An Efficient One-Pot Synthesis of Bis-Indolylmethanes Containing Pyrazolyl Catalyzed by Brønsted Acidic Ionic Liquid Under Solvent-Free Conditions

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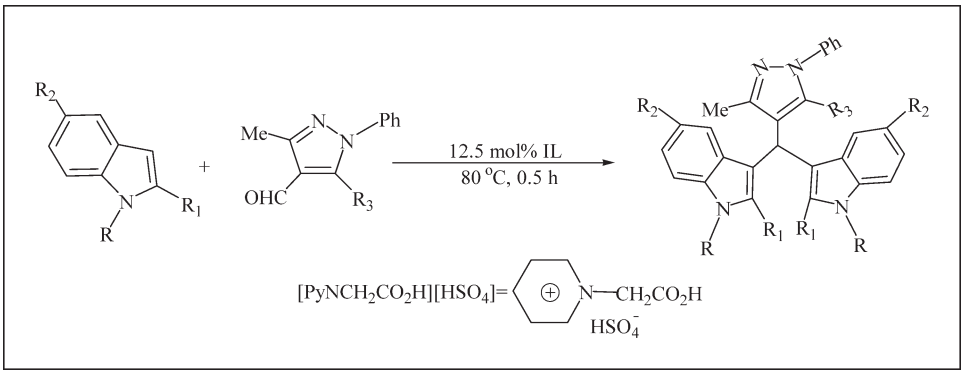

Brønsted acidic ionic liquid [$PyNCH_2CO_2H$][HSO_4] was found to be an effective catalyst for the condensation reactions of indoles with various 4-formylpyrazoles to afford the corresponding bis-indolylmethanes containing pyrazole under solvent-free conditions. The satisfactory results were obtained with excellent yields, short reaction time, and simplicity in the experimental procedure.

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INTRODUCTION

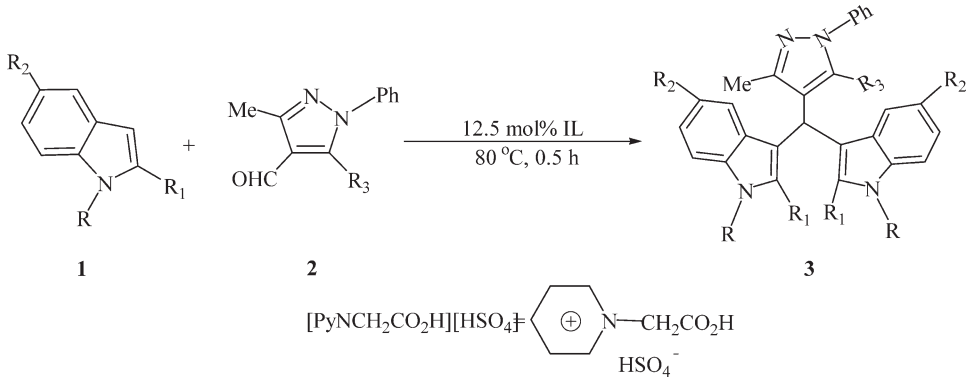
In recent years, bis-indolylmethanes have received much attention due to their potential applications in the pharmaceutical and agrochemical industries [1]. Consequently, numerous methods describing the preparation of bis-indolylmethanes have been reported in the literature using protic acids or Lewis acids as catalyst including $AlPW_{12}O_{40}$ [2], $LiClO_4$ [3], Zeokarb-225 [4], oxone [5], $HClO_4$-SiO_2 [6], oxalic acid [7], HTP or supported HTP [8] and so on. However, some of the previously reported methods suffer from several setbacks, such as expensive and highly toxic catalysts, long reaction time, and low yield. To avoid these limitations, there is a need for simple environmentally friendly procedures for the preparation of bis-indolylmethanes.

Recently, ionic liquids (ILs) have attracted increasing interest in the context of Green Chemistry owing to their advantageous properties [9,10]. Due to their unique biological properties, pyrazole derivatives have attracted much attention [11]. In continuation of our interest in ILs applications for green chemistry [12], we studied the possibility to synthesize bis-indolylmethanes containing pyrazolyl using 4-formylpyrazole instead of ordinary aldehydes as substrates and using Brønsted acidic ionic liquid [$PyNCH_2CO_2H$][HSO_4] as catalyst under solvent-free conditions. Here, an efficient and practical method for the synthesis of target compounds is described and none of them has yet been reported in the literature (Scheme 1).

