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Synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones catalyzed by Tartaric acid in aqueous media

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Abstract

An efficient and green synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones using tartaric acid as a catalyst for the reaction of aromatic aldehydes, ethylacetoacetate and hydroxylamine hydrochloride in water as solvent is described. This protocol offers several advantages such as atom efficiency, short reaction time, easy work-up and simple reaction condition.

Keyword: Aromatic aldehyde, ethylacetoacetate, hydroxylamine hydrochloride, water, tartaric acid catalyst, 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones.

Introduction

Organic reactions in aqueous media have attracted much attention due to its nonflammable, nontoxic, low volatility, unique reactivity and selectivity. Water is the cheapest and most non toxic solvent in the world. Organic reactions in water as a solvent are ecofriendly chemical process. It will reduce use of harmful organic solvents and the reaction carried out under mild conditions. Water as reaction media is one of the major parts of green chemistry[1-2].

Number of excellent review about organic reactions in water and synthesis of heterocyclic compounds has been published[3]. Water is used in living systems for metabolic reactions and present abundantly on our planet; hence water is referred as a universal solvent. It also helps to enhance the reaction rate because of polarity and hydrogen bonding. There is need to replace toxic solvents by greener solvents because in industrial processes huge amount of solvent get wasted.

Recently as per green chemistry[4] concerned number of methods developed in organic synthesis, such as solvent free synthesis, use of ionic liquids[5], microwave irradiation and ultrasound irradiation etc. All above methods has its own merits and limitation, but for large scale synthesis and minimizing pollution, water as a solvent is one of the best solutions. Water and mixtures of water with organic solvents are commonly used as solvents for a large variety of organic reactions[6]. K. Surendra and co-workers[7] report oxidation of sulphides to sulphoxides in aqueous media. Enzymic oxidation of glucose, aerobic oxidation of benzylic alcohols, to the corresponding aldehydes or ketones in water was developed by Kit-Ho Tong and co-workers[8]. Dambacher and co-workers report that Wittig reactions accelerated in an aqueous media[9].

Synthesis of isoxazole has focused due to their wide range of biological activities. Isoxazole is a heterocyclic compound with an oxygen atom next to the nitrogen as an important class of medicinal chemistry because of their diversified biological applications. Some natural products found isoxazole rings such as ibotenic acid. Isoxazoles also used for synthesis of number of drugs, including the COX-2 inhibitor. An isoxazolyl group is also found in many beta-lactamase-resistant antibiotics. Organic compounds containing isoxazol ring showed biologically activities such as anticonvulsant, antifungal[10], analgesic, antitumor[11], antimicrobial, antinociceptive[12], anti-inflammatory, anticancer, antiviral, antituberculosis, antimycobacterial and treatment of patients with active arthritis. Isoxazole containing moiety also can be used in optical recording and nonlinear optical research. Isoxazol structural unit are medicinally useful agents such as protein-tyrosine phosphatase inhibitor etc.

There is increasing interest in the development of new methodologies for the synthesis of isoxazole moiety due to wide importance in medicinal, industrial and in the fields of synthetic organic chemistry. A number of synthetic strategies have been developed for the preparation of isoxazole derivatives using sodium benzoate[13], sodium silicate[14], sodium sulfide[15], DABCO and pyridine[16], sodium citrate[17], sodium tetraborate[18], sodium saccharin[19], sodium ascorbate as a catalyst. In recent years, some new methods such as solid state grinding, solid state heating, microwave irradiation and under ultrasound irradiation have been reported. The synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4*H*)-ones by visible light in aqueous ethanol has been reported[20]. Synthesis of 2,3,6,6a-tetrahydrofuro[3,4] isoxazol-4 (3a)-one was reported[21].

However, these methods have its own merits as well as demerits such as expansive catalyst and solvent, harsh reaction condition, longer reaction time, poor yields and low selectivity. Nowadays

several modifications has made to minimizes these problems, but still there is a need to develop better method for synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones. In continuation of our work, a green approach for the one pot synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones using tartaric acid as a catalyst using aromatic aldehydes, ethylacetoacetate and hydroxylamine hydrochloride in aqueous media has been reported (figure-1).

