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Efficient and Eco-Friendly Synthesis of Dihydropyrimidinones, Bis(indolyl)methanes, and *N*-Alkyl and *N*-Arylimides in Ionic Liquids

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Dihydropyrimidinones, bis(indolyl)methanes, and *N*-alkyl and *N*-arylimides were synthesized efficiently under mild reaction conditions in the presence of two types of ionic liquids. In each section, effects of different ILs on the yield of reactions were investigated. The use of ionic liquids offer improvements for the synthesis of title compounds with regard to the yield of products, simplicity in operation, short reaction times and green aspects by avoiding toxic catalyst and organic solvents.

Keywords: Ionic liquid, Dihydropyrimidinones, Bis(indolyl)methanes, *N*-Substituted cyclic imides, Green chemistry

INTRODUCTION

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) **1** and their sulfur analogues have been reported to possess diverse pharmacological properties such as antiviral, antibacterial and antihypertensive activity, as well as efficacy as calcium channel modulator and α_{1a}-antagonists [1]. As an example, the betzelladine alkaloid containing the DHPM core unit is particularly notable, as found to be a potent HIV gp-120-CD_4-inhibitor [2]. The conventional method for the synthesis of DHPMs is the one-pot three-component reaction of an aldehyde, a β-ketoester, and urea (or thiourea) in the presence of an acidic catalyst, known as the Biginelli reaction from the name of its inventor [3]. Due to the importance of DHPMs, the Biginelli reaction for their synthesis has attracted renewed attention and many improved procedures have been reported. Many of the reported methods employ catalysts such as Brønsted acids [4], Lewis acids [5], solid supports [6], ammonium salts [7], LiBr [8], CAN [9], and ionic liquids [10].

Indole and its derivatives are important intermediates in organic synthesis and exhibit various physiological properties and pharmacological activities [11] such as beneficial estrogen metabolism promoter [12], inhibitor for human prostate cancer cells [13], and radical scavengers [14]. Over the past decade, a number of natural products containing bis(indolyl)methane (BIM) **2** moieties have been isolated from marine sources indeed [15]. Therefore, there is a great deal of interest in the synthesis of these classes of compounds. Among different methods used, synthesis toward the reaction of indole with aldehydes or ketones catalyzed by an acidic reagent, have gained much attention. Several catalysts have been reported for this reaction such as protic acids [16], Lewis acids [17], heterogeneous acidic catalyst [18] and reagents like iodine [19], NBS [20], potassium hydrogen sulfate [21], CAN [22], and hexamethylenetetramine-bromine [23]. However, many of these methods still suffer from some drawbacks such as long

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reaction time, expensive reagents, low yields of products, high catalyst loading, corrosive reagents, and large amounts of solid supports which would eventually result in the production of large amounts of toxic waste. For these reasons, superior catalysts, which are cheap, less toxic, easily available, air stable and water-tolerant, are desirable.

Imide derivatives constitute an important class of organic compounds which have been widely used in biology [24], synthetic [25] and polymer chemistry [26]. Because of a variety of industrial and pharmaceutical applications of imides, study of their chemistry is very important. For example, a number of imide derivatives are applied in therapies of tuberculosis, or as growth stimulant of grains and plants, fungicide, and herbicide [24]. Popular method for the synthesis of imide derivatives involves dehydrative condensation of an anhydride and an amine at high temperature followed by cyclization of the corresponding amic acid in the presence of acidic reagents [27].

Ionic liquids (ILs) are attracting increasing attention as alternative solvents for a wide range of catalytic and organic reactions [28]. Among versatile ILs, acidic ILs are of special interest, the first generation of this type of ILs are chloroaluminates which have been broadly studied [28]. However, the mentioned ILs are undergo hydrolysis in water and this lead to undesired side reactions and causing considerable potential for corrosion, so these problems limits their applications. Therefore, non-chloroalominate ILs, which are air and moisture stable, have been developed and applied in acid catalyzed reactions [29].

EXPERIMENTAL

General

Products were identified by their physical and spectroscopic data. Melting points were obtained in open capillary tubes on an Electrothermal 9200 apparatus and are not corrected. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. IR spectra were recorded as KBr pellets on a Shimadzu IR-470 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 300 DRX AVANCE instrument at 300 and 75 MHz, respectively. The ILs [Hmim]Tfa and [Hmim]HSO_4 were prepared according to the procedure reported in literature [30], and other ionic liquids and reagents were purchased from Merck chemical company in high-grade quality.

