Journal of Saudi Chemical Society (2016) **20**, 517–522

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

[Bmim]BF_4 ionic liquid: An efficient reaction medium for the one-pot multi-component synthesis of 2-amino-4, 6-diphenylpyridine-3-carbonitrile derivatives

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Received 6 April 2012; accepted 22 July 2012
Available online 7 September 2012

KEYWORDS

Pyridine derivatives;
One-pot synthesis;
[Bmim][BF_4];
Ionic liquid

Abstract One-pot condensation from aromatic aldehyde, methyl ketone, malononitrile and ammonium acetate in the presence of the ionic liquid (IL), 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF_4]), affords the corresponding 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives. This method has the advantage of short routine, high yields and being environmentally-friendly. Here, the need for catalyst is avoided through the use of catalytically active ionic liquid as solvent. Furthermore, the possible mechanism is also proposed.

1. Introduction

Due to the increase in environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures that avoid the use of harmful organic solvents. One of the most important principles of the green chemistry is the elimination of hazardous solvents in chemical synthesis and avoids using toxic solvents and the generation of wastes. Ionic liquids (ILs) have become popular as novel and promising solvents for the organic synthesis due to their inherent features. Along with their chemical and physical properties which make a careful choice of cation/anion, they have also been used as designer reaction media. ILs are ionic compounds in which, at least the cation is an organic type of cation. ILs contain only ionic species and sometimes are known as molten salt, however while a molten salt is generally thought to refer to a high-melting, highly viscous and very corrosive medium, ionic liquids are already liquid at low temperatures (< 100 °C) and have relatively low viscosity. The apparently somewhat arbitrary line drawn between molten salts and ILs at a melt temperature of 100 °C can be justified by the abrupt improvement in the range of applications for liquid salts below this temperature. Even though some examples are known in which high-temperature salt melts have been successfully used as reaction media for synthetic applications,

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Peer review under responsibility of King Saud University.

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http://dx.doi.org/10.1016/j.jscs.2012.07.011

only a liquid range below 100 °C can enable the versatile substitution of conventional, organic solvents by ionic liquid (Wasserscheid and Keim, 2000).

The main properties of ILs for their applications are the following: to a difference of the classical organic solvents, ILs are known to have a negligible vapor pressure below their decomposition temperature. This is the main reason why ILs are considered as environmental friendly solvents. The thermal stability of ILs is limited by the strength of their hetero-atom–carbon and their hetero atom–hydrogen bonds, respectively. The nature of the ILs, containing organic cations, restricts upper stability temperatures; pyrolysis generally occurs between 350 and 450 °C, if no other lower temperature decomposition pathways are accessible. In most cases, decomposition occurs with complete mass loss and volatilization of the component fragments. Many ILs possess the ability to dissolve a wide range of inorganic and organic compounds. This is important for dissolving disparate combinations of reagents into the same phase. ILs are considered to be polar solvents, but can be non coordinating (mainly depending on the ionic liquid anions). The polarity of many ILs is intermediate between water and chlorinated organic solvents and varies, depending on the nature of the ionic liquid components. Several processes would be impossible with conventional solvents because of their limited liquid range or miscibility. Of even greater potential is the use of ILs for chemical synthesis because the charged nature of these solvents can influence the synthesis itself. ILs often have wide electrochemical potential windows, they have reasonably good electrical conductivity. The electrochemical window of an ionic liquid is influenced by the stability of the cation against electrochemical reduction-processes and the stability of the anion against oxidation-processes. ILs are safe for hanging. The catalytic properties in organic and inorganic syntheses have been widely described (Corma and García, 2003; Olivier-Bourbigou and Magna, 2002).

