# **RSC Advances**

## PAPER

Cite this: RSC Adv., 2014, 4, 727

# Brønsted acid-surfactant-combined catalyst for the Mannich reaction in water<sup>+</sup>

Tao Chang,\* Leqin He, Li Bian, Haiyan Han, Mingxia Yuan and Xiaorui Gao\*

A series of Brønsted acid-surfactant-combined catalysts (BASCs) functionalised with different acids have been synthesized and applied to catalyze the three-component Mannich reaction with aldehyde, acetone and amine at 25 °C in water. The effects of cation tail length and ions of the ionic liquid and the recyclability of the catalysts and BASC acidity ( $H_0$ ) were investigated. The results demonstrated that the 3-(N,N-dimethyloctylammonium) propanesulfonic acid toluene sulfate ([DOPA][Tos]) provide the best catalytic activity because of the formation of emulsions during the reaction. The catalytic procedure was simple and the catalyst could be recycled 9 times by simple separating processes without noticeably decreasing the catalytic activity.

Received 29th August 2013 Accepted 6th November 2013

DOI: 10.1039/c3ra44726j

www.rsc.org/advances

## 1. Introduction

Organic synthesis in water has received much attention, not only because unique reactivity and selectivity are exhibited in water but also because it is an economical and environmentally benign solvent.<sup>1</sup> However, one major disadvantage in the use of water is that most organic compounds are insoluble in water. To circumvent this disadvantage, surfactant-type catalysts, which solubilize organic materials or form micellar dispersion with them in water, have been used.<sup>2–4</sup>

The Mannich reaction is one of the most important carboncarbon bond formation reactions in organic synthesis and an atom-economic reaction.<sup>5</sup> β-Amino carbonyl compounds are very useful compounds as building blocks in the synthesis of pharmaceuticals and natural products that can be easily formed *via* the Mannich reaction.<sup>6</sup> Many systems have been investigated as the catalysts for the Mannich reaction over the past decades, such as Lewis acids,<sup>7-11</sup> bases,<sup>12-15</sup> Brønsted acids<sup>16-23</sup> and organic compounds,<sup>24,25</sup> which often suffer from the drawbacks of long reaction times, harsh reaction conditions, toxicity and difficulty in product separation. Therefore, the search for new and green catalysts is still being actively pursued.

In recent years, ionic liquid have attracted extensive interest in green synthesis. Compared to traditional liquid acid catalyst, Brønsted acidic ionic liquids have tunable structures. Using Brønsted acidic ionic liquids as catalysts for Mannich reaction have also been reported in these years.<sup>16–23</sup> However, Brønsted acidic ionic liquids with imidazole or triphenylphosphine as the

cation were relatively expensive, which hinders their industrial application. In addition, many of these procedures need the tedious and energy-consuming vacuum distillation for the recovery of catalytically active ionic liquids. Thus, it is necessary to synthesize less expensive, halogen-free and water-soluble ionic liquid. Fang et al. reported that 3-(N,N-dimethyldodecylammonium) propanesulfonic acid hydrogen sulfate ([DDPA][HSO<sub>4</sub>]) shows good catalytic performance for this reaction,<sup>19</sup> many factors such as the structure and acidity of the catalysts have not been studied well. In this paper, a series of BASCs functioned with *p*-toluenesulfonic acid have been synthesized and applied to catalyze the three-component Mannich reaction in water. The relationship between structure, acidity and catalytic activity was investigated in detail. It was proved that the anions of BASCs had a decisive influence on the catalytic performance and the longchain BASCs reveal excellent activity because of formation of emulsion during the reaction process (Scheme 1).

