Divergent Synthesis of Linear and Angular Furocoumarin Acetic Acids from Phloroglucinol

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Abstract: Linear and angular furocoumarins can be obtained starting from phloroglucinol in a versatile, simple, direct, and efficient way, as demonstrated in the divergent syntheses described here. The key step is the alkali-mediated rearrangement of 4-halomethylcoumarins to benzofuran-3-acetic acids via α,β-unsaturated acids and the key intermediates are benzodipyrones, which, depending on their substitution, can either give or fail to give the ring-contraction reaction.

Key words: Pechmann reaction, furocoumarin acetic acids, ring-contraction reaction, divergent synthesis

Furocoumarins are an important class of natural and synthetic compounds and are widely studied for pharmacological and industrial applications.[1] In particular, these compounds are important as photochemotherapeutic agents and are used to cure a variety of skin diseases. This application is possible due to their ability to intercalate in the double-stranded DNA and to undergo photoaddition to thymine, thereby blocking cell growth and replication.[2]

During the course of our research into the synthesis and subsequent study of these heterocyclic compounds, we previously focused our attention on a convenient contraction reaction of the coumarin pyrone ring to give a benzofuran when position 4 is occupied by a chloromethyl chain. The reaction involves an alkali-mediated rearrangement of the coumarin via α,β-unsaturated acids.[3] This behavior allowed us to obtain, in a very direct and efficient way, a wide range of furocoumarin derivatives that are extremely difficult to prepare by other methods and, for this reason, have not been studied in any detail in terms of their pharmacological potential.[4] The preparation of these compounds involves the use of asymmetric dipyrones, one of the pyrone rings is 4-chloromethyl-substituted and the other cannot be transformed under the alkaline conditions used.

The 4-chloromethyl substituted pyrone nucleus linked to a benzene ring can often be obtained in one step by reaction of the phenolic precursor and ethyl 4-chloroacetoacetate under Pechmann conditions.[5] In an analogous way a large number of hydroxycoumarins, which can be prepared in a similar way or by alternative methods,[6] could be used to obtain a wide variety of asymmetric dipyrones in which the second pyrone nucleus would be 4-chloromethyl-substituted.

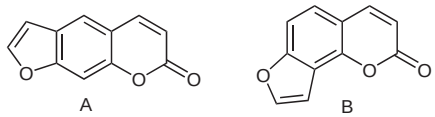

Figure 1 Linear and angular furocoumarins. A) Psoralen: furo[3,2-*g*]coumarin. B) Angelicin: furo[2,3-*h*]coumarin.

In the present work, we describe an interesting example to illustrate the application and synthetic possibilities of this contraction reaction; namely the synthesis, starting from phloroglucinol, of linear and angular (psoralens and angelicins, respectively, Figure 1) furocoumarin acetic acids (Scheme 1). The reaction between phloroglucinol (**1**) and ethyl 4-chloroacetoacetate under Pechmann conditions leads to 4-chloromethylcoumarin **4**[5] and linear and angular dipyrones (compounds **2** and **3**, respectively).[7] The angular dipyrone is obtained in much larger quantities in relation to the linear dipyrone as position 8 is the preferred position for the electrophilic substitution of coumarins under these conditions.[8] On the other hand, dichlorodipyrones are not obtained, but instead the phenolic hydroxyl displaces the chloro substituent from the closest chloromethyl group, leading to the formation of the furan ring. When compound **3** is treated under the appropriate alkaline conditions (0.1 N NaOH) to give ring contraction of the 4-chloromethyl-substituted pyrone ring, the ring contracts and the other pyrone ring in the molecule is hydrolyzed to give with 78% yield the linear benzodifuran **5**,[9] which has a substitution pattern that has not previously been reported in the literature. It would only be necessary to replace the chloro substituent in the chloromethyl group with, for example, a hydroxyl group (simply by an aqueous treatment with a yield of 72%) to make the pyrone ring, now with a hydroxymethyl substituent (compound **6**), resistant to ring contraction under the aforementioned alkaline conditions. In this way, alkaline treatment of **6** only leads to hydrolysis of the second pyrone ring and transposition of the double bond to give the furan ring of psoralen **7**[10] with 70.5% yield.

