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Micelle Catalyzed Synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones in Aqueous media: A green approach

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ABSTRACT:

A greener, simple and more efficient method has been developed for the synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones by using aqueous media of nano-size micelle catalyst. 10mole% SDS and SLES are found to be more effective for the synthesis of desired products. The present method is found to be more efficient, easier, and environmentally benign. The main advantages of method are greener, atom efficient, simple reaction condition.

KEYWORDS: 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones, aromatic aldehydes, ethyl acetoacetate, hydroxylamine hydrochloride, micelle, water.

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INTRODUCTION:

Today, organic reaction in water attracts great intension of every chemist with the interest of environment. As water has some intriguing properties such as nontoxic, nonflammable, low viscosity, low volatility, with unique reactivity and selectivity, now a day it is been used as solvent for the organic reaction¹⁻². The major hurdle of water as solvent for organic reaction is the poor solubility i.e most of the organic compounds are hydrophobic in nature hence it restrict water as a solvent ability. To overcome such hurdle now a day many researcher has been carried out organic reaction in micellar solution. Surfactant in water at critical micelle concentration (CMC) forms micelle that increases the solubility of organic substrate in water and also orients the substrate in such way that it enhances the selectivity as well as rate of reaction³.

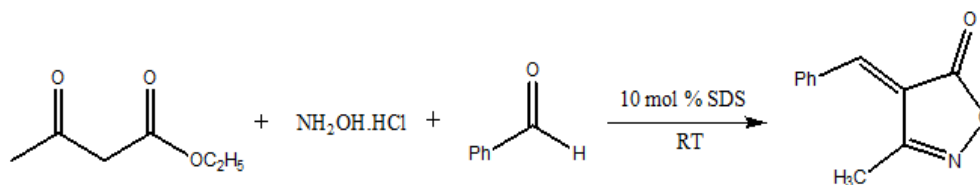
Recently, Paprocki et.al published excellent review about multicomponent reactions in aqueous micelles⁴. Surfactant at particular concentration forms micelle behaves like nano-reactors shows unique features than other type of catalysis.

Multicomponent reactions (MCRs) have obtained a great attention today as the number of applications in medicinal, drug discovery, natural product synthesis⁵. A name reaction like Mannich⁶, Biginelli⁷, Kabachnik-Fields⁸, Strecker⁹, Kinugasa¹⁰, Hantzsch¹¹ were successfully carried out in micellar solution.

The compounds of isoxazole has wide range of biological activities due to presence of hetero atom like oxygen and nitrogen atom results into excellent medicinal application. Isoxazole compound shows antifungal¹², antiviral, antitumour¹³, antinociceptive¹⁴, anti-tuberculosis, analgesics like biological activity. Such a interesting properties would boost everyone to find the new methodology in the development of synthesis of isoxazole moiety.

Therefore, several protocols have been proposed to Synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones such as sodium benzoate¹⁵, sodium silicates¹⁶, sodium sulfide¹⁷, sodium citrate¹⁸, sodium tetraborate¹⁹, aqueous ethanol²⁰, tartaric acid²¹, and ionic liquids²². Also by using visible light in aqueous ethanol has been reported. Some of the above mentioned conditions possess shortcomings, such as slow rates and limited substrate scope and the combination of solvents and long reaction time makes this method environmentally hazardous. But, still there is need of development of a simple, safe, environmentally benign, and more efficient method for the synthesis 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones of reaction is a rewarding challenge. In continuation of our work to carried out organic transformation in micellar solution²³⁻²⁴. Herein green route have been proposed for the synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones in aqueous micelle.

Scheme 1

**MATERIALS AND METHODS:**

All reagents were obtained from commercial sources Sigma Aldrich. Column chromatography was performed using 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 maybe incorrect. The products were also characterized by comparison of their melting point with literature values.

