

Stability of Electron Deficient Activated Nitronates under Neutral and Lewis Acid Catalyzed Conditions. Facile Nitronate Cycloaddition Reactions to the Magnesium Alkoxides of Allylic Alcohols Leading to Isoxazolidines and Isoxazolines

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Received 13 August 1998; revised 9 September 1998; accepted 11 September 1998

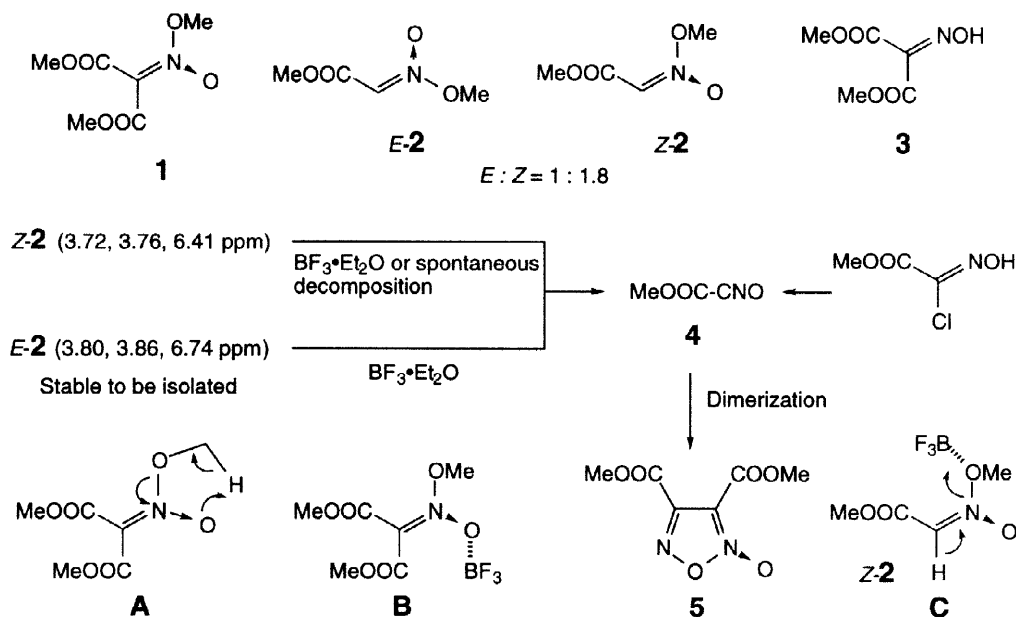
Abstract: *N*-Methoxy-*N*-[bis(methoxycarbonyl)methylene]amine *N*-oxide and *N*-methoxy-*N*-(methoxycarbonylmethylene)amine *N*-oxide as electron-deficient activated nitronates, show an exceptionally high reactivity to the magnesium alkoxides of allylic alcohols. Isoxazolidines or isoxazolines are formed as cycloadducts, depending upon the substitution pattern of the allylic alcohols. When the latter C-monosubstituted nitronate is treated with a catalytic amount of boron trifluoride etherate, the corresponding nitrile oxide is smoothly generated through β -elimination of methanol. © 1998 Elsevier Science Ltd. All rights reserved.

Alkyl or silyl nitronates derived from primary nitroalkanes are well known to undergo cycloaddition reactions with activated alkenes to form *N*-alkoxy- or *N*-silyloxy-substituted isoxazolidines¹ which then undergo spontaneous² or acid catalyzed³ elimination of alcohol (or silanol) to produce isoxazolines. So, with this cycloaddition/elimination sequence, C-monosubstituted nitronates can be synthetic equivalents of nitrile oxides 1,3-dipoles. It is also known that C-monosubstituted electron-deficient nitronates are converted into nitrile oxides by treatment with a strong protonic or a Lewis acid.⁴ Nitronates show a reactivity similar to that of nitrones, and nitrones are one of the 1,3-dipoles which have been successfully developed to catalyzed asymmetric versions.⁵⁻¹¹ Therefore, catalyzed asymmetric nitronate cycloadditions could be open if an appropriate combination of nitronate and Lewis acid is selected.

Like nitrones, nitronates would be activated by electron-withdrawing substituent(s) on the carbon even toward electron-poor alkenes,¹² and such activated nitronates should be favored in the study of nitrile oxide cycloaddition equivalents. However, electron-deficient nitronates are often unstable; half life times are usually shorter than a few days, and sometimes a few hours.^{2,13} The typical decomposition pattern is the irreversible sigmatropic fragmentation producing a carbonyl compound and an oxime.¹⁴ In this work, we examined the stability of ester-activated nitronates under uncatalyzed and Lewis acid catalyzed conditions and also tried to find reactive dipolarophiles toward these unstable nitronates.

