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Highly efficient oxidation of 2-imidazoline-5-carboxylic derivatives to imidazole-5-carboxylic derivatives by dioxygen

Yue Huang, Xiaodong Zu, Fan Wu, Jinyi Xu, Xiaoming Wu, Hequan Yao *

State key Laboratory of Natural Medicines and department of Medicinal Chemistry, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, PR China

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ABSTRACT

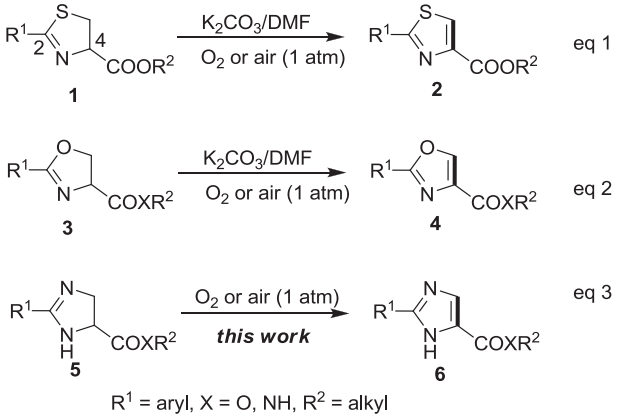
A highly efficient and environmental-benign oxidation by dioxygen (or air) as the sole oxidant was first applied for the conversion of 2-imidazoline-5-carboxylic derivatives to imidazole-5-carboxylic derivatives in very good and excellent yields. The substituent effect on 2-imidazoline ring was investigated. This protocol was also suitable for the synthesis of 2-imidazoles in relatively large scale.

1. Introduction

Nitrogen-containing heterocyclic compounds, such as thiazoles, oxazoles, and imidazoles are important motifs of pharmaceuticals and functional materials, which attracted much attention of synthetic community.[1,2] Typically, thiazoles, oxazoles, and imidazoles with carboxylic functional groups at 4 or 5-position are often found in a number of naturally occurring products and synthetic molecules with interesting biological activities, such as antiviral, antifungal, antibacterial, antihypertensive, anti-inflammatory, and anti-tumor activities.[2–4]

In the past decades, many approaches have been developed for the synthesis of azoles including imidazoles. Among these, oxidative dehydrogenation of imidazolines to imidazoles was one of the most general and reliable methods for the preparation of imidazoles. Up to date, various reaction systems, such as DBU/$CBrCl_3$,[5] Zn–Al_2O_3,[6] Ni,[7] Se,[8] Pd/C,[9] MnO_2,[10] $BaMnO_4$,[11] DMSO/$(COCl)_2$,[12] $KMnO_4/Al_2O_3$,[13] *o*-iodoxybenzoic acid (IBX),[14] (diacetoxiodo)benzene (DIB)/K_2CO_3,[15] $NaIO_4$–Mn(salophen)Cl,[16] and $KMnO_4/SiO_2$[17] are proved to be very useful for the oxidative dehydrogenation of imidazolines. However, all above systems have at least one or more drawbacks, such as low yields of products, excess amount of reagents, expensive reagents or catalysts, and hazardous reaction conditions. Also, the drawbacks of some reagents, which are toxic or difficult to dispose somewhat limit their further application to the synthesis of the desired products. For an economical and environmental viewpoint, a clean, and efficient oxidation process is thus extremely valuable and will be more applicable to industrial application.

In 2011, Wang and Blechert disclosed one example on the photocatalyzed oxidation of 2-imidazoline using carbon nitride and dioxygen (0.5 MPa).[18] Recently, we have demonstrated more simple method for the oxidation of 2-thiazolines and 2-oxazolines using dioxygen as a sole oxidant (Scheme 1, Eq. 1 and Eq. 2).[19] In this paper, we wish to extend our environmental-benign system to the oxidation of 2-imidazoline-5-carboxylic derivatives.[20] (Eq. 3).



Scheme 1. Oxidation of 2-azolines to azoles with dioxygen.

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

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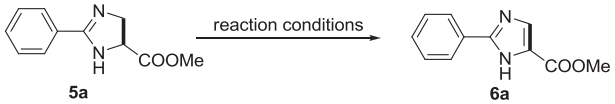
2. Results and discussion

We chose **5a** as a substrate bearing 5-carboxylate group under the conditions we previous used for the oxidation of 2-thio(oxa) zoline-carboxylates, in which potassium carbonate (3 equiv) was used as a base, anhydrous DMF was used as a solvent and dioxygen or air was used as a sole oxidant. As shown in Table 1, high yields of the desired product **6a** could be achieved under either air or O_2 atmosphere (entries 1–4). Remarkably shorter reaction time was needed for molecular oxygen or air to fully oxidize **5a** at 100 °C than at 80 °C. We also demonstrated the reaction was less effective in other solvents (entries 5–10). Although we reported that the oxidation for 2-azoline-4-carboxylates was stepwise based on the isolated intermediates,[19a] we were not able to observe any intermediate in this case, even at lower temperature or in shorter reaction time. This may be explained that the intermediate is not stable enough to be seen or isolated under the oxidation condition.

