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SnX_2 Promoted Cyclization of β-Nitro-β,γ-unsaturated Ketones Into 3-(2-Haloalkyl)-5-aryl Isoxazoles

Muhammad Ehtisham Ibraheem Khan,[a] Lu Wang,[a, b] Benedetta Bassetti,[a] Marino Petrini,*[a] and Alessandro Palmieri*[a]

Herein we report an easy and fruitful methods to synthesize 3-(2-haloalkyl)-5-aryl isoxazoles starting from β-nitro-β,γ-unsaturated ketones. The reaction was promoted by the presence of tin (II) chloride or bromide and products were obtained in good yields and in short reaction time. Moreover, we extended our methodology to flow chemical conditions, and we also tested the usefulness of halogenated isoxazoles to obtain amino and ether derivatives.

1. Introduction

The isoxazole moiety can be largely found in many compounds widely known for their enhanced biological profile. The pharmacophoric attributes of the isoxazole ring has favoured its presence in many drugs of totally synthetic origin but has also spurred the development of natural products-isoxazole hybrids (Figure 1).[1]

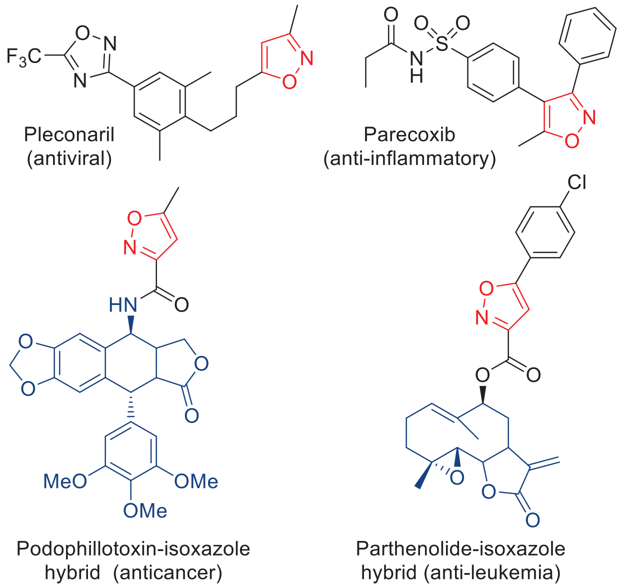
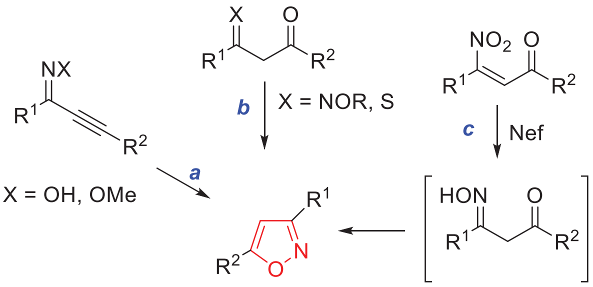


Figure 1. Isoxazole-based drugs.

Over the years, an increasing number of synthetic protocols have been developed to access differently substituted isoxazoles.[2] In many of these processes, the regiochemical control of the obtained isoxazole is not easy achievable being affected by stereo electronic factors as in the 1,3-dipolar cycloaddition of nitrile oxides with substituted alkynes.[3] Even more complicated is the preparation of Regio defined isoxazoles starting from unsymmetrical 1,3-dicarbonyl compounds or 1,3-dinitroalkanes.[4] In this context, a truly Regio defined synthesis of these heterocyclic derivatives is only possible starting from precursors embedding the nitrogen atom in a fixed position thus enabling the formation of a single product in the cyclization step (Scheme 1).

The metal-catalysed cyclization of alkynyloxime derivatives (route a) provides an efficient entry to functionalized isoxazoles via the classical activation of the triple bond.[5] The utilization of *O*-substituted monoxime of 1,3-diketones can be converted into isoxazoles exploiting a simple condensation reaction (route b)[6] but a related process carried out on 3-thioxoketones occurs through the oxidative insertion of an azido group.[7] Finally, the oxime moiety can be readily installed in a suitable framework starting from β-nitroenones by a reductive Nef reaction using tin(II) chloride (route c).[8] The generated oxime intermediate undergoes a domino cyclization process leading to the expected isoxazole compound. Developing the synthetic significance of β-nitroenones, we recently introduced a procedure for the Regio



Scheme 1. Synthetic approaches to Regio defined isoxazoles.

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[a] M. E. I. Khan, L. Wang, Dr. B. Bassetti, Prof. Dr. M. Petrini, Prof. Dr. A. Palmieri
Green Chemistry Group, School of Sciences and Technology, Chemistry Division, University of Camerino, ChIP Research Center, Via Madonna delle Carceri, snc, Camerino (MC) 62032, Italy
E-mail: marino.petrini@unicam.it
alessandro.palmieri@unicam.it

[b] L. Wang
School of Chemistry and Chemical Engineering, Liaocheng University, Liaocheng 252059, China

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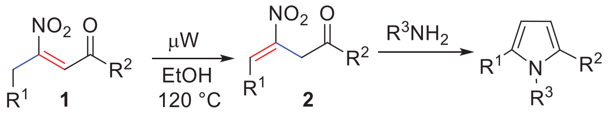
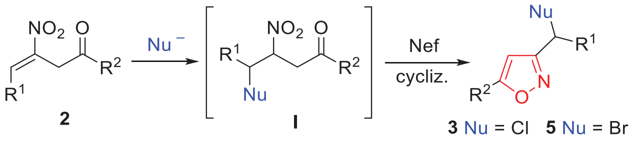


Scheme 2. Regio isomerization of β-nitroenones.



Scheme 3. Synthetic approaches to side arm functionalized isoxazoles.

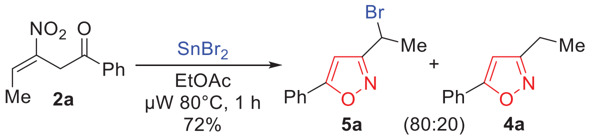
isomerization of β-nitroenones **1** to the parent β-nitro-β,γ-unsaturated ketones **2** (Scheme 2).[9] This transformation can be achieved by direct microwave irradiation of β-nitroenones and the resulting ketones **2** have been applied for the preparation of trisubstituted pyrrole derivatives.

The presence of an isolated nitroalkenyl moiety in compounds **2** opens up new scenarios for the preparation of azole derivatives. Thus, we sought for a synthetic protocol enabling the direct preparation of side arm functionalized isoxazoles exploiting the general strategy depicted in Scheme 3. The conjugate addition of nucleophilic species to nitroalkenes **2** would give an intermediate **I** which in the same conditions undergoes a Nef reaction followed by a cyclization to the isoxazole ring **3** or **5**.

Following our previous findings on the preparation of 3,5-disubstituted isoxazoles using β-nitroenones as substrates (Scheme 1, route c), we decided to preliminarily test the introduction of a halogen atom at the "benzylic" position of the isoxazole unit using SnX_2 as halide source and reductant for the subsequent Nef process. The interest in 3-(2-haloalkyl) isoxazole derivatives stems from their potential utilization in the preparation of new natural products-isoxazole hybrids exploiting the electrophilic character of the carbon-halogen bond particularly useful in coupling processes.[1a] In this context, it should be observed that 3-(2-haloalkyl) isoxazoles are mainly obtained by halogenation of the corresponding primary alcohols[10] or halogen bearing open chain precursors,[11] but a direct assembling of these heterocycles from nonhalogenated compounds is practically unprecedented. In this paper, we present a straightforward preparation of functionalized 3-(2-haloalkyl)-5-aryl isoxazoles from β-nitro-β,γ-unsaturated ketones using tin(II) halides as single reagents under microwave activation.

