Synthesis of 3-Alkenylated Indole and *Bis*(indol-3-yl) Derivatives Catalyzed by Sulfonic Acid Functionalized Ionic Liquid Under Ultrasound Irradiation

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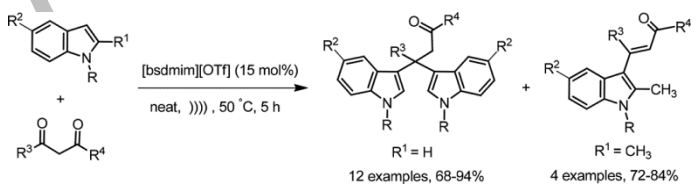
Abstract

A simple and efficient protocol has been developed for the synthesis of 3-alkenylated indoles and *bis*(indol-3-yl) derivatives by sulfonic acid functionalized ionic liquids (SFIL) catalyzed reaction of indole with 1,3-diketones/3-ketoesters under solvent free ultrasound irradiation. Good to excellent yields (68-94%) are obtained in ultrasonication. The product of the reaction is dependent on the substituent at C-2-position of indole. The catalyst is reusable and recyclable up to four cycles without significant loss of its catalytic activity. Compared with conventional heating, sound wave activation has the considerable advantages such as shorter reaction times, easy work-up, higher yields and mild conditions.

GRAPHICAL ABSTRACT



KEYWORDS: Sulfonic acid functionalized ionic liquids, Solvent-free condition, 3-Alkenylated indoles, *Bis*(indol-3-yl) derivatives

INTRODUCTION

Indole moiety is a privileged structural subunit present in several pharmaceuticals and natural products.[1] Among various substituted indoles, 3-substituted indoles are most commonly used as building blocks for the synthesis of various compounds that exhibit physiological properties such as antiinflammatory, antifungal, anticancer, antibacterial, analgesic, antidepressant etc.[2] Consequently, development of efficient synthetic methods for selective functionalization of indoles at the C-3 position has become topic of significant interest to the synthetic chemists.[3] Several methods have been developed for the synthesis of *bis*(indolyl)alkanes, cyclopenta[*b*]indoles using different catalysts,[4] whereas very few reports are available for the synthesis of 3-alkenylated indoles.

Functionalized ionic liquids (FILs) have gained considerable interest as a catalyst in synthesis of organic compounds due to their unique properties such as operational simplicity, non-corrosiveness, greater selectivity, reusability, environmental compatibility and ease of isolation.[5] By amending the structure of cation or anions, their chemical and physical properties can be altered to influence the outcomes of the reaction. These fascinating materials have shown excellent results for various organic transformations as catalysts and reagents. Reaction of indole with acetylacetone in the presence of sulfonic acid functionalized ionic liquid is reported to give 3-alkenylated product[6] at lower

temperature whereas *bis*(indolyl)carbonyl derivatives are obtained at higher temperature.[7]

On the other hand, use of ultrasound has been explored for enhancing the reaction rates and yields/selectivity under milder conditions.[8] In recent years, a great attention has been focused on developing synthetic method by combining alternative energy sources with ionic liquids. In this direction ionic liquids and ultrasound irradiation provide very good opportunity to develop efficient methods for different organic transformation.[9] Continuing our interest in application of functionalized ionic liquids (FILs),[10] herein, we disclose our results for the synthesis of 3-alkenylated indoles and *bis*(indol-3-yl) derivatives by sulfonic acid functionalized ionic liquids (SFIL) catalyzed reaction of indole with 1,3-diketones/3-ketoesters under solvent-free ultrasound irradiation (**Scheme 1**).

RESULTS AND DISCUSSION

Initially, we performed a series of experiments to find the optimum reaction condition for the reaction of indole (**1a**) with acetylacetone (**2a**) to give 4,4-*bis*(1*H*-indol-3-yl)pentan-2-one (**3aa**) using *p*-TSA, CF_3SO_3H [bsdmim][PF_6], [bsdmim][HSO_4] and [bsdmim][OTf] as catalysts. As can be seen from **Table 1**, the best yield of **3aa** (78%) was obtained using 15 mol % of sulfonic-functionalized ionic liquids [bsdmim][OTf] after 24 h at room temperature under solvent free condition (**Table 1**, entry 8). The yield of **3aa** slightly increased by increasing the reaction temperature to 50 °C but further

increase in temperature to 80 °C led to reduction in the yield of 3**aa** (**Table 1**, entries 10, 11).

