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REGULAR ARTICLE

KSCN and K_2CO_3 mediated one-pot synthesis of cyclopropanyl coumarin derivatives

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Abstract. A novel and efficient one-pot method has been developed for the synthesis of cyclopropanes by the cyclization of 4-bromomethylcoumrains, benzaldehydes and active methylene groups in 1:1 acetonitrile and water solvent in the presence of KSCN and K_2CO_3 as a catalyst at room temperature for 2-5 h. The significant attraction of this procedure is environmentally benign, simple procedure, the ready accessibility of the catalyst, excellent yield and mild reaction conditions. The structure of the target molecule (4b) was confirmed by X-ray diffraction.

Keywords. Bromomethylcoumarin; Cyclopropane; KSCN; K_2CO_3; Aryl/hetrocyclic aldehydes and activemethylenes.

1. Introduction

Cyclopropanes are important synthetic intermediates to access various valuable heterocyclic compounds.[1] They are widely applied in many organic transformations as intermediates[2,3] that are investigated extensively as an antibiotic,[4] antiviral,[5] antitumor,[6] neurochemical,[7] and antifungal activities.[8] Although rare, cyclopropane containing natural products have been isolated and investigated for their biological and pharmacological activities.[9] Therefore, the use of cyclopropane derivatives as building blocks continues to receive a great deal of attention from pharmaceutical companies. Some notable cyclopropane embedded drugs are foretinib (c-Met inhibitor),[10] isoxaflutole (inhibitor of HPPD),[11] and Trpv1 agonist (treatment for various diseases)[12] (Figure 1).

Plenty of powerful synthetic routes have been developed to access cyclopropane derivatives from (i) transition metal-catalyzed addition of carbenes to olefins,[13] (ii) oxidative cyclopropanation reaction of alkynyl sulfone with styrene,[14] (iii) the reaction of diazo compounds with alkenes,[15] (iv) cycloaddition reaction between enoldiazoacetate and imines,[16] (v) cross-coupling of styrene with acetyl ketones,[17] (vi) the reaction among α-halogenated compounds, benzaldehydes and active methylene groups.[18]

However, the last reaction is the most applied methodology to synthesize cyclopropane derivatives. In the past years, few methods have been proposed based on ylides of nitrogen,[19] sulfonium,[20] phosphorous,[21] tellurium,[22] and arsonium[23] as a reagent for the synthesis of cyclopropane derivatives. Many of these methodologies suffer from drawbacks such as the use of expensive and toxic catalysts, high temperature, long reaction time and harsh conditions. Thus, it is desirable to develop a new protocol for the synthesis of cyclopropane derivatives in one pot.

The coumarin is probably one of the most ubiquitous moieties in nature.[24] A vast number of natural and synthetic coumarin derivatives have been associated with valuable biological activities. [25–27] Among them, 4-methyl coumarin derivatives have attracted much attention because of their parent biological activities such as antidiabetic,[28] antidepressant,[29] antibacterial,[30] antiinflammatory,[31] anticancer,[32] antioxidant,[33] and COX inhibitor.[34] Based on the aforementioned facts, it is pivotal to design these two important moieties by blending distinct pharmacophoric groups of pharmacological relevance into a single framework to

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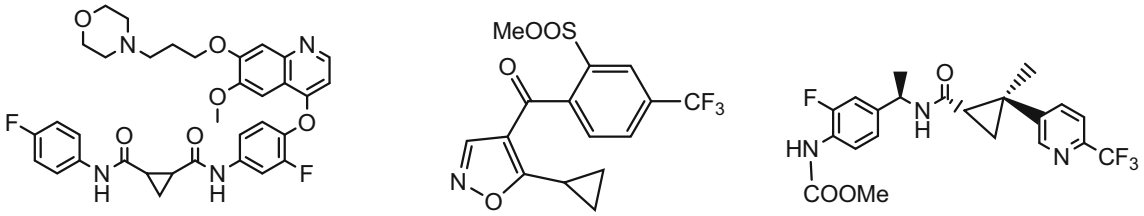


Figure 1. Examples of some cyclopropane based pharmacologically active molecules.

improve their medicinal properties and finally build stairways into a drug library.

KSCN being of low cost, environmentally benign and its operational simplicity have attracted several research groups. They have been used as thiocyanating agent and cyanating agent in various organic reactions such as in the formation of isothiocyanates, thiols, thioethers, phosphorothioates and other cyclized products.[35] Potassium carbonate is an inexpensive, commercially available, easy to handle that has recently been utilized as a catalyst in organic synthesis.[36]

Hence, we wish to report a one-pot synthesis of cyclopropanylcoumarin derivatives from 4-bromomethylcoumarins, benzaldehydes and active methylene groups under mild conditions that provide a facile execution for the synthesis of cyclopropanylcoumarins.

