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Reaction of Alkyl 2-Bromoalkanoates with Zinc and Arylglyoxales

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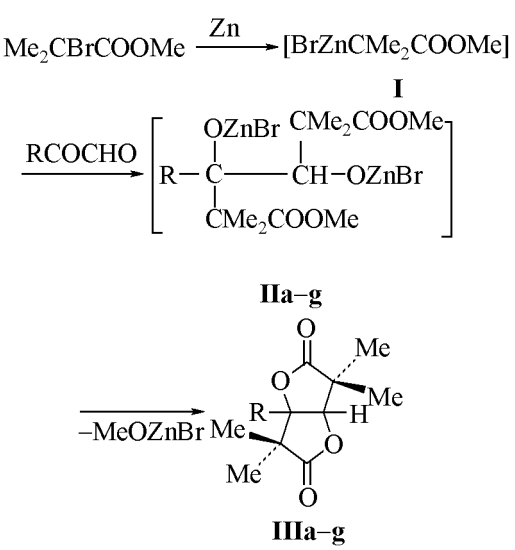
Abstract—Methyl 2-bromo-2-methylpropionate reacts with zinc and arylglyoxals under conditions of Reformatsky reaction in ether-HMPA mixture to afford 1-aryl-4,4,8,8-tetramethyl-2,6-dioxabicyclo[3.3.0]-octane-3,7-diones in 68–85% yield. Methyl 2-bromopropionate reacts with zinc and 4-bromophenylglyoxal in the same way giving the bicyclic product in 28% yield. The bromination of 1-(4-tolyl)-4,4,8,8-tetramethyl-2,6-dioxabicyclo[3.3.0]octane-3,7-dione with bromosuccinimide results in successive replacement of hydrogens in the tolyl moiety by bromine. The calculation of formation enthalpy for stereoisomers of compounds obtained in AM1 approximation predicts the highest stability for chair-type conformation with eclipsed position of substituents at C^1 and C^5 atoms.

α-Diketones are known to enter into Reformatsky reaction with organozinc reagents by one or both carbonyl groups [1, 2]. We did not find published evidence on application arylglyoxals to this reaction [3–5]. In this connection we studied the reaction of alkyl 3-bromoalkanoates with zinc and arylglyoxals.

It turned out that under common conditions of Reformatsky reaction (in ether–benzene medium) the alkyl 2-bromoalkanoate did not react with zinc (first stage of Reformatsky reaction did not occur) in the presence of arylglyoxals. The reaction course is sharply change when instead of benzene is used HMPA. Under these conditions (in ether–HMPA mixture) at the ratio, for instance, of methyl 2-bromo-2-methylpropionate, zinc, and arylglyoxal of 2.2 : 4 : 1 occurred a vigorous reaction yielding 1-aryl-4,4,8,8-tetramethyl-2,6-dioxabicyclo[3.3.0]octane-3,7-diones (**IIIa–g**) (see table).

The initially arising Reformatsky reagent **I** attacks both carbonyl groups of arylglyoxals providing zinc alcoholate **IIa–g**, a derivative of dimethyl 3-aryl-3,4-dihydroxy-2,2,5,5-tetramethylhexanedicarboxylate. Then the zinc bromide alcoholate **IIa–g** under the reaction conditions undergoes spontaneous cyclization to afford bicyclic products **IIIa–g** in 68–85% yield. The composition and structure of compounds **IIIa–g** were proved by elemental analyses, IR and ^{1}H NMR spectroscopy. In the IR spectra is present a characteristic absorption band of lactone carbonyl group around 1790 cm^{-1}. In the ^{1}H NMR spectra appear the characteristic proton signals (δ, ppm) in the regions 5.00–5.10 and 0.83–1.37 belonging respectively to



(**II, III**), R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-EtC_6H_4 (**c**), 4-*t*-BuC_6H_4(d), 4-FC_6H_4 (**e**), 4-ClC_6H_4 (**f**), 4-BrC_6H_4 (**g**).

the methine proton from CHO group and protons in methyls.

Then we studied the reaction of methyl 2-bromopropionate with zinc and 4-bromophenylglyoxal. The reaction was vigorous and exothermic, but the expected bicyclic product, 1-(4-bromophenyl)-4,8-dimethyl-2,6-dioxabicyclo[3.3.0]octane-3,7-dione, (**V**) was isolated in 20% yield.

