Facile and green method for the synthesis of 4-amino-1,2-dihydrobenzo [4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles catalysed by ammonium acetate

Lingjun Hu[a], Zhajun Zhan[a], Min Lei[b]* and Lihong Hu[a,b]

[a]*College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, P. R. China*

[b]*Shanghai Research Center for Modernization of Traditional Chinese Medicine, Shanghai Institute of Materia Medica, Shanghai 201203, P. R. China*

A facile and green method for the synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-6-carbonitrile derivatives has been developed by one-pot condensation of 2-aminobenzimidazole, aldehydes, and malononitrile catalysed by ammonium acetate in ethanol. The inexpensive and readily available catalyst and easy workup is environmentally friendly.

Keywords: 2-aminobenzimidazole, aldehydes, malononitrile, green chemistry, muti-component reactions

Multi-component reactions (MCRs) are significant and useful organic reactions, which refer to a chemical reaction where three or more compounds react to form a single product.[1–5] Recently, MCRs have become powerful tools in modern synthetic chemistry due to their efficiency and convenience in the construction of multiple new bonds in one-pot processes.[6–8] Efforts are being made to find and develop new MCRs.

Imidazo[1,2-*a*]pyrimidines and their analogues have a wide range of applications, such as benzodiazepine receptor agonists,[9] antiviral,[10] antitumor,[11] and antimicrobial agents.[12,13] Moreover, pyrimido[1,2-*a*]benzimidazoles represent a pharmaceutically important class of compounds because of their diverse range of biological activities.[14–16] Therefore, preparation of these heterocyclic compounds has gained great importance in organic synthesis.

In recent years, several methods have been reported for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives via multi-component condensations of 2-aminobenzimidazole, aldehydes, and malononitrile.[14–16] To improve the yields of this three-component condensation reaction, a number of catalysts and techniques, such as microwaves,[17–19] MgO,[20] C_5H_5N,[21] Et_3N,[22–24] Me_2NH,[23] and N_2H_4,[26] have been used. However, these methods are limited by drawbacks, such as long reaction times, poor yields, harsh reaction conditions or the use of toxic catalysts. Consequently, better conditions are required.

NH_4OAc is cheap, nontoxic, and stable and it is used widely in organic synthesis. Earlier work in our laboratory established that NH_4OAc can efficiently catalyse the multi-component condensation reaction of 4-hydroxyquinolin-2(1*H*)-one, aldehydes, and malononitrile.[27] Therefore, we investigated whether NH_4OAc could catalyse the condensation of 2-aminobenzimidazole, aldehydes, and malononitrile. Preliminary experiments revealed that the condensation of 2-aminobenzimidazole, aldehyde, and malononitrile can react smoothly to give benzo[4,5]imidazo[1,2-*a*]pyrimidine products in the presence of NH_4OAc in good yields. Hence, we now report a green, efficient, and rapid procedure for the one-pot synthesis of 4-amino-1,2-dihydro-benzo[4,5]imidazo[1,2-*a*]pyrimidine-6-carbonitrile derivatives by using NH_4OAc as the catalyst in excellent yields (Scheme 1).

Scheme 1

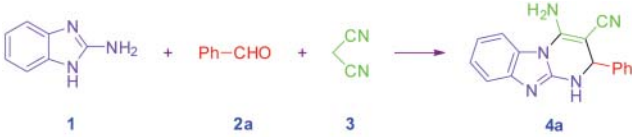
* Correspondent. E-mail: mlei@mail.shcnc.ac.cn

Firstly, the mixture of 2-aminobenzimidazole **1**, benzaldehyde **2a**, and malononitrile **3** was chosen as the model reaction to detect whether the use of NH_4OAc was efficient and the results are summarised in Table 1.