In the present communication, we would like to report the preparation, isolation, and characterization of methyl nitronates derived from methyl nitroacetate and dimethyl nitromalonate. The stability test under uncatalyzed or Lewis acid catalyzed conditions has been investigated. Beside the known decomposition through irreversible sigmatropic fragmentation,^{2,14} a new nitrile oxide generation by β -elimination of nitronates under neutral conditions was discovered. This nitrile oxide generation is accelerated by a catalytic amount of Lewis acid catalyst. Magnesium alkoxides of allylic alcohols showed high reactivity to these electron deficient nitronates to give either isoxazolidines or isoxazolines depending upon the substituents of the allylic alcohols.

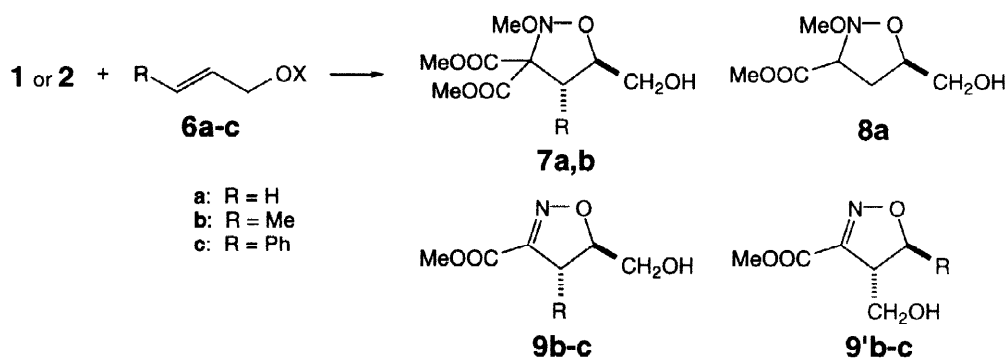
Nitronates are usually *in situ* generated and directly used in cycloadditions with an excess amount of dipolarophiles. The most convenient preparation method of nitronates is the *O*-methylation of "enolizable" nitroalkanes with diazomethane.² Thus, two nitronic esters, *N*-methoxy-*N*-[bis(methoxycarbonyl)methylene]amine *N*-oxide (**1**) and *N*-methoxy-*N*-(methoxycarbonylmethylene)amine *N*-oxide (**2**), were prepared by *O*-methylation, with diazomethane at a low temperature, of dimethyl nitromalonate and methyl nitroacetate, respectively. Diester nitronate **1** could be isolated as colorless solid,¹⁵ but a fairly rapid decomposition took place in chloroform at room temperature. In 2 days in deuteriochloroform,¹⁶ nitronate **1** was entirely consumed to give oxime **3** through an irreversible sigmatropic fragmentation (**A** in Scheme 1). Because of this instability, cycloadditions of **1** with dipolarophiles were quite limited. Only poor yields of cycloadducts were produced in uncatalyzed reactions with a variety of dipolarophiles such as norbornene, methyl acrylate, dimethyl maleate, ethyl vinyl ether, and allyl alcohol (in all cases equivalent amounts were used). However, the magnesium alkoxide of allyl alcohol **6a** (X = MgBr) showed an exceptionally high reactivity to **1** producing dimethyl isoxazolidine-3,3-dicarboxylate **7a** in a quantitative yield (Scheme 2). This indicates that the reaction of nitronates with allylic alcohols can be highly accelerated by the presence of magnesium ion.¹⁷ However, the magnesium alkoxide of crotonyl alcohol **6b** (X = MgBr) was much less reactive. Increasing steric hindrance at the reaction site may be a major reason for the decreased reactivity.



Scheme 1

The monoester nitronate **2** was also isolable,^{18,19} but quite labile. Especially, the major isomer of **2** (isomer ratio = 1.8:1) underwent a faster decomposition than the other isomer (decomposed in 4 days at room temperature in deuteriochloroform)¹⁶ than the minor isomer. Consequently, the minor isomer remained was isolated in a pure form¹⁸ after purification by column chromatography. Decomposition product of the major isomer was not sigmatropic fragmentation product, but 3,4-bis(methoxycarbonyl)-1,2,5-oxadiazole *N*-oxide (**5**), formed by the dimerization of methoxycarbonylformonitrile oxide (**4**) generated from **2** by the β -elimination of methanol. This will be discussed below. Due to the close resemblance of spectral data, structures of two geometrical isomers of nitronates **2** could not be distinguished. We temporarily assigned the more stable (minor) isomer to be the *E*-isomer *E*-**2** on the basis of the anticipated relative stability: the less stable (major) *Z*-isomer *Z*-**2** may have a geometry more favored for both β -elimination and fragmentation reactions.²⁰

