Catalysis
Science & Technology

RSC Publishing

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View Article Online
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Cite this: DOI: 10.1039/c3cy20856g

A benign synthesis of 2-amino-4*H*-chromene in aqueous medium using hydrotalcite (HT) as a heterogeneous base catalyst†

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Received 12th December 2012,
Accepted 9th April 2013

DOI: 10.1039/c3cy20856g

www.rsc.org/catalysis

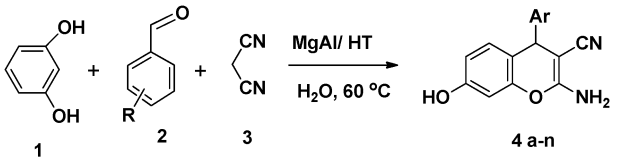
A simple and environmentally benign synthesis of 2-amino-4*H*-chromene is described using hydrotalcite as a solid base catalyst in aqueous medium. The catalysts were prepared by a co-precipitation method and well characterized by various techniques such as XRD, FT-IR, SEM and the basicity was found using the phenol adsorption method. The reusability of the catalyst, use of water as a green solvent and easy isolation of the product along with good yields make the present protocol sustainable and advantageous compared to conventional methods.

Introduction

It is well known that one pot multicomponent reactions are always better than multistep syntheses,[1] as they require minimal workup and desired products can be obtained in one pot often in quantitative yields. In addition, use of water for the organic reactions has been an important and fertile area of research in recent years.[2]

2-Amino-4*H*-chromenes and their derivatives are of significant importance as they possess a wide range of biological activities such as mutagenicity,[3] antimicrobial,[4] antiproliferative,[5] sex pheromone,[6] antitumor,[7] cancer therapy and central nervous system activity.[8] Several protocols have been reported for the synthesis of 2-amino-4*H*-chromenes and their derivatives using malononitrile, resorcinol and aldehyde. Various catalysts such as piperidine,[9] triethyl amine,[10] aqueous K_2CO_3,[11] cetyltrimethylammonium bromide (CTABr),[12] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[13] $Ca(OH)_2$,[14] HT/MW[15] and basic ionic liquids[16] have been used for these reactions. Recently, electrochemically induced multicomponent condensation of resorcinol, malononitrile and aldehyde in propanol in an undivided cell in the presence of NaBr as an electrolyte was reported.[17] Most of these reported protocols require a long reaction time, high temperature, and use of organic solvents, and have problems associated with the reusability of catalysts. In order to make the reaction simple and green, it is important to use environmentally friendly medium for the organic reactions, and combination of heterogeneous catalysts and water is the most demanding combination for catalytic reactions.

In continuation of our efforts to develop efficient protocols for the various organic transformations using heterogeneous catalysts,[18,19] we herein report Mg/Al hydrotalcite (HT) to catalyze the three component reaction of resorcinol, aldehyde and malononitrile under mild conditions (Scheme 1). The Mg–Al hydrotalcite is found to be an efficient catalyst for the synthesis of 2-amino-4*H*-chromene in aqueous medium. Among the heterogeneous basic catalysts, hydrotalcite is a versatile material used as a catalyst for several organic transformations such as multicomponent reaction of malononitrile, aldehyde and nitro methane,[20a] hydroxylation of phenol,[20b] aldol and Knoevenagel condensation,[21] polymerization,[22] cycloaddition reaction of nitroso



R = H, 2-Cl, 3-Cl, 4-Cl, 4-NO_2, 3-NO_2, 2-thiophene, 4-Me, 4-OMe, 4-OH, 2,5-$(OMe)_2$, 3,4-$(OMe)_2$, 4-F, 4-Br

Scheme 1 Synthesis of chromenes using hydrotalcite in aqueous medium.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cy20856g

and azo-alkenes,[23] homocoupling reaction,[24] Michael reaction[25] and Baeyer–Villiger oxidation.[26]

The synthesized Mg/Al hydrotalcite heterogeneous catalysts were characterized by XRD (X-ray diffraction), FT-IR (Fourier transform Infrared spectroscopy) and SEM (scanning electron microscopy). The basicity of hydrotalcite was measured by the phenol adsorption method[27] and it was found to show a maximum basicity of 0.131 mmol g^{-1} with a Mg/Al molar ratio of 5.0. Thus this catalyst was chosen for optimizing the reaction conditions (ESI†).

