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Tandem 6π-Electrocyclization and Cycloaddition of Nitrodienes to Yield Multicyclic Nitroso Acetals

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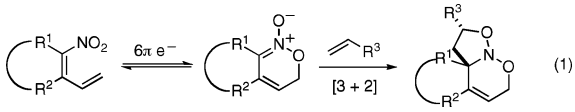
Pericyclic reactions are among the most versatile transformations in synthetic organic chemistry. In a single step, pericyclic reactions rapidly generate molecular complexity from simpler starting materials, often with predictable and well-defined stereochemical outcomes. An even more powerful effect is generated when more than one pericyclic reaction is combined in a domino process, wherein the product of the first reaction serves as a substrate for the subsequent reaction(s).[1] Among the known pericyclic reactions, electrocyclization has been studied relatively less exhaustively than, for example, cycloaddition or sigmatropic rearrangement, despite its synthetic potential for the assembly of complex six-membered-ring cyclic compounds.[2] In this context, we became particularly interested in the possible 6π-electrocyclizations of nitrodienes, examples of which are absent from the literature.[3] The resulting nitronates are well-established substrates for dipolar cycloaddition,[4] suggesting the potential for domino electrocyclization/dipolar cycloaddition. Herein, we disclose the first example of a 6π-electrocyclization of nitrodienes and subsequent [3 + 2] cycloadditions of the resulting nitronates to form tricyclic nitroso acetals with well-defined stereochemistry (eq 1).



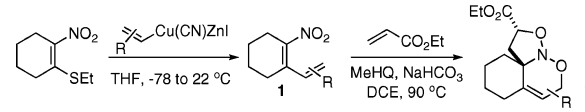
(1)

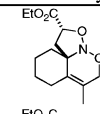
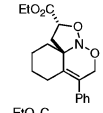
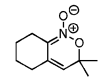
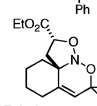
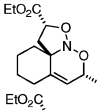
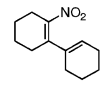
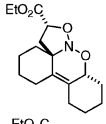
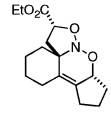
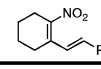
The closest examples to the 6π-electrocyclization of nitrodienes are the six-electron, five-atom electrocyclizations of nitrostyrenes, nitrostilbenes, and nitrobiphenyls under reductive deoxygenation conditions to generate indoles and carbazoles.[5] Denmark et al. developed a powerful protocol for the formation of nitronate dipoles through hetero-Diels−Alder reactions of nitroalkenes and subsequent dipolar cycloadditions;[6] they have applied this elegant methodology toward the construction of several multicyclic alkaloid natural products.[7] In addition, formal [4 + 1] cycloadditions of sulfur ylides and nitroalkenes, generating nitronate intermediates, have been reported very recently.[8] Finally, there are rare examples of sigmatropic rearrangements of γ,δ-unsaturated nitroalkenes providing cyclic nitronates that undergo further reactions.[9]

As we launched our investigation into the possibility of 6π-electrocyclization of nitrodienes, it immediately became apparent that the preparation of nitrodienes with the requisite internal *cis*-olefin geometry would be a challenge. Locking the internal double bond into a ring, by tethering the R^1 and R^2 units, presented itself as a practical solution. In addition, literature precedents portended that the equilibrium between the nitrodiene and nitronate would lie unfavorably;[10] we designed to overcome this problem by trapping the nitronate products in situ with dipolarophiles.

Pleasingly, our synthetic plan was realized as described (Table 1). Conjugate addition/elimination of zinc cuprates, derived from readily accessible vinyl halides, into 2-thioethyl nitrocyclohexene[11] provided ready access to the desired nitrodienes.[12] Both 2-bromopropene and α-bromostyrene readily formed their expected nitrodienes (**1a** and **1b**, respectively); upon heating in the presence of ethyl acrylate at 90 °C, both nitrodienes underwent rearrangement and exoselective dipolar cycloaddition[13] to form their anticipated nitroso acetal products (entries 1 and 2).[14] Unexpectedly, the δ,δ-dimethylnitrodiene prepared from 1-bromo-2-methylpropene spontaneously rearranged to the corresponding nitronate **2** during chromatography over SiO_2 (entry 3, 86% isolated yield); this nitronate smoothly underwent the subsequent [3 + 2] cycloaddition to produce the nitroso acetal **3c** in 91% yield.

Table 1. Syntheses of Nitrodienes, Nitronates, and Nitroso Acetals[a]



entry	halide	nitrodiene **1** isolated yield (%)	nitroso acetal **3** isolated yield (%)
1		 **1a** 81%	 **3a** 79%
2		 **1b** 77%	 **3b** 78%
3		 **2** 86%	 **3c** 91%[b]
4		 **1d** 53%	 **3d** 60% 1.6:1 dr
5		 **1e** 83%	 **3e** 78% 5.2:1 dr
6		 **1f** 88%	 **3f** 79%
7[c]		 **1g** 87%	— 0%

[a] Experimental details are provided in the Supporting Information. [b] Reaction performed in CH_2Cl_2 at 22 °C. [c] Use of either *cis*- or *trans*-β-bromostyrene produced **1g**.

