A General Synthetic Procedure for N-Unsubstituted Isoxazolidines *via* Nitrone-Olefin Cycloaddition. Remarkable Catalytic Effect of Bu_2SnO

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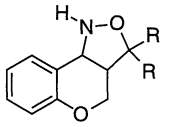
The remarkable catalysis of Bu_2SnO for nitrone formation in the nitrone-olefin cycloaddition reaction has been discovered, and has led to the development of a general method for the synthesis of N-unsubstituted isoxazolidine derivatives.

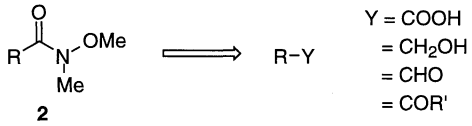
In an effort to develop new chiral auxiliaries for a certain set of asymmetric syntheses, we have selected benzopyrano-isoxazolidine **1** as a prototypical auxiliary for two reasons:



1

(i) N-acyl-N,O-dialkylhydroxylamine derivatives, such as **2**, are known to be converted to acids, aldehydes, ketones and alcohols by a single operation,[1] and (ii) a variety of isoxazolidine derivatives can be prepared by [3+2] cycloaddition of nitrones and olefins.[2] (Scheme 1)

Scheme 1.

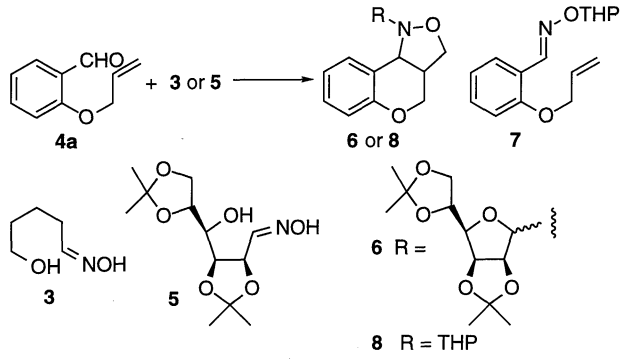


2

The dipolar cycloaddition is a reliable procedure for construction of isoxazolidines, but no generally applicable method for the synthesis of N-unsubstituted isoxazolidines has been developed.[3-6] In this Letter, we would like to describe our finding on the remarkable catalysis of Bu_2SnO for the formation of N-THP-nitrones that is involved in the cycloaddition reaction.

For our purpose a large quantity of **1** was needed and the application of reported methods met only with limited success. Although 2-allyloxybenzaldehyde **4a** cleanly reacted with the (D)-mannose-derived hydroxyoxime **5** [5] to give a mixture of isomeric cycloadducts **6** after 20 hours' heating in xylene in 84% yield, this procedure has been impractical for a large scale preparation. The application of this procedure to 5-hydroxypentanal oxime **3** [6] gave intractable mixture. (Scheme 2)

Scheme 2.



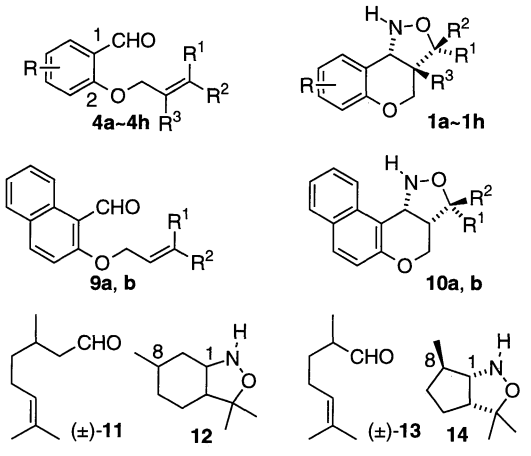
Then, several catalysts were tested to facilitate the reaction. Basic catalysts had no effect and acidic catalysts, such as PPTS, led to the formation of the THP-oxime **7** instead of the expected **8**.[7] Finally we found Bu_2SnO acted quite well as a catalyst for the transformation.

Thus, in the presence of less than 5 mol% of Bu_2SnO, an equimolar mixture of **3** and **4** afforded a diastereomeric mixture of the cycloadduct **8** after several hours' heating in toluene. The cycloadduct **8**, without purification, was hydrolyzed under mild

Table 1. Synthesis of N-Unsubstituted Isoxazolidine -1. Intramolecular Nitrone-Olefin Cyclization

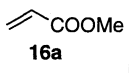
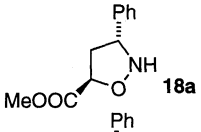
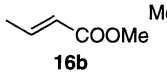
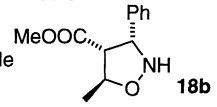
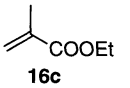
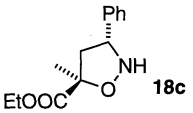
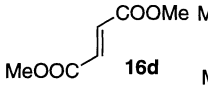
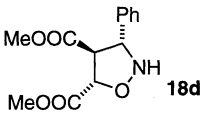
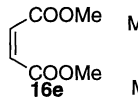
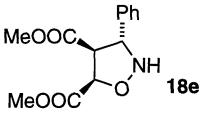
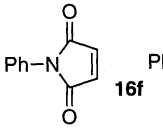
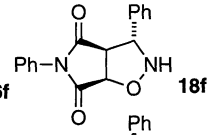
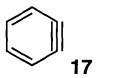
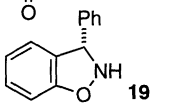
Entry	Olefin aldehyde	R^1, R^2, R^3	Product	Yield/%
1	**4a** (R = H)	H, H, H	**1a**	80
2	**4b** (R = H)	Me, Me, H	**1b**	90
3	**4c** (R = H)	H, Ph, H	**1c**	85
4	**4d** (R = H)	H, H, Me	**1d**	68
5	**4e** (R =3-MeO)	Me, Me, H	**1e**	89
6	**4f** (R =3-MeO)	H, H, H	**1f**	72
7	**4g** (R =5-NO_2)	Me, Me, H	**1g**	92
8	**4h** (R =5-NO_2)	H, H, H	**1h**	91
9	**9a**	Me, Me, ---	**10a**	82
10	**9b**	H, H, ---	**10b**	79
11	citrolellal **11**		**12**	76[a]
12	melonal **13**		**14**	80

