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Metal-free synthesis of 4-(methylthio)isoxazoles with acetylenic oximes and dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSM)

Chengqun Chen* and Zihan Deng

Department of Chemical Engineering, Fuzhou University Zhicheng College, Fuzhou, P.R. of China
Email: chenchq03@yeah.net

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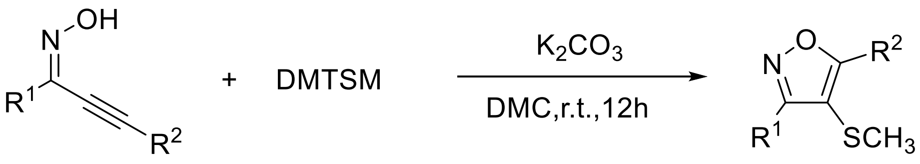
Abstract

An efficient protocol for the synthesis of 4-(methylthio)isoxazoles, by way of the reaction of differentially functionalized acetylenic oximes with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSM) under mild, metal-free conditions is described and affords the products in moderate to good yields.



Keywords: 4-(Methylthio)isoxazole, acetylenic oxime, DMTSM, metal-free

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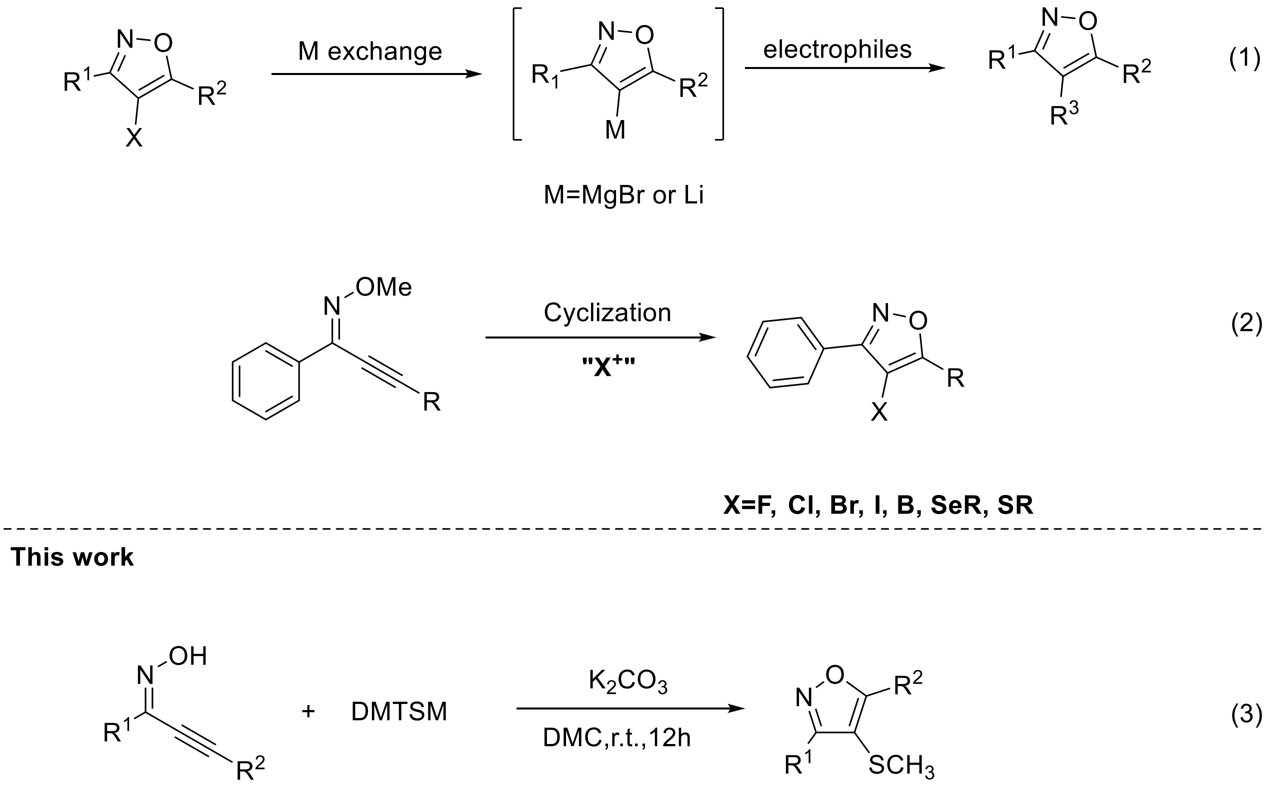
Introduction

As well-known heterocycles, the isoxazole skeleton acts as a key structural framework and pharmacophore, showing diverse biological activities and serving as important privileged architectures in materials science and pharmaceuticals[1-3]. Sulfur serves as a ubiquitous constituent in biologically active natural products and medicinal molecules[4, 5]. Moreover, the substitution of heterocyclic rings with sulfenylated derivatives represents a valuable strategy to modulate substituent trajectories, thereby optimizing complementarity and fitting within the ligand-binding pocket during drug design[6].

