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MICROWAVE-ASSISTED SYNTHESIS OF PHENYLISOXAZOLE DERIVATIVES VIA 1,3-DIPOLAR CYCLOADDITION

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Abstract – In this paper, an efficient method was developed to prepare phenylisoxazoles *via* metal-free microwave-assisted 1,3-dipolar cycloaddition reaction. Thirty derivatives were synthesized under the optimal condition and identified by NMR and HRMS. The yield was good from 30% to 93%.

INTRODUCTION

Phenylisoxazole is a crucial heterocyclic skeleton, which was mainly used in bioorganic chemistry for its wide range of pharmacological properties.[1] As shown in **Figure 1**, Isoxathion is a broad-spectrum insecticide in agricultural field.[2] Flucloxacillin could effectively use for staphylococcal and streptococcal infections.[3] Valdecoxib is a prominently representative COX-2 inhibitor.[4] It is an excellent choice to treat chronic arthritis pain and acute pain.[5] Recent studies showed that compound A6B3C2 had antithrombotic activity.[6] Shin and co-authors found that compound KRIBB3 performed as anti-proliferative activity by inhibiting microtubule polymerization.[7] In addition, compound XN05 could induce BEL-7402 cells apoptosis by disrupting microtubule assembly.[8] These highly active molecules indicate that phenylisoxazole derivatives have been widely adopted in discovering new bioactive compounds. Therefore, many groups are interested in this framework.[9]

In recent years, microwave irradiation (MW) has attracted much attention in organic synthesis. It has been considered as one of the most simple, green, and environmentally friendly method.[10] Under the condition of MW, lots of slow and tricky reaction could be quickly accomplished. Furthermore, MW could improve the yiled and selectivity.[11] For example, Maksimenko and co-authors reported a regiospecific, and simple Cu(I)-catalyzed MW reaction to prepare isoxazoles.[12] Similarly, Ibrahim and co-authors used this condition to synthesize benzimidazolone-based isoxazoles with remarkable yield.[13] In 2021, Gläsel and co-authors described a new microwave-assisted cycloaddition of diacetylenes with phosphines with more than 90% yield.[14] These results suggested that microwave radiation could accelerate cycloaddition

reaction and increase the yield.[15]

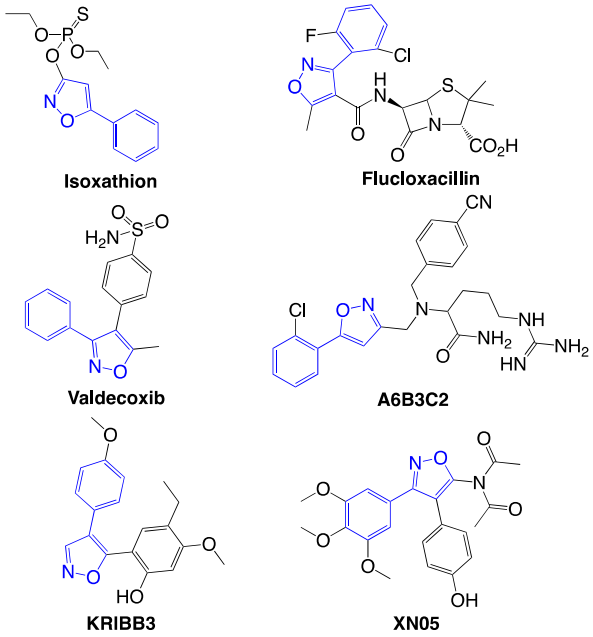


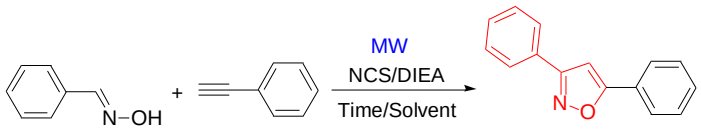
Figure 1. Biologically active skeleton contains phenylisoxazole skeleton

Our group has been focused on the development of new heterocyclic compounds for many years.[16] In 2019, we reported microwave-assisted cycloaddition reaction of 7-azaindole.[17] Recently, we synthesized phenylpyrimidine derivatives *via* Suzuki-Miyaura reaction under MW condition.[18] Based on the broad biological acitivity of phenylisoxazole derivatives and our previous research, we are interested in developing new method to synthesize phenylisoxazoles. In literature, the usual strategy to prepare phenylisoxazoles is metal catalysis. However, it has some disadvantages such as high cost and metal pollution.[19] In this paper, we will describe our efforts to synthesize phenylisoxazoles *via* 1,3-dipolar cycloaddition reaction under microwave radiation.