General Procedure for the Synthesis of DHPMs

A mixture of aldehyde (1 mmol), β-dicarbonyl compound (1 mmol) and urea or thiourea (1.5 mmol) were mixed with [Hmim]Tfa (0.2 g) and placed in a round bottomed flask. The mixture was heated at 50 °C. After the completion of the reaction, which was indicated by TLC (eluent: *n*-hexane/ethyl acetate: 3/1), cold water was added and the precipitated product was separated by simple filtration. If needed, the crude product was recrystallized from ethyl acetate/*n*-hexane or ethanol.

General Procedure for the Synthesis of BIMs in Ionic Liquids

Aldehyde (2 mmol), and indole (1 mmol) were mixed with ionic liquid (0.2 g) and placed in a round bottomed flask. The mixture was stirred at room temperature. After the completion of the reaction confirmed by TLC (eluent: *n*-hexane/ethyl acetate: 3/1), cold water was added and the precipitated product was separated by simple filtration. Finally the crude product was recrystallized from ethyl acetate/*n*-hexane or ethanol.

General Procedure for the Synthesis of *N*-Alkyl- and *N*-Arylimides

Aromatic or aliphatic amine (1 mmol), and phthalic anhydride derivative (1 mmol) were added to ionic liquid (0.2 g). The mixture was stirred at 80 ºC for the appropriate time (see Table 6). After completion of the reaction which indicated by TLC (eluent: *n*-hexane/ethyl acetate: 2/1), the mixture was cooled to room temperature. Water (2 × 5 ml) was added and decanted. Finally the solid residue was recrystallized from ethanol.

3i. IR (KBr) (ν_{max}, cm^{-1}): 1766, 1709.6, 1072, 734.6. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.94 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 2.13 (m, 1H, CH), 3.53 (brs, 2H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 20.09 (2C), 27.61, 46.14, 127.55, 129.67, 140.02, 163.87 ppm. MS (EI, 70 eV): m/z (%): 341 (30) [M^+], 298 (100), 214 (60).

3j. IR (KBr) (ν_{max}, cm^{-1}): 1766.6, 1700.0, 1050, 747. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.96 (t, ^{3}J = 7.44 Hz, 3H, CH_3),

1.72 (m, 2H, CH_2), 3.68 (t, ^3J = 7.2 Hz, 2H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.2, 21.6, 40.4, 127.6, 129.5, 140.0, 163.6 ppm. MS (EI, 70 eV): m/z (%): 327 (60) [M^+], 298 (100), 214 (45).

3e. IR (KBr) (ν_{max}, cm^{-1}): 1768, 1695, 1046, 719. ^1H NMR (300 MHz, $CDCl_3$) δ = 0.94 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 2.14 (m, 1H, CH), 3.52 (d, 2H, ^3J = 7.39 Hz), 7.71-7.87 (m, 4H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 20.15 (2C), 27.69, 46.16, 127.56, 129.61, 140.05, 163.88. MS (EI, 70 eV): m/z (%): 203 (75) [M^+], 159 (100), 76 (55).

3k. IR (KBr) (ν_{max}, cm^{-1}): 3476, 2968, 1760, 1718, 1692, 1518, 1483. ^1H NMR (300 MHz, DMSO-*d_6*) δ = 2.37 (s, 3H, CH_3), 7.32 (brs, 3H, Ar-H), 8.0-8.35 (m, 4H, Ar-H) ppm. ^{13}C NMR (75 MHz, DMSO-*d_6*) δ = 21.20, 123.77, 124.11, 127.53, 129.54, 129.80, 132.40, 135.2, 135.84, 137.10, 138.22, 166.30, 166.81 ppm. MS (EI, 70 eV): m/z (%): 281 (100) [M^+], 252 (70), 236 (100), 191 (100), 165 (80), 148 (55), 120 (50).

