Organic Reactions in Ionic Liquids: Ionic Liquid-Accelerated Cyclocondensation of α-Tosyloxyketones with 2-Aminopyridine

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Abstract: The room temperature ionic liquid *n*-butylpyridinium tetrafluoroborate ($BPyBF_4$) is used as a 'green' recyclable alternative to classical molecular solvents for the cyclocondensation of α-tosyloxyketones with 2-aminopyridine. Significant rate enhancements and improved yields have been observed.

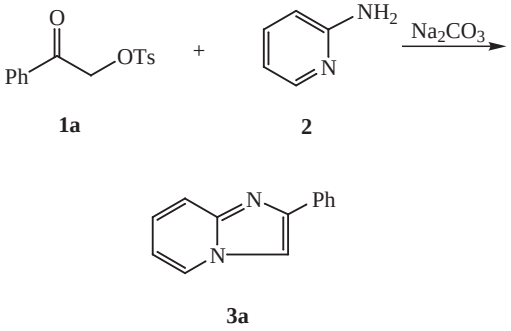
Key words: ionic liquid, 2-aminopyridine, α-tosyloxyketones, cyclocondensation

Room temperature ionic liquids (RTIL) are a new class of solvents. 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. Recently, room temperature ionic liquids are attracting increasing interest as environmentally benign reaction media for synthetic organic chemistry.[1] To date some of the more important reactions which have been carried out and investigated in ionic liquids are, for example, Friedel–Crafts reactions,[2] alkylations,[3] hydrogenations,[4] Diels–Alder reactions,[5] Wittig reactions,[6] Heck reactions,[7] Michael additions,[8] Suzuki reactions,[9] epoxidations,[10] 1,3-dipolar cycloaddition reactions,[11] oxidation of aromatic aldehydes,[12] the Knoevengel, and Robinson annulation reactions,[13] etc.

Our recent interest has been in the area of clean synthesis using α-tosyloxyketones to replace lachrymatory and toxic α-haloketones for the synthesis of five-membered heterocycles.[14] As part of a programme to investigate the range of organic reactions possible in ionic liquids, we were interested in the reaction of α-tosyloxyketones with 2-aminopyridine to form imidazo[1,2-*a*]pyridine derivatives in ionic liquids. Imidazo[1,2-*a*]pyridine derivatives have been widely used as long-acting local anesthetic[15] and antiulcer agents,[16] for whitening fine fabrics,[17] as anthelmintic or bacteriostatic agents,[18] and as fluorescent materials.[19] They are also versatile intermediates for synthetic transformations.[20]

For this study, butylpyridinium tetrafluoroborate ($BPyBF_4$), 1-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$) and 1-butyl-3-methylimidazolium hexafluorophosphorate ($BMImPF_6$) were synthesized according to the procedures reported in the literature.[21]

First, we examined the efficacy of different ionic liquids in the cyclocondensations of α-tosyloxyacetophenone (**1a**) with 2-aminopyridine (**2**) (Scheme 1, Table 1). The results summarized in Table 1 show that $BPyBF_4$ give the best results in terms of yield and reaction times. As can be seen from Table 1, the ionic liquids can truly be compared with classical molecular solvents, with the advantage of rate acceleration and increase of yield. For example, using the classical molecular solvents, such as acetonitrile, the preparation of 2-phenylimidazo[1,2-*a*] pyridine (**3a**) needs refluxing for 6 hours.[22] But, the same reaction was successful in the ionic liquid $BPyBF_4$ at room temperature in only 1 hour and gave a higher yield.



Scheme 1

Table 1 Cyclocondensation of α-Tosyloxyacetophenone (**1a**) with 2-Aminopyridine (**2**) in Different Solvents to form **3a**

Entry[a]	Solvent	Reaction Temp (°C)	Reaction Time (h)	Yield (%)[b]
1	MeCN	80	6	70
2	$BPyBF_4$	25	1	81
3	$BMImBF_4$	25	3	72
4	$BMImPF_6$	25	3	75

[a] All reactions were run with α-tosyloxyacetophenone (**1a**; 1 mmol), 2-aminopyridine (**2**; 1.2 mmol) and Na_2CO_3 (0.55 mmol) in 2 mL of solvent.

[b] Isolated yield based on α-tosyloxyacetophenone (**1a**).

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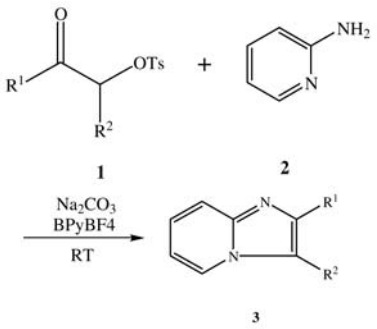
The scope of the cyclocondensation of various α-tosyloxyketones **1** with 2-aminopyridine (**2**) in $BPyBF_4$ was investigated. We found that the cyclocondensation of α-tosyloxyketones **1** with 2-aminopyridine (**2**) occurred easily in $BPyBF_4$ at room temperature in the presence of sodium carbonate to form the corresponding imidazo[1,2-*a*]pyridine derivatives **3** (Scheme 2, Table 2).



