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# Double Hetero-Michael Addition of *N*-Substituted Hydroxylamines to Quinone Monoketals: Synthesis of Bridged Isoxazolidines

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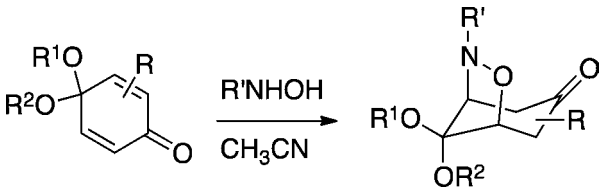
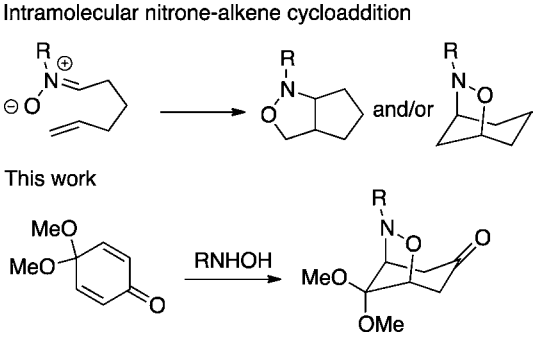
## ABSTRACT




**A general synthesis of bridged isoxazolidines from a double hetero-Michael addition of *N*-substituted hydroxylamines to quinone monoketals has been developed. The different addition order of *N*-benzylhydroxylamine and *N*-Boc hydroxylamine is also discussed. Moreover, the various functionalities in the isoxazolidine products allow facile derivatization.**

Isoxazolidines are important synthetic intermediates that have attracted attention in organic synthesis[1] and drug discovery.[2] Furthermore, natural products containing the isoxazolidine moiety have also been isolated from marine sponges[3] and plants.[4] Reductive cleavage[5] of the labile N−O bond in isoxazolidines produces 1,3-amino alcohols, which are also of synthetic value.[6] The most employed method for synthesis of isoxazolidines is

**Scheme 1.** Synthesis of Bridged Isoxazolidines

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(1) For a review, see: Frederickson, M. *Tetrahedron* **1997**, *53*, 403.

(2) (a) Palmer, G. C.; Ordy, M. J.; Simmons, R. D.; Strand, J. C.; Radov, L. A.; Mullen, G. B.; Kinsolving, C. R.; Georgiev, V.; Mitchell, J. T.; Allen, S. D. *Antimicrob. Agents Chemother.* **1989**, *33*, 895. (b) Burton, G.; Clarke, G. J.; Douglas, J. D.; Eglington, A. J.; Frydrych, C. H.; Hinks, J. D.; Hird, N. W.; Hunt, E.; Moss, S. F.; Naylor, A.; Nicholson, N. H.; Pearson, M. J. *J. Antibiot.* **1996**, *49*, 1266. (c) Minter, A. R.; Brennan, B. B.; Mapp, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 10504. (d) Ishiyama, H.; Tsuda, M.; Endo, T.; Kobabyashi, J. *Molecules* **2005**, *10*, 312. (e) Rescifina, A.; Chiacchio, M. A.; Corsaro, A.; De Clercq, E.; Iannazzo, D.; Mastino, A.; Piperno, A.; Romeo, G.; Romeo, R.; Valveri, V. *J. Med. Chem.* **2006**, *49*, 709.

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the 1,3-dipolar cycloaddition of nitrones to alkenes.[7] Intramolecular nitrone–alkene cycloaddition provides fused and/or bridged isoxazolidines,[8] which can equilibrate under thermal conditions[9] (Scheme 1). Bridged isoxazolidines are a good source of *syn*-1,3-amino alcohols, which often serve as critical precursors to many biologically active compounds, such as glucosidase inhibitor *N*-octyl-4-*epi*-*β*-valienamine (NOEV),[10] anti-influenza drug Tamiflu,[11] and antiangiogenic natural product cortistatin A[12] (Figure 1). Herein, we report a synthesis of bridged bicyclic isoxazolidines via a double hetero-Michael addition of *N*-substituted hydroxylamines to quinone monoketals (Scheme 1).

