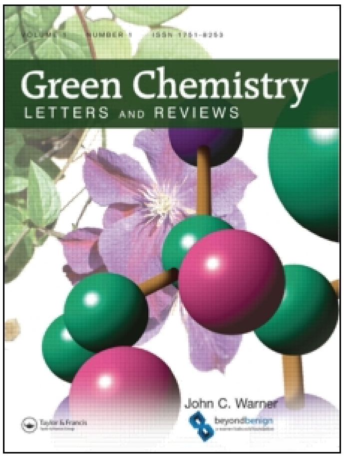

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Cellulose sulfuric acid: reusable catalyst for solvent-free synthesis of bis(indolyl)methanes at room temperature

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RESEARCH ARTICLE

Cellulose sulfuric acid: reusable catalyst for solvent-free synthesis of bis(indolyl)methanes at room temperature

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Bis(indolyl)methanes were synthesized from indole and aldehydes under solvent-free conditions using cellulose sulfuric acid (CSA) as a catalyst at room temperature. CSA is easily prepared and it was also found that this catalyst could be recovered quantitatively and reused without much loss of catalytic activity.

Keywords: cellulose sulfuric acid; bis(indolyl)methanes; solvent-free condition; room temperature synthesis

Introduction

Indole derivatives are well known to possess various biological activities, which are generally used in pharmaceuticals, antioxidatives and so on (*1*). Bis(indolyl)methanes have abundant pharmacological and biological properties (*2*), therefore, there is great interest in the synthesis of these compounds (*3–5*). Synthetically, the reaction of 1*H*-indole with aldehyde or ketones produces azafulvenium salts that react further with a second molecule to form bis(indolyl)methanes (*6*). However, acid-catalyzed condensations of indole with carbonyl compounds have been used for the preparation of bis(indolyl)methanes.

The synthesis of bis(indolyl)methanes require excess protic acids (*7*) and Lewis acids (*7*) and the drastic conditions. To abate the disposal of the excess acids and to improve the condensation reaction of indole and aldehydes, a number of catalytic systems have been tested such as rare earth perfluorooctanoate [RE(PFO)$_3$] (*8*), trichloro-1,3,5-triazine (*9*), hexamethylenetetramine-bromine (*10*), ion-exchange resin (*11*), ionic liquids in conjugation with In(OTf)$_3$ or FeCl$_3$. 6H$_2$O (*12*), ZrOCl$_2$ (*13*), ZrCl$_4$ (*14*), antimony(III) sulfate (*15*), and Ph$_3$CCl (*16*) were also found to promote this reaction. Recently, phosfate zirconia (*17*), heteropoly acids (*18*), fluoroboric acid (*19*), silica sulfuric acid (*20*), ZrOCl$_2$.2H$_2$O/SiO$_2$ (*21*), and protic solvents (*22*) have also been found to promote the synthesis of bis(indolyl)methanes.

These reported methods for the synthesis of bis(indolyl)methanes were suffering with various limitations, such as, usage of expensive reagents (*23–25*), excess of catalyst (*26*), long reaction time (*10,23,26*), and low yield of products (*26*). Today, synthetic chemists are focusing on the eco-friendly methods in the field of catalytic and synthetic chemistry. The application of solvent-free reaction conditions in organic chemistry has been explored extensively within the last decade. It has been demonstrated to be an efficient technique for various organic reactions. Solvent-free conditions often lead to a remarkable decrease in reaction time, increased yields, easier workup, and enhancement of regio and stereo selectivity of reaction which matches with the green chemistry protocol (*27*). A mild and efficient catalyst for the synthesis of bis(indolyl)methanes is highly desirable. In view of current interest in catalytic processes, there is a merit in developing synthesis of bis(indolyl)methanes using inexpensive, mild and non-polluting reagents. The introduction of reusable catalysts and solvent-free reaction paths are preferred, so as to minimize environmental pollution due to the usage of hazardous solvents and their disposal. The limitations of current methods, along with the demand for greener alternatives prompted us to develop a new method for the synthesis of bis(indolyl)methanes. In continuation of our research on the development of green methodologies for the synthesis of heterocyclic compounds (*28*), we report here an efficient and green method for the synthesis of bis(indolyl)methanes at room temperature using cellulose sulfuric acid (CSA) as a catalyst (Scheme 1). This condensation reaction probably proceeds through the activation of a carbonyl group by CSA as well as the indole moiety by H$^+$ at the reaction interface (Scheme 2).

