DOI: 10.1002/ejoc.201101465

Synthesis of 4-Hydroxy-2-oxazolidinones Catalyzed by Tin Alkoxides

Ryota Kojima,[a] Satoshi Sawamoto,[a] Aritomo Okamura,[a] Hiroki Takahashi,[a] Shinji Tsunoi,[a] and Ikuya Shibata*[a]

Keywords: Heterocycles / Tin / Ketones / Isocyanates / Diastereoselectivity

Synthesis of 4-hydroxy-2-oxazolidinone derivatives was accomplished from the reaction of α-hydroxy ketones with isocyanates in the presence of a catalytic amount of a tin alkoxide. The reactions proceeded under mild conditions and are highly atom economical.

Introduction

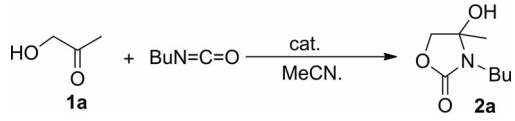
2-Oxazolidinones[1] are important heterocyclic compounds that are useful as intermediates in organic synthesis and as biologically active compounds.[2] The reaction of α-hydroxy ketones with isocyanates to give 2-oxazolidinonones is highly atom economical. Recently, reactions under microwave irradiation have been reported by Tamariz et al.,[3] in which *exo*-methylene-type oxazolidinones were produced. We present here the tin-catalyzed reaction of α-hydroxy ketones with isocyanates under mild conditions to produce 4-hydroxy-2-oxazolidinones. In the catalytic reaction, the nucleophilic Sn–O and Sn–N bonds work very well as active catalytic species.[4]

Results and Discussion

Initially, the reaction involving acetoin (**1a**) and *n*-butyl isocyanate was examined, as shown in Table 1. Without a catalyst, no reaction proceeded at 80 °C for 3 h (Table 1, Entry 1). In the presence of the tin catalyst (10 mol-%), 4-hydroxy-4-methyl-1,3-oxazolidin-2-one (**2a**) was obtained (Table 1, Entries 2–4). Although heating conditions caused effective reactions, microwave irradiation also gave desired **2a** in only 5 min (Table 1, Entries 5 and 6). THF solvent was also useful (Table 1, Entry 7).

Next, the reactions were performed by using various α-hydroxy ketones **1** and isocyanates and were catalyzed by $Bu_2Sn(OMe)_2$ under microwave irradiation (Table 2). In the reaction of **1a**, 4-hydroxy-1,3-oxazolidin-2-one (**2b**) was obtained (Table 2, Entry 2). Thus, aliphatic and aromatic isocyanates were applicable. Secondary alcohol **1b** also reacted with isocyanate to give the corresponding oxazolidinones **2c**–**2e**, in which *trans*-dimethyl-substituted ones predominated (Table 2, Entries 3–5). Sterically hindered tertiary alcohol **1c** was also reactive under the conditions and gave tetrasubstituted oxazolidinone **2f** (Table 2, Entry 6). Thus, from these reactions, products possessing labile α-aminal functionalities were obtained. In almost cases, the desired products were obtained in only 5 min.

Table 1. Effects of catalysts.[a]



Entry	Catalyst	Conditions	Yield / %
1	none	80 °C, 3 h	trace
2	$Bu_2Sn{=}O$	80 °C, 3 h	62
3	Bu_3SnOMe	80 °C, 3 h	68
4	$Bu_2Sn(OMe)_2$	80 °C, 3 h	72
5	Bu_3SnOMe	MW, 110 °C, 5 min[b]	81
6	$Bu_2Sn(OMe)_2$	MW, 110 °C, 5 min[b]	87
7	$Bu_2Sn(OMe)_2$	MW, 110 °C, 5 min[b,c]	61

[a] The reaction was carried out with **1a** (1 mmol), BuN=C=O (1 mmol), and the catalyst (0.1 mmol) in MeCN (1 mL). [b] 30 W. [c] THF (1 mL) was used as the solvent.

