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Reactions of 1-Bromo-1-nitro-3,3,3-trichloropropene with Acetylacetone and Cyclohexane-1,3-dione

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Abstract—Reactions of 1-bromo-1-nitro-3,3,3-trichloropropene with acetylacetone, dihydroresorcinol, and dimedone afforded substituted dihydrofuran and hexahydrobenzofurans containing nitro and trichloromethyl functionalities. Their structure was established by spectroscopic (IR, UV, ^{1}H, $^{13}C-\{^{1}H\}$ NMR) methods and X-ray diffraction analysis.

Keywords: 1-bromo-1-nitro-3,3,3-trichloropropene, acetylacetone, 1,3-cyclohexanedione, Michael reaction, heterocyclization

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Synthesis of furan and benzofuran derivatives is of interest due to important applications of these compounds. 2-Nitrofuran derivatives are widely used as antibacterial agents (furacillin, furadoninum, furazolidone, etc.) [1]. Benzofuran ring is contained in molecules of amiodarone (anti-anginal and anti-arrhythmic agent) as well as phenicaberanum and khellinum (antispasmodic activity) [2]. The practical significance of trichloromethyl-containing compounds should also be noted, among which the most known is chloral hydrate used as an anticonvulsant agent [2].

Methods for the synthesis of 2-nitrodihydrofurans and 2-nitrohexahydrobenzofurans are scarce; they are mainly based on the reactions of β-bromo-β-nitrostyrenes [3–10], β,β-dinitrostyrenes [11] and β-bromo-β-nitroacrylates [12] with β-diketones occurring in the presence of bases [Et_3N, MeONa, AcONa, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), *N*,*N*-diisopropylethylamine (DIPEA)].

We have studied reactions of *Z*-1-bromo-1-nitro-3,3,3-trichloropropene **1** [13] with acyclic (acetylacetone) and cyclic (dihydroresorcinol, dimedone) β-diketones leading to the formation of previously unknown dihydrofuran **2** and hexahydrobenzofurans **3** and **4** functionalized with nitro and trichloromethyl groups (Scheme 1).

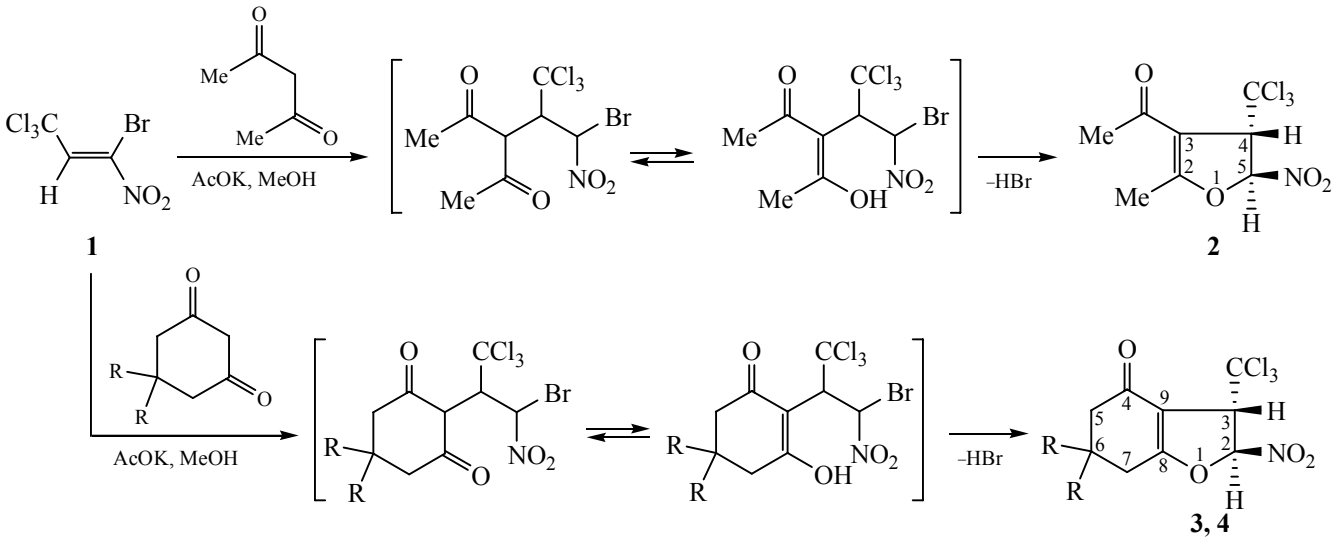
Variation of the bases (Et_3N, MeONa, AcOK), solvents (benzene, methanol), temperature (boiling, ambient or lower temperature) and the reaction time (from several hours to days) showed that the reaction proceeds successfully in anhydrous methanol in the presence of an equimolar amount of potassium acetate at room temperature (3 days) or under reflux (2 h).

