Synthesis and Reactions of 2-(4-Oxochromen-3-yl) benzothiazolium and -benzoxazolium Bromides

Renata Gašparová[1*], Mário Kleštinec[2], Pavol Koiš[2], Margita Lácová[2]

[1]Department of Chemistry, Faculty of Natural Sciences, University of St. Cyril and Methodius, Námestie Jozefa Herdu 2, Sk-917 01 Trnava, Slovak Republic
[2]Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, Mlynská dolina CH-2, SK-842 15 Bratislava, Slovak Republic

[*]gasparor@ucm.sk

Abstract

Benzothiazolium and benzoxazolium bromides 4, 5 were synthesized either by one-pot condensation of substituted 4-oxochromene-3-carboxaldehydes 1 with 2-methylbenzothiazole (2a) or 2-methylbenzoxazole (2b) and benzyl bromide or by condensation of 1 with 2-methylbenzothiazolium or 2-methylbenzoxazolium bromides 3 under microwave irradiation or by the classical heating. The advantage of microwave irradiation in comparison with classical reactions was reflected in the significantly reduced reaction time and increased yields. Reactions of resulting benzothiazolium salt 4b with primary and secondary amines led to 2-substituted derivatives 6 or phenylpyrazolo[3,4-*b*]pyridine 7.

Keywords: benzoxazolium bromides, benzothiazolium bromodes, microwave irradiation, 4-oxochromene-3-carboxaldehydes

Introduction

3-Substituted 4-oxochromene derivatives are known as useful building blocks for various heterocycles due to their reactivity towards nucleophiles or ability to rearrange under mild conditions. (Abass 2003, Stankovičová 2001). A large number of 4-oxochromene derivatives occur widely in nature and exhibit variety of biological activities, e.g. antialgal (Kráľová 1998), antifungal, antiparasitic (Caujolle 1993) or antimycobacterial (Gašparová 1997). Many benzothiazole derivatives were tested for a different biological activity (Kráľová 1994, Sutoris 1988) and also examined for their plant growth regulating properties. They may stimulate the plant regeneration, activity of peroxidases, the prolongation of growth and may induce the dediferentiation and morphogenesis in *in vitro* conditions (Davies 1995).

In connection with this, and as an extension of our studies on the synthesis of chromene derivatives (Krutošíková 2000, Melykian 1993, Gáplovský 2000), we decided to synthesize new 4-oxochromene-derived benzothiazolium and benzoxazolium salts **4, 5** under microwave irradiation as well as at the classical conditions and investigate some reactions of prepared compounds **4** with primary and secondary amines to obtain new derivatives **6** and **7**. The effects of bromides 4, 5 were tested on the germination and early growth of cucumber and corn seedlings. The most effective compounds with stimulating activity on cucumber seedlings was 4a, 4f and the best retardant activity on corn seedlings showed 5b and 4b (Henselová 2008).

Experimental

Elemental analyses and ^{1}H NMR spectra were used to characterize all products. Melting points of products were determined on a Kofler hot plate apparatus and are uncorrected. All solvents were pre-distilled and dried appropriately prior to use. Elemental analyses were determined using a Carlo Erba Instrumentazione 1106-Elemental analyzer. ^{1}H NMR spectra were obtained on a 300 MHz spectrometer VARIAN GEMINI 2000 in DMSO-*d*6 at 100 °C or CF_3COOH-*d*, tetramethylsilane being the internal reference. IR spectra were measured on a Specord 75IR spectrometer in nujol. All microwave experiments were performed in a Lavis–1000 MultiQuant laboratory microwave oven using a power output of 270 W. The apparatus was adapted for laboratory application with magnetic stirring and an external reflux condenser. The course of reactions was monitored by TLC chromatography in ethyl acetate – n-hexane. The protocol in (Nohara 1974) was followed for the synthesis of 4-oxochromene-3-carboxaldehydes and in (Kráľová 1998, Gašparová 1997) for benzothiazolium and benzoxazolium salts by the classical procedure.

3-Benzyl-2-methylbenzothiazolium bromide (3a)

A stirred mixture of 2-methylbenzothiazole (**2a**) (0.5 g, 3.35 mmol) and benzylbromide (0.573 g, 3.35 mmol) in anhydrous nitromethane (2 mL), or acetonitrile (2 mL) was irradiated for 20 min at 270 W in microwave oven. Pale-green precipitate was diluted by acetone, filtered off and dried. Yield: 55 % (acetonitrile) or 70 % (nitromethane). The product was identical to that prepared by classical method (Kráľová 1998, Gašparová 1997).

Synthesis of 3-Benzyl-2-[(4-oxochromen-3-yl) ethenyl] benzothiazolium and – benzoxazolium bromides 4,5

Method A

A stirred mixture of 4-oxochromene-3-carboxaldehyde (**1a**) (1 mmol), 2-methylbenzothiazole (**2a**) (1 mmol) and benzylbromide (1 mmol) in anhydrous nitromethane (2 mL) was irradiated at 270 W. After cooling, the solid product was filtered off, washed with warm acetone and crystallized (acetonitrile).

