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SODIUM SACCHARIN AS A CLEAN AND EFFICIENT CATALYST FOR THE SYNTHESIS OF 4-ARYLIDENE-3-METHYLISOXAZOL-5(4*H*)-ONES *VIA* ONE-POT THREE-COMPONENT REACTION IN AQUEOUS MEDIUM

Hamzeh Kiyani*, **Fatemeh Ghorbani**

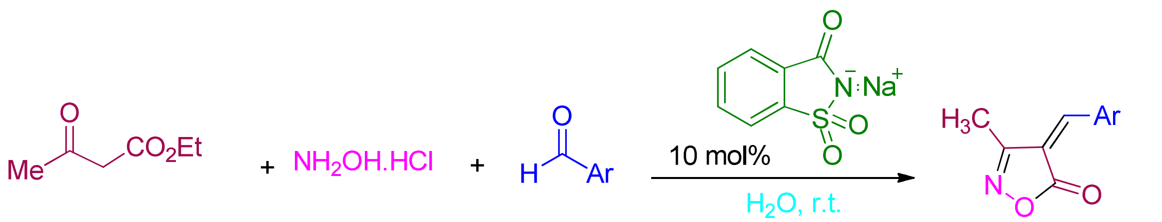
School of Chemistry, Damghan University, 36715-364, Damghan, Iran
**E-Mail: hkiyani@du.ac.ir, Tel.: +98-2325235431; Fax: +98-2325235431*

Abstract
As a result of one-pot three-component reaction of ethyl acetoacetate with hydroxylamine hydrochloride and various aromatic aldehydes using sodium saccharin as a catalyst in water, a green and environmentally benign solvent, 4-arylidene-3-methylisoxazol-5(4*H*)-ones were obtained in high yields. The advantage of this method is efficient, clean, easy work-up, high yields, and shorter reaction time.

Keywords: Sodium saccharin, isoxazol-5(4*H*)-ones, three-component reaction

Introduction
Isoxazol five-membered ring is one of the components some of natural and medicinal active molecules and their derivatives show interesting biological activity as well[i]. Isoxazol derivatives are found to possess biological and pharmaceutical activities such as 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 unit 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]. Some of the photochromic compounds such as diarylethenes possessing an isoxazol moiety[xxi]. In the framework some of the liquid crystals, the isoxazol ring also can be found[xxii]. Isoxazols have also worked as versatile building blocks in organic synthesis.
Multicomponent reactions (MCRs) have been developed widely as powerful strategy and useful tool to create various chemical compounds. Also these processes diminish the synthetic steps, and amount of waste produced, which are significant factors in "green" chemistry [xxiii-xxiv]. Moreover, MCRs in water will be one of the most appropriate approaches which will run into the necessities of green chemistry[xxv].
Saccharin, is a distinguished heterocyclic compound and used in the form of sodium or calcium salt. Saccharin is used in a variety of beverages and foods such as soft drinks, fruit juice drinks, processed fruits, chewing gum and confectionary, gelatin desserts, juices, jams, toppings, sauces,

and dressings. It is also used in cosmetics, pharmaceutical products and other non-food applications such as nickel electroplating brightener, and nutritive and nonnutritive sweetener resources[xxvi-xxxiii]. Furthermore, sodium saccharin in combination of tetrabutylammonium iodide has been used for trimerization of isocyanates[xxxiv]. As recently reported[xxxv-xxxvii], arylmethylene isoxazol-5(4*H*)-ones were prepared by using of sodium benzoate[xxv], sodium sulfide[xxxvi], as well as sodium silicate[xxxvii]. Also we synthesized the same arylmethylene isoxazol-5(4*H*)-ones by using of sodium ascorbate[xl] and sodium citrate[xli] as the catalyst. 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, to the best of our knowledge, no reports that include the use of sodium saccharin for condensation of aromatic aldehydes, ethyl acetoacetate (EAA), and hydroxylamine hydrochloride (Scheme 1) have been reported. At the same time, we hoped to establish that sodium saccharin could be suitable for synthesis of **4a-o** compounds (Scheme 1).



Scheme1. Synthetic route for the target compounds **4**.