Obviously, this one-pot process occurs analogously to the reaction of cyclohexane-1,3-diones with 2-alkyl-(aryl)-1-bromo-1-nitroethenes [3–10], i.e. via the initial formation of the Michael adduct and subsequent heterocyclization by intramolecular *O*-alkylation accompanied with HBr elimination.

IR spectra of compounds **2**–**4** contained the absorption bands of conjugated multiple bond C=C (1630–1645 cm^{-1}) and carbonyl (1680–1690 cm^{-1}) groups, as well as of non-conjugated nitro group (ν_{as} = 1580, ν_{s} = 1360–1365 cm^{-1}). The value of $\Delta\nu$ (210–215 cm^{-1}) is characteristic of the nitro group with geminally located electron-withdrawing substituent, oxygen atom of the dihydrofuran ring [14, 15].

In the ^{1}H NMR spectra of **2**–**4** the signals of methine protons $CHNO_2$ (6.04–6.21 ppm) and $CHCCl_3$ (4.64–4.71 ppm) appeared as singlets, which may indicate their transoid location. It is known that the value of the vicinal constants of spin-spin interaction

Scheme 1.



R = H (**3**), Me (**4**).

for *trans*-positioned protons of cyclopentane ring is about 0 Hz [16].

^{13}C–{^{1}H} NMR spectra of compounds **2**–**4** contained the signals of carbon atoms of all structural fragments. The correct assignment of the signals of C^4, C^5 (for compound **2**) and C^2, C^3 (for compounds **3** and **4**) atoms was made by means of ^{1}H–^{13}C HMQC NMR spectroscopy. For example, in the HMQC spectrum of compound **3** a correlation between the signals of $CHNO_2$ (6.19 ppm) and C^2 atom (106.58 ppm) was observed. In addition, a correlation between the signals of $CHCCl_3$ proton (4.64 ppm) and the corresponding carbon atom C^3 (66.84 ppm) was found (Fig. 1).

Absorption band at λ_{max} = 249–251 nm (ε = 8100–9100 L mol^{-1} cm^{-1}) observed in the UV spectra of compounds **2**–**4** was characteristic of the conjugated system –O–C=C–C=O [17].

Data of X-ray diffraction analysis of 2-nitro-4-oxo-3-(trichloromethyl)-2,3,4,5,6,7-hexahydrobenzofuran **3** (Fig. 2) showed that six- and five-membered rings in its molecule have a *chair* and an *envelope* conformations, respectively, wherein the C^2 atom is out of

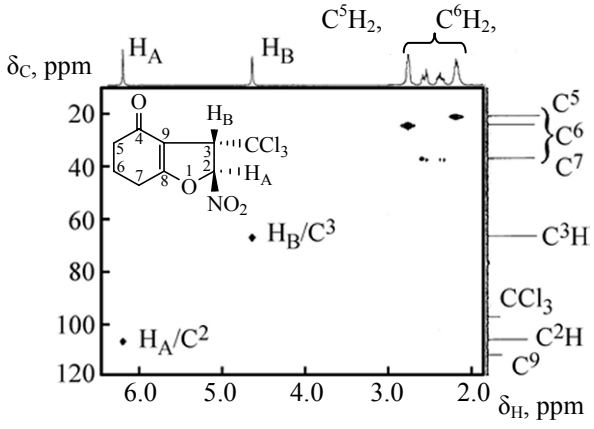


Fig. 1. ^{1}H–^{13}C HMQC NMR spectrum of compound **3** in $CDCl_3$ solution.

