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SHORT COMMUNICATIONS

Synthesis of 6-Aryl-4-[(3-aryl-1*H*-pyrazol-5-yl)methylidene]-4,5-dihydropyridazin-3-ols

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Abstract—The reaction of 5-aryl-3-(chromen-3-ylmethylidene)furan-2(3*H*)-ones with hydrazine led to the formation of 6-aryl-4-{[3-(2-hydroxyphenyl)-1*H*-pyrazol-5-yl]methylidene}-4,5-dihydropyridazin-3-ols.

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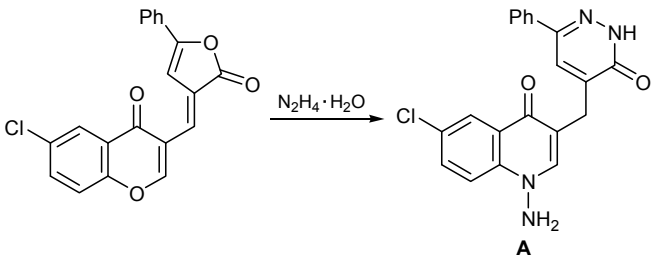
3-(Chromen-3-ylmethylidene)furan-2(3*H*)-ones attract particular interest from the viewpoint of modern organic chemistry. These compounds contain two pharmacophoric fragments which can be readily modified to obtain other useful derivatives.

We have studied the reaction of substituted 3-(chromen-3-ylmethylidene)furan-2(3*H*)-ones **1a**–**1c** [1] with hydrazine. We have found the only reported example of such reaction [2] which leads to the formation of 1-amino-6-chloro-3-[(3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)methyl]quinolin-4(1*H*)-one **A** (Scheme 1). The moderate yield (45%) of the product, as well as the lack of ^{13}C NMR data, makes the structure proposed in [2] doubtful. The reaction scheme and the structure of *N*-amino derivative **A** given in [2] are not typical of compounds containing a chromene fragment. We believe that the reaction scheme implying substitution of the phenolic hydroxy group (in structure like **B**; Scheme 2) with the formation of an *N*-aminopyridinone system is erroneous.

By reacting 3-(chromen-3-ylmethylidene)furan-2(3*H*)-ones **1a**–**1c** with hydrazine hydrate we obtained products that differed from those described in [2]. On the basis of spectral data, they were identified as 6-aryl-4-{[3-(2-hydroxyphenyl)-1*H*-pyrazol-5-yl]-methylidene}-4,5-dihydropyridazin-3-ols **2a**–**2c**. Their ^1H NMR spectra contained an upfield singlet at δ 2.40–2.49 ppm from methylene protons in the pyridazine ring, singlets at δ 6.45–6.58 and 6.94–7.04 ppm due to proton at the exocyclic double bond and proton on C^4 of the pyrazole ring, respectively, two broadened singlets at δ 3.35–3.28 and 4.87–4.92 ppm due to hydroxy protons, and a singlet at δ 10.75–10.84 ppm due to NH proton in the pyrazole ring. These data in combination with the number and position of signals in the ^{13}C NMR spectra fully confirmed the proposed structure of **2a**–**2c**.

Scheme 1.



A

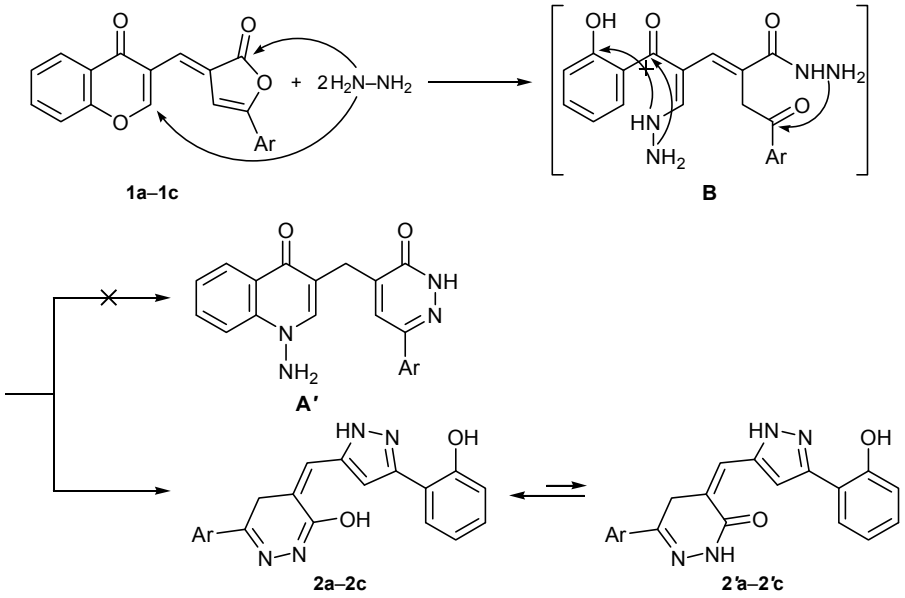
A probable reaction mechanism involves opening of the furan and pyran rings by the action of two hydrazine molecules and double intramolecular ring closure in intermediate **B** with elimination of two water molecules (Scheme 2). The existence of tautomers **2′a**–**2′c** is not supported by spectral data. No alternative reaction paths were observed.