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 for the synthesis of 4-arylmethylene-3-methyl-isoxazol-5(4*H*)-ones: A mixture of ethyl acetoacetate (0.130 g, 1 mmol), hydroxylamine hydrochloride (0.07 g, 1 mmol) and sodium saccharin (10 mol%) in 5 mL of distilled water was stirred at room temperature for 10 min, then corresponding aromatic or heterocyclic aldehyde (1 mmol) was added to the mixture. The reaction mixture was stirred at ambient temperature for mentioned time in Table 2. After completion of reaction (monitored by TLC), the precipitate was filtered off, and washed with cold distilled water and dried in air to get pure products. For further purification of title compounds which can be recrystallization in the ethanol (95%). The catalyst was recovered by evaporation of solvent from filtrated solution after each run. The same catalyst was utilized to synthesize further derivatives. Spectral data for the some compounds as follows:

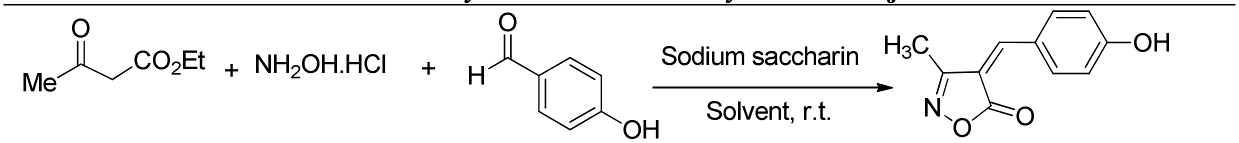
4-benzylidene-3-methylisoxazol-5(4*H*)-one (4a), Pale yellow solid, ^1H NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 3H), 7.46 (s, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.61-7.64 (m, 1H), 8.38 (dd, *J* = 1.3, 7.4 Hz, 2H).
3-methyl-4-(4-methylbenzylidene)isoxazol-5(4*H*)-one (4c), pale yellow solid, ^1H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.48 (s, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.42 (s, 1H), 8.32 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 11.6, 22.1, 118.2, 129.8, 129.9, 134.2, 145.8, 150.2, 161.4, 168.3.
3-methyl-4-(thiophen-2-ylmethylene)isoxazol-5(4*H*)-one (4f), yellow solid, ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 7.29 (t, *J* = 4.8 Hz, 1H), 7.64 (s, 1H), 7.95 (d, *J* = 4.8 Hz, 1H), 8.13 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.5, 114.6, 128.9, 136.5, 139.2, 139.6, 141.5, 160. 7, 168.7.
3-methyl-4-(thiophen-3-ylmethylene)isoxazol-5(4*H*)-one (4g), yellow solid, ^1H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 7.42 (dd, *J* = 5.2, 2.8 Hz, 1H), 7.49 (s, 1H), 7.95 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.99 (dd, *J* = 2.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 117.0, 126.8, 131.5, 135.2, 139.4, 140.9, 161.3, 168.5.
4-(3-hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4i), yellow solid, ^1H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 7.95 (s, 1H), 9.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.7, 118.9, 119.9, 121.8, 125.8, 130.2, 134.1, 152.3, 157.8, 162.6, 168.2.
4-(4-(dimethylamino)benzylidene)-3-methylisoxazol-5(4*H*)-one (4k), red solid, ^1H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.19 (s, 6H), 6.75 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.24 (s, 1H), 8.43 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 40.1, 110.9, 111.5, 121.5, 137.7, 149.3, 154.2, 161.7, 170.2.

