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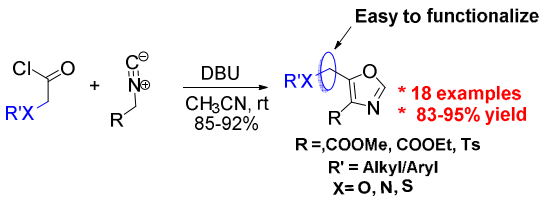

Journal Name

ARTICLE

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Introduction

Oxazoles represent an important class of five membered heterocycles, occuring as substructural units in a wide variety of biologically active compounds[1] (Diazonamide A (**1**)[1i] and Leucamide A (**2**)[1j], pharmaceuticals[2] (Ostreogrycin-A (**3**) Fig-1) and molecular sensors.[3] Oxazoles are also popular as valuable precursors in many useful synthetic transformations.[4] In recent years, 4,5-disubstituted oxazoles have received considerable attention from both synthetic and medicinal chemists, mainly due to their significant therapeutic potential in treating various diseases such as inflammation, cancer and asthma.[5-6] 4,5-Disubstituted oxazoles as a class are a potent and selective inhibitor of the stress-activated kinase p38α[7], cyclooxygenate-II (COX-II), cyclooxygenase-1 (COX-1) and anti-tumor necrosis factor (Anti-TNF).[8]

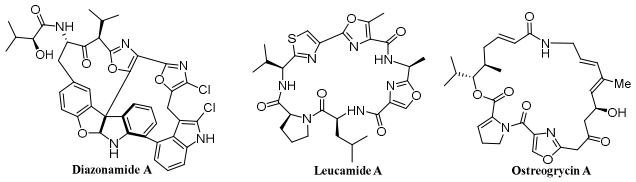

Figure 1. Oxazole containing biologically active compounds.

Owing to their medicinal value, a number of synthetic methods have been developed to construct 4,5-disubstituted oxazoles.[9]

Among these methods, the most classical procedure is the cyclocondensation of acetyl chloride and monosubstituted tosyl methyl isocyanides developed by van Lausen *et. al.* (Fig-2 eq-1).[10a] Later, Yu and Stevens groups reported improved syntheses in ionic liquids and an automated flow reactor system respectively.[10b-c] In addition, Miller group devised a new route which involves the regioselective C2 silylation followed by metalation of oxazoles at C5 position (Fig-2 eq.-2).[10d]

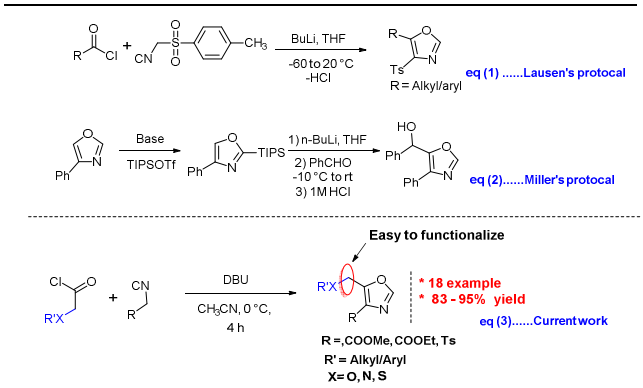

Figure. 2 Scheme depicting previous reports on the synthesis of 4,5-disubstituted oxazoles along with present study.

While all these useful methods provide convenient access to 4,5-disusbtituted oxazoles, there are certain limitations associated with them, such as harsh reaction conditions, multistep synthesis, and difficulties in further functionalization, especially at C5 position of oxazoles. Therefore, development of a mild and efficient approach to 4,5-disubstituted oxazoles is still highly desirable.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

