SHORT PAPER

J. Chem. Research (S),
2003, 645–647

Synthesis of 2-arylimidazo[1,2-*a*]pyrimidines by the Chichibabin synthesis in ionic liquids†

Danqian Xu*, Baoyou Liu and Mei Zheng

Laboratory of Green Chemistry and Synthetic Technology, Zhejiang University of Technology, Hangzhou 310 032, P. R. China

A series of 2-arylimidazo[1,2-*a*]pyrimidines has been synthesised in excellent yields by the Chichibabin synthesis in room temperature ionic liquids.

Keywords: ionic liquids, Chichibabin synthesis, fused imidazoles, fused pyrimidines

Room temperature ionic liquids (RTILs) have gained considerable attention in the last decade as possible environmentally benign media in various organic synthetic processes owing to their unique chemical and physical properties.[1] Many organic reactions have been shown to proceed in good yields and high efficiency in RTILs, which including oxidations, hydrogenations, C–C and C–O cleavage reactions, and C–C and C–heteroatom coupling reactions (*e.g.*, Diels–Alder reactions, Friedel–Crafts reactions, Heck reactions, *etc.*). Furthermore, several studies on the applications of RTILs for heterocyclic synthesis have been reported since 2000,[2] including the Biginelli reaction,[3] Beckmann rearrangement,[4] Pechmann reaction[5] Bischler-Napieralski reaction[6] and so on. The extensive use of RTILs in the synthesis of heterocyclic compounds is quite significant since many of those compounds are useful as drug, pesticide and dyestuff intermediates or products.

Our recent research has been in the area of environmentally clean synthesis of pharmaceutically useful compounds. As part of a program to investigate the synthesis of heterocyclic compounds in ionic liquids, we have studied the preparation of 2-arylimidazo[1,2-*a*]pyrimidine compounds, which show pharmaceutical activity, in particular antimicrobial effects.[7] Usually, they have been synthesised according to Chichibabin's method by cyclocondensation of 2-aminopyrimidine with α-bromoacetophenones. The solvent used could be ethanol[7] and DMF[8]. Long reaction times or reflux temperatures have always been necessary, and yields never outstanding. To explore the possibility of this cyclocondensation in ionic liquids, the following RTILs were used: 1-*n*-butyl-3-methyl imidazolium tetrafluoroborate ($BMImBF_4$), 1-ethyl-3-methylimidazolium tetrafluoroborate ($EMImBF_4$), and *N*-butylpyridinium tetrafluoroborate ($BPyBF_4$), which were synthesised according to literature procedures.[9]

First, we examined the efficiency of different ionic liquids in the cyclocondensation of α-bromo-4-chloroacetophenone (**1a**) with 2-aminopyrimidine (**2**) (Scheme 1). For the sake of comparison, reactions in some typical molecular solvents are also included; the results are listed in Table 1. As can be seen from Table 1, when the ionic liquids $BMImBF_4$, $BPyBF_4$ and $EMImBF_4$ were used as solvents, the yields were 82%, 86% and 79% respectively (entries 1–3), while when the reactions were carried out under similar conditions but using traditional molecular solvents DMF, acetonitrile and ethanol, the yields fell to 55%, 42% and 26% respectively (entries 4, 6, 8); higher yields in traditional solvents could only be obtained when longer reaction times and elevated temperatures were used (entries 5, 7, 9), which showed that the ionic liquids can truly be compared with conventional molecular solvents, with the advantages of acceleration of reaction rate and increase of yield.

Table 1 Cyclocondensation of α -bromo-4-chloroacetophenone (**1a**) with 2-aminopyrimidine (**2**) in different solvents

Entry[a]	Solvent	Reaction time/h	Reaction temp./°C	Yield/%[b]
1	$BMImBF_4$	3	25	82
2	$BPyBF_4$	3	25	86
3	$EMImBF_4$	3	25	79
4	DMF	3	25	55
5	DMF	6	reflux	86
6	MeCN	3	25	42
7	MeCN	6	reflux	89
8	EtOH	3	25	26
9	EtOH	6	reflux	59

[a]All the reactions were run with α-bromo-4-chloroacetophenone (5 mmol), 2-aminopyrimidine (5 mmol) in solvent (10 ml) in the presence of sodium carbonate (5mmol). [b]Isolated yield of pure product.

