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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

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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*-ααδ9) 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*-ααδ9 (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]

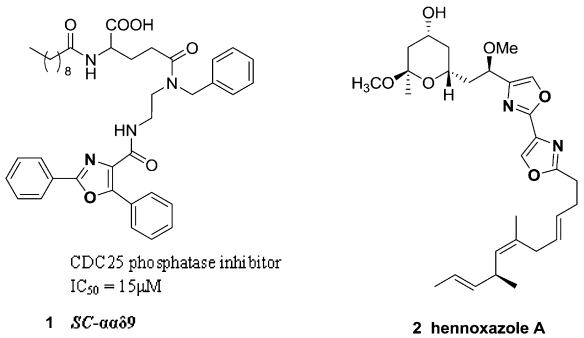

Fig. 1. Examples of oxazole-containing bioactive molecules.

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).

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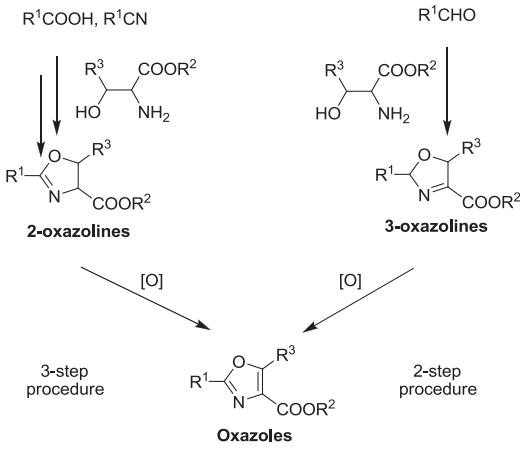
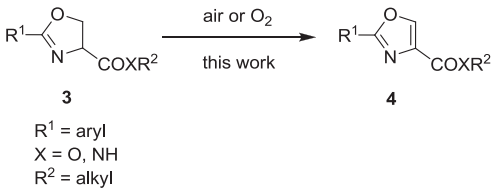


Scheme 1. General methods for the synthesis of oxazoles.



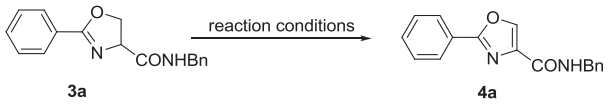
Scheme 2. The oxidation of 2-oxazolines to oxazoles using dioxygen as the sole oxidant.

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).

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 1
The screening of reaction conditions[a,b]

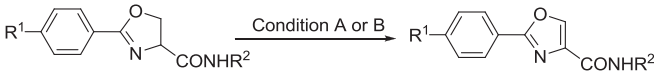


3a 4a

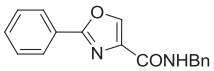
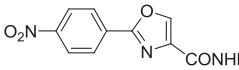
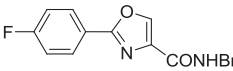
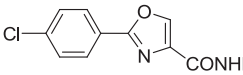
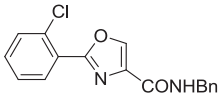
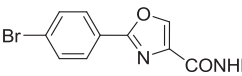
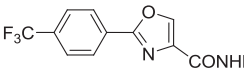
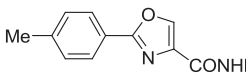
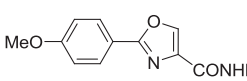
Entry	Conditions	*T* (°C)	Time (h)	Yield[c] (%)
1	DMF, K_2CO_3, 4 Å MS, O_2	80	24	41
2	DMF, K_2CO_3, 4 Å MS, O_2	100	15	89
3	DMF, K_2CO_3, 4 Å MS, O_2	120	6	92
4[d]	DMF, K_2CO_3, 4 Å MS, O_2	120	10	90
5[e]	DMF, K_2CO_3, 4 Å MS, O_2	120	16	88
6	DMF, K_2CO_3, 4 Å MS, air	100	24	77
7	DMF, K_2CO_3, 4 Å MS, 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.