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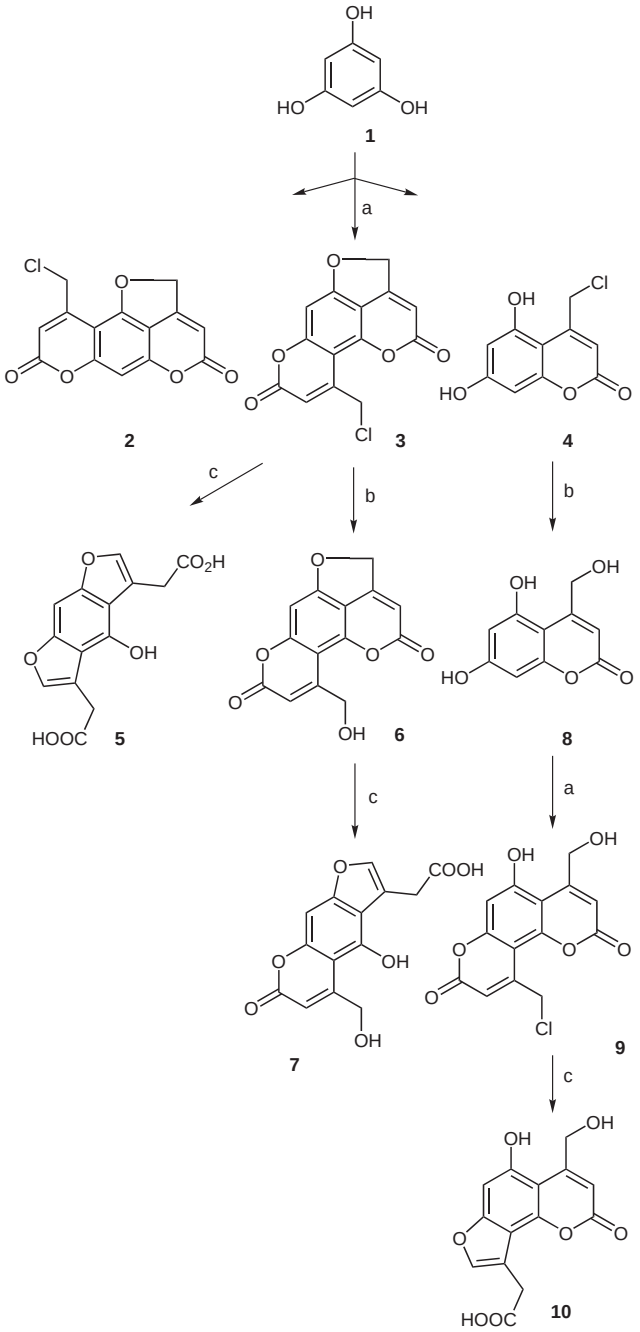
If we synthesize the second ring of the 4-chloromethyl-substituted pyrone on a previously formed coumarin that is unsubstituted or substituted with a different group in this position, then the furan contraction only occurs in one case. This approach was used in the transformation of coumarin **4**. Treatment with water replaces the chloro substituent with a hydroxy group to give the hydroxymethyl-coumarin **8**.

Treatment of this compound with ethyl chloroacetoacetate under Pechmannn conditions led with a 84.5% yield to the asymmetric dipyrone **9**. This dipyrone enabled a selective contraction to be performed in an alkaline medium on only one of the two pyrone rings to give in 78% yield, the angelicin (**10**).[11]

This means that the key step, the contraction of the 4-chloromethyl-substituted pyrane nucleus to the 4-carboxymethyl-substituted furan ring, can be carried out through a very easy, general, and efficient procedure. The application of this synthetic method will enable the preparation of a large series of these types of compounds, which were designed in order to evaluate their properties as photochemotherapeutic agents.



Scheme 1 *Reagents and conditions*: (a) ethyl 4-chloroacetate, H_2SO_4, r.t., 12 h; (b) H_2O, reflux, 48 h; (c) 0.1 N NaOH, 0 °C, 30 min.

