

One-pot Synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4*H*)-ones Catalyzed by Sodium Benzoate in Aqueous Media: A Green Chemistry Strategy

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Multicomponent condensation reactions (MCRs) have recently been discovered to be a powerful method for the synthesis of structurally diverse chemical libraries of drug-like heterocyclic compounds, since the products are formed in a single step and diversity can be achieved by simply varying each component.¹ The search and discovery for new MCRs on one hand, and the full exploitation of the already known multicomponent reactions on the other hand, is therefore of considerable current interest.² One such MCR that belongs to the latter category is the isoxazol-5(4*H*)-ones derivatives synthesis.³

Isoxazole derivatives have attracted increasing interest due to their significant pharmaceutical and therapeutic properties, such as hypoglycemic, immunosuppressive, anti-inflammatory, and anti-bacterial activity.⁴ In addition, isoxazole derivatives have served as a versatile building block in organic synthesis.⁵ The traditional synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones derivatives were carried out in two steps.⁶ At first step, ethyl acetoacetate reacts with hydroxylamine hydrochloride to afford oxime, and further ring closing bring product 3-methyl-isoxazol-5(4*H*)-one. And then, the Knoevenagel reactions between 3-methyl-isoxazol-5(4*H*)-one and aromatic aldehydes produce 3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones. In recent years, some new methods (such as solid state grinding,⁷ solid state heating⁷ and MCR^{8,9}) have been reported, each affording variable yields of condensation compounds in solution or under solvent-free conditions. Using the methods indicated above, there were still some limitations, such as large amount of catalyst, the long reaction time, low yields, the strict reactive condition (grinding or high temperature), and needed other special conditions (such as ultrasound irradiation). Hence, the introduction of efficient and new methods based on green methodology is still in demand.

Sodium benzoate is a common, safe, food preservative and antimicrobial agent. Sodium benzoate works well in acidic media to inhibit yeasts, molds, and bacterial growth, which is classified in the United States as Generally Recognized as Safe (GRAS) and its use in food is permitted up to the maximum level of 0.1%.¹⁰ In spite of its usefulness in a variety of products¹¹ and cheapness, its ability of catalysis has been neglected for a long time, sodium benzoate has been reported as a catalyst only in one organic reaction to our knowledge.¹² Therefore, the study of sodium benzoate as environmentally benign catalyst is in demand.

In continuation of our interest in catalysis,¹³ we wish to report one-pot synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones through three-component reaction catalyzed by sodium benzoate in water at room temperature.

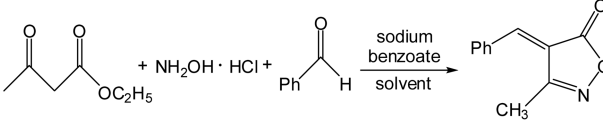
Experimental

General Procedure for the Synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4*H*)-ones. A mixture of ethyl acetoacetate (20 mmol), hydroxylamine hydrochloride (20 mmol) and sodium benzoate (2 mmol) in water (5 mL) were stirred for 10 min, after then aromatic aldehyde (20 mmol) was added, and the mixture was further stirred till the completion of the reaction (monitored by TLC). The product was filtered off and washed with cold 5% aqueous ethanol (2 × 30 mL), and recrystallized from EtOH (95%) to afford the pure product. All products are known compounds and identified by physical data (M.P.) with those reported in the literature.

Results and Discussion

In order to investigate the influence of the solvents, the reaction was carried out in various solvents and also under solvent-free condition. The reaction between benzaldehyde, ethyl acetoacetate, hydroxylamine hydrochloride was selected as model. As shown in Table 1, the reaction proceeded well in water (Table 1, entry 1), whereas in the other solvents or under solvent-free condition the reaction proceeded difficultly. Enhancing the rate of the reaction and purity of the product in water could be attributed to the increment of sodium benzoate's basicity and hydrophobic interactions. Carrying out organic synthesis in aqueous phase is highly challenging both from the synthetic view point and also from the impact of the environmental pollution.¹⁴ Apart from being environmentally friendly, water possesses some unique properties that are different from other solvents thus making it a very good reaction medium for organic synthesis. Consequently, the remainder of reactions were carried out in water.