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

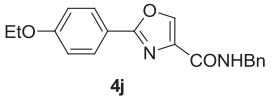
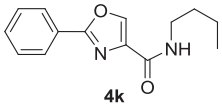
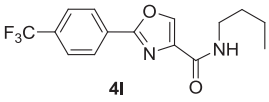
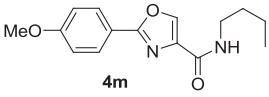
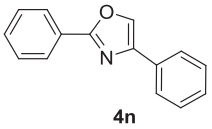
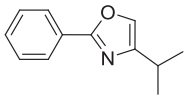


3a-o 4a-o

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

(*continued on next page*)

Table 2 (*continued*)

Entry	Product	Condition[b]	Time (h)	Yield[c] (%)
10	 **4j**	A B	6 8	69 60
11	 **4k**	A B	6.5 8	82 80
12	 **4l**	A B	6 8	80 77
13	 **4m**	A B	6 7	61 50
14	 **4n**	B	48	67
15	 **4o**	B	36	0[d]

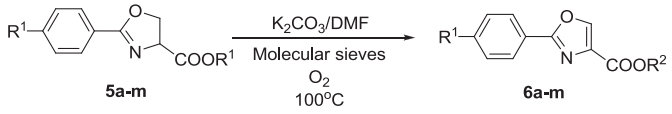
[a] Reactions were performed in DMF on a 0.2 mmol scale with K_2CO_3(3 equiv) and molecular sieves (200 wt %).
[b] Condition A: the reaction was performed with O_2 (balloon). Condition B: the reaction was open to air.
[c] Isolated yields after flash chromatography.
[d] Compound **4o** was not observed after 36 h.

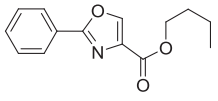
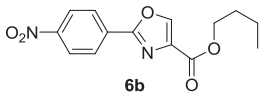
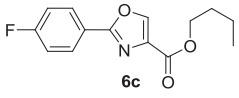
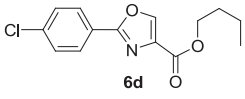
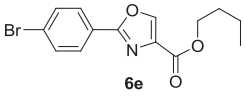
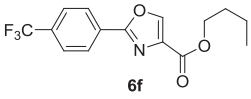
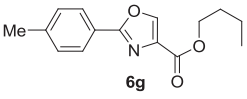
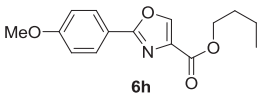
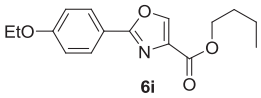
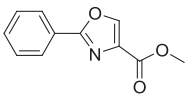
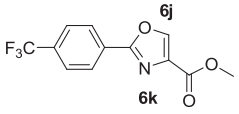
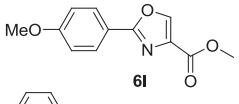
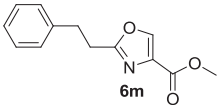
be fully complete in less than 8 h (entries 1–13, conditions A and B). Good to excellent yields of the corresponding products were achieved for all substrates bearing electron-deficient aryl groups (entries 2–7 and 12), while moderate yields for the ones bearing electron-rich aryl groups (entries 8–10 and 13). These results indicated that electron-deficient group at 2-postion of the 2-oxazoline ring could facilitate the oxidation. When the reactions were conducted in air, similar yields of corresponding products were obtained (entries 1–13, condition B). Oxidation of the substrate **3n** bearing benzene group at 4-position under this condition for 48 h successfully afforded the desired product **4n** in 67% yield (entry 14), while that of the one bearing alkyl group (**3o**) at 4-position failed to give the desired product **4o** (entry 15).

Next, we examined the oxidation of substrates bearing carboxylate group at 4-position. We first tried to decrease the reaction temperature and use pure dioxygen in order to suppress the hydrolysis of ester group, which could be caused by the tiny amount of water generated during the reaction. We found that the reaction proceeded smoothly and **6a** was obtained in 70% yield when **5a** was treated at 100 °C (see Supplementary data S2 and S3). As shown in Table 3, all substrates bearing aryl groups at 2-postion could be converted to the corresponding products in moderate yields (entries 1–12). The results in Table 3 also indicate similar pattern about the influence of substitutions on the benzene ring as shown in Table 2. To our disappointment, the substrate bearing alkyl group underwent decomposition under this condition (entry 13).

