JOC The Journal of Organic Chemistry

UT DALLAS

Subscriber access provided by UNIV OF TEXAS DALLAS

Article

Synthesis of 4-Sulfenyl Isoxazoles through AlCl3-Mediated Electrophilic Cyclization and Sulfenylation of 2-Alkyn-1-one O-Methyloximes

Wen-Chao Gao, Yu-Fei Cheng, Hong-Hong Chang, Xing Li, Wen-Long Wei, and Peng Yang

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b00256 • Publication Date (Web): 13 Mar 2019

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of 4-Sulfenyl Isoxazoles through $AlCl_3$-Mediated Electrophilic Cyclization and Sulfenylation of 2-Alkyn-1-one *O*-Methyloximes

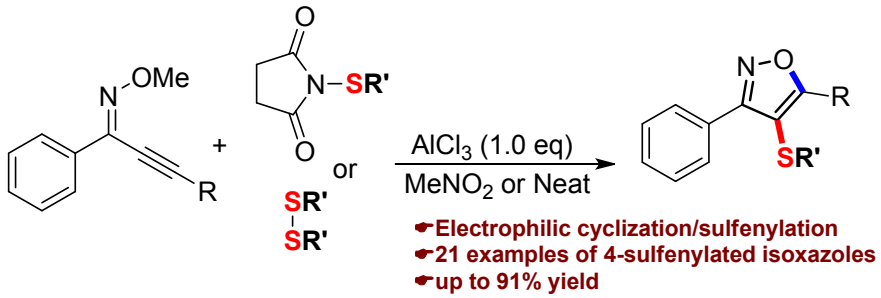
Wen-Chao Gao,[a]* Yu-Fei Cheng,[a] Hong-Hong Chang,[a] Xing Li,[a] Wen-Long Wei[a] and Peng Yang[b]*

[a] College of Biomedical Engineering, Taiyuan University of Technology, Taiyuan 030024, P. R. China

[b] College of Chemistry, Chemical Engineering and Material Science, Shandong Normal University, Jinan 250014, P. R. China

*E-mail: gaowenchao@tyut.edu.cn; yangpeng@sdnu.edu.cn

Abstract: An efficient method for the synthesis of 4-sulfenyl isoxazoles has been developed via $AlCl_3$-mediated electrophilic cyclization/sulfenylation of 2-alkyn-1-one *O*-methyloximes. Remarkably, *N*-arylsulfanylsuccinimides are employed as electrophiles for the construction of 4-arylsulfanyl isoxazoles, and 4-alkylsulfanyl isoxazoles are accessed with dialkyl disulfides as electrophiles.

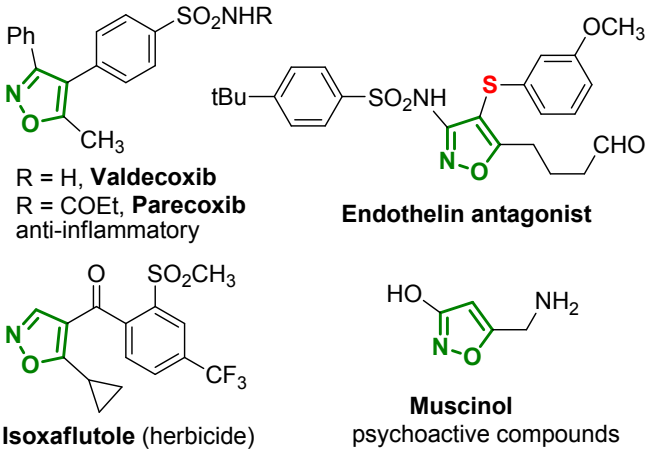


Introduction

Isoxazole skeleton is an important framework and a critical pharmacophore with a variety of biological activities (Figure 1),[1] and it ranked 33rd in frequency among the 351 ring systems found in marketed drugs according to a recent survey.[2] Sulfur is also a ubiquitous element in biologically active natural products and medicinal molecules,[3] and

replacement of heterocycle rings with sulfenylated ones provides a useful way to modulate substituent trajectories for optimizing complementarity and fitting within a ligand binding pocket in drug design.[4] Although many synthetic methods have been developed to construct functionalized isoxazole derivatives,[5] the synthetic route to access 4-sulfenyl isoxazoles has been less studied. A representative and conventional synthetic route for 4-sulfenyl isoxazoles was the reaction of thiosulfonates or disulfides with 4-isoxazolyl anion species, which was generated at low temperature under strong basic conditions (Scheme 1, eq 1).[6]

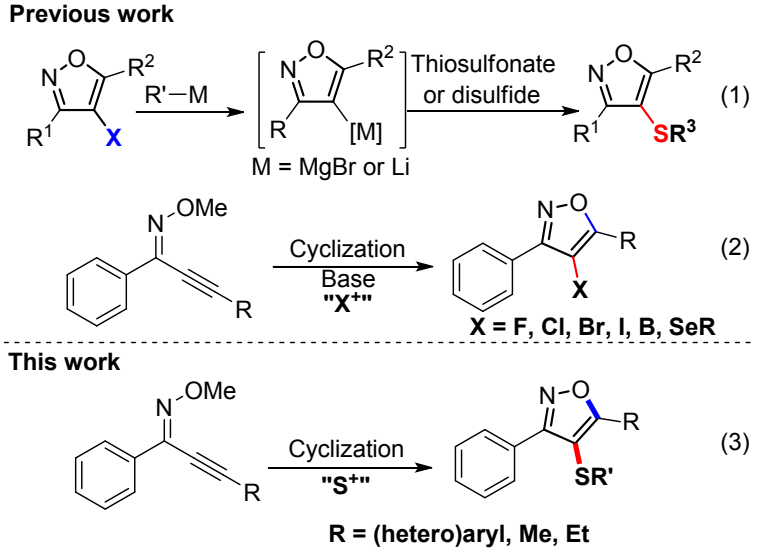
Figure 1. Examples Containing Isoxazole Skeleton



Since the pioneer work for the synthesis of 4-iodo isoxazoles via electrophilic cyclization of 2-alkyn-1-one *O*-methyloximes was developed by Larock,[7] electrophilic cyclization of oximes employing different electrophiles has become a powerful protocol to building 4-functionalized isoxazoles,[8] due to its easy availability of starting materials, high efficiency and excellent regioselectivity. A series of isoxazole derivatives such as 4-fluoro, selenyl, and boryl isoxazoles have been successfully accessed using this

protocol (Scheme 1, eq 2).[8c-e] However, the electrophilic sulfenylation of 2-alkyn-1-one *O*-methyloximes, which can enable the construction of 4-sulfenyl isoxazoles, seems feasible but never been established. Principally this is attributed to the sulfenylation/halogenation of alkynyl derivatives with traditional *S*-electrophile (e.g. sulfenyl choloride), which is competitive to electrophilic cyclization and cannot be avoided properly.[9] As our continuous work in the preparation of sulfur-containing compounds,[10] herein we would like to report the electrophilic sulfenylation of 2-alkyn-1-one *O*-methyloximes using *N*-sulfanylsuccinimides or disulfides as electrophiles, which could access the synthesis of 4-sulfenyl isoxazoles under mild reaction conditions.

