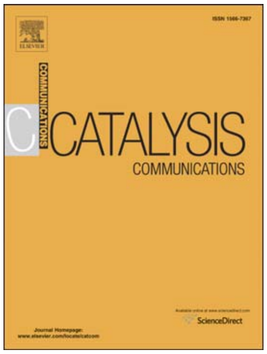

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Tetramethyl guanidinium chlorosulfonate as a highly efficient and recyclable organocatalyst for the preparation of bis(indolyl)methane derivatives

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Abstract

The synthesis and characterization of a novel superbase ionic liquid, tetramethylguanidinium chlorosulfonate, is described. The guanidine ionic liquid (GIL) was characterized by FT-IR and NMR spectroscopies, and wide-angle X-ray scattering techniques, as well as thermogravimetric analysis. The GIL functions as an effective, environmentally benign, and recyclable catalyst for the synthesis of various bis(indolyl)methanes in outstanding yields (90–96%), within short reaction times; further, no chromatographic purification step for the product is required.

*Keywords***:** Bis(indolyl)methanes; Organocatalysis; Chlorosulfonic acid; Ionic liquid; Tetramethylguanidine

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1. Introduction

Currently, many researchers are focusing on the development of green chemical methods to reduce waste, environmental hazards, cost, and energy consumption by using eco-friendly reagents and reaction conditions, which are of great importance in chemical synthesis and engineering. In addition, the realization of multiple transformations in a single operation is highly compatible with the goals of green and sustainable chemistry. In terms of public concern, the use of environmentally benign solvents such as water or the deployment of solvent-free conditions represents a highly potent and green chemical protocol from the viewpoints of both cost-effectiveness and ease of synthesis.

Synthetic heterocyclic compounds play an important role in organic and medicinal chemistry. Indole is an important nitrogen heterocyclic compound (NHC), with a variety of natural and synthetic derivatives displaying various biological properties [1]. Among them, bis(indolyl)methanes (BIMs) are an important class of NHCs possessing diverse pharmacological activities such as antimicrobial [2,3], anti-inflammatory [4], anti-oxidant [5], and anticancer [6] activities; further, BIMs can aid the inhibition cancer cell growth through the induction of apoptosis and metastasis [7]. In addition, indole–carbazole derivatives act as triplet energy materials [8], while oxidized BIMs are used as dyes [9] and colorimetric sensors [10,11]. In view of these important applications, there is increasing interest in the preparation of BIMs.

An important approach for the direct synthesis of BIMs is based on the electrophilic substitution of indole with carbonyl compounds in the presence of Brønsted or Lewis acids [12–14], heteropolyacids [15], and ionic liquids (ILs) such as $FeCl_3$-basedILs [16], [bmim][BF_4], [bmim][PF_6] [17], [bmim][$MeSO_4$] (bmim = 1-butyl-3-methylimidazolium) [18], guanidinium ILs [19], and secondary amine-based ILs [20]. The majority of the Lewis acids are highly moisture sensitive and may form stable complexes with the lone pair of electrons at nitrogen, sometimes decomposing in the presence of certain ligands in the reaction media. Accordingly, an excess of Lewis acid is required, which often results in poor reaction progress and by-product formation. To solve the abovementioned problems, it is necessary to identify mild reaction conditions using stable and reusable catalysts for the preparation of BIMs.

Advances in ILs and the related methodologies are centered on improving the efficiency of ILs, which is necessary for application in both sustainable and environmentally friendly methods; such protocols are the most important objectives of the renewable chemical industry [21]. Various GILs can be prepared by simply neutralizing tetramethylguanidine (TMG) with an equimolar amount of carboxylic acid, fluorinated carboxylic acid, nitric acid, or sulfuric acid [22]. These TMG-based ILs have recently drawn much attention because they behave as green solvents and show outstanding performance in catalysis and eco-friendly synthesis. Akbari et al. synthesized four GILs and used them for the Boc protection of amines [22]. Li et al. also prepared three GILs and used them in the Heck reaction with a palladium support [23]. Recently, Carrera et al. demonstrated a different approach by neutralizing TMG with amino acids such as *L*-alanine, *L*-phenylalanine, and *DL*-tryptophan [24]. Very recently, Lei et al. [25] prepared 1,1,3,3-tetramethylguanidinium imidazole ([TMG][IM]) and employed it for the absorption and desorption of CO_2. Numerous GILs have been prepared, mostly by the neutralization of TMG with acids, and employed as catalysts as well as solvents. The reaction time for GIL formation is typically 2 h; however, only a few GILs are formed as solids, while the others appear as liquids or semisolids, which makes their separation from the reaction mixture more difficult. Nonetheless, while GILs are conceptually eco-friendly, nontoxic, and recyclable solvents and/or catalysts, there is a need for alternatives that are easily separable from the reaction mixture and can be used as catalysts in organic reactions.

