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Ultrasound-assisted Method for the Synthesis of 3-Methyl-4-arylmethylene Isoxazole-5(4*H*)-ones Catalyzed by Imidazole in Aqueous Media

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In the present study, an attempt has been made to synthesize 3-methyl-4-arylmethylene isoxazole-5(4*H*)-one derivatives through sonication of hydroxylamine hydrochloride, ethyl acetoacetate and benzaldehyde derivatives in the presence of imidazole as a novel and effective catalyst in aqueous media. This green reaction under ultrasound irradiation has advantageous compared to conventional procedures in view of its shorter reaction times, high isolated yields, avoidance of using organic solvents, simple experimental procedure and workup and energy conservation. A combination of the advantages of ultrasound irradiation, homogeneous catalyst and aqueous media provides an important methodology for carrying out catalytic transformations.

Keywords: Isoxazoles, Ultrasound irradiation, Imidazole, Catalyst, Water

INTRODUCTION

Isoxazole derivatives are important organic heterocycles possessing various pharmacological activities. Organic compounds containing isoxazole can act as fungicidal, anticonvulsant, analgesic, antimicrobial, antioxidant, anti-obesity, herbicidal, nematicidal, protein kinase C (PKC) inhibitory, as well as antimycobacterial agent [1-3]. Hence, these molecules are attractive target for the synthesis. More recently, the most straight forward synthesis of isoxazole heterocycles involving the one-pot reactions of an aldehyde, hydroxylamine hydrochloride and a β-ketoester in the presence of different types of catalysts, has been reported [4-8]. Ghosh and *et al*. have been developed green synthesis of 3-methyl-4-arylmethylene isoxazole-5(4*H*)-ones by visible light *via* multicomponent reaction of aromatic aldehydes, ethyl acetoacetate, hydroxylamine hydrochloride, and sodium acetate in aqueous ethanol [6]. The salient features of their research protocol include operational simplicity, high yields and clean reaction conditions.

On the other hand, the ultrasound irradiation has been established as an important synthetic strategy. In general, organic reactions under sonication are more advantageous compared to classical methods in view of its shorter reaction times, higher yields, simple experimental procedure and workup and energy conservation [9]. Moreover, homogeneous catalysts under sonochemical conditions are well-known as an important technique for the organic transformations. Despite some difficulties in separating the homogeneous catalysts from the final reaction product, homogeneous catalytic processes are the first choice for the chemists because of their high activity and selective chemical reactions with high yields and simplicity in the experimental procedure. Examples of these homogeneous catalysts include mineral acids and bases, organic acids and bases and transition metal compounds [10]. Imidazole is a commercially available and efficient basic catalyst in several reactions including synthesis of pyranopyrazoles in aqueous medium [11], the acylation of cellulose [12] and the monoacylation of symmetrical diamines [13].

The present work is devoted to the ultrasonic assisted synthesis of 3-methyl-4-arylmethylene isoxazole-5(4*H*)-ones by three-component condensation of aldehyde derivatives with hydroxylamine hydrochloride and ethyl

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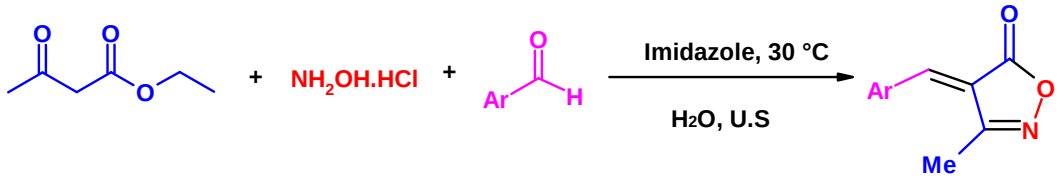


Scheme 1. Synthesis of 3-methyl-4-arylmethylene isoxazole-5(4*H*)-ones using imidazole under ultrasound

acetoacetate in the presence of imidazole in aqueous solutions (Scheme 1).

EXPERIMENTAL PROCEDURES AND MATERIALS

Chemicals were purchased from the Merck and Fluka Chemical Companies in high purity. All materials were of commercial reagent grade. IR spectra were recorded as KBr pellets on a Perkin-Elmer 781 spectrophotometer and on an Impact 400 Nicolet FTIR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX-400 Avanced spectrometer. The melting points were determined by a Yanagimoto micro melting point apparatus. A Bandelin Sonorex Super 10P Ultrasonic Bath (water) (with a frequency of 35 kHz and a nominal power 100 W) was used. The purity determination of the substrates and reaction monitoring were accomplished by thin layer chromatography (TLC) on silica gel polygram SILG/UV 254 plates.

