ORGANIC LETTERS

2010
Vol. 12, No. 15
3456−3459

Facile Preparation of Oxazole-4-carboxylates and 4-Ketones from Aldehydes using 3-Oxazoline-4-carboxylates as Intermediates

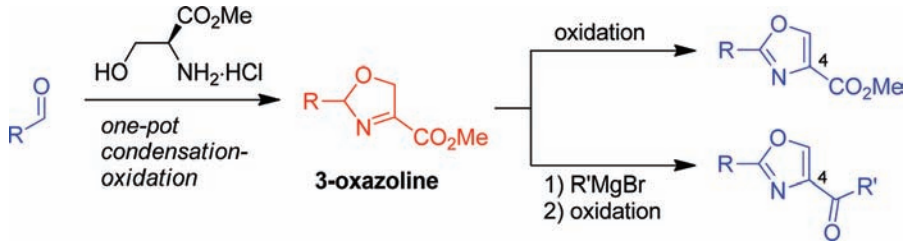
Kenichi Murai, Yusuke Takahara, Tomoyo Matsushita, Hideyuki Komatsu, and Hiromichi Fujioka*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan

fujioka@phs.osaka-u.ac.jp

Received June 3, 2010

ABSTRACT



A novel 2-step synthesis of oxazole-4-carboxylates from aldehydes was developed, which is characterized by the utilization of 3-oxazoline-4-carboxylates as synthetic intermediates. The facile preparation of 4-keto-oxazole derivatives from 3-oxazoline-4-carboxylates based on their interesting reactivity toward Grignard reagents is also described.

Oxazole is an important heterocycle, and many oxazole-containing natural products, such as disorazole A[1] and hennoxiazole A[2] (Figure 1), display attractive biological activities.[3] As for their structures, 2,4-disubstituted oxazoles are found in a number of natural products, and most of the substituents at the oxazole 4-position are esters and their derivatives, because naturally occurring oxazoles are considered to be derived from amino acids such as serine and threonine.[1a]

Oxazole-4-carboxylates are recognized as useful intermediates and have been used in various total syntheses.[1a,4] General synthetic methods for them include the following 3-step procedure: (1) condensation of carboxylic acids with serine methyl ester to afford amide alcohols, (2) dehydrative

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10.1021/ol1012789
Published on Web 07/07/2010

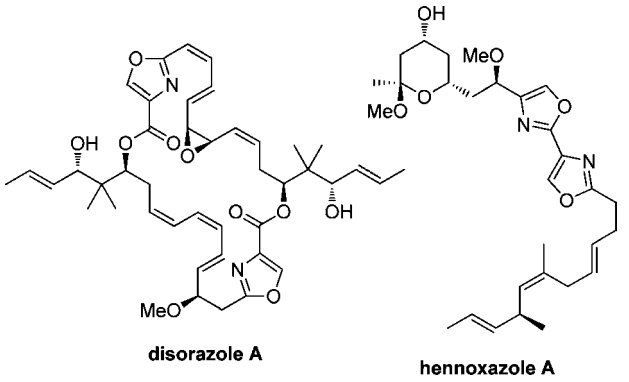
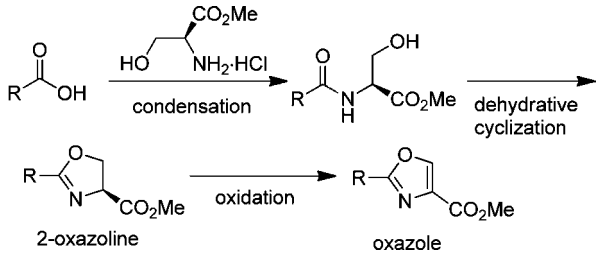


Figure 1. Examples of oxazole-containing natural products.

cyclization to obtain 2-oxazolines,[5] and (3) oxidation to the oxazoles (Scheme 1).[6] The Robinson−Gabriel-type cyclization, which includes side-chain oxidation and subsequent

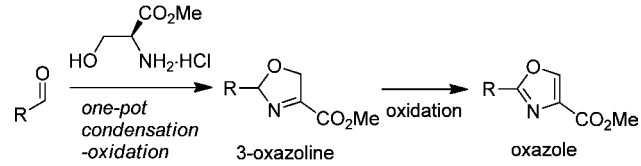
Scheme 1. General Method



cyclodehydration of amide alcohols, is also employed.[7,8] Although such transformations are well-developed, they require 3 steps, and expensive reagents are necessary for some of the dehydrative cyclizations. Therefore, developing a novel efficient synthesis of oxazole-4-carboxylates is still desirable.

