



Research Article

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Synthesis of pyrazolo [3,4-b] pyridines using basic ionic liquid [bmIm]OH

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ABSTRACT

Basic ionic liquid catalyzed synthesis of various pyrazolo [3, 4-b] pyridines were synthesized by cyclocondensation of 5-amino-3 aryl -1-H phenylpyrazoles, p-substituted benzoylacetone nitriles and some aryl aldehydes by using basic ionic liquid, [bmIm]OH. It acts as a base catalyst. Comparative study of triethylamine and [bmIm]OH. and ammonium acetate was studied. Reusability of catalyst with good yields under green reaction conditions is the salient feature of this synthetic method.

Keywords: pyrazolo [3, 4-b] pyridines; [bmIm]OH, benzoylacetone nitriles; aryl aldehydes; triethylamine, base catalyst.

INTRODUCTION

A multicomponent reaction (MCR) can create highly complex molecules from readily available starting materials without the complicated purification operations thus MCR are resource and time effective and economically favorable processes in diversity generation [1-3]]. Three component condensation with heterocyclic amine, various aldehydes and nitriles or isocyanate was reported [4].

The pyrazolo [3, 4-b] pyridine derivative exhibited biological activities [5-8]. Synthesis of pyrazolo [3, 4-b] pyridine derivatives were reported using Michael addition of 5-amino-3-methyl or 5-amino-3-phenyl pyrazole and benzoylacetone nitrile [9-10]. Recently synthesis of pyrazolo [3, 4-b] pyridines from 5-amino-3 aryl-1-H phenylpyrazoles and benzoylacetone nitriles and aldehydes using ammonium acetate were reported. [11].

Recently, there has been considerable interest in the use of ionic liquids as an environmentally benign reaction media due to its unique properties such as a wide liquid range, good solvating ability, tunable polarity, high thermal stability, negligible vapour pressure and ease of recyclability [12-13]. Basic ionic liquids are getting more interest because they showed more advantages such as catalytic efficiency and recycling of the ionic liquid than the combination of inorganic base and ionic liquid for some base catalyzed processes [14]. A basic ionic liquid [bmIm]OH has been successfully applied to catalyze the Michael addition of active methylene compounds to α,β -unsaturated ketones, esters and nitriles [15]. [bmIm]OH have been extensively applied in different organic reactions such as Heck reaction [16], (Li, et. al., 2006) Henry reaction, Aldol condensation [17-18], Diels-Alder reaction [19], heterocyclic synthesis [20].

Knowing all these aspects we have decided to investigate the possibility of formation of pyrazolo [3, 4-*b*] pyridine using [bmIm]OH as a catalyst and reaction media.

EXPERIMENTAL SECTION

*General Procedure for preparation of 3,4,6-triaryl-1-H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile*

To a solution of 5-aminopyrazole (1 mmol) and aroylacetonitrile (1.05 mmol) and aryl aldehyde (1.05 mmol) in [bmIm]OH (30 mol %), and the resulting reaction mixture was stirred at room temperature till completion of reaction (4h). After completion of the reaction (confirm by TLC), cold water added to reaction mixture and stirred for 30 min to get solid compound which was filtered and dried under vacuum. product was purified by recrystallisation using ethanol to get the pure compound. Aqueous layer was evaporated under reduced pressure at 90 °C to obtain pure ionic liquid.

Analytical data for synthesized compounds

3,6-Bis(4-Methylphenyl)-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (5a). ¹H NMR: (DMSO-*d*₆) 2.54 (s, 6H, 2CH₃), 7.39 (m, 5H, Ar-H), 7.55 (m, 2H, Ar-H), 7.95 (m, 2H, Ar-H), 8.42 (d, 2H, J = 8.4 Hz, Ar-H), 8.83 (s, 1H, C4H); IR: (KBr): 2227, 1453, 1519, 1170 cm⁻¹.

3,6-Bis(4-Methylphenyl)-4-(4-fluorophenyl)-1-phenyl-1H-pyrazolo [3, 4-*b*] pyridine-5-carbonitrile (5b). ¹H NMR: (CDCl₃) 2.56(s, 6H, 2CH₃), 7.39-7.51 (m, 9H, Ar-H), 7.55 (m, 2H, Ar-H), 7.74 (d, 2H, J = 8.4 Hz, Ar-H), 7.95 (d, 2H, J = 8.4 Hz, Ar-H), 8.42 (d, 2H, J = 8.6 Hz, Ar-H); IR: (KBr): 2224, 1453, 1519, 1170 cm⁻¹.