RESULTS AND DISCUSSION

Various reaction parameters, such as reaction time, temperature, and the molar ratio of ionic liquid to the substrate were studied using the reaction of indole with 5-chloro-4-formyl-3-methyl-1-phenylpyrazole as a model and the results were presented in Table 1. The influence of the molar ratio of ionic liquid to the substrate was examined for the model reaction first. Raising the molar ratio of ionic liquid/substrate from 0 to 12.5 resulted in increasing in yield from 0 to 99% (entries 1–5), while the molar ratio of ionic liquid to the substrate over 12.5 resulted in decreasing in yield (entry 6). Then the effect of reaction time on yield was investigated (entries 5 and 7–10). The results showed the reaction nearly tend to equilibrium after 30 min. Excessively prolonged time did not change the yield significantly. At last, the influence of the reaction temperature on the yield was also investigated (entries 10–13). It was clear that the highest yield was provided when the reaction temperature was

Scheme 1



80°C. Therefore, the best condition uses 0.125:2:1 mole ratio of ionic liquid, indole, and 4-formylpyrazole at 80°C for 30 min.

To examine the scope and generality of this procedure, we extended the methodology to different indoles and 4-formylpyrazoles. The results were presented in Table 2. In general, the reaction proceeded easily and the corresponding adducts were isolated in excellent yields. A proposed reaction mechanism for the condensation reactions of indoles with 5-chloro-4-formyl-3-methyl-1-phenylpyrazole was presented in Scheme 2. The 5-chloro-4-formyl-3-methyl-1-phenylpyrazole was first activated by proton and then carried out electron rich β-position of indole ring. After loss of water, an intermediate **4** was generated. Then the intermediate 4 was served as an electrophile to attack a second molecule of indole to form the product.

In conclusion, we described an efficient and simple method for the synthesis of a series of novel bis-indolylmethanes containing pyrazole using 4-formylpyrazole instead of ordinary aldehydes as substrate and using Brønsted acidic ionic liquid $[PyNCH_2CO_2H][HSO_4]$ as catalyst under solvent-free conditions. Hence, a clean and environmentally friendly strategy for the synthesis of bis-indolylmethanes is developed. At the same time, it is an important supplement to the existing methods for the synthesis of bis-indolylmethanes.

EXPERIMENTAL

Melting points were determined using a Büchi B-540 instrument and are uncorrected. The IR spectra were obtained as potassium bromide pellets with a FTS-40 spectrometer (BIO-RAD). The ^{1}H-NMR spectra were measured on a Varian Inova-400 spectrometer using TMS as an internal standard in $CDCl_3$ or DMSO-d_6. Elemental analysis (C, H, N) was performed on a Perkin-Elmer Analyzer 2400. The Brønsted acidic ionic liquid $[PyNCH_2CO_2H][HSO_4]$ was synthesized according to previous literature [13].

General procedure for the synthesis of bis-indolylmethane containing pyrazolyl. A mixture of 5-chloro-4-formyl-3-methyl-1-phenylpyrazole (1 mmol), indole (2 mmol), and Brønsted acidic ionic liquid $[PyNCH_2CO_2H][HSO_4]$ (0.125 mmol) was reacted at 80°C for 0.5 h under solvent-free conditions. After cooling, the reaction mixture was poured onto crushed ice (30 g). The resulting precipitate was filtered under suction, and then recrystallized from ethanol to afford the pure product **3a**. The same procedure was used for the synthesis of products **3b–j**. The physicochemical data for the synthesized compounds are as shown below.

Bis-(indol-3-yl)(5-chloro-3-methyl-1-phenylpyrazol-4-yl) methane (3a). Mp 196–198°C. IR (KBr): 3372, 2921, 1610, 1512, 1479, 1366, 738 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.99 (s, 3H, CH_3), 5.83 (s, 1H), 6.87–7.58 (m, 15H, ArH), 10.87 (brs, 2H, NH); Anal Calcd for $C_{27}H_{21}N_4Cl$: C, 74.22; H, 4.84; N, 12.82. Found: C, 74.36; H, 4.89; N, 12.74.

