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Hetero Diels–Alder Reactions of Nitrosoamidines: An Efficient Method for the Synthesis of Functionalized Guanidines

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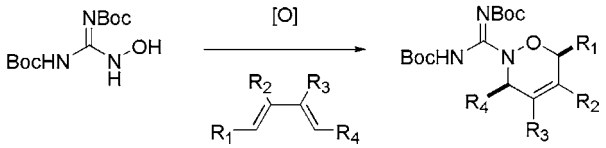
ABSTRACT



Hetero Diels–Alder reactions of transient nitrosoamidines are reported. Transient nitrosoamidines are formed by oxidation of protected *N*-hydroxylguanidines and are trapped in situ by 1,3-dienes to give [4 + 2] cycloadducts in good yields and regioselectivity. The resultant cycloadducts are versatile intermediates for the formation of functionalized guanidines.

Nitroso heterodienophiles (i.e., R−N═O) have been widely used since the initial discovery by Wichterle over 50 years ago.[1] Kirby[2] later significantly advanced this methodology from a synthetic standpoint, through the development of transient acylnitroso dienophiles (i.e., RCO−N═O).[3] Very reactive acylnitroso species could thus be generated by the oxidation of hydroxamic acids and trapped in situ with a variety of 1,3-dienes. The increased reactivity of acylnitroso intermediates in normal electron-demand Diels−Alder reactions occurs because the electron-withdrawing acyl group lowers the LUMO energy of the dienophile. This methodology has since been used as the key step in a wide range of natural product syntheses[4] and has expanded to include a number of structurally diverse derivatives including iminonitroso,[5] α-chloronitroso,[6] cyanonitroso,[7] vinylnitroso,[8] and most recently *P*-nitroso phosphine oxide[9] heterodienophiles, each with varying degrees of utility in [4 + 2] cycloaddition reactions. We now report the reactivity and synthetic utility of transient nitrosoamidines as heterodienophiles.

The increasing number of structurally diverse guanidine compounds with biological relevancy[10] highlights a need for new strategies to address the significant synthetic challenges associated with the introduction and manipulation of substituted guanidines. Our interest in the synthesis of func-

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(2) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1−24.
(3) For reviews of nitroso Diels−Alder reactions, see: (a) Vogt, P. F.; Miller, M.J. *Tetrahedron* **1998**, *54*, 1317−1348. (b). Streith, J.; Defoin, A. *Synthesis* **1994**, 1107−1117. (c) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087−3128.
(4) For representative examples, see: (a) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583−4592. (b) Carbanal-Duvillard, I.; Berrien, J. F.; Royer, J. *Tetrahedron: Asymmetry* **2000**, *12*, 2525−2532. (c) Zhang, D.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 755−759. (c) Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4602−4611. (d) Ledford, B. E.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 11811−11812. (e) Kibayashi, C.; Aoyagi, S.; *Synlett* **1995**, 873−879. (f) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444−458. (g) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089−5090.
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(7) Horsewood, P. K.; Kirby, G. W. *J. Chem. Soc., Perkin Trans.* **1980**, 1587−1591.
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(9) (a) Ware, R. W.; King, S. B. *J. Am. Chem. Soc.* **1999**, *121*, 6769−6770. (b) Ware, R. W.; King, S. B. *J. Org. Chem.* **2000**, *65*, 8725−8729. (c) Ware, R. W.; King, S. B. *J. Org. Chem.* **2002**, *67*, 6174−6180.
(10) For reviews of guanidine natural products, see: Berlink, R. G. S *Nat. Prod. Rep.* **2002**, *19*, 617−649 and references therein.

