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One-pot synthesis of 4-alkyl-2-amino-4*H*-chromene derivatives

DOI 10.1515/hc-2015-0077
Received April 14, 2015; accepted April 28, 2015

Abstract: A one-pot synthesis of 4-alkyl-2-amino-4*H*-chromene derivatives by base-initiated reactions of aliphatic aldehydes, malononitrile, and resorcinol in water is described.

Keywords: cyano compounds; heterocycles; Knoevenagel condensation; Michael addition; pyrans.

Introduction

2-Amino-4*H*-pyrans are attractive molecules because of their diverse biological activity, which includes antibacterial [1–5], fungicidal [6], molluscicidal [7–8], and anticancer [9–14] properties. Among them, 4-aryl-4*H*-chromenes receive special attention as potent apoptosis inducing agents possessing vascular targeting activity [10, 11]. These compounds are tubulin inhibitors, binding at or close to the binding site of colchicine, possessing vascular targeting activity and showing high activity in several anticancer animal models [11]. In contrast to the preparation of the 4-aryl derivatives, the synthesis of 4-alkyl-4*H*-chromenes is poorly represented in the literature.

Results and discussion

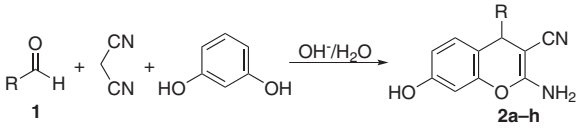
In earlier published works, there are two approaches to the synthesis of 4-alkyl-2-amino-4*H*-chromenes. The first involves the reaction of 2-(2-acyl- or 2-nitrovinyl) phenols and malononitrile that leads to the 4-acyl- or 4-nitromethyl-2-amino-4*H*-chromenes [15–17]. The second variant is based on the base-initiated reaction between 3,4-unsubstituted coumarins and malononitrile followed by ring-opening and ring-closing reactions [13, 14, 18]. However, these methods are not suitable for the synthesis of simple 4-alkyl-2-amino-4*H*-chromenes.

A common method for the synthesis of 2-amino-4-aryl-4*H*-chromene-3-carbonitriles and similar compounds is the three-component condensation of malononitrile, aromatic aldehyde, and phenol or cyclic 1,3-dicarbonyl compound in various solvents [11, 19, 20]. Using this approach to obtain new derivatives of 2-amino-4*H*-chromenes, we investigated the reaction of aliphatic aldehydes **1**, malononitrile and resorcinol, that gave 4-alkyl-2-amino-7-hydroxy-4*H*-chromene-3-carbonitriles **2a–h** in 23–76% yields (Scheme 1).

Low yields of compounds **2a,b** are apparently due to the resorcinol-aldehyde condensations. The structures of compounds **2a–h** were confirmed by IR, NMR spectroscopy, and mass spectrometry.

Conclusions

In this paper, we described the eco-friendly synthesis of 4-alkyl-2-amino-4*H*-chromene derivatives using the methodology of a multicomponent synthesis. There are several articles that describe the synthesis of 4-alkyl-2-amino-4*H*-chromene derivatives **2c,h** using ultrasound irradiation and Fe_3O_4 or MgO nanoparticles as catalyst [21–24]. However, their NMR data (^{13}C NMR data in particular) and melting points are different from ours and incorrect. Accordingly, this article describes the method of synthesis of 4-alkyl-2-amino-4*H*-chromene derivatives for the first time.



2a: R = H; **2b**: R = Me; **2c**: R = Pr; **2d**: R = *i*-Pr; **2e**: R = *n*-C_5H_{11}; **2f**: R = $CH(CH_2CH_3)_2$; **2g**: R = *n*-C_6H_{13}; **2h**: R = *n*-C_7H_{15};

Scheme 1 One-pot synthesis of 4-alkyl-2-amino-4*H*-chromene derivatives **2a–h**.

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Experimental

The reaction progress was monitored and the purity of compounds was analyzed by TLC on Silufol UV-254 plates (development by UV irradiation, exposure to iodine vapor, or thermal decomposition). IR spectra were recorded on an IR Fourier spectrophotometer FSM-1202 using mulls in mineral oil. The ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker DRX-500 (500 and 125 MHz, respectively) in DMSO-d_6. Mass spectra were taken on a Finnigan MAT INCOS-50 instrument (EI, 70 eV).

