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SYNTHESIS OF NEW DIFUROCOUMARINS

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5,7-Dihydroxy-4-methyl- and 5,7-dihydroxy-4-trifluoromethylcoumarins are starting compounds in the synthesis of new 10-methyl-8H-difuro[2,3-f;2,3-h]-8-ones and 10-trifluoromethyl-8H-difuro-[2,3-f;2,3-h]chromen-8-ones with high yields.

Keywords: difurocoumarins, 10-methyl-8H-difuro[2,3-*f*;2,3-*h*]chromen-8-one, Fries rearrangement, cyclization.

Preparations based on furocoumarins and their derivatives have been used successively in the treatment of various blood diseases [1]. Certain furocoumarins, containing angelicin and allopsoralen fragments in the molecule, form only monoadducts with DNA molecules [2] and can presumably exhibit the lower photo- and genotoxicity characteristic of this class [3-5].

In this paper we report on the synthesis of new furocoumarins containing not only angelicin and allopsoralen fragments but also hydrocarbon and ester substituents.

The number of papers on the synthesis of difuro[2,3-*f*;2,3-*h*]chromen-8-ones is extremely limited.

Thus, Singh and coworkers were able to synthesize 2,5,10-trimethyl-8H-difuro[2,3-*f*;2,3-*h*]chromen-8-one and 2,5-dimethyl-8H-difuro[2,3-*f*;2,3-*h*]chromen-8-one [6]. The starting compounds were 5,7-dihydroxy- and 4-methyl-5,7-dihydroxycoumarins, which were alkylated with allyl bromide. The obtained ethers were subjected to a Claisen rearrangement followed by cyclization of the rearrangement products in the presence of acid. The synthesized compounds were dehydrogenated with Pd/C in diphenyl ether to the corresponding 2,5-dimethyl-8H-difuro[2,3-*f*;2,3-*h*]chromen-8-ones. The total yield of the difurocoumarins including the four stages amounted to 15% [6].

In [2] a different method was proposed for the cyclization of the product of the Claisen rearrangement: Protection of the hydroxyl groups by acylation, bromination of the obtained compound, and subsequent alkaline cyclization of the 6,8-bisdibromopropyl derivative to difurocoumarin with an overall yield of 2%.

It should be noted that the methods described only gave difurocoumarins with methyl substituents and only at the α-positions of the furan rings. Moreover, the yields of the final products were low.

We have developed new methods for the synthesis of difuro[2,3-*f*;2,3*h*]chromen-8-one and its substituted derivatives. In particular, by using base-catalyzed cyclization of the acylmethyl ethers of dihydroxycoumarins **2** and Fries rearrangement of the chloroacetates of the dihydroxycoumarins, we obtained good yields of 10-methyl-8H-difuro[2,3-*f*;2,3-*h*]chromen-8-one and its derivatives **3-5**,

We synthesized the initial 5,7-dihydroxycoumarins **1** by the familiar procedure from phloroglucinol and the corresponding acetoacetic esters [7, 8].

For the production of dufurocoumarins containing methyl and phenyl substituents at the β-positions of the furan rings we used the method and conditions that we used earlier in the synthesis of various monofurocoumarins [9]. The 5,7-dihydroxycoumarins were alkylated with chloroacetone and

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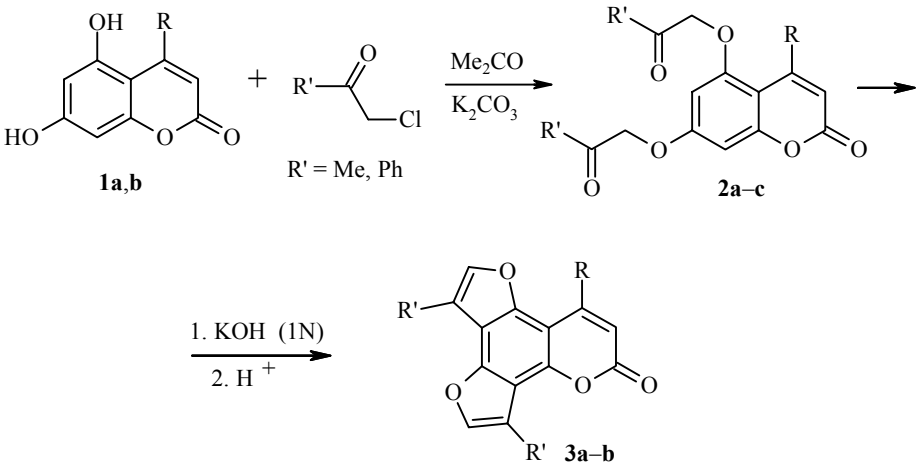
α-chloroacetophenone in the presence of potassium carbonate, and the obtained acylmethyl ethers were submitted to base-catalyzed cyclization in a water–alcohol solution of potassium hydroxide. It should be noted that the yields of the difurocoumarins obtained according to this scheme hardly differed at all from the yields of the monofurocoumarins that we synthesized earlier by this method (65-85%).