2. Results and Discussion

To explore the feasibility of our idea, preliminary experiments involving the reaction of **2a** with tin(II) chloride dihydrate were carried out and the obtained results summarized in Table 1. Inspired by our previous work,[8] we initially screened the reaction using ethyl acetate as the solvent and in the presence of different amounts of $SnCl_2{\cdot}2H_2O$ at room temperature (entries *a*–*c*). The reaction completed after 8 h both in the presence of 2 and 3 equiv. of $SnCl_2{\cdot}2H_2O$. On the other hand, 1.5 equiv. of $SnCl_2{\cdot}2H_2O$ were insufficient for the complete conversion of **2a** into **3a** and **4a**, which were isolated in 55% of total yield after 8 h and no further progress was observed by allowing the reaction to stir for a longer time. Successively, we screened the reaction using 2 equiv. of $SnCl_2{\cdot}2H_2O$ in different solvents (entries *d*–*f*). Dichloromethane (DCM) led to a less efficient reaction, while toluene or 2-methyltetrahydrofuran (2-MeTHF) proved completely ineffective. Finally, different reaction temperatures were examined (entries *g*–*j*). At 50 °C the conversion completed in 2.5 h with just a slight better yield (65% versus 62%), vice versa under reflux conditions the reaction accomplished in 1 h and **3a** and **4a** were isolated in 72% of total yield and in an 80:20 ratio. Under microwaves condition at 80 °C we observed an improvement in the yield to 78%. It is important to note that although the reaction temperature of entries *h* and *i* are comparable (77 °C versus 80 °C), the higher yield of the latter is presumably due to the more efficient energy transfer occurring under microwave irradiation.[12] A further increase of the temperature to 100 °C produced a degradation of the reaction with a lowering of both the yield to 68% and **3a**:**4a** ratio to 75:25.



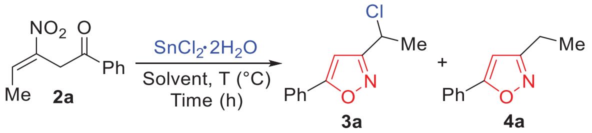
Scheme 4. Synthesis of the brominated isoxazole **5a**.

Then, aiming to access to the analogues brominated isoxazole derivatives, the optimized reaction conditions (entry *j*) were tested replacing $SnCl_2{\cdot}2H_2O$ with $SnBr_2$.To our delight, the conversion of **2a** into **5a** and **4a** occurred with a similar efficiency since **5a** and **4a** were obtained in 72% of total yield and in an 80:20 ratio (Scheme 4).

Next, to confirm the efficiency of our methodology a variety of nitroalkenes **2** were converted into the corresponding isoxazole derivatives. It is important to highlight that halogenated/non-halogenated products were easily separated by flash column chromatography except for the isoxazole derivative **5c** which resulted inseparable from **4c**. It is also worth to note that the introduction of an aromatic system in R^1 (**2k**; R^1 = *p*-Tol, R^2 = Ph) involves a reversal of the reaction trend. In fact, the non-halogenated isoxazole was isolated as the main or single reaction product using $SnCl_2{\cdot}2H_2O$ or $SnBr_2$ respectively. The observed result is probably due to the reduced electrophilic character of the double bond caused by its extensive conjugation with the aromatic system. In all examples displayed in Table 2, the resulting isoxazoles were isolated from satisfactory to good overall yields independently from the presence of aryl, heteroaryl and alkyl ketone moieties.

A plausible rationalization concerning the formation of halogenated/non-halogenated isoxazoles would involve two simultaneous and competitive reaction mechanisms. In partic-

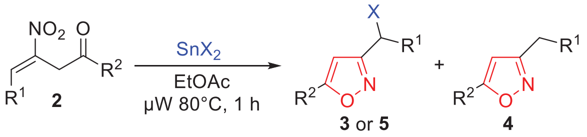
Table 1. Optimization studies.



Entry	Solvent	Temp. (°C)	Time (h)	Total Yield (%)[e] of 3a and 4a (ratio)
a[a]	EtOAc	r.t.	8	62 (75:25)
b[b]	EtOAc	r.t.	8	55 (70:30) + **2a**
c[c]	EtOAc	r.t.	8	63 (76:24)
d[a]	DCM	r.t.	8	22 (65:35) + **2a**
e[a]	2-MeTHF	r.t.	8	**2a**
f[a]	Toluene	r.t.	8	**2a**
g[a]	EtOAc	50 °C	2.5	65 (79:21)
h[a]	EtOAc	Reflux	1	72 (80:20)
i[a),d)]	EtOAc	80 °C	1	78 (80:20)
j[a),d)]	EtOAc	100 °C	0.5	68 (75:25)

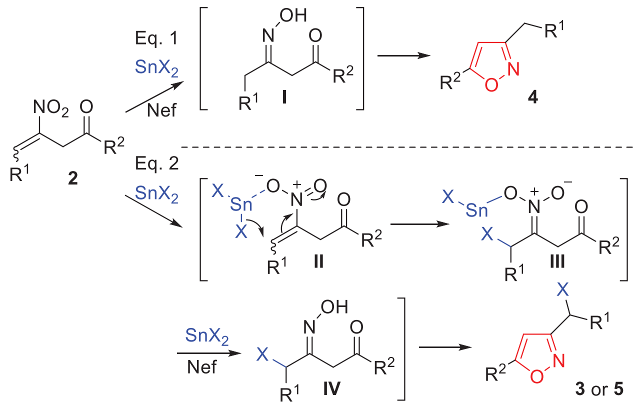
[a] Reaction performed in the presence of 2 eq. of $SnCl_2·H_2O$. [b] Reaction performed in the presence of 1.5 eq. of $SnCl_2·H_2O$. [c] Reaction performed in the presence of 2.5 eq. of $SnCl_2·H_2O$. [d] Reaction performed under Microwave conditions. [e] Yield of pure isolated products (**3a** and **4a** were separated by flash column chromatography).

Table 2. Substrate scope investigation.



R1	R^2	X	Overall Yield (%)[a]		Ratio[b]
Me	Ph	Cl	**3a** + **4a**	78	(80:20)
Me	Ph	Br	**5a** + **4a**	72	(80:20)
Me	2-Thiophene	Cl	**3b** + **4b**	81	(78:22)
Me	2-Thiophene	Br	**5b** + **4b**	61	(82:18)
Me	2-Furane	Cl	**3c** + **4c**	68	(79:21)
Me	2-Furane	Br	**5c** + **4c**	57	(80:20)
Me	2-(*N*-Methylpyrrole)	Cl	**3d** + **4d**	58	(70:30)
Me	2-(*N*-Methylpyrrole)	Br	**5d** + **4d**	45	(80:20)
n-Bu	*t*-Bu	Cl	**3e** + **4e**	76	(80:20)
n-Bu	*t*-Bu	Br	**5e** + **4e**	53	(100:0)
n-Bu	4-MeOC_6H_4	Cl	**3f** + **4f**	82	(78:22)
n-Bu	4-MeOC_6H_4	Br	**5f** + **4f**	55	(80:20)
$Ph(CH_2)_2$	Ph	Cl	**3g** + **4g**	85	(75:25)
$Ph(CH_2)_2$	Ph	Br	**5g** + **4g**	64	(75:25)
Et	4-BrC_6H_4	Cl	**3h** + **4h**	82	(78:22)
Et	4-BrC_6H_4	Br	**5h** + **4h**	70	(78:22)
$CH_3(CH_2)_5$	4-MeC_6H_4	Cl	**3i** + **4i**	86	(70:30)
$CH_3(CH_2)_5$	4-MeC_6H_4	Br	**5i** + **4i**	63	(70:30)
$CH_3(CH_2)_7$	2-Naphthyl	Cl	**3j** + **4j**	82	(68:32)
$CH_3(CH_2)_7$	2-Naphthyl	Br	**5j** + **4j**	65	(79:21)
p-Tol	Ph	Cl	**3k + 4k**	40	(4:96)
p-Tol	Ph	Br	**5k + 4k**	41	(0:100)

[a] Total yield and ratio of halogenated/non-halogenated products. [b] Ratio of halogenated/non-halogenated products.



Scheme 5. Probable reaction mechanism.

