Microwave Assisted One-pot Synthesis of 2-Amino-4*H*-chromenes and Spiropyrano[2,3-*d*]pyrimidine

Mahmoud, Alaa F.*[a] Abd El-Latif, Fathy F.[b] Ahmed, Amira M.[b]

[a] *Faculty of Pharmacy and Pharmaceutical Industries, Sinai University, El-Areesh, North Sinai, Egypt*
[b] *Department of Chemistry, Faculty of Science, El Minia University, El Minia, Egypt*

A convenient and efficient method using microwave assisted one pot synthesis reactions for synthesis of 4*H*-benzo[*f*]chromenes by the reaction of aromatic aldehydes with a mixture of malononitrile and naphthols was examined. The synthesis of spiropyrano[2,3-*d*]pyrimidines by the reaction of isatin with malononitrile and barbituric acid and/or thiobarbituric acid was investigated. The versatility of the method was also examined through the reaction of aromatic aldehydes and malononitrile with various reagents.

Keywords microwave, 2,7-dihydroxynaphthalene, malononitrile, 2-aminochromene, spiropyrano[2,3-*d*] pyrimidine

Introduction

2-Aminochromenes are an important class of heterocyclic compounds having important biological activities. During the last decade, such compounds have shown interesting pharmacological properties including, antimicrobial,[1] antiviral,[2,3] mutagenicity,[4] antiproliferative,[5] sex hormone,[6] antitumor,[7] cancer therapy,[8,9] and central nervous system activities.[10] 2-Aminochromenes were also used as biodegradable agrochemicals and components of many natural products.[11-14]

Recently, several procedures for the preparation of 2-aminochromenes have been described.[15,16] Various catalysts such as piperidine,[17,18] morpholine,[19] CTACI (cetyltrimethylammonium chloride),[20] TEBA (triethylbenzylammonium chloride),[21] and alumina[22] have been used for this preparation. However, most of the reported methods require prolonged reaction time, stoichiometric reagents, toxic solvents but generate only moderate yields of the product.

The development of an efficient methodology of preparing 2-aminochromenes is highly essential. The most straightforward synthesis of this heterocyclic system involves three-component coupling of aromatic aldehyde, malononitrile and activated phenol catalyzed by a base.

With the increasing public concern over environmental degradation, the use of environmentally benign solvents like water and solvent-free reactions represents very powerful green chemical technology procedures from both the economical and synthetic point of view. They have many advantages, such as reduced pollution, lower cost and simplicity in processing, which are beneficial to the industry as well as to the environment.

Microwave heating has been known for accelerating the organic reactions.[23-26] Cyclocondensation reactions in "dry media" leading to heterocyclic systems have been performed under microwave irradiation.[27-31] The reactions were carried out in a neat or solvent-free state under microwave irradiation help to generate products not attainable through classical heating methods.

Experimental

All melting points were measured with a Gallenkamp melting point apparatus and uncorrected. ^{1}H NMR were recorded in DMSO with Varian EM-390 and Brokers MW 400 spectrometers at ambient temperature. Chemical shifts are relative to TMS. IR spectra were registered with a Shimadzu 400 spectrometer in KBr pellets. Mass spectra (EI=70 eV) were recorded directly with a Finnigan 50 spectrometer. Elemental analysis was carried out at the Micro-analytical Laboratories of the Faculty of Science, Cairo University.

The maximum power of microwave irradiation was optimized by carrying out the same reaction at different Watt powers. Microwave radiations at 300 W gave the highest yield, and therefore microwave power of 300 W was chosen as the optimum power.

General procedure for the synthesis of 4*H*-benzo[*f*]-chromene 4a—4d

An equimolar mixture of an aldehyde **1a**—**1c**, malononitrile **2a** and a naphthol **3a**, **3b** with a few drops of TEA was thoroughly mixed and irradiated at 300 W in a Samsung M9245 microwave for 1—3 min (the reactions were monitored by TLC). Then, the reaction mixture was cooled, triturated with methanol and the

* E-mail: afmahmoud@su.edu.eg, afmahmoud@yahoo.com; drfathyfahim@yahoo.com
Received April 14, 2009; revised May 20, 2009; accepted June 25, 2009.

 © 2010 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

solid formed was collected by filtration and crystallized from the appropriate solvent.

2-Amino-3-cyano-6-hydroxy-4-phenyl-4*H*-benzo[*f*]chromene (4a) Pale green solid, yield 82%, m.p. 295—297 ℃ (from DMF); ^{1}H NMR δ: 4.93 (s, 1H, H-1), 6.92 (br, 2H, NH_2), 6.82—7.97 (m, 10H, Ar-H); 9.83 (s, 1H, OH); IR (KBr) v: 3492 (O—H); 3376, 3279 (NH_2), 2192 (CN) cm^{-1}; MS *m/z* (%): 314 (M^+, 23). Anal. calcd for $C_{20}H_{14}N_2O_2$ (314.34): C 76.42, H 4.49, N 8.91; found C 76.61, H 4.32, N 8.75.

