Selective O-glucosylation of 4,7-dihydroxycoumarin

Valery F. Traven*[a], Lidija S.Krasavina[a] , Elena Yu. Dmitrieva[a] and Edward A. Carberry[b]

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

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

Abstract: Selective glucosylation of 4,7-dihydroxycoumarin **1** has been studied. Different acidity of 4- and 7-hydroxyl functions provides the corresponding synthetic paths. Interaction of 4,7-hydroxycoumarin monosodium salt with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide **2** in DMFA followed by the product deacetylation provides 4-O-(β-D-glucopyranosyl)-7-hydroxycoumarin **3**. Interaction of 4-benzyloxy-7-hydroxycoumarin **4** with **2** followed by the product deacetylation and debenzylation provides 7-O-(β-D-glucopyranosyl)-4-hydroxycoumarin **5**.

Introduction

Natural coumarins are well known for their biological effect (1,2). Series of glucosyloxycoumarins have also been isolated. Their structure and biological activity have been studied (3-5). 4-Phenyl-coumarinyl glucosides have been found to provide antiinflammatory activity (6). Umbellyferyl glucosides showed an antirithmic activity (1). The most of more than 60 isolated coumarinyl glicosides belong to the 7-hydroxycoumarin derivatives which contain one, two or three alkylated (glucosylated) hydroxyl functions at positions 4, 5, 6 or 8 (5).

Synthetic availability of corresponding glucosides depends on selectivity of glucosylation steps. Nevertheless, there are no reports in literature where selective glucosylation of polyhydroxycoumarins have been studied. Potential difficulties of directed coumarinyl glucoside synthesis can be illustrated by attempts of selective O-alkylation of 6,7-dihydroxycoumarin (7) and concurrence of O/C-alkylation of 4,7-dihydroxycoumarin (8,9).

Results and Discussion

We have developed synthetic paths of selective glucosylation of 4,7-dihydroxycoumarin **1** based on the 4-and 7-hydroxyl function different acidities: pKa values have been reported to be equal to 4.74 and 9,46 respectively (11). Change of base strength turned to be the key to undertake selective electrophilic reactions at the hydroxyl function at position 4. For example, protection of this hydroxyl function via

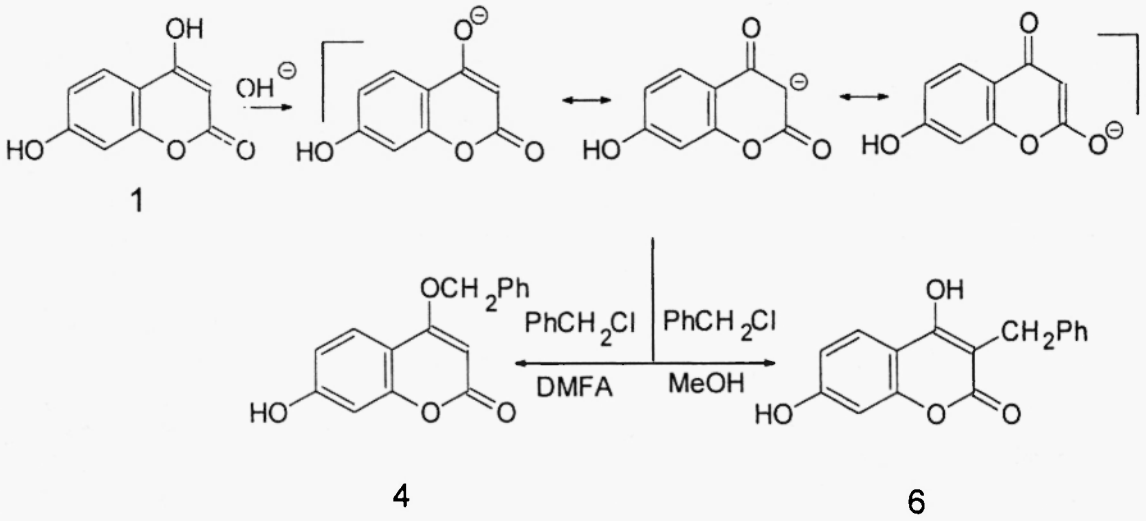
alkylation reaction can provide regiospecific glucosylation of hydroxyl group located at position 7.

Nevertheless, starting with 4 hydroxyl group benzylation of **1** we could not get good results when known procedures (8,9) had been used . On opposite to Buckle et al. data (8), we have found benzylation of **1** by benzyl chloride in DMFA in the presence of NaH at 100°C to provide, besides 4 hydroxyl alkylation, formation of several subside products - mono-, di- and tri-benzylated substrates. Benzylation of **1** at lower temperature (65°C) led to decrease of conversion of starting compounds, but it did not increase selectivity of benzylation at 4 hydroxyl function.

