A New Short Way to Furocoumarins

Valery F. Traven*[a], Dmitrii V.Kravtchenko[a], Tatjana A. Chibisova[a], Sergei V. Shorshnev[a], Robert Eliason[b] and Darren H. Wakefield[b]

a: Department of Organic Chemistry, D.Mendeleev University of Chemical Technology of Russia, 125047 Moscow, Russia

b: Department of Chemistry, Southwest State University, 56258 Marshall, MN, USA

Abstract: The Fries rearrangement of hydroxycoumarin chloroacetates provides a new short way to furocoumarins. 7-Hydroxycoumarin chloroacetates have been transformed in the presence of $AlCl_3$ into the proper dihydrofuro[2,3-h]coumarin-9-ones in high yields. 8-Substituted-7-hydroxycoumarin chloroacetates undergo into dihydrofuro[2,3-g]coumarin-6-ones in the presence of $AlCl_3$. 4-Hydroxycoumarin chloroacetate has been transformed into the dihydrofuro[2,3-c]coumarin-3-one in the same conditions. Reduction of all dihydrofurocoumarinones followed by dehydration provide the proper furocoumarins in good yields. This new way to furocoumarins is mostly suitable for angelicin derivatives synthesis. All new coumarin derivatives have been characterised by NMR and mass spectra.

Introduction

Derivatives of the 2H-1-benzopyran-2-one (coumarin) belong to one of the most widespread classes of natural products. Many of them show a significant biological activity. For example, some furocoumarins (e.g. psoralens and angelicins) are useful in treatment of human skin diseases (1,2). Even though several methods for the preparation of unsubstituted in furan ring furocoumarins have been elaborated (3-13), some of these methods provide rather low yields, others have laborious procedures to carry out. Some schemes to furocoumarins contain a step of furan ring formation in strong alkaline solution, others include decarboxylation step. Both steps take place at the high temperatures and do not provide good yields of final products.

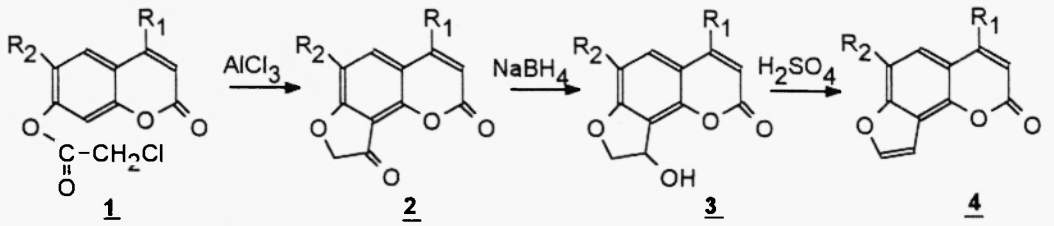
We reported previously a new way to 4-methylangelicin based on transformation of 7-hydroxy-8-bromoacetyl-4-methylcoumarin (14). After cyclization of the latter we have prepared 4-methyldihydrofuro[2,3-h]coumarin-9-one. Reduction of the 4-methyldihydrofuro[2,3-h]coumarin-9-one followed by a dehydration step has resulted the angelicin derivative.

In this paper we report a new way to dihydrofurocoumarinones excluding halogenation step. Chloroacetoxycoumarins undergo a Fries rearrangement with formation of the corresponding dihydrofurocoumarinones. This unusual Fries reaction provides a convenient short synthesis of furocoumarins. It involves three steps only (starting from chloroacetoxycoumarins) and goes in the most cases with good yields of final products.

Results and Discussion

Angelicins which have no substituents in furan ring have been synthesized by the following scheme 1.

scheme 1



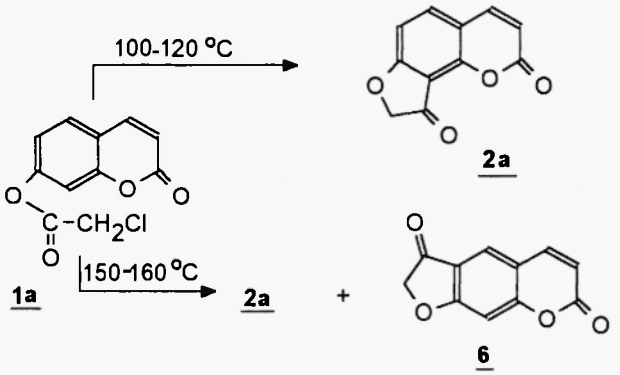
1 2 3 4

a:R_1=R_2=H; b:R_1=Me, R_2=H; c:R_1=Me, R_2=Et; d:R_1=Me, R_2=Cl

7-Chloroacetoxycoumarins 1a-d undergo Fries rearrangement with formation of the corresponding dihydrofuro[2,3-h]coumarin-9-ones. The temperature of this hydroxycoumarin chloroacetate transformation is found to be less (near 120°C) than hydroxycoumarin acetates Fries rearrangement (140-150°C). However, the rearrangement of 1d took place only at 160°C because of electron-withdrawing effect of chlorine. No intermediate products have been found in the rearrangement of chloroacetates 1a-c. On the other hand, rearrangement of 1d has provided 6-chloro-8-chloroacetyl-7-hydroxy-4-methylcoumarin 5 as an intermediate. The reaction mixture after Fries rearrangement of 1d was treated then with excess of K_2CO_3 in acetone. Cyclization of 6-chloro-8-chloroacetyl-7-hydroxy-4-methylcoumarin 5 provided the increased yield of 6-chloro-4-methyldihydrofuro[2,3-h]coumarin-9-one 2d.

