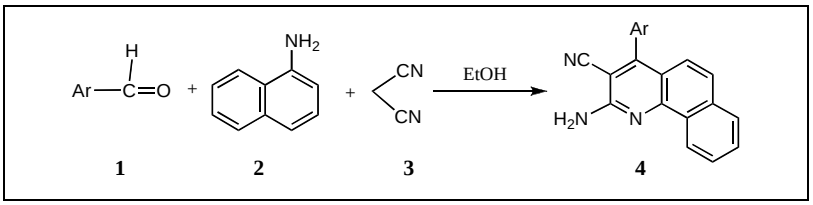
A Facile One-pot Synthesis of 2-Amino-4-arylbenzo[*h*]quinoline-3-carbonitrile Derivatives without Catalyst

Shujiang Tu,* Runhong Jia, Junyong Zhang, Yan Zhang, Bo Jiang.

Department of Chemistry, Xuzhou Normal University, Key Laboratory of Biotechnology on Medical Plant, Xuzhou; Jiangsu, 221116, P. R. China

Received July 6, 2006



A series of 2-amino-4-arylbenzo[*h*]quinoline-3-carbonitrile derivatives were synthesized by one-pot condensation of aromatic aldehyde, α-naphthylamine and malononitrile in ethanol without catalyst. This multicomponent reaction has the notable advantages of short route, high yield and convenient operation.

J. Heterocyclic Chem., **44**, 735 (2007).

INTRODUCTION

The rapid assembly of molecular diversity is an important goal of synthetic organic chemistry and one of the key paradigms of modern drug discovery. One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials. In addition to the intrinsic atom economy and selectivity underlying such reactions, simpler procedures and equipment, time and energy savings, as well as environmental friendliness have all led to a sizable effort to design and implement MCRs in both academia and industry [1-4].

The quinoline ring system exists in natural products, especially alkaloids [5-7], and much attention has still been paid to the synthesis of quinoline derivatives because of their pharmacological properties. Especially, the benzoquinoline skeleton is found in many substances with industrial applications or biological activity [8-10]. Furthermore, they are effective against infectious microbes, have produced some improvements in Alzheimer's disease, and display good antipsychotic activity. Besides, benzoquinoline derivatives have marked anti-Parkinson activity and are used in the chemotherapy of the mind [11].

Synthesis of compounds of benzoquinoline series has been well documented [12-15]. Anderson and co-workers synthesized benzoquinoline by the condensation of malononitrile with aromatic aldehydes and alkyl ketones in the presence of ammonium acetate [16,17]. Chkanikov and co-workers synthesized dihydrobenzoquinoline by α-naphthylamine and 1,1-dicyano-2,2-bis(trifluoromethyl) ethylene [18]. However, the synthesis of 4-arylbenzoquinoline derivatives using aromatic aldehyde, naphthylamine and malononitrile as starting materials has not been reported yet. In order to enlarge the libraries of 4-arylbenzo[*h*]quinoline and explore the new classes of biological active compounds, herein we report a facile three-component one-pot synthesis of 2-amino-4-arylbenzo[*h*]quinoline-3-carbonitrile derivatives by the reaction of aromatic aldehyde, α-naphthylamine and malononitrile in ethanol (Scheme 1).

RESULTS AND DISCUSSION

Choosing an appropriate solvent is of importance for successful synthesis. In order to search for the optimum solvent, the reaction of 4-chlorophenyl aldehyde **1a**, α-naphthylamine **2** and malononitrile **3** was examined using glycol, DMF, glacial acetic acid and ethanol as solvent respectively at 80 °C. The results were summarized in Table 1, which showed that the reaction using ethanol as solvent resulted in higher yield and shorter reaction time (Entry 4 of Table 1). Therefore, ethanol was chosen as the optimum solvent.

The products were synthesized by equimolecular amounts of aromatic aldehyde, α-naphthylamine and malononitrile without catalyst in ethanol. After refluxing for 5-8 hours at 80 °C, the 2-amino-4-arylbenzo[*h*]quinoline-3-carbonitrile derivatives were obtained in high yields (80-96%). The results are listed in Table 2.

