Russian Journal of Organic Chemistry, Vol. 37, No. 7, 2001, pp. 1008–1012. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 7, 2001, pp. 1058–1062.

New Synthesis of 8-Alkoxycarbonylangelicins

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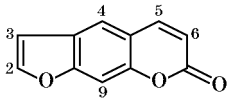
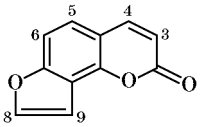
Received July 5, 1999

Abstract—A new procedure was developed for the synthesis of 8-alkoxycarbonylangelicins by base-catalyzed cyclization of *ortho*-acyl(hydroxy)coumarins with haloacetic acid esters. The procedure was successfully applied to prepare a series of new 8-alkoxycarbonyl- and 8-acylangelicins.

Furocoumarin derivatives are well known as compounds exhibiting phototherapic activity in the treatment of a series of skin diseases. There are also data on their bactericide and fungicide activity [1]. In addition, numerous publications appeared in the recent years on the use of furocoumarins and their analogs for blood disinfection [2, 3]. Especially strong activity was demonstrated by psoralene derivatives.



Psoralene



Angelicin

However, the presence in the psoralene molecule of two double bonds ($C^2=C^3$ and $C^5=C^6$) capable of forming [2 + 2]-cycloaddition products with DNA pyrimidine bases makes its derivatives difunctional reagents [4, 5]; as a result, they can exhibit genotoxicity and increase the risk of cancer [1, 6]. Therefore, numerous studies in the field of photochemotherapic drugs are concerned with search for new compounds capable of forming monoadducts with DNA bases. Much attention is given to angelicin derivatives which are polyfunctional reagents [7]. In particular, a large number of methylangelicins were synthesized and tested. They showed a considerable activity and a lower genotoxicity, as compared to psoralenes [8–10]. Furocoumarins having electron-acceptor substituents, including carbonyl-containing groups, in the furan or pyran ring also attract interest. These compounds are characterized by low geno- and phototoxicity and are also promising for photochemotherapy [11].

The known method of synthesis of 8-alkoxycarbonylangelicins and 2-alkoxycarbonylpsoralenes is based on the condensation of *ortho*-acyl(hydroxy)-coumarins with diethyl bromomalonate by the action of potassium carbonate in a polar aprotic solvent (e.g., acetone, 2-butanone, or ethyl acetate) [12]. The reaction is carried out in one step, for intermediate ester readily undergoes intramolecular cyclization followed by aromatization to give the corresponding furocoumarin. The condensation with diethyl bromomalonate is accompanied by decarboxylation of one ester group. This scheme is applied to the synthesis of only lower (mainly ethyl) esters of angelicin-8-carboxylic and psoralene-2-carboxylic acids. Various alkyl furocoumarincarboxylates could be prepared by the condensation scheme given below from the corresponding haloacetic acid esters. However, we have found no information on such reactions in the literature.

While studying new schemes for preparation of furocoumarins and their heteroanalogs [13], we obtained new data on the synthesis of angelicins containing an ester group in position *8*. As starting compounds we used 8-acyl-7-hydroxycoumarins **I**–**III**. The condensation of coumarins **I**–**III** with haloacetic acid esters in the presence of potassium carbonate was found to be a convenient route to angelicines having an ester substituent. With the use of ethyl bromoacetate we succeeded in obtaining 8-ethoxycarbonylfurocoumarins in one step with a yield of 40–50%. In the synthesis of compounds **XXI** and **XXII** we also isolated 25–30% of ethoxycarbonylmethoxy derivatives **X** and **XI** (Scheme 1).

The general character of the proposed procedure was demonstrated with the synthesis of cholesteryl

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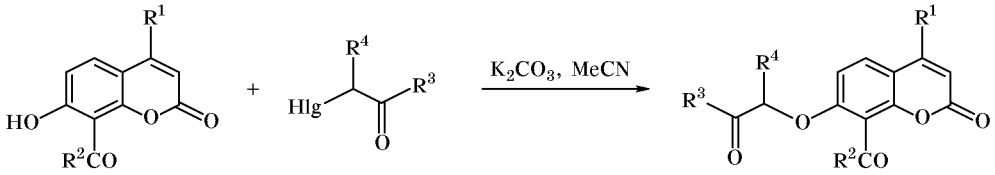
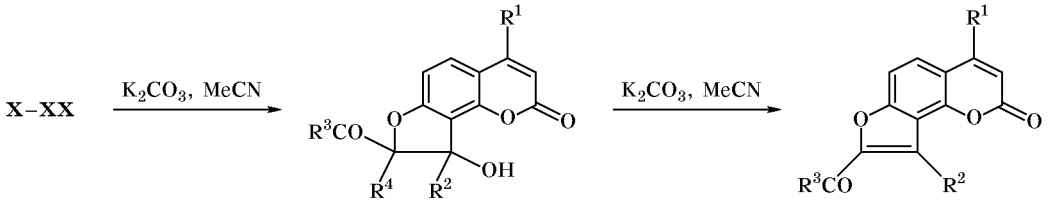
Scheme.



