Triphenylphosphine (PPh_3) Catalyzed Erlenmeyer Reaction for Azlactones under Solvent-free Conditions

Alapati Mohan Lakshmi Punna Rao,[a,b]* Abburi Sridhar Rao,[a,b] Mukkamala Saratchandra Babu,[a] and M. Krishnaji Rao[b]

[a]Department of Chemistry, GITAM Institute of Science, GITAM University, Visakhapatnam 530045, India
[b]Quality Control Department, Unit-II, DIVIS Laboratories Ltd., Visakhapatnam 531163, India
*E-mail: mohan.alapati9@gmail.com

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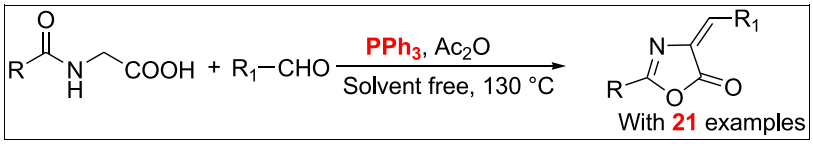

This study presents triphenylphosphine catalyzed process for the synthesis of azlactones and their derivatives using hippuric and substituted aromatic aldehydes. The methodology also found to be effective for the synthesis of azlactones from 5-(2,6-dichlorophenyl)-3-methyl-1,2-oxazol-4-yl carbonyl amino acetic acid and offers several advantages such as solvent-free conditions, excellent yields, simple procedure, mild conditions, and reduced environmental consequences.

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INTRODUCTION

Oxazolones are an important class of heterocyclic compounds because of their wide range of biological properties, such as their peptides [1], analgesic [2], antibacterial and antifungal [3], biosensors [4], anti-obesity [5], anticancer [6], antimicrobial [7], antitumor [8], and antidiabetic activities [9]. Moreover, they are used in the asymmetric synthesis of amino acids [10] and in active site titration of enzymes [11]. Because of their biological importance, many synthetic routes are proposed for oxazolones.

The most well-known route for the synthesis of azlactones, involves the direct condensation of aromatic aldehydes and hippuric acid with a stoichiometric amount of fused sodium acetate as a base in the presence of acetic anhydride as the dehydrating agent, which is known as Erlenmeyer–Plochl reaction [12,13]. Further number of methods have been used for the synthesis of oxazolones such as Nano-MgO [14], $Bi(OTf)_3$ [15], $Pb(OAc)_2$ [16], I_2 [17], K_3PO_4 [18], Al_2O_3–H_3BO_3 [19], $Bi(OAc)_3$ [20], $[C_6(MIm)_2]_2W_{10}O_{32}$, $2H_2O$ [21], Montmorillonite K-10 [22], and alumina [23], instead of sodium acetate. Microwave-assisted reactions have also been employed successfully in the synthesis of the oxazolones [24]. Most of the reported methods are suitable for the synthesis of oxazolones and their derivatives, but these methods require high temperature, longer reaction times results in unsatisfactory yields. In this regard, a simple, efficient, and environmentally friendly method is highly desirable for the synthesis of azlactones.

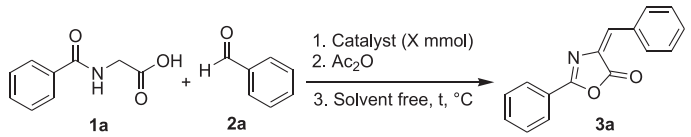
Triphenylphosphine (PPh_3) has been reported as environmentally friendly, mild, and commercially available catalyst in several organic transformations such as the traditional Morita Baylis–Hillman reaction [25], synthesis of o-vinyloximes [26], [3 + 2] cycloaddition reactions [27], Michael Addition [28], and Reductive Cyclization [29]. In this report, we have adopted the eco-friendly PPh_3 as catalyst for the synthesis 4-arylidene-2-phenyl-5(4*H*)-oxazolones and 4-(substitutedarylidene)-2-[5-(2,6-dichlorophenyl)-3-methyl isoxazol-4-yl]oxazol-5(4*H*)-one.

RESULT AND DISCUSSION

First, to investigate the reaction conditions for the synthesis of substituted oxazolones, we have chosen the reaction of hippuric acid, aromatic aldehydes under solvent-free condition as a model reaction (Scheme 1), and the results are summarized in Table 1.

