Darzens synthesis of 2,2-dichloro-3-(2-furyl)-3-hydroxypropionic acid derivatives

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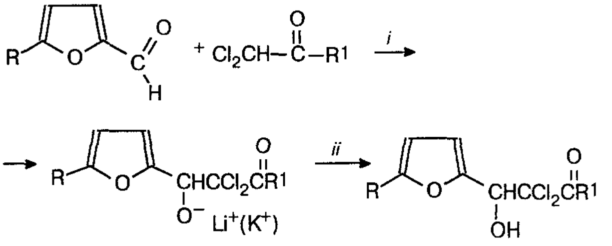
Esters and amides of 2,2-dichloro-3-(2-furyl)-3-hydroxypropionic acid were prepared by the reaction of furfural with dichloroacetic acid derivatives under the conditions of the Darzens condensation. The structures of the reaction products were confirmed by their ^{1}H NMR and IR spectra and chemical transformations.

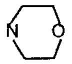
Key words: furfural, dichloroacetic acid esters and amides, esters and amides of 2,2-dichloro-3-(2-furyl)-3-hydroxy-propionic acid, Darzens reaction.

We have previously reported[1] the reaction of 2-thiophenecarboxaldehyde with dichloroacetic acid esters under the conditions of the Darzens condensation. In this work, the results of the investigation of the reaction of furfural with esters and amides of dichloroacetic acid to give the corresponding esters (**1—3**) and amides (**4—6**) of 3-furyl-3-hydroxy-2,2-dichloropropionic acid are presented. It should be noted that the application of *t*-BuOK as a base instead of BuLi increases the yields of the final products by 15—20 %.



1—6

1: R = H, R^1 = OMe; **2**: R = H, R^1 = OEt; **3**: R = H, R^1 = OPr-*n*;

4: R = H, R^1 = NEt$_3$; **5**: R = H, R^1 =  **6**: R = Me, R^1 = NEt$_2$;

i. BuLi or Bu^{t}OK *ii.* HCl

The structures of products **1—6** were confirmed by their IR and ^{1}H NMR spectra. The presence of the singlet signal of the methyne proton at 5.23 ppm no matter which ester was used for the reaction, and also the presence of the broadened singlet signal of the hydroxyl group at 3.60—4.73 ppm in the ^{1}H NMR spectra of compounds **1—3** both confirm the formation of α,α–dichlorohydrins. The IR spectroscopy data also give additional confirmation of the structures of compounds **1—6**. In the spectra of the studied compounds in the condensed phase the bands of νOH 3484—3435, νC=O 1632 (**4—6**), 1770—1750 (**1—3**), and νCCl$_2$ 760 cm^{-1} are present. The furan ring is characterized by the following set of bands: 3200—3100 cm^{-1} (ν(=CH)); 1590, 1500 cm^{-1} (ν of cycle); 1155, 1070, 1020 (β(=CH)); 950, 870, 820, 760 (γCH + β of the ring).[2] The bands in the range of 1270 cm^{-1} (ν(C=O)) and 1100—1000 cm^{-1} (ν(C—O)) are characteristic of the ester group. In the ^{1}H NMR spectrum of compound **4** in CCl$_4$ the methyne and hydroxyl groups appear as doublets at 5.30 and 4.40 ppm, respectively, with ^3J = 5 Hz. Saturation of a solution of compound **4** in CCl$_4$ with hydrogen chloride transforms the doublets of the CH and OH groups in the ^{1}H NMR spectrum into singlets at 5.23 and 4.23 ppm, respectively. One of the possible reasons for these changes in the ^{1}H NMR spectra is the presence of a hydrogen bond. To verify this assumption and to reveal the type of hydrogen bond the IR spectra of solutions of compounds **4** and **5** in CCl$_4$ were studied. In fact, in dilute solutions of these compounds bands at 3500 cm^{-1} (νOH$_{\text{bound}}$, strong), and 3610 cm^{-1} (νOH$_{\text{free}}$, very weak) are observed in the hydroxyl group region. The ratio of the intensities of these bands remains constant upon further dilution of the solution. This fact makes it possible to conclude that the molecules of compounds **4** and **5** exist mainly in a form with an intramolecular hydrogen bond (IHB). The magnitude of the shift of the hydroxyl band, νOH (110 cm^{-1}) corresponds to the IHB with a six-membered ring formed by the O—H...O=C bonds.[3]

