1002 Chinese Chemical Letters Vol. 14, No. 10, pp 1002– 1004, 2003
http://www.imm.ac.cn/journal/ccl.html

Synthesis of 2-Arylimidazo[1, 2-a]pyrimidines in Ionic Liquids

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Abstract: Room temperature ionic liquids were used as a "green" recyclable alternative to conventional solvents in the synthesis of pharmaceutically useful compounds 2-arylimidazo[1, 2-a] pyrimidines through Tschotschibabin reaction of α-bromoacetophenones with 2-aminopyrimidine in good yields.

Keywords: Room temperature ionic liquids, Tschotschibabin reaction, 2-aminopyrimidine, α-bromoacetophenones, 2-arylimidazo[1, 2-a]pyrimidines.

Our recent research focused on the synthesis of heterocyclic compounds, since many of these compounds are used in the pharmaceutical, pesticide and dyestuff chemistry. As a part of our program, we are interested in the synthesis of 2-arylimidazo[1, 2-a]pyrimidine compounds, which showed antimicrobial effects[1]. Usually, they were synthesized according to Tschotschibabin reaction by cyclocondensation of 2-aminopyrimidine with the appropriate α-bromoacetophenones. DME[2], ethanol[3], acetone[4] and DMF[5] were used as the solvents. Long reaction time was necessary while the yield was not very favorable. Since the room temperature ionic liquids (RTILs) are being more and more regarded as clean solvents and many organic reactions have proceeded on the use of RTILs with good yields and selectivity[6], the versatility of RTILs stimulated us to explore the possibility of the cyclocondensation reaction of α-bromoacetophenones with 2-aminopyrimidine in RTILs. The RTILs used in this paper were 1-*n*-butyl-3-methyl-imidazolium tetrafluoroborate ($BMImBF_4$), 1-ethyl-3-methylimidazolium tetrafluoro-borate ($EMImBF_4$) and N-butylpyridium tetrafluoroborate ($BPyBF_4$), which were synthesized according to the literatures[7].

The cyclocondensation reactions of α-bromoacetophenones **1** with 2-amino-pyrimidine **2** to form 2-arylimidazo[1, 2-a]pyrimidines **3** (**Scheme 1**) were carried out using RTILs as solvents and the results were summarized in **Table 1**. Thus, several α-bromoacetophenones **2** containing various substituents, such as chloro, fluoro, bromo, nitro, methyl, methoxyl and phenyl, were successfully reacted with 2-aminopyrimidine **1** in the presence of sodium carbonate to form corresponding 2-arylimidazo[1, 2-a] pyrimidines **3** in good yields. The reactions were usually completed within 3-6 hours, and proceeded at room temperature except entry 11 which needed a little higher

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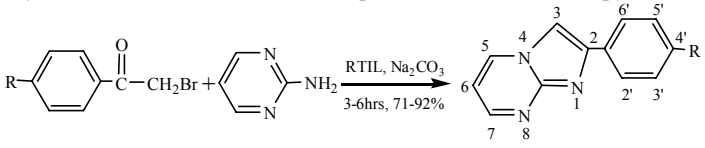
temperature for higher yield. All the RTILs chosen here can act as solvents, among them $BPyBF_4$ is the most favorable for the α-bromoacetophenones without strong electron-withdrawing groups in the *para* position (entry 1-8, 13, 14).

For comparion, some results reported in literature are also summarized in **Table 1**. The yields of compounds **3a~f, 3g** were 70%,70%,70%,65%,70% and 70% respectively in literature[3]. The reactions were run in absolute alcohol and refluxed for 4 hours; the compound **3d** was obtained in acetone at room temperature overnight in 72% yield[4]; according to literature[2], compound **3b** was obtained in refluxing DME for 48 hours, but the yield was not reported. These results suggested that the RTILs have many advantages over conventional solvents, such as shorter reaction time and better yields.