RESULTS AND DISCUSSION

Initially, we chose the commercially available benzaldoxime **1a** (1 mmol) and phenylacetylene **2a** (1.2 mmol) as starting materials. And we also used *N*-chlorosuccimide (NCS) (2.2 mmol) and *N*,*N*-diisopropylethylamine (DIEA) (1 mmol) to study the reaction in dichloromethane (DCM) under microwave irradiation at 40 °C for 5 min to obtain product **3a** with 38% yield (Table 1, entry 1). In order to increase yield, different solvents were investigated under the condition such as dioxane, DMF, DMSO, THF, and toluene (Table 1, entries 2-6). DMF gave the highest yield with 45% (Table 1, entry 3). Subsequently, the influence of temperature was evaluated.

Table 1. Optimization of the 1,3-dipolar cycloaddition



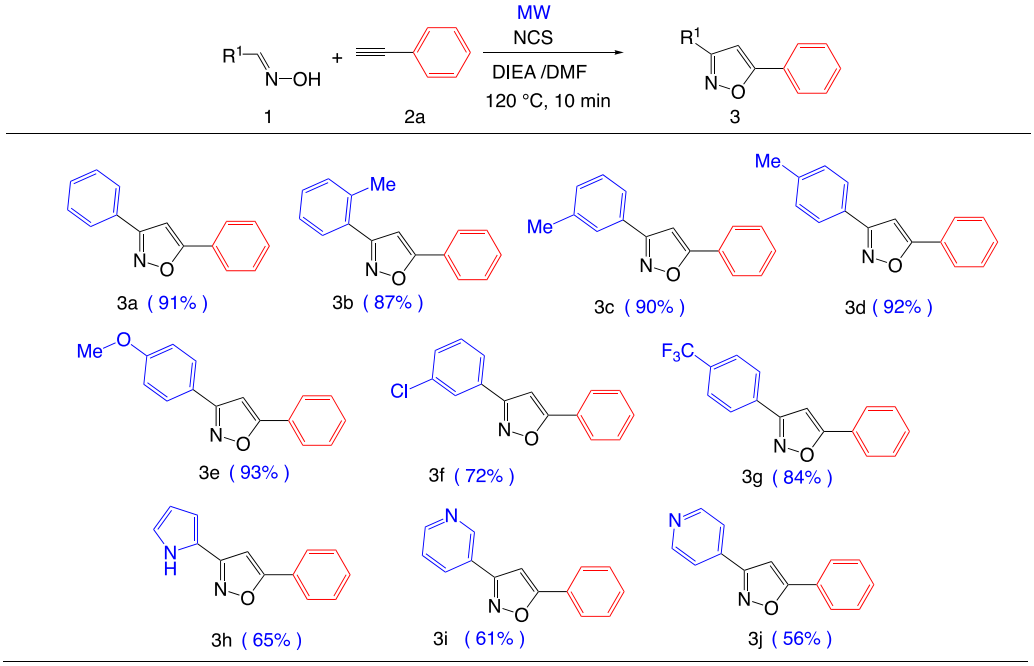
1a **2a** **3a**

Entry	Solvent	T (°C)	Time (min)	Yield (%)[a,b]
1	DCM	40	5	38
2	dioxane	40	5	23
3	DMF	40	5	45
4	DMSO	40	5	14
5	THF	40	5	31
6	toluene	40	5	20
7	DMF	60	5	48
8	DMF	80	5	54
9	DMF	100	5	68
10	DMF	120	5	73
11	DMF	140	5	73
12	DMF	160	5	71
13	DMF	120	5	3[c]
14	DMF	120	50	24[d]
15	DMF	120	0.5	53
16	DMF	120	1	58
17	DMF	120	1.5	60
18	DMF	120	2.5	67
19	DMF	120	7.5	81
20	DMF	120	10	91
21	DMF	120	15	90
22	DMF	120	20	88

[a] Reagents: **1a** (1 mmol), **2a** (1.2 mmol), NCS (2.2 mmol), DIEA (1 mmol), Solvent (2 mL);
[b] Isolated yields;
[c] Reagents: **1a** (1 mmol), **2a** (1.2 mmol), NCS (2.2 mmol), DIEA (1 mmol), DMF (2 mL), 120 °C, 5 min;
[d] Reagents: **1a** (1 mmol), **2a** (1.2 mmol), NCS (2.2 mmol), DIEA (1 mmol), DMF (2 mL), 120 °C, 50 min.

The yield was sharply increased accomplishing with the increase of reaction temperature (Table 1, entries 7-12). In order to compare the conventional method with microwave irradiation, we tried the reaction at 120 ℃ (Conventional heating method) for 5 min to give 3% yield (Table 1, entry 13). When the reaction time was prolonged to 50 min, the yield reached to 24% (Table 1, entry 14). To reduce energy consumption, we chose 120 ℃ under microwave irradiation (Table 1, entry 10) as the optimum condition. At last, MW time was studied for green chemistry. From 0.5 min to 20 min (Table 1, entries 15-22), the isolated yield was increased. The highest yield was 91% at 10 min. After screening various condition in Table 1, we determined that the optimal condition was DMF as solvent at 120 °C for MW 10 min (Table 1, entry 20).