2-Amino-3-cyano-4-(2-chlorophenyl)-6-hydroxy-4*H*-benzo[*f*]chromene (4b) Buff solid, yield 75%, m.p. 260—262 ℃ (decomp., from toluene/methanol); ^{1}H NMR δ: 5.52 (s, 1H, H-4), 6.83 (br, 2H, NH_2), 6.89—7.45 (m, 9H, ArH), 9.92 (s, 1H, OH); IR (KBr) v: 3490 (O—H), 3380, 3256 (NH_2), 2196 (CN) cm^{-1}; MS *m/z* (%): 348 (M^+, 90), 350 (M^++2, 28). Anal. calcd for $C_{20}H_{13}ClN_2O_2$ (348.78): C 68.87, H 3.76, N 8.03, Cl 10.16; found C 68.77, H 3.65, N 8.10, Cl 10.26.

2-Amino-3-cyano-4-(4-chlorophenyl)-6-hydroxy-4*H*-benzo[*f*]chromene (4c) Buff solid, yield 75%, m.p. 286—288 ℃ (decomp., from toluene/methanol); ^{1}H NMR δ: 5.09 (s, 1H, H-4), 6.90 (br, 2H, NH_2), 6.89—7.87 (m, 9H, ArH), 9.90 (s, 1H, OH-9); IR (KBr) v: 3495 (O—H), 3370, 3260 (NH_2), 2190 (CN) cm^{-1}; MS *m/z* (%): 348 (M^+, 91), 350 (M^++2, 29). Anal. calcd for $C_{20}H_{13}ClN_2O_2$ (348.78): C 68.87, H 3.76, N 8.03, Cl 10.16; found C 68.77, H 3.65, N 8.10, Cl 10.26.

2-Amino-3-cyano-4-(2-chlorophenyl)-4*H*-benzo[*f*]chromene (4d) Colorless solid, yield 83%, m.p. 256—258 ℃ (from dioxane); ^{1}H NMR δ: 4.85 (s, 1H, H-4), 6.55 (br, 2H, NH_2), 6.65—7.75 (m, 10H, ArH); IR (KBr) v: 3368, 3269 (NH_2), 2196 (CN) cm^{-1}; MS *m/z* (%): 332 (M^+, 66), 334 (M^++2, 21). Anal. calcd for $C_{20}H_{13}ClN_2O$ (332.78): C 72.18, H 3.94, N 8.42, Cl 10.65; found C 72.07, H 3.90, N 8.30, Cl 10.60.

General procedure for the synthesis of 4*H*,10*H*-chromeno[8,7-*h*]chromene (6a, 6b)

A mixture of aromatic aldehyde **1b, 1d** (10 mmol), malononitrile **2** (10 mmol) and 1,5-naphthalenediol **5** (5 mmol) with a few drops of TEA was thoroughly mixed and irradiated at 300 W in a Samsung M9245 microwave for 5—6 min (the reactions were monitored by TLC). Then, the reaction mixture was cooled, triturated with methanol and the solid formed was collected by filtration and crystallized from the appropriate solvent.

2,8-Diamino-4,10-di(2-chlorophenyl)-3,9-dicyano-4*H*,10*H*-chromeno[8,7-*h*] chromene (6a) Yellow powder, yield 82%, m.p. 295—297 ℃ (decom., from DMF); ^{1}H NMR δ: 5.43 (s, 2H, H-4, H-10), 7.12 (br.s, 4H, $2NH_2$), 7.29—7.94 (m, 12H, ArH); IR (KBr) v: 3324, 3196 (NH_2), 2200 (CN) cm^{-1}; MS *m/z* (%): 536 (M^+, 26), 538 (M^++2, 8). Anal. calcd for $C_{30}H_{18}Cl_2N_4O_2$ (537.40): C 67.05, H 3.38, N 10.43, Cl 13.19; found C 67.23, H 3.22, N 10.52, Cl 13.02.

2,8-diamino-3,9-dicyano-4,10-di(2-methoxyphenyl)-4*H*,10*H*-chromeno[8,7-*h*]chromene (6b) Yellow powder, yield 84%, m.p. 215—217 ℃ (decomp., from methanol/DMF); ^{1}H NMR δ: 3.69 (s, 6H, $2OCH_3$), 5.25 (s, 2H, H-4, H-10), 7.02 (br.s, 4H, $2NH_2$), 7.21—7.96 (m, 12H, ArH); IR (KBr) v: 3330, 3192 (NH_2), 2188 (CN) cm^{-1}; MS *m/z* (%): 528 (M^+, 11). Anal. calcd for $C_{32}H_{24}N_4O_4$ (528.56): C 72.72, H 4.58, N 10.60; found C 72.53, H 4.42, N 10.72.

General procedure for the synthesis of 2-amino-4*H*-chromene (7a, 7b)

A mixture of aromatic aldehyde **1b, 1d** (5 mmol), malononitrile **2** (5 mmol) and resorcinol **7a** and/or 4-chlorobenzene-2,4-diol **7b** (5 mmol) with a few drops of TEA was thoroughly mixed and irradiated at 300 W in a Samsung M9245 microwave for 5—6 min (the reactions were monitored by TLC). After cooling, the reaction mixture was triturated with methanol, and the solid formed was collected by filtration and crystallized from the appropriate solvent.

