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The Implication of Electrocatalysis in MCR Strategy: Electrocatalytic Multicomponent Transformation of Cyclic 1,3-Diketones, Aldehydes and Malononitrile into Substituted 5,6,7,8-Tetrahydro-4*H*-Chromenes

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The electrochemically induced catalytic multicomponent transformation of cyclic 1,3-diketones, aldehydes and malononitrile in alcoholic solvents results in the formation of substituted 5,6,7,8-tetrahydro-4*H*-chromenes in 85–95% yields. The reaction is performed in an undivided cell in the presence of sodium bromide as an electrolyte. The application of this efficient electrocatalytic method to the formation of tetrahydro-4*H*-chromenes is beneficial for diversity-oriented large-scale processes. The novel concept of an electrocatalytic multicomponent reaction is also ecologically sound. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2006)

Introduction

The development of multicomponent reactions (MCRs) designed to produce elaborate biologically active compounds has become an important area of research in organic, combinatorial and medicinal chemistry.[1] The MCR strategy offers significant advantages over conventional linear-type syntheses because of its flexible, convergent and atom efficient nature.[2]

Among the heterocycles, functionally substituted 4*H*-chromenes (or 4*H*-benzo[b]pyranes) have received considerable attention in the field of medicinal chemistry because of their wide range of useful biological properties, which include spasmolitic-, diuretic-, anticoagulant-, anticancer- and antianaphylactic activities.[3] The current interest in 4*H*-chromene derivatives bearing a nitrile functionality, especially 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles, arises from their potential application in the treatment of human neurodegenerative disorders.[4]

The known multicomponent procedures for the synthesis of 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles employ a three-component condensation of cyclic 1,3-diketones, aryl aldehydes and malononitrile, and is performed under a variety of reaction conditions. The first set of procedures utilize ethanol as the solvent and piperidine,[5] piperidine/ammonium acetate[6] or triethylamine[7] as the catalysts. The yields of the desired products are in the range of 50–60%, and if the reaction is heated to reflux the yields increase to 70–85%. The second set of methods includes the catalysis of the three components with alkyl ammonium salts in water,[8] their catalysis with (*S*)-proline in water or water/ethanol mixtures,[9] or the use of [bmim][BF_4] as a combined solvent/catalyst system.[10] Although these catalytic MCRs afford the corresponding 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles in higher yields (75–95%), they suffer from prolonged reaction times (3–10 h) and high reaction temperatures (up to 90 °C). Finally, Devi and Bhuyan reported the solid state three-component condensation of cyclic 1,3-diketones, aryl aldehydes and malononitrile into the corresponding adduct under microwave irradiation, but the reaction necessitates a temperature of 70–85 °C in the microwave reactor. Furthermore, recrystallization of the crude reaction mixture from ethanol is required.[11] Thus, each of the known MCR methods for the synthesis of 5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles has its merits, but they also suffer from at least one limitation that may include moderate yields, long reaction times, harsh reaction conditions, effluent pollution or tedious work-up procedures.

The advances in electrosynthesis in the last few decades has provided organic chemists with a new and versatile synthetic device of great promise.[12] Despite the significant synthetic potential and ecological advantages of electrochemical methods, the practical usage of the electrochemical procedure is often limited on account of its technical complexity and generally long processing times. In the course of our study on the electrochemical transformation of organic compounds,[13] we have found a new type of electrochemical transformation, namely the electrocatalytic

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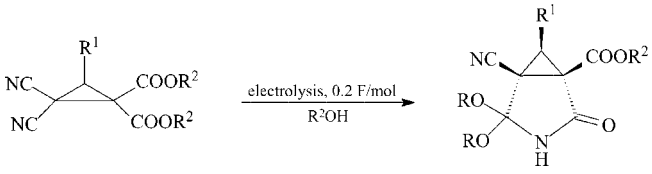
chain transformation of organic compounds induced by a catalytic amount of an electrogenerated base in an undivided cell. The recent example of this type of procedure, which was discovered by us, is the stereoselective electrocatalytic chain transformation of 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates into (1*R*,5*R*,6*R*)*-6-substituted-4,4-dialkoxy-5-cyano-2-oxo-3-azabicyclo[3.1.0]-hexane-1-carboxylates (Scheme 1).[14]



Scheme 1.

