

FULL PAPER

Silica supported-boron sulfonic acid: a versatile and reusable catalyst for synthesis of bis(indolyl)methane in solvent free and room temperature conditions

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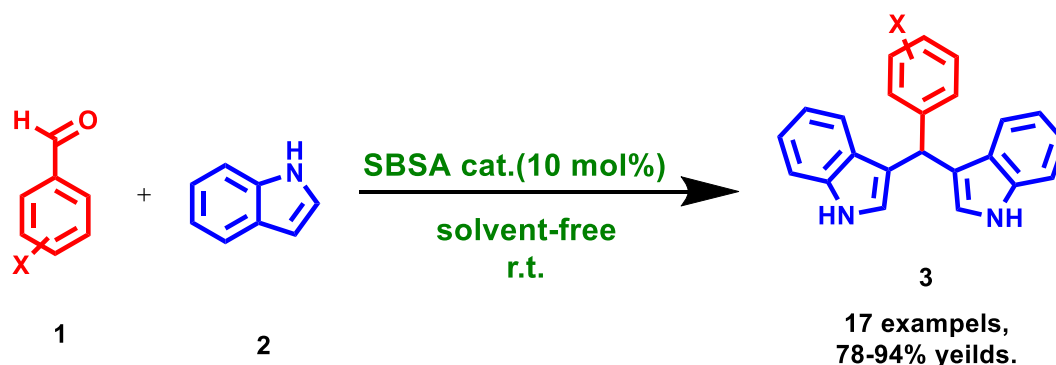
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ABSTRACT: Silica supported-boron sulfonic acid (SBSA) was used as a cheap and mild Bronsted acidic in the reaction of indole with aldehydes to afford the corresponding bis(indolyl)methanes in solvent free grinding and room temperature. The catalyst is also effective in the reaction in good yields. This methodology offers several advantages, such as good yields, reusability of catalyst, short reaction times, simple procedure, and mild conditions. The catalyst can be recovered and reused without loss of activity. The work-up of the reaction consists of a simple filtration, followed by concentration of the crude product and purification.

KEYWORDS: Indole, Bis(indolyl)methane, Boron Sulfonic Acid, Aldehyde, Synthesis, Solvent-free, Green Chemistry.

GRAPHICAL ABSTRACT:



1 - Introduction

Recently, use of heterogeneous catalysts have been extensively studied and have been demonstrated to be highly efficient catalysts in organic synthesis [1]. Solid acids are important class of heterogeneous catalysts because of easily application capabilities, simplicity in handling, decreased reactor and plant corrosion problems, and are more environmentally safe and available [2]. Among a number of different solid acid catalysts, silica supported-boron sulfonic acid with both protic and Lewis acidic sites

were shown to be the most active and recyclable catalyst [3]. Indoles and its derivatives are important heterocyclic compounds that used as pharmaceutical industry [4], agrochemicals [5], and material sciences [6]. Among these compounds, bis(indolyl) methanes (BIMs) contain two indole or substituted indole moieties has attracted much interest in recent years due to important biological activities [7], and bioactive metabolites [8]. Thus, the synthesis of bis(indolyl)methanes has received an

increasing attention in recent years. A common synthetic methods for preparation of bis(indolyl)methane derivatives included reaction of indole with various carbonyl compounds in the presence of different catalyst [9]. In the previous work, in the case of catalyst generally difficult to handle, stoichiometric amount maybe needed, and require tedious aqueous work-up, along with the use of environmentally harmful organic solvents. Due to the important key role of bis(indolyl)methanes in organic chemistry, chemists are looking for new approaches for the synthesis of bis(indolyl)methanes. Therefore, provide the simpler method seems necessary. A solid state based mechanochemical process conforms to most of the aspects of green chemistry and thus is appealing for use in the organic synthesis. In continuation of our previous report [10-15], In the recent years various catalytic systems have been developed for synthesis of indole derivatives including: such as 1-Carboxymethyl-3-methylimidazolium chloride, ([BMIm]BF₄-LiCl) [2], 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride Brønsted acidic ionic liquids (BAIL), and Fe₃O₄@silica sulfuric acid and Fe₂O₃/VO₂ magnetic nanoparticles, Dipyrindine cobalt chloride organo metallic compound, Sulfonylbis(1,4-phenylene)bissulfamic acid (SPSA) and also Silica Boron Sulfonic Acid were used as catalyst in Similar multi-component reactions (MCRs) .[16-22]. we described a mild and solvent free mechanochemical path for the synthesis of bis(indolyl)methanes from indole and aldehyde using silica supported-boron sulfonic acid as a new and versatile and reusable catalyst at solvent free and room temperature.

