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Synthesis of 6-Aryl-3,3-dimethyl-5-phenyl-2,3,5,6-tetrahydropyran-2,4-diones

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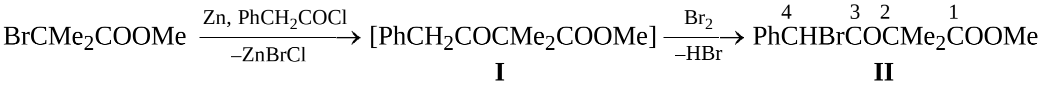
Abstract—Zinc enolates obtained from methyl 4-bromo-2,2-dimethyl-3-oxo-4-phenylbutanoates and zinc react with aromatic aldehydes to form 6-aryl-3,3-dimethyl-5-phenyl-2,3,5,6-tetrahydropyran-2,4-diones as a single geometric isomer.

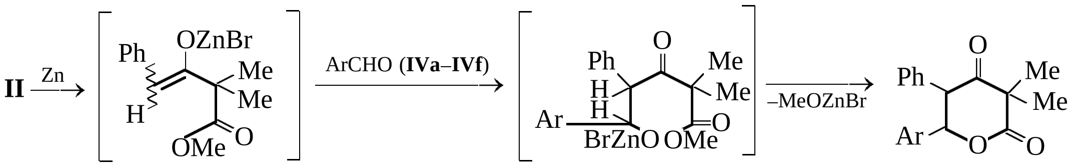
In view of the practical importance of substituted 2,3,5,6-tetrahydropyran-2,4-diones [1–3], as well as the scarcity of information about 2,3,5,6-tetrahydropyran-2,4-diones with a 5-phenyl-substituted heteriring [3–5], we have developed a new synthetic approach to such compounds. To this end, we first reacted methyl α-bromoisobutyrate with phenylacetyl chloride with zinc in ether–benzene, 1 : 2, to obtain methyl 4-phenyl-3-oxobutanoate (**I**) and then converted the latter, without isolation, in CCl medium, to bromo derivative **II**.



$$\mathrm{BrCMe_2COOMe} \xrightarrow[-\mathrm{ZnBrCl}]{\mathrm{Zn,\ PhCH_2COCl}} [\mathrm{PhCH_2COCMe_2COOMe}] \xrightarrow[-\mathrm{HBr}]{\mathrm{Br_2}} \mathrm{Ph\overset{4}{C}HBr\overset{3}{C}O\overset{2}{C}Me_2\overset{1}{C}OOMe}$$

I **II**

Further on methyl 4-bromo-2,2-dimethyl-4-phenyl-3-oxobutanoate (**II**) was reacted with zinc and aromatic aldehydes in ether–ethyl acetate, 1 : 3.



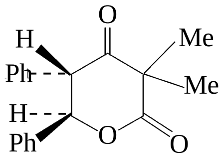
III **Va–Vf** **IVa–IVf**

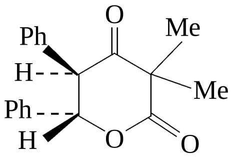
IV–**VI**, Ar = Ph (**a**), 4-ClC_6H_4 (**b**), 2,4-$Cl_2C_6H_3$ (**c**), 2-BrC_6H_4 (**d**), 4-BrC_6H_4 (**e**), 3-$NO_2C_6H_4$ (**f**).

Zinc enolate **III** formed by the Reformatskii reaction regioselectively reacted with aldehydes **IVa**–**IVf** to form intermediates **Va**–**Vf** which then cyclized into the target compounds, 6-aryl-3,3-dimethyl-5-phenyl-2,3,5,6-tetrahydropyran-2,4-diones **VIa**–**VIf**.

The reaction with *m*-nitrobenzaldehyde was performed in steps, i.e. first bromo derivative **II** was reacted with zinc to obtain zinc enolate **III** and then the latter was mixed with aldehyde in the absence of zinc.

The yields of the final products were 32–55%. The structure of compounds **VIa**–**VIf** was proved by elemental analysis and IR and ^{1}H NMR spectroscopy. The IR spectra contain characteristic absorption bands at 1720–1730 and 1745–1765 cm^{-1} from the ketone and lactone carbonyls. The ^{1}H NMR spectra of compounds **VIa**–**VIf** (see table) show characteristic signals at 3.75–3.99 and 5.53–6.16 ppm from the HC^5 and HC^6 protons, respectively ($J_{HC^5C^6H}$ ~10–11 Hz). These data suggest that the reaction products are formed as a single geometric isomer. To assess the preferred structure of this isomer, we performed quantum-chemical calculations of the molecular geometries of possible isomers by the MO LCAO method in the MNDO–PM3 approximation (MOPAC. Ver. 6.0. Public).


A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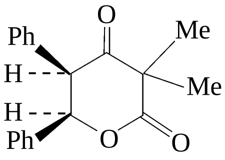
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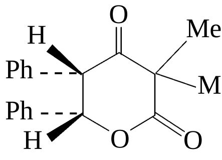
D

	A	**B**	**C**	**D**
$-\Delta_fH$, kJ mol^{-1}	295.28	295.27	287.13	287.13
Angle, deg	170.27	170.27	53.92	53.92
J, Hz	12.7	12.7	4.9	4.9

According to the calculations, the most stable are structures **A** and **B** with a transoid position of the phenyl groups. By the Karplus equation with Butner–Bie parameters we calculated the $J_{HC^5C^6H}$ contants, using the HC^{5}C^{6}H dihedral angles. Comparison of the calculated $J_{HC^5C^6H}$ values with experimental shows that the synthesized compounds have structures like **A** and **B**.

