

## Synthesis of *bis*-indolymethanes, *tris*-indolymethanes and 3, 3'-diindolyloxindole derivatives using cellulose sulfuric acid as the biodegradable solid acid catalyst under heterogeneous condition

Heshmatollah Alinezhad,\* Asefeh Hagh Haghighi  
Faculty of Chemistry, Mazandaran University, Babolsar, Iran.

**Abstract:** Reaction of indoles with structurally diverse aldehydes and ketones in the presence of catalytic amount of cellulose sulfuric acid as the heterogeneous, reusable and efficient catalyst gave the corresponding *bis*-indolyl methanes, *tris*-indolyl methanes and 3, 3'-diindolyloxindole derivatives in good to excellent yields at room temperature.

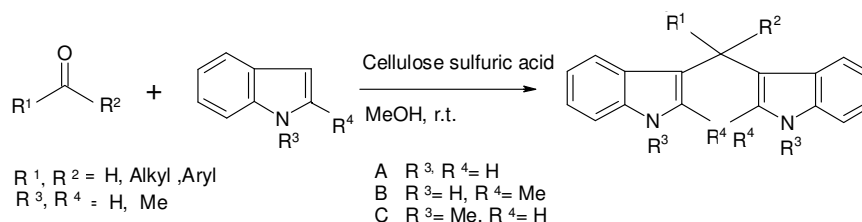
**Keywords:** Aldehydes; Ketones; Cellulose sulfuric acid; *Bis*-indolymethanes; *Tris*-indolyl methanes; 3, 3'-Diindolyloxindole derivatives.

### Introduction

Indoles and its derivatives are well known as biologically active substances. Among various indole derivatives, diindolylmethane (DIMS) and related compounds exhibit a wide range of biological activities such as antibacterial and antitumor properties [1]. One of the simple and direct methods for the synthesis of these compounds is the reaction of 2 equiv. of indoles with carbonyl group in the presence of either protic or Lewis acids. Several methods for this purpose have been reported using catalysts such as: Zeolites [2], CuBr<sub>2</sub> [3], Lanthanid triflates [4,5], ion exchange resin [6], aminosulfonic acid [7], NaHSO<sub>4</sub>/LiClO<sub>4</sub> [8], molibdatophosphoric acid [9], AlPW<sub>12</sub>O<sub>40</sub> [10], 12-tungstophosphoric acid supported on zirconia [11], ZrOCl<sub>2</sub>·8H<sub>2</sub>O [12].

However, there are some drawbacks in these catalytic systems including the long reaction times [13], low

yield of products [14], use of expensive Lewis acids [15], using toxic catalyst [16], tedious conditions for catalyst preparation [17], and use of expensive organic polymer chains as support in catalysts. Due to the applications of indole derivatives in pharmacology, medicinal and biochemistry, it is necessary to find an efficient catalyst for the synthesis of these compounds. Cellulose sulfuric acid [18], is an efficient, nonvolatility, recyclable, non explosive, easy to handle thermally robust and superior proton source for organic reactions. Here in, we report the use of cellulose sulfuric acid as a catalyst in the electrophilic substitutions of indole and substituted indoles with a variety of aldehydes and ketones to afford bis(indolyl)methanes, tris(indolyl) methanes and 3,3'-diindolyloxindole derivatives at room temperature with high to excellent yields (Scheme1).



**Scheme 1**

\*Corresponding author. Fax: +98(112)5342302;  
E-Mail: heshmat@umz.ac.ir

## Results and Discussion

At first, we studied the reaction of benzaldehyde with indole (1:2 molar ratio) in order to optimize the reaction conditions with respect to solvent, time, temperature and catalyst (Table 1,2). Initial screening studies identified methanol as the optimal solvent for this reaction.

Organic solvents such as CH<sub>3</sub>CN, THF and EtOH were also proved effective with longer reaction time (Table 1). We found that 2.5 mol% of cellulose sulfuric acid was sufficient to give the most satisfactory result (92% yield) within 15 min at room temperature in MeOH.

**Table 1.** Optimization of Solvent and Reaction Time in the Reaction of Benzaldehyde with Indole in the Presence of Cellulose Sulfuric Acid<sup>a</sup>

Entry	Solvent	Time (h)	Yield (%)
1	THF	3	90
2	CH <sub>3</sub> CN	2	92
3	EtOH	1.5	90
4	MeOH	0.25	92

<sup>a</sup> All reactions were carried out at room temperature and molar ratio of indole:carbonyl compound was 2:1 and 0.05 g cellulose sulfuric acid was used.