1 a R = Me, **b** R = CF_3; **2, 3 a** R = R' = Me, **b** R = Me, R' = Ph, **c** R = CF_3, R' = Me

We realized the synthesis of the diacetoxy-substituted difurocoumarin **6** according to Scheme 1. Acylation of the dihydroxycoumarin **1a** with chloroacetyl chloride was used on account of the strong resinification of the reaction mixture under mild conditions with gentle heating in DMF, whereas in the acylation of monohydroxycoumarins the reaction is conducted with boiling in chloroacetyl chloride. The bischloroacetate of dihydroxycoumarin **4** was then submitted to the Fries rearrangement, and the reaction product was treated with a solution of sodium acetate in acetic anhydride. Earlier we used this method for the production of acetoxy derivatives in the synthesis of various monofurocoumarins [10]. The required compound **6** was synthesized with a yield of 61%, calculated in the initial dihydroxycoumarin.

Scheme 1

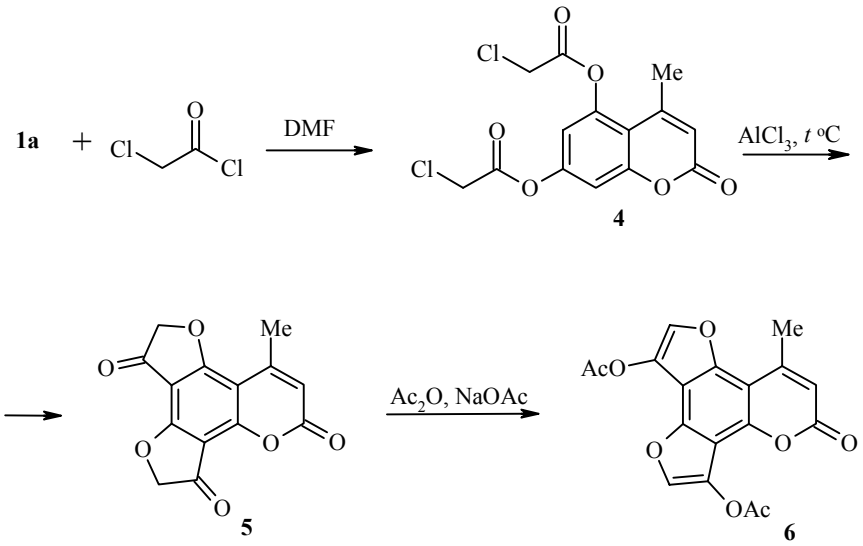
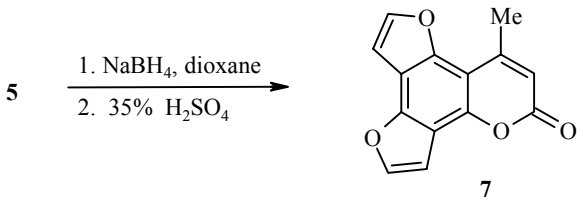


TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Yield, %
		C	H		
2a	$C_{16}H_{16}O_6$	63.11 / 63.15	5.22 / 5.30	154-155	67
2b	$C_{26}H_{20}O_6$	72.79 / 72.89	4.68 / 4.71	225-226	71
2c	$C_{16}H_{13}F_3O_6$	53.58 / 53.64	3.63 / 3.66	175	64
3a	$C_{16}H_{12}O_4$	71.60 / 71.64	4.57 / 4.51	271-273	73
3b	$C_{26}H_{16}O_4$	79.47 / 79.58	4.08 / 4.11	220-221	76
3c	$C_{16}H_9F_3O_4$	59.56 / 59.64	2.85 / 2.82	203	70
4	$C_{14}H_{10}Cl_2O_6$	48.66 / 48.72	2.96 / 2.92	174-175	84
5	$C_{14}H_8O_6$	61.65 / 61.77	2.98 / 2.96	285-286	85
6	$C_{18}H_{12}O_8$	60.65 / 60.68	3.35 / 3.39	235-236	86
7	$C_{14}H_8O_4$	69.88 / 70.00	3.38 / 3.36	242-243	34

For the synthesis of unsubstituted difurocoumarin **7** we reduced the difuranone **5**, and we then dehydrated the obtained product. The required compound was isolated with a yield of 35%.