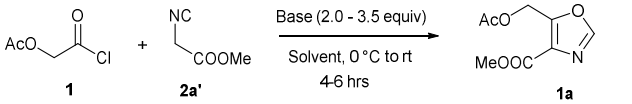
Acid chlorides have long been renowned for their reactivity in numerous synthetic transformations, particularly their reactivity in [2+2] and [4+2] cycloadditions, reductive couplings, SN_2 substitutions as well as both nucleophilic and electrophilic additions. Our current research is focused on the synthesis of various azetidin-2-ones using [2+2] cycloaddition reactions of imines with in situ generated ketenes from acid chlorides.[11] As a continuation of the same research program which uses acid chlorides as precursors, herein we wish to report an efficient and practical synthesis of 4,5-disubstituted oxazole *via* [3+2] cycloaddition reactions of isocyanides with alkyloxy/aryloxy acid chlorides in presence of a base. This methodology works with broad spectrum of acid chlorides including the ones containing heteroatoms such as oxygen, nitrogen and sulphur. These 4,5-disubstituted oxazoles could in turn be functionalized at C5 position.

Results and Discussion

Initially, the synthesis of 4,5-disubstituted oxazole was examined using acetoxyacetyl chloride **1** and methyl 2-isocyanoacetate **2a'** as the model substrate. Our first attempt by treating acetoxyacetyl chloride **1** (0.5 mmol) and methyl 2-isocyanoacetate **2a'** (0.5 mmol) in presence of anhydrous K_2CO_3 (2.0 equiv) in dry DCM at room temperature was unsuccessful (Table-1 entry-1). Use of different bases such as Cs_2CO_3, Et_3N and DBU in dichloromethane too failed to yield the desired product **1a** (Table-1 entries 1-4). However, 20% yield of the product 4,5-disubstituted oxazole **1a** was isolated when reaction was performed in anhydrous CH_3CN in the presence of K_2CO_3 (2.0 equiv) at room temperature under argon atmosphere (Table-1, entry 5). Furthermore, **1a** was isolated in 35% yield by using 2.0 equiv of Et_3N in CH_3CN at room temperature (Table-1, entry-6). The poor performance of the reactions at room temperature, possibly may be due to the polymerization of ketene generated *in situ* from acid chloride.[12] Therefore, we attempted reaction at lower temperature and a sharp increase in the yield (53%) of **1a** was observed when reaction was performed at 0 °C (Table-1, entry 7). To our delight, a much better yield (76%) of **1a** was obtained when DBU (2.0 equiv) was employed as a base (Table-1, entry-8). Notably, the conversion and the yields were affected dramatically by amount of DBU employed, and the best result (95%) was obtained by employing 3.5 equiv. of DBU (Table-1, entry 9). Further increase or decrease in the amount of DBU did not give a better yield (Table-1, entry 10 & 11). Stronger bases such as KOH, NaOMe and KO^{t}Bu were found less effective to promote the reaction (Table-1, entries 12-14) and furnished lower yields of desired **1a**. It was plausibly due the enolization of acetate group of the substrate (**1**) and product (**1a**) in the presence of strong bases which led to the formation of undesired side products. However, strong bases were equally effective as DBU with substrates containing no acetate group (For details, see supporting information). Furthermore, the cycloaddition reaction of **1** and **2a'** were tried in different solvents such as *N,N* dimethyl formamide (DMF), dimethylsulfoxide (DMSO), tetrahydrofuran (THF) and 1,4-dioxane but most of them were found less efficient, resulting **1a** in inferior yields (Table-1, entries 15-18). Unsurprisingly, no product was obtained in protic solvents such as MeOH and EtOH (entries 19 & 20).

With optimal conditions in hand (Table-1, entry 9), the scope of the reaction with respect to various acid chlorides and isocyanide components was investigated. Methyl 2-isocyanoacetate effectively reacted with acid chlorides bearing both aliphatic and aromatic groups. Methoxyacetyl chloride **2**, phenoxy and benzyloxyacetyl chlorides (**3** & **4**) also gave corresponding 4,5-disubstitiuted oxazoles **2a**, **3a**, and **4a** in good yields. Nitrogen containing acid chlorides (PhthNCH$_2$COCl, **5**) on treatment with methyl 2-isocyanoacetate (**2a'**) produced corresponding oxazole **5a** in 92% yield.