Functionalized nitrogen-heterocycles play a predominant role in medicinal chemistry. The pyridine nucleus is prevalent in numerous natural products and is extremely important in the chemistry of biological systems. It plays a key role catalyzing both biological and chemical systems. Many pyridine derivatives are of commercial interest and find application in areas where bioactivity is important, as in medicinal drugs (Challa et al., 2014). Some of them have been used as herbicides, fungicides, pesticides, medicines, and dyes (Lohray et al., 2004; Merja et al., 2004; Chaki et al., 1995; Thomae et al., 2007). Several cyanopyridine moiety compounds show interesting pharmacological and chemotherapeutic activities, such as anticancer, antitubercular (Kanjariya et al., 2004), antimicrobial (Popat et al., 2004), etc. Recently, 2-aminopyridine derivatives (Fig. 1) have been identified as novel 1KK-β inhibitors (Murata et al., 2003), A_{2A} adenosine receptor antagonists (Mantri et al., 2008), potent inhibitor of HIV-1 integrase (Deng et al., 2007), and so on. Therefore, the synthesis of 2-amino-3-cyanopyridine derivatives continues to attract much interest in organic chemistry.

Various preparation methods of 2-amino-4,6-diphenylpyridine-3-carbonitrile have been reported. The common method used in the preparation of 2-amino-4,6-diphenylpyridine-3-carbonitrile involves the chalcone or carbonyl compound condensation with malononitrile and ammonium acetate by conventional heating in the presence of ethyl alcohol as a solvent. A series of 2-amino-3-cyanopyridine derivatives have been prepared by one-pot condensation from malononitrile, aromatic aldehyde, methyl ketone and ammonium acetate under microwave irradiation without solvent (Shi et al., 2005). A new series of 2-amino-3-cyano-4-tetrazoloquinolinylpyridine derivatives have been synthesized by the one-pot cyclocondensation reaction of a tetrazolo[1,5-*a*]quinoline-4-carbaldehyde, malononitrile, a heterocyclic/aromatic methyl ketone and ammonium acetate (Mungra et al., 2009). Recently, it has been reported that chalcones on condensation with malononitrile and ammonium acetate in the presence of ionic liquid ethylammonium nitrate affords the corresponding 2-amino-4,6-diphenylpyridine-3-carbonitrile. The ionic liquid is recycled and reused several times (Sarda et al., 2009). A family of 2-amino-3-cyanopyridine derivatives were synthesized using [Yb(PFO)$_3$] (Tang et al., 2011). These reported methods suffered from several drawbacks like prolonged reaction times, low yields, harsh reaction conditions, critical isolation procedures, and expensive catalysts. Consequently, there is room for further innovation toward milder reaction conditions, shorter reaction time and better yield which is achieved using ionic liquid [Bmim][BF$_4$].

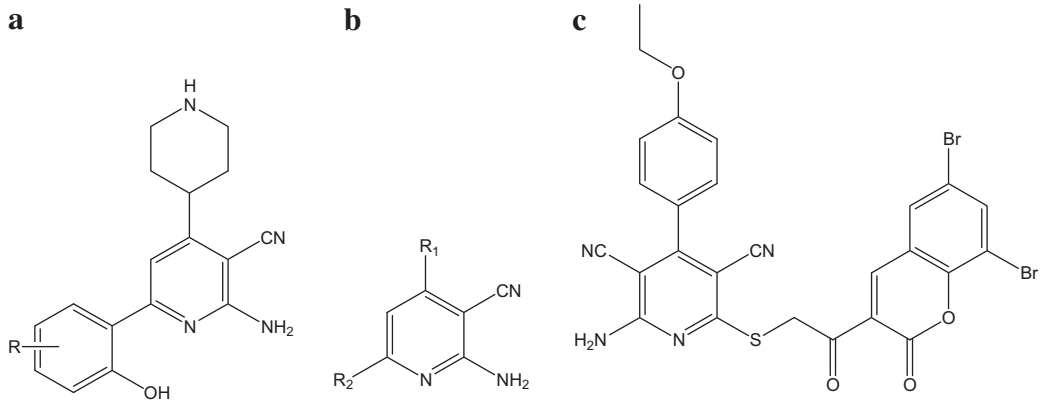


Figure 1 (a) 1KK-β inhibitors (b) A_{2A} adenosine receptor antagonists (c) potent inhibitor of HIV-1 integrase.

