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Acidic Brønsted ionic liquids catalyzed the preparation of 2-amino-3-cyanopyridine derivatives under ambient and solvent-free conditions

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Abstract

The acidic ionic liquids, 2-pyrrolidonium hydrogensulfate, *N*-methyl-2-pyrrolidonium hydrogensulfate, triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate and (4-sulfobutyl) tris (4-sulfophenyl) phosphonium hydrogensulfate catalyzed one-pot four-component condensation between aromatic aldehydes, substituted acetophenones, malononitrile and ammonium acetate to afford corresponding 2-amino-3-cyanopyridine derivatives. This synthetic method has the remarkable advantages such as mild reaction conditions and good isolated yields, short reaction time, and use of green catalysts.

Keywords: acidic ionic liquids, aromatic aldehydes, acetophenones, malononitrile, ammonium acetate.

1. Introduction

Ionic liquids (ILs), because of their low volatility, non-flammability, capability to dissolve various organic and inorganic compounds, and potentially recyclable properties, have attracted considerable attention as environmentally friendly reaction media in the green organic synthesis [1-4].

The designs of multi-component reactions (MCRs) for the synthesis of diverse groups of compounds, especially the ones that are biologically active, have commanded great attention in green organic synthesis [5-9].

2-amino-3-cyanopyridines are known as IKK-β-inhibitors [10]. They have been identified to possess multiple biological activities such as antifungal [11], antitumor [12], antiviral [13], antibacterial [14], antimicrobial [15], anti-inflammatory [16] as well as antihypertensive [17] properties. Hence, in consequence of the aforementioned biological significances of these versatile structural motifs, a number of procedures have been reported on this topic like microwave or ultrasound irradiation [18-21], Fe_3O4 [22], Cellulose-SO_3H [23], DMF [24], acetic acid[25],Cu/C[26],{Fe_3O_4@SiO_2@(CH_2)3Im}$C(CN)_3$ [27],

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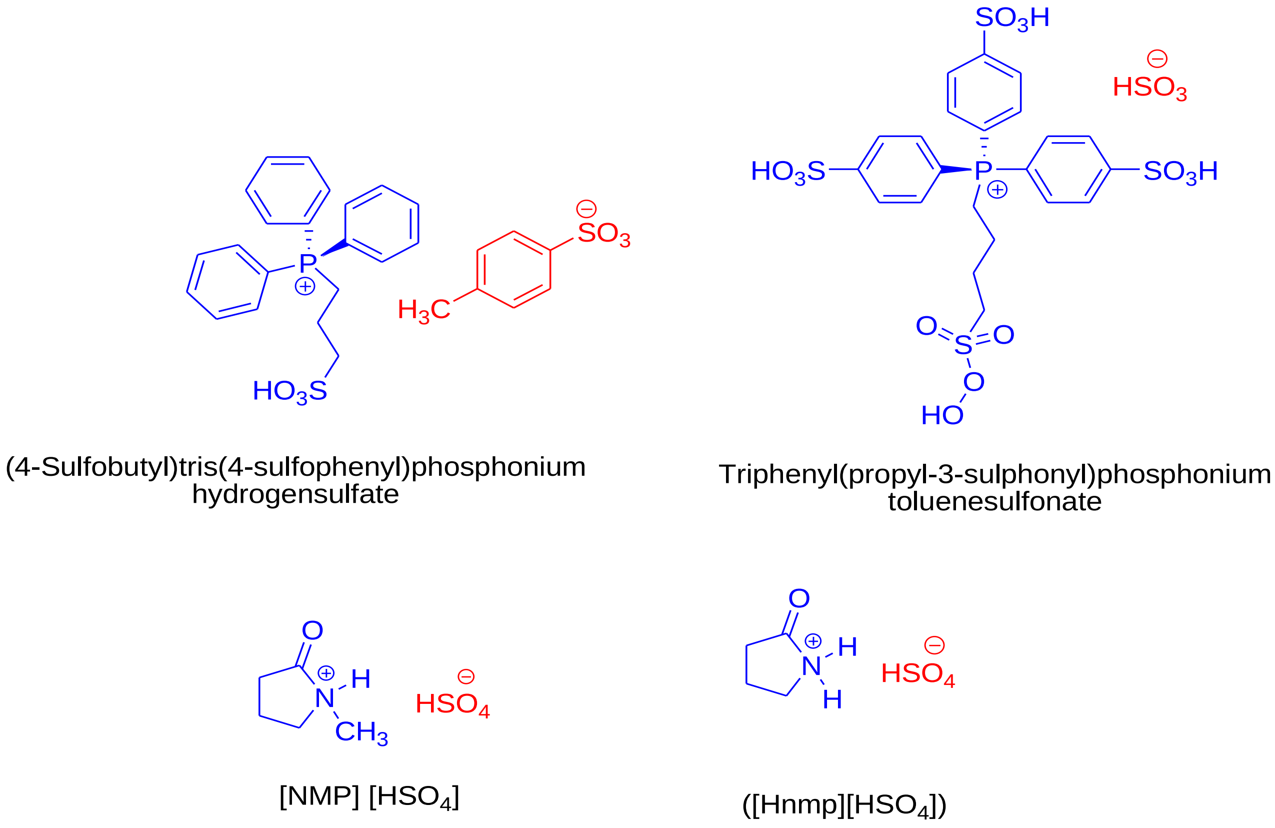
hexadecyldimethyl benzyl ammonium bromide and triethylamine [28], and using earth Lewis acid catalyst [29]. Although, several catalyst and protocol have been studied for the preparation of the 2-amino-3-cyanopyridine derivatives, the methods suffer from one or more imperfection such as multi-steps reaction pathway [30], high temperature and microwave assistance [31,32], toxic solvent [33], long reaction times and harsh reaction conditions with low yields. In the light of these facts, surveying a straightforward and newer recyclable catalytic environmentally congruous approach for the synthesis of these compounds is still demanded and an interesting mission to the methodologists and would be valuable.

