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碘介导下通过氧化性 C—O 键形成合成异噁唑类化合物

侯 姣[a] 张新婷[a] 于文全*,[a] 常俊标*,[a]
([a]郑州大学化学与分子工程学院 郑州 450001)

摘要 通过碘介导的氧化性 C—O 键形成反应由易得的 *α*,*β*-不饱和肟合成了一系列单、双和三取代(芳基、烷基和/或烯基)的异噁唑类化合物. 该合成方法具有不使用过渡金属、操作简单、反应条件温和、反应时间短, 以及底物适用范围广等优点.

关键词 异噁唑; 碘; *α*,*β*-不饱和肟; C—O 键形成

I_2-Mediated Oxidative C—O Bond Formation for the Synthesis of Isoxazoles

Hou, Jiao[a] Zhang, Xinting[a] Yu, Wenquan*,[a] Chang, Junbiao*,[a]
([a] *College of Chemistry and Molecular Engineering*, *Zhengzhou University*, *Zhengzhou 450001*)

Abstract A variety of mono-, di-, and tri-substituted (aryl, alkyl, and/or alkenyl) isoxazoles were synthesized from readily accessible *α*,*β*-unsaturated oximes via I_2-mediated oxidative C—O bond formation. The features of this synthetic approach include no use of transition metals, simple operation, mild reaction conditions, short reaction time, and broad substrate scope.

Keywords isoxazole; iodine; *α*,*β*-unsaturated oxime; C—O bond formation

1 Introduction

Isoxazole is an important five-membered aromatic heterocyclic skeleton[1] widely distributed in biologically active natural and synthetic products. Moreover, its derivatives are also used extensively as insecticides or fungicides in agrochemistry[2] and as masked 1,3-dicarbonyl equivalents in organic synthesis.[3] Consequently, various methods have been developed for the synthesis of isoxazoles.[1,4] Among them, oxidative cyclization of readily accessible *α*,*β*-unsaturated oxime precursors is one of the most straightforward synthetic pathways to access isoxazoles. Such transformations have been previously accomplished[5] using reagents, such as $Pb(OAc)_4$, [$Py_4Co(HCrO_4)_2$], 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), MnO_2, 2-iodoxybenzoic acid (IBX), $Cu(OAc)_2/O_2$, tetrabutyl-ammonium iodide/*tert*-butyl hydroperoxide (TBAI/TBHP). Despite of the existing methods, it is still of importance to develop new convenient and environmentally-benign protocols for isoxazole synthesis under mild reaction conditions.

As a commercial available, inexpensive and eco-friendly reagent, molecular iodine has been extensively used in oxidative C—C and C—N bond construction through direct C—H functionalization.[6] Although a number of oxidative C—O bond formation reactions have been developed using a combination of catalytic amount of iodine (or iodide) with peroxides.[7] Such transformations employing molecular iodine as the sole oxidant are only rarely studied. Zhang and coworkers[8] reported an I_2-meditated oxazole synthesis under basic conditions from *α*-bromoketones and benzylamines via *α*-aminoketones. Qu group[9] disclosed an iodine-promoted *α*-C—H oxidation of pyrrolidines to produce N,O-acetals. Earlier, we[10] also described the synthesis of 1,3,4-oxadiazoles and oxazoles via I_2-mediated oxidative C—O bond formation. Inspired by the previous work, in this paper we envisioned the synthesis of isoxazoles from readily accessible *α*,*β*-unsaturated oximes employing molecular iodine[11] as the sole oxidant. By contrast, the present synthetic approach has advantages such as simple operation, mild reaction conditions, short reaction time, and broad substrate scope.

* Corresponding authors. E-mail: wenquan_yu@zzu.edu.cn; changjunbiao@zzu.edu.cn
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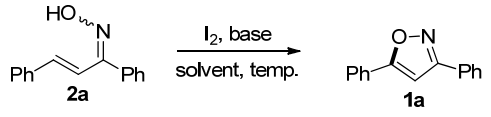
2 Results and discussion

First, we investigated I_2-mediated oxidative cyclization of chalcone oxime **2a** to synthesize isoxazole **1a**. The required substrate **2a** was readily obtained through the condensation of chalcone with hydroxylamine hydrochloride in EtOH at the reflux temperature. Initial solvent screening (Table 1, Entries 1～4) revealed that this transformation proceeds well in dimethyl sulfoxide (DMSO). In the presence of K_2CO_3 as base, the reaction was complete within 1 h at 40 ℃ producing the desired product **1a** in 72% yield (Entry 4). Increasing the temperature to 60 ℃ could accelerate the transformation and resulted in a better yield (Entry 5); while the yield of **1a** was slightly decreased at 80 ℃ (Entry 6). It is also demonstrated that 1.2 equiv. of iodine is optimal (Entry 5) and the yield will be affected by either lower (Entries 7～8) or higher (Entry 9) amount of the oxidant. No further improvement was observed when Cs_2CO_3, K_3PO_4 or MeONa was used as bases instead of K_2CO_3 (Entries 10～12). Replacement of K_2CO_3 with triethylamine only resulted in a trace amount of the product (Entry 13).

