A Facile One-Pot Synthesis of 3,5-Disubstituted Isoxazole Derivatives Using Hydroxy (Tosyloxy) Iodobenzene

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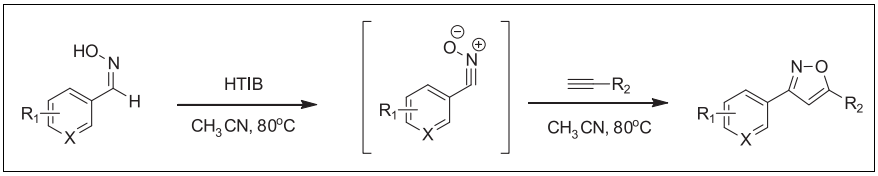

Hydroxy (tosyloxy) iodobenzene (HTIB), a hypervalent iodine reagent, has been extensively used for oxidative transformations. We have developed a one-pot synthesis wherein aldoximes when reacted with alkynes in the presence of HTIB result in the direct formation of isoxazoles. This simple and straightforward reaction allows for ease of purification while leading to the formation of high purity 3,5-disubstituted isoxazoles in moderate yields.

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INTRODUCTION

Aromatic heterocycles such as isoxazoles are valuable synthetic templates in organic and medicinal chemistry. Several isoxazoles have been used as key intermediates for the synthesis of complex organic molecules. The isoxazole moiety is a part of several commercial drugs including antidepressants [1], anti-inflammatory agents [2], antibiotics [3], and antifungal agents [4]. Because of the commercial applications of isoxazoles, there has been an immense interest in developing convenient methodologies for the synthesis of this heterocycle. A few prominently reported methods for the synthesis of asymmetric 3,5-disubstituted isoxazoles include the condensation of 1,3-dicarbonyl compounds with hydroxylamine [5], solid phase methods that involve anchoring a nitrile oxide precursor onto resins [6], and 1,3-dipolar cycloaddition reactions that use 1,1-disubstituted bromoalkenes as alkyne equivalents for regioselective synthesis [7]. However the disadvantages of these methods include low yields, formation of side products, and nonselective synthesis of regioisomers.

A commonly used approach for isoxazole synthesis involves the 1,3-dipolar cycloaddition reaction of nitrile oxides with terminal alkynes [8]. Aldoximes that serve as established precursors for obtaining nitrile oxides can be conveniently generated using reported methodologies [9] that either utilize halogenating reagents [10], direct oxidizing reagents [11], or hypervalent iodine reagents [12]. Conventional methods use halogenating reagents such as *N*-bromosuccinimide [13], *N*-chlorosuccinimide [14], sodium hypochlorite [15], and *tert*-butyl hypochlorite [16]. However, the use of halogenating reagents for the synthesis of asymmetric 3,5-disubstituted isoxazoles involves a two-step synthetic protocol necessitating an additional base treatment and the need for temperature control to optimize reaction yields. Direct oxidizing agents such as ceric ammonium nitrate, lead (IV) acetate, potassium ferricyanide, magtrieve (CrO_2), and manganese dioxide have also been used to yield asymmetric 3,5-disubstituted isoxazoles [17]. However these reagents also suffer from certain disadvantages that include harsh reaction conditions, leading to the formation of significant amounts of corresponding aldehydes from aldoximes thereby lowering the overall yields of this reaction.

The hypervalent iodine reagent diacetoxy iodobenzene (DIB) has been reported to react with several substituted aldoximes resulting in the formation of their corresponding nitrile oxide intermediates that in turn have been used to synthesize isoxazolines following a reaction with alkenes and isoxazoles following a reaction with alkynes [18]. However, hypervalent iodine reagents also have the potential to induce deoximation of aldoximes, thereby suppressing the formation of nitrile oxides [19]. The scope of a hypervalent iodine reagent hydroxy (tosyloxy) iodobenzene (HTIB), also known as Koser's reagent, for the *in situ* formation of nitrile oxide and its intramolecular dipolar cycloaddition for the preparation of isoxazole and isoxazoline derivatives has been recently explored by Yao and co-workers [20]. We have explored and report the scope of this reagent, for the conversion of aldoximes to nitrile oxides followed by their subsequent reactivity with a substituted alkyne resulting in the intermolecular synthesis of 3,5-disubstituted isoxazoles. Our results demonstrate the applicability and identify limitations of this HTIB-mediated formation of 3,5 disubstituted isoxazoles.