3-Benzyl-2-[(4-oxochromen-3-yl) ethenyl] benzothiazolium bromide (4a)

Yield 0.36 g (76 %); React. time 10 min; m.p. 215 - 217 °C (acetonitrile). Anal. Calcd. for $C_{25}H_{18}BrNO_2S$ (476.4) C, 63.03; H 3.81; N 2.94; S 6.73; Br 16.77. Found C, 63.218; H 3.86; N 2.82; S 6.35; Br 17.06 %. IR: 1655 (ν /C=O/), 1618 (ν /C=C/). ^{1}H NMR δ_H DMSO-d_6 : 9.17 (s,1H, H-2) ; 8.69 (d, 1H, *J*(9,10) = 15.66, H-9); 8.59 (d, 1H, *J*(7',6') = 7.69, H-7'); 8.31 (d, 1H, *J*(4',5') = 8.24, H-4'); 8.21 (d, 1H, *J*(5,6) = 7.69, H-5); 8.11 (d, 1H, *J*(10,9) = 15.66, H-10); 7.81 - 7.89 (m, 3H, H-6, H-7, H-5'); 7.77 (d, 1H, *J*(8,7) = 8.24, H-8); 7.71 (t, 1H, *J*(6',5') = 7.97, *J*(6',7') = 7.14, H-6'); 7.39 (s, 5H, C_6H_5); 6.15 (s, 2H, CH_2). The compounds **4b-5e** were prepared similarly.

3-Benzyl-2-[(6-methyl-4-oxochromen-3-yl) ethenyl] benzothiazolium bromide (4b)

Yield 68 %; React. time 8 min; m.p. 171 - 173 °C (acetonitrile). Anal. Calcd. for $C_{26}H_{20}BrNO_2S$ (490.4) C, 63.89; H 4.11; N 2.86; S 6.54; Br 16.30. Found C, 63.68; H 4.32; N 2.73; S 6.38; Br 16.58 %. IR:1660 (ν /C=O/), 1615 (ν /C=C/). ^{1}H NMR δ_H DMSO-d_6 : 9.18 (s, 1H, H-2); 8.70 (d, 1H, *J*(9,10) =15.4, H-9); 8.52 (d,1H, *J*(7',6') = 10, H-7'); 8.35 (d, 1H, *J*(4',5') = 9.8, H-4'); 8.07 (d, 1H, *J*(10,9) = 15.4, H-10); 7.96 (d, 1H, *J*(5,7) = 1.7, H-5); 7.80 -

7.89 (m, 2H, H-7, H-5'); 7.71 - 7.72 (m, 2H, H-8, H-6'); 7.40 (s, 5H, C_6H_5); 6.15 (s, 2H, CH_2); 2.47 (s, 3H, CH_3).

3-Benzyl-2-[(6-chloro-4-oxochromen-3-yl) ethenyl] benzothiazolium bromide (4c)

Yield 76 %; React. time 8 min; m.p. 242 – 245 °C (acetonitrile). Anal. Calcd. for $C_{25}H_{17}BrClNO_2S$ (510.8) C, 58.78; H 3.35; N 2.74; S 6.28; Br 15.64; Cl 6.94. Found C, 58.25; H 3.42; N 2.61; S 6.06; Br 15.21; Cl 6.58 %. IR: 1652 (ν /C=O/), 1608 (ν /C=C/), 785 (ν /C-Cl/). ^{1}H NMR δ_H CF_3COOH-*d*: 9.01 (s, 1H, H-2); 8.74 (d, 1H, *J*(9,10) = 15.38, H-9); 8.33 - 7.76 (m, 8H, H-5, H-7, H-8, H-10, H-4', H-5', H-6', H-7'); 7.51 - 7.31 (m, 5H, C_6H_5); 6.11 (s, 2H, CH_2).

3-Benzyl-2-[(6-bromo-4-oxochromen-3-yl) ethenyl] benzothiazolium bromide (4d)

Yield 81 %; React. time 7 min; m.p. 253 – 256 °C (acetonitrile). Anal. Calcd. for $C_{25}H_{17}Br_2ClNO_2S$ (555.3) C, 54.08; H 3.09; N 2.52; S 5.77; Br 28.78. Found C, 53.84; H 3.12; N 2.47; S 5.68; Br 29.12 %. IR: 1648 (ν /C=O/), 1600 (ν /C=C/), 700 (ν /C-Br/). ^{1}H NMR δ_H DMSO-d_6 : 9.21 (s, 1H, H-2); 8.66 (d, 1H, *J*(9,10) =15.5, H-9); 8.52 (d, 1H, *J*(7',6') = 8, H-7'); 8.34 (d, 1H, *J*(4',5') = 8, H-4'); 8.24 (d, 1H, *J*(5,7) = 1.9, H-5); 8.06 (d, 1H, *J*(10,9) =15.6, H-10); 8.01 (dd, 1H, *J*(7,8) = 7.2, *J*(7,5) = 2, H-7); 7.79 - 7.88 (m, 3H, H-8, H-5', H-6') 7.37 - 7.41 (m, 5H, C_6H_5); 6.16 (s, 2H, CH_2).

