NEW TRANSFORMATIONS OF DIETHOXYCARBONYL SUBSTITUTED HYDROXYCYCLOHEXANONES

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Abstract. The reactions of diethoxycarbonyl substituted hydroxycyclohexanones (β-ketols) with hydroxylamine hydrochloride in the presence of two equivalents of potassium bicarbonate were studied. It has been established that, depending on the electronic nature of the substituent in the benzene ring, as a result of the reactions can be formed the corresponding ketoxime or the heterocyclic product – ethyl-6-hydroxy-6-methyl-3-oxo-4-aryl-1,3,4,5,6,7-hexahydrobenzo[c]isoxazole carboxylate. The structure of all synthesized compounds was proved by modern physical methods of analysis. The spatial orientation of the substituents in the cyclohexane ring in one of the reaction products was established by X-ray diffraction.

Keywords: β-ketols, hydroxylamine, ketoximes, hexahydrobenzo[c]isoxazoles.

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1. Introduction

Dialkyl(diacetyl)substituted hydroxycyclohexanones (β-ketols) due to the presence of extensive resources base as available aromatic aldehydes and methyleneactive dicarbonyl compounds, high chemical potential caused by the presence of the o xo groups of different types, are valuable building blocks of organic synthesis (Dyachenko, 2011, 2012, 2014, 2015; Gein, 2004, 2005; Hote & Lokhande, 2014; Ismiyev, 2013, 2019; Maharramov, 2011, 2016; Magerramov et al., 2013) and have properties, of practical importance (Abiyeva et al., 2018; Gein, 2007, 2019).

2. Results and discussion

In this work, in order to identify new directions for the transformation of diethyl-2-aryl-4-hydroxy-4-methyl-6-oxo-cyclohexane-1,3-dicarboxylates, we studied their reactions with hydroxylamine hydrochloride in the presence of two equivalents of potassium hydrogen carbonate.

It was found that in ethanol at 60°C the interaction of diethyl-2-aryl-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylates (1) with hydroxylamine hydrochloride (2) in the presence of two equivalents of potassium bicarbonate (KHC03), followed by neutralization of the reaction medium with hydrochloric acid, leads to the corresponding ketoxime (3) (Scheme 1):
Scheme 1.

Structure (3) was confirmed by NMR spectroscopy (Fig. 1, Fig. 2).

However, the reaction of β-ketols (4,5) with hydroxylamine hydrochloride in the presence of two equivalents of potassium hydrogen carbonate (KHCO₃) without subsequent neutralization of the reaction mixture with hydrochloric acid leads to heterocyclic derivatives - ethyl-6-hydroxy-6-methyl-3-oxo-4-aryl-1,3,4,5,6,7-hexahydrobenzo[c]isoxazole carboxylates (6,7) (Scheme 2).

Scheme 2.

Structure (6) was confirmed by NMR spectroscopy (Fig. 3, Fig. 4).

From the comparison of the reactions performed, it can be concluded that the electron-withdrawing chlorine and nitro groups located in the benzene ring contribute to the realization of heterocyclization. It is likely that under the influence of these groups in the oximes formed at the initial stage, imino-enamine tautomeration occurs, leading to intermediate (A), which subsequently turns into an intermediate-anion (B). In this intermediate, free rotation around the C — N bond is possible, therefore, oxygen of the hydroxylamine spatially approaches the ethoxycarbonyl group and intramolecular heterocyclization becomes possible (Scheme 3):

Scheme 3.
Figure 1. $^1$H NMR spectra of compound (3)

Figure 2. $^{13}$C NMR spectra of compound (3)
Figure 3. $^1$H NMR spectra of compound (6)

Figure 4. $^{13}$C NMR spectra of compound (6)
In the case of compound (1), in the benzene ring of which there is an electrodonor methoxy group, similar tautomerism probably does not occur, therefore, the hydroxyl of the oxime group and the ethoxycarbonyl group are spatially maximally distant, and at a similar spatial orientation of these groups heterocyclization is impossible.

The structure of compounds (3) and (6,7) was proved by IR and NMR spectroscopy, as well as by results of X-ray diffraction for compound (6).

The molecular structure of compound (6) was shown on Fig. 3 and Fig. 4.

The molecular structure of compound (6) was confirmed as well as by X-ray diffraction (Fig. 5).

