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Highly efficient chemoselective construction of 2,2-dimethyl-6-substituted 4-piperidones *via* multi-component tandem Mannich reaction in ionic liquids†

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The room temperature ionic liquid [bmim][PF$_6$] has been demonstrated to be an efficient and recyclable medium for highly chemoselective synthesis of 2,2-dimethyl-6-substituted 4-piperidones *via* a L-proline catalyzed tandem Mannich reaction of ammonia, aldehydes and acetone, and good yields were achieved for aryl and alkyl aldehydes.

Room-temperature ionic liquids (RTILs) have recently been highlighted as effective replacements of traditional organic solvents.[1–2] The attractiveness of RTILs as reaction media is attributed to their favorable physicochemical properties, such as negligible vapor pressure, low volatility, tunable polarity and miscibility with organic or inorganic compounds. The ionic nature of RTILs ensures that catalysts that are ionic or possess polar or ionic groups can be readily immobilized, separated and recycled through a biphasic operation without laborious catalyst modification or work up, thereby providing a convenient solution to both the solvent emission and catalytic recycling problem. Numerous catalytic reactions have proven feasible in a variety of ionic liquids with facile catalyst recovery and reuse.[1–2] Of particular note is that many reactions in RTILs displayed enhanced reactivities and selectivities, some of which were not readily accomplished in common organic solvents.[3] For example, Xiao and coworkers found that RTILs could significantly improve the regioselectivity of Pd-catalyzed Heck arylation of electron-rich olefins.[3a–b] Lee *et al.* observed dramatic enhancement of catalytic activity in RTILs in their study of Friedel–Crafts alkenylation of arenes with alkynes.[3c] Alper and coworkers reported that Pd-catalyzed cyclocarbonylation of enynols with thiols could be successfully conducted in ionic liquids, which was not possible in normal organic solvents.[3d] More recently, we disclosed that Ru-TsDPEN catalyst displayed unprecedented reactivity and high enantioselectvity in the asymmetric hydrogenation of quinolines in neat RTIL, and employing RTIL as the reaction medium not only facilitates the recyclability, but also enhances the stability and selectivity of the catalyst.[3e]

Functionalized 4-piperidones are versatile building blocks for the preparation of a range of piperidine derivatives, which are important frameworks in a large number of bioactive natural products and pharmaceuticals.[4] Moreover, many piperidones themselves are an integral part of many biologically active compounds.[5] Consequently, much effort has been devoted to the efficient construction of these useful compounds, and many successful examples can now be found in the literature.[6] However, most attention has focused on the synthesis of 2-substituted and 2,6-disubstituted 4-piperidones, and there are few methods available for the synthesis of 2,2,6-trisubstituted 4-piperidones.[7] During our recent research on using versatile and cheap ammonia to activate direct aldol reaction of aldehydes and ketones, we unexpectedly found that 2,2-dimethyl-6-aryl-4-piperidones could be readily prepared through a tandem Mannich reaction in room temperature ammonia solution.[8] However, this chemistry is limited to hydroxybenzaldehydes, pyrrole-2-carboxyaldehyde and indole-3-carboxyaldehyde. Therefore, a more efficient and practical method for the preparation of 2,2,6-trisubstituted 4-piperidones is still highly desirable. Herein we wish to report that the use of RTIL [bmim][PF$_6$] in a tandem Mannich reaction of aldehydes, acetone and ammonia in the presence of L-proline additive enhances the chemoselectivity dramatically, providing the desired 2,2-dimethyl-6-substituted 4-piperidones in high yields. Moreover, the ionic liquid phase containing L-proline catalyst could be easily recycled for several times without loss of reactivity and chemoselectivity.

