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A Mild and Chemoselective Method for the Reduction of Conjugated Isoxazolines to β-Hydroxy Ketones

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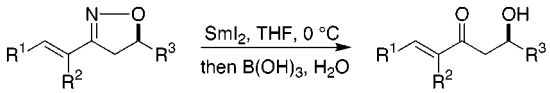
ABSTRACT

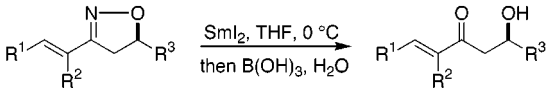


A new procedure for the selective reduction of conjugated Δ^2-isoxazolines to the corresponding unsaturated β-hydroxy ketones is described. The use of SmI_2 as the reducing agent and $B(OH)_3$ to hydrolyze the resulting imine results in a mild, convenient, and chemoselective protocol for this otherwise difficult transformation and complements existing methodology for the preparation of β-hydroxy ketones via nitrile oxides.

Δ^2-Isoxazolines constitute of a class of heterocycles that are most commonly assembled by dipolar cycloaddition reaction of a nitrile oxide and alkene. Their conversion to β-hydroxy carbonyls provides a powerful alternative to classic carbonyl addition methods for the preparation of stereochemically well-defined aldol adducts.[1] This transformation is commonly accomplished by reduction of the isoxazoline with Raney Ni,[2] $TiCl_3$,[3] and $Mo(CO)_6$[4] or by oxidation with ozone.[5] These conditions often afford the desired products in good yield and with complete stereochemical integrity. Although these methods are often compatible with highly functionalized molecules,[6] they uniformly fail when confronted with the challenge of effecting reduction of *conjugated* 3-vinyl-substituted Δ^2-isoxazolines without concomitant reduction of the α,β-unsaturated olefin.

We now report mild and highly selective conditions for the reduction of conjugated isoxazolines to the corresponding unsaturated β-hydroxy ketones. This protocol routinely provides the desired product in good yield and shows remarkable functional group tolerance. Furthermore, this reduction is surprisingly chemoselective for conjugated isoxazolines and provides a valuable means of selective isoxazoline reduction (Scheme 1).

Scheme 1



During the course of a recent total synthesis of the epothilone natural products, we encountered the limitations of the existing methods when faced with the conversion of conjugated isoxazolines to β-hydroxy ketones.[7] To the best of our knowledge, there has been only one report of such a transformation involving conjugated isoxazolines: Torssell and co-workers found that isoxazoline *N*-alkylation followed by electrochemical reduction afforded the desired, conjugated ketone in 30−40% overall yield.[8]

(1) (a) Curran, D. P. *Adv. Cycloaddit.* **1988**, *1*, 129−189. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Chemistry*; VCH: Stuttgart, 1988.

(2) (a) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826. (b) Curran, D. P.; Scanga, S. A.; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474−3478.

(3) Andersen, S. H.; Sharma, K. K.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2241.

(4) Baraldi, P. G.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, D. *Synthesis* **1987**, 276.

(5) Jäger, V.; Grund, H.; Buss, V.; Schwab, W. Müller, I. *Bull. Chem. Soc. Belg.* **1983**, *92*, 1039.

(6) For examples, see: (a) McGarvery, G. J.; Mathys, J. A.; Wilson, K. J. *J. Org. Chem.* **1996**, *61*, 5704−5705. (b) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946−7968.

(7) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611−3612.

(8) Isager, P.; Thomsen, I.; Torssell, K. G. B. *Acta Chem. Scand.* **1990**, *44*, 806.

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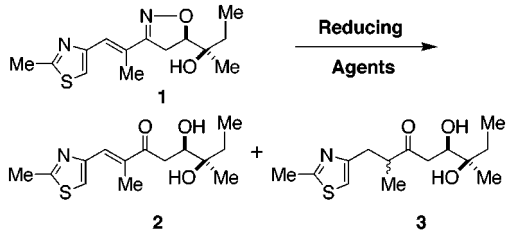
Using isoxazoline **1** as a model compound in a series of investigations, we surveyed the existing methods for reduction and conversion to the corresponding unsaturated, β-hydroxy ketones and documented their limitations as shown in Table 1. In a related study, we also attempted the selective reduction of 3-alkynyl-substituted Δ^2-isoxazolines and encountered similar difficulties.[9]

Table 1. Reduction of Conjugated Isoxazoline **1**[a]



entry	reagent	solvent	% **2**[a]	% **3**
1	$Mo(CO)_6$	CH_3CN/H_2O	45	20[b]
2	Raney Ni	$EtOH/H_2O$		100
3	SmI_2	THF/H_2O		100
4	SmI_2, then $B(OH)_3/H_2O$	THF	>90	<2[c]

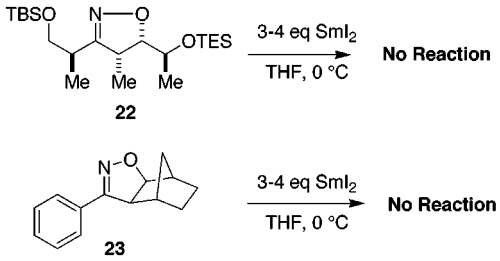
[a] Product ratios determined by ^1H NMR analysis. [b] The starting isoxazoline **1** was present as 35% of the product mixture. [c] The remaining material was the unreacted isoxazoline.

