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PAPER

Direct transition-metal-free intramolecular C–O bond formation: synthesis of benzoxazole derivatives†

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A direct base-mediated intramolecular carbon-oxygen bond formation has been developed without a transition-metal catalyst. In the presence of 2.0 equiv of K_2CO_3 in DMSO at 140 °C, the intramolecular cyclization of *o*-haloanilides affords benzoxazoles in high yields. A mechanism *via* an initial formation of a benzyne intermediate followed by nucleophilic addition to form the C–O bond has been proposed.

Introduction

Benzoxazoles are frequently found in a diverse array of compounds, including biologically and therapeutically active agents,[1] a wide range of natural products,[2] and functional materials.[3] Therefore, the construction of these heterocycles has received much attention. The conventional method for the synthesis of 2-substituted benzoxazoles is *via* condensation of *ortho*-aminophenols and aldehydes or carboxylic acid derivatives under oxidative conditions.[4] Although these transformations are widely used in the preparation of benzoxazoles, there remain many drawbacks to overcome such as the use of highly toxic reagents, strong acids and, in some cases, harsh reaction conditions.[4,5] To develop more milder, novel and sustainable processes for the assembly of the benzoxazole ring system, much effort has been devoted to the survey of the transition metal-catalyzed intramolecular *O*-arylation of *ortho*-haloanilides. Among the different catalysts, inexpensive and nontoxic copper[6] and iron[7] provide the efficient and straightforward means for this carbon-heteroatom cross-coupling reaction.

The intramolecular addition reaction of a benzyne by side-chain nucleophiles to generate benzo-fused heterocycles is another useful synthetic strategy introduced independently by Huisgen[8] and Bunnett[9] in the 1950s. This methodology has potential advantages over the transition metal-catalyzed cross-coupling reactions, avoiding the generation of the waste and hazards associated with metal.[10] Despite this protocol being successfully employed in the synthesis of various heterocycles by using aryne-tethered nitrogen,[11] oxygen,[11b,12] or sulfur nucleophiles[13] in common laboratory practice, it is recognized that this procedure is especially problematic for large-scale operations with some disadvantages: rather low reaction temperatures, the use of excess strong base (generally potassium amide in liquid ammonia or *n*-BuLi in hexane), inconvenience in handling and workup, moderate yields, or a relatively narrow scope of substrates.[12] Herein, we report metal-free weak base-mediated intramolecular carbon-oxygen bond formation reaction of *ortho*-haloanilides to afford synthetically valuable benzoxazole derivatives under mild conditions.

Results and discussion

N-(2-Iodo-4-methylphenyl)benzamide (**1a**) derived from benzoylation of 2-iodo-4-methylbenzenamine, was selected as a model substrate for the metal-free intramolecular *O*-arylation reaction. To optimize the reaction conditions, we examined different bases, solvents and temperature. Some results from that study are summarized in Table 1. At first, the intramolecular C–O coupling reaction of **1a** was examined by using potassium carbonate (K_2CO_3, 2.0 equiv) as the base in DMSO at 100 °C for 48 h. To our delight, the desired product benzoxazole **2a** was smoothly obtained in 94% yield (entry 1, Table 1). To explore the possibility of metal impurities in the commercially available potassium carbonate that would potentially induce this transformation,[14] we analyzed K_2CO_3 using inductively coupled plasma atomic emission spectroscopy (ICP-AES). 1–3 ppm of Fe, Co and Mg were detected in the base. However, the reaction efficiency was reduced when 10 mol% $CoBr_2$ or $FeCl_3$ was added to the reaction mixture. On the other hand, different sources of K_2CO_3 and purified K_2CO_3 were used with new glassware, almost the same results were obtained. Based on the above experiments, we concluded that the presence of trace metal impurities were not involved in this carbon-oxygen bond formation reaction. We then carried out a set of experiments to reveal the crucial role of the reaction temperature (entries 1–3, Table 1). At a higher temperature, the reaction time was significantly shortened (8 h *vs.* 48 h, entries 3 and 1, Table 1) giving comparable yield to the reaction at 100 °C. A brief survey of reaction medium showed that use of polar solvent such as DMF, water, or a co-solvent of DMSO and water gave no products (entries 4, 5 and 7, Table 1). The reaction carried out in the nonpolar solvent toluene didn't proceed