Scheme 1. Different Methods for the Synthesis of 4-Functionalized Isoxazoles

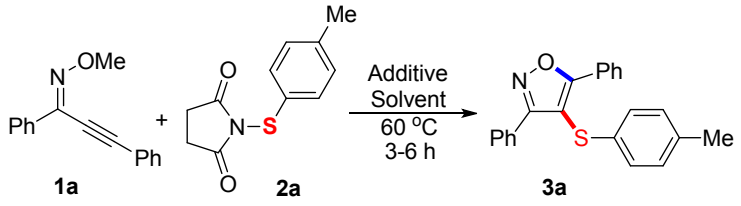


Results and Discussion

We commenced our study with the reaction of 2-alkyn-1-one *O*-methyloxime **1a** and *N*-tolylsulfanylsuccinimde **2a** using $ClCH_2CH_2Cl$ (DCE) as solvent. In the absence of any

additives, neither of starting materials were consumed (entry 1). The desired 4-tolylsulfanyl isoxazole **3a** was produced in 67% yield (entry 2) when 1.0 equiv of $AlCl_3$ was employed. Further investigation on the reaction solvents showed that CH_3NO_2 was the optimal solvent for this transformation (entries 3-7), and **3a** could be isolated in 86% yield (entry 7). Lowering the amount of $AlCl_3$ would resulted in the decrease of yield of **3a** (entry 8). Other kinds of additives such as $ZnCl_2$, BF_3•Et_2O, $FeCl_3$, trifluoroacetic acid (TFA), and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) were all tried for this reaction, while none of them gave a better result than $AlCl_3$ (entries 9-13). Attempts to increase or lower the reaction temperature lead to the decrease of reaction efficiency (entries 14 and 15). We also attempted this cyclization using the known *S*-electrophiles **4** and **5**, however, the formation of disulfides or chlorothiolation of C-C triple bond was detected as major process (entries 16 and 17). In addition, the disulfide **6** was also tested for this cyclization, and the desired product **3a** was only afford in 32% yield (entry 18).

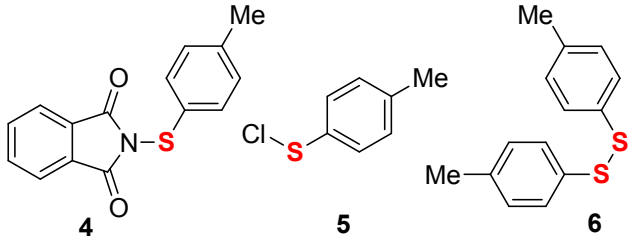
Table 1. Optimization of Reaction Conditions[a]



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

Entry	Additive (eq)	Solvent	Yield[b](%)
1	--	DCE	0
2	$AlCl_3$ (1.0)	DCE	67
3[c]	$AlCl_3$ (1.0)	CH_2Cl_2	32
4	$AlCl_3$ (1.0)	$CHCl_3$	86

5	$AlCl_3$ (1.0)	MeCN	46
6	$AlCl_3$ (1.0)	Toluene	12
7	$AlCl_3$ (1.0)	CH_3NO_2	91 (86[d])
8	$AlCl_3$ (0.75)	CH_3NO_2	78
9	$ZnCl_2$ (1.0)	CH_3NO_2	0
10	BF_3•Et_2O (1.0)	CH_3NO_2	3
11	$FeCl_3$ (1.0)	CH_3NO_2	6
12	TFA (1.0)	CH_3NO_2	0
13	DBU (1.0)	CH_3NO_2	0
14[e]	$AlCl_3$ (1.0)	CH_3NO_2	67
15[f]	$AlCl_3$ (1.0)	CH_3NO_2	74
16[g]	$AlCl_3$ (1.0)	CH_3NO_2	16
17[h]	$AlCl_3$ (1.0)	CH_3NO_2	10
18[i]	$AlCl_3$ (1.0)	CH_3NO_2	32

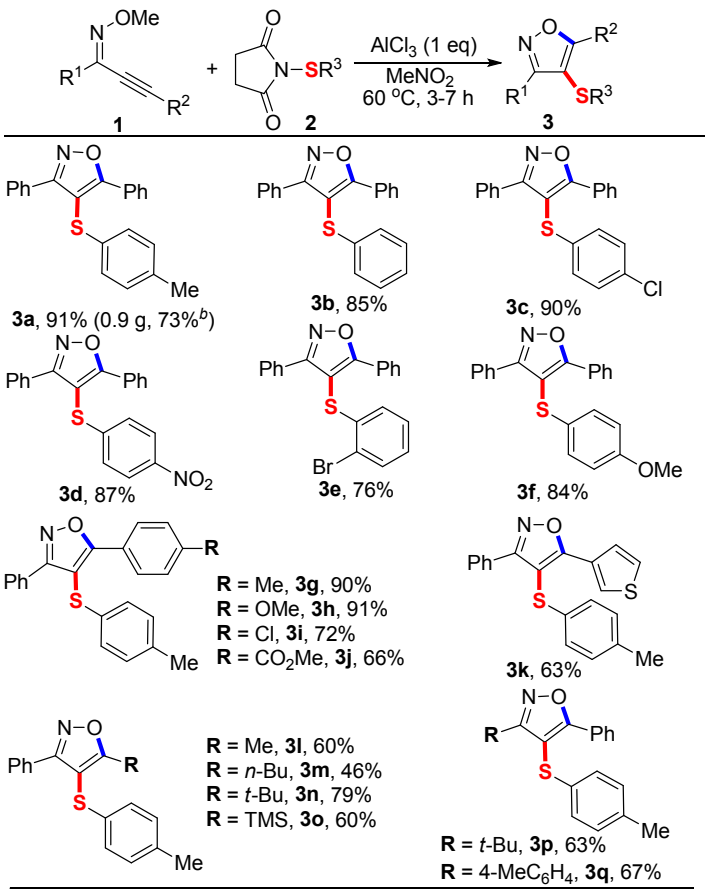


[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.225 mmol), and additive (0.15 mmol) in solvent (1.5 mL) at 60 °C for 3-6 h. [b] Yield determined by GC analysis using *n*-dodecane as the internal standard. [c] The reaction was run at reflux. [d] Isolated yield. [e] Reaction temperature: 45 °C. [f] Reaction temperature: 90 °C. [g] **2a** was replaced by **4**. [h] **2a** was replaced by **5**. [i] **2a** was replaced by **6**.

