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Synthesis of Structural Fragments of Natural 3-Phenoxycoumarins

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Abstract—The synthesis of substituted and unsubstituted 3-phenoxycoumarins is described.

Keywords: 3-phenoxycoumarins, synthesis

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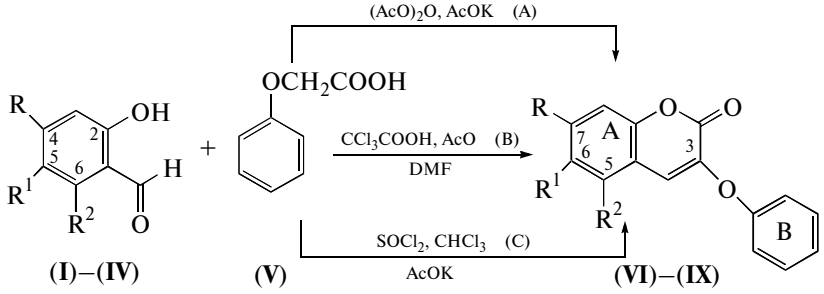
Natural coumarin and phenoxycoumarin bioregulators have a broad range of physiological activity and are a fertile field for chemical modifications [1].

Traditionally, substituted and unsubstituted 3-phenoxycoumarins are synthesized using the Perkin reaction [2], the Edgeworin synthesis procedure [3], the Kostanetsky–Robinson reaction, or modified versions of them [4].

The most common method used to synthesize phenoxycoumarins containing *O*-aryl substituents in the 3 position is the interaction of the appropriate aldehydes with phenoxyacetic acids and their functional derivatives. Compounds possessing antimicrobial [2], herbicidal, fungicidal, and insecticidal activity, as well as activity against dermatophytes [5], were identified during the study of biological activity.

RESULTS AND DISCUSSION

The known biological activity of natural and synthetic 3-phenoxycoumarins prompted us to develop convenient and efficient methods for synthesizing these compounds. We used three methods, A, B, and C (Scheme) for the synthesis of substituted and unsubstituted 3-phenoxycoumarins, which are analogues of natural compounds.



(I), **(VI)** R=R[1]=R[2]=H
(II), **(VII)** R=OAc, R[1]=R[2]=H
(III), **(VIII)** R=R[2]=H, R[1]=Br
(IV), **(IX)** R=H, R[1]=R[2]=–CH=CH–CH=CH–

Scheme.

According to method A, the appropriate salicylaldehyde **(I)**–**(IV)** phenoxyacetic acid **(V)** was condensed in the Perkin reaction [1]. In method B, starting compounds were condensed in dimethylformamide in the presence of trichloroacetic acid and acetic anhydride according to the Edgeworin synthesis procedure [3]. In method C, the starting materials were refluxed in dry chloroform in the presence of thionyl chloride and potassium acetate.

Comparison of results for the three methods of 3-phenoxycoumarin **(VI)**–**(IX)** synthesis shows that in the conditions used in Edgeworin synthesis (B), the reaction occurs in milder conditions and gives higher yields (20–80%) than in methods A and C and is hardly accompanied at all by resinification or the formation of by-products.

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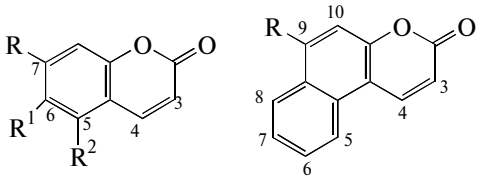
It should be noted that the synthesis in method A results in the formation of by-products **(VIIa)**–**(IXa)** along with the desired products, while the synthesis in method C leads to resinification. Those by-products do not contain *O*-aryl substituents in position 3.



(**VIIa**) R=OAc, R^1=R^2=H (**IXa**) R=H

(**VIIIa**) R^1=Br, R=R^2=H

Product mixtures formed in the reaction were separated by fractional crystallization.

When applying method B, refluxing the reaction mixture for 30–32 h leads to the formation of 3-phenoxycoumarins **(VI)**–**(IX)** with high yields (20–80%). These products are easily detectable on a TLC plate under UV light.

The resulting 3-phenoxycoumarins **(VI)**–**(IX)** are colorless crystalline compounds soluble in various organic solvents and insoluble in water. Due to blue or violet fluorescence under UV light, these compounds are easily detectable.

The structure of the new 3-substituted phenoxycoumarins was confirmed by ^{1}H NMR spectroscopy, using acetone-d_6 as a solvent.

Signals of methine protons of the pyrone cycle (H4) are the most characteristic signals in the spectra. They appear as singlets in a low field at 7.43 ppm. In the case of 5-unsubstituted phenoxycoumarins (R^2 = H), protons at position 5 give doublets at 7.3–7.9 ppm with spin–-spin coupling constants (SSCC) of 2 Hz. In ^{1}H NMR spectra of 7-acetoxycoumarins **(VII)**, a three-proton peak of the acetyl group appears at 2.31 ppm instead of the hydroxyl group signal. Protons H2' and H6' of ring B give a multiplet signal at 7.40–7.47 ppm, while the characteristic signals of H3', H4' and H5' protons are at 7.15–7.28 ppm.

So, comparison of the results of 3-phenoxycoumarin synthesis by different methods shows that the second method (B) provides the formation of the desired compounds with the highest yields and without the formation of by-products.