By comparing the effect of catalyst in this category of reactions, we found that cellulose sulfuric acid is an efficient catalyst compare to recently reported solid acid catalysts from the view point of easy preparation

from available and nontoxic starting materials, application of catalytic amount of this catalyst (2.5 mol%) and shorter required reaction time (Table 2).

**Table 2:** Reaction of Indole and Benzaldehyde in the Presence of Different Catalysts

Entry	Catalyst	Condition	Time (h)	Catalyst content	Ref
1	InCl <sub>3</sub>	CH <sub>3</sub> CN	4	0.2 mol	[13]
2	TPA-ZrO <sub>2</sub>	Solvent- free	0.5	0.25 mol%	[11]
3	La(OTf) <sub>3</sub>	EtOH/H <sub>2</sub> O	12	0.1M solution	[4]
4	ZrOCl <sub>2</sub> .8H <sub>2</sub> O	Solvent- free	40min	5 mol%	[12]
5	AlPW <sub>12</sub> O <sub>40</sub>	CH <sub>3</sub> CN	0.25	2 mol%	[10]
6	NH <sub>4</sub> Cl	Solvent- free	0.5	0.5 mmol	[19]
7 <sup>a</sup>	Cellulose sulfuric acid	MeOH	0.25	2.5 mol%	----

<sup>a</sup>The reaction was carried out at r.t. and molar ratio of indole: benzaldehyde was 2:1 and 0.05 g (2.5 mol %) cellulose sulfuric acid was used.

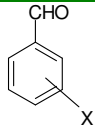
Reactions were carried out in the simplest manner, only by stirring the mixture of indole, an aldehyde or ketone and cellulose sulfuric acid as catalyst at room

temperature. A series of aliphatic, aromatic and heteroaromatic aldehydes and ketones underwent electrophilic substitution reaction with indole, 1-methyl

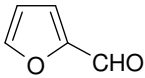
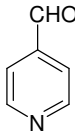
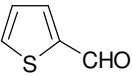
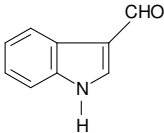
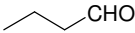
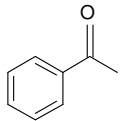
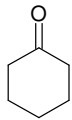
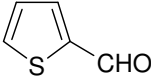
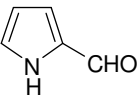
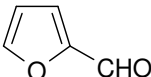
indole and 2-methyl indole smoothly to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields. The results are summarized in (Table 3). By controlling the molar ratio of indole, condensation of a dialdehyde i.e terephthalaldehyde to the corresponding DIMS (Table 3, entries 11, 20)

was successfully achieved. In this method, tris-indolylmethanes was produced using indole-3-carbaldehyde as an aldehyde (Table 3, entries 26, 34). Also we have reported 3,3'-diindolyloxindole derivatives by the reaction between isatin and indoles using this procedure (Table 3, entries 3, 38).

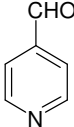
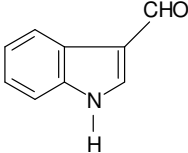
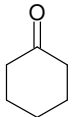
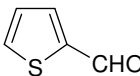
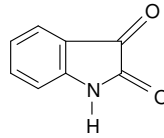
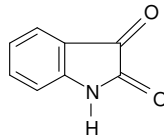
**Table 3.** Synthesis of Bis and Tris-indolylmethanes and 3,3'-Diaryloxindole Derivatives by Condensation of Indoles and Carbonyl Compounds Catalyzed by Cellulose Sulfuric Acid<sup>a</sup>

Entry	Aldehydes/Ketones	Indoles	Time(min)	Yield (%) <sup>b</sup>	Ref.
	 $\text{X}$				
1	H	A	15	92	[11]
2	4-OH	A	5	92	[10]
3	4-Cl	A	20	88	[11]
4	2-Cl	A	25	87	[18]
5	3-Cl	A	30	93	[20]
6	4-Me	A	20	93	[11]
7	4-OMe	A	30	95	[11]
8	4-Br	A	15	96	[21]
9	4-NO <sub>2</sub>	A	90	98	[11]
10	4-CN	A	70	98	[11]
11 <sup>c</sup>	4-CHO	A	5	82	[21]
12	H	B	5	97	[11]
13	4-OH	B	Im. <sup>d</sup>	94	[10]
14	4-Cl	B	10	89	[11]
15	4-Me	B	5	93	[11]
16	4-OMe	B	5	95	[11]
17	4-Br	B	5	96	[22]

