



A Green Method for the Synthesis of Bis(indolyl)methanes, Tris(indolyl)methanes and 3,3'-Diindolyloxindole Derivatives Using β -Cyclodextrin Sulfuric Acid in Water

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Abstract: β -Cyclodextrin sulfuric acid as a green Lewis acid catalyst has been applied for the preparation of bis(indolyl)methanes, tris(indolyl)methanes and 3,3'-diindolyloxindole derivatives by the condensation of indoles with various carbonyl compounds in aqueous media with high to excellent yields.

Key words: Carbonyl compounds, β -Cyclodextrin sulfuric acid, Bis(indolyl)methanes, Tris(indolyl)methanes, 3,3'-Diindolyloxindoles.

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1. Introduction

Indoles have attracted much interest in diverse areas of chemistry [1 -3]. Bis(indolyl)alkanes are familiar due to their pharmacological and biological importance. Bis(indolyl)alkanes moiety are widely occurs in various natural products obtained from marine sponge alkaloids [4]. These compounds also show antibacterial activity [5]. In particular, bis(indolyl)methanes are the most active substances for promoting beneficial estrogen metabolism and also it could be effective on the proliferation and induction of apoptosis in human cancer cells [6]. Numerous methods have been reported for the synthesis of bis(indolyl)methanes using variety of reagents such as Alum ($KAl(SO_4)_2 \cdot 12H_2O$) [7], I_2 [8],

Ph_3CCl [9], hexamethylenetetramine–bromine [10], molybdato-phosphoric acid [11], $ZrOCl_2 \cdot 8H_2O$ -silica gel [12], $ZrOCl_2$ [13], TPA- ZrO_2 [14], $AlPW_{12}O_{40}$ [15], Sb_2SO_4 [16], $ZrCl_4$ [17], NH_4Cl [18] and TiO_2 nanoparticles [19].

One way for reducing the use of harmful organic solvents is carrying out the reactions in aqueous conditions. In the present article, we report a facile route using β -Cyclodextrin sulfuric acid (β -CDSA) as an efficient catalyst for the synthesis of bis(indolyl)methanes, tris(indolyl)methanes and 3,3'-diindolyloxindole derivatives in aqueous media. β -CDSA is non-explosive, easy handling, eco- friendly, stable and recoverable solid acid catalyst.

2. Experimental

2.1 General

Materials were purchased from Merck. The reactions were monitored by TLC using silica gel plates and the products were purified by column chromatography on silica gel (Merck, 230-400 mesh) and were identified by comparison of their spectra (^1H NMR and FT-IR) and physical data with those of the authentic samples. ^1H NMR spectra were recorded with Bruker DRX-300 AVANCE (300 MHz) spectrometers using CDCl_3 as solvent. FT-IR spectra were recorded on a Pye-unicam SP 1100 spectrophotometer.

2.2 Synthesis of β -cyclodextrin sulfuric acid

To a magnetically stirred mixture of β -cyclodextrin (5 g) in CHCl_3 (20 mL), chlorosulfonic acid (1.00 g, 9 mmol) was added dropwise at 0°C during 2 h. The mixture was stirred for 2 h to remove HCl from reaction vessel. Then, the mixture was filtered, washed with methanol (30 mL) and dried at room temperature to obtain β -cyclodextrin sulfuric acid as white powder (5.28 g). Using acid-base titration, we determined the number of H^+ site of β -cyclodextrin- SO_3H that was 0.52 meq/g.

2.4 General procedure for preparation of bis(indolyl)methanes

To the mixture of indole (2.0 mmol) and an aldehyde or a ketone (1 mmol) in 5 mL water, β -cyclodextrin sulfuric acid (0.05 g) was added and the mixture was stirred at 60°C until the disappearance of the starting materials.

After completion of the reaction, as indicated by

TLC, EtOAc was added to the reaction mixture. Organic phase was separated and dried over Na_2SO_4 . Removing of solvent gives pure products. The products were identified by melting point, IR and ^1H NMR data.