General Procedure for the Synthesis of 3-Methyl-4-arylmethylene isoxazole-5(4*H*)-ones

A mixture of 4-methoxy benzaldehyde (1 mmol, 0.13 g), ethyl acetoacetate (1 mmol, 0.13 g), hydroxylamine hydrochloride (1 mmol, 0.69 g) and imidazole (5 mol%, 0.03 g) as catalyst in distilled water (5 ml) in a 50 ml round-bottomed flask irradiated under sonication at 30 °C. Precipitate is gradually formed during the reaction. After completion of the reaction (monitored by TLC; petroleum ether-ethyl acetate 1:1), the precipitate was filtered off and washed with cold distilled water (3 ml) and dried in the air to obtain the solid products. The crude product was crystallized from EtOH to afford the pure product in high yield. Spectral data for some compounds are as follows:

Spectral and Physical Data of Selected Compounds

3-Methyl-4-(4-methoxybenzylidene)isoxazol-5(4H)-one (4a). Yellow powder; M.P$_{rep.}$ (°C): 174; M.P$_{lit.}$ (˚C): 173-176; IR (KBr) υ (cm^{-1}): 3100 (=CH), 2977 (CH), 1730 (C=O), 1590, 1431 (C=C), 1266, 1179 (C-O); ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 2.35 (s, 3H, CH$_3$), 3.92 (s, 3H, CH$_3$O), 7.02 (d, ^{3}J = 8.8 Hz, 2H, ArH), 7.26 (s, 1H, ═CH), 8.46 (d, ^{3}J = 8.8 Hz, 2H, ArH).

3-Methyl-4-(2-methoxybenzylidene) isoxazol-5(4H)-one (4b). Yellow powder; M.P$_{rep.}$ (°C): 137-139; M.F: $C_{12}H_{11}NO_3$; R$_f$ (in petroleum ether:ethylacetate; 1:1 (v/v)): 0.89; UV (CHCl$_3$) λ$_{max}$ (nm): 392; IR (KBr) υ (cm^{-1}): 3100 =CH), 2938 (CH), 1733 (C=O), 1593, 1479 (C=C), 1256, 1170 (C-O); ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 2.35 (s, 3H, CH$_3$), 3.94 (s, 3H, CH$_3$O), 6.95 (d, 1H,^{3}J = 8 Hz, ArH), 7.10 (t, 1H, ^{3}J = 11 Hz, ArH), 7.56 (t, 1H, ^{3}J = 8 Hz, ArH), 8.11 (s, 1H, =CH), 8.92 (d, 1H, ^{3}J = 11 Hz, ArH); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 11.6, 50.0, 111.1, 115.6, 119.6, 126.2, 129.6, 146.7, 150.6, 153.7, 161.5, 168.7.

3-Methyl-4-(3-hydroxy-4-methoxybenzylidene)isoxazol-5(4H)-one (4h). Orange powder; M.P$_{rep.}$ (°C): 187-189; M.F: $C_{12}H_{11}NO_4$; R$_f$ (in petroleum ether:ethylacetate; 1:1 (v/v)): 0.48; UV (CHCl$_3$) λ$_{max}$ (nm): 396; IR (KBr) υ (cm^{-1}): 3283 (OH), 3100 (=CH), 2844 (CH), 1696 (C=O), 1571, 1445 (C=C), 1260, 1190 (C-O); ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 2.35 (s, 3H, CH$_3$), 4.12 (s, 3H, CH$_3$O), 5.58-8.03 (s, 1H, OH), 6.97 (d, 1H, ^{3}J = 8.4 Hz, ArH), 7.37 (s, 1H,═CH), 8.05 (d, 1H, ^{4}J = 2 Hz, ArH), 8.19 (d, 1H, ^{3}J = 8.4 Hz, ArH); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 11.7, 55.9, 110.0, 118.3, 120.1, 121.2, 133.4, 136.3, 144.1, 159.8, 161.6, 168.4.

4-(4-(Dimethylamino)benzylidene)-3-methylisoxazol-5(4H)-one (4i). Red powder; M.P$_{rep.}$ (°C): 224; M.P$_{lit.}$ (°C): 226-228; IR (KBr) υ (cm^{-1}): 3080 (=CH), 2915 (CH), 1716 (C=O), 1590, 1530 (C=C), 1300 (C-O); ^{1}H NMR (CDCl$_3$,

400 MHz) δ (ppm): 2.27 (s, 3H, CH_3), 3.16 (s, 6H, $N(CH_3)_2$), 6.72 (d, ^3J = 8.4 Hz, 2H, ArH), 7.26 (s, 1H, =CH), 8.43 (d, ^3J = 8.4 Hz, 2H, ArH).

