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# ORGANOCATALYZED THREE-COMPONENT SYNTHESIS OF ISOXAZOL-5(4*H*)-ONES UNDER AQUEOUS CONDITIONS

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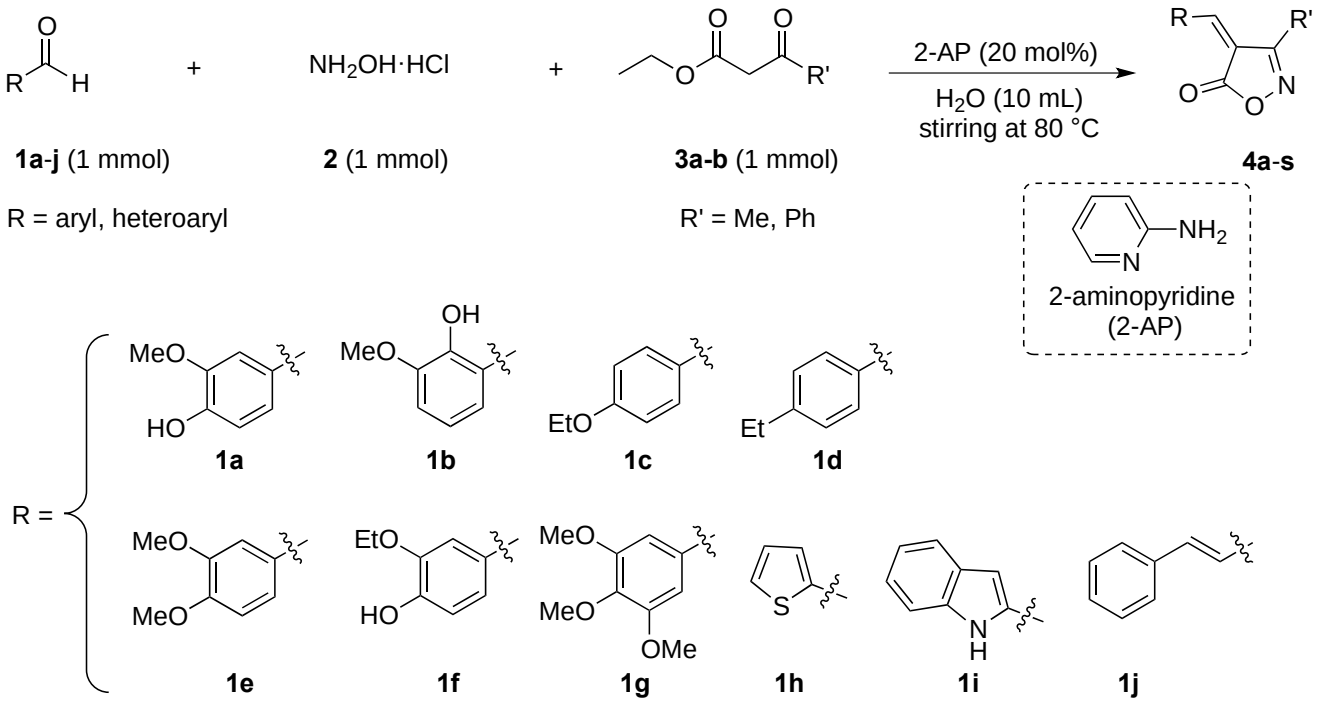
**Abstract** – The three-component cyclocondensation was performed using various frequently available aryl/heteroaryl aldehydes, hydroxylamine hydrochloride, and *β*-ketoesters in water as a green reaction medium at 80 °C. In this reaction, isoxazol-5(4*H*)-ones were obtained in the presence of 2-aminopyridine as an efficient and low-cost organocatalyst. The present methodology offers sustainable approach with appreciable yields of the desired heterocycles. This procedure has expectant features, including shorter reaction times, easy separation of pure products, avoiding the hazardous organic solvents, simplicity experimental procedure, operationally simple, and eco-friendly. The heterocyclic structures were characterized using physical properties and analysis of spectral data.

Isoxazoles are the top 10% most commonly used heterocycles in drug discovery.[1] Derivatives of this attractive five-membered heterocyclic ring are found in various natural and medicinal products.[1] Isoxazol-5(4*H*)-ones, on the other hand, have widely been shown antibacterial, antifungal, androgen receptor antagonist, tyrosinase inhibitory, SIRT1 inhibitory, anti-obesity, anti-HIV, antioxidant, anticancer, fungicide and insecticide properties activities.[2] As reported, the compounds have been studied in photovoltaic cells,[3] monochromatic terahertz difference frequency,[4] and laser dyes.[5] Isoxazol-5(4*H*)-ones are a representative class of isoxazoles that have been used as precursors in the synthesis of other interesting organic molecules.[6] The cyclization of *O*-propioloyl/propargylic oximes,[7] the reaction of ethyl acetoacetate and hydroxylamine hydrochloride followed condensation with aromatic aldehydes, and condensation of 1,3-dicarbonyls with benzaldoximes[8] are straightforward methods used to synthesis of isoxazol-5(4*H*)-ones. Significant development has been made in reviewing different routes for the construction of an isoxazol-5(4*H*)-one skeleton.[9]