An equimolar mixture of olefinic aldehyde and **3** was heated with Bu_2SnO (5 mol%) in toluene (entry 1, 2, 3 ,7, 8, 11, 12) or in benzene (entry 4, 5, 6, 9, 10) under reflux. Resulting adduct was hydrolyzed with 2 M HCl and EtOH at room temperature (entry 1~10) or with 1.1eq. $HClO_4$ in MeOH at 60 °C (entry 11, 12).
[a] Trans: cis = 2:1.



acidic conditions to provide **1** in 80% overall yield. In this way, **1a** and **1b** have become readily available.[8] The scope and limitations of this catalytic reaction were examined using various olefinic aldehydes. (Table 1 and 2) As is clear from Table 1, each salicylaldehyde derivative with a substituted allyl group or with an electronically different substituent on the aromatic ring afforded a single isomer of benzopyrano-isoxazolidine.[9] Citronellal **11** gave rise to a mixture of trans and cis fused heterocycles **12** in a ratio of 2:1, whereas melonal **13** afforded the single cis isomer **14**.[9]

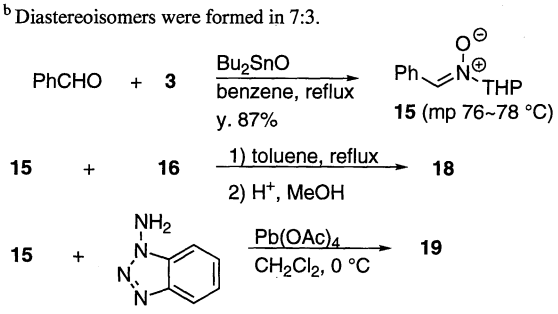
Table 2. Synthesis of N-Unsubstituted Isoxazolidine - 2. Intrermolecular Nitrone-Olefin Cycloaddition

Entry	Olefin	Iisoxazolidine	Yield/%
1	 **16a**	 **18a**	89[a]
2	 **16b**	 **18b**	81
3	 **16c**	 **18c**	80
4	 **16d**	 **18d**	85[b]
5	 **16e**	 **18e**	88
6	 **16f**	 **18f**	79
7	 **17**	 **19**	87

A mixture of **15** and dipolarophile (1.5eq.) was heated in toluene under reflux for 4~6 h (except for entry 7). Crude reaction mixture was concentrated and hydrolyzed with 1.1eq. $HClO_4$ in MeOH or EtOH (entry 3) at 60 °C for 1 h.

[a] Diastereoisomers were formed in 8:2.

[b] Diastereoisomers were formed in 7:3.



Under the influence of Bu_2SnO the reaction of benzaldehyde and **3** afforded stable Z-nitrone **15**,[10] which reacted with activated olefins[11] to give N-unsubstituted isoxazolidine derivatives in high yields after hydrolysis. (Table 2) In every case an isoxazolidine was obtained with high regio- and stereoselectivity (>10:1) except for entries 1 and 4, where diastereomers were formed with low selectivity.[10] It should be noted that the opposite regioselectivity was observed for the methyl crotonate cycloaddition compared to those of methyl acrylate and ethyl methacrylate (entries 1~3). Again without the Bu_2SnO catalyst nitrone **15** could not be obtained.

In summary, Bu_2SnO was found to be a good catalyst for the formation of THP-nitrone from various aldehydes which resulted in a practical synthetic procedure of N-unsubstituted isoxazolidine drivatives via [3+2] cycloaddition reaction.

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References and Notes

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7 With PPTS catalyst, the reaction of **4a** and **5** afforded the cycloadduct **6** in 88% yield after 2 h' reflux in toluene.

8 A. Abiko, O. Moriya, S. A. Filla, and S. Masamune, *Angew. Chem.* in press.

9 Structures of **1a** and **1b** were determined by X-ray analysis, whereas **1c~1h** and **10** were assumed by analogy.
12: Stereochemistry of the ring juncture was assigned on the basis of the coupling constant of H-1 (cis: br, W_H = 5Hz, trans: dt, J = 3.4, 10.0 and 10.0 Hz). However that of the C-8 methyl group was not determined. **14**: $J_{H1\text{-}H5}$ = 8.3 Hz, $J_{H1\text{-}H8}$ = 5.4 Hz.

10 Stereochemistry of the nitrone **15** and the products were elucidated by N.O.E. experiment and/or comparison of the coupling constants with the reported value for the related compounds. cf: R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968); R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **102**, 736 (1969).

11 The reaction with unactivated olefins, such as 1-octene, resulted in the rearragement of the nitrone **15** to the THP-oxime after prolonged heating.