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Unexpected formation of pyridazine-5,6-dione derivatives in the reactions of 3-arylhydrazono-2,4-dioxo-4-pentafluorophenylbutanoates with hydrazines

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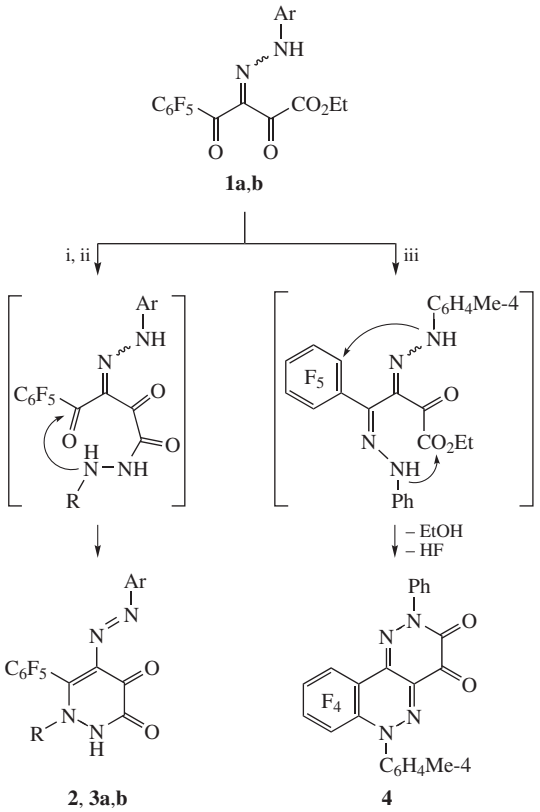
The reactions of 3-arylhydrazono-2,4-dioxo-4-pentafluorophenylbutanoates with hydrazine hydrate and phenylhydrazine resulted in the formation of 4-arylazo-3-pentafluorophenyl-1,2-dihydro-5*H*,6*H*-pyridazine-5,6-diones or 6-aryl-2-phenyl-7,8,9,10-tetrafluoro-2,3,4,6-tetrahydropyridazino[4,3-*c*]cinnoline-3,4-dione.

In the reactions of 4-alkyl(aryl)-2,4-dioxobutanoates, including fluorinated compounds, with hydrazines, cyclocondensation at a β-dicarbonyl fragment with the formation of substituted pyrazoles is the main process.[1,2] In these reactions, the primary attack occurs at the α-carbonyl carbon atom because intermediate 2-arylhydrazono-4-oxobutanoates were isolated in a number of cases. There is no published data on changes in the reaction paths on the introduction of various substituents at the 3-position of 2,4-dioxobutanoates. 3-Arylhydrazono-substituted 4-alkyl(aryl, polyfluoroalkyl)-2,4-dioxoesters are no exception; they also form pyrazole derivatives in reactions with hydrazines.[2,3]

We studied the reactions of 3-arylhydrazono-2,4-dioxo-4-pentafluorophenylbutanoates **1a**,**b** with hydrazine hydrate and phenylhydrazine and found that substituted pyridazine-5,6-diones **2**, **3a**,**b**, which resulted from the addition of a dinucleophile at the γ-dicarbonyl fragment, were the main isolated products of these reactions. The structures of the resulting compounds were determined based on elemental analysis data and IR, NMR and mass spectra.†

The mass spectra of compounds **2**, **3a**,**b** exhibited peaks due to molecular ions. In addition, in the case of compound **2**, an intense peak of $[M - 20]^+$ (I = 70.32%), which corresponds to the ion of 6-(4-methoxyphenyl)-7,8,9,10-tetrafluoro-2,3,4,6-tetra-



Scheme 1 *Reagents and conditions*: i, $NH_2NH_2 \cdot H_2O$, $MeCO_2H$, 20 °C, 1 h; ii, NH_2NHPh, Et_2O, reflux, 3 h; iii, NH_2NHPh, EtOH, reflux, 10 min.

† New isolated compounds **2**, **3a**,**b**, **4** were characterised by elemental analyses, IR, ^{1}H NMR (400 MHz, Me_4Si) and ^{19}F NMR (75.0 MHz, C_6F_6) spectroscopy and mass spectrometry (EI, 70 eV).