Water as a universal solvent in which the vast majority of interactions occur in living systems have other unique properties, including abundance, cost-effectiveness, non-flammability, availability, non-hazardous, non-toxic, uniquely redox-stable, clean, and recyclable medium. Thus, water is preferred compared to organic solvents. For these reasons, the implementation of synthetically useful chemical reactions in the aquatic medium has attracted the attention of many chemists from the point of view of green chemistry as well as economically.[11]

Recently, 2-aminopyridine (2-AP) has been used as commercial availability, low cost, environmental friendliness, and reusability organocatalyst for the synthesis of various heterocyclic molecules, including tetrahydro-4*H*-chromenes,[12] polyfunctionalized 4*H*-pyrans,[13] 1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxamide, 1*H*-pyrazolo[1,2-*b*]phthalazine, 4*H*-pyrano[2,3-c]pyrazole, and 4*H*-benzo[*g*]chromenes.[14] In this work, the catalytic effect of 2-AP toward synthesis of isoxazol-5(4*H*)-ones (**4a**-**s**) has been explored *via* a three-component cyclocondensation of aryl/heteroaryl aldehydes (**1a**-**j**), hydroxylamine hydrochloride (**2**) and *β*-ketoesters (**3a**-**b**) (Scheme 1).

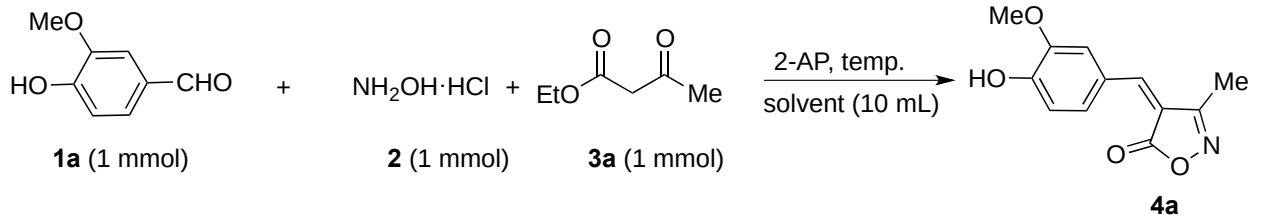



**Scheme 1.** Three-component cyclocondensation for the synthesis of isoxazol-5(4*H*)-ones (**4a**-**s**) in the presence of 2-AP

Firstly, the multicomponent reaction of vanillin (**1a**), hydroxylamine hydrochloride (**2**), and ethyl acetoacetate (**3a**) was selected as the model reaction. The effect of various parameters such as solvents, amounts of catalyst, and temperatures was checked on the reaction (Table 1). When the reaction was

performed without the use of a catalyst in water, it did not complete and the 4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (**4a**) was obtained with only 5% yield (Table 1, Entry 1). Under this condition, the change of other parameters did not cause a significant change on the reaction time or the yield of the reaction. After this result, it was decided to use a catalyst. By adding catalytic amounts of 2-aminopyridine (2-AP) to the reaction mixture in water at room temperature, an improvement in the reaction time and yield was obtained (Table 1, Entry 2). Other amounts of catalyst, solvents, and various temperatures were investigated. Based on these studies we concluded that the best result in the synthesis of desired heterocyclic product can be obtained when the reaction was carried out in the presence of 20 mol% of the 2-AP catalyst in water medium at 80 ºC (Table 1, entry 8).

**Table 1.** Screening the reaction conditions for the synthesis of 4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (**4a**)




**1a** (1 mmol) **2** (1 mmol) **3a** (1 mmol) **4a**

| Entry | 2-AP (mol%) | Solvent | Temp. / °C | Time / min. | Isolated yields / % |
|---|---|---|---|---|---|
| 1 | - | $H_2O$ | 25 | 65 | 5 |
| 2 | 5 | $H_2O$ | 25 | 55 | 15 |
| 3 | 10 | $H_2O$ | 25 | 51 | 30 |
| 4 | 15 | $H_2O$ | 25 | 48 | 36 |
| 5 | 20 | $H_2O$ | 25 | 45 | 45 |
| 6 | 20 | $H_2O$ | 50 | 30 | 65 |
| 7 | 20 | $H_2O$ | 70 | 30 | 88 |
| 8[a] | **20** | **$H_2O$** | **80** | **30** | **96** |
| 9 | 25 | $H_2O$ | 90 | 30 | 97 |
| 10 | 30 | $H_2O$ | 90 | 30 | 97 |
| 11 | 20 | EtOH | reflux | 30 | 70 |
| 12 | 20 | EtOH:$H_2O$ (1:1) | reflux | 30 | 93 |
| 13 | 20 | *n*-hexane | reflux | 30 | 0 |
| 14 | 20 | acetone | reflux | 30 | 5 |
| 15 | 20 | MeCN | reflux | 30 | 10 |
| 16 | 20 | EtOAc | reflux | 30 | 20 |
| 17 | 20 | MeOH | reflux | 30 | 70 |
| 18 | 20 | solvent-free | 90 | 30 | 55 |