Thus, in the reaction of compounds **1a**–**1c** with hydrazine, the most reactive is the carbonyl carbon atom in the aromatic fragment which is subjected to attack of the β-amino group of hydrazine. This is consistent with published data [3–5].

Compounds 2a–2c (*general procedure***).** A mixture of 0.01 mol of compound **1a**–**1c** and 0.02 mol of hydrazine hydrate in 12 mL of ethanol was stirred for 30–50 min at 35–40°C. The crystalline solid was filtered off and recrystallized from propan-2-ol.

4-{[3-(2-Hydroxyphenyl)-1*H*-pyrazol-5-yl]methylidene}-6-phenyl-4,5-dihydropyridazin-3-ol (2a).

Scheme 2.



Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**).

Yield 87%, mp 160–162°C. ^{1}H NMR spectrum, δ, ppm: 2.49 s (2H, 5-H), 3.28 br.s (1H, OH), 4.91 br.s (1H, OH), 6.45 s (1H, 5′-CH), 7.04 s (1H, 4′-H), 6.91–7.85 m (9H, H_{arom}), 10.81 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.0 (C^5), 98.1–136.1 (C_{arom}), 156.4 (C^6), 168.5 (COH), 170.1 (COH). Found, %: C 70.12; H 4.73; N 16.05. $C_{20}H_{16}N_4O_2$. Calculated, %: C 69.76; H 4.68; N 16.27.

4-{[3-(2-Hydroxyphenyl)-1*H*-pyrazol-5-yl]methylidene}-6-(4-methylphenyl)-4,5-dihydropyridazin-3-ol (2b). Yield 79%, mp 173–175°C. ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 2.47 s (2H, 5-H), 3.31 br.s (1H, OH), 4.87 br.s (1H, OH), 6.52 s (1H, 5′-CH), 7.01 s (1H, 4′-H), 7.15 d (2H, $CH_3C_6\mathbf{H}_4$, J = 8.1 Hz), 7.28 d (2H, $CH_3C_6\mathbf{H}_4$, J = 8.1 Hz), 7.35–7.49 m (4H, H_{arom}), 10.84 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 26.9 (CH_3), 42.1 (C^5), 99.9–136.8 (C_{arom}), 153.2 (C^6), 167.3 (COH), 169.4 (COH). Found, %: C 69.97; H 5.34; N 16.12. $C_{21}H_{18}N_4O_2$. Calculated, %: C 70.38; H 5.06; N 15.63.

4-{[3-(2-Hydroxyphenyl)-1*H*-pyrazol-5-yl]methylidene}-6-(4-methoxyphenyl)-4,5-dihydropyridazin-3-ol (2c). Yield 83%, mp 179–181°C. ^{1}H NMR spectrum, δ, ppm: 2.40 s (2H, 5-H), 3.35 br.s (1H, OH), 3.73 s (3H, OCH_3), 4.92 br.s (1H, OH), 6.58 s (1H, 5′-CH), 6.94 s (1H, 4′-H), 6.99–7.34 m (4H, H_{arom}), 7.03 d (2H, $CH_3OC_6\mathbf{H}_4$, J = 8.1 Hz), 7.31 d (2H, $CH_3OC_6\mathbf{H}_4$, J = 8.1 Hz), 10.75 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 43.4 (C^5), 58.3 (OCH_3), 98.1–136.7 (C_{arom}), 155.9 (C^6), 167.6 (**C**OCH_3), 168.1 (COH), 169.9 (COH). Found, %: C 67.65; H 5.32; N 15.43. $C_{21}H_{18}N_4O_3$. Calculated, %: C 67.37; H 4.85; N 14.96.

The ^{1}H NMR spectra were recorded on a Varian NB System 400 spectrometer (400 MHz for ^{1}H) at 20–25°C using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Analytical TLC was performed on Silufol UV-254 plates; eluent hexane–ethyl acetate–chloroform (2:2:1); spots were visualized by treatment with iodine vapor. The melting points were measured in open capillaries. The elemental analyses were obtained with a Vario Micro cube Elementar CHNS analyzer.

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