Study on the synthesis of some (un)substituted 2-amino-4-aryl-7-hydroxy-4*H*-chromene-3-carbonitriles in the water medium

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Abstract

An efficient and simple synthesis of substituted 2-amino-4*H*-chromene-3-carbonitriles was developed by the one-pot and three-component reaction of a mixture of corresponding substituted benzaldehydes, resorcinol, and malononitrile in the presence of sodium carbonate solution as a catalyst at room temperature.

Keywords: 4*H*-Chromene; One-pot reaction; Multi-Component Reaction; Propargyl Ether; Single-crystal X-ray structure.

1. Introduction

Recently, the multi-component coupling reactions (MCRs) are interesting in organic synthesis due to their conveniences and benefits [1]. In these reactions, three or more starting materials react with each other to form a product, where all or most of the atoms contribute to the newly formed product. Essentially, in an MCR, a product is created by putting components or members together according to a cascade of elementary chemical reactions [1]. Histologically, the MCRs were discovered by Adolph Strecker in1860 [2] with the synthesis of α-amino acid, involving the reaction of potassium cyanide, ammonium chloride, and an aldehyde to make an alpha amino acid, and nowadays are continuously developed organic synthetic laboratories everywhere [3, 4].

The organic reactions that are carried out in an aqueous medium and at room temperature are of great interest to synthetic chemists [5, 6]. Water is the environmental, nonflammable, non-hazardous, inexpensive, and naturally available solvent. Water also gives the benefits of simple workup and purification by simple phase separation techniques. Therefore, organic reactions carried out in aqueous media are an attractive and interesting area of the of green chemistry [7, 8]. Also, the performance of the organic reactions at room temperature also helps mitigate the decomposition of the product (if available) or the formation of unwanted products [9].

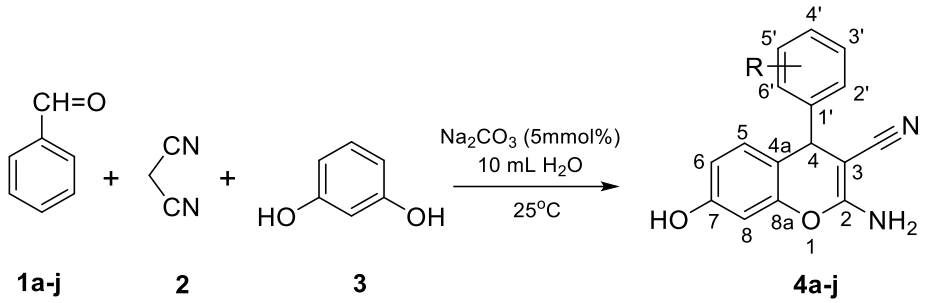
4*H*-Chromene derivatives and compounds with chromene moiety have notable usage in organic synthesis due to their biological activities [10]. These compounds function as the important pharmacophores, which are associated with a broad range of pharmacological activities. They are antimicrobial [11], hypolipidemic [12], anti-inflammatory [13, 14], anti-proliferative [15], antioxidant [11, 16], anticoagulant [17], and antileishmanial [18], antitumor [15], anti-diabetic [19], cytotoxicity [10, 20], and anticancer [16, 20] agents.

It's known that 2-amino-4H-chromene compounds have been synthesized from (un)substituted benzaldehydes, malononitrile, and (un)substituted resorcinols [21, 22]. Chromene ring is formed in the presence some inorganic and organic catalysts, such as K_2CO_3 in water [23], Ca $(OH)_2$ [24], nano ZnO [25], nanocrystalline MgO in aqueous media [26], silica gel supported polyamine [27], ammonium acetate [28], potassium phthalimide [29]. Some ionic liquids are also used as catalysts for this purpose, for examples, [2-Eim]OAc [30], basic ionic liquids from triethylenetetramine or ethylenediamine and TFA [31]. Even monodisperse Pd nanomaterials anchored graphene oxide [32] and bimetallic Pd-Ru/graphene oxide based catalysts [33] are also applied in the one-pot three-component synthesis of 2-amino-4*H*-chromene derivatives. In some cases, the 4*H*-chromene ring is closed in one-pot and solvent-free synthesis using grindstone chemistry [34] (by simple grinding). Bovine serum albumin is also used as a catalyst in a domino reaction for the synthesis of 2-amino-4H-chromene derivatives [35]. Even 2,2,2-trifluoroethanol is used, too, as a metal-free and reusable medium in a facile and efficient synthesis of 2-amino-3-cyano-4H-chromenes and tetrahydrobenzo[*b*]pyrans [36]. The ultrasound irradiation is applied under procedure without catalyst [37] or catalyzed by Fe_3O_4-functionalized nanoparticles with chitosan [38], by glycine in aqueous medium under sonic conditions [39], or by electrochemically induced multi-component condensation in the presence of NaBr [40].

