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Cyclocondensation of Hydroxylamine with 1,3-Bis(het)arylmonothio 1,3-Diketones and 1,3-Bis(het)aryl-3-(methylthio)-2-propenones: Synthesis of 3,5-Bis(het)arylisoxazoles with Complementary Regioselectivity

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Efficient routes for the regioselective synthesis of 3,5-bis-(het)arylisoxazoles with complementary regioselectivity have been developed. The methods involve the cyclocondensation of hydroxylamine hydrochloride with either 1,3-bis(het)aryl-monothio-substituted 1,3-diketones **1** or with 3-methylthio-1,3-bis(het)aryl-2-propenones **2** under various reaction conditions. In the first protocol, diketones **1** were treated with hydroxylamine hydrochloride in the presence of sodium acetate/acetic acid (pH 2.2) in refluxing ethanol/benzene to give 3,5-bis(het)arylisoxazoles **5**, in which the het(aryl) moiety attached to thiocarbonyl group of the monothio-substituted 1,3-diketones is installed at the 3-position. On the other hand, the reaction of hydroxylamine hydrochloride with 3-(methylthio)-1,3-bis(het)aryl-2-propenones **2** in the presence of barium hydroxide in refluxing ethanol gave 3,5-bis-(het)arylisoxazoles **6** with complementary regioselectivity in high yields. A probable mechanism for the formation of regioisomeric isoxazoles **5** and **6** from precursors **1** and **2** has been suggested.

Introduction

Isoxazole and its derivatives constitute an important class of five membered heterocycles[1] because this structural motif is present in numerous biologically active natural products (ibotenic acid, muscimol, isoxazole-4-carboxylic acid), pharmaceuticals (such as bextra, valdecoxib, leflunomide, and cloxacillin),[1–3] and functional materials.[3c,3g] Substituted isoxazoles are potent and selective agonists of human cloned dopamine D4 receptors, and they show a broad range of biological activities[3a–3f,3h] such as GABA antagonist, analgesic, antiviral, antimicrobial, hypoglycemic, ulcerogenic, and anticancer activities, and also, as agrochemicals, herbicidal[3e] and antifungal[3e,3i,3j] activities.

Isoxazole derivatives also serve as versatile building blocks[4] in organic synthesis,[3c] as they can be converted into several useful functionalities, such as β-hydroxy ketones, β-hydroxynitriles, γ-amino alcohols, and α,β-unsaturated oximes.[1,1g,4] Therefore the development of new methods for the synthesis of these heterocycles is an area of considerable interest.

Numerous synthetic approaches for the construction of the isoxazole framework have been reported,[1,2] and among them, the two most prevalent methods are: (i) [3+2] dipolar cycloadditions between alkynes (or alkenes) and nitrile oxides;[1,2b,3,4g,5] and (ii) cyclocondensation of hydroxylamine with 1,3-dicarbonyl compounds[1,3i,6b] or other three-carbon 1,3-electrophilic variants[6a–6c] (i.e., α,β-unsaturated ketones,[4e,6c,6d] enamino ketones,[6e] β-chlorovinyl ketones,[6f] β-alkylthioenones,[6g,6h] and ynones[6i,6j]). Although the [3+2] cycloaddition method is highly convergent and versatile, it suffers from several limitations, such as low yields of products, side-reactions due to competing dimerization of nitrile oxide,[1b,1f,5a,5b] and, frequently, poor regioselectivity.[1b,7] Similarly, the classical reaction of unsymmetrically substituted 1,3-dicarbonyl compounds with hydroxylamine usually results in the formation of regioisomeric mixtures of isoxazoles.[1] Therefore, several useful and elegant methods for regioselective synthesis of isoxazoles have been developed in recent years. Fokin's group has reported routes to 3,5-/3,4-disubstituted and 3,4,5-trisubstituted isoxazoles based on the copper-[8a,8b] or ruthenium-[8c]catalysed [3+2] cycloaddition of various nitrile oxides with terminal/internal alkynes. Similarly, Larock[9a,9b] has described iodine-catalysed electrophilic cyclization of *O*-methyloximes of acetylenic ketones to give 3,5-substi-

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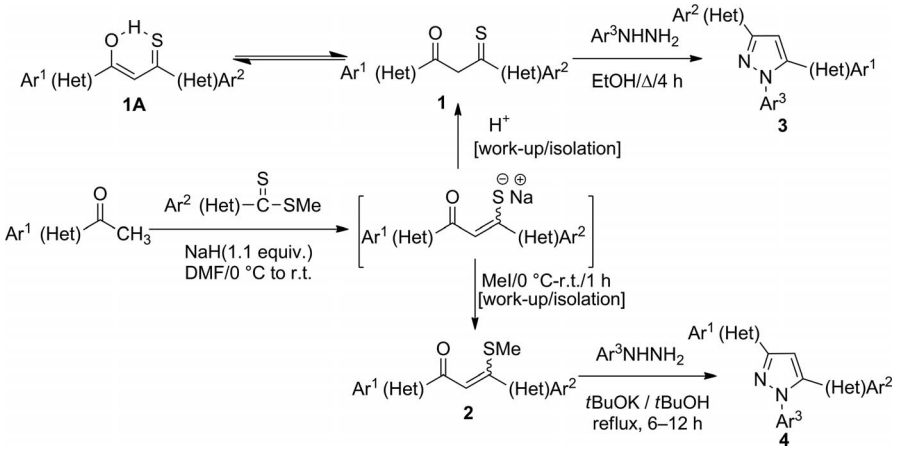
tuted-4-iodooxazoles, which can be transformed further into 3,4,5-substituted isoxazoles by palladium-catalysed cross-coupling.[9b,9c] In parallel strategies, Miyata and coworkers have developed a practical synthesis of 3,5-disubstituted isoxazoles by silver-catalysed cyclization of *O*-benzylalkynyloxime ethers,[10a] along with a gold-catalysed domino reaction of *O*-allylalkynyloxime ethers involving cyclization and subsequent Claisen-type rearrangement to give trisubstituted isoxazoles in a highly regioselective manner.[10b] Other recently published methods include the iodocyclization of *N*-alkoxycarbonyl-*O*-propargylic hydroxylamines;[11a] a sequential iron- and palladium-catalysed transformation of propargyl alcohols into *N*-protected propargylhydroxylamines, and their subsequent cyclization and coupling with various aryl iodides to give trisubstituted isoxazoles in a multistep one-pot reaction;[11b] base-catalysed cyclocondensation of activated nitromethylene compounds with dipolarophiles;[3c,12a–12c] zinc-triflate-catalysed aerobic cross-dehydrogenative coupling (CDC) of alkynes with nitrones;[13a] hypervalent-iodine-induced cycloaddition of nitrile oxides to alkynes;[13b–13d] *N*-heterocyclic-carbene-catalysed 1,3-dipolar cycloaddition of nitrile oxides and alkynes;[5f] and dipolar cycloaddition of acetylenic boronates[4g,14] and silaacetylenes[5j] with nitrile oxides. A completely regioselective synthesis of unsymmetrically 3,5-disubstituted isoxazoles by the reaction of the 1,4-dianions of oximes derived from α-alkyl ketones with various amides/esters has also been described by Olofson[15a,15b] and others.[15c] Efforts have also been made to improve the regioselectivity of the reaction of hydroxylamine with three-carbon components by altering the electrophilicity of the terminal carbons in these intermediates,[16] or by controlling the reaction conditions by changing the pH of the medium,[17] or by the introduction of a leaving group (such as a bromo or benzotriazolyl moiety) at the α-position of α,β-unsaturated ketones, which would allow the in situ transformation of the initially formed oxazolines into aromatic isoxazoles.[18] Nevertheless, new methods for the efficient and regioselective synthesis of substituted isoxazoles from readily accessible precursors are highly desirable.

