

Synthesis of 5-Aryl-2,2-dimethyl-4-oxaspiro[5,5]undecane-1,3-diones by Reformatsky Reaction

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Abstract—Alkyl 3-(1-bromocyclohexyl)-2,2-dimethyl-3-oxopropanoates react with zinc and aromatic aldehydes to yield 5-aryl-2,2-dimethyl-4-oxaspiro[5,5]undecane-1,3-diones.

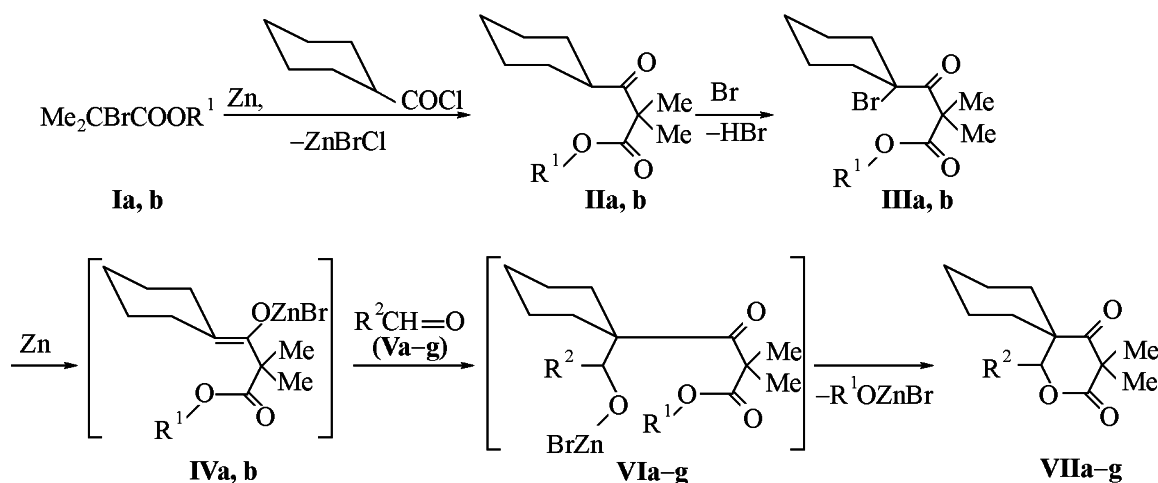
In extension of the study on Reformatsky reaction as a method for building up a system of 2,3,5,6-tetrahydro-2,4-pyrandione [1, 2] we carried out an investigation of reaction between alkyl 3-(1-bromocyclohexyl)-2,2-dimethyl-3-oxopropanoates (**IIa, b**), zinc and aromatic aldehydes **Va–g**. The initial bromoketoesters **IIa, b** were prepared by reaction of methyl or ethyl α -bromoisobutyrate (**Ia, b**) with zinc and cyclohexanecarbonyl chloride followed by bromination in the acetic acid solution of methyl or ethyl 2,2-dimethyl-3-oxo-3-cyclohexylpropanoates (**IIa, b**) (see the scheme).

Our study revealed that alkyl 3-(1-bromocyclohexyl)-2,2-dimethyl-3-oxopropanoates were capable to react with zinc in the ether–ethyl acetate (1:2) medium affording a new zinc enolate **IV** that reacted with aromatic aldehydes **Va–g**. The arising bromo-

zinc alcoholate **VI** spontaneously underwent cyclization into substituted tetrahydro-2,4-pyandiones containing a spiro carbon in the 5 position of the pyran ring. Thus 5-aryl-2,2-dimethyl-4-oxaspiro[5,5]undecane-1,3-diones (**VIIa–g**) were prepared (see table).

The final products were obtained in 42–72% yield. Their composition and structure were proved by elemental analysis, ^1H NMR and IR spectra. In the ^1H NMR spectra appear the characteristic proton signals (δ , ppm) in 5.53–5.81, 1.34–1.47, 0.60–2.07 regions. The resonances belong respectively to methine proton (CHO), methyl groups protons (Me_2C), and those of the cyclohexane ring. In the IR spectra absorption bands are present from the keto group in 1715–1720 cm^{-1} region and from the lactone carbonyl at 1740–1770 cm^{-1} .

Scheme.