Thus, hippuric acid (**1a**) (14 mmol) was treated with benzaldehyde (**2a**) (11.6 mmol) under solvent free at 130°C without any catalyst. The product was not obtained (Table 1, entry 1). Therefore, our efforts were focused on the search for a suitable base catalyst. Initially, NH_4OAc (5 mol%) was chosen as a catalyst to carry out this reaction. As a result, long reaction times with poor yields were observed (Table 1, entry 2). In addition, the catalytic activity of other catalysts such as K_2CO_3, $Ca(OAc)_2$, $CaCO_3$, $Yb(OTf)_3$, and $Cu(OTf)_2$ were tested (Table 1, entries 3–7). Under the same conditions, triphenylphosphine was found to be the excellent catalyst for azlactone synthesis. On the other hand, $Yb(OTf)_3$ shows moderate catalytic activity , and K_2CO_3 and $Cu(OTf)_2$ give the unsatisfactory yields. Encouraged by these results, we turned our attention to find out the effect of amount of catalyst; reaction temperature and time were investigated (Table 1, entries 8–14). Amounts of 5, 10, and 15 mol% of PPh_3 were used, and it was found that 10 mol% of PPh_3 was enough to accomplish the reaction (Table 1, entry 9).

Scheme 1. Model reaction.



When catalyst loading was dropped to 5 mol%, only 73% of the desired product was afforded (Table 1, entry 8). Further, reaction temperature was also studied; the reaction at room temperature did not result in desired product (Table 1, entry 11). The yield 63% was low at 120°C (Table 1, entry 12), and increasing the temperature did not help to obviously improve the yield (Table 1, entries 13–14). Moreover, the reaction could be performed on a large scale and gave satisfactory yield (Table 1, entry 9). Finally, we achieved an optimized condition using 10 mol% of PPh_3 as the catalyst at 130°C.

With the optimized conditions in hand, we focused our study on different benzaldehydes for the synthesis of wide range of azlactone derivatives. In this reaction (Scheme 2), we have used hippuric acid and aromatic aldehydes derivatives. As shown in Table 2, both the electron-donating (Table 2, entries 2–5) and the electron-withdrawing (Table 2, entries 6–10) substitutions on aromatic aldehydes were effective for the reaction, providing the products good to excellent yields under the optimized conditions.

Encourage by their results, we further switch hippuric acid to 5-(2,6-dichlorophenyl)-3-methylisoxazole-4-carboxylic acid with aromatic aldehyde derivatives that were investigated under the same reaction conditions. The results are summarized in Table 3. It was observed that a variety of aromatic aldehydes was effective for this reaction and afforded the corresponding products in good yields (Scheme 3).

To excellent a suitable mechanism was for the synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolone **3a** as shown in Scheme 4.

On the basis of the above results and previous reports [30], a plausible mechanism was proposed and shown in Scheme 4. This mechanism involves the initial activation of carboxylic group of hippuric acid **1a** using acetic anhydride, followed by cyclization to form **A**, which was confirmed by proton nuclear magnetic resonance (^{1}H NMR), carbon-13 nuclear magnetic resonance (^{13}C NMR), and electrospray ionization mass spectrometry (ESI-MS). Deprotonation of **A** in presence of triphenylphosphine affords anion **B**. Compound **C** was formed by the nucleophilic attack of **B** on the carbonyl carbon of **2a** followed by the protonation. Finally, dehydration of compound **C** furnished the corresponding product **3a**.

In conclusion, we have demonstrated a practical application of PPh_3 catalyzed Erlenmeyer reaction under solvent-free condition, with a wide range of substrate scope even hydroxy substituted aldehydes can undergo the desired condensation affording quantitative yields. In addition, the notable advantages of this procedure are (a) no need of neutralization and (b) no need of further purification. The reactions are conducted under mild conditions to afford 4-arylidene-2-phenyl-5(4)-oxazolones and 4-(substituted arylidene)-2-[5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl] oxazol-5(4*H*)-ones in good to excellent yields. These results suggests that PPh_3 is eco-friendly and cheap catalyst and can be employed for industrial applications for the synthesis of wide range of heterocyclic compounds.

Table 1

Synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones (**3a**) under different optimization conditions.