With the optimal conditions in hand (Table 1, entry 7), we explored the substrate scope of this cyclization reaction. As is shown in Table 2, a series of *N*-arylsulfanylsuccinimides, regardless of electron-donating or -withdrawing group on the

phenyl ring, could efficiently induce the cyclization to produce the desired 4-isoxazolyl sulfides in good to excellent yields (**3a**-**f**). Notably, the present transformation could be effectively scaled up to gram scale despite slight decrease in reaction efficiency (73% yield of **3a**). Next, the influence of electronic effects on the aromatic rings directly linked to the triple bond of the alkynone *O*-methyloximes was examined. The results demonstrated that substrates bearing electron-donating groups (Me and MeO) could give better yields than the ones with electron-withdrawing groups (**3g**, **h** vs **3i, j**), and the thienyl group could also be tolerated in this transformation (**3k**). The structure of **3i** was further confirmed by X-ray crystallographic analysis. When the aromatic ring tethered to the triple bond was replaced by alkyl or silyl group, the reaction could still work well, despite a little decrease in reaction efficiency (**3l-o**). Additionally, the variation on the *O*-methyloxime moiety were also tried, and products containing either the bulkyl *tert*-butyl group or substituted phenyl ring attached to the *O*-methyloxime moiety were afforded in moderate yields.

Table 2. Synthesis of 4-Arylsulfanyl Isoxazoles[a]

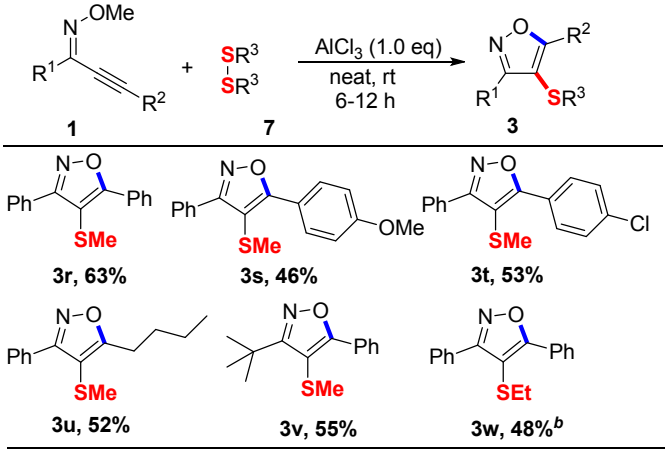


[a] Reaction conditions: **1** (0.15 mmol), **2** (0.225 mmol), $AlCl_3$ (0.15 mmol), $MeNO_2$ (1.5 mL), at 60 °C for 3-7 h. Isolated yields are shown. [b] The reaction was run on a 3.6 mmol scale.

Notably, methyl sulfides are valuable units in modern pharmaceutical science (e.g., Thioridazine and Simetryn), and many synthetic methods have been developed to introduce the "MeS" group to organic molecules.[11] In our initial attempt to the synthesis of 4-sulfenyl isoxazoles, when *N*-methylthiosuccinimide was subjected to the cyclization process, no desired 4-methylthio isoxazoles were detected under the optimized conditions. Fortunately, inspired by Zeni's work,[12] it was found that in the presence of $AlCl_3$, the dimethyl disulfide could induce the cyclization to access 4-methylthio isoxazoles under neat conditions (For details, see SI). The generality of this cyclization/methylthiolation

was also tested (Table 3), and all the 4-isoxazolyl methyl sulfides could be produced in moderate yields (**3r-v**). Furthermore, the diethyl disulfide could also be served as an electrophile to induce the cyclization of 2-alkyn-1-one oxime **1a** to afford **3w** in 48% yield.

Table 3. Synthesis of 4-Alkylsulfanyl Isoxazoles[a]

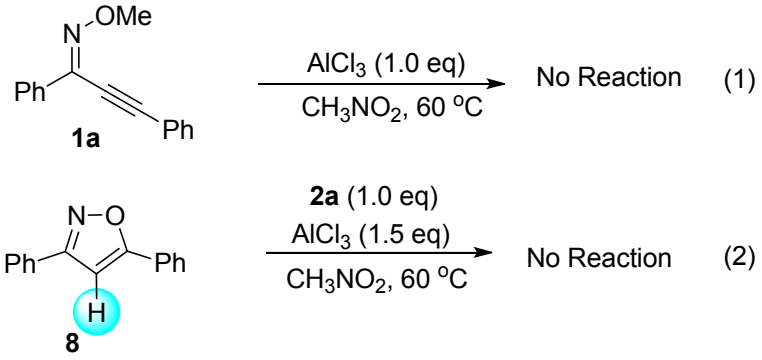


[a] Reaction conditions: **1** (0.15 mmol), **7** (0.225 mmol), $AlCl_3$ (0.15 mmol), stirred at room temperature for 6-12 h. Isolated yields are shown. [b] The reaction was run in DCE (1.5 mL) at 60 °C.

To give a clear understanding of the mechanism, several control experiments were consequently carried out. When the oxime **1a** was submitted to $AlCl_3$-mediated reaction in the absence of *N*-arylsulfanylsuccinimides (**2a**) (Scheme 2, eq 1), or likewise when the same substrate reacted with **2a** in the absence of $AlCl_3$ (Table 1, entry 1), no cyclized product was detected in both reactions. Furthermore, the reaction of 4-unsubstituted isoxazoles **8** with **2a** could not give any product under standard conditions (Scheme 2, eq 2). These results indicated that the sulfenylation and cyclization process probably underwent simultaneously. In addition, the reaction mixture was also detected using MS

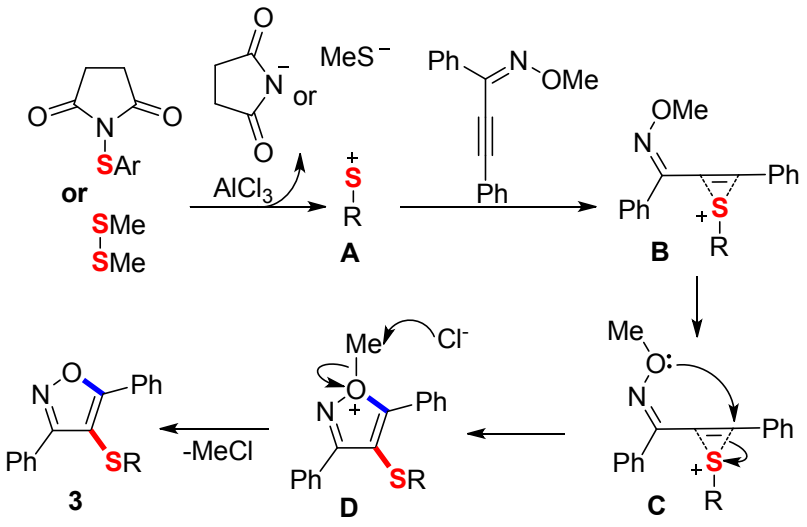
analysis, and the signal of a sulfenium cation intermediate $[358.13]^+$ was obviously captured (for details, see SI), which further confirmed that the cyclization was induced by *S*-electrophiles.

