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One-Pot Three-Component Synthesis of 3-Methyl-4-Arylmethylene-Isoxazol-5(4H)- Ones Catalyzed by Sodium Sulfide

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ONE-POT THREE-COMPONENT SYNTHESIS OF 3-METHYL-4-ARYLMETHYLENE-ISOXAZOL-5(4H)-ONES CATALYZED BY SODIUM SULFIDE

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GRAPHICAL ABSTRACT



Abstract 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones were synthesized by the convenient three-component reaction of ethyl acetoacetate, hydroxylamine hydrochloride, and aromatic aldehydes catalyzed by sodium sulfide in the presence of ethanol at room temperature. The advantages of this procedure were mild reaction conditions, high yields, short reaction time, and operational simplicity.

Keywords Sodium sulfide; 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones; one-pot synthesis

INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry because these reactions increase the efficiency by combining several operational steps without the isolation of intermediates or change in the conditions.¹ MCRs have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.² The search and discovery for new MCRs on one hand and the full exploitation of the already known multicomponent reactions on the other hand are therefore of considerable current interest.³ One such MCR that belongs to the latter category is the synthesis of isoxazol-5(*4H*)-ones derivatives.

Isoxazol-5(4H)-ones compounds have attracted increasing interest due to their significant pharmaceutical and therapeutic properties, such as hypoglycemic, immunosuppressive, anti-inflammatory, and anti-bacterial activities.⁴ In addition, isoxazole derivatives have served as a versatile building block in organic synthesis.⁵ The traditional synthesis of

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3-methyl-4-arylmethylene-isoxazol-5(4H)-ones derivatives were carried out in two steps.⁶ In the first step, ethyl acetoacetate reacts with hydroxylamine hydrochloride to afford an oxime, and further ring closure forms the product 3-methyl-isoxazol-5(4H)-one. And then, the Knoevenagel reactions between 3-methyl-isoxazol-5(4H)-one and aromatic aldehydes produce 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones. In recent years, some new methods (such as solid-state grinding,⁷ solid-state heating,⁷ 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 the long reaction time, low yields, and the strict reactive condition (grinding or high temperature), and they needed other special conditions, such as ultrasound irradiation. Hence, the introduction of efficient and new methods is still in demand.

Sodium sulfide is probably one of the oldest and most widely used industrial chemicals and has been used as a catalyst in some reactions.¹⁰ In continuation of our interest in catalysis,¹¹ we wish to report one-pot synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones through a three-component reaction catalyzed by sodium sulfide. In this study, the procedure showed various advantages such as mild reaction conditions, high yields, short reaction time, and operational simplicity.

RESULTS AND DISCUSSION

In order to explore the feasibility of some different catalysts, the reaction between benzaldehyde, ethyl acetoacetate, and hydroxylamine hydrochloride in ethanol was selected as model. As shown in Table 1, only sodium sulfide was effective in catalyzing the reaction, and others did not work. The basicity of different catalysts itself sometimes plays an important role in the high catalytic activity in base-catalyzed reactions. However, mention must be made here that hydroxylamine hydrochloride was active and would react with the base tempestuously (effervescently). Sodium sulfide was found to be the best since it resulted in the highest yield of the desired product.



Table 1 Screening of different catalysts for the condensation reaction

^aThe reaction was carried out in ethanol (5 mL) with catalysts (5 mol%) for 2.5 h. ^bIsolated yield.

Entry	Solvent ^a	Yield (%) ^b
1	C ₂ H ₅ OH	80
2	Cyclohexane	70
3	1, 4-dioxane	37
4	Acetone	Trace
5	H ₂ O	Trace
6	Solvent-free	42

 Table 2 Effect of solvents on the condensation catalyzed by sodium sulfide

^aThe reaction was carried out in solvents (5 mL) with catalysts (5 mol%) for 2.5 h. ^bIsolated yield.

To investigate the influence of the solvents, the model reaction was carried out in various solvents and also under solvent-free condition. As shown in Table 2, the reaction proceeded well in ethanol (Table 2, entry 1), and also proceeded well in cyclohexane (Table 2, entry 2), whereas in the other solvents or under solvent-free conditions, the reaction proceeded dissapointingly. When water was used, the reaction was unsuccessful (Table 2, entry 5). The reason might be that the solution of sodium sulfide was strong alkaline and would react with hydroxylamine hydrochloride, which was the same with the base in Table 1. Consequently, the remainder of reactions were carried out in ethanol.

MCR strategies offer significant advantages over conventional linear-type syntheses. In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components. However, the sequence of feed-in sometimes plays an important role in MCRs. In this reaction, there was no product when ethyl acetoacetate, hydroxylamine hydrochloride, and aromatic aldehyde were added simultaneously in the presence of the catalyst. When, ethyl acetoacetate, hydroxylamine hydrochloride, and the catalyst were stirred for 10 min, followed by the addition of aromatic aldehyde, the reaction proceeded smoothly to high yield.