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The yields and the spectral characteristics of the synthesized substances are presented in Tables 1-3.

TABLE 2. The ^{1}H NMR Spectra of Compounds **2-7**

Compound	Chemical shifts, δ, ppm (*J*, Hz)*
1	2
2a	2.16 (3H, s, 7-OCH$_2$–CO–C$\underline{H}_3$); 2.17 (3H, s, 5-OCH$_2$–CO–C$\underline{H}_3$); 2.57 (3H, d, J = 0.9, 4-CH$_3$); 4.92 (2H, s, 7-OC$\underline{H}_2$–CO–CH$_3$); 4.98 (2H, s, 5-OC$\underline{H}_2$-CO–CH$_3$); 6.02 (1H, dd, J = 0.9, 3-H); 6.44 (1H, d, $J_{6,8}$ = 2.5, 6-H); 6.53 (1H, d, $J_{8,6}$ = 2.5, 8-H)
2b	2.83 (3H, d, $J_{CH_3,3\text{-}H}$ = 1.1, 4-CH$_3$); 5.66 (2H, s, 7-O–CH$_2$–); 5.72 (2H, s, 5-O–CH$_2$–); 6.03 (1H, dd, $J_{3\text{-}H,\text{-}CH_3}$ = 1.1, 3-H); 6.69 (1H, d, $J_{8,6}$ = 1.8, 8-H); 6.73 (1H, d, $J_{6,8}$ = 1.8, 6-H); 7.52-7.73 (6H, m, 2×(*m*-, *p*-Ph)); 7.99-8.06 (4H, m, 2×(*o*-Ph))
2c	2.27 (3H, s, 7-OCH$_2$–CO–C$\underline{H}_3$); 2.28 (3H, s, 5-OCH$_2$–CO–C$\underline{H}_3$); 4.63 (2H, s, 7-OC$\underline{H}_2$–CO–CH$_3$); 4.67 (2H, s, 5-OC$\underline{H}_2$–CO–CH$_3$); 6.26 (1H, d, $J_{8,6}$ = 2.5, 8-H); 6.43 (1H, d, $J_{6,8}$ = 2.5, 6-H); 6.71 (1H, s, 3-H)

TABLE 2 (continued)

1	2
3a	2.45 (3H, d, $J_{6\text{-}CH_3,5\text{-}H}$ = 1.3, 6-CH_3), 2.47 (3H, d, $J_{3\text{-}CH_3,2\text{-}H}$ = 1.3, 3-CH_3), 2.74 (3H, d, $J_{10\text{-}CH_3,9\text{-}H}$ = 1.2, 10-CH_3), 6.33 (1H, dd, $J_{9\text{-}H,\ 10\text{-}CH_3}$ = 1.2, 9-H), 7.87 (1H, dd, $J_{5\text{-}H,6\text{-}CH_3}$ = 1.2, 5-H), 7.93 (1H, dd, $J_{2\text{-}H,3\text{-}CH_3}$ = 1.2, 2-H).
3b	2.79 (3H, d, $J_{10\text{-}CH_3,9\text{-}H}$ = 1.2, 10-CH_3); 6.36 (1H, dd, $J_{9\text{-}H,10\text{-}CH_3}$ = 1.2, 9-H); 7.44-7.54 (6H, m, *m*-, *p*-Ph); 7.66-7.68 (2H, m, *o*-Ph); 7.88-7.91 (2H, m, *o*-Ph'); 8.22 (1H, s, 5-H); 8.49 (1H, s, 2-H)
3c	2.42 (3H, d, *J* = 1.3, 6-CH_3); 2.43 (3H, d, *J* = 1.3, 3-CH_3); 6.98 (1H, s, 9-CH_3); 7.88 (1H, d, *J* = 1.3, 5-CH_3); 7.94 (1H, d, *J* = 1.3, 2-CH_3)
4	2.51 (3H, d, $J_{\text{-}CH_3,3\text{-}H}$ = 1.2, 4-CH_3); 4.30 (2H, s, 7-CO–C$\underline{H}_2$–Cl); 4.33 (2H, s, 5-CO–C$\underline{H}_2$–Cl); 6.24 (1H, dd, $J_{3\text{-}H,\text{-}CH_3}$ = 1.2, 3-H); 6.97 (1H, d, $J_{8,6}$ = 2.0, 8-H); 7.16 (1H, d, $J_{6,8}$ = 2.0, 6-H)
5	2.55 (3H, d, *J* = 1.2, 10-CH_3); 5.01 (2H, s, 5-H); 5.07 (2H, s, 2-H); 6.28 (1H, dd, *J* = 1.2, 9-H)
6	2.42 (3H, s, 6-OC(O)C$\underline{H}_3$); 2.43 (3H, s, 3-OC(O)C$\underline{H}_3$); 2.75 (3H, d, *J* = 0.2, 10-CH_3); 6.41 (1H, dd, *J* = 0.2, 9-H); 8.28 (1H, s, 5-H); 8.38 (1H, s, 3-H)
7	2.87 (3H, d, *J* = 1.9, 10-CH_3); 6.26 (1H, dd, *J* = 1.9, 9-CH_3); 7.11 (1H, d, *J* = 2.0, 6-CH_3); 7.21 (1H, d, *J* = 2.0, 3-CH_3); 7.70 (1H, d, *J* = 2.0, 5-CH_3); 7.70 (1H, d, *J* = 2.0, 2-CH_3)

