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Ionic liquid N-ethylpyridinium hydrogen sulfate as an efficient catalyst for designing indole scaffolds and their antimicrobial behavior

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ABSTRACT

Ionic liquid N-ethylpyridinium hydrogen sulfate has been prepared, characterized and used as an efficient recyclable catalyst for the synthesis of a series of indoles and bis(indolyl)methanes. Latter have been further explored for their potential antimicrobial activity against *E coli* and *Bacillus*. The ionic liquid used was recycled in the end and its recovery was facilitated by water. Use of water was beneficial in terms of avoiding organic solvents, providing facile recovery of the products and affording the recycling of the catalyst.

***Keywords**: Indoles, Bis(indolyl)methanes, Ionic liquids, Aqueous media, N-ethylpyridinium hydrogen sulfate.*

1. Introduction

Ionic liquids [1] have recently emerged as effective substitute for volatile organic solvents for exploring the greener aspect of synthesis in different chemical reactions. Recently, their importance is manifested in variety of chemical reactions such as hydroformylation [2], hydrodimerization [3], Diels-Alder reaction [4], esterification [5] and ring closing metathesis [6]. They have also been increasingly used in catalysis [7] and electrochemical devices [8]. Few of their remarkable properties include negligible vapor pressure, low coordination ability, high thermal stability and good solvating power. Ionic liquids are task specific in nature and hence can be tuned according to the requirement of the reaction. These liquids mostly can be recovered and recycled in the end to offer comparable performance in chemical transformations. Similarly, water is also a green solvent used in organic synthesis. It has replaced many organic solvents in the field of organic synthesis [9]. Different reactions such as halogenations, free radical polymerization, hydro-alkoxylation, Cope rearrangement and Diels-Alder reaction have been reported in aqueous media [10].

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Indole and their derivatives [11] are important intermediates in organic synthesis due to their potential applications [12] in pharmaceutical chemistry, agrochemicals and material science. Indole derivatives are used as psychotropic [13], anti-inflammatory [14], anticancer, antineoplastic [15] and DNA-intercalation [16] agents. They are also important constituents of many drugs that are used for the treatment of type-2 diabetes [17] and HIV type-1 infection [18]. Indoles constitute very important class of therapeutic molecules and are likely to replace many existing pharmaceuticals in the future. Various catalysts, including Lewis [19], Bronsted [20] and solid acidic [21] catalysts, have been employed for the synthesis of indoles. Different methodologies including solid phase synthesis [22] and ionic liquid mediated reactions [23] have also been used for their preparation. Few indole derivatives, such as bis(indolyl)methanes, are applied [24] in medicinal science for the preparation of agrochemicals and in the synthesis of pharmaceuticals. Due to our interest in ionic liquid mediated organic transformations [25] and our recent focus on heterocyclic chemistry in unconventional media [26], we set out to use N-ethylpyridinium hydrogensulfate $[EtPy]HSO_4$ as a catalyst for the synthesis of indole and bis(indolyl)methanesand study their antimicrobial behavior.

2. Experimental

All the chemicals were purchased from Sigma Aldrich beside ethyliodide and pyridine, which were purchased from CDH India and were of the analytical grade. Reaction monitoring was performed on TLC plates that were prepared by adsorbing silica gel-G on glass plates. Spot visualization was accomplished by iodine adsorption in iodine chamber. FTIR spectra of the synthesized compounds were recorded on the Agilent Technology FTIR spectrometer ranging from 500-4000 cm^{-1} using KBr palates. ^{1}HNMR was recorded on the Bruker Advance-III 400 MHz spectrometer in $CDCl_3$/DMSO-d_6 solvent using TMS as the internal standard.

2.1. Synthesis of N-ethylpyridinium hydrogen sulfate [EtPy][HSO4]:

Ionic liquid was prepared by analogous methods reported in literature [27]. Pyridine (20 mmol) was refluxed with ethyl iodide (40 mmol) for 12 h to obtain N-ethylpyridinium iodide. The crude product obtained was washed with diethyl ether to remove unreacted ethyl iodide and was dried under vacuum to obtain ethylpyridinium iodide [EtPy]I. In the next step [EtPy]I (0.017 mol) was taken in round bottom flask that was cooled to 0-5 °C in DCM (10 mL) followed by the drop wise addition of sulfuric acid (0.5 mL)and stirred at room temperature for 5h. Solvent was evaporated under reduced pressure to obtain brownish yellow liquid N-ethylpyridinium hydrogen sulfate.