## 2. Materials and methods

#### 2.1 Materials

The <sup>1</sup>H NMR, <sup>13</sup>C NMR spectra were detected on a Bruker AC-P 300 spectrometer, in  $D_2O$  and DMSO-d. The Hammett acidity of BASCs was measured using Perkin Elmer Lambda 35 UV-vis spectra with a basic indicator by literature.<sup>26</sup> The ESI-MS was detected on a Esquire 6000 mass spectrometer. All chemicals were obtained from commercial suppliers. They were of AR grade and used without further purification. The catalysts of 1a–e were synthesized according to the literature.<sup>27</sup>

#### 2.2 Catalyst preparation

The SO<sub>3</sub>H-fuctionalized ionic liquids were prepared according to the literature with some changes.<sup>27</sup> A typical procedure was as follow: 1,3-propanesultone (5.0 ml, 0.06 mol) was dissolved in



View Article Online

View Journal | View Issue

Key Laboratory for Resource Exploration Research of Hebei Province, College of science, Hebei University of Engineering, 199 South Guangming Road, Handan, Hebei 056038, China. E-mail: changt03@sina.com; gxr\_1320@sina.com; Tel: +86-310-8578796

<sup>†</sup> Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra44726j



Scheme 1 Structure of the Brønsted acid-surfactant-combined ionic liquids

15 ml ethyl acetate, and *N*,*N*-dimethyloctylamine (15.5 ml, 0.06 mol) was dropped slowly into the previous solution. The mixture was stirred for 3 h at 55 °C and the reaction mixture was filtered to get the white precipitate. The precipitate was washed with ethyl acetate and diethyl ether twice and dried at 100 °C for 10 h, giving *n*-OctMe<sub>2</sub>N-PS as a white power.

*n*-OctMe<sub>2</sub>N-PS: yield: 95%, a white solid, mp: 178 °C, <sup>1</sup>H NMR (400 M, D<sub>2</sub>O):  $\delta = 0.68$  (t, 3H), 1.09–1.17 (m, 10H), 1.57 (s, 2H), 2.02 (m, 2H), 2.78 (t, 2H), 2.90 (s, 6H), 3.11–3.14 (m, 2H), 3.25–3.28 (m, 2H), <sup>13</sup>C NMR (100 M, D<sub>2</sub>O): 13.60, 18.27, 21.90, 22.16, 25.56, 28.28, 31.14, 47.41, 62.07, 64.40.

*n*-DodecMe<sub>2</sub>N-PS: yield: 96%, a white solid, mp: 244 °C, <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O):  $\delta$  0.81 (t, 3H), 1.23 (s, 18H), 1.69 (s, 2H), 2.11–2.15 (m, 2H), 2.86 (t, 2H), 3.052 (s, 6H), 3.23–3.27 (m, 2H), 3.39–3.44 (m, 2H), <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O):  $\delta$  13.88, 18.35, 22.22, 22.67, 26.11, 29.10, 29.52, 29.88, 29.74, 29.82, 29.97, 32.00, 47.41, 50.87, 61.92, 63.93.

The mixture of the zwitterion with equal mole of toluenesulfonic acid was stirred for 5 h at 110  $^{\circ}$ C without solvent, after reaction, the white viscous emulsion was dried under vacuum at 100  $^{\circ}$ C for 30 min, cooled and got a white solid product.

[DOPA][Tos]: yield: 97%, a white solid, mp: 76 °C, <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O): 0.67 (t, 3H), 1.08–1.15 (m, 10H), 1.53–1.57 (m, 2H), 1.97–2.04 (m, 2H), 2.20 (s, 3H), 2.77 (t, 2H), 2.88 (s, 6H), 3.08–3.12 (m, 2H), 3.22–3.26 (m, 2H), 7.17 (d, 2H), 7.49 (d, 2H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O): 13.78, 18.25, 20.71, 21.08, 23.37, 25.73, 28.55, 28.69, 31.40, 47.39, 50.48, 62.13, 64.41, 125.55, 129.41, 140.29, 141.84. ESI-MS: calcd for  $C_{20}H_{37}NS_2O_6 m/z$  [M –  $C_7H_7SO_3$ ]<sup>+</sup>: 280.4; found: 280.4.