I–IV, $\text{R}^1 = \text{Me}$ (**a**), Et (**b**); **VI**, $\text{R}^1 = \text{Me}$ (**a**), Et (**b–g**); **V–VII**, $\text{R}^2 = 4\text{-BrC}_6\text{H}_4$ (**a**), $4\text{-ClC}_6\text{H}_4$ (**b**), $2,4\text{-Cl}_2\text{C}_6\text{H}_3$ (**c**), $2\text{-FC}_6\text{H}_4$ (**d**), $4\text{-FC}_6\text{H}_4$ (**e**), $4\text{-CH}_3\text{OC}_6\text{H}_4$ (**f**), $3,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3$ (**g**).

Yields, physical constants, IR and ^1H NMR spectra, and elemental analyses of 5-aryl-2,2-dimethyl-4-oxaspiro[5,5]-undecane-1,3-diones (**VIIa–g**)

Compd. no.	Yield, %	mp, °C	IR spectrum (ν , cm^{-1})		^1H NMR spectrum (δ , ppm)			
			CO ket.	CO lact.	R^2	Me_2C	$(\text{CH}_2)_5$	$-\text{CHO}-$
VIIa	58	171–172	1715	1740	7.32 d, 7.62 d (4H, 4- BrC_6H_4)	1.36 s, 1.46 s	0.60–2.05 m	5.61 s
VIIb	64	170–171	1720	1750	7.37 d, 7.42 d (4H, 4- ClC_6H_4)	1.34 s, 1.46 s	0.62–2.07 m	5.62 s
VIIc	54	182–183	1725	1770	7.49 d, 7.55 s, 7.60 d (3H, 2,4- $\text{Cl}_2\text{C}_6\text{H}_3$)	1.37 s, 1.47 s	0.67–2.02 m	5.81 s
VIIId	42	128–129	1720	1760	7.20–7.57 m (4H, 2- FC_6H_4)	1.36 s, 1.47 s	0.74–2.04 m	5.80 s
VIIE	72	162–163	1720	1750	7.22 d.d, 7.42 d.d (4H, 4- FC_6H_4)	1.35 s, 1.46 s	0.66–2.03 m	5.67 s
VIIIf	40	131–132	1720	1750	3.80 s (3H, MeO), 6.96 d, 7.29 d (4H, 4- MeOC_6H_4)	1.35 s, 1.44 s	0.71–2.00 m	5.55 s
VIIg	41	145–147	1720	1760	3.79 s (6H, MeO), 6.90 d, 6.92 s, 6.97 d [3H, 3,4-(MeO) $_2\text{C}_6\text{H}_3$]	1.35 s, 1.46 s	0.76–2.01 m	5.53 s

Compd. no.	Found, %		Formula	Calculated, %	
	C	H		C	H
VIIa	59.26	5.85	$\text{C}_{18}\text{H}_{21}\text{BrO}_3$	59.19	5.80
VIIb	67.48	6.63	$\text{C}_{18}\text{H}_{21}\text{ClO}_3$	67.39	6.60
VIIc	60.68	5.62	$\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{O}_3$	60.85	5.67
VIIId	70.95	6.88	$\text{C}_{18}\text{H}_{21}\text{FO}_3$	71.03	6.95
VIIE	71.15	6.92	$\text{C}_{18}\text{H}_{21}\text{FO}_3$	71.03	6.95
VIIIf	72.01	7.71	$\text{C}_{19}\text{H}_{24}\text{O}_4$	72.13	7.65
VIIg	69.21	7.52	$\text{C}_{20}\text{H}_{26}\text{O}_5$	69.34	7.57

EXPERIMENTAL

^1H NMR spectra of compounds **IIa**, **b**, **IIIa**, **b** in CCl_4 solution were registered on RYa-2310 instrument (60 MHz), and those of compounds **VIIa–g** in $\text{DMSO}-d_6$ solution on spectrometer Bruker AM-300 (300 MHz), internal reference TMS. IR spectra of individual compounds were recorded on UR-20 spectrophotometer.