As part of our ongoing research programme directed towards the design and development of new methods for the synthesis of substituted and condensed five- and six-membered heterocycles using polarized ketene dithioacetals and other organosulfur compoundsa as versatile three-carbon 1,3-bielectrophilic building blocks,[19] we have previously reported the highly regioselective synthesis of 5-(or 3-)methylthio-3-(or 5-)-substituted pyrazoles[20a] and 5-(or 3-)methylthio-3-(or 5-)arylisoxazoles[17b] by cyclocondensation of α-oxoketene dithioacetals (or β-oxadithioesters) with arylhydrazines and hydroxylamine, respectively, under different conditions. In a continuation of these studies, we became interested in 1,3-substituted-monothio 1,3-diketones of the general structure **1**,[21,22] and the corresponding 1,3-bis(het)aryl-3-(methylthio)-2-propenones **2**, a new class of potentially useful three-carbon 1,3-bielectrophile building blocks that are virtually unexplored.[22e–22g] Based on these intermediates, we have recently reported efficient regioselective synthesis of unsymmetrically substituted 1-aryl-3,5-bis(het)aryl pyrazoles **3** and **4** with complementary regioselectivity by cyclocondensation of either **1** or **2** with arylhydrazines under different conditions (Scheme 1).[23a] Encouraged by these results, and by our ongoing interest in these newly developed organosulfur building blocks (**1** and **2**),[23b,23c] we became interested in exploring the reaction of hydroxylamine with β-thioxo ketones **1** and the corresponding β-(methylthio)-2-propenones **2**, with a view to developing regioselective syntheses of unsymmetrically substituted 3,5-bis(het)arylisoxazoles **5** and **6** based on these intermediates (Tables 1 and 2). We have achieved this goal, and our results are reported in this paper.

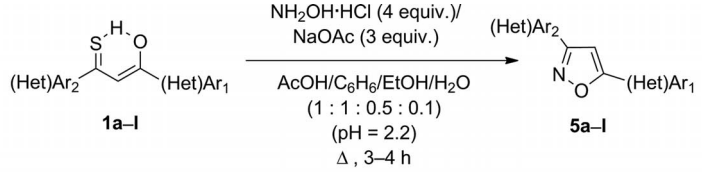
Results and Discussion

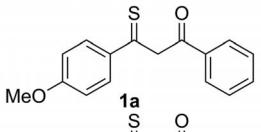
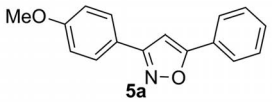
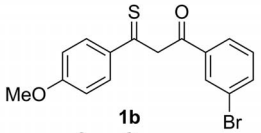
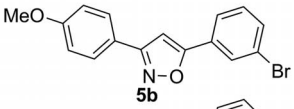
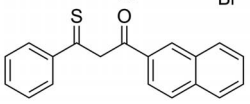
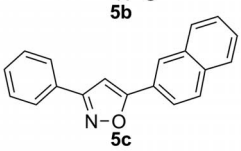
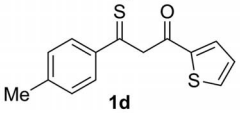
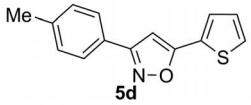
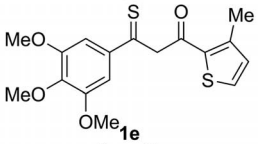
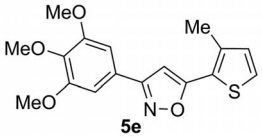
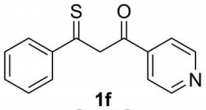
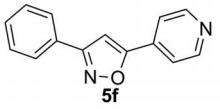
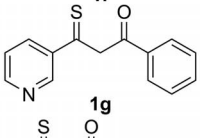
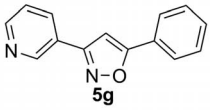
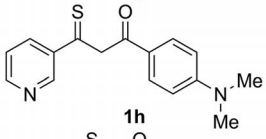
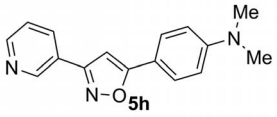
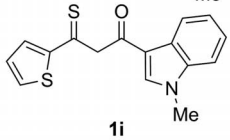
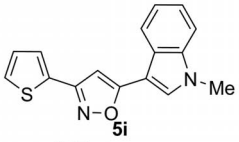
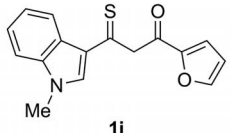
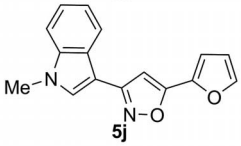
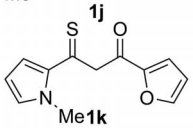
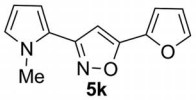
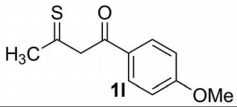
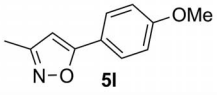
Monothio β-diketones **1a**–**1l** were prepared in good yields, by modification of an earlier reported procedure,[22a–22d] by condensation of aryl/heteroaryl methyl ketones with various aryl/heteroaryl dithioesters in the presence of sodium hydride as base (Scheme 1).[23a] These 1,3-



Scheme 1. Synthesis of 1,3-bis(het)arylpyrazoles **3** and **4** with complementary regioselectivity from precursors **1** and **2**.

Table 1. Regioselective synthesis of 3,5-bis(het)arylisoxazoles **5a**–**5l** from 1,3-monothio β-diketones **1a**–**1l**.

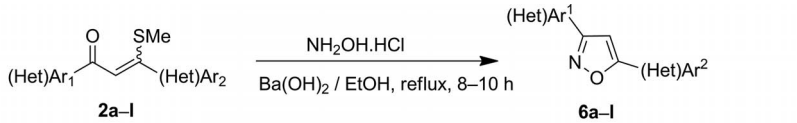


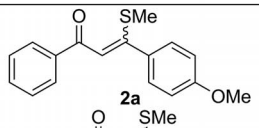
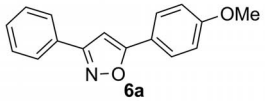
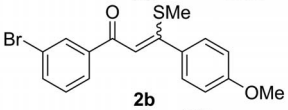
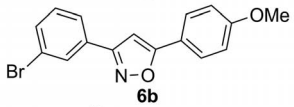
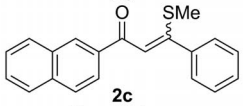
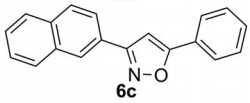
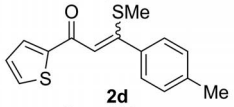
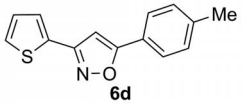
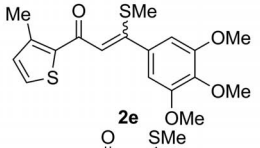
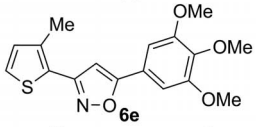
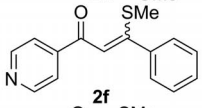
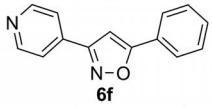
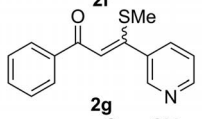
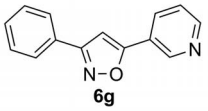
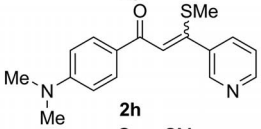
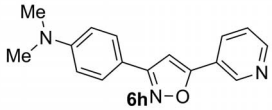
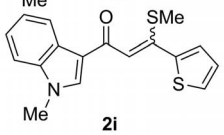
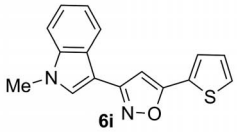
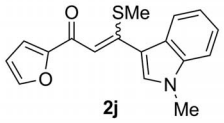
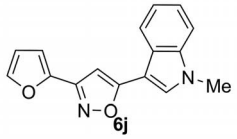
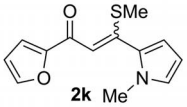
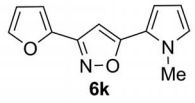
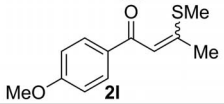
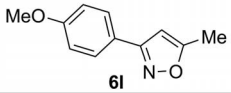
Entry[a]	1	Yield (%) 1	5	Yield (%) 5
1	 **1a**	85	 **5a**	82
2	 **1b**	79	 **5b**	84
3	 **1c**	76	 **5c**	80
4	 **1d**	80	 **5d**	88
5	 **1e**	86	 **5e**	79
6	 **1f**	75	 **5f**	95
7	 **1g**	78	 **5g**	86
8	 **1h**	82	 **5h**	92
9	 **1i**	64	 **5i**	79
10	 **1j**	78	 **5j**	78
11	 **1k**	81	 **5k**	87
12	 **1l**	60	 **5l**	77

[a] Reaction conditions:
1 (10 mmol), $NH_2OH·HCl$ (40 mmol) in NaOAc / AcOH / C_6H_6 / EtOH / H_2O, reflux, 3-4 h

substituted monothio diketones were directly converted into the corresponding β-methylthio-β-het(aryl)enones (i.e., **2a**–**2l**) by in situ alkylation of thiolate salts with methyl iodide under similar conditions.[23a] Monothio 1,3-diketones **1a**–**1l** and β-alkylthioenones **2a**–**2l** were characterized with the help of spectral and analytical data, which showed that monothio β-diketones **1a**–**1l** exist in enol form **1A**.[23a]

Table 2. Regioselective synthesis of 3,5-bis-(het)arylisoxazoles **6a**–**6l** from 3-(methyl)thiopropenones **2a**–**2l**.



