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Catalysis by cellulose sulfuric acid as a bio-supported and recyclable solid acid: Synthesis of 3-substituted indoles through Michael addition

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ABSTRACT

Michel addition of indoles with olefins in the presence of cellulose sulfuric acid as catalysts afford the corresponding 3-substituted indoles in excellent yields and short reaction times is described. The reaction work up is simple and the catalyst can be easily separated from the reaction mixture and reused in subsequent reaction.

Keywords: cellulose sulfuric acid, indole, Michael addition, α,β-unsaturated compounds

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INTRODUCTION

The indole ring is widely present in a variety of biologically active compounds and has become an important structural component in many pharmaceutical agents owing to the great structural diversity of biologically active indoles.[1-7] Various indole derivatives occur in many pharmacologically and biologically active compounds.[8-11] Among them 3-substituted indoles are important building blocks for the synthesis of biologically active compounds and natural products.[12-16] Consequently, many procedures have been developed for the synthesis of 3-substituted indoles. The simple and direct method for the synthesis of 3-alkylated indoles involves the conjugate addition of indoles to α,β-unsaturated compounds in the presence of protic[16-19], Lewis acid[20-26] and metal complexes[27-30]. However, many of these procedures involved strong acidic conditions, expensive reagents and longer reaction times, low yields of products and uneasy handling, which necessitate the development of an alternative route for the synthesis of these biologically active molecules.

Biopolymers, especially cellulose and its derivatives[31] have some unique properties, which make them attractive alternatives for conventional organic or inorganic supports for catalytic applications. Cellulose is a biodegradable material, can be obtained from renewable resources and has potential as a catalyst to yield clean, efficient and fast reactions. Recently, cellulose sulfuric acid has emerged as a promising biopolymer solid support acid catalyst for acid-catalyzed reactions, such as the synthesis of α-aminonitriles[32] imidazoazines,[33] and quinolines.[34] CSA can be easily prepared by the reaction of inexpensive cellulose with chlorosulfonic acid.[32-34]

In recent years, the direction of science and technology is shifting more towards environmentally friendly and sustainable resources and processes and reusable catalysts in organic synthesis. Thus, natural biopolymers are attractive candidates in the search for such solid support catalysts.[35,36]

MATERIALS AND METHODS

Melting points are uncorrected and were obtained in open capillary tubes in sulphuric acid bath. TLC checking was done on plastic sheets coated with silica gel GF-254 (Merck). Flash column chromatography was performed over silica gel (mesh 230–400) and hexane/ethyl acetate combination was used as the eluent. ^{1}H NMR and ^{13}C NMR spectra were determined in DMSO-d_6 solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. IR spectra were recorded using Perkin-Elmer model 1700 instrument in KBr phase. MS spectra were obtained on a mass spectrometer.

Preparation of cellulose sulfuric acid:

To a magnetically stirred mixture of 5.00 g of cellulose (DEAE for column chromatography, Merck) in 20 ml of *n*-hexane, 1.00 g of chlorosulfonic acid (5.4 mmol) was added dropwise at 0 °C during 2 h. HCl gas was removed from the reaction vessel immediately. After the addition was complete, the mixture was stirred for 2 h. Then, the mixture was filtered and washed with 30 ml of acetonitrile and dried at room temperature to obtain 3.15 g cellulose sulfuric acid as white powder.

General procedure for the synthesis of 3-substituted indoles (3):

A mixture of α,β-unsaturated carbonyl compounds (**2**) (1 mmol), indoles (**1**) (1 mmol) and cellulose sulfuric acid (0.1 g) in 4 mL of dry acetonitrile was stirred at refluxing temperature for 40-45 min. The reaction was monitored by thin-layer chromatography (TLC). After complete conversion, the reaction mixture was filtered while hot, washed with CH_2Cl_2 (8 mL) and the cellulose sulfuric acid catalyst recovered. The filtrate evaporated, under reduced pressure and purified by silica-gel column chromatography to afford pure product.