3-Benzyl-2-[(6-nitro-4-oxochromen-3-yl) ethenyl] benzothiazolium bromide (4e)

Yield 81 %; React. time 4.5 min; m.p. 294 – 297 °C (acetonitrile). Anal. Calcd. for $C_{25}H_{17}BrN_2O_4S$ (521.4) C, 57.59; H 3.28; N 5.37; S 6.15; Br 15.33. Found C, 57.32; H 3.35; N 5.14; S 5.95; Br 14.82 %. IR: 1660 (ν /C=O/), 1605 (ν /C=C/), 1340 (ν /NO_2). ^{1}H NMR δ_H DMSO-d_6 : 9.36 (s, 1H, H-2); 8.80 (d, 1H, *J*(5,7) = 2.9, H-5); 8.74 (d, 1H, *J*(9,10) =15.0, H-9); 8.63 (dd, 1H, *J*(7,8) = 9.15, *J*(7,5) = 2.9, H-7); 8.59 (d, 1H, *J*(7',6') = 8.55, H-7'); 8.37 (d, 1H, *J*(4',5') =8.24, H-4'); 8.11 (d, 1H, *J*(10,9) =.15, H-10); 8.05 (d, 1H, *J*(8,7) = 9.15, H-8); 7.79 - 7.92 (m, 2H, H-5', H-6'); 7.33 - 7.46 (m, 5H, C_6H_5); 6.21 (s, 2H, CH_2).

3-Benzyl-2-[(6-hydroxy-4-oxochromen-3-yl) ethenyl] benzothiazolium bromide (4f)

Yield 63 %; React. time 15 min; m.p. 232 – 235 °C (acetonitrile). Anal. Calcd. for $C_{25}H_{18}BrNO_3S$ (492.4) C, 60.98; H 3.68; N 2.84; S 6.51; Br 16.23. Found C, 60.68; H 3.62; N 3.02; S 6.01; Br 16.72 %. IR: 3355 (*v* /OH), 1659 (*v* /C=O/), 1615 (*v* /C=C/). ^{1}H NMR δ_H CF_3COOH-*d*: 10.21 (bs, 1H, OH); 9.05 (s, 1H, H-2); 8.77 (d, 1H, *J*(9,10) = 15.3, H-9); 7.89 - 7.53 (m, 6H, H-5, H-7, H-8, H-4', H-7', H-10); 7.46 – 7.31 (m, 7H, H-5', H-6', C_6H_5); 6.14 (s, 2H, CH_2).

3-Benzyl-2-[(7-hydroxy-4-oxochromen-3-yl)ethenyl] benzothiazolium bromide (4g)

Yield 45 %; React. time 5 min; m.p. 231 – 233 °C (acetonitrile). Anal. Calcd. for $C_{25}H_{18}BrNO_3S$ (492.4) C, 60.98; H 3.68; N 2.84; S 6.51; Br 16.23. Found C, 60.39; H 3.28; N 2.35; S 6.32; Br 16.09 %. IR: 3375 (*v* /OH), 1660 (*v* /C=O/), 1620 (*v* /C=C/). ^{1}H NMR δ_H CF_3COOH-*d*: 10.19 (bs, 1H, OH); 9.01 (s, 1H, H-2); 8.71 (d, 1H, *J*(9,10) = 15.3, H-9); 7.84-7.46 (m, 6H, H-5, H-6, H-8, H-4', H-7', H-10); 7.42 – 7.22 (m, 7H, H-5', H-6', C_6H_5); 6.12 (s, 2H, CH_2).

3-Benzyl-2-[(7,8-dimethyl-4-oxochromen-3-yl) ethenyl] benzothiazolium bromide (4h)

Yield 79 %; React. time 3.5 min; m.p. 255 – 258 °C (acetonitrile). Anal. Calcd. for $C_{27}H_{22}BrNO_2S$ (504.4) C, 64.29; H 4.40; N 2.78; S 6.36; Br 15.84. Found C, 64.03; H 4.49; N 2.54; S 6.48; Br 16.02 %. IR: 1660 (/C=O/), 1605 (*v* /C=C/). ^{1}H NMR δ_H CF_3COOH-*d*: 9.11 (s, 1H, H-2); 8.87 (d, 1H, *J*(9,10) = 15.4, H-9); 8.52 – 7.69 (m, 7H, H-5, H-6, H-4', H-5', H-6', H-7', H-10); 7.24 (s, 5H, C_6H_5); 6.12 (s, 2H, CH_2); 2.53 (s, 3H, CH_3); 2.34 (s, 3H, CH_3).

