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Isomerizable (*E*/*Z*)-alkynyl-*O*-methyl oximes employing TMSCl–NCS in chlorinative cyclization for the direct synthesis of 4-chloroisoxazoles†

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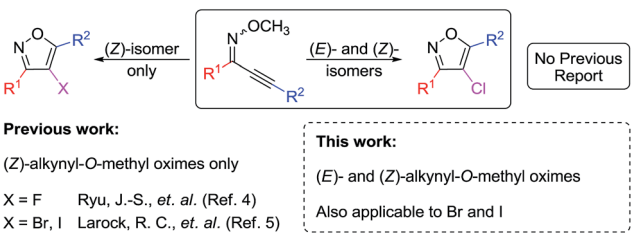
For the first time, 4-chloroisoxazoles are directly synthesized in moderate to excellent yields from (*E*/*Z*)-alkynyl-*O*-methyl oximes *via* chlorinative cyclization. The synthesis employs the combination of *N*-chlorosuccinimide (NCS) and chlorotrimethylsilane (TMSCl) in nitromethane solvent where chlorine (Cl_2) and hydrochloric acid (HCl) are generated *in situ*. In addition, the current protocol is applicable to the synthesis of 4-bromo- and 4-iodoisoxazoles when *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS), respectively, are employed in place of NCS. The current method can improve the overall efficiency of the preparation of 4-haloisoxazoles starting from the step where alkynyl-*O*-methyl oximes are prepared since (*E*)-isomers can isomerize and cyclize under the conditions.

Introduction

Isoxazoles are an important structural motif[1] found in many biologically active compounds and currently marketed drugs, such as valdecoxib and oxacillin, a non-steroidal anti-inflammatory drug and a β-lactamase-resistant antibiotic drug, respectively. Pertaining to the medicinal properties of compounds, several studies have shown that the inclusion of halogen atoms can improve their biological activities as compared to the non-halogenated variants.[2] Due to these important pharmacological aspects of halogenated compounds and the roles the isoxazole nucleus plays in medicinal chemistry, preparative methods for halogenated isoxazoles are of interest among organic and medicinal chemists. Furthermore, the halogen atoms in halogenated isoxazoles can serve as synthetic handles for a variety of C–C and C–heteroatom bond formations *via* cross-coupling reactions,[3] thus facilitating further functionalization and increasing the molecular diversity.

One of the most widely used strategies for the construction of the 4-haloisoxazole nucleus in general is the cyclization of (*Z*)-alkynyl-*O*-methyl oximes mediated by electrophilic halogens, which are presently available only for the preparation of 4-fluoro-, 4-bromo- and 4-iodoisoxazoles. As illustrated in Scheme 1, Ryu[4] recently utilized the combination of a gold catalyst and an electrophilic fluorine source to synthesize 4-fluoroisoxazoles from (*Z*)-only alkynyl-*O*-methyl oximes. Previously, Larock[5] also showed that reagents such as Br_2 and ICl could be employed to synthesize 4-bromo- and 4-iodoisoxazole derivatives, respectively, *via* the cyclization of also (*Z*)-only alkynyl-*O*-methyl oximes.

For the synthesis of 4-chloroisoxazole derivatives, no procedure has been reported to date for the direct cyclization from alkynyl-*O*-methyl oximes. The current synthesis of 4-chloroisoxazole derivatives relies on the chlorination of 4-unsubstituted isoxazole compounds under strongly acidic (NCS and sulfuric acid in refluxing acetic acid) or oxidative (hydrogen chloride and hydrogen peroxide in refluxing acetic acid) conditions.[6] In this work, we aim to search for the new method which could prepare 4-chloroisoxazoles by direct conversion of alkynyl-*O*-methyl oximes, which would provide a useful and concise synthetic access to such compounds. We recently reported a halogenation procedure for aromatic compounds



Scheme 1 Halogenative cyclization strategy employed in the synthesis of 4-haloisoxazoles.

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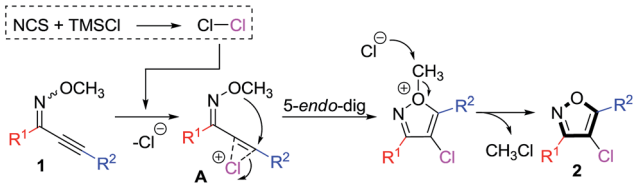
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of compounds **1a–1u**, **2a–2u** and **3d**. See DOI: 10.1039/c6ra09396e



Scheme 2 Proposed mechanism of the reaction.

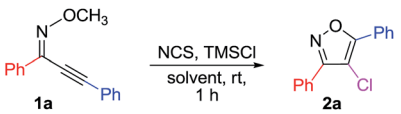
which relies on the *in situ* generation of interhalogen species (X–Cl) and hydrochloric acid (HCl) from chlorotrimethylsilane (TMSCl) and *N*-halosuccinimide (NXS) in wet acetonitrile.[7] For the combination of TMSCl and *N*-chlorosuccinimide (NCS), we hypothesized that chlorine (Cl_2) generated under the conditions may enable the direct formation of 4-chloroisoxazoles *via* electrophilic Cl_2-induced cyclization, thus constituting the first direct synthesis of 4-chloroisoxazoles *via* chlorinative cyclization of alkynyl-*O*-methyl oximes (Scheme 2). In addition, we also envisioned that the inherently acidic conditions may be advantageous in isomerizing the normally unreactive (*E*)-alkynyl-*O*-methyl oximes to the (*Z*)-isomers appropriate for the cyclization.

Results and discussion

We started the investigation of our proposed cyclization of alkynyl-*O*-methyl oximes with compound **1a** which was obtained only as (*Z*)-isomer after purification and can be prepared in good overall yield from benzaldehyde and phenylacetylene.[8] Compound **1a** was subjected to different conditions as summarized in Table 1.

We first applied our original conditions[7] to substrate **1a** in commercial-grade CH_3CN at rt for 1 h (entry 1) which resulted in only 17% conversion. We next studied the effects of other solvents. Changing the solvent from CH_3CN to CH_3NO_2 resulted in a significantly improved conversion (53%, entry 2). Next, more TMSCl (1.0 equiv.) was employed but this resulted in a slightly lower conversion (46%, entry 3), which may have been due to the concentration effect. Therefore, the concentration of the substrate was lowered to 0.1 M (entry 4) which led to >99% conversion to product **2a**. After the optimal concentration was established, we next investigated additional solvents, including THF and DCM, both of which were found to be less effective, giving lower conversions than in CH_3NO_2 (entries 5–6). We next attempted the reaction in CH_3NO_2 with lower equivalent of TMSCl (0.5 equiv.) and found the conversion dropping to 52% (entry 7). Additionally, we attempted the reaction with NCS only (entry 8) and TMSCl only (entry 9) and no reaction occurred in either case. This indicated that both reagents were required for the successful conversion of the substrate. Moreover, this outcome also supported the proposed mechanism of formation of product (Scheme 2), which required chlorine, generated from combination of NCS and TMSCl, to induce the cyclization by activating the triple bond. Therefore, the optimal conditions required the reaction to be conducted in CH_3NO_2 at room temperature using 1.1 equiv. of NCS and 1.0 equiv. of TMSCl at 0.1 M concentration of substrate for 1 h.

Table 1 Optimization for the cyclization of (*Z*)-alkynyl-*O*-methyl oximes **1a**

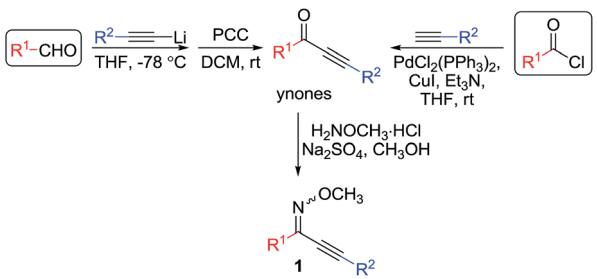


Entry	NCS (equiv.)	TMSCl (equiv.)	[**1a**] (M)	Solvent	Conversion[a] (%)
1	1.1	0.1	0.4	CH_3CN	17
2	1.1	0.1	0.4	CH_3NO_2	53
3	1.1	1.0	0.4	CH_3NO_2	46
4	1.1	1.0	0.1	CH_3NO_2	>99
5	1.1	1.0	0.1	THF	68
6	1.1	1.0	0.1	DCM	28
7	1.1	0.5	0.1	CH_3NO_2	52
8	1.1	—	0.1	CH_3NO_2	NR
9	—	1.0	0.1	CH_3NO_2	NR

[a] Conversions were determined by ^{1}H NMR.