This unique electrochemical procedure utilizes a simple undivided cell and is valuable for large-scale processes because of its catalytic nature and the use of a cheap and environmentally responsible chemical reagent – electricity. The use of the described electrocatalytic methodology in base-activated MCRs is highly promising as it allows for the combination of the synthetic virtues of the conventional MCR strategy with the ecological benefits and convenience of the facile electrocatalytic procedure.

Results and Discussion

In the present study we report our results on the electrocatalytic multicomponent chain transformation of cyclic 1,3-diketones, aryl aldehydes and malononitrile into 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles under mild conditions by electrolysis in an undivided cell. The reaction is performed in alcoholic solvents in the presence of sodium bromide as an electrolyte (Scheme 2).

First, to evaluate the synthetic potential of the proposed procedure and to optimize the electrolytic conditions, the electrocatalytic multicomponent transformation of cyclohexane-1,3-dione (**1a**), benzaldehyde (**2a**) and malononitrile into 4*H*-chromene **3a** was studied (Table 1).

Table 1. Electrocatalytic transformation of cyclohexane-1,3-dione (**1a**), benzaldehyde (**2a**) and malononitrile into 4*H*-chromene **3a**.[a]

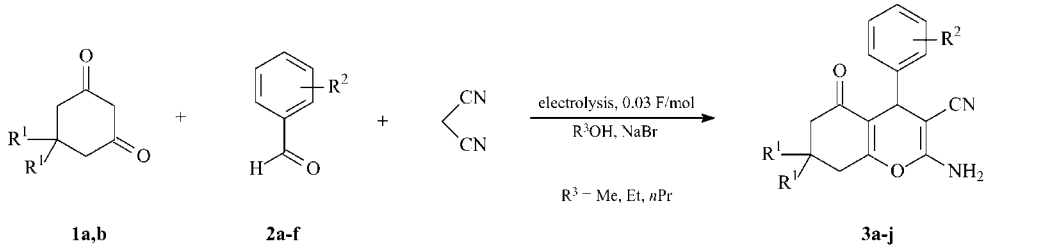
I [mA]	Current density [mA/cm^2]	Time [min]	Alcohol	Electricity passed [F/mol]	Yield of **3a** [%][b]
5	1	100	EtOH	0.03	67
10	2	50	EtOH	0.03	73
20	4	25	EtOH	0.03	87
50	10	10	EtOH	0.03	76
20	4	25	MeOH	0.03	74
20	4	25	*n*PrOH	0.03	95

[a] **1a** (10 mmol), **2a** (10 mmol), malononitrile (10 mmol), NaBr (1 mmol), alcohol (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20 °C. [b] Yield of isolated product obtained by filtration of the reaction mixture.

Excellent conversions of the starting compounds were obtained under 4 mA/cm^2 and 10 mA/cm^2 current densities after 0.03 F/mol of electricity had been passed. The current density 4 mA/cm^2 (I = 20 mA, electrode surface 5 cm^2) was found to be optimal for the electrochemically induced chain process and allowed for the highest yield of 4*H*-chromene **3a**. An increase in the current density up to 10 mA/cm^2 (I = 50 mA) resulted in a slight decrease in the reaction yield, and may be a result of the activation of the undesired direct electrochemical processes that lead to oligomerization of the starting material.

After electrolysis, 4*H*-chromene **3a** was directly crystallized from the reaction mixture. As for the alcoholic solvents, the use of *n*PrOH is preferred when the products are filtered directly after electrolysis.[15] Under the optimal conditions (current density 4 mA/cm^2, 0.03 F/mol passed, *n*PrOH as solvent) the electrolysis of cyclic diketones **1a** and **1b**, aryl aldehydes **2a**–**f** and malononitrile in an undivided cell affords 4*H*-chromenes **3a**–**j** in yields of 85–95% at ambient temperature over a 25 min reaction period (Table 2).