2. Experimental

2.1 *General information*

Melting points were determined on an electric melting point apparatus. ^{1}H NMR spectra were recorded on Jeol 400 and 500 MHz whereas ^{13}C NMR was recorded on 100 and 125 MHz in DMSO-d_6 and $CDCl_3$ solvents using TMS as an internal standard. Mass spectra were recorded by LC-MS Thermo LCQ fleet and high-resolution mass spectra (HRMS) were recorded by ion-electron spray. Analytical thin-layer chromatography (TLC) was performed using aluminium backed silica gel plates coated with 0.2 mm thickness of silica gel. Elemental analysis was performed on an elemental Vario Micro Cube rapid CHN analyzer.

2.1a *Typical experimental procedure for the synthesis of (4a-n)*: 4-Bromomethylcoumarins (1 mmol) and potassium thiocyanate (97 mg, 1 mmol) were stirred at room temperature in 1:1 acetonitrile and water (10 mL) for 10 min. Aldehydes (1 eq), active methylene compounds (1 eq) and potassium carbonate (100 mg, 1.5 eq) are added to the reaction mixture and stirred at room temperature for 3 h (completion of the reaction was monitored by TLC). The solid compound separated was filtered, dried and recrystallized from ethanol.

2.2 *Spectral details*

2-(6-Methyl-2-oxo-2*H*-chromen-4-yl)-3-phenylcyclopropane-1,1-dicarbonitrile (4a) Yield 85%; Brown solid; M.p. 260-262 °C; IR (ATR, cm^{-1}): 1726 (C=O), 2250 (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.75 (dd, 1H, J = 9.2 Hz, J = 1.2 Hz), 4.28 (d, 1H, J = 8.8 Hz,) 6.50 (s, 1H), 7.15-7.38 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 16.3, 24.6, 34.6, 111.0, 111.4, 115.7, 118.3, 123.0, 126.3, 128.3, 130.0, 133.0, 134.6, 137.7, 140.0, 142.2, 144.5, 150.4, 153.1, 160.0 ppm; LCMS m/z: $[M+H]^+$ Cald For $C_{21}H_{15}N_2O_2$ 327.1; Found 327.1; Anal. Calcd for $C_{21}H_{14}N_2O_2$: C, 77.29; H, 4.32; N, 8.58 Found: C, 77.25; H, 4.28; N, 8.53

2-(2,3-Dimethoxyphenyl)-3-(6,8-dimethyl-2-oxo-2*H*-chromen-4-yl)cyclopropane-1,1-dicarbonitrile (4b) Yield 85%; Brown solid; M.p. 284-286 °C; IR (ATR, cm^{-1}): 1730 (C=O), 2230 (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.46 (s, 3H), 3.63 (dd, 1H, J = 9.2 Hz, J = 1.2 Hz), 3.77 (d, 1H, J = 9.2 Hz,) 3.92 (s, 3H), 4.06 (s, 3H), 6.42 (d, 1H, J = 0.8 Hz) 6.80 (t, 1H), 7.06-7.33 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 15.7, 21.2, 34.1, 34.7, 56.0, 61.2, 114.7, 116.2, 119.2, 120.9, 123.5, 124.3, 127.1, 134.6, 135.7, 145.9, 149.0, 150.3, 152.8, 159.9 ppm; HRMS m/z: $[M+Na]^+$ Cald For $C_{24}H_{20}N_2O_4Na$ 423.1321; Found 423.1318; Anal. Calcd for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00 Found: C, 72.20; H, 5.01; N, 6.99.

2-(6-(Tert-butyl)-2-oxo-2*H*-chromen-4-yl)-3-(4-chlorophenyl)cycopropane-1,1-dicarbonitrile (4c) Yield 80%; White solid; M.p. 300-302 °C; IR (ATR, cm^{-1}): 1715 (C=O), 2210 (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 9H); 4.36 (dd, 1H, J = 10.0 Hz, J = 1.2 Hz), 4.53 (d, 1H), 6.26 (d, 1H, J = 0.8 Hz), 7.16-7.45 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 22.2, 31.3, 34.7, 46.3, 111.7, 113.1, 114.0, 116.7, 117.5, 119.5, 125.0, 129.8, 129.9, 131.2, 136.1, 145.4, 149.8, 150.8, 152.0, 161.2 ppm; HRMS m/z: $[M+H]^+$ Cald for $C_{24}H_{20}ClN_2O_2$ 403.1213; Found 403.1207; Anal. Calcd for $C_{24}H_{19}ClN_2O_2$: C, 71.55; H, 4.75; N, 6.95 Found: C, 71.53; H, 4.72; N, 6.92