Therefore, in this article, we report on the synthesis of some (un)substituted 2-amino-7-hydroxy-4*H*-chromene-3-carbonitriles *via* a one-pot three-component reaction in aqueous media (Scheme 1).

2. Results and discussion

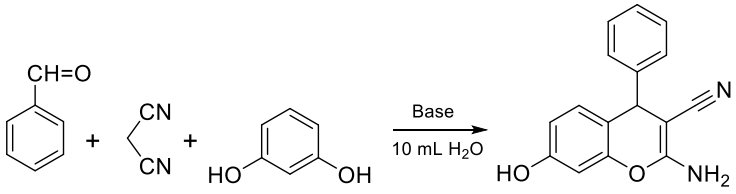
For the purpose of applying an environmental and cheap solvent, we used water as a solvent in the synthesis of compounds of (un)substituted 2-amino-7-hydroxy-4-aryl-4*H*-chromene-3-carbonitriles. The model reaction was made with unsubstituted benzaldehyde **1a**. The base, reaction time and reaction temperature optimizations for yields are listed in Table 1. The different inorganic and organic basic catalysts were used in the catalyst surveys, such as NaOH, $NaHCO_3$, Na_2CO_3, K_2CO_3, ammonium acetate, dimethylamino pyridine (DMAP), triethylamine and piperidine and the reactions were examined in water at room temperature.



Scheme 1. Synthetic route for substituted 2-amino-7-hydroxy-4-aryl-4*H*-chromene-3-carbonitriles. Condition reactions: *see* Table 2.

In general, the inorganic bases gave the product **4a** in higher yields (Entries 1−4), while the organic bases gave the product **4a** in lower yields (Entries 5−8). We found that sodium carbonate (with 0.1 equivalent amount, Entries 3) in 10 mL of water provided the target product **4a** in 90% yield. Therefore, sodium carbonate was chosen for further investigations in water at different times and temperatures (Entries 8−15).

Table 1. One-pot synthesis of 4*H*-chromene in presence of various bases [a]



Entry	Bases (equiv)	Time (min)	Temp. (°C)	Yield of **4a** [b] (%)
1	NaOH (0.1)	2	25	58
2	$NaHCO_3$ (0.1)	2	25	65
3	Na_2CO_3 (0.1)	2	25	90
4	K_2CO_3 (0.1)	2	25	76
5	Ammonium acetate (0.1)	2	25	67
6	DMAP (0.1)	2	25	50
7	Et_3N (0.1)	2	25	45
8	Piperidine (0.1)	2	25	55
9	Na_2CO_3 (0.05)	2	25	90
10	Na_2CO_3 (0.15)	2	25	88
11	Na_2CO_3 (0.2)	2	25	87
12	Na_2CO_3 (0.1)	2	70	80
13	Na_2CO_3 (0.1)	2	Reflux	70
14	Na_2CO_3 (0.1)	3	25	91
15	Na_2CO_3 (0.1)	4	25	90

[a] Reaction conditions: The reaction was performed by using 2 mmol of **1**, 2 mmol of **2**, and 2 mmol of **3** in the presence of 10 mol % or 5 mol% of basic additive in 10 mL of water under different temperature conditions. [b] Isolated yields.

