

THREE-COMPONENT SYNTHESIS OF MONO AND BIS 4,5-DIHYDROPYRANO[3,2- C]CHROMENES AND 4,5-DIHYDROPYRANO[4,3- B]PYRANS CATALYZED BY SODIUM BENZENESULFINATES AS A GREEN ORGANOCATALYST

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Abstract: Mono and bis 4,5-dihydropyrano[3,2-*c*]chromene and 4,5-dihydropyrano[4,3-*b*]pyran derivatives were synthesized by three-component reaction of aromatic aldehydes, malononitrile and 4-hydroxycoumarin or 4-hydroxy-6-methylpyrone, in the presence of catalytic amounts of sodium benzenesulfinates, as a organocatalyst, in H₂O/EtOH, at reflux. High conversions, short reaction times, cleaner reaction profiles and usage of a stable and also inexpensive catalyst are some of the advantages of this method.

Keywords: Sodium benzenesulfinates; Mono and bis 4,5-dihydropyrano[3,2-*c*]chromenes; Mono and bis 4,5-dihydropyrano[4,3-*b*]pyrans; Three-component reactions.

Introduction

Multi-component reactions (MCRs) have emerged as an attractive and powerful strategy for organic synthesis.^{1,2} MCRs are highly flexible,

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supplying the opportunity of building up complex molecules with exceptional synthetic efficiency, frequently with high stereo selectivity, from simple and easily available substrates.³⁻⁸ Hence, MCRs are considered a clean and practical protocol for the synthesis of polyfunctionalized heterocyclic compounds (PFHC).⁹

It is not surprising that the synthesis of these compounds has received considerable attention, because PFHC play important roles in the synthesis of a large number of biologically active molecules.^{10,11} In the recent years, a great deal of research into PFHC has permitted the synthesis of bis-heterocyclic compounds that show various biological activities, such as antibacterial, fungicidal, tuberculostatic, and antiamebic properties.¹²⁻¹⁴

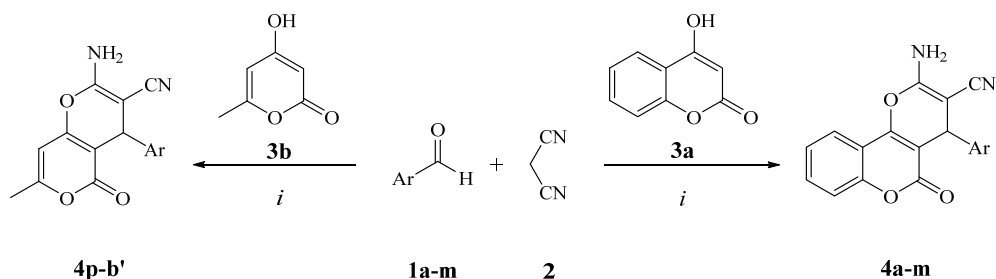
Among these aforementioned compounds, 4,5-dihydropyrano[3,2-*c*]chromene and 4,5-dihydropyrano[4,3-*b*]pyran derivatives have received much attention, due to their remarkable molecular structures and important biological¹⁵ and pharmacological¹⁶ applications. Therefore, considerable attention has been focused on the development of environmentally friendly procedures to synthesize dihydropyranochromene and dihydropyrano[4,3-*b*]pyran derivatives, by three-component reaction of aromatic aldehydes, malononitrile and 4-hydroxycoumarin or 4-hydroxy-6-methylpyrone. Various catalytic systems such as potassium phthalimide-*N*-oxyl (POPINO),¹⁷ high surface area MgO,¹⁸ 3-hydroxypropanaminium acetate (HPAA),¹⁹ trisodium citrate,²⁰ hexamethylenetetramine (HMT),²¹ ammonium acetate,²² 1,4-diazabicyclo[2.2.2]octane (DABCO)²³ and KF/Al₂O₃²⁴ have been reported for synthesis these compounds. We previously reported synthesis these compounds in the presence of crown ether complex cation ionic liquids (CECILs) as catalyst.²⁵ Each of these methods has its own advantages, but there are also major drawbacks, as the use of toxic organic solvents, expensive catalysts, difficult work up, high reaction time, and low yields. The finding a simple and green synthesis of

dihydropyranochromene and dihydropyranopyran derivatives is therefore very necessary.