RESULTS AND DISCUSSION

Initial studies were carried out by reaction of 4-methoxy benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and hydroxylamine hydrochloride (1 mmol) in the presence of imidazole under various reaction conditions.

The ultrasound assisted reaction to obtain 4a was examined using a variety of solvents and the results were summarized in Table 1. As shown in Table 1, H_2O proved to be the solvent of choice for all future studies. Therefore, enhancement effect on the reaction rate and yield by combining homogeneous catalyst with ultrasound is presented as an alternative methodology for the production of isoxazoles. Liquids irradiated with ultrasound can

Table 1. Screening of Solvent Effect on the Model Reaction under Ultrasound Irradiation at 30 °C

Entry	Solvent	Time (min)	Yield (%)	
			with US	without US
1	H_2O	25	96	60
2	Ethanol	25	70	30
3	Methanol	25	47	25
4	EtOH:H_2O (1:1)	25	70	40
5	DCM	25	37	15

Table 2. Effect of Catalyst on the Model Reaction under Ultrasound Irradiation

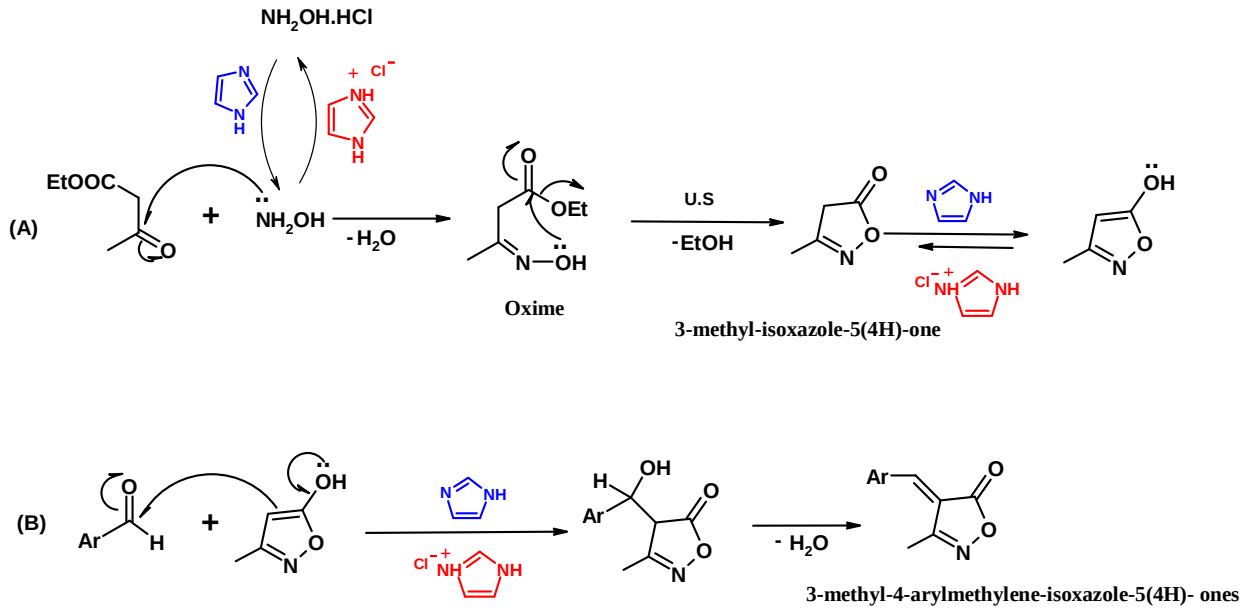
Entry	Catalyst (mol%)	Time (min)	Yield (%)
1	None	120	30
2	NaOH (5)	25	44
3	KOH (5)	25	40
4	Na_2CO_3 (5)	25	40
5	$NaHCO_3$ (5)	25	30
6	NEt_3 (5)	25	35
7	Imidazole (3)	25	78
8	Imidazole (4)	25	86
9	Imidazole (5)	25	96
10	Imidazole (6)	25	95

Table 3. Preparation of Different Isoxazole-5(4*H*)-ones Catalyzed by Imidazole in Ultrasonic Conditions

