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Acetal Chlorination with MnO_2-Trimethylchlorosilane

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Abstract: *α-Chloroacetals are obtained in almost quantitative yields, by treating acetals with MnO_2-trimethylchlorosilane in CH_3OH:CH_3CN (1:1). The halogenation is explained by a ligand-transfer process on an enolether intermediate, mediated by a Mn(IV)-chloride species.*

INTRODUCTION

The α-halogenation of aldehydes is a troublesome task and generally gives poor yields, being complicated by competing reactions.[1] Better results have been obtained by halogenating the corresponding enol derivatives, such as the vinyl silylethers.[2] The α-halo aldehydes, however, are unstable products and in order to prevent polymerizations,[3] their transformation into the corresponding acetals is recommended for storage. Since these latter derivatives are also useful for dehydrohalogenations[3,4] and aldol condensations,[5] their direct synthesis is a valuable synthetic goal. A number of methods for the preparation of α-chloroacetals has been developed,[3,4,6] but unsatisfactory yields are generally obtained, through complicated procedures.[7] The reported most convenient systems use molecular halogens[7] or N-haloimides[8] on a mixture of vinylacetate and alcohol, even if the step of the enol esterification gives poor yields.[7]

We now report on an almost quantitative chlorination of acetals by MnO_2-trimethylchlorosilane (TMCS). The reagent has been previously employed in the chlorination of alkenes[9,10] and ketones,[11] and the intervention of Mn(IV) and Mn(III) chloride species, working through a ligand-transfer process, has been suggested.[9-12] As far as we know, the halogenation of acetals by a metal chloride has been attempted only with $CuCl_2$ or $CuBr_2$, but with low conversions and poor yields.[13]

Result and Discussion

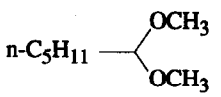
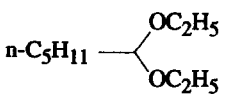
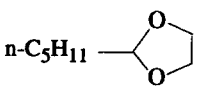
The treatment of aliphatic aldehydes with MnO_2-TMCS in acetic acid, tetrahydrofurane, acetonitrile, or dimethylformamide as solvents, produces α-monochlorination together with polymerization, dichlorination and carbonyl oxidation. Since we observed that, in the absence of solvent, this reagent oxidizes primary aliphatic alcohols to a mixture of acetals and α-chloroacetals,[14] we tried the direct chlorination of acetals with MnO_2-TMCS. On using 1,1-dimethoxyhexane as substrate and a number of solvents, the highest yields of α-chloroacetal are obtained in methanol/acetonitrile (1:1), although the product is accompanied by considerable amount of methylester (see Table 1). A generally favourable effect on the reaction course is observed on adding soluble salts to the reaction mixture.

The effectiveness, which is higher on using $MnCl_2$ (Table 1), may be explained on assuming that the metallic cation complexes the acetal group, and hinders the aldehydic hydrogen abstraction, thus preventing the oxidation to methylester; besides, the salt addition increases the substrate conversion rate. With respect to methyl derivatives, ethyl acetals give a lower yield of α-chloroacetals, whereas dioxolanic derivatives produce large amount of ester (Table 2).

TABLE 1. The effect of added salts on the reaction of the hexanal dimethyl acetal (10 mmoles) with MnO_2-TMCS.

Salt (mmoles)	α-Chloroacetal yield (%)	α-Chloroacetal /ester ratio
/	81	13
$MnCl_2$ (2.5)	91	35
$MnCl_2$ (5)	95	56
LiCl (5)	85	14
LiCl (10)	91	29
$LiNO_3$ (10)	82	12
NEt_4Cl (10)	75	7
$Zn(OAc)_2$ (5)	91	44
$MgCl_2$ (5)	86	26