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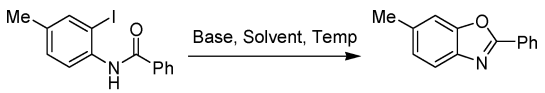
Table 1 Optimization of base-mediated intramolecular C–O bond formation of amide **1a**[a]



1a **2a**

entry	base	solvent	temp (°C)	time (h)	yield[b] (%)
1	K_2CO_3	DMSO	100	48	94
2	K_2CO_3	DMSO	120	24	88
3	K_2CO_3	DMSO	140	8	92
4	K_2CO_3	DMF	120	48	0
5	K_2CO_3	H_2O	120	48	0
6	K_2CO_3	Toluene	120	48	0
7[c]	K_2CO_3	DMSO/H_2O	120	48	0
8	Na_2CO_3	DMSO	140	36	40
9	Cs_2CO_3	DMSO	140	36	82
10	Et_3N	DMSO	140	36	0
11	$K_3PO_4{\cdot}3H_2O$	DMSO	140	36	74

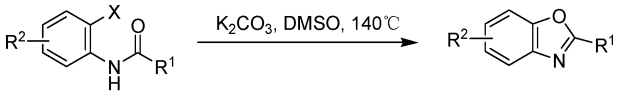
[a] Conditions: 1.0 equiv of *o*-haloanilide, 2.0 equiv of base, solvent (0.2 M). [b] Yield of isolated product after chromatography. [c] A mixture solvent of DMSO and H_2O (v/v = 1) was used.

(entry 6, Table 1). DMSO as the stronger polar solvent proved to be the most effective for this coupling (entries 1–3, Table 1). Finally, other bases such as Na_2CO_3, Cs_2CO_3, Et_3N and $K_3PO_4{\cdot}3H_2O$ were examined, K_2CO_3 provided better results (entries 8–11, Table 1). Noteworthy was the fact that this reaction was insensitive to air and moisture, hence, there was no need for an inert atmosphere.

With the optimized reaction conditions in hand, we prepared a large range of benzoxazole derivatives to explore the generality of the present reaction (Table 2). As shown in Table 2, this method is efficient for the synthesis of a number of benzoxazoles **2** in good to excellent yields. The nature of the substituent R^1 directly linked to the carbonyl moiety was very important to the reaction outcome. Although *o*-iodoanilide substrates bearing various different aromatic substituents can smoothly be converted to the desired products in moderate to excellent yields (entries 1, 3, 4, 6–8, 10–14 and 16–18, Table 2), the electronic nature of the aromatic motifs had a great effect on the yields. In general, a variety of electron neutral, rich aromatic and heteroaromatic substrates were efficiently transformed into the corresponding benzoxazoles in excellent yields (entries 1, 3, 4, 6–8, 17 and 18, Table 2). The presence of relatively electron withdrawing *o*- and *p*-chlorophenyl substituents did not have much effect and led to similar results (entries 10 and 11, Table 2), whereas, for substrates with stronger electron-withdrawing functional groups on aromatic rings (with the exception of -CN, entry 14), the yield decreased significantly (entries 12, 13 and 16, Table 2). Haloanilide with an (*E*)-styryl substituent R^1 gave the corresponding product in 78% yield (entry 19, Table 2). In contrast to aromatic and styryl substituents, halobenzamides with vinyl or aliphatic functional groups R^1 provided a trace amount of the products (entries 20 and 21, Table 2), the most of the starting materials were unchanged and recovered from the reaction mixture. Interestingly, steric hindrance seemed not to hamper the reaction, the benzoxazoles can be obtained in excellent yields (entries 4, 7 and 11, Table 2).