Table-1 Optimization of reaction conditions[a]



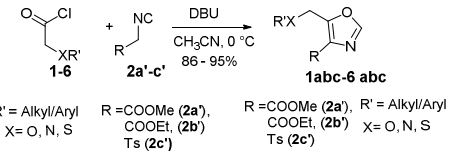
1 2a' 1a

Entry	Base/equiv	Solvent	Temp °C	Time (h)	Yield (%)[b]
1	K_2CO_3 (2)	DCM	rt	6	No reaction
2	Cs_2CO_3 (2)	DCM	rt	6	No reaction
3	Et_3N (2)	DCM	rt	6	No reaction
4	DBU (2)	DCM	rt	6	No reaction
5	K_2CO_3 (2)	CH_3CN	rt	6	20%
6	Et_3N (2)	CH_3CN	rt	6	35%
7	Et_3N (2)	CH_3CN	0 °C	6	53%
8	DBU (2)	CH_3CN	0 °C	6	76%
9	DBU (3.5)	CH_3CN	0 °C	4	95 %
10	DBU (3.0)	CH_3CN	0 °C	4	84%
11	DBU (4.0)	CH_3CN	0 °C	4	91%
12	KOH (3.5)	CH_3CN	0 °C	4	25%
13	NaOMe (3.5)	CH_3CN	0 °C	4	41%
14	*t*-BuOK (3.5)	CH_3CN	0 °C	4	36%
15	DBU (3.5)	DMSO	0 °C	4	45 %
16	DBU (3.5)	DMF	0 °C	4	32 %
17	DBU (3.5)	THF	0 °C	4	65 %
18	DBU (3.5)	1,4-dioxane	0 °C	4	51 %
19	DBU (3.5)	MeOH	0 °C	4	No reaction
20	DBU (3.5)	EtOH	0 °C	4	No reaction

[a] All reactions were carried out on 0.5 mmol of acetoxyacetyl chloride (**1**), 0.5 mmol of methylisocyanoacetate (**2a'**). [b] Isolated yield

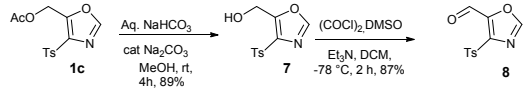
Identical yield (91%) of **6a** was obtained when thiophenylacetyl chloride (**6**) was subjected to similar reaction condition. Also worthy of note is the observation that in place of methyl 2-isocyanoacetate (**2a'**) both ethyl 2-isocyanoacetate (**2b'**) and tosylmethyl isocyanide (TosMIC, **2c'**) readily participated in cycloaddition with various acid chlorides to give corresponding oxazoles (**1b,c-5b,c**) in very good yields.

Table 2 Substrate scope for 4,5-disubstituted oxazole formation[a, b]



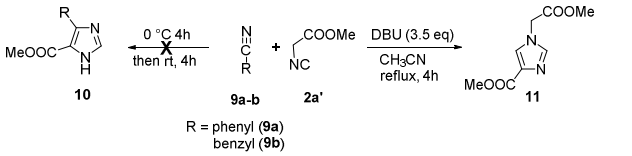
[a] The reaction was carried out with 0.5 mmol of acid chlorides, 0.5 mmol of isocyanides in the presence of DBU (1.75 mmol) in 5 mL of CH_3CN for 4 hrs; [b] Isolated yield.

This initial success propelled us to investigate the versatility of present method. 5-formyl oxazole **8** which can be considered to be an intermediate of high utility can undergo various reactions such as Grignard, Aldol, Wittig, and reductive amination to give functionalized oxazoles. Similar 5-formyl oxazole have already been used as an advance intermediate in the preparation of biologically active compound which is known to posses CRTH2 receptor activity.[13] This synthetically important intermediate was easily prepared in two step process from **1c** (Scheme-1). The hydrolysis of acetate group of **1c** using aqueous sodium bicarbonate solution in MeOH gave intermediate **7** which underwent smooth Swern oxidation to furnish 5-formyl-4-tosyl oxazole **8** in 87% yield.



