One pot synthesis of Bis-coumarin derivatives by using mixture of dodecyl benzene sulfonic acid and sodium benzyl dodecyl sulphateas an efficient catalyst in water

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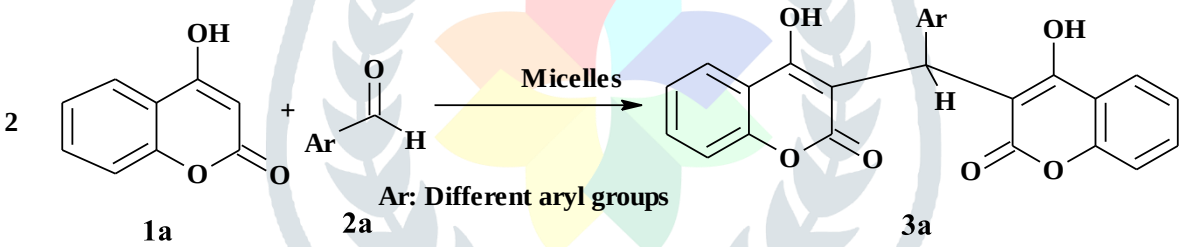
ABSTRACT:

Bis-coumarin derivatives have been synthesized by using mixture of dodecyl benzene sulfonic acid and sodium benzyl dodecyl sulphate as an effective catalyst. The merits of the method are shorter reaction time, aqueous media, easy workup procedure, non-toxic catalyst, better yield and cost-effective method. Micellar medium is not toxic, eco-friendly, less expensive and recyclable.

IndexTerms - Bis-Coumarin, dodecyl benzene sulfonic acid, sodium benzyl dodecyl sulphate,Catalysis, Green Chemistry.



Scheme: Synthesis of Bis-coumarin

INTRODUCTION

Coumarin derivatives are reported a s biological active heterocyclic compounds which act as anticoagulant, anti-HIV, antihypertensive, analgesic, anti-inflammatory, antihypertensive and anti-arrhythmia agents [1]. Along with biological applications coumarin are significant organic fluorescent materials [2], hence they are used in high tech application such as laser dyes, sensor for medical diagnostics and as fluorescent brightening agents [3]. Large number of coumarin derivatives are demanded by synthetic organic chemistry due to their various applications [4]. Many shortcomings are observed during synthesis of coumarin like use of organic solvents, laborious workup, increasing cost of reaction, long reaction time with low yields. Reported methods involves acid catalysts like $In(OTf)_3$, $LiClO_4$, $KHSO_4$, montmorillonite and iodine [5,11].

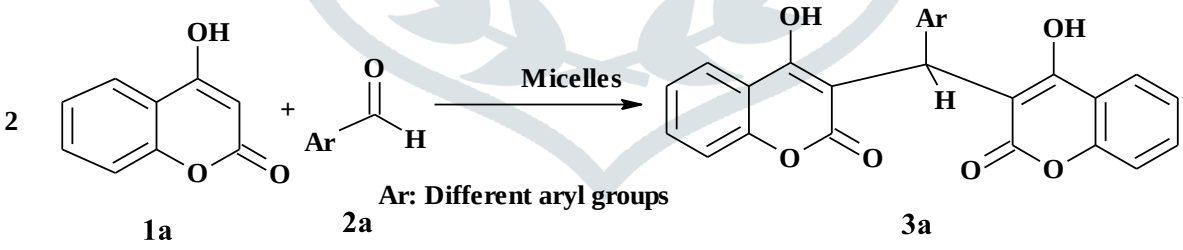
Water is used as solvent in wide range of reactions like pericyclic Reactions, reactions of carbenes, reactions of carbocations and carbanion equivalent, oxidation-reduction reactions etc. Water is not only cost effective but also lack mutagenic, explosive, carcinogenic properties. Recently, reactions in aqueous medium plays a very important role in synthetic organic chemistry. Organic moieties are lipophilic in nature

and this makes organic phase separation easy from water. In addition, higher heat capacity of water helps to control reaction temperature rather than in organic solvents. These features of water make easy and clean work up of reactions. Water has not only unique chemical and physical properties but also easily available solvent. Still, many reactions are not possible in aqueous medium basically due to insolubility of organic content into water and many catalysts and intermediates are not compactible with water. These drawbacks can be overcome by using surfactants as a catalyst for organic synthesis. Solubility of organic material is improved due to micellization of long organic chain of surfactants in water.