[DDPA][Tos]: yield: 96%, a white solid, mp: 86 °C, <sup>1</sup>H NMR (400 MHz, DMSO-d): 0.86 (t, 3H), 1.25 (s, 18H), 1.64 (s, 2H), 1.94– 1.98 (m, 2H), 2.29 (s, 3H), 2.49 (t, 2H), 2.99 (s, 6H), 3.21–3.25 (m, 2H), 3.35–3.39 (m, 2H), 7.14 (d, 2H), 7.50 (d, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-d): 13.93, 18.69, 20.77, 21.65, 22.09, 25.78, 28.88, 38.74, 38.95, 39.35, 39.57, 39.70, 39.99, 47.66, 49.95, 61.88, 62.93, 125.47, 128.53, 138.23, 144.69, 144.73. ESI-MS: calcd for  $C_{24}H_{45}NS_2O_6 m/z [M - C_7H_7SO_3]^+: 336.5;$  found: 336.5.

#### 2.3 The Hammett acidity of BASCs

The Hammett acidity  $(H_0)$  function can be calculated by the equation below:  $H_0 = pK(I_{aq}) + lg([I]_s/[IH^+]_s)$ . Here, "I" represents the indicator base,  $[IH^+]_s$  and  $[I]_s$  are respectively the molar concentrations of the protonated and unprotonated forms of the indicator. The value of  $[I]_s/[IH^+]_s$  was determined

and calculated through UV-visible spectrum. In the experiment, 4-nitroaniline ( $pK_a = 0.99$ ) was chosen as the basic indicators and ethanol as the solvent. The maximum absorbance of unprotonated form of 4-nitroaniline was observed at 371 nm in ethanol. With the increase of acidity of the BASCs, the absorbance of the unprotonated form of the basic indicator decreased, whereas the protonated form of the indicator could not be observed because of its small molar absorptivity and its location, so the  $[I]_{\rm s}/[{\rm IH}^+]_{\rm s}$  can be determined from the differences of measured absorbance after the addition of catalysts and  $H_0$  can be calculated.

## 2.4 General procedure for Mannich reaction catalyzed by BASCs

In a typical procedure, to a reaction tube charged with catalyst (0.1 mmol) in 1.5 ml of water was added aldehyde (1.0 mmol), aniline (1.0 mmol), ketone (1.0 mmol). The mixture was then stirred at 25 °C. After completion, the precipitated product was collected by centrifugation and decantation and the catalyst solution could be reused directly in the next run without purification.

## 3. Results and discussion

#### 3.1 Acidity of BASCs

The Hammett acidity  $(H_0)$  function can effectively express the acidity strength of an acid in organic solvents. The  $H_0$  of the catalysts was summarized in Table 1. As shown in Table 1,

| Table 1 | The $H_0$ of different ionic liquids in ethanol <sup>a</sup> |                  |        |         |       |  |
|---------|--|------------------|--------|---------|-------|--|
| Entry   | Catalyst system  | A <sub>max</sub> | [I](%) | [IH](%) | $H_0$ |  |
| 1       | Blank  | 0.6556           | 100    | 0       | _     |  |
| 2       | [MPSIM][Br]  | 0.4691           | 71.50  | 28.50   | 1.39  |  |
| 3       | [MPSIM][HSO4]  | 0.4488           | 68.46  | 31.54   | 1.33  |  |
| $4^b$   | [MPSIM][H <sub>2</sub> PO <sub>4</sub> ]                     | _                | _      |         | _     |  |
| 5       | [MPSIM][Tos]   | 0.4861           | 74.15  | 25.85   | 1.45  |  |
| 6       | [MPSIM][CH <sub>3</sub> SO <sub>3</sub> ]                    | 0.4649           | 70.91  | 29.09   | 1.37  |  |
| 7       | [BPSIM][Tos]   | 0.4794           | 73.12  | 26.88   | 1.42  |  |
| 8       | [DOPA][Tos]  | 0.4527           | 69.05  | 30.95   | 1.34  |  |
| 9       | [DDPA][Tos]  | 0.4543           | 69.29  | 30.71   | 1.34  |  |

<sup>*a*</sup> Condition for UV-vis spectra measurement: solvent: ethanol, indicator: 4-nitroaniline (p $K_a$  = 0.99), 54 μmol l<sup>-1</sup>; BASCs: 35 mmol l<sup>-1</sup>, 25 °C. <sup>*b*</sup> No protonation.