3-(2-Nitro-1-phenylethyl)-1*H*-indole (3a): Off white solid; mp 99-101 °C (lit[30] 99 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.85-5.05 (m, 2H), 5.16-5.20 (m, 1H), 7.00 (s, 1H), 9.99-7.40 (m, 9H), 8.05 (s, 1H, NH). MS (ESI): m/z ([M+H]+): 267.1.

3-(1-(4-Chlorophenyl)-2-nitroethyl)-1*H*-indole (3b)[28]; Oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.91 (dd, J=7.2, 11.6 Hz, 1H), 5.05 (dd, J=8.2, 12.4 Hz, 1H), 5.20 (t, J=8.0 Hz, 1H), 7.00-7.35 (m, 9H), 8.10 (brs, 1H); m/z ([M+H]+): 301.1.

3-(1-(3,4-Dichlorophenyl)-2-nitroethyl)-1H-indole (3c); Red solid; mp 132-134 °C (lit[27] 135-137 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.80-4.85 (dd, J=8.1, 12.3 Hz, 1H), 4.91-4.97 (dd, J=7.9, 12.00 Hz, 1H), 5.08 (t, 1H), 6.92 (s, 1H), 7.02-7.10 (m, 2H), 7.17 (t, 1H), 7.30-7.36 (m, 4H), 8.37 (s, 1H); MS (ESI): m/z ([M+H]+): 334.4.

3-(1-(4-bromophenyl)-2-nitroethyl)-1H-indole (3d)[27]; Oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.89 (dd, J=7.8, 11.9 Hz, 1H), 5.05 (dd, J=7.6, 12.4 Hz, 1H), 5.02 (t, J=8.0 Hz, 1H), 7.01-7.46 (m, 9H), 8.11 (brs, 1H); MS (ESI): m/z ([M+2]): 346.2.

3-(2-Nitro-1-*o*-tolylethyl)-1*H*-indole (3e) Brown solid**;** mp 139-143 °C (lit[28] 142-147 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.49 (s, 3H), 4.92-4.99 (d, 1H), 5.10 (d, J=8.5 Hz, 1H), 5.5 (t, J=8.2 Hz, 1H), 6.95 (s, 1H), 7.16-7.20 (m, 1H), 7.19-7.27 (m, 4H), 7.30 (t, J=8.8 Hz, 1H), 7.41-7.43 (d, J=7.8 Hz, 1H), 7.57 (d, J=8.0 Hz 1H), 8.10 (s, 1H, 1H); MS (ESI): m/z ([M+H]+): 281.2.

3-(1-(4-methoxyphenyl)-2-nitroethyl)-1H-indole (3f); Off white solid**;** mp 145-148 (lit[28] 149-150 °C); ^{1}H NMR (CDCl3, 400 MHz) δ 3.80 (s, 3H), 4.90 (d, J=8.4, 1H), 5.05 (d, J=7.9, Hz, 1H), 5.14 (t, J=8.0 Hz, 1H), 6.81-7.45 (m, 9H), 8.02 (brs, 1H); MS (ESI): m/z ([M+H]+): 297.3.

5-Chloro-3-(1-(3,4-dichlorophenyl)-2-nitroethyl)-1*H*-indole (3g)
Pink solid; mp 145-147 °C (lit[27] 149-150 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.82-4.87 (d, J=8.6 Hz, 1H), 4.95 (d, J=8.0 Hz, 1H), 4.02 (t, J=7.8 Hz, 1H), 6.99 (s, 1H), 7.10-7.14 (m, 2H), 7.20 (d, J=8.0 Hz, 1H), 7.32-7.37 (m, 3H), 8.67 (s, 1H). MS (ESI): m/z ([M+H]+): 369.3.