Scheme 2

In fact, simple stirring of a mixture of α-tosyloxyketones **1**, 2-aminopyridine (**2**) and sodium carbonate in $BPyBF_4$ at room temperature for about one hour gave, after extraction with diethyl ether, the desired imidazo[1,2-*a*]pyridines **3** in good yields. All reactions exhibited pronounced rate accelerations and good yields were obtained for the isolated products **3**. The results are summarized in Table 2. The products were characterized by ^1H NMR, IR and melting points which were consistent with the literature data.

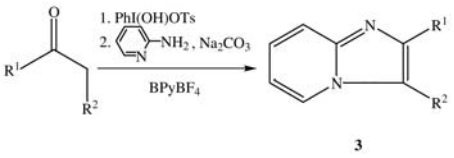
The ionic liquid can be typically recovered by extracting out the product first and filtering the suspension to remove residual sodium carbonate and precipitated sodium tosylate followed by vacuum drying. The recovered solvent can be reused with no appreciable decrease in yield. The results are summarized in Table 3.

Table 3 Results Obtained Using Recycled Ionic Liquid

Entry	Product	Cycle	Yield (%)[a]
1	**3a**	1	81
2	**3a**	2	82
3	**3a**	3	80

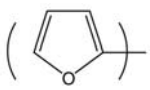
[a] Isolated yield based on α-tosyloxyketones **1**.

As part of a programme to investigate the scope of organic reactions possible in ionic liquids, recently, we found that α-tosyloxylation of ketones can be performed by treatment of ketones with [hydroxy(tosyloxy)iodo]benzene (HTIB) in ionic liquids.[23] Hence, we envisaged that imidazo[1,2-*a*]pyridines **3** could be directly prepared by a one-pot procedure through treatment of ketones with HTIB and 2-aminopyridine (**2**) successively in $BPyBF_4$. Our experiments showed a one-pot procedure for the preparation of imidazo[1,2-*a*]pyridine derivatives **3** by cyclocondensation of ketones with [hydroxy(tosyloxy)iodo]benzene and 2-aminopyridine (**2**) in ionic liquid ($BPyBF_4$) was successful (Scheme 3). The results are summarized in Table 4.



Scheme 3

Table 2 Cyclocondensation of α-Tosyloxyketones **1** with 2-Aminopyridine (**2**) in $BPyBF_4$

Product	R^1	R^2	Yield (%)[a]	Mp (°C)[b]	Lit. mp (°C)
3a	Ph	H	81	130–132	135[24]
3b	4-FC_6H_4	H	90	158–160	165–166[25]
3c	4-ClC_6H_4	H	79	200–202	205–206[26]
3d	4-BrC_6H_4	H	77	210–212	215–216[27]
3e	4-MeC_6H_4	H	72	140–141	144–145[26]
3f	4-$MeOC_6H_4$	H	90	133–134	137–138[26]
3g	Ph	Me	72	153–154	158–160[28]
3h		H	76	92–94	90–91[26]

[a] Isolated yield based on α-tosyloxyketones **1**.
[b] Melting points are uncorrected.

Table 4 One-Pot Synthesis of Imidazo[1,2-*a*]pyridines **3** in $BPyBF_4$

Entry	R^1	R^2	Yield (%)[a]
1	Ph	H	81
2	4-FC_6H_4	H	85
3	4-ClC_6H_4	H	74

[a] Isolated yield based on ketone.

In conclusion, room temperature ionic liquid $BPyBF_4$ is an attractive clean synthetic alternative to classical molecular solvents for cyclocondensation of α-tosyloxyketones **1** with 2-aminopyridine (**2**) and give significant rate accelerations and improved yields of products. Separation of products from the ionic liquids is very straight forward, as is recycling of the ionic liquid.

IR spectra were recorded as KBr pellets on VECTOR-22 IR Spectrophotometer. ^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometer in $CDCl_3$ using TMS as an internal standard.

2-Phenylimidazo[1,2*a*]pyridine (3a); Typical Procedure

α-Tosyloxyacetophenone (**1a**; 0.29 g, 1 mmol), 2-aminopyridine (**2**; 0.11 g, 1.2 mmol), and Na_2CO_3 (0.06 g, 0.55 mmol) were added to $BPyBF_4$ (2 mL). The resulting mixture was stirred at r.t. for 1 h. Subsequently, the reaction mixture was extracted with Et_2O (6 × 10 mL). The remaining ionic liquid suspension was filtered, and reused after drying in vacuum. The combined ethereal solution was evaporated under reduced pressure. The crude product was purified by preparative TLC (EtOAc–cyclohexane, 1:2) to give **3a** (0.156 g, 81%) as a white solid.

IR (KBr): 1633 cm^{-1} (C=N).

^{1}H NMR: δ = 6.76–6.79 (t, *J* = 6.7 Hz, 1 H), 7.15–7.19 (m, 1 H), 7.32–7.35 (t, 1 H), 7.42–7.46 (m, 2 H), 7.63–7.65 (d, *J* = 9.0 Hz, 1 H), 7.86 (s, 1 H), 7.95–7.97 (t, 2 H), 8.11–8.13 (d, *J* = 6.8 Hz, 1 H).