Our research work is aimed to improve conditions like mild and environment benign procedure, recyclability, overall cost-effective material for synthesis of Bio-coumarin. Significantly surfactants are used in organic synthesis due to its properties like less expensive, ecofriendly, reactive and easy to handle. In this research work, micellar media (mixture of dodecyl benzene sulfonic acid and sodium benzyl dodecyl sulphate) is efficiently used for synthesis of Bis-coumarin from coumarin and different aldehydes reactions. Many reactions like Suzuki reaction, Heck reaction, cyclisation reactions etc. were carried out strictly under anhydrous conditions but recently these reactions were reported in aqueous medium with higher yields than in previous one. Similar attempt of satisfying maximum "Green Chemistry" concept has been carried out in this paper to explore application of micellar media in synthetic chemistry.

RESULTS AND DISCUSSION

Initially, reaction was attempted by p-toluenesulfonic acid promoted the condensation reaction of coumarin 2a with benzaldehyde in reflux benzene to afford biscoumarin1 in a moderate yield with some decomposed by-products. Same condensation carried out using mixture of dodecyl benzene sulfonic acid and sodium benzyl dodecyl sulphateand unexpectedly better yields were observed in aqueous media as represented in **Scheme 1**.



Scheme 1: Synthesis of Bis-coumarin

Condensation of coumarin 2a with variety of aromatic aldehydes gave corresponding biscoumarins 3a in more than 92 % yields as reported in **Table 3** under same conditions. Reaction was clean with better yields due to aqueous media. Electron-rich aromatic aldehydes like 4-methoxyphenylaldehyde was taken more time to complete reaction with satisfied yields (entry3 of Table 2) whereas electron-withdrawing aromatic aldehyde like 4-nitrophenylaldehyde was taken shorter time to complete reaction (entry 2 of Table 2).

Many reactive substrates, intermediates, catalysts, reagents and products are not compatible with water. This drawback can be improved by using surfactant as a solubilizing agent. The solubility of organic substrates is enhanced due to micellization of surfactant in water. Since from last few decades, many literatures are existing on organic reaction in micellar media.In this methodology, major principles of

"Green Chemistry" have been fulfilled to protect human health and environment with achieving commercial viability. This is urgent need of the world due to increased industrial revolution. Hence, scientists are working to explore alternative methodologies with ecofriendly reaction media, less toxicity and least by products with avoiding use of volatile and toxic organic solvents. Importantly, this catalyst not only suitable in aqueous medium but also it can be recycled and used effectively and efficiently for such type of reactions. The uses of environmentally benign solvent, catalystand eco-friendly for synthetic transformations. Therefore, this investigation is utmost important and effective methodology for the different organic transformation to fulfill need of "Green Chemistry".

- In order to investigate the catalyst efficiency for the condensation of 4-hydroxycoumarin and benzaldehyde different catalysts were screened and dodecyl sulphate and its sodium salt in water were found to be best catalyst for bis-coumarin synthesis. Results of bis-coumarin synthesis by using different catalyst are summarized in **Table. 1**

Table 1. Optimization of catalyst for the synthesis of bis-coumarin.

Entry	Catalyst	Time (min)	Yield (Bis-coumarin)
1	p-TSA	112	50 (60)
2	Sulphuric acid	55	61 (54)
3	Phosphoric acid	50	62 (67)
4	Phosphomolybdic acid	40	75 (70)
5	BDS and salt	30	88 (87)

REAGENT AND CONDITIONS: 4-Hydroxycoumarin, aldehyde / ketone (1 mmole), catalyst (0.12 mmole), water 3 ml, temperature: 25 ^{o}C.

In order to find out role of catalyst in synthesis of bis-coumarin synthesis we proposed a probable mechanism for bis-coumarin **Figure 1**, In order to investigate the feasibility of theses synthesis methodology for the synthesis of bis-coumarin from 4-hydroxycoumarin with aldehydes, we extended the reaction of 4-hydroxy coumarin with electron donating and electron withdrawing aldehydes under similar conditions furnishing the respective bis-coumarin in short reaction time with very high yield. The optimized results are summarized in **Table 2**.

Figure 1: Proposed mechanism for bis-coumarin synthesis.