2 - EXPERIMENTAL

2.1 - Typical procedure for the synthesis of silica supported-boron sulfonic acid

A 50 mL suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution (water) and an alkali trap. Boric acid (1.55 g, 25.0mmol) was charged in the flask and chlorosulfonic acid (8.74 g, ca. 5.0 mL, and 75.0mmol in 5.0 mL CH₂Cl₂) was added dropwise over a period of 1h at room temperature under N₂ gas. HCl evolved immediately. After completion of the addition, the mixture was shaken for 85 min, while the residual HCl was eliminated by suction. The mixture was washed with diethyl ether to remove the unreacted chlorosulfonic acid and then 14.4 g SiO₂ was added a mixed. Finally, dried and grayish solid material was obtained in 95.6 % yield (21.6 g).

2.1 - Typical procedure for the synthesis of bis(indolyl)methane

In a mortar, 1.0 mmol of aldehyde, 2.0 mmol of indole and 10 mol % of silica supported-boron sulfonic acid is ground together with a pestle for appropriate times at room temperature. The progress of the reaction was monitored by TLC. Upon completion of the reaction the mixture of reaction worked-up of with a simple filtration by CHCl₃, followed by concentration of the crude product. The pure product was obtained by plate chromatography (silica gel, n-hexane-ethyl acetate, 3:1). The spectroscopic and analytical data for selected compounds are presented below.

2.3 - Spectral data for a selected bis(indolyl)methane

Bis(3-indolyl)-(2,4 dichlorophenyl)methane (3a): IR (KBr): ν = 3473 (NH), 2872, 1581, 1463, 1407, 1332, 1211, 1093, 857, 784, 730 (N-H) cm^{-1} . ^1H NMR (CDCl_3): δ = 6.30 (s, 1H), 6.59 (s, 2H, NH), 7.07 (m, 2H), 7.13 (m, 2H), 7.22 (t, J = 7.58 Hz, 1H), 7.35 (d, J = 8.15 Hz, 2H), 7.48 (d, J = 2.04 Hz, 1H), 7.49 (d, J = 7.92 Hz, 2H), 7.83 (br s, 2H, NH) ppm.

3,3-Bis(1H-indol-3-yl)-nitrophenylmethane (3b): ^1H NMR (CDCl_3) (δ , ppm): 6.00 (s, 1H), 6.69 (s, 2H), 7.04 (t, J = 7.51 Hz, 2H), 7.21 (t, J = 7.28 Hz, 2H), 7.35 (d, J = 7.93 Hz, 2H), 7.40 (d, J = 8.53 Hz, 2H), 7.52 (d, J = 8.69 Hz), 8.01 (br s, 2H, NH), 8.15 (d, J = 8.72 Hz, 2H).

Bis(3-indolyl)-(2-chlorophenyl)methane (3c): IR (KBr): ν = 3463 (NH), 1603, 1453, 1332, 1215, 1097, 1036, 733 (N-H) cm^{-1} . ^1H NMR (CDCl_3): δ = 6.36 (s, 1H), 6.62 (s, 2H), 7.05 (t, J = 7.14 Hz, 2H), 7.11 (t, J = 7.46 Hz, 1H), 7.21-7.27 (m, 4H), 7.36 (d, J = 8.12 Hz, 2H), 7.43-7.46 (m, 3H), 7.86 (br s, 2H, NH) ppm.

Bis(3-indolyl)-(4-methylphenyl)methane (3d): IR (KBr): ν = 3409 (NH), 3055, 2965, 1600, 1509, 1455, 1216, 1090, 733 (N-H) cm^{-1} . ^1H NMR (CDCl_3): δ = 2.33 (s, 3H, 4'-CH₃), 5.98 (s, 1H), 6.8 (s, 2H), 7.05-7.56 (m, 12H, Ar-H), 8.09 (br s, 2H, NH) ppm.

3,3-Bis(1H-indol-3-yl)-3-nitrophenylmethane (3i): ^1H NMR (CDCl_3) (δ , ppm): 6.01 (s, 1H), 6.67 (s, 2H), 7.04 (t, J = 7.10 Hz, 2H), 7.21 (t, J = 7.23 Hz, 2H), 7.38 (t, J = 9.07 Hz, 4H), 7.43 (t, J = 7.92 Hz, 1H), 7.70 (d, J = 7.64 Hz), 7.97 (br s, 2H, NH), 8.09 (m, 1H), 8.22 (s, 1H).

