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A Sustainable Green Approach for Synthesis of Bis(indolyl) Methanes in Ionic Liquid

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ABSTRACT

A novel and eco-friendly synthetic protocol has been established to prepare bisindolyl methanes using an easily recyclable ionic liquid and a minimal amount of sulfuric acid. This synthetic approach involves coupling two indole molecules with aromatic aldehydes under mild conditions. The developed synthetic route has remarkable benefits like high percentage yields, shorter time of reaction, and straightforward product isolation. Additionally, the employed ionic liquid was effectively recycled which indicates the sustainability of the synthetic approach.

Keywords: Ionic Liquid (ILs), HEMImBr (1-(hydroxymethyl)-3-methyl-1H-imidazol-3-ium bromide) Bis(indolyl) Methanes.

INTRODUCTION

Green chemistry is crucial for the present and the future because it offers a valuable concept for environmentally sound protection. The principles of green chemistry must be considered by chemists, researchers, and the pharmaceutical industry while creating the reaction mechanism and choosing the catalyst. Using green chemistry techniques, we may reduce waste, utilize less harmful chemicals, receive the atom economy, and protect the environment.

However, the limited solubility of synthesized BIMs in aqueous solvents presents a challenge. To minimize this issue, phase transfer catalysts such as ionic liquids are increasingly recognized as potential environmentally friendly catalysts and solvents due to their low vapour pressure, thermal and chemical stability, solvating ability, and ease of recycling. Ionic liquids are formed by combining pyridinium or imidazolium cations with different inorganic or organic anions to create liquid salts, they have a lot of potential uses in different fields such as electrochemistry[1], catalysis[2], biocatalysis, chemical engineering, and synthesis of heterocyclic compounds[3].

Heterocycles are important structural components in both marketed pharmaceuticals and drug discovery targets, with nitrogen-containing

rings playing a particularly significant role in drug development due to their diverse pharmacological and therapeutic properties[4].

Bis(indolyl)alkanes are a significant class of organic nitrogen compounds obtained from natural sources that have been shown to contribute to biological activity[5,6]. They serve as a desirable framework in pharmaceutical chemistry and have been demonstrated to exhibit a range of pharmacological actions, including antimicrobial[7], Antifungal[8], Antioxidant[9], anti-HIV[10], anti-inflammatory activities[11] and Anticancer[12] activities.

Recently, several techniques for employing multicomponent processes to create bis(indolyl) alkanes have been found. such as Immobilized ionic liquids on Fe_3O_4 nanoparticles[13], Chitosan supported ionic liquid (CSIL)[14], $[(CH_2)_4SO_3HMIM][HSO_4]$[15], Silica-Supported Acidic Ionic Liquid[16], Dabco-Base Ionic Liquids[17], Tetracationic Ammonium Salts[18], Transition metal base ionic liquid[19], $[bmim][MeSO_4]$[20], Morpholinium bisulfate[21], Pentafluorophenyl ammonium triflate[22], tetracationic acidic organic salt[23] this catalyst has been used to synthesize these compounds.

However, there is scope for improvement in developing a low-cost, cleaner, and environmentally friendly approach with a quicker reaction time.

This paper describes a modest, easy, green, and successful technique for manufacturing BIMs at 80^0C utilising 1(2-hydroxyethyl)-3-methylimidazolium bromide as a solvent and a few drops of Sulfuric acid as a catalyst.

MATERIALS AND METHODS

All common reagents and solvents were purchased from commercial suppliers and were not purified further. Ionic Liquids were synthesized using some modifications previously reported in the literature[24,25]. The reaction progress was monitored by carrying out thin layer chromatography (TLC) using silica gel plates, and Melting points were measured using the Digital Analab Scientific Instrument. The FT-IR spectra were recorded using an Alpha II Bruker spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance Neo 500 MHz spectrometer in $CDCl_3$ or DMSO-d_6. Mass spectra were performed on a Waters Q-ToF Micro LC-MS spectrometer.

EXPERIMENTAL

Preparation of ILs

Pyridine (1 mol)/1 Methyl imidazole (1 mol) and 1-bromopropane (1.1 mol)/2 Bromoethanol (1.1 mol) were placed in a 50 mL two-necked round-bottomed flask. The flask was then placed in an oil bath and heated to 90°C. The mixture was then stirred continuously for 45 to 60 minutes. The formation of the ionic liquid was confirmed by ^{1}H NMR, ^{13}C CMR, and MS spectroscopy. The excess starting compounds were removed by extracting the mixture with 5 mL of ethyl acetate. The final compound was then dried in a vacuum oven at 80°C for 4 hours.