3l.. IR (KBr) (ν_{max}, cm^{-1}): 1772, 1707, 1397, 1306, 1255. ^1H NMR (300 MHz, DMSO-d_6) δ = 0.86 (t, ^3J = 7.2 Hz, 3H, CH_3), 1.26 (m, 2H, CH_2), 1.49-1.89 (m, 2H, CH_2), 3.54 (t, ^3J = 7.25 Hz, 2H, CH_2), 7.89 (d, ^3J = 7.71 Hz, 1H, Ar-H), 8.13 (s, 1H, Ar-H), 8.27 (d, ^3J = 7.71 Hz, 1H, Ar-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 13.88, 19.93, 30.35, 37.75, 123.36, 123.66, 132.38, 135.20, 135.58, 167.53, 167.55 ppm. MS (EI, 70 eV): m/z (%): 247 (100) [M^+], 230 (25), 204 (100), 191 (55), 174 (100), 148 (100), 120 (30), 75 (50).

3m. IR (KBr) (ν_{max}, cm^{-1}): 3420, 2942, 1758, 1700, 16891452, 1429. ^1H NMR (300 MHz, DMSO-*d_6*) δ = 2.92 (t, ^3J = 7.1 Hz, 2H, CH_2), 3.82 (t, ^3J = 7.1 Hz, 2H, CH_2), 7.15-7.28 (m, 5H, Ar-H), 7.95 (d, ^3J = 7.6 Hz, 1H, Ar-H), 8.18 (s, 1H, Ar-H), 8.34 (d, ^3J = 7.6 Hz, 1H, Ar-H), 13.72 (brs, 1H, COOH) ppm. ^{13}C NMR (75 MHz, DMSO-*d_6*) δ = 34.05, 123.41, 123.79, 126.90, 128.87, 129.06, 132.30, 135.15, 135.69, 136.66, 138.59, 166.19, 167.26 ppm. MS (EI, 70 eV): m/z (%): 295 (75) [M^+], 278 (20), 204 (100), 177 (60), 148 (65), 120 (25), 104 (100), 91 (75).

3n. IR (KBr) (ν_{max}, cm^{-1}): 3489, 3058, 1788, 1721, 1702, 1504, 1486, 1398. ^1H NMR (300 MHz, DMSO-*d_6*) δ = 745-7.57 (m, 5H, Ar-H), 8.08 (d, ^3J = 7.65 Hz, 1H, Ar-H), 8.30 (s, 1H, Ar-H), 8.41 (d, ^3J = 7.65 Hz, 1H, Ar-H), 13.78 (brs, 1H, COOH) ppm. ^{13}C NMR (75 MHz, DMSO-*d_6*) δ = 123.82, 124.23, 127.77, 128.68, 129.35, 132.17, 132.45, 135.32, 135.91, 136.85, 166.25, 166.73 ppm. MS (EI, 70 eV): m/z (%): 267 (100) [M^+], 250 (20), 223 (70), 178 (30), 148 (20).

3o. IR (KBr) (ν_{max}, cm^{-1}): 3490, 3032, 1782, 1711, 1700, 1434, 1395, 1352. ^1H NMR (300 MHz, DMSO-d_6) δ = 4.90 (s, 2H, CH_2), 727-7.48 (m, 5H, Ar-H), 8.01 (d, ^3J = 7.85 Hz, 1H, Ar-H), 8.49 (d, ^3J = 7.85 Hz, 1H, Ar-H), 8.58 (s, 1H, Ar-H) ppm. ^{13}C NMR (75 MHz, DMSO-*d_6*) δ = 41.55, 123.67, 124.01, 127.93, 128.74, 129.01, 132.44, 135.29, 135.81, 136.77, 136.84, 165.77, 167.36 ppm. MS (EI, 70 eV): m/z (%): 281 (100) [M^+], 252 (100), 224 (50), 208 (100), 190 (30), 174 (100), 148 (75), 104 (60), 91 (30), 65 (50).

RESULTS AND DISCUSSION

In continuation of our work on green and efficient synthesis of heterocyclic compounds [31], here we examined two types of ILs (Fig. 1) for the synthesis of DHPMs, BIMs, and *N*-alkyl and *N*-arylimides.

We started the three-component Biginelli condensation by examining the effect of ILs on yield and time of the typical reaction of benzaldehyde, urea and ethyl acetoacetate at 50 °C. The results are shown in Table 1. As indicated, four common

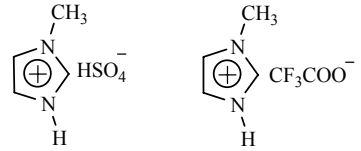


Fig. 1. Structures of ILs used.