To establish suitable experimental conditions for this tandem Mannich reaction we first tried the reaction of benzaldehyde **1a** with acetone and ammonia in ethanol. Ammonia gas was bubbled into 1 mL ethanol for 5 min, followed by the addition of **1a** (1 mmol, 102 µL) and acetone (10 mmol, 0.75 mL) at room temperature. The mixture was stirred at room temperature, and the reaction went to completion in 20 h. The crude ^{1}H NMR spectrum indicated the formation of four products **2a–5a** in a ratio of 4 : 1 : 23 : 1. The major one corresponded to the aldol product **4a** (79%), and the chemoselectivity of the desired 2,2-dimethyl-6-phenyl-4-pyrilidinone **2a** was only 13% (Table 1, entry 1). Replacing ethanol with ethylene glycol led to the production of **3a–5a** in a ratio of 1 : 11 : 2, and no **2a** was observed (Table 1, entry 2). Recent reports disclosed that Mannich reaction could be promoted in RTILs.[9] Subsequently, we examined the reaction in a series of RTILs. To our delight, the use

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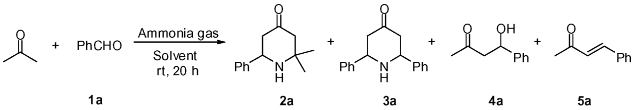
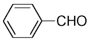
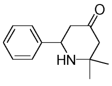
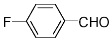
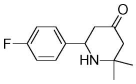
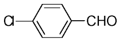
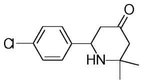
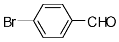
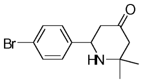
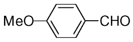
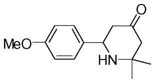
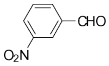
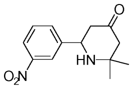
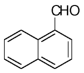
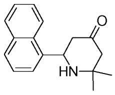
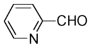
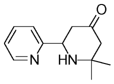
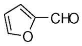
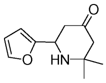
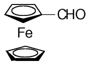
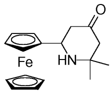
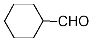
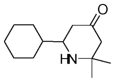
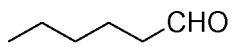
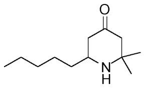
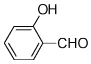
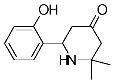
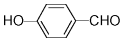
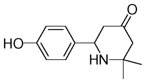
Table 1 Reaction condition optimization using different solvents and catalysts[a]



Entry	Solvent	Catalyst	**2a : 3a : 4a : 5a**[b]
1	Ethanol	none	14 : 3 : 80 : 3
2	Ethylene glycol	none	0 : 7 : 79 : 14
3	[dmpim][NTf_2]	none	55 : 30 : 10 : 5
4	[emim][NTf_2]	none	74 : 16 : 5 : 5
5	[bmim][Cl]	none	41 : 0 : 56 : 3
6	[bmim][BF_4]	none	67 : 0 : 30 : 3
7	[bmim][PF_6]	none	**78 : 9 : 9 : 4**
8	[bmim][PF_6]	PhCOOH (20 mol%)	78 : 9 : 11 : 2
9	[bmim][PF_6]	PhOH (20 mol%)	79 : 4 : 15 : 2
10	[bmim][PF_6]	$InCl_3$ (20 mol%)	84 : 9 : 5 : 2
11	[bmim][PF_6]	L-proline (20 mol%)	**93 : 1 : 0 : 6**
12[c]	[bmim][PF_6]	L-proline (20 mol%)	84 : 8 : 0 : 8

[a] Reaction conditions: 1.0 mL solvent (bubbled with ammonia gas for 5 min), **1a** (1.0 mmol), acetone (10.0 mmol, 0.75 mL), room temperature, 20 h. [b] Determined by ^1H NMR based on the integration of the relevant peaks of the crude products. [c] 5 equiv. acetone was used.