As a continuation of our ongoing research on the development of green methodologies [26], we describe a new TMG IL that can be used as a catalyst for the electrophilic substitution of substituted indoles with various substituted aromatic aldehydes (Scheme 1). The reactions proceeded to completion within a few minutes, with high yields (90–96%) of BIMs. The IL could be reused up to three times without any apparent decrease in catalytic activity. The reused catalyst did not affect the product selectivity. To the best of our knowledge, there are no reports on the synthesis of new TMG IL species and their applicability for the electrophilic substitution reaction of indoles with aldehydes.

2. Experimental

2.1. General

Indole, 2-methylindole (both purchased from Sigma-Aldrich Co., USA), 5-bromoindole, TMG (both purchased from Alfa Aesar), and various substituted aldehydes (Sigma-Aldrich Co., USA) were used without further purifications. All the experiments were carried out under neat conditions; pre-coated silica gel plates (Merck, Germany) developed with iodine were used for analytical thin-layer chromatography (TLC). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian INOVA 400 NMR spectrometer. Chemical shift values were relative to tetramethylsilane (TMS; Me_4Si). The data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, m = multiplet, brs = broad singlet), coupling constant *J*(Hz). FTIR spectra were recorded on a Shimadzu IR Prestige 21 spectrometer at r.t. The samples were analyzed as KBr discs in the range 3500–500 cm^{-1}.

2.2. Synthesis of TMG IL

A 50-mL reaction flask was charged with a solution of TMG (2 mmol) in CH_2Cl_2 (15 mL). To the resulting solution was added chlorosulfonic acid (2 mmol) in CH_2Cl_2 (10 mL) over a period of 5 min at 0 °C. After the addition was complete, the reaction mixture was stirred at room temperature for 40 min. At this point, the reaction mixture was concentrated by rotary evaporation; the concentrated mixture was then washed with CH_2Cl_2 (30 mL) and dried by rotary evaporation at 70 °C to afford TMG IL as a colorless solid (Scheme 1).

TMG IL: white solid, mp 40–42 °C and decomposition point (by thermogravimetric analysis (TGA)) 287.2 °C. IR (KBr): ν (cm^{-1}) 3284, 3115, 1650, 1608, 1558, 1415, 1162, 1070, 885, 733, 657, 598; ^1H NMR (400 MHz, D_2O): δ (ppm) 2.81 (s, 12H, $–CH_3 \times 4$); ^{13}C NMR (100 MHz, D_2O): δ (ppm) 161.5, 38.8; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.74 (s, 2H, $–NH_2$) 2.85 (s, 12H, $–CH_3 \times 4$); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 161.3, 39.3. Anal. cacld for $C_5H_{14}N_3O_3SCl$: C, 25.92; H, 6.09; N, 18.14. Found: C, 26.96; H, 6.01; N, 19.57.

2.3. General procedure for synthesis of BIMs

To a mixture of indole, 2-methylindole, or 5-bromoindole (2 mmol) and aldehyde (1 mmol) in a 50-mL reaction flask equipped with a magnetic stirring bar was added the IL (3 mol %); the resulting reaction mixture was stirred at r.t. After completion of the reaction (monitored by TLC), the product was extracted with 20 mL of ethyl acetate (EA). The solvent was evaporated under reduced pressure, and the obtained solid was washed with hexane and recrystallized from ethanol to afford the product. The insoluble IL was separated by simple filtration, washed twice with EA, and then dried under vacuum before reuse. All the previously known products afforded spectral and physical data consistent with those reported in the literature for samples prepared using previously reported methods. The new products were characterized by their melting points, as well as IR, ^{1}H NMR, and ^{13}C NMR spectra. Detailed descriptions of reaction times, yields, melting points, and spectral data for all compounds **1–36** are given in Supporting Information.

