Microwave-Assisted Reactions: Three Component Process for the Synthesis of 2-Amino-2-chromenes Under Microwave Heating

Ramadan A. Mekheimer and Kamal U. Sadek*

Department of Chemistry, Faculty of Science, El-Minia University, El-Minia 61519, Egypt
*E-mail: kusadek@yahoo.com

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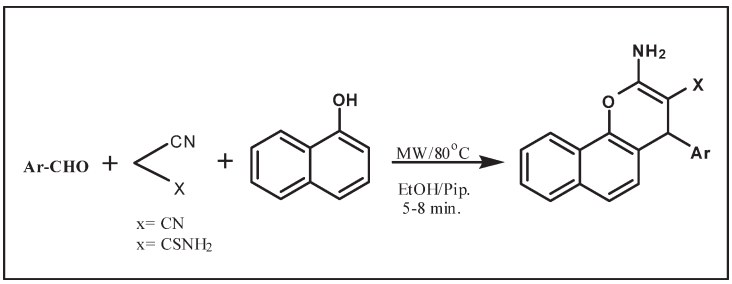

A simple and efficient three component process for the synthesis of 2-amino-2-chromenes utilizing the reaction of aryl aldehydes **1a–1h** with active methylenes **2a,b** and 1-naphthol **3** in refluxing ethanol/piperidine under microwave-heating is described.

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INTRODUCTION

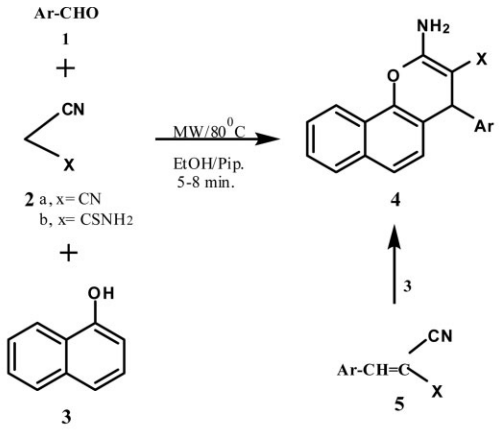
Substituted 2-amino-2-chromenes have received considerable attention due to their importance as pigments, cosmetics, potential agrochemicals, and being the main constituents of many natural products [1–5]. Accordingly, their synthesis has received much attention from organic chemists. These compounds are generally prepared by multicomponent condensation of aromatic aldehyde **1**, active methylene derivatives **2** and activated phenol or naphthol **3** in the presence of piperidine using acetonitrile or ethanol as a solvent under conventional heating for periods ranging from 2–3 h in moderate yields [6–9]. Also, relatively benign reagents such as cetyltrimethylammonium chloride (CTACl) and basic alumina in water have been used [10]. Thus, substituted 2-amino-2-chromenes **4** will be produced in moderate to good yields by heating a mixture of **1**, **2**, and **3** in water in the presence of a catalytic amount of CTACl for 6 h under reflux. It is obvious that, most of these require prolonged reaction time, reagents in stoichiometric amounts and provide moderate yields of the product. Recently [11], a three component condensation in MeOH in the presence of nanosized magnesium oxide as a catalyst at room temperature has been reported. Although, this process is efficient and convenient, the usage of MeOH as a solvent for the reaction and work-up is not recommended due to the toxicity.

In recent years, there has been extensive effort to adapt green technologies in synthetic organic chemistry, so as to minimize waste production, material and energy consumption, and the use of hazardous compounds. Microwave-assisted reactions have received great interest because of their simplicity in operation, enhanced reaction rates, products with high purity, and better yields compared to those conducted by conventional heating [12–14]. Also, a three-component one step reaction is of great interest for cost savings due to raw materials consumption, energy use, and time. We do believe that combining microwave heating technique with a three-component one step reaction will be beneficial and interesting. In continuation to our interest for the synthesis of azoles, azines, and fused rings [15–17], we report herein the synthesis of 2-amino-2-chromenes *via* three-component synthesis by using microwave technique.

RESULTS AND DISCUSSION

The synthesis of 2-amino-2-chromenes under conventional heating technique requires prolonged reaction time and affords moderate yields of products. Conducting a three-component synthesis of these target molecules under microwave irradiation and, to the best of our knowledge, has never been published before. Thus, when a mixture of benzaldehyde **1a**, malononitrile **2a** and α-naphthol **3** in 10 mL of ethanol and in the presence of piperidine as a catalyst was refluxed in a microwave labstation for 5 min at 80°C, the corresponding 2-amino-2-chromene derivative **4a** was obtained in almost quantitative yield (Scheme 1). The structure of the formed product was established by spectral and analytical data and also by comparison with authentic sample synthesized by reaction of benzylidene malononitrile **5** with α-naphthol under conventional heating [18]. Thus,

Scheme 1



1,4, 5	Ar	X	Time (min.)	Yield (%)
a	C_6H_5	CN	5	93
b	4-OCH_3-C_6H_4	CN	5	94
c	4-Cl-C_6H_4	CN	5	88
d	4-NO_2-C_6H_4	CN	10	85
e	3-pyridyl	CN	5	95
f	4-pyridyl	CN	5	89
g	H	CN	5	94
h	2-furyl	$CSNH_2$	5	93

Three component synthesis of 2-amino-2-chromenes.

