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SYNTHESIS OF ARYLMETHYLIDENE-ISOXAZOL-5(4*H*)-ONES IN WATER CATALYZED BY SODIUM CITRATE

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Abstract
A series of 4-arylmethylene-3-methylisoxazol-5(4*H*)-ones have been prepared in high yields, under aqueous conditions, *via* cyclocondensation of aromatic aldehydes with ethyl acetoacetate and hydroxylamine hydrochloride in the presence of sodium citrate. The merits of this method are efficient, clean, green, easy work-up, high yields, and shorter reaction time.

Keywords: Isoxazol, three-component reaction, sodium citrate, green

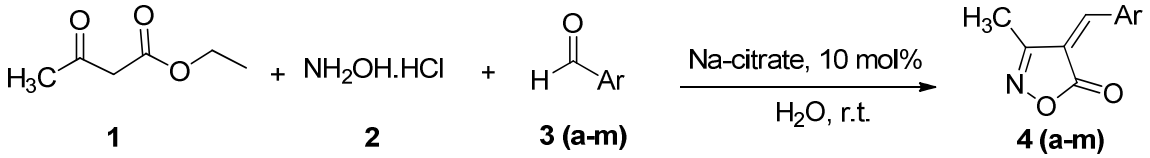
Introduction

Isoxazol structural unit represent class of heterocyclic compounds with biological activities and medicinally useful agents such as protein-tyrosine phosphatase 1B (PTP1B) inhibitory[i], anticonvulsant[ii],antifungal[iii], HDAC inhibitory[iv], analgesic[v], antitumor[vi], antioxidant[vii], antimicrobial[viii], COX-2 inhibitory[ix], nematicidal[x], antinociceptive[xi], anti-inflammatory[xii], anticancer[xiii], antiviral[xiv], antituberculosis[xv], antimycobacterial[xvi], treatment of leishmaniasis[xvii], and treatment of patients with active arthritis[xviii]. Furthermore, isoxzolone core also can be used as the bases for the design and construction of merocyanine dyes, which are used in optical recording and nonlinear optical research[xix-xx]. On the other hand, multicomponent reactions (MCRs) have a special place in the pharmaceuticalowing to their characteristics of convergence, efficiency, facile completing, and usually high yield of products[xxi-xxiv]. Also, MCRs in water will be one of the most appropriate approaches which will run into the necessities of green chemistry[xxv].

Sodium citrate (Na-citrate) as an organic salt with the low molecular weight and low-toxicity widely have been used as acidulate, flavoring and safe organic preservative in pharmaceutical and food industry including meat, fish, poultry and beverage as an economical and safe food additive and stabilizing agent. This salt inhibits the growth of tongue bacteria including H_2S-producing bacteria, opportunistic pathogenic bacteria, and coagulase-negative staphylococci[xxvi-xxx] and having antibacterial activities against various food-borne pathogens. Na-citrate plus sodium diacetates been used for improving steak color, oxidation stability, moisture retention, and tenderness has also been used[xxxi]. In addition, Na-citrate has been used for preparationof nanoparticles in aqueous solution[xxxii], Au@Ag nanocrystals[xxxiii], Pt nanoparticles[xxxiv], preparation

of glass–silver nanodisk core–shell composite[xxxv], CaP nanocrystals in CaP-suspensions[xxxvi], generation of Ag nanowires[xxxvii], and is one of the most commonly used as complexing agents for electrode position copper indium diselenide (CIS) thin films[xxxviii], increasing efficiency platinum catalyst for methanol oxidation[xxxix], and desulphurization-crystallization agent for recovering lead from lead battery pastes[xl].

As recently reported[xli-xliii], arylmethylene isoxazol-5(4*H*)-ones were prepared by using of sodium benzoate, sodium silicate, and sodium sulfide as a catalyst. Also we synthesized the same arylmethylene isoxazol-5(4*H*)-ones by using of sodium ascorbate as a catalyst[xliv]. With this methodology as background, we attempted to develop an alternative catalyst for the preparation of arylmethylene isoxazol-5(4*H*)-ones. Although 4*H*-isoxazol-5-ones were synthesized so far[xli-xlvi] to the best of our knowledge, no reports that include the use of Na-citrate for condensation of aromatic aldehydes, ethyl acetoacetate (EAA), and hydroxylamine hydrochloride have been reported. We herein report preparation of 4*H*-isoxazol-5-ones, **4** (**a**-**m**), by one-pot three-component condensation of aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride using of Na-citrate, as a green and reusable catalyst in water as a solvent at room temperature (Scheme 1).