Entry	Ar	Product	Time (min) /yield (%)	M.p. (lit. mp) [Ref.]
1	4-OMe-C_6H_4	4a	25/95	174-175 (173-174) [4a]
2	2-OMe-C_6H_4	4b	30/93	137-139
3	3,4-$(OMe)_2$-C_6H_3	4c	40/90	134-135 (135) [6]
4	4-OH-C_6H_4	4d	30/92	214-215 (213-215) [4a]
5	3-OH-C_6H_4	4e	30/90	202-203 (202-203) [4a]
6	2-OH-C_6H_4	4f	47/92	197-199 (198-199) [4a]
7	4-Me-C_6H_5	4g	70/88	130-133 (130-132) [4a]
8	3-OH-4-OMe-C_6H_3	4h	30/89	187-189
9	4-$N(CH_3)_2$-C_6H_4	4i	30/91	224-226 (226-228) [4a]
10	C_6H_5	4j	90/80	141-143 (141-142) [4a]
11	3-Indole-carboxaldehyde	4k	45/87	243-244 (240) [6]
12	2-Tiophen	4l	40/86	144-145 (144-146) [4a]

Table 4. Comparison of Imidazole with other Catalysts for the Synthesis of 4a

Entry	Catalyst (g)	Condition	Yield (%)	Time (min)	Ref.
1	Na_2S	EtOH/r.t.	88	90	[15]
2	Pyridine	EtOH/reflux	71	180	[16]
3	Sodium benzoate	H_2O/r.t.	87	90	[8b]
4	Sodium saccharin	H_2O/r.t.	91	50	[4a]
5	Potassium phthalimide	H_2O/r.t.	96	70	[5]
6	Boric acid	H_2O/r.t.	92	50	[4b]
7	Sodium silicate	H_2O/r.t.	91	90	[8a]
8	DL-Tartaric acid	H_2O/r.t.	60	85	[4c]
9	Visible light	Aqueous ethanol	82	10	[6]
10	Imidazole	H_2O/U.S	95	25	This work



Scheme 2. The plausible mechanism for the formation of 4-arylmethylene isoxazole-5(4*H*)-ones

produce cavitations, namely, formation, growth, and implosive collapse of tiny bubbles. Cavitation generates localized microscopic "hot spots" with transient high temperatures and pressures to induce favorable conditions for chemical reactions [14].

Subsequently, the effects of catalysts were investigated for this model reaction. The results are shown in Table 2. The catalytic activity of imidazole was evident when the trace product was obtained in the absence of the catalyst (Table 2, entry 1). Moreover, the various alkaline catalysts were studied for their activities in the model reaction (Table 2, entries 2-6). However, imidazole was identified as an effective catalyst for the syntheses of 3-methyl-4-arylmethylene isoxazole-5(4*H*)-ones under ultrasound irradiations. Next, we further turned to test the effect of catalyst loading. It was found that the highest yield was obtained using 5 mol% catalyst (Table 2, entry 9). Higher amounts of catalyst did not lead to significant change in the reaction yields (Table 2, entry 10).

After optimization of the reaction conditions, aromatic aldehyde derivatives were treated with hydroxylamine hydrochloride and ethyl acetoacetate in the presence of a catalytic amount of imidazole in water under sonication. The results are shown in Table 3. In all cases, the conversion was completed under sonication with excellent yields of desired products.

Then, we compared our catalytic data with that found in the literature. Comparison of the results shows a better catalytic activity of imidazole to sonochemical synthesis of isoxazoles (Table 4).

The formation of the products can be explained by a plausible reaction mechanism as shown in Scheme 2. In the first step, the imidazole helps to generate NH_2OH from $NH_2OH.HCl$, and the nucleophilic attack of the amino group of hydroxylamine on the carbonyl carbon of the ethyl acetoacetate resulted in intermediate oxime. Then cyclization of intermediate oxime was performed for the synthesis of 3-methyl-isoxazole-5(4*H*)-one under ultrasound irradiation. In the second step, in the presence of imidazole, the Knoevenagel condensation reaction between 3-methyl-isoxazole-5(4*H*)-ones and aromatic aldehydes leads to formation of 3-methyl-4-arylmethylene-isoxazole-5(4*H*)-ones [5,6].

CONCLUSIONS

In summary, a simple, efficient and environmentally benign method for the sonochemical synthesis of 3-methyl-

4-arylmethylene-isoxazol-5(4*H*)-one derivatives by the use of homogeneous catalytic system has been described. Excellent yields, the use of a cost effective catalyst for the synthesis of isoxazoles, practicability and operational simplicity are the important features of this method.

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