NMR Structural Study and Stereoselective Synthesis of 2-Substituted and 2,2-Disubstituted 5-Dichloroacetamido-5-methyl-1,3-dioxanes

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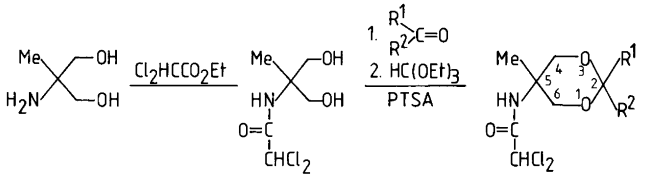
Several 1,3-dioxanes (**3**)–(**15**) have been synthesized by a stereoselective method from 2-dichloroacetamido-2-methyl-1,3-propanediol (**2**) and appropriate carbonyl compounds in the presence of triethyl orthoformate. Compound **2** was prepared from 2-amino-2-methyl-1,3-propanediol (**1**) by selective acylation. The configurations and conformations of 1,3-dioxanes were confirmed by ^{1}H and ^{13}C NMR spectroscopy and some selected 2D experiments. In all cases the 5-methyl group is equatorial. The cyclization reaction leads stereoselectively to the epimers where the conformationally more demanding group at the 2 position is equatorial.

Relatively little attention has been paid to the synthesis and structural study of 2,5,5-tri-[1-3] and 2,2,5,5-tetra-substituted[1a] 1,3-dioxanes. In this report a stereoselective method for preparing 2-mono- and 2,2-di-substituted 5-dichloroacetamido-5-methyl-1,3-dioxanes is described together with their ^{1}H and ^{13}C NMR spectroscopic characterizations.

Results and discussion

Syntheses. Compounds **3–15** were prepared from 2-dichloroacetamido-2-methyl-1,3-propanediol (**2**) and a carbonyl compound in the presence of triethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid (Scheme 1). The reactions proceeded to completion in 2–8 h at reflux as



Scheme 1. **1** **2** **3–15**

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Table 1. Physical properties for the 1,3-dioxanes (**3–15**).

Compound	R^1	R^2	Yield/%	M.p./°C	Elemental analyses
3	Me	Me	70	111–112[a]	$C_9H_{15}NO_3Cl_2$: C, H, N
4	Et	Et	72	103–104[a]	Found: C, 45.71; H, 6.76; N, 4.83. Calc. for $C_{11}H_{19}NO_3Cl_2$: C, 46.49; H, 6.73; N, 4.92
5	Me	Et	50	106–109[a]	$C_{10}H_{17}NO_3Cl_2$: C, H, N
6	*c*-C_5H_9	*c*-C_5H_9	44	101–102[a]	$C_{12}H_{17}NO_3Cl_2$: C, H, N
7	*c*-C_6H_{11}	*c*-C_6H_{11}	65	103–105[b]	$C_{13}H_{19}NO_3Cl_2$: C, H, N
8	*c*-C_7H_{13}	*c*-C_7H_{13}	28	69– 71[b]	$C_{14}H_{21}NO_3Cl_2$: C, H, M
9	H	PhCH=CH-Ph	46	158–160[a]	$C_{15}H_{17}NO_3Cl_2$: C, H, N
10	H	Ph	97	165–166[c]	$C_{13}H_{15}NO_3Cl_2$: C, H, N
11	H	*o*-$EtOC_6H_4$	87	183–184[c]	$C_{15}H_{19}NO_3Cl_2$: C, H, N
12	H	*m*-ClC_6H_4	89	118–121[c]	$C_{14}H_{14}NO_3Cl_3$: C, H, N
13	H	*p*-$MeOC_6H_4$	85	149–152[b]	Found: C, 49.80; H, 5.06; N, 3.99. Calc. for $C_{14}H_{17}NO_3Cl_2$: C, 50.32; H, 5.13; N, 4.19
14	Me	Ph	68	160–163[a]	Found: C, 52.26; H, 5.35; N, 4.22; Calc. for $C_{14}H_{17}NO_3Cl_2$: C, 52.84; H, 5.38; N, 4.40
15	Me	*p*-BrC_6H_4	77	156–159[a]	$C_{14}H_{16}NO_3BrCl_2$: C, H, N

[a]Recrystallized from ether. [b]Recrystalized from benzene–ether. [c]Recrystallized from benzene.

shown by thin-layer chromatography [silica gel; benzene–ethanol (4:1)]. Aldehydes required shorter and ketones longer reaction times. After the reaction mixtures had been evaporated solid products (**3–15**) were obtained which were recrystallized from the solvents shown in Table 1. The crystalline products were always stereohomogeneous, i.e. stereoselective condensation had occurred in all cases.