This reaction may occur *via* a condensation, elimination, addition, cyclization, dehydrogenization mechanism (Scheme 2). The condensation between aromatic aldehyde **1** and α-naphthylamine **2** gives Schiff base **5** which further undergoes *in situ* Michael addition reaction with malononitrile **3** to yield intermediate **6**, followed by the elimination of α-naphthylamine to form the intermediate product **7** which undergoes intermolecular cyclization, isomerisation, dehydrogenization, finally affords **4**.

Table 1

Solvent Optimization of synthesis **4a** at 80 °C

Entry	Solvent	Time (h)	Y ield (%)[a]
1	glycol	6	67
2	HOAc	7	72
3	DMF	7	74
4	EtOH	5	85

[a] Yields of isolated compounds.

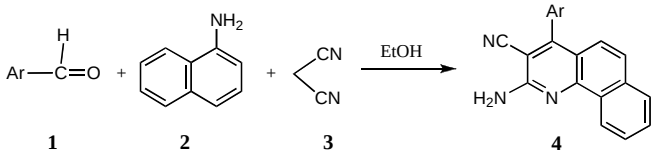
Table 2

Synthesis of **4**

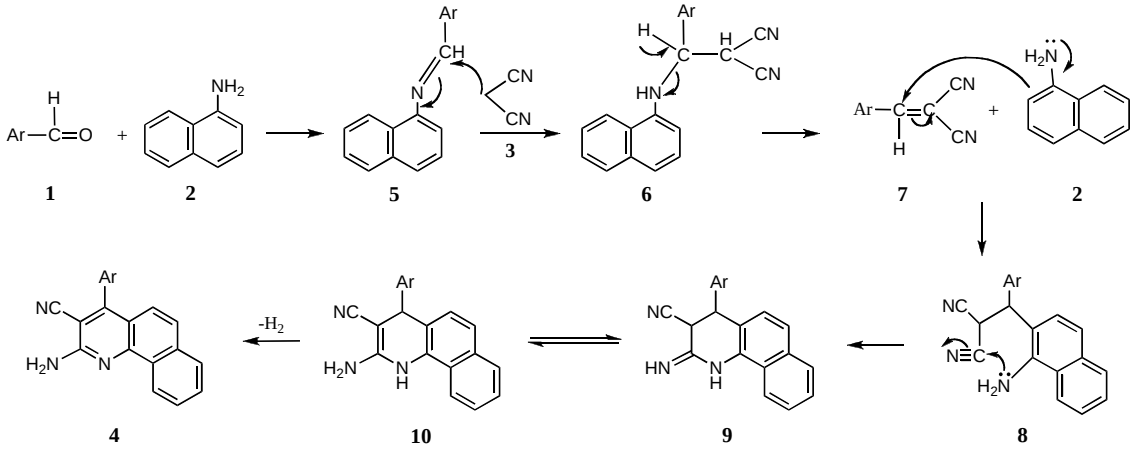
Product	Ar	Time (h)	Yield (%)[a]	Mp (℃)[b]
4a	4-ClC_6H_4	5	85	236-239
4b	4-BrC_6H_4	8	80	244-246
4c	4-FC_6H_4	5	89	194-196
4d	2-ClC_6H_4	7	92	239-242
4e	3,4-$Cl_2C_6H_3$	5	90	246-249
4f	2,4-$Cl_2C_6H_3$	6	90	298-300
4g	4-$NO_2C_6H_4$	8	95	247-248
4h	3-$NO_2C_6H_4$	8	95	280-283
4i	3-NO_2-4-OHC_6H_3	5	96	273-274

[a] Yields of isolated compounds; [b] Melting points are uncorrected.

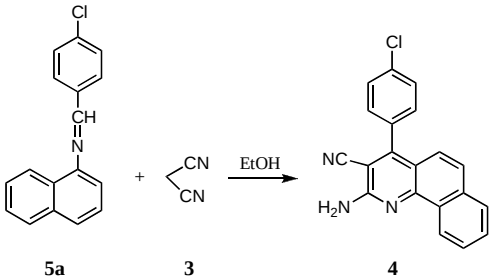
Scheme 1



Scheme 2



Scheme 3



To test the mechanism described above, the reaction of Schiff base **5a** and malononitrile **3** was carried out in EtOH under identical conditions (Scheme 3). The target compound **4a** was obtained with yield similar to the one-pot reaction. However, when the reaction of the intermediate product **7a** and α-naphthylamine **2** was carried out in EtOH under identical conditions, the yield was lower than the one-pot reaction. This result supported the proposed mechanism.

