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# Design of task-specific ionic liquid, 1-(ethylaceto acetate)-1-(2-hydroxyethyl) piperidinium tetrachloroaluminate for multicomponent synthesis of 3,3′-disubstituted oxindoles

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Abstract We have designed and synthesized an efficient novel task-specific ionic liquid, 1-(ethylaceto acetate)-1-(2-hydroxyethyl) piperidinium tetrachloroaluminate $[EAHEPiPY]^+$ $[AlCl_4]^-$. Its catalytic efficiency was explored for multicomponent reaction of isatin(s), malononitrile, and indole(s) furnished corresponding 3,3′-disubstituted oxindoles via tandem Knoevenagel/Michael addition reaction in excellent yield at 80 °C in mixed solvent system, water: ethanol (80:20%).

Graphical Abstract
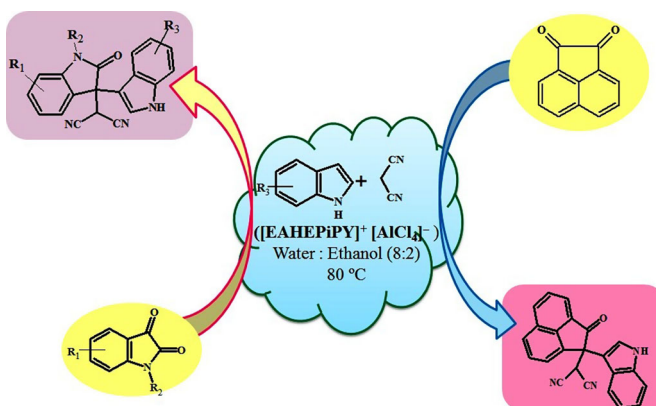
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Introduction

The continual upsurge in designing and exploring efficient methods for generation
of molecular complexity and diversity with predefined functionality from simple
starting material urges chemists to develop effective tools for their arsenal [1, 2]. In
this context, multicomponent reactions (MCRs) have attracted considerable
attention for their ability to generate carbon–carbon and carbon–hetero atom bonds
along with added advantages viz simple procedure, high efficiency, economy, time
and energy conservation, environmental friendliness, and atom economy resulting
in substantial minimization of waste, labor, and production cost in industrial
application [3–11]. It is noteworthy that most MCRs proceed through the
Knoevenagel Michael cascade pathway for building complex, cyclic, and
spirocyclic molecular scaffolds [12, 13]. These attractive features have amplified
their popularity in scientific community [14].

Oxindoles bearing a tetra substituted carbon center at 3-position (i.e. 3,3′-
disubstituted) is a valuable structural motif, found in many natural products,
biologically active alkaloids, and pharmacological agents [15–21]. Amongst them,
special attention is received by 3-methyl azaarene substituted oxindoles owing to
their unique biological activities and crucial role as key building blocks in organic
synthesis [17–19]. Often, these motifs are constructed by direct addition of various
nucleophiles to isatin(s) [20]. It is worthy to note that substituted isatin analogues
constitute valuable building blocks for organic scaffolds used in flourimetric metal
sensing [21] and potential pharmaceuticals with a wide range of biological activities
such as anti-microbial [22], anti-tumor [23–26], anti-tubercular [27, 28], anti-
malarial [29], anti-HIV [30], and anti-bacterial [31].

Recently, Tao He and co-workers reported the synthesis of 3,3′-disubstituted
oxindoles via α-amylase catalyzed one pot multicomponent reaction of isatin,
malononitrile, and indole. However, the major drawback was long reaction time,
5 days [32]. Hence, development of an efficient and eco-friendly method for
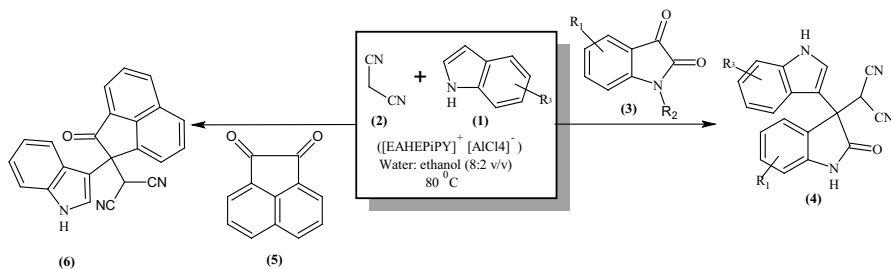synthesis of 3,3′-disubstituted oxindoles is highly warranted.