As shown in Table 1, only 35% yield of the corresponding product **4a** was obtained when the mixture of 2-aminobenzimidazole **1**, benzaldehyde **2a**, and malononitrile **3** was stirred under reflux temperature for 120 min in the absence of NH_4OAc (Table 1, entry 1). However, the yield was improved greatly (83%) when the reaction was carried out under similar conditions in the presence of 5 mol% NH_4OAc. This study demonstrated that NH_4OAc could catalyse the condensation of 2-aminobenzimidazole **1**, benzaldehyde **2a**, and malononitrile **3** for the synthesis of 4-amino-2-phenyl-1,2-dihydrobenzo[4,5] imidazo[1,2-*a*]pyrimidine-3-carbonitrile **4a** efficiently. Then, the amount of NH_4OAc was changed from 0 to 30 mol%, showing that yields of **4a** were improved as the amount of NH_4OAc increased from 0 to 10 mol%, and the yields were maintained as the amount of NH_4OAc increased from 10 to 30 mol%. Therefore, 10 mol% of NH_4OAc was considered to be the most suitable for efficient reaction.

Having established the optimised reaction conditions, we then successfully synthesised a variety of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **4** (Table 2). A series of aromatic aldehydes were selected to undergo the reaction in the presence of 10 mol% NH_4OAc in EtOH at the reflux temperature. As shown in Table 2, benzaldehydes carrying either electron-donating or electron-withdrawing substituents could react efficiently with excellent

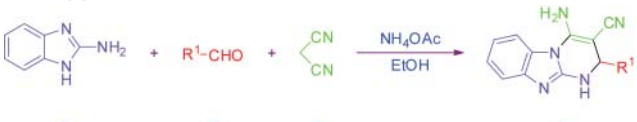
Table 1 Optimisation of the condensation of 2-aminobenzimidazole **1**, benzaldehyde **2a**, and malononitrile **3**[a]



Entry	NH_4OAc/mol%)	Time/min	Yield of **4a**/%[b]
1	none	120	35
2	3	60	60
3	5	40	83
4	10	30	91
5	20	30	91
6	30	30	88

[a]Conditions: 2-aminobenzimidazole **1** (5 mmol), benzaldehyde **2a** (5.5 mmol), malononitrile **3** (5.5 mmol), EtOH (10 mL), reflux temperature.
[b]Isolated yield.

Table 2 Synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **4**[a]



Entry	R^1	Time/min	Product **4**	Yield/%[b]
1	C_6H_5 **2a**	30	**4a**	91
2	4-MeC_6H_4 **2b**	30	**4b**	88
3	4-$MeOC_6H_4$ **2c**	60	**4c**	86
4	4-ClC_6H_4 **2d**	20	**4d**	93
5	3-ClC_6H_4 **2e**	20	**4e**	94
6	2-ClC_6H_4 **2f**	20	**4f**	94
7	4-HOC_6H_4 **2g**	60	**4g**	80
8	4-NCC_6H_4 **2h**	20	**4h**	92
9	4-Pyridyl **2i**	20	**4i**	88

[a] Conditions: 2-aminobenzimidazole **1** (5 mmol), aldehyde **2** (5.5 mmol), malononitrile **3** (5.5 mmol), EtOH (10 mL), reflux temperature.
[b] Isolated yield.

yields (80–94%) (Table 2, entries 1–8). Therefore, the effect of the substituents on the benzene ring showed no obvious effect on this conversion. As shown in Table 2, this experimental procedure has the ability to tolerate a variety of functional groups, such as methyl, methoxyl, hydroxyl, cyano, and halides. Furthermore, 4-pyridinecarboxaldehyde could react smoothly to give the corresponding products **4i** in good yields (88%) (Table 2, entry 9). Note that all of the condensations were complete within 60 min and the products **4** could be obtained simply by filtration from the reaction medium.