The increasing importance of substituted isoxazoles has promoted the development of new synthetic methods. In the past years, numerous approaches to construct functionalized isoxazole derivatives have been reported[2, 7]; however, the synthetic pathway towards 4-sulfenyl isoxazoles remains relatively underexplored. A classic and representative synthetic approach for 4-sulfenyl isoxazoles involves the reaction of thiosulfonates or disulfides with 4-isoxazolyl anions, which are generated in situ under strong basic conditions at low temperature (Scheme 1, eq 1). [8, 9]



Scheme 1. Different methods for the synthesis of 4-sulfenyl isoxazoles.

Building on Larock's pioneering work[10] in the synthesis of 4-iodo isoxazoles via electrophilic cyclization of 2-alkyn-1-one O-methyloximes, electrophilic cyclization of oximes using diverse electrophiles has emerged as a robust protocol for constructing 4-functionalized isoxazoles (Scheme 1, eq 2).[11-16] This approach is distinguished by its readily available starting materials, operational efficiency, and exceptional regioselectivity. Specifically, electrophilic sulfenylation of 2-alkyn-1-one O-methyloximes with N-sulfanylsuccinimides or disulfides as electrophiles enables the synthesis of 4-sulfenyl isoxazoles under mild reaction conditions, expanding the scope of this methodology to sulfur-containing heterocycles.[16]

Dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTSM) stands out as a remarkable electrophilic methylthiolating reagent, offering unique advantages including safety, crystallinity, and ease of handling[17-19]. In recent years, the application of dimethyl(methylthio)sulfonium salts has been investigated in direct alkylthiolation[20], cycloaddition reactions[21-23], and C–C bond formation [24]. Herein, we describe a novel and practical approach for the synthesis of 4-(methylthio)isoxazole from acetylenic oximes and DMTSM under ambient temperature conditions.

Results and Discussion

The initial study commenced by adding 1, 3-diphenylprop-2-yn-1-one oxime and DMTSM to acetonitrile, and the substrate mixture was stirred at ambient temperature under an air atmosphere. After 12 hours of reaction, the target compound 4-(methylthio)-3, 5-diphenylisoxazole **3a** was successfully synthesized with a yield of 33%. To enhance the yield of this transformation, the influence factors of solvents, reaction temperature, base, and catalysts were successively investigated (Table 1).

Table 1. Optimization of Reaction Conditions[a]

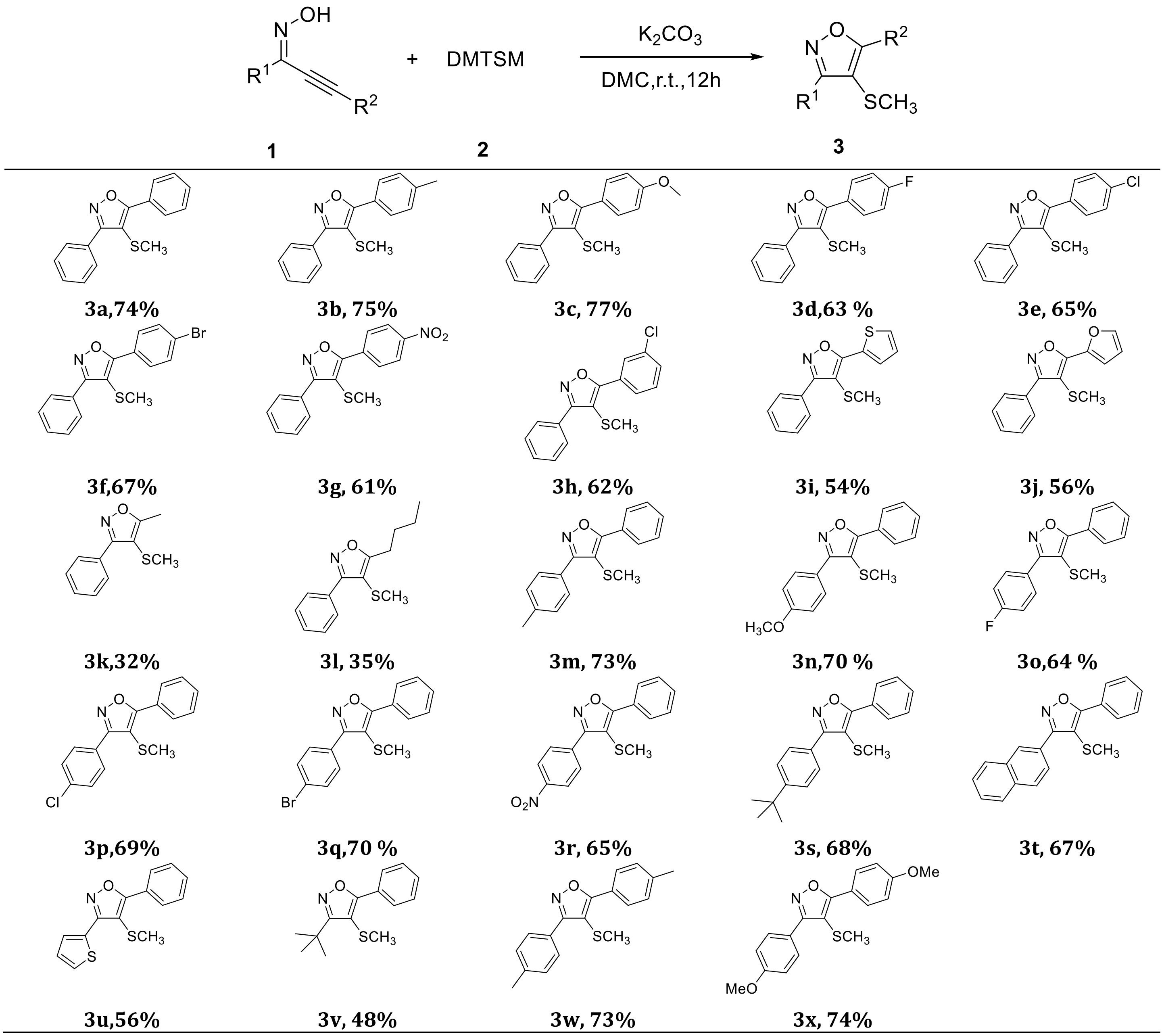
Entry	Solvent	Temp (℃)	Base	catalyst	Yield (%)[b]
1	MeCN	r.t.	None	-	33
2	DCM	r.t.	None	-	42
3	DCE	r.t.	None	-	38
4	THF	r.t.	None	-	15
5	Dioxane	r.t.	None	-	8
6	DCM	40	None	-	35
7	DCM	55	None	-	30
8	DCM	70	None	-	14
9	DCM	r.t.	AcONa	-	23
10	DCM	r.t.	tBuOK	-	28
11	DCM	r.t.	Na_2CO_3	-	67
12	DCM	r.t.	K_2CO_3	-	74
13	DCM	r.t.	K_2CO_3	CuI	73
14	DCM	r.t.	K_2CO_3	$Cu(OAc)_2$	71
15	DCM	r.t.	K_2CO_3	$FeCl_3$	72