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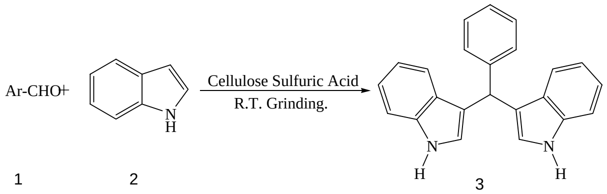


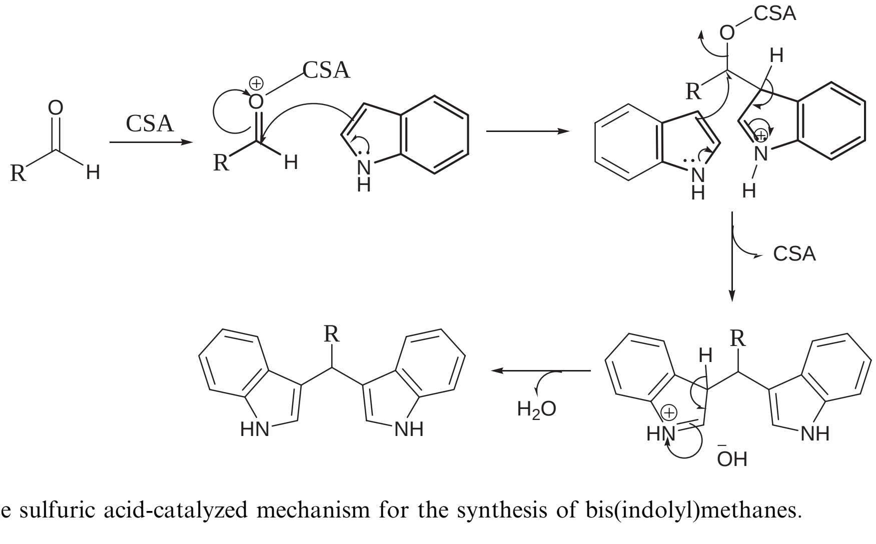
Scheme 1. Condensation reaction of bis(indolyl)methanes at room temperature using cellulose sulfuric acid as a catalyst.

Cellulose is one of the most abundant natural materials in the world and it has been widely studied during the past decades in organic transformations (*29,30*). Cellulose is a biodegradable material, can be obtained from renewable resources and has potential as a catalyst to yield clean, efficient and fast reactions. CSA, a non-hygroscopic solid acid catalyst, is an efficient and environmentally benign catalyst for the synthesis of bis(indolyl)methanes.

Result and discussion

In this report (Scheme 1), we describe an efficient method for the synthesis of bis(indolyl)methanes using CSA. This method does not need expensive reagents or special care to exclude moisture from the reaction medium. The reaction proceeded efficiently and smoothly at room temperature, and the products were obtained in excellent yields. Furthermore, the reaction conditions are very mild and no by-products were observed. In order to synthesis bis(indolyl)methanes under solvent-free conditions, we have chosen the condensation reaction of benzaldehyde and indole using CSA as a catalyst as a model reaction. A mixture of (2.0 mmol) indole, (1.0 mmol) benzaldehyde and (0.1g) CSA was ground using a mortar and pestle. The reaction mixture was ground at room temperature until the reaction was complete (monitored by thin layer chromatography TLC). Surprisingly, complete conversion was observed within 8 min. When compared with various reported catalyst and reaction paths, it was observed that the solid state solvent-free process with the CSA catalyst resulted in better yield and with a shorter reaction time at room temperature (Table 1). This clearly indicates the beneficial effect of mechanochemical grinding in the presence of CSA. The scope of the reaction was monitored with respect to various substituted aldehydes and indoles under these reaction conditions. The nature of the substituents on the aromatic ring showed some effect on this conversion. The nitro substituted aryl aldehydes required longer reaction times to produce comparable yields than those of their simple and electron-rich counterparts.

The CSA catalyst was able to be recycled and reused efficiently. To check the reusability of the catalyst, the product obtained by the reaction of indole with benzaldehyde was dissolved in ethanol. The catalyst was filtered and washed with ethanol repeatedly, dried and reused for the reaction of indole with the same aldehydes (Table 2, entry 1). It was found that the catalyst could be recycled at least twice without loss of much activity. The versatility of this method was confirmed by the synthesis of bis(indolyl)methanes from various aromatic aldehydes (Table 2). In summary, the electrophilic addition reaction of indole with aldehydes was successfully carried out in the presence of a catalytic amount of CSA at room temperature. The salient features of this procedure are easy handling, cleaner reaction profile, short reaction time, improved yields, and an economic and environmentally friendly process, which makes it a useful and attractive process for the rapid synthesis of substituted bis(indolyl)methanes.



Scheme 2. Cellulose sulfuric acid-catalyzed mechanism for the synthesis of bis(indolyl)methanes.

Table 1. Comparison data of benzaldehyde derivative (Table 2, entry 1) with different catalysts at room temperature.

