5,6,7,8-Tetrafluoro-4-hydroxycoumarin derivatives in reactions with *o*-phenylenediamine

Ya. V. Burgart, K. V. Shcherbakov, V. I. Saloutin, and O. N. Chupakhin*

I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy Sciences, 20 ul. S. Kovalevskoi, 620219 Ekaterinburg, Russian Federation. Fax: +7 (343 2) 74 5954. E-mail: saloutin@ios.uran.ru

The reactions of 5,6,7,8-tetrafluoro-4-hydroxycoumarin derivatives with *o*-phenylenediamine occur with pyrone heterocycle cleavage and formation of substituted benzodiazepin-2-ones. 5,6,7,8-Tetrafluoro-4-hydroxycoumarin affords 4-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one, 3-acetimidoyl-5,6,7,8-tetrafluoro-4-hydroxycoumarin produces 3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)-4-methyl-1,2-dihydro-1*H*-1,5-benzodiazepin-2-one, and 3-acetyl-5,6,7,8-tetrafluoro-4-hydroxycoumarin yields both these heterocycles.

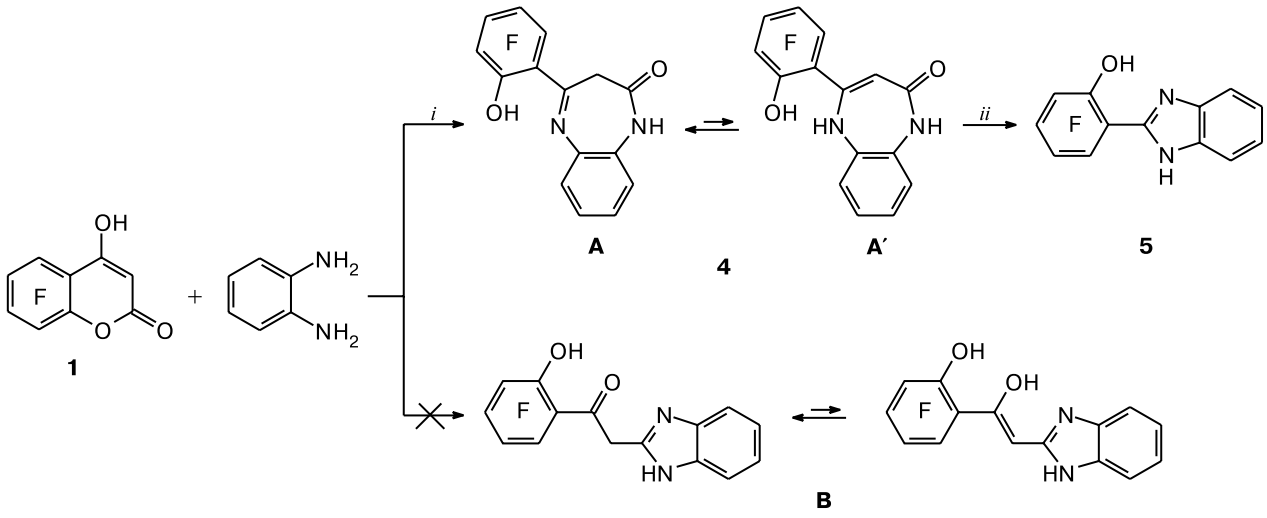
Key words: 5,6,7,8-tetrafluoro-4-hydroxycoumarin, *o*-phenylenediamine, benzodiazepin-2-one.

Substances having biological activity and being successfully used in medicine were found among coumarin derivatives (both synthetic and isolated from natural raw materials).[1,2] However, fluorine-containing coumarins remained poorly studied to the recent time, because they are difficult to access. We developed the methods for syntheses of compounds of the 5,6,7,8-tetrafluoro-4-hydroxycoumarin group[3] and studied their reactions with ammonia and morpholine. These reactions involve aromatic nucleophilic substitution of fluorine atoms at position 7 as the main process.[4]

In this work, we studied the reactions of 5,6,7,8-tetrafluoro-4-hydroxycoumarin (**1**) and its 3-acetyl- (**2**) and 3-acetimidoyl-substituted (**3**) derivatives with *o*-phenylenediamine.