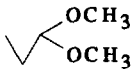
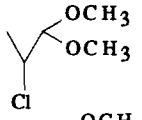
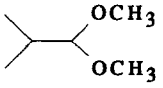
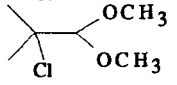
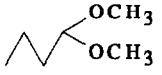
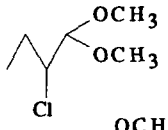
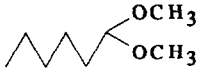
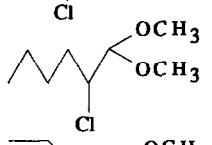
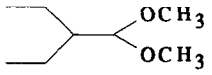
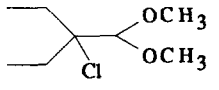
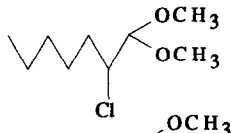
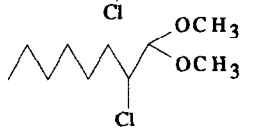
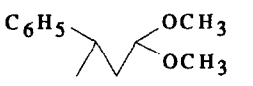
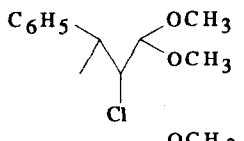
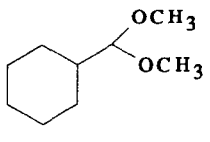
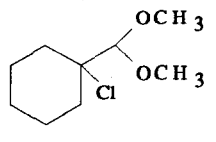
TABLE 2. The effect of the alkyl acetal group on the reaction yields.

Substrate	α-Chloroacetal yield (%)
	95
	87
	48[a]

a) Percentage of unreacted acetal: 23%; percentage of ester: 13%.

Dimethylacetals or the corresponding aldehydes (10 mmoles) have thus been treated with stoichiometric amounts of the title reagent and 5 mmoles of $MnCl_2$ in acetonitrile/methanol (1:1). The reaction has been

TABLE 3. Acetals chlorination with MnO_2- TMCS.

Substrate	Product	α-Chloroacetal Yield(%)[a]
		99 (89)
		98 (93)
		99 (97)
		95 (89)
		90 (69)
		94 (78)
		95 (83)
		91 (61)
		94 (63)

a) In parenthesis are reported the yields obtained starting from the parent aldehydes.

thermostatted at 40°C, a temperature that gives better yields and chemoselectivity. The α-chloroacetals are obtained in very high yields on starting from acetals, and in significatively lower yields from aldehydes, especially from the more hindered ones (Table 3). The reaction is generally fast the conversion for 1,1-dimethoxyhexane, for example, being about 95% just after one hour .

A substrate lacking of α-hydrogens, such as benzaldehyde dimethylacetal, is slowly oxidated to methylester (65% yield, after 48 hours). Starting from differently alkylsubstituted ketones, partial conversions and mixtures of α-chloroketones and α-chloroketals are obtained; therefore these substrates have not been studied further.

Even if Cl_2 may be generated from the treatment of manganese(IV)-oxide with an acidic chloride carrier (hydrochloric acid,[15] for example), molecular chlorine is ruled out as the halogenating species, since on using Cl_2, under equivalent reaction conditions, considerable amounts of ester are produced. Definitive support comes from the comparative halogenation of norbornene with the two reagents;[9] whereas molecular chlorine produces many products through rearrangement and solvent addition processes, MnO_2-TMCS affords only 1,2 dichloro adducts, a result that does not agree with an ionic pathway.

Previously, we suggested that MnO_2 reacts with TMCS generating a Mn(IV)-Cl[16] species,[9,11] together with hexamethyldisiloxane (eq. 1); we also observed that in the presence of $MnCl_2$ in dimethylformamide as solvent, a Mn(III)-Cl complex arises by comproportionation between Mn(IV) and Mn(II) species (eq. 2).[10]

$$(1) \qquad MnO_2 + 4\,(CH_3)_3SiCl \longrightarrow MnCl_4 + 2\,(CH_3)_3SiOSi(CH_3)_3$$

$$(2) \qquad Mn(IV) + Mn(II) \longrightarrow Mn(III) + Mn(III)$$

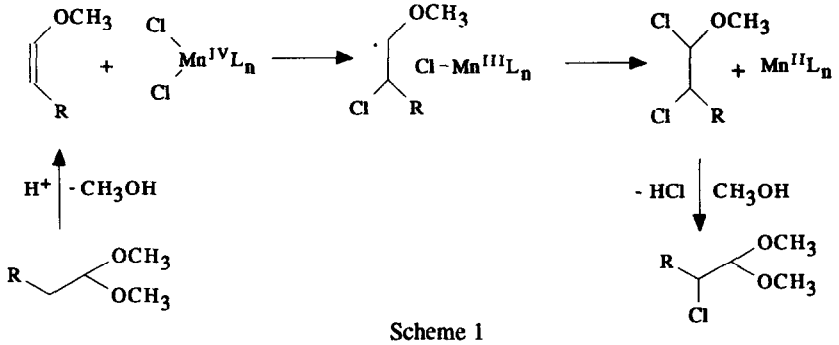
A comproportionation process and so a Mn(III)-Cl species as the halogenating reagent, could agree with the present results. However, on generating Mn(III)-Cl from $Mn(OAc)_3$ and TMCS, very different results are obtained on starting from 1,1-dimethoxyhexane; great amounts of methyl ester are produced (49%), and on adding $MnCl_2$ to the reaction mixture, the oxidation is suppressed, but the conversion is only 54%. Owing to this different behaviour, we suggest a Mn(IV)-Cl species as the chlorinating intermediate.

