Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient and Facile Synthesis of 3-Amino-1-aryl-9H-fluorene-2,4-dicarbonitrile Under Solvent-Free Conditions

Liangce Rong [a b], Hongxia Han [a], Hong Jiang [b] & Shujiang Tu [a b]

[a] College of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, China

[b] Key Laboratory of Biotechnology for Medicinal Plant, Xuzhou, Jiangsu, China

Version of record first published: 04 Sep 2009

To cite this article: Liangce Rong, Hongxia Han, Hong Jiang & Shujiang Tu (2009): Efficient and Facile Synthesis of 3-Amino-1-aryl-9H-fluorene-2,4-dicarbonitrile Under Solvent-Free Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:19, 3493-3499

To link to this article: http://dx.doi.org/10.1080/00397910902779298

Synthetic Communications®, 39: 3493–3499, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902779298

Taylor & Francis
Taylor & Francis Group

Efficient and Facile Synthesis of 3-Amino-1-aryl-9*H*-fluorene-2,4-dicarbonitrile Under Solvent-Free Conditions

Liangce Rong,[1,2] Hongxia Han,[1] Hong Jiang,[2] and Shujiang Tu[1,2]
[1]College of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, China
[2]Key Laboratory of Biotechnology for Medicinal Plant, Xuzhou, Jiangsu, China

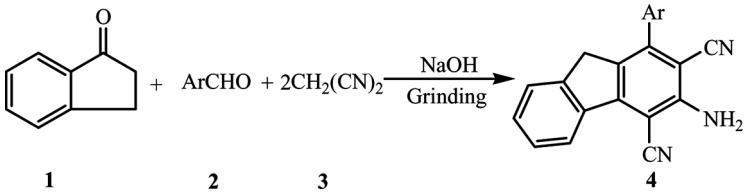
Abstract: A versatile and efficient route to 3-amino-1-aryl-9*H*-fluorene-2,4-dicarbonitrile via multicomponent reactions of 1-indanone, aromatic aldehydes, and malononitrile under solvent-free conditions using NaOH as the catalyst is described. This method provides several advantages over alternative procedures such as mild, solvent-free conditions at ambient temperature and direct isolation of the products in good yields.

Keywords: Fluorene, grinding, multicomponent reactions, solvent-free, synthesis

In this new century, green chemistry has become a major driving force for organic chemists to develop environmentally benign routes to a myriad of materials.[1] One of the green synthetic methods, solvent-free organic synthesis, has garnered much attention from organic chemists. This method has many advantanges, such as high efficiency and selectivity, easy separation and purification, and mild reaction conditions, and these benefit industry as well as the environment.[2]

Multicomponent reactions, an important class of organic tandem reactions, are one-pot processes with at least three components that form

Received April 28, 2008.
Address correspondence to Liangce Rong, College of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, China. E-mail: lcrong2005@yahoo.com



Scheme 1. The reaction of 1-indanone, aromatic aldehydes, and malononitrile under solvent-free conditions.

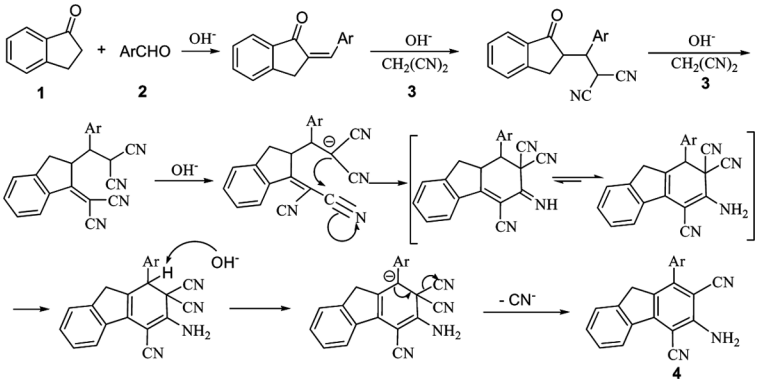
a single product, which incorporates most or even all of the starting materials.[3] The huge interest for such multicomponent reactions during the recent years has been oriented toward developing combinatorial chemistry procedures because of the high efficiency and convenience of these reactions in comparison with multistage procedures.