RESULTS AND DISCUSSION

A convenient one-pot protocol describing the synthesis of 3,5-disubstituted isoxazoles has been developed. In this reaction, nitrile oxide intermediates are obtained from aromatic aldoximes following a treatment with HTIB and are further reacted *in situ* with substituted alkynes to obtain 3,5-disubstituted isoxazoles. We investigated the feasibility of this HTIB-mediated generation of nitrile oxides from substituted aromatic aldoximes (Table 1, entries 1–10) and validated it following the subsequent trapping of these reactive intermediates using ethyl propiolate to yield several ethyl 3-(substituted phenyl) isoxazole-5-carboxylates (Table 1, compounds **4a–4j**). The effect of electron-withdrawing and electron-donating substituents on the reactivity of the aldoxime was also studied. Five different electron-withdrawing substituents (Table 1, entries 1–5) on the aldoxime yielded corresponding isoxazole products (**4a–4e**) in moderate yields ranging from 50 to 64%. However, the presence of electron-donating substituents (Table 1, entries 6 and 7) displayed either negligible (**4f**) or no product (**4g**) formation. In the case of disubstitution (Table 1, entries 8 and 9), the presence of an electron-withdrawing substituent appears to override the effects of an electron-donating substituent (**4h**), thereby yielding around 65% of the 3,5-disubstituted isoxazoles. The formation of a corresponding 3,5-disubstituted isoxazole product (**4j**) following the use of a heterocyclic aldoxime (Table 1, entry 10) also highlights the utility of this method for such substituents.

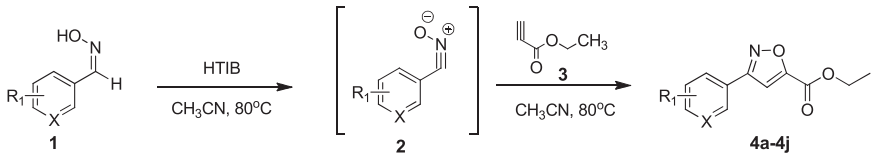
In an attempt to explore the feasibility of this methodology with aliphatic alkynes, the nitrile oxide intermediates obtained from aromatic aldoximes, following a treatment with HTIB, were reacted with mono-substituted and di-substituted alkynes to produce di-substituted and tri-substituted isoxazoles in moderate yields (45–60%, Table 2, entries 1–3). The use of a heteroaromatic aldoxime (Table 2, entry 4) also resulted in the formation of a tri-substituted product (Table 2, compound **8d**) when reacted with dimethyl-2-butynedioate.

We have also explored the feasibility of this HTIB-mediated methodology for studying the reactivity of *para*-substituted benzaldoxime with *para*-substituted phenyl alkynes resulting in the formation of 3,5-disubstituted isoxazoles (Table 3, entries 1–10). It was observed that the nature of a *para*-substituent on the aldoxime influenced its reactivity. The presence of an electron donating benzyloxy substituent (Table 3, entry 10) on the aldoxime gave a low 9% yield of the corresponding isoxazole. However, electron-withdrawing substituents (Table 3, entries 1–9) on the aldoxime yielded products (**12a–12i**) ranging from 30 to 57%. This study thus highlights that the formation of a reactive nitrile oxide intermediate from aromatic aldoximes appears to be suppressed in the presence of electron-donating substituents.

The reaction condition thus developed can be used to synthesize, in moderate yields, 3,5-disubstituted isoxazoles that possess electron-withdrawing substituents on the aromatic aldoxime. It is possible that the moderate yields observed were a result of a competing *in situ* alkynyl iodinium species formation [21]. Deoximation of the

Table 1

HTIB-mediated synthesis of 3,5-disubstituted isoxazoles using ethyl propiolate.

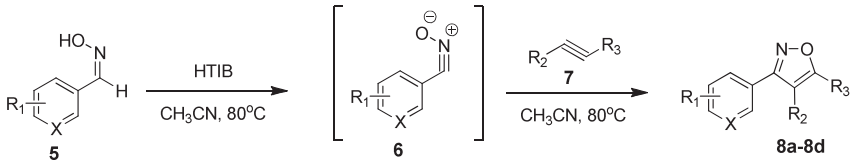


Entry	X	R_1	Product	Yield[a]
1	–CH–	4–F	**4a**	62
2	–CH–	4–CI	**4b**	56
3	–CH–	4–CF_3	**4c**	64
4	–CH–	4–NO_2	**4d**	50
5	–CH–	4–NO_2	**4e**	60
6	–CH–	4–OCH_2Ph	**4f**	14
7	–CH–	4–OCH_3	**4g**	No product
8	–CH–	2–OCH_3, 4–NO_2	**4h**	65
9	–CH–	3–F, 4–NO_2	**4i**	74
10	–N–	–H	**4j**	55

[a]Isolated yields.

Table 2

HTIB-mediated synthesis of 3,5-disubstituted isoxazoles/3,4,5-trisubstituted isoxazoles using substituted alkynes.

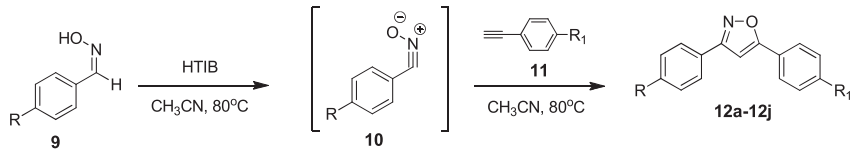


Entry	X	R_1	R_2	R_3	Product	Yield (%)[a]
1	–CH–	4–CI	–H	$–CH_2OH$	**8a**	45
2	–CH–	4–F	$–COOCH_3$	$–COOCH_3$	**8b**	60
3	–CH–	4–CI	–H	$–COCH_3$	**8c**	55
4	–N–	–H	$–COOCH_3$	$–COOCH_3$	**8d**	50

[a]Isolated yields.

