Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 77 (10) 1345–1352 (2012)
JSCS–4356
UDC 547.747+542.913+547.53:
544.4:66–911.4+54.71
Original scientific paper

A clean and efficient L-proline-catalyzed synthesis of polysubstituted benzenes in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate

SHUBHA JAIN, BALWANT S. KESHWAL* and DEEPIKA RAJGURU

School of Studies in Chemistry, Vikram University, Ujjain, Madhya Pradesh-456010, India

(Received 11 December 2011, revised 20 June 2012)

Abstract: A clean and efficient synthesis of polysubstituted benzenes has been developed *via* sequential vinylogous Michael addition and nucleophilic cyclization reactions of arylethylidenemalonodinitriles with arylidenemalonodinitriles in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) employing L-proline as a catalyst.

Keywords: polysubstituted benzenes; organocatalysis; ionic liquids; green chemistry.

INTRODUCTION

Polysubstituted benzenes are very useful compounds in organic synthetic chemistry, natural product chemistry, medicinal chemistry and material science.[1] Consequently, enormous numbers of procedures have been developed for their synthesis. Electrophilic[2] or nucleophilic substitutions,[3] coupling reactions catalyzed by transition metals[4], and metalation functionalization reactions[5] are considered as traditional approaches. Later, benzannulation reactions including the [3+2+1] Dötz Reaction,[6] [4+2] cycloaddition,[7] [3+3] cyclocondensation,[8] [5+1] benzannulation of alkenoyl ketene-acetals and nitroalkane,[9] and [4+2] annulation strategy from the Baylis–Hillman Reaction[10] have been developed in recent years.

Milart *et al.* described piperidine-catalyzed cyclocondensations of arylethylidene and arylidenemalonodinitriles in acetonitrile.[11] Recently, Xue *et al.*[12] and Su *et al.*[13] reported base-catalyzed cyclocondensations of vinyl malononitriles and nitro-olefins. Xin *et al.*[14] prepared polysubstituted benzenes *via* sequential Michael addition, Knoevenagel condensation and nucleophilic cyclization reactions of chalcones with active methylene compounds in guanidinium ionic liquids. Very recently, Helmy *et al.*[15] achieved the synthesis of polyfunctionally-substituted benzenes by the reaction of the malononitrile dimer with enaminones

* Corresponding author. E-mail: bskeshwal2@gmail.com
doi: 10.2298/JSC111211067J

and arylidenemalononitrile in acetic acid in the presence of ammonium acetate. These approaches have received growing interest due to their short sequence and regioselectivity, however; it is still of prime interest and great importance to explore efficient and clean synthetic approaches.

In recent years, ionic liquids, due to their unique properties such as good solvating ability, high thermal stability, negligible vapour pressure, variable polarity, non-flammability and recyclability, have been widely used as "green" solvents for many organic reactions, including transition metal and bio-catalyzed reactions,[16] but they have not been frequently used as the media for organocatalyst catalyzed reactions. Organic reactions catalyzed by small molecule organocatalysts have become very attractive in recent years.[17–20] Quinine, ephedrine, 2-(*S*)-[(phenylamino)methyl]-4-(*S*)-hydroxypyrrolidine and 2-(*S*)-(diphenylhydroxymethyl)piperidine and its 1-t-butoxycarbonyl (1-Boc) derivatives have all been previously used as the catalysts for Michael additions, but they gave been only moderate enantiomeric excess (ee) values.[21–25] Loh *et al.*[26] described the excellent results observed for L-proline-catalyzed aldol reactions in imidazolium-based ionic liquids. Rasalkar very recently described the L-proline-catalyzed Michael addition of ketones to nitrostyrene.[27] In this study, several ionic liquids were tested and 1-(methoxyethyl)-3-methylimidazolium methanesulphonate ([MOEMIM]OMs) was found to be the best. In order to achieve good yields, it was necessary to prolong the reaction time up to 60 h and the catalyst loading had to be increased to 40 mol % to achieve 75 % ee. Hagiwara[28] described organocatalyst-catalysed additions of aliphatic aldehydes to methyl vinyl ketone in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF6]). 2-(*S*)-(Morpholinomethyl)pyrrolidine was found to be the best organocatalyst, but the yields of the product were only average with 11–51 % ee. Kotrusz[29] found that L-proline in ionic liquids is a very good catalyst for Michael addition of aliphatic aldehydes and ketones to β-nitrostyrenes. They also described L-proline-catalyzed Michael additions of thiophenols to α,β-unsaturated compounds in [bmim][PF_6].[30] Moreover, L-proline, a natural amino acid, is non-toxic, inexpensive and is available in very pure form.