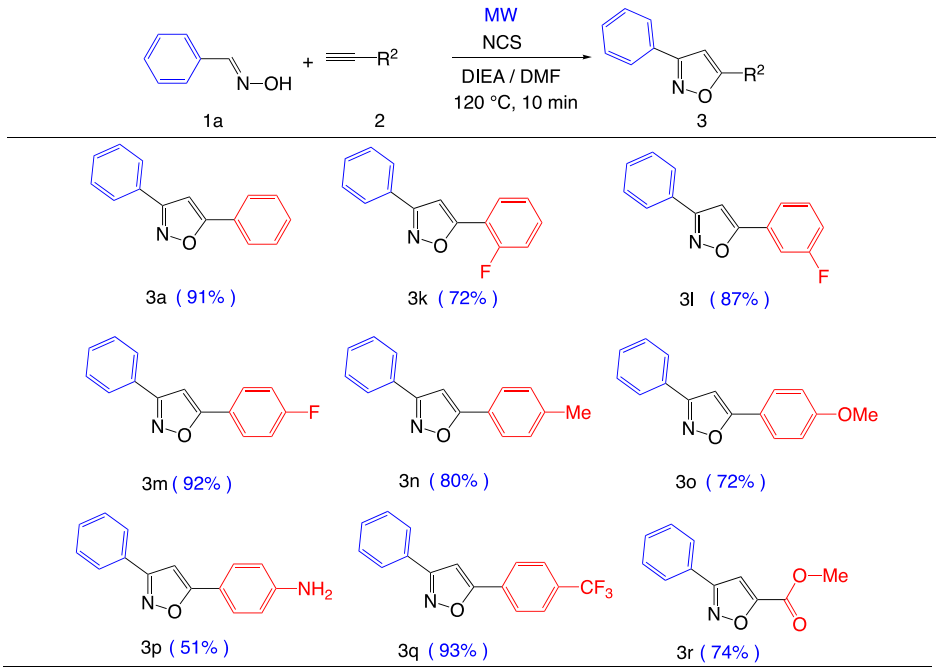
Table 2. 1, 3-Dipolar cycloaddition of **1** and **2a**[a,b]



[a] Reagents: **1** (1 mmol), **2a** (1.2 mmol), NCS (2.2 mmol), DIEA (1 mmol), DMF (2 mL);
[b] Isolated yields.

With the best condition in hand, we discussed the range of different substituted aryloxime **1**. As shown in Table 2, the corresponding yields with *ortho*-methyl group (**3b**), *meta*-methyl group (**3c**), and *para*-methyl group (**3d**) were 87%, 90%, and 92%, respectively. In addition, we found that the electron-donating group -OMe (**3e**) could produce the product with 93% yield and the electron withdrawing group -Cl (**3f**) and -CF_3 (**3g**) gave the yields 72% and 84%. To expand the scope of this 1,3-dipolar cycloaddition, heterocyclic substituted oxime **1** was also used in this reation. Interestingly, the products with 2-pyrrole (**3h**), 3-pyridine (**3i**), and 4-pyridine (**3j**) could be otained with satisfactory yield from 56% to 65%.

Table 3. 1, 3-Dipolar cycloaddition of **1a** and **2**[a,b]

