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Reaction of Methyl 1-Bromocycloalkanecarboxylates with Zinc and Ethyl 5-Aryl-3-oxo-2,2-diethylpent-4-enoates

N. F. Kirillov[a], **E. A. Nikiforova**[a], **P. A. Slepukhin**[b], **and M. I. Vakhrin**[a]

[a] *Perm' State University, ul. Bukireva 15, Perm', 614990 Russia*
e-mail: kirillov@psu.ru

[b] *Postovsky Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences, Yekaterinburg, Russia*

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Abstract—Methyl 1-bromoalkanecarboxylates react with zinc and ethyl 5-aryl-3-oxo-2,2-diethylpent-4-enoates to form ethyl 2-(10-aryl-6-oxo-7-oxaspiro[4.5]dec-8-en-8-yl)-2-ethylbutanoates and ethyl 2-(5-aryl-1-oxo-2-oxaspiro[5.5]undec-3-en-3-yl)-2-ethylbutanoates.

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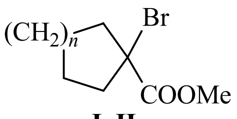
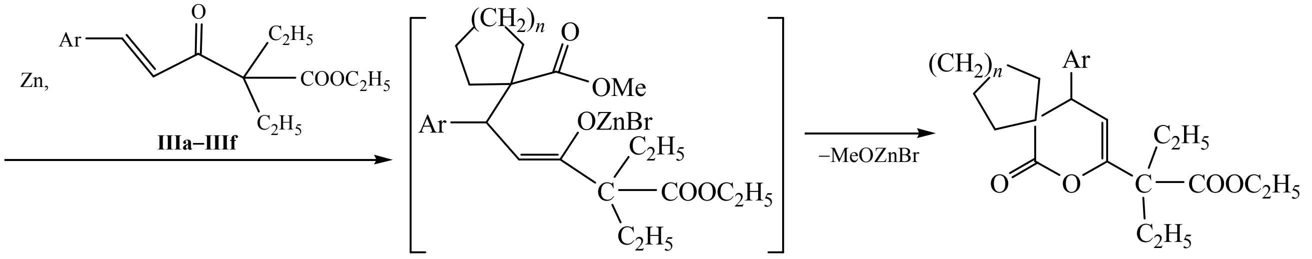
The Reformatsky reagents add to α,β-unsaturated ketones in the 1,2- as well as in the 1,4-positions of the conjugated system. The products of 1,4-addition undergo cyclization to unsaturated lactones, the dihydropyran-2-one derivatives [1, 2].

It was established previously that in the reactions of alicyclic Reformatsky reagents with 1,3-diarylprop-2-en-1-ones substituted spirodihydropyranones were formed [3, 4]. Developing these studies we have investigated the reactions of Reformatsky reagents prepared from methyl 1-bromocyclopentane **I** and 1-bromocyclohexane **II**-carboxylates and zinc with ethyl 5-aryl-3-oxo-2,2-diethylpent-4-enoates **IIIa–IIIf**. Our studies showed that organozinc reagents add to compounds **IIIa–IIIf** in the 1,4 position of –C=C-C=O fragment to form the intermediates **IVa–IVd** and **Va–Vf**. In the course of the reaction these intermediates due to attack of the oxygen atom on the ester carbonyl carbon atom undergo cyclization to substituted spyrodihydropyran-2-ones, in particular, to ethyl 2-(10-aryl-6-oxo-7-oxaspiro[4.5]dec-8-en-8-yl)-2-ethylbutanoates **VIa–VId** and ethyl 2-(5-aryl-1-oxo-2-oxaspiro[5.5]undec-3-en-3-yl)-2-ethylbutanoates **VIIa–VIIf**. In both cases a bromozincmethylate molecule is liberated.



I, II



IVa–IVd, Va–Vf **VIa–VId, VIIa–VIIf**

I, IV, VI: $n = 1$; **II, V, VII**: $n = 2$; **III–VII**: Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-BrC_6H_4 (**c**), 4-ClC_6H_4 (**d**); **III, V, VII**: Ar = 3-BrC_6H_4 (**e**), 2-FC_6H_4 (**f**).