Scheme-1 synthesis of 5-formyl oxazole from **1c**

Next, in order to expand the scope of the present methodology, we examined the reaction of aryl cyanides (**9a**, **9b**) with methyl 2-isocyanoacetate **2a'** under standard conditions (Scheme-2) to prepare 4,5-disubstituted imidazole **10.**[14] But, unfortunately, no desired products (**10a-b)** were observed. However, when the reaction mixture was refluxed the cyclodimerization of isocyanide takes place to form **11** in 95% yield along with unreacted aryl cyanides (**9a-b)**. The spectral data of **11** is in good agreement with previously reported value.[15]



Scheme-2 reaction of aryl cyanides (**9a-b**) with isocyanide (**2a**)

The formation of 4,5-disubstituted oxazoles may be explained by two pathways. In pathway **A**, initially anionic form of **2a'**, undergoes addition on acid chloride **1** give intermediate **13.** This intermediate **13** then undergoes enolization, followed by

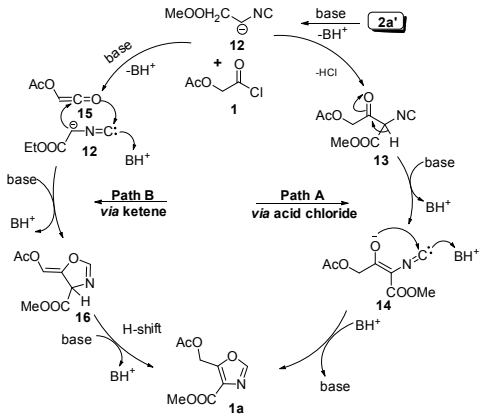


Figure 3. Mechanism of [3+2] cycloaddition of acid chloride and isocyanide towards 4,5-disubstituted oxazoles.

nucelophillic attack on carbene form of **14** leading to the formation of 4,5-disubstituted oxazole **1a**. Another possible mechanistic pathway could be *via* ketene mechanism. The ketene **15** generated *in situ* from the acid chloride undergoes a [3+2] cycloaddition with **12** to yield intermediate **16** which undergoes 1,3 H-shift to give **1a**

Conclusions

In summary, 4,5-disubstituted oxazole construction was achieved in very good yields from readily available acid chlorides and isocyanides under very mild conditions. Moreover, this method was applied to the synthesis of 5-formyl oxazole**.** Work to exploit the potential of 5-formyl oxazoles for further functionalization to yield valuable intermediates is underway and findings will be disclosed in due course of time. The ready availability of starting materials, broad substrate scope, and operational simplicity makes the present method an attractive option for the synthesis of the oxazole skeleton.

Experimental

General: The reagents, chemicals and solvents were either purchased from commercial suppliers or prepared and purified by standard techniques. Column chromatography was carried out using silica gel 100-200 mesh. Infrared spectra were recorded using a FT-IR spectrophotometer and values reported

in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded with 300, 400 and 500 MHz NMR instruments with tertramethylsilane (TMS) as an internal standard. High-resolution mass spectra (ESI-HRMS) were recorded on ESI-QTOP mass spectrometer.

Typical experimental procedure for the synthesis of 4,5-disubstituted oxazoles: A solution of acid chlorides (0.5 mmol) in dry CH_3CN (2 mL) was slowly added to a mixture of isocyanides (0.5 mmol) and DBU (1.75 mmol) in dry CH_3CN (4 mL) at 0 °C. The reaction mixture was allowed to stir for additional 4 hrs at same temperature. The reaction mixture was quenched with water (6 mL) and the mixture was diluted with ethylacetate (10 mL). The organic layer was separated and washed with aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic layer was dried over anhydrous sodium sulphate and solvent was removed under reduced pressure to produce crude 4,5-disubstituted oxazole, which was on purification using 100-200 mesh silica gel, gave pure 4,5-disubstituted oxazoles in very good yields.

Methyl 5-(acetoxy methyl)-oxazole-4-carboxylate (1a):
95% yield, colourless oil; IR (KBr), 3475, 2957, 1747, 1622, 1517, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H), 5.45 (s, 2H), 3.93 (s, 3H), 2.11 (s, 3H): ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.04, 161.35, 152.23, 150.51, 129.54, 55.11, 52.36, 20.48. HRMS (ESI, Orbitrap) calcd for $C_8H_9NO_5$ [M+Na], 222.03734; found 222.03728.