As part of our continuing interest in the development of new synthetic methods in organic synthesis [34,35], in this paper we would like to report applications of some acidic ionic liquids such as 2-pyrrolidonium hydrogensulfate ([Hnmp][HSO_4]), *N*-methyl-2-pyrrolidonium hydrogensulfate ([NMP][HSO_4]), triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate and (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate as catalysts (Figure 1) in a four-component reaction for the synthesis of 2-amino-3-cyanopyridine derivatives (Scheme 1).



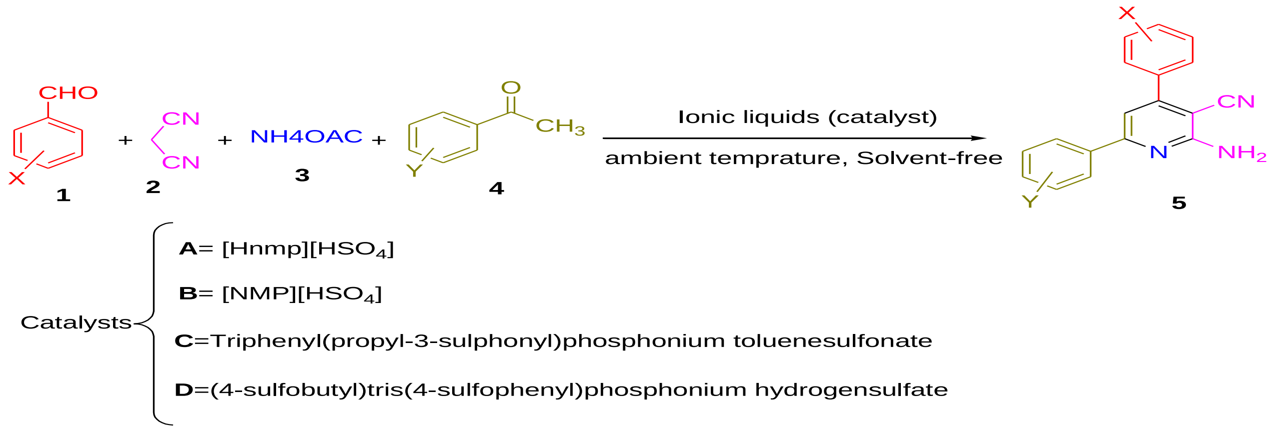
(4-Sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate

Triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate

[NMP] [HSO_4]

([Hnmp][HSO_4])

Figure 1. The molecular structure of acidic Brønsted ionic liquids**:** [NMP][HSO_4], triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate, (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate and [Hnmp][HSO_4].