Table 2 L-Proline catalyzed tandem Mannich reaction of aldehydes with acetone and ammonia in [bmim][PF_6][a]

Entry	Aldehydes	Products	Yields (%)[b]
1	 **1a**	 **2a**	85
2	 **1b**	 **2b**	84
3	 **1c**	 **2c**	79
4	 **1d**	 **2d**	81
5	 **1e**	 **2e**	75
6	 **1f**	 **2f**	65
7	 **1g**	 **2g**	69
8	 **1h**	 **2h**	71
9	 **1i**	 **2i**	68
10	 **1j**	 **2j**	65
11	 **1k**	 **2k**	66
12	 **1l**	 **2l**	61
13	 **1m**	 **2m**	80
14	 **1n**	 **2n**	78

[a] Reaction conditions: [bmim][PF_6] (1.0 mL) (bubbled with ammonia gas for 5 min), aldehydes (1.0 mmol), acetone (10 mmol, 0.75 mL) and L-proline (23 mg, 0.20 mmol), room temperature, 20 h. [b] Isolated yield.

of [dmpim][NTf_2] led to 55% chemoselectivity favoring the formation of **2a** (Table 1, entry 3). A slightly better chemoselectivity was observed in [emim][NTf_2], but using [bmim][Cl] gave rise to a lower chemoselectivity (Table 1, entries 4–5). Much better results were achieved in both [bmim][BF_4] and [bmim][PF_6], and [bmim][PF_6] proved to be the most suitable solvent, affording the best chemoselectivity of 78% (Table 1, entries 6–7). We speculate that RTILs may favor the formation of imine and consequently result in the preferential occurrence of Mannich reaction over aldol reaction. The different chemoselectivities obtained may be attributed to the different viscosity of RTILs or NH_3-solubility.

In an attempt to further improve the chemoselectivity of the reaction, it seems that the use of catalyst is necessary. Then several acid catalysts were tested. While benzoic acid, phenol or $InCl_3$ failed to provide significant improvement (Table 1, entries 8–10), we found that with L-proline (20 mol%) as catalyst the tandem Mannich reaction in IL proceeded effectively to give the desired product **2a** in 85% isolated yield with very good chemoselectivity (93%) (Table 1, entry 11). This result is in good agreement with the previous reports that L-proline could efficiently catalyze Mannich reactions.[9a,10] However decreasing the amount of acetone led to a poor chemoselectivity (Table 1, entry 12).

With these encouraging results in hand, we turned to explore the scope of the reaction using different aldehydes as substrates under the optimized reaction conditions. The results are summarized in Table 2. Aryl aldehydes underwent effective tandem Mannich reaction in [bmim][PF_6] regardless of the nature of the substituents on the aryl ring, affording the desired products in moderate to good yields (Table 2, entries 1–7). The heteroaromatic aldehydes also proved to be viable substrates (Table 2, entries 8–9). Interestingly, ferrocenecarboxyaldehyde could be subjected to the tandem Mannich reaction as well, giving the product in 65% yield (Table 2, entry 10). The reactions of aliphatic aldehydes gave rise to 2,2-dimethyl-6-substituted 4-piperidones in 61–66% yields (Table 3, entries 11–12). In addition, aryl aldehydes with a hydroxy group at *ortho* or *para* position also exhibited high reactivity, and the corresponding piperidones were formed in 80%, 78% yields, respectively (Table 2, entries 13–14). The structure of **2m** was determined by X-ray crystallography, confirming the product formed (Fig. 1).[11] The space group is $P\bar{1}$ with 4 molecules in a cell. There are two independent molecules of **2m** in an asymmetric unit, and only one is shown in Fig. 1.