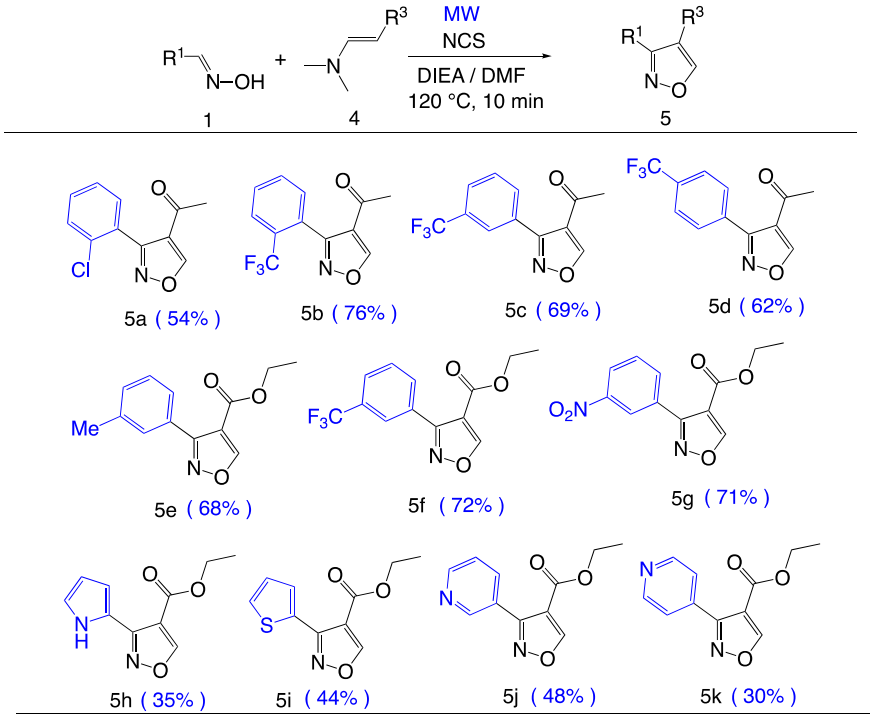


[a] Reagents: **1a** (1 mmol), **2** (1.2 mmol), NCS (2.2 mmol), DIEA (1 mmol), DMF (2 mL);
[b] Isolated yields.

As shown in Table 3, different substituted alkynes **2** were explored. When the substituent of R^2 was -F, the correponding products positions of *ortho* (**3k**), *meta* (**3l**), and *para* (**3m**) were obtained with 72%, 87%, and 92% yields, respectively. The *para*-substitution was the given the best yiled for the presence of steric hindrance. Moreover, the yield of electron-withdrawing group (-CF_3, **3q**) was the highest (93%) and electron-donating groups such as -Me (**3n**), -OMe (**3o**), -NH_2 (**3p**) were reduced to 80%, 72%, 51%, respectively. At last, the ester-substituted alkynes also could provide the corresponding product **3r** with 74% yield.

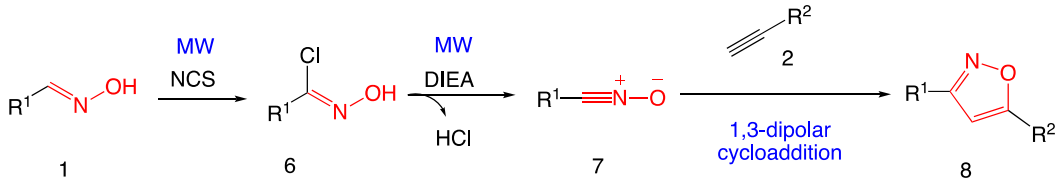
To discuss the tolerance of this reaction, we tried to prepare 3,4-disubstituted phenylisoxazoles. As shown in Table 4, 4-dimethylaminobut-3-en-2-one (**4a**) was used to synthesize compounds **5a-5d**. The yields were from 54% to 76%. Compared **5a** with **5b**, the electron-withdrawing group could give higher yield. The *ortho*-substituted product (**5b**) was more favor than *meta* and *para* substituted derivatives (**5c** and **5d**). And then, (3-dimethylamino)acrylic acid ethyl ester (**4b**) was served to expand the scope of the reaction system. Fortunately, compounds **5e-5g** were obtained with 68%-72% yields. Meanwhile, four kinds of heterocyclic substituted compound **1** were studied with compound **4b**. However, the yields (**5h-5k**) were 30%-48%, which were much lower than the phenyl products **5a-5g**.

Table 4. 1, 3-Dipolar cycloaddition of **1** and **4**[a,b]



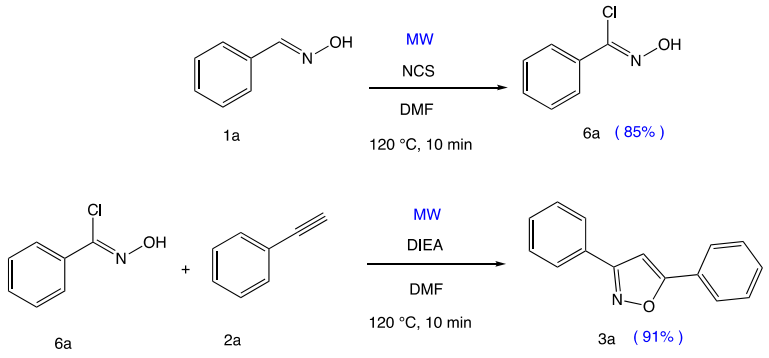
[a] Reagents: **1** (1 mmol), **4** (1.2 mmol), NCS (2.2 mmol), DIEA (1 mmol), DMF (2 mL);
[b] Isolated yields.

In 2013, Rodrigues and co-authors proposed a reasonable mechanism of 1,3-dipolar cycloaddition.[20] On the basis of the previous report, we described a similar mechanism in **Scheme 1**. Firstly, NCS chlorinated oxime **1** to obtain compound **6**. Subsequently, the key intermediate nitrile oxide **7** was formed under the base DIEA. After addition of alkyne **2**, the final products were synthesized through 1,3-dipolar cycloaddition.