With these encouraging results, we evaluated the substrate scope. As shown in Table 2, various 2-imidazoline-5-carboxylates[20] with aryl groups could be converted to the corresponding products and all reactions could complete in less than 10 h using molecular oxygen as an oxidant (entries 1–12, condition A). Good to excellent yields of the corresponding products were achieved for all substrates bearing electron-deficient or halo-substituted aryl groups (entries 3–6), while moderate yields for the ones bearing electron-rich aryl groups (entries 7–9). An exception was that **6b** bearing 4-nitrophenyl substituent at 2-position was obtained in relatively low yield after flash column chromatography. Although the reaction of **5b** was clean, the poor solubility of **6b** in various organic solvents, such as EtOAc, CH_2Cl_2, Et_2O, and $CHCl_3$, might cause incomplete extraction from the reaction mixture and incomplete elution from the column, leading to the relatively low isolated yield of **6b**. No obvious hydrolysis of the ester groups was observed in all cases. The good yields could also maintain for the substrates with slightly bulky esters (entries 10–12). When the reactions were conducted with air, the corresponding products were also obtained in good yields, albeit longer reaction time was required (entries 1–12, condition B). These results in Table 2 indicated that electron-deficient aryl group on 2-imidazoline ring could facilitate this oxidation process, which is consistent with our previous results.[19a,19b]

Next, we examined the oxidation of the substrates bearing carboxamide group at 5-position. We first tried to conduct the reaction with pure dioxygen as an oxidant (entries 1–4, Table 3). Very interestingly, the reactions did not proceed as well as we expected. The substrate **7a** was not fully consumed even after prolonged reaction time (36 h). Considering that the carboxamide group is stable under basic condition, we then tried strong base, such as NaOH to promote this reaction. To our delight, the yield of **8a** could rise to 97% and the reaction time could be dramatically reduced to 1 h and when NaOH was used as a base (entries 5, Table 3). It seems that 3 equiv of NaOH were required to maintain the high yield based on the results that **7a** could not completely converted to the desired product when 1 or 2 equiv of NaOH were employed (entries 6 and 7). The reactions also proceeded smoothly to afforded **8a** in

Table 1
The screening of reaction conditions of oxidation of imidazoline-5-carboxylate[a,b]

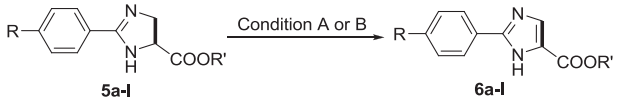


5a 6a

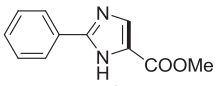
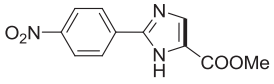
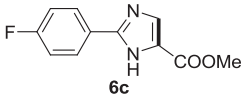
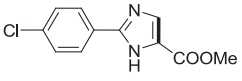
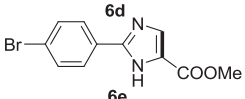
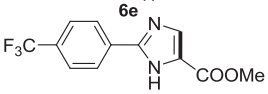
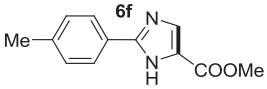
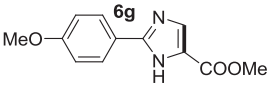
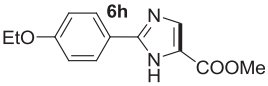
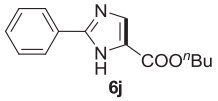
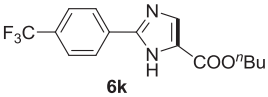
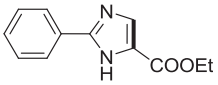
Entry	Conditions	Temp (°C)	Time (h)	Yield[c] (%)
1	DMF, K_2CO_3, O_2	80	10	91
2	DMF, K_2CO_3, air	80	16	91
3	DMF, K_2CO_3, O_2	100	2.5	93
4	DMF, K_2CO_3, air	100	5	89
5	DME, K_2CO_3, O_2	Reflux	24	26
6	DME, K_2CO_3, air	Reflux	24	24
7	DCM, K_2CO_3, O_2	Reflux	24	Trace
8	DCM, K_2CO_3, air	Reflux	24	Trace
9	CH_3CN, K_2CO_3, O_2	Reflux	24	21
10	CH_3CN, K_2CO_3, air	Reflux	24	20

[a] Reactions were performed on a 0.5 mmol scale (102 mg) with inorganic bases (3 equiv) and molecular sieves (4 Å, ca. 200 wt %, 204 mg).
[b] The reaction was performed with O_2 (balloon) or open to air.
[c] Isolated yields.

