Ring Transformation of 3-Halo-4-methoxycoumarins into Pyrazoles with Hydrazines

Hikari Morita

Mitsubishi Rayon Co., Ltd., Daikoku-cho, Tsurumi-ku, Yokohama-shi 2300053, Japan

Kazuho Harada

School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 1088641, Japan

Yoshihisa Okamoto* and Kaname Takagi

Center of Liberal Arts and Sciences, Kitasato University, Kitasato, Sagamihara-shi, Kanagawa-ken 2288555, Japan

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3-Chloro- and 3-bromo-4-methoxycoumarins **1a,b** were readily transformed into 4-halo-5-(2-hydroxyphenyl)-3-oxo-2,3-dihydropyrazoles **2a,b** with hydrazines. In the reaction of **1a,b** with excess hydrazine and phenylhydrazine in boiling ethanol, unexpected 4-hydrazono-3-(2-hydroxyphenyl)-2-pyrazolin-5-ones **3**, **5** were obtained. The structure of **3** was determined by X-ray diffraction analysis.

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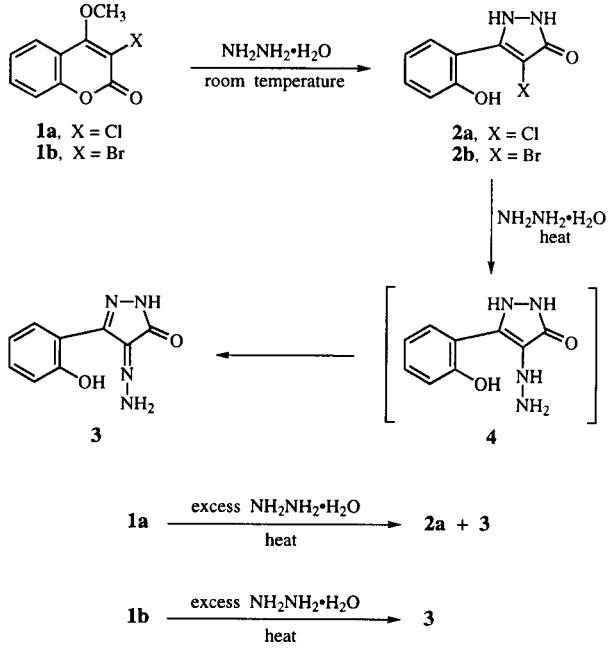
It is well known that certain coumarins are transformed into 5-(2-hydroxyphenyl)pyrazoles [1] and 6-(2-hydroxyphenyl)pyrimidines [2] on the reaction with hydrazines and amidines, respectively. In a previous paper [3], we described that 4-hydroxy and 4-methoxy-3-nitrocoumarins readily underwent similar ring transformation with hydrazines and amidines to give pyrazoles and pyrimidines, owing to the strong electron-withdrawing group at the 3-position of the coumarin ring. We also reported that 3-halo-4-methoxycoumarins were susceptible to nucleophilic attack by amidines and thiourea to give pyrimidine derivatives [4,5]. In continuation of these studies, we examined the reactions of 3-chloro- and 3-bromo-4-methoxycoumarins **1a,b** with hydrazines. We now report the facile ring transformation of **1a,b** into 4-halo-5-(2-hydroxyphenyl)pyrazolones and the formation of the unexpected 4-hydrazono-5-(2-hydroxyphenyl)pyrazolinones caused by air oxidation in the reaction process.

Treatment of **1a,b** with hydrazine hydrate (1:1 molar ratio) in ethanol at room temperature afforded 4-halo-5-(2-hydroxyphenyl)-3-oxo-2,3-dihydropyrazoles **2a,b** in 71 and 73% yields, respectively (Scheme 1).

Scheme 1



The structural elucidation of **2a,b** was based on elemental analyses and spectral data. Especially, the pmr spectra of **2a,b** showed a signal due to the phenolic hydroxy proton (each 10.00 ppm, 1H, br, s) in addition to the signals corresponding to the ring nitrogen proton, ring amido proton and aromatic protons. These observations indicate that the O1-C2 bond fission of **1a,b** occurred by nucleophilic attack of hydrazine to generate the proposed pyrazole ring system. Indeed, **2a,b** are easily soluble in a diluted sodium hydroxide solution.