3. Results and Discussion

3.1. Characterization of the new TMG IL

A simple stoichiometric reaction of TMG with chlorosulfonic acid under mild conditions afforded a colorless solid after evaporation of the solvents, without using any specific purification procedures. The spectrum (see Fig. S1 in Supporting Information) showed O=S=O asymmetric and symmetric stretching peaks at 1162 and 1070 cm^{-1}, respectively, and an S–O stretching peak at 733 cm^{-1}, which precisely confirmed the SO_3 group linkage. Further, the C=N vibrations at 1650 cm^{-1}indicated the presence of an imine. The abovementioned peaks confirmed the IL identity, and were in good agreement with the reported data [27].

The ^{1}H and ^{13}C NMR spectra of TMG IL were also recorded (Fig. 1). The ^{1}H NMR spectrum (Fig. 1(a)) of the TMG IL shows a single peak at 2.81 ppm, assigned to methyl protons. Note that the guanidinium protons are observed in D_2O as HDO at 4.5 ppm, because of H-D exchange. However, when recording the ^{1}H NMR spectrum in DMSO-d_6 (Fig. 1(c)), the guanidinium protons are observed at 7.47 ppm, together with the methyl protons at 2.85 ppm, indicating that the $ClSO_3H$ proton migrated to TMG. The absence of observable peaks between 11 ppm and 14 ppm further confirms this migration. In addition, no peaks indicating the existence of unreacted $ClSO_3H$ are observed. In the ^{13}C NMR spectra (Figs. 1(b) and 1(d)), two peaks are observed at 161.5 and 38.8 ppm in D_2O, and at 161.3 and 39.7 ppm in DMSO-d_6, which are attributed to C=N and –N–CH_3 carbons, respectively. Gao et al. [27] reported a TMG IL structure with the positive charge on the carbon atom; if this were true, the carbon peak in the ^{13}C NMR would appear at 44–45 ppm. However, in Figs. 1(b) and 1(d), no peaks at 44–45 ppm were observed, indicating that the positive charge is located on the nitrogen atom; this was confirmed by the presence of the imine carbon peak at 161.5 ppm in Fig. 1(b) and at 161.3 ppm in Fig. 1(d). The TMG IL was also characterized by powder X-ray diffraction (XRD) (Fig. 2(a)). The XRD pattern showed characteristic diffraction peaks of the IL, indicating a crystalline structure. Moreover, the characteristic peaks at 2θ = 25°–80° indicate a SO_3 group, confirming that this IL contains an SO_3 functionality [28]. The thermal stability of the TMG IL, as measured by thermogravimetric analysis (TGA), is shown in Fig. 2(b). Complete degradation occurred between 265 and 365 °C, indicating that the IL is stable up to 250 °C.

3.3. Application of TMG IL for the synthesis of BIMs

The synthesis of BIMs can be classified as a pseudo three-component reaction (TCR), i.e., two molecules of indole react with one molecule of aldehyde. In general, TCRs usually require high reaction temperatures, long reaction times, high catalyst loadings, and exotic reagents to promote the formation of the desired product. To avoid these problems, TCRs can be carried out with suitable promoters, which are inexpensive, easily available, and recyclable. Initially, BIMs were prepared in the presence of an inexpensive superbase TMG, in which case the product yield was low. The reaction was carried out with $ClSO_3H$, but this resulted in charring; as a result, we could not identify the products. We next proposed that the low yields could be improved if TMG and $ClSO_3H$ were combined to form the new ionic liquid TMG IL, which could be applied to the synthesis of BIMs. Gratifyingly, the reactions proceeded smoothly in high yields. The synergetic effect of the TMG IL reactions results in better yields as compared to those obtained with individual TMG or $ClSO_3H$. First, the reactions were carried out in different organic solvents such as CH_3CN, CH_2Cl_2, and THF. While these solvents smoothly facilitated the reaction with acceptable yields (85%), long reaction times (2–3 h) were required. Subsequently, we decided to carry out the reaction under neat conditions; in this case, the reaction proceeded to completion within 40 min, affording the product in quantitative yield (96%).

