MODIFIED COUMARINS. 21. SYNTHESIS OF NEOFLAVONES PRODUCED BY *Marila pluricostata* AND THEIR DERIVATIVES

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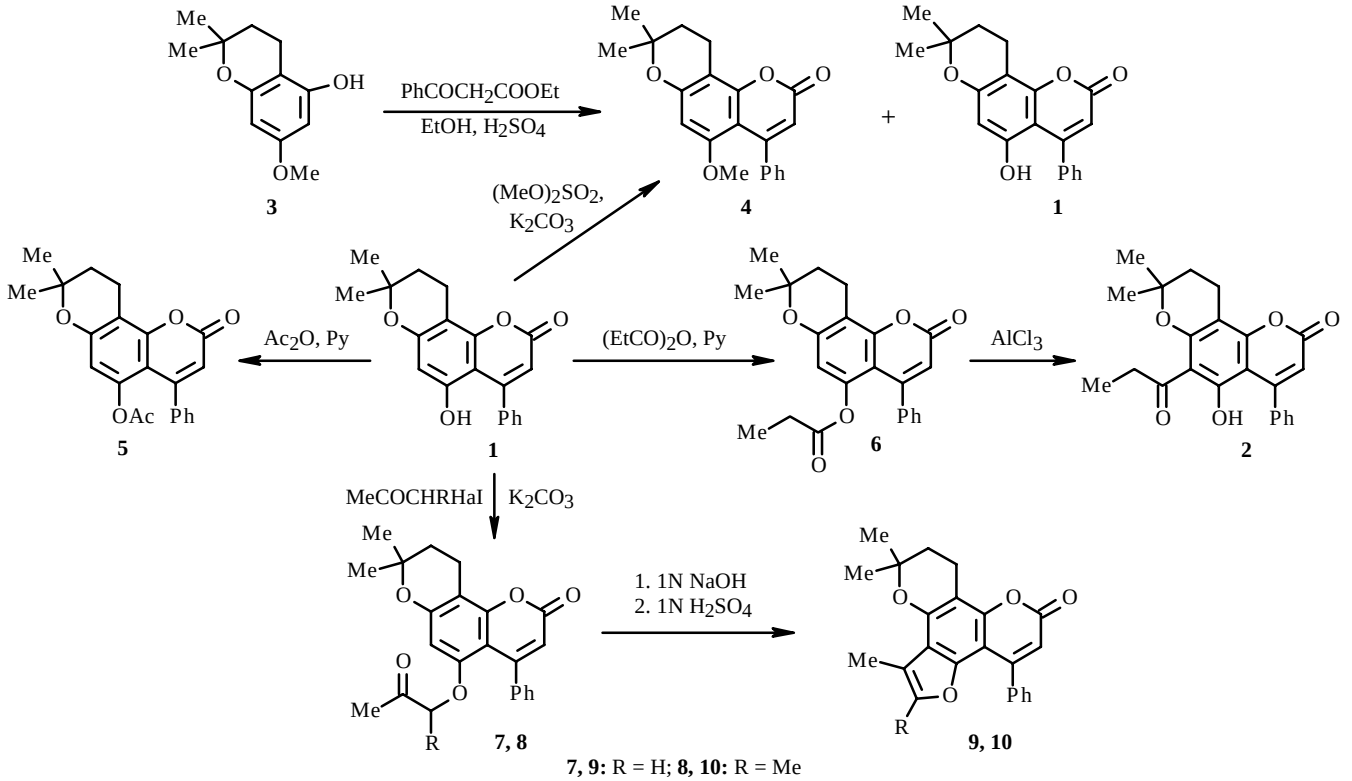
Natural neoflavones 5-hydroxy-8,8-dimethyl-4-phenyl-9,10-dihydropyrano[2,3-f]chromen-2-one and 5-hydroxy-8,8-dimethyl-6-propionyl-4-phenyl-9,10-dihydropyrano[2,3-f]chromen-2-one and their derivatives were synthesized.

Key words: coumarins, 4-phenylcoumarins, neoflavones, pyranocoumarins, furocoumarins.

Neoflavones form a group of compounds based on the 4-phenylcoumarin skeleton that are widely distributed in nature [1, 2]. Several neoflavones including 5-hydroxy-8,8-dimethyl-4-phenyl-9,10-dihydropyrano[2,3-*f*]chromen-2-one (**1**) and 5-hydroxy-8,8-dimethyl-6-propionyl-4-phenyl-9,10-dihydropyrano[2,3-*f*]chromen-2-one (**2**) were isolated from leaves of *Marila pluricostata* (Clusiaceae) [3]. Some of these compounds possess cytotoxic [3] and anti-HIV activity [4]. A synthesis of **1** and **2** has also been reported [3]. Coumarin **1** was prepared by cyclization in acidic medium of 5,7-dihydroxy-8-(3-methylbut-2-enyl)-4-phenylcoumarin; **2**, by Friedel—Krafts acylation of **1** with propionylchloride in the presence of $AlCl_3$.