The νOH absorption in the condensed phase of compounds **4** and **5** is observed at significantly lower

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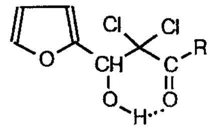
Table 1. IR and ^1H NMR data for the compounds synthesized

Compound	IR spectrum[a] (ν/cm^{-1})	^1H NMR spectrum (δ, ppm, *J*/ Hz)
1	3490, 3160, 3130, 2965, 2880, 1760, 1615, 1505, 1440, 1385, 1260, 1155, 1075, 1020, 870, 825, 755	3.80 (s, 3 H, OCH_3),; 4.63 (br.s, 1 H, OH); 5.23 (s, 1 H, CH); 6.20 (q, 1 H, H-4, $^3J_{4,5}$ = 1.8); 6.30 (d, 1 H, H-3, $^3J_{3,4}$ = 3.4); 7.20 (d, 1 H, H-5, $^4J_{3,5}$ = 0.8)
2	3500, 3155, 3135, 2965, 2890, 1755, 1505, 1470, 1390, 1270, 1255, 1155 1070, 1020, 870, 820, 750	1.30 (t, 3 H, $CH_2C\underline{H}_3$); 4.23 (q, 2 H, $C\underline{H}_2CH_3$); 4.73 (br.s, 1 H, OH); 5.23 (s, 1 H, CH); 6.23 (q, 1 H, H-4, $^3J_{4,5}$ = 1.8); 6.30 (d, 1 H, H-3, $^3J_{3,4}$ = 3.4); 7.23 (d, 1 H, H-5, $^4J_{3,5}$ = 0.8)
3	3155, 3135, 2980, 2890, 1760, 1500, 1470, 1380, 1265, 1155, 1080, 1065, 1020, 930, 870, 825, 755	0.93 (t, 3 H, $C\underline{H}_3CH_2CH_2$); 1.23—2.16 (m, 2 H, $CH_3C\underline{H}_2CH_2$); 3.60 (br.s, 1 H, OH); 4.10 (t, 2 H, $CH_3CH_2C\underline{H}_2$); 5.23 (s, 1 H, CH); 6.23 (q, 1 H, H-4, $^3J_{4,5}$ = 1.8); 6.33 (d, 1 H, H-3, $^3J_{3,4}$ = 3.4); 7.23 (d, 1 H, H-5, $^4J_{3,5}$ = 0.8)
4	3440, 1630, 1590, 1505, 1465, 1380, 1270, 1215, 1155, 1090, 1080, 1020, 950, 860, 825, 760	0.90 и 0.95 (2 t, 6 H, $N(CH_2C\underline{H}_3)_2$); 3.40 и 3.80 (2 q, 4 H, $N(C\underline{H}_2CH_3)_2$); 4.40 (d, 1 H, OH, ^3J = 5.0); 5.30 (d, 1 H, CH, ^3J = 5.0); 6.26 (q, 1 H, H-4, $^3J_{4,5}$ = 1.8); 6.46 (d, 1 H, H-3, $^3J_{3,4}$ = 3.4); 7.33 (d, 1 H, H-5, $^4J_{3,5}$ = 0.8)
5	3435, 1640, 1595, 1500, 1675, 1650, 1380, 1280, 1255, 1120, 1075, 1010, 855, 765	3.30—4.0 (m, 8 H, $N(CH_2CH_2)_2O$); 4.43 (br.s, 1 H, OH); 5.36 (s, 1 H, CH); 6.26 (q, 1 H, H-4, $^3J_{4,5}$ = 1.8); 6.43 (d, 1 H, H-3, $^3J_{3,4}$ = 3.4); 7.26 (d, 1 H, H-5, $^4J_{3,5}$ = 0.8)