When half reduce the concentration of this catalyst was done, the yield of **4a** did not change (in 90% yield in Entry 9).

We found that increasing amounts of this catalyst, from 0.1 equiv (Entry 3) to 0.15 equiv (Entry 10) to 0.2 equiv (Entry 11), lead to reduce the slight reaction yields (88% in Entry 10 and 87% in the Entry 11). On the other hand, raising the temperature of the reaction from 25°C (Entry 3) to 70°C (Entry 12) to the reflux-heating method (Entry 13) lead to reduced product yields of **4a**, to 80% and 70%, respectively. The reaction time does not significantly change the yields of the products. For examples, in Entries 14 and 15, the yields of **4a** were 91% (for 180 min) and 90% (for 240 min), respectively. Hence, sodium carbonate in the amount of 0.05 equiv in 10 mL of water is used in the synthesis of all the other chromenes **4b-l** (Table 2).

The absorption band that appeared in regions at ν=3500–3450 cm^{-1} belonged to the hydroxyl group and two other absorption bands that appeared in regions 3420–3250 cm^{-1} in IR spectra of 4*H*-chromenes **4a-l** confirmed the presence of the amino group in these molecules. The nitrile functional group had the absorption band at 2203–2188 cm^{-1}. All ^{1}H NMR spectra of chromenes **4a-l** had characteristic signal at δ=4.95–4.50 ppm with an integral height of one proton; this signal belongs to proton on position 4 and could be used as the identification sign for 4*H*-pyrans and 4*H*-chromenes. In addition, the chemical shift appearing at δ=9.70–9.60 ppm confirmed the presence of hydroxyl group on position 7 of chromene ring. The amino group on position 2 of chromenes **4a-l** had resonance signal at δ=6.84–6.83 ppm. The carbon atom at position 2 had chemical shift downfield at δ=161.4–160.1 ppm due to the electron-withdrawing influence of oxygen atom in chromene ring. The carbon atom in the nitrile group showed a resonance signal at δ=121.2–119.6 ppm. This evidence proved that chromenes **4a-l** have been formed through three component reaction between substituted benzaldehydes **1a-l**, malononitrile **2** and resorcinol **3** in the presence of sodium carbonate as a catalyst.

Table 2. Sodium carbonate catalyzed the one-pot synthesis of 4*H*-chromene derivatives (**4a-l**)[a]

Entry	R		Time (hrs)	Temp. (°C)	Yield [b] (%)
1	H	**4a**	2	25	90
2	4-NO_2	**4b**	2	25	88
3	3-NO_2	**4c**	2	25	78
4	2,4-dichloro	**4d**	2	25	89
5	4-Cl	**4e**	2	25	84
6	3-Cl	**4f**	2	25	76
7	2-Cl	**4g**	2	25	92
8	4-Me	**4h**	2	25	77
9	4-iPr	**4i**	2	25	62
10	4-OMe	**4j**	2	25	79
11	3-OMe	**4k**	2	25	62
12	2-OMe	**4l**	2	70	76

[a] Reaction conditions: The reaction was performed by using 2 mmol of **1a-l**, 2 mmol of **2**, and 2 mmol of **3** in the presence of 5 mol% of sodium carbonate in 10 mL of water at room temperature conditions. [b] Isolated yields.

3. Experimental

Melting points were determined by open capillary method on STUART SMP3 instrument (BIBBY STERILIN, UK) and are uncorrected. IR spectra (KBr disc) were recorded on an Impact 410 FT-IR Spectrometer (Nicolet, USA). ^{1}H and ^{13}C NMR spectra were recorded on Avance Spectrometer AV500 (Bruker, Germany) at 500.13 MHz and 125.77 MHz, respectively, using DMSO-d_6 as solvent and TMS as an internal standard. All analytical thin-layer chromatography (TLC) was performed on silica gel 60 $WF_{254}S$ aluminum sheets (Merck, Germany) and was visualized with UV light. Chemical reagents in high purity were purchased from the Merck Chemical Company. All materials were of commercial reagent grade.

