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Alkyl Nitrites: Novel Reagents for One-Pot Synthesis of 3,5-Disubstituted Isoxazoles from Aldoximes and Alkynes

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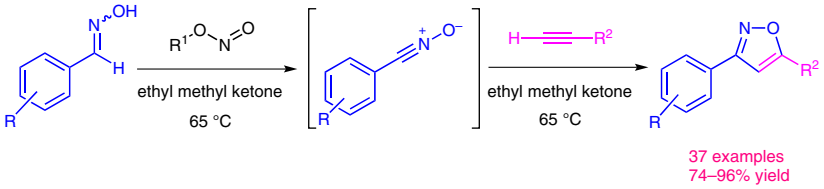

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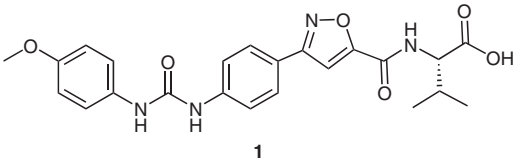
Abstract An efficient, one-pot approach has been described for the synthesis of 3,5-disubstituted isoxazoles from substituted aldoximes (mixture of *E* and *Z*) and alkynes, using alkyl nitrites under conventional heating conditions. The key nitrile oxide intermediates that are required for the synthesis of isoxazoles are formed by treatment of substituted aldoxime with either *tert*-butyl nitrite or isoamyl nitrite. The generated nitrile oxides underwent *in situ* [3+2] dipolar cycloaddition to the substituted alkynes to give 3,5-disubstituted isoxazoles regioselectively in high to excellent yields. The developed synthetic methodology was applied for the synthesis of a previously reported potent hDGAT1 inhibitor.

Key words isoxazoles, nitrile oxides, aldoximes, *tert*-butyl nitrite, isoamyl nitrite

Isoxazole and its derivatives are privileged heterocyclic intermediates that exist in various natural products,[1] biologically active compounds,[2] and functional materials.[3] The isoxazole core exhibits anti-inflammatory (Valdecoxib),[4] antibiotic (Oxacillin),[5] antirheumatic (leflunomide),[6] antidepressant (isocarboxazid),[7] anticancer,[8] and antifungal (micafungin)[9] properties. Traditionally, 3,5-disubstituted isoxazoles have been synthesized by the [3+2] dipolar cycloaddition of alkynes to nitrile oxides generated from oximes or dehydrohalogenation of hydroxymoyl halides. Dang and co-workers synthesized 3,5-disubstituted isoxazoles by the treatment of an aldoxime with *n*-butyl lithium and diethyl oxalate followed by dehydration with an acid.[10] Perumal and co-workers reported $AuCl_3$-catalyzed cycloisomerization of various α,β-acetylenic oximes, leading to the formation of isoxazoles.[11] Thus, aldoximes were established as precursors for the generation of nitrile oxides *in situ* either by utilizing halogenating reagents such as *N*-bromosuccinimide,[12] *N*-chlorosuccinimide,[13] sodium hypochlorite,[14] and *tert*-butyl hypochlorite,[15] or by using direct oxidizing agents such as magtrieve (CrO_2),[16] potassium ferricyanide ($K_3Fe(CN)_6$),[17] manganese dioxide (MnO_2),[18] cerium(IV) ammonium nitrate (CAN),[19] or lead acetate ($Pb(OAC)_4$),[20] or by using hypervalent iodine reagents such as (diacetoxyiodo)benzene (DIB),[21] hydroxyl(tosyloxy)iodobenzene (HTIB),[22] or phenyliodine bis(trifluoroacetate) (PIFA).[23] However, these reagents suffer from certain drawbacks such as the requirement for excess reagents, toxic transition metals, harsh reaction conditions, poor regioselectivity, formation of aldehydes as side product and low synthetic yields. Therefore, the development of a regioselective and metal-free synthetic methodology for 3,5-disubstituted isoxazoles is highly desirable.

We recently reported the synthesis of hDGAT1 inhibitor 3-phenylisoxazole-5-carboxamide derivative **1** with 16% overall yield (Figure 1) by using ethyl 3-(4-nitrophenyl)isoxazole-5-carboxylate (**7**) as the key precursor.[24] However, compound **7** was synthesized in low yield (51%) in two steps. Our main objective was to improve the overall yield of **1** by enhancing the yield of **7**. Alkyl nitrites are commonly utilized for the oxidation of amines to their diazonium salts.[25] Therefore, we envisaged the oxidation of aldoximes by alkyl nitrites to their corresponding nitrile oxides and their subsequent [3+2] cycloaddition to the terminal alkynes, resulting in the formation of 3,5-disubstituted isoxazole derivatives. Herein, we report the exploitation of *tert*-butyl nitrite (**3**) and isoamyl nitrite (**4**) towards the synthesis of 3,5-disubstituted isoxazoles.

At the outset, we initiated the investigation by using commercially available alkyl nitrites, *tert*-butyl nitrite (**3**) and isoamyl nitrite (**4**) as oxidizing agent (due to their acceptable boiling points of 63 and 99 °C, respectively) to generate **5**, which was expected to take part in [3+2] cycloaddition with the terminal alkyne **6** resulting in the for-



1

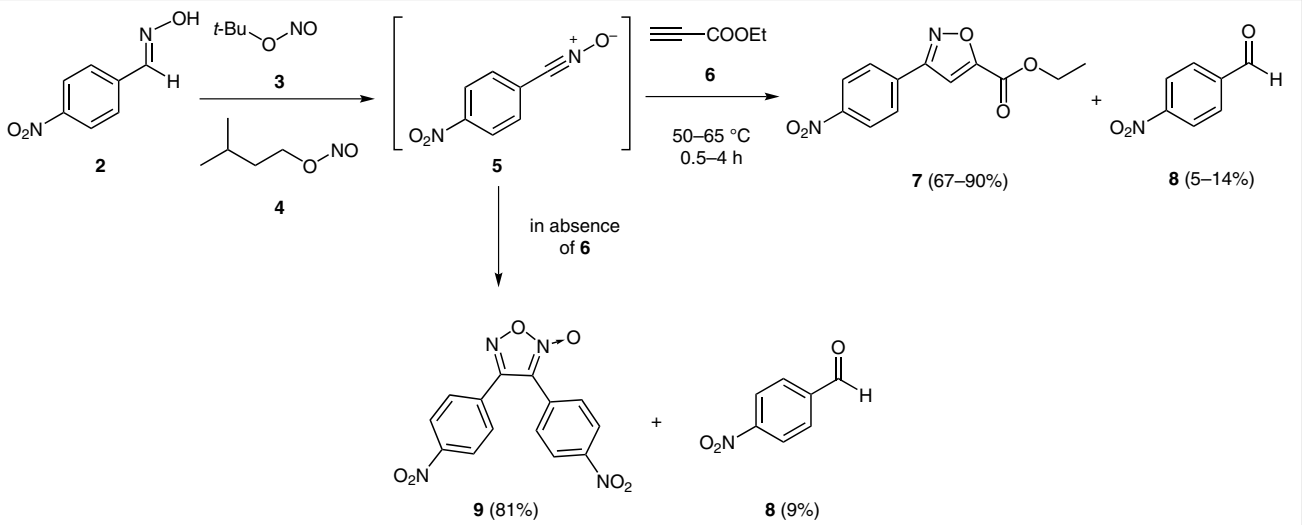
in vitro (hDGAT1 IC50 = 63 nM)
in vivo (TG reduction at 3 mpk = 90%)

Figure 1 3-Phenylisoxazole-5-carboxamide derivative **1** as hDGAT1 inhibitor

mation of 3,5-disubstituted isoxazole derivatives (Scheme 1). The starting materials, i.e., aldoximes required for the synthesis of isoxazoles, were synthesized from aldehydes by using reported procedures.[26] First, we attempted the reaction of aldoxime **2** (1.0 mol equiv) and alkyne **6** (1.1 mol equiv) in the presence of alkyl nitrite **3** (1.1 mol equiv) in tetrahydrofuran (THF) at 50 °C for 4 hours. To our surprise, the reaction resulted in the formation of the desired isoxazole **7** in 75% yield along with 10% 4-nitrobenzaldehyde **8** as deoximated product (Table 1, entry 1). As shown in Table 1, different reaction conditions were probed to improve the yield of compound **7**. The use of alkyne **6** (1.5 mol equiv) and alkyl nitrite **3** (1.5 mol equiv) afforded isoxazole **7** in a 73% yield along with 11% of deoximated product **8** (entry 2). The formation of nitrile oxide intermediate **5** was confirmed by isolation of dimerized product 3,4-di-4-nitrophenylfuroxan **9** (81% yield) along with 9% of aldehyde **8**, when the reaction was carried out in the absence of alkyne **6** (entry 3). Hence, subsequent experiments were carried out by using an equimolar amount of aldoxime **2**, with alkyl nitrite **3** (1.1 equiv) and alkyne **6** (1.1 mol equiv.; entries 4–14).

Replacing the conventional heating conditions with microwave irradiation at 300 MW did not improve the product yield (Table 1, entry 4). The lower yield of **7** was observed along with formation of deoximated product **8**, when solvents such as acetonitrile, toluene, and ethylene dichloride were used (entries 5, 6, and 7, respectively). Use of ethyl methyl ketone in the reaction resulted in improved yield of **7** along with small amounts of deoximated product **8** (entry 8). The above experimental data suggests formation of isoxazole **7** along with deoximated product **8**, thus limiting the scope of reaction with *tert*-butyl nitrite **3**.