To evaluate effect of amount of catalyst on the condensation, we investigated its efficiency in the model reaction. The yield was 88%, when sodium benzoate was 10 mol % (Table 2, entry 3). More catalyst was added, whereas there were no increment in the yields. When 1 mol % catalyst was used the yield was high to 82%, but sodium benzoate was cheap and environmentally benign, so the optimum amount

Table 1. Effect of solvents on the condensation catalyzed by sodium benzoate


Entry	Solvent ^a	Amount (mol %)	Yield (%) ^b
1	H ₂ O	5	84
2	C ₂ H ₅ OH	5	60
3	Cyclohexane	5	58
4	1,4-Dioxane	5	28
5	Acetone	5	Trace
6	Solvent-free	5	51

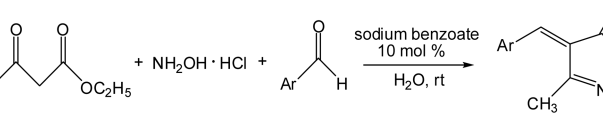
^aThe reaction was carried out in 5 mL of solvents for 2.5 h. ^bIsolated yield.

of catalyst was 10 mol %.

After optimising the reaction conditions, aromatic aldehydes were treated with ethyl acetoacetate and hydroxylamine hydrochloride in the presence of sodium benzoate in water. All of the results are shown in Table 3. The yields varied because of the difference of substitutional group of aromatic aldehydes. The aromatic aldehydes with electron-donating group afforded the target products in high yields and purity in short time (Table 3, entries 3-6). Steric hindrance seems to have some effects on the efficiency of this transformation, shown in entries 4-5. Ortho substituted aromatic aldehyde reacted sluggishly, which required comparatively longer reaction time with low yield (Table 3, entry 4). However,

Table 2. Effect of catalyst amount on the condensation catalyzed by sodium benzoate

Entry	Amount (mol %)	Yield (%) ^a
1	1	82
2	5	84
3	10	88
4	12.5	84
5	15	83

^aThe reaction was carried out in H₂O (5 mL) for 2.5 h.**Table 3.** Synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones in the presence of sodium benzoate


Compd.	Ar	Time (h)	Yield (%) ^a	mp (°C)	
				Found	Reported ⁸
1	C ₆ H ₅	2.5	88	141-143	142-144
2	2-Furyl	3.0	75	237-241	240-242
3	4-CH ₃ OC ₆ H ₄	1.5	87	175-177	178-179
4	2-OHC ₆ H ₄	2.5	79	198-201	198-202
5	4-OHC ₆ H ₄	1.5	89	214-216	215-218
6	3-CH ₃ O-4-OHC ₆ H ₃	1.5	86	211-214	212-214
7	C ₆ H ₅ CH=CH	2.0	96	172-174	173-178
8	2-ClC ₆ H ₄	6.5	NR ^b	-	-
9	2,4-Cl ₂ C ₆ H ₃	6.5	NR ^b	-	-

^aIsolated yield. ^bNo reaction.

aromatic aldehydes with an electron-withdrawing group failed to convert to the target products (Table 3, entries 8-9). It is important to note that heterocyclic aldehyde (Table 3, entry 2) and α,β -unsaturated aldehyde (Table 3, entry 7) underwent smoothly with ethyl acetoacetate and hydroxylamine hydrochloride giving moderate or excellent yields of the corresponding products.

We have provided a facile and efficient method for the one-pot three-component synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones in the presence of sodium benzoate in water. The attractive features of this procedure were cleaner reaction profiles, operational simplicity, high yields and short reaction time, all of the advantages made this procedure to be much more competitive than previously reported ones.

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