



ORIGINAL ARTICLE

Morpholinium bisulfate [morH][HSO₄]: An efficient and reusable catalyst for the synthesis of bis(indolyl)methanes



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Abstract Morpholinium bisulfate [morH][HSO₄] ionic liquid was found to be an effective catalyst for the condensation reaction of indoles with carbonyl compound at room temperature. Present methodology has several merits such as mild reaction condition, inexpensive catalyst, stable at room temperature and it was also found that this catalyst could be recovered quantitatively and reused without much loss of catalytic activity.

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1. Introduction

Room temperature ionic liquids (RTILs) emerging as greener alternative reaction media as well as catalyst towards conventional organic solvents which is an important part of today's drive towards sustainable chemistry (Sheldon, 2005). Ionic liquids (ILs) were introduced because of their unique chemical and physical properties of non-volatility, non-flammability, thermal stability, and ease of recyclability (Yadav et al., 2005)

In the past several years, great deal of attention has been given towards imidazolium based ionic liquids *viz*

[bmim]Br (Wu et al., 2009), [bmim]BF₄ (Park and Lee, 2009), [bmim]NTf₂ (Vale et al., 2009), [hmim]PF₆ (Sarma and Prajapati, 2008), [mim'-OH][OMs] (Shinde et al., 2008), [Hbim]BF₄ (Siddiqui et al., 2005). Although the unique advantage of ionic liquid as reaction media and catalyst they have not been applied in industries probably due to high cost of ionic liquids, difficulty in separation or recycling. Therefore, cost-effective and environmentally practicable ionic liquids are gaining significant importance.

Bis(indolyl)methanes, indole and its derivatives are known as an important class of heterocyclic compounds and bioactive intermediates in R&D and pharmaceutical industry (Sundberg, 1996). Bis(indolyl)methanes are found in cruciferous plants and are known to promote beneficial estrogen metabolism and induce apoptosis in human cancer cell (Glasby, 1975). Therefore, there is great interest in the synthesis of these compounds (Chakrabarty et al., 2002; Reddy et al., 2003). Synthetically, the reaction of 1*H*-indole with aldehydes or ketones

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produces azafulvenium salts that react further with a second 1*H*-indole molecule to form bis(indol-3-yl)methanes (Remers, 1972).

In recent years, synthesis of this class of molecules under mild conditions have been reported with promoters, such as Montmorillonite clay K-10 (Chakrabarty et al., 2004), trichloro-1,3,5-triazine (Sharma et al., 2004), AlPW₁₂O₄₀ (Firouzabadi et al., 2005), sodium dodecyl sulfate (SDS) (Deb and Bhuyan, 2005), ZrCl₄ (Zhang et al., 2005), H₂NSO₃H (Li et al., 2006), I₂ (Bandgar and Shaikh, 2003), zeolites (Kart-hik et al., 2004), bentonite (Penieres et al., 2003), In(OTf)₃/ionic liquid (Ji et al., 2003), CuBr₂ (Mo et al., 2005), Dy(OTf)₃/ionic liquid (Mi et al., 2004), HClO₄-SiO₂ (Kamble et al., 2007), InCl₃ (Pradhan et al., 2005), MW/Lewis acids (FeCl₃, BiCl₃, InCl₃, ZnCl₂, CoCl₂) (Xia et al., 2004), NaHSO₄ and Amberlyst-15 (Ramesh et al., 2003), sulfated zirconia (Reddy et al., 2005), ZrOCl₂/SiO₂ (Firouzabadi et al., 2006), silica sulfuric acid (SSA) (Zolfigol et al., 2008), TiO₂ (Hosseini, 2007), (NH₄)₂HPO₄ (Dabiri et al., 2007), acidic ionic liquid (Hagiwara et al., 2007), NaBF₄ (Kamble et al., 2007), metal hydrogen sulfates (Niknam et al., 2006), tetrabutylammonium tribromide (Lin et al., 2006), superacid SO₄²⁻/TiO₂ (Zeng and Ji, 2006), NBS (Koshima and Matsuoka, 2002), Ph₃CCl (Khalafi et al., 2008), H₃PW₁₂O₄₀ (Azizi et al., 2007), LiClO₄ (Mehrazma et al., 2006), and Bi(NO₃)₃·5H₂O (Khodaei et al., 2008). However, many of the above-mentioned catalytical systems are corrosive and often cause heavy environmental pollution because of the difficult separation from the reaction medium. Furthermore, the reactions require long reaction times and often give unsatisfactory yields. Most of the existing methods involve toxic metal ions and solvent, high cost, and cumbersome work-up procedures. Consequently, new procedures that address these drawbacks are desirable.

2. Experimental

All the melting points were recorded in open capillaries. The IR spectra were recorded on FT/IR-410 type (A) spectrophotometer in KBr and adsorptions are expressed in cm⁻¹. ¹H NMR spectra were measured in DMSO-*d*₆ solution on a Bruker spectrophotometer at 400 MHz. Electron-spray ionization mass spectra (ES-MS) were recorded on a Water-Micro mass Quattro-II spectrometer.