4,6-Bis(4-Chlorophenyl)-3-(4-methylphenyl)-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile(5c). ¹H NMR (CDCl₃) 2.48(s, 3H, CH₃), 7.02-7.63 (m, 11H, Ar-H), 7.74 (d, 2H, J = 8.4 Hz, Ar-H), 7.94 (d, 2H, J = 8.7 Hz, Ar-H), 8.35 (d, 2H, J = 8.4 Hz, Ar-H); IR: (KBr): 2223, 1453, 1519, 1170 cm⁻¹.

3,6-Bis(4-chlorophenyl)-4-(4-fluorophenyl)-1-phenyl-1H-pyrazolo[3, 4-*b*] pyridine-5-carbonitrile (5d). ¹H NMR (CDCl₃) 7.02-7.50 (m, 9H, Ar-H), 7.62 (d, 2H, J = 8.4 Hz, Ar-H), 7.76 (d, 2H, J = 8.7 Hz, Ar-H), 7.98 (d, 2H, J = 8.4 Hz, Ar-H), 8.42 (d, 2H, J = 8.7 Hz, Ar-H). IR: (KBr): 2223, 1453, 1519, 1170 cm⁻¹.

6-(4-Bromophenyl)-3-(4-chlorophenyl)-4-(4-fluorophenyl)-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (5e). ¹H NMR: (CDCl₃) 7.02-7.63 (m, 11H, Ar-H), 7.74 (d, 2H, J = 8.7 Hz, Ar-H), 7.94 (d, 2H, J = 8.4 Hz, Ar-H), 8.35 (d, 2H, J = 8.7 Hz, Ar-H), 8.42 (d, 2H, Ar-H); IR: (KBr): 2223, 1453, 1520, 1166 cm⁻¹.

6-(4-Bromophenyl)-3-(4-chlorophenyl)-4-(4-cyanophenyl)-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (5f). ¹H NMR: (DMSO-*d*₆) 7.03-7.14 (m, 4H, Ar-H), 7.39-7.74 (m, 8H, Ar-H), 7.89-8.24(m, 5H, Ar-H); IR: (KBr): 2219, 1453, 1515, 1169 cm⁻¹.

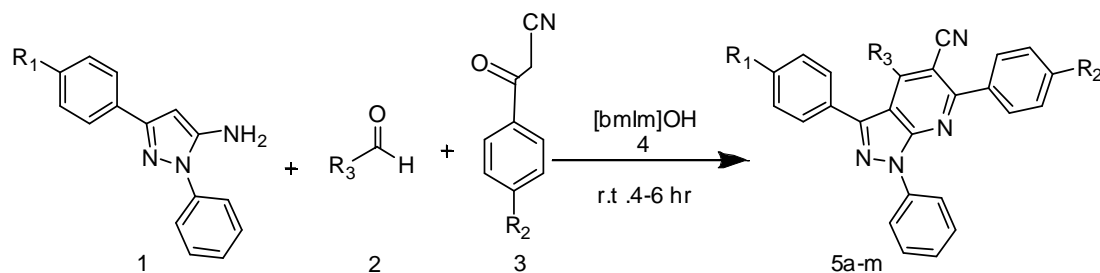
4,6-Bis(4-Chlorophenyl)-3-(4-methylphenyl)-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile(5g). ¹H NMR: (CDCl₃) 2.48 (s, 3H, CH₃), 7.02-7.63 (m, 11H, Ar-H), 7.74 (d, 2H, J = 8.4 Hz, Ar-H), 7.94 (d, 2H, J = 8.7 Hz, Ar-H), 8.35 (d, 2H, J = 8.4 Hz, Ar-H); IR: (KBr): 2223, 1453, 1519, 1170 cm⁻¹.

3-(4-Bromophenyl)-4,6-bis(4-chlorophenyl)-1-phenyl-1H-pyrazolo [3, 4-*b*] pyridine-5-carbonitrile (5h). ¹H NMR: (CDCl₃) 7.01 (d, 2H, J = 8.7 Hz, Ar-H), 7.13 (d, 2H, J = 8.4 Hz, Ar-H), 7.20 (m, 4H, Ar-H), 7.36 (t, 1H, J = 7.2 Hz, Ar-H), 7.53 (m, 4H, Ar-H), 7.98 (d, 2H, J = 8.4 Hz, Ar-H), 8.29 (d, 2H, J = 7.8 Hz, Ar-H); IR: (KBr): 2232, 1462, 1512, 1157 cm⁻¹.