IR spectrum for compound **4a** revealed both amino and cyano groups at ν_{max} 3400 and 2200 cm^{-1}, respectively. ^1H NMR spectrum of this product revealed signals that are in accord with the proposed structure. It reveals signals at $\delta = 4.77$ (s, 1H, 4H-pyran); 6.8 (br, s, 2H, NH_2), 6.93 (d, $J = 8$ Hz, 1H, H-5), 7.08–7.23 (m, 5H, Ar—H); 7.33–7.43 (m, 3H, Ar—H), 7.52 (d, $J = 8$ Hz, 1H, H-7), 8.10 (d, $J = 8$ Hz, 1H, H-10). ^{13}C NMR revealed signals at $\delta = 40.92$, 61.06, 108.50, 116.6, 120.80, 123.20, 124.80, 125.90, 126.80, 126.92, 127.80, 129.10, 129.50, 133.22, 133.40, 142.90, 143.30, 158.60. To examine the aromatic aldehyde substrate effect on the rate and overall yield, various aldehydes **1b–1d** were used under the aforementioned reaction conditions. From the results, we can see that all reactions proceeded smoothly to afford the corresponding 2-amino-2-chromene derivatives **4b–4d** in high yield. Slightly diminished yields were observed when the substituent is an electron withdrawing group.

To examine the scope of such techniques, heteroaryl and aliphatic aldehydes **1e–1h** were also used and the corresponding 2-amino-2-chromene derivatives **4e–4h** were obtained in high yields. The structure assigned for the reaction products were established based on analytical and spectral data (*cf*. Experimental part for details). Cyanothioacetamide (**2b**) was also examined as an active methylene compound and the corresponding 2-amino-2-chromen **4h** was obtained.

In conclusion, in green chemistry it is generally recognized that the best reaction requires no solvent. In our procedure we used a little amount of ethanol compared to the quantities of starting materials. Refluxing under microwave technique in the presence of this little amount of solvent perform a homogenous heating, which prevents charring of neat samples and offers a simple and high yield process for the synthesis of 2-amino-2-chromene derivatives.

EXPERIMENTAL

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The reactions were conducted in milestone START-Labstation for microwave enhanced chemistry provided with a sensor for adjusting the temperature and a refluxing condenser. IR spectra (KBr) were measured with a Schimadzu Model 470 spectrophotometer.

^{1}H NMR (300 MHz) and ^{13}C NMR (100 MHz) spectra were measured on a Varian spectrometer using DMSO-d_6 as solvent and TMS as internal Standard, chemical shifts are expressed as δ ppm. Analytical data were determined on the Microanalytical Data Unit at Cairo University. Compounds **4g,4h** were found identical with authentic samples [18].

General procedure for the synthesis of 2-amino-2-chromenes (4a–4g). A solution of the appropriate aldehyde **1**, α-naphthol (**2**) and active methylene **3** (0.01 mol) in ethanol (10 mL), and catalytic amount of piperidine (2 drops) was heated under reflux in a milestone labstation at 80°C for a period of 5–8 min. Upon standing at room temperature a solid product was formed which was collected by filtration to afford compounds **4a–4g**. An additional amount of products were obtained *via* evaporation of the solvent under reduced pressure.

2-Amino-3-cyano-4-phenyl-4H-benzo[h]chromene (4a). Compound **4a** (93%) was obtained as colorless crystals (ethanol). M.P. 179–180°C. *Anal*. Calcd. for $C_{20}H_{14}N_2O$ (298.35): C, 80.52; H, 4.73; N, 9.40. Found: C, 80.40; H, 4.63; N, 9.50. IR (KBr): 3420 (NH_2); 2200 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.77 (s, 1H, 4H-pyran); 6.8 (br, s, 2H, NH_2), 6.93 (d, J = 8 Hz, 1H, H-5), 7.08–7.23 (m, 5H, Ar—H); 7.33–7.43 (m, 3H, Ar—H), 7.52 (d, J = 8 Hz, 1H, H-7), 8.10 (d, J = 8 Hz, 1H, H-10).