Scheme 1. The synthesis of 2-amino-3-cyano pyridinederivatives

2. Experimental

General:

All reagents were purchased from Merck and Aldrich and used without further purification. The acidic ionic liquids such as 2-pyrrolidonium hydrogensulfate [36], *N*-methyl-2-pyrrolidonium hydrogensulfate [37], triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate [38] and (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate [39] were prepared according to literature. All yields refer to isolated products after purification. NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400 MHz for ^{1}H, 100 MHz for ^{13}C). IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica-gel Poly Gram SIL G/UV 254 plates.

2.1. Synthesis of 2-amino-3-cyanopyridine derivatives under solvent-free conditions

The mixture of the aldehydes (1.0 mmol), substituted acetophenones (1.0 mmol), malononitrile (1.0 mmol), ammonium acetate (1.5 mmol) and ionic liquids containing[Hnmp][HSO_4] (30 mol%), [NMP][HSO_4] (30 mol%), triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate (30 mol%) and (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate (30 mol%) as acidic catalysts was stirred under ambient and solvent-free conditions for the specific time. After completion of the reaction, 5 mL of water was added to the mixture. The ionic liquid was dissolved in water, and filtered for separation of the crude product. The separated product was washed twice with water (2×5 mL). The resultant precipitate was isolated by filtration, washed with cold ethanol carefully, and recrystallized from tetrahydrofuran.

Spectroscopic data of new products are given below:

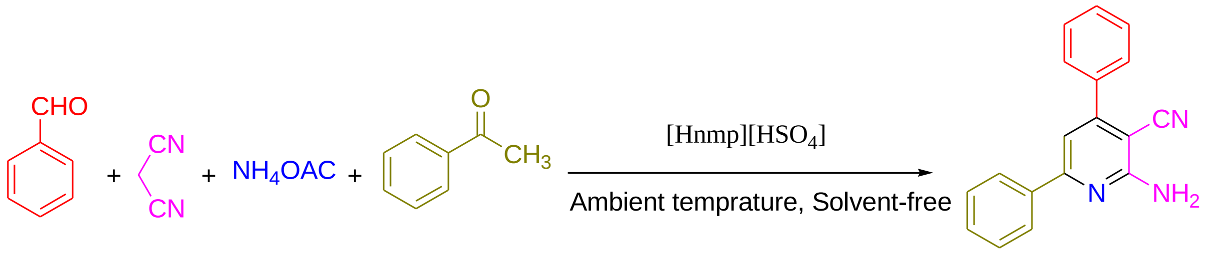
2-amino-3-cyano-4-(2,3-dichlorophenyl)-6-(4-methoxyphenyl)pyridine (Table 2, Entry 8): mp 145-147 ºC; IR (KBr): ν_{max} = 3462, 3356, 2219, 1004, 1515 cm^{-1}; ^{1}HNMR ($CDCl_3$,400MHz): δ = 3.9 (s, 3H,CH_3), 5.38 (s, 2H, NH_2), 6.96-7.02 (m, 2H, Ar), 7.10 (s, 1H, Ar), 7.29-7.31 (m, 1H, Ar), 7.35-7.37 (m, 1H, Ar); ^{13}CNMR ($CDCl_3$, 100MHz): δ = 55.47, 111.07, 113.7, 114.2, 116.2, 127.6, 128.4, 128.9, 130.0, 130.6, 131.3, 134.1, 138.1, 152.3, 159.4, 159.6, 161.6.

2-amino-3-cyano-4-(3,4,5-trimethoxyphenyl)-6-(4-methoxyphenyl)pyridine (Table 2, Entry 9): mp 166-168 ºC; IR (KBr): ν_{max} = 3357, 2206, 1005-1508 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400MHz): δ = 3.90 (s, 3H, CH_3), 3.95(s, 9H, CH_3), 5.4 (s, 2H, NH_2), 6.87 (s, 2H, Ar), 7.02 (d, 2H, Ar, *J* = 8.0 Hz), 7.1 (s, 1H, Ar), 8.01 (d, 2H, Ar, *J* = 8.0 Hz); ^{13}CNMR ($CDCl_3$, 100MHz): δ = 55.4, 56.3, 61.0, 87.2, 105.4, 110.1, 114.2, 114.2, 117, 128.8, 130.3, 132.4, 139.2, 153.4, 154.8, 159.3, 160.2, 161.5.