Entry	Catalysts	Solvents	Time (min.)	Yield (%)
1	$ZrCl_4$	CH_3CN	35	91
2	$ZrOCl_2$	CH_3CN	35	89
3	$Sb_2(SO_4)_3$	MeOH	90	96
4	Ph_3CCl	Grinding	20	90
5	$La(PFO)_3$	EtOH	30	90
6	[Hmim] HSO_4	neat	15	90
7	[Hmim] TF_4	neat	10	90
8	Cellulose Sulfuric Acid	neat	8	93

Entry 1–7 – as reported in literature.

Experimental section

Melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded on FT/IR-410 type (A) spectrophotometer in KBr. ^{1}HNMR spectra were measured in DMSO-d6 solution on a Bruker spectrophotometer at 400 MHz. Electron-spray ionization mass spectra (ES-MS) were recorded on a Water-Micro mass Quattro-II spectrometer.

Preparation of cellulose sulfuric acid (CSA)

To a magnetically stirred mixture of 5 g of cellulose (DEAE for column chromatography, Merck) in 20 ml of *n*-hexane, 1.00 g of chlorosulfonic acid (9 mmol) was added dropwise at 0°C over two hours. HCl gas was removed from the reaction vessel immediately. After the addition was complete, the mixture was stirred for two hours at room temperature. The mixture was then filtered and washed with 30 ml of acetonitrile and dried at room temperature to obtain 5.47 g CSA as a white powder. This white homogeneous solid acid is very stable and is not affected by air, water and light. The sulfur content of the sample obtained by conventional elemental analysis, was 0.68 mmol/g. The number of H^+ sites on the CSA catalyst was determined by acid-base titration and found to be 0.65 meq/g. This value corresponds to about 0.96% of the sulfur content, indicating that most of the sulfur species on the sample are in the form sulfonic acid groups (*29,30*).

General procedure for the synthesis of bis(indolyl)methanes

CSA (0.1 g) was added to a mixture of (2.0 mmol) indole and (1.0 mmol) aldehyde in a mortar. The reaction mixture was ground at room temperature using a pestle for appropriate time. Upon completion of the reaction (TLC) ethanol (20 mL) was added and the reaction mixture and the mixture was filtered. The catalyst was washed with ethanol (2 × 10 mL). The obtained filtrate was evaporated using a rotary evaporator. The removal of solvent from the combined filtrate gave the product in almost pure form. The obtained compounds were analyzed and the results were compared with literature values.

Spectroscopic data

3,3'-Bis(indolyl) phenylmethane (1). IR (KBr): 3478, 3019, 1601, 1522, 1456, 1419, 1215, 1093, 1017, 757, 669 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ ppm): 5.89 (1H, s), 6.67 (2H, s), 7.09–7.58 (13H, m), 7.94 (2H, bs, NH); ES-MS E/Z 322(M^+).

3,3'-Bis(indolyl)-4-methylphenylmethane (2). IR (KBr): 3480, 3020, 1602, 1512, 1456, 1417, 1215, 1091, 1021,759, 669 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ ppm): 2.31 (3H, s), 5.84 (1H, s), 6.64 (2H, s), 6.85–7.40 (12H, m), 7.94 (2H, bs, NH); ES-MS E/Z 336(M^+).

3,3'-Bis(indolyl)-4-methoxyphenylmethane (3). IR (KBr): 3480, 3019, 2838, 1610, 1509, 1455, 1456, 1417, 1336, 1216, 1091, 1033, 759 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ ppm): 3.77 (3H, s), 5.84 (1H, s), 6.64 (2H, d), 6.83 (2H, d), 7.03 (2H, t),7.2 (2H, t); 7.26–7.40 (6H, m), 7.89 (2H, bs, NH); ES-MS E/Z 352(M^+).

3,3'-Bis(indolyl)-3,4-dimethoxyphenylmethane (4). IR (KBr): 3480, 3020, 1604, 1512, 1456, 1418, 1336, 1216, 1091, 1033, 759 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ ppm): 3.76 (3H, s), 3.85 (3H, s), 5.83 (1H, s), 6.65 (2H, d), 6.78 (2H, d), 7.0 (3H, t), 7.17 (2H, t), 7.29–7.43 (4H, m), 7.91 (2H, bs, NH); ES-MS E/Z 382(M^+).

3,3'-Bis(indolyl)-4-chlorophenylmethane (5). IR (KBr): 3478, 3020, 2927, 1600, 1523, 1456, 1417, 1216, 1091, 1015, 759, 670 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ ppm): 5.88 (1H, s), 6.63 (2H, brs), 7.00–7.70 (12H, m), 7.92 (2H, bs, NH); ES-MS E/Z 322(M^+).

3,3'-Bisindolyl(2-furfuryl)methane (10). IR (KBr): 3477, 3019, 2399, 1600, 1456, 1419, 1216, 1093, 1021, 757, 670 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ ppm): 5.94 (1H, s), 6.06 (1H, d), 6.30 (1H, d), 6.87 (1H, d), 7.08 (2H, t), 7.17(2H, t), 7.29–7.48 (5H, m),7.95 (2H, bs, NH); ES-MS E/Z 312(M^+).

