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A convenient and greener synthesis of bis(indolyl)methanes in surfactant medium under microwave irradiation

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ABSTRACT

An efficient, versatile and environmental friendly being one-pot approach for the synthesis of highly substituted bis(indolyl)methane (BIMs) derivatives has been described under microwave irradiation in surfactant medium. Without application of additional reagent or catalyst makes this methodology green, simple and user friendly.

KEYWORDS

Bis(indolyl)methanes;
Surfactant medium;
AOT (sodium *bis* -2-ethyl hexyl sulphosuccinate);
Microwave irradiation;
Knoevenagel condensation;
Michael addition.

INTRODUCTION

With the development of industrialization, organic chemists have been confronted with a new challenge of finding novel methods in organic synthesis that can reduce and finally eliminate the impact of volatile organic solvents and hazardous toxic chemicals on the environment. So, use of nontoxic, environmental friendly and inexpensive protocol has attracted considerable interest recently. The development of novel synthetic route to facilitate the preparation of specific molecules is an intense area of research. In this regard, efforts have been constantly made to develop new methodologies that are efficient and more compatible with the environment. One of the most desirable approaches to address this challenge is a search for surrogates for commonly employed organic solvents from various health and environmental reasons[1]. From the green chemistry point of view, water would be the perfect solvent to carry out chemical reaction since it is safe, nontoxic, and inexpensive and which possess no threat to the environment[2]. However, water is rarely used or even considered as a solvent for organic reactions. One of the principal reasons is undoubtedly the limited solubility of most organic compounds in pure water. Since solubility is important factor for good reactivity, alternative for improving the solubility of organic substrates that may ultimately help in expanding the scope of water-based organic synthesis have been investigated[3]. Incorporation of surface active agents (surfactants) in aqueous media has been proved to enhance the reactivity of water mediated reactions[4].

Bis(indolyl)methane moieties are found in a large number of natural products, which have shown a broad spectrum of biological properties for example antitumor[5], antifungal[6], antibiotic[7], anti-inflammatory and antibacterial activities[8]. BIMs exhibit inhibitory activity on lung cancer cells[9], inhabit bladder cancer[10], active against colon cancer[11] and are also exploit as tranquilizers[12], antiangiogenic and cytotoxic agents[13]. Due to such biological and pharmaceutical importance the synthesis of bis(indolyl)methanes and its derivatives is receiving considerable attention.

Recently, many synthetic methods for preparing these compounds have been reported by using variety of reagents such as acetic acid, InCl$_3$[14], In(OTf)$_3$[15], diamminium hydrogen phosphate[16], InF$_3$[17], Dy(OTf)$_3$[18], Ln(OTf)$_3$[19], LiClO$_4$[20], FeCl$_3$[21], NBS[22], KHSO$_4$[23], NaHSO$_4$. SiO$_2$[24], PPh$_3$. HClO$_4$ (TPP)[25], CAN[26], zeolites[27], clay[28], I$_2$[29], etc. However, some of these methodologies have some disadvantages, such as low yields, prolonged reaction time, harsh reaction condition, use of organic solvents and the requirement of stiochiometric amount of catalyst. So, the development of simple, convenient and environmental friendly approaches are still demanding for the preparation of bis(indolyl)methanes.

Microwave chemistry has an edge over conventional heating for conducting chemical reactions, and it emerge as the preferred technology for performing chemical synthesis relating to lead development in pharmaceutical and biotechnology companies[30]. Microwave activation as a non-conventional energy source has become an important method that can be used to carry out a wide range of reactions in very short reaction time and in high yields.

However, to the best of our knowledge, reports related to the synthesis of bis(indolyl)methanes in surfactant medium promoted by microwave irradiation has not been published till date. We herein report a green, one-pot, efficient synthesis of BIMs under microwave irradiation in surfactant medium.