2-amino-3-cyano-4-(3,4,5-trimethoxyphenyl)-6-(4-nitrophenyl)pyridine (Table 2, Entry 10): mp 243-245 ºC; IR (KBr): ν_{max} = 3366, 2214, 1129-1518 cm^{-1}; ^{1}HNMR ($CDCl_3$,400 MHz): δ = 3.98 (s, 9H, CH_3), 5.52 (s, 2H, NH_2), 6.80 (s, 2H, Ar), 6.91 (s, 1H, Ar), 7.78 (d, 2H, Ar, *J*=8.0 Hz), 8.41 (d, 2H, Ar, *J* = 12.0 Hz); ^{13}CNMR ($CDCl_3$, 100MHz): δ = 56.4, 61.0, 94.4, 96.0, 105.8, 115.3, 115.7, 119.4, 124.2, 129.6, 132.1, 139.5, 143.4, 148.5, 150.6, 153.5.

3. Results and Discussion

To optimize reaction conditions, the condensation between benzaldehyde, acetophenone, malononitrile and ammonium acetate in the presence of 2-pyrrolidonium hydrogensulfate ([Hnmp][HSO_4]) was selected as a model systems (Scheme 2) (Table 1). The reaction was carried out with different amount of [Hnmp][HSO_4] as catalyst (10, 20, 30, 40 mol %) under ambient and solvent-free conditions (Table 1). As it can been clearly seen, 30 mol % of [Hnmp][HSO_4] as catalyst afforded the corresponding product in 5 min with 93% of yield (Table 1, Entry 3). In continuation of our study, optimization conditions of ionic liquids, [NMP][HSO_4], Triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate and (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate, in the mentioned model were investigated. According to the Table 1 and its general optimization procedure, 30 mol% of [NMP][HSO_4], 30 mol% of Triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate and 30 mol% of (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate as catalysts under ambient and solvent-free conditions was chosen (Table 1).



Scheme 2. Model reaction for the synthesis of 2-amino-4,6-diphenylnicotinonitrile**.**

Table 1. Optimization amount of A: [Hnmp][HSO_4], B: [NMP][HSO_4], C: triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate, D: (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate as catalysts in four-component synthesis of 2-amino-3-cyano-4,6-diphenylpyridine from the reaction of benzaldehyde, acetophenone, malononitrile and ammonium acetate under solvent-free and ambient conditions

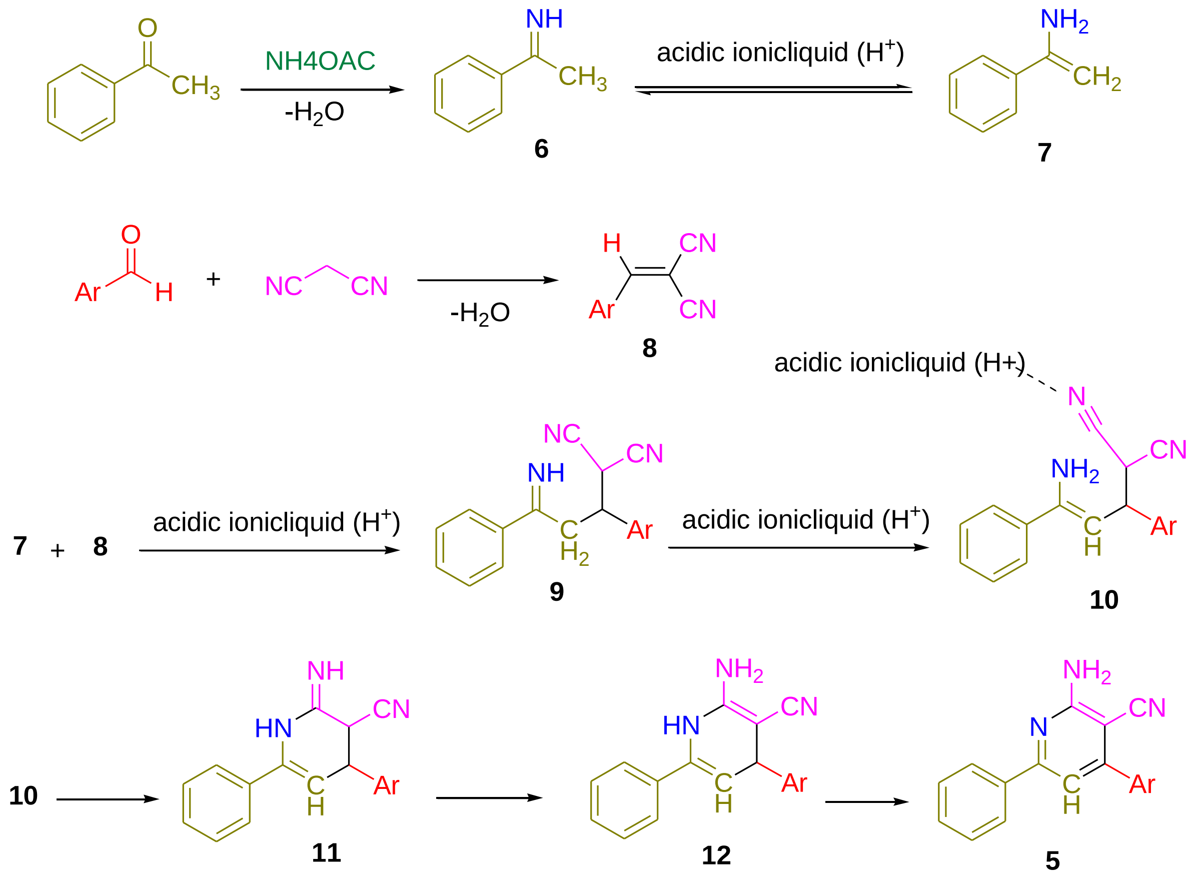
Entry	Catalyst (mol%)				Time (min)				Isolated Yield (%)			
	A	B	C	D	A	B	C	D	A	B	C	D
1	10	10	10	10	30	30	30	30	50	52	54	51
2	20	20	20	20	8	10	8	10	80	79	80	78
3	30	30	30	30	5	6	5	7	93	92	94	92
4	40	40	40	40	5	6	5	7	94	93	95	92

