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ARTICLE TYPE

Synthesis of Substituted Oxazoles from Enamides

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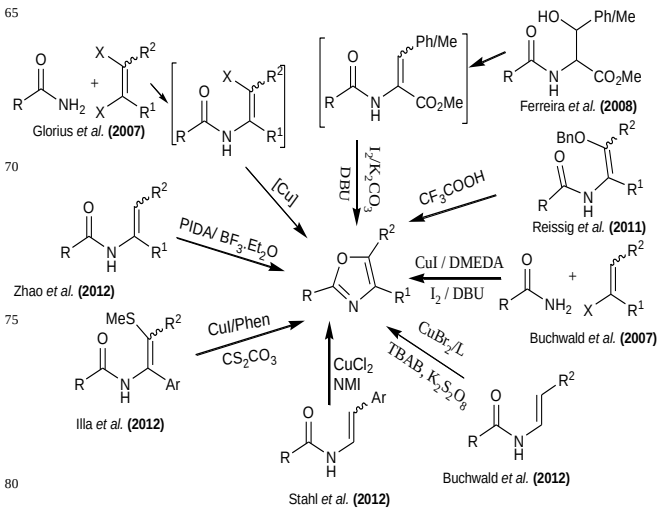
Annulation of enamides into 2,5- and 2,4,5-substituted oxazoles by NBS/Me_2S in the presence of mild base has been achieved. The reaction conditions are simple and tolerant to wide varieties of substituents including both electron-donating and withdrawing groups to produce oxazoles in one-pot without further purification of the intermediate.

Introduction

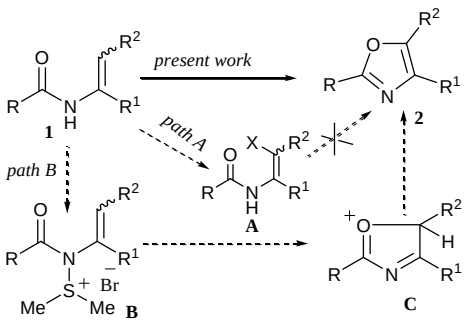
Oxazoles are important precursors in many organic transformations and exist as key structural motifs in many natural products.[1] They also exhibit diverse range of pharmacological properties such as antifungal, antiviral, antibacterial, antileukemia, cytotoxic activities, enzyme inhibitory activities and peripheral analgesic activities.[2] Different substitutions to this heterocycle, propound a new avenue for drug development and other applications in material science.[2,3] Therefore, impressive synthetic efforts have been made to achieve widely substituted oxazoles. The synthetic routes to oxazoles can be broadly classified as: (i) intramolecular oxidative cyclization of acyclic precursors to oxazoles, and (ii) transition metal catalyzed functionalization of oxazole ring to the desired derivatives. Although the cyclodehydration of 2-acylamino-ketones, esters, or amides in the presence of Lewis or Brønsted acid (known as Robinson-Gabriel condensation),[4] is a classical approach to construct various oxazole skeletons, the method suffers from drawbacks such as harsh reaction conditions, use of strong Brønsted acid and moderate functional group tolerance.[5] As a response to these challenges, several modifications have been continuously documented in recent literature. Cyclization of enamides has been emerged as potential method to enable varieties of oxazoles.[6] Indeed, enamides with vinylic functionalization undergo base- or acid-mediated cyclization to the corresponding oxazoles (Scheme 1). In this regard, several reports have been disclosed. For instance, Buchwald and his co-workers described the sequential copper-catalysed amidation of vinyl halides, followed by iodine-promoted cyclization to achieve tri- substituted oxazoles.[6d] Glorius and his co-workers have developed a copper-catalysed preparation of 2,5-disubstituted oxazoles from the reaction of primary amides with 1,2-dihaloalkenes, which expected to involve β-haloenamides intermediate.[6e] Reissig and his co-workers investigated acid catalysed annulations of β-alkoxy-β-ketoenamides in to substituted oxazoles.[6f] Ferreira and his co-workers used a multistep process to synthesize 2,4,5-substituted oxazoles from amino acid derivatives.[6g,h] In a recent report, Wendlandt and Stahl reported the $CuCl_2$/NMI (2 equiv. each)-mediated intramolecular cyclization of enamides (without vinylic C-H functionalization) at 140°C.[6i] Later, Cheung and Buchwald demonstrated a $CuBr_2$/ethyl nicotinate-catalyzed oxidative cyclization of enamides to synthetically difficult 2,5-substituted oxazoles via vinylic C-H bond functionalization.[5] Du and Zhao prepared substituted oxazoles from phenyliodine diacetate (PIDA)-mediated intramolecular cyclization of enamides in the presence of $BF_3.Et_2O$.[6j] It may be mentioned here that although this method is suitable to achieve a series of 2,4,5-trisubstituted oxazoles, but its scope was less extended to produce 2,5-disubstitituted oxazoles.[6j] Illa and her co-workers used thio-substituted enamides for cyclization to the corresponding oxazoles in the presence of copper iodide and 1,10-phenanthroline.[6k] Very recently, Bathula and his co-worker described the NBS-mediated synthesis of substituted oxazoles from *N*-acylated amino acid derivatives through iterative bromination and debromination process.[6l]



Scheme 1. Reported synthesis of 2,5 and 2,4, 5-substituted oxazoles by cyclization of enamides/preformed enamides.

In view to these useful methods it may be envisaged that the depicted transformations are mostly substrate specific (leading to either 2,5-or 2,4,5-substitituted oxazoles) and/or associated with intricacy in generation of selective staring materials (i.e. β-halo or β-mercapto or β-benzyloxy enamides) to produce either 2,5 or 2,4,5-substituted oxazoles. Moreover, employment of a single method to produce both 2,5 or 2,4,5-substituted oxazoles is less literature precedent. Consequently, the increasing demand of functionalized oxazoles indeed garners interest for an efficient and practical method for their preparation.