2.1. General procedure for the synthesis of bis(indolyl)methanes (3a-q)

Mixture of aldehyde (1 mmol) and indole (2 mmol) was taken in mortar in the presence of morpholinium bisulfate

(10 mol%) and was stirred vigorously for appropriate time at room temperature. The course of the reaction was monitored by TLC. After completion of the reaction, the mixture was quenched with ice cold water and solid product obtained was collected by filtration. Further purification was accomplished by recrystallization from ethanol to afford final product which was in full agreement with the spectral data.

2.1.1. 3,3' Bis(indolyl) phenylmethane (3a)

IR (KBr, cm⁻¹): 3478, 3019, 1601, 1522, 1456, 1419, 1215, 1093, 1017, 757, 669 cm⁻¹; PMR (CDCl₃): δH 5.89(s, 1H), 6.67(s, 2H), 7.09–7.58(m, 13H), 7.94(bs, 2H, NH); ES-MS E/Z 322(M⁺).

2.1.2. 3,3' Bis(indolyl)-4-methylphenylmethane (3b)

IR (KBr): 3480, 3020, 1602, 1512, 1456, 1417, 1215, 1091, 1021, 759, 669 cm⁻¹; PMR (CDCl₃): δH 2.31(s, 3H), 5.84(s, 1H), 6.64(s, 2H), 6.85–7.40(m, 12H), 7.94(bs, 2H, NH); ES-MS E/Z 336(M⁺).

2.1.3. 3,3' Bis(indolyl)-4-chlorophenylmethane (3d)

IR (KBr, cm⁻¹): 3478, 3020, 2927, 1600, 1523, 1456, 1417, 1216, 1091, 1015, 759 670; PMR. (CDCl₃): δH 5.88 (s, 1H), 6.63 (brs, 2H), 7.00–7.70(m, 12H), 7.92(bs, 2H, NH); ES-MS E/Z 322(M⁺).

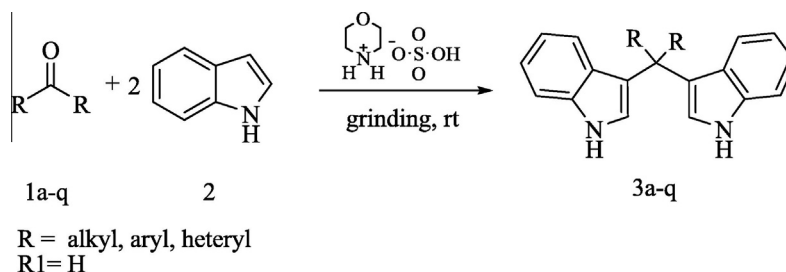
2.1.4. 3,3' Bisindolyl(2-furfuryl)methane (3o)

IR (KBr): 3477, 3019, 2399, 1600, 1456, 1419, 1216, 1093, 1021, 757, 670 cm⁻¹; PMR (CDCl₃): δH 5.94 (s, 1H), 6.06 (d, 1H), 6.30(d, 1H), 6.87(d, 1H), 7.08(t, 2H), 7.17(t, 2H), 7.29–7.48(m, 5H), 7.95(bs, 2H, NH); ES-MS E/Z 312(M⁺).

3. Results and discussion

In the present work highly inexpensive, reusable, mild morpholinium bisulfate [morH][HSO₄] ionic liquid was implemented as a catalyst for the synthesis of (BIMs) by the reaction of aldehyde and indole. The reaction was carried out by grinding at room temperature (Scheme 1). This catalyst in comparison to the reported ionic liquids with Brønsted acidic counter ions can be prepared from inexpensive starting materials and is quite stable at room temperature (Hajipour et al., 2008).

Choosing an appropriate solvent is of crucial importance for successful organic synthesis. Therefore, we initially investigated the effect of solvent on the synthesis of bis(indolyl)methanes (Table 2). The reaction of 4-Cl-benzaldehyde (1 mmol), and indole (2 mmol) considered as model reaction (Table 3, entry 3d) and was examined in the presence of [morH][HSO₄] as catalyst under various solvent. From the results we observe



Scheme 1

Table 1 Optimization of catalyst.

Entry	Catalyst (mol%)	Time (min)	Yield (%) ^a
1	0	30	–
2	2	30	75
3	5	10	87
4	10	05	96
5	15	05	94
6	20	12	95

^a Isolated yields.

that, the use of solvents retards the rate of reaction which ultimately resulted in decrease in the product yield with prolonged reaction time (Table 1, entries 1–5). When we carry out the reaction solvent-free by grinding at room temperature in the presence of [morH][HSO₄], the reaction proceeds smoothly by giving 96% of yield (Table 1, entry 6). After complete optimization, [morH][HSO₄] was found to be the appropriate catalyst for this reaction (Table 1, entry 6).

