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Short Communication

Ultrasound assisted green synthesis of bis(indol-3-yl)methanes catalyzed by 1-hexenesulphonic acid sodium salt

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ABSTRACT

1-Hexenesulphonic acid sodium salt as catalyst for green synthesis of bis(indol-3-yl)methanes was described. The reaction of indole with various aldehydes in water using ultrasound irradiation at ambient temperature for appropriate time using 1-hexenesulphonic acid sodium salt furnish the desired product in good to excellent yield. Utilization of aqueous medium, simple reaction conditions, isolation, and purification makes this manipulation very interesting from an economic and environmental perspective.

1. Introduction

Interest in indole-containing structures stems from their widespread occurrence in molecules that exhibit significant activity against several bacteria and viruses [1]. In addition, bis-indolylalkane derivatives have been used as bioactive metabolites of terrestrial and marine origin [2]. Various oxyindole derivatives are used as potential anticancer agents [3]. Medicinal chemists repeatedly twirl indole based compounds as a target pharmacophores for the development of therapeutic agents [4]. Bis(indolyl)-methanes are most active cruciferous substances for promoting beneficial estrogen metabolism and inducing apoptosis in human cancer cell [5].

The acid-catalyzed reaction of electron rich heterocyclic compounds with *p*-dimethyl amino benzaldehyde knowns as the Ehrlich test [6–8] for π-electron rich heterocycles such as pyrroles and indoles. Analogous to Ehrlich test, indoles with other aromatic or aliphatic aldehydes and ketones produces azafulvenium salts. The azafulvenium salts can undergo further addition with a second indole molecule to afford bis(indol-3-yl)methanes [9].

In the organic synthesis and reactions, increasing attention is being focused on green chemistry using environmentally benign reagents and conditions, particularly solvent-free procedures [10] which often lead to clean, eco-friendly and highly efficient procedures involving simplified work-up. Organic reactions in water or aqueous media have attracted great interest [11–13]. With tightened regulatory pressure focusing on organic solvents, the search for alternatives is of increasing importance. In this respect, the development of water-tolerant catalyst has rapidly become an area of intense research. Surprisingly however, there are only four reports for synthesis of indole and its derivatives in net water using oxalic acid [14], Meldrum's acid [15], [Cu(3,4-tmtppa)($MeSO_4$)$_4$] [16] and $H_3PW_{12}O_{40}$ [17].

Ultrasound irradiation has been established as an significant technique in synthetic organic chemistry [18–21]. Shorter reaction time is the main benefit of ultrasound-assisted reactions. Simple experimental procedure, high yields, improved selectivity and clean reaction of many ultrasound induced organic transformations offers additional convenience in the field of synthetic organic chemistry. Also bis(indol-3-yl)methanes synthesis under ultrasound irradiation [22–24] but all these method having some drawbacks like prolonged reaction time, lower yield and expensive catalyst due to this we have expand this method in under ultrasound irradiation in aqueous media with our catalyst.

We herein, report an eco-friendly, facile and efficient methodology for the synthesis of bis(indol-3-yl)methanes. The 1-hexenesulphonic acid sodium salt [25,26] liberates corresponding acid with extreme wide applications such as sulphonation of alkanes [27] etc. However, there are no examples of 1-hexenesulphonic acid sodium salt as a catalyst in the organic transformation.

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2. Experimental

Melting points were determined on a Veego apparatus and are uncorrected. Infrared spectra were recorded on a Bruker spectrophotometer in a KBr disc, and the absorption bands are expressed in cm^{-1}. ^1H NMR spectra were recorded on a Varian AS 400 MHz spectrometer in $CDCl_3$/DMSO-d_6, chemical shifts (δ) are in ppm relative to TMS, and coupling constants (J) are expressed in Hertz (Hz). Mass spectra were taken on a Macro mass spectrometer (Waters) by electro-spray method (ES). Bandelin Sonorex (with a frequency of 35 kHz and a nominal power 200 W) ultrasonic bath was used for ultrasonic irradiation. Built-in heating, 30–80 °C thermostatically adjustable. The reaction vessel placed in side the ultrasonic bath containing water.

