Asian Journal of Chemistry; Vol. 23, No. 3 (2011), 1273-1275

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

# Ionic Liquid, [bmim]Br, as An Efficient Promoting Medium for Synthesis of 2-Amino-3,5-dicarbonitrile-6-thiopyridines

A. DAVOODNIA[1], P. ATTAR[1,*], H. ESHGHI[2], A. MORSALI[1], N. TAVAKOLI-HOSEINI[1] and A. TAVAKOLI-NISHABURI[1]

[1]Department of Chemistry, Faculty of Sciences, Islamic Azad University-Mashhad Branch, Mashhad, Iran
[2]Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

*Corresponding author: Fax: +98 511 8424020; Tel: +98 511 8417015; E-mail: attar_paria@yahoo.com

(*Received*: 3 May 2010; *Accepted*: 8 November 2010) AJC-9285

A simple, efficient and rapid method for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridines through one-pot multi-component reaction of a variety of aryl aldehydes with malononitrile and thiophenol in the presence of ionic liquid 1-butyl-3-methylimidazolium bromide, [bmim]Br, as an efficient promoting medium without the use of any catalyst has been developed. This method has the advantages of good yields, milder reaction conditions, no catalyst and environmentally benign procedure.

**Key Words: [Bmim]Br, Ionic liquids, Multi-component reactions, 2-Amino-3,5-dicarbonitrile-6-thiopyridines.**

## INTRODUCTION

Multi-component reactions have recently received the attention of organic chemists because of the many advantages these reactions offered over conventional multi-step synthesis as well as their potential applications in medicinal chemistry for the generation of diverse scaffolds and combinatorial libraries for drug development[1-4]. In this type of reactions three or more components are reacted to form ideally one product, which contains the essential parts of all the initial reactants. Multicomponent reactions contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Therefore, the discovery for new multi-component reactions and improving the already known multi-component reactions are of considerable interest.

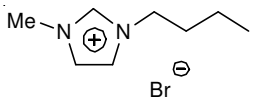
The presence of the pyridine ring system in a number of natural products, vitamins and pharmacologically significant molecules[5] has made it a prime target for scientific research. In particular, 2-amino-3,5-dicarbonitrile-6-thiopyridines exhibit diverse pharmacological activities and are useful as antiprion[6], antihepatitis B virus[7], antibacterial[8] and anti-cancer[9] agents. In addition, they serve as potassium channel openers for the treatment of urinary incontinence[10]. Recently, some of these compounds have been recognized as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia, asthma, kidney disease, epilepsy and cancer[11].

These compounds are generally synthesized *via* one-pot three-component condensation of an aldehyde, malononitrile and a thiol in the presence of several catalysts such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or triethylamine[12], piperidine[13], 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU)[14], silica nanoparticle[15], [bmim][OH][16], $ZnCl_2$[17] and $H_3BO_3$[18]. However, some of these methodologies encounter some limitations, such as long reaction times, unsatisfactory yields, harsh reaction conditions, requirement of expensive catalysts and hazardous organic solvents. Thus, alternative procedures with more general applicability, considerably faster reaction with high yields and environmentally friendly conditions are still in demand.

The development of environmentally friendly catalysts and solvents for organic chemistry is an area of considerable importance. From both economical and environmental points of view, the use of non-volatile solvents and non-metallic catalysts is very promising. In the last few years room temperature ionic liquids (RTILs), especially those based on 1,3-dialkylimidazolium cations[19], have been recognised as a possible environmentally benign alternative to chemical volatile solvents because of their unique properties, such as non-volatility, non-flammability and high thermal stability[20].

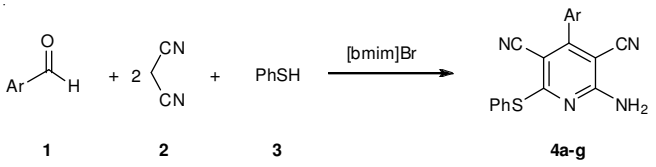
As part of our current studies on the development of new routes for the synthesis of organic compounds in ionic liquids[21-25], herein we wish to report a green and rapid methodology for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridines in ionic liquid 1-butyl-3-ethylimidazolium bro-

mide, [bmim]Br (Fig. 1) as an efficient promoting medium without the use of any catalyst (**Scheme-I**).




[bmim][Br]

Fig. 1. Ionic liquid structure




**Scheme-I:** Synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridines

## EXPERIMENTAL

All compounds were known and their physical and spectroscopic data were compared with those of authentic samples and found to be identical. [Bmim]Br was prepared according to the literature procedure[26]. Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The $^1$H NMR (500 MHz) spectra were recorded on Bruker DRX500 spectrometer.

**General procedure for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridines:** A mixture of aromatic aldehyde (2 mmol), malononitrile (4 mmol), thiophenol (2 mmol) and [bmim]Br (1.2 mmol) was heated on the oil bath at 120 ºC for a few minutes. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and then *t*-BuOH was added. The precipitated solid was filtered off, recrystallized from *t*-BuOH and washed with *n*-hexane to give compounds **4a-g** in good yields.