Regarding the aryl halide moiety, it is obvious that *o*-bromoanilides afforded inferior results to their iodo analogues (entries 2, 5, 9, 15, 22 and 24–26, Table 2), despite the fact that

Table 2 Direct base-mediated synthesis of benzoxazole derivatives[a]



1 **2**

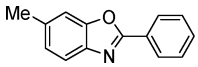
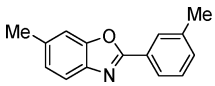
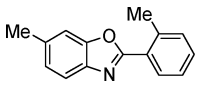
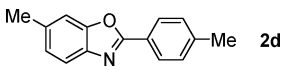
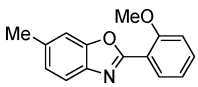
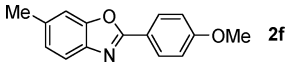
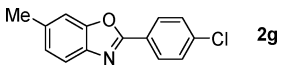
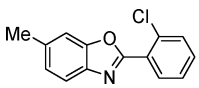
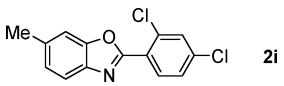
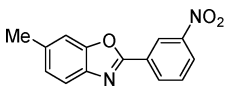
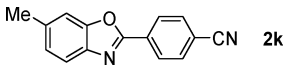
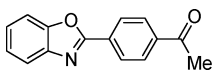
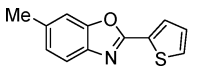
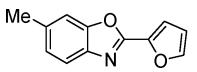
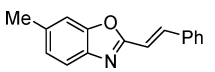
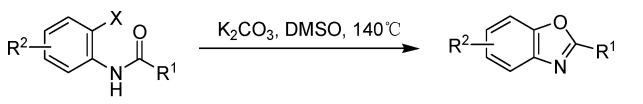
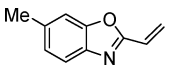
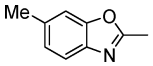
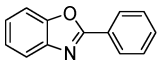
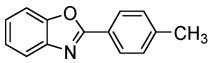
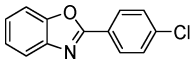
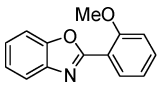
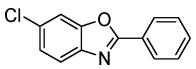
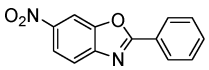
entry	X	benzoxazole	yield (%)[b]
1	I	 **2a**	92 (86)[c]
2	Br		61
3	I	 **2b**	97
4	I	 **2c**	96
5	Br		58
6	I	 **2d**	92
7	I	 **2e**	86
8	I	 **2f**	96
9	Br		93
10	I	 **2g**	83
11	I	 **2h**	94
12	I	 **2i**	43
13	I	 **2j**	41
14	I	 **2k**	96
15	Br		66
16	I	 **2l**	29
17	I	 **2m**	84
18	I	 **2n**	82
19	I	 **2o**	78

Table 2 *(Contd.)*



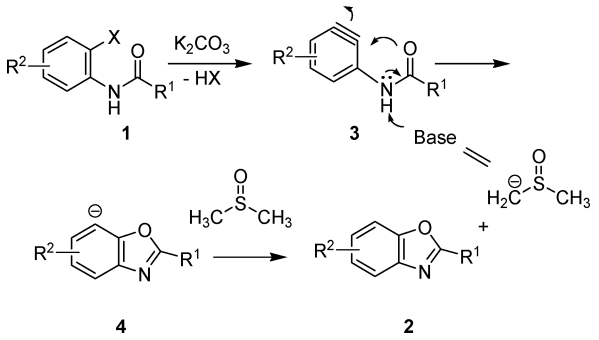
1 **2**

entry	X	benzoxazole	yield (%)[b]
20[d]	I	 **2p**	trace
21[d]	I	 **2q**	<10
22	Br	 **2r**	55 (46)[e]
23	Cl		18
24	Br	 **2s**	93
25	Br	 **2t**	64
26	Br	 **2u**	42
27	I	 **2v**	92
28[f]	I	 **2w**	0

[a] Conditions: 1.0 equiv of *o*-haloanilide (0.3 mmol), 2.0 equiv of K_2CO_3, DMSO (0.2 M), 140 °C for 8–48 h. [b] Yield of isolated product after chromatography. [c] 2.0 mmol of *o*-haloanilide was used. [d] Most of the starting materials were unchanged and recovered from the reaction mixture. [e] The value in the parenthesis is an isolated yield of the corresponding product with *t*-BuOK as a base. [f] Most of the starting materials were unchanged and recovered from the reaction mixture.

