An Improved Procedure for the Three-Component Synthesis of Highly Substituted Pyridines Using Ionic Liquid

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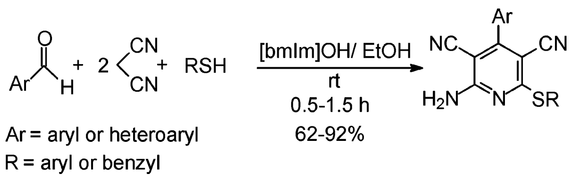
Received January 4, 2007



A basic ionic liquid, [bmIm]OH, efficiently promotes a one-pot, three-component condensation of aldehydes, malononitrile, and thiophenols to produce highly substituted pyridines in high yields at room temperature. This reaction does not involve any hazardous organic solvent and toxic catalyst. The ionic liquid is recovered and recycled for subsequent reactions.

The pyridine nucleus is of considerable interest as this ring is the key constituent in a range of bioactive compounds, both naturally occurring and synthetic, and often of considerable complexity.[1] Thus, the synthesis of highly substituted pyridines has attracted much attention, and a number of procedures have been developed[2] using a variety of protocols, such as hetero-Diels−Alder reaction of 3-siloxy-1-aza-1,3-butadienes with electron-deficient acetylenes;[2a] three-component condensation of aldehyde, malononitrile, and thiol;[2b] ruthenium-catalyzed cycloisomerization of 3-azadienynes;[2c] Mannich reaction of aldehydes and iminium salts;[2d] Vilsmeier−Haack reaction of α-hydroxyketenedithioacetals;[2e] 6π-azaelectrocyclization of azatrienes;[2f] catalytic oxidation of 1,4-dihydropyridines by $RuCl_3/O_2$;[2g] carbon transfer reaction of functionalized oxazolidines and their open-chain enamine tautomers to enamine nucleophiles;[2h] [4+2] cycloadditions of oximinosulfonates;[2i] conversion of conjugated oximes under Vilsmeier conditions;[2j,k] reaction of *N*-methylene-*tert*-butylamine with enamines;[2l] Diels−Alder reaction of 2*H*-1,4-oxazinones with acetylenic compounds;[2m] and conversion of ketene dithioacetals to substituted pyridines.[2n] Among these, one of the very convenient approaches which attracted our attention is the three-component condensation of aldehyde, malononitrile, and thiol to the highly substituted pyridines developed by Evdokimov et al.[2b] However, one of the serious limitations of this procedure is formation of considerable amounts of a side product, enaminonitrile, reducing the yields of pyridines to 20−48%, using bases such as DABCO and Et_3N in ethanol under reflux. As a part of our continuing program to explore the novel uses of ionic liquids in organic reactions,[3] we discovered that our recently reported task-specific ionic liquid, [bmIm]OH,[3a] completely suppressed this side reaction of enaminonitrile formation and raised the yields (isolated) of pyridines to the level of 62−92% (Scheme 1).

The experimental procedure is very simple. A mixture of an aromatic aldehyde, malononitrile, and ionic liquid, [bmIm]OH, was stirred at room temperature. After an exothermic reaction, a solid product appeared which was dissolved with ethanol. Thiophenol was then added, and the reaction mixture was stirred for a period of time until completion of the reaction (TLC). Usual workup and purification by recrystallization provided the pure pyridine. The residual ionic liquid was rinsed with ethyl acetate, dried under a vacuum, and recycled.

A wide range of substituted aromatic as well as heteroaromatic aldehydes underwent this three-component condensation with malononitrile and several substituted thiophenols by this procedure to produce 2-amino-3,5-dicyano-6-sulfanyl pyridines. The results were summarized in Table 1. Several functionalities such as Cl, Br, NO_2, SMe, OH, methylenedioxy, and OMe were found to be compatible under the reaction conditions. However, in contrast to the findings of Evdokimov et al.,[2b] aliphatic aldehydes did not produce the pyridines; instead, gummy products of unidentified constituents were isolated. Accordingly, also aliphatic thiols remained inert in this reaction. When *o,o*-disubstituted aldehydes (entries 18 and 19) were used in this condensation process, the corresponding 1,4-dihydropyridines were obtained in high yields.