[a] Optimized reaction conditions.

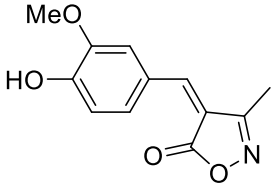
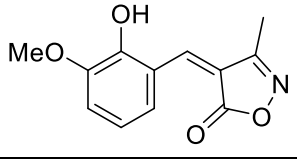
After optimization of the reaction conditions, the influence of the optimized conditions was studied on different aldehydes. It was observed that aldehydes bearing electron-donating groups at the different positions on the phenyl ring react better and faster leading to the corresponding isoxazol-5(4*H*)-one

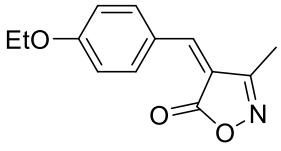
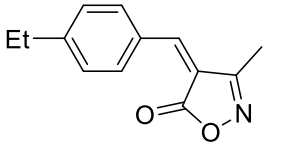
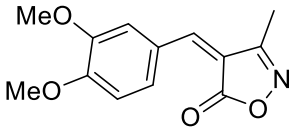
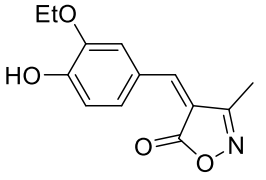
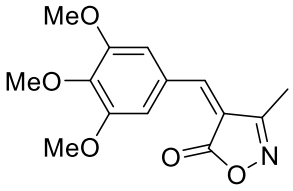
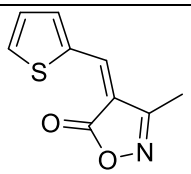
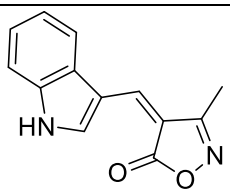
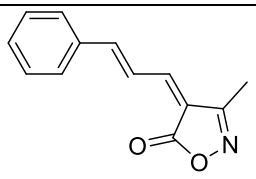
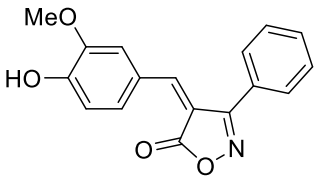
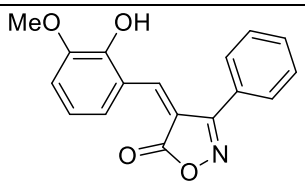
products (**4a**-**g**) in good to excellent isolated yields (Table 2, Entries 1-7). In addition, when ethyl benzoylacetete (**3b**) were used as a *β*-ketoester reactant the corresponding isoxazol-5(4*H*)-ones (**4k**-**q**) were formed in high isolated yields (Table 2, Entries 11-17). Heterocyclic aldehydes such as thiophene-2-carbaldehyde and indole-3-carbaldehyde showed high efficiency in this cyclocondensation (Table 2, entries 8, 9, 18, and 19). When an α,β-unsaturated aldehyde such as cinnamaldehyde was also used as one of the precursors in the reaction, the desired heterocyclic compound (**4j**) was obtained in excellent yields (Table 2, Entry 10) The use of substituted benzaldehydes containing electron-withdrawing groups and aliphatic aldehydes in this experiment was not successful.