Sodium benzenesulfonates (SBSs) have been used in many organic reactions as traceless linker,²⁶ as nucleophile²⁷ and as catalyst.²⁸ According to our knowledge, SBSs have never used as catalyst in the synthesis of dihydropyranochromene and dihydropyranopyran derivatives. In this work, we expose a method to synthesize these compounds in H₂O/EtOH by using inexpensive and commercially available SBSs as catalyst, working under reflux.

Results and Discussion

SBSs was used as a green and effective organocatalyst in the synthesis of 4,5-dihydropyrano[3,2-*c*]chromene (**4a-m**) and 4,5-dihydropyrano[4,3-*b*]pyran derivatives (**4p-b'**) by using three-component reaction of aromatic aldehydes (**1a-m**), malononitrile (**2**) and 4-hydroxycoumarin (**3a**) or 4-hydroxy-6-methylpyrone (**3b**), in H₂O/EtOH and at reflux (Scheme 1).



i: H₂O/EtOH (7mL/3mL), 4-Chloro SBS (10 mol%), reflux

Scheme 1. Three-component reaction of aromatic aldehydes (**1a-m**), malononitrile (**2**) and 4-hydroxycoumarin (**3a**) or 4-hydroxy-6-methylpyrone (**3b**).

The optimization of the reaction conditions was made by using a model, the reaction between benzaldehyde (**1a**), malononitrile (**2**) and 4-hydroxycoumarin (**3a**) (Table 1). When the three-component reaction was

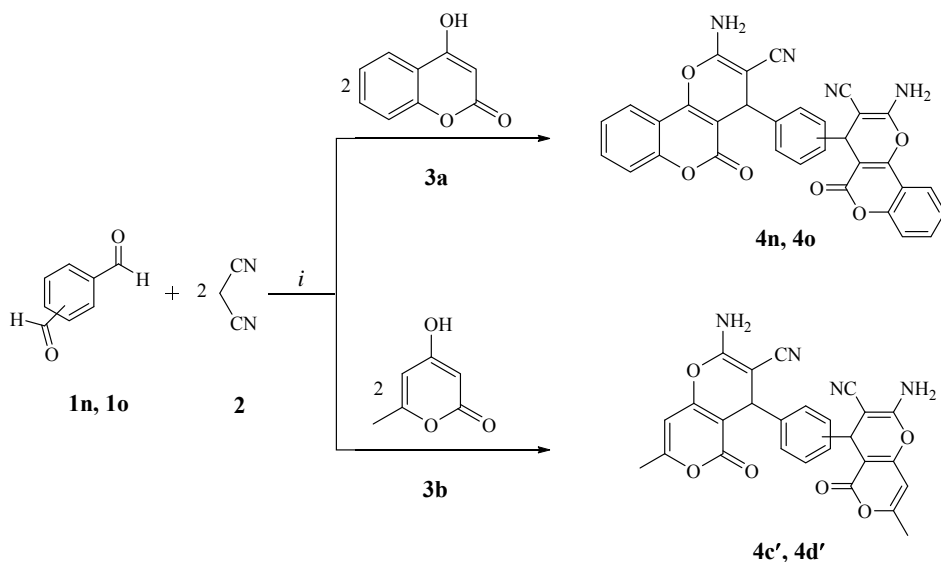
carried out in the presence of 4-chloro SBS (10 mol%), in H₂O/EtOH, at reflux, the yield towards 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile **4a** was obtained in 91% yield after 12 minutes reaction time. Different solvents were also tested, such as H₂O, EtOH, AcOEt, MeCN and toluene; the best results in terms of reaction time and yield of the desired product **4a** was obtained in H₂O/EtOH (Table 1, entries 1-6). SBS and 4-methyl SBS were also tested as catalyst (Table 1, entries 7-8). Decreasing the catalyst loading from 10 to 4 mol% significantly lowered the yield of the reaction (Table 1, entries 9-11).