Entry[a]	2	Yield (%) 2	6	Yield (%) 6
1	 **2a**	76	 **6a**	80
2	 **2b**	67	 **6b**	74
3	 **2c**	73	 **6c**	87
4	 **2d**	72	 **6d**	71
5	 **2e**	78	 **6e**	75
6	 **2f**	72	 **6f**	86
7	 **2g**	73	 **6g**	86
8	 **2h**	75	 **6h**	79
9	 **2i**	72	 **6i**	73
10	 **2j**	92	 **6j**	74
11	 **2k**	78	 **6k**	80
12	 **2l**	86	 **6l**	70

[a] Reaction conditions:
2 (10 mmol), $NH_2OH{\cdot}HCl$ (40 mmol), $Ba(OH)_2$ (30 mmol) in EtOH, reflux, 8–12 h

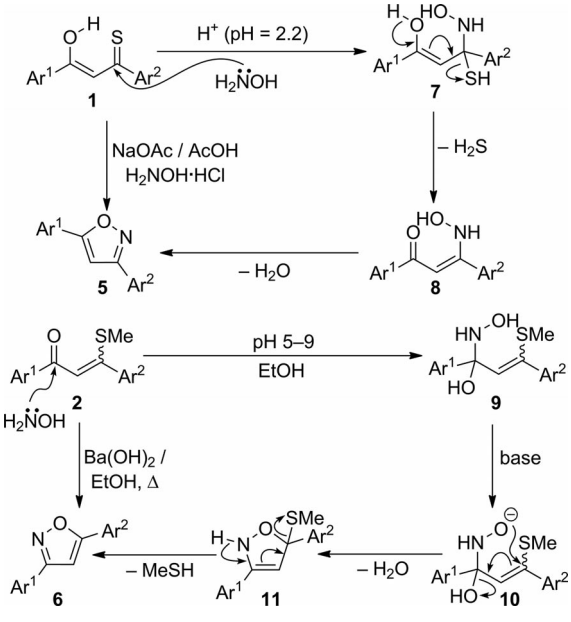
The reaction of unsymmetrically substituted monothio 1,3-diketone **1a** with hydroxylamine hydrochloride was first examined under various conditions with a view to obtaining either of the unsymmetrically substituted isoxazoles **5a** or **6a** in a regiocontrolled fashion. The use of bases such as sodium carbonate, sodium hydrogen carbonate, or sodium ethoxide in refluxing ethanol led only to the formation of intractable mixtures of products, along with unreacted starting material **1a** (with Na_2CO_3 or $NaHCO_3$). Under neutral conditions, **1a** was recovered unchanged with no trace of any product. However, when **1a** was treated with hydroxylamine hydrochloride in the presence of sodium acetate in a mixture of acetic acid, benzene, ethanol, and water (1:1:0.5:0.1; pH = 2.2) at reflux, a single product was isolated after work-up of the reaction, which was characterized as 3-(4-methoxyphenyl)-5-phenylisoxazole (**5a**; Table 1, entry 1), on the basis of its spectral and analytical data and by comparison of its melting point with that reported in the literature.[24] Similarly, the corresponding 1-(4-methoxyphenyl)-3-(3-bromophenyl)monothio 1,3-diketone (**1b**), with two different substituents on two aryl groups, also gave the corresponding 3-(4-methoxyphenyl)-5-(3-bromophenyl)isoxazole (**5b**) in good yield, in a highly regioselective manner (Table 1, entry 2). The regiochemistry of **5b** was further confirmed from its X-ray diffraction data (Figure S1). Isoxazoles **5a** and **5b** are apparently formed by attack of the amino functionality of hydroxylamine onto the thiocarbonyl group of **1a** to form the Ar–C=N bond of isoxazoles. 1-Phenyl-3-(2-naphthyl)-monothio-1,3-diketone (**1c**) also reacted in a similar manner with hydroxylamine under these conditions to give exclusively 3-phenyl-5-(2-naphthyl)-isoxazole (**5c**) in 80% yield (Table 1, entry 3). Similarly, 3,5-(het)arylisoxazoles **5d**–**5h** bearing one aryl and one heteroaryl group could also be prepared in high yields as single regioisomers under the same conditions, starting from the corresponding aryl/heteroaryl 1,3-monothio diketones (i.e., **1d**–**1h**; Table 1, entries 4–8). Further diversity was added by the regioselective introduction of two different heteroaryl groups at the 3- and 5-positions of the isoxazole framework by subjecting 1,3-bis(het)-aryl monothio diketone precursors **1i**–**1k** to the same reaction conditions. This led to the formation of 3,5-bis(het)-arylisoxazoles **5i**–**5k** in high overall yields (Table 1, entries 9–12).

As an example of the extension of this methodology for the synthesis of alkyl-substituted isoxazoles, 3-methyl-5-(4-methoxyphenyl)isoxazole (**5l**) was also obtained in good yield from the corresponding methyl-substituted monothio 1,3-diketone (i.e., **1l**) under similar conditions (Table 1, entry 12). The structures and regiochemistry of these newly synthesized isoxazoles were confirmed with the help of spectral and analytical data, and also by the X-ray diffraction data of isoxazoles **5b** and **5e** (Figure S2).

Having developed a completely regioselective synthesis of 3,5-bis(het)arylisoxazoles **5a**–**5l** from 1,3-substituted monothio diketones **1a**–**1l**, we became interested in developing appropriate reaction conditions for the synthesis of 1,3-disubstituted isoxazoles **6a**–**6l** with complementary regiochemistry, starting from the same 1,3-monothio 1,3-diketone precursors **1a**–**1l**, by treating them with hydroxylamine under various reaction conditions. However, all our attempts to achieve this goal were unsuccessful, and only intractable mixtures of products were formed. We therefore turned our attention to β-(methylthio)-β-(het)arylenones **2a**–**2l**,[23a] which are easily accessible from various active-methylene ketones in a one-pot reaction involving base-induced thioacylation with dithioesters followed by alkylation (Scheme 1).

As a model experiment, enone **2a** was subjected to cyclization with hydroxylamine hydrochloride under different conditions, varying the solvent, the base, and the temperature. After a few unsuccessful attempts, we did indeed obtain the regioisomeric 3-phenyl-5-(4-methoxyphenyl)isoxazole (**6a**) exclusively in 80% yield, by treatment of 1,3-diarylenone **2a** with hydroxylamine hydrochloride in the presence of barium hydroxide in refluxing ethanol (Table 2, entry 1). The structure of isoxazole **6a** was confirmed with the help of spectral and analytical data, and by comparison of its melting point with that reported in the literature.[25] These reaction conditions were found to be generally applicable for the synthesis of other regioisomeric 3,5-diaryl-isoxazoles (**6b** and **6c**), 3,5-aryl/heteroaryl-isoxazoles (**6d**–**6h**), and 3,5-bis(heteroaryl)isoxazoles **6i**–**6k**, along with methyl arylisoxazole **6l**, in excellent yields (Table 2, entries 2–12). In every case, the formation of only one regioisomer **6** was observed, and no trace of the other isomer (**5a**–**5l**) was isolated. The structures of newly synthesized isoxazoles **6a**–**6l** were confirmed from their ^1H NMR, ^{13}C NMR, and HRMS spectra, along with X-ray diffraction data for isoxazoles **6b** and **6e** (Figures S39–S42).