Material and Methods

All reagents were obtained from commercial sources Sigma Aldrich. Column chromatography was performed using Acme silica gel (100-200 mesh). The reaction is monitored on TLC using pre-coated plates (silica gel on aluminum, Merck). Melting points were measured in open glass capillaries and may be incorrect. ^{1}H NMR was recorded at room temperature on a 200 MHz in $CDCl_3$ using TMS as internal standard. IR spectra (using KBr pellets) were obtained with a Varian 640FT-IR instrument. The products were also characterized by comparison of their melting point with literature values.

Synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones (4a-p): The solution of ethyl acetoacetate (0.130 g, 1 mmol) and hydroxylamine hydrochloride (0.07 g, 1 mmol) in 10 ml of distilled water was stirred for 10 min at room temperature. Then aromatic aldehyde (1 mmol) and catalyst DL-Tartaric acid (5 mol %) was added to the reaction mixture. The reaction mixture was stirred at room temperature for appropriate time (table-1) till solid mass appeared. Reaction is monitored by TLC and after completion of reaction the crude product was filtered and washed with cold distilled water and dried. After evaporation of filtrate the catalyst DL-Tartaric acid obtain as it is water soluble, which may be reused several times to carry out the same experiment. Crude products were recrystallized from ethanol to obtain pure product 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones (**4a-i**). The product is further purified by column chromatography using ethyl acetate:n-hexane (2:8) as an eluent. The obtained products were identified by comparison with authentic samples, ^{1}HNMR, ^{13}C NMR, IR, Mass spectra and their reported melting points (table-1).

4-benzylidene-3-methylisoxazol-5(4H)-one (4a): White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 7.45 (s, 1H), 7.53 (t, 2H), 7.61-7.64 (m, 1H), 8.36 (dd, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.6, 119.7, 129.9, 130.4, 132.2, 133.8, 134.0, 149.9, 161.3, 167.6, 168.2. MS, *m/z* (% Rel. intensities): 187.97(M^+), 147.06, 128, 88.98, 81.03.

4-(4-chlorobenzylidene)-3-methylisoxazol-5(4H)-one (4b): 1H NMR (400 MHz, $CDCl_3$): δ2.30(s, 3H), 7.37 (d, 1H), 7.37 (t, 1H), 7.47 (d, 1H), 7.49 (s, 1H), 8.30 (s, 1H), 8.33(s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.6, 77.03, 120.0, 129.3, 129.4, 130.7, 135.0, 140.4, 140.1, 161.1, 167.8.

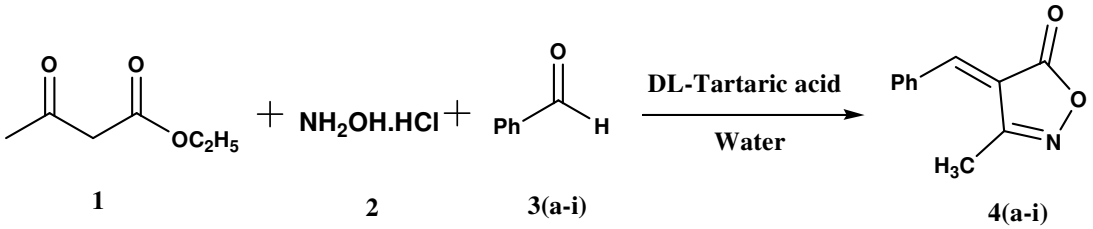
4-(4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (4c): ^{1}H NMR (400 MHz, $CDCl_3$): δ2.29(s, 3H), 3.39(s, 3H), 7.01 (t, 2H), 7.36 (m, 1H), 8.42 (dd, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.6, 55.72, 114.6, 116.1, 126.3, 133.8, 136.9, 149.3, 161.2, 164.6, 168.7. MS, *m/z* (% Rel. intensities): 217.01(M^+), 200.23, 159.13, 110.08, 89.02.

