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Synthesis of 2,3-Dihydroisoxazoles from Propargylic *N*-Hydroxylamines via Zn(II)-Catalyzed Ring-Closure Reaction

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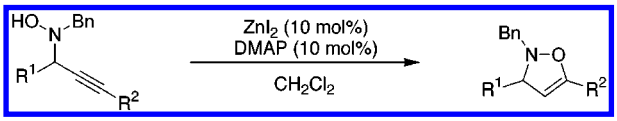
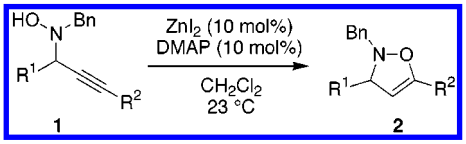
ABSTRACT



A novel cyclization reaction of propargylic *N*-hydroxylamines to 2,3,5-trisubstituted 2,3-dihydroisoxazoles in the presence of catalytic amounts (10 mol %) of ZnI_2 and DMAP is reported. The methodology provides a mild new approach to this useful class of substituted heterocycles that complements extant methods. The unique reactivity of the propargylic *N*-hydroxylamine substrates in the presence of Zn(II) and DMAP may have additional applications in other, related alkyne cyclization reactions.

2,3-Dihydroisoxazoles represent a class of heterocycles that may be employed as useful building blocks for synthesis.[1] Most commonly they are prepared in the laboratory through either the 1,3-dipolar cycloaddition reaction of nitrones and alkynes or the condensation reaction of *N*-hydroxylamines and α,β-unsaturated ketones. Although cycloaddition reactions can provide ready access to 2,3-dihydroisoxazoles, they typically furnish regioisomeric mixtures of adducts.[1f] In principle, the intramolecular cyclization of propargylic *N*-hydroxylamines can also provide direct access to 2,3,5-trisubstituted 2,3-dihydroisoxazoles. Surprisingly, such a transformation has not been investigated and, to the best of our knowledge, lacks precedence. Nevertheless, the development of such a cyclization reaction under mild, catalytic conditions would considerably facilitate access to this synthetically useful class of dihydroisoxazoles. We have recently reported a novel, mild, catalytic method for the preparation of propargylic *N*-hydroxylamines from nitrones and terminal acetylenes.[2] Key to this method is the in situ generation of a Zn-alkynilide under mild conditions (23 °C; toluene, MeCN, or Et_2O). Thus, in the presence of catalytic $Zn(OTf)_2$ and Et_3N, terminal alkynes undergo addition to nitrones at room temperature in high yields to give propargylic *N*-hydroxylamines. In optimizing and studying these addition reactions, we had observed the formation of 2,3-dihydroisoxazoles as minor side products under certain conditions. In the context of our interest in developing methods for heterocycle synthesis,[3] herein we document that in the presence of catalytic ZnI_2 and DMAP (10 mol % each), propargylic *N*-hydroxylamines undergo 5-endo-dig cyclization to the corresponding 2,3-dihydroisoxazoles in good yields (Scheme 1).[4] The cyclization is demonstrated to be general for a wide range of propargylic *N*-hydroxylamines.

Scheme 1. Cyclization of the Propargylic *N*-Hydroxylamines to 2,3-Dihydroisoxazoles



In a series of studies by McDonald, homopropargylic alcohols have been shown to participate in metal-mediated

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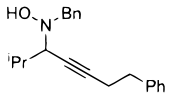
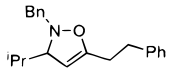
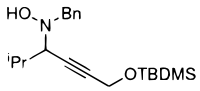
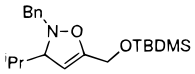
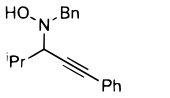
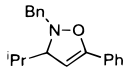
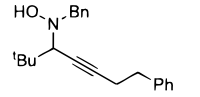
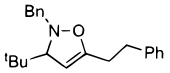
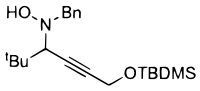
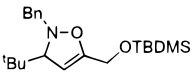
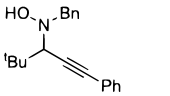
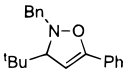
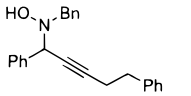
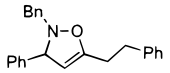
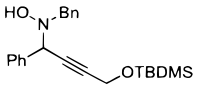
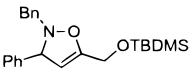
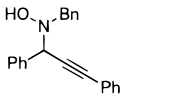
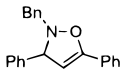
(Mo and Cr) cyclization reactions to furnish 2,3-dihydrofurans.[5] The cyclization reactions of alkynyl allylic alcohols to the corresponding furans under basic conditions have been the subject of investigations by Marshall in the context of synthetic studies aimed at 2,5-furanocyclic natural products.[6] Additionally, Marshall has documented the Ag(I)-catalyzed isomerization of allenones to furans along with allenyl carbinols to 2,5-dihydrofurans.[7] The 5-exo-trig iodocyclization reaction of allylic *O*-silylated *N*-hydroxylamines using NIS has been reported to give iodo-substituted isoxazolidines in 55−91% yields.[8,9] By contrast, the direct cyclization reaction of propargylic *N*-hydroxylamines to 2,3-dihydroisoxazoles, however, has not been examined.