Using these optimized conditions, the scope and efficiency of the reaction were explored for the synthesis of a wide variety of 2-amino-3-cyanopyridine derivatives from the reaction between aromatic aldehydes, substituted acetophenones, malononitrile and ammonium acetate (Table 2). The wide ranges of substituted and structurally diverse aldehydes and acetophenones synthesize the corresponding products in high to excellent yields using the four Brønsted acidic ionic liquids as catalysts (Table 2).

Table 2 Four-component synthesis of 2-amino-3-cyano pyridinederivatives from the reaction of aromatic aldehydes (1 mmol), substituted acetophenones (1 mmol), malononitrile (1 mmol), ammonium acetate (1.5 mmol) in the presence of A: [Hnmp][HSO_4](30 mol %), B: [NMP][HSO_4] (30 mol %), C: triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate (30 mol %) and D: (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate (30 mol %) as catalysts under ambient and solvent-free conditions

Entry	X	Y	Time (min)				Yield (%)^a				Melting Point m.p (°C)/ Lit. m.p (°C)[Ref]
			A	B	C	D	A	B	C	D	
1	H	H	5	6	5	7	93	92	94	92	189-190/(186-187) [40]
2	4-Cl	H	5	6	4	7	93	94	96	93	237-238/(233-235) [40]
3	4-Cl	4-OH	6	5	6	6	92	92	91	90	265-266/(266-267) [40]
4	4-Cl	4-CH_3O	5	7	8	7	94	93	96	93	194-196/(195-196) [40]
5	4-Cl	4-Cl	7	6	7	8	93	90	92	90	249-251/(248-250) [41]
6	4-CH_3	4-Br	6	4	8	6	94	92	91	92	240/(235-237) [41]
7	3,4,5-$(CH_3O)_3$	4-F	5	8	6	5	90	91	90	91	238-239/(235-237) [41]
8	2,3-Cl_2	4-CH_3O	6	6	7	8	93	91	91	92	145-147
9	3,4,5-$(CH_3O)_3$	4-CH_3O	4	7	7	8	89	94	92	94	166-168
10	3,4,5-$(CH_3O)_3$	4-NO_2	7	6	6	7	89	90	91	91	243-245

According to the literature survey [40], the suggested mechanism for the formation of the products is shown in Scheme 3. This transformation can be proceeded through imine, enamine, Knoevenagel condensation, cycloaddition, Michael addition, aromatization.