Use of methanol as a solvent resulted also in formation of mixture of alkylation products. We have isolated 3-benzyl-4,7-dihydroxycoumarin **6** as main product in the benzylation procedure in the presence of sodium bicarbonate. Earlier Anker and Massicot reported predomination of 3-benzyl-7-benzyloxy-4-hydroxycoumarin formation in similar conditions, when compound **1** had been treated by benzyl chloride in methanol in the presence of potassium carbonate (9).

We have prepared 4-benzyloxy-7-hydroxycoumarin **4** by benzylation of **1** in dimethylformamide in the presence of sodium carbonate at 50°C; compound **6** has also been isolated as a subside product in these conditions. Structures of compounds **4** and **6** have been approved by their ^{1}H NMR and mass spectra. There is no 3-H proton signal in ^{1}H NMR spectrum of **6** and singlet of CH_2 protons in it is seen in a stronger field: at 4.02 ppm instead of 5.14 ppm in the spectrum of compound **4**.

scheme 1



Mass spectra of both **4** and **6** contain molecular ion peaks (m/z 268) and benzyl ion peaks (m/z 91). Compound **6** mass spectrum is also specified by the peak of O=C=C-CH_2-Ph (m/z 131), which is impossible (and is not seen) in mass spectrum of **4**.

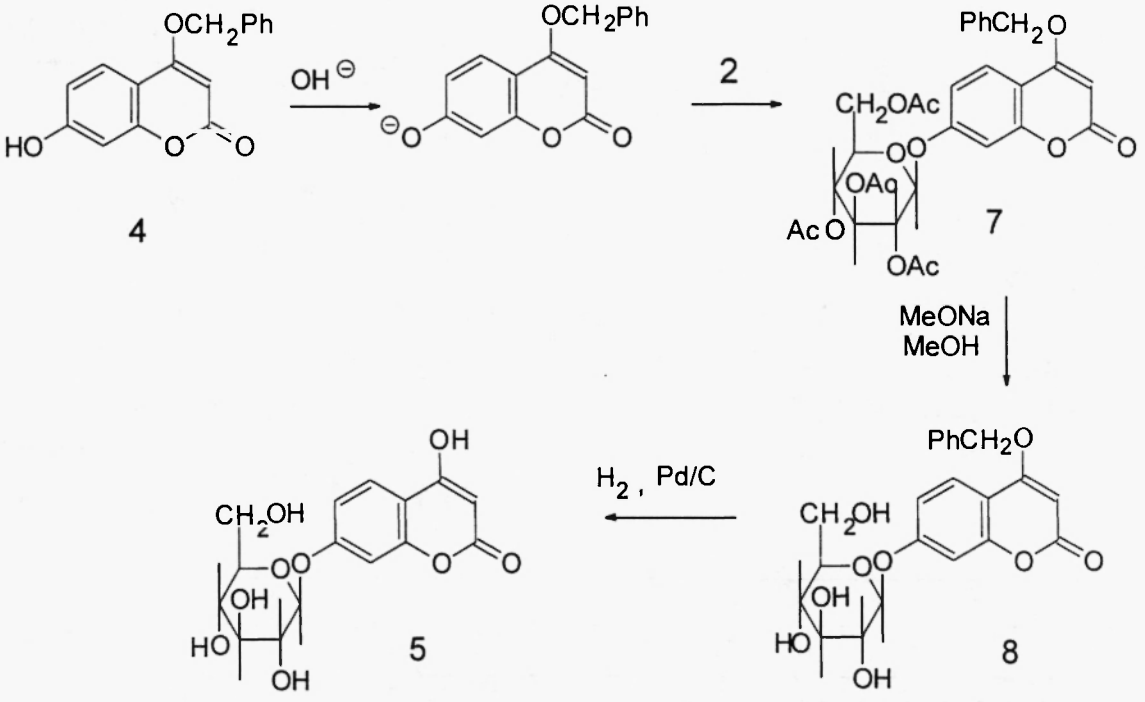
The found results of benzylation are in accordance with effective resonance delocalization of negative charge in ionized form of 4,7-dihydroxycoumarin **1** as it is shown on the scheme 1.