We then investigated the use of isoamyl nitrite **4**, which is another commercially available oxidant, because its higher boiling point (99 °C) compared with **3** would allow higher reaction temperature conditions. To optimize and identify the best set of conditions, we scouted six distinct experiments for isoxazole synthesis from aldoxime **2** (1.0 mol equiv) and alkyne **6** (1.1 mol equiv) in the presence of **4** (1.1 mol equiv) at 65 °C for 2 hours in different solvents (Table 1, entries 9–14). The improvement in the yield (83%) of **7** along with reduced amounts of deoximated product **8** was observed in THF (entry 9), whereas when the reaction was run in acetonitrile, toluene or ethylene dichloride, **7** was furnished in comparable yields (77–79%; entries 10–12). Finally, best yield of **7** (90%) was obtained when the reaction was carried out with ethyl methyl ketone as solvent (entry 13). However, microwave irradiation at 300 MW for 0.5 hour at 65 °C in ethyl methyl ketone did not improve the yield of **7** (entry 14). Therefore, isoamyl nitrite **4** (1.1 equiv) found to be the best reagent in combination with **2** (1.0 equiv) and **6** (1.1 equiv) in ethyl methyl ketone as solvent for the synthesis of **7** (Scheme 1). Our study was restricted to the applicability of commercially available alkyl nitrites **3** and **4** because the other commercial alkyl nitrites are either low-boiling liquids or gases.



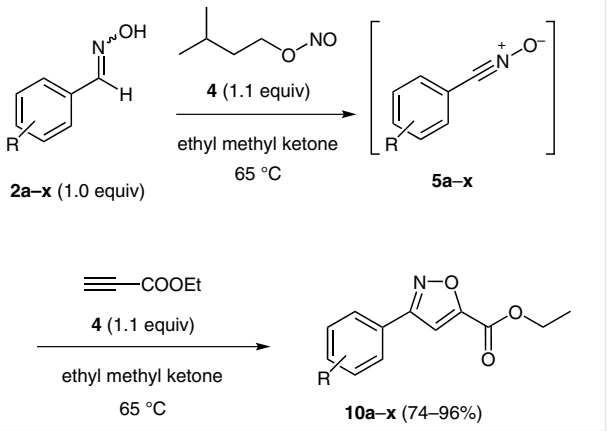
Scheme 1 Synthesis of ethyl 3-(4-nitrophenyl)isoxazole-5-carboxylate (**7**) and 3,4-di-4-nitrophenylfuroxan **9**

With the optimized reaction conditions in hand (Table 1, entry 13), we explored the application of **4** for the synthesis of isoxazole derivatives **10a–x** (Scheme 2). To understand the steric and electronic effects of substituents on the aromatic aldoximes, we selected substituted phenyl aldoximes having an electron-withdrawing (**2b–l**) or electron-donating (**2m–x**) group at either the *ortho*-, *meta*-, or *para*-position. The *para*-substituted phenyl aldoximes gave the desired isoxazoles **10f**, **10i**, **10l**, **10o**, **10r**, **10u**, and **10x** (Table 2, entries 6, 9, 12, 15, 18, 21, 24, respectively) in high yields (88–96%).

Table 1 Optimization Studies

Entry	Alkyl nitrite	Solvent	Temp (°C)	Time (h)	Yield (%)[e]	Yield of **8** (%)[e]
1	**3**	THF[a]	50	4.0	75 (**7**)	10
2	**3**	THF[b]	50	4.0	73 (**7**)	11
3	**3**	THF[c]	50	4.0	81 (**9**)	9
4	**3**	THF[d]	50	0.5	67 (**7**)	13
5	**3**	acetonitrile[a]	50	4.0	69 (**7**)	11
6	**3**	toluene[a]	50	4.0	71 (**7**)	10
7	**3**	ethylene dichloride[a]	50	4.0	67 (**7**)	14
8	**3**	ethyl methyl ketone[a]	50	4.0	81 (**7**)	7
9	**4**	THF[a]	65	2.0	83 (**7**)	5
10	**4**	acetonitrile[a]	65	2.0	78 (**7**)	8
11	**4**	toluene[a]	65	2.0	79 (**7**)	6
12	**4**	ethylene dichloride[a]	65	2.0	77 (**7**)	8
13	**4**	ethyl methyl ketone[a]	65	2.0	90 (**7**)	–
14	**4**	ethyl methyl ketone[d]	65	0.5	80 (**7**)	7

[a] Reaction conditions: **2** (1.0 equiv), **3** or **4** (1.1 equiv), **6** (1.1 equiv).
[b] Reaction conditions: **2** (1.0 equiv), **3** (1.5 equiv), **6** (1.5 equiv).
[c] Reaction conditions: **2** (1.0 equiv), **3** (1.1 equiv).
[d] Reaction carried out in microwave.
[e] Isolated yield after purification.



Scheme 2 One-pot synthesis of 3,5-disubstituted isoxazoles **10a–x**

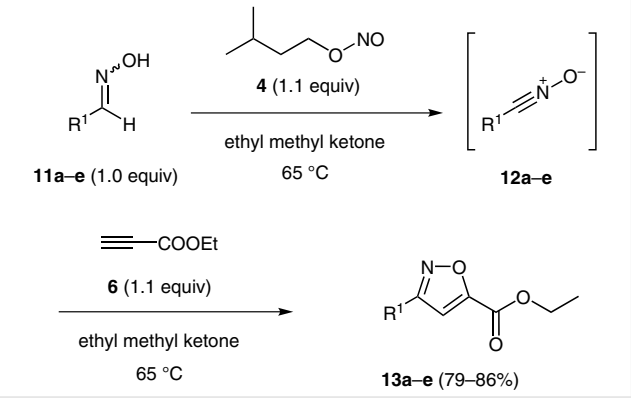
The presence of a *meta*-substituent on the phenyl aldoxime also resulted in the formation of the desired products **10c**, **10e**, **10h**, **10k**, **10n**, **10q**, **10t**, and **10w** in good yields ranging from 83 to 89% (Table 2, entries 3, 5, 8, 11, 14, 17, 20, 23, respectively). On the other hand, *ortho*-substituents on the phenyl aldoxime afforded the corresponding isoxazole compounds **10b**, **10d**, **10g**, **10j**, **10m**, **10p**, **10s**, and **10v** in slightly lower yields ranging from 74 to 81% (entries 2, 4, 7, 10, 13, 16, 19, 22, respectively). In case of the *ortho*-substituted aldoximes, around 4–9% corresponding deoximated products were obtained along with the desired product. However, formation of deoximated side-products was not observed in the case of *meta*- or *para*-substituted aldoximes. Electron-withdrawing as well as electron-donating aldoximes gave similar results. As a result, the steric effects, with regards to the proximity of the substituents to the reaction site, appear to play a far greater role in determining product yields compared with the electronic effects of the phenyl substituents on aldoximes **2a–x**.

Table 2 One-Pot Synthesis of 3,5-Disubstituted Isoxazoles **10a–x**[a]

Entry	**2**	R	Time (h)	Yield of **10** (%)[b]
1	**2a**	H	2	87 (**10a**)
2	**2b**	2-NO_2	2	76 (**10b**)
3	**2c**	3-NO_2	2	86 (**10c**)
4	**2d**	2-F	2	74 (**10d**)
5	**2e**	3-F	2	85 (**10e**)
6	**2f**	4-F	2	94 (**10f**)
7	**2g**	2-Br	2	75 (**10g**)
8	**2h**	3-Br	2	86 (**10h**)
9	**2i**	4-Br	2	94 (**10i**)
10	**2j**	2-CF_3	2	74 (**10j**)
11	**2k**	3-CF_3	2	87 (**10k**)
12	**2l**	4-CF_3	2	93 (**10l**)
13	**2m**	2-Me	3	75 (**10m**)
14	**2n**	3-Me	3	84 (**10n**)
15	**2o**	4-Me	3	90 (**10o**)
16	**2p**	2-OMe	3	77 (**10p**)
17	**2q**	3-OMe	3	83 (**10q**)
18	**2r**	4-OMe	3	88 (**10r**)
19	**2s**	2-Ph	3	81 (**10s**)
20	**2t**	3-Ph	3	89 (**10t**)
21	**2u**	4-Ph	3	96 (**10u**)
22	**2v**	2-OPh	3	77 (**10v**)
23	**2w**	3-OPh	3	85 (**10w**)
24	**2x**	4-OPh	3	90 (**10x**)

[a] Reaction conditions: **2a–x** (1.0 equiv), **4** (1.1 equiv), **6** (1.1 equiv).
[b] Isolated yield after purification.

We then studied the substrate scope of the reaction by using heterocyclic and aliphatic aldoximes for the synthesis of isoxazole derivatives **13a–e** (Scheme 3). On treatment of 2-pyridyl aldoxime **11a** with **4** and **6**, the desired isoxazole **13a** was afforded in 86% yield (Table 3, entry 1). However, the 3-pyridyl analogue **13b** (entry 2) and 4-pyridyl analogue **13c** (entry 3) were obtained from the corresponding aldoximes in 80 and 79% yields, respectively. Replacing the pyridine aldoxime with five-membered thiophene aldoxime **11d** furnished the desired isoxazole **13d** in 82% yield (entry 4). Isobutyraldehyde oxime (**11e**) afforded the corresponding isoxazole **13e** in 81% yield (entry 5). Our current methodology, which is extended to heterocyclic and aliphatic aldoximes, readily afforded the corresponding isoxazoles in excellent yields.