To determine the appropriate concentration of TMG IL, we investigated the model reaction at different catalyst loadings of 1.0, 2.0, 3.0, and 4.0 mol%, which afforded product yields of 65%, 72%, 96%, and 96%, respectively. The product yield remained constant at 96% when the catalyst was increased from 3.0 to 4.0 mol%, indicating that a 3.0 mol% loading was sufficient for optimal results considering the reaction time and product yield (Fig. 3(a)).

After optimization of the reaction conditions, additional reactions of indole and its derivatives with various substituted aromatic aldehydes were carried out in the presence of 3 mol% TMG IL under neat conditions to establish the generality of this methodology; the results are summarized in the Experimental section. All the reactions proceeded smoothly to afford the products in good yields. Both electron-donating and electron-withdrawing substituents on the indole moiety were suitable for the reaction, and the corresponding substituted products were successfully isolated .2-Methylindole afforded a lower product yield as compared to 5-bromoindole and indole because of the methyl substituent at the 2-position. Aromatic aldehydes containing electron-donating, electron-withdrawing, and halogen substituents on the aromatic ring were utilized successfully in the reaction, and the desired products were obtained in high yields within a very short time. The reaction did not proceed with ketones because of their lower reactivity and higher stability as compared to aldehydes.

The merits of TMG IL were compared with those of other reported ILs for the synthesis of BIMs. Very recently, Das et al. [20] reported the use of secondary amine-based ILs for the synthesis of BIMs using microwave irradiation, an additional energy source for product formation, as well as column chromatography for product isolation. In 2009, Rad-Moghadam

[19] demonstrated the synthesis of BIMs promoted by [TMGT] and [TMGTf] ILs (TMGT: *N*,*N*,*N*,*N*-tetra methyl guanidinium trifluoroacetate; TMGTf: *N*,*N*,*N*,*N*-tetra methyl guanidinium triflate). In that study, [TMGT] was found to be superior to [TMGTf]. For [TMGT], the TMG is neutralized with trifluoroacetic acid (TFA), which is a good chemical reagent for organic transformations. The synthesis of BIMs was possible only under drastic conditions in the case of using [TMGTf]. In addition, Yadav et al. [17] reported the synthesis of BIMs using [bmim]BF_4 or [bmim]PF_6 over a reaction time of almost 270 min, and with 92% yield. Chakraborti et al. [18] also reported the synthesis of BIMs in 95% yield using a [bmim][$MeSO_4$] IL, which required a tedious work-up procedure. Compared to the abovementioned ILs, the new TMG IL described here is superior for the synthesis of BIMs; this is because of the high yields and the non-requirement of drastic reaction conditions, additional energy sources (i.e., microwave, ultrasonication), and laborious work-up procedures. The full comparison is summarized in Table1.

The reusability of the TMG IL was also examined for the preparation of compound **1** from the reaction of indole with benzaldehyde. The catalyst was easily recovered by the addition of EA to the reaction mixture; the insoluble TMG IL could be separated by simple filtration, washing twice with EA (30 mL), and drying in vacuum. The catalyst displayed good reusability after three runs (Fig. 3(b)).

The structures of all the compounds were confirmed using IR, ^{1}H, and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectra, the –NH proton signal appeared as a singlet at 10.37–7.68 ppm. The Ar–CH proton signal also appeared as a singlet at 6.27–5.28 ppm, confirming product formation; the remaining proton signals were observed in the expected regions. In the ^{13}C NMR spectrum, the

Ar–CH carbon signal was observed at 54.1–36.8 ppm, confirming the formation of BIMs [29] (see Supporting Information).