In order to screen the effect of solvent, the model reaction was kept at 50 °C using 15 mol % [bsdmim][OTf] in different solvents such as CH_3CN, H_2O, EtOH, dichloroethane (DCE), toluene, but no improvement in the yield of **3aa** was observed (**Table 1**, entries 12-16). Finally, the model reaction was performed under ultrasound irradiation in solvent-free conditions and to our surprise; **3aa** was obtained in 94% yield after 5 h (**Table 1**, entry 17). The higher yield in shorter reaction time under ultrasound irradiation may be attributed to the phenomenon of cavitation produced by ultrasound.[11] Encouraged by the results for model reaction, we probed the scope of the reaction of substituted indoles with variety of 1,3-dicarbonyl compounds. As evidenced by the results in **Table 2**, 2-unsubstituted indoles such as indole (**1a**), 5-methoxyindole (**1b**), 5-fluoroindole (**1c**), 5-bromoindole (**1d**), 5-cyanoindole (**1e**) and *N*-methylindole (**1f**) smoothly reacted with different 1,3-dicarbonyl compounds such as acetylacetone (**2a**), methyl acetoacetate (**2b**) and ethyl acetoacetate (**2c**) to give corresponding *bis*(indolyl)carbonyl compounds (**3aa-fc**) in good to excellent yields (**Table 2**, entries 1-16). Structure of all the compounds was elucidated by NMR (^1H and ^{13}C) and mass spectrometry data. When 2-methylindole (**1g**) was reacted with various 1,3-dicarbonyl compounds (**2a-d**) under similar conditions corresponding 3-alkenylated indole derivatives (**4ga-gd**) were obtained rather than the expected *bis*(indol-3-yl) derivatives under these conditions (**Table 2**, entries 17-20). Increased steric hindrance caused by C-2

substituent may be responsible for the exclusive formation of 3-alkenylated indole derivatives from C-2 substituted indoles.

The recyclability of catalyst [bsdmim][OTf] is highly preferable for a green process. We investigated this issue by using model reaction of **1a** and **2a** under the optimal conditions (**Table 1**, entry 17). After completion of reaction, the crude product **3aa** was extracted with ethyl acetate (3 × 5 mL) and then **1a** and **2a** were added into the catalytic system for next runs. As shown in **Figure 1**, the recovered catalyst was reused up to four cycles without significant decrease in the yields of the product **3aa**.

Based on the results and literature reports, a plausible mechanism of the reaction is depicted in **Scheme 2**. Initially, indole (**1**) attacks the activated carbonyl group of 1,3-dicarbonyl compound (**2**) to give intermediate **A**. Depending on the substituent R^1, intermediate **A** then either undergoes acid catalyzed substitution with another indole molecule to give *bis*(indol-3-yl) derivatives (**3**) or elimination of water to give 3-alkenylated indole derivative (**4**).

CONCLUSION

In summary, we have described a solvent-free method for the synthesis of 3-alkenylated indoles and *bis*(indol-3-yl) derivatives by the reaction of indoles with 1,3-dicarbonyl compounds using catalytic amount of acidic ionic liquid [bsdmim][OTf] under ultrasonic irradiation. The notable features of this protocol are simple operation, high yields, shorter reaction times, reusability of catalyst, mild and metal free nature of reaction. The

formation of product is dependent on the C-2-substitution in indole. Combined use of ionic liquid and ultrasound makes this procedure an improved alternative to the available synthetic methodologies.

EXPERIMENTAL

All solvents and chemicals were procured from Alfa-Aesar, SD Fine Chemicals, Spectrochem Chemicals Pvt. Ltd, Merck, Sigma-Aldrich and were used as received. The progress of the reactions was monitored by thin-layer chromatography (TLC) carried out on silica-coated aluminum plates coated with fluorescent indicator F254. Melting points were recorded using a MPA120 EZ-Melt automated melting point apparatus and were uncorrected. The IR spectra were recorded with KBr on ABB Bomem MB3000 FTIR spectrophotometer. The NMR spectra were recorded on a Bruker Advance 400 MHz NMR spectrometer using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts values are reported as values in ppm relative to TMS as internal standard and abbreviations for multiplicity of chemical shift values are s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. All the synthesized compounds were purified by column chromatography using silica gel (60–120 mesh).

