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Synthesis of 2-amino-4-phenyl-6-(phenylsulfanyl)-3, 5-dicyanopyridines by tandem reaction

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Abstract A novel basic ionic liquid, 1-(2-aminoethyl)pyridinium hydroxide, containing both Brønsted base and Lewis base sites has been used as an efficient catalyst for the synthesis of 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5-dicyanopyridines. The condensation and oxidation tandem reaction of aldehydes, malononitrile, and thiols, performed in aqueous ethanol, afforded reasonable to good yields within 30–60 min. After the reaction, the catalyst could be recycled and reused. A possible mechanism to account for the tandem reaction is proposed.

Keywords 2-Amino-4-phenyl-6-(phenylsulfanyl)-3,5-dicyanopyridine · Synthesis · Basic ionic liquid · Catalyst · Tandem reaction

Introduction

The pyridine ring is an important constituent of a wide range of naturally occurring and synthetic bioactive compounds, pharmaceuticals, and functional materials [1]. Among these, substitution of the 6-position of the pyridine ring with thio-containing groups furnishes a class of medicinally significant compounds, for example antiprion agents [2, 3], non-nucleoside agonists of the human adenosineA1 receptor [4], and an inhibitor of HIV-1 integrase [5]. Substituted pyridine derivatives are important heterocyclic compounds, because many have biological activity as potential antimicrobial and anti-inflammatory agents, acetylcholinesterase inhibitors, analgesics, bactericides, and muscle relaxants [6–8].

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Several methods for synthesis of substituted pyridines have been reported in recent years. One convenient method involving three-component coupling of aldehydes, malononitrile, and thiols in the presence of bases and Lewis acids, for example triethylamine [6], 1,8-diazabicyclo[5.4.0]undec-7-ene [7], piperidine and tetrabutylammonium hydroxide [8], $ZnCl_2$ [9], silica nanoparticles [10], $KF–Al_2O_3$ [11], TBAF [12], have led to the direct formation of these compounds.

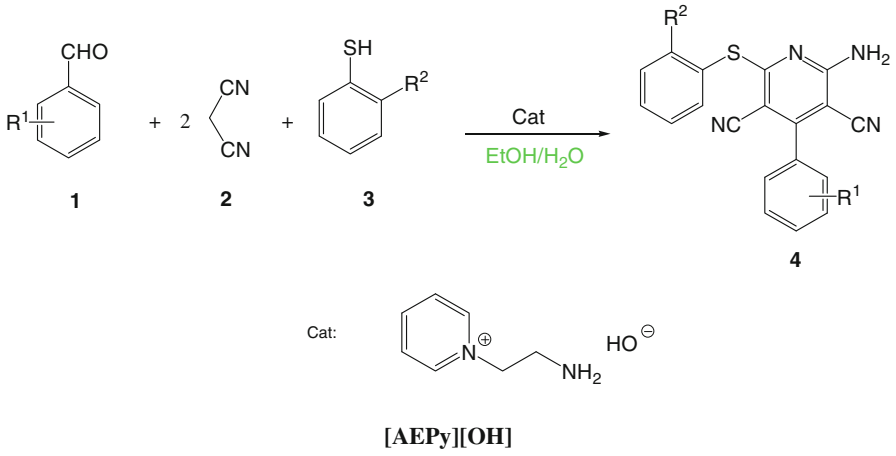
In recent years, functionalized ionic liquids have attracted increasing attention because of their specific properties, for example negligible vapor pressure, wide liquid range, and high thermal stability, etc., making them a more environmentally benign alternative to volatile organic solvents and/or catalysts [13]. Their use as reaction media and/or catalytic systems eliminates both the solvent emission and catalytic recycling problems of traditional chemical procedure. In addition, basic functionalized ionic liquids have been found to have dual function (solvent and catalyst) in multi-component reactions (MCRs) [14], affording higher yields and selectivity than traditional catalysts. In fact, use of basic ionic liquids as catalysts is a topic with ongoing activity, and the development and investigation of such ionic liquids for multi-component reactions is, currently, extremely important. However, very few papers have reported the synthesis of 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5-dicyanopyridines in the presence of ionic liquids. Ranu et al. [15] first used the basic ionic liquid [bmim]OH as novel reaction medium to produce highly substituted pyridines. Very recently, Tian and Guo reported synthesis of 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5-dicyanopyridines by using the imidazolium-based ionic liquid $[bmim]BF_4$ as reaction medium [16]. In fact, searching for new, readily available, and environmentally benign catalysts for these compounds is still being actively pursued.