Synthesis Methods for Bis(Indolyl)Methanes-

A mixture of Indole (2 mmol), aromatic aldehyde (1 mmol) and HEMImBr 2 mL in a 50 mL round bottom flask in the presence of 2 drops of sulfuric acid, is heated at 80°C in an oil bath for 23-28 minutes. When the reaction is completed (monitored by TLC), the reaction mixture is allowed to cool at room temperature. Then add approximately 10 g of crushed ice to the above mixture. The solid product obtained is filtered, washed thoroughly with ice-cold water and dried. Subsequently, the product purification by recrystallization using hot ethanol. Then, the obtained filtrate after the isolation of the product was subjected to evaporation under reduced pressure to recover the ionic liquid. The ionic liquid was then dried in a vacuum oven for 2 h and subsequently used for the next experimental cycle.

Spectral data

propyl pyridinium bromide (PPBr)

^{1}H NMR (500 MHz, DMSO): δ (ppm) 0.23-0.26(3H, t.), 1.33-1.38(2H, m), 4.22-4.25 (2H, t), 8.88-8.90(2H, d.), 7.93-7.97(2H, t.), 8.88-8.90 (1H, t.). ^{13}C NMR (125 MHz, DMSO): 10.11,28.90, 62.42,128.15,144.72, 145.24. Mass (m/z): 202.16.

N-(2-hydroxyethyl) pyridinium bromide (HEPBr)

^{1}H NMR (500 MHz, DMSO): δ (ppm) 3.93-3.97 (2H, q), 4.85-4.87 (2H, t), 5.32(1H, s), 8.26-8.29 (2H, q), 8.72-8.75(1H, t), 9.22-9.23 (2H, d) ^{13}C NMR (125 MHz, DMSO): 35.69, 51.92, 59.20, 122.53, 123.20, 136.66. Mass (m/z): 207.13.

1 methyl 3 propyl imidazolium bromide (PMImBr)

^{1}H NMR (500 MHz, DMSO): δ (ppm) 0.11-0.14(3H, t), 1.11-1.15(2H, m), 3.30(3H, s), 3.49-3.52 (2H, t), 6.95-6.96(1H,d), 6.99-7.00 (1H, d), 9.23

(1H, s). ^{13}C NMR (125 MHz, DMSO): 39.71, 111.13, 119.12, 119.39, 119.83, 119.94, 122.11, 123.62, 126.89, 130.52, 131.33, 136.71, 143.11. Mass (m/z): 205.07.

1-(hydroxymethyl)-3-methyl-1H-imidazol-3-ium bromide (HEMImBr)

^{1}H NMR (500 MHz, DMSO): δ (ppm) 3.70-3.71(2H, t), 3.87 (3H, s), 4.23-4.25(2H, t), 5.08 (1H, s), 7.75-7.78(2H, d), 9.22(1H, s) ^{13}C NMR (125 MHz, DMSO): 35.69, 51.92, 59.20, 122.53, 123.20, 136.66. Mass (m/z): 192.14.

3,3'-(4 chloro Phenylmethylene) bis(1H-indole) (3c)

IR υ_{max} cm^{-1}: 3300, 3177, 2976, 1662, 1572, 1444, 1282. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86(1H, s), 6.64(2H, s), 6.99-7.02(2H, t), 7.15-7.18(2H, t), 7.34-7.36(4H, d), 7.22-7.27 (4H, m), 7.92(2H, s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): 39.64, 111.10, 119.25, 119.37, 119.83, 122.10, 123.58, 126.90, 128.37, 130.08, 131.81, 136.71, 142,56. Mass (m/z): 357.09.

3,3'-(4 hydroxy Phenylmethylene) bis(1H-indole) (3d)

IR υ_{max} cm^{-1}: 3501, 3350, 3110, 2981, 1640, 1455,1226. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.58 (1H, s), 5.82(1H, s), 6.65-6.66(2H, q), 6.73-6.75 (2H, m), 6.98-7.01(2H, t), 7.14-7.17(2H, t), 7.19-7.21(2H,d), 7.34-7.39(4H,s), 7.90(2H, s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): 39.36, 111.00, 115.04, 119.22, 119.98, 120.05, 121,93, 123.49, 127.06, 129.83, 136.42, 136.73, 153.80. Mass (m/z): 305.24.