## RESULTS AND DISCUSSION

It is well-known that choosing an appropriate solvent and reaction temperature is crucially important for an efficient organic synthesis. To find the optimal conditions, the synthesis of 2-amino-4-(4-chlorophenyl)-3,5-dicarbonitrile-6-(thiophenyl)pyridine (**4d**) was selected as a model reaction. Therefore, a mixture of 4-chlorobenzaldehyde, malononitrile and thiophenol was heated under various reaction conditions. The corresponding results are summarized in Table-1. As shown in this table, at 110 ºC under solvent-free conditions and without the use of any catalyst no product could be detected even after 1 h (entry 7). Also, the reaction was carried out in various solvents (entries 1-6). As shown, no product could be detected in $CHCl_3$ and $CH_3CN$ as solvent (entries 1 and 2) and only trace amount of the product **4d** was obtained in EtOH or $H_2O$ (entries 3 and 4), while, in comparison to conventional solvents, good results were obtained in [bmim]Br (entries 5 and 6). The yield increased as the reaction temper-ature was raised and at 120 ºC the products **4d** was obtained in good yield. Subsequently, therefore, all reactions were carried out in [bmim]Br and at 120 ºC as optimal conditions.

TABLE-1
RESULTS OF THE SYNTHESIS OF COMPOUND **4d** IN DIFFERENT SOLVENTS

| Entry | Solvent | Reaction temp. (ºC) | Time (min) | Yield (%)* |
|---|---|---|---|---|
| 1 | $CHCl_3$ | Reflux | 60 | None |
| 2 | $CH_3CN$ | Reflux | 60 | None |
| 3 | EtOH | Reflux | 60 | Trace |
| 4 | $H_2O$ | Reflux | 60 | Trace |
| 5 | [bmim]Br | 85 | 30 | 74 |
| 6 | [bmim]Br | 120 | 6 | 82 |
| 7 | Solvent-free | 110 | 60 | None |

*Isolated yields.

In order to evaluate the generality of this model reaction we then prepared a range of 2-amino-3,5-dicarbonitrile-6-thiopyridines under the optimized reaction conditions. In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in good yields. The results are summarized in Table-2.

TABLE-2
SYNTHESIS OF 2-AMINO-3,5-DICARBONITRILE-6-THIOPYRIDINES[a]

| Entry | Ar | Products[b] | Time (min) | Yield[c] (%) | m.p. (ºC) | |
|---|---|---|---|---|---|---|
| | | | | | Found | Reported |
| 1 | $C_6H_5$ | **4a** | 12 | 75 | 210-212 | 216-218 [17] |
| 2 | 3-$BrC_6H_4$ | **4b** | 4 | 86 | 254-256 | 256-258 [16] |
| 3 | 4-$BrC_6H_4$ | **4c** | 5 | 78 | 250-252 | 255-257 [14] |
| 4 | 4-$ClC_6H_4$ | **4d** | 6 | 82 | 230-232 | 222-225 [16] |
| 5 | 4-$HOC_6H_4$ | **4e** | 5 | 84 | 306-308 | 314-316 [18] |
| 6 | 4-$MeOC_6H_4$ | **4f** | 5 | 79 | 247-249 | 242-243 [18] |
| 7 | 4-$MeC_6H_4$ | **4g** | 5 | 83 | 213-215 | 208-211 [16] |

[a]2 mmol aromatic aldehyde, 4 mmol malononitrile and 2 mmol thiophenol in 1.2 mmol [bmim]Br at 120 ºC. [b]All the products were characterized by $^1$H NMR and IR spectral data and comparision of their melting points with those of authentic samples. [c]Isolated yields.

## Conclusion

A very simple and efficient method is developed for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridines through one pot multi-component reaction of an aryl aldehyde, malononitrile and thiophenol in the presence of ionic liquid 1-butyl-3-methylimidazolium bromide, [bmim]Br, as an efficient promoting medium without the use of any catalyst. Compared with other methods, this new method has the advantages of easier workup, milder reaction conditions, no catalyst and a more environmentally benign procedure.

## REFERENCES

1. N.K. Terret, M. Gardner, D.W. Gordon, R.J. Kobylecki and J. Steele, *Tetrahedron*, **51**, 8135 (1995).
2. A. Dandia, R. Singh, P. Sarawgi and S. Khaturia, *Chin. J. Chem.*, **24**, 950 (2006).
3. L.A. Thomson and J.A. Ellman, *Chem. Rev.*, **96**, 555 (1996).
4. A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, **39**, 3168 (2000).

