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# SYNTHESIS OF 2,2-DICHLORO-1-ALKANOLS

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Abstract : 2,2-Dichloro-1-alkanols were prepared conveniently by sodium borohydride reduction of 2,2-dichloroaldehydes.

*Dedicated to Professor Gottfried Heinisch on the occasion of his 60th birthday.*

β-Halogenated alcohols are valuable bifunctional substrates in synthetic organic chemistry. β-Halogenated primary alcohols are primarily known as β-monohalo and β,β,β-trihalo derivatives. β-Monohaloalcohols are mostly known for their synthetic potential related to epoxide formation while β,β,β-trihaloalcohols are used as inductively activated ethanol derivatives ($X_3CCH_2OH$).

2,2,2-Trihaloalcohols are frequently applied in organic synthesis as protecting agents for alcohols[1,2] and carboxyl groups[3,4]. 2,2,2-Trichloroethanol and, to a lesser extent, 2,2,2-tribromoethanol are mostly used for this purpose. The 2,2,2-trihaloalcohols are

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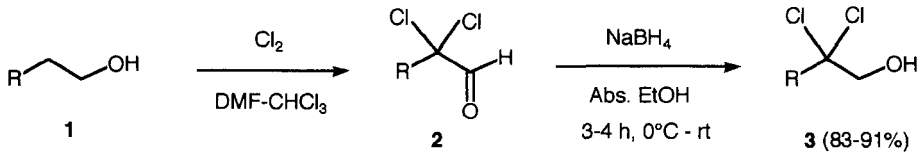


R = Et, n-Pr, n-Bu, N-Hex, n-Oct



sometimes first converted into the 2,2,2-trihaloethylchloroformates by reaction with phosgene in benzene[5]. These chloroformates suitably protect hydroxyl[5], thiol[6] and amino[5,7] groups. In all cases mentioned above, the protecting group can be easily removed by treatment with Zn[2,4,5] or by means of electrolysis,[6,8] depending on the nature of the functional group.

Surprisingly, 2,2-dichloro-1-alkanols **3** seem to have been neglected in the literature. Only 2,2-dichloro-1-pentanol **3** (R=n-Pr) was formed in an unspecified yield as an undesired side-product of the reaction of 2,2-dichloropentanoyl chloride with one equivalent of lithium tri-tert.butoxyaluminium hydride in tetrahydrofuran at -70°C, while the target 2,2-dichloropentanal **2** (R=n-Pr) was only obtained in low yield (isolation by preparative gas chromatography).[9] Only one primary β,β-dibromoalcohol, i.e. 2,2-dibromo-1-propanol, seems to be synthesized previously by sodium borohydride reduction of the corresponding α,α-dibromoaldehyde in THF in the presence of a catalytic amount of triethylamine.[10]

Due to the fact that 2,2-dichloro-1-alkanols might be suitable inductively β,β-activated alcohols for use in a variety of applications, we would like to report on their easy synthesis from 2,2-dichloroaldehydes **2**. As a matter of fact, their application for the synthesis of activated esters, useful for enzyme mediated chiral synthesis of carboxylic acids or esters, is under investigation in our research.

2,2-Dichloroaldehydes **2** are easily accessible by reaction of the corresponding alcohols **1** with chlorine gas in dimethylformamide-chloroform at 65-70°C.[11,12]

Reaction of 2,2-dichloroaldehydes **2** with 1-2 molar equivalents of sodium borohydride in ethanol at 0°C for 3-4 hours, during which the temperature slowly increased to

Table 1 : Synthesis of 2,2-Dichloroaldehydes **2** and 2,2-Dichloro-1-alkanols **3**

| | R | Compound **2** | | Reaction Conditions (Reduction) | Compound **3** | |
|---|---|---|---|---|---|---|
| | | yield (%) | Bp. | | yield (%) crude (dist.) | Bp. |
| a | $C_2H_5$ | 78 | 37°C/27 mmHg | 1 equiv. $NaBH_4$ EtOH, 4h, 0°C → rt | 87 (70) | 56-60°C/13-14 mmHg |
| b | n-$C_3H_7$ | 66 | 56-60°C/14 mmHg | 1.1 equiv. $NaBH_4$ EtOH, 3h, 0°C → rt | 80 (69) | 72-75°C/11-12 mmHg or 78-81°C/17-18 mmhg |
| c | n-$C_4H_9$ | 66 | 74-77°C/54 mmHg | 2 equiv. $NaBH_4$ EtOH, 4h, 0°C → rt | 87 (68) | 25-27°C/0.01 mmHg |
| d | n-$C_6H_{13}$ | 67 | 83-85°C/11 mmHg | 1.2 equiv. $NaBH_4$ EtOH, 3.5h, 0°C → rt | 91 (83) | 108-110°C/10 mmHg |
| e | n-$C_8H_{17}$ | 68 | 60-69°C/0.02 mmHg | 1.2 equiv. $NaBH_4$ EtOH, 3h, 0°C → rt | 83 (68) | 81-82°C/0.2 mmHg |

ambient temperature, afforded excellent crude yields (83-91%) of 2,2-dichloro-1-alkanols **3** in acceptable purities, suitable for further use (> 96%). Pure samples of dichloroalcohols **3** were obtained after vacuum distillation. Table 1 gives a compilation of the synthesis of 2,2-dichloroaldehydes **2** and 2,2-dichloro-1-alkanols **3**.