Scheme1. One-pot three-component condensation of ethyl acetoacetate (**1**), hydroxylamine hydrochloride (**2**), and aromatic aldehydes (**3**) using sodium citrate (Na-citrate)

Experimental

All the reagents and chemicals were obtained from commercial sources and used without further purification. Melting points were measured on a Buchi 510 melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT-IR 8300 Spectrophotometer using KBr pellets technique. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature on a BRUKER AVANCE DRX-400 MHz spectrophotometer using $CDCl_3$ as a solvent and TMS as an internal standard. The purity of new synthesized compounds and development of reactions was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F_{254} aluminum sheets, visualized by UV light.

General procedure: A mixture of equimolar quantities of ethyl acetoacetate (1 mmol) and hydroxylamine hydrochloride (1 mmol) were stirred in 5 mL of water for 10 min. Then aromatic aldehyde (1 mmol), 10 mol% of Na-citrate was added and the reaction mixture was stirred at room temperature for specified time mentioned in Table 2. The solid product formed was isolated by simple filtration and washed with water (5 mL). The purity of products obtained was confirmed by TLC and spectral techniques. The filtrate was evaporated to remove water leaving catalyst. The same catalyst was utilized to synthesize further derivatives. If necessary, further purification was performed by recrystallization from suitable solvent to give desired compounds in high yield.

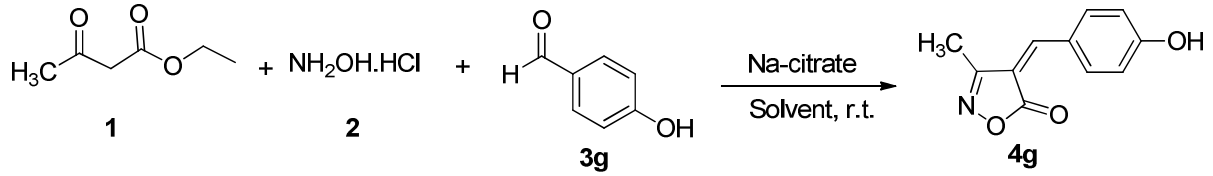
Results and discussion

The synthesis of isoxazols has been carried as shown in Scheme 1. At first, in a simple three-component reaction equimolar quantity of ethyl acetoacetate (**1**), hydroxylamine hydrochloride (**2**) and benzaldehyde (**3a**) were treated at room temperature in presence of catalytic amount of Na-citrate in water. This reaction leads to compound **4a** in good yields. Compound **4a**[xli-xliv] has been described in literature. The structure of the compound **4a** was determined from the spectral and physical data. The ^{1}H NMR spectrum of **4a** showed two singlet peaks at δ 2.34 for the methyl group and δ 7.46 ppm for proton of the C═C bond. Aromatic protons of **4a** resonate as triplet at 7.55, doublet of doublets at 8.38 and multiplets at region of δ 7.61-7.64 ppm. Also, recording the melting point of the compound **4a** and fixed with authentic sample showed **4a** has been formed.

In order to explore for the optimum amounts of catalyst, the reaction of ethyl acetoacetate (**1**), hydroxylamine hydrochloride (**2)** and 4-hydroxybenzaldehyde (**3g**) as a model was carried out in water with different amounts of Na-citrate ranging from 5 to 20 mol% at room temperature (Table 1). As shown in Table 1, when the amount of Na-citrate was increased from 5 to 10 mol%, the yield of **4g** was improved from 83 to 93% (Table 1, entries 1-2). However, no significant increase in the yield of **4g** was observed as the amount of Na-citrate was further raised to 20 mol% (Table 1, entries 3-4). Therefore, the amount of 10 mol% Na-citrate was chosen as the catalyst for these reactions.

Moreover, to search for the optimal solvent, the synthesis of **4g** was performed by using solvents of water, tetrahydrofuran (THF), ethanol, hexane, and water-ethanol mixture (Table 1, entries 5-9) at room temperature and the results are summarized in Table 1. As shown in Table 1, the reaction in water resulted in higher yields and shorter reaction time than others. So water was chosen as the appropriate solvent. Hence, all further reactions were carried out using 10 mol% of Na-citrate in water at room temperature.

Table1: Synthesis of **4g** in the presence of different solvents and amounts of catalyst[a]



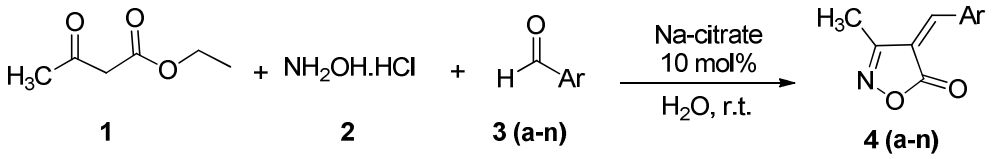
1 **2** **3g** **4g**

Entry	Solvent	Amounts of catalyst	Time (min)	Yield (%)[b]
1	Water	5	120	70
2	Water	10	120	90
3	Water	15	120	90
4	Water	20	120	85
5	Ethanol	10	120	40
6	1,4-Dioxane	10	150	31
7	Hexane	10	150	25
8	Water/ethanol (1:1)	10	120	65
9	Solvent free	10	160	40

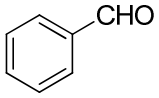
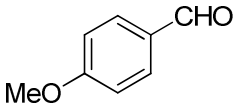
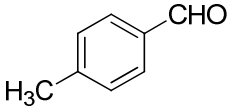
[a] Reaction was performed with equimolar quantities of reactants in 5 mL solvent.
[b]Isolated yields.

