ISSN: 0974 - 7516 Volume 11 Issue 3

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 11(3), 2015 [083-090]

Synthesis of 3,4-dihydropyrano[*c*]chromene derivatives under catalyst-free conditions

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ABSTRACT

Given the importance of chromene moiety, which is an essential pharmacophore in many antimicrobial, antiviral, antivascular, antifungal, antioxidant, anti-inflammatory, estrogenic, anticancer and anti-HIV agents, development of environmentally benign and practically simpler methods are highly desirable. Unlike many base catalyzed synthesis of 3,4-dihydropyrano[3,2-*c*]chromenes by multicomponent reaction of aldehydes, malononitrile, and 4-hydroxy coumarin which has potential to generate many byproducts, we have reported herein a catalyst-free method so synthesize the same. Comparison of two-component and three-component strategy led us to conclude that three component reaction generated bis-coumarin as byproduct while two-component reaction did not give any side reaction.

KEYWORDS

3,4-dihydropyrano [3,2-*c*]chromenes; Catalyst-free; Chromatography-free; Green.

INTRODUCTION

Chromene is an interesting scaffold that constitute the basic backbone of many polyphenols which are widely found in natural alkaloids, flavonoids, anthocyanins,[1] and many other biologically important compounds (Figure 1).[2] Many natural and synthetic chromene derivatives possess antimicrobial,[3] antiviral,[4] antivascular,[5] antifungal,[6] antioxidant,[7] anti-inflammatory,[8] estrogenic,[9] anticancer[10] and anti-HIV[11] activities. Additionally, dihydropyrano[*c*]chromenes have found application in the treatment of neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease.[12] Nevertheless, they have found applications in cosmetics, pigments[13] and photoactive materials.[14] As a result, development of new methodology for the synthesis of dihydropyrano[*c*]chromenes attracts interests from synthetic community.

The most common route for the synthesis of 3,4-dihydropyrano[3,2-*c*]chromenes is *via* three component reaction of aldehyde 2, malononitrile or ethyl cyanoacetate 3 and 4-hydroxycoumarin 4 (Scheme 1) in the presence of a base catalyst. But there are too many possibilities in a base catalyzed reaction that include (a) competitive Knoevenagel condensation of the aldehyde with both malononitrile and 4-hydroxycoumarin, and (b) competitive addition of both malononitrile and 4-hydroxycoumarin to the Knoevenagel products to give at least two undesired products (Figure 2).

The synthesis of 3,4-dihydropyrano[*c*] chromenes are known to be catalyzed by acid, base and ammonium salts.[15-27] While acid catalyzed synthesis 3,4-

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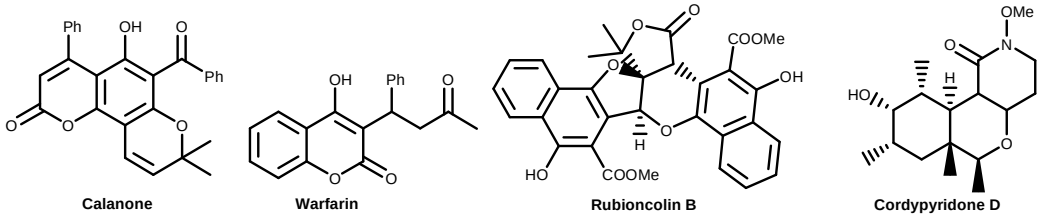


