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Catalyst-Free Cascade Synthesis of Densely Functionalized Chromenes in Water

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An expeditious and environmental friendly, general protocol has been developed for the synthesis of 2-amino-3-cyano-4*H*-chromenes *via* cascade Knoevenagel-Michael-intramolecular cyclization in water. Pure solid products were obtained by simple filtration technique. The aqueous catalyst-free reactions lead to high product yield at room temperature.

Keywords: Green Synthesis, Cascade reaction, Water media, Knoevenagel condensation, Chromenes.

INTRODUCTION

Complete elimination of hazardous solvents or replacement with innocuous solvent is one of the main aspect of Green Chemistry [1]. Among various solvents used as reaction media, water is the primary choice because of its advantageous properties such as naturally occurring, economically cheaper, non-flammable and innocuous nature [2-4]. Further, significant enhancement in the rate of several reactions was observed in water, owing to hydrophobic interactions that induce favourable aggregation of polar components [5]. In addition to this, the use of water as a solvent allows simple isolation of products by filtration, extraction and distillation processes [6].

The cascade reactions involve two or more sequential bond-formation that occurs without modification of reaction conditions, to obtain complex molecular structures starting from simple building blocks [7,8]. Hence, these reactions have gained increasing interest in greener chemical synthesis, because they introduce elegance and efficiency to synthetic strategies [9]. Chromenes are significant fused heterocycles, present in broad range of natural products and pharmaceuticals [10,11]. Functionalized chromene scaffolds are known to display potent pharmacological activities, such as antioxidant, antifungal, antimicrobial, antiviral, antitubercular, antiproliferative and anticancer properties [12,13]. Owing to their importance, a wide range of synthetic protocols have been developed for the synthesis of chromene derivatives using catalysis [14-18], photochemical activation [19], microwave irradiation [20,21], ultrasound activation [22] and under ionic liquids [23], deep eutectic solvents [24], aqueous media [25-28] and under solvent-free catalyst free conditions [29,30]. Despite satisfactory results, most of these methods need to overcome from limitations such as harsh reaction conditions, tedious work-up and purification procedures, lack of substrate generality and thus, the development of an efficient environmental friendly protocol with more general applicability is of great importance from the synthetic organic and Green Chemistry viewpoint.

With the aim to develop greener methodology for organic transformations, the present contribution focuses on a general protocol for the synthesis of densely functionalized chromenes *via* Cascade Knoevenagel-Michael addition-intramolecular cyclization reaction.

EXPERIMENTAL

All chemicals were procured from commercial suppliers and used without further purification. Melting points were recorded on Stuart SMP3 melting point apparatus and are uncorrected. NMR spectra were recorded as a solution in DMSO-d_6 at 400 MHz instrument with tetramethylsilane as an internal standard. Chemical shifts (δ) are given in parts per million and coupling constant *J*-values are given in Hz. Elemental analysis was performed using a Perkin Elmer, Series II, 2400 analyzer. Thin Layer Chromatography (TLC) was performed on silica gel 60 F_{254} (Merck).

General procedure for the synthesis of compounds 4a-i: A mixture of salicylaldehyde (1 mmol) and malononitrile (2 mmol) was taken in a 25 mL round-bottomed flask containing water (5 mL). The suspension formed was stirred at room temperature for a suitable time (Table-1). The formed precipitate was then filtered and washed with 3 × 10 mL water and dried under vacuum to obtain pure product. Purity and structure of all the products are supported by TLC analysis, melting point determination and NMR characterization (**Scheme-I**).

2-(2-Amino-3-cyano-4*H*-chromen-4-yl)malononitrile (4a): Colour: white solid; Anal. calcd. (found) % for $C_{13}H_8N_4O$: C, 66.10 (65.94); H, 3.41 (3.37); N, 23.72 (23.66). ^{1}H NMR (DMSO-d_6) δ: 4.61 (d, 1H, *J* = 4 Hz), 5.11 (1H, d, *J* = 4 Hz), 7.16 (1H, d, *J* = 8Hz), 7.31 (1H, t, *J* = 7.5 Hz), 7.45-7.49 (m, 2H), 7.55 (s, 2H); ^{13}C NMR (DMSO-d_6) δ: 32.3, 38.2, 49.6, 112.5, 112.8, 116.8, 117.9, 119.3, 125.2, 130.0, 130.3, 150.4, 163.9.

