

Chemistry of 2-Ylidenefuran-3(2*H*)-ones: XIX.* Reaction of 5-Aryl-2-(oxoylidene)furan-3(2*H*)-ones with Carboxylic Acid Hydrazides

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Received March 16, 2006

Abstract—2-[2-(4-Chlorophenyl)-2-oxoethylidene]-5-phenylfuran-3(2*H*)-one and methyl (5-aryl-3-oxo-2,3-dihydrofuran-2-ylidene)acetates react with carboxylic acid hydrazides to give the corresponding 3-substituted 2-acyl-6-aryl-3-hydroxy-2,3-dihydropyridazin-4(1*H*)-ones. Specificities of the product structure are discussed.

DOI: 10.1134/S1070428007060115

It was found previously that reactions of 2-ylidenefuran-3(2*H*)-ones with hydrazine and aryl- or hetarylhydrazines are quite versatile: they lead to the formation of hydrazino derivatives of 3-oxofuran [2] and cyclic azoles or azines, e.g., 3-acylpyrazoles [3–6], 3-(3-oxopyrazol-5-yl)pyrazoles [6, 7], or substituted pyridazin-4(1*H*)-ones [3, 6, 8, 9]. Published data on reactions of acylhydrazines with five-membered 2-ylidene-2,3-dihydro-3-oxo heterocycles are limited to our short communications [10–12]. In the present work we examined reactions of 2-oxoylidenefuran-3(2*H*)-ones with carboxylic acid hydrazides and their derivatives in comparison with simpler hydrazines.

The direction of the reaction of 5-aryl-2-(oxoylidene)furan-3(2*H*)-ones **Ia–Ic** with carboxylic acid hydrazides depended on neither substrate nor reagent structure. Methyl (5-aryl-3-oxo-2,3-dihydrofuran-2-ylidene)acetates **Ia** and **Ib** [13, 14] and 2-[2-(4-chlorophenyl)-2-oxoethylidene]-5-phenylfuran-3(2*H*)-one (**Ic**) [15] reacted with acetic, benzoic, *p*-methoxybenzoic, *p*-nitrobenzoic, and salicylic acid hydrazides in ethanol on heating for a short time (10–30 min) under reflux to give 44–86% of 3-substituted 2-acyl-6-aryl-3-hydroxy-2,3-dihydropyridazin-4(1*H*)-ones **IIa–IIIh** (Scheme 1); the products were identified on the basis of spectral data in comparison with known 4-oxopyri-

dazines [6, 9]. Compounds **II** exist in solution as two tautomers **A** and **B**. From the reaction mixtures we also isolated small amounts of 1,2-diacylhydrazines **III** which were identified by comparison with authentic samples.