2-(2-Chloro-6-fluorophenyl)-3-(6-methoxy-2-oxo-2H-chromen-4-yl)cyclopropane-1,1-dicarbonitrile (4d) Yield 75%; White solid; M.p. 270-272 °C; IR (ATR, cm^{-1}): 1732 (C=O), 2220 (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (d, 1H, J = 8.8 Hz), 3.75 (d, 1H, J = 8 Hz), 3.91 (s, 3H), 6.53 (d, 1H), 7.08-7.42 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 31.4, 37.37, 55.9, 106.0, 111.5, 115.3, 115.6, 117.4, 118.0, 119.0, 120.6, 126.5, 132.3, 132.4, 144.8, 148.1, 156.7, 159.6, 160.6, 163.1 ppm; HRMS m/z: $[M+H]^+$ Cald For $C_{21}H_{13}ClFN_2O_3$ 395.0599; Found 395.0582; Anal. Calcd for $C_{21}H_{12}ClFN_2O_3$: C, 76.58; H, 5.00; N, 3.31 Found: C, 76.52; H, 4.90; N, 3.29

2-(6,7-Dimethyl-2-oxo-2*H*-chromen-4-yl)-3-(4-(methylsufonyl)phenyl)cyclopropane-1,1-dicarbonitrile (4e) Yield 80%; Yellow solid; M.p. 270-272 °C; IR (ATR, cm^{-1}): 1718 (C=O), 2242 (CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H), 2.20 (s, 3H), 3.07 (s, 3H), 4.31 (d, 1H, J = 9.2 Hz), 4.66 (dd, 1H, J = 2.4 Hz, 9.2 Hz), 6.93 (s, 1H), 7.26 (d, 1H), 7.41 (d, 1H), 7.53 (s, 1H) 7.71 (d, J = 6.8 Hz, 2H) 8.09 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 22.2, 42.2, 58.8, 58.9, 63.0, 113.8, 118.8, 122.9, 129.7, 131.7, 151.8, 152.0, 160.2 ppm; LCMS m/z: $[M+H]^+$ Cald For $C_{23}H_{19}N_2O_4S$ 419.1; Found 419.1; Anal. Calcd for $C_{23}H_{18}N_2O_4S$: C, 66.00; H, 4.34; N, 6.69 Found: C, 66.07; H, 4.32; N, 6.63

2-(7-Benzyl-2-oxo-2*H*-chromen-4-yl)-3-(2,3-dimethoxyphenyl)cyclopropane-1,1-dicarbonitrile (4f) Yield 82%; White solid; M.p. 258-260 °C; IR (ATR, cm^{-1}): 1725 (C=O), 2230 (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.53 (d, J = 8.8 Hz, 1H), 3.68 (d, J = 8.8 Hz, 1H), 3.93 (s, 3H), 3.40 (s, 3H), 4.09 (s, 2H), 6.44 (s, 1H), 6.75 (s, 1H), 7.18-7.42 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 34.3, 34.4, 41.4, 56.0, 61.2, 114.7, 117.0, 117.9, 119.3, 123.3, 124.3, 126.8, 129.0, 133.9, 138.8, 139.7, 145.7, 148.9, 152.3, 152.8, 159.6 ppm; LCMS m/z: $[M+H]^+$ Cald For $C_{29}H_{23}N_2O_4$ 463.2; Found 463.2; Anal. Calcd for $C_{29}H_{22}N_2O_4$: C, 75.31; H, 4.79; N, 6.06 Found: C, 75.32; H, 4.72; N, 6.10

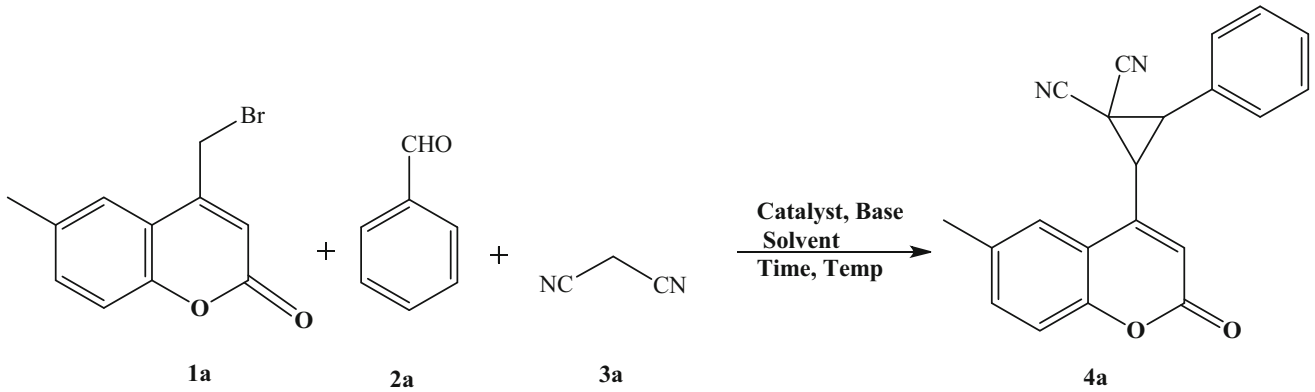
2-(6,8-Dimethyl-2-oxo-2*H*–chromen-4-yl)-3-(5-ethylthiophen-2-yl)cyclopropane-1,1-dicarbonitrile (4g) Yield 75%; Yellow solid; M.p. 240-242 °C; IR (ATR, cm^{-1}): 1728 (C=O), 2240 (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, J = 8.8 Hz, 3H), 2.39 (m, 2H), 2.78 (s, 3H), 2.80 (s, 3H), 3.76 (d, 1H, J = 8.4 Hz), 4.12 (dd, J = 8.5, 2.0 Hz, 1H), 6.06 (d, 1H), 6.34-6.37 (m, 2H), 6.52 (d, 1H), 7.36 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 14.4, 20.9, 23.3, 26.1, 34.0, 38.2, 113.1, 115.1, 115.3, 121.8, 124.1, 128.6, 129.6, 130.1, 135.3, 138.8, 144.9, 149.0, 150.3, 152.1, 159.4 ppm; LCMS m/z: $[M+H]^+$ Cald For $C_{22}H_{19}N_2O_2S$ 375.1; Found 375.1; Anal. Calcd for $C_{22}H_{18}N_2O_2S$: C, 70.57; H, 4.85; N, 7.48 Found: C, 70.55; H, 4.87; N, 7.49