2-Amino-3-cyano-4-(4-methoxyphenyl)-4H-benzo[h]chromene (4b). Compound **4b** (94%) was obtained as yellow crystals (ethanol). M.P. 188–189°C. *Anal*. Calcd. for $C_{21}H_{16}N_2O_2$ (328.36): C, 76.80; H, 4.91; N, 8.53. Found: C, 76.70; H, 4.80; N, 8.33. IR (KBr): 3430 (NH_2); 2200 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.90 (s, 3H, OCH_3), 4.54 (s, 1H, 4H-pyran), 6.82 (br, s, 2H, NH_2), 7.0 (d, J = 8 Hz, 1H, H-5), 7.10–7.22 (m, 4H, Ar—H), 7.39–7.40 (m, 3H, Ar—H), 7.53 (d, J = 8 Hz, 1H, H-7), 8.12 (d, J = 8 Hz, 1H, H-10).

2-Amino-3-cyano-4-(4-chlorophenyl)-4H-benzo[h]chromene (4c). Compound **4c** (94%) was obtained as yellow crystals (ethanol). M.P. 232–234°C. *Anal*. Calcd. for $C_{20}H_{13}ClN_2O$ (332.78): C, 72.18; H, 3.94; Cl, 10.65; N, 8.42. Found: C, 72.10; H, 3.70; Cl, 10.50; N, 8.20. IR (KBr): 3450 (NH_2); 2200 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.55 (s, 1H, 4H-pyran), 6.70 (br, s, 2H, NH_2), 7.1 (d, J = 8 Hz, 1H, H-5), 7.21–7.33 (m, 4H, Ar—H), 7.40–7.45 (m, 3H, Ar—H), 7.56 (d, J = 8 Hz, 1H, H-7), 8.15 (d, J = 8 Hz, 1H, H-10).

2-Amino-3-cyano-4-(4-nitrophenyl)-4H-benzo[h]chromene (4d). Compound **4d** (85%) was obtained as yellow crystals (ethanol). M.P. 240–241°C. *Anal*. Calcd. for $C_{20}H_{13}N_3O_3$ (343.34): C, 69.96; H, 3.82; N, 12.24. Found: C, 69.80; H, 3.92; N, 12.13. IR (KBr): 3440 (NH_2), 2220 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.58 (s, 1H, 4H-pyran), 6.79 (br, s, 2H, NH_2), 7.18 (d, J = 8 Hz, 1H, H-5), 7.25–7.41 (m, 4H, Ar—H), 7.46–7. 51 (m, 3H, Ar—H), 7.61 (d, J = 8 Hz, 1H, H-7), 8.21 (d, J = 8 Hz, 1H, H-10).

2-Amino-3-cyano-4-(3-pyridyl)-4H-benzo[h]chromene (4e). Compound **4e** (95%) was obtained as yellow crystals (ethanol). M.P. 240–241°C. *Anal*. Calcd. for $C_{19}H_{13}N_3O$ (299.33): C, 76.24; H, 4.38; N, 14.04. Found: C, 76.10; H, 4.50; N, 14.00. IR (KBr): 4310 (NH_2); 2220 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.90 (s, 1H, 4H-pyran); 7.11 (d, J = 8 Hz, 1H, H-5 or H-6), 7.22 (s, 2H, NH_2); 7.33 (dd, J = 8 Hz and 4.5 Hz, pyridine H-5); 7.50–7.70 (m, 4H, H-6 or H-5, H-7, H-8, and pyridine H-6), 7.89 (d, J = 8 Hz, 1H, H-7 or H-10); 8.24 (d, J = 8 Hz,1H, H-7 or H-10), 8.46 (d, J = 4.5 Hz, 1H, pyridine H-4), 8.55 (s, 1H, pyridine H-2).

2-Amino-3-cyano-4-(4-pyridyl)-4H-benzo[h]chromene (4f). Compound **4f** (93%) was obtained as yellow crystals (ethanol). M.P. 200–202°C. *Anal*. Calcd. for $C_{19}H_{13}N_3O$ (299.33): C, 76.24; H, 4.38; N, 14.04. Found: C, 76.13; H, 4.34; N, 14.24. IR (KBr): 3354 (NH_2); 2220 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.97 (s, 1H, 4H-pyran), 7.14 (d, J = 8 Hz, 1H, H-5 or H-6), 7.27 (m, 4H, pyridine H-3, pyridine H-5 and NH_2), 7.56–7.73 (m, 2H, H-8 or H-9), 7.66 (d, J = 8 Hz, 1H, H-6 or H-5), 7.80 (d, J = 8 Hz, 1H, H-7 or H-10), 8.22 (d, J = 8 Hz, 1H, H-7, or H-10), 8.52 (d, 2H, J = 5 Hz, pyridine H-2 and H-6).

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