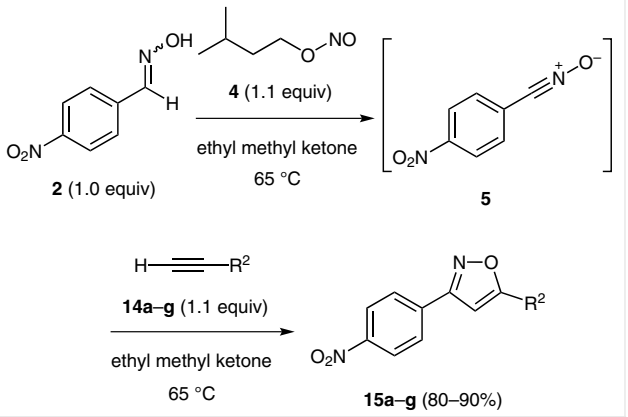
Scheme 3 One-pot synthesis of 3,5-disubstituted isoxazoles **13a–e**

Table 3 One-Pot Synthesis of 3,5-Disubstituted Isoxazoles **13a–e**[a]

Entry	**11**	R^1	Time (h)	Yield of **13** (%)[b]
1	**11a**	2-pyridyl	3	86 (**13a**)
2	**11b**	3-pyridyl	3	80 (**13b**)
3	**11c**	4-pyridyl	3	79 (**13c**)
4	**11d**	thiophen-3-yl	3	82 (**13d**)
5	**11e**	3-isopropyl	3	81 (**13e**)

[a] Reaction conditions: **11a–e** (1.0 equiv), **4** (1.1 equiv), **6** (1.1 equiv).
[b] Isolated yield after purification.

Finally, to explore the scope of the reaction with respect to alkynes, we selected aldoxime **2**, having an electron-withdrawing nitro group, and altered the nature of the alkyne (Scheme 4). The reaction of aldoxime **2** with phenylacetylene (**14a**) under the optimized conditions resulted in the formation of the desired isoxazole **15a** in 81% yield (Table 4, entry 1). Similarly, 4-fluorophenylacetylene (**14b**) and 4-methoxyphenylacetylene (**14c**) afforded **15b** and **15c** with 82 and 80% yields, respectively (entries 2 and 3). The scope of this reaction was further extended by using *tert*-butylacetylene (**14d**) and cyclohexylacetylene (**14e**) to furnish **15d** and **15e** with 88 and 87% yields, respectively (entries 4 and 5). Cycloaddition of polar alkyne such as 1-hydroxyprop-2-yne (**14f**) with aldoxime **2** yielded **15f** in 85% yield (entry 6), whereas but-3-yn-2-one (**14g**) afforded **15g** in 90% yield (entry 7). Thus, aliphatic acetylenes as well as aromatic acetylenes were well tolerated under the present reaction conditions.



Scheme 4 One-pot synthesis of 3,5-disubstituted isoxazoles **15a–g** from aldoxime **2** and substituted terminal alkynes **14a–g**

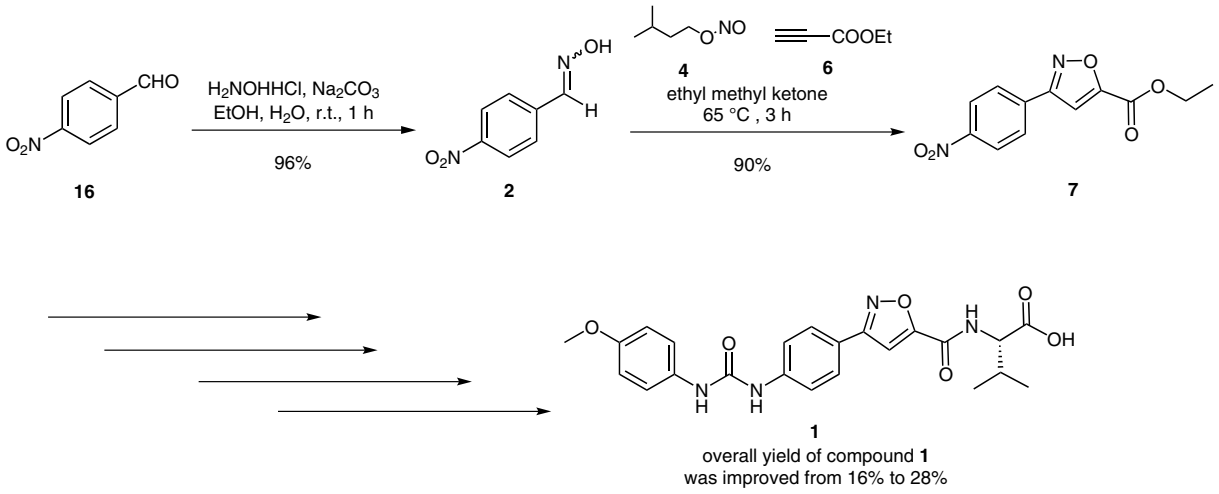
Table 4 One-Pot Synthesis of 3,5-Disubstituted Isoxazoles **15a–g**[a]

Entry	**14**	R^2	Time (h)	Yield of **13** (%)[b]
1	**14a**	Ph	4	81 (**15a**)
2	**14b**	4-FC_6H_4	4	82 (**15b**)
3	**14c**	4-$MeOC_6H_4$	5	80 (**15c**)
4	**14d**	*tert*-butyl	4	88 (**15d**)
5	**14e**	cyclohexyl	5	87 (**15e**)
6	**14f**	CH_2OH	3	85 (**15f**)
7	**14g**	COMe	3	90 (**15g**)

[a] Reaction conditions: **2** (1.0 equiv), **4** (1.1 equiv), **6** (1.1 equiv).
[b] Isolated yield after purification.

The developed synthetic methodology was implemented for the synthesis of hDGAT1 inhibitor **1** (Scheme 5), and we were pleased to find that the overall yield of **1** was improved from 16 to 28% by using this novel transformation.[24]

The regioselectivity of all the 3,5-disubstituted isoxazoles **10a–x**, **13a–e**, and **15a–g** synthesized by using the synthetic protocol described above was established on the basis of available precedence.[27] ^{1}H NMR analysis of synthesized analogues **10a–y**, **13a–e**, and **15a–g** each showed a singlet signal in the region of 6.2–7.8 ppm, characteristic of isoxazole proton (C_4-H) and the corresponding isoxazole carbon (C_4) appeared in the range of 96–111 ppm in the ^{13}C NMR spectrum, confirming the formation of 3,5-disubstituted isoxazoles with complete regioselectivity.



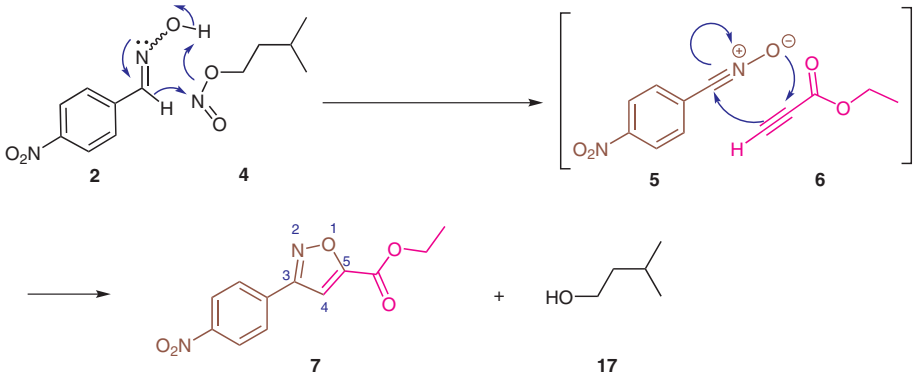
Scheme 5 Synthesis of 3-phenylisoxazole-5-carboxamide derivative **1** from isoxazole **7** with overall improved yield

We propose a probable mechanism for the synthesis of isoxazole **7** by oxidation of aldoxime **2** using alkyl nitrite **4** to nitrile oxide **5** following cycloaddition to alkyne **6** *in situ* (Scheme 6). Support for the alkyl nitrite **4** mediated oxidation of aldoxime **2** proceeding through a seven-membered transition state to nitrile oxide **5** came from the formation of isoamyl alcohol **17**, which was confirmed by the observed mass fragment at *m*/*z* 88 by GCMS analysis of the reaction mass. The formed nitrile oxide **5**, on further [3+2] cycloaddition to alkyne **6** *in situ*, furnished isoxazole **7** (*m*/*z* 262), which was confirmed by GCMS analysis, with the 3,5-disubstituted regioselectivity supported by ^{1}H NMR analysis of isolated isoxazole **7**.

