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Facile Synthesis of Ureas in Ionic Liquid

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Abstract: The reaction of isocyanates with aliphatic and aromatic amines in the 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (bmimBF_4) ionic liquid in good to excellent yields is described. Due to its insolubility, the desired urea solids could be recovered by simple filtration from the ionic liquid after reaction.

Keywords: Ionic liquid, isocyanates, amines, ureas.

The urea functional group is of importance in a wide range of biological compounds such as enzyme inhibitors[1] and pseudopeptides[2]. Substituted ureas are widely applied in fine chemical industry, especially pesticides[3] and pharmaceuticals[4].

Many investigations have been made to search for an efficient and practical method to synthesize ureas. The typical procedure for the synthesis of ureas is treating isocyanates with primary or secondary amines in organic solvents[5]. In the presence of transition metal catalysts, selenium[6] or sulfur[7] compounds, symmetrical, unsymmetrical and even cyclo-ureas can be prepared by reacting primary amine or ammonia with carbon monoxide. Nevertheless, these classical methods are not environmentally benign for involving a gas substrate or a large number of volatile organic solvents. On the other hand, with the development of solid phase synthesis, solid phase urea synthesis[8] has attracted considerable attention in urea-containing combinational libraries. It is regretting that a favorite resin is not easy in many times.

Room-temperature ionic liquids as clean solvents and catalysts have shown their promising potentials in organic synthesis. And their utility in hydrogenation[9], Diels-Alder[10] and Heck reaction[11] *etc*. has been demonstrated. They will probably play important roles on green chemistry for that they are nonvolatile, recyclable, easy to handle, and nonexplosive. In case the product soluble in the ionic phase, it can be separated by extraction with ether[12].

Herein we wish to report a convenient synthesis of ureas from isocyanates and amines in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (bmimBF_4) ionic liquid (**Scheme 1**). All the products are obtained in good to excellent yields.

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Scheme 1

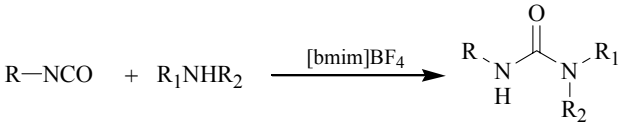
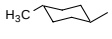
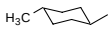


Table 1 Synthesis of ureas in ($bmimBF_4$) ionic liquid

Entry	R	R_1	R_2	Time (h)	Temp.	Yield (%)	mp (℃)
1	$PhCH_2CH_2$	*n*-C_7H_{15}	H	0.1	r.t.	96	76-79
2						95	
3						97	
4	$PhCH_2CH_2$	*n*-$C_{10}H_{21}$	H	0.1	r.t.	98	85-87
5	$PhCH_2CH_2$	cyclohexyl	H	0.2	r.t.	84	122-123
6	$PhCH_2CH_2$	piperidyl		2.0	50℃	81	78-79
7	$PhCH_2CH_2$	*p*-CH_3-Ph	H	1.0	r.t.	98	165-166
8	$PhCH_2CH_2$	*o*-CH_3-Ph	H	1.0	r.t.	92	154-156
9	Ph	$PhCH_2CH_2$	H	0.1	r.t.	98	154-5(153-4)[13]
10	Ph	morpholino		2.0	80℃	81	162-164
11	Ph	*m*-Cl-Ph	H	3.0	r.t.	92	185-187
12		Ph	H	1.5	r.t.	98	209-11(210 –1)[14]
13		*o*-CH_3-Ph	H	1.5	r.t.	98	212-214
14		*p*-Br-Ph	H	2.0	r.t.	91	184-186

The results are summarized in **Table 1**. Almost in all the case the mechanism of the formation of the urea derivatives is nucleophilic addition, when this method was used. Aliphatic primary amines afforded excellent yields and the reaction time was only 0.1 h. The electron-donating inductive effect of aliphatic groups promoted the reactions. The reactions with aliphatic secondary amines, such as piperidine and morpholine, were sluggish (2-3 h at 50℃ and 80℃ respectively), due to the steric hindrance (entries 6, 10). In the case of aromatic amines with electron-withdrawing substituent took longer reaction time (entries 12, 14). The resulting products are characterized by ^1H NMR, IR , MS spectroscopy and elemental analysis.

In view of 'green chemistry', reuse of the catalyst and solvent is preferable. From the results shown in **Table 1** (entries 1-3), with the recovered ($bmimBF_4$) ionic liquid the yields were almost the same as in the first run.

In conclusion, we have demonstrated that ($bminBF_4$) ionic liquid acts as an alternative medium for the formation of urea derivatives in high yields. The ionic liquid can be reused without impacting on yields.

Experimental

The thermometer was uncorrected. ^{1}H NMR spectra were determined in $CDCl_3$ or DMSO-d_6 on a Bruker 400 MHz spectrometer with TMS as the internal standard. J-values were given in Hz. IR spectra were recorded on a Bruker Vector-22 infrared spectrometer. Mass spectral data were obtained by electron ionization on HP5989B MS spectrometer. C,H,N were analyzed on a Carlo Erba 1110 elemental analyzer.