![Figure 5](image)

**Figure 5.** Molecular structure of (6) in anisotropic approximation with 30% of ellipsoids probability and selected bond lengths and angles: O1 C1 1.394(3), O1 N1 1.420(3), N1 C7 1.361(4), C1 C2 1.419(4), C2 C7 1.347(4), O2 C1 1.220(4), C5 1.434(4)Å; C1 O1 N1 107.2(2), C7 N1 O1 106.5(2), O1 C1 C2 107.3(2), C7 C2 C1 107.0(2), C7 N1 O1 111.5(3)°

**Crystal data:** C17H18ClNO5, M 351.77, monoclinic, space group P21, a = 6.2865(4), b =13.0756(9), c = 10.4731(7)Å, β = 96.705(2)°, V = 855.0(1)Å³, Z = 2, dc = 1.366 g cm⁻³, μ = 0.25 mm⁻¹, F(000) = 368, crystal size ca. 0.27 × 0.32 × 0.33 mm. The intensity data were collected within the range of 1.96 ≤ θ ≤ 27.5° using Mo-Kα radiation (λ = 0.71078 Å). The intensities of 9396 reflections were collected (3919 unique reflections, Rmerg = 0.041). The structure was solved by direct methods and refined as a racemic twin with 2 component (basf =0.378) by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the Bruker SHELXTL program package (Sheldrick, 2001). Atoms of OC₂H₃ group are disordered over two positions A and B with multiplicity 0.58 and 0.42 respectively. All CH hydrogen atoms were placed at calculated positions and refined as ‘riding’ model; hydrogen atoms by heteroatom are found from DF synthesis and refined isotropically. Convergence was obtained at R1 = 0.0413 and wR2 = 0.0816 for 2841 observed reflections with I ≥ 2σ(I), R1 = 0.0653 and wR2 = 0.0875, GOF = 0.984 for 3919 independent reflections, 245 parameters, the largest and minimal peaks in the final difference map 0.20 and −0.20 e/Å³. In structure (6)
oxazole cycle is planar (mean deviation from plane is 0.023 Å) and cyclohexene ring has twisted nonplanar configuration. Bond lengths and angles in oxazole correspond to an intermediate values between single and double bonds that indicate conjugation in these systems. The N1 atom has pyramidal environment with sum of bond angles around N1 atom of 329(2)º. In the crystal molecules of compound (6) are associated in 3D net by hydrogen bonds NH···O and OH···O type with following parameters: N1-H1N 0.95(4), N1···O3a 2.877(3) Å, N1-H1N···O3a 164(3)º; O3 H4O 0.81(4), O3 O2b 2.779(3) Å, O3 O2b 163(4)º (by letters a and b are market atoms which is connected by symmetry operations x+1, y, z and 2-x, y-0.5, 1-z respectively).  

3. Experimental part

The $^1$H and $^{13}$C NMR spectrum were measured on a Bruker AC-300 MHs spectrometer at 300 and 75 MHs, respectively in a (CD$_3$)$_2$SO solution, residual signals of solvent were used as a standard. The IR spectra were run on a Varian 3600 FT-IR Excalibur Series FTIR spectrometer in KBr pellets. Elemental analysis for C, H and N was performed on a Carlo Erba 1106 analyzer. The experimental data for (6) were obtained at 296(2) K on a Bruker APEX-II CCD automatic three-circle diffractometer (MoKα, graphite monochromator, CCD detector, ω-scanning, 2θmax = 49.42º). All calculations were carried out using the SHELXT software suite (Sheldrick, 2001). The initial positions of the hydrogen atoms were found from the difference synthesis of electron density, and were geometrically calculated and clarified using the rider model with Uizo = nUeq carrier atom (n = 1.5 for methyl groups, n = 1.2 for other hydrogen atoms). The structure was clarified by full-matrix least squares in the anisotropic approximation for non-hydrogen atoms in F2.  

The melting points were measured on a Kofler hot stage and were not adjusted. The purity of the synthesized compounds was checked by TLC on Silufol UV-254 plates, eluent–acetone–hexane (1:1), development in iodine vapor, UV detector.

**Diethyl 6-hidroxy-4-hydroxyimino-6-methyl-2-(4-chlorophenyl) cyclohexane-1,3-dicarboxylate (3)**

To a solution of 10 mmol of compound (1) in 15 ml of ethanol were added 20 mmol of hydroxylamine hydrochloride and 20 mmol of potassium hydrogen carbonate. The mixture was stirred for 8 hours at 60-65°C, then the hot solution was filtered, the filtrate was cooled, diluted with distilled water (15 ml), titrated with concentrated HCl until neutral. The precipitated crystals were filtered off, recrystallized from ethanol. Yield 63%, m.p. 212 °C.