Table 1 Optimization of the reaction conditions for the synthesis of isoxazole **1a**[a]



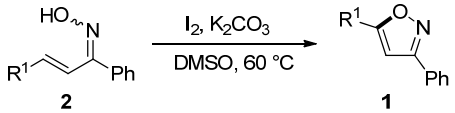
Entry	I_2/equiv.	Base	Solvent	Temp./℃	Time/h	Yield[b]/%
1	1.2	K_2CO_3	EtOH	60	0.5	40
2	1.2	K_2CO_3	1,4-Dioxane	102	3	Trace
3	1.2	K_2CO_3	CH_2Cl_2	40	3	Trace
4	1.2	K_2CO_3	DMSO	40	1	72
5	**1.2**	**K_2CO_3**	**DMSO**	**60**	**0.5**	**81**
6	1.2	K_2CO_3	DMSO	80	0.5	76
7	0.8	K_2CO_3	DMSO	60	1	65
8	1.0	K_2CO_3	DMSO	60	1	74
9	1.4	K_2CO_3	DMSO	60	0.5	77
10	1.2	Cs_2CO_3	DMSO	60	0.5	79
11	1.2	K_3PO_4	DMSO	60	0.5	78
12	1.2	MeONa	DMSO	60	0.5	61
13	1.2	NEt_3	DMSO	60	3	Trace

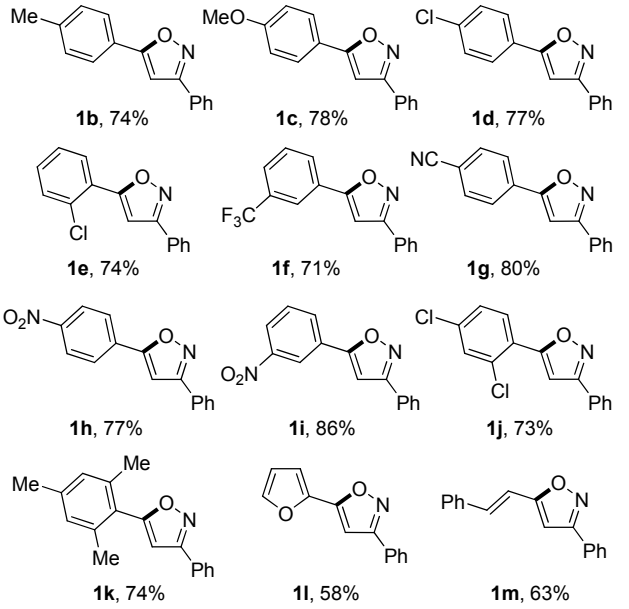
[a] Optimal reaction conditions (Entry 5): **2a** (1.0 equiv.), I_2 (1.2 equiv.), K_2CO_3 (3.0 equiv.), DMSO, 60 ℃. [b] Isolated yields.

Under the optimal reaction conditions (Table 1, Entry 5), the substrate scope of this synthetic method was examined. The present reaction is compatible with both electron-donating groups (EDGs) and electron-withdrawing groups (EWGs) on the phenyl ring at R^1 position regardless of the substitution positions (Table 2, **1b** ～ **1i**). 2,4-Dichlorophenyl and 2,4,6-trimethylphenyl substituted oximes were also smoothly converted to the expected products **1j**～**1k**. 2-Furyl (**1l**) and styryl isoxazoles (**1m**) were synthesized in satisfactory yields as well.

