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ORIGINAL PAPER

Green route for the synthesis of 3-substituted indoles using [bmim]-HSO_4 as non-halogenated ionic liquid

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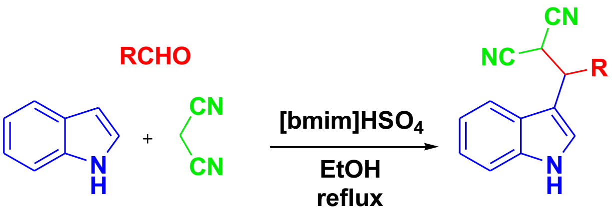
Abstract

In this paper, an effective procedure is reported for the synthesis of 3-substituted indoles via the one-pot three-component reaction of an aldehyde, malononitrile or ethyl cyanoacetate and indole in the presence of [bmim]HSO_4 in ethanol under reflux condition. The advantages of this protocol are the synthesis of some novel 3-substituted indoles containing furyl, 4-hydroxyphenyl, and styryl nuclei that are very important in pharmaceutical and drug discovery research in comparison to previously reported results, and the use of non-halogenated ionic liquid.

Graphic abstract



Keywords One-pot · 3-Substituted indoles · [bmim · HSO_4 · Ionic liquid

Introduction

Multi-component reactions (MCRs) are synthetic methodologies for the preparation of compound libraries, which is pivotal focal point of research activity in the field of modern medicinal and combinatorial chemistry [1, 2]. These reactions are offering many advantages, as they allow the simple operation by which organic structures with impressive molecular complexity can be assembled into target molecules with high variability, atom efficiency, and high reaction yield [3–7].

3-Substituted indoles are important chemical intermediates and pharmaceutical precursors [8] and pharmacologically active analogues of synthetic ergine, gramine, and sumatriptan production (Scheme 1), and as aromatase and integrase inhibitors for breast cancer and HIV-1 therapies, respectively [9].

Existing protocols for the preparation of 3-substituted indoles suffer from disadvantages including long reaction times, high temperatures, and the requirement for stoichiometric reagent quantities, or deliver unsatisfactory yields or utilize homogeneous catalysts with associated product separation issues [10–13]. Lately, many researchers have been focused on the application of ionic liquids (ILs) in organic reactions both as solvent and as catalyst [14–16]. Owing to this property, ILs became very important materials that can be selected for the chemical synthesis such as the providing of 3-substituted indoles [17]. Also, halogenated ILs are commercially available, but are of limited interest to industry due to environmental and health reasons [18].

New active, low cost and green catalysts employing earth abundant elements are thus sought for operation under mild

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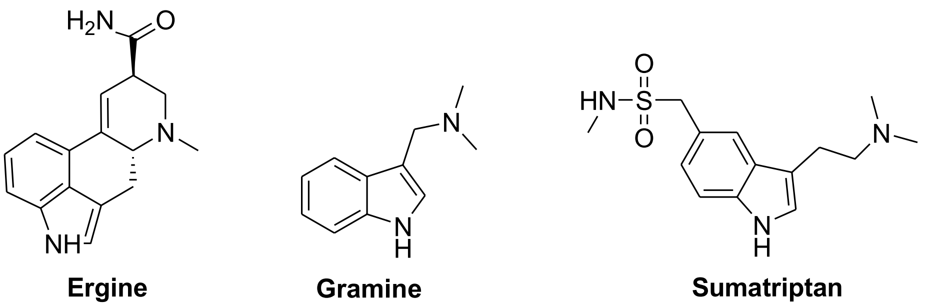
Scheme 1



Scheme 2

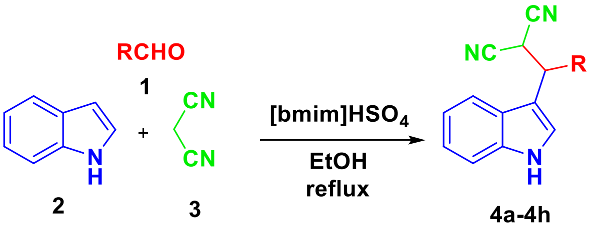


Table 1 Optimization of the catalyst amount in the synthesis of **4e**

Entry	Catalyst/mol%	Yield/%[a]
1	Free	Trace
2	10	79
3	15	90
4	20	95
5	25	95

[a] Reaction condition: benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), [bmim]HSO_4, and in 5.0 cm^3 refluxing ethanol