Table 1. Optimization of the model reaction between benzaldehyde (**1a**), malononitrile (**2**) and 4-hydroxycoumarin (**3a**).

Entry	Solvent	Catalyst	Catalyst (mol %)	Time (min)	Yield (%)
1	H ₂ O/EtOH (7mL/3mL)	4-chloro SBS	10	12	91
2	Water (10 mL)	4-chloro SBS	10	18	85
3	Ethanol (10 mL)	4-chloro SBS	10	15	89
4	Ethyl acetate (10 mL)	4-chloro SBS	10	40	80
5	Acetonitrile (10mL)	4-chloro SBS	10	38	81
6	Toluene (10 mL)	4-chloro SBS	10	80	60
7	H ₂ O/EtOH (7mL/3mL)	SBS	10	23	89
8	H ₂ O/EtOH (7mL/3mL)	4-methyl SBS	10	30	85
9	H ₂ O/EtOH (7mL/3mL)	4-chloro SBS	8	20	85
10	H ₂ O/EtOH (7mL/3mL)	4-chloro SBS	6	26	81
11	H ₂ O/EtOH (7mL/3mL)	4-chloro SBS	4	35	78

According to the obtained data, we decided to apply this method for the synthesis of 4,5-dihydropyrano[3,2-*c*]chromene (**4a-m**) and 4,5-dihydropyrano[4,3-*b*]pyran derivatives (**4p-b'**) by three component reaction of aromatic aldehydes (**1a-m**), malononitrile (**2**) and 4-hydroxycoumarin (**3a**) or 4-hydroxy-6-methylpyrone (**3b**), in H₂O/EtOH, at reflux, in the presence of 4-chloro SBS (Table 2).

The versatility of the reaction was explored further by extending the procedure to the synthesis of bis-4,5-dihydropyrano[3,2-*c*]chromene (**4n**, **4o**) and bis-4,5-dihydropyrano[4,3-*b*]pyran derivatives (**4c'**, **4d'**). When para and meta phthalaldehyde (**1n**, **1o**) was treated with two equiv. malononitrile and 4-hydroxycoumarin (**3a**) or 4-hydroxy-6-methylpyrone (**3b**) under similar conditions, the reaction proceeded quickly to give the corresponding bis-4,5-dihydropyrano[3,2-*c*]chromenes (**4n**, **4o**) and bis-4,5-dihydropyrano[4,3-*b*]pyrans (**4c'**, **4d'**) in high yield (Table 2 and Scheme 2).

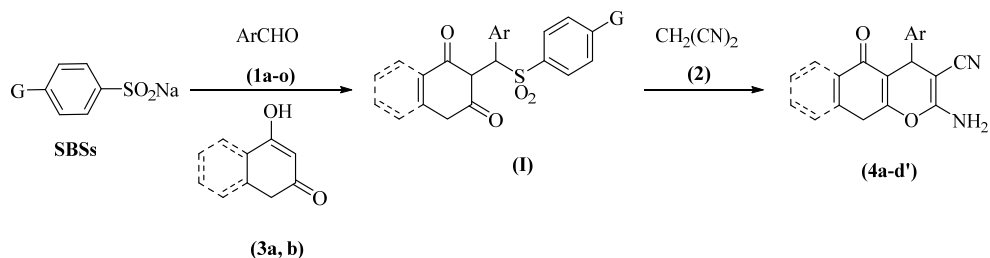


Scheme 2. Synthesis of bis-4,5-dihydropyrano[3,2-*c*]chromene (**4n**, **4o**) and bis-4,5-dihydropyrano[4,3-*b*]pyran derivatives (**4c'**, **4d'**).

According to some authors^{26,28} condensation of sodiumbenzenesulfonates, aromatic aldehydes (**1a-o**) and 4-hydroxycoumarin (**3a**) or 4-hydroxy-6-methylpyrone (**3b**), provided compound **I**. Subsequent coupling of **I** with malononitrile (**2**) gave the expected products **4a-4d'** (mono and bis 4,5-dihydropyrano[3,2-*c*]chromene and 4,5-dihydropyrano[4,3-*b*]pyran derivatives) (Scheme 3).

