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Fischer Indole Synthesis in Brønsted Acidic Ionic Liquids: A Green, Mild, and Regiospecific Reaction System

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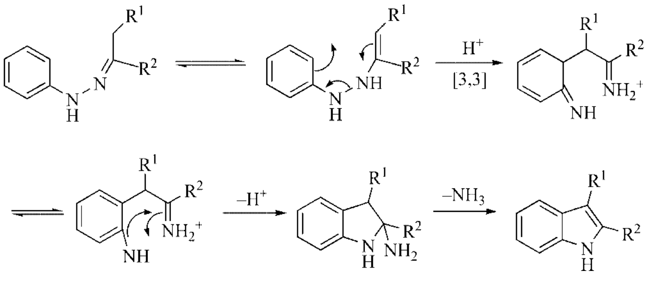
A novel one-pot Fischer indole synthesis approach has been developed by using Brønsted acidic ionic liquids as dual solvent-catalysts. Yields of 83–97 % were obtained after reaction in $BMImHSO_4$ at 70–110 °C in 0.5–6 h, and exclusive formation of 2,3-disubstituted indoles was observed in the reaction of alkyl methyl unsymmetrical ketones. The indoles produced could be conveniently separated from the reaction mixture without any volatile organic solvents, and the $BMImHSO_4$ could be readily reused without efficiency loss after simple treatment involving only 1 equiv. of HCl for neutralization followed by filtration.

1. Introduction

The indole ring system is probably the most ubiquitous heterocycle that represents an important structural component in many pharmacologically active compounds. Although many methods have been developed for the synthesis of indoles,[1] Fischer indole synthesis is still one of the most versatile and widely employed methodologies for the preparation of indole intermediates and biologically active compounds.[2] It can be regarded as the elimination of ammonia from the *N*-arylhydrazone of a ketone through a [3,3] sigmatropic rearrangement with an acid catalyst (Scheme 1).[3] Since its discovery in the 1880s by Emil Fischer, various catalysts have been used to effect the cyclization of arylhydrazones derived from ketones. Alternative catalysts, including Brønsted acids (H_2SO_4, HCl, PPA, AcOH),[4] Lewis acids ($ZnCl_2$, $TiCl_4$, PCl_3),[5] and solid acids (zeolite, montmorillonite clay),[6] have been reported for the synthesis of the indole nucleus, but the search for new catalysts is still being actively pursued because the reported Brønsted and Lewis acids are environmentally unfriendly, hazardous, or difficult to reuse, and they are usually required in large amounts. For example, PCl_3 is needed in equimolar quantity, PPA in 8–9-fold excess by weight, and $ZnCl_2$ is used in as large as a 3-fold excess. Although utilization of solid acids may solve the above problems, solid acids′ own shortcomings limit their application to some degree such as restricted accessibility of the matrix-bound acidic sites, rapid deactivation, and decrease of activity site per area. In addition, traditional organic solvents are still used which can have a considerable environmental impact. Noncatalytic Fischer indole syntheses have also been studied in different solvents such as ethylene glycol, diethylene glycol, and tetralin; however, high temperatures above 200 °C are required for such a cyclization.[7]



Scheme 1. The mechanism for Fischer indole synthesis with an acid catalyst.

The development of one-pot approaches to the indole scaffold is attracting considerable attention because of their significance from both economical and ecological points of view. These methods usually directly start from a single, commercially available precursor, which obviates the preparation or isolation of the unstable arylhydrazones (Scheme 2). Some reported examples within this context are listed below: (1) one-pot synthesis of 5-substituted *N*,*N*-dimethyltryptamine with the use of 4% H_2SO_4;[8] (2) one-pot synthesis of 1,2,3,4-tetrahydrocarbazole, which involves the use of trifluoroacetic anhydride and the recycling of trifluoroacetic acid;[9] (3) one-pot synthesis of the indole scaffold by using K-10 montmorillonite as a catalyst in MeOH.[6c] Clearly, in spite of the diverse synthetic approaches developed so far, it is hoped that environmentally