6	3450, 3010, 1635, 1570, 1470, 1450, 1385, 1365, 1285, 1230, 1085, 1035, 855, 805	0.93—1.43 (m, 6 H, $N(CH_2C\underline{H}_3)_2$); 2.26 (s, 3 H, CH_3); 3.0—4.10 (m, 4 H, $N(C\underline{H}_2CH_3)_2$); 4.43 (s, 1 H, OH); 5.13 (s, 1 H, CH); 5.76—5.83 (m, 1 H, H-4); 6.16 (d, 1 H, H-3, $^3J_{3,4}$ = 3.8)
7	3265, 1765, 1715, 1600, 1540, 1510, 1470, 1380, 1260, 1230, 1165, 1145, 1110, 1080, 1015, 990, 960	0.86 (t, 3 H, $OCH_2CH_2C\underline{H}_3$); 1.36—2.06 (m, 2 H, $OCH_2C\underline{H}_2CH_3$); 4.23 (t, 2 H, $OC\underline{H}_2CH_2CH_3$); 6.47 (s, 1 H, CH); 6.50 (q, 1 H, H-4, $^3J_{4,5}$ = 1.5); 6.63 (d, 1 H, H-3, $^3J_{3,4}$ = 3.4); 7.26—8.13 (m, 9 H, H-5, NH, naphthyl protons)
8	3310, 1740, 1655, 1540, 1500, 1465, 1380, 1350, 1280, 1215, 1155, 1110, 1080, 1025	1.0 (t, 6 H, $N(CH_2C\underline{H}_3)_2$); 3.06—4.06 (m, 4 H, $N(C\underline{H}_2CH_3)_2$); 6.33 (q, 1 H, H-4, $^3J_{4,5}$ = 1.6); 6.56 (br.s, 2 H, CH, H-3, $^3J_{3,4}$ = 3.3); 7.20—8.03 (m, 9 H, H-5, NH, naphthyl protons)
9	3155, 3125, 1765, 1620, 1445, 1315, 1280, 1260, 1160, 1085, 1025, 905, 890, 855	0.1 (s, 9 H, 3 CH_3); 3.83 (s, 3 H, OCH_3); 5.33 (s, 1 H, CH); 6.26 (q, 1 H, H-4, $^3J_{4,5}$ = 1.1); 6.43 (d, 1 H, H-3, $^3J_{3,4}$ = 3.7); 7.30 (d, 1 H, H-5, $^4J_{3,5}$ = 0.8)
10	3150, 3130, 1765, 1620, 1445, 1260, 1165, 1120, 1025, 900, 855	0.1 (s, 9 H, 3 CH_3); 1.0 (t, 3 H, $OCH_2CH_2C\underline{H}_3$); 1.43—2.06 (m, 2 H, $OCH_2C\underline{H}_2CH_3$); 4.13 (t, 2 H, $OC\underline{H}_2CH_2CH_3$); 5.30 (s, 1 H, CH); 6.10 (q, 1 H, H-4, $^3J_{4,5}$ = 1.0); 6.26 (d, 1 H, H-3, $^3J_{3,4}$ = 3.2); 7.20 (d, 1 H, H-5, $^4J_{3,5}$ = 0.7)
11	3155, 3125, 1740, 1500, 1460, 1440, 1385, 1365, 1315, 1260, 1215, 1160, 1095, 1020, 925, 905, 885, 850	0.1 (s, 9 H, 3 CH_3); 1.23 (t, 6 H, $N(CH_2C\underline{H}_3)_2$); 3.1—3.73 (m, 4 H, $N(C\underline{H}_2CH_3)_2$); 5.50 (s, 1 H, CH); 6.20 (q, 1 H, H-4, $^3J_{4,5}$ = 1.1); 6.33 (d, 1 H, H-3, $^3J_{3,4}$ = 3.2); 7.23 (d, 1 H, H-5, $^4J_{3,5}$ = 0.6)
12	3260, 1615, 1470, 1380, 1370, 1310, 1250, 1160, 1070, 1025, 930, 890	4.93 (br.s, 1 H, OH); 6.00—6.51 (m, 3 H, CH, H-3, H-4); 7.33—7.60 (m, 1 H, H-5)

