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REGULAR ARTICLE

Pyruvic acid-catalyzed one-pot three-component green synthesis of isoxazoles in aqueous medium: a comparable study of conventional heating versus ultra-sonication

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Abstract. A mild and efficient route for the one-pot synthesis of isoxazole derivatives has been developed using pyruvic acid as a catalyst under an aqueous medium. The reaction was carried out under conventional as well as ultrasonic conditions to afford the desired product in good yield. The features of this protocol are the use of environmental-friendly, commercially available, biodegradable catalyst, use of biologically safe solvent, simple experimental procedure and short reaction times. The given protocol can be a better alternative for the synthesis of 4*H*-isoxazol-5-one derivatives as compared to traditional methods.

Keywords. 4*H*-isoxazol-5-one; pyruvic acid; aldehyde; ultrasound irradiation; green chemistry; multicomponent reaction (MCR).

1. Introduction

A realization of the fundamental importance of nitrogen-containing heterocycles in pharmaceutical and medicinal chemistry captivated researchers across the world. These heterocycles are the core building block of several pharmaceutically active natural products. Furthermore, 59% of the approved small molecule drugs by the US FDA contain nitrogen heterocycles, which ranks them as the most privileged and momentous heterocycles by a medicinal chemist.[1] Among these, isoxazole and its derivatives are an important class of oxygen- and nitrogen-containing heterocycles with several applications in organic chemistry, medicinal chemistry and the pharmaceutical industry.[2,3] Isoxazole derivatives are well-known for their widespread biological and pharmacological activities such as antifungal,[4] analgesic,[5] antitumor,[6] antioxidant,[7] antimicrobial,[8] COX-2 inhibitor,[9] anti-inflammatory,[10] antiviral,[11] antimycobacterial,[12] anti-HIV,[13] androgen antagonists,[14] antibiotic,[15] antihypertensive,[16] antimalarial,[17] antirheumatic,[18] antianginal,[19] anticonvulsant,[20] anti-obesity,[21] anti-osteoporotic,[22] nematicidal agents,[23] antiprotozoal,[24] hypoglycemic,[25] antituberculosis[26] and bronchodilating agent.[27] Furthermore, isoxazole derivatives have also been used for the design and manufacture of merocyanine dyes with applications in optical recording and nonlinear optical research,[28] liquid crystalline materials,[29] light-conversion molecular devices[30] and as a filter dye in photographic films.[31] The isoxazole moiety is also a structural backbone of a variety of natural products like cycloserine,[32] pantherine,[33] ibotenic acid and isoxazol-4-carboxylic acid.[32] Some of the interesting compounds with isoxazole moiety are shown in Figure 1. Because of their diverse applications in multi-disciplinary fields, the development of new synthetic strategies for the synthesis of isoxazole derivatives has received great attention in organic synthesis.

In the literature, there are many methods to prepare this class of compounds. The most common method

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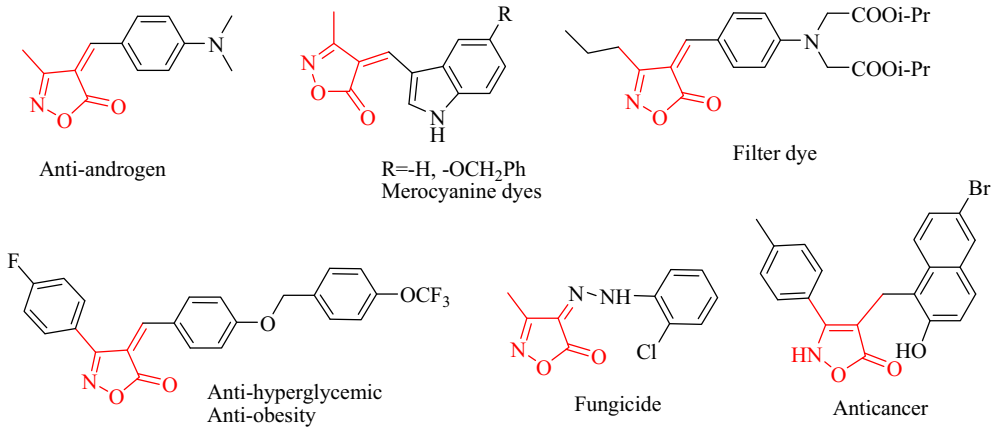


