REACTIONS OF 4-HYDROXYCOUMARIN WITH HETEROCYCLIC ALDEHYDES

RENATA GAŠPAROVÁ[1], KATARÍNA KOTLEBOVÁ[1], MARGITA LÁCOVÁ[2]

[1]*Department of Chemistry, University of SS. Cyril and Methodius, J. Herdu 2, Trnava, SK-917 01, Slovak Republic (gasparor@ucm.sk)*
[2]*Department of Organic Chemistry, Comenius University, Mlynská dolina CH-2, Bratislava, SK-842 15, Slovak Republic (lacova@fns.uniba.sk)*

Abstract: Reactions of 4-hydroxycoumarin **1** with heterocyclic aldehydes **2-4** led to bis-4-hydroxycoumarin derivatives **5-7** under microwave irradiation as well as under the classical heating. The subsequent reactions of products **5-7** are described. 4,4'-Epoxydicoumarins **8**, **9** were prepared by the reaction of **5-7** in acetic acid / *p*-toluenesulfonic acid medium. Compound **10** was prepared by the reaction of **5** in acetic anhydride in the presence sodium acetate. Dioxocine-1,15-dione **11** was prepared by the reaction of **6** with dichloromethane in sodium hydroxide-toluene.

Key words: coumarin, 4-oxo-4*H*-chromene, furan, furo[3,2-*b*]pyrrole, microwave

1. Introduction

Coumarins are biologicaly active compounds with antifungal, antineoplastic, antibacterial, spasmolytic or cytotoxic activity (STANCHEV *et al*., 2007; JUNG *et al.*, 2004). 4-Hydroxycoumarin **1** and its derivatives, e.g. warfarin and dicoumarol are known as anticoagulants.

4-Hydroxycoumarin **1** reacts with aromatic or aliphatic aldehydes to give bis-4-hydroxycoumarin derivatives (GIOVANI *et al*., 1991; MANOLOV *et al*., 2006; MAO *et al*., 2002), which are interesting for their biological activity and they can serve as intermediates for synthesis of various heterocycles (HAMDI *et al.*, 2008; YAMASHITA *et al*., 1987).

2. Experimental

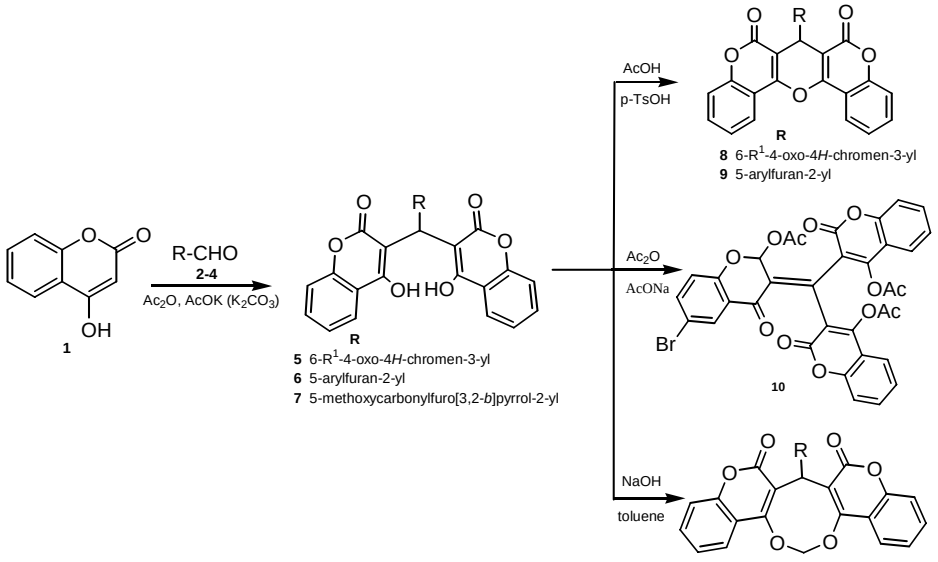
Melting points of products were determined on a Kofler hot plate apparatus and are uncorrected. All solvents were predistilled and dried appropriately prior to use. ^{1}H NMR spectra were obtained on a 300 MHz spectrometer VARIAN GEMINI 2000 in $CDCl_3$ or DMSO-d_6 or CF_3COOD with tetramethylsilane as an internal standard.

All microwave experiments were performed in a Panasonic NN-E205 type microwave oven. The apparatus was adapted for laboratory applications; n-hexane was used as coolant for the condenser.