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In this investigation, we took a different approach to the synthesis of **1** and **2**.

We used 7-methoxy-2,2-dimethylchroman-5-ol (**3**) [5] as the starting material. It is known that use of **3** in the Pechmann condensation causes demethylation of the product as a side reaction [5]. Reaction of **3** and ethylbenzoylacetate in the presence of conc. H_2SO_4 as the condensing agent produced a mixture of **1** and 5-methoxy-8,8-dimethyl-4-phenyl-9,10-dihydropyrano[2,3-*f*]chromen-2-one (**4**), which was easily separated by basic extraction.

Acetylation of **1** with acetic anhydride in pyridine gave acetoxycoumarin **5**. Methoxy derivative **4** was also prepared by methylation of **1** with dimethylsulfate in the presence of anhydrous potash.

Coumarin **1** was used as a key intermediate in the synthesis of natural neoflavone **2**. Acylation of **1** by propionic anhydride in pyridine produced 5-propionoxycoumarin **6**. Fries rearrangement of **5** in the presence of anhydrous $AlCl_3$ at 120°C formed 6-propionylneoflavone **2**.

Hydroxycoumarin **1** was also used as starting material for synthesizing of 5,5-dimethyl-6,7-dihydrofuro[2,3-*f*]-pyrano[2,3-*h*]chromen-9-ones. The MacLeod method was used to annelate the furan ring to the dihydropyranocoumarin system [6]. Alkylation of **1** under Williamson conditions using chloroacetone and 3-chlorobutan-2-one formed oxoethers **7** and **8**, respectively, which were heated with NaOH solution (1 N) and then hydrolyzed with acid to cyclize smoothly and in high yields to 5,5-dimethyl-11-phenyl-6,7-dihydrofuro[2,3-*f*]pyrano[2,3-*h*]chromen-9-ones **9** and **10**, respectively.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck 60 F254 plates with elution by $CHCl_3$:CH_3OH (9:1). Melting points were determined on a Kofler block. IR spectra were measured on a Nicolet Nexus 475 FTIR; PMR spectra, on Varian VXR-300 and Mercury 400 spectrometers at 300 and 400 MHz, respectively, relative to TMS (internal standard). Elemental analyses of all compounds agreed with those calculated.

Chromanol **3** was prepared as before [5].

8,8-Dimethyl-4-phenyl-9,10-dihydropyrano[2,3-*f*]chromen-2-ones 1 and 4. A solution of **3** (4.50 g, 20 mmol) and ethylbenzoylacetate (3.6 mL, 20 mmol) in ethanol (10 mL) was stirred vigorously and treated dropwise with conc. H_2SO_4 (20 mL). The resulting mixture was held at 50°C for 4 h, left overnight at room temperature, and transferred into icewater (100 mL). The resulting precipitate was dissolved in $CHCl_3$ (50 mL) and treated with NaOH solution (1 N, 2 × 50 mL) and saturated NaCl solution. The organic phase was dried with anhydrous $MgSO_4$. The solvent was removed in vacuo in a rotary evaporator. The oily residue was crystallized from CH_3OH to afford **4**. The combined extracts of the alkaline solution were acidified to pH 4. The resulting precipitate of **1** was filtered off and crystallized from CH_3OH.

5-Hydroxy-8,8-dimethyl-4-phenyl-9,10-dihydropyrano[2,3-*f*]chromen-2-one (1). Yield 4.42 (63%), $C_{20}H_{18}O_4$, mp 317-318°C (lit. [3] 274-275°C).

IR spectrum (KBr, cm^{-1}): 3248, 1702, 1690, 1592, 1562, 1440, 1428, 1360, 1160, 1112.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.82 (6H, s, 2×CH_3-8), 1.56 (2H, t, J = 6.8, CH_2-9), 2.56 (2H, t, J = 6.8, CH_2-10), 5.67 (1H, s, H-3), 6.37 (1H, s, H-6), 7.20 (2H, m, H-2′, H-6′), 7.34 (3H, m, H-3′, H-4′, H-5′), 10.38 (1H, s, OH-5).

5-Methoxy-8,8-dimethyl-4-phenyl-9,10-dihydropyrano[2,3-*f*]chromen-2-one (4). Yield 2.32 g (32%), $C_{21}H_{20}O_4$, mp 133-134°C.

