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Cycloaddition/Ring Opening of 3-Unsubstituted Cyclic Nitronates, Isoxazoline and 5,6-Dihydro-4*H*-1,2-oxazine *N*-Oxides, as Synthetic Equivalents of Functionalized Nitrile Oxides

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Abstract: ω-Halo-α-nitropropane and -butane are cyclized with a base to form cyclic nitronates as labile 1,3-dipoles. They can be trapped by a variety of monosubstituted ethenes to give 3-(2-hydroxyethyl)isoxazolines or perhydroisoxazolo[2,3-*b*]*o*-oxazines depending upon the ring size of nitronates. The latter ring-fused heterocycles are transformed by treatment with an acid into 3-(3-hydroxypropyl)isoxazolines in good yields. Therefore, these cyclic nitronates are useful synthetic equivalents of functionalized nitrile oxides. Isolation of 5,6-dihydro-4*H*-1,2-oxazine *N*-oxide and their regio- and stereoselective cycloadditions are also discussed.

1,3-Dipolar cycloadditions of C-monosubstituted nitronates to alkenes produce isoxazolidine derivatives which then undergo β-elimination to give isoxazolines under acidic conditions.[1] Accordingly, through this cycloaddition/β-elimination sequence, nitronates can be a useful synthetic equivalent of nitrile oxides.[2] Importance of nitrile oxide cycloaddition is based on the high synthetic potential of isoxazolines in which a variety of important functionalities are masked such as β-hydroxy ketones, γ-amino alcohols, 1,3-diols, α,β-unsaturated ketones, and others.[3] Nitrile oxides having an additional functionality are required in synthetic point of view, but such examples are quite limited.[2,4]

Since nitronates should have a reactivity similar to nitrones, it is expected that their cycloadditions can be catalyzed by a Lewis acid catalyst.[5] However, no successful examples are known so far for the Lewis acid catalyzed nitronate cycloadditions;[1c] in the presence of a strong Lewis acid such as boron trifluoride etherate, nitronates are converted to nitrile oxides through β-elimination.[2] In the preceding paper,[6] we have reported the facile cycloadditions of electron-deficient nitronates to the magnesium alkoxides of allylic alcohols, while the nitrile oxide generation is a fast reaction when catalyzed by boron trifluoride etherate. Therefore, reactive nitronates with a higher stability under Lewis acid catalyzed conditions are required to achieve the Lewis acid catalyzed nitronate cycloadditions.

From these standpoints, we planed to utilize 3-unsubstituted cyclic nitronates; they would be a useful synthetic equivalent of nitrile oxides functionalized by a hydroxyalkyl group. High synthetic utility of cyclic nitronates has been well established by a series of pioneering works by Denmark.[7] His reaction includes the initial step of [4+2] hetero Diels-Alder type cycloaddition of nitroalkenes with electron rich alkenes to form cyclic nitronates which are utilized for the subsequent 1,3-dipolar cycloadditions. 3-Substituted cyclic nitronates are readily accessible by dehydrohalogenation of ω-halo-α-nitroalkanes with a base, but either synthesis or reaction of 3-unsubstituted cyclic nitronates is rare.[8]

In the present communication, we would like to report the preparation of cyclic nitronates from 3-iodo-1-nitropropane and 4-iodo-1-nitrobutane by action with a base. These 1,3-dipoles can be trapped with a variety of monosubstituted ethenes to give 3-(2-hydroxyethyl)isoxazolines or perhydroisoxazolo[2,3-*b*]*o*-

