



One-pot Green Procedure for the Mannich Reaction Catalyzed by a Task-specific Ionic Liquid

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ABSTRACT

A three-component Mannich-type reaction of aromatic aldehydes, aromatic amines, and ketones was catalyzed by a novel task-specific ionic liquid, 4-(3-sulfopropyl) morpholinium hydrogen sulfate ($[\text{C}_3\text{SO}_3\text{Hnm}]\text{HSO}_4$) at room temperature to give various β -amino carbonyl compounds in good yields. The products could simply be separated from catalyst/ethanol, and the catalytic system could be recycled and reused for six times without noticeably decreasing catalytic activity.

Keywords: Mannich reaction, task-specific ionic liquid, catalyst.

1. INTRODUCTION

The Mannich reaction occupies an important position in the field of organic synthesis and has been one of the most important reactions in organic chemistry [1-5]. The β -amino carbonyl compounds are important synthetic intermediates for various pharmaceuticals and natural products [6-8]. The increasing popularity of the Mannich reaction has been fueled by ubiquitous nature of nitrogen-containing compounds in drugs and natural products [9-11]. The conventional catalysts for the classical Mannich reaction of aldehydes, ketones and amines involve mainly organic and mineral acids like proline [12-14], acetic acid [15], p-dodecylbenzenesulfonic acid [16] and some Lewis acids [17]. They often suffer from a variety of disadvantages, such as long reaction times, harsh reaction

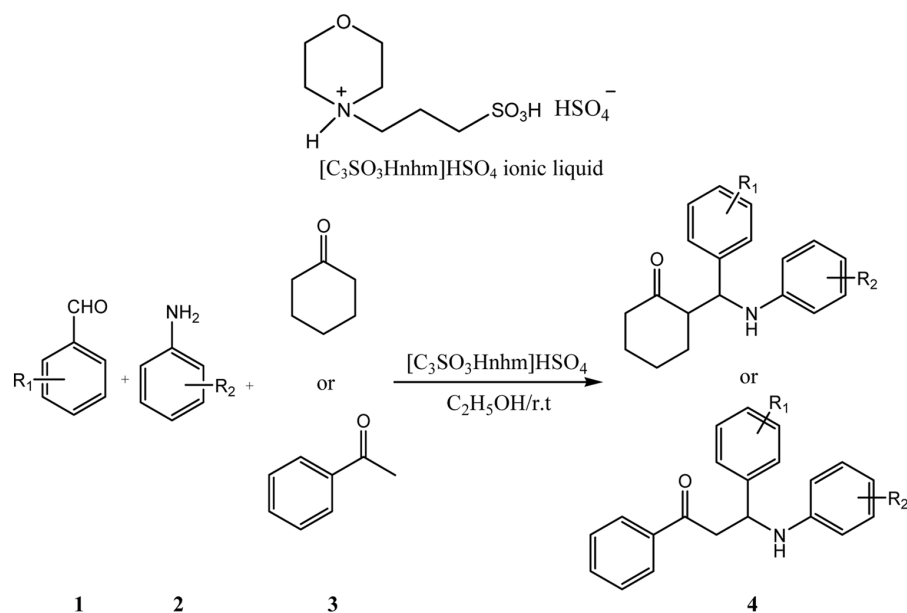
conditions, toxicity and pollution. Besides that, the separation of products from catalytic system is also difficult. Therefore, the development of a catalytic system that may be stable, easily separable, and reusable is highly desirable.