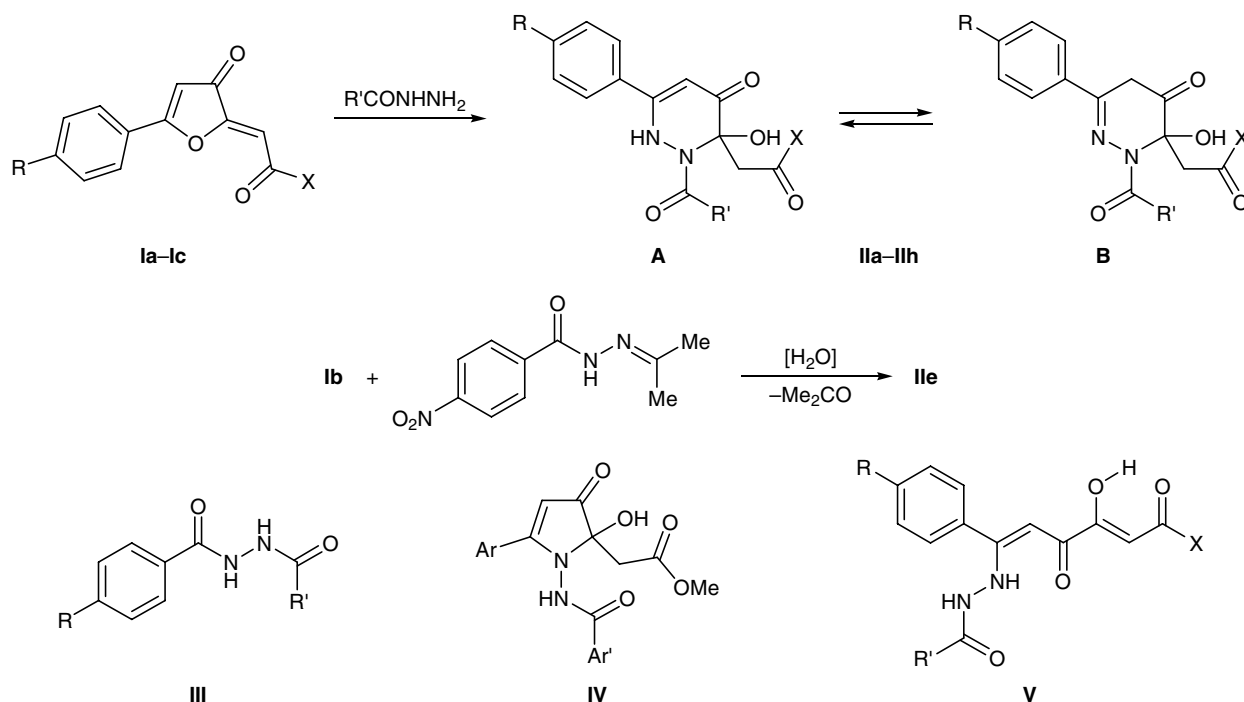
Pyridazinone **IIe** was also synthesized by reaction of *N'*-isopropylidene-4-nitrobenzohydrazide with methyl (3-oxo-5-phenyl-2,3-dihydrofuran-2-ylidene)acetate (**Ib**) under analogous conditions. It should be noted that other *N'*-ylidene-substituted hydrazides, e.g., *N'*-benzylidene-4-nitrobenzohydrazide, failed to react with furanylidene acetate **Ib**.

Initially [16, 17], we erroneously assigned some pyridazin-4(1*H*)-ones **II** the structure of (1-aroyle-amino-5-aryl-2-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrol-2-yl)acetates **IV** (Ar = 4-RC₆H₄, Ar' = R', X = OMe). The ¹H NMR spectra of compounds **II** in chloroform-*d* contain a downfield signal at δ 7.95–8.15 ppm which belongs to the N¹H proton in tautomer **A**; this signal disappears completely upon addition of trifluoroacetic acid due to fast proton exchange.

Presumably, the reaction of carboxylic acid hydrazides with furanones **Ia–Ic** involves nucleophilic attack by the hydrazide NH₂ group [or NH group of the enamino tautomer of *N'*-isopropylidene-4-nitrobenzohydrazide, NHC(Me)=CH₂] at the electrophilic C⁵ atom of the furan ring in **I**. Intermediate enehydrazino-

* For communication XVIII, see [1].

Scheme 1.



I, X = OMe, R = Me (**a**), H (**b**); X = 4-ClC₆H₄, R = H (**c**); **II**, X = OMe, R = R' = Me (**a**); R = Me, R' = Ph (**b**); R = H, R' = Ph (**c**), 2-HOC₆H₄ (**d**), 4-O₂NC₆H₄ (**e**); X = 4-ClC₆H₄, R = H, R' = Ph (**f**), 4-MeOC₆H₄ (**g**), 2-HOC₆H₄ (**h**).

carbonyl structure **V** (Scheme 1) undergoes intramolecular heterocyclization at the NH group of the acylhydrazine moiety to give pyridazin-4(1*H*)-ones **II**. The hydroxy group in salicylic acid hydrazide does not participate in the reaction with furanones **I**, and the corresponding products (pyridazinones **II****d** and **II****h**) have unchanged hydroxy group in the aromatic ring. Regioselective nucleophilic attack by hydrazides at the electron-deficient C⁵ atom in compound **I**, despite the presence of other electrophilic centers (C², C^{2'}, C³), indicates that the reaction is likely to be orbital-controlled [18].