Methyl 2,2-dimethyl-3-oxo-3-cyclohexylpropanoate (IIa). To 10 g of fine zinc turnings in 25 ml of anhydrous ether and 5 ml of anhydrous ethyl acetate was added 0.1 mol of methyl α -bromoisobutyrate and 0.1 mol of cyclohexanecarbonyl chloride. The mixture was boiled for 1 h, decanted, and hydrolyzed with water. The organic layer was separated, dried on calcined sodium sulfate, the solvent was distilled off, and the reaction product was twice distilled in a vacuum. Yield 51%, bp 134–135°C (5 mm Hg), d_4^{20} 1.0197, n_D^{20} 1.4584. IR spectrum (ν , cm^{-1}): 1730, 1750 ($\text{C}=\text{O}$). ^1H NMR spectrum (δ ,

ppm): 0.83–1.93 m [10H, $(\text{CH}_2)_5$], 1.16 s (6H, CH_3), 2.29 m (1H, $\text{CHC}=\text{O}$), 3.56 s (3H, CH_3O). Found, %: C 67.74; H 9.45. $\text{C}_{12}\text{H}_{20}\text{O}_3$. Calculated, %: C 67.89; H 9.50.

Ethyl 2,2-dimethyl-3-oxo-3-cyclohexylpropanoate (IIb) was prepared similarly to compound **IIa** proceeding from compound **Ib**. Yield 53%, bp 129–131°C (10 mm Hg), d_4^{20} 1.0016, n_D^{20} 1.4525. IR spectrum (ν , cm^{-1}): 1715, 1730 ($\text{C}=\text{O}$). ^1H NMR spectrum (δ , ppm): 0.78–1.88 m [10H, $(\text{CH}_2)_5$], 1.13 t (3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.13 s (6H, CH_3), 2.33 m (1H, $\text{CHC}=\text{O}$), 4.05 q (2H, OCH_2CH_3). Found, %: C 68.91; H 9.82. $\text{C}_{13}\text{H}_{22}\text{O}_3$. Calculated, %: C 68.99; H 9.80.

Methyl 3-(1-bromocyclohexyl)-2,2-dimethyl-3-oxopropanoate (IIIa). To a solution of 0.1 mol of compound **IIa** in 25 ml of acetic acid was added at stirring 0.11 mol of bromine. The mixture was heated for 1.5 h on a water bath, then the solvent was distilled off, and the reaction product was distilled in

a vacuum. Yield 68%, bp 162–164°C (11 mm Hg), mp 62–63°C (from petroleum ether). IR spectrum (ν , cm^{-1}): 1715, 1730, 1760 ($\text{C}=\text{O}$). ^1H NMR spectrum (δ , ppm): 0.73–2.16 m [10H, $(\text{CH}_2)_5$], 1.28 s (6H, CH_3), 3.49 s (3H, OCH_3). Found, %: C 49.35; H 6.49; Br 27.26. $\text{C}_{12}\text{H}_{19}\text{BrO}_3$. Calculated, %: C 49.50; H 6.58; Br 27.44.

Ethyl 3-(1-bromocyclohexyl)-2,2-dimethyl-3-oxopropanoate (IIIb) was prepared in the same way as compound **IIIa** starting with compound **IIb**. Yield 74%, bp 155–157°C (7 mm Hg), mp 36–38°C (from petroleum ether). IR spectrum (ν , cm^{-1}): 1715, 1730, 1760 ($\text{C}=\text{O}$). ^1H NMR spectrum (δ , ppm): 0.84–2.21 m [10H, $(\text{CH}_2)_5$], 1.09 t (3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.29 s (6H, CH_3), 3.99 q (2H, OCH_2CH_3). Found, %: C 51.01; H 6.96; Br 25.97. $\text{C}_{13}\text{H}_{21}\text{BrO}_3$. Calculated, %: C 51.16; H 6.94; Br 26.18.

5-R-2,2-dimethyl-4-oxaspiro[5,5]undecane-1,3-diones (VIIa–g). To a mixture of 6 g of fine zinc turnings, catalytic amount of HgCl_2 , 10 ml of

anhydrous ethyl ether, and 15 ml of anhydrous ethyl acetate was added dropwise at stirring a mixture of 0.02 mol of methyl or ethyl 3-(1-bromocyclohexyl)-2,2-dimethyl-3-oxopropanoate and 0.021 mol of an appropriate aldehyde in 20 ml of a mixed solvent. Then the reaction mixture was boiled for 1 h, cooled, decanted, hydrolyzed with 5% hydrochloric acid, the organic layer was separated, and from the water layer the products were twice extracted with ether. The combined organic solutions were dried with calcined sodium sulfate, the solvents were distilled off, and the final products **VIIa–g** were twice recrystallized from petroleum ether (bp 40–70°C) (see table).

REFERENCES

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