Ionic liquids, being recognized as environmentally benign media, have been widely applied in many reactions as catalysts or dual catalyst-solvent due to their low vapor pressure, reusability and high thermal and chemical stability [18-21]. The introduction of Brønsted-acidic functional groups into cations or anions of ionic liquids, especially the SO_3H -functional groups, obviously enhanced their acidities and water solubilities [22-24]. Therefore, Brønsted-acidic ionic liquids can be used as highly efficient acid catalysts

[25-28]. Moreover, their polar nature makes them useful for use under solvent-free conditions. An ever-increasing interest has focused on Brønsted-acidic ionic liquids for catalytic reactions where catalyst is in one phase and product in another, which makes product-isolation easy and catalyst-reuse convenient. Yue et al. [29] synthesized the acidic catalyst [Py][CF₃COO] (pyridinium trifluoroacetate) and used it in the Mannich reaction. Li and coworkers [30] reported three-component Mannich reactions catalyzed by a recyclable carboxyl-functionalized ionic liquid ([cmmim][BF₄]) in aqueous [bmim][BF₄] under mild conditions. Saboo et al. [31] reported that Brønsted acidic ionic liquids containing 1-methylimidazolium and triphenylphosphonium cations and p-toluenesulfonic acid (PTSA) and trifluoroacetic acid (TFA) anions catalyzed Mannich reactions. However, these types of ionic liquids are relatively expensive, which hinders their industrial applications. However, Brønsted-

acidic ionic liquids with imidazole or triphenylphosphine as cation are relatively expensive, which hinders their industrial applications. Furthermore, typical ionic liquids consist of halogen containing anions (such as [PF₆]⁻ and [BF₄]⁻) which in some regard limits their “greenness” [32-34]. Thus, it is necessary to synthesize less expensive and halogen-free ionic liquids, which can be used straightforwardly with simple procedure.

Here, we developed a facile, efficient and environmentally friendly protocol for preparation of β-amino carbonyl compounds using a novel multi-SO₃H functionalized halogen-free ionic liquid [C₃SO₃Hnhm]HSO₄ (Scheme 1). The reactions proceeded efficiently under mild conditions and products were isolated with ease compared to many previously reported catalysts. The results showed that the novel catalyst had a wide range of application for different substrates and products could be obtained conveniently in excellent yields.



Scheme 1. Mannich-type reaction catalyzed by [C₃SO₃Hnhm]HSO₄.

2. MATERIALS AND METHODS

All starting chemicals (AR grade) were purchased from commercial suppliers and used without further purification. The functionalized ionic liquid $[C_3SO_3Hnhm]HSO_4$ was synthesized according to literature procedures [35]. Melting points were determined on a Thomas Hoover capillary apparatus and were uncorrected. The IR spectra were recorded with a Bomem Michelson model 102 FTIR. 1H NMR spectra were recorded on Bruker DRX (500 MHz) spectrometer. Elemental analyses were performed on a Yanagimoto MT3CHN recorder. Mass spectra were obtained with automated FININIGAN Trace Ultra-Trace DSQ GC/MS spectrometer.

2.1 General Experimental Procedures

To a stirred solution of aldehyde (10 mmol) 1, aniline (10 mmol) 2, ketone (10 mmol) 3 in 6 mL of ethanol was added $[C_3SO_3Hnhm]HSO_4$ (1 mmol) and stirring was continued at room temperature for the appropriate time. After completion of the reaction, as indicated by TLC, the precipitated crude product was collected by filtration and the solids were washed with ethanol. Recrystallization from ethanol-acetone (v/v = 1:1) then afford the pure Mannich base 4. The filtrated

containing $[C_3SO_3Hnhm]HSO_4$ could be reused directly in the next run without further purification. The target substrates were characterized by elemental analysis. Their 1H NMR, IR, and physical data (m.p.) were consistent with those reported in the literature.

3. RESULTS AND DISCUSSIONS

Solubility experiments showed that the SO_3 -functionalized ionic liquid is miscible with methanol and relatively readily soluble in polar solvents such as ethanol, and acetone, and they are partially immiscible with no-polar solvents such as alkanes, and aromatic hydrocarbons. In the initial catalytic activity experiments, different solvents were screened for three-component Mannich-type reactions. Herein the reaction of benzaldehyde, cyclohexanone, and aniline was selected as the model reaction. As shown in Table 1, Mannich-type reactions could proceed effectively in polar organic solvents, such as methanol and ethanol (entries 1, 2), and $[C_3SO_3Hnhm]HSO_4/C_2H_5OH$ was found to be the most effective catalyst/solvent system and gave the highest yield of 86% (entry 2) among the solvents selected.