As Limaye (15) and Shah et al. (16) reported, the Fries rearrangement of 7-acetoxycoumarin at the lower temperature (120-140°C) results in 7-hydroxy-8-acetylcoumarin, but 7-hydroxy-6-acetylcoumarin was also isolated at the higher temperature (160°C) (15-16). We have found the same results for the Fries rearrangement of 7-chloroacetoxycoumarin 1a: at the 100-120°C the rearrangement resulted only in dihydrofuro[2,3-h]coumarin-9-one 2a, but at the 150°C dihydrofuro[2,3-g]coumarin-6-one 6 have also been formed and separated by a column chromatography (see scheme 2).

scheme 2

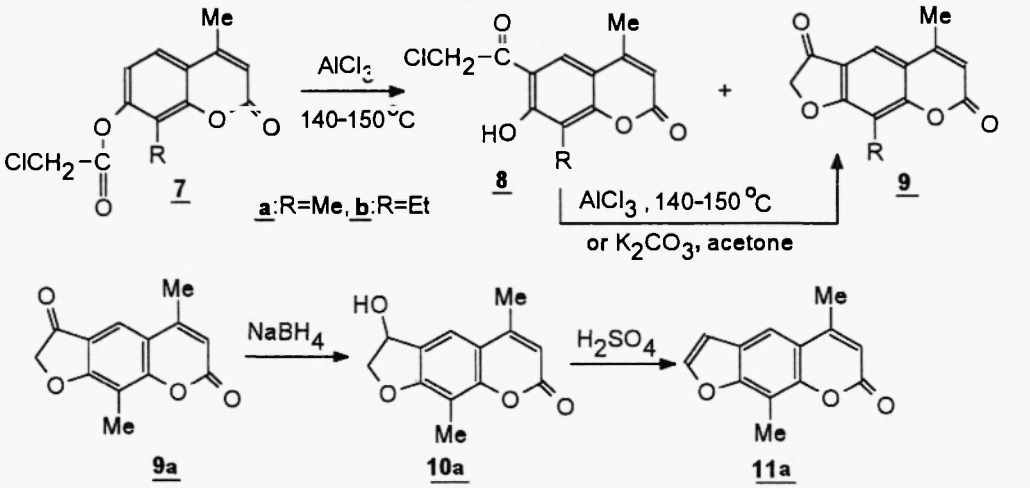


1a 2a

Reduction of dihydrofurocoumarinones **2** with $NaBH_4$ in dioxane and dehydration of the resulted alcohols **3** with H_2SO_4 provided the corresponding angelicins **4**.

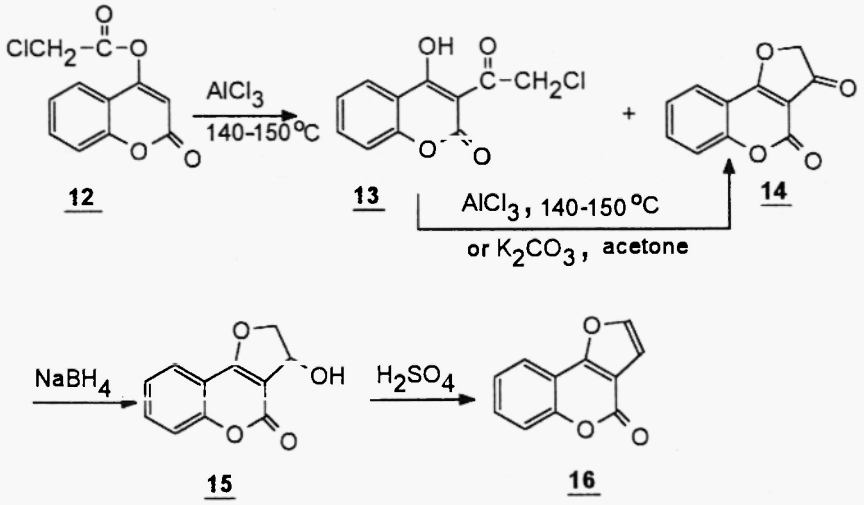
Two products were isolated in the Fries rearrangement of 7-chloroacetoxy-8-ethyl-4-methylcoumarin **7b**: 6-chloroacetyl-7-hydroxy-8-ethyl-4-methylcoumarin **8b** and 8-ethyl-4-methyldihydrofuro[2,3-g]coumarin-6-one **9b** in the ratio 1:1. Two products with the same ratio have also been found in the Fries rearrangement of 7-chloroacetoxy-4,8-dimethylcoumarin **7a**. The reaction mixture after Fries rearrangement was treated with excess of K_2CO_3 in acetone. Intermediate 6-chloroacetyl-7-hydroxy-4,8-dimethylcoumarin **8a** underwent to the 4,8-dimethyldihydrofuro[2,3-g] coumarin-6-one **9a** via cyclization. The linear furocoumarin, 4,9-dimethylpsoralen **11a** has then been prepared via reduction and dehydration steps (see scheme 3).

scheme 3



The Fries rearrangement of 4-chloroacetoxycoumarin **12** yielded also two products: 3-chloroacetyl-4-hydroxycoumarin **13** and dihydrofuro[2,3-c]coumarin-3-one **14** in the ratio 2:1. The furocoumarin-2H-furo[2,3-c]-1-benzopyran-2-one **16** has been prepared via reduction and dehydration steps (see scheme 4).

scheme 4



The chloroacetylhydroxycoumarins **8b** and **13** were transformed to the dihydrofurocoumarinones **9b** and **14** respectively by heating in the presence of K_2CO_3 in acetone or by heating in the presence of excess of $AlCl_3$ (conditions of the Fries reaction).