The procedure is easy to carry out and the workup procedure is simple. In this experiment, we found that this

protocol could be applied to aromatic aldehydes with electron-withdrawing groups, but not to aromatic aldehydes with electron-donating groups. Therefore, we concluded that the electronic nature of the substituent of aldehyde has an effect on this reaction. In order to obtain 4-unsubstituted benzo[*h*]quinoline and 4-alkyl benzo[*h*]-quinoline, the aromatic aldehyde was replaced by formaldehyde and aliphatic aldehydes (such as pentanal and butyraldehyde), unfortunately, the anticipated product were not obtained. When the α-naphthylamine was replaced by β-naphthylamine prepared by the reaction of aromatic aldehyde and malononitrile under the same reaction conditions, unfortunately, the anticipated result were not attained.

In conclusion, we have disclosed a facile method for the synthesis of benzo[*h*]quinoline-3-carbonitrile derivatives. Although the reaction has some limitations, it offered a new method with the notable advantages of short route, high yield and easy workup procedure for the synthesis of benzoquinoline scaffold.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a TENSOR 27 spectrometer in KBr. ^{1}H NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using DMSO-d_6 as solvent and TMS as internal standard. Elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument.

General procedure for 2-amino-4-arylbenzo[*h*]quinoline-3-carbonitrile derivatives (4). A mixture of the appropriate aromatic aldehyde **1** (2 mmol), α-naphthylamine **2** (2 mmol), malononitrile **3** (2 mmol) was refluxed in ethanol (8 mL) and stirred at 80 °C (oil bath temperature) for 5-8 hours in a ventilating arrangement. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature, after 8 hours, filtered to give the crude product, which was further purified by recrystallization from EtOH (**4a**-**4i**). All the products were characterized by IR, ^{1}H NMR and elemental analysis.

2-Amino-4-(4-chlorophenyl)benzo[*h*]quinoline-3-carbonitrile (4a). This compound was obtained as yellow solid (alcohol); ir (potassium bromide): 3482, 3376, 2219, 1628, 1506, 1450, 1419, 1291, 1090, 1014, 840, 823, 768 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.04 (d, 1H, J = 8.0 Hz, ArH), 7.92 (d, 1H, J = 7.6 Hz, ArH), 7.76-7.69 (m, 4H, ArH), 7.24 (s, 2H, NH_2), 7.19 (t, 3H, J = 8.8 Hz, ArH), 7.16 (d, 1H, J = 8.8 Hz, ArH). *Anal.* Calcd. for $C_{20}H_{12}ClN_3$: C, 72.84; H, 3.67; N, 12.74. Found: C, 72.91; H, 3.72; N, 12.81.

2-Amino-4-(4-bromophenyl)benzo[*h*]quinoline-3-carbonitrile (4b). This compound was obtained as yellow solid (alcohol); ir (potassium bromide): 3487, 3376, 2218, 1627, 1505, 1449, 1419, 1391, 1290, 1238, 1073, 1010, 836, 822, 800, 766 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.04 (d, 1H, J = 8.0 Hz, ArH), 7.92 (d, 1H, J = 7.6 Hz, ArH), 7.85 (d, 2H, J = 8.4 Hz, ArH), 7.75-7.72 (m, 2H, ArH), 7.57-7.50 (m, 3H, ArH), 7.24 (s, 2H, NH_2), 7.16 (d, 1H, J = 8.8 Hz, ArH). *Anal.* Calcd. for $C_{20}H_{12}BrN_3$: C, 64.19; H, 3.23; N, 11.23. Found: C, 64.25; H, 3.31; N, 11.29.

2-Amino-4-(4-fluorophenyl)benzo[*h*]quinoline-3-carbonitrile (4c). This compound was obtained as yellow solid (alcohol); ir (potassium bromide): 3488, 3375, 2219, 1628, 1507,1450, 1420, 1405, 1294, 1228, 1160, 1096, 848, 823, 802, 770 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.05 (d, 1H, J = 8.0 Hz, ArH), 7.92 (d, 1H, J = 7.2 Hz, ArH), 7.76-7.68 (m, 2H, ArH), 7.63-7.46 (m, 5H, ArH), 7.20 (s, 2H, NH_2), 7.17 (d, 1H, J = 8.8 Hz, ArH). *Anal.* Calcd. for $C_{20}H_{12}FN_3$: C, 76.67; H, 3.86; N, 13.41. Found: C, 76.70; H, 3.81; N, 13.49.