For establishing the best reaction conditions, synthesis of 2-(phenyl (phenyl-amino) methyl) cyclohexanone was first

Table 1. Effect of the $[C_3SO_3Hnhm]HSO_4$ /solvent on Mannich-type reaction^a.

Entry	Catalyst/solvent	Isolated yield (%)
1	$[C_3SO_3Hnhm]HSO_4/CH_3OH$	83
2	$[C_3SO_3Hnhm]HSO_4/C_2H_5OH$	86
3	$[C_3SO_3Hnhm]HSO_4/CH_2Cl_2$	62
4	$[C_3SO_3Hnhm]HSO_4/C_6H_6$	45

^a Reaction conditions: benzaldehyde (10 mmol), cyclohexanone (10 mmol), aniline (10 mmol), $[C_3SO_3Hnhm]HSO_4$ (1.0 mmol) r.t., 6 h.

studied. Therefore the reaction of benzaldehyde (10 mmol), cyclohexanone (10 mmol) and aniline (10 mmol) in ethanol catalyzed under various amount of $[\text{C}_3\text{SO}_3\text{Hnhm}]\text{HSO}_4$ at room temperature was examined. The efficiency of the reaction was mainly affected by the amount of the

catalyst (Table 2). The yields of the Mannich base clearly increased as the amount of $[\text{C}_3\text{SO}_3\text{Hnhm}]\text{HSO}_4$ increased (Entries 1-5). The optimal amount of $[\text{C}_3\text{SO}_3\text{Hnhm}]\text{HSO}_4$ was 10 mol% (Entry 5), the higher amount of the catalyst did not increase the yield noticeably (Entry 6).

Table 2. Effect of amount of $[\text{C}_3\text{SO}_3\text{Hnhm}]\text{HSO}_4$ on Mannich reaction^a.

Entry	Catalyst (mol%)	Reaction time (h)	Isolated yield (%)
1	0	24	0
2	2	6	42
3	6	6	58
4	8	6	71
5	10	6	86
6	15	6	86
7	10	2	53
8	10	8	86

^a Reaction conditions: benzaldehyde (10 mmol), cyclohexanone (10 mmol), aniline (10 mmol), r.t., 6 h, ethanol is used as a solvent.

Then, the scope of the Mannich-type reaction with other aromatic aldehydes (1), aromatic amines (2) and ketones (3) was investigated catalyzed by $[\text{C}_3\text{SO}_3\text{Hnhm}]\text{HSO}_4$ under the optimized reaction conditions (Table 3). In general, the reaction proceeded smoothly at room temperature to give the corresponding products in reasonable to good yields ranged from 81% to 92%. Compared with the other methods and catalysts, the separation procedure of products and catalyst from the reactor was easier. For aromatic aldehydes carrying either electron-withdrawing or electron-donating substituents could facilitate the Mannich-type reaction, and gave almost the same yields (entries 5-9). It should be noted that aryl aldehydes bearing a strong electron-donating group facilitated the Mannich-type reaction (entries 13, 14, 15). In the case of anilines,

it is noteworthy that both the electron-donating and weak electron-withdrawing substituents were advantageous to the Mannich reaction.

Compared with traditional solvents and catalysts, task-specific acidic ionic liquids are easily reused, which is superior to the use of conventional solvents and catalysts. The recycling performance of $[\text{C}_3\text{SO}_3\text{Hnhm}]\text{HSO}_4$ in the reaction of benzaldehyde, cyclohexanone, and aniline was investigated. After the reaction, the products were isolated from the catalytic system by filtration. The filtrate (ethanol media containing the catalyst) was reused in the next run without further purification, and the catalytic system could be recycled and reused six times without noticeably decreasing catalytic activity, as shown in Figure 1.