The probable mechanism for the formation of regioisomeric isoxazoles **5** and **6** from the corresponding 1,3-mono-



Scheme 2. Probable mechanism for the formation of regioisomeric isoxazoles **5** and **6** from **1** and **2**.

thio ketone and 3-(methylthio)propenone precursors **1** and **2** upon reaction with hydroxylamine under different conditions is shown in Scheme 2. Thus, at lower pH, under acidic conditions, monothio diketone **1** is present mainly in the enolic form, which means that the thiocarbonyl group is the only possibility for the point of initial nucleophilic attack by hydroxylamine. Intramolecular heterocyclization via intermediates **7**–**8** then gives isoxazoles **5** exclusively, in which the het(aryl) group attached to the thiocarbonyl group in **1** is installed at the 3-position. On the other hand, under basic conditions (pH 5–9), 3-(methylthio)propenones **2** undergo intial nucleophilic attack by hydroxylamine at the carbonyl group to give only the regioisomeric isoxazoles (i.e., **6**) after subsequent intramolecular cyclization via intermediates **9**–**11** (Scheme 2).[17,18,26,27]

Conclusions

In summary, we have demonstrated that 1,3-bis(het)arylmonothio 1,3-diketones **1** are versatile three-carbon 1,3-electrophilic components for the highly regioselective synthesis of 3,5-diaryl/(het)aryl isoxazoles **5**, by cyclocondensation with hydroxylamine under controlled reaction conditions. Furthermore, it was also possible to achieve the synthesis of 3,5-diaryl/(het)aryl isoxazoles **6** with complimentary regiochemistry, by using β-(methylthio)-β-aryl/(het)arylenones **2** as three-carbon components, and treating them with hydroxylamine in the presence of barium hydroxide. Both monothio 1,3-diketones and β-(methylthio)propenone precursors **1** and **2** are readily accessible from a large variety of active methylene ketones in high yields, and so there is great scope for the incorporation of diverse aryl/(het)aryl motifs into the product isoxazoles in a highly regioselective fashion and in excellent yield. Further work to investigate the mechanism of these regioselective processes, and also to use them for the synthesis of pharmaceutically important targets is currently underway.

Experimental Section

General Information: All chemicals were bought from commercial suppliers, and were used without further purification. Solvents were dried according to standard procedures. All reactions were monitored by thin-layer chromatography using Merck TLC Silica gel plates, which were visualized with UV light. Column chromatography was carried out using Merck silica gel (100–200 mesh). Nuclear magnetic resonance spectra were recorded using a 400 MHz Fourier transform NMR spectrometer with $CDCl_3$ as solvent. Chemical shifts are reported in ppm on the δ scale, using residual solvent protons as internal standard (δ = 7.26 for $CDCl_3$ in ^1H NMR spectra; δ = 77.16 for $CDCl_3$ in ^{13}C NMR spectra). Coupling constants are reported as *J* values in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), m (multiplet), and br (broad). Infrared spectra were recorded using an FTIR instrument, and HRMS spectra were recorded with a Q-TOF mass spectrometer. Melting points were recorded using an electrothermal capillary melting-point apparatus.

General Procedure for the Preparation of 1,3-Bis(het)arylmonothio β-Diketones 1a–1l: 1,3-Bis(het)arylmonothio β-diketones were prepared following our earlier reported procedure[23a] by reaction of the corresponding (hetero)aryl methyl ketone (3.0 mmol) with the appropriate (hetero)aryl dithioesters (3.0 mmol) using sodium hydride (0.25 g, 6.3 mmol) in DMF (10 mL), and subsequent work-up. Known 1,3-bis(het)aryl-3-(methylthio)-2-propenones **1b**, **1e**, **1f**, **1j**, and **1l** were characterized by comparison of their spectral and analytical data with literature data.[23a] The spectral and analytical data of unknown 1,3-monothio diketones **1a**, **1c**, **1d**, **1g**–**1i**, and **1k** are given below.

3-(4-Methoxyphenyl)-1-phenyl-3-thioxopropan-1-one (1a): Red solid, m.p. 61–63 °C. R_f = 0.59 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2926, 1599, 1550, 1174, 773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 15.98 (s, 1 H), 8.00 (d, *J* = 7.2 Hz, 2 H), 7.90 (d, *J* = 8.8 Hz, 2 H), 7.55–7.49 (m, 3 H), 7.44 (s, 1 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.5, 178.1, 162.8, 138.5, 135.7, 132.5, 129.0, 128.9, 127.2, 113.9, 108.8, 55.6 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}O_2S$ $[M + H]^+$ 271.0793; found 271.0787.

1-(Naphthalen-3-yl)-3-phenyl-3-thioxopropan-1-one (1c): Red solid, m.p. 100–102 °C. R_f = 0.59 (1.5:8.5 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3047, 1545, 1447 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 15.36 (s, 1 H), 8.58 (d, *J* = 1.4 Hz, 1 H), 8.03 (dd, *J* = 8.4, 1.4 Hz, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 7.94 (s, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.88–7.85 (m, 2 H), 7.63–7.44 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.9, 179.7, 145.8, 135.5, 133.1, 133.0, 131.3, 129.6, 128.8, 128.75, 128.70, 128.6, 128.0, 127.1, 127.0, 123.3, 111.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{14}OS$ $[M + H]^+$ 291.0844; found 291.0838.

1-(Thiophen-2-yl)-3-thioxo-3-*p*-tolylpropan-1-one (1d): Red solid, m.p. 96–98 °C. R_f = 0.6 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2918, 1557, 1410, 1240 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 13.67 (s, 1 H), 7.84 (dd, *J* = 3.8, 1.0 Hz, 1 H), 7.68 (d, *J* = 8.2 Hz, 2 H), 7.64 (dd, *J* = 4.8, 1.0 Hz, 1 H), 7.29 (s, 1 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 7.16 (dd, *J* = 4.8, 3.8 Hz, 1 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 176.1, 142.5, 141.8, 141.4, 132.8, 130.5, 129.4, 128.6, 126.9, 110.6, 21.5 ppm. HRMS (ESI): calcd. for $C_{14}H_{12}OS_2$ $[M + H]^+$ 261.0408; found 261.0399.

1-Phenyl-3-(pyridin-3-yl)-3-thioxopropan-1-one (1g): Red solid, m.p. 90–92 °C. R_f = 0.43 (3:7 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2927, 1631, 1585, 1534 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 14.52 (s, 1 H), 9.21 (dd, *J* = 2.0, 0.4 Hz, 1 H), 8.77 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.30 (ddd, *J* = 8.0, 2.0, 1.6 Hz, 1 H), 7.81–7.79 (m, 2 H), 7.54–7.49 (m, 1 H), 7.47–7.43 (m, 3 H), 7.42 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 178.1, 153.0, 148.6, 145.0, 134.7, 132.0, 131.6, 128.8, 127.0, 123.8, 110.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{11}NOS$ $[M + H]^+$ 242.064; found 242.0639.

1-[4-(Dimethylamino)phenyl]-3-(pyridin-3-yl)-3-thioxopropan-1-one (1h): Red solid, m.p. 118–120 °C. R_f = 0.41 (3:7 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2923, 1583, 1549, 1482, 1246, 1087, 840 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 16.29 (s, 1 H), 9.16 (s, 1 H), 8.71 (d, *J* = 5.2 Hz, 1 H), 8.23–8.21 (m, 1 H), 7.98 (d, *J* = 6.0 Hz, 2 H), 7.43–7.39 (m, 1 H), 7.36 (d, *J* = 3.2 Hz, 1 H), 6.64 (d, *J* = 6.0 Hz, 2 H), 3.07 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.3, 172.3, 153.5, 152.1, 148.0, 134.2, 133.1, 132.1, 129.6, 123.7, 111.0, 106.3, 40.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{16}N_2OS$ $[M + H]^+$ 285.1062; found 285.1060.