Finally, we applied this protocol to the synthesis of trisubstituted oxazole **9**, a key synthetic intermediate of *SC*-ααδ9, as shown in Scheme 3. A coupling between 1-benzyl-5-methoxyl-

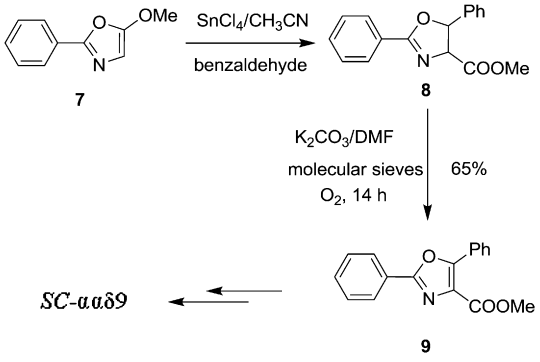
Table 3
Oxidation of 2-oxazoline-4-carboxylates to oxazole-4-carboxylates by dioxygen[a]



Entry	Product	Time (h)	Yield[b] (%)
1	 **6a**	8	70
2	 **6b**	7	68
3	 **6c**	8	68
4	 **6d**	8	70
5	 **6e**	8	71
6	 **6f**	8	74
7	 **6g**	7	67
8	 **6h**	7	51
9	 **6i**	8	50
10	 **6j**	7	60
11	 **6k**	7	62
12	 **6l**	5.5	43
13	 **6m**	3	Decomp.[c]

[a] Reactions were performed in DMF on a 0.2 mmol scale with K_2CO_3(3 equiv) and molecular sieves (200 wt %).
[b] Isolated yields after flash chromatography.
[c] Compound **6m** was found to be decomposed at rt–100 °C after 3 h.

oxazole (**7**) and benzaldehyde gave 2,4,5-trisubstituted oxazoline **8**. The following oxidation of **8** also successfully proceeded under O_2/K_2CO_3/DMF condition for 14 h to afford **9** in 65% yield.



Scheme 3. Synthesis of the key intermediate, oxazole **9** of *SC*-ααδ9.

3. Conclusions

We have first developed a clean, economical, and efficient oxidation of 2-oxazolines to oxazoles by dioxygen as the sole oxidant in moderate to good yields. We have also applied this methodology to the preparation of the key intermediate for *SC*-ααδ9, a CDC25 phosphatase inhibitor as an anticancer agent. This process is mild, environmental-benign, and could provide a useful method for the preparation of oxazole-containing molecules or natural products. Further investigations of this methodology for other heterocycles and synthetic application of this protocol are now underway and will be reported in due course.

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 or EI ionization. Mp data were measured with micro melting point apparatus. Melting points were uncorrected. IR spectra were recorded on a FTIR spectrometer (KBr).

4.2. General procedure for the synthesis of oxidation of 2-oxazolines

2-Oxazoline (0.2 mmol) was dissolved in anhydrous DMF (2 mL). Then molecular sieves (4 Å, 200 wt %) and K_2CO_3 (83 mg, 0.6 mmol) were added and the reaction mixture was stirred with a O_2 balloon at 100 °C or 120 °C for 3–24 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 residue was purified by flash chromatography on silica gel to afford oxazole.

*4.2.1. N-Benzyl-2-phenyloxazole-4-carboxamide (**4a**).* White solid; mp: 150–151 °C; IR (KBr) 3302, 3139, 3062, 3038, 2956, 2920, 2855, 1654, 1606, 1591, 1518, 1488, 1449, 1384, 1333, 1256, 1181, 1109, 1058, 745, 706, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (d, 2H, J=6.0 Hz), 7.30–7.40 (m, 6H), 7.46–7.50 (m, 3H), 8.01–8.05 (m, 2H), 8.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 159.5, 139.9, 137.0, 136.2, 130.0, 127.9, 127.7, 126.9, 126.5, 125.6, 42.1; MS (ESI) m/z 279.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{17}H_{14}N_2O_2+H]^+$ 279.1127, found 279.1128.