Table 3

HTIB-mediated synthesis of 3,5-disubstituted isoxazoles using substituted aromatic alkynes.



Entry	R	R_1	Product	Yield (%)[a]
1	$–NO_2$	–H	**12a**	45
2	$–NO_2$	–F	**12b**	44
3	$–NO_2$	$–CF_3$	**12c**	47
4	–F	$–CF_3$	**12d**	35
5	$–CF_3$	$–CF_3$	**12e**	55
6	–CI	$–CF_3$	**12f**	57
7	$–NO_2$	$–CH_3$	**12g**	30
8	$–NO_2$	$–OCH_3$	**12h**	49
9	$–NO_2$	$–C(CH_3)_3$	**12i**	36
10	$–OCH_2Ph$	–H	**12j**	9

[a]Isolated yields.

starting aldoximes in the presence of hypervalent iodine reagents [19] resulting in the reduction of nitrile oxide formation can provide yet another explanation for the moderate yields of the resulting 3,5-disubstituted isoxazoles. This reaction condition, utilizing HTIB, appears to have limited utility for synthesizing 3,5-disubstituted isoxazoles possessing electron-donating substituents on the aromatic aldoxime. However, a detailed study to gauge the scope of electron-donating substituents is warranted because of the limited number of examples covered herein.

The advantage of this simplistic HTIB protocol for the synthesis of 3,5-disubstituted isoxazoles lies in the ease of reaction workup that involves a sequential evaporation of the solvent used, followed by a trituration of the subsequently obtained solid in ethanol and eventually conducting a simple filtration to obtain the desired isoxazoles as a solid. The yields reported herein are those following this simplified workup that does not necessitate any column chromatographic purification. The structures of all the synthesized isoxazoles were established from their spectral (^{1}H NMR, ^{13}C NMR, and HRMS) data. Interestingly, in each case only the 3,5-disubstituted regioisomer was obtained, as is evident from the ^{1}H NMR data.

CONCLUSIONS

In summary, an alternate intermolecular one-pot synthesis of 3,5-disubstituted isoxazoles has been

achieved. This reaction proceeds via a reactive nitrile oxide intermediate synthesized *in situ* by reacting a substituted aromatic aldoxime with HTIB, which on subsequent coupling with either an aliphatic or aromatic alkyne leads to the formation of corresponding 3,5-disubstituted isoxazole. The presence of an electron-withdrawing substituent on the aromatic aldoxime leads to moderate yields of the corresponding isoxazoles. However, aromatic aldoximes possessing electron-donating substituents exhibit poor reactivity and negligible yields. The reagent, HTIB, used in this reaction is readily available, stable, and can be handled without any special care.

EXPERIMENTAL

Unless mentioned otherwise, all reactions were performed under atmosphere. Unless otherwise specified, all reagents were obtained from Aldrich (St. Louis, MO) and solvents were obtained from Thomas Baker (Mumbai, India) and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer (300 MHz; Billerica, MA) operating at 300 and 75 MHz for ^{1}H and ^{13}C, respectively using either $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts, δ, are reported in parts per million (ppm) relative to solvent resonance: $CDCl_3$, δ 7.26 (^{1}H NMR), and 77.3 (^{13}C NMR); DMSO-d_6, δ 2.50 (^{1}H NMR), and 40.2 (^{13}C NMR). Multiplicities are indicated by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), and m (multiplet). Coupling constants, *J*, are reported in Hertz. High resolution mass spectra were obtained on Bruker Daltonics ESI-QTOF instrument equipped with an ESI interface. Melting points have been determined on a manually operated Veego (VMP-1; Mumbai, India) melting point apparatus and are reported uncorrected. Analytical HPLC was obtained on a Waters Alliance 2695 HPLC system (Milford, MA) fitted with a PDA detector using either method A or method B as follows:

HPLC solvents
A1: acetonitrile
B1: 0.01 *M* NH_4OAc + 0.5% TEA, pH 5.0 with AcOH
B2: 0.1% trifluoroacetic acid
HPLC columns
Column 1: Ascentis TM Express (50 × 4.6 mm I.D.), 2.7 μm operated at 1 mL/min, detection at 288 nm
Column 2: Kromasil 250 × 4.6 mm, 3.5 μm, C18 operated at 1 mL/min, detection at 276 nm
HPLC methods
Method A: Elution with 20–80% linear gradient of A1 in 6 min followed by 20–80% linear gradient of B1 in 1 min that is continued using an isocratic elution with 80% B1 for 3 min using Column 1.
Method B: Elution with 10–90% linear gradient of A1 in 20 min followed by 10–90% linear gradient of B2 in 2 min that is continued using an isocratic elution with 90% B2 for 8 min using Column 2.

The aldoximes used for synthesis were prepared in-house using a reported procedure and characterized completely using ^{1}H NMR and mass spectrometry. General procedures used for the synthesis of these aromatic aldoximes (procedure A) and its subsequent conversion to 3,5-disubstitured isoxazoles (procedure B) are provided in the following sections.