2. Experimental section

2.1. Apparatus and analysis

All chemicals were purchased from Aldrich Chemical Co. and solvents were used without further purification. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates. Visualization of the developed chromatogram was performed by UV light (254 nm). Column chromatography was performed on silica gel 90, 200–300 mesh. Melting points were determined with Shimadzu DS-50 thermal analyser. ^{1}H NMR spectra were recorded on Bruker AM 300 (300 MHz) using TMS as the internal standard. FT-IR spectra were obtained as KBr discs on Bruker spectrometer. Mass spectra were determined on a Varion-Saturn 2000 GC/MS instrument. Elemental analyses were measured by means of Perkin Elmer 2400 CHN elemental analyzer flowchart.

3. Chemistry

3.1. General procedure for the synthesis of 2-amino-4-(4-chlorophenyl)-6-phenylpyridine-3-carbonitrile (4a)

The ionic liquid [Bmim][BF_4] (2 mL) was added to a mixture of 4-chlorobenzaldehyde (**1a**, 1 mmol), acetophenone (**2a**, 1 mmol), malononitrile (1 mmol) and ammonium acetate (8 mmol) and the reaction mixture was heated at 60 °C for the appropriate time. After reaction completion (monitored by TLC) the reaction mixture was poured onto 50 mL of ice-cold water. The resulting solid (**4a**) was filtered, washed with cold water, and recrystallized in ethyl alcohol. The aqueous layer was distilled at 80 °C under vacuum to remove water, leaving behind the ionic liquid (about 90%), which was recycled several times. The crude residue was purified by column chromatography using hexane–ethyl acetate (9:1) as eluent to give the corresponding compounds **4a–4l**. The products were characterized by IR, ^{1}H NMR, mass and elemental analyses.

4. Results and discussion

In continuation of our work on the development of simple and environmentally friendly experimental procedures using readily available reagents and catalysts for the synthesis of biologically active molecules, such as 3,4-dihydropyrimidin-2(*1H*)-ones/-thiones/imines (Mansoor et al., 2011), β-amino ketone compounds (Mansoor et al., 2015), amidoalkyl naphthols (Mansoor et al., 2016), we became interested in the possibility of developing a one-pot synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives by the reaction of aromatic aldehyde, methyl ketone, malononitrile and ammonium acetate in the presence of [Bmim][BF_4] (Scheme 1). In this paper, we wish to highlight our finding about the multi-component reaction using [Bmim][BF_4] as a solvent.

Table 1 Synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile (**4a**) in various solvents.[a]

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	C_2H_5OH	Reflux	9	78
2	CH_3OH	Reflux	10	46
3	CH_3CN	Reflux	12	80
4	Toluene	Reflux	8	60
5	CH_2Cl_2	Reflux	14	64
6	DMSO	Reflux	8	74
7	[Bmim][BF_4]	Stirred at R.T	9	72
8	[Bmim][BF_4]	Stirred at 60 °C	4	92,89,90,88[c]
9	[Bmim][BF_4]	Stirred at 80 °C	4	84

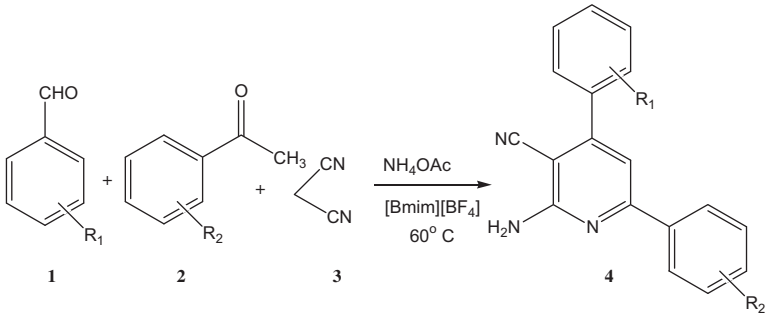
[a] Reaction conditions: benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol) and ammonium acetate (8 mmol).
[b] Isolated yields.
[c] Catalyst was reused four times.

