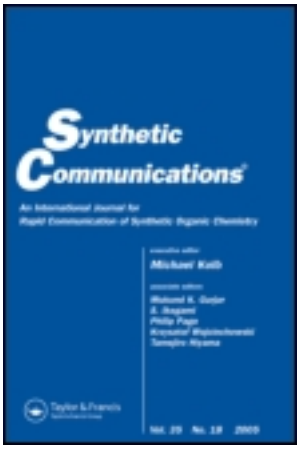

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Organic Reactions in Ionic Liquids: Ionic Liquid-Accelerated One-Pot Synthesis of 2-Arylimidazo[1,2-a]pyrimidines

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Organic Reactions in Ionic Liquids: Ionic Liquid-Accelerated One-Pot Synthesis of 2-Arylimidazo[1,2-a]pyrimidines

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Abstract: The room-temperature ionic liquid n-butylpyridinium tetrafluoroborate ($BPyBF_4$) is used as a recyclable alternative to classical molecular solvents in the one-pot synthesis of 2-arylimidazo[1,2-a]pyrimidines by reaction with ketones, [hydroxy(tosyloxy)iodo]benzene, and 2-aminopyrimidine. Significant rate enhancements and improved yields have been observed.

Keywords: 2-Aminopyrimidine, 2-arylimidazo[1,2-a]pyrimidine, ionic liquid, one-pot synthesis

Imidazo[1,2-a]pyrimidine derivatives constitute an important class of organic compounds that have been widely used as azo dyes,[1] fabric whiteners,[2] and antimicrobial agents.[3] In addition they possess an antagonistic activity against that of purines.[4] Despite their wide applicability, feasible routes for their synthesis are limited. Typically, they are synthesized by the cyclocondensation of 2-aminopyrimidine with the suitable α-bromoacetophenones in solvents such as DME,[5] ethanol,[6] acetone,[7] and DMF.[8] Unfortunately, a long reaction time is necessary and the yield is poor. In addition, α-bromoacetophenones are lachrymatory, toxic, and not readily available. Therefore, the development of a mild, efficient, environmentally friendly method to

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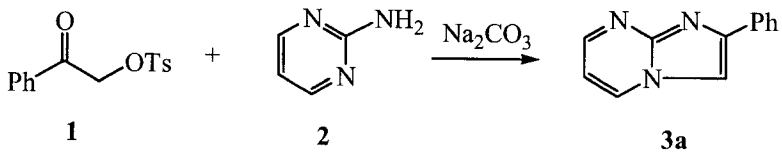


Scheme 1.

prepare 2-arylimidazo[1,2-a]pyrimidines is still presently significant in organic synthesis.

In recent years, the use of room-temperature ionic liquids has attracted increasing interest as a recyclable alternative to classical molecular solvents in synthetic organic chemistry. Many reports have been published showing improved reaction yields and rates.[9] Our recent interest has been in the development of new synthetic methods using ionic liquids as reaction media and promoters.[10] As part of a program to investigate the range of possible organic reactions in ionic liquids, we studied the one-pot reaction of ketones, [hydroxy(tosyloxy)iodo]benzene (HTIB), and 2-aminopyrimidine to form imidazo[1,2-a]pyrimidine derivatives.

In this study, n-butylpyridinium tetrafluoroborate ($BPyBF_4$), 1-butyl-3-methyl-imidazolium tetrafluoroborate ($BMImBF_4$), and 1 -butyl-3-methylimidazolium hexafluorophosphate ($BMImPF_6$) were synthesized according to the procedures reported in the literature.[11]

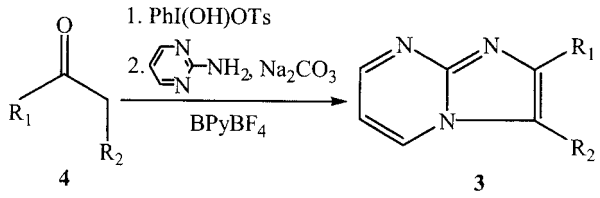
At first, we examined the efficacy of different ionic liquids in the cyclocondensation of α-tosyloxyacetophenone (**1**) with 2-aminopyrimidine (**2**) (Scheme 1). The results summarized in Table l showed that $BPyBF_4$ gave the best results in terms of yield and reaction time. As shown in Table 1, the ionic liquids, compared with classical molecular solvents, had the advantage of rate acceleration and increased yields. For example, the preparation of 2-phenylimidazo[1,2-a]pyrimidine (**3a**) needed refluxing for 6 h in the classical molecular solvents, such as ethanol; however, in ionic liquid

Table 1. Effect of solvent on the cyclocondensation of α-tosyloxyacetophenone with 2-aminopyrimidine

Entry[a]	Solvent	Reaction temperature (°C)	Reaction time (h)	Yield[b] (%)
1	Ethanol	80	6	70
2	$BPyBF_4$	25	1	82
3	$BMImBF_4$	25	1	72
4	$BMImPF_6$	25	1	71

[a]All reactions were run with α-tosyloxyacetophenone, 1 mmol; 2-aminopyrimidine, 1.2 mmol; and sodium carbonate, 0.55 mmol in 2 mL of solvent.