Figure 1. Isoxazole scaffold-containing interesting compounds.

for the synthesis of isoxazoles involves one-pot multicomponent reactions (MCRs) of aromatic aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride using various catalysts.[34–55] MCRs have been discovered to be a powerful synthetic tool for the synthesis of several natural products and biologically active compounds. MCRs have received significant advantages over conventional synthetic methodologies. This ensures good yields, high atom economy and low costs, reduction in reaction times, minimization of waste, energy, labour, operational simplicity and avoidance of tedious purification processes.[56–58] A combination of MCR, green solvent like water and the use of non-conventional energy sources like ultrasound irradiation are important features of an ideal green synthesis.[59–63]

The use of ultrasound irradiation to speed up the organic reactions has long been known in both academia and industry. The chemical and physical effects of ultrasound come from acoustic cavitations such as the formation, growth and implosive collapse of bubbles in a liquid. The cavitation collapse creates drastic conditions inside the medium for an extremely short time and temperatures of 2000–5000 K, as well as pressure up to 1800 atm inside the collapsing cavity, have been produced under ultrasonic conditions. The cavitation effect produces effective physical, chemical and biological transformations. Thus ultrasound irradiation has been employed in synthetic organic chemistry, medicinal chemistry and material sciences.[64–68]

A number of catalysts have been used in one-pot MCRs for the synthesis of isoxazole scaffold including sodium acetate,[34] potassium hydrogen phthalate,[35] tetrabutylammonium perchlorate,[36] *N*-bromosuccinimide,[37] sodium benzoate,[38] boric acid,[39] pyridinium *p*-toluenesulfonate,[40] 1,4-diazabicyclo[2.2.2]octane,[41] 4-aminobenzene-1-sulfonic acid,[42] cerium chloride heptahydrate,[43] antimony trichloride,[44] iodine,[45] 2-hydroxy-5-sulfobenzoic acid,[46] potassium phthalimide,[47] pyridine,[48] NaH_2PO_4,[49] Ag/SiO_2,[50] phosphotungstic acid,[51] nano-MgO,[52] itaconic acid,[53] sodium sulphide,[54] citric acid,[55] hydroxyapatite nanoparticles[69] and deep eutectic solvents.[70] The gold-catalyzed cyclization of *O*-propioloyl oxime *via* intermolecular arylidene group transfer,[71] reaction of 1,3-dicarbonyl compounds with benzaldoximes derivatives,[72] two-step condensation of 3-Phenylisoxazol-5-one with aryl halide in the presence of KF/alumina,[73] cycloadditions of ethyl benzoyl nitromethane or 2-nitroacetate with alkenes or terminal alkynes[74] were reported.

Although many of these protocols suffer from drawbacks and limitations such as strongly acidic or basic conditions, low yields, long reaction times, the use of toxic reagents, harsh reaction conditions, the use of expensive catalysts and tedious workup procedures that restricts their scope in practical applications. Moreover, compared to the commonly used organic solvents, water is the ideal green solvent for organic reactions, because of its cost-efficiency, abundance, easy handling, high stability, non-flammability, environmental compatibility and nontoxicity.[75]

Considering the above points, there is still a need for novel and greener methodologies to fulfil the increasing demands of modern synthetic chemistry, which avoid harsh reaction conditions and allow an efficient route for the synthesis of isoxazole derivatives. Recently, we have reported pyruvic acid as a highly efficient catalyst for the synthesis of bis(indolyl)methanes.[76] This finding provoked us to evaluate the catalytic potential of pyruvic acid in the synthesis

of isoxazol-5(4*H*)-one derivative. Our literature survey revealed that there is no report on the use of pyruvic acid as a catalyst in the synthesis of isoxazol-5(4*H*)-one derivative; hence to explore its catalytic utility, herein we report the synthesis of isoxazol-5(4*H*)-one derivative *via* the one-pot, a three-component process catalyzed by pyruvic acid under conventional and ultrasound irradiation.