EXPERIMENTAL

The IR spectra were measured on a UR-20 spectrophotometer for individual compounds. The ^{1}H NMR spectra were measured for solutions of compounds **II** and **VIa**–**VIf** in CDCl$_3$ on a Tesla BS-567A instrument (100 MHz).

Methyl 4-bromo-2,2-dimethyl-3-oxo-4-phenylbutanoate (II). A mixture of 0.2 mol of methyl α-bromoisobutyrate and 0.2 mol of phenylacetyl chloride was added to 25 g of finely cut zinc in 100 ml of ether and 30 ml of ethyl acetate. The resulting mixture was refluxed for 20 min, decanted from zinc, and hydrolyzed with water. The organic layer was dried with sodium sulfate, and the solvent was removed.

Yields, melting points, ^{1}H NMR spectra, and elemental analyses of 6-aryl-3,3-dimethyl-5-phenyl-2,3,5,6-tetrahydropyran-2,4-diones **VIa**–**VIf**

Comp. no.	Yield, %	mp, °C	^{1}H NMR spectrum, δ, ppm (*J*, Hz)					Found, %		Formula	Calculated, %	
			CMe$_2$	C*H*Ph	CH	CH*Ph*	R	C	H		C	H
VIa	32	129–130	1.44 s, 1.54 s	3.84 d (*J* 10)	5.57 d (*J* 10)	6.70–6.95 m	7.03 s (Ph)	77.46	6.10	$C_{19}H_{18}O_3$	77.53	6.16
VIb	45	112–113	1.46 s, 1.55 s	3.75 d (*J* 11)	5.54 d (*J* 11)	6.71–6.94 m	7.00–7.10 m (4-ClC$_6$H$_4$)	69.33	5.15	$C_{19}H_{17}ClO_3$	69.41	5.21
VIc	55	138–140	1.49 s, 1.60 s	3.93 d (*J* 11)	6.0 d (*J* 11)	6.71–6.77 m	7.05–7.24 m (2,4-Cl$_2$ · C$_6$H$_3$)	62.73	4.37	$C_{19}H_{16}Cl_2O_3$	62.83	4.44
VId	40	123–125	1.49 s, 1.60 s	3.99 d (*J* 11)	6.16 d (*J* 11)	6.74–6.80 m	7.01–7.18 m (2-BrC$_6$H$_4$)	61.09	4.55	$C_{19}H_{17}BrO_3$	61.14	4.59
VIe	48	125–127	1.46 s, 1.56 s	3.76 d (*J* 11)	5.53 d (*J* 11)	6.69–6.79 m	6.79–7.24 m (2-BrC$_6$H$_4$)	61.08	4.54	$C_{19}H_{17}BrO_3$	61.14	4.59
VIf	50	161–162	1.48 s, 1.59 s	3.78 d (*J* 11)	5.65 d (*J* 11)	6.69–6.72 m	7.06–7.24 m (3-NO$_2$C$_6$H$_4$)	67.17	5.00	$C_{19}H_{17}NO_5$	67.25	5.05

The product was distilled in a vacuum; bp 130–140 (2–5) mm Hg, n_D^{20} 0 1.5040. Bromine, 0.14 mol, was added dropwise with stirring and heating on a water bath to a solution of methyl 2,2-dimethyl-4-phenyl-3-oxobutanoic acid in 50 ml of CCl_4. The mixture was heated on a water bath until HBr no longer evolved. The solvent was removed by distillation, and the reaction product was doubly crystallized from CCl_4. Yield 60%, mp 65–67°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.26 s, 1.43 s (6H, CMe_2), 3.41 s (3H, OMe), 5.58 s (1H, CH), 7.12–7.34 m (5H, Ph). Found, %: C 52.10; H 5.01. $C_{13}H_{15}BrO_3$. Calculated, %: C 52.19; H 5.05.

6-Aryl-3,3-dimethyl-5-phenyl-2,3,5,6-tetrahydropyran-2,4-diones VIa–VIe. A mixture of 0.05 mol of methyl 4-bromo-2,2-dimethy-4-phenyl-3-oxobutanoate (**II**) and 0.045 mol of aldehyde was added to 10 g of finely cut zinc in 10 ml of ether and 30 ml of ethyl acetate. The resulting mixture was refluxed for 30 min, hydrolyzed with 10% HCl, and extracted with ether. The organic layer was washed to neutral, dried with sodium sulfate, and the solvent was removed. The final products were purified by double crystallization from petroleum ether and CCl_4.

Compound VIf. Methyl 4-bromo-2,2-dimethy-4-phenyl-3-oxobutanoate (**II**), 0.05 mol, was added to 10 g to activated finely cut zinc in 20 ml of ether and 20 ml of ethyl acetate. The resulting mixture was refluxed for 30 min and decanted from zinc, after which 0.035 mol of aldehyde was added to the solution. Further workup was performed as described for compounds **VIa**–**VIe**. The final product was purified by double crystallization from petroleum ether and CCl_4.

ACKNOWLEDGMENTS

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