Intermolecular cyclocondensation of arylchloropyruvates in the synthesis of 2,3-dihydrofuran-3,5-dicarboxylic acid derivatives

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Methyl arylchloropyruvates undergo intermolecular self-condensation in the presence of a catalytic amount of a base under high-temperature conditions (~250°C) with the formation of 3,4-diaryl-2-oxo-2,3-dihydrofuran-3,5-dicarboxylic acid derivatives.

Key words: furanones, γ-butyrolactones, arylchloropyruvates, Darzens condensation, X-ray diffraction analysis.

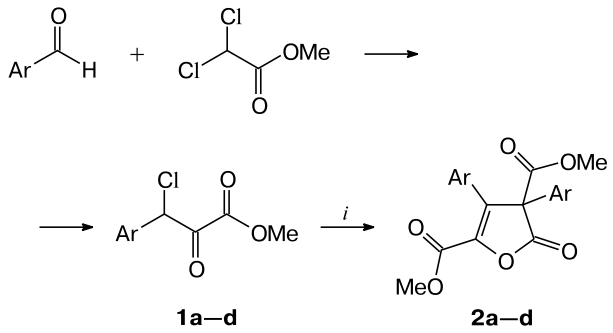
Substituted dihydrofuranones (or γ-butyrolactones) are important synthetic intermediate products in organic synthesis and usually are encountered as structural parts of natural biologically active compounds, receptors, and medicines.[1] Apart from that, compounds containing a γ-butyrolactone fragment have a long history of pharmacological activity, including muscarinic (pilocarpine)[2] and antimuscarinic action (Kaiser lactones),[3] convulsive (picrotoxin, β-substituted γ-butyrolactones) and anticonvulsive activities (α-alkyl-substituted γ-butyrolactones),[4] carcinogenic[5] and anti-tumor[6] activities, as well as the ability to modulate sensory thresholds in the body.[7]

Though such furanones can be synthesized by a number of described methods,[3,8] the multi-step character of the processes, poor availability of starting reagents, and low yields of final products make impossible their use for the synthesis of functionally substituted derivatives or limit their application.

Earlier, we have shown that the reaction of dichloroacetates with aromatic aldehydes under the Darzens condensation conditions in the presence of a base proceeded, depending on the character of substituents in the aromatic ring of benzaldehyde, with the formation of either arylchloroglycidates, or arylchloropyruvates **1**, or a mixture of these products.[9,10] As a rule, a standard treatment of these reaction mixtures included the washing with the concentrated solution of NaCl, extraction with toluene or chloroform, drying the organic layer with $MgSO_4$, and purification of reaction products by distillation *in vacuo* using an oil pump (0.01—0.02 Torr)[9,10] or by column chromatography on silica gel.[9]

It was found[9,10] that a prolonged heating during vacuum distillation using a water-jet pump (12—16 Torr) of crude arylchloropyruvates **1a—d** isolated from the reaction mixtures led to a partial intermolecular self-condensation with the formation of furan-5-ones **2a—d** (Scheme 1).

Scheme 1



1a—d **2a—d**

Ar = Ph (**a**), 4-ClC_6H_4 (**b**), 4-BrC_6H_4 (**c**), 4-FC_6H_4 (**d**)

Conditions: *i*. ~250 °C, 2 h.

The formation of furan-5-ones **2a—d** was indicated by the presence in the ^1H NMR spectrum of two singlets from the methyl protons of the ester groups. The IR spectrum exhibited the bands for three carbonyl groups in the region

* Dedicated to Academician of the Russian Academy of Sciences N. S. Zefirov on the occasion of his 80th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2865—2868, December, 2015.

of 1733—1813 cm^{-1}, one of which (1805—1813 cm^{-1}) belonging to the lactone carbonyl fragment.[11]