**Table 3** continued.

18	4-NO <sub>2</sub>	B	30	93	[11]
19	4- CN	B	10	95	[11]
20 <sup>c</sup>	4- CHO	C	5	87	[21]
21 <sup>e</sup>	4-Br	C	20	96	[22]
22 <sup>e</sup>	4-Cl	C	20	93	[22]
23		A	30	98	[18]
24		A	20	88	[23]
25		A	20	97	[22]
26		A	10	93	[11]
27		A	20	94	[18]
28		A	50	70	[21]
29		A	40	78	[22]
30		B	10	98	[22]
31		B	5	83	[21]
32		B	10	96	[21]

**Table 3** continued.

33		B	7	91	[21]
34		B	5	82	[11]
35		B	15	82	[22]
36		C	10	90	[22]
37		A	120	88	[24]
38		B	10	85	[24]

<sup>a</sup>All reactions were carried out at room temperature and molar ratio of indole:carbonyl compound was 2:1 and 0.05 g cellulose sulfuric acid was used.

<sup>b</sup>Yields refer to isolated yield and all products were characterized by IR and <sup>1</sup>H NMR.

<sup>c</sup>The molar ratio of aldehyde: indole was 1:4.

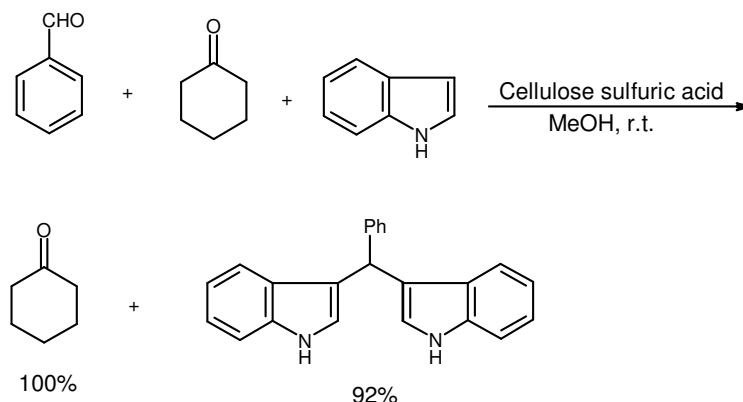
<sup>d</sup>Immediately.

<sup>e</sup>Reactions were carried out at 50<sup>o</sup>C.

By comparing of the results obtained from different indoles, the required reaction times of different aldehydes with 2-methyl indole are shorter than indole under the same reaction conditions. In addition, we found that some aldehydes and ketones react with 1-methyl indole hardly under the present methodology and after a prolonged reaction time most of the starting materials were remained.

However, this method is more effective for aldehydes with electron donating substituents compare to the electron withdrawing groups in the aromatic rings.

This procedure is also highly chemoselective for aldehydes. For example, when a 1:1 mixture of benzaldehyde and cyclohexanone was allowed to react with indole in the presence of cellulose sulfuric acid in MeOH, it found that only phenyl-3, 3'-bis-(indolyl) methane was obtained, while cyclohexanone did not give the corresponding product under this reaction conditions (Scheme 2).



Scheme 2.

## Conclusions

The present procedure provides a simple, convenient and efficient method for the preparation of bis-indolyl methanes from a variety of carbonyl compounds.

The simplicity, mild reaction condition, high yields of products, easy work up procedure make it the preferred method for the preparation of different kind of bis(1H-indole-3-yl) alkanes. The important feature of this methodology is the use of cellulose sulfonic acid as a biodegradable catalyst. All these, make this procedure a useful and an attractive method for the synthesis of indole derivatives.

## Experimental

### General

Materials were purchased from Merck. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck, 230-400 mesh) and were identified by comparison of their spectra ( $^1\text{H}$  NMR and FTIR) and physical data with those of the authentic samples.  $^1\text{H}$  NMR spectra were recorded with Bruker DRX-500 AVANCE (500 MHz) and Bruker DRX-300 AVANCE (300 MHz) spectrometers, using  $\text{CDCl}_3$  as solvent. IR spectra were recorded on a Pye-unicam SP 1100 spectrophotometer. The catalyst cellulose sulfonic acid was prepared by an established procedure [18].