4-Hydroxycoumarin **1** was found to react with *o*-phenylenediamine on refluxing in toluene to form product **4** (Scheme 1). According to the data of elemental analysis, IR spectroscopy, and NMR spectroscopy, the structures of 4-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one (**A**) or 2-substituted benzimidazole **B** can be ascribed to compound **4**.

Scheme 1



i. Toluene, Δ. *ii*. Conc. H_2SO_4, Δ.

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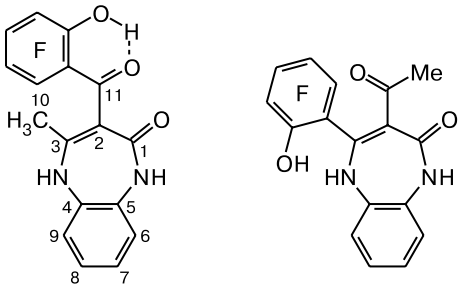
Mass spectrometric study was carried out to establish the structure of compound **4**. The mass spectrum of product **4** contains the peak of the molecular ion *m/z* 324 (86%) and the maximum (100%) peak *m/z* 282 corresponding to 2-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)benzimidazole (**5**). A tendency of decreasing the heterocycle size is characteristic of the mass spectrometric behavior of 1,5-benzodiazepin-2-ones[5] and, hence, the mass spectra of these compounds contain intense peaks of the corresponding benzimidazoles.

It is known that the character of mass spectrometric fragmentation of 1,5-benzodiazepines is similar to their thermal or acid decomposition.[1,5] In fact, refluxing of compound **4** in concentrated sulfuric acid yields benzimidazole **5** as the main product (Scheme 1).

According to the ^{1}H and ^{19}F NMR spectroscopic data, benzodiazepinone **4** in DMSO-d_6 exists as a mixture of tautomers **A** and **A´** in a ratio of 4 : 1.

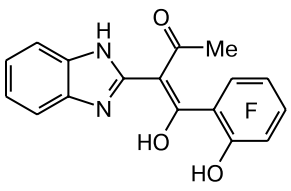
Benzodiazepin-2-one **4** is formed due to the substitution of the hydroxy group of coumarin **1** by one of the amino groups of *o*-phenylenediamine and the C—O bond cleavage in the pyrone cycle under the action of the second amino group.

Under similar conditions, 3-acetyl-4-hydroxycoumarin (**2**) reacts with *o*-phenylenediamine to form a mixture of products from which benzodiazepin-2-one **4** and compound **6** can be isolated (Scheme 2). According to the data of elemental analysis, IR spectrum, and ^{1}H and ^{19}F NMR spectra, three equally probable structures can be ascribed to the latter: 3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)-4-methyl-1,2-dihydro-1*H*-1,5-benzodiazepin-2-one (**C**), 3-acetyl-4-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)-1,2-dihydro-1*H*-1,5-benzodiazepin-2-one (**D**), or 3-(benzimidazol-2-yl)-4-(3,4,5,6-tetrafluoro-2-hydroxy-4-hydroxyphenyl)but-3-en-2-one (**E**).