RESULT AND DISCUSSION

In continuation of our efforts to explore newer reactions for the synthesis of heterocyclic compounds[31], we decided to explore the synthesizing of bis(indolyl)methanes under microwave irradiation in presence of surfactant. The reaction of indole **(1)** and benzaldehyde **(2a)**, in surfactant medium under microwave irradiation has been considered as a standard model reaction. Initially the reaction was carried out at 60 W and 25 °C for 5 min it furnished a solid product in a low yields (32 %). Compound was identified by the analytical and spectra data. The presence of a singlet at δ 5.81 and a broad singlet at δ 7.83 in ^{1}H NMR and picks at 3403 cm^{-1} and 1639 cm^{-1} in IR spectra clearly indicate the formation of **(4a)**. In an attempt to improve the yield, we further optimized the reaction condition by altering watt, temperature and time. This conversion was found to be even slower and gave lower yield of the product even if we used 100 W and 50 °C temperature; 10 min. Best result was achieved by using 175 W, 70 °C, for 6 min. In order to optimize the reaction condition we have screened a number of different surfactant on the model reaction. However, when the same reaction was conducted under similar condition using by CPC (cetylpyridinium chloride) or SDS (sodium dodecyl sulphate) as a surfactant it gave less yield of product (TABLE 1 entry 1, 2), best yield (88 %) was achieved by using AOT (sodium *bis* -2-ethyl hexyl sulphosuccinate) as surfactant under microwave-irradiation (TABLE 1, entry 3). Among SDS, CPC and AOT, the latter accelerate the reaction better, presumably due to the stronger binding of the AOT with the substrate, which is expected as AOT has more hydrocarbon content in the core region than SDS or CPC[32].

TABLE 1 : Optimization of the reaction condition under microwave irradiation and conventional methods in presence of different surfactants

	Microwave			Conventional		
Entry	Surfactant	Time (min)	Yields (%)	Surfactant	Time (h)	Yields (%)
1	SDS	8	78	DBSA	1	90[33]
2	CPC	8	82	[Fe(DS)$_3$]	6	90[34]
3	AOT	6	88	AOT	2	80 [Present work]

Reaction condition: Indole (2 mmol), benzaldehyde (1 mmol).

Under the condition described above [H$_2$O-AOT, 70 °C, 175 W] scope of the reaction was examined (TABLE 2). From TABLE 2 it is evident that aromatic aldehydes bearing electron withdrawing group react faster than electron donating substituent. It was also found that the reaction of isatin **(3)** and indole **(1)** furnished 3, 3/-di(indolyl)oxindoles under similar condition gave good to higher yield. However, when the aliphatic aldehydes were applied to this reaction, no expected products were obtained. All the products were analytically pure and structures were determined by the spectral methods (ir, nmr, mass) and the physical data (mp) with those in literature[29,35-37].

Furthermore, we decided to study of reusability of AOT in our optimized reaction condition. After the separation of products, the AOT-containing aqueous medium was reused in the next five runs without any further purification and no significant drops in product yields was observed.

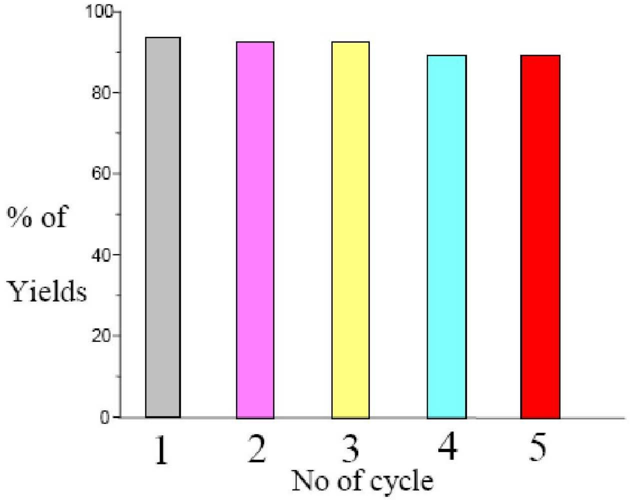
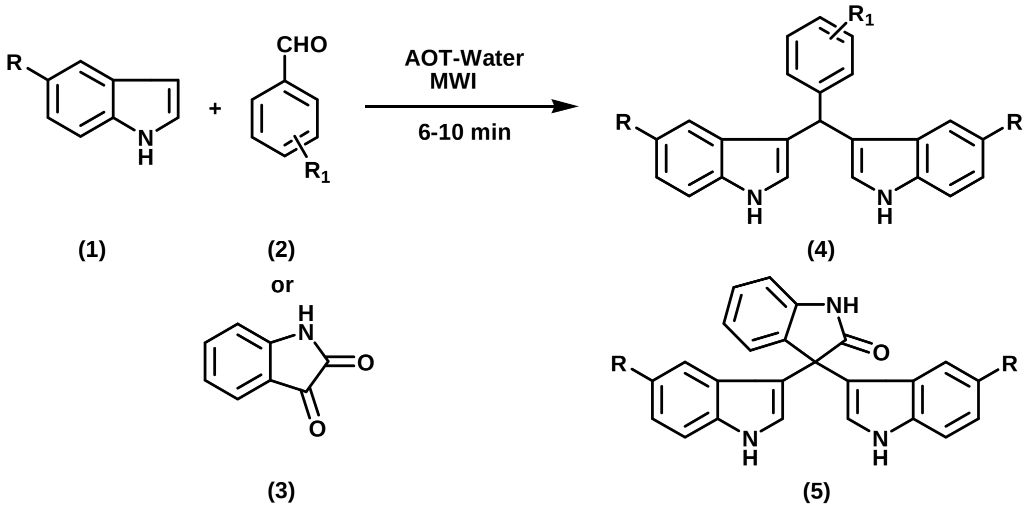