For mono-δ-substituted nitrodienes, an additional stereogenic center is formed. For instance, the δ-*n*-butyl nitrodiene **1d** resulted in a 1.6:1 mixture of two diastereoisomers upon reaction with ethyl acrylate (entry 4). Conversely, the 2-cyclohexenyl nitrocyclohexene **1e** smoothly rearranged to the corresponding nitronate and formed the tetracyclic nitroso acetal **3e** with improved selectivity (5.2:1, entry 5). The nitrodiene **1f**, featuring a cyclopentenyl group, provided even better

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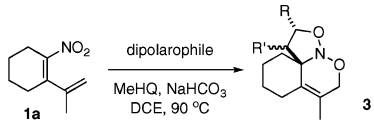
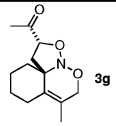
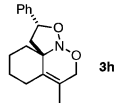
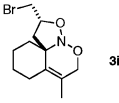
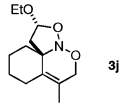
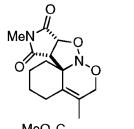
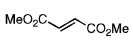
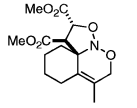
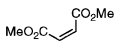
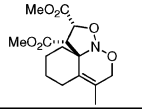
selectivity: we obtained the tetracycle **3f** as a single diastereoisomer in 79% isolated yield (entry 6). Apparently, ethyl acrylate approached the nitronate dipole preferentially from the face of its δ-hydrogen atom.[14] The δ-phenyl-substituted nitrodiene **1g** was recalcitrant to the rearrangement, presumably because of its exceptional stability stemming from the extensively conjugated framework (entry 7).

The scope of the dipolarophile partners was further investigated (Table 2). Another electron-deficient olefin, methyl vinyl ketone, was smoothly incorporated into the cascade sequence, forming the nitroso acetal **3g** in good yield with reasonable diastereoselectivity (entry 1). Styrene (electron-neutral) was also an excellent dipolarophile, providing the nitroso acetal **3h** as a single diastereoisomer in 88% yield (entry 2). Allyl bromide also proved to be a viable dipolarophile, albeit with poorer diastereoselectivity (entry 3). Gratifyingly, ethyl vinyl ether (electron-rich) was also an excellent dipolarophile, yielding the nitroso acetal **3j** (62%) as a single diastereoisomer (entry 4). *N*-Methylmaleimide underwent the dipolar cycloaddition in a highly efficient and stereoselective manner (entry 5). The trans-disubstituted olefin dimethyl fumarate was an excellent dipolarophile (entry 6), as was its cis isomer, dimethyl maleate (entry 7).

Table 2. Electrocyclization/Cycloadditions of Nitrodiene **1a**

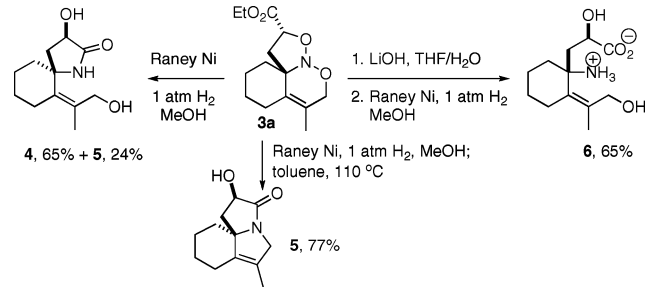


entry	dipolarophile	nitroso acetal **3**	yield[a]	exo/endo
1		 **3g**	79	5:1
2		 **3h**	88	exo only
3		 **3i**	63	1.3:1
4		 **3j**	62	exo only
5		 **3k**	80	exo only
6		 **3l**	81	exo only
7		 **3m**	64	exo only[b]

[a] Isolated yields after chromatographic purification. [b] The reaction yielded **3m** accompanied by 18% of **3l**.

The nitroso acetals served as versatile starting materials for the construction of complex amino alcohol derivatives. For instance, subjecting **3a** to standard Raney Ni hydrogenolysis conditions, we generated the spirocyclic amide **4** in 65% yield, along with the tricyclic minor product **5** (Scheme 1).[15] Hydrogenolysis of **3a**, followed by heating the crude reaction mixture under reflux in toluene, produced the tricyclic amide **5** in 77% isolated yield. Saponification of the ethyl ester prior to hydrogenolysis precluded amide formation, resulting in isolation of the amino dihydroxy acid **6** after exposure to Raney Ni. Therefore, reduction of the nitroso acetal is a versatile and powerful reaction modality capable of following several potential reaction pathways without loss of the stereochemical information gained from the tandem electrocyclization/dipolar cycloaddition.

Scheme 1. Selective Hydrogenolyses of the Nitroso Acetal **3a**



In summary, we have developed a new transformation: the 6π-electrocyclization of nitrodienes and subsequent capture of the intermediate nitronates through dipolar cycloaddition. In this one-pot domino process, two rings are formed with one quaternary center generated; the products are isolated, typically as single diastereoisomers, in good to excellent yields. Hydrogenolysis of the resulting nitroso acetal products provides highly functionalized, synthetically useful structures. We are currently investigating expanding the substrate scope to acyclic systems, as well as unveiling other latent pericyclic reactivities of the nitroalkenes.

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Supporting Information Available: Representative experimental procedures; spectral data for all new compounds (PDF); crystallographic data for **2** and **3a** (CIF). This information is available free of charge via the Internet at http://pubs.acs.org.

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(13) The presence of both $NaHCO_3$ and methyl hydroquinone (MeHQ) improved the efficiency of the reaction, presumably because MeHQ acted as a stabilizer (reducing decomposition of the nitrodiene) and the bicarbonate sequestered trace acid. Denmark, S. E.; Gomez, L. *J. Org. Chem.* **2003**, *68*, 8015.
(14) Structures **2** and **3a** were confirmed through X-ray crystallographic analysis. The relative stereochemistry of **3f** (and the major adducts for **3d** and **3e**) was rigorously established based on NOE data and comparison to the spectra of the nitroso acetal **3a**. See the Supporting Information for details.
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