## Experimental Section

$^1$H NMR spectra (270 MHz) and $^{13}$C NMR spectra (68 MHz) were run with a Jeol JNM-EX270 NMR spectrometer. IR spectra were recorded with a Perkin Elmer model 1310 spectrophotometer. Mass spectra were obtained with a Varian MAT 112 mass spectrometer (70 eV) using a GC-MS coupling or the direct inlet mode. 2,2-Dichloroaldehydes **2** were synthesized by chlorination of alcohols **1** with chlorine gas in a dimethylformamide-chloroform mixture.[11,12]

## Synthesis of 2,2-dichloro-1-alkanols **3**

A mechanically stirred solution of 0.1 mol of 2,2-dichloroaldehyde **2** in 150 ml of absolute ethanol was treated portionwise with 0.1-0.2 mol of sodium borohydride over a period of 10 minutes at ice bath temperature. Stirring was continued for 3-4 hours during which the solution reached ambient temperature. The reaction mixture was poured in water (200 ml) and extracted three times with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. The residue was distilled in vacuo to afford pure 2,2-dichloro-1-alkanols **3** (Table 1).

## 2,2-Dichloro-1-butanol **3a**

$^1$H NMR (270 MHz, $CDCl_3$) δ : 1.18 (3H, t, J=7.3 Hz, $C\underline{H}_3$); 2.25 (2H, q, J=7.3 Hz, $CH_3C\underline{H}_2$); 3.91 (1H, broad s, O<u>H</u>); 3.92 (2H, s, $C\underline{H}_2OH$). $^{13}$C NMR (68 MHz, $CDCl_3$) : δ 9.27 ($\underline{C}H_3$); 36.82 ($CH_3\underline{C}H_2$); 71.84 ($\underline{C}H_2OH$); 95.40 ($\underline{C}Cl_2$). IR (NaCl, $cm^{-1}$) : $\nu_{OH}$ 3358 (broad). Mass spectrum (70 eV) m/z (%) : 142/4/6 ($M^+$, 1); 111/3/5 (63); 110/2/4(100); 78/80(11); 76/8(11); 75/7(53); 71(45); 53(13); 51(13); 49(28); 43 (43); 42(17); 41(82).

Elem. anal. $C_4H_8Cl_2O$ : Calc. C 33.59%, H 5.64%; found C 33.25%, H 5.37%.

2,2-Dichloro-1-pentanol **3b**

$^1$H NMR (270 MHz, $CDCl_3$) : δ 1.00 (3H, t, J=7.3 Hz, $C\underline{H}_3$); 1.68 (2H, m, $CH_3C\underline{H}_2$); 2.20 (2H, t, J=7.3 Hz, $CH_3CH_2C\underline{H}_2$); 2.80 (1H, broad s, O<u>H</u>); 3.90 (2H, s, $C\underline{H}_2OH$). $^{13}$C NMR (68 MHz, $CDCl_3$) : δ 13.57 ($\underline{C}H_3$); 18.28 ($CH_3\underline{C}H_2$); 45.62 ($CH_3CH_2\underline{C}H_2$); 72.07 ($\underline{C}H_2OH$); 94.46 ($\underline{C}Cl_2$). IR (NaCl, cm-1); $\nu_{OH}$ 3382 (broad). Mass spectrum (70 eV) m/z (%) : no $M^+$; 125/127/129(56); 124/126/128(70); 91(46); 90(11); 89 (100); 85(21); 80(7); 78(24); 76(12); 75(16); 67(20); 65(23); 63(58); 61(11); 57(23); 55(68); 53(34); 51(12); 49(12); 45(28); 43(63); 42(13); 41(66).