Scheme 1. Proposed mechanism

In order to study the transformation of this mechanism, we conducted experiments. Under the optimized conditions (Table 1, entry 18), benzaldehyde oxime **1a** was converted to compound **6a** with 85% yield at the presence of NCS. The NMR spectra of **6a** was consistent with the literature.[21] At last, compound **6a** reacted with phenylacetylene **2a** under the microwave irradiation at 120 ℃ to give the required product **3a** in 91% yield (Scheme 2). The successful complementary experiments in **Scheme 2** proved the correctness of the proposed reaction mechanism.



Scheme 2. Complementary experiments

CONCLUSION

Generally, we developed a new synthetic method to synthesize phenylisoxazole *via* microwave-assisted 1,3-dipolar cycloaddition. This protocol was used DMF as solvent at 120 ℃ for 10 min. Thirty phenylisoxazole derivatives were successfully prepared with 30%-93% yields. This method provides a fast and economical route to obtain various substituted phenylisoxazoles. Further studies are still underway in our lab.

EXPERIMENTAL

All commercial materials were used without further purification. Melting points were determined on a Kofler apparatus as uncorrected values. Analytical thin-layer chromatography was performed on precoated 250 μm layer thickness silica gel 60 F254 plates and visualized with UV light. Column chromatography was performed using silica gel 300-400 mesh. ^{1}H NMR and ^{13}C NMR spectra were measured on 400 MHz spectrometer in DMSO-d_6 or $CDCl_3$ with chemical shift (δ) given in parts per million (ppm) relative to TMS as internal standard and recorded at 25 °C. The high resolution mass spectra (HRMS) were obtained with an electrospray ionization (ESI) using the mass spectrometer QStar Elite (Applied Biosystems SCIEX). The microwave-assisted reaction was performed on a Discover SP microwave reactor-CEM.

Dissolve the corresponding mixture of oxime **1** (2 mmol), enyne **2** or **4** (1.2 mmol), NCS (2.2 mmol), and DIEA (1 mmol) in DMF (3 mL) in a 5 mL microwave glass bottle. Then the microwave bottle was sealed and irradiated in a microwave reactor at 120 ℃ for 10 min, and the absorbance was set to "very high". After cooling, the reaction mixture was extracted with EtOAc (3×20 mL). The combined organic phase was dried over magnesium sulfate, concentrated under reduced pressure, and the crude residue was purified by silica gel column chromatography to give the product **3** and **5**.

3,5-Diphenylisoxazole (3a) Light yellow solid; 91% yield; mp: 129.8-131.2 ℃; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.86 (m, 4H), 7.52 – 7.44 (m, 6H), 6.84 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 163.1, 131.0, 130.8, 129.8, 129.6, 129.1, 127.4, 127.1, 126.1, 99.1; ESI-HRMS $C_{15}H_{11}NO$ ($[M+H]^+$): calcd 222.0913, found 222.0919. Spectral properties were in accordance with the literature.[22]

5-Phenyl-3-(*o*-tolyl)isoxazole (3b) Colorless oil; 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.58 (s, 1H), 7.54 – 7.49 (m, 3H), 7.38 – 7.32 (m, 3H), 6.72 (s, 1H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169. 6, 163.7, 137.0, 134.6, 131.1, 130.2, 129.8, 129.5 (d, *J* = 4.9 Hz), 129.0, 127.5, 126.0, 125.9, 100.2, 21.1; ESI-HRMS $C_{16}H_{13}NO$ ($[M+H]^+$): calcd 236.1069, found 236.1070.

5-Phenyl-3-(*m*-tolyl)isoxazole (3c) White solid; 90% yield; mp: 69.3-71.2 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 2H), 7.71 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.54 – 7.43 (m, 3H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 6.83 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 163.1, 138.7, 130.8, 130.2, 129.0, 129.0, 128.9, 127.5, 127.5, 125.9, 124.0, 97.6, 21.5; ESI-HRMS $C_{16}H_{13}NO$ ($[M+H]^+$): calcd 236.1069, found 236.1066.

5-Phenyl-3-(*p*-tolyl)isoxazole (3d) White solid; 92% yield; mp: 115.5-116.4 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.54 – 7.41 (m, 3H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.81 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 163.0, 140.2, 130.2 129.7, 129.0, 127.5, 126.7, 126.3, 125.9, 97.5, 21.5; ESI-HRMS $C_{16}H_{13}NO$ ($[M+H]^+$): calcd 236.1069, found 236.1066.

3-(4-Methoxyphenyl)-5-phenylisoxazole (3e) White solid; 93% yield; mp: 109.0-112.4 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 4H), 7.54 – 7.41 (m, 3H), 7.06 – 6.97 (m, 2H), 6.78 (s, 1H), 3.87 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 162.6, 161.0, 130.2, 129.0, 128.2, 127.5, 125.8, 121.6, 114.3, 97.3, 55.4; ESI-HRMS $C_{16}H_{13}NO_2$ ($[M+H]^+$): calcd 252.1019, found 252.1020.