Bis-(indol-3-yl)(3-methyl-5-phenoxyl-1-phenylpyrazol-4-yl) methane (3b). Mp 209–210°C; IR (KBr): 3365, 2911, 1609, 1552, 1454, 1362, 737 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.99 (s, 3H, CH_3), 5.58 (s, 1H), 6.76–7.59 (m, 20H, ArH), 10.75 (brs, 2H, NH) Anal Calcd for $C_{33}H_{26}N_4O$: C, 80.14; H, 5.30; N, 11.33. Found: C, 80.26; H, 5.39; N, 11.24.

Bis-(2-methylindol-3-yl)(5-chloro-3-methyl-1-phenylpyrazol-4-yl)methane (3c). Mp 196–198°C; IR (KBr): 3385, 2921, 1599, 1502, 1459, 1356, 742 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6):

Table 1

Effect of different reaction conditions for condensation of 3a.[a]

Entry	Temperture (°C)	Time (min)	Catalyst (mol%)	Yield (%)[b]
1	100	120	0	0
2	100	120	2.5	32
3	100	120	5	58
4	100	120	10	89
5	100	120	12.5	99
6	100	120	15	94
7	100	10	12.5	68
8	100	20	12.5	87
9	100	60	12.5	99
10	100	30	12.5	98
11	35	30	12.5	43
12	55	30	12.5	81
13	80	30	12.5	98

[a] Reaction conditions: indole (2 mmol), 5-chloro-4-formyl-3-methyl-1-phenylpyrazole (1 mmol) and catalyst.
[b] Isolated yields.

Table 2

$[PyNCH_2CO_2H][HSO_4]$-catalyzed one-pot synthesis of the bis-indolylmethanes containing pyrazole 3.[a]

Product	R	R^1	R^2	R^3	Yields (%)[b]
3a	H	H	H	Cl	98
3b	H	H	H	C_6H_5O	94
3c	H	CH_3	H	Cl	92
3d	H	CH_3	H	C_6H_5O	91
3e	H	CH_3	H	*p*-Cl-C_6H_4O	87
3f	H	H	CH_3O	Cl	94
3g	H	H	Br	C_6H_5O	85
3h	CH_3	H	H	Cl	98
3i	CH_3	H	H	C_6H_5O	93
3j	CH_3	H	H	*p*-Cl-C_6H_4O	89

[a] Reaction conditions: 4-formylpyrazoles (1mmol), indole or substituted indoles (2 mmol), catalyst (12.5 mol%), 0.5 h, 80 °C.
[b] Isolated yields.

δ = 1.88 (s, 3H, CH_3), 2.03 (s, 6H, 2×CH_3), 5.56 (s, 1H), 6.89–7.73 (m, 13H, ArH), 10.51 (brs, 2H, NH); Anal Calcd for $C_{29}H_{25}N_4Cl$: C, 74.91; H, 5.42; N, 12.05. Found: C, 74.76; H, 5.49; N, 12.16.

Bis-(2-methylindol-3-yl)(3-methyl-5-phenoxyl-1-phenylpyrazol-4-yl)methane (3d). Mp 280–281°C; IR (KBr): 3377, 2910, 1597, 1503, 1455, 1363, 744 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.80 (s, 3H, CH_3), 1.94 (s, 6H, 2×CH_3), 5.56 (s, 1H), 6.32–7.55 (m, 18H, ArH), 10.51 (brs, 2H, NH); Anal Calcd for $C_{35}H_{30}N_4O$: C, 80.43; H, 5.79; N, 10.72. Found: C, 80.26; H, 5.69; N, 10.84.

Bis-(2-methylindol-3-yl)(5-(4-chlorophenoxyl)-3-methyl-1-phenylpyrazol-4-yl)methane (3e). Mp 269–272°C; IR (KBr): 3375, 2912, 1594, 1503, 1484, 1380, 735 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.00 (s, 3H, CH_3), 2.12 (s, 6H, 2×CH_3), 5.71 (s, 1H), 6.07–7.55 (m, 17H, ArH), 10.51 (brs, 2H, NH); Anal Calcd for $C_{35}H_{29}N_4OCl$: C, 75.46; H, 5.25; N, 10.06. Found: C, 75.36; H, 5.19; N, 10.24.