[b]Isolated yield based on α-tosyloxyacetophenone.



Scheme 2.

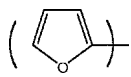
($BPyBF_4$), the reaction took place at room temperature for 1 h and gave a higher yield.

Previously, we had found that α-tosyloxylation of ketones can be perfomed by treatment of ketones with HTIB in ionic liquids.[10b] As a consequence of this finding, we reasoned that imidazo[1,2-a]pyrimidines could be directly prepared by a one-pot procedure through the treatment of ketones with HTIB and 2-aminopyrimidine successively in $BPyBF_4$. Our experiments showed this one-pot procedure for the preparation of imidazo[1,2-a]pyrimidine derivatives was indeed successful (Scheme 2). The results are summarized in Table 2.

In fact, all reactions exhibited pronounced rate acceleration, and good yields were also obtained for isolated products (**3**). All the products were characterized by ^{1}H-NMR, IR, and mp, which were consistent with literature data.

The ionic liquid could be typically recovered by first extracting out the product with an organic solvent; followed by filtering the ionic liquid, which contained residual insoluble sodium carbonate and sodium tosylate; then drying in vacuum. The recovered solvent could be reused several times

Table 2. One-pot synthesis of imidazo[1,2-a]pyrimidines (**3**) through the cyclocondensation of ketones with HTIB and 2-aminopyrimidine in $BPyBF_4$

Product	R_1	R_2	Yield[a] (%)	Mp[b] (°C)	Lit. mp (°C)
3a	Ph	H	80	190–192	195[5]
3b	*p*-FC_6H_4	H	85	236–238	239[5]
3c	*p*-ClC_6H_4	H	83	266–268	270[5]
3d	*p*-BrC_6H_4	H	81	218–221	224[5]
3e	*p*-$CH_3C_6H_4$	H	75	236–238	242[6]
3f	*p*-$CH_3OC_6H_4$	H	72	188–190	190[4]
3g	Ph	Me	76	206–208	211[12]
3h		H	73	208–210	212–214[13]

[a]Isolated yield based on ketone.
[b]Melting points were uncorrected.

Table 3. Results obtained using recycled ionic liquid

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

[a]Isolated yield based on acetophenone.

without appreciable decrease in yield. The representative results are summarized in Table 3.

In conclusion, we have provided a convenient synthetic method for imidazo[1,2-a]pyrimidine derivatives by the cyclocondensation of ketones with HTIB and 2-aminopyrimidine in room-temperature ionic liquid, $BPyBF_4$, by a one-pot procedure. In comparison with reported methods in the literature, the present method has some advantages, such as more environmental friendliness, enhanced reaction rates, mild reaction conditions, simple manipulation, ready isolation of the product, and higher yields. Moreover, the ionic liquid can be recycled without decrease of yield.

EXPERIMENTAL

IR spectra were recorded as KBr pellets on a Vector-22 spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker 400-MHz spectrometer using $CDC1_3$ as the solvent with TMS as an internal standard.

Procedure for synthesis of 2-phenylimidazo[1,2-a]pyrimidine (3a): α-Tosyloxy acetophenone (0.29 g, 1 mmol), 2-aminopyrimidine (0.11 g, 1.2 mmol) and sodium carbonate (0.06 g, 0.55 mmol) were added to $BPyBF_4$ (2 mL). The resulting mixture was stirred at room temperature for 1 h. Subsequently, the reaction media was extracted with ethyl acetate (6 × 10 mL). The remaining ionic liquid solution was filtered and reused. The combined ethyl acetate solution was evaporated under reduced pressure. The crude product was purified by preparative TLC (ethyl acetate) to give **3a** (0.16 g, 82% yield) as a white solid.