The scope of the cyclocondensation of α-bromoacetophenones (**1**) with 2-aminopyrimidine (**2**) in ionic liquids was next

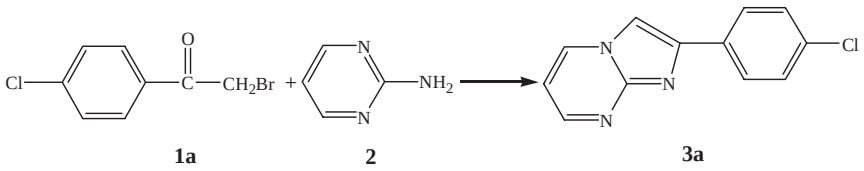
Table 2 Synthesis of 2-arylimidazo[1,2-*a*]pyrimidines (**3**) *via* cyclocondensation of α-bromoacetophenones (**1**) with 2-aminopyrimidine (**2**) in RTILs[a]

Entry	Products	RTIL	Reaction time/h	Yield/%[b] [Lit.]	M.p. (°C) [Lit.]
1	**3a**	$BMImBF_4$	3	82 [70[10]][c]	280 [274[11]]
2	**3a**	$BPyBF_4$	3	86	280
3	**3a**	$EMImBF_4$	3	79	280
4	**3b**	$BMImBF_4$	3	83	241 [239[12]][d]
5	**3b**	$BPyBF_4$	3	84	241
6	**3b**	$EMImBF_4$	3	81	241
7	**3c**	$BMImBF_4$	4	78 [70[10]]	279 [279[11]]
8	**3c**	$BPyBF_4$	4	81	279
9	**3d**	$BMImBF_4$	4	79 [72[13]][e]	>360[>360[13]]
10	**3d**	$BPyBF_4$	4	77	>360
11	**3e**	$BPyBF_4$	6	84 [70[10]]	231 [242[10]]
12	**3f**	$BPyBF_4$	6	71 [70[10]]	182 [183[12]]
13	**3g**	$BMImBF_4$	4	78	269 [260[14]]
14	**3g**	$BPyBF_4$	4	92 [70[10]]	269
15	**3h**	$BMImBF_4$	4	60	279 [244[10]]
16	**3h**	$BPyBF_4$	4	77	279
17	**3i**	$BMImBF_4$	4	72	190
18	**3i**	$BPyBF_4$	4	76	190
19	**3j**	$BMImBF_4$	6	63	261 [260[7]]
20	**3j**	$BPyBF_4$	6	78 [70[10]]	261
21	**3j**	$EMImBF_4$	6	76	261
22	**3k**	$BMImBF_4$	3	75	181 [195[12]]

[a]The experimental procedure was not further optimised. [b]Isolated yield of pure product. [c]Reaction in absolute alcohol, reflux for 4 hours. [d]Reaction in DME, reflux for 48 hours, no yield reported. [e]Reaction in acetone, at room temperature overnight.

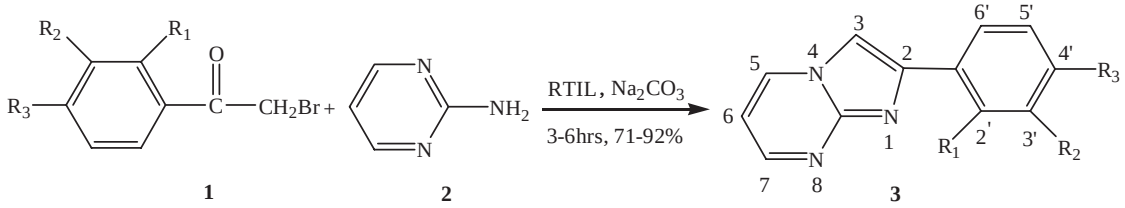
* To receive any correspondence. E-mail: chrc@zjut.edu.cn

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



1a **2** **3a**

Scheme 1 Synthesis of 2-(4-chlorophenyl)imidazo[1,2-*a*]pyrimidine



1 **2** **3**

	R_1	R_2	R_3		R_1	R_2	R_3
a	H	H	Cl	**g**	H	H	C_6H_5
b	H	H	F	**h**	Cl	H	Cl
c	H	H	Br	**i**	H	Cl	H
d	H	H	NO_2	**j**	H	NO_2	H
e	H	H	CH_3	**k**	H	H	H
f	H	H	OCH_3				