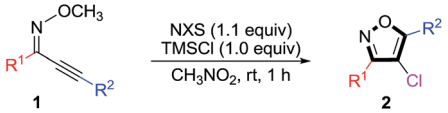
With the optimal conditions in hand, we began to study the scope of alkynyl-*O*-methyl oximes, beginning with R^1 and R^2 as aryl groups. The preparation of these substrates started from ynones, which could be prepared by lithium acetylide addition to aldehydes followed by oxidation of the resulting propargylic alcohols[8] or by Sonogashira coupling between acid chlorides and terminal alkynes.[9] The condensation of ynones with methoxyamine hydrochloride salt[10] then afforded the corresponding alkynyl-*O*-methyl oximes in moderate to good overall yields (Scheme 3). Substrates employed in Table 2 ($R^1 = R^2 =$ aryl groups) were obtained only as (*Z*)-isomers after purification while almost all substrates employed in Table 3 (R^1 = alkyl groups, R^2 = Ph or alkyl groups) were obtained as (*E*/*Z*)-isomeric mixtures. The results of the cyclization of these compounds are summarized below.

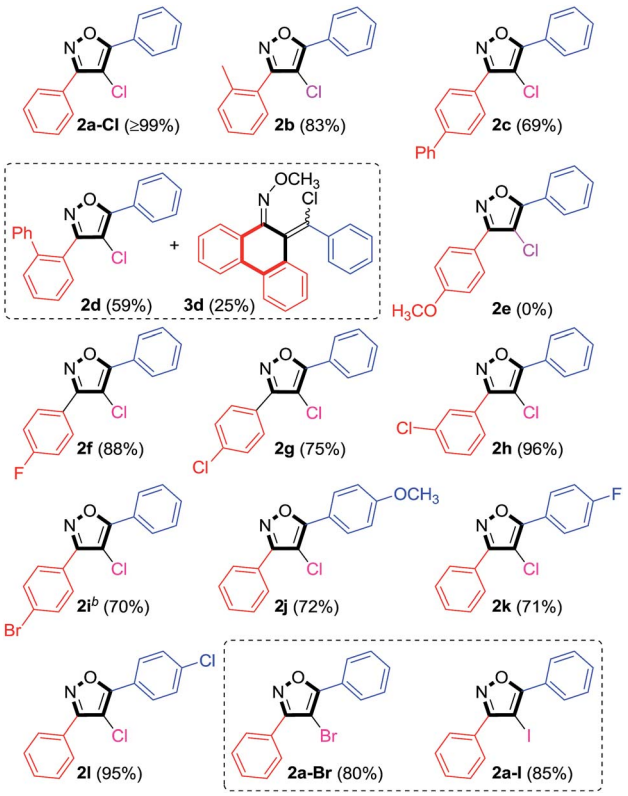
As shown in Table 2, in most cases the reactions proceeded under mild conditions (rt, 1 h). For the substrate with $R^1 = R^2 =$ Ph groups, the reaction afforded quantitative yield of the desired product (**2a-Cl**). We then varied the electronic property of R^1 while keeping R^2 as the phenyl group. With R^1 being an electronically neutral *o*-tolyl ring, the cyclization proceeded to afford the corresponding 4-chloroisoxazole **2b** in 83% yield. We



Scheme 3 Preparation of alkynyl-*O*-methyl oximes **1**.[8–10]

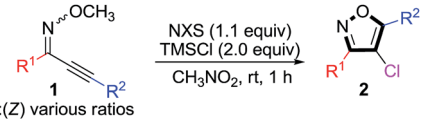
Table 2 Scope of intramolecular cyclization of (*Z*)-alkynyl-*O*-methyl oximes **1**[a]

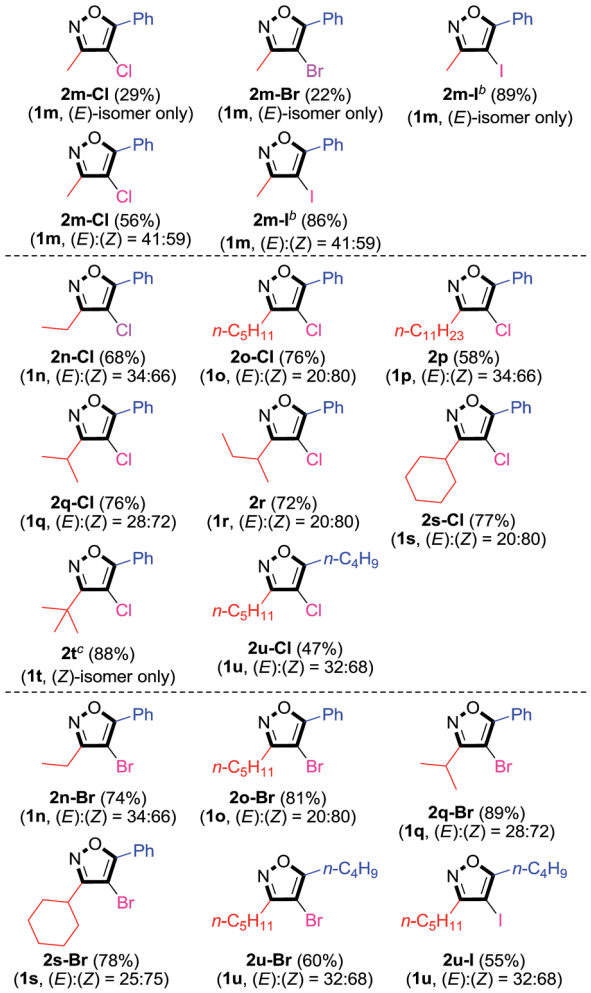




[a] Isolated yields. [b] The reaction required heating at reflux for 1 h.

Table 3 Intramolecular cyclization of mixtures of (*E*/*Z*)-alkynyl-*O*-methyl oximes **1**[a]





[a] Isolated yields. [b] Reaction time was 5 h. [c] 1.0 equiv. of TMSCl was employed.

next attempted the reactions with substrates containing mildly electron-withdrawing biphenyl systems. For the substrate containing the *p*-biphenyl group (**1c**), the desired product (**2c**) was obtained uneventfully in 69%. For the *o*-biphenyl substrate (**1d**), the desired product (**2d**) was obtained in 59% along with 25% of by-product **3d** formed *via* the intramolecular cyclization by the adjacent *o*-phenyl ring. This result showed the tethered *o*-biphenyl group to be the competing nucleophile (leading to **3d**), although the reaction with the methoxy oxygen as the nucleophile (leading to **2d**) was still more prevalent. The structure of by-product **3d** was proposed and confirmed by ^{1}H and ^{13}C NMR spectroscopy, both 1D and 2D techniques, as well as HRMS, however, the geometry of the vinyl chloride could not be conclusively assigned. In case of R^1 = *p*-OMe-phenyl group, the reaction proceeded to give no desired cyclized product (**2e**), instead the formation of complex mixture was observed. We speculated that when R^1 = aryl group containing electron-donating substituent, it became competitive in reacting with the electrophilic chlorine and underwent other undesired reaction pathways under the conditions faster than the cyclization. Next, substrates with R^1 = *p*-F-, *p*-Cl- and *m*-Cl-phenyl groups were examined. The reactions proceeded uneventfully to give the desired products **2f**, **2g**, and **2h** in 88%, 75% and 96% yields, respectively. In these cases, the halogen atom at the *meta*-position of the aryl ring of R^1 seemed to facilitate the cyclization to a greater degree. For the substrate containing *p*-Br-phenyl group (**1i**), the reaction was more sluggish and required reflux for 1 h for a complete conversion to afford product **2i** in 70% yield. We next explored substrates containing a variety of R^2 while keeping R^1 = Ph (**1j–1l**). With R^2 = *p*-OMe-phenyl group (**1j**), the reaction proceeded smoothly to give the

desired product **2j** in 72% yield. This result was in contrast to the result of substrate **1e**, in which many side-reactions occurred and no desired product was observed due to the competitive reactions occurring on the electron-rich aryl ring. The successful outcome of substrate **1j** illustrated that the *p*-OMe-phenyl substituent of the alkyne helped stabilizing the chloronium ion intermediate (**A**, Scheme 2) which eventually led to the desired product **2j**. For substrates **1k** and **1l** containing R^2 = *p*-F- and *p*-Cl-phenyl groups, the reactions afforded the desired 4-chloroisoxazole products **2k** and **2l** in 71% and 95% yields, respectively. Additionally, our method was applicable for the synthesis of other 4-haloisoxazole derivatives, requiring appropriate *N*-halosuccinimides. Thus, (*Z*)-alkynyl-*O*-methyl oxime **1a** could be conveniently transformed in good to excellent yields to both 4-bromoisoxazole **2a-Br** (80%) and 4-iodoisoxazole **2a-I** (85%).