2-Amino-4-(2-chlorophenyl)-3-cyano-7-hydroxy-4*H*-chromene (8a) Colorless needles, yield 84%, m.p. 185—187 ℃ (from ethanol); ^{1}H NMR δ: 5.05 (s, 1H, H-4), 6.85 (br.s, 2H, NH_2), 6.85—7.35 (m, 7H, ArH), 10.35 (s, 1H, OH); IR (KBr) v: 3405 (O—H), 3440, 3180 (NH_2), 2200 (CN) cm^{-1}; MS *m/z* (%): 298 (M^+, 38), 300 (M^++2, 12). Anal. calcd for $C_{16}H_{11}ClN_2O_2$ (298.72): C 64.33, H 3.71, N 9.38; found C 62.53, H 4.42. N 10.72.

2-Amino-6-chloro-3-cyano-7-hydroxy-4-(2-methoxyphenyl)-4*H*-chromene (8b) Brown powder, yield 75%, m.p. 257—259 ℃ (from ethanol); ^{1}H NMR δ: 3.80 (s, 3H, CH_3), 5.00 (s, 1H, H-4), 6.70 (s, 2H, NH_2), 6.80—7.80 (m, 6H, ArH), 10.50 (s, 1H, OH); IR (KBr) v: 3400 (O—H), 3340, 3180 (NH_2), 2190 (CN) cm^{-1}; MS *m/z* (%): 328 (M^+, 35), 330 (M^++2, 10). Anal. calcd for $C_{17}H_{13}ClN_2O_3$ (328.75): C 62.11, H 3.99, N 8.52, Cl 10,78; found C 61.88, H 4.23, N 8.53, Cl 11.0.

General procedure for the synthesis of spiro[indole-3,5'-pyrano[2,3-*d*]pyrimidine 10a—10h

A mixture of isatin or bromoisatin **8a**, **8b** (5 mmol), malononitrile or ethyl cyanoacetate **2a**, **2b** (5 mmol) and barbituric or thiobarbituric acid **9a**, **9b** (5 mmol) with a few drops of TEA was mixed and irradiated at 300 W in a Samsung M9245 microwave for 5—6 min (the reactions were monitored by TLC). Then, the reaction mixture was cooled, triturated with methanol, and the solid formed was collected by filtration and crystallized from the appropriate solvent.

7'-Amino-6'-cyano-2,2',4'-trioxo-1,1',2,2',3',4'-hexahydrospiroindole-3,5'-pyrano[2,3-*d*]pyrimidine (10a) Yellow powder, yield 84%, m.p. 264—266 ℃, (from ethanol). ^{1}H NMR δ: 6.95 (s, 2H, NH_2), 6.85—7.35 (m, 4H, ArH), 10.05 (s, 1H, NH), 11.05 (s, 1H, NH), 11.35 (s, 1H, NH); IR (KBr) v: 3353—3305 (NH, NH_2), 2204 (CN), 1710—1725 (C=O) cm^{-1}; MS *m/z* (%): 323 (M^+, 21). Anal calcd for $C_{15}H_9N_5O_4$ (323.26): C 55.73, H 2.81, N 21.66; found C 55.39, H 3.41, N

 © 2010 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

21.53.

7'-Amino-5-bromo-6'-cyano-2,2',4'-trioxo-1,1',2,2',3',4'-hexahydrospiroindole-3,5'-pyrano[2,3-*d*]pyrimidine (10b) Pale violet, yield 72%, m.p. 220—222 ℃ (from ethanol); ^{1}H NMR δ: 6.85 (s, 2H, NH_2), 6.80—7.40 (m, 3H, ArH), 10.00 (s, 1H, NH), 11.00 (s, 1H, NH), 11.25 (s, 1H, NH); IR (KBr) *v*: 3350—3310 (NH, NH_2), 2210 (CN), 1710—1715 (C=O) cm^{-1}; MS *m/z* (%): 401 (M^+, 45), 403 (M^++2, 48). Anal. calcd for $C_{15}H_8BrN_5O_4$ (402.16): C 44.80, H 2.01, N 17.41, Br 19.87; found C 44.39, H 2.11, N 17.52, Br 19.63.

7'-Amino-6'-cyano-2,4'-dioxo-2'-thioxo-1,1',2,2',3',4'-hexahydrospiroindole-3,5'-pyrano[2,3-*d*]pyrimidine (10c) Pale buff, yield 79%, m.p. 235—237 ℃ (from dioxane); ^{1}H NMR δ: 6.82 (s, 2H, NH_2), 6.88—7.52 (m, 4H, ArH), 10.10 (s, 1H, NH), 11.15 (s, 1H, NH), 11.35 (s, 1H, NH); IR (KBr) *v*: 3350—3310 (NH, NH_2), 2208 (CN), 1710—1725 (C=O's) cm^{-1}; MS *m/z* (%): 339 (M^+, 94), 341 (M^++2, 4.4). Anal. calcd for $C_{15}H_9N_5O_3S$ (339.33): C 53.09, H 2.67, N 20.64, S 9.45; found C 53.19, H 2.59, N 20.57, S 9.33.

7'-Amino-5-bromo-6'-cyano-2,4'-dioxo-2'-thioxo-1,1',2,2',3',4'-hexahydrospiroindole-3,5'-pyrano[2,3-*d*]pyrimidine (10d) Pale violet, yield 76%, m.p. 246—248 ℃ (from ethanol); ^{1}H NMR δ: 6.85 (s, 2H, NH_2), 6.88—7.52 (m, 3H, ArH), 10.15 (s, 1H, NH), 11.10 (s, 1H, NH), 12.25 (s, 1H, NH); IR (KBr) *v*: 3350—3310 (NH, NH_2), 2210 (CN), 1715—1725 (C=O's) cm^{-1}; MS *m/z* (%): 417 (M^+, 100), 419 (M^++2, 97.9), 421 (4.8). Anal. calcd for $C_{15}H_8BrN_5O_3S$ (418.22): C 43.08, H 1.93, N 16.75, Br 19.11, S 7.67; found C 43.19, H 2.01, N 16.62, Br 19.17, S 7.61.