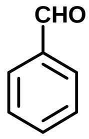
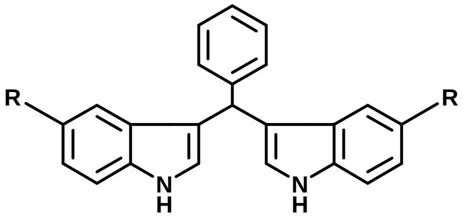
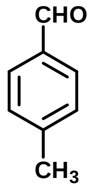
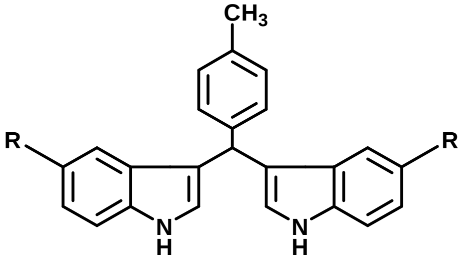
Figure 1 : Reusability of the surfactant in the model reaction

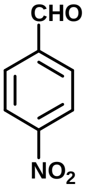
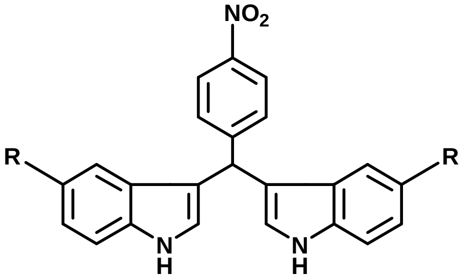
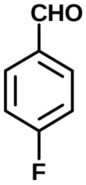
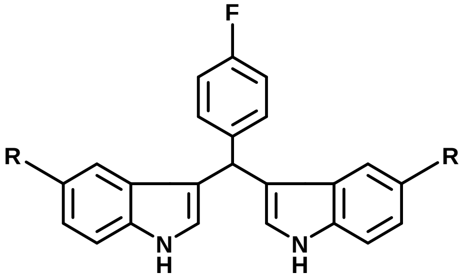
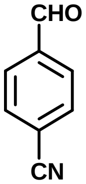
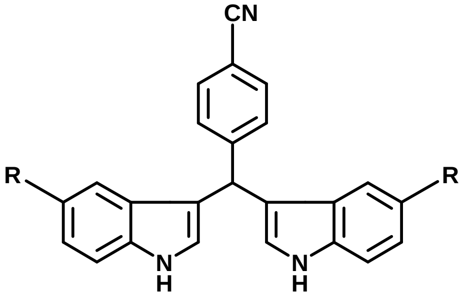
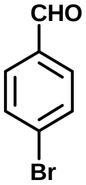
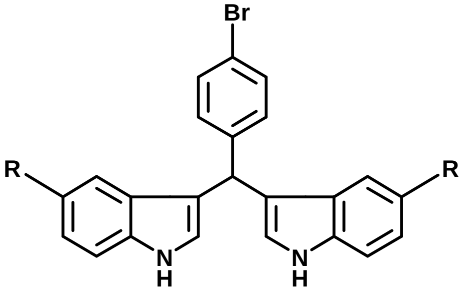
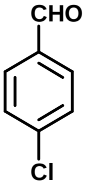
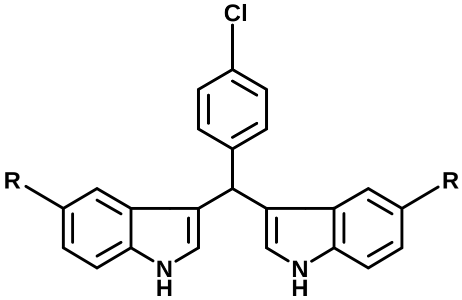
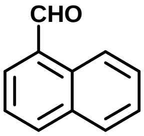
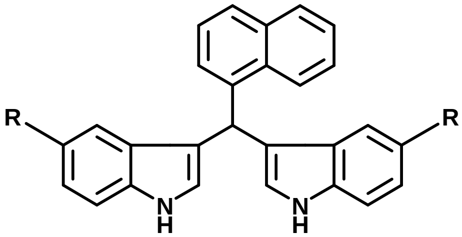


