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

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Abstract—Methyl 1-bromocyclohexanecarboxylate reacts with zinc in the presence of cyclohexanecarbonyl chloride to give methyl 1-(cyclohexylcarbonyl)cyclohexanecarboxylate. Treatment of the latter with bromine leads to formation of methyl 1-(1-bromocyclohexylcarbonyl)cyclohexanecarboxylate which reacts with zinc and aromatic aldehydes, yielding 16-aryl-15-oxadispiro[5.1.5.3]hexadecane-7,14-diones.

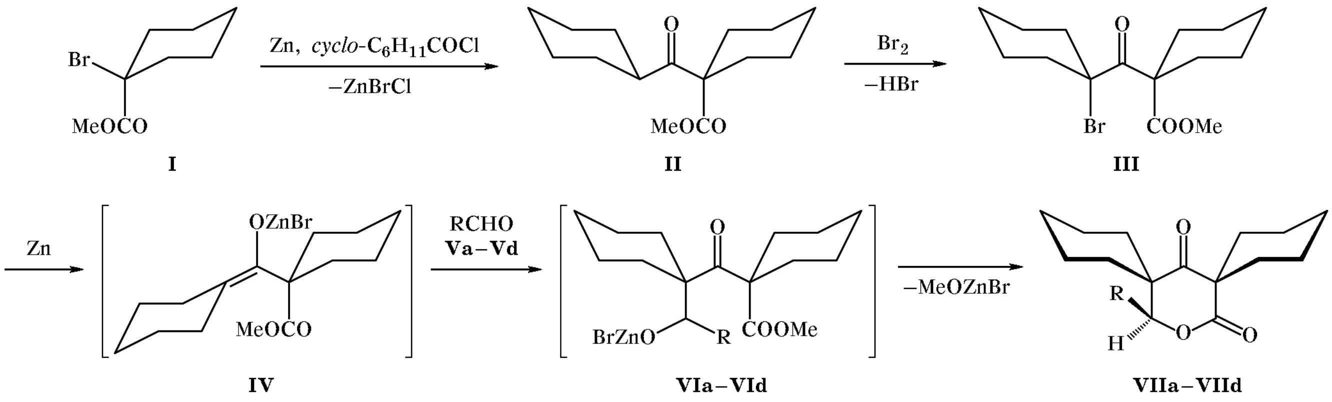
We recently synthesized substituted tetrahydropyran-2,4-diones containing a spiro-carbon atom in position *3* of the pyran ring [1]. In the present communication we report on the use of Reformatsky reaction to build up the cyclic system of 2,3,5,6-tetrahydro-2,4-pyrandiones containing two spiro-carbon atoms in positions *3* and *5* of the pyran ring. The target compounds were synthesized as shown in Scheme 1. The first stage was the reaction of methyl 1-bromocyclohexanecarboxylate (**I**) with zinc and cyclohexanecarbonyl chloride which afforded methyl 1-(cyclohexylcarbonyl)cyclohexanecarboxylate (**II**). Bromination of ester **II** gave methyl 1-(1-bromocyclohexylcarbonyl)cyclohexanecarboxylate (**III**). The latter was brought into Reformatsky reaction with zinc to obtain intermediate **IV** which was treated with aromatic aldehydes **Va**–**Vd**. Alkoxides **VIa**–**VId** thus formed underwent spontaneous cyclization in ether–ethyl acetate, yielding 34–40% of 16-aryl-15-oxadispiro[5.1.5.3]hexadecane-7,14-diones **VIIa**–**VIId** as final products (Scheme 1).

The structure of compounds **VII** was proved by elemental analysis and IR and ^{1}H NMR spectroscopy. The IR spectra of **VII** contained absorption bands typical of ketone (1720 cm^{-1}) and lactone carbonyl groups (1750–1760 cm^{-1}). Signals at δ 5.51–5.77 and 0.57–2.17 ppm in the ^{1}H NMR spectra were assigned, respectively, to the CHO proton and methylene protons of the cyclohexane rings.

EXPERIMENTAL

The ^{1}H NMR spectra of solutions of compounds **II** and **VIIb** in CCl$_4$ were recorded on an RYa-2310 spectrometer at 60 MHz; the spectra of compounds **III**, **VIIa**, **VIIc**, and **VIId** were obtained from

Scheme 1.



V–VII, R = Ph (**a**), 4-FC$_6$H$_4$ (**b**), 4-ClC$_6$H$_4$ (**c**), 2,4-Cl$_2$C$_6$H$_3$ (**d**).

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solutions in DMSO-d_6 on a Bruker AM-300 instrument (300 MHz). Tetramethylsilane was used as internal reference. The IR spectra were measured on a UR-20 instrument from neat substances.