Based on these experimental results one can suggest the following steps in the Fries rearrangement of chloroacetoxycoumarins: the first step includes "normal" Fries rearrangement of hydroxycoumarin chloroacetate and results in ortho-chloroacetylhydroxycoumarin derivative; the second step includes cyclization of ortho-chloroacetylhydroxycoumarin derivative to corresponding dihydrofurocoumarinone.

^{1}H-NMR spectra

All ^{1}H-NMR spectra were recorded on a Varian Gemini-200 spectrometer at 200 MHz in acetone-d_6 solution using TMS as internal standard. Chemical shifts are given in ppm.

The most characteristic signal of all dihydrofurocoumarinones is a singlet of methylene group which appears in a lower field compared to methylene group signal of chloroacetoxycoumarins.

^{1}H-NMR spectra of hydroxydihydrofurocoumarins **3**, **10a**, **15** are worth of additional comments. The protons of methylene group are not equivalent to each other. They appear as doublets of doublets and have the same large geminal coupling constants (near 11 Hz), but different coupling constants due to the proton which is geminal to hydroxyl group. Signal of this proton appears as a multiplet. Hydroxyl group proton of the compounds **3** has a doublet form due to its interaction with geminal proton, but in the case of **10a** and **15** its signal is not identified because of the same shifts as protons of methylene group.

Furan ring protons of final furocoumarins appear as doublets with coupling constants equal near to 2 Hz. Proton at α-position in furan ring appears in lower field compared to the β-proton due to oxygen electron-withdrawing effect. Proton 9-H of furan ring in angelicin derivatives **4a-b** is also coupled (coupling constant near 1 Hz) due to proton 6-H of coumarin ring.

Mass spectra

All mass spectra were scanned on a SSQ-710 (Finnigan MAT) spectrometer at the energy of ionising electrons equal to 70 ev.

Molecular ions of chloroacetoxycoumarins have low intensity peaks (near 20%), but they produce the highest intensity peaks losing chloroketene fragment.

Dihydrofurocoumarinones **2a-d**, **6**, **9a-b** and **14** have the highest intensity parent peaks in the electron-impact mass spectra. Their molecular ions lose then carbon monoxide or HCO fragments.

Hydroxydihydrofurocoumarins **3a-d**, **10a** and **15** have also the highest intensity parent peaks. Their molecular ions decompose under electron impact in three directions: with lose of carbon monoxide, HCO or OH fragments.

The final furocoumarins **4b**, **11a** and **16** have the highest intensity parent peaks, but the **4a**, **4c** and **4d** peaks are lower by intensity, 80, 94 and 97 %, respectively. The furocoumarin molecular ions decompose under electron impact in two directions: with lose of carbon monoxide or HCO fragments.

Experimental

Synthesis of chloroacetoxycoumarins

Dry pyridine (0.5 ml) was slowly added to the mixture of hydroxycoumarin (10 g) and 15 ml of chloroacetyl chloride. After refluxing for 40 min the reaction mixture was cooled and treated then with ice water. The crude product was collected, washed with water and recrystallized from methanol as colourless needles.

1a: yield 85%; mp 167-168°C (lit. (17) 163-164°C (EtOH)); ^{1}H-NMR (acetone-d_6, J/Hz), 4.57 (s, 2H, -CH_2-), 6.37 (d, 1H, 3-H, $J_{3,4}$=9.5), 7.12 (d, 1H, 8-H, $J_{8,6}$=2.1), 7.18 (dd, 1H, 6-H, $J_{6,5}$=8.3, $J_{6,8}$=2.1), 7.71 (d, 1H, 5-H, $J_{5,6}$=8.3), 7.95 (d, 1H, 4-H, $J_{4,3}$=9.5).

1b: yield 85%; mp 180-181°C (lit. (17) 181-182°C (EtOH)); ^{1}H-NMR (acetone-d_6, J/Hz), 2.50 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 4.60 (s, 2H, -CH_2-), 6.30 (d, 1H, 3-H, $J_{3,Me}$=1.2), 7.19 (d, 1H, 8-H, $J_{8,6}$=2.1), 7.22 (dd, 1H, 6-H, $J_{6,5}$=9.1, $J_{6,8}$=2.1), 7.83 (d, 1H, 5-H, $J_{5,6}$=9.1).

1c: yield 85%; mp 162-163°C; ^{1}H-NMR (acetone-d_6, J/Hz), 1.22 (tr, 3H, Me, $J_{Me,-CH_2-}$=7.6), 2.50 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 2.68 (q, 2H, -CH_2-, $J_{-CH_2-,Me}$=7.6), 4.67 (s, 2H, -CH_2-), 6.30 (d, 1H, 3-H, $J_{3,Me}$=1.2), 7.20 (s, 1H, 8-H), 7.74 (s, 1H, 5-H).