2-(3-Bromopyridin-2-yl)-3-(6,8-dimethyl-2-oxo-2*H*-chromen-yl)cyclopropane-1,1-dicarbonitrile (4h) Yield 80%; Brown solid; M.p. 276-278 °C; IR (ATR, cm^{-1}): 1715 (C=O), 2218 (CN); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.39 (s, 3H), 4.58 (d, 1H, J = 9.0 Hz), 4.90 (dd, 1H, J = 9.0 Hz, J = 0.8 Hz), 6.79 (s, 1H), 7.44 (s, 1H), 7.59 (s, 1H), 7.80 (d, J = 8.5 Hz, 1H), 8.02 (s, 1H), 8.68 (d, J = 2.0 Hz 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6, 21.1, 33.3, 34.0, 46.2, 113.0, 113.2, 116.3, 117.9, 122.6, 126.1, 128.0, 128.3, 134.1, 135.5, 140.3, 142.5, 147.1, 150.0, 152.0, 159.9 ppm; LCMS m/z: $[M-H]^+$ Cald For $C_{21}H_{14}BrN_3/O_2$: M/Z = 418.0; Found 418.0; Anal. Calcd for $C_{21}H_{14}BrN_3O_2$: C, 60.02; H, 3.36; N, 10.00 Found: C, 59.98; H, 3.30; N, 10.02

2-(6-Methoxy-2-oxo-*2H*-chromen-4-yl)-3-(4-oxo-*4H*-chromen-2-yl)cyclopropane-1,1-dicarbonitrile (4i) Yield 65%; Brown solid; M.p. 238-240 °C; IR (ATR, cm^{-1}): 1740 (C=O), 2240 (CN); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.44 (dd, 1H, J = 9.2 Hz), 3.73 (d, 1H, J = 9.0 Hz), 4.01 (m, 3H), 6.21 (s, 1H), 7.09-7.12 (m, 2H), 7.38-7.43 (m, 2H), 7.57 (d, 1H), 7.73 (s, 1H), 7.26-7.93 (m, 2H), 7.81-8.01 (m, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 11.9, 16.9, 20.9, 61.0, 115.2, 115.9, 118.8, 122.6, 122.9, 123.8, 124.3, 125.2, 125.6, 125.8, 130.8, 134.3, 136.0, 141.9, 147.4, 153.9, 156.1, 164.6, 172.4, 175.9 ppm; HRMS m/z: $[M+Na]^+$ Cald For $C_{24}H_{14}N_2O_5Na$ 433.0800; Found 433.0788; Anal. Calcd for $C_{24}H_{14}N_2O_5$: C, 70.24; H, 3.44; N, 6.83 Found: C, 69.58; H, 3.47; N, 6.80

2-(6-Ethyl-2-oxo-2*H*-chromen-4-yl)-3-(1-methyl-1*H*-imidazol-2-yl)cyclopropane-1,1-dicarbonitrile (4j) Yield 70%; Yellow solid; M.p. 234-236 °C; IR (ATR, cm^{-1}): 1715 (C=O), 2218 (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, 3H, J = 7.2 Hz,); 2.78 (q, 2H, J = 7.6 Hz), 3.63 (d, 1H, J = 8.0 Hz), 3.92 (s, 1H), 4.42

Table 1 Optimization conditions for the synthesis of **4a**.



