Facile, eco-friendly and one-pot synthesis of 3,4-disubstituted isoxazol-5(4H)-ones using starch solution as a reaction media

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A one-pot three-component reaction of ethyl acetoacetate with hydroxylamine hydrochloride and various aromatic aldehydes has been developed using starch solution as a reaction media. Starch solution has been employed as an environmentally benign and commercially available catalytic system for this synthesis. This cyclo-condensation reaction has been performed in aqueous ethanol as an environmentally benign solvent at 90°C as well as under microwave irradiation (MWI, 300 W) giving 3,4-disubstituted isoxazol-5(4H)-one derivatives in excellent yields. The use of a nontoxic, reusable and biodegradable catalytic system is one of the superior advantages of this protocol. The superior features of the present methodology are mild reaction conditions, excellent yields, high atom-economy, easy work-up process, short reaction times and use of microwave irradiation conditions.

Keywords: Isoxazol-5(4H)-one, starch solution, one-pot, multi-component, microwave irradiation (MWI)

Recently, the expansions of green protocols that are environmentally benign and pollution free have received substantial levels of consideration because of the increasing tendency of the chemical industry towards greener unit processes. Green chemistry can be recognized as a pioneering approach, which widely reports intrinsic atom economy, energy savings, waste reduction, easy work-ups and the avoidance of hazardous chemicals. Now-a-days multi-component reactions (MCRs) have received much attention in the field of organic and medicinal chemistry, because the strategies of multi component reaction offer significant advantages over conventional synthetic methodologies.

Isoxazole scaffolds are an important class of heterocyclic compounds and they are predominant in nature and display a wide range of biological and pharmaceutical activities such as anti-inflammatory, antibacterial, antifungal, antitumor, antioxidant, antiviral, anti-tubercular and anti-HIV. In the literature, α, β-unsaturated isoxazol-5(4H)-one derivatives have been prepared via a three-component condensation of β-oxoesters, hydroxylamine hydrochloride and aromatic aldehydes by use of catalytic amounts of sodium benzoate, Na2S, DABCO, N-bromosuccinimide (NBS), potassium hydrogen phthalate (KHP), Ag/SiO2, 2-Hydroxy-5-sulfobenzoic acid (2-HSBA), tartaric acid, potassium phthalimide (PPI), pyridine and boric acid. All listed above protocols suffer from one or more drawbacks such as prolonged reaction time, use of organic solvents, strong acid or base catalysts, expensive catalyst and harsh reaction conditions. Thus, the development of new environmental friendly, more effective procedure for the synthesis of isoxazole scaffolds and carrying out organic reactions in water is of significant interest.

Now-a-days, organocatalysis is being energetically pursued because of their attractive merits like high efficiency, inexpensive and environmentally benign reagents, the transition metals-free conditions, experimental simplicity, potential for large scale reaction and the easily recoverability. Starch solution is an efficient, mild, inexpensive and bio-degradable catalytic system. Hazeri and co-workers have reported the use of starch solution as a catalyst for the preparation of tetrahydro[β]pyran and 3,4-dihydropyrano[c]chromene derivatives in excellent yield. Our literature survey revealed that there is no report on the use of starch solution as a catalyst in the synthesis of isoxazol-5(4H)-one derivatives. For the first time, we disclose the application of starch solution as an efficient organocatalyst for the preparation of isoxazol-5(4H)-one derivatives through the one-pot three-component reaction of ethyl acetoacetate, hydroxylamine hydrochloride and aromatic aldehydes under conventional thermal as well as microwave irradiation (MWI) (Scheme I).
Results and Discussion