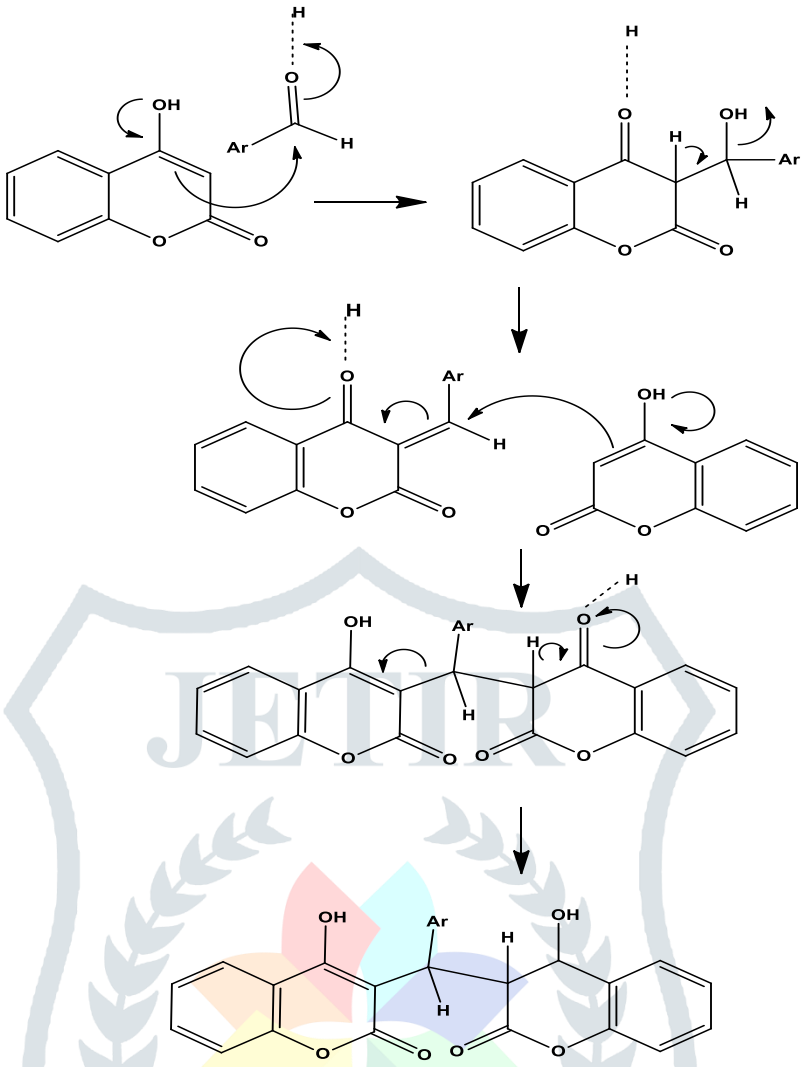


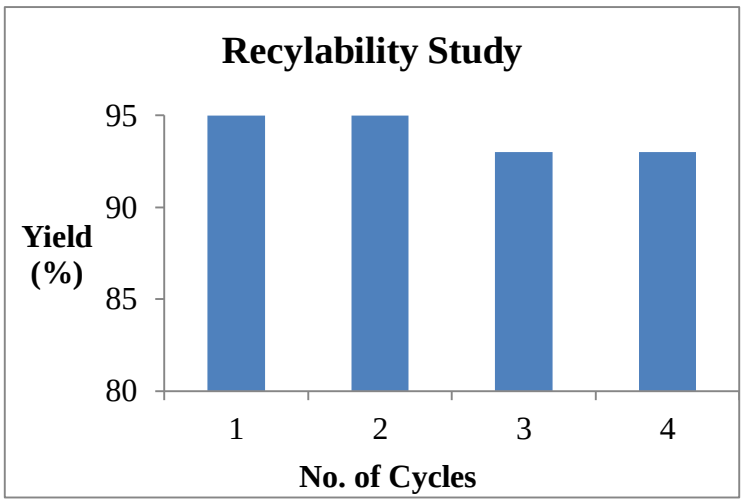
Table 2: Synthesis of bis-coumarin derivatives from 4-hydroxy coumarin and different aldehydes

Sr. No	Ar	Time
1	Ph	35
2	4-NO_2-Ph	25
3	4-MeO-Ph	50
4	4-Cl-Ph	45
5	4-Br-Ph	45
6	4-Me-Ph	35

A result of **Table 2** clearly indicates that catalyst tolerates the effect of electron donor and acceptor substitute in the formation of products.

The study of recyclability of reaction media revealed that the reaction media could be recycled and reused for four successive cycles offering the identical conversions and slight loss in yield (**Figure 2**). Upon end of the reaction the product was extracted using diethyl ether and thus separated micellar media were reused for the next cycle.

Figure 2: Recyclability of catalyst for bis-coumarin synthesis.



