

Green synthesis of bis(indolyl)methanes in water using sulfonic acid functionalized silica (SiO₂-Pr-SO₃H)

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ABSTRACT

Bis(indolyl)methanes are important group of bioactive metabolites of terrestrial and marine regions. They were synthesized by different methods. Herein, a clean, one-pot synthesis of bis(indolyl)methane derivatives by cyclo-condensation reaction of indole and various aldehydes using Sulfonic acid functionalized silica (SiO₂-Pr-SO₃H) in aqueous media is reported. The advantages of this new method were simple operation, good yields, short reaction times and easy work-up. Sulfonic acid functionalized silica as an efficient heterogeneous solid acid catalyst could be prepared by simple operation from commercially available cheap starting materials such as silica. It catalyzes various organic reactions and could be easily removed, recovered and reused without significant loss of activity.

Keywords: Bis(indolyl)methane, SiO₂-Pr-SO₃H, Green synthesis, Multicomponent reaction (MCRs).

1. Introduction

Heterocyclic compounds containing indole moiety are one of the most fruitful and extensively developing materials of heterocyclic chemistry. These compounds exhibit various kinds of biological activities [1, 2].

Among them, bis(indolyl)methanes are important group of bioactive metabolites of terrestrial and marine regions. Bis- and trisindolylmethanes are synthesized by different methods [3]. These materials inhibit the growing of bladder [4], renal [5], lung [6], colon [7, 8], mammary tumor [9], prostate [10], breast tumor cells [11] and also have antitumorigenic activity [12], serve as topoisomerase II_α catalytic inhibitors [13], serve as inhibitors of the platelet-derived growth factor receptor kinase [14], exhibit antimicrobial and antifungal activities [15], exhibit antibiotic activity [16] and antibacterial activity [17].

A variety of synthetic methods for the preparation of the bis-indolylmethanes, using protic or Lewis acids, have been reported in the literature, employing protic acids and Lewis acids such as LiClO₄ [18], InCl₃ [19], lanthanide triflates [20], *N*-bromosuccinimide, NBS [21], I₂ [11], KHSO₄ [22], montmorillonite K-10 [23], HY-zeolite [24], rare-earth perfluorooxanoates,

[RE(PFO)₃] [25], NaHSO₄/amberlyst-15 [26], [bnmim][HSO₄] [27], ZrOCl₄ [28], Ph₃CCl [29], [hmim][HSO₄] [30], and ZrCl₄ [31]. However, some of the reported methods have the drawbacks such as using the expensive and not environmentally friendly reagents, longer reaction time and low yields of products.

However, with a view to circumvent the harmful effects associated with conventional organic solvents and hazardous catalysts, we thought it would be profitable to replace them with a green aqueous solution.

Designing of MCRs in water is another attractive area in green chemistry [32], because water is a cheap, safe, and environmentally benign solvent. There is need for developing MCRs in water with a suitable catalyst and without the use of any harmful organic solvents.

The application of heterogeneous catalysts to carry out various organic transformations has great importance in organic synthesis. These catalysts can conveniently be handled and removed from the reaction mixture, making the experimental procedure simple and ecofriendly.

To expand our effort toward environmentally benign synthesis and on the application of heterogeneous solid catalyst in organic synthesis [33-37], we have decided to investigate the catalytic activity of sulfonic acid

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functionalized silica ($\text{SiO}_2\text{-Pr-SO}_3\text{H}$) as a highly efficient heterogeneous acid catalyst toward the synthesis of bis(indolyl)methanes in water media.

2. Experimental

2.1. Materials

GC-Mass analysis was performed on a GC-Mass model: 5973 network mass selective detector, GC 6890 Agilent. IR spectra were recorded from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The ^1H NMR (250 MHz) was run on a Bruker DPX.

2.2. Preparation of catalyst

To SiO_2 (20 g) in dry toluene (50 mL), (3-mercaptopropyl)trimethoxysilane (25 mL) was added and the reaction mixture was refluxed for 24 h. After this period, the mixture was filtered to obtain 3-mercaptopropylsilica which was washed with acetone and dried. The 3-mercaptopropylsilica (20 g) was oxidized with H_2O_2 (50 ml) and one drop of H_2SO_4 in methanol (20 mL) for 24 h at room temperature and then the mixture was filtered and washed with H_2O and acetone to obtain $\text{SiO}_2\text{-Pr-SO}_3\text{H}$ catalyst.