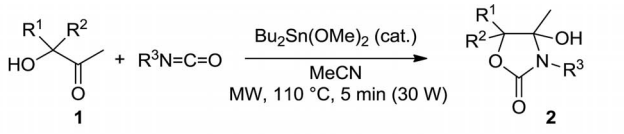
A plausible catalytic cycle is described in Scheme 1. The Sn–O and Sn–N bonds bear high nucleophilicity.[5] Initially, tin methoxide reacts with α-hydroxy ketone **1** to give α-stannoxy ketone **A**. The Sn–O bond of **A** adds to an isocyanate to form stannyl carbamate **B**.[6] The resulting Sn–N bond adds to the remaining carbonyl moiety intramolecularly. The Sn–O bond of cyclized product **C** reacts with starting α-hydroxy ketone **1**. As a result, 4-hydroxy-4-methyl-1,3-oxazolidin-2-one (**2**) is obtained with the regeneration of catalytic species **A**.[7]

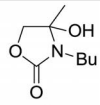
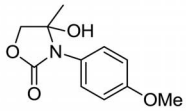
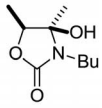
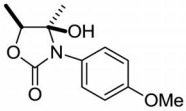
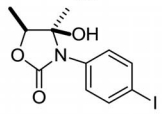
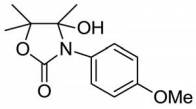
When benzoin (**3**) was used as a starting material, *trans*-4,5-diphenyl-substituted oxazolidinone **4** was obtained under heating conditions in 76% yield with high diastereo-

[a] Research Center for Environmental Preservation, Osaka University,
2-4 Yamadaoka, Suita, Osaka, 565-0871, Japan
Fax: +81-(6)6879-8978
E-mail: shibata@epc.osaka-u.ac.jp

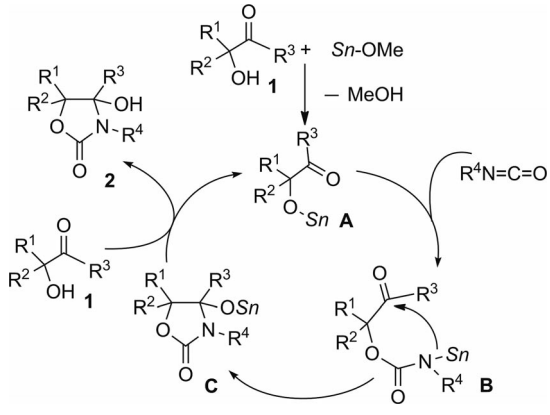
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101465.

Table 2. Reaction with α-hydroxy ketones **1** and isocyanates.[a]



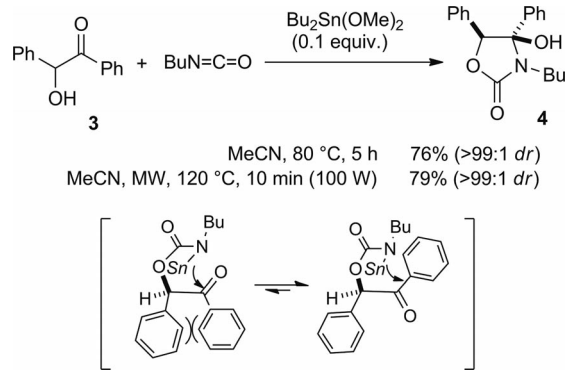
Entry	R^1	R^2		R^3	Product	Yield / %
1	H	H	**1a**	Bu	 **2a**	87
2	H	H	**1a**	PMP	 **2b**	89
3	Me	H	**1b**	Bu	 **2c**	84 (72:28 *dr*)
4	Me	H	**1b**	PMP	 **2d**	90 (77:23 *dr*)
5	Me	H	**1b**	*p*-IC_6H_4	 **2e**	51 (79:21 *dr*)[b]
6	Me	Me	**1c**	PMP	 **2f**	72

[a] The reaction was carried out with **1** (1 mmol), BuN=C=O (1 mmol), and $Bu_2Sn(OMe)_2$ (0.1 mmol) in MeCN (1 mL). [b] Major stereoisomer was confirmed by X-ray crystallography.[8]



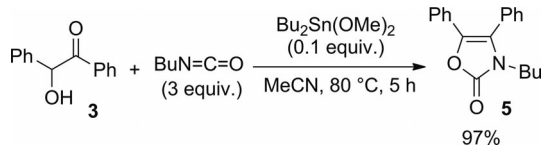
Scheme 1. Plausible cyclization mechanism.

selectivity (Scheme 2). The stereochemistry of the main product was determined by X-ray crystallography.[8] This high diastereoselectivity can be explained in terms of the steric repulsion between the two phenyl groups in the cyclization step and further by the formation of the thermodynamically stable 4,5-diphenyl-substituted structure.