Scheme 2

investigated, and the reaction was found to be general. Several α-bromoacetophenones containing various substituents, such as fluoro, chloro, bromo, nitro, phenyl, methyl and methoxyl, were successfully reacted to form corresponding 2-arylimidazo[1,2-*a*]pyrimidines (**3**) (Scheme 2). In fact, simple stirring of a mixture of α-bromoacetophenone (**1**), 2-aminopyrimidine (**2**) and sodium carbonate in ionic liquid at room temperature gave, after work up and isolation, the desired 2-arylimidazo[1,2-*a*]pyrimidine (**3**), the results are summarised in Table 2 which includes some results from the literature for comparison. The products were all characterised by melting points; for the products whose melting points were inconsistent with the literature (**3e**, **3g**, **3h**, **3k**) or when there are no literature data (**3i**), elemental analyses, IR, ^{1}H NMR and MS were used to further characterize and the data are reported in the Experimental section. As can be seen from Table 2, all reactions exhibited pronounced rate accelerations and good yields were obtained.

Besides, the ionic liquids could be typically recovered by filtering to remove product followed by vacuum drying. The recovered solvent can be reused with no appreciable decrease in yield at least six times except only small mechanical loss. The results are summarised in Table 3.

We have demonstrated that RTILs are promising alternative solvents for the cyclocondensation reaction of 2-aminopyrimidine with α-bromoacetophenones to prepare some 2-arylimidazo[1,2-*a*]pyrimidines. It can afford good yields under mild conditions within limited time. The product can easily be separated from the reaction mixture by dilution first and then filtration. RTILs could be used at least six times without apparent drop in efficiency except a little mechanical loss of quantity. The present method has some obvious advantages over traditional methods, including the simplicity of the methodology, ease of product isolation and higher yields; RTILs promise to have broad application in the field of organic synthesis. Further investigation of the uses of RTILs in organic reactions is still under way in our laboratory.

Table 3 Results obtained using recycled ionic liquid $BPyBF_4$ for synthesis of compound **3a**

Entry	Cycle	Yield/%
1	Fresh	86
2	1	89
3	2	87
4	3	86
5	4	86
6	5	86
7	6	85

Experimental

Melting points (uncorrected) were detected on a microscopic melting point apparatus, ^{1}H NMR spectroscopy were obtained on a Bruker Avance 500 (DMSO-d_6, TMS as internal standard), IR spectra were recorded as KBr pellets on a Bruker Equinox 55 spectrometer, Mass spectra were recorded on a Varian CP 3800/Saturn 2000 GC/MS, Element analyses were obtained using a Carlo Erba EA 1106 instrument. The purity of products was analysed by HPLC.

Synthesis of 2-arylimidazo[1, 2-a]pyrimidines in RTILs: typical procedure: α-Bromo-4-chloroacetophenone (**1a**, 1.17 g, 5 mmol), 2-aminopyrimidine (**2**, 0.47 g, 5 mmol), sodium carbonate (0.53 g, 5 mmol), ionic liquid ($BPyBF_4$, 10 ml) were added successively into a 20 ml round-bottomed two-necked flask with mechanical stirrer. Then the reaction mixture was stirred for the stated time (Table 1) at room temperature. The reaction process was monitored by thin layer chromatography (TLC, silica gel 254, eluted hexane: ethyl acetate, 2:1). After completion of the reaction, the mixture was poured into ice-water mixture (10 ml) with vigorous stirring to precipitate the product 2-(4-chlorophenyl)imidazo[1,2-*a*]pyrimidine **3a**. After filtration of the product, the filtrate was evaporated to remove the water under reduced pressure and the remaining ionic liquid could be reused for another experiment. A pure sample was obtained by further crystallization from DMF or alcohol or by preparative TLC (silica gel 254, eluted ethyl acetate) to give **3a** (0.99 g, 86% in yield), m.p. 280 °C (lit.[11] 274 °C). Found: C, 62.47; H, 3.52; N, 18.33. $C_{12}H_8ClN_3$ requires C, 62.76; H, 3.51; N, 18.30 %.

Compound **3e**: m.p. 231 °C (lit.[10] 242 °C). IR: 1612, 1521, 1485, 1353, 1080 cm^{-1}; ^{1}H NMR: 7.02 (1H, dd, $J_{5,6}$ = 6.7 Hz, $J_{6,7}$ = 4.1 Hz, H_6) 7.27 (2H, d, J = 8.0 Hz, $H_{3'}H_{5'}$) 7.89 (2H, d, J = 8.0 Hz, $H_{2'}H_{6'}$) 8.30 (1H, s, H_3) 8.50 (1H,dd, $J_{5,7}$ = 1.8 Hz, H_7) 8.92 (1H,dd,H_5); MS:

m/z 209 (100), 210 (44), 211 (26), 194 (2), 181 (6),140 (3), 130 (7), 115 (4), 89 (7), 77 (6), 63 (6). Found: C, 74.28; H, 5.31; N, 20.12. $C_{13}H_{11}N_3$ requires C, 74.62; H, 5.30; N, 20.08 %.