3-Benzyl-2-[(8-chloro-6-methyl-4-oxochromen-3-yl) ethenyl] benzothiazolium bromide (4i)

Yield 79 %; React. time 6 min; m.p. 255 – 258 °C (acetonitrile). Anal. Calcd. for $C_{26}H_{19}BrClNO_2S$ (524.8) C, 59.50; H 3.65; N 2.67; S 6.11; Br 15.22 ; Cl 6.75. Found C, 59.30; H 3.57; N 2.76; S 5.89; Br 15.84; Cl 6.25 %. IR: 1662 (*v* /C=O/), 1600 (*v* /C=C/), 770 (*v* /C-Cl/). ^{1}H NMR δ_H DMSO-d_6 : 9.29 (s, 1H, H-2); 8.70 (d, 1H, *J*(9,10) = 15.7, H-9); 8.52 (d, 1H, *J*(7',6') = 8.7, H-7'); 8.36 (d, 1H, *J*(4',5') = 8.6, H-4'); 8.08 (d, 1H, *J*(10,9) =15.7, H-10); 7.83-7.92 (m, 4H, H-5, H-7, H-5', H-6'); 7.39 (s, 5H, C_6H_5); 6.16 (s, 2H, CH_2); 2.46 (s, 3H, CH_3).

3-Benzyl-2-[(7,8-dihydroxy-4-oxochromen-3-yl) ethenyl] benzothiazolium bromide (4j)

Yield 57 %; React. time 7 min; m.p. 239 – 242 °C (acetonitrile). Anal. Calcd. for $C_{25}H_{18}BrNO_4S$ (508.4) C, 59.06; H 3.57; N 2.76; S 6.31; Br 15.72. Found C, 58.64; H 3.73; N 2.65; S 6.03; Br 15.23 %. IR: 3550, 3500 (*v*/OH), 1664 (*v* /C=O/), 1625 (*v* /C=C/). ^{1}H NMR δ_H CF_3COOH-*d*: 10.25 (bs, 2H, OH); 8.98 (s, 1H, H-2); 8.84 (d, 1H, *J*(9,10) = 15.5, H-9); 8.32 – 7.87 (m, 7H, H-5, H-6, H-4', H-5', H-6', H-7', H-10); 7.45 (s, 5H, C_6H_5); 6.00 (s, 2H, CH_2).

3-Benzyl-2-[(4-oxochromen-3-yl) ethenyl] benzoxazolium bromide (5a)

Yield 54 %; React. time 2.5 min; m.p. 221 – 223 °C (acetonitrile). Anal. Calcd. for $C_{25}H_{18}BrNO_3$ (460.3) C, 65.23; H 3.94; N 3.04; Br 17.36. Found C, 64.94; H 3.82; N 3.04; Br 17.56 %. IR: 1658 (*v* /C=O/), 1615 (*v* /C=C/). ^{1}H NMR δ_H DMSO-d_6 : 9.29 (s, 1H, H-2); 8.52 (d, 1H, *J*(9,10) = 15.68, H-9); 8.33 (d, 1H, *J*(10,9) = 15.65, H-10); 8.22 (dd, 1H, *J*(5,6) = 7.92, *J*(5,7)=1.65, H-5); 8.14 (d, 1H, *J*(4',5') = 7.44, H-4'); 8.06 (d, 1H, *J*(7',6') = 7.42, H-7'); 7.89-7.97 (m, 1H, H-7); 7.73-7.86 (m, 4H, H-6, H-8, H-5', H-6'); 7.36 - 7.86 (m, 5H, C_6H_5); 5.98 (s, 2H, CH_2).

3-Benzyl-2-[(6-methyl-4-oxochromen-3-yl) ethenyl] benzoxazolium bromide (5b)

Yield 51 %; React. time 3 min; m.p. 175 – 177 °C (acetonitrile). Anal. Calcd. for $C_{26}H_{20}BrNO_3$ (474.4) C, 65.83; H 4.25; N 2.95; Br 16.85. Found C, 66.07; H 4.72; N 3.03; Br 16.62 %. IR: 1648 (*v* /C=O/), 1610 (*v* /C=C/). ^{1}H NMR δ_H DMSO-d_6 : 9.20 (s, 1H, H-2); 8.73 (d, 1H, *J*(9,10) =15.6, H-9); 8.61 (d, 1H, *J*(7',6') = 9.7, H-7'); 8.55 (d, 1H, *J*(4',5') = 9.8, H-4'); 8.11 (d, 1H, *J*(10,9) = 15.6, H-10); 7.91 (d, 1H, *J*(5,7) = 2.1, H-5); 7.84 - 7.72 (m, 4H, H-7, H-8, H-5', H-6'); 7.39 (s, 5H, C_6H_5); 6.17 (s, 2H, CH_2); 2.44 (s, 3H, CH_3).