Incorporation of a methyl group to the carbon-carbon double bond of the substrate led to a 3,4,5-trisubstituted

Table 2 Substrate scope of the R^1 group[a]



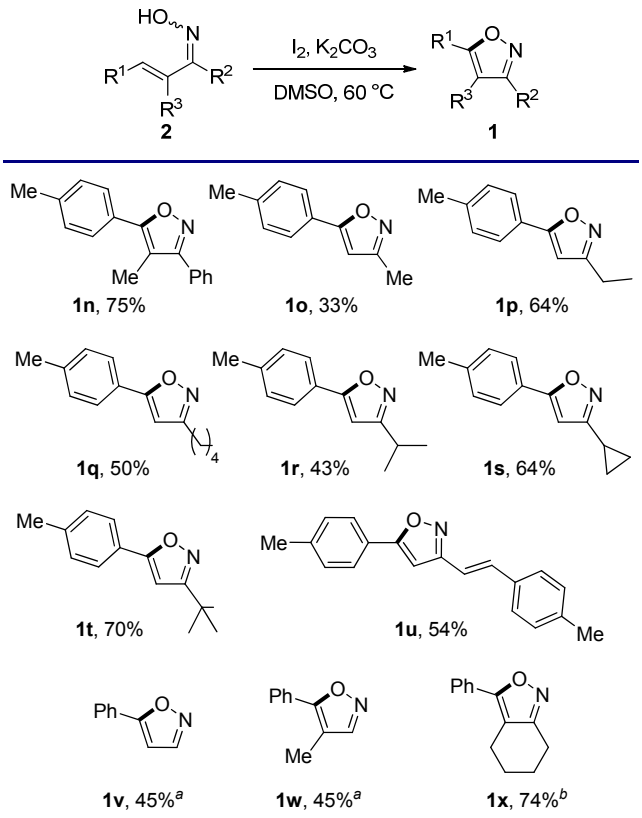


[a] Reaction conditions: **2** (1 mmol), I_2 (1.2 mmol), K_2CO_3 (3 mmol), DMSO (3 mL), 60 °C, 0.5 h (isolated yields).

isoxazole product (Table 3, **1n**). Encouraged by the success of 3,5-diaryl isoxazole synthesis, we sought to further extend the substrate scope by replacing the aromatic R^2 substituents with aliphatic and alkenyl ones. These *α*,*β*-unsaturated oximes were all successfully cyclized into the desired products (**1o**～**1u**) under the optimal oxidative cyclization conditions. Generally, these substrates resulted in lower yields than the ones with aryl groups at the R^2 position. The relatively low yield of **1o** might be due to side reactions caused by the *α*-methyl group of the oxime in the presence of iodine.[12] Mono- and disubstituted isoxazoles without R^2 substitution (R^2=H) were obtained from the corresponding cinnamaldehyde oxime precursors in moderate yields (**1v**～**1w**) as well. Moreover, this reaction is also amenable for 2-benzylidenecyclohexanone oxime substrate (**2x**) to produce the fused-ring isoxazole **1x**.

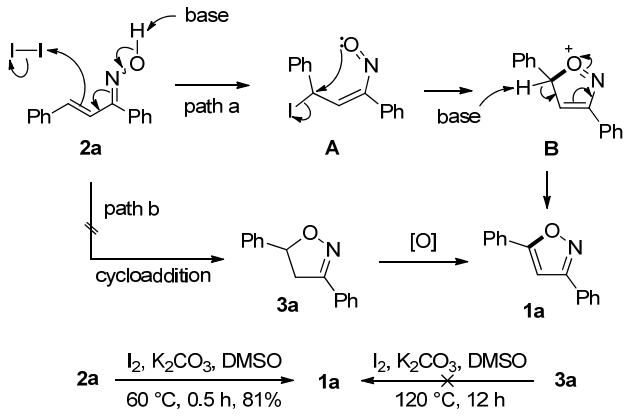
Based on these experimental results along with our previous work,[10a,13] tentative reaction mechanisms for this I_2-mediated oxidative cyclization of *α*,*β*-unsaturated oximes to isoxazoles are proposed (Scheme 1). Taking the formation of product **1a** as an example, the oxidative iodination of oxime **2a** under basic condition gives a plausible iodo species **A** (path a). Then, a S_N2'-type cyclization of intermediate **A** followed by base-promoted deprotonation produces the isoxazole framework **1a**. Another possible isoxazoline intermediate **3a** (via path b) was not observed during the reaction. Control experiments also indicated that treatment of isolated **3a**[14] with iodine under the standard reaction conditions (or at even higher temperature) failed to produce the expected isoxazole **1a**. These

Table 3 Substrate scope of the R^2 and R^3 groups[a]



[a] Reaction conditions: **2** (1 mmol), I_2 (1.2 mmol), K_2CO_3 (3 mmol), DMSO (3 mL), 60 °C, 0.5 h (isolated yields). [a] The reaction was carried out at 80 °C. [b] 1.5 mmol of I_2 was used.

observations rule out a cycloaddition-oxidative aromatization mechanism (path b).