Heating the individual compounds **1a—d** at 200—250 °C for 3 h does not lead to the formation of furan-5-ones **2a—d**. Only in the case of compound **1a**, a desired compound **2a** was isolated in low yield. Carrying out the self-condensation of arylchloropyruvates **1a—d** at the same temperatures, but in the presence of a small amount of a base, gave the corresponding furan-5-ones **2a—d** in higher yields than in the case of self-condensation of crude arylchloropyruvates **1a—d** observed in the course of distillation. Carrying out the reaction in the presence of an equimolar amount of a base at high temperature (above 200 °C) leads to a difficult to separate mixtures of products, whereas at relatively low temperatures (0—65 °C), as it was shown earlier, to different condensation products,[12—14] including those of intermolecular self-condensation, depending on the character of a base and reaction conditions.[15]

The structure of the self-condensation products was also confirmed by X-ray diffraction studies of furanone **2a** (Fig. 1).

Compound **2a** crystallizes in the centrosymmetric space group $P2_1/n$, the independent part of the unit cell contains one molecule. The five-membered oxygen-containing (dihydrofuran) heterocycle is planar (within 0.027(4) Å), the acetyl substituent at carbon atom C(5) lies in the plane of the heterocycle (the torsion angle O(1)—C(5)—C(51)—O(52) is 7.2(5)°). The phenyl substituent at atom C(4) is turned from the plane of the heterocycle (the torsion angle C(5)—C(4)—C(41)—C(46) is 57.4(6), the dihedral angle between the planes of the rings is 58.3(2)°), the acetyl and the phenyl substituents at atom C(3) are also turned relative to the plane of the heterocycle (the dihedral angles between their planes and the plane of the five-membered ring are 83.8(3) and 77.4(2)°, respectively). The presence of bulky substituents at the atoms of heterocycle does not lead to the distortion of the main geometric parameters of the molecule: its bond distances lie within the standard values for this type of the bonds.

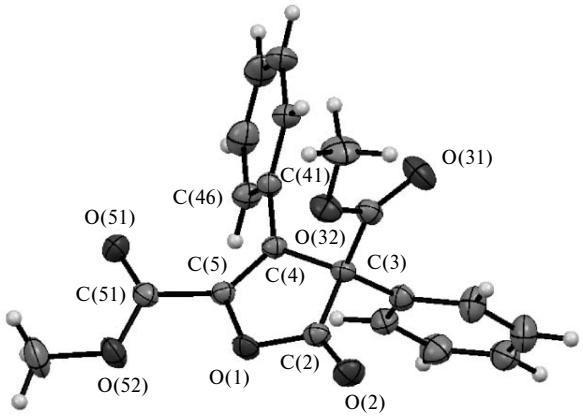
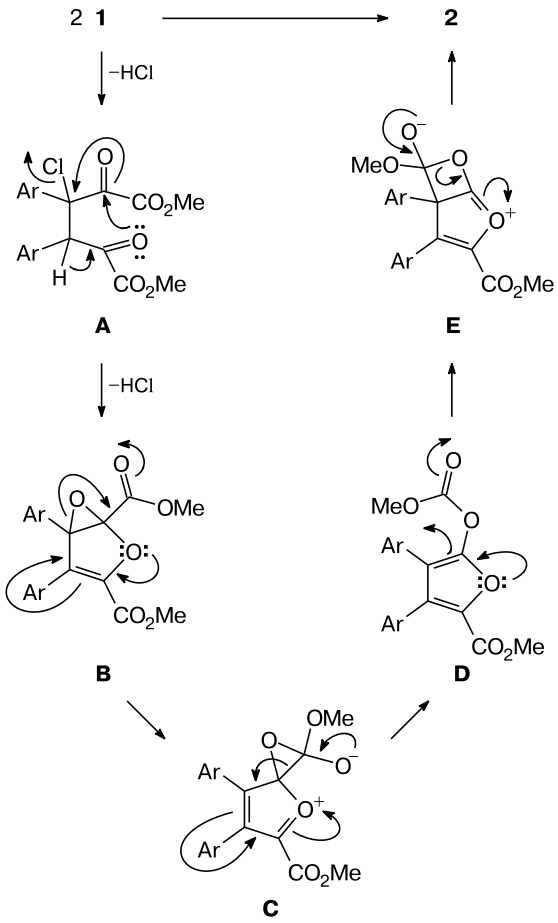


Fig. 1. Molecular geometry of **2a** in crystal.