The low yield of compound **V** is due apparently to side processes involving Zn(OH)Br elimination from

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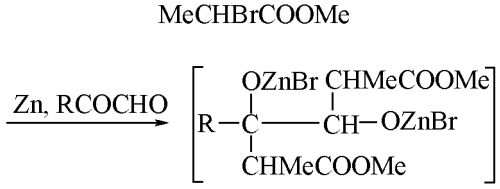
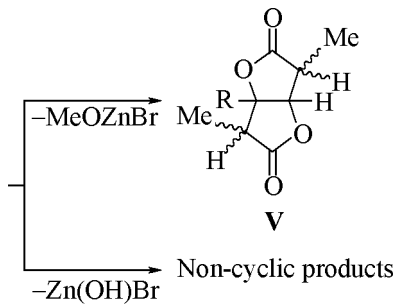
Yields, constants, ^{1}H NMR spectra, and elemental analyses of 1-aryl-4,4,8,8-tetramethyl-2,6-dioxabicyclo[3.3.0]octane-3,7-diones **IIIa**–**j**

Compd. no.	Yield, %	mp, °C	^{1}H NMR spectrum, δ, ppm			Found, %		Formula	Calculated, %	
			Ar	CHO	CMe_2, CMe_2	C	H		C	H
IIIa	70	139–141	7.38 s (Ph)	5.08 s	0.87 s, 0.92 s, 1.25 s, 1.33 s	69.92	6.52	$C_{16}H_{18}O_4$	70.06	6.61
IIIb	85	170–171	2.30 s (Me), 7.17 s (4-MeC_6H_4)	5.03 s	0.83 c, 0.87 s, 1.20 s, 1.28 s	70.51	6.85	$C_{17}H_{20}O_4$	70.82	6.98
IIIc	77	120–121	1.17 t, 2.60 q (Et), 7.17 s (4-EtC_6H_4)	5.00 s	0.85 s, 0.89 s, 1.20 s, 1.30 s	71.39	7.20	$C_{18}H_{22}O_4$	71.51	7.33
IIId	71	185–186	1.27 s (*t*-Bu), 7.30 s (4-*t*-BuC_6H_4)	5.07 s	0.86 s, 0.90 s, ~1.20 s, 1.30 s	72.52	7.80	$C_{20}H_{26}O_4$	72.70	7.93
IIIe	83	160–161	6.90–7.60 m (4-FC_6H_4)	5.10 s	0.86 s, 0.90 s, 1.20 s, 1.30 s	65.55	5.77	$C_{16}H_{17}FO_4$	65.74	5.86
IIIf	68	221–222	7.33 s (4-ClC_6H_4)	5.03 s	0.87 s, 0.90 s, 1.22 s, 1.33 s	62.12	5.43	$C_{16}H_{17}ClO_4$	62.25	5.54
IIIg	81	220–221	7.27 d, 7.53 d (4-BrC_6H_4)	5.03 s	0.86 s, 0.90 s, 1.20 s, 1.30 s	54.31	4.73	$C_{16}H_{17}BrO_4$	54.41	4.85
IIIh	70	143–145 (decomp.)	4.37 s ($BrCH_2$), 7.37 s (4-$BrCH_2C_6H_4$)	5.00 s	0.86 s, 0.90 s, 1.21 s, 1.33 s	55.48	5.12	$C_{17}H_{19}BrO_4$	55.60	5.22
IIIi	65	150–152 (decomp.)	6.60 s (Br_2CH), 7.37 d, 7.53 d (4-$Br_2CHC_6H_4$)	5.03 s	0.86 s, 0.90 s, 1.22 s, 1.33 s	45.52	3.96	$C_{17}H_{18}Br_2O_4$	45.77	4.07
IIIj	78	222–223 (decomp.)	7.43 d, 8.00 d (4-$Br_3CC_6H_4$)	5.07 s	0.90 s, 0.93 s, 1.27 s, 1.37 s	38.64	3.10	$C_{17}H_{17}Br_3O_4$	38.89	3.26

intermediate **IV** furnishing unsaturated compounds with acyclic structure. We failed to isolate and reliably identify these compounds. After separation of compound **V** the remaining liquid was subjected to distillation that resulted in its decomposition and tarring.



IV



V

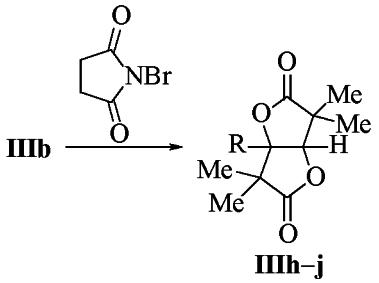
R = 4-BrC_6H_4.

In the ^{1}H NMR spectrum of compound **V** besides the proton signals of the main geometrical isomer (see EXPERIMENTAL) appear additional peaks, in particular, a doublet at δ 1.30 ppm [$(CH_3)_2CH$] obviously evidencing the presence of the minor geometrical isomer (the corresponding isomer ratio is 10 : 1).