Table 2. Three-component reaction of aromatic aldehydes (**1a-o**), malononitrile (**2**) and 4-hydroxycoumarin (**3a**) or 4-hydroxy-6-methylpyrone (**3b**).

M. P. reported (°C)	M. P. observed (°C)	Yield (%)	Time (min)	Ar	Activated C-H acid	Compd. No.
4a	3a	C ₆ H ₅	12	91	259-261	261-263 [17]
4b	3a	4-Cl-C ₆ H ₄	10	92	265-268	265-267 [17]
4c	3a	2,4-(Cl) ₂ -C ₆ H ₃	8	93	253-255	256-258 [23]
4d	3a	4-Br-C ₆ H ₄	10	91	246-248	247-250 [23]
4e	3a	2-Br-C ₆ H ₄	11	91	293-296	295-297 [21]
4f	3a	4-NO ₂ -C ₆ H ₄	8	92	250-251	250-252 [17]
4g	3a	3-NO ₂ -C ₆ H ₄	11	91	264-266	263-265 [17]
4h	3a	4-CH ₃ -C ₆ H ₄	15	90	258-260	257-259 [17]
4i	3a	4-CH ₃ O-C ₆ H ₄	17	89	232-234	235-237 [17]
4j	3a	Furan-2-yl	17	89	250-253	253-255 [17]
4k	3a	Thiophen-2-yl	18	88	227-229	226-230 [23]
4l	3a	Pyridin-2-yl	13	90	257-259	—
4m	3a	Pyrrole-2-yl	15	90	278-280	—
4n	3a	p-Phthalaldehyde	20	91	>300	—
4o	3a	m-Phthalaldehyde	22	90	278-281	281-283 [21]
4p	3b	C ₆ H ₅	13	90	233-235	234-236 [22]
4q	3b	4-Cl-C ₆ H ₄	10	91	230-231	231-232 [24]
4r	3b	2,4-(Cl) ₂ -C ₆ H ₃	8	92	233-234	234-235 [24]
4s	3b	4-Br-C ₆ H ₄	10	90	220-222	223-225 [24]
4t	3b	2-Br-C ₆ H ₄	10	91	271-273	271-273 [25]
4u	3b	4-NO ₂ -C ₆ H ₄	8	92	215-217	215-218 [22]
4v	3b	3-NO ₂ -C ₆ H ₄	10	91	229-232	232-233 [24]
4w	3b	4-CH ₃ -C ₆ H ₄	17	90	222-223	224-225 [22]
4x	3b	4-CH ₃ O-C ₆ H ₄	20	89	202-204	202-205 [22]
4y	3b	Furan-2-yl	17	89	220-222	223-224 [22]
4z	3b	Thiophen-2-yl	18	89	240-243	242-244 [22]
4a'	3b	Pyridin-2-yl	13	90	222-224	—
4b'	3b	Pyrrole-2-yl	15	90	221-224	—
4c'	3b	p-Phthalaldehyde	23	90	>300	—
4d'	3b	m-Phthalaldehyde	25	89	>300	—



Scheme 3. Proposed synthesis mechanism of mono and bis 4,5-dihydropyrano[3,2-*c*]chromene and 4,5-dihydropyrano[4,3-*b*]pyran derivatives

Experimental

General

All chemicals and reagents used were of analytical grade or were chemically pure, and were supplied by Merck and Sigma Aldrich Co. (Germany). Melting points were measured on an Electrothermal-9100 apparatus and are uncorrected. IR spectra were recorded on a Bruker FT-IR Tensor 27 infrared spectrophotometer. ¹H NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer. ¹³C NMR spectra were recorded on the same instruments at 100 MHz using TMS as an internal standard. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical procedure for the preparation of mono and bis 4,5-dihydropyrano[3,2-*c*]chromene (4a-o) and mono and bis 4,5-dihydropyrano[4,3-*b*]pyran derivatives (4p-d')

A mixture of aromatic aldehydes (**1a-m**) (2 mmol) or para and meta phthalaldehyde (**1n**, **1o**) (1 mmol), malononitrile (**2**) (2 mmol) and 4-hydroxycoumarin (**3a**) or 4-hydroxy-6-methylpyrone (**3b**) (2 mmol), and sodium 4-chloro benzenesulfinate (10 mol%) in H₂O/EtOH (7mL/3mL) was refluxed for in the reported time in Table 2 (the progress of the reaction being monitored by TLC and hexane/ethyl acetate was used as an eluent).