Table 2 The effect of different temperature in the synthesis of **4e**

Entry	Temp.	Time/h	Yield/%[a]
1	r.t.	6.0	10
2	Reflux	1.0	95

[a] Reaction condition: benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), [bmim]HSO_4 (20 mol%), and in 5.0 cm^3 refluxing ethanol

Table 3 The effect of varying solvent in the synthesis of **4e**

Entry	Solvent	Yield/%[a]
1	Free	60
2	MeOH	67
3	*n*-Hexane	55
4	EtOH	95
5	CH_2Cl_2	40

[a] Reaction condition: benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), [bmim]HSO_4 (20 mol%), and in 5.0 cm^3 refluxing solvent at 1.0 h

reaction conditions. In this communication, we enclosed the synthesis of 3-substituted indoles via the one-pot three-component reaction of aldehydes, malononitrile or ethyl cyanoacetate and indole in the presence of [bmim]HSO_4 in ethanol under reflux condition (Scheme 1) (Scheme 2).

Results and discussion

To achieve optimization reaction condition, benzaldehyde, indole, and malononitrile was mixed in ethanol without ionic liquid that desired product was resulted in low yield ($<10\%$). The model reaction was repeated in the presence of different amounts of [bmim]HSO_4 such as 5, 10, 15, 20, and 25 mol%. The best results were found in 20 mol% of the ionic liquid. The increasing of ionic liquid amount to 25 mol% did not effect to reaction yield (Table 1).

Also, we examined model reaction in different solvent such as CH_2Cl_2, *n*-hexane, H_2O, MeOH, EtOH, and without solvent, in different temperatures as well as ambient temperature (Tables 2, 3). However, the best reaction condition was obtained in 20 mol% of [bmim]HSO_4 and in ethanol as green solvent under reflux condition.

To generalize this optimizing reaction condition, as shown in Table 1, a variety of aldehydes, malononitrile, indole, and [bmim]HSO_4 were readily converted to the corresponding 3-substituted indoles in good-to-excellent isolated yields over short reaction times in ethanol under reflux condition. To investigate the substituent effect, a wide variety of aldehydes containing an electron withdrawing (-F and -NO_2) or electron donating (-OH and -Me) group were utilized. Found that aryl aldehydes both bearing electron donating groups and with electron withdrawing groups react in sufficient condition and short reaction time (Table 1). On the other hand, the yields of obtained products were good-to-excellent without formation of any side products such as bis(indolyl) methanes that are normally obtained under acids condition. In each case, the reaction media is clean and this one-pot, three-component procedure revealed some improvements and advantages over existing methods. However, a significant fraction of this present work is the application of [bmim][HSO$_4$] as non-halogenated ILs, which are not only commercially available, but also greener and non-toxic candidate for the synthesis of 3-substituted indoles rather than the halogenated ILs. The other features of this new method are simple isolation and purification of the products, reusable catalyst and synthesis of three new derivative compounds (Table 4).

Proposed mechanism [19] for the synthesis of 3-substituted indoles has also been shown in Scheme 2. At first, malononitrile as a relatively acidic compound with pK_A of 11 is ionized to malononitrile anion **5**. Then ionic liquid activated-aldehyde **1** react with malononitrile anion **5** in Knoevenagel condensation reaction to afford arylidene compound **6**. Michael reaction indole **2** with **6** give intermediate **7** following H-shift to obtain 3-substituted indole **4** (Scheme 3).