6-Fluoro-3-(2-nitro-1-phenylethyl)-1*H*-indole (3h)[27]

Brown liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.99 (d, *J*=,7.8 Hz 1H), 5.00 (d, *J*=8.0 Hz 1H), 5.13 (t, *J*=7.8 Hz 1H), 6.76-6.82 (m, 1H), 6.95-6.70 (m, 2H), 7.21-7.30 (m, 6H), 8.07 (s, 1H); MS (ESI): m/z ([M+H]+): 285.4.

3-(1-(3,4-Dichlorophenyl)-2-nitroethyl)-6-fluoro-1*H*-indole (3i)

Pink solid; mp 130-132 °C (lit[27] 135-138 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.90 (d, *J*=7.8 Hz ,1H), 5.00 (d, *J*=8.0 Hz, 1H), 5.10 (t, *J*=7.6 Hz, 1H), 6.90 (d, *J*=7.6 Hz, 1H), 6.90-7.02 (m, 1H), 7.03 (d, *J*=8.0 Hz, 1H), 7.13-7.18 (m, 2H), 7.38- 7.41 (m, 2H), 8.51 (brs, 1H); MS (ESI): m/z ([M+H]+): 353.3.

3-(1-(Furan-2-yl)-2-nitroethyl)-1*H*-indole (3j)[29]

Oil; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 4.91 (dd, *J*=7.8, 12.2 Hz, 1H), 5.08 (dd, *J*=8.2, 12.2 Hz, 1H), 5.22 (t, *J*=8.0 Hz, 1H), 6.15-6.19 (m, 1H), 6.32-6.35 (m, 1H), 7.10-7.32 (m, 6H), 8.11 (brs, 1H); MS (ESI): m/z ([M+H]+): 257.5.

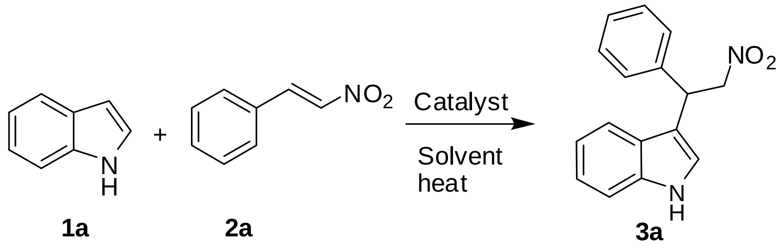
3-(1-(3,4-Dichlorophenyl)-2-nitroethyl)-5-fluoro-1*H*-indole (3k)

Pale red solid; mp 131-133 °C (lit[27] 128-133 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.83 (d, *J*=7.8 Hz, 1H), 4.98 (d, *J*=8.6 Hz, 1H), 5.08 (t, *J*=7.2, Hz, 1H), 6.80-6.85 (m, 1H), 6.99-7.02 (m, 2H), 7.13 (d, *J*=8.2, Hz, 1H), 7.25 (d, *J*=8.2, Hz, 1H), 7.36 (d, *J*=7.8 Hz, 2H), 8.47 (brs, 1H); MS (ESI): m/z ([M+H]+): 353.6.

RESULTS AND DISCUSSION

Initially, we examined the reaction of indole (**1a**) with nitrostyrene (**2a**) in the presence of Montmorillonite-K10 in CH_3CN at 60 °C for 1 h when the desired 3-(2-nitro-1-phenylethyl)-1H-indole (**3a**) was isolated in 25% yield (entry 1, Table 1). While the yield of **3a** was increased when Amberlite IR 400 was used in place of Montmorillonite-K10 (entry 2, Table 1) the maximum yield however was achieved using Cellulose sulfuric acid (entry 3, Table 1) indicating its most suitability for the present reaction. The use of other solvents was also examined (entries 4-6, Table 1) among which MeOH, EtOH and CH_2Cl_2 was found to be effective. Nevertheless, being inexpensive and readily available green catalyst Cellulose sulfuric acid was chosen for further study on the present cellulose sulfuric acid mediated condensation reaction. To test the recyclability of the catalyst used cellulose sulfuric acid was recovered by simple filtration and reused in the same reaction when **3a** was isolated without significant loss of its yield. The yield of **3a** was found to be 94, 92 and 85 after 1st, 2nd and 3rd recovery and reuse of the catalyst. Overall, the combination of cellulose sulfuric acid in CH_3CN was found to be optimal for the preparation of **3a.**