*5-Hydroxy-4-(4-methoxyphenylazo)-3-pentafluorophenyl-1*H,*6*H*-pyridazin-6-one* **2**. A 40% hydrazine hydrate solution (0.25 ml) was added to a solution of ester **1a** (444 mg, 1 mmol) in glacial acetic acid (10 ml). The reaction mixture was stirred at room temperature for 1 h. Next, distilled water (20 ml) was added. The precipitate formed was filtered off. After column chromatography on silica gel (eluent: chloroform–methanol in a 10:1 ratio), 189 mg (49%) of compound **2** was obtained; mp 230 °C. ^{1}H NMR [$(CD_3)_2CO$] δ: 3.83 (s, 3H, OMe), 7.35 (m, 4H, C_6H_4), 8.17 (br. s, 1H, NH), 14.47 (br. s, 1H, OH). ^{19}F NMR [$(CD_3)_2CO$] δ: 0.24 (m, 2F), 9.47 (m, 1F), 22.93 (m, 2F). IR (Vaseline oil, ν/cm^{-1}): 3527, 3167 (NH, OH), 1673 (C=O), 1597, 1579, 1526, 1499 (NH, C=C, C=N, N=N). IR (0.01 mmol cm^{-3} in $CHCl_3$, ν/cm^{-1}): 3684, 3621, 3389, 1578 (NH, OH), 1684 (C=O), 1600, 1524, 1502 (NH, C=C, C=N, N=N). MS, m/z (I_{rel}, %): 412 (24.27) $[M]^+$, 392 (70.32), 364 (5.54), 307 (7.54), 295 (21.70), 278 (10.87), 264 (9.79), 135 (38.82), 107 (100.00), 92 (25.92), 77 (36.34), 64 (14.46). Found (%): C, 49.29; H, 2.16; F, 22.67; N, 13.35. Calc. for $C_{17}H_9F_5N_4O_3$ (%): C, 49.53; H, 2.20; F, 23.04; N, 13.59.

*4-(4-Methoxyphenylazo)-3-pentafluorophenyl-2-phenyl-1,2-dihydro-5*H,*6*H*-pyridazine-5,6-dione* **3a** (general procedure). Phenylhydrazine (108 mg, 1 mmol) was added to a solution of ester **1a** (444 mg, 1 mmol) in diethyl ether (10 ml). The reaction mixture was refluxed for 3 h, and the solvent was evaporated. After column chromatography on silica gel (eluent: chloroform), 225 mg (42%) of product **3a**, mp 177–178 °C, was obtained. ^{1}H NMR ($CDCl_3$) δ: 3.84 (s, 3H, Me), 6.91–7.75 (m, 9H, C_6H_4, Ph), 14.17 (br. s, 1H, NH). ^{19}F NMR ($CDCl_3$) δ: 1.20 (m, 2F), 11.61 (m, 1F), 22.15 (m, 2F). IR (Vaseline oil, ν/cm^{-1}): 3257, 1590 (NH), 1682, 1650 (C=O), 1611, 1560, 1515 (C=C, C=N, N=N). MS, m/z (I_{rel}, %): 488 (100) $[M]^+$, 411 (8.93), 195 (47.88), 167 (6.61), 121 (21.13), 107 (23.78), 105 (13.14), 92 (18.50), 91 (14.80), 78 (7.87), 77 (65.24), 65 (13.69). Found (%): C, 56.50; H, 2.49; F, 19.58; N, 11.29. Calc. for $C_{23}H_{13}F_5N_4O_3$ (%): C, 56.57; H, 2.68; F, 19.45; N, 11.47.

hydro-2*H*-pyridazino[4,3-*c*]cinnoline-3,4-dione formed by the aromatic replacement of the *ortho*-fluorine atom in the pentafluorophenyl substituent by the amino group of the arylhydrazone fragment with the elimination of the HF molecule, was observed. This is a characteristic reaction of the test compounds containing arylhydrazone and pentafluorophenyl groups.[3] The other most important peaks can correspond to the products of stepwise degradation of the ion of the resulting tricyclic pyridazocinnoline system.[4]

The cyclocondensation of esters **1a**,**b** with phenylhydrazine is a regiodirected reaction because it results in the formation of heterocycles from the same regioisomeric series. It is likely that this results from the primary addition of a dinucleophile at the ester group of the parent ester. The regioisomeric structure of pyridazinodiones **3a**,**b** was demonstrated by the impossibility of their intramolecular cyclisation to pyridazocinnolines **4**. It is evident that, unlike alternative pyridazine-3,4-diones, pyridazine-5,6-diones **3a**,**b** cannot close to form a cinnoline ring. We failed to perform the cyclisation of compounds **3a**,**b**. The proposed isomeric structure of pyridazinodiones **3a**,**b** was additionally supported by the absence of a $[M - HF]^+$ peak, which was observed in the case of pyridazinodione **2**, from the mass spectra of compounds **3a**,**b**.