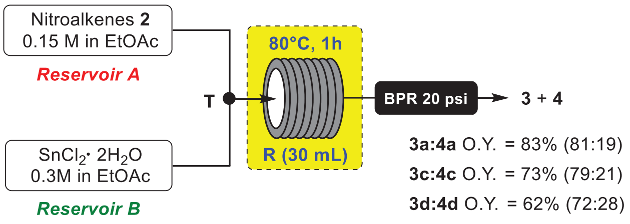
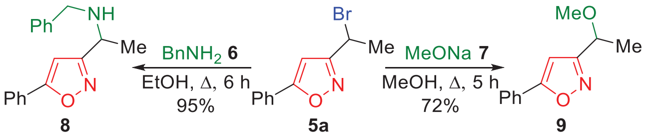


Figure 2. Flow chemical approach.

ular, nitroalkene **2** can undergo the preliminary reductive Nef reaction affording the oxime **I** which cyclizes into the target **4** (Scheme 5, Equation 1), similarly on what previously observed with β-nitroenones **1**.[8,13] Alternatively, **2** plausibly coordinates tin dihalide to give adduct **II**, which transfer a halide atom to the carbon-chain backbone giving **III**, that by the classical reductive Nef reaction leads the oxime **IV** and subsequently the target isoxazole **3** or **5** (Scheme 5, Equation 2).

Later on, in order to test the automation of the process, we extended the batch optimized reaction conditions to the flow chemical approach. However, due to the poor solubility of the $SnBr_2$ in EtOAc the study was limited to the chlorinated derivatives. To this scope, we studied the conversion of **2a**, **2c**, and **2d** into the respective products, by means of the FlowLab system of Uniqsis.[14] The apparatus consists of two HPLC pumps working at 15 mL/h each, two reservoirs respectively filled with ethyl acetate solutions of **2** (0.15 M, reservoir A) and $SnCl_2 \cdot 2H_2O$ (0.3 M, reservoir B), a T-connector **T**, a heated reactor station equipped with a 30 mL PTFE coil reactor **R** set at 80 °C, and a back pressure regulator (BPR) set at 20 psi (Figure 2). The target products were isolated in slightly higher yields, probably due to the superior mass and energy transfer efficiency of the flow approach compared to the batch one. On the contrary no substantial change in the halogenated/nonhalogenated ratio was observed.

Finally, according to previous literature,[15] we tested the applicability of this class of products by reacting **5a** with benzylamine **6** and sodium methoxide **7**. Pleasingly, both reactions afforded the corresponding substituted products in 95% and 72% of yield respectively (Scheme 6).



Scheme 6. Exploration studies on the reactivity of isoxazole **5a**.

3. Conclusion

In conclusion, we developed a new efficient synthesis of brominated and chlorinated isoxazoles starting from easily accessible starting materials such β-nitro-β,γ-unsaturated ketones. The protocol permits to synthesize the title targets in good yields and in short reaction time (1 h), even in the presence of sensible organic structure such as furan, pyrrole and thiophene. Moreover, the use of a green solvent such ethyl acetate reduces the environmental impact of our protocol.[16] Finally, we have demonstrated both that our methodology can be extended to flow chemical conditions for an easy process automation, and the utility of halogenated isoxazoles to obtain amino and ether derivatives.

Supporting Information

General Remarks: ^{1}H NMR analyses were recorded at 400 MHz on a Varian Mercury Plus 400. ^{13}C NMR analyses were recorded at 100 MHz. IR spectra were recorded with a Perkin Elmer FTIR spectrometer Spectrum Two UATR. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. GS-MS analyses were obtained on a Hewlett-Packard GC/MS 6890 N that works with the EI technique (70 eV). Microwave irradiations were performed by means of a Biotage Initiator. Flow chemical reactions were performed by means of FlowLab system of Uniqsis. Compounds **2** were prepared by following reported procedures.[17]

General procedure for synthesizing compounds 3 and 5. A solution of the nitroalkene **2** (1 mmol) and the proper tin(II) halide (2 mmol) in ethyl acetate (13 mL) was irradiated, by means of a Biotage Initiator microwave oven, at 80 °C for 1 h. Then, the solution was transferred into a separatory funnel, treated with a 0.5 N aqueous solution of HCl (30 mL), extracted by fresh EtOAc (3×30 mL), and the collected organic phase was dried using anhydrous Na_2SO_4. Finally, the sodium sulphate was removed by filtration and the solvent evaporated under reduced pressure. Then, reaction crude was purified by flash column chromatography (Hexane:EtOAc = 95:5) furnishing the pure product **3** (or **5**).

Flow general procedure. The appropriate nitroalkene **2a**, **2c**, or **2d** (1.5 mmol) was taken up in EtOAc (10 mL) and filled into Reservoir A, and tin(II) chloride dihydrate (3 mmol) was taken up in EtOAc (10 mL) and filled into Reservoir B. The two solutions were simultaneously pumped with a flow rate of 15 mL/h for each pump into a T-connector before passing through a 30 mL PTFE coil reactor heated at 80 °C (residence time 1 h), and the outflow was dropped into a flask containing 30 mL of a stirring

0.5 N aqueous solution of HCl. The two layers were separated, the aqueous one was extracted with fresh EtOAc (3×30 mL), and the collected organic phase was dried using anhydrous Na_2SO_4. Finally, after the filtration of Na_2SO_4 and the evaporation of the solvent under reduced pressure, the reaction crude was purified by flash column chromatography (Hexane:EtOAc = 95:5) furnishing the pure product **3a**, **3c** or **3d**.

Spectroscopic data of compound 3a-k.

3-(1-Chloroethyl)-5-phenylisoxazole 3a. Pale yellow oil. IR (neat): 3132, 3065, 1616, 1592, 1574, 1451, 1059, 947, 762, 688, 673 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.81–7.76 (m, 2H), 7.51–7.43 (m, 3H), 6.63 (s, 1H), 5.20 (q, 1H, J = 6.9 Hz), 1.91 (d, 3H, J = 6.9 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 170.7, 166.1, 130.5, 129.1, 127.2, 126.0, 98.0, 49.0, 24.5. GC-MS (70 eV): *m/z* (%) 209 ([M + 2^{+}], 26), 207 ([M^{+}], 83), 172 (72), 105 (100), 77 (66), 63 (51), 51 (29). Anal. Calcd for $C_{11}H_{10}ClNO$ (207.66): C, 63.62; H, 4.85; N, 6.75. Found: C, 63.66; H, 4.82; N, 6.77.

3-(1-Chloroethyl)-5-(thiophen-2-yl)isoxazole 3b. Pale yellow oil. IR (neat): 3111, 3062, 1599, 1470, 1446, 1229, 849, 791, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51 (dd, 1H, J = 3.7, 1.2 Hz), 7.45 (dd, 1H, J = 5.0, 1.2 Hz), 7.12 (dd, 1H, J = 5.0, 3.7 Hz), 6.49 (s, 1H), 5.17 (q, 1H, J = 6.9 Hz), 1.89 (d, 3H, J = 6.9 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 166.1, 165.7, 129.0, 128.4, 128.2, 127.4, 97.7, 48.8, 24.5. GC-MS (70 eV): *m/z* (%) 215 ([M + 2^{+}], 34), 213 ([M^{+}], 100), 178 (58), 111 (98), 63 (60), 39 (54). Anal. Calcd for C_9H_8ClNOS (213.68): C, 50.59; H, 3.77; N, 6.56; S, 15.00. Found: C, 50.62; H, 3.80; N, 6.54; S, 14.97.

3-(1-Chloroethyl)-5-(furan-2-yl)isoxazole 3c. Pale yellow oil. IR (neat): 3136, 1645, 1625, 1542, 1445, 1012, 888, 743, 721, 591 cm^{--1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.54 (dd, 1H, J = 1.7, 0.6 Hz), 6.90 (dd, 1H, J = 3.5, 0.6 Hz), 6.55 (s, 1H), 6.53 (dd, 1H, J = 3.5 Hz, 1.7 Hz), 5.17 (q, 1H, J = 6.9 Hz), 1.89 (d, 3H, J = 6.9 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 165.8, 162.3, 144.4, 143.1, 112.1, 110.9, 97.6, 48.7, 24.5. GC-MS (70 eV): *m/z* (%) 199 ([M + 2^{+}], 197 ([M^{+}], 100), 162 (34), 135 (14), 95 (76), 63 (50), 39 (29). Anal. Calcd for $C_9H_8ClNO_2$ (197.62): C, 54.70; H, 4.08; N, 7.09. Found: C, 54.67; H, 4.06; N, 7.07.