The main aim of the current work was to explore the use of L-proline as a catalyst in ionic liquid media for Michael additions of arylethylidenemalonodinitriles to arylidenemalonodinitriles that could provide a clean synthetic route to polysubstituted benzenes.

RESULTS AND DISCUSION

When the reactions of arylethylidenemalonodinitriles **1** and arylidenemalonodinitrile **2** were performed in the presence of 10 mol % L-proline in [bmim][PF_6] at 60 °C, the polysubstituted benzene derivatives **3** were obtained in high yields.

In an initial study, the reaction of 2-(1-phenylethylidene)malononitrile (**1a**) and 2-(4-nitrobenzylidene)malononitrile (**2a**) was used as a model reaction to optimize the reaction conditions. The reaction was first performed in [bmim][PF_6] in the absence of L-proline. No reaction occurred at room temperature or at 60 °C. Similar reactions were then attempted in the presence of 5, 10 and 20 mol % of L-proline. The results from Table I (entries 4, 7 and 9) showed that 10 mol % L-proline at 60 °C in [bmim][PF_6] was sufficient to push the reaction forward. Higher loadings of the catalyst did not improve the reaction conditions greatly. To find the optimum reaction temperature, the reaction was first performed with 10 mol % L-proline at room temperature, which yielded only traces of the product, and then at 40, 60 and 80 °C, which resulted in the isolation of **3a** in 64, 76 and 72 % yields (Table I, entries 5–8), respectively. Thus, 10 mol % L-proline and a reaction temperature at 60 °C were the optimal conditions. Furthermore, to determine the most suitable media for the reaction, the model reaction was performed in various ionic liquids as well as in the conventional organic solvent ethanol (Table I, entries 10–14). The best results in terms of reaction time and yield were obtained in [bmim][PF_6].

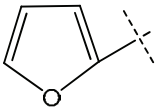
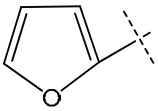
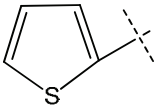
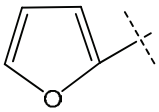
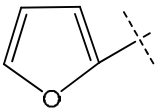
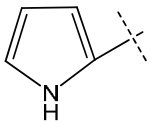
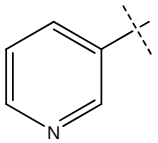
TABLE I. L-Proline-catalyzed synthesis of **3a** under different reaction conditions; r.t. – room temperature; [bmim][PF_6] – 1-butyl-3-methylimidazolium hexafluorophosphate; [bmim]Br – 1-butyl-3-methylimidazolium bromide; [hmim][PF_6] – 1-Hexyl-3-methylimidazolium hexafluorophosphate; [omim][BF_4] – 1-Octyl-3-methylimidazolium hexafluoroborate

Entry	Solvent	Amount of catalyst, mol %	*T* / °C	Time, h	Yield, %
1	[bmim][PF_6]	0	r.t.	10	0
2	[bmim][PF_6]	0	60	10	0
3	[bmim][PF_6]	5	r.t.	10	Trace
4	[bmim][PF_6]	5	60	10	43
5	[bmim][PF_6]	10	r.t.	10	Trace
6	[bmim][PF_6]	10	40	10	64
7	[bmim][PF_6]	10	60	4	76
8	[bmim][PF_6]	10	80	4	72
9	[bmim][PF_6]	20	60	4	78
10	[bmim][PF_6]	10	60	4	75
11	[bmim]Br	10	60	6	58
12	[hmim][PF_6]	10	60	6	61
13	[omim][BF_4]	10	60	4	72
14	EtOH	10	80	8	54