Figure 1 : Biologically active molecules containing chromene

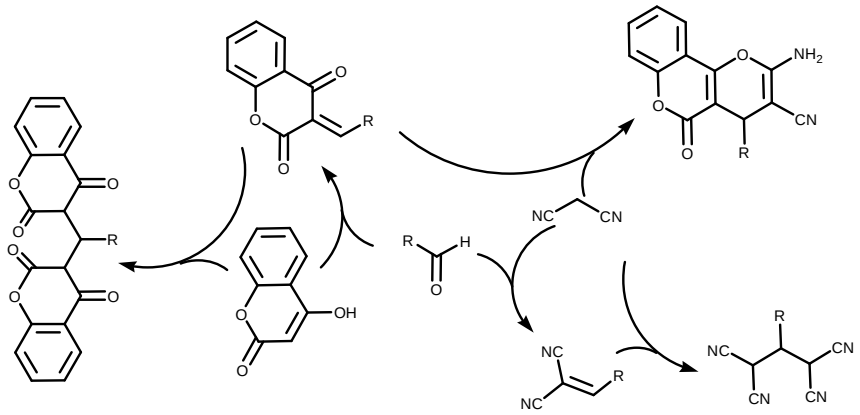


Figure 2 : Possible MCR pathways

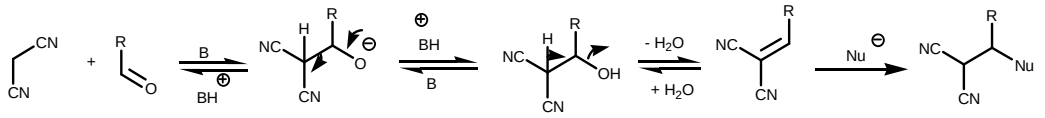
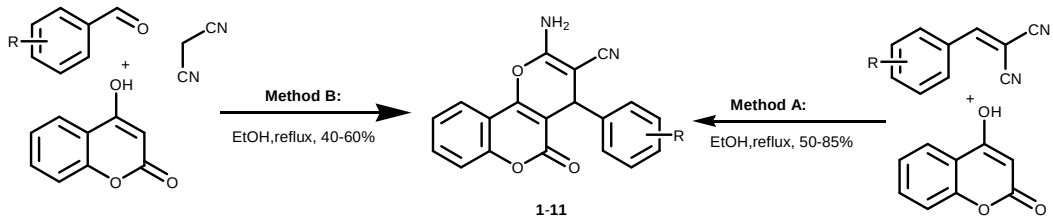


Figure 3 : Reversibility of knoevenagel reaction



Scheme 1 : Synthesis of dihydropyran[*c*]chromenes

dihydropyrano[*c*]chromenes can be accomplished at room temperature, it leads to formation of undesired byproducts due to competing Knoevenagel reaction of 4-hydroxycoumarin and malononitrile with aldehyde. Heravi et al.[24] observed that selection of catalyst is very crucial to synthesize dihydropyrano[3,2-*c*]chromenes and avoid the formation of undesired bis-coumarins in the reaction of 4-hydroxycoumarin, aldehydes and ethyl cyanoacetate catalyzed by heteropoly acids. On the other hand, base catalysis of this reaction requires high temperature possibly to avoid the reversibility of the Knoevenagel product (Figure 3) which works as Michael acceptor for incoming nucleophile (in this case 4-hydroxycoumarin).

Khurana and co-workers[15] reported the synthesis of 3,4-dihydropyrano[3,2-*c*]chromenes 1 catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in water under reflux condition, while Balalaie and co-workers[16] used a catalytic amount (10 mol%) of diammonium hydrogen phosphate (DAHP) to achieve the same transformation at room temperature. Use of task-specific ionic liquids (ILs),[17] and metal oxide nanoparticles[18] as a catalysts for the synthesis of 3,4-dihyropyrano[*c*] chromenes 1 by three-component condensation reaction of aldehydes, malononitrile and 4-hydroxycoumarin also required reflux temperature. Bihani et al.[19] recently reported the use of Amberlyst A21 as a resin bound reusable catalyst for green synthesis of

pyrano[*c*]chromenes derivatives at room temperature. Given the fact that most of the base catalyzed reactions worked only at reflux temperature and mechanistically, they are prone to give other products, we were curious to know if addition of 4-hydroxy coumarin to the Knoevenagel product in two component fashion works better to achieve 3,4-dihydropyrano[3,2-*c*]chromenes. For that purpose, we carried out both three component and two component synthesis 3,4-dihydropyrano [3,2-*c*]chromenes without any base at reflux conditions. Our observations are summerized in the Scheme 1.

EXPERIMENTAL

Materials and methods

The commercially available chemicals and reagents were used without further purification. Compounds were purified by crystallization using hot ethanol. Melting points were determined by using open capillary tube on a melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin Elmer 983 spectrophotometer and the values are expressed as ν_{max} cm^{-1}. ^{1}HNMR (400 MHz) and ^{13}CNMR (100 MHz) spectra were recorded on an FT-NMR Bruker Avance II 400 MHz spectrometer using DMSO-d_6 as solvent and TMS as internal standard, unless otherwise stated. Mass spectra were obtained from Waters ZQ 4000 mass spectrometer by the ESI method, while the elemental analyses of the compounds were performed on a Perkin-Elmer-2400 CHN/S analyzer. Silica gel G (Merck) was used for thin-layer chromatography (TLC). TLC plates were visualized by putting the plate in an iodine chamber or UV or sulphuric acid spray followed by heating on a hot plate.