1a **2a** **3a** **4a**

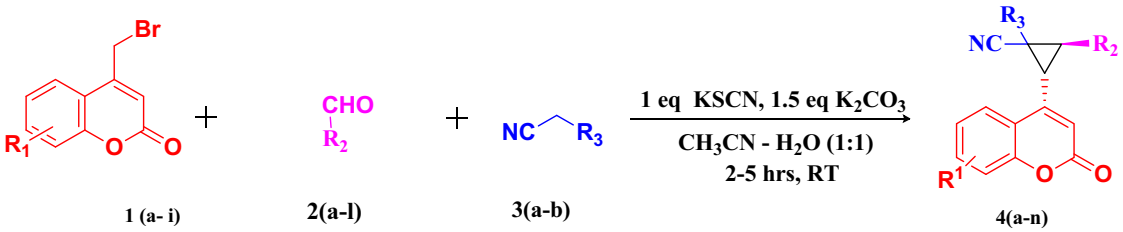
Entry	Base	Equivalence	Thiocyanate (1 eq)	Solvents	Time (h)	Temperature (°C)	Yield (%)
1	…	…	…	Ethanol	24	RT	–
2	DIPEA	1.5	KSCN	Ethanol	24	RT	trace
3	DIPEA	1.5	NH_4SCN	Ethanol	24	RT	–
4	DBU	1.5	KSCN	Ethanol	10	RT	–
5	Pyridine	1.5	KSCN	Ethanol	24	RT	–
6	$NaOC_2H_5$	1.5	KSCN	Ethanol	24	RT	–
7	NaOH	1.5	KSCN	Ethanol	24	RT	–
8	TEA	1.5	KSCN	Ethanol	24	RT	15
9	K_2CO_3	1.5	KSCN	Ethanol	24	RT	50
10	K_2CO_3	1.5	KSCN	Xylene	24	RT	30
11	K_2CO_3	1.5	KSCN	CH_3CN	7	RT	60
12	K_2CO_3	1.5	KSCN	DMSO	3	RT	–
13	K_2CO_3	1.5	KSCN	DMF	3	RT	–
14	K_2CO_3	1.5	KSCN	CH_3CN-H_2O (1:1)	3	RT	85
15	K_2CO_3	2.0	KSCN	CH_3CN -H_2O (1:1)	2	RT	85
16	K_2CO_3	1.0	KSCN	CH_3CN -H_2O (1:1)	6	RT	20
17	K_2CO_3	1.5	KSCN	THF-H_2O (1:1)	5	RT	35
18	K_2CO_3	1.5	KSCN	Ethanol-H_2O (1:1)	5	RT	30
19	K_2CO_3	1.5	KSCN	CH_3CN-H_2O (1:1)	10	50	40
20	K_2CO_3	1.5	KSCN	CH_3CN-H_2O(1:1)	10	60	10
21	K_2CO_3	1.5	KSCN	CH_3CN-H_2O (1:1)	10	80	10

(d, 1H, J = 8.0 Hz), 6.44 (s, 1H), 7.08 (d, 2H, J = 8.0 Hz), 7.35 (d, 1H, J = 9.0 Hz), 7.49-7.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 15.3, 28.3, 29.6, 33.0, 33.5, 111.3, 111.3, 116.0, 117.5, 122.2, 124.1, 128.8, 133.2, 137.2, 141.5, 144.9, 151.9, 159.6 ppm; LCMS m/z: $[M+H]^+$ Cald For $C_{20}H_{17}N_4O_2$ 345.1; Found 345.1; Anal. Calcd for $C_{20}H_{16}N_4O_2$: C, 69.55; H, 4.96; N, 16.22 Found: C, 69.58; H, 4.94; N, 16.20

2-(6-Methoxy-2-oxo-2*H*-chromen-4-yl)-3-(1-methyl-1*H*-imidazol-2-yl)cyclopropane-1,1-dicarbonitrile (4k) Yield 75%; Brown solid; M.p. 238-240 °C; IR (ATR, cm^{-1}): 1710 (C=O), 2230 (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57 (d, 1H, J = 8.0 Hz), 3.83 (s, 3H), 3.92 (s, 3H), 4.35 (d, 1H, J = 7.2 Hz), 6.69 (s, 1H), 7.08 (d, 2H, J = 2.0 Hz), 7.42 (d, 1H, J = 8.8 Hz), 7.53 (m, 1H), 7.63 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 15.3, 29.7, 33.1, 61.3, 111.3, 111.4, 113.2, 115.9, 117.5, 122.3, 124.1, 128.9, 133.3, 135.8, 137.2, 152.0, 154.0, 160.4 ppm; HRMS m/z: $[M+H]^+$ Cald For $C_{19}H_{15}N_4O_3$ 347.1144; Found 347.1134;

2-(6-Bromo-2-oxo-2H-chromen-4-yl)-3-(4-methoxyphenyl)cyclopropane-1,1-dicarbonitrile (4l) Yield 80%; Brown solid; M.p. 280-282 °C; IR (ATR, cm^{-1}): 1730 (C=O), 2210 (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (dd, 1H, J = 10 Hz, J = 2.5 Hz), 3.86 (d, 1H, J = 10.5 Hz,), 4.00 (s, 3H), 6.70 (s, 1H), 6.86-6.88 (m, 1H), 7.04 (d, 2H, J = 3.5 Hz), 7.28 (t, J = 6.0 Hz, 1H), 7.50-7.52 (m, 2H), 7.75 (t, 2H, J = 3.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.9, 16.3,

Table 2. Synthesis of (**4a-n**).