MATERIALS AND METHODS

Monitoring of the progress of the reactions and the identification of synthesized compounds was performed by TLC on Silufol UV-254 plates (eluent, benzene : ethanol, 9 : 1). ^{1}H NMR spectra were recorded on a Unity-400+ device (Varian, United States, 400 MHz) in acetone-d_6 (δ, ppm; *J*, Hz). Tetramethylsilane was used as an internal standard.

Elemental analysis was performed on the instrument for microdetection of carbon, hydrogen, and halogen (Russia). Aldehydes **(I)**–**(IV)** by Reakhim (Russia) were used. Phenoxyacetic acid **(V)** prepared according to procedure [6]. Other chemical agents were produced by Reahim (Russia) and Khimreaktivkomplekt (Uzbekistan).

Synthesis of compounds VI–IX. ***Method A.*** A mixture of an appropriate aldehyde **(I)**–**(IV)** (10 mmol), acid **(V)** (10 mmol), acetate (2.95 g, 30.1 mmol), and acetic anhydride (10.3 mL) was refluxed for 18–19 h. After the reaction mixture was cooled, the precipitate that formed was filtered off and recrystallized from ethanol.

3-Phenoxy-2*H*-chromen-2-on (VI). Yield 0.41 g (17.2%), R_f = 0.44, mp 108–110°C (lit. mp 110°C [3]). Found, %: C 75.5, H 4.2. $C_{15}H_{10}O_3$ (M 238). Calculated, %: C 75.6, H 4.2. ^{1}H NMR: 7.63 (1 H, dd, *J* 8.2; 2.4, H8), 7.55 (1 H, td, *J* 8.2; 2.4, H6), 7.43 (1 H, s, H4), 7.40–7.47 (2 H, m, H2', H6'), 7.38 (H, dd, *J* 8.2; 2.4, H5), 7.34 (1 H, dd, *J* 8.3; 2.4, H7), 7.15–7.25 (3 H, m, H3', H4', H5').

7-Acetoxy-3-phenoxy-2*H*-chromen-2-on (VII). Yield 0.21 g (7.2%), R_f = 0.53, mp 140–143°C. Found, %: C 69.0, H .0. $C_{17}H_{12}O_5$ (296). Calculated, %: 68.9, 4.0. ^{1}H NMR: 7.69 (1 H, s, H4), 7.50 (1H, d, *J* 8.4, H5), 7.40–7.45 (2 H, m, H2', H6'), 7.18–7.25 (3 H, m, H3', H4', H5'), 7.12 (H, d, *J* 2.2, H8), 7.01 (H, dd, *J* 8.3; 2.2, H6), 2.31 (H, s, H7).

6-Bromo-3-phenoxy-2*H*-chromen-2-on (VIII). 0.57 g (18%), R_f = 0.62, mp 153–155°C. Found, %: C 56.6, H 2.4, Br 49.0. $C_{15}H_9BrO_3$ (M 317). Calculated, %: C 56.8, H2.8, Br 48.8. ^{1}H NMR: 7.95 (H, d, *J* 2.2 2.2, H5), 7.92 (1 H, s, H4), 7.62 (1 H, dd, *J* 8.2 8.2; 2.4, H7), 7.41–7.46 (2 H, m, H2', H6'), 7.32 (1 H, d, *J* 2.3 2.3, H8), 7.15–7.25 (3 H, m, H3', H4', H5').

3-Phenoxy-2H-benzo[f]chromen-2-on (IX). Yield 0.32 g (11.5%), R_f = 0.31, mp 113–115°C. Found, %: C 79.2, H 4.0. $C_{19}H_{12}O_3$ (M 288). Calculated, %: C 79.2, H 4.2. ^{1}H NMR: 8.50 (1 H, s, H4), 8.28 (1 H, dd, *J* 8.3 8.3; 2.4, H5), 7.85 (1 H, d, *J* 8.3 8.3, H9), 7.83 (1 H, dd, *J* 8.3 8.3; 2.4, H8, 7.61 (1 H, td, H7), 7.50 (1 H, td, H6), 7.45 (1 H, d, *J* 8.3 8.3, H10), 7.40-7.46 (2 H, m, H2', H6'), 7.15-7.28 (3 H, m, H3', H4', H5').

Method B. A mixture of an appropriate aldehyde **(I)**–**(IV)** (10 mmol), phenoxyacetic acid **(V)** (10 mmol), dimethylformamide (5 mL), trichloroacetic acid (10 g), and acetic anhydride (10.3 mL) was refluxed for 30–32 h. After that, the reaction mixture was diluted with cold water, and the precipitated solid was filtered off and recrystallized from ethanol.

Yields: 1.90 g (80%) for compound **(VI)**, 0.59 g (20%) for **(VII)**; 1.12 g (35.5%) for **(VIII)**; 1.44 g (52.2%) for **(IX)**.

Method C. Thionyl chloride (0.72 mL, 10 mmol) was added to phenoxyacetic acid (**V**) (10 mmol) at 0°C. Then, an appropriate aldehyde (**I**)–(**IV**) (1.06 mL, 10 mmol), dry chloroform (1 mL, 10 mmol), and potassium acetate were added at room temperature. The resulting mixture was refluxed for 60–65 h. After that, the reaction mixture was diluted with cold water, and the precipitated solid was filtered off and recrystallized from ethanol.

Yields: 1.24 g (52%) for compound (**VI**); 0.75 g (25.6%) for (**VII**); 0.60 g (19%) for (**VIII**); 1.38 g (50%) for (**IX**).

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