Procedure A: preparation of aromatic aldoximes. To a solution of the aromatic aldehyde (1.0 equiv) in ethanol, pyridine (1.5 equiv) and hydroxylamine hydrochloride (2.0 equiv) were added sequentially, and the reaction mixture was refluxed overnight. The reaction mixture was concentrated *in vacuo*, and the residue was taken in water and extracted using ethyl acetate. The organic layer was dried over sodium sulfate and evaporated *in vacuo* to yield a solid product that was subsequently recrystallized from ethyl acetate and petroleum ether to afford the desired aromatic aldoxime.

Procedure B: preparation of 3,5-disubstitured isoxazoles. Hydroxy (tosyloxy) iodobenzene (1.3 equiv) was added to a solution of the aromatic aldoxime (1.0 equiv) in acetonitrile, and the mixture was stirred at 80°C for 5 min. Subsequently the alkyne (2.0 equiv) was added to this reaction mixture and stirred for an additional 2 h at 80°C. Following completion of this reaction, the solvent was removed under reduced pressure, the residue was subsequently triturated with ethanol, and the resulting solid was filtered and dried under vacuum to yield the title compounds (**4a–4j**, **8a–8d**, and **12a–12j**).

Ethyl 3-(4-fluorophenyl)isoxazole-5-carboxylate (4a). Reaction with 4-fluorobenzaldehyde oxime (0.50 g, 3.59 mmol) and ethyl propiolate (0.72 mL, 7.18 mmol) afforded compound **4a** (0.52 g, 62%) as a white solid, mp 126–128°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.82 (d, J = 9.0 Hz, 2H, phenyl), 7.21 (s, 1H, isoxazole), 7.16 (d, J = 9.0 Hz, 2H, phenyl), 4.46 (q, J = 6.0 Hz, 2H, CH_2), 1.43 (t, J = 6.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 162.5, 161.2, 156.8, 129.0, 128.9, 124.4, 116.5, 116.2, 107.3, 62.5, 14.3; HRMS (ESI+) calcd. for $C_{12}H_{11}FNO_3$ $[M+H]^+$ 236.0717, found 236.0707 (error 4.23 ppm); HPLC: retention time 5.18 min, purity 95.73% (method A).

Ethyl 3-(4-chlorophenyl)isoxazole-5-carboxylate (4b). Reaction with 4-chlorobenzaldehyde oxime (0.50 g, 3.21 mmol) and ethyl propiolate (0.65 mL, 6.42 mmol) afforded compound **4b** (0.45 g, 56%) as a white solid, mp 135–137°C (lit [17]: 136–138°C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.77 (d, J = 9.0 Hz, 2H. phenyl), 7.46 (d, J = 9.0 Hz, 2H, phenyl), 7.22 (s, 1H, isoxazole), 4.46 (d, J = 6.0 Hz, 2H, CH_2), 1.43 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 161.3, 156.8, 136.8, 129.5 (2C), 128.2 (2C), 126.6, 107.3, 62.5, 14.3; HRMS (ESI+) calcd. for $C_{12}H_{11}ClNO_3$ $[M+H]^+$ 252.0422, found 252.0420 (error 0.79 ppm); HPLC: retention time 5.84 min, purity 99.27% (method A).

Ethyl 3-(4-(trifluoromethyl)phenyl)isoxazole-5-carboxylate (4c). Reaction with 4-(trifluoromethyl)benzaldehyde oxime (0.5 g, 2.64 mmol) and ethyl propiolate (0.53 mL, 5.28 mmol) afforded compound **4c** (0.48 g, 64%) as a white solid, mp 124–126°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.95 (d, J = 9.0 Hz, 2H, phenyl), 7.73 (d, J = 9.0 Hz, 2H, phenyl), 7.28 (s, 1H, isoxazole), 4.44 (d, J = 7.2 Hz, 2H, CH_2), 1.43 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.6, 156.6, 132.7, 132.3, 131.5, 127.3 (2C), 126.2, 126.1, 107.3, 62.6, 14.2; HRMS (ESI+) calcd. for $C_{13}H_{11}F_3NO_3$ $[M+H]^+$ 286.0686, found 286.0676 (error 3.49 ppm); HPLC: retention time 6.02 min, purity 99.16% (method A).

Ethyl 3-(4-nitrophenyl)isoxazole-5-carboxylate (4d). Reaction with 4-nitrobenzaldehyde oxime (0.5 g, 3.01 mmol) and ethyl propiolate (0.61 mL, 6.02 mmol) afforded compound **4d** (0.39 g, 50%) as a white solid, mp 152–154°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, J = 9.0 Hz, 2H, phenyl), 8.03 (d, J = 9.0 Hz, 2H, phenyl), 7.32 (s, 1H, isoxazole), 4.47 (q, J = 6.0 Hz, 2H, CH_2), 1.44

(t, J = 6.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 160.7, 155.9, 148.6, 133.5, 127.4 (2C), 123.9 (2C), 106.8, 62.2, 13.7; HRMS (ESI+) calcd. for $C_{12}H_{11}N_2O_5$ $[M+H]^+$ 263.0662, found 263.0668 (error 2.28 ppm); HPLC: retention time 4.98 min, purity 99.61% (method A).