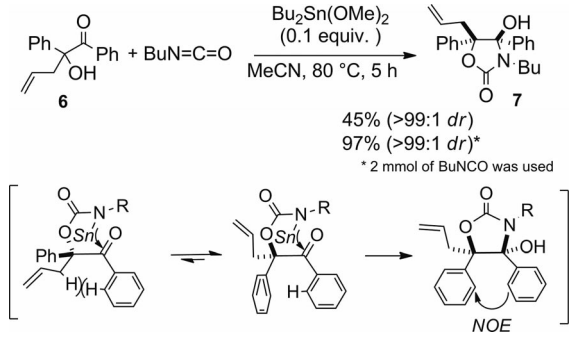
Scheme 2. Reaction with the use of benzoin (**3**).

When an excess amount of isocyanate was treated with **3**, a cyclized product involving internal tetrasubstituted alkene **5** was obtained selectively (Scheme 3). This is because of β-elimination from aminal product **4**.[9]



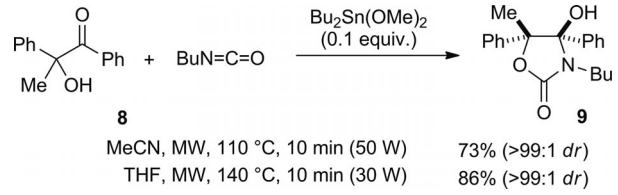
Scheme 3. Reaction with the use of benzoin (**3**).

The reaction using allyldiphenyl-substituted substrate **6** afforded product **7**. In contrast to the formation of **4**, the 4,5-diphenyl substituents were oriented *cis* in product **7** (Scheme 4). The stereochemistry of **7** was determined by an NOE study. This stereoselective reaction is explained in terms of steric repulsion between the allyl and *vic*-phenyl group in the cyclization step.[10]



Scheme 4. Reaction with the use of allyl-substituted benzoin **6**.

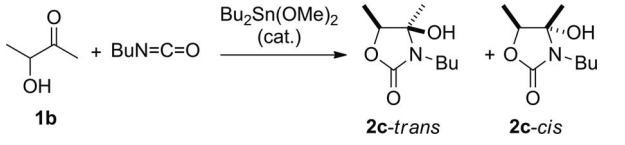
The reaction of methyldiphenyl-substituted **8** proceeded effectively under MW irradiation, and *cis*-4,5-diphenyl-substituted product **9** was also obtained (Scheme 5).[8]



Scheme 5. Reaction with the use of methyl-substituted benzoin **8**.

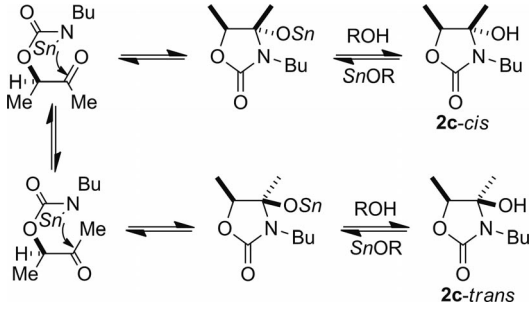
In contrast to the reaction for diphenyl-substituted substrates **3**, **6**, and **8** (Schemes 2, 4, and 5), the diastereoselectivity of the reaction by using dimethyl-substituted substrate **1b** was dependent on the conditions (Table 3). Thus, under microwave irradiation in polar solvent (Table 2, Entry 3) or heating conditions (Table 3, Entry 1), *trans*-dimethyl-substituted oxazolidinone **2c**-*trans* was obtained predominantly. On the other hand, heating for a short time in THF (Table 3, Entry 2) afforded *cis*-4,5-dimethyl-substituted isomer **2c**-*cis* as a major product. Prolonged reaction time increased the ratio of **2c**-*trans* (Table 3, Entry 3). Thus, it was assumed that a reversible reaction occurred in the reaction of **1b** (Scheme 6).[11] At the initial stage, **2c**-*cis* is formed as a kinetically controlled product. Heating conditions or prolonged reaction time results in the formation of thermodynamically stable **2c**-*trans*.[12]