I–III **IV–IX** **X–XX**

I, **II**, **X**, **XII**–**XX**, R^1 = Me; **III**, **XI**, R^1 = H; **I**, **XII**, **XIII**, **XV**, **XVII**, R^2 = Me; **II**, **XIV**, **XVIII**–**XX**, R^2 = Et; **III**, **XI**, R^2 = Ph; **IV**, **V**, **X**, **XI**, **XIII**, **XIV**, R^3 = OEt; **VI**, **XII**, R^3 = $C_{27}H_{45}O$; **VII**, **XV**, **XVIII**, R^3 = Me; **VIII**, **XVI**, **XIX**, R^3 = Ph; **IX**, **XVII**, **XX**, R^3 = 4-$CH_3C_6H_4$; **IV**, **VI**–**XII**, **XV**–**XX**, R^4 = H; **V**, **XIII**, **XIV**, R^4 = CO_2Et; **IV**, **V**, **VII**–**IX**, Hlg = Br; **VI**, Hlg = Cl.



XXI–XXX

XXI, **XXIII**–**XXX**, R^1 = Me; **XXII**, R^1 = H; **XXI**, **XXIII**, **XXV**–**XXVII**, R^2 = Me; **XXII**, R^2 = Ph; **XXIV**, **XXVIII**–**XXX**, R^2 = Et; **XXI**, **XXII**, **XXIV**, R^3 = OEt; **XXIII**, R^3 = $C_{27}H_{45}O$; **XXV**, **XXVIII**, R^3 = Me; **XXVI**, **XXIX**, R^3 = Ph; **XXII**, **XXX**, R^3 = 4-$CH_3C_6H_4$.

angelicin-8-carboxylate (**XXIII**) as an example. Cholesteryl esters of 7-alkoxycoumarin-3-carboxylic acids were previously synthesized as potential mesomorphic compounds [14]. In addition, cholesteryl esters derived from coumarin- and furocoumarincarboxylic acids are of interest for preparation of photosensitive monomolecular Langmuir–Blodgett films.

It seems hardly promising to involve in the above condensation dicholesteryl bromomalonate or mixed chlolesteryl ethyl bromomalonate, for these reagents are difficultly accessible. Moreover, in the reaction with chlolesteryl ethyl bromomalonate it is impossible to predict which of the ester groups will undergo decarboxylation. Our attempts to obtain ester **XXIII** by acylation of cholesterol with the corresponding carboxylic acid or carbonyl chloride were unsuccessful. Also, the alkylation of furocoumarincarboxylic acid potassium salt with cholesteryl *p*-toluenesulfonate gave no desired product. We succeeded in preparing cholesteryl 4,9-dimethylangelicin-8-carboxylate (**XXIII**) only by condensation of coumarin **I** with cholesteryl chloroacetate according to the general procedure described above. The isolated and purified product showed a strong ability to form monomolecular Langmuir–Blodgett films with high performance.

The proposed conditions ensured smooth condensation of acyl(hydroxy)coumarins **I**–**III** with α-haloketones **VII**–**IX** and diethyl bromomalonate (**V**). The products were furocoumarins **XXI** and **XXIV**–**XXX** which are promising as phototherapic agents. The condensation in the system potassium carbonate–acetonitrile takes a considerably shorter time and provides greater yield of the target products. For example, the yield of compound **XXI** from diethyl bromomalonate was 83% in 1 h against 43% in 6 h under the conditions described in [12]. The yields of acylangelicins **XXV**–**XXX** from bromo ketones were 65–85%, and the reaction time was 3–4 h (cf. 12–18 h [15]).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) in $CDCl_3$ using TMS as internal reference. The mass spectra (70 eV) were obtained on a Finnigan-MAT SSQ-710 instrument. The progress of reactions was monitored by TLC on Silufol UV-254 plates using chloroform as eluent. Preparative chromatographic separations were performed on silica gel with chloroform as eluent.