3-(4-Bromophenyl)-6-(4-chlorophenyl)-4-(4-cyanophenyl)-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (5i). ¹H NMR: (CDCl₃) 7.07 (d, 2H, J = 8.4 Hz, Ar-H), 7.11 (d, 2H, J = 8.7 Hz, Ar-H), 7.30 (t, 1H, Ar-H), 7.41 (d, 2H, J = 8.4 Hz, Ar-H), 7.70 (d, 2H, J = 8.4 Hz, Ar-H), 7.54 (m, 4H, Ar-H), 7.89 (d, 2H, J = 8.7 Hz, Ar-H), 8.29 (d, 2H, J = 7.8 Hz, Ar-H); IR: (KBr): 2230, 1462, 1596, 1157 cm⁻¹.

RESULTS AND DISCUSSION

We studied the representative reaction for preparation of 5a from 5-aminopyrazole (1) aryl aldehyde (2) and aroylacetonitrile (3) in Basic ionic liquid [bmIm]OH. (scheme1)

**Scheme 1. Synthesis of pyrazolo [3, 4-b] pyridine**

The optimal reaction condition was developed using the different combination of solvent and mole % [bmIm]OH at room temperature for 4 hour under various conditions. The pyrazolo [3, 4-b] pyridine derivative 5a was obtained in 67% yield when reaction was carried out using 10mole % [bmIm]OH in ethanol at R.T. for 4 hour its structure was determined by NMR and Mass spectra. By using the traditional bases such as, triethylamine, ammonium acetate forms the desired product in 69 and 82% respectively (table2). . When solvents tetrahydrofuran, acetonitrile, acetone, in presence of 10 mole% catalyst, the desired product 5a was afforded in 52%, 51%, 64%, respectively, Surprisingly with DMF, as solvent the relative yield of the reaction was produced in 27% yield. When we used the 30 mole % [bmIm] OH in absence of solvent at room temperature the yield of the product was improved dramatically to 91%. This clearly indicates that [bmIm]OH served as base in this condensation reaction. The condensation product obtained by simple water work up followed by recrystallisation in good yield the results were shown in Table 1.

Table 1 Optimization of reaction condition

Solvent	mole% [bmIm]OH	Reaction time	% yield
Ethanol	10mole %	4h	67
DMF	10mole %	4h	52
ACN	10mole %	4h	32
THF	10mole %	4h	20
[bmIm]OH	30mole %	4h	91

Under these optimized conditions we next explored the scope of one pot synthesis of pyrazolo [3, 4-b] pyridine (5) as shown in Table 3 various substituted 5-aminopyrazole (1) aroylacetonitrile (2) and aryl aldehyde (3) were employed as reaction substrates and the reaction can afford the corresponding pyrazolo [3, 4-b] pyridine derivatives in good yields regardless of the different substitution on the aromatic ring of the substrates..

Table 2. Comparative yields of pyrazolo [3, 4-b] pyridine [bmIm]OH, NH₄(OAc)₂, Et₃N

	R ¹	R ²	R ³	%yield [bmIm]OH	%yield NH ₄ (OAc)	%yield Et ₃ N
5a	CH ₃	CH ₃	H	88	80	70
5b	CH ₃	CH ₃	p-FC ₆ H ₄	89	82	71
5c	CH ₃	Cl	p-ClC ₆ H ₄	87	81	69
5d	Cl	Cl	p-FC ₆ H ₄	90	82	72
5e	Cl	Br	p-FC ₆ H ₄	91	85	69
5f	Cl	Br	p-CNC ₆ H ₄	83	79	66
5g	Cl	Br	p-ClC ₆ H ₄	92	88	77
5h	Br	Cl	p-ClC ₆ H ₄	90	83	67
5i	Br	Cl	p-CNC ₆ H ₄	89	78	68
5j	Br	Cl	p-OMeC ₆ H ₄	91	77	72
5k	Br	Br	C ₆ H ₅	93	77	72
5l	CH ₃	CH ₃	2-Thienyl	91	82	71
5m	CH ₃	CH ₃	Furyl	94	84	73