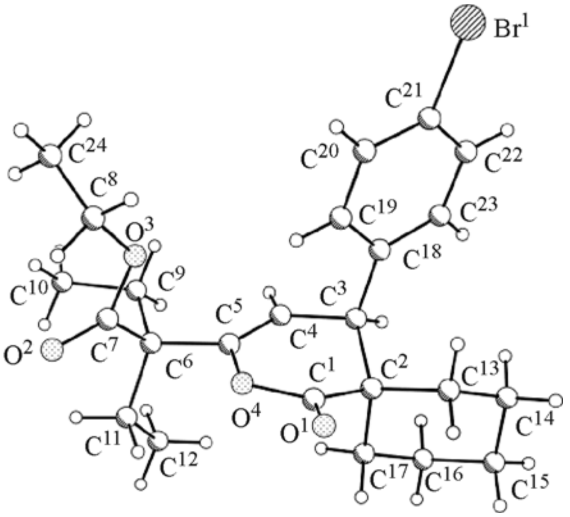


Fig. 1. General view of compound **VIIc** according to X-ray data.

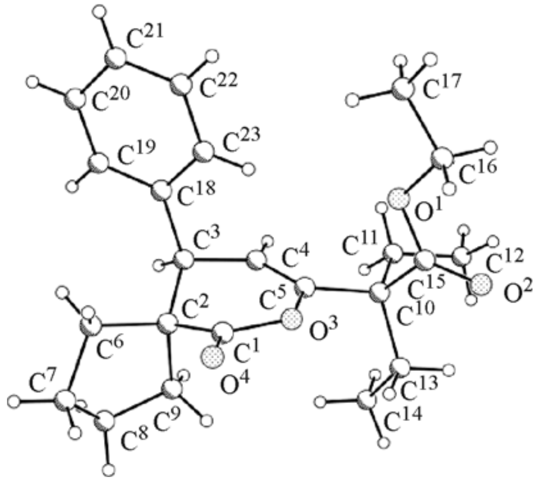


Fig. 2. General view of compound **VIa** according to X-ray data.

The composition and structure of the compounds obtained were confirmed by elemental analysis and the IR and ^{1}H NMR spectroscopy. In the IR spectra of compounds **VIa–VId** and **VIIa–VIIf** characteristic bands of C=C bonds at 1675–1690 cm^{-1} and of the ester and lactonic carbonyls at 1735–1750 cm^{-1} and 1755–1775 cm^{-1} respectively were observed. ^{1}H NMR spectra contain one set of signals among which the doublets of dihydropyran cycle protons at 3.22–3.38 and 5.35–5.41 ppm are most characteristic. In the ^{1}H NMR spectra of compounds **VIa–VId** unlike the spectra of substances **VIIa–VIIf** signals of methylene protons of the ethoxy groups give clearly expressed 10-component multiplet with the integral intensity corresponding to two protons. At the saturation of the resonance of methylene protons of the ethoxy group of compound **VIc** the signal of the methylene group proton converts in two doublets with chemical shifts of 4.19 and 4.23 ppm and the coupling constant $J = 15.0$ Hz. It shows that these protons are nonequivalent.

Structure of the compounds **VIa** and **VIIc** was established by the XRD study. It was shown that these substances crystallize in centrosymmetric group of the $P2_1/c$ symmetry of the monoclinic crystal system with close parameters of the unit cells. Interatomic distances and bond angles of the cyclic esters synthesized are close to the standard values. General view and numbering of atoms in the structural experiment are presented in Figs. 1, 2. The symmetry of ethyl substituents in the side chain of dihydropyran ring in both compounds is distorted. Corresponding torsion angles for compound **VIa** are C^{5}C^{10}C^{11}C^{12} 178.07°, C^{5}C^{10}C^{13}C^{14} 66.26°. For compound **VIIc** these values are C^{5}C^{6}C^{9}C^{10} 175.37°, C^{5}C^{6}C^{11}C^{12} –66.00°.