When **1a** was heated with an excess of hydrazine hydrate in ethanol for 6 hours, orange-yellow crystals **3** were isolated together with **2a** (58% yield). Similar reaction of **1b** with hydrazine hydrate gave only **3**. The mass and elemental analysis of **3** established its molecular formula as $C_9H_8N_4O_2$ (mw, 204) which corresponded to a compound formed by condensation of 1 mole of **1a** with 2 moles of hydrazine with elimination of methanol, hydrochloric acid and hydrogen (each 1 mole). The ir spectra of **3** showed an absorption band at 1680 cm^{-1} attributable to the amido-carbonyl group. This suggests that **3** does not have a coumarin ring (unsaturated lactone), but a pyrazolone nucleus (cyclic amide). Finally, an

X-ray analysis was performed on the crystals of **3**, and the structure was determined to be 4-hydrazono-3-(2-hydroxyphenyl)-2-pyrazolin-5-one (**3**) (Figure 1, Tables I and II). The pmr spectrum of **3** is consistent with the proposed structure. Especially, the signals for the amino protons were observed at lower field (11.21 and 11.87 ppm), and this may indicate the formation of a hydrogen bond between the terminal amino hydrogen of the hydrazono group and the oxygen of the ring carbonyl group.

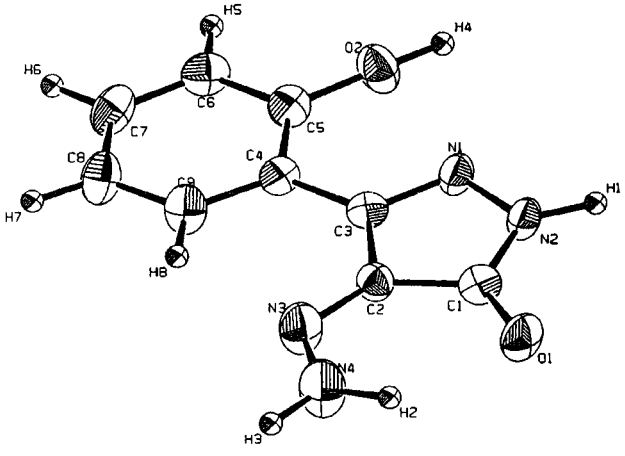


Figure 1. X-ray Structure of **3**.

Table I

Position Parameters and Equivalent Isotropic Thermal Parameters of **3** with Their Estimated Standard Deviations in Parentheses

Atom	x	y	z	B_{eq}
O(1)	-0.2589(7)	0.973(1)	0.4848(2)	4.1(3)
O(2)	0.1493(6)	0.114(1)	0.3760(2)	4.2(3)
N(1)	0.0076(7)	0.518(1)	0.4204(2)	3.1(3)
N(2)	-0.0182(8)	0.724(1)	0.4561(2)	3.1(3)
N(3)	-0.4660(8)	0.627(1)	0.4008(3)	4.5(4)
N(4)	-0.5685(9)	0.803(2)	0.4226(3)	5.9(4)
C(1)	-0.195(1)	0.795(2)	0.4568(3)	2.9(4)
C(2)	-0.292(1)	0.622(2)	0.4179(3)	2.9(4)
C(3)	-0.154(1)	0.453(1)	0.3970(3)	2.6(4)
C(4)	-0.172(1)	0.246(2)	0.3557(3)	2.8(4)
C(5)	-0.019(1)	0.101(2)	0.3426(3)	3.2(4)
C(6)	-0.040(1)	-0.095(2)	0.3037(3)	3.7(4)
C(7)	-0.208(1)	-0.146(2)	0.2778(3)	4.0(4)
C(8)	-0.360(1)	-0.007(2)	0.2899(3)	4.1(4)
C(9)	-0.339(1)	0.191(2)	0.3289(3)	4.0(4)

A possible mechanism for the formation of **3** is explained as follows. The pyrazolones **2a,b** are initially formed by nucleophilic attack of hydrazine on the α-pyrone ring of **1a,b**, and the subsequent substitution of hydrazine at the 4-position of **2a,b** gives 4-hydrazinopyrazolone **4** as an intermediate (Scheme 1) which is finally oxidized in air into **3**. In fact, when heated with an excess of hydrazine hydrate in ethanol, **2a,b** afforded, as expected, **3** in good yields.