[a] The IR spectra of compounds **5—8** were obtained for suspensions in liquid paraffin; the others were obtained in thin films.

[b] The ^1H NMR spectrum of compound **5** was recorded in $CDCl_3$, those for compounds **7**, **8** were recorded in CD_3CN-d_3, and the other spectra were recorded in CCl_4 solutions.

frequencies than that in solution, evidently due to intermolecular hydrogen bonding (I—HB). In accordance with the conclusion of the presence of IHB in solutions of compounds **4** and **5**, the values of νC=O 1632 cm^{-1} (**4**) and 1646 cm^{-1} (**5**) are lower than those of halogenated tertiary amides **4**.

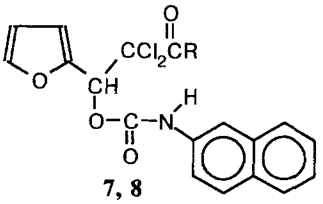


4, 5

It was of significant interest to perform a similar investigation of esters **1—3**. However, the data obtained for solutions of compounds **1—3** cannot be unequivocally interpreted at this moment and require further study.

In addition to spectral methods, the structures of α,α-dichlorohydrins **1—6** were confirmed by their reactions with β-naphthylisocyanate, $ClSiMe_3$, and KOH.

Crystalline urethanes **7** and **8**, were prepared from ester **3** and amide **4**, respectively, by reaction with naphthylisocyanate in the presence of Et_3N.

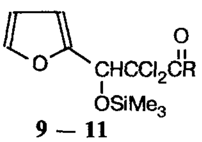


7, 8

R = OPr-*n* (**7**), NEt$_2$ (**8**)

In the IR spectrum of compound **8** the absorption band (AB) of νOH disappears and new intense ABs at 3265, 1765, 1715, and 1540 cm^{-1} appear as a result of deformational vibrations of NH and valent vibrations of the C=O bonds of the amide and urethane groups and of ν of the NH group, respectively. Comparison of the IR spectra of compounds **3** and **7** reveals almost the same change in patterns (Table 1). The absence of the singlet signals of the OH groups and the appearance of multiplet signals in the aromatic region 7.20—8.00 ppm for the naphthyl group in the ^{1}H NMR spectra of compounds **7** and **8** also indicate the formation of urethanes in the reaction of α,α-dichlorohydrins **3** and **4** with naphthylisocyanate.

The reaction of α,α-dichlorohydrins **1**, **3**, and **4** with $ClSiMe_3$ in the presence of pyridine affords silyl ethers **9—11**, respectively.

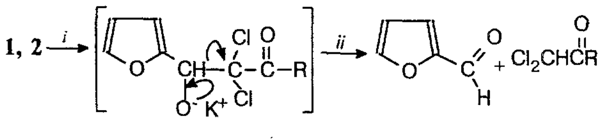


9 — 11

R = OMe (**9**), OPr-*n* (**10**), NEt$_2$ (**11**)

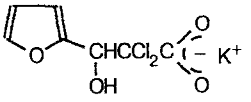
In contrast to the starting alcohols, the silyl ethers **9** and **10** are stable and do not undergo any changes during prolonged storage.