2-Amino-4-(2-chlorophenyl)benzo[*h*]quinoline-3-carbonitrile (4d). This compound was obtained as yellow solid (alcohol); ir (potassium bromide): 3488, 3352, 2230, 1627, 1507, 1451, 1417, 1405, 1296, 1142, 1050, 826, 801, 768, 758 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.04 (d, 1H, J = 7.6 Hz, ArH), 7.92 (d, 1H, J = 7.2 Hz, ArH), 7.78-7.55 (m, 7H, ArH), 7.31 (s, 2H, NH_2), 6.93 (d, 1H, J = 9.2 Hz, ArH). *Anal.* Calcd. for $C_{20}H_{12}ClN_3$: C, 72.84; H, 3.67; N, 12.74. Found: C, 72.89; H, 3.59; N, 12.84.

2-Amino-4-(3,4-dichlorophenyl)benzo[*h*]quinoline-3-carbonitrile (4e). This compound was obtained as yellow solid (alcohol); ir (potassium bromide): 3489, 3369, 2221, 1626, 1506, 1453, 1422, 1406, 1361, 1294, 1253, 1159, 1130, 1031, 923, 879, 827, 816, 802, 766 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.04 (d, 1H, J = 7.6 Hz, ArH), 7.94-7.92 (m, 2H, ArH), 7.91 (s, 1H, ArH), 7.78-7.55 (m, 2H, ArH), 7.58-7.56 (m, 2H, ArH), 7.28 (s, 2H, NH_2), 7.16 (d, 1H, J = 9.2 Hz, ArH). *Anal.* Calcd. for $C_{20}H_{11}Cl_2N_3$: C, 65.95; H, 3.04; N, 11.54. Found: C, 65.87; H, 3.12; N, 11.66.

2-Amino-4-(2,4-dichlorophenyl)benzo[*h*]quinoline-3-carbonitrile (4f). This compound was obtained as yellow solid (alcohol); ir (potassium bromide): 3478, 3349, 2229, 1626, 1499, 1450, 1421, 1409, 1382, 1294, 1139, 1099, 1048, 826, 800, 764 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.03 (s, 1H, ArH), 7.92 (s, 1H, ArH), 7.81-7.74 (m, 5H, ArH), 7.58 (d, 1H, J = 7.2 Hz, ArH), 7.36 (s, 2H, NH_2), 6.96 (d, 1H, J = 6.4 Hz, ArH). *Anal.* Calcd. for $C_{20}H_{11}Cl_2N_3$: C, 65.95; H, 3.04; N, 11.54. Found: C, 65.85; H, 3.18; N, 11.67.

2-Amino-4-(4-nitrophenyl)benzo[*h*]quinoline-3-carbonitrile (4g) This compound was obtained as yellow solid (alcohol); ir (potassium bromide): 3487, 3376, 2218, 1628, 1505, 1450, 1420, 1405, 1349, 1295, 1265, 860, 801, 770 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.05 (d, 1H, J = 7.6 Hz, ArH), 8.49 (d, 2H, J = 8.8 Hz, ArH), 7.94-7.87 (m, 3H, ArH), 7.76-7.72 (m, 2H, ArH), 7.57 (d, 1H, J = 8.8 Hz, ArH), 7.33 (s, 2H, NH_2), 7.09 (d, 1H, J = 9.2 Hz, ArH). *Anal.* Calcd. for $C_{20}H_{12}N_4O_2$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.66; H, 3.48; N, 16.39.

2-Amino-4-(3-nitrophenyl)benzo[*h*]quinoline-3-carbonitrile (4h). This compound was obtained as yellow solid (alcohol); ir (potassium bromide): 3489, 3372, 2218, 1612, 1505, 1451, 1407, 1348, 1293, 1245, 1146, 1086, 884, 807, 769 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.05 (d, 1H, J = 7.6 Hz, ArH), 8.50-8.44 (m, 2H, ArH), 8.05 (d, 1H, J = 8.0 Hz, ArH), 7.97 (s, 1H, ArH), 7.95-7.92 (m, 1H, ArH), 7.78-7.70 (m, 2H, ArH), 7.57 (d, 1H, J = 9.2 Hz, ArH), 7.32 (s, 2H, NH_2), 7.14 (d, 1H, J = 8.8 Hz, ArH). *Anal.* Calcd. for $C_{20}H_{12}N_4O_2$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.64; H, 3.59; N, 16.48.