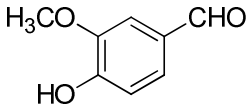
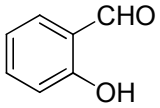
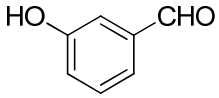
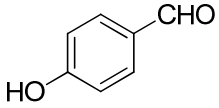
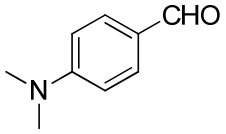
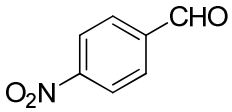
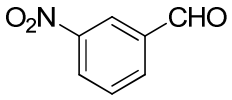
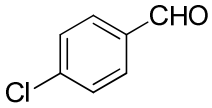
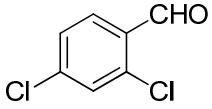
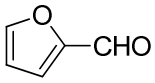
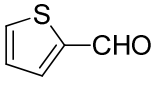
Based on these optimized conditions, the reactions proceeded efficiently. The efficacy of this protocol was well evaluated using a wide range of aldehydes a series of compounds **4** were synthesized with this simple procedure. The results were summarized in Table 2. Nature and position of functional groups on phenyl ring were affected yields of products and reaction times. The results indicated that aromatic aldehydes bearing electron-donating groups such as $–OCH_3$, $-CH_3$, -OH, and $-N(Me)_2$ are suitable for this reaction and corresponding products were prepared in high yields (Table 2, entries 2-8). It seems that, crowded steric of the hydroxyl group in 2-hydroxybenzaldehyde give rise to that yield slightly lower and reaction time is a little longer (Table 2, entry 5). However, aromatic aldehydes containing electron-withdrawing functional groups, such as chlorine or nitro were ineffective and did not proceed under the optimized reaction conditions. Therefore, they are not suitable for the reaction (Table 2, entries 9-11). The current reaction was more examined using heterocyclic aromatic aldehydes such as furan, 2-thiophenecarbaldehyde and 3-thiophenecarbaldehyde. In this case, the reaction well proceed with high yields.
Also, in search to reusability of the catalyst in water after completion of the reaction, the filtrate that remained catalyst was subjected to evaporation under reduced pressure and the recycled solid catalyst was applied as such for the consecutive runs in three series of the same model reaction under the optimized conditions for up to three runs (1^{th} use: 90%, isolated yield, 2^{th} use: 86% isolated yield, and 3^{th} use: 82% isolated yield). Decreasing the yield is probably related to slight reduction in the catalytic activity of the catalyst or decreasing the amount of catalyst recovery which is attributed to the handling.

Table 2: Synthesis of arylmethylene-isoxazol-5(4*H*)-ones **4**[a]



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

Entry	Ar	Product	Yield[b] (%)	Time (min)	mp (°C)[c] Found	mp (°C)[c] Reported
1	 **1a**	**4a**	85	120	139-141	141-143
2	 **1b**	**4b**	91	60	174-175	174-176
3	 **1c**	**4c**	87	75	131-132	-

4	 **1d**	**4d**	92	90	214-215	211-214
5	 **1e**	**4e**	85	140	198-199	198-201
6	 **1f**	**4f**	90	120	198-201	-
7	 **1g**	**4g**	90	120	213-215	214-216
8	 **1h**	**4h**	89	90	225-227	-
9	 **1i**	**4i**	trace	600	-	-
10	 **1j**	**4j**	trace	750	-	-
11	 **1k**	**4k**	trace	750	-	-
12	 **1l**	**4l**	trace	900	-	-
13	 1m	**4m**	87	120	238-240	238-241
14	 **1n**	**4n**	90	110	145-147	-

[a]Reaction conditions: Ethyl acetoacetate (1 mmol), aromatic aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol) in water (5 mL) stirring at room temperature.
[b] Isolated yields.

[c] Melting points are listed in the references xl-xliv.

Conclusion

In summary, the efficient and clean synthesis of isoxazols *via* a one-pot, three-component condensation of ethyl acetoacetate, aryl aldehydes, and hydroxylamine hydrochloride in the presence of Na-citrate at room temperature has been developed. The reaction exhibited merits such as mild conditions; easy wok-up, completion reaction in shorter reaction times, reuse of catalyst, safe, and using of water from the ecologically point of view.

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