In the context our investigations of the Zn(II)- and amine-catalyzed addition reaction of terminal acetylenes to nitrones, we carried out a series of investigations in which the structure of the amine base was systematically varied. As we have previously noted, the use of Et_3N or Hünig's base leads to generation of a putative Zn-acetylide that subsequently participates in additions to nitrones and imines. When pyridine was employed under otherwise identical conditions ($Zn(OTf)_2$, 23 °C, CH_2Cl_2), the starting nitrone and terminal acetylene could be recovered quantitatively. This observation suggested that pyridine is insufficiently basic to effect deprotonation of terminal alkyne·Zn(II) complex. Interestingly, however, when this same mixture of $Zn(OTf)_2$, pyridine, acetylene, and nitrone was treated with Hünig's base, rapid formation of a product (91%) was observed that was subsequently shown to correspond to a 2,3-dihydroisoxazole. In subsequent studies (vide infra), we established that the 2,3-dihydroisoxazoles isolated from these test reactions were generated as secondary products from the first-formed propargylic *N*-hydroxylamines. We have subsequently investigated a one-pot procedure for acetylide addition to nitrones to give propargylic *N*-hydroxylamines with cyclization to give 2,3-dihydroisoxazoles; however, at the current level of development this has not been possible. Nonetheless, we have found that treatment of propargylic *N*-hydroxylamines with ZnI_2 and DMAP in CH_2Cl_2 at 23 °C afforded clean conversion to 2,3-dihydroisoxazoles.

As shown in Table 1, a wide range of propargylic *N*-hydroxylamines participate in this transformation to afford heterocyclic products in good yields. The workup of the

Table 1. Cyclization Reaction of Propargylic *N*-Hydroxylamines[a]

Entry	Hydroxylamine	Time, Yield	Product
1		1 h 95%	
2		26 h 94%	
3		3 h 94%	
4		1 h 97%	
5		28 h 93%	
6		2 h 91%	
7		1 h 92%	
8		32 h 82%	
9		4 h 91%	

[a] Conditions: 10 mol % of ZnI_2 and 10 mol % of DMAP were added to a solution of propargylic *N*-hydroxylamine in CH_2Cl_2 at 23 °C. The reaction mixture was stirred for the time indicated above before it was quenched by partitioning between CH_2Cl_2 and an aqueous ammonium chloride solution. Yields are of the pure isolated compounds.

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(4) 5-Endo-dig cyclizations were discussed in the original formulation of Baldwin's rules and constitute an allowed process, see: (a) Baldwin,J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738. (c) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silbermann, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun*. **1976**, 736. (c) Baldwin, J. *Rules for Ring Closure*, Ciba Foundation Symposium 53, Furhter Perspectives in Organic Chemistry; Elsevier: New York, 1978; p 85.

(5) (a) Bowman, J. L.; McDonald, F. E *J. Org. Chem*. **1998**, *60*, 3680. (b) McDonald, F. E.; Bowman, J. L *Tetrahedron Lett*. **1996**, 4675. (c) McDonald, F. E.; Connolly, C. B.; Gleason, G. G. *J. Org. Chem*. **1993**, *58*, 6952.

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(7) (a) Marshalll, J. A.; Yu, B. C. *J. Org. Chem*. **1994**, *59*, 324. (b) Marshall, J. A. Bartley, G. S. *J. Org. Chem*. **1994**, *59*, 7169.

(8) (a) Fiumana, A.; Lombardo, M.; Trombini, C. *J. Org. Chem*. **1997**, *62*, 5623.

(9) For a recently reported example involving the intramolecular 5-endo-trig cyclization reaction of 2-alkynyl anilides to indoles, see: Ma, C.; He, X.; Liu, X.; Cook, J. M. *Tetrahedron Lett*. **2000**, *41*, 2781.

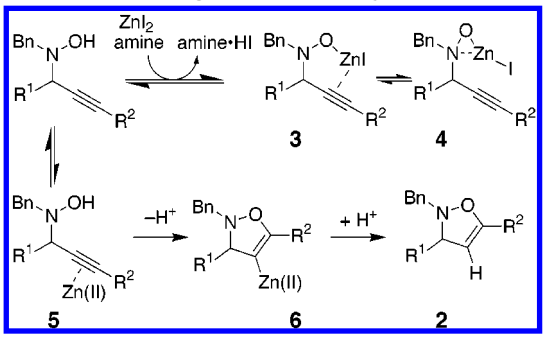
reaction is experimentally straightforward, as a simple acidic aqueous workup allows for the separation of the reactants (Zn(II) and DMAP) from the product. With the exception of those substrates incorporating propargylic silyl ethers (entries 2, 5, and 8) the cyclization reactions are observed to proceed in 1−4 h (Table 1).