EXPERIMENTAL

IR spectra of compounds **VIa–VId** and **VIIa–VIIf** were recorded on a Specord-75IR spectrometer as mulls in mineral oil. ^{1}H NMR spectra were taken on a Mercury Plus-300 (300 MHz) spectrometer in $CDCl_3$ with reference TMS.

XRD studies were carried out on an automatic Xcalibur 3 diffractometer with CCD detector according to the standard procedure [Mo*K* radiation, 295(2) K, graphite monochromator, w-scanning]. For the analysis of compound **VIIc** the colorless single crystal of dimensions 0.31×0.23×0.13 mm was used, and in the case of compound **VIa** the colorless single crystal of dimensions 0.25×0.20×0.15 mm was studied. The correction for the extinction of compound **VIIc** was made analytically using the polyhedron crystal model [5]. For compound **VIa** no correction was made. Solving and refining of structures was carried out by SHELXL-97 software [6]. The structures were solved by the direct method and refined by the full-matrix root-mean-square method with respect to F^2 in the anisotropic approximation for all non-hydrogen atoms. Hydrogen atoms were revealed by the peaks of spatial electronic density and included in refining in the isotropic approximation in the *rider* model. Main crystallographic data and the parameters of refining of structures are listed in the table.

Main parameters of the X-ray experiments

Compound	VIIc	VIa
Formula	$C_{24}H_{31}BrO_4$	$C_{23}H_{30}O_4$
Molecular weight	463.40	370.47
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a, Å	11.1706(3)	15.4759(7)
b, Å	12.9526(3)	11.2863(11)
c, Å	15.9457(4)	12.6735(8)
α, deg	90	90
β, deg	94.611(2)	107.711(5)
γ, deg	90	90
V, Å^3	2299.69(10)	2108.7(3)
Z	4	4
d_{calc}, g cm^{-3}	1.338	1.167
μ, mm^{-1}	1.813	0.078
Scanning range, deg	$2.80 \le \theta \le 30.52$	$2.76 \le \theta \le 28.30$
Number of measured independent reflections (R_{int})	13349/6606 (0.0141)	10328/5024 (0.0205)
Number of reflections with $I > 2\sigma(I)$	3815	2534
Completeness (for θ, deg)	97.3% (26.00)	98.2% (26.00)
Number of refined parameters	271	247
S	1.001	1.008
R_1 [by $I > 2\sigma(I)$]	0.0323	0.0458
wR_2 [by $I > 2\sigma(I)$]	0.0773	0.1278
R_1 (by all reflections)	0.0625	0.0948
wR_2 (by all reflections)	0.0804	0.1390
$\Delta e/e$ Å^{-3}	0.358/–0.464	0.277/–0.242

X-ray data were deposited in the Cambridge center of crystallographic data, CCDC numbers 842114 and 842115. These data are accessible free and may be requested by the address www.ccdc.cam.ac.uk/data_request/cif.

Ethyl 2-(10-aryl-6-oxo-7-oxaspiro[4.5]dec-8-en-8-yl)-2-ethylbutanoates VIa–VId and ethyl 2-(5-aryl-1-oxo-2-oxaspiro[5.5]undec-3-en-3-yl)-2-ethylbutanoates VIIa–VIIf. A mixture of 23 mg-equiv of fine zinc turnings, the catalytic amount of mercury chloride, 5 mmol of ethyl 5-aryl-3-oxo-2,2-diethylpent-4-enoate, 5.3 mmol of methyl 1-bromocyclopentane- or methyl 1-bromocyclohexanecarboxylate, 20 ml of benzene, 5 ml of ethyl acetate, and 1 ml of HMPA was boiled for 4 h, cooled, decanted from the excess of zinc, and decomposed with 5% hydrochloric acid. Organic layer was separated, and water layer was two times extracted with ethyl acetate. After drying the extract over anhydrous sodium sulfate solvents were removed and compounds **VIa–VId** or **VIIa–VIIf** were crystallized from ethanol.