Attempts were also made to synthesize the dioxanes **3–15** from the diols and oxo compounds using P_4O_{10}[4,5] or concentrated sulphuric acid[6] as the dehydrating agent. Under these conditions yields of only a few per cent were obtained.

2-Dichloroacetamido-2-methyl-1,3-propanediol (**2**) was obtained by selective acylation of 2-amino-2-methyl-1,3-propanediol (**1**) with ethyl dichloroacetate at reflux.[7] This was the method of choice since other methods also acylate the hydroxy groups to give triacyl derivatives. The selectivity of this acylation with ethyl dichloroacetate arises because (i) the solubility of **1** in this reagent is very low and (ii) the acid amide precipitates from the reaction mixture as soon as it is formed. This phenomenon shifts the equilibrium toward acid amide formation.

Configurational and conformational assignments. Eliel and Enanoza[2] proved previously with ^1H NMR and IR spectroscopy that the acetamido group at position 5 adopts predominantly the axial orientation which is stabilized by intramolecular hydrogen bonding. Therefore only the relative orientations of the substituents at position 2 of **5** and **9–15** need be assigned. The NMR data (Tables 2 and 3), in comparison with earlier data[1,8–14] together with present double resonance (D-NOE) (**10**)[15,16] and 2D NOESY and heteronuclear COSY experiments **5** and **14**, made possible the determination of the configurations and conformations (chair form) of the prepared 1,3-dioxanes.

First, the irradiation of the 5-methyl singlet of **10** produced intensity changes in the D-NOE spectrum of both the axial and equatorial orientation of this methyl group. Secondly, irradiation of the H(2)-singlet of **10** produced a positive NOE effect on the $H(4,6_{ax})$ proton signal while the $H(4,6_{eq})$ signal showed a negative effect. Therefore H(2) must be axially oriented.[17] Accordingly, from the similarity of the NMR parameters (Tables 1 and 2) compounds **9–13** all have an equatorial substituent at position 2 and an axial dichloroacetamido group at position 5.

Table 2. ^{1}H NMR data (δ) for compounds **3–15**. Solvent $CDCl_3$ ($\delta_{SiMe_4} = 0$).

Compound	Me(5)	NH	$CHCl_2$	H(4,6$_{eq}$)	H(4,6$_{ax}$)	
3[a]	1.31	6.94	5.87	3.95[b]	3.64[b]	1.46(ax), 1.42(eq)
4[a]	1.31	6.99	5.86	3.92[c]	3.70[c]	0.96 and 1.65(eq),[d] 0.87 and 1.83(ax[d]
5a[a]	1.31	6.98	5.86	3.94[e]	3.73[e]	1.40(ax), 0.98 and 1.68(eq[d]
5b[a]	1.36	6.95	5.86	3.94[c]	3.68[c]	1.625(eq), 0.91 and 1.185(ax[d]
6[f]	1.32	6.95	5.82	3.95	3.56	1.7
7[f]	1.32	7.00	5.91	3.95	3.65	1.5–1.8
8[f]	1.30	6.95	5.85	3.86	3.59	1.5–1.8
9[f]	1.36	7.05	5.92	4.29	3.61	5.15(H-2,[g] 6.20,[g,h] 6.90,[h] 7.45(Ph)
10[f]	1.36	7.02	5.87	4.29	3.65	5.44(H-2), 7.45(Ph)
11[a]	1.37	7.10	5.91	4.33[i]	3.76[i]	5.91(H-2); EtO: 1.43 and 4.07;[j] Ar: 6.87;[k,l] 6.98;[k,m,n] 7.31;[l,n,o] 7.59[m,o]
12[f]	1.29	7.1	5.9	4.40	3.66	5.47(H-2); Ar: 7.5(4H), 8,0(1H)
13[a]	1.36	7.04	5.89	4.33[p]	3.71[p]	5.44(H-2), 3.81(CH_3O); Ar: 6.90,[q] 7.40[q]
14[a]	1.13	7.10	5.90	3.97[r]	3.47[r]	1.53(Me-2); Ph: 7.34(1 H), 7.40(2 H), 7.41(2 H)
15[f]	1.16	7.1	5.91	3.93	3.37	1.52(Me-2); Ph: 7.30,[s] 7.56[s]