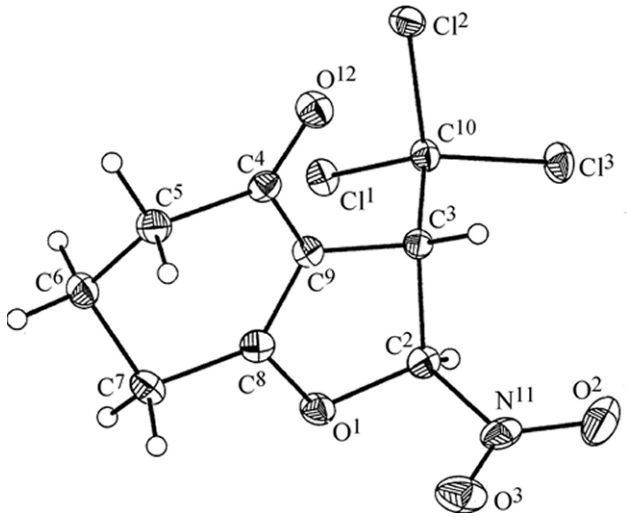


Fig. 2. General view of the molecule of **3** (p = 50%).

the plane O^1–C^8–C^9–C^3. Values of torsion angles $O^1C^2C^3C^9$ and $C^8O^1C^2C^3$ are 15.03° and –15.04°, respectively. Nitro and trichloromethyl groups are *trans*-positioned relative to the dihydrofuran ring [$N^{11}C^2C^3C^{10}$ = 136.78(13)°], which is consistent with the data of ^{1}H NMR spectroscopy. Note that the value of the bond lengths, bond and torsion angles for the first synthesized compound **3** is quite close to the corresponding parameters in the molecules of its analogs previously studied by X-ray diffraction [8–10, 18].

EXPERIMENTAL

Spectral studies and elemental analysis were performed at the Center for Joint Use of Herzen State Pedagogical University of Russia.

^{1}H, ^{13}C–{^{1}H}, and ^{1}H–^{13}C HMQC NMR spectra were obtained on a Jeol ECX-400A instrument operating at 399.78 (^{1}H) and 100.525 MHz (^{13}C) in a chloroform-d_1 solution with respect to the signals of residual solvent protons. IR spectra were recorded on a Shimadzu FTIR spectrometer IRPrestige-21 in chloroform (40 mg/mL). Electron absorption spectra were registered on a Shimadzu UV2401PC spectrophotometer (quartz cells, l = 0.101 cm, c ~ 3.0–3.5 × 10^{-4} mol/L) in ethanol solution. The reaction progress was monitored by thin layer chromatography using Silufol UV-254 plates, developing with iodine vapor or ultraviolet irradiation (λ = 254 nm).

X-Ray diffraction studies were performed on a SMART APEX II CCD diffractometer (MoK_α-radiation, graphite monochromator, ω-scanning). The crystals of **3** were monoclinic; the unit cell parameters were as follows: $C_9H_8Cl_3NO_4$, M 300.51, space group $P2_1/c$, a = 12.6608(7), b = 8.2182(5), c = 11.8792(7) Å, β = 112.8290(10)°, V = 1139.20(12) Å^3, d_{calc} = 1.752 g/cm^3, μ = 8.05 mm^{-1}, F(000) 608. The structure was solved by the direct method and refined by full-matrix anisotropic approximation with respect to F^2_{hkl} using SHELXTL PLUS software [19, 20]. Positions of the hydrogen atoms were found from the difference Fourier syntheses and refined in isotopic approximation.

1-Bromo-1-nitro-3,3,3-trichloropropene was prepared as described in [13].

3-Acetyl-2-methyl-5-nitro-4-(trichloromethyl)-4,5-dihydrofuran (2). A solution of 0.55 g (5.57 mmol) of potassium acetate in 10 mL of anhydrous methanol was added to a solution of 1.50 g (5.57 mmol) of 1-bromo-1-nitro-3,3,3-trichloropropene **1** and 0.56 g (5.57 mmol) of acetylacetone in 5 mL of anhydrous methanol. After reflux for 2 h the reaction mixture was poured into crushed ice. The resulting emulsion was extracted with chloroform (50 mL), The extract was dried with calcium chloride, the desiccant was filtered off, and the filtrate was evaporated to give 1.05 g of orange oil which was chromatographed on silica gel. Compound **2** was isolated from the fraction eluted with benzene. Yield 0.18 g (11%), colorless crystals, mp 109–111°C (ethanol–water, 4 : 1). IR spectrum ($CHCl_3$), ν, cm^{-1}: 1690 (C=O), 1630 (C=C), 1580, 1365 (NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.37 s (3H, MeC=O), 2.42 s (3H, Me), 4.71 s (1H, $CHCCl_3$), 6.04 s (1H, $CHNO_2$). ^{13}C–{^{1}H} NMR spectrum ($CDCl_3$), δ_C, ppm: 14.66 (Me), 29.89 (MeC=O), 69.48 (C^4), 98.39 (CCl_3), 105.21 (C^5), 113.30 (C^3), 169.47 (C^2), 192.39 (C=O). UV spectrum (EtOH), λ_{max}, nm (ε, L mol^{-1} cm^{-1}): 250 (8100). Found, %: C 33.48; H 2.91. $C_8H_8Cl_3NO_4$. Calculated, %: C 33.30; H 2.79.