Scheme 2. Control Experiments



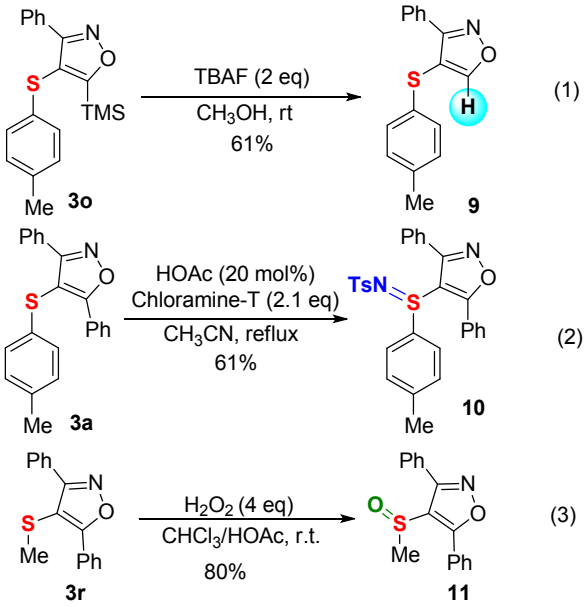
Based on these experimental results, a possible reaction mechanism was proposed in Scheme 3. The activation of *N*-arylsulfanylsuccinimides or dimethyl disulfide with $AlCl_3$ would give sulfenium cation **A**, which could react with C-C triple bond to form intermediate **B**. Subsequently, intramolecular cyclization via nucleophilic attack of oxygen to the activated Csp resulted in the formation of intermediate **D**, which underwent demethylation to afford the desired 4-isoxazolyl sulfides **3**.

Scheme 3. Proposed Reaction Mechanism



Diversified derivation is further demonstrated using the obtained 4-sulfenyl isoxazoles. For example, desilylation of **3o** proceeded smoothly to access the 3-unsubsituted 4-sulfenyl isoxazoles **9** (Scheme 4, eq 1). Furthermore, using different oxidative conditions, the 4-sulfenyl isoxazoles products could be successfully transformed to either *N*-tosyl sulfilimine **10** or 4-sulfinyl isoxazole **11**.

Scheme 4. Derivation of 4-sulfenyl isoxazoles



Conclusions

In summary, this work provides a simple and practical protocol to 4-sulfenylated isoxazoles, which were formed through $AlCl_3$-mediated electrophilic cyclization/sulfenylation of 2-alkyn-1-one *O*-methyloximes. *N*-Arylsulfanylsuccinimides were used as electrophiles for 4-arylsulfanyl isoxazoles whereas the 4-alkylsulfanyl ones were accessed by employing dialkyl disulfides as electrophiles instead. For the mechanism studies, the key sulfenium cation was obviously detected by MS analysis. The diversified derivation of desired products expressed the synthetic potential for 4-sulfur-containing isoxazoles construction. Further study on the application of this methodology and biological activities of these isoxazolyl sulfides is underway.

Experimental Section

General. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz), were recorded using NMR spectrometers with $CDCl_3$ as the solvent. Chemical shifts (δ) were measured in ppm and referenced to the deuterated chloroform (^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.00 ppm). High-resolution mass spectrometry (HRMS) was performed on a Q-TOF spectrometer instrument with an ESI source. Melting points were measured with a RD-II type melting point apparatus (uncorrected). X-ray structural analysis was obtained with an X-ray single-crystal diffractometer. Commercially available reagents were used without further purification. 2-Alkyn-1-one *O*-methyloximes[8] and *N*-Sulfanylsuccinimides[10] are prepared following previous reports. Petroleum ether (PE), where used, has the boiling point range of 60−90 °C. For column chromatography, silica gel (200−300 mesh) was used with EtOAc and PE as eluent.

General Procedure for the Synthesis of 3a-q.

In a 10 mL flask, under ambient atmosphere, the solution of 3-diphenylprop-2-yn-1-one *O*-methyl oxime (**1a**, 0.15 mmol), *N*-tolylthiosuccinimides (**2a**, 0.225 mmol, 1.5 equiv) and $AlCl_3$ (0.15 mmol, 1.0 equiv) in CH_3NO_2 (1.5 mL) was stirred at 60 °C using oil bath for 6 h. After that time, the residue was purified by chromatography column on silica gel or preparative TLC to afford the desired product **3a**.

*Gram scale synthesis of **3a***. In a 25 mL flask, under ambient atmosphere, the solution of 3-diphenylprop-2-yn-1-one *O*-methyl oxime (**1a**, 3.6 mmol, 0.85 g), *N*-tolylthiosuccinimides (**2a**, 5.4 mmol, 1.2 g) and $AlCl_3$ (3.6 mmol, 0.48 g) in CH_3NO_2 (6 mL) was stirred at 60 °C using oil bath for 12 h. The resulted reaction mixture was diluted with CH_2Cl_2 (30 mL), and washed with H_2O (10 mL×3). The organic phase was dried with anhydrous Na_2SO_4, concentrated under vacuum and purified by chromatography column to afford **3a** (0.90 g, 73% yield).

3,5-Diphenyl-4-(*p*-tolylthio)isoxazole (3a)

Yield: 46.8 mg (91%); time: 3 h; yellow solid; m.p. 82-84 ^oC; TLC, R_f = 0.37 (PE:EtOAc = 19:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.16-8.13 (m, 2H), 7.81 (dd, 2H, J = 7.6 Hz, J = 1.2 Hz), 7.50-7.39 (m, 6H), 7.05-6.98 (m, 4H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 172.2, 165.1, 135.8, 132.5, 130.9, 130.1, 130.0, 128.8, 128.53, 128.47, 128.2, 127.4, 127.0, 126.2, 102.3, 20.9; HRMS (ESI) m/z calcd for $C_{22}H_{18}NOS$ $[M + H]^+$: 344.1104, found: 344.1102.

3,5-Diphenyl-4-(phenylthio)isoxazole (3b)

Yield: 41.9 mg (85%); time: 3 h; yellow solid; m.p. 88-90 °C; TLC, R_f = 0.35 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15-8.11 (m, 2H), 7.80 (dd, 2H, J = 7.6 Hz, J = 1.2 Hz), 7.49-7.47 (m, 3H), 7.42-7.39 (m, 3H), 7.22 (t, 2H, J = 7.6 Hz), 7.12 (t, 3H, J = 8.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.4, 165.1, 136.1, 131.0, 130.0, 129.3, 128.8, 128.5, 128.1, 127.4, 127.0, 126.0, 125.9, 101.8; HRMS (ESI) m/z calcd for $C_{21}H_{16}NOS$ $[M + H]^+$: 330.0947, found: 330.0941.

4-((4-Chlorophenyl)thio)-3,5-diphenylisoxazole (3c)

Yield: 49.0 mg (90%); time: 3.5 h; white solid; m.p. 124-126 °C; TLC, R_f = 0.40 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13-8.09 (m, 2H), 7.78 (dd, 2H, J = 7.6 Hz, J = 1.2 Hz), 7.50-7.41 (m, 6H), 7.19 (d, 2H, J = 8.8 Hz), 7.03 (d, 2H, J = 8.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.5, 164.9, 134.6, 131.9, 131.1, 130.1, 129.4, 128.9, 128.6, 128.4, 127.9, 127.4, 127.2, 126.8, 101.4; HRMS (ESI) m/z calcd for $C_{21}H_{15}ClNOS$ $[M + H]^+$: 364.0557, found: 364.0558.