In the beginning, to achieving the optimization reaction conditions, first we performed the reaction between ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1.0 mmol) and benzaldehyde (1 mmol) as the model reaction. The use of different amounts of catalyst (1, 2, 3, 4, and 5 mL) at different temperatures (RT to 90°C) were investigated (Table I). From the results table, we concluded that the low conversion of the product was observed in the absence of the catalyst at room temperature as well as at 90°C (Table I, entries 1 and 2), which indicated that the catalyst was necessary for this transformation. In the next step, the reaction was carried out with various amounts of catalyst from 1 to 5 mL at different temperature range between RT to 90°C. It was found that, by increasing the amount of catalyst and rising the temperature, the yield of 4-benzylidene-3-methylisoxazol-5(4H)-one (1) was improved (Table I, entries 3-13). Hence, the best result was obtained by performing the reaction in the presence of 4 mL starch solution at 90°C. Next, we have performed this condensation reaction under microwave irradiation (MWI) using 4 mL starch solution as a catalytic system (Table I, entries 14-16). Surprisingly, the best result was obtained by performing the reaction at 300 W. In addition, the higher amount of starch solution does not have any significant effect on product yield and reaction time (Table I, entry 17). Compared to conventional heating, reaction under microwave irradiation shows higher efficiency in terms of product yields and reaction times (Table II).

Then the generalization of the protocol was evaluated using various aromatic aldehydes under optimized reaction conditions. It is found that, aromatic substrates having electron-donating functional groups afforded good to high yields of products (Table II). In addition, the reaction with electron rich heterocyclic aldehydes also preceded smoothly with high yields with less reaction times (Table II, entries 13 and 18). It is important to note that the aldehydes with electron-withdrawing (-NO₂) as well as ring deactivating (-Cl, -F, -Br) groups and deficient heterocyclic aldehyde like pyridine-2-carbaldehyde are not favored under these conditions (Table II, entries 8, 12, 14, 15, 17 and 20). Accordingly, it is concluded that the electronic nature of the functional groups and their position on aryl aldehydes have various effects on this reaction. The reaction was clean, and no chromatographic separation was required because no impurities were observed. After completion of the reaction, the solid product was collected by simple filtration and if required then recrystallized from ethanol to afford pure products. The desired pure products were characterized by comparison of their physical and spectroscopic data (melting points, IR, mass, ¹H and ¹³C NMR) with those of known compounds in the literature. For example, the ¹H NMR spectrum of compound 2 exhibited a sharp singlet signal at δ 2.25 due to the methyl group in the isoxazol unit. Two doublets at δ 6.95 (J = 8.76 Hz) and δ 8.45 (J = 8.8 Hz), which assigned four protons of aromatic ring. Also, the ¹H NMR showed one singlet signal at δ 7.78 for the =CH proton between the isoxazol and aromatic rings. In addition, proton of 4-OH exhibited

### Table I — Optimization of the reaction conditions

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<tr>
<th>Entry</th>
<th>Catalyst Amount (mL)</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yield%</th>
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<td>17</td>
<td>5.0</td>
<td>300 W (MWI)</td>
<td>8</td>
<td>92</td>
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*Isolated yields*
singlet at δ 11.06. The $^{13}$C NMR spectrum displayed the isoxazol ring carbons C=O and C=N at δ 168.80 and 163.82 respectively, which confirmed the isoxazol unit. The signal at δ 11.25 corresponds to the CH$_3$ group. The other carbon signals were observed at the expected chemical shifts.

Although the exact mechanism of this transformation is not completely clear, a possible reaction mechanism is proposed based on these results and the provided mechanism in the literature (Scheme II). According to the proposed reaction mechanism, at first, the nucleophilic attack of the amino group of hydroxylamine hydrochloride on the carbonyl carbon of the ethyl acetoacetate in the presence of starch solution resulted in intermediate oxime (A). The aldehyde is attacked by intermediate oxime (A) and subsequent Knoevenagel adduct (B) is formed. Then oxygen attacks on carbon of ester moiety to give (C), which undergoes proton transfer and losing one ethanol molecule to corresponding products (1-20).

The catalyst was recovered by the evaporation of water from the filtrate under vacuum. The recovered 4 mL starch solution was reused four times with slightly decreasing in its activity (Figure 1 and Figure 2). Decreasing the yield is probably related to a minor reduction in the efficiency of the catalyst or a decrease in the amount of the catalyst recycled, which is accredited to the handling.

