SHORT PAPER

J. Chem. Research (S),
2003, 614–615

Organic reactions in ionic liquids: cyclocondensation of α-bromoketones with 2-aminopyridine†

Yuan-Yuan Xie[b], Zhen-Chu Chen[a,b*] and Qin-Guo Zheng[c]

[a]*Ningbo Institute of Technology, Zhejiang University, Ningbo, 315104, P.R.China*

[b]*Department of Chemistry, Zhejiang University (Xi-Xi campus), Hangzhou, 310028, P.R.China*

[c]*Pharmaceutical Sciences Research Institute, Aston University, Aston Triangle, Birmingham B4 7ET, UK*

The room temperature ionic liquid 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$), is used as a 'green' recyclable alternative to classical molecular solvents for the cyclocondensation of α-bromoketones with 2-aminopyridine to form 2-arylimidazo[1,2-a]pyridines with rate accelerations and improved yields.

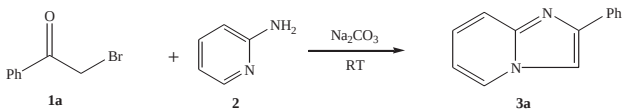
Keywords: ionic liquid, 2-aminopyridine, α-bromoketones, cyclocondensation, 2-arylimidazo[1,2-a]pyridines

Room temperature ionic liquids (RTIL) are a new class of solvents. They are composed entirely of ions and appear to be undemanding to manufacture. These solvents possess a number of interesting properties, especially their lack of vapour pressure, a widely accessible temperature range with lack of flammability and ease of reuse. Compared with classical molecular solvents, room temperature ionic liquids are used as environmentally benign reaction media for synthetic organic chemistry. This use has been the subject of considerable recent attention. To date, some of the more important reactions have been carried out and investigated in ionic liquids.[1]

As part of a programme to investigate the range of organic reactions possible in ionic liquids, we were interested in cyclocondensation of α-bromoketones with 2-aminopyridine to form imidazo[1,2-a]pyridine derivatives.[2] Imidazo[1,2-a]pyridine derivatives have been widely used as long-acting local anesthetics,[3] and antiulcer compounds,[4] for whitening fine fabrics,[5] for anthelmintic or bacteriostatic activities,[6] and as fluorescent materials.[7]

For this study, 1-*n*-butylpyridinium tetrafluoroborate ($BPyBF_4$), 1-*n*-butyl-3-methyl- imidazolium tetrafluoroborate ($BMImBF_4$) and 1-*n*-butyl-3-methylimidazolium hexafluorophosphorate ($BMImPF_6$) were, respectively, synthesised according to the procedures reported in the previous literature.[8] The ionic liquids were dried *in vacuo* at 60°C for 15–20 hours.

First, we examined the efficacy of different ionic liquids in the cyclocondensations of α-bromoacetophenone (**1a**) with 2-aminopyridine (**2**) (Scheme 1). The results summarised in Table 1 show that $BMImBF_4$ gives the best results in terms of yield and reaction times.



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

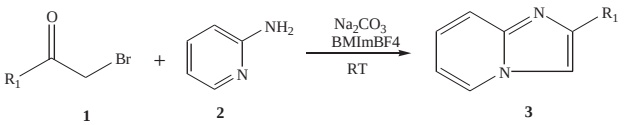
Scheme 1

Then, the scope of the cyclocondensation of various α-bromoketones (**1**) with 2-aminopyridine (**2**) in $BMImBF_4$ was investigated. We found that the cyclocondensation of α-bromoketones (**1**) with 2-aminopyridine (**2**) occurred easily and was complete within 1 hour in $BMImBF_4$ at room temperature in the presence of sodium carbonate to form corresponding imidazo[1,2-a]pyridine derivatives (**3**) in good yields(Scheme 2). The results are summarised in Table 2. The products were characterised by ^1H NMR, IR and m.p., which were consistent with literature data. The reaction was found to be general applicable to aromatic or heteroaromatic ketones. Several acetophenones containing various substituents, such as fluoro, chloro, bromo, methyl, methoxyl and phenyl groups reacted successfully. As usual, we also examined the recovery and reuse of the ionic liquid. We found that the ionic liquid, $BMImBF_4$ can typically be recovered by extracting the product with ether from the reaction mixture and filtering to remove insoluble sodium carbonate and precipitated sodium bromide. The recovered solvent could be reused with no appreciable decrease in yield. The results are summarised in Table 2 (Entries 10–11).