MS: m/z (%) 280/282, (1 Cl), (M+, 23), 204 (-O=C=CHCl, 100), 189 (-O=C=CHCl, -Me, 80), 161 (-O=C=CHCl, -Me, -CO, 41), 203 (-O=C-CH_2Cl, 16).

1d: yield 70%; mp 219-220°C; ^{1}H-NMR (acetone-d_6, J/Hz), 2.54 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 4.71 (s, 2H, -CH_2-), 6.40 (d, 1H, 3-H, $J_{3,Me}$=1.2), 7.40 (s, 1H, 8-H), 7.96 (s, 1H, 5-H).

MS: m/z (%) 286/288, (2 Cl), (M+, 10), 210/212, (1 Cl), (-O=C=CHCl, 100), 182/184, (1 Cl), (-O=C=CHCl, -CO, 65).

7a: yield 85%; mp 158-159°C; ^{1}H-NMR (acetone-d_6, J/Hz), 2.25 (s, 3H, 8-Me), 2.49 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 4.69 (s, 2H, -CH_2-), 6.32 (d, 1H, 3-H, $J_{3,Me}$=1.2), 7.19 (d, 1H, 6-H, $J_{6,5}$=8.6), 7.69 (d, 1H, 5-H, $J_{5,6}$=8.6).

MS: m/z (%) 266/268, (1 Cl), (M+, 24), 190 (-O=C=CHCl, 100), 162 (-O=C=CHCl, -CO, 100), 161 (-O=C=CHCl, -HCO, 33).

7b: yield 85%; mp 135-136°C; ^{1}H-NMR (acetone-d_6, J/Hz), 1.16 (tr, 3H, Me, $J_{Me,-CH_2-}$=7.7), 2.49 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 2.80 (q, 2H, -CH_2-, $J_{-CH_2-,Me}$=7.7), 4.69 (s, 2H, -CH_2-), 6.33 (d, 1H, 3-H, $J_{3,Me}$=1.2), 7.19 (d, 1H, 6-H, $J_{6,5}$=8.8), 7.69 (d, 1H, 5-H, $J_{5,6}$=8.8).

MS: m/z (%) 280/282, (1 Cl), (M+, 22), 204 (-O=C=CHCl, 100), 189 (-O=C=CHCl, -Me, 75).

12: yield 80%; mp 153-155°C (lit. (18) 156.5-158°C (benzene)); ^{1}H-NMR (acetone-d_6, J/Hz), 4.83 (s, 2H, -CH_2-), 6.54 (s, 1H, 3-H), 7.34-7.45 (m, 2H, 6-H and 8-H), 7.68-7.89 (m, 2H, 7-H and 5-H).

Fries rearrangement of chloroacetoxycoumarins 1a-c

The mixture of chloroacetoxycoumarin (0.016 mole) and anhydrous aluminium chloride (0.052 mole) was heated in an oil bath at 100-120°C for 25-35 min. The cooled reaction mixture was poured into cold dilute HCl. The crude solids, thus obtained, were washed with water and recrystallized from glacial acetic acid as light yellow crystals of **2a-c**.

2a: yield 60%; mp 251-252°C; ^{1}H-NMR (acetone-d_6, J/Hz), 4.83 (s, 2H, -CH_2-), 6.34 (d, 1H, 3-H, $J_{3,4}$=9.8), 7.15 (d, 1H, 6-H, $J_{6,5}$=8.5), 7.97 (d, 1H, 5-H, $J_{5,6}$=8.5), 8.01 (d, 1H, 4-H, $J_{4,3}$=9.8).

MS: m/z (%) 202 (M+, 100), 174 (-CO, 32), 173 (-HCO, 27), 145 (-$CHCO_2$, 34).

2b: yield 70%; mp 257-258°C; ^{1}H-NMR (acetone-d_6, J/Hz), 2.49 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 4.81 (s, 2H, -CH_2-), 6.23 (d, 1H, 3-H, $J_{3,Me}$=1.2), 7.14 (d, 1H, 6-H, $J_{6,5}$=8.8), 8.08 (d, 1H, 5-H, $J_{5,6}$=8.8).

MS: m/z (%) 216 (M+, 100), 188 (-CO, 44), 159 (-CO, -HCO, 35), 131 (-2CO, -HCO, 15).

2c: yield 75%; mp 243-244°C; ^{1}H-NMR (acetone-d_6, J/Hz), 1.29 (tr, 3H, Me, $J_{Me,-CH_2-}$=7.7), 2.50 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 2.76 (q, 2H, -CH_2-, $J_{-CH_2-,Me}$=7.7), 4.85 (s, 2H, -CH_2-), 6.21 (d, 1H, 3-H, $J_{3,Me}$=1.2), 7.91 (s, 1H, 5-H).

MS: m/z (%) 244 (M+, 100), 216 (-CO, 85), 187 (-CO, -HCO, 20), 229 (-Me, 79), 201 (-Me, -CO, 98), 173 (-Me, -2CO, 26).