Ethyl 5-(acetoxy methyl)-oxazole-4-carboxylate (1b):
93% yield, Brown colour liquid, IR (KBr), 3474, 2956, 1747, 1623, 1517, 1441 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 5.46 (s, 2H), 4.39 (q, *J* = 7.1, 14.2 Hz, 2H), 2.11 (s, 3H), 1.39 (t, *J* = 7.1, 14.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.14, 161.35, 152.23, 150.51, 148.77, 129.81, 77.42, 77.00, 76.57, 55.11, 52.36, 20.48. HRMS (ESI, Orbitrap): calcd for $C_9H_{12}NO_5$ $[M+H]^+$ 214.07100 found 214.07161.

(4-tosyloxazol-5-yl)methyl acetate (1c):
Yield: 91%; white solid, M.P. 85-87 °C; IR (KBr), 3453, 1744, 1595, 1499, 1234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.85 (s, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 5.54 (s, 2H), 2.45 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.80, 150.78, 149.52, 145.28, 138.50, 136.16, 129.83, 128.20, 54.51, 21.54, 20.37; HRMS (ESI, Orbitrap): calcd for $C_{13}H_{14}NO_5S$ $[M+H]^+$ 296.05872 found 296.05864.

Methyl 5-(methoxymethyl)oxazole-4-carboxylate (2a):
Yield: 86%, colourless oil; IR (KBr) 3412, 2956, 1741, 1680, 1517, 1440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 4.83 (s, 2H), 3.95 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.13, 150.41, 129.45, 63.37, 58.75, 52.304; HRMS (ESI, Orbitrap): calcd for $C_7H_{10}NO_4$ $[M+H]^+$ 172.06043 found 172.06054.

Ethyl 5-(methoxymethyl)oxazole-4-carboxylate (2b):
Yield: 93%; colourless oil, IR (KBr), 3465, 3128, 1720, 1613, 1376, 1282 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 4.82 (s, 2H), 4.39 (q, *J* = 14.2, 7.14 Hz, 2H), 3.42 (s, 3H), 1.40 (t, *J* = 14.3, 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.14, 154.15, 150.21, 129.46, 63.16, 61.11, 58.39, 13.95; HRMS (ESI, Orbitrap): calcd for $C_8H_{11}NO_4$ [M+Na] 208.05803 found 208.05785.

5-(methoxymethyl)-4-tosyloxazole (2c):
Yield : 90% light brown solid, M.P. 93-95 °C; IR (KBr) 3149, 2928, 1597, 1505, 1325 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 1H), 7.84 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 4.88 (s, 1H), 3.46 (s, 2H), 2.44 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.60, 150.78, 145.18, 136.54, 129.88, 128.20, 62.74, 58.82, 21.59; HRMS (ESI, Orbitrap): calcd for $C_{12}H_{14}NO_4S$ $[M+H]^+$ 268.06435 found 268.06388.

Methyl 5-(phenoxymethyl)oxazole-4-carboxylate (3a):
Yield 85%; yellow oil; IR (KBr) 3481, 3132, 1722, 1597, 1493, 1346 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.34-7.28 (m, 2H), 7.02-7.00 (m, 3H), 5.46 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.60, 157.65, 153.29, 150.53, 129.48, 121.70, 114.74, 59.46, 52.23; HRMS (ESI, Orbitrap): calcd for $C_{12}H_{12}NO_4$ $[M+H]^+$ 234.07663 found 234.07582.

Ethyl 5-(phenoxymethyl)oxazole-4-carboxylate (3b):
Yield: 92%; white solid, M.P. 74-75 °C; IR (KBr) 3390, 3120, 1712, 1629, 1501, 1324, 1196 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.30 (dd, *J* = 11.7, 4.3 Hz, 2H), 7.04 - 6.97 (m, 3H), 5.46 (s, 2H), 4.43 (q, *J* = 14.2, 7.1 Hz, 2H), 1.40 (t, *J* = 14.2, 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.12, 157.65, 153.09, 150.45, 129.69, 129.42, 121.62, 114.70, 61.34, 59.49, 14.03; HRMS (ESI, Orbitrap): calcd for $C_{13}H_{14}NO_4$ $[M+H]^+$ 248.09228 found 248.09180.

