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Copper(II)-catalyzed oxidation of 4-carboxythiazolines and 4-carboxyoxazolines to 4-carboxythiazoles and 4-carboxyoxazoles

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ABSTRACT

A mild copper(II)-catalyzed oxidation of 4-carboxythiazolines and 4-carboxyoxazolines to 4-carboxythiazoles and 4-carboxyoxazoles has been developed. Various substrates with alkyl or aryl substitutions at 2-position on azoline ring could be smoothly oxidized to the desired products in good to excellent yields. Moreover, the hydrolysis of the ester group could be avoided under this method.

1. Introduction

The 4-carboxythiazole and 4-carboxyoxazole moieties are prevalent scaffolds in a number of naturally occurring and synthetic molecules with attractive biological activities, such as antiviral, antifungal, antibacterial, and anti-tumor activities.[1,2] It was proposed that 4-carboxythiazoles and 4-carboxyoxazoles could be incorporated into natural products by the nonribosomal peptide synthase mediated cyclization of cysteine and serine or threonine-containing peptides, followed by an oxidation with typical oxidase.[3] In the past few decades, oxidation of 4-carboxythiazolines and 4-carboxyoxazolines to 4-carboxythiazoles and 4-carboxyoxazoles using synthetic oxidants has attracted much attention from synthetic community due to the interesting bioactivities of the compounds bearing these scaffolds.

Up to date, various approaches, such as excess amount of activated MnO_2,[4] NiO_2,[5] $CBrCl_3$/DBU,[6] DDQ,[7] NBS/peroxide,[8] have been reported to efficiently oxidize 4-carboxythiazolines and 4-carboxyoxazolines to 4-carboxythiazoles and 4-carboxyoxazoles (Fig. 1, Eq. 1). Recently we disclosed an environmental-benign method for those conversions using molecular dioxygen as a sole oxidant (Fig. 1, Eq. 2).[9] The major disadvantage of our method is that

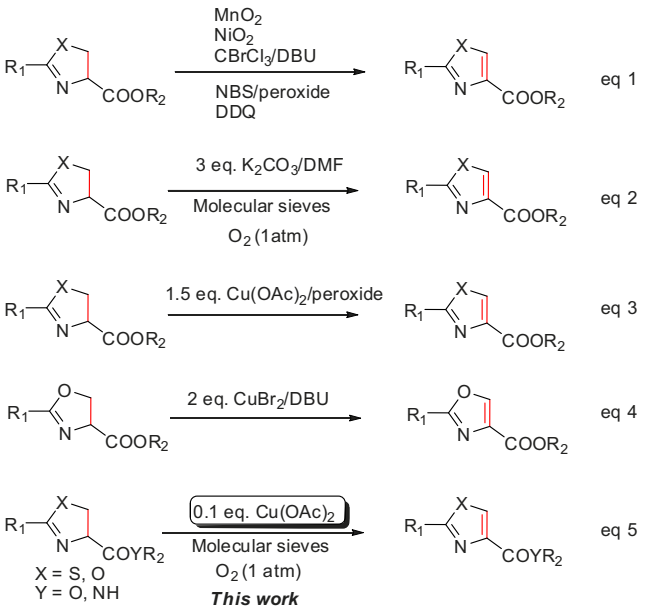

Fig. 1. Oxidation of 4-carboxythiazolines and 4-carboxyoxazolines to 4-carboxythiazoles and 4-carboxyoxazoles.

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the hydrolysis of ester groups could be observed due to the use of inorganic bases even though molecular sieves was used, leading to the relatively low yields of the desired products. About 2 decades ago, Meyers et al. developed a stoichiometric copper(II) mediated oxidation of 4-carboxythiazolines and 4-carboxyoxazolines to 4-carboxythiazoles and 4-carboxyoxazoles in good yields, in which peroxide was also used to initiate the reaction (Fig. 1, Eq. 3).[10] Barrish and Singh described a novel procedure using $CuBr_2$ (2 equiv) and DBU for the oxidation of 4-carboxyoxazolines to 4-carboxyoxazoles in moderate to good yields (Fig. 1, Eq. 4), in which the reaction mechanism was proposed.[11] However, to the best of our knowledge, no approach using a catalytic amount of $Cu(OAc)_2$ for the oxidation of these substrates has ever been reported so far.