IR (KBr): $\bar{\nu}$= 3428, 3052, 1637, 1488, 1320 and 1175 cm^{-1} (Fig. S3). ^{1}HNMR (DMSO-d_6, 400MHz): δ= 1.55 (t, 2H, *J*= 7.3), 4.76 (q, 3H, *J*= 7.3), 8.13-8.10 (m, 2H), 8.64-8.60 (m, 1H), 9.23 (m, 2H) (Fig. S6).

2.2. General procedure for the synthesis of indole derivatives using [EtPy][HSO4]

Hydrazones (5 mmol) were mixed with ionic liquid (5 mmol) at room temperature and then stirred at 120 °C for 30 minutes. After completion of the reaction as monitored via TLC, distilled H_2O (10 mL) was added and contents were cooled to room temperature. The crude solid obtained was filtered and washed with water to get the desirable indole. The wet solid was dried at 40 °C for 16 h and then recrystallized in ethanol to obtain the pure product.

Spectral data for 2,3,4,9-tetrahydrocarbazole (Table 1, entry 1, Figs. S10 and S11)

IR (KBr): $\bar{\nu}$= 3398, 3052, 2929, 2851, 1622, 1443, 1238, 1145, 739 cm^{-1}. ^{1}HNMR (DMSO-d_6, 400MHz): δ= 7.47 (s, 1H, NH), 7.18-7.05 (m, 4H, ArH), 2.65 (m, 4H, Non Aromatic), 1.87 (m, 4H, Non Aromatic).

2.3. General procedure for the synthesis of bis(indolyl)methanes using [EtPy][HSO4]

Indole (10 mmol) and substituted aldehydes (5 mmol) were added to distilled water (7mL) followed by the addition of N-ethylpyridinium hydrogen sulfate (100 mg) and stirred at 80 °C for 40 minute. After the completion of reaction as monitored by TLC, contents were cooled to room temperature and then poured into ice cold distilled water (7 mL). The solid obtained was filtered, washed with water and dried in vacuum at 60 °C to obtain the crude product that was recrystallized in ethanol.

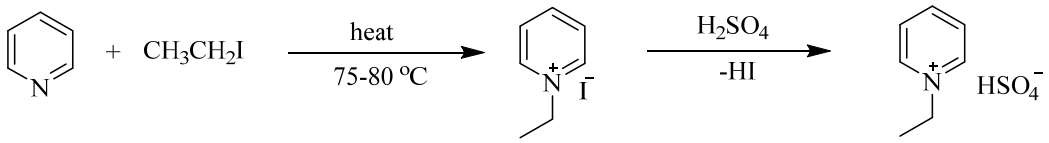
Spectral data for 3,3′(phenylmethylene)bis(1*H*-indole) (Table 2, entry 1, Figs. S12 and S13)

IR (KBr): $\bar{\nu}$= 3305, 2921, 2851, 1618, 1484, 1331, 1261, 1074, 776 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6): δ= 10.4 (s, 2H, NH), 7.42-7.12 (m, 9H, ArH), 7.19-7.11 (m, 2H, ArH), 7.08-7.06 (m, 2H, ArH), 6.99-6.71 (m, 2H, CH), 5.80 (s, 1H, CH).

3. Results and Discussion

Our first task was to prepare the Brønsted acidic ionic liquid [EtPy]HSO_4, which was prepared by quarternization of pyridine with ethyl iodide [27] followed by acidification of quarternary salt. This strategy is mostly adopted to prepare the pyridine or imidazole based ionic liquids [28]. At first pyridine was heated with ethyl iodide at 75-80 °C to obtain N-ethylpyridinium iodide (Scheme 1). Then, 1 mol eq. of sulfuric acid was added at room temperature to obtain N-ethylpyridinium hydrogen sulfate. The resulting compound is a viscous liquid with brownish color that tends to solidify at lower temperature giving a brownish orange solid (below 20 °C).

The formation of product was indicated by the change in physical state (solid product isolated from liquid substrates) and by TLC; and confirmed by IR and ^{1}HNMR analysis (Figs. S1-S6).



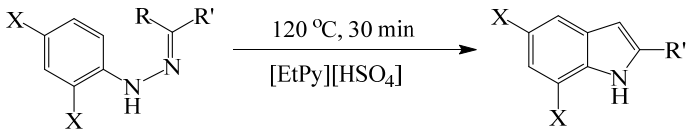
Scheme 1. Synthesis of ionic liquid [EtPy]HSO_4.

N-Ethylpyridinium iodide upon addition of sulfuric acid (1 Mol Eq.) turns into a liquid state with the evolution of a gas (fumes of HI). On performing the TLC analysis, the product spot does not move at all and no corresponding spot either to pyridine or to ethyl iodide was observed (Fig. S7). Even after increasing the polarity of the mobile phase (ethyl acetate in n-hexane) up to 30%, no rise in product spot was observed. This confirms the absence of both of the reactants in the final product. Careful analysis of IR spectrum reveals characteristic peaks at 1637, 1488, and 1175cm^{-1} (Fig. S3). These peaks are absent in the IR spectrum of pyridine or ethyl iodide clearly indicating the change in nature of C=N stretching and in –CH bending of alkyl side chain (Figs. S1 and S2). ^{1}HNMR spectrum (Fig. S6) further confirms the synthesis of N-ethylpyridinium hydrogen sulfate. Pyridine showed peaks at δ 6.69, 7.06, 8.05 (Fig. S4) in the ^{1}HNMR spectrum that are shifted downfield to δ 8.10, 8.62 and 9.23 respectively after the product formation. Also the ^{1}HNMR spectrum of ethyl iodide (Fig. S5) shows a quartet at δ 3.14 and this peak shifts downfield to δ 4.7 due to the de-shielding caused by the quaternary nitrogen atom in [EtPy]HSO_4. Finally, the ionic exchange was determined by acid base titration using phenolphthalein as an indicator.

Once the ionic liquid was prepared, we next set to probe its role for the synthesis of indole derivatives via cyclization of phenyl hydrazones. Later were prepared by the reaction of phenyl hydrazine with different carbonyl compounds in presence of [EtPy]HSO_4 as a catalyst (see experimental, Supporting Table-S1). Hydrazones were cyclized in ionic liquid at 120 °C to afford the corresponding indole derivatives. In a typical example 2,3,4,9-tetrahydrocarbazole was prepared and characterized via FT-IR and ^{1}HNMR spectroscopic techniques. FT-IR spectrum (Fig. S10) of this compound shows a peak at 3398 cm^{-1} was assigned to NH stretching. Similarly peaks at 3052 cm^{-1} was most likely due to =C-H stretching, 2929-2851 cm^{-1} due to C-H stretching and 1238-1145 cm^{-1} due to C-N stretching. ^{1}HNMR spectrum of the compound (Fig. S11) also confirmed the formation of the product where singlet at δ 7.47 arise due to NH proton of a cyclic pyrrole ring and multiplet at δ 7.18-7.05 for aromatic protons confirming the product formation. Once the formation of 2-cyclohexyl-1H-indole was confirmed in this reaction, we next synthesized other indole derivatives by adopting the same methodology, and the results are compiled in Table 1. It was observed that yields for the indoles from 2,4-dinitrophenyl products were lower probably due to the deactivation of aromatic ring by –NO_2 group that may decrease the electron density on N-atom and hence decreasing its tendency for the nucleophilic attack on –CHO group.

To extend the applicability of the method we further synthesized bis(indolyl)methanes by the electrophilic addition of aldehydes to indole. First we synthesized 3,3′(phenylmethylene)bis(1*H*-indole) by reacting indole (10 mmol) with benzaldehyde (5 mmol) in ethanol by adding catalytic amount of [EtPy]HSO_4.