3-(3-Chlorophenyl)-5-phenylisoxazole (3f) White solid; 72% yield; mp: 113.2-114.5 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 3H), 7.80 – 7.74 (m, 1H), 7.54 – 7.41 (m, 5H), 6.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 161.9, 135.0, 130.9, 130.5, 130.3, 130.1, 129.1, 127.2, 127.0, 125.9, 124.9, 97.4; ESI-HRMS $C_{15}H_{10}ClNO$ ($[M+H]^+$): calcd 256.0523, found 256.0519.

5-Phenyl-3-(4-(trifluoromethyl)phenyl)isoxazole (3g) White solid; 84% yield; mp: 70.0-72.3 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.88 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.58 – 7.49 (m, 3H), 6.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 161.9, 132.6, 132.1, 131.7, 130.5, 129.1, 127.2, 126.0 (q, *J* = 3.9 Hz), 125.3, 122.5, 97.4; ESI-HRMS $C_{16}H_{10}F_3NO$($[M+H]^+$):calcd 290.0787, found 290.0787.

5-Phenyl-3-(1*H*-pyrrol-2-yl)isoxazole (3h) Pink solid; 65% yield; mp: 122.2-124.3 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 – 7.84 (m, 2H), 7.62 – 7.49 (m, 4H), 7.31 (d, *J* = 4.8 Hz, 1H), 6.96 (td, *J* = 2.8, 1.6 Hz, 1H), 6.68 (m,1H), 6.23 – 6.17 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.2 145.7, 124.7, 123.9, 121.9, 120.8, 117.5, 116.5, 108.6, 107.7, 98.8; ESI-HRMS $C_{13}H_{10}N_2O$ ($[M+H]^+$): calcd 211.0865, found 211.0862.

3-(5-Phenylisoxazol-3-yl)pyridine (3i) Light yellow solid; 61% yield; mp: 138.2-139.7 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (dd, *J* = 2.0, 0.8 Hz, 1H), 8.74 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.36 – 8.27 (m, 1H), 7.98 – 7.89 (m, 2H), 7.72 (s, 1H), 7.64 – 7.53 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.6, 161.0, 151.7, 148.0, 134.5, 131.2, 129.9, 127.1, 126.1, 125.1, 124.7, 99.1; ESI-HRMS $C_{14}H_{10}N_2O$ ([M+H]$^+$): calcd 223.0865, found 223.0871.

4-(5-Phenylisoxazol-3-yl)pyridine (3j) Light yellow solid; 56% yield; mp: 163.2-164.8 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.8, 1.6 Hz, 2H), 7.89 – 7.81 (m, 2H), 7.76 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.56 – 7.46 (m, 3H), 6.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.4, 161.1, 150.6, 136.6, 130.7 129.2, 127.0, 125.9, 121.0, 97.3; ESI-HRMS $C_{14}H_{10}N_2O$ ([M+H]$^+$): calcd 223.0865, found 223.0869.

5-(2-Fluorophenyl)-3-phenylisoxazole (3k) White solid; 72% yield; mp: 66.2-68.6 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 1H), 7.92 – 7.88 (m, 2H), 7.51 – 7.47 (m, 3H), 7.46 – 7.41 (m, 1H), 7.30 (m, 1H), 7.22 (m, 1H), 7.04 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 163.3, 160.3, 158.3, 131.7 (d, *J* = 8.4 Hz), 130.2, 129.1 (d, *J* = 8.4 Hz), 127.8, 127.0, 124.8 (d, *J* = 2.9 Hz), 116.4 (d, *J* = 17.1 Hz), 116.0 (d, *J* = 9.7 Hz), 101.8 (d, *J* = 8.6 Hz); ESI-HRMS $C_{15}H_{10}FNO$ ([M+H]$^+$): calcd 240.0819, found 240.0815.

5-(3-Fluorophenyl)-3-phenylisoxazole (3l) Light yellow solid; 87% yield; mp: 69.3-71.2 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 2H), 7.63 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.49 (dd, *J* = 5.2, 2.0 Hz, 3H), 7.47 – 7.44 (m, 1H), 7.20 – 7.13 (m, 1H), 6.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 164.1 (d, *J* = 11.5 Hz), 163.2, 162.1 (d, *J* = 7.1 Hz), 130.9 (d, *J* = 6.6 Hz), 130.3, 129.4 (d, *J* = 7.0 Hz), 129.1, 126.9, 121.7, 117.3 (d, *J* = 17.1 Hz), 112.9 (d, *J* = 18.5 Hz), 98.4; ESI-HRMS $C_{15}H_{10}FNO$ ([M+H]$^+$): calcd 240.0819, found 240.0815.