Although the monoester nitronate **2** showed a higher reactivity than diester nitronate **1** toward ethyl acrylate, ethyl vinyl ether, allyl and crotyl alcohols, yields of cycloadducts were not satisfactory either. A mixture of isoxazolidines and/or isoxazolines was produced in less than 20% of combined yields when a mixture of stereoisomers of **2** was employed (equivalent amounts of dipolarophile). It should be noted that the pure *Z*-isomer *Z*-**2** isolated is inert to both allyl and crotyl alcohols (Scheme 2). Presumably either the *E*-isomer *E*-**2** was more reactive than *Z*-**2** or nitrile oxide **4** as the decomposition product participated in the reaction. In this case also, the magnesium alkoxides of allylic alcohols **6a-c** ($X = \text{MgBr}$) were excellent dipolarophiles to produce isoxazolidine **8a** ($R = \text{H}$) from allyl alkoxide (**6a**) and regioisomeric mixtures of isoxazolines **9b,c** and **9'b,c** ($R = \text{Me}$ and Ph) from crotyl and cinnammyl alkoxides (**6b,c**). Elimination of methanol from the initial isoxazolidines depends upon the existence of substituent at the 4 position. High rate acceleration in the magnesium ion mediated nitronene cycloadditions to allylic alcohols has been reported by our group.¹⁷



Dipole	R	X	Temp/°C	Time/h	Product	Yield/% ^a	Ratio ^b
1	H	MgBr	rt	1	7a	100	-
	Me	MgBr	rt	48	7b	trace	-
2 <i>E</i> - 2 : <i>Z</i> - 2 = 1:1.8	H	MgBr	rt	3	8a	82	-
	Me	MgBr	rt	5	9b+9'b	80	6.8:1
<i>E</i> - 2	H	H	rt	48	-	0	-
	Me	H	rt	48	-	0	-
	H	MgBr	rt	1	8a	100	-
	Me	MgBr	rt	3	9b+9'b	100	7.1:1
	Ph	MgBr	rt	5	9c+9'c	80	5.5:1

^aIsolated yields. ^bBased on ¹H NMR spectrum.

Scheme 2

In the presence of a catalytic amount (10 mol%) of boron trifluoride etherate, decomposition of the diester nitronate **1** leading to oxime **3** was suppressed. This would be rationalized that coordination of the Lewis acid catalyst to the nitronate oxygen²¹ deactivates the irreversible sigmatropic fragmentation because of the lowered basicity of the coordinated oxygen atom (**B** in Scheme 1). On the other hand, both isomers of monoester nitronate **2** underwent a smooth decomposition in the presence of a catalytic amount of boron trifluoride etherate at room temperature.⁴ The decomposition product formed in a quantitative yield was the nitrile oxide dimer **5**, the authentic sample of which was prepared from nitrile oxide **4** as shown in Scheme 1. Thus, the monosubstituted nitronate **2** undergoes either spontaneous or Lewis acid catalyzed β -elimination giving the corresponding nitrile oxide **4** (**C** in Scheme 1), the catalyzed reaction being much faster.

Coordination of Lewis acid to the methoxyl oxygen of nitronate **2** would accelerate the β -elimination of the methoxyl moiety. However, we believe that, in the reactions of **2** with the magnesium alkoxides of allylic alcohols **6**, not nitrile oxide **4** but nitronate **2** is responsible for the formation of isoxazolines **9**. Reasons are that (1) the reaction with allyl substrate **6a** ($X = \text{MgBr}$) produced isoxazolidine derivative **8a**,

and (2) the reaction of nitrile oxide **4** with **6b** ($X = \text{MgBr}$) is not a high yield reaction. Lewis acidity of the magnesium ion of the substrates **6** ($X = \text{MgBr}$) would be insufficient to mediate such a nitrile oxide generation; the reactivity of magnesium alkoxides of allylic alcohols is faster than the rate of β -elimination. This indicates that use of a weak Lewis acid catalyst would lead to effective Lewis acid catalysis in nitronate cycloadditions.

Relation between the acidity of Lewis acid catalyst and the rate of nitrile oxide generation is now under investigation.