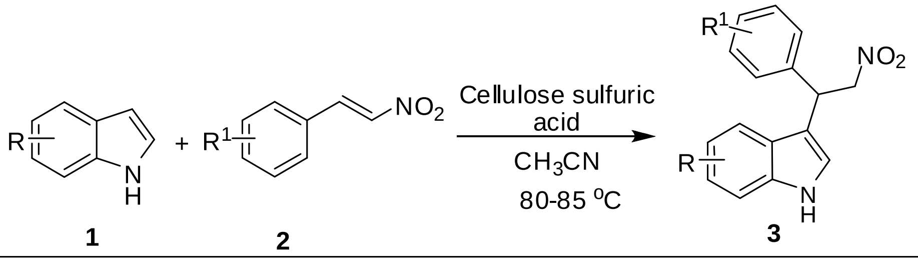
Table 1 Optimization of the reaction conditions[a]

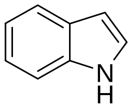
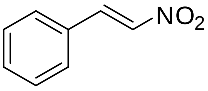
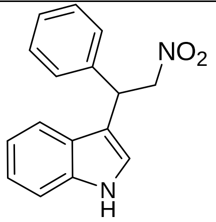
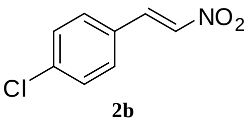
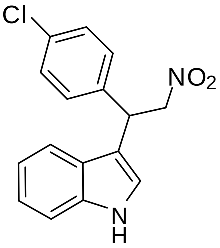
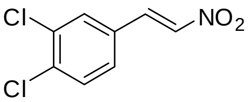
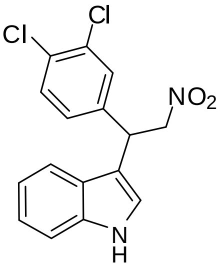
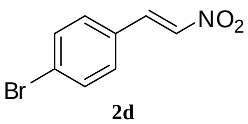
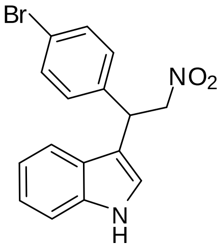
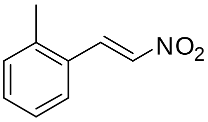


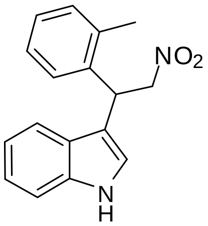
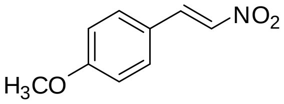
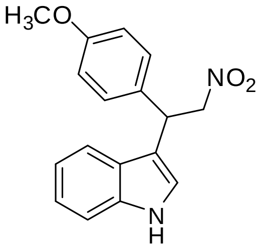
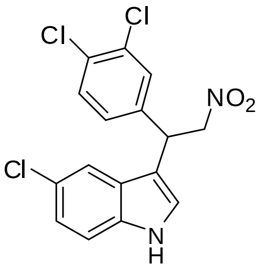
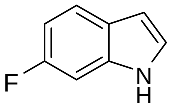
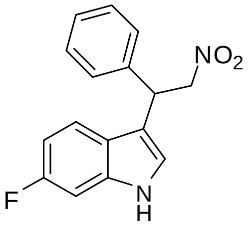
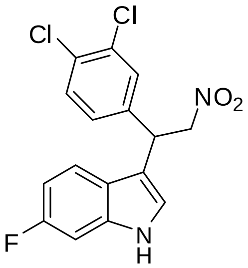
Entry	Catalyst	Solvent	T °C; t (h)	%Yield[b,c]
1	Montmorillonite-K10 (50% w/w)	CH_3CN	80-85;2	25
2	Amberlite IR 400	CH_3CN	80-85;2	38
3	Cellulose sulfuric acid (0.02 mmol)	CH_3CN	80-85;0.45	95 (94, 92, 85)[d]
4	Cellulose sulfuric acid (50% w/w)	CH_3OH	63-68; 0.45	50
5	Cellulose sulfuric acid (50% w/w)	C_2H_5OH	77-80; 0.45	65
6	Cellulose sulfuric acid (50% w/w)	CH_2Cl_2	38-42; 0.45	78