In recent years, we have synthesized several compounds using this technique.[4] Herein, we report the preparation of 3-amino-1-aryl-9*H*-fluorene-2,4-dicarbonitrile derivatives under solvent-free conditions.

Fluorene and fluorene derivatives are important compounds and have different types of biological activities, such as anti-inflammatory[5] and antitumor activites.[6] The literature reports that the tetrahydrobenzo[*a*]-fluorine compounds also inhibit bone loss or bone resorption.[7] Recently, we found an efficient and facile method to synthesize this compound by a multicomponent reaction under solvent-free conditions. 1-Indanone **1**, aromatic aldehydes **2**, and malononitrile **3** were blended together in a mortar and ground at room temperature (Scheme 1). The reaction completed within a very short time (1–3 min), and a series of 3-amino-1-aryl-9*H*-fluorene-2,4-dicarbonitrile derivatives could be gained with good yields. The results of the reaction are listed in Table 1. The structures of the

Table 1. Synthetic results of compounds **4**

Entry	Ar	Time (min)	Product	Yield (%)	Mp (°C)
1	4-$CH_3C_6H_4$	2	**4a**	81	269–270
2	4-$CH_3OC_6H_4$	2	**4b**	80	215–217
3	3,4-$(CH_3O)_2C_6H_3$	3	**4c**	75	219–221
4	4-FC_6H_4	2	**4d**	82	266–268
5	4-BrC_6H_4	3	**4e**	78	246–248
6	4-ClC_6H_4	2	**4f**	83	259–260
7	2-ClC_6H_4	2	**4g**	80	293–294
8	3-ClC_6H_4	2	**4h**	76	263–265
9	2,4-$Cl_2C_6H_3$	1	**4i**	87	265–267
10	3,4-$Cl_2C_6H_3$	1	**4j**	77	277–279



Scheme 2. Plausible mechanism of 3-amino-1-aryl-9*H*-fluorene-2,4-dicarbonitrile formation.

products were confirmed on the basis of infrared (IR), ^{1}H NMR spectroscopic data, and elemental analysis, and the formation of compound **4** could be explained by a possible mechanism presented in Scheme 2.

In conclusion, we have developed a rapid and highly efficient method for the synthesis of 3-amino-1-aryl-9*H*-fluorene-2,4-dicarbonitrile via the reaction of different aromatic aldehydes, 1-indanone, and malononitrile under solvent-free conditions. Particularly valuable features of this method include the greater yields of the products, mild reaction conditions, and reduced environmental impact, which make it a useful and attractive process for the synthesis of these important compounds.

EXPERIMENTAL

General Procedure

Melting points were uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr. ^{1}H NMR spectra were obtained in dimethylsulfoxide (DMSO)-d_6 solution with Me_4Si as internal standard using a Bruker 400-MHz spectrometer. Elemental analyses were carried out using a Perkin-Elmer 240 II analyzer.

General Procedure for the Syntheses of 3-Amino-1-aryl-9*H*-fluorene-2,4-dicarbonitrile

The general procedure is as follows: 1-indanone **1** (2 mmol), aromatic aldehyde **2** (2 mmol), malononitrile **3** (5 mmol), and NaOH (0.2 g) were

added to a mortar. The mixture was ground with a pestle at room temperature. The reaction was completed within 1–3 min, and the reaction mixture was poured into water. The product was filtered, dried, and recrystallized from 95% ethanol.

Data

3-Amino-1-*p*-tolyl-9*H*-fluorene-2,4-dicarbonitrile (**4a**)

Mp: 269–270°C. IR (KBr) *v*: 3470, 3372, 3234, 3036, 2894, 2208, 1632, 1564, 1516, 1476, 1447, 1398, 1376, 1305, 1267, 1186, 1155, 1100, 826, 758, 726 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 2.42 (3H, s, CH_3), 3.70 (2H, s, CH_2), 6.73 (2H, s, NH_2), 7.38 (2H, d, $J = 8.0$ Hz, ArH), 7.48 (2H, d, $J = 8.0$ Hz, ArH), 7.53 (2H, t, $J = 7.2$ Hz, ArH), 7.63 (1H, d, $J = 6.8$ Hz, ArH), 8.35 (1H, d, $J = 7.6$ Hz, ArH). Anal. calcd. for $C_{22}H_{15}N_3$: C, 82.22; H, 4.70; N, 13.08. Found: C, 82.40; H, 4.63; N, 13.01.