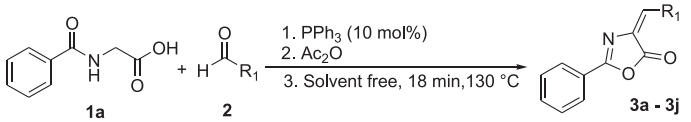
Entry	Catalyst (mol %)	Temperature (°C)	Time (min)	Yield (%)[a]
1	—	130	50	ND[b]
2	NH_4OAc (5)	130	60	25
3	K_2CO_3 (5)	130	55	32
4	$Ca(OAc)_2$ (5)	130	50	50
5	$CaCO_3$ (5)	130	50	45
6	$Yb(OTf)_3$ (5)	130	50	75
7	$Cu(OTf)_2$ (5)	130	50	ND[b]
8	PPh_3 (5)	130	18	73
9	PPh_3 (10)	130	18	95
10	PPh_3 (15)	130	18	94
11	PPh_3 (10)	25	60	ND[b]
12	PPh_3 (10)	120	35	63
13	PPh_3 (10)	135	18	92
14	PPh_3 (10)	140	18	89

[a]Isolated yield after column chromatography.
[b]No product was detected.

EXPERIMENTAL

All chemicals were purchased from Merck (Kenilworth, NJ) or Sigma-Aldrich (St. Louis, MO). All compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Melting point (m.p.): Buchi-530 capillary apparatus; open capillary method and are uncorrected. IR spectra: Shimadzu IR-Affinity spectrometer, KBr disks; ν in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra: Bruker Advance DPX 400 MHz; at 400(^{1}H) and 100 (^{13}C) spectrometer in $CDCl_3$; DMSO-d_6; δ in parts per million, TMS as internal standard, j in Hz. Data

Scheme 2. Preparation of product **3a–3j**.



reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in Hertz, integration assignment]. ESI-MS: JEOL SX 102/DA-6000 mass spectrometer; in m/z.

General Procedure for Synthesis of 4-arylidene-2-phenyl-5 (4*H*)-oxazolones (3a). To the aromatic aldehyde (1.63 g, 11.6 mmol), hippuric acid (2.5 g, 14 mmol), anhydrous acetic anhydride (3.14 g, 31 mmol), and 10 mol% triphenylphosphine. The reaction mixture was stirred at 130°C for 18 min under solvent-free condition. After completion of the reaction (thin-layer chromatography monitoring), reaction mixture was cooled to room temperature, 5 mL of 95% ethyl alcohol was added, and a yellow solid was obtained. The yellow solid was filtered off and washed with water and recrystallized from acetone to afford 4-arylidene-2-phenyl-5(4)-oxazolones (**3a**) in 94% yield.

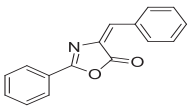
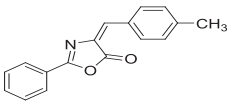
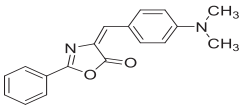
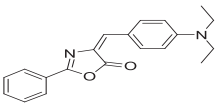
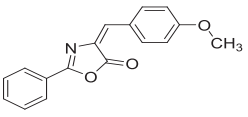
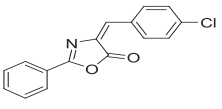
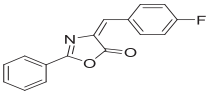
General Procedure for Synthesis of 4-benzylidene-2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)oxazol-5(4*H*)-one (5a). To the aromatic aldehyde (1.63 g, 11.6 mol), 4-benzylidene-2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)oxazol-5(4*H*)-one (5.6 g, 14 mmol), anhydrous acetic anhydride (3.14 g, 31 mol), and 10 mol % triphenylphosphine. The reaction mixture was stirred at 130°C for 18 min under solvent-free condition. After completion of the reaction (thin-layer chromatography monitoring), reaction mixture was cooled to room temperature, 5 mL of 95% ethyl alcohol was added, and a pale-yellow solid was obtained. The pale-yellow solid was filtered off and washed with water and recrystallized from acetone to afford 4-benzylidene-2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)oxazol-5(4*H*)-one (**5a**) in 91% yield.

2-phenyloxazol-5(4H)-one (A). Yield 84%. m.p: 84–86°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.42 (s, 2H, methylene CH_2), 7.48–7.51 (m, 2H, Ar-H), 7.58 (t, J = 7.2 Hz, 2H, ArH), 7.99–8.00 (m, 1H, ArH), ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 55.0, 125.8, 127.8, 128.8, 132.8, 163.5, 175.9; ESI-MS: m/z 162.20 $[M+1]^+$.

