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SHORT COMMUNICATIONS

Synthesis of 8a-Chlorotetrahydropyrrolo[1,2-*a*]pyrazine-1,6,7-(2*H*)-triones from 3-Methylidenepiperazin-2-ones and Oxalyl Chloride

A. V. Chervyakov[a], M. V. Dmitriev[a], and A. N. Maslivets[a]*

[a] *Perm State University, ul. Bukireva 15, Perm, 614990 Russia*
**e-mail: koh2@psu.ru*

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Abstract—(*Z*)-1-Aryl-3-(2-aryl-2-oxoethylidene)piperazin-2-ones react with oxalyl chloride at cooling with the formation of (*Z*)-2-aryl-8-[hydroxy(aryl)methylidene]-8a-chlorotetrahydropyrrolo[1,2-*a*]pyrazine-1,6,7(2*H*)-triones. At heating HCl is eliminated from them to produce 8-aroyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-1,6,7(2*H*)-triones.

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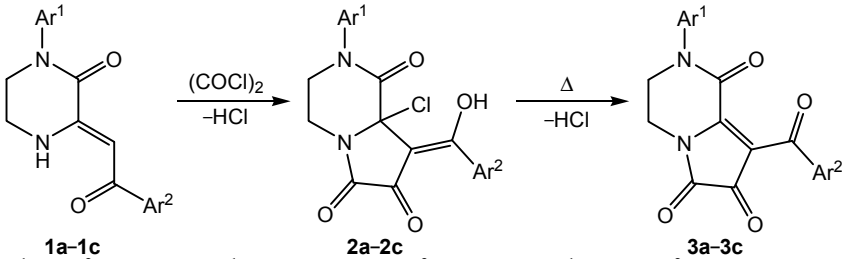
Heterocyclic enaminoketones in the reaction with oxalyl chloride form hetareno[*e*]pyrrole-2,3-diones [1–4] or 4-heterylfuran-2,3-diones [4, 5]. All reactions involve several stages, but intermediate products were not isolated.

At the reaction of 3-methylenepiperazin-2-ones with oxalyl chloride at 110–111°C we obtained new class of hetareno[*e*]pyrrole-2,3-diones, pyrrolo[1,2-*a*]pyrazine-1,6,7-triones [6]. Milder conditions of the reaction made it possible to isolate the intermediate of this reaction.

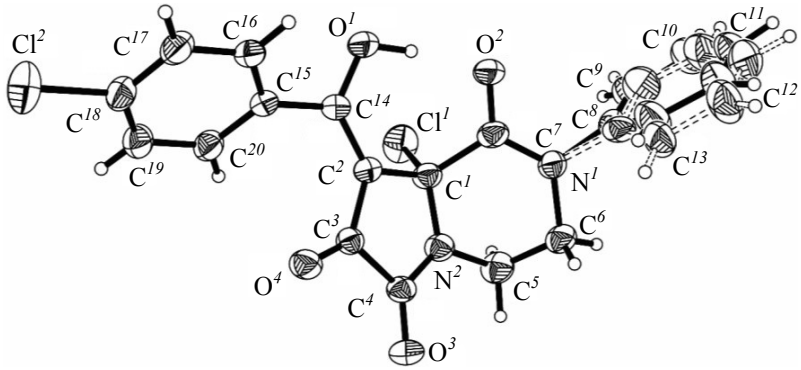
As a result of reaction of (*Z*)-1-aryl-3-(2-aryl-2-oxoethylidene)piperazin-2-ones **1a–1c** with oxalyl chloride in anhydrous toluene during 4–8 h at 5–20°C we obtained (*Z*)-2-aryl-8-[hydroxy(aryl)methylidene]-8a-chlorotetrahydropyrrolo[1,2-*a*]pyrazine-1,6,7(2*H*)-triones **2a–2c**, whose structure was confirmed by X-ray diffraction (XRD) analysis by an example of compound **2c** (see the figure). At boiling of compounds **2a–2c** in anhydrous toluene for 2–3 h (till the end of HCl evolution) 8-aroyl-3,4-dihydropyrrolo[1,2-*a*]-pyrazine-1,6,7(2*H*)-triones **3a–3c** were obtained, identified by comparing with authentic compounds prepared by method [6].