Table 3. Preparation of β -amido ketones using $[\text{C}_3\text{SO}_3\text{Hnhm}]\text{HSO}_4$ as catalyst^a.

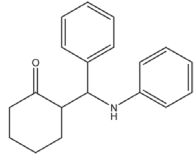
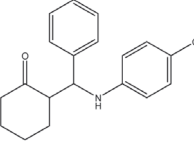
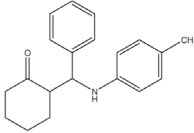
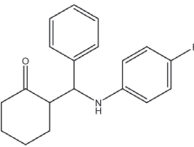
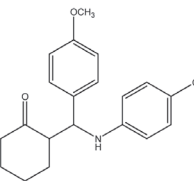
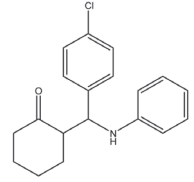
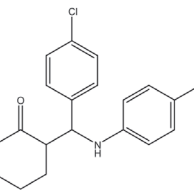
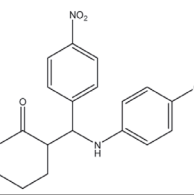
Entry	R ₁	R ₂	3	Product	Yield (%) ^b	mp (°C) (lit mp) [ref]
1	H	H	(CH ₂) ₅ CO		86	114-115 (115-116) [36]
2	H	4-Cl	(CH ₂) ₅ CO		84	136-137 (137-138) [37]
3	H	4-CH ₃	(CH ₂) ₅ CO		90	117-118 (116-118) [37]
4	H	4-Br	(CH ₂) ₅ CO		81	98-99 (97-98) [38]
5	4-CH ₃ O	4-Cl	(CH ₂) ₅ CO		83	122-123 (122-123) [36]
6	4-Cl	H	(CH ₂) ₅ CO		82	133-134 (134-135) [38]
7	4-Cl	4-Cl	(CH ₂) ₅ CO		85	96-97 (95-96) [38]
8	4-NO ₂	4-Cl	(CH ₂) ₅ CO		86	135-136 (136-137) [38]

Table 3. (Continue)

Entry	R ₁	R ₂	3	Product	Yield (%) ^b	mp (°C) (lit mp) [ref]
9	4-NO ₂	4-CH ₃	(CH ₂) ₅ CO		88	138-139 (137-138) [36]
10	H	H	C ₆ H ₅ COCH ₃		91	168-169 (169-171) [39]
11	H	4-Cl	C ₆ H ₅ COCH ₃		85	170-171 (170-171) [39]
12	H	4-CH ₃	C ₆ H ₅ COCH ₃		92	169-170 (170-171) [39]
13	4-CH ₃ O	H	C ₆ H ₅ COCH ₃		89	150-151 (151-152) [37]
14	4-CH ₃ O	4-Cl	C ₆ H ₅ COCH ₃		83	116-117 (116-118) [39]
15	4-CH ₃ O	4-CH ₃	C ₆ H ₅ COCH ₃		92	161-162 (160-162) [39]
16	4-NO ₂	H	C ₆ H ₅ COCH ₃		83	107-108 (107-110) [40]

