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Oxidation of 4-carboxylate thiazolines to 4-carboxylate thiazoles by molecular oxygen

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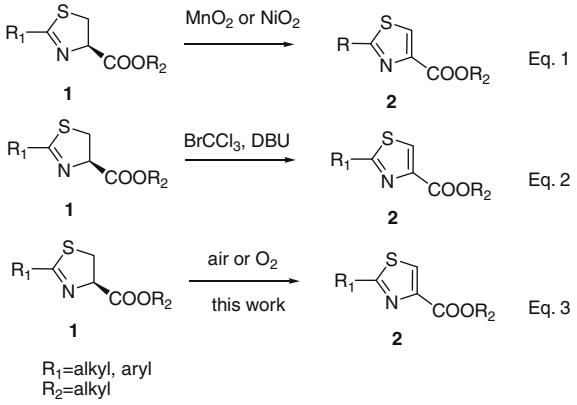
ABSTRACT

A facile and environment-benign oxidation by molecular oxygen was applied for the conversion of 4-carboxylate thiazolines to 4-carboxylate thiazoles. The substituent effect on thiazoline ring was investigated. It was found that electron-poor group on the thiazoline ring could facilitate the oxidation.

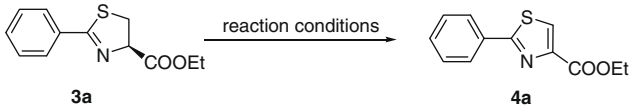
Thiazoles are important building blocks for preparing various pharmaceuticals. Recently, many natural products containing thiazole moiety were isolated and most of them exhibit considerable cytotoxicities and anti-tumor potentials.[1] It is presumed that, in organism, thiazole could be synthesized through a condensation between amino acid and cysteine, followed by an oxidation by oxidase.[2] A variety of protocols have been reported for the oxidation of thiazoline to thiazole.[3–6] For example, activated manganese dioxide (MnO_2),[3] nickel oxide (NiO_2)[4] and $CBrCl_3$/DBU[5] can oxidize thiazoline to thiazole in excellent yields (Scheme 1, Eqs. 1 and 2). Although these reagents are quite effective for this conversion, excessive amount of activated MnO_2 or NiO_2 are needed, and $CBrCl_3$ is harmful to the environment. Up to date, few environment-benign methods and further investigations for this conversion have been explored.[7] Herein, we report an oxidation of 4-carboxylate thiazolines to 4-carboxylate thiazoles using molecular oxygen as an oxidant (Scheme 1, Eq. 3).

We screened the reaction conditions for this conversion using **3a** as the substrate. Choosing potassium carbonate as the base and anhydrous DMF as the solvent, very low conversion was observed and low yield of the desired product **4a** was obtained at room temperature (Table 1, entry 1). It was found that the reaction was stepwise and the intermediate alcohol **6**, which was fully characterized,[8] could be isolated. The low yield was due to the incomplete consumption of **3a** and the incomplete dehydration of **6**. When the reaction temperature was increased to 60 °C (entry 2), **4a** was acquired in 52% yield. Although **3a** was fully consumed at this temperature, **6** was not fully dehydrated to furnish **4a**. When the reaction was performed at 80 °C or 100 °C, **6** disappeared after 2 h and the desired product **4a** was obtained in 67% and 66% yields, respectively (entries 3 and 4). At higher temperatures (entries 3 and 4), **4a** was found to be partially hydrolyzed, which could be accounted for by the fact that tiny amount of water was generated during the reaction. In order to suppress the hydrolysis of the ester



Scheme 1. Synthesis of thiazole from thiazoline.

Table 1
The screening of reaction conditions[a, 7]



Entry	Conditions	*T* (°C)	Time (h)	Yield[b]
1	DMF, K_2CO_3	rt	24	12
2	DMF, K_2CO_3	60	6	52
3	DMF, K_2CO_3	80	2	67
4	DMF, K_2CO_3	100	2	66
5	DMF, K_2CO_3, 4 Å MS	80	2	77
6	DMF, K_2CO_3, 4 Å MS	100	2	76
7	DMF, K_2CO_3, 4 Å MS	80	2	79[c]
8	DMF, $NaHCO_3$, 4 Å MS	80	6	75
9	EtOH, $NaHCO_3$, 4 Å MS	78	24	37
10	EtOH, K_2CO_3, 4 Å MS	78	8	66

[a] Reactions were performed on a 0.5 mmol scale with inorganic bases (3 equiv) and open to air.
[b] Isolated yields after flash column chromatography.
[c] The reaction was performed with O_2 (balloon).