Table 2
Oxidation of 2-imidazoline-5-carboxylates to imidazole-5-carboxylates[a,b]

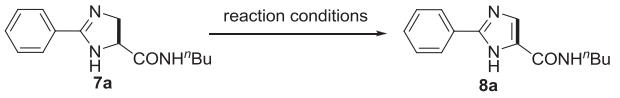


5a-l 6a-l

Entry	Product	Condition[b]	Time (h)	Yield[c] (%)
1	 6a	A	2.5	93
		B	10	89
2	 6b	A	10	67
		B	13	61
3	 6c	A	5	84
		B	11	87
4	 6d	A	5	94
		B	8	91
5	 6e	A	6	95
		B	8	93
6	 6f	A	2.5	93
		B	5	91
7	 6g	A	4	92
		B	11	87
8	 6h	A	7	73
		B	21	73
9	 6i	A	9	73
		B	27	74
10	 6j	A	4	92
		B	8	94
11	 6k	A	2	90
		B	2.5	94
12	 6l	A	4	92
		B	10	90

[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 %) at 100 °C.
[b] Condition A: the reaction was performed with O_2 (balloon). Condition B: the reaction was open to air.
[c] Isolated yields.

Table 3
The screening of reaction conditions of oxidation of imidazoline-5-carboxylamide[a,b]



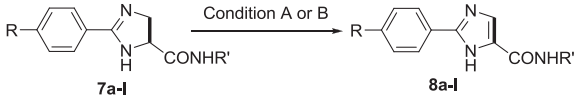
Entry	Conditions	Temp (°C)	Time (h)	Yield[c] (%)
1	K_2CO_3 (3 equiv), O_2	80	36	23
2	K_2CO_3 (3 equiv), O_2	100	36	27
3	K_2CO_3 (3 equiv), O_2	120	36	40
4[d]	K_2CO_3 (3 equiv), O_2	120	36	35
5	NaOH (3 equiv), O_2	120	1	97
6	NaOH (2 equiv), O_2	120	24	80
7	NaOH (1 equiv), O_2	120	24	62
8	NaOH (3 equiv), O_2	100	1	93
9	NaOH (3 equiv), O_2	80	1	95
10	NaOH (3 equiv), O_2	60	1	97
11	NaOH (3 equiv), air	60	1	95

[a] Reactions were performed on a 0.5 mmol scale (123 mg) with inorganic bases (3 equiv).
[b] The reaction was performed with O_2 (balloon) or open to air.
[c] Isolated yields.
[d] Molecular sieves (4 Å, ca. 200 wt %, 246 mg) was added.

excellent yields with either O_2 or air in the presence of 3 equiv of NaOH at lower temperatures (entries 8–11).

With the optimized conditions in hand, the oxidation of various 2-imidazoline-5-carboxamides to imidazole-5-carboxamides was then examined as shown in Table 4. All substrates (**7a**–**l**) bearing electron-deficient or electron-rich aryl groups at 2-position could be converted to the corresponding products (**8a**–**l**) in nearly quantitative yields under the optimized conditions (entries 1–12). The reactions were quite efficient as all substrates could be fully consumed in less than 2 h. The substituent on carboxamide group did not much affect this conversion. Very gratifyingly, no obvious difference was observed when air was used as an oxidant.

Table 4
Oxidation of 2-imidazoline-5-carboxylamides to imidazole-5-carboxylamides by dioxygen[a,b]



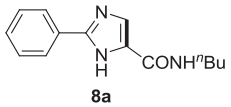
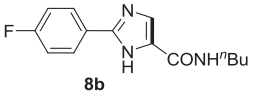
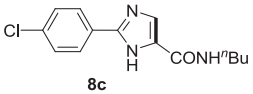
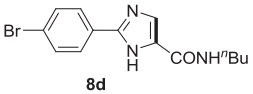
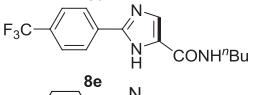
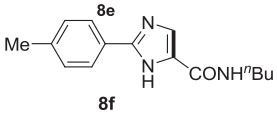
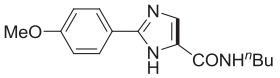
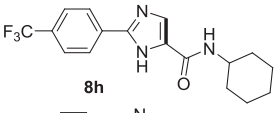
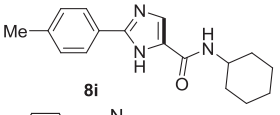
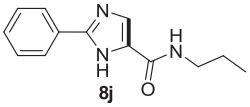
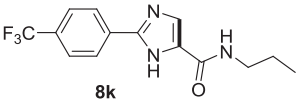
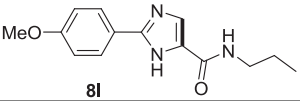
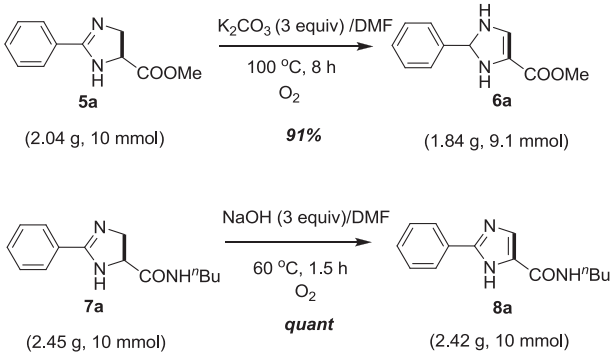
Entry	Product	Condition[b]	Time (h)	Yield[c] (%)
1	 **8a**	A	1	97
		B	1	95
2	 **8b**	A	1	93
		B	1	92
3	 **8c**	A	1	92
		B	1	91
4	 **8d**	A	2	93
		B	2	93
5	 **8e**	A	1	95
		B	1	92
6	 **8f**	A	1	95
		B	1	92