Ionic liquids were initially introduced as a green media but nowadays considered
as "green" catalysts due to their green aspects such as non-volatility, thermal
stability, reusability, and operational simplicity [33–41]. Their high polarity and the
ability to solubilize both inorganic and organic compounds can enhance rate of
reaction and provide higher selectivity compared to conventional solvents [42–45].
It is noteworthy that some physicochemical properties of ILs depend upon the type
and proportion of halide ion [46, 47]. ILs with metal halide anions exhibit marked
Lewis acidity, especially those based on chloroaluminate anions [48–52]. Hence,
considering the advantages of ILs, we decided to synthesize novel task-specific
ionic liquid (TSIL) comprising $AlCl_4^-$ anion, 1-(ethylaceto acetate)-1-(2-

hydroxyethyl) piperidinium Tetrachloroaluminate; [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ for the synthesis of 3,3′- disubstituted oxindoles from isatin(s), malononitrile and indole(s).

Results and discussion

In continuation of our interest in development of multicomponent strategies through Knoevenagel/Michael cascade reactions [53–56], herein we report an expeditious method for synthesis of 3,3′-disubstituted oxindoles via a multicomponent reaction of isatin(s), malononitrile, and indole(s) using catalytic amount of [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ in water: ethanol (80: 20 v/v) at 80 °C (Scheme 1).

Initially, attempts were focused towards design and synthesis of eco-friendly, homogeneous, acidic ionic liquid, 1-(ethylaceto acetate)-1-(2-hydroxyethyl) piperidinium Tetrachloroaluminate [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ (Fig. 1). The reaction of 1-(2-Hydroxyethyl) piperidine with ethyl chloroacetate at 80 °C in acetonitrile for 12 h resulted into the formation of 1-(ethylaceto acetate)-1-(2-hydroxyethyl) piperidinium chloride, [EAHEPiPY]$^+$ Cl$^-$ followed by reaction with AlCl$_3$ in methanol at 40 °C for 4 h furnished TSIL (Scheme 2), characterized by IR, ^{1}H, ^{13}C, ^{27}Al NMR, ESI-MS, and TGA analysis.

Scheme 1 Synthesis of combinatorial library of 3,3′-disubstituted oxindoles

Fig. 1 Dual functionalized task specific ionic liquid (TSIL) [EAHEPiPY]$^+$ [AlCl$_4$]$^-$
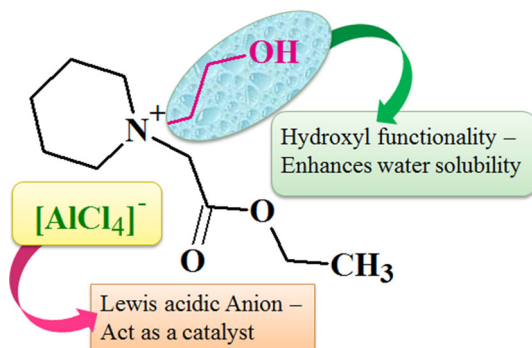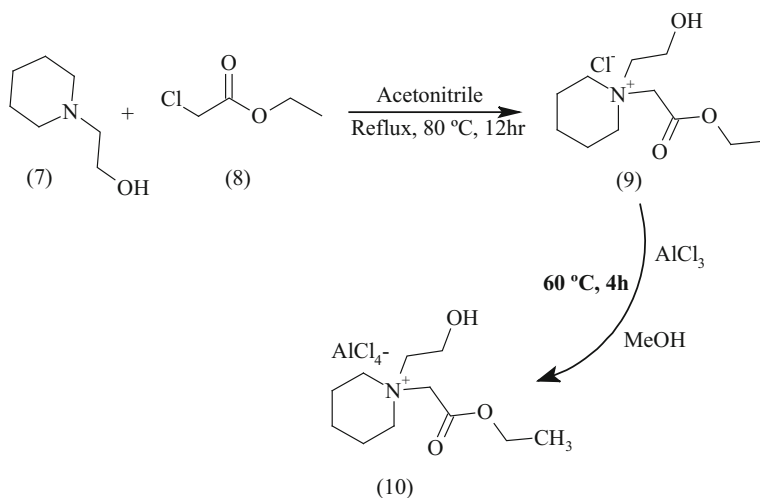
Scheme 2 Synthesis of novel [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ as TSIL