Scheme 1 Proposed mechanisms

3 Conclusions

In summary, we have developed a convenient method for isoxazole synthesis of via I_2-mediated oxidative intramolecular C—O bond formation under transition-metal-free conditions. The required *α*,*β*-unsaturated oxime substrates were readily prepared via the condensation of *α*,*β*-unsaturated ketones with hydroxylamine hydrochloride. This operationally simple protocol is broadly applicable to a wide range of *α*,*β*-unsaturated oximes providing a facile access to diverse mono-, di-, and tri-substituted (aryl, alkyl, and/or alkenyl) isoxazoles within short reaction times under mild reaction conditions.

4 Experimental section

4.1 General information

^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz (100 MHz for ^{13}C NMR) spectrometer. Chemical shift values are given with tetramethylsilane (TMS) as an internal standard. Melting points were determined on a micro-melting point apparatus without corrections. Infrared (IR) spectra were obtained on an FT-IR spectrometer. High-resolution mass spectra (HRMS-ESI) were obtained on a Q-TOF Mass Spectrometer. Flash column chromatography was performed over silica gel 200～300 mesh. Ethanol was refluxed with magnesium and iodine, and then distilled; and DMSO was dried over 4 Å molecular sieves prior to use.

4.2 Preparation of *α*,*β*-unsaturated oxime substrates 2

A reaction mixture of the *α*,*β*-unsaturated ketone[13] (or aldehyde, 1.5 mmol) and hydroxylamine hydrochloride (156.4 mg, 2.25 mmol) in EtOH (10 mL) was heated to reflux. If the condensation was not complete within 3 h, another portion of hydroxylamine hydrochloride (156.4 mg, 2.25 mmol) was added. After the reaction was complete, the solvent was evaporated. The resulting residue was dissolved in EtOAc (15 mL) and washed by brine (30 mL). The separated aqueous layer was extracted by EtOAc (15 mL×2). All the organic layers were combined, dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel chromatography using a mixture of EtOAc and petroleum ether (PE) as eluent to afford substrate **2** in 30%～96% yields.

4.3 Synthesis of isoxazoles 1

A stirred solution of substrate **2** (1.0 mmol) in DMSO (3 mL) was treated with iodine (1.2 mmol), followed by addition of K_2CO_3 (3.0 mmol). The reaction mixture was stirred at 60 ℃ for 0.5 h. After cooled to room temperature, it was treated with 5% $Na_2S_2O_3$ (15 mL), followed by addition of brine (20 mL) and then extracted with EtOAc (15 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated and purified through silica gel column chromatography using a mixture of EtOAc and PE as eluent to afford isoxazole **1**.

3,5-Diphenylisoxazole (**1a**): Yield 179 mg, 81%. White solid, m.p. 141～142 ℃ (lit.[15] m.p. 143.4 ℃); R_f=0.43 [*V*(EtOAc)∶*V*(PE)=5∶95]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.88～7.83 (m, 4H), 7.50～7.44 (m, 6H), 6.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 170.4, 163.0, 130.2, 130.0, 129.1, 129.0, 128.9, 127.4, 126.8, 125.8, 97.5; IR (film) *ν*: 3048, 2921, 2851, 1571, 1487, 1461, 1450 cm^{-1}; HRMS calcd for $C_{15}H_{12}NO$ $[M+H]^+$ 222.0913, found

222.0924.

3-Phenyl-5-(*p*-tolyl)isoxazole (**1b**): Yield 174 mg, 74%. White solid, m.p. 137～138 ℃ (lit.[15] m.p. 136～138 ℃); R_f=0.43 [*V*(EtOAc)∶*V*(PE)=5∶95]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.87～7.85 (m, 2H), 7.73～7.70 (m, 2H), 7.49～7.44 (m, 3H), 7.28～7.26 (m, 2H), 6.76 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 170.6, 162.9, 140.5, 129.9, 129.7, 129.2, 128.9, 126.8, 125.7, 124.7, 96.9, 21.5; IR (film) *v*: 3028, 2963, 1610, 1577, 1499, 1460, 1436 cm^{-1}; HRMS calcd for $C_{16}H_{14}NO$ [M+H]$^+$ 236.1070, found 236.1085.

5-(4-Methoxyphenyl)-3-phenylisoxazole (**1c**): Yield 196 mg, 78%. White solid, m.p. 125～126 ℃ (lit.[4a] mp 125～126 ℃); R_f=0.23 [*V*(EtOAc)∶*V*(PE)=5∶95]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.87～7.84 (m, 2H), 7.77 (td, *J*=9.6, 2.8 Hz, 2H), 7.50～7.44 (m, 3H), 6.99 (td, *J*=9.6, 2.4 Hz, 2H), 6.70 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 170.3, 162.9, 161.1, 129.9, 129.2, 128.9, 127.4, 126.8, 120.3, 114.4, 96.1, 55.4; IR (film) *v*: 3005, 2966, 2839, 1614, 1579, 1519, 1502, 1464, 1441 cm^{-1}; HRMS calcd for $C_{16}H_{14}NO_2$ [M+H]$^+$ 252.1019, found 252.1027.

