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Reaction of methyl 1-(2-bromo-4-methoxy-1,4-dioxobutyl)cyclohexanecarboxylate with zinc and aromatic aldehydes

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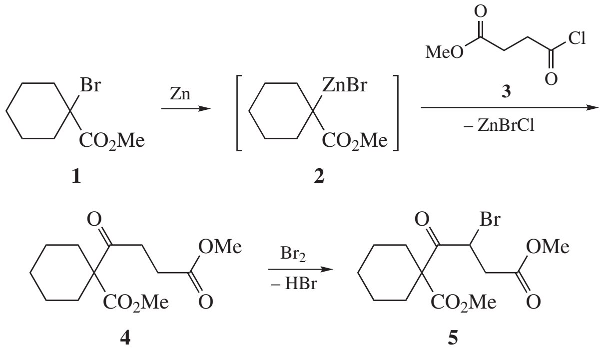
Treatment of methyl 1-(2-bromo-4-methoxy-1,4-dioxobutyl)cyclohexanecarboxylate with zinc followed by aromatic aldehydes affords methyl 1-(2-aryl-5-oxotetrahydrofuran-3-carbonyl)cyclohexanecarboxylates.

The Reformatsky reagents, derived from β-bromo γ-oxo esters and zinc, react with aromatic aldehydes to give tetrahydropyran-2,4-diones.[1–4] In continuation of these studies aiming to prepare analogous compounds containing an ester group (see Schemes 1 and 2), we converted methyl 1-(2-bromo-4-methoxy-1,4-dioxobutyl)cyclohexanecarboxylate **5** into the corresponding organozinc Reformatsky reagent **6**, and coupled the latter with aromatic aldehydes. Compound **5** was obtained by the Reformatsky protocol using methyl 1-bromocyclohexanecarboxylate **1** and methyl 4-chloro-4-oxobutanoate **3** as the reactants followed by bromination of the intermediate methyl 1-(4-methoxy-1,4-dioxobutyl)cyclohexanecarboxylate **4** (Scheme 1).[†]

In fact, the Reformatsky reagent **6** added to the carbonyl group of aromatic aldehydes **7a**,**b** giving zinc bromide alkoxides **8a**,**b**. In the course of the reaction, the latter underwent cyclization into terahydrofuran derivatives **9a**,**b** upon elimination of zinc bromide methoxide. The IR spectra of these compounds have the absorption bands of the carbonyl groups at 1700, 1735, 1780–1785 cm^{-1}. Appearance of the carbonyl group absorption band at 1780–1785 cm^{-1} is typical of five-membered furanone moiety rather than six-membered pyranone one in **10a**,**b**, whose oscillation should be in a region of 1735 cm^{-1} (see ref. 5). The products **9a**,**b** have structures of methyl 1-(2-aryl-5-oxotetrahydrofuran-3-carbonyl) cyclohexanecarboxylates (Scheme 2).[‡]



Scheme 1

[†] The IR spectra of compounds **4**, **5** in a thin layer and **9a**,**b** from mulls in mineral oil were measured on a Spectrum Two PerkinElmer Fourier spectrometer. The ^{1}H NMR spectra were recorded at 300 MHz on a Varian Mercury Plus-300 instrument in CDCl$_3$ with TMS as an internal standard. Quantum-chemical calculations were carried out using the program package 'Firefly'[6] on the PSU-Tesla supercomputer of Scientific-educational Center of Parallel and Distributive Calculations of Perm State University.