In this Letter, we report a novel 2-step synthesis of oxazole-4-carboxylates from aldehydes (Scheme 2). It involves a one-pot condensation−oxidation of aldehydes and serine or threonine methyl ester to give 3-oxazoline-4-carboxylates and then subsequent oxidation to obtain the oxazole-4-carboxylates. This method is characterized by the utilization of 3-oxazoline-4-carboxylates as novel synthetic

Scheme 2. This Work



intermediates in contrast to the previous methods that use 2-oxazoline-4-carboxylates. To the best of our knowledge, this is the first general method that uses aldehydes as starting materials for oxazole-4-carboxylates.[9] Aldehydes are one of the most popular functional groups and are readily prepared by a number of methods. The present method shortens the steps needed to access oxazoles compared with previous methods. The method can also provide various oxazoles including biologically active natural products.

Recently, we developed a novel method for obtaining 2-imidazolines via a one-pot condensation−oxidation involving aldehydes and 1,2-diamines.[10] This reaction chemoselectively proceeds under mild conditions at a low reaction temperature (0 °C−rt) with *N*-bromosuccinimide (NBS). During the course of our study on the oxidative synthesis of heterocycles, we examined the one-pot condensation−oxidation of heptanal (**1a**) and serine methyl ester hydrochloride (**2a**) with *N*-chlorosuccinimide (NCS) in the presence of DABCO and expected formation of the 2-oxazoline-4-carboxylate **4a**. However, 3-oxazoline-4-carboxylate **3a** was selectively obtained (Scheme 3). Although the one-pot and stepwise condensation−oxidation of aldehydes and amino alcohols has been previously reported, these methods provided 2-oxazolines[11] or a mixture of 2-oxazolines and 3-oxazolines.[12] On the other hand, this type of reaction using ester-substituted amino alcohols, such as the serine methyl ester, and the selective formation of 3-oxazolines has not

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(7) (a) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604. (b) Brain, C. T.; Paul, J. M. *Synlett* **1999**, 1642. (c) Pulici, M.; Quartieri, F.; Felder, E. R. *J. Comb. Chem.* **2005**, *7*, 463.

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(9) For limited examples of the oxidation of 2-aryl-oxazolidines derived from aldehydes to give oxazoles, see: Badr, M. Z. A.; Aly, M. M.; Fahmy, A. M.; Mansour, M. E. Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1844.

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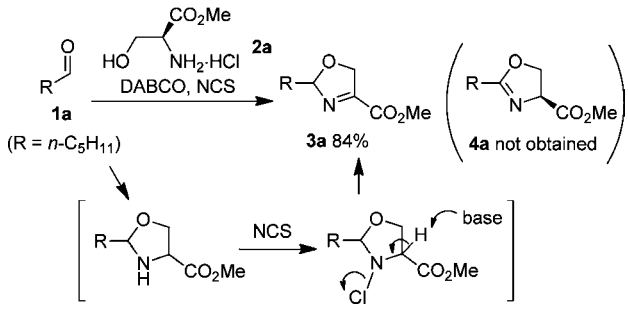
(11) (a) Schwekendiek, K.; Glorius, F. *Synthesis* **2006**, 2996. (b) Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474. (c) Sayama, S. *Synlett* **2006**, 1479.

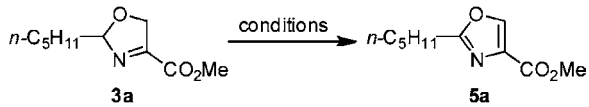
Scheme 3. Formation of the 3-Oxazoline-4-carboxylate **3a**



been reported. Our result is the first example of the one-pot condensation−oxidation of such ester-substituted amino alcohols and aldehydes to selectively afford the 3-oxazolines. This transformation involves formation of the *N*,*O*-acetal (namely, the oxazolidine), *N*-chlorination, and subsequent E2 elimination. In the final step, deprotonation at the α-position of the ester selectively occurs to give the 3-oxazoline-4-carboxylate **3a**.

Although 2-oxazolines are useful synthetic intermediates for oxazoles, there are a few reports on the synthetic utility of 3-oxazolines.[13] Hence, we examined several oxidative conditions to obtain oxazole **5a** from 3-oxazoline **3a**. These results are summarized in Table 1. We first examined the

Table 1. Oxidation of 3-Oxazoline **3a** to Oxazole **5a**



entry	conditions	yield (%)
1	$BrCCl_3$ (1.2 equiv), DBU (2.0 equiv)/ CH_2Cl_2, rt, 22 h	no reaction
2	MnO_2 (10 equiv)/benzene, reflux, 16 h	no reaction
3	DDQ (2.2 equiv)/toluene, reflux, 14 h	decomposition
4	CAN (2.2 equiv)/CH_3CN, reflux, 24 h	decomposition
5	NBS (1.2 equiv), K_2CO_3 (1.2 equiv)/ DCE, reflux, 30 min	84
6	NBS (1.2 equiv), TEA (1.2 equiv)/ DCE, reflux, 6 h	no reaction

combination of $BrCCl_3$ and DBU, which is widely used for the oxidation of 2-oxazoline-4-carboxylates to oxazoles. However, this method was not suitable for 3-oxazoline **3a** and resulted in no reaction judged by TLC (entry 1). MnO_2 also resulted in no reaction (entry 2). DDQ and CAN resulted in decomposition of the starting material (entries 3 and 4).