[a] Reaction conditions: **1a** (0.5 mmol), DMTSM (0.6 mmol), base (0.75 mmol) , catalyst(0.05 mmol) and solvent (2 mL) under air for 12 h.

[b] Isolated yields.

DCM =dichloromethane, DCE = dichloroethane, THF =tetrahydrofuran.

Table 2. Substrate scope of various acetylenic oximes[a]



3a,74% **3b, 75%** **3c, 77%** **3d,63 %** **3e, 65%**

3f,67% **3g, 61%** **3h, 62%** **3i, 54%** **3j, 56%**

3k,32% **3l, 35%** **3m, 73%** **3n,70 %** **3o,64 %**

3p,69% **3q,70 %** **3r, 65%** **3s, 68%** **3t, 67%**

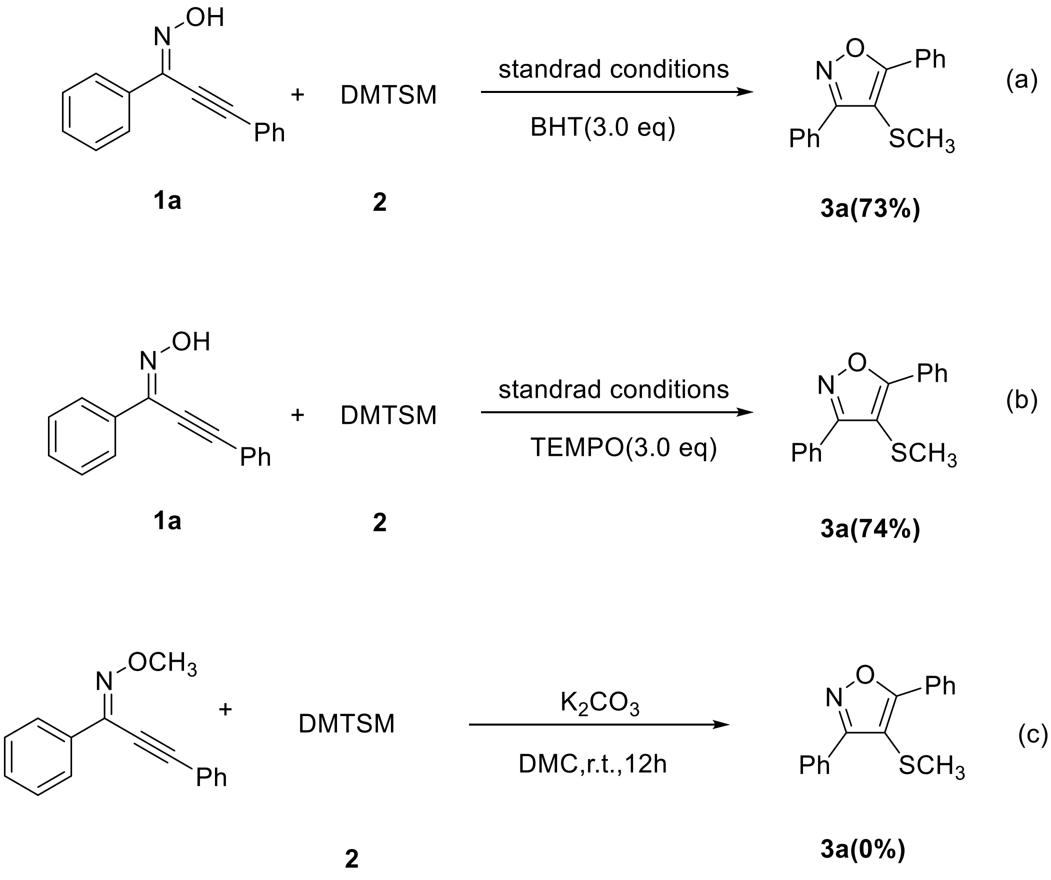
3u,56% **3v, 48%** **3w, 73%** **3x, 74%**

