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Six-Membered Cyclic Nitronates as 1,3-Dipoles in Formal [3 + 3]-Cycloaddition with Donor–Acceptor Cyclopropanes. Synthesis of New Type of Bicyclic Nitrosoacetals

**Evgenia O. Gorbacheva,[†,‡] Andrey A. Tabolin,[*,†] Roman A. Novikov,[†]
Yulia A. Khomutova,[†] Yulia V. Nelyubina,[§] Yury V. Tomilov,[†] and Sema L. Ioffe[*,†]**

*N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
Leninsky prosp. 47, Moscow 119991, Russian Federation, Higher Chemical College,
D.I. Mendeleev University of Chemical Technology of Russia, Miusskaya sq. 9,
Moscow 125047, Russian Federation, and A.N. Nesmeyanov Institute of Organoelement
Compounds, Russian Academy of Sciences, Vavilov str. 28, Moscow 119991,
Russian Federation*

iof@ioc.ac.ru

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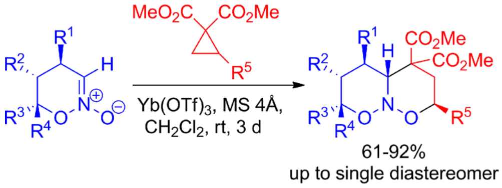
ABSTRACT



The first formal [3 + 3]-cycloaddition of nitronates with donor–acceptor cyclopropanes is reported. The reaction is catalyzed by ytterbium trifluoromethanesulfonate and leads to hitherto unknown bicyclic nitrosoacetals, possessing two annelated six-membered rings.

In the recent years there has been extensive development in the chemistry of donor–acceptor cyclopropanes (DACs).[1] The reactivity of the banana σ-bond C,C of these substrates is comparable to that of the π-bond C,C of Michael acceptors. Homo-Michael nucleophilic addition accompanies cyclopropane ring opening (Scheme 1, eq 1).[2] Formal [3 + 2]-cycloadditions ([3 + 2]-annelations) with multiple bonds where DACs act as 1,3-dipoles is another intriguing field (eq 2). Such transformations involved a wide range of dipolarophiles, including silylenolates,[3] siloxy-alkynes,[4] indoles,[5] aldehydes,[6] imines,[7] pyridines,[8] nitriles.[9]

Our interest in DAC chemistry is encouraged by their annelation capability due to the possible involvement of cyclic nitronates **1** (see Scheme 2) as the reaction partners.

[†] N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences.

[‡] D.I. Mendeleev University of Chemical Technology of Russia.

[§] A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences.

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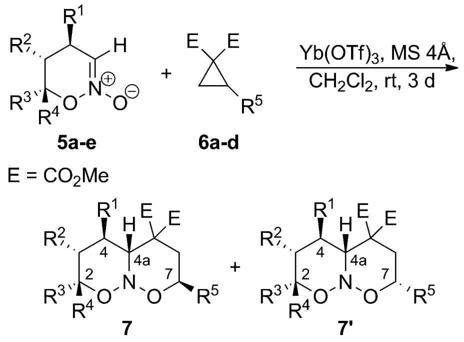
Recently a similar transformation, namely homocycloaddition of DACs with nitrones, was described by Kerr et al.[10] Further studies from that and other groups deepened the reaction understanding allowing the synthesis of various tetrahydro-1,2-oxazines,[11] including those in asymmetric mode.[12]

Utilization as 1,3-dipoles in [3 + 2]-cycloaddition is one of the most explored reactivities of nitronates.[13] In the 1990s Denmark's and Rosini's groups accomplished several total syntheses based on similar transformations.[13,14] This approach began with the synthesis of cyclic nitronates **1** (Scheme 2). Its cycloaddition with alkenes further led to the formation of bicyclic nitrosoacetals **2**. Reductive unmasking of the amine group triggered the formation of various amino-alcohol derivatives **3**, which were further transformed into target products. Undoubtedly [3 + 2]-cycloaddition itself can provide only nitrosoacetals **2** containing a five-membered isoxazolidine ring. Consequently successful involvement of nitronates **1** in a reaction with DACs should open the access to nitrosoacetals **4**, including hitherto unknown bicyclic ones possessing two six-membered rings.