In conclusion, we have developed a novel methodology for the synthesis of 3,5-disubstituted isoxazoles with complete regioselectivity by using commercially available alkyl nitrites by the reaction of aldoximes and terminal alkynes. In general, it was observed that the steric effects govern the desired product formation over the electronic effects. The formation of the deoximated product as a side-product was observed to be restricted to the *ortho*-substituted aldoximes over *meta*- or *para*-substituted aldoximes. A variety of functional groups on the aromatic ring of the aldoxime as well as aldoximes derived from heterocyclic rings were well tolerated under the present reaction conditions. Therefore, the present mild and metal-free reaction methodology offers an attractive alternative to the existing methodologies. The biological activity of all synthesized isoxazole analogues will be evaluated in due course.

Reagents and starting materials, including compounds **2r**, **11a**, **11b**, **11c**, and **11e**, were obtained commercially and used without prior purification.

Unless mentioned otherwise all reactions were performed under open air. ^{1}H, ^{13}C NMR spectra were recorded with a Bruker spectrometer (300 or 400 MHz) using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts, δ, are reported in ppm relative to the solvent peak. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants, *J*, are reported in hertz. High-resolution mass spectra (HRMS) were obtained with a Bruker Daltonics ESI-QTOF instrument equipped with an ESI interface. Melting points were determined with a manually operated Veego (VMP-1)



Scheme 6 Plausible reaction mechanism for the synthesis of isoxazole **7**

melting-point apparatus and are reported uncorrected. Flash chromatography was conducted with a Teledyne Isco advances CombiFlash® Rf automated flash chromatography system (Lincoln, USA) equipped with a UV variable dual-wavelength, software selectable (200–360 nm), using prefabricated RediSep Flash Column silica columns. The aldoximes used for synthesis were prepared in-house by using a reported procedure and characterized completely based on ^{1}H NMR spectroscopy and mass spectrometry.

Synthesis of Aldoximes; General Procedure

To a mixture of hydroxylamine hydrochloride (15.88 mmol, 1.2 equiv) in EtOH (4 mL) and water (20 mL) was added sodium carbonate (15.88 mmol, 1.2 equiv) and the mixture was stirred for 5 min to obtain a clear solution. To this, the appropriate aldehyde (13.23 mmol, 1.0 equiv) was added and the solution was stirred at r.t. for 0.5–1 h; the progress of the reaction was monitored by TLC. After addition of water (30 mL), the resulting solids were filtered and dried to obtain the corresponding aldoximes. When the solid did not precipitate out of the reaction, the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to obtain the corresponding aldoximes, which were used without further purification.

Benzaldehyde Oxime (2a)[28]

Yield: 1.0 g (88%); colorless liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.24 (s, 1 H, OH), 8.14 (s, 1 H, N=CH), 7.60–7.57 (m, 2 H, Ar-H), 7.44–7.37 (m, 3 H, Ar-H).

MS (ESI+): m/z = 122.1 $[M + H]^+$.

2-Nitrobenzaldehyde Oxime (2b)[29]

Yield: 0.98 g (86%); off-white solid; mp 127–129 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.78 (s, 1 H, OH), 8.40 (s, 1 H, N=CH), 8.04 (d, J = 7.8 Hz, 1 H, Ar-H), 7.88 (d, J = 7.8 Hz, 1 H, Ar-H), 7.76 (d, J = 7.8 Hz, 1 H, Ar-H), 7.67–7.62 (m, 1 H, Ar-H).

MS (ESI+): m/z = 167 $[M + H]^+$.

3-Nitrobenzaldehyde Oxime (2c)[30]

Yield: 1.0 g (91%); off-white solid; mp 122–124 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.64 (s, 1 H, OH), 8.40 (t, J = 1.8 Hz, 1 H, Ar-H), 8.31 (s, 1 H, N=CH), 8.20 (dd, J = 1.8 Hz, 1 H, Ar-H), 8.03 (d, J = 7.8 Hz, 1 H, Ar-H), 7.68–7.65 (m, 1 H, Ar-H).

MS (ESI+): m/z = 165 $[M - H]^-$.

4-Nitrobenzaldehyde Oxime (2)[31]

Yield: 21 g (96%); off-white solid; mp 127–129 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.85 (s, 1 H, OH), 8.31 (s, 1 H, N=CH), 8.26 (d, J = 9.0 Hz, 2 H, Ar-H), 7.85 (d, J = 9.0 Hz, 2 H, Ar-H).

MS (ESI+): m/z = 376.1 $[M + H]^+$.

2-Fluorobenzaldehyde Oxime (2d)[32]

Yield: 2 g (89%); white solid; mp 64–66 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.59 (s, 1 H, OH), 8.22 (s, 1 H, N=CH), 7.74 (t, J = 7.5 Hz, 1 H, Ar-H), 7.47–7.41 (m, 1 H, Ar-H), 7.29–7.21 (m, 2 H, Ar-H).

MS (ESI+): m/z = 140.1 $[M + H]^+$.

3-Fluorobenzaldehyde Oxime (2e)[33]

Yield: 3.6 g (80%); white solid; mp 102–104 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.45 (s, 1 H, OH), 8.16 (s, 1 H, N=CH), 7.49–7.37 (m, 3 H, Ar-H), 7.25–7.18 (m, 1 H, Ar-H).

MS (ESI+): m/z = 140 $[M + H]^+$.

4-Fluorobenzaldehyde Oxime (2f)[34]

Yield: 4.12 g (92%); white solid; mp 82–84 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.67 (s, 1 H, OH), 8.05 (t, J = 8.7 Hz, 2 H, Ar-H), 7.43 (s, 1 H, N=CH), 7.27 (t, J = 8.7 Hz, 2 H, Ar-H).

MS (ESI+): m/z = 140 $[M + H]^+$.

2-Bromobenzaldehyde Oxime (2g)[35]

Yield: 3.8 g (88%); off-white solid; mp 101–103 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.70 (s, 1 H, OH), 8.31 (s, 1 H, N=CH), 7.81–7.78 (m, 1 H, Ar-H), 7.69–7.65 (m, 1 H, Ar-H), 7.44–7.39 (m, 2 H, Ar-H).

MS (ESI+): m/z = 200 $[M + H]^+$.

3-Bromobenzaldehyde Oxime (2h)[33]

Yield: 3.18 g (84%); off-white solid; mp 74–76 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.46 (s, 1 H, OH), 8.14 (s, 1 H, N=CH), 7.77–7.76 (m, 1 H, Ar-H), 7.62–7.55 (m, 2 H, Ar-H), 7.45–7.33 (m, 1 H, Ar-H).

MS (ESI+): m/z = 199.9 $[M + H]^+$.

4-Bromobenzaldehyde Oxime (2i)[31]

Yield: 3.9 g (90%); pale-brown liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.38 (s, 1 H, OH), 8.13 (s, 1 H, N=CH), 7.63–7.55 (m, 4 H, Ar-H).

MS (ESI+): m/z = 199.9 $[M + H]^+$.

2-(Trifluoromethyl)benzaldehyde Oxime (2j)[36]

Yield: 3.7 g (85%); off-white solid; mp 51–53 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.87 (s, 1 H, OH), 8.30 (s, 1 H, N=CH), 8.01 (d, J = 7.5 Hz, 1 H, Ar-H), 7.79 (d, J = 7.5 Hz, 1 H, Ar-H), 7.71 (t, J = 7.5 Hz, 1 H, Ar-H), 7.63 (t, J = 7.5 Hz, 1 H, Ar-H).

MS (ESI+): m/z = 190.1 $[M + H]^+$.

3-(Trifluoromethyl)benzaldehyde Oxime (2k)[33]

Yield: 4 g (92%); off-white solid; mp 84–86 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.54 (s, 1 H, OH), 8.27 (s, 1 H, N=CH), 7.92–7.90 (m, 2 H, Ar-H), 7.74 (d, J = 8.1 Hz, 1 H, Ar-H), 7.67 (t, J = 8.1 Hz, 1 H, Ar-H).

MS (ESI+): m/z = 189.9 $[M + H]^+$.

4-(Trifluoromethyl)benzaldehyde Oxime (2l)[36]

Yield: 3.8 g (87%); colorless liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.65 (s, 1 H, OH), 8.25 (s, 1 H, N=CH), 7.78 (dd, J = 8.4 Hz, 4 H, Ar-H).

MS (ESI+): m/z = 189.9 $[M + H]^+$.

2-Methylbenzaldehyde Oxime (2m)[36]

Yield: 4.2 g (93%); pale-brown liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.28 (s, 1 H, OH), 8.32 (s, 1 H, N=CH), 7.62 (d, J = 7.2 Hz, 1 H, Ar-H), 7.29–7.18 (m, 3 H, Ar-H), 2.37 (s, 3 H, Ar-CH_3).

MS (ESI+): m/z = 136 $[M + H]^+$.

3-Methylbenzaldehyde Oxime (2n)[30]

Yield: 3.9 g (87%); off-white solid; mp 59–61 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.18 (s, 1 H, OH), 8.09 (s, 1 H, N=CH), 7.38 (d, J = 8.4 Hz, 2 H, Ar-H), 7.30 (t, J = 7.5 Hz, 1 H, Ar-H), 7.18 (d, J = 7.5 Hz, 1 H, Ar-H), 2.31 (s, 3 H, Ar-CH_3).

MS (ESI+): m/z = 136 $[M + H]^+$.

4-Methylbenzaldehyde Oxime (2o)[30]

Yield: 5.3 g (94%); off-white solid; mp 75–77 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.11 (s, 1 H, OH), 8.09 (s, 1 H, N=CH), 7.48 (d, J = 8.1 Hz, 2 H, Ar-H), 7.20 (d, J = 8.1 Hz, 2 H, Ar-H), 2.30 (s, 3 H, Ar-CH_3).