*4.2.2. N-Benzyl-2-(4-nitrophenyl)oxazole-4-carboxamide (**4b**).* Yellow solid; mp: 148–149 °C; IR (KBr) 3421, 3110, 3082, 2950, 1657, 1590, 1557, 1512, 1454, 1431, 1347, 1291, 1119, 1068, 862, 854, 749, 714, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (d, 2H, J=6.0 Hz), 7.32–7.39 (m, 6H), 8.20 (d, 2H, J=9.0 Hz), 8.34 (d, 2H, J=9.0 Hz), 8.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 159.3, 149.1, 142.2, 138.0, 137.8, 131.9, 128.8, 127.9, 127.7, 127.5, 124.2, 43.2; MS (ESI) m/z 324.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{17}H_{13}N_3O_4+H]^+$ 324.0984, found 324.0979.

*4.2.3. N-Benzyl-2-(4-fluorophenyl)oxazole-4-carboxamide (**4c**).* 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}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (d, 2H, J=6.0 Hz), 7.16 (t, 2H, J=8.7 Hz), 7.30–7.39 (m, 6H), 8.02 (t, 2H, J=8.7 Hz), 8.26 (s, 1H); ^{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.

*4.2.4. N-Benzyl-2-(4-chlorophenyl)oxazole-4-carboxamide (**4d**).* White solid; 135–137 °C; IR (KBr) 3332, 3109, 2938, 1655, 1606, 1596, 1518, 1483, 1456, 1406, 1385, 1256, 1175, 1108, 1093, 1057, 1013, 838, 734, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (d, 2H, J=6.0 Hz), 7.26–7.46 (m, 6H), 7.62 (d, 2H, J=6.4 Hz), 7.99 (d, 2H, J=6.4 Hz), 8.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 160.4, 141.1, 138.0, 137.4, 137.3, 129.2, 128.8, 127.9, 127.9, 127.6, 125.1, 43.1; MS (ESI) m/z 313.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{17}H_{13}ClN_2O_2+H]^+$ 313.0733, found 313.0738.

*4.2.5. N-Benzyl-2-(2-chlorophenyl)oxazole-4-carboxamide (**4e**).* White solid; mp: 79–80 °C; IR (KBr) 3335, 3139, 3068, 3032, 2926, 2855, 1650, 1594, 1516, 1454, 1436, 1384, 1335, 1237, 1103, 1045, 1025, 774, 733, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (q, 2H, J=6.0 Hz), 7.29–7.45 (m, 8H), 7.52 (dd, 1H, J=1.6 , 7.6 Hz), 7.95 (dd, 1H, J=1.6 , 7.6 Hz), 8.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 159.4, 141.3, 138.0, 137.1, 132.9, 131.7, 131.3, 131.1, 128.7, 127.9, 127.6, 126.9, 125.5, 43.1; MS (ESI) m/z 313.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_{17}H_{13}ClN_2O_2+H]^+$ 313.0737, found 313.0738.

*4.2.6. N-Benzyl-2-(4-bromophenyl)oxazole-4-carboxamide (**4f**).* White solid; mp: 133–134 °C; IR (KBr) 3329, 3038, 2936, 2861, 1656, 1595, 1519, 1494, 1480, 1401, 1328, 1277, 1256, 1173, 1107, 1070, 1010, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (d, 2H, J=6.0 Hz), 7.31–7.39 (m, 6H), 7.60 (d, 2H, J=8.6 Hz), 7.88 (d, 2H, J=8.6 Hz), 8.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 160.3, 141.1, 137.9, 137.4, 132.2, 128.8, 128.1, 127.9, 127.6, 125.7, 125.5, 43.1; MS (ESI) m/z 357.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_{17}H_{13}BrN_2O_2+H]^+$ 357.0233, found 357.0233.