Table 2. Cellulose sulfuric acid: reusable catalyst for solvent-free synthesis of bis(indolyl)methanes at room temperature.

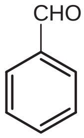
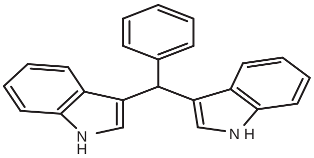
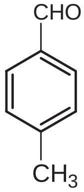
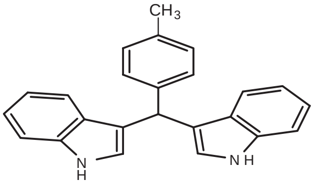
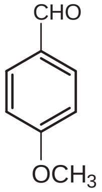
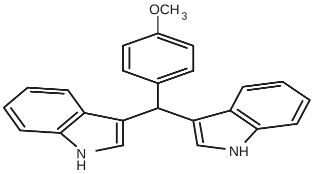
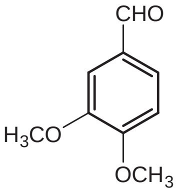
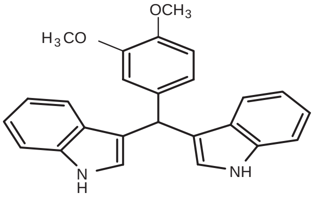
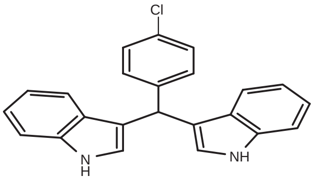
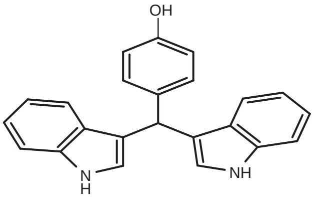
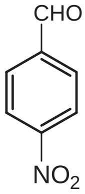
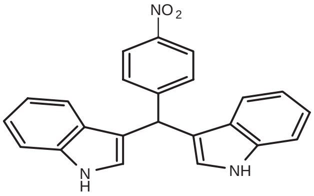
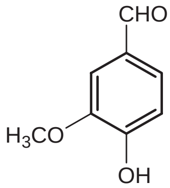
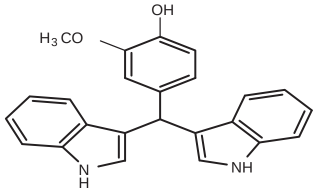
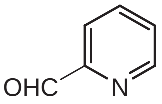
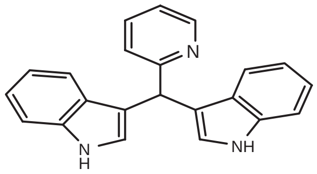
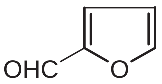
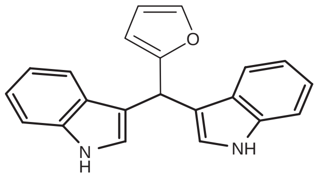
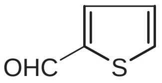
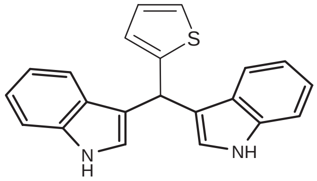
Entry	Ar	Product	Time (min)	Yield (%)	M.P. (°C)[a]
1			(8,10,13)[b]	(93,92,90)[b]	123–125 (lit.123–125) (*13*)
2			16	91	98–100 (lit. 96–98) (*13*)
3			20	90	190–192 (lit. 190–192) (*13*)
4			22	91	196–198 (lit. 196–197) (*20*)
5			10	95	120–122 (lit. 120–122) (*20*)
6			20	87	124–126 (lit. 124–125) (*13*)
7			08	95	222–224 (lit. 221–223) (*13*)

Table 2. (*Continued*)

Entry	Ar	Product	Time (min)	Yield (%)	M.P. (°C)[a]
8			26	91	112–114 (lit. 111–112) (*13*)
9			18	85	137–139 (lit. 96–98) (*13*)
10			22	88	320–322 (lit. 320–323) (*13*)
11			28	86	150–152 (lit. 150–153) (*22*)

[a]Melting points compared with physical data in lit.

[b]The same catalyst used for each of the three runs.

Conclusion

In conclusion, this synthetic method describes a simple and highly efficient dehydration process for the synthesis of indole derivatives at room temperature. Synthesis of bis(indolyl)methanes through the electrophilic substitution of indoles with aldehydes using CSA as an environmentally benign catalyst at room temperature has been successfully performed.

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