Table 3. Effect of the conditions in the reaction of **1b**.[a]



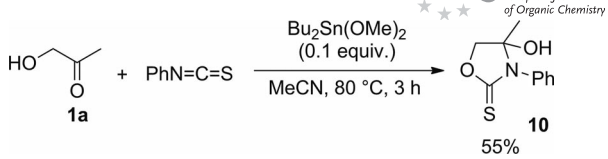
Entry	Conditions	Yield / %	Ratio *trans*/*cis*
1	MeCN, 80 °C, 3 h	81	76:24
2	THF, 60 °C, 15 min	87	8:92
3	THF, 60 °C, 60 min	89	26:74

[a] The reaction was carried out with **1b** (1 mmol), BuN=C=O (1 mmol), and $Bu_2Sn(OMe)_2$ (0.1 mmol), in solvent (1 mL).



Scheme 6. Reversible reaction of acetoin **1b**.

Other than isocyanates, isothiocyanate (RN=C=S) could be used as an electrophile (Scheme 7). The addition occurred across the C=N group of the isothiocyanate.[13] Thus, oxazolidin-2-thione **10** was obtained selectively. Similar to the case of isocyanates, the α-aminal moiety was involved.



Scheme 7. Reaction with isothiocyanate.

Conclusions

In summary, various nitrogen heterocyclic compounds were obtained from α-hydroxy ketones **1**. The advantage of the presented reactions is that they are highly atom economical where no side product was obtained at all.

Experimental Section

Representative Procedure for the Preparation of 2-Oxazolidinones under Heating: A 10-mL round-bottomed flask was flame dried under reduced pressure. Under an atmosphere of nitrogen, $Bu_2Sn(OMe)_2$ (0.0295 g, 0.1 mmol), MeCN (1.0 mL), α-hydroxy ketone **1** (1.0 mmol), and the isocyanate (1.0 mmol) were added. The mixture was heated at reflux (80 °C) and stirred for 3 h. The reaction was quenched with H_2O (0.5 mL), and the layers were quickly separated. The aqueous phase was further extracted with diethyl ether, and the combined extracts were dried with sodium sulfate and concentrated. The crude product was then purified by flash column chromatography (hexane/EtOAc, 9:1 to 3:7). The desired product was obtained with an eluent mixture of hexane/EtOAc = 7:3.

Representative Procedure for the Preparation of 2-Oxazolidinones under Microwave Irradiation: A 5-mL vial was flame dried under reduced pressure. Under an atmosphere of nitrogen, $Bu_2Sn(OMe)_2$ (0.0295 g, 0.1 mmol), MeCN (1.0 mL), α-hydroxy ketone **1** (1.0 mmol), and the isocyanate (1.0 mmol) were added. The vial was sealed with a septum and was set in the microwave reactor. The mixture was stirred under microwave irradiation at 30 W for 5 min. The reaction temperature was measured by an IR sensor. A representative temperature profile is shown in the Supporting Information. After the reaction, the mixture was quenched with H_2O (0.5 mL), and the layers were quickly separated. The aqueous phase was further extracted with diethyl ether, and the combined extracts were dried with sodium sulfate and concentrated. The crude product was then purified by flash column chromatography (hexane/EtOAc, 9:1 to 3:7). The desired product was obtained with an eluent mixture of hexane/EtOAc = 7:3.

Recrystallization of **2e**, **4**, and **9** was performed from hexane with the addition of a small amount of Et_2O.

Supporting Information (see footnote on the first page of this article): Experimental and characterization data of all new compounds.

Acknowledgments

This research was supported by the Ministry of Education, Science, Sports, and Culture, Japan, the Japan Securities Scholarship Foundation and the Naito Foundation.

[1] a) M. E. Dyen, D. Swern, *Chem. Rev.* **1967**, *67*, 197–246; b) S. Ozaki, *Chem. Rev.* **1972**, *72*, 457–456; c) R. Maggi, C. Bertolotti, E. Orlandini, C. Oro, G. Sartori, M. Selva, *Tetrahedron Lett.* **2007**, *48*, 2131–2134.