3-(1-Chloroethyl)-5-(1-methyl-1H-pyrrol-2-yl)isoxazole 3d. Pale yellow oil. IR (neat): 3127, 1608, 1462, 1445, 1057, 721, 603 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.77–6.73 (m, 1H), 6.67 (dd, 1H, J = 3.9, 1.7 Hz), 6.34 (s, 1H), 6.19 (dd, 1H, J = 3.9, 2.6 Hz), 5.17 (q, 1H, J = 6.9 Hz), 3.87 (s, 3H), 1.90 (d, 3H, J = 6.9 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 165.6, 164.7, 127.0, 121.2, 112.8, 108.9, 96.8, 48.9, 36.5, 24.5. GC-MS (70 eV): *m/z* (%) 212 ([M + 2^{+}], 33), 210 ([M^{+}], 100), 120 (40), 108 (78), 53 (17). Anal. Calcd for $C_{10}H_{11}ClN_2O$ (210.66): C, 57.02; H, 5.26; N, 13.30. Found: C, 57.06; H, 5.24; N, 13.28.

5-(*tert*-Butyl)-3-(1-chloropentyl)isoxazole 3e. Pale yellow oil. IR (neat): 3134, 1589, 1488, 1462, 1429, 1276, 981, 798, 761, 736 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.00 (s, 1H), 4.94 (t, 1H, J = 7.3 Hz), 2.05 (q, 2H, J = 7.3 Hz), 1.56–1.30 (m, 4H), 1.34 (s, 9H), 0.91 (t, 3H, J = 7.0 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 182.1, 164.6, 96.7, 54.0, 37.7, 33.0, 29.0, 28.7, 22.1, 14.0. GC-MS (70 eV): *m/z* (%) 229 ([M^{+}], 12), 186 (30), 173 (100), 166 (85), 152 (51), 56 (47), 41 (51). Anal. Calcd for $C_{12}H_{20}ClNO$ (229.75): C, 62.73; H, 8.77; N, 6.10. Found: C, 62.70; H, 8.75; N, 6.12.

3-(1-Chloropentyl)-5-(4-methoxyphenyl)isoxazole 3f. Pale yellow solid; m.p. = 40–42 °C. IR (neat): 3130, 1611, 1511, 1456, 1436, 1252, 1176, 1023, 840, 792, 758, 733, 522 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71 (d, 2H, J = 9.0 Hz), 6.97 (d, 2H, J = 9.0 Hz), 6.48 (s, 1H), 5.01 (t, 1H, J = 7.3 Hz), 3.85 (s, 3H), 2.17–2.07 (m, 2H), 1.60–1.29 (m, 4H), 0.91 (t, 3H, J = 7.1 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 170.6, 165.5, 161.4, 127.6, 120.1, 114.5, 96.5, 55.5, 53.7, 37.8, 28.7, 22.1, 14.0. GC-MS (70 eV): *m/z* (%) 281 ([M + 2^{+}], 8), 279 ([M^{+}], 25), 244 (83), 223 (66), 217 (45), 161 (25), 135 (100), 77 (31). Anal. Calcd for $C_{15}H_{18}ClNO_2$ (279.76): C, 64.40; H, 6.49; N, 5.01. Found: C, 64.37; H, 6.51; N, 4.98.

3-(1-Chloro-3-phenylpropyl)-5-phenylisoxazole 3 g. Yellow solid; m.p. = 53–55 °C. IR (neat): 3129, 3054, 1612, 1574, 1468, 1451, 764, 698, 687, 510 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.81–7.75 (m, 2H), 7.51–7.43 (m, 3H), 7.35–7.28 (m, 2H), 7.26–7.19 (m, 3H), 6.63 (s, 1H), 5.02 (t, 1H, J = 7.3 Hz), 2.97–2.77 (m, 2H), 2.47 (q, 2H, J = 7.4 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 170.8, 165.3, 140.1, 130.6, 129.1, 128.7, 128.6, 127.2, 126.5, 126.0, 98.1, 52.8, 39.4, 32.6. GC-MS (70 eV): *m/z* (%) 297 ([M^{+}], 17), 193 (100), 131 (18), 105 (34), 81 (41), 77 (31). Anal. Calcd for $C_{18}H_{16}ClNO$ (297.78): C, 72.60; H, 5.42; N, 4.70. Found: C, 72.63; H, 5.39; N, 4.68.

5-(4-Bromophenyl)-3-(1-chloropropyl)isoxazole 3 h. Pale yellow solid; m.p. = 47–49 °C. IR (neat): 3131, 1605, 1491, 1458, 1433, 1067, 1006, 845, 837, 789, 763, 706, 502 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65–7.54 (m, 4H), 6.60 (s, 1H), 4.96 (t, 1H, J = 7.1 Hz), 2.20–2.10 (m, 2H), 1.08 (t, 3H, J = 7.3 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 169.5, 165.5, 132.4, 127.4, 126.1, 124.9, 98.4, 55.0, 31.4, 11.1. GC-MS (70 eV): *m/z* (%) 302 ([M + 2^{+}], 7, 300 ([M^{+}], 20), 273 (100), 271 (74), 185 (31), 183 (31), 155 (23), 157 (25), 76 (21), 75 (21), 41 (38). Anal. Calcd for $C_{12}H_{11}BrClNO$ (300.58): C, 47.95; H, 3.69; N, 4.66. Found: C, 47.98; H, 3.71; N, 4.64.

3-(1-Chloroheptyl)-5-(*p*-tolyl)isoxazole 3i. Pale yellow solid; m.p. = 30–32 °C. IR (neat): 3131, 1618, 1513, 1462, 1439, 948, 826, 812, 797, 766, 621, 502 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67 (d, 2H, J = 7.9 Hz), 7.26 (d, 2H, J = 7.9 Hz), 6.55 (s, 1H), 5.02 (t, 1H, J = 7.3 Hz), 2.40 (s, 3H),), 2.15–2.07 (m, 2H), 1.61–1.21 (m, 8H), 0.88 (t, 3H, J = 6.8 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 170.8, 165.5, 140.8, 129.8, 125.9, 124.6, 97.3, 53.7, 38.1, 31.7, 28.7, 26.5, 22.7, 21.6, 14.2. GC-MS (70 eV): *m/z* (%) 291 ([M^{+}], 15), 256 (46), 200 (45), 206 (81), 186 (60), 119 (100), 91 (60), 41 (28). Anal. Calcd for $C_{17}H_{22}ClNO$ (291.82): C, 69.97; H, 7.60; N, 4.80. Found: C, 70.01; H, 7.62; N, 4.82.

3-(1-Chlorononyl)-5-(naphthalen-2-yl)isoxazole 3j. Pale yellow solid; m.p. = 53–55 °C. IR (neat): 3132, 1606, 1589, 1467, 1439, 937, 889, 863, 833, 794, 753, 727, 614, 469 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.30 (s, 1H), 7.95–7.77 (m, 4H), 7.59–7.49 (m, 2H), 6.73 (s, 1H), 5.07 (t, 1H, J = 7.3 Hz), 2.16 (q, 2H, J = 7.3 Hz), 1.65–1.16 (m, 12H), 0.88 (t, 3H, J = 6.7 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 170.7, 165.7, 134.1, 133.1, 129.0, 128.8, 128.0, 127.5, 127.1, 125.8, 124.5, 122.9, 98.3, 53.7, 38.1, 31.9, 29.4, 29.3, 29.0, 26.6, 22.8, 14.2. GC-MS (70 eV): *m/z* (%) 357 ([M + 2^{+}], 13), 355 ([M^{+}], 38), 320 (50), 292 (51), 256 (52), 243 (93), 222 (71), 181 (30), 155 (100), 127 (97), 27 (41). Anal. Calcd for $C_{22}H_{26}ClNO$ (355.91): C, 74.24; H, 7.36; N, 3.94. Found: C, 74.21; H, 7.39; N, 3.96.