We next tested our hypothesis that our protocol could isomerize (*E*)-alkynyl-*O*-methyl oximes and then cyclize to the desired 4-chloroisoxazoles by preparing (*E*)-**1m**,[11] which was the only easily accessible oxime as the pure (*E*)-isomer. In further optimizing the conditions, we found that an additional equivalent of TMSCl was beneficial in facilitating the isomerization of (*E*/*Z*)-isomeric substrates. We then subjected (*E*)-**1m** to 1.1 equiv. of NCS and 2.0 equiv. of TMSCl in CH_3NO_2 at rt and found that the desired isoxazole **2m-Cl** could be obtained in 29% yield. The reaction of (*E*)-**1m** was also attempted with NBS, which afforded the corresponding **2m-Br** in 22% yield. In both cases, side-reactions were also observed. Surprisingly, when NIS was employed in the reaction at rt for 5 h, the corresponding **2m-I** was gratifyingly obtained in excellent yield (89%) with much less side-reactions. The results of these three reactions clearly supported our hypothesis that our protocol could facilitate the isomerization of the normally non-cyclizable (*E*)-alkynyl-*O*-methyl oxime to the (*Z*)-isomer, which could readily cyclize to the desired isoxazole products under the reaction conditions, thus enabling the preparation of 4-haloisoxazoles from both (*E*)- and (*Z*)-alkynyl-*O*-methyl oximes. These results also suggested that the outcome of the reactions seemed to depend on the nature of *N*-halosuccinimide. We next applied our protocol to mixture of (*E*/*Z*)-alkynyl-*O*-methyl oximes **1m** (R^1 = CH_3, (*E*) : (*Z*) = 41 : 59) using NCS and NIS as shown in Table 3. In these cases, isoxazoles **2m-Cl** and **2m-I** were obtained in 56% and 86% yields, respectively. The scope of the substrates was further studied with starting materials **1n** to **1u**, which were prepared (R^1 = alkyl group, R^2 = Ph or alkyl group, Table 3) and obtained as mixtures of (*E*)- and (*Z*)-isomers in varying ratios, except for **1t** which was obtained only as the (*Z*)-isomer; the results are summarized in Table 3.

With R^1 = Et, *O*-methyl oxime **1n** ((*E*) : (*Z*) = 34 : 66) was transformed to isoxazole **2n-Cl** in 68% yield. For substrates with longer 1° alkyl groups, R^1 = *n*-C_5H_{11} (**1o**; (*E*) : (*Z*) = 20 : 80) and R^1 = *n*-$C_{11}H_{23}$ (**1p**; (*E*) : (*Z*) = 34 : 66), the reactions led to the corresponding products **2o-Cl** and **2p** in 76% and 58% yields, respectively. These results showed that longer R^1 alkyl chains could tolerate the reaction conditions well to provide the products in moderate to good yields. We then looked at R^1 = 2° alkyl groups, substrates **1q** (R^1 = *i*-Pr; (*E*) : (*Z*) = 28 : 72), **1r** (R^1 = *s*-Bu; (*E*) : (*Z*) = 20 : 80) and **1s** (R^1 = cyclohexyl; (*E*) : (*Z*) = 20 : 80) underwent the reactions uneventfully to give isoxazoles **2q-Cl** (76%), **2r** (72%) and **2s-Cl** (77%) in good yields. Finally, R^1 = 3° alkyl group was investigated. Thus, the reaction of *O*-methyl oxime **1t** (R^1 = *t*-Bu), obtained only as (*Z*)-isomer, proceeded to provide the corresponding product **2t** in 88% yield. In this case, the reaction, which started with only the (*Z*)-isomer of **1t**, needed only 1.0 equiv. of TMSCl for a complete conversion to deliver the product in excellent yield. The result implied that no additional TMSCl was needed for the HCl generation to assist in the (*E*) → (*Z*) isomerization process. In the reaction of **1t**, TMSCl was consumed only for the generation of Cl_2 to facilitate the cyclization, which further substantiated our hypothesis regarding the role of TMSCl. Although the yield of **2t** was high, it was still inferior compared to **2a** (R^1 = Ph, 99%, Table 2). These results showed the general trend of the reaction regarding yields of products as related to the effect of R^1 (with R^2 = Ph) as followed: Ph > 3° > 2° > 1° > CH_3. Finally, the substrate with both R^1 = R^2 = alkyl groups was studied in compound **1u** (R^1 = *n*-C_5H_{11}, R^2 = *n*-C_4H_9, (*E*) : (*Z*) = 32 : 68) which was transformed to 4-chloroisoxazole **2u-Cl** in 47% yield. This latter result also showed the general trend in yields of products related to R^1 and R^2 as followed: R^1 = R^2 = aryl > R^1 = alkyl, R^2 = aryl > R^1 = R^2 = alkyl.

The yields of 4-chloroisoxazoles **2n-Cl** (68%) and **2q-Cl** (76%) in Table 3 further proved that the (*E*)-alkynyl-*O*-methyl oximes in the mixtures of substrates **1n** and **1q** were isomerized and cyclized to the desired products since the yields obtained for each case were higher than the proportions of (*Z*)-isomer in the starting materials. As exemplified with alkynyl-*O*-methyl oxime **1m**, our method was applied to prepare 4-bromo- and 4-iodoisoxazoles from other alkynyl-*O*-methyl oximes. As shown in Table 3, alkynyl-*O*-methyl oxime **1n** ((*E*) : (*Z*) = 34 : 66) was converted to the corresponding 4-bromoisoxazole **2n-Br** in 74% yield while alkynyl-*O*-methyl oxime **1o** ((*E*) : (*Z*) = 20 : 80) was also converted smoothly to product **1o-Br** in 81% yield. Similarly, compound **1q** ((*E*) : (*Z*) = 28 : 72) underwent the reaction to the corresponding 4-bromoisoxazole (**2q-Br**) in 89% yield. In case of compound **1s** ((*E*) : (*Z*) = 25 : 75), the reaction produced the desired product (**2s-Br**) in 78% yield. Finally, for substrate **1u** ((*E*) : (*Z*) = 32 : 68), the reactions with NBS and NIS produced the corresponding products **2u-Br** and **2u-I** in 60% and 55% yields, respectively. Among these cases, yields of products **2m-Cl**, (from (*E*/*Z*)-**1m**), **2o-Cl**, **2p**, **2r**, **2s-Cl**, **2u-Br** and **2u-I** were slightly lower than the proportions of the (*Z*)-isomers present in the starting materials. However, as the conversions of the (*Z*)-starting materials could not always be quantitative, it could be implicated that the (*E*)-isomers could isomerize and cyclize, thus contributing to the overall yields of products. Moreover, the isomerization-cyclization process of the (*E*)-isomers could be supported by the yields of products **2n-Cl**, **2q-Cl**, **2n-Br**, **2o-Br**, **2q-Br**, **2s-Br** and **2m-I** (from (*E*/*Z*)-**1m**) as they were greater than or equal to the proportions of the (*Z*)-isomers present in the starting materials. The strongest cases to support such isomerization process were demonstrated in the reactions of pure (*E*)-**1m** which gave isoxazoles **2m-Cl**, **2m-Br** and **2m-I** in 29%, 22% and 89% yields, respectively (Table 3).

Conclusions

We have developed the first method for the direct conversion of alkynyl-*O*-methyl oximes to 4-chloroisoxazoles *via* chlorinative cyclization. This is also the first method which could be employed for both (*E*)- and (*Z*)-alkynyl-*O*-methyl oximes. This is due to the fact that the unreactive (*E*)-isomers can be isomerized and cyclized under the reaction conditions. The current method therefore constitutes a protocol having higher efficiency than the previous methods, and can be employed for mixtures of both (*E*/*Z*)-alkynyl-*O*-methyl oximes. The protocol conveniently employs the combination of TMSCl and NCS in nitromethane at room temperature, which produces Cl_2 and HCl *in situ* to promote the cyclization to furnish 4-chloroisoxazole products in moderate to excellent yields. This method is effectively applicable to a broad range of substrates and is also appropriate for the preparation of 4-bromo- and 4-iodoisoxazole derivatives simply by using NBS and NIS instead of NCS.