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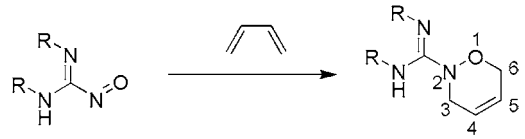
tionalized guanidines[11] has prompted us to consider alternative methods for guanidine synthesis. We envisaged that a nitrosoamidine **1** could serve as a precursor for the formation of highly functionalized guanidines and provide a new entry point for the synthesis of complex guanidine targets. Although nitrosoamidines **1** are likely to be less reactive than acylnitroso compounds, the amidinyl group of **1** should be sufficiently electron-withdrawing to facilitate a hetero Diels−Alder reaction with 1,3-dienes in a synthetically useful manner. Thus, reaction of **1** with a diene would lead to the formation of cycloadduct **2** (Scheme 1). Moreover,

Scheme 1

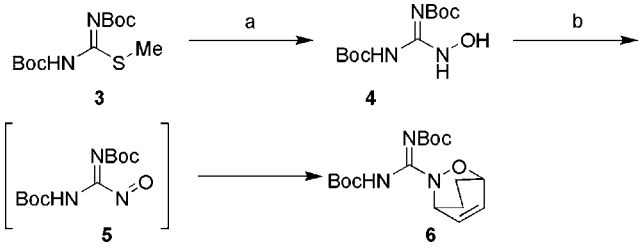


1 **2**

by comparison with the results of acylnitroso reactions, regioselective additions should also be possible with substituted 1,3-dienes. The functionality of oxazinyl amidines **2** provides multiple opportunities for synthetic elaboration, including reductive cleavage of the N2−O1 bond, C6−O1 bond cleavage, and alkene functionalization.

N,*N*′-Bis-Boc-*N*″-hydroxylguanidine **4** was chosen as a suitable nitrosoamidine precursor, since Boc substituents are one of the most widely used guanidine-protecting groups,[12] and their presence should further enhance the electron-withdrawing capacity of the amidinyl group, leading to greater reactivity in the Diels−Alder cycloaddition. Compound **4** can be synthesized in moderate yield from *N*,*N*′-bis-Boc-*S*-methylisothiourea[13] **3** via guanylation[14] of hydroxylamine hydrochloride with stoichiometric $HgCl_2$ and Amberlyst A21 exchange resin in acetonitrile (Scheme 2).

Scheme 2 [a]



[a] Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, $HgCl_2$, Amberlyst A21, 12 h, 61%; (b) Bu_4NIO_4, 1,3-cyclohexadiene, CH_2Cl_2, 61%.

A variety of conditions have been developed for acylnitroso chemistry, but the most commonly used procedures involve mild periodate-based oxidants or the Swern protocol. Analogous conditions were used in the test reaction of **4** with 1,3-cyclohexadiene and Bu_4NIO_4 as the oxidant in anhydrous CH_2Cl_2 at room temperature. Complete disappearance of the starting material occurred after 8 h, yielding cycloadduct **6** in 61% isolated yield, presumably via the transient nitrosoamidine **5**. Although nitrosoamidine **5** was not directly observed,[15] cycloadduct **6** is formally the product of a [4 + 2] cycloadddition reaction between **5** and 1,3-cyclohexadiene. An extensive optimization study was subsequently performed and revealed that slow addition of **4** in small portions over 2 h to a stirred solution of a stoichiometric amount of oxidant and 1,3-cyclohexadiene was found to produce cycloadduct **6** in as high as 85% yield using Pr_4NIO_4[16] in MeOH and produced satisfactory results under a variety of conditions. Interestingly, the use of Pr_4NIO_4 led to consistently higher product yields than were obtained using Bu_4NIO_4. Investigation into increasing the concentration of both the diene and oxidant from 1.1 to 5 equiv, respectively, had no apparent effect on the reaction. The use of Dess−Martin reagent in CH_2Cl_2 or $CHCl_3$ was found to be a suitable replacement for Pr_4NIO_4 providing similar, though slightly diminished, yields.

The scope of the reaction was investigated using a series of symmetrical 1,3-dienes employing the optimized conditions[17] (Table 1). Cyclic dienes locked in the required and reactive *s-cis* conformation were found to react rapidly with **5** to produce the cycloadducts at room temperature (Table 1, entries 1 and 2). On the other hand, for reactions with acyclic dienes in which free rotation about the C−C σ bond of the diene can occur, maximal yields were obtained when the reactions were conducted at 0 °C (Table 1, entries 3 and 4). The origin of this difference is not clear at this point.