3-(Chloro(p-tolyl)methyl)-5-phenylisoxazole 3k. Pale yelow solid; m.p. = 112–114 °C. IR (neat): 3130, 1612, 1574, 1551, 1466, 1450, 1381, 764, 743, 688, 509 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.78–7.73 (m, 2H), 7.47–7.38 (m, 5H), 7.22–7.17 (m, 2H), 6.61 (s, 1H), 6.17 (s, 1H), 2.36 (s, 3H). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 170.8, 165.3, 139.1, 135.5, 130.6, 129.7, 129.1, 127.5, 126.0, 98.7, 54.8, 21.3. GC-MS (70 eV):

m/z (%) 285 ([M + 2$^+$], 7), 283 ([M$^+$], 20), 248 (100), 220 (46), 205 (40), 204 (35), 105 (68), 77 (69), 51 (18). Anal. Calcd for $C_{17}H_{14}ClNO$ (283.76): C, 71.96; H, 4.97; N, 4.94. Found: C, 71.99; H, 4.95; N, 4.97.

Spectroscopic data of compound 4a-k.

3-Ethyl-5-phenylisoxazole 4a. Yellow waxy solid. IR (neat): 1616, 1575, 1451, 1421, 947, 762, 688 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.78–7.73 (m, 2H), 7.49–7.38 (m, 3H), 6.39 (s, 1H), 2.74 (q, 2H, J = 7.6 Hz), 1.32 (t, 3H, J = 7.6 Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 169.7, 165.9, 130.1, 129.0, 127.8, 125.9, 99.0, 19.8, 12.9. GC-MS (70 eV): m/z (%) 173 ([M+], 98), 131 (13), 105 (100), 77 (56), 68 (19), 51 (18). Anal. Calcd for $C_{11}H_{11}NO$ (173.21): C, 76.28; H, 6.40; N, 8.09. Found: C, 76.31; H, 6.38; N, 8.11.

3-Ethyl-5-(thiophen-2-yl)isoxazole 4b. Yellow oil. IR (neat): 3110, 1601, 1459, 1422, 1024, 849, 798, 701 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.48 (dd, 1H, J = 3.7, 1.2 Hz), 7.42 (dd, 1H, J = 5.1, 1.2 Hz), 7.10 (dd, 1H, J = 5.1, 3.7 Hz), 6.25 (s, 1H), 2.72 (q, 2H, J = 7.6 Hz), 1.31 (t, 3H, J = 7.6 Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 165.9, 164.7, 129.7, 128.1, 127.8, 126.8, 98.8, 19.7, 12.8. GC-MS (70 eV): m/z (%) 179 ([M$^+$], 100), 151 (20), 111 (99), 68 (27), 39 (39). Anal. Calcd for C_9H_9NOS (179.24): C, 60.31; H, 5.06; N, 7.81; S, 17.89. Found: C, 60.34; H, 5.08; N, 7.84; S, 17.92.

3-Ethyl-5-(furan-2-yl)isoxazole 4c. Yellow oil. IR (neat): 3134, 1645, 1544, 1444, 1012, 889, 899, 742, 591 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.51 (dd, 1H, J = 1.8, 0.7 Hz), 6.86 (dd, 1H, J = 3.5, 0.7 Hz), 6.52 (dd, 1H, J = 3.5 Hz, 1.8 Hz), 6.31 (s, 1H), 2.73 (q, 2H, J = 7.6 Hz), 1.30 (t, 3H, J = 7.6 Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 165.6, 161.4, 144.0, 143.7, 112.0, 110.2, 98.6, 19.7, 12.8. GC-MS (70 eV): m/z (%) 163 ([M$^+$], 98), 135 (18), 108 (20), 95 (100), 68 (27), 39 (24). Anal. Calcd for $C_9H_9NO_2$ (163.18): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.28; H, 5.54; N, 8.60.

3-Ethyl-5-(1-methyl-1H-pyrrol-2-yl)isoxazole 4d. Yellow oil. IR (neat): 2125, 1610, 1488, 1460, 1421, 1306, 1057, 722 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 6.74–6.72 (m, 1H), 6.62 (dd, 1H, J = 3.8, 1.8 Hz), 6.18 (dd, 1H, J = 3.8, 2.6 Hz), 6.10 (s, 1H), 3.86 (s, 3H), 2.72 (q, 2H, J = 7.6 Hz),1.31 (t, 3H, J = 7.6 Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 165.4, 163.8, 126.5, 121.8, 112.1, 108.7, 98.2, 53.5, 36.5, 19.7. GC-MS (70 eV): m/z (%) 176 ([M$^+$], 100), 133 (29), 108 (74), 106 (34), 93 (18), 53 (19), 39 (17). Anal. Calcd for $C_{10}H_{12}N_2O$ (176.22): C, 68.16; H, 6.86; N, 15.90. Found: C, 68.20; H, 6.88; N, 15.89.

5-(*tert*-Butyl)-3-pentylisoxazole 4e. Pale yellow oil. IR (neat): 1595, 1492, 1461, 1422, 1366, 1278, 982, 794 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 5.76 (s, 1H), 2.62–2.56 (m, 2H), 1.70–1.56 (m, 2H), 1.39–1.23 (m, 4H), 1.32 (s, 9H), 0.90 (t, 3H, J = 7.0 Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 180.9, 164.0, 97.9, 32.8, 31.6, 29.0, 28.2, 26.3, 22.5, 14.1. GC-MS (70 eV): m/z (%) 195 ([M$^+$], 5), 166 (20), 152 (84), 139 (100), 82 (29), 57 (26), 40 (32). Anal. Calcd for $C_{12}H_{21}NO$ (195.31): C, 73.80; H, 10.84; N, 7.17. Found: C, 73.77; H, 10.82; N, 7.18.

5-(4-Methoxyphenyl)-3-pentylisoxazole 4f. Pale yellow solid; m.p. = 37–39 °C. IR (neat): 3133, 1312, 1512, 1465, 1428, 1249, 1177, 1025, 835, 797, 526 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.69 (d, 2H, J = 9.0 Hz), 6.96 (d, 2H, J = 9.0 Hz), 6.24 (s, 1H), 3.85 (s, 3H), 2.72–2.62 (m, 2H), 1.78–1.63 (m, 2H), 1.45–1.30 (m, 4H), 0.90 (t, 3H, J = 6.7 Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 169.6, 164.9, 161.1, 127.5, 120.7, 114.5, 97.9, 55.5, 31.5, 28.2, 26.2, 22.5, 14.1. GC-MS (70 eV): m/z (%) 245 ([M$^+$], 29), 202 (32), 189 (100), 161 (12), 135 (42), 77 (11). Anal. Calcd for $C_{15}H_{19}NO_2$ (245.32): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.48; H, 7.83; N, 5.73.

5-Phenyl-3-(3-phenylpropyl)isoxazole 4 g. Yellow oil. IR (neat): 3062, 1574, 1497, 1451, 1420, 762, 689, 494 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.76 (dd, 2H, J = 8.1, 1.6 Hz), 7.49–7.40 (m, 3H), 7.33–7.18 (m, 5H), 6.37 (s, 1H), 2.77–2.70 (m, 4H), 2.11–2.01 (m, 2H). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 169.8, 164.4, 141.7, 130.1, 129.1, 128.7, 128.6, 127.8, 126.1, 125.9, 99.2, 35.4, 30.1, 25.8. GC-MS (70 eV): m/z (%) 263 ([M$^+$], 33), 262 (75), 159 (100), 131 (43), 105 (46), 91 (67), 77 (55), 65 (21). Anal. Calcd for $C_{18}H_{17}NO$ (263.34): C, 82.10; H, 6.51; N, 5.32. Found: C, 82.13; H, 6.49; N, 5.30.