4-((4-Nitrophenyl)thio)-3,5-diphenylisoxazole (3d)

Yield: 48.8 mg (87%); time: 3.5 h; yellow solid; m.p. 128-130 °C; TLC, R_f = 0.33 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (t, 4H, J = 8.8 Hz), 7.76 (dd, 2H, J = 7.6 Hz, J = 1.2 Hz), 7.52-7.38 (m, 6H), 7.21 (d, 2H, J = 8.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 173.1, 164.8, 145.8, 145.6, 131.5, 130.4, 129.0, 128.7, 128.2, 127.6, 127.3, 126.4, 126.3, 125.4, 124.5, 124.4, 99.4; HRMS (ESI) m/z calcd for $C_{21}H_{15}N_2O_3S$ $[M + H]^+$: 375.0798, found: 375.0788.

4-((2-Bromophenyl)thio)-3,5-diphenylisoxazole (3e)

Yield: 46.4 mg (76%); time: 7 h; yellow solid; m.p. 149-151 °C; TLC, R_f = 0.35 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10-8.06 (m, 2H), 7.79 (dd, 2H, J = 7.6 Hz, J = 2.0 Hz), 7.53 (dd, 1H, J = 7.6 Hz, J = 1.2 Hz), 7.50-7.46 (m, 3H), 7.43-7.40 (m, 3H), 7.11 (t, 1H, J = 8.8 Hz), 6.98 (t, 1H, J = 9.2 Hz), 6.84 (d, 1H, J = 8.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.8, 164.9, 137.3, 133.1, 131.2, 130.1, 128.9, 128.6, 128.1, 127.9, 127.4, 126.8, 126.7, 126.2, 120.5, 101.3; HRMS (ESI) m/z calcd for $C_{21}H_{15}BrNOS$ $[M + H]^+$: 408.0052, found: 408.0063.

4-((4-Methoxyphenyl)thio)-3,5-diphenylisoxazole (3f)

Yield: 45.2 mg (84%); time: 4 h; yellow solid; m.p. 76-78 °C; TLC, R_f = 0.32 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20-8.16 (m, 2H), 7.83 (d, 1H, J = 1.6 Hz), 7.81 (d, 1H, J = 2.0 Hz), 7.50-7.48 (m, 3H), 7.44-7.41 (m, 3H), 7.03 (d, 2H, J = 8.8 Hz), 6.74 (d, 2H, J = 8.8 Hz), 3.73 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 171.8, 165.0, 158.3, 130.9, 129.9, 128.8, 128.62, 128.59, 128.5, 128.3, 127.5, 127.1, 126.5, 115.0, 103.5, 55.3; HRMS (ESI) m/z calcd for $C_{22}H_{18}NO_2S$ $[M + H]^+$: 360.1053, found: 360.1060.

3-Phenyl-5-(*p*-tolyl)-4-(*p*-tolylthio)isoxazole (3g)

Yield: 48.2 mg (90%); time: 3 h; yellow solid; m.p. 106-108 °C; TLC, R_f = 0.35 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, 2H, J = 8.4 Hz), 7.72 (dd, 2H, J = 7.6 Hz, J = 1.6 Hz), 7.34-7.31 (m, 3H), 7.18 (d, 2H, J = 8.4 Hz), 6.96-6.90 (m, 4H), 2.31 (s, 3H), 2.18 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.4, 165.1, 141.4, 135.7, 132.7, 130.1, 129.9, 129.5, 128.5, 128.4, 127.3, 126.1, 124.3, 115.3, 101.5, 21.5,

20.9; HRMS (ESI) m/z calcd for $C_{23}H_{20}NOS$ $[M + H]^+$: 358.1260, found: 358.1254.

5-(4-Methoxyphenyl)-3-phenyl-4-(*p*-tolylthio)isoxazole (3h)

Yield: 50.3 mg (90%); time: 3 h; white solid; m.p. 107-109 ^oC; TLC, R_f = 0.41 (PE:EtOAc = 19:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, 2H, J = 9.2 Hz), 7.79 (dd, 2H, J = 8.0 Hz, J = 1.6 Hz), 7.44-7.37 (m, 3H), 7.05-6.95 (m, 6H), 3.85 (s, 3H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 172.2, 165.1, 161.6, 135.6, 132.8, 130.1, 129.9, 129.1, 128.5, 128.4, 125.9, 119.7, 114.2, 100.4, 55.3, 20.9; HRMS (ESI) m/z calcd for $C_{23}H_{20}NO_2S$ $[M + H]^+$: 374,1209, found: 374.1217.

5-(4-Chlorophenyl)-3-phenyl-4-(*p*-tolylthio)isoxazole (3i)

Yield: 40.7 mg (72%); time: 7.5 h; yellow solid; m.p. 112-114 ^oC; TLC, R_f = 0.42 (PE:EtOAc = 19:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, 2H, J = 8.8 Hz), 7.72 (d, 2H, J = 8.0 Hz), 7.34 (t, 5H, J = 8.8 Hz), 6.95 (d, 2H, J = 8.4 Hz), 6.90 (d, 2H, J = 8.4 Hz), 2.18 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 171.0, 165.2, 137.1, 136.0, 132.1, 130.2, 130.0, 129.1, 128.6, 128.5, 128.0, 126.2, 125.4, 102.8, 20.9; HRMS (ESI) m/z calcd for $C_{22}H_{17}ClNOS$ $[M + H]^+$: 378.0714, found: 378.0719.

Methyl 4-(3-phenyl-4-(p-tolylthio)isoxazol-5-yl)benzoate (3j)

Yield: 39.7 mg (66%); time: 4 h; yellow liquid; TLC, R_f = 0.32 (PE:EtOAc = 19:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, 2H, J = 8.0 Hz), 8.13 (d, 2H, J = 8.0 Hz), 7.81 (d, 2H, J = 7.2 Hz), 7.48-7.39 (m, 3H), 7.04-6.96 (m, 4H), 3.94 (s, 3H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 170.8, 166.3, 165.3, 140.0, 136.1, 131.95, 131.90, 130.9, 130.2, 130.1, 129.9, 128.6, 128.5, 128.0, 127.6, 127.3, 126.5, 52.4, 20.9; HRMS (ESI) m/z calcd for $C_{24}H_{20}NO_3S$ $[M + H]^+$: 402.1158, found: 402.1152.

3-Phenyl-5-(thiophen-3-yl)-4-(*p*-tolylthio)isoxazole (3k)

Yield: 33.0 mg (63%); time: 3.5 h; yellow solid; m.p. 76-78 ^{o}C; TLC, R_f = 0.36 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (dd, 1H, J = 2.8 Hz, J = 1.2 Hz), 7.85-7.81 (m, 3H), 7.45-7.39 (m, 4H), 7.06-6.99 (m, 4H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 169.2, 164.8, 135.9, 132.2, 130.1, 130.0, 128.50, 128.48, 128.1, 127.9, 127.3, 126.4, 126.1, 126.0, 125.2, 101.0, 33.7, 28.6, 20.8; HRMS (ESI) m/z calcd for $C_{20}H_{16}NOS_2$ $[M + H]^+$: 350.0668, found: 350.0667.