3.1. General procedure for synthesis of 7-hydroxy-4H-chromene-3-carbonitriles and analytical data

To a mixture of substituted benzaldehyde **1a-i** (2 mmol), malononitrile **2** (2 mmol), and resorcinol **3** (2 mmol) in 5 mL of water was added a solution sodium carbonate (2.12 mg, 0.5 mmol) of in 5 mL of water. The reaction mixture was stirred for 2 hrs at room temperature (the reactions were monitored by TLC). Separated solid product was filtered, washed by water and recrystallized from mixture of 96% ethanol and toluene to afford the titled chromene-3-carbonitriles **4a-l**. The characterizations of these 2-amino-7-hydroxy-4-aryl-4*H*-chromene-3-carbonitriles **4a-l** are as follows.

*3.1.1. 2-Amino-7-hydroxy-4-phenyl-4H-chromene-3-carbonitrile (**4a**)*

Ivory white solids. M.p. 235–236°C (from 96% ethanol/toluene 1:1), ref [40]: 234–237°C; IR (KBr), ν (cm^{-1}): 3500,

3427, 3350, 2192, 1647, 1600, 1520, 1145, 1104; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.70 (s, 1H, 7-OH), 7.31 (t, 2H, *J* = 7.5 Hz, H-3′ & H-5′), 7.21 (t, 1H, *J* = 7.5 Hz, H-4′), 7.17 (d, 2H, *J* = 7.5 Hz, H-2′ & H-6′), 6.86 (s, 2H, 2-NH_2), 6.81 (d, 1H, *J* = 8.5 Hz, H-5), 6.49 (dd, 1H, *J* = 8.5, 2.5 Hz, H-6), 6.42 (d, 1H, *J* = 2.5 Hz, H-8), 4.63 (s, 1H, H-4); ^{13}C NMR (125.77 MHz, DMSO-d_6), δ (ppm): 160.7 (C-2), 157.6 (C-7), 149.3 (C-8a), 146.8 (C-1′), 130.4 (C-5), 129.1 (C-3′ & C-5′), 127.9 (C-2′ & C-6′), 127.1 (C-4′), 121.1 (C≡N), 114.2 (C-4a), 112.9 (C-6), 102.7 (C-8), 56.8 (C-3), 40.5 (C-4).

*3.1.2. 2-Amino-7-hydroxy-4- (4-nitrophenyl)-4H-chromene-3-carbonitrile (**4b**)*

Yellow crystals. M.p. 205–206°C (from 96% ethanol/toluene 1:1), ref [21]: 211–213°C; IR (KBr), ν (cm^{-1}): 3460, 3335, 3210, 2188, 1640, 1582, 1510, 1346, 1157, 1103; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.79 (s, 1H, OH), 8.20 (d, 2H, *J* = 8.75 Hz, H-3’ & H-5’), 7.46 (d, 2H, *J* = 8.75 Hz, H-2’ & H-6’), 7.03 (s, 2H, 2-NH_2), 6.82 (d, *J* = 8.0 Hz, 1H, H-5), 6.51 (dd, *J* = 8.25, 2.25 Hz, 1H, H-6), 6.46 (d, 1H, *J* = 2.5 Hz, H-8), 4.87 (s, 1H, H-4); ^{13}C NMR (125.77 MHz, DMSO-d_6), δ (ppm): 160,9 (C-2); 158,0 (C-7); 154,2 (C-8a); 149,4 (C-1′); 146,8 (C-4′); 130,4 (C-5); 129,2 (C-2′ & C-6′); 124,5 (C-3′ & C-5′); 120,8 (C≡N); 113,1 (C-4a); 112,8 (C-6); 102,9 (C-8); 55,6 (C-3); 40,1 (C-4).