IR spectrum (KBr, cm^{-1}): 1706, 1685, 1620, 1590, 1430, 1350, 1140.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.37 (6H, s, 2×CH_3-8), 1.87 (2H, t, J = 6.8, CH_2-9), 2.81 (2H, t, J = 6.8, CH_2-10), 3.37 (3H, s, OMe-5), 5.81 (1H, s, H-3), 6.18 (1H, s, H-6), 7.23 (2H, m, H-2′, H-6′), 7.36 (3H, m, H-3′, H-4′, H-5′).

5-Acetoxy-8,8-dimethyl-4-phenyl-9,10-dihydropyrano[2,3-*f*]chromen-2-one (5). A solution of **1** (0.96 g, 3 mmol) in absolute pyridine (2 mL) was treated with acetic anhydride (1 mL). The reaction mixture was held at room temperature for 24 h. The resulting precipitate was filtered off and crystallized from propan-2-ol. Yield 0.98 g (90%), $C_{22}H_{20}O_5$, mp 138-139°C.

IR spectrum (KBr, cm^{-1}): 1745, 1708, 1690, 1620, 1580, 1455, 1340, 1130.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85 (6H, s, 2×CH_3-8), 1.60 (2H, t, J = 6.6, CH_2-9), 2.64 (3H, s, CH_3COO-5), 2.52 (2H, t, J = 6.6, CH_2-10), 6.09 (1H, s, H-3), 6.71 (1H, s, H-6), 7.23 (2H, m, H-2′, H-6′), 7.37 (3H, m, H-3′, H-4′, H-5′).

5-Methoxy-8,8-dimethyl-4-phenyl-9,10-dihydropyrano[2,3-*f*]chromen-2-one (4). A hot solution of **1** (0.96 g, 3 mmol) in absolute acetone (20 mL) was treated with freshly calcined potash (1.24 g, 9 mmol), stirred vigorously, heated (50-56°C), and treated with dimethylsulfate (0.46 mL, 3.3 mmol). The reaction mixture was held for 2 h with heating and vigorous stirring (course of reaction monitored by TLC). When the reaction was complete the mixture was cooled to room temperature, transferred to icewater (100 mL), and acidified to pH 4. The precipitate was filtered off and crystallized from CH_3OH. Yield 0.87 g (86%).

8,8-Dimethyl-5-propionoxy-4-phenyl-9,10-dihydropyrano[2,3-*f*]chromen-2-one (6) was prepared analogously to **5** using **1** (1.61 g, 5 mmol), absolute pyridine (2 mL), and propionic anhydride (0.96 mL, 7.5 mmol). Yield 1.55 g (82%), $C_{23}H_{22}O_5$, mp 143-144°C.

IR spectrum (KBr, cm^{-1}): 1742, 1705, 1695, 1620, 1580, 1455, 1340, 1130.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85 (6H, s, 2×CH_3-8), 1.30 (3H, t, J = 7.2, CH_3-3″), 1.60 (2H, t, J = 6.6, CH_2-9), 2.51 (2H, t, J = 6.6, CH_2-10), 2.64 (2H, q, J = 7.2, CH_2-2″), 6.08 (1H, s, H-3), 6.71 (1H, s, H-6), 7.23 (2H, m, H-2′, H-6′), 7.37 (3H, m, H-3′, H-4′, H-5′).

5-Hydroxy-8,8-dimethyl-4-phenyl-6-propionyl-9,10-dihydropyrano[2,3-*f*]chromen-2-one (2). A ground mixture of **6** (1.13 g, 3 mmol) and $AlCl_3$ (1.20 g, 9 mmol) was held at 120°C for 1 h, cooled, and treated with HCl solution (1 N, 100 mL). The resulting precipitate was filtered off and crystallized from CH_3OH. Yield 0.71 g (63%), $C_{23}H_{22}O_5$, mp 286-287°C (lit. [3] 274-275°C).

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.84 (6H, s, 2×CH_3-8), 1.38 (3H, t, J = 7.2, CH_3-3″), 1.62 (2H, t, J = 6.6, CH_2-9), 2.59 (2H, t, J = 6.6, CH_2-10), 2.85 (2H, q, J = 7.2, CH_2-2″), 5.93 (1H, s, H-3), 7.20 (2H, m, H-2′, H-6′), 7.35 (3H, m, H-3′, H-4′, H-5′), 13.20 (1H, br.s, OH-5).

8,8-Dimethyl-5-(2-oxopropoxy)-4-phenyl-9,10-dihydropyrano[2,3-*f*]chromen-2-one (7) was prepared analogously to **4** from **1** (1.61 g, 5 mmol), anhydrous potash (2.07 g, 15 mmol), and chloroacetone (0.44 mL, 5.5 mmol). Yield 1.63 g (86%), $C_{23}H_{22}O_5$, mp 171-172°C.