3. Result and discussion

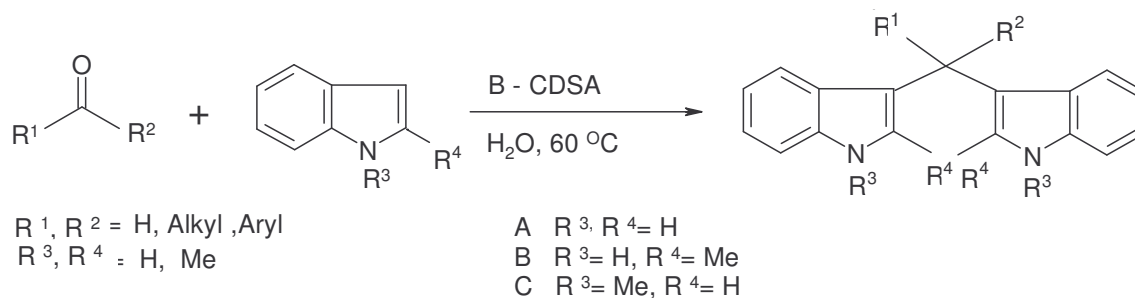
At first in order to get the best experimental reaction condition, we have chosen the reaction of 1H-indole and benzaldehyde (2:1 molar ratio respectively) for the synthesis of 3,3'-bis(indolyl)phenylmethane in the presence of β -cyclodextrin sulfuric acid in aqueous condition as a standard model reaction.

We have investigated the model reaction at different temperatures and different concentrations of catalyst to obtain the best condition. The results indicated that 0.05 g of β -cyclodextrin sulfuric acid (2.5 mol%) was sufficient to obtain the most appropriate result (98 % yield) at 60°C in water (Table 1, Entry 1). Complete conversion was observed within 20 min under this optimized reaction condition monitored by TLC. The reaction was then extended towards a variety of aryl and heteroaryl

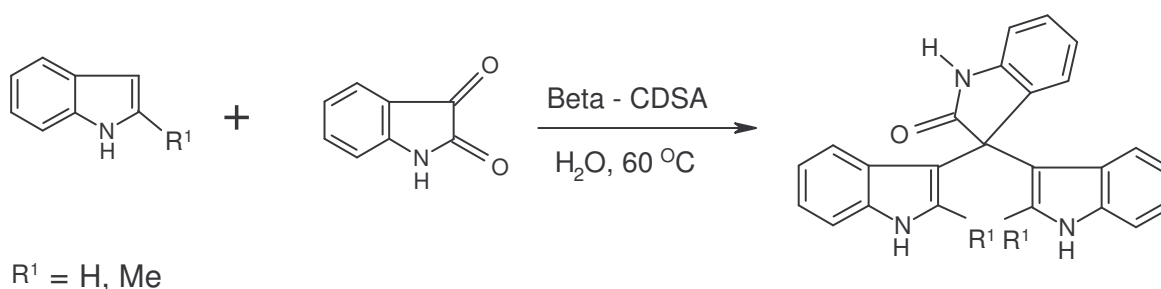
aldehydes/ketones with indoles (indole, 2- methyl indole, 1- methyl indole).

By this method, we compared the reactivity of indole and 2-methylindole in the reaction with various carbonyl compounds.

As shown in Table 1, the required reaction time for the reaction of aldehydes and ketones with 2-methyl indole was shorter in compare with indole in the same reaction condition. As it is expected, due to the steric crowding in corresponding DIMS, aliphatic and aromatic ketones (Table1, entries 28, 29, 35) reacted with longer reaction time and their yields of products was lower.



Scheme 1. Reaction of carbonyl compound with indoles in the presence of β -CDSA.



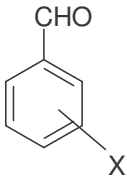
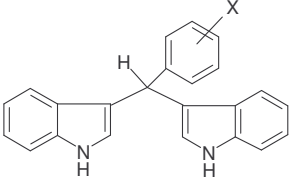
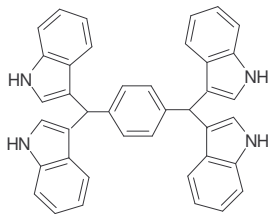
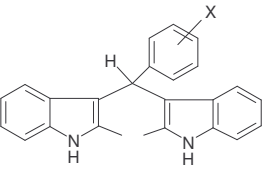
Scheme 2. Reaction of isatin with indoles in the presence of β -CDSA.