Ethyl 3-(3-nitrophenyl)isoxazole-5-carboxylate (4e). Reaction with 3-nitrobenzaldehyde oxime (0.5 g, 3.01 mmol) and ethyl propiolate (0.61 mL, 6.02 mmol) afforded compound **4e** (0.47 g, 60%) as a white solid, mp 125–127°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H, phenyl), 8.34 (dd, J = 9.0, 6.0 Hz, 1H, phenyl), 8.21 (d, J = 6.0 Hz, 1H, phenyl), 7.70 (t, J = 9.0 Hz, 1H, phenyl), 7.34 (s, 1H, isoxazole), 4.47 (q, J = 6.0 Hz, 2H, CH_2), 1.44 (t, J = 6.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.2, 156.5, 148.8, 132.6, 130.5, 129.9, 125.2, 121.9, 107.2, 62.7, 14.2; HRMS (ESI+) calcd. for $C_{12}H_{11}N_2O_5$ $[M+H]^+$ 263.0662, found 263.0671 (error 3.42 ppm); HPLC: retention time 5.03 min, purity 96.11% (method A).

Ethyl 3-(4-(benzyloxy)phenyl)isoxazole-5-carboxylate (4f). Reaction with 4-(benzyloxy)benzaldehyde oxime (0.2 g, 2.20 mmol) and ethyl propiolate (0.44 mL, 4.40 mmol) afforded compound **4f** (0.04 g, 14%) as an off-white solid, mp 112–114°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.79 (d, J = 9.0 Hz, 2H, phenyl), 7.41 (m, 5H, phenyl), 7.28 (s, 1H, isoxazole), 7.08 (d, J = 9.0 Hz, 2H, phenyl), 5.14 (s, 2H, OCH_2), 4.47 (d, J = 6.0 Hz, 2H, CH_2), 1.45 (t, J = 6.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 160.7, 160.6, 156.9, 136.4, 128.7 (2C), 128.3 (2C), 128.2, 127.5 (2C), 120.7, 115.4 (2C), 107.2, 70.1, 62.3, 14.2; HRMS (ESI+) calcd. for $C_{19}H_{18}NO_4$ $[M+H]^+$ 324.1230, found 324.1242 (error 3.70 ppm); HPLC: retention time 6.38 min, purity 95.79% (method A).

Ethyl 3-(2-methyl-4-nitrophenyl)isoxazole-5-carboxylate (4h). Reaction with 2-methyl-4-nitrobenzaldehyde oxime (0.5 g, 2.20 mmol) and ethyl propiolate (0.44 mL, 4.40 mmol) afforded compound **4h** (0.49 g, 65%) as a white solid, mp 92–94°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.26 (d, J = 1.5 Hz, 1H, phenyl), 8.14 (dd, J = 2.1, 8.4 Hz, 1H, phenyl), 7.90 (d, J = 8.7 Hz, 1H, phenyl), 7.80 (s,1H, isoxazole), 4.40 (q, J = 6.9 Hz, 2H, CH_2), 2.55 (s, 3H, Ar-CH_3), 1.33 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.7, 160.7, 156.7, 148.7, 139.7, 134.0, 131.7, 126.2, 121.7, 110.9, 62.8, 21.3, 14.5; HRMS (ESI+) calcd. for $C_{13}H_{13}N_2O_5$ $[M+H]^+$ 277.0819, found 277.0829 (error 3.60 ppm); HPLC: retention time 5.42 min, purity 98.10% (method A).

Ethyl 3-(3-fluoro-4-nitrophenyl)isoxazole-5-carboxylate (4i). Reaction with 3-fluoro-4-nitrobenzaldehyde oxime (0.5 g, 2.72 mmol) and ethyl propiolate (0.55 mL, 5.44 mmol) afforded compound **4i** (0.56 g, 74%) as a white solid, mp 144–146°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.30 (t, J = 9.0 Hz, 1H, phenyl), 8.18 (d, J = 9.0 Hz, 1H, phenyl), 8.04 (d, J = 9.0 Hz, 1H, phenyl), 8.00 (s, 1H, isoxazole), 4.45 (q, J = 6.0 Hz, 2H, CH_2), 1.38 (t, J = 6.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.2, 160.7, 155.9, 153.2, 137.8, 134.7, 127.3, 123.2, 117.1, 108.5, 62.4, 13.9; HRMS (ESI+) calcd. for $C_{12}H_{10}FN_2O_5$ $[M+H]^+$ 281.0568, found 281.0576 (error 2.84 ppm); HPLC: retention time 5.07 min, purity 98.09% (method A).