Scheme 3. The suggested mechanism for the formation of the products 2-amino-3-cyano pyridinederivatives

We also investigated the recycling of the ionic liquids under ambient and solvent-free conditions using the model reaction of benzaldehyde, acetophenones, malononitrile, and ammonium acetate in the presence of [Hnmp][HSO_4] (30 mol%), [NMP][HSO_4] (30 mol%), triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate (30 mol%) and (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate (30 mol%) (Table 2, Entry 1). After completion of the reaction, water was added and the precipitated mixture was filtered off for separation of crude products. After washing the solid products with water completely, the water containing ionic liquid (IL is soluble in water) was evaporated under reduced pressure and ionic liquid was recovered and reused (Figure 2). The recovered catalysts were reused four runs with lowest decrease in activity.

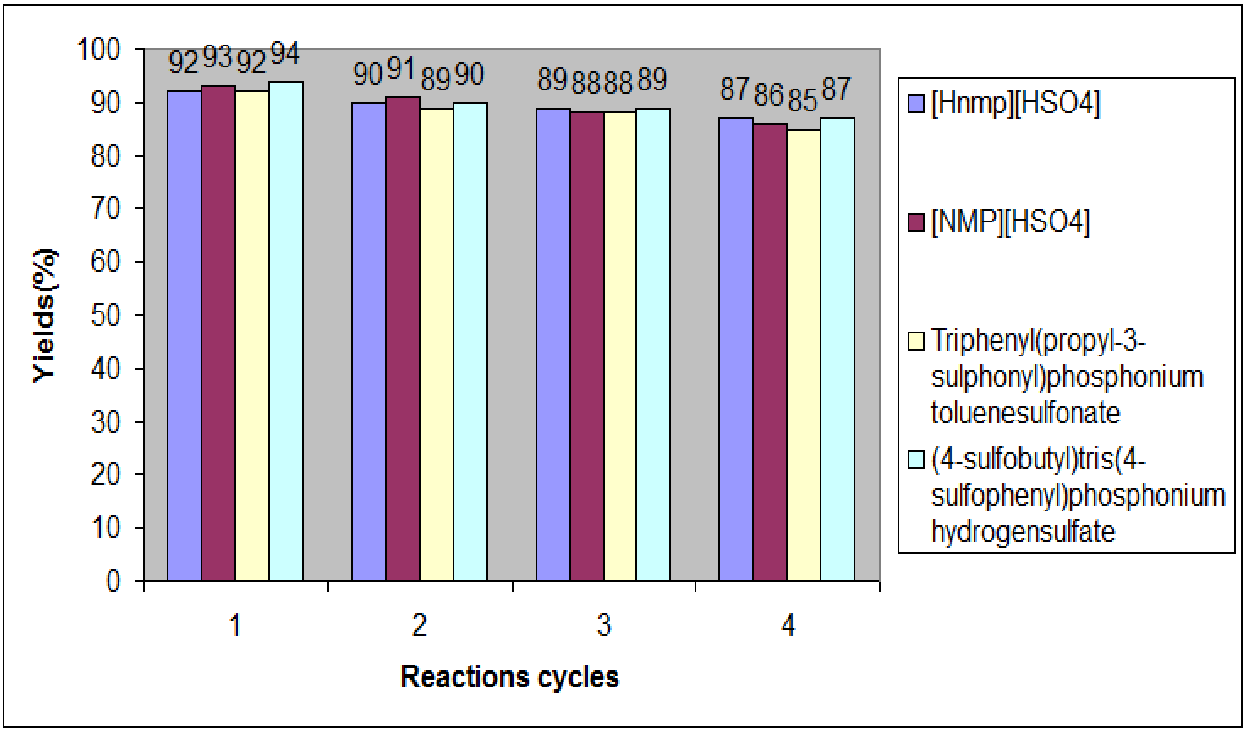


Figure 2. The recycling of the ionic liquids as catalyst

In order to assess the efficiency and generality of this methodology, the obtained result from the reaction of benzaldehyde, acetophenones, malononitrile and ammonium acetate with catalyst **A**, **B**, **C**, and **D** by this method has been compared with those of the previously reported methods (Table 3). It was found that the present method is convincingly superior to the reported methods with respect to reaction time, yield of the product and amount of the catalyst.