Very likely enolethers,[17] which can be formed by an acid catalysed elimination of an alcohol molecule from the acetals, are the intermediates of the halogenation process. The higher reaction rate observed on adding $MnCl_2$ (a Lewis acid) agrees with a faster catalyzed enolether formation. Under the reported conditions, the equilibrium between the enol intermediate and the starting acetal is not effective; on substituting, indeed, CH_3OH by the same amount of CD_3OD as solvent, no α-deuterated product (NMR analysis) is detected.

This observation also indicates that enolethers cannot derive from α-chloroacetals, which instead easily exchange an alkoxy group, when a different alcohol is introduced in the system after the reaction end. All the above evidences agree with the process shown in Scheme1.

The enolether intermediate, which may be considered an activated alkene, is halogenated, as soon as it is formed, by a Mn(IV)-Cl species through a ligand transfer process giving rise to a 1,2-dichloro-1-methoxy-alkane.[9] This product easily reacts with the alcohol solvent, yielding the α-chloroacetal.

The method[18] produces monochlorination exclusively, and can be employed in preparative scale reactions with comparable yields (see experimental part). It is advantageous with respect to other procedures since preparation of acetals is a very simple and easy process. Furthermore, since mild ways for acetals deprotection have been developed,[19] the method is useful for aldehydes chlorination.



Scheme 1

Experimental Part

The ^1H NMR spectra have been recorded on a Bruker FP80 and a Varian XL200 spectrometers. Substrates, reagents and solvents are standard grade commercial products, and have been used without further purification.

General procedure for the preparation of acetals.[20] To a solution of aldehyde (200 mmoles) and trimethyl orthoformate (200 mmoles) in CH_3OH (20 ml), a catalytic amount of Dowex^R 50W or p-toluenesulphonic acid is added. No temperature control of the reaction system is operative. After complete conversion (GC monitoring) of the aldehyde, the mixture is diluted with n-hexane (20 ml), washed with a NaOH solution (H_2O 90 ml and NaOH 5% 10 ml) and dried over Na_2SO_4. The acetal is isolated by distillation under nitrogen. The isolation of cyclohexan-carboxyaldehyde dimethylacetal occurs by elimination of the solvent at room temperature, since this product easily polymerizes on distillation. The yields are almost quantitative.

General procedures for the preparation of α-chloro acetals. In a double necked round bottom flask (50 ml), fitted with a dropping funnel, a condenser and a $CaCl_2$ valve, CH_3CN (5 ml), CH_3OH (5 ml) and $MnCl_2$ (5 mmoles) are added. When $MnCl_2$ is completely dissolved, MnO_2 Merck (>90% activated, precipitated)[21] (11 mmoles) and the acetal (10 mmoles) are added. The stirred mixture is thermostatted at 40°C and TMCS (44 mmoles) is poured, all at once, from the dropping funnel. A vigorous boiling is soon observed while the mixture becomes a dark-brown solution, thereof visible spectrum is characterized by the two maxima at 490 nm and 311 nm. The mixture turns colourless, about six hours later, and then is diluted with n-hexane (15 ml) and poured in 50 ml of a NaOH solution (H_2O 35 ml and NaOH 5% 15 ml).[22] After phase separation, the aqueous layer is again washed with 15ml of n-hexane. The organic extracts are collected, dried on Na_2SO_4 and then evaporated at 20-40 mmHg. Crude products can be further purified by distillation. The same procedure has been followed starting from aldehydes.

Special cases.- a) With 2-ethylbutyraldehyde dimethyl acetal the reaction is thermostatted at 15°C, since at 40°C the transformation occurs very quickly but with lower yield (82%); *b)* With 3-phenylbutyraldehyde dimethyl acetal the amount of MnO_2-TMCS is increased to 12 mmoles and 48 mmoles respectively, since under the general reaction conditions, the conversion is not completed.