MS (ESI+): m/z = 136 $[M + H]^+$.

2-Methoxybenzaldehyde Oxime (2p)[36]

Yield: 3.6 g (81%); colorless liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.22 (s, 1 H, OH), 8.29 (s, 1 H, N=CH), 7.65 (dd, J = 1.8 Hz, 1 H, Ar-H), 7.37 (t, J = 8.7 Hz, 1 H, Ar-H), 7.06 (d, J = 8.1 Hz, 1 H, Ar-H), 6.95 (t, J = 7.5 Hz, 1 H, Ar-H), 3.81 (s, 3 H, OCH_3).

MS (ESI+): m/z = 152 $[M + H]^+$.

3-Methoxybenzaldehyde Oxime (2q)[30]

Yield: 4 g (90%); colorless liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.24 (s, 1 H, OH), 8.10 (s, 1 H, N=CH), 7.33 (t, J = 8.1 Hz, 1 H, Ar-H), 7.16 (d, J = 7.5 Hz, 2 H, Ar-H), 6.94 (dd, J = 2.1, 7.2 Hz, 1 H, Ar-H), 3.76 (s, 3 H, OCH_3).

MS (ESI+): m/z = 152 $[M + H]^+$.

[1,1′-Biphenyl]-2-carbaldehyde Oxime (2s)[37]

Yield: 2.8 g (86%); colorless liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.30 (s, 1 H, OH), 7.89–7.83 (m, 2 H, N=CH, Ar-H), 7.57–7.39 (m, 5 H, Ar-H), 7.35–7.30 (m, 3 H, Ar-H).

MS (ESI+): m/z = 198 $[M + H]^+$.

[1,1′-Biphenyl]-3-carbaldehyde Oxime (2t)[36]

Yield: 3.7 g (85%); colorless liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.30 (s, 1 H, OH), 8.22 (s, 1 H, N=CH), 7.85 (s, 1 H, Ar-H), 7.68 (d, J = 7.5 Hz, 3 H, Ar-H), 7.62 (d, J = 7.5 Hz, 1 H, Ar-H), 7.52–7.46 (m, 3 H, Ar-H), 7.41–7.36 (m, 1 H, Ar-H).

MS (ESI+): m/z = 198 $[M + H]^+$.

[1,1′-Biphenyl]-4-carbaldehyde Oxime (2u)[36]

Yield: 3.8 g (88%); colorless liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.29 (s, 1 H, OH), 8.19 (s, 1 H, N=CH), 7.77–7.66 (m, 6 H, Ar-H), 7.48 (t, J = 7.8 Hz, 2 H, Ar-H), 7.38 (t, J = 7.2 Hz, 1 H, Ar-H).

MS (ESI+): m/z = 198 $[M + H]^+$.

2-Phenoxybenzaldehyde Oxime (2v)[38]

Yield: 3.76 g (87%); colorless liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.45 (s, 1 H, OH), 8.21 (s, 1 H, N=CH), 7.84 (d, J = 7.5 Hz, 1 H, Ar-H), 7.44–7.36 (m, 3 H, Ar-H), 7.22 (t, J = 7.5 Hz, 1 H, Ar-H), 7.12 (t, J = 7.2 Hz, 1 H, Ar-H), 6.98–6.94 (m, 3 H, Ar-H).

MS (ESI+): m/z = 214 $[M + H]^+$.

3-Phenoxybenzaldehyde Oxime (2w)[39]

Yield: 3.6 g (84%); colorless liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.31 (s, 1 H, OH), 8.12 (s, 1 H, N=CH), 7.48–7.31 (m, 4 H, Ar-H), 7.20–7.15 (m, 2 H, Ar-H), 7.07–7.01 (m, 3 H, Ar-H).

MS (ESI+): m/z = 214 $[M + H]^+$.

4-Phenoxybenzaldehyde Oxime (2x)[39]

Yield: 3.9 g (91%); colorless liquid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.14 (s, 1 H, OH), 8.12 (s, 1 H, N=CH), 7.60 (d, J = 8.4 Hz, 2 H, Ar-H), 7.40 (t, J = 8.1 Hz, 2 H, Ar-H), 7.18 (t, J = 7.5 Hz, 1 H, Ar-H), 7.03 (dd, J = 8.1 Hz, 4 H, Ar-H).

MS (ESI+): m/z = 214 $[M + H]^+$.

Thiophene-3-carbaldehyde Oxime (11d)[30]

Yield: 3.1 g (91%); pale-brown solid; mp 120–122 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.53 (s, 1 H, OH), 8.23 (s, 1 H, N=CH), 7.58–7.53 (m, 2 H, Ar-H), 7.49 (s, 1 H, Ar-H).

MS (ESI+): m/z = 127.9 $[M + H]^+$.

3,4-Di-4-nitrophenylfuroxan (9)[40]

To a solution of aldoxime **2** (200 mg, 1.65 mmol, 1.0 equiv) in ethyl methyl ketone (10 mL) was added alkyl nitrite **4** (155 mg, 1.32 mmol, 1.1 equiv) and the reaction mixture was stirred at 65 °C for 4 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc–*n*-hexane, 2:8 v/v) to afford **9**.

Yield: 160 mg (81%); pale-yellow solid; mp 198–200 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (t, J = 8.0 Hz, 4 H, Ar-H), 7.61 (t, J = 8.0 Hz, 4 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7 (Ar-CNO_2), 169.8 (Ar-CNO_2), 153.8 (C=N), 148.33 (C=N), 131.60, 129.31 (2C), 129.19 (2C), 128.17, 124.16 (2C), 123.98 (2C).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_9N_4O_6^+$: 329.0522; found: 329.0530.

Synthesis of 3,5-Disubstituted Isoxazoles 10a–x, 13a–e, and 15a–g; General Procedure

To a solution of the appropriate aldoxime (1.2 mmol, 1.0 equiv) in ethyl methyl ketone (10 mL) was added appropriately substituted alkyne (1.32 mmol, 1.1 equiv) followed by alkyl nitrite **4** (1.32 mmol, 1.1 equiv). After 5 min stirring at r.t., the turbid reaction mixture became a clear solution and the reaction mixture was stirred at 65 °C until the aldoxime had been consumed. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc–*n*-hexane, 1:9 v/v) to afford the desired compound.

Ethyl 3-Phenylisoxazole-5-carboxylate (10a)[39]

Yield: 311 mg (87%); off-white solid; mp 47–49 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.84 (m, 2 H, Ar-H), 7.51–7.49 (m, 3 H, Ar-H), 7.27 (s, 1 H, isoxazole-H), 4.48 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.44 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.96 (C=O), 160.95 (C=N), 156.82 (isoxazole-CO), 130.56, 129.09 (2C), 128.00, 126.86 (2C), 107.35 (isoxazole-CH), 62.34 (OCH_2), 14.16 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}NO_3^+$: 218.0817; found: 218.0830.

Ethyl 3-(2-Nitrophenyl)isoxazole-5-carboxylate (10b)

Yield: 240 mg (76%); pale-brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.8 Hz, 1 H, Ar-H), 7.79–7.67 (m, 3 H, Ar-H), 7.06 (s, 1 H, isoxazole-H), 4.48 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.45 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.66 (C=O), 160.61 (C=N), 156.50 (isoxazole-CO), 148.27 (Ar-CNO_2), 133.38, 132.39, 131.86, 124.88, 123.42, 109.69 (isoxazole-CH), 62.50 (OCH_2), 14.14 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}N_2O_5^+$: 263.0668; found: 263.0683.

Ethyl 3-(3-Nitrophenyl)isoxazole-5-carboxylate (10c)[23]

Yield: 271 mg (86%); white solid; mp 126–128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 1.5 Hz, 1 H, Ar-H), 8.36 (dd, *J* = 1.5, 8.1 Hz, 1 H, Ar-H), 8.24 (d, *J* = 7.8 Hz, 1 H, Ar-H), 7.72 (t, *J* = 7.8 Hz, 1 H, Ar-H), 7.36 (s, 1 H, isoxazole-H), 4.50 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.46 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.81 (C=O), 161.15 (C=N), 156.42 (isoxazole-CO), 148.69 (Ar-CNO_2), 132.53, 130.33, 129.76, 125.15, 121.87, 107.08 (isoxazole-CH), 62.63 (OCH_2), 14.15 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}N_2O_5^+$: 263.0668; found: 263.0676.

Ethyl 3-(4-Nitrophenyl)isoxazole-5-carboxylate (7)[24]

Yield: 285 mg (90%); white solid; mp 151–153 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.7 Hz, 2 H, Ar-H), 8.05 (d, *J* = 8.7 Hz, 2 H, Ar-H), 7.34 (s, 1 H, isoxazole-H), 4.50 (q, *J* = 6.9 Hz, 2 H, OCH_2), 1.46 (t, *J* = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.86 (C=O), 161.18 (C=N), 156.40 (isoxazole-CO), 149.02 (Ar-CNO_2), 133.96, 127.81 (2C), 124.38 (2C), 107.28 (isoxazole-CH), 62.66 (OCH_2), 14.15 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}N_2O_5^+$: 263.0668; found: 263.0678.