In seeking a new protocol for this reduction, we were attracted by recent reports by Keck and by Marco-Contelles of SmI_2-induced N−O bond cleavage in hydroxamic acids and cyclic hydroxylamines, respectively.[10] We observed that treatment of conjugated isoxazoline **1** with 3−4 equiv of SmI_2 at 0 °C in degassed THF, followed by workup of the reaction mixture with H_2O and boric acid, achieved selective reduction of the conjugated isoxazoline and subsequent imine hydrolysis. Under these conditions neither competing reduction of the conjugated C=C, hydroxyl elimination, nor retro-aldol products were observed. Moreover, these reaction conditions proved tolerant of a wide range of functionality in the reduction substrates.[11]

The substrates that form the basis of this study and that are amenable to selective reduction are illustrated in Table 2. Alkynyl-substituted isoxazolines **4** and **5** are cleanly transformed to the corresponding ynones (entries 1 and 2). The phenylvinyl-substituted isooxazoline **6** participates in the selective reduction (entry 3). Functionality rich substrates **8** and **9** smoothly undergo the desired reduction in good yield (entries 5 and 6) and underscore the wide compatibility of the conditions with functionality common to advanced intermediates in complex molecule synthesis. Thus olefins (entry 7), free hydroxyl groups (entry 9), and conjugated esters (entry 9) survive the isoxazoline reduction unscathed. Even a primary, allylic TES ether is untouched (entry 8), in contrast to our experiences with the Raney Ni and $Mo(CO)_6$ procedures in which silyl ether deprotection was occasionally observed.

Further investigation produced an unexpected observation that suggested the possibility of chemoselective reductions of differentially substituted isoxazolines (Scheme 2). In this respect, we were surprised to observe that the reduction conditions used above were not applicable to the reduction of isoxazolines that were not conjugated to a vinyl or alkynyl group. Thus, isoxazoline **22** does not undergo N−O bond cleavage even upon warming the reaction to room temperature.[12] Likewise aromatic substrate **23** was also resistant to reduction at 0 °C.[13] These results prompted us to examine the reduction of a conjugated isoxazoline in competition with reduction of an otherwise identical saturated substrate. In

Scheme 2



(9) We have recently reported the first preparation of propargylic isoxazolines by nitrile oxide cycloaddition of alkyne-substituted nitrile oxides: Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, in press.

(10) (a) Keck G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *41*, 7419 (b) Chiara, J.; Destabel, C.; Gallego, P.; Marco-Contelles, J. *J. Org. Chem.* **1996**, *61*, 359.

(11) **Representative Procedure.** To the isoxazoline (0.334 mmol, 1.00 equiv) in 12 mL of degassed THF at 0 °C was added SmI_2 (0.1 M in THF, 12 mL, 1.2 mmol, 3.6 equiv) slowly, maintaining a dark blue−green color throughout the reaction. After the addition was complete, additional SmI_2 (1 mL) was added to the dark blue solution, and stirring was continued for 20 min at 0 °C. After the reaction was quenched with O_2 to give a bright yellow solution, H_2O (8 mL) and $B(OH)_3$ (0.3 g) were added, and the mixture was stirred for 30 min at room temperature. Following the addition of Et_2O (10 mL) and careful separation of the layers to avoid an emulsion, the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic solutions were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (6:1 hexanes/EtOAc) afforded the β-hydroxyketone (75%) as a colorless oil.

(12) Upon warming isoxazoline **22** to room temperature in the presence of 6 equiv of SmI_2 for 8 h, we recovered the starting isoxazoline, albeit contaminated with decomposition products. The expected β-hydroxy ketone was not observed. This substrate is cleanly reduced to the hydroxy ketone under Curran's conditions (Raney Ni, H_2) in 96% yield.

(13) Upon warming isoxazoline **23** to room temperature in the presence of 6 equiv of SmI_2, we observed formation of the expected product along with significant amounts of the corresponding retro-aldol product.

(14) It is likely that the selectivity that is observed results from the difference in reduction potential of the substrate as a function of the substitution of the isoxazoline at C(3). Calculations (PC Spartan Pro, Wavefunction, Inc.) of the LUMO energies of isoxazolines **i**−**iii** revealed the ranking to be **iii** > **ii** > **i**, consistent with the observed reactivity trends in which **i** undergoes reduction preferentially over **ii** and above all over **iii**.