In our previous work, novel, efficient, recyclable, and eco-friendly SO_3H-functional acidic ionic liquids were designed and prepared successfully. Their catalytic performance in MCRs was also investigated [17, 18]. In continuation of our work on the study of ionic liquid-catalyzed MCRs, we synthesized some 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5- dicyanopyridines in the presence of an novel basic ionic liquid, 1-(2-aminoethyl)pyridinium hydroxide ([AEPy][OH]) in aqueous ethanol. Thio-groups were introduced to the 6-position of the pyridines ring by three-component tandem reaction of aldehydes, malononitrile, and thiols (Scheme 1).

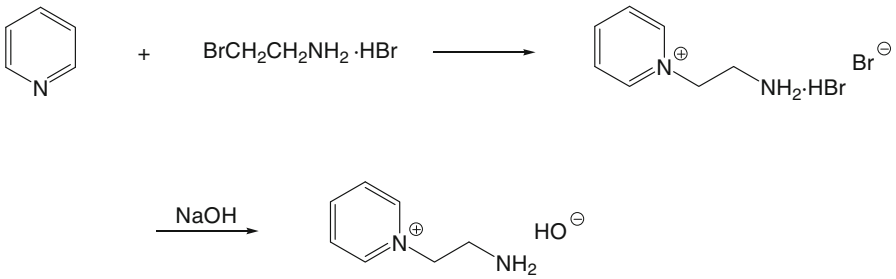
Results and discussion

The synthetic approach used a basic ionic liquid, 1-(2-aminoethyl)pyridinium hydroxide ([AEPy][OH]), which contains a Brønsted base as the cation and a Lewis base as the anion, in the two-step reaction (Scheme 2). The catalyst is a light yellow oil which dissolves in such polar solvents as water, CH_3OH, C_2H_5OH, CH_3CN, and acetone, and partly dissolves in non-polar solvents, for example CH_2Cl_2, ether, and benzene.

In initial experiments on catalytic activity, benzaldehyde, malononitrile, and thiophenol were used as model reactants in 1:1 (*v*/*v*) $EtOH–H_2O$ at room temperature for different lengths of time to investigate catalytic performance (Table 1).



Scheme 1 Synthesis of 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5-dicyanopyridine



Scheme 2 Preparation of 1-(2-aminoethyl)pyridinium hydroxide [AEPy][OH]

It was shown that almost no desired product could be detected when a mixture of benzaldehyde, malononitrile, and thiophenol was stirred at room temperature for 180 min in the absence of basic ionic liquids (entry 1), which indicated that the catalysts were absolutely necessary for this one-pot three-component tandem reaction. Among these catalysts, [AEPy][OH] was the best for this tandem reaction under these conditions; the optimized reaction conditions are listed in Table 1 (entry 5).

Subsequently, the reusability of [AEPy][OH] and two other basic ionic liquids in the same model condensation reaction was investigated for economic and environmental reasons (Fig. 1). On completion of the reaction the product was separated by filtration and the filtrate containing the catalyst was reused in the next run without further purification. The results showed the three basic ionic liquids could be reused six times with little decrease of the yields.

To optimize the reaction conditions, different polar solvents were then selected as reaction medium. The results are summarized in Table 2. Among the six reaction media, this type of reaction was accomplished successfully in polar solvents, for example CH_3CN, EtOH, and 1:1 (*v*/*v*) EtOH–H_2O. The chemical industry is under considerable pressure to replace many of the volatile organic compounds (VOCs)

Table 1 Effect of different catalysts on the synthesis of α-aminophosphonates

Entry	Catalyst	Molar ratio (mol %)	Time (min)	Yield (%)
1	–	–	180	–
2	[AEPy][OH]	3	30	35
3	[AEPy][OH]	5	30	62
4	[AEPy][OH]	8	30	71
5	[AEPy][OH]	10	30	85
6	[AEPy][OH]	12	30	85
7	[AEPy][OH]	15	30	86
8	[BPy][OH]	10	30	45
9	[BMIM][OH]	10	30	56
10	[TMA][OH]	10	30	35
11	[TBA][OH]	10	30	32

Reaction conditions: benzaldehyde (10 mmol), malononitrile (20 mmol), thiophenol (10 mmol), 10 mL EtOH–H_2O, r.t.