Experimental

General procedure

Commercial grade chemicals were used without further purification, unless otherwise specified. All solvents were used as received. Oven-dried glassware (110 °C at least for 2 h) was used for all reactions. Crude reaction mixtures were concentrated under reduced pressure on a rotary evaporator. Column chromatography was performed using silica gel 60 (particle size 0.06–0.2 mm; 70–230 mesh ASTM). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F_{254} aluminum sheets. Nuclear magnetic resonance (NMR) spectra were recorded in deuterochloroform ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6) with 300 and 600 MHz spectrometers. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm, δ), relative to tetramethylsilane (TMS) as the internal reference. Coupling constants (J) are reported in hertz (Hz). Infrared spectra were measured using an FT-IR spectrometer and are reported in cm^{-1}. High-resolution mass spectra (HRMS) were obtained using a time-of-flight (TOF) instrument.

General procedure for the preparation of (*Z*)-alkynyl-*O*-methyl oximes 1a–u

The solution of 1,3-diphenylprop-2-yn-1-one (561.2 mg, 2.72 mmol, 1.0 equiv.) in MeOH (12.0 mL, 4.5 mL $mmol^{-1}$) was added sequentially with $MeONH_2 \cdot HCl$ (469.6 mg, 5.44 mmol, 2.0 equiv.), Na_2SO_4 (864.3 mg, 5.44 mmol, 2.0 equiv.), and pyridine (1.2 mL, 14.9 mmol, 5.5 equiv.). The resulting reaction mixture was stirred overnight and quenched by addition of water. The mixture was then extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator. The crude product was purified by SiO_2 column chromatography (2% EtOAc–hexane) to afford (*Z*)-1,3-diphenylprop-2-yn-1-one *O*-methyl oxime (**1a**) (340.3 mg, 53%).

(*Z*)-1,3-Diphenylprop-2-yn-1-one *O*-methyl oxime (1a).[5b] Yield 340.3 mg (53%, white solid); mp 44.9–45.1 °C; IR (neat): ν_{max} 3058, 2936, 2820, 2213, 1444, 1337, 1048 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00–7.97 (m, 2H), 7.68–7.65 (m, 2H), 7.47–7.39 (m, 6H), 4.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 133.5, 132.1, 129.6, 129.5, 128.38, 128.36, 126.4, 121.7, 101.1, 79.4, 63.0; HRMS (ESI) calcd for $C_{16}H_{14}NO$ $(M + H)^+$ 236.1070, found 236.1060.

(*E*)-3-Phenyl-1-(*o*-tolyl)prop-2-yn-1-one *O*-methyl oxime (1b).[5b] Yield 17.5 mg (14%, yellow oil); IR (neat): ν_{max} 3749, 3058, 2934, 2818, 1689, 1046, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.45 (m, 3H), 7.31–7.15 (m, 6H), 4.05 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 136.8, 133.4, 132.1, 131.0, 129.5, 129.4, 129.1, 128.4, 125.9, 121.8, 101.2, 80.7, 63.0, 20.8; HRMS (ESI) calcd for $C_{17}H_{16}NO$ $(M + H)^+$ 250.1226, found 250.1235.

(*Z*)-1-([1,1′-Biphenyl]-4-yl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (1c). Yield 105.5 mg (40%, white solid); mp 111.7–112.1 °C; IR (neat): ν_{max} 3364, 2923, 2852, 2349, 2216, 1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00–7.97 (m, 2H), 7.66–7.62 (m, 6H), 7.48–7.37 (m, 6H), 4.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 140.4, 139.6, 132.5, 132.1, 129.5, 128.8, 128.4, 127.6, 127.1, 127.0, 126.9, 121.7, 101.2, 79.4, 63.1; HRMS (ESI) calcd for $C_{22}H_{18}NO$ $(M + H)^+$ 312.1383, found 312.1374.

(*E*)-1-([1,1′-Biphenyl]-2-yl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (1d). Yield 100.2 mg (28%, colorless oil); IR (neat): ν_{max} 3059, 2935, 2210, 1951, 1443, 1044, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.55 (m, 1H), 7.42–7.28 (m, 7H), 7.24–7.10 (m, 4H), 7.06–7.03 (m, 2H), 3.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 141.3, 140.9, 133.0, 131.9, 130.6, 129.7, 129.5, 129.4, 129.1, 128.2, 128.0, 127.4, 127.1, 121.6, 101.5, 80.5, 62.9; HRMS (ESI) calcd for $C_{22}H_{18}NO$ $(M + H)^+$ 312.1383, found 312.1384.

(*Z*)-1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (1e).[12] Yield 279.1 mg (63%, white solid); mp 63.2–63.4 °C; IR (neat): ν_{max} 2935, 2899, 2838, 2213, 1944, 1606, 1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90–7.85 (m, 2H), 7.64–7.61 (m, 2H), 7.42–7.35 (m, 3H), 6.96–6.91 (m, 2H), 4.13 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 139.5, 132.1, 129.4, 128.4, 127.9, 126.2, 121.8, 113.8, 100.8, 79.5, 62.9, 55.3; HRMS (ESI) calcd for $C_{17}H_{16}NO_2$ $(M + H)^+$ 266.1176, found 266.1179.

(*Z*)-1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (1f).[4a] Yield 72.8 mg (26%, yellow oil); IR (neat): ν_{max} 2937, 2901, 2214, 1602, 1046 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92–7.87 (m, 2H), 7.62–7.59 (m, 2H), 7.39–7.33 (m, 3H), 7.10–7.05 (m, 2H), 4.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (d, J_{C-F} = 248 Hz), 138.8, 132.1, 129.7 (d, J_{C-F} = 3 Hz), 129.6, 128.4 (d, J_{C-F} = 5 Hz), 128.3, 121.6, 115.4 (d, J_{C-F} = 22 Hz), 101.3, 79.2, 63.1; HRMS (ESI) calcd for $C_{16}H_{13}FNO$ $(M + H)^+$ 254.0976, found 254.0973.

(*Z*)-1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (1g).[5b] Yield 80.1 mg (30%, colorless oil); IR (neat): ν_{max} 2935, 2891, 2213, 1489, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.7 Hz, 2H), 7.62–7.59 (m, 2H), 7.42–7.35 (m, 5H), 4.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 135.7, 132.2, 132.1, 129.7, 128.6, 128.5, 127.7, 121.6, 101.5, 79.0, 63.2; HRMS

(ESI) calcd for $C_{16}H_{13}ClNO$ $(M + H)^+$ (Cl-35) 270.0680, found 270.0668.

(*Z*)-1-(3-Chlorophenyl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (1h). Yield 59.1 mg (28%, colorless oil); IR (neat): ν_{max} 3063, 2937, 2818, 2217, 1594, 1328, 1043, 821, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.81 (dd, $J = 7.2$, 1.8 Hz, 1H), 7.65–7.62 (m, 2H), 7.44–7.31 (m, 5H), 4.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 135.3, 134.4, 132.1, 129.7, 129.60, 129.58, 128.4, 126.3, 124.7, 121.5, 101.6, 78.9, 63.3; HRMS (ESI) calcd for $C_{16}H_{13}ClNO$ $(M + H)^+$ (Cl-35) 270.0680, found 270.0683.

(*Z*)-1-(4-Bromophenyl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (1i). Yield 97.0 mg (24%, colorless oil); IR (neat): ν_{max} 2925, 2853, 2370, 2213, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83–7.79 (m, 2H), 7.64–7.52 (m, 4H), 7.45–7.36 (m, 3H), 4.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 132.5, 132.1, 131.5, 129.6, 128.4, 127.9, 123.9, 121.5, 101.5, 78.9, 63.2; HRMS (ESI) calcd for $C_{16}H_{13}BrNO$ $(M + H)^+$ (Br-79) 314.0175, found 314.0170.

(*Z*)-3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one *O*-methyl oxime (1j).[5b] Yield 82.0 mg (52%, colorless oil); IR (neat): ν_{max} 3058, 2962, 2935, 2837, 2208, 1604, 1249, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94–7.91 (m, 2H), 7.60–7.55 (m, 2H), 7.43–7.38 (m, 3H), 6.93–6.88 (m, 2H), 4.15 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 140.1, 133.8, 133.7, 129.6, 128.3, 126.5, 114.1, 113.7, 101.6, 78.6, 63.0, 55.3; HRMS (ESI) calcd for $C_{17}H_{15}NNaO_2$ $(M + Na)^+$ 288.0995, found 288.0996.