General Procedure For Synthesis Of 3-Alkenylated Indoles And *Bis*(Indol-3-Yl) Derivatives

Indole **1** (1.0 mmol), 1,3-dicarbonyl compound **2** (0.6 mmol) and 1-butylsulfonic-2,3-dimethylimidazolium trifluoromethanesulfonate, [bsdmim][OTf] (15 mol %) were mixed in a 25 mL round-bottom flask. The reaction mixture was sonicated in a digital

ultrasonicator at 50 °C for 5 h. Then, the mixture was cooled to room temperature, extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the residue was purified by chromatography on silica gel (gradient eluent of 5-10% EtOAc in hexanes, *v/v*) to give the desired product.

4,4-Di(1H-Indol-3-Yl)Pentan-2-One (3aa)

White solid. m.p = 214–216 °C (Lit.[7] 223-225 °C); IR (KBr): 3394, 1690, 1342, 748 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm = 10.16 (s, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.06 (t, *J* = 2.6 Hz, 2H), 6.91 (dd, *J* = 9.9, 5.1 Hz, 2H), 6.75 – 6.52 (m, 2H), 3.05 (s, 2H), 1.86 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 209.2, 137.3, 126.0, 122.0, 121.4, 120.9, 120.5, 118.2, 111.6, 53.4, 37.6, 31.9, 27.2; HRMS (ESI) *m/z* $C_{21}H_{21}N_2O^+$ $[M + H]^+$ calcd for 317.1648, found 317.1646.

SUPPLEMENTAL MATERIAL

Experimental detail for synthesis of the catalyst 1-butylsulfonic-2,3-dimethylimidazolium trifluoromethanesulfonate [bsdmim][OTf], ^1H and ^{13}C NMR spectra associated with 3-alkenylated indoles (**3**) and *bis*(indol-3-yl) derivatives (**4**) can be found via the ‘‘Supplementary Content’’ section of this article’s webpage.

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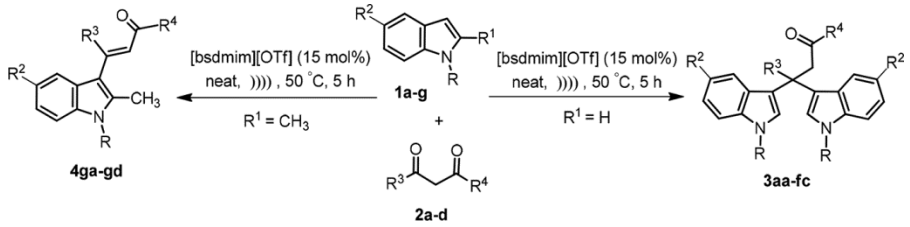
Table 1 Optimization of reaction conditions for **3aa**[a]

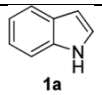
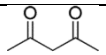
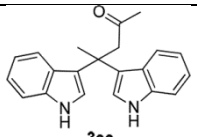
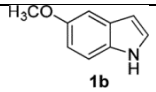
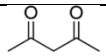
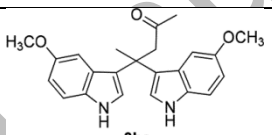
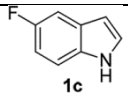
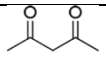
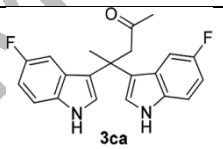
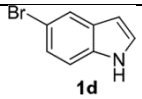
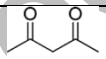
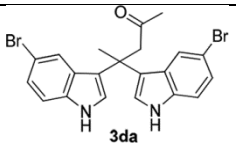
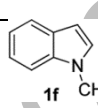
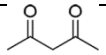
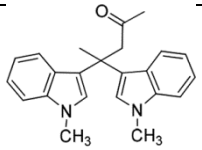
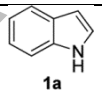
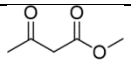
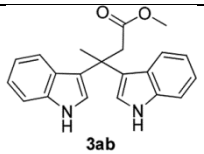
Entry	Catalyst (mol %)	Temp. (°C)	Solvent	(%) Yield[b]
1	[bsdmim][PF_6] (10)	25	-	33
2	[bsdmim][HSO_4] (10)	25	-	56
3	[bsdmim][OTf] (10)	25	-	72
4	pTSA (10)	25	-	50
5	CF_3SO_3H (10)	25	-	64
6	-	25	-	NR[c]
7	[bsdmim][OTf] (5)	25	-	56
8	[bsdmim][OTf] (15)	25	-	78
9	[bsdmim][OTf] (20)	25	-	76
10	[bsdmim][OTf] (15)	50	-	82
11	[bsdmim][OTf] (15)	80	-	67
12	[bsdmim][OTf] (15)	50	CH_3CN	65
13	[bsdmim][OTf] (15)	50	H_2O	48
14	[bsdmim][OTf] (15)	50	EtOH	Trace
15	[bsdmim][OTf] (15)	50	DCE	45
16	[bsdmim][OTf] (15)	50	Toluene	63
17	[bsdmim][OTf] (15)	50	-	94[d]