Ethyl-7'-amino-2,2',4'-trioxo-1,1',2,2',3',4'-hexahydrospiroindole-3,5'-pyrano[2,3-*d*]pyrimidine-6'-carboxylate (10e) Brown powder, yield 84%, m.p. 184—186 ℃ (from methanol); ^{1}H NMR δ: 1.35 (t, *J*=7.2 Hz, 3H, CH_3), 3.50 (q, *J*=8.0 Hz, 2H, CH_2), 6.83 (s, 2H, NH_2), 6.85—7.35 (m, 4H, ArH), 9.50 (s, 1H, NH), 10.05 (s, 1H, NH), 10.35 (s, 1H, NH); IR (KBr) *v*: 3353—3305 (NH, NH_2), 1697, 1700—1725 (C=O) cm^{-1}; MS *m/z* (%): 370 (M^+, 76). Anal. calcd for $C_{17}H_{14}N_4O_6$ (370.32): C 55.14, H 3.81, N 15.13; found C 55.29, H 3.75, N 15.23.

Ethyl-7'-amino-5-bromo-6'-cyano-2,2',4'-trioxo-1,1',2,2',3',4'-hexahydrospiroindole-3,5'-pyrano[2,3-*d*]pyrimidine-6'-carboxylate (10f) Pale brown powder, yield 87%, m.p. 230—232 ℃ (from methanol); ^{1}H NMR δ: 1.38 (t, *J*=6.0 Hz, 3H, CH_3), 3.70 (q, *J*=8.0 Hz, 2H, CH_2), 6.85 (s, 2H, NH_2), 6.85—7.35 (m, 3H, ArH), 9.75 (s, 1H, NH), 10.35 (s, 1H, NH), 10.65 (s, 1H, NH); IR (KBr) *v*: 3353—3305 (NH, NH_2), 1697, 1700—1725 (C=O's) cm^{-1}; MS *m/z* (%): 448 (M^+, 100), 450 (M^++2, 97.9). Anal. calcd for $C_{17}H_{13}BrN_4O_6$ (449.21): C 45.55, H 2.92, N 12.47, Br 17.79; found C 45.33, H 2.75, N 12.27, Br 17.68.

Ethyl-7'-amino-6'-cyano-2,4'-dioxo-2'-thioxo-1,1',2,2',3',4'-hexahydrospiroindole-3,5'-pyrano[2,3-*d*]-pyrimidine-6'-carboxylate (10g) Yellowish green powder, yield 72%, m.p. 240—242 ℃ (from ethanol); ^{1}H NMR δ: 1.38 (t, *J*=7.2 Hz, 3H, CH_3), 3.57 (q, *J*=8.0 Hz, 2H, CH_2), 6.75 (s, 2H, NH_2), 6.85—7.35 (m, 4H, ArH), 9.70 (s, 1H, NH), 10.25 (s, 1H, NH), 10.55 (s, 1H, NH); IR (KBr) *v*: 3353—3305 (NH, NH_2), 2204 (CN), 1700—1725 (C=O's) cm^{-1}; MS *m/z* (%): 386 (M^+, 94), 388 (M^++2, 4.3). Anal. calcd for $C_{17}H_{14}N_4O_5S$ (386.38): C 52.84, H 3.65, N 14.50, S 8.30; found C 52.75, H 3.75, N 14.43, S 8.33.

Ethyl-7'-amino-5-bromo-2,4'-dioxo-2'-thioxo-1,1',2,2',3',4'-hexahydrospiroindole-3,5'-pyrano[2,3-*d*]-pyrimidine-6'-carboxylate (10h) Brown powder, yield 79%, m.p. 250—252 ℃ (from ethanol); ^{1}H NMR δ: 1.35 (t, *J*=6.0 Hz, 3H, CH_3), 3.55 (q, *J*=8.0 Hz, 2H, CH_2), 6.72 (s, 2H,NH_2), 6.88—7.37 (m, 3H, ArH), 9.75 (s, 1H, NH), 10.35 (s, 1H, NH), 10.50 (s, 1H, NH); IR (KBr) *v*: 3353—3305 (NH, NH_2), 1700—1725 (C=O's) cm^{-1}; MS *m/z* (%): 464 (M^+, 100), 466 (M^++2, 98.7), 468 (4.4). Anal. calcd for $C_{17}H_{13}BrN_4O_5S$ (465.28): C 43.88, H 2.82, N 12.04, Br 17.17, S 6.89; found C 43.79, H 2.75, N 12.17, Br 17.08, S 6.85.