[a]JEOL GX-400 (400 MHz). [b]J −11.7 Hz. [c]J −12.0 Hz. [d]J 7.5 Hz. [e]J −11.8 Hz. [f]JEOL C-60-HL (60 MHz). [g]J 4.5 Hz. [h]J 16.5 Hz. [i]J −11.4 Hz. [j]J 7.0 Hz. [k]J 0.9 Hz. [l]J 7.0 Hz. [m]J 7.7 Hz. [n]J 8.7 Hz. [o]J 1.8 Hz. [p]J −11.4 Hz. [q]J 9.0 Hz. [r]J −11.3 Hz. [s]J 8.5 Hz.

Table 3. ^{13}C NMR chemical shifts for **3–5**, **11**, **13** and (**14**.

Compound	C(2)	C(4,6)	C(5)	CH_3(5)	$CHCl_2$	C=O	R^1, R^2
3	98.4	66.6	51.1	17.35	67.0	164.1	28.6(ax), 18.4(eq)
4	101.5	66.0	51.0	17.4	66.9	163.9	8.0 and 30.2(eq), 7.0 and 21.2(ax)
5a	99.6	66.5	51.2	17.2	66.9	164.0	7.3 and 34.6(eq), 16.7(ax)
5b	100.5	66.1	51.0	17.55	66.9	164.0	24.8(eq), 8.3 and 23.5(ax)
11	97.2	73.6	51.3	17.0	67.0	164.15	14.9 and 64.0(CH_3CH_2O); Ar: 155.9, 130.5, 126.9, 125.8, 120.8, 111.9
13	102.1	73.4	51.2	17.0	67.0	164.2	55.4(CH_3O); Ar: 160.4, 129.9, 127.5, 113.9
14	101.1	67.6	51.1	16.9	67.1	164.15	32.0(eq); Ph: 139.3, 129.0(2C), 128.2, 126.6(2C)

The 2D NOESY spectrum of **14** showed a strong interaction between the axial H(4,6) and the phenyl and CH_3(5) protons. Therefore, **14** has a configuration in which the 2-phenyl group is axial and the 5-methyl group equatorial. The axial character of the 2-phenyl group in **14** as well as in **15** is already indicated by the highfield resonance of the 5-methyl groups (1.13 and 1.16 ppm, respectively). Similarly, the 2D NOESY spectrum of **5** shows a strong interaction between both equatorial and axial H(4,6) and the 5-methyl group and between the axial H(4,6) and the 2-methyl group. Therefore the former methyl group is equatorial and the latter axial. The ^{1}H,^{13}C-heteronuclear COSY spectrum of **5** was used to assign the signals of the protons and carbons connected to each other.

The crystalline products epimerize rapidly in solution (e.g. in $CDCl_3$ which is slightly acidic). The epimerization equilibria are in agreement with the relative conformational energies of the substituents at position 2.[18,19]

Experimental

^{1}H NMR spectra were recorded for solutions in $CDCl_3$ at ambient temperature on JEOL C-60-HL (60 MHz) and JEOL GX-400 (400 MHz) NMR spectrometers. ^{13}C NMR spectra and the 2D NOESY and ^{1}H,^{13}C-heteronuclear COSY spectra were recorded in the same solvent on the latter instrument. D-NOE experiments were run on a Bruker WM-250 (250 MHz) instrument.

2-Dichloroacetamido-2-methyl-1,3-propanediol (**2**). A mixture of one equivalent of 2-amino-2-methyl-1,3-propanediol (**1**) and 1.5 equivalents of ethyl dichloroacetate was refluxed for 5 h. As the reaction proceeded, the crystalline product began to precipitate out. The white crystals were separated, washed with light petroleum and recrystallized from EtOH: m.p. 177–180 °C, yield 82 %. Anal. $C_6H_{11}Cl_2NO_3$: C, H, N.

1,3-Dioxanes **3–15**. A mixture of one equivalent of **2**, 1.1 equivalents of triethyl orthoformate and 1.1 equivalents of a carbonyl compound was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid for 2–8 h. The excess triethyl orthoformate and carbonyl compound were removed under reduced pressure. The products were recrystallized from the solvents shown in Table 1.

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