The issue of regioselectivity of the cycloaddition is a complicating feature in the reactions of **5** with unsymmetric dienes. Following the same general procedure as for the reaction with symmetric dienes, a number of cycloadducts were produced in good yield and excellent regioselectivity (Table 2). In the case of acylnitroso compounds, it is postulated that electronic dissymmetry in the LUMO of the dienophile accounts for the high levels of regioselectivity

(11) (a) Batey, R. A.; Powell, D. A. *Chem. Commun.* **2001**, 2362−2363. (b) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913−2916. (c) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133−136. (d) Powell, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.* **2003**, *68*, 2300−2309.

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(13) Bergeron, R. J.; McManis, J. S. *J. Org. Chem.* **1987**, *52*, 1700−1711.

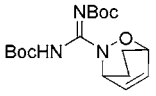
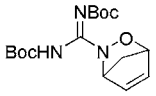
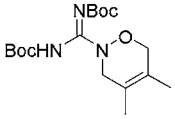
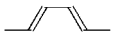
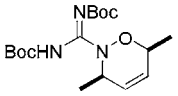
(14) For discussion of the term guanylation see ref 11d and references therein.

(15) Until recently no methods existed for the direct observation of acylnitroso species in solution. Time-resolved infrared spectroscopy has recently been employed in the direct detection of acylnitroso compounds in solution. See: Cohen, A. D.; Zeng, B.; King, S. B.; Toscano, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1444−1445.

(16) Crystalline Pr_4NIO_4 is conveniently prepared by treatment of equimolar amounts of Pr_4NOH and HIO_4 in water; see: Keck, G. E.; Fleming, S. A. *Tetrahedron Lett.* **1978**, *19*, 4763−4766.

(17) **General Procedure for Cycloaddition of 2.** A stirred solution of diene (1.1 equiv) and Pr_4NIO_4 (1.1 equiv) in MeOH was cooled to 0 °C in an ice−water bath, and to this was added **4** in small portions over 2 h. The solution was allowed to warm to room temperature over 12 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated sodium thiosulfate and brine and dried with $MgSO_4$. The solvent was removed under vacuum, and the resulting product was purified by silica gel chromatography.

Table 1. Reaction of **4** with Symmetric 1,3-Dienes in the Presence of Pr_4NIO_4

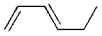
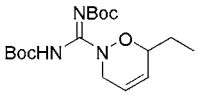
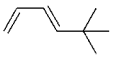
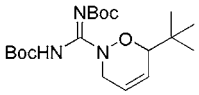
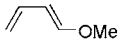
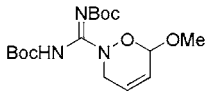
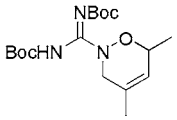
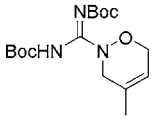
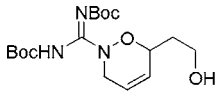
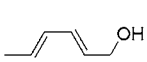
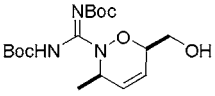
entry	diene	product	yield (%)[a]
1			85
2			81
3			78
4			78

[a] Isolated yields

observed in most reactions. The observed regioselectivity was found to be consistent with that of other nitroso dienophiles[18] with 1-subsituted dienes reacting to form the cycloadduct where the proximal regioisomer dominates (Table 2, entries 1−3 and 6), whereas 2-substituted dienes preferentially form the distal isomers (Table 2, entry 5). The nomenclature employed to describe the regiochemistry of these cycloadducts is the same as that employed by Boger.[19] The proximal regioisomer is the one in which the diene substituent is closest to oxygen and the distal isomer is that with the substituent furthest from oxygen. Increased steric hindrance at the 1-position of the 1,3-dienes did not appreciably alter the regioselectivity, as shown by the comparison of ethyl- and *tert*-butyl-substituted dienes (Table 2, entries 1 and 2). The presence of a strongly electron-donating substituent at the 1-position of the diene gave excellent results, with only one regioisomer detected by ^{1}H NMR (Table 2, entry 3). Dienes with electron-withdrawing substituents failed in their reaction with **4**, indicating that this reaction falls into the class of normal electron-demand Diels−Alder reactions. Thus, ethyl sorbate, sorbic acid, and sorbic aldehyde produced none of the desired cycloadduct with only decomposition of **4** observed even when a large excess of diene was used and under numerous temperature profiles.