Glucosylation of **4** has then been carried out in reaction of compound **4** sodium salt with acetobromoglucose **2** in acetone. 7-O-(β-D-2,3,4,6-tetra-O-acetylglucopyranosyl)-4-benzyloxycoumarin **7** has been isolated as a main product. Mass spectrum of **7** is specified by molecular ion peak (m/z 599), O-acetyl glucose fragment ion peak (m/z 331) (which is formed due to scission of C-O glucoside bond) and benzyl ion peak (m/z 91).

Deacetylation of **7** has been undertaken both by sodium methylate treatment and with use of ion exchange resin AV-17. 7-O-(β-D-glucopyranosyl)-4-benzyloxycoumarin **8** has been prepared in both cases in good yield. Doublet of anomeric proton at 5.1 ppm is definitely seen in ^{1}H NMR spectrum with value of splitting constant J = 7.3 Hz providing β-orientation of coumarinyloxy fragment in glucoside **8**. Mass spectrum of **8** contains molecular ion peak (m/z 431), aglycone ion peak (m/z268) and benzyl ion peak (m/z 91).

Debenzylation of **8** has been undertaken by hydrogenolysis of O-C bond over Pd/C catalyst with formation of 7-O-(β-D-glucopyranosyl)-4-hydroxycoumarin **5** as it is shown on scheme 2.

scheme 2



^{1}H NMR and mass spectral data agree with the proposed structure of the final product **5**. Signals of the glucopyranose protons are seen at 3.36-3.88 ppm in its ^{1}H NMR spectrum. Doublet of anomeric proton is located at 5.03 ppm with splitting constant value J=7.3 Hz with accordance to β-configuration. The coumarin ring protons are specified by signals at 6.78-7.80 ppm.

We have found selectivity of glucosylation to be rather similar to that of benzylation. This similarity provides a way of direct glucosylation of the compound **1** at 4-hydroxyl group without any

protection of 7-hydroxyl function. Interaction of 4,7-dihydroxycoumarin sodium salt with acetobromoglucose **2** in DMFA at 50-55°C results in predominant 4-hydroxyl group glucosylation. 4-O-(β-D-2,3,4,6-tetra-O-acetylglucopyranosyl)-7-hydroxycoumarin **9** has been isolated from reaction mixture by column preparative chromatography. Formation of 4,7-dihydroxy-3-(β-D-2,3,4,6-tetra-O-acetylglucopyranosyl)coumarin can also be suggested by TLC analysis of subside products of the reaction mixture.

Mass spectrum of compound **9** is in accordance with the proposed structure. Molecular ion peak (m/z 509), O-acetylglucopyranosyl fragment ion peak (m/z 331) and aglycone ion (m/z 178) have been detected in the mass spectrum. Deacetylation of compound **9** has been undertaken via its sodium methoxide treatment with formation of 4-O-(β-D-glucopyranosyl)-7-hydroxycoumarin **3**. ^{1}H NMR and mass spectral data agree with the proposed structure of the final product **3**. Signals of glucose fragment protons are located in ^{1}H NMR spectrum in region at 3.28-4.04 ppm. Coumarin ring is specified by signals at 6.71-7.80 ppm. Doublet of anomeric proton located at 5.22 ppm with splitting constant J equal to 7.0 Hz provides β-orientation of coumarinyloxy fragment in carbohydrate cycle.

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded with 200 Mhz Brucker spectrometer in acetone-d_6 solution using tetramethylsilane as internal standard. Mass spectra were scanned on a SSQ-710 (Finnigan MAT) spectrometer at the energy of ionizing electrons equal to 70 eV. Thin layer chromatography has been done on Silufol UV-254 sheets using as an eluent one of the following systems: A - isopropanol/benzene/ammonia solution (with 10/5/2 ratio) and B - chloroform/acetone (with 9/1 ratio) with iodine development of the chromatogramms.

4-Benzyloxy-7-hydroxycoumarin **4**: 0.6 ml (5 mmol) of benzyl chloride was added dropwise to the solution of 0.89 g (5 mmol) of 4,7-dihydroxycoumarin **1** and 0.42 g (5 mmol) of sodium bicarbonate in 5 ml of DMFA and 2 ml of water; reaction mixture was stirred then at 45-50°C for 10 hours (TLC control with system B) and poured into water; unreacted **1** was washed out by hot water from the product precipitate; compounds **4** and 6 were separated and purified by column chromatography -

4, yield 35% , mp 242-243°C (Lit.(9) 243-244°C), R_f 0.34 (system B); ^{1}H NMR ($CDCl_3$, J/Hz), d: 5.64 (s, 1H, 3-H), 7.73 (d, 1H, 5-H, $J_{5,6}$=8.8), 6.75 (dd, 1H, 6-H, $J_{6,5}$=8.8, $J_{6,8}$=2.9), 6.80 (d, 1H, 8-H, $J_{8,6}$=2.9), 5.14 (s, 2H, -O-CH_2-), 7.42 (s, 5H, Ph).