2-chloropropionaldehyde dimethyl acetal

B.p.: 48-50°C /(14-15 mmHg); Litt. 86°C /(100 mmHg)[23]

^1H NMR ($CDCl_3$) :1.45 (3H, d, CH_3-CCl); 3.4 (6H, s, 2xOCH_3); 3.6-4.0 (1H, m, -CHCl-); 4.3 [1H, d, -CH$(OR)_2$].

Found : C, 43.4; H, 8.1; Cl, 25.6. $C_5H_{11}ClO_2$ requires C, 43.33; H, 8.00; Cl, 25.58%.

2-chloroisobutyraldehyde dimethyl acetal
B.p.: 42-45°C /(14-15 mmHg);
^{1}H NMR ($CDCl_3$): 1.5 (6H, s, 2xCH_3); 3.55 (6H, s, 2xOCH_3); 4.15 [1H, s, -CH$(OR)_2$].
Found : C, 47.2; H, 8.6; Cl, 23.1. $C_6H_{13}ClO_2$ requires C, 47.22; H, 8.59; Cl, 23.23%.

2-chlorobutyraldehyde dimethyl acetal
B.p.: 61-63°C /(14-15 mmHg). Litt. 67-70°C /(16 mmHg)[24]
^{1}H NMR ($CDCl_3$): 1.5 (3H, t, -CH_3); 1.3-2.2 (2H, m, -CH_2-); 3.4 (6H, s, 2xOCH_3); 3.6-4.0 (1H, m, -CHCl-); 4.3 [1H, d, -CH$(OR)_2$].
Found: C, 47.2; H, 8.6; Cl, 23.2. $C_6H_{13}ClO_2$ requires C, 47.22; H, 8.59; Cl, 23.23%.

2-chlorohexanal dimethyl acetal
B.p: 48-50°C / 0.7 mmHg.
^{1}H NMR ($CDCl_3$): 0.9 (3H, t, CH_3-C-); 1.1-2.0 (6H, m, C-$(CH_2)_3$-CCl); 3.4 (6H, s, 2xOCH_3); 3.6-4.0 (1H, m, CHCl-); 4.3 [1H, d, -CH$(OR)_2$].
Found : C, 53.2, H, 9.5; Cl, 19.7. $C_8H_{17}ClO_2$ requires C, 53.18; H, 9.48; Cl, 19.62%.

2-chloro-2-ethylbutyraldehyde dimethyl acetal
B.p.: 40-42°C / 0.6 mmHg.
^{1}H NMR ($CDCl_3$): 0.85 (6H, t, 2xCH_3); 1.7 (4H, q, 2xCH_2); 3.4 (6H, s, 2xOCH_3); 4.15 [1H, s, -CH$(OR)_2$].
Found : C, 53.2; H, 9.5; Cl, 19.5. $C_8H_{17}ClO_2$ requires C, 53.18; H, 9.5; Cl, 19.5%.

2-chloroheptanal dimethyl acetal
B.p.: 58-60°C / 0.7 mmHg.
^{1}H NMR ($CDCl_3$) : 0.9 (3H, t, CH_3-C); 1.1-2.0 (8H, m, C(CH_2)-CCl); 3.4 (6H, s, 2xOCH_3); 3.6-4.0 (1H, m, -CHCl); 4.3 [1H, d, -CH$(OR)_2$].
Found: C, 55.6; H, 9.8 ; Cl, 18.3. $C_9H_{19}ClO_2$ requires C, 55.52; H, 9.84; Cl, 18.21%.

2-chlorooctanal dimethyl acetal
B.p.: 72-74°C / 0.8 mmHg.
^{1}H NMR ($CDCl_3$): 0.9 (3H, t, CH_3-C); 1.1-2.0 (10H, m, C$(CH_2)_5$-CCl); 3.4 (6H, s, 2xOCH_3); 3.6-4.0 (1H, m, CHCl-); 4.3 [1H, d, -CH$(OR)_2$].
Found: C, 57.6; H, 10.2; Cl, 17.0. $C_{10}H_{21}ClO_2$ requires C, 57.54; H, 10.14; Cl, 16.99%.