In continuation of seeking a mild and economical oxidation process, we focused on the copper(II)-catalyzed oxidation of 4-carboxythiazolines and 4-carboxyoxazolines. We decided on this reaction for the known reason that Cu(I) could be oxidized to Cu(II) by molecular dioxygen.[12] Herein, we wish to describe this result (Fig. 1, Eq. 5).

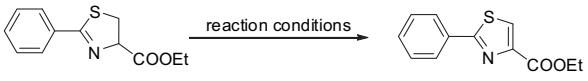
2. Results and discussion

To begin with, we chose **1a** bearing carboxylate group at 4-position as a model substrate. The results were shown in Table 1. It was found that the oxidation of **1a** could be realized in anhydrous DMF when 0.1 equiv of $Cu(OAc)_2$ was used as a catalyst at low temperatures (40–100 °C, entries 1–4). Gratifyingly, **1a** could be fully converted to the desired thiazole **2a** in 92% isolated yield in 12 h when the reaction temperature was raised to 120 °C (entry 5). The yield of **2a** was found to dramatically decrease when anhydrous CH_3CN or EtOH was used as solvent (entries 6 and 7). Other copper(II) catalysts, such as $CuCl_2$, $CuSO_4\cdot 5H_2O$ and $Cu(OAc)_2\cdot 2H_2O$, were examined as catalysts for this reaction and proven to be effective for the oxidation of **1a** (entries 8–10), albeit in relatively lower yields of **2a**. Meanwhile, a lower loading of catalyst or omitting the use of molecular sieves would reduce the yield of **2a** (entries 11–13). Next, we conducted the contrastive experiments. It was found that only about 10% yield of **2a** (by ^1H NMR) was acquired when the reaction was carried out with 0.1 equiv of catalyst under argon atmosphere (entry 14), while over 90% isolated yield of **2a** was obtained with a stoichiometric amount of $Cu(OAc)_2$ (entry 15). No product was observed in the absence of a copper catalyst (entry 16), indicating that copper catalyst played an important role in this reaction.

With the optimized condition in hand, we set out to explore the substrate scope. As shown in Table 2, various 4-carboxythiazolines with aryl or alkyl groups at 2-position could be converted to the corresponding products in high yields and all reactions could complete in 24 h (entries 1–16). We also found that the substitution on thiazole ring would influence the efficiency of the oxidation. For example, for those substrates with electron-rich benzyl substitutions at 2-position (entries 2–4) or formamides (entries 12–16) at 4-postion, prolonged reaction time was generally needed for the substrates to be fully consumed. It is noteworthy that the substrates with alkyl groups also proceeded smoothly to afford the desired products in good yields under the optimized condition (entries 10 and 11), while often in low to moderate yields under our previous method (K_2CO_3/O_2/DMF). Notably, no obvious hydrolysis of the ester group was observed for each case. No desired product was produced for the substrate with alkyl group at 4-position (entry 17), suggesting that the carboxylic substitution at 4-position was critical for this conversion, which is consistent with the mechanism proposed in the literature.

Using the optimized condition, the oxidation of various

Table 1
The screening of reaction conditions[a]

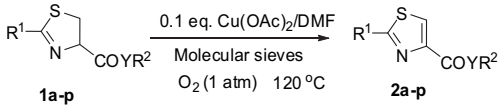


1a **2a**

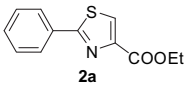
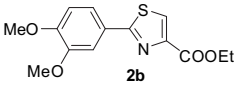
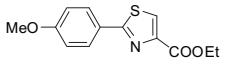
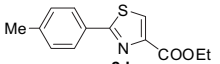
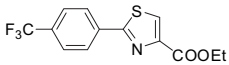
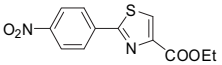
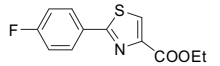
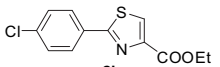
Entry	Conditions	T (°C)	Time (h)	Yield[b] (%)
1	O_2, $Cu(OAc)_2$, DMF, MS	40	24	40
2	O_2, $Cu(OAc)_2$, DMF, MS	60	24	50
3	O_2, $Cu(OAc)_2$, DMF, MS	80	24	68
4	O_2, $Cu(OAc)_2$, DMF, MS	100	24	72
5	O_2, $Cu(OAc)_2$, DMF, MS	120	12	92
6	O_2, $Cu(OAc)_2$, CH_3CN, MS	Reflux	36	20
7	O_2, $Cu(OAc)_2$, EtOH, MS	Reflux	36	40
8	O_2, $CuCl_2$, DMF, MS	120	36	45
9	O_2, $CuSO_4\cdot 5H_2O$, DMF, MS	120	12	84
10	O_2, $Cu(OAc)_2\cdot 2H_2O$, DMF, MS	120	12	80
11	O_2, $Cu(OAc)_2$, DMF, MS	120	12	65[c]
12	O_2, $Cu(OAc)_2$, DMF, MS	120	24	88[c]
13	O_2, $Cu(OAc)_2$, DMF	120	12	70
14	Ar, $Cu(OAc)_2$, DMF, MS	120	12	10[e]
15	O_2, $Cu(OAc)_2$, DMF, MS	120	12	90[d,e]
16	O_2, DMF, MS	120	24	Trace