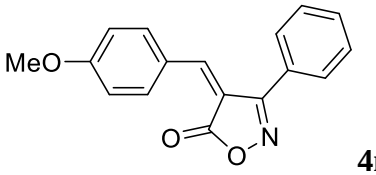
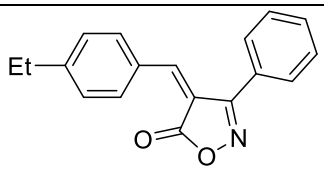
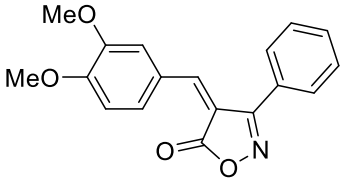
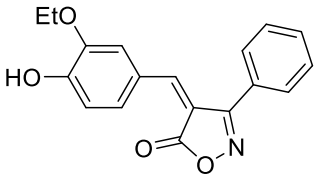
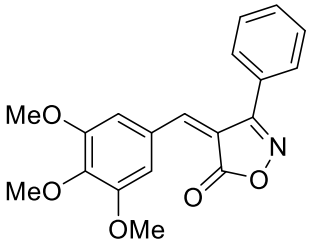
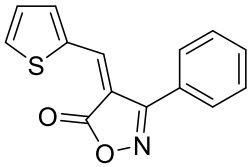
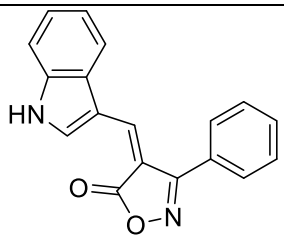
The structures of the isoxazol-5(4*H*)-ones **4a**-**s** were deduced on the basis spectroscopic data. For example, the $^{1}$H NMR (300 MHz, DMSO-$d_6$) spectrum of 4-(4-ethoxybenzylidene)-3-methyl-isoxazol-5(4*H*)-one **(4c)** exhibited a sharp singlet at δ 2.27 ppm as arising from the methyl group. A triplet signal was observed for the three H atoms of the methyl group of ethoxy substituent at δ = 1.38 ppm. The characteristic signal for the $CH_2$ of ethoxy group was observed at δ 4.42 as a quartet. A singlet at δ = 7.82 ppm was observed for the vinylic proton between to rings. The protons of the phenyl ring were located at δ 7.12 and 8.51 ppm as two clear and separate doublet peaks due to the *para* pattern. The $^{1}$H decoupled $^{13}$C NMR spectrum of **4c** displayed five signals readily recognized as arising from two methyl (δ = 11.7 and 14.9), a $CH_2O$ (δ = 64.4 ppm), a $C{=}O_{isoxazol}$ group (δ = 169.1 ppm), and a imine of isoxazol ring (δ = 164.1) as well as five distinct resonances at δ 115.4, 126.1, 137.4, 151.6, and 162.7 ppm in agreement with the proposed structure.

To recover the catalyst, after completion of the reaction, the reaction mixture was filtered and the solvent of the filtrate solution containing the catalyst was evaporated under vacuum. After drying, the catalyst was reused in the model reaction, and the reaction was performed up to three times with good to high yield (Table 2, Entry 1).

**Table 2.** Synthesis of various derivatives of isoxazol-5(4*H*)-ones (**4a**-**s**)

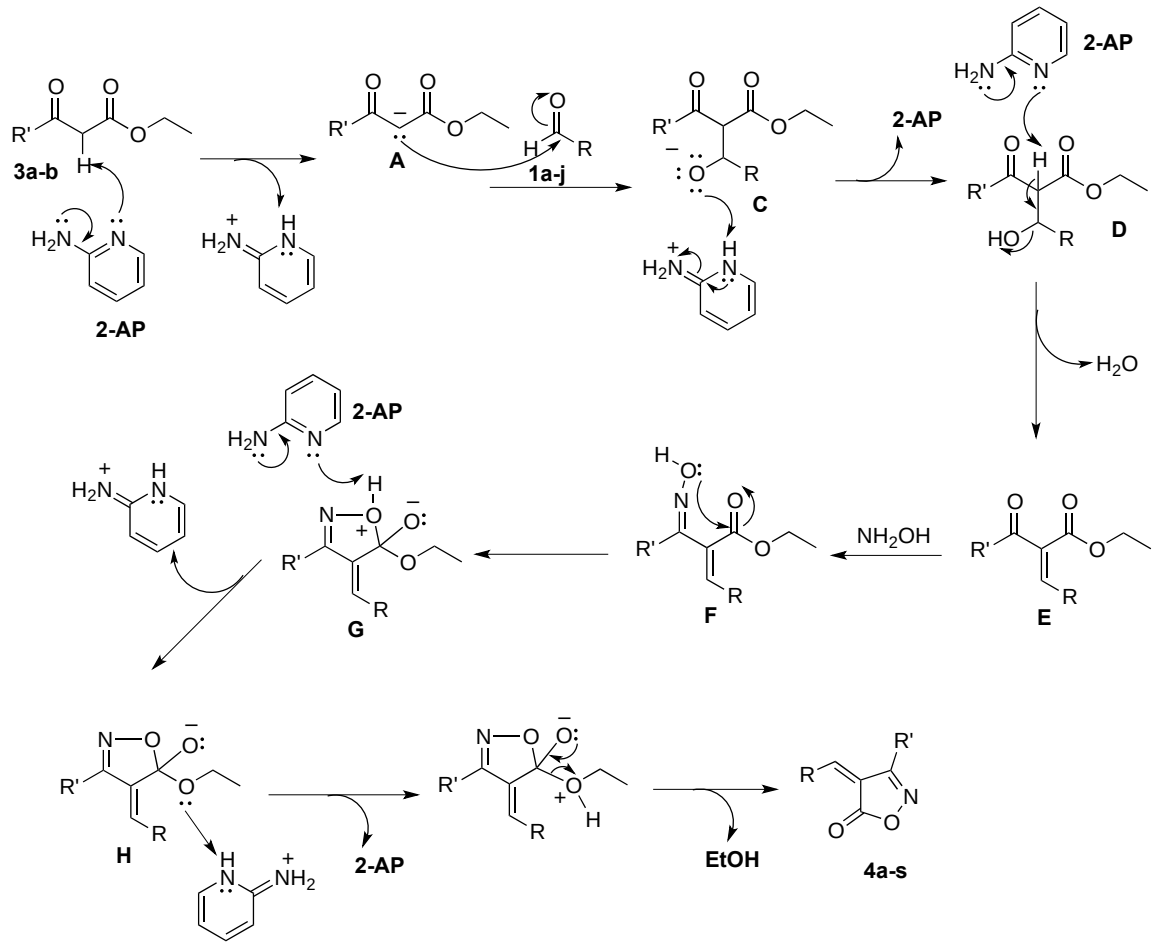
| Entry | Structure of isoxazolone | Time (min) | Isolated yields (%) | Mp (°C) | |
|---|---|---|---|---|---|
| | | | | Found | Reported [ref.] |
| 1 |  **4a** | 30 | 96 (94, 89, 87)[a] | 214-216 | 213-215[9v] |
| 2 |  **4b** | 45 | 83 | 220-222 | 213-215[9r] |