1-(1-Methyl-1*H*-indol-3-yl)-3-(thiophen-2-yl)-3-thioxopropan-1-one (1i): Red solid, m.p. 122–124 °C. R_f = 0.51 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2926, 1558, 1507, 1449 cm^{-1}. ^1H NMR (400 MHz,

$CDCl_3$): δ = 15.87 (s, 1 H), 8.43–8.41 (m, 1 H), 7.92 (s, 1 H), 7.81 (dd, J = 3.8, 1.2 Hz, 1 H), 7.58 (dd, J = 5.2, 1.2 Hz, 1 H), 7.39 (s, 1 H), 7.36–7.32 (m, 3 H), 7.16 (dd, J = 5.2, 3.8 Hz, 1 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.3, 170.2, 141.0, 138.4, 133.8, 130.9, 129.2, 128.6, 125.5, 124.6, 123.5, 122.9, 122.1, 110.4, 106.7, 33.7 ppm. HRMS (ESI): calcd. for $C_{16}H_{13}NOS_2$ [M + H]$^+$ 300.0517; found 300.0499.

1-(Furan-2-yl)-3-(1-methyl-1*H*-pyrrol-2-yl)-3-thioxopropan-1-one (1k): Red solid, m.p. 48–50 °C. R_f = 0.46 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2938, 1614, 1539, 1390 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.55 (s, 1 H), 7.58 (s, 1 H), 7.21 (s, 1 H), 7.14 (d, J = 3.8 Hz, 1 H), 6.95 (dd, J = 8.0, 3.8 Hz, 1 H), 6.91 (s, 1 H), 6.57 (t, J = 1.6 Hz, 1 H), 6.18 (t, J = 3.6 Hz, 1 H), 4.08 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.0, 164.0, 150.1, 145.7, 140.3, 133.7, 115.5, 114.7, 112.9, 108.7, 106.3, 38.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{11}NO_2S$ [M + H]$^+$ 234.0589; found 234.0580.

General Procedure for the Preparation of 1,3-Bis(het)aryl-3-(methylthio)-2-propenones 2a–2l: The 1,3-bis(het)aryl-3-(methylthio)-2-propenones were prepared following our earlier reported procedure[23a] by reaction of the corresponding (hetero)aryl methyl ketones (3.0 mmol) with the appropriate (hetero)aryl dithioesters (3.0 mmol) using sodium hydride (0.25 g, 6.3 mmol) in DMF (10 mL), followed by treatment with methyl iodide (0.28 mL, 4.5 mmol) and subsequent work-up. Known 1,3-bis(het)aryl-3-(methylthio)-2-propenones **2b**, **2e**, **2f**, **2j**, and **2l** were characterized by comparison of their spectral and analytical data with literature data.[23a] The spectral and analytical data of unknown 1,3-bis(het)aryl-3-(methylthio)-2-propenones **2a**, **2c**, **2d**, **2g**–**2i**, and **2k** are given below.

(*E*/*Z*)-3-(4-Methoxyphenyl)-3-(methylthio)-1-phenylprop-2-en-1-one (2a): *E*/*Z* = 77:23. Pale yellow semi-solid. R_f = 0.45 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2925, 1608, 1499, 1248, 1015, 773 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.96 (m, 1.54 H), 7.85–7.83 (m, 0.46 H), 7.52–7.34 (m, 3 H), 7.28 (d, J = 8.8 Hz, 2 H), 7.08 (s, 0.77 H), 6.95 (d, J = 8.8 Hz, 1.54 H), 6.81 (d, J = 8.8 Hz, 0.46 H), 6.56 (s, 0.23 H), 3.84 (s, 2.31 H), 3.76 (s, 0.69 H), 2.43 (s, 0.69 H), 1.99 (s, 2.31 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9, 188.5, 164.6, 161.1, 160.5, 160.2, 139.2, 138.8, 132.2, 131.2, 131.1, 130.1, 129.9, 129.6, 128.6, 128.5, 128.3, 128.1, 119.2, 115.6, 114.1, 113.7, 55.5, 55.3, 16.9, 16.5 ppm. HRMS (ESI): calcd. for $C_{17}H_{16}O_2S$ [M + H]$^+$ 285.0949; found 285.0942.

(*E*/*Z*)-3-(Methylthio)-1-(naphthalen-3-yl)-3-phenylprop-2-en-1-one (2c): *E*/*Z* = 87:13. Yellow solid, m.p. 134–136 °C. R_f = 0.4 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2926, 1630, 1532, 1482 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.4.5 (br. s, 0.87 H), 8.37 (br. s, 0.13 H), 8.09 (dd, J = 8.6, 1.6 Hz, 0.87 H), 7.93–7.79 (m, 2.87 H), 7.58–7.42 (m, 3.87 H), 7.38–7.36 (m, 1.39 H), 2.49 (s, 0.4 H), 1.97 (s, 2.6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.6, 188.3, 164.8, 160.9, 138.9, 137.9, 136.4, 136.1, 135.3, 132.7, 132.5, 129.9, 129.5, 129.4, 129.2, 129.1, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 126.7, 124.6, 124.4, 119.3, 116.2, 16.7, 16.5 ppm. HRMS (ESI): calcd. for $C_{20}H_{16}OS$ [M + H]$^+$ 305.1000; found 305.0995.

(*E*)-3-(Methylthio)-1-(thiophen-2-yl)-3-*p*-tolylprop-2-en-1-one (2d): Yellow solid, m.p. 86–88 °C. R_f = 0.40 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2920, 1616, 1541, 1410 cm^{-1}. ^{1}H NMR (400 MHz, [D_6]-DMSO): δ = 7.98 (dd, J = 3.8, 1.0 Hz, 1 H), 7.93 (dd, J = 4.4, 1.0 Hz), 7.29 (d, J = 8.2 Hz, 2 H), 7.26 (d, J = 8.2 Hz, 2 H), 7.19 (dd, J = 4.4, 3.8 Hz, 1 H), 2.36 (s, 3 H), 1.89 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.1, 164.8, 146.3, 139.1, 135.8, 132.8, 130.5, 129.4, 128.1, 128.0, 119.0, 21.4, 16.9 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}OS_2$ [M + H]$^+$ 275.0564; found275.0557.

(*E*/*Z*)-3-(Methylthio)-1-phenyl-3-(pyridin-3-yl)prop-2-en-1-one (2g): *E*/*Z* = 73:27. Yellow solid, m.p. 64–66 °C. R_f = 0.40 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2922, 1631, 1579, 1534 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.15 (d, J = 1.6 Hz, 0.73 H), 9.0 (d, J = 1.6 Hz, 0.27 H), 8.72 (dd, J = 4.8, 1.6 Hz, 0.73 H), 8.62 (dd, J = 4.8, 1.6 Hz, 0.27 H), 8.26 (ddd, J = 8.0, 2.0, 1.6 Hz, 0.73 H), 8.02 (ddd, J = 8.0, 2.0, 1.6 Hz, 0.27 H), 7.46–7.38 (m, 2.92 H), 7.33–7.29 (m, 3.08 H), 7.06 (s, 0.73 H), 6.53 (s, 0.26 H), 2.47 (s, 0.81 H), 1.97 (s, 2.18 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.4, 186.7, 167.2, 163.3, 152.7, 152.6, 149.9, 149.5, 138.5, 137.5, 135.9, 135.6, 134.5, 134.0, 129.6, 129.2, 128.9, 128.5, 128.4, 128.0, 123.7, 123.4, 118.4, 115.4, 16.8, 16.6 ppm. HRMS (ESI): calcd. for $C_{15}H_{13}NOS$ [M + H]$^+$ 356.0796; found 356.0791.