C

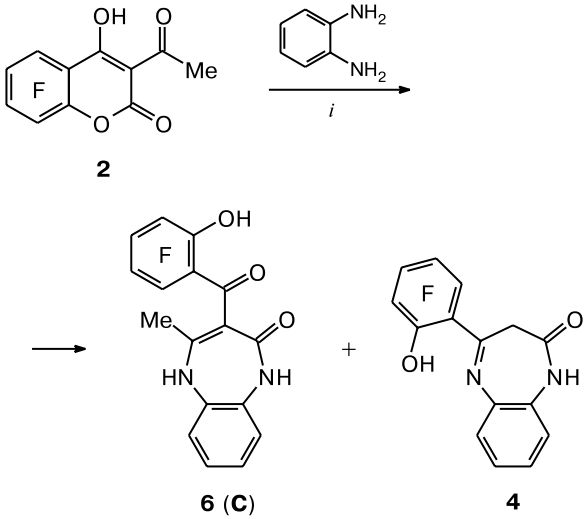
D



E

Based on the ^{13}C NMR spectroscopic data, we chose benzodiazepin-2-one **C**, since the spectrum of product **6** in DMSO-d_6 contains two low-field signals corresponding to the resonance absorption of the carbon atom of the amide group (singlet at δ_C 168.85) and carbonyl carbon atom at the fluorobenzoyl residue (doublet at δ_C 160.63 ($J_{C,F}$ = 1 Hz)).

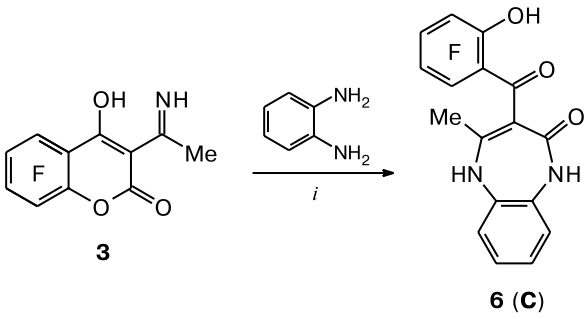
Scheme 2



i. Toluene, Δ.

A product, whose physicochemical characteristics are identical to those of benzodiazepin-2-one **6**, was isolated from the products of the reaction of 3-acetimidoyl-4-hydroxycoumarin (**3**) with *o*-phenylenediamine in boiling toluene (Scheme 3). Under these conditions, we failed to obtain heterocycles **D** and **E** bearing the acetyl substituent from 3-acetimidoyl-4-hydroxycoumarin (**3**), which confirms additionally the above conclusion about the structure of compound **6**.

Scheme 3



i. Toluene, Δ.

Benzodiazepin-2-one **6** is formed, most likely, due to the condensation of one of the amino groups of *o*-phenylenediamine at the acetyl or acetimidoyl fragment of the corresponding coumarins **2** and **3** and pyrone heterocycle cleavage under the action of the second amino group. However, this is not the single reaction route, which is indicated by medium yields of benzodiazepin-2-one **6** and isolation of benzodiazepin-2-one **4** as a by-product from the reaction of coumarin **2**. Compound **4** can be formed due to transformations of both coumarin **1**, which is synthesized from 3-acetylcoumarin **2**, and as a product of decomposition of intermediately formed benzodiazepin-2-one **D**.

It is known that the reactions of 3-oxo esters with *o*-phenylenediamine are characterized by the formation of 1,5-benzodiazepin-2-one. Thus, in these reactions coumarins **1—3** behave as 1,3-dicarbonyl compounds.

Thus, we have shown that 5,6,7,8-tetrafluoro-4-hydroxycoumarin and its 3-acyl-substituted analogs can serve as the starting substances for syntheses of other heterocyclic systems.

Experimental

IR spectra were recorded on a Perkin Elmer Spectrum One spectrometer in the 4000—400 cm^{-1} interval using Nujol mulls. ^1H (400 MHz), ^{13}C (100.6 MHz, relatively to $SiMe_4$), and ^{19}F (75 MHz, relatively to C_6F_6) NMR spectra were measured on a Bruker DRX-400 spectrometer. Elemental analysis was carried out on a Perkin Elmer PE 2400 analyzer (series II CHNS-O EA 1108). Mass spectra were obtained on a Varian MAT-311A instrument.

Starting 4-hydroxycoumarins **1—3** were synthesized according to known procedures.[3]

Reactions of coumarins 1—3 with *o*-phenylenediamine (general procedure). *o*-Phenylenediamine (1.62 g, 15 mmol) was added to a solution of coumarin **1—3** (10 mmol) in toluene (30 mL). The mixture was refluxed for 6 h. The precipitate that formed was filtered off and recrystallized from the corresponding solvent.