2-Nitro-4-oxo-3-(trichloromethyl)-2,3,4,5,6,7-hexahydrobenzofuran (3). A solution of 0.55 g (5.57 mmol) of potassium acetate in 10 mL of anhydrous methanol was added to a solution of 1.50 g (5.57 mmol) of 1-bromo-1-nitro-3,3,3-trichloropropene **1** and 0.62 g (5.57 mmol) of dihydroresorcinol in 5 mL of anhydrous methanol. After refluxing for 2 h, the reaction mixture was poured into crushed ice. The precipitate was filtered off. Yield 0.72 g (43%), beige crystals, mp 139–140°C (ethanol–water, 4 : 1). IR spectrum ($CHCl_3$), ν, cm^{-1}: 1680 (C=O), 1645 (C=C), 1580, 1360 (NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.19 m (2H, C^6H_2), 2.37–2.57 m (2H, C^5H_2), 2.76 m (2H, C^7H_2), 4.64 s (1H, $CHCCl_3$), 6.19 s (1H, $CHNO_2$). ^{13}C–{^{1}H} NMR spectrum ($CDCl_3$), δ_C, ppm: 20.69 (C^6), 24.04 (C^7), 37.06 (C^5), 66.84 (C^3), 97.69 (CCl_3), 106.58 (C^2), 112.54 (C^9), 180.80 (C^8), 191.83 (C=O). UV spectrum (EtOH), λ_{max}, nm (ε, L mol^{-1} cm^{-1}): 251 (9100). Found, %: C 35.72; H 2.81; N 4.17. $C_9H_8Cl_3NO_4$. Calculated, %: C 35.97; H 2.68; N 4.66.

6,6-Dimethyl-2-nitro-4-oxo-3-(trichloromethyl)-2,3,4,5,6,7-hexahydrobenzofuran (4). A solution of 0.55 g (5.57 mmol) of potassium acetate in 10 mL of anhydrous methanol was added to a solution of 1.50 g (5.57 mmol) of 1-bromo-1-nitro-3,3,3-trichloropropene **1** and 0.78 g (5.57 mmol) of dimedone in 5 mL of anhydrous methanol. The reaction mixture was maintained for 72 h at room temperature and poured into crushed ice. The precipitate was filtered off. Yield 0.43 g (24%), beige crystals, mp 120–122°C (ethanol–water, 4 : 1). IR spectrum ($CHCl_3$), ν, cm^{-1}: 1680

(C=O), 1645 (C=C), 1580, 1365 (NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.16 s (3H, Me), 1.24 s (3H, Me), 2.29 d (1H, C^5H_2, ^2J 16.3), 2.41 d (1H, C^5H_2, ^2J 16.3), 2.62 s (2H, C^7H_2), 4.64 s (1H, $CHCCl_3$), 6.21 s (1H, $CHNO_2$). $^{13}C-\{^1H\}$ NMR spectrum ($CDCl_3$), δ_C, ppm: 28.22 (Me), 28.66 (Me), 34.21 (C^6), 37.66 (C^7), 51.52 (C^5), 66.93 (C^3), 97.74 (CCl_3), 106.79 (C^2), 111.37 (C^9), 179.88 (C^8), 191.46 (C=O). UV spectrum (EtOH), λ_{max}, nm (ε, L mol^{-1} cm^{-1}): 249 (8900). Found N, %: 3.83. $C_{11}H_{12}Cl_3NO_4$. Calculated N, %: 4.26.

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