Ethyl 2-(8-acetyl-4-methyl-2-oxo-2*H*-chromen-7-yloxy)acetate (X) and ethyl 4,9-dimethyl-2-oxo-2*H*-furo[2,3-*h*]chromene-8-carboxylate (XXI). To a solution of 0.5 g (2.3 mmol) of 8-acetyl-7-hy-

droxy-4-methylcoumarin (**I**) and 1.58 g (0.01 mmol) of potassium carbonate in 40 ml of anhydrous acetonitrile, heated to the boiling point, we added dropwise under vigorous stirring a solution of 0.39 g (2.3 mmol) of ethyl bromoacetate (**IV**) in 15 ml of anhydrous acetonitrile. The mixture was stirred for 21–24 h under reflux, cooled to room temperature, and evaporated under reduced pressure. Potassium carbonate in the residue was neutralized by adding 10% hydrochloric acid to pH 2–3. The precipitate was filtered off, washed with water, dried in air, and subjected to column chromatography on silica gel using chloroform as eluent. We isolated 0.26 g (40%) of compound **XXI** and 0.17 g (25%) of compound **X**.

Compound **X**. R_f 0.10 (chloroform), mp 114–115°C (from EtOH) [10]. ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, $CH_2C\mathbf{H}_3$, J = 7.02 Hz), 2.40 d (3H, 4-CH_3, J = 1.22 Hz), 2.66 s (3H, $COCH_3$), 4.26 q (2H, $OC\mathbf{H}_2CH_3$, J = 7.02 Hz), 4.75 s (2H, OCH_2), 6.18 d (1H, 3-H, J = 1.22 Hz), 6.75 d (1H, 6-H, J = 8.84 Hz), 7.55 d (1H, 5-H, J = 9.14 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 304 (55) $[M]^{+\cdot}$, 203 (100) $[M-CO_2Et-CO]^+$. $C_{16}H_{16}O_6$.

Compound **XXI**. R_f 0.30 (chloroform), mp 191–192°C (from EtOH) [12]. ^{1}H NMR spectrum, δ, ppm: 1.46 t (3H, $CH_2C\mathbf{H}_3$, J = 7.04 Hz), 2.50 d (3H, 4-CH_3, J = 0.92 Hz), 2.90 s (3H, 9-CH_3), 4.47 q (2H, CH_2, J = 7.04 Hz), 6.29 d (1H, 3-H, J = 0.92 Hz), 7.46 d (1H, 6-H, J = 8.84 Hz), 7.64 d (1H, 5-H, J = 8.86 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 286 (100) $[M]^{+\cdot}$. $C_{16}H_{14}O_5$. Compound **XXI** was also obtained from coumarin **I** and diethyl bromomalonate, yield 0.54 g (83%).

Ethyl 2-(8-benzoyl-2-oxo-2*H*-chromen-7-yloxy)-acetate (XI) and ethyl 2-oxo-9-phenyl-2*H*-furo-[2,3-*h*]chromene-8-carboxylate (XXII) were synthesized in a similar way from coumarin **III** and ethyl bromoacetate.

Compound **XI**. Yield 0.16 g (29%), R_f 0.11 (chloroform), mp 121–123°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH_3, J = 7.14 Hz), 4.19 q (2H, $OC\mathbf{H}_2CH_3$, J = 7.14 Hz), 4.65 s (2H, OCH_2), 6.27 d (1H, 3-H, J = 9.58 Hz), 6.78 d (1H, 6-H, J = 8.68 Hz), 7.65 d (1H, 4-H, J 9.58 Hz), 7.91 d.d (2H, *o*-H, ^3J = 7.02, ^4J = 1.20 Hz), 7.59–7.35 m (4H, 5-H, *m*-H, *p*-H). Mass spectrum, *m*/*z* (I_{rel}, %): 352 (26) $[M]^{+\cdot}$. Found, %: C 68.06; H 4.56. $C_{20}H_{16}O_6$. Calculated, %: C 68.18; H 4.58.