Table 1 Cyclocondensation of α-bromoacetophenone with 2-aminopyridine in different ionic liquids

Entry[a]	Solvent	Reaction temperature/°C	Reaction time/h	Yield[b]/%
1	$BPyBF_4$	25	1	72
2	$BMImBF_4$	25	1	82
3	$BMImPF_6$	25	1	70

[a]All reactions were run with α-bromoacetophenone 1mmol, 2-aminopyridine 1.2mmol and sodium carbonate 0.55mmol in 2ml solvent.
[b]Isolated yield based on α-bromoacetophenone.



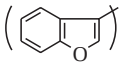
1 **2** **3**

Scheme 2

In ionic liquids, rate enhancement and yield improvement have been reported for many reactions. Also, our experimental results showed that ionic liquids can be compared with classical molecular solvents giving the advantage of rate acceleration and increase of yield. For example, using the classical molecular solvents, such as acetonitrile, the preparation of 2-(4-fluorophenyl)imidazo[1,2-a]pyridine (3b) needs refluxing for 24 hours and the yield was only 37%.[18] But the same reaction was successful in ionic liquid ($BMImBF_4$) at room temperature in only 1 hour and gave a higher yield (76%).

* To receive any correspondence. E-mail: zhenchuc@mail.hz.zj.cn
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 2 Cyclocondensation of α-bromoketones with 2-aminopyridine in $BMImBF_4$

Entry	Product	R_1	Yield[a]/%	M.p.[b]/°C	Lit.M.p./°C
1	**3a**	Ph	82	130–132	135[9]
2	**3b**	*p*-FC_6H_4	76	158–160	165–166[10]
3	**3c**	*p*- ClC_6H_4	70	200–202	205–206[11]
4	**3d**	*p*- BrC_6H_4	73	210–212	215–216[12]
5	**3e**	*p*- $CH_3C_6H_4$	72	140–141	144–145[11]
6	**3f**	*p*-$CH_3OC_6H_4$	71	133–134	137–138[11]
7	**3g**	*p*-$C_6H_5C_6H_4$	67	210–212	215–216[13]
8	**3h**		65	92–94	90–91[11]
9	**3i**		56	220–224	226[14]
10	**3a**[c]	Ph	82	130–132	135[9]
11	**3a**[d]	Ph	80	130–132	135[9]

[a] Isolated yield based on α-bromoketone.
[b] Melting points are uncorrected.
[c] Second run using recycled ionic liquid.
[d] Third run using recycled ionic liquid .

In conclusion, room temperature ionic liquid $BMImBF_4$ is an attractive clean synthetic alternative to classical molecular solvents for cyclocondensation of α-bromoketones with 2-aminopyridine and gives significant rate accelerations and improved yields. Separation of products from the ionic liquids is very straight forward, as is recycling of the ionic liquid.

Experimental

IR spectra were recorded as KBr pellets on a Vector-22 infrared spectrophotometer. ^1H NMR spectra were recorded on a Bruker-400MHz spectrometer using $CDCl_3$ as the solvent with TMS as an internal standard.

Typical procedure for synthesis of 2-arylimidazo[1,2-a]pyridine **(3a):** α-Bromo acetophenone (0.199g, 1 mmol), 2-aminopyridine (0.11g, 1.2 mmol), and sodium carbonate (0.06g, 0.55 mmol) were added to $BMImBF_4$ (2 ml). The resulting mixture was stirred at room temperature for 1 hour. Subsequently, the reaction media was extracted with ethyl ether (6×10 ml). The remaining ionic liquid solution was filtered, and reused. The combined ethereal solution was evaporated under reduced pressure. The crude product was purified by preparative TLC (ethyl acetate/cyclohexane=1:2) to give **3a** (0.16g , 82% yield) as a white solid.