Scheme 1 Cyclocondensation of α-bromoacetophenones **1** with 2-aminopyrimidine **2** in RTILs



1 **2** **3**

a: R=Cl; **b**: R=F; **c**: R=Br; **d**: R=NO_2; **e**: R=CH_3; **f**: R=OCH_3; **g**: R=C_6H_5

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

Entry	Product	RTIL	Reaction time (hrs)	Reaction temp. (□)	Isolated yield (%)	Yield in lit.* (%)
1	**3a**	$BMImBF_4$	3	25	82	70[3]
2	**3a**	$BPyBF_4$	3	25	86	
3	**3a**	$EMImBF_4$	3	25	79	
4	**3b**	$BMImBF_4$	3	25	83	no[2]
5	**3b**	$BPyBF_4$	3	25	84	
6	**3b**	$EMImBF_4$	3	25	81	
7	**3c**	$BMImBF_4$	4	25	78	70[3]
8	**3c**	$BPyBF_4$	4	25	81	
9	**3d**	$BMImBF_4$	4	25	79	70[3], 72[4]
10	**3d**	$BPyBF_4$	4	25	77	
11	**3e**	$BPyBF_4$	6	50	84	65[3]
12	**3f**	$BPyBF_4$	6	25	71	70[3]
13	**3g**	$BMmlBF_4$	4	25	78	70[3]
14	**3g**	$BPyBF_4$	4	25	92	

lit.3: Reaction in absolute alcohol, reflux for 4 hours. lit.2: Reaction in DME, reflux for 48 hours, no yield was reported. lit.4: Reaction in acetone, at room temperature overnight.

Table 2 Yields of **3a,** using recycled ionic liquid $BPyBF_4$ as solvent

Entry	RTIL(times of runing)	Yield (%)
1	Fresh	86
2	Recycled (1)	89
3	(2)	87
4	(3)	86
5	(4)	86
6	(5)	86
7	(6)	85

The RTILs could be recovered easily by vacuum drying, and the recovered RTILs

could be reused at least six times without decrease in yield (**Table 2**).

Experimental

Melting points were detected on a microscope melting point detector and the thermometer was uncorrected, ^{1}H NMR spectroscopy were obtained on a Bruker Avance 500(DMSO-d_6, TMS as internal standard), IR spectra were recorded (KBr pellets) on a Bruker Equinox 55 spectrometer, MS were recorded on a Varian MS spectrometer. The purity of products was analyzed by HPLC.

Typical Procedure was as follows: α-Bromo-4-chloroacetophenone (**1a**, 1.17 g, 5 mmol), 2-aminopyrimidine (**2**, 0.47 g, 5 mmol), sodium bicarbonate (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 proceeded for 3 hrs 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 (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 ionic liquid was evaporated to remove the water under reduced pressure for recycling. A pure sample was obtained by recrystallization from DMF or alcohol or by preparative TLC (silica gel 254, eluted with ethyl acetate) to give **3a** (0.99 g, 86% yield, mp 273~275, 274 in literature[8]). The spectroscopic data were consistent with literature. IR (KBr, cm^{-1}) 1610, 1499, 1090, 791; MS (*m/z*, %) 231(35), 229(100), 194(13), 167(19), 140(12), 114(7), 89(5); ^{1}H NMR (500MHz, δ ppm) 7.06(s, 1H, H-6), 7.52(d, 2H, *J*=7.0 Hz, H-3′,5′), 8.01 (d, 2H, H-2′,6′), 8.39(s, 1H, H-3), 8.54 (s, 1H, H-7) , 8.95(d, 1H, H-5).

In summary, RTILs can be an alternative solvents to prepare 2-aryl-imidazo[1, 2-a]pyrimidines with Tschotschibabin reaction in mild conditions with shorter reaction time and higher yield. Further studies on Tschotschibabin reaction in ionic liquids are under way in our lab.

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Received 14 October, 2002