Methyl 1-(cyclohexylcarbonyl)cyclohexanecarboxylate (II). Fine turnings of zinc, 10 g, were mixed with 25 ml of anhydrous ether and 5 ml of anhydrous ethyl acetate, and a mixture of 0.1 mol of methyl cyclohexanecarboxylate and 0.1 mol of cyclohexanecarbonyl chloride in 30 ml of the same solvents was added dropwise. The mixture was refluxed for 1 h, separated from excess zinc (by decanting), and treated with water. The organic phase was separated, dried with anhydrous sodium sulfate, and evaporated. The product was distilled under reduced pressure. Yield 61%. bp 163–165°C (10 mm), mp 49–50°C (from petroleum ether). IR spectrum, ν, cm^{-1}: 1715, 1750 (C=O). ^1H NMR spectrum, δ, ppm: 3.52 s (3H, OCH_3), 2.38 m (1H, 1′-H), 0.58–2.11 m (20H, cyclohexyl). Found, %: C 71.21; H 9.45. $C_{15}H_{24}O_3$. Calculated, %: C 71.39; H 9.59.

Methyl 1-(1-bromocyclohexylcarbonyl)cyclohexanecarboxylate (III). Bromine, 0.11 mol, was added with stirring to a solution of 0.1 mol of compound **II** in 25 ml of acetic acid. The mixture was heated for 1.5 h on a water bath, excess bromine and acetic acid were distilled off, and the product was recrystallized twice from petroleum ether (bp 40–70°C). Yield 62%. mp 67–68°C. IR spectrum, ν, cm^{-1}: 1720, 1735, 1750, 1760 (C=O). ^1H NMR spectrum, δ, ppm: 3.65 s (3H, OCH_3), 1.16–2.16 m (20H, cyclohexyl). Found, %: C 54.53; H 6.82; Br 23.95. $C_{15}H_{23}BrO_3$. Calculated, %: C 54.39; H 7.00; Br 24.12.

16-Aryl-15-oxadispiro[5.1.5.3]hexadecane-7,14-diones VIIa–VIId. To a mixture of 6 g of zinc (prepared as fine turnings), a catalytic amount of mercury(II) chloride, 10 ml of anhydrous diethyl ether, and 25 ml of anhydrous ethyl acetate we added dropwise with stirring a mixture of 0.02 mol of compound **III** and 0.021 mol of aldehyde **Va**–**Vd** in 35 ml of the same solvent mixture. The reaction mixture was refluxed for 1 h, cooled, separated from excess zinc (by decanting), and treated with 5% hydrochloric acid. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The extract was combined with the organic phase, dried over anhydrous sodium sulfate, and evaporated. Products **VIIa**–**VIId** were recrystallized from petroleum ether–ethyl acetate.

16-Phenyl-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione (VIIa). Yield 34%. mp 158–159°C. IR spectrum, ν, cm^{-1}: 1720, 1750 (C=O). ^1H NMR spectrum, δ, ppm: 7.32–7.64 m (5H, Ph), 5.51 s (1H, CHO), 0.64–2.16 m (20H, cyclohexyl). Found, %: C 77.05; H 8.12. $C_{21}H_{26}O_3$. Calculated, %: C 77.27; H 8.03.

16-(4-Fluorophenyl)-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione (VIIb). Yield 38%. mp 176–177°C. IR spectrum, ν, cm^{-1}: 1720, 1755 (C=O). ^1H NMR spectrum, δ, ppm: 7.18–7.45 m (4H, C_6H_4), 5.59 s (1H, CHO), 0.60–2.17 m (20H, cyclohexyl). Found, %: C 73.08; H 7.28. $C_{21}H_{25}FO_3$. Calculated, %: C 73.23; H 7.32.

16-(4-Chlorophenyl)-15-oxadispiro[5.1.5.3]hexadecane-7,14-dione (VIIc). Yield 40%. mp 211–212°C. IR spectrum, ν, cm^{-1}: 1720, 1750 (C=O). ^1H NMR spectrum, δ, ppm: 7.39 d (2H, H_{arom}), 7.37 d (2H, H_{arom}), 5.54 s (1H, CHO), 0.57–2.16 m (20H, cyclohexyl). Found, %: C 69.75; H 7.07; Cl 9.68. $C_{21}H_{25}ClO_3$. Calculated, %: C 69.89; H 6.98; Cl 9.82.

16-(2,4-Dichlorophenyl)-15-oxadispiro[5.1.5.3]-hexadecane-7,14-dione (VIId). Yield 36%. mp 220–221°C. IR spectrum, ν, cm^{-1}: 1720, 1760 (C=O). ^1H NMR spectrum, δ, ppm: 7.60 d (1H, H_{arom}), 7.53 s (1H, H_{arom}), 7.49 d (1H, H_{arom}), 5.77 s (1H, CHO), 0.62–2.17 m (20H, cyclohexyl). Found, %: C 63.87; H 6.05; Cl 17.72. $C_{21}H_{24}Cl_2O_3$. Calculated, %: C 63.80; H 6.12; Cl 17.94.

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