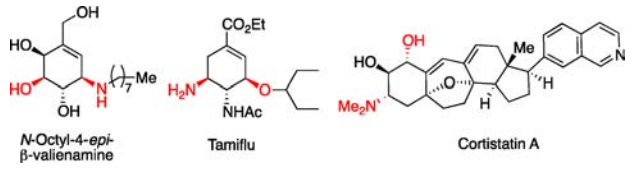


**Figure 1.** *syn*-1,3-Amino alcohol/ether-containing bioactive compounds.

Quinone monoketals are regiospecifically differentiated quinone equivalents that can be easily made from phenols in a single step by the Tamura–Pelter protocol.[13] They have been widely used in the synthesis of structurally complex molecules.[14] Because quinone monoketals possess unsaturated keto and allylic ketal moieties, it is known that they can undergo 1,4-,[15] 1,2-[16] nucleophilic addition and $S_N2'$[17] addition with a variety of nucleophiles (O, N, S, C, etc.). As part of our interest in the nucleophilic addition to quinone monoketals, we recently developed a one-pot synthesis of indoles via condensation of quinone monoketals and aliphatic hydrazine hydrochlorides via 1,2-addition.[18] We envisioned that an *N*-substituted hydroxylamine would favor 1,4-addition and eventually lead to the bridged isoxazolidine system. A literature search reveals that hydroxylamine ($NH_2OH$) reacted with santonin to afford a side product isoxazolidine through a double conjugate addition.[19] However, it is known that condensation of hydroxylamine with quinone monoketals did not provide the double conjugate addition product, but instead led to nitroso products through a 1,2-addition and an ensuing aromatization.[20] Although hydroxylamine and monosubstituted hydrazines lead to 1,2-addition with quinone monoketals, it occurred to us that an *N*-substituted hydroxylamine would favor a double hetero-Michael addition to afford isoxazolidines.

Gratifyingly, when quinone monoketal ketal **2a** was subjected to treatment with *N*-benzylhydroxylamine hydrochloride **1a** in acetonitrile in the presence of DBU, bridged isoxazolidine **3aa** was obtained in 97% yield. With this result in hand, we explored the scope of the reaction with a variety quinone monoketals and *N*-substituted hydroxylamines (Table 1). Quinone monoketals are readily accessible in one step from phenols,[13,21] while

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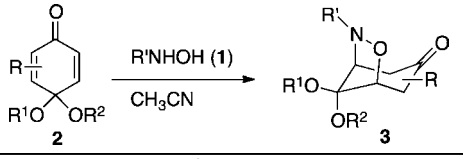
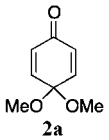
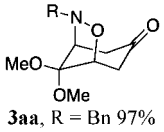
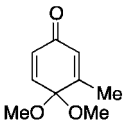
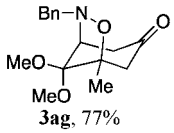
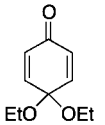
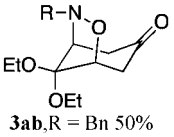
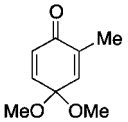
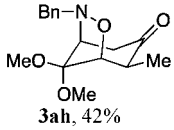
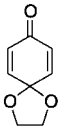
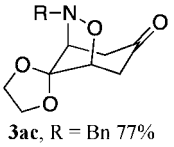
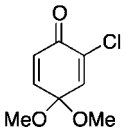
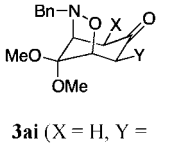
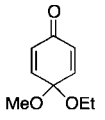
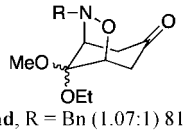
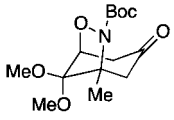
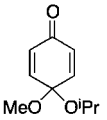
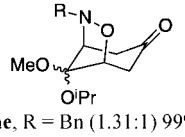
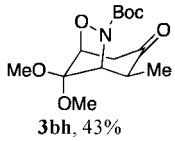
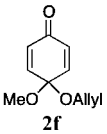
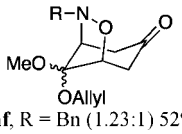
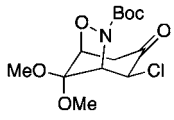
**Table 1.** Synthesis of Bridged Isoxazolidines