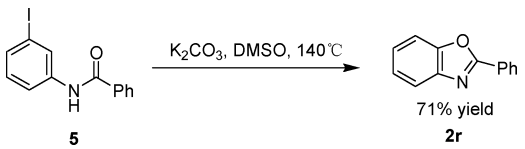
in some cases the yield was comparable (entries 8 and 9, 6 and 24, Table 2). *o*-Chloroanilide showed the poorest tendency to undergo this transformation, giving only 18% isolated yield (entry 23, Table 2). In addition, R^2 substituents on the haloarene were essential to the reaction. For instance, aromatic amides bearing H, Me or Cl substituents furnished the corresponding products in good yields (entries 1, 22 and 27, Table 2), whereas for the substrate with strong electron-withdrawing functional groups ($-NO_2$), no product was obtained (entry 28, Table 2).

A proposed reaction mechanism for base-mediated intramolecular C–O coupling of *o*-haloanilides to benzoxazole derivatives is shown in Scheme 1. In nucleophilic aromatic substitution, the formation of the addition intermediate is usually the rate-determining step, so the ease of C–X bond breaking does not affect the rate and the order of reactivity is often Cl > Br > I.[15] Obviously an aromatic nucleophilic substitution process is inconsistent with our experimental results (entries 1, 22 and 23, Table 2). This reaction presumably occurred by an initial formation of a benzyne intermediate **3** in the presence of a base,[11c,16] which was trapped by furan through [2+4] cycloaddition reaction[17] in an additional experiment. An intramolecular nucleophilic



Scheme 1 Proposed mechanism for the base-mediated intramolecular *O*-arylation of *o*-haloanilides.

addition[11–13,18] of amide to **3** afforded carbanion[18] intermediate **4**, followed by subsequent protonation by DMSO to give the final products **2**. To prove the benzyne-type mechanism,[12b] the substrate *m*-iodoanilide **5** was used to conduct this transformation under the optimized reaction condition, benzoxazole **2r** was obtained in 71% yield (eqn (1)).



5 **2r** (1)

Conclusions

In summary, we have established an efficient and practical method for direct base-promoted intramolecular *O*-arylation of *o*-haloanilides to afford benzoxazoles in good to excellent yields. Particular valuably, without the addition of any exogenous transition metal catalysts, this easy-to-handle and environmentally benign chemical process is suitable for large-scale synthesis, providing a valuable synthetic protocol for industrial applications.

Experimental

Chemicals and solvents were all purchased from commercial suppliers and used without further purification. All reactions were carried out under an air atmosphere in dried glassware. ^{1}H NMR spectra were recorded on a Bruker-300 or 400 MHz spectrometer, ^{13}C NMR spectra were recorded at 75 or 100 MHz. Chemical shifts (δ) are given in parts per million (ppm) downfield relative to $CDCl_3$. Coupling constants are given in hertz (Hz). Unless otherwise stated deuterochloroform was used as solvent. In assignment of the ^{1}H NMR spectra, multiplicities and abbreviations used are as follows: Ar = aromatic, Ph = phenyl, d = doublet, dd = doublet of doublets, m = multiplet, q = quartet, s = singlet, t = triplet. High-resolution mass spectra were recorded on a Bruker BIO TOF Q mass spectrometer.

General procedures for direct metal-free intramolecular C–O bond formation of *o*-haloanilides (Tables 1 and 2)

A two-necked dried round-bottomed flask was charged with *o*-haloanilide substrates (0.3 mmol, 1.0 equiv) and K_2CO_3 (82.8 mg, 0.6 mmol, 2.0 equiv). The flask was then equipped with a thermometer and water-cooled reflux condenser, and 1.5 mL

DMSO (5 mL mmol^{-1} *o*-haloanilide substrate) was added *via* syringe. The mixture was then heated to 140 °C with stirring under an air atmosphere until the starting material had been consumed as judged by TLC. The reaction mixture was cooled to room temperature, quenched with water (5 mL), and diluted with ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with (2 × 5 mL) ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel (H), eluting with 2–5% ethyl acetate/petroleum ether.