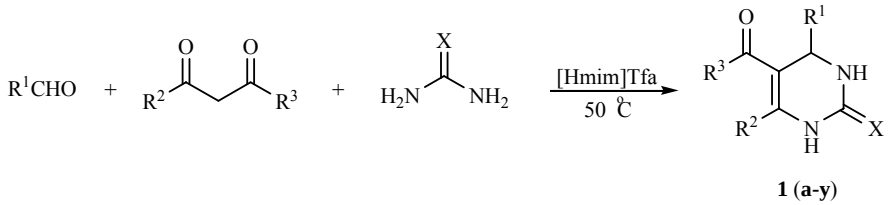
Table 1. Effect of Different ILs on the Reaction of Benzaldehyde, Ethyl Acetoacetate and Urea at 50 °C

Entry	Ionic liquid	Time (h)	Yield (%)[a]
1	[Hmim]Tfa	0.5	92
2	[Hmim]HSO_4	4	90
3	[Hmim]OTs	12	84
4	[bmim]Br	12	30
5	[bmim]PF_6	12	45
6	[bmim]BF_4	12	40
7	TBAB	12	20

[a]Isolated yield.

types of ILs were used (entries 4-7), but the best result was obtained in [Hmim]Tfa. On the basis of these findings, we focused our attention on the application of [Hmim]Tfa for the Biginelli reaction.

In a similar fashion, a variety of aromatic, aliphatic and heterocyclic aldehydes underwent three-component condensation smoothly to afford a wide range of substituted DHPMs (Scheme 1, Table 2). Many pharmacologically



Scheme 1

Table 2. Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones in [Hmim]Tfa

Entry	DHMP	R^1	R^2	R^3	X	Yield (%)[a]	Time (min)	M.p. (°C)[b]
1	**1a**	C_6H_5	Me	OEt	O	90	40	200-201
2	**1b**	4-$MeOC_6H_4$	Me	OEt	O	92	55	198-201
3	**1c**	4-ClC_6H_4	Me	OEt	O	89	50	209-211
4	**1d**	4-$O_2NC_6H_4$	Me	OEt	O	91	80	206-207
5	**1e**	3-$O_2NC_6H_4$	Me	OEt	O	87	70	227-228
6	**1f**	4-FC_6H_3	Me	OEt	O	93	90	185-186
7	**1g**	3,4-$(MeO)_2C_6H_3$	Me	OEt	O	85	45	176-177
8	**1h**	C_6H_5-CH=CH	Me	OEt	O	83	90	232-235
9	**1i**	*n*-C_3H_7	Me	OEt	O	80	80	157-158
10	**1j**	*n*-C_6H_{13}	Me	OEt	O	85	85	150-153
11	**1k**	2-Furyl	Me	OEt	O	82	90	210-212
12	**1l**	C_6H_5	Me	OMe	O	90	50	207-209
13	**1m**	4-$O_2NC_6H_4$	Me	OMe	O	94	85	234-236
14	**1n**	4-$MeOC_6H_4$	Me	OMe	O	89	40	192-193
15	**1o**	4-ClC_6H_4	Me	OMe	O	91	45	204-206
16	**1p**	3-$O_2NC_6H_4$	Me	OMe	O	92	60	278-280
17	**1q**	C_6H_5	Ph	OEt	O	85	50	158-160
18	**1r**	C_6H_5	Me	Me	O	90	45	232-235
19	**1s**	4-$MeOC_6H_4$	Me	Me	O	92	30	177-179
20	**1t**	4-$O_2NC_6H_4$	Me	Me	O	93	55	229(dec)
21	**1u**	C_6H_5	Me	OEt	S	96	70	204-206
22	**1v**	4-$MeOC_6H_4$	Me	OEt	S	94	85	138-140
23	**1w**	3-$O_2NC_6H_4$	Me	OEt	S	95	70	206-207
24	**1x**	C_6H_5	Me	Me	S	89	90	184 dec
25	**1y**	3-HOC_6H_4	Me	OEt	S	88	80	182-183

[a]Isolated yield. [b]The products were characterised by comparison of their spectroscopic and physical data with authentic samples synthesised by reported procedures [31d].

relevant substitution patterns on the aromatic ring were introduced with efficiency by using this procedure. Most importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted well under the reaction conditions to give the corresponding DHPMs in high to quantitative yields. Acid sensitive aldehydes like furfural also worked well without the formation of any side product (Table 2, entry 13). This method is even effective with aliphatic and α-β-unsaturated aldehydes, which normally show extremely low conversions in the Biginelli reaction (Table 2, entries 8-10). Thiourea has been used with similar success to produce the corresponding thio-derivatives of DHPMs, which are also of much interest with respect to their biological activities [32]. Decreased reaction times and temperature, joining with improving the yields are among other advantages of this method. Unlike most of the reported methods, this procedure does not require any further promoter and this is because of the dual solvent-catalyst activity of [Hmim]Tfa.