Experimental Procedure:

MATERIALS AND METHODS:

All commercial material reagents and solvents were purchased from S.D. fine chemicals Ltd., (India) and were used without purification. Mixture of dodecyl benzene sulfonic acid and sodium benzyl dodecyl sulphate was purchased from Sigma Aldrich. Column chromatography was performed using silica gel 60-120 mesh size. All melting points were obtained by Bamslead Electrothermal 9200 apparatus and are uncorrected. The reaction was monitored by TLC using 0.25 mm E-Merck silica gel 60 F254 precoated plates, which were visualized with UV light. 1H and 13C NMR spectra were recorded in DMSO on a Bruker 400 MHz spectrometer. Infrared spectra were recorded on a Bruker FT-IR Equinax-55 spectrophotometer in KBr with absorption in cm^{-1}.

GENERAL EXPERIMENTAL PROCEDURE

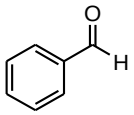
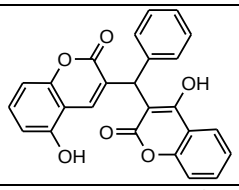
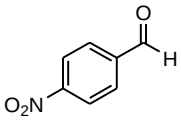
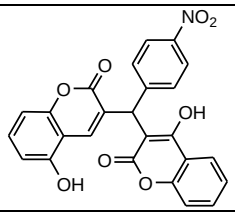
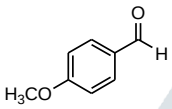
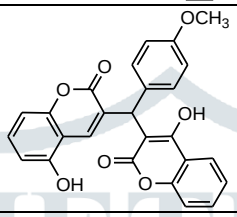
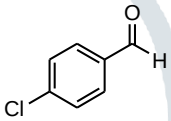
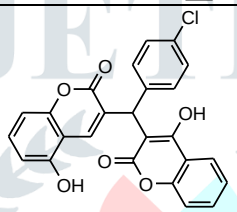
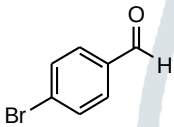
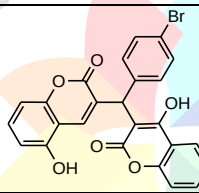
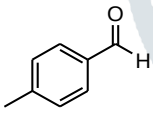
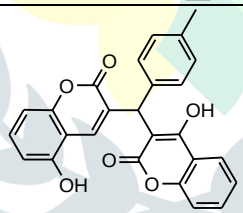
GENERAL EXPERIMENTAL PROCEDURE FOR BIS-COUMARIN

A mixture of 4-hydroxycoumarin (2 mmol), an aromatic aldehyde (1 mmol) and BDS (0.12 mmol, 57.6 mg) in H_2O (3 ml) were stirred at 25°C for the appropriate times (**Tables 2**). Upon completion of the reaction, monitored by TLC product was extracted in diethyl ether, micelles was recycled and crude product crystallized from ethanol.

EXPERIMENTAL AND ANALYSIS:

- All the temperatures are expressed in degree centigrade (^oC).
- All the melting points are uncorrected and have been recorded by capillary method.
- Room temperature wherever mentioned corresponds to 28-32 oC.
- Experimental part of this project report has been written in detail so as to ensure qualitative and quantitative reproduction of the compounds synthesized.

Table 3: Spectral data of synthesized bis-coumarin derivatives.

Sr. No.	Aldehydes 2a	Product 3a	Yield	M.P.
1			92	148-150
2			98	236
3			96	246-247
4			94	256-257
5			93	267-268
6			97	266-268

CONCLUSION:

In this project, Greener, efficient and environment friendly method have been developed for synthesis of various bis-coumarin alkanes by using micelles in water. The advantageous of the present method are higher yields, shorter reaction time and ease of reaction procedure.

ACKNOWLEDGEMENT:

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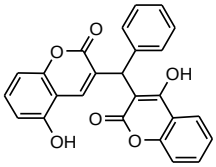
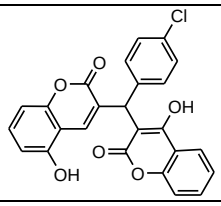
Spectral data of representative bis-coumarin

Structure	IR (KBr) cm^{-1}	1H NMR ($CDCl_3$) ppm	C^{13} NMR ($CDCl_3$) ppm	EIMS m/z
	3035, 1661, 1604 and 761	6.18 (1H, s, CH) and 7.1–8.3 (13H, m, 13×CH)	16.25, 91.23, 104.52, 107.093, 116.32, 117.91, 123.50, 124.22, 126.12, 126.94, 128.50, 129.723, 132.45, 139.63, 163.35, 165.44	411.75
	3031, 1672, 1614, 1092, 765	6.11 (1H, s, CH) and 7.3–8.2 (12H, m, 12×CH);	δ 16.48, 90.43, 105.51, 107.25, 115.28, 117.91 123.42, 125.60,126.20, 126.94, 129.62, 130.58, 133.13, 139.63, 163.35, 166.85;	445.69

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