Dihydrofuro[2,3-g]coumarin-6-one 6

Fries rearrangement of 7-chloroacetoxycoumarin **1a** has been carried out at 150-160°C by the standard procedure. The crude reaction mixture contained dihydrofuro[2,3-h]coumarin-9-one **2a** and dihydrofuro[2,3-g]coumarin-6-one **6** in the ratio 4:1 (by NMR spectra). Compound **6** was separated by column chromatography (silica gel 40/100, $CHCl_3$) and recrystallized from glacial acetic acid as light yellow crystals.

6: yield 6%; mp 245-246°C; ^{1}H-NMR (acetone-d_6, J/Hz), 4.84 (s, 2H, -CH_2-), 6.37 (d, 1H, 3-H, $J_{3,4}$=9.9), 7.11 (s, 1H, 9-H), 8.01 (s, 1H, 5-H), 8.06 (d, 1H, 4-H, $J_{4,3}$=9.9).

MS: m/z (%) 202 (M+, 100), 174 (-CO, 40), 145 (-CO, -HCO, 60), 173 (-HCO, 30), 144 (-2HCO, 14).

Fries rearrangement of chloroacetoxycoumarins 1d, 7a, 7b, 12

Fries rearrangements of chloroacetoxycoumarins **1d, 7a, 7b, 12** have been done by the standard procedure. The crude reaction mixture contained two compounds-dihydrofurocoumarinone and chloroacetylhydroxycoumarin.

The crude reaction mixture (5 g) after Fries rearrangement was dissolved in 50 ml dry acetone and treated with excess of K_2CO_3 for 40 min at 30°C, and poured then into cold dilute HCl. Dihydrofurocoumarinones **2d, 9a, 9b, 14**, thus obtained, were recrystallized as light yellow crystals.

2d: yield 20%; mp 244-245°C (AcOH); ^{1}H-NMR (acetone-d_6, J/Hz), 2.53 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 4.96 (s, 2H, -CH_2-), 6.31 (d, 1H, 3-H, $J_{3,Me}$=1.2), 8.14 (s, 1H, 5-H).

MS: m/z (%) 250/252, (1 Cl), (M+, 100), 222/224, (1 Cl), (-CO, 84), 193/195, (1 Cl), (-CO, -HCO, 59), 149/151, (1 Cl), (-2CO, -HCO, 17).

9a: yield 60%; mp 246-247°C (AcOH); ^{1}H-NMR (acetone-d_6, J/Hz), 2.32 (s, 3H, 9-Me), 2.53 (d, 3H, 4-Me, $J_{Me,3}$=1.4), 4.85 (s, 2H, -CH_2-), 6.28 (d, 1H, 3-H, $J_{3,Me}$=1.4), 7.87 (s, 1H, 5-H).

MS: m/z (%) 230 (M+, 100), 202 (-CO, 94), 173 (-CO, -HCO, 82), 145 (-2CO, -HCO, 28), 201 (-HCO, 30).

9b: yield 60%; mp 180°C (MeOH); ^{1}H-NMR (acetone-d_6, J/Hz), 1.24 (tr, 3H, Me, $J_{Me,-CH_2-}$=7.6), 2.53 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 2.88 (q, 2H, -CH_2-, $J_{-CH_2-,Me}$=7.6), 4.86 (s, 2H, -CH_2-), 6.28 (d, 1H, 3-H, $J_{3,Me}$=1.1), 7.88 (s, 1H, 5-H).

MS: m/z (%) 244 (M+, 100), 216 (-CO, 37), 201 (-CO, -Me, 45) 229 (-Me, 60), 187 (-Me, -H_2C=C=O, 10).

14: yield 50%; mp 231°C (MeOH); ^{1}H-NMR (acetone-d_6), 5.07 (s, 2H, -CH_2-), 7.46-7.57 (m, 2H, 7-H and 9-H), 7.89-8.06 (m, 2H, 8-H and 6-H).

MS: m/z (%) 202 (M+, 100), 174 (-CO, 5), 173 (-HCO, 5), 172 (-H_2CO, 10), 144 (-H_2CO, -CO, 27), 116 (-H_2CO, -2CO, 17).

Chloroacetylhydroxycoumarins **5**, **8a**, **13** were separated by preparative TLC or column chromatography (silica gel 40/100, $CHCl_3$) and recrystallized as white crystals.

5: mp 220°C (decomp.) ($CHCl_3$); ^{1}H-NMR (acetone-d_6, J/Hz), 2.53 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 5.31 (s, 2H, -CH_2-), 6.31 (d, 1H, 3-H, $J_{3,Me}$=1.2), 8.11 (s, 1H, 5-H), 14.29 (s, 1H, -OH).

MS: m/z (%) 286/288, (2 Cl), (M+, 20), 250/252, (1 Cl), (-HCl, 20), 237/239, (1 Cl), (-CH_2Cl, 100).

8b: yield 20%; mp 183°C (MeOH); ^{1}H-NMR (acetone-d_6, J/Hz), 1.18 (tr, 3H, Me, $J_{Me,-CH2-}$=7.6), 2.53 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 2.86 (q, 2H, -CH_2-, $J_{-CH2-,Me}$=7.6), 5.28 (s, 2H, -CH_2-), 6.24 (d, 1H, 3-H, $J_{3,Me}$=1.1), 8.30 (s, 1H, 5-H), 12.49 (s, 1H, -OH).