5-(4-Chlorophenyl)-3-phenylisoxazole (**1d**): Yield 196 mg, 77%. White solid, m.p. 179～180 ℃ (lit.[16] mp 178～179 ℃); R_f=0.40 [*V*(EtOAc)∶*V*(PE)=5∶95]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.88～7.84 (m, 2H), 7.78 (td, *J*=2.4 Hz, 9.2 Hz, 2H), 7.50～7.45 (m, 5H), 6.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 169.2, 163.1, 136.3, 130.1, 129.3, 128.9, 128.7, 127.1, 126.8, 125.9, 97.8; IR (film) *v*: 3104, 1612, 1485, 1458, 1438, 1409 cm^{-1}; HRMS calcd for $C_{15}H_{11}ClNO$ [M+H]$^+$ 256.0524, found 256.0537.

5-(2-Chlorophenyl)-3-phenylisoxazole (**1e**)[5a]: Yield 189 mg, 74%. White solid, m.p. 60～62 ℃; R_f=0.41 [*V*(EtOAc)∶*V*(PE)=5∶95]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.01～7.99 (m, 1H), 7.90～7.87 (m, 2H), 7.52～7.43 (m, 4H), 7.42～7.34 (m, 2H), 7.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 162.9, 131.7, 130.8, 130.8, 130.1, 129.4, 129.0, 128.9, 127.2, 126.9, 126.2, 102.4; IR (film) *v*: 3067, 2922, 1602, 1575, 1480, 1461, 1446 cm^{-1}; HRMS calcd for $C_{15}H_{11}ClNO$ [M + H] $^+$ 256.0524, found 256.0533.

3-Phenyl-5-(3-(trifluoromethyl)phenyl)isoxazole (**1f**): Yield 205 mg, 71%. White solid, m.p. 115～116 ℃; R_f= 0.38 [*V*(EtOAc)∶*V*(PE)=5∶95]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.08 (s, 1H), 8.03 (d, *J*=7.6 Hz, 1H), 7.89～7.86 (m, 2H), 7.71 (d, *J*=7.6 Hz, 1H), 7.65～7.61 (m, 1H), 7.51～7.47 (m, 3H), 6.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.7, 163.1, 131.6 (J_{C-F}=33 Hz), 130.2, 129.7, 129.0, 128.9 (J_{C-F}=1 Hz), 128.7, 128.1, 126.8, 126.7 (J_{C-F}=4 Hz), 123.7 (J_{C-F}=271 Hz), 122.7 (J_{C-F}=4 Hz), 98.5; IR (film) *v*: 3106, 1621, 1577, 1446, 1420, 1402, 1325 cm^{-1}; HRMS calcd for $C_{16}H_{11}F_3NO$ [M+H]$^+$ 290.0787, found 290.0784.

4-(3-Phenylisoxazol-5-yl)benzonitrile (**1g**)[4j]: Yield 197 mg, 80%. White solid, m.p. 202～203 ℃; R_f=0.45 [*V*(EtOAc)∶*V*(PE)=15∶85]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.95～7.93 (m, 2H), 7.87～7.84 (m, 2H), 7.79～7.77 (m, 2H), 7.51～7.48 (m, 3H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.1, 163.2, 132.8, 131.1, 130.4, 129.0, 128.5, 126.8, 126.2, 118.2, 113.6, 99.6; IR (film) *v*: 3106, 2921, 2851, 2229, 1596, 1495, 1462, 1437 cm^{-1}; HRMS calcd for $C_{16}H_{11}N_2O$ [M+H]$^+$ 247.0866, found 247.0876.

5-(4-Nitrophenyl)-3-phenylisoxazole (**1h**): Yield 205 mg, 77%. Yellow solid, m.p. 230～232 ℃ (lit.[4b] m.p. 225～227 ℃); R_f=0.13 [*V*(EtOAc)∶*V*(PE)=15∶85]; ^{1}H NMR (400 MHz, DMSO) *δ*: 8.44～8.42 (m, 2H), 8.21～8.19 (m, 2H), 7.96～7.94 (m, 3H), 7.61～7.56 (m, 3H); ^{13}C NMR (100 MHz, DMSO) *δ*: 168.0, 163.4, 148.6, 132.7, 131.0, 129.7, 128.5, 127.2, 127.1, 125.1, 102.0; IR (film) *v*: 3106, 1574, 1516, 1489, 1462, 1438, 1339 cm^{-1}; HRMS calcd for $C_{15}H_{11}N_2O_3$ [M+H]$^+$ 267.0764, found 267.0764.