After completion of the reaction, the reaction mixture was poured into ice-cold water; the crude product was filtered, dried and recrystallized from ethanol.

2-Amino-5-oxo-4-(pyridin-2-yl)-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile (4l):

White powder; IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3376, 3280 (NH₂), 2192 (CN), 1670 (C=O), 1603, 1571 (C=C); ¹H NMR (400 MHz, DMSO-d₆) δ_{H} : 8.52-7.31 (m, 10H, CH-Ar, NH₂), 4.43 (s, 1H, CH); ¹³C NMR (100 MHz, DMSO-d₆) δ_{C} : 161.2 (C=O), 159.7, 155.3, 152.8, 150.5, 149.7, 140.2, 137.2, 133.5, 126.6, 125.4, 123.1, 120.5, 118.4, 114.2 (CN), 104.5, 57.6, 37.3; Anal. calcd. for C₁₈H₁₁N₃O₃: C, 68.14; H, 3.49; N, 13.24%. Found: C, 67.93; H, 3.30; N, 13.05%.

2-Amino-5-oxo-4-(1H-pyrrol-2-yl)-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile (4m):

Yellow powder; IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3457, 3387, 3312 (NH, NH₂), 2192 (CN), 1677 (C=O), 1600, 1577 (C=C); ¹H NMR (400 MHz, DMSO-d₆) δ_{H} : 11.22 (s, 1H, NH), 7.86-7.42 (m, 7H, CH-Ar), 6.87 (s, 2H, NH₂), 5.23 (s, 1H, CH); ¹³C NMR (100 MHz, DMSO-d₆) δ_{C} : 162.2 (C=O), 160.1, 154.2, 153.2, 150.1, 137.3, 135.0, 133.6, 132.1, 130.6, 127.3, 125.2, 124.0, 113.3 (CN), 104.2, 58.7, 33.1; Anal. calcd. for C₁₇H₁₁N₃O₃: C, 66.88; H, 3.63; N, 13.76%. Found: C, 66.67; H, 3.45; N, 13.57%.

4,4'-(1,4-Phenylene)bis(2-amino-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile) (4n):

White powder; IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3472, 3327 (NH₂), 2192 (CN), 1677 (C=O), 1606, 1574 (C=C); ¹H NMR (400 MHz, DMSO-d₆) δ_{H} : 7.83-7.48 (m, 12H, CH-Ar), 7.41 (s, 4H, NH₂), 4.45 (s, 2H, CH); ¹³C NMR (100 MHz, DMSO-d₆) δ_{C} : 162.0 (C=O), 159.3, 158.9, 151.6, 138.5, 135.0, 132.2, 129.1, 126.0, 122.7, 120.1, 114.0 (CN), 101.6, 57.5, 32.5; Anal. calcd. for

$C_{32}H_{18}N_4O_6$: C, 69.31; H, 3.27; N, 10.10%. Found: C, 69.10; H, 3.09; N, 9.93%.

2-Amino-7-methyl-5-oxo-4-(pyridin-2-yl)-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (4a'):

Yellow powder; IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3408, 3394 (NH₂), 2192 (CN), 1670 (C=O), 1587, 1523 (C=C); ¹H NMR (400 MHz, DMSO-d₆) δ_{ppm} : 8.26 (s, 2H, NH₂), 7.54-7.22 (m, 4H, CH-Ar), 6.12 (s, 1H, CH), 4.37 (s, 1H, CH), 2.38 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ_{ppm} : 162.4 (C=O), 160.1, 158.8, 151.5, 150.1, 140.2, 136.5, 126.0, 121.0, 114.1 (CN), 101.2, 99.5, 57.8, 35.6, 20.8 (CH₃); Anal. calcd. for C₁₅H₁₁N₃O₃: C, 64.05; H, 3.94; N, 14.94%. Found: C, 63.87; H, 3.77; N, 14.76%.

