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Synthesis of 16-Aryl-15-oxadispiro[5.1.5.3]hexadecane-7,14-diones by Reformatsky Reaction

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Abstract—Methyl 1-bromocyclohexanecarboxylate reacted with zinc and aromatic aldehydes in two steps to afford 16-aryl-15-oxadispiro[5.1.5.3]hexadecane-7,14-diones; methyl 1-[aryl(hydroxy)methyl]cyclohexanecarboxylates were also formed as by-products.

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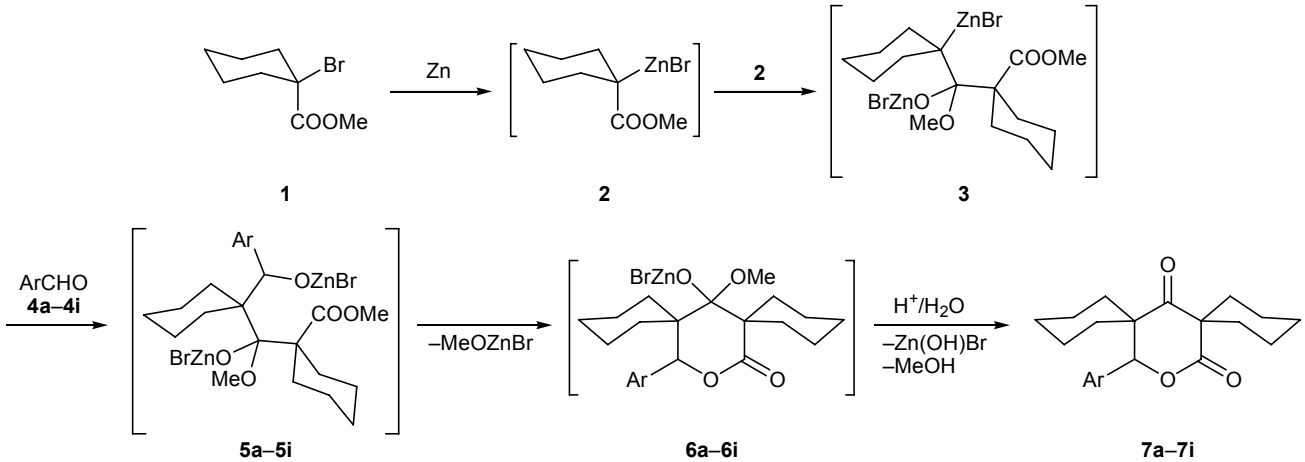
2,4-Dioxotetrahydropyran fragment is a structural unit of some biologically active natural compounds [1]. Substituted spirotetrahydropyran-2,4-diones were found to exhibit analgesic activity [2, 3]. Dispiropyran-2,4-diones were synthesized previously by reaction of bromo oxo esters with zinc and aromatic aldehydes [4–7]. The reaction of methyl 1-bromocyclohexanecarboxylate (**1**) with zinc and nitrobenzaldehydes in two steps afforded 16-nitrophenyl-15-oxadispiro-[5.1.5.3]hexadecane-7,14-diones [8] instead of the expected normal reaction products, hydroxy esters. In order to obtain new substituted dispiro pyran-2,4-diones, compound **1** was brought into reaction with zinc and aromatic aldehydes under analogous conditions; as a result, we isolated 16-aryl-15-oxadispiro[5.1.5.3]-hexadecane-7,14-diones **7a**–**7i** (Scheme 1).

Two schemes of formation of compounds **7a**–**7i** are possible. According to the first scheme, bromo ester **1** reacts with zinc to give Reformatsky reagent **2** whose homocoupling in the absence of other electrophiles yields new Reformatsky reagent **3**. Analogous self-condensation of Reformatsky reagents has been reported in [9], and its probability is higher for sterically hindered substrates. After addition of aromatic aldehyde **4a**–**4i**, intermediate **3** adds to the carbonyl group of **4** with formation of intermediate **5a**–**5i** which undergoes spontaneous cyclization to bromozinc hemiketal **6a**–**6i**, and hydrolysis of the latter yields final

Scheme 1.