4-benzylidene-2-phenyloxazol-5(4H)-one (3a). Yield 94%. m.p: 168–170°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 6.84–6.85 (m, 1H, ArH), 7.23 (s, 1H, benzylidene CH), 7.61–7.65 (m, 3H, ArH), 7.69–7.73 (t, 1H, ArH), 8.10 (s, 1H, ArH), 8.11 (d, J = 7.6 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 114.2, 117.5, 120.6, 125.1, 127.3, 127.9, 129.3, 133.5, 148.0, 149.9, 162.2, 166.5; ESI-MS: m/z 249 $[M+1]^+$ *Anal*. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.15; H, 4.43; N, 5.61.

Table 2

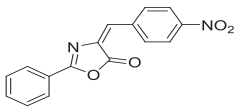
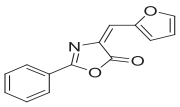
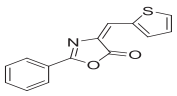
Erlenmeyer–Plochl reaction of substituted aromatic aldehydes with hippuric acid promoted by PPh_3 (**3a–3j**).

S. No	Product	R_1	Yield (%)[a]
3a		Ph	94
3b		4-MePh	86
3c		4-N(Me)$_2$Ph	92
3d		4-N(Et)$_2$Ph	96
3e		4-OMePh	90
3f		4-ClPh	83
3g		4-FPh	86

(*Continued*)

Table 2

(Continued)

S. No	Product	R_1	Yield (%)[a]
3h		4-NO_2Ph	91
3i		2-furyl	80
3j		2-thionyl	86

[a]Isolated yield after column chromatography.

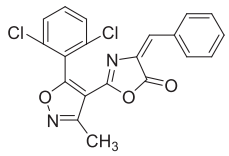
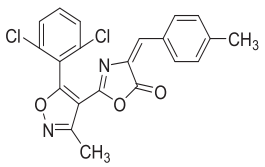
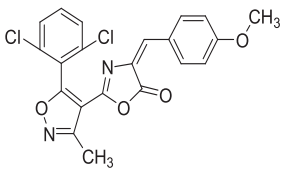
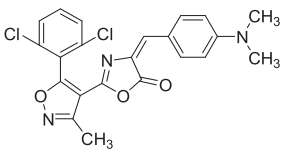
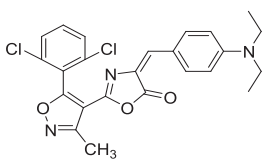
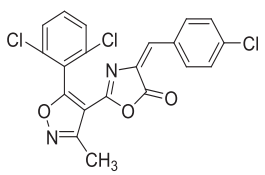
4-(4-methylbenzylidene)-2-phenyloxazol-5(4H)-one (3b). Yield 86%. m.p: 146–148°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.39 (s, 3H, CH_3), 7.25 (s,1H, benzylidene CH), 7.29 (d, J = 8.0 Hz 2H, ArH), 7.52–7.65 (m, 3H, ArH), 8.12 (d, J = 8.1 Hz 2H, ArH), 8.12–8.17(m, 2H, ArH) ; ^{13}C NMR (100 MHz, DMSO, δ, ppm): 22.8, 125.4, 128.2, 128.6, 130.0, 131.4, 133.1, 133.5, 133.6, 134.9, 142.0, 163.5, 167.2; ESI-MS: m/z 264 $[M+1]^+$ *Anal*. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.58; H, 4.95; N, 5.34.

4-(4-(dimethylamino)benzylidene)-2-phenyloxazol-5(4H)-one (3c). Yield 92%. m.p: 213–216°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 3.16 (s, 6H, 2xCH_3), 6.85 (d, J = 8.4 Hz, 2H, ArH), 7.16(s, 1H, benzylidene CH), 7.50–7.57 (m, 3H, ArH), 8.21–8.26(m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 38.6, 110.3, 122.8, 126.4, 127.3, 128.1, 128.8, 132.2, 134.6, 154.6, 161.5, 168.4; ESI-MS: m/z 293 $[M+1]^+$ *Anal*. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.91; H, 5.54; N, 9.60.

4-(4-(diethylamino)benzylidene)-2-phenyloxazol-5(4H)-one (3d). Yield 96%. m.p: 193–195°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 1.01 (t, 6H, 2×CH_3), 3.01 (s, 4H, 2xCH_2), 6.81 (d, J = 8.8 Hz, 2H, ArH), 7.14(s, 1H, benzylidene CH), 7.52–7.59 (m, 3H, ArH), 8.16–8.21(m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 20.1, 34.6, 114.6, 123.6, 125.3, 127.3, 128.6, 128.8, 131.4, 134.1, 156.3, 163.4, 169.4; ESI-MS: m/z 321 $[M+1]^+$ *Anal*. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.93; H, 6.32; N, 8.76.