(*Z*)-3-(4-Fluorophenyl)-1-phenylprop-2-yn-1-one *O*-methyl oxime (1k). Yield 133.4 mg (54%, colorless oil); IR (neat): ν_{max} 3449, 2938, 2213, 1506, 1234, 1048, 836, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96–7.93 (m, 2H), 7.66–7.59 (m, 2H), 7.45–7.40 (m, 3H), 7.13–7.05 (m, 2H), 4.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (d, $J_{C-F} = 250$ Hz), 139.7, 134.1 (d, $J_{C-F} = 9$ Hz), 133.4, 129.7, 128.4, 126.4, 117.8 (d, $J_{C-F} = 4$ Hz), 115.8 (d, $J_{C-F} = 22$ Hz), 100.0, 79.2, 63.0; HRMS (ESI) calcd for $C_{16}H_{13}NOF$ $(M + H)^+$ 254.0976, found 254.0975.

(*Z*)-3-(4-Chlorophenyl)-1-phenylprop-2-yn-1-one *O*-methyl oxime (1l).[13] Yield 63.2 mg (34%, colorless oil); IR (neat): ν_{max} 3455, 2071, 1638, 1335, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93–7.91 (m, 2H), 7.57–7.54 (m, 2H), 7.43–7.36 (m, 5H), 4.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 135.7, 133.3, 129.7, 128.8, 128.4, 126.4, 120.2, 99.8, 80.3, 63.1; HRMS (ESI) calcd for $C_{16}H_{13}ClNO$ $(M + H)^+$ (Cl-35) 270.0680, found 270.0686.

4-Phenylbut-3-yn-2-one *O*-methyl oxime (1m).[5b] Yield 157.4 mg (69%, $(E) : (Z) = 41 : 59$, colorless oil); IR (neat): ν_{max} 3580, 2925, 2855, 2309, 1731, 1462, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.49 (m, 2H), 7.40–7.29 (m, 3H), 3.98 (s, 2.11H, minor), 3.97 (s, 3H), 2.13 (s, 3H), 2.09 (s, 2.11H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1 (minor), 137.2, 131.9, 131.7 (minor), 129.2, 128.8 (minor), 128.2, 121.8 (minor), 121.5, 98.9, 90.0 (minor), 85.4 (minor), 80.9, 62.2 (minor), 62.0, 20.4, 16.4 (minor); HRMS (ESI) calcd for $C_{11}H_{12}NO$ $(M + H)^+$ 174.0913, found 174.0917.

(*E*)-4-Phenylbut-3-yn-2-one *O*-methyl oxime (1m).[5b] Yield 81.9 mg (22%, colorless oil); ^1H NMR (300 MHz, $CDCl_3$) δ 7.52–7.49 (m, 2H), 7.34–7.29 (m, 3H), 3.98 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 131.9, 129.0, 128.3, 121.9, 90.1, 85.4, 62.4, 16.6; HRMS (ESI) calcd for $C_{11}H_{12}NO$ $(M + H)^+$ 174.0913, found 174.0917.

1-Phenylpent-1-yn-3-one *O*-methyl oxime (1n). Yield 126.2 mg (73%, $(E) : (Z) = 34 : 66$, colorless oil); IR (neat): ν_{max} 3559, 3058, 2927, 2851, 2370, 1947, 1725, 1265, 1095 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.54–7.51 (m, 2H), 7.39–7.32 (m, 3H), 3.98 (s, 3H), 2.52 (q, $J = 7.8$ Hz, 1.02H, minor), 2.44 (q, $J = 7.8$ Hz, 2H), 1.25–1.20 (m, 3H); ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.52 (m, 2H), 7.43–7.33 (m, 3H), 3.99 (s, 3H), 2.53 (q, $J = 7.5$ Hz, 1.02H, minor), 2.45 (q, $J = 7.8$ Hz, 2H), 1.28–1.20 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 142.7, 131.9, 131.8, 129.2, 128.8, 128.2, 121.9, 121.6, 99.5, 91.3, 84.0, 80.0, 62.3, 62.1, 27.8, 22.5, 11.6, 10.3; HRMS (ESI) calcd for $C_{12}H_{13}NNaO$ $(M + Na)^+$ 210.0889, found 210.0879.

(*Z*)-1-Phenyloct-1-yn-3-one *O*-methyl oxime (1o). Yield 145.4 mg (97%, $(E) : (Z) = 20 : 80$, yellow oil); IR (neat): ν_{max} 3902, 3750, 2957, 2930, 2858, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.48 (m, 2H), 7.38–7.31 (m, 3H), 3.972 (s, 3H), 3.965 (s, 0.74H, minor), 2.49 (t, $J = 7.5$ Hz, 0.49H, minor), 2.40 (t, $J = 7.5$ Hz, 2H), 1.73–1.63 (m, 2H), 1.39–1.33 (m, 4H), 0.93–0.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 141.9, 132.0, 131.8, 129.2, 128.9, 128.3, 122.0, 121.7, 99.4, 90.9, 84.5, 80.3, 62.3, 62.1, 34.2, 31.4, 31.0, 29.1, 26.7, 25.5, 22.3, 13.9; HRMS (ESI) calcd for $C_{15}H_{20}NO$ $(M + H)^+$ 230.1539, found 230.1549.

1-Phenyltetradec-1-yn-3-one *O*-methyl oxime (1p). Yield 206.1 mg (65%, $(E) : (Z) = 34 : 66$, dark brown oil); IR (neat): ν_{max} 2925, 2854, 2208, 1464, 1047, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.48 (m, 2H), 7.38–7.30 (m, 3H), 3.96 (s, 3H), 2.49 (t, $J = 7.5$ Hz, 1.04H, minor), 2.39 (t, $J = 7.5$ Hz, 2H), 1.72–1.60 (m, 2H), 1.33–1.26 (m, 16H), 0.88 (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 142.0, 132.1, 131.9, 129.3, 128.9, 128.3, 122.1, 121.8, 99.5, 91.0, 84.5, 80.3, 62.3, 62.2, 34.3, 31.9, 29.6, 29.5, 29.30, 29.27, 28.9, 27.0, 25.9, 22.6, 14.1; HRMS (ESI) calcd for $C_{21}H_{32}NO$ $(M + H)^+$ 314.2478, found 314.2487.

4-Methyl-1-phenylpent-1-yn-3-one *O*-methyl oxime (1q). Yield 502.0 mg (92%, $(E) : (Z) = 28 : 72$, light yellow oil); IR (neat): ν_{max} 2968, 2936, 2213, 1444, 1034, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.50 (m, 2H), 7.40–7.30 (m, 3H), 3.96 (s, 3H), 3.40 (sept, $J = 6.9$ Hz, 0.38H, minor), 2.73 (sept, $J = 6.9$ Hz, 1H), 1.23 (d, $J = 6.9$ Hz, 6H), 1.16 (d, $J = 6.9$ Hz, 2.28H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 146.8, 132.0, 131.8, 129.2, 128.8, 128.2, 122.0, 121.8, 100.1, 92.0, 82.4, 78.8, 62.2, 62.0, 33.3, 26.8, 20.4, 19.4; HRMS (ESI) calcd for $C_{13}H_{16}NO$ $(M + H)^+$ 202.1226, found 202.1229.

4-Methyl-1-phenylhex-1-yn-3-one *O*-methyl oxime (1r). Yield 194.5 mg (89%, $(E) : (Z) = 20 : 80$, yellow oil); IR (neat): ν_{max} 3525, 2965, 2934, 2876, 2210, 1457, 1041, 755, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.49 (m, 2H), 7.40–7.31 (m, 3H), 3.97 (s, 3H), 3.95 (s, 0.75H, minor), 3.24 (sex, $J = 6.6$ Hz, 0.25H, minor), 2.48 (sex, $J = 6.9$ Hz, 1H), 1.77–1.41 (m, 2H), 1.21 (d, $J = 6.6$ Hz, 3H), 1.14 (d, $J = 6.9$ Hz, 0.75H, minor), 0.94 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 146.2, 132.1, 131.9, 129.2, 128.8, 128.3, 122.1, 121.8, 100.0, 91.6, 82.6, 78.8, 62.2, 62.1, 40.2, 33.7, 27.6, 27.2, 18.4, 17.4, 11.8, 11.7; HRMS (ESI) calcd for $C_{14}H_{18}NO$ $(M + H)^+$ 216.1383, found 216.1390.