General procedure for the synthesis of 4,5-dihydropyrano[3,2-c]chromene (method a)

In a flamed dried 25 mL round bottom flask equipped with a magnetic bar and condenser was added aldehyde (1 mmol) and malononitrile (1 mmol) in ethanol (5 mL) and stirred at refluxed temperature. Upon formation of the α,α-dicyanoolefin as indicated in the TLC plate, it was filtered and recrystallized from ethanol to get almost quantitative yield. Then the α,α-dicyanoolefin was added to a solution of 4-hydroxycoumarin (1 mmol) in ethanol (5 mL) and stirred under refluxed temperature. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was brought to room temperature. The precipitate was filtered and purified by re-crystallization from ethanol.

General procedure for the synthesis of 4,5-dihydropyrano[3,2-c]chromene (method b)

In a flamed dried 25 mL round bottom flask equipped with a magnetic bar and condenser was added aldehyde (1 mmol), malononitrile (1 mmol) and 4-hydroxycoumarin (1 mmol) in ethanol (10 mL) and stirred under refluxed temperature. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was brought to room temperature. The precipitate was filtered and purified by re-crystallization from ethanol.

Spectral data of the compounds

2-Amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3 carbonitrile, 1

White solid; m.p.[23] 261-263°C; IR (KBr): ν 3383, 3303, 3191, 2190, 1712, 1675, 1606 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.48 (s, 1H), 7.20-7.30 (m, 4H), 7.45-7.54 (m, 4H), 7.71 (t, J = 7.6 Hz, 1H), 7.88 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.70, 56.5, 103.06, 115.45, 117.01, 119.74, 122.90, 124.07, 127.58, 128.49, 128.93, 129.31, 130.99, 141.39, 152.45, 164.39, 167.70; ESI-MS: *m/z* 351 $[M+1]^+$, 373 $[M+Na]^+$; Elemental Analysis for $C_{19}H_{11}ClN_2O_3$: Calculated C 65.06, H 3.16, N 7.99; Found C 65.10, H 3.21, N 8.10.

2-Amino-4-(3-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile, 2

White solid; m.p.[15] 242-243°C; IR (KBr): ν 3371, 3310, 3193, 2200, 1710, 1650, 1601 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.47 (s, 1H), 7.21-7.33 (m, 3H), 7.47-7.58 (m, 5H), 7.69 (t, J = 7.6 Hz, 1H), 7.81 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.20, 57.22, 103.56, 113.32, 117.01, 119.45, 123.03, 125.20, 126.99, 127.56, 128.01, 130.76, 133.42, 133.60, 146.12, 152.51, 154.23, 158.50, 160.13; ESI-MS: *m/z* 373 $[M+Na]^+$. Elemental Analysis for $C_{19}H_{11}ClN_2O_3$: Calculated C 65.06, H 3.16, N 7.99; Found C 65.10, H 3.18, N 8.01.

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2-Amino-4-(4-bromophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile, 3

Solid;m.p.[15] 253-255°C; IR (KBr): ν 3390, 3303, 3191, 2196, 1712, 1672, 1619 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.46 (s, 1H), 7.22-7.35 (m, 2H), 7.44-7.50 (m, 6H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.8 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.34, 57.34, 103.28, 103.35, 115.62, 116.54, 119.064, 120.189, 122.47, 124.65, 129.00, 130.60, 132.98, 142.71, 157.88, 159.50, 164.47, 166.88; ESI-MS: *m/z* 395.19 $[M+]^+$, 418 $[M+Na]^+$; Elemental Analysis for $C_{19}H_{11}BrN_2O_3$: Calculated C 57.74, H 2.81, N 7.09; Found C 57.79, H 2.86, N 7.12.