The formation of furan-5-ones **2** can be presumably represented by the scheme of intermolecular condensation including a cascade of reactions (Scheme 2): 1) the nucleophilic substitution of a chlorine atom in one of the molecules with the carbon atom C(3) of the other molecule of arylchloropyruvate with the formation of compound **A**, 2) first, the closure of the five-membered and, then, the three-membered rings with the formation of compound **B**,[16,17] 3) the migration of the ester group as a result of several intramolecular rearrangements involving the intermediate compounds[18,19] **C**, **D**, and **E**.

Scheme 2



Note that compounds **2a**,**b** have been synthesized earlier[20,21] from arylchloropyruvates **1a**,**b**, but under more complex experimental conditions. The authors[20] prepared these compounds using copper salts ($CuCl_2$, $CuBr_2$) on a SiO_2 support in chlorobenzene at 130 °C, as well as obtained compound **2a** by the reaction of $CuCl_2$ with cyanoepoxide in acetonitrile at low temperatures. Lactone **2a** was obtained[21] by photooxidation of 2,5-di(methoxycarbonyl)-3,4-diphenylcyclopentadienone with subsequent dehydration.

The found by us thermal intermolecular self-condensation of arylchloropyruvates opens the access to 3,4-diaryl-2-oxo-2,3-dihydrofuran-3,5-dicarboxylic acid derivatives without application of metal catalysts and other expensive reagents.

Experimental

Melting points were determined on Boetius heating stage. IR spectra for all the compounds were recorded on a Bruker Vector-22 Fourier-transform spectrometer in KBr pellets. Electron ionization mass spectra were obtained on a ThermoQuest/Finnigan Trace MS quadrupole mass spectrometer, the samples were injected through a system of direct injection with water cooling; high-precision mass spectra were obtained on a Finnigan MAT 212 high-precision mass spectrometer. ^{1}H NMR spectra were recorded on Bruker AVANCE 400 and Bruker AVANCE 500 spectrometer. Chemical shifts are given relative to the signals of the solvents used.

Synthesis of 2,3-dihydrofuran-3,5-dicarboxylic acid derivatives (2) (general procedure). ***A.*** Potassium *tert*-butoxide (10 mmol) was slowly added to a mixture of an equimolar amount of the corresponding dichloroacetate (10 mmol) and an aromatic aldehyde (10 mmol) in anhydrous toluene (30 mL) with stirring at 0—10 °C under dry argon. The reaction mixture was allowed to stand at room temperature for 14 h and quenched with a 25% aqueous solution of NaCl (20 mL). After thorough shaking, the organic layer was separated, the aqueous layer was extracted with toluene (2×15 mL). The combined organic extracts were dried with $MgSO_4$, the solvent was evaporated. The residue was heated at ~250—270 °C for 2 h and cooled. Then, the reaction mixture was diluted with diethyl ether (10 mL), the crystals formed were filtered and recrystallized from Pr^{i}OH.

B. An equimolar amount of a base (5% aqueous solution of KOH (5.6 mL) was added to methyl 3-aryl-3-chloro-2-oxopropionate (5 mmol), the reaction mixture was extracted with toluene (2×25 mL). The organic layer was washed with water (2×25 mL) and dried with $MgSO_4$, the solvent was evaporated. The residue was heated at a high temperature (250—270 °C) for 2 h. After cooling, the reaction mixture was treated with diethyl ether to isolate crystals.