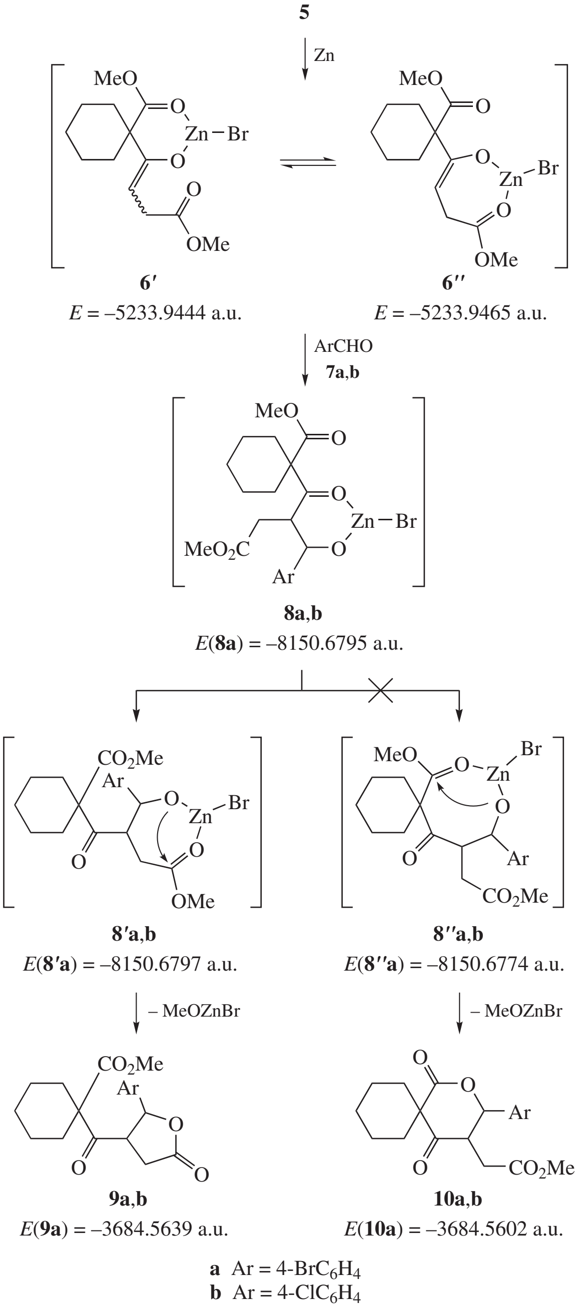
Methyl 1-(4-methoxy-1,4-dioxobutyl)cyclohexanecarboxylate **4**. A mixture of methyl 4-chloro-4-oxobutanoate **3** (15 g, 0.1 mol) and methyl 1-bromocyclohexanecarboxylate **1** (24.3 g, 0.11 mol) in anhydrous ethyl acetate (50 ml) was added dropwise to zinc powder (9.8 g) in anhydrous ethyl acetate (10 ml). The mixture was refluxed for 1 h, cooled and treated with water and 10% hydrochloric acid. The organic layer was separated, the water layer was twice extracted with ethyl acetate. The combined extracts were washed with water and dried with anhydrous Na$_2$SO$_4$. The solvent was removed and the product was distilled *in vacuo*. Yield 14.4 g (56%), bp 160–163 °C (10 Torr), n_D^{20} 1.4688, d_4^{20} 1.1219. IR (ν/cm^{-1}): 1739, 1726, 1715 (C=O). ^{1}H NMR, δ: 1.20–2.28 [m, 10H, (CH$_2$)$_5$], 2.52 (t, 2H, C^{3}H$_2$, J 6.8 Hz), 2.77 (t, 2H, C^{2}H$_2$, J 6.8 Hz), 3.62 (s, 3H, MeO), 3.69 (s, 3H, MeO). Found (%): C, 61.11; H, 7.74. Calc. for C$_{13}$H$_{20}$O$_5$ (%): C, 60.92; H, 7.87.

Methyl 1-(2-bromo-4-methoxy-1,4-dioxobutyl)cyclohexanecarboxylate **5**. Bromine (6.7 g, 2.2 ml, 0.042 mol) was added to a solution of compound **4** (10.3 g, 0.04 mol) in anhydrous acetic acid (30 ml). The mixture was heated for 1 h, and after removing the solvent and the excess of bromine the product was distilled *in vacuo*. Yield 9.0 g (67%), bp 176–179 °C (8 Torr), n_D^{20} 1.4944, d_4^{20} 1.3668. IR (ν/cm^{-1}): 1746, 1730, 1721 (C=O). ^{1}H NMR, δ: 1.02–2.34 [m, 10H, (CH$_2$)$_5$], 2.61 and 3.05 (2m, 2H, CH$_2$), 3.62 (s, 3H, MeO), 3.69 (s, 3H, MeO), 4.91 (m, 1H, CH). Found (%): C, 46.75; H, 5.54; Br, 23.59. Calc. for C$_{13}$H$_{19}$BrO$_5$ (%): C, 46.58; H, 5.71; Br, 23.84.

[‡] *Methyl 1-(2-aryl-5-oxotetrahydrofuran-3-carbonyl)cyclohexanecarboxylates* **9a**,**b**. A mixture of zinc powder (1 g), catalytic amount of mercuric chloride, methyl 1-(2-bromo-4-methoxy-1,4-dioxobutyl)cyclohexanecarboxylate **5** (3.7 g, 11 mmol), aromatic aldehyde **7** (10 mmol), anhydrous ethyl acetate (10 ml) and anhydrous benzene (10 ml) was heated for 2 h, cooled and treated with water and 10% hydrochloric acid. The organic layer was separated, the water layer was twice extracted with ethyl acetate. The combined extracts were washed with water and dried with anhydrous sodium sulfate. Then the solvent was removed and the product was recrystallized from methanol.

Methyl 1-[2-(4-bromophenyl)-5-oxotetrahydrofuran-3-carbonyl)]cyclohexanecarboxylate **9a**. Yield 2.17 g (53%), mp 110–111 °C. IR (ν/cm^{-1}): 1700, 1735, 1780 (C=O). ^{1}H NMR, δ: 1.06–2.23 [m, 10H, (CH$_2$)$_5$], 2.72 (t, 2H, C^{4}H$_2$, J 7.5 Hz), 3.35 (s, 3H, MeO), 3.59 (m, 1H, C^{3}H), 5.51 (d, 1H, C^{2}H, J 5.0 Hz), 7.07 (d, 2H, H$_{Ar}$, J 8.7 Hz), 7.29 (d, 2H, H$_{Ar}$, J 8.7 Hz). Found (%): C, 55.93; H, 5.03; Br, 19.38. Calc. for C$_{19}$H$_{21}$BrO$_5$ (%): C, 55.76; H, 5.17; Br, 19.52.