Figure 2 displays the overlay FTIR spectrum of AlCl$_3$ (a), [EAHEPiPY]$^+$ Cl$^-$ (b), and [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ (c). In spectra (b) and (c), a sharp stretching frequency band observed at 1746 cm^{-1} attributed to –C=O Stretching of ester group in cation. In the IR spectrum of [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ the band at 1634 cm^{-1} (observed in IR spectrum of AlCl$_3$) was disappeared and new band at 1651 cm^{-1} was observed confirms the formation of [AlCl$_4$]$^-$ anion in the ionic liquid. The ^{1}H and ^{13}C NMR of the TSIL was also in good agreement with its structure. In ^{27}Al NMR spectrum of
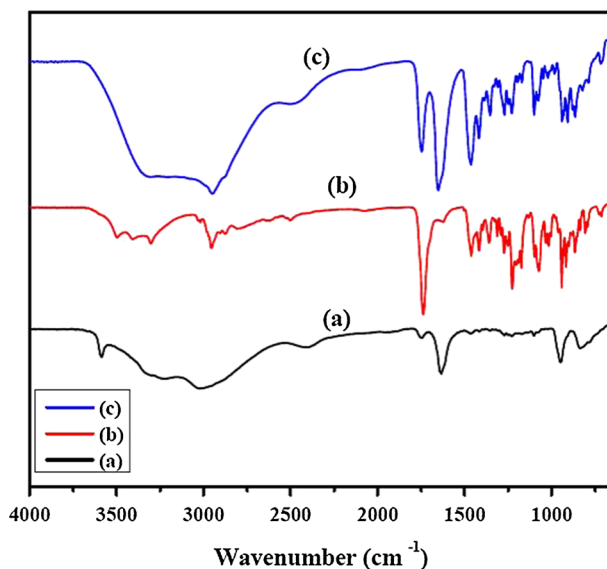

Fig. 2 IR spectrum of AlCl$_3$ (*a*), [EAHEPiPy]$^+$ Cl$^-$ (*b*) and [EAHEPiPy]$^+$ [AlCl$_4$]$^-$ (*c*)
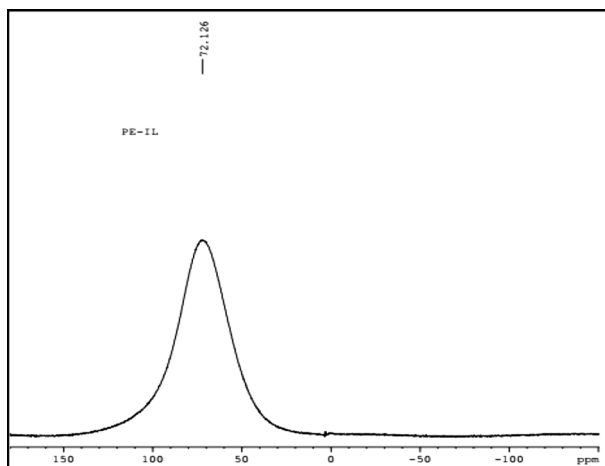
Fig. 3 ^{27}Al NMR spectrum of TSIL, [EAHEPiPy]$^+$ [AlCl$_4$]$^-$

TSIL (Fig. 3), the signal at δ 72.12 ppm highlighted presence of Al in tetrahedral geometry attributed to anion, [AlCl$_4$]$^-$ [57, 58]. Moreover, in the mass spectrum of TSIL, the peak appeared at m/z 169 also supported formation of AlCl$_4^-$ anion.