3-Benzyl-2-[(6-chloro-4-oxochromen-3-yl) ethenyl] benzoxazolium bromide (5c)

Yield 38 %; React. time 15 min; m.p. 275 – 278 °C (acetonitrile). Anal. Calcd. for $C_{25}H_{17}BrClNO_3$ (494.8) C, 60.69; H 3.46; N 2.83; Br 16.15; Cl 7.17. Found C, 60.64; H 3.82; N 2.81; Br 16.19; Cl 7.05 %. IR: 1658 (*v* /C=O/), 1605 (*v* /C=C/), 800 (*v* /C-Cl/). ^{1}H NMR δ_H CF_3COOH-*d*: 9.04 (s, 1H, H-2); 8.80 (d, 1H, *J*(9,10) = 15.2, H-9); 8.61- 7.96 (m, 8H, H-5, H-7, H-8, H-10, H-4', H-5', H-6', H-7'); 7.52- 7.39 (m, 5H, C_6H_5); 6.11 (s, 2H, CH_2).

3-Benzyl-2-[(6-bromo-4-oxochromen-3-yl) ethenyl] benzoxazolium bromide (5d)

Yield 41 %; React. time 12 min; m.p. 277 – 279 °C (acetonitrile). Anal. Calcd. for $C_{25}H_{17}Br_2NO_3$ (539.2) C, 55.69; H 3.18; N 2.60; Br 29.64. Found C, 55.92; H 3.31; N 2.73; Br 29.18 %. IR: 1660 (*v* /C=O/), 1620 (*v* /C=C/), 720 (*v* /C-Br/). ^{1}H NMR δ_H CF_3COOH-*d*: 9.25 (s, 1H, H-2); 8.73 (d, 1H, *J*(9,10) =15.43, H-9); 8.58 - 8.05 (m, 8H, H-5, H-7, H-8, H-10, H-4', H-5', H-6', H-7'); 7.41 (s, 5H, C_6H_5); 6.22 (s, 2H, CH_2).

3-Benzyl-2-[(7-hydroxy-4-oxochromen-3-yl) ethenyl] benzoxazolium bromide (5e)

Yield 42 %; React. time 10 min; m.p. 203 – 205 °C (acetonitrile). Anal. Calcd. for $C_{25}H_{18}BrNO_4$ (476.3) C, 63.04; H 3.81; N 2.94; Br 16.77. Found C, 62.84; H 3.69; N 2.87; Br 17.03 %. IR: 3290 (*v* /OH) 1670 (*v* /C=O/), 1620 (*v* /C=C/). ^{1}H NMR δ_H CF_3COOH-*d*: 10.26 (bs, 1H, OH); 9.17 (s, 1H, H-2); 8.76 (d, 1H, *J*(9,10) = 15.6, H-9); 7.88 - 7.53 (m, 6H, H-5, H-6, H-8, H-4', H-7', H-10); 7.46 – 7.20 (m, 7H, H-5', H-6', C_6H_5); 6.23 (s, 2H, CH_2).

Microwave Condensation of 4-Oxochromene-3-carboxaldehydes 1 with 3-Benzyl-2-methylbenzothiazolium and -benzoxazolium Bromides 3

Method B

A stirred mixture of 4-oxochromene-3-carboxaldehydes **1** (1 mmol) and 3-benzyl-2-methylbenzothiazolium bromide (**3a**) or 3-benzyl-2-methylbenzothiazolium bromide (**3b**) (1 mmol) in anhydrous nitromethane (2 mL) was irradiated at 270 W over the period as stated in Table 1. The products were isolated and purified in the manner identical to the method A.

Classical Condensation methods

Method C

A of 4-oxochromene-3-carboxaldehyde (**1a**) (1 mmol), 2-methylbenzothiazole (**2a**) or 2-methylbenzoxazole (**2b**) (1 mmol) and benzylbromide (1 mmol) in anhydrous nitromethane (2 mL) was was refluxed for 6 hours at 90 – 100 °C under argon atmosphere. After cooling, the solid products were isolated and purified in the manner identical to the method A.

Method D

A mixture of 4-oxochromene-3-carboxaldehydes **1** (1 mmol) and 3-benzyl-2-methylbenzothiazolium bromide (**3a**) or 3-benzyl-2-methylbenzothiazolium bromide (**3b**) (1 mmol) in anhydrous nitromethane (2 mL) was refluxed for 6 hours at 90 – 100 °C under argon atmosphere. The products were isolated and purified in the manner identical to the method A.