Ethyl 3-(pyridin-2-yl)isoxazole-5-carboxylate (4j). Reaction with picolinaldehyde oxime (0.5 g, 4.09 mmol) and ethyl propiolate (0.82 mL, 8.18 mmol) afforded compound **4j** (0.49 g, 55%) as a yellow solid, mp 70–72°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.73 (d, J = 4.8 Hz, 1H, phenyl), 8.09 (d, J = 8.1 Hz, 1H, phenyl), 7.99 (m, 1H, phenyl), 7.66 (s, 1H, isoxazole), 7.55 (m, 1H, phenyl), 4.39 (q, J = 7.0 Hz, 2H, CH_2), 1.34 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.0, 161.2, 156.6, 150.6, 146.9, 138.2, 126.1, 122.2, 108.5, 62.7, 14.4; HRMS (ESI+) calcd. for $C_{11}H_{11}N_2O_3$ $[M+H]^+$ 219.0764, found 219.0757 (error 3.19 ppm); HPLC: retention time 3.75 min, purity 99.11% (method A).

(3-(4-chlorophenyl)isoxazol-5-yl)methanol (8a). Reaction with 4-chlorobenzaldehyde oxime (0.25 g, 1.60 mmol) and propargyl alcohol (0.18 mL, 3.20 mmol) afforded compound **8a** (0.15 g, 45%) as a white solid, mp 98–100°C (lit [22]: 98–100°C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.72 (d, J = 9.0 Hz, 2H, phenyl), 7.43 (d, J = 9.0 Hz, 2H, phenyl), 6.54 (s, 1H, isoxazole), 4.82 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 161.7, 136.3, 131.7, 129.4, 129.0, 128.2, 127.4, 100.0, 56.7; HRMS (ESI+) calcd. for $C_{10}H_9ClNO_2$ $[M+H]^+$ 210.0316, found 210.0319 (error 1.42 ppm); HPLC: retention time 3.43 min, purity 97.25% (method A).

Dimethyl 3-(4-fluorophenyl)isoxazole-4,5-dicarboxylate (8b). Reaction with 4-fluorobenzaldehyde oxime (0.25 g, 1.79 mmol) and dimethyl-2-butynedioate (0.43 mL, 3.58 mmol) afforded compound **8b** (0.33 g, 60%) as a white solid, mp 110–112°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.71 (d, J = 9.0 Hz, 2H, phenyl), 7.39 (m, 2H, phenyl), 3.94 (s, 3H, CH_3), 3.84 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.2, 163.1, 161.5, 160.4, 156.4, 130.9, 130.8, 123.2, 116.9, 116.7, 115.6, 54.1, 53.8; HRMS (ESI+) calcd. for $C_{13}H_{11}FNO_5$ $[M+H]^+$ 280.0616, found 280.0620 (error 1.42 ppm); HPLC: retention time 4.84 min, purity 99.41% (method A).

1-(3-(4-Chlorophenyl)isoxazol-5-yl)ethanone (8c). Reaction with 4-chlorobenzaldehyde oxime (0.25 g, 1.60 mmol) and 3-butyne-2-one (0.25 mL, 3.20 mmol) afforded compound **8c** (0.19 g, 55%) as a white solid, mp 133–135°C (lit [23]: 134–136°C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.99 (m, 3H, 2H-phenyl, 1H-isoxazole), 7.63 (d, J = 8.4 Hz, 2H, phenyl), 2.61 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 186.9, 166.9, 162.3, 135.9, 129.8 (2C), 128.9 (2C), 126.9, 107.5, 27.9; HRMS (ESI+) calcd. for $C_{11}H_9ClNO_2$ $[M+H]^+$ 222.0316, found 222.0324 (error 3.60 ppm); HPLC: retention time 4.92 min, purity 99.35% (method A).

Dimethyl 3-(pyridin-2-yl)isoxazole-4,5-dicarboxylate (8d). Reaction with picolinaldehyde oxime (0.25 g, 2.04 mmol) and dimethyl-2-butynedioate (0.23 mL, 4.08 mmol) afforded compound **8d** (0.29 g, 50%) as a white solid, mp 90–92°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.67 (m, 1H, phenyl), 8.02 (m, 2H, phenyl), 7.57 (m, 1H, phenyl), 3.94 (s, 3H, CH_3), 3.84 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.8, 161.1, 158.3, 156.1, 150.6, 145.9, 138.5, 126.5, 122.7, 117.1, 54.1, 53.6; HRMS (ESI+) calcd. for $C_{12}H_{11}N_2O_5$ $[M+H]^+$ 263.0662, found 263.0671 (error 4.18 ppm); HPLC: retention time 3.66 min, purity 99.97% (method A).

3-(4-Nitrophenyl)-5-phenylisoxazole (12a). Reaction with 4-nitrobenzaldehyde oxime (0.25 g, 1.50 mmol) and phenylacetylene (0.32 mL, 3.00 mmol) afforded compound **12a** (0.18 g, 45%) as a white solid, mp 224–226°C (lit [24]: 226–228°C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.42 (d, J = 9.0 Hz, 2H, phenyl), 8.22 (d, J = 9.0 Hz, 2H, phenyl), 7.95 (m, 2H, phenyl) 7.80 (s, 1H, isoxazole), 7.60 (m, 3H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 161.2, 148.6, 134.6, 128.0 (2C), 127.8, 126.7, 126.2 (2C), 125.4 (2C), 124.3 (2C), 98.9; HRMS (ESI+) calcd. for $C_{15}H_{11}N_2O_3$ $[M+H]^+$ 267.0764, found 267.0776 (error 4.49 ppm); HPLC: retention time 6.09 min, purity 97.46% (method A).