(*E*/*Z*)-1-[4-(Dimethylamino)phenyl]-3-(methylthio)-3-(pyridin-3-yl)-prop-2-en-1-one (2h): *E*/*Z* = 80:20. Yellow solid, m.p. 98–100 °C. R_f = 0.42 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2926, 1608, 1507 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.17 (dd, J = 2.0, 0.6 Hz, 0.8 H), 8.97 (dd, J = 2.2, 0.8 Hz, 0.2 H), 8.71 (dd, J = 4.4, 1.6 Hz, 0.8 H), 8.57 (dd, J = 4.8, 1.6 Hz, 0.2 H), 8.26 (dt, J = 8.0, 2.0 Hz, 0.8 H), 8.0 (dt, J = 8.0, 2.2 Hz, 0.2 H), 7.39 (ddd, J = 8.0, 4.4, 0.6 Hz, 0.8 H), 7.29–7.21 (m, 2.2 H), 7.04 (s, 0.8 H), 6.74 (d, J = 8.8 Hz, 1.6 H), 6.53 (d, J = 8.8 Hz, 0.4 H), 6.39 (s, 0.2 H), 3.02 (s, 4.8 H), 2.93 (s, 1.2 H), 2.46 (s, 0.6 H), 2.10 (s, 2.4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.3, 186.5, 169.9, 164.4, 152.4, 152.0, 151.7, 151.2, 149.9, 149.4, 135.9, 135.6, 135.0, 134.5, 130.5, 129.6, 126.0, 124.2, 124.6, 123.2, 117.7, 114.1, 111.8, 111.3, 40.5, 40.2, 17.4,16.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{18}N_2OS$ [M + H]$^+$ 299.1218; found 299.1218.

(*E*/*Z*)-1-(1-Methyl-1*H*-indol-3-yl)-3-(methylthio)-3-(thiophen-2-yl)-prop-2-en-1-one (2i): *E*/*Z* = 76:24. Yellow solid, m.p. 51–53 °C. R_f = 0.53 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2918, 1608, 1524, 1407 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.0 Hz, 0.76 H), 7.70 (dd, J = 4.0, 1.6 Hz, 0.24 H), 7.68 (dd, J = 3.6, 1.2, 0.76 Hz), 7.55 (dd, J = 5.2, 1.2, 0.76 Hz), 7.52–7.51 (m, 0.72 H), 7.37 (d, J = 8.0 Hz, 0.76 H), 7.33–7.27 (m, 0.96 H), 7.25 (d, J = 1.2 Hz, 0.76 H), 7.23–7.21 (m, 0.72 H), 7.12 (s, 0.76 H), 7.10–7.06 (m, 1 H), 3.85 (s, 2.3 H), 3.78 (s, 0.7 H), 2.50 (s, 0.7 H), 2.16 (s, 2.3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.0, 179.5, 157.8, 154.6, 147.2, 146.9, 137.2, 132.3, 132.2, 131.8, 130.5, 130.1, 129.1, 128.1, 127.9, 126.5, 126.0, 122.9, 122.5, 121.4, 121.1, 120.7, 120.3, 118.2, 114.4, 112.9, 112.7, 110.0, 109.8, 33.3, 17.4, 16.9 ppm. HRMS (ESI): calcd. for $C_{17}H_{15}NOS_2$ [M + H]$^+$ 314.0670; found 314.0658.

(*E*/*Z*)-1-(Furan-2-yl)-3-(1-methyl-1*H*-pyrrol-2-yl)-3-(methylthio)-prop-2-en-1-one (2k): *E*/*Z* = 70:30. Yellow solid, m.p. 65–67 °C. R_f = 0.56 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2916, 1574, 1505, 1471 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.45 (m, 1 H), 7.11 (dd, J = 3.6, 0.8 Hz, 0.7 H), 7.05 (dd, J = 3.4, 0.4 Hz, 0.3 H), 6.98 (s, 0.7 H), 6.71–6.69 (m, 0.6 H), 6.66 (dd, J = 2.4, 2.0 Hz, 0.7 H), 6.46 (dd, J = 3.6, 2.0 Hz, 0.7 H), 6.44 (dd, J = 3.4, 2.0 Hz, 0.3 H), 6.29 (dd, J = 3.8, 2.0 Hz, 0.3 H), 6.13 (dd, J = 3.6, 2.0 Hz, 0.7 H), 6.10–6.09 (m, 1.0 H), 3.55 (s, 2.1 H), 3.41 (s, 0.9 H), 2.39 (s, 0.9 H), 1.85 (s, 2.1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.4, 174.5, 155.4, 154.5, 154.2, 153.4, 145.7, 145.4, 130.1, 128.9, 125.9, 124.4, 120.0, 116.1, 113.9, 112.5, 112.4, 112.2, 110.8, 108.2, 108.1, 34.3, 34.2, 16.9, 15.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{13}NO_2S$ [M + H]$^+$ 248.0745; found 248.0740.

General Procedure for the Synthesis of 3-Methyl/(het)aryl-5-(het)-arylisoxazoles 5a–5l from Monothio 1,3-Diketones 1a–1l: A solution of sodium acetate (0.06 g, 9 mmol) and hydroxylamine hydrochloride (0.1 g, 12 mmol) in water (10 mL) was added to a stirred solution of 1-aryl/heteroaryl-3-thioxo-3-alkyl/aryl/heteroaryl prop-

an-1-one **1** (3 mmol) in benzene (100 mL) and AcOH (100 mL). The reaction mixture was made homogeneous by the addition of EtOH (55 mL), and then it was heated at reflux for 3–4 h (monitored by TLC). The mixture was then concentrated to dryness under reduced pressure, and the residue was extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was washed with water (2 × 100 mL) and brine (1 × 100 mL), and dried using anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give crude isoxazoles **5**, which were purified by column chromatography on silica gel using hexane/EtOAc as eluent.

3-(4-Methoxyphenyl)-5-phenylisoxazole (5a): White solid, m.p. 120–122 °C (ref.[28a] 120 °C). R_f = 0.52 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2935, 1609, 11457, 1257, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.79 (m, 4 H), 7.50–7.42 (m, 3 H), 7.0 (d, J = 8.8 Hz, 2 H), 6.77 (s, 1 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 162.7, 161.2, 130.3, 129.1, 128.3, 127.7, 126.0, 121.8, 114.5, 97.4, 55.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{13}NO_2$ $[M + H]^+$ 252.1025; found 252.1015.

5-(3-Bromophenyl)-3-(4-methoxyphenyl)isoxazole (5b): White solid, m.p. 116–118 °C. R_f = 0.48 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2926, 1611, 1522, 1436, 1200 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.78 (d, J = 8.8 Hz, 2 H), 7.75 (d, J = 8.4 Hz, 1 H), 7.56 (d, J = 8.4 Hz, 1 H), 7.34 (t, J = 8.0 Hz, 1 H), 7.00 (d, J = 8.8 Hz, 2 H), 6.77 (s, 1 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 162.7, 161.1, 133.0, 130.5, 129.4, 128.8, 128.2, 124.3, 123.1, 121.4, 114.4, 98.1, 55.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{12}BrNO_2$ $[M + Na]^+$ 351.9949; found 351.9949.

5-(Naphthalene-2-yl)-3-phenylisoxazole (5c): Off-white solid, m.p. 129–130 °C. R_f = 0.79 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3049, 2922, 1615, 1566 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.37 (s, 1 H), 7.95 (d, J = 8.8 Hz, 2 H), 7.92–7.87 (m, 4 H), 7.56 (dd, J = 6.4, 3.2 Hz, 2 H), 7.52 (d, J = 8.8 Hz, 3 H), 6.95 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 162.1, 133.0, 132.1, 129.0, 128.2, 127.94, 127.88, 127.7, 126.9, 126.3, 126.0, 125.9, 124.6, 123.7, 121.9, 96.9 ppm. HRMS (ESI): calcd. for $C_{19}H_{13}NO$ $[M + Na]^+$ 294.0895; found 294.0897.

5-(Thiophen-2-yl)-3-*p*-tolyisoxazole (5d): White solid, m.p. 68–70 °C. R_f = 0.62 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3101, 2915, 1599, 1423 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.0 Hz, 2 H), 7.55 (d, J = 2.4 Hz, 1 H), 7.45 (d, J = 4.4 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 4.0 Hz, 1 H), 6.67 (s, 1 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 162.9, 140.2, 129.6, 129.4, 128.0, 127.9, 126.9, 126.7, 126.1, 97.2, 21.4 ppm. HRMS (ESI): calcd. for $C_{14}H_{11}NOS$ $[M + Na]^+$ 264.0459; found 264.0459.