**Experimental Section**

All analytical grade chemicals, unless otherwise specified, were purchased from commercial sources. Samsung modified domestic microwave oven was used to carried out all the reactions. The products were characterized by a comparison of their physical data and melting points with those of known samples or by their spectral data. Melting points were measured on an Optimelt MPA 100 melting point apparatus and are uncorrected. FT-IR spectra were recorded on a Perkin-Elmer FT-IR 377 spectrometer using KBr. $^1$H NMR spectra were recorded on Bruker AV 400 MHz spectrometer using DMSO-$d_6$ as solvent and TMS as the internal reference. Mass spectra were recorded at Advion expression CMS, USA. Acetone was used as mobile phase, and electron spray ionization (ESI) used as ion source. Elemental analysis was performed on a CHN elemental analyser. The progress of reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F$_{254}$ aluminium sheets, visualized by UV light.
General procedure for preparation of starch solution (catalyst)

Starch (2 g) was added to water (25 mL) with magnetic stirring at 25°C. After 30 min, the solution was filtered to remove insoluble starch (amylose). The filtered solution was used for synthesis of 3,4-disubstituted isoxazol-5(4H)-one derivatives.

General procedure for the synthesis of 3,4-disubstituted isoxazol-5(4H)-ones, 1-20

A mixture of hydroxylamine hydrochloride (1 mmol), ethyl acetoacetate (1 mmol) and starch solution (4 mL) was stirred at RT for 15 min, followed by addition of aromatic aldehydes (1 mmol) into the reaction mixture. The reaction mixture was stirred at 90°C or irradiated under microwave (300 W), until the reaction was completed. The reaction was monitored by TLC analysis. After completion of the reaction, the precipitate was separated by simple filtration, washed with cold distilled water and dried in air. Crude products were purified by recrystallization from ethanol (95%) to afford pure compounds. The solvent from the filtrate was evaporated under vacuum until it became 4 mL and reused for the four subsequent runs. The identity of the known products was confirmed by comparison of their spectroscopic data and physical properties with those from available data.
4-Benzylidene-3-methylisoxazol-5(4H)-one, 1: White solid. IR (KBr): 3232, 2363, 1734, 1559, 1358, 1297, 1179 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δH 2.27 (s, 3H, CH₃), 7.46 (s, 1H, =CH), 7.55 (t, J = 7.8 Hz, 2H, ArH), 7.61-7.64 (m, 1H, ArH), 8.38 (dd, J = 1.3, 7.4 Hz, 2H, ArH); ¹³C NMR (100 MHz, DMSO-d₆): δC 11.55, 114.61, 118.17, 126.55, 137.41, 152.65, 163.03, 168.62; ESI-MS: m/z for (187.19): 187.2 (M⁺), 188.2 (M+1)⁺.

4-(Hydroxybenzylidene)-3-methylisoxazol-5(4H)-one, 2: Red solid. IR (KBr): 3590, 1744, 1550, 1532, 1427, 1188, 1099, 870 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δH 2.25 (s, 3H, CH₃), 6.82 (d, J = 9.14 Hz, 2H, ArH), 7.67 (s, 1H, =CH), 8.42 (d, J = 8.26 Hz, 2H, ArH), 11.46 (s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d₆): δC 11.28, 116.87, 119.52, 124.14, 136.12, 151.15, 155.23, 164.42, 168.42; ESI-MS: m/z for (203.19): 203.1 (M⁺), 204.2 (M+1)⁺.

4-(Dimethylamino)benzylidene)-3-methylisoxazol-5(4H)-one, 3: Red solid. IR (KBr): 1734, 1589, 1530, 1429, 1180, 1096, 874 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δH 2.14 (s, 3H, CH₃), 3.14 (s, 6H, N(CH₃)₂), 6.86 (d, J = 9.16 Hz, 2H, ArH), 7.63 (s, 1H, =CH), 8.47 (d, J = 8.20 Hz, 2H, ArH); ¹³C NMR (100 MHz, DMSO-d₆): δC 11.27, 45.32, 108.98, 118.59, 121.95, 137.52, 150.44, 151.32, 162.08, 169.79; ESI-MS: m/z for (230.26): 230.2 (M⁺), 253.2 (M+Na)⁺.