Results and discussion

XRD of the Mg/Al: 5.0 hydrotalcite clearly indicates the crystalline nature of the catalyst (Fig. 1). The presence of both sharp and diffuse non-basal reflections was taken as an indication of a partially disordered structure.

Initially, multicomponent reaction of benzaldehyde, resorcinol and malononitrile was chosen as the model reaction. Effects of various reaction parameters such as the influence of hydrotalcites with various Mg/Al molar ratios, the influence of solvents, the influence of catalyst concentration and the effect of temperature were studied to optimize the reaction conditions (Table 1).

It is important to note that Mg/Al hydrotalcite with a molar ratio of 5.0 was found to be the effective catalyst for the three component reaction of benzaldehyde, resorcinol and malononitrile affording a very good yield of the desired products. It was noteworthy that, in the absence of the catalyst no significant product formation was observed under similar reaction conditions (Table 1, entry 1).

The solvent plays an important role in the catalyst activity (Table 1). We have investigated the effect of various protic, aprotic and non-polar solvents on the three component reaction of resorcinol, malononitrile and benzaldehyde (Table 1, entries 8–18). Under solvent free conditions the reaction did not take place even after prolonged reaction time (Table 1, entry 9). In non-polar solvents such as 1,4-dioxane, *n*-hexane, diethyl ether and toluene, the reaction did not take place, whereas in the case of polar aprotic solvents such as acetonitrile, THF and DMF, the yield of the reaction was found to be very low (<20%, Table 1, entries 12–14). In the case of polar protic solvents such as ethanol and isopropanol (IPA) (Table 1, entries 10 and 11), the yield of the desired product was moderate (19–25%). From Table 1 it's clear that water was the best choice as solvent (Table 1, entries 2–5 and 21).

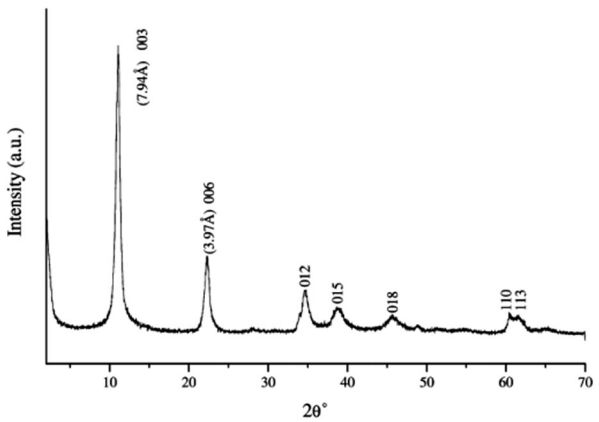


Fig. 1 XRD profile of Mg/Al HT.

Table 1 Optimization of reaction parameters[a]

Entry	Catalyst[b] (% w/w)	Reaction conditions	Yield[c] (%)
1	No catalyst	H_2O, 60 °C, 24 h	0
2	Mg/Al: 2.0 HT (15)	H_2O, 60 °C, 4 h	65
3	Mg/Al: 3.0 HT (15)	H_2O, 60 °C, 4 h	72
4	Mg/Al: 4.0 HT (15)	H_2O, 60 °C, 4 h	78
5	Mg/Al: 5.0 HT (15)	H_2O, 60 °C, 4 h	95
6	Mg/Al: 5.0 HT (5)	H_2O, 60 °C, 4 h	32
7	Mg/Al: 5.0 HT (10)	H_2O, 60 °C, 4 h	56
8	Mg/Al: 5.0 HT (20)	H_2O, 60 °C, 4 h	95
9	Mg/Al: 5.0 HT (15)	No solvent, 60 °C, 4 h	0
10	Mg/Al: 5.0 HT (15)	Ethanol, 60 °C, 4 h	25
11	Mg/Al: 5.0 HT (15)	Isopropanol, 60 °C, 4 h	19
12	Mg/Al: 5.0 HT (15)	ACN, 60 °C, 4 h	Trace
13	Mg/Al: 5.0 HT (15)	DMF, 60 °C, 4 h	18
14	Mg/Al: 5.0 HT (15)	THF, 60 °C, 4 h	Trace
15	Mg/Al: 5.0 HT (15)	2-Me-THF, 60 °C, 4 h	Trace
16	Mg/Al: 5.0 HT (15)	1,4-Dioxane, 60 °C, 4 h	0
17	Mg/Al: 5.0 HT (15)	Hexane, 60 °C, 4 h	0
18	Mg/Al: 5.0 HT (15)	Diethyl ether, 60 °C, 4 h	0
19	Mg/Al: 5.0 HT (15)	Toluene, 60 °C, 4 h	0
20	Mg/Al: 5.0 HT (15)	H_2O, 30 °C, 24 h	0
21	Mg/Al: 5.0 HT (15)	H_2O, 80 °C, 4 h	96