2.3. General procedure for the synthesis of bis(indolyl)methanes 3a-j

A mixture of indole **1** (2 mmol, 0.35 g), appropriated aromatic aldehydes **2a-j** (1 mmol) and catalyst ($\text{SiO}_2\text{-Pr-SO}_3\text{H}$) (0.1 g) was stirred in refluxing water (5 ml) for appropriated time as mentioned in Table 1. The progress of reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature; the crude product was dissolved in hot ethanol and after filtration of catalyst and cooling of the filtrate, the pure crystals of bis(indolyl)methanes were obtained. The recovered catalyst could be washed with diluted acid solution, water and acetone. After drying, it could be reused without noticeable loss of reactivity.

Selected spectral data

3,3'-Bisindolyl(phenyl)methane (3a):

m.p= 123-124°C. IR (KBr): $\bar{\nu}$ = 3395, 3052, 1615, 1489, 1452, 1417, 1335, 1217, 1090, 1006, 745, 698 cm^{-1} . ^1H NMR (250 MHz, DMSO-d_6): δ = 5.87 (s, 1H, Ar-CH), 6.61-6.20 (s, 2H), 6.96-7.02 (m, 2H), 7.12-

7.19 (m, 2H), 7.22-7.39 (m, 6H), 7/83 (s, 2H, 2NH) ppm. GC-Mass: m/z(%)= 322 [M^{+}], 245, 205, 122, 105, 77.

3,3'-Bisindolyl-4-fluorophenylmethane (3g):

m.p= 79-81°C, IR (KBr): $\bar{\nu}$ = 3408, 3053, 1601, 1547, 1054, 1454, 1416, 1337, 1216, 1154, 1124, 1092, 788, 743 cm^{-1} . ^1H NMR (250 MHz, CDCl_3): δ = 5.84 (s, 1H, H-8), 6.57 (s, 2H, H-2 and H-2'), 7.13-7.19 (m, 4H, Ar-CH), 7.23-7.36 (m, 8H, Ar-CH), 7.84 (brs, 2H, 2NH) ppm. GC-Mass: m/z (%)= 340 [M^{+}], 245, 222, 170, 122.

3,3'-bisindolyl-4-methylphenylmethane (3i):

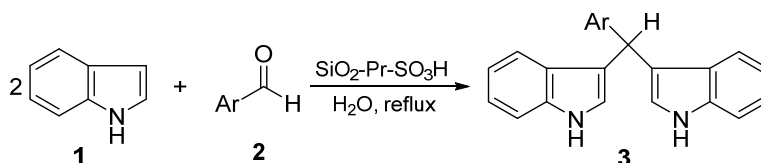
m.p= 94-96°C, IR (KBr): $\bar{\nu}$ = 3408, 3048, 1615, 1547, 1508, 1485, 1453, 1336, 1182, 1039, 1008, 779, 742 cm^{-1} . ^1H NMR (250 MHz, CDCl_3): δ = 2.35 (s, 3H, CH_3), 5.81 (s, 1H, H-8), 6.53 (s, 2H, H-2 and H-2'), 6.97-7.28 (m, 11H), 7.36 (d, 2H, Ar-CH), 7.67 (brs, 2H, 2NH) ppm. GC-Mass: m/z(%)= 336 [M^{+}], 245, 218, 168, 122.

3. Results and discussion

In the present work, we evaluated the reaction of indole with various aldehydes using $\text{SiO}_2\text{-Pr-SO}_3\text{H}$ as a catalyst. In the first step we screened the optimized conditions by using water as solvent and solvent-free condition. The reaction was attempted by coupling of indole **1** with benzaldehyde **2a** in the presence of $\text{SiO}_2\text{-Pr-SO}_3\text{H}$ under solvent-free conditions at room temperature. The results revealed the product **3a** was obtained in 87% yield at 8 minutes. We investigated water media to achieve complete conversion. Therefore, indole **1** was treated with benzaldehyde **2a** in the presence of $\text{SiO}_2\text{-Pr-SO}_3\text{H}$ using water as solvent at 100°C. The desired product **3a** was obtained in 15 minutes and 96% yield (Scheme 1).

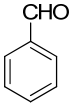
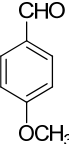
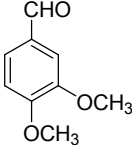
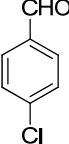
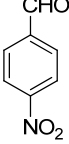
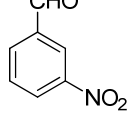
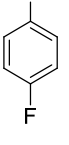
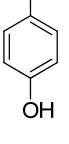
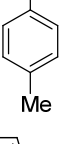
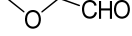
Consequently refluxing in water was the optimized reaction condition and our further experiments were performed under this condition. In the second step, we turned our attention toward various aromatic aldehydes **2a-j** (Table 1). As can be seen in Table 1, the results revealed that the reaction of different aldehydes **2a-j** with indole **1** was performed in very short reaction times (5-20 minutes) and in high yields (87-96%).