5-Methyl-3-phenyl-4-(*p*-tolylthio)isoxazole (3l)

Yield: 25.3 mg (60%); time: 6 h; yellow oil liquid; TLC, R_f = 0.37 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87-7.84 (m, 2H), 7.43-7.37 (m, 3H), 7.04 (d, 2H, J = 8.0 Hz), 6.95 (d, 2H, J = 8.4 Hz), 2.52 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 175.3, 165.1, 135.7, 132.7, 129.94, 129.90, 128.5, 128.4, 128.1, 126.3, 103.5, 20.8, 11.7; HRMS (ESI) m/z calcd for $C_{17}H_{16}NOS$ $[M + H]^+$: 282.0947, found: 282.0948.

5-Butyl-3-phenyl-4-(*p*-tolylthio)isoxazole (3m)

Yield: 22.3 mg (46%); time: 7 h; yellow liquid; TLC, R_f = 0.38 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (dd, 2H, J = 7.6 Hz, J = 2.0 Hz), 7.41-7.37 (m, 3H), 7.03 (d, 2H, J = 8.0 Hz), 6.94 (d, 2H, J = 8.4 Hz), 2.89 (t, 2H, J = 9.6 Hz) , 2.27 (s, 3H), 1.75-1.66 (m, 2H), 1.41-1.34 (m, 2H), 0.90 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 178.9, 163.2, 135.6, 133.0, 129.9, 129.8, 128.5, 128.1, 126.2, 102.8, 29.3, 25.7, 22.3, 20.8, 13.6; HRMS (ESI) m/z calcd for $C_{20}H_{22}NOS$ $[M + H]^+$: 324.1417, found: 324.1415.

5-(*tert*-Butyl)-3-phenyl-4-(*p*-tolylthio)isoxazole (3n)

Yield: 38.3 mg (79%); time: 4.5 h; yellow solid; m.p. 75-77 °C; TLC, R_f = 0.37 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, 2H, J = 7.2 Hz), 7.39-7.34 (m, 3H), 7.01 (d, 2H, J = 8.0 Hz), 6.89 (d, 2H, J = 8.4 Hz), 2.26 (s, 3H), 1.49 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 183.6, 165.1, 135.1, 133.9, 129.8, 129.7, 128.4, 128.3, 125.5, 100.7, 34.9, 28.5, 20.8; HRMS (ESI) m/z calcd for $C_{20}H_{22}NOS$ $[M + H]^+$: 324.1417, found: 324.1415.

3-Phenyl-4-(*p*-tolylthio)-5-(trimethylsilyl)isoxazole (3o)

Yield: 30.5 mg (60%); time: 3 h; yellow solid; m.p. 68-70 °C; TLC, R_f = 0.45 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, 2H, J = 8.4 Hz), 7.36 (t, 3H, J = 7.6 Hz), 7.01 (d, 2H, J = 8.0 Hz), 6.90 (d, 2H, J = 8.0 Hz), 2.26 (s, 3H), 0.39 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 184.0, 162.5, 135.3, 133.7, 129.8, 129.7, 128.42, 128.38, 128.1, 125.9, 114.7, 20.8, 1.9; HRMS (ESI) m/z calcd for $C_{19}H_{22}NOSSi$ $[M + H]^+$: 340.1186, found: 340.1189.

3-(*tert*-Butyl)-5-phenyl-4-(*p*-tolylthio)isoxazole (3p)

Yield: 30.5 mg (63%); time: 3.5 h; yellow solid; m.p. 72-74 °C; TLC, R_f = 0.40 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (dd, 2H, J = 7.6 Hz, J = 1.6 Hz), 7.42-7.39 (m, 3H), 7.04 (d, 2H, J = 8.0 Hz), 6.94 (d, 2H, J = 8.4 Hz), 2.27 (s, 3H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.6, 135.2, 133.3, 130.6, 129.9, 128.6, 127.3, 127.2, 125.2, 101.0, 33.7, 28.6, 20.8; HRMS (ESI) m/z calcd for $C_{20}H_{22}NOS$ $[M + H]^+$: 324.1417, found: 324.1418.

5-Phenyl-3-(*p*-tolyl)-4-(p-tolylthio)isoxazole (3q)

Yield: 36 mg (67%); time: 5.5 h; yellow solid; m.p. 99-101 oC; TLC, Rf = 0.38 (PE:EtOAc = 19:1); 1H NMR (CDCl3, 400 MHz): δ 8.15-8.12 (m, 2H), 7.72 (d, 2H, J = 7.6 Hz), 7.48-7.45 (m, 3H), 7.21 (d, 2H, J = 7.6 Hz), 7.05-6.99 (m, 4H), 2.37 (s, 3H), 2.27 (s, 3H); 13C NMR ($CDCl_3$, 100 MHz): δ 172.2, 165.1, 140.0, 135.7, 132.7, 130.8, 130.1, 129.2, 128.8, 128.4, 127.4, 127.1, 126.1, 125.3, 102.2, 21.4, 20.9; HRMS (ESI) m/*z* calcd for $C_{23}H_{20}NOS$ $[M + H]^+$: 358.1260, found: 358.1251.

General Procedure for the Synthesis of 3r-w.

In a 10 mL flask, under ambient atmosphere, the solution of 3-diphenylprop-2-yn-1-one *O*-methyl oxime (**1a**, 0.15mmol), dimethyl disulfide (**2a**, 0.3 mmol, 2.0 equiv) and $AlCl_3$ (0.15 mmol, 1.0 equiv) was stirred at room temperature for 6 h. After that time, the residue was purified by chromatography column on silica gel or preparative TLC to afford the desired product **3r**. For the synthesis of **3w**, the reaction mixture was dissolved in 1,2-dichloroethane (1.5 mL) and stirred at 60 °C for 12 h.

4-(Methylthio)-3,5-diphenylisoxazole (3r)

Yield: 24.8 mg (62%); time: 6 h; yellow solid; m.p. 66-68 °C; TLC, R_f = 0.36 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (dd, 2H, J = 8.4 Hz, J = 2.0 Hz), 8.02-7.99 (m, 2H), 7.54-7.50 (m, 6H), 2.11 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 169.7, 164.1, 130.5, 129.9, 128.7, 128.6, 128.4, 127.5, 127.4, 106.7, 19.0; HRMS (ESI) m/z calcd for $C_{16}H_{13}NOSNa$ $[M + Na]^+$: 290.0610, found: 290.0609.

