Unexpected Course of the Intramolecular Darzens Condensation of Dichloroacetoxybenzaldehyde. A Novel One-step Synthesis of 2,2-Dichloro-3-(2-hydroxyphenyl)-3-(2-formylphenoxy) propionic Acid

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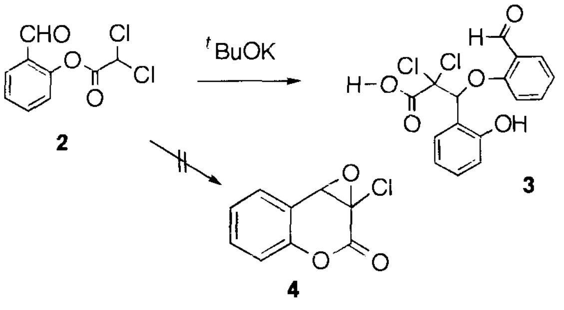
The reaction of *ortho*-di (**2**) and monochloroacetoxybenzaldehyde (**1**) with ^{t}BuOK and/or $NaN(SiMe_3)_2$ under Darzens condensation conditions leads to 2,2-dichloro-3-(2-hydroxyphenyl)-3-(2-formylphenoxy) propionic acid (**3**) and 3-chlorocoumarin (**8**) depending on number of chlorine atoms in the starting aldehydes (**1**, **2**).

The Darzens reaction, the classical procedure for the preparation of glycidic esters by condensation of aldehydes or ketones with α-chlorocarboxylic esters in the presence of various bases, has been known since 1892.[1] At the present time, Darzens reaction is used for the synthesis of heterocyclic systems such as aziridines,[2] furans,[3] lactones,[4] dioxines[5] and so on. We have been studying the reactions of aldehydes[6] with active hydrogen compounds and reported on the Darzens type condensation of carbonyl compounds with the derivatives of dichloroacetic acid,[7] and dichloromethyl ketones.[8]

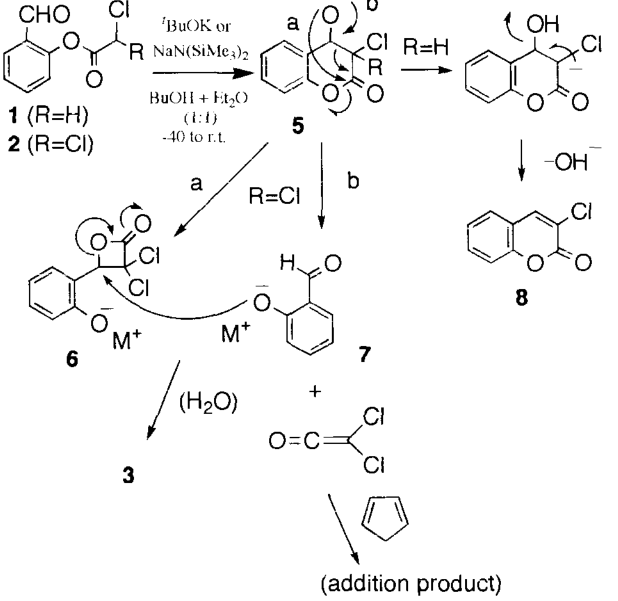
It is well known that the monochloromethyl and dichloromethyl groups in acetic acid derivatives play the main role in defining the direction of reactions with aldehydes under Darzens condensation, with the formation of glycidic esters and α-chloroglycidic ester or their isomeric 3-chloropropionic acid derivatives.[7,8] A question arouse, how will be changed the direction of the reaction if mono- or dichloroacetoxy groups and an aldehyde group exist in the same molecule? In order to answer to this question and as an extension of the previous works,[3-6] we investigated the behavior of 2-mono- (**1**) and 2-dichloroacetoxybenzaldehydes (**2**) under the conditions of Darzens condensation.

Treatment of dichloroacetoxy compound (**2**) with potassium *t*-butoxide gave an unusual product, 2,2-dichloro-3-(2-hydroxyphenyl)-3-(2-formylphenoxy)-propionic acid (**3**)[9] in 68% yield instead of an expected Darzens condensation product (**4**)(Scheme 1).



Scheme 1.

The mechanism of the formation of **3** can be explained as shown in Scheme 2. At the first stage, cyclized intermediate **5** would take place. In the case of dichloroacetate **2**, the reaction would give β-lactone intermediate **6**, *o*-formylphenoxide **7**, and dichloroketene via the transfer of electrons from the intermediate **5** as shown by arrows a and b. The formation of β-lactone **6** is known in intermolecular Darzens type condensation.[4] The reaction of the phenoxide **7** with the β-lactone **6** would give the final product **3**. The formation of dichloroketene under this reaction condition was proved by the experiment where the reaction was carried out in the presence of an equal quantity of cyclopentadiene to give a cycloaddition product, 7,7-dichlorobicyclo [3.2.0]hept-2-en-6-one.[1]



Scheme 2.

The structure of compound **3** was established by X-ray structure determination (Figure 1).[11]

The X-ray analysis showed that the geometry and packing of molecules in crystal cell are determined by the developed system of strong intermolecular hydrogen bonds OH(2)...O(6) 1.79(2)Å, OH(5)...O(16) 2.02(2)Å, OH(6)...O(1) 2.06(2)Å, which formed with the participation of solvated molecule of *t*-BuOH and inter-molecular CH(3)...O(2) 2.444(18)Å, CH(3)...O(2) 2.310(17)Å, CH(3)...O(2) 2.41(2)Å hydrogen bonds.