EXPERIMENTAL:***Synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones (Table 2, 1-9)***

The solution of ethyl acetoacetate (1 mmol) and hydroxylamine hydrochloride (1 mmol) in 10 mole% SDS solution of 10 cm³ was stirred for 10 min at room temperature. Then aromatic aldehyde (1 mmol) 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. 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 their reported melting points (table-1).

RESULTS AND DISCUSSION:

In order to find new greener, environmentally benign route for the synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones, we carried out the reaction of ethyl acetoacetate, hydroxylamine hydrochloride and aromatic benzaldehyde at room temperature as a model reaction (Table-1, entry-1). Off course, the reaction is well proceeded in the water (Table 1, entry 1) but the reaction is found to be very sluggish because of poor solubility of aldehyde in water. Enhancing the rate of reaction is major challenging interest for the study. When such reaction is carried out in micellar system an abrupt change in the speed and yield of the product was found.

It is intriguing to note that the presence of water immiscible reactants within the hydrophobic core of micellar media boost the rate of reaction. To evaluate effect of various surfactant of different

concentration has been carried out. The cationic surfactant CTAB of different concentration were first screened (Table 1, entry 2, 3) and the yield of the product was found good about 67% and 78% in just 50 minutes. Then, in order to check the versatility of micellar solution some nonionic surfactant like TX-100 also used for the reaction with 80% yield of the product was obtained. (Table 1, entry 4). However, more surprising result was obtained when same reaction carried in anionic 10 mole% SDS micelle gives 92% (Table 1, entry 6) and SLES micelle gives 90% (Table 1, entry 6) in 50 minutes.

Table 1, Effect of different micelles on the formation of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones.

Entry	Various solvents	Concentration (mole%)	Yields (%)
1	Water	-	35
2	CTAB	5	67
3	CTAB	10	78
4	TX-100	10	80
5	SDS	5	83
6	SDS	10	92
7	SLES	10	90

Reaction condition: ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), benzaldehyde (1 mmol) and Various Micellar solution (10cm³), Reaction time 50 minute.

After optimizing the reaction conditions, aromatic aldehydes were treated with ethyl acetoacetate and hydroxylamine hydrochloride in the presence of 10 mol% SDS in water. All the obtained results for different aromatic aldehydes are shown in Table 2. The yield of product are varied because of the effect of nature of different substituted group present on the aromatic aldehyde. The aromatic aldehydes with electron donating group facilitate the reaction faster with high yield of the products in short time (Table 2 entries 3-6). The ortho-substituted aromatic aldehyde shows longer reaction time compared to para-substituted aldehydes.

Table 2, Synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones in presence of 10 mole% SDS micelle.

Sr. No.	Ar	Time (min)	Yields(%)	MP (°C)	
				Found	Reported
	C ₆ H ₅	50	92	142-146	142-144
2	2-Furyl	65	70	240-244	240-242
3	4-CH ₃ OC ₆ H ₄	30	87	176-179	178-179
4	2-OHC ₆ H ₄	40	88	199-204	198-202
5	4-OH C ₆ H ₄	30	93	213-216	215-218
6	3CH ₃ O-4OH C ₆ H ₃	30	91	212-214	212-214
7	C ₆ H ₅ CH=CH	70	90	172-174	173-178
8	2-Cl C ₆ H ₄	180	NR	-	-
9	2,4-C C ₆ H ₃	180	NR	-	-

^a Isolated yield

NR- No reactions in given time,

Reaction condition: ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), benzaldehyde (1 mmol) and 10 mole% SDS solution (10cm³).

However, aromatic aldehyde with an electron withdrawing group shows sluggish the formation of desired product Table-2 entries 8, 9). Heterocyclic aldehyde and α β unsaturated aldehyde reacts smoothly with ethyl acetoacetate and hydroxylamine giving moderate to excellent yield.

CONCLUSION:

Here we have reported a simple and efficient method for the condensation of three component one pot synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4H)-ones in presence of 10 mole% SDS micelle. The main features of this method is environmentally benign, simple workup, short reaction time.

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