1-Cyclohexyl-3-phenylprop-2-yn-1-one *O*-methyl oxime (1s). Yield 427.2 mg (87%, $(E) : (Z) = 20 : 80$, yellow oil); IR (neat):

ν_{max} 2929, 2854, 2817, 2217, 1574, 1444, 1044, 754, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.50 (m, 2H), 7.38–7.31 (m, 3H), 3.964 (s, 3H), 3.956 (s, 0.73H), 3.10 (tt, J = 11.7, 3.0 Hz, 0.24H, minor), 2.41 (tt, J = 11.7, 3.3 Hz, 1H), 1.90–1.15 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 146.2, 132.0, 131.8, 129.2, 128.8, 128.2, 122.1, 121.8, 100.0, 91.7, 83.2, 79.4, 62.3, 62.1, 42.9, 36.8, 30.6, 29.4, 25.8, 25.7, 25.6; HRMS (ESI) calcd for $C_{16}H_{20}NO$ $(M + H)^+$ 242.1539, found 242.1543.

(*Z*)-4,4-Dimethyl-1-phenylpent-1-yn-3-one *O*-methyl oxime (1t).[5a] Yield 379.2 mg (90%, dark brown oil); IR (neat): ν_{max} 2968, 2931, 2818, 2215, 1363, 1051, 755, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.52 (m, 2H), 7.40–7.31 (m, 3H), 3.97 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 132.0, 129.1, 128.3, 122.0, 100.3, 79.3, 62.2, 36.9, 28.2; HRMS (ESI) calcd for $C_{14}H_{18}NO$ $(M + H)^+$ 216.1383, found 216.1389.

Dodec-7-yn-6-one *O*-methyl oxime (1u). Yield 281.9 mg (80%, $(E) : (Z) = 32 : 68$, colorless oil); IR (neat): ν_{max} 2957, 2928, 2856, 2349, 1821, 1739, 1457, 1053, 799 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.89 (s, 1.42H, minor), 2.43 (t, J = 7.2 Hz, 2H), 2.38–2.34 (m, 1.95H, minor), 2.27 (t, J = 7.2 Hz, 2H), 1.62–1.52 (m, 4H), 1.48–1.42 (m, 2H), 1.36–1.28 (m, 4H), 0.94–0.89 (m, 6H); ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.89 (s, 1.42H, minor), 2.44 (t, J = 6.9 Hz, 2H), 2.39–2.33 (m, 1.95H, minor), 2.24 (t, J = 7.8 Hz, 2H), 1.62–1.26 (m, 10H), 0.95–0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 142.2, 102.0, 92.6, 75.9, 72.3, 61.8, 34.3, 31.3, 30.9, 30.2, 29.0, 26.5, 25.4, 22.2, 21.81, 21.77, 19.1, 18.8, 13.7, 13.3; HRMS (ESI) calcd for $C_{13}H_{24}NO$ $(M + H)^+$ 210.1852, found 210.1857.

General procedure for the synthesis of 4-haloisoxazoles 2a–l (Table 2) and 2t (Table 3)

To the solution of (*Z*)-alkynyl-*O*-methyl oxime **1a** (71.1 mg, 0.30 mmol, 1.0 equiv.) in nitromethane (3.0 mL, 10.0 mL $mmol^{-1}$) was added with NCS (45.8 mg, 0.33 mmol, 1.1 equiv.), followed by TMSCl (38.4 μL, 0.30 mmol, 1.0 equiv.). The reaction was monitored by TLC until completion. It was then diluted with water and extracted with EtOAc, dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator. The crude product was purified by SiO_2 column chromatography (10% EtOAc–hexane) to afford 4-chloro-3,5-diphenylisoxazole (**2a-Cl**) (76.5 mg, ≥99%).

General procedure for the synthesis of 4-haloisoxazoles 2m–u (Table 3, except 2t)

To the solution of alkynyl-*O*-methyl oxime **1m** ($(E) : (Z)$ = 41 : 59) (62.3 mg, 0.36 mmol, 1.0 equiv.) in nitromethane (3.6 mL, 10.0 mL $mmol^{-1}$) was added with NCS (52.8 mg, 0.40 mmol, 1.1 equiv.), followed by TMSCl (91.0 μL, 0.72 mmol, 2.0 equiv.). The reaction was monitored by TLC until completion. It was then diluted with water and extracted with EtOAc, dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator. The crude product was purified by SiO_2 column chromatography (2% EtOAc–hexane) to afford 4-chloro-3-methyl-5-phenylisoxazole (**2m**) (39.1 mg, 56%).

4-Chloro-3,5-diphenylisoxazole (2a-Cl).[6a] Yield 76.5 mg (≥99%, white solid); mp 65.7–65.9 °C; IR (neat): ν_{max} 3055, 2923, 2853, 1492, 1459, 1448, 1397, 1127, 767, 706, 690 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.02–7.99 (m, 2H), 7.86–7.80 (m, 2H), 7.65–7.57 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.8, 160.4, 131.2, 130.7, 129.4, 129.1, 128.1, 126.6, 126.4, 125.5, 104.2; HRMS (ESI) calcd for $C_{15}H_{11}ClNO$ $(M + H)^+$ (Cl-35) 256.0524, found 256.0517.

4-Bromo-3,5-diphenylisoxazole (2a-Br).[5b] Yield 88.9 mg (80%, yellow solid); mp 126.1–126.5 °C; IR (neat): ν_{max} 3449, 3053, 1613, 1447, 1115, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12–8.08 (m, 2H), 7.89–7.86 (m, 2H), 7.54–7.52 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 162.1, 130.7, 130.2, 128.8, 128.63, 128.58, 127.8, 127.0, 126.8, 89.5; HRMS (ESI) calcd for $C_{15}H_{11}NOBr$ $(M + H)^+$ (Br-79) 300.0019, found 300.0010.

4-Iodo-3,5-diphenylisoxazole (2a-I).[5b] Yield 103.8 mg (85%, white solid); mp 161.4–161.6 °C; IR (neat): ν_{max} 3457, 2069, 1638, 1446, 765 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.04–8.00 (m, 2H), 7.76–7.72 (m, 2H), 7.66–7.57 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.6, 164.8, 131.0, 130.3, 129.2, 128.84, 128.80, 128.5, 127.6, 126.9, 59.5; HRMS (ESI) calcd for $C_{15}H_{11}INO$ $(M + H)^+$ (I-127) 347.9880, found 347.9877.

4-Chloro-5-phenyl-3-(*o*-tolyl)isoxazole (2b). Yield 64.9 mg (83%, colorless oil); IR (neat): ν_{max} 3611, 3063, 2925, 2854, 1448, 1389, 767, 689 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.04–8.01 (m, 2H), 7.65–7.57 (m, 3H), 7.50–7.34 (m, 4H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.9, 162.0, 137.1, 131.2, 130.6, 130.4, 129.9, 129.4, 126.2, 126.1, 125.9, 125.6, 105.4, 19.4; HRMS (ESI) calcd for $C_{16}H_{13}ClNO$ $(M + H)^+$ (Cl-35) 270.0680, found 270.0690.

3-([1,1′-Biphenyl]-4-yl)-4-chloro-5-phenylisoxazole (2c). Yield 47.8 mg (69%, white solid); mp 136.3–136.7 °C; IR (neat): ν_{max} 3453, 3058, 2921, 2851, 2126, 1420, 768, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01–7.98 (m, 2H), 7.93–7.90 (m, 2H), 7.69–7.64 (m, 2H), 7.59–7.55 (m, 2H), 7.49–7.37 (m, 5H), 7.31 (tt, J = 7.2, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 160.4, 143.1, 140.2, 130.6, 128.9, 128.6, 127.8, 127.4, 127.2, 126.6, 126.5, 126.3, 104.6; HRMS (ESI) calcd for $C_{21}H_{15}ClNO$ $(M + H)^+$ (Cl-35) 332.0837, found 332.0842.

3-([1,1′-Biphenyl]-2-yl)-4-chloro-5-phenylisoxazole (2d). Yield 63.0 mg (59% as a colorless oil). IR (neat): ν_{max} 3060, 3027, 1591, 1447, 1391, 1129, 766, 742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.95–7.92 (m, 2H), 7.63–7.43 (m, 7H), 7.34–7.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 162.8, 142.2, 140.1, 130.9, 130.42, 130.36, 129.2, 128.8, 128.1, 127.3, 126.4, 126.2, 125.5, 106.2; HRMS (ESI) calcd for $C_{21}H_{15}ClNO$ $(M + H)^+$ (Cl-35) 332.0837, found 332.0833.