2-Amino-4-(4-hydroxy-3-nitrophenyl)benzo[*h*]quinoline-3-carbonitrile (4i). This compound was obtained as yellow solid (alcohol); ir (potassium bromide): 3487, 3368, 3267, 2220, 1625, 1508, 1452, 1411, 1365, 1320, 1248, 1167, 1081, 838,

807, 764 cm^{-1}; ^1H nmr (DMSO-d_6): δ 11.59 (s, 1H, OH), 9.03 (d, 1H, J = 7.6 Hz, ArH), 8.10 (s, 1H, ArH), 7.93 (d, 1H, J = 7.6 Hz, ArH), 7.76-7.69 (m, 3H, ArH), 7.58 (d, 1H, J = 9.2Hz, ArH), 7.37 (d, 1H, J = 8.8 Hz, ArH), 7.26 (d, 1H, J = 7.2 Hz, ArH), 7.24 (s, 2H, NH_2). *Anal*. Calcd. for $C_{20}H_{12}N_4O_3$: C, 67.41; H, 3.39; N, 15.72. Found: C, 67.49; H, 3.31; N, 15.68.

Acknowledgments. We are grateful to the financial support from the National Natural Science Foundation of China (No. 20672090), Natural Science Foundation of the Jiangsu Province (No. BK2006033). Six Kinds of Professional Elite Foundation of the Jiangsu Province (No. 06-A-039).

REFERENCES AND NOTES

[1] Ramón, D. J.; Miguel, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602.

[2] Orru, R. V. A.; Greef, M. *de Synthesis*, **2003**, 1471.

[3] Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screening*, **2001**, *4*, 1.

[4] Weber, L.; Illgen, K.; Almstetter, M. *Synlett*, **1999**, 366.

[5] Kametani, T.; Kasai, H. In *Studies in Natural Products Chemistry*, Atta-ur-Rahman, Ed, Elsevier Scientific Publishing Co.: Amsterdam, 1989, Vol 3, p385.

[6] Yates, F. S. In *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W. Ed, Pergamon Press, Oxford, UK, 1984, Vol 2, p511.

[7] Sainsbury, M. In *Rodd's Chemistry of Carbon Compounds*, Coffey, S. Ed, Elsrvier Scientific Publishing Co.: Amsterdam, 1978, Part G, p171.

[8] Newkome, G. R. Paudler, W. W. *Contemporary Heterocyclic Chemistry. Syntheses, Reactions, and Applications*, Wiley: New York, 1982, p200.

[9] Gilchrist, T. L. *Heterocyclic Chemistry*, 2nd Ed, Longman Scientific & Technical: Essex, UK, 1992, p152.

[10] Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*, 3rd Ed, Chapman & Hall: London, 1995, p120.

[11] Campos, P. J.; Añón, E.; Carmen, M. M.; Tan, C. Q.; Rodríguez, M. A. *Tetrahedron*, **1998**, *54*, 6929.

[12] Kozlov, N. G.; Basalaeva, L. I. Russian *J. Org. Chem.*, **2003**, *39*, 718.

[13] Kozlov, N. G.; Sauts, R. D.; Gusak, K. N. Russ. *J. Org. Chem.* **2000**, *36*, 531.

[14] Otto, H. H.; Rinus, O.; Schmelz, H. *Monatsh. Chem.* **1979**, *110*, 115.

[15] Komarov, K. V.; Chkanikov, N. D.; Sereda, S. V.; Antipin, M. Yu.; Struchkov, Yu. T.; Kolomiets, A. F.; Fokin, A. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1988**, *8*, 1917.

[16] Kambe, S.; Saito, K. *Synthesis,* **1980**, 366.

[17] Anderson, D. R.; Stehle, N. W.; Kolodziej, S. A.; Reinhard, E. J.; PCT Int. Appl. 2004, WO 2004055015 A1 20040701, *Chem. Abstr.*, **2004**, *141*, 89018.

[18] Komarov, K. V.; Chkanikov, N. D.; Galakhov, M. V.; Kolomiets, A. F.; Fokin, A. V. *J. Fluorine Chem.* **1990**, *47*, 59.