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Surfactant-assisted synthesis of bis(indolyl)methanes in water

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Abstract

An environmentally friendly synthesis method for bis(indolyl)methanes has been developed in the presence of sodium lauryl ether sulfate (SLES), electrophilic substitution reactions of indoles with aldehydes were accomplished in water as solvent at room temperature without any Bronested or Lewis acid catalysts.

Keywords: Sodium lauryl ether sulfate; Bis(indolyl) methanes; Indoles; Aldehydes

Indoles and bis(indolyl)methanes (BIMs) are important class of heterocyclic compounds in the pharmaceutical as well as synthetic chemistry [1,2]. They are important antibiotics in the field of pharmaceuticals [3] or the precursor of bioactive metabolites of terrestrial and marine origin [4–6]. They are also know as antitumor compounds [7,8] and are effective in the prevention of cancer and found in cruciferous plants and known to promote beneficial estrogen metabolism and induce apoptosis in human cancer cell [9]. In the analytical chemistry they can be used as anion receptors [10] or in solid-phase extraction [11].

Due to importance of bis(indolyl)methanes in pharmaceutical chemistry, their synthesis have received increasing attention. Several methods have been reported in the literature for the preparation of bis(indolyl)methanes from indoles and aldehydes or ketones using protic acids [12–17] and Lewis acids [18–23]. Many Lewis acids like BF_3 and $AlCl_3$ promote this type of reaction but they generate harmful wastes, which pose environmental problems.

Use of environmentally friendly reaction medium is one of the fundamental principles of green chemistry [24]. Water as a reaction solvent has received much attention in synthesis of organic compounds, because it would be considerably safe, non-toxic, environmentally friendly, and cheap compared to organic solvents [25]. Moreover, when a water soluble catalyst is used, the insoluble products can be separated by simple filtration and the catalyst system can be recycled. Using water as solvent in the synthesis of BIMs is accompanied with some problems; the most common and noticeable of these problems are low solubility of reactants and sensitivity of Lewis acids to the water. These problems can be solved to some extent using water tolerant Lewis acids such as metal triflate and surfactant-type Lewis and Bronested acids or using surfactant assisted reactions [26–30].

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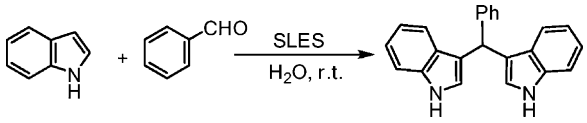


Scheme 1. The reaction of indole with benzaldehyde as a model reaction.

Table 1
Effect of amount of SLES on the reaction yield of 3,3′-bis(indolyl)phenylmethane.[a]

Entry	Mol%	Yield (%)[b]
1	None	N.R
2	5	80
3	10	93
4	15	74
5	20	70

[a] Indole (2.0 mmol), benzaldehyde (1.0 mmol) in the presence of different amount of SLES.
[b] Isolated yield.

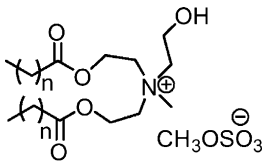
In order to develop a new method for the synthesis of bis(indolyl)methanes we report here the surfactant assisted synthesis of bis(indolyl)methanes from the condensation of various aldehydes and indoles in water as solvent at room temperature in the absence of any catalyst.

To optimize the reaction conditions, the reaction of indole and benzaldehyde was selected as the model reaction. Model reaction has been carried out at room temperature in water as solvent (Scheme 1).

To find the optimum amount of SLES, the yields of the model reaction using various amounts of SLES (5, 10, 15 and 20 mol%) were obtained and compared. The results were summarized in Table 1. From these results, it can be concluded that the yields of reaction in the presence small amount of SLES were good to high and the optimum amount of surfactant was 10 mol%, the desired product was obtained in 93% yield within 2.5 h. Presence of surfactant is essential for this reaction and the reaction did not occur in the absence of SLES even after a long time (Table 1, entry 1).