3. General procedure

A mixture of 1*H*-indole (1 mmol), aldehyde (2 mmol) and 1-hexenesulphonic acid sodium salt (10 mol%) was dissolved in minimum quantity of water with constant stirring. Further the reaction mass was irradiated under ultrasonic irradiation at ambient temperature for appropriate time (Table 3). The progress of reaction was monitored by TLC. After the completion of reaction the coloured product obtained was filtered and recrystallized from ethanol to get the pure product.

4. Results and discussion

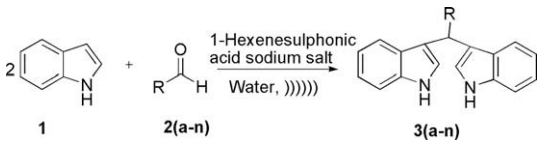
In the continuation of our research work of developing methods in various organic transformations [28–31]. Herein, we have developed methodology for the synthesis of bis(indol-3-yl)methanes using 1-hexenesulphonic acid sodium salt, which makes use of milder condition over the reported procedure as depicted in Scheme 1.

The methodology developed is simple with good to excellent yields. We first compared the catalyst effect on different solvents for synthesis of bis(indol-3-yl)methanes using 1-hexenesulphonic acid sodium salt and the results are summarized in Table 1.

In a typical experiment, the reaction of indole (1) and benzaldehyde (2a) in water was carried in the presence of 1-hexenesulphonic acid sodium salt to afford the corresponding bis(indol-3-yl)methanes (**3a**). Using lower amount of catalyst resulted in lower yields, while higher amount of catalyst did not affect the reaction times and yields and in the absence of catalyst, the yield of the product was not found. The best results were obtained using 10 mol% of catalyst (yield = 94%). The reaction proceeds smoothly at ambient temperature with 10 mol% of catalyst and completes within 45 min (Table 2, **entry 6**). We kept catalyst concentration constant and used different solvents like toluene, dichloromethane, acetonitrile:water (8:2), methanol, and ethanol afforded a lower yields. We have also studied the sonochemical effect on model reaction by using different solvents. In all cases, the experimental results show that the reaction times are shorter and the yields of the products are higher under sonication. Based on the results of this study, it seems that the ultrasound irradiation improves the reaction times and yields. The obtained results summarized in (Table 1, **entries 1–6**). These results suggest that water is the best solvent for synthesis of bis(indol-3-yl)methanes; it may be due to catalyst having greater solubility in water than in any organic solvent.

Furthermore, effect of catalyst load on reaction time and yield is explored in Table 2. The best result is obtained with 10 mol% of the catalyst. After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aryl aldehydes with indol. The results are shown in Table 3. The newly synthesized compounds were compared (melting point, MS, NMR, and IR) with compounds that were prepared by using the literature method [32] (Scheme 1. This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds.

The probable mechanism [23,33] of the reaction is shown in Scheme 2. The mechanistic part shows 1-hexenesulphonic acid sodium salt liberates corresponding acid when dissolved in water, which activates the aldehyde towards electrophilic attack of indole to generate aza-Michael intermediate. Later on aza-Michael of 1*H*-indole furnishes desired bis(indol-3-yl)methanes.



Scheme 1. Synthesis of bis(indol-3-yl) methanes.

Table 1
Optimization of solvent effect on the model reaction.

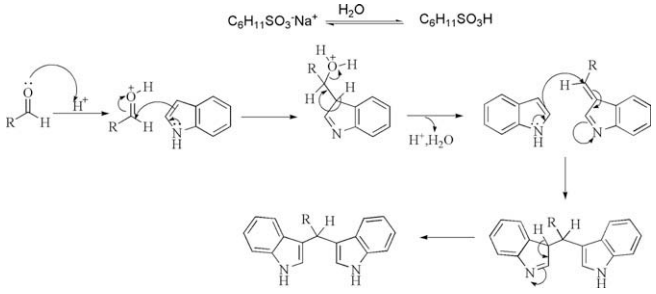
Entry	Solvent	With US[a]		Without US[b]	
		Time (min)	Yield[c] (%)	Time (min)	Yield[c] (%)
1	Toluene	45	25	120	20
2	Dichloromethane	45	34	120	28
3	Acetonitrile:water (8:2)	45	65	120	53
4	Methanol	45	72	120	60
5	Ethanol	45	78	120	70
6	Water	45	94	120	85

[a] Reaction of benzaldehyde with 1*H*-Indole in presence of 1-hexenesulphonic acid sodium salt (10 mol%) under ultrasonic waves for 45 min.
[b] Reaction of benzaldehyde with 1*H*-Indole in presence of 1-hexanesulphonic acid sodium salt (10 mol%) under reflux condition for 120 min.
[c] Isolated yield.