An attempt to obtain individual compounds by reaction of methyl bromoacetate with zinc and 4-bromophenylglyoxal was unsuccessful.

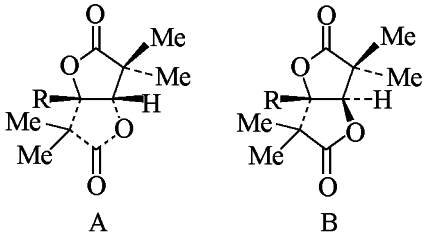
To extend the series of bicyclic compounds **III** we studied the reaction of compound **IIIb** with bromosuccinimide. It turned out that we were able by controlling the reagents ratio to replace selectively hydrogen atoms in the methyl group of the tolyl substituent one by one and to obtain in succession 1-(4-bromomethylphenyl)- (**IIIh**), 1-(4-dibromomethylphenyl)- (**IIIi**), and 1-(4-tribromomethylphenyl)- (**IIIj**) -4,4,8,8-tetramethyl-2,6-dioxabicyclo-[3.3.0]octane-3,7-diones.

The yields of compounds **IIIh–j** amount to 65–78% (see table). Their composition and structure were proved by elemental analyses, IR and ^{1}H NMR spectra that are consistent with the data characteristic of this type compounds.



III, R = 4-$BrCH_2C_6H_4$ (**h**), 4-$Br_2CHC_6H_4$ (**i**), 4-$Br_3CC_6H_4$ (**j**).

Compounds **IIIa–g** synthesized may presumably exist as two diastereomers (A) and (B) with *S,S*- and *S,R*-configuration of carbon atoms C^1 and C^5 respectively. However IR and ^1H NMR spectroscopy are not sufficient for determination of their spatial structure. To solve this problem we carried out calculation of formation enthalpy for (A) and (B) stereoisomers of bicycle **IIIa** with the use of semiempirical method SCF MO LCAO in AM1 approximation [6]. According to calculations the stereoisomer (A) with *S*,5*S*-configuration of the chiral centers is considerably more stable than isomer (B) with *S*,5*R*-configuration as follows from comparison of their formation enthalpy, equal to –564.5 and –412.9 kJ mol^{-1} respectively. Assuming that from the reaction under study result the most stable isomers, then compounds **IIIa–g** have (A) structure of *chair* type with eclipsed position of substituents at C^1 and C^5 atoms.



EXPERIMENTAL

^1H NMR spectra of compounds **IIIa–j** dissolved in CCl_4 + $CDCl_3$ (1 : 1) were registered on spectrometer PYa-2310 (60 MHz), internal reference TMS. IR spectra were recorded on spectrophotometer UR-20 from individual compounds.

Quantum-chemical calculations were carried out on PC Pentium 200MMX with the use of software package MOPAC 7.0 [6] with complete optimization of geometrical parameters.

1-Aryl-4,4,8,8-tetramethyl-2,6-dioxabicyclo-[3.3.0]octane-3,7-diones (IIIa–g). To 6.5 g of fine zinc turnings in 10 ml of ether and 10 ml of HMPA was added 0.055 mol of methyl 2-bromo-2-methylpropionate and 0.025 mol of arylglyoxal in 10 ml of ether. On completion of reaction the mixture was heated for 30 min, cooled, hydrolyzed with 5% hydrochloric acid, and extracted with ether. The organic layer was dried with anhydrous sodium sulfate, the solvents were distilled off, and the final products were recrystallized from methanol.

Compounds **IIIh–j** were obtained by bromination of 0.01 mol of compound **IIIb** in 20 ml of CCl_4 with 0.01, 0.02, and 0.032 mol of bromosuccinimide respectively. The reaction products **IIIh, i** were recrystallized from methanol, compound **IIIj** from a mixture acetone–methanol (1 : 5).

1-(4-Bromophenyl)-4,8-dimethyl-2,6-dioxabicyclo[3.3.0]octane-3,7-dione (V) was prepared similarly to compounds **IIIa–g** using as initial reagent methyl 2-bromopropionate. Yield 20%, mp 180–181°C. IR spectrum, cm^{-1}: 1790 (C=O). ^1H NMR spectrum (δ, ppm): 7.43 d, 7.27 d (4H, 4-BrC_6H_4), 4.77 s (1H, CHO), ~2.90 m (2H, C<u>H</u>Me), 1.20 d, 0.97 d (6H, CH<u>Me</u>). Found, %: C 51.50; H 3.94. $C_{14}H_{13}BrO_4$. Calculated, %: C 51.71; H 4.03.

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