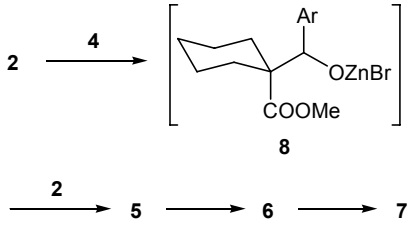


4–**7**, Ar = Ph (**a**), 4-BrC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 2,4-$Cl_2C_6H_3$ (**d**), 4-FC_6H_4 (**e**), 3-BrC_6H_4 (**f**), 2-$O_2NC_6H_4$ (**g**), 3-$O_2NC_6H_4$ (**h**), 4-$O_2NC_6H_4$ (**i**).

16-aryl-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione **7a**–**7i** (Scheme 1).

An alternative reaction path involves reaction of Reformatsky reagent **2** with aromatic aldehyde **4** with formation of intermediate **8** which undergoes attack by the second molecule **2**. The subsequent transformations of intermediate **5** thus formed are the same as in the first scheme (Scheme 2).

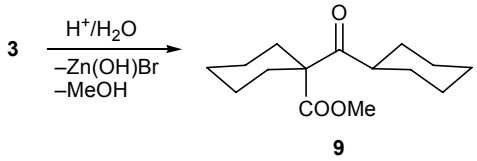
Scheme 2.



Analogous mechanism was proposed in [10] for the reaction of Reformatsky reagent derived from ethyl bromoacetate with carbonyl compounds. This reaction afforded δ-hydroxy-β-ketoesters as a result of addition of the Reformatsky reagent to the carbonyl group and subsequent attack by the second Reformatsky reagent molecule on the primary adduct, followed by hydrolysis. The reaction was called by the authors "double Reformatsky reaction." The formation of pyrandiones via cyclization of products resulting from double attack by organomagnesium compounds was observed in the reaction of ethyl α-bromoisobutyrate with magnesium and aromatic aldehydes [11].

To determine whether the reaction follows one or another scheme, methyl 1-bromocyclohexanecarboxylate (**1**) was treated with zinc without addition of aromatic aldehyde. After hydrolysis, we isolated methyl 1-(cyclohexylcarbonyl)cyclohexanecarboxylate (**9**) (Scheme 3).

Scheme 3.



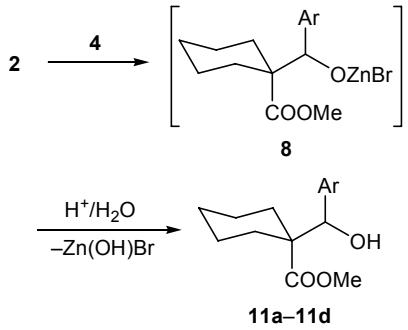
Compound **9** was synthesized previously by reaction of Reformatsky reagent **2** with cyclohexanecarbonyl chloride [4]. Therefore, we concluded that the described reaction follows the first path through intermediates **3**, **5**, and **6**.

The reaction conditions were optimized by carrying out the reaction in the absence of aldehyde component, by heating a mixture of bromo ester **1** and zinc in boiling benzene; samples were withdrawn after heating for 0.5, 1, 2, 3, and 4 h. The samples were subjected to hydrolysis and extraction, the solvent was distilled off from the extract, and the residue was analyzed by GC/MS to determine the ratio of compound **9** and methyl cyclohexanecarboxylate (**10**) formed by hydrolysis of Reformatsky reagent **2**; the results are given below. It is seen that heating for 3 h is sufficient to ensure the maximum yield of **3**.

Reaction time, h	0.5	1	2	3	4
Fraction of **9**, %	5.6	31.0	61.3	77.9	79.2
Fraction of **10**, %	94.4	69.0	38.7	22.1	20.8

Reformatsky reagent **2** present in the reaction mixture reacted with aromatic aldehydes to give methyl 1-[aryl(hydroxy)methyl]cyclohexanecarboxylates **11a**–**11d** (Scheme 4).

Scheme 4.



Compound **11b** was also isolated when the reaction was carried out with simultaneous addition of the initial reactants. Regardless of the ratio of 4-bromobenzaldehyde (**4b**) and methyl 1-bromocyclohexanecarboxylate, no tetrahydropyrandione **7b** was isolated, which also indicated that the reaction followed Scheme 1.