6-Methyl-2-phenylbenzo[*d*]oxazole (2a)[6c,6e]. Mp 93–94 °C; IR (KBr): ν (cm^{-1}) 3053, 2955, 2915, 2846, 1614, 1552, 1479, 1446, 1335, 1246, 1175, 1125, 1096, 1052, 1020; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31–8.24 (m, 2H), 7.68 (d, 1H, J = 8.2 Hz), 7.58–7.51 (m, 3H), 7.41 (t, 1H, J = 0.6 Hz), 7.20 (ddd, 1H, J = 8.1, 1.5, 0.6 Hz), 2.53 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.6, 151.1, 140.0, 135.6, 131.3, 128.9, 127.5, 127.4, 125.8, 119.4, 110.8, 21.8. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{14}H_{11}NNaO$ 232.0738; found 232.0736.

6-Methyl-2-*m*-tolylbenzo[*d*]oxazole (2b). Mp 96–97 °C; IR (KBr): ν (cm^{-1}) 3050, 3018, 2916, 2849, 1614, 1552, 1479, 1446, 1425, 1335, 1288, 1272, 1245, 1170, 1124, 1051, 1020; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71 (s, 1H), 7.63 (m, 2H), 7.38 (t, 1H, J = 0.6 Hz), 7.32–7.26 (m, 1H), 7.19 (d, 1H, J = 7.5 Hz), 7.14 (d, 1H, J = 8.0 Hz), 2.51 (s, 3H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.7, 150.3, 139.8, 138.7, 135.5, 130.7, 129.3, 129.1, 127.1, 126.2, 124.4, 119.1, 111.2, 22.1, 21.9. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{15}H_{13}NNaO$ 246.0895; found 246.0891.

6-Methyl-2-*o*-tolylbenzo[*d*]oxazole (2c). Mp 94–95 °C; IR (KBr): ν (cm^{-1}) 3014, 2955, 2919, 2853, 1609, 1545, 1485, 1453, 1378, 1328, 1269, 1166, 1120, 1027; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13–8.08 (m, 1H), 7.62 (d, 1H, J = 8.0 Hz), 7.54–7.50 (m, 1H), 7.38–7.26 (m, 3H), 7.15 (d, 1H, J = 8.0 Hz), 2.75 (s, 3H), 2.50 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.0, 149.3, 141.8, 138.9, 134.4, 131.8, 130.9, 129.9, 127.3, 126.6, 126.1, 119.9, 109.8, 22.2, 21.6. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{15}H_{13}NNaO$ 246.0895; found 246.0897.

6-Methyl-2-*p*-tolylbenzo[*d*]oxazole (2d). Mp 103–104 °C; IR (KBr): ν (cm^{-1}) 3052, 3022, 2916, 2853, 1619, 1556, 1499, 1480, 1409, 1334, 1287, 1249, 1179, 1115, 1052, 1015; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13–8.11 (m, 2H), 7.62 (d, 1H, J = 8.0 Hz), 7.37 (s, 1H), 7.33–7.31 (m, 2H), 7.15 (d, 1H, J = 8.0 Hz), 2.50 (s, 3H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.7, 150.9, 141.7, 139.9, 135.2, 129.5, 127.4, 125.6, 124.6, 119.6, 110.6, 21.7, 21.5. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{15}H_{13}NNaO$ 246.0895; found 246.0893.

2-(2-Methoxyphenyl)-6-methylbenzo[*d*]oxazole (2e)[6e]. Mp 74–75 °C; IR (KBr): ν (cm^{-1}) 3018, 2963, 2936, 2919, 2837, 1605, 1596, 1579, 1532, 1479, 1447, 1432, 1421, 1333, 1300, 1268, 1253, 1186, 1157, 1119, 1063, 1033, 1021; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (dd, 1H, J = 8.0, 2.0 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.49–7.43 (m, 1H), 7.37 (t, 1H, J = 0.6 Hz), 7.16–7.04 (m, 3H), 3.98 (s, 3H), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8, 158.3, 150.5, 139.9, 135.2, 132.4, 131.0, 125.4, 120.6, 119.5, 116.3, 111.9, 110.5, 56.1, 21.8. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{15}H_{13}NNaO_2$ 262.0844; found 262.0851.