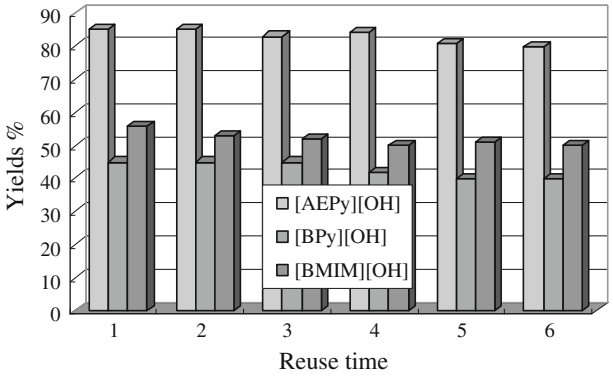


Fig. 1 The reusability of three basic ionic liquids

that are currently used as solvents in organic synthesis. To overcome these problems, one approach is to use the water as environmentally benign medium. Considering the reaction rate and yield, a 1:1 mixture of EtOH and H_2O was confirmed to be the optimum medium.

This condensation reaction with different aldehydes, malononitrile, and thiols in the presence of [AEPy][OH] as catalyst was then investigated under the optimized reaction conditions described above; the results are presented in Table 3. It is readily apparent that this one-pot, three-component condensation was complete within 30–60 min and the products were isolated, by filtration, in reasonable to good yields ranging from 76–89 %. Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents afforded good yields of 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5-dicyanopyridine. For thiols it was noteworthy that compounds with substituents in both the 2-position (entries 10–14) and the 4-position (entry 15, 16) reacted smoothly in this tandem procedure.

Table 2 [AEPy][OH]-catalyzed model reaction in different solvents

Entry	Solvent	Time (min)	Isolated yield (%)
1	H_2O	30	65
2	DMF	30	56
3	EtOH	30	85
4	CH_3CN	30	86
5	CH_2Cl_2	30	26
6	EtOH–H_2O	30	85

Reaction conditions: benzaldehyde (10 mmol), malononitrile (20 mmol), thiophenol (10 mmol), 10 mL solvents, r.t.

Table 3 [BDMAP][OH]-catalyzed three-component reaction

Entry	R_1	R_2	Time (min)	Isolated yields (%)	mp (°C) [Ref.][a]
1	4-CH_3O	H	30	85	238–240 [7]
2	4-CH_3	H	30	86	206–208 [11]
3	4-OH	H	30	84	310–312 [7]
4	H	H	30	85	216–218 [8]
5	4-F	H	30	83	250–252 [8]
6	4-Cl	H	30	85	220–222 [8]
7	3-Br	H	30	81	253–255 [6]
8	3-OCH_3-4-OH	H	30	89	216–218 [11]
9	4-NO_2	H	60	80	286–288 [11]
10	4-CH_3O	2-NH_2	30	80	229–231 [8]
11	4-CH_3	2-NH_2	30	81	206–208 [8]
12	4-OH	2-NH_2	45	76	176–178 [8]
13	H	2-NH_2	30	85	216–218 [6]
14	4-Cl	2-NH_2	45	89	231–233 [8]
15	H	4-CH_3	30	86	234–236 [7]
16	4-Cl	4-CH_3	30	88	242–244 [7]

Reaction conditions: benzaldehyde (10 mmol), malononitrile (20 mmol), thiophenol (10 mmol), solvent 10 mL EtOH–H_2O, r.t.