In continuation of our work on enamide synthesis,[7] we here in disclose a metal-free, practical approach to generate 2, 5- and 2, 4, 5-substituted oxazoles from easily accessible enamides in one-pot under mild reaction conditions. Our strategy involves the use of NBS-Me_2S (Corey-Kim reagent)-mediated intramolecular cyclization of substituted enamides in the presence of mild base to produce desired oxazoles (Scheme 2).



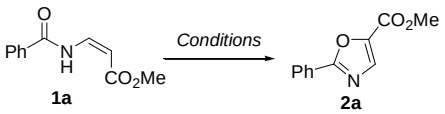
Scheme 2. Present approach to oxazoles from enamide.

Results and Discussion

In the past years, we have developed the Pd-catalyzed amidation of electron deficient alkenes[7a] and alkynes[7b] to generate *Z*-enamides. Possible intramolecular hydrogen bonding between the amido N-H proton and carbonyl oxygen in the intermediate might be responsible for *Z*-selectivity of the reaction. Since synthetically difficult 2,5 oxazoles are the key structural motifs in many natural products as well as pharmaceuticals,[5] direct synthesis of substituted oxazoles from our enamides sparked to be important. Moreover, intramolecular cyclization of such electron deficient enamides to required oxazoles is less literature precedent; which stimulates us to develop a suitable protocol to access such oxazoles. We started our investigation with the intramolecular cyclization of enamide (**1a**) to the corresponding oxazole (Table 1) following the analogous procedure reported by Ferreira and his co-worker.[6g, h] Thus, when **1a** was treated with I_2/K_2CO_3/DBU in THF at 80°C (Table 1, entry 1), surprisingly oxazole **2a** was not produced rather enamide **1a** isomerised to thermodynamically more stable *E*-enamide (e.g. **3**) exclusively. Reaction of **1a** in the presence of 3 equiv. of NBS in DCE at 100 °C[6l] did not result the oxazole (**2a**); rather β-bromoenamide was produced (Table 1, entry 3). Furthermore, following the similar reaction conditions reported by Yoshimura,[6a] when **1a** was heated with NBS and triethyl amine in benzene under reflux condition, no reaction takes place, albeit *cis-trans* isomerised enamide was isolated (Table 1, entry 4). An attempt to acid catalysed annulations of enamide **1a** to **2a** by employing the similar procedure reported by Reissig[6f] was found to be unsuccessful.

This failure persuaded us to modify the reaction conditions to prepare 2,5-substituted oxazoles. After several experimentations, we observed that the solvent plays a vital role in the cyclization process. For instance, when, enamide **1a** was treated with I_2 in the presence of base in non-polar solvent such as toluene, only β-iodoenamide was obtained (Table 1, entry 2). This may be due to the poor insolubility of the base in toluene. However, when a mixture of solvents such as toluene and DMF (3:1) was taken to improve the solubility of the base and reagents 2,5-disubstituted oxazole was achieved in 33% yield (Table 1, entry 5). Replacing the oxidant I_2 to *N*-bromo succinimide (NBS) results in negligible yield of **2a** (Table 1, entry 9). However, addition of dimethyl sulphide along with NBS (Corey-Kim reagent) to the reaction mixture in the presence of mild base such as K_2CO_3 at 70°C improves the yield of oxazole **2a** substantially (79%) (Table 1, entry 10). Further screening of bases such as ^{t}BuOK, Cs_2CO_3, KOH, Et_3N and DBU did not lead to better yield of oxazole (Table 1, entries 19-22). It may be noted that, under controlled reaction conditions, when **1a** was treated with NBS-Me_2S in the absence of base, mixture of *cis-trans* β-bromoenamides (from NMR) were obtained (Table 1, entry 23). Undesirably, treatment of isolated β-bromoenamides (**A**) with K_2CO_3 at 70°C did not

Table 1. Optimization of reaction conditions [a]

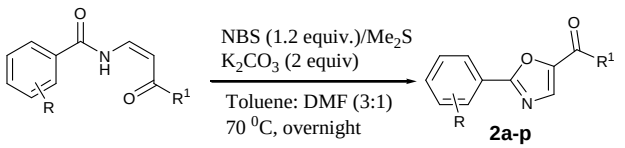


Entry	Oxidant	Base	Additive	Solvent	Yield (%),(**2a**)
1[b]	I_2	K_2CO_3/DBU	--	THF	0
2[c]	I_2	K_2CO_3	--	toluene	0
3[c]	NBS	--	--	DCE	0
4	NBS	Et_3N	--	benzene	NR
5	I_2	K_2CO_3	--	toluene/DMF	33
6	Br_2	K_2CO_3	--	toluene/DMF	12
7	ICl	K_2CO_3	--	toluene/DMF	NR
8	Chloramine-T	K_2CO_3	--	toluene/DMF	NR
9	NBS	K_2CO_3	--	toluene/DMF	10
10	**NBS**	**K_2CO_3**	**Me_2S**	**toluene/DMF**	**79**
11	NBS	K_2CO_3	Me_2S	toluene	17
12[b]	NBS	K_2CO_3	Me_2S	DMF	0
13[b]	NBS	K_2CO_3	Me_2S	DMSO	0
14[b]	NBS	K_2CO_3	Me_2S	THF	0
15	NBS	K_2CO_3	Me_2S	H_2O	0
16[c]	NBS	K_2CO_3	Me_2S	toluene/H_2O	0
17	NBS	K_2CO_3	Me_2S	toluene/DMF	NR
18	NBS	K_2CO_3	Me_2S	toluene/DMSO	22
19	NBS	KOH	Me_2S	toluene/DMF	37
20	NBS	^{t}BuOK	Me_2S	toluene/DMF	0
21	NBS	Et_3N	Me_2S	toluene/DMF	0
22	NBS	DBU	Me_2S	toluene/DMF	0
23[c]	NBS	--	Me_2S	toluene/DMF	0
24	NBS	K_2CO_3	Me_2S	DCE	NR