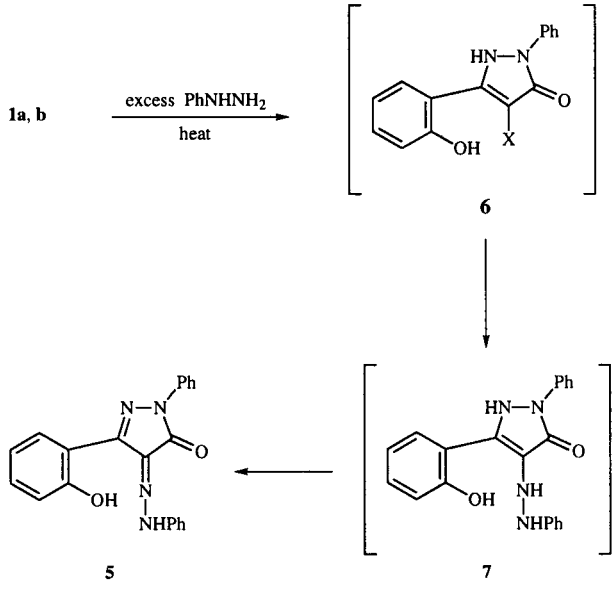
Table II

Selected Bond Lengths and Bond Angles

Bond Length (Å)		Bond Angle (°)	
O(1)-C(1)	1.251(8)	O(1)-C(1)-N(2)	127.3(7)
O(2)-C(5)	1.348(8)	O(1)-C(1)-C(2)	127.9(7)
N(1)-N(2)	1.394(7)	N(1)-N(2)-C(1)	113.0(5)
N(1)-C(3)	1.319(8)	N(1)-C(1)-C(2)	104.7(6)
N(2)-C(1)	1.349(8)	C(1)-C(2)-C(3)	105.6(6)
N(3)-N(4)	1.312(8)	C(2)-C(3)-N(1)	109.2(7)
N(3)-C(2)	1.312(8)	C(2)-N(3)-N(4)	117.3(7)
C(1)-C(2)	1.451(9)		
C(2)-C(3)	1.459(9)		
C(3)-C(4)	1.468(9)		

Phenylhydrazine did not react with **1a,b** in ethanol at room temperature. However, upon heating with an excess of phenylhydrazine in ethanol for 7 hours, **1a,b** led to 3-(2-hydroxyphenyl)-1-phenyl-4-phenylhydrazono-2-pyrazolin-5-one (**5**) in 29 and 33% yields, respectively (Scheme 2). The structure of **5**, analogous to that of **3**, was determined on the basis of analytical and spectral data. Scheme 2 shows the reaction pathway from **1a,b** to **5**. This is a similar mechanism as that proposed for the formation of **3** from the reaction of **1a,b** with hydrazine. The pyrazolone **6** initially formed is converted to intermediate **7** which is oxdized to **5**.

Scheme 2



For the ring transformation of **1a,b** into the pyrazolone derivatives, we propose a possible mechanism as shown in Scheme 3. Hydrazine should initially react with **1a,b** at C4 (not at C2) which is most sensitive to the nucleophile [6], to give the 4-hydrazinocoumarins **8** (R = H). Further nucleophilic attack of hydrazine at C2 of **8** leads to the ring opened hydrazine adducts **9** (R = H) which cyclize to the pyrazoles **2a,b** with the loss of hydrazine. In the struc-

ture of **8**, intramolecular attack of the terminal amino group of the 4-position to C2, which can also produce the pyrazolones **2a,b**, may be sterically difficult. In the reaction of **1a,b** with phenylhydrazine, the same reaction mechanism is possible; it comprises the first attack of the primary amino group of phenylhydrazine at C4 of **1a,b** to give **8** (Scheme 3, R = Ph). However, the ring transformation process in this case (**8** → **9** → **6**; R = Ph) requires the heating with an excess of phenylhydrazine because of the low nucleophilicity of phenylhydrazine. Under these conditions, the resulting pyrazolones **6** may immediately undergo further reactions with phenylhydrazine to provide **7** and then **5**.