[a] Reaction conditions: **1a** (1 mmol), catalyst (0.1 mmol, 0.1 equiv), and 4 Å molecular sieves (100% wt) in anhydrous solvent (2 mL) charged with a balloon of molecular dioxygen or argon.
[b] Isolated yields of **2a** after flash column chromatography.
[c] $Cu(OAc)_2$ (0.05 equiv) was used.
[d] $Cu(OAc)_2$ (1 equiv) was used.
[e] Compound **1a** (3 mmol) was used.

Table 2
Copper(II) catalyzed oxidation of thiazolines derivatives[a]

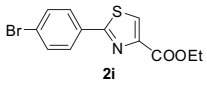
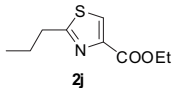
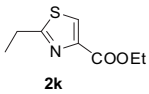
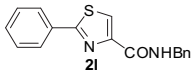
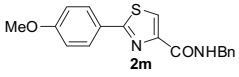
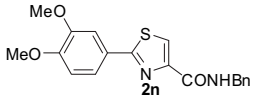
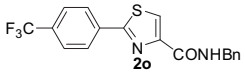
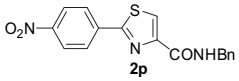
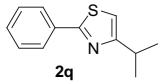


1a-p **2a-p**

Entry	Product	Time (h)	Yield[b] (%)
1	 **2a**	12	92
2	 **2b**	40	84
3	 **2c**	20	83
4	 **2d**	20	85
5	 **2e**	12	86
6	 **2f**	10	81
7	 **2g**	12	84
8	 **2h**	12	76

(*continued on next page*)

Table 2 (*continued*)

Entry	Product	Time (h)	Yield[b] (%)
9	 **2i**	12	93
10	 **2j**	12	81
11	 **2k**	12	83
12	 **2l**	24	85
13	 **2m**	24	87
14	 **2n**	30	84
15	 **2o**	24	78
16	 **2p**	24	71
17	 **2q**	24	NR

[a] Reaction conditions: thiazole substrate (0.5 mmol), $Cu(OAc)_2$ (0.1 equiv) and 4 Å molecular sieves (100% wt) in 1.0 mL of anhydrous DMF charged with a balloon of molecular dioxygen.
[b] Isolated yield.

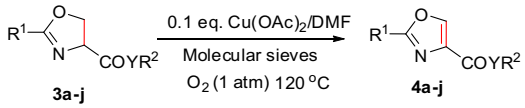
4-carboxyoxazolines to 4-carboxyoxazoles was then examined. We found that all 4-carboxyoxazolines could be converted to the corresponding products in good to excellent yields (entries 1–10). Generally, longer reaction time is needed for oxazolines than thiazolines. Methyl ester was also found to be tolerated under this reaction condition, further demonstrating that this reaction condition is really mild. The results in Table 3 also indicated a similar pattern about the influence of substitutions on oxazoline ring as shown in Table 2.

Finally, we investigated whether this protocol was suitable for the synthesis of 4-carboxythiazole or 4-carboxyoxazole in relatively large scale. Indeed, Treatment of 5 mmol of **1a** and **3a** under the optimized condition smoothly provided the desired products **2a** and **4a** in 88% and 81% isolated yields, respectively (Fig. 2).