Table 3

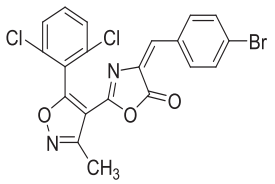
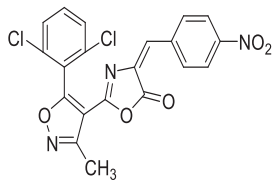
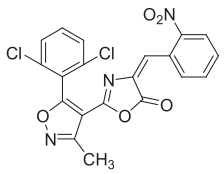
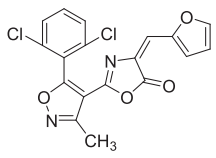
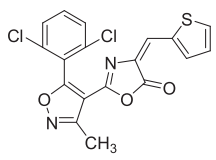
Erlenmeyer–Plochl reaction of substituted aromatic aldehydes with 5-(2,6 dichloro phenyl)-3-methylisoxazole-4-carboxylic acid promoted by PPh_3 (**5a–5k**)

S. No	Product	R_1	Yield (%)[a]
5a		Ph	91
5b		4-MePh	88
5c		4-MeOPh	90
5d		4-N$(Me)_2$Ph	89
5e		4-N$(Et)_2$Ph	87
5f		4-ClPh	89

(*Continued*)

Table 3

(Continued)

S. No	Product	R_1	Yield (%)[a]
5g		2-BrPh	80
5h		4-NO_2Ph	85
5i		2-NO_2Ph	75
5j		2-furyl	90
5k		2-thionyl	92

[a]Isolated yield after column chromatography.

4-(4-methoxybenzylidene)-2-phenyloxazol-5(4H)-one (3e). Yield 90%. m.p: 160–163°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 3.78(s, 3H, OCH_3), 6.83(d, J = 8.6 Hz, 2H, ArH), 7.24(s, 1H, benzylidene CH), 7.46–7.53(m, 3H, ArH), 8.09–8.14 (m, 2H, ArH), 8.12 (d, J = 8.7 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 56.2, 114.6, 125.2, 126.6, 127.9, 128.6, 131.2, 131.8, 132.9, 135.1, 158.3, 162.6, 167.6; ESI-MS: m/z 280 $[M+1]^+$ *Anal*. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.16; H, 4.65; N, 5.01.

4-(4-chlorobenzylidene)-2-phenyloxazol-5(4H)-one (3f). Yield 83%. m.p: 205–207°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 7.14 (s, 1H, benzylidene CH), 7.39 (d, J = 8.0 Hz, 2H, ArH), 7.51–7.60 (m, 3H, ArH), 8.14–8.17 (m, 3H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 124.6, 128.4, 129.4, 129.6, 130.4, 132.1, 133.52, 133.55, 133.7, 137.4, 162.7, 168.5; ESI-MS: m/z 284 $[M+1]^+$ *Anal*. Calcd for $C_{16}H_{10}Cl\ NO_2$: C, 67.74; H, 3.55; Cl, 12.50; N, 4.94. Found: C, 67.70; H, 3.54; Cl, 12.52; N, 4.97.

4-(4-fluorobenzylidene)-2-phenyloxazol-5(4H)-one (3g). Yield 86%. m.p: 162–164°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 7.14–7.17 (m, 2H,), 7.21 (s, 1H, benzylidene CH), 7.48–7.55(m, 3H, ArH), 8.11 (d, J = 7.6 Hz, 2H, ArH), 8.26–8.31(m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 118.3, 118.9, 125.3, 128.1, 128.6, 129.8, 130.6, 132.4, 133.9, 135.1, 135.6, 161.4, 163.6, 167.9; ESI-MS: m/z 268 $[M+1]^+$ *Anal*. Calcd for $C_{16}H_{10}FNO_2$: C, 71.91; H, 3.77; Cl, 7.11; N, 5.24. Found: C, 71.88; H, 3.78; Cl, 7.12; N, 5.25.