5-(4-Fluorophenyl)-3-phenylisoxazole (3m) Light yellow solid; 92% yield; mp: 138.2-140.9 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 4H), 7.51 – 7.45 (m, 3H), 7.23 – 7.14 (m, 2H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 164.9, 163.0 (d, *J* = 28.6 Hz), 130.2, 128.9 (d, *J* = 39.3 Hz), 128.4, 128.0 (d, *J* = 7.4 Hz), 126.9, 123.9, 116.3 (d, *J* = 17.3 Hz), 97.37; ESI-HRMS $C_{15}H_{10}FNO$ ([M+H]$^+$): calcd 240.0819, found 240.0815.

3-Phenyl-5-(*p*-tolyl)isoxazole (3n) White solid; 80% yield; mp: 129.8-131.2 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.44 (m, 3H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.78 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 163.0, 140.6 , 130.0, 129.7, 129.2, 128.9, 126.8, 125.8, 124.8, 96.9, 21.6; ESI-HRMS $C_{16}H_{13}NO$ ([M+H]$^+$): calcd 236.1069, found 236.1066.

5-(4-Methoxyphenyl)-3-phenylisoxazole (3o) Light yellow solid; 72% yield; mp: 106.1-108.2 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.81 – 7.75 (m, 2H), 7.52 – 7.44 (m, 3H), 7.05 – 6.97 (m, 2H), 6.71 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 150.4, 149.0, 124.0, 123.5, 123.2, 122.0, 121.5, 116.3, 111.6, 97.0, 64.4; ESI-HRMS $C_{16}H_{13}NO_2$ ([M+H]$^+$): calcd 252.1019,

found 252.1015.

4-(3-Phenylisoxazol-5-yl)aniline (3p) Earth-yellow solid; 51% yield; mp: 108.1-110.7 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 2H), 7.66 (d, *J* = 6.8 Hz, 2H), 7.48 (s, 3H), 6.81 – 6.61 (m, 3H), 3.97 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 162.9, 148.4, 129.8, 129.5, 128.9, 127.4, 126.8, 117.9, 114.9, 95.2; ESI-HRMS $C_{15}H_{12}N_2O$ ($[M+H]^+$): calcd 237.1022, found 237.1020.

3-Phenyl-5-(4-trifluoromethylphenyl)isoxazole (3q) Light yellow solid; 93% yield; mp: 166.1-167.9 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.90 – 7.85 (m, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.54 – 7.47 (m, 3H), 6.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 163.2, 132.1, 131.8, 130.6, 130.3, 129.0, 128.7, 126.9, 126.1 (q, *J* = 4.1 Hz), 125.1, 99.0; ESI-HRMS $C_{16}H_{10}F_3NO$ ($[M+H]^+$): calcd 290.0787, found 290.0784.

3-Phenylisoxazole-5-carboxylic acid methyl ester (3r) White solid; 74% yield; mp: 86.4-87.8 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.96 (m, 2H), 7.94 (s, 1H), 7.55 (dd, *J* = 6.8, 3.6 Hz, 3H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3, 160.7, 157.2, 131.3, 129.7, 127.9, 127.3, 108.5, 53.4; ESI-HRMS $C_{11}H_9NO_3$ ($[M+H]^+$): calcd 204.0655, found 204.0656.

1-[3-(2-Chlorophenyl)-isoxazol-4-yl]ethanone (5a) Light yellow solid; 54% yield; mp: 65.5-67.3 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.52 – 7.49 (m, 1H), 7.46 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.39 (dd, *J* = 10.4, 4.0 Hz, 1H), 2.34(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 162.2, 159.0, 133.9, 131.3, 131.1, 129.8, 127.5, 126.9, 122.3, 29.0; ESI-HRMS $C_{11}H_8ClNO_2$ ($[M+H]^+$): calcd 222.0316, found 222.0314.

1-[3-(2-Trifluoromethylphenyl)isoxazol-4-yl]ethanone (5b) White solid; 76% yield; mp: 82.7-84.8 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.86 – 7.77 (m, 1H), 7.71 – 7.58 (m, 2H), 7.49 – 7.38 (m, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 162.0, 159.0, 131.6, 131.3, 130.0, 129.7, 129.4, 126.7 (q, *J* = 4.9 Hz), 124.9, 122.3, 29.1; ESI-HRMS $C_{12}H_8F_3NO_2$ ($[M+H]^+$): calcd 278.0399, found 278.0395.

1-[3-(3-Trifluoromethylphenyl)isoxazol-4-yl]ethanone (5c) Light yellow oil; 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.03 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 163.8, 159.8, 132.9, 130. 8 (q, *J* = 32.5 Hz), 128.8, 128.2, 126.7, 125.2, 122.5, 120.5, 29.7; ESI-HRMS $C_{12}H_8F_3NO_2$ ($[M+Na]^+$): calcd 278.0399, found 278.0392.