[a] Reaction condition: benzaldehyde (3 mmol), resorcinol (3 mmol), malononitrile (3 mmol). [b] Weight percentage of the catalyst with respect to resorcinol. [c] Isolated yield after chromatography.

Variation of the catalyst loading from 0 and 20 wt% had different effects on the catalytic activity (Table 1 entries 5–8) with the best performance being observed with an Mg/Al molar ratio of 5 (Table 1, entries 2–5). The reaction was carried out using 5 and 20 wt% of the catalysts, which provided the desired product along with side products (not isolated).[28] An increase in the catalyst loading to 15 wt% resulted in an increase in the yield (95%) of the desired product. Further increase in the catalyst loading has no profound effect on the yield of the desired product. The temperature has also a profound effect with no reaction taking place at room temperature (30 °C). Further increase in the temperature to 60 °C makes the reaction almost quantitative (Table 1, entry 20). However a further increase in the temperature did not show any significant enhancement in the yield of the desired product (Table 1, entry 20 *vs.* 21).

Encouraged by these results, we extended the scope of this reaction to a range of aldehydes (Table 2, entries 1–14) under optimized reaction conditions and the corresponding 2-amino-4*H*-chromenes **4a**–**n** were obtained in excellent yields (Table 2). As expected, functional groups such as nitro (Table 2, entries 7 and 8) which have a strong electron withdrawing inductive effect (−I) as well as a mesomeric effect (−R) give excellent yields (91–95%) of the desired products, whereas electron donating groups such as –OH, –OMe, –Me, –Cl, –Br, –F (Table 2, entries 2–6, 12–14) at the *ortho* or *para* position of the aldehyde group give slightly lower yields. The electron withdrawing group makes the carbonyl more vulnerable toward

Table 2 2-Amino-4*H*-chromene synthesis in aqueous medium[a]

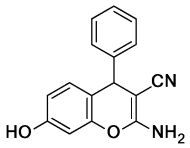
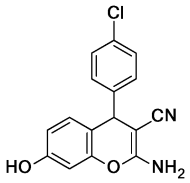
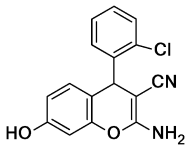
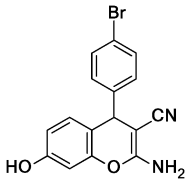
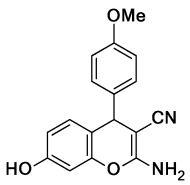
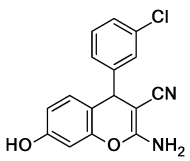
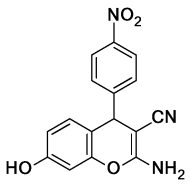
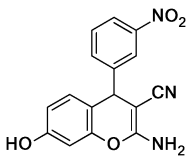
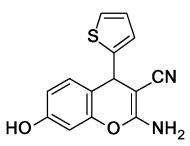
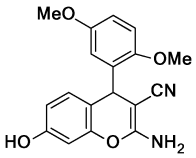
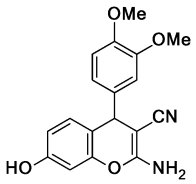
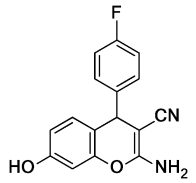
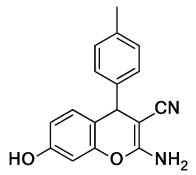
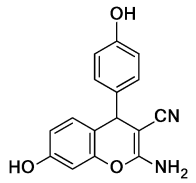
	Aldehyde	Product				m.p. (°C)	
Entry	R	Structure	Code	Time (h)	Yield[b] (%)	Found	Reported
1	–H		**4a**	4	95	234–235	234–236[11b]
2	–4-Cl		**4b**	5	90	159–161	160–162[16]
3	–2-Cl		**4c**	4.5	87	96–98	96–98[16]
4	–4-Br		**4d**	5	85	224–226	225–227[16]
5	–4-OMe		**4e**	6	75	112–114	112–114[16]
6	–3-Cl		**4f**	4	95	176–178	NR[c]
7	–4-NO_2		**4g**	3	96	210–212	NR[c]
8	–3-NO_2		**4h**	4	92	188–190	NR[c]
9	Thiophene substituted benzaldehyde		**4i**	4.5	90	216–218	NR[c]