3-Amino-1-(4-methoxyphenyl)-9*H*-fluorene-2,4-dicarbonitrile (**4b**)

Mp: 215–217°C; IR (KBr) *v*: 3469, 3346, 3232, 2931, 2836, 2215, 2180, 1638, 1610, 1546, 1513, 1460, 1394, 1305, 1277, 1253, 1175, 1104, 1032, 829, 755, 723 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.72 (2H, s, CH_2), 3.81 (3H, s, CH_3O), 6.71 (2H, s, NH_2), 6.96 (2H, d, $J = 8.4$ Hz, ArH), 7.12 (2H, d, $J = 8.4$ Hz, ArH), 7.33 (2H, d, $J = 8.0$ Hz, Hz, ArH), 7.64 (1H, d, $J = 6.8$ Hz, ArH), 8.35 (1H, d, $J = 7.6$ Hz, ArH). Anal. calcd. for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.46. Found: C, 78.48; H, 4.55; N, 12.26.

3-Amino-1-(3,4-dimethoxyphenyl)-9*H*-fluorene-2,4-dicarbonitrile (**4c**)

Mp: 219–221°C; IR (KBr) *v*: 3480, 3355, 3234, 2939, 2852, 2211, 2182, 1638, 1570, 1544, 1519, 1451, 1421, 1308, 1258, 1240, 1157, 1136, 1022, 811, 758, 721 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.77 (2H, s, CH_2), 3.81 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.71 (2H, s, NH_2), 7.20 (1H, s, ArH), 7.52 (2H, t, $J = 8.0$ Hz, ArH), 7.58 (1H, d, $J = 8.0$ Hz, ArH), 7.65 (1H, d, $J = 6.8$ Hz, ArH), 8.23 (1H, d, $J = 8.4$ Hz, ArH), 8.36 (1H, d, $J = 8.0$ Hz, ArH). Anal. calcd. for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66. N, 11.44. Found: C, 75.38; H, 4.60; N, 11.38.

3-Amino-1-(4-fluorophenyl)-9*H*-fluorene-2,4-dicarbonitrile (**4d**)

Mp: 266–268°C (lit.[8] 264–266°C); IR (KBr) *v*: 3458, 3364, 3250, 2942, 2817, 2211, 1641, 1602, 1561, 1541, 1513, 1475, 1456, 1304, 1228, 1157, 1100, 844, 756, 720 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.71 (2H, s, CH_2), 6.79 (2H, s, NH_2), 7.42 (2H, t, $J = 8.8$ Hz, ArH), 7.54 (2H, dd $J = 7.2$ Hz, $J = 8.8$ Hz, ArH), 7.65 ~ 7.68 (3H, m, ArH), 8.36 (1H, d, $J = 8.0$ Hz, ArH). Anal. calcd. for $C_{21}H_{12}FN_3$: C, 77.53; H, 3.72; N, 12.92. Found: C, 77.72; H, 3.65; N, 12.83.

3-Amino-1-(4-bromophenyl)-9*H*-fluorene-2,4-dicarbonitrile (**4e**)

Mp: 246–248°C (lit.[8] 257–259°C); IR (KBr) *v*: 3464, 3361, 3230, 2928, 2840, 2218, 1633, 1575, 1559, 1494, 1476, 1449, 1394, 1375, 1303, 1264, 1156, 1078, 1010, 830, 755, 720 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.71 (2H, s, CH_2), 6.82 (2H, s, NH_2), 7.53 (2H, t, $J = 7.2$ Hz, ArH), 7.56 (2H, d, $J = 8.4$ Hz, ArH), 7.64 (1H, d, $J = 6.8$ Hz, ArH), 7.78 (2H, d, $J = 8.4$ Hz, ArH), 8.36 (1H, d, $J = 7.2$ Hz, ArH). Anal. calcd. for $C_{21}H_{12}BrN_3$: C, 65.30; H, 3.13; N, 10.88. Found: C, 65.48; H, 3.05; N, 10.76.