4.1. Effect of the solvent

The reaction was performed in various solvents to identify the best solvent condition. A range of solvents such as ethanol, methanol, acetonitrile, toluene, dichloromethane, DMSO, and [Bmim][BF_4] were examined and [Bmim][BF_4] emerged as the solvent of choice in terms of reaction kinetics and product yields (Table 1). The scope and generality of this reaction is illustrated with respect to various aromatic aldehydes and aromatic ketones (Table 2).

4.2. Synthesis of various 2-amino-4,6-diphenylpyridine-3-carbonitrile compounds

When a mixture of aromatic aldehyde **1**, methyl ketone **2**, malononitrile **3** and ammonium acetate was heated at 60 °C in ionic liquid [Bmim][BF_4] (Scheme 1), the reactions were almost completed in 4–5.5 h. The reaction mixtures were then washed with a small amount of ethanol. The crude products were



Scheme 1 One-pot synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile.

Table 2 Synthesis of various 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives in [Bmim][BF_4], ionic liquid.[a]

Entry	R_1	R_2	Product	Time (h)	Yield (%)[b]	Mp (°C)
1	4-Cl	H	**4a**	4.0	92	208–210
2	4-Br	H	**4b**	4.5	94	176–178
3	4-F	H	**4c**	4.0	85	170–172
4	4-CH_3	H	**4d**	4.5	88	218–220
5	4-OCH_3	H	**4e**	5.0	78	184–186
6	H	4-F	**4f**	4.5	86	156–158
7	H	4-CH_3	**4g**	4.0	83	206–208
8	H	4-OCH_3	**4h**	4.0	85	214–216
9	H	4-Cl	**4i**	4.5	90	188–190
10	4-Cl	4-OCH_3	**4j**	5.0	88	194–196
11	4-OCH_3	4-OCH_3	**4k**	5.5	85	160–162
12	4-Cl	4-F	**4l**	5.0	88	166–168

[a] Reaction conditions: benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol) and ammonium acetate (8 mmol) and the reaction mixture was heated at 60 °C for the appropriate time.
[b] Isolated yields.

purified by recrystallization from 95% ethanol to afford products with good yields (78–94%). The main results for the synthesis of these compounds are given in Table 2. It is seen that this procedure has the advantage of short routine, good yields, convenient workup and being environmentally friendly. The identity of the product was determined by IR, ^{1}H NMR, mass and elemental analyses.

*4.3. Spectral data for the synthesized 2-amino-4,6-diphenylpyridine-3-carbonitrile compounds (**4a–4l**)*

*4.3.1. 2-Amino-4-(4-chlorophenyl)-6-phenylpyridine-3-carbonitrile (**4a**)*

IR (KBr, cm^{-1}): 3442 and 3312 (NH_2), 3177 (ArH), 2211 (CN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.04–8.16 (2H, m, ArH), 7.58 (2H, d, J = 8.0 Hz, ArH), 7.40–7.47 (3H, m, ArH), 7.18 (1H, s, CH), 7.00 (2H, d, J = 8.4 Hz, ArH), 6.88 (2H, s, NH_2). MS(ESI): m/z 306 $(M+H)^+$; Anal. Calcd for $C_{18}H_{12}ClN_3$: C, 70.72; H, 3.93; N, 13.75. Found: C, 70.62; H, 3.88; N, 13.79.

*4.3.2. 2-Amino-4-(4-bromophenyl)-6-phenylpyridine-3-carbonitrile (**4b**)*

IR (KBr, cm^{-1}): 3455 and 3308 (NH_2), 3165 (ArH), 2214 (CN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.02–8.10 (2H, m, ArH), 7.55 (2H, d, J = 7.8 Hz, ArH), 7.48–7.49 (3H, m, ArH), 7.16 (1H, s, CH), 7.21 (2H, d, J = 8.2 Hz, ArH), 6.96 (2H, s, NH_2). MS(ESI): m/z 350 $(M+H)^+$; Anal. Calcd for $C_{18}H_{12}BrN_3$: C, 61.73; H, 3.43; N, 12.00. Found: C, 61.66; H, 3.49; N, 12.12.