*3.1.3. 2-Amino-7-hydroxy-4- (3-nitrophenyl)-4H-chromene-3-carbonitrile (**4c**)*

Pale yellow crystals. M.p. 211–213°C (from 96% ethanol/toluene 1:1), ref [21]: 189–191°C; IR (KBr), ν (cm^{-1}): 3500, 3429, 3300, 2188, 1647, 1582, 1510, 1346, 1154, 1047; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.79 (s, 1H, 7-OH), 8.10 (ddd, *J* = 8.0, 2.0, 1.5 Hz, 1H, H-4′), 8.04 (t, *J* = 2.0 Hz, 1H, H-2′), 7.67 (dt, *J* = 7.75, 1.5 Hz, 1H, H-6′), 7.64 (t, *J* = 7.75 Hz, 1H, H-5′), 7.04 (s, 2H, 2-NH_2), 6.86 (d, *J* = 8.5 Hz, 1H, H-5), 6.52 (dd, *J* = 8.5, 2.5 Hz, 1H, H-6), 6.46 (d, *J* = 2.5 Hz, 1H, H-8), 4.92 (s, 1H, H-4); ^{13}C NMR (125.77 MHz, DMSO-d_6), δ (ppm): 161.0 (C-2), 158.0 (C-7), 149.4 (C-8a), 149.1 (C-3′), 148.4 (C-1′), 134.8 (C-6′), 130.8 (C-2′), 130.5 (C-5), 122.3 (C-5′), 122.2 (C-4′), 120.8 (C≡N), 113.2 (C-4a), 113.0 (C-6), 102.9 (C-8), 55.8 (C-3), 40.3 (C-4).

*3.1.4. 2-Amino-7-hydroxy-4- (2,4-dichlorophenyl)-4H-chromene-3-carbonitrile (**4d**)*

Pale yellow crystals. M.p. 189–191°C (from 96% ethanol/toluene 1:1); ref [41]: 256–258°C; IR (KBr), ν (cm^{-1}): 3500, 3470, 3300, 3254, 3050, 2186, 1628, 1580, 1503, 1154, 1046; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.78 (s, 1H, 7-OH), 7.58 (d, *J* = 2.0 Hz, 1H, H-3′), 7.40 (dd, *J* = 8.25, 2.0 Hz, 1H, H-5′), 7.22 (d, *J* = 8.25 Hz, 1H, H-6′), 6.97 (s, 2H, 2-NH_2), 6.73 (d, *J* = 8.5 Hz, 1H, H-5), 6.50 (dd, *J* = 8.5, 2.5 Hz, 1H, H-6), 6.43 (d, *J* = 2.5 Hz, 1H, H-8), 5.14 (s, 1H, H-4); ^{13}C NMR (125.77 MHz, DMSO-d_6), δ (ppm): 161.0 (C-2), 158.0 (C-7), 149.5 (C-8a), 142.4 (C-1′), 133.3 (C-2′), 132.7 (C-4′), 132.6 (C-6′), 129.7 (C-3′), 129.6 (C-5), 128.5 (C-5′), 120.6 (C≡N), 113.1 (C-4a), 112.4 (C-6), 102.8 (C-8), 54.9 (C-3), 37.4 (C-4).

*3.1.5. 2-Amino-7-hydroxy-4- (4-chlorophenyl)-4H-chromene-3-carbonitrile (**4e**)*

Pale yellow crystals. M.p. 238–240°C (from 96% ethanol/toluene 1:1), ref [40]: 162–164°C; IR (KBr), ν (cm^{-1}): 3467, 3341, 3262, 2191, 1697, 1640, 1510, 1157, 1109; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.72 (s, 1H, 7-OH), 7.38 (dt, 2H, *J* = 8.75, 2.25 Hz, H-2′ & H-6′), 7.20 (dt, 2H, *J* = 8.75, 2.25 Hz, H-3′ & H-5′), 6.91 (s, 2H, 2-NH_2), 6.79 (d, *J* = 8.5 Hz, 1H, H-5), 6.50 (dd, *J* = 8.5, 2.5 Hz, 1H, H-6), 6.41 (d, 1H, *J* = 2.5 Hz, H-8), 4.67 (s, 1H, H-4); ^{13}C NMR (125.77 MHz, DMSO-d_6), δ (ppm): 160.2 (C-2), 157.2 (C-7), 148.8 (C-8a), 145.3 (C-1′), 131.2 (C-4′), 129.9 (C-5), 129.3 (C-2′ & C-6′), 128.5 (C-3′ & C-5′), 120.5 (C≡N), 113.2 (C-4a), 112.5 (C-6), 102.2 (C-8), 55.8 (C-3), 39.0 (C-4).