(2-Amino-3-cyano-8-methoxy-4*H*-chromen-4-yl)malononitrile (4b): Colour: white solid; Anal. calcd. (found) % for $C_{14}H_{10}N_4O_2$: C, 63.15 (63.27); H, 3.79 (3.72); N, 21.04 (20.92). ^{1}H NMR (DMSO-d_6) δ: 3.88 (s, 3H), 4.60 (d, 1H, *J* = 2.5 Hz), 5.05 (d, 1H, 2.5 Hz), 7.02 (d, 1H, *J* = 7.5 Hz), 7.10 (d, 1H, *J* = 8 Hz), 7.19-7.23 (m, 1H), 7.53 (s, 2H); ^{13}C NMR (DMSO-d_6) δ: 32.6, 37.4, 48.9, 55.9, 112.9, 113.1, 113.3, 118.9, 119.6, 119.9, 125.1, 139.3, 147.3, 163.7.

2-(2-Amino-3-cyano-7-methoxy-4*H*-chromen-4-yl)-malononitrile (4c): Colour: pale yellow solid; Anal. calcd. (found) % for $C_{14}H_{10}N_4O_2$: C, 63.15 (63.29); H, 3.79 (3.68); N, 21.04 (20.90). ^{1}H NMR (DMSO-d_6) δ: 3.80 (s, 3H), 4.52 (d, 1H, *J* = 4Hz), 5.04 (d, 1H, *J* = 3.5 Hz), 6.70 (d, 1H, *J* = 2.4 Hz), 6.90 (d, 1H, *J* = 8.5 Hz), 7.41 (d, 1H, *J* = 8 Hz), 7.49 (s, 2H); ^{13}C NMR (DMSO-d_6) δ: 34.5, 38.9, 57.2, 103.3, 111.5, 113.7, 114.7, 115.3, 121.1, 131.7, 152.8, 162.3, 165.3.

2-(2-Amino-6-chloro-3-cyano-4*H*-chromen-4-yl)malononitrile (4d): Colour: white solid; Anal. calcd. (found) % for $C_{13}H_7N_4OCl$: C, 57.69 (57.77); H, 2.61 (2.54); N, 20.70 (20.58). ^{1}H NMR (DMSO-d_6) δ: 4.62 (d, 1H, *J* = 4 Hz), 5.15 (d, 1H, *J* = 3.5 Hz), 7.19 (d, 1H, *J* = 8.5Hz), 7.47 (d, 1H, *J* = 8.5 Hz), 7.59 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 32.8, 37.3, 48.9, 113.2, 113.4, 118.8, 119.6, 120.4, 128.9, 129.0, 130.5, 149.1, 163.7.

2-(2-Amino-3-cyano-6-nitro-4*H*-chromen-4-yl)malononitrile (4e): Colour: pale brownish solid; Anal. calcd. (found) % for $C_{13}H_7N_5O_3$: C, 55.52 (55.60); H, 2.51 (2.39); N, 24.90 (24.76). ^{1}H NMR (DMSO-d_6) δ: 4.81 (d, 1H, *J* = 4 Hz), 5.23 (d, 1H, *J* = 3.5 Hz), 7.40 (d, 1H, *J* = 9 Hz), 7.81 (s, 2H), 8.30 (d, 1H, *J* = 8.5 Hz), 8.53 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 32.9, 37.2, 49.0, 113.1, 113.2, 118.4, 119.2, 119.7, 125.7, 126.3, 144.3, 154.6, 163.2.

2-(2-Amino-3-cyano-8-methoxy-6-nitro-4*H*-chromen-4-yl)malononitrile (4f): Colour: pale brownish solid; Anal. calcd. (found) % for $C_{14}H_9N_5O_4$: C, 54.02 (54.16); H, 2.91 (2.78); N, 22.50 (22.41). ^{1}H NMR (DMSO-d_6) δ: 4.00 (s, 3H), 4.77 (d, 1H, *J* = 4Hz), 5.21 (d, 1H, *J* = 3.5Hz), 7.82 (s, 2H), 7.91 (s, 1H), 8.10 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 32.6, 37.4, 49.1, 57.2, 108.3, 113.1, 113.2, 116.5, 119.2, 119.8, 144.2, 144.4, 148.2, 163.3.