[a] Reaction conditions: A mixture of enamide (100 mg), oxidant (1.2 equiv), additive (0.1 mL), in solvent (4 mL) was heated at 70 °C for overnight. [b] Mixture of *E* and *Z*-enamides (**3**) forms. [c] β-haloenamide (**4**) forms. NR: no reaction.

produce the expected oxazole with the complete recovery of starting material i.e. β-bromoenamide. Thus, we speculate that under our mild reaction conditions, intermediate **B** may form,[8] which subsequently undergo facile intramolecular reaction leading to the intermediate **C** (Scheme 2). Aromatization of the intermediate **C** produces the desired oxazole **2a**. Among the tested solvents combination of toluene and DMF (3:1) turned out to be the best solvent for the annulation reaction and hence it was selected as the solvent in the following tests. Furthermore, it may be mentioned here that when *E*-enamide was taken as a reactant, oxazole **2a** was isolated with similar yield; which indicates that the stereochemistry of enamide does not affect the yield of oxazole.

Table 2. Synthesis of 2,5-disubstituted oxazoles [a]



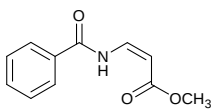
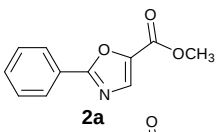
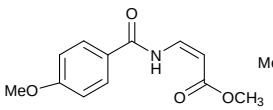
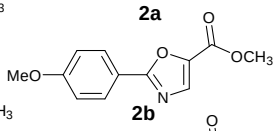
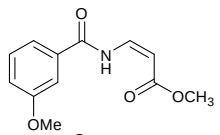
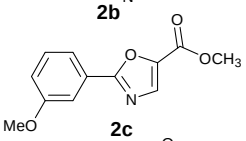
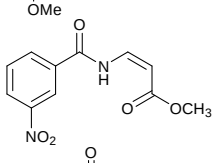
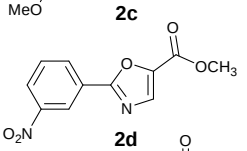
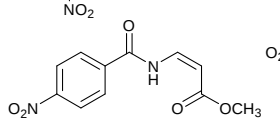
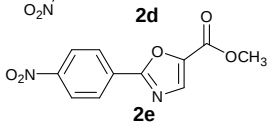
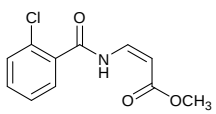
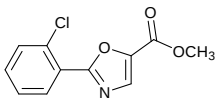
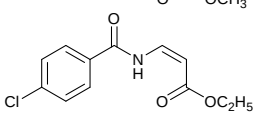
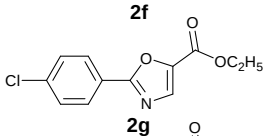
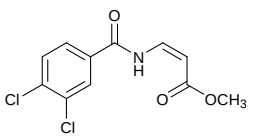
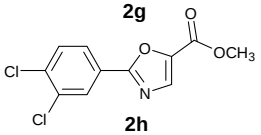
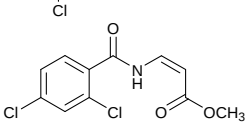
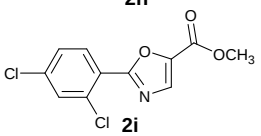
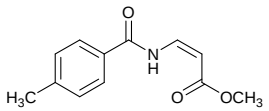
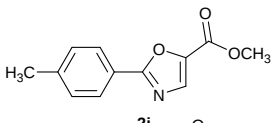
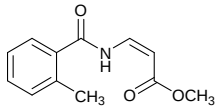
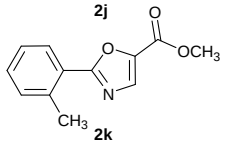
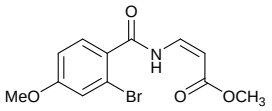
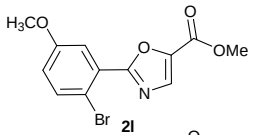
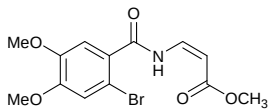
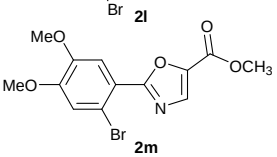
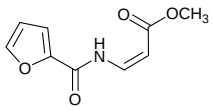
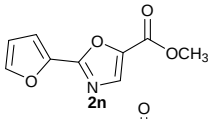
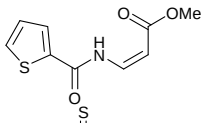
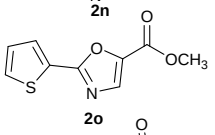
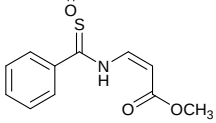
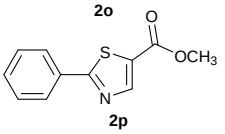
Entry	enamide	oxazole	yield (%)
1		 **2a**	79
2		 **2b**	76
3		 **2c**	81
4		 **2d**	80
5		 **2e**	76
6		 **2f**	83
7		 **2g**	86
8		 **2h**	93
9		 **2i**	85

Table 2. *Continued …….*

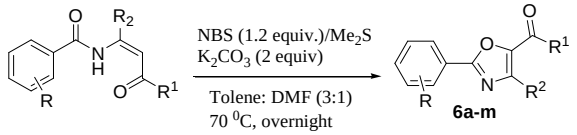
Entry	enamide	oxazole	yield (%)
10		 **2j**	91
11		 **2k**	81
12		 **2l**	74
13		 **2m**	81
14		 **2n**	71
15		 **2o**	75
16		 **2p**	69