*4.3.3. 2-Amino-4-(4-fluorophenyl)-6-phenylpyridine-3-carbonitrile (**4c**)*

IR (KBr, cm^{-1}): 3462 and 3307 (NH_2), 3184 (ArH), 2201 (CN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.11–8.12 (2H, m, ArH), 7.66 (2H, d, J = 7.6 Hz, ArH), 7.48–7.49 (3H, m, ArH), 7.25 (1H, s, CH), 7.11 (2H, d, J = 8.0 Hz, ArH), 6.96 (2H, s, NH_2). MS(ESI): m/z 290 $(M+H)^+$; Anal. Calcd for $C_{18}H_{12}FN_3$: C, 74.74; H, 4.15; N, 14.53. Found: C, 74.68; H, 4.10; N, 14.59.

*4.3.4. 2-Amino-4-(4-methylphenyl)-6-phenylpyridine-3-carbonitrile (**4d**)*

IR (KBr, cm^{-1}): 3477 and 3312 (NH_2), 3180 (ArH), 2208 (CN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.16–8.19 (2H, m, ArH), 7.69 (2H, d, J = 7.4 Hz, ArH), 7.42–7.48 (3H, m, ArH), 7.21 (1H, s, CH), 7.17 (2H, d, J = 8.0 Hz, ArH), 6.90 (2H, s, NH_2), 2.23 (3H, s, CH_3). MS(ESI): m/z 286 $(M+H)^+$; Anal. Calcd for $C_{19}H_{15}N_3$: C, 80.00; H, 5.26; N, 14.74. Found: C, 80.10; H, 5.33; N, 14.70.

*4.3.5. 2-Amino-4-(4-methoxyphenyl)-6-phenylpyridine-3-carbonitrile (**4e**)*

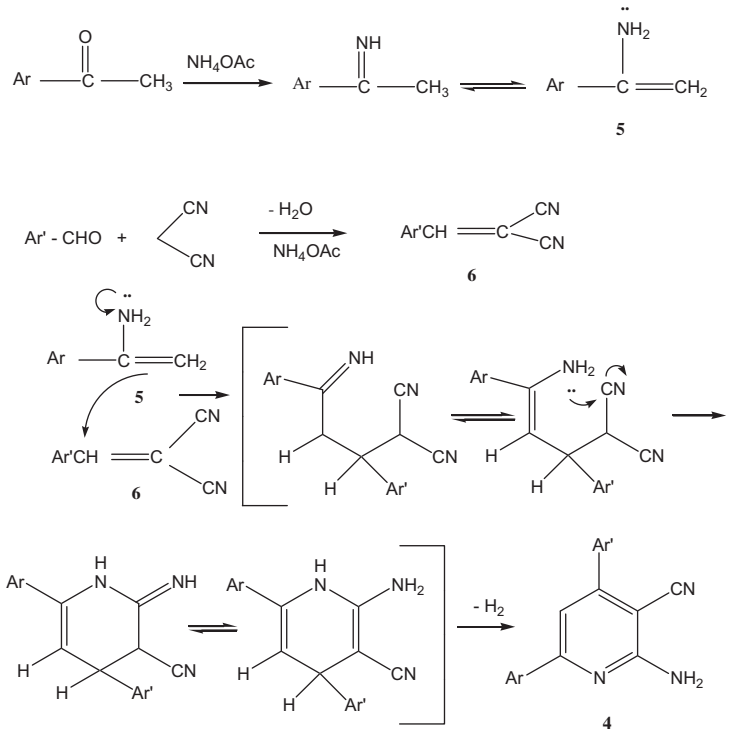
IR (KBr, cm^{-1}): 3469 and 3303 (NH_2), 3180 (ArH), 2201 (CN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.16–8.19 (2H, m, ArH), 7.60 (2H, d, J = 7.9 Hz, ArH), 7.41–7.46 (3H, m, ArH), 7.20 (1H, s, CH), 7.12 (2H, d, J = 8.1 Hz, ArH), 6.93 (2H, s, NH_2), 3.81 (3H, s, OCH_3). MS(ESI): m/z 302 $(M+H)^+$; Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.75; H, 4.98; N, 13.95. Found: C, 75.70; H, 4.93; N, 13.90.