Synthesis of 2-amino-4-(4-chlorophenyl)-6-(2-thienyl)-nicotinonitrile (11)

4-Chlorobenzaldehyde **1c** (5 mmol), malononitrile **2** (5 mmol) and 2-acetylthiophene (5 mmol) were thoroughly mixed with ammonium acetate (10 mmol) and irradiated at 300 W in a Samsung M9245 microwave for 3 min (the reactions were monitored by TLC). The solid formed was collected and crystallized from dioxane to give yellow powder, yield 82%, m.p. 230—232 ℃ (from dioxane); ^{1}H NMR δ: 6.90 (s, 2H, NH_2), 6.75 (s, 1H, H-3), 6.85—7.77 (m, 7H, ArH+thienyl H); IR (KBr) *v*: 3350—3305 (NH_2), 2200 (CN) cm^{-1}; MS *m/z* (%): 311 (M^+, 33), 313 (M^++2, 11). Anal. calcd for $C_{16}H_{10}ClN_3S$ (311.79): C 61.63, H 3.23, N 13.48, Cl 11.37, S 10.28; found C 61.51, H 3.05, N 13.64, Cl 11.51, S 10.42.

Synthesis of 2-amino-4-(2-bromophenyl)-6-(2-thienyl)-nicotinonitrile (12)

2-Bromobenzaldehyde **1e** (5 mmol), malononitrile **2** (5 mmol), 2-acetyl thiophene (5 mmol) and ammonium acetate (10 mmol) were thoroughly mixed and irradiated at 300 W in a Samsung M9245 microwave for 3 min (the reactions were monitored by TLC). The solid formed was collected and crystallized from ethanol to give yellow powder, yield 77%, m.p. 240—242 ℃; ^{1}H NMR δ: 6.83 (s, 2H, NH_2), 6.88 (s, 1H, H-3), 6.85—7.35 (m, 7H, ArH+thienyl H); IR (KBr) *v*: 3370 (NH_2), 2210 (CN) cm^{-1}. Anal. calcd for $C_{16}H_{10}BrN_3S$ (356.24): C 53.94, H 2.83, N 11.80, Br 22.43, S 9.00; found C 53.86, H 2.69, N 11.95, Br 22.25, S 9.19.

Synthesis of 6-amino-5-cyano-4-(4-chlorophenyl)-2,3'-bipyridine (13)

4-Chlorobenzaldehyde **1c** (5 mmol), malononitrile **2** (5 mmol), 3-acetylpyridine (5 mmol) and ammonium acetate (10 mmol) were thoroughly mixed and irradiated

 © 2010 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

at 300 W in a Samsung M9245 microwave for 3 min (the reactions were monitored by TLC). The solid formed was collected and crystallized from dioxane to give yellow powder, yield 82%, m.p. 230—232 ℃; ^{1}H NMR δ: 7.25 (s, 2H, NH_2), 7.35 (s, 1H, H-3), 7.55—8.75 (m, 7H, ArH+pyridyl H); IR (KBr) v: 3380—3350 (NH_2), 2200 (CN) cm^{-1}. Anal. calcd for $C_{17}H_{11}ClN_4$ (306.75): C 66.56, H 3.61, N 18.26, Cl 11.56; found C 66.38, H 3.43, N 18.51, Cl 11.74.

Synthesis of 6-amino-7-cyano-8-(2-chlorphenyl)-3-hydroxy-8*H*-pyrano[3,2-*c*]pyridazine (14)

2-Chlorobenzaldehyde **1b** (5 mmol), malononitrile **2a** (5 mmol), pyridazine-3,5-diol (5 mmol) and a few drops of TEA were thoroughly mixed and irradiated at 300 W in a Samsung M9245 microwave for 3 min (the reactions were monitored by TLC). The solid formed was collected and crystallized from ethanol to give pale yellow powder, yield 78%, m.p. 238—240 ℃; ^{1}H NMR δ: 4.90 (s, 1H, H8), 7.25 (s, 2H, NH_2), 7.55—8.15 (m, 4H, ArH+H4), 8.88 (s, 1H, OH); IR (KBr) v: 3370 (NH_2), 2210 (CN) cm^{-1}; MS m/z (%): 300 (M^+, 29), 302 (M^++2, 7). Anal. calcd for $C_{14}H_9ClN_4O_2$ (300.70): C 55.90, H 3.02, N 18.63, Cl 11.79; found C 55.78, H 3.19, N 18.51, Cl 11.74.

Results and discussion

In continuation of our efforts to develop efficient environmentally benign protocols for the synthesis of various heterocycles through one pot multi-component reactions,[32-35] we report herein the synthesis of amino(benzo)chromenes through three component condensation of aromatic aldehydes, malononitrile and phenols or naphthols.

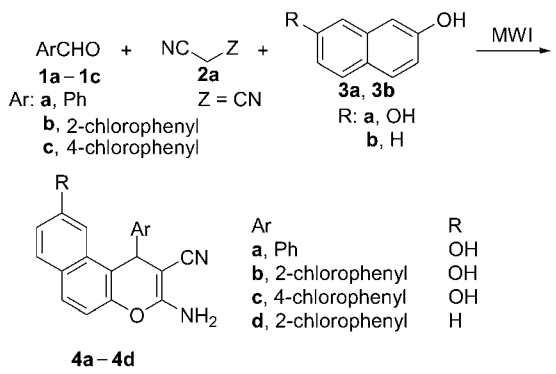
An earlier attempt to synthesize benzochromenes from 2,7-naphthalenediol and arylmethylidenemalononitrile has failed.[35] We were interested in studying new approaches in which 2,7-dihydroxynaphthalene reacted with aldehyde and malononitrile in a three-component condensation system in the presence of a catalytic amount of triethylamine in ethanolic solution to afford amino(benzo)chromenes.[36]

In conjugation of this work, we report herein further investigation to clear this conflict of results. We found that condensation of 2,7-dihydroxynaphthalene **3a**, benzaldehyde **1a** and malononitrile **2a** under microwave irradiation and solvent free condition afforded 2-amino-3-cyano-6-hydroxy-4-phenyl-4*H*-benzo[*f*]chromene **4a** (Scheme 1). The formation of **4a** was explained through the formation of the phenylmethylenemalononitrile, then 2,7-dihydroxynaphthalene attacks on the β-carbon of the phenylmethylenemalononitrile to yield an acyclic Michael adduct which undergoes intramolecular cyclization to compound **4a**.