Having produced a variety of cycloadducts in good overall yield and regioselectivity, our attention turned toward generating useful guanidine-containing compounds by simple transformations of the initial cycloadducts. Perhaps the most important such transformation is N−O bond reduction, which for cycloadducts **6** would result in the formation of hydroxycyclohexenyl guanidine **7**. A number of standard reductive

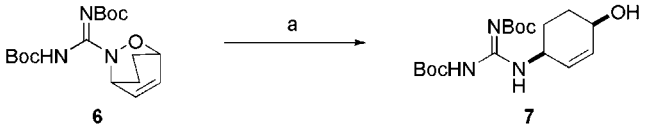
Table 2. Reaction of **4** with Unsymmetric 1,3-Dienes in the Presence of Pr_4NIO_4

entry	diene	major product	yield (%)[a]	ratio[b]
1			75	85:15
2			79	83:17
3			86	≥98:2
4			70	≥98:2
5			71	81:19
6			74	91:9
7			60	≥98:2

[a] Isolated yield. [b] Regioisomeric ratio was determined by ^{1}H NMR of the crude reaction mixtures.

procedures were attempted to cleave the N−O bond of **6**, including $Mo(CO)_6$,[20] $LiAlH_4$,[21] Zn in acetic acid,[22] and hydrogenation over Raney nickel,[23] without success. However, reduction of **6** to **7** could be accomplished in high yield with the use of Na(Hg) amalgam[24] (Scheme 3).

Scheme 3 [a]



6 **7**

[a] Reagents and conditions: (a) Na(Hg) amalgam, Na_2HPO_4, EtOH, 95%.

Alternatively, N−O bond cleavage can be achieved following alkene reduction. Hydrogenation of **6** over Pearl-

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(19) Boger, D. L.; Patel, M.; Takusagawa, F. *J. Org. Chem.* **1985**, *50*, 1911−1916.
(20) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3358.
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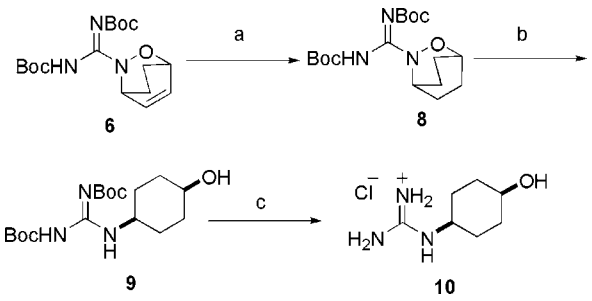
(22) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876−2882.

man's catalyst gave **8**, which then underwent facile reduction to **9** via hydrogenation over Raney nickel. Subsequent Boc deprotection under acidic conditions generated guanidine **10** as an HCl salt (Scheme 4)

Scheme 4 [a]



[a] Reagents and conditions: (a) H_2, $Pd(OH)_2$ MeOH, 73%; (b) H_2, Raney Ni, MeOH, 91%; (c) 2 M HCl, MeOH, 89%.

In conclusion, nitrosoamidines constitute a new class of substituted N═O heterodienophiles. *N*-Protected hydroxylguanidines can be oxidized in the presence of 1,3-dienes to generate transient nitrosoamidines that undergo rapid [4 + 2] cycloaddition. Optimal conditions for the oxidation utilize Pr_4NIO_4 in MeOH at 0 °C. The cycloadducts are formed in good yields, and in reactions with unsymmetrical dienes, a strong preference for the proximal isomer is observed with 1-substituted dienes and for the distal isomer with 2-substituted dienes. These regioselectivity patterns are similar to those observed with acylnitroso Diels−Alder adducts. The cycloadducts are versatile intermediates for further elaboration, and applications of their utility in complex guanidine target synthesis, such as the batzelladine alkaloids, will be reported in due course.

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

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