IR spectrum (KBr, cm^{-1}): 1710, 1692, 1602, 1552, 1424, 1380, 1360, 1164, 1134, 1108.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.83 (6H, s, 2×CH_3-8), 1.59 (2H, t, J = 6.4, CH_2-9), 2.21 (3H, s, CH_3-3″), 2.60 (2H, t, J = 6.4, CH_2-10), 4.88 (3H, s, CH_2-1″), 5.79 (1H, s, H-3), 6.52 (1H, s, H-6), 7.21 (2H, m, H-2′, H-6′), 7.36 (3H, m, H-3′, H-4′, H-5′).

8,8-Dimethyl-5-(1-methyl-2-oxoproproxy)-4-phenyl-9,10-dihydropyrano[2,3-*f*]chromen-2-one (8) was prepared analogously to **4** from **1** (1.61 g, 5 mmol), anhydrous potash (2.07 g, 15 mmol), and 3-chloro-2-butanone (0.56 mL, 5.5 mmol) as a yellow oil and was used for further transformations without additional purification.

5,5-Dimethyl-11-phenyl-6,7-dihydrofuro[2,3-*f*]pyrano[2,3-*h*]chromen-9-ones 9 and 10. A solution of **7** or **8** (3 mmol) in propan-2-ol (10 mL) was treated with NaOH solution (1 N, 10 mL). The reaction mixture was heated at 80-90°C for 3 h (course of reaction monitored by TLC). After the reaction was complete the mixture was cooled to room temperature, transferred to water (100 mL), and acidified to pH 4. The resulting precipitate was filtered off and crystallized from propan-2-ol.

3,5,5,-Trimethyl-11-phenyl-6,7-dihydrofuro[2,3-*f*]pyrano[2,3-*h*]chromen-9-one (9). Yield 1.01 g (94%), $C_{23}H_{20}O_4$, mp 248-249°C.

IR spectrum (KBr, cm^{-1}): 1726, 1692, 1610, 1568, 1466, 1420, 1384, 1358, 1312, 1160, 1118, 1104.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.84 (6H, s, 2×CH_3-5), 1.65 (2H, t, J = 6.4, CH_2-6), 2.45 (3H, s, CH_3-3), 2.80 (2H, t, J = 6.4, CH_2-7), 5.93 (1H, s, H-10), 7.21 (2H, m, H-2′, H-6′), 7.37 (3H, m, H-3′, H-4′, H-5′), 7.55 (1H, d, J = 1.6, H-2).

2,3,5,5-Tetramethyl-11-phenyl-6,7-dihydrofuro[2,3-*f*]pyrano[2,3-*h*]chromen-9-one (10). Yield 1.02 g (91%), $C_{24}H_{22}O_4$, mp 162°C.

IR spectrum (KBr, cm^{-1}): 1722, 1692, 1612, 1568, 1444, 1380, 1352, 1310, 1222, 1160, 1088.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.84 (6H, s, 2×CH_3-5), 1.64 (2H, t, J = 6.4, CH_2-6), 2.38, 2.39 (6H, 2s, CH_3-3, CH_3-2), 2.78 (2H, t, J = 6.4, CH_2-7), 5.90 (1H, s, H-10), 7.22 (2H, m, H-2′, H-6′), 7.38 (3H, m, H-3′, H-4′, H-5′).

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REFERENCES

1. R. D. H. Murray, *Progress in the Chemistry of Organic Natural Products*, Vol. 83, in: *The Naturally Occurring Coumarins*, Springer, Vienna and New York (2002).
2. M. M. Garazd, Ya. L. Garazd, and V. P. Khilya, *Khim. Prir. Soedin.*, 47 (2003).
3. J. L. Lopez-Perez, D. A. Olmedo, E. del Olmo, Y. Vasquez, P. N. Solis, M. P. Gupta, and A. San Feliciano, *J. Nat. Prod.*, **68**, 369 (2005).
4. L. M. Bedoya, M. Beltran, R. Sancho, D. A. Olmedo, S. Sanchez-Palomino, E. del Olmo, J. L. Lopez-Perez, E. Munoz, A. San Feliciano, and J. Alcami, *Bioorg. Med. Chem. Lett.*, **15**, 4447 (2005).
5. Ya. L. Garazd, M. M. Garazd, and V. P. Khilya, *Khim. Prir. Soedin.*, 352 (2004).
6. J. K. MacLeod and B. R. Worth, *Tetrahedron Lett.*, 237 (1972).