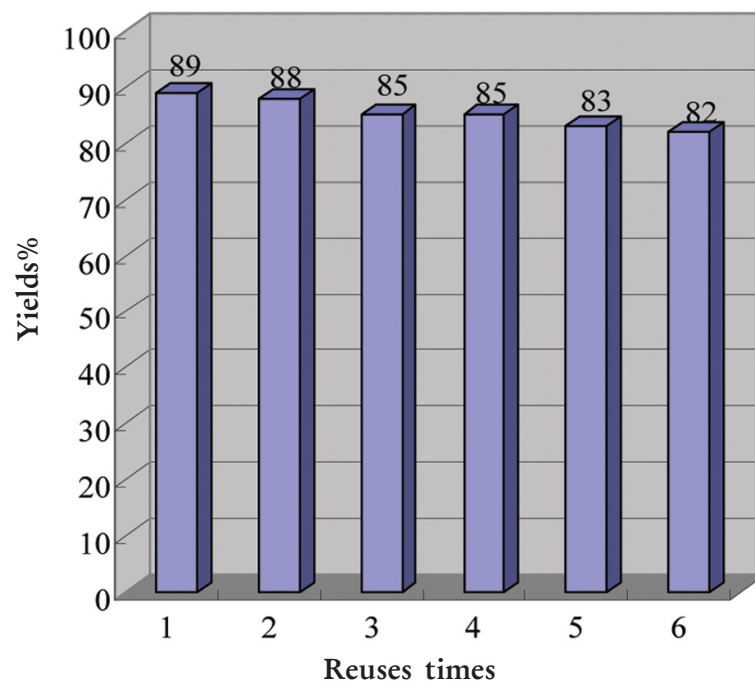


Figure 1. Reusability of $[C_3SO_3Hnhm]HSO_4$.

4. CONCLUSIONS

In summary, it was demonstrated that an acidic, readily available, economic catalyst, $[C_3SO_3Hnhm]HSO_4$, was a highly efficient and reuseable catalyst for the Mannich reaction at room temperature, offering practical convenience in product separation from the reaction medium. The raw materials were cheaper than acidic ionic liquids having an imidazolium or triphenylphosphonium cation. Therefore, we believe that the new synthetic method reported here provides an environmentally green procedure that may be suitable for industrial applications.

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REFERENCES

- [1] Chen X.H., Dong S.X., Qiao Z., Zhu Y., Xie M.S., Lin L.L. and Liu X.M., Guanidine organocatalyst for the asymmetric Mannich-type reaction between alpha-isothiocyanato imide and sulfonyl imines, *Chem. Eur. J.*, 2011; 17: 2583-2586.
- [2] Yu J.P., Miao Z.W. and Chen R.Y., Highly efficient asymmetric vinylogous Mannich reaction induced by O-pivaloylated D-galactosylamine as the chiral auxiliary, *Org. Biomol. Chem.*, 2011; 9: 1756-1762.
- [3] Candeias N.R., Montalbano F., Cal P.M.S.D. and Gois P.M.P., Boronic acids and esters in the Petasis-Borono Mannich multicomponent reaction, *Chem. Rev.*, 2011; 110: 6169-6193.
- [4] Xu X.F., Qian Y., Yang L.P. and Hu W.H., Cooperative catalysis in highly enantioselective Mannich-type three-