5-(4-Bromophenyl)-3-propylisoxazole 4 h. Pale yellow solid; m.p. = 46–48 °C. IR (neat): 3113, 1608, 1492, 1461, 1421, 1397, 1071, 1010, 945, 829, 822, 799, 493 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.64–7.55 (m, 4H), 6.37 (s, 1H), 2.71–2.65 (m, 2H), 1.79–1.68 (m, 2H), 1.01 (t, 3H, J = 7.4 Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 168.6, 164.8, 132.3, 127.3, 126.7, 124.4, 99.7, 28.2, 21.8, 13.9. GC-MS (70 eV): m/z (%) 269 ([M + 2]$^+$, 18), 267 ([M$^+$], 17), 239 (97), 237 (100), 185 (29), 183 (33), 157 (13), 155 (13), 76 (15), 41 (18). Anal. Calcd for $C_{12}H_{12}BrNO$ (266.14): C, 54.16; H, 4.55; N, 5.26. Found: C, 54.19; H, 4.52; N, 5.28.

3-Heptyl-5-(*p*-tolyl)isoxazole 4i. Pale yellow waxy solid. IR (neat): 3141, 1616, 1602, 1516, 1455, 1468, 1431, 1420, 947, 825, 788, 728, 501 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.65 (d, 2H, J = 8.2 Hz), 7.25 (d, 2H, J = 8.2 Hz), 6.31 (s, 1H), 2.71–2.66 (m, 2H), 2.39 (s, 3H), 1.76–1.60 (m, 2H), 1.46–1.20 (m, 8H), 0.88 (t, 3H, J = 7.0 Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 169.8, 164.8, 140.3, 129.7, 125.8, 125.2, 98.7, 31.9, 29.3, 29.1, 28.5, 26.3, 22.8, 21.6, 14.2. GC-MS (70 eV): m/z (%) 257 ([M$^+$], 16), 214 (17), 186 (53), 173 (100), 119 (31), 91 (19), 41 (11). Anal. Calcd for $C_{17}H_{23}NO$ (257.38): C, 79.33; H, 9.01; N, 5.44. Found: C, 79.30; H, 8.99; N, 5.42.

5-(Naphthalen-2-yl)-3-nonylisoxazole 4j. Pale yellow solid; m.p. = 59–61 °C. IR (neat): 3129, 1589, 1466, 1438, 1420, 863, 790, 748, 726, 471 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 8.29 (s, 1H), 7.97–7.76 (m, 4H), 7.60–7.47 (m, 2H), 6.49 (s, 1H), 2.78–2.69 (m, 2H), 1.79–1.68 (m, 2H), 1.49–1.17 (m, 12H), 0.88 (t, 3H, J = 6.8 Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 169.7, 165.0, 134.0, 133.3, 128.9, 128.8, 128.0, 127.3, 127.0, 125.6, 125.1, 123.1, 99.7, 30.0, 29.6, 29.5, 29.4, 29.3, 28.6, 26.3, 22.8, 14.3. GC-MS (70 eV): m/z (%) 321 ([M$^+$], 17), 236 (18), 222 (53), 209 (100), 181 (13), 155 (30), 127 (33), 41 (14). Anal. Calcd for $C_{22}H_{27}NO$ (321.46): C, 82.20; H, 8.47; N, 4.36. Found: C, 82.23; H, 8.45; N, 4.38.

3-(4-Methylbenzyl)-5-phenylisoxazole 4k. White solid; m.p. = 60–62 °C. IR (neat): 3125, 1611, 1592, 1573, 1450, 765, 758, 688, 481 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.74–7.69 (m, 2H), 7.46–7.39 (m, 3H), 7.22–7.11 (m, 4H), 6.27 (s, 1H), 4.02 (s, 2H), 2.34 (s, 3H). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 170.0, 164.0, 136.6, 134.4, 130.1, 129.6, 129.0, 128.9, 127.7, 125.9, 99.6, 32.3, 21.2. GC-MS (70 eV): m/z (%) 250 ([M + 1$^+$], 43), 249 ([M$^+$], 99), 144 (36), 106 (45), 105 (100), 79 (37), 77 (99), 51 (39). Anal. Calcd for $C_{17}H_{15}NO$ (249.31): C, 81.90; H, 6.06; N, 5.62. Found: C, 81.94; H, 6.03; N, 5.64.

Spectroscopic data of compound 5a-j.

3-(1-Bromoethyl)-5-phenylisoxazole 5a. Pale yellow solid; m.p. = 43–45 °C. IR (neat): 3131, 1612, 1591, 1574, 1461, 1063, 927, 770, 692, 677. cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.81–7.73 (m, 2H), 7.51–7.39 (m, 3H), 6.63 (s, 1H), 5.23 (q, 1H, J = 7.0 Hz), 2.08 (d, 3H, J = 7.0 Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): δ = 170.7, 166.4, 130.5, 129.1, 127.2, 125.9, 98.4, 37.3, 25.1. GC-MS (70 eV): m/z (%) 253 ([M + 2$^+$], 24), 251 ([M$^+$], 25), 172 (100), 105 (42), 77 (54), 51 (22). Anal.

Calcd for $C_{11}H_{10}BrNO$ (252.11): C, 52.41; H, 4.00; N, 5.56. Found: C, 52.44; H, 3.98; N, 5.58.

3-(1-Bromoethyl)-5-(thiophen-2-yl)isoxazole 5b. Yellow oil. IR (neat): 3101, 1602, 1445, 1425, 849, 790, 704, 688 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.52$ (dd, 1H, $J = 3.7$, 1.1 Hz), 7.46 (dd, 1H, $J = 5.0$, 1.1 Hz), 7.12 (dd, 1H, $J = 5.0$, 3.7 Hz), 6.49 (s, 1H), 5.20 (q, 1H, $J = 7.0$ Hz), 2.07 (d, 3H, $J = 6.9$ Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): $\delta = 166.4$, 165.7, 129.0, 128.4, 128.2, 127.4, 98.2, 37.0, 25.1. GC-MS (70 eV): *m/z* (%) 259 ([M + 2$^+$], 66), 257 ([M$^+$], 67), 178 (100), 111 (99), 39 (30). Anal. Calcd for C_9H_8BrNOS (258.13): C, 41.88; H, 3.12; N, 5.43; S, 12.42. Found: C, 41.91; H, 3.10; N, 5.44; S, 12.40.

3-(1-Bromoethyl)-5-(furan-2-yl)isoxazole 5c obtained as inseparable mixture 80:20 with 3-Ethyl-5-(furan-2-yl)isoxazole 4c. Yellow oil. IR (neat): 3134, 1647, 1627, 1542, 1445, 1192, 1012, 888, 794, 742, 680, 590 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.54$ (dd, 1H, $J = 1.7$, 0.6 Hz)-***5c***, 7.51 (dd, 1H, $J = 1.8$, 0.7 Hz)-***4c***, 6.90 (dd, 1H, $J = 3.5$, 0.6 Hz)-***5c***, 6.86 (dd, 1H, $J = 3.5$, 0.7 Hz)-***4c***, 6.55 (s, 1H)-***5c***, 6.53 (dd, 1H, $J = 3.5$ Hz, 1.8 Hz)-***5c***, 6.52 (dd, 1H, $J = 3.5$ Hz, 1.8 Hz)-***4c***, 6.31 (s, 1H)-***4c***, 5.20 (q, 1H, $J = 6.9$ Hz)-***5c***, 2.73 (q, 2H, $J = 7.6$ Hz)-***4c***, 2.05 (d, 3H, $J = 7.0$ Hz)-***5c***, 1.30 (t, 3H, $J = 7.6$ Hz)-***4c***. ^{13}C{H} NMR (CDCl$_3$, 100 MHz): $\delta = 166.0$–***5c***, 165.6–***4c***, 162.1–***5c***, 161.4–***4c***, 144.3–***5c***, 144.0–***4c***, 143.8–***5c***, 143.7–***4c***, 112.0–***4c***,111.9–***5c***, 110.2–***4c***,110.0–***5c***, 98.6–***4c***, 97.9–***5c***, 36.7–***5c***, 24.9–***5c***, 19.7–***4c***, 12.8–***4c***. GC-MS (70 eV)-***5c***: *m/z* (%) 243 ([M + 2$^+$], 59), 241 ([M$^+$], 61), 162 (100), 95 (99), 81 (27), 67 (18), 39 (33). GC-MS (70 eV)-***4c***: *m/z* (%) 163 ([M$^+$], 98), 135 (18), 108 (20), 95 (100), 68 (27), 39 (24).