2-Amino-7-methyl-5-oxo-4-(1H-pyrrol-2-yl)-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (4b'):

White powder; IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3407, 3392, 3292 (NH, NH₂), 2192 (CN), 1670 (C=O), 1600, 1568 (C=C); ¹H NMR (400 MHz, DMSO-d₆) δ_{H} : 11.63 (s, 1H, NH), 7.45 (d, ³J_{HH}=4 Hz, CH-Ar), 7.22 (s, 2H, NH₂), 6.88-6.56 (m, 2H, CH-Ar), 6.09 (s, 1H, CH), 4.44 (s, 1H, CH), 2.21 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ_{C} : 163.0 (C=O), 160.3, 153.3, 150.2, 137.0, 134.6, 133.2, 131.5, 126.2, 114.0 (CN), 105.2, 58.5, 34.2, 20.8 (CH₃); Anal. calcd. for C₁₄H₁₁N₃O₃: C, 62.45; H, 4.12; N, 15.61%. Found: C, 62.26; H, 3.95; N, 15.44%.

4,4'-(1,4-Phenylene)bis(2-amino-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile) (4c'):

White powder; IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3407, 3358 (NH₂), 2192 (CN), 1670 (C=O), 1593, 1523 (C=C); ¹H NMR (400 MHz, DMSO-d₆) δ_{ppm} : 8.49-7.09 (m, 8H, CH-Ar, NH₂), 6.27 (s, 2H, CH), 4.40 (s, 2H, CH), 2.19 (s, 6H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ_{ppm} : 162.9 (C=O), 160.6, 159.8, 150.5, 140.4, 132.4, 120.1, 114.8 (CN), 99.5, 58.0, 37.4, 20.9 (CH₃); Anal.

calcd. for $C_{26}H_{18}N_4O_6$: C, 64.73; H, 3.76; N, 11.61%. Found: C, 64.54; H, 3.58; N, 11.44%.

4,4'-(1,3-Phenylene)bis(2-amino-7-methyl-5-oxo-4H,5H-pyran[4,3-b]pyran-3-carbonitrile) (4d'):

White powder; IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3360, 3312 (NH_2), 2192 (CN), 1664 (C=O), 1580, 1542 (C=C); ^1H NMR (400 MHz, DMSO- d_6) δ_{ppm} : 8.49-7.09 (m, 8H, CH-Ar, 2 NH_2), 6.29 (s, H, CH), 6.25 (s, H, CH), 4.40 (s, H, CH), 4.22 (s, H, CH), 2.20 (s, 3H, CH_3), 2.02 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{ppm} : 163.0 (C=O), 162.8 (C=O), 160.9, 160.5, 159.2, 158.3, 151.2, 150.8, 141.0, 140.6, 132.3, 130.9, 121.0, 120.7, 114.6 (CN), 113.8 (CN), 101.0, 99.5, 58.2, 57.6, 37.4, 36.9, 21.3 (CH_3), 20.9 (CH_3); Anal. calcd. for $C_{26}H_{18}N_4O_6$: C, 64.73; H, 3.76; N, 11.61%. Found: C, 64.53; H, 3.57; N, 11.42%.

Conclusions

In summary, we have reported the use of sodium benzenesulfonates as an effective organocatalyst, for obtaining mono and bis 4,5-dihydropyrano[3,2-*c*]chromene and 4,5-dihydropyrano[4,3-*b*]pyran derivatives by the three component reaction of aromatic aldehydes, malononitrile and 4-hydroxycoumarin or 4-hydroxy-6-methylpyrone. These reactions were carried out in $\text{H}_2\text{O}/\text{EtOH}$ at reflux. High yields, operational simplicity, and clean reaction conditions are advantages of this procedure that make it a useful practical process for the synthesis of these compounds.

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