4. Conclusions

A simple, highly efficient, and green procedure for the synthesis of BIMs in the presence of a novel TMG IL catalyst, under solvent-free conditions, has been described. This low-cost protocol has several advantages, including a clean reaction medium (solvent-free), use of easily available chemicals, high yields, and easy work-up procedures. This protocol provides the synthetic chemists with a rapid and efficient method for preparing nitrogen-containing heterocycles. In addition, the structure of the novel TMG IL is confirmed by FTIR and NMR spectroscopic analyses, XRD techniques, and TGA.

Acknowledgements

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Captions

Scheme caption

Scheme 1. Preparation of BIMs by the reaction of indoles and aldehydes in the presence of a TMG IL catalyst.

Figure captions

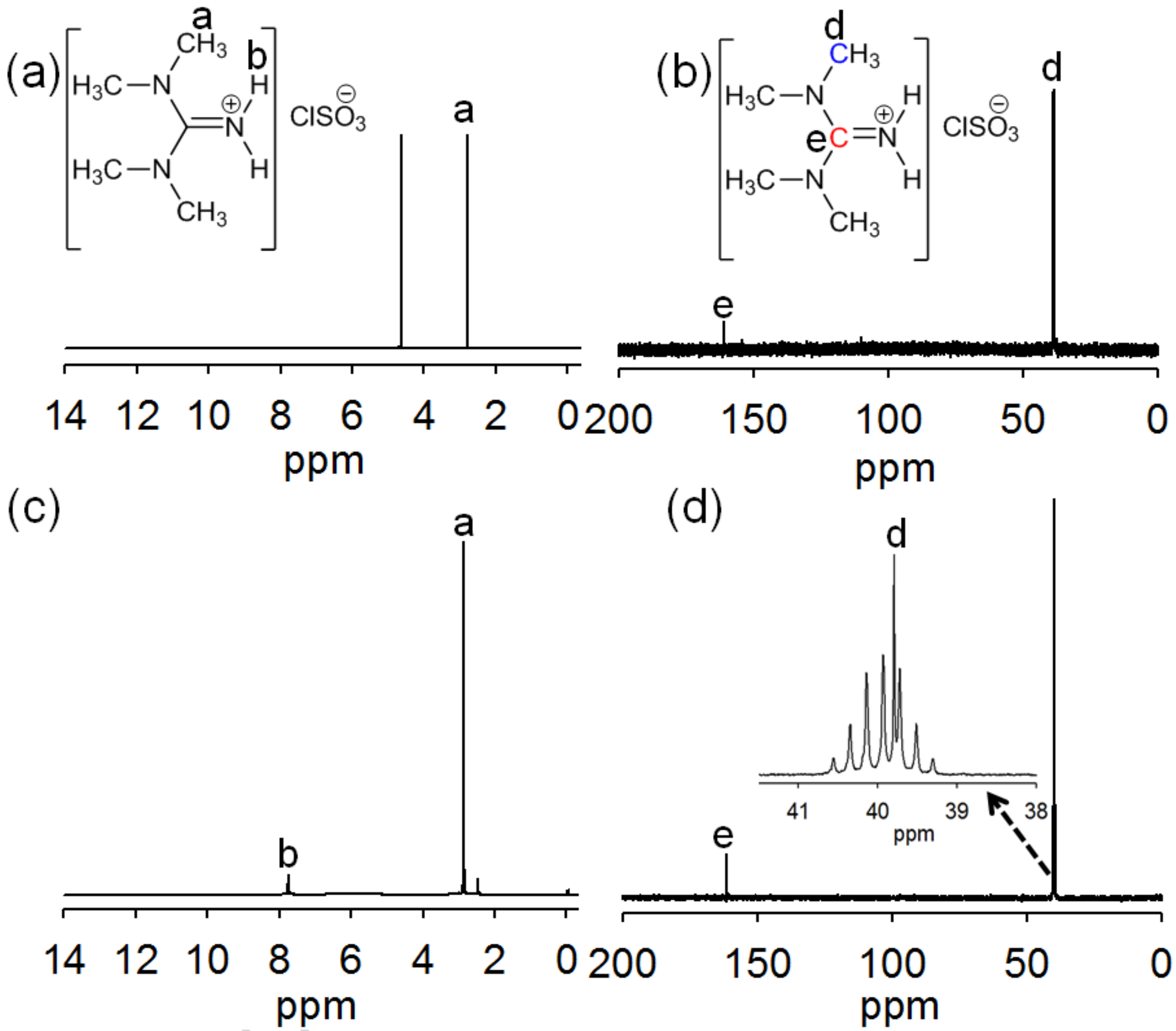
Fig. 1. ^{1}H and ^{13}CNMR spectra of TMG IL measured in D_2O [(a) and (b)] and DMSO-d_6 [(c) and (d)].

