

Reformatsky Reaction of Methyl 1-Bromocycloalkanecarboxylates with α -Dicarbonyl Compounds

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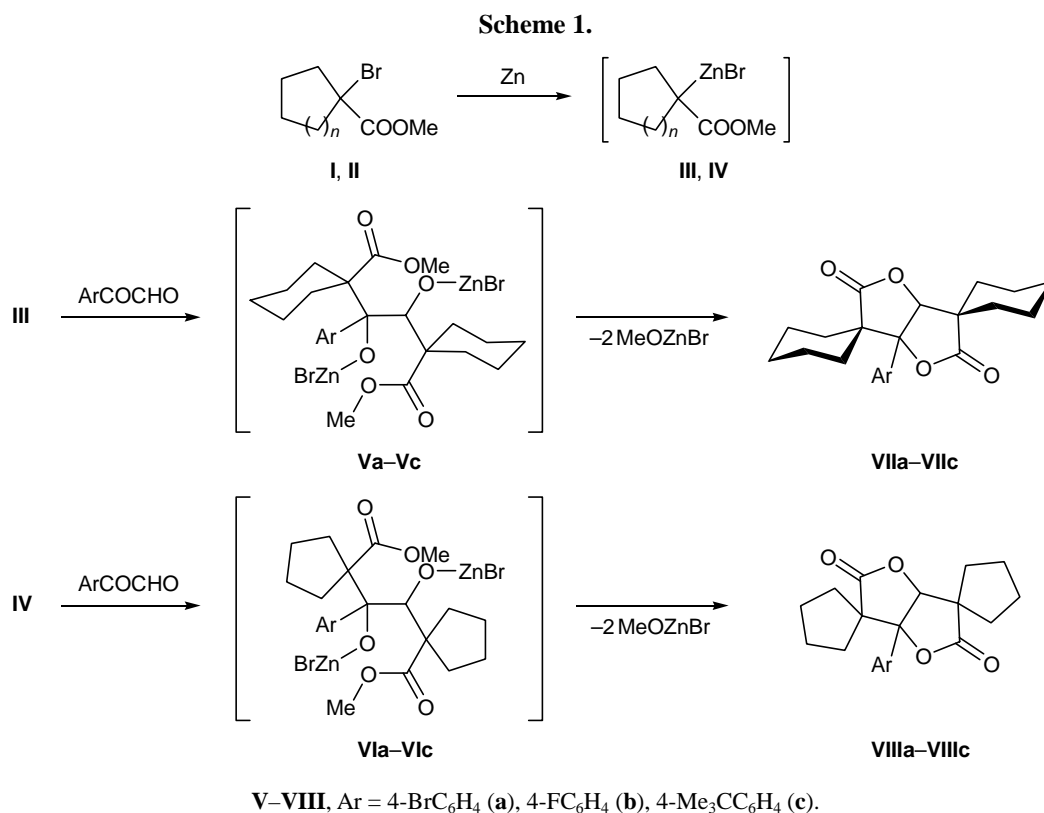
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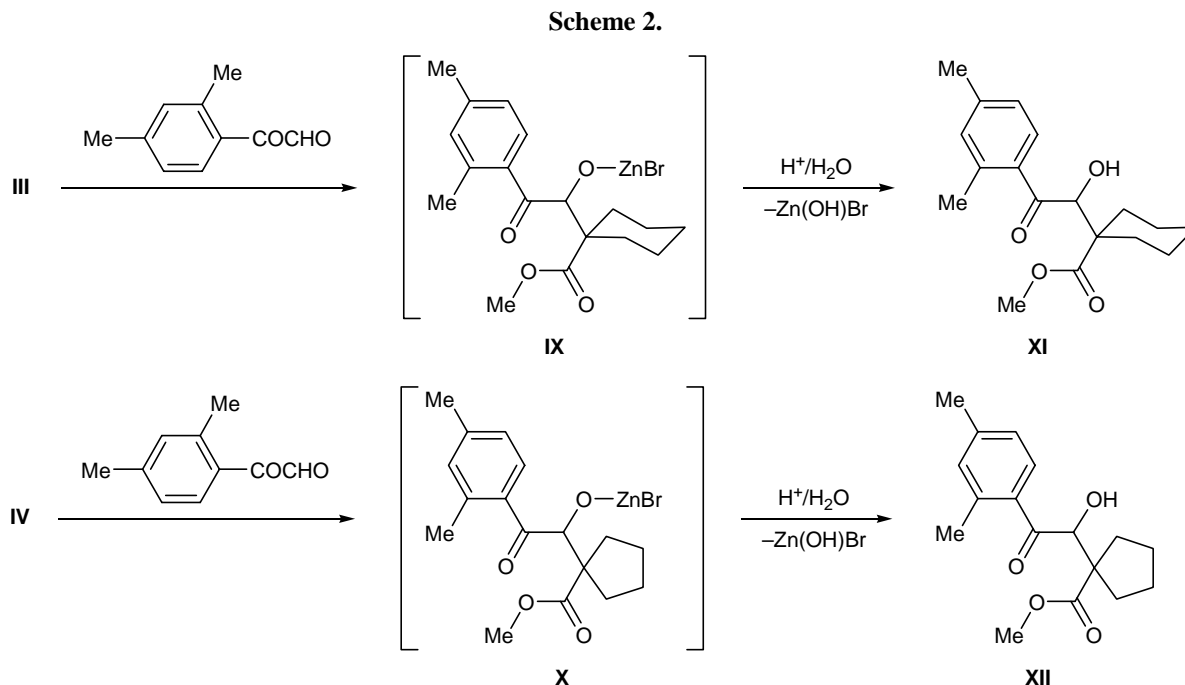
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Abstract—Reformatsky reactions of methyl 1-bromocyclohexanecarboxylate and methyl 1-bromocyclopentanecarboxylate with 2-aryl-2-oxoacetaldehydes involve both carbonyl groups of the latter and result in formation of 3a-aryl-3,3:6,6-bis(pentamethylene)- and 3a-aryl-3,3:6,6-bis(tetramethylene)tetrahydrofuro[3,2-*b*]furan-2,5-diones. The reaction with 2-(2,4-dimethylphenyl)-2-oxoacetaldehyde gives acyclic products, methyl 1-[1-hydroxy-2-(2,4-dimethylphenyl)-2-oxoethyl]cyclohexanecarboxylate and methyl 1-[1-hydroxy-2-(2,4-dimethylphenyl)-2-oxoethyl]cyclopentanecarboxylate, while with benzil methyl 1-(4-hydroxy-1-oxo-3,4-diphenyl-2-oxaspiro[4.5]dec-3-yl)cyclohexanecarboxylate and methyl 1-(4-hydroxy-1-oxo-3,4-diphenyl-2-oxaspiro[4.4]non-3-yl)cyclopentanecarboxylate are obtained.