Ethyl 2-(6-oxo-10-phenyl-7-oxaspiro[4.5]dec-8-en-8-yl)-2-ethylbutanoate (VIa). Yield 0.78 g (42%), mp 74–75°C. IR spectrum, ν, cm^{-1}: 1690 (C=C), 1740 (C=O)$_{est}$, 1779 (C=O)$_{lact}$. ^{1}H NMR spectrum, δ, ppm: 0.79 t. 0.82 t (6H, $2CH_2CH_3$, J 7.5 Hz), 1.27 t (3H, OCH_2CH_3, J 7.5 Hz), 1.18–2.09 m [12H, $(CH_2)_4$, $2CH_2CH_3$], 3.26 d (1H, C^{19}H, J 6.3 Hz), 4.13–4.25 m (2H, OCH_2CH_3), 5.41 d (1H, =C^{9}H, J 6.3 Hz), 7.11 d, 7.25 t, 7.27 t (5H, Ph, J 8.1 Hz). Found, %: C 74.78, H 8.02. $C_{23}H_{30}O_4$. Calculated, %: C 74.56, H 8.16.

Ethyl 2-[10-(4-methylphenyl)-6-oxo-7-oxaspiro[4.5]dec-8-en-8-yl]-2-ethylbutanoate (VIb). Yield 0.83 g (43%), mp 123–124°C. IR spectrum, ν, cm^{-1}: 1695 (C=C), 1735 (C=O)$_{est}$, 1775 (C=O)$_{lact}$. ^{1}H NMR spectrum, δ, ppm: 0.78 t, 0.82 t (6H, $2CH_2CH_3$, J 7.2 Hz), 1.27 t (3H, OCH_2CH_3, J 6.9 Hz), 1.26–2.06 m [12H, $(CH_2)_4$, $2CH_2CH_3$], 2.30 s (3H, Me), 3.22 d (1H, C^{10}H, J 6.0 Hz), 4.13–4.25 m (2H, OCH_2CH_3). 5.39 d (1H, =C^{9}H, J 6.0 Hz), 7.00 d, 7.07 d (4H, 4-MeC_6H_4, J 8.1 Hz). Found, %: C 75.18, H 8.23. $C_{24}H_{32}O_4$. Calculated, %: C 74.97, H 8.39.

Ethyl 2-[10-(4-bromophenyl)-6-oxo-7-oxaspiro-[4.5]dec-8-en-8-yl]-2-ethylbutanoate (VIc). Yield 1.08 g (48%), mp 91–92°C. IR spectrum, ν, cm^{-1}: 1680 (C=C), 1740 (C=O)$_{est}$, 1775 (C=O)$_{lact}$. ^{1}H NMR spectrum, δ, ppm: 0.78 t, 0.82 t (6H, $2CH_2CH_3$, J 7.5 Hz), 1.27 t (3H, OCH_2CH_3, J 7.2 Hz), 1.21–2.09 m [12H,

$(CH_2)_4$, $2CH_2CH_3$], 3.22 d (1H, $C^{10}H$, *J* 6.3 Hz), 4.14–4.25 m (2H, OCH_2CH_3), 5.38 d (1H, $=C^9H$, *J* 6.3 Hz), 6.99 d, 7.39 d (4H, $4\text{-}BrC_6H_4$, *J* 8.4 Hz). Found, %: C 61.69; H 6.29, Br 17.55. $C_{23}H_{29}BrO_4$. Calculated, %: C 61.47, H 6.50, Br 17.78.