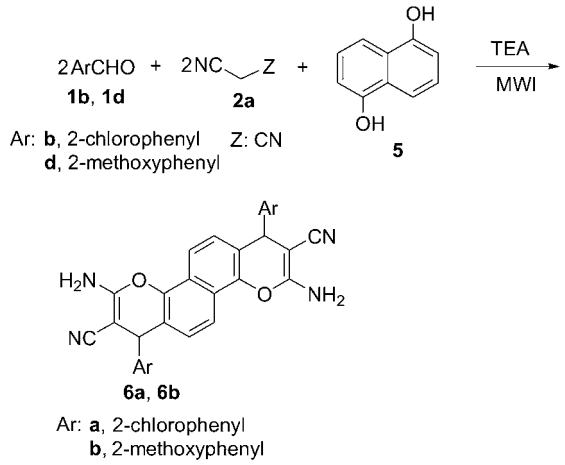
To explore the scope and versatility of this method, various similar reactions were investigated using different aromatic aldehydes **1a**—**1c** with malononitrile **2a** and 2,7-dihydroxynaphthalene **3a** or β-naphthol **3b** yielding different 4*H*-benzo[*f*]chromene **4b** — **4d** (Scheme 1). The structures of previously known compounds were confirmed by spectroscopic methods and elemental analysis (see Experimental).

In order to expand the scope of the present method under the above optimized reaction conditions, the reaction of *o*-chlorobenzaldehyde **1b** and malononitrile **2a** with 1,5-naphthalenediol **5** in a molar ratio of 2∶2∶1 was investigated under the previous condition to afford the diadduct 2,8-diamino-4,10-di(2-chlorophenyl)-3,9-dicyano-4*H*,10*H*-chromeno[8,7-*h*]chromene **6a** (Scheme 2). The IR spectrum for compound **6a** revealed both amino and cyano functions at 3324, 3196 and 2200 cm^{-1}, respectively. ^{1}H NMR spectrum of this product revealed signals that are in agreement with the proposed structure. For example, there is a singlet at δ 5.43 with integration of two protons for H-4 and H-10 protons as indication for the diadduct formation. Similarly, *o*-methoxybenzaldehyde **1d**, malononitrile **2a** and 1,5-naphthalenediol **5** were allowed to react under the same condition to yield 2,8-diamino-3,9-dicyano-4,10-di(2-methoxyphenyl)-4*H*,10*H*-chromeno[8,7-*h*]chromene **6b**.

Scheme 1



Scheme 2



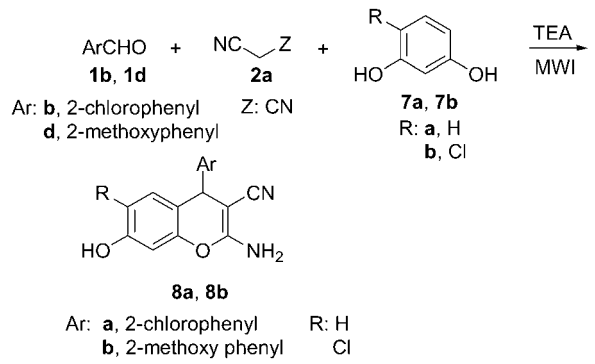
To examine the scope of such technique, aromatic aldehyde **1b**, **1d**, malononitrile **2a** and resorcinol **7a** or 4-chlorobenzene-1,3-diol **7b** were also used and the

 © 2010 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

CHINESE JOURNAL OF CHEMISTRY

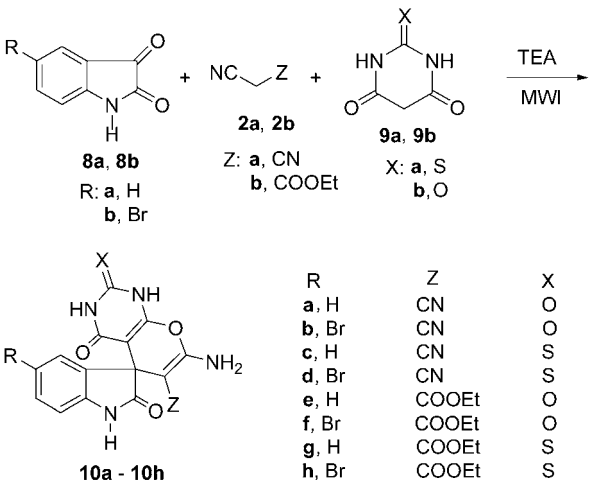
corresponding 2-amino-chromene derivatives **8a**, **8b** were obtained in high yields (Scheme 3). The IR spectrum for compound **8a** revealed hydroxyl, amino and cyano functions at 3440, 3180 and 2200 cm^{-1}, respectively. ^1H NMR spectrum of this product revealed signals that are in accord with the proposed structure. For example, there are three singlets at δ 5.05 for H-4 proton, at 6.85 for NH_2 protons and at 10.50 for OH proton. There was no effect by increasing the reaction ratio from 1∶1∶1 to 2∶2∶1, and the only isolated product was the single adduct **7a**, **7b**.