References and Note

- 1 Tufariello, J. J.; *Nitrone* as Chapt. 9 of *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A. Ed.; A Wiley-Interscience Publication: New York, 1984; Vol. 2, pp 83-168.
- 2 Breuer, E.; Aurich, H. G.; Nielsen, A.; *Nitrones, nitronates and nitroxides*, Patai, S.; Rappoport, Z. Ed.; John Wiley & Sons: Chichester, 1989; Chapt. 2 and 3, pp 139-312.
- 3 (a) Boron trifluoride catalyzes the cycloaddition of nitronic esters. Levina, I. S.; Mortikova, E. I.; Kamernitzky, A. V. *Synthesis*, **1974**, 562-563. (b) Torssell, K. B. G.; Hazell, A. C.; Hazell, R. G. *Tetrahedron* **1985**, *41*, 5569-5576. (c) Tartakovskii, V. A.; Savost'yanova, I. A.; Novikov, S. S. *Zh. Org. Khim.*, **1968**, *4*, 240-243.
- 4 Wade, P. A.; Amin, N. V.; Yen, H.-K.; Price, D. T.; Huhn, G. F. *J. Org. Chem.* **1984**, *49*, 4595-4601.
- 5 (a) Jensen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *Helv. Chim. Acta* **1997**, *80*, 2039-2046. (b) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471-2477. (c) Gothelf, K. V.; Jørgensen, K. A. *Acta Chem. Scand.* **1996**, *50*, 652. (d) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59-64. (e) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687-5991.
- 6 Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346-355.
- 7 Sanchez-Blanco, A. I.; Gothelf, K. V.; Jørgensen, K. A. *Tetrahedron Lett.* **1997**, *38*, 7923-7926.
- 8 Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *Tetrahedron Lett.* **1996**, *37*, 5947-5950.
- 9 (a) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840-5841. (b) Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett.* **1997**, 1039-1040.
- 10 (a) Seerden, J.-P. G.; Boeren, M. M. M.; Scheeren, H. W. *Tetrahedron* **1997**, *53*, 11843-11852. (b) Seerden, J.-P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett.* **1994**, *35*, 4419-4422.
- 11 Ukaji, Y.; Taniguchi, K.; Sada, K.; Inomata, K. *Chem. Lett.* **1997**, 547-548.
- 12 Huisgen, R.; Seidle, H.; Brüning, I. *Chem. Ber.* **1969**, *102*, 1102-1116.
- 13 Kornblum, K.; Brown, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 2681-2687.
- 14 The irreversible sigmatropic fragmentation of nitronates is known as an important preparative method of oximes (Ref. 2).
- 15 After treatment of dimethyl nitromalonate with diazomethane (1.1 equiv) in diethyl ether at $-78\text{ }^{\circ}\text{C}$ for 5 min and at $0\text{ }^{\circ}\text{C}$ for 10 min, the ether was evaporated in vacuo below rt. The solid residue was crystallized from diethyl ether - hexane to give **1** in 95%: Colorless plate, mp $39 - 40\text{ }^{\circ}\text{C}$. ^1H NMR (CDCl_3) $\delta = 3.88, 3.88, \text{ and } 3.89$ (each 3H, s, Me); ^{13}C NMR (CDCl_3) $\delta = 53.38, 53.51, 54.34, 93.05, 158.79, \text{ and } 159.93$. Found: C, 36.18; H, 5.21; N, 10.41%. Calcd for $\text{C}_4\text{H}_7\text{NO}_4$: C, 36.10; H, 5.30; N, 10.52%. This nitronate **1** can be stored unchanged for weeks in a freezer under nitrogen.
- 16 The decomposition was monitored by ^1H NMR spectrum. Deuteriochloroform was filtered through a short column packed with basic alumina and then used for the stability test.
- 17 For the magnesium ion mediated nitronate cycloadditions to allylic alcohols, see: Kanemasa, S.; Tsuruoka, T.; Wada, E. *Tetrahedron Lett.* **1993**, *34*, 87-90.
- 18 The diethyl ether solution of diazomethane (1.1 equiv) is slowly added to methyl nitroacetate at $-10\text{ }^{\circ}\text{C}$ for 20 min. The mixture was stirred for 1 h at the same temperature, followed by evaporation at $0\text{ }^{\circ}\text{C}$. The residue was chromatographed on silica gel (ethyl acetate - hexane = 3:1 v/v) to give a mixture of *Z*- and *E*-isomers of **2** in 82% (1.8:1): ^1H NMR (CDCl_3) *Z*-isomer: $\delta = 3.72, 3.76$ (each 3H, s, Me), and 6.41 (1H, s, CH=); *E*-isomer: $\delta = 3.80, 3.86$ (each 3H, s, Me), and 6.74 (1H, s, CH=). ^{13}C NMR (CDCl_3) *Z*-isomer: $\delta = 51.95, 52.51, 105.82, \text{ and } 159.60$; *E*-isomer: $\delta = 52.13, 53.28, 104.23, \text{ and } 160.37$.
- 19 Greé, R.; Carrié, R. *Bull. Soc. Chim. Fr.*, **1975**, 1314-1318.
- 20 The *O*-methyl substituent of nitronate *Z*-**2** is located close to the *N*-oxide oxygen due to the steric hindrance to the adjacent methoxycarbonyl group so that the fragmentation reaction may be easier.
- 21 Interaction of Lewis acid with nitrones has been reported (Kanemasa, S.; Uemura, T.; Wada, E. *Tetrahedron Lett.* **1992**, *33*, 7889-7892).