Methyl 1-[2-(4-chlorophenyl)-5-oxotetrahydrofuran-3-carbonyl)]cyclohexanecarboxylate **9b**. Yield 1.75 g (48%), mp 90–91 °C. IR (ν/cm^{-1}): 1700, 1735, 1785 (C=O). ^{1}H NMR, δ: 1.02–2.20 [m, 10H, (CH$_2$)$_5$], 2.72 (t, 2H, C^{4}H$_2$, J 7.5 Hz), 3.34 (s, 3H, MeO), 3.61 (m, 1H, C^{3}H), 5.51 (d, 1H, C^{2}H, J 5.0 Hz), 7.06 (d, 2H, H$_{Ar}$, J 8.4 Hz), 7.29 (d, 2H, H$_{Ar}$, J 8.4 Hz). Found (%): C, 62.71; H, 5.87; Cl, 9.61. Calc. for C$_{19}$H$_{21}$ClO$_5$ (%): C, 62.55; H, 5.80; Cl, 9.72.



Scheme 2

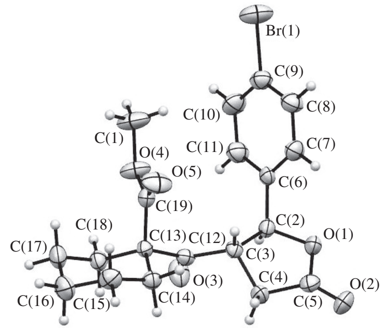


Figure 1 General view of the molecule **9a** based on the X-ray data with 50% probability thermal ellipsoids.

The structure of compounds obtained was ultimately established by the X-ray study of a single crystal of compound **9a** (Figure 1).§ This compound crystallizes in the centrosymmetric space group. Bond lengths and bond angles are within deviations from the standard values. Both carbonyl bonds of the COOR moieties are 1.192(3) Å long, the lengths of the ketone C=O and C–Br bonds are 1.211(3) and 1.900(2) Å, respectively. The cyclohexyl fragment acquires a *chair* conformation with axial position of the COOMe group, the tetrahydrofuran cycle exists in an *envelope* conformation with deviation from the plane of the C(3) atom and *trans*-location of substituents at C(2) and C(3) atoms. There are not essential short-cut intermolecular contacts in the crystal packing.

To explain the regioselectivity of the process, we performed the non-empirical calculations of geometric and electronic characteristics of possible intermediates (Ar = 4-BrC$_6$H$_4$) by the B3LYP/6-31(d) method. The calculated values of total energies E (a.u.) of possible intermediates and reaction products are shown in Scheme 2. The Reformatsky reagent **6** very likely exists in the form of zinc-enolate and is stabilized by coordination of zinc with the ester carbonyl oxygen (intermediates **6′** and **6″**, while intermediate **6″** is 5.5 kJ mol^{-1} more stable).

The addition of an aromatic aldehyde to the Reformatsky reagent affords intermediate **8a** stabilized by coordination of zinc at the ketone carbonyl oxygen. Further on, intermediate **8a** turns into intermediate **8′a** as far as furan ring closure should be promoted by coordination of zinc at the ester carbonyl oxygen. Elimination of MeOZnBr from intermediate **8′a** leads ultimately to furanone **9a**. Intermediate **8″a**, a precursor of pyrandione **10a**, is 6.3 kJ mol^{-1} less stable than **8′a**. Moreover, pyrandione **10a** is also 9.7 kJ mol^{-1} less stable than furanone **9a**.

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§ The X-ray diffraction analysis of compound **9a** was performed at 295(2) K on an Xcalibur S (Oxford diffraction) automatic single crystal diffractometer with graphite monochromated MoKα (λ = 0.71073 Å) radiation. The extinction correction was introduced by multi-scanning method (μ = 2.328 mm^{-1}).

Crystal data. The colourless single crystals (C$_{19}$H$_{21}$BrO$_5$, M = 409.27), triclinic, a = 7.81270(10), b = 10.7584(18) and c = 11.670(2) Å; α = = 85.04(3)°, β = 77.46(3)°, γ = 68.860(9)°, V = 893.0(2) Å^3, Z = 2, space group P1, 3564 independent reflections collected (R_{int} = 0.0268), including 2123 with $I > 2\sigma(I)$. The solution and refinement of the structure were carried out using the SHELXTL software package.[7] The final refinement converged to R_1 = 0.0346 [$I > 2\sigma(I)$].

CCDC 995474 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2014.