[2] a) G. Cardillo, M. Orena, S. Sandri, C. Tomashini, *Tetrahedron* **1987**, *43*, 2505–2512; b) A. V. Rama Rao, T. G. Murali Dhar, T. K. Chakraborty, M. K. Gurjar, *Tetrahedron Lett.* **1988**, *29*, 2069–2072; antibacterial drugs: c) M. R. Barbachyn, D. K. Hutchinson, S. J. Brickner, M. H. Cynamon, J. O. Kilburn, S. P. Klemens, S. E. Glickman, K. C. Grega, S. K. Hendges, D. S. Toops, C. W. Ford, G. E. Zurenko, *J. Med. Chem.* **1996**, *39*, 680–685.

[3] Dehydrated cyclic products were obtained under MW irradiation at 120 °C, 90 min (200 W); a) C. González-Romero, P. Bernal, F. Jiménez, M. del Carmen Cruz, A. Fuentes-Benites, A. Benavides, R. Bautista, J. Tamariz, *Pure Appl. Chem.* **2007**, *79*, 181–191; b) B. M. Santoyo, C. González-Romero, O. Merino, R. Martínez-Palou, A. Fuentes-Benites, H. A. Jiménez-Vázquez, F. Delgado, J. Tamariz, *Eur. J. Org. Chem.* **2009**, 2505–2518; c) O. Merino, B. M. Santoyo, L. E. Montiel, H. A. Jiménez-Vázquez, L. G. Zepeda, J. Tamariz, *Tetrahedron Lett.* **2010**, *51*, 3738–3742.

[4] For examples of the synthetic uses of organotin compounds, see: a) A. Baba, I. Shibata, M. Yasuda in *Comprehensive Organometallic Chemistry III*, vol. 9, ch. 8 (Eds.: R. H. Crabtree, D. Michael, P. Mingos), Elsevier, Oxford, **2006**, pp. 341–380; b) M. Pereyre, P. J. Quintard, A. Rahm in *Tin in Organic Synthesis*, Butterworth, London, **1987**, pp. 261–285; c) A. G. Davies in *Organotin Chemistry*, VCH, Weinheim, **1997**, pp. 166–193.

[5] Sn–O and Sn–N bonds bear high nucleophilicity. In some cases, their nucleophilicity is higher than that of the corresponding free alcohols and amines: E. W. Abel, D. A. Armitage, D. B. Brady, *Trans. Faraday Soc.* **1966**, *62*, 3459–3462.

[6] a) A. G. Davies, T. N. Mitchell, W. R. Symes, *J. Chem. Soc. C* **1966**, 1311–1315; b) A. Baba, H. Kishiki, I. Shibata, H. Matsuda, *Organometallics* **1985**, *4*, 1329–1333.

[7] Tin-catalyzed cycloadditions with the use of epoxides has been reported: I. Shibata, A. Baba, H. Iwasaki, H. Matsuda, *J. Org. Chem.* **1986**, *51*, 2177–2184.

[8] CCDC-822458 (for **2e**), -840180 (for **4**), and -822457 (for **9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] In the reaction of Scheme 2, product **5** was not formed during isolation. Although the exact reason for the formation of **5** is not clear, we suppose that, for example, by using an excess amount of isocyanate, formation of the carbamate of the cyclized product would accelerate the elimination to give **5**.

[10] In the cyclization of allyldiphenyl-substituted tin adducts, we have already reported that diphenyl substituents prefer to orient in a *cis* fashion. I. Shibata, R. Kojima, S. Tsunoi, T. Nozaki, T. Watanabe, A. Ninomiya, M. Yasuda, A. Baba, *Org. Biomol. Chem.* **2010**, *8*, 2009–2011.

[11] Tamariz et al. also propose a similar equilibrium: R. Martinez, H. A. Jiménez-Vázquez, J. Tamariz, *Tetrahedron* **2000**, *56*, 3857–3866.

[12] For the reaction of diphenyl-substituted substrates **3**, **6**, and **8**, the diastereoselectivity was not changed by the conditions. Because the Ph group is bulkier than the Me group, the use of **3**, **6**, and **8** would not cause a reversible reaction in contrast to the case of **1b**.

[13] In the cycloaddition of epoxides, the addition occurred across the C=S group of the isothiocyanate.[7]

Received: October 8, 2011
Published Online: November 8, 2011

