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A convenient synthesis of furo[3,2-*c*]coumarins by a tandem alkylation/intramolecular aldolisation reaction

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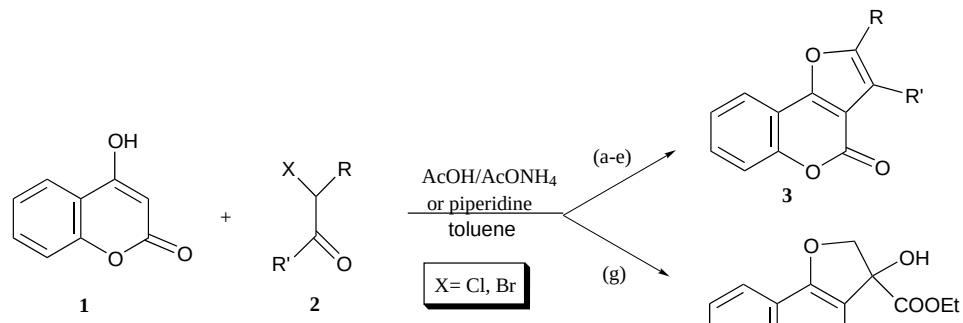
Abstract—A simple and efficient synthesis of furo[3,2-*c*]coumarin derivatives from 4-hydroxycoumarin and α-haloketones via a tandem *O*-alkylation/cyclisation protocol is described.

The 4-hydroxycoumarin fragment occurs in many synthetic and natural products, which are used clinically as drugs and pesticides[1] as well as oral anticoagulants[2] and rodenticides.[3] These important applications have generated considerable interest in this ring system and various 2,3- or 3,4-fused polycycles or open chain derivatives have been synthesised. While many efforts have been made to synthesise 3-alkyl-4-hydroxycoumarin derivatives,[4] only a few studies have focussed on the synthesis of linearly or angularly fused tricyclic complex systems. All the reported procedures referring to this particular system require vigorous reaction conditions and laborious preparation.[5]

This paper describes a simple and easy route to new angular furocoumarins **3** differentially substituted on the five-membered ring, starting from 4-hydroxycoumarin **1**. The reaction is also interesting because the framework of these systems is entirely present in the coumestans (6*H*-benzofuro[3,2-*c*]benzopyran-6-ones), a class of physiologically active natural compounds such as wedelolactone, medicagol, psoraldin, isopsoraldin, erosnin, and many others.[6]

The idea arose from the observation that the highly reactive enolic moiety of **1** can easily be utilised, together with selected building blocks, in the construction of angular or linear polyheterocycles. With this in mind, we chose the double electrophile α-haloketones **2** (Scheme 1). In fact, for the entries (**a**–**e**), treatment of **1** with the ambident reagents **2** produced the expected cycloadducts **3** in good yield (70–77%).[7] The reaction



	a	b	c	d	e	f	g
R	H	H	H	H	Me	Ph	H
R'	Me	Ph	*p*-BrC_6H_4	*p*-$OMeC_6H_4$	Ph	Ph	CO_2Et

Scheme 1.