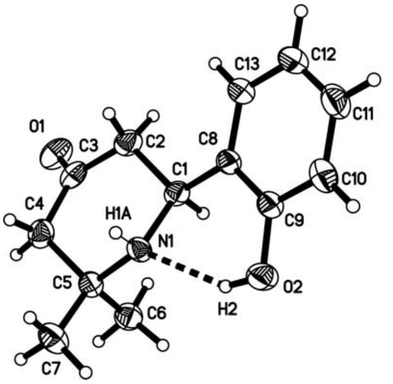
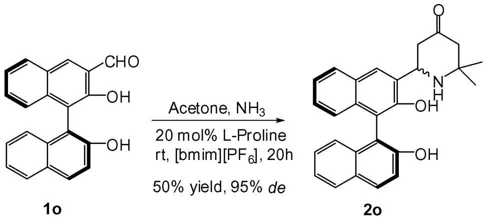


Fig. 1 X-Ray structure of **2m** (30%).

This attractive protocol could be applied to the diastereoselective tandem Mannich reaction of the chiral aryl aldehyde **1o** derived from (*S*)-BINOL (Scheme 1). The desired diastereomeric piperidone was obtained in 50% yield with excellent selectivity (20 : 1). Considering the versatile applications of BINOL in the design of chiral ligands, the resulting chiral piperidone may be exploited for the development of a new class of chiral ligands.



Scheme 1 Diastereoselective tandem Mannich reaction in [bmim][PF$_6$].

Having established the viability of this reaction, attention was then switched to the recyclability of the ionic liquid and catalyst. The insolubility of [bmim][PF$_6$] and L-proline in Et$_2$O offered a possibility of recycling both. We carried out the study by using **1a** as the model substrate. When the reaction finished in 20 h, the volatiles were removed *in vacuo* and the mixture was extracted with Et$_2$O. The residue was then subjected to the next batch of catalytic reaction to give the desired product. The catalyst system could be used consecutively for five times, but the yield decreased gradually (Table 3).

In summary, we have developed an efficient route for the construction of 2,2-dimethyl-6-substituted 4-piperidones *via* a four-component tandem Mannich reaction using the RTIL [bmim][PF$_6$] as the solvent at room temperature. The ionic liquid not only serves as a reaction medium, but also significantly enhances the chemoselectivity. The advantages of this methodology are: (1) easily available and low-cost starting materials, (2) easy operation, (3) recyclability of catalyst, and (4) mild reaction conditions. These advantages make this process potentially useful for industrial applications.

Table 3 Recycling of [bmim][PF$_6$]/L-proline system for tandem Mannich reaction[a]

Run	1	2	3	4	5
Yield (%)[b]	85	84	80	77	75

[a] Reaction conditions: [bmim][PF$_6$] (1.0 mL) (bubbled with ammonia gas for 5 min), **1a** (1.0 mmol), acetone (10.0 mmol, 0.75 mL) and L-proline (23 mg, 0.20 mmol), room temperature, 20 h. [b] Isolated yield.

Acknowledgements

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11 X-Ray crystallographic study of **2m**: Compound **2m**: ($C_{13}H_{17}NO_2$, $M_r = 219.28$) triclinic system space group $P\bar{1}$ (No. 2), $a = 5.7313(7)$ Å, $b = 11.8701(14)$ Å, $c = 18.407(2)$ Å, $\alpha = 72.324$ (2)°, $\beta = 85.809$ (2)°, $\gamma = 79.963$ (2)°, $V = 1174.6(2)$ Å^3, $Z = 4$, $\rho_{calc} = 1.240$ mg m^{-3}, $T = 294(2)$ K, $\mu = 0.083$ mm^{-1}, $F(000) = 472$, Mo-Kα radiation ($\lambda = 0.71073$ Å), colorless plate 0.30 × 0.26 × 0.24 mm. 11 208 reflections were collected on a Bruker-AXS SMART CCD diffractometer with 5412 reflections > $2\sigma(I)$, parameters 293, goodness of fit on F^2 1.016, $R_1 = 0.0528$, w$R_2 = 0.1274$. Further crystallographic data for **2m** have been deposited with the Cambridge Crystallographic Data Centre. CCDC number 259948. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b926498a.