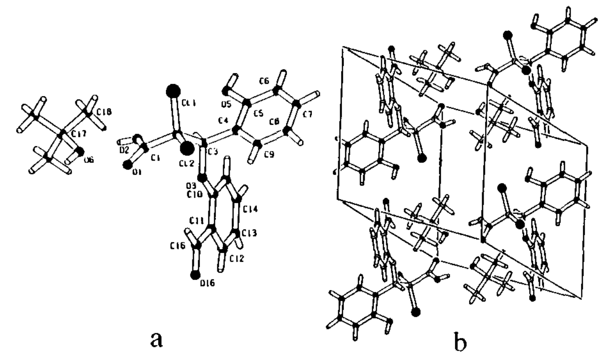


Figure 1. X-ray crystal structure of 2,2-dichloropropionic acid (**3**). a) ORTEP view of the molecular structure of **3**.
b) Stereoscopic view of the unit cell of **3**, with dotted lines showing hydrogen bonds.

In contrast to the dichloromethyl derivative **2**, monochlorocarbonyl compound **1** under the same condition leads to the formation of 3-chlorocoumarin **8**.[12] The yield of this reaction dramatically increased (from 54% to 91%) when $NaN(SiMe_3)_2$ was used instead of ^{t}BuOK. The formation of **8** can be explained by the mechanism via the prototropic shift of **5** and the subsequent dehydroxylation, as shown in Scheme 2.

References and Notes

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9 2,2-Dichloro-3-(2-hydroxyphenyl)-3-(2-formylphenyl)propionic acid (**3**): A solution of ^{t}BuOK, prepared from potassium 1.0 g (0.026 g-atom) and anhydrous ^{t}BuOH (25 mL), was added at -40 ^oC under argon atmosphere to a solution of compound **2** 6.0 g (0.026 mol) in 20 mL ether. The reaction mixture was kept at -40 ^oC for 1.5 h and was stirred at room temperature for 8 h. The solvent was removed in vacuum by rotatory evaporator. Brine was added to the residue and the mixture was extracted with chloroform (3x30 mL). The extract was dried over $MgSO_4$. The residue became crystals at r.t. during 2 days and was recrystallized from ^{i}PrOH to give 3.8 g (68%) of **3**: m.p. 114-115 ^oC; ^1H NMR ($(CD_3)_2CO$) δ 1.35 (9H, s, $C(CH_3)_3$, 6.96 (1H, s, CH), 7.05-7.92 (8H, m, $2C_6H_4$), 9.42 (H, broad S, OH), 10.7 (1H, s, CHO), 12.1 (1H, s, COOH); ^{13}C NMR $(CD_3)_2CO)$ δ 29.72 (C_{18}, q.sep, $^1J_{CH}$=147.5 Hz, $^3J_{CH}$=5.0 Hz); 68.33 (C_{17}, sep, $^2J_{CH}$=4.2), 75.17 (C_3, d, $^1J_{CH}$=152.7), 94.72 (C_2, s), 164.59 (C_1, s), 187.78 (CHO, dt, $^1J_{CH}$= 181.1 $^3J_{CH}$=2.3), aromatics: 158.36 (C_{11}, s), 155.27 (C_{10}, s), 124.58 (C_4, s) 118.79 (C_5, s), 113.23 (dd, $^1J_{CH}$=161.5, $^3J_{CH}$=7.7), 114.51 (dd, $^1J_{CH}$=158.6 $^3J_{CH}$=7.6), 118.85 (dd, $^1J_{CH}$=162.0, $^3J_{CH}$=7.8), 120.94 (dd,$^1J_{CH}$=164.0, $^3J_{CH}$= 7.5), 126.85 (dd, $^1J_{CH}$=160.4, $^3J_{CH}$=8.6), 129.13 (br.d, $^1J_{CH}$=160.1), 130.00 (ddd, $^1J_{CH}$=158.8, $^3J_{CH}$=8.9, $^2J_{CH}$= 1.9), 135.09 (dd, $^1J_{CH}$=161.3, $^3J_{CH}$=8.1).

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11 Crystal data for **3**: $C_{16}H_{12}O_5Cl_2 \cdot C_4H_{10}O$, M=235.06 · 74.12, monoclinic, $P2_1/n$, a=10.04(1), b=10.35(1), c=11.36(9) Å, β=71.21(2), V=1059(5) $Å^3$, Z=2, D_{calc}=1.30 g/cm^3, μ(CuKα)=30.27 cm^{-1}, R=0.042 (Rw=0.066), unique reflections=3737.

12 3-Chlorocoumarine **8**: m.p. 122-123 ^oC; ^{13}C NMR $(CD_3)_2CO)$ δ 117.56 C_5, dd, $^1J_{CH}$=166.9 Hz, $^3J_{CH}$=8.0 Hz), 119.64 (C_{10}, br.s), 123.54 (C_3, d, $^3J_{CH}$=4.9); 125.59 (C_8, dd, $^1J_{CH}$=163.4, $^3J_{CH}$=7.9), 127.84 (C_5, ddd, $^1J_{CH}$= 163.0, $^3J_{CH}$=7.8, $^2J_{CH}$=3.0), 132.39 (C_7, dd, $^1J_{CH}$= 163.8, $^3J_{CH}$=7.8), 140.24 (C_4, dd, $^1J_{CH}$=167.1, $^3J_{CH}$= 5.2), 157.22 (C_2, d, $^3J_{CH}$=8.3).