5-(3-Nitrophenyl)-3-phenylisoxazole (**1i**)[17]: Yield 229 mg, 86%. White solid, m.p. 182～183 ℃; R_f=0.48 [*V*(EtOAc)∶*V*(PE)=15∶85]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.67 (s, 1H), 8.24 (d, *J*=2.8 Hz, 2H), 7.88～7.50 (m, 6H), 7.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.7, 163.3, 148.6, 131.3, 130.4, 130.3, 129.0, 128.9, 128.5, 126.8, 124.6, 120.8, 99.2; IR (film) *v*: 3133, 2974, 2882, 1531, 1458, 1436, 1349 cm^{-1}; HRMS calcd for $C_{15}H_{11}N_2O_3$ [M+H]$^+$ 267.0764, found 267.0779.

5-(2,4-Dichlorophenyl)-3-phenylisoxazole (**1j**)[18]: Yield 211 mg, 73%. White solid, m.p. 121～123 ℃; R_f=0.45 [*V*(EtOAc)∶*V*(PE)=5∶95]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.95 (d, *J*=8.4 Hz, 1H), 7.89～7.87 (m, 2H), 7.55 (d, *J*=2.0 Hz, 1H), 7.51～7.47 (m, 3H), 7.42～7.39 (m, 1H), 7.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 165.6, 163.0, 136.3, 132.3, 130.7, 130.2, 130.1, 129.0, 128.8, 127.7, 126.8, 124.8, 102.6; IR (film) *v*: 3072, 2923, 1598, 1551, 1480, 1460, 1438 cm^{-1}; HRMS calcd for $C_{15}H_{10}Cl_2NO$ [M+H]$^+$ 290.0134, found 290.1052.

5-Mesityl-3-phenylisoxazole (**1k**)[19]: Yield 195 mg, 74%. Colorless syrup; R_f=0.50 [*V*(EtOAc)∶*V*(PE)=5∶95]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.90～7.87 (m, 2H), 7.48～7.46 (m, 3H), 6.96 (s, 2H), 6.54 (s, 1H), 2.33 (s, 3H), 2.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 170.5, 162.2, 139.9, 137.9, 129.9, 129.3, 128.9, 128.5, 126.8, 124.7, 102.1, 21.2, 20.3; IR (film) *v*: 3136, 2975, 1617, 1579, 1463, 1442, 1398 cm^{-1}; HRMS calcd for $C_{18}H_{18}NO$ [M+H]$^+$ 264.1383, found 264.1385.

5-(Furan-2-yl)-3-phenylisoxazole (**1l**): Yield 122 mg, 58%. White solid, m.p. 71～73 ℃ (lit.[20] m.p. 76～77 ℃); R_f=0.39 [*V*(EtOAc)∶*V*(PE)=5∶95]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.87～7.83 (m, 2H), 7.56 (dd, *J*= 2.0, 0.8 Hz, 1H), 7.50～7.44 (m, 3H), 6.94 (dd, *J*=3.6, 0.4 Hz, 1H), 6.75 (s, 1H), 6.55 (q, *J*=1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 162.6, 162.0, 144.1, 143.2, 130.1, 128.9, 128.7, 126.8, 111.9, 110.5, 97.1; IR (film) *v*: 3117, 2919, 1622, 1554, 1458, 1439, 1400 cm^{-1}; HRMS calcd for $C_{13}H_{10}NO_2$ [M+H]$^+$ 212.0706, found 212.0706.

(*E*)-3-Phenyl-5-styrylisoxazole (**1m**): Yield 156 mg, 63%. White solid, m.p. 135～137 ℃ (lit.[21] m.p. 135 ℃); R_f=0.51 [*V*(EtOAc)∶*V*(PE)=5∶95]; ^{1}H NMR

(400 MHz, $CDCl_3$) δ: 7.85～7.82 (m, 2H), 7.55～7.53 (m, 2H), 7.49～7.44 (m, 3H), 7.42～7.32 (m, 4H), 6.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9, 162.7, 135.5, 134.9, 129.9, 129.2, 129.1, 128.9, 128.9, 127.1, 126.8, 113.1, 99.5; IR (film) v: 3060, 2922, 1575, 1537, 1495, 1445, 1420 cm^{-1}; HRMS calcd for $C_{17}H_{14}NO$ $[M+H]^+$ 248.1070, found 248.1061.