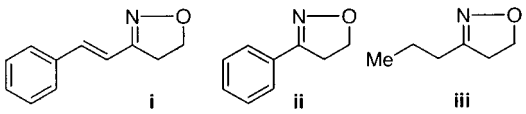
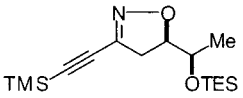
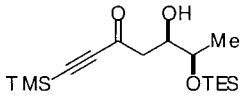
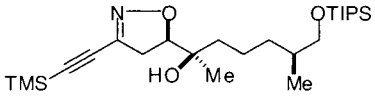
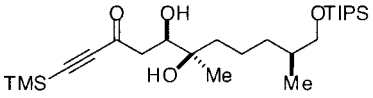
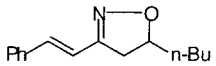
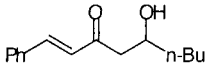
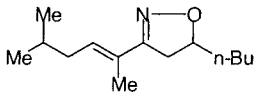
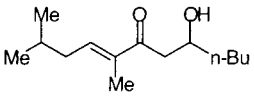
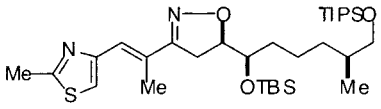
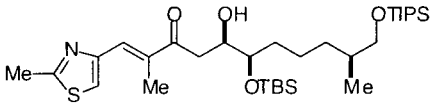
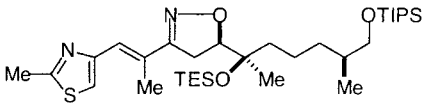
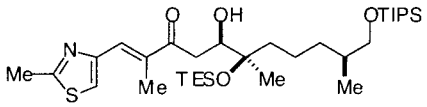
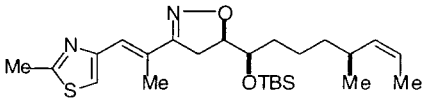
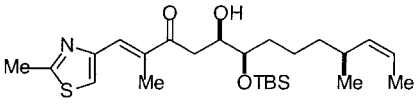
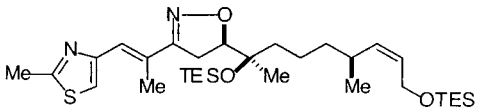
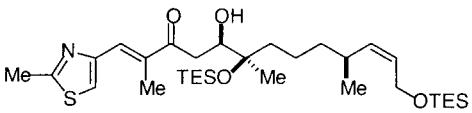
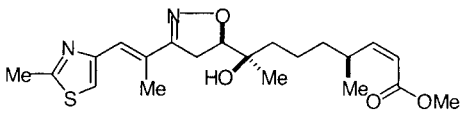
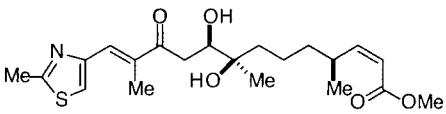


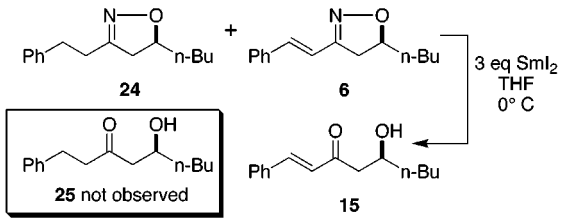
Table 2. Reduction of Conjugated Isoxazolines to β-Hydroxy Ketones with SmI_2[a]

entry	isoxazoline	product	yield[b]
1	 **4**	 **13**	84 %
2	 **5**	 **14**	62 %
3	 **6**	 **15**	89 %
4[c]	 **7**	 **16**	81 %
5	 **8**	 **17**	72 %
6	 **9**	 **18**	75 %
7	 **10**	 **19**	75 %
8	 **11**	 **20**	87 %
9	 **12**	 **21**	56 %[d]

[a] Reactions were performed by the addition of 3−4 equiv of SmI_2 (0.1 M in THF) to the isoxazoline in THF at 0 °C, followed by workup with H_2O and $B(OH)_3$. Typical reaction times were 5−45 min. [b] Isolated yields following purification by column chromatography on silica gel. [c] This reaction was performed at 23 °C for 8 h. [d] The balance of the reaction mass was recovered isoxazoline **12**.

this regard, the addition of 3 equiv of SmI_2 to a 1:1 mixture of **6** and **24** effected chemoselective reduction, providing only the conjugated β-hydroxy ketone derived from **6** (Scheme 3). No trace of the saturated β-hydroxy ketone **25** derived from **24** was observed. The ability to differentiate between such isoxazolines provides a promising method for the utilization of substrates containing multiple isoxazolines moieties by effecting selective heterocycle cleaveage.[14]

Scheme 3



In conclusion, we have described the mild, efficient, and chemoselective reduction of unsaturated isoxazolines to the corresponding conjugated β-hydroxy ketones. This protocol provides the first general method for the selective reduction of this class of isoxazolines and fills an important gap in the supporting methodology for the nitrile oxide approach to β-hydroxyl carbonyls.[15]

Acknowledgment. Support has been provided by generous funds from the ETH-Z, Hoffmann-LaRoche, Merck, and Novartis. J.W.B. thanks the National Science Foundation (U.S.) for a predoctoral fellowship.

OL015885D

(15) All compounds have been satisfactorily characterized by appropriate ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, mass spectrometry, $[\alpha]_D$, and elemental analyses.