6, yield 5% , mp 252.5-253 °C (Lit. (9) 253-254°C), R_f 0.61 (system B), ^{1}H NMR ($CDCl_3$, J/Hz), d: 7.62 (d, 1H, 5-H, $J_{5,6}$=8.8), 6.78 (dd, 1H, 6-H, $J_{6,5}$=8.8, $J_{6,8}$=2.9), 7.10 (d, 1H, 8-H, $J_{8,6}$=2.9), 4.2 (s, 2H, -CH_2-), 7.35 (s, 5H, Ph).

3-Benzyl-4,7-dihydroxycoumarin **6**: 0.23 ml (2 mmol) of benzyl chloride was added dropwise to the solution of 0.35 g (2 mmol) of **1** and 0.17 g (2 mmol) of sodium bicarbonate in 15 ml of methanol; reaction mixture was stirred then at boiling for 10 hours; methanol was partly distilled off, precipitate

was washed by hot water from unreacted **1** and recrystallized from alcohol - **6**, yield 10%, mp 252.5-253°C

7-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-benzyloxycoumarin **7**: 0.41 g of **2** was added slowly to solution of 0.27 g of **4** in mixture of 0.9 ml of 5% aqueous sodium hydroxide and 3 ml of acetone; reaction mixture was stirred then for 48 hours at room temperature; precipitate was filtered off and dissolved in chloroform; this solution was washed by 2% aqueous sodium hydroxide from unreacted **4**; chloroform was distilled off and precipitate was recrystallized from ethanol -

7, yield 66%, mp 198-199°C, R_f 0.49 (system B); ^{1}H NMR (acetone-d_6, J/Hz), δ : 5.69 (s, 1H, 3-H), 7.77 (d, 1H, 5-H, $J_{5,6}$=8.6), 6.89 (dd,1H, 6-H, $J_{6,5}$=8.6, $J_{6,8}$=2.4), 6.93 (d, 1H, 8-H, $J_{8,6}$=2.4), 2.04, 2.06, 2.10, 2.11 (s, 12 H, Acetyl), 5.19, 5.32 (c, 2H, -O-CH_2-Ph, -O-CH_2-Ac), 5.11- 5.32, 4.13- 4.33, 3.90 (m, 7H, glucopyranosyl), 7.43 (m, 5H, Ph).

7-O-(β-D-glucopyranosyl)-4-benzyloxycoumarin **8**: 2M sodium methylate solution in methanol was added to solution of 0.11 g (1.8 mmol) of **7** in 25 ml of methanol for the final pH equal to 7.5-8.0; reaction mixture has been kept then at room temperature for a night and treated by ion exchange resin KU-2 for the final pH equal to 7.0; compound **8** was separated by concentration of the solvent and recrystallization of resulted precipitate from ethanol -

8, yield 79.5%, mp 138-139°C, R_f 0.25 (system A); ^{1}H NMR (acetone-d_6, J/Hz), d : 5.77 (s, 1H, 3-H), 7.80 (d, 1H, $J_{5,6}$=8.8), 6.87 (dd, 1H, 6-H, $J_{6,5}$=8,8, $J_{6,8}$=2,4), 7.00 (d, 1H, 8-H, $J_{8,6}$=2.4), 5.37 (s, 2H, -O-CH_2-Ph), 7.43 (s, 5H, Ph), 4.20-4.62, 3.46-3.74, 3.93 (m, 7H, glucopyranosyl).

7-O-(β-D-glucopyranosyl)-4-hydroxycoumarin **5**: mixture of 0.109 g (2.5 mmol) of **8** in 50 ml of methanol and 0.08 g of catalyst Pd/C was stirred in presence of hydrogen at room temperature for 8 hours; compound **5** was separated by concentration of the solvent and recrystallization of resulted precipitate from acetone -

5, yield 52%, mp 247-248°C, R_f 0.10 (system A); ^{1}H NMR (D_2O, J/Hz), d : 7.80 (d, 1H, 5-H, $J_{5,6}$=8.8), 6.87 (dd, 1H, 6-H, $J_{6,5}$=8.8, $J_{6,8}$=2.1), 6.78 (1H, 8-H, $J_{8,6}$=2.1), 5.03 (d, 1H, 1'-H, $J_{1',2'}$=7.3), 3.36-3.88, 5.19 (m, 6H, Glucopyranosyl), ^{1}H NMR ($CDCl_3$, J/Hz), d: 5.64 (s, 1H, 3-H), 7.73 (d, 1H, 5-H, $J_{5,6}$=8.8), 6.75 (dd, 1H, 6-H, $J_{6,5}$=8.8, $J_{6,8}$=2.9), 6.80 (d, 1H, 8-H, $J_{8,6}$=2.9), 5.14 (s, 2H, -O-CH_2-), 7.42 (s, 5H, Ph); signal of 3-H is not seen due H/D exchange in D_2O.