Bis(3-(2-methylindolyl))-(4-chlorophenyl)methane (3l): IR (KBr): ν = 3387 (NH), 2915, 1614, 1461, 1305, 1012, 741 (N-H) cm^{-1} . ^1H NMR (CDCl_3): δ = 2.05 (s, 6H), 5.96 (s, 1H), 6.86-7.26 (m, 12H, Ar-H), 7.78 (br s, 2H, NH) ppm.

Bis(3-(2-methylindolyl))-(2,4-dichlorophenyl)methane (3m): IR (KBr): ν = 3398 (NH), 2926, 1659, 1584, 1463, 1104, 741 (N-H) cm^{-1} . ^1H NMR (CDCl_3): δ = 2.23 (s, 6H), 6.33 (s, 1H), 7.07 (t, J = 7.42 Hz, 2H), 7.14 (t, J = 9.66 Hz, 2H), 7.25 (t, J = 7.49 Hz, 2H), 7.29 (d, J = 8.35 Hz, 1H), 7.40 (d, J = 8.33 Hz, 1H), 7.45 (d, J = 8.23 Hz, 2H), 7.60 (s, 1H), 7.95 (br s, 2H, NH) ppm.

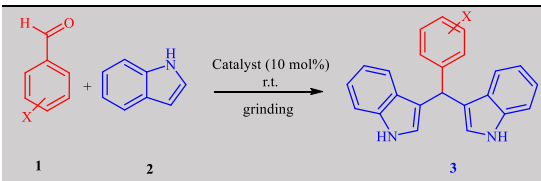
Bis(3-(2-methylindolyl))-4-(methylphenyl)methane (3n): IR (KBr): ν = 3398 (NH), 3044, 1611, 1458, 1010, 736 (N-H) cm^{-1} . ^1H NMR (CDCl_3): δ = 2.06 (s, 6H), 2.34 (s, 3H), 5.97 (s, 1H), 6.84-7.06 (m, 8H), 7.16 (d, J = 7.78 Hz, 2H), 7.24 (d, J = 8.04 Hz, 2H), 7.75 (br s, 2H, NH) ppm.

3 - RESULT AND DISCUSSION

The silica supported-boron sulfonic acid catalyzed reaction between 4-chloro benzaldehyde and indole was chosen as a simple model reaction to evaluate the effects of solvent and the amounts of catalyst. In the first step we have tried solvents such as H₂O, CHCl₃, C₂H₅OH, CH₃CN, CH₂Cl₂, Et₂O, and acetone. The same reaction was performed in solvent free conditions at room temperature. All the ingredients of the reaction were taken in a mortar, mixed thoroughly and ground well at room temperature. We found that in solvent free

conditions, the yield of product was enhanced to 88 after 60 minutes at room temperature (Table 1, entry 8).

Table 1. Influence of the solvent on the synthesis of bis(indolyl)methane.



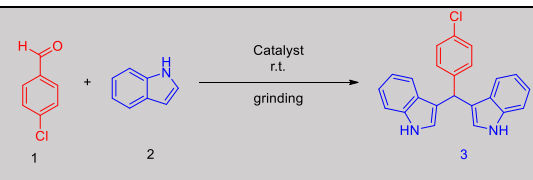
Entry	Solvent	Time (min)	Yield (%) ^c
1	H ₂ O ^b	140	50
2	CHCl ₃	50	84
3	C ₂ H ₅ OH	75	73
4	CH ₃ CN	45	80
5	CH ₂ Cl ₂	55	82
6	Et ₂ O	50	81
7	acetone	170	65
8	Free-solvent	60	88

^aReaction conditions: 4-chloro benzaldehyde (1.0 mmol), indole (2.0 mmol), 10 mol % of silica supported-boron sulfonic acid and room temperature.

^b 50 °C. ^cIsolated yield.

The influence of amount of silica supported-boron sulfonic acid was also examined. The results (Table 2) shown, the yield of bis(indolyl)methane production was depended on amount of silica supported-boron sulfonic acid. Significant proceed of the reaction was also observed in the presence of 10 mol% of catalyst as the product was yielded 98% after 50 min.

Table 2. Screening of amount of silica supported-boron sulfonic acid for the reaction of 4-chloro benzaldehyde with indole



Entry	Amount of catalyst (%)	Time (min)	Yield (%) ^b
1	1	120	80
2	3	85	80
3	5	80	87
4	10	50	98
5	15	50	90
6	20	20	92

^aReaction conditions: 4-chloro benzaldehyde (1.0 mmol), indole (2.0 mmol), and room temperature.