Reactions of 4 with *N*-bases

3-[2-(3-benzyl-1,3-benzothiazol-2(3*H*)-ylidene)ethylidene]- 2-(morpholin-1-yl)-4*H*-chroman -4-one (6a)

The mixture of 3-benzyl-2-(6-methyl-4-oxochromen-3-yl)ethenylbenzothiazolium bromide (**4b**) (1 mmol) and morpholine (2 mmol) was refluxed in ethanol (20 mL) at 80 – 90 °C. Then the reaction mixture was cooled, the red crystals were filtered off and crystallized (ethanol). Yield 0.32 g (65 %); React. time 1 h; m.p. 161 – 162 °C. Anal. Calcd. for $C_{30}H_{28}N_2O_3S$ (496.6) C, 72.55; H 5.66; N 5.64; S 6.45. Found C, 72.39; H 5.46; N 5.55; S 6.55. IR: 1668 (*v* /C=O/), 1642, 1630(*v* /C=C/), 1268 (*v* /C-N/). ^{1}H NMR δ_H DMSO-d_6: 7.49 (d, 1H, *J*(9,10) = 12.2, H-9);. 7.30-7.41 (m, 4H, H-4', H-5', H-6', H-7'); 7.10 - 7.21 (m, 5H, C_6H_5); 7.71 (d, 1H, *J*(5,7) =1.6, H-5); 7.68 (dd, 1H, *J*(7,8) = 8.21, *J*(7,5) = 1,95 H-7); 6.89 (d, 1H, *J*(8,7) = 8.24, H-8); 5.86 (d, 1H, *J*(10,9) =12.3, H-10); 5.62 (s, 1H, H-2); 5.13 (s, 2H, CH_2); 3.21 –3.40 (m, 4H, H-3", H-5"); 2.42 –2.81 (m, 4H, H-2", H-6"); 2.29 (s, 3H, CH_3). Products **6b** and **7** were prepared similarly.

3-[2-(3-benzyl-1,3-benzothiazol-2(3*H*)-ylidene) ethylidene]- 2-(piperidin-1-yl)-4*H*-chroman-4-one (6b)

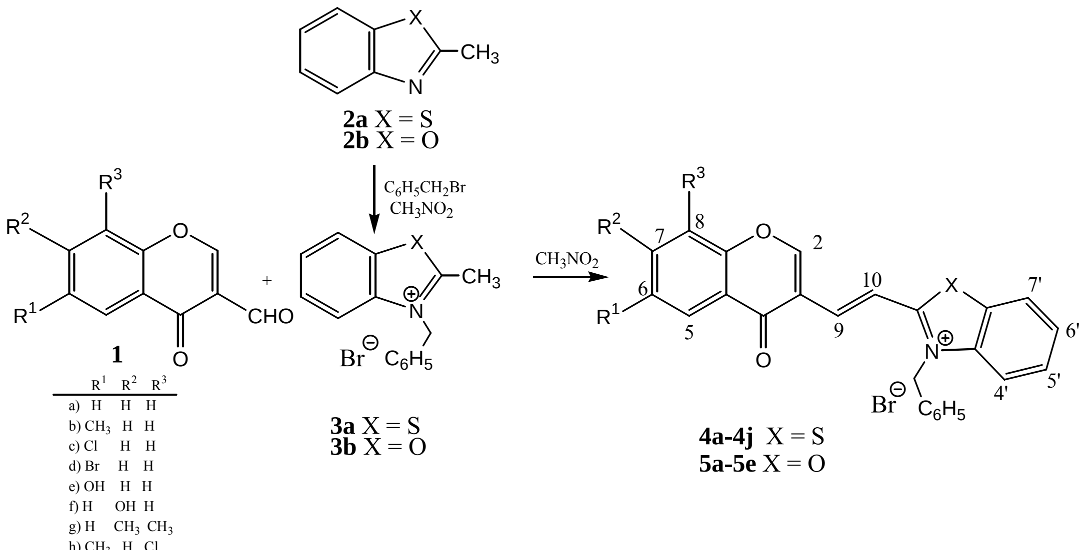
Yield 69 %; React. time 1 h; m.p. 182 – 184 °C (ethanol). Anal. Calcd. for $C_{31}H_{30}N_2O_2S$ (494.6) C, 75.27; H 6.11; N 5.66; S 5.48. Found C, 75.39; H 5.98; N 5.68; S 5.37 %. IR: 1670 (*v* /C=O/), 1640, 1630 (*v* /C=C/), 1270 (*v* /C-N/). ^{1}H NMR δ_H DMSO-d_6: 7.30-7.38 (m, 4H, H-4', H-5', H-6', H-7'); 7.11 - 7.23 (m, 5H, C_6H_5); 7.72 (d, 1H, *J*(5,7) =1.6, H-5); 7.45 (d, 1H, *J*(9,10) = 12.4, H-9);. 7.66 (dd, 1H, *J*(7,8) = 8.24, *J*(7,5) = 2.01 H-7); 6.77 (d, 1H, *J*(8,7) = 8.24, H-8); 5.92 (d, 1H, *J*(10,9) =12.4, H-10); 5.64 (s, 1H, H-2); 5.13 (s, 2H, CH_2); 2.37 – 2.49 (m, 4H, H-2", H-6"); 2.29 (s, 3H, CH_3); 1.51 - 1.60 (m, 4H, H-3", H-5"); 1.72 -1.78 (m, 2H, H-4").