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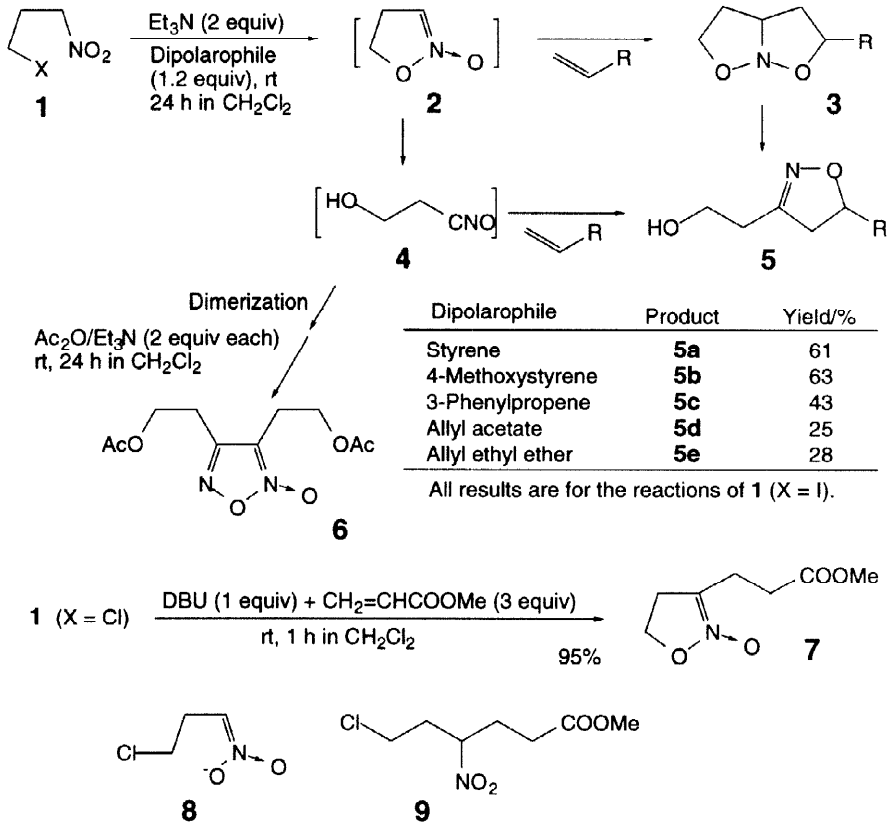
oxazines depending upon the ring size of nitronates. The latter ring-fused isoxazolidines are transformed by treatment with an acid into 3-(3-hydroxypropyl)isoxazolines in quantitative yields. Therefore, these cyclic nitronates are useful synthetic equivalents of functionalized nitrile oxides.

When 3-iodo-1-nitropropane (**1**, X = I)[9] was treated with triethylamine (2 equiv) in dichloromethane in the presence of styrene (1.2 equiv) at rt for 24 h, 3-(2-hydroxyethyl)-5-phenylisoxazoline (**5a**) was obtained regioselectively in 61% yield (Scheme 1). 4-Methoxystyrene as dipolarophile provided the best yield, but the maximum yield for cycloadduct **5b** was only 63%. Although single regioisomers were produced in all cases, trapping with less reactive alkenes such as 3-phenylpropene (43%), allyl acetate (25%), and allyl ethyl ether (28%) was rather ineffective (1.2 equiv in all cases). Two mechanisms are possible for the formation of **5**: By action with triethylamine, **1** cyclizes to form isoxazoline *N*-oxide (**2**) which then undergoes either cycloaddition giving nitronate cycloadducts **3** or generation of nitrile oxide **4** through ring opening by β-elimination. We believe that the isoxazoline cycloadducts **5** have been produced via a nitrile oxide route on the basis of the following informations: (1) no trace of nitronate cycloadducts **3** was detected, (2) β-elimination of **3** should not be easy under the reaction conditions, (3) isoxazolidine ring is quite stable under basic conditions as observed for compounds **12**, (4) the dimer of nitrile oxide **4** was produced as acetylated derivative **6** (30% yield) in the presence of acetic anhydride without dipolarophile.