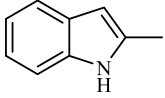
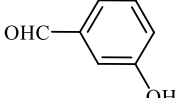
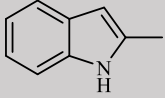
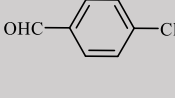
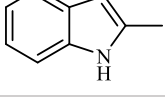
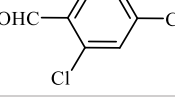
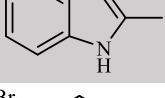
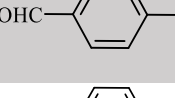
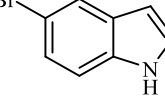
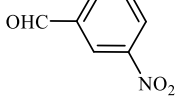
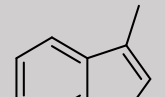
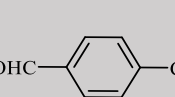
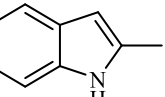
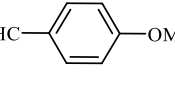
^bIsolated yield.

Eventually, a large number of bis(indolyl)methane was synthesized by the reaction of benzaldehyde with indole in solvent free grinding and room temperature with excellent yields under optimized reaction conditions. Results are summarized in Table 3.

A reasonable mechanism for the reaction is outlined in Scheme 1. The reaction of indole with aldehydes proceeded through the successive intermediates of related carbinols. The sulfonic acid groups on the catalyst are involved in salt formation with indolylcarbinols. Owing to their instability in acidic conditions, the indolylcarbinols lose water, generating the salts of indoleninium species, which act as electrophiles towards a second molecule of indole, giving the corresponding bis(indolyl)methanes.

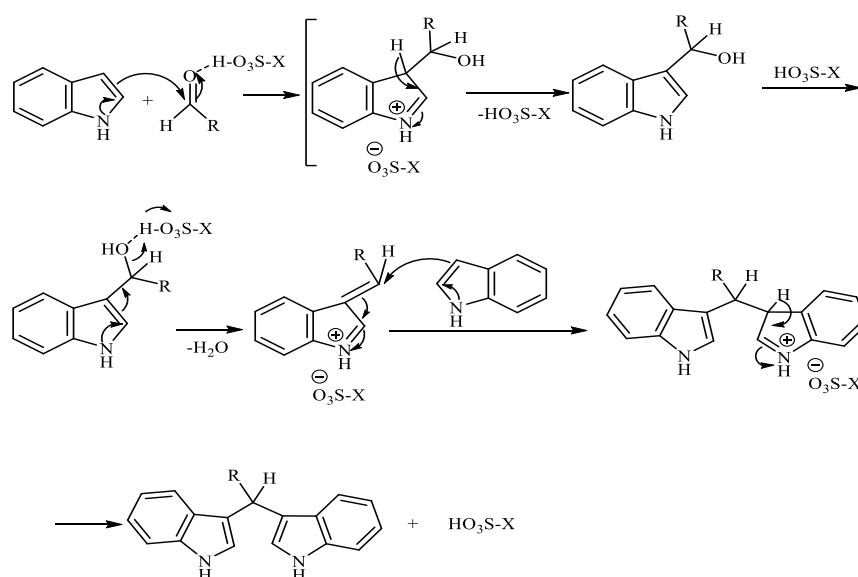
Table 3. Synthesis of bis(indolyl)methane

Entry	Indol	Aldhyde	Product a	Time (min)	Yieldb (%)	m.p. (°C)	[ref.]
1			3a	70	88%	78-80	[23]
2			3b	110	78%	217-219	[24]
3			3c	90	86%	74-76	[23]
4			3d	130	88%	95-97	[25]
5			3e	140	91%	132-133	[26]
6			3f	55	92%	121-132	[27]
7			3g	50	90%	126-128	[27]
8			3h	120	84%	140-142	[28]
9			3i	55	89%	217-219	[28]
10			3j	65	79%	196-198	[29]

11			3k	130	89%	118-120	[27]
12			3l	65	91%	145-147	[30]
13			3m	55	71%	215-216	[27]
14			3n	100	94%	92-94	[23]
15			3o	90	90%	217-219	[27]
16			3p	200	N.R	-	-
17			3q	180	79	186-188	[27]

^aAll the products are known compounds and were characterized by comparison of NMR spectral data and melting points with those reported in the literature.

^bIsolated yield.



Scheme 1. Proposed mechanism for the synthesis of bis(indolyl)methane.

4 – CONCLUSIONS

In conclusion, a simple and efficient reaction for the synthesis of bis(indolyl)methane has been developed using silica supported-boron sulfonic acid in solvent free grinding and room temperature.

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