MS: m/z (%) 280/282, (1 Cl), (M+, 25), 244 (-HCl, 15), 231 (-CH_2Cl, 100).

13: yield 25%; mp 155-156°C (acetone); ^{1}H-NMR (acetone-d_6), 5.10 (s, 2H, -CH_2-), 7.39-7.54 (m, 2H, 6-H and 8-H), 7.85-8.14 (m, 2H, 7-H and 5-H), 16.37 (s, 1H, -OH).

MS: m/z (%) 238/240, (1 Cl), (M+, 15), 203 (-Cl, 100), 189 (-CH_2Cl, 85).

Cyclization of 6-chloroacetyl-7-hydroxy-8-ethyl-4-methylcoumarin 8b in the presence of $AlCl_3$

The mixture of compound **8b** (1 g, 3.5 mmole) and anhydrous aluminium chloride (1.56 g, 11.7 mmole) was heated at 140-150°C in an oil-bath for 30-40 min. The crude solid of **9b** was poured into cold dilute HCl and recrystallized then from MeOH. M.p. 180°C. Yield 0.43 g (50%).

Cyclization of 6-chloroacetyl-7-hydroxy-8-ethyl-4-methylcoumarin 8b in the presence of K_2CO_3

The compound **8b** (1 g, 3.5 mmole) was dissolved in acetone and K_2CO_3 was added. The mixture was stirred for 10 min. at room temperature. The product (**9b**) after acetone evaporation was recrystallized from MeOH. M.p. 180°C. Yield 0.7 g (80%).

Cyclization of 3-chloroacetyl-4-hydroxycoumarin **13** to dihydrofuro[2,3-c]coumarin-3-one **14** have been done in the presence of $AlCl_3$ and K_2CO_3 similar to previous procedures.

Reduction of dihydrofurocoumarinones (synthesis of hydroxydihydrofurocoumarins)

Dihydrofurocoumarinone (4.6 mmole) was dissolved in 1,4-dioxane and treated with excess of $NaBH_4$ under cooling. Methanol (0.5 ml) was added to the reaction mixture along the reaction. The mixture was stirred for 1 hour at 30°C (TLC control), and poured then into dilute HCl. The product was extracted by chloroform. Light yellow needles were separated after partial chloroform evaporation. Yield 85-90%.

3a: mp 135-136°C; ^{1}H-NMR (acetone-d_6, J/Hz), 4.54 (dd, 1H, 8a-H, J_{gem}=10.7, $J_{8a,9}$=2.2), 4.71 (dd, 1H, 8b-H, J_{gem}=10.7, $J_{8b,9}$=6.5), 5.02 (d, 1H, 9-OH, $J_{9\text{-}OH,9}$=5.8), 5.70 (ddd, 1H, 9-H, $J_{9,8b}$=6.5, $J_{9,9\text{-}OH}$=5.8, $J_{9,8a}$=2.2), 6.20 (d, 1H, 3-H, $J_{3,4}$=9.5), 6.84 (d, 1H, 6-H, $J_{6,5}$=8.2), 7.58 (d, 1H, 5-H, $J_{5,6}$=8.2), 7.92 (d, 1H, 4-H, $J_{4,3}$=9.5).

MS: m/z (%) 204 (M+, 100), 187 (-OH, 85), 176 (-CO, 19), 175 (-HCO, 19).

3b: mp 209-210°C; ^{1}H-NMR (acetone-d_6, J/Hz), 2.44 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 4.53 (dd, 1H, 8a-H, J_{gem}=11.0, $J_{8a,9}$=2.5). 4.70 (dd, 1H, 8b-H, J_{gem}=11.0, $J_{8b,9}$=6.6), 4.96 (d, 1H, 9-OH, $J_{9\text{-}OH,9}$=5.5), 5.68 (ddd, 1H, 9-H, $J_{9,8b}$=6.6, $J_{9,9\text{-}OH}$=5.5, $J_{9,8a}$=2.5), 6.10 (d, 1H, 3-H, $J_{3,Me}$=1.1), 6.84 (d, 1H, 6-H, $J_{6,5}$=8.4), 7.68 (d, 1H, 5-H, $J_{5,6}$=8.4).

MS: m/z (%) 218 (M+, 100), 201 (-OH, 10), 173 (-OH, -CO, 12), 190 (-CO, 17), 161 (-CO, -HCO, 7).

3c: mp 205-206°C; ^{1}H-NMR (acetone-d_6, J/Hz), 1.23 (tr, 3H, Me, $J_{Me,\text{-}CH_2\text{-}}$=7.5), 2.44 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 2.70 (q, 2H, -CH_2-, $J_{\text{-}CH_2\text{-},Me}$=7.5), 4.56 (dd, 1H, 8a-H, J_{gem}=10.7, $J_{8a,9}$=2.2), 4.72 (dd, 1H, 8b-H, J_{gem}=10.7, $J_{8b,9}$=6.2), 4.98 (d, 1H, 9-OH, $J_{9\text{-}OH,9}$=5.0), 5.68 (ddd, 1H, 9-H, $J_{9,8b}$=6.2, $J_{9,9\text{-}OH}$=5.0, $J_{9,8a}$=2.2), 6.09 (d, 1H, 3-H, $J_{3,Me}$=1.2), 7.52 (s, 1H, 5-H).