To compare the merits of this catalytic method with those of previously reported ones, results of the formation of **4e** were compiled in the presence of a variety of acidic catalysts. From the results given in Table 5, the advantages of our method are evident, regarding the catalyst amounts, which are very important in the chemical industry especially when they are combined with easy separation, short reaction time and high yield accompanied by the synthesis of some new compounds **4f**, **4g**, and **4h** (Table 1), shows that our procedure is a good achievement besides previously reported studies.

Conclusion

In summary, [bmim]HSO$_4$ has been used for the first time as an effective ionic liquid for the synthesis of polysubstituted pyrroles through one-pot, three-components reaction of indole, aldehydes, and malononitrile. Mild reaction conditions, wide substrate scope, excellent functional group tolerance, good overall yields, use of an inexpensive, not halogenated IL, and environmentally benign catalyst are the key advantages of the present method.

Experimental

Melting points were measured using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on Perkin Elmer FT-IR spectrometer scanning between 4000 and 400 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-300 MHz NMR instrument. Mass spectra were taken on an Agilent 5973 Network Mass Selective Detector instrument.

General procedure for the preparation of 3-substituted indoles

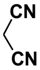
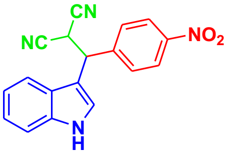
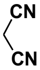
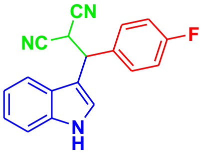
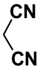
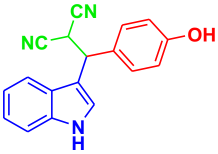
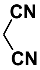
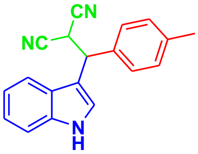
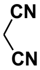
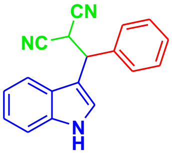
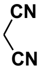
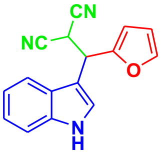
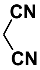
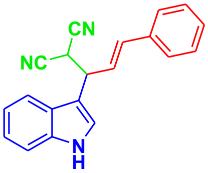
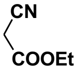
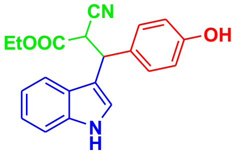
To a mixture of the aldehyde (1 mmol), malononitrile or ethyl cyanoacetate (1 mmol), indole (1 mmol) in 5.0 cm^3 ethanol was added [bmim]HSO$_4$) (20 mol%). The reaction mixture was stirred and heated under reflux condition for 1–1.5 h and the reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. The precipitate was filtered off and recrystallized from ethanol to afford the desired compound.

The synthesis of compounds **4e** was also used to assess the reusability of the [bmim]HSO$_4$ catalyst. After separation of the product, the moderate liquor containing a solution of [bmim][HSO$_4$] in ethanol was evaporated. Then, the residue was solved in 15 cm^3 water and 15 cm^3 dichloromethane was added and the catalyst was extracted by separatory funnel. Aqueous layer containing IL was evaporated and IL was obtained after drying on oven for 3 h and used in the synthesis of **4e** for some runs. The catalyst could be reused at least four times without appreciable loss of efficiency, yield of **4e** (run no.): 95% (1), 88% (2), 88% (3), 83% (4).

2-[(Furan-2-yl)(1*H*-indol-3-yl)methyl]malononitrile (4f, $C_{16}H_{11}N_3O$) To 0.096 g furfural (1.0 mmol), 0.066 g malononitrile (1.0 mmol), and 0.117 g indole (1.0 mmol) dissolved in 5.0 cm^3 EtOH and 0.047 g [bmim]HSO$_4$) (0.2 mmol) was added. The mixture was refluxed for 75 min, cooled, and filtered. Recrystallization from ethanol afforded 0.214 g (82%) **4f**. White solid; m.p.: 98–100 °C; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 4.42$ (d, $J = 6.8$ Hz, 1H), 4.88 (d, $J = 6.7$ Hz, 1H), 6.07 (d, $J = 3.5$ Hz, 1H), 6.86 (dd, $J = 3.5$ Hz, 1.8 Hz, 1H), 7.13 (t, $J = 7.4$ Hz, 1H), 7.20–7.28 (m, 2H), 743–7.52 (m, 3H), 8.34 (s, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 28.3$, 41.4, 107.6, 111.1, 111.9, 112.9, 113.4, 113.8, 119.9 ppm; IR (KBr): $\bar{\nu} = 3414$, 2840, 2225, 1605, 1582, 1458 cm^{-1}.