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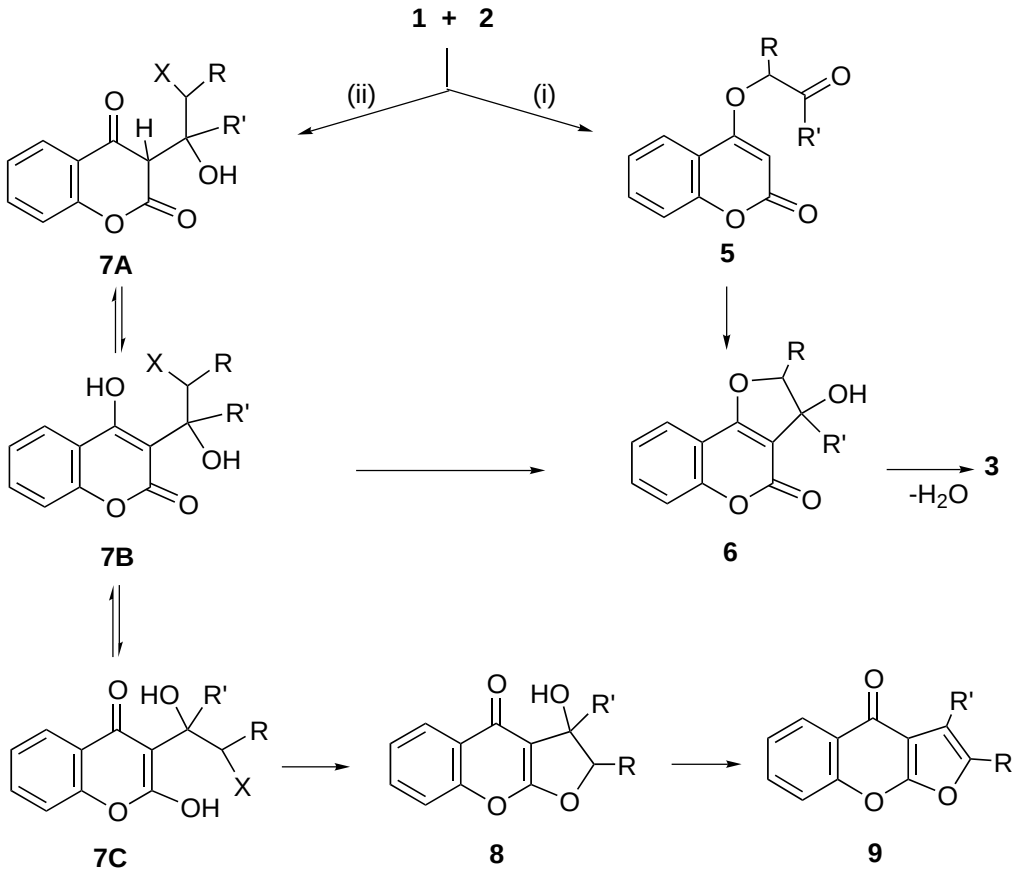
was carried out in glacial AcOH/$AcONH_4$ or piperidine in refluxing toluene/EtOH (4:1). In entry **f**, the desired cycloaddition failed: desyl chloride **2f** and **1** were recovered unreacted. This failure can be attributed to the presence of the bulky phenyl substituent in the α-position. In entry **g**, however, the reaction of **1** with **2g** under similar conditions (AcOH/$AcONH_4$, refluxing toluene/EtOH) gave the dihydrofuran derivative **4** in high yield (90%).[7] It must be noted that chemoselective cyclisation is favoured at the carbonyl-C, rather than at the ester-C, in accordance with accepted rules.[8] The stability of the α-hydroxyester **4** is remarkable and it can be recrystallised and stored without any decomposition. Moreover, it cannot be converted into the corresponding derivative **3g**. Treatment of the isolated **4** with acids or bases did not promote any dehydration and, at the end, compound **4** was unaltered.

All the compounds synthesised were characterised by their ^1H and ^{13}C NMR, and IR spectra, as well as by elemental analyses.[9] IR spectra of compounds **3a–e** and **4** contain bands at 1735–1755 cm^{-1} which are characteristic of the stretching vibrations of the coumarin carbonyl group. For compound **4** $C{=}O_{ester}$ and OH bands were also observed at 1702 cm^{-1} and at 3331 cm^{-1}, respectively. In the ^1H NMR spectrum of the dihydro derivative **4** the signal related to the OH appears at δ 6.54 and exchanges with D_2O; the methylene protons are split into an AB quartet centred at δ 4.90 due to the generation of a new chiral carbon. An X-ray crystallographic analysis carried out on **3b** also confirmed the structure of compounds **3**.[10]

Formation of **3** can proceed following two different pathways (Scheme 2). Firstly, (i), through dehydration of **6** obtained by intramolecular C–C bond formation of the initial adduct **5**. Alternatively, (ii), by the tautomeric form **7B** of the aldol product **7A**, which is subjected to a 5-*exo*-*trig* cyclisation to give **6** through intramolecular O–C bond formation and dehydration, in a manner which follows the well-known Feist–Benary synthesis[11] of 3-carbonyl substituted furans. The latter reaction pathway also implies a partial change in the direction of cyclisation. A similar process should occur, at least partially, for the tautomeric form **7C** through the lactone carbonyl oxygen to give linear policyclic fused heterocycles such as **8** or **9**.

The existence of the 4-hydroxycoumarin/2-hydroxychromone tautomerism[12] has been demonstrated, for instance, by the treatment of 4-hydroxycoumarin with diazomethane, which afforded a mixture of 4-methoxycoumarin and 2-methoxychromone.[13] Since products **8** and **9** were not observed, it can be assumed that **3** is formed through pathway (i). In confirmation of this, the X-ray of 3-phenylfuro[3,2-*c*]coumarin **3b** showed the phenyl substituent exclusively in the 3-position.[10]



Scheme 2.