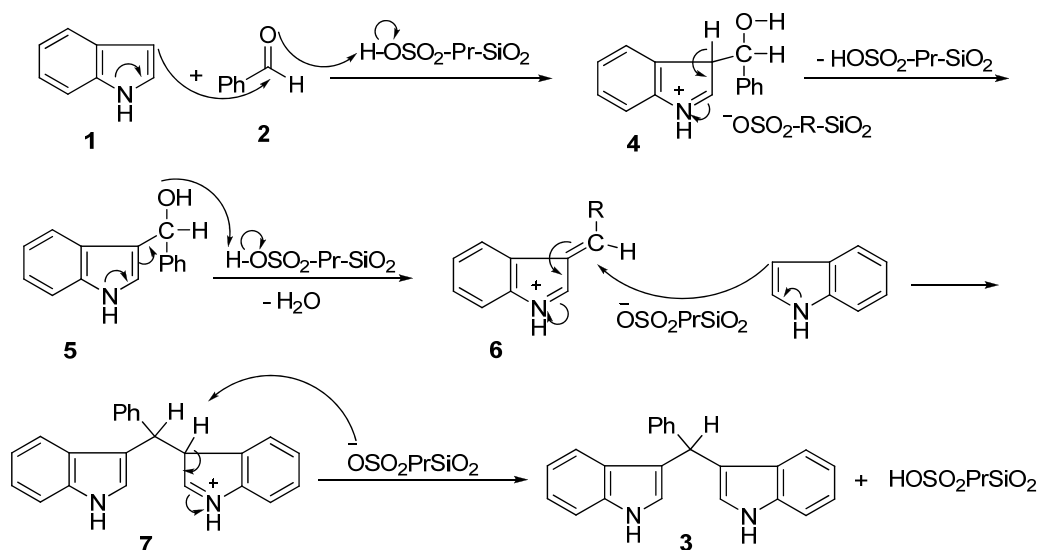
The proposed reaction mechanism was illustrated in Scheme 2. First, the carbonyl of aldehydes **2** is activated by acid catalyst. Then the C_3 position of indole **1** attacks to the carbonyl group of aldehyde and



Scheme 1. Synthesis of Bis(indolyl)methanes using $\text{SiO}_2\text{-Pr-SO}_3\text{H}$.

Table 1. Synthesis of bis(indolyl)methanes **3a-j** catalyzed by SiO₂-Pr-SO₃H in water.

Entry	Aldehyde	Product	Time/min	Yield/%	m.p. (°C)		Ref.
					Found	Reported	
1		3a	15	96	123-124	124-125	[41]
2		3b	5	93	187-189	188-190	[42]
3		3c	5	91	197-199	199-200	[42]
4		3d	15	87	75-77	76-77	[42]
5		3e	15	90	230-232	222-228	[43]
6		3f	15	88	215-217	217-219	[42]
7		3g	10	90	79-81	80-82	[44]
8		3h	5	95	120-122	121-123	[42]
9		3i	20	93	94-96	95-97	[42]
10		3j	15	90	320-322	324-326	[44]



Scheme 2. A plausible mechanism of the reaction.

subsequently generates intermediate compound 4 which loses its proton and produces the adduct product 5. In the presence of catalyst, the intermediate 5 is dehydrated to give the compound 6. Then the second indole molecule combines to 6 via a Michael condensation and produces intermediate 7 which finally is dehydrated to give bis indole system 3.

To investigate the efficiency of the $\text{SiO}_2\text{-Pr-SO}_3\text{H}$, we compared other reported synthesis methods and the results were summarized in Table 2. As shown in Table 2, using $\text{SiO}_2\text{-Pr-SO}_3\text{H}$ as catalyst offers several advantages such as excellent yields, short reaction times, a simple procedure and work-up and using water as a green solvent in contrast with other methods.

Sulfonic acid functionalized silica as an efficient heterogeneous solid acid catalyst can be prepared by simple operation from commercially available cheap starting materials such as silica. For the preparation of this solid acid catalyst, acid sites have been incorporated into silica surface by grafting method [38, 39]. The silica surface was first grafted with (3-mercaptopropyl)trimethoxysilane (MPTS) and then the thiol functionalities were then oxidized into sulfonic acid groups by hydrogen peroxide (Scheme 3).