MS: m/z (%) 246 (M+, 100), 218 (-CO, 20), 231 (-Me, 56), 203 (-Me, -CO, 27).

3d: mp 235-237°C; ^{1}H-NMR (acetone-d_6, J/Hz), 2.47 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 4.63 (dd, 1H, 8a-H, J_{gem}=10.6, $J_{8a,9}$=2.2), 4.82 (dd, 1H, 8b-H, J_{gem}=10.6, $J_{8b,9}$=6.2), 5.17 (d, 1H, 9-OH, $J_{9\text{-}OH,9}$=6.0), 5.76 (ddd, 1H, 9-H, $J_{9,8b}$=6.2, $J_{9,9\text{-}OH}$=6.0, $J_{9,8a}$=2.2), 6.19 (d, 1H, 3-H, $J_{3,Me}$=1.2), 7.66 (s, 1H, 5-H).

MS: m/z (%) 252/254, (1 Cl), (M+,100), 224/226, (1 Cl), (-CO, 25), 195/197, (1 Cl), (-CO, -H_2O, 23), 237/239, (1 Cl), (-Me, 10).

10a: mp 207-208°C; ^{1}H-NMR (acetone-d_6, J/Hz), 2.22 (s, 3H, 9-Me), 2.44 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 4.48 (dd, 1H, 7a-H, J_{gem}=10.4. $J_{7a,6}$=3.2), 4.71 (dd, 1H, 7b-H, J_{gem}=10.4, $J_{7b,6}$=6.6), 4.57 (m, 1H, 6-OH), 5.48 (dd, 1H, 6-H, $J_{6,7b}$=6.6, $J_{6,7a}$=3.2), 6.10 (d, 1H, 3-H, $J_{3,Me}$=1.2), 7.64 (s, 1H, 5-H).

MS: m/z (%) 232 (M+, 100), 215 (-OH, 60), 187 (-OH, -CO, 44), 204 (-CO, 32), 175 (-CO, -HCO, 16), 214 (-H_2O, 34), 185 (-H_2O, -HCO, 33).

15: mp 165-167°C; ^{1}H-NMR (acetone-d_6, J/Hz), 4.70 (dd, 1H, 4a-H, J_{gem}=10.7, $J_{4a,3}$=2.2), 4.91 (dd, 1H, 4b-H, J_{gem}=10.7, $J_{4b,3}$=6.8), 4.74 (m, 1H, 3-OH), 5.42 (dd, 1H, 3-H, $J_{3,4b}$=6.8, $J_{3,4a}$=2.2), 7.36-7.43 (m, 2H, 7-H and 9-H), 7.68-7.78 (m, 2H, 8-H and 6-H).

MS: m/z (%) 204 (M+, 100), 187 (-OH, 60), 143 (-OH, -CO_2, 44), 176 (-CO, 66), 147 (-CO, -HCO, 57), 175 (-HCO, 66), 146 (-2HCO, 82).

Dehydration of hydroxydihydrofurocoumarins (synthesis of furocoumarins)

Hydroxydihydrofurocoumarin (4.6 mmole) was added to the mixture of 5 ml ethanol and 45 ml of 30 % H_2SO_4. The mixture was heated in a water-bath for 30 min and poured into ice water. The crude product was recrystallized from methanol as needles. Yield 80-85%.

4a: white needles, mp 139-140°C (lit. (10) 140-142°C (MeOH)); ^{1}H-NMR (acetone-d_6, J/Hz), 6.39 (d, 1H, 3-H, $J_{3,4}$=9.8), 7.21 (dd, 1H, 9-H, $J_{9,8}$=2.2, $J_{9,6}$=1.0), 7.54 (dd, 1H, 6-H, $J_{6,5}$=8.2, $J_{6,9}$=1.0), 7.63 (d, 1H, 5-H, $J_{5,6}$=8.2), 8.08 (d, 1H, 8-H, $J_{8,9}$=2,2), 8.92 (d, 1H, 4-H, $J_{4,3}$=9.8).

MS: m/z (%) 186 (M+, 80), 158 (-CO, 100), 130 (-2CO, 13), 102 (-3CO, 33).

4b: white needles, mp 189°C (lit. (10) 189°C (MeOH)); ^{1}H-NMR (acetone-d_6, J/Hz), 2.55 (d, 3H, 4-Me, $J_{Me,3}$=1.4), 6.29 (d, 1H, 3-H, $J_{3,Me}$=1.4), 7.19 (dd, 1H, 9-H, $J_{9,8}$=2.1, $J_{9,6}$=0.9), 7.54 (dd, 1H, 6-H, $J_{6,5}$=8.8, $J_{6,9}$=0.9), 7.72 (d, 1H, 5-H, $J_{5,6}$=8.8), 7.98 (d, 1H, 8-H, $J_{8,9}$=2.1).

MS: m/z (%) 200 (M+, 100), 172 (-CO, 65), 171 (-HCO, 48).

4c: light yellow solid, mp 182-183°C; ^{1}H-NMR (acetone-d_6, J/Hz), 1.36 (tr, 3H, Me, $J_{Me,-CH2-}$=7.4), 2.54(d, 3H, 4-Me, $J_{Me,3}$=1.0), 2.99 (q, 2H, -CH_2-, $J_{-CH2-,Me}$=7.4), 6.26 (d, 1H, 3-H, $J_{3,Me}$=1.0), 7.18 (d, 1H, 9-H, $J_{9,8}$=2.2), 7.54 (s, 1H, 5-H), 7.99 (d, 1H, 8-H, $J_{8,9}$=2.2).