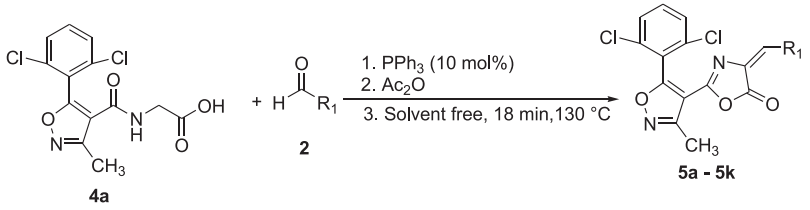
4-(4-nitrobenzylidene)-2-phenyloxazol-5(4H)-one (3h). Yield 91%. m.p: 238–240°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 7.12 (s, 1H, benzylidene CH), 7.51–7.62 (m, 3H, ArH), 8.21 (d, J = 7.6 Hz, 2H, ArH), 8.31–8.45 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 121.9, 125.0, 127.6, 128.8, 129.5, 132.5, 134.2, 136.6, 139.1, 148.6, 165.7, 166.8; ESI-MS: m/z 295 $[M+1]^+$ *Anal*. Calcd for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.28; H, 3.45; N, 9.53.

4-((furan-2-yl)methylene)-2-phenyloxazol-5(4H)-one (3i). Yield 80%. m.p: 172–174°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 6.84–6.85 (m, 1H, ArH), 7.23 (s, 1H, benzylidene CH), 7.61–7.65 (m, 3H, ArH), 7.69–7.73 (t, 1H, ArH), 8.10 (s, 1H, ArH), 8.11 (d, J = 7.6 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 114.2, 117.5, 120.6, 125.1, 127.3, 127.9, 129.3, 133.5, 148.0, 149.9, 162.2, 166.5; ESI-MS: m/z 240 $[M+1]^+$ *Anal*. Calcd for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.23; H, 3.82; N, 5.89.

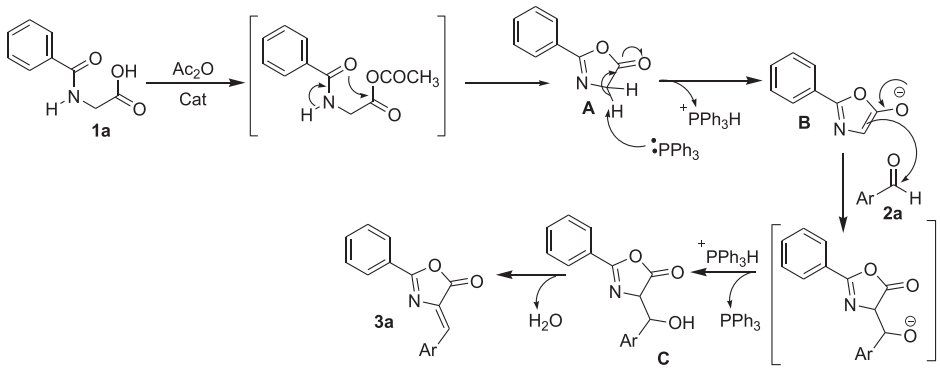
2-phenyl-4-((thiophen-2-yl)methylene)oxazol-5(4H)-one (3j). Yield 86%. m.p: 156–159°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 7.26 (t, 1H), 7.62–7.74 (m, 4H, ArH), 7.86 (*d*, J = 3.2 Hz, 1H), 8.01–8.10 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 124.9, 125.1, 127.7, 128.2, 129.3, 130.1, 133.4, 136.3, 136.7, 137.1, 161.6, 166.2; ESI-MS: m/z 256 $[M+1]^+$ *Anal*. Calcd for $C_{14}H_9NO_2S$: C, 65.87; H, 3.55; N, 5.49. Found: C, 65.92; H, 3.53; N, 5.46.

4-benzylidene-2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)oxazol-5(4H)-one (5a). Yield 91%. m.p: 166–168°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.86(s, 3H, CH_3), 7.21(s, 1H, benzylidene CH), 7.31(t, 2H, ArH), 7.66(d, J = 7.2 Hz, 1H, ArH), 7.72–7.77(m, 3H, ArH); ^{13}C

Scheme 3. Preparation of product **5a–5k**.



Scheme 4. Plausible mechanism.



NMR (100 MHz, DMSO, δ, ppm): 13.8, 105.2, 127.3, 128.7, 129.2, 131.42, 131.45, 131.6, 132.4, 132.9, 133.4, 134.9, 156.4, 158.3, 166.2, 172.5; ESI-MS: m/z 399 $[M]^+$ *Anal*. Calcd for $C_{20}H_{12}Cl_2N_2O_3$: C, 60.17; H, 3.03; N, 7.02. Found: C, 60.11; H, 3.07; N, 7.04.