Having established the optimal conditions for the reaction, various kinds of arylethylidenemalonodinitriles **1** and arylidenemalonodinitriles **2** were reacted to give the corresponding polyfunctionalyzed benzene derivatives **3**, and representative examples are shown in Table II. All of compounds **1** and **2** gave the expected products in good to high yields under same reaction conditions, regardless of whether they bore electron-withdrawing groups or electron-donating groups.

Thus, it was found that the same product could be synthesized from different arylethylidene- and arylidenemalonodinitriles with no substantial difference in yields under the given reaction conditions (Table II, entries 1 and 2).

TABLE II. L-Proline-catalyzed synthesis of polysubstituted benzenes **3** in [bmim][PF_6]

Entry	Ar	Ar′	Product	Time, h	Yield, %	M.p. (Lit.), °C
1	C_6H_5	4-$NO_2C_6H_4$	**3a**	3.5	76	242 (244–246)[11]
2	4-$NO_2C_6H_4$	C_6H_5	**3a**	3.5	65	244 (244–246)[11]
3	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	**3b**	4	54	350 (352–353)[11]
4	C_6H_5	2-$CH_3OC_6H_4$	**3c**	3	85	166 (168–169)[14]
5	C_6H_5		**3d**	3.5	82	> 350
6	4-$O_2NC_6H_4$		**3e**	3	85	277–278
7	4-$O_2NC_6H_4$		**3f**	3	79	272–273
8			**3g**	3	84	318
9			**3h**	4	72	329
10			**3i**	4	79	315

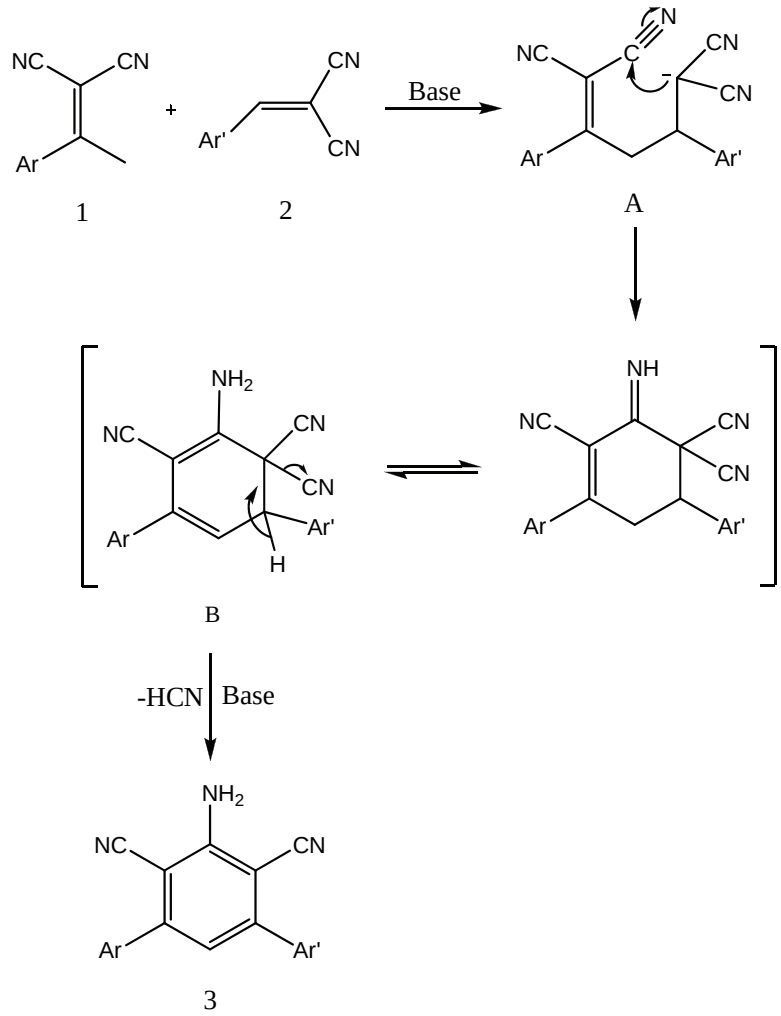
Furthermore, some heteroarylidenemalononitriles were reacted with aryl- or heteroarylethylidenemalononitriles under the same reaction conditions. Surprisingly, these reactions afforded the corresponding benzene derivatives containing heteroaromatic substituents in good yields (Table II, entries 5–10).