Table 4 (*continued*)

Entry	Product	Condition[b]	Time (h)	Yield[c] (%)
7	 **8g**	A	2	91
		B	2	96
8	 **8h**	A	1	94
		B	1.5	94
9	 **8i**	A	1	93
		B	1	91
10	 **8j**	A	1	92
		B	1	90
11	 **8k**	A	1	94
		B	1	94
12	 **8l**	A	1	92
		B	1	90

[a] Reactions were performed in DMF on a 0.5 mmol scale with NaOH (3 equiv) at 60 °C.
[b] The reaction was performed with O_2 (balloon) or open to air.
[c] Isolated yields.

Finally, we set this protocol to the oxidation of 2-imidazole-5-caboxylic derivatives in relatively large scale under the optimized conditions. Indeed, treatment of 10 mmol of **5a** under O_2/K_2CO_3/DMF condition at 100 °C for 8 h smoothly provided the corresponding product **6a** in 91% isolated yield. Similarly, treatment of 10 mmol of **7a** under O_2/NaOH/DMF condition at 60 °C for only 1.5 h afforded **8a** in almost quantitative isolated yield. These results clearly indicate that our protocol is suitable for the synthesis of imidazole-5-carboxylic derivatives in large scale (Scheme 2).



Scheme 2. The scalable oxidation of 2-imidazolines to 2-imidazoles by dioxygen.

3. Conclusions

We have first developed an efficient oxidation of 2-imidazoline-5-carboxylic derivatives to imidazole-5-carboxylic derivatives by dioxygen (1 atm) in very good to excellent yields. This process is mild, environmental-benign and could provide a practical method for the preparation of imidazole-containing molecules or natural products. Moreover, our protocol could be applied to the synthesis

of imidazole-5-carboxylic derivatives in large scale, which must be quite attractive to pharmaceutical industry. Further investigations of this methodology for other heterocycles are now underway and will be reported in due course.

4. Experimental

4.1. General experimental

NMR spectra were recorded on a BRUKER-ACF-300 spectrometer 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) or DMSO-d_6 (δ=39.51) was used as internal standard and spectra were obtained with complete proton decoupling. HRMS data were obtained on an Agilent 1100-LC-MSD-Trap/SL spectrometer using ESI ionization. Mp data were measured with a MEL-TEMP II micro melting point apparatus. IR spectra were recorded on a BRUKER FT-IR TENSOR27 spectrometer (KBr).

4.2. General procedure for the oxidation of 2-imidazoline-5-carboxylates

To a solution of 2-imidazoline-5-carboxylate (0.5 mmol, 1 equiv) in anhydrous DMF (5 mL) were added K_2CO_3 (207 mg, 1.5 mmol, 3 equiv) and molecular sieves (4 Å, 200 wt %). The reaction mixture was stirred with an O_2 balloon or open to air at 100 °C for 2.5–27 h. The resulting solution was diluted with ethyl acetate and 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 imidazole-5-carboxylate as a solid.

*4.2.1. Methyl 2-phenylimidazole-5-carboxylate (**6a**).* White solid; mp 212–214 °C; IR (KBr) 3442, 3079, 2944, 1728, 1655, 1561, 1457, 1435, 1384, 1284, 1127, 770, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 3.91 (s, 3H), 7.41–7.42 (m, 3H), 7.81 (s, 1H), 7.90–7.93 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.0, 147.8, 130.3, 129.4, 129.2, 126.0, 125.3, 125.3, 51.5; HRMS (ESI) calcd for $[C_{11}H_{11}N_2O_2+H]^+$ 203.0815, found 203.0821.