[a] Reaction conditions: **1a** (0.5 mmol), DMTSM (0.6 mmol), K_2CO_3 (0.75 mmol) and DCM (2 mL) under air for 12 h.

An initial solvent screening was performed to evaluate dichloromethane (DCM), dioxane, 1,2-dichloroethane (DCE), and tetrahydrofuran (THF) as reaction media (Table 1, entries 2–5). Reactions were conducted at room temperature without the addition of base. Notably, dichloromethane (DCM) proved to be the optimal solvent, furnishing the desired product in 42% yield—outperforming other tested media. 1, 2-Dichloroethane (DCE) yielded 38%, whereas polar aprotic solvents tetrahydrofuran (THF) and dioxane afforded significantly lower yields of 15% and 8%, respectively. These results highlight DCM's superior performance in facilitating this transformation compared to the evaluated solvents. Additionally, increasing the reaction temperature was found to decrease the product yield (Table 1, entries 6–8). To accelerate the reaction, various bases were evaluated (Table 1, entries 9–12). Potassium carbonate (K_2CO_3) afforded superior results compared to sodium carbonate (Na_2CO_3), sodium acetate (AcONa), and tert-butoxide (t-BuOK). This outcome was primarily attributed to the degradation of DMTSM by the strong base. Meanwhile, catalysts such as CuI, $Cu(OAc)_2$, and $FeCl_3$ showed no significant effect on the reaction (Table 1, entries 13–15). Through systematic optimization, the reaction conditions detailed in Table 1, entry 11, enabled the synthesis of the product with an optimal yield of 74%. After that, a number of acetylenic oximes bearing different aryl groups were used to react with DMTSM, affording the 4-(methylthio)isoxazoles in varied yields (Table 2).

For R^2 being benzene or substituted benzene rings, satisfactory yields were achieved. Notably, para-substituted benzene rings with electron-donating groups ($-CH_3$, $-OCH_3$) afforded yields of 75% and 77% (Table 2, **3b-3c**), respectively, whereas the presence of electron-withdrawing groups (-F, -Cl, -Br, $-NO_2$) on the benzene ring led to a moderate decrease in yields(Table 2, **3d-3h**). Heterocyclic or aliphatic substituents (R^2) led to a notable drop in yields(Table 2, **3i-3j**), with methyl and n-butyl groups yielding merely 32% and 35%(Table 2, **3k-3l**), respectively. This suggests that aromatic systems are more favorable for the reaction than aliphatic or heterocyclic counterparts.

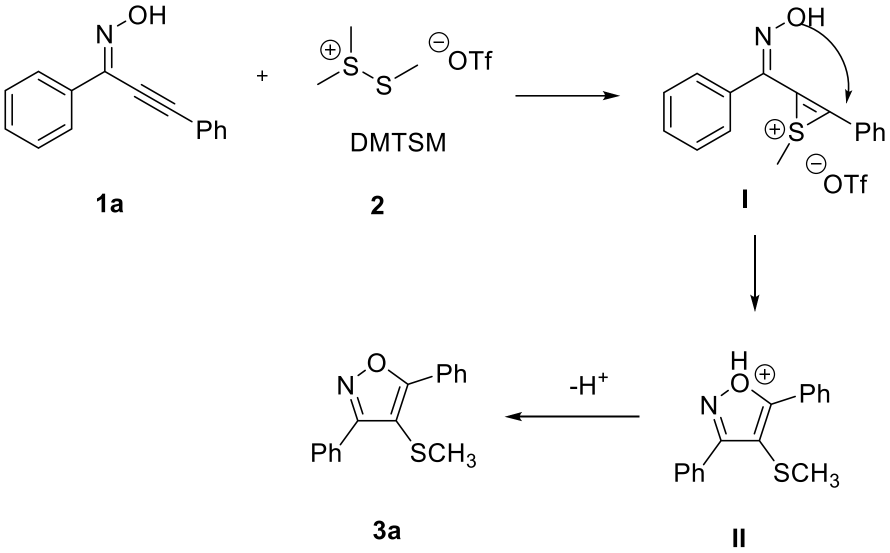
When R^1 is a para-substituted phenyl group or naphthyl ring, the reaction affords comparable yields(Table 2, **3m-3t**). Noteworthily, electron-withdrawing substituents like fluoro and nitro cause slight yield reductions to 64% and 65%, respectively. Similar to the trend observed for R^1, the yields decline appreciably when R^2 is a heterocycle or alkyl substituent(Table 2, **3u-3v**). When both R^1 and R^2 are p-tolyl or p-methoxyphenyl groups, the reaction also affords good yields (Table 2, **3w-3x**).