*3.1.6. 2-Amino-7-hydroxy-4- (3-chlorophenyl)-4H-chromene-3-carbonitrile (**4f**)*

Pale yellow crystals. M.p. 192-196°C (from 96% ethanol/toluene 1:1); ref [41]: 106–109°C; IR (KBr), ν (cm^{-1}): 3500, 3465, 3328, 3254, 3050, 2190, 1640, 1580, 1503, 1154, 1044; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.81 (s, 1H, 7-OH), 7.35 (t, *J* = 7.75 Hz, 1H, H-5′), 7.28 (dt, *J* = 7.75, 1.0 Hz, 1H, H-4′), 7.21 (br. s, 1H, H-2′), 7.15 (d, *J* = 7.75 Hz, 1H, H-6′), 6.96 (s, 2H, 2-NH_2), 6.83 (d, *J* = 8.5 Hz, 1H, H-5), 6.51 (dd, *J* = 8.5, 2.0 Hz, 1H, H-6), 6.43 (d, *J* = 2.0 Hz, 1H, H-8), 4.69 (s, 1H, H-4); ^{13}C NMR (125.77 MHz. DMSO-d_6), δ (ppm): 160.9 (C-2), 157.7 (C-7), 149.3 (C-8a), 149.3 (C-1′), 133.6 (C-3′), 131.1 (C-5′), 130.4 (C-5), 127.6 (C-2′), 127.2 (C-4′), 126.7 (C-6′), 121.0 (C≡N), 113.5 (C-4a), 113.0 (C-6), 102.8 (C-8), 56.1 (C-3), 49.1 (C-4).

*3.1.7. 2-Amino-7-hydroxy-4- (2-chlorophenyl)-4H-chromene-3-carbonitrile (**4g**)*

Pale yellow crystals. M.p. 216–217°C (from 96% ethanol/toluene 1:1); ref [21]: 184–186°C; IR (KBr), ν (cm^{-1}): 3465, 3328, 3254, 3050, 2190, 1640, 1580, 1503, 1154, 1044; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.73 (s, 1H, 7-OH), 7.42 (dd, 1H, *J* = 7.75, 1.25 Hz, H-3′), 7.31 (td, 1H, *J* = 7.5, 1.0 Hz, H-6′), 7.25 (td, 1H, *J* = 7.75, 1.75 Hz, H-4′), 7.19 (dd, 1H, *J* = 7.5, 2.0 Hz, H-5′), 6.92 (s, 2H, 2-NH_2), 6.74 (d, 1H, *J* = 8.5 Hz, H-5), 6.48 (dd, 1H, *J* = 8.5, 2.5 Hz, H-6), 6.41 (d, 1H, *J* = 2.5 Hz, H-8), 5.14 (s, 1H, H-4); ^{13}C NMR (125.77 MHz, DMSO-d_6), δ (ppm): 160.5 (C-2), 157.3 (C-7),

149.0 (C-8a), 142.8 (C-1′), 131.8 (C-5), 130.8 (C-2′), 129.7 (C-3′), 129.2 (C-4′), 128.5 (C-5′), 127.8 (C-6′), 120.3 (C≡N), 112.5 (C-6 & C-4a), 102.2 (C-8), 54.9 (C-3), 37.2 (C-4).