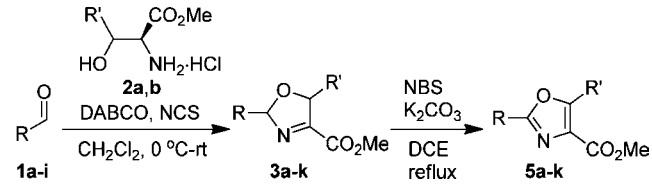
(12) Favreau, S.; Lizzani-Cuvelier, L.; Loiseau, M.; Duñach, E.; Fellous, R. *Tetrahedron Lett.* **2000**, *41*, 9787.

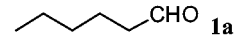
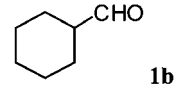
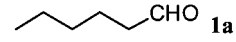
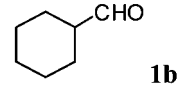
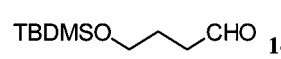
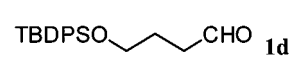
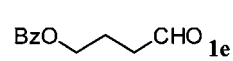
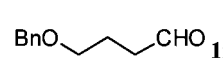
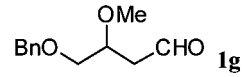
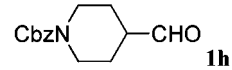
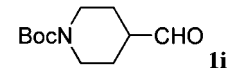
(13) (a) Dömling, A.; Bayler, A.; Ugi, I. *Tetrahedron* **1995**, *51*, 755. (b) Hua, D. H.; Khiar, N.; Zhang, F.; Lambs, L. *Tetrahedron Lett.* **1992**, *33*, 7751.

As a result of this screening, NBS was found to be an effective oxidant, and oxazole **5a** was obtained in 84% yield in the presence of K_2CO_3. On the other hand, in the presence of triethylamine, the reaction did not proceed (entry 6).[14]

With the optimized reaction conditions in hand, the generality of the reactions for forming 3-oxazolines **3a**−**3k** and oxazoles **5a**−**5k** was investigated. As shown in Table 2, the yields were uniformly good to excellent. As well as **2a** (entries 1 and 2), the threonine methyl ester hydrochloride (**2b**) was evaluated (entries 3 and 4). As functional groups, TBDMSO, TBDPSO, BzO, BnO, MeO, Cbz, and Boc were found to be tolerant (entries 5−11). For the oxidation of **3** to **5**, some modification of the reaction conditions was

Table 2. Synthesis of Oxazole-4-carboxylates from Aldehydes via 3-Oxazoline-4-carboxylates[a,b]



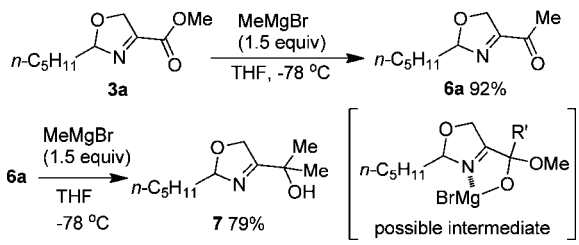
entry	RCHO	R'		yield (%)
1	 1a	H	**3a**	84
			5a	86
2	 1b	H	**3b**	82
			5b	86
3	 1a	Me	**3c**	83
			5c	97
4	 1b	Me	**3d**	84
			5d	95
5	 1c	H	**3e**	82
			5e	83[c]
6	 1d	H	**3f**	90
			5f	89
7	 1e	H	**3g**	89
			5g	88
8	 1f	H	**3h**	87
			5h	70[c,d]
9	 1g	H	**3i**	96
			5i	71[c,e]
10	 1h	H	**3j**	91
			5j	89[c]
11	 1i	H	**3k**	84
			5k	76

[a] Conditions (**1** to **3**): **2** (1.1 equiv), DABCO (3 equiv), and NCS (1.1 equiv). [b] Conditions (**3** to **5**): NBS (1.2 equiv) and K_2CO_3 (1.2 equiv) (unless otherwise noted). [c] Additive: MS 4 Å. [d] Conditions (**3** to **5**): NIS (2.0 equiv). [e] Conditions (**3** to **5**): NIS (4.0 equiv).

needed: molecular sieves were added for **5e**, **5h**, **5i**, and **5j**; NIS was used instead of NBS and K_2CO_3 for **5h** and **5i**. It is noteworthy that oxazoles **5f** and **5i** were synthetic interemediates for the oxazole-containing natural products such as hennoxazole A[4d] and disorazole C.[4b] Contrary to the reported methods that needed 3 steps to prepare **5f** or **5i** from the corresponding carboxylic acids as shown in Scheme 1, our method was able to provide them from readily available aldehydes in 2 steps and good yields.