Results and Discussion

Water mediated reaction are great demand for the organic reactions. It act as ecofriendly reaction media in industrial process. Recently number of researcher works to minimize use expensive catalyst and hazardous chemicals. The use of DL-Tartaric acid in organic synthesis is focused as an mild Lewis acid catalyst which is readily available, inexpensive, non-toxic, catalyst. Number of organic transformations using tartaric acid has reported such as enantioselective heterogeneous catalysis[22], synthesis of dihydroquinolines[23], nephrosteranic acid[24], methyl amino acids[25] etc. Tartaric acid–choline chloride based deep eutectic solvent used in Clauson-Kaas reaction of aromatic amines and 2,5-dimethoxytetrahydrofuran[26,27]. Nickel powder modified with NaBr-tartaric acid used in hydrogenation of methyl acetoacetate.

Tartaric acid is a diprotic aldaric acid. It occurs naturally in many plants, particularly grapes and bananas. It is used as an antioxidant and used in the discovery of chemical chirality.

In continuation of our work to develop better method for the synthesis of heterocyclic compounds[28,29], we have designed a ecofriendly reaction methods for the synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones using water as a reaction medium (figure-1).

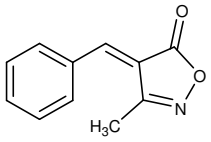
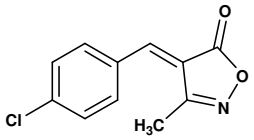
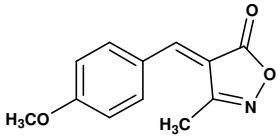
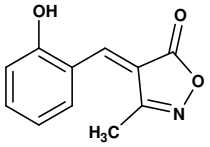
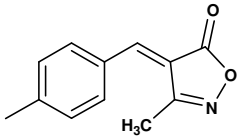
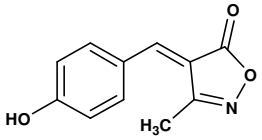
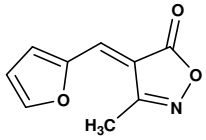
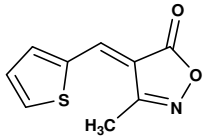
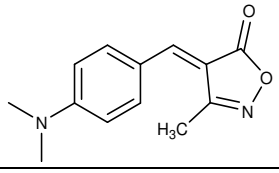


1 **2** **3(a-i)** **4(a-i)**

(Scheme-I)

Figure-1

Table-1
Synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones[a]

Entry	Product	Color of product	Reaction time (min)	Yield (%)[b]	Melting Point (Reported M.P.)[c]
4a		Brown solid	100	88	144 (140-142)[17]
4b		Orange yellow solid	120	80	128-130
4c		Dark Yellow solid	60	85	179-180
4d		Yellow solid	100	78	187 (196-198)[17]
4e		Pale Yellow solid	60	80	130 (135-136)[17]
4f		Yellow solid	110	78	202 (212-215)[17]
4g		Orange solid	90	84	228 (237-238)[17]
4h		Yellow solid	100	85	145 (145-147)[17]
4i		Red solid	85	85	198 (225-227)[17]

[a]**Reaction conditions:** Ethyl acetoacetate (1 mmol), aromatic aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol) and catalyst, DL- Tartaric acid (5 mol%) in 10 ml of distilled water (5 mL) stirring at room temperature. [b]Isolated yield [c] Reported melting point.

Initially, in order to optimize the reaction conditions, we have chosen a model reaction of ethyl acetoacetate (1 mmol) and hydroxylamine hydrochloride (1 mmol) and benzaldehyde (1 mmol). In addition reaction is carried out in aqueous medium successfully implemented (figure-1).

If we compared this model reaction by using different catalyst, which is previously reported, found that catalyst had a

significant effect on the product yield. In absence of catalyst there is very poor yield is observed. Neat reaction only leads to condensation product of acetoacetate with hydroxylamine hydrochloride to afford ethyl 3-(hydroxyimino)butanoate. This clarified the need of catalyst for the formation of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones.