2-Amino-4-(4-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile, 4

White solid; m.p.[27] 257-259°C; IR (KBr): 3404, 3330, 3199, 2204, 1709, 1675, 1531 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.67 (s, 1H), 7.23-7.58 (m, 5H), 7.61 (s, 2H), 7.71-7.77(m, 1H), 7.90-7.94 (m, 1H), 8.18 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.46, 58.25, 102.54, 112.78, 116.59, 119.41, 122.25, 123.31, 123.34, 124.57, 130.86, 133.50, 133.94, 145.55, 147.79, 151.33, 154.32, 158.02, 159.90; ESI-MS: *m/z* 361 $[M+]^+$, 362 $[M+1]^+$; Elemental Analysis for $C_{19}H_{11}N_3O_5$: Calculated C 63.16, H 3.07, N 11.63; Found 63.21, H 3.10, N 11.69.

2-Amino-4-(3-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile, 5

White solid; m.p.[28] 261-263°C; IR (KBr): ν 3409, 3330, 3197, 2209, 1703, 1672, 1533 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.72 (s, 1H), 7.45- 7.52 (m, 3H), 7.55 (s, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 6.8 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.56, 56.85, 103.56, 113.78, 116.59, 119.21, 122.24, 123.31, 123.34, 124.69, 130.85, 133.50, 134.74, 145.45, 147.79, 152.23, 154.35, 158.08, 160.20; ESI-MS: *m/z* 362 $[M+1]^+$; Elemental Analysis for $C_{19}H_{11}N_3O_5$: Calculated C 63.16, H 3.07, N, 11.63; Found C 63.20, H 3.12, N 11.70.

2-Amino-4-(4-hydroxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile, 6

White solid; m.p.[29] 264-265°C; IR (KBr): ν 3416, 3387, 3309, 3198, 2203, 1686, 1606, 1507 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.31 (s, 1H), 6.67 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.33 (s, 1H), 7.423-7.702 (m, 2H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 6.8 Hz, 1H), 9.36 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.08, 58.29, 104.43, 112.95, 115.12, 116.47, 119.35, 122.33, 124.57, 128.64, 132.73, 133.65, 151.98, 152.90, 156.41, 157.82, 159.48; ESI-MS: *m/z* 355 $[M+Na]^+$; Elemental Analysis for $C_{19}H_{12}N_2O_4$: Calculated C 68.67, H 3.64, N 8.43; Found C 68.69, H 3.68, N 8.49.

2-Amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile, 7

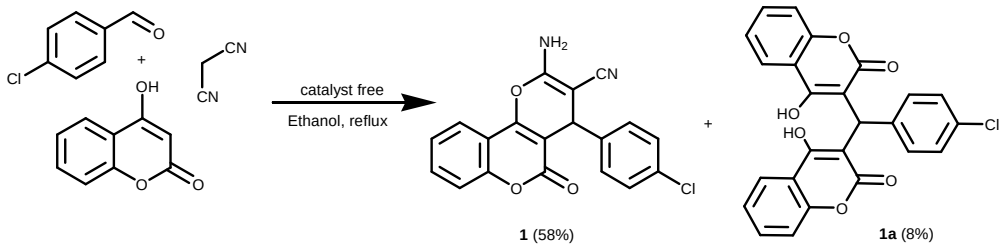
White solid; m.p.[15] 253-256°C; IR (KBr): ν 3376, 3290, 3184, 2203, 1712, 1672, 1606 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.45 (s, 1H), 7.21-7.32 (m, 5H), 7.41-7.51 (m, 2H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 7.4 Hz, 1H), 8.3 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.90, 57.90, 103.93, 112.89, 116.50, 119.21, 122.42, 127.08, 127.58, 128.47, 132.87, 143.28, 152.07, 153.36, 157.92, 159.49; ESI-MS: *m/z* 317.12 $[M+1]^+$, 339 $[M+Na]^+$, Elemental Analysis for $C_{19}H_{12}N_2O_3$: Calculated C 72.15, H 3.82, N 8.86; Found C 72.18, H 3.89, N 8.90.

2-Amino-5-oxo-4-(p-tolyl)-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile, 8

White solid; m.p.[30] 223-225°C; IR (KBr): ν 3389, 3309, 3189, 2198, 1712, 1670, 1617 cm^{-1}; ^1H NMR (400 MHz, DMSO- d_6): δ 2.24 (s, 3H), 4.38 (s, 1H), 7.23-7.30 (m, 4H), 7.38 (s, 2H), 7.44-7.55 (m, 2H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 20.43, 35.67, 47.22, 103.46, 115.40, 119.83, 122.88, 124.03, 126.48, 128.26, 130.89, 139.07, 142.22, 152.38, 153.44, 158.71, 159.43; ESI-MS: *m/z* 331 $[M+1]^+$, 353 $[M+Na]^+$; Elemental Analysis for $C_{20}H_{14}N_2O_3$: Calculated C 72.72, H 4.27, N 8.48; Found C 72.76, H 4.31, N 8.50.