* The ^{1}H NMR spectra were recorded in DMSO-d_6 (compounds **2a**,**b**, **3a-c**, **5**, and **6**) and $CDCl_3$ (compounds **2c**, **4**, and **7**).

TABLE 3. Mass-spectral Dissociation of the Synthesized Compounds

Com-pound	*m/z* (I_{rel}, %)
2a	304 [M^+] (100), 261 [M^+–CH_3CO] (45)
2b	428 [M^+] (32), 105 [M^+–PhCO] (100)
2c	358 [M^+] (46), 315 [M^+–CH_3CO] (28), 287 [M^+–CH_3CO, –CO] (21), 247 [M^+–CH_3CO, –CO,–C_2O] (100)
3a	268 [M^+] (77), 240 [M^+–CO] (100)
3b	392 [M^+] (100), 364 [M^+–CO] (88)
3c	322 [M^+] (83), 294 [M^+–CO] (100), 265 [M^+–CO, –HCO] (20)
4	349 [M^++1] (4), 317 [M^+–CO] (3)
5	272 [M^+] (100), 244 (M^+–CO] (65), 215 [M^+–CO, –HCO] (79)
6	356 [M^+] (5), 314 [M^+–CH_2CO] (28), 272 [M^+–CH_2CO, –CH_2CO] (100)
7	240 [M^+] (75), 212 [M^+–CO] (100)

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker AC-200 spectrometer (200 MHz) with TMS as internal standard. The mass spectra were obtained on a Finnigan MAT SSQ-710 instrument at 70 eV. The reactions were monitored by TLC in Silufol UV-254 plates. Chromatographic separation was realized on silica gel 60 (Merck) with $CHCl_3$ as eluent.

5,7-Bis(acetonyloxy)-4-methyl-2H-chromen-2-one (2a). To a solution of 4-methyl-5,7-dihydroxycoumarin **1a** (3.0 g, 15.6 mmol) in the smallest amount of DMF we added chloroacetone (3.0 g, 32.8 mmol) and anhydrous potassium carbonate (5 g). The mixture was stirred for 5 h. It was then poured into of water (250 ml) with vigorous stirring for 15 min. The precipitated product was filtered off and washed with several portions of water. The substance was purified by boiling in ethanol. After drying 3.18 g of the product was obtained.

5,7-Bis(benzoylmethoxy)-4-methyl-2H-chromen-2-one (2b). The compound was obtained from compound **1a** and α-chloroacetophenone by analogy with compound **2a**.

5,7-Bis(acetonyloxy)-4-(trifluoromethyl)-2H-chromen-2-one (2c). The compound was obtained by analogy with compound **2a** from compound **1b** and chloroacetone and was purified on a chromatographic column.

3,6,10-Trimethyl-8H-difuro[2,3-*f*;2,3-*h*]chromen-8-one (3a). We boiled compound **2a** (2 g, 6.58 mmol) for 6 h with a reflux condenser with stirring in a 1 N solution of potassium hydroxide (75 ml), and we cooled the mixture to room temperature. The reaction mass was then acidified to pH 3 with 1 N hydrochloric acid with stirring. It was cooled for 1 h to complete the crystallization. The precipitate was filtered off and washed by boiling in methanol (15 ml). We obtained 1.29 g of the product **3a**.

10-Methyl-3,6-diphenyl-8H-difuro[2,3-*f*;2,3-*h*]chromen-8-one (3b). The compound was obtained from compound **2b** by analogy with compound **3a**.