We also carried out the reaction of indole with 4-chlorobenzaldehyde in the presence of different ILs at room temperature. The results are shown in Table 3. Among the ILs examined, $[Hmim]HSO_4$ proved to be the most effective. Similar results were observed in [Hmim]Tfa but with longer reaction time. Utilization of other ILs was found to be quite unsatisfactory. It is worthy to note that, in the absence of ILs, the reaction did not yield any product at room temperature even after a long reaction time (Table 3, entry 8). So as the next step, we focused our attention on the synthesis of a number of BIMs in $[Hmim]HSO_4$ and [Hmim]Tfa at room temperature (Scheme 2).

As shown in Table 4, a series of aromatic, aliphatic and heterocyclic aldehydes underwent electrophilic substitution reaction with indole smoothly to afford a wide range of substituted BIMs in good to excellent yields. Manipulation of

Table 3. Effect of Different ILs on the Reaction of 4-Chlorobenzaldehyde, and Indole at Room Temperature

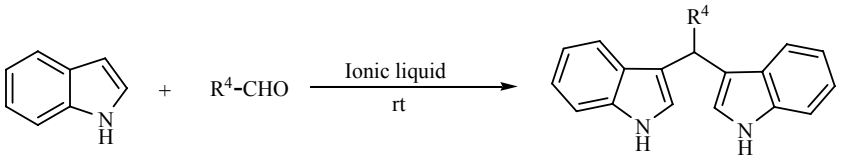
Entry	Ionic liquid	Time (h)	Yield (%)
1	[Hmim]Tfa	0.3	86
2	$[Hmim]HSO_4$	0.2	93
3	[Hmim]OTs	3	70
4	[bmim]Br	12	40
5	$[bmim]PF_6$	12	60
6	$[bmim]BF_4$	12	65
7	TBAB	12	30
8	-[a]	24	-

[a]The reaction was carried out in the absence of any IL.

different functional groups in the final product was easily achieved with high efficiency by using this procedure. Furthermore, unsaturated aldehydes, such as cinnamaldehyde, gave the corresponding BIMs without polymerization under the above reaction conditions (Table 4, entry 8).

For the synthesis of *N*-alkyl- and *N*-arylimides, the model reaction of phthalic anhydride and aniline was investigated under different conditions. The results are represented in Table 5. As seen, when the reactions were carried out in organic solvents, no satisfactory results were obtained. However, good results were obtained by conducting the reaction in $[Hmim]HSO_4$ and [Hmim]Tfa ILs. It is worthy to note that the reaction was not completed in the absence of ILs (Table 5, entry 6).

Then we focused on the synthesis of our desired compounds under the optimized conditions. When a mixture of amine, phthalic anhydride derivative, and IL were heated at 80 ºC the desired imides were obtained (Scheme 3). The reactions were progressed smoothly and products were obtained in good to excellent yields in sufficient time (Table 6).



Scheme 2

Table 4. Synthesis of Bis(indolyl)methanes by the Reaction of Aromatic Aldehydes and Indole in ILs

