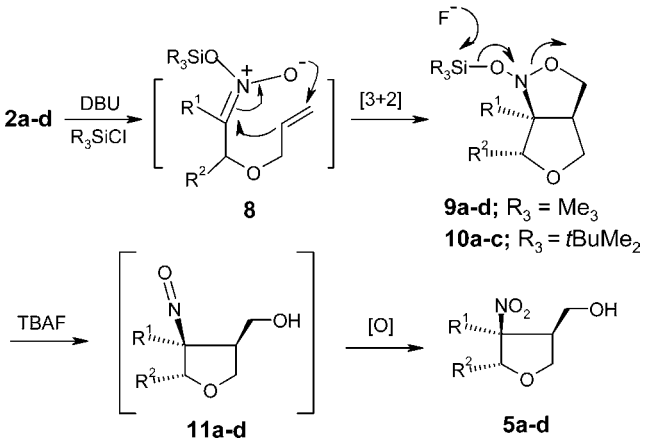
When *aci*-nitro anions **2a**−**d** obtained by oxa-Michael addition of allylic alcohol to nitroalkenes **1a**−**d** with Bu^{t}OK/THF were hydrolyzed by addition of an excess of (2 M) HCl, an unprecedented transformation took place leading to the formation of *exo*-nitro alcohols **5** in 5−23% yield together with the Michael adducts **6**; starting from **2a**, the corresponding alkoxy ketone **7a** arising from Nef reaction[7] was also isolated in 5% yield (Scheme 2).

Scheme 2. Hydrolysis of *aci*-Nitro Anions **2** with 2 M HCl



Although yields were not optimized in this standard reaction condition, we noticed that nitro alcohols **5** were isolated as a pure diastereoselective form; an intramolecular [3 + 2] cycloaddition of nitronic acids followed by an oxidative ring cleavage of the cycloadduct intermediate should account for the overall transformation. To confirm that nitro alcohols **5** result from 1,3-dipolar cycloaddition and therefore to enlarge the scope of this potential new stereoselective preparation of functionalized tetrahydrofurans, we decided to study the reactivity of the corresponding silyl nitronates **8** (Table 1).

Table 1. Transformation of Silylnitronates **7** into Nitro Alcohols **5**



entry	2	R^1	R^2	R_3	**9**[a], **10**[b](%)	**5** (%)
1	**2a**	-$(CH_2)_4$-		Me_3	**9a** (100)	**5a** (47)
2	**2a**	-$(CH_2)_4$-		$tBuMe_2$	**10a** (84)	**5a** (47)
3	**2b**	Me	C_5H_{11}	Me_3	**9b** (96)	**5b** (48)
4	**2b**	Me	C_5H_{11}	$tBuMe_2$	**10b** (93)	**5b** (48)
5	**2c**	Me	Ph	Me_3	**9c** (98)	**5c** (37)
6	**2c**	Me	Ph	$tBuMe_2$	**10c** (69)	**5c** (37)
7	**2d**	Me	Me	Me_3	**9d** (72)	**5d** (50)

[a] Crude products. [b] Products purified by flash chromatography on silica gel.

β-Nitro allyl ethers **6** were first reacted with Me_3SiCl (2 equiv) and DBU (1.2 equiv) in CH_2Cl_2 at 0 °C to smoothly afford *N*-(trimethylsilyloxy)isoxazolidines **9** in 55−86% yield; this [3 + 2] cycloaddition is related to the well-documented intramolecular silylnitronate olefin cycloaddition (ISOC reaction).[1b,5]

The tendency of silyl nitronates to cycloadd smoothly in a 1,3-dipolar fashion to the alkene moiety was enhanced by

(6) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599. Westle W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Marcel Dekker: New York, 1982; Vols. 1 and 2. Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309−3362. Steele, J. *Contemp. Org. Synth.* **1994**, *1*, 95−111. Mori, M.; Uesaka, N.; Saitoh, F.; Shibasaki, M. *J. Org. Chem.* **1994**, *59*, 5643−5649. Pinder, A. R. *The Alkaloids*; Grundon, M. F., Ed.; Chemical Society: London, 1982; Vol. 12. Shao, Z.; Chen, J.; Tu, Y.; Li, L.; Zhang, H. *Chem. Commun.* **2003**, 1918−1919 and references therein; Kitagawa, O.; Miyagi, S.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *J. Org. Chem.* **2003**, *68*, 3184−3189.

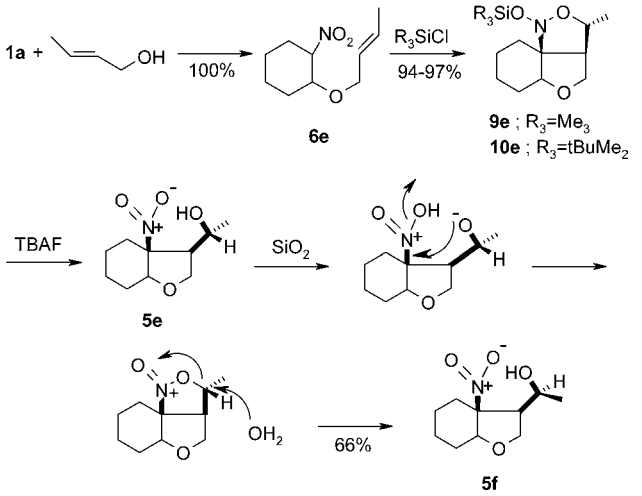
(7) Noland, W. E. *Chem. Rev.* **1955**, *55*, 137−55; Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017−1047.

the increased yields (89−100%) obtained when DBU/Me_3SiNMe_2 was used as the silylating reagent.