The thermal stability of the catalyst was studied by thermogravimetric analysis (TGA) and differential thermogravimetry (DTG) analysis in the temperature range of 25 to 600 °C in an air atmosphere at 10 °C/min. The TGA/DTA plot of AlCl$_3$, [EAHEPiPY]$^+$ Cl$^-$ and [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ is depicted in Fig. 4. The total loss of 70% for AlCl$_3$ sample in the temperature range 25–600 °C is due to physically adsorbed water (endothermic peak at 184 °C in DTA). In comparison, The TG/DTA plot of [EAHEPiPY]$^+$ Cl$^-$ and [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ shows the total weight loss of 90 and 88%, which can be divided into three different regions in the temperature ranges 25–200, 200–500 and 500–600 °C. Initial weight loss of 25 and 8% in the temperature range 25–200 °C may be observed due to the elimination of physically
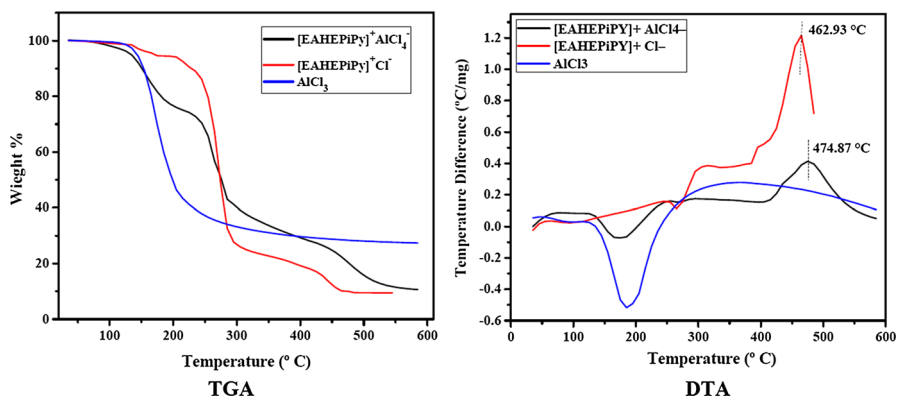

Fig. 4 TGA/DTA Comparison plot of AlCl$_3$, [EAHEPiPy]$^+$ Cl$^-$ and [EAHEPiPy]$^+$ [AlCl$_4$]$^-$

adsorbed water [59, 60]. The second weight loss of 70 and 43% correspond to the slope in the TG curve is due to exothermic decomposition of organic moiety, i.e. cation. The decomposition of cation is shifted to higher temperature in the $[EAHEPiPY]^+$ $[AlCl_4]^-$, which is confirmed by the progressive shift of the exotherm in DTA plot to higher temeperature (475 °C) from $[EAHEPiPY]^+$ Cl^- (465 °C). Therefore, we conclude that the decomposition behavior is strongly influenced by the presence of Al and a soft interaction exists between $[EAHEPiPY]^+$ $[AlCl_4]^-$ complex. The third weight loss of 13 and 20 in the temperature range 500–600 °C is due to elimination of residual carbonaceous species.

After this primary success, attention was then focused towards application of synthesized TSIL as a catalyst for synthesis of 3,3′-disubstituted oxindoles. In the pilot experiment, the model multicomponent reaction of isatin, malononitrile, and indole was investigated with respect to optimization of parameters such as efficiency and molar proportion of catalyst. Screening of catalyst for model reaction was carried out employing ammonium acetate, sulphamic acid, p-TSA, L–proline, cellulose–SO₃H, PEG–SO₃H, $[EAHEPiPY]^+$ $[AlCl_4]^-$ (entries 1–11, Table 1) in 20 mol% loading. The results summarized in Table 1, clearly revealed the high catalytic activity of synthesized TSIL to yield desired 3,3′-disubstituted oxindoles in excellent yield (88%) in a short reaction time (7 h) as compared to the literature (120 h) [32]. Further the loading effect of catalyst on the reaction indicated that 15 mol% of $[EAHEPiPY]^+$ $[AlCl_4]^-$ was sufficient to furnish desired product in excellent yield (entry 10; Table 1). When the catalyst loading was decreases up to 5 and 10 mol % then the yield of product also decreases with increasing reaction time (entries 8 and 9; Table 1), whereas with an increase in catalyst loading to 20 mol % (entry 11; Table 1), no significant change in the yield of product was observed.