Fig. 2. (a) XRD pattern and (b) thermogram of TMG IL.

Fig. 3. Effect of the amount (a) and recycle (TMG IL = 3.0 mol%) (b) of TMG IL on the yield of compound **1**. Conditions: indole = 2 mmol and benzaldehyde= 1 mmol.

Table caption

Table 1. Comparison of various ILs and normal catalyst for the synthesis of BIMs.


(a)
a
b
H_3C-N
CH_3
$ClSO_3^{\ominus}$
a
14 12 10 8 6 4 2 0
ppm
(b)
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e
$ClSO_3^{\ominus}$
d
e
200 150 100 50 0
ppm
(c)
a
b
14 12 10 8 6 4 2 0
ppm
(d)
d
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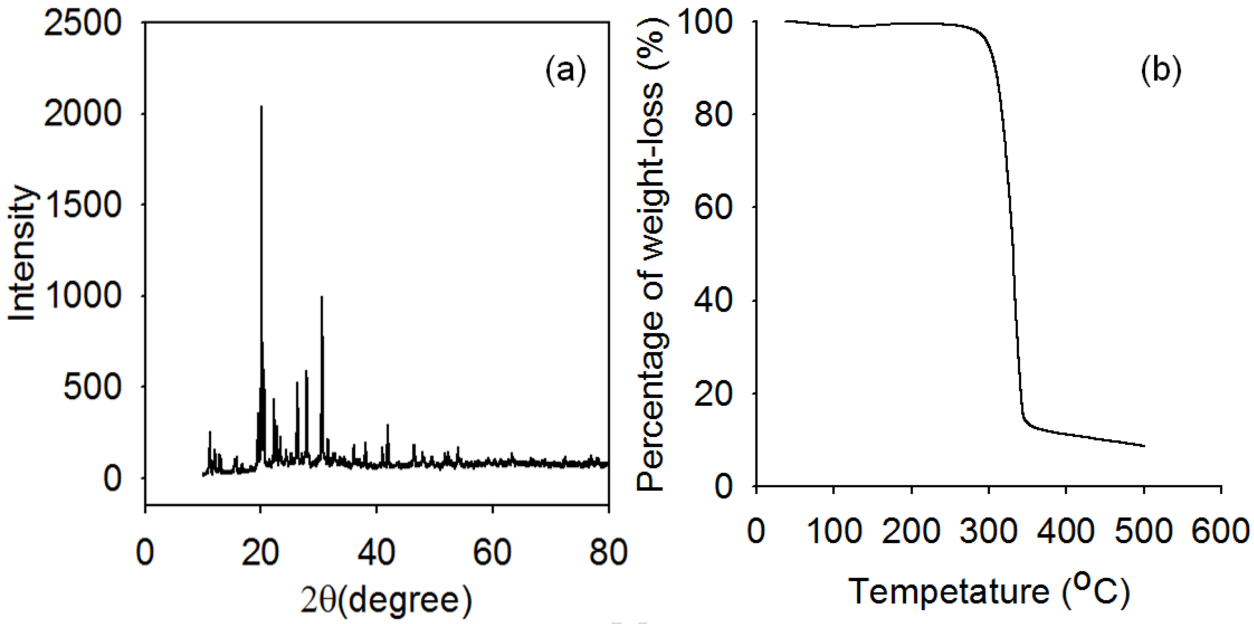
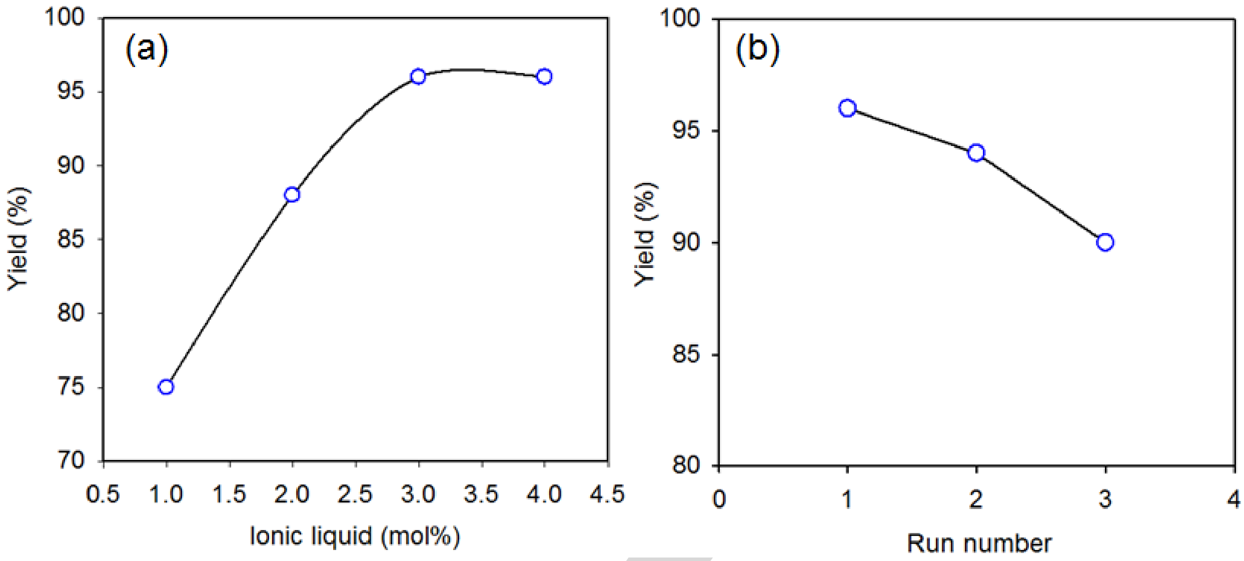
ppm
e
200 150 100 50 0
ppm