- component reaction of a diazoacetophenone with an alcohol and an imine, *Chem. Commun.*, 2011; 47: 797-799.
- [5] Hayashi Y., Urushima T., Tsuboi W. and Shoji M., L-proline-catalyzed enantioselective one-pot cross-Mannich reaction of aldehydes, *Nat. Protoc.*, 2007; 2: 113-118.
- [6] Balasubramaniam S. and Aidhen I.S., The growing synthetic utility of the weinreb amide, *Synthesis.*, 2008; 3707-3738.
- [7] Kojima T., Sugano K., Onoue S., Murase N., Sato M., Kawabata Y. and Mano T., Solid form selection of zwitterionic 5-HT₄ receptor agonist, *Int. J. Pharm.*, 2008; 350: 35-42.
- [8] Jadhav A.S., Pathare D.B. and Shingare M.S., A validated stability indicating RP-LC method for nitazoxanide, a new antiparasitic compound, *Chromatographia.*, 2007; 66: 595-600.
- [9] Aytemir M.D. and Ozcelik B., A study of cytotoxicity of novel chlorokojic acid derivatives with their antimicrobial and antiviral activities, *Eur. J. Med. Chem.*, 2010; 45: 4089-4095.
- [10] Kumar A., Kumar M. and Gupta M.K., An efficient organocatalyzed multicomponent synthesis of diaryl-methanes via Mannich type Friedel-Crafts reaction, *Tetrahedron Lett.*, 2009; 50: 7024-7027.
- [11] Luo H.T., Kang Y.R., Nie H.Y. and Li M.Y., Sulfamic acid as a cost-effective and recyclable catalyst for beta-amino carbonyl compounds synthesis, *J. Chin. Chem. Soc.*, 2009; 56: 186-195.
- [12] List B., Pojarliev P., Biller W.T. and Martin H.J., The proline-catalyzed direct asymmetric three-component Mannich reaction: Scope, optimization, and application to the highly enantioselective synthesis of 1, 2-amino alcohols, *J. Am. Chem. Soc.*, 2002; 124: 827-833.
- [13] List B., The direct catalytic asymmetric three-component Mannich reaction, *J. Am. Chem. Soc.*, 2000; 122: 9336-9337.
- [14] Duthaler R.O., Proline-catalyzed asymmetric alpha-amination of aldehydes and ketones - An astonishingly simple access to optically active alpha-hydrazino carbonyl compounds, *Angew. Chem. Int. Ed.*, 2003; 42: 975-978.
- [15] Mogilaiah K. and Kankaiah G., Synthesis and antibacterial activity of novel Mannich bases containing 1,8-naphthyridine moiety, *Indian J. Heterocycl. Chem.*, 2002; 11: 283-286.
- [16] Manabe K., Mori Y. and Kobayashi S., Three-component carbon-carbon bond-forming reactions catalyzed by a Bronsted acid-surfactant-combined catalyst in water, *Tetrahedron.*, 2001; 57: 2537-2544.
- [17] Kobayashi S., Hamada T. and Manabe K., The catalytic asymmetric Mannich-type reactions in aqueous media, *J. Am. Chem. Soc.*, 2002; 124: 5640-5641.
- [18] Imanzadeh G.H., Tavana M.M., Zamanloo M.R. and Mansoori Y., Aza-Michael addition of isatin and phthalimide to symmetrical fumaric esters in ionic liquid media, *Chin. J. Chem.*, 2009; 27: 389-396.
- [19] Yan J.C., Zhou L. and Wang L., Amination reactions of aryl halides with nitrogen-containing reagents catalyzed by CuI in ionic liquid, *Chin. J. Chem.*, 2008; 26: 165-169.
- [20] Zhao G.Y., Jiang T., Gao H.X., Han B.X., Huang J. and Sun D.H., Mannich reaction using acidic ionic liquids as catalysts and solvents, *Green Chem.*, 2004; 6: 75-77.