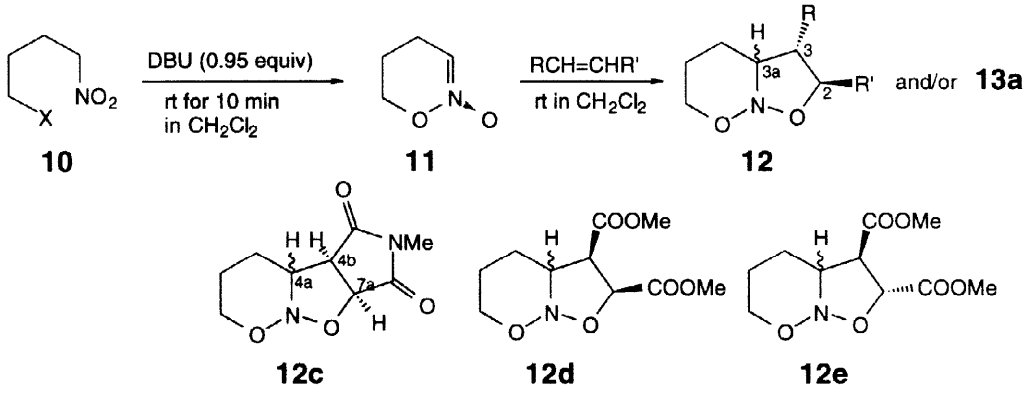
Dipolarophile	Product	Yield/%
Styrene	**5a**	61
4-Methoxystyrene	**5b**	63
3-Phenylpropene	**5c**	43
Allyl acetate	**5d**	25
Allyl ethyl ether	**5e**	28

All results are for the reactions of **1** (X = I).

Scheme 1

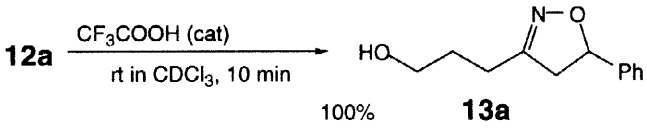
Electron deficient alkenes could not be used successfully to trap nitronate **2** (or nitrile oxide **4**).[10] For example, when nitronate generation was carried out from 3-chloro-1-nitropropane (**1**, X = Cl) and DBU in the presence of methyl acrylate, the 3-alkylated nitronate **7** was produced quantitatively as highly stable compound. DBU and **1** (X = Cl) would generate a high concentration of nitronate anion **8** which can be smoothly trapped by the acrylate to give Michael adduct **9**; the subsequent base-mediated cyclization gives **7**.

High stability of **7** indicates that the unsubstitution at 3-position of **2** is the major reason for its instability under basic conditions. Actually, isolation of the 3-unsubstituted nitronate **2** was rather difficult. Since β-elimination of **2** leading to nitrile oxide **4** should be accelerated by a base, use of excess base should be avoided to isolate the base-labile nitronate **2**. Thus, **1** (X = I) was reacted with an amount slightly less than 1 equiv of DBU at rt for 10 min to give **2** (20% yield based on ^{1}H NMR) together with the unreacted **1**. However, separation and isolation of pure **2** through column chromatography failed.[11] This ready β-elimination may be favored because of its *Z*-geometry of the cyclic nitronate moiety of **2** in which the imine hydrogen at 3-position is antiperiplanar to the leaving oxygen group.[12]



Dipolarophile	Time/h	Product	R, R' in Dipolarophile	Yield/%	Isomer ratio
Styrene	18	**12a**	R = H, R' = Ph	52	3,3a-*trans* only
Methyl acrylate	3	**12b**	R = H, R' = COOMe	75	3,3a-*trans*/*cis* = 91:9
N-Methylmaleimide	10 min	**12c**	RR' = CON(Me)CO	90	4a,4b-*trans*/*cis* = 78:22
Dimethyl maleate	24	**12d**	R = R' = COOMe (*Z*)	42	3,3a-*trans* only
Dimethyl fumarate	3	**12e**	R = R' = COOMe (*E*)	81	53:47[a]

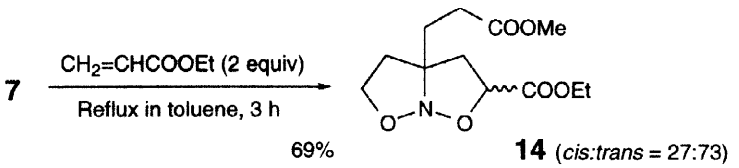
All results are for the reactions of **10** (X = I). [a] Stereochemistry unidetified.