2-(4-Methoxyphenyl)-6-methylbenzo[*d*]oxazole (2f)[19]. Mp 90–91 °C; IR (KBr): ν (cm^{-1}) 3060, 3022, 2990, 2971, 2913, 2834, 1618, 1604, 1580, 1557, 1503, 1434, 1420, 1335, 1321, 1305, 1287, 1258, 1241, 1185, 1176, 1120, 1059, 1024; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (d, 2H, J = 8.0 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.39 (t, 1H, J = 0.6 Hz), 7.21 (m, 1H), 7.12 (d, 2H, J = 8.0 Hz), 3.98 (s, 3H), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.2, 162.3, 150.7, 142.1, 135.2, 129.4, 127.6, 119.8, 119.6, 116.3, 110.4, 55.5, 21.6. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{15}H_{13}NNaO_2$ 262.0844; found 262.0847.

2-(4-Chlorophenyl)-6-methylbenzo[*d*]oxazole (2g)[6e]. Mp 151–152 °C; IR (KBr): ν (cm^{-1}) 3076, 3021, 2920, 1612, 1590, 1547, 1480, 1456, 1400, 1329, 1279, 1244, 1159, 1125, 1108, 1087, 1051, 1007; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, 2H, J = 7.8 Hz), 7.71 (d, 1H, J = 8.0 Hz), 7.52 (d, 2H, J = 7.8 Hz), 7.41 (t, 1H, J = 0.6 Hz), 7.19 (m, 1H), 2.52 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1, 150.8, 142.0, 137.8, 135.7, 129.3, 128.9, 127.7, 124.8, 119.8, 116.2, 21.8. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{14}H_{10}ClNNaO$ 266.0349; found 266.0353.

2-(2-Chlorophenyl)-6-methylbenzo[*d*]oxazole (2h)[6e]. Mp 78–79 °C; IR (KBr): ν (cm^{-1}) 3049, 2916, 2853, 1617, 1605, 1565, 1531, 1483, 1456, 1432, 1417, 1331, 1307, 1272, 1253, 1159, 1124, 1084, 1041, 1022; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14–8.11 (m, 1H), 7.71 (d, 1H, J = 8.0 Hz), 7.57–7.53 (m, 1H), 7.46–7.36 (m, 3H), 7.21–7.17 (m, 1H), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.6, 151.1, 139.8, 136.3, 133.6, 131.9, 131.6, 127.7, 127.1, 126.6, 126.1, 120.1, 111.1, 22.1. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{14}H_{10}ClNNaO$ 266.0349; found 266.0351.

2-(2,4-Dichlorophenyl)-6-methylbenzo[*d*]oxazole (2i). Mp 97–98 °C; IR (KBr): ν (cm^{-1}) 3064, 2916, 2849, 1604, 1585, 1562, 1485, 1459, 1384, 1329, 1252, 1126, 1104, 1089, 1031; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15–8.12 (d, 1H, J = 8.5 Hz), 7.71–7.62 (m, 3H), 7.41 (t, 1H, J = 0.6 Hz), 7.16 (m, 1H), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.7, 152.1, 140.1, 136.3, 135.7, 134.3, 133.4, 132.1, 131.7, 128.3, 127.3, 121.1, 110.8, 22.3. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{14}H_9Cl_2NNaO$ 299.9959; found 299.9963.

6-Methyl-2-(3-nitrophenyl)benzo[*d*]oxazole (2j)[20]. Mp 140–142 °C; IR (KBr): ν (cm^{-1}) 3095, 3037, 2915, 2853, 1607, 1551, 1523, 1473, 1349, 1240, 1132, 1102, 1050; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.37 (s, 1H), 8.16 (m, 1H), 7.76–7.63 (m, 3H), 7.39 (t, 1H, J = 0.6 Hz), 7.16 (m, 1H), 2.50 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.7, 152.1, 148.9, 140.1, 134.2, 133.4, 130.5, 128.3, 127.1, 122.1, 121.7, 121.1, 110.8, 22.3. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{14}H_{10}N_2NaO_3$ 277.0589; found 277.0592.