the Brønsted acidities of the BASCs with different anions were determined (entries 2–6), and the order of  $H_0$  was as follows: [MPSIM][HSO<sub>4</sub>] > [MPSIM][CH<sub>3</sub>SO<sub>3</sub>] > [MPSIM][Br] > [MPSIM]-[Tos], which were in accordance with the acidities of the anions. The effect of the cations in the BASCs on their acidity was also investigated (entries 5, 7–9), the order of  $H_0$  was as follows: [DDPA][Tos] = [DOPA][Tos] > [BPSIM][Tos] > [MPSIM][Tos], which indicted that the length of carbon chain in cations can also influence acidities of BASCs, the longer of the catalyst chain, the stronger acidity.

#### 3.2 Catalyst screening for the Mannich reaction

The Mannich reaction of benzaldehyde, aniline and cyclohexanone was chosen as the model reaction to test the catalytic activities of BASCs, and the results were summarized in Table 2. It was found that, the anions of BASCs had a decisive influence on the catalytic performance of the BASCs (entries 1-5). [MPSIM][H<sub>2</sub>PO<sub>4</sub>] facilitated very poor conversion, because of weak acidity (entry 3). BASCs with organic anions showed higher catalytic activity for the reaction than that of inorganic anion (entries 4, 5 vs. 1-3 and 7, 8 vs. 9, 10), which was inconsistent with the acidity order of the Brønsted acid. Among all the anions, the Tos<sup>-</sup> show the best catalytic reactivity. The difference was attributed to the fact that the bulky anion Tos<sup>-</sup> can promote contact between the reactant and catalyst. The cations also had an important influence on the catalytic performance with the same anion (entries 6, 9, 10 and 11). These results demonstrated that the long-chain was crucial for efficient catalysis. As shown in Fig. 1, the reaction mixture became white turbid emulsions during the reaction, the formation of white turbid mixtures was important for good yields, which accelerated the reaction,4 and the catalysts with short-chain do not form emulsion (see Fig. S1<sup>†</sup>). With the same cation of [DOPA]-[HSO<sub>4</sub>] and [DOPA][Tos], both of which can be form emulsion, the [DOPA] Tos] exhibited better activity than that of [DOPA]-[HSO<sub>4</sub>], which proved the importance of the anion further (entries 7, 8 vs. 9, 10). After the reaction, the precipitated product was collected easily.

Table 2 Influence of catalytic system on the Mannich reaction in aqueous media $^{\rm a}$ 

| Entry | Catalyst system                           | Time/h | Yield/% <sup>b</sup> |
|-------|---|--------|----------------------|
| 1     | [MPSIM][Br]                               | 7      | 49                   |
| 2     | [MPSIM][HSO <sub>4</sub> ]                | 7      | 57                   |
| 3     | [MPSIM][H <sub>2</sub> PO <sub>4</sub> ]  | 7      | 43                   |
| 4     | [MPSIM][Tos]                              | 7      | 88                   |
| 5     | [MPSIM][CH <sub>3</sub> SO <sub>3</sub> ] | 7      | 62                   |
| 6     | [BPSIM][Tos]                              | 6      | 80                   |
| 7     | [DOPA][HSO4]                              | 3      | 58                   |
| 8     | [DOPA][HSO4]                              | 4.5    | 75                   |
| 9     | [DOPA][Tos]                               | 3      | 75                   |
| 10    | DOPATOS                                   | 4.5    | 89                   |
| 11    | [DDPA][Tos]                               | 4.5    | 85                   |

<sup>*a*</sup> Reaction conditions: 1.0 mmol benzaldehyde, 1.0 mmol aniline and 1.0 mmol cyclohexanone, catalyst: 0.1 mmol, 1.5 ml H<sub>2</sub>O, 25 °C. <sup>*b*</sup> Others are benzylideneaniline and a small amount of raw material.



Fig. 1 Different stages of Mannich reaction catalyzed by catalyst [DOPA][Tos], left: during the reaction; right: at the end of reaction.