*4.2.2. Methyl 2-(4-nitrophenyl)imidazole-5-carboxylate (**6b**).* Yellow solid; mp 286–288 °C; IR (KBr) 3446, 3021, 2937, 1605, 1550, 1485, 1341, 1201, 1121, 1084, 855, 777 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 8.27–8.37 (m, 5H), 13.61 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.6, 147.6, 145.8, 136.0, 129.4, 126.8, 124.6, 51.7; HRMS (ESI) calcd for $[C_{11}H_{10}N_3O_4+H]^+$ 248.0666, found 248.0673.

*4.2.3. Methyl 2-(4-fluorophenyl)imidazole-5-carboxylate (**6c**).* White solid; mp 205–208 °C; IR (KBr) 3446, 3168, 2937, 1697, 1516, 1436, 1341, 1201, 1121, 1084, 855, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.14 (t, J=7.7 Hz, 2H), 7.79 (s, 1H), 7.90 (t, J=7.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.5, 163.3, 161.3, 146.5, 136.4, 133.2, 128.9, 128.1, 128.0, 126.9, 125.5, 116.4, 116.1, 51.4; HRMS (ESI) calcd for $[C_{11}H_{10}FN_2O_2+H]^+$ 221.0721, found 221.0727.

*4.2.4. Methyl 2-(4-chlorophenyl)imidazole-5-carboxylate (**6d**).* White solid; mp 210–212 °C; IR (KBr) 3347, 3068, 2958, 1710, 1483, 1367, 1266, 1157, 1091, 842, 804 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.42 (d, J=8.5 Hz, 2H), 7.81 (s, 1H), 7.90 (d, J=8.5 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.0, 146.5, 134.1, 129.3, 129.1, 128.7, 127.7, 125.9, 51.5; HRMS (ESI) calcd for $[C_{11}H_9ClN_2O_2+H]^+$ 237.0425, found 237.0431.

*4.2.5. Methyl 2-(4-bromophenyl)imidazole-5-carboxylate (**6e**).* White solid; mp 238–240 °C; IR (KBr) 3469, 3167, 2954, 1717, 1598, 1479, 1336, 1196, 1115, 1067, 840, 804 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.57 (d, J=7.9 Hz, 2H), 7.81 (s, 1H), 7.82 (d, J=7.9 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.2, 146.3, 136.1, 132.3, 129.4, 127.8, 125.7, 122.7, 51.5; HRMS (ESI) calcd for $[C_{11}H_9BrN_2O_2+H]^+$ 280.9920, found 280.9924.

*4.2.6. Methyl 2-(4-trifluoromethylphenyl)imidazole-5-carboxylate (**6f**).* White solid; mp 230–232 °C; IR (KBr) 3375, 3107, 2943, 1686, 1556, 1498, 1429, 1207, 1160, 1065, 849, 808 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 7.86 (d, J=7.1 Hz, 2H), 8.07 (s, 1H), 8.22 (d, J=7.1 Hz, 2H), 13.45 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.1, 163.2, 145.9, 133.9, 130.0, 129.5, 129.1, 128.8, 126.3, 125.6, 122.8, 51.6; HRMS (ESI) calcd for $[C_{12}H_{10}F_3N_2O_2+H]^+$ 271.0689, found 271.0696.

*4.2.7. Methyl 2-(4-tolylphenyl)imidazole-5-carboxylate (**6g**).* White solid; mp 212–214 °C; IR (KBr) 3232, 3025, 2946, 1721, 1693, 1499, 1345, 1278, 1164, 1012, 829 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.90 (s, 3H), 7.21 (d, J=8.1 Hz, 2H), 7.79 (s, 1H), 7.80 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.5, 147.5, 138.9, 133.1, 129.8, 127.6, 125.8, 125.1, 51.4, 21.3; HRMS (ESI) calcd for $[C_{12}H_{13}N_2O_2+H]^+$ 217.0972, found 217.0972.

*4.2.8. Methyl 2-(4-methoxyphenyl)imidazole-5-carboxylate (**6h**).* White solid; mp 213–215 °C; IR (KBr) 3464, 3018, 2986, 1718, 1615, 1501, 1435, 1345, 1295, 1196, 843, 795 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.89 (s, 3H), 6.91 (d, J=8.7 Hz, 2H), 7.83 (s, 1H), 7.85(d, J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.4, 129.8, 127.5, 125.0, 123.0, 114.6, 114.0, 113.8, 55.7, 51.4; HRMS (ESI) calcd for $[C_{12}H_{13}N_2O_3+H]^+$ 233.0921, found 233.0925.

*4.2.9. Methyl 2-(4-ethoxyphenyl)imiazole-5-carboxylate (**6i**).* White solid; mp 272–274 °C; IR (KBr) 3449, 3086, 2927, 1722, 1616, 1501, 1481, 1385, 1282, 1198, 1042, 846 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, J=7.0 Hz, 3H), 3.91 (s, 1H), 4.07 (q, J=7.0 Hz, 2H), 6.94 (d, J=8.6 Hz, 2H), 7.77(s, 1H), 7.86 (d, J=8.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.6, 147.4, 136.5, 132.9, 127.3, 124.9, 122.8, 115.1, 63.6, 51.4, 15.0; HRMS (ESI) calcd for $[C_{13}H_{15}N_2O_3+H]^+$ 247.1077, found 247.1085.