| | | | | | |
|---|---|---|---|---|---|
| 3 |  **4c** | 25 | 92 | 144-147 | 139-140[9v] |
| 4 |  **4d** | 40 | 87 | 88-90 | New |
| 5 |  **4e** | 40 | 92 | 162-165 | 152-159[9v] |
| 6 |  **4f** | 30 | 94 | 123-125 | 135-138[9v] |
| 7 |  **4g** | 40 | 93 | 172-173 | 171-173[9r] |
| 8 |  **4h** | 35 | 89 | 138-140 | 144-146[9p] |
| 9 |  **4i** | 50 | 90 | 250-255 | 244-245[9y] |
| 10 |  **4j** | 40 | 96 | 175-178 | 177-179[9r] |
| 11 |  **4k** | 25 | 92 | 213-215 | Not reported[2a] |
| 12 |  **4l** | 50 | 85 | 213-215 | New |

| | | | | | |
|---|---|---|---|---|---|
| 13 |  **4m** | 20 | 97 | 158-160 | 168-169[9j] 174[9t] |
| 15 |  **4n** | 35 | 93 | 118-120 | New |
| 15 |  **4o** | 35 | 89 | 167-170 | 185[9t] |
| 16 |  **4p** | 30 | 92 | 150-152 | Not reported[2a] |
| 17 |  **4q** | 35 | 88 | 157-160 | Not reported[2a] |
| 18 |  **4r** | 25 | 95 | 183-187 | 196,[9t] 226-228[9j] |
| 19 |  **4s** | 45 | 95 | 212-215 | New |

[a] The isolated yields of the model reaction after three uses of the recovered catalyst for 30 min.

The proposed mechanism for the synthesis of isoxazol-5(4*H*)-ones is shown in Scheme 2. At first, acidic proton of *β*-ketoster is abstracted by 2-AP and enolate **A** was formed. The aldehyde group is then attacked by the anion **A** and after eliminating the water, 2-arylidene intermediate **E** is obtained. The $H_2NOH{\cdot}HCl$ attacks the carbonyl group of **E** to form the oxime intermediate **F**, which then undergoes intramolecular cyclization and then after the loss of an ethanol molecule lead to the final heterocycles **4a-s**.




**Scheme 2.** Plausible mechanism for the synthesis of isoxazol-5(4*H*)-ones (**4a**-**s**) catalysed by 2-AP

A comparison of the efficiency of this method with some organocatalyzed reported methods is presented in Table 3. The method is competitive with previously reported methods in terms of the reaction yields and reaction times as well as the amounts of catalyst.