5-(4-Fluorophenyl)-3-(4-nitrophenyl)isoxazole (12b). Reaction with 4-nitrobenzaldehyde oxime (0.25 g, 1.50 mmol) and 4-fluorophenylacetylene (0.34 mL, 3.00 mmol) afforded compound

12b (0.18 g, 45%) as a white solid, mp 206–208°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.38 (d, J = 8.7 Hz, 2H, phenyl), 8.07 (d, J = 8.7 Hz, 2H, phenyl), 7.87 (m, 2H, phenyl), 7.23 (m, 2H, phenyl), 6.87 (s, 1H, isoxazole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 165.7, 161.3, 148.7, 135.1, 128.1, 127.9, 127.7 (2C), 124.3 (2C), 123.3, 116.6, 116.3, 97.3; HRMS (ESI+) calcd. for $C_{15}H_{10}FN_2O_3$ $[M+H]^+$ 285.0670, found 285.0682 (error 4.20 ppm); HPLC: retention time 6.18 min, purity 98.54% (method A).

3-(4-Nitrophenyl)-5-(4-(trifluoromethyl)phenyl)isoxazole (12c). Reaction with 4-nitrobenzaldehyde oxime (0.25 g, 1.50 mmol) and 4-trifluoromethylphenylacetylene (0.49 mL, 3.00 mmol) afforded compound **12c** (0.23 g, 47%) as an off-white solid, mp 186–188°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.38 (d, J = 9.0 Hz, 2H, phenyl), 8.08 (d, J = 9.0 Hz, 2H, phenyl), 8.00 (d, J = 8.1 Hz, 2H, phenyl), 7.80 (d, J = 8.4 Hz, 2H, phenyl), 7.03 (s, 1H, isoxazole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 161.4, 148.8, 134.8, 132.6, 132.1, 129.9, 127.7 (2C), 126.2 (3 C), 125.4, 124.3 (2C), 98.9; HRMS (ESI+) calcd. for $C_{16}H_{10}F_3N_2O_3$ $[M+H]^+$ 335.0638, found 335.0641 (error 0.89 ppm); HPLC: retention time 6.85 min, purity 97.24% (method A).

3-(4-Fluorophenyl)-5-(4-(trifluoromethyl)phenyl)isoxazole (12d). Reaction with 4-fluorobenzaldehyde oxime (0.25 g, 1.79 mmol) and 4-trifluoromethylphenylacetylene (0.29 mL, 3.58 mmol) afforded compound **12d** (0.19 g, 35%) as a white solid, mp 112–114°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.13 (d, J = 9.0 Hz, 2H, phenyl), 7.97 (m, 4H, phenyl), 7.84 (s, 1H, isoxazole), 7.44 (d, J = 9.0 Hz, 2H, phenyl); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.7, 162.4, 162.1, 130.9, 130.8, 130.5, 129.5, 129.4, 126.8 (2C), 126.1, 125.3, 122.7, 116.9, 116.6, 100.9; HRMS (ESI+) calcd. for $C_{16}H_{10}F_4NO$ $[M+H]^+$ 308.0693, found 308.0696 (error 0.97 ppm); HPLC: retention time 6.97 min, purity 99.72% (method A).

3,5-bis(4-(Trifluoromethyl)phenyl)isoxazole (12e). Reaction with 4-(trifluoromethyl) benzaldehyde oxime (0.25 g, 1.32 mmol) and 4-trifluoromethylphenylacetylene (0.21 mL, 2.64 mmol) afforded compound **12e** (0.26 g, 55%) as a white solid, mp 154–156°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.15 (m, 4H, phenyl), 7.96 (m, 5H, 4 H-phenyl, 1H-isoxazole); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.1, 162.2, 132.6, 131.8, 131.3, 130.6, 127.9 (2C), 126.8 (4 C), 126.7 (2C), 126.4, 125.1, 101.2; HRMS (ESI+) calcd. for $C_{17}H_{10}F_6NO$ $[M+H]^+$ 358.0661, found 358.0674 (error 3.63 ppm); HPLC: retention time 5.70 min, purity 99.04% (method A).

3-(4-Chlorophenyl)-5-(4-(trifluoromethyl)phenyl)isoxazole (12f). Reaction with 4-chlorobenzaldehyde oxime (0.25 g, 1.60 mmol) and 4-trifluoromethylphenylacetylene (0.26 mL, 3.20 mmol) afforded compound **12f** (0.29 g, 57%) as a white solid, mp 120–122°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.13 (d, J = 8.1 Hz, 2H, phenyl), 7.96 (d, J = 8.4 Hz, 4H, phenyl), 7.86 (s, 1H, isoxazole), 7.65 (d, J = 8.4 Hz, 2H, phenyl); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.8, 162.4, 135.6, 130.9, 130.7, 130.5, 129.8 (2C), 128.8 (2C), 127.6, 126.8 (2C), 126.1, 122.5, 100.9; HRMS (ESI+) calcd. for $C_{16}H_{10}ClF_3NO$ $[M+H]^+$ 324.0399, found 324.0398 (error 0.30 ppm); HPLC: retention time 22.55 min, purity 98.97% (method B).