*3.1.8. 2-Amino-7-hydroxy-4- (4-methylphenyl)-4H-chromene-3-carbonitrile (**4h**)*

Pale yellow solids. M.p. 208–210°C (from 96% ethanol/toluene 2:1), ref [40]: 182–184°C; IR (KBr), ν (cm^{-1}): 3454, 3320, 3256, 3200, 2195, 1638, 1587, 1503, 1152, 1047; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.72 (s, 1H, 7-OH), 7.17 (d, 2H, *J* = 8.0 Hz, H-2′ & H-6′), 7.11 (d, 2H, *J* = 8.0 Hz, H-3′ & H-5′), 6.88 (s, 2H, 2-NH_2), 6.84 (d, 1H, *J* = 8.5 Hz, H-5), 6.49 (dd, 1H, *J* = 8.5, 2.5 Hz, H-6), 6.46 (d, 1H, *J* = 2.5 Hz, H-8), 4.63 (s, 1H, H-4), 3.40 (s, 3H, 4′-CH_3); ^{13}C NMR (125.77 MHz, DMSO-d_6), δ (ppm): 160.6 (C-2), 157.5 (C-7), 149.3 (C-8a), 143.9 (C-1′), 136.2 (C-4′), 130.4 (C-5), 129.6 (C-2′ & C-6′), 127.8 (C-3′ & C-5′), 121.1 (C≡N), 114.4 (C-4a), 112.8 (C-6), 102.6 (C-8), 56.9 (C-3), 40.1 (C-4), 21.1 (4′-CH_3).

*3.1.9. 2-Amino-7-hydroxy-4- (4-isopropylphenyl)-4H-chromene-3-carbonitrile (**4i**)*

Ivory white crystals. M.p. 228–230°C (from 96% ethanol/toluene 2:1); IR (KBr), ν (cm^{-1}): 3313, 3300, 3171, 2194, 1639, 1584, 1570, 1155, 1104; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.67 (s, 1H, 7-OH), 7.17 (d, 2H, *J* = 8.0 Hz, H-2′ & H-6′), 7.08 (d, 2H, *J* = 8.0 Hz, H-3′ & H-5′), 6.83 (s, 2H, 2-NH_2), 6.82 (d, 1H, *J* = 9.0 Hz, H-5), 6.49 (dd, 1H, *J* = 8.25, 2.25 Hz, H-6), 6.41 (d, 1H, *J* = 2.5 Hz, H-8), 4.58 (s, 1H, H-4), 2.84 [septet, 1H, *J* = 7.0 Hz, 3-**CH** $(CH_3)_2$, 1.18 [d, 6H, *J* = 7.0 Hz, 3-CH (**CH_3**)$_2$]; ^{13}C NMR (125.77 MHz, DMSO-d_6), δ (ppm): 160.7 (C-2), 157.5 (C-7), 149.3 (C-8a), 147.1 (C-4′), 144.3 (C-1′), 130.4 (C-5), 127.7 (C-2′ & C-6′), 127.0 (C-3′ & C-5′), 121.2 (C≡N), 114.4 (C-4a), 112.8 (C-6), 102.6 (C-8), 56.9 (C-3), 39.5 (C-4), 33.5 [4′-**CH** $(CH_3)_2$], 24.3 [4′-CH (**CH_3**)$_2$].

*3.1.10. 2-Amino-7-hydroxy-4- (4-methoxyphenyl)-4H-chromene-3-carbonitrile (**4j**)*

Yellow crystals. M.p. 225–227°C (from 96% ethanol/toluene 2:1); ref [40]: 110−112°C; IR (KBr), ν (cm^{-1}): 3550, 3420, 3358, 2196, 1642, 1592, 1570, 1158, 1110; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.66 (s, 1H, 7-OH), 7.08 (t, 2H, *J* = 8.25 Hz, H-2′ & H-6′), 6.87 (t, 2H, *J* = 8.25 Hz, H-3′ & H-5′), 6.80 (s, 2H, 2-NH_2), 6.78 (d, *J* = 8.5 Hz, 1H, H-5), 6.48 (dd, *J* = 8.5, 2.5 Hz, 1H, H-6), 6.40 (d, 1H, *J* = 2.5 Hz, H-8), 4.57 (s, 1H, H-4), 3.72 (s, 3H, 4-OCH_3); ^{13}C NMR (125.77 MHz, DMSO-d_6), δ (ppm): 160.1 (C-2), 158.0 (C-7), 156.9 (C-8a), 148.8 (C-4′), 138.5 (C-1′), 129.9 (C-5), 128.4 (C-2′ & C-6′), 120.7 (C≡N), 114.1 (C-4a), 113.9 (C-3′ & C-5′), 112.3 (C-6), 102.1 (C-8), 56.6 (C-3), 55.0 (4′-OCH_3), 39.0 (C-4).