3,6-Dimethyl-10-(trifluoromethyl)-8H-difuro[2,3-*f*;2,3-*h*]chromen-8-one (3c). The compound was obtained from compound **2c** by analogy with compound **2a**. After acidification the reaction mass was extracted with chloroform, and the solvent was evaporated. The product was purified on a chromatographic column.

5,7-Bis(chloroacetoxy)-4-methyl-2H-chromen-2-one (4). To a solution of compound **1a** (3 g, 15.6 mmol) in DMF (10 ml) we added chloroacetyl chloride (4 ml, 47.96 mmol). The mixture was stirred with heating at 65-70°C for 5 h. The reaction mass was poured onto ice. The precipitate was stirred for 15 min on a magnetic stirrer to complete hydrolysis of the chloroacetyl chloride, filtered, and washed with several portions of water. After drying we obtained 4.52 g of the product, which can be used in the next reaction without further purification.

10-Methyl-2,3,5,6-tetrahydro-(8H)-difuro[2,3-*f*;2,3*h*]chromene-3,6,8-trione (5). In a dry flat-bottom flask we mixed thoroughly ground dichloroacetate **4** (4 g, 11.6 mmol) and anhydrous aluminum chloride (6.20 g, 46.4 mmol). The mixture was heated on an oil bath at 120-130°C (bath temperature) for 1 h. After cooling the dark-brown reaction mixture, crushed iced (100 g) and then 1 N hydrochloric acid (20 ml) were added to the flask. The mixture was stirred vigorously on a magnetic stirrer until a uniform precipitate had formed. The precipitate was filtered off, washed with several portions of water, dried, and purified by boiling in ethanol. We obtained 2.37 g of the dry product.

3,6-Diacetoxy-10-methyl-8H-difuro[2,3-*f*;2,3-*h*]chromen-8-one (6). A mixture of the trione **5** (0.5 g, 1.84 mmol) and acetic anhydride (5 ml) was heated on a water bath in the presence of an excess of sodium acetate for 1 h. The reaction mass was poured into a beaker of ice. The precipitate was filtered off and washed with water. We obtained 0.56 g of the dry analytically pure product.

10-Methyl-8H-difuro[2,3-*f*;2,3-*h*]chromen-8-one (7). To a solution of difurocoumarin **5** (1 g, 3.68 mmol) in dioxane (15 ml) and methanol (0.5 ml) we added in portions an excess of sodium borohydride while stirring on a magnetic stirrer. The reaction mass was stirred for 6 h while fresh portions of sodium borohydride were added. The solvent was distilled, 35% sulfuric acid (25 ml) was added, the mixture was heated on a water bath for 2 h, and it was then poured into cold water (50 ml). The precipitate was filtered off, washed with water, dried, and purified by vacuum sublimation. We obtained 0.3 g of the product.

REFERENCES

1. F. P. Gasparro (editor), *Psoralen DNA Photobiol.*, CRC Press, Boca Raton, (1988), 1, 2.
2. S. Caffieri, A. Moor, G. Beijersbergen, F. Dall'Acua, A. Guiotto, A. Chilin, and P. Rodighiero, *Z. Naturforsch.*, **50B**, 1257 (1995).
3. H. Honigsmann, E. Jaschke, F. Gschnait, W. Brenner, P. Fritsch, and K. Wolff, *Br. J. Dermatol.*, **101**, 369 (1979).
4. A. Tanew, B. Ortel, K. Rappersberger, and H. Honigsmann, *J. Am. Acad. Dermatol.*, **18**, 333 (1988).

5. D. Averbeck, *Photochem. Photobiol.*, **50**, 859 (1989).
6. K. Singh, S. K. Banerjee, and C. K. Atal, *Indian J. Chem.*, **20B**, 108 (1981).
7. H. Von Pechman and B. Cohen, *Berichte*, **17**, 2187 (1884).
8. V. Bayer, R. Pastor, and A. Carabon, *J. Fluorine Chem.*, **20(2)**, 187 (1982).
9. V. F. Traven, R. V. Rozhkov, A. Yu. Tolmachev, N. A. Kuznezova, N. Ya. Podhaluzina, and E. A. Carberry, *Heterocycl. Commun.*, **3**, 339 (1997).
10. V. F. Traven, D. V. Kravtchenko, T. A. Chibisova, S. V. Shorshnev, R. Eliason, and D. H. Wakerfield, *Heterocycl. Commun.*, **2**, 345 (1996).