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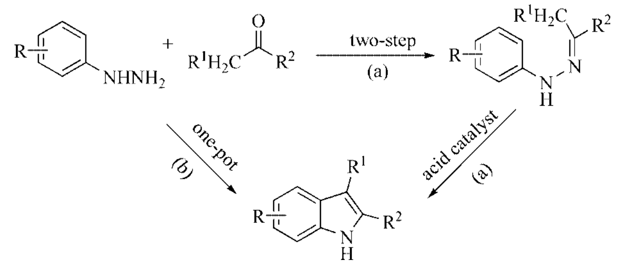
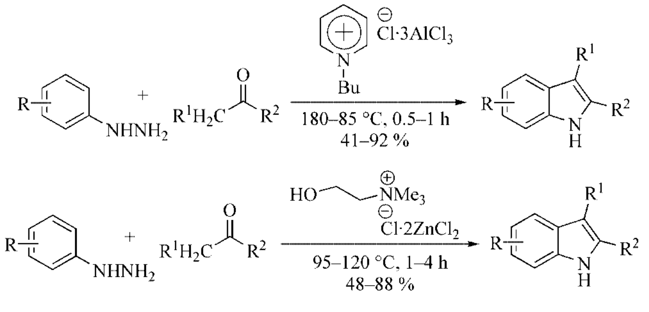
friendly one-pot options will be adopted and it seems possible. Recently, with the development of ionic liquids, there have been reports concerning the one-pot Fischer indole synthesis in Lewis acidic ionic liquids such as 1-butylpyridinium chloride·$3AlCl_3$ or choline chloride·$2ZnCl_2$ (Scheme 3).[10]

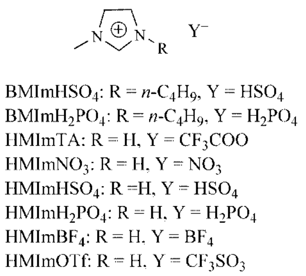


Scheme 2. The Fischer indole synthesis with (a) conventional two-step route and (b) one-pot method.



Scheme 3. The Fischer indole synthesis with the use of Lewis acidic ionic liquids.

With the approach to minimize the use of hazardous materials or volatile solvents in reactions, ionic liquids have attracted much attention because of their advantageous properties, which include negligible vapor pressure, high thermal stability, large electrochemical window, and easy of recycling.[11] In recent years, ionic liquids have been widely researched in many organic reactions for the replacement of traditional solvents or catalysts.[12] In particular, the task-specific ionic liquids (TSILs), in which a functional group is covalently tethered to the cation or anion, further enlarges the application scope of ionic liquids in chemistry.[13] Brønsted acidic ionic liquids (BAILs) are one kind of TSILs, which contain a Brønsted acid functionalized component in the cation or anion. Because of their unique features, such as their nonvolatility, flexibility, noncorrosiveness, and immiscibility with nonpolar organic solvents, they have exhibited great potential as alternatives to conventional acids in acid-catalyzed reactions, such as Fischer esterification,[14] acetalization of carbonyls,[15] dimerization of α-methylstyrene,[16] alkylation of phenol with TBA,[17] and Mannich reactions.[18] In contrast to conventional acids and Lewis acidic ionic liquids, the BAILs have their own advantages as follows: (1) their "greenness" features make them environmentally benign and safe; (2) they are air- and moisture-stable; (3) their preparation procedures are relatively simple and the acidity can be adjusted by the careful choice of the cation or anion; (4) product isolation from these BAILs is easy and the remaining BAILs can be readily recycled. Here, we first report a green, mild, and regiospecific reaction system for the one-pot Fischer indole synthesis by using BAILs. In the reaction process, no other organic solvents or catalysts are used and the BAILs act as dual solvent-catalysts. The BAILs used are depicted in Figure 1.



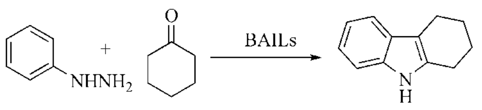
$BMImHSO_4$: $R = n\text{-}C_4H_9$, $Y = HSO_4$
$BMImH_2PO_4$: $R = n\text{-}C_4H_9$, $Y = H_2PO_4$
HMImTA: R = H, $Y = CF_3COO$
$HMImNO_3$: R = H, $Y = NO_3$
$HMImHSO_4$: R = H, $Y = HSO_4$
$HMImH_2PO_4$: R = H, $Y = H_2PO_4$
$HMImBF_4$: R = H, $Y = BF_4$
HMImOTf: R = H, $Y = CF_3SO_3$

Figure 1. The chemical structures of the BAILs used.