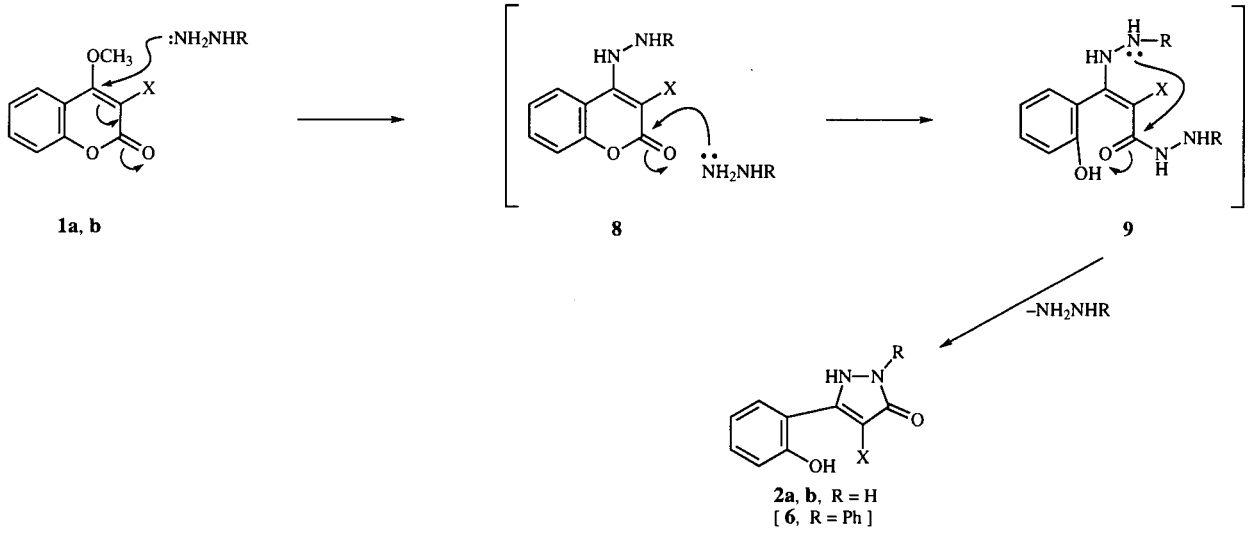
Compound **2a** was obtained in 71% yield, (1.04 g), mp 206-207° dec; ir (potassium bromide): 1638 cm^{-1}; pmr (deuteriodimethyl sulfoxide): 3.55 (1H, br, NH), 6.83-7.00 (2H, m, arom), 7.15-7.30 (1H, m, arom), 7.32-7.50 (1H, m, arom), 10.00 (1H, br, OH), 13.00 (1H, br, NH); ms: m/z 212, 210 (M^+), 175 (M^+-Cl).

Anal. Calcd. for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.77; H, 3.50; N, 13.43.

Compound **2b** was obtained in 73% yield (1.31 g), mp 152-153°; ir (potassium bromide): 1618 cm^{-1}; pmr (deuteriodimethyl sulfoxide): 3.44 (1H, br, NH), 6.85-7.00 (2H, m, arom), 7.21-7.27 (1H, m, arom), 7.42-7.44 (1H, m, arom), 10.00 (1H, br, OH), 12.25-13.10 (1H, br, NH); ms: m/z 256, 254 (M^+), 175 (M^+-Br).

Anal. Calcd. for $C_9H_7BrN_2O_2$: C, 42.38; H, 2.77; N, 10.98. Found: C, 42.58; H, 2.89; N, 10.77.

Scheme 3



EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point apparatus and are uncorrected. The ir spectra were recorded on a JASCO IRA-1 spectrophotometer. The pmr spectra were determined with a Varian VXR-300 spectrometer using tetramethylsilane as the standard. The mass spectra were recorded using a JMS D-100 apparatus. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

4-Halo-5-(2-hydroxyphenyl)-3-oxo-2,3-dihydropyrazoles **2a,b**.

A mixture of **1a,b** (7 mmoles) and hydrazine hydrate (0.35 g, 7 mmoles) in ethanol (30 ml) was stirred at room temperature for 5 hours. After removal of the solvent under reduced pressure, the residue was treated with 5% sodium hydroxide solution (20 ml) and the resulting solution was filtered. The filtrate was acidified with acetic acid, and the precipitates were collected by filtration and washed with water. Recrystallization from a mixture of ethanol and water gave **2a,b**.