The structure of the newly synthesized compounds was confirmed by their elemental analyses and IR and ^{1}H NMR spectra, and the structure of compound **7h** was unambiguously determined by X-ray analysis (see figure). Compound **7h** crystallized in a centrosymmetric space group belonging to monoclinic crystal system. All bond lengths and bond angles in molecule **7h** are consistent with the corresponding reference values. The cyclohexane fragments appear in a *chair* conformation, and the pyran ring adopts a distorted *boat* conformation. The $C^9C^{10}C^7O^3$ fragment is essentially twisted (deviations of atoms from the mean-

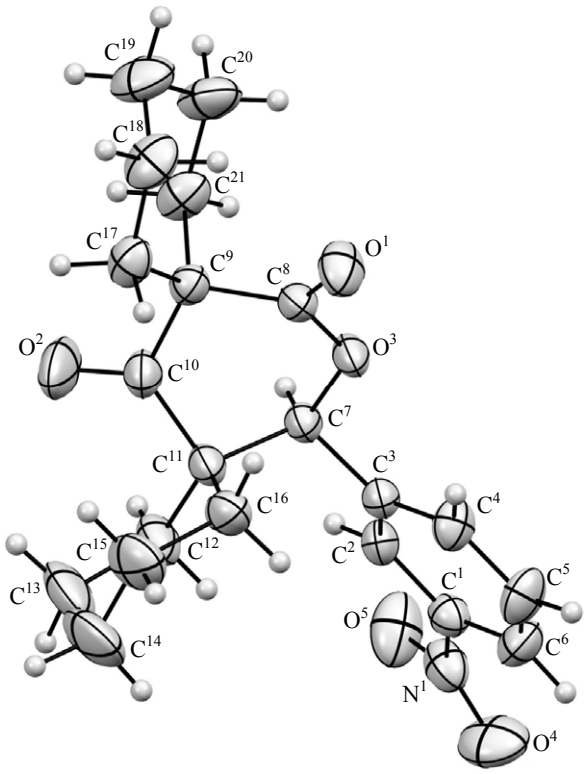
square plane range from +0.09 to –0.09 Å). The C^{11} and C^{8} atoms deviate from the plane formed by the other four ring atoms by 0.73 and 0.35 Å, respectively. The *m*-nitrophenyl substituent is oriented pseudo-equatorially. Molecules **7h** in crystal are linked to each other through van der Waals interactions.

Compounds **7a**, **7b**, **7g**–**7i**, **9a**, and **9b** showed analgesic activity comparable or exceeding the activity of the reference analgesic metamizole sodium.

EXPERIMENTAL

The IR spectra were recorded from samples dispersed in mineral oil on a Perkin Elmer Spectrum Two spectrometer with Fourier transform. The ^{1}H NMR spectra were measured on a Varian Mercury Plus-300 spectrometer (300 MHz) from solutions in $CDCl_3$ (**7b**, **7f**, **11a**, **11b**) or DMSO-d_6 (**11c**, **11d**) using tetramethylsilane as internal reference. Gas chromatographic–mass spectrometric analysis was performed on an Agilent Technologies 7890B instrument [HP-5MS capillary column, 30 m × 0.25 mm, film thickness 0.25 μm; injector temperature 250°C, oven temperature programming from 200°C (7 min) at a rate of 25 deg/min to 300°C (4 min); carrier gas helium, flow rate 1 mL/min, split ratio 100 : 1; a.m.u. range 16–350].