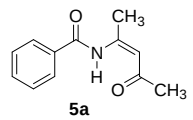
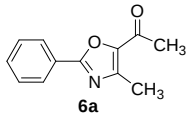
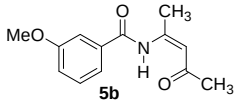
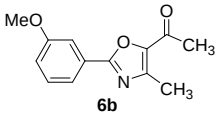
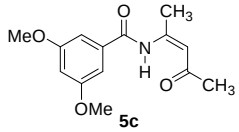
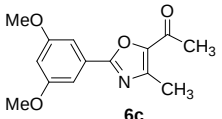
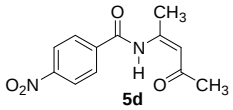
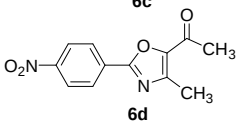
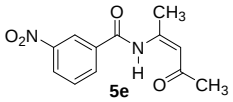
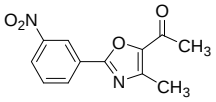
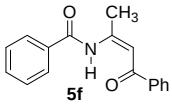
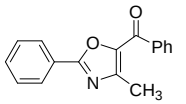
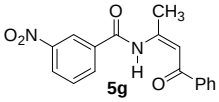
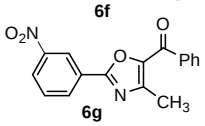
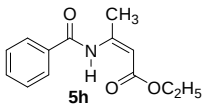
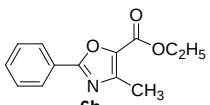
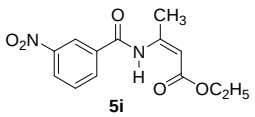
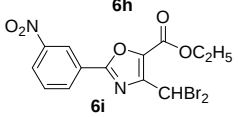
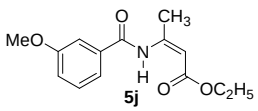
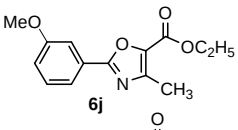
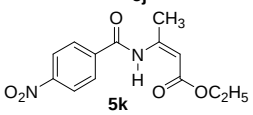
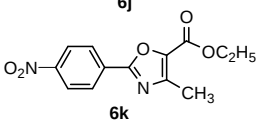
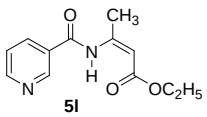
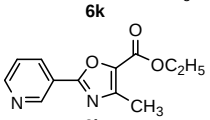
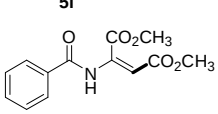
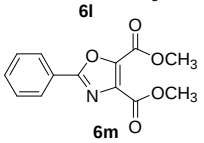
[a] Reaction conditions: A mixture of enamide (100 mg), NBS (1.2 equiv), Me_2S (0.1 mL), in 2 mL of Toluene : DMF (3:1) was heated at 70 °C for overnight.

With the optimized reaction conditions, we turned our attention to investigate the substrate scope of the annulation reaction. We observed that under our optimized reaction conditions, substrates with electron-donating or -withdrawing substituents to the aromatic ring were successfully transformed to 2,5-substituted oxazoles in one-pot with good to excellent yield (Table 2). Heteroaromatic enamides also afford the heteroaryl substituted oxazoles in good yield. 2,5-disubstituted thioxazole (**2p**) was also obtained from the cyclization of the corresponding thioenamide in appreciable yield (Table 2, entry 16). Unfortunately, however, the reaction did not afford the corresponding oxazole when we use *N*-styrylbenzamides; which indicates that the presence of electron withdrawing group at the β-position in the enamide is indispensible for the reaction to occur.

Substrate scope of the annulation reaction was further explored with the α- and β-substituted enamides to achieve 2,4,5-substituted oxazoles. Substituted enamides were prepared from the carbonylation of readily accessible enamines following the similar procedure reported elsewhere. As expected, under our optimized reaction conditions, 2,4,5 trisubstituted oxazoles (**6a-m**) were obtained in good to excellent yield under the optimized reaction conditions (Table 3). Notably, different substituents to

Table 3. Synthesis of 2,4,5-substituted oxazoles [a]



Entry	enamide	oxazole	yield (%)
1	 5a	 6a	88
2	 5b	 6b	86
3	 5c	 6c	90
4	 5d	 6d	82
5	 5e	 6e	92
6	 5f	 6f	62
7	 5g	 6g	86
8	 5h	 6h	88
9	 5i	 6i	47
10	 5j	 6j	82
11	 5k	 6k	87
12	 5l	 6l	64
13[b]	 5m	 6m	67

[a] Reaction conditions: A mixture of enamide (100 mg), NBS (1.2 equiv), Me_2S (0.1 mL), in 4 mL of toluene:DMF (3:1) was heated at 70 °C for overnight. [b] stirred at 70 °C for 24 h and only **6i** was isolated.

the aromatic ring did not affect the reaction to produce 2,4,5-trisubstituted oxazoles in moderate to good yield. Notably, electron- donating and -withdrawing groups α- to the enamides do not affect the reaction to occur.

Conclusions

In conclusion, we have developed a transition metal-free protocol for the direct transformation of enamide into 2,5-substituted oxazoles in moderate to good yield. The reaction conditions are very mild and simple and do not require any inert atmosphere to result good yield of the oxazoles. Mechanistic insight suggest that the reaction may proceeds through the in-situ formation of oxazolium intermediate (e.g. **C**), which subsequently oxidized to oxazoles. Furthermore, the present method is a suitable protocol to produce 2,4,5-trisubstituted oxazoles in good to excellent yield. The presence of electron withdrawing β-substituent in the enamide is indispensible for the reaction to occur.

Experimental

General Methods: Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance III instrument at 400 and 100 MHz, respectively. IR spectra were recorded by Perkin Elmer Spectrophotometer. MS and HRMS data were recorded by the mass spectrometry service of CDRI, Lucknow and NISER Bhubaneswar. The reactions were monitored by thin-layer chromatography (TLC). Column chromatography was performed over silica gel (Rankem, India, particle size 60-120 mesh), using ethyl acetate-petroleum ether (60-80°C) mixture as eluent.