Pyridazinones **II** showed a pronounced bacteriostatic activity against *Staphylococcus aureus* P-209 and *Escherichia coli* M₁₇ [10].

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord M-80 spectrometers from samples dispersed in mineral oil. The ¹H NMR spectra were measured on RYa-2310 (60 MHz), Bruker AC-300 (300 MHz), and Bruker DRX-500 (500 MHz) instruments using CDCl₃, DMSO-*d*₆, or DMSO-*d*₆-CF₃COOH (10:1) as solvent and HMDS or TMS as internal reference. The ¹³C NMR spectrum of compound **II****g** was obtained on

a JEOL EX90A FT-NMR spectrometer (22 MHz) in CDCl₃ using TMS as internal reference. The mass spectra (electron impact, 70 eV) were recorded on a Kratos MS-30 mass spectrometer (United Kingdom) with direct sample admission into the ion source (emission current 1000 mA, vaporizer temperature 100–120°C). The progress of the reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using benzene–diethyl ether–acetone (10:9:1) as eluent; spots were visualized by treatment with iodine vapor.

Initial 5-aryl-2-(oxoylidene)furan-3(2*H*)-ones **Ia–Ic** were prepared by the procedures described in [13–15].

2-Acyl-6-aryl-3-hydroxy-2,3-dihydropyridazin-4(1*H*)-ones IIa–IIh (general procedure). *a.* A mixture of equimolar amounts (5.0 mmol) of compound **Ia–Ic** and the corresponding carboxylic acid hydrazide in 100–150 ml of ethanol was stirred on heating until it became homogeneous and was then heated under reflux for 10–30 min (TLC). The solvent was distilled off, and the residue was recrystallized from ethanol, acetonitrile, or chloroform–hexane (1:1) to obtain compounds **IIa–IIh** as colorless crystals. Recrystallization of the residue from toluene gave a small amount of 1,2-diacylhydrazine **III**.

b. Compound **Iie** was also synthesized by reaction of **Ib** with *N'*-isopropylidene-4-nitrobenzohydrazide, following an analogous procedure.

Methyl [2-acetyl-3-hydroxy-6-(4-methylphenyl)-4-oxo-1,2,3,4-tetrahydropyridazin-3-yl]acetate (IIa). Yield 0.70 g (44%), mp 149–150°C (decomp., from ethanol). ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 2.12 s (3H, 4-CH₃C₆H₄), 2.45 s (3H, COCH₃), 3.42 d.d (2H, 3-CH₂, *J* = 15.8 Hz), 3.72 s (3H, COOCH₃), 4.05 s (2H, 5-H, tautomer **B**), 7.30–7.95 m (4H, C₆H₄). Found, %: C 60.54; H 5.89; N 8.61. C₁₆H₁₈N₂O₅. Calculated, %: C 60.37; H 5.70; N 8.80.

Methyl [2-benzoyl-3-hydroxy-6-(4-methylphenyl)-4-oxo-1,2,3,4-tetrahydropyridazin-3-yl]acetate (IIb). Yield 1.50 g (79%), mp 139–140°C (decomp., from acetonitrile). ¹H NMR spectrum (CDCl₃), δ, ppm: 2.31 s (3H, 4-CH₃C₆H₄), 3.65 d.d (2H, 3-CH₂, *J* = 9.2 Hz), 3.71 s (3H, COOCH₃), 5.82 s (1H, 5-H, tautomer **A**), 7.05–7.89 m (9H, C₆H₄, C₆H₅), 7.95 s (1H, 1-H). Found, %: C 66.20; H 5.48; N 7.22. C₂₁H₂₀N₂O₅. Calculated, %: C 66.31; H 5.30; N 7.36.