5. M. Balasubramanian and J.G. Keay, in eds.: In: A.R. Katritzky, C.W. Rees and E.V.F. Scriven, Comprehensive Heterocyclic Chemistry II, Pergamon Press: London, Vol. 5, Ch. 6, pp. 245-300 and references cited therein (1996).
6. (a) T.R.K. Reddy, R. Mutter, W. Heal, K. Guo, V.J. Gillet, S. Pratt and B. Chen, *J. Med. Chem*., **46**, 607 (2006); (b) B.C.H. May, J.A. Zorn, J. Witkop, J. Sherrill, A.C. Wallace, G. Legname, S.B. Prusiner and F.E. Cohen, *J. Med. Chem*., **50**, 65 (2007).
7. H. Chen, W. Zhang, R. Tam and A.K. Raney, PCT Int. Appl. WO 2005058315 A1 20050630 (2005).
8. S.B. Levy, M.N. Alekshun, B.L. Podlogar, K. Ohemeng, A.K. Verma, T. Warchol, B. Bhatia, T. Bowser and M. Grier, U.S. Patent, 2005124678 A1 20050609 (2005).
9. M.T. Cocco, C. Congiu, V. Lilliu and V. Onnis, *Eur. J. Med. Chem.*, **40**, 1365 (2005).
10. H. Harada, S. Watanuki, T. Takuwa, K. Kawaguchi, T. Okazaki, Y. Hirano and C. Saitoh, PCT Int. Int. WO 2002006237 A1 20020124 (2002).
11. B.B. Fredholm, A.P. Ijzerman, K.A. Jacobson, K.N. Klotz and J. Linden, *Pharmacol. Rev*., **53**, 527 (2001).
12. (a) N.M. Evdokimov, A.S. Kireev, A.A. Yakovenko, M.Y. Antipin, I.V. Magedov and A.J. Kornienko, *Org. Chem*., **72**, 3443 (2007); (b) N.M. Evdokimov, I.V. Magedov, A.S. Kireev and A. Konienko, *Org. Lett*., **8**, 899 (2006).
13. K. Guo, M.J. Thompson, T.R.K. Reddy, R. Mutter and B. Chen, *Tetrahedron*, **63**, 5300 (2007).
14. R. Mamgain, R. Singh and D.S. Rawat, *J. Heterocycl. Chem*., **46**, 69 (2009).
15. S. Banerjee and G. Sereda, *Tetrahedron Lett*., **50**, 6959 (2009).
16. B.C. Ranu, R. Jana and S. Sowmiah, *J. Org. Chem*., **72**, 3152 (2007).
17. M. Sridhar, B.C. Ramanaiah, C. Narsaiah, B. Mahesh, M. Kumaraswamy, K.K.R. Mallu, V.M. Ankathi and P.S. Rao, *Tetrahedron Lett*., **50**, 3897 (2009).
18. P.V. Shinde, S.S. Sonar, B.B. Shingate and M.S. Shingare, *Tetrahedron Lett*., **51**, 1309 (2010).
19. (a) J.D. Holbrey and K.R. Seddon, *J. Chem. Soc. Dalton Trans*, **13**, 2133 (1999); (b) J.G. Huddleston, A.E. Visser, W.M. Reichert, H.D. Willauer, G.A. Broker and R.D. Rogers, *Green Chem*., **3**, 156 (2001); (c) A.C. Cole, J.L. Jensen, I. Ntai, K.L.T. Tran, K.J. Weaver, D.C. Forbes and J.H. Davis Jr., *J. Am. Chem. Soc*., **124**, 5962 (2002); (d) L.C. Branco, J.N. Rosa, J.J.M. Ramos and C.A.M. Afonso, *Chem. Eur. J*., **8**, 3671 (2002).
20. (a) T. Welton, *Chem. Rev*., **99**, 2071 (1999); (b) P. Wasserscheid and W. Keim, *Angew. Chem. Int. Ed*., **39**, 3772 (2000); (c) J. Dupont, C.S. Consorti and J. Spencer, *J. Braz. Chem. Soc*., **11**, 337 (2000).
21. A. Davoodnia, M.M. Heravi, L. Rezaei-Daghigh and N. Tavakoli-Hoseini, *Monatsh. Chem*., **140**, 1499 (2009).
22. A. Davoodnia, M. Bakavoli, R. Moloudi, M. Khashi and N. Tavakoli-Hoseini, *Chin. Chem. Lett*., **21**, 1 (2010).
23. A. Davoodnia, M.M. Heravi, Z. Safavi-Rad and N. Tavakoli-Hoseini, *Synth. Commun*., **40**, 2588 (2010).
24. A. Davoodnia, M.M. Heravi, L. Rezaei-Daghigh and N. Tavakoli-Hoseini, *Chin. J. Chem*., **28**, 429 (2010).
25. A. Davoodnia, S. Allameh, A.R. Fakhari and N. Tavakoli-Hoseini, *Chin. Chem. Lett*., **21**, 550 (2010).
26. R.S. Varma and V.V. Namboodiri, *Chem. Commun*., **7**, 643 (2001).

**THE 3RD EUROPEAN PROCESS INTENSIFICATION CONFERENCE**

**20 — 23 JUNE, 2011**

**MANCHESTER, U.K.**

*Contact:*
Rosemary Cragg, Conference Officer, IChemE, Davis Building, Rugby, Warwickshire, CV21 3HQ U.K.
Tel: +44-(0)1788-578214, Fax: +44-(0)1788-560833,
E-mail:rcragg@icheme.org, web site http://www.icheme.org/EPIC2011/