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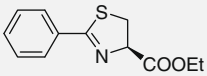
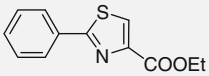
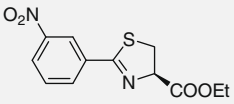
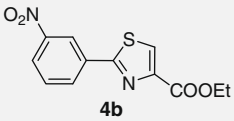
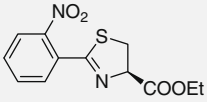
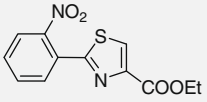
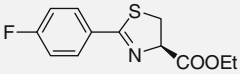
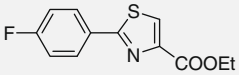
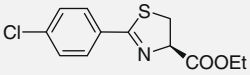
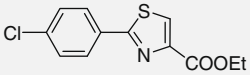
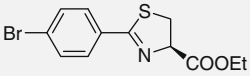
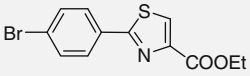
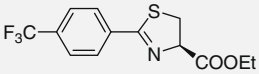
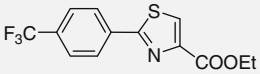
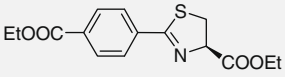
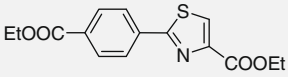
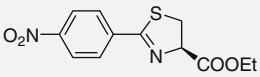
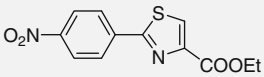
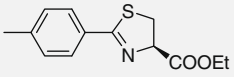
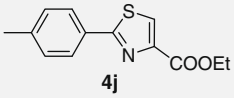
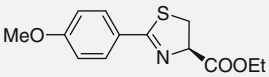
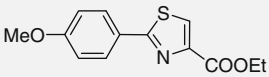
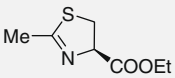
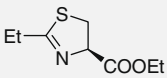
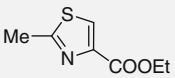
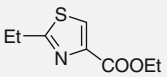
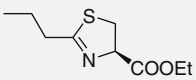
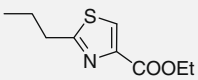
Table 2
Oxidation of 4-carboxylate thiazolines to 4-carboxylate thiazoles by molecualr oxygen

Entry[a]	Substrate (**3a–p**)	Time (h)	Method[b]	Product (**4a–p**)	Yield[c] (%)
1	 **3a**	2	A	 **4a**	77
2	 **3b**	2	A	 **4b**	82
3	 **3c**	2	A	 **4c**	83
4	 **3d**	2	A	 **4d**	80
5	 **3e**	2	A	 **4e**	83
6	 **3f**	2	A	 **4f**	81
7	 **3g**	2	A	 **4g**	91
8	 **3h**	2	A	 **4h**	80
9	 **3i**	2	A	 **4i**	77
10	 **3j**	2.5	A	 **4j**	80
11	 **3k**	2.5	A	 **4k**	56
12	 **3l**	24 7	A B	 **3m**	23[d] 67
13	 **4l**	6	B B	 **4m**	69
14	 **3n**	6	B	 **4n**	67

[a] Reactions were performed in DMF on a 0.5 mmol scale with K_2CO_3(3 equiv) and molecular sieves (4 Å, 200 wt %).[9]
[b] A: the reaction was open to air; B: the reaction was performed with O_2 (balloon).
[c] Isolated yields after flash column chromatography.
[d] The starting material was not completely consumed after 24 h.

group in **4a**, we added molecular sieves (4 Å, 200 wt %) to absorb the water generated during the reaction. Gratifyingly, under the new condition the yield of **4a** was increased significantly (entries 5 and 6). When molecular oxygen, in lieu of air, was used as the oxidant, **4a** was obtained in 79% yield, which is close to that obtained with air (entry 7). The reactions were rather slow when $NaHCO_3$ was used as the base or anhydrous EtOH was used as the solvent (entries 8–10).