Scheme 3



For further investigation for the scope of this efficient and simple procedure, the reaction of isatin or bromoisatin **8a**, **8b**, malononitrile or ethyl cyanoacetate **2a**, **2b** with barbituric or thiobarbituric acid **9a**, **9b** was examined (Scheme 4). The reaction of isatin **8a**, malononitrile **2a** and barbituric acid **9a** afforded the compound assigned by spectral and elemental data to be 7'-amino-6'-cyano-2,2',4'-trioxo-1,1',2,2',3',4'-hexahydro spiroindole-3,5'-pyrano[2,3-*d*]pyrimidine (**10a**) (see Experimental).

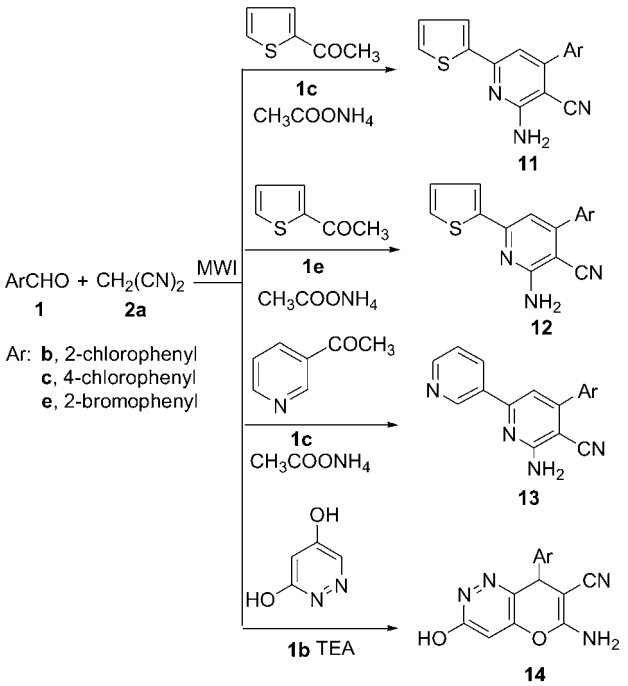
Scheme 4



The feasibility of employing different derivatives of the above reaction components was also investigated, and we obtained different 6'-cyano-2,2',4'-trioxo-1,1',2,2',3',4'-hexahydrospiroindole-3,5'-pyrano[2,3-*d*]pyrimidine and 6'-cyano-2,4'-dioxo-2'-thioxo-1,1',2,2',3',4'-hexahydrospiroindole-3,5'-pyrano[2,3-*d*]-pyrimidine **10b**—**10i** in excellent yields. The spectroscopic data for the prepared compounds add a sharp evidence for their formation (see Experimental).

Encouraged with the above satisfactory results, the reaction of 4-chlorobenzaldehyde **1c**, malononitrile **2a** with 2-acetylthiophene in the presence of ammonium acetate afforded 2-amino-4-(4-chlorophenyl)-6-(2-thienyl) nicotinonitrile **11** (Scheme 5). The IR spectrum for compound **11** revealed both amino and cyano functions in 3350—3305 and at 2200 cm^{-1}, respectively. ^1H NMR spectrum of this product revealed signals that are in accord with the proposed structure. For example, there are two singlets at δ 6.90 for NH_2 protons and at 6.75 for H-5 proton (see Experimental). The formation of **11** was expected to proceed via initial condensation of aldehyde with malononitrile to afford an arylidine, which further undergoes *in situ* Michael addition with 1-arylethenamine obtained by treating aromatic ketone with ammonia from ammonium acetate to yield an intermediate, which is cyclized and subsequently dehydrogenated to afford the final product.

Scheme 5



Also, the reaction of 2-bromobenzaldehyde (**1e**), malononitrile (**2a**) with 2-acetylthiophene in the presence of ammonium acetate yielded 2-amino-4-(2-bromophenyl)-6-(2-thienyl) nicotinonitrile (**12**). The reaction of 4-chlorobenzaldehyde (**1c**), malononitrile (**2a**) with 2-acetylpyridine in the presence of ammonium acetate afforded 6-amino-4-(4-chlorophenyl)-5-cyano-2,3'-bipyridine (**13**). The condensation of 2-chlorobenzaldehyde (**1b**), malononitrile (**2a**) with pyridazine-3,5-diol yielded 6-amino-8-(2-chlorophenyl)-7-cyano-

 © 2010 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

3-hydroxy-8*H*-pyrano[3,2-*c*]pyridazine (**14**) (Scheme 5).