Table 1. Synthesis of indoles from phenylhydrazones using ionic liquid [EtPy]HSO_4.[a]



X = H, -NO_2

R' = alkyl, aryl
R = H, Alkyl

Entry	X	R	R′	Yield (%)
1	H	Cyclohexyl (Including R and R′)		86
2	H	-CH_3	-(2-OH)C_6H_4	80
3	H	-CH_3	-CH_2CH_3	64
4	H	-CH_3	- CH_2Br	84
5	-NO_2	-CH_3	-C_6H_5	65
6	-NO_2	-CH_3	-(2-OH)C_6H_4	63
7	-NO_2	-CH_3	-CH_2Br	73

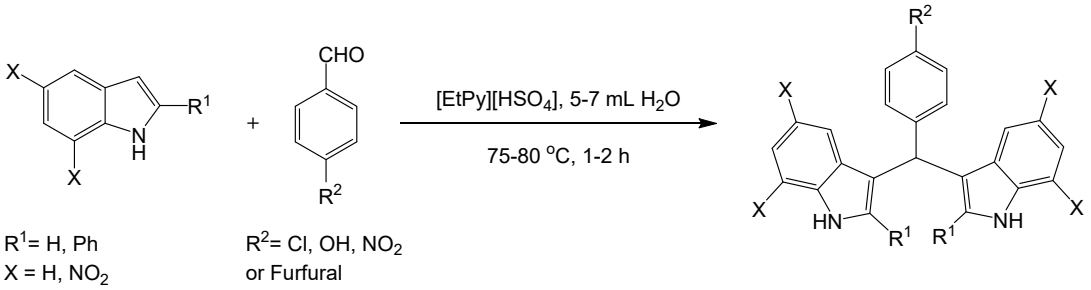
[a]Reaction conditions: All the reactions were performed by treating 1 mmol of hydrazone, 1 mmol of [EtPy][HSO_4] with continuous stirring at 120 °C for 30 minutes.

Crude product obtained was finally recrystallized in ethanol and characterized by IR and ^{1}HNMR analysis. IR spectrum of the product does not show any peak at 1700 cm^{-1}(Fig. S12) indicating the complete absence of aldehyde. While observing the ^{1}HNMR spectrum of the product, characteristic peak at δ 5.80 (singlet) is observed (Fig. S13) due to formation of new –CH bond in the product. After characterizing the product, different solvents including water were explored for the process (Table S2). The use of water was found to be beneficial for the reaction in terms of avoiding the organic solvents and assisting in facile product recovery. Finally, variety of substituted aldehydes were reacted with indoles in presence of the ionic liquid N-ethylpyridinium hydrogen sulfate (in water) to produce corresponding bis(indolyl)methanes (Table 2).

It must be noted that substituent at position 2- was found to decrease the yield of the product, probably due to the steric effect observed. Moreover, presence of –NO_2 also was found to decrease the yield that may result in electron deficiency on indole ring making it less suitable for the nucleophilic attack on aldehydeic group. The activity of the catalyst was compared with other catalysts reported in literature, and it was found to provide almost the same yields within a very short time (Table 3).

The catalyst was recovered and recycled in the end (See supplementary information). After the completion of the reaction, obtained mass was filtered to remove the crude product. The clear liquid having pH 3-4 was obtained and acidic pH indicated that catalyst had its activity and the potential to be reused. Hence, the compound [EtPy]HSO_4 was isolated by evaporation of water under reduced pressure. The resulting viscous liquid was dried at 50-60 °C and reused for the preparation of bis(indolyl)methanes (The yields for three runs were 74, 68 and 60%, respectively) by the optimized method and results are compiled.

Table 2. Comparative yields of bis(indolyl)methanes obtained from indole and aldehydes in aqueous media using [EtPy]HSO_4.[a]



Entry	X	R_1	R_2	Time (h)	Yield (%)
1	H	H	H	1	84
2	H	H	Cl	1	68
3	H	H	OH	1.5	75
4	H	H	NO_2	1	65
5	NO_2	C_6H_5	Cl	2	52
6	H	H	Furfural	1	78

[a]Reaction conditions: All reaction were performed using 10 mmol of indole, 5 mmol of aldehyde in presence of 100 mg N-ethylpyridinium hydrogen sulfate in water at 80 °C for the specified time period.

Table 3. Comparison of yields of 3,3′-Bis(indolyl)phenylmethane with various catalyst under different reaction conditions.