In accordance with the mechanism delineated by Evdokinov et al.,[2b] the first step of this process involves the Knoevenagel condensation of an aldehyde with malononitrile to form the corresponding Knoevenagel product (A). The second molecule of malononitrile then undergoes Michael addition to A followed by simultaneous thiolate addition to C≡N of the adduct and cyclization to dihydropyridine (B) which on aromatization and oxidation (air) under the reaction conditions leads to pyridine (Scheme 2). It may be speculated that the difference in basicity of [bmIm]OH used in this reaction compared to DABCO and Et_3N[2b] may play a crucial role in suppressing the enaminonitrile formation,[2b] and a systematic investigation regarding the precise

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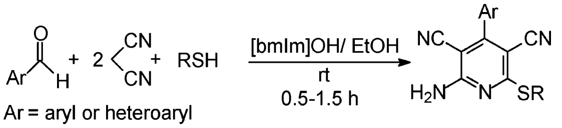
[1] (a) Boger, D. L.; Nakahara, S. *J. Org. Chem.* **1991**, *56*, 880. (b) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517. (c) Zhang, T. Y.; Stout, J. R.; Keay, J. G.; Scriven, E. F. V.; Toomey, J. E.; Goe, G. L. *Tetrahedron* **1995**, *51*, 13177. (d) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752.

[2] (a) Fletcher, M. D.; Hurst, T. E.; Miles, T. J.; Moody, C. J. *Tetrahedron* **2006**, *62*, 5454. (b) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. *Org. Lett.* **2006**, *8*, 899. (c) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 4592. (d) Winter, A.; Risch, N. *Synthesis* **2003**, 2667. (e) Thomas, A. D.; Asokan, C. V. *Tetrahedron Lett.* **2002**, *43*, 2273. (f) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumara, S. *J. Org. Chem.* **2001**, *66*, 3099. (g) Mashraqui, S. H.; Karnik, M. A. *Tetrahedron Lett.* **1998**, *39*, 4895. (h) Singh, K.; Singh, J.; Singh, H. *Tetrahedron* **1998**, *54*, 935. (i) Renslo, A. R.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 7840. (j) Vijn, R. J.; Arts, H. J.; Green, R.; Castelijns, A. M. *Synthesis* **1994**, 573. (k) Ahmed, S.; Baruah, R. C. *Tetrahedron Lett.* **1996**, *37*, 8231. (l) Komatsu, M.; Ohgishi, H.; Takamatsu, S.; Ohshiro, Y.; Agawa, T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 213. (m) Van Aken, K. J.; Lux, G. M.; Deroover, G. G.; Meerpoel, L.; Hoornaert, G. J. *Tetrahedron* **1994**, *50*, 5211. (n) Anabha, E. R.; Nirmala, K. N.; Thomas, A.; Asokan, C. V. *Synthesis* **2007**, 428.

[3] (a) Ranu, B. C.; Banerjee, S. *Org. Lett.* **2005**, *7*, 3049. (b) Ranu, B. C.; Banerjee, S.; Jana, R. *Tetrahedron* **2007**, *63*, 776 and references cited therein.