Ethyl 2-[6-oxo-10-(4-chlorophenyl)-7-oxaspiro[4.5]dec-8-en-8-yl]-2-ethylbutanoate (VId). Yield 0.97 g (47%), mp 98–99°C. IR spectrum, ν, cm^{-1}: 1680 (C=C), 1740 $(C=O)_{est}$, 1755 $(C=O)_{lact}$. ^1H NMR spectrum, δ, ppm: 0.78 t, 0.82 t (6H, $2CH_2CH_3$, *J* 7.5 Hz), 1.27 t (3H, OCH_2CH_3, *J* 7.2 Hz), 1.21–2.08 m [12H, $(CH_2)_4$, $2CH_2CH_3$], 3.24 d (1H, $C^{10}H$, *J* 6.0 Hz), 4.14–4.25 m (2H, OCH_2CH_3). 5.38 d (1H, $=C^9H$, *J* 6.0 Hz), 7.05 d, 7.24 d (4H, $4\text{-}ClC_6H_4$, *J* 8.7 Hz). Found, %: C 68.44, H 7.06, Cl 8.53 $C_{23}H_{29}ClO_4$. Calculated, %: C 68.22, H 7.22, Cl 8.76.

Ethyl 2-(1-oxo-5-phenyl-2-oxaspiro[5.5]yndec-3-en-3-yl)-2-ethylbutanoate (VIIa). Yield 0.88 g (46%), mp 85–86°C. IR spectrum, ν, cm^{-1}: 1690 (C=C), 1745 $(C=O)_{est}$, 1775 $(C=O)_{lact}$. ^1H NMR spectrum, δ, ppm: 0.77 t, 0.81 t (6H, $2CH_2CH_3$, *J* 7.5 Hz), 1.24 t (3H, OCH_2CH_3, *J* 7.5 Hz), 0.95–2.10 m [14H, $(CH_2)_5$, $2CH_2\cdot CH_3$], 3.35 d (1H, C^5H, *J* 6.5 Hz), 4.13 q (2H, OCH_2CH_3). 5.25 d (1H, $=C^4H$, *J* 6.5 Hz), 6.92–7.27 m (5H, Ph). Found, %: C 75.22, H 8.51. $C_{24}H_{32}O_4$. Calculated, %: C 74.97, H 8.39.

Ethyl 2-[5-(4-methylphenyl)-1-oxo-2-oxaspiro[5.5]yndec-3-en-3-yl]-2-ethylbutanoate (VIIb). Yield 0.82 g (41%), mp 112–113°C. IR spectrum, ν, cm^{-1}: 1695 (C=C), 1750 $(C=O)_{est}$, 1765 $(C=O)_{lact}$. ^1H NMR spectrum, δ, ppm: 0.77 t, 0.81 t (6H, $2CH_2CH_3$, *J* 7.5 Hz), 1.25 t (3H, OCH_2CH_3, *J* 7.2 Hz), 1.00–2.10 m [14H, $(CH_2)_5$, $2CH_2CH_3$], 2.30 s (2H, Me), 3.35 d (1H, C^5H, *J* 6.3 Hz), 4.17 q (2H, OCH_2CH_3, *J* 7.2 Hz), 5.29 d (1H, $=C^4H$, *J* 6.3 Hz), 6.98 d, 7.07 d (4H, $4\text{-}MeC_6H_4$, *J* 8.4 Hz). Found, %: C 75.48, H 8.71. $C_{25}H_{34}O_4$. Calculated, %: C 74.34, H 8.60.

Ethyl 2-[5-(4-bromophenyl)-1-oxo-2-oxaspiro[5.5]undec-3-en-3-yl]-2-ethylbutanoate (VIIc). Yield 1.09 g (47%), mp 84–85°C. IR spectrum, ν, cm^{-1}: 1690 (C=C), 1750 $(C=O)_{est}$, 1765 $(C=O)_{lact}$. ^1H NMR spectrum, δ, ppm: 0.77 t, 0.82 t (6H, $2CH_2CH_3$, *J* 7.5 Hz), 1.25 t (3H, OCH_2CH_3, *J* 7.2 Hz), 0.90–2.12 m [14H, $(CH_2)_5$, $2CH_2CH_3$], 3.36 d (1H, C^5H, *J* 6.6 Hz), 4.17 q (2H, OCH_2CH_3, *J* 7.2 Hz). 5.28 d (1H, $=C^4H$, *J* 6.6 Hz), 6.97 d, 7.39 d (4H, $4\text{-}BrC_6H_4$, *J* 8.4 Hz). Found, %: C 62.42, H 6.55, Br 17.03. $C_{24}H_{31}BrO_4$. Calculated, %: C 62.20, H 6.74, Br 17.24.