We recently reported that classical Reformatsky reactions with 2-aryl-2-oxoacetaldehydes lead to formation of fused bis-lactones [1]. In the present work we examined reactions of α -dicarbonyl compounds with organozinc reagents **III** and **IV** derived from

methyl 1-bromocyclohexanecarboxylate (**I**) and methyl 1-bromocyclopentanecarboxylate (**II**), respectively. We found that compounds **III** and **IV** react with 2-aryl-2-oxoacetaldehydes at both carbonyl groups of the latter and that intermediate bromozinc alkoxides **Va–Vc** and





Vla–Vlc undergo spontaneous cyclization to afford fused spiro bis-lactones, 3a-aryl-3,3:6,6-bis(pentamethylene)- and 3a-aryl-3,3:6,6-bis(tetramethylene)-tetrahydrofuro[3,2-*b*]furan-2,5-diones **VIIa–VIIc** and **VIIIa–VIIIc**, respectively (Scheme 1, see table).

The structure of products **VIIa–VIIc** and **VIIIa–VIIIc** was confirmed by the data of elemental analysis and IR and NMR spectroscopy. The IR spectra of **VIIa–VIIc** and **VIIIa–VIIIc** characteristically contained two lactone carbonyl bands at 1760–1775 and

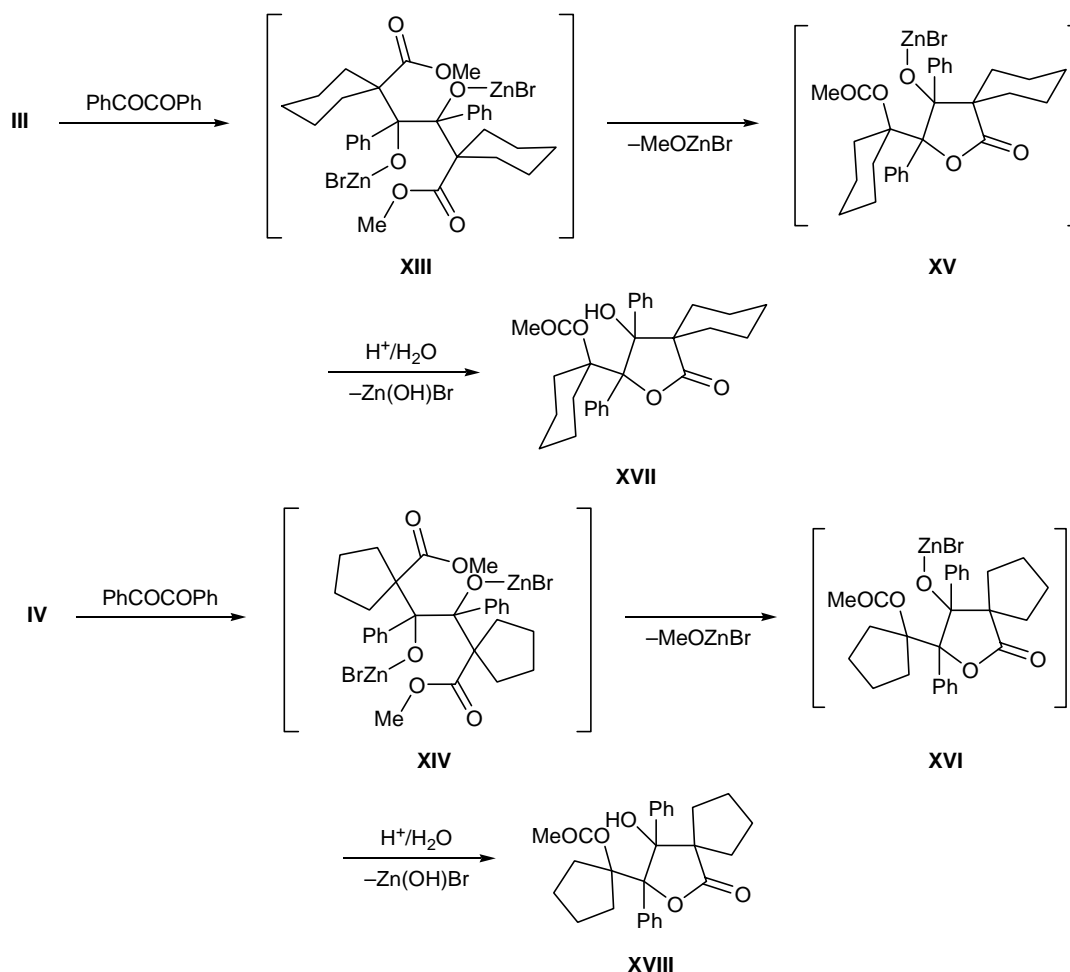
1780–1795 cm^{-1} . In the ¹H NMR spectra, the 6a-H signal (CHO) appeared at δ 5.22–5.78 ppm.

Introduction of a substituent into the *ortho* position of 2-aryl-2-oxoacetaldehyde increases steric hindrances to attack by organozinc compound. As a result, compounds **III** and **IV** react with 2-(2,4-dimethylphenyl)-2-oxoacetaldehyde only at the aldehyde carbonyl group, and intermediates **IX** and **X** do not undergo cyclization. The final products were acyclic methyl 1-[1-hydroxy-2-(2,4-dimethylphenyl)-2-oxo-