- [21] Yue C.B., Aromatic compounds Mannich reaction using economical acidic ionic liquids based on morpholinium salts as dual solvent-catalysts, *Synth. Commun.*, 2010; **40**: 3640-3647.
- [22] Cole A.C., Jensen J.L., Ntai I., Tran K.L.T., Weaver K.J., Forbes D.C., James J. and Davis H., Novel bronsted acidic ionic liquids and their use as dual solvent-catalysts, *J. Am. Chem. Soc.*, 2002; **124**: 5962-5963.
- [23] Arfan A. and Bazureau J.P., Efficient combination of recyclable task specific ionic liquid and microwave dielectric heating for the synthesis of lipophilic esters, *Org. Process Res. Dev.*, 2005; **9**: 743-748.
- [24] Wasserscheid P., Sessing M. and Korth W., Hydrogen sulfate and tetrakis (hydrogensulfato) borate ionic liquids: synthesis and catalytic application in highly Bronsted-acidic systems for Friedel-Crafts alkylation, *Green Chem.*, 2002; **4**: 134-138.
- [25] Li L., Xu L.W., Ju Y.D. and Lai G.Q., Asymmetric direct Aldol reactions catalyzed by a simple chiral primary diamine-Bronsted acid catalyst in/on water, *Synth. Commun.*, 2009; **39**: 764-774.
- [26] Dabiri M., Salehi P., Baghbanzadeh M. and Nikcheh M.S., Water-Accelerated selective synthesis of 1,2-disubstituted benzimidazoles at room temperature catalyzed by Bronsted acidic ionic liquid, *Synth. Commun.*, 2008; **38**: 4272-4281.
- [27] Niralwad K.S., Shingate B.B. and Shingare M.S., Ultrasound-assisted one-pot synthesis of octahydroquinazolinone derivatives catalyzed by acidic ionic liquid [tbmin]Cl₂/AlCl₃, *J. Chin. Chem. Soc.*, 2010; **57**: 89-92.
- [28] Niknam K. and Damya M., 1-Butyl-3-methylimidazolium hydrogen sulfate [bmim] HSO₄: An efficient reusable acidic ionic liquid for the synthesis of 1,8-dioxo-octahydroxanthenes, *J. Chin. Chem. Soc.*, 2009; **56**: 659-665.
- [29] Cai B.Y., Yi T.F., Zhu C.B. and Liu G., Mannich reaction catalyzed by a novel catalyst under solvent-free conditions, *J. Ind. Eng. Chem.*, 2009; **15**: 653-656.
- [30] Li J.Z., Peng Y.Q. and Song G.H., Mannich reaction catalyzed by carboxyl-functionalized ionic liquid in aqueous media, *Catal. Lett.*, 2005; **102**: 159-162.
- [31] Sahoo S., Joseph T. and Halligudi S.B., Mannich reaction in Bronsted acidic ionic liquid: A facile synthesis of beta-amino carbonyl compounds, *J. Mol. Catal. A: Chem.*, 2006; **244**: 179-182.
- [32] Garcia M.T., Gathergood N. and Scammells P.J., Biodegradable ionic liquids - Part II. Effect of the anion and toxicology, *Green Chem.*, 2005; **7**: 9-14.
- [33] Gathergood N., Garcia M.T. and Scammells P.J., Biodegradable ionic liquids: Part I. Concept, preliminary targets and evaluation, *Green Chem.*, 2004; **6**: 166-175.
- [34] Fraga-Dubreuil J., Bourahla K., Rahmouni M., Bazureau J.P. and Hamelin J., Catalysed esterifications in room temperature ionic liquids with acidic counteranion as recyclable reaction media, *Catal. Commun.*, 2002; **3**: 185-190.
- [35] Huang B.H., Li Z.J., Shi N., Xu X.L., Zhang K. and Fang Y.X., Functionalized acidic ionic liquid with morpholinium cation: synthesis, characterization and catalysis performance in esterification, *Chin. J. Org. Chem.*, 2009; **29**: 770-775.

- [36] Yang Y.Y., Shou W.G. and Wang Y.G., Synthesis of beta-amino carbonyl compounds via a Zn(OTf)₂-catalyzed cascade reaction of anilines with aromatic aldehydes and carbonyl compounds, *Tetrahedron*, 2006; **62**: 10079-10086.
- [37] Yi W.B. and Cai C., Mannich-type reactions of aromatic aldehydes, anilines, and methyl ketones in fluorous biphasic systems created by rare earth (III) perfluorooctane sulfonates catalysts in fluorous media, *J. Fluorine. Chem.*, 2006; **127**: 1515-1521.
- [38] Fang D., Fei Z.-H. and Liu Z.L., Functionalized ionic liquid as the recyclable catalyst for Mannich-type reaction in aqueous media, *Catal. Commun.*, 2009; **10**: 1267-1270.
- [39] Yi L., Zou J.H., Lei H.S. and He Q.L., The Mannich reaction of butanone, aromatic-aldehydes and aromatic-amines, *Synth. Commun.*, 1991; **21**: 2109-2117.
- [40] Akiyama T., Takaya J. and Kagoshima H., Bronsted acid-catalyzed Mannich-type reactions in aqueous media, *Adv. Synth. Catal.*, 2002; **344**: 338-347.