(9*Z*)-10-(Chloro(phenyl)methylene)phenanthren-9(10*H*)-one *O*-methyl oxime (3d). Yield 27.6 mg (25%, yellow solid); mp 159.7–161.2 °C; IR (neat): ν_{max} 3059, 2935, 2819, 1935, 1599, 1442, 1051, 767, 736, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 7.5 Hz, 1H), 7.59–7.40 (m, 4H), 7.33–7.11 (m, 7H), 6.96 (d, J = 8.1 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 139.5, 139.1, 137.9, 137.8, 137.6, 136.3, 131.3, 130.7, 130.3, 130.1, 129.5, 129.2, 128.2, 128.1, 127.9, 127.7, 127.0, 126.9, 121.0, 62.9; HRMS (ESI) calcd for $C_{22}H_{17}ClNO$ $(M + H)^+$ (Cl-35) 346.0993, found 346.0986.

4-Chloro-3-(4-fluorophenyl)-5-phenylisoxazole (2f). Yield 69.3 mg (88%, white solid); mp 89.9–90.4 °C; IR (neat): ν_{max}

3053, 1902, 1607, 1127, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07–8.04 (m, 2H), 7.93–7.88 (m, 2H), 7.56–7.51 (m, 3H), 7.26–7.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (d, $J_{C-F} = 249$ Hz), 164.3, 159.9, 130.7, 130.3 (d, $J_{C-F} = 8$ Hz), 128.9, 126.6, 126.4, 123.6 (d, $J_{C-F} = 3$ Hz), 115.9 (d, $J_{C-F} = 22$ Hz), 104.4; ESI-HRMS calcd for $C_{15}H_{10}ClFNO$ $(M + H)^+$ (Cl-35) 274.0430, found 274.0419.

4-Chloro-3-(4-chlorophenyl)-5-phenylisoxazole (2g). Yield 103.2 mg (75%, white solid); mp 92.3–93.5 °C; IR (neat): ν_{max} 3357, 3063, 2924, 2854, 2349, 1603, 1419 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06–8.02 (m, 2H), 7.85 (d, $J = 8.4$ Hz, 2H), 7.56–7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 159.7, 136.5, 130.7, 129.5, 129.0, 128.9, 126.5, 126.3, 125.8, 104.4; HRMS (ESI) calcd for $C_{15}H_{10}Cl_2NO$ $(M + H)^+$ (Cl-35) 290.0134, found 290.0138.

4-Chloro-3-(3-chlorophenyl)-5-phenylisoxazole (2h). Yield 83.4 mg (96%, white solid); mp 86.6–86.8 °C; IR (neat): ν_{max} 3059, 2936, 2326, 1439, 1378, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07–8.04 (m, 2H), 7.92–7.91 (m, 1H), 7.82–7.79 (m, 1H), 7.57–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 159.5, 134.7, 130.7, 130.3, 130.0, 129.0, 128.9, 128.2, 126.5, 126.3, 126.2, 104.4; HRMS (ESI) calcd for $C_{15}H_{10}Cl_2NO$ $(M + H)^+$ (Cl-35) 290.0134, found 290.0126.

3-(4-Bromophenyl)-4-chloro-5-phenylisoxazole (2i). Yield 23.4 mg (70%, white solid); mp 109.0–109.3 °C; IR (neat): ν_{max} 3504, 2127, 1985, 1924, 1640, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07–8.04 (m, 2H), 7.81–7.78 (m, 2H), 7.66 (d, $J = 8.4$ Hz, 2H), 7.57–7.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 159.8, 132.0, 130.7, 129.7, 128.9, 126.5, 126.30, 126.27, 124.9, 104.3; HRMS (ESI) calcd for $C_{15}H_{10}BrClNO$ $(M + H)^+$ (Cl-35) (Br-79) 333.9629, found 333.9637.

4-Chloro-5-(4-methoxyphenyl)-3-phenylisoxazole (2j). Yield 51.2 mg (72%, white solid); mp 97.5–97.8 °C; IR (neat): ν_{max} 3160, 3068, 2952, 2846, 1773, 1694, 1189, 833, 687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04–8.00 (m, 2H), 7.90–7.87 (m, 2H), 7.52–7.50 (m, 3H), 7.06–7.02 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 161.3, 160.6, 130.2, 128.7, 128.21, 128.16, 127.5, 119.2, 114.3, 103.1, 55.4; HRMS (ESI) calcd for $C_{16}H_{13}ClNO_2$ $(M + H)^+$ (Cl-35) 286.0629, found 286.0627.

4-Chloro-5-(4-fluorophenyl)-3-phenylisoxazole (2k). Yield 50.3 mg (71%, white solid); mp 94.8–95.0 °C; IR (neat): ν_{max} 3451, 2134, 2030, 1638, 1239, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09–8.04 (m, 2H), 7.90–7.87 (m, 2H), 7.53–7.51 (m, 3H), 7.26–7.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9 (d, $J_{C-F} = 251$ Hz), 163.3, 160.8, 130.4, 128.80, 128.78 (d, $J_{C-F} = 9$ Hz), 128.3, 127.3, 122.8 (d, $J_{C-F} = 3$ Hz), 116.2 (d, $J_{C-F} = 22$ Hz), 104.4; HRMS (ESI) calcd for $C_{15}H_{10}ClFNO$ $(M + H)^+$ (Cl-35) 274.0430, found 274.0439.

4-Chloro-5-(4-chlorophenyl)-3-phenylisoxazole (2l). Yield 52.1 mg (95%, white solid); mp 105.9–106.1 °C; IR (neat): ν_{max} 3463, 3068, 2344, 2127, 1131, 834, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94–7.90 (m, 2H), 7.82–7.77 (m, 2H), 7.46–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 160.8, 136.7, 130.3, 129.2, 128.8, 128.2, 127.7, 127.2, 124.9, 104.9; HRMS (ESI) calcd for $C_{15}H_{10}Cl_2NO$ $(M + H)^+$ (Cl-35) 290.0134, found 290.0130.

4-Chloro-3-methyl-5-phenylisoxazole (2m-Cl).[14] Yield 39.1 mg (56%, white solid); mp 35.7–36.2 °C; IR (neat): ν_{max} 3749, 3610, 2930, 2152, 1699, 1409, 767, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00–7.96 (m, 2H), 7.51–7.45 (m, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 159.4, 130.3, 128.8, 126.5, 126.1, 105.8, 9.8; HRMS (ESI) calcd for $C_{10}H_9ClNO$ $(M + H)^+$ (Cl-35) 194.0367, found 194.0363.

4-Bromo-3-methyl-5-phenylisoxazole (2m-Br).[15] Yield 12.0 mg (22%, yellow oil); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–8.01 (m, 2H), 7.52–7.47 (m, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 160.6, 130.4, 128.8, 127.9, 126.8, 126.6, 91.1, 10.8.

4-Iodo-3-methyl-5-phenylisoxazole (2m-I).[5b] Yield 50.7 mg (89%, yellow oil); IR (neat): ν_{max} 3058, 2936, 2820, 2213, 1444, 1337, 1048 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.99–7.96 (m, 2H), 7.61–7.56 (m, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 163.2, 130.8, 129.2, 127.0, 126.9, 60.9, 12.3; HRMS (ESI) calcd for $C_{10}H_9INO$ $(M + H)^+$ (I-131) 285.9723, found 285.9723.

4-Chloro-3-ethyl-5-phenylisoxazole (2n-Cl). Yield 70.7 mg (68%, colorless oil); IR (neat): ν_{max} 3062, 2979, 2939, 1713, 1594, 1448, 1072, 940, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01–7.98 (m, 2H), 7.54–7.47 (m, 3H), 2.76 (q, $J = 7.8$ Hz, 2H), 1.36 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 162.6, 130.3, 128.8, 126.6, 126.3, 105.2, 18.4, 11.4; HRMS (ESI) calcd for $C_{11}H_{11}ClNO$ $(M + H)^+$ (Cl-35) 208.0524, found 208.0515.

4-Bromo-3-ethyl-5-phenylisoxazole (2n-Br). Yield 74.1 mg (74%, colorless oil); IR (neat): ν_{max} 3063, 2978, 2939, 1573, 1412, 1063, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04–8.01 (m, 2H), 7.54–7.48 (m, 3H), 2.75 (q, $J = 7.5$ Hz, 2H), 1.36 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 164.3, 130.4, 128.8, 126.8, 126.7, 90.4, 19.2, 11.5; HRMS (ESI) calcd for $C_{11}H_{11}BrNO$ $(M + H)^+$ (Br-79) 252.0019, found 252.0029.