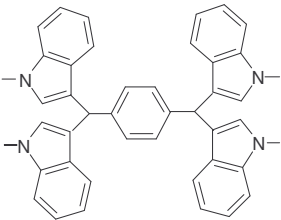
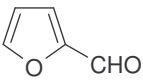
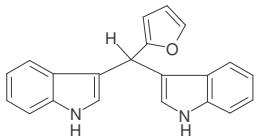
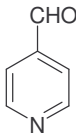
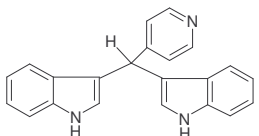
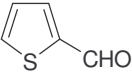
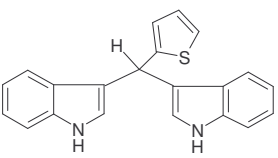
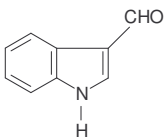
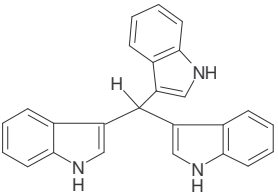
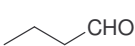
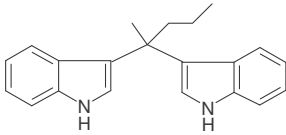
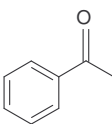
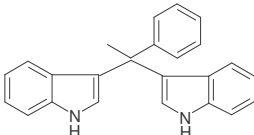
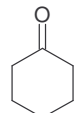
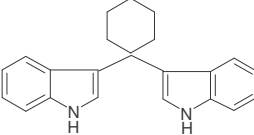
Various substituted aryl aldehydes were used for the synthesis of bis(indolyl)methanes having different substituents. It was found that; electron donating substituent requires shorter time where as electron withdrawing substituent requires longer time for the completion of reaction. Furthermore, the reaction of indole and 2-methylindole with indole-3-carbaldehyde as an aldehyde in the presence of β -CDSA furnished good to excellent yields of the resulting tris(indolyl)methanes (Table 1, entries 26 and 34). Also we here report the synthesis of 3,3'-

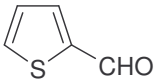
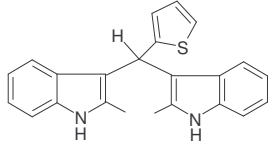
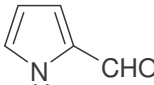
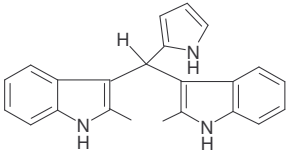
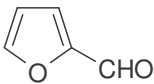
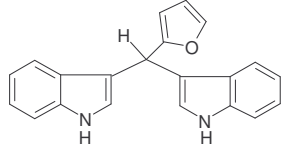
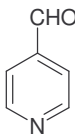
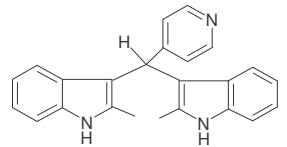
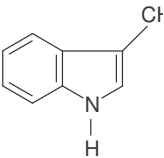
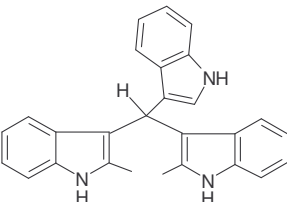
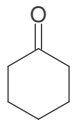
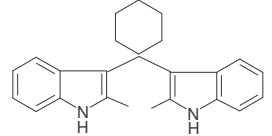
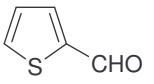
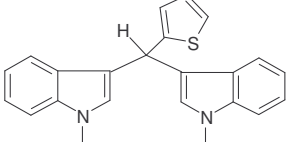
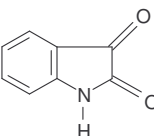
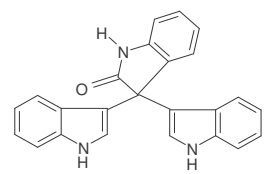
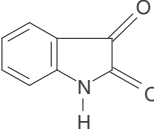
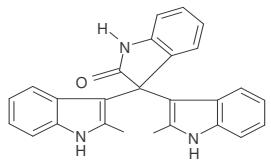
diindolyloxindole derivatives by the reaction between isatin and indoles using this procedure (Scheme 2, Table 1, entries 37, 38).

Scheme 3 shows the catalytic application of β -CDSA throughout the predicted mechanistic pathway for the preparation of DIMs. The reaction proceeds via the formation of azafulvenium salt which further reacts with the second indole to afford bis(indolyl)methanes by losing water and releasing β -CDSA.