2-Phenylimidazo[1,2-*a*]pyridine (3a); One-Pot Typical Procedure

Acetophenone (0.12 g, 1 mmol) and HTIB (0.392 g, 1 mmol) were added successively with efficient stirring to $BPyBF_4$ (2 mL). The resulting mixture was stirred for 1 h at 90 °C, and then the reaction mixture was cooled to r.t. 2-Aminopyridine (**2**; 0.11 g, 1.2 mmol), and Na_2CO_3 (0.06 g, 0.55 mmol) were added and the mixture was stirred at r.t. for 1 h. Subsequently, the reaction mixture was extracted with Et_2O (6 × 10 mL) and the combined ethereal solution was evaporated under reduced pressure. The crude product was purified by preparative TLC (EtOAc–cyclohexane, 1:2) to give **3a** (0.16 g, 82%) as a white solid.

2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridine (3b)

IR: 1634 cm^{-1} (C=N).

^{1}H NMR: δ = 6.77–6.81 (t, *J* = 6.8 Hz, 1 H), 7.10–7.18 (m, 3 H), 7.62–7.64 (d, *J* = 9.1 Hz, 1 H), 7.81 (s, 1 H), 7.91–7.95 (m, 2 H), 8.11–8.13 (d, *J* = 6.8 Hz, 1 H).

2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridine (3c)

IR: 1634 cm^{-1} (C=N).

^{1}H NMR: δ = 6.77–6.81 (t, *J* = 6.7 Hz, 1 H), 7.17–7.21 (m, 1 H), 7.39–7.42 (m, 2 H), 7.61–7.64 (d, *J* = 9.1 Hz, 1 H), 7.84 (s, 1 H), 7.88–7.90 (m, 2 H), 8.11–8.13 (d, *J* = 6.8 Hz, 1 H).

2-(4-Bromophenyl)imidazo[1,2-*a*]pyridine (3d)

IR: 1634 cm^{-1} (C=N).

^{1}H NMR: δ = 6.78–6.81 (t, *J* = 6.7 Hz, 1 H), 7.17–7.21 (m, 1 H), 7.55–7.57 (m, 2 H), 7.61–7.64 (d, *J* = 9.1 Hz, 1 H), 7.82 (s, 1 H), 7.82–7.85 (m, 2 H), 8.10–8.12 (d, *J* = 6.8 Hz, 1 H).

2-(4-Methylphenyl)imidazo[1,2-*a*]pyridine (3e)

IR: 1633 cm^{-1} (C=N).

^{1}H NMR: δ = 2.39 (s, 3 H), 6.76–6.79 (t, *J* = 6.7 Hz, 1 H), 7.15–7.18 (t, *J* = 7.9 Hz, 1 H), 7.24–7.26 (d, *J* = 8.2 Hz, 2 H), 7.63–7.65 (d, *J* = 9.0 Hz, 1 H), 7.83 (s, 1 H), 7.85–7.87 (d, *J* = 8.1 Hz, 2 H), 8.10–8.12 (d, *J* = 6.7 Hz, 1 H).

2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridine (3f)

IR: 1634 cm^{-1} (C=N).

^{1}H NMR: δ = 3.86 (s, 3 H), 6.74–6.78 (t, *J* = 6.8 Hz, 1 H), 6.97–6.99 (d, *J* = 6.8 Hz, 2 H), 7.13–7.17 (t, *J* = 7.9 Hz, 1 H), 7.60–7.62 (d, *J* = 9.1 Hz, 1 H), 7.78 (s, 1 H), 7.89–7.90 (d, *J* = 6.8 Hz, 2 H), 8.10–8.11 (d, *J* = 6.8 Hz, 1 H).

3-Methyl-2-phenylimidazo[1,2-*a*]pyridine (3g)

IR: 1634 cm^{-1} (C=N).

^{1}H NMR: δ = 2.65 (s, 3 H), 6.84–6.88 (t, *J* = 6.8 Hz, 1 H), 7.16–7.20 (t, *J* = 7.9 Hz, 1 H), 7.34–7.37 (m, 1 H), 7.45–7.49 (m, 2 H), 6.64–6.67 (d, *J* = 9.1 Hz, 1 H), 7.80–7.82 (m, 2 H), 7.90–7.92 (d, *J* = 6.8 Hz, 1 H).

2-(2-Furyl)imidazo[1,2-*a*]pyridine (3h)

IR: 1636 cm^{-1} (C=N).

^{1}H NMR: δ = 6.51–6.52 (m, 1 H), 6.78–6.81 (t, *J* = 6.8 Hz, 1 H), 6.91 (d, *J* = 3.2 Hz, 1 H), 7.17–7.21 (t, *J* = 7.8 Hz, 1 H), 7.47–7.48 (t, *J* = 0.8 Hz, 1 H), 7.60–7.63 (d, *J* = 9.1 Hz, 1 H), 7.80 (s, 1 H), 8.10–8.12 (d, *J* = 6.8 Hz, 1 H).

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