The 3-oxazoline-4-carboxylates have three electrophilic functional groups that include an ester, an imine, and an *N*,*O*-acetal.[15] Therefore, their reactivity with nucleophiles was of interest. To explore the synthetic utility of the 3-oxazoline-4-carboxylates, we examined their reaction with Grignard reagents. When MeMgBr (1.5 equiv) was added to the solution of **3a** at −78 °C and the reaction was quenched at the same temperature, MeMgBr was found to only react with the ester of the three possible electrophilic functional groups. Very interestingly, the methyl ketone **6a** was obtained in 92% yield (Scheme 4). We also confirmed the reaction of

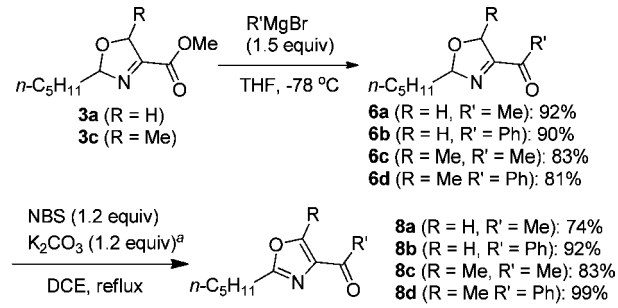
Scheme 4. Reaction of **3a** with MeMgBr



the ketone **6a** with MeMgBr to give the tertiary alcohol **7** (Scheme 4). Therefore, we assumed that a chelated metal complex intermediate (Scheme 4) could be involved that would prevent the addition of more than 1 equiv of reagent to form the alcohol, although further detailed investigations of the selective formation of the ketone are needed.

This interesting reactivity of the 3-oxazoline-4-carboxylates was useful for preparation of the 4-keto-oxazole derivatives (Scheme 5). Thus, the reaction of **3a** and **3c** with MeMgBr or PhMgBr gave the corresponding ketones **6a**−**6d** in good yields. The following oxidation also successfully proceeded under NBS/K_2CO_3 conditions to give the 4-keto-oxazole derivatives **8a**−**8d**. In the case of compound **6a**, the modified conditions using molecular sieves as an additve were effective. This transformation was facile compared with

Scheme 5. Preparation of the 4-Keto-oxazole Derivatives



[a] MS 4 Å was added for **8a**.

the previous report using the Weinreb amide for 4-keto-oxazole synthesis.[4e]

In conclusion, we have developed a novel 2-step approach for oxazole-4-carboxylates from aldehydes using 3-oxazoline-4-carboxylates as synthetic intermediates. It was also found that the interesting reactivity of the 3-oxazoline-4-carboxylates with Grignard reagents provided an easy preparation of 4-keto-oxazole derivatives. The availability of various aldehydes and the simplicity of the developed method can provide broad synthetic options for the synthesis of oxazole derivatives. Further detailed investigations including the one-pot transformation of aldehydes to oxazoles,[16] and applications for the total synthesis of natural products are now underway.

Acknowledgment. This work was financially supported by Grant-in-Aid for Scientific Research (B) and for Young Scientists (B) from JSPS.

Supporting Information Available: Experimental details and detailed spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The reaction without any base also afforded oxazole **5a**; however, an inseparable byproduct was also produced. The reaction probably proceeded via bromination of the 5-position of 3-oxazolines or nitrogen atom and then aromatization. K_2CO_3 was used as an acid scavenger for HBr formed in situ.

(15) For examples of the reaction of 1,3-oxazolidines with Grignard reagents, see: (a) Steinig, A. G.; Spero, D. M. *J. Org. Chem.* **1999**, *64*, 2406. (b) Yamauchi, T.; Takahashi, H.; Higashiyama, K. *Heterocycles* **1998**, *48*, 1813. (c) Wu, M. J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340. (d) Takahashi, H.; Chida, Y.; Yoshii, T.; Suzuki, T.; Yanaura, S. *Chem. Pharm. Bull.* **1986**, *34*, 2071.

(16) Several attempts at the one-pot transformation of aldehydes to oxazoles have failed at this stage.