4-O-(β-D-2,3,4,6-tetra-O-acetylglucopyranosyl)-7-hydroxycoumarin 9: 3.14 g (7.6 mmol) of **2** was added to solution of 1.36 g (7.6 mmol) of **1** and 0.65 g (7.6 mmol) of sodium bicarbonate in mixture of 20 ml of DMFA and 5 ml of water; reaction mixture was stirred then at 50-55°C for 10 hours and poured into water; unreacted **1** was then extracted from precipitate by 5% sodium bicarbonate solution; compound 9 was separated by colunm chromatography (silicagel, eluent - chloroform/acetone = 9/1) and recrystallization from ethanol -

9, yield 20%, mp 205-206°C, R_f 0.68 (system A), 0.32 (system B); ^1H NMR ($CDCl_3$, J/Hz), d : 5.77 (s, 1H,3-H), 7.80 (d, 1H, 5-H, $J_{5,6}$=8.8), 6.80 (dd, 1H, 6-H, $J_{6,5}$=8.8, $J_{6,8}$=2.4), 6.85 (d, 1H, 8-H, $J_{8,6}$=2.4), 2.06, 2.06, 2.07, 2.11 (s, 12H, Acetyl), 5.11-5.48, 3.95, 4.17-4.33 (m, 7H, Glucopyranosyl).

4-O-(β-D-Glucopyranosyl)-7-hydroxycoumarin **3**: 2M sodium methylate solution in methanol was added to solution of 0.1 g (2 mmol) of **9** in 25 ml of methanol for the final pH equal to 7.5-8.0; reaction mixture has been kept then at room temperature for a night and treated by ion exchange resin KU-2 for the final pH equal to 7.0; compound **3** was separated by concentration of the solvent and recrystallization of resulted precipitate from ethanol -

3, yield 80%, mp 237-238°C, R_f 0.15 (system A); ^1H NMR (DMSO-d_6, J/ Hz), d : 5.77 (s, 1H, 3-H), 7.80 (d, 1H, 5-H, $J_{5,6}$=8.8), 6.80 (dd, 1H, 6-H, $J_{6,5}$=8.8, $J_{6,8}$=2.0), 6.71 (d, 1H, 8-H, $J_{8,6}$=2.0), 5.05 (d, 1H, 1'-H, $J_{1',2'}$=7.0), 3.28-4.04, 5.22 (m, 6H, Glucopyranosyl).

Conclusions

Selective glucosylation of 4,7-dihydroxycoumarin is based on different acidity of its two hydroxyl functions. This compound is directly glucosylated at 4-hydroxyl group when both hydroxyl groups are unprotected. 7-Hydroxyl group is glucosylated when 4-hydroxyl function is protected via 4-benzyloxy-7-hydroxycoumarin formation.

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.

References

(1) N.P.Maksjutina, Rastitel'nie Lekarstvennie sredstva, Zdorovje, Kiev, 1985

(2) D.A.Muravjeva, Farmakognosija, Medizina, Moskva, 1978

(3) R.D.H.Murray, The Natural Coumarins, Occurence, Chemistry and Biochemistry, Wiley Interscience, New York, 1982

(4) R.D.H.Murray, Nat. Prod. Reports, 6, 551 (1989)

(5) E.X.Batirov, M.P.Yuldashev and V.M.Malikov, Khimija prirodnih soedinenii, 577 (1990)

(6) R.Mata, F.Calzada and M.P.Garcia, J. Nat. Prod., 50, 866 (1987)

(7) K.W.Merz, W.Hagemann, Arch. Pharm., 282 (1944)

(8) D.R. Buckle, D.J.Outed and J.W.Ross, J. Med. Chem. 22, 159 (1979)

(9) D.Anker and J.C. Massicot, Bull. Soc. Chem. France, 2181 (1969)

(10) O.S. Wolfbeis and G. Uray, Monatshefte fur Chem., 109, 123 (1978)

(11) A.K. Bauer and R. Schoder, Arch. Pharm. 53, 259 (1929)

Received June 5, 1996