1 (a- i) **2(a-l)** **3(a-b)** **4(a-n)**

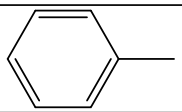
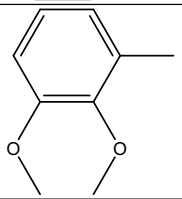
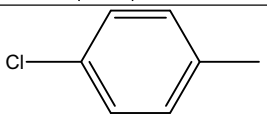
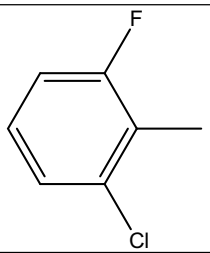
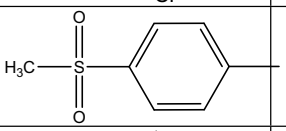
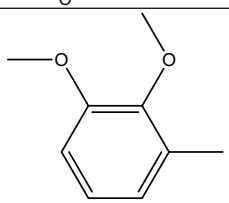
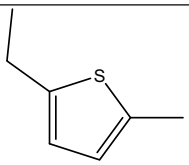
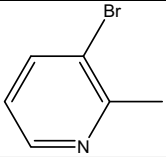
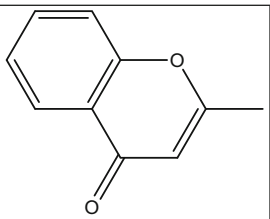
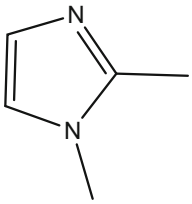
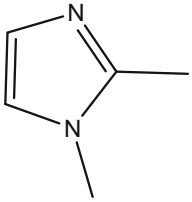
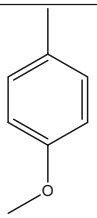
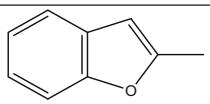
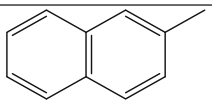
Entry	R_1	R_2	R_3	Product	Time (hrs)	Yield (%)
1	6-Methyl		CN	**4a**	2	85
2	6,8-di-Methyl		CN	**4b**	3	85
3	6-*tert*-Butyl		CN	**4c**	2.3	80
4	6-Methoxy		CN	**4d**	5	75
5	6,7-di-Methyl		CN	**4e**	3.5	80
6	7-Benzyl		CN	**4f**	5	82
7	6,8-di-Methyl		CN	**4g**	3.5	75
8	6,8-di-Methyl		CN	**4h**	3.5	80

Table 2. continued

9	6-Methoxy		CN	**4i**	3	65
10	6-Ethyl		CN	**4j**	3.5	70
11	6-Methoxy		CN	**4k**	4	75
12	6-Bromo		CN	**4l**	4	80
13	6-Chloro		CN	**4m**	3.5	72
14	6-Methyl		$COOC_2H_5$	**4n**	5	74

21.0, 52.0, 113.9, 114.5, 117.9, 121.9, 122.7, 125.9, 129.7, 130.3, 131.8, 136.2, 138.0, 138.4, 145.4, 149.0, 151.7, 158.5, 161.0 ppm; HRMS m/z: $[M+H]^+$ Cald For $C_{21}H_{14}BrN_2O_3$ 421.0188; Found 421.0186; Anal. Calcd for $C_{21}H_{13}BrN_2O_3$: C, 59.88; H, 3.11; N, 6.65 Found: C, 59.85; H, 3.09; N, 6.69

2-(Benzofuran-2-yl)-3-(6-chloro-2-oxo-2*H*-chromen-4-yl)cyclopropane-1,1-dicarbonitrile (4m) Yield 72%; White solid; M.p. 212-214 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63 (d, 1H, J = 8.5 Hz), 4.75 (dd, 1H, J = 8.5 Hz, J = 2.0 Hz), 6.43 (s, 1H), 7.10-7.22 (m, 3H), 7.35-7.41 (m, 4H), 7.73 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.7, 16.3, 25.2, 111.7, 114.7, 115.7, 118.3, 120.9, 123.0, 123.8, 124.3, 127.1, 128.9, 130.5, 133.9, 142.9, 152.0, 154.2, 158.4, 163.8 ppm; LCMS m/z: $[M+H]^+$ Cald For $C_{22}H_{12}ClN_2O_3$ 387.1; Found 387.1; Anal. Calcd for $C_{22}H_{11}ClN_2O_3$: C, 68.32; H, 2.87; N, 7.24 Found: C, 68.29; H, 2.89; N, 2.84

Ethyl-1-cyano-2-(6-methyl-2-oxo-2*H*-chromen-4-yl)-3-(naphthalene-2-yl)cyclopropanecarboxylate (4n): Yield 74%; Brown solid; M.p. 260-262 °C; IR