Table 2 (*continued*)

Entry	Aldehyde R	Product Structure	Code	Time (h)	Yield[b] (%)	m.p. (°C) Found	m.p. (°C) Reported
10	–2,5-$(OMe)_2$		**4j**	6	86	198–200	NR[c]
11	–3,4-$(OMe)_2$		**4k**	6	88	215–217	NR[c]
12	–4-F		**4l**	5	91	186–188	187–189[16]
13	–4-Me		**4m**	6	87	180–182	182–184[16]
14	–4-OH		**4n**	5.5	83	248–250	NR[c]

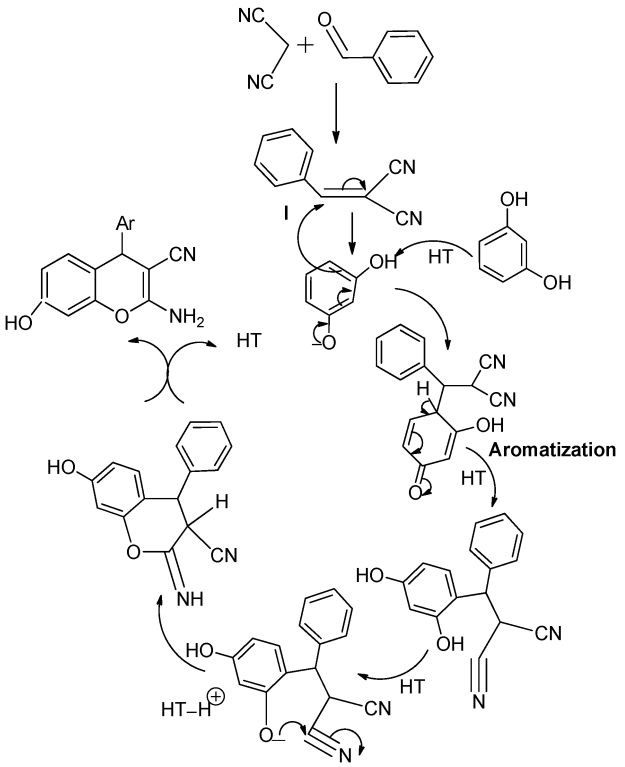
[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, IR and MS data. [b] Yields refer to pure products after silica gel column chromatography. [c] Not reported (melting point not available in the literature).

nucleophilic attack. The probable reaction mechanism for the synthesis of 2-amino-4*H*-chromene using hydrotalcite is given in Scheme 2. The first step of the mechanism involves the Knoevenagel condensation between aldehyde and malononitrile (basic sites of the catalyst abstract an acidic proton of malononitrile and then subsequent attack on the carbonyl group furnishes condensed product I).[29] In the second step Michael addition of resorcinol and condensed product I affords the desired product after rearomatization and intramolecular cyclization. During the formation of the 2-amino-4*H*-chromenes, the formation of 2-amino-5-hydroxy-4*H*-chromeme cannot be ruled out, but the product was not observed, this may be due to the steric hindrance of the phenyl group and the hydroxyl group which makes the molecule less stable.