#### 3.3 Effect of the catalyst amount on Mannich reaction

Fig. 2 shows the effect of the catalyst amount with increasing of the molar ratio of catalyst [DOPA][Tos]. When the loading of catalyst increased from 2% to 12%, the yield of product increased sharply from 55% to 90%. At a catalyst loading of 10 mol%, the best result can be obtained. Further increasing the amount of catalyst, the yield increase slightly, therefore 10 mol% was selected as the best loading of catalyst amount.

#### 3.4 Reusability of [DOPA][Tos] for Mannich reaction

The recycling performance of the catalyst in the Mannich reaction was also investigated. After the reaction, the products were isolated from the catalytic system by centrifugation and decantation. The catalyst solution was reused in the next run without further purification. As shown in Fig. 3, the catalyst can be reused at least nine times without appreciable decrease in yield.

# 3.5 The catalytic activities for Mannich reaction catalyzed by [DOPA][Tos]

To further extend the scope of the reaction, the other aromatic aldehyde and aromatic amine were utilized as substrates in the



Fig. 2 Effect of the catalyst amount on Mannich reaction. Reaction conditions: 1.0 mmol benzaldehyde, 1.0 mmol aniline and 1.0 mmol cyclohexanone, 1.5 ml  $H_2O$ , 25 °C.



Fig. 3 Reuses performance of the catalyst [DOPA][Tos]. Reaction conditions: 1.0 mmol benzaldehyde, 1.0 mmol aniline and 1.0 mmol cyclohexanone, catalyst: 0.1 mmol, 1.5 ml  $H_2O$ , 25 °C.

 Table 3
 The catalytic activities for Mannich reaction in aqueous media<sup>a</sup>

| 0<br>+ | NH2<br>R <sup>1</sup> + | $ \begin{array}{c} \text{CHO} \\ \text{CHO} \\ \text{Catalyst} \\ \text{25°C. H}_2\text{O} \end{array} $ | $O HN R^{1}$ |
|--------|-------------------------|--|--------------|
| Entry  | $R^1$                   | $R^2$  | Yield/%      |
| 1      | Н                       | Н  | 89           |
| 2      | Н                       | $o-NO_2$   | 86           |
| 3      | Н                       | $m-NO_2$   | 83           |
| 4      | Н                       | p-NO <sub>2</sub>  | 85           |
| 5      | н                       | o-Cl   | 87           |
| 6      | Н                       | <i>p</i> -OMe  | 84           |
| 7      | <i>p</i> -Cl            | Н  | 89           |
| 8      | <i>p</i> -OMe           | Н  | 75           |
| 9      | <i>p</i> -Cl            | o-Cl   | 89           |
| 10     | <i>p</i> -Cl            | <i>p</i> -OMe  | 88           |

 $^a$  Reaction conditions: 1.0 mmol aldehyde, 1.0 mmol amine and 1.0 mmol cyclohexanone, catalyst [DOPA][Tos]: 0.1 mmol, 1.5 ml H<sub>2</sub>O, 25 °C, 6 h.

Mannich reaction in the presence of catalyst [DOPA][Tos]. The results were summarized in Table 3. In general, the reaction proceeded smoothly at room temperature in water to give the corresponding products in reasonable to good yields ranged from 75% to 89%. Aromatic aldehydes and anilines carrying either electron-withdrawing or electron-donating substituents could carry out the reaction. In case of anilines, both of the electron-donating and weak electron-withdrawing substituents were advantageous to the Mannich reaction.

## 4. Conclusion

In summary, a series of BASCs functionalised with toluenesulfonic acid were prepared and behaved as the recyclable catalyst for the three-component Mannich reaction with aldehyde, acetone and amine at room temperature in water. The results demonstrated that the [DOPA][Tos] provide the best catalytic activity because of the formation of emulsions. The catalytic procedure was simple and the catalyst could be recycled 9 times by simple separating processes without noticeably decreasing the catalytic activity.

## Acknowledgements

We acknowledge the financial support by the Science Foundation of Hebei province (no. B2012402001, B2012402064) and the National Natural Science Foundation of China (no. 51202054).