The success of the above reactions prompted an investigation of the recyclability of catalyst and ionic liquid. This study was realized using the reaction of **1a** and **2a** in [bmim][PF_6] as a model system. After completion of the reaction, the product was extracted with diethyl ether. The recovered ionic liquid containing L-proline was then used for the next reaction run. Again, the product **3a** was obtained in better yield. Following four consecutive reaction cycles there was a slight decrease in the yield (Table III).

TABLE III. Recycling of the catalyst and ionic liquid in the synthesis of **3a**

Run	1	2	3	4
Yield, %	86	84	82	78

Although the detailed mechanism of the above reaction has not yet been clarified, the formation of polysubstituted benzene derivatives **3** could be tentatively explained by the pathway presented in Scheme 1.



Scheme 1. Tentative pathway for the formation of the polysubstituted benzene derivatives **3**.

In the first step, adduct **A** is obtained according to the vinylogous Michael addition of **1** to arylidenemalononitrile. The addition is followed by the Thorpe

cyclization of the Michael product **A** to the cyclohexadiene system **B**.[11] The deprotonation of **B** with *N*-methylimidazole, already contained in imidazolium-based ionic liquids,[31] followed by the elimination of CN which may occur in the last step afforded the final product **3**. The HCN formed in the reaction is neutralized with the reaction medium that is basic in nature.[32] The neutralization of HCN with the reaction media causes a continuous decrease in the yields while recycling the catalyst contained in the ionic liquid.

The synthesis of **3a** was taken as a representative example to show the advantage of the method employed in this study over previously reported procedures. As shown in Table IV, the reaction catalyzed by L-proline in the ionic liquid [bmim][PF_6] gave a comparable yield and took a shorter time than the other method.

TABLE IV. Comparison of the present method with other reported protocols for the synthesis of **3a**

Entry	Catalyst	Conditions	Time, h	Yield, %
1	L-Proline	[bmim][PF_6], 60 °C	3.5	76[a]
2	Piperidine	CH_3CN, reflux	3	77[11]
3	–	Guanidinium ionic liquid, 60 °C	5	32[14]

[a]This work

CONCLUSIONS

In summary, a new efficient and clean method for the synthesis of polyfunctionalized benzenes has been established *via* sequential Michael addition and cyclocondensation of arylethylidenemalononitriles with arylidenemalononitriles using L-proline as a catalyst in an ionic liquid, [bmim][PF_6]. According to this methodology, a series of complex aryl compounds such as *m*-terphenyls and benzenes linked to heteroaromatics could be obtained in satisfactory yields. The simplicity, high yields, mild reaction conditions, easy work-up and reusable solvent and catalyst make it a preferred procedure for the preparation of polysubstituted benzenes.

EXPERIMENTAL

General

Chemicals were purchased from Merck and Sigma-Aldrich as "synthesis grade" and were used without further purification. Melting points were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on a Perkin-Elmer-1430 spectrophotometer using KBr pellets. The ^{1}H- and ^{13}C-NMR spectra were obtained at 400 MHz and 100 MHz, respectively, on a Bruker Avance WM-400 spectrometer using DMSO-d_6 as the solvent and TMS as an internal standard. The MS spectra were recorded on a Micromass ZMD ESI (70 eV) system. Elemental analysis was performed using a Carlo Erba-1108 analyzer.