With the above results taken into consideration and the mechanistic data on the electrocatalytic chain cyclizations of tetracyanocyclopropanes[16] and 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates,[14] the following mechanism for the electrocatalytic chain transformation of cyclic diketones **1**, aryl aldehydes **2**, and malononitrile into substi-



1a,b **2a-f** **3a-j**

a R^1 = H
b R^1 = Me

a R^2 = H; **b** R^2 = 4-Me;
c R^2 = 4-MeO; **d** R^2 = 4-Cl;
e R^2 = 3-Br; **f** R^2 = 4-NO_2

a $R^1 = R^2$ = H; **b** R^1 = H, R^2 = 4-Me;
c R^1 = H, R^2 = 4-MeO; **d** R^1 = H, R^2 = 4-Cl;
e R^1 = H, R^2 = 3-Br; **f** R^1 = H, R^2 = 4-NO_2;
g R^1 = Me, R^2 = H; **h** R^1 = Me, R^2 = 4-MeO;
i R^1 = Me, R^2 = 3-Br; **j** R^1 = Me, R^2 = 4-NO_2;

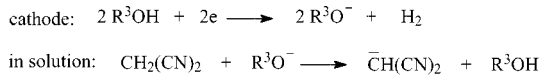
Scheme 2.

Table 2. Electrocatalytic transformation of cyclic diketones **1a** and **1b**, aryl aldehydes **2a**–**f** and malononitrile into 4*H*-chromenes **3a**–**j**.[a]

Cyclic 1,3-diketone	Aldehyde	Current density [mA/cm^2]	Time [min]	Electricity passed [F/mol]	4*H*-Chromene	Yield of **3** [%][b]
1a	**2a**	4	25	0.03	**3a**	95
1a	**2b**	4	25	0.03	**3b**	86
1a	**2c**	4	25	0.03	**3c**	91
1a	**2d**	4	25	0.03	**3d**	85
1a	**2e**	4	25	0.03	**3e**	93
1a	**2f**	4	25	0.03	**3f**	87
1b	**2a**	4	25	0.03	**3g**	84
1b	**2c**	4	25	0.03	**3h**	84
1b	**2e**	4	25	0.03	**3i**	88
1b	**2f**	4	25	0.03	**3j**	85

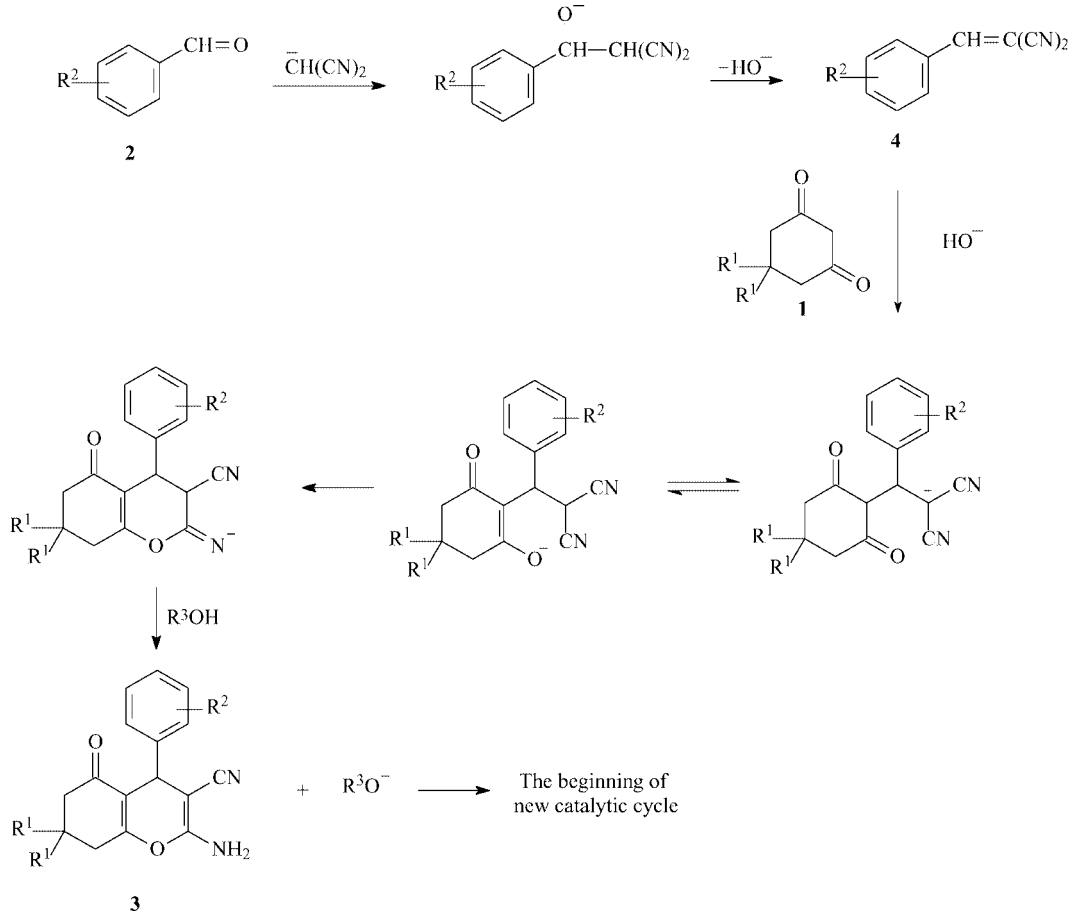
[a] **1a** and **1b** (10 mmol), **2a**–**f** (10 mmol), malononitrile (10 mmol), NaBr (1 mmol), *n*PrOH (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20 °C. [b] Yield of isolated product obtained by filtration of the reaction mixture.