Compound **3g**: m.p. 269 °C (lit.[14] 260 °C). IR: 1613,1519, 1498,1078 cm^{-1}; ^1H NMR: 7.07 (1H, dd, $J_{5,6}$ = 6.6 Hz, $J_{6,7}$ = 4.2 Hz, H_6) 7.38 (1H, t, J = 7.2 Hz, $H_{4'}$) 7.49 (2H, J = 7.2 Hz, $H_{3'}$,$H_{5'}$) 7.74 (2H, d, J = 7.2Hz, $H_{2'}$,$H_{6'}$) 7.79 (2H, J = 8.4 Hz, $H_{3'}$,$H_{5'}$) 8.1 (2H, d, J = 8.2 Hz, $H_{2'}$,$H_{6'}$), 8.44 (1H, s, H_3) 8.54 (1H, d, $J_{5,7}$ = 1.9 Hz, H_7), 8.98 (1H, dd,H_5); MS: *m/z* 271 (100), 272 (21), 273 (2), 243 (28), 216 (11), 192 (31), 164 (10), 138 (10), 53 (12). Found: C, 79.28; H, 4.85; N, 15.46; $C_{18}H_{13}N_3$ requires C, 79.68; H, 4.83; N, 15.49 %.

Compound **3h**: m.p. 279 °C (lit.[10] 244 °C). IR: 1610, 1500, 1045, 710 cm^{-1}; ^1H NMR: 7.09 (1H, dd, $J_{5,6}$ = 6.6 Hz, $J_{6,7}$ = 4.1 Hz, H_6), 7.56 (1H, dd, J = 8.5 Hz, $H_{5'}$), 7.72 (1H, s, $H_{3'}$), 8.30 (1H, d, $H_{6'}$), 8.58 (2H, d, H_3, H_7) 9.01 (1H, t, H_5); MS: *m/z* 263 (100), 265 (74), 264 (37), 228 (40), 184 (14), 174 (12), 168 (10). Found: C, 54.30; H, 2.66; N, 15.89 $C_{12}H_7Cl_2N_3$ requires C, 54.57; H, 2.67; N, 15.91 %.

Compound **3i**: m.p. 190 °C. IR: 1617, 1499, 1082, 789 cm^{-1}; ^1H NMR: 7.07 (1H, dd, $J_{5,6}$ = 6.7 Hz, $J_{6,7}$ = 4.0 Hz, H_6), 7.41 (1H, d, J = 8.2 Hz, $H_{4'}$), 7.49 (1H, t, $J_{4'5'}$ = 8.0 Hz, $J_{5'6'}$ = 7.7Hz, $H_{5'}$) 7.96 (1H, d, $H_{6'}$), 8.05 (1H, s, $H_{2'}$), 8.47 (1H, s, H_3), 8.56 (1H, dd, H_7), 8.96 (1H, dd, $J_{5,7}$ = 1.8 Hz, H_5);MS: *m/z* 229 (100), 231 (35), 230 (21), 194 (20), 167 (11), 140 (14), 114 (6), 97 (7), 75 (10). Found: C, 62.46; H, 3.51; N, 18.34. $C_{12}H_8ClN_3$ requires C, 62.76; H, 3.51; N, 18.30 %.

Compound **3k**: m.p. 181 °C (lit.[12] 195 °C). IR: 1638, 1597, 1501, 1059 cm^{-1}; ^1H NMR: 7.53 (3H, m, $H_2H_6H_{4'}$), 7.59 (2H, t, J = 7.7 Hz, $H_{3'}$,$H_{5'}$) 8.01 (2H, d, J = 7.5 Hz, $H_{2'}$,$H_{6'}$) 8.70 (1H, s, H_3) 8.92 (1H, d, $J_{5,7}$ = 1.9 Hz, H_7) 9.26 (1H, dd, $J_{5,6}$ = 6.5 Hz, H_5); MS: *m/z* 195 (100), 196 (18), 168 (15), 141 (12), 116 (12), 89 (11), 79 (9), 63 (8). Found: C, 73.46; H, 4.65; N, 21.49. $C_{12}H_9N_3$ requires C, 73.83; H, 4.65; N, 21.52 %.

Received 30 January 2003; accepted 30 July 2003
Paper 03/1724

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