2. Results and Discussion

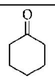
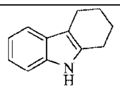
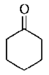
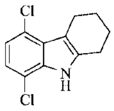
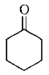
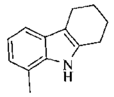
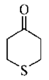
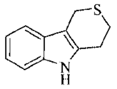
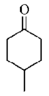
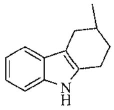
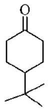
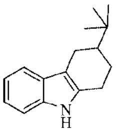
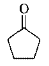
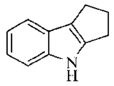
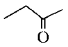
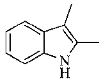
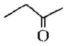
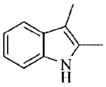
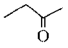
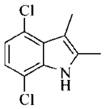
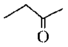
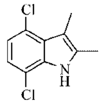
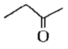
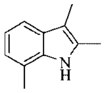
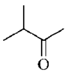
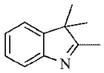
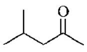
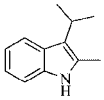
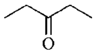
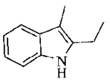
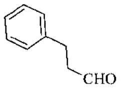
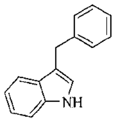
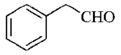
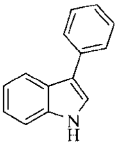
Initially the one-pot Fischer indole synthesis of phenylhydrazine with cyclohexanone was carried out as a model reaction in various BAILs. As shown in Table 1 all of the BAILs tested proved catalytically active in the indole synthesis under mild reaction conditions with yields in the range of 81–92%. The best result was obtained in $BMImHSO_4$, in which the reaction was performed at 70 °C and 92% yield of 1,2,3,4-tetrahydrocarbazole was obtained after 1 h (Entry 1). Even at room temperature, yields of 89% and 82% could also be obtained in $BMImHSO_4$ and $BMImH_2PO_4$, respectively (Entries 2 and 5). The results indicate that BAILs have a high catalytic activity for the Fischer indole synthesis. On the other hand, the catalytic performance of BAILs is dependent on the character of the cation and anion. For BAILs with HSO_4^- and $H_2PO_4^-$ as counteranions, the imidazolium cation with a *n*-butyl group on the alkyl side chain was more advantageous to the reac-

Table 1. The one-pot Fischer indole synthesis of phenylhydrazine with cyclohexanone to afford 1,2,3,4-tetrahydrocarbazole in various BAILs.



Entry	BAILs	Time [h]	*T* [°C]	Yield [%]
1	$BMImHSO_4$	1	70	92
2	$BMImHSO_4$	5	room temp.	89
3	$HMImHSO_4$	1	70	82
4	$BMImH_2PO_4$	1	70	89
5	$BMImH_2PO_4$	14	room temp.	82
6	$HMImH_2PO_4$	0.75	100	80
7	HMImTA	1	70	87
8	$HMImBF_4$	1	70	85
9	$HMImNO_3$	7	100	81
10	HMImOTf	1.5	100	82

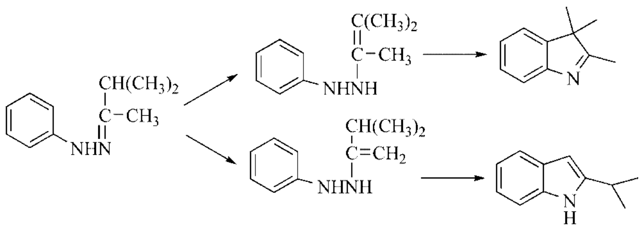
Table 2. One-pot synthesis of Fischer indoles from ketones/aldehydes and phenylhydrazines (substituted phenylhydrazines) in $BMImHSO_4$.[19-31]