Dimethyl 2-oxo-3,4-diphenyl-2,3-dihydrofuran-3,5-dicarboxylate (2a). ***A.*** (0.51 g, 29%) was obtained from benzaldehyde (1.06 g, 10.0 mmol) according to the procedure described above.

B. Compound **2a** (1.06 g, 64%) was obtained from arylchloropyruvate **1a**[9,10] (2.00 g, 9.4 mmol) according to the procedure described above.

White crystals. M.p. 167—168 °C (Pr^{i}OH) (Ref. 21: m.p. 171 °C). IR (KBr), ν/cm^{-1}: 3443, 2997, 2953, 1805, 1752, 1733, 1651, 1498, 1441, 1335, 1260, 1242, 1205, 1191, 1127, 1018, 1002, 979, 927, 772, 748, 709, 699, 691, 609. ^{1}H NMR ($CDCl_3$), δ: 3.80 (s, 3 H, OCH_3); 3.82 (s, 3 H, OCH_3); 7.07—7.09 (m, 2 H, Ph); 7.28—7.37 (m, 8 H, Ph). ^{1}H NMR (DMSO-d_6), δ: 3.73 (s, 3 H, OCH_3); 3.84 (s, 3 H, OCH_3); 7.13—7.15 (d, 2 H, J = 7.0 Hz); 7.31—7.38 (m, 5 H, Ph); 7.43—7.44 (m, 3 H, Ph). MS, *m/z* (*I* (%)): 353 (10), $[M]^+$ 352 (31), 308 (28) 265 (44), 237 (48), 233 (20), 194 (55), 178 (100), 176 (48), 166 (35), 165 (35), 152 (350, 151 (33), 150 (25), 126 (22), 115 (41), 91 (40).

Crystals of compound **2a** suitable for X-ray diffraction studies were obtained by recrystallization from isopropyl alcohol. Colorless crystals, m.p. 167—168 °C, $C_{20}H_{16}O_6$, M = 352.33 monoclinic, at 296 K a = 9.386(3), b = 9.657(3), c = 19.198(6) Å, β = 99.584(5)°, V = 1715.8(9) Å^3, Z = 4, space group $P2_1/n$, d_{calc} = 1.364 g cm^{-3}, μ = 0.101 mm^{-1}, F(000) = 736. Parameters of unit cell and experimental data were obtained at T = 296 K on a Bruker Smart APEX II CCD automated diffractometer (λ(Mo-Kα) = 0.71073 Å, ω-scan technique), 2θ < 54°, R_{int} = 0.034. From 13744 measured reflections, 3701 were independent, the number of observed reflections with $I > 2\sigma(I)$ was 1754. Absorption was included using the SADABS program.[22] The structure was solved by direct method using the SIR program[23] and refined by the full-matrix least-squares method using the SHELXL97 program.[24]. Hydrogen atoms were calculated geometrically and refined using a riding model. All the calculations were carried out using the WinGX[25] and APEX2[26] programs. The final R-factor values: R 0.0748, wR_2 0.2284, GOOF = 1.01, number of refined parameters 238. Crystallographic data for the structure **1** were deposited with the Cambridge Crystallographic Data Center (http://www.ccdc.cam.ac.uk; CCDC 1407989).

Dimethyl 3,4-bis(4-chlorophenyl)-2-oxo-2,3-dihydrofuran-3,5-dicarboxylate (2b). ***A.*** Compound **2b** (0.44 g, 21%) was obtained from 4-chlorobenzaldehyde (1.40 g, 10.0 mmol) according to the described procedure.

B. Compound **2b** (1.02 g, 64%) was obtained from **1b**[9,10] (2.00 g, 8.1 mmol) according to the procedure described above.