The X-ray diffraction data for compound **7h** were obtained at 293(2) K on an Xcalibur R automatic diffractometer with a CCD detector according to standard procedure (MoK_α radiation, ω-scanning with a step of 1°) [12] from a 0.6 × 0.6 × 0.5-mm fragment of a yellow prismatic single crystal. A correction for absorption was applied empirically according to SCALE3 ABSPACK algorithm [12]. Monoclinic crystal system, space group $P2_1/c$; $C_{21}H_{25}NO_5$; unit cell parameters: a = 12.5406(19), b = 12.206(2), c = 12.515(2) Å; β = 95.731(14)°; V = 1906.1(5) Å^3; Z = 4. Total of 10264 reflection intensities were measured, including 4412 independent reflections and 3531 reflections with $I > 2\sigma(I)$ (completeness 99.9% for θ < 26.00°). The structure was solved directly and was refined against F^2 by the full-matrix least-squares procedure in anisotropic approximation for all non-hydrogen atoms. The positions of hydrogen atoms were refined according to the riding model in isotropic approximation with dependent thermal parameters. All calculations were performed using SHELX97 software suite [13]. Final divergence factors R_1 = 0.0503, wR_2 = 0.1310 [for reflections with $I > 2\sigma(I)$] and R_1 = 0.0628, wR_2 = 0.1399 (for all reflections); goodness of fit 1.038; maximum and minimum residual electron density peaks 0.254 and –0.241 $\bar{e}$ Å^{-3}. The set of X-ray diffraction data for compound **7h** was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 1057390) and is available at *www.ccdc.cam.ac.uk/data_request/cif*.



Structure of the molecule of 16-(3-nitrophenyl)-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione (**7h**) according to the X-ray diffraction data. Non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%.

Compounds 7a–7i and 11a–11d (*general procedure*). A mixture of 2.5 g of zinc, 5.53 g (25 mmol) of bromo ester **1**, a catalytic amount (5 mg) of $HgCl_2$, and 40 mL of benzene was heated for 3 h under reflux. The mixture was cooled, 10 mmol of aldehyde **4a**–**4i** was added, and the mixture was heated for 2 h under reflux. After cooling, the mixture was treated with 5% aqueous acetic acid, the organic phase was separated and dried over Na_2SO_4, and the solvent was distilled off. The crystalline product (**7a**–**7i**) was recrystallized from ethyl acetate. Treatment of the residue with methanol led to crystallization of compound **11a**–**11d** which was recrystallized from methanol.

16-Phenyl-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione (7a). Yield 1.57 g (48%), mp 167–168°C.

16-(4-Bromophenyl)-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione (7b). Yield 2.11 g (52%), mp 215–216°C. IR spectrum, ν, cm^{-1}: 1742, 1710 (C=O).

^{1}H NMR spectrum, δ, ppm: 0.73–2.20 m [20H, $(CH_2)_5$], 5.16 s (1H, 16-H), 7.21 d (2H, H_{arom}, J = 8.4 Hz), 7.52 d (2H, H_{arom}, J = 8.4 Hz). Found, %: C 62.10; H 6.28; Br 19.94. $C_{21}H_{25}BrO_3$. Calculated, %: C 62.23; H 6.22; Br 19.71.

16-(4-Chlorophenyl)-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione (7c). Yield 1.62 g (45%), mp 210–211°C; published data [4]: (mp 211–212°C.

16-(2,4-Dichlorophenyl)-15-oxadispiro[5.1.5.3]-hexadecane-7,14-dione (7d). Yield 1.03 g (26%), mp 219–220°C; published data [4]: mp 220–221°C.

16-(4-Fluorophenyl)-15-oxadispiro[5.1.5.3]-hexadecane-7,14-dione (7e). Yield 2.00 g (58%), mp 176–177°C.

16-(3-Bromophenyl)-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione (7f). Yield 2.47 g (61%), mp 145–146°C. IR spectrum, ν, cm^{-1}: 1741, 1710 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.80–2.24 m [20H, $(CH_2)_5$], 5.18 s (1H, 16-H), 7.28 d (1H, H_{arom}, J = 7.4 Hz), 7.29 t (1H, H_{arom}, J = 7.4 Hz), 7.53 d (1H, H_{arom}, J = 7.4 Hz), 7.54 s (1H, H_{arom}). Found, %: C 62.38; H 6.16; Br 19.54. $C_{21}H_{25}BrO_3$. Calculated, %: C 62.23; H 6.22; Br 19.71.

16-(2-Nitrophenyl)-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione (7g). Yield 1.60 g (43%), mp 197–198°C; published data [8]: mp 198–199°C.

16-(3-Nitrophenyl)-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione (7h). Yield 2.08 g (56%), mp 188–189°C.

16-(4-Nitrophenyl)-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione (7i). Yield 1.93 g (52%), mp 194–196°C; published data [8]: mp 195–196°C.