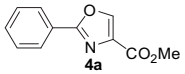
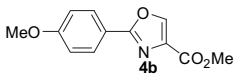
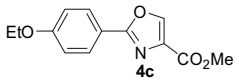
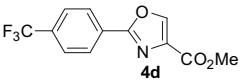
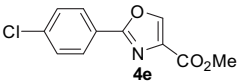
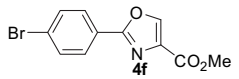
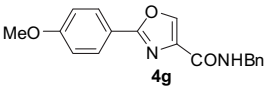
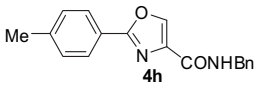
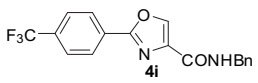
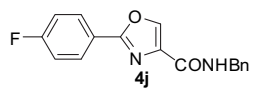
3. Conclusions

In summary, we have first developed a copper(II) catalyzed oxidation of 4-carboxythiazolines or 4-carboxyoxazolines to 4-carboxythiazoles or 4-carboxyoxazoles in good to excellent yields. The reaction demonstrated broad substrate scope and good substitution tolerance. Compared to the well-established protocols, this process is atom-economical, safe, and easy to handle. Further

Table 3
Copper(II) catalyzed oxidation of oxazolines derivatives[a]



3a-j **4a-j**

Entry	Poduct	Time (h)	Yield[b] (%)
1	 **4a**	24	82
2	 **4b**	24	81
3	 **4c**	24	88
4	 **4d**	24	81
5	 **4e**	24	82
6	 **4f**	24	75
7	 **4g**	24	86
8	 **4h**	24	80
9	 **4i**	24	83
10	 **4j**	24	76

[a] Reaction conditions: oxazole substrate (0.5 mmol), $Cu(OAc)_2$ (0.1 equiv) and 4 Å molecular sieves (100% wt) in 1.0 mL of anhydrous DMF charged with a balloon of molecular dioxygen.
[b] Isolated yield.

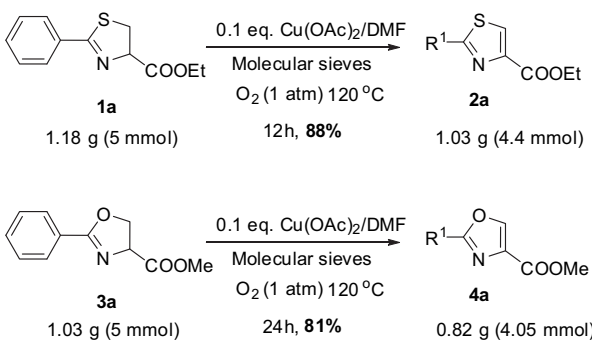


Fig. 2. The scalable synthesis of **2a** and **4a** under the optimized condition.

investigations of this methodology for other hetereocycles and synthetic application of this protocol are now underway in our laboratory.

4. Experimental

4.1. General experimental

All solvents were distilled prior to use unless otherwise noted. NMR spectra were recorded for ^{1}H NMR at 300 MHz and for ^{13}C NMR at 75 MHz. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard (δ=0) and data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), and coupling constant in hertz. For ^{13}C NMR, TMS (δ=0) or $CDCl_3$ (δ=77.25) was used as internal standard and spectra were obtained with complete proton decoupling. Low-resolution MS and HRMS data were obtained using ESI ionization. Mp data were measured with micro melting point apparatus. Melting points were uncorrected. IR spectra were recorded on an FTIR spectrometer (KBr).

4.2. General procedure for the synthesis of 4-carboxythiazolines or 4-carboxyoxazolines

To a solution of 4-carboxythiazoline or 4-carboxyoxazoline (0.5 mmol) in anhydrous DMF (1 mL) were added molecular sieves (4 Å, 100% wt) and $Cu(OAc)_2$ (9.1 mg, 0.05 mmol). The reaction mixture was stirred with an O_2 balloon at 120 °C for 10–24 h. The resulting mixture 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 residue was purified by flash chromatography on silica gel to afford 4-carboxythiazole or 4-carboxyoxazole.

*4.2.1. Ethyl 2-phenylthiazole-4-carboxylate (**2a**).* Colorless oil; IR (KBr) 3126, 2932, 2896, 1728, 1466, 1368, 930, 871, 770, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.26–8.02 (m, 5H), 4.44 (q, 2H, J=7.0 Hz), 1.14 (t, 3H, J=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 161.4, 148.0, 131.4, 130.6, 129.2, 128.5, 126.9, 61.4, 14.3; MS (ESI) m/z 234.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{12}H_{11}NO_2S+H]^+$ 234.0583, found 234.0582.