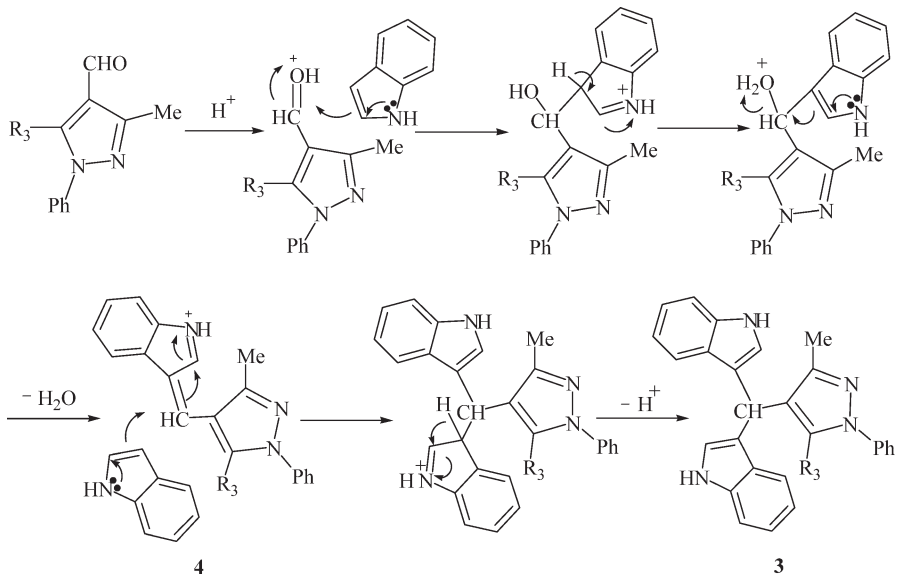
Bis-(5-methoxylindol-3-yl)(5-chloro-3-methyl-1-phenyl pyrazol-4yl)methane (3f). Mp 125–127°C; IR (KBr): 3386, 2968, 1578, 1502, 1484, 1365, 783 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.96 (s, 3H, CH_3), 3.63 (s, 6H, 2×OCH_3), 5.73 (s, 1H), 6.73–7.56 (m, 13H, ArH), 10.72 (brs, 2H, NH); Anal Calcd for $C_{29}H_{25}N_4O_2Cl$: C, 70.08; H, 5.07; N, 11.27. Found: C, 70.22; H, 4.98; N, 11.14.

Bis-(5-bromoindol-3-yl)(3-methyl-5-phenoxyl-1-phenyl pyrazol-4-yl)methane (3g). Mp 175–177°C; IR (KBr): 3424, 2923, 1594, 1503, 1454, 1380, 751 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.99 (s, 3H, CH_3), 5.57 (s, 1H), 6.64–7.75 (m, 16H, ArH), 11.00 (brs, 2H, NH); Anal Calcd for $C_{33}H_{24}N_4OBr_2$: C, 60.76; H, 3.71; N, 8.59. Found: C, 60.88; H, 3.78; N, 8.74.

Bis-(1-methylindol-3-yl)(5-chloro-3-methyl-1-phenylpyrazol-4yl)methane (3h). Mp 190–193°C;IR (KBr): 2930, 1595, 1492, 1462, 1371, 740 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.99 (s, 3H, CH_3), 3.78 (s, 6H, 2×CH_3), 5.83 (s, 1H), 6.96–7.58 (m, 15H, ArH); Anal. Calcd for $C_{29}H_{25}N_4Cl$: C, 74.91; H, 5.42; N, 12.05. Found: C, 74.76; H, 5.49; N, 12.21.

Bis-(1-methylindol-3-yl)(3-methyl-5-phenoxyl-1-phenylpyrazol-4yl)methane (3i). Mp 184–186°C; IR (KBr): 2929, 1596, 1579, 1470, 1368, 739 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.11 (s, 3H, CH_3), 3.61 (s, 6H, 2×CH_3), 5.62 (s, 1H),

Scheme 2



6.57–7.58 (m, 20H, ArH); Anal Calcd for $C_{35}H_{30}N_4O$: C, 80.43; H, 5.79; N, 10.72. Found: C, 80.56; H, 5.71; N, 10.84.

Bis-(1-methylindol3-yl)(5-(4-chlorophenoxyl)-3-methyl-1-phenylpyrazol-4-yl)methane (3j). Mp 172–174°C.IR (KBr): 2915, 1584, 1563, 1494, 1378, 735 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): $\delta = 2.17$ (s, 3H, CH_3), 3.60 (s, 6H, $2\times CH_3$), 5.62 (s, 1H), 6.40–7.56 (m, 19H, ArH); Anal. Calcd for $C_{35}H_{29}N_4OCl$: C, 75.46; H, 5.25; N, 10.06. Found: C, 75.28; H, 5.18; N, 10.24.

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