Yields, constants, IR and ¹H NMR spectra, and elemental analyses of 3a-aryl-3,3:6,6-bis(pentamethylene)- and 3a-aryl-3,3:6,6-bis(tetramethylene)tetrahydrofuro[3,2-*b*]furan-2,5-diones **VIIa–VIIc** and **VIIIa–VIIIc**

Comp. no.	Yield, %	mp, °C	IR spectrum, ν_{CO} , cm^{-1}	¹ H NMR spectrum, δ , ppm	Found, %		Formula	Calculated, %	
					C	H		C	H
VIIa	28	194–195	1765, 1780	0.50–2.40 m (20H, C ₆ H ₁₀), 5.25 s (1H, CHO), 6.85–7.75 m (4H, 4-BrC ₆ H ₄)	60.81	5.73	C ₂₂ H ₂₅ BrO ₄	60.98	5.82
VIIb	31	190–191	1770, 1790	0.60–2.30 m (20H, C ₆ H ₁₀), 5.22 s (1H, CHO), 6.75–7.55 m (4H, 4-FC ₆ H ₄)	71.12	6.61	C ₂₂ H ₂₅ FO ₄	70.95	6.77
VIIc	39	202–203	1765, 1780	0.62–2.19 m (20H, C ₆ H ₁₀), 1.35 s (9H, Me ₃ C), 5.78 s (1H, CHO), 7.35–7.50 m (4H, 4-Me ₃ CC ₆ H ₄)	75.89	8.43	C ₂₆ H ₃₄ O ₄	76.07	8.35
VIIIa	35	212–213	1760, 1780	0.55–2.34 m (16H, C ₅ H ₈), 5.35 s (1H, CHO), 6.88–7.74 m (4H, 4-BrC ₆ H ₄)	59.09	5.14	C ₂₀ H ₂₁ BrO ₄	59.27	5.22
VIIIb	32	180–181	1775, 1785	0.65–2.25 m (16H, C ₅ H ₈), 5.31 s (1H, CHO), 6.73–7.58 m (4H, 4-FC ₆ H ₄)	69.60	6.08	C ₂₀ H ₂₁ FO ₄	69.75	6.15
VIIIc	42	166–167	1775–1795	0.90–2.14 m (16H, C ₅ H ₈), 1.35 s (9H, Me ₃ C), 5.52 s (1H, CHO), 7.41 d and 7.47 d (4H, 4-Me ₃ CC ₆ H ₄)	75.18	7.77	C ₂₄ H ₃₀ O ₄	75.36	7.91

Scheme 3.



ethyl)cyclohexanecarboxylate (XI) and methyl 1-[1-hydroxy-2-(2,4-dimethylphenyl-2-oxoethyl)]-cyclopentanecarboxylate (XII) (Scheme 2).

Phenyl groups in the molecule of benzil do not hamper reactions of compounds III and IV at both carbonyl groups to give intermediate bromozinc alkoxides XIII and XIV. However, double intramolecular cyclization of XIII and XIV is hindered, and the reaction stops after the first cyclization stage leading to intermediates XV and XVI. As final products, we isolated methyl 1-(4-hydroxy-1-oxo-3,4-diphenyl-2-oxaspiro[4.5]dec-3-yl)cyclohexanecarboxylate (XVII) and methyl 1-(4-hydroxy-1-oxo-3,4-diphenyl-2-oxaspiro[4.4]non-3-yl)cyclopentanecarboxylate (XVIII), respectively (Scheme 3).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from neat substances. The ¹H NMR spectra of compounds VIIa, VIIb, VIIIa, VIIIb, XII, XVII, and

XVIII were obtained from solutions in CDCl₃ on an RYa-2310 instrument; the ¹H NMR spectra of VIIc, VIIIc, and XI were measured on a Bruker DRX-500 spectrometer (500 Hz) from solutions in DMSO-*d*₆-CCl₄ (1:3); tetramethylsilane was used as internal reference.