*4.2.2. Ethyl 2-(3,4-dimethoxyphenyl)thiazole-4-carboxylate (**2b**).* White solid; mp 94–95 °C; IR (KBr) 3094, 2985, 1726, 1599, 1522, 1466, 1366, 1343, 1248, 1028, 861, 807, 763 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 6.89–7.61 (m, 3H), 4.45 (q, 2H, J=7.1 Hz), 3.99 (t, 3H), 3.94 (t, 3H), 1.43 (t, 3H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 161.5, 151.2, 149.2, 147.7, 126.5, 125.9, 120.3, 110.9, 109.4, 61.5, 56.1, 56.0, 14.3; MS (ESI) m/z 294.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{14}H_{15}NO_4S+H]^+$ 294.0794, found 294.0790.

*4.2.3. Ethyl 2-(4-methoxyphenyl)thiazole-4-carboxylate (**2c**).* White solid; mp 91–93 °C; IR (KBr) 3136, 2968, 2926, 2837, 1726, 1607, 1525, 1441, 1369, 1258, 1209, 1027, 836, 796, 682 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8. 09 (s, 1H), 6.94–7.96 (m, 4H), 4.44 (q, 2H, J=7.2 Hz), 3.86 (t, 3H), 1.42 (t, 3H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 161.6, 161.5, 147.8, 28.4, 126.2, 125.7, 114.2, 61.4, 55.4, 14.3; MS (ESI) m/z 264.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_{13}H_{13}NO_3S+H]^+$ 264.0689, found 264.0687.

*4.2.4. Ethyl 2-p-tolylthiazole-4-carboxylate (**2d**).* Colorless oil; IR (KBr) 3139, 2957, 2902, 1723, 1613, 1464, 1365, 879, 789, 710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.24–7.91 (m, 4H), 4.44 (q, 2H, J=7.1 Hz), 2.38 (t, 3H), 1.39(t, 3H, J=7.1Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 161.5, 147.8, 141.0, 130.1, 129.6, 128.6, 126.7, 61.4, 21.4, 14.3; MS (ESI) m/z 248.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{13}H_{13}NO_2S+H]^+$ 248.0740, found 248.0742.

*4.2.5. Ethyl 2-(4-(trifluoromethyl)phenyl)thiazole-4-carboxylate (**2e**).* White solid; mp 97–99 °C; IR (KBr) 3135, 1724, 1617, 1459, 1369, 1249, 1109, 852, 794 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.26–8.15 (m, 4H), 4.45 (q, 2H, J=7.1 Hz), 1.45 (t, 3H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 161.2, 148.5, 135.8, 132.0, 127.9, 127.2, 126.0,125.9, 125.9, 61.7, 14.3; MS (ESI) m/z 302.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{13}H_{10}F_3NO_2S+H]^+$ 302.0457, found 302.0457.

*4.2.6. Ethyl 2-(4-nitrophenyl)thiazole-4-carboxylate (**2f**).* Yellow solid; mp 143–144 °C; IR (KBr) 3443, 1721, 1516, 1336, 1205, 851, 794 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, 2H, J=8.7 Hz), 8.28 (s, 1H), 8.20 (d, 2H, J=8.7 Hz), 4.47 (q, 2H, J=7.2 Hz), 1.45 (t, 3H, J=7.2 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 $[M+H]^+$; HRMS (ESI) calcd for $[C_{12}H_{10}N_2O_4S+H]^+$ 279.0434, found 279.0437.

*4.2.7. Ethyl 2-(4-fluorophenyl)thiazole-4-carboxylate (**2g**).* White solid; mp 70–72 °C; IR (KBr) 3105, 2979, 1721, 1594, 1518, 1464, 1368, 1245, 1102, 861, 793 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8. 14 (s, 1H), 7.00–8.03 (m, 4H), 4.45 (q, 2H, J=7.1 Hz), 1.33 (t, 3H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 165.9, 162.5, 161.4, 148.1, 129.0, 128.9, 127.0, 116.2, 116.0, 61.5, 14.3; MS (ESI) m/z 252.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_{12}H_{10}FNO_2S+H]^+$ 252.0489, found 252.0487.