Scheme 2. Control Experiments.

To investigate the reaction mechanism, several control experiments were conducted. First, butylated hydroxytoluene (BHT) and 2, 2, 6, 6-Tetramethylpiperidin-1-oxyl(TEMPO) were used as a radical inhibitor in the reaction (Scheme 2, **a-b**), and no significant effect on the isolated yield was observed. When 1,3-diphenylprop-2-yn-1-one O-methyl oxime was used as the substrate in the reaction with 2 under standard conditions, the desired product 3a was not obtained (Scheme 2, **c**).

Based on these results, the reaction mechanism was proposed as follows: the sulfonium group transfer from DMTSM to 1, 3-diphenylprop-2-yn-1-one oxime generates the intermediate episulfonium ion (I), Subsequently, the formation of the cyclic intermediate (II) was achieved through the intramolecular cyclization reaction. Ultimately, the anticipated product was generated through deprotonation.



Scheme 3. Plausible reaction mechanism for the hydrolysis reaction.

Conclusions

In summary, we herein describe a straightforward and efficient protocol for the synthesis of 4-(methylthio)isoxazoles through the reaction of acetylenic oximes with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSM) under mild, metal-free conditions. This transformation accommodates a wide array of functional groups on the aromatic ring, yielding the corresponding products in moderate to good yields.

Experimental Section

General procedure for the synthesis of 4-(methylthio)isoxazole. At room temperature, to a solution of alkyne oxime (0.5mmol, 1 equiv) in CH_2Cl_2 (2 mL), DMTSM (0.6mmol, 1.2 equiv) and K_2CO_3 (0.75mmol, 1.5 equiv) were added into the solvent. The mixture was stirred for 12h (TLC monitored). The reaction mixture was extracted with CH_2Cl_2 after adding the saturated brine. Then the organic phase was combined and dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo, the crude product was purified by column chromatography, eluting with petroleum ether/ethyl acetate to afford the desired products.

4-(Methylthio)-3,5-diphenylisoxazole(3a).[16] Yellow solid (99mg, 74%); mp 66-68 ℃. IR(KBr) 3051, 2962, 1624, 1167, 1028cm^{-1};^{1}H NMR (400 MHz, CDCl$_3$): δ 8.24 (dd, *J* 8.4 Hz, *J* 2.0 Hz, 2H), 7.99-7.95 (m, 2H), 7.53-7.46 (m, 6H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.9, 164.2, 130.3, 129.8, 128.7, 128.6, 128.4, 127.6, 127.1, 106.6, 19.0. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for C$_{16}$H$_{14}$NOS: 268.0796, found: 268.0791.

4-(Methylthio)-3-phenyl-5-(*p*-tolyl)isoxazole(3b). White solid (105mg, 75%); mp 109-114 ℃. IR(KBr) 3047, 2958, 1618, 1173, 1017cm^{-1};^{1}H NMR (400 MHz, CDCl$_3$): δ 8.23 (d, *J* 8.8 Hz, 2H), 8.20-8.16 (m, 2H), 7.53-7.49 (m, 3H), 7.21 (d, *J* 8.2 Hz, 2H), 2.82 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.9, 163.9, 130.9,130.2, 129.5, 128.8, 128.6, 127.7, 127.3, 126.7, 105.8,21.6, 15.4. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for C$_{17}$H$_{16}$NOS: 282.0939, found: 282.0947.

5-(4-Methoxyphenyl)-4-(methylthio)-3-phenylisoxazole(3c).[16] White solid (114mg, 77%); mp 91-95 ℃. IR(KBr) 3035, 2837, 1613, 1165, 1014cm-^{1};^{1}H NMR (400 MHz, CDCl$_3$): δ 8.19 (d, J 9.2 Hz, 2H), 8.00-7.96 (m, 2H), 7.53-7.50 (m, 3H), 7.04 (d, *J* 8.8 Hz, 2H), 3.89 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.3, 163.5, 160.7, 128.7, 128.3, 127.8, 127.5, 126.8, 120.2, 113.2, 104.0, 54.4, 19.1. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for C$_{17}$H$_{16}$NO$_2$S: 298.0886, found: 298.0896.