tuted 4*H*-chromenes **3** is proposed. The initiation step of the catalytic cycle begins with the deprotonation of a molecule of alcohol at the cathode, which leads to the formation of an alkoxide anion. The subsequent reaction between the alkoxide anion and malononitrile gives rise to the malononitrile anion (Scheme 3).



Scheme 3.

Knoevenagel condensation of the malononitrile anion with aryl aldehyde **2** then takes place with the elimination of a hydroxide anion and formation of arylidenemalononitrile **4**.[17] The hydroxide-promoted Michael addition of cyclic diketone **1** to electron deficient Knoevenagel adduct **4** followed by intramolecular cyclization affords **3** with the regeneration of the alkoxide anion as the last step. The catalytic chain process then continues by the interaction of the



Scheme 4.

alkoxide with the next molecule of malononitrile (Scheme 4). Thus, the generation of even a single molecule of the alkoxide anion at the cathode is theoretically sufficient for the total conversion of equimolar quantities of cyclic diketone, aryl aldehyde and malononitrile into the corresponding 4*H*-chromenes.

Conclusions

In conclusion, the simple electrocatalytic system can produce, under neutral and mild conditions, a fast and selective multicomponent transformation of 1,3-diketones, aldehydes and malononitrile into 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles in excellent yields. This novel electrocatalytic chain process offers an efficient and convenient way to generate cyano-functionalized 5,6,7,8-tetrahydro-4*H*-chromenes, which are promising small-molecule compounds that have various biomedical applications which include its use as a therapeutic in human neurodegenerative disorders. The electrocatalytic procedure utilizes simple equipment and an undivided cell; it is easily carried out and is valuable in environmentally benign diversity-oriented large-scale processes. This efficient electrocatalytic approach to the 4*H*-chromene system represents a novel synthetic concept for multicomponent reactions, and allows for the combination of the synthetic virtues of conventional MCRs with ecological benefits and convenience; therefore, this MCR strategy brings us a step closer to the notion of an "ideal synthesis".[18]

Further investigations in the electrocatalytic multicomponent methodology that leads to different heterocyclic systems of biomedical importance are underway and new results are soon to be reported.

Experimental Section

General Remarks: All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H- and ^{13}C NMR spectra were recorded with a Bruker WM-250 spectrometer at ambient temperature. Chemical shift values are relative to Me_4Si. Mass-spectra (EI = 70 eV) were obtained directly with a Finningan MAT INCOS 50 spectrometer.

Typical Electrolysis Procedure: A solution of cyclic 1,3-diketone (10 mmol), aryl aldehyde (10 mmol), malononitrile (0.66 g, 10 mmol) and sodium bromide (0.1 g, 1 mmol) in the appropriate alcoholic solvent (20 mL) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode and an iron cathode at 20 °C under a constant current density of 4 mA/cm^2 (I = 20 mA, electrodes square 5 cm^2) until the catalytic quantity of 0.03 F/mol of electricity was passed (time is 25 min). After the electrolysis was finished, the solution was filtered to isolate the solid product, which was then rinsed with an ice-cold ethanol/water solution (9:1, 3 mL), and dried under reduced pressure.