*4.2.8. Ethyl 2-(4-chlorophenyl)thiazole-4-carboxylate (**2h**).* White solid; mp 88–89 °C; IR (KBr) 3134, 1724, 1460, 1364, 1336, 1086, 836, 793 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.26–7.97 (m, 4H), 4.43 (q, 2H, J=7.1 Hz), 1.37 (t, 3H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 161.3, 148.0, 136.7, 131.2, 129.1, 128.9, 127.0, 61.5, 14.3; MS (ESI) m/z 268.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_{12}H_{10}ClNO_2S+H]^+$ 268.0194, found 268.0192.

*4.2.9. Ethyl 2-(4-bromophenyl)thiazole-4-carboxylate (**2i**).* White solid; mp 89–91 °C; IR (KBr) 3122, 2985, 1724, 1470, 1363, 1209, 1098, 832, 795 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.25–7.89 (m, 4H), 4.46 (q, 2H, J=7.1 Hz), 1.40 (t, 3H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 161.3, 148.2, 139.7, 132.1, 130.1, 127.2, 125.1, 61.6, 14.4; MS (ESI) m/z 312.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_{12}H_{10}BrNO_2S+H]^+$ 311.9688, found 311.9684.

*4.2.10. Ethyl 2-propylthiazole-4-carboxylate (**2j**).* Colorless oil; IR (KBr) 2963, 2932, 2867, 1733, 1716, 1485, 1363, 1229, 1204, 1100, 1020, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 4.42 (q, 2H, J=7.1 Hz), 3.04 (t, 2H, J=7.7 Hz), 1.81 (m, 2H), 1.39 (t, 3H, J=7.1 Hz), 1.02 (t, 3H, J=7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 161.5, 146.8, 126.8, 61.3,35.5, 23.5, 14.1, 14.0; MS (ESI) m/z 200.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_9H_{13}NO_2S+H]^+$ 200.0740, found 200.0739.

*4.2.11. Ethyl 2-ethylthiazole-4-carboxylate (**2k**).* Colorless oil; IR (KBr) 2977, 2926, 2853, 1734, 1460, 1368, 1235, 1205, 1098, 1020, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 4.42 (q, 2H, J=7.8 Hz), 3.10 (q, 2H, J=7.5 Hz), 1.39 (t, 6H, J=6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 161.4, 146.7, 126.7, 61.3, 27.0, 14.3, 14.2; MS (ESI) m/z 186.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_8H_{11}NO_2S+Na]^+$ 208.0403, found 208.0402.

*4.2.12. N-Benzyl-2-phenylthiazole-4-carboxamide (**2l**).* White solid; mp 62–64 °C; IR (KBr) 3303, 3097, 2920, 1654, 1479, 1465, 1384, 1233, 1054, 1027, 765, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.81 (s, 1H), 7.42–7.92 (m, 5H), 7.24–7.35 (m, 5H), 4.67 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 161.1, 150.7, 138.2, 132.8,

130.7, 129.1, 128.8, 127.9, 127.5, 126.7, 123.2, 43.4; MS (ESI) *m/z* 295.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{17}H_{14}N_2OS+H]^+$ 295.0899, found 295.0900.

*4.2.13. N-Benzyl-2-(4-methoxyphenyl)thiazole-4-carboxamide (**2m**).* White solid; mp 128–130 °C; IR (KBr) 3345, 2938, 2825, 1648, 1610, 1480, 1304, 1253, 1110, 838,706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.82 (s, 1H), 6.93–7.88 (m, 4H), 7.29–7.39 (m, 5H), 4.68 (d, 2H), 3. 86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 161.6, 160.6, 150.3, 138.2, 128.7, 128.2, 127.9, 127.5, 125.6, 122.3, 114.4, 55.5, 43.4; MS (ESI) *m/z* 325.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{18}H_{16}N_2O_2S+H]^+$ 325.1005, found 325.0999.

*4.2.14. N-Benzyl-2-(3,4-dimethoxyphenyl)thiazole-4-carboxamide (**2n**).* White solid; mp 98–100 °C; IR (KBr) 3398, 3091, 2920, 2849, 1659, 1465, 1437, 1268, 1243, 1024, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.80 (s, 1H), 6.88–7.47 (m, 3H), 7.26–7.37 (m, 5H), 4.68 (d, 2H), 3. 93 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 161.1, 151.3, 150.4, 149.3, 138.3, 128.7, 127.8, 127.5, 125.9, 122.6, 120.1, 111.1, 109.2, 56.1, 55.0, 43.3; MS (ESI) *m/z* 355.1 $[M+H]^+$; HRMS (ESI) calcd for $[C1_9H_{18}N_2O_3S+H]^+$ 355.1104, found 355.1106.