4-(4-methylbenzylidene)-2-[5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)]oxazol-5(4H)-one (5b). Yield 88%. m.p: 156–159°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 2.38 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 7.15 (d, J = 6.3 Hz, 2H, ArH), 7.19 (s, 1H, benzylidene CH), 7.55 (d, J = 6.6 Hz, 2H, ArH), 7.75–7.84 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO, δ, ppm): 13.7, 21.6, 105.2, 127.3, 128.6, 129.6, 130.5, 130.7, 132.6, 133.0, 134.8, 142.3, 155.8, 158.1, 166.2, 174.8; ESI-MS: m/z 414 $[M+1]^+$ *Anal*. Calcd for $C_{21}H_{14}$ $Cl_2N_2O_3$: C, 61.03; H, 3.41; N, 6.78. Found: C, 61.09; H, 3.38; N, 6.75.

4-(4-methoxybenzylidene)-2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)oxazol-5(4H)-one (5c). Yield 90%. m.p: 156–159°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 2.87(s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.87 (d, J = 9.0 Hz, 2H, ArH), 7.21 (s, 1H, benzylidene CH), 7.67 (d, J = 9.0 Hz, 2H, ArH), 7.75–7.81 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO, δ, ppm): 13.5, 21.6, 105.4, 127.3, 128.6, 129.8, 130.4, 130.6, 131.4, 132.8, 133.1, 134.7, 142.5, 155.7, 158.3, 166.3, 174.6; ESI-MS: m/z 430 $[M+1]^+$ *Anal*. Calcd for $C_{21}H_{14}$ $Cl_2N_2O_4$: C, 58.76; H, 3.29; N, 6.53. Found: C, 58.79; H, 3.28; N, 6.52.

4-(4-(dimethylamino)benzylidene)-2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)oxazol-5(4H)-one(5d). Yield 89%. m.p: 232–234°C. ^{1}H NMR (300 MHz, DMSO) δ: 2.34 (s, 3H, CH_3), 2.98 (s, 6H, 2xCH_3), 7.18 (d, J = 8.1 Hz, 2H, ArH), 7.22 (s, 1H, benzylidene CH), 7.58 (d, J = 8.4 Hz, 2H, ArH), 7.75–7.83 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO) δ : 13.8, 22.4, 40.1, 74.2, 105.9, 111.4, 121.6, 126.6, 127.9, 128.3, 130.8, 133.6, 134.8, 136.1, 152.2, 153.5, 158.2, 167.2, 173.2, 203.1. ESI-MS: m/z 443 $[M+1]^+$ *Anal*. Calcd for $C_{22}H_{17}$ $Cl_2N_3O_3$: C, 59.74; H, 3.87; N, 9.50. Found: C, 59.66; H, 3.93; N, 9.52.

4-(4-(diethylamino)benzylidene)-2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)oxazol-5(4H)-one (5e). Yield 87%. m.p: 244–246°C. ^{1}H NMR (300 MHz, DMSO) δ: 1.18 (t, 6H, 2xCH_3), 2.81 (s, 3H, CH_3), 3.46 (q, 4H, 2xCH_2), 6.52 (d, J = 9.0 Hz, 2H, ArH), 7.08 (s, 1H, benzylidene CH), 7.55 (d, J = 9.0 Hz, 2H, ArH), 7.72–7.79 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO) δ : 12.6, 13.6, 44.1, 105.3, 111.5, 120.5, 124.7, 127.8, 128.8, 132.6, 133.6, 134.8, 135.3, 150.4, 152.5, 157.9, 166.7, 173.1; ESI-MS: m/z 471 $[M+1]^+$ *Anal*. Calcd for $C_{24}H_{21}Cl_2N_3O_3$: C, 61.29; H, 4.50; N, 8.93. Found: C, 61.23; H, 4.54; N, 5.91.

4-(4-chlorobenzylidene)-2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)oxazol-5(4H)-one (5f). Yield 89%. m.p: 161–163°C. ^{1}H NMR (300 MHz, DMSO) δ : 2.86 (s, 3H, CH_3), 7.24 (s, 1H, benzylidene CH), 7.36 (d, J = 8.7 Hz, 2H, ArH), 7.61 (d, J = 8.4 Hz, 2H, ArH), 7.73–7.84 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO) δ: 13.7, 105.0, 127.1, 128.8, 129.1, 129.7, 131.9, 132.3, 133.1, 133.8, 134.9, 136.4, 156.8, 158.1, 165.8, 175.4; ESI-MS: m/z 433 $[M+1]^+$ *Anal*. Calcd for $C_{20}H_{11}Cl_3N_2O_3$: C, 55.39; H, 2.56; N, 5.86. Found: C, 70.23; H, 3.82; N, 5.89.