4-(Hydroxybenzylidene)-3-methylisoxazol-5(4H)-one, 4: Yellowish orange solid. IR (KBr): 3443, 3232, 2363, 1734, 1559, 1358, 1297, 1179, 669 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δH 2.25 (s, 3H, CH₃), 6.95 (d, J = 8.76 Hz, 2H, ArH), 7.78 (s, 1H, =CH), 8.45 (d, J = 8.80 Hz, 2H, ArH), 11.06 (s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d₆): δC 11.25, 118.48, 119.38, 120.65, 121.34, 125.25, 129.80, 133.57, 151.98, 157.35, 162.21, 169.71; ESI-MS: m/z for (203.19): 203.1 (M⁺), 204.2 (M+1)⁺.

3-Methyl-4-(4-methoxyphenyl)methyleneisoxazole-5(4H)-one, 5: Yellow solid. IR (KBr): 3246, 2362, 1734, 1594, 1269, 1176, 860 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δH 2.25 (s, 3H, CH₃), 3.89 (s, 3H, OCH₃), 7.14 (d, J = 8.96 Hz, 2H, ArH), 7.85 (s, 1H, =CH), 8.51 (d, J = 8.96 Hz, 2H, ArH); ¹³C NMR (100 MHz, DMSO-d₆): δC 11.30, 46.22, 115.63, 123.45, 132.19, 151.19, 154.93, 162.29, 168.97; ESI-MS: m/z for (217.22): 217.1 (M⁺), 218.3 (M+1)⁺.

3-Methyl-4-(4-methoxybenzylidene)isoxazol-5(4H)-one, 6: Light yellow solid. IR (KBr): 3245, 2322, 1737, 1547, 1334, 1300, 1166, 672 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δH 2.33 (s, 3H, CH₃), 2.48 (s, 3H, OCH₃), 7.36 (d, J = 8.0 Hz, 2H, ArH), 7.42 (s, 1H, =CH), 8.32 (d, J = 8.4 Hz, 2H, ArH); ¹³C NMR (100 MHz, DMSO-d₆): δC 11.60, 22.12, 118.26, 128.81, 129.97, 134.21, 141.83, 156.70, 162.46, 168.38; ESI-MS: m/z for (201.22): 201.1 (M⁺), 224.2 (M+Na)⁺.

4-(Hydroxybenzylidene)-3-methylisoxazol-5(4H)-one, 7: Yellow solid. IR (KBr): 3443, 3232, 2363, 1734, 1559, 1358, 1297, 1179, 669 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δH 2.25 (s, 3H, CH₃), 6.95 (d, J = 8.76 Hz, 2H, ArH), 7.78 (s, 1H, =CH), 8.45 (d, J = 8.80 Hz, 2H, ArH), 11.06 (s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d₆): δC 11.25, 114.56, 118.38, 121.34, 125.25, 129.80, 134.57, 151.98, 158.35, 162.21, 168.71; ESI-MS: m/z for (203.19): 203.1 (M⁺), 204.2 (M+1)⁺.

3-Methyl-4-(2,3-dimethoxyphenyl)methyleneisoxazole-5(4H)-one, 9: Yellow solid. IR (KBr): 3260, 2362, 1698, 1524, 1268, 1125, 668 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δH 2.29 (s, 3H, CH₃), 3.86 (s, 6H, 2OCH₃), 7.06 (d, J = 7.82 Hz, 1H, ArH), 7.36 (d, J = 7.64 Hz, 1H, ArH), 7.99 (s, 1H, =CH), 8.22 (d, J = 9.08 Hz, 1H, ArH); ¹³C NMR (100 MHz, DMSO-d₆): δC 11.13, 56.00, 61.67, 118.83, 119.26, 123.34, 123.70, 125.63, 145.12, 149.85, 152.15, 162.44, 168.87; ESI-MS: m/z for (247.25): 247.2 (M⁺), 248.3 (M+1)⁺.
3-Methyl-4-(2,5-dimethoxyphenyl)methyleneisoxazole-5(4H)-one, 10: Orange solid. IR (KBr): 3230, 2362, 1730, 1596, 1237, 1045, 668 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) H 2.25 (s, 3H, CH\(_3\)), 3.75 (s, 3H, OCH\(_3\)), 3.87 (s, 3H, OCH\(_3\)), 7.11-7.27 (m, 2H, ArH), 8.01 (s, 1H, =CH), 8.41 (d, \(J = 8.04\) Hz, 1H, ArH); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) C 11.12, 55.50, 56.50, 112.84, 115.78, 117.79, 120.79, 123.23, 148.21, 152.26, 154.43, 162.12, 169.01; ESI-MS: \(m/z\) for (247.25): 247.2 (M\(^+\)), 248.2 (M+1\(^+\)).