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(7) A solution of **1** (300 mg, 2.4 mmol) in H_2SO_4 was stirred at r.t. for 20 min. Then, ethyl 4-chloroacetoacetate (1.60 mL, 1.95 g, 11.89 mmol) was added dropwise and the reaction was stirred at r.t. overnight. Ice (50 mL) was added, the solution was filtered, and the precipitate was washed with cold H_2O until the washings were pH 7. The residue was purified by silica gel column chromatography (hexane–EtOAc, 4:1 to 3:2) to afford **2** (16 mg, 2.5% yield), **3** (104 mg, 15.0% yield), and **4** (220 mg, 41.0% yield), all as pure white solids.
10-Chloromethyl-8*H*-8-oxofuro[4,3,2-*e*]pyran[3,2-*g*]coumarin(**2**): mp 243–244 °C. IR (KBr): 2960, 1684, 1639, 1590, 1390, 1208, 1109, 1074, 856 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 4.93 (s, 2 H, CH_2Cl), 5.90 (d, *J* = 2.1 Hz, 2 H, H-2), 6.20 (t, *J* = 2.1 Hz, 1 H, H-3), 6.56 (s, 1 H, H-9), 7.03 (s, 1 H, H-6). MS: *m/z* (%) = 292 (2) [M + 2]$^+$, 290 (15) [M$^+$], 178 (86), 163 (69), 135 (10).
10-Chloromethyl-8*H*-8-oxofuro[4,3,2-*d*,*e*]pyran[3,2-*h*]coumarin(**3**): mp 266–267 °C. IR (KBr): 2960, 1684,

1639, 1590, 1390, 1208, 1109, 1074, 856 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 5.11 (s, 2 H, CH_2Cl), 5.82 (d, *J* = 2.0 Hz, 2 H, H-4), 6.31 (t, *J* = 2.0 Hz, 1 H, H-3), 6.58 (s, 1 H, H-9), 7.03 (s, 1 H, H-6). MS: *m/z* (%) = 292 (0.5) $[M + 2]^+$, 290 (3) $[M^+]$, 220 (1.6), 142 (1.7), 104 (3), 79 (25), 54 (51), 46 (80), 33 (100).

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(9) **Synthesis of 3,5-Bis(carboxymethyl)-4-hydroxyfuro[3,2-*f*]benzofuran (5)**
A mixture of **3** (100 mg, 0.344 mmol) in 0.1 N NaOH (10 mL) was stirred at 0 °C for 30 min. Then, 3 N HCl was added to give pH 6.0 at the same temperature. The resulting brown precipitate was filtered off and washed with cold H_2O until the washings were pH 7. The residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 9:1 to 4:1) to give **5** (77 mg, 78.0%); mp 147 °C (dec.). IR (KBr): 3520, 2949, 2840, 1746, 1620, 1599, 1422, 1128, 1080, 830 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.74 and 3.77 (2 s, 2 + 2 H, 2 CH_2), 6.73 (s, 1 H, H-8), 7.67 and 7.69 (2 s, 1 + 1 H, H-2 and H-6), 9.99 (br s, 1 H, OH), 12.31 (br s, 2 H, 2 COOH). MS: *m/z* (%) = 290 (0.2) $[M^+]$, 261 (12), 247 (58), 231 (12), 203 (100), 201 (15), 164 (5).

(10) 6-Carboxymethyl-5-hydroxy-4-hydroxymethylfuro[3,2-*g*]coumarin (**7**): mp 290 °C (dec.). IR (KBr): 3550, 2930, 2800, 1715, 1595, 1430, 1100, 1080, 835 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 3.84 (s, 2 H, CH_2CO), 4.76 (s, 2 H, CH_2OH), 6.05 (s, 1 H, H-3), 6.88 (s, 1 H, H-9), 7.96 (s, 1 H, H-7), 9.45 (br s, 1 H, OH), 11.05 (br s, 2 H, 2 OH). MS: *m/z* (%) = 291 (9) $[M + 1]^+$, 290 (100) $[M^+]$, 272 (15), 246 (20), 205 (10).

(11) 9-Carboxymethyl-5-hydroxy-4-hydroxymethylfuro[2,3-*h*]coumarin (**10**): mp 285 °C (dec.). IR (KBr): 2949, 2840, 1716, 1599, 1432, 1108, 1088, 832 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 3.80 (s, 2 H, CH_2CO), 4.72 (s, 2 H, CH_2OH), 6.08 (s, 1 H, H-3), 6.79 (s, 1 H, H-6), 7.58 (s, 1 H, H-8), 10.80 (br s, 3 H, 3 OH). MS: *m/z* (%) = 291 (8) $[M + 1]^+$, 290 (100) $[M^+]$, 272 (18), 246 (9), 228 (15).