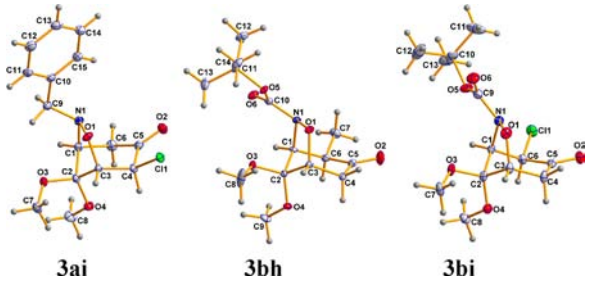



2 3

| quinone monoketal | product (% yield)[a] | quinone monoketal | product (% yield)[a] |
|---|---|---|---|
|  **2a** |  **3aa**, R = Bn 97%<br>**3ba**, R = Boc 99%<br>**3ca**, R = Me 62%<br>**3da**, R = Ac 76% |  **2g** |  **3ag**, 77% |
|  **2b** |  **3ab**,R = Bn 50%<br>**3bb**, R = Boc 96% |  **2h** |  **3ah**, 42% |
|  **2c** |  **3ac**, R = Bn 77%<br>**3bc**, R = Boc 88% |  **2i** |  **3ai** (X = H, Y = Cl) + **3ai'**(X = Cl, Y = H), 32% (2:1) |
|  **2d** |  **3ad**, R = Bn (1.07:1) 81%<br>**3bd**, R = Boc (1.23:1) 93% | **2g** |  **3bg**, 40% |
|  **2e** |  **3ae**, R = Bn (1.31:1) 99%<br>**3be**, R = Boc (4:1) 86% | **2h** |  **3bh**, 43% |
|  **2f** |  **3af**, R = Bn (1.23:1) 52%<br>**3bf**, R = Boc (1.14:1) 68% | **2i** |  **3bi**, 16% |

[a] Isolated yield.

*N*-hydroxylamines are commercially available. Since *N*-benzylhydroxylamine (**1a**) and *N*-Boc hydroxylamine (**1b**) gave better yields than *N*-methylhydroxylamine (**1c**) and *N*-acetylhydroxylamine (**1d**), we used the former to test the generality of quinone monoketals. Unsubsituted quinone monoketals generally gave good to excellent yields. Among them, mixed quinone monoketals gave a mixture of isomers as a result of a lack of facial selectivity. Their ratio was calculated from the proton NMR of the product mixture. According to NOESY, the major isomers are those where the nucleophiles approach from the less hindered (methoxy) face. The double Michael addition is affected by the substitution on the double bonds; monosubstituted quinone monoketals generally gave moderate yields. For a reaction between monosubstituted quinone monoketals and *N*-substituted hydroxylamines, the chemoselectivity of both nucleophiles (N vs O) and electrophiles (substituted enone vs unsubstituted enone) determines which products are obtained. Although the yields of double Michael products are moderate, the unambiguous structure elucidation by X-ray diffraction and NOESY would shed light on the order of the double hetero-Michael addition. It is well-known that *N*-substituted hydroxylamines can act as ambident nucleophiles, which readily alkylate on nitrogen but often acylate and phosphorylate on oxygen.[22] For *N*-alkylhydroxylamine, the first conjugate addition would be the N addition to the more electrophilic double bond.[19b,23] 2-Methyl- and 3-methyl-quinone monoketal gave only one regioisomer as the product since the more electrophilic double bond is also the sterically less hindered (cf. **3ag** and **3ah**). On the other hand, for 2-chloro-quinone monoketal, an inseparable mixture of regioisomers was obtained as the product. In this case, the more electrophilic double bond is the one with a chloro substituent, which is also more sterically hindered. The opposite electronic and steric effect results in a mixture of regioisomers. 3-Chloroquinone monoketal gave decomposition. No desired bridged isoxazolidine can be isolated, presumably due to displacement of the chloro substituent and subsequent decomposition. We then evaluated *N*-Boc hydroxylamine as a nucleophile. It has been shown that *N*-Boc hydroxylamine can act as both an oxygen and a nitrogen nucleophile in various reactions, sometimes leading to a mixture of both products.[24] Compared to *N*-benzylhydroxylamine, steric effect plays a more important role in the addition of *N*-Boc hydroxylamine since the oxygen added to the less hindered double bonds, even in the 2-chloro-quinone monoketal case (cf. **3bg**–**3bi**, Figure 2).[25]