Synthesis of the starting ylidenemalonodinitriles

The required arylidene- and arylethylidenemalonodinitriles were obtained *via* the Knoevenagel reaction of the corresponding aldehyde or ketone with malononitrile, as reported in the literature.[33]

*General procedure for the synthesis of polysubstituted benzenes **3***

To a glass vial charged with L-proline (10 mol %) were added [bmim][PF_6] (5 ml), arylethylidenemalononitrile **1** (1 mmol) and arylidenemalononitrile **2** (1 mmol). The reaction mixture was stirred at 60 °C for 3–4 h. After completion of the reaction (as monitored by TLC), the product was extracted with diethyl ether (4×15 mL) to give the ionic liquid containing L-proline. The recovered ionic liquid containing L-proline was then used for the next reaction run. The combined ether extracts were concentrated and chromatographed on a SiO_2 column using 8:2 hexane/ethyl acetate in all cases. The products were isolated as pure materials. The structures of the already known products were confirmed by their melting point and ^{1}H-NMR spectra and new compounds were fully characterized.

SUPPLEMENTARY MATERIAL

Analytic and spectral data of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgment. We thank the Director, SAIF, Punjab University, Chandigarh, for the NMR and MS spectral data.

И З В О Д

ЕФИКАСНА СИНТЕЗА ПОЛИСУПСТИТУИСАНИХ ДЕРИВАТА БЕНЗЕНА, КАТАЛИЗОВАНА L-ПРОЛИНОМ, У ЈОНСКОЈ ТЕЧНОСТИ [bmim][PF_6]

SHUBHA JAIN, BALWANT S. KESHWAL и DEEPIKA RAJGURU

[1]*School of Studies in Chemistry, Vikram University, Ujjain, Madhya Pradesh-456010, India*

Развијена је ефикасна синтеза полисупституисаних деривата бензена поступком винилне Мајклове адиције и реакције нуклеофилне циклизације арил-етилиденмалонодинитрила и арилиденмалонодинитрила, катализоване L-пролином, у јонској течности [bmim][PF_6].

(Примљено 11. децембра 2011, ревидирано 20. јуна 2012)

REFERENCES

1. a) D. Astruc, *Modern Arene Chemistry*, Wiley-VCH, Weinheim, Germany, 2002; b) J. Q. Wang, M. Gao, K. D. Miller, G. W. Sledge, Q. H. Zheng, *Bioorg. Med. Chem. Lett.* **16** (2006) 4102
2. a) G. Olah, *Friedel-Crafts and Related Reactions*, Vols. I–IV, Wiley Interscience, New York, 1963; b) D. E. Pearson, C. A. Buehler, *Synthesis* (1972) 533
3. a) M. B. Smith, J. March, *Advanced Organic Chemistry*, 5th ed., Wiley Interscience, New York, 2001, Ch. 13, p. 850; b) E. Buncel, J. M. Dust, F. Terrier, *Chem. Rev.* **95** (1995) 2261
4. J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **102** (2002) 1359
5. V. Snieckus, *Chem. Rev.* **90** (1990) 879