According to XRD data compound **2c** crystallized in a centrosymmetric space group of monoclinic crystal system as a solvate with toluene in a ratio 1 : 1. The pyrrole ring is flat. The piperazine ring is in a *sofa* conformation with the deviation of atom C^5 from the plane of the other atoms of the cycle by 0.56 Å. The enol hydroxy group forms a strong intramolecular hydrogen bond with the lactam carbonyl group. The phenyl cycle is disordered (displacement of the cycle in the plane) by two positions with close occupancy. Significantly shortened intermolecular contacts were not found in the crystal.



1a–1c **2a–2c** **3a–3c**

$Ar^1 = Ar^2 = Ph$ (**a**); $Ar^1 = C_6H_4Me$-4, $Ar^2 = Ph$ (**b**); $Ar^1 = Ph$, $Ar^2 = C_6H_4Cl$-4 (**c**).



General arrangement of the molecule of (*Z*)-8-[hydroxy(4-chlorophenyl)methylidene]-2-phenyl-8a-chlorotetrahydropyrrolo[1,2-*a*]-pyrazine-1,6,7(2*H*)-trione **2c** according to XRD data represented in thermal ellipsoids of 30% probability.

The described reaction is the first example of the isolation of the intermediate compound in the synthesis of hetareno[*e*]pyrrole-2,3-diones or 4-heterylfuran-2,3-diones. Due to the stability and easy way of isolation of the intermediate compound it is possible to synthesize pyrrolo[1,2-*a*]pyrazine-1,6,7(2*H*)-triones in two stages with higher yields and purity than in the one-stage method of synthesis.

(*Z*)-8-[Hydroxy(phenyl)methylidene]-2-phenyl-8a-chlorotetrahydropyrrolo[1,2-*a*]pyrazine-1,6,7-(2*H*)-trione (2a). To a solution of 0.50 g (1.71 mmol) of compound **1a** in 25 mL of anhydrous toluene was added 0.22 mL (2.57 mmol) of oxalyl chloride, the mixture was stirred for 8 h at 20°C, the precipitate was filtered off and dried in a vacuum. Yield 94%, mp 147–149°C (from toluene). IR spectrum, ν, cm^{-1}: 3059 br (OH), 1744 (C^6=O), 1697 (C^7=O), 1604 (C^1=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.08 m (2H, C^4H_2), 4.17 m (2H, C^3H_2), 7.19–7.64 group of signals ($8H_{arom.}$), 7.87 d [2H, 2 *o*-CH in C(OH)Ph, *J* 7.2 Hz]. Found, %: C 62.87; H 3.89; N 7.14. $C_{20}H_{15}ClN_2O_4$. Calculated, %: C 62.75; H 3.95; N 7.32.

(*Z*)-8-[Hydroxy(phenyl)methylidene]-2-(4-methylphenyl)-8a-chlorotetrahydropyrrolo[1,2-*a*]pyrazine-1,6,7(2*H*)-trione (2b). To a solution of 1.00 g (3.26 mmol) of compound **1b** in 25 mL of anhydrous toluene was added 0.41 mL (4.90 mmol) of oxalyl chloride, the mixture was stirred till compound **1b** fully dissolved, the reaction mixture was held for 4 h at 5°C, the precipitate was filtered off, dried in a vacuum. Yield 81%, mp 119–120°C (from toluene). IR spectrum, ν, cm^{-1}: 3185 br (OH), 1716 (C^6=O), 1694 (C^7=O), 1586 (C^1=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.37 s (3H, CH_3), 3.85 m (2H, C^4H_2), 4.11 m (2H, C^3H_2), 7.12–7.56 group of signals ($7H_{arom}$), 7.76 d [2H, 2 *o*-CH in C(OH)Ph, *J* 7.9 Hz]. Found, %: C 63.76; H 4.28; N 6.99. $C_{21}H_{17}ClN_2O_4$. Calculated, %: C 63.56; H 4.32; N 7.06.

(*Z*)-8-[Hydroxy(4-chlorophenyl)methylidene]-2-phenyl-8a-chlorotetrahydropyrrolo[1,2-*a*]pyrazine-1,6,7(2*H*)-trione (2c). To 0.50 g (1.53 mmol) of compound **1c** in 25 mL of anhydrous toluene was added 0.20 mL (2.30 mmol) of oxalyl chloride, the mixture stirred till compound **1c** fully dissolved, the reaction mixture was held for 8 h at 5°C, the precipitate was filtered off, dried in a vacuum. Yield 84%, mp 153–155°C (from toluene). IR spectrum, ν, cm^{-1}: 3058 br (OH), 1752 (C^6=O), 1699 (C^7=O), 1588 (C^1=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.90 m (2H, C^4H_2), 4.11 m (2H, C^3H_2), 7.14–7.75 group of signals ($7H_{arom}$), 8.03 d [2H, 2 *o*-CH in $C(OH)C_6H_4Cl$-4, *J* 8.5 Hz]. Found, %: C 57.59; H 3.25; N 6.54. $C_{20}H_{14}Cl_2N_2O_4$. Calculated, %: C 57.57; H 3.38; N 6.71.

X-ray diffraction analysis of compound **2c** was performed on a single-crystal diffractometer Xcalibur Ruby [295(2) K, MoK_α-radiation, ω-scanning with a step 1°]. The extinction was accounted for empirically using the algorithm SCALE3 ABSPACK [7]. Crystals of monoclinic crystal system: *a* 9.106(2), *b* 16.073(4), *c* 17.203(4) Å, β 92.76(2)°, *V* 2514.9(10) $Å^3$, space group $P2_1/n$, *Z* 4. The structure was solved by software Superflip [8] and refined with full-matrix least-squares method in an anisotropic approximation for all non-hydrogen atoms with the application of software SHELXL-2014 [9] and OLEX2 [10]. Hydrogen atom of OH group was refined independently in an isotropic approximation. At the refinement of other hydrogen atoms *rider* model was applied. Final parameters of refinement are as follows: R_1 0.0614, wR_2 0.1403 [for 2781 reflections with $I > 2\sigma(I)$]; R_1 0.1473, wR_2 0.1905 (for all 6058 independent reflections), *S* 1.021.

Full set of crystallographic data was deposited in Cambridge Crystallographic Data Centre under the number CCDC 1536814 and may be requested by the link: www.ccdc.cam.ac.uk.

8-Benzoyl-2-phenyl-3,4-dihydropyrrolo[1,2-*a*]-pyrazine-1,6,7(2*H*)-trione (3a). 0.50 g (1.31 mmol) of compound **2a** in 17 mL of anhydrous toluene was boiled for 2 h (till the end of HCl evolution), the solvent was distilled off in a vacuum on a rotary evaporator. Yield 98%, mp 150–151°C (from toluene) (150–151°C [6]).

Compounds **3b** and **3c** were synthesized similarly.

8-Benzoyl-2-(4-tolyl)-3,4-dihydropyrrolo[1,2-*a*]-pyrazine-1,6,7(2*H*)-trione (3b). Yield 97%, mp 148–149°C (from toluene) (147–148°C [6]).

2-Phenyl-8-(4-chlorobenzoyl)-3,4-dihydro-pyrrolo[1,2-*a*]pyrazine-1,6,7(2*H*)-trione (3c). Yield 98%, mp 201–202°C (from toluene). IR spectrum, ν, cm^{-1}: 1755 (C^6=O), 1728 (C^7=O), 1665 (C^1=O, COPh). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.90 m (2H, C^4H_2), 4.10 m (2H, C^3H_2), 7.27–7.44 group of signals (5H, Ph), 7.56 d [2H, 2 *m*-CH in COC_6H_4Cl-4, *J* 8.7 Hz], 8.01 d (2H, 2 *o*-CH in COC_6H_4Cl-4, *J* 8.8 Hz). Found, %: C 63.20; H 3.35; N 7.38. $C_{20}H_{13}ClN_2O_4$. Calculated, %: C 63.09; H 3.44; N 7.36.

IR spectra were recorded on a spectrophotometer Perkin Elmer Spectrum Two in mineral oil. ^{1}H NMR spectra were registered on a spectrometer Bruker Avance III (working frequency 500 MHz), internal reference TMS. Elemental analysis was performed on an analyzer vario Micro cube. The homogeneity of compounds was confirmed by TLC (Silufol plates, eluents benzene–ethyl acetate, 5 : 1, spots visualized by iodine vapor), optimization of reaction conditions was attained using ultra-HPLC method (on an instrument Waters ACQUITY UPLC I-Class, column Acquity UPLC BEH C18 1.7 μm, mobile phase acetonitrile–water, flow rate 0.3–0.6 mL/min, detector ACQUITY UPLC PDA eλ Detector).

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