*2.1 General procedure for **5** and **6***

A) Classical heating. A mixture of 4-hydroxycoumarin **1** (0.002 mol) and 6-R-4-oxo-4*H*-chromen-3-carbaldehyde **2** (or 5-arylfuran-2-carbaldehyde **3**) (0.001 mol) in acetic

anhydride (15 cm^3), in the presence of a catalytic amount of K_2CO_3 (or AcOK) was heated at 80 ºC for 3.5 h. After cooling the solid product was filtered off and crystallized from ethanol.



Scheme 1

B) Microwave method. A mixture of 4-hydroxycoumarin **1** (0.002 mol) and 6-R-4-oxo-4*H*-chromen-3-carbaldehyde **2** (or 5-arylfuran-2-carbaldehyde **3**) (0.001 mol) in acetic anhydride (4 cm^3), in the presence of a catalytic amount of K_2CO_3 (or AcOK) was irradiated in microwave oven for 4 min. The work-up was the same as described above.

2.1.1 3,3'-[(4-oxo-4H-chromen-3-yl)methylene]bis(4-hydroxy-2-oxo-2H-chromen-2-one) ***5a***

For $C_{28}H_{16}O_8$ (480.4): Mp: 275-280 °C; react. time 3.5h (A), 4min (B); yield: 81% (A), 82% (B); ^{1}H NMR ($CDCl_3$): 6.01 (d, 1H, CH J = 1.5 Hz); 7.34-7.36 (m, 1H, H-6); 7.39 (dd, 4H, H-8´, H-8´´, H-6´, H-6´´, ^3J = 7.97 Hz); 7.46 (d, 1H, H-8, J = 8.25 Hz); 7.59-7.61 (m, 2H, H-7´, H-7´´); 7.67 (m, 1H, H-7); 7.92 (d, 1H, H-2, J = 1.7 Hz); 8.04 (dd, 2H, H-5´, H-5´´, J = 7.9 Hz); 8.11 (dd, 1H, H-5, J = 7.9 Hz); 11.50 (bs, 2H, OH)

2.1.2 3,3'-[(6-Methyl-4-oxo-4H-chromen-3-yl)methylene]bis(4-hydroxy-2-oxo-2H-chromen-2-one) ***5b***

For $C_{29}H_{19}O_8$ (495.5): Mp: 276-278 °C; react. time 3.5h (A); yield: 79% (A); ^{1}H NMR (DMSO-d_6): 2.38 (s, 3H, CH_3); 6.07 (d, 1H, CH, J = 1.5 Hz); 7.19 (dd, 2H, H-8´, H-8´´, J = 7.5, 1.1 Hz); 7.24 (dd, 2H, H-6´, H-6´´, J = 7.5, 0.9 Hz); 7.46 (ddd, 2H,

H-7´, H-7´´, *J* = 8.2 , 1.5 Hz); 7.47-7.50 (m, 1H, H-7); 7.55 (dd, 1H, H-8, *J* = 8.6, 1.6 Hz); 7.69 (d, 1H, H-5, *J* = 1.5 Hz); 7.78 (dd, 2H, H-5´, H-5´´, *J* = 7.9, 1.5 Hz); 7.83 (d, 1H, H-2, *J* = 1.5 Hz); 17,2 (bs, 2H, OH)

2.1.3 3,3´-[(5-(4-Chlorophenyl)furan-2-yl)methylene]bis(4-hydroxy-2H-chromen-2-one) ***6a***

For $C_{29}H_{17}ClO_7$ (512.9): Mp: 265-269 °C; react. time 93h (A), 1.5h (B); yield: 68% (A), 70% (B); ^{1}H NMR (DMSO-d_6): 5.15 (s, 1H, CH); 6.52 (d, 1H, H – 4, *J* = 3.3 Hz); 6.91 (d, 1H, H – 3, *J* = 3.3 Hz); 7.41 (d, 2H, Ar - H, *J* = 8.5 Hz); 7.54 – 7.57 (m, 6H, Ar – H); 7.77 (ddd, 2H, H – 7´, *J* = 8.7, 1.2 Hz); 8.43 (dd, 2H, H – 5´, *J* = 8.5, 1.3 Hz).

2.1.4 3,3´-[(5-(4-Nitrophenyl)furan-2-yl)methylene]bis(4-hydroxy-2H-chromen-2-one) ***6b***

For $C_{29}H_{17}NO_9$ (457.5): Mp: 317-319 °C; react. time 51h (A), 1.5h (B); yield: 60% (A), 62% (B); ^{1}H NMR (DMSO-d_6): 5.19 (s, 1H, CH); 6.65 (d, 1H, H – 4, *J* = 3.3 Hz); 7.23 (d, 1H, H – 3, *J* = 3.3 Hz); 7.54 – 7.57 (m, 8H, Ar - H); 7.82 – 7.84 (m, 5H, Ar - H); 8.24 (d, 2H, H –8´´, *J* = 8.3 Hz).