Entry	Catalysts	Solvents	Temp. (°C)	Time (h)	Yield (%)	Ref.
1	[EtPy]HSO_4	Solvent free	80	40 min	84	This work
2	InF_3. H_2O	Aqueous	r.t.	10	99	[29]
3	CAN	EtOH	r.t.	2	93	[30]
4	Amberlyst-15	DCM	r.t.	2.5	89	[31]
5	Zeolite	DCM	r.t.	3	85	[32]

The activity of the catalyst was found to decrease gradually which may be due to decrease in its acidic strength that may occur during its extraction from water or due to trapping of some other impurities generated during the course of earlier reactions.

Finally, the antibacterial property of bis (indolyl) methanes was studied against *E coli* (gram negative) and *Bacillus* (gram positive) at different concentrations (750 µg/mL, 500 µg/mL and 250 µg/mL) (See supplementary information). The compounds which were subjected to antibacterial studies include 3,3′-(4-hydroxyphenylmethylene)bis(1-*H*-indole), 3,3′-(4-hydroxyphenylmethylene)bis(5,7-Dinitro-2-phenyl-1*H*-indole), 3,3′-(4-chlorophenylmethylene)bis(1-*H*-indole) and 3,3′-(4-chlorophenylmethylene)bis(5,7-Dinitro-2-phenyl-1-*H*-indole). All these compounds were active against the bacteria at a concentration of 250 µg/mL (Fig. 1). Among all these compounds; 3,3′-(4-hydroxyphenylmethylene)bis(1-*H*-indole) was found to be most effective against *E coli* and *Bacillus* at a concentration of 250 µg/mL with a maximum zone of inhibition measuring 24mm and 21 mm respectively. The antibacterial potential of this compound was probably due to the presence of the phenolic group that might play an important role in absorbing reactive oxygen species (ROS) that causes damage to the defense mechanism of body in large concentrations.

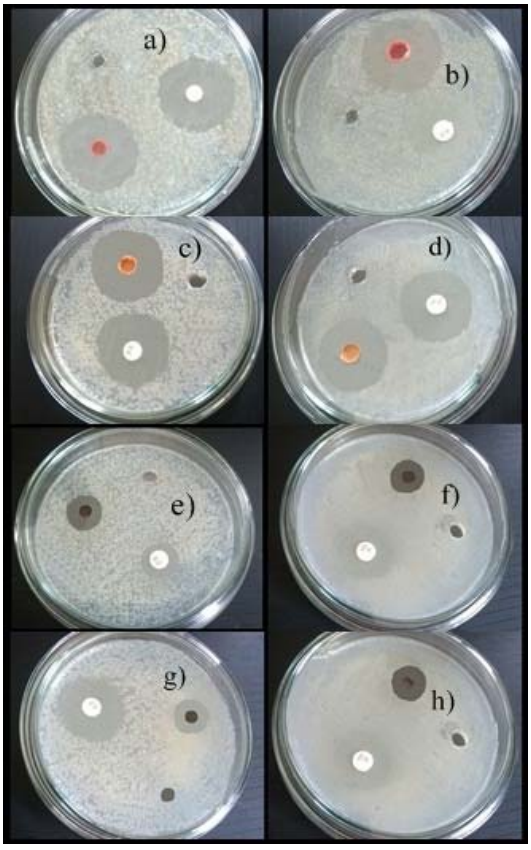


Fig. 1. Antibacterial potential of (a) 3,3′(4-hydroxyphenyl methylene)bis(1H-indole) against E. coli (b) against Bacillus (c) 3,3′(4-chlorophenylmethylene)bis(1H-indole) against E. coli (d) against Bacillus (e) 3,3′(4-chlorophenylmethylene) bis(5,7-dinitro-2-phenyl-1H-indole) against E. coli (f) against Bacillus (g) 3,3′(4-hydrophenyl methylene)bis(5.7-dinitro-2-phenyl-1H-Indole) against E. coli and (h) against Bacillus.

4. Conclusion

To conclude, we have prepared ionic liquid [EtPy]HSO_4 and used it as an efficient and recyclable catalyst for developing a simple procedure for the synthesis of indole derivatives and bis(indolyl)methanes. Water was also used as a solvent during the synthesis of bis(indolyl)methanes and its use was beneficial to provide facile recovery of the product and for the recycling of the used catalyst. The synthesized bis(indolyl)methaneswere also found to possess antibacterial potential against *E coli* and *Bacillus*.

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