Ethyl 3-(2-Fluorophenyl)isoxazole-5-carboxylate (10d)

Yield: 251 mg (74%); white solid; mp 37–39 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.02 (m, 1 H, Ar-H), 7.53–7.45 (m, 1 H, Ar-H), 7.40 (d, *J* = 3.6 Hz, 1 H, Ar-H), 7.31–7.19 (m, 2 H, Ar-H, isoxazole-H), 4.49 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.46 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.94 (C=O), 160.80 (C=N), 158.34 (Ar-CF), 156.78 (isoxazole-CO), 132.34, 129.08, 124.79, 116.60, 116.20, 109.87 (isoxazole-CH), 62.35 (OCH_2), 14.16 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}FNO_3^+$: 236.0723; found: 236.0733.

Ethyl 3-(3-Fluorophenyl)isoxazole-5-carboxylate (10e)

Yield: 287 mg (85%); white solid; mp 80–82 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.56 (m, 2 H, Ar-H), 7.51–7.44 (m, 1 H, Ar-H), 7.25–7.17 (m, 2 H, Ar-H, isoxazole-H), 4.48 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.46 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.66 (C=O), 162.03 (Ar-CF), 161.27 (C=N), 156.65 (isoxazole-CO), 130.86, 129.95, 122.65, 117.69, 114.05, 107.26 (isoxazole-CH), 62.46 (OCH_2), 14.15 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}FNO_3^+$: 236.0723; found: 236.0729.

Ethyl 3-(4-Fluorophenyl)isoxazole-5-carboxylate (10f)[23]

Yield: 317 mg (94%); white solid; mp 140–142 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.82 (m, 2 H, Ar-H), 7.23–7.16 (m, 3 H, isoxazole-H, Ar-H), 4.48 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.45 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.77 (C=O), 162.03 (Ar-CF), 161.10 (C=N), 156.72 (isoxazole-CO), 128.92, 128.81, 124.25, 116.41, 116.12, 107.15 (isoxazole-CH), 62.39 (OCH_2), 14.14 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}FNO_3^+$: 236.0723; found: 236.0731.

Ethyl 3-(2-Bromophenyl)isoxazole-5-carboxylate (10g)

Yield: 223 mg (75%); light-brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (t, *J* = 1.2 Hz, 2 H, Ar-H), 7.47–7.45 (m, 1 H, Ar-H), 7.42 (s, 1 H, isoxazole-H), 7.39–7.34 (m, 1 H, Ar-H), 4.49 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.46 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.00 (C=O), 160.12 (C=N), 156.80 (isoxazole-CO), 133.71, 131.55, 131.38, 128.48, 127.80, 122.24 (Ar-CBr), 110.67 (isoxazole-CH), 62.41 (OCH_2), 14.19 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}BrNO_3^+$: 295.9922; found: 295.9928.

Ethyl 3-(3-Bromophenyl)isoxazole-5-carboxylate (10h)[41]

Yield: 256 mg (86%); white solid; mp 90–92 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (t, *J* = 1.8 Hz, 1 H, Ar-H), 7.79 (d, *J* = 7.8 Hz, 1 H, Ar-H), 7.63 (dd, *J* = 7.8, 0.9 Hz, 1 H, Ar-H), 7.38 (t, *J* = 7.8 Hz, 1 H, Ar-H), 7.26 (s, 1 H, isoxazole-H), 4.49 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.46 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.76 (C=O), 161.29 (C=N), 156.61 (isoxazole-CO), 133.54, 130.64, 129.94, 129.86, 125.43, 123.19 (Ar-CBr), 107.19 (isoxazole-CH), 62.46 (OCH_2), 14.16 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}BrNO_3^+$: 295.9922; found: 295.9931.

Ethyl 3-(4-Bromophenyl)isoxazole-5-carboxylate (10i)[12,17]

Yield: 277 mg (94%); white solid; mp 128–130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.63 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.25 (s, 1 H, isoxazole-H), 4.48 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.45 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.07 (C=O), 161.23 (C=N), 156.65 (isoxazole-CO), 132.36 (2C), 128.34 (2C), 126.93, 125.00 (Ar-CBr), 107.11 (isoxazole-CH), 62.44 (OCH_2), 14.15 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}BrNO_3^+$: 295.9922; found: 295.9927.

Ethyl 3-[2-(Trifluoromethyl)phenyl]isoxazole-5-carboxylate (10j)[39]

Yield: 224 mg (74%); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 6.6 Hz, 1 H, Ar-H), 7.67 (s, 3 H, Ar-H), 7.16 (s, 1 H, isoxazole-H), 4.49 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.46 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.96 (C=O), 160.45 (C=N), 156.69 (isoxazole-CO), 132.10, 131.83 (q, $^2J_{C–F}$ = 33.2 Hz), 130.25, 129.08, 126.56, 126.05 (q, $^3J_{C–F}$ = 3.03 Hz), 121.75 (q, $^1J_{CF3}$ = 272.5 Hz), 110.52 (isoxazole-CH), 62.46 (OCH_2), 14.15 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO_3^+$: 286.0691; found: 286.0698.

Ethyl 3-[3-(Trifluoromethyl)phenyl]isoxazole-5-carboxylate (10k)[39]

Yield: 262 mg (87%); white solid; mp 52–54 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (s, 1 H, Ar-H), 8.06 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.77 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.65 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.31 (s, 1 H, isoxazole-H), 4.49 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.46 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.83 (C=O), 161.50 (C=N), 156.56 (isoxazole-CO), 131.90, 130.05 (q, $^2J_{C–F}$ = 33.1 Hz), 129.73, 128.89 (q, $^3J_{C–F}$ = 3.5 Hz), 127.21, 123.77, 123.72 (q, $^1J_{CF3}$ = 272.9 Hz), 107.12 (isoxazole-CH), 62.52 (OCH_2), 14.15 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO_3^+$: 286.0691; found: 286.0700.

Ethyl 3-[4-(Trifluoromethyl)phenyl]isoxazole-5-carboxylate (10l)[21,23]

Yield: 281 mg (93%); white solid; mp 125–127 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.76 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.31 (s, 1 H, isoxazole-H), 4.49 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.46 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.83 (C=O), 161.51 (C=N), 156.56 (isoxazole-CO), 132.62 (q, $^2J_{C–F}$ = 33.4 Hz), 131.42 (q, $^3J_{C–F}$ = 3.6 Hz), 127.23 (4C), 126.13 (q, $^1J_{CF3}$ = 272.4 Hz), 107.24 (isoxazole-CH), 62.53 (OCH_2), 14.15 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO_3^+$: 286.0691; found: 286.0702.

Ethyl 3-(2-Tolyl)isoxazole-5-carboxylate (10m)[10]

Yield: 257 mg (75%); white solid; mp 45–47 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.42–7.32 (m, 3 H, Ar-H), 7.15 (s, 1 H, isoxazole-H), 4.49 (q, *J* = 7.2 Hz, 2 H, OCH_2), 2.50 (s, 3 H, Ar-CH_3), 1.46 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.56 (C=O), 160.18 (C=N), 156.92 (isoxazole-CO), 136.95, 131.23, 130.01, 129.47, 127.65, 126.18, 109.96 (isoxazole-CH), 62.32 (OCH_2), 21.06 (Ar-CH_3), 14.17 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO_3^+$: 232.0974; found: 232.0977.

Ethyl 3-(3-Tolyl)isoxazole-5-carboxylate (10n)[10]

Yield: 289 mg (84%); white solid; mp 58–60 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (s, 1 H, Ar-H), 7.63 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.38 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.30 (m, 1 H, Ar-H), 7.26 (s, 1 H, isoxazole-H), 4.48 (q, *J* = 7.2 Hz, 2 H, OCH_2), 2.44 (s, 3 H, Ar-CH_3), 1.45 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.07 (C=O), 160.83 (C=N), 156.85 (isoxazole-CO), 138.91, 131.33, 128.98, 127.86, 127.44, 124.00, 107.43 (isoxazole-CH), 62.32 (OCH_2), 21.37 (Ar-CH_3), 14.17 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO_3^+$: 232.0974; found: 232.0981.

Ethyl 3-(4-Tolyl)isoxazole-5-carboxylate (10o)[10]

Yield: 309 mg (90%); white solid; mp 51–53 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.5 Hz, 2 H, Ar-H), 7.31 (d, *J* = 7.5 Hz, 2 H, Ar-H), 7.25 (s, 1 H, isoxazole-H), 4.48 (q, *J* = 6.6 Hz, 2 H, OCH_2), 2.43 (s, 3 H, Ar-CH_3), 1.46 (t, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.91 (C=O), 160.76 (C=N), 156.88 (isoxazole-CO), 140.82, 129.78 (2C), 126.75 (2C), 125.14, 107.32 (isoxazole-CH), 62.30 (OCH_2), 21.46 (Ar-CH_3), 14.17 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO_3^+$: 232.0974; found: 232.0979.

Ethyl 3-(2-Methoxyphenyl)isoxazole-5-carboxylate (10p)

Yield: 252 mg (77%); white solid; mp 57–59 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.44 (m, 2 H, Ar-H), 7.10–7.02 (m, 2 H, Ar-H, isoxazole-H), 4.48 (q, *J* = 7.2 Hz, 2 H, OCH_2), 3.94 (s, 3 H, OCH_3), 1.45 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.56 (C=O), 159.78 (C=N), 157.19 (2C, Ar-C-OCH_3, isoxazole-CO), 131.81, 129.41, 121.01, 116.85, 111.42, 111.06 (isoxazole-CH), 62.16 (OCH_2), 55.57 (OCH_3), 14.21 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO_4^+$: 248.0923; found; 248.0932.