5-(phenoxymethyl)-4-tosyloxazole (3c):
Yield: 87%; brown solid, 122-124 °C; IR (KBr) 3146, 1593, 1493, 1324, 1230, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.86 (s, 1H), 7.34 (d, *J* = 7.5 Hz, 3H), 7.03 (d, *J* = 8.5 Hz, 2H), 5.51 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.53, 151.05, 150.39, 145.33, 138.42, 136.20, 130.29, 129.91, 129.64, 129.36, 128.28, 122.02, 115.00, 59.01, 21.64; HRMS (ESI, Orbitrap): calcd for $C_{17}H_{16}NO_4S$ $[M+H]^+$ 330.37824 found 330.07960.

Methyl 5-(benzyloxymethyl)oxazole-4-carboxylate (4a):
Yield 92%, colourless oil, IR (KBr), 3468, 1744, 1595, 1499, 1234 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.34-7.19 (m, 5H), 4.92 (s, 2H), 4.62 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.73, 154.63, 150.33, 137.11, 128.41, 127.97, 127.83, 72.99, 61.07, 52.22; HRMS (ESI, Orbitrap): calcd for $C_{13}H_{14}NO_4$ $[M+H]^+$ 248.09173 found 248.09154.

Ethyl 5-(benzyloxymethyl)oxazole-4-carboxylate (4b):
Yield 95%, yellow oil; IR (KBr) 3452, 1738, 1720, 1613, 1518, 1375 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.35 - 7.26 (m, 5H), 4.92 (s, 2H), 4.61 (s, 2H), 4.38 (q, *J* = 14.3, 7.1 Hz, 2H), 1.38 (t, *J* = 14.3, 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.32, 154.33, 150.28, 136.99, 128.37, 127.91, 127.77, 72.94,

61.28, 61.15, 14.11; HRMS (ESI, Orbitrap): calcd for $C_{14}H_{16}NO_4$ $[M+H]^+$ 262.10346 found 262.10737.

5-(benzyloxymethyl)-4-tosyloxazole (4c):
Yield 87%, brown sticky solid, 64-65 °C; IR (KBr) 3157, 2922, 1600, 1503, 1331 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.82 (s, 1H), 7.40 - 7.29 (m, 7H), 4.98 (s, 2H), 4.65 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.74, 150.70, 145.08, 138.10, 136.96, 136.51, 129.80, 128.39, 128.28, 128.14, 127.96, 127.82, 73.15, 60.62, 21.55; HRMS (ESI, Orbitrap): calcd for C18H18NO4S $[M+H]^+$ 344.09118 found 344.09535.

Methyl 5-((1,3-dioxoisoindolin-2-yl)methyl)oxazole-4-carboxylate (5a):

Yield: 92%; brown solid; 139-141 °C; IR (KBr) 3465, 1713, 1509, 1422, 1282, 1088, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 - 7.88 (m, 2H), 7.81 - 7.75 (m, 3H), 5.32 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.19, 161.60, 152.32, 149.81, 134.34, 131.78, 123.64, 52.35, 32.61; HRMS (ESI, Orbitrap): calcd for $C_{14}H_{11}N_2O_5$ $[M+H]^+$ 287.06625 found 287.06361.

Ethyl 5-((1,3-dioxoisoindolin-2-yl) methyl)oxazole-4-carboxylate (5b):
Yield: 91%; brown solid; 114-116 °C; IR (KBr) 3464, 1712, 1511, 1396, 1184, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 - 7.90 (m, 2H), 7.79 - 7.77 (m, 3H), 5.33 (s, 2H), 4.46 (q, *J* = 14.3, 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.22, 161.42, 152.12, 149.78, 134.34, 131.79, 123.64, 61.54, 32.66, 14.26; HRMS (ESI, Orbitrap): calcd for $C_{15}H_{13}N_2O_5$ $[M+H]^+$ 301.08080 found 301.08079.