MS: m/z (%) 228 (M+, 94), 200 (-CO, 49), 185 (-CO, -Me, 100), 213 (-Me, 84), 185 (-Me, -CO, 100).

4d: light yellow solid, mp 209-210°C; ^{1}H-NMR (acetone-d_6, J/Hz), 2.57 (d, 3H, 4-Me, $J_{Me,3}$=1.0), 6.35 (d, 1H, 3-H, $J_{3,Me}$=1.0), 7.29 (d, 1H, 9-H, $J_{9,8}$=2.2), 7.77 (s, 1H, 5-H), 8.11 (d, 1H, 8-H, $J_{8,9}$=2.2).

MS: m/z (%) 234/236, (1 Cl), (M+, 97), 206/208, (1 Cl), (-CO, 100), 171 (-CO, -Cl, 37), 205/207, (1 Cl), (-HCO, 85).

11a: light pink solid, mp 204-205°C (lit. (19) 206°C (MeOH)); ^{1}H-NMR (acetone-d_6, J/Hz), 2.54 (s, 3H, 9-Me), 2.54 (d, 3H, 4-Me, $J_{Me,3}$=1.4), 6.26 (d, 1H, 3-H, $J_{3,Me}$=1.4), 7.01 (d, 1H, 6-H, $J_{6,7}$=2.2), 7.90 (s, 1H, 5-H), 7.95 (d, 1H, 7-H, $J_{7,6}$=2.2).

MS: m/z (%) 214 (M+, 100), 186 (-CO, 68), 185 (-HCO, 89).

16: white needles, mp 92-93°C (lit. (20) 93°C (MeOH)); ^{1}H-NMR (acetone-d_6, J/Hz), 7.07 (d, 1H, 3-H, $J_{3,4}$=2.2), 7.41-7.96 (m, 4H, 6-H-9-H), 8.01 (d, 1H, 4-H, $J_{4,3}$=2.2).

MS: m/z (%) 186 (M+, 100), 158 (-CO, 10), 130 (-2CO, 10), 158 (-3CO, 28).

Conclusions

The Fries rearrangement of hydroxycoumarin chloroacetates provides a new short way for furocoumarin synthesis. It is mostly effective for angelicin derivative preparation.

Acknowledgements

This work was generously funded by the Highest Education State Committee of Russian Federation (program "Fine Organic Synthesis") and by the Otto Bremer Foundation (via Prof.Ed.Carberry project).

References

(1) F.Dall`Acqua, D.Vedaldi, S.Caffieri, A.Guiotto, P.Rodighiero, F.Baccichetti, F.Carlassare, and F.Bordin, J. Med. Chem.,24, 178 (1981)

(2) A.Guiotto, P.Rodighiero, P.Manzini, G.Pastorini, F.Bordin, F.Baccichetti, F.Carlassare, D.Vedaldi, F.Dall`Acqua, M.Tamaro, G.Recchia and M.Cristofolini, J. Med. Chem.,27, 959 (1984)

(3) E.Spath and M.Pailer, Chem. Ber., 67, 1212 (1934)

(4) E.Spath and M.Pailer, Chem. Ber., 68, 940 (1935)

(5) C.Antonello, Gazz. Chim. Ital., 88, 430 (1958)

(6) Y.Kawase, M.Nakayama and H.Tamatsukurd, Bull. Chem. Soc. Jpn., 35, 149 (1962)

(7) R.M.Naik and V.M.Thakor, J. Org. Chem., 22, 1696 (1957)

(8) R.Aneja, S.K.Mukerjee and T.R.Seshadri, Tetrahedron, 4, 256 (1958)

(9) N.H.Pardanani and K.N.Trivedi, J. Indian Chem. Soc., 48, 339 (1971)

(10) R.J.Bhayani and V.M.Thakor, J. Indian Chem. Soc., 67, 71 (1990)

(11) E.Zubia, F.R.Luis, G.M.Massanet and I.G.Collado, Tetrahedron, 48, 4239 (1992)

(12) Y.R.Lee, Tetrahedron, 51, 3087 (1995)

(13) W.D.Wulff, J.S.MeCallum and F.-A.Kunng, J. Am. Chem. Soc., 110, 7419 (1988)

(14) V.F.Traven, D.V.Kravtchenko and T.A.Chibisova, Mendeleev Commun., 1, 21 (1995)

(15) D.B.Limaye, Chem. Ber., 65, 375 (1932)

(16) D.N.Shah and N.M.Shah, J. Org. Chem., 19, 1681 (1954)

(17) L.R.Row and T.R.Seshadri, Proc. Indian Acad. Sci., 11A, 206 (1940)

(18) R.B.Zhurin and N.S.Vulf'son, J. Gen. Chem. USSR (Engl. Transl), 31, 806 (1961)

(19) G.Caporale and A.M.Bareggi, Gazz. Chim. Ital., 98, 444, (1968)

(20) V.N.Dholakia and K.N.Trivedi, J. Indian Chem. Soc., 43, 804, (1966)

Received June 5, 1996