5-(4-Fluorophenyl)-4-(methylthio)-3-phenylisoxazole(3d). White solid (90mg, 63%); mp 71-74 ℃. IR(KBr) 3053, 2870, 1642, 1160, 1008cm^{-1};^{1}H NMR (400 MHz, CDCl$_3$): δ 8.24-8.20 (m, 2H), 7.96-7.91 (m, 2H), 7.60-7.51 (m, 3H), 3.89 (s, 3H), 7.24-7.16 (m, 2H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ.169.57-169.54(d, *J* 3Hz), 163.5, 161.8, 158.7, 130.6, 129.9, 129.8, 127.77-127.71(d, *J 6Hz*), 124.9, 122.0, 118.81-118.59(d, *J*.3Hz), 105.5, 17.4. ^{19}F NMR (376 MHz, CDCl$_3$) δ -110.01. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for C$_{16}$H$_{13}$FNOS: 286.0674, found: 286.0696.

5-(4-Chlorophenyl)-4-(methylthio)-3-phenylisoxazole(3e).[16] White solid (98mg, 65%); mp 80-83 ℃. IR(KBr) 3037, 2954, 1646, 1153, 1087cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.16 (d, *J* 8.8 Hz, 2H), 8.00-7.97 (m, 2H), 7.54-7.49 (m, 5H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.9, 160.2, 138.1, 128.6, 128.4, 128.0, 127.7, 127.6, 126.7, 126.3, 109.7, 18.8. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for C$_{16}$H$_{13}$ClNOS: 302.0398, found: 302.0401.

5-(4-Bromophenyl)-4-(methylthio)-3-phenylisoxazole(3f). White solid (116mg, 67%); mp 84-87 ℃. IR(KBr) 3028, 2866, 1620, 1158, 1025cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, *J* 8.7 Hz, 2H), 7.31 (d, *J* 8.5 Hz, 2H), 7.25−7.19 (m, 5H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.2, 168.5, 136.2, 130.4, 130.2, 128.8, 128.7, 127.4, 126.5, 125.7, 107.0, 18.3. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for C$_{16}$H$_{13}$BrNOS: 345.9901, found: 345.9896.

4-(Methylthio)-5-(4-nitrophenyl)-3-phenylisoxazole(3g). Light yellow solid (95mg, 61%); mp 87−90 ℃. IR(KBr) 3050, 2961, 1627, 1179, 1012cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.42 (d, *J* 8.9 Hz, 2H),8.15 (d, *J* 8.7 Hz, 2H), 7.99−7.95 (m, 2H), 7.58−7.50 (m, 3H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.6, 162.9, 148.5, 130.6, 129.6, 128.9, 127.8, 125.9, 124.3, 107.1, 21.1. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for C$_{16}$H$_{13}$N$_2$O$_3$S:313.0640, found: 313.0641.

5-(3-Chlorophenyl)-4-(methylthio)-3-phenylisoxazole(3h). White solid (93mg, 62%); mp 89−92 ℃. IR(KBr) 3044, 2906, 1623, 1173, 782cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.07-8.03 (m, 2H), 7.97 (d, *J* 8.7 Hz, 2H), 7.58-7.49 (m, 5H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.5, 163.1, 147.4, 130.1, 129.6, 129.1, 127.8, 126.5, 125.9, 125.1, 124.4, 107.2, 20.0. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for C$_{16}$H$_{13}$ClNOS: 302.0409, found: 302.0401.

4-(Methylthio)-3-phenyl-5-(thiophen-2-yl)isoxazole(3i). Light yellow solid solid (74mg, 54%); mp =60-64 ℃. IR(KBr)= 3102, 2892, 1632, 1171, 1026, 711 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.88 (d, J 3.7 Hz, 2H), 7.67−7.61 (m, 3H), 7.54−7.49 (m, 3H), 7.22 (dd, J 5.0, 3.8 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ=164.4, 162.0, 130.1, 130.0, 129.3, 128.5, 127.9, 127.3, 127.1, 126.4, 104.1, 19.7. HRMS (ESI) (m/z): [M+H]$^+$ calcd. for C$_{14}$H$_{12}$NOS$_2$: 274.0364, found: 274.0355.

5-(Furan-2-yl)-4-(methylthio)-3-phenylisoxazole(3j). Light yellow solid solid (72mg, 56%); mp 60-63 ℃. IR(KBr) 3025, 2943, 1636, 1114, 1007, 742cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.82 (dd, J 1.7, 0.7 Hz, 1H), 7.65−7.62 (m, 2H), 7.53−7.49 (m, 3H), 7.30 (d, *J* 3.6 Hz, 1H), 6.65(dd, *J* 3.6, 1.8 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.5, 161.3, 139.6, 135.2, 129.3, 127.9, 127.6, 126.2, 119.1, 114.4, 103.6, 15.9. HRMS (ESI) (*m/z*): [M+H]+ calcd. for $C_{14}H_{12}NO_2S$: 258.0589, found: 258.0583.