4-(Furan-2-ylmethylene)-3-methylisoxazole-5(4H)-one, 13: Yellow solid. IR (KBr): 3464, 2212, 1851, 1578, 1395, 1238, 1218, 768 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) H 6.46 (s, 2H, ArH), 7.96 (s, 1H, =CH), 8.97 (d, \(J = 8.81\) Hz, 1H, ArH), 9.90 (s, 1H, OH), 11.06 (s, 1H, OH); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) C 11.62, 115.66, 127.17, 128.97, 131.22, 138.92, 142.11, 162.62, 169.09(MS) (ESI) \(m/z\) for (177.16): 177.1 (M\(^+\)), 178.2 (M+1\(^+\)).

3-Methyl-4-(3,4-dihydroxyphenyl)methyleneisoxazole-5(4H)-one, 16: Yellow solid. IR (KBr): 3474, 2362, 1754, 1588, 1391, 1258, 1214, 764 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) H 6.42 (s, 2H, ArH), 7.96 (s, 1H, =CH), 8.97 (d, \(J = 8.81\) Hz, 1H, ArH), 9.90 (s, 1H, OH), 11.06 (s, 1H, OH); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) C 11.62, 115.66, 127.17, 128.97, 131.22, 138.92, 142.11, 162.62, 169.40; ESI-MS: \(m/z\) for (219.19): 219.2 (M\(^+\)), 220.3 (M+1\(^+\)).

3-Methyl-4-(thiophen-2-ylmethylene)isoxazole-5(4H)-one, 18: Yellow solid. IR (KBr): 3474, 2362, 1754, 1588, 1391, 1258, 1214, 764 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) H 3.23 (s, 3H, CH\(_3\)), 7.29 (t, \(J = 8.41\) Hz, 1H), 7.64 (s, 1H, =CH), 7.95 (d, \(J = 8.88\) Hz, 1H), 8.13 (d, \(J = 8.81\) Hz, 1H); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) C 11.50, 114.61, 127.47, 128.9, 130.52, 139.27, 141.54, 162.72, 168.79; ESI-MS: \(m/z\) for (193.22): 193.1 (M\(^+\)), 216.2 (M+Na\(^+\)).

4-(4-Hydroxy-3-methoxybenzylidene)-3-methylisoxazole-5(4H)-one, 19: Yellow solid. IR (KBr): 3444, 3220, 2261, 1751, 1565, 1397, 1259, 1211, 760 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) H 2.14 (s, 3H, CH\(_3\)), 3.72 (s, 3H, OCH\(_3\)), 6.42 (s, 2H, ArH), 7.96 (s, 1H, =CH), 8.97 (d, \(J = 8.41\) Hz, 1H, ArH), 10.56 (s, 1H, OH); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) C 11.17, 46.17, 111.02, 114.57, 117.01, 122.87, 132.14, 143.94, 152.22, 158.10, 162.63, 169.40; ESI-MS: \(m/z\) for (233.22): 233.3 (M\(^+\)), 234.2 (M+1\(^+\)).

Conclusions

In summary, we have developed an efficient method for the one-pot, three component synthesis of various 3,4-disubstituted isoxazol-5(4H)-one derivatives catalyzed by starch solution. This protocol is very simple from the experimental point of view and would permit easy access to large families of 3,4-disubstituted isoxazol-5(4H)-ones. The use of a green and recyclable catalytic system, high yield of products with high purity, simple work-up process, avoiding the use of hazardous organic solvents, aqueous conditions and a simple work-up procedure make the present method a valuable contribution in accord with green chemistry principles.

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References