Compound **XXII**. Yield 0.34 g (54%), R_f 0.28 (chloroform), mp 168–170°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH_3, J = 7.12 Hz), 4.30 q (2H, CH_2, J = 7.14 Hz), 6.34 d (1H, 3-H, J = 9.64 Hz), 7.75 d (1H, 4-H, J = 9.64 Hz), 7.46–7.56 m (7H, H_{arom}, 5-H, 6-H). Mass spectrum, *m*/*z* (I_{rel}, %): 334 (100) $[M]^{+\cdot}$. Found, %: C 71.83; H 4.21. $C_{20}H_{14}O_5$. Calculated, %: C 71.85; H 4.22.

Cholesteryl 4,9-dimethyl-2-oxo-2*H*-furo[2,3-*h*]-chromene-8-carboxylate (XXIII) was synthesized from coumarin **I** and cholesteryl chloroacetate. Yield 0.38 g (25%), R_f 0.43 (chloroform), mp 229–230°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 0.70 s (3H, 18-CH_3), 0.87 d [6H, $CH(C\mathbf{H}_3)_2$, J = 6.40 Hz], 0.93 d (3H, 21-CH_3, J = 6.00 Hz), 1.09 s (3H, 19-CH_3), 2.50 d (3H, 4-CH_3, J = 1.06 Hz), 2.90 s (3H, 9-CH_3), 4.93 m (1H, 3-H, cholesteryl), 5.44 d (1H, 6-H, cholesteryl, J = 4.14 Hz), 6.29 d (1H, 3-H, J = 1.06 Hz), 7.45 d (1H, 6-H, J = 8.82 Hz), 7.63 d (1H, 5-H, J = 8.82 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 627 (40) $[M+1]^{+\cdot}$, 369 (60) $[C_{27}H_{46}]^+$, 259 (100) $[C_{14}H_{11}O_5]^+$. Found, %: C 78.43; H 8.69. $C_{41}H_{54}O_5$. Calculated, %: C 78.56; H 8.68.

Ethyl 9-ethyl-4-methyl-2-oxo-2*H*-furo[2,3-*h*]-chromene-8-carboxylate (XXIV) was synthesized from coumarin **II** and diethyl bromomalonate. Yield 0.52 g (81%), mp 174–175°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 1.38 t (3H, CH_2CH_3, J = 7.48 Hz), 1.45 t (3H, $OCH_2C\mathbf{H}_3$, J = 7.12 Hz), 2.50 d (3H, 4-CH_3, J = 0.92 Hz), 3.38 q (2H, CH_2, J = 7.46 Hz), 4.47 q (2H, OCH_2, J = 7.14 Hz), 6.29 d (1H, 3-H, J = 0.94 Hz), 7.46 d (1H, 6-H, J = 8.84 Hz), 7.64 d (1H, 5-H J = 8.84 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 300 (100) $[M]^{+\cdot}$. Found, %: C 67.91; H 5.36. $C_{17}H_{16}O_5$. Calculated, %: C 67.99; H 5.37.

8-Acetyl-4,9-dimethyl-2*H*-furo[2,3-*h*]chromen-2-one (XXV) was synthesized from coumarin **I** and bromoacetone. Yield 0.38 g (65%), mp 231–232°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 2.51 d (3H, 4-CH_3, J = 1.14 Hz), 2.92 s (3H, 9-CH_3), 2.63 s (3H, $COCH_3$), 6.30 d (1H, 3-H, J = 1.14 Hz), 7.43 d (1H, 6-H, J = 8.84 Hz), 7.67 d (1H, 5-H, J = 8.86 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 256 (100) $[M]^{+\cdot}$. Found, %: C 70.26; H 4.68. $C_{15}H_{12}O_4$. Calculated, %: C 70.31; H 4.72.

8-Benzoyl-4,9-dimethyl-2*H*-furo[2,3-*h*]chromen-2-one (XXVI) was synthesized as described above for compound **XXI** from coumarin **I** and phenacyl bromide. Yield 0.58 g (79%), mp 208–209°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 2.52 d (3H, 4-CH_3, J = 1.08 Hz), 2.93 s (3H, 9-CH_3), 6.31 d (1H, 3-H, J = 1.08 Hz), 7.46 d (1H, 6-H, J = 8.84 Hz), 7.49–7.64 m (3H, *m*-H, *p*-H), 7.68 d (1H, 5-H, J = 8.86 Hz), 8.05 d.d (2H, *o*-H, ^3J = 8.20, ^4J = 1.70 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 318 (95) $[M]^{+\cdot}$, 317 (100) $[M-H]^+$. Found, %: C 75.43; H 4.41. $C_{20}H_{14}O_4$. Calculated, %: C 75.46; H 4.43.