**Table 3.** Comparison of the efficiency of 2-AP for three-component synthesis of **4a** and **4f** with some reported methods

| Entry | Catalyst (mol%)/conditions | Time (min)/ yield (%) for **4a** | Time (min)/ yield (%) for **4f** | Ref. |
|---|---|---|---|---|
| 1 | sodium acetate (100)/EtOH:$H_2O$ (1:1 v/v), h$\nu$ | 10/68 | - | 9a |
| 2 | boric acid (10)/$H_2O$, rt | 85/95 | 70/91 | 9d |
| 3 | salicylic acid (15)/$H_2O$, rt | 100/93 | 165/89 | 9o |
| 4 | pyridine (100)/SF[a], 105 ºC | - | 60/77 | 9j |
| 5 | DABCO[b] (39)/EtOH, rt then reflux | - | 50-200/24-87 | 2a |
| 6 | potassium phthalimide (10)/$H_2O$, rt | 70/95 | 70/91 | 9k |
| 7 | 2-HSBA[c] (15)/$H_2O$, rt | 70/96 | - | 9m |
| 8 | sulfanilic acid (20)/$H_2O$, rt | 70/94 | 95/88 | 9p |
| 9 | 2-AP (20)/$H_2O$, 80 ºC | 30/96 | 20/97 | This work |

[a]Solvent free, [b]1,4-Diazabicyclo[2.2.2]octane, [c]2-Hydroxy-5-sulfobenzoic acid

In this research, isoxazol-5(4*H*)-ones as interesting five-membered heterocycles have been synthesized successfully *via* the one-pot three-component cyclocondensation of aryl/heteroaryl aldehydes, hydroxylamine hydrochloride, and ethyl acetoacetate or ethyl benzoylacetate. The reactions were promoted in the presence of 2-AP as an organocatalyst at 80 ºC. The products were obtained under benign conditions in good to high yields. Other merits of this method are the reusability of catalyst, efficacy, relatively shorter reaction times, simple workup procedure, cost-effectiveness, no use of hazardous solvents, and purification without chromatographic methods.

## EXPERIMENTAL

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification, with the exception of liquid aldehydes, which were distilled before using. The well-known products were characterized by comparison of their physical data with those of known samples or by their spectral data. Melting points were measured on a Büchi 510 melting point apparatus and are uncorrected. Proton nuclear magnetic resonance ($^1$H NMR) and carbon-13 nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Varian INOVA 300 MHz spectrometer. FT-IR spectra were recorded on a Perkin Elmer RXI spectrometer. The development of reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 $F_{254}$ aluminum sheets, visualized by UV light. Elemental microanalyses were performed on an Elementar Vario EL III analyzer.

**General procedure for the synthesis of isoxazol-5(4*H*)-ones (4a-s) catalyzed by 2-AP.** The appropriate aldehyde (**1a-j**, 1 mmol), hydroxylamine hydrochloride (**2**, 1 mmol), *β*-ketoester (**3a-b**, 1 mmol), and 2-AP as a catalyst (20 mol%) was stirred in $H_2O$ (10 mL) at 80 ºC. After completion of the reaction as indicated by TLC analysis, the precipitated products were filtered off, washed with cold water and dried at room temperature. If necessary, the crude products were purified by recrystallization from EtOH. The filtrate contains a catalyst. After evaporation of solvent from the filtrate, the catalyst was remained and was used for consecutive runs.

**4-(4-Hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4a).** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.28 (s, 3H, $CH_3$), 3.91 (s, 1H, OH), 3.90 (s, 3H, $OCH_3$), 7.14 (d, $J$ = 8.6, 1H, Ar-H), 7.76 (s, 1H, H-vinyl), 7.92 (d, $J$ = 8.6, 1H, Ar-H), 8.22 (s, 1H, Ar-H), 9.61 (s, 1 H, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 11.4, 56.2, 111.8, 114.7, 127.2, 128.7, 129.5, 146.4, 151.8, 153.6, 168.6, 170.3.

**4-(2-Hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4b).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.28 (s, 3H, $CH_3$), 3.40 (s, 1H, OH), 3.88 (s, 3H, $OCH_3$), 6.90 (dd, $J$ = 8.1, 2H, Ar-H), 7.26 (d, $J$ = 8.1, 1H, Ar-H), 8.34 (d, $J$ = 8.1, 1H, Ar-H), 8.13 (s, 1H, H-vinyl); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 11.7, 56.6, 117.2, 118.0, 119.1, 120.2, 123.8, 145.4, 148.2, 149.9, 162.6, 168.6.

**4-(4-Ethoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4c).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.38 (t, $J$ = 6.9 Hz, 3H, $CH_3$), 2.27 (s, 3H, $CH_3$), 4.42 (q, $J$ = 6.9 Hz, 2H, $OCH_2$), 7.12 (d, $J$ = 9.0 Hz, 2H, Ar-H), 7.82 (s, 1H, H-vinyl), 8.51 (d, $J$ = 8.7 Hz, 2H, Ar-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 11.7, 14.9, 64.4, 115.4, 126.1, 137.4, 151.6, 162.7, 164.1, 169.1.