General procedure for the synthesis of oxazoles. To a reaction mixture of enamide (100 mg), recrystalised NBS (1.2 equiv) and K_2CO_3 (2 equiv) in 4 mL of toluene: DMF (3:1), Me_2S (0.1 mL) was added. The reaction mixture was stirred at room temperature for 30 min and subsequently heated at 70 °C for overnight. Then the reaction mixture was cooled to room temperature, diluted with ethyl acetate and water. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was subjected to column chromatography on silica gel [ethyl acetate/petroleum ether (60-80 °C)] to get the pure oxazoles.

Methyl 2-phenyloxazole-5-carboxylate[9] **(2a):** Yield: 78 mg (79%), white crystalline solid, mp 85-87 ºC. IR (KBr): 3114, 3030, 2952, 2849, 1712, 1630, 1579, 1535, 1473, 1447, 1348, 1308, 1246, 1205, 1142, 1093 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.19-8.15 (m, 2H), 7.87 (s, 1H), 7.57-7.48 (m, 3H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 158.2 (s), 142.0 (s), 135.5 (d), 131.6 (d), 128.9 (d), 127.2 (d), 126.3, 52.2 (q). MS (ESI, +ve) m/z (relative intensity) 204.06 ($[M + H]^+$, 100%).

Methyl 2-(4-methoxyphenyl)oxazole-5-carboxylate (2b): Yield: 75 mg (76 %), white crystalline solid, mp 114-115 ºC. IR (KBr): 3154, 3098, 3002, 2949, 2834, 1731, 1611, 1586, 1489, 1436, 1358, 1307, 1254, 1193, 1150, 1024 cm^{-1}. ^1H NMR (400

MHz, $CDCl_3$): δ 8.11-8.07 (m, 2H), 7.82 (s, 1H), 7.01- 6.99(m, 2H, 3.94 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 162.3, 158.3, 141.5, 135.6, 129.0, 118.9, 114.3, 55.4, 52.1. ^{1}HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_4^+$[M + H]$^+$ 234.0766, found 234.0765.

Methyl 2-(3-methoxyphenyl)oxazole-5-carboxylate (2c): Yield: 79 mg (80 %), white crystalline solid, mp 120-122 ºC. IR (KBr): 3439, 3002, 2951, 2845, 1735, 1579, 1534, 1470, 1435, 1355, 1307, 1263, 1219, 1194, 1151, 1090, 1039 cm^{-1} . ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.78-7.74 (m, 1H),7.68-7.65 (m, 1H), 7.42 (t, 1H, *J* = 8 Hz), 7.11-7.07 (m, 1H), 3.97 (s, 3H), 3.91 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 159.9, 158.2, 142.0, 135.5, 130.0, 127.4, 119.7, 118.4, 111.6, 55.5, 52.2. MS (ESI, +ve) m/z (relative intensity) 234.12 ([M + H]$^+$, 100%).

Methyl 2-(3-nitrophenyl)oxazole-5-carboxylate (2d): Yield: 80 mg (81 %), white crystalline solid, mp 125-127 °C. IR (KBr): 3115, 3061, 2986, 2915, 2862, 1725, 1635, 1589, 1528, 1396, 1345, 1302, 1252, 1156, 1013 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (m, 1H), 8.52-8.47 (m, 1H), 8.42-8.37 (m, 1H), 7.92 (s, 1H), 7.75 (t, 1H, *J* = 8 Hz), 4.00 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 157.9, 148.6, 142.9, 135.5, 132.6, 130.2, 127.9, 123.1, 122.1, 52.5. IR (KBr): 3115, 3061, 2986, 2915, 2862, 1725, 1635, 1589, 1528, 1396, 1345, 1302, 1252, 1156, 1013.cm^{-1} MS (ESI, +ve) m/z (relative intensity) 248.14 ([M + H]$^+$, 100%).

Methyl 2-(4-nitrophenyl)oxazole-5-carboxylate (2e): Yield: 75 mg (76 %), white crystalline solid, mp 117-118 ºC. IR (KBr): 3065, 2975, 2858, 1719, 1639, 1586, 1528, 1386, 1342, 1312, 1263, 1165, 1068, 1013 cm.$^{-1}$ ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41-8.35 (m, 4H), 7.93 (s, 1H), 4.00 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 157.8, 149.4, 143.1, 135.6, 131.6, 128.1, 124.2, 52.5. MS (ESI, +ve) m/z (relative intensity) 248.11 ([M + H]$^+$, 100%).

Methyl 2-(2-chlorophenyl)oxazole-5-carboxylate (2f): Yield: 82 mg (83 %), white crystalline solid, mp 92-94°C. IR (KBr): 3064, 2921, 2851, 1728, 1586, 1527, 1450, 1356, 1303, 1151. cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (dd, 1H, J_1 = 7.6 Hz, J_2 =1.6 Hz), 7.94 (s, 1H), 7.58-7.54 (m, 1H), 7.49-7.38 (m, 2H), 3.98 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 158.1, 142.3, 135.1, 133.2, 132.1, 131.4, 131.4, 126.9, 125.2, 52.3. MS (ESI, +ve) m/z (relative intensity) 238.01 ([M + H]$^+$, 100%).

Ethyl 2-(4-chlorophenyl)oxazole-5-carboxylate (2g): Yield: 85 mg (86 %), white crystalline solid, mp 85-86 °C. IR (KBr): 3062, 2925, 2856, 1716, 1629, 1583, 1535, 1461, 1349, 1312, 1156.cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, 2H, J_1 = 6.8 Hz, J_2 = 2 Hz), 7.85 (s, 1H), 7.49 (dd, 2H, J_1 = 6.8 Hz, J_2 = 2 Hz), 4.43 (q, 2H, *J* = 6.8 Hz), 1.42 (t, 3H, *J* = 6.8 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 157.7, 142.4, 137.9, 135.3, 129.3, 128.5, 124.8, 61.5, 14.2. MS (ESI, +ve) m/z (relative intensity) 252.28 ([M + H]$^+$, 100%).