To achieve highest level of green chemistry, the model reaction was carried out in universal solvent, water (entry 1, Table 2). However, desired product was

Table 1 Screening of catalyst for synthesis of 3,3′-disubstituted oxindole

Sr. no.	Catalyst	Solvent	mol%	Time (h)	Yield (%)
1	Amonium Acetate	Ethanol	100	8	78
2	Amonium Acetate	Ethanol	20	10	81
3	Sulphamic acid	Ethanol	20	8	82
4	p-TSA	Ethanol	20	10	81
5	L–proline	Ethanol	20	12	76
6	Cellulose–SO₃H	Ethanol	20	10	80
7	PEG–SO₃H	Ethanol	20	10	80
8	$[EAHEPiPY]^+$ $[AlCl_4]^-$	Ethanol	5	9	84
9	$[EAHEPiPY]^+$ $[AlCl_4]^-$	Ethanol	10	9	85
10	$[EAHEPiPY]^+$ $[AlCl_4]^-$	Ethanol	15	7	88
11	$[EAHEPiPY]^+$ $[AlCl_4]^-$	Ethanol	20	8	88

Reaction conditions: isatin (1 mmol), malononitrile (1 mmol), indole (1 mmol) solvent: 5 mL ethanol, temp.: 80 °C

Table 2 Screening of solvent for synthesis of 3,3′-disubstituted oxindole

Sr. no.	Solvent	Time (h)	Yield (%)
1	Water	7	68
2	Water:ethanol (9:1)	7	71
3	Water:ethanol (8:2)	7	91
4	Water:ethanol (7:3)	7	84
5	Water:ethanol (6:4)	7	84
6	Water:ethanol (5:5)	8	85
7	Water:ethanol (4:6)	9	81
8	Water:ethanol (3:7)	10	84
9	Water:ethanol (2:8)	10	76
10	Water:ethanol (1:9)	10	85
11	Ethanol	9	83

Reaction conditions: isatin (1 mmol), malononitrile (1 mmol), indole (1 mmol, catalyst:[EAHEPiPY]$^+$ [AlCl$_4$]$^-$ (15 mol%), temperature: 80 °C, solvent: 5 mL

obtained in low yield (68%) due to scanty solubility of reactant in it. In continuation with our experience in a mixed solvent system [61–64], we envisaged that water:ethanol system may be effective to improve the yield. Hence, the reaction was then carried out in the presence of different proportions of said mixed solvent system (entries 2–10, Table 2). Pleasingly, H$_2$O: C$_2$H$_5$OH (80:20, v/v) (entry 3, Table 2) was found to be superior in terms of yield and reaction time. The work-up for these reactions involves only filtration and a simple washing with ethanol resulted highly pure desired product and confirmed by IR, ^{1}H, ^{13}C NMR and HRMS.

From Table 2 it seems that optimized reaction conditions for model reaction is use of 15 mol% of [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ in 80:20:: water:ethanol v/v (entry 3; Table 2). In IL catalysis, the task specific functionalities play important role in one or either way such as H-bonding, co-ordination, micellization, etc. Hence, to scrutinize effect of hydroxyl group in cation of ionic liquid, the model reaction was carried out using the catalyst lacking hydroxyl functionality viz 1-(ethylaceto acetate)-1-methyl piperidinium tetrachloroaluminate [EANMPiPy]$^+$ [AlCl$_4$]$^-$ employing optimized reaction conditions. However, product was obtained in low yield even after longer reaction time was employed (entry 2; Table 3). Further, to investigate effect of AlCl$_4^-$ anion in ionic liquid, the model reaction was performed in the presence of 15 mol% of [EAHEPiPY]$^+$ Cl$^-$. Notably the desired product was

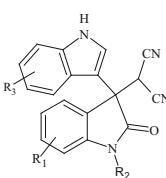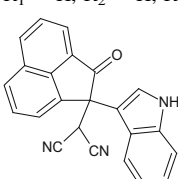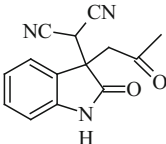**Table 3** Screening of TSIL with its subparts separately for the synthesis of 3,3′-oxiindole derivatives

Entry	Catalyst (mol %)	Time (h)	Yield (%)
1	[EAHEPiPY]$^+$[AlCl$_4$]$^-$ (15)	7	91
2	[EANMPiPy]$^+$[AlCl$_4$]$^-$ (15)	10	78
3	[EAHEPiPY]$^+$ Cl$^-$ (15)	12	36
4	AlCl$_3$ (15)	9	77
5	[EAHEPiPY]$^+$ Cl$^-$ (15)/AlCl$_3$ (15)	10	76

Reaction conditions: isatin (1 mmol), malononitrile (1 mmol), indole (1 mmol), Temperature: 80 °C. Solvent: water:ethanol (80:20%, v/v, 5mL)

obtained in only 36% yield (entry 3, Table 3). On the other hand, when model reaction was carried out in the presence of 15 mol% of $AlCl_3$, the desired product was obtained in 77% yield (entry 4, Table 3). Afterwards, in order to investigate combinatorial effect of $AlCl_3$ and $[EAHEPiPY]^+ Cl^-$ on the model reaction, the reaction was carried out using 15 mol% each (entry 5, Table 3) of these counterparts and observed that there was no significant change in the yield and reaction time. It may be due to no formation of $[EAHEPiPY]^+ AlCl_4^-$ as time required for formation of the said anion is 4 h.