2-((4-tosyloxazol-5-yl)methyl)isoindoline-1,3-dione (5c):
Yield: 87% ; white solid, 204-206 °C; IR (KBr) 3426, 1721, 1596, 1392, 1150, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.3 Hz, 2H), 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.77 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.72 (s, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 5.43 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.07, 150.42, 145.28, 136.27, 134.42, 131.72, 129.94, 128.57, 123.72, 32.01, 21.72; HRMS (ESI, Orbitrap): calcd for $C_{19}H_{15}N_2O_5S$ $[M+H]^+$ 383.06962 found 383.06999.

Methyl 5-((phenylthio)methyl)oxazole-4-carboxylate (6a):
Yield: 91%; yellow oil; IR (KBr) 3058, 1727, 1609, 1521, 1354, 1048, 955 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.40 - 7.34 (m, 2H), 7.31 - 7.23 (m, 3H), 4.45 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.79, 155.46, 149.77, 133.42, 132.17, 129.05, 127.88, 52.14, 29.26; HRMS (ESI, Orbitrap): calcd for $C_{12}H_{11}NO_3SNa$ $[M+Na]^+$ 272.03519 found 272.03560.

Ethyl 5-((phenylthio)methyl)oxazole-4-carboxylate (6b):
Yield: 93%; yellow oil; IR (KBr) 2923, 1718, 1608, 1374, 1315, 1045 cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ 7.77 (s, 1H), 7.39 - 7.35 (m, 2H), 7.27 - 7.24 (m, 3H), 4.46 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 159.03, 149.66, 132.08, 129.03, 127.82, 61.26, 29.25, 14.22; HRMS (ESI, Orbitrap): calcd for $C_{13}H_{14}NO_3S$ $[M+H]^+$ 264.06889 found 268.0637.

5-((phenylthio)methyl)-4-tosyloxazole (6c):
Yield: 83%; brown solid, 86-88 °C; IR (KBr) 2922, 1587, 1404, 1323, 1145, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.71 (s, 1H), 7.42 - 7.39 (m, 2H), 7.34 - 7.28 (m, 5H), 4.54 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.76, 150.23, 145.12, 136.55, 136.36, 133.39, 132.14, 130.03, 129.89, 129.27, 128.30, 128.01, 28.85, 21.74; HRMS (ESI, Orbitrap): calcd for $C_{17}H_{15}NO_3S_2$ $[M+H]^+$ 346.05661 found 346.05525.

(4-tosyloxazol-5-yl)methanol (7):
Yield: 89%; brown sticky solid, IR (KBr) 23541, 1593, 1506, 1323, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.92 (d, *J* = 8.3 Hz, 2H), 7.81 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.99 (s, 2H), 3.35 (bs, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.83, 150.27, 145.51, 136.99, 136.18, 130.07, 128.19, 54.64, 21.72; HRMS (ESI, Orbitrap): calcd for $C_{11}H_{11}NO_4SNa$ $[M+Na]^+$ 276.03010 found 276.03018.

4-tosyloxazole-5-carbaldehyde (8):
Yield: 87%; brown semi solid; IR (KBr) 3412, 2922, 1691, 1608, 1457, 1151cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.97 (s, 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.29, 153.00, 130.36, 128.94, 126.42, 114.80, 22.51; HRMS (ESI, Orbitrap): calcd for $C_{11}H_{19}NO_4SNa$ $[M+Na]^+$ 274.01445 found 274.01449.

Methyl 1-(2-methoxy-2-oxoethyl)-1H-imidazole-4-carboxylate (11)
Yield: 95%; white solid; 141-143 °C; IR (KBR) 3462, 1716, 1533, 1342, 1180, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.52 (s, 1H), 4.75 (s, 2H), 3.85 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 167.24, 163.02, 138.78, 133.86, 126.25, 53.01, 51.65, 48.12; HRMS (ESI, Orbitrap): calcd for $C_8H_{11}N_2O_4$ $[M+H]^+$ 199.07133 found 199.07139

Acknowledgements

The authors thank the Department of Science and Technology (DST) New Delhi, India, for financial support. The authors are grateful to the Director, CSIR-IICT for providing the necessary infrastructure. D. K. T. is grateful to Dr. P. M. Chincholkar for his valuable suggestions.

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