Kiyani et al. and other group reported various catalysts for the synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones. All above methods has its own merits and limitation. Our attempts started with the use of cheaper catalyst in addition with ecofriendly reaction condition. Surprisingly, when DL-Tartaric acid catalyst was used as catalysts, the reaction was completed in a shorter time with excellent yield of desired product. The use of DL-Tartaric acid catalyst is best for optimum yield and reaction time (table-2).

Table-2
Effect of catalyst

Entry	Catalyst[a]	Reaction time[b]	Yield[c]
1	Sodium citrate	(120 min.) [17]	85%
2	Sodium saccharian	(100 min.) [19]	90%
3	Sodium benzoate	(150 min.) [13]	88%
4	DL-Tartaric acid	100 min.	88%

[a]**Reaction conditions:** Ethyl acetoacetate (1 mmol), aromatic aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol) and catalyst (5 mol%) in 10 ml of distilled water (5 mL) stirring at room temperature. [b]Reported reaction methods, [c]Isolated yield.

Further, to know the precise role of a solvent, model reaction was performed under different solvent. There was no product formation observed in the absence of solvent. As the selection of an appropriate reaction medium model reaction was screened by various solvents in the presence of DL-Tartaric at room temperature. The results show that the effectiveness of solvents on the product yield. The use of ethanol, methanol, acetonitrile, DMF and water gave as good as same yields. The best conversion was observed when the reaction was performed in water using DL-Tartaric acid as a catalyst (table-2, entry 4) based on these results; water was then selected as the medium for the further investigations. In this reaction method, it was observed that 10 mL of water is sufficient to carry out the reaction efficiently.

Reaction is carried out in two steps, first ethyl acetoacetate reacts with hydroxylamine hydrochloride to afford ethyl 3-(hydroxyimino) butanoate. In second step Knoevenagel reactions between aromatic aldehydes and ethyl 3-(hydroxyimino)butanoate, obtained 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones product.

The DL-Tartaric acid is cheap therefore no need for recycle in small scale, for large scale operations recyclability of the catalyst is important as an industrial concern. DL-Tartaric acid can be recycled and reused three cycles to carry out the same experiment to obtain desired product (table-3). To determine the appropriate ratio of DL-Tartaric acid for a model reaction, it is observed that 10 mol % catalysts is sufficient and further increase in catalyst mol% there is no increase yield of product (table-4).

Table-3
Recycle of catalyst DL-Tartaric acid[a]

Entry	Yield[b]		
	Cycle-I	Cycle-II	Cycle-III
4a	88	80%	72%
4b	80	75%	70%
4c	85	78%	74%

[a]**Reaction conditions:** Ethyl acetoacetate (1 mmol), aromatic aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol) and DL-tartaric acid (5 mol%) in 10 ml of distilled water (5 mL) stirring at room temperature, [b]Isolated yield.

Table-4
Effect of mole% of DL-Tartaric acid

Entry	mole% of DL-Tartaric acid[a]	Reaction time	Yield[b]
1	2 mole %	135 min.	65 %
2	5 mole %	120 min.	80 %
3	7 mole %	100 min.	82 %
4	**10 mole %**	**100 min**	**85 %**
5	15 mole %	100 min	88 %
6	20 mole %	100 min	88 %

[a]**Reaction conditions:** Ethyl acetoacetate (1 mmol), aromatic aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol) and catalyst (1-10 mol%) in 10 ml of distilled, water (5 mL) stirring at room temperature. [b]Isolated yield

In a reaction of ethyl acetoacetate (1 mmol) and hydroxylamine hydrochloride (1 mmol) in 10 ml of distilled water was stirred for 10 min at room temperature. Then aromatic aldehyde (1 mmol) and catalyst DL-Tartaric acid (10 mol %) was added to the reaction mixture. The reaction mixture was stirred at room temperature for one to two hours; the result was summarized in table-1. After evaporation of filtrate the catalyst DL-Tartaric acid obtained, as it is water soluble, which may be reused several times to carry out the same experiment. The similar procedure was used for synthesis of different isoxazols (4a-i).