Typical one-pot procedure for synthesis of 2-phenylimidazo[1,2-a]pyrimidine (3a): Acetophenone (0. 12 g, 1 mmol) and HTIB (0.392 g, 1 mmol) were added successively to $BPyBF_4$ (2 mL) with efficient stirring. The resulting mixture was stirred for 1 h at 90°C and then cooled to room temperature. After that, 2-aminopyrimidine (0.11 g, 1.2 mmol) and sodium carbonate (0.06 g, 0.55 mmol) were added, and the mixture was stirred at room temperature for 1 h. Subsequently, the reaction media was extracted with ethyl acetate

(6 × 10 mL). The combined ethyl acetate solution was evaporated under reduced pressure. The crude product was purified by preparative TLC (ethyl acetate) to give **3a** (0.155 g, 80% yield) as a white solid.

SPECTROSCOPIC DATA

2-Phenylimidazo[1,2-a]pyrimidine (3a): This compound was obtained as a white solid. IR (cm^{-1}) 1634 (C═N); ^{1}H-NMR, ppm: δ 6.85–6.88 (m, 1H), 7.34–7.37 (t, $J = 7.4$ Hz, 1H), 7.41–7.45 (t, $J = 7.6$ Hz, 2H), 7.87 (s, 1H), 8.00–8.02 (d, $J = 7.2$ Hz, 2H), 8.49–8.52 (m, 2H).

2-(4-Fluorophenyl)imidazo[1,2-a]pyrimidine (3b): This compound was obtained as a white solid. IR (cm^{-1}) 1615 (C═N); ^{1}H-NMR, ppm: δ 6.86–6.89 (m, 1H), 7.12–7.16 (t, $J = 8.7$ Hz, 2H), 7.78 (s,1H), 7.99–8.03 (m, 2H), 8.42–8.44 (m, 1H), 8.53–8.54 (m, 1H).

2-(4-Chlorophenyl)imidazo[1,2-a]pyrimidine (3c): This compound was obtained as a white solid. IR (cm^{-1}) 1614 (C═N); ^{1}H-NMR, ppm: δ 6.93–6.96 (m, 1H), 7.42–7.44 (d, $J = 8.5$ Hz, 2H), 7.85 (s, 1H), 7.94–7.96 (d, $J = 8.5$ Hz, 2H), 8.47–8.50 (m, 1H), 8.59–8.60 (m, 1H).

2-(4-Bromophenyl)imidazo[1,2-a]pyrimidine (3d): This compound was obtained as a white solid. IR (cm^{-1}) 1613 (C═N); ^{1}H-NMR, ppm: δ 6.87–6.90 (m, 1H), 7.57–7.59 (d, $J = 8.4$ Hz, 2H), 7.82 (s, 1H), 7.90–7.92 (d, $J = 8.5$ Hz, 2H), 8.42–8.44 (m, 1H), 8.55–8.56 (m, 1H).

2-(4-Methylphenyl)imidazo[1,2-a]pyrimidine (3e): This compound was obtained as a white solid. IR (cm^{-1}) 1616 (C═N); ^{1}H-NMR, ppm: δ 2.40 (s, 3H), 6.83–6.86 (m, 1H), 7.25–7.27 (d, $J = 7.7$ Hz, 2H), 7.79 (s, 1H), 7.91–7.93 (d, $J = 8.0$ Hz, 2H), 8.41–8.43 (m, 1H), 8.52–8.53 (m, 1H).

2-(4-Methoxyphenyl)imidazo[1,2-a]pyrimidine (3f): This compound was obtained as a white solid. IR (cm^{-1}) 1618 (C═N); ^{1}H-NMR, ppm: δ 3.86 (s, 3H), 6.82–6.85 (m, 1H), 6.97–7.00 (m, 2H), 7.74(s, 1H), 7.95–7.99 (m, 2H), 8.39–8.42 (m, 1H), 8.50–8.51 (m, 1H).

2-Pheny1-3-Methylimidazo[1,2-a]pyrimidine (3g): This compound was obtained as a yellow solid. IR (cm^{-1}) 1610 (C═N); ^{1}H-NMR, ppm: δ 2.64 (s, 3H), 7.01–7.03 (t, $J = 5.0$ Hz, 1H), 7.41–7.43 (m, 1H), 7.48–7.52 (t, $J = 7.4$ Hz, 2H), 7.87–7.88 (d, $J = 7.2$ Hz, 2H), 8.35–8.36 (d, $J = 6.8$ Hz, 1H), 8.58–8.60 (d, $J = 2.8$ Hz, 1H).

2-(2-Furanyl)imidazo[1,2-a]pyrimidine (3h): This compound was obtained as a yellow solid. IR (cm^{-1}) 1632 (C═N); ^{1}H-NMR, ppm: δ 6.35–6.63

(m, 1H), 6.92–6.95 (m, 1H), 7.06–7.09 (m, 1H), 7.78 (s, 1H), 8.14–8.15 (m, 1H), 8.54–8.56 (m, 1H), 8.95–8.99 (m, 1H).

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