Results and discussion

In the present work, using a three-component, one-pot method, arylmethylene isoxazol-5(4*H*)-ones (**4a**-**o**) were obtained *via* condensation reaction of ethyl acetoacetate (EAA), hydroxylamine hydrochloride and available aryl aldehydes in the presence of water and sodium saccharin, with the high yield and purity. The results are summarized in Table 2. In the beginning, condensation of the 4-hydroxybenzaldehyde (**3j**) with ethyl acetoacetate (**1**) and hydroxylamine hydrochloride in water mediated by sodium saccharin at room temperature resulted in the formation title compound **4j** in high yield (Table 2, entry 10). Since the synthesized compound is known[xxxv-xli] its melting point is measured and compared with the previously reported demonstrated that **4j** is formed. Given this result, we have encouraged to conduct the other reactions, with the aim to obtain the suitable compounds. In order to optimize the reaction conditions, the reaction by using 4-hydroxybenzaldehyde (**3j**), EAA (**1**), and $NH_2OH.HCl$ (**2**) as a model, in the presence of different amounts of catalyst, water and various solvents was performed at room temperature (Table 1).
As can be seen in Table 1, increasing the amount of sodium saccharin from 10 to 15 and 20 mol% had no significant improvement in the efficiency of the reaction. Also, we thought of varying the nature of solvent to increase the reaction yield, and we carried out reactions in several solvents (Table 1). The use of organic solvents had no noticeable effect on the efficiency of the reaction. Probably the low yields obtained in organic solvents are due to a low solubility of sodium saccharin in these solvents. When the reaction using catalytic amounts of sodium

saccharin in distilled water at ambient temperature is performed, the yield of compound **4j** significantly improved. This clearly shows the effect of solvent on the reaction. With increasing solvent polarity, the yield and rate increases. Reaction in the solvent-free conditions also did not lead to satisfactory results. When the reaction was carried out in the absence of catalyst, small amounts of the product were observed. 10 mol% Catalyst and water as solvent, the best results have been achieved. Thus, 10 mol% sodium saccharin, water as solvent and room temperature were selected as the optimal conditions and the other reactions were performed in these conditions. Selection of water as a solvent has several beneficial including safety, non-toxicity, low cost, availability, being green and environmentally friendly.

Table1: Effect of solvents and catalyst amounts on the synthesis of **4j**[a]



1 **2** **3j** **4j**

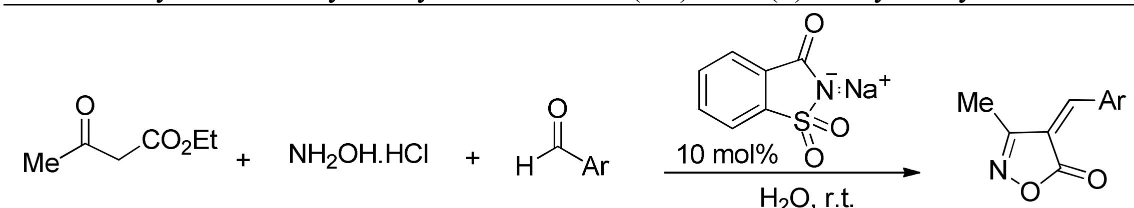
Entry	Solvent	Amounts of catalyst (mol%)	Time (min)	Yield (%)[b]
1	Water	2.5	120	88
2	Water	5	120	93
3	Water	10	120	96
4	Water	15	120	96
5	Water	20	120	95
6	Ethanol	10	120	70
7	Acetone	10	160	30
8	1,4-Dioxane	10	180	40
9	Hexane	10	180	40
10	Water/ethanol (1:1)	10	120	80
11	Solvent free	10	180	35

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

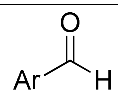
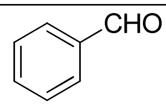
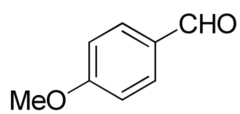
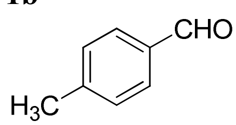
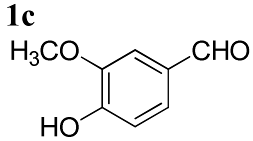
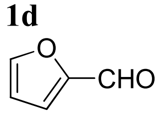
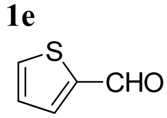
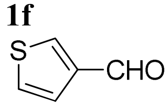
By using the optimized conditions described above, condensation reactions to produce the other compounds were studied. The results can be found in Table 2. According to Table 2, a range of aryl aldehydes substituted with electron donor and electron acceptor groups has been used. Aromatic aldehydes possessing electron-donating groups, the corresponding products with very high yield and with shorter reaction times have established (Table 2, entries 2-4 and 8-11). When aromatic aldehydes containing electron-withdrawing groups such as nitro and chlorine can be used, only trace amounts of the corresponding products to be formed. It is evident that electron rich aromatic aldehydes and π-excessive heterocyclic systems such as furan-2-carbaldehyde (**1e**), thiophene-2-carbaldehyde (**1f**), and thiophene-3-carbaldehyde (**1g**) reacted with EAA and hydroxylamine hydrochloride to afford high yields of products (Table 2, entries 5-7). Furthermore, for π-deficient heterocyclic aldehyde, pyridine-2-carbaldehyde (**1o**), there was no product formation even after 12 h under the optimized reaction conditions (Table 2, entry 15). These results indicate that the electron-releasing and electron-withdrawing substituents, which would affect the reaction. It appears that in this reaction, the steric factors also represent its effectiveness. For instance, when the salicylaldehyde reacted with EAA and hydroxylamine hydrochloride, the relatively less yield of the desired product is formed. The low is probably due to the crowded steric of the hydroxyl group.