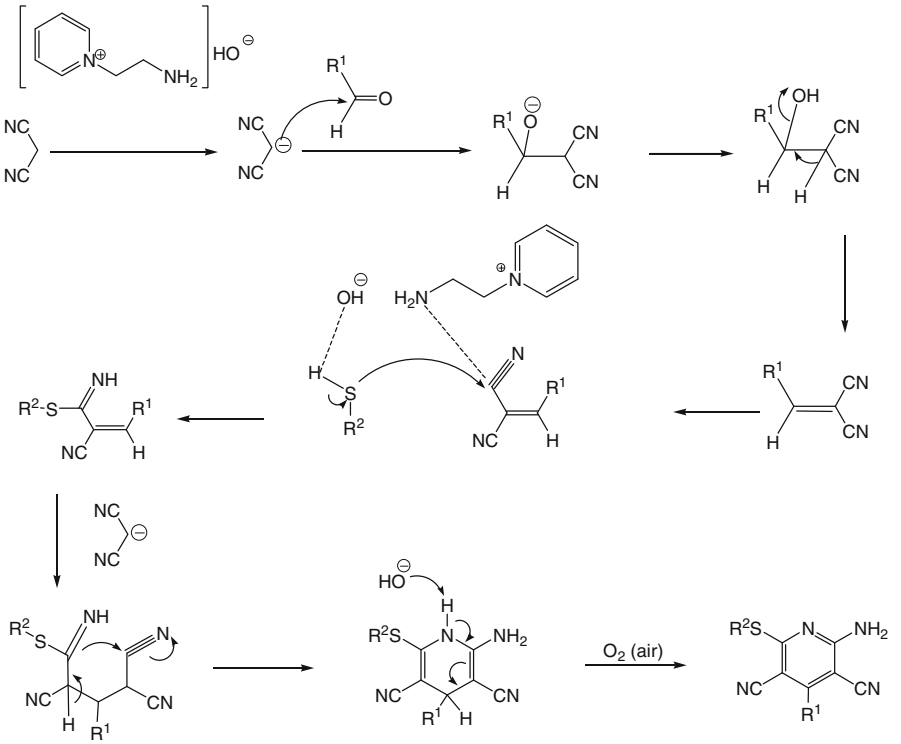
[a] The products were identified by ^{1}H NMR, and by comparison of physical data (m.p) with those reported in the literature

The results obtained with benzaldehyde, malononitrile, and thiophenol under the optimized conditions were compared with literature results reported for use of other catalysts in this reaction. Table 4 shows that the novel basic ionic liquid [AEPy][OH] was a relatively a good catalyst for synthesis of 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5-dicyanopyridine.

Last, with the above experimental results to hand, a plausible mechanism of this tandem reaction is proposed in Scheme 3. This is different from those proposed elsewhere. It is suggested that both reactants and intermediates are activated by the cation and anion of [AEPy][OH].

Table 4 Comparison of our results with those from previously reported methods

Entry	Catalyst	Reaction conditions	Time	Yield (%) [Ref.]
1	DBU	10 % H_2O in EtOH/35 °C	15 min	80 [7]
2	Piperidine	EtOH/reflux	3 h	88 [8]
3	$ZnCl_2$	EtOH/reflux or EtOH/MW	2 h or 2 min	65 [9]
4	$KF.Al_2O_3$	EtOH/r.t.	30 min	87 [11]
5	[bmim]OH	EtOH/r.t.	1.1 h	92 [15]
6	[bmim]BF_4	50 °C	30 min	82 [16]
7	[AEPy][OH]	1:1 (*v*/*v*) EtOH–H_2O/r.t.	30 min	85 [This work]



Scheme 3 Possible mechanism of the tandem reaction

Conclusions

In summary, a readily available, bi-functional alkaline ionic liquid [AEPy][OH] containing Brønsted and Lewis base sites has been used as a novel catalyst for the tandem synthesis of 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5-dicyanopyridine; thio-groups were, therefore, introduced into the pyridine ring. The merit of this anion–cation cooperative catalytic methodology is that it is simple, highly efficient, and environmentally benign.