By taking the optimization of solvent effect into account we further investigated the quantity of catalyst required for the reaction. Same reaction of 4-Cl-benzaldehyde and indole was chosen as model reaction (Table 3, entry 3d). The results showed that the reaction did not proceed in the absence of the catalyst. As we implement 2–5 mol% of catalyst the reaction proceeds smoothly by giving 75–87% of the yield within 30–10 min. After increasing the percentage of the catalyst the yields were also found to be increased (Table 2, entries 2–6). But 10 mol% of the catalyst gave exclusively better results because molecules present in the 10 mol% of the catalyst are sufficient to carry out the catalytical role. Higher amount of the catalyst did not improve the yield to greater extent because as the yield was not increasing by the increase in the catalyst quantity that means only 10 mol% of the catalyst was involved and used during the reaction by the reactants to give final product. Thus, 10 mol% of catalyst was found to be sufficient amount of the catalyst for better results (Table 2, entry 4).

In order to explore the applicability and scope of the methodology a wide range of structurally diverse and functionalized aromatic, aliphatic and heteroaromatic aldehydes were examined, which underwent very rapid condensation in good to excellent yields (Table 3, entries 3a–q).

In terms of electronic effect and nature of substituent on aromatic, and hetero aromatic aldehydes we do not observe

Table 2 Optimization of solvent effect.^a

Entry	Solvent ^b :Catalyst ^c	Time (min)	Yield ^d (%)
1	Water:[morH][HSO ₄]	60	28
2	DCM:[morH][HSO ₄]	60	37
3	THF:[morH][HSO ₄]	60	64
4	EtOH:[morH][HSO ₄]	60	82
5	CH ₃ CN:[morH][HSO ₄]	60	73
6	[morH][HSO ₄] ^c	12	96 ^e

^a Reaction condition: 4-Cl-benzaldehyde (1 mmol), indole (2 mmol), [morH][HSO₄] (10 mol%) stirred at RT.^b 5 mL of solvent was used.^c 10 mol% of morpholinium bisulfate.^d Yields were isolated.^e Reaction was stirred vigorously at RT.**Table 3** Characterization of Bis(indolyl)methanes in the presence of [morH][HSO₄].

Entry	Aldehydes	Time (min)	Yield (%) ^a	MP ^b (°C)
3a	H	5	97	124–126
3b	4-CH ₃	8	94	96–98
3c	4-OCH ₃	8	95	97–99
3d	4-Cl	5	96	104–106
3e	2-Cl	5	95	71–73
3f	4-F	5	97	73–75
3g	4-NO ₂	10	93	223–225
3h	3-NO ₂	15	92	267–269
3j	4-OH	12	94	123–125
3k	2-OH	15	93	> 300
3l	Cinnam aldehyde	15	92	101–103
3o	Furan-2-carbaldehyde	25	83	320–322
3p	Thiophene-2-carbaldehyde	27	81	152–154
3q	2-Piperanaldehyde	20	85	100–102

^a Isolated yield.^b The spectroscopic and physical data of obtained products were compared with the literature data (Vale et al., 2009; Wu et al., 2009).**Table 4** Reusability of the catalyst.^b

Runs	Time (min)	Yield ^a
Fresh	25	97
1	25	97
2	27	95
3	30	94

^a Yields were isolated.

any strong obvious effect on time and yield of the product. In other words, when electron-donating groups (–OCH₃, –CH₃, –OH) and electron-withdrawing groups (–Cl, –NO₂, –F) were employed the reaction proceeds smoothly with shorter reaction time and gives good to excellent yields. Results with hetero aromatic aldehydes were also found to be satisfactory (Table 3, entries 3o and 3p).

The reactions were carried out in the simplest manner, only by grinding the mixture of aldehydes, indole and catalytical amount of [morH][HSO₄]. The preparation of catalyst was also very cheap which was prepared at room temperature.

The recovery and reuse of solvent and catalyst are highly preferable in terms of green synthetic process. Therefore, with the success of above reaction methodology, we continued our research by studying reusability of [morH][HSO₄] (Table 4). Reaction of benzaldehyde (1 mmol) and indole (2 mmol) was chosen as model reaction for this investigation. The results showed the catalytic activity of the catalyst did not show any significant decrease even after three runs (Table 4). The catalyst can also be reused even after three runs for the same model reaction.

4. Conclusion

In conclusion, we have used mild, efficient and effective methodology for the synthesis of bis(indolyl)methanes in presence of the morpholinium bisulfate as catalyst [morH][HSO₄]. The use of highly inexpensive, mild with high catalytical activity

is another advantage of this method. In contrast to other acids, storage and handling of this catalyst do not need special precautions and it can be stored on the bench top for weeks without losing its catalytic activity.

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