*3.1.11. 2-Amino-7-hydroxy-4- (3-methoxyphenyl)-4H-chromene-3-carbonitrile (**4k**)*

Yellow crystals. M.p. 177–179°C (from 96% ethanol/toluene 1:1); IR (KBr), ν (cm^{-1}): 3550, 3420, 3358, 2196, 1642, 1592, 1571, 1151, 1035; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.68 (s, 1H, 7-OH), 7.22 (t, 1H, *J* = 7.25 Hz, H-5′), 6.84 (s, 2H, 2-NH_2), 6.83 (d, 1H, *J* = 7.5 Hz, H-4′), 6.78 (dd, 1H, *J* = 7.0, 2.0 Hz, H-6′), 6.73 (s, 1H, H-2′), 6.72 (d, 1H, *J* = 7.5 Hz, H-5), 6.49 (dd, 1H, *J* = 8.25, 2.25 Hz, H-6), 6.41 (d, 1H, *J* = 2.0 Hz, H-8), 4.59 (s, 1H, H-4), 3.34 (s, 3H, 3′-OCH_3); ^{13}C NMR (125.77 MHz, DMSO-d_6), δ (ppm): 160.3 (C-2), 159.3 (C-7), 157.1 (C-3′), 148.8 (C-8a), 147.9 (C-1′), 129.8 (C-5), 129.7 (C-5′), 120.6 (C-6′), 119.6 (C≡N), 113.6 (C-4a), 113.5 (C-2′), 112.3 (C-4′), 111.5 (C-6), 102.1 (C-8), 54.9 (C-3), 56.1 (C-3), 54.9 (3′-OCH_3), 39.9 (C-4).

*3.1.12. 2-Amino-7-hydroxy-4- (2-methoxyphenyl)-4H-chromene-3-carbonitrile (**4l**)*

Ivory white crystals. M.p. 218–220°C (from 96% ethanol/toluene 2:1), ref [42]: 222–224°C; IR (KBr), ν (cm^{-1}): 3477, 3340, 3250, 3191, 2203, 1643, 1587, 1502, 1157, 1053; ^{1}H NMR (500.13 MHz, DMSO-d_6), δ (ppm): 9.62 (s, 1H, 7-OH), 7.19 (td, 1H, *J* = 8.0, 1.5 Hz, H-6′), 6.99 (td, 1H, *J* = 7.5, 1.5 Hz, H-5′), 6.89 (td, 1H, *J* = 7.25, 1.0 Hz, H-4′), 6.84 (d, 1H, *J* = 9.0 Hz, H-5), 6.78 (s, 2H, 2-NH_2), 6.74 (d, 1H, *J* = 8.5 Hz, H-5), 6.46 (dd, 1H, *J* = 8.5, 2.5 Hz, H-6), 6.39 (d, 1H, *J* = 2.5 Hz, H-8), 4.99 (s, 1H, H-4), 3.34 (s, 3H, 2′-OCH_3); ^{13}C NMR (125.77 MHz, DMSO-d_6), δ (ppm): 161.4 (C-2), 157.4 (C-7), 156.8 (C-2′), 149.6 (C-8a), 134.6 (C-5), 129.7 (C-6′), 129.0 (C-4′), 128.4 (C-5′), 121.2 (C≡N), 114.5 (C-1′), 112.7 (C-4a), 112.0 (C-6), 102.6 (C-8), 56.1 (C-3), 55.8 (2′-OCH_3), 34.0 (C-4).

Conclusions

The use of sodium carbonate as a catalyst in water as the reaction medium in the synthesis of 2-amino-7-hydroxy-4*H*-chromene-3-carbonitriles **4a-l** opens a new direction in chromene chemistry. This synthetic procedure for these chromene-3-carbonitrile ring is a cheap, efficient and simple method.

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