**4-(4-Ethylbenzylidene)-3-methylisoxazol-5(4*H*)-one (4d).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.23 (t, $J$ = 7.5, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$), 2.72 (q, $J$ = 7.5 Hz, 2H, $CH_2$-), 7.45 (d, $J$ = 8.1 Hz, 2H, Ar-H), 7.93 (s, 1H, H-vinyl), 8.39 (d, $J$ = 8.1 Hz, 2H, Ar-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 11.8, 15.4, 28.9, 118.1, 128.9, 130.8, 134.5, 151.6, 152.1, 162.7, 168.5; Anal. Calcd for $C_{13}H_{13}NO_2$ (%): C, 72.54; H, 6.09; N, 6.51. Found: C, 72.56; H, 6.11; N, 6.48.

**4-(3,4-Dimethoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4e).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.25 (s, 3H, $OCH_3$), 3.91 (s, 3H, $OCH_3$), 7.78 (s, 1H, H-vinyl), 7.16 (d, $J$ = 8.4, 1H, Ar-H), 7.96 (dd, $J$ = 8.7, 1H, Ar-H), 8.47 (d, $J$ = 8.4, 1H, Ar-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 55.9, 56.5, 111.9, 114.4, 116.4, 126.3, 127.8, 128.7, 131.3, 153.8, 155.2, 164.7, 169.3.

**4-(3-Ethoxy-4-hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4f).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.39 (t, $J$ = 6.9, 3H, $CH_3$), 2.22 (s, 3H, $CH_3$), 4.09 (q, $J$ = 6.6 Hz, 2H, $CH_2$-), 6.95 (d, $J$ = 7.2, 2H, Ar-H), 7.82 (d, $J$ = 8.4, 2H), 7.66 (s, 1H, H-vinyl), 7.81 (d, $J$ = 8.4, 2H, Ar-H), 8.47 (s,1H, Ar-H), 10.66 (s, 1H, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 11.6, 14.9, 64.3, 114.0, 116.2, 118.0, 125.5, 131.9, 147.1, 152.1, 154.5, 162.6, 169.4.

**3-Methyl-4-(3,4,5-trimethoxybenzylidene)isoxazol-5(4*H*)-one (4g).** $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 2.29 (s, 3H, $CH_3$), 3.87 (s, 6H, *meta*-$CH_3O$), 3.84 (s, 3H, *para*-$CH_3O$), 7.89 (s, 1H, ArCH═), 8.02 (s, 2H, Ar-H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 11.8, 56.5, 60.9, 112.5, 117.6, 128.4, 143.4, 152.2, 152.9, 162.7, 168.9.

**4-((1*H*-Indol-3-yl)methylene)-3-methylisoxazol-5(4*H*)-one (4i).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.39 (s, 3H, $CH_3$), 8.12 (s, 1H, ArCH═), 9.51 (s, 1H, H of indole ring), 7.30-7.36 (m, 2H, Ar-H), 7.58-7.63 (m, 2H, Ar-H), 12.80 (s, N-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 11.6, 109.3, 113.1, 113.6, 119.2, 123.0, 124.4, 128.4, 136.8, 138.9, 140.8, 162.1, 170.8.

**3-Methyl-4-(3-phenylallylidene)isoxazol-5(4*H*)-one (4j).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.25 (s, 3H, $CH_3$), 7.49-7.52 (m, 4H, Ar-H), 7.68-7.73 (m, 2H, Ar-H, H-vinyl), 7.82 (dd, $J$ = 3.6, 11.4 Hz, 1H, H-alkene), 8.15 (dd, $J$ = 3.6, 11.7 Hz, 1H, H-alkene).

**4-(4-Hydroxy-3-methoxybenzylidene)-3-phenylisoxazol-5(4*H*)-one (4k).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 3.86 (s, 3H, $CH_3$), 6.95 (d, $J$ = 8.4 Hz, 1H, Ar-H), 7.75-7.67 (m, 6H, Ar-H), 7.90 (d, $J$ = 6.6 Hz, 1H), 8.49 (s, 1H, H-vinyl), 10.90 (s, 1H, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 56.1, 113.1, 116.3, 117.6, 125.4, 128.0, 129.3, 129.6, 131.2, 132.6, 147.9, 153.9, 154.8, 164.8, 169.5.

**4-(2-Hydroxy-3-methoxybenzylidene)-3-phenylisoxazol-5(4*H*)-one (4l).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 3.86 (s, 3H, $OCH_3$), 6.95 (dd, *J* = 8.1 Hz, 1H, Ar-H), 7.27 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.63-8.42 (m, 5H, Ar-H), 8.21 (s, 1H, H-vinyl), 8.43 (d, *J* = 8.1 Hz, 1H, Ar-H), 10.3. (s, 1H, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 56.7, 116.2, 118.5, 119.2, 120.4, 124.1, 127.8, 129.7, 131.5, 147.5, 148.2, 150.2, 164.9, 168.7; Anal. Calcd for $C_{17}H_{13}NO_4$ (%): C, 69.15; H, 4.44; N, 4.74. Found: C, 69.18; H, 4.46; N, 4.77.