Our study started from the model reaction of 1,2-oxazine-*N*-oxide **5a** with DAC **6a** (Table 1). Upon treatment with catalytic amounts of ytterbium triflate in the presence of molecular sieves, transformation proceeded to target **7aa** in pretty good yield with excellent stereoselectivity.[15] Lewis acid screening (see Supporting Information for details) revealed that the reaction can be equally catalyzed by scandium triflate. Use of nickel perchlorate decreased the reaction rate. Copper(II) triflate allowed acceleration but led to some decomposition products even in the presence of the acid scavenger, 2,6-di-*tert*-butyl-4-methylpyridine. Traditional Lewis acids ($SnCl_4$, $TiCl_4$) led only to the decay products. $AgBF_4$ failed to catalyze the reaction. Of note is the importance of molecular sieves or use of nonhydrated Lewis acids: $Yb(OTf)_3 \cdot 6H_2O$ in the absence of MS 4Å decreases the yield of annelation product **7aa** to 39%, presumably due to partial hydrolysis of starting nitronate **5a**.

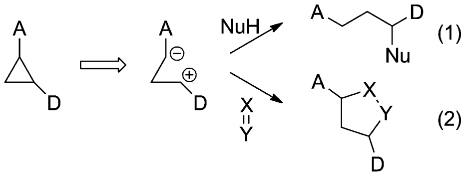
Table 1. Formal [3 + 3] Cycloaddition of Nitronates **3** with DAC **4**



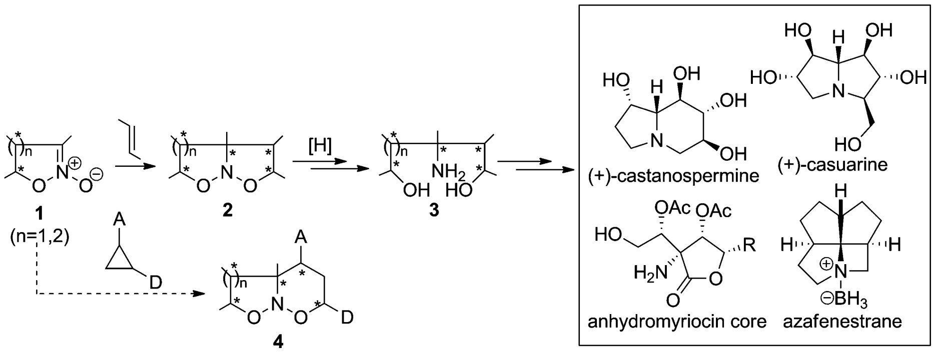
5	6	7	R^1	R^2	R^3	R^4	R^5	yield, %	7:7′
a	*a*	*aa*	An[a]	H	Me	Me	Ph	91	only **7**
b	*a*	*ba*	ClPh[b]	H	Me	Me	Ph	61	only **7**
c	*a*	*ca*	Ph	H	Ph	H	Ph	67	3.5:1
d	*a*	*da*	An	H	*n*-Pr	H	Ph	85	11:5:1[c]
e	*a*	*ea*	An	$-(CH_2)_4-$		H	Ph	80	only **7**
a	*b*	*ab*	An	H	Me	Me	ClPh	92	only **7**
a	*c*	*ac*	An	H	Me	Me	An	77	only **7**
a	*d*	*ad*	An	H	Me	Me	Th[d]	70	only **7**

[a] An = 4-MeOC_6H_4-. [b] ClPh = 4-ClC_6H_4-. [c] Unknown adduct. [d] Th = 2-thienyl.

Scheme 1. Reactivity Modes of Donor–Acceptor Cyclopropanes



Scheme 2. Cyclic Nitronates in Total Synthesis[a]



[a] * = chiral center.

The applicability of the reaction was tested on an array of nitronates **5** and DACs **6** (Table 1, Figure 1). Good yields were achieved for products shown in the Table 1, while the stereoselectivity depended on the nitronate structure. 6,6-Dimethyl substituted substrates **5a,b** gave products **7aa–ad,ba** as single diastereomers. 6-Monosubstituted substrates **5c,d** led to a diastereomeric mixture of products **7** and **7′** with the same relative configuration at bridgehead carbon C-4a and ring carbons C-2 and C-4. 3-Methyl substituted nitronate **5f** (Figure 1) failed to undergo the annelation even in refluxing toluene apparently due to steric reasons. 6-Alkoxy-substituted nitronates **5g,h** led to a complex mixture of products.

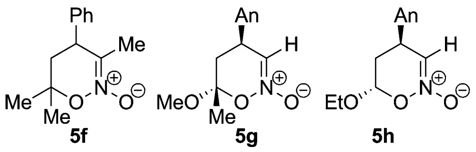


Figure 1. Nitronates, tried in [3 + 3]-annelation unsuccessfully.