4-(3,4,5,6-Tetrafluoro-2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one (4). The yield was 75% (from coumarin **1**) and 25% (from coumarin **2**), m.p. 246—248 °C (from acetone). Found (%): C, 55.45; H, 1.92; F, 23.49; N, 8.71. $C_{15}H_8F_4N_2O_2$. Calculated (%): C, 55.57; H, 2.17; F, 23.44; N, 8.64. IR, ν/cm^{-1}: 2900 (OH); 1686 (C=ONH); 3205, 3082, 1608 (NH); 1654 (C=N); 1563, 1526 (C=C_{arom}); 1007 (C—F_{arom}). ^1H NMR (DMSO-d_6), δ: **A** (80%), 3.51 (s, 2 H, CH_2); 7.23—7.44 (m, 4 H, C_6H_4); 10.74 (s, 1 H, NH); 13.38 (br.s, 1 H, OH); **A´** (20%), 4.42 (t, 1 H, CH=, J = 1.9 Hz); 6.72—6.85 (m, 4 H, C_6H_4); 8.25 (s, 1 H, NH); 8.77 (d, 1 H, NH, J = 1.9 Hz); 11.1 (br.s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: **A** (80%), −8.94—(−8.80) (m, 1 F); 0.20—0.29 (m, 1 F); 8.62—8.74 (m, 1 F); 20.17—20.27 (m, 1 F); **A´** (20%), −8.59—(−8.51) (m, 1 F); 1.66—1.76 (m, 1 F); 4.95—5.06 (m, 1 F); 19.37—19.46 (m, 1 F). MS (EI, 70 eV), m/z (I_{rel} (%)): 324 $[M]^+$ (86), 282 $[C_{13}H_6F_4N_2O]$ (100), 134 [HN − C_6H_4 − NH − CO] (21), 90 $[C_6H_4N]$ (14), 65 $[C_5H_5]$ (16).

4-Methyl-3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)-1,2-dihydro-1*H*-1,5-benzodiazepin-2-one (6). The yield was 65% (from coumarin **3**) and 45% (from coumarin **2**), m.p. 230—232 °C (from ethanol). Found (%): C, 55.42; H, 2.85; F, 20.82; N, 7.90. $C_{17}H_{10}F_4N_2O_3$. Calculated (%): C, 55.75; H, 2.75; F, 20.75; N, 7.65. IR, ν/cm^{-1}: 3149, 3093, 1620 (NH); 2721, 2602 (OH); 1678 (CONH); 1649 (Ar^FCO); 1566 (C=C); 1517, 1460 (C=C_{arom}); 1023, 1012 (C—F_{arom}). ^1H NMR (DMSO-d_6), δ: 2.64 (s, 3 H, Me); 5.09 (s, 1 H, OH); 7.30—7.62 (m, 4 H, C_6H_4); 10.85 (br.s, 2 H, 2 NH). ^{19}F NMR (DMSO-d_6), δ: −3.63—(−3.48) (m, 1 F); 1.91—2.02 (m, 1 F); 7.96—8.10 (m, 1 F); 17.60—17.68 (m, 1 F). ^{13}C NMR (DMSO-d_6), δ: 168.85 (s, C(1)); 88.36 (s, C(2)); 151.33 (s, C(3)), 134.61 (s, C(4), C(5)), 123.31 (s, C(6), C(9)), 113.81 (s, C(7), C(8)), 13.36 (s, C(10)), 160.63 (d, C(11), $J_{C,F}$ = 1.0 Hz).

2-(3,4,5,6-Tetrafluoro-2-hydroxyphenyl)benzimidazole (5). A solution of benzodiazepin-2-one **4** (0.25 g, 0.8 mmol) in concentrated H_2SO_4 (20 mL) was heated at 100 °C for 3 h. The reaction mixture was poured into water (50 mL). The precipitate that formed was filtered off and dried. After recrystallization from ethanol, benzimidazole **5** was obtained in 52% yield (0.11 g), m.p. 270 °C (subl.); *cf.* Ref. 3.

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