With the optimized reaction conditions in hand, we explored the generality of this method by using various substituted isatin(s) with malononitrile and indole(s) (Entries 1–12, Table 4). Isatins containing both electron-withdrawing

Table 4 Synthesis of combinatorial library of 3,3′-disubstituted oxindoles

Entry	Code	Product	Time (h)	Yield (%)
1	4a	R_1 = H, R_2 = H, R_3 = H	7	91
2	4b	R_1 = 5I, R_2 = H, R_3 = H	7	90
3	4c	R_1 = 5Cl, R_2 = H, R_3 = H	7	94
4	4d	R_1 = 5OCH$_3$, R_2 = H, R_3 = H	6	78
5	4e	R_1 = 5NO$_2$, R_2 = H, R_3 = H	6	88
6	4f	R_1 = 5CH$_3$, R_2 = H, R_3 = H	6	90
7	4g	R_1 = 5Br, R_2 = H, R_3 = H	5	95
8	4h	R_1 = H, R_2 = C$_2$H$_5$, R_3 = H	5	66
9	4i	R_1 = H, R_2 = H, R_3 = 5Br	5	89
10	4j	R_1 = H, R_2 = H, R_3 = 5OCH$_3$	5	88
11	4k	R_1 = H, R_2 = H, R_3 = 5CH$_3$	5	87
12	4 l	R_1 = H, R_2 = H, R_3 = 7CH$_3$	5	95
13	6a		6	75
14	7a		12	46

Reaction conditions: isatin (s)/acenaphthoquinone (1 mmol), malononitrile (1 mmol), indole (1 mmol), catalyst: 15 mol%. Temperature: 80 °C, solvent: water: ethanol (80:20%, v/v, 5 mL)

and electron-donating substrates in their structure reacts smoothly to afford corresponding 3,3′-disubstituted oxindoles in good yields in shorter reaction time (Entries 1–8, Table 4). To explore the scope of present method, reactions using substituted indoles viz 5-methoxy, 5-bromo, 5-methyl, and 7-methyl indole were carried out. Gratifyingly, all reactions proceeded smoothly, furnishing corresponding products in good yields (Entries 9–12, Table 4). Encouraged by this success, for versatility of the method acenaphthoquinone was then selected. The reaction proceeded smoothly under optimized reaction conditions, furnishing desired products in excellent yield (Entry 13; Table 4). Thus, the present method is a versatile method for synthesis of 3,3′-disubstituted oxindoles.

Conclusion

We have synthesized novel TSIL, 1-(ethylaceto acetate)-1-(2-hydroxyethyl) piperidinium Tetrachloroaluminate $[EAHEPiPY]^+$ $[AlCl_4]^-$ and explored its catalytic efficiency for the synthesis of 3,3′-disubstituted oxindoles. The present method provides a sustainable route for the synthesis of 3,3′-oxindoles from reaction of carbonyl compound with malononitrile and indole(s) in the water:ethanol (80:20 v/v) system. Versatility of the method was proved by using various substituted isatins and acenaphthoquinone. The attractive features of the methods are the use of novel homogeneous task-specific ionic liquids, easy isolation of products, high yields, atom economy, versatile method due to excellent substrate scope, use of green mixed solvent system (water:ethanol), less reaction time than the reported method, and does not require tedious purification techniques such as column chromatography.