Methyl 2-(3,4-dichlorophenyl)oxazole-5-carboxylate (2h): Yield: 92 mg (93 %), white crystalline solid, mp 97-98 ºC. IR (KBr): 3086, 2952, 2921, 2845, 1733, 1627, 1580, 1524, 1452, 1396, 1304, 1198, 1139, 1031. cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, 1H, *J* = 2 Hz), 7.99 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2 Hz), 7.86 (s, 1H), 7.60 (dd, 1H, J1 = 8.4 Hz, J2 = 1.6 Hz), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 157.9, 142.5, 135.5, 133.6, 131.1, 128.9, 126.1, 126.0, 97.6, 52.4. HRMS (ESI) m/z calcd for $C_{11}H_8Cl_2NO_3^+$[M + H]$^+$ 271.9881, found 271.9876.

Methyl 2-(2,4-dichlorophenyl)oxazole-5-carboxylate (2i): Yield: 84 mg (85%), white crystalline solid, mp 104-105 °C. IR (KBr): 3070, 2921, 2851, 1739, 1725, 1633, 1465, 1426, 1351, 1311, 1151.cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, 1H, *J* = 8.8 Hz), 7.93 (s, 1H), 7.58 (d, 1H, *J* = 1.2 Hz), 7.40 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2 Hz), 3.98 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 158.0, 142.4, 137.8, 135.1, 133.9, 132.1, 131.3, 127.5, 123.7, 52.4. HRMS (ESI) m/z calcd for $C_{11}H_8Cl_2NO_3^+$[M + H]$^+$ 271.9881, found 271.9876.

Methyl 2-*p*-tolyloxazole-5-carboxylate (2j): Yield: 90 mg (91%), white crystalline solid, mp 64-65 ºC. IR (KBr): 3109, 3002, 2957, 2918, 2851, 1714, 1613, 1570, 1542, 1486, 1437, 1352, 1310, 1246, 1182, 1148.cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, 2H, *J* = 8.4 Hz), 7.85 (s, 1H), 7.30 (m, 2H), 3.96 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 158.3, 142.2, 141.7, 135.6, 129.6, 127.2, 123.6, 52.2, 21.6. HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_3^+$[M + H]$^+$ 218.0817, found 218.0832.

Methyl 2-*o*-tolyloxazole-5-carboxylate (2k): Yield: 80 mg (81%), white crystalline solid, mp 68-69 ºC. IR (KBr): 3120, 2954, 2918, 2840, 1734, 1716, 1627, 1586, 1525, 1485, 1451, 1353, 1304, 1190, 1147, 997.cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13-8.08 (m, 1H), 7.89 (s, 1H), 7.44-7.37 (m, 1H), 7.35-7.29 (m, 2H), 3.96 (s, 3H), 2.73 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 158.3, 141.5, 138.4, 135.2, 131.8, 131.1, 129.5, 126.1, 125.3, 52.2, 22.0. HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_3^+$[M + H]$^+$218.0817, found 218.0807.

Methyl 2-(2-bromo-5-methoxyphenyl)oxazole-5-carboxylate (2l): Yield: 73 mg (74 %), dark brown gummy liquid. IR (neat): 3109, 3008, 2951, 2840, 1735, 1571, 1524, 1460, 1436, 1344, 1309, 1231, 1194, 1150, 1039, 1017 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.62 (d, 1H, *J* = 8.8 Hz), 7.53 (d, 1H, *J* = 1.2 Hz), 6.93 (dd, 1H, , J_1 = 9.2 Hz J_2 = 3.2 Hz), 3.97 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 158.7, 158.1, 142.3, 135.5, 134.9, 127.7, 119.0, 116.2, 111.9, 55.7, 52.3. HRMS (ESI) m/z calcd for $C_{12}H_{11}BrNO_4^+$[M + H]$^+$311.9871, found 311.9850.

Methyl 2-(2-bromo-4,5-dimethoxyphenyl)oxazole-5-carboxylate (2m): Yield: 80 mg (81 %), dark brown semi solid, IR (neat): 3308, 3070, 2951, 2918, 2845, 1712, 1629, 1586, 1493, 1459, 1432, 1248, 1205, 1078, 1041cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.53 (s, 1H), 7.17 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 158.2, 151.6, 148.3, 141.9, 135.0, 119.2, 117.1, 113.3, 112.9, 56.3, 56.2, 52.3. MS (ESI, +ve) m/z (relative intensity) 341.8 ([M + H]$^+$, 100%).

Methyl 2-(furan-2-yl)oxazole-5-carboxylate[10] **(2n):** Yield: 70 mg (71 %), white crystalline solid, mp 1112-114 ºC. IR (KBr):

3386, 3127, 2921, 2850, 1736, 1628, 1581, 1517, 1436, 1350, 1308, 1256, 1195, 1195, 1151, 1096, 1014 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.63 (t, 1H, *J* = 1.2 Hz), 7.22 (t, 1H, *J* = 2 Hz), 6.58 (q, 1H, *J* = 1.8 Hz), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 156.5, 145.7, 141.9, 141.4, 135.4, 114.2, 112.2, 52.3. MS (ESI, +ve) m/z (relative intensity) 194.22 ($[M + H]^+$, 100%).