For a typical reaction, 1.5 mL ionic liquid, 1 mmol 2-phenylethyl isocyanate and 1 mmol heptyl amine were successively charged into the flask, and then the content was stirred at room temperature for 0.1 h. The product precipitated out and 2 mL water was added to facilitate the filtration. The crude product was filtrated, washed with water (1 mL×2) and recrystallized from ethyl acetate. The room temperature ionic liquid ($bmimBF_4$) was dried under vacuum for the next run.

N-n-Heptyl-N'-(2-phenylethyl)urea (entry 1) mp 76 -79℃ ^{1}H NMR ($CDCl_3$, δppm) 0.90(t, 3H, J=7.2), 1.30 (s, 8H), 1.45-1.48(m, 2H), 2.83 (t, 2H, J=6.8), 3.09-3.14(m, 2H), 3.44-3.49(m, 2H), 4.24(s, H), 4.30(s, 1H), 7.21-7.35(m, 5H); IR (KBr, cm^{-1}) 3352.8, 3314.4, 2955.2, 2928.8, 2856.6, 1619.5, 1575.1, 699.9, 630.4; MS *m/z* 262(M^+). Anal. Calcd. for $C_{16}H_{26}N_2O$: (%) C 73.24, H 9.99, N 10.68. Found: C 73.24, H 9.92, N 10.82.

N-Morpholino-N'-phenylurea (entry 10) mp 162-164℃ ^{1}H NMR ($CDCl_3$, δppm) 3.49 (t, 4H, J=4.8), 3.75 (t, 3H, J=4.8), 6.42(s, 1H), 7.05-7.09(m, 1H), 7.28-7.38(m, 4H); IR (KBr, cm^{-1}) 3270.4, 2953.6, 2918.2, 2858.4, 1635.6, 1539.9, 1500.3, 1444.9, 1415.0, 1303.3, 1250.8, 1114.5, 992.9, 873.8, 746.8, 692.1; MS *m/z* 206 (M^+). Anal. Calcd. for $C_{11}H_{14}N_2O_2$: (%) C 64.06, H 6.84, N 13.58. Found: C 64.26, H 6.80, N 13.76.

N-(3-Chlorophenyl)-N'-phenylurea (entry 11) mp 185-187℃ ^{1}H NMR (DMSO-d_6, δppm) 6.97-7.03(m, 2H), 7.25-7.32(m, 4H), 7.45-7.46(m, 2H), 7.71(s, 1H), 8.73(s, 1H), 8.86(s, 1H); IR (KBr, cm^{-1}) 3354.9, 3198.6, 3140.5, 3088.7, 1655.6, 1598.4, 1553.7, 1445.1, 1234.8, 768.4, 700.0; MS *m/z* 246 (M^+). Anal. Calcd. for $C_{13}H_{11}ClN_2O$: (%) C 63.29, H 4.49, N 11.36. Found: C 63.48, H 4.52, N 11.08.

N-(4-Methylcyclohexyl)-N'-(2-methylphenyl)urea (entry 13) mp 212-214 ℃ ^{1}H NMR ($CDCl_3$, δppm) 0.88 (d, 3H, J=6.8Hz), 1.03-1.12(m, 4H), 1.28 -1.31(m, 1H), 1.69-1.71(m, 2H), 1.99-2.01(m, 2H), 2.29(s, 3H), 3.60-3.62(m, 1H), 4.34 (d, 1H, J=8.4Hz), 5.85(s, 1H), 7.13-7.15(m, 1H), 7.17-7.26(m, 2H), 7.35-7.37(m, 1H); IR (KBr, cm^{-1}) 3319.2, 2946.5, 2849.4, 1635.2, 1570.0, 659.5; MS *m/z* 246(M^+). Anal. Calcd. for $C_{15}H_{22}N_2O$: (%) C 73.13, H 9.00, N 11.37. Found: C 73.35, H 8.95, N 11.58.

N-(4-Bromophenyl)-N'-(4-methylcyclohexyl)urea (entry 14) mp 284-286 ℃ ^{1}H NMR (DMSO-d_6, δppm) 0.87 (d, 3H, J=6.4Hz), 0.97-1.00(m, 2H), 1.08-1.18(m, 2H), 1.31-1.33(m, 1H), 1.65-1.68(m, 2H), 1.83-1.87(m, 2H), 6.01-6.03(d, 1H, J=7.2Hz), 7.32-7.38(m, 4H), 8.41(s, 1H); IR (KBr, cm^{-1}) 3327.5, 2946.2, 1629.3, 1583.5, 1569.4, 1486.9, 663.2; MS *m/z* 310(M^+). Anal. Calcd. for $C_{14}H_{19}BrN_2O$: (%) C 54.03, H 6.15, N 9.00. Found: C 53.91, H 6.20, N 9.07.

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15. The data of compounds in entries 4-8 have been submitted to CCL editorial office.

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