Ethyl 3-(3-Methoxyphenyl)isoxazole-5-carboxylate (10q)[10]

Yield: 271 mg (83%); white solid; mp 102–104 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 7.5 Hz, 3 H, Ar-H), 7.25 (s, 1 H, isoxazole-H), 7.05–7.02 (m, 1 H, Ar-H), 4.48 (q, *J* = 7.2 Hz, 2 H, OCH_2), 3.88 (s, 3 H, OCH_3), 1.45 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.89 (C=O), 160.92 (C=N), 160.07 (Ar-C-OCH_3), 156.80 (isoxazole-CO), 130.16, 129.19, 119.34, 116.68, 111.75, 107.46 (isoxazole-CH), 62.35 (OCH_2), 55.43 (OCH_3), 14.16 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO_4^+$: 248.0923; found: 248.0927.

Ethyl 3-(4-Methoxyphenyl)isoxazole-5-carboxylate (10r)[10]

Yield: 288 mg (88%); white solid; mp 83–85 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.21 (s, 1 H, isoxazole-H), 7.00 (d, *J* = 8.4 Hz, 2 H, Ar-H), 4.47 (q, *J* = 6.9 Hz, 2 H, OCH_2), 3.88 (s, 3 H, OCH_3), 1.45 (t, *J* = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.56 (C=O), 161.40 (C=N), 160.67 (Ar-C-OCH_3), 156.90 (isoxazole-CO), 128.31 (2C), 120.44, 114.47 (2C), 107.16 (isoxazole-CH), 62.29 (OCH_2), 55.40 (OCH_3), 14.17 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO_4^+$: 248.0923; found: 248.0934.

Ethyl 3-[(1,1′-biphenyl)-2-yl]isoxazole-5-carboxylate (10s)

Yield: 242 mg (81%); white solid; mp 64–66 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 6.9 Hz, 1 H, Ar-H), 7.59–7.46 (m, 3 H, Ar-H), 7.38–7.36 (m, 3 H, Ar-H), 7.27–7.26 (m, 2 H, isoxazole-H, Ar-H), 6.20 (s, 1 H, Ar-H), 4.37 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.37 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.74 (C=O), 159.46 (C=N), 156.78 (isoxazole-CO), 141.59 (Ar-C-OCH_3), 140.00, 130.63, 130.21, 129.93, 129.36 (2C), 128.47 (2C), 127.81, 127.77, 126.93, 110.46 (isoxazole-CH), 62.12 (OCH_2), 14.07 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO_3^+$: 294.1130; found: 294.1135.

Ethyl 3-[(1,1′-biphenyl)-3-yl]isoxazole-5-carboxylate (10t)

Yield: 266 mg (89%); white solid; mp 63–65 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (br. s, 1 H, Ar-H), 7.83 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.74 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.66 (d, *J* = 7.5 Hz, 2 H, Ar-H), 7.58 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.50 (t, *J* = 7.2 Hz, 2 H, Ar-H), 7.42 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.33 (s, 1 H, isoxazole-H), 4.48 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.45 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.95 (C=O), 161.02 (C=N), 156.81 (isoxazole-CO), 142.23, 140.21, 129.56, 129.31, 128.92 (2C), 128.50, 127.83, 127.21 (2C), 125.68, 125.61, 107.44 (isoxazole-CH), 62.38 (OCH_2), 14.18 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO_3^+$: 294.1130; found: 294.1137.

Ethyl 3-[(1,1′-biphenyl)-4-yl]isoxazole-5-carboxylate (10u)

Yield: 286 mg (96%); white solid; mp 112–114 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.70 (dd, *J* = 8.4, 7.2 Hz, 4 H, Ar-H), 7.50 (t, *J* = 7.2 Hz, 2 H, Ar-H), 7.41 (dd, *J* = 7.2 Hz, 2 H, Ar-H), 7.31 (s, 1 H, isoxazole-H), 4.50 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.47 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.67 (C=O), 160.99 (C=N), 156.83 (isoxazole-CO), 143.38, 140.05, 128.94 (2C), 127.94, 127.75 (2C), 127.29 (2C), 127.11 (2C), 126.82, 107.35 (isoxazole-CH), 62.36 (OCH_2), 14.18 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO_3^+$: 294.1130; found: 294.1141.

Ethyl 3-(2-Phenoxyphenyl)isoxazole-5-carboxylate (10v)

Yield: 223 mg (77%); white solid; mp 97–99 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 1.5 Hz, 1 H, Ar-H), 7.46–7.36 (m, 4 H, Ar-H), 7.26–7.15 (m, 2 H, isoxazole-H, Ar-H), 7.04 (d, *J* = 8.1 Hz, 2 H, Ar-H), 6.96 (d, *J* = 8.1 Hz, 1 H, Ar-H), 4.45 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.42 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.29 (C=O), 160.08 (C=N), 157.00 (Ar-C-OAr), 156.25 (isoxazole-CO), 155.12, 131.79, 130.05 (2C), 129.65, 124.04, 123.74, 119.49, 119.17 (2C), 118.93, 110.60 (isoxazole-CH), 62.21 (OCH_2), 14.17 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO_4^+$: 310.1079; found: 310.1083.

Ethyl 3-(3-Phenoxyphenyl)isoxazole-5-carboxylate (10w)

Yield: 246 mg (85%); white solid; mp 62–64 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 10.2 Hz, 1 H, Ar-H), 7.49–7.43 (m, 2 H, Ar-H), 7.39–7.37 (m, 2 H, Ar-H), 7.22 (s, 1 H, isoxazole-H), 7.17–7.08 (m, 2 H, Ar-H), 6.92 (d, *J* = 8.1 Hz, 2 H, Ar-H), 4.47 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.45 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.51 (C=O), 161.04 (C=N), 158.06 (Ar-C-OAr), 156.74, 156.58 (isoxazole-CO), 130.53, 129.97 (2C), 129.63, 123.86, 121.56, 120.71, 119.22 (2C), 116.94, 107.42 (isoxazole-CH), 62.40 (OCH_2), 14.16 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO_4^+$: 310.1079; found: 310.1092.

Ethyl 3-(4-Phenoxyphenyl)isoxazole-5-carboxylate (10x)

Yield: 261 mg (90%); white solid; mp 55–57 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.81 (d, *J* = 8.7 Hz, 2 H, Ar-H), 7.41 (t, *J* = 8.1 Hz, 2 H, Ar-H), 7.23–7.17 (m, 2 H, isoxazole-H, Ar-H), 7.11–7.08 (m, 4 H, Ar-H), 4.48 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.46 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.38 (C=O), 160.88 (C=N), 159.65 (Ar-C-OAr), 156.84 (isoxazole-CO), 156.11, 129.99 (2C), 128.51 (2C), 124.18, 122.58, 119.69 (2C), 118.64 (2C), 107.21 (isoxazole-CH), 62.36 (OCH_2), 14.18 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO_4^+$: 310.1079; found: 310.1088.

Ethyl 3-(Pyridin-2-yl)isoxazole-5-carboxylate (13a)[23]

Yield: 306 mg (86%); white solid; mp 59–61 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 3.6 Hz, 1 H, Py-H), 8.14 (d, *J* = 7.5 Hz, 1 H, Py-H), 7.84 (t, *J* = 7.5 Hz, 1 H, Py-H), 7.60 (s, 1 H, isoxazole-H), 7.40 (t, *J* = 6.3 Hz, 1 H, Py-H), 4.48 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.45 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.82 (C=O), 160.98 (C=N), 156.76 (isoxazole-CO), 149.91, 147.48, 137.02, 124.95, 121.75, 108.30 (isoxazole-CH), 62.32 (OCH_2), 14.14 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}N_2O_3^+$: 219.0770; found: 219.0776.

Ethyl 3-(Pyridin-3-yl)isoxazole-5-carboxylate (13b)[42]

Yield: 285 mg (80%); pale-brown solid; mp72–74 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.06 (d, *J* = 1.5 Hz, 1 H, Py-H), 8.75 (d, *J* = 1.5 Hz, 1 H, Py-H), 8.21 (d, *J* = 7.5 Hz, 1 H, Py-H), 7.46 (dd, *J* = 4.8 Hz, 1 H, Py-H), 7.32 (s, 1 H, isoxazole-H), 4.50 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.46 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.50 (C=O), 160.51 (C=N), 156.53 (isoxazole-CO), 151.54, 147.88, 134.16, 124.29, 123.95, 106.96 (isoxazole-CH), 62.56 (OCH_2), 14.14 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}N_2O_3^+$: 219.0770; found: 219.0775.

Ethyl 3-(Pyridin-4-yl)isoxazole-5-carboxylate (13c)[42]

Yield: 282 mg (79%); pale-brown solid; mp 120–122 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 (d, *J* = 5.7 Hz, 2 H, Py-H), 7.74 (d, *J* = 5.7 Hz, 2 H, Py-H), 7.32 (s, 1 H, isoxazole-H), 4.50 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.47 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.82 (C=O), 161.13 (C=N), 156.41 (isoxazole-CO), 150.78 (2C), 135.45, 120.92 (2C), 107.11 (isoxazole-CH), 62.61 (OCH_2), 14.14 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}N_2O_3^+$: 219.0770; found: 219.0774.