4-(6-Methylbenzo[*d*]oxazol-2-yl)benzonitrile (2k)[6b]. Mp 203–204 °C; IR (KBr): ν (cm^{-1}) 3022, 2917, 2223, 1617, 1598, 1544, 1483, 1407, 1333, 1283, 1246, 1055, 1011; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (d, 2H, J = 8.0 Hz), 7.81 (d, 2H, J = 8.0 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.42 (s, 1H), 7.23 (d, 1H, J = 8.0 Hz), 2.55 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4, 151.2, 139.7, 136.8, 132.6, 131.3, 127.7, 126.4, 119.8, 118.2, 114.4, 110.9, 21.9. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{15}H_{10}N_2NaO$ 257.0691; found 257.0695.

1-(4-(Benzo[*d*]oxazol-2-yl)phenyl)ethanone (2l). Mp 112–114 °C; IR (KBr): ν (cm^{-1}) 3054, 2954, 2918, 2849, 1721, 1611, 1560, 1548, 1453, 1411, 1376, 1344, 1277, 1245, 1109, 1059, 1012; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.34 (d, 2H, J = 8.0 Hz), 8.19 (d, 2H, J = 8.0 Hz), 7.83–7.79 (m, 1H), 7.64–7.60 (m, 1H), 7.54–7.41 (m, 2H), 3.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 161.9, 150.8, 142.0, 132.5, 131.0, 130.1, 127.5, 125.7, 124.9, 120.4, 110.8, 29.7. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{15}H_{11}NNaO_2$ 260.0687; found 260.0691.

6-Methyl-2-(thiophen-2-yl)benzo[*d*]oxazole (2m)[6c,6e]. Mp 74–76 °C; IR (KBr): ν (cm^{-1}) 3072, 3057, 2916, 2857, 1613, 1589, 1507, 1490, 1476, 1415, 1368, 1329, 1270, 1248, 1227, 1206, 1124, 1090, 1044, 1004; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (dd, 1H, J = 4.0, 1.0 Hz), 7.58 (d, 1H, J = 8.0 Hz), 7.51 (dd, 1H, J = 5.0, 1.0 Hz), 7.33–7.31 (m, 1H), 7.17–7.12 (m, 2H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.5, 150.7, 139.7, 135.5, 129.8, 129.7, 129.5, 128.1, 125.9, 119.1, 110.5, 21.7. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{12}H_9NNaOS$ 238.0303; found 238.0308.

2-(Furan-2-yl)-6-methylbenzo[*d*]oxazole (2n)[6e]. Mp 52–53 °C; IR (KBr): ν (cm^{-1}) 3060, 2919, 2849, 1681, 1626, 1592, 1524, 1484, 1457, 1309, 1249, 1156, 1087, 1060, 1005; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.64 (dd, 1H, J = 2.0, 0.5 Hz), 7.61 (d, 1H, J = 8.0 Hz), 7.34–7.33 (m, 1H), 7.22 (dd, 1H, J = 3.5, 0.5 Hz), 7.17–7.13 (m, 1H), 6.59 (dd, 1H, J = 3.5, 2.0 Hz), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.8, 150.4, 145.4, 142.7, 139.4, 135.7, 126.0, 119.4, 113.7, 112.1, 110.6, 21.7. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{12}H_9NNaO_2$ 222.0531; found 222.0538.

6-Methyl-2-styrylbenzo[*d*]oxazole (2o)[6e]. Mp 70–71 °C; IR (KBr): ν (cm^{-1}) 3056, 3037, 3018, 2916, 2849, 2360, 1643, 1575, 1531, 1482, 1445, 1337, 1242, 1189, 1156, 1117, 1071; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, 1H, J = 16.5 Hz), 7.59–7.56 (m, 3H), 7.43–7.31 (m, 4H), 7.12 (dd, 1H, J = 8.0, 1.0 Hz), 7.04 (d, 1H, J = 16.5 Hz), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.7, 140.4, 138.8, 135.7, 135.2, 132.6, 129.6, 128.9, 127.4, 125.7, 119.2, 114.0, 110.4, 21.8. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{16}H_{13}NNaO$ 258.0895; found 258.0899.