An important norm for heterogeneous catalysis is the reusability of the catalyst. To study the catalyst reusability, reaction of resorcinol, benzaldehyde and malononitrile was carried out on Mg/Al: 5.0 hydrotalcite several times. After the reaction was completed, the catalyst was filtered under vacuum, washed with ethyl acetate, and dried at 60 °C. The recovered catalyst could be reused more than four reaction cycles with significant loss in catalytic activity (Fig. 2, for the first cycle 95% and for the fourth cycle 61% yield).

Conclusion

In conclusion, we have reported an efficient protocol for one pot multicomponent reaction of resorcinol, malononitrile and aldehyde for the synthesis of 2-amino-4*H*-chromenes catalyzed by hydrotalcite using water as solvent. The present protocol was found to be efficient providing higher yields of the desired products. This procedure offers several advantages including mild reaction conditions, reusability of the catalyst, high yield of products as well as a simple experimental procedure, which make it an attractive process for the synthesis of 2-amino-4*H*-chromenes and their derivatives. The catalyst has the advantage



Scheme 2 Plausible mechanism for the chromene synthesis.

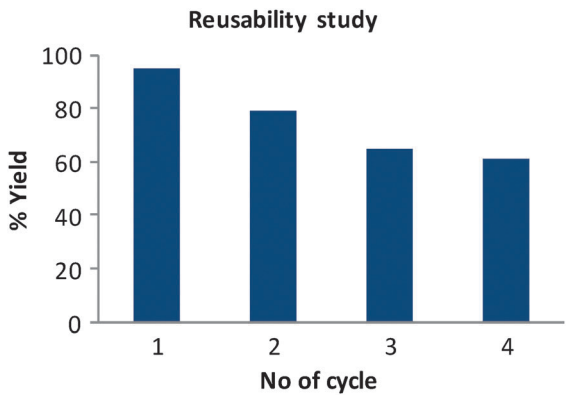


Fig. 2 Reusability of the catalyst.

of being inexpensive, non-hazardous, easily prepared and heterogeneous in nature, which makes the protocol economically viable for the synthesis of titled compounds.

Experimental section

All chemicals were obtained from Sigma-Aldrich Company and used as received. Powder X-ray diffraction (XRD) patterns of the catalyst were recorded using a Philips 1050 diffractometer using graphite monochromatized Cu-Kα radiation over a 2θ range of 10–90°. BET surface area measurements were carried out by the acetic acid adsorption method. Basicity of the catalyst was found using the phenol adsorption method. The melting points were determined using a digital melting point apparatus and are uncorrected. The FTIR spectra were recorded using a Perkin Elmer (Spectra 100) spectrometer by a KBr pellet technique. ^{1}H NMR spectra were recorded on a JEOL-300 MHz NMR spectrometer using TMS as an internal standard.

General procedure for synthesis of chromene

A mixture of resorcinol (0.330 g, 3 mmol), malononitrile (0.198 g, 3 mmol), and aldehyde (3 mmol) was taken in a 25 mL round bottom flask containing 10 mL of water. The Mg/Al-HT (15 wt%) catalyst with respect to resorcinol was then added to the reaction flask and the contents were stirred. The reaction mixture was heated for an appropriate time as mentioned in Table 1. The progress of the reaction was monitored by thin layer chromatography (ethyl acetate/pet ether: 30%). After reaction was completed, the reaction mixture was allowed to cool at room temperature. The crude product was extracted with ethyl acetate. The organic layer was washed with water (25 mL), dried with anhydrous Na_2SO_4, the solvent evaporated under vacuum and the crude product recrystallized from ethanol. Characterization data for selected compounds are provided below:

2-Amino-3-cyano-7-hydroxy-4-(3-chloro)-4*H* chromene (4f). m.p.: 176–178 °C. IR (KBr): 3440 (OH), 3246 (NH_2), 2970 (ArCH), 2235 (CN), 1645, 1580 (aromatic), 1149 (C-O) cm^{-1}. ^{1}H NMR (300 MHz DMSO-d_6) δ: 4.68 (s, 1H, CH), 6.41 (d, 1H, J = 2.2 Hz, *ortho* to Ar-OH), 6.51 (dd, 1H, J = 8.4 and 2.2 Hz, *ortho* to Ar-OH), 6.81 (d, 1H, J = 2.2 Hz, *meta* to Ar-OH), 6.94 (s, 2H, NH_2), 7.14–7.37 (m, 4H, H-ArCl), 9.77 (s, 1H, OH). ^{13}C NMR (75 MHz DMSO-d_6) δ ppm: 160.82, 157.76, 149.30, 133.62, 131.03, 130.35, 127.57, 127.15, 126.64, 120.95, 113.41, 113.02, 102.73, 62.50; MS m/z (%): 300, 299, 282, 263, 232, 187 (100).

2-Amino-3-cyano-7-hydroxy-4-(4-nitrophenyl)-4*H* chromene (4g). Yellow solid. Yield 96%, m.p. 210–212 °C. IR (KBr): 3474 (OH), 3336 (NH_2), 2980 (ArCH) 2188 (CN), 1645, 1580 (aromatic), 1459 (NO_2), 1150, 1112 (C-O) cm^{-1}; ^{1}H NMR (300 MHz DMSO-d_6) δ: 4.90 (s, 1H, CH), 6.44 (d, 1H, J = 2.5 Hz, *ortho* to Ar-OH), 6.51 (dd, 1H, J = 8.4 and 2.5 Hz, *ortho* to Ar-OH), 6.79 (d, 1H, J = 8.4 Hz, *meta* to Ar-OH) 7.04 (s, 2H, NH_2) 7.46 (d, 2H, J = 8.8 Hz, *meta* to Ar-NO_2), 8.18 (d, 2H, J = 8.8 Hz, *ortho* to Ar-NO_2), 9.82 (s, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ ppm: 160.87, 158.01, 154.20, 149.34, 146.74, 130.38, 129.14, 124.43, 120.79, 113.10, 112.73, 102.86, 55.58; MS m/z (%): 308 (M + 30), 293, 278, 263, 262 (100), 251, 252, 243, 187.

2-Amino-3-cyano-7-hydroxy-4-(3-nitrophenyl)-4*H* chromene (4h). m.p.: 188–192 °C. IR (KBr): 3451 (OH), 3336 (NH_2), 3243, 2985 (ArCH), 2190 (CN), 1625, 1550 (aromatic), 1353, 1450 (NO_2), 1150, 1054 (C-O) cm^{-1}. ^{1}H NMR (300 MHz DMSO-d_6) δ: 4.90 (s, 1H, CH), 6.44 (d, 1H, J = 2.5 Hz, *ortho* to Ar-OH), 6.50 (dd, 1H, J = 8.4 and 2.5 Hz, *ortho* to Ar-OH), 6.83 (d, 1H, J = 8.4 Hz, *meta* to Ar-OH), 7.04 (s, 2H, NH_2), 7.60–8.8 (m, 4H, Ar-NO_2), 9.82 (s, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ ppm: 160.91, 157.91, 149.33, 149.09, 148.37, 134.73, 130.78, 130.39, 122.28, 122.17, 120.76, 113.10, 112.97, 102.80, 62.44; MS m/z (%): 308 (M + 30), 293, 278, 263, 262 (100), 251, 252, 243, 187 (100).

2-Amino-3-cyano-7-hydroxy-4-(2-thiophene)-4*H* chromene (4i). Yellow solid. Yield 90%, m.p. 216–218 °C. IR (KBr): 3448 (OH),

3350 (NH_2), 2963 (ArCH), 2193 (CN), 1654, 1506 (aromatic), 706 (C-S) cm^{-1}; ^1H NMR (300 MHz DMSO-d_6) δ: 4.97 (s, 1H, CH), 6.38 (d, 1H, J = 2.4 Hz, *ortho* to Ar-OH), 6.52 (dd, 1H, J = 8.4 and 2.4 Hz, *ortho* to Ar-OH), 7.34 (d, 1H, Ar-S), 6.91–6.98 (m, 5H, NH_2, 1H-ArOH and 2H-Ar-S), 9.82 (s, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ ppm: 160.76, 157.72, 151.87, 148.95, 130.27, 127.19, 125.45, 120.92, 113.96, 112.86, 102.65, 56.93; MS *m*/*z* (%): 272, 271, 270, 254, 244, 206, 187 (100), 163, 149.