*4.2.15. N-Benzyl-2-(4-(trifluoromethyl)phenyl)thiazole-4-carboxamide (**2o**).* White solid; mp: 105–108 °C; IR (KBr) 3341, 2927, 1654, 1544, 1485, 1409, 1254, 1065, 848, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.80 (s, 1H), 7.66–8.03 (m, 4H), 7.25–7.39 (m, 5H), 4.68 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 160.1, 151.5, 139.9, 136.4, 131.1, 130.7, 128.6, 127.8, 127.5, 127.4, 127.1, 126.4, 125.8, 125.7, 42.8; MS (ESI) *m/z* 363.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{18}H_{13}F_3N_2OS+H]^+$ 363.0773, found 363.0772.

*4.2.16. N-Benzyl-2-(4-nitrophenyl)thiazole-4-carboxamide (**2p**).* Yellow solid; mp 146–148 °C; IR (KBr) 3410, 2920, 1650, 1597, 1480, 1345, 1257, 1104, 850, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.89 (s, 1H), 8.09–8.32 (m, 4H), 7.26–7.37 (m, 5H), 4.60 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 160.8, 151.6, 148.8, 139.9, 138.3, 128.7, 128.0, 127.8, 127.3, 126.8, 124.9, 42.8; MS (ESI) *m/z* 340.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{17}H_{13}N_3O_3S+H]^+$ 340.0750, found 340.0742.

*4.2.17. Methyl 2-phenyloxazole-4-carboxylate (**4a**).* White solid; mp: 81–81.5 °C; IR (KBr) 3156, 3103, 3003, 2950, 2855, 1718, 1571, 1442, 1317, 1258, 1204, 1143, 1127, 1057, 1001, 780, 713, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.10–8.14 (m, 3H), 7.46–7.50 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 160.8, 127.2, 142.8, 142.8, 133.4, 130.2, 127.8, 127.8, 125.9, 125.4, 51.2; MS (ESI) *m/z* 204.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_{11}H_9NO_3+H]^+$ 204.0662, found 204.0655.

*4.2.18. Methyl 2-(4-methoxyphenyl)oxazole-4-carboxylate (**4b**).* White solid; mp: 111–112 °C; IR (KBr) 3162, 3103, 3026, 2956, 2850, 1742, 1616, 1502, 1440, 1323, 1269, 1250, 1129, 1151, 1123, 1018, 829 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.05 (d, 2H, *J*=7.2 Hz), 6.98 (d, 2H, *J*=7.2 Hz), 3.95 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 162.6, 162.0, 161.9, 143.3, 134.2, 128.6, 119.1, 114.2, 55.4, 52.1; MS (ESI) *m/z* 234.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_{12}H_{11}NO_4+H]^+$ 234.0759, found 234.0761.

*4.2.19. Methyl 2-(4-ethoxyphenyl)oxazole-4-carboxylate (**4c**).* White solid; mp: 110–112 °C; IR (KBr) 3144, 2920, 2843, 1753, 1615,1500, 1384, 1324, 1259, 1192, 1143, 1118, 1036, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (t, 3H, *J*=6.9 Hz), 3.95 (s, 3H), 4.09 (q, 2H, *J*=6.9 Hz), 6.94–8.05 (m, 4H), 8.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 162.7,161.9, 161.4, 143.3, 128.6, 118.9, 114.7, 63.7, 52.2, 14.7; MS (ESI) *m/z* 248.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{13}H_{13}NO_4+H]^+$ 248.0917, found 248.0920.

*4.2.20. Methyl2-(4-(trifluoromethyl)phenyl)oxazole-4-carboxylate (**4d**).* White solid; mp: 123–124 °C; IR (KBr) 3135, 3087, 2968, 1728, 1442, 1414, 1384, 1328, 1257, 1201, 1176, 1151, 1074, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.24 (d, 2H, *J*=8.4 Hz), 7.75 (d, 2H, *J*=8.4 Hz), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 161.1, 144.3, 134.8, 133.0, 132.6, 129.5, 127.2, 126.0, 125.9, 125.9, 125.8, 125.5, 121.8, 52.3; MS (ESI) *m/z* 272.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_{12}H_8F_3NO_3+H]^+$ 272.0538, found 272.0529.