Representative spectroscopic data: 2-Phenylimidazo[1,2-a] pyridine **(3a):** IR (cm^{-1}) 1633 (C=N). ^1H NMR, ppm: δ 6.78 (t, *J* = 6.7Hz, 1H), 7.17 (t, *J* = 7.9Hz, 1H), 7.34 (t, *J* = 7.4Hz, 1H), 7.44 (t, *J* = 7.6Hz, 2H), 7.64 (d, *J* = 9.0Hz, 1H), 7.86 (s, 1H), 7.96 (d, *J* = 8.2Hz, 2H), 8.12 (d, *J* = 6.8Hz, 1H).

2-(2-Benzofuranyl) imidazo[1,2-a]pyridine **(3i):** IR (cm^{-1}) 1639 (C=N). ^1H NMR, ppm: δ 6.80–6.84 (m, 1H), 7.24 (m, 2H), 7.30 (m, 2H), 7.52 (d, *J* = 8.1Hz 1H), 7.64 (m, 2H), 7.98 (s, 1H), 8.14 (d, *J* = 6.8Hz, 1H).

Received 7 October 2002; accepted 7 July 2003
Paper 02/1576

References

1 (a) T. Welton, *Chem. Rew.* 1999, **99**, 2071; (b) P. Wassercheid and W. Keim, *Angew. Chem. Int. Ed. Engl.*, 2000, **39**, 3772; (c) M. Freemantle, *Chem. Eng. News*, 2001, **79(1)**, 21; (d) J. Dupont, R.F. de Souza, P.A.Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667; (e) D.B. Zhao, M. Wu, Y. Kou and E. Min, *Catalysis Today*, 2002, **74**, 157.
2 Y.Y. Xie, Z.C. Chen and Q.G. Zheng *Synthesis*, 2002, **11**,1505. We prepared imidazo[1,2-a]pyridine by reaction of α-tosyloxyketones with 2-aminopyridine
3 B. Dubinsky, D.A. Shriver, P.J. Sanfilippo, J.B. Press, A.J. Tobia and M. E. Rosenthale, *Drug. Dev. Res.*, 1990, **21**, 277.
4 (a) Y. Katsura, S. Nishino, Y. Inoue, M. Tomoi and H. Takasugi, *Chem. Pharm. Bull.*, 1992, **40**, 371; (b) J.E. Starrett, T.A. Montzka, A.R. Crosswell and R.L. Cavanagh, *J. Med. Chem.*, 1989, **32**, 2204.
5 E.C. Louis, *U. S.* 2785133, cf. C.A.: 1957, **51**, P9175a.
6 M.H. Fisher and A. Lusi, *J. Med. Chem.*, 1972, **15**, 982.
7 H. Tomoda, T. Hirano, S. Saito, T. Mutai and K. Araki, *Bull. Chem. Soc. Jap.*, 1999, **72**, 1327.
8 (a) P. BonhÔte, A.P. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Grätzel, *Inorg. Chem.*, 1996, **35**, 1168; (b) P.A.Z. Suarez, J.E.L. Dillius, S. Einloft, R.F. de Souza and J. Dupont, *Polyhedron* 1996, **15**, 1217.
9 *Beilstein* 28 **I**62, **II**239.
10 Ya.G. Balon, M.D. Shulman, V.A. Smirnov, M.M. Yukhnomenko and M.A. Yukhomenko, *Zh. Org. Khim.* 1990, **26**, 1566.
11 A.R. Katritzky, G.Q. Qiu, Q.H. Long, H.Y. He and P.J. Steel, *J. Org. Chem.*, 2000, **65**, 9201.
12 V.A. Artyomov, A.M. Shestopalov and V.P. Litvinov, *Synthesis*, 1996, **8**, 927.
13 Ng. Ph. Buu-Hoï, Ng. Hóan and R. Royer, *Bull. Soc. Chim., Fr.*, 1950, 489-493.
14 R. Royer, E. Bisagni and C. Hudry, *Bull. Soc. Chim. Fr.*, 1961, 933-938.