*4.3.6. 2-Amino-4-phenyl-6-(4-fluorophenyl)-pyridine-3-carbonitrile (**4f**)*

IR (KBr, cm^{-1}): 3458 and 3302 (NH_2), 3177 (ArH), 2212 (CN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.04–8.09 (2H, m, ArH), 7.69 (2H, d, J = 8.0 Hz, ArH), 7.46–7.49 (3H, m, ArH), 7.21 (1H, s, CH), 7.17 (2H, d, J = 7.7 Hz, ArH), 6.88 (2H, s, NH_2). MS(ESI): m/z 290 $(M+H)^+$; Anal. Calcd for $C_{18}H_{12}FN_3$: C, 74.74; H, 4.15; N, 14.53. Found: C, 74.70; H, 4.12; N, 14.57.

*4.3.7. 2-Amino-4-phenyl-6-(4-methylphenyl)-pyridine-3-carbonitrile (**4g**)*

IR (KBr, cm^{-1}): 3455 and 3311 (NH_2), 3177 (ArH), 2211 (CN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.11–8.15 (2H, m, ArH), 7.64 (2H, d, J = 7.4 Hz, ArH), 7.48–7.51 (3H, m, ArH), 7.19 (1H, s, CH), 7.11 (2H, d, J = 8.0 Hz, ArH), 6.88 (2H, s, NH_2), 2.22 (3H, s, CH_3). MS(ESI): m/z 286 $(M+H)^+$; Anal. Calcd for $C_{19}H_{15}N_3$: C, 80.00; H, 5.26; N, 14.74. Found: C, 80.08; H, 5.31; N, 14.79.



Scheme 2 Mechanism of the formation of 2-amino-4,6-diphenylpyridine-3-carbonitrile.

*4.3.8. 2-Amino-4-phenyl-6-(4-methoxylphenyl)-pyridine-3-carbonitrile (**4h**)*

IR (KBr, cm^{-1}): 3468 and 3300 (NH_2), 3184 (ArH), 2200 (CN). ^1H NMR (300 MHz, DMSO-d_6): δ 8.00–8.06 (2H, m, ArH), 7.55 (2H, d, J = 8.2 Hz, ArH), 7.38–7.44 (3H, m, ArH), 7.19 (1H, s, CH), 7.14 (2H, d, J = 8.4 Hz, ArH), 6.88 (2H, s, NH_2), 3.81 (3H, s, OCH_3). MS(ESI): m/z 302 $(M+H)^+$; Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.75; H, 4.98; N, 13.95. Found: C, 75.79; H, 4.95; N, 13.93.

*4.3.9. 2-Amino-4-phenyl-6-(4-chlorophenyl)-pyridine-3-carbonitrile (**4i**)*

IR (KBr, cm^{-1}): 3438 and 3309 (NH_2), 3179 (ArH), 2213 (CN). ^1H NMR (300 MHz, DMSO-d_6): δ 8.04–8.16 (2H, m, ArH), 7.58 (2H, d, J = 8.0 Hz, ArH), 7.42–7.49 (3H, m, ArH), 7.19 (1H, s, CH), 7.00 (2H, d, J = 7.6 Hz, ArH), 6.89 (2H, s, NH_2). MS(ESI): m/z 306 $(M+H)^+$; Anal. Calcd for $C_{18}H_{12}ClN_3$: C, 70.72; H, 3.93; N, 13.75. Found: C, 70.66; H, 3.98; N, 13.70.

*4.3.10. 2-Amino-4-(4-chlorophenyl)-6-(4-methoxyphenyl)-pyridine-3-carbonitrile (**4j**)*

IR (KBr, cm^{-1}): 3451 and 3311 (NH_2), 3172 (ArH), 2198 (CN). ^1H NMR (300 MHz, DMSO-d_6): δ 8.08–8.10 (2H, m, ArH), 7.61 (2H, d, J = 8.0 Hz, ArH), 7.44–7.46 (2H, m, ArH), 7.20 (1H, s, CH), 7.11 (2H, d, J = 8.6 Hz, ArH), 6.90 (2H, s, NH_2), 3.79 (3H, s, OCH_3). MS(ESI): m/z 336 $(M+H)^+$; Anal. Calcd for $C_{19}H_{14}ClN_3O$: C, 67.97; H, 4.17; N, 12.52. Found: C, 67.90; H, 4.12; N, 12.58.

