Proline-Promoted Efficient Synthesis of 4-Aryl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromene-2,5-diones in Aqueous Media

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Received 29 December 2007

Abstract: The reaction of 4-hydroxycoumarin with Meldrum's acid and benzaldehydes in aqueous media in the presence of proline (10 mol%) led to 4-aryl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromene-2,5-diones in good yields.

Key words: chromene, proline, aqueous media, Meldrum's acid, 4-hydroxycoumarin, benzaldehydes

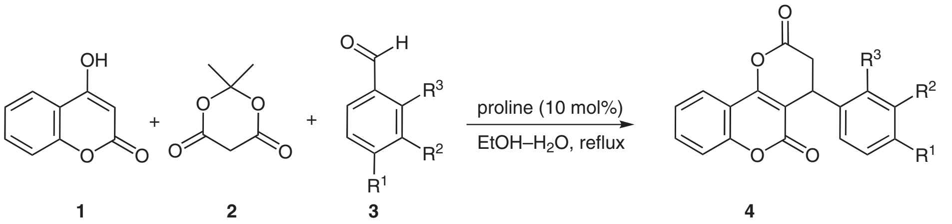
Chromenes constitute a major class of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents.[1,2] The key bicyclic ring system of chromenes has inspired a number of different synthetic approaches.[3,4] Substituted 4*H*-chromenes are a new class of anticancer compounds.[5] Many studies have been reported on the synthesis of the chromene ring system.[6,7]

As part of our current studies[8–12] on the development of new routes to heterocyclic systems, we now report an efficient synthetic route to functionalized chromenes in aqueous media. Thus the reaction of 4-hydroxycoumarin (**1**) with Meldrum's acid (**2**) and benzaldehydes **3** in 50% aqueous EtOH in the presence of proline (10 mol%) led to 4-aryl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromene-2,5-diones **4** in good yields (Table 1).

Structures of compounds **4a**–**g** were assigned by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For example, the ^{1}H NMR spectrum of **4a** exhibited a characteristic ABM system for the CH_2CH moiety. The resonances of the carbonyl groups in the ^{13}C NMR spectrum of **4a** appear at $\delta = 161.2$ and 164.7 ppm. The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 292$. The ^{1}H NMR and ^{13}C NMR spectra of **4b**–**g** are similar to those of **4a** except for the benzene moieties, which show characteristic signals in the appropriate regions of the spectra.

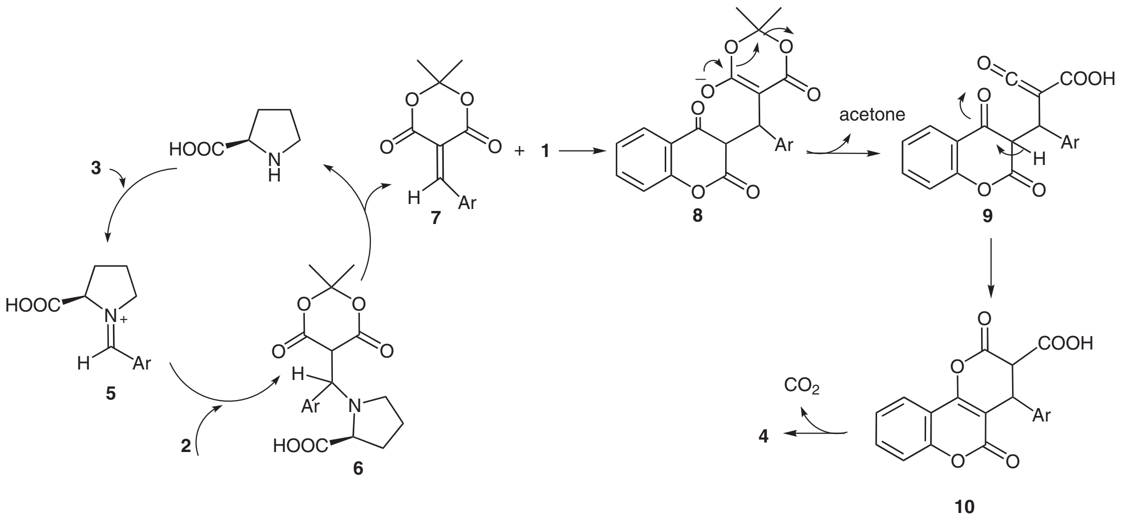
A tentative mechanism for this transformation is proposed in Scheme 1. It is conceivable that the initial event is the formation of iminium ion **5** from proline and the aldehyde **3**, which undergoes Knoevenagel condensation with Meldrum's acid to produce intermediate **7**. This intermediate is subsequently attacked by 4-hydroxycoumarin to generate **8**. Intermediate **8** first loses acetone to give ketene **9**,