2,2-Dichloro-1-hexanol **3c**

$^1$H NMR (270 MHz, $CDCl_3$) : δ 0.95 (3H, t, J=7.3 Hz, $CH_3$); 1.39 (2H, sextet, J=7.3 Hz, $CH_3C\underline{H}_2$); 1.62 (2H, quintet, J=7.3 Hz, $C\underline{H}_2CH_2CCl_2$); 2.22 (2H, t, J=7.3 Hz, $C\underline{H}_2CCl_2$); 2.78 (1H, s, OH); 3.90 (2H, s, $C\underline{H}_2OH$). $^{13}$C NMR (68 MHz, $CDCl_3$) : δ 13.85 ($CH_3$); 22.25 ($CH_3\underline{C}H_2$); 26.97 ($\underline{C}H_2CH_2Cl_2$); 43.39 ($\underline{C}H_2CCl_2$); 72.13 ($CH_2OH$); 94.70 ($CCl_2$). IR (NaCl, $cm^{-1}$); $\nu_{OH}$ 3387 (broad). Mass spectrum (70 eV) m/z (%) : no $M^+$; 149(7); 139/141/143(7); 104/6(5); 95(9); 93(8); 86(6); 81(16); 75 (10); 69(10); 59(7); 58(5); 57(7); 55(20); 49(10); 44(20); 43(13); 42(10); 41(8); 40 (6); 40(100); 39(5).

Elem. anal. $C_6H_{12}Cl_2O$ : calc. C 42.13%, H 7.07%; found C 42.34%, H 7.31%.

2,2-Dichloro-1-octanol **3d**

$^1$H NMR (270 MHz, $CDCl_3$) : δ 0.90 (3H, t, J=7.3 Hz, $CH_3$); 1.20-1.44 (6, m, $CH_3(C\underline{H}_2)_3$); 1.64 (2H, quintet, J=7.3 Hz, $C\underline{H}_2CH_2CCl_2$); 2.21 (2H, t, J=7.3 Hz, $C\underline{H}_2CCl_2$); 2.49 (1H, broad s, OH); 3.90 (2H, s, $C\underline{H}_2OH$). $^{13}$C NMR (68 MHz, $CDCl_3$) : δ 14.03 ($CH_3$); 22.53 ($CH_3\underline{C}H_2$); 24.78 ($CH_3CH_2\underline{C}H_2$); 28.72 ($CH_3(CH_2)_2\underline{C}H_2$); 31.55 ($CH_3(CH_2)_3\underline{C}H_2$); 43.59 ($\underline{C}H_2CCl_2$); 72.09 ($CH_2OH$); 94.72 ($CCl_2$). IR (NaCl, $cm^{-1}$) $\nu_{OH}$ 3374 (broad). Mass spectrum (70 eV) m/z (%) : no $M^+$; 131/3(13); 109(41); 95(76); 91(16); 89(22); 88(11); 87(22); 86(11); 85(11); 84(17); 83(13); 82(10); 78/80(16); 71(12); 70(68); 69(41); 68(33); 67(22); 57(35); 56(19);

55(84); 53(10); 43(100); 42(50); 41(89).

Elem. anal. $C_8H_{16}Cl_2O$ : calcd. C 48.26%, H 8.10%; found C 48.74%, H 8.63%.

2,2-Dichloro-1-decanol **3e**

$^1H$ NMR (270 MHz, $CDCl_3$) : δ 0.89 (3H, t, J=7.3 Hz, $CH_3$); 1.19-1.40 (10H, m, $CH_3(CH_2)_5CH_2$); 1.64 (2H, quintet, J=7.3 Hz, $CH_2CH_2CCl_2$); 2.21 (2H, t, J=7.3 Hz, $CH_2CCl_2$); 2.59 (1H, t, J=7.3 Hz, OH); 3.90 (2H, d, J=7.3 Hz, $CH_2OH$). $^{13}C$ NMR (68 MHz, $CDCl_3$); δ 14.09 ($CH_3$); 22.66 ($CH_3CH_2$); 24.85 ($CH_3CH_2CH_2$); 29.07 ($CH_3(CH_2)_2CH_2$); 29.18 ($CH_3(CH_2)_3CH_2$); 29.34 ($CH_3(CH_2)_4CH_2$); 31.84 ($CH_3(CH_2)_5CH_2$); 43.61 ($CH_2CCl_2$); 72.09 ($CH_2OH$); 94.73 ($CCl_2$). IR (NaCl, $cm^{-1}$) $\nu_{OH}$ 3381. Mass spectrum (70 eV) m/z (%) : no $M^+$; 137(31); 123(23); 117(10); 115 (14); 103(14); 102(14); 101(17); 98(18); 97(18); 96(23); 95(16); 83(21); 82(12); 81 (41); 71(20); 70(36); 69(40); 68(11); 67(25); 57(76); 56(51); 55(75); 54(12); 53(10); 43(100); 42(26); 41(87).

Elem. anal. $C_{10}H_{20}Cl_2O$ : calcd. C 52.87%, H 8.87%; found C 53.23%, H 9.18%.

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