10.1021/jo070015g CCC: $37.00

SCHEME 1. Synthesis of Pyridines



Ar = aryl or heteroaryl
R = aryl or benzyl

SCHEME 2. Plausible Mechanism of 1,4-Dihydropyridine and Pyridine Formation

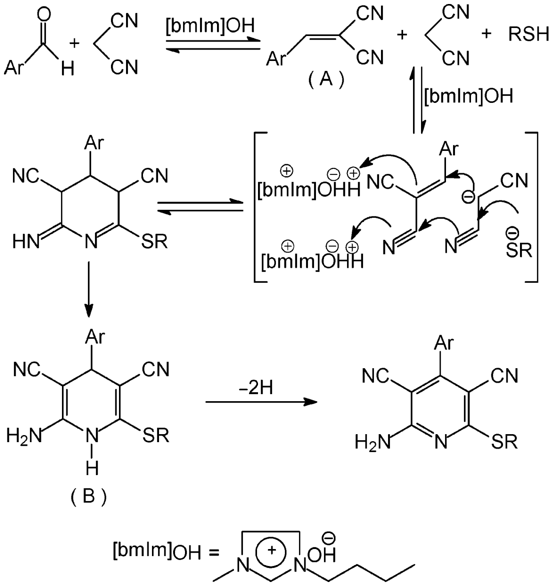
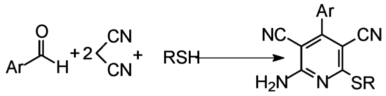
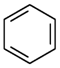
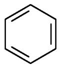
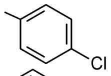
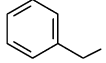
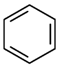
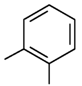
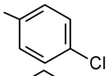
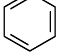
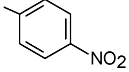
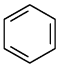
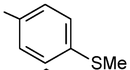
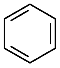
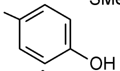
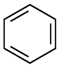
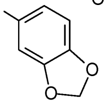
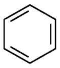
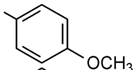
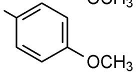
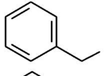
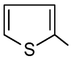
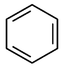
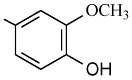
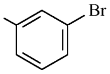
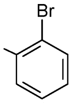
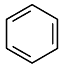
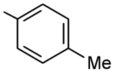
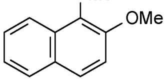
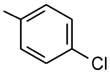
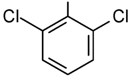
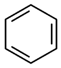
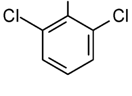
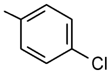


TABLE 1. Synthesis of Substituted Pyridines Catalyzed by [bmIm]OH



entry	Ar	R	time (h)	yield (%)[a]	mp (°C)	ref
1			1.1	92	216 - 218	2b
2			1.5	65	228 - 230	4
3			1.5	72	193 - 195	4
4			1.7	62	224 - 225	2m
5			1.5	87	222 - 224	2m
6			2.0	67	287 - 289	2b
7			1.7	62	254 - 256	
8			1.5	87	315 - 316	2b
9			1.7	87	234 - 236	5
10			1.5	82	238 - 240	2b
11			2.0	75	228 - 230	6b
12			1.5	82	208 - 210	4
13			2.0	81	218 - 220	
14			1.5	65	256 - 258	
15			1.2	74	242 - 244	
16			1.5	87	208 - 211	2m
17			2.0	72	257 - 260	
18			1.0	95[b]	319 - 320	2b
19			1.0	94[b]	334 - 335	

[a] Yields refer to those of pure isolated products characterized by IR, ^{1}H, ^{13}C, and mass spectroscopic data. [b] Substituted 1,4-dihydropyridine.

function of [bmIm]OH has been undertaken. The presence of ionic liquid, [bmIm]OH, is essential, as in the absence of this ionic liquid the reactions did not proceed at all. The use of other ionic liquids such as [bmIm]Br or [bmIm]BF$_4$ failed to push the reaction to the pyridine stage, and the reaction was stopped at an intermediate step with the formation of compound A. Presumably, the reactions of *o,o*-disubstituted aldehydes (entries 18 and 19) were arrested at the 1,4-dihydropyridine stage as further aromatization did not occur due to steric hindrance at the 4-position by two ortho substituents at the aromatic ring.