3-Amino-1-(4-chlorophenyl)-9*H*-fluorene-2,4-dicarbonitrile (**4f**)

Mp: 259–260°C (lit.[8] 275–277°C); IR (KBr) *v*: 3464, 3361, 3229, 2938, 2842, 2217, 1633, 1576, 1560, 1493, 1477, 1449, 1393, 1374, 1302, 1263, 1155, 1078, 1010, 830, 755, 720 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.70 (2H, s, CH_2), 6.81 (2H, s, NH_2), 7.52 (2H, t, $J = 6.8$ Hz, ArH), 7.56 (2H, d, $J = 8.4$ Hz, ArH), 7.63 (1H, d, $J = 7.2$ Hz, ArH), 7.78 (2H, d, $J = 8.4$ Hz, ArH), 8.36 (1H, d, $J = 6.8$ Hz, ArH). Anal. calcd. for $C_{21}H_{12}ClN_3$: C, 73.79; H, 3.54; N, 12.29. Found: C, 73.58; H, 3.61; N, 12.40.

3-Amino-1-(2-chlorophenyl)-9*H*-fluorene-2,4-dicarbonitrile (**4g**)

Mp: 293–294°C; IR (KBr) *v*: 3404, 3358, 3250, 2841, 2821, 2212, 2181, 1621, 1597, 1570, 1542, 1521, 1507, 1488, 1447, 1436, 1398, 1308, 1267, 1156, 1101, 785, 753, 720 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.54 (2H, dd, $J_1 = 22.4$ Hz, $J_2 = 22.4$ Hz, CH_2), 6.88 (2H, s, NH_2), 7.51–7.61 (5H, m, ArH), 7.64 (1H, d, $J = 7.2$ Hz, ArH), 7.71 (1H, d, $J = 7.6$ Hz, ArH), 8.37 (1H, d, $J = 7.6$ Hz, ArH). Anal. calcd. for $C_{21}H_{12}ClN_3$: C, 73.79; H, 3.54; N, 12.29. Found: C, 73.56; H, 3.63; N, 12.38.

3-Amino-1-(3-chlorophenyl)-9*H*-fluorene-2,4-dicarbonitrile (**4h**)

Mp: 263–265°C; IR (KBr) *v*: 3462, 3356, 3237, 2941, 2837, 2213, 1635, 1561, 1542, 1501, 1487, 1474, 1448, 1307, 1266, 1259, 1101, 801, 748, 723 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.72 (2H, s, CH_2), 6.81 (2H, s, NH_2), 7.52 (1H, d, $J = 7.2$ Hz, ArH), 7.57 (2H, d, $J = 8.0$ Hz, ArH), 7.62 (2H, d, $J = 6.8$ Hz, ArH), 7.66 (1H, d, $J = 6.8$ Hz, ArH), 7.72 (1H, s, ArH), 8.37 (1H, d, $J = 6.8$ Hz, ArH). Anal. calcd. for $C_{21}H_{12}ClN_3$: C, 73.79; H, 3.54; N, 12.29. Found: C, 73.90; H, 3.48; N 12.20.

3-Amino-1-(2,4-dichlorophenyl)-9*H*-fluorene-2,4-dicarbonitrile (**4i**)

Mp: 265–267°C (lit.[8] 267–269°C); IR (KBr) *ν*: 3467, 3363, 3242, 2216, 1714, 1635, 1572, 1560, 1485, 1444, 1382, 1306, 1262, 1100, 801, 751, 717 cm^{-1};^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.56 (2H, s, CH_2), 6.91 (2H, s, NH_2), 7.51–7.61 (5H, m, ArH), 7.92 (1H, d, $J = 2.0$ Hz, ArH), 8.34 (1H, d, $J = 7.2$ Hz, ArH). Anal. calcd. for $C_{21}H_{11}Cl_2N_3$: C, 67.04; H, 2.95; N, 11.17. Found: C, 67.22; H, 2.88; N, 11.09.