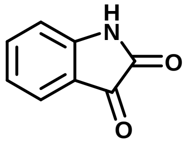
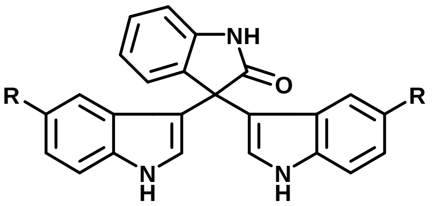
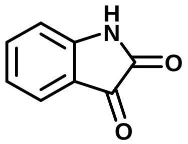
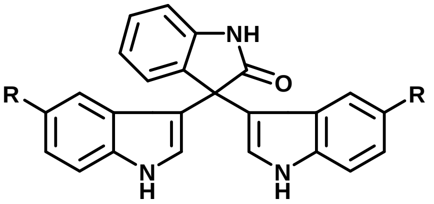
Reagent and Condition: (i) AOT-Water, MW 175 W, 70 °C, 6-10 min

Scheme 1

TABLE 2 : The reaction of indole with aromatic aldehydes or isatin under microwave irradiation in presence of AOT-water.

Entry	2	R	Product	Time (min)	Yield (%)a
1		H		6	88[29]
2		H		9	86[29]

Entry	2	R	Product	Time (min)	Yield (%)[a]
3		H		6	92[29]
4		H		7	86
5		H		6	87[35]
6		H		6	88[36]
7		H		8	85[29]
8		H		10	82

Entry	2	R	Product	Time (min)	Yield (%)^a
9		H		6	87[37]
10		OCH_3		8	89[37]

^{a}Isolated yields

EXPERIMENTAL SECTION

All the experiments were carried out in MATTHEWS, NC- MADE IN USA. MODEL-DISCOVER-S. MODEL NO-NP-1009, Microwaves Digester in sealed vessel. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Spectrum BX FT-IR, Perkin Elmer (υ_{max} in cm^{-1}) on KBr disks. ^{1}H NMR and ^{13}C NMR (400 MHz and 100 MHz respectively) spectra were recorded on Bruker Avance II-400 spectrometer. Mass spectra were recorded on Waters ZQ-2695. CHN were recorded on CHN-OS analyzer (Perkin Elmer 2400, Series II). Silica gel G (E-mark, India) was used for TLC. Hexane refers to the fraction boiling between 60 and 80 °C.

General procedure

A mixture of indole 1 (2 mmol), aryl aldehydes (1 mmol) **(2)** or isatin **(3)** (1 mmol) in aqueous solution of AOT (15 mmol, 5 ml) was irradiated under microwave at 175 watt and 70 °C for the appropriate time mentioned in the TABLE 2. After completion of the reaction (TLC), it was cooled to room temperature and extracted with chloroform (3 × 10 ml). The combined organic extract was washed with water (3 × 10 ml), brine solution and dried (Na_2SO_4). The solvent was removed in vacuum and the crude product was purified by column chromatography over silica gel using ethyl acetate – hexane (2:8) as eluent.

CONCLUSION

In conclusion, we have developed a hitherto unreported, easy, general and straight forward protocol for the synthesis of substituted bis(indolyl)methanes by Knoevenagel condensation followed by Michael addition reaction from readily and widely available substrate (indole and aromatic aldehydes) employing microwave irradiation under surfactant medium. In the light of its operational simplicity, simple purification procedure and high yields makes this protocol is superior to the existing methods.

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