5-(4-Methoxyphenyl)-4-(methylthio)-3-phenylisoxazole (3s)

Yield: 20.5 mg (46%); time: 7 h; white solid; m.p. 92-94 °C; TLC, R_f = 0.38 (PE:EtOAc

= 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, 2H, J = 9.2 Hz), 8.00-7.97 (m, 2H), 7.52-7.50 (m, 3H), 7.04 (d, 2H, J = 8.8 Hz), 3.89 (s, 3H), 2.11 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 169.7, 164.1, 161.2, 129.8, 128.9, 128.6, 128.4, 120.2, 114.1, 105.0, 55.4, 19.0; HRMS (ESI) m/z calcd for $C_{17}H_{16}NO_2S$ $[M + H]^+$: 298.0896, found: 298.0882.

5-(4-Chlorophenyl)-4-(methylthio)-3-phenylisoxazole (3t)

Yield: 23.9 mg (53%); time: 24 h; yellow solid; TLC, R_f = 0.36 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, 2H, J = 8.8 Hz), 8.00-7.97 (m, 2H), 7.53-7.49 (m, 5H), 2.10 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 168.6, 164.2, 136.6, 130.0, 129.1, 128.7, 128.6, 128.5, 128.3, 125.9, 107.0, 18.9; HRMS (ESI) m/z calcd for $C_{16}H_{12}ClNOSNa$ $[M + H]^+$: 302.0401, found: 302.0423.

5-Butyl-4-(methylthio)-3-phenylisoxazole (3u)

Yield: 19.3 mg (52%); time: 7 h; yellow liquid; TLC, R_f = 0.37 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (dd, 2H, J = 8.0 Hz, J = 4.0 Hz), 7.48 (t, 3H, J = 4.0 Hz), 2.92 (t, 2H, J = 8.0 Hz), 2.09 (s, 3H), 1.80-1.70 (m, 2H), 1.50-1.40 (m, 2H), 0.97 (t, 3H, J = 8.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 176.6, 162.3, 129.8, 129.0, 128.6, 127.9, 126.4, 106.6, 29.7, 25.6, 22.3, 19.5, 13.7; HRMS (ESI) m/z calcd for $C_{14}H_{18}NOS$ $[M + H]^+$: 248.1104, found: 248.1105.

3-(*tert*-Butyl)-4-(methylthio)-5-phenylisoxazole (3v)

Yield: 20.3 mg (55%); time: 9 h; yellow liquid; TLC, R_f = 0.35 (PE:EtOAc = 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, 2H, J = 7.6 Hz), 7.50-7.46 (m, 3H), 2.19 (s, 3H),

1.53 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 172.2, 170.0, 130.3, 128.7, 127.8, 126.9, 106.2, 33.6, 28.5, 19.8; HRMS (ESI) m/z calcd for $C_{14}H_{18}NOS$ $[M + H]^+$: 248.1104, found: 248.1100.

4-(Ethylthio)-3,5-diphenylisoxazole (3w)

Yield: 23.9 mg (51%); time: 9.5 h; yellow liquid; TLC, R_f = 0.31 (PE:EtOAc = 19:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.25 (d, 2H, J = 6.4 Hz), 8.00 (d, 2H, J = 6.4 Hz), 7.52-7.50 (m, 6H), 2.51-2.48 (m, 2H), 1.01 (t, 3H, J = 7.2 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 170.3, 164.5, 130.5, 129.8, 128.7, 128.54, 128.48, 127.6, 127.4, 104.8, 29.8, 14.3; HRMS (ESI) m/z calcd for $C_{17}H_{16}NOS$ $[M + H]^+$: 282.0947, found: 282.0952.

Synthesis of 9. To TBAF (0.2 mmol, 2 equiv) in THF solution (1M) was added 0.1 mmol of **3o** in 1 mL of CH_3OH at room temperature. The reaction was allowed to stir at room temperature for 2 hours until the starting material was consumed. After the reaction, the resulting mixture was diluted with EtOAc (30 mL), washed with H_2O (10 mL × 3), dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (eluent: PE/EtOAc = 19:1) to give the desired **9**. Yield: 24.4 mg (61%); time: 2 h; yellow liquid; TLC, R_f = 0.39 (PE:EtOAc = 19:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.49 (s, 1H), 7.80-7.77 (m, 2H), 7.37-7.32 (m, 3H), 7.01-6.96 (m, 4H), 2.21 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 163.1, 162.0, 136.7, 131.8, 130.05, 130.03, 129.6, 128.6, 128.2, 128.0, 127.7, 109.1, 20.9; HRMS (ESI) m/z calcd for $C_{16}H_{14}NOS$ $[M + H]^+$: 268.0791, found: 268.0797.

Synthesis of *N*-tosyl sulfilimine 10. To a mixture of **3a** (0.1 mmol) and Chloramine-T

(0.21 mmol, 2.1 eq) in CH_3CN (1 mL) was added AcOH (20 mol%) slowly and the mixture was stirred at reflux for 18 hours. After that time, the resulting mixture was diluted with EtOAc (30 mL), washed with H_2O (10 mL × 3), dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (eluent: PE/EtOAc = 7:3) to give the desired **10**. Yield:31.2 mg (61%); time: 18 h; white solid; m.p. 114-116 °C; TLC, R_f = 0.28 (PE:EtOAc = 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (d, 2H, J = 7.6 Hz), 7.71 (d, 2H, J = 7.6 Hz), 7.58 (t, 3H, J = 7.6 Hz), 7.52 (t, 2H, J = 7.2 Hz), 7.36 (t, 1H, J = 7.6 Hz), 7.27 (d, 2H, J = 8.0 Hz), 7.19 (s, 2H), 7.10 (d, 2H, J = 7.6 Hz), 6.95 (d, 2H, J = 7.6 Hz), 2.34 (s, 3H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 174.3, 163.2, 141.9, 141.8, 141.1, 132.4, 130.4, 129.70, 129.68, 129.2, 129.1, 129.0, 128.2, 126.5, 126.3, 126.0, 125.7, 124.7, 109.7, 21.4, 21.1. HRMS (ESI) m/z calcd for $C_{29}H_{24}N_2O_3S_2$ $[M+H]^+$: 513.1301, found: 513.1304.

Synthesis of 4-sulfinyl isoxazole 11. To H_2O_2 (0.17 mL, 0.4 mmol, 4 equiv) contained in a 10 mL round-bottomed flask was slowly added 0.1 mmol of **3r** in 2 mL of HOAc/$CHCl_3$ (1:1) at room temperature. The reaction vessel was allowed to stir at room temperature about 15 hours until the starting material was consumed. After that, the resulting mixture was diluted with EtOAc (30 mL), washed with H_2O (10 mL × 3), dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (eluent: PE/EtOAc = 7:3) to give the desired **11**. Yield:34.0 mg (80%); time: 15 h; yellow solid; m.p. 152-154 °C; TLC, R_f = 0.22 (PE:EtOAc = 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-8.03 (m, 2H), 7.97 (dd, 2H, J = 7.6 Hz, J = 1.6 Hz), 7.60-7.54

(m, 6H), 2.72 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 172.6, 162.8, 131.9, 130.8, 129.9, 129.1, 129.0, 127.7, 125.9, 116.7, 37.8. HRMS (ESI) m/z calcd for $C_6H_{14}NO_2S$ $[M+H]^+$: 284.0340, found :284.0336.