Target product composition was established by means of elemental analyses or HRMS. Structures were determined by 2D NMR and X-ray data (for **7ba,ca,da,ea,7′ca**, Figure 2). Nitrosoacetals **7aa–ad,ba** at room temperature exhibit two sets of signals in ^{1}H and ^{13}C NMR that are attributed to the conformation equilibrium (Figure 3, Scheme 3). The dominant is the double chair conformation **7-1** with *trans*-ring junction. Other conformations to be expected are those with a *cis*-junction: **7-2** and **7-3**. Both of these arise from nitrogen and ring inversions. Coupling constant analysis reveals that the minor conformation is **7-2**. Such domination of the *trans*-junction in nitrosoacetals **7aa–ad,ba,ea** is intriguing because such a structure lacks the stabilizing anomeric interaction in the O–N–O moiety. Indeed, 6-ring-5-ring-annelated nitrosoacetals **8** are known to adopt a conformation with the *cis*-junction, with the N–O bond of the six-membered ring being pseudoaxial with respect to the five-membered ring.[16]

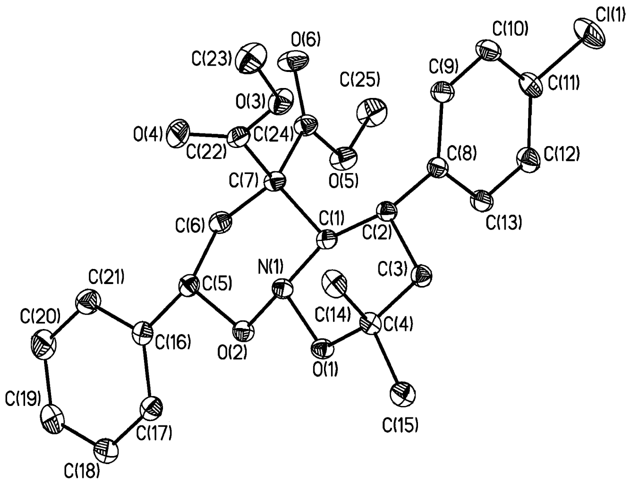
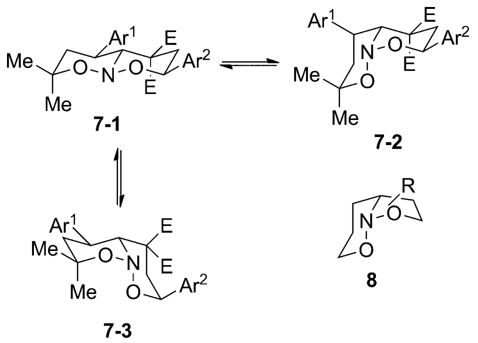


Figure 2. ORTEP drawing for **7ba**.

Scheme 3. Conformational Equilibrium of Nitrosoacetals **5**



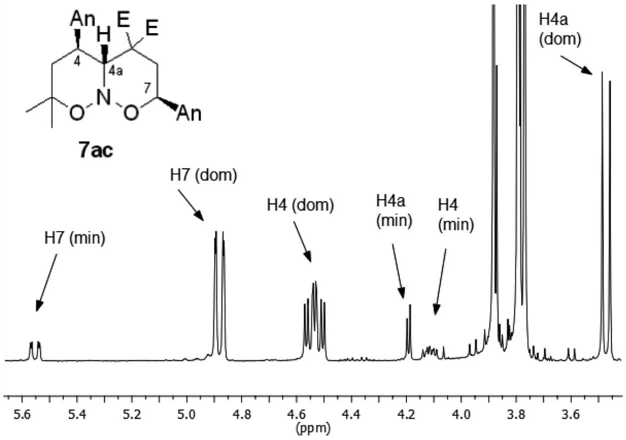


Figure 3. Part of ^{1}H NMR spectra for **7ac**.

In conclusion here we reported the synthesis of bicyclic nitrosoacetals **7** by means of ytterbium triflate mediated annelation of cyclic nitronates **5** with DACs **6**. Our next

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efforts will be focused on broadening the reaction scope, including stereochemical regularities, and investigation of the chemistry of adducts **7**.

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Supporting Information Available. Experimental procedures, analytical data and copies of NMR spectra, cif files for compounds **7ba**,**ca**,**da**,**ea**,**7′ca**. This material is available free of charge via the Internet at http://pubs.acs.org.

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