3,3'-(4 nitro Phenylmethylene) bis(1H-indole) (3e)

IR υ_{max} cm^{-1}: 3250, 2920, 2847, 1578, 1438, 1382, 1237. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 (1H,s), 6.68(2H,s), 7.01-7.04(2H,d), 7.18-7.25(2H,t), 7.32-7.34(2H,d), 7.37-7.39(2H,d), 7.49-7.51(2H,d), 8.00(2H,d,NH), 8.13-8.14(2H,d). ^{13}C NMR (125 MHz, $CDCl_3$): 40.22, 111.26, 118.17, 119.57, 119.64, 122.38, 123.63, 126.67, 129.54, 136.71, 151.83. Mass (m/z): 367.26.

3,3'-(4 methoxy Phenylmethylene) bis(1H-indole) (3f)

IR υ_{max} cm^{-1}: 3422, 2931, 1645, 1461, 1287, 1220. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (3H, s), 5.82(1H, s), 6.51(2H, s), 6.79-6.81 (2H,d), 6.97-7.00(2H, t), 7.13-7.16(2H, t), 7.22-7.24 (2H, t), 7.31-7.32 (2H, d), 7.36-7.38 (2H, d), 7.85 (2H, s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): 39.36, 55.23, 11.04, 113.59, 119.20, 120.00, 120.06, 121.90, 123.54, 127.09, 129.62, 136.26, 136.73, 157.93. Mass (m/z): 352.04.

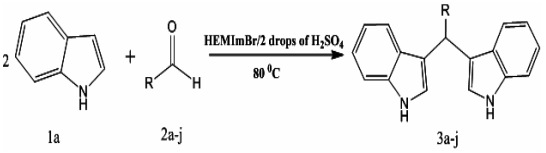
3,3'-(2 nitro Phenylmethylene) bis(1H-indole) (3g)

IR(ATR) υ_{max} cm^{-1}: 3311,3104,2981,1662, 1562,1572,1455,1265,1170. ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.65(2H, s), 6.70(1H, s), 7.03-7.06 (2H, t), 7.14-7.28(2H, m), 7.35-7.38 (3H, m) 7.41-7.45 (4H, m), 7.86-7.91 (1H, d), 7.91 (2H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 34.82, 102.63, 111.05, 111.18, 117.71, 119.57, 119.75, 119.82, 120.74, 122.00, 122.25, 123.85, 124.14, 124.38, 126.79, 127.22, 131.10, 132.34, 136.70, 138.01, 149.85 Mass (m/z): 367.35.

RESULT AND DISCUSSION

The outcomes of our study demonstrate the production of Synthesised bis(indolyl)alkanes by the interaction between indoles and aldehydes, facilitated by the addition of 2 drops of sulfuric acid in the ionic liquid HEMImBr (Scheme 1).

In our first attempt, we combined two indole molecules with benzaldehyde at 80°C, using 10 mol% tartaric acid as a catalyst, and conducted the reaction without the use of a solvent. The reaction was complete after 150 min, yielding product 3a at a yield of 57%. To improve the conversion, we switched to a solvent-free, 80^{0}C, 20 mol% tartaric acid treatment of indole (1a) with benzaldehyde (2a). This time, the reaction needed 135 min to complete, and the obtained yield was 62% (Table 1).



Scheme 1

Table 1: The optimization of the indole-benzaldehyde coupling

Sr. No	Solvent	Catalyst	Temperature^{0}C	Time	Yield%
1	-	Tartaric Acid (10%)	80	150	57
2	-	Tartaric Acid (20%)	80	135	62
3	Ethanol	Tartaric Acid (10%)	80	240	72
4	Ethanol	Tartaric Acid (20%)	80	240	85
5	PPBr	-	80	60	70
6	PMImBr	-	80	50	75
7	PPBr	Tartaric Acid (10%)	80	78	74
8	PPBr	Tartaric Acid (20%)	80	72	79
9	PMImBr	Tartaric Acid (10%)	80	70	78
10	PMImBr	Tartaric Acid (20%)	80	60	82
11	PPBr	H_2SO_4 (2 Drops)	80	43	84
12	PMImBr	H_2SO_4 (2 Drops)	80	37	86
13	HEPBr	-	80	40	82
14	HEMImBr	-	80	38	84
15	HEPBr	H_2SO_4 (2 Drops)	80	35	89
16	HEMImBr	H_2SO_4 (2 Drops)	80	28	95

