Tetrahedron 67 (2011) 2066–2071

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Environmental-benign oxidation of 2-oxazolines to oxazoles by dioxygen as the sole oxidant

Yue Huang[a], Lijun Ni[a], Haifeng Gan[a], Yu He[a], Jinyi Xu[a], Xiaoming Wu[b], Hequan Yao[a,c,*]

[a] Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, No. 24 Tongjiaxiang, Nanjing 210009, Jiangsu, PR China
[b] Center for Drug Discovery, China Pharmaceutical University, 24 Tongjia Xiang, Nanjing 210009, PR China
[c] Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, PR China

ARTICLE INFO

Article history:
Received 3 December 2010
Received in revised form 14 January 2011
Accepted 18 January 2011
Available online 22 January 2011

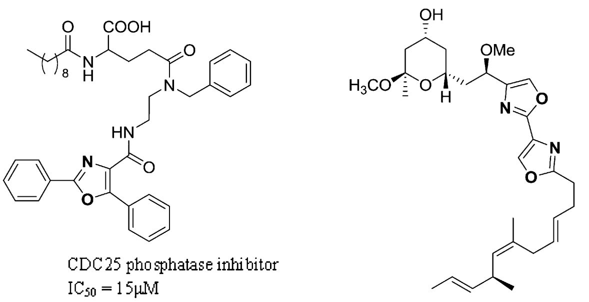
Keywords:
Oxidation
2-Oxazolines
Oxazoles
Dioxygen
Environmental-benign

ABSTRACT

A facile and environment-benign oxidation by dioxygen as the sole oxidant was applied for the conversion of 2-oxazolines to oxazoles. The substituent effect on 2-oxazoline ring was investigated. The use of this methodology for the synthesis of a key intermediate of a CDC25 phosphatase inhibitor (*SC*-$\alpha\alpha\delta$9) as an anticancer agent was also described.

1. Introduction

Oxazoles are prevalent substructures in a number of naturally occurring and synthetic molecules, which show attractive biological activities, such as antiviral, antifungal, antibacterial, and antitumor activities (Fig. 1).[1] For example, *SC*-$\alpha\alpha\delta$9 (1), an oxazole-containing small molecule, was found to be a potent CDC25 phosphatase inhibitor.[1f] Natural product Hennoxazole A (2), first isolated from the marine sponge, displays predominant antiviral activity against herpes simplex type I.[1g] It was proposed that oxazoles could be incorporated into natural products by the nonribosomal peptide synthase mediated cyclisation of serine or threonine-containing peptides.[2] As a consequence, most of the substituents at 4-position of oxazole ring are ester or their derivatives. Up to date, a variety of protocols have been reported for the synthesis of oxazoles. Among them, the most common route for the synthesis of oxazoles is a three-step procedure that relies on caboxylate acids or nitriles and amino alcohols as starting materials.[3] Recently, Fujioka and Graham independently developed a novel two-step process of oxazoles from aldehydes and amino alcohols. Specially, the final steps of above methods are the oxidation of 2-oxazolines or 3-oxazolines to oxazoles (Scheme 1).[4]



1 *SC*-$\alpha\alpha\delta$9 **2 hennoxazole A**

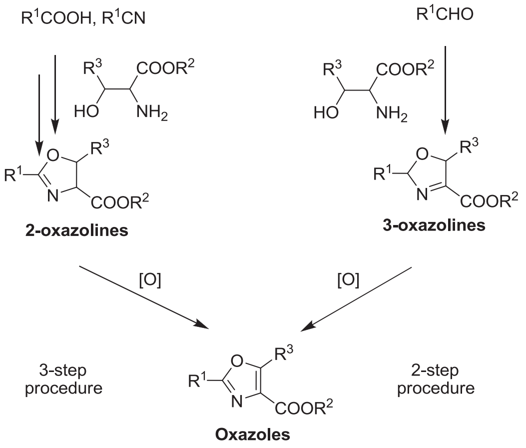
Fig. 1. Examples of oxazole-containing bioactive molecules.

Various oxidants, such as activated manganese dioxide (MnO_2),[5] nickel oxide (NiO_2),[6] $CBrCl_3$/DBU,[7] DDQ,[8] NBS/peroxide,[9] and copper/peroxide,[10] etc. can oxidize 2-oxazolines to oxazoles, while NBS/K_2CO_3 and $CBrCl_3$/DBU can convert 3-oxazolines to oxazoles (Scheme 2). Most of the above methods are effective for these oxidations. However, they have at least one or more drawbacks, such as low yields, excess amount of reagents, expensive reagents, and hazardous reaction conditions.[11] Very recently, we first reported an efficient environmental-benign method for oxidation of 2-thiazolines to thiazoles.[12] In this letter, we wish to apply this method to the oxidation of 2-oxazolines to oxazoles (Scheme 2). To the best of our knowledge, no method for oxidation of 2-oxazolines to oxazoles using dioxygen has been described so far.

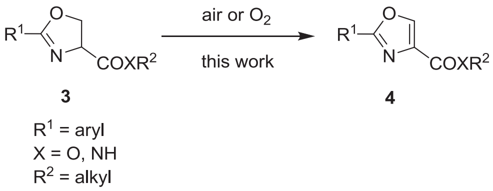
---

[*] Corresponding author. Tel.: +86 25 83271042; e-mail address: hyao@cpu.edu.cn (H. Yao).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.01.050



Scheme 1. General methods for the synthesis of oxazoles.