Apart from this Pyruvic acid is the most vital α-oxocarboxylic acid and plays a fundamental role in energy metabolism in living organisms. It effectively reduces cholesterol,[77] improves exercise endurance capacity,[78] serves as a potent antioxidant,[79] reduces anoxic injury and free radical formation.[80]

2. Experimental

2.1 *Materials*

All the chemicals were purchased from commercial sources and used without further purification. Probe sonicator (Model ATP- 250 Athena Technology) was used for ultrasound irradiation. Thin-layer chromatography (TLC) was performed on silica gel $60F_{254}$ (0.25 mm thickness) plates, which were visualized under short (254 nm) and long (365 nm) UV light. Column chromatography was performed using silica gel 100–200 mesh size. Melting points (Mp) were determined in open capillary tubes using paraffin oil bath and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on 500 and 125 MHz NMR spectrometer, respectively using $CDCl_3$ and DMSO-d_6 as solvent. Chemical shifts δ are reported in ppm relative to Me_4Si internal standard. The multiplicity of signals is designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). FT-IR was recorded on the IR-Affinity1 Shimadzu DRS-8000A instrument. High-resolution mass spectra (HRMS) were obtained using micromass-Q-TOF machine operating in electrospray ionization (ESI) mode.

2.2 *General procedure for the synthesis of 4a-i under ultrasound irradiation condition*

A mixture of benzaldehyde (0.50 g, 4.71 mmol), hydroxylamine hydrochloride (0.33 g, 4.71 mmol), ethyl acetoacetate (0.61 g, 4.71 mmol) and pyruvic acid catalyst (0.02 g, 0.023 mmol) in water (10 mL) were sonicated at 50 °C for the indicated time. After the completion of the reaction (TLC check), the reaction mixture was cooled to room temperature and extracted using ethyl acetate (2 X 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography using ethyl acetate: *n*-hexane (20-40%) as the eluent to yield the pure product

2.2a *(Z)-4-benzylidene-3-methylisoxazol-5(4H)-one (4a)*: Yellow solid; M.p.: 140-142 °C; IR (KBr): 3475, 3053, 2322, 1732, 1620, 1454, 1352, 1220, 1124, 879, 763, 689, 574 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 8.42 (d, J = 7.6 Hz, 2H), 7.97 (s, 1H), 7.68-7.65 (m, 1H), 7.59 (t, J = 7.6 Hz, 2H), 2.30 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO) δ 168.31, 162.71, 152.14, 134.39, 134.05, 132.92, 129.73, 129.36, 129.04, 119.33, 11.78 ppm; HRMS (ESI) m/z: calcd for $C_{11}H_{10}NO_2$ $[M+H]^+$ 188.0706 found 188.0705.

2.2b *(Z)-4-(4-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (4b)*: Yellow solid; M.p.: 212-214 °C; IR (KBr): 3261, 3037, 1728, 1552, 1301, 1232, 1132, 999, 894, 775, 561 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 11.06 (s, 1H), 8.46 (d, J = 8.8 Hz, 2H), 7.81 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 2.26 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO) δ 169.32, 164.34, 162.78, 152.05, 138.03, 125.05, 116.64, 114.32, 11.78 ppm; HRMS (ESI) m/z: calcd for $C_{11}H_{10}NO_3$ $[M+H]^+$ 204.0655 found 206.0645.

2.2c *(Z)-3-methyl-4-(4-methylbenzylidene) isoxazol-5(4H)-one (4c)*: Light yellow solid; M.p.: 134-136 °C; IR (KBr): 3458, 3095, 2594, 1732, 1600, 1508, 1408, 1354, 1111, 879, 775, 588 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, J = 8.2 Hz, 2H), 7.39 (s, 1H), 7.33 (d, J = 8.1 Hz, 2H), 2.45 (s, 3H), 2.30 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.22, 161.20, 149.93, 145.76, 134.16, 131.04, 129.93, 118.50, 22.11, 11.71 ppm; HRMS (ESI) m/z: calcd for $C_{12}H_{12}NO_2$ $[M+H]^+$ 202.0862 found 202.0861.