In addition to SLES, we screened the effect of other surfactants such as cetyl trimethylammonium bromide (CTAB), tetradecyl trimethyl ammonium bromide (TTAB), dodecyl trimethyl ammonium bromide (DTAB), and Esterquat (Scheme 2), on the time and yield of the model reaction (Table 2). As can be seen from this table SLES performs better than other surfactants regard to time and yield of the reaction.

Based on these observations we extended the study to the reaction of indoles with other aldehydes all the results were summarized in Table 3.



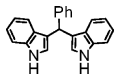
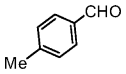
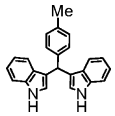
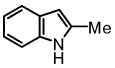
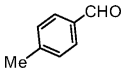
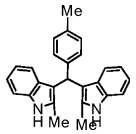
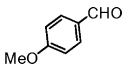
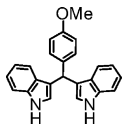
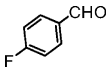
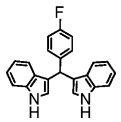
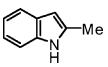
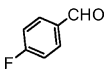
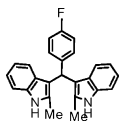
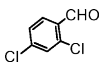
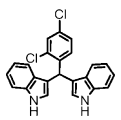
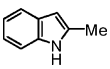
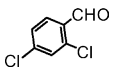
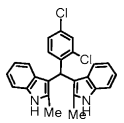
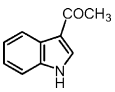
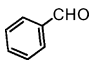
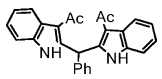
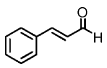
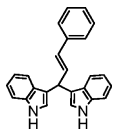
Scheme 2. Chemical structure of Esterquate as a cationic surfactant.

Table 2
Effect of different surfactants on the reaction time and yield of 3,3′-bis(indolyl)phenylmethane.[a]

Entry	Surfactant (10 mol%)	Time (h)	Yield (%)
1	TTAB	7	35
2	DETAB	7	30
3	CTAB	7	30
4	Esterquat	5	37
5	SLES	2.5	93

[a] Indole (2.0 mmol), benzaldehyde (1.0 mmol) in the presence of 10 mol% of various surfactants.

Table 3
Synthesis of bis(indolyl)methanes via the condensation of indoles with aldehydes using SLES in aqueous media at room temperature.

Entry	Indole	Benzaldehyde	Product	Time (h)	Yield (%)[a,b]
1				2.5	93
2				2.5	94
3				1.0	70
4				5.0	85
5				5	90
6				4	86
7				1	90
8				5	80
9				5	73
10				3	70
11			–	5	–
12		CH_3CHO	–	5	–

[a] Yields refer to isolated products.
[b] All the products gave satisfactory spectroscopic (IR, ^1H, and ^{13}C NMR) analysis.

SLES forms micelles in water and can dissolves insoluble starting materials. The dissolved material reacted gradually on stirring the reaction mixture at room temperature and was complete in 2.5–5 h giving 70–94% yields of bis(indolyl)methanes.

In conclusion, we have presented a green procedure for the synthesis of bis(indolyl)methanes from indoles and aromatic aldehydes in the presence of SLES in water as green solvent. The present procedure has many advantages such as mild conditions, easy operation procedures and environment friendly.

General experimental procedure for synthesis of bis(indolyl)methanes: To a mixture of indole (2 mmol), aldehyde (1 mmol) in water (5 mL), SLES (10 mol%) was added and stirred at room temperature. The mixture became emulsive and the product gradually precipitated. The progress of reaction monitored by TLC and the reaction went to completion in appropriate time (Table 3). After completion of the reaction the almost pure insoluble bis(indoly)-methane was filtered and recrystallized from suitable solvent like ethanol–water for further purification.

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