5-Methyl-4-(methylthio)-3-phenylisoxazole(3k). Yellow liquid (33mg, 32%). IR(KBr)= 3019, 2870, 1602, 1162, 1007cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ =8.06(dd, *J* 7.7, 1.6 Hz, 2H), 7.51−7.44 (m, 3H), 2.61 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.7, 163.1, 132.1, 130.2, 129.0, 128.6, 107.4, 15.3, 12.4. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for $C_{11}H_{12}NOS$: 206.0630, found: 206.0634.

5-Butyl-4-(methylthio)-3-phenylisoxazole(3l). Yellow liquid (43mg, 35%). IR(KBr) 3043, 2930, 1616, 1173, 1010cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.01 (dd, *J* 8.0, 4.0 Hz, 2H), 7.51−7.48 (m, 3H), 2.90 (t, *J* 8.0 Hz, 2H), 2.11 (s, 3H), 1.80-1.70 (m, 2H), 1.46-1.35 (m, 2H), 0.89 (t, 3H, *J* 8.0 Hz). ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.5, 161.3, 139.6, 135.2, 129.3, 127.9, 127.6, 126.2, 119.1, 114.4, 103.6, 15.9. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for $C_{14}H_{18}NOS$: 248.1099, found: 248.1104.

4-(Methylthio)-5-phenyl-3-(*p*-tolyl)isoxazole(3m).White solid (103mg, 73%); mp 107-111 °C. IR(KBr) 3061, 2922, 1634, 1177, 1025cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.10 (d, *J* 8.6 Hz, 2H), 7.66 (d, J 7.9 Hz, 2H), 7.62−7.60(m, 3H), 7.14 (d, *J* 7.9 Hz, 2H), 2.46 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.4, 163.6, 134.2, 131.5, 129.3, 128.7, 128.7, 127.5, 126.2, 124.6, 106.6, 21.4, 18.0. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for $C_{17}H_{16}NOS$: 282.0956, found: 282.0947.

3-(4-Methoxyphenyl)-4-(methylthio)-5-phenylisoxazole(3n). White solid (104mg, 70%); mp 77-81 °C. IR(KBr) 3027, 2968, 1625, 1123, 1017, 824cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.14−8.10 (m, 2H), 7.95(d, *J* 8.7 Hz, 2H), 7.55−7.51 (m, 3H), 7.03 (d, *J* 8.9 Hz, 2H),3.87 (s, 3H) , 2.37 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ=168.5, 161.3, 160.6, 131.5, 130.2, 128.8, 126.2, 123.2, 120.6, 119.9, 106.5, 55.3, 15. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for $C_{17}H_{16}NO_2S$: 298.0902, found: 298.0896.

3-(4-Fluorophenyl)-4-(methylthio)-5-phenylisoxazole(3o). Light yellow solid solid (91mg, 64%); mp 86-89 °C. IR(KBr) 3045, 2903, 1639, 1228, 1154, 1026cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.16−8.12 (m, 2H), 7.98 (dd, *J* 8.7, 5.3 Hz, 2H), 7.58−7.52 (m, 3H), 8.22−8.18 (m, 2H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.3, 162.6, 131.9, 130.7, 129.08, 128.0, 127.8, 127.7, 126.3, 105.1, 15.5. ^{19}F NMR (376 MHz, CDCl$_3$) δ -114.3. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for $C_{16}H_{13}FNOS$: 286.0690, found: 286.0696.

3-(4-Chlorophenyl)-4-(methylthio)-5-phenylisoxazole(3p). Light yellow solid solid (104mg, 69%); mp 72-74 °C. IR(KBr) 3027, 2876, 1623, 1167, 1009cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.07−8.03 (m, 2H), 7.93(d, *J* 8.4 Hz, 2H), 7.52−7.41 (m, 5H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.3, 162.6, 131.9, 130.7, 129.1, 128.0, 127.8, 127.7, 126.3, 105.1, 15.5. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for $C_{16}H_{13}ClNOS$: 302.0395, found: 302.0401.

3-(4-Bromophenyl)-4-(methylthio)-5-phenylisoxazole(3q). White solid (121mg, 70%); mp 64-67 °C. IR(KBr) 3041, 2967, 1625, 1168, 1012, 822cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.08−8.06 (m, 2H), 7.95 (d, *J* 8.6 Hz, 2H), 7.55−7.46 (m, 5H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.9, 162.4, 130.9, 130.7, 129.3, 127.8, 126.8, 125.5, 124.8, 124.0, 105.1, 15.6. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for $C_{16}H_{13}BrNOS$: 345.9890, found: 345.9896.