*4.2.7. N-Benzyl-2-(4-trifluoromethylphenyl)oxazole-4-carboxamide (**4g**).* 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}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (d, 2H, J=6.0 Hz), 7.31–7.39 (m, 6H), 7.73 (d, 2H, J=8.4 Hz), 8.15 (d, 2H, J=8.4 Hz), 8.32 (s, 1H); ^{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.

*4.2.8. 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 2.41 (s, 3H), 4.65 (d, 2H, J=6.0 Hz), 7.28–7.39 (m, 8H), 7.91 (d, 2H, J=8.4 Hz), 8.24 (s, 1H); ^{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.

*4.2.9. N-Benzyl-2-(4-methoxyphenyl)oxazole-4-carboxamide (**4i**).* 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 3.86 (s, 3H), 4.64 (d, 2H, J=6.0 Hz), 6.96 (d, 2H, J=8.7 Hz), 7.27–7.38 (m, 6H), 7.95 (d, 2H, J=8.7 Hz), 8.21 (s, 1H); ^{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.

*4.2.10. N-Benzyl-2-(4-ethoxyphenyl)oxazole-4-carboxamide (**4j**).* White solid; mp: 125–126 °C; IR (KBr) 3305, 3092, 3032, 2973, 2938, 1651, 1611, 1595, 1517, 1499, 1475, 1445, 1392, 1330, 1254, 1167, 115, 1041, 842, 826 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (t, 3H, J=7.0 Hz), 4.09 (q, 2H, J=7.0 Hz), 4.65 (d, 2H, J=6.0 Hz), 6.95 (d, 2H, J=8.8 Hz), 7.29–7.38 (m, 6H), 7.94 (d, 2H, J=8.8 Hz), 8.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 161.3, 160.7, 140.3, 138.1, 137.0, 128.7, 128.3, 127.9, 127.5, 119.1, 114.8, 63.7, 43.1, 14.7; MS (ESI) m/z 323.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{19}H_{18}N_2O_3+H]^+$ 323.1386, found 323.1390.

*4.2.11. N-Butyl 2-phenyloxazole-4-carboxamide (**4k**).* White solid; mp: 111–112 °C; IR (KBr) 3315, 3125, 3097, 2956, 2929, 2859, 1655, 1593, 1560, 1522, 1449, 1384, 1304, 1287, 1258, 1104, 1058, 1023, 778, 705, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, 3H, J=7.2 Hz), 1.44 (h, 2H, J=7.2 Hz), 1.65 (p, 2H, J=7.4 Hz), 3.46 (q, 2H, J=6.8 Hz), 7.08 (s, 1H), 7.46–7.51 (m, 3H), 8.03–8.07 (m, 2H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 160.6, 140.6, 137.5, 131.0, 128.9, 126.7, 126.6, 38.8, 31.7, 20.1, 13.7; MS (ESI) m/z 245.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{14}H_{16}N_2O_2+H]^+$ 245.1284, found 245.1285.

*4.2.12. N-Butyl 2-(trifluoromethyl)phenyloxazole-4-carboxamide (**4l**).* White solid; mp: 150.5–151 °C; IR (KBr) 3315, 3133, 3097, 2967, 2935, 2879, 2867, 1654, 1622, 1592, 1522, 1415, 1321, 1255, 1165, 1135, 1073, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, J=7.2 Hz), 1.44 (h, 2H, J=7.2 Hz), 1.64 (p, 2H, J=6.8 Hz), 3.47 (q, 2H, J=6.6 Hz), 7.02 (s, 1H), 6.75 (d, 2H, J=8.4 Hz), 8.16 (d, 2H, J=8.4 Hz), 8.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 159.9, 141.3, 137.9, 132.8, 132.4, 129.8, 126.9, 125.9, 125.9, 125.9, 125.8, 125.5, 121.9, 38.8, 31.7, 20.1, 13.7; MS (ESI) m/z 313.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{15}H_{15}F_3N_2O_2+H]^+$ 313.1163, found 313.1158.

