Regioselective Synthesis of Furo[3,2-*c*][1]benzopyran-4-one and Furo[3,2-*c*]quinolin-4-one

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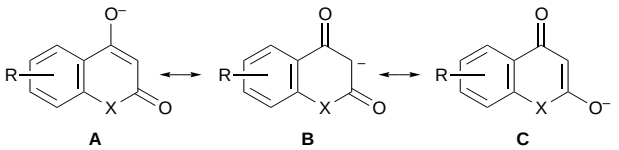
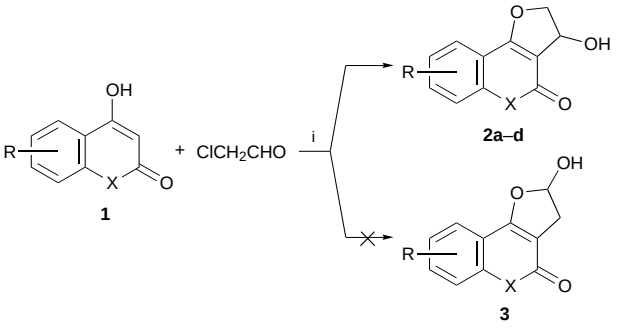
4-Hydroxycoumarins and 4-hydroxy-1-methyl-2-quinolone react with chloroacetaldehyde in the presence of aqueous potassium carbonate to give 3-hydroxy-2,3-dihydrofuro derivatives (60–75%) which on treatment with aqueous hydrochloric acid provide furo[3,2-*c*]coumarins and the hitherto unreported 5-methylfuro[3,2-*c*]quinolin-4-one in nearly quantitative yields.

Recently we have reported[1] a simple route to the regioselective synthesis of 2-alkylfuro[3,2-*c*][1]benzopyran-4-ones and 2-alkylfuro[3,2-*c*]quinolin-3-ones. This prompted us to undertake a study to synthesise furo[3,2-*c*][1]benzopyran-4-ones and furo[3,2-*c*]quinolin-4-ones devoid of any substitution on the furan ring from the reaction of 4-hydroxycoumarins and 4-hydroxyquinolones, respectively, with chloroacetaldehyde. The results are reported here.



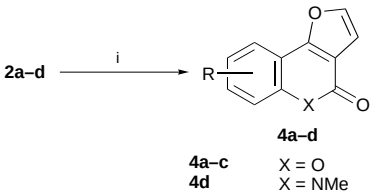
The compound **1** in the presence of a base may exist as an ambident anion (canonical forms **A**, **B** and **C**). It is widely known to undergo *O*-alkylation[1–3] under classical (acetone–K_2CO_3) conditions and partial *C*-alkylation[4] in phase-transfer-catalysed reactions with hydroxide base. Thus initially it was a reasonable expectation that we would obtain product **2** through *O*-alkylation and cyclisation and/or product **3** through *C*-alkylation and cyclisation. To this end, 4-hydroxycoumarin (**1a**) in water was treated with chloroacetaldehyde in the presence of potassium carbonate at room temperature for 1.5 h. A white solid was obtained in 73% yield which was characterised as 3-hydroxy-2,3-dihydrofuro[3,2-*c*][1]benzopyran-4-one (**2a**).



	R	X	Time (*t*/h)	Yield (%)
2a	H	O	1.5	73
2b	8-Me	O	3.5	75
2c	6-Me	O	3.0	70
2d	H	NMe	5.0	60

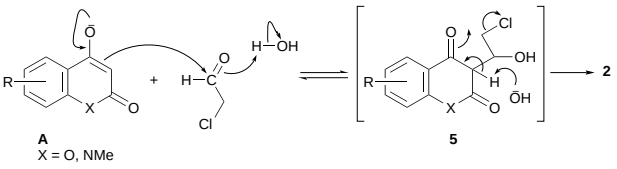
Scheme 1 *Reagents and conditions:* i, K_2CO_3–H_2O, room temperature

Other substrates **1b–d** were similarly treated to give the products **2b-d** in 60–75% yields. Products **2a–c** were then treated with hydrochloric acid (1 M) to provide the furo[3,2-*c*][1]benzopyran-4-ones **4a–c** in almost quantitative yields (Scheme 2). It was necessary to use 6 M hydrochloric acid in the case of **2d** to convert it (in 96% yield) into the product furo[3,2-*c*]quinolin-4-one **4d**.



Scheme 2 *Reagents and conditions:* i, HCl–H_2O, heat

The formation of products **2** from **1** may easily be explained by the reversible nucleophilic addition of a coumarin-4-olate anion to the carbonyl group of chloroacetaldehyde to give an intermediate **5** (not isolated) followed by base-catalysed intramolecular cyclisation leading to products **2** (Scheme 3). It may be noted that the nucleophilic addition to the carbonyl group of the chloroacetaldehyde is facilitated by the electron-withdrawing inductive effect of the chlorine, and that in water the equilibrium is strongly in favour of the hydrate. This methodology failed when reactions were attempted with substrates such as 3-hydroxycoumarin, 3-hydroxy-2-quinolone and 7-hydroxycoumarin. Perhaps the reversible nucleophilic addition step from **1** to **5** is important. In the case of 3-hydroxycoumarin and 3-hydroxy-2-quinolone, the equilibrium is perhaps not in favour of the intermediate and thus cyclisation is precluded.



Scheme 3

Furo[3,2-*c*][1]benzopyran-4-one (**4a**) has been prepared[6] earlier from the reaction of 4-hydroxycoumarin and malic acid in four steps. Furo[3,2-*c*][1]benzopyran-4-one and furo[3,2-*c*]quinoline-4-one derivatives obtained from the thermal rearrangement always carry a substituent at the furan ring (2-position). Thus the present procedure provides a simple method for the regioselective synthesis of furo[3,2-*c*][1]benzopyran-4-one and furo[3,2-*c*]quinolin-4-one devoid of any substitution on the furan ring.

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Techniques used: UV, IR, ^{1}H and ^{13}C NMR, mass spectrometry, elemental analysis, TLC, column chromatography

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