Table 1 Reaction of 4-Hydroxycoumarin (**1**) with Meldrum's Acid (**2**) and Benzaldehydes **3**



3	4	R^1	R^2	R^3	Yield of **4** (%)
3a	**4a**	H	H	H	94
3b	**4b**	H	Br	H	92
3c	**4c**	Me	H	H	85
3d	**4d**	OMe	H	H	83
3e	**4e**	Cl	H	H	78
3f	**4f**	H	H	Cl	75
3g	**4g**	H	H	Me	81

SYNLETT 2008, No. 8, pp 1153–1154
Advanced online publication: 16.04.2008
DOI: 10.1055/s-2008-1072656; Art ID: D41207ST



Scheme 1

and then undergoes cyclization and decarboxylation to produce **4**.

In conclusion, we have described a convenient route to 4-aryl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromene-2,5-diones from 4-hydroxycoumarin, Meldrum's acid, and benzaldehydes in aqueous media in the presence of proline (10 mol%). The functionalized chromenes reported in this work may be considered as potentially useful synthetic intermediates because they possess atoms with different oxidation states. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The simplicity of the present procedure makes it an interesting alternative to other approaches.

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(12) **4-Phenyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromene-2,5-dione (4a)**
To a stirred solution of benzaldehyde (0.21 g, 2 mmol) and Meldrum's acid (0.29 g, 2 mmol) in 50% aq EtOH (10 mL) were added 4-hydroxycoumarin (0.32 g, 2 mmol) and proline (11.5 mg, 10 mol%). The reaction mixture was stirred at reflux for 40 min. After completion of the reaction (monitored by TLC), the precipitate was collected by filtration and washed by cold 50% aq EtOH (5 mL) to afford **4a**, yield 0.55 g (94%); white powder; mp 169–171 °C. IR (KBr): 1788 (C=O), 1707 (C=O), 1630, 1104 cm^{-1}. ^{1}H NMR (500.1 MHz, CDCl$_3$): $\delta = 3.15$ (dd, $^2J = 16.2$ Hz, $^3J = 1.7$ Hz, 1 H, CH), 3.21 (dd, $^2J = 16.2$ Hz, $^3J = 7.6$ Hz, 1 H, CH), 4.54 (dd, $^3J = 7.6$ Hz, $^3J = 1.7$ Hz, 1 H, CH), 7.26–7.29 (m, 3 H, 3 CH), 7.31 (d, $^3J = 6.8$ Hz, 1 H, CH), 7.32 (d, $^3J = 6.9$ Hz, 1 H, CH), 7.36–7.39 (m, 2 H, 2 CH), 7.62 (t, $^3J = 7.3$ Hz, 1 H, CH), 7.92 (dd, $^3J = 8.2$ Hz, $^4J = 1.6$ Hz, 1 H, CH). ^{13}C NMR (125.7 MHz, CDCl$_3$): $\delta = 36.3$ (CH$_2$), 36.4 (CH), 106.8 (C), 113.9 (C), 117.3 (CH), 123.2 (CH), 125.1 (CH), 127.1 (2 CH), 128.5 (CH), 129.7 (2 CH), 133.4 (CH), 139.8 (C), 153.6 (C), 157.7 (C), 161.2 (C=O), 164.7 (C=O). MS (EI): *m/z* (%) = 292 (8) [M$^+$], 264 (5), 249 (5), 111 (18), 95 (18), 85 (30), 71 (58), 57 (100), 43 (94). Anal. Calcd (%) for $C_{18}H_{12}O_4$ (292.29): C, 73.97; H, 4.14. Found: C, 73.70; H, 4.31. All other compounds isolated possessed spectroscopic and analytical data in agreement with their proposed structures.