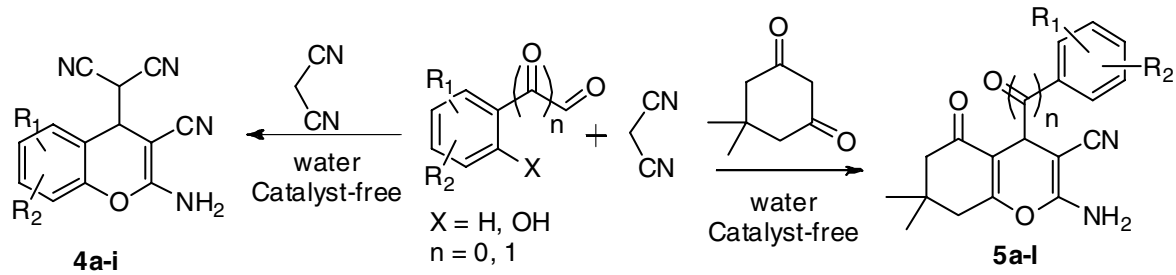
2-(2-Amino-8-bromo-6-chloro-3-cyano-4*H*-chromene-4-yl)malononitrile (4g): Colour: pale yellowish solid; Anal. calcd. (found) % for $C_{13}H_6N_4OBrCl$: C, 44.67 (44.74); H, 1.73 (1.66); N, 16.03 (15.90). ^{1}H NMR (DMSO-d_6) δ: 4.67 (d, 1H, *J* = 4 Hz), 5.15 (d, 1H, *J* = 3.5 Hz), 7.60 (s, 1H), 7.75 (s, 2H), 7.92 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 32.7, 37.7, 49.4, 111.1, 113.2, 119.2, 121.8, 128.6, 129.4, 133.3, 146.3, 163.4.

2-(2-Amino-6-bromo-3-cyano-4*H*-chromene-4-yl)malononitrile (4h): Colour: White solid; Anal. calcd. (found) % for $C_{14}H_9BrN_4O_2$: C, 48.72 (48.66); H, 2.63 (2.55); N, 16.23 (16.08). ^{1}H NMR (DMSO-d_6) δ: 4.61 (d, 1H, *J* = 3.5 Hz), 5.13 (d, 1H, *J* = 4 Hz), 7.13 (d, 1H, *J* = 9.0 Hz), 7.53-7.59 (m, 3H), 7.72 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 32.4, 36.7, 48.4, 112.7, 112.9, 116.4, 118.6, 119.1, 120.3, 131.4, 131.9, 149.0, 163.2.

TABLE-1
SYNTHESIS OF 2-AMINO-3-CYANO-4*H*-CHROMENES (**4a-I**)

Compound	R_1	R_2	Reaction time (min)[a]	Yield[b] (%)	m.p. (°C)	
					Found	Lit.
4a	H	H	10	94	152	150-153 [31]
4b	8-OCH_3	H	10	91	161	161 [30]
4c	7-OCH_3	H	25	88	150	150 [30]
4d	6-Cl	H	10	96	154	151-154 [26]
4e	6-NO_2	H	10	89	179	180-181 [26]
4f	6-NO_2	8-OCH_3	10	90	190	190 [30]
4g	6-Cl	8-Br	10	91	174	174 [30]
4h	6-Br	8-OCH_3	10	86	160	160-162 [32]
4i	6-I	8-I	10	88	198	198 [30]

[a]Reactions were monitored by TLC; [b]Isolated yield.



Scheme-I: Cascade synthesis of 2-amino-3-cyano-4*H*-chromene derivatives involved in the current work

TABLE-2
SYNTHESIS OF 2-AMINO-3-CYANO-4*H*-CHROMENE DERIVATIVES (**5a-i**)