With the optimized condition in hand, we then examined the oxidation of a variety of 2-substituted thiazolines and the results are summarized in Table 2. We found that various thiazole derivatives with aryl groups could be obtained using this protocol (entries 1–11). The substrates with aryl groups generally afforded the desired products in moderate to good yields, although prolonged reaction time was required for substrates bearing electron-rich aryl groups (entries 10 and 11). However, for the substrates with alkyl substituent at 2-position, the reaction proceeded sluggish and most of the substrates were not consumed even after 24 h (entry 12). Gratifyingly, higher yields could be achieved for substrates with alkyl group when molecular oxygen was used instead of air (entries 12–14). These results shown in Table 2 indicated that electron-deficient group at 2-postion of the thiazoline ring could facilitate the oxidation.

In conclusion, we have developed a clean and facile oxidation of 4-carboxylate thiazolines to 4-carboxylate thiazoles by molecular oxygen in moderate to good yields. This process is mild and environment-benign. Moreover, this work could provide a useful method for the preparation of thiazole-containing building blocks. Further investigations of this methodology for synthesis of thiazole-containing natural products are in progress and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.091.

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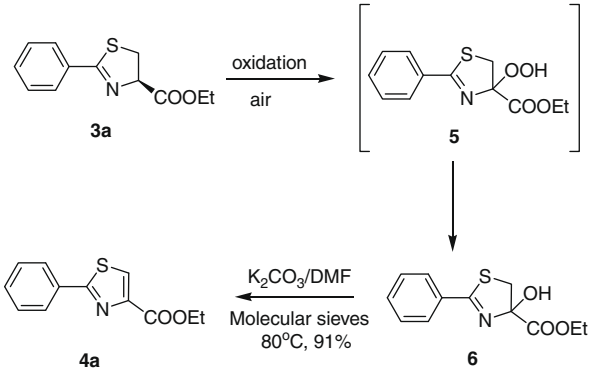
8. The intermediates **5** and **6** could be observed on TLC. Compound **6** was characterized by IR, ^1H NMR, ^{13}C NMR and ESI-HRMS. Mp 105–107 °C; IR(KBr): 3415, 3137, 3002, 2834, 1754, 1590, 1189, 1112, 766, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 3.54 (d, 1H, J = 12.0 Hz), 4.01 (d, 1H, J = 12.0 Hz), 4.32 (m, 3H), 7.40–7.45 (m, 2H), 7.49–7.54 (m, 1H), 7.89 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 170.9, 132.4, 132.1, 128.7, 105.4, 62.9, 40.6, 14.01; MS(ESI) m/z 252.0 $(M+H)^+$; HRMS(ESI) m/z calcd for $[C_{12}H_{14}NO_3S]^+$ 252.0689, found 252.0694; **6** could be smoothly dehydrated to **4a** in 91% yield using K_2CO_3 in DMF at 80 °C for 1 h.



9. *Typical experimental procedure for oxidation of thiazolines:* Ethyl 2-(4-nitrophenyl)thiazoline-4-carboxylate **3i** (140 mg, 0.5 mmol) was dissolved in anhydrous DMF (5 mL). Then molecular sieves (4 Å, 280 mg, 200 wt %) and K_2CO_3 (207 mg, 1.5 mmol) were added and the reaction mixture was stirred at 80 °C for 2 h. The resulting solution was diluted with ethyl acetate and the solution was washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The result residue was purified by flash chromatography on silica gel to afford 107 mg (77%) of ethyl 2-(4-nitrophenyl)thiazole-4-carboxylate **4i** as a yellow solid. Mp 158–159 °C; IR(KBr): 3443, 1721, 1516, 1336, 1205, 851, 794 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, 3H, J = 7.2 Hz), 4.47 (q, 2H, J = 7.2 Hz), 8.20 (d, 2H, J = 8.7 Hz), 8.28 (s, 1H), 8.33 (d, 2H, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 161.0, 148.9, 148.8, 138.1, 128.5, 127.6, 124.3, 61.7, 14.3; MS(ESI) m/z 279.0 $(M+H)^+$.