2-Phenylbenzo[*d*]oxazole (2r)[6c,12b]. Mp 101–102 °C; IR (KBr): ν (cm^{-1}) 3057, 2952, 2917, 2845, 1615, 1551, 1470, 1445, 1342, 1316, 1288, 1240, 1196, 1144, 1052, 1021, 1002; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (dd, 2H, J = 5.6, 2.1 Hz), 7.86–7.79 (m, 1H), 7.67–7.53 (m, 4H), 7.44–7.36 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.1, 150.8, 142.2, 131.4, 128.9, 127.6, 127.2, 125.1, 124.6, 120.1, 110.6. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{13}H_9NNaO$ 218.0582; found 218.0585.

2-*p*-Tolylbenzo[*d*]oxazole (2s)[21]. Mp 116–117 °C; IR (KBr): ν (cm^{-1}) 3052, 3021, 2914, 2849, 1620, 1555, 1500, 1470, 1449, 1408, 1344, 1311, 1286, 1241, 1197, 1176, 1139, 1115, 1053, 1016; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.49 (d, 2H, J = 8.2 Hz), 7.76–7.73 (m, 1H), 7.55–7.52 (m, 1H), 7.33–7.28 (m, 4H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.7, 151.1, 142.6, 142.4, 130.0, 128.0, 125.3, 125.2, 124.9, 120.3, 110.8, 22.0. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{14}H_{11}NNaO$ 232.0738; found 232.0742.

2-(4-Chlorophenyl)benzo[*d*]oxazole (2t)[6b]. Mp 150–151 °C; IR (KBr): ν (cm^{-1}) 3084, 3056, 1616, 1594, 1552, 1482, 1451, 1403, 1342, 1293, 1273, 1243, 1196, 1174, 1106, 1090, 1055, 1011; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, 2H, J = 7.8 Hz), 7.84–7.77 (m, 1H), 7.65–7.57 (m, 1H), 7.52 (d, 2H, J = 7.8 Hz), 7.44–7.36 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1, 150.8, 142.0, 137.8, 129.3, 128.9, 125.7, 125.4, 124.8, 120.1, 110.6. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{13}H_8ClNNaO$ 252.0192; found 252.0195.

2-(2-Methoxyphenyl)benzo[*d*]oxazole (2u)[6e]. Mp 53–55 °C; IR (KBr): ν (cm^{-1}) 3045, 2978, 2841, 1644, 1616, 1603, 1580, 1503, 1452, 1420, 1344, 1319, 1303, 1254, 1242, 1187, 1059, 1019; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (dd, 1H, J = 7.7, 1.8 Hz), 7.90–7.83 (m, 1H), 7.66–7.60 (m, 1H), 7.58–7.52 (m, 1H), 7.42–7.35 (m, 2H), 7.17–7.11 (m, 2H), 4.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.6, 158.5, 150.4, 142.2, 132.8, 131.3, 124.9, 124.3, 120.7, 120.3, 116.2, 112.1, 110.5, 56.2. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{14}H_{11}NNaO_2$ 248.0687; found 248.0689.

6-Chloro-2-phenylbenzo[*d*]oxazole (2v)[6b]. Mp 107–108 °C; IR (KBr): ν (cm^{-1}) 3089, 3060, 3006, 1616, 1552, 1460, 1448, 1425, 1331, 1284, 1262, 1229, 1048, 1021; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.23–8.16 (m, 2H), 7.64 (d, 1H, J = 8.5 Hz), 7.55 (d, 1H, J = 1.9 Hz), 7.57–7.45 (m, 3H), 7.30 (dd, 1H, J = 8.5, 1.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.7, 151.0, 140.9, 131.8, 130.7, 129.0, 127.7, 126.8, 125.3, 120.5, 111.2. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{13}H_8ClNNaO$ 252.0192; found 252.0197.

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