Methyl (2-benzoyl-3-hydroxy-4-oxo-6-phenyl-1,2,3,4-tetrahydropyridazin-3-yl)acetate (IIc). Yield 1.43 g (78%), mp 118–119°C (decomp., from ethanol). ¹H NMR spectrum (CDCl₃), δ, ppm: 3.63 d.d (2H, 3-CH₂, *J* = 8.5 Hz), 3.73 s (3H, COOCH₃), 5.37 s (1H, 5-H, tautomer **A**), 7.33–8.05 m (10H, C₆H₅), 8.10 s (1H, 1-H). Found, %: C 65.32; H 5.18; N 7.49. C₂₀H₁₈N₂O₅. Calculated, %: C 65.57; H 4.95; N 7.65.

Methyl [3-hydroxy-2-(2-hydroxybenzoyl)-4-oxo-6-phenyl-1,2,3,4-tetrahydropyridazin-3-yl]acetate (IId). Yield 1.41 g (74%), mp 120–121°C (decomp., from chloroform–hexane, 1:1). IR spectrum, ν, cm⁻¹: 3422 (N–H); 1730 (C=O, ester); 1711 (C⁴=O); 1665, 1647, 1620 (C=O, amide; C=C, C=C_{arom}). ¹H NMR spectrum, δ, ppm: in DMSO-*d*₆: 3.65 m (5H, 3-CH₂-COOCH₃), 5.84 s (1H, 5-H, tautomer **A**), 7.06–8.10 m (10H, C₆H₅, C₆H₄, 1-H), 10.35 br.s (1H, C₆H₄OH); in DMSO-*d*₆-CF₃COOH (10:1): 3.70 d.d and 4.06 d.d (1H each, 3-CH₂, *J* = 9.6 Hz), 3.78 s (3H, COOCH₃), 5.90 s (1H, 5-H, tautomer **A**), 7.12–8.17 m (9H, C₆H₅, C₆H₄), 10.65 br.s (1H, HOC₆H₄). Mass spectrum, *m/z* (*I*_{rel}, %): 382 (3) [*M*]⁺, 351 (0.5) [*M* – CH₃O]⁺, 281 (56) [*M* – CH₃O – CH₂CO]⁺, 263 (3) [*M* – CH₃O – CH₂CO – H₂O – H]⁺, 161 (88) [C₆H₅C(=NH)CH₂CONH]⁺, 160 (5) [C₆H₅C₃H₃N₂O]⁺, 121 (100) [HOC₆H₄C≡O]⁺, 103 (6) [C₆H₅C≡N]⁺, 93 (18) [HOC₆H₄]⁺, 77 (14) [C₆H₅]⁺. Found, %: C 62.74; H 4.85; N 7.46. C₂₀H₁₈N₂O₆. Calculated, %: C 62.82; H 4.74; N 7.33. *M* 382.

Methyl [3-hydroxy-2-(4-nitrobenzoyl)-4-oxo-6-phenyl-1,2,3,4-tetrahydropyridazin-3-yl]acetate (IIe). Yield 1.77 g (86%) (*a*), 1.38 g (67%) (*b*), mp 153–154°C (decomp., from ethanol). IR spectrum, ν, cm⁻¹: 3385 (N–H); 3280 (O–H); 1734 (C=O, ester); 1716 (C⁴=O); 1678, 1656, 1635 (C=O, amide; C=C, C=C_{arom}). ¹H NMR spectrum (CDCl₃), δ, ppm: 3.77 s (3H, COOCH₃), 3.82 d.d (2H, 3-CH₂, *J* = 9.8 Hz), 5.62 s (1H, 5-H, tautomer **A**), 6.11 s (1H, 3-OH), 7.25–8.08 m (9H, C₆H₅, C₆H₄), 8.17 s (1H, 1-H). Found, %: C 58.70; H 4.32; N 9.88. C₂₀H₁₇N₃O₇. Calculated, %: C 58.39; H 4.17; N 10.21.