White crystals. M.p. 113—114 °C (Ref. 20: m.p. 120 °C). IR (KBr), ν/cm^{-1}: 3444, 2952, 1805, 1750, 1731, 1648, 1594, 1495, 1435, 1403, 1337, 1260, 1242, 1209, 1188, 1124, 1098, 1015. 996, 976, 919, 904, 823, 799, 768, 758, 741, 727, 621, 509. 499, 482. ^{1}H NMR ($CDCl_3$), δ: 3.82 (s, 3 H, OCH_3); 3.83 (s, 3 H, OCH_3); 7.04 (d, 2 H, J = 8.4 Hz); 7.22 (d, 2 H, J = 8.4 Hz); 7.28 (d, 2 H, J = 8.4 Hz); 7.34 (d, 2 H, J = 8.4 Hz). ^{1}H NMR (DMSO-d_6), δ: 3.76 (s, 3 H, OCH_3); 3.87 (s, 3 H, OCH_3); 7.18 (d, 2 H, J = 8.6 Hz); 7.40 (d, 2 H, J = 8.6 Hz); 7.44 (d, 2 H, J = 8.6 Hz); 7.54 (d, 2 H, J = 8.6 Hz). MS, *m/z* (*I* (%)): 422 (36), 421 (10), $[M]^+$ 420 (48), 378 (23), 377 (9), 376 (33), 363 (16), 362 (11), 361(23), 335 (70), 334 (23), 333 (84), 307 (71), 306 (22), 305 (84), 273 (19), 264 (66), 263 (22), 262 (84), 246 (73), 212 (46), 199 (60), 191 (70), 176 (68), 150 (55), 149 (78), 139 (100), 125 (63).

Dimethyl 3,4-bis(4-bromophenyl)-2-oxo-2,3-dihydrofuran-3,5-dicarboxylate (2c) was obtained according to the procedure ***B*** described above from compound **1c**[9,10] (2.00 g, 6.9 mmol). The yield of compound **2c** was 1.05 g (60%).

Light brown crystals. M.p. 99—100 °C. IR (KBr), ν/cm^{-1}: 2953, 1814, 1766, 1737, 1589, 1488, 1436, 1398, 1334, 1274, 1204, 1174, 1115, 1071, 1011, 964, 931, 824, 758, 508. ^{1}H NMR (DMSO-d_6), δ: 3.72 (s, 3 H, OCH_3); 3.83 (s, 3 H, OCH_3); 7.07 (d, 2 H, J = 8.8 Hz); 7.29 (d, 2 H, J = 8.4 Hz); 7.54 (d, 2 H, J = 8.4 Hz); 7.63 (d, 2 H, J = 8.8 Hz).

Dimethyl 3,4-bis(4-fluorophenyl)-2-oxo-2,3-dihydrofuran-3,5-dicarboxylate (2d) was obtained by method ***B*** from compound **1d**[27] (2.00 g, 8.7 mmol). The yield of compound **2d** was 1.21 g (72%).

Brown crystals. M.p. 119—121 °C. IR (KBr), ν/cm^{-1}: 3440, 2958, 1805, 1750, 1733, 1603, 1511, 1436, 1339, 1261, 1241, 1165, 1126, 1016, 1002, 836, 592, 536. NMR ^{1}H NMR ($CDCl_3$), δ: 3.82 (s, 3 H, OCH_3); 3.83 (s, 3 H, OCH_3); 6.99 (dd, 2 H, J = 8.6 Hz, J = 8.6 Hz); 7.06 (dd, 2 H, J = 8.6 Hz, J = 8.6 Hz); 7.09 (dd, 2 H, J = 9.0 Hz, J = 5.3 Hz); 7.27 (dd, 2 H, J = 9.0 Hz, J = 5.3 Hz).

This work was financially supported by the Russian Science Foundation (Priority Direction of Studies "Fundamental Scientific Studies and Scientific Search by the Personal of Existing Research Laboratories (Departments)" (Project No. 14-23-00073).

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Received May 22, 2015;
in revised form October 22, 2015