Methyl 1-[hydroxy(phenyl)methyl]cyclohexanecarboxylate (11a). Yield 0.30 g (12%), mp 69–70°C. IR spectrum, ν, cm^{-1}: 3525 (OH), 1698 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.05–2.20 m [10H, $(CH_2)_5$], 2.93 s (1H, OH), 3.65 s (3H, OMe), 4.61 s (1H, CH), 7.16–7.33 m (5H, H_{arom}). Found, %: C 72.67; H 8.18. $C_{15}H_{20}O_3$. Calculated, %: C 72.55; H 8.12.

Methyl 1-[(4-bromophenyl)(hydroxy)methyl]-cyclohexanecarboxylate (11b). Yield 0.52 g (16%), mp 93–94°C. IR spectrum, ν, cm^{-1}: 3489 (OH), 1721 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.05–2.23 m [10H, $(CH_2)_5$], 2.95 s (1H, OH), 3.66 s (3H, OMe), 4.58 s (1H, CH), 7.07 d (2H, H_{arom}, J = 7.2 Hz), 7.42 d (2H, H_{arom}, J = 7.2 Hz). Found, %: C 55.29; H 5.96; Br 24.25. $C_{15}H_{19}BrO_3$. Calculated, %: C 55.06; H 5.85; Br 24.42.

Methyl 1-[(4-chlorophenyl)(hydroxy)methyl]-cyclohexanecarboxylate (11c). Yield 0.37 g (13%), mp 77–78°C. IR spectrum, ν, cm^{-1}: 3532 (OH), 1705 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.95–2.25 m [10H, $(CH_2)_5$], 3.55 s (3H, OMe), 4.55 s (1H, CH), 5.52 s (1H, OH), 7.18 d (2H, H_{arom}, J = 7.8 Hz), 7.33 d (2H, H_{arom}, J = 7.8 Hz). Found, %: C 63.85; H 6.62; Cl 12.41. $C_{15}H_{19}ClO_3$. Calculated, %: C 63.71; H 6.77; Cl 12.54.

Methyl 1-[(2,4-dichlorophenyl)(hydroxy)methyl]cyclohexanecarboxylate (11d). Yield 0.35 g (11%), mp 100–101°C. IR spectrum, ν, cm^{-1}: 3548 (OH), 1711 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.95–2.42 m [10H, $(CH_2)_5$], 3.60 s (3H, OMe), 5.04 s (1H, CH), 5.72 s (1H, OH), 7.41 d (1H, H_{arom}, J = 7.8 Hz), 7.45 d (1H, H_{arom}, J = 7.8 Hz), 7.50 s (1H, H_{arom}). Found, %: C 56.88; H 5.85; Cl 22.17. $C_{15}H_{18}Cl_2O_3$. Calculated, %: C 56.80; H 5.72; Cl 22.35.

Reaction of methyl 1-bromocyclohexanecarboxylate with zinc. A mixture of 5.0 g of zinc, 11.06 g (50 mmol) of ester **1**, and 5 mg of $HgCl_2$ in 80 mL of benzene was heated for 4 h under reflux, and 10-mL samples were withdrawn after 0.5, 1, 2, 3, and 4 h. Each sample was cooled and hydrolyzed with 5% acetic acid. The organic phase was separated, and the aqueous phase was extracted with three portions of ethyl acetate. The extracts were combined with the organic phase and dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was analyzed by GC/MS. The residual reaction mixture was treated in a similar way, and vacuum distillation gave methyl 1-(cyclohexylcarbonyl)cyclohexanecarboxylate, bp 160–168 (10 mm), mp 48–50°C (from hexane).

Reaction of methyl 1-bromocyclohexanecarboxylate with zinc and 4-bromobenzaldehyde. A mixture of 2.5 g of zinc, 5.53 g (12 mmol) of ester **1**, 10 mmol of 4-bromobenzaldehyde (**4b**), and 5 mg of $HgCl_2$ in 40 mL of benzene was heated for 3 h under reflux. The mixture was treated with 5% acetic acid, the organic phase was separated and dried over Na_2SO_4, the solvent was distilled off, and the residue was treated with methanol to isolate 1.77 g (54%) of compound **11b**.

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