| IR (KBr) spectrum, γ, cm$^{-1}$; 1690 (C=N), 1719 (CO), 3284 (NOH) | [1] $^1$H NMR (300 MHz, (CD$_3$)$_2$SO, δ, ppm); 0.86 (t, J=7.2 Hz, 3H), 0.94 (t, J=7.2 Hz, 3H), 1.22 (s, 3H), 1.99 (d, J=14.4 Hz, H), 2.99 (d, J=11.6 Hz, H), 3.30 (d, J=14.4 Hz, H), 3.39 (d, J=11.6 Hz, H), 3.46 (d, J=11.6 Hz, H), 3.68 (s, OCH$_3$, 3H), 3.75-3.85 (m, OCH$_2$, 2H), 4.43 (s, OH), 6.80 (d, J=9 Hz, 2Harom), 7.17 (d, J=9 Hz, 2Harom) | $^{13}$C NMR (75 MHz, (CD$_3$)$_2$SO, δ, ppm); 14.29, 29.1, 37.48, 43.37, 54.13, 55.39, 57.38, 59.94, 70.51, 113.59, 130.02, 130.80, 153.79, 158.40, 170.14, 171.73 |
| Found, %: C 61.13, H 6.98, N 3.61; C$_{20}$H$_{27}$NO$_7$. Calculated, %: C 61.06, H 6.92, N 3.56 |
Ethyl-6-hydroxy-6-methyl-3-oxo-4-aryl-1,3,4,5,6,7-
hexahydrobenzo[c]isoxazole carboxylates (6,7)

To a solution of 10 mmol of compound (4,5) in 15 ml of ethanol was added 20 mmol of hydroxylamine hydrochloride and 20 mmol of potassium hydrogen carbonate. The mixture was stirred for 8 hours at 60-65°C, then the hot solution was filtered, ethanol was distilled off. The precipitated crystals were washed with water, dried, recrystallized from ethanol. Received

Ethyl-6-hydroxy-6-methyl-3-oxo-4-(4-chlorophenyl)-1,3,4,5,6,7-
hexahydrobenzo[c]isoxazole carboxylate (6), yield 73%, m.p.176°C
1H NMR (300 MHz, (CD3)2SO, δ, ppm); 1.00 (t, J=7.2 Hz, 3H), 1.22 (s, 3H), 1.99 (d, J=14.4 Hz, H), 2.99 (d, J=11.6 Hz, H), 1.28 (s, 3H), 2.50 (d, J=11.6 Hz, H), 2.70 (d, J=9.0 Hz, H), 2.90 (d, 18.0 Hz, H), 3.44 (d, J=9.0 Hz, OH), 3.93 ( m, OCH2, CH, 3H), 7.17 ( s, 2Harom), 7.30 ( s, 2Harom)
13C NMR (75 MHz, (CD3)2SO, δ, ppm); 14.47, 28.14, 36.96, 37.73, 58.73, 60.19, 69.52, 128.44, 130.59, 131.54, 140.24, 163.83, 169.86, 171.61
Found, %: C 58.10, H 5.20, N 4.02; C17H18ClNO5. Calculated, %: C 58.04, H 5.16, N 3.98

Ethyl-6-hydroxy-6-methyl-3-oxo-4-(3-nitrophenyl)-1,3,4,5,6,7-
hexahydrobenzo[c]isoxazole carboxylate (7), yield 69%, m.p.169 °C
1H NMR (300 MHz, (CD3)2SO, δ, ppm); 1.00 (t, J=7.2 Hz, 3H), 1.22 (s,3H), 1.99 (d, J=14.4 Hz, H), 2.99 (d, J=11.6 Hz, H), 1.28 (s, 3H), 2.50 (d, J=11.6 Hz, H), 2.70 (d, J=9.0 Hz, H), 2.90 (d, 18.0 Hz, H), 3.44 (d, J=9.0 Hz, OH), 3.93 ( m, OCH2, CH, 3H), 7.60 (d, Harom), 7.77 ( d, Harom), 8.10 (d, Harom), 8.20 (d, Harom)
13C NMR (75 MHz, (CD3)2SO, δ, ppm); 14.47, 28.14, 36.96, 37.73, 58.73, 60.19, 70.23, 122.42, 123.33, 130.46, 136.25, 143.61, 148.11, 164.18, 169.97, 171.54
Found, %: C 56.40, H 5.10, N 7.82; C20H27NO7. Calculated, %: C 56.35, H 5.01, N 7.73

4. Conclusion

Thus, by studying the reactions of diethyl-2-aryl-4-hydroxy-4-methyl-6-
oxocyclohexane-1,3-dicarboxylates with hydroxylamine hydrochloride, we found that, depending on the electronic nature of the substituent in the benzene ring, can occur condensation with the formation of the corresponding oxime, as well as heterocyclization into the isoxazole ring.

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