Table 1 Synthesis of bis(indolyl)methanes, tris(indolyl)methanes and 3,3'-diindolyloxindole derivatives by the condensation of indoles and carbonyl compounds catalyzed by β -CDSA in water

Entry	Aldehydes/ Ketones	Indoles	Products ^a	Time (min)	Yield (%) ^b	Ref.
	 \underline{X}					
1	H	A	H	20 (23) ^c	98	[14]
2	4-OH	A	4-OH	10	94	[15]
3	4-Cl	A	4-Cl	20	95	[14]
4	2-Cl	A	2-Cl	25	90	[18]
5	3-Cl	A	3-Cl	40	96	[20]
6	4-Me	A	4-Me	20	96	[14]
7	4-OMe	A	4-OMe	45	92	[14]
8	4-Br	A	4-Br	20	96	[21]
9	4-NO ₂	A	4-NO ₂	100	95	[14]
10	4-CN	A	4-CN	80	98	[14]
11 ^d	4-CHO	A		7	85	[22]
						
12	H	B	H	8	98	[14]
13	4-OH	B	4-OH	5	94	[15]
14	4-Cl	B	4-Cl	10	92	[14]
15	4-Me	B	4-Me	7	92	[14]
16	4-OMe	B	4-OMe	10	96	[14]
17	4-Br	B	4-Br	8	96	[23]

18	4-NO ₂	B	4- NO ₂	45	90	[14]
19	4- CN	B	4- CN	20	96	[14]
20 ^d	4- CHO	C		10	87	[22]
21	4-Br	C	4- Br	20	96	[21]
22	4-Cl	C	4-Cl	20	95	[21]
23		A		35	98	[23]
24		A		30	88	[23]
25		A		25	97	[21]
26		A		12	91	[14]
27		A		25	92	[18]
28		A		60	72	[21]
29		A		50	78	[21]

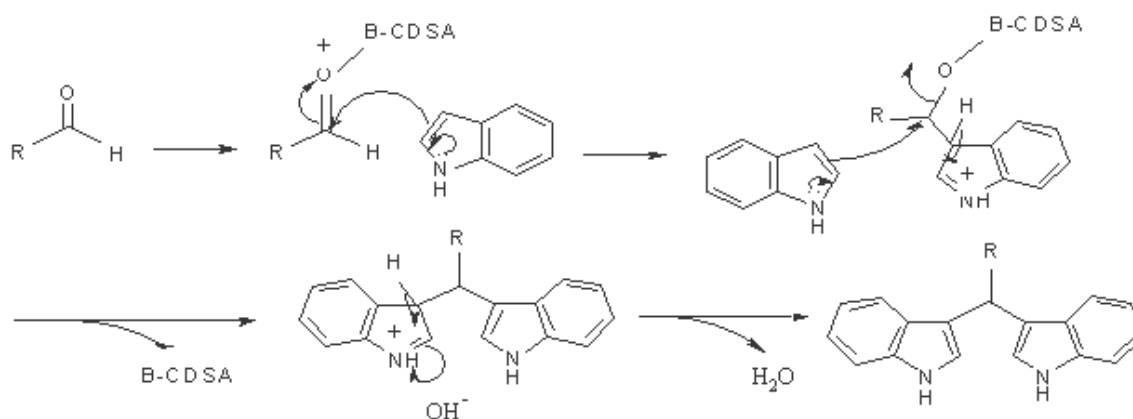
30		B		10	96	[21]
31		B		5	85	[22]
32		B		10	98	[22]
33		B		10	97	[22]
34		B		6	82	[14]
35		B		20	84	[21]
36		C		10	90	[21]
37		A		130	89	[24]
38		B		15	88	[24]

^a All yields refer to isolated products.

^b All products were characterized by IR and ¹H NMR.

^c Recovered catalyst.

^d The molar ratio of aldehyde: indole was 1:4.



Scheme 3. Mechanistic pathway for the preparation of DIMs.

4. Conclusion

In conclusion, we have provided a powerful and convenient procedure for the preparation of bis(indolyl)methanes, tris(indolyl)methanes and 3,3'-diindolyloxindole derivatives. Mild reaction condition, improved yields of the products, using friendly process and easy work up procedure are the merits of this procedure.

Acknowledgements

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