Figure 1

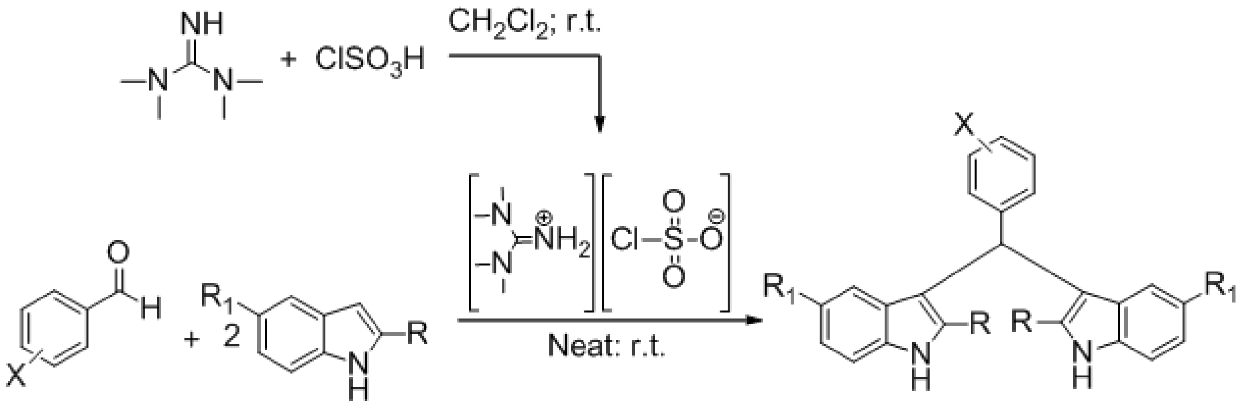


2500
2000
1500
1000
500
0
Intensity
(a)
0
20
40
60
80
2θ(degree)
100
80
60
40
20
0
Percentage of weight-loss (%)
(b)
0
100
200
300
400
500
600
Tempetature (^{O}C)