*4.2.10. n-Butyl 2-phenylimidazole-5-carboxylate (**6j**).* White solid; mp 123–124 °C; IR (KBr) 3448, 3137, 2959, 1714, 1638, 1529, 1489, 1384, 1181, 716, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J=7.0 Hz, 3H), 1.36–1.49 (m, 2H), 1.66–1.76 (m, 2H), 4.31 (q, J=6.5 Hz, 2H), 7.37–7.38 (m, 3H), 7.81 (s, 1H), 7.92–7.93 (m, 2H), 10.32 (br, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.5, 146.8, 133.0, 129.8, 128.8, 126.1, 125.3, 124.8, 63.1, 30.4, 18.7, 13.6; HRMS (ESI) calcd for $[C_{14}H_{17}N_2O_2+H]^+$ 245.1285, found 245.1296.

*4.2.11. n-Butyl 2-(4-trifluoromethylphenyl)imidazole-5-carboxylate (**6k**).* White solid; mp 216–218 °C; IR (KBr) 3447, 3024, 2941, 1722, 1622, 1501, 1438, 1283, 1169, 1095, 852, 836 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.89–0.97 (m, 3H), 1.37–1.48 (m, 2H), 1.65–1.73 (m, 2H), 4.23–4.24 (m, 2H), 7.85 (d, J=8.0 Hz, 2H), 8.05 (s, 1H), 8.21 (d, J=8.0 Hz, 2H), 13.42 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.8, 145.9, 133.9, 130.0, 129.6, 129.1, 126.4, 126.2, 126.1, 122.8, 63.8, 30.9, 19.1, 13.9; HRMS (ESI) calcd for $[C_{15}H_{16}F_3N_2O_2+H]^+$ 313,1158, found 313.1175.

*4.2.12. Ethyl 2-phenylimidazole-5-carboxylate (**6l**).* White solid; mp 111–112 °C; IR (KBr) 3463, 3144, 2995, 1715, 1638, 1571, 1488, 1369,

1285, 1185, 716, 697 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.49 (t, J=6.7 Hz, 3H), 4.27 (q, J=6.7 Hz, 2H), 7.40–7.51 (m, 3H), 7.97–7.98 (m, 2H), 8.12 (s, 1H), 13.13 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.9, 147.3, 133.6, 130.3, 129.4, 129.2, 125.9, 125.3, 60.0, 14.8; HRMS (ESI) calcd for $[C_{12}H_{13}N_2O_2+H]^+$ 217.0972, found 217.0982.

4.3. Typical procedure for the oxidation of 2-imidazoline-5-carboxamides

To a solution of 2-imidazoline-5-carboxamide (0.5 mmol, 1 equiv) in anhydrous DMF (5 mL) was added NaOH (60 mg, 1.5 mmol, 3 equiv). The reaction mixture was stirred with an O_2 balloon or open to air at 60 °C for 1–2 h. The resulting solution was diluted with dichloromethane, 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 imidazole-5- carboxamide as a solid.

*4.3.1. N-n-Butyl-2-phenylimidazole-5-carboxamide (**8a**).* White solid; mp 220–222 °C; IR (KBr) 3341, 3059, 2958, 1629, 1554, 1457, 1400, 1349, 1287, 1143, 779, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J=7.3 Hz, 3H), 1.37–1.50 (m, 2H), 1.58–1.69 (m, 2H), 3.50 (q, J=6.8 Hz, 2H), 7.35–7.49 (m, 3H), 7.51 (s, 1H), 7.65 (s, 1H), 8.08 (d, J=7.0 Hz, 2H), 12.67 (br, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.5, 146.0, 137.8, 130.5, 129.2, 129.1, 125.8, 120.6, 38.4, 32.1, 20.1, 14.2; HRMS (ESI) calcd for $[C_{14}H_{18}N_3O+H]^+$ 244.1444, found 244.1458.

*4.3.2. N-n-Butyl-2-(4-fluorophenyl)imidazole-5-carboxamide (**8b**).* White solid; mp 170–173 °C; IR (KBr) 3412, 3181, 2961, 1639, 1579, 1494, 1373, 1226, 1162, 842, 814 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J=7.3 Hz, 3H), 1.38–1.51 (m, 2H), 1.59–1.70 (m, 2H), 3.50 (q, J=6.8 Hz, 2H), 7.13 (t, J=8.6 Hz, 2H), 7.46 (s, 1H), 7.63 (s, 1H), 8.08 (t, J=8.6 Hz, 2H), 12.48 (br, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.4, 162.4, 161.1, 145.2, 137.7, 128.0, 127.9, 127.2, 120.7, 116.3, 116.0, 38.3, 32.1, 20.1, 14.1; HRMS (ESI) calcd for $[C_{14}H_{17}FN_3O+H]^+$ 262.1350, found 262.1362.