2-Amino-4-(4-methoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile, 9

White solid; m.p.[31] 242-245°C; IR (KBr): ν?3370, 3297, 3191, 2196, 1712, 1679, 1606, 1507 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.70 (s, 3H), 4.38 (s,1H), 6.85 (d, *J* = 8.4Hz, 2H), 7.15 (d, *J* = 8.4 Hz,



Scheme 2 : One-step catalyst-free synthesis of dihydropyran[*c*]chromene

2H), 7.37 (s, 2H), 77.44-7.50 (m, 2H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.11, 54.99, 58.11, 104.22, 111.91, 112.96, 113.79, 116.52, 119.26, 119.80, 122.40, 124.63, 128.71, 132.83, 135.35, 152.04, 153.04, 157.84, 158.26, 159.49; ESI-MS: *m/z* 347.73 $[M+1]^+$; Elemental Analysis for $C_{20}H_{14}N_2O_4$: Calculated C 69.36, H 4.07, N 8.09; Found C 69.40, H 4.12, N 8.11.

2-Amino-4-(4-(dimethylamino)phenyl)-5-oxo-4,5-dihydropyrano[3,2-c] chromene-3-carbonitrile, 10

Solid; m.p.[15] 224-226°C; IR (KBr): ν 3380, 3287, 3189, 2198, 1716, 1677, 1606, 1509 cm^{-1}; ^{1}H NMR (400 MHz, DMSO- d_6): δ 2.84 (s, 6H), 4.29 (s, 1H), 6.63 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.31 (s, 2H), 43-7.49 (m, 2H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 8 Hz,1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 35.95, 40.12, 58.37, 104.60, 112.32, 112.97, 116.48, 119.40, 122.35, 124.61, 128.15, 130.86, 132.72, 149.51, 151.95, 152.72, 157.83, 159.51; ESI-MS: *m/z* 359 $[M+]^+$, 382 $[M+Na]^+$; Elemental Analysis for $C_{21}H_{17}N_3O_3$: Calculated C 70.18, H 4.77, N 11.69; Found C 70.21, H 4.80, N 11.71.

2-Amino-4-(3,4-dimethoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile, 11:

Solid; m.p.[32] 225-227°C; IR (KBr): ν 3330, 3220, 3176, 2190, 1715, 1666, 1606, 1513 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.45 (s, 6H), 4.14 (s, 1H), 6.48 (dd, *J* = 1.6, 8 Hz, 1H), 6.58-6.62 (m, 2H), 7.11 (s, 2H), 7.17-7.23 (m, 2H), 7.41-7.45 (m, 1H), 7.63 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.39, 55.41, 58.07, 104.00, 111.48, 111.78, 112.89, 116.47, 119.29, 119.56, 122.50, 124.65, 132.88, 135.75, 147.85, 148.39, 152.00, 153.16, 157.87, 159.62; ESI-MS: *m/z* 377 $[M+1]^+$; Elemental Analysis for $C_{21}H_{16}N_2O_5$: Calculated C 67.02, H 4.28, N 7.44; Found C 67.08, H 4.32, N 7.49.

TABLE 1 : Solvent effect on the synthesis of dihydropyran[*c*] chromene *via* Scheme 1 [a]

Entry	Solvent	Time (h)	Yield %[b]	
			One-step method	Two-step method
1	H_2O	24	-	-
2	CH_2Cl_2	16		
2	CH_3CN	24	-	-
3	THF	24	-	-
4	MeOH	24	16	35
5	Ethanol	16	80	80

3,32 -(4-Chlorophenyl)methylenebis-(4-hydroxycoumarin), 1a

White crystalline solid; mp 251–254 °C[33]; IR (KBr): 3030, 1671, 1602, 1092 and 768 cm^{-1}; ^{1}H NMR ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.12 (s, 1H) and 7.28–8.22 (m, 12H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.46, 90.44, 105.53, 107.24, 115.29, 117.89, 123.44, 125.60, 126.22, 126.92, 129.63, 130.59, 133.15, 139.62, 163.37 and 166.82; Elemental Analysis for $C_{25}H_{15}ClO_6$: Calculated C 67.20, H, 3.38; Found C 67.18; H, 3.40.