Entry	Hydrazine R	Ketone / aldehyde	Indole	T [°C]	Time [h]	Yield [%]	Mp [°C] Found	Mp [°C] Reported
1	H			70	1	92	116–118	118–119[19]
2	2,5-Cl_2			70	0.5	94	90–92	91–93[20]
3	2-CH_3			70	0.5	96	93–94	93–95[19]
4	H			70	1	97	157–159	158–160[21]
5	H			70	1	83	109–110	108–111[22]
6	H			70	1	94	126–127	126–127[23]
7	H			70	3	90	101–103	102–104[24]
8	H			70	3	89	106–107	107[19]
9	H			100	1	88		
10	2,5-Cl_2			70	6	88	90–91	90–91[25]
11	2,5-Cl_2			100	1	88		
12	2-CH_3			70	0.5	90	75–76	76–77[26]
13	H			70	2	91	oil	oil[27]
14	H			110	2	85	oil	oil[28]
15	H			70	3	83	64–65	65–66[29]
16	H			70	0.5	87	103–105	104–106[30]
17	H			70	0.5	88	83–85	84–86[31]

tion than the cation with a hydrogen on the N atom of the imidazolium, 92%, 89% and 82%, 80% yields, respectively (Entry 1 versus Entry 3 and Entry 4 versus Entry 6). For BAILs with the same $[HMIm]^+$ countercation, the catalytic performance of $HMImNO_3$ and HMImOTf were worse than that of the others; phenylhydrazone was formed in the first step, but the [3,3] sigmatropic rearrangement at 70 °C, required for the completion of the one-pot Fischer indole synthesis, did not occur. An elevated temperature of 100 °C and a longer reaction time were required (Entries 9–10) to complete the synthesis. On the basis of the obtained results, $BMImHSO_4$ was found to be superior in terms of activity and yield.

The results of a series of Fischer indole syntheses in $BMImHSO_4$ are summarized in Table 2. The products were characterized by IR, ^1H NMR spectroscopic, and MS analysis, which were consistent with the literature data. As can been seen, $BMImHSO_4$ proved to be highly catalytically active for the one-pot conversion of the ketones/aldehydes and hydrazines to their corresponding indoles at 70–110 °C in 83–97% yields within 6 h. The results are better than those previously reported in Lewis acidic ionic liquid systems[10] and suggest that $BMImHSO_4$ would be a more suitable catalytic system for Fischer indole synthesis. Within the operating conditions, the nature of the substrates was taken into account for the temperature/time parameter. When the temperature was increased, the maximum yield was reached more quickly: for a 30 °C rise in temperature, the reaction time was shortened from 3 h to 1 h (Entry 8 versus Entry 9), and from 6 h to 1 h (Entry 10 versus Entry 11). Moreover, a relatively elevated temperature promoted the completion of the one-pot conversion: the [3,3] sigmatropic rearrangement of the corresponding phenylhydrazone from phenylhydrazine and 4-methyl-2-pentanone occurred rapidly at 110 °C, but did not occur to any extent at 70 °C (Entry 14).

An important issue of the Fischer indole synthesis is the selectivity of the cyclization of the phenylhydrazones derived from unsymmetrical ketones. In previous studies on the Fischer indole synthesis of the phenylhydrazone of isopropyl methyl ketone, a mixture of 2,3,3-trimethylindole and 2-isopropylindole was obtained in different acidic conditions (Scheme 4).[32a] In our studies, in all cases a single more substituted indole was obtained (Entries 8–14), which indicates that $BMImHSO_4$ has a high selectivity as a catalyst. Reports have shown that the direction of cyclization is governed by the acidity of the reaction medium.[32,1a] Lower acid concentrations or weaker acids promote cyclization towards the more branched carbon and higher acid concentrations or stronger acids enhance the extent of cyclization at the less branched position. Therefore, $BMImHSO_4$ should provide a weak acid system for the Fischer indole synthesis and result in a more branched carbon in the indole ring.



Scheme 4. Acid-catalyzed Fischer indole reaction from an unsymmetrical ketone.