*4.3.3. N-n-Butyl-2-(4-chlorophenyl)imidazole-5-carboxamide (**8c**).* White solid; mp 174–175 °C; IR (KBr): 3396, 3137, 2959, 1642, 1582, 1484, 1383, 1286, 1131, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J=7.3 Hz, 3H), 1.38–1.51 (m, 2H), 1.60–1.70 (m, 2H), 3.50 (q, J=6.7 Hz, 2H), 7.42 (d, J=8.5 Hz, 2H), 7.48 (s, 1H), 7.62 (s, 1H), 8.04 (d, J=8.5 Hz, 2H), 12.67 (br, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.4, 144.9, 137.9, 133.7, 129.4, 129.3, 127.4, 121.0, 38.3, 32.1, 20.1, 14.2; HRMS (ESI) calcd for $[C_{14}H_{17}ClN_3O+H]^+$ 278.1055, found 278.1067.

*4.3.4. N-n-Butyl-2-(4-bromophenyl)imidazole-5-carboxamide (**8d**).* White solid; mp 173–174 °C; IR (KBr) 3375, 3132, 2957, 1646, 1579, 1509, 1480, 1384, 1287, 1200, 1131, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J=7.3 Hz, 3H), 1.36–1.44 (m, 2H), 1.54–1.62 (m, 2H), 3.44 (q, J=6.7 Hz, 2H), 7.10 (s, 1H), 7.44 (d, J=8.4 Hz, 2H), 7.61 (d, J=8.4 Hz, 2H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.4, 145.0, 137.9, 132.2, 129.7, 127.7, 122.3, 121.0, 38.3, 32.1, 20.1, 14.2; HRMS (ESI) calcd for $[C_{14}H_{17Br}N_3O+H]^+$ 322.0550, found 322.0561.

*4.3.5. N-n-Butyl-2-(4-trifluoromethylphenyl)imidazole-5-carbo-xamide (**8e**).* White solid; mp 193–194 °C; IR (KBr) 3404, 3137, 2962, 1632, 1581, 1522, 1438, 1325, 1219, 1140, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J=7.3 Hz, 3H), 1.38–1.52 (m, 2H), 1.61–1.72 (m, 2H), 3.53 (q, J=6.7 Hz, 2H), 7.54 (s, 1H), 7.67 (s, 1H), 7.70 (d, J=8.3 Hz, 2H), 8.26 (d, J=8.3 Hz, 2H), 13.15 (br, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3, 144.4, 138.3, 134.2, 129.6, 129.2, 128.8, 126.2, 122.8, 121.5, 38.4, 32.0, 20.1, 14.1; HRMS (ESI) calcd for $[C_{15}H_{17}FN_3O+H]^+$ 312.1318, found 312.1331.

*4.3.6. N-n-Butyl-2-(4-methylphenyl)imidazole-5-carboxamide (**8f**).* White solid; mp 198–202 °C; IR (KBr) 3342, 3139, 2953, 1630, 1557, 1462, 1383, 1296, 1148, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J=7.3 Hz, 3H), 1.25–1.50 (m, 2H), 1.58–1.69 (m, 2H), 2.39 (s, 3H), 3.49 (q, J=6.7 Hz, 2H), 7.25 (d, J=8.2 Hz, 2H), 7.50 (s, 1H), 7.62 (s, 1H), 7.92 (d, J=8.2 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.0, 145.9, 138.1, 137.0, 129.2, 127.3, 125.2, 120.0, 37.9, 31.6, 20.8, 19.6, 13.6; HRMS (ESI) calcd for $[C_{15}H_{20}N_3O+H]^+$ 258.1601, found 258.1613.

*4.3.7. N-n-Butyl-2-(4-methoxyphenyl)imidazole-5-carbox-amide (**8g**).* White solid; mp 182–183 °C; IR (KBr) 3475, 3118, 2965, 1632, 1570, 1552, 1473, 1299, 1207, 1182, 834, 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J=7.3 Hz, 3H), 1.40–1.48 (m, 2H), 1.53–1.62 (m, 2H), 3.44 (q, J=6.7 Hz, 2H), 3.87 (s, 3H), 6.97 (d, J=8.8 Hz, 2H), 7.15 (s, 1H), 7.52 (d, J=8.8 Hz, 2H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.6, 160.1, 146.2, 137.4, 127.3, 123.3, 120.2, 114.6, 55.6, 38.4, 32.1, 20.1, 14.1; HRMS (ESI) calcd for $[C_{15}H_{20}N_3O_2+H]^+$ 274.1550, found 274.1564.