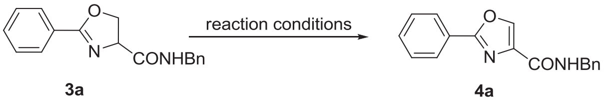


Scheme 2. The oxidation of 2-oxazolines to oxazoles using dioxygen as the sole oxidant.

2. Results and discussion

We began the investigation using **3a** bearing carboxamide at 4-position as the substrate with previously developed conditions for oxidation of 2-thiozolines, in which potassium carbonate (3 equiv) was used as the base, anhydrous DMF was used as the solvent, and dioxygen was used as the sole oxidant (Table 1). Low yield (41%) of the desired product **4a** was acquired when the reaction was performed at 80 °C, while under the same conditions 2-thiazolines could be completely converted to thiazoles (entry 1).[12] It was found that this conversion was also stepwise as we described before (see Supplementary data S1). Although most of **3a** was consumed at this temperature, the intermediate alcohol was not fully dehydrated even after 24 h, leading to the low yield of **4a**. As we knew that the dehydration could be accelerated by raising the reaction temperature, we then increased the reaction temperature to 100 °C and 120 °C. We were delighted to observe that the reactions were quite successful and **4a** was obtained in 89% and 92% yields, respectively (entries 2 and 3). The yield of **4a** was slightly decreased when 2 equiv or 1 equiv of K_2CO_3 was used (entries 4 and 5). It is worth noting that the reactions also proceeded smoothly in air, although prolonged reaction time was required (entries 6 and 7). Changing base and solvent or omitting molecular sieves resulted in lower yields of **4a** (entries 8–12). Finally, we conducted a contrastive experiment under argon, in which **3a** could not be oxidized to **4a**, confirming that dioxygen plays a key role in this oxidation (entry 13).

Table 1
The screening of reaction conditions[a,b]



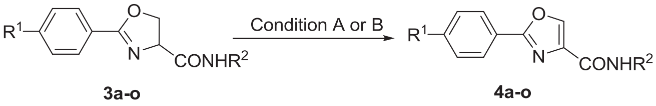
3a **4a**

Entry	Conditions	*T* (°C)	Time (h)	Yield[c] (%)
1	DMF, K_2CO_3, 4 Å MS, O_2	80	24	41
2	DMF, K_2CO_3, 4 Å MS, O_2	100	15	89
3	DMF, K_2CO_3, 4 Å MS, O_2	120	6	92
4[d]	DMF, K_2CO_3, 4 Å MS, O_2	120	10	90
5[e]	DMF, K_2CO_3, 4 Å MS, O_2	120	16	88
6	DMF, K_2CO_3, 4 Å MS, air	100	24	77
7	DMF, K_2CO_3, 4 Å MS, air	120	8	90
8	DMF, K_2CO_3, O_2	80	24	41
9	DMF, K_2CO_3, O_2	100	14	82
10	DMF, K_2CO_3, O_2	120	6	83
11	EtOH, K_2CO_3, 4 Å MS, O_2	Reflux	24	Trace
12	DMF, $NaHCO_3$, 4 Å MS, O_2	120	24	18
13	DMF, K_2CO_3, 4 Å MS, argon	120	16	0

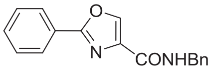
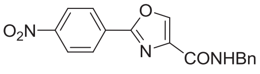
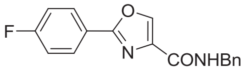
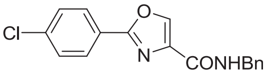
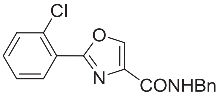
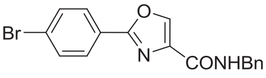
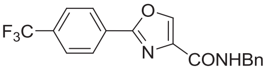
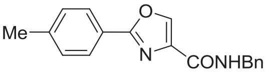
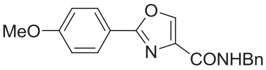
[a] Reactions were performed on a 0.2 mmol scale with inorganic bases (3 equiv).
[b] The reaction was performed with O_2 (balloon) or open to air.
[c] Isolated yields after flash chromatography.
[d] K_2CO_3 (2 equiv) was used.
[e] K_2CO_3 (1 equiv) was used.

With the optimized conditions in hand, we set out to explore the substrate scope. As shown in Table 2, various 2-oxazolines-4-carboxamides with aryl groups could be converted to the corresponding products in high yields using dioxygen or air and all substrates could

Table 2
Oxidation of 2-oxazoline-4-carboxamides to oxazole-4-carboxamides by dioxygen or air[a]



3a-o **4a-o**

Entry	Product	Condition[b]	Time (h)	Yield[c] (%)
1	 **4a**	A B	6 8	92 90
2	 **4b**	A B	6 8	79 78
3	 **4c**	A B	6 8	92 91
4	 **4d**	A B	6 8	85 87
5	 **4e**	A B	6 8	79 81
6	 **4f**	A B	6 8	87 87
7	 **4g**	A B	6 7.5	87 84
8	 **4h**	A B	6 8	81 80
9	 **4i**	A B	6 8	65 60

(*continued on next page*)