2-Benzoyl-3-[2-(4-chlorophenyl)-2-oxoethyl]-3-hydroxy-6-phenyl-2,3-dihydropyridazin-4(1*H*)-one (II*f*). Yield 1.59 g (71%), mp 162–163°C (decomp., from acetonitrile). ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 3.55 d.d (2H, 3-CH₂, *J* = 16.4 Hz), 4.95 s (2H, 5-H, tautomer **B**, 72%), 7.05 s (1H, 5-H, tautomer **A**, 28%), 7.55–8.10 m (15H, C₆H₅, C₆H₄, 1-H). Found, %: C 67.06; H 4.45; Cl 7.81; N 6.10. C₂₅H₁₉ClN₂O₄. Calculated, %: C 67.19; H 4.29; Cl 7.93; N 6.27.

3-[2-(4-Chlorophenyl)-2-oxoethyl]-3-hydroxy-2-(4-methoxybenzoyl)-6-phenyl-2,3-dihydropyridazin-4(1*H*)-one (II*g*). Yield 2.00 g (85%), mp 180–181°C (decomp., from ethanol). ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 3.66 d.d (2H, 3-CH₂, *J* = 16.0 Hz), 3.84 s (3H, MeO, tautomer **B**), 3.85 s (3H, MeO, tautomer **A**), 4.72 s (2H, 5-H, tautomer **B**, 64%), 7.06 s (1H, 5-H, tautomer **A**, 36%), 7.50–8.10 m (14H, C₆H₅, C₆H₄, 1-H). ¹³C NMR spectrum (CDCl₃), δ_C, ppm: 45.9 (C⁵, tautomer **B**), 49.1 (3-CH₂), 55.2 (CH₃O), 91.8 (C³), 93.3 (5-H, tautomer **A**), 113.6–176.7 (C_{arom}, C⁶, 1-C=O), 194.3 and 197.2 (C⁴, tautomers **A** and **B**), 203.2 (4-ClC₆H₄CO). Found, %: C 65.79; H 4.15; Cl 7.52; N 6.03. C₂₆H₂₁ClN₂O₅. Calculated, %: C 65.48; H 4.44; Cl 7.43; N 5.87.

3-[2-(4-Chlorophenyl)-2-oxoethyl]-3-hydroxy-2-(2-hydroxybenzoyl)-6-phenyl-2,3-dihydropyridazin-4(1*H*)-one (II*h*). Yield 1.46 g (63%), mp 172–173°C (decomp., from ethanol). ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 3.54 d.d (2H, 3-CH₂, *J* = 17.2 Hz), 4.91 s (2H, 5-H, tautomer **B**, 78%), 6.95 s (1H, 5-H, tautomer **A**, 22%), 7.25–8.08 m (14H, C₆H₅, C₆H₄, 1-H), 10.30 s (1H, 2-HOC₆H₄). Found, %: C 64.70; H 4.28; Cl 7.48; N 5.91. C₂₅H₁₉ClN₂O₅. Calculated, %: C 64.87; H 4.14; Cl 7.66; N 6.05.

1,2-Dibenzoylhydrazine (III*a*). Yield 0.18 g (15%), mp 241–242°C (decomp., from toluene). Mass spectrum, *m/z* (*I*_{rel}, %): 240 (23) [*M*]⁺, 136 (1) [C₆H₅CONHNH₂]⁺, 121 (2) [C₆H₅CONH₂]⁺, 105 (100)

$[\text{C}_6\text{H}_5\text{C}\equiv\text{O}]^+$, 77 (44) $[\text{C}_6\text{H}_5]^+$, 51 (15). Found, %: C 70.12; H 4.94; N 11.73. $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$. Calculated, %: C 69.99; H 5.03; N 11.66. M 240.

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