In conclusion, a NH_4OAc-catalysed synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **4** from 2-aminobenzimidazole **1**, aldehydes **2**, and malononitrile **3** has been described. The catalyst NH_4OAc is not only readily available and cheap, but also much safer and more practical in comparison to the reported catalysts. Undoubtedly, all the advantages of the reactions make this procedure a useful addition to the present methodologies for heterocyclic synthesis.

Experimental

Melting points were measured by a WRS-1B micromelting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX 300 instrument or Bruker AMX 400 instrument using solvent peaks as DMSO-d_6 solutions. HRESIMS were determined on a Micromass Q-Tof Global mass spectrometer and ESIMS were run on a Bruker Esquire 3000 Plus Spectrometer. TLC was performed on GF254 silica gel plates (Yantai Huiyou Inc., China).

Synthesis of **4a**–**i***; general procedure*

A mixture of aldehyde **2** (5.5 mmol), malononitrile **3** (5.5 mmol), and NH_4OAc (10 mol%) in EtOH (10 mL) was stirred for 5 min. Then 2-aminobenzimidazole **1** (5 mmol) was added and mixture was heated to reflux for an appropriate time (Table 2). After completion of the reaction (TLC), the solid was collected by filtration, purified via recrystallisation from ethanol to give 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **4**.

4-Amino-2-(4-hydroxyphenyl)-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**4g**): Yield: 93%; white solid; m.p. 215 °C (Dec.). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.07 (s, 1H), 6.70 (d, *J* = 8.0 Hz, 2H), 6.75 (s, 2H), 6.97 (t, *J* = 7.6 Hz, 1H), 7.02–7.12 (m, 3H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 8.45 (brs, 1H), 9.44 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 52.93, 62.54, 112.34, 115.25, 115.95, 119.19, 119.70, 123.20, 127.27, 129.29, 133.13, 143.63, 148.91, 151.73, 157.06. MS (ESI): *m/z* = 304 ([M + H]$^+$). HRMS (ESI) calcd for $C_{17}H_{14}N_5O$ [M + H]$^+$ 304.1193; found 304.1187.

4-Amino-2-(4-cyanophenyl)-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**4h**): Yield: 92%; yellow solid; m.p. 215 °C (Dec.). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.36 (s, 1H), 6.94 (s, 2H), 6.99 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 8.71 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 52.70, 60.73, 110.57, 112.50, 116.18, 118.58, 118.93, 120.02, 123.44, 126.87, 129.20, 132.80, 143.48, 148.23, 149.37, 151.47. MS (ESI): *m/z* = 313 ([M + H]$^+$). HRMS (ESI) calcd for $C_{18}H_{13}N_6$ [M + H]$^+$ 313.1196; found 313.1189.

4-Amino-2-(pyridin-4-yl)-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**4i**): Yield: 88%; yellow solid; m.p. 215 °C (Dec.). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.28 (s, 1H), 6.95 (s, 2H), 6.99 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.21–7.27 (m, 3H), 7.61 (d, *J* = 7.8 Hz, 1H), 8.49–8.55 (m, 2H), 8.72 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 52.04, 60.35, 112.52, 116.22, 118.96, 120.05, 120.79, 123.46, 129.20, 143.48, 149.48, 150.09, 151.31, 151.39. MS (ESI): *m/z* = 289 ([M + H]$^+$). HRMS (ESI) calcd for $C_{16}H_{13}N_6$ [M + H]$^+$ 289.1196, found 289.1192.

This work was supported by the National Natural Science Foundation of China (grants 30925040, 81102329), the Chinese National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program" (grant 2011ZX09307-002-03), and the Science Foundation of Shanghai (grant 12XD14057).