2-Amino-5-Oxo-4-Phenyl-5,6,7,8-Tetrahydro-4*H*-Chromene-3-Carbonitrile (3a): White solid. Yield 2.52 g (95%). M.p. 238–240 °C (lit. m.p.[19] 239–241 °C). ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 1.80–2.05 (m, 2 H, CH_2), 2.15–2.35 (m, 2 H, CH_2), 2.55–2.66 (m, 2 H, CH_2), 4.17 (s, 1 H, CH), 6.97 (s, 2 H, NH_2), 7.10–7.20 (m, 3 H, Ar), 7.22–7.31 (m, 2 H, Ar) ppm.

2-Amino-4-(4-Methylphenyl)-5-Oxo-5,6,7,8-Tetrahydro-4*H*-Chromene-3-Carbonitrile (3b): White solid. Yield 2.41 g (86%). M.p. 223–225 °C. ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 1.83–2.05 (m, 2 H, CH_2), 2.17–2.33 (m, 2 H, CH_2 and 3H, CH_3), 2.54–2.66 (m, 2 H, CH_2), 4.16 (s, 1 H, CH), 6.91 (s, 2 H, NH_2), 7.01–7.12 (m, 4 H, Ar) ppm. ^{13}C NMR (62.53 MHz, [D$_6$]DMSO): δ = 19.7, 20.5, 26.4, 34.9, 36.2, 58.32, 113.9, 119.7, 126.9 (2 C), 128.7 (2 C), 135.5, 141.8, 158.4, 164.1, 195.7 ppm. MS: *m*/*z* (%) = 280 (48) [M]$^+$, 265 (36), 199 (14), 189 (100), 147 (11), 115 (22), 91 (22), 65 (21), 55 (16), 44 (16). IR (KBr): $\tilde{\nu}$ = 3408, 3322, 2916, 2200, 1684, 1608, 1508, 1386, 1208, 1000 cm^{-1}. $C_{17}H_{16}N_2O_2$ (280.33): calcd. C 72.84, H 5.75, N 9.99; found C 72.75, H 5.84, N 9.91.

2-Amino-4-(4-Methoxyphenyl)-5-Oxo-5,6,7,8-Tetrahydro-4*H*-Chromene-3-Carbonitrile (3c): White solid. Yield 2.69 g (91%). M.p. 195–197 °C (lit. m.p.[8a] 193–195 °C). ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 1.78–1.98 (m, 2 H, CH_2), 2.18–2.30 (m, 2 H, CH_2), 2.53–2.63 (m, 2 H, CH_2), 3.69 (s, 3 H, OCH_3), 4.12 (s, 1 H, CH), 6.82 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 3-H$_{Ar}$, 5-H$_{Ar}$), 6.92 (s, 2 H, NH_2), 7.05 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 2-H$_{Ar}$, 6-H$_{Ar}$) ppm.

2-Amino-4-(4-Chlorophenyl)-5-Oxo-5,6,7,8-Tetrahydro-4*H*-Chromene-3-Carbonitrile (3d): White solid. Yield 2.55 g (85%). M.p. 226–228 °C (lit. m.p.[8a] 226–229 °C). ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 1.77–2.03 (m, 2 H, CH_2), 2.22–2.32 (m, 2 H, CH_2), 2.55–2.63 (m, 2 H, CH_2), 4.18 (s, 1 H, CH), 7.03 (s, 2 H, NH_2), 7.17 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 3-H$_{Ar}$, 5-H$_{Ar}$), 7.32 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 2-H$_{Ar}$, 6-H$_{Ar}$) ppm.

2-Amino-4-(3-Bromophenyl)-5-Oxo-5,6,7,8-Tetrahydro-4*H*-Chromene-3-Carbonitrile (3e): White solid. Yield 3.20 g (93%). M.p. 242–243 °C (lit. m.p.[20] 243–244 °C). ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 1.82–1.98 (m, 2 H, CH_2), 2.23–2.34 (m, 2 H, CH_2), 2.55–2.65 (m, 2 H, CH_2), 4.19 (s, 1 H, CH), 7.06 (s, 2 H, NH_2), 7.16 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, 6-H$_{Ar}$), 7.24 (t, $^3J_{1H,H}$ = 7.9 Hz, $^3J_{2H,H}$ = 7.9 Hz, 1 H, 5-H$_{Ar}$), 7.30 (s, 1 H, 2-H$_{Ar}$), 7.37 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, 4-H$_{Ar}$) ppm.