4-(Methylthio)-3-(4-nitrophenyl)-5-phenylisoxazole(3r). White solid (101mg, 65%); mp 104-106 °C. IR(KBr) 3041, 2959, 1643, 1523, 1186, 1012, 844cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.40−8.38 (m, 2H), 8.11 (d, *J* 8.7 Hz, 2H), 8.01 (d, *J* 7.2 Hz, 2H), 7.62−7.53 (m, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.2, 162.0, 147.4, 132.3, 129.6, 129.1, 1127.8, 126.5, 125.1, 122.9, 106.8, 15.7. HRMS (ESI) (*m/z*): [M+H]$^+$ calcd. for $C_{16}H_{13}N_2O_3S$: 313.0635, found: 313.0641.

3-(4-(*tert*-Butyl)phenyl)-4-(methylthio)-5-phenylisoxazole(3s). White solid (110mg, 68%); mp 101-103 °C. IR(KBr) 3057, 2906, 1609, 1388, 1162, 822cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.10 (d, J8.6 Hz, 2H), 7.80 (d, J8.6 Hz, 2H), 7.34−7.28 (m, 3H), 7.14 (d, J 7.2 Hz, 2H), 2.40 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$) δ

170.0, 165.6, 158.3, 130.6, 129.6, 128.5, 128.4, 127.1, 125.2, 125.0, 107.6, 35.4, 31.0, 15.6. HRMS (ESI) (m/z): $[M+H]^+$ calcd. for $C_{20}H_{22}NOS$: 324.1424, found: 324.1417.

4-(Methylthio)-3-(naphthalen-2-yl)-5-phenylisoxazole(3t). Yellow liquid (106mg, 67%). IR(KBr) 3053, 2952, 1610, 1161, 1008, 805cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49−8.45 (m, 1H), 7.90 (d, *J* 7.2 Hz, 2H), 7.84−7.82 (m, 1H), 7.80−7.73 (m, 2H), 7.70−7.64 (m, 1H), 7.55−7.49 (m, 5H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 169.5, 131.1, 129.5, 127.6, 125.9, 107.1, 33.4, 28.6, 19.1. HRMS (ESI) (*m/z*): $[M+H]^+$ calcd. for $C_{20}H_{16}NOS$: 318.0940, found: 318.0947.

4-(Methylthio)-5-phenyl-3-(thiophen-2-yl)isoxazole(3u). White solid (76mg, 56%); mp 66-68 ℃. IR(KBr) 3107, 2963, 1628, 1174, 1003, 707cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* 7.3 Hz, 2H), 7.61−7.50 (m, 5H), 7.19 (dd, J 5.1, 3.7 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.6, 156.3, 130.2, 128.8, 127.9, 127.8, 127.7, 126.8, 126.4, 125.3, 104.5, 15.5. HRMS (ESI) (*m/z*): $[M+H]^+$ calcd. for $C_{14}H_{12}NOS_2$: 274.0355, found: 274.0355.

3-(*tert*-Butyl)-4-(methylthio)-5-phenylisoxazole(3v).[16] Yellow liquid (59mg, 48%). IR(KBr) 3035, 2900, 1612, 1385, 1174, 1017cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, 2H, J 7.6 Hz), 7.51-7.46 (m, 3H), 2.19 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 169.5, 131.1, 129.5, 127.6, 125.9, 107.1, 33.4, 28.6, 19.1. HRMS (ESI) (*m/z*): $[M+H]^+$ calcd. for $C_{14}H_{18}NOS$: 248.1103, found: 248.1104.

4-(Methylthio)-3,5-di-*p*-tolylisoxazole(3w). White solid (108mg, 73%); mp 189-192 ℃. IR(KBr) 3055, 2920, 2863, 1633, 1455, 1171, 1018cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* 8.1 Hz, 2H), 7.78 (d, *J* 8.1Hz, 2H), 7.35-7.28 (m, 4H), 2.45 (s, 3H), 2.44 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 164.5, 139.1, 137.4, 129.5, 129.3, 128.6, 125.9, 124.0, 123.8, 106.1, 22.1, 22.0, 19.5. HRMS (ESI) (*m/z*): $[M+H]^+$ calcd. for $C_{18}H_{18}NOS$: 296.1110, found: 296.1104.

3,5-Bis(4-methoxyphenyl)-4-(methylthio)isoxazole(3x). White solid (121mg, 74%); mp 116-119 ℃. IR(KBr) 3057, 2933, 1629, 1488, 1167, 1025,828cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* 8.1 Hz, 2H), 7.71 (d, J 8.7Hz, 2H), 7.05−7.00 (m, 4H), 3.87 (s, 3H), 3.86 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 163.3, 162.1, 130.3, 130.0, 127.4, 124.8, 121.0, 119.0, 115.0, 105.2, 55.7, 55.6, 21.4. HRMS (ESI) (*m/z*): $[M+H]^+$ calcd. for $C_{18}H_{18}NO_3S$: 328.1011, found: 328.1002.

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Supplementary Material

Supplementary material is available on the publisher’s website along with the published article.

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