Trichloroisocyanuric Acid Oxidation of 2-Chloro Aldehyde Acetals to 2-Chloro Acid Esters

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2-Chloro acid methyl esters were prepared in good yields treating 2-chloro aldehyde dimethyl acetals with trichloroisocyanuric acid in DMF. Aldehyde dimethyl acetals with the 2-halogen on a tertiary carbon atom were poorly reactive and could be oxidized effeciently only after their transformation into 1,3-dioxolanes.

2-Halogenated carboxylic acid derivatives are useful synthetic intermediates,[1] and are usually prepared by halogenation of carboxylic acids, acyl chlorides, or anhydrides through their enolic form.[2] Esters can be also halogenated after conversion to enolate ions or to ketene silyl acetals.[3]

An alternative route to 2-halo acid esters is the oxidation of 2-halo aldehyde acetals,[4] but, as far as we know, this procedure has been rarely investigated.[5] Since we have developed efficient procedures for the preparation of 2-chloro and 2-bromo aldehyde dimethyl acetals,[6] their oxidation to 2-halo acid esters appeared to be an immediate and attractive synthetic route. We now report that this transformation is satisfactorily accomplished with trichloroisocyanuric acid (TCIA). This inexpensive reagent has been widely and successfully used for chlorination processes[7a] and for alcohol,[7b] ether,[7c] and acetal[7d] oxidations.

Results and Discussion

TCIA oxidation of 2-chlorohexanal dimethyl acetal (**5**) was tested in a number of solvents (CH_2Cl_2, CH_3OH, CH_3CO_2H, DMF, and THF), but good results were only obtained in DMF; 2-chlorocarboxylic acid methyl ester **15** was, however, accompanied by large amounts of the 2,2-dichloro ester (Table 1, Entry 1). The addition of a little water to the reaction mixture significantly reduced 2,2-dichloro ester formation (Table 1, Entry 3) and improved the 2-chloro ester yields, these yields further increased on adding, at the same time, cyanuric acid (Table 1, Entry 5), which also transforms a violent reaction, especially on a large scale, into a smoother one.

A series of 2-chloro aldehyde dimethyl acetals was thus submitted to TCIA oxidation under the conditions of Entry 5 in Table 1, affording the corresponding 2-chloro carboxylic acid methyl esters in high yields (Table 2). The procedure was effective only for aliphatic aldehyde acetals, since benzylic chlorination competed in the case of aromatic substrates (**11**).

Aldehyde dimethyl acetals with the 2-halogen on a tertiary carbon atom (**3** and **8**) were poorly reactive, owing to steric hindrance; on replacing the chlorine with a bromine atom the reactivity completely disappeared. After their transformation into the corresponding 1,3-dioxolanes **4** and **9**,[8] however, the 2-chlorocarboxylic acid esters **15** and