General procedure for the synthesis of 4-alkyl-2-amino-7-hydroxy-4*H*-chromene-3-carbonitriles 2

A solution of resorcinol (10 mmol) and KOH (10 mmol) in water (10 mL) was added to a mixture of aliphatic aldehyde **1** (10 mmol) and malononitrile (10 mmol) in water (10 mL). The mixture was stirred at room temperature for 60 min. The resulting precipitate was filtered, washed with water, dried, and crystallized from benzene or mixture of benzene and isopropanol.

2-Amino-7-hydroxy-4*H*-chromene-3-carbonitrile (2a) This compound was obtained in 23% yield (0.43 g) as a pale yellow solid; mp 198–199°C (dec); ^{1}H NMR: δ 3.32 (s, 2H, CH_2), 6.34 (d, 1H, J = 2.4 Hz, CH), 6.52 (dd, 1H, J = 8.3 Hz, J = 2.4 Hz, CH), 6.70 (s, 2H, NH_2), 6.96 (d, 1H, J = 8.3 Hz, CH), 9.60 (s, 1H, OH). IR: 3413, 3325, 3221 (NH_2, OH), 2179 (CN), 1632 cm^{-1} (C=C); MS: *m/z* (%) 188 [M]$^+$ (56), 187 [M–1]$^+$ (100). Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.29; N, 14.89. Found: C, 63.69; H, 4.42; N, 14.73.

2-Amino-7-hydroxy-4-methyl-4*H*-chromene-3-carbonitrile (2b) This compound was obtained in 38% yield (0.77 g) as a white solid; mp 159–160°C (dec); ^{1}H NMR: δ 1.25 (d, 3H, J = 6.7 Hz, CH_3), 3.46 (q, 1H, J = 6.7 Hz, CH), 6.33 (d, 1H, J = 2.4 Hz, CH), 6.55 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz, CH), 6.65 (s, 2H, NH_2), 7.06 (d, 1H, J = 8.4 Hz, CH), 9.59 (s, 1H, OH); IR: 3436, 3328, 3210 (NH_2, OH), 2180 (CN), 1637 cm^{-1} (C=C); MS: *m/z* (%) 202 [M]$^+$ (5), 187 [M–15]$^+$ (100). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.53; H, 4.89; N, 13.86.

2-Amino-7-hydroxy-4-propyl-4*H*-chromene-3-carbonitrile (2c) This compound was obtained in 65% yield (1.49 g) as a white solid; mp 145–146°C (mp 160–162°C [24]); ^{1}H NMR: δ 0.82 (t, 3H, J = 7.3 Hz, CH_3), 1.01–1.09 (m, 1H, CH_2), 1.20–1.27 (m, 1H, CH_2), 1.47–1.59 (m, 2H, CH_2), 3.44 (t, 1H, J = 5.0 Hz, CH), 6.34 (d, 1H, J = 2.4 Hz, CH), 6.55 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz, CH), 6.69 (s, 2H, NH_2), 7.01 (d, 1H, J = 8.4 Hz, CH), 9.59 (s, 1H, OH); ^{13}C NMR: δ 161.2, 156.8, 149.9, 128.7, 121.1, 114.1, 112.0, 102.2, 54.5, 40.4, 33.7, 17.5, 14.0; IR: 3434, 3340, 3217 (NH_2, OH), 2178 (CN), 1647 cm^{-1} (C=C); MS: *m/z* (%) 230 [M]$^+$ (5), 187 [M–43]$^+$ (100). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.59; H, 6.23; N, 12.28.

2-Amino-7-hydroxy-4-isopropyl-4*H*-chromene-3-carbonitrile (2d) This compound was obtained in 72% yield (1.66 g) as a white solid; mp 196–198°C; ^{1}H NMR: δ 0.70 (d, 3H, J = 6.8 Hz, CH_3), 0.82 (d, 3H, J = 6.8 Hz, CH_3), 1.77 (d sept, 1H, J = 6.8 Hz, J = 3.6 Hz, CH), 3.25 (d, 1H, J = 3.5 Hz, CH), 6.36 (d, 1H, J = 2.4 Hz, CH), 6.55 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz, CH), 6.74 (s, 2H, NH_2), 6.97 (d, 1H, J = 8.4 Hz, CH), 9.58 (s, 1H, OH). IR: 3439, 3345, 3218 (NH_2, OH), 2178 (CN), 1639 cm^{-1} (C=C); MS: *m/z* (%) 230 [M]$^+$ (2), 187 [M–43]$^+$ (100). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.75; H, 6.18; N, 12.21.