2-Amino-3-cyano-7-hydroxy-4-(2,5-dimethoxy)-4*H* chromene (4j). Light yellow solid. Yield 86%, m.p. 198–200 °C. IR (KBr): 3448 (OH), 3345 (NH_2), 2963 (aromatic CH), 2194 (CN), 1643, 1508 (aromatic) cm^{-1}, 1130, 1149, 1242, 1265 (C-O) cm^{-1}; ^1H NMR (300 MHz DMSO-d_6) δ: 3.63 (s, 3H, OMe), 3.70 (s, 3H, OMe), 4.90 (s, 1H, CH), 6.37 (d, 1H, J = 2.2 Hz, *ortho* to Ar-OH), 6.44 (dd, 1H, J = 8.4 and 2.5 Hz, *ortho* to Ar-OH), 6.50 (d, 1H, J = 2.5 Hz, 6H-Ar-OMe), 6.73–6.93 (m, 5H, NH_2, 1H-*meta* to ArOH and 2H-*ortho* to -OMe), 9.67 (s, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ ppm: 161.34, 157.34, 153.74, 151.04, 149.53, 135.76, 129.61, 121.11, 115.48, 114.20, 113.29, 112.58, 112.01, 102.50, 67.84, 56.72, 55.66; MS: *m*/*z* (%): 324, 323, 322, 294, 258, 216, 187 (100).

2-Amino-3-cyano-7-hydroxy-4-(3,4-dimethoxy)-4*H* chromene (4k). Light yellow solid. Yield 88%, m.p. 217–219 °C. IR (KBr): 3448 (OH), 3345 (NH_2), 2963 (ArCH), 2194 (CN), 1643, 1508 (aromatic) cm^{-1}, 1130, 1149, 1242, 1265 (C-O); ^1H NMR (300 MHz DMSO-d_6) δ: 3.70 (s, 6H, OMe), 4.56 (s, 1H, CH), 6.39 (d, 1H, J = 2.2 Hz, *ortho* to Ar-OH), 6.48 (dd, 1H, J = 8.4 and 2.2 Hz *ortho* to Ar-OH), 6.64–6.89 (m, 6H, NH_2, 1H-*meta* to ArOH and 3H-Ar(OMe)2), 9.78 (s, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ ppm: 160.59, 157.38, 149.12, 139.31, 130.29, 121.12, 119.82, 114.38, 112.71, 112.47, 111.75, 108.36, 106.72, 102.52, 55.91, 56.34; MS: *m*/*z* (%): 324, 323, 322, 294, 258, 216, 187 (100).

2-Amino-3-cyano-7-hydroxy-4-(4-hydroxy)-4*H* chromene (4n). Yellow solid. Yield 83%, m.p. 248–250 °C, IR (KBr): 3479 (OH), 3349 (NH_2), 3218, 2980 (ArCH), 2184 (CN), 1645, 1587 (aromatic), 1459 (NO_2), 1152 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 4.40 (s, 1H, CH), 6.37 (d, 1H, J = 2.2 Hz, *ortho* to Ar-OH), 6.46 (dd, 1H, J = 8.4 and 2.2 Hz, *ortho* to Ar-OH), 6.68 (d, 2H, J = 8.4 Hz, *ortho* to Ar′-OH), 6.92 (d, 2H, J = 8.4 Hz, *meta* Ar′-OH), 6.75–6.78 (m, 3H, NH_2 and *meta* to Ar-OH), 9.27 (s, 1H, OH). 9.82 (s, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ ppm: 160.49, 157.33, 156.49, 149.19, 137.25, 130.34, 128.82, 121.24, 115.67, 114.75, 112.71, 102.50, 57.18; MS *m*/*z* (%): 281, 280, 279, 264, 252, 215, 187 (100), 171.

Acknowledgements

S.R.K. is grateful to CSIR, New Delhi, India, for the award of Senior Research Fellowships.

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