3-Amino-1-(3,4-dichlorophenyl)-9*H*-fluorene-2,4-dicarbonitrile (**4j**)

Mp: 277–279°C; IR (KBr) *ν*: 3456, 3361, 3251, 2890, 2202, 1640, 1601, 1564, 1514, 1476, 1451, 1303, 1226, 1154, 842, 756 cm^{-1};^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.71 (2H, s, CH_2), 6.76 (2H, s, NH_2), 7.36–7.66 (6H, m, ArH), 8.36 (1H, d, $J = 7.2$ Hz, ArH). Anal. calcd. for $C_{21}H_{11}Cl_2N_3$: C, 67.04; H, 2.95; N, 11.17. Found: C, 67.20; H, 2.90; N, 11.11.

ACKNOWLEDGMENTS

We thank the Natural Science Foundation of Jiangsu Education Department (No. 08KJB150017) and the PeiYu Foundation (No. 07PYL06) of Xuzhou Normal University for financial support.

REFERENCES

1. Anastas, P.; Williamson, T. *Green Chemistry: Frontiers in Benign Chemical Synthesis and Procedure*; Oxford Science Publications, New York, 1998.
2. Tanaka, K.; Toda, F. Solvent-free organic synthesis. *Chem. Rev.* **2000**, *100*, 1025–1074.

3. (a) Hulme, C.; Gore, V. Multi-component reactions: Emerging chemistry in drug discovery from xylocain to crixivan. *Curr. Med. Chem.* **2003**, *10*, 51–80; (b) Orru, R. V. A.; de Greef, M. Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. *Synthesis* **2003**, 1471–1499; (c) Domling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3220; (d) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. Strategies for heterocyclic construction via novel multicomponent reactions based on isocyanides and nucleophilic carbenes. *Acc. Chem. Res.* **2003**, *36*, 899–907; (e) Zhu, J. Recent developments in the isonitrile-based multicomponent synthesis of heterocycles. *Eur. J. Org. Chem.* **2003**, *7*, 1133–1144; (f) Domling, A. Recent advances in isocyanide-based multicomponent chemistry. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306–313.
4. (a) Rong, L. C.; Li, X. Y.; Wang, H. Y.; Shi, D. Q.; Tu, S. J. An efficient and facile synthesis of 2-amino-4,6-diarylbenzene-1,3-dicarbonitrile and 1,2-dihydro-2-oxo-4,6-diaryl-pyridine-3-carbonitrile under solvent-free conditions. *Chem. Lett.* **2006**, *35*, 1314–1315; (b) Rong, L. C.; Wang, H. Y.; Shi, J. W.; Yang, F.; Yao, H.; Tu, S. J.; Shi, D. Q. An efficient and facile procedure for the synthesis of 4,6-diaryl-2(1*h*)-pyridones under solvent-free conditions. *J. Heterocyclic Chem.* **2007**, *44* (10), 1505–1508; (c) Rong, L. C.; Han, H. X.; Yang, F.; Yao, H.; Jiang, H.; Tu, S. J. An efficient one-pot synthesis of 2-amino-4,6-diarylbenzene-1,3-dicarbonitrile under solvent-free conditions. *Synth. Commun.* **2007**, *37* (21), 3767–3772.
5. Ishihara, T.; Kakuta, H.; Moritani, H.; Ugawa, T.; Sakamoto, S.; Tsukamoto, S. I.; Yanagisawa, I. Syntheses and biological evaluation of novel quinuclidine derivatives as squalene synthase inhibitors. *Bioorg. Med. Chem.* **2003**, *11*, 2403–2414.
6. Skalova, L.; Nobilis, M.; Szotakova, B.; Kondrova, E.; Savlik, M.; Wosol, V.; Pichard, G. L.; Maser, E. Carbonyl reduction of the potential cytostatic drugs benfluron and 3,9-dimethoxy-benfluron in human in vitro. *Biochem. Pharm.* **2002**, *64*, 297–305.
7. Bryant, H. U.; Cullinan, G. J. Preparation of tetrahydrobenzo[*a*]fluorene compounds for inhibiting bone loss or bone resorption. US patent 5821253 A 13, 1998; *Chem. Abstr.* **1998**, *129*, 302558.
8. Wang, X. S.; Zhang, M. M.; Li, Q.; Yao, C. S.; Tu, S. J. An improved and clean procedure for the synthesis of one-donor poly-acceptors systems containing 2,6-dicyanoamine moiety in aqueous media catalyzed by TEBAC in the presence and absence of K_2CO_3. *Tetrahedron* **2007**, *63*, 5265–5273.