### General procedure for preparation of bis(indolyl)methanes:

To the mixture of indole (2 mmol), aldehyde or ketone (1 mmol) in MeOH, cellulose sulfonic acid (0.05 g, 0.025 mmol) was added and the mixture stirred at room

temperature for an appropriate time (Table 3). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with MeOH and filtered. The filtrate was evaporated under reduced pressure to afford crude product which was then purified by column chromatography and eluted with ethyl acetate and petroleum ether mixture (1:9) to afford the pure product (70-98%, Table 3). The products were identified by melting point, IR and  $^1\text{H}$  NMR data.

## Acknowledgments

Financial support of this work from the Research Council of Mazandaran University is gratefully acknowledged.

## References

- [1] Drasar, B. S.; Hill, M. J. *Human Intestinal Flora*. Academic press. New York, 1974.
- [2] Li, J.; Zhou, M.; Li, B.; Zhang, G. *Synth. Commun.* **2004**, *34*, 275.
- [3] Mo, L. P.; Ma, Z. C.; Zhang, Z. H. *Synth. Commun.* **2005**, *35*, 1997.
- [4] Xia, M.; Wang, S.; Yuan, W. *Synth. Commun.* **2004**, *34*, 3175.
- [5] Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467.
- [6] Feng, X.; Guan, C.; Zhao, C. *Synth. Commun.* **2004**, *34*, 487.
- [7] Li, J. T.; Dai, H. G.; Xu, W. Z.; Li, T. S. *Ultrason. Sonochem.* **2006**, *13*, 24.
- [8] Yadav, J. S.; Reddy, B. V. S.; Mueth, C. V. S R.; Kumar, G. M.; Madan, C. *Synthesis* **2001**, 783.

- [9] Zolfigol, M. A.; Salehi, P.; Shiri, M. *Phosphorus Sulfur Silicon Rel. Elements* **2004**, 178,149.
- [10] Firouzabadi, H.; Iranpoor, N.; Jafari, A. A. *J. Mol. Catal. A* **2006**, 244, 168.
- [11] Satam, J. R.; Parghi, K. D.; Jayaram, R. V. *Catal. Commun.* **2008**, 9, 1071.
- [12] Firouzabadi, H.; Iranpoor, N.; Jafarpour, M.; Jafari, A. A. *J. Mol. Catal. A* **2006**, 253, 249.
- [13] Babu, G.; Sridhar, N.; Perumal, P. T. *Synth. Commun.* **2000**, 30, 1609.
- [14] Reddy, A. V.; Ravinder, K.; Reddy, V. L. N.; Goud, T. V.; Ravikant, V.; Venkateswarlu, Y. *Synth. Commun.* **2003**, 33, 3687.
- [15] Mi, X.; Luo, S.; Hea, J.; Chenga, J. P. *Tetrahedron Lett.* **2004**, 45, 4567.
- [16] Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett.* **2003**, 44, 1959.
- [17] Wang, L.; Han, J.; Tian, H.; Sheng, J.; Fan, Z.; Tang, X. *Synlett* **2005**, 337.
- [18] Shaabani, A.; Rahmati, A.; Badri, Z. *Catal. Commun.* **2008**, 9, 13.
- [19] Azizian, J.; Teimouri, F.; Mohammadzadeh, M. R. *Catal. Commun.* **2007**, 8, 1117.
- [20] Pasha, M. A.; Jayashankara, V. P. *J. Pharmacol. Toxicol.* **2006**, 1(6), 585.
- [21] Zolfigol, M. A.; Salehi, P.; Shiri, M.; Tanbakouchian, Z. *Catal. Commun.* **2007**, 8, 173.
- [22] Azizi, N.; Torkian, L.; Saidi, M. R. *J. Mol. Catal. A: Chem.* **2007**, 275, 109.
- [23] Kamble, V. T.; Kadam, K. R.; Joshi, N. S.; Muley, D. B. *Catal. Commun.* **2007**, 8, 498.
- [24] Azizian, J.; Mohammadi, A. A.; Karimi, N.; Mohammadzadeh, M. R.; Karimi, A. R. *Catal. Commun.* **2006**, 7, 752.