2-chloro-3-phenylbutyraldehyde dimethyl acetal
B.p.: 88-98°C / 0.8 mmHg.
^{1}H NMR (C_6D_6): 1.3 (3H, q, CH_3-C); 3.0-3.2 (6H, m, 2x-OCH_3); 3.4 (1H, m, C_6H_5-C<u>H</u>-CCl); 4.0-4.3 [2H, m, -CHCl-, -CH$(OR)_2$]; 7.2 (5H, m, -C_6H_5).
Found: C, 63.1; H, 7.5; Cl, 15.6. $C_{12}H_{17}ClO_2$ requires C, 63.02; H, 7.49; Cl, 15.50%.

1-chlorocyclohexanecarboxaldehyde dimethyl acetal
B.p.: 55-58°C / 0.7 mmHg.
^{1}H NMR ($CDCl_3$) : 1.4-2.0 (10H, m, -C_6H_{10}); 3.55 (6H, s, 2xCH_3); 4.1 [1H, s, -CH$(OR)_2$].
Found: C, 64.9; H, 7.1; Cl, 14.8. $C_{13}H_{17}ClO_2$ requires C, 64.86; H, 7.12; Cl, 14.73%.

Preparative scale reaction. Starting from hexanal dimethyl acetal (10.22 g, 70 mmoles), MnO_2 (6.69 g, 77 mmoles), TMCS (33.46 g, 308 mmoles) and $MnCl_2$ (4.40 g, 35 mmoles) in CH_3CN (35 ml)-CH_3OH (35 ml), the corresponding α-chloroacetal is obtained in 94% yield, being 75 its ratio with the methylester, while the recovered

starting material is 3%.

Chlorination of norbornene with MnO_2-TMCS. MnO_2 (11 mmoles) and norbornene (10 mmoles) are added to a solution of $MnCl_2$ (5 mmoles) in CH_3CN-CH_3OH (1:1, 10 ml). To the mixture, vigorously stirred and thermostatted at 40°C, TMCS (44 mmoles) is rapidly added, giving rise to the dark-brown colour. After fading the mixture is worked up as described above. The only products obtained are trans-1,2-dichloronorbornane (yield 76%) and exo-cis-1,2-dichloronorbornane (yield 19%).

Chlorination of hexanal dimethyl acetal with Cl_2. In a solution of hexanal dimethyl acetal (10 mmoles), LiCl (20 mmoles) and TMCS (24 mmoles) in CH_3CN-CH_3OH (1:1, 10 ml), Cl_2 is slowly bubbled in about 2 hours at 40°C. The yields of α-chloroacetal and methylhexanoate have been 75% and 17% respectively.

Chlorination of norbornene with Cl_2. Chlorine is slowly bubbled (2h) in a solution of norbornene (10 mmoles), LiCl (20 mmoles) and TMCS (22 mmoles) in CH_3CN:CH_3OH (1:1, 10 ml). Nortricyclylchloride (yield 29%) and many other chlorinated and methoxylated products have been produced.

Chlorination of hexanal dimethyl acetal with $Mn(OAc)_3$-TMCS. To a suspension of $Mn(OAc)_3$ (21 mmoles) in CH_3CN-CH_3OH (1:1, 10 ml), vigorously stirred and termostatted at 40°C, the acetal (10 mmoles) is introduced, immediately followed by TMCS(63 mmoles) addition all in a while. Usual work-up afford methyl hexanoate 49% and α-chloroacetal 46%. In the presence of $MnCl_2$ (5 mmoles), the yields are 1.2% and 45% respectively, while the conversion is lowered to 54%.

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18. On substituting TMCS by trimethylbromosilane (TMBS) high yields of α-bromoacetals are obtained, without added salts; starting from 1,1-dimethoxyhexane, for example, yields are 94% (84% starting from hexanal), while methylester is <1%. In this case, however, the reaction must proceed through an ionic mechanism since from norbornene the MnO_2-TMBS reagent system gives a very complex pattern of products. Molecular bromine is very likely involved in these transformations.
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21. Other types of commercial MnO_2 have been tested, giving the same products distribution pattern,but lower conversions, likely owing to a lower purity grade.
22. To recover the anhydrous $MnCl_2$, the mixture, after colour fading, is diluted with CH_2Cl_2 (20 ml). The precipitated salt is filtered off; dioxane (10 ml) is then added to the filtrate to help a further precipitation of $MnCl_2$. After filtration, the organic phase is treated as described above.
23. Beilstein 1, I, 335.
24. Beilstein 1, IV, 3239.