Treatment of compounds **1** and **4** with a methanolic KOH solution leads not to the desired α-chloroepoxide or isomeric α-chloroketone, but to other products, whose composition depends on the reaction temperature. Thus, at 20 °C or after a short period (5 min) of heating to boiling the dichlorohydrins decompose with splitting at the C(2)—C(3) bonds to give the starting materials.



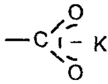
i. KOH, MeOH, 20 °C; *ii.* MeOH, (–MeOK), 20 °C.

Treatment of esters **1** and **2** with a methanolic KOH solution at *ca.* 0 °C for 72 h afforded a quantitative yield of a crystalline compound, that had the structure of the potassium salt of 3-(2-furyl)-3-hydroxy-2,2-dichloropropionic acid (**12**).



12

In the ^{1}H NMR spectrum of compound **12** the signals of ester groups are absent. In the IR spectrum the intense ABs of the ester group at 1760 and 1740 cm^{-1} totally disappear, however, there are two new bands at 1620 and 1370 cm^{-1} which were tentatively assigned to the symmetrical and asymmetrical vibrations of the


$-\mathrm{C}\overset{O}{\underset{O}{\langle}}{}^{-}\ \mathrm{K}^+$ group, respectively.[5]

Experimental

The ^{1}H NMR spectra were recorded with a Varian T-60 instrument. Chemical shifts are given relative to tetramethylsilane. The IR spectra were recorded with UR-20 and Specord-75 IR spectrometers (Carl Zeiss, Iena). Melting points were determined under a microscope with a Boetius apparatus.

Methyl 2,2-dichloro-3-(2-furyl)-3-hydroxypropionate (1). A solution of *t*-BuOK, prepared from potassium (4.0 g) and anhydrous *t*-BuOH (150 mL) was added at –40 °C under argon to a solution of furfural (9.8 g, 0.102 mol) and methyl dichloroacetate (14.6 g, 0.102 mol) in a mixture of anhydrous ether and *t*-BuOH (1:1, 100 mL). The reaction mixture was kept at –40 °C for 1.5 h, poured onto ice and acidified with dilute HCl to pH *ca.* 7. The organic layer was separated and the aqueous layer was extracted with ether (3×100 mL) and dried over $MgSO_4$. The solvent was removed and the residue was distilled *in vacuo* to give compound **1** (10.5 g).

Compounds **2—6** were prepared in a similar way from furfural and the derivatives of dichloroacetic acid in the presence of equimolar amounts of *t*-BuOK (Tables 1 and 2).

Table 2. Characteristics of the compounds prepared

Compound	Yield (%)	B.p./°C (*p*/ Torr) or M.p.[a]/°C	Found/Calculated (%) C	H	Cl	N	Molecular formula
1	43.4	102—106 (0.03)	39.96 40.21	3.20 3.35	29.40 29.67	—	$C_8H_8Cl_2O_4$
2	40.2	112 (0.04)	42.35 42.73	3.60 3.95	27.75 28.03	—	$C_9H_{10}Cl_2O_4$
3	44.1	103—105 (0.9)	44.65 44.89	4.28 4.49	26.31 26.56	—	$C_{10}H_{12}Cl_2O_4$
4	66.9	67—68	46.70 47.18	5.10 5.36	25.01 25.32	4.75 5.00	$C_{11}H_{15}Cl_2NO_3$
5	30.6	109—110	44.54 44.79	4.58 4.41	23.86 24.04	4.47 4.75	$C_{11}H_{13}Cl_2NO_4$
6	43.5	52.5—54	48.91 49.02	5.59 5.78	24.01 24.12	4.69 4.76	$C_{12}H_{17}Cl_2NO_2$
7	25.8	88—89	57.59 57.84	4.32 4.36	16.29 16.26	3.40 3.21	$C_{21}H_{19}Cl_2NO_5$
8	30.1	59—60	58.61 58.83	4.72 4.90	15.49 15.79	6.09 6.23	$C_{22}H_{22}Cl_2N_2O_4$
9	53.4	105—110 (0.08)	42.29 42.47	5.01 5.14	22.56 22.79	—	$C_{11}H_{16}Cl_2O_4Si$
10	45.01	90—94 (0.08)	45.89 46.05	5.72 5.90	20.69 20.91	—	$C_{13}H_{20}Cl_2O_4Si$
11	80.6	48—49	47.59 47.76	6.29 6.53	20.01 20.14	3.72 3.98	$C_{14}H_{23}Cl_2NO_3Si$
12[b]	45.4	187—189	31.53 31.96	1.77 1.90	26.59 26.96	—	$C_7H_5Cl_2O_4K$