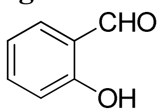
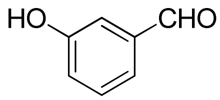
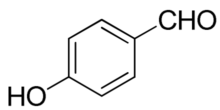
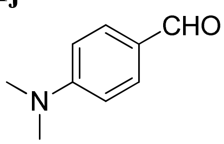
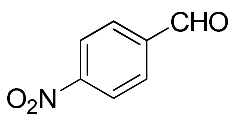
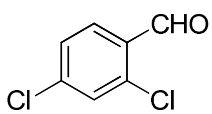
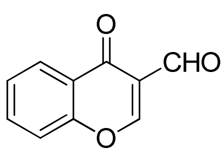
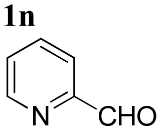
Although the exact mechanism of this transformation is not completely clear, a plausible reaction mechanism is proposed based on these results and provided mechanism in literature (Scheme 2). At first, the nucleophilic attack of amino of hydroxylamine hydrochloride at the carbonyl carbon of the EAA (**1**) resulted in intermediate oxime **5**. The removal of hydrogen by sodium saccharin, give rise to the carbon anion **6** is created. The aldehyde was attacked by carbon anion and subsequent reaction Knoevenagel, **7** is formed. Then oxygen attacks on ester carbonyl carbon to give **8** which undergoes proton transfer and losing one ethanol molecule to corresponding products.