In general, the reactions were very clean and high yielding. No side products were detected in any reaction except that with piperanaldehyde (entry 9) where a small amount (<5%) of enaminonitrile was formed. All the products were crystalline compounds and were easily identified by their melting points and spectroscopic data.

The highly substituted pyridine derivatives are of intense attention because of their potential for biological activities, and thus an efficient procedure for their synthesis is of high importance. The present procedure using a basic ionic liquid, [bmIm]OH, in place of conventional bases[2b] provides a selective, high yielding one-pot synthesis of highly substituted pyridines through a three-component condensation process. Significantly, the formation of a side product, enaminonitrile,[2b] was virtually eliminated. The other advantages of this procedure are the use of no hazardous organic solvent in the reaction and the reusability of ionic liquids. Encouraged by these results, we are pursuing further application of ionic liquids for such useful transformations.

Experimental Section

General Experimental Procedure for the Synthesis of Substituted Pyridines. Representative Procedure for 2-Amino-4-phenyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (Entry 1, Table 1). A mixture of benzaldehyde (106 mg, 1 mmol), malononitrile (132 mg, 2 mmol), and the basic ionic liquid, [bmIm]OH[3a]

(80 mg, 0.5 mmol), was stirred at room temperature. Immediately, an exothermic reaction took place and a solid product appeared. This solid was dissolved in a minimum amount (0.5 mL) of ethanol (possibly, the function of ethanol is just to carry out the reaction in a solution phase), and the solution was stirred for 30 min after which thiophenol (110 mg, 1 mmol) was added. The reaction mixture was stirred for another 30 min (TLC) until completion of the reaction. Ethanol was evaporated under reduced pressure, and the residue was extracted with ethyl acetate (3 × 10 mL). Evaporation of solvent left the crude solid which was recrystallized (acetonitrile) to furnish crystals (mp 216−218 °C) of 2-amino-4-phenyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (301 mg, 92%). The spectroscopic data (IR, ^{1}H NMR, and ^{13}C NMR) are in good agreement with the reported values.[4] The remaining ionic liquid was rinsed with ethyl acetate, dried under a vacuum, and reused for four runs after which a fresh ionic liquid was added to compensate the loss during washing by ethyl acetate. This procedure was followed for all the reactions listed in Table 1. Although this procedure was described with a 1 mmol scale, 10 mmol scale reactions also provided uniform results.

Many of these products are known compounds and were easily identified by comparison of their spectroscopic data and mp's with those reported (refs in Table 1). The unknown compounds were properly characterized by their spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, HRMS) data. The purity of all compounds was also checked by ^{1}H NMR, ^{13}C NMR, and HRMS.

Acknowledgment. This investigation has enjoyed the financial support of a grant [01(1936)/04/EMR-II] by CSIR, New Delhi. R.J. is thankful to CSIR and S.S. thanks the Indian Academy of Sciences for their fellowships.

Supporting Information Available: Spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, and HRMS) data and ^{13}C NMR spectra of all products in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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[4] Reddy, R. K. T.; Mutter, R.; Heal, W.; Guo, K.; Valerie, J.; Pratt, S.; Chen, B. *J. Med. Chem*. **2006**, *49*, 607.

[5] Chang, L. C.; Von-Kuenzel, J. K.; Kriegner, T.; Spangersberg, R. F.; Roerink, S. F.; Van-den, H. G.; Beukers, M. W.; Brussee, J.; Ijzerman, A. P. *J. Med. Chem.* **2005**, *48*, 2045.

[6] Rosentreter, U.; Henning, R.; Bauser, M.; Kraemer, T.; Vaupel, A.; Huebsch, W.; Dembowsky, K.; Salcher-Schraufstaetter, O.; Stasch, J.-P.; Krahn, T.; Perzborn, E. PCT Int. Appl. WO 2001025210 A2.