Ethyl 3-(Thiophen-3-yl)isoxazole-5-carboxylate (13d)

Yield: 288 mg (82%); off-white solid; mp 56–58 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (s, 1 H, thiophene-H), 7.56 (d, *J* = 4.8 Hz, 1 H, thiophene-H), 7.47 (d, *J* = 2.7 Hz, 1 H, thiophene-H), 7.17 (s, 1 H, isoxazole-H), 4.47 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.45 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.67 (C=O), 158.79 (C=N), 156.76 (isoxazole-CO), 129.27, 127.22, 125.85, 125.42, 107.64 (isoxazole-CH), 62.35 (OCH_2), 14.16 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}NO_3S^+$: 224.0376; found: 224.0380.

Ethyl 3-Isopropylisoxazole-5-carboxylate (13e)

Yield: 341 mg (81%); pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 1 H, isoxazole-H), 4.42 (q, *J* = 7.2 Hz, 2 H, OCH_2), 3.16–3.11 (m, 1 H, $(CH_3)_2CH$), 1.40 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.31 (d, *J* = 7.2 Hz, 6 H, $(CH_3)_2CH$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.13 (C=O), 160.08 (C=N), 156.97 (isoxazole-CO), 107.56 (isoxazole-CH), 62.08 (OCH_2), 26.48 (CH), 21.62 (2C, $(CH_3)_2CH$), 14.10 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{14}NO_3^+$: 184.0974; found: 184.0979.

3-(4-Nitrophenyl)-5-phenylisoxazole (15a)[43]

Yield: 261 mg (81%); white solid; mp 221–223 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.41 (d, *J* = 8.8 Hz, 2 H, Ar-H), 8.21 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.94 (d, *J* = 2.0 Hz, 2 H, Ar-H), 7.80 (s, 1 H, isoxazole-H), 7.62–7.56 (m, 3 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.49 (isoxazole-CO), 161.10 (C=N), 148.34 (Ar-C-NO_2), 134.65, 130.63, 129.23 (2C), 127.80 (2C), 126.54, 125.58 (2C), 124.26 (2C), 98.94 (isoxazole-CH).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}N_2O_3^+$: 267.0770; found: 267.0772.

5-(4-Fluorophenyl)-3-(4-nitrophenyl)isoxazole (15b)[23]

Yield: 281 mg (82%); white solid; mp 207–209 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.38 (d, *J* = 8.8 Hz, 2 H, Ar-H), 8.15 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.97 (dd, *J* = 5.6 Hz, 2 H, Ar-H), 7.74 (s, 1 H, isoxazole-H), 7.43 (t, *J* = 8.8 Hz, 2 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.79 (isoxazole-CO), 162.64 (Ar-C-F), 161.41 (C=N), 148.59 (Ar-C-NO_2), 134.69, 128.34 (2C), 128.03 (2C), 124.61 (2C), 123.43, 116.86, 116.64, 99.18 (isoxazole-CH).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{10}FN_2O_3^+$: 285.0675; found: 285.0687.

5-(4-Methoxyphenyl)-3-(4-nitrophenyl)isoxazole (15c)[23]

Yield: 286 mg (80%); white solid; mp 173–175 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.40 (d, *J* = 8.8 Hz, 2 H, Ar-H), 8.18 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.87 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.64 (s, 1 H, isoxazole-H), 7.14 (d, *J* = 8.8 Hz, 2 H, Ar-H), 3.84 (s, 3 H, OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_2O_4^+$: 297.0875; found: 297.0884.

5-(*tert*-Butyl)-3-(4-nitrophenyl)isoxazole (15d)[44]

Yield: 262 mg (88%); white solid; mp 155–157 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.35 (d, *J* = 8.8 Hz, 2 H, Ar-H), 8.14 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.02 (s, 1 H, isoxazole-H), 1.36 (s, 9 H, $(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.95 (C=N), 160.30 (isoxazole-CO), 148.53 (Ar-C-NO_2), 135.67, 127.56 (2C), 124.14 (2C), 96.65 (isoxazole-CH), 32.97 ($(CH_3)_3C$), 28.83 (3C, $(CH_3)_3$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_3^+$: 247.1083; found: 247.1087.

5-Cyclohexyl-3-(4-nitrophenyl)isoxazole (15e)

Yield: 286 mg (87%); white solid; mp125–127 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.34 (d, *J* = 8.8 Hz, 2 H, Ar-H), 8.13 (d, *J* = 8.8 Hz, 2 H, Ar-H), 6.99 (s, 1 H, isoxazole-H), 2.92–2.87 (m, 1 H, cyclohexyl), 2.04–2.01 (m, 2 H, cyclohexyl), 1.78–1.74 (m, 2 H, cyclohexyl), 1.69–1.66 (m, 1 H, cyclohexyl), 1.52–1.34 (m, 4 H, cyclohexyl), 1.30–1.21 (m, 1 H, cyclohexyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.54 (C=N), 160.33 (isoxazole-CO), 148.52 (Ar-C-NO_2), 135.68, 127.56 (2C), 124.14 (2C), 97.28 (isoxazole-CH), 36.42, 31.15 (2C), 25.74, 25.63 (2C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_3^+$: 273.1239; found: 273.1241.

[3-(4-Nitrophenyl)isoxazol-5-yl]methanol (15f)[45]

Yield: 226 mg (85%); pale-yellow solid; mp 118–120 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.35 (d, *J* = 8.8 Hz, 2 H, Ar-H), 8.16 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.11 (s, 1 H, isoxazole-H), 5.78 (t, *J* = 6.0 Hz, 1 H, OH), 4.65 (d, *J* = 6.0 Hz, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.51 (C=N), 160.10 (isoxazole-CO), 148.15 (Ar-C-NO_2), 134.80, 127.70 (2C), 124.03 (2C), 100.12 (isoxazole-CH), 54.90 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9N_2O_4^+$: 221.0562; found: 221.0566.

1-[3-(4-Nitrophenyl)isoxazol-5-yl]ethanone (15g)[46]

Yield: 253 mg (90%); white solid; mp 158–160 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.40 (d, *J* = 8.8 Hz, 2 H, Ar-H), 8.24 (d, *J* = 8.8 Hz, 2 H, Ar-H), 8.12 (s, 1 H, isoxazole-H), 2.63 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 185.97 (C=O), 166.80 (C=N), 161.20 (isoxazole-CO), 148.50 (Ar-C-NO_2), 133.70, 127.91 (2C), 124.11 (2C), 107.12 (isoxazole-CH), 27.26 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9N_2O_4^+$: 233.0562; found: 233.0566.

(*S*)-2-(3-{4-[3-(4-Methoxyphenyl)ureido]phenyl}isoxazole-5-carboxamido)-3-methylbutanoic Acid (1)[24]

To a solution of (*S*)-methyl-2-[3-(4-aminophenyl)isoxazole-5-carboxamido]-3-methylbutanoate (4 g, 12.62 mmol, 1.0 equiv) in THF (20 mL) was added 4-methoxyphenylisocyanate (1.98 g, 13.25 mmol, 1.1 equiv) and the reaction mixture was stirred at r.t. for 5 h. The precipitated solid was filtered and dried to obtain the ester compound (5.3 g) as a white solid. To a solution of the ester (5.3 g, 11.37 mmol, 1. 0 equiv) in THF (25 mL) was added 1 M LiOH solution (5.68 mL, 56.86 mmol, 5.0 equiv) and the mixture was stirred at r.t. for 12 h. The solvent was evaporated under reduced pressure to obtain a residue, which was diluted with water and acidified with concd HCl to pH 2. The precipitated solid was filtered and dried to afford the desired compound **1**.

Yield: 4.63 g (81%); off-white solid; mp 220–222 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.61 (br. s, 1 H, OH), 9.00 (s, 1 H, NH), 8.91 (d, J = 8.1 Hz, 1 H,CONH), 8.68 (s, 1 H, NH), 7.81 (d, J = 8.7 Hz, 2 H, Ar-H), 7.67 (s, 1 H, isoxazole-H), 7.60 (d, J = 8.7 Hz, 2 H, Ar-H), 7.36 (d, J = 8.7 Hz, 2 H, Ar-H), 6.85 (d, J = 8.7 Hz, 2 H, Ar-H), 4.28–4.23 (t, J = 7.2 Hz, 1 H, NHCH), 3.70 (s, 3 H, OCH_3), 2.23–2.16 (m, 1 H, $CH(CH_3)_2$), 0.95 (dd, J = 4.2 Hz, 6 H, $(CH_3)_2$).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.95 (C=O), 163.90 (C=N), 162.74 (NHC=O), 156.65 (isoxazole-CO), 155.18 (Ar-C-OCH_3), 153.13 (NHCONH), 142.82, 133.08, 128.03 (2C), 121.28, 120.75 (2C), 118.70 (2C), 114.58 (2C), 105.19 (isoxazole-CH), 58.67 (CHNH), 55.75 (OCH_3), 30.05 ($CH(CH_3)_2$), 19.78 (CH_3), 19.21 (CH_3).

HRMS (ESI+): m/z calcd for $C_{23}H_{25}N_4O_6^+$: 453.1774; found 453.1778.

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Supporting Information

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