RESULTS AND DISCUSSION

For the pilot reaction, we stirred a mixture of malononitrile (1 mmol) and 4-chlorobenzaldehyde (1 mmol) in 10 mL ethanol at reflux temperature to afford the electron deficient olefin, α,α-dicyanoolefins in just 5 min. The crystalline Knoevenagel product was recrystallized from ethanol and added to a solution of 4-hydroxycoumarin (1 mmol) at reflux temperature and complete conversion was observed in 16 h. After cooling, the solid precipitate was filtered to get the crude product which was re-crystallized from ethanol to afford a pure white solid product 1 in 80% yield. When a stoichiometric mixture of all the three reactants were stirred together in ethanol at reflux temperature for 16

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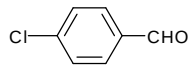
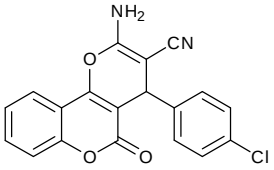
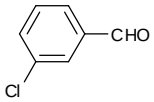
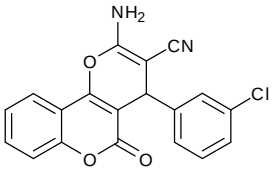
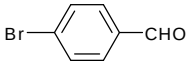
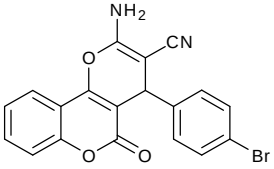
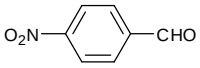
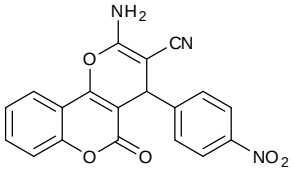
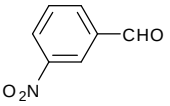
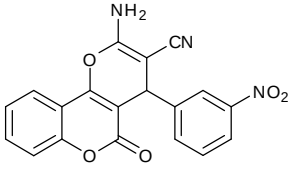
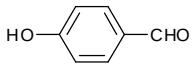
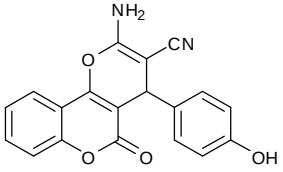
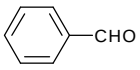
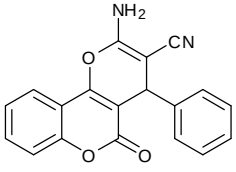
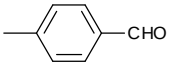
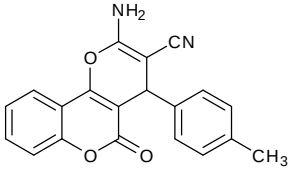
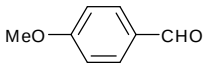
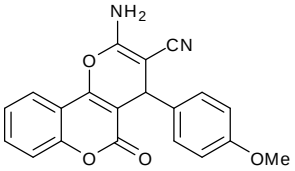
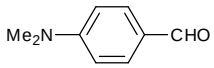
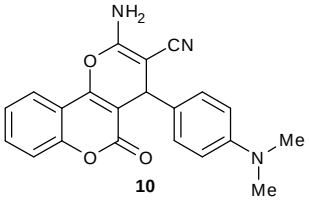
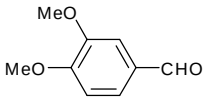
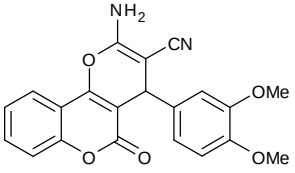
TABLE 2 : Synthesis of dihydropyran[*c*]chromenes *via* scheme 1[a,b]

Entry	R	Product	t/h	Yield[c] (%)	
				Method A	Method B
1		 **1**	16	80	58
2		 **2**	17	79	55
3		 **3**	16	82	56
4		 **4**	15	79	60
5		 **5**	15	75	56
6		 **6**	16	85	52
7		 **6**	22	70	58
8		 **8**	24	77	55

9		 **9**	24	63	60
10		 **10**	16	74	49
11		 **11**	26	50	47

[a]***Method A: α,α*-dicyanoolefins (1 mmol), 4-hydroxycoumarin (1 mmol) at reflux in ethanol;** [b]***Method B: aldehydes* (1 mmol), malononitrile (1 mmol), and 4-hydroxycoumarin (1 mmol) at reflux in ethanol;** [c]**Yield of the recrystallized product.**

h, we were surprised to find as many as three byproducts along with the desired dihydropyran[*c*]chromene in 58% yield. After analysing the major byproduct obtained by employing the three-component protocol with IR, ^{1}HNMR, ^{13}CNMR and elemental analysis, we could confirm the formation of bis-coumarin in 8% yield in the pilot reaction.