*4-(4-Methylphenylazo)-3-pentafluorophenyl-2-phenyl-1,2-dihydro-5*H*,6*H*-pyridazine-5,6-dione* **3b**. After recrystallisation from ethanol, 225 mg (46%) of product **3b**, mp 161–162 °C, was obtained. ^{1}H NMR ($CDCl_3$) δ: 2.36 (s, 3H, Me), 6.96–7.73 (m, 9H, C_6H_4, Ph), 14.15 (br. s, 1H, NH). ^{19}F NMR ($CDCl_3$) δ: 1.21 (m, 2F), 11.64 (m, 1F), 22.09 (m, 2F). ^{13}C NMR (100 MHz, Me_4Si, $CDCl_3$) δ: 21.6 (Me), 113.3, 118.4, 119.4, 123.6, 128.2, 129.4, 130.3, 143.1, 50.7, 152.2, 137.2–145.9 (m, C_6F_5), 190.1 (C^6), 205.7 (C^5). IR (Vaseline oil, ν/cm^{-1}): 3264, 1595 (NH), 1688, 1650 (C=O), 1614, 1550, 1523 (C=C, C=N, N=N). IR (0.01 mmol cm^{-3} in $CHCl_3$, ν/cm^{-1}): 3684, 3621, 1597 (NH), 1683, 1662 (C=O), 1613, 1530 (C=N, N=N). MS, *m*/*z* (I_{rel}, %): 472 (100) $[M]^+$, 395 (12.11), 248 (17.67), 119 (25.82), 109 (10.11), 91 (15.35), 77 (60.76), 65 (11.59). Found (%): C, 58.32; H, 2.83; F, 20.55; N, 11.62. Calc. for $C_{23}H_{13}F_5N_4O_2$ (%): C, 58.48; H, 2.77; F, 20.11; N, 11.86.

6-(4-Methylphenyl)-2-phenyl-7,8,9,10-tetrafluoro-2,3,4,6-tetrahydropyridazino[4,3-c]cinnoline-3,4-dione **4**. Phenylhydrazine (1.43 ml, 2.9 mmol) was added to a solution of ester **1b** (1.247 g, 2.9 mmol) in ethanol (25 ml). The reaction mixture was boiled for 10 min and then cooled to 20 °C. The resulting precipitate was filtered off and washed with chloroform. 189 mg (54%) of product **4**, mp 244–245 °C, was obtained. ^{1}H NMR [$(CD_3)_2SO$] δ: 2.34 (s, 3H, Me), 7.31–7.73 (m, 9H, C_6H_4, Ph). ^{19}F NMR [$(CD_3)_2SO$] δ: 2.68 (m, 1F), 14.97 (m, 1F), 20.28 (m, 1F), 30.75 (m, 1F). IR (Vaseline oil, ν/cm^{-1}): 1683, 1665, 1650 (C=O, C=N). Found (%): C, 58.74; H, 2.63; F, 16.01; N, 12.16. Calc. for $C_{23}H_{12}F_4N_4O_2$ (%): C, 58.98; H, 2.58; F, 16.23; N, 11.96.

The presence of two weak-field signals of two carbonyl carbon atoms (C^5, C^6) in the ^{13}C NMR spectrum of compound **3b** indicates that products **3a**,**b** have pyridazine-5,6-dione structures.

According to IR-spectroscopic data (one high-frequency absorption band of the carbonyl group), pyridazine **2** occurs in an hydrazono-enol form in a $CHCl_3$ solution or in a solid state, unlike N-phenyl-substituted pyridazines **3a**,**b**, which occur as azo-keto tautomers. The low-frequency shift of carbonyl group absorption bands in the IR spectra of heterocycles **2**, **3a**,**b** is due to their conjugation with other C=C and C=N bonds.

Pyridazino[4,3-*c*]cinnoline **4** was prepared by the reaction of ester **1b** with phenylhydrazine in boiling ethanol. It is likely that, under the specified conditions, ester **1b** initially reacted with a dinucleophile at the γ-carbonyl (this reaction site can be activated under conditions of a proton-donor solvent). Next, the intermediate underwent consecutive cyclisation reactions to form the pyridazino[4,3-*c*]cinnoline system.

Considerable electron density redistribution due to the presence of pentafluorophenyl and arylhydrazone substituents can be responsible for the unusual behaviour of esters **1** in the reactions with hydrazines. Evidently, this redistribution decreases the probability of a nucleophilic attack of the α-carbonyl carbon atom by the amino groups of hydrazine, as is the case with 2,4-dioxobutanoates and their derivatives.[1,2]

Thus, we found that 3-arylhydrazono-4-pentafluorophenyl-2,4-dioxobutanoates **1** can undergo cyclocondensation with dinucleophilic reagents at the γ-dicarbonyl fragment, unlike their fluoroalkyl and nonfluorinated analogues and unsubstituted 2,4-dioxobutanoates.

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