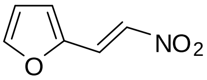
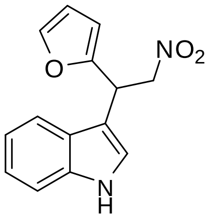
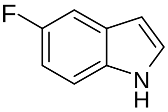
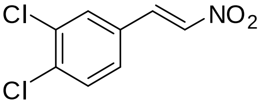
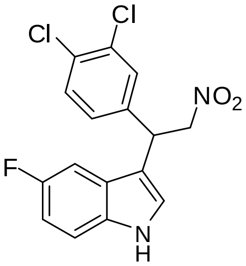
[a] *All the reactions were carried out by using indole (1 mmol), β-nitrostyrene (**2**) (1 mmol), Cellulose sulfuric acid (50% w/w), CH_3CN (5 mL) at 80-85 °C.;* [b] *Identified by ^{1}H NMR and MS.;* [c] *Isolated yields.;* [d] *Catalyst was reused for additional three runs and figures within parentheses indicate the corresponding yield for each run.*

Table 2. Cellulose sulfuric acid catalyzed synthesis of 3-substituted indoles in acetonitrile (Scheme 1).[a]



Entry	Indole (**1**)	Nitroolefins (**2**)	Product (**3**)[b]	Yield[c] (%)
1	 **1a**	 **2a**	 **3a**	95
2	**1a**	 **2b**	 **3b**	90
3	**1a**	 **2c**	 **3c**	88
4	**1a**	 **2d**	 **3d**	92
5	**1a**	 **2e**		90

			 **3e**	
6	**1a**	 **2f**	 **3f**	88
7	**1b**	**2c**	 **3g**	88
8	 **1c**	**2a**	 **3h**	88
9	**1c**	**2c**	 **3i**	85

10	**1a**	 **2g**	 **3j**	92
11	 **1d**	 **2h**	 **3k**	90

[a] *All the reactions were carried out using indole (1mmol); nitroolefins (1 mmol); cellulose sulfuric acid (50% w/w); 80-90 °C and 45-50 mins.*
[b] *All the compounds are known, characterized by ^{1}H NMR, and mass spectral analysis, and compared with the authentic samples.*
[c] *Isolated yield*

Having the optimized reaction conditions in hand we then examined the generality and scope of the present cellulose sulfuric acid mediated reaction in CH_3CN. Thus, a range of β-Nitrostyrene (**2**) was initially reacted with **1a** and the results are summarized in Table 2. Various electron donating groups e.g. Cl, Br and Me (entries 2-5, Table 2) present on the aryl ring of nitrostyrene were well tolerated. The uses of heteroaromatic styrene (entries 11, Table 2) were also successful and afforded the desired 3-substituted indole in good yields. The reaction proceeded smoothly with other indoles e.g. **1b-d** as well (entries 7-10 and 11, Table 2). All products were characterized by comparison of their melting points, ^{1}H NMR, and mass spectra (MS) with those of authentic samples.

CONCLUSION

In summary, cellulose sulfuric acid as an efficient, eco-friendly, reusable, bio-supported proton source catalyst has been prepared and employed for the synthesis 3-substituted indoles. Excellent yields, simple experimental procedure, use of nontoxic, noncorrosive and inexpensive solid acid catalyst are important features of this new protocol to prepare 3-substituted indoles.

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