6. a) K. H. Dotz, P. Tomuschat, *Chem. Soc. Rev.* **28** (1999) 187; b) H. Wang, J. Huang, W. D. Wulff, A. L. Rheingold, *J. Am. Chem. Soc.* **125** (2003) 8980; c) A. V. Vorogushin, W. D. Wulff, H. Hansen, *J. Am. Chem. Soc.* **124** (2002) 6512
7. a) L. V. R. Bonaga, H. C. Zhang, A. F. Moretto, H. Ye, D. A. Gauthier, J. Li, G. C. Leo, B. E. Maryanoff, *J. Am. Chem. Soc.* **127** (2005) 3473; b) S. Saito, Y. Yamamoto, *Chem. Rev.* **100** (2000) 2901
8. a) P. Langer, G. Bose, *Angew. Chem. Int. Ed.* **42** (2003) 4033; b) A. R. Katritzky, J. Li, L. Xie, *Tetrahedron* **55** (1999) 8263
9. a) X. Bi, D. Dong, Q. Liu, W. Pan, L. Zhau, B. Li, *J. Am. Chem. Soc.* **127** (2005) 4578; b) O. Barun, S. Nandi, K. Panda, H. Ila, H. Junjappa, *J. Org. Chem.* **67** (2002) 5398
10. M. J. Lee, K. Y. Lee, S Gowrisankar, J. N. Kim, *Tetrahedron Lett.* **47** (2006) 1355
11. P. Milart, J. Wilamowski, J. J. Sepiol, *Tetrahedron* **54** (1998) 15643
12. D. Xue, J. Li, Z. T. Zhang, J. G. Deng, *J. Org. Chem.* **72** (2007) 5443
13. W. Su, K. Ding, Z. Chen, *Tetrahedron Lett.* **50** (2009) 636
14. X. Xin, Y. Wang, W. Xu, Y. Lin, H. Duan, D. Dong, *Green Chem.* **12** (2010) 893
15. N. M. Helmy, F. E. M. El-Baih, M. A. Al-Alshaikh, M. S. Moustafa, *Molecules* **16** (2011) 298
16. a) H. Olivier-Bourbigou, L. Magma, *J. Mol. Catal. A: Chem.* **419** (2002) 182; b) J. Dupont, R. F. de-Souza, P. A. Z. Suarez, *Chem. Rev.* **102** (2002) 3667; c) P. Wasserscheid, T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim, (2003); d) R. Sheldon, *Chem. Commun.* (2001) 2399; e) C. E. Song, *Chem. Commun.* (2004) 1033; f) J. S. Loh, L. C. Feng, H. Y. Yang, J. Y. Yang, *Tetrahedron Lett.* **43** (2002) 8741
17. B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **122** (2000) 2395
18. B. List, *Tetrahedron* **58** (2002) 5573
19. H. Grőger, J. Wilken, *Angew. Chem. Int. Ed.* **40** (2001) 529
20. P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **40** (2001) 3727
21. H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **103** (1981) 417
22. C. Agami, N. Platzer, C. Puchot, H. Sevestre, *Tetrahedron* **43** (1987) 1091
23. T. Mukaiyana, A. Ikegawa, K. Suzuki, *Chem. Lett.* (1981) 165
24. K. Suzuki, A. Ikegawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **55** (1982) 3277
25. S. Kobayashi, C. Ogawa, M. Kawamura, M. Sugiura, *Synlett* (2001) 983
26. J. S. Loh, L. C. Feng, H. Y. Yang, J. Y. Yang, *Tetrahedron Lett.* **43** (2002) 8741
27. M. S. Rasalkar, M. K. Potdar, S. S. Mohile, M. M. Salunkhe, *J. Mol. Catal., A* **235** (2005) 267
28. H. Hagiwara, T. Okabe, T. Hoshi, T. Suzuki, *J. Mol. Catal., A* **214** (2004) 167
29. P. Kotrusz, S. Toma, H. G. Schmalz, A. Adler, *Eur. J. Org. Chem.* (2004) 1577
30. P. Kotrusz, S. Toma, *ARKIVOC* (2006) 100
31. M. Meciarova, M. Cigan, S. Toma, A. Gaplovsky, *Eur. J. Org. Chem.* **26** (2008) 4408
32. HCN is among the most toxic and rapidly acting of all poisonous substances. Exposure to high doses may be followed by almost instantaneous collapse, rapid cessation of respiration and death. Readers are suggested to take all necessary precautions when working with this procedure.
33. a) D. Xue, Y. C. Chen, X. Cui, Q. W. Wang, J. Zhu, J. G. Deng, *J. Org. Chem.* **70** (2005) 3584; b) S. Suresh, S. Jagir, *Green Chem. Lett. Rev.* **2** (2009) 189; c) C. Mukhopadhyay, A. Datta, *Synth. Comm.* **38** (2008) 2103.