2.2d *(Z)-4-(2-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (4d)*: Yellow solid; M.p.: 198-200 °C; IR (KBr): 3192, 1955, 1753, 1602, 1458, 1267, 1095, 902, 773, 580 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 11.01 (s, 1H), 8.74 (dd, J = 8.0, 1.2 Hz, 1H), 8.09 (s, 1H), 7.51-7.48 (m, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.94 (m, 1H), 2.26 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO) δ 168.75, 162.63, 160.12, 145.49, 137.23, 132.78, 119.94, 119.57, 116.90, 116.61, 11.68 ppm; HRMS (ESI) m/z: calcd for $C_{11}H_{10}NO_3$ $[M+H]^+$ 204.0655 found 204.0653.

2.2e *(Z)-4-(3,4-dimethoxybenzylidene)-3-methylisoxazol-5(4H)-one (4e)*: Yellow solid; M.p.: 134-136 °C; IR (KBr): 3446, 3097, 2846, 1732, 1508, 1244, 1111, 995, 881, 777, 565 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, J = 2.1 Hz, 1H), 7.60 (dd, J = 8.5, 2.1 Hz, 1H), 7.33 (s, 1H), 6.96 (d, J = 8.5 Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.02, 161.35, 154.58, 149.81, 149.09, 131.23, 126.38, 116.28, 115.06, 110.71, 56.23, 56.19, 11.68 ppm; HRMS (ESI) m/z: calcd for $C_{13}H_{14}NO_4$ $[M+H]^+$ 248.0917 found 248.0916.

2.2f *(Z)-4-(4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (4f)*: Yellow solid; M.p.: 174-176 °C; IR (KBr): 3448, 3034, 2833, 2357, 1732, 1514, 1435, 1269, 1176, 875, 775, 563 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 8.9 Hz, 2H), 7.35 (s, 1H), 7.02 (d, J = 9.0 Hz, 2H), 3.92 (s, 3H), 2.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.80, 164.62, 161.29, 149.35, 136.99, 125.84, 116.40, 114.69, 55.74, 11.71 ppm; HRMS (ESI) m/z: calcd for $C_{12}H_{12}NO_3$ $[M+H]^+$ 218.0811 found 218.0810.

2.2g *(Z)-4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (4g)*: Yellow solid; M.p.: 214-216 °C; IR (KBr): 3273, 3005, 2140, 1936, 1732, 1558, 1313, 1284, 1184, 1001, 889, 756, 563 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 10.81 (bs, 1H), 8.53 (d, J = 1.9 Hz, 1H), 7.92 (dd, J = 8.4, 1.9 Hz, 1H), 7.80 (s, 1H), 6.97 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H), 2.26 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO) δ 169.50, 162.78, 154.36, 152.38, 147.95, 132.09, 125.52, 117.14, 116.30, 114.14, 56.00, 11.78 ppm; HRMS (ESI) m/z: calcd for $C_{12}H_{12}NO_4$ $[M+H]^+$ 234.0760 found 234.0759.

2.2h *(Z)-4-(3-hydroxy-4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (4h)*: Orange solid; M.p.: 212-214 °C; IR (KBr): 3282, 3057, 2015, 1697, 1570, 1516, 1448, 1288, 1136, 1010, 881, 779, 569 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.6, 2.1 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.30 (s, 1H), 6.98 (d, J = 8.6 Hz, 1H), 5.69 (s, 1H), 4.02 (s, 3H), 2.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.55, 161.24, 151.81, 149.59, 145.59, 129.09, 126.48, 119.54, 117.08, 110.60, 56.26, 11.70 ppm; HRMS (ESI) m/z: calcd for $C_{12}H_{12}NO_4$ $[M+H]^+$ 234.0760 found 234.0763.

2.2i *(Z)-4-((1H-indol-3-yl)methylene)-3-methylisoxazol-5(4H)-one (4i)*: Brown solid; M.p.: 240-242 °C; ^1H NMR (500 MHz, DMSO) δ 12.81 (s, 1H), 9.52 (s, 1H), 8.20-8.15 (m, 2H), 7.63-7.60 (m, 1H), 7.35-7.33 (m, 2H), 2.35 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO) δ 170.88, 162.20, 140.97, 139.00, 136.85, 128.45, 124.43, 123.05, 119.33, 113.62, 113.14, 109.29, 11.70 ppm; HRMS (ESI) m/z: calcd for $C_{13}H_{11}N_2O_2$ $[M+H]^+$ 227.0815 found 227.0817.