References

1 Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. *Farmaco* **2002**, *57*, 715.
2 Smith, W. P.; Sollins, L. S.; Howes, D. P.; Cherry, C. P.; Starkey, D. I.; Cobley, N. K. *J. Med. Chem.* **1998**, *41*, 787.
3 Martinez, A. G.; Marck, L. J. *J. Bioorg. Med. Chem. Lett.* **1997**, *7*, 3165.
4 Dell, C. P.; Smith, C. W. *EP 537949*, **1993** [*Chem. Abstr.* **1993**, *119*, 139102d.]
5 Bianchi, G.; Tava, A. *Agric. Biol. Chem*. **1987**, *51*, 2001.
6 Mohr, S. J.; Chirigios, M. A.; Fuhrman, F. S.; Pryor, J. W. *Cancer Res.* **1975**, *35*, 3750.
7 Anderson, D. R.; Hegde, S.; Reinhard, E.; Gomez, L.; Vernier, W. F.; Lee, L.; Liu, S.; Sambandam, A.; Sinder, P. A.; Masih, L. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1587.
8 Skommer, J.; Wlodkowic, D.; Matto, M.; Eray, M.; Pelkonen, J. *Leukemia Res*. **2006**, *30*, 322.
9 Wang, J. L.; Liu, D.; Zhang, Z.; Shan, S.; Han, X.; Srinvasula, S. M.; Croce, C. M.; Alnemeri, E. S.; Huang, Z. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 7124.
10 Eiden, F.; Denk, F. *Arch. Pharm. Weinhein Ger.* (*Arch. Pharm.*) **1991**, *324*, 353.
11 Hafez, E. A.; Elnagdi, M. H.; Elagamey, A. G. A.; ElTaweel, F. M. A. A. *Heterocycles* **1987**, *26*, 903.
12 Sofan, M. A.; Elnagdi, M. H.; ElTaweel, F. M. A. A. *Liebigs. Ann. Chem.* **1989**, 935.
13 Varma, R. S.; Dahiya, R. *J. Org. Chem*. **1998**, *63*, 8038.
14 ElAgrody, A. M.; ElHakiem, M. H.; Abd El-Latif, M. S.; Fakery, A. H.; El-Sayed, E. S. M.; El-Ghareab, K. A. *Acta Pharm.* **2000**, *50*, 111.
15 Yavari, I.; Djahaniani, H.; Nasiri, F. *Synthesis* **2004**, 679.
16 Yavari, I.; Djahaniani, H.; Nasiri, F. *Tetrahedron* **2003**, *59*, 9409.
17 Kemnitzer, W.; Kasibhatla, S.; Jiang, S.; Zhang, H.; Zhao, J.; Lia, S.; Xu, L.; Crogan-Grundy, C.; Denis, R.; Barriault, N.; Villacourt, L.; Charron, S.; Dodd, J.; Attardo, G.; Labrique, D.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cia, S. X. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4645.
18 Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, W.; Lia, S.; Xu, L.; Crogan-Grundy, C.; Denis, R.; Barriault, N.; Villacourt, L.; Charron, S.; Dodd, J.; Attardo, G.; Labrique, D.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cia, S. X. *J. Med. Chem.* **2004**, *47*, 6299.
19 Dyachenko, V. D.; Chernega, A. N. *Russ. J. Org. Chem.* **2006**, *42*, 567.
20 Ballini, R.; Bosica, G.; Conforti, M. L.; Maggi, R.; Mazzacanni, A.; Righi, P.; Sartori, G.; *Tetrahedron* **2001**, *57*, 1395.
21 Shi, D. Q.; Zhang, S.; Zhuang, Q. Y.; Tu, S. J.; Hu, H. W. *Chin. J. Org. Chem.* **2003**, *23*, 809 (in Chinese).
22 Maggi, R.; Ballini, R.; Sartori, G.; Sartorio, R. *Tetrahedron Lett.* **2004**, *45*, 2297.
23 Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.
24 Varma, R. S. *Green Chem.* **1999**, *1*, 43.
25 Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578.
26 Baghurst, D. R.; Mingos, B. K. *Chem. Soc. Rev.* **1991**, *20*, 1.
27 Varma, R. S. *J. Heterocycl. Chem.* **1999**, *36*, 1565.
28 Shi, L.; Wang, M.; Fan, C. A.; Zhang, F. M.; Tu, Y. Q. *Org. Lett.* **2003**, *5*, 3515.
29 Shi, L.; Wang, M.; Fan, C. A.; Zhang, F. M.; Tu, Y. Q. *Org. Lett.* **2004**, *6*, 1001.
30 Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327.
31 Hamelin, J.; Bazureau, J. P.; Texier-Boullet, F., In *Microwaves in Organic Synthesis*, Ed.: Loupy, A., Wiley-VCH, Weinheim, Germany, **2002**, p. 253.
32 Abdel-Latif, F. F.; Mashaly, M. M.; Mekheimer, R.; Abdel-Aleem, T. B. *Z. Naturforsch* **1993**, *48b*, 817.
33 Abdel-Latif, F. F.; Shaker, R. M. *Bull. Soc. Chem. Fr.* **1991**, *127*, 87.
34 Abdel-Latif, F. F.; Shaker, R. M.; Abdel-Aziz, N. S. *Heterocycl. Commun.* **1997**, *3*, 245.
35 Elagamey, A. G. A.; El-Taweel, F. M. A. A.; Sowellim, S. Z. A.; Sofan, M. A.; Elnagdi, M. H. *Collect. Czech. Chem. Commun.* **1990**, *55*, 424.
36 Shestopalov, A. M.; Emelianova, Y. M.; Nesterov, V. N. *Russ. Chem. Bull., Intl. Ed*. **2002**, *51*, 2238.

(E0904145 Lu, Y.)

 © 2010 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim