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LETTERS TO THE EDITOR

# Synthesis of New 2-Substituted 5-Hydroxypyrano[2,3-*d*][1,3]oxazine-4,7-diones

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**Abstract**—The reaction of carboxylic acid amides with malonyl chloride in acetonitrile or tetrahydrofuran without heating leads to the formation of previously unknown 2-substituted 5-hydroxypyrano[2,3-*d*][1,3]oxazines. The structure of the obtained compounds was established by high resolution mass spectrometry, NMR spectroscopy, and X-ray analysis.

**Keywords:** pyrano[2,3-*d*][1,3]oxazine, malonyl chloride, X-ray analysis

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Oxo derivatives of 1,3-oxazines are important reagents for organic synthesis. Molecules of 1,3-oxazin-4-ones possess three electrophilic centers, and their reactions with nucleophiles lead to the formation of various acyclic and heterocyclic compounds, in particular malonamic acid derivatives exhibiting hypotensive activity [1] and 1,2,4-triazoles with antiviral activity [2]. On the other hand, related fused structures, pyranooxazines, have been poorly studied.

Ziegler and Meindl [3] previously reported the reaction of carboxylic acid amides **2a** and **2b** with malonyl chloride (**1**), which led to the formation of 2-substituted 4-hydroxypyrano[3,4-*e*][1,3]oxazine-5,7diones **3a** and **3b** (Scheme 1). The reactions were carried out under fairly harsh conditions, on heating without a solvent.

In continuation of studies in this field, amides **2a**–**2h** were reacted with malonyl chloride **1** at a molar ratio of 1 : 2 in acetonitrile or tetrahydrofuran 20–25°C. The isolated products were characterized by high-resolution mass spectrometry and NMR. According to the HRMS data, compounds **4a** and **4b** had the same elemental compositions as pyranooxazines **3a** and **3b** described in [3]. However, the X-ray analysis of a single crystal of *p*-bromophenyl derivative **4e** (Fig. 1) showed that the isolated compounds are representatives of previously unknown heterocyclic system, pyrano[2,3-*d*][1,3]-oxazines **4a**–**4h** [4] (Scheme 1).

Thus, we have found that carboxylic acid amides **2a**–**2h** react with 2 equiv of malonyl chloride in acetonitrile or tetrahydrofuran at room temperature to afford 2-substituted 5-hydroxypyrano[2,3-*d*][1,3]-oxazine-4,7-diones [5]. The presence of five electrophilic centers in their molecules makes them valuable substrates for reactions with various nucleophiles and potential precursors to new privileged heterocyclic structures.

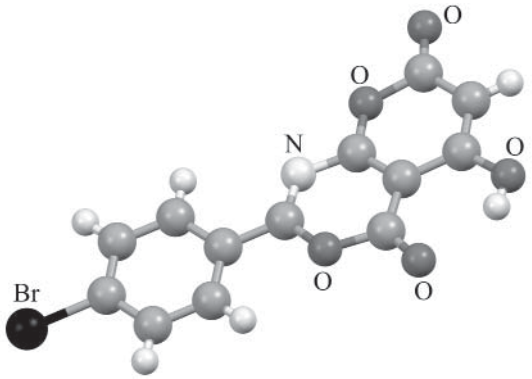
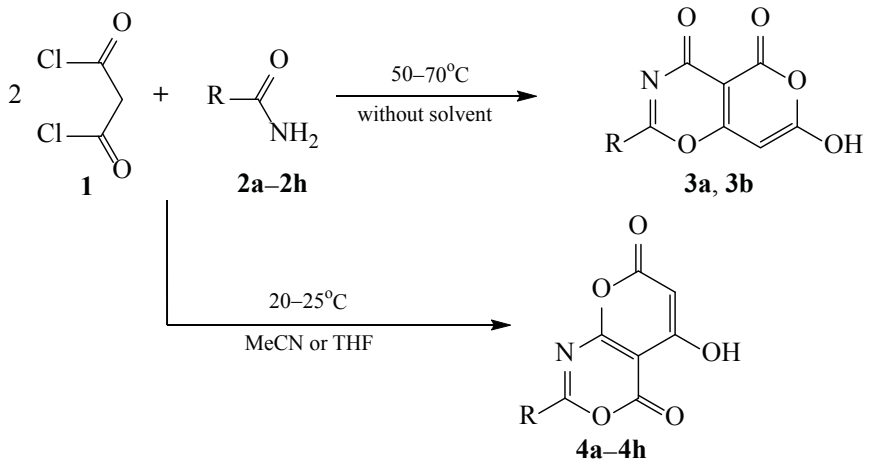



**Fig. 1.** Structure of the molecule of 2-(4-bromophenyl)-5-hydroxypyrano[2,3-*d*][1,3]oxazine-4,7-dione (**4e**) in crystal according to the X-ray diffraction data.

**Scheme 1.**




R = Ph (**a**), 4-$MeC_6H_4$ (**b**), 4-$MeOC_6H_4$ (**c**), 4-$NO_2C_6H_4$ (**d**), 4-$BrC_6H_4$ (**e**), 3-$MeOC_6H_4$ (**f**), PhCH=CH (**g**), furan-2-yl (**h**).

**5-Hydroxy-2-phenylpyrano[2,3-*d*][1,3]oxazine-4,7-dione (4a).** A solution of 9.4 g (20 mmol) of malonyl chloride in 25 mL of anhydrous tetrahydrofuran was slowly added dropwise to a cold suspension of 4 g (10 mmol) of amide **2a** in 25 mL of anhydrous tetrahydrofuran. Amide **2a** dissolved during the addition process. The mixture was stirred for 18 h at room temperature, and the precipitate was filtered off, washed with tetrahydrofuran, and dried. Yield 5.7 g (67%), mp 218–220°C. $^1$H NMR spectrum, δ, ppm: 5.50 s (1H, 6-H), 7.52 m (2H, Ph), 7.79 m (1H, Ph), 8.20 m (2H, Ph), 12.77 br.s (1H, OH). $^{13}$C NMR spectrum, $\delta_C$, ppm: 88.53, 93.38, 127.32, 128.07, 131.59, 135.01, 154.43, 154.68, 165.87, 167.59, 168.46. Mass spectrum: *m*/*z* 256.0248 [*M* – H]$^-$; calculated for $C_{13}H_6NO_5$: 256.0251.

Compounds **4b**–**4h** were synthesized in a similar way.

**5-Hydroxy-2-(4-methylphenyl)pyrano[2,3-*d*]-[1,3]oxazine-4,7-dione (4b).** Yield 5.79 g (72%), mp 210–212°C. $^1$H NMR spectrum, δ, ppm: 2.44 s (3H, Me), 5.47 s (1H, 6-H), 7.46 d (2H, $H_{arom}$, *J* = 8.3 Hz), 8.09 d (2H, $H_{arom}$, *J* = 8.3 Hz), 12.65 br.s (1H, OH). $^{13}$C NMR spectrum, $\delta_C$, ppm: 21.53, 88.66, 93.32, 129.46, 130.08, 130.51, 143.77, 154.39, 154.64, 165.92, 167.72, 168.59. Mass spectrum: *m*/*z* 270.0401 [*M* – H]$^-$; calculated for $C_{14}H_8NO_5$: 270.0408.

**5-Hydroxy-2-(4-methoxyphenyl)pyrano[2,3-*d*]-[1,3]oxazine-4,7-dione (4c).** Yield 5.94 g (78%), mp 221–223°C. $^1$H NMR spectrum, δ, ppm: 3.81 s (3H, MeO), 5.53 s (1H), 6.97 d (2H, $H_{arom}$, *J* = 8.8 Hz), 7.85 d (2H, $H_{arom}$, *J* = 8.8 Hz), 12.84 br.s (1H, OH). $^{13}$C NMR spectrum, $\delta_C$, ppm: 49.66, 89.27, 93.73, 115.39, 129.83, 131.81, 154.38, 159.93, 163.49, 165.63, 167.68, 168.77. Mass spectrum: *m*/*z* 286.0341 [*M* – H]$^-$; calculated for $C_{14}H_8NO_6$: 286.0357.

**5-Hydroxy-2-(4-nitrophenyl)pyrano[2,3-*d*][1,3]-oxazine-4,7-dione (4d).** Yield 4.15 g (57%), mp 214–216°C. $^1$H NMR spectrum, δ, ppm: 5.57 s (1H, 6-H), 8.15 d (2H, $H_{arom}$, *J* = 8.8 Hz), 8.42 d (2H, $H_{arom}$, *J* = 8.8 Hz), 13.30 s (1H, OH). $^{13}$C NMR spectrum, $\delta_C$, ppm: 83.07, 89.83, 124.65, 129.56, 139.35, 150.30, 159.59, 159.99, 163.97, 168.72, 170.97. Mass spectrum: *m*/*z* 301.0114 [*M* – H]$^-$; calculated for $C_{13}H_6N_2O_7$: 301.0102.

**2-(4-Bromophenyl)-5-hydroxypyrano[2,3-*d*][1,3]-oxazine-4,7-dione (4e).** Yield 4.15 g (62%), mp 220–222°C. $^1$H NMR spectrum, δ, ppm: 5.52 s (1H, 6-H), 7.86 d (2H, $H_{arom}$, *J* = 8.5 Hz), 8.10 d (2H, $H_{arom}$, *J* = 8.5 Hz), 12.89 br.s (1H, OH). $^{13}$C NMR spectrum, $\delta_C$, ppm: 89.77, 93.92, 128.28, 129.53, 131.13, 133.04, 154.13, 159.78, 165.04, 167.36, 168.74. Mass spectrum: *m*/*z* 333.9357 [*M* – H]$^-$; calculated for $C_{13}H_6NO_5Br$: 333.9357.

**5-Hydroxy-2-(3-methoxyphenyl)pyrano[2,3-*d*][1,3]-oxazine-4,7-dione (4f).** Yield 5.33 g (70%), mp 224–226°C. $^1$H NMR spectrum, δ, ppm: 3.87 s (3H, MeO), 5.50 s (1H, 6-H), 7.35 m (1H), 7.56 pseudo-t (1H, *J* = 7.8 Hz), 7.62 m (1H), 7.78 m (1H, $H_{arom}$), 12.77 br.s (1H, OH). $^{13}$C NMR spectrum, $\delta_C$, ppm: 55.98, 89.87, 93.69, 113.36, 121.62, 121.82, 130.29, 131.10, 154.19, 159.75, 160.07, 165.54, 167.40, 168.52. Mass spectrum: *m*/*z* 286.0361 [*M* – H]$^-$; calculated for $C_{14}H_8NO_6$: 286.0357.

**5-Hydroxy-2-(2-phenylethenyl)pyrano[2,3-*d*][1,3]-oxazine-4,7-dione (4g).** Yield 5.04 g (65%), mp 110–112°C. $^1$H NMR spectrum, δ, ppm: 5.60 s (1H, 6-H), 7.05 d (1H, CH=CH, $J$ = 16.1 Hz), 7.47 m (3H, $H_{arom}$), 7.88 m (2H, $H_{arom}$), 7.99 d (1H, CH=CH, $J$ = 16.1 Hz), 12.86 br.s (1H, OH). $^{13}$C NMR spectrum, $\delta_C$, ppm: 89.59, 93.33, 118.47, 128.65, 129.59, 132.02, 134.33, 146.88, 154.33, 159.89, 166.21, 167.43, 168.68. Mass spectrum: $m/z$ 282.0409 $[M - H]^-$; calculated for $C_{15}H_8NO_5$: 282.0408.

**2-(Furan-2-yl)-5-hydroxypyrano[2,3-*d*][1,3]-oxazine-4,7-dione (4h).** Yield 6.77 g (76%), mp 178–180°C. $^1$H NMR spectrum, δ, ppm: 5.45 s (1H), 6.91 d (1H, $H_{Fu}$, $J$ = 3.8 Hz), 7.75 d (1H, $H_{Fu}$, $J$ = 3.8 Hz), 8.25 s (1H, $H_{Fu}$), 12.73 br.s (1H, OH). $^{13}$C NMR spectrum, $\delta_C$, ppm: 89.40, 93.14, 114.55, 122.19, 143.76, 151.01, 153.71, 157.47, 159.74, 167.50, 168.61. Mass spectrum: $m/z$ 246.0037 $[M - H]^-$; calculated for $C_{11}H_4NO_6$: 246.0044.

The $^1$H and $^{13}$C NMR spectra were recorded from solutions in DMSO-$d_6$ on a Bruker Avance III spectrometer at 400 and 100 MHz, respectively; the chemical shifts were measured relative to the residual proton and carbon signals of the solvent. The high resolution mass spectra (negative electrospray ionization) were obtained with a Bruker micrOTOF instrument. The purity of the isolated compounds was checked, and the progress of reactions was monitored, by TLC on Silica gel 60 F254 plates (Merck) using ethanol–ethyl acetate (4 : 1) as eluent; spots were visualized under UV light. The melting points were measured in capillary tubes and are uncorrected.

**X-Ray analysis of compound 4e.** The X-ray diffraction data for compound **4e** were obtained at the Center for X-Ray Diffraction Studies (St. Petersburg State University) on a Supernova diffractometer (Dual, Cuatzero, Atlas) at 100(2) K. Single crystals of **4e** were grown from a solution in acetonitrile. The structure was solved using Olex2 [6], SHELXS [7], and SHELXL [8]. Monoclinic crystal system, $C_{13}H_6NO_5Br$, $M$ 336.10, space group $P2_1/c$ (no. 14); unit cell parameters: $a$ = 8.7492(2), $b$ = 11.0703(3), $c$ = 12.0221(3) Å; β = 95.733(3)°; $V$ = 1158.59(5) Å$^3$; $Z$ = 4; μ(Mo$K_\alpha$) = 3.568 mm$^{-1}$; $d_{calc}$ = 1.927 g/cm$^3$. Total of 11 710 reflection intensities were measured in the range $6.624° \le 2\theta \le 55°$), including 2661 independent reflections ($R_{int}$ = 0.0400, $R_\sigma$ = 0.0317) which were used in all calculations; final divergence factors: $R_1$ = 0.0275 [reflections with $I > 2\sigma(I)$], $wR_2$ = 0.0658 (all independent reflections). The X-ray diffraction data were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1 941 265).

## CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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