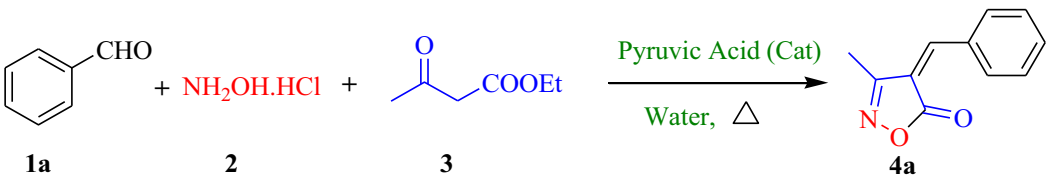
2.3 *General procedure for the synthesis of 4a-i under the conventional condition*

A mixture of benzaldehyde (0.5 g, 4.71 mmol), hydroxylamine hydrochloride (0.327 g, 4.71 mmol), ethyl acetoacetate (0.613 g, 4.71 mmol) and pyruvic acid catalyst (0.02 g, 0.023 mmol) in water (10 mL) were refluxed for the indicated time. After the completion of the reaction (TLC check), the reaction mixture was cooled to room temperature and extracted using ethyl acetate (2 X 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography using ethyl acetate: *n*-hexane (20-40%) as the eluent to yield the pure product.

3. Results and Discussion

In order to optimize the reaction conditions, the model reaction was performed using benzaldehyde (**1a**), hydroxylamine hydrochloride (**2**) and ethyl acetoacetate (**3**) in the presence of different amounts of catalyst in an aqueous medium and the results are summarized in Table 1. Firstly, the reaction conditions were optimized under conventional heating and the progress of the reaction was monitored by TLC analysis. When the reaction was conducted in water without pyruvic acid catalyst, the reaction did not proceed until 2 h (Table 1, entry 1). Performing the same reaction in the presence of 2 mol% pyruvic acid catalyst in an aqueous medium at R.T. and at 50 °C led to the formation of a trace amount of **4a** after 2 h (Table 1, entries 2, 3). In order to improve the results, the catalyst amount was increased to 5 mol% and the reaction mixture was stirred at 60 °C and 80 °C for 2 h. This showed a considerable impact on the yield (Table 1, entries 4, 5). Improvement in the reaction profile in terms of the yield was observed at higher temperatures (Table 1, entry 6). Finally, it was found that 5 mol% of pyruvic acid catalyst was sufficient to obtain the desired product **4a** in 86% yield after 2.5 h stirring at refluxed temperature (Table 1, entry 6). Increasing

Table 1. Optimization of the reaction condition under conventional heating[a].



1a **2** **3** **4a**

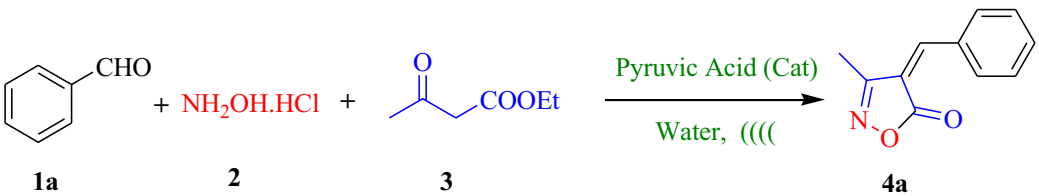
Entry	Catalyst (mol %)	Temp (°C)	Time (h)	% Yield[b]
1	0	R.T.	2	NR[c]
2	2	R.T.	2	Trace
3	2	50	2	Trace
4	5	60	2	40
5	5	80	2	73
6	**5**	**100**	**2.5**	**86**
7	10	100	2.5	86
8	5	100	3	85
9	5	100	3.5	86

[a]The reactions were carried out on 5.0 mmol scale; 1 equivalents of each benzaldehyde, hydroxylamine hydrochloride and ethyl acetoacetate were employed. [b]Isolated yield. [c]No reaction.

the reaction time and catalyst load to 10 mol% did not show any great change in the reaction profile (Table 1, entries 7–9).