Experimental

Melting points were determined by use of an X_6-Data microscope apparatus. IR spectra were acquired on a Bruker Vector 22 spectrometer and are expressed in cm^{-1} (KBr). ^1H NMR spectra were acquired on a Bruker DRX300 (300 MHz) spectrometer. ^{13}C NMR spectra were acquired on a Bruker DRX300 (75.5 MHz) spectrometer. Elemental analysis was performed with a Perkin–Elmer C elemental analyzer. Mass spectra were acquired with an automated Finnigan TSQ Quantum Ultra AM (Thermal) LC–MS spectrometer. All chemicals (AR grade) were commercially available and used without further purification.

Synthesis of 1-(2-aminoethylhydrobromide)pyridinium bromide

To a solution of 7.91 g pyridine (0.10 mol) in 30 mL acetonitrile was added 20.49 g 2-bromoethylamine hydrobromide (0.10 mol). The mixture was stirred under nitrogen for 2 h at 80–85 °C. On completion, the solvent was removed by distillation and the residue was washed with ethanol (10 mL × 3) to furnish 90 % yield of a white solid product, mp 170–172 °C.

Synthesis of 1-(2-aminoethyl)pyridinium hydroxide [AEPy][OH]

To a solution of 14.2 g of the above intermediate (0.05 mol) in 50 mL ethanol was added 4 g NaOH (0.10 mol). The mixture was then stirred for 6 h at room temperature. Solvents were then removed by evaporation in vacuo and the residue was extracted with dry ethanol. The salts thus separated were filtered and the solvents were removed by evaporation. The yellow oil obtained was washed successively with chloroform and ether. After drying for 2 h in vacuo at 80 °C, 96 % yield of [AEPy][OH] was obtained. Selected spectral data for the pyridinium-based basic ionic liquid [AEPy][OH] are:

^1H NMR (300 MHz, D_2O): $\delta = 3.25$ (t, 2H, $J = 6.3$ Hz, N–C–CH_2–NH_2), 4.49 (t, 2H, $J = 6.3$ Hz, N–CH_2–C–NH_2), 7.38 (m, 2H, Py–H), 7.75 (m, 1H, Py–H), 8.65 (d, 2H, $J = 7.5$ Hz, Py–H) ppm; MS: $m/z = 140.19$ (M^+).

General procedure for synthesis of 2-amino-4-phenyl-6-(phenylsulfanyl)-3, 5-dicyanopyridines

In a typical experiment, aldehyde (10 mmol) and malononitrile (20 mmol) in 10 mL 1:1 (*v*/*v*) EtOH–H_2O were added, with stirring, to [AEPy][OH] (1.0 mmol) in a round-bottomed flask. The mixture was stirred at room temperature for 1 min and then the thiol (10 mmol) was added. The mixture was stirred continuously. On completion, monitored by TLC, the solid was separated by filtration and dried under vacuum. The product was identified by ^1H NMR, and physical data (m.p.) compared with those in the literature. The catalyst [AEPy][OH] contained in the filtrate could be used for subsequent cycles without any treatment. All products were characterized by IR, ^1H NMR, and m.p., by comparison with literature data (Table 4).

Selected data for compounds **4**

2-Amino-4-(4-chlorophenyl)-6-(phenylsulfanyl)pyridine-3,5-dicarbonitrile (entry 6, $C_{19}H_{11}N_4SCl$)

Yellow solid; m.p. 220–222 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.87 (brs, 2H, NH), 7.69–7.49 (m, 9H, Ar–H).

2-Amino-4-phenyl-6-(2-aminophenyl)sulfanylpyridine-3,5-dicarbonitrile (entry 13, $C_{19}H_{13}N_5S$)

Yellow solid; m.p. 216–218 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.62 (brs, 2H, NH), 7.55–6.60 (m, 9H, Ar–H), 5.35 (brs, 2H, NH).

2-Amino-4-phenyl-6-(4-tolyl)sulfanylpyridine-3,5-dicarbonitrile (entry 15, $C_{19}H_{11}N_4SCl$)

Yellow solid; m.p. 234–236 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.80 (brs, 2H, NH), 7.56–7.54 (m, 5H, Ar–H), 7.47 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.30 (d, $J = 7.8$ Hz, 2H, Ar–H), 2.37 (s, 3H, CH_3).

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