Apart from the mild conditions of the process and its excellent results, the simplicity of product isolation and the possibility to recycle the BAILs offer a significant advantage. Because $BMImHSO_4$ is miscible with water and the desired indoles are insoluble in water, the indole products can be directly separated by adding water into the synthetic system after the reaction is complete. The remaining $BMImHSO_4$ can then be recycled after removal of water under vacuum, where some solid material was found in $BMImHSO_4$. According to the mechanism of Fischer indole synthesis, 1 equiv. of NH_3 is produced in the reaction, which can coordinate with HSO_4^- to form ammonium hydrogen sulfate, which is insoluble in $BMImHSO_4$. With the repeated use of $BMImHSO_4$ for a series of reactions, ammonia will accumulate and reduce the efficiency of the reaction as observed by a decrease in the yield. Alternatively, the indole products were isolated by adding water and 1 equiv. HCl, followed by the similar operation as above; in this case, the recycled $BMImHSO_4$ could be reused with

Table 3. Recycling of $BMImHSO_4$ in the synthesis of 1,2,3,4-tetrahydrocarbazole.

Run	$BMImHSO_4$[a]		$BMImHSO_4$[b]	
	t [h]	Yield [%]	*t* [h]	Yield [%]
1	1	92	1	92
2	1.5	89	1	91
3	2.5	82	1	91
4	5.0	74	1	92
5	7	trace	1	90

[a] Product isolation by adding H_2O. [b] Product isolation by adding H_2O and 1 equiv. HCl.

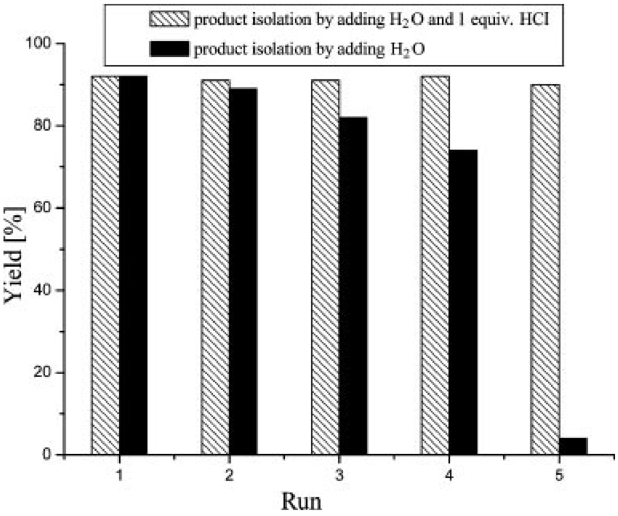


Figure 2. The results of Fischer indole synthesis with the use of recycled $BMImHSO_4$.

no appreciable decrease in the yield except for only small mechanical loss (Table 3 and Figure 2). IR analysis with the use of pyridine as a probe molecule[33] showed that the wavenumber of the characteristic band corresponding to coordination at Brønsted acid sites increased from 1540 cm^{-1} for pyridine/HCl to 1543 cm^{-1} for BMImHSO$_4$/pyridine/HCl, and 1551 cm^{-1} for fresh and recycled BMImHSO$_4$/pyridine (Figure 3), which demonstrated that the added HCl acted just as an NH$_3$ capture. Therefore, an overall process for the one-pot Fischer indole synthesis can be envisaged as shown in Figure 4.

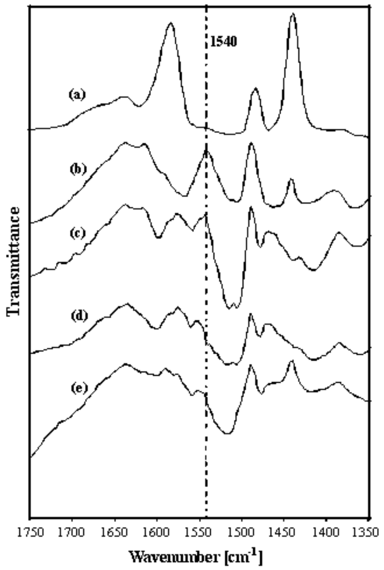


Figure 3. FTIR spectra: (a) pure pyridine; (b) pyridine + HCl (2:1 by vol.); (c) BMImHSO$_4$ + pyridine + HCl (2:1:1 by vol.); (d) BMImHSO$_4$ + pyridine (2:1 by vol.); (e) recycled BMImHSO$_4$ (by adding H$_2$O and equiv.-HCl) + pyridine (2:1 by vol.).