2-[(*E*)-1-(1*H*-Indol-3-yl)-3-phenylallyl]malononitrile (4g, $C_{20}H_{15}N_3$) To 0.132 g cinnamaldehyde (1.0 mmol), 0.066 g malononitrile (1.0 mmol), and 0.117 g indole (1.0 mmol) dissolved in 5.0 cm^3 EtOH and 0.047 g [bmim]HSO$_4$) (0.2 mmol) was added. The mixture was refluxed for 67 min, cooled, and filtered. Recrystallization from ethanol afforded 0.213 g (72%) **4g**. Yellow solid; m.p.: 110–112 °C; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 4.14$ (d, $J = 6.8$ Hz, 1H), 4.51 (d, $J = 6.8$ Hz, 1H), 6.36 (dd, $J = 15.42$ Hz, 7.53 Hz, 2H), 7.17–7.50 (m, 10H), 8.36 (s, 1H) ppm; ^{13}C NMR

Table 4 Synthesis of 3-substituted indoles using [bmim]HSO_4

Entry	Aldehyde	Nitrile	Product	Time /min	Yield /%	M.p. /°C [Lit.]
1	4-NO_2-C_6H_4CHO		 **4a**	70	86	165-167 [19]
2	4-F-C_6H_4CHO		 **4b**	65	94	110-114 [20]
3	4-OH-C_6H_4CHO		 **4c**	80	88	170-172 [21]
4	4-Me-C_6H_4CHO		 **4d**	65	82	118-120 [21]
5	C_6H_5CHO		 **4e**	60	95	79-80 [19]
6	Furfural		 **4f**	75	82	98-100
7	*trans*- $C_6H_5CH=CHCHO$		 **4g**	67	72	110-112
8	4-OH-C_6H_4CHO		 **4h**	70	64	95-97