## References

- 1 M. O. Simon and C. J. Li, Chem. Soc. Rev., 2012, 41, 1415.
- 2 B. Pawar, V. Padalkar, K. Phatangare, S. Nirmalkar and A. Chaskar, *Chem. Commun.*, 2011, 1641.
- 3 J. H. Li, Y. F. Tang, Q. W. Wang, X. F. Li, L. F. Cun, X. M. Zhang, J. Zhu, L. C. Li and J. G. Deng, *J. Am. Chem. Soc.*, 2012, **134**, 18522.
- 4 B. Y. Zhang, Z. X. Jiang, X. Zhou, S. M. Lu, J. Li, Y. Liu and C. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 13159.
- 5 A. A. Jafari, F. Moradgholi and F. Tamaddon, *Eur. J. Org. Chem.*, 2009, 1249.
- 6 G. P. Lu and C. Cai, Catal. Commun., 2010, 11, 745.
- 7 S. Kobayashi and H. Ishitani, Chem. Rev., 1999, 99, 1069.
- 8 R. Muller, H. Goesmann and H. Waldmann, *Angew. Chem.*, *Int. Ed.*, 1999, **38**, 184.
- 9 M. Wu, H. W. Jing and T. Chang, *Catal. Commun.*, 2007, 8, 2217.
- 10 C. X. Zhang, J. C. Dong, T. M. Cheng and R. T. Li, *Tetrahedron Lett.*, 2001, 42, 461.
- 11 T. Ollevier, E. Nadeau and A.-A. Guay-begin, *Tetrahedron Lett.*, 2006, 47, 8351.
- 12 H. Wu, X. M. Chen, Y. Wan, L. Ye, H. Q. Xin, H. H. Xu, C. H. Yue, L. L. Pang, R. Ma and D. Q. Shi, *Tetrahedron Lett.*, 2009, **50**, 1062.
- 13 W. J. Hao, B. Jiang, S. J. Tu, X. D. Cao, S. S. Wu, S. Yan, X. H. Zhang, Z. G. Han and F. Shi, *Org. Biomol. Chem.*, 2009, 7, 1410.
- 14 P. Goswami and B. Das, Tetrahedron Lett., 2009, 50, 2384.
- 15 W. Shen, L. M. Wang and H. Tian, *J. Fluorine Chem.*, 2008, **129**, 267.
- 16 Y. S. Wu, J. W. Cai, Z. Y. Hu and G. X. Lin, *Tetrahedron Lett.*, 2004, 45, 8949.
- 17 K. Manabe and S. Kobayashi, Org. Lett., 1999, 1, 1965.
- 18 D. Fang, J. Luo and X. L. Zhou, Catal. Lett., 2007, 116, 76.
- 19 D. Fang, Z. H. Fei and Z. L. Liu, *Catal. Commun.*, 2009, **10**, 1267.
- 20 N. Azizi, L. Torkian and M. R. Saidi, Org. Lett., 2006, 8, 2079.
- 21 G. Zhao, T. Jiang, H. Gao, B. Han, G. Huang and D. Sun, *Green Chem.*, 2004, **6**, 75.
- 22 J. Li, Y. Peng and S. Gong, Catal. Lett., 2005, 102, 159.
- 23 S. Sahoo, T. Joseph and S. B. Halligudi, *J. Mol. Catal. A: Chem.*, 2006, **244**, 179.

#### View Article Online RSC Advances

- 24 Y. Hayashi, W. Tsuboi and N. Suzuki, *J. Am. Chem. Soc.*, 2003, **125**, 11208.
- 25 S. Mitsumori, H. Zhang, P. H. Y. Cheong, K. N. Houk, F. Tanaka and S. F. Barbas, *J. Am. Chem. Soc.*, 2006, **128**, 1040.
- 26 Y. W. Zhao, J. X. Long, F. G. Deng, X. F. Liu, Z. Li, C. G. Xia and J. J. Peng, *Catal. Commun.*, 2009, 10, 732.
- 27 S. W. Liu, L. Li, S. T. Yu, C. X. Xie, F. S. Liu and Z. L. Song, *Chin. J. Catal.*, 2010, **31**, 1433.

### Paper