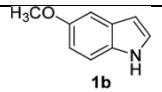
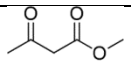
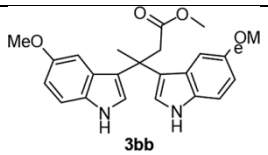
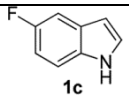
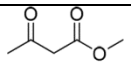
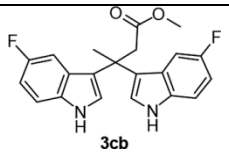
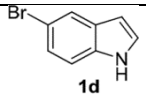
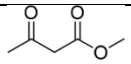
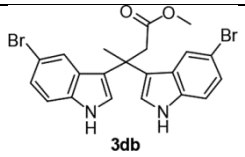
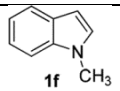
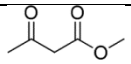
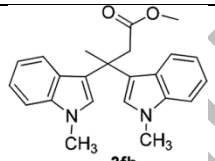
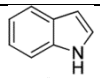
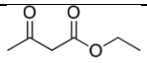
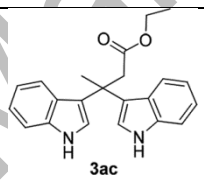
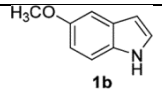
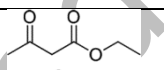
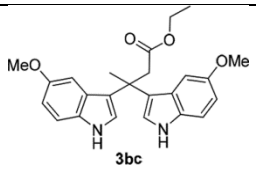
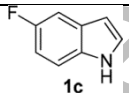
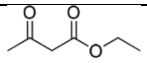
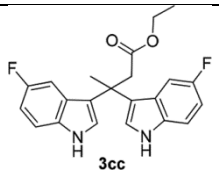
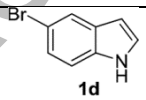
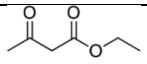
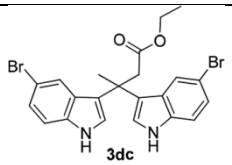
[a]Reaction conditions: Indole (1.0 mmol), acetylacetone (0.6 mmol), 24 h. [b]Isolated yield.

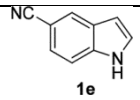
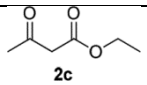
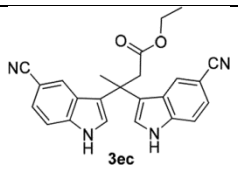
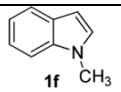
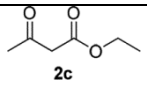
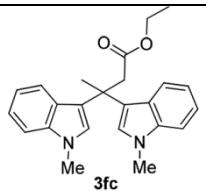
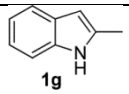
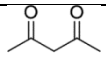
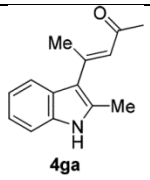
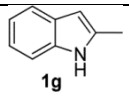
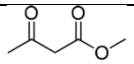
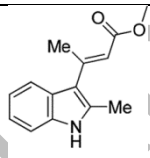
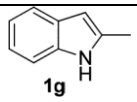
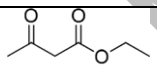
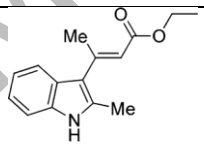
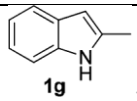
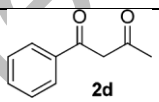
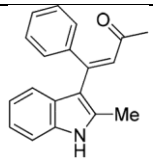
[c]NR = No reaction. [d]Under ultrasound irradiations (50W, 40 KHz) after 5 h.