These results obtained at conventional conditions (Table 1) led us to explore an alternative procedure to prepare product **4a** in higher yield. In this sense, we choose ultrasound as an alternative energy source to provide a selective reaction. Thus, the same reaction condition was applied for the reaction under ultrasound irradiation; however, product **4a** was not obtained in the absence of pyruvic acid catalyst at R.T. (Table 2, entry 1). By increasing the catalyst load to 2 and 5 mol% at 40 °C, the desired product **4a** was obtained in 25% and 71% yield, respectively (Table 2, entries 2, 3). To check the effect of temperature on reaction profile, we increased temperature to 50 °C, which resulted in the formation of the product in 90% yield in 15 min (Table 2, entry 4). No improvement

Table 2. Optimization of the reaction condition under ultrasonic irradiation[a].



1a **2** **3** **4a**

Entry	Catalyst (mol %)	Temp (°C)	Time (min)	% Yield[b]
1	0	R.T.	10	NR[c]
2	2	40	15	25
3	5	40	15	71
4	**5**	**50**	**15**	**90**
5	10	50	20	90
6	5	60	20	89

[a]The reactions were carried out on 5.0 mmol scale; 1 equivalents of each benzaldehyde, hydroxylamine hydrochloride and ethyl acetoacetate were employed. [b]Isolated yield. [c]No reaction.

was observed in the reaction profile by increasing the catalyst loading, temperature and time (Table 2, entries 5, 6). Thus, the optimum reaction condition for the reaction was found, when the benzaldehyde (**1a**) was sonicated in water at 50 °C with hydroxylamine hydrochloride (**2**) and ethyl acetoacetate (**3**) in the presence of 5 mol% pyruvic acid catalyst for 15 minutes which afforded isoxazole derivative **4a** in 90% yield (Table 2, entry 4).

The optimum reaction condition is applied to a variety of differently substituted aldehydes and the results obtained are summarized in Table 3. We notice that whatever the nature of the substituent and its position yields remain very good and vary between 73 to 90% (Table 3, entries 1–9). Moreover, it is observed that the mono, as well as di-substituted aldehydes, reacts smoothly to give corresponding 4*H*-isoxazol-5-ones derivatives in good yields. Phenolic aldehyde like vanillin and isovanillin also condensed efficiently to afford 4*H*-isoxazol-5-one derivative **4g** and **4h** in comparative yields (Table 3, entries 7, 8). In addition to benzaldehydes, indole-based aldehyde like Indole-3-carboxaldehyde also condensed efficiently to afford isoxazole derivative **4i** in good yield (Table 3, entry 9).

As shown in Table 3, the reactions were carried out under the ultrasound irradiation method happens comparatively at faster rates with higher yields

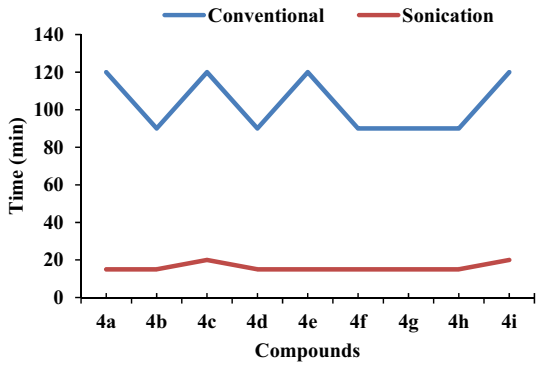
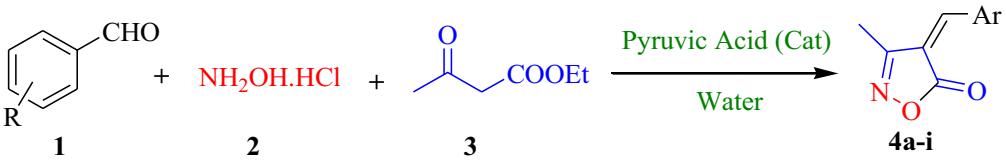


Figure 2. Time required for reaction under conventional and sonication method.

(Figure 2). While the same reactions were carried out under conventional heating, require a longer time and gave lower yields. Notably, a similar effect was seen in all reactions and it was evident that ultrasound irradiation can speed up the reaction considerably to reduce the reaction time with high yields. Thus, we found that ultrasonic irradiation was very effective and useful in our work, which was superior to the conventional method with respect to yields and reaction time. Moreover, although earlier reported methods are quite suitable with respect to reaction yield many of them were carried out at drastic conditions or require expensive catalysts. Furthermore, several previously

Table 3. Synthesis of 4*H*-isoxazol-5-one derivatives using pyruvic acid catalyst[a].