*4.3.11. 2-Amino-4-(4-methoxyphenyl)-6-(4-methoxyphenyl)-pyridine-3-carbonitrile (**4k**)*

IR (KBr, cm^{-1}): 3466 and 3355 (NH_2), 3222 (ArH), 2200 (CN). ^1H NMR (300 MHz, DMSO-d_6): δ 8.14 (2H, d, J = 8.4 Hz, ArH), 7.54 (2H, d, J = 8.0 Hz, ArH), 7.16 (1H, s, CH), 7.07 (2H, d, J = 8.4 Hz, ArH), 7.03 (2H, d, J = 8.6 Hz, ArH), 6.87 (2H, s, NH_2), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3). MS(ESI): m/z 332 $(M+H)^+$; Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.51; H, 5.14; N, 12.69. Found: C, 72.55; H, 5.17; N, 12.66.

*4.3.12. 2-Amino-4-(4-chlorophenyl)-6-(4-fluorophenyl)-pyridine-3-carbonitrile (**4l**)*

IR (KBr, cm^{-1}): 3450 and 3300 (NH_2), 3170 (ArH), 2210 (CN). ^1H NMR (300 MHz, DMSO-d_6): δ 8.09–8.18 (2H, m, ArH), 7.66 (2H, d, J = 8.2 Hz, ArH), 7.39–7.45 (2H, m, ArH), 7.22 (1H, s, CH), 7.00 (2H, d, J = 7.6 Hz, ArH), 6.93 (2H, s, NH_2). MS(ESI): m/z 324 $(M+H)^+$; Anal. Calcd for $C_{18}H_{11}ClFN_3$: C, 66.78; H, 3.40; N, 12.99. Found: C, 66.74; H, 3.36; N, 12.92.

The IR spectrum of compound **4a** exhibited absorption at 3442 cm^{-1} (asymmetric N–H stretching) and 3312 cm^{-1} (symmetric N–H stretching) for – NH_2, 2211 cm^{-1} for – CN, 3177 cm^{-1} for ArH. The ^1H NMR spectra of compound **4a** showed the absence of the aldehyde proton, moreover singlets at δ 6.88 ppm and multiplets at δ 7.40–8.16 ppm appeared for amine and aromatic protons, respectively. Mass spectra of compound **4a** gave molecular ion peak at m/z 306 $(M+H)^+$ corresponding to molecular formula $C_{18}H_{12}ClN_3$. The elemental analysis values are in good agreement with the theoretical data. Similarly, all these compounds were characterized on

the basis of spectral studies. The reaction may proceed *via* imine **5** formed from aldehyde and ammonium acetate, imine **5** reacts with arylidenemalononitrile **6** (from condensation of aromatic aldehyde with malononitrile), followed by cycloaddition, isomerization, aromatization to afford the 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives **4** (Scheme 2).

5. Conclusions

In summary, we have developed a straightforward and efficient method for the preparation of 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives by one-pot reaction of aldehydes, ketones, malononitrile and ammonium acetate in the presence of [Bmim][BF_4]. This method tolerates most of the substrates, and the catalyst can be reused at least four times without significant loss of activity.

Acknowledgements

The authors are grateful to C. Abdul Hakeem College Management, Dr. W. Abdul Hameed, Principal and Dr. M. S. Dastageer, Head of the Research Department of Chemistry for the facilities and support from the DST-FIST (Government of India) sponsored Laboratory and also for encouragement during the process of carrying out this work. The authors wish to thank to Dr. A. Abdul Rahuman, Unit of Nanotechnology and Bioactive Natural Products, for useful discussion and encouragement.

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