We have carried out a number of control experiments that provide insight into the mechanistic aspects of the novel cyclization reaction and highlight the unique aspects of the combination of ZnI_2 and DMAP as catalysts. As highlighted above, although the combination of Hünig's base and $Zn(OTf)_2$ leads to the addition reaction of terminal acetylenes and nitrones, this reagent combination does not lead to cyclization of the propargylic *N*-hydroxylamine during the reaction times (4−8 h) that have been employed for the nitrone addition reactions. Only in the presence of $Zn(OTf)_2$ and pyridine, with the latter present either at the outset of the reaction or after formation of the propargylic *N*-hydroxylamine adducts, could the formation of heterocyclic adduct be observed. This led us to suspect that a complex formed between DMAP and Zn(II) has the special ability to activate both the *N*-hydroxylamine and the C−C triple bond toward the cyclization reaction. Indeed, only upon prolonged stirring (>28 h) could any 2,3-dihydroisoxazole be observed (5%) upon treatment of starting propargylic *N*-hydroxylamine with Hünig's base and $Zn(OTf)_2$. Although our initial studies employed $Zn(OTf)_2$ in the cyclization reaction, we have observed that $ZnCl_2$, $ZnBr_2$, and ZnI_2 promote heterocycle formation from propargylic *N*-hydroxylamines, with ZnI_2 affording product at the fastest rate.

A series of control experiments were conducted to examine and preclude proton-catalyzed processes. In this regard, we were unable to induce the cyclization of propargylic *N*-hydroxylamines in the presence of triflic acid. Additionally, the combination of other Lewis acids ($BF_3{\cdot}OEt_2$, $AlCl_3$, $Cu(OTf)_2$, $Mg(OTf)_2$, and $Sn(OTf)_2$) along with DMAP or Hünig's base did not lead to the formation of 2,3-dihydroisoxazoles. Heating a solution of the propargylic *N*-hydroxylamines in toluene or CH_2Cl_2 returned starting material. To establish that the reaction was not proceeding through a mechanism in which the propargylic *N*-hydroxylamine undergoes $C_{sp}-C_{sp^3}$ bond cleavage to give the corresponding terminal acetylene and nitrone followed by a recombination through a dipolar cycloaddition reaction to give 2,3-dihydroisoxazoles directly, a crossover experiment was conducted. Thus, treatment of a 1:1 mixture of the *N*-hydroxylamines from entries 6 and 7 (Table 1) under the reaction conditions we have described (10 mol % of ZnI_2, and DMAP, CH_2Cl_2, 23 °C) gave a 1:1 mixture of 2,3-dihydroisoxazoles expected from intramolecular cyclization and none resulting from cross-reactivity.

The mechanistic details of the process we have described are currently under scrutiny in order to determine the nature of the reactive species involved. In our working hypothesis, we speculate that the resting state of the Zn(II) is a coordination complex that results from association of the *N*-hydroxylamine and the Zn(II) (Scheme 2, cf. **3** and **4**).[10]

Scheme 2. Working Model for the Cyclization Reaction



In either form, however, we speculate the Zn(II) is precluded from participating in the necessary complexation and activation of the alkyne C≡C for subsequent cyclization (**5**). It would seem reasonable that the nature of amine and counterions affects the equilibrium between free and coordinated Zn(II), thereby influencing the rate of cyclization.

In summary, we have developed a novel cyclization reaction of propargylic *N*-hydroxylamines to 2,3-dihydroisoxazoles under mild conditions in the presence of catalytic amounts (10 mol %) of ZnI_2 and DMAP. The method described provides a new approach to this useful class of substituted heterocycles that complements extant methods. The intriguing reactivity of the substrates in the presence of Zn(II) and DMAP may have additional applications in related alkene or alkyne cyclization reactions. Further investigations of this process are ongoing and will be reported as results are forthcoming.

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Supporting Information Available: Full characterization and experimental procedures for the synthesis of the propargylic *N*-hydroxylamines, the 2,3-dihydroisoxazoles products, and control experiments. This material is available free of charge via the Internet at http://pubs.acs.org/.

OL006095R

(10) The coordination chemistry of *N*-hydroxylamines has been investigated by Wiegardt, see: Wiedgardt, K.; Hofer, E.; Holzbach, W.; Nuber, B.; Weiss, J. *Inorg. Chem.* **1980**, *19*, 2927.