2-Amino-4-(4-Nitrophenyl)-5-Oxo-5,6,7,8-Tetrahydro-4*H*-Chromene-3-Carbonitrile (3f): Yellowish solid. Yield 2.71 g (87%). M.p. 234–236 °C (lit. m.p.[8a] 234–235 °C). ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 1.78–2.05 (m, 2 H, CH_2), 2.24–2.33 (m, 2 H, CH_2), 2.55–2.64 (m, 2 H, CH_2), 4.32 (s, 1 H, CH), 7.16 (s, 2 H, NH_2), 7.42 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 2-H$_{Ar}$, 6-H$_{Ar}$), 8.15 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 3-H$_{Ar}$, 5-H$_{Ar}$) ppm.

2-Amino-7,7-Dimethyl-5-Oxo-4-Phenyl-5,6,7,8-Tetrahydro-4*H*-Chromene-3-Carbonitrile (3g): White solid. Yield 2.47 g (84%). M.p. 225–226 °C (lit. m.p.[21] 224–225 °C). ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 0.92 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 2.14 (d, $^2J_{H,H}$ = 16.1 Hz, 1 H, CH), 2.24 (d, $^2J_{H,H}$ = 16.1 Hz, 1 H, CH), 2.39 (s, 2 H, CH_2), 4.15 (s, 1 H, CH), 6.99 (s, 2 H, NH_2), 7.10–7.21 (m, 3 H, Ar), 7.22–7.30 (m, 2 H, Ar) ppm.

2-Amino-4-(4-Methoxyphenyl)-7,7-Dimethyl-5-Oxo-5,6,7,8-Tetrahydro-4*H*-Chromene-3-Carbonitrile (3h): White solid. Yield 2.72 g (84%). M.p. 207–209 °C (lit. m.p.[21] 207–208 °C). ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 0.93 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 2.08 (d, $^2J_{H,H}$ = 16.3 Hz, 1 H, CH), 2.23 (d, $^2J_{H,H}$ = 16.3 Hz, 1 H, CH), 2.44 (s, 2 H, CH_2), 3.86 (s, 3 H, OCH_3), 4.10 (s, 1 H, CH), 6.82 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 3-H$_{Ar}$, 5-H$_{Ar}$), 6.92 (s, 2 H, NH_2), 7.03 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 2-H$_{Ar}$, 6-H$_{Ar}$) ppm.

2-Amino-4-(3-Bromophenyl)-7,7-Dimethyl-5-Oxo-5,6,7,8-Tetrahydro-4*H*-Chromene-3-Carbonitrile (3i): White solid. Yield 3.28 g

(88%). M.p. 225–227 °C (lit. m.p.[20] 225–226 °C). ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 0.94 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 2.10 (d, $^2J_{H,H}$ = 15.9 Hz, 1 H, CH), 2.24 (d, $^2J_{H,H}$ = 15.9 Hz, 1 H, CH), 2.51 (s, 2 H, CH_2), 4.19 (s, 1 H, CH), 7.07 (s, 2 H, NH_2), 7.15 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 6-H_{Ar}), 7.25 (t, $^3J_{1H,H}$ = 7.8 Hz, $^3J_{2H,H}$ = 7.8 Hz, 1 H, 5-H_{Ar}), 7.29 (s, 1 H, 2-H_{Ar}), 7.37 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 4-H_{Ar}) ppm.

2-Amino-7,7-Dimethyl-4-(4-Nitrophenyl)-5-Oxo-5,6,7,8-Tetrahydro-4*H*-Chromene-3-Carbonitrile (3j): Yellowish solid. Yield 2.88 g (85%). M.p. 208–209 °C (lit. m.p.[21] 209–210 °C). ^{1}H NMR: δ = 0.94 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 2.08 (d, $^2J_{H,H}$ = 16.0 Hz, 1 H, CH), 2.25 (d, $^2J_{H,H}$ = 16.0 Hz, 1 H, CH), 2.53 (s, 2 H, CH_2), 4.35 (s, 1 H, CH), 7.19 (s, 2 H, NH_2), 7.43 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 2-H_{Ar}, 3-H_{Ar}), 8.14 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 3-H_{Ar}, 5-H_{Ar}) ppm.

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