3-(2-Hydroxy-5-methylbenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine (7)

Yield 60 %; React. time 1 h; m.p. 142 – 144 °C (ethanol). Anal. Calcd. for $C_{21}H_{17}N_3O_2$ (343.4) C, 73.38; H 4.99; N 12.23. Found C, 73.22; H 4.84; N 12.27 %. IR: 3230 (*ν* /OH), 1695 (*ν* /C=O/), 1639 (*ν* /C=N/). ^{1}H NMR δ_H DMSO-d_6: 10.51 (bs, 1H, OH); 8.94 (d, 1H, *J*(2,4) = 1.9, H-2); 8.47 (d, 1H, *J*(4,2) = 1.9, H-4); 8.26 (dd, 2H, *J*(3",2") =7.6, *J*(3",5") =1.1, H-3", H-5"); 7.55 (m, 3H, H-2", H-4", H-6"); 7.39 (d, 1H, J(6',4') = 0.8, H-6'); 7.38 (dd, 1H, *J*(4',3') = 7.7, *J*(4',6') = 0.8, H-4'); 7.04 (d, 1H, *J*(3',4') = 7.7, H-3'); 2.72 (s, 3H, CH_3); 2.28 (s, 3H, CH_3).

Results and Discussion

Substituted 2-[(4-oxochromen-3-yl)-ethenyl]benzothiazolium bromides 4a – 4j and 2-[(4-oxochromen-3-yl)-ethenyl]benzoxazolium bromides 5a - 5e were synthesized in two microwave-assisted methods (Scheme 1). The one-pot condensation of substituted 4-oxochromene-3-carboxaldehydes 1a – 1i with 2-methylbenzothiazole (2a) and benzylbromide in nitromethane under microwave irradiation for 3.5 - 15 min gave 45 – 81 % yields of 4a – 4j. Using 2-methylbenzoxazole (2b) led to 38 – 54 % of 5a – 5e after 2.5 – 15 min irradiation (Method A, Table 1).



Scheme 1

3-Benzyl-2-methylbenzothiazolium bromide 3a and 3-benzyl-2-methylbenzoxazolium bromide (3b) as the starting material were more efficient components for the condensation than 2–methylbenzothiazole 2a (or 2–methylbenzoxazole 2b) – benzylbromide. When aldehydes 1a – 1i were condensed with separately prepared 3-benzyl-2-methylbenzothiazolium bromide 3a in nitromethane under microwave irradiation for 5 – 8 min, products 4a – 4j were obtained in 56 – 90 % yields. Condensation of 1 with 3-benzyl-2-methylbenzoxiazolium bromide 3b gave 52 -77 % yields of 5a – 5e (Method B, Table 1).

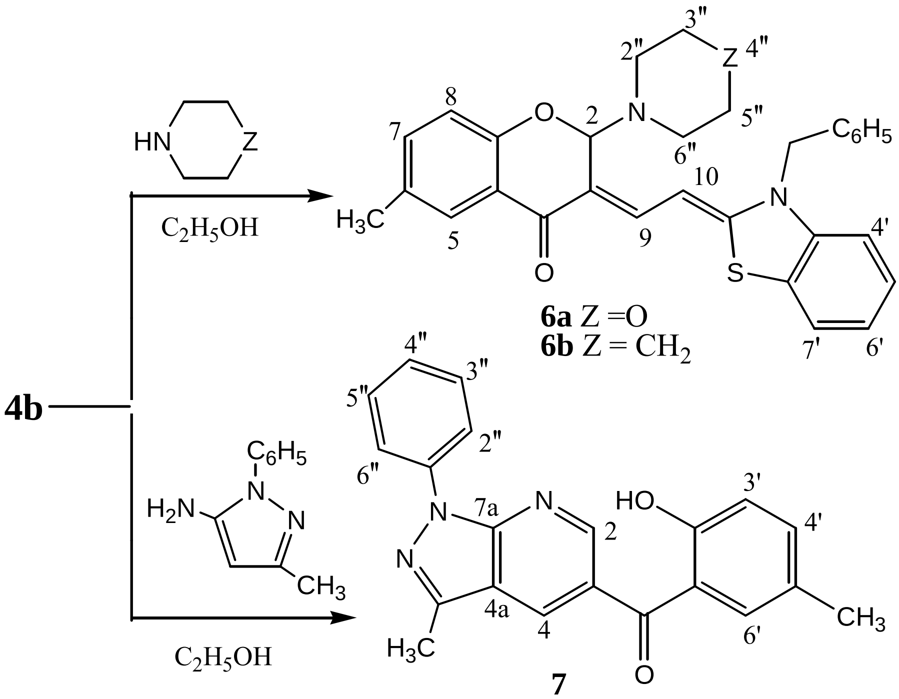
Classical one-pot reaction in the same reaction medium requires the heating at 100 °C to give lower yields of 4a - 4j (42 – 78 %) and 5a – 5e (30 – 49 %), respectively and the reaction time was prolonged to 4 – 5.5 h (Method C, Table1). Classical heating of the mixture of 1 and 3 in nitromethane at 100 °C yielded 4a – 4j (50 – 82 %) and 5a – 5e (50 – 71 %), respectively after 3 – 5 h (Method D, Table 1).