Received 13 September 2012; accepted 26 October 2012
Paper 1201514 doi: 10.3184/174751912X13528011362074
Published online: 5 December 2012

References

1 I. Ugi, A. Domling and B. Werner, *J. Heterocycl. Chem.*, 2000, **37**, 647.
2 G. Shanthi and P.T. Perumal, *Tetrahedron Lett.*, 2009, **50**, 3959.
3 S. Shirakawa and S. Kobayashi, *Org. Lett.*, 2006, **8**, 4939.
4 H. Zhang, Z. Zhou, Z. Yao, F. Xu and Q. Shen, *Tetrahedron Lett.*, 2009, **50**, 1622.
5 M.C. Bagley and M.C. Lubinu, *Synthesis*, 2006, 1283.
6 M.M. Heravi, B. Baghernejad and H.A. Oskooie, *Tetrahedron Lett.*, 2009, **50**, 767.
7 X. Huang and T. Zhang, Tetrahedron Lett., 2009, **50**, 208.
8 S. Cui, J. Wang and Y. Wang, *Org. Lett.*, 2008, **10**, 1267.
9 G. Trapani, M. Franco, A. Latrofa, G. Genchi, V. Iacobazzi, C.A. Ghiani, E. Maciocco and G. Liso, *Eur. J. Med. Chem.*, 1997, **32**, 83.
10 A. Gueiffieri, Y. Blache, J.P. Chapat, E.M.E. Elhakmaoui, G. Andrei, R. Snoeck, E. De Clercq, O. Chavignon, J.C. Teulade and F. Fauvelle, *Nucleosides Nucleotides*, 1995, **14**, 551.
11 L. Dalla-Via, O. Gia, S.M. Magno, A. Da Settimo, A.M. Marini, G. Primofiore, F. Da-Settimo and S. Salaerno, *Il Farmaco.*, 2001, **65**, 159.
12 Y. Rival, G. Grassy and G. Michel, *Chem. Pharm. Bull.*, 1992, **40**, 1170.
13. Y. Rival, G. Grassy, A. Tauduo and R. Ecalle, *Eur. J. Med. Chem.*, 1991, **26**, 13.
14 J.E. De-Araujo, J.P. Huston and M. Brandao, *Eur. J. Pharmac.*, 2001, **432**, 43.
15 N. Wonda and Z. Michal, *Arch. Pharm.*, 1999, **337**, 249.
16 G. Trapani, M. Farnco, A. Latrofa, G. Genchi and V. Iacobazzi, *Eur. J. Med. Chem.*, 1997, **32**, 83.
17 A. Dandia, R. Singh, A.K. Jain and D. Singh, *Synth. Commun.*, 2008, **38**, 3543.
18 G. Liu, Q. Shao, S. Tu, L. Cao, C. Li, D. Zhou and B. Han, *J. Heterocycl. Chem.*, 2008, **45**, 1127.
19 A. Dandia, P. Sarawgi, A.L. Bingham, J.E. Drake, M.B. Hursthouse, M.E. Light and R. Ratnani, *J. Chem. Res.*, 2007, 155.
20 H. Sheibani and F. Hassani, *J. Heterocycl. Chem.*, 2011, **48**, 915.
21 Y.R. Ibrahim, *J. Chem. Res.*, 2009, **8**, 495
22 M.D. Wendt, A. Kunzer, R.F. Henry, J. Cross and T.G. Pagano, *Tetrahedron Lett.*, 2007, **48**, 6360.
23 B. Insuasty, A. Salcedo, R. Abonia, J. Quiroga, M. Nogueras and A. Sanchez, *Heterocycl. Commun.*, 2002, **8**, 287.
24 F.A. Bassyouni and I.I. Ismail, *Afinidad.*, 2011, **58**, 375.
25 S.A. Komykhov, S.K. Ostras, A.R. Kostanyan, S.M. Desenko, D.V. Orlov and H. Meier, *J. Heterocycl. Chem.*, 2005, **42**, 1111.
26 E.I. El-Desoky, S. Aboul-Fetouh and M.A. Metwally, *J. Chem. Technol. Biotechnol.*, 1996, **67**, 153.
27 M. Lei, L. Ma and L. Hu, *Tetrahedron Lett.*, 2011, **52**, 2597.