In order to study the effect of solvent on the reaction, we screened out the pilot reaction with various solvents at reflux temperature (TABLE 1) under stepwise and one step conditions. Keeping greener context in mind, we initially tried the reaction of *p*-chlorobenzaldehyde (1 mmol), malononitrile (1 mmol) and 4-hydroxycoumarin (1 mmol) in water, but reaction did not work under either one step or stepwise conditions even at reflux temperature. As can be seen from the TABLE 1, the solvent our initial choice, i.e ethanol, was found to be the solvent of choice as it gave the best yield.

To draw out a general conclusion regarding reactivity and efficiency of one-step and two-step methods, we explored the substrate scope of both the protocols (TABLE 2) using various substituted aldehydes having electron withdrawing and electron donating substituents on the phenyl ring. While reaction worked extremely well in all the cases for two-step reaction, yield of the products obtained in one-step protocol were comparatively lower. The yields of the reaction in one-step protocol could not be increased by increasing the reaction time. The aryl aldehydes with strong +M-effect (entries 9 and 11) took longer time for complete conversion and were inferior on yield. Incidentally, we did not come across formation of any bis-coumarin product in the two-step protocol.

CONCLUSIONS

In conclusion, we have reported a catalyst-free and green method for the synthesis of 4,5-dihydropyrano[3,2-*c*]chromene derivatives *via* a two-component reaction of an electron deficient alkene, α,α-dicyanoolefins, and 4-hydroxycoumarin and compared the yield with three component reaction of aldehydes, malononitrile, and 4-hydroxy coumarin. While three-component strategy gave bis-coumarin as one of the byproducts, two component synthesis was distinctly superior with better yields and no byproducts. Use of green approach by not employing any hazardous and expensive catalyst, no chromatographic purification, no hazardous solvent make our protocol highly applicable.

REFERENCES

[1] Q.Ren, W.Y.Siau, Z.Du, K.Zhang, J.Wang; Chem.Eur.J., **17**, 7781 **(2011)**.

[2] L.V.Hester, Z.Wei, H.Tore, P.J.T.Floris, A.Karl; J.Org.Biomol.Chem., **1**, 1953 **(2003a)**; E.Henry, A.M.Indwiani; Ind.J.Chem., **10**, 240 **(2010b)**; M.Curini, G.Cravotto, F.Epifano, G.Giannone; Curr.Med.Chem., **13**, 199 **(2006c)**; E.Melliou, P.Magiatis, S.Mitaku, A.L.Skaltsounis, E.Chinou, I.Chinou; J.Nat.Prod., **68**, 78 **(2005d)**; R.D.H.Murray, J.Mendez, R.A.Brown; 'The Natural Coumarins', Wiley; New York **(1982e)**.

[3] B.S.Chetan, M.S.Nimesh, P.P.Manish, G.P.Ranjan; J.Serb.Chem.Soc., **77**, 1 **(2012)**.

[4] J.Mori, M.Iwashima, M.Takeuchi, H.Saito; Chem.Pharm.Bull., **54**, 391 **(2006)**.

[5] G.Henriette, L.Lorraine, H.Bettina, D.Clemence, K.Dong, K.Irenej; Mol.Cancer.Ther., **3**, 1375 **(2004)**.

[6] T.Suresh, V.Arunima, K.Atin, G.Sandeep, V.R.Prarthana, R.K.Ganesh; Acta.Pol.Pharm., **67**, 423 **(2010)**.

[7] M.Milan, M.Mirjana, B.Desanka, M.Sanja, N.Neda, M.Vladimir; Int.J.Mol.Sci., **12**, 2822 **(2011)**.

[8] K.Nitin, K.Sushil, G.Himanshu, P.K.Sharma; World Res.J.Biochem., **1**, 1 **(2012)**.