*4.3.8. N-Cyclohexyl-2-(4-trifluoromethylphenyl)imidazole-5-carboxamide (**8h**).* White solid; mp 242–244 °C; IR (KBr) 3399, 3162, 2961, 1647, 1581, 1516, 1441, 1330, 1284, 1162, 849, 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26–1.40 (m, 5H), 1.67–1.81 (m, 3H), 2.04–2.05 (m, 2H), 4.01–4.10 (m, 1H), 7.43 (s, 1H), 7.67 (s, 1H), 7.70 (d, J=8.1 Hz, 2H), 8.26 (d, J=8.1 Hz, 2H), 13.13 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.9, 143.9, 137.7, 133.6, 129.1, 128.7, 128.3, 127.9, 126.1, 125.9, 125.7, 122.3, 121.2, 47.2, 32.5, 25.1, 24.8; HRMS (ESI) calcd for $[C_{17}H_{19}F_3N_3O+H]^+$ 338.1475, found 338.1490.

*4.3.9. N-Cyclohexyl-2-(4-methylphenyl)imidazole-5-carboxamide (**8i**).* White solid; mp 246–248 °C; IR (KBr) 3448, 3156, 2936, 1624, 1552, 1496, 1372, 1205, 1129, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–1.47 (m, 5H), 1.64–1.77 (m, 3H), 2.01–2.05 (m, 2H), 2.39 (s, 1H), 3.97–3.98 (m, 1H), 7.43 (s, 1H), 7.67 (s, 1H), 7.24 (d, J=8.2 Hz, 2H), 7.37 (s, 1H), 7.61 (s, 1H), 7.92 (d, J=8.2 Hz, 2H), 11.84 (br, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.2, 145.6, 138.1, 137.0, 129.2, 127.3, 125.2, 120.0, 47.1, 32.5, 25.2, 24.9, 20.8; HRMS (ESI) calcd for $[C_{17}H_{22}N_3O+H]^+$ 284.1757, found 284.1759.

*4.3.10. N-n-Propyl-2-phenylimidazole-5-carboxamide (**8j**).* White solid; mp 230–234 °C; IR (KBr) 3464, 3142, 2964, 1629, 1561, 1457, 1347, 1295, 1147, 781, 693 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.88 (t, J=7.3 Hz, 3H), 1.46–1.59 (m, 2H), 3.21 (q, J=6.7 Hz, 2H), 7.35–7.50 (m, 3H), 7.71 (s, 1H), 7.87 (s, 1H), 8.04 (d, 2H), 12.91 (br, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.0, 145.7, 137.1, 130.0, 128.7, 128.6, 125.3, 120.2, 40.0, 22.7, 11.3; HRMS (ESI) calcd for $[C_{13}H_{16}N_3O+H]^+$ 230.1288, found 230.1289.

*4.3.11. N-n-Propyl-2-(4-trifluoromethylphenyl)imidazole-5-carboxamide (**8k**).* White solid; mp 230–232 °C; IR (KBr) 3449, 3204, 2973, 2891, 1638, 1560, 1550, 1431, 1384, 1328, 1160, 1126, 842, 706 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.88 (t, J=7.3 Hz, 3H), 1.47–1.58 (m, 2H), 3.22 (q, J=6.6 Hz, 2H), 7.81 (s, 1H), 7.86 (d, J=8.1 Hz, 2H), 7.95 (s, 1H), 8.21 (d, J=8.1 Hz, 2H), 13.21 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.4, 144.5, 138.3, 134.2, 130.0, 129.3, 129.2, 128.8, 128.4, 126.4, 126.2, 122.8, 119.2, 121.5, 40.5, 23.2, 11.8; HRMS (ESI) calcd for $[C_{14}H_{15}F_3N_3O+H]^+$ 298.1162, found 298.1164.

*4.3.12. N-n-Propyl-2-(4-methoxyphenyl)imidazole-5-carboxamide (**8l**).* White solid; mp 198–200 °C; IR (KBr) 3205, 3058, 2959, 1632, 1571, 1524, 1437, 1385, 1311, 1208, 834, 796 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.92 (t, J=7.3 Hz, 3H), 1.53–1.61 (m, 2H), 3.25 (q, J=6.2 Hz, 2H), 3.85 (s, 3H), 7.07 (d, J=8.5 Hz, 2H), 7.69 (s, 1H), 7.97 (s, 1H), 7.98 (d, J=8.5 Hz, 2H), 12.79 (s, 1H); ^{13}C NMR (75 MHz,

DMSO-d_6) δ 162.3, 160.1, 146.4, 137.4, 127.3, 123.3, 120.2, 114.6, 55.6, 40.5, 23.2, 11.8; HRMS (ESI) calcd for $[C_{14}H_{18}N_3O_2+H]^+$ 260.1394, found 260.1409.

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Supplementary data

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