Scheme 2

Six-membered nitronate, 5,6-dihydro-4*H*-1,2-oxazine *N*-oxide (**11**), was similarly generated and trapped with styrene: Reaction of 4-iodo-1-nitrobutane (**10**, X = I) with triethylamine (2 equiv) at rt for 72 h in the presence of styrene (1.2 equiv) gave a mixture of ring-fused isoxazolidine **12a** and isoxazoline **13a** in 52 and 7% yields respectively (Scheme 2). The nitronate cycloadduct **12a** could be easily transformed into 3-(3-hydroxypropyl)-5-phenylisoxazoline (**13a**) in a quantitative yield by treatment with a catalytic amount of trifluoroacetic acid at rt for a short time.[2] When **10** (X = I) was treated with an amount slightly less than 1 equiv of DBU at rt for 10 min, nitronate **11**[13] was isolated in 80% yield. This nitronate **11**, a colorless liquid with a fairly high stability, was applied to the reactions with a variety of dipolarophiles. Monosubstituted alkenes such as styrene and methyl acrylate showed a moderate reactivity; 2,3a-*trans*-isomers of ring-fused isoxazolidines **12a,b** having a substituent at 2-position were produced as a single or major diastereomer. *N*-Methylmaleimide was highly reactive to give a stereoisomeric mixture of **12c** in a high yield, the major isomer of which was assigned as 4a,4b-*trans*-structure (*exo*-isomer) on the basis of the NOE spectrum between H-4a/H-4b of the minor diastereomer.[14] Reactions with dimethyl maleate and fumarate were both absolutely stereospecific; although the maleate adduct **12d** was a single 3,3a-*trans*-stereoisomer, a low isomer ratio of stereoisomeric mixture of **12e** was produced from the fumarate.

As mentioned above, the 3-alkylated nitronate **7** was quantitatively obtained in the reaction of **1** (X = Cl) with methyl acrylate. Although this nitronate **7** was not highly reactive, it underwent cycloaddition with an excess amount of ethyl acrylate under reflux in toluene to give a stereoisomeric mixture (2,3a-*cis:trans* = 27:73) of 2,3a-disubstituted nitronate cycloadduct **14**.



Lewis acid catalyzed cycloadditions of cyclic nitronates with electron deficient alkenes are under progress. Results will be reported elsewhere in due time.

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9. 3-Chloro-1-nitropropane (**1**, X = Cl) and 4-chloro-1-nitrobutane (**10**, X = Cl) are less reactive starting materials because cyclization of the nitronate anions is very slow. Yields of **5**, **12**, **13** are always less than 10% and the starting chloro compounds **1** and **10** are mostly recovered unchanged.
10. When **1** (X = I) was treated with triethylamine (2 equiv) and methyl acrylate (1.2 equiv) at rt in dichloromethane, the corresponding isoxazoline was produced in 17% yield.
11. During the separation procedure by column chromatography on silica gel, most of **2** decomposes.
12. Similar thermal or base induced β-elimination leading to β-hydroxy nitriles is known: (a) Christl, M.; Mattauch, B.; Irngartinger, H.; Goldmann, A. *Chem. Ber.* **1986**, *119*, 950-959. (b) Das, N. B.; Torssell, K. B. G.; *Tetrahedron*, **1983**, *39*, 2247-2253. (c) De Sarlo, F.; Brandi, A.; Goti, A.; Guarna, A.; Rovero, P. *Heterocycles*, **1983**, *20*, 511-518. (d) Kozikowski, A. P.; Ghosh, A. K.; *J. Am. Chem. Soc.* **1982**, *104*, 5788-5789.
13. After the reaction was complete, the dichloromethane was concentrated in vacuo at rt. Hexane was added and the precipitate was removed by filteration. The filtrate was evaporated in vacuo to give the residue which contained almost pure **11**. The nitronate **11** may be stored for weeks in a freezer and one week in deuteriochloroform at rt.
14. The minor isomer of **12c** shows a clear NOEs between H-4a/H-4b and H-4b/H-7a (H-4a: $\delta = 3.79^{m}$, H-4b: 3.43^{dd}, H-7a: 5.12^{d}) to be identified as 4a,4b-*cis*-isomer (*endo*-isomer).