2-Amino-7-hydroxy-4-pentyl-4*H*-chromene-3-carbonitrile (2e) This compound was obtained in 75% yield (1.94 g) as a white solid; mp 132–133°C; ^{1}H NMR: δ 0.80 (t, 3H, J = 6.9 Hz, CH_3), 1.01–1.60 (m, 8H, $(CH_2)_4$), 3.45 (t, 1H, J = 4.8 Hz, CH), 6.33 (d, 1H, J = 2.1 Hz, CH), 6.54 (dd, 1H, J = 8.4 Hz, J = 2.1 Hz, CH), 6.68 (s, 2H, NH_2), 7.01 (d, 1H, J = 8.4 Hz, CH), 9.59 (s, 1H, OH). IR: 3420, 3339, 3220 (NH_2, OH), 2174 (CN), 1646 cm^{-1} (C=C); MS: *m/z* (%) 258 [M]$^+$ (3), 187 [M–71]$^+$ (100). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.82; H, 6.97; N, 10.73.

2-Amino-7-hydroxy-4-(pentan-3-yl)-4*H*-chromene-3-carbonitrile (2f) This compound was obtained in 70% yield (1.81 g) as a white solid; mp 182–183°C; ^{1}H NMR: δ 0.78 (t, 3H, J = 7.4 Hz, CH_3), 0.91 (t, 3H, J = 7.4 Hz, CH_3), 1.08–1.27, 1.32–1.39 (m, 5H, $2CH_2$, CH), 3.48 (d, 1H, J = 3.0 Hz, CH), 6.35 (d, 1H, J = 2.4 Hz, CH), 6.55 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz, CH), 6.71 (s, 2H, NH_2), 6.94 (d, 1H, J = 8.4 Hz, CH), 9.58 (s, 1H, OH); IR: 3437, 3342, 3224 (NH_2, OH), 2182 (CN), 1646 cm^{-1} (C=C); MS: *m/z* (%) 258 [M]$^+$ (1), 187 [M–71]$^+$ (100). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.88; H, 6.92; N, 10.71.

2-Amino-4-hexyl-7-hydroxy-4*H*-chromene-3-carbonitrile (2g) This compound was obtained in 76% yield (2.07 g) as a white solid; mp 119–120°C; ^{1}H NMR: δ 0.82 (t, 3H, J = 6.8 Hz, CH_3), 0.97–1.59 (m, 10H, $(CH_2)_5$), 3.44 (t, 1H, J = 4.7 Hz, CH), 6.33 (d, 1H, J = 2.4 Hz, CH), 6.54 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz, CH), 6.68 (s, 2H, NH_2), 7.00 (d, 1H, J = 8.4 Hz, CH), 9.59 (s, 1H, OH); IR: 3431, 3341, 3221 (NH_2, OH), 2184 (CN), 1644 (C=C); MS: *m/z* (%) 272 [M]$^+$ (2), 187 [M–85]$^+$ (100). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.43; H, 7.37; N, 10.36.

2-Amino-4-heptyl-7-hydroxy-4*H*-chromene-3-carbonitrile (2h) This compound was obtained in 68% yield (1.95 g) as a white solid; mp 117–118°C (mp 124–126°C [24]); ^{1}H NMR: δ 0.83 (t, 3H, J = 7.0 Hz, CH_3), 0.92–1.62 (m, 12H, $(CH_2)_6$), 3.44 (t, 1H, J = 4.9 Hz, CH), 6.34 (d, 1H, J = 2.4 Hz, CH), 6.54 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz, CH), 6.68 (s, 2H, NH_2), 7.00 (d, 1H, J = 8.4 Hz, CH), 9.02 (br.s, 1H, OH); IR: 3432, 3348, 3227 (NH_2, OH), 2179 (CN), 1645 cm^{-1} (C=C); MS: *m/z* (%) 286 [M]$^+$ (1), 187 [M–99]$^+$ (100). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.23; H, 7.90; N, 9.95.

Acknowledgments: This research was supported by the Presidential Grant of the Russian Federation for Young Scientists (MK-6312.2015.3).

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