Entry	R	Compound	Conventional Heating (100 °C)		Ultrasonication (50 °C)	
			Time (h)	% Yield[b]	Time (min)	% Yield[b]
1[c]	H	**4a**	2	85	15	90
2[c]	4-OH	**4b**	1.5	80	15	85
3[c]	4-Me	**4c**	2	88	20	92
4[c]	2-OH	**4d**	1.5	85	15	90
5[c]	3,4-di-OMe	**4e**	2	88	15	92
6[c]	4-OMe	**4f**	1.5	81	15	88
7[c]	3-OMe,4-OH	**4g**	1.5	83	15	85
8	3-OH,4-OMe	**4h**	1.5	85	15	90
9[c]	Indole-3-carboxaldehyde	**4i**	2	73	20	78

[a]The reactions were carried out on 5.0 mmol scale; 1 equivalents of each aldehyde, hydroxylamine hydrochloride, ethyl acetoacetate and 5 mol% pyruvic acid catalyst were employed. [b]Isolated yield. [c]All compounds are known and their spectroscopic and physical data is consistent with those of authenticating samples.[34,39,40]

reported reactions are performed in volatile organic solvents, which are not environmentally friendly. Thereby, we propose the use of pyruvic acid as a catalyst and water as a biologically and environmentally safe solvent to provide an eco-friendly and economical procedure for the synthesis of 4*H*-isoxazol-5-one derivatives, which can be afforded in 15 to 20 min.

As described in Figure 3 we have proposed a plausible reaction mechanism for the pyruvic acid-catalyzed one-pot multicomponent reaction between aromatic aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride in an aqueous medium. Initially, acidic proton of pyruvic acid interacts with the carbonyl oxygen of ethyl acetoacetate, which activates the carbonyl group to facilitate nucleophilic attack of the amino group of hydroxylamine followed by dehydration, resulting in the formation of oxime **A**. The keto-enol tautomerism of oxime **A** results in the formation of intermediate **B**. The activated methylene carbon of intermediate **B** then shows nucleophilic attack on the carbonyl carbon of the aromatic aldehyde which is also activated by pyruvic acid catalyst under sonication followed by dehydration gives intermediate **C**. The formed intermediate **C** eventually undergoes cyclisation by the intramolecular attack of oxygen atom of hydroxyl group to ester carbonyl with the elimination of ethanol molecule to form intermediate **D**. Intermediate **D** on de-protonation results into desired product 3-methyl-4-arylmethylene isoxazole-5(4*H*)-one.

The reusability of catalyst was investigated through a series of sequential condensations of 4-hydroxybenzaldehyde, hydroxylamine hydrochloride and ethyl acetoacetate in the presence of pyruvic acid as a model reaction under ultra-sonication. After completion of the reaction, the reaction mixture was extracted using