Whereas crude *N*-(trimethylsilyloxy)isoxazolidines **9a**−**d** were stable enough[8] to provide satisfactory spectroscopic data, *N*-(*tert*-butyldimethylsilyloxy)isoxazolidines **10a**−**c** could be easily purified by flash chromatography.

With these isoxazolidines in hand, we looked at the TBAF-promoted desilylation to find a general and unprecedented oxidative cleavage affording 3-nitro-4-hydroxymethyl tetrahydrofurans **5**; only one diastereomer having three consecutive stereogenic centers was obtained in fair to good yields. As previously shown, the *cis* relationship between R^1 and R^2 is the result of 1,3-allylic strain in the nitronate[2] coupled with the stereoselective cycloaddition fixing the NO_2 function in a *cis* orientation to the hydroxymethyl group after fragmentation. It is worth noting that bicyclic compound **5e**,[9] obtained with 66% yield from **1a** and crotonic alcohol, can be totally epimerized at the carbon bearing the hydroxy group to give **5f**, probably via an intramolecular transesterification during chromatography on silica gel (Scheme 3).

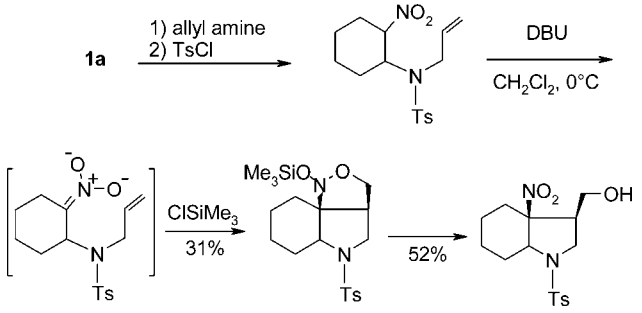
Scheme 3. Epimerization of Compound **5e** into **5f**



The crucial point in this new transformation is the in situ oxidative ring cleavage of the isoxazolidine intermediate, which does not need addition of any specific metallic or organometallic oxidant. From a mechanistic point of view, although oxidation of nitroso compounds to the corresponding nitro derivatives usually requires powerful oxidants,[10] they are likely to be intermediates in our transformation. Indeed, we have been able to isolate and fully characterize nitroso intermediate **11a**, which gave a spontaneous uncatalyzed aerobic oxidation to furnish the expected hydroxymethyl nitro tetrahydrofuran **5a** in quantitative yield (followed by NMR) (Table 1).

Silylation of nitronate **12a**, obtained by aza Michael addition of tosylallylamine to **1a** afforded *N*-(silyloxy)-isoxazolidine **13a** in 31% yield, diastereoselectively transformed into 3-nitro 4-hydroxymethyl pyrrolidine **14a** after desilylation (52% yield, Scheme 4).

Scheme 4. Transformation of Nitronate **12** into Pyrrolidine **14**



In conclusion, the work reported herein provides an efficient route to silyloxyisoxazolidines **9a**−**e**, **10a**−**c**,**e**, and **13a**, which are subsequently desilylated and oxidized into 3-nitro 4-hydroxymethyl heterocycles **5a**−**f** and **14a**. Improvements for increasing the yield of the direct transformation of nitronates **2** or **12** into nitro alcohols **5** or **14** are currently under investigation. Moreover, the improved methods for the conversion of the nitro functionality[11] stress the potential interest in this diastereoselective formation of highly functionalized furans and pyrrolidines.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) To our knowledge, *N*-trimethylsilyloxyisoxazolidines have only scarcely been characterized by ^1H NMR when the ISOC reaction was conducted in $CDCl_3$ in an NMR tube (see ref 5b), whereas *N*-trimethylsilyloxysilabicyclic isoxazolidine derivatives gave satisfactory NMR data: Kudoh, T.; Ishikawa, T.; Shimizu, Y.; Saito, S. *Org. Lett.* **2003**, *5*, 3875−3878.

(9) The relative stereochemistry of the stereocenter bearing the hydroxy group in **5e** was deduced from NOESY experiments performed on **10e**.

(10) Hassner, A.; Heathcock, C. *J. Org. Chem.* **1964**, *29*, 1350−1355. Jorgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1987**, 1405−1406. Boyer, J. H. *Chem. Rev.* **1980**, *80*, 495−561. Ashok, K.; Scaria, P. M.; Kamat, P. V.; George, M. V. *Can. J. Chem.* **1987**, *65*, 2039−2049. McKillop, A.; Tarbin, J. A. *Tetrahedron* **1987**, *43*, 1753−1758.

(11) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1−18. Pereekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M.; Efremov, D. A. *Nitroalkenes*; Wiley: New York, 1994.