Table 2
Screening of catalyst concentration on model reaction[a].

Entry	Catalyst (mol%)	Yield[b] (%)
1	0	No reaction
2	2	24
3	4	36
4	6	58
5	8	80
6	10	94
7	12	94

[a] Reaction of benzaldehyde with 1*H*-Indole in presence of 1-hexanesulphonic acid sodium salt (10 mol%) in water under ultra sonic waves for 45 min.
[b] Isolated yield.



Scheme 2. Proposed mechanism of reaction.

Table 3
Characterization data[a] of bis(indol-3-yl)methanes (3a–3n).

Entry	Aldehyde	Time (min)	Yield[b,c] (%)	MP (°C)	
				Found	Lit.
3a	Benzaldehyde	45	94	123–124	124 [34]
3b	2-Chlorobenzaldehyde	55	88	73–75	74 [34]
3c	3-Chlorobenzaldehyde	60	92	74–75	74 [35]
3d	4-Chlorobenzaldehyde	40	92	76–77	78 [32]
3e	4-Hydroxy-3-methoxy benzaldehyde	60	82	109–111	111 [35]
3f	4-Hydroxybenzaldehyde	60	85	122–123	124 [32]
3g	4-Nitrobenzaldehyde	40	90	221–222	220[32]
3h	4-Methylbenzaldehyde	65	84	97–98	96[35]
3i	4-Methoxybenzaldehyde	60	88	188–189	189 [32]
3j	Benzo[1,3]dioxale-5-benzaldehyde	65	90	100–102	102 [36]
3k	Furan-2-carbaldehyde	50	83	320–321	322[32]
3l	Heptanal	45	80	68–70	68 [34]
3m	Piconaldehyde	60	87	99–100	97 [32]
3n	Thiophene-2-carbaldehyde	60	90	150–153	152 [35]

[a] Reaction of aldehyde with 1*H*-Indole in presence of 1-hexenesulphonic acid sodium salt (10 mol%) in water under ultrasound irradiation.
[b] Isolated yield.
[c] Compounds were characterised by ^{1}H NMR, MS spectral data and were compared with the reference compounds [37].

5. Conclusion

1-Hexenesulphonic acid sodium salt in aqueous media was found to be mild and effective catalyst in green synthesis of bis(indol-3-yl)methanes under ultrasonic irradiation. This catalyst provides clean, conversion; greater selectivity and easy work-up make this protocol practical and economically attractive.

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[37] Spectral data of reprehensive compounds (**3d**) ^{1}H NMR (400 MHz, $CDCl_3$): 5.86 (s, 1H, Ar–CH), 6.65 (s, 2H), 7.02 (t, 2H, *J* = 7.6 Hz), 7.18 (t, 2H, *J* = 7.6 Hz), 7.26–7.38 (m, 8H), 7.93 (br s, 2H, NH); MS *m*/*z*. 357 (M^+) 359 (M+2). (**3j**) ^{1}H NMR (400 MHz, $CDCl_3$): 5.80 (s, 1 H), 5.90 (s, 2 H), 6.66 (d, 2 H, *J* = 1.2 Hz), 6.72 (d, 1 H, *J* = 8.6 Hz), 6.83 (d, 2 H, *J* = 7.8 Hz), 7.01 (t, 2H, *J* = 7.8 Hz), 7.16 (t, 2 H, *J* = 7.2 Hz), 7.35 (d, 2 H, *J* = 8.4 Hz), 7.4 (d, 2 H, *J* = 8.1 Hz), 7.89 (br, s, 2 H, NH). ES-MS *m*/*z* = 356 (M^+).