5-aminopyrazole was prepared using the literature method (Jachak et.al. 2005). 5-aminopyrazole with chloro, bromo and methyl substituent on the 3-phenyl group are used for the reactions with aroylacetonitrile (2) and aryl aldehyde (3). Substrates with an electron-donating group on the aromatic ring of the aldehyde (3), for example substrates with methyl, methoxy, group's gave less yields than electron-withdrawing group such as Fluoro, chloro, bromo. Heterocyclic aldehydes gave better yields as compare to aromatic aldehydes. While substrates with a chloro group in the phenyl ring of benzoylacetonitrile gave the corresponding product in good yield 84-87% as compare bromo group in the phenyl ring of benzoylacetonitrile, there is no remarkable effect observed when chloro and bromo replaced by methyl group in the phenyl ring of benzoylacetonitrile under typical reaction conditions.(table2).

The reusability of ionic liquid was the more advantageous aspect, the ionic liquid used in the reaction was recovered from aqueous layer and washed with diethyl ether to remove any organic impurities and dried under vacuum to get the pure ionic liquid and reused for the above reactions. We have tested reusability of ionic liquid for compound **5k**, upon use of five times, showed no loss of its activity and does not vary yield notably of final product.

CONCLUSION

We have developed an environmental friendly new single step method for the synthesis of pyrazolo [3, 4-b] pyridine using reusable basic ionic liquid [bmIm]OH as a catalyst and itself reaction medium as well. Present methodology offer benefits such as easily available catalyst, easy reaction protocol, better yield and reusability of catalyst. This method gives better yield than triethylamine and ammonium acetate method.

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REFERENCES

- [1] Ramon, D. J. Yus, M. **2005**. *Angew Chem.Int.Ed.Engl* 44, 1602.
- [2] Orru, R. V. A. **2006** *QSAR Comb Sci* 25,417.
- [3] Marek, I. **2005** *Tetrahedron* 61, 11309.
- [4] Ugi, I. **2001** *Pure Appl. Chem* 73,187.
- [5] Elnagdi, M.; Elmoghayar, M.; Elgemeie, G.; *Adv. Heterocyclic Chem.* **1987**, 41,
- [6] Elnagdi, M.; Elmoghayar, M.; Elgemeie, G.; *Adv. Heterocyclic Chem.* **1990**, 48, 223
- [7] Masui, M.; Kavakami, M.; Nakajima, M.; Hara, S.; Ito, H.; Ueda, M.; *Drug. Dev. Res.*, **1990**, 20, 453.
- [8] Quiroga, J.; Alvarado M.; Insuasty B.; and Moreno, R.; *J.Heterocyclic Chem.* **1999**, 36, 1311
- [9] Quiroga, J.; Cruz S.; Insuasty, B.; and Abonia, R.; *J.Heterocyclic Chem.* **2001**, 38, 53
- [10] Kabbe, H.J. Widdig, A. 1982. *Angew. Chem., Int. Ed. Engl.* 21, 247.
- [11] Jachak, M. N.; Avhale, A. B.; Ghotekar, B.K.; Kendre, D.B.; Toche, R.B. *J. Heterocyclic Chem* **2008**, 45, 1221
- [12] Welton, T. **1999**, *Chemical Review.* 99,2071.
- [13] Earle, M. J., Katdare, S. P., Seddon, K. R. **2000**, *Pure Appl.Chem.*72, 1391.
- [14] Formentin, P., Garcia, H., Leyva, A. **2004**, *J.Mol. Catal.A., Chem.*214,137.
- [15] Ranu, B. C., Jana, R. **2006**, *Eur. J. Org. Chem.*, 3767.
- [16] Li, S., Lin, H., Xie, S., Zhang, S., Xu, J. **2006**, *Org. Lett.* 8, 391.
- [17] Jiang, T., Gao, H., Han, B., Zhao, G., Chang, Y., Wu, W., Gao, L., Yang, G. **2004**, *Tetrahedron Lett.* 45, 2699.
- [18] Zhu, A., Jiang, T., Wang, D., Han, B., Liu, L., Haung, J., Zhang, J., Sun, D. **2005**, *GreenChem.* 7, 514.
- [19] Janus, E., Maciejewski, I. G., Skib, M. L., Pernak, J. **2006**, *Tetrahedron Lett.* 47, 4079.
- [20] Potewar, T. M., Siddiqui, S. A., Lahoti, R. J., Shrinivasan, K. V. **2007**, *Tetrahedron Lett.*48, 1721.