5-(3-Methylthiophen-2-yl)-3-(3,4,5-trimethoxyphenyl)isoxazole (5e): Brown solid, m.p. 63–65 °C. R_f = 0.70 (3:7 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2930, 1589, 1235 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 5.2 Hz, 1 H), 7.07 (s, 2 H), 6.96 (d, J = 5.2 Hz, 1 H), 6.57 (s, 1 H), 3.95 (s, 6 H), 3.90 (s, 3 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 162.6, 153.6, 139.8, 138.3, 131.5, 126.8, 124.4, 123.6, 104.2, 98.0, 60.9, 56.3, 15.7 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}NO_4S$ $[M + Na]^+$ 354.0776; found 354.0778.

4-(3-Phenylisoxazol-5-yl)pyridine (5f): Dark yellow solid, m.p. 121–123 °C. R_f = 0.32 (3:7 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2922, 1580, 1403, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.78–8.69 (m, 2 H), 7.88–7.84 (m, 2 H), 7.75 (d, J = 5.2 Hz, 1 H), 7.71 (d, J = 5.2 Hz, 1 H), 7.50–7.45 (m, 3 H), 7.02 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 163.2, 134.2, 130.4, 129.0, 128.5, 127.0, 126.8, 125.9, 97.3 ppm. HRMS (ESI): calcd. for $C_{14}H_{10}N_2O$ $[M + H]^+$ 223.0871; found 223.0872.

3-(5-Phenylisoxazol-3-yl)pyridine (5g): Off-white solid, m.p. 107–108 °C. R_f = 0.55 (3:7 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2946, 1571, 1449, 765 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.08 (d, J = 1.2 Hz, 1 H), 8.71 (d, J = 1.2 Hz, 1 H), 8.21 (d, J = 8.0 Hz, 1 H), 7.88–7.84 (m, 2 H), 7.62–7.46 (m, 3 H), 7.44 (dd, J = 8.0, 4.8 Hz, 1 H), 6.87 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 160.6, 151.2, 148.1, 134.2, 130.7, 129.2, 127.3, 126.1, 125.5, 123.9, 97.3 ppm. HRMS (ESI): calcd. for $C_{14}H_{10}N_2O$ $[M + H]^+$ 223.0871; found 223.0871.

***N*,*N*-Dimethyl-4-[3-(pyridine-3-yl)isoxazole-5-yl]benzenamine (5h):** Pale yellow solid, m.p. 157–159 °C. R_f = 0.59 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2960, 1608, 1465, 1248, 790 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.06 (br. s, 1 H), 8.66 (br. d, J = 3.2 Hz, 1 H), 8.12 (dt, J = 8.0, 2.0 Hz, 1 H), 7.73 (d, J = 8.8 Hz, 2 H), 7.42 (dd, J = 8.0, 4.8 Hz, 1 H), 6.84 (s, 1 H), 6.76 (d, J = 8.8 Hz, 2 H), 3.02 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 163.2, 151.8, 150.8, 147.1, 133.0, 128.0, 124.2, 123.9, 116.2, 112.2, 98.3, 40.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}N_3O$ $[M + H]^+$ 266.1293; found 266.1286.

1-Methyl-2-[3-(thiophen-2-yl)isoxazole-5-yl]-1*H*-indole (5i): Yellow crystalline solid, m.p. 115–117 °C. R_f = 0.73 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2916, 1620, 1453, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.0 (d, J = 8.0 Hz, 1 H), 7.64 (s, 1 H), 7.55 (d, J = 2.8 Hz, 1 H), 7.44–7.40 (m, 2 H), 7.37–7.29 (m, 2 H), 7.14 (dd, J = 4.8, 3.6 Hz, 1 H), 6.64 (s, 1 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 157.8, 137.2, 131.4, 128.8, 127.6, 127.2, 127.1, 124.8, 122.9, 121.3, 120.1, 110.0, 103.8, 95.2, 33.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{12}N_2OS$ $[M + Na]^+$ 303.0568; found 303.0568.

2-[5-(Furan-2-yl)isoxazol-3-yl]-1-methyl-1*H*-indole (5j): Off-white solid, m.p. 108–110 °C. R_f = 0.28 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2922, 1643, 1573, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (dd, J = 7.2, 1.0 Hz, 1 H), 7.56 (dd, J = 1.6, 1.0 Hz, 1 H), 7.51 (s, 1 H), 7.38–7.26 (m, 3 H), 6.94 (d, J = 3.2 Hz, 1 H), 6.72 (s, 1 H), 6.56 (dd, J = 3.2, 1.6 Hz, 1 H), 3.84 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 158.5, 144.0, 143.8, 137.5, 129.3, 125.7, 122.9, 121.8, 121.1, 112.0, 110.3, 109.7, 104.6, 97.4, 33.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{12}N_2O_2$ $[M + Na]^+$ 287.0796; found 287.0796.

5-(Furan-2-yl)-3-(1-methyl-1*H*-pyrrol-2-yl)isoxazole (5k): Brown viscous liquid. R_f = 0.50 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2946, 1643, 1569, 1458, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 1 H), 6.91 (d, J = 3.2 Hz, 1 H), 6.77 (s, 1 H), 6.60 (s, 2 H), 6.54 (t, J = 1.2 Hz, 1 H), 6.20 (s, 1 H), 3.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 156.7, 144.0, 143.3, 126.7, 122.0, 112.6, 111.9, 110.3, 108.3, 98.1, 37.1 ppm. HRMS (ESI): calcd. for $C_{12}H_{10}N_2O_2$ $[M + H]^+$ 215.0821; found 215.0820.

5-(4-Methoxyphenyl)-3-methylisoxazole (5l): Off-white solid, m.p. 90–92 °C (ref.[28b] 92–93 °C). R_f = 0.83 (3:7 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2932, 1608, 1432, 1254,787 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, J = 8.0 Hz, 2 H), 6.97 (d, J = 8.0 Hz, 2 H), 6.22 (s, 1 H), 3.80 (s, 3 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 164.5, 163.0, 129.7, 124.4, 116.5, 101.2, 57.9, 13.9 ppm. HRMS (ESI): calcd. for $C_{11}H_{11}NO_2$ $[M + H]^+$ 190.0868; found 190.0870.

General Procedure for the Synthesis of Regioisomeric 3-(Het)aryl-5-methyl/(het)arylisoxazoles 6a–6l from 3-(Methylthio)-1,3-substituted 2-Propenones 2a–2l: Hydroxylamine hydrochloride (0.1 g, 12 mmol) was added to a stirred suspension of $Ba(OH)_2$ (0.15 g, 9 mmol) in

EtOH (95%; 30 mL), and then a solution of 3-methylthio-1-aryl/heteroaryl-3-alkyl/aryl/heteroaryl propenone (3 mmol) in ethanol (10 mL) was added. The reaction mixture was heated at reflux with stirring for 8–10 h (monitored by TLC). The mixture was then concentrated to dryness under reduced pressure, and the residue was extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was washed with water (2 × 100 mL) and brine (1 × 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give crude isoxazoles **6**, which were purified by column chromatography on silica gel using hexane/EtOAc as eluent.

5-(4-Methoxyphenyl)-3-phenylisoxazole (6a): White solid, m.p. 124–126 °C (ref.[28c] 126–127 °C). R_f = 0.51 (1.5:8.5 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2940, 1609, 1449, 1265, 773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.80 (m, 4 H), 7.51–7.43 (m, 3 H), 7.0 (d, J = 8.8 Hz, 2 H), 6.77 (s, 1 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 162.4, 160.8, 129.9, 128.8, 128.0, 127.4, 125.6, 121.5, 114.2, 97.1, 55.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{12}NO_2$ $[M + Na]^+$ 351.9949; found 351.9948.

3-(3-Bromophenyl)-5-(4-methoxyphenyl)isoxazole (6b): White solid, m.p. 112–114 °C. R_f = 0.51 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2968, 1616, 1451, 1257, 781 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.0 (t, J = 1.6 Hz, 1 H), 7.80–7.75 (m, 3 H), 7.59–7.56 (m, 1 H), 7.34 (t, J = 8.0 Hz, 1 H), 7.00 (d, J = 9.2 Hz, 2 H), 6.68 (s, 1 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 161.9, 161.4, 133.0, 131.5, 130.6, 130.0, 127.6, 125.5, 123.1, 120.2, 114.6, 96.1, 55.6 ppm. HRMS (ESI): calcd. for $C_{16}H_{13}NO_2$ $[M + H]^+$ 252.1025; found 252.1019.