2.1.5 3,3´-({5-[4-(3-Trifluoromethyl)phenyl]furan-2-yl}methylene)bis(4-hydroxy-2H-chromen-2-one) ***6c***

For $C_{30}H_{17}F_3O_7$ (546.5): Mp: 257-260 °C; react. time 70h (A), 1.5h (B); yield: 50% (A), 51% (B); ^{1}H NMR (DMSO-d_6): 5.17 (s, 1H, CH); 6.65 (d, 1H, H – 4, *J* = 3.3 Hz); 7.11 (d, 1H, H – 3, *J* = 3.3 Hz); 7.58 – 7.61 (m, 5H, Ar - H); 7.77 – 7.83 (m, 5H, Ar - H); 8.44 (d, 2H, H –8´´, *J* = 8.4 Hz).

2.1.6 3,3´-[(5-(4-Iodophenyl)furan-2-yl)methylene]bis(4-hydroxy-2H-chromen-2-one) ***6d***

For $C_{29}H_{17}IO_7$ (604.4): Mp: 248-252 °C; react. time 70h (A), 1.5h (B); yield: 51% (A), 53% (B); ^{1}H NMR (DMSO-d_6): 5.14 (s, 1H, CH); 6.52 (d, 1H, H – 4, *J* = 3.3 Hz); 6.92 (d, 1H, H – 3, *J* = 3.3 Hz); 7.35 (d, 2H, Ar - H, *J* = 8,7 Hz); 7.51 – 7.59 (m, 4H, H-6´,H-8´); 7.73 (d, 2H, Ar-H *J* = 8.7 Hz); 7.83 (ddd, 2H, H – 7´, *J* = 8.7, 1.5 Hz); 8.42 (dd, 2H, H – 5´, *J* = 8.4, 1.2 Hz).

2.2 Synthesis of Methyl 2-[bis(4-hydroxy-2H-chromen-3-yl)methyl]-4H-furo[3,2-b]pyrrole-5-carboxylate ***7***

A) Classical heating. A mixture of 4-hydroxycoumarin **1** (0.002 mol) and methyl 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate **4** (0.001 mol) in pyridine (15 cm^3) was heated at 105 ºC for 3 h. After cooling the solid product was filtered off and crystallized from ethanol.

B) Microwave method. A mixture of 4-hydroxycoumarin **1** (0.002 mol) and 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate **4** (0.001 mol) in pyridine (4 cm^3) was irradiated in microwave oven for 3 min. The work-up was the same as described above.

For $C_{27}H_{15}O_9N$ (497.4): Mp: 275-280 °C; react. time 3h (A), 3 min (B); yield: 52% (A), 56% (B); ^{1}H NMR (DMSO-d_6): 3.89 (s, 3H, CH_3); 6.90 (s, 1H, CH); 7.33-7.40 (m, 4H, Ar-H); 7.71-7.79 (m, 2H, Ar-H); 7.97 (m, 2H, Ar-H); 8.28 (s, 1H, H-3); 8.66 (s, 1H, H-6); 9.05 (s, 1H, NH); 12.46 (d, 2H, 2 OH).

*2.3 General procedure for **8** and **9***

Compound **5** (or **6**) (0.2 mmol) in acetic acid (5 cm^3) and catalytic amount of p-toluenesulfonic acid was heated at 80°C. After cooling the solid was filtered off and crystallized in ethanol.

*2.3.1 3,3´-[(4-Oxo-4H-chromen-3-yl)methylene]-4,4´-epoxydicoumarin **8***

For $C_{28}H_{14}O_7$ (462.4): Mp: 330-335 °C; react. time 2.5h; yield: 92%; ^{1}H NMR (DMSO-d_6): 4.77 (s, 1H, CH; 7.41-7.42 (m, 1H, H-6); 7.51-7.78 (m, 4H, H-8´, H-8´´, H-6´, H-6´´); 7.66 (d, 1H, H-8, *J* = 8,4 Hz); 7.76-7.78 (m, 3H, H-7´, H-7´´); 7.88 (d, 1H, H-5, *J* = 7,8 Hz); 8.45 (d, 2H, H-5´, H-5´´, *J* = 7.8 Hz); 8.71 (s, 1H, H-2).