The structure of 4-benzylidene-3-methylisoxazol-5(4H)-one (4a) was determined from the spectral and physical data. The ^{1}H NMR spectrum of 4a showed singlet peaks at δ 2.32 for the methyl group and doublet for C=C bond at δ 8.36. Aromatic protons of 4a resonate as triplet at 7.37 and multiples at region of δ 7.43-7.53. ^{13}C NMR spectrum of compound 4a showed characteristic signals at 119.7 for C=CH-Ar, 161.3 for C=N, and 168.2 ppm, for C=O of the isoxazol ring. The mass spectra show intense peak at 187.93 (M^{+}) confirms formation of 4-benzylidene-3-methylisoxazol-5(4H)-one (4a). Similarly all other synthesized compound was identified by melting point and comparison with the reported melting point.

Mechanism of this reaction is to be fully clarified (figure-2), here a simple condensation of ethylacetoacetate and hydroxyl

amine takes place in aqueous condition without heating the reaction mass in presence of tartaric acid to give the ethyl 3-(hydroxyimino)butanoate. This will further undergo condensation product with aromatic aldehyde to form intermediate followed by the intramolecular cyclization to afford the desired product.

It is observed that yields of electron rich aldehydes are giving good yields than electron-deficient aldehydes. The rate of condensation reactions increased in presence of protic solvent which enforced hydrophobic interactions in aqueous media along with polarity of solvent enhance the rate of reaction.

Conclusion

In summary, we reported a simple, eco-friendly, three-component one pot reaction for the synthesis of green an efficient synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones using tartaric acid as a catalyst. This protocol offers several advantages such as atom efficiency, short reaction time, simple work-up and simple reaction condition. Use of water as ecofriendly solvent and cheap DL-tartaric acid catalyst makes this method superior as compare to other reported methods.

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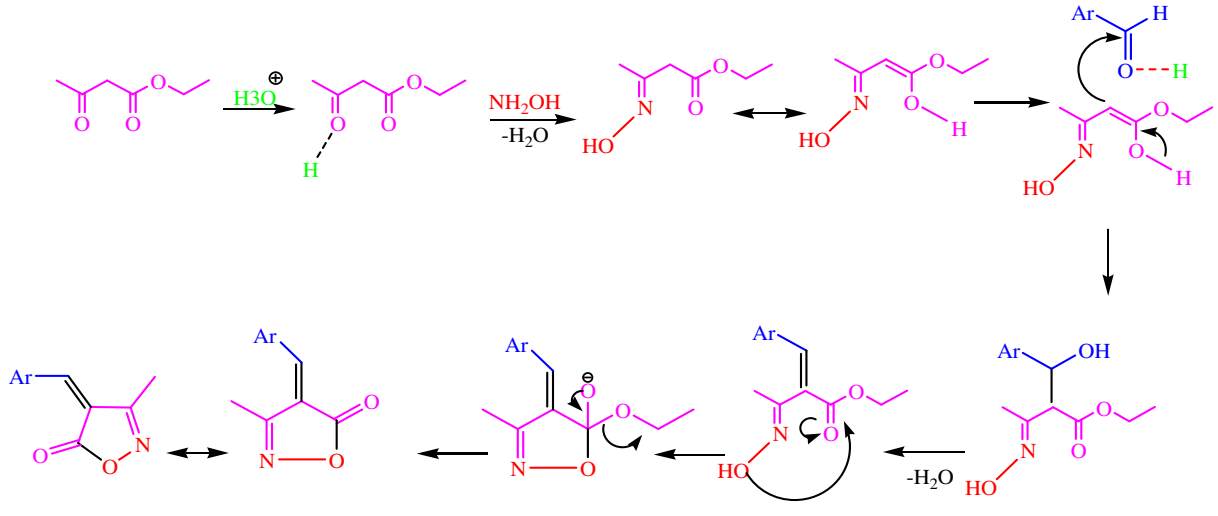

Plausible mechanistic pathway for the formation of 4-arylidene-3-phenylisoxazol-5-ones

Figure-2

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