4,9-Dimethyl-8-(4-toluoyl)-2*H*-furo[2,3-*h*]chromen-2-one (XXVII) was synthesized as described above for compound **XXI** from coumarin **I** and 4-methylphenacyl bromide. Yield 0.65 g (85%), mp 248–249°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 2.47 s (3H, $C_6H_4C\mathbf{H}_3$), 2.51 d (3H, 4-CH_3, J = 1.22 Hz), 2.92 s (3H, 9-CH_3), 6.31 d (1H, 3-H, J = 1.22 Hz), 7.34 d (2H, *m*-H, J = 8.00 Hz), 7.45 d (1H, 6-H, J = 8.84 Hz), 7.67 d (1H, 5-H, J = 8.84 Hz), 7.97 d (2H, *o*-H, J = 8.0 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 332 (35) $[M]^{+\cdot}$, 317 (100) $[M-CH_3]^+$. Found, %: C 75.82; H 4.85. $C_{21}H_{16}O_4$. Calculated, %: C 75.89; H 4.85.

8-Acetyl-9-ethyl-4-methyl-2*H*-furo[2,3-*h*]chromen-2-one (XXVIII) was synthesized as described above for compound **XXI** from coumarin **II** and bromoacetone. Yield 0.39 g (67%), mp 193–194°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 1.36 t (3H, $CH_2C\mathbf{H}_3$, J = 7.38 Hz), 2.50 d (3H, 4-CH_3, J = 1.18 Hz), 2.63 s (3H, $COCH_3$), 3.38 q (2H, CH_2, J = 7.38 Hz), 6.32 d (1H, 3-H, J = 1.18 Hz), 7.43 d (1H, 6-H, J = 8.82 Hz), 7.66 d (1H, 5-H, J = 8.84 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 270 (100) $[M]^{+\cdot}$. Found, %: C 71.07; H 5.21. $C_{16}H_{14}O_4$. Calculated, %: C 71.10; H 5.22.

8-Benzoyl-9-ethyl-4-methyl-2*H*-furo[2,3-*h*]chromen-2-one (XXIX) was synthesized as described above for compound **XXI** from coumarin **II** and phenacyl bromide. Yield 0.57 g (80%), mp 207–208°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 1.44 t (3H, $CH_2C\mathbf{H}_3$, J = 7.42 Hz), 2.52 d (3H, 4-CH_3, J = 0.96 Hz), 3.40 q (2H, CH_2, J = 7.42 Hz), 6.32 d (1H, 3-H, J = 0.96 Hz), 7.45 d (1H, 6-H, J = 8.82 Hz), 7.53–7.63 m (3H, *m*-H, *p*-H), 7.69 d (1H, 5-H, J = 8.84 Hz), 8.05 d.d (2H, *o*-H, ^3J = 8.30, ^4J = 1.58 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 332 (72) $[M]^{+\cdot}$, 317 (100) $[M-CH_3]^+$. Found, %: C 75.85; H 4.83. $C_{21}H_{16}O_4$. Calculated, %: C 75.89; H 4.85.

9-Ethyl-4-methyl-8-(4-toluoyl)-2*H*-furo[2,3-*h*]chromen-2-one (XXX) was synthesized as described above for compound **XXI** from coumarin **II** and 4-methylphenacyl bromide. Yield 0.62 g (83%), mp 206–207°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 1.43 t (3H, $CH_2C\mathbf{H}_3$, J = 7.42 Hz), 2.46 s (3H, $C_6H_4C\mathbf{H}_3$), 2.51 d (3H, 4-CH_3, J = 0.92 Hz), 3.39 q (2H, CH_2, J = 7.42 Hz), 6.30 d (1H, 3-H, J = 0.92 Hz), 7.33 d (2H, *m*-H, J = 8.02 Hz), 7.44 d (1H, 6-H, J = 8.80 Hz), 7.67 d (1H, 5-H, J = 8.84 Hz), 7.97 d (2H, *o*-H, J = 8.02 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 346 (22) $[M]^{+\cdot}$, 331 (100) $[M-CH_3]^+$. Found, %: C 76.25; H 5.23. $C_{22}H_{18}O_4$. Calculated, %: C 76.29; H 5.24.

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