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

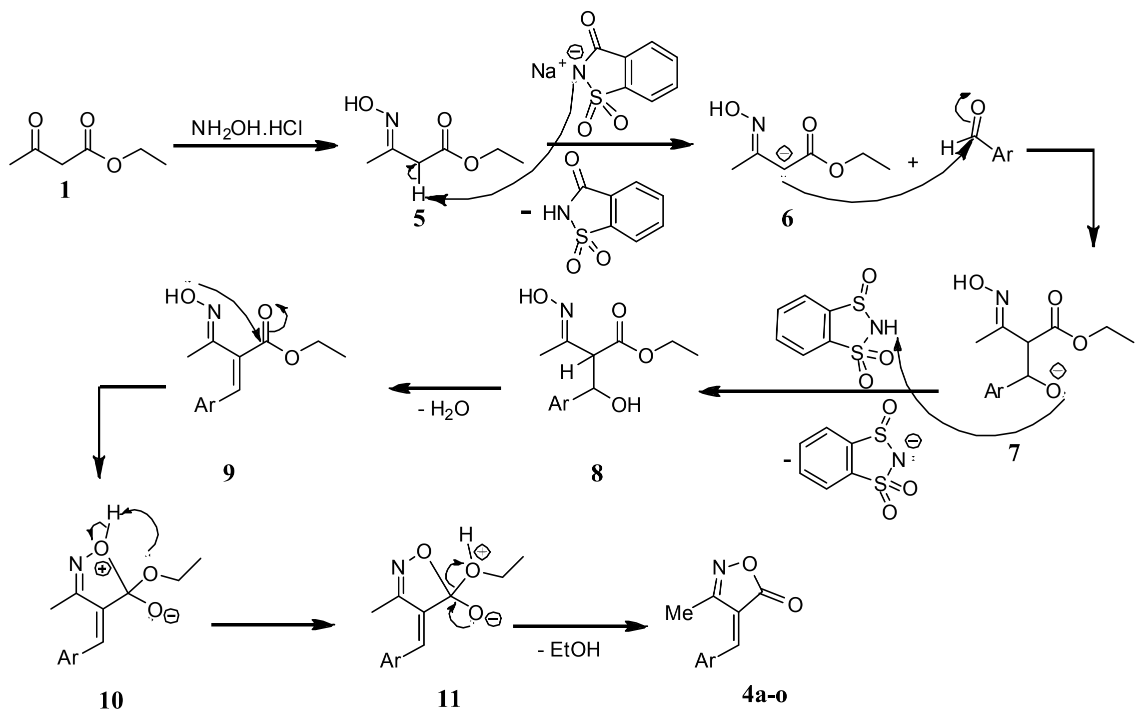


1 **2** **3a-o** **4a-o**

Entry		Product	Yield[b] (%)	Time (min)	mp (˚C)[c] Found	mp (˚C)[c] Reported
1	 **1a**	**4a**	90	100	141-142	141-143
2	 **1b**	**4b**	91	50	173-175	174-176
3	 **1c**	**4c**	90	75	130-132	-
4	 **1d**	**4d**	94	60	214-215	211-214
5	 **1e**	**4e**	88	100	240-241	238-241
6	 **1f**	**4f**	91	60	144-146	-
7		**4g**	90	60	145-147	-

	1g					
8	 **1h**	**4h**	82	120	198-199	198-201
9	 **1i**	**4i**	92	110	202-203	-
10	 **1j**	**4j**	96	115	213-215	214-216
11	 **1k**	**4k**	90	85	226-228	-
12	 **1l**	**4l**	trace	900	-	-
13	 **1m**	**4m**	trace	1440	-	-
14	 **1n**	**4n**	91	80	242-243	241
15	 **1o**	**4o**	-	900	-	-

[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 xxxv-xlii.



Scheme 2: The plausible mechanism for the formation of desired compounds (**4a**-**o**).

To evaluate the reusability of the catalyst, three series of reactions using 4-hydroxybenzaldehyde, ethyl acetoacetate, hydroxylamine hydrochloride, and catalyst recovery were carried out (1th use: 92%, isolated yield, 2th use: 85% isolated yield, and 3th use: 75% isolated yield).

To compare the effectiveness of sodium saccharin with other catalysts in the synthesis of 4-arylmethylene-3-methyl-isoxazol-5(4*H*)-ones, results of the reaction of 4-methoxybenzaldehyde, EAA, and $NH_2OH.HCl$ have tabulated in Table 3. With respect to results, compared to the previously reported methods, sodium saccharin is relatively better in terms of reaction times and yields.

Table 3: Comparing the result of the reaction of EAA, $NH_2OH.HCl$, and $4\text{-}CH_3OC_6H_4CHO$ using sodium saccharin with the results reported catalysts.

Catalyst/conditions	Catalyst amount (mol%)	Time (min)	Yield (%)	Ref.
Na_2S/EtOH/r.t.	5	90	88	xxxvii
Pyridine/EtOH/reflux	100	180	71	xxxvi
Catalyst free/grinding	0	48	61	xxxvi
Catalyst free/105-110 ˚C	0	15	66	xxxvi
Pyridine/H_2O/ultrasound	100	60	82	xxxvi
Sodium benzoate/H_2O/r.t.	10	90	87	xxxv
Sodium silicate/ H_2O/r.t.	5	90	91	xxxvi
Sodium saccharin/H_2O/r.t.[a]	10	50	91	-

[a] This work

Conclusion

In summary, sodium saccharin shows good catalytic activity for the preparation of 4-arylmethylene-3-methyl-isoxazol-5(4*H*)-ones and gives high yields under above mentioned conditions. Also, an efficient, safe, green and facial protocol for the synthesis of isoxazol-5(4*H*)-ones by a one-pot MCR of hydroxylamine hydrochloride, ethyl acetoacetate, aryl aldehydes, and catalytic amount of sodium saccharin in water at room temperature has been developed. The catalyst is simple, readily available. Also this method is simple and possesses advantageous such as environmentally friendly, easy workup, green, simplicity, relatively better yields, and shorter reaction times.

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