**4-(4-Ethoxybenzylidene)-3-phenylisoxazol-5(4*H*)-one (4m).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.37 (t, *J* = 6.9 Hz, 3H, $CH_3$), 4.18 (q, *J* = 6.9 Hz, 2H, $OCH_2$), 7.11 (d, *J* = 8.7 Hz, 2H), 7.62-7.71 (m, 5H, Ar-H), 7.62 (s, 1H, H-vinyl), 8.48 (d, *J* = 8.7 Hz, 2H, Ar-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 14.8, 64.5, 114.5, 115.1, 115.4, 125.9, 127.8, 129.7, 131.3, 137.9, 153.4, 164.4, 164.6, 169.1.

**4-(4-Ethylbenzylidene)-3-phenylisoxazol-5(4*H*)-one (4n).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.21 (t, *J* = 7.5 Hz, 3H, $CH_3$), 2.70 (q, *J* = 7.8 Hz, 2H, $CH_2$-), 7.41 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.62-7.72 (m, 5H, Ar-H), 7.78 (s, 1H, H-vinyl), 8.33 (d, *J* = 8.1 Hz, 2H, Ar-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 15.4, 29.4, 35.5, 114.9, 129.1, 130.6, 134.8, 152.5, 153.4, 162.1, 168.0; Anal. Calcd for $C_{18}H_{15}NO_2$ (%): C, 77.96; H, 5.45; N, 5.05. Found: C, 77.98; H, 4.44; N, 5.08.

**4-(3,4-Dimethoxybenzylidene)-3-phenylisoxazol-5(4*H*)-one (4o).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 3.84 (s, 3H, $OCH_3$), 3.91 (s, 3H, $OCH_3$), 8.91 (s, 1H, H-vinyl), 7.15 (d, *J* = 8.4, 1H, Ar-H), 8.02 (dd, *J* = 8.7, 1H, Ar-H), 7.62-7.69 (m, 6H, Ar-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 55.9, 56.5, 111.9, 114.4, 116.4, 126.3, 127.8, 128.7, 129.7, 131.3, 131.9, 148.8, 153.8, 155.2, 164.7, 169.3.

**4-(3-Ethoxy-4-hydroxybenzylidene)-3-phenylisoxazol-5(4*H*)-one (4p).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.39 (t, *J* = 6.9 Hz, 3H, $CH_3$), 4.12 (q, *J* = 6.6 Hz, 2H, $CH_2$), 6.96 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.86 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.64 (m, 6H, Ar-H), 8.51 (s, 1H, H-vinyl), 10.86 (s, 1H, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 15.0, 64.4, 112.9, 116.3, 118.5, 125.4, 127.9, 129.3, 129.6, 131.2, 132.6, 147.1, 153.9, 155.1, 164.8, 169.6.

**3-Phenyl-4-(3,4,5-trimethoxybenzylidene)isoxazol-5(4*H*)-one (4q).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 3.85 (s, 9H, $CH_3O$), 7.99 (s, 2H, Ar-H), 7.67-7.76 (m, 6H, Ar-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 56.5, 60.9, 112.8, 116.6, 127.6, 128.7, 129.3, 129.7, 131.4, 143.7, 152.8, 153.9, 164.6, 170.8.

**3-Phenyl-4-(thiophen-2-ylmethylene)isoxazol-5(4*H*)-one (4r).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.40 (dd, *J* = 3.9, 1H, H of thiophen ring), 7.63-7.74 (m, 5H, Ar-H), 8.41 (dd, *J* = 3.9 Hz, 1H, H of thiophen ring), 8.31 (t, *J* = 3.1 Hz, 1H, H of thiophen ring), 8.12 (s, 1H, ArCH═); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 2.0, 127.7, 129.1, 129.5, 129.7, 131.4, 136.7, 142.8, 143.7, 145.2, 163.8, 169.2.

**4-((1*H*-Indol-3-yl)methylene)-3-phenylisoxazol-5(4*H*)-one (4s).** $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.07 (s, 1H, ArCH═), 9.61 (s, 1H, H of indole ring), 7.26-7.77 (m, 9H, Ar-H), 12.95 (s, 1H, N-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 107.5, 113.4, 113.8, 118.7, 123.4, 124.6, 128.3, 128.7, 129.8, 131.1, 137.0,

139.9, 141.6, 164.2, 171.1; Anal. Calcd for $C_{18}H_{12}N_2O_2$ (%): C, 74.99; H, 4.20; N, 9.72. Found: C, 75.02; H, 4.22; N, 9.75.

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