*4.2.13. N-Butyl 2-(4-methoxyphenyl)oxazole-4-carboxamide (**4m**).* White solid; mp: 111–111.5 °C; IR (KBr) 3323, 3139, 2957, 2924, 2861, 1650, 1616, 1593, 1523, 1501, 1422, 1384, 1305, 1251, 1185, 1170, 1030, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, 3H, J=6.9 Hz), 1.43 (h, 2H, J=6.9 Hz), 1.62 (p, 2H, J=7.2 Hz), 3.45 (q, 2H, J=6.7 Hz), 3.87 (s, 3H), 6.98 (d, 2H, J=9.0 Hz), 7.06 (s, 1H), 7.98 (d, 2H, J=9.0 Hz), 8.17 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 161.5, 160.7, 140.0, 137.3, 128.3, 119.4, 114.3, 55.4, 38.8, 31.7, 20.1, 13.7; MS (ESI) m/z 275.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{15}H_{18}N_2O_3+H]^+$ 275.1387, found 275.1390.

*4.2.14. 2,4-Diphenyloxazole (**4n**)*[13]. White solid; mp: 98–100 °C; IR (KBr) 2963, 1554, 1489, 1447, 1401, 1261, 1096, 1022, 942, 930, 802, 756, 718, 706, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (t, 1H, J=7.2 Hz), 7.42–7.50 (m, 5H), 7.85 (d, 2H, J=7.3 Hz), 7.98 (s, 1H), 8.15–8.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.4, 129.4, 127.9, 127.8, 127.1, 126.9, 125.5, 124.6; MS (ESI) m/z 222.1 $[M+H]^+$; HRMS (EI) calcd for $[C_{15}H_{11}NO]^+$ 221.0841, found 221.0853.

*4.2.15. Butyl 2-phenyloxazole-4-carboxylate (**6a**).* White solid; mp: 50.5–51 °C; IR (KBr) 2959, 2926, 2872, 2853, 1738, 1573, 1558, 1487, 1467, 1450, 1390, 1323, 1259, 1155, 1115, 764, 750, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, J=7.5 Hz), 1.46 (h, 2H, J=7.5 Hz), 1.77 (p, 2H, J=7.1 Hz), 4.71 (t, 2H, J=6.8 Hz), 7.47–7.50 (m, 3H), 8.10–8.14 (m, 2H), 8.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 161.4, 143.5, 134.7, 131.1, 128.8, 126.9, 126.5, 65.1, 30.7, 19.1, 13.7; MS (ESI) m/z 246.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{14}H_{18}NO_3+H]^+$ 246.1133, found 246.1125.

*4.2.16. Butyl 2-(4-nitrophenyl)oxazole-4-carboxylate (**6b**).* Yellow solid; mp: 91–92 °C; IR (KBr) 3133, 2957, 2934, 2867, 1723, 1611, 1566, 1531, 1345, 1293, 1250, 1162, 1113, 1057, 863, 856, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, 3H, J=7.4 Hz), 1.47 (h, 2H, J=7.4 Hz), 1.78 (p, 2H, J=7.4 Hz), 4.39 (t, 2H, J=7.4 Hz), 8.30 (d, 2H, J=8.9 Hz), 8.34 (s, 1H), 8.35 (d, 2H, J=8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 159.3, 148.2, 143.6, 134.4, 130.8, 126.7123.2, 64.4, 29.7, 18.1, 12.7; MS (ESI) m/z 291.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{14}H_{14}N_2O_5+H]^+$ 291.0980, found 291.0976.