1-[3-(4-Trifluoromethylphenyl)isoxazol-4-yl]ethanone (5d) White solid; 62% yield; mp: 100.2-102.8 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 163.8, 159.9, 132.2 (q, *J* = 25.1 Hz), 131.1, 130.0, 125.3, 120.7, 29.7; ESI-HRMS $C_{12}H_8F_3NO_2$ ($[M+H]^+$): calcd 256.0579, found 256.0565.

(3-*m*-Tolyl)isoxazole-4-carboxylic acid ethyl ester (5e) Colorless transparent oil; 68% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.28 (m, 2H), 4.29 (q, *J* = 7.2 Hz, 2H),

2.42 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.4, 161.0, 137.9, 130.9, 130.0, 128.1, 127.1, 126.7, 113.1, 61.1, 21.4, 14.1; ESI-HRMS $C_{13}H_{13}NO_3$ ($[M+H]^+$): calcd 232.0968, found 232.0969.

3-(3-Trifluoromethylphenyl)isoxazole-4-carboxylic acid ethyl ester (5f) Colorless transparent oil; 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.09 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 161.0, 160.2, 132.9, 130.8 (q, *J* = 32.5 Hz), 128.8, 128.2, 127.9, 125.2, 122.5, 113.2, 61.4, 14.1; ESI-HRMS $C_{13}H_{10}F_3NO_3$ ($[M+H]^+$): calcd 286.0685, found 286.0675.

3-(3-Nitrophenyl)isoxazole-4-carboxylic acid ethyl ester (5g) White solid; 71% yield; mp: 77.2-79.8 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.74 (t, *J* = 2.0 Hz, 1H), 8.37 (m, 1H), 8.21 – 8.13 (m, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 160.6, 159.5, 148.1, 135.4, 129.3, 129.1, 124.9, 124.8, 113.1, 61.6, 14.1; ESI-HRMS $C_{10}H_{10}N_2O_3$ ($[M+Na]^+$): calcd 285.0481, found 285.0477.

3-(1*H*-Pyrrol-2-yl)isoxazole-4-carboxylic acid ethyl ester (5h) Pink solid; 35% yield; mp: 60.1-62.3 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 9.64 (s, 1H), 7.03 (dd, *J* = 3.6, 2.8 Hz, 1H), 6.18 (dd, *J* = 4.0, 2.4Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.6, 161.2, 152.8, 118.0, 117.9, 114.6, 111.7, 107.9, 61.5, 14.5; ESI-HRMS $C_{10}H_{10}N_2O_3$ ($[M+H]^+$): calcd 207.0764, found 207.0762.

(3-Thiophen-2-yl)isoxazole-4-carboxylic acid ethyl ester (5i) Light yellow solid; 44% yield; mp: 44.7-46.2 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.08 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.81 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.25 (dd, *J* = 5.2, 4.0 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.9, 148.8, 144.2, 125.8, 124.2, 122.8, 122.1, 109.7, 69.3, 31.6; ESI-HRMS $C_{10}H_9NO_3S$ ($[M+H]^+$): calcd 224.0375, found 224.0376.

(3-Pyridin-3-yl)isoxazole-4-carboxylic acid ethyl ester (5j) White solid; 48% yield; mp: 89.1-91.2 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (s, 1H), 8.87 (dd, *J* = 2.0, 0.8 Hz, 1H), 8.73 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.21 – 8.09 (m, 1H), 7.56 (m, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.7, 160.7, 158.9, 151.5, 149.8, 137.5, 124.0, 123.8, 113.2, 61.4, 14.4; ESI-HRMS $C_{11}H_{10}N_2O_3$ ($[M+H]^+$): calcd 219.0764, found 219.0762.

(3-Pyridin-4-yl)isoxazole-4-carboxylic acid ethyl ester (5k) Light yellow solid; 30% yield; mp: 62.3-64.1 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.75 (dd, *J* = 4.8, 1.6 Hz, 2H), 7.74 (dd, *J* = 4.4, 1.6 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 160.5, 159.3, 149.8, 135.4, 123.8, 113.2, 61.5, 14.1; ESI-HRMS $C_{11}H_{10}N_2O_3$ ($[M+H]^+$): calcd 219.0764, found 219.0761.

Benzaldehyde oxime (2 mmol) and NCS (1.2 mmol) were mixed and stirred in DMF (3 mL) at room

temperature for 1 h. After the combined organic layer was concentrated to dryness in vacuo, the product was purified by silica gel column chromatography (petroleum ether: EtOAc= 12:1) to give **6a**.

(*Z*)-*N*-Hydroxybenzimidoyl chloride (6a) Yellow oil; 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.50 (m, 3H), 7.85 (dd, J = 8.0, 1.6 Hz, 2H), 8.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 132.5, 130.7, 128.5, 127.2. Spectral properties were in accordance with the literature.[21]

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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