Methyl 2-(thiophen-2-yl)oxazole-5-carboxylate[10] **(2o):** Yield: 74 mg (75 %), white crystalline solid, mp 108-110 ºC. IR (KBr): 3085, 3008, 2963, 2920, 2840, 1734, 1697, 1583, 1560, 1482, 1359, 1300, 1192, 1144cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, 1H, J_1 = 3.6 Hz, J2 = 1.2 Hz), 7.81 (s, 1H), 7.55 (dd, 1H, J_1 = 4 Hz, J_2 = 1.2 Hz), 7.17 (dd, 1H, J_1 = 5 Hz, J_2 = 4 Hz), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 158.1, 141.4, 135.6, 130.4, 129.9, 128.7, 128.3, 52.2. MS (ESI, +ve) m/z (relative intensity) 210.1 ($[M + H]^+$, 100%).

Methyl 2-phenylthiazole-5-carboxylate (2p): Yield: 68 mg (69 %) as yellow crystalline solid, mp 115-116 ºC. IR (KBr): 3058, 2991, 2944, 2924, 2834, 1707, 1625, 1517, 1454, 1312, 1252, 1194, 1150, 1093cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.03-7.98 (m, 2H), 7.53-7.48 (m, 3H), 3.95 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 161.8, 149.3, 132.8, 131.2, 129.1, 128.5, 126.9, 52.5. HRMS (ESI) m/z calcd for $C_{11}H_{10}NO_2S^+$[M + H]$^+$ 220.0432, found 220.0427.

1-(4-Methyl-2-phenyloxazol-5-yl)ethanone[6j] **(6a):** Yield: 87 mg (88%), white crystalline solid. mp 61-63 °C. IR (KBr): 3322, 3058, 3002, 2952, 2918, 2845, 1670, 1595, 1536, 1440, 1381, 1264, 1145, 1075.cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.14-8.10 (m, 2H), 7.55-7.47 (m, 3H), 2.58 (s, 3H), 2.57 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 161.4, 146.3, 145.1, 131.6, 128.9, 127.1, 126.3, 27.5, 13.8. MS (ESI, +ve) m/z (relative intensity) 202.14 ($[M + H]^+$, 100%).

1-(2-(3-Methoxyphenyl)-4-methyloxazol-5-yl)ethanone (6b): Yield: 85 mg (86%), yellow crystalline solid, mp 66-68 ºC. IR (KBr): 3064, 3002, 2923, 2837, 1677, 1582, 1527, 1469, 1433, 1387, 1358, 1322, 1277, 1236, 1182, 1141, 1080, 1042cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.73-7.69 (m, 1H), 7.65-7.62 (m, 1H), 7.42 (t, 1H, J = 8 Hz), 7.10-7.06 (m, 1H), 3.90 (s, 3H), 2.58 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 159.9, 146.2, 130.1, 119.6, 118.1, 111.7, 55.5, 27.5, 13.8. HRMS (ESI) m/z calcd for $C_{13}H_{14}NO_3^+$[M + H]$^+$232.0974, found 232.0972.

1-(2-(3,5-Dimethoxyphenyl)-4-methyloxazol-5-yl)ethanone (6c): Yield: 89 mg (90%), yellow crystalline solid, mp 69-71 ºC. IR (KBr): 3360, 3081, 3002, 2938, 2840, 1715, 1675, 1593, 1535, 1460, 1426, 1384, 1355, 1257, 1205, 1157, 1063 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1H), 7.25 (s, 1H), 6.63 (t, 3H, *J* = 2.0 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 2.58 (s, 3H), 2.57 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 161.1, 146.2, 127.9, 118.8, 104.9, 104.2, 97.3, 55.7, 55.6, 27.5, 13.8. HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_4^+$ [M + H]$^+$ 262.1079, found 262.1070.

1-(4-Methyl-2-(4-nitrophenyl)oxazol-5-yl)ethanone (6d): Yield: 81 mg (82 %), yellow crystalline solid, mp 83-84 ºC. IR (KBr): 3443,3054, 2923, 2836, 1676, 1581, 1537, 1470, 1433, 1387, 1358, 1322, 1276, 1235, 1182, 1140, 1080, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.39-8.35 (m, 2H), 8.32-8.28 (m, 2H), 2.61 (s, 3H), 2.60 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 187.4, 158.9, 149.3, 146.5, 145.8, 131.7, 127.9, 124.3, 27.6, 13.7. HRMS (ESI) m/z calcd for $C_{12}H_{11}N_2O_4^+$[M + H]$^+$ 247.0719, found 247.0713.

1-(4-Methyl-2-(3-nitrophenyl)oxazol-5-yl)ethanone (6e): Yield: 91 mg (92 %), yellow crystalline solid, mp 78-79 ºC. IR (KBr): 3075, 2919, 2840, 1677, 1573, 1520, 1384, 1347, 1307, 1260, 1079 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (t, 1H, *J* = 1.2 Hz), 8.47 (s, 1H), 8.45 (s, 1H), 7.73 (t, 1H, *J* = 8 Hz), 2.62 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.5, 158.8, 148.6, 146.3, 145.6, 132.6, 130.2, 128.0, 125.9, 121.9, 27.7, 13.7. HRMS (ESI) m/z calcd for $C_{12}H_{11}N_2O_4^+$ [M + H]$^+$ 247.0719, found 247.0713.

(4-Methyl-2-phenyloxazol-5-yl)(phenyl)methanone (6f): Yield: 61 mg (62 %), off-white crystalline solid, mp 62-64 ºC. IR (KBr): 3059, 2921, 2865, 1641, 1597, 1537, 1477, 1448, 1382, 1355, 1299, 1264, 1175, 1125 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15-8.06 (m, 4H), 7.66-7.51 (m, 6H), 2.65 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 182.7, 161.8, 149.2, 144.8, 137.3, 132.8, 131.7, 129.3, 129.0, 128.5, 127.2, 14.3. MS (ESI, +ve) m/z (relative intensity) 264.11 ($[M + H]^+$, 100%).