3-(Naphthalen-2-yl)-5-phenylisoxazole (6c): Yellow solid, m.p. 128–129 °C. R_f = 0.80 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3118, 1566, 1449, 823, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (br. s, 1 H), 8.03 (dd, J = 8.4, 1.6 Hz, 1 H), 7.95–7.92 (m, 2 H), 7.89–7.87 (m, 3 H), 7.55–7.48 (m, 5 H), 6.97 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 163.1, 134.2, 133.4, 130.4, 129.2, 128.9, 128.6, 128.0, 127.6, 127.1, 126.8, 126.7, 126.6, 126.0, 124.1, 97.7 ppm. HRMS (ESI): calcd. for $C_{19}H_{13}NO$ $[M + Na]^+$ 294.0895; found 294.0898.

3-(Thiophen-2-yl)-5-p-tolylisoxazole (6d): White solid, m.p. 66–68 °C. R_f = 0.65 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2918, 1599, 1432, 797 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.0 Hz, 2 H), 7.50 (dd, J = 3.6, 1.2 Hz, 1 H), 7.42 (dd, J = 5.2, 1.2 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 2 H), 7.12 (dd, J = 5.2, 3.6 Hz, 1 H), 6.68 (s, 1 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 158.2, 140.8, 131.1, 129.8, 127.8, 127.6, 127.4, 125.9, 124.6, 97.0, 21.6 ppm. HRMS (ESI): calcd. for $C_{14}H_{11}NOS$ $[M + Na]^+$ 264.0460; found 264.0460.

3-(3-Methylthiophen-2-yl)-5-(3,4,5-trimethoxyphenyl)isoxazole (6e): Yellow solid, m.p. 77–79 °C. R_f = 0.73 (3:7 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2933, 1620, 1450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, J = 4.8 Hz, 1 H), 7.05 (s, 2 H), 6.97 (d, J = 4.8 Hz, 1 H), 6.64 (s, 1 H), 3.94 (s, 6 H), 3.89 (s, 3 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 158.4, 153.7, 140.0, 138.2, 131.6, 125.9, 124.7, 122.6, 103.3, 98.5, 61.0, 56.3, 15.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}NO_4S$ $[M + Na]^+$ 354.0776; found 354.0778.

4-(5-Phenylisoxazol-3-yl)pyridine (6f): Pale yellow solid, m.p. 125–127 °C. R_f = 0.31 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3110, 2935, 1555, 1441, 756, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.76 (d, J = 4.8 Hz, 2 H), 7.85 (d, J = 8.0 Hz, 2 H), 7.75 (d, J = 4.8 Hz, 2 H), 7.50 (d, J = 8.0 Hz, 3 H), 6.88 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 161.1, 136.6, 130.4, 129.1, 129.0, 127.0, 126.8, 125.9, 97.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{10}N_2O$ $[M + H]^+$ 223.0871; found 223.0870.

3-(3-Phenylisoxazol-5-yl)pyridine (6g): Off-white solid, m.p. 140–142 °C (ref.[28c] 143–144 °C). R_f = 0.58 (3:7 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2922, 1609, 1404 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.09 (br. s, 1 H), 8.70 (d, J = 4.8 Hz, 1 H), 8.15 (d, J = 8.0 Hz, 1 H), 7.89–7.87 (m, 2 H), 7.50–7.49 (m, 3 H), 7.45 (dd, J = 8.0, 4.8 Hz, 1 H), 6.93 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 163.1, 151.0, 147.1, 132.9, 130.3, 129.0, 128.7, 126.9, 123.8, 123.7, 98.5 ppm. HRMS (ESI): calcd. for $C_{14}H_{10}N_2O$ $[M + H]^+$ 223.0871; found 223.0873.

***N*,*N*-Dimethyl-4-[5-(pyridin-3-yl)isoxazol-3-yl]benzenamine (6h):** White solid, m.p. 143–145 °C. R_f = 0.52 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2895, 1616, 1524, 791 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.06 (d, J = 1.2 Hz, 1 H), 8.68 (dd, J = 4.4, 1.2 Hz, 1 H), 8.19 (dt, J = 8.0, 2.0 Hz, 1 H), 7.70 (d, J = 8.8 Hz, 2 H), 7.41 (ddd, J = 8.0, 3.2, 0.4 Hz, 1 H), 6.75 (d, J = 8.8 Hz, 2 H), 6.64 (s, 1 H), 3.04 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 160.4, 151.7, 150.9, 148.1, 134.2, 127.3, 125.9, 123.9, 115.0, 111.9, 94.3, 40.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}N_3O$ $[M + H]^+$ 266.1293; found 266.1288.

1-Methyl-2-[5-(thiophen-2-yl)isoxazol-3-yl]-1*H*-indole (6i): Pale yellow solid, m.p. 98–100 °C. R_f = 0.76 (3:7 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3103, 2919, 1620, 1387 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.0 (d, J = 7.8 Hz, 1 H), 7.43 (d, J = 7.8 Hz, 1 H), 7.35–7.09 (m, 6 H), 6.52 (s, 1 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3, 141.3, 138.7, 137.3, 132.9, 126.7, 125.9, 122.4, 120.3, 120.0, 119.5, 115.9, 111.3,110.0, 109.6, 104.6, 32.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{12}N_2OS$ $[M + Na]^+$ 303.0568; found 303.0569.

2-[3-(Furan-2-yl)isoxazol-5-yl]-1-methyl-1*H*-indole (6j): Off-white solid, m.p. 122–124 °C. R_f = 0.31 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3114, 2925, 1630, 1562 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.0 Hz, 1 H), 7.65 (s, 1 H), 7.58 (s, 1 H), 7.41–7.28 (m, 3 H), 6.95 (d, J = 6.8 Hz, 1 H), 6.68 (s, 1 H), 6.55 (d, J = 2.0 Hz, 1 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 158.5, 144.0, 143.8, 137.5, 129.3, 125.7, 122.8, 121.8, 121.1, 112.0, 110.3, 109.7, 104.6, 97.4, 33.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{12}N_2O_2$ $[M + Na]^+$ 287.0796; found 287.0792.

3-(Furan-2-yl)-5-(1-methyl-1*H*-pyrrol-2-yl)isoxazole (6k): White solid, m.p. 76–78 °C. R_f = 0.71 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3127, 2933, 1612, 1457 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56 (br. s, 1 H), 6.93 (d, J = 3.6 Hz, 1 H), 6.77 (br. s, 1 H), 6.7 (d, J = 3.2 Hz, 1 H), 6.54 (d, J = 1.2 Hz, 1 H), 6.50 (s, 1 H), 6.20 (t, J = 3.2 Hz, 1 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 155.1, 144.5, 143.9, 127.0, 121.3, 112.7, 111.9, 110.2, 108.9, 96.1, 36.5 ppm. HRMS (ESI): calcd. for $C_{12}H_{10}N_2O_2$ $[M + H]^+$ 215.0821; found 215.0822.

3-(4-Methoxyphenyl)-5-methylisoxazole (6l): Off-white solid, m.p. 112–114 °C (ref.[28d] 111–112 °C). R_f = 0.77 (2:8 EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3070, 2926, 1662, 1452 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.2 Hz, 2 H), 6.96 (d, J = 8.2 Hz, 2 H), 6.23 (s, 1 H), 3.85 (s, 3 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 164.6, 163.3, 130.5, 124.3, 116.6, 101.9, 57.7, 14.7 ppm. HRMS (ESI): calcd. for $C_{11}H_{11}NO_2$ $[M + H]^+$ 190.0868; found 190.0867.

Supporting Information (see footnote on the first page of this article): Scanned copies of ^1H and ^{13}C NMR spectra of compounds **1a**, **1c**, **1d**, **1g**–**1i**, **1k**, **2a**, **2c**, **2d, 2g**–**2i**, **2k**, **5a**–**5l**, and **6a**–**6l** and also ORTEP diagrams of crystal structure of **5b**, **6b**, **5e**, and **6e**.

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