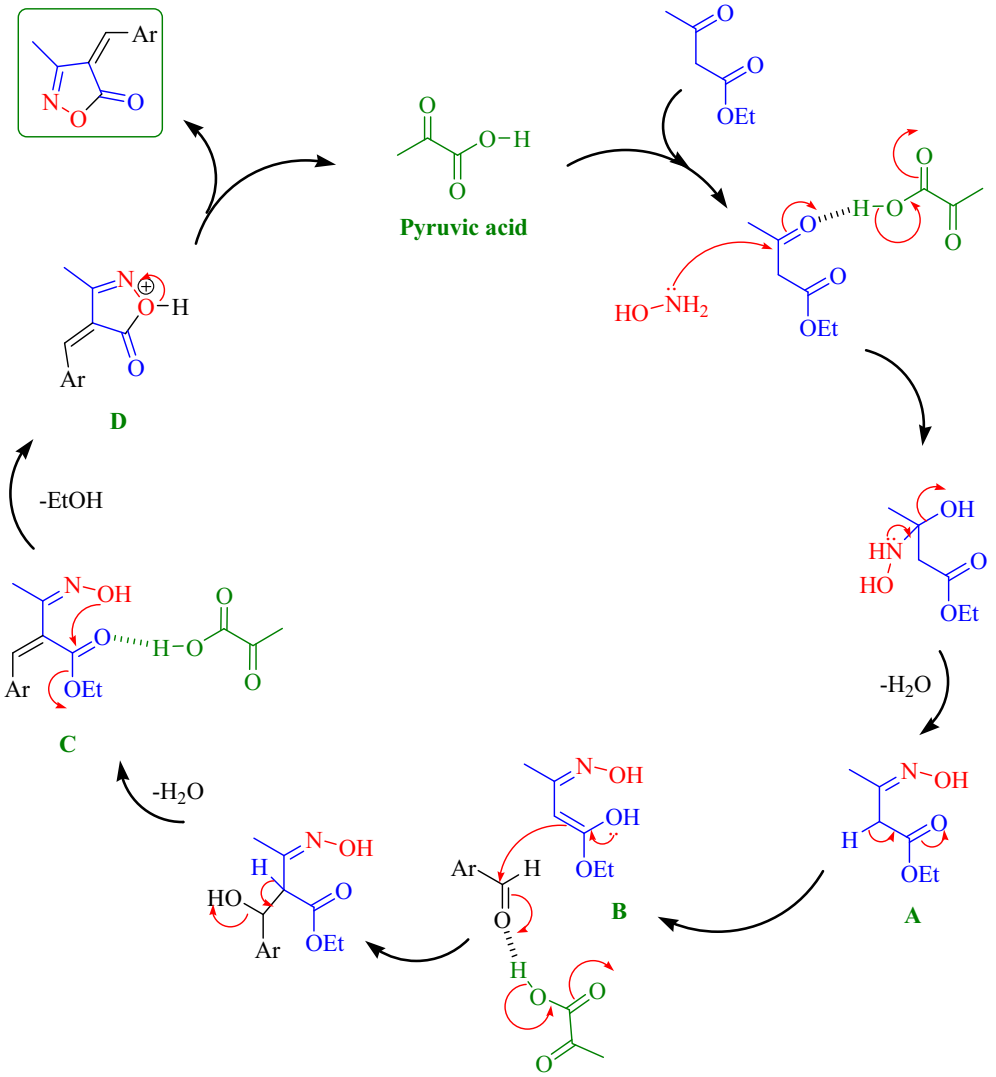


Figure 3. Plausible mechanism for the formation of isoxazoles using pyruvic acid catalyst.

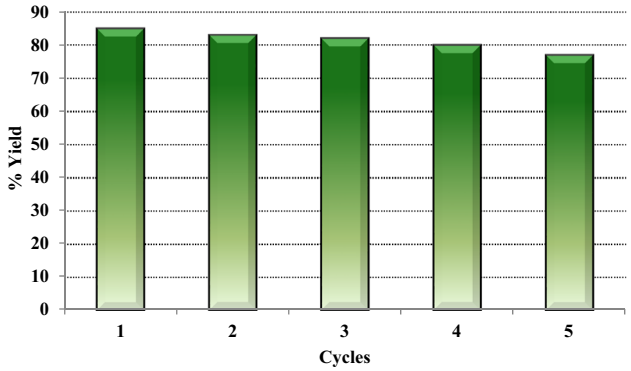


Figure 4. Reusability study of pyruvic acid catalyst under ultrasound irradiations.

ethyl acetate and an aqueous layer was used again for the model reaction without the addition of a catalyst. The obtained results revealed that the catalyst could be reused five consecutive cycles without any pre-treatment and with a negligible decrease in activity (Figure 4).

4. Conclusions

We describe here a new, efficient process for the synthesis of 3-methyl-4-arylmethylene isoxazole-5(4*H*)-ones by a one-pot multicomponent reaction between aromatic aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride catalysed by pyruvic acid as a benign, commercially available, inexpensive catalyst. The essential advantages of this method are simplicity of use, good yields and short reaction times, use of non-toxic solvent and non-conventional energy source and eco-friendly method. We believe that the present protocol is a convenient and efficient alternative to the existing traditional methods.

Supplementary Information (SI)

The Supplementary Information contains all the ^{1}H NMR, ^{13}C NMR, IR and HRMS spectra's of synthesized compounds. Supplementary Information is available at www.ias.ac.in/chemsci.

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