Figure


(a)
Yield (%)
100
95
90
85
80
75
70
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
Ionic liquid (mol%)
(b)
Yield (%)
100
95
90
85
80
0
1
2
3
4
Run number

Figure



Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
X	H	2-CN	4-OH	3,4-OH	2-Cl	2-Br	3-Br	4-Br	4-Me	4-OMe	3,5-OMe	4-NO$_2$
R	H	H	H	H	H	H	H	H	H	H	H	H
R$_1$	H	H	H	H	H	H	H	H	H	H	H	H
Yield (%)	96	93	92	90	95	93	95	96	91	90	94	96

Compound	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
X	H	2-CN	4-OH	3,4-OH	2-Cl	2-Br	3-Br	4-Br	4-Me	4-OMe	3,5-OMe,	4-NO$_2$
R	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me
R$_1$	H	H	H	H	H	H	H	H	H	H	H	H
Yield (%)	94	94	93	91	95	94	95	96	91	92	94	96

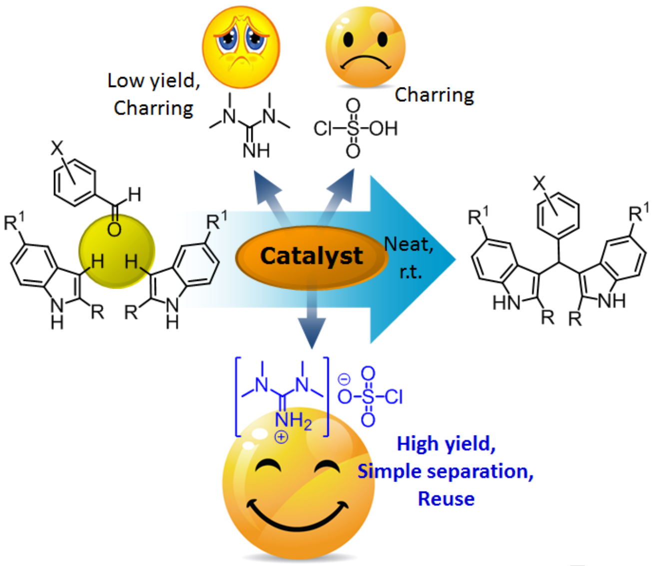
Compound	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
X	H	2-CN	4-OH	3,4-OH	2-Cl	2-Br	3-Br	4-Br	4-Me	4-OMe	3,5-OMe,	4-NO$_2$
R	H	H	H	H	H	H	H	H	H	H	H	H
R$_1$	Br	Br	Br	Br	Br	Br	Br	Br	Br	Br	Br	Br
Yield (%)	96	93	92	90	95	94	95	96	91	92	94	96

Scheme 1

Table 1. Comparison of various ILs and normal catalyst for the synthesis of BIMs.

Entry	IL (amount)	Condition	Time (min)	Yield (%)	Ref.
1	Secondary amine based ILs (10mol %)	Microwave	3	99	20
2	[TMGT][TMGT$_f$] (1 mL)	Neat	15	93	19
3	[bmim]BF$_4$or [bmim]PF$_6$ (2 mL)	Neat	270	87	17
4	[bmim][MeSO$_4$] (5 mol %)	Neat	20	92	18
5	Pyridinium tribromide (2 mol %)	CH_3CN	20	96	30
6	Dodecylbenzenesulfonic Acid (30 mol %)	H_2O	18	97	31
7	TMG IL (3mol %)	Neat	40	96	This work

Graphical Abstract



Highlights

- ▸Novel tetramethylguanidineionic liquid (TMG IL) is synthesized and well characterized.
- ▸The TMG IL is an excellent organocatalyst for the synthesis of bisindolylmethanes.
- ▸Bisindolylmethanes are obtained in quantitative yields at environmentally benign conditions.
- ▸ The TMG IL catalyst is recyclable without losing its catalytic activity.