**3ai** **3bh** **3bi**

**Figure 2.** X-ray crystal structures of **3ai**, **3bh**, and **3bi**.

The order of the cyclization was further supported by isolation of the mono-Michael addition product **4** and its cyclization to bridged isoxazolidine **3ah** (Scheme 2).

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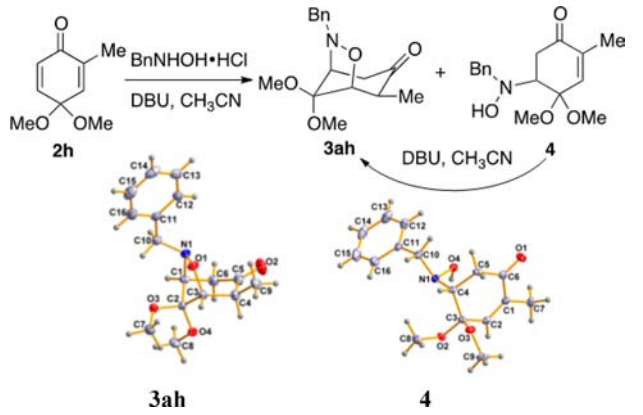
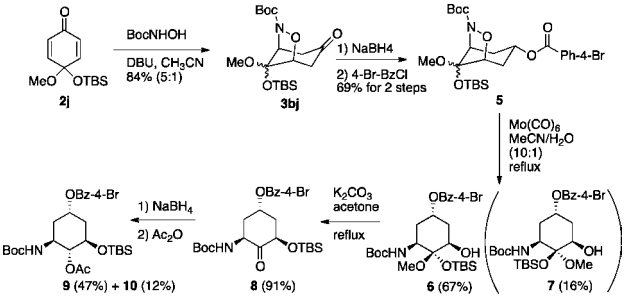
**Scheme 2.** Isolation of Mono-Michael Addition Intermediate




The bridged isoxazolidines are rich in various functionalities, such as two differentiable carbonyl groups (one as its ketal form), which are ready for further transformation. As an example, synthesis of an aminocyclitol derivative is shown in Scheme 3.

Aminocyclitols are cyclohexanes with at least one amino group and three or more additional hydroxyl goups on the ring.[26] They possess a variety of biological activities.[27] From mixed quinone monoketal **2j**,[13,28] double Michael addition afforded a mixture of inseparable facial isomers of **3bj**. Reduction of the keto group and subsequent acylation afforded **5** in 69% yield. $Mo(CO)_6$-mediated cleavage of the N−O bond[29] led to separable alcohol **6** (67%) and **7** (16%). From **6**, $K_2CO_3$-catalyzed transsilylation[30] afforded ketone **8** in 91% yield. Reduction of ketone **8** followed by acetylation gave two separable aminocyclitol derivatives **9** (47%) and its C-2 epimer **10** as a minor product (see the Supporting Information). The structure of **9** was confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information).[31] The relative stereochemistry in the three consecutive chiral centers in **9** is in accord with that of Tamiflu, NOEV, and cortistatin A (cf. Figure 1).

**Scheme 3.** Synthesis of Aminocyclitol Derivative




In summary, we have developed an expedient synthesis of bridged isoxazolidines from a double hetero-Michael addition of *N*-substituted hydroxylamines to quinone monoketals. This method complements the existing nitrone−alkene cycloaddition route. The various functionalities in the isoxazolidines allow facile derivatization. Application of this method to the synthesis of bioactive compounds is underway.

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**Supporting Information Available.** Experimental details 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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(31) X-ray data have been deposited with the Cambridge Crystallographic Database, deposition numbers 931741 (**3ah**), 919302 (**3ai**), 919301 (**3bh**), 919300 (**3bi**), 931740 (**4**), and 921687 (**9**).

The authors declare no competing financial interest.