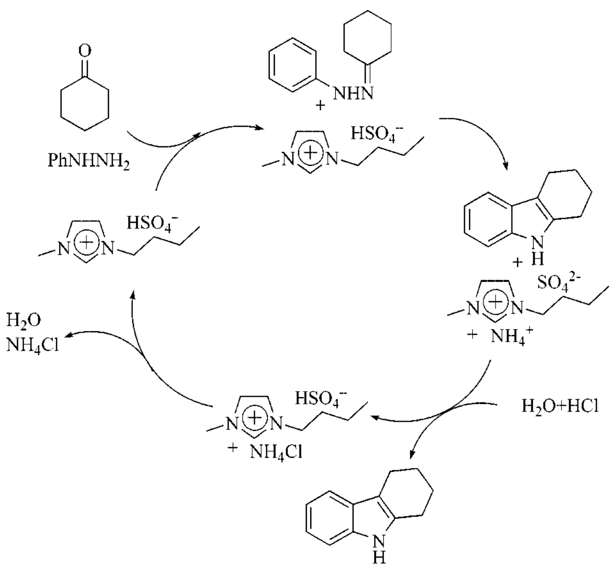


Figure 4. Reaction–isolation-recycle process for the one-pot Fischer indole synthesis in BMImHSO$_4$.

3. Conclusion

In this paper, we describe a new method for the one-pot synthesis of the Fischer indole scaffold with the use of ecofriendly solvent BAILs which act as catalysts as well. The products are obtained in a BMImHSO$_4$ medium in high yield, good purity, and without further purification. In unsymmetrical cases, regiospecific formation of a single product with more substitutes in the indole ring is obtained, which indicates that the BMImHSO$_4$ provides a weak acid system for synthesis of indoles and has a high selectivity as a catalyst. Compared with the conventional acid catalysts and Lewis acidic ionic liquids, the present BMImHSO$_4$-mediated Fischer indole synthesis conditions are quite mild and efficient, the isolation–recycle process is convenient and environmentally benign, and the BMImHSO$_4$ can be reused without any loss of efficiency. The developed method may open new opportunities and alternatives of great interest in the design and synthesis of naturally occurring indole skeletons.

4. Experimental Section

General: Brønsted acidic ionic liquids were prepared according to the reported procedures[14,18] including BMImHSO$_4$, HMImHSO$_4$, BMImH$_2$PO$_4$, HMImH$_2$PO$_4$, HMImTA, HMImBF$_4$, HMImNO$_3$, and HMImOTf. Melting points were measured with a Buchi Melting Point B-545. ^{1}H NMR spectra were recorded with a Varian PLUS 400 (TMS as internal standard). IR spectra were obtained with a Bruker Equinox 55. GC–MS spectra were recorded with an Agilent 6890N/5973N.

General Procedure for the Synthesis of Indoles: The Brønsted acidic ionic liquid BMImHSO$_4$ (5 mL) was mixed with cyclohexanone (0.49 g, 5.0 mmol) in a 20 mL flask, and phenylhydrazine (0.54 g, 5.0 mmol) was added. The mixture was then stirred at 70 °C for 1 h. Reaction progress was monitored by GC–MS. After completion, the reaction mixture was cooled to room temperature and HCl (0.5 M, 10 mL) was added. The obtained 1,2,3,4-tetrahydrocarbazole was filtered off, washed with water, and dried. The remaining BMImHSO$_4$ phase was reused after removal of water under vacuum and filtered off NH$_4$Cl. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.88–1.91 (m, 4 H), 2.71–2.73 (m, 4 H), 7.05–7.13 (m, 2 H, H$_{\text{arom.}}$), 7.27 (d, J = 10.4 Hz, 1 H, H$_{\text{arom.}}$), 7.46 (d, J = 7.2 Hz, 1 H, H$_{\text{arom.}}$), 7.66 (br. s, 1 H, NH) ppm. IR (KBr): 3399 (NH), 3051 (ArH), 2926, 2848, 1446, 737 cm^{-1}. MS (EI): m/z: 171[M]$^+$.

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