Ethyl 2-[5-(4-chlorophenyl)-1-oxo-2-oxaspiro-[5.5]yndec-3-en-3-yl]-2-ethylbutanoate (VIId). Yield 0.82 g (39%), mp 83–84°C. IR spectrum, ν, cm^{-1}: 1695 (C=C), 1745 $(C=O)_{est}$, 1765 $(C=O)_{lact}$. ^1H NMR spectrum, δ, ppm: 0.77 t, 0.82 t (6H, $2CH_2CH_3$, *J* 7.5 Hz), 1.25 t (3H, OCH_2CH_3, *J* 7.2 Hz), 0.98–2.12 m [14H, $(CH_2)_5$, $2CH_2CH_3$], 3.37 d (1H, C^5H, *J* 6.3 Hz), 4.17 q (2H, OCH_2CH_3, *J* 7.2 Hz). 5.28 d (1H, $=C^4H$, *J* 6.3 Hz), 7.03 d, 7.24 d(4H, $4\text{-}ClC_6H_4$, *J* 8.4 Hz). Found, %: C 68.96, H 7.67, Cl 8.29. $C_{24}H_{31}ClO_4$. Calculated, %: C 68.80, H 7.46, Cl 8.46.

Ethyl 2-[5-(3-bromorophenyl)-1-oxo-2-oxaspiro-[5.5]yndec-3-en-3-yl]-2-ethylbutanoate (VIIe). Yield 1.00 g (43%), mp 97–98°C. IR spectrum, ν, cm^{-1}: 1690 (C=C), 1750 $(C=O)_{est}$, 1775 $(C=O)_{lact}$. ^1H NMR spectrum, δ, ppm: 0.79 t, 0.83 t (6H, $2CH_2CH_3$, *J* 7.2 Hz), 1.25 t (3H, OCH_2CH_3, *J* 6.9 Hz), 1.05–2.13 m [14H, $(CH_2)_5$, $2CH_2CH_3$], 3.34 d (1H, C^5H, *J* 6.6 Hz), 4.19 q (2H, OCH_2CH_3, *J* 6.9 Hz). 5.27 d (1H, $=C^4H$, *J* 6.6 Hz), 7.03 d, 7.14 t, 7.26 s, 7.36 d (4H, $3\text{-}BrC_6H_4$, *J* 7.8 Hz). Found, %: C 62.46, H 6.89, Br 17.53. $C_{24}H_{31}BrO_4$. Calculated, %: C 62.20, H 6.74, Br 17.24.

Ethyl 2-[1-oxo-5-(2-fluorophenyl)-2-oxaspiro[5.5]-yndec-3-en-3-yl]-2-ethylbutanoate (VIIf). Yield 1.05 g (52%), mp 83–84°C. IR spectrum, ν, cm^{-1}: 1675 (C=C), 1740 $(C=O)_{est}$, 1770 $(C=O)_{lact}$. ^1H NMR spectrum, δ, ppm: 0.78 t, 0.82 t (6H, $2CH_2CH_3$, *J* 7.5 Hz), 1.25 t (3H, OCH_2CH_3, *J* 7.2 Hz), 0.98–2.12 m [14H, $(CH_2)_5$, $2CH_2CH_3$], 3.38 d (1H, C^5H, *J* 6.6 Hz), 4.18 q (2H, OCH_2CH_3, *J* 7.2 Hz). 5.30 d (1H, $=C^4H$, *J* 6.6 Hz), 6.92–7.10 m (4H, $2\text{-}FC_6H_4$, *J* 7.8 Hz). Found, %: C 71.39, H 7.94. $C_{24}H_{31}FO_4$. Calculated, %: C 71.62, H 7.76.

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