The ^{1}H NMR spectra displayed a well distinguishable intensive singlet signal of H-2 protons in 9.01 – 9.36 ppm range and singlet signals of methylene group in 5.98 – 6.21 ppm range. Both these signals are characteristic for chromene system protons in case when the chromene ring is substituted by strong electron withdrawing group at C-3. Stereochemistry of the salts 4 and 5 at their olefinic double bond is *trans*, which is evident from the signals and coupling constans. Signals of H-9 protons occurred in 8.52 - 8.87 ppm range and due to H-10 protons at 8.06 – 8.33 ppm. Both signals occured as doublets with the coupling constants of 15,5 Hz. The chemical shifts and the multiplicity confirmed the proposed structures.

Table **1** Comparisons among microwave one-pot reaction of **1** with **2** and benzyl bromide (Method A), microwave condensation of **1** with **3** (Method B), classical one-pot reaction of **1** with **2** and benzyl bromide (Method C) and classical condensation of **1** with **3** (Method D).

	Microwave-assisted conditions				Classical conditions			
	Method A		Method B		Method C		Method D	
	React. time (min)	Yield (%)	React. time (min)	Yield (%)	React.time (h)	Yield (%)	React.time (h)	Yield (%)
4a	10	76	8	83	5	68	4	71
4b	8	68	7	80	4.5	63	3	68
4c	8	76	5.5	85	5	69	3.5	77
4d	7	81	5	90	4.5	72	3.5	82
4e	4.5	81	5	87	4	78	3	80
4f	15	63	8	79	5	60	4	71
4g	5	45	5	56	4	42	3	50
4h	3.5	79	5	87	4	70	3	78
4i	6	79	7.5	88	5	73	4	76
4j	7	57	6	73	5.5	55	4.5	64
5a	2.5	54	5	77	5.5	49	4	71
5b	3	51	4.5	70	5.5	47	4.5	66
5c	15	38	9	55	6	30	5	50
5d	12	41	8.5	52	6	36	5	50
5e	10	42	8	59	5	40	4	58

The oxochromene derivatives undergo nucleophilic attack on C-2 position of the chromene ring, followed by double bond shift in the presence of alcohols, primary or secondary amines to yield 2-alkoxy, 2-alkylamino or 2-dialkylamino substituted derivatives (Stankovičová 1997, Tolmachev 1990). Some of 2-ethoxy-3-(2-alkylthio-6-benzothiazolylaminomethylene)-4*H*-chroman-4-ones showed significant antimicrobial activity (El-Shaaer 1998).



Scheme 2

Therefore we investigated the reaction of prepared salt **4b** with secondary amines (morpholine and piperidine), which showed that nucleophilic attack was realized on the C-2 site of chromene ring without opening the pyrone system. Morpholine and piperidine underwent 1,4-addition to chromene salts **4** and formed products **6a** and **6b**, respectively (Scheme 2). This fact is in agreement with the similar 1,4-addition of piperidine on 4-oxochromene-3-carboxylic acids already described by Ghosh (Ghosh 1981). ^{1}H NMR spectra of compounds **6a** and **6b** had no occurrence of signal for phenolic OH-group, which could be a good evidence of the pyrone ring opening. From the comparison of chromene and benzothiazole ^{1}H NMR spectra signals of **4b** with the corresponding signals of **6a** and **6b**, the reasonable changes in the structure of both **6a** and **6b**, caused by the absence of positive charge in the structure of **6a** and **6b** are evident.

Compound 7 was prepared by treatment of the benzothiazole salts 4b with 5-amino-3-methyl-1-phenylpyrazole (Scheme 2). The benzothiazolium moiety of 4b is split off and the electrophilic substitution on pyrazole ring is followed by the cyclisation resultings pyridin cycle. Product 7 was already obtained by the direct reaction of 6-methyl-4-oxochromene-3-carboxaldehyde with 5-amino-3-methyl-1-phenylpyrazole in ethanol and p-toluensulfonic acid as catalyst (Lácová 2005). ^{1}H NMR spectrum confirmed structure of 7, based on missing signals of H-2, CH_2 and benzothiazole-bonded protons, as well as on the presence of one broad signal of OH group at 10.51 ppm.

Acknowledgement

The authors are grateful for financial support to the Science and Technology Assistance Agency by way of project No. APVV-0006-07 and to the VEGA Grant Agency of Slovak Ministry of Education by way of projects No. 1/1005/09 and 1/0448/09

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