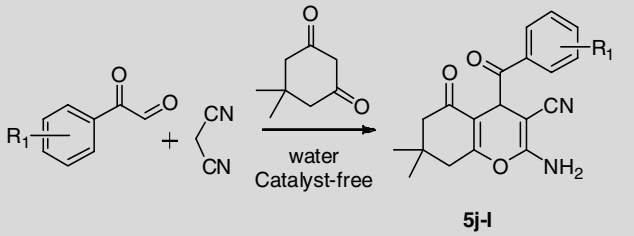
Entry	R_1	Reaction time[a] (A+B) (min)[b]	Yield[c] (%)	m.p. (°C)	
				Found	Reported
5a	H	20+10	91	230	226-228 [33]
5b	4-CH_3	45+20	86	214	209-211 [33]
5c	2-Cl	30+20	87	215	212-213 [34]
5d	4-Cl	10+10	94	206	202-203 [33]
5e	4-OCH_3	75+30	90	200	197-199 [33]
5f	3-NO_2	10+10	93	213	212-215 [18]
5g	4-NO_2	10+10	88	177	175-176 [17]
5h	4-F	10+10	92	196	198-200 [35]
5i	4-OH	120	Trace	–	–

[a]Reactions were monitored by TLC; [b]Reaction time before the addition of dimedone (A) and that for completion of the reaction after the addition of dimedone (B); [c]Isolated yield.

2-(2-Amino-3-cyano-6,8-diiodo-4*H*-chromen-4-yl)malononitrile (4i): Colour: Brownish solid; Anal. calcd. (found) % for $C_{13}H_6N_4OI_2$: C, 31.99 (32.08); H, 1.24 (1.18); N, 11.48 (11.37). ^{1}H NMR (DMSO-d_6) δ: 4.54 (d, 1H, J = 4 Hz), 5.09 (d, 1H, J = 3.5 Hz), 7.71 (s, 2H), 7.82 (s, 1H), 8.2 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 32.8, 37.4, 49.5, 87.7, 90.2, 113.3, 119.2, 121.5, 137.8, 146.9, 150.2.

General procedure for the synthesis of compounds 5a-l: A mixture of benzaldehyde/arylglyoxal (1 mmol) and malononitrile (1 mmol) was taken in a 25 mL round bottomed flask containing water (5 mL). The suspension formed was stirred at room temperature for a suitable time given in Tables 2 and 3. Further, dimedone (2 mmol) was added and continued stirring for a suitable time. Formed precipitate was then filtered and washed with 3 × 10 mL water and dried under vacuum to obtain pure product. Purity and structure of all the products are supported by TLC analysis, melting point determination and NMR characterization (**Scheme-I**).

TABLE-3
SYNTHESIS OF 2-AMINO-3-CYANO-4*H*-CHROMENE DERIVATIVES (**5j-l**)



5j-l

Entry	R_1	Reaction time[a] (A + B) (min)[b]	Yield[c] (%)	m.p. (°C)
5j	4-CH_3	60 + 40	68	176
5k	4-Cl	45 + 30	76	184
5l	4-F	45 + 30	74	188

[a]Reactions were monitored by TLC; [b]Reaction time before the addition of dimedone (A) and that for completion of the reaction after the addition of dimedone (B); [c]Isolated yield

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5a): Colour: White solid; Anal. calcd. (found) % for $C_{18}H_{18}N_2O_2$: C, 73.45 (73.35); H, 6.16 (6.02); N, 9.52 (9.38). ^{1}H NMR (DMSO-d_6) δ: 0.96 (s, 3H), 1.10 (s, 3H), 2.06-2.30 (m, 4H), 4.25 (s, 1H), 6.41 (s, 2H), 7.13-7.43 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 28.0, 29.3, 31.0, 34.0, 51.6, 54.3, 118.0, 124.8, 127.6, 128.5, 128.7, 140.1, 156.8, 176.2, 190.4.

2-Amino-7,7-dimethyl-5-oxo-4-(*p*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5b): Colour: White solid; Anal. calcd. (found) % for $C_{19}H_{20}N_2O_2$: C, 74.00 (73.89); H, 6.54 (6.40); N, 9.08 (8.93). ^{1}H NMR (DMSO-d_6) δ: 0.1.01 (s, 3H), 1.11 (s, 3H), 2.14-2.19 (m, 2H), 2.29 (s, 3H), 2.48 (s, 2H), 4.32 (s, 1H), 5.63 (s, 2H), 7.02-7.10 (m, 4H); ^{13}C NMR (DMSO-d_6) δ: 20.3, 27.1, 28.7, 32.1, 35.6, 50.6, 58.7, 113.1, 120.3, 127.2, 129.5, 136.1, 142.3, 158.8, 162.6, 182.3, 196.1.