Table 3. Comparison of the efficiency of [Hnmp][HSO_4], [NMP][HSO_4], triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate and (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate with other reported catalysts in literature

Entry	Catalyst	Conditions	Time	Isolated Yield (%) [Ref]
1	[Yb(PFO)$_3$](5 mol%)	Ethanol (2 mL), reflux	90 min	90 [40]
2	[TBBDA] (0.05 g)	100 ºC	10 min	90 [41]
3	[PBBS] (0.05 g)	100 ºC	10 min	85[41]
4	No catalyst	TFE, reflux	6 h	90 [42]
5	Cu/C	CH_3CN	6 h	91[26]
6	{Fe_3O_4@SiO_2@(CH2)3Im}C$(CN)_3$	Solvent-free, 100 ºC	40 min	86[27]
7	[Hnmp][HSO_4] (30 mol%)	Solvent-free, r.t	5 min	93 (Present work)
8	[NMP][HSO_4](3 mol%)	Solvent-free, r.t	6 min	92 (Present work)
9	Triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate (30 mol%)	Solvent-free, r.t	5 min	94 (Present work)
10	(4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate (30 mol%)	Solvent-free, r.t	7 min	92 (Present work)

Conclusions

In conclusion, acidic ionic liquids were prepared from commercially available and inexpensive starting materials, catalyzed efficiently synthesis of 2-amino-3-cyanopyridine derivatives under solvent-free conditions. The simplicity of the procedure, eco-friendly, non-volatile, easy handling, and safety of catalyst are the advantages of these methods. These methods not only afford the products in excellent yields but also avoid the problems associated with catalyst cost, and pollution. The mentioned ionic liquids show priority relative to other catalysts in the literature.

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References

[1] P. Wasserscheid, T. Welton, Ionic Liquids in Synthesis (Wiley-VCH, Weinheim, 2008)

[2] P. Wasserscheid, W. Keim, *Angew. Chem. Int. Ed.* **39** (2000) 3773.

[3] M. Golmohammadi Afkham, A. Elhampour, F. Nemati *J. Appl. Chem.* **10** (2016) 55.

[4] N. Nowrouzi, S. Keshtegar *J. Appl. Chem.* **11** (2016) 115.

[5] A. Nefzi, J. M. Ostresh, R. A. Houghten, *Chem. Rev.* **97** (1997) 449.

[6] L. A. Thompson, *Curr. Opin. Chem. Biol.* **4** (2000) 324.

[7] A. Dömling, *Curr. Opin. Chem. Biol.* **6** (2002) 306.

[8] M. M. Hosseini, E. Kolvari, M. Vahidian, R. Bagheri *J. Appl. Chem.* **11** (2017) 109.

[9] F. Mohamadpour, M. Lashkari, M. T. Maghsoodlou, R. Heydari, *J. Appl. Chem.* **10** (2016) 79.

[10] T. Murata, M. Shimada, S. Sakakibara, T. Yoshino, H. Kadono, T. Masuda, M. Shimazaki, T. Shintani, K. Fuchikami, K. Sakai, H. Inbe, K. Takeshita, T. Niki, M. Umeda, K. B. Bacon, K. B. Ziegelbauer, T. B. Lowinger, *Bioorg. Med. Chem. Lett.* **13** (2003) 913.

[11] A. R. Gholap, K. S. Toti, F. Shirazi, R. Kumari, M. K. Bhat, M. V. Deshpande, K. V. Srinivasan, *Bioorg. Med. Chem.* **15** (2007) 6705.

[12] F. Zhang, Y. Zhao, L. Sun, L. Ding, Y. Gu, P. Gong, *Eur. J. Med. Chem.* **46** (2011) 3149.

[13] A. G. Hammam, N. A. A. EI-Hafez, W. H. Midura, M.*Z.* Mikolajczyk, *Naturforschung B: J. Chem. Sci.* **55** (2000) 417.

[14] S. G. Konda, V. T. Khedkar, B. S. Dawane, *J. Chem. Pharm. Res.* **2** (2010) 187.

[15] D. C. Mungra, M. P. Patel, R. G. Patel, *Arkivoc* xiv (2009) 64.

[16] T. Murata, M. Shimada, S. Sakakibara, T. Yoshino, T. Masuda, T. Shintani, H. Sato, Y. Koriyama, K. Fukushima, N. Nunami, M.Yamauchi, K. Fuchikami, H. Komura, A. Watanabe, K. B. Ziegelbauer, K. B. Bacon, T. B. Lowinger, *Bioorg. Med. Chem. Lett.* **14** (2004) 4019.