[9] N.Jain, J.Xu, M.K.Ramesh, F.Du, G.Jian-Zhong, E.Pacia; J.Med.Chem., **52**, 544 **(2009)**.

[10] M.K.Aliaa, M.K.Manal, K.A.Eman, A.H.Heba; Int.J.Pharm.Res.Dev., **4**, 310 **(2012)**.

[11] C.K.Denish, K.P.Hetal, K.G.Nilesh; Asian J.Bio.Pharm.Res., **2**, 126 **(2012)**.

[12] W.O.Foye; 'Principi di Chemico Farmaceutica', Piccin; Padora, Italy, 416 **(1991a)**; L.L.Andreani, E.Lapi; Bull.Chim.Farm., **99**, 583 **(1960b)**; Y.L.Zhang, B.Z.Chen, K.Q.Zheng, M.L.Xu, X.H.Lei, X.B.Yaoxue; Chem.Abstr., **17**, 17 **(1982c)**; L.Bonsignore, G.Loy, D.Secci, A.Calignano; Eur.J.Med.Chem., **28**, 517 **(1993d)**.

[13] G.P.Ellis, A.Weissberger, E.C.Taylor; Chapter II; *In The Chemistry of Heterocyclic Compounds Chromenes, Chromanes and Chromones*; Eds.; John Wiley: New York, NY, 11 **(1977)**.

[14] D.Arnesto, W.M.Horspool, N.Martin, A.Ramos, C.Seaone; J.Org.Chem., **54**, 3069 **(1989)**.

[15] J.M.Khurana, B.Nand, P.Saluja; Tetrahedron, **66**, 5637 **(2010)**.

[16] S.Abdolmohammadi, S.Balalaie; Tetrahedron Lett., **48**, 3299 **(2007)**.

[17] J.Zheng, Y.Li; Mendeleev Commun., **21**, 280 **(2011)**.

[18] H.Mehrabi, M.Kazemi-Mireki; Chin.Chem.Lett., **22**, 1419 **(2011)**.

[19] M.Bihani, P.P.Bora, G.Bez; J.Chem., **16**, 419 **(2013)**.

[20] M.Kidwai, S.Saxena; Syn.Commun., **36**, 2737 **(2006)**.

[21] S.Khodabakhshi, B.Karami, K.Eskandari, S.J.Hoseini; C.R.Chimie, **17**, 35 **(2013)**.

[22] G.Zhang, Y.Zhang, J.Yan, R.Chen, S.Wang, Y.Ma, R.Wang; J.Org.Chem., **77**, 878 **(2012)**.

[23] A.T.Khan, M.Lal, S.Ali, M.M.Khan; Tetrahedron Lett., **52**, 5327 **(2011)**.

[24] M.M.Heravi, S.Sadjadi, N.M.Haj, H.A.Oskooie, F.F.Bamoharram; Catal. Commun., **10**, 1643 **(2009)**.

[25] J.M.Khurana, S.Kumar; Tetrahedron Lett., **50**, 4125 **(2009)**.

[26] V.D.Dyachenko, A.N.Chernega; Rus. J.Org.Chem., **42**, 585 **(2006)**.

[27] U.P.Tarpada, B.B.Thummar, D.K.Raval; J.Saudi Chem.Soc., doi:10.1016/j.jscs.2012.07.014., **(2013)**.

[28] G.Md.Dekamin, Md.Eslami, A.Maleki; Tetrahedron, **69**, 1074 **(2013)**.

[29] S.Jain, D.Rajguru, B.S.Keshwal, A.D.Acharya; ISRN Org.Chem., 1 **(2013)**.

[30] S.Kanakaraju, B.Prasanna, S.Basavoju, G.V.P.Chandramouli; Arabian J.Chem., doi:10.1016/j.arabjc.2013.10.014., **(2013)**.

[31] H.J.Wang, J.Lu, Z.H.Zhang; Monatsh Chem., **141**, 1107 **(2010)**.

[32] K.Tabatabaeian, H.Heidari, M.Mamaghani, O.N.Mahmoodi; Appl.Organometal.Chem., **26**, 56 **(2012)**.

[33] M.Kidwai, V.Bansal, P.Mothsra, S.Saxena, R.K.Somvanshi, S.Dey, T.P.Singh; J.Mol.Catal.A: Chem., **268**, 76 **(2007)**.