4-Chloro-3-pentyl-5-phenylisoxazole (2o-Cl). Yield 64.1 mg (76%, yellow oil); IR (neat): ν_{max} 2957, 2927, 2855, 2149, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01–7.97 (m, 2H), 7.52–7.42 (m, 3H), 2.71 (t, $J = 7.5$ Hz, 2H), 1.82–1.71 (m, 2H), 1.46–1.31 (m, 4H), 0.94–0.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 162.5, 130.3, 128.8, 126.6, 126.2, 105.3, 31.3, 26.6, 24.6, 22.3, 13.9; HRMS (ESI) calcd for $C_{14}H_{17}ClNO$ $(M + H)^+$ (Cl-35) 250.0993, found 250.1005.

4-Bromo-3-pentyl-5-phenylisoxazole (2o-Br). Yield 47.9 mg (81%, colorless oil); IR (neat): ν_{max} 3065, 2930, 2860, 1445, 1410, 1060, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–8.01 (m, 2H), 7.53–7.48 (m, 3H), 2.71 (t, $J = 7.5$ Hz, 2H), 1.82–1.72 (m, 2H), 1.46–1.33 (m, 4H), 0.95–0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 163.8, 130.4, 128.8, 126.9, 126.7, 90.6, 31.4, 26.8, 25.4, 22.3, 13.9; HRMS (ESI) calcd for $C_{14}H_{17}BrNO$ $(M + H)^+$ (Br-79) 294.0488, found 294.0499.

4-Chloro-5-phenyl-3-undecylisoxazole (2p). Yield 48.6 mg (58%, colorless oil); IR (neat): ν_{max} 2924, 2854, 1594, 1449, 1072, 766, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01–7.97 (m, 2H), 7.52–7.45 (m, 3H), 2.71 (t, $J = 7.5$ Hz, 2H), 1.81–1.71 (m, 2H), 1.44–1.26 (m, 16H), 0.88 (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 162.5, 130.3, 128.8, 126.6, 126.3, 105.3, 31.9, 29.6, 29.5, 29.3, 29.21, 29.20, 27.0, 24.6, 22.7, 14.1; HRMS (ESI) calcd for $C_{20}H_{29}ClNO$ $(M + H)^+$ (Cl-35) 334.1932, found 334.1938.

4-Chloro-3-isopropyl-5-phenylisoxazole (2q-Cl). Yield 62.1 mg (76%, colorless oil); IR (neat): ν_{max} 3063, 2973, 2934, 1448,

1131, 768, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, J = 7.8, 2.1 Hz, 2H), 7.53–7.44 (m, 3H), 3.13 (sept, J = 7.2 Hz, 1H), 1.40 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 162.8, 130.3, 128.8, 126.6, 126.4, 104.7, 26.0, 20.2; HRMS (ESI) calcd for $C_{12}H_{13}ClNO$ $(M + H)^+$ (Cl-35) 222.0680, found 222.0685.

4-Bromo-3-isopropyl-5-phenylisoxazole (2q-Br). Yield 78.4 mg (89%, colorless oil); IR (neat): ν_{max} 3062, 2972, 2931, 2878, 1948, 1447, 1036, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04–8.00 (m, 2H), 7.52–7.48 (m, 3H), 3.11 (sept, J = 6.9 Hz, 1H), 1.41 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 164.4, 130.4, 128.7, 126.9, 126.8, 89.9, 26.6, 20.4; HRMS (ESI) calcd for $C_{12}H_{13}BrNO$ $(M + H)^+$ (Br-79) 266.0175, found 266.0179.

3-(*sec*-Butyl)-4-chloro-5-phenylisoxazole (2r). Yield 42.7 mg (72%, colorless oil); IR (neat): ν_{max} 3526, 2968, 2934, 2877, 2152, 1449, 1131, 768, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, J = 7.8, 2.1 Hz, 2H), 7.53–7.44 (m, 3H), 2.95 (sex, J = 7.2 Hz, 1H), 1.91 (sept, J = 7.5 Hz, 1H), 1.71 (sept, J = 7.2 Hz, 1H), 1.38 (d, J = 7.2 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 162.7, 130.3, 128.8, 126.7, 126.3, 104.9, 32.6, 27.5, 17.9, 11.7; HRMS (ESI) calcd for $C_{13}H_{15}ClNO$ $(M + H)^+$ (Cl-35) 236.0837, found 236.0845.

4-Chloro-3-cyclohexyl-5-phenylisoxazole (2s-Cl).[14] Yield 50.6 mg (77%, white solid); mp 63.9–64.5 °C; IR (neat): ν_{max} 3065, 2930, 2854, 1960, 1448, 1129, 768, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, J = 7.8, 1.8 Hz, 2H), 7.51–7.42 (m, 3H), 2.80 (tt, J = 11.7, 3.3 Hz, 1H), 2.06–2.02 (m, 2H), 1.90–1.85 (m, 2H), 1.78–1.58 (m, 3H), 1.48–1.25 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 162.5, 130.2, 128.7, 126.6, 126.3, 104.7, 35.3, 30.4, 26.1, 25.8; HRMS (ESI) calcd for $C_{15}H_{17}ClNO$ $(M + H)^+$ (Cl-35) 262.0993, found 262.0991.

4-Bromo-3-cyclohexyl-5-phenylisoxazole (2s-Br). Yield 91.1 mg (78%, yellow oil); IR (neat): ν_{max} 3064, 2929, 2853, 1447, 1414, 1070, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03–7.99 (m, 2H), 7.51–7.46 (m, 3H), 2.77 (tt, J = 11.7, 3.6 Hz, 1H), 2.07–2.03 (m, 2H), 1.90–1.85 (m, 2H), 1.78–1.57 (m, 3H), 1.48–1.25 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 164.1, 130.3, 128.7, 126.8, 126.7, 89.9, 35.9, 30.6, 26.1, 25.8; HRMS (ESI) calcd for $C_{15}H_{17}BrNO$ $(M + H)^+$ (Br-79) 306.0488, found 306.0498.

3-(*tert*-Butyl)-4-chloro-5-phenylisoxazole (2t). Yield 138.6 mg (88%, colorless oil); IR (neat): ν_{max} 3063, 2973, 2935, 2873, 1574, 1050, 768, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99–7.96 (m, 2H), 7.52–7.43 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 163.7, 130.3, 128.7, 126.7, 126.5, 104.4, 33.2, 27.7; HRMS (ESI) calcd for $C_{13}H_{15}ClNO$ $(M + H)^+$ (Cl-35) 236.0837, found 236.0841.

5-Butyl-4-chloro-3-pentylisoxazole (2u-Cl). Yield 43.4 mg (47%, colorless oil); IR (neat): ν_{max} 2958, 2932, 2863, 2152, 1610, 1122, 1053, 891 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.74 (t, J = 7.5 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 1.73–1.66 (m, 4H), 1.43–1.30 (m, 6H), 0.96–0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 161.4, 105.9, 31.4, 28.8, 26.6, 24.9, 24.6, 22.3, 22.1, 13.9, 13.6; HRMS (ESI) calcd for $C_{12}H_{21}ClNO$ $(M + H)^+$ (Cl-35) 230.1306, found 230.1297.

4-Bromo-5-butyl-3-pentylisoxazole (2u-Br). Yield 49.3 mg (60%, colorless oil); IR (neat): ν_{max} 2958, 2932, 2863, 1602, 1466, 1416, 1057, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.74 (t, J = 7.5 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 1.75–1.63 (m, 4H), 1.43–1.31 (m, 6H), 0.96–0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 162.4, 91.5, 31.4, 28.9, 26.7, 25.5, 25.3, 22.3, 22.1, 13.9, 13.6; HRMS (ESI) calcd for $C_{12}H_{21}BrNO$ $(M + H)^+$ (Br-79) 274.0801, found 274.0808.

5-Butyl-4-iodo-3-pentylisoxazole (2u-I). Yield 49.3 mg (55%, yellow oil); IR (neat): ν_{max} 2957, 2931, 2862, 1587, 1465, 1047, 894, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.77 (t, J = 7.5 Hz, 2H), 2.59 (t, J = 7.5 Hz, 2H), 1.75–1.63 (m, 4H), 1.43–1.31 (m, 6H), 0.96–0.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 164.3, 58.9, 31.3, 29.2, 27.0, 26.6, 26.5, 22.3, 22.1, 13.9, 13.6; HRMS (ESI) calcd for $C_{12}H_{21}INO$ $(M + H)^+$ (I-131) 322.0662, found 322.0655.

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