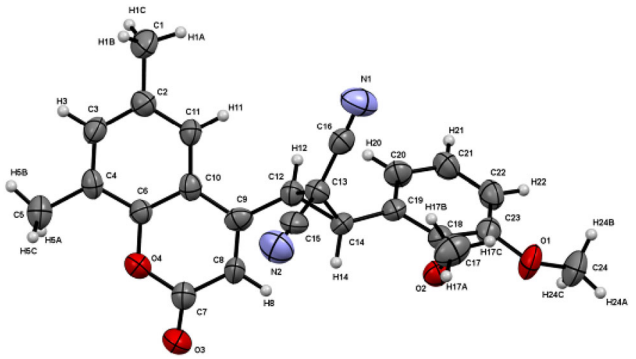


Figure 2. ORTEP diagram of the molecule **4b** at 50% probability.

(ATR, cm^{-1}): 1730 (C=O), 2235 (CN); ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, 3H, J = 6.8 Hz), 2.46 (s, 3H), 3.71 (dd, 1H, J = 8.4 Hz, J = 1.2 Hz), 3.95 (d, 1H, J = 8.8 Hz), 4.03-4.09 (m, 2H), 6.53 (d, 1H, J = 1.6 Hz), 7.26-7.93 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 21.1, 29.2, 36.1, 63.4, 115.6, 117.4, 123.8, 125.6, 127.0, 127.7, 127.9, 128.0, 129.3, 133.4, 133.5, 134.6, 146.8, 151.7, 155.0, 160.0, 163.4 ppm; Anal. Calcd for $C_{29}H_{22}N_2O_4$: C, 76.58; H, 5.00; N, 3.31 Found: C, 76.52; H, 4.90; N, 3.29

3. Results and Discussion

4-Bromomethylcoumarins were prepared as per literature reports.[37] We initiated this study by investigating the cyclization reaction of 4-bromomethyl-6-methylcoumarin (**1a**), malanonitrile (**2a**) and benzaldehyde (**3a**). When the model reaction was not treated with a catalyst in ethanol at room temperature for 24 h, (**4a**) was not detected (entry 1, Table 1). When the reaction was performed with DIPEA and NH_4SCN at room temperature for 24 h, the desired product (**4a**) was obtained only in trace yield (entry 3, Table 1). When the reaction was performed with DIPEA and KSCN at room temperature for 24 h, the desired product (**4a**) was obtained only in 10% yield (entry 2, Table 1). The reaction was performed in the presence of various bases such as DBU, pyridine, $NaOC_2H_5$, NaOH, TEA and K_2CO_3 to test their catalytic activities (entry 4-9, Table 1). Among these bases, K_2CO_3 was found to be the most effective catalyst and yielded the target compound (**4a**) in 50% yield (entry 9, Table 1).