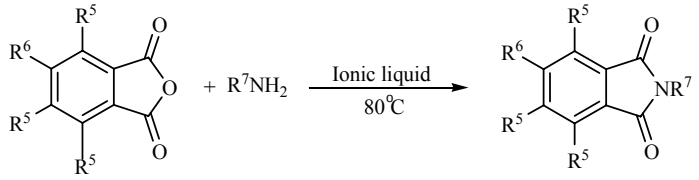
Entry	R^4	[Hmim]Tfa		[Hmim]HSO_4		M.p. (ºC)	
		Yield (%)	Time (min)	Yield (%)	Time (min)	Found	Reported
1	C_6H_5	90	10	90	15	123-124	126-127 [17c]
2	4-$MeOC_6H_4$	92	15	92	20	93-95	95-97 [17c]
3	4-ClC_6H_4	89	15	89	15	106-108	104-105 [17c]
4	4-$O_2NC_6H_4$	91	15	91	20	220-223	222-224 [17c]
5	3-$O_2NC_6H_4$	87	20	87	20	267	265-266 [17c]
6	4-FC_6H_3	93	15	93	25	72-73	72-74 [17c]
7	C_6H_5-CH=CH	83	25	83	40	100-102	99 [17c]
8	*n*-C_6H_{13}	85	30	85	40	65-67	66-68 [17c]
9	2-Furyl	82	30	82	40	>300	322 [17c]
10	2-$O_2NC_6H_4$	90	20	90	20	140-142	141-143 [17c]
11	2-ClC_6H_4	94	20	94	25	70-71	72-74 [17c]
12	4-MeC_6H_4	89	10	89	15	96-97	95-97 [17c]
13	4-HOC_6H_4	91	10	91	15	123-124	122-124 [17c]
14	2-HOC_6H_4	92	15	92	15	>300	349 [17c]

[a]Isolated yield.

Table 5. Effect of Temperature and Time on the Synthesis of *N*-Phenyl Phthalimide

Entry	Medium	Temperature (°C)	Time (h)	Yield (%)[b]
1	CH_2Cl_2	40	12	-
2	CH_3OH	60	12	-
3	CH_3CH_2OH	70	12	-
4	$C_6H_5CH_3$	100	12	20
5	CH_3CN	60	12	-
6	-[a]	80	12	15
7	TBAB	80	12	25
8	[bmim]Br	80	12	30
9	[bmim]PF_6	80	12	50
10	[bmim]BF_4	80	12	45
11	[Hmim]Tfa	80	3	85
12	[Hmim]HSO_4	80	2.5	89

[a]Reaction was carried out under neat condition. [b]Isolated yield.



3 (a-o)

Scheme 3

Table 6. Synthesis of *N*-alkyl- and *N*-arylphthalimides in Different ILs

Product	R^5	R^6	R^7	[Hmim]Tfa		[bmim]HSO_4		M.p. (°C)	
				Time (h)	Yield (%)[a]	Time (h)	Yield (%)[a]	Found	Reported
3a	H	H	C_6H_5	2.5	85	3	89	209-210	208-209 [33]
3b	H	H	$C_6H_5CH_2$	3	90	3.5	84	118-120	118.5-119.5 [34]
3c	H	H	4-BrC_6H_4	2.5	90	3	90	203-205	204-205 [35]
3d	H	H	1-Naphthyl	4	87	4	87	182-183	182-183 [35]
3e	H	H	*iso*-Butyl	2	84	3	84	90-92	-
3f	Cl	Cl	C_6H_5	3	88	4	82	275-276	273-275 [36]
3g	Cl	Cl	1-Naphthyl	3.5	91	4	88	239-240	237-239 [36]
3h	Cl	Cl	4-BrC_6H_4	3	84	3.5	87	335-336	334-336 [36]
3i	Cl	Cl	*iso*-Butyl	3	87	3.5	86	171-172	-
3j	Cl	Cl	*n*-Propyl	1.5	85	2.5	91	162-163	-
3k	H	CO_2H	4-$H_3CC_6H_4$	2	90	2	85	256-258	-
3l	H	H	*n*-Butyl	1.5	89	1.5	87	134-135	-
3m	H	CO_2H	$C_6H_5CH_2CH_2$	2	57	1.5	90	204-206	-
3n	H	CO_2H	C_6H_5	3	90	3	85	>260	-
3o	H	CO_2H	$C_6H_5CH_2$	2.5	85	3	87	200-202	-

[a]Isolated yield.

The procedure was applicable to aliphatic as well as aromatic amines containing different functionalities, such as methyl, nitro and chloro groups.

CONCULSIONS

Three important types of heterocyclic compounds were synthesized efficiently in two types of acidic ILs. In all cases, the products can be separated conveniently from the reaction system in high purity and no chromatographic method need for their isolation. Another advantage of these methods is that the reaction conditions were mild and the products were obtained in excellent yields. We believe this method, with respect to the green chemistry regards, could be adopted for

the synthesis of DHPMs, BIMs, and *N*-alkyl and *N*-arylimides.

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