Acknowledgments

We acknowledge the financial support from the Key Research and Development Program of Shanxi Province (international cooperation) (No. 201803D421093) and the National Natural Science Foundation of China (No. 21602126).

Supporting Information

Condition optimization for the synthesis of **3r**, MS study for the synthesis of **3a**, crystal structure of **3i** and the corresponding data, copies of ^{1}H and ^{13}C NMR spectra, found in the SI.

References

(1) Zhu, J.; Mo, J.; Lin, H.; Chen, Y.; Sun, H. The Recent Progress of Isoxazole in Medicinal Chemistry. *Bioorg. Med. Chem.* **2018**, *26*, 3065-3075.

(2) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845-5859.

(3) (a) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals To Reveal Opportunities for Drug Design and Discovery. *J. Med. Chem.* **2014**, *57*, 2832-2842. (b) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry. *Curr. Top. Med. Chem.* **2016**, *16*, 1200-1216.

(4) Beno, B. R.; Yeung, K.-S.; Bartberger, M. D.; Pennington, L. D.; Meanwell, N. A. A Survey of the Role of Noncovalent Sulfur Interactions in Drug Design. *J. Med. Chem.*

2015, *58*, 4383-4438.

(5) (a) Morita, T.; Yugandar, S.; Fuse, S.; Nakamura, H. Recent Progresses in the Synthesis of Functionalized Isoxazoles. *Tetrahedron Lett.* **2018**, *59*, 1159-1171. (b) Hu, F.; Szostaka, M. Recent Developments in the Synthesis and Reactivity of Isoxazoles: Metal Catalysis and Beyond. *Adv. Synth. Catal.* **2015**, *357*, 2583-2614.

(6) (a) Morita, T.; Fuse, S.; Nakamura, H. Generation of an 4-Isoxazolyl Anion Species: Facile Access to Multifunctionalized Isoxazoles. *Angew. Chem. Int. Ed.* **2016**, *55*, 13580-13584. (b) Kanda, Y.; Takahashi, T.; Araki, Y.; Konoike, T.; Mihara, S.; Fujimoto, M. Discovery and Synthesis of a Potent Sulfonamide ET_B Selective Antagonist. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1875-1878.

(7) Waldo, J. P.; Larock, R. C. Synthesis of Isoxazoles via Electrophilic Cyclization. *Org. Lettt.* **2005**, *7*, 5203-5205.

(8) (a) Waldo, J. P.; Larock, R. C. The Synthesis of Highly Substituted Isoxazoles by Electrophilic Cyclization: An Efficient Synthesis of Valdecoxib. *J. Org. Chem.* **2007**, *72*, 9643-9647. (b) Kaewsri, W.; Thongsornkleeb, C.; Tummatorn, J. ;Ruchirawat, S. Isomerizable (E/Z)-alkynyl-*O*-methyl oximes employing TMSCl-NCS in chlorinative cyclization for the direct synthesis of 4-chloroisoxazoles. *RSC Adv.* **2016**, *6*, 48666-48675. (c) Jeong, Y.; Kim, B.-I; Lee, J. K.; Ryu, J.-S. Direct Synthesis of 4-Fluoroisoxazoles through Gold-Catalyzed Cascade Cyclization-Fluorination of 2-Alkynone *O*-Methyl Oximes, *J. Org. Chem.* **2014**, *79*, 6444-6455. (d) Sperança, A.; Godoi, B.; Zeni, G. Iron(III) Chloride/Diorganyl Diselenides: A Tool for Intramolecular Cyclization of Alkynone *O*-Methyloximes. *J. Org. Chem.* **2013**, *78*, 1630-1637. (e) Tu, K. N.; Hirner, J. J.; Blum, S. A. Oxyboration with and without a Catalyst: Borylated Isoxazoles via B-O σ-Bond Addition. *Org. Lett.* **2016**, *18*, 480-483.

(9) (a) Iwasaki, M.; Fujii, T.; Nakajima, K.; Nishihara, Y. Iron-Induced Regio- and Stereoselective Addition of Sulfenyl Chlorides to Alkynes by a Radical Pathway, *Angew. Chem. Int. Ed.* **2014**, *53*, 13880-13884. (b) Huang, H.; Fan, J.; He, G.; Yang, Z.; Jin, X.;

Liu, Q.; Zhu, H. Generation of Oxazolidine-2,4-diones Bearing Sulfur-Substituted Quaternary Carbon Atoms by Oxothiolation/Cyclization of Ynamides, *Chem. Eur. J.* **2016**, *22*, 2532-2538.

(10) (a) Gao, W.-C.; Cheng, Y.-F.; Shang, Y.-Z.; Chang, H.-H.; Li, X.; Zhou, R.; Qiao, Y.; Wei, W.-L. Copper(II)-Catalyzed Four-Component Oxysulfonylation/Diazenylation: Synthesis of α-Arylhydrazo-β-keto Sulfones, *J. Org. Chem.* **2018**, *83*, 11956-11962. (b) Gao, W.-C.; Liu, T.; Cheng, Y.-F.; Chang, H.-H.; Li, X.; Zhou, R.; Wei, W.-L.; Qiao, Y. $AlCl_3$-Catalyzed Intramolecular Cyclization of *N*-Arylpropynamides with *N*-Sulfanylsuccinimides: Divergent Synthesis of 3-Sulfenyl Quinolin-2-ones and Azaspiro[4,5]trienones, *J. Org. Chem.* **2017**, *82*, 13459-13467. (c) Liu, T.; Tian, J.; Gao, W.-C.; Chang, H.-H.; Liu, Q.; Li, X.; Wei, W.-L. Intermolecular Sulfenoamination of Alkenes with Sulfonamides and *N*-Sulfanylsuccinimides to Access β-Sulfonylamino Sulfides and Dihydrobenzothiazines, *Org. Biomol. Chem.* **2017**, *15*, 5983-5992. (d) Gao, W.-C.; Liu, T.; Zhang, B.; Li, X.; Wei, W.-L.; Liu, Q.; Tian, J.; Chang, H.-H. Synthesis of 3‑Sulfenylated Coumarins: $BF_3{\cdot}Et_2O$‑Mediated Electrophilic Cyclization of Aryl Alkynoates Using N−Sulfanylsuccinimides, *J. Org. Chem.* **2016**, *81*, 11297-11304.

(11) Wang, M.; Qiao, Z.; Zhao, J.; Jiang, X. Palladium-Catalyzed Thiomethylation via a Three-Component Cross-Coupling Strategy, *Org. Lett.* **2018**, *20*, 6193–6197, and references therein.

(12) Bilheri, F. N.; Stein, A. L.; Zeni, G. Synthesis of Chalcogenophenes via Cyclization of 1,3-Diynes Promoted by Iron(III) Chloride and Dialkyl Dichalcogenides, *Adv. Synth. Catal.* **2015**, *357*, 1221-1228.