2-Amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5c): Colour: White solid; Anal. calcd. (found) % for $C_{18}H_{17}N_2O_2Cl$: C, 65.75 (65.69); H, 5.21 (5.11); N, 8.52 (8.44). ^{1}H NMR (DMSO-d_6) δ: 0.98 (s, 3H), 1.12 (s, 3H), 2.13-2.24 (m, 2H), 2.56 (s, 2H), 4.67 (s, 1H), 7.08 (s, 2H), 7.13-7.34 (m, 4H); ^{13}C NMR (DMSO-d_6) δ: 27.2, 28.3, 32.2, 35.1, 50.4, 58.4, 113.7, 115.1, 115.6, 119.9, 129.3, 129.4, 140.5, 141.2, 158.8, 160.0, 162.2, 196.1.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5d): Colour: White solid; Anal. calcd. (found) % for $C_{18}H_{17}N_2O_2Cl$: C, 65.75 (65.66); H, 5.21 (5.09); N, 8.52 (8.40). ^{1}H NMR (DMSO-d_6) δ: 0.92 (s, 3H), 1.03 (s, 3H), 2.07-2.29 (m, 4H), 4.19 (s, 1H), 7.08 (s, 2H), 7.15-7.17 (d, 2H), 7.33-7.36 (d, 2H); ^{13}C NMR (DMSO-d_6) δ: 27.0, 28.3, 31.8, 35.6, 50.2, 58.0, 112.8, 119.9, 128.8, 129.2, 131.6, 144.4, 158.6, 162.9, 196.1.

2-Amino-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile (5e): Colour: White solid; Anal. calcd. (found) % for $C_{19}H_{20}N_2O_3$: C, 70.35 (70.24); H, 6.21 (6.06); N, 8.64 (8.52). ^{1}H NMR (DMSO-d_6) δ: 1.04 (s, 3H), 1.13 (s, 3H), 2.16-2.22 (m, 2H), 2.47 (s, 2H), 3.77 (s, 3H), 4.30 (s, 1H), 5.60 (s, 2H), 6.84 (d, 2H, J = 8Hz), 7.14 (d, 2H, J = 8 Hz).

2-Amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5f): Colour: White solid; Anal. calcd. (found) % for $C_{18}H_{17}N_3O_4$: C, 63.71 (63.56); H, 5.05 (4.91); N, 12.38 (12.26). ^{1}H NMR (DMSO-d_6) δ: 1.05 (s, 3H), 1.11 (s, 3H), 2.20-2.25 (m, 2H), 2.47 (s, 2H), 4.49 (s, 1H), 6.24 (s, 2H), 7.47-7.66 (m, 2H), 8.06-8.11 (m, 2H).

2-Amino-6,6,8,8-tetrahydro-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4*H*-chromene-3-carbonitrile (5g): Colour: Pale brownish solid; Anal. calcd. (found) % for $C_{18}H_{17}N_3O_4$: C, 63.71 (63.58); H, 5.05 (4.89); N, 12.38 (12.23).^{1}H NMR

(DMSO-d_6) δ: 0.95 (s, 3H), 1.08 (s, 3H), 2.13-2.27 (m, 4H), 4.29 (s, 1H), 6.61 (s, 2H), 7.17-7.41 (m, 4H); ^{13}C NMR (DMSO-d_6) δ: 28.8, 33.8, 39.6, 40.9, 51.5, 53.9, 118.5, 123.2, 124.8, 129.0, 145.9, 149.3, 156.9, 178.1, 190.5.

2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5h): Colour: White solid; Anal. calcd. (found) % for $C_{18}H_{17}N_2O_2F$: C, 69.22 (69.04); H, 5.49 (5.41); N, 8.97 (8.86).^{1}H NMR (DMSO-d_6) δ: 0.93 (s, 3H), 1.16 (s, 3H), 1.96-2.32 (m, 4H), 4.22 (s, 1H), 6.91 (s, 2H), 7.11-7.42 (m, 4H); ^{13}C NMR (DMSO-d_6) δ: 28.8, 33.7, 39.6, 40.8, 51.5, 54.4, 114.0, 118.3, 124.8, 129.7, 136.1, 156.7, 162.2, 176.2, 190.4.