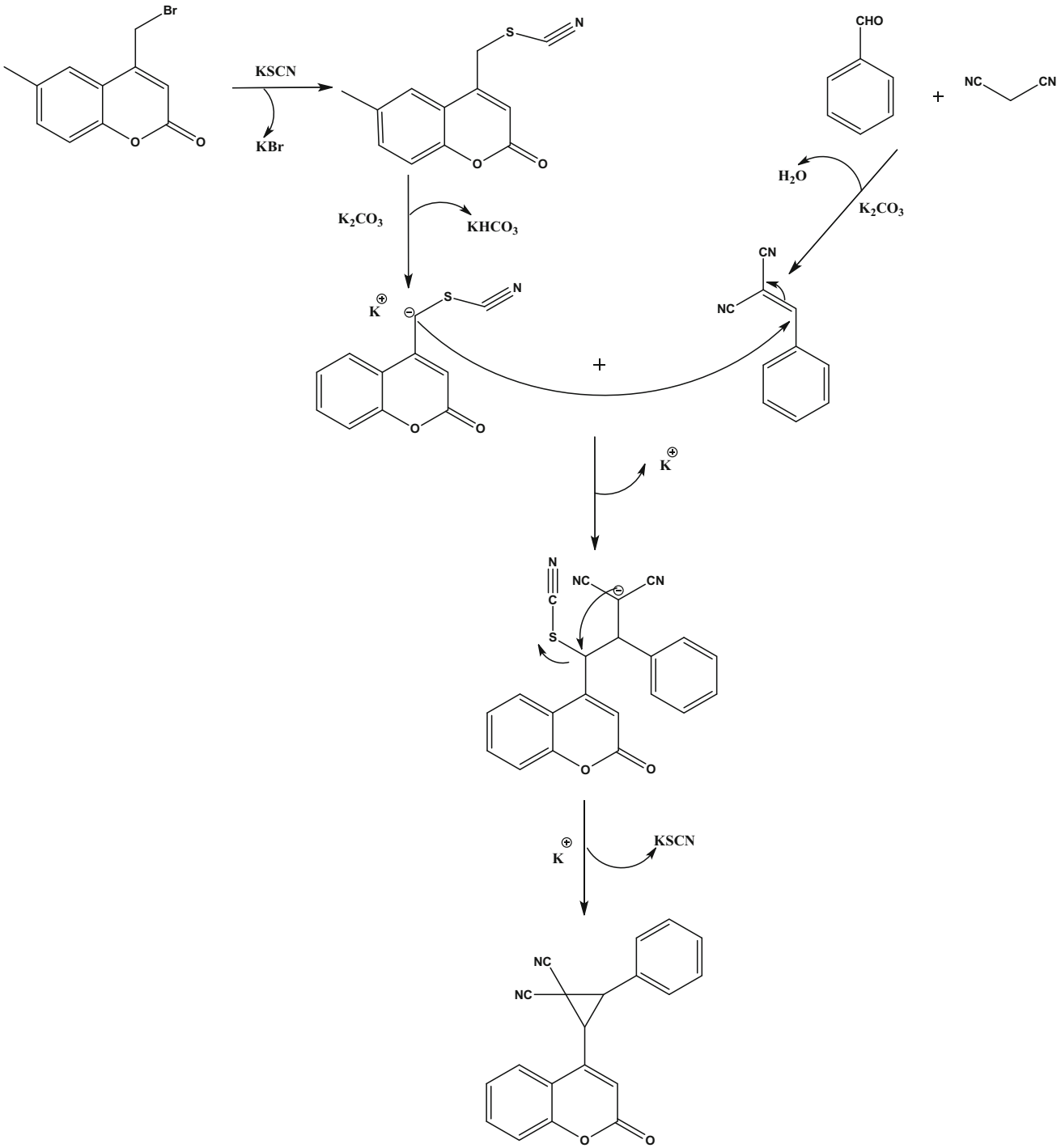
Next, we screened the reaction conditions with a range of solvents. Among all, acetonitrile and water (1:1) revealed to be a better solvent and afforded the desired product in high yield (entry 14, Table 1). Further attempt to increase or decrease K_2CO_3 loading (1.5 equiv) caused the lower yield of the product (**4a**) (entries 15-16, Table 1). The effect of temperature is also investigated. Rising temperature to 50 °C, 60 °C and 80 °C didn't improve the yield, but on the contrary, a lower yield was obtained (entries 19-21, Table 1). Therefore, RT (approximately 25 °C) was chosen as a proper temperature for the model reaction. Thus, the use of K_2CO_3 (1.5 equiv) and KSCN (1.0 equiv) in (1:1) acetonitrile and water at room temperature for 24 h are the optimized reaction condition for the cyclization (Table 2).

With the optimal conditions in hand, we examined the scope of 4-bromomethylcoumarins, aldehydes and active methylene groups. 4-Bromomethylcoumarins containing all kinds of substituent including electron-donating (6-methyl, 6-*tert*-butyl, 6-methoxy, 7-benzyl, 6-ethyl) and electron-withdrawing groups (6-bromo and 6-chloro) work well to furnish products in excellent yields. Disubstituted 4-bromomethylcoumarins (6,7-dimethyl and 6,8-dimethyl) at diverse positions also furnish the products in excellent yields. We next turned our attention to explore the scope of aldehydes. As expected, aromatic aldehydes and heterocyclic aldehydes with electron-donating groups on the aromatic and heterocyclic ring showed more reactivity than electron-withdrawing groups. We then proceeded to investigate the scope of active methylene groups. Malononitrile and ethyl cyanoacetate underwent the reaction smoothly to give the products excellent yields. The structure of (**4b**) was unambiguously confirmed by single-crystal X-ray structure (Figure 2) determination.[38]

A plausible explanation for the formation of cyclopropanyl coumarin derivatives is illustrated (Scheme 1). The first step proceeds with *in situ* generations of two intermediates by nucleophilic substitution of 4-bromomethylcoumarin by potassium thiocyanate to afford 4-thiocyanoto-methylcoumarin and arylidenemalononitrile by condensation of substituted aldehydes with nitrile. In the second step, an anion formed at the alpha position of the coumarin of the thiocyanato-4-methycoumarin is performing a 1,4-addition to yield an anionic Michael adduct that can subsequently be cyclized by displacing the thiocyanate group to form the targeted cyclopropane.[39]

4. Conclusions

In short, we have developed an efficient protocol for the preparation of cyclopropanes through a multicomponent reaction from 4-bromomethyl coumarins, benzaldehydes and active methylene groups. This versatile protocol features an excellent yield and a



Scheme 1. Plausible mechanism for the synthesis of cyclopropanylcoumarin.

broad substrate scope with inexpensive and nontoxic KSCN and K_2CO_3 as a catalyst with easy workup procedures.

Supplementary Information (SI)

Experimental detail, spectral detail, ^{1}H NMR, ^{13}C NMR, LCMS and HRMS spectra are available at www.ias.ac.in/chemsci.

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Compliance with ethical standards

Conflict of interest The authors confirm that this article content has no conflict of interest

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