3-(4-Nitrophenyl)-5-(p-tolyl)isoxazole (12g). Reaction with 4-nitrobenzaldehyde oxime (0.25 g, 1.50 mmol) and 4-methylphenylacetylene (0.35 g, 3.00 mmol) afforded compound **12g** (0.12 g, 30%) as a white solid, mp 178–180°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.41 (d, J = 8.7 Hz, 2H, phenyl), 8.19 (d, J = 8.7 Hz, 2H, phenyl), 7.82 (d, J = 8.1 Hz, 2H, phenyl), 7.72 (s, 1H, isoxazole), 7.40 (d, J = 8.4 Hz, 2H, phenyl), 2.39 (s, 3H, Ar-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.1, 161.6, 148.8, 141.2, 135.1, 130.3 (2C), 128.3 (2C), 126.0 (2C), 124.8 (2C), 124.3, 98.9, 21.5; HRMS (ESI+) calcd. for $C_{16}H_{13}N_2O_3$ $[M+H]^+$ 281.0921, found 281.0931 (error 3.55 ppm); HPLC: retention time 20.52 min, purity 99.89% (method B).

5-(4-Methoxyphenyl)-3-(4-nitrophenyl)isoxazole (12h). Reaction with 4-nitrobenzaldehyde oxime (0.25 g, 1.50 mmol) and 4-ethynyl anisole (0.39 mL, 3.00 mmol) afforded compound **12h** (0.21 g, 49%) as a white solid, mp 173–175°C (lit [24]: 172–175°C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.36 (d, J = 8.7 Hz, 2H, phenyl), 8.06 (d, J = 8.7 Hz, 2H, phenyl), 7.81 (d, J = 8.7 Hz, 2H, phenyl), 7.04 (d, J = 8.7 Hz, 2H, phenyl), 6.79 (s, 1H, isoxazole), 3.90 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 162.4, 162.1, 148.8, 133.8, 127.6, 127.5, 127.0, 124.2 (2C), 123.6, 114.5 (2C), 114.2, 96.1, 55.4; HRMS (ESI+) calcd. for $C_{16}H_{13}N_2O_4$ $[M+H]^+$ 297.0870, found 297.0872 (error 0.67 ppm); HPLC: retention time 6.08 min, purity 97.63% (method A).

5-(4-(tert-Butyl)phenyl)-3-(4-nitrophenyl)isoxazole (12i). Reaction with 4-nitrobenzaldehyde oxime (0.25 g, 1.50 mmol) and 4-(*tert*-butyl)phenylacetylene (0.54 mL, 3.00 mmol) afforded compound **12i** (0.17 g, 36%) as a white solid, mp > 230°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (d, J = 9.0 Hz, 2H, phenyl), 8.21 (d, J = 8.7 Hz, 2H, phenyl), 7.86 (d, J = 8.4 Hz, 2H, phenyl), 7.74 (s,1H, isoxazole), 7.62 (d, J = 8.4 Hz, 2H, phenyl), 1.33 (s, 9H, $(CH_3)_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.3, 162.0, 151.3, 147.9, 134.3, 128.3 (2C), 126.6 (2C), 125.9 (2C), 124.9 (2C), 122.5, 100.9, 34.3, 31.3 (3 C); HRMS (ESI+) calcd. for $C_{19}H_{19}N_2O_3$ $[M+H]^+$ 323.1390, found 323.1387 (error 0.92 ppm); HPLC: retention time 22.13 min, purity 99.89% (method B).

3-(4-(Benzyloxy)phenyl)-5-(4-(trifluoromethyl)phenyl)isoxazole (12j). Reaction with 4-(benzyloxy)benzaldehyde oxime (0.25 g, 1.10 mmol) and phenylacetylene (0.24 mL, 2.20 mmol) afforded compound **12j** (0.038 g, 9%) as an off-white solid, mp 144–146°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.91 (dd, J = 1.5, 8.1 Hz, 2H, phenyl), 7.87 (d, J = 9.0 Hz, 2H, phenyl), 7.56 (m, 3H, phenyl), 7.49 (d, J = 6.9 Hz, 2H, phenyl), 7.38 (m, 4H, 3H-phenyl, 1H-isoxazole) 7.19 (d, J = 8.7 Hz 2H, phenyl), 5.19 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 162.6, 160.2, 136.6, 130.2, 128.9 (2C), 128.7 (2C), 128.2 (2C), 128.1 (2C), 127.5 (2C), 125.8 (2C), 121.9, 115.2 (2C), 97.3, 70.1; HRMS (ESI+) calcd. for $C_{22}H_{18}NO_2$ $[M+H]^+$ 328.1332, found 328.1329 (error 0.91 ppm); HPLC: retention time 7.22 min, purity 99.76% (method A).

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