3-(1-Bromoethyl)-5-(1-methyl-1H-pyrrol-2-yl)isoxazole 5d. Pale yellow solid; m.p. = 45–47 °C. IR (neat): 3126, 1607, 1487, 1461, 1444, 1309, 1056, 723, 603 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 6.76$–6.73 (m, 1H), 6.67 (dd, 1H, $J = 3.9$, 1.7 Hz), 6.33 (s, 1H), 6.19 (dd, 1H, $J = 3.9$, 2.6 Hz), 5.20 (q, 1H, $J = 6.9$ Hz), 3.87 (s, 3H), 2.07 (d, 3H, $J = 7.0$ Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): $\delta = 165.9$, 164.7, 127.0, 121.2, 112.8, 109.0, 97.3, 37.2, 36.6, 25.1. GC-MS (70 eV): *m/z* (%) 256 ([M + 2$^+$], 97), 254 ([M$^+$], 100), 175 (18), 120 (26), 108 (81), 39 (29). Anal. Calcd for $C_{10}H_{11}BrN_2O$ (255.11): C, 47.08; H, 4.35; N, 10.98. Found: C, 47.05; H, 4.33; N, 11.00.

3-(1-Bromopentyl)-5-(*tert*-butyl)isoxazole 5e. Yellow oil. IR (neat): 3131, 1589, 1487, 1462, 1429, 1366, 1276, 980, 915, 796, 753, 733 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 6.01$ (s, 1H), 4.98 (dd, 1H, $J = 8.2$, 6.7 Hz), 2.24–2.05 (m, 2H), 1.56–1.23 (m, 4H), 1.34 (s, 9H), 0.90 (t, 3H, $J = 7.1$ Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): $\delta = 182.0$, 164.9, 97.2, 43.7, 38.0, 33.0, 30.0, 28.9, 22.0, 14.0. GC-MS (70 eV): *m/z* (%) 275 ([M + 2$^+$], 12), 273 ([M$^+$], 12), 219 (79), 217 (81), 194 (90), 166 (98), 152 (100), 136 (26), 108 (28), 87 (84), 41 (66). Anal. Calcd for $C_{12}H_{20}BrNO$ (274.20): C, 52.56; H, 7.35; N, 5.11. Found: C, 52.59; H, 7.33; N, 5.09.

3-(1-Bromopentyl)-5-(4-methoxyphenyl)isoxazole 5f. Yellow solid; m.p. = 38–40 °C. IR (neat): 3129, 1608, 1509, 1455, 1434, 1253, 1175, 1022, 840, 790, 726, 604, 521 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.71$ (d, 2H, $J = 9.0$ Hz), 6.97 (d, 2H, $J = 9.0$ Hz), 6.48 (s, 1H), 5.04 (t, 1H, $J = 7.4$ Hz), 3.85 (s, 3H), 2.33–2.10 (m, 2H), 1.59–1.32 (m, 4H), 0.91 (t, 3H, $J = 7.1$ Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): $\delta = 170.6$, 165.8, 161.4, 127.6, 120.1, 114.5, 97.0, 55.5, 43.3, 38.2, 30.0, 22.0, 14.0. GC-MS (70 eV): *m/z* (%) 325 ([M + 2$^+$], 12), 323 ([M$^+$], 12), 269 (26), 267 (27), 244 (100), 202 (35), 160 (17), 135 (93), 77 (26). Anal. Calcd for $C_{15}H_{18}BrNO_2$ (324.22): C, 55.57; H, 5.60; N, 4.32. Found: C, 55.60; H, 5.62; N, 4.30.

3-(1-Bromo-3-phenylpropyl)-5-phenylisoxazole 5 g. Pale yellow solid; m.p. = 77–79 °C. IR (neat): 3126, 3054, 1612, 1574, 1451, 973, 910, 767, 757, 697, 676, 505, 500 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.81$–7.76 (m, 2H), 7.51–7.44 (m, 3H), 7.34–7.27 (m, 2H), 7.25–7.19 (m, 3H), 6.61 (s, 1H), 5.03 (dd, 1H, $J = 8.3$, 6.4 Hz), 2.96–2.87 (m, 1H), 2.85–2.74 (m, 1H), 2.63–2.46 (m, 2H). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): $\delta = 170.8$, 165.5, 140.0, 130.6, 129.2, 128.8, 128.7, 127.2, 126.5, 126.0, 98.5, 42.3, 39.7, 33.8. GC-MS (70 eV): *m/z* (%) 343 ([M + 2$^+$], 14), 341 ([M$^+$], 13), 262 (53), 239 (97), 237 (100), 172 (29), 130 (30), 105 (74), 91 (80), 77 (53), 65 (20). Anal. Calcd for $C_{18}H_{16}BrNO$ (342.24): C, 63.17; H, 4.71; N, 4.09. Found: C, 63.20; H, 4.69; N, 4.07.

5-(4-Bromophenyl)-3-(1-bromopropyl)isoxazole 5 h. Yellow solid; m.p. = 59–61 °C. IR (neat): 3126, 3058, 1603, 1456, 1431, 1396, 1067, 1006, 945, 838, 924, 789, 674, 662, 497 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.68$–7.56 (m, 4H), 6.61 (s, 1H), 4.99 (t, 1H, $J = 7.3$ Hz), 2.31–2.16 (m, 2H), 1.09 (t, 3H, $J = 7.3$ Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): $\delta = 169.5$, 165.7, 132.4, 127.4, 126.2, 124.9, 98.9, 44.7, 31.8, 12.6. GC-MS (70 eV): *m/z* (%) 347 ([M + 4]$^+$, 16), 345 ([M + 2$^+$], 32), 343 ([M$^+$], 16), 319 (49), 317 (100), 315 (51), 266 (71), 264 (76), 185 (62), 183 (61), 157 (51), 155 (41), 76 (30), 41 (51). Anal. Calcd for $C_{12}H_{11}Br_2NO$ (345.03): C, 41.77; H, 3.21; N, 4.06. Found: C, 41.80; H, 3.19; N, 4.04.

3-(1-Bromoheptyl)-5-(*p*-tolyl)isoxazole 5i. Pale yellow solid; 28–30 °C. IR (neat): 3131, 1617, 1598, 1462, 1433, 947, 821, 792, 727, 503 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.67$ (d, 2H, $J = 8.3$ Hz), 7.26 (d, 2H, $J = 8.3$ Hz), 6.55 (s, 1H), 5.06 (t, 1H, $J = 7.5$ Hz), 2.40 (s, 3H), 2.29–2.10 (m, 2H), 1.60–1.20 (m, 8H), 0.88 (t, 3H, $J = 6.5$ Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): $\delta = 170.8$, 165.7, 140.8, 129.8, 125.9, 124.6, 97.7, 43.3, 38.4, 31.7, 28.6, 27.8, 22.7, 21.6, 14.2. GC-MS (70 eV): *m/z* (%) 337 ([M + 2$^+$], 10), 335 ([M$^+$], 11), 295 (18), 293 (18), 256 (96), 251 (36), 249 (37), 214 (27), 186 (68), 119 (100), 91 (49), 41 (18). Anal. Calcd for $C_{17}H_{22}BrNO$ (336.27): C, 60.72; H, 6.59; N, 4.17. Found: C, 60.75; H, 6.62; N, 4.19.