Table 2 Synthesis of 3-alkenylated indoles and *bis*(indol-3-yl) derivatives using [bsdmim][OTf] under ultrasound irradiation.[a]



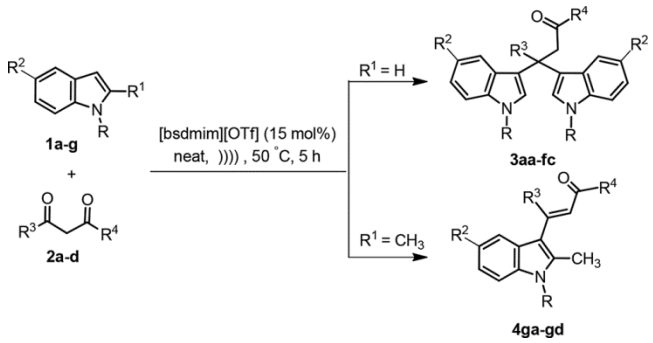
Entry	1	2	¾	Yield (%)[b]
1	 1a	 2a	 3aa	94
2	 1b	 2a	 3ba	81
3	 1c	 2a	 3ca	76
4	 1d	 2a	 3da	76
5	 1f	 2a	 3fa	82
6	 1a	 2b	 3ab	89

7	 1b	 2b	 3bb	70
8	 1c	 2b	 3cb	80
9	 1d	 2b	 3db	78
10	 1f	 2b	 3fb	74
11	 1a	 2c	 3ac	75
12	 1b	 2c	 3bc	68
13	 1c	 2c	 3cc	73
14	 1d	 2c	 3dc	70

15	 1e	 2c	 3ec	86
16	 1f	 2c	 3fc	75
17	 1g	 2a	 4ga	84
18	 1g	 2b	 4gb	80
19	 1g	 2c	 4gc	78
20	 1g	 2d	 4gd	72

[a]Reaction conditions: indole (1.0 mmol), acetylacetone (0.6 mmol), ultrasound irradiation (50W, 40 KHz) 5 h, 50 °C. [b]Isolated yield

Scheme 1. Synthesis of 3-alkenylated indoles and *bis*(indol-3-yl) derivatives catalyzed by SO_3H-IL under ultrasound irradiation.



Scheme 2. Plausible reaction mechanism.

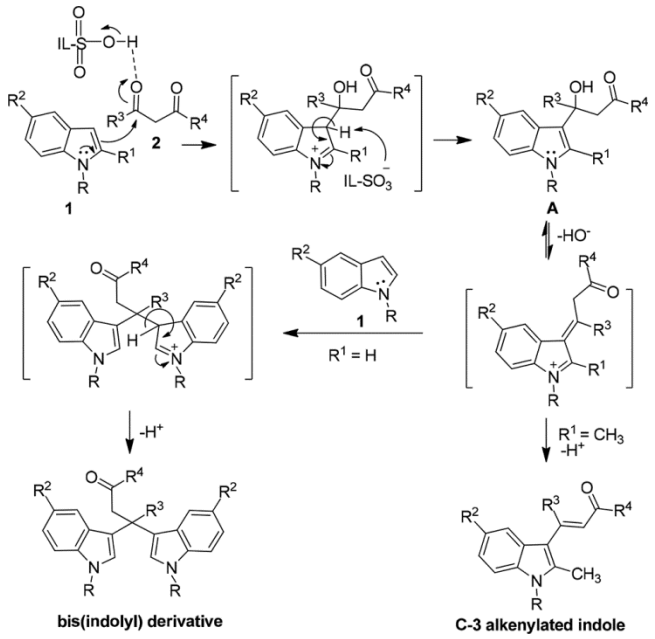


Figure 1. Recyclability study of [bsdmim][OTf] in the synthesis of **3aa**.