4-(4-bromobenzylidene)-2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)oxazol-5(4H)-one (5g). Yield 80%. m.p: 168–170°C. ^{1}H NMR (300 MHz, DMSO) δ: 2.86 (s, 3H,

CH_3), 7.21 (s, 1H, benzylidene CH) 7.52–7.56 (m, 4H, ArH), 7.76–7.78 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO) δ: 13.4, 105.1, 125.4, 127.0, 128.9, 129.8, 131.9, 132.1, 132.5, 133.6, 133.9, 134.6, 156.8, 158.2, 165.6, 175.6; ESI-MS: m/z 479 $[M+1]^+$ *Anal.* Calcd for $C_{20}H_{11}BrCl_2N_2O_3$: C, 50.24; H, 2.32; N, 5.86. Found: C, 50.29; H, 2.28; N, 5.85.

4-(4-nitrobenzylidene)-2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)oxazol-5(4H)-one (5h). Yield 85%. m.p: 170–173°C. ^{1}H NMR (300 MHz, DMSO) δ: 2.89 (s, 3H, CH_3), 7.31 (s, 1H, benzylidene CH), 7.76–7.86 (m, 3H, ArH), 7.87 (d, J = 9.0 Hz, 2H, ArH), 8.11–8.15 (m, 2H, ArH); ^{13}C NMR (75 MHz, DMSO) δ: 13.6, 103.8, 123.8, 127.2, 127.5, 128.8, 132.8, 133.0, 134.3, 134.9, 139.5, 148.0, 155.5, 158.4, 165.8 176.3; ESI-MS: m/z 445 $[M+1]^+$ *Anal*. Calcd for $C_{20}H_{11}Cl_2N_3O_5$: C, 54.07; H, 2.50; N, 9.46. Found: C, 54.13; H, 2.46; N, 9.44.

4-(2-nitrobenzylidene)-2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)oxazol-5(4H)-one (5i). Yield 75%. m.p: 179–181°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.88 (2, 3H, CH_3), 7.18 (s, 1H, benzylidene CH), 7.64–7.74 (m, 5H, ArH), 7.95 (d, J = 5.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 13.3, 104.8, 125.4, 126.7, 128.1, 128.2, 128.6, 132.6, 134.5, 136.3, 136.6, 137.0, 154.7, 157.4, 165.0, 174.8; ESI-MS: m/z 445 $[M+1]^+$ *Anal*. Calcd for $C_{20}H_{11}Cl_2N_3O_5$: C, 54.07; H, 2.50; N, 9.46. Found: C, 54.11; H, 2.48; N, 9.44.

2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)-4-((furan-2-yl)methylene)oxazol-5(4H)-one (5j). Yield 90%. m.p: 216–218°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.91 (s, 3H, CH_3), 6.67–6.71 (m, 2H, ArH), 7.14 (s, 1H, benzylidene CH), 7.72–7.75 (m, 3H, ArH), 7.98 (d, J = 1.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 13.3, 104.8, 114.0, 116.1, 118.0, 120.1, 126.9, 128.1, 128.4, 132.7, 134.5, 134.6, 147.9, 155.4, 157.6, 165.1, 174.9; ESI-MS: m/z 390 $[M+1]^+$ *Anal*. Calcd for $C_{18}H_{10}Cl_2N_2O_4$: C, 55.55; H, 2.59; N, 7.20. Found: C, 55.50; H, 2.63; N, 7.21.

2-(5-(2,6-dichlorophenyl)-3-methylisoxazol-4-yl)-4-((thiophen-2-yl)methylene)oxazol-5(4H)-one (5k). Yield 92%. m.p: 196–198°C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.88 (2, 3H, CH_3), 7.18 (s, 1H, benzylidene CH), 7.64–7.74 (m, 5H, Ar-H), 7.95 (d, J = 5.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 13.3, 104.8, 125.4, 126.7, 128.1, 128.2, 128.6, 132.6, 134.5, 136.3, 136.6, 137.0, 154.7, 157.4, 165.0, 174.8; ESI-MS: m/z 406 $[M+1]^+$ *Anal*. Calcd for $C_{18}H_{10}Cl_2N_2O_3S$: C, 53.35; H, 2.49; N, 6.91. Found: C, 53.33; H, 2.46; N, 6.96.

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