2-Amino-7,7-dimethyl-4-(4-methylbenzoyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5j): White solid. Anal. calcd. (found) % for $C_{20}H_{20}N_2O_3$: C, 71.41 (71.29); H, 5.99 (6.07); N, 8.33 (8.21). ^{1}H NMR (DMSO-d_6) δ: 1.02 (s, 3H), 1.11(s, 3H), 2.13-2.26 (m, 2H), 2.42 (s, 3H), 2.46-2.58 (m, 2H), 4.91 (s, 1H), 7.25 (br. s, 2H), 7.37 (d, 2H, *J* = 7.5 Hz), 8.00 (d, 2H, *J* = 7.8 Hz). ^{13}C NMR (DMSO-d_6) δ: 21.7, 26.8, 29.2, 32.9, 36.0, 50.1, 52.7, 111.2, 119.6, 129.6, 129.7, 133.6, 144.5, 160.5, 164.4, 196.5, 198.4.

2-Amino-4-(4-chlorobenzoyl)-7,7-dimethyl-5-oxo-5,6,-7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5k): White solid. Anal. calcd. (found) % for $C_{19}H_{17}N_2O_3Cl$: C, 63.96 (63.80); H, 4.80 (4.91); N, 7.85 (7.76). ^{1}H NMR (DMSO-d_6) δ: 1.05 (s, 3H), 1.12 (s, 3H), 2.13-2.29 (m, 2H), 2.44-2.53 (m, 2H), 5.02 (s, 1H), 7.22 (br. s, 2H), 7.62 (d, 2H, *J* = 7.5Hz), 8.13 (d, 2H, *J* = 8 Hz); ^{13}C NMR (DMSO-d_6) δ: 26.6, 29.2, 32.9, 36.3, 49.9, 52.4, 110.9, 119.5, 129.4, 131.3, 139.0, 160.5, 164.6, 196.6, 198.2.

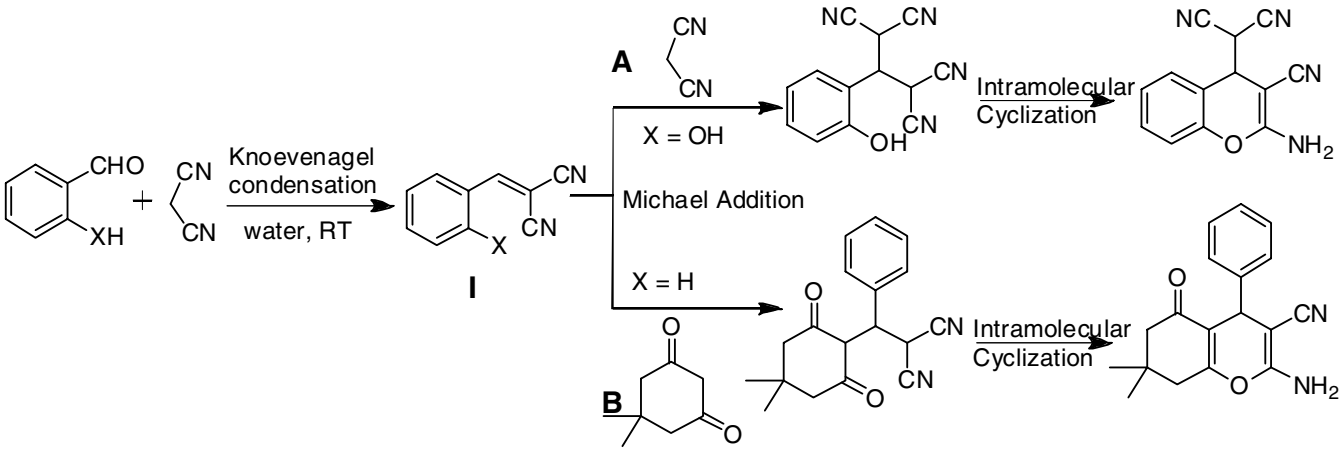
2-Amino-4-(4-fluorobenzoyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5l): White solid. Anal. calcd. (found) % for $C_{19}H_{17}N_2O_3F$: C, 67.05 (66.92); H, 5.03 (4.90); N, 8.23 (8.09). ^{1}H NMR (DMSO-d_6) δ: 1.02 (s, 3H), 1.09 (s, 3H), 2.14-2.28 (m, 2H), 2.49-2.60 (m, 2H), 5.01 (s, 1H), 7.27 (br. s, 2H), 7.40 (d, 2H, *J* = 7.5 Hz), 8.22 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (DMSO-d_6) δ: 26.9, 29.1, 32.9, 36.2, 50.0, 52.4, 111.1, 116.2, 119.6, 132.5, 132.9, 132.9, 160.6, 164.5, 196.6, 197.7.