4-Hydrazono-3-(2-hydroxyphenyl)-2-pyrazolin-5-one (**3**).

a) A mixture of **1a** (1.47 g, 7 mmoles) and hydrazine hydrate (1.00 g, 20 mmoles) in ethanol (30 ml) was heated under reflux for 6 hours. After removal of the solvent, the residue was treated with 5% sodium hydroxide solution. The insoluble orange crystals were filtered, washed with water and recrystallized from a mixture of ethanol and water to yield 0.35 g (25%) of **3**, mp 211-212°; ir (potassium bromide): 1680 cm^{-1}; pmr (deuteriodimethyl sulfoxide): 6.89-6.95 (2H, m, arom), 7.25-7.31 (1H, m, arom), 8.11 (1H, d, arom), 10.76 (1H, s, OH), 11.21 and 11.87 (each 1H, d, NH_2), 12.00 (1H, s, NH); ms: m/z 204 (M^+), 187, 176.

Anal. Calcd. for $C_9H_8N_4O_2$: C, 52.99; H, 3.95; N, 27.46. Found: C, 53.09; H, 3.87; N, 27.54.

The filtrate was acidified with acetic acid and the precipitates were collected by filtration, washed with water and recrystallized from a mixture of ethanol and water to yield 0.8 g (58%) of **2a**.

b) A mixture of **1b** (1.7 g, 7 mmoles) and hydrazine hydrate (1.00 g, 20 mmoles) in ethanol (30 ml) was heated for 6 hours.

After removal of the solvent, the residue was treated with a diluted sodium hydroxide solution. The insoluble red crystals were collected, washed with water and recrystallized from a mixture of ethanol and water to give **3** (0.18 g, 12%), mp 211-212°. An additional crystalline product was not obtained from the filtrate.

c) A mixture of **2a,b** (7 mmoles) and hydrazine hydrate (1.00 g, 20 mmoles) in ethanol (30 ml) was treated in the same manner as described above to give **3** (yields: 81% from **2a**, 65% from **2b**).

3-(2-Hydroxyphenyl)-1-phenyl-4-(phenylhydrazono)-2-pyrazolin-5-one (**5**).

A mixture of **1a,b** (7 mmoles) and phenylhydrazine (2.16 g, 20 mmoles) in ethanol (30 ml) was heated for 7 hours. After removal of the solvent, the residue was treated with 5% sodium hydroxide solution. The insoluble orange crystals were collected, washed with water and dried. Recrystallization from ethyl acetate gave **5** (yields: 0.73 g (29%) from **1a**); 0.81 g (33%) from **1b**, mp 190-191°; ir (potassium bromide): 1660 cm^{-1}; pmr (deuteriochloroform): 7.01-7.09 (2H, m, arom), 7.29-7.36 (3H, m, arom), 7.45-7.51 (6H, m, arom), 7.92-7.95 (2H, m, arom), 8.46-8.49 (1H, m, arom), 10.73 (1H, s, OH), 14.31 (1H, s, NH); ms: m/z 356 (M^+), 279, 273, 105, 77.

Anal. Calcd. for $C_{21}H_{16}N_4O_2$: C, 70.85; H, 4 53; N, 15.74. Found: C, 70.87; H, 4.56; N, 15.72.

X-Ray Analysis of **3**.

A prism crystal having approximate dimensions of 0.2 x 0.1 x 0.1 mm was mounted on a Rigaku AFC-5R diffractometer, and the cell parameters and the intensity data were measured with graphite-monochromated CuKα (λ = 1.54179Å) radiation at 23°. Approximate atomic coordinates were obtained by the direct method using MITHRIL [7]. The parameters of non-hydrogen atoms were refined by the full-matrix least-squares method with anisotropic temperature factors. The hydrogen atoms were located from a difference Fourier synthesis, and refined with isotropic temperature factors. The crystal data of **3** are as follows: Chemical formula $C_9H_8N_4O_2$; M.W. 204.19; monoclinic; space group $P2_1/c$; Z = 4; unit cell dimensions a = 7.356(7)Å, b = 5.068(9)Å, c = 24.816(6)Å, β = 94.70(5)°, γ = 101.17(1)°, V = 922(3)°A^3; D_{cal} = 1.471 gcm^{-3}; μ (CuKα) = 8.73 cm^{-1}. Of the total of 2065 reflections up to the 2 θ range of 140.1°(unique reflections: 1919), 601 were measured as above the 3 σ (1) level and were used. The final R value was 0.056. A perspective drawing of the molecular structure of **3** is shown in Figure 1. The positional parameters for **3** are listed in Table I. The selected bond lengths and bond angles for **3** are listed in Table II.

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