*4.2.21. Methyl 2-(4-chlorophenyl)oxazole-4-carboxylate (**4e**).* White solid; mp: 152–154 °C; IR (KBr) 3103, 2914, 2849, 1736, 1642, 1492, 1370, 1314, 1282, 1214, 1117, 1093, 1062, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.44–8.06 (m, 4H), 3.96 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 161.6, 143.9, 137.5, 130.0, 129.2, 128.5, 128.1, 52.3; MS (ESI) *m/z* 238.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_{11}H_8ClNO_3+H]^+$ 238.0259, found 238.0265.

*4.2.22. Methyl 2-(4-bromophenyl)oxazole-4-carboxylate (**4f**).* White solid; mp: 154–156 °C; IR (KBr) 3109, 2920, 2849, 1736, 1642,1484, 1369, 1314, 1279, 1262, 1117, 1092, 1011, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.60–7.99 (m, 4H), 3.96 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 166.6, 143.9, 134.5, 132.2, 128.3, 125.9, 125.2, 52.3; MS (ESI) *m/z* 282.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{11}H_8BrNO_3+H]^+$ 281.9760, found 281.9761.

*4.2.23. N-Benzyl-2-(4-methoxyphenyl)oxazole-4-carboxamide (**4g**).* White solid; mp: 134–136 °C; IR (KBr) 3305, 3116, 3080, 1650, 1612, 1592, 1514, 1498, 1452, 1439, 1384, 1331, 1256, 1183, 1166, 1101, 1027, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.95 (d, 2H, *J*=8.7 Hz), 7.27–7.38 (m, 6H), 6.96 (d, 2H, *J*=8.7 Hz), 4.64 (d, 2H, *J*=6.0 Hz), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 161.5, 160.7, 140.4, 138.0, 137.0, 128.7, 128.3,127.9, 127.5, 119.3, 114.3, 55.4, 43.1; MS (ESI) *m/z* 309.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{18}H_{16}N_2O_3+H]^+$ 309.1230, found 309.1234.

*4.2.24. N-Benzyl-2-p-tolyloxazole-4-carboxamide (**4h**).* White solid; mp: 137–138 °C; IR (KBr) 3341, 3133, 3038, 2920, 2855, 1655, 1593, 1519, 1500, 1458, 1384, 1325, 1255, 1109, 1060, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.91 (d, 2H, *J*=8.4 Hz), 7.28–7.39 (m, 8H), 4.65(d, 2H, *J*=6.0 Hz), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 160.7, 141.5, 140.6, 138.1, 137.1, 129.6, 128.7, 127.9, 127.6, 126.6, 123.9, 43.1, 21.5; MS (ESI) *m/z* 293.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{18}H_{16}N_2O_2+H]^+$ 293.1281, found 293.1285.

*4.2.25. N-Benzyl-2-(4-(trifluoromethyl)phenyl)oxazole-4-carboxamide (**4i**).* White solid; mp: 117–118 °C; IR (KBr) 3320, 2938, 1654, 1621, 1597, 1525, 1504, 1435, 1415, 1325, 1259, 1171, 1127, 1083, 853, 790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.15 (d, 2H, *J*=8.4 Hz), 7.73 (d, 2H, *J*=8.4 Hz), 7.31–7.39 (m, 6H), 4.67 (d, 2H, *J*=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 160.0, 141.7, 137.9, 137.7, 132.8, 132.4, 129.7, 128.8, 128.5, 127.9, 127.6, 126.9, 125.9, 125.9, 125.5, 121.9, 43.1; MS (ESI) *m/z* 347.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{18}H_{13}F_3N_2O_2+H]^+$ 347.0999, found 347.1002.

*4.2.26. N-Benzyl-2-(4-fluorophenyl)oxazole-4-carboxamide (**4j**).* White solid; mp: 122–123.5 °C; IR (KBr) 3306, 2944, 1652,1610, 1595, 1520, 1499, 1384, 1325, 1240, 1113, 846, 815, 742, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.02 (t, 2H, *J*=8.7 Hz), 7.30–7.39 (m, 6H), 7.16 (t, 2H, *J*=8.7 Hz), 4.65 (d, 2H, *J*=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 162.7,160.6, 160.4, 140.9, 140.9, 137.9, 137.2, 128.9, 128.7, 128.5,127.9, 127.6, 122.9, 122.9,

116.3, 116.0, 43.1; MS (ESI) *m*/*z* 297.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{17}H_{13}FN_2O_2+H]^+$ 297.1038, found 297.1034.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.016.

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