RESULTS AND DISCUSSION

At the outset, 1:2 molar reaction of salicylaldehyde and malononitrile was investigated as a probe reaction by stirring the reactants in water at ambient temperature. The suspension of reactants in water turned to white precipitate within 10 min of stirring. Thin layer chromatography using 30 % ethyl acetate in petroleum ether confirmed completion of the reaction. The pure solid product was obtained by simple filtration of reaction mixture, followed by washing with water without any further purification. The product was identified by spectroscopic techniques and by comparison with an authentic sample. As expected, the reactants underwent a series of bond forming reactions to yield product **4a**. With the intention to compare the efficiency of the current heterogeneous protocol with homogeneous solution reaction, the exemplary reaction was carried out in solution state using numerous solvents *viz*. ethanol, methanol, tetrahydrofuran, ethyl acetate and dichloromethane. Interestingly, it was found that the reaction proceeds very slowly to give trace amount of products in organic solvents, which form homogeneous solution.

With the aim to explore the scope of the following protocol, a series of salicylaldehyde derivatives were reacted with 1:2 moles of malononitrile in water to obtain chromene derivatives. The results are summarized in Table-1. It was found that salicylaldehydes attached to functional groups with electron donating and withdrawal effects underwent smooth reaction to yield desired products with high conversion rate within few minutes of stirring.

In order to expand the generality of the current uncatalyzed cascade Knoevenagel-Michael-intramolecular cyclization protocol, the aqueous reaction of benzaldehyde with malononitrile and dimedone was revisited. Initially, the reaction was carried out through one-pot three-component addition of reactants and monitored by TLC. Upon completion of the reaction, the pure products were obtained using column chromatography. Only trace amount of desired chromene was formed (9 %), (which is in agreement with the reported literature [17,34]), with the formation of benzylidene malononitrile (20 %) and 2,2′-(phenylmethylene)*bis*(3-hydroxycyclohex-2-enone) (30 %) as major products. Further, the attempt to obtain compound **5a** was successful by treating benzylidene malononitrile with dimedone in water. Thus, with the aim to obtain desired product, sequential addition of aldehyde and malononitrile followed by dimedone was attempted in water. The desired product was obtained in 91 % yield by simple filtration of the precipitate without further purification. Encouraged by this successful result, synthesis of diverse 2-amino-3-cyano-4*H*-



Scheme-II: Proposed mechanism of current cascade protocol

chromenes (**5a-i**) was undertaken in water at room temperature and the results are presented in Table-2. The aromatic aldehydes bearing both electron withdrawing and electron donating groups were found to undergo smooth transformation to yield the desired chromene derivatives in high percentage of conversion.

Furthermore, the applicability of current protocol was extended to the synthesis of functionalized chromenes through the sequential reaction of arylglyoxals with malononitrile followed by dimedone in one-pot. The products were obtained in moderate yield in aqueous media at ambient temperature (Table-3).

Based on the experimental results and available literature, plausible mechanism depicting the series of events for current cascade reaction is proposed in **Scheme-II**. The condensation of aldehyde and malononitrile lead to formation of corresponding benzylidenemalononitrile (**I**), which act as an electron deficient Michael acceptor. Another molecule of malononitrile (path A) or dimedone (path B) attacks the electron deficient (**I**) to give Michael addition product, which undergoes simultaneous intramolecular cyclization reaction to produce corresponding chromene derivative.

Conclusion

An efficient, environmental friendly, one-pot approach for the synthesis of 2-amino-3-cyano-4*H*-chromenes has been developed using water as a reaction medium. High percentage of conversion of reactants to (2-amino-3-cyano-4*H*-chromene-4-yl)malononitrile derivatives were achieved through single step addition. Further, synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives and 2-amino-4-(benzoyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives were achieved through sequential addition of reactants in one-pot. The current uncatalyzed cascade Knoevenagel-Michael-Intramolecular cyclization approach circumvents several limitations accompanying with previously reported catalytic protocols.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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