*4.2.17. Butyl 2-(4-fluorophenyl)oxazole-4-carboxylate (**6c**).* White solid; mp: 55.5–56 °C; IR (KBr) 3153, 3086, 2963, 2934, 2875, 1728, 1611, 1501, 1475, 1415, 1400, 1321, 1287, 1247, 1226, 1159, 1119, 1055, 847, 824, 815 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, J=7.5 Hz), 1.46 (h, 2H, J=7.5 Hz), 1.77 (p, 2H, J=7.50 Hz), 4.37 (t, 2H, J=6.8 Hz), 7.17 (t, 2H, J=8.7 Hz), 8.12 (t, 2H, J=8.7 Hz), 8.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 161.8, 160.6, 160.3, 142.5, 133.7, 128.2, 128.0, 121.8, 121.8, 115.2, 114.9, 64.1, 29.7, 18.1, 12.7; MS (ESI) m/z 264.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{14}H_{14}FNO_3+H]^+$ 264.1031, found 264.1031.

*4.2.18. Butyl 2-(4-chlorophenyl)oxazole-4-carboxylate (**6d**).* White solid; mp: 82–83 °C; IR (KBr) 3138, 3097, 2963, 2920, 2897, 2867, 1724, 1608, 1486, 1474, 1404, 1317, 1248, 1162, 1109, 1093, 1013, 835, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, J=7.5 Hz), 1.44 (h, 2H, J=7.5 Hz), 1.76 (p, 2H, J=7.2 Hz), 4.37 (t, 2H, J=6.7 Hz), 7.46 (d, 2H, J=8.7 Hz), 8.06 (d, 2H, J=8.7 Hz), 8.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 161.2, 143.6, 137.4, 134.8, 129.2, 128.1, 125.0, 65.1, 30.7, 19.1, 13.7; MS (ESI) m/z 280.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{14}H_{14}ClNO_3+H]^+$ 280.0734, found 280.0735.

*4.2.19. Butyl 2-(4-bromophenyl)oxazole-4-carboxylate (**6e**).* White solid; mp: 95–95.5 °C; IR (KBr) 3134, 3086, 2961, 2926, 2867, 1720, 1606, 1482, 1401, 1384, 1340, 1317, 1249, 1158, 1107, 1071, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, J=7.5 Hz), 1.46 (h, 2H, J=7.5 Hz), 1.76 (p, 2H, J=7.2 Hz), 4.37 (t, 2H, J=6.9 Hz), 7.62 (d, 2H, J=8.4 Hz), 7.99 (d, 2H, J=8.4 Hz), 8.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 161.2, 143.7, 134.8, 132.1, 128.3, 125.8, 125.4, 65.2, 30.7, 19.1, 13.7; MS (ESI) m/z 324.0 $[M+H]^+$; HRMS (ESI) calcd for $[C_{14}H_{14}BrNO_3+H]^+$ 324.0232, found 324.0232.

*4.2.20. Butyl 2-(4-trifluoromethylphenyl)oxazole-4-carboxylate (**6f**).* White solid; mp: 65–66 °C; IR (KBr) 3140, 2963, 2935, 2867, 1730, 1567, 1467, 1414, 1324, 1247, 1166, 1134, 1109, 1071, 858, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, J=7.5 Hz), 1.48 (h, 2H, J=7.5 Hz), 1.77 (p, 2H, J=6.9 Hz), 4.39 (t, 2H, J=6.8 Hz), 7.74 (d, 2H, J=8.4 Hz), 8.25 (d, 2H, J=8.4 Hz), 8.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 143.1, 134.1, 129.9, 128.6, 127.8, 126.2, 125.0, 124.9, 124.9, 124.5, 120.9, 64.3, 29.7, 18.1, 12.7; MS (ESI) m/z 314.1 $[M+H]^+$; HRMS (EI) calcd for $[C_{15}H_{14}F_3NO_3]^+$ 313.0926, found 313.0924.

*4.2.21. Butyl 2-p-tolyloxazole-4-carboxylate (**6g**).* White solid; mp: 61–62 °C; IR (KBr) 3127, 3080, 2962, 2932, 2873, 1724, 1608, 1561,

1502, 1473, 1321, 1260, 1167, 1105, 1018, 823, 804 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, J=7.5 Hz), 1.46 (h, 2H, J=7.5 Hz), 1.77 (p, 2H, J=7.2 Hz), 2.41 (s, 3H), 4.24 (t, 2H, J=6.8 Hz), 7.28 (d, 2H, J=8.1 Hz), 8.01 (d, 2H, J=8.1 Hz), 8.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 161.5, 143.3, 141.5, 134.5, 129.5, 126.8, 123.8, 65.0, 30.7, 21.5, 19.1, 13.7; MS (ESI) m/z 260.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{15}H_{17}NO_3+H]^+$ 260.1282, found 260.1281.