[17] J. J. Baldwin, E. L. Engelhardt, R. Hirschmann, G. S. Pontic, J. G. Atkinson, Wasson, B. K. Sweet, C. S. Scriabine, A, *J. Med. Chem.* **23** (1980) 65.

[18] F. Shi, V. Tu, F. Fang, T. Li, *Arkivoc* **137** (2005).

[19] S. J. Tu, H. Jiang, Q. Y. Zhuang, C. B. Miao, D. Q. Shi, X. S. W. J. Zhou, S. J. Ji, Z. L. Shen, *J. Organomet. Chem.* **691** (2006) 1356.

[20] W. J. Zhou, S. J. Ji, Z. L. Shen, *J. Organomet. Chem.* **691** (2006) 1356.

[21] R. Gupta, A. Jain, M. Jain, R. Joshi, *Bull. Korean Chem. Soc.* **31** (2010) 3180.

[22] M. M. Heravi, S. Y. S. Beheshtiha, M. Dehghani, N. Hosseintash, *J. Iran. Chem. Soc.* **12** (2015) 2075.

[23] S. S. Mansoor, K. Aswin, K. Logaiya, P. N. Sudhan, S. Malik, *Res. Chem. Intermed.* **40** (2014) 871.

[24] Wang, Y. C. Gao, *Chin. J. Org. Chem.* **23** (2003) 488.

[25] A. N. Vasiliev, Y. S. Kayukov, O. E. Nasakin, A. N. Lyshchikov, V. N. Nesterov, O. V. Kayukova, O. V. Poulkherovskaya, *Chem. Heterocycl. Compd.* **37** (2001) 309.

[26] R. Khalifeh, M. Ghamari, *J. Braz. Chem. Soc.* **27** (2016) 759.

[27] M. A. Zolfigol, M. Kiafara, M. Yariea, A. Taherpourb, M. Saeidi-Rada, *RSC Adv.* **6** (2016) 50100.

[28] T. S. Jin, A. Q. Wang, F. Shi, L. S. Han, L. B. Liu, T. S. Li, *Arkivoc* xiv (2006) 78.

[29] J. Tang, L. Wang, Y. Yao, L. Zhang, W. Wang, *Tetrahedron Lett.* **52** (2011) 509.

[30] A. S. Girgis, A. Kalmouch, H. M. Hosni, *Amino Acids* **26** (2004) 139.

[31] F. Shi, S. J. Tu, F. Fang, T. J. Li, *Arkivoc* (2005) 137.

[32] P. G othawal, G. Malhotra, Y. K. Srivastava, *E-J. Chem.* **8** (2011) 119.

[33] S. Kambe, K. Saito, *Synthesis* (1980) 366.

[34] E. Mollashahi, H. Gholami, M. Kangani, M. Lashkari, MT. Maghsoodlou, *Heteroatom Chem.* **26** (2016) 322.

[35] N. Hazeri, M.T. Maghsoodlou, F. Mir, M. Kangani,H. Saravani, E. Molashahi, *Chin. J. Catal.* **35** (2014) 391.

[36] C. Zhang, X-Y. Pan, M-J. Yu, L. Jin, G. Wu, *Chem. Eng. J.* **209** (2012) 464.

[37] V.S. Patil, V.S. Padalkar, A.S.Chaudhari, N. Sekar, *Catal. Sci. Technolo.* **2** (2012) 1681.

[38] C. Cole, J.L. Jensen, I. Nati, K.L.T. Tran, K.J. Weaver, D. Forbes, *J. Am. Chem. Soc.* **124** (2002) 5962.

[39] B. Shaohua, C. Lu, J. Yongjun, Y. Jianguo, *Chin. J. Chem.* **28** (2010) 2119.

[40] J. Tang, L. Wang, Y. Yao, L. Zhang, W. Wang, *Tetrahedron Lett.* **52** (2011) 509.

[41] R. Ghorbani-Vaghei, Z. Toghraei-Semiromi, R. Karimi-Nami, *C. R. Chimie.* **16** (2013) 1111.

[42] S. Khaksar, M. Yaghoobi, *J. Fluorine Chem.* ***142*** *(2012) 41.*