3a-Aryl-3,3:6,6-bis(pentamethylene)- and 3a-aryl-3,3:6,6-bis(tetramethylene)tetrahydrofuro[3,2-*b*]furan-2,5-diones VIIa–VIIc and VIIIa–VIIIc (general procedure). A mixture of 0.03 mol of methyl 1-bromocyclohexanecarboxylate or methyl 1-bromocyclopentanecarboxylate and 0.01 mol of 2-aryl-2-oxoacetaldehyde in 10 ml of benzene was added to a mixture of 3 g of zinc (prepared as fine turnings), 10 ml of diethyl ether, 10 ml of benzene, and 1 ml of HMPA. The mixture was heated for 1.5 h, cooled, treated with 5% hydrochloric acid, and extracted with diethyl ether. The extract was dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was recrystallized from ethyl acetate. The

yields, melting points, IR and ^1H NMR spectral parameters, and elemental analyses of compounds **VIIa–VIIc** and **VIIIa–VIIIc** are given in table.

Methyl 1-[1-hydroxy-2-(2,4-dimethylphenyl)-2-oxoethyl]cyclohexanecarboxylate (XI) and methyl 1-[1-hydroxy-2-(2,4-dimethylphenyl)-2-oxoethyl]cyclopentanecarboxylate (XII) were synthesized in a similar way.

Compound **(XI)**. Yield 55%, mp 88–89°C (from petroleum ether). IR spectrum, ν , cm^{-1} : 1665, 1720 (C=O); 3460 (OH). ^1H NMR spectrum, δ , ppm: 0.98–1.90 m (20H, C_6H_{10}); 2.31 s and 2.33 s (6H, 2,4- $\text{Me}_2\text{C}_6\text{H}_3$); 3.25 s (3H, MeO); 4.89 d (1H, CHO); 5.21 d (1H, OH); 7.10 d, 7.11 s, and 7.55 d (3H, 2,4- $\text{Me}_2\text{C}_6\text{H}_3$). Found, %: C 70.88; H 8.02. $\text{C}_{18}\text{H}_{24}\text{O}_4$. Calculated, %: C 71.03; H 7.95.

Compound **(XII)**. Yield 65%, bp 203–207°C (6 mm). IR spectrum, ν , cm^{-1} : 1675, 1720 (C=O); 3470 (OH). ^1H NMR spectrum, δ , ppm: 0.85–1.75 m (16H, C_5H_8), 2.30 s and 2.33 s (6H, 2,4- $\text{Me}_2\text{C}_6\text{H}_3$), 3.23 s (3H, MeO), 4.78 d (1H, CHO), 5.05 br.s (1H, OH), 7.08–7.50 m (3H, 2,4- $\text{Me}_2\text{C}_6\text{H}_3$). Found, %: C 70.49; H 7.52. $\text{C}_{17}\text{H}_{22}\text{O}_4$. Calculated, %: C 70.32; H 7.64.

1-(4-Hydroxy-1-oxo-3,4-diphenyl-2-oxaspiro[4.5]dec-3-yl)cyclohexanecarboxylate (XVII) and methyl 1-(4-hydroxy-1-oxo-3,4-diphenyl-2-oxaspiro[4.4]non-3-yl)cyclopentanecarboxylate (XVIII) were synthesized as described above for compounds **VII** and **VIII** using 1,2-diphenylethane-1,2-dione as initial compound.

Compound **(XVII)**. Yield 33%, mp 237–238°C (from ethyl acetate). IR spectrum, ν , cm^{-1} : 1690, 1730. ^1H NMR spectrum, δ , ppm: 0.47–1.87 m (20H, C_6H_{10}), 3.29 s (3H, MeO), 7.00–7.82 m (10H, H_{arom}), 8.37 br.s (1H, OH). Found, %: C 75.17; H 7.49. $\text{C}_{29}\text{H}_{34}\text{O}_5$. Calculated, %: C 75.30; H 7.41.

Compound **(XVIII)**. Yield 44%, mp 235–237°C (ethyl acetate). IR spectrum, ν , cm^{-1} : 1690, 1730. ^1H NMR spectrum, δ , ppm: 0.75–1.78 m (16H, C_5H_8), 3.36 s (3H, MeO), 7.00–7.70 m (10H, H_{arom}), 8.40 br.s (1H, OH). Found, %: C 74.81; H 6.78. $\text{C}_{27}\text{H}_{30}\text{O}_5$. Calculated, %: C 74.63; H 6.96.

REFERENCE

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