4-Methyl-3-phenyl-5-(*p*-tolyl)isoxazole (**1n**): Yield 187 mg, 75%. White solid, m.p. 95～96 ℃; R_f = 0.43 [V(EtOAc)∶V(PE)=5∶95]; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69～7.64 (m, 4H), 7.52～7.46 (m, 3H), 7.31 (d, J= 8.0 Hz, 2H), 2.42 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.9, 163.7, 139.7, 129.6, 129.5, 129.3, 128.7, 128.4, 126.8, 125.7, 108.1, 21.4, 9.3; IR (film) v: 3033, 2965, 2919, 1616, 1596, 1513, 1459, 1421 cm^{-1}; HRMS calcd for $C_{17}H_{16}NO$ $[M+H]^+$ 250.1226, found 250.1238.

3-Methyl-5-(*p*-tolyl)isoxazole (**1o**)[4c]: Yield 57 mg, 33%. White solid, m.p. 82～83 ℃; R_f=0.38 [V(EtOAc)∶V(PE)=5∶95]; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.65～7.62 (m, 2H), 7.26～7.23 (m, 2H, overlaps with the peak of chloroform), 6.30 (s, 1H), 2.39 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 160.3, 140.2, 129.5, 125.6, 124.8, 99.5, 21.4, 11.5; IR (film) v: 3034, 2922, 2854, 1618, 1601, 1514, 1441, 1415 cm^{-1}; HRMS calcd for $C_{11}H_{12}NO$ $[M+H]^+$ 174.0913, found 174.0913.

3-Ethyl-5-(*p*-tolyl)isoxazole (**1p**): Yield 120 mg, 64%. White solid, m.p. 40～42 ℃; R_f=0.38 [V(EtOAc)∶V(PE)=5∶95]; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66～7.64 (m, 2H), 7.26～7.24 (m, 2H, overlaps with the peak of chloroform), 6.33 (s, 1H), 2.73 (q, J=7.6 Hz, 2H), 2.39 (s, 3H), 1.32 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7, 165.7, 140.1, 129.5, 125.6, 124.9, 98.2, 21.4, 19.6, 12.7; IR (film) v: 3032, 2979, 2924, 1616, 1597, 1513, 1456, 1425 cm^{-1}; HRMS calcd for $C_{12}H_{14}NO$ $[M+H]^+$ 188.1070, found 188.1079.

3-Pentyl-5-(*p*-tolyl)isoxazole (**1q**): Yield 115 mg, 50%. White semi-solid, R_f=0.50 [V(EtOAc)∶V(PE)=5∶95]; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66～7.64 (m, 2H), 7.26～7.24 (m, 2H), 6.32 (s, 1H), 2.69 (t, J=7.6 Hz, 2H), 2.39 (s, 3H), 1.74～1.67 (m, 2H), 1.40～1.34 (m, 4H), 0.93～0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 164.7, 140.1, 129.5, 125.6, 125.0, 98.5, 31.4, 28.0, 26.1, 22.4, 21.4, 13.9; IR (film) v: 3033, 2924, 2859, 1615, 1597, 1514, 1459, 1422 cm^{-1}; HRMS calcd for $C_{15}H_{20}NO$ $[M+H]^+$ 230.1539, found 230.1540.

3-Isopropyl-5-(*p*-tolyl)isoxazole (**1r**): Yield 87 mg, 43%. Yellow semi-solid; R_f=0.44 [V(EtOAc)∶V(PE)=5∶95]; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66～7.64 (m, 2H), 7.26～7.23 (m, 2H, overlaps with the peak of chloroform), 6.34 (s, 1H), 3.10 (h, J=7.0 Hz, 1H), 2.39 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9, 169.6, 140.1, 129.5, 125.6, 125.0, 96.9, 26.6, 21.8, 21.4; IR (film) v: 3035, 2966, 2918, 1617, 1597, 1513, 1460, 1422 cm^{-1}; HRMS calcd for $C_{13}H_{16}NO$ $[M+H]^+$ 202.1226, found 202.1226.