After optimizing the reaction conditions, aromatic aldehydes were treated with ethyl acetoacetate and hydroxylamine hydrochloride in the presence of sodium sulfide in ethanol. All of the results are presented in Table 3. The yields varied greatly because of the difference in the substitutional group of aromatic aldehydes. The aromatic aldehydes with electron-donating group afforded the target products in high yield and purity in short time (Table 3, entries 3–6), while aromatic aldehydes with an electron-withdrawing group failed to convert to the target products (Table 3, entries 8 and 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 high yields of the corresponding products.

In Scheme 1, we proposed a feasible mechanism for the reaction. Ethyl acetoacetate reacted with hydroxylamine hydrochloride to afford oxime, and it was difficult for oxime to close the ring to achieve 3-methyl-isoxazol-5(4H)-one. When intermediate **a** lost one hydrogen atom, the methylene would convert to be the carbon anion **b**. Then, aromatic aldehydes attacked carbon anion and the Knoevenagel reactions occurred. After losing one ethanol molecule, ring-closing brought the product 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones.

О ОС ₂ H ₅ + NH ₂ OH•	HCI + Ar	$\begin{array}{c} 0 \\ H \end{array} \xrightarrow{ Na_2S \bullet 9H_2O} \\ \hline H \end{array} \xrightarrow{ Hanol, r.t. }$	$Ar \longrightarrow 0 \\ CH_3 \\ mp (°C)$	
Ar	Time (h)	Yield (%) ^a	Found	Reported ⁸
C ₆ H ₅	2.5	80	141–143	142–144
2-Furyl	2.0	72	238-241	240-242
4-CH ₃ OC ₆ H ₄	1.5	88	174-176	178-179
2-OHC ₆ H ₄	1.5	91	198-200	198-202
4-OHC ₆ H ₄	1.0	87	214-216	215-218
Vanillin	1.5	89	212-215	212-214
$C_6H_5CH = CH$	2.5	88	171-173	173-178
2-ClC ₆ H ₄	6.5	NR ^b		
2, 4-Cl ₂ C ₆ H ₃	6.5	NR ^b	—	_
	Ar $C_{6}H_{5}$ 2-Furyl 4-CH_{3}OC_{6}H_{4} 2-OHC_{6}H_{4} 4-OHC_{6}H_{4} Vanillin $C_{6}H_{5}CH = CH$ 2-CIC_{6}H_{4} 2, 4-Cl_{2}C_{6}H_{3}	$\begin{array}{c cccc} & & & & & \\ & & & & \\ & & $	$\begin{array}{c cccc} & & & & & & & & & & & \\ \hline & & & & & & &$	$\begin{array}{c cccc} & & & & & & & & & & & & & & & & & $

Table 3 Synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones in the presence of sodium sulfide

^aIsolated yield.

^bNo reaction.

In order to show the merit of sodium sulfide in comparison with other catalysts used for the same reaction, we have tabulated some of the results in Table 4. As is evident from the results, although some reactions took more than 12 h, the yield was the highest with a shorter reaction time in the presence of sodium sulfide. Mention must be made here that other procedures were strict and complicated.

Table 4 Condensation catalyzed by different catalysts

	O + NH ₂ OH • HCl + OC ₂ H ₅ H ₃ CO		Catalys	t H ₃ CO	O CH ₃
Entry	Catalyst and conditions	Amount (mol%)	Time (h)	Yield (%) ^a	Reference
1	Na ₂ S/EtOH/r.t.	5	1.5	88	This work
2	Pyridine/EtOH/reflux	100	3	71	Zhang et al. (2008)9
3	Catalyst free/grinding	0	0.8 ^b	61	Zhang et al. (2008)7
4	Catalyst free/105-110 °C	0	0.25 ^b	66	Zhang et al. (2008)7
5	Pyridine/H ₂ O/ultrasound	100	1 ^c	82	Cheng et al. (2009) ⁸

^aIsolated yield.

^bThe mixture was allowed to stand 12 h after the completion of the reaction.

^cThe mixture was allowed to stand overnight after the completion of the reaction.



Scheme 1

CONCLUSION

We have provided a facile and efficient method for the synthesis of 3-methyl-4arylmethylene-isoxazol-5(4H)-ones in the presence of sodium sulfide. Owing to its operational simplicity, high yields, and short reaction time, this method is better than other currently examined reactions.

EXPERIMENTAL

All reagents were purchased and used without further purification. Melting points were determined using XT-4 micro melting point apparatus.

A mixture of 20 mmol ethyl acetoacetate, 20 mmol hydroxylamine hydrochloride, and 1 mmol sodium sulfide in ethanol (5 mL) were stirred for 10 min, then 20 mmol aromatic aldehyde was added, and the mixture was further stirred until the completion of the reaction (monitored by TLC). The product was filtered off and washed with cold 5% aqueous ethanol (2 \times 30 mL), and recrystallized from EtOH (95%) to afford the pure product.

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