The surface of catalyst was analyzed by different method such as TGA, BET and CHN methods which were demonstrated that the organic groups (propyl sulfonic acid) were immobilized into the pores [40]. The catalyst can be reused several times without considerable loss of reactivity.

The FT-IR of the catalyst showed the O-H stretch and vibrations of the surface hydroxyl groups and physisorbed water as a broad peak at $3000\text{-}3700\text{ cm}^{-1}$. The peaks around $1000\text{-}1250\text{ cm}^{-1}$ were attributed to the asymmetric stretching modes of Si-O-Si groups,

SO_3^- stretching vibration (1161 cm^{-1}), and $\text{O}=\text{S}=\text{O}$ (1032 cm^{-1}) stretching in SO_3H group. The weak bands at around 2800 and 2950 cm^{-1} were assigned to the C-H symmetric and asymmetric stretching of alkyl groups.

4. Conclusions

In this work we introduced an efficient, a clean, and a simple method for the preparation bis(indolyl) methanes using readily available starting materials and $\text{SiO}_2\text{-Pr-SO}_3\text{H}$ as heterogeneous catalyst. The advantages of this new method were simple operation, good yields, short reaction times and easy work-up. In addition, $\text{SiO}_2\text{-Pr-SO}_3\text{H}$ could be recovered from the crude product by simple filtration and reused without loss of activity.

Acknowledgements

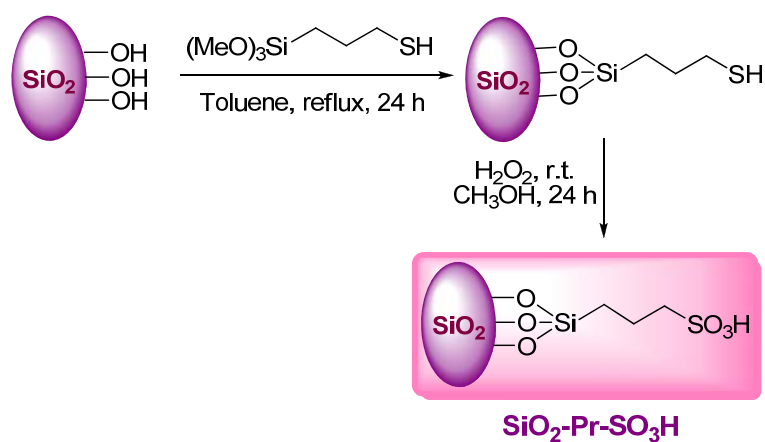
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Table 2. Comparison of different catalysts in the synthesis of **3a**.

Entry	Catalyst	Solvent	Yield/%	Time	Ref.
1	In(OTf) ₃	CH ₃ CN	71-86	25-35 min	[45]
2	K-10	AcOH	52-96	5 min-6 h	[46]
3	CAN	CH ₃ CN	81-92	0.5-1.5 h	[43]
4	Amberlyst-35	CH ₂ Cl ₂	51-94	6-24 h	[47]
5	InF ₃	H ₂ O	81-99	10-17 h	[48]
6	CuBr ₂	CH ₃ CN	38-95	15-480 min	[49]
7	HMTAB	H ₂ O	85-93	1.5-2.5 h	[42]
8	SbCl ₃	CH ₂ Cl ₂	42-95	0.45-9 h	[50]
9	TPA-ZrO ₂	-	82-94	30-60 min	[51]
10	H ₆ P ₂ W ₁₈ O ₆₂	-	45-98	15-150 min	[52]
11	HBF ₄ -SiO ₂	-	65-94	10-50 min	[44]
12	H ₃ PW ₁₂ O ₄₀	H ₂ O	78-92	1-8 h	[53]
13	ZnO	-	63-99	20-120 min	[54]
14	PO ₄ ³⁻ /ZrO ₂	-	51.2-93	20-240 min	[55]
15	La(NO ₃) ₃ .H ₂ O	-	96-98	30-120 min	[56]
16	Fe(DS) ₃ ^a	H ₂ O	73-97	2-12 h	[57]
17	PEG-Sulfonic acid	MeOH	83-96	2-9 h	[41]
18	SiO ₂ -Pr-SO ₃ H	H ₂ O	86-96	5-20 min	This work

^aFerric dodecyl Sulfonate.**Scheme 3.** Synthesis of sulfonic acid functionalized silica.

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