3-Cyclopropyl-5-(*p*-tolyl)isoxazole (**1s**): Yield 128 mg, 64%. White solid, m.p. 66～67 ℃; R_f=0.41 [V(EtOAc)∶V(PE)=5∶95]; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, J=8.0 Hz, 2H), 7.24 (d, J=8.0 Hz, 2H), 6.12 (s, 1H), 2.38 (s, 3H), 2.07～2.00 (m, 1H), 1.08～1.03 (m, 2H), 0.87～0.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7, 166.9, 140.2, 129.5, 125.6, 124.9, 96.2, 21.4, 8.0, 7.4; IR (film) v: 3014, 2919, 2850, 1616, 1596, 1514, 1428 cm^{-1}; HRMS calcd for $C_{13}H_{14}NO$ $[M+H]^+$ 200.1070, found 200.1066.

3-(*tert*-Butyl)-5-(*p*-tolyl)isoxazole (**1t**): Yield 151 mg, 70%. White solid, m.p. 73～75 ℃; R_f=0.55 [V(EtOAc)∶V(PE)=5∶95]; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66～7.64 (m, 2H), 7.25～7.23 (m, 2H), 6.37 (s, 1H), 2.39 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.6, 169.5, 140.0, 129.5, 125.6, 125.0, 96.8, 32.0, 29.5, 21.4; IR (film) v: 3032, 2957, 2919, 1617, 1598, 1513, 1469, 1456, 1446 cm^{-1}; HRMS calcd for $C_{14}H_{18}NO$ $[M+H]^+$ 216.1383, found 216.1395.

(*E*)-3-(4-Methylstyryl)-5-(*p*-tolyl)isoxazole (**1u**): Yield 149 mg, 54%. White solid, m.p. 189～191 ℃; R_f=0.46 [V(EtOAc)∶V(PE)=5∶95]; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, J=8.0 Hz, 2H), 7.43 (d, J=8.4 Hz, 2H), 7.27 (d, J=8.0 Hz, 2H), 7.21～7.17 (m, 3H), 7.13～7.09 (m, 1H), 6.69 (s, 1H), 2.40 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 162.3, 140.4, 139.0, 135.7, 133.1, 129.61, 129.5, 126.9, 125.7, 124.7, 115.2, 95.8, 21.5, 21.3; IR (film) v: 3020, 2988, 1611, 1593, 1513, 1505, 1429 cm^{-1}; HRMS calcd for $C_{19}H_{18}NO$ $[M+H]^+$ 276.1383, found 276.1396.

5-Phenylisoxazole (**1v**)[4f]: According to General procedure B, the reaction was performed at 80 ℃. Yield 65 mg, 45%. Colourless oil; R_f=0.36 [V(EtOAc)∶V(PE)=5∶95]; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, J=1.6 Hz, 1H), 7.81～7.79 (m, 2H), 7.49～7.42 (m, 3H), 6.52 (d, J=1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 150.8, 130.2, 129.0, 127.2, 125.8, 98.6; IR (film) v: 3063, 2925, 2854, 2218, 1616, 1591, 1571, 1497, 1458 cm^{-1}; HRMS calcd for C_9H_8NO $[M+H]^+$ 146.0600, found 146.0600.

4-Methyl-5-phenylisoxazole (**1w**): According to General procedure B, the reaction was performed at 80 ℃. Yield 72 mg, 45%. Colorless oil; R_f=0.51 [V(EtOAc)∶V(PE)=5∶95]; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.14 (s, 1H), 7.73～7.71 (m, 2H), 7.50～7.40 (m, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1, 153.4, 129.4, 128.8, 128.2, 126.6, 109.4, 8.9; IR (film) v: 3062, 2931, 1630, 1600, 1576, 1462, 1446 cm^{-1}; HRMS calcd for $C_{10}H_{10}NO$ $[M+H]^+$ 160.0757, found 160.0766.

3-Phenyl-4,5,6,7-tetrahydrobenzo[*c*]isoxazole (**1x**): According to general procedure, 0.5 h later, another portion of iodine (0.3 mmol, with 0.6 mmol of K_2CO_3) was added, and then the reaction mixture was kept stirring for another 0.5 h. Yield 147 mg, 74%. White solid, m.p. 57～58 ℃; R_f=0.31 [V(EtOAc)∶V(PE)=5∶95]; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.74 (d, J=7.6 Hz, 2H), 7.46 (t, J=7.6 Hz, 2H), 7.39 (t, J=7.2 Hz, 1H), 2.79～2.78 (m, 4H), 1.87～1.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:

169.3, 150.8, 130.2, 129.0, 127.2, 125.8, 98.6; IR (film) *v*: 3062, 2917, 2850, 1624, 1504, 1440, 1418 cm^{-1}; HRMS calcd for $C_{13}H_{14}NO$ $[M+H]^+$ 200.1070, found 200.1071.

Supporting Information Copies of ^1H NMR and ^{13}C NMR spectra of compounds **1**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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