On the basis of the above results, the reaction leading to **3** is unhindered when the nearby α-carbon of **2** is not particularly bulky. This can prevent the *O*-alkylation process and/or the following 5-*exo*-*trig* cyclisation. When this condition is satisfied, the resulting hydroxyl group on the tertiary carbon atom or in the benzylic position is easily expelled as water, under the conditions used, to give **3**. The unsuccessful dehydration of **4** to give **3g**, however, reflects the well-known difficulties that α-hydroxy-acids or -esters have in losing water intramolecularly.

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7. *A typical experimental procedure for the preparation of **3** and **4***. A toluene solution of the appropriate α-haloketone **2** (4 mmol) was added to a solution of 4-hydroxycoumarin **1** (0.65 g, 4 mmol) and AcOH/$AcONH_4$ (20 mmol) in toluene/EtOH abs. (50 ml; 40:10). The mixture was stirred for 1 h and the solvent evaporated under reduced pressure. The oily residue was treated with cold water (30 ml) and the precipitate was filtered off, washed with water (50 ml) and recrystallised from EtOH to give **3a–e** or **4**.
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9. Selected data: **3a**: mp 135°C; IR (Nujol): $\nu = 1747$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Mz, rt): $\delta = 2.30$ (s, 3H, CH_3), 7.24–7.82 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 Mz, rt): $\delta = 8.2$, 102.1, 112.5, 116.8, 119.6, 120.5, 124.6, 130.1, 142.5, 151.8, 156.9, 158.2. Anal. $C_{12}H_8O_3$ requires (%) C, 72.88; H, 4.03. Found (%) C, 73.08; H, 4.12. Compound **3b**: mp 177°C; IR (Nujol): $\nu = 1739$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Mz, rt): $\delta = 7.35$–7.89 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 Mz, rt): $\delta = 107.8$, 110.6, 112.1, 120.1, 124.8, 125.3, 128.0, 128.3, 128.5, 129.0, 131.3, 143.3, 151.9, 157.0, 158.1. Anal. $C_{17}H_{10}O_3$ requires (%) C, 77.85; H, 3.84. Found (%) C, 77.98; H, 3.92. Compound **3c**: mp 198°C; IR (Nujol): $\nu = 1747$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Mz, rt): $\delta = 7.33$–7.91 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 Mz, rt): 107.7, 112.0, 116.1, 120.8, 121.3, 121.5, 124.2, 124.9, 128.4, 130.5, 131.4, 143.4, 152.0, 157.2, 158.2. Anal. $C_{17}H_9BrO_3$ requires (%) C, 59.85; H, 2.66. Found (%) C, 60.08; H, 2.82. Compound **3d**: mp 166°C; IR (Nujol): $\nu = 1740$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Mz, rt): $\delta = 3.88$ (s, 3H, OCH_3), 6.98–7.87 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 Mz, rt): $\delta = 54.7$, 107.1, 112.3, 114.7, 121.3, 121.6, 124.3, 125.0, 128.4, 130.6, 131.3, 143.3, 152.0, 157.5, 158.2, 160.9. Anal. $C_{18}H_{12}O_4$ requires (%) C, 73.97; H, 4.14. Found (%) C, 74.08; H, 4.21. Compound **3e**: mp 150°C; IR (Nujol): $\nu = 1735$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Mz, rt): $\delta = 2.50$ (s, 3H, CH_3), 7.30–7.85 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 Mz, rt): $\delta = 12.8$, 107.8, 112.4, 116.5, 120.4, 124.5, 127.8, 128.4, 129.5, 130.8, 143.8, 149.4, 152.0, 153.2, 157.0, 158.1. Anal. $C_{12}H_8O_3$ requires (%) C, 78.25; H, 4.38. Found (%) C, 78.48; H, 4.50. Compound **4**: mp 134°C; IR (Nujol): $\nu = 1755$, 1702 cm^{-1}; ^{1}H NMR ($DMSO_{d6}$, 300 Mz, rt): $\delta = 1.11$ (t, 3H, CH_3, $J = 7.1$ Hz), 4.20 (q, 2H, OCH_2, $J = 7.1$ Hz), 4.90 (ABq, 2H, CH_{2ring}, $J = 10.7$ Hz), 6.54 (s, 1H, OH), 7.41–7.81 (m, 4H); ^{13}C NMR ($DMSO_{d6}$, 75 Mz, rt): $\delta = 14.8$, 61.9, 79.8, 86.1, 106.5, 111.74, 117.1, 123.4, 124.9, 134.7, 155.0, 157.6, 167.9, 170.7. Anal. $C_{14}H_{12}O_6$ requires (%) C, 60.87; H, 4.38. Found (%) C, 61.08; H, 4.52.
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