[a] Compounds **4—8**, and **11** were recrystallized from an ethanol—isopropanol (1:1) mixture, compound **12** was recrystallized from hexane. [b] Elemental analysis data: K, 14.57/14.86.

An attempt to synthesize compounds **1—6** according to the reported procedure[1] by the interaction of furfural with dichloroacetic acid derivatives in the presence of BuLi did not improve the yields of the final products.

***n*-Propyl 2,2-dichloro-3-(2-furyl)-3-(β-naphthylcarbamoyloxy)propionate (7).** A mixture of dichlorohydrin **3** (3.8 g, 0.014 mol), β-naphthylisocyanate (2.4 g, 0.014 mol), and Et_3N (1.4 g, 0.014 mol) was refluxed in anhydrous benzene (10 mL) for 3 h. The reaction mixture was washed with water, extracted with $CHCl_3$ (3×50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was recrystallized twice from hexane to give compound **7** (1.6 g).

Compound **8** was obtained from equimolar amounts of dichlorohydrin **4**, naphthylisocyanate, and Et_3N as described for **7**.

Methyl 2,2-dichloro-3-furyl-3-trimethylsiloxypropionate (9). Pyridine (2.6 g, 0.03 mol) was added to a solution of dichlorohydrin **1** (7.2 g, 0.03 mol) and $ClSiMe_3$ (5.5 g, 0.03 mol) in anhydrous ether (100 mL) at 0 °C. After 2 h pyridine hydrochloride was filtered off, the solvent was removed, and the residue was distilled *in vacuo* (an oil pump).

Compounds **10** and **11** were prepared from equimolar amounts of dichlorohydrin **3**, **4**, $ClSiMe_3$, as described for **9**.

Reaction of KOH with 2,2-dichloro-*N*,*N*-diethyl 3-furyl-3-hydroxypropionamide at heating or at 20 °C. Dichlorohydrin **4** (5.0 g, 0.018 mol) was added to a solution of KOH (1 g) in MeOH (20 mL) and the mixture was refluxed for 5 min. After removal of the solvent the residue was treated with diluted HCl, extracted with ether (3×50 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo*, the residue was dissolved in ethanol (20 mL), 2,4-dinitrophenylhydrazine (2.8 g, 0.014 mol) and several drops of conc. H_2SO_4 were added to the solution (the necessary amount of 2,4-dinitrophenylhydrazine was calculated from the ^1H NMR spectrum of the reaction mixture). The precipitated crystals were filtered off to give furfural 2,4-dinitrophenylhydrazone (2.3 g, 59.8%), m.p. 200—202 °C (from acetic acid; *cf.* Ref. 6).

The filtrate was washed with 5 % aqueous $NaHCO_3$, and extracted with ether (3×50 mL). After removal of the solvent and distillation of the residue *in vacuo* *N*,*N*-diethyl dichloroacetamide was obtained, b.p. 88—89 °C (0.99 Torr, *cf.* Ref. 7).

Potassium 2,2-dichloro-3-furyl-3-hydroxypropionate (12). Compound **1** (4.0 g, 0.016 mol) was added to a solution of KOH (1 g) in MeOH (20 mL) at 0°C, the reaction mixture was kept at this temperature for 72 h. After removal of the solvent salt **12** was obtained.

Salt **12** was also obtained from dichlorohydrin **2** in a similar way.

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