*4.2.22. Butyl 2-(4-methoxyphenyl)oxazole-4-carboxylate (**6h**).* White solid; mp: 57–58 °C; IR (KBr) 3138, 2963, 2861, 1726, 1614, 1585, 1501, 1399, 1384, 1256, 1176, 1153, 1025, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, 3H, J=7.5 Hz), 1.46 (h, 2H, J=7.5 Hz), 1.77 (p, 2H, J=7.1 Hz), 3.87 (s, 3H), 4.36 (t, 2H, J=6.7 Hz), 6.98 (d, 2H, J=6.9 Hz), 8.06 (d, 2H, J=6.9 Hz), 8.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 160.9, 160.5, 142.1, 133.5, 127.6, 118.2, 113.2, 64.0, 54.4, 29.7, 18.1, 12.7; MS (ESI) m/z 276.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{15}H_{17}NO_4+H]^+$ 276.1229, found 276.1230.

*4.2.23. Butyl 2-(4-ethoxyphenyl)oxazole-4-carboxylate (**6i**).* White solid; mp: 60–61 °C; IR (KBr) 3168, 3133, 2963, 2935, 2873, 1743, 1649, 1608, 1576, 1502, 1476, 1395, 1321, 1312, 1260, 1175, 1114, 1042, 844, 804 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, 3H, J=7.5 Hz), 1.41–1.58 (m, 5H), 1.76 (p, 2H, J=7.1 Hz), 4.09 (q, 2H, J=9.5 Hz), 4.36 (t, 2H, J=7.5 Hz), 6.95 (d, 2H, J=8.8 Hz), 8.03 (d, 2H, J=8.8 Hz), 8.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 161.5, 161.3, 143.0, 134.5, 128.6, 119.0, 114.7, 65.0, 63.6, 30.7, 19.1, 14.7, 13.7; MS (ESI) m/z 290.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{16}H_{19}NO_4+H]^+$ 290.1383, found 290.1387.

*4.2.24. Methyl 2-phenyloxazole-4-carboxylate (**6j**).* 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 3.96 (s, 3H), 7.46–7.50 (m, 2H), 8.10–8.14 (m, 3H), 8.30 (s, 1H); ^{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.

*4.2.25. Methyl 2-(4-(trifluoromethyl)phenyl)oxazole-4-carboxylate (**6k**).* 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 3.98 (s, 3H), 7.75 (d, 2H, J=8.4 Hz), 8.24 (d, 2H, J=8.4 Hz), 8.34 (s, 1H); ^{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.

*4.2.26. Methyl 2-(4-methoxyphenyl)oxazole-4-carboxylate (**6l**).* 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 3.87 (s, 3H), 3.95 (s, 3H), 6.98 (d, 2H, J=7.2 Hz), 8.05 (d, 2H, J=7.2 Hz), 8.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 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.

*4.2.27. Methyl 2,5-diphenyloxazole-4-carboxylate (**9**).* White solid; mp: 73–75 °C; IR (KBr) 3068, 2944, 2932, 2855, 1720, 1711, 1564, 1491, 1447, 1358, 1227, 1217, 1099, 775, 767, 708, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.49–7.55 (m, 6H), 8.13–8.18 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 159.8, 155.3, 131.1, 130.8, 130.4, 128.8, 128.5, 128.0, 127.0, 126.9, 126.4, 52.3; MS (ESI) m/z 280.1 $[M+H]^+$; HRMS (ESI) calcd for $[C_{17}H_{13}NO_3+H]^+$ 280.0965, found 280.0968.

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Supplementary data

Supplementary data related to this article can be found online, at doi:10.1016/j.tet.2011.01.050.

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