Scheme 3

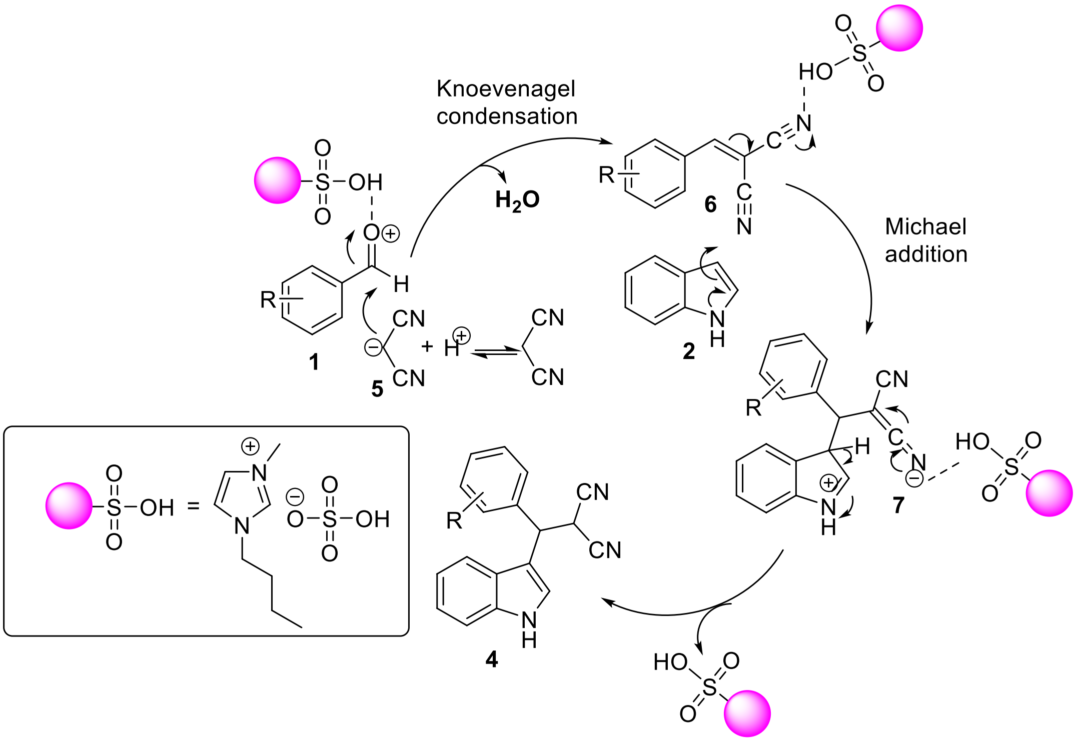


Table 5 Comparison of efficiency of [bmim]HSO_4 and the others acidic catalysts in the synthesis of **4e**

Entry	Catalyst	Time/h	Temp./°C	Solvent	Yield/%	Ref
1	Copper(II) sulfonato salen complex (5 mol%)	6	60	H_2O	96	[10]
2	Bis(*N*-*t*-butyl-pyrrole-2-aldiminato)copper(II) (5 mol%)	12	30	H_2O	96	[22]
3	PEG-200 (1.5 g)	28	r.t	H_2O	95	[11]
4	$H_5PW_{10}V_2O_{40}VOx/SBA\text{-}15\text{-}NH_2$ (0.03 g)	0.3	50	–	95	[19]
5	[bmim]HSO_4 (20 mol%)	1	reflux	EtOH	95	This work

(75 MHz, $CDCl_3$): $\delta = 28.6$, 42.0, 111.7, 112.5, 113.1, 114.2, 120.3, 120.9, 121.8, 123.5, 126.2, 126.4, 127.4, 28.5, 128.9, 129.2, 130.1, 135.2, 143.9 ppm; IR (KBr): $\bar{\nu} = 3413$, 3060, 2257, 1550, 1458 cm^{-1}.

Ethyl 2-cyano-3-(4-hydroxyphenyl)-3-(1*H*-indol-3-yl) propanoate (4h, $C_{20}H_{18}N_2O_3$) To 0.122 g 4-hydroxybenzaldehyde (1.0 mmol), 0.113 g ethyl 2-cyanoacetate (1.0 mmol), and 0.117 g indole (1.0 mmol) dissolved in 5.0 cm^3 EtOH and 0.047 g [bmim]HSO_4) (0.2 mmol) was added. The mixture was refluxed for 70 min, cooled, and filtered. Recrystallization from ethanol afforded 0.213 g (64%) **4h**. Yellow solid; m.p.: 95–97 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.02$–1.06 (m, 6H), 3.44 (s,1H), 3.49 (s, 1H), 3.98–4.03 (m, 4H), 4.40 (d, $J = 7.4$, 1H), 4.56 (d, $J = 7.4$, 1H), 5.38 (d, $J = 7.5$, 1H), 5.50 (d, $J = 7.4$, 1H), 6.84–6.92 (m, 4H), 7.04–7.76 (m, 12H), 7.80–7.88 (m, 2H), 8.35 (s, 1H), 8.37 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$, 14.0, 41.9, 42.4, 42.9, 43.6, 62.7, 111.4, 111.7, 112.5, 112.9, 115.6, 116.5, 116.9, 117.4, 118.6, 119.7, 120.8, 121.2, 121.9, 122.5, 122.9, 123.4, 126.7, 127.4, 127.9, 135.8, 136.2, 145.2, 145.6, 160.2, 160.8, 168.8, 169.5 ppm; IR (KBr): $\bar{\nu} = 3383$, 3059, 2261, 1558, 1459 cm^{-1}.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00706-021-02782-y.

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