We then attempted the same reaction using 10% and 20% mole proportion of tartaric acid under ethanol as a solvent at 80^{0}C. Then, both reactions were completed in 240 min, with 72% and 85% yields, respectively. Additionally, we conducted the reaction without a catalyst, using propyl pyridinium bromide and 3-propyl 1 methyl imidazolium bromide, and observed a slightly higher yield (70% and 75%). When tartaric acid was added to both ionic liquids at 10% and 20%, we saw an increase in yield.

We turned to strong acids such as sulfuric acid to improve the yield. We observed that in both ionic liquids (PPBr and PMImBr), a significant elevation in the yield of the product was observed. With the addition of sulfuric acid as a catalyst, we obtained yields of 84% and 86% using PPBr and PMImBr, respectively, and we also found that the reaction time decreased from 50 min without a catalyst to 38 min with the sulfuric acid catalyst in PMImBr ionic liquid.

In addition to the previously reported results, we explored using two alternative ionic liquids, HEPBr and HEMImBr, to synthesize bisindolyl methanes. Interestingly, even without the addition of a catalyst, both ionic liquids promoted the reaction with 82% and 84% yields. However, adding two drops of sulfuric acid to either ionic liquid (HEPBr or HEMImBr) led to a significant enhancement in product yield, reaching 89% and 95%, respectively. Furthermore, the reaction times were reduced to 35 min for HEPBr and 28 min for HEMImBr, demonstrating the synergistic effect of the ionic liquid and sulfuric acid.

In considering these encouraging findings, we moved on to investigate the connection between indole and other aromatic aldehydes. The required BIMs may be efficiently produced by combining indole with various substituted aldehydes. (entry 3a-3j in Table 2).

The reusability of the ionic liquids (ILs) and catalyst was evaluated. The product, being insoluble in water, was easily separated. The residual solution comprising ionic liquids (ILs) was separated by applying decreased pressure at a temperature of 80^{0}C. It was thereafter subjected to drying for two hours in a vacuum oven at 70^{0}C. The resulting product was then used again for the same synthesis process. Both the ILs and the catalyst exhibited reusability with only a slight decrease in their activity. Table 3 displays the findings.

Table 2: Analytical data of BIMs (3a–3j) catalyzed by 2 drops of H_2SO_4 in HEMImBr

Sr. No	Carbonyl Compound	Product	Time (Min)	Yield(%)	m.p^{0}C
1	C_6H_5-CHO(2a)	3a	28	95	124-125
2	p-BrC_6H_4-CHO(2b)	3b	27	93	110–112
3	p-ClC_6H_4-CHO(2c)	3c	25	94	84-85
4	p-OHC_6H_4-CHO(2d)	3d	27	90	122-124
5	p-$NO_2C_6H_4$-CHO(2e)	3e	23	95	220-222
6	p-$OCH_3C_6H_4$-CHO(2f)	3f	25	94	177-179
7	o-NO_2C_6H4-CHO(2g)	3g	27	89	139-140
8	o-ClC_6H_4-CHO(2h)	3h	28	84	73-74
9	p-FC_6H_4-CHO(2i)	3i	27	88	102-104
10	Isatin(2j)	3j	23	92	308-310

Table 3: Recyclability of Ionic liquid and catalyst

No. of Cycles	Fresh	Run 1	Run 2	Run 3
Yieldsa	95	93	90	88
Time (Min)	38	38	39	40

"Reaction conditions: Indole (2 mmol) and Benzaldehyde (1 mmol); ILs and catalyst; temp: 80°C; aisolated yields

CONCLUSION

HEMImBr proved to be an effective and easy-to-use green solvent in synthesizing Bis indolyl methane. We used two drops of sulfuric acid as a catalyst to get high yields from Indole and many different types of aldehydes, which reduced the use of organic volatile solvents. With this one-pot synthesis, the reaction time was fast, the solvent was cheap, nontoxic, and easily synthesized, and the yields were high since the products were easily separated. As a result, this research gives future researchers interested in investigating these frameworks a feasible, quick, and affordable method.

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Conflict of interest

The author declared that there is no conflict of interest related to this article.

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