3-(1-Bromononyl)-5-(naphthalen-2-yl)isoxazole 5j. Pale yellow solid; m.p. = 50–52 °C. IR (neat): 3122, 1610, 1586, 1564, 1469, 1445, 907, 823, 800, 794, 754, 561, 482 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 8.31$ (s, 1H), 7.96–7.79 (m, 4H), 7.60–7.51 (m, 2H), 6.73 (s, 1H), 5.10 (t, 1H, $J = 7.5$ Hz), 2.33–2.13 (m, 2H), 1.66–1.20 (m, 12H), 0.88 (t, 3H, $J = 6.7$ Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): $\delta = 170.7$, 165.9, 134.1, 133.2, 129.0, 128.8, 128.0, 127.6, 127.1, 125.8, 124.5, 123.0, 98.7, 43.2, 38.5, 31.9, 29.4, 29.3, 28.9, 27.9, 22.8, 14.2. GC-MS (70 eV): *m/z* (%) 401 ([M + 2$^+$], 18), 399 ([M$^+$], 17), 320 (100), 289 (33), 287 (34), 222 (66), 180 (18), 155 (92), 127 (88), 41 (20). Anal. Calcd for $C_{22}H_{26}BrNO$ (400.36): C, 66.00; H, 6.55; N, 3.50. Found: C, 66.03; H, 6.57; N, 3.51.

***N*-benzyl-1-(5-phenylisoxazol-3-yl)ethan-1-amine 8**. Clear oil. IR (neat): 3307, 3129, 1615, 1573, 1452, 758, 742, 699, 684, 606 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.82$–7.75 (m, 2H), 7.51–7.40 (m, 3H), 7.37–7.20 (m, 5H), 6.57 (s, 1H), 4.11 (q, 1H, $J = 6.7$ Hz), 3.82–3.71 (m, 2H), 2.02 (bs, 1H), 1.49 (d, 3H, $J = 6.7$ Hz). ^{13}C{H} NMR (CDCl$_3$, 100 MHz): $\delta = 170.1$, 168.1, 139.8, 130.2, 129.1, 128.6, 128.4, 127.7, 127.2, 125.9, 97.3, 51.6, 49.7, 21.8. GC-MS (70 eV): *m/z* (%) 173 (54), 132 (17), 106 (56), 91 (100), 77 (21), 65 (15). Anal. Calcd for $C_{18}H_{18}N_2O$ (278.36): C, 77.67; H, 6.52; N, 10.06. Found: C, 77.69; H, 6.50; N, 10.05.

3-(1-Methoxyethyl)-5-phenylisoxazole 9. Clear oil. IR (neat): 3127, 3065, 1615, 1592, 1574, 1467, 1451, 1118, 1097, 1061, 976, 763, 689, 520 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.81$–7.75 (m, 2H), 7.48–7.40 (m, 3H), 6.54 (s, 1H), 4.56 (q, 1H, $J = 6.6$ Hz), 3.32 (s, 3H), 1.53

(d, 3H, $J = 6.6$ Hz). $^{13}C\{H\}$ NMR ($CDCl_3$, 100 MHz): $\delta = 170.3$, 166.6, 130.3, 129.1, 127.6, 125.9, 96.9, 71.7, 56.9, 21.2. GC-MS (70 eV): m/z (%) 203 ([M^+], 4), 173 (65), 131 (6), 105 (19), 77 (24), 59 (100), 51 (13), 29 (12). Anal. Calcd for $C_{12}H_{13}NO_2$ (203.24): C, 70.92; H, 6.45; N, 6.89. Found: C, 70.89; H, 6.43; N, 6.91.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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[1] a) J. Wang, D.-B. Wan, L.-L. Sui, T. Luan, *Arabian J. Chem.* **2024**, *17*, 105794; b) Y. Shinde, B. Khairnar, S. Bangale, *ChemistrySelect* **2024**, *9*, e202401423; c) G. C. Arya, K. Kaur, V. Jaitak, *Eur. J. Med. Chem.* **2021**, *221*, 113511; d) G. N. Pairas, F. Perperopoulou, P. G. Tsoungas, G. Varvounis, *ChemMedChem* **2017**, *12*, 408.

[2] a) F. De Sarlo, F. Machetti, *Org. Biomol. Chem.* **2023**, *21*, 7255; b) C. P. Pandhurnekar, H. C. Pandhurnekar, A. J. Mungole, S. S. Butoliya, B. G. Yadao, *J. Heterocyclic Chem.* **2023**, *60*, 537; c) S. Das, K. Chanda, *RSC Adv.* **2021**, *11*, 32680; d) T. Morita, S. Yugandar, S. Fuse, H. Nakamura, *Tetrahedron Lett.* **2018**, *59*, 1159.

[3] T. V. Hansen, P. Wu, V. V. Fokin, *J. Org. Chem.* **2005**, *70*, 7761.

[4] a) D. Long, Y. Qin, Q. Wu, X. Zou, Z. Zhou, *J. Struct. Chem.* **2019**, *60*, 1339; b) R. Ballini, F. Bigi, E. Gogni, R. Maggi, G. Sartori, *J. Catal.* **2000**, *191*, 348; c) W. M. Best, E. L. Ghisalberti, M. Powell, *J. Chem. Res., Synop.* **1998**, *7*, 388.

[5] a) M. M. Evarts, Z. H. Strong, M. J. Krische, *Org. Lett.* **2023**, *25*, 5907; b) M. Duan, G. Hou, Y. Zhao, C. Zhu, C. Song, *J. Org. Chem.* **2022**, *87*, 11222; c) C. Li, J. Li, F. Zhou, C. Li, W. Wu, *J. Org. Chem.* **2019**, *84*, 11958; d) X. Liu, D. Hong, Z. She, W. H. Hersh, B. Yoo, Y. Chen, *Tetrahedron* **2018**, *74*, 6593.

[6] a) K. Akagawa, K. Kudo, *J. Org. Chem.* **2018**, *83*, 4279; b) Y. Ning, Y. Otani, T. Ohwada, *J. Org. Chem.* **2018**, *83*, 203.

[7] P. Mary Antony, G. L. Balaji, P. Iniyavan, H. Ila, *J. Org. Chem.* **2020**, *85*, 15422.

[8] M. E. I. Khan, T. L. Cassini, M. Petrini, A. Palmieri, *Org. Biomol. Chem.* **2024**, *22*, 3299.

[9] E. Chiurchiù, S. Xhafa, R. Ballini, G. Maestri, S. Protti, A. Palmieri, *Adv. Synth. Catal.* **2020**, *362*, 4680.

[10] a) A. Iraji, N. Sheikhi, M. Attarroshan, G. R. S. Ardani, M. Kabiri, A. N. Bafghi, F. Kobarfard, Z. Rezaei, M. Khoshneviszadeh, A. Foroumadi, S. S. Mirfazli, *Bioorg. Chem.* **2022**, *129*, 106140; b) K. İbiş, E. Nalbat, B. Çalışkan, D. C. Kahraman, R. Cetin-Atalay, E. Banoglu, *Eur. J. Med. Chem.* **2021**, *221*, 113489.

[11] M. A. P. Martins, A. P. Sinhorin, A. da Rosa, A. F. C. Flores, A. D. Wastowski, C. M. P. Pereira, D. C. Flores, R. A. F. P. Beck, S. Brondani, W. Cunico, H. G. Bonacorso, N. Zanatta, *Synthesis* **2002**, 2353.

[12] C. O. Kappe, A. Stadler, D. Dallinger, in *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, 2nd ed., **2012**, Vol. *52*.

[13] For a recent review on the Nef reaction see: R. Ballini, M. Petrini, *Adv. Synth. Catal.* **2015**, *357*, 237.

[14] https://www.uniqsis.com/paProductsDetail.aspx?ID=FlowLab.

[15] a) H. J. Kim, J. H. Lee, *Heterocycles* **1994**, *38*, 1383; b) H. JinKim, Y. JuLee, *Synth. Commun.* **1998**, *28*, 3527; c) V. I. Potkina, N. A. Bumaginb, A. V. Kletskova, S. K. Petkevicha, P. V. Kurmanc, *Russ. J. Org. Chem.* **2016**, *52*, 1661.

[16] D. Prat, J. Hayler, A. Wells, *Green Chem.* **2014**, *16*, 4546.

[17] B. Bassetti, R. Ballini, M. Petrini, A. Palmieri, *Adv. Synth. Catal.* **2023**, *365*, 13.

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