Experimental

Materials and methods

1-(2-Hydroxyethyl) piperidine (Alfa Aesar), ethyl chloroacetate (Sigma-Aldrich), aluminium (III) chloride $(AlCl_3)$ (spectrochem), various substituted isatins (Alfa Aesar), acenaphthaquinone (Sigma-Aldrich), malononitrile (spectrochem), and indole(s) (Sigma-Aldrich and Alfa Aesar), were used as received and were used without further purification. Melting points were measured by open capillary. IR spectra were recorded on a Perkin–Elmer FT-IR 783 spectrophotometer. NMR spectra were recorded on a Bruker AC-300 spectrometer in DMSO-d_6 using tetramethylsilane as internal standard. High resolution mass spectra (HRMS) were performed on Thermo Scientific Q–Exactive, Accela 1250 pump, instrument. ^{27}Al NMR spectrum was recorded on Bruker AV-400 spectrometer from IISc Bangalore. ESI–MS was recorded on Shimadzu LCMS–2020.

Typical procedure for the preparation of 1-(2-ethoxy-2-oxoethyl)-1-(2-hydroxyethyl) piperidinium tetrachloroaluminate ([EAHEPiPY]$^+$ [AlCl$_4$]$^-$)

Preparation of 1-(ethylaceto acetate)-1-(2-hydroxyethyl) piperidinium chloride ([EAHEPiPY]$^+$ Cl$^-$)

A solution of 1-(2-Hydroxyethyl) piperidine (5 g, 0.038 mol) and ethyl chloroacetate (4.70 g, 0.038 mol) in acetonitrile (40 mL) was refluxed for 12 h. The white crystalline needles formed (9 g, 94% yield) were filtered after cooling, and washed with diethyl ether. The obtained residue was then washed with acetonitrile (10 mL), ethyl acetate (20 mL), and diethyl ether (20 mL) to remove traces of starting materials. Further, it was dried under reduced pressure to afford white crystals of 1-(2-ethoxy-2-oxoethyl)-1-(2-hydroxyethyl) piperidinium chloride ([EAHEPiPY]$^+$ Cl$^-$).

Preparation of 1-(ethylaceto acetate)-1-(2-hydroxyethyl) piperidinium tetrachloroaluminate [EAHEPiPY]$^+$ [AlCl$_4$]$^-$

100 mL round bottom flask was equipped with 1-(2-ethoxy-2-oxoethyl)-1-(2-hydroxyethyl) piperidinium chloride ([EAHEPiPY]$^+$ Cl$^-$) (3 g, 0.012 mol) in methanol (20 mL). Then powdered aluminium (III) chloride (AlCl$_3$) (1.59 g, 0.012 mol) was added with constant stirring. The mixture was then stirred at 40 °C for 4 h to afford 1-(ethylaceto acetate)-1-(2-hydroxyethyl) piperidinium Tetrachloroaluminate [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ (4.428 g, 96%). Confirmation of [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ was done by using spectral techniques viz IR, ^{1}H, ^{13}C, ^{27}Al NMR, ESI–MS and TGA analysis.

Spectral data: Viscous liquid, 4.43 g (96%), IR (KBr) (Figure S1): 2948, 2497, 1746, 1651, 1463, 1418, 1353, 1271, 1229, 1100, 1077, 940, 907, 865 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ (ppm) (Figure S2): 4.72 (t, 3H, J = 4.8 and 5.7 Hz), 4.60 (s, 3H), 4.07 (t, 3H, J = 5.4 and 5.4 Hz), 3.65–3.71 (m, 4H) 1.82–1.87 (m, 6H), 1.56–1.62 (m, 3H), ^{13}C NMR (75 MHz, DMSO-d$_6$): δ (ppm) (Figure S3): 162.08, 62.31, 61.23, 58.78, 53.17, 20.84, 19.60; ESI–MS (Figure S5): +ve mode 239 [M + Na]$^+$, −ve mode: 169 [M + H]$^+$.

General procedure for the synthesis of 3,3′-disubstituted oxindoles

In a 100 mL round bottom flask, a mixture of isatin(s)/acenaphthaquinone (1.0 mmol) and malononitrile (1.0 mmol) in 5 mL water:ethanol (8:2 v/v) was stirred at room for ten minutes. Then indole(s) (1.0 mmol) and 15 mol % of [EAHEPiPY]$^+$ [AlCl$_4$]$^-$ were added. The resultant reaction mixture was stirred at 80 °C until completion of reaction for the time mentioned in Table 4. The progress of reaction was monitored by TLC. Precipitated product was isolated by filtration and recrystallized in hot ethanol to furnish pure product. Confirmation of products was done by spectral techniques viz IR, ^{1}H, ^{13}C NMR and HRMS analysis.

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