(4-Methyl-2-(3-nitrophenyl)oxazol-5-yl)(phenyl)methanone (6g): Yield: 85 mg (86 %), yellow crystalline solid, mp 78-79 ºC. IR (KBr): 3446, 3092, 2957, 2924, 2857, 1643, 1597, 1525, 1447, 1384, 1348, 1311, 1266, 1175, 1135, 1107 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (t, 1H, *J* = 2 Hz), 8.45-8.36 (m, 2H), 8.07-8.03 (m, 2H), 7.76-7.55 (m, 4H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.7, 159.2, 148.9, 148.7, 145.3, 137.0, 133.1, 132.5, 130.2, 129.2, 128.6, 128.0, 125.8, 122.1, 14.2. MS (ESI, +ve) m/z (relative intensity) 331.06 ($[M + Na]^+$, 100%).

Ethyl 4-methyl-2-phenyloxazole-5-carboxylate[11] **(6h):** Yield: 87 mg (88%), colorless oil. IR (neat): 3060, 2916, 2835, 1724, 1608, 1543, 1466, 1392, 1347, 1252, 1245, 1158, 1107, 1037 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.14-8.10 (m, 2H), 7.51-7.47 (m, 3H), 4.41 (q, 2H, *J* = 7.2 Hz), 2.54 (s, 3H), 1.42 (t, 3H, *J* = 7.2 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 158.8, 147.06, 137.4, 131.4, 128.8, 127.1, 126.4, 61.0, 14.3, 13.5. MS (ESI, +ve) m/z (relative intensity) 232.12 ($[M + H]^+$, 100%).

Ethyl 4-(dibromomethyl)-2-(3-nitrophenyl)oxazole-5-carboxylate (6i): Yield: 73 mg (47%); yellow crystalline solid, mp 128-130 ºC. IR (KBr): 3422, 3109, 2991, 2921, 2851, 1731, 1603, 1520, 1476, 1415, 1388, 1340, 1308, 1249, 1162, 1108, 1015cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.04 (t, 1H, *J* = 1.6 Hz), 8.59-8.55 (m, 1H), 8.46-8.41 (m, 1H), 7.75 (t, 1H, *J* = 8 Hz), 7.32 (s, 1H), 4.52 (q, 2H, *J* = 7.2 Hz), 1.49 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (s), 157.0 (s), 148.7 (s), 147.5 (s), 133.3 (s), 133.1 (d), 130.2 (d), 127.3 (s), 126.5 (d),

122.4 (d), 62.5 (t), 27.5 (d), 14.2 (q). MS (ESI, +ve) m/z (relative intensity) 434.76 ([M + H]$^+$, 50%).

Ethyl 2-(3-methoxyphenyl)-4-methyloxazole-5-carboxylate[12] **(6j):** Yield: 81 mg (82%), white solid, mp 75-76 ºC. IR (KBr): 3065, 2929, 2829, 1711, 1605, 1540, 1469, 1397, 1348, 1272, 1235, 1152, 1108, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 1H, *J* = 8 Hz), 7.63 (d, 1H, J = 1.6 Hz), 7.38 (t, 1H, *J* = 8 Hz), 7.05 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2 Hz), 4.41 (q, 2H, *J* = 7.2 Hz), 3.88 (s, 3H), 2.54 (s, 3H), 1.42 (t, 3H, *J* =7.2 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 159.8, 158.8, 147.0, 137.4, 129.9, 127.5, 119.7, 118.1, 111.5, 61.0, 55.5, 14.3, 13.5. MS (ESI, +ve) m/z (relative intensity) 262.14 ([M + H]$^+$, 100%).

Ethyl 4-methyl-2-(4-nitrophenyl)oxazole-5-carboxylate (6k): Yield: 86 mg (87%), yellow crystalline solid, mp 122-123 ºC IR (KBr): 3105, 3064, 2980, 2922, 2851, 1730, 1639, 1603, 1521, 1390, 1341, 1309, 1250, 1162, 1107, 1015cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36-8.29 (m, 4H), 4.45 (q, 2H, *J* = 7.2 Hz), 2.58 (s, 3H), 1.44 (t, 3H, *J* = 7.2 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 158.5, 149.2, 147.3, 138.6, 131.8, 128.0, 124.2, 61.4, 14.3, 13.4. HRMS (ESI) m/z calcd for $C_{13}H_{13}N_2O_5^+$ [M + H]$^+$ 277.0824, found 277.0819.

Ethyl 4-methyl-2-(pyridin-3-yl)oxazole-5-carboxylate[6e] **(6l):** Yield: 63 mg (64 %) as yellow oil. IR (neat): 3075, 2929, 2784, 1772, 1708, 1640, 1426, 1371, 1297, 1246, 1189, 1006cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (s, 1H), 8.79 (s, 1H), 8.40 (d, 1H, *J* = 8 Hz), 7.46 (s, 1H), 4.44 (q, 2H, *J* = 7.2 Hz), 2.57 (s, 3H), 1.44 (t, 3H, *J* = 7.2 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 158.6, 151.9, 148.3, 147.0, 138.0, 134.2, 123.7, 61.3, 14.3, 13.4. MS (ESI, +ve) m/z (relative intensity) 233.05 ([M + H]$^+$, 100%).

2-Phenyl-oxazole-4,5-dicarboxylic acid dimethyl ester[13] **(6m):** Yield: 66 mg (67 %), white solid, mp 78-79 ºC. IR (KBr): 3061, 2923, 2825, 1729, 1615, 1520, 1459, 1387, 1338, 1279, 1225, 1142, 1102, 1033cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21-8.16 (m, 2H), 7.58-7.48 (m, 3H), 4.02 (s, 3H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 161.0, 157.3, 141.9, 137.2, 132.2, 129.0, 127.5, 125.3, 53.0, 52.9. MS (ESI, +ve) m/z (relative intensity) 262.12 ([M + H]$^+$, 100%).

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Notes and references

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