*2.3.2 3,3´-[(5-(4-Nitrophenyl)furan-2-yl)methylene]-4,4´-epoxydicoumarin **9***

For $C_{28}H_{14}O_7$ (439.4): Mp: 322-325 °C; react. time 6h; yield: 62%; ^{1}H NMR (DMSO-d_6): 5.41 (s, 1H, CH); 6.58 (d, 1H, H – 4, *J* = 3.4 Hz); 7.10 (d, 1H, H – 3, *J* = 3.4 Hz); 7.35 – 7.50 (m, 6H, Ar - H); 7.62 – 7.74 (m, 4H, Ar - H); 8.10 – 8.13 (m, 2H, H – 3´, 5´).

*2.4 Synthesis of 2,4´,4´´-triacethyl-3-[bis(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl]-chromen-4-one **10***

A mixture of 4-hydroxycoumarin **1** (0.002 mol) and 6-bromo-4-oxo-4*H*-chromen-3-carbaldehyde **2** in acetic anhydride (5 cm^3) and catalytic amount of sodium acetate was heated at 80 ºC for 4.5 h. After cooling the solid product was filtered off and crystallized from ethanol.

For $C_{34}H_{21}BrO_{12}$ (701.4): Mp: 158-163 °C; yield: 66%; ^{1}H NMR ($CDCl_3$): 2.09 (s, 3H, CH_3); 2 x 2.18 (s, 3H, CH_3); 7.12 (d, 1H, H-8, *J* = 8.5 Hz); 7.35-7.41 (m, 4H, H-6´, H-6´´, H-8´, H-8´´); 7.63-7.67 (m, 2H, H-7´, H-7´´); 7.66 (d, 1H, H-5, *J* = 2.4 Hz); 7.78 (s, 1H, H-2); 7.96-8.07 (m, 3H, H-5´, H-5´´, H-7).

*2.5 Synthesis of 16-[5-(4-Iodophenyl)furan-2-yl]-1H,15H,16H-dibenzopyrano[3,4-g:4'3'-d]dioxocine-1,15-dione **11***

A mixture of compound **6d** (0.4 mmol), dichloromethane (0.8 mmol) and sodium hydroxide (0.8 mmol) in toluene (3 cm^3) was heated at 60°C for 117 h. After cooling the solid was filtered off and crystallized in ethanol.

For $C_{30}H_{17}IO_7$ (616.4): Mp: ›350 °C; yield: 47%; ^{1}H NMR (CF_3COOD): 4.36 (s, 2H, CH_2); 5.32 (s, 1H, CH); 6.57 (d, 1H, H – 3, *J* = 3.3 Hz); 7.26 –7.51 (m, 9H, H – 4, Ar - H); 7.64 – 7.70 (m, 2H, H -3´,5´); 8.10 – 8.13 (m, 2H, H - 2´´, 12´´).

3. Results and discussion

Reaction of **1** with 6-substituted 4-oxo-4*H*-chromene-3-carbaldehydes **2** led to bis(4-hydroxy-2-oxo-2*H*-chromen-2-ones **5** in 79-81% yields after 3.5h of heating. Microwave-assisted method gave the comparable yield of **5a** (82%), but the reaction time was remarkably shortened (4min). The use of 5-arylfuran-2-carbaldehydes **3** in reaction with **1** led to derivatives **6** in 50-68 % yields.. The effect of microwave irradiation was manifested in the remarkable shortening of reaction time from 51-93 h under classical heating to 1.5h in microwave oven.

When 4-hydroxycoumarin **1** was treated with methyl 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate **4** in pyridine either by classical heating for 3h or in microwave oven for 4 min, product 7 was obtained in comparable yields (52% and 56%, respectively).

Epoxycoumarins **8** and **9** were obtained in 92% and 62 % yields, respectively by the dehydratation of **5** or **6** in acetic acid / p-toluenesulfonic acid medium.

The heating of 4-hydroxycoumarin **1** and 6-bromo-4-oxo-4*H*-chromen-3-carbaldehyde in acetic anhydride led to 3-acetyloxy derivative **10** in 66% yield.
Dioxocine-1,15-dione **11** was prepared in 47% yield by reaction of **6d** with dichloromethane and sodium hydroxide in toluene. The reaction required long reaction time (117 h). The pursuit to shorter the reaction time by the influence of microwave irradiation was not successful and only decomposition polymeric product was isolated. All structures were confirmed by ^{1}H NMR spectra.

4. Conclusions

4-Hydroxycoumarin **1** reacted with heterocyclic aldehydes **2**-**4** to give bis-derivatives **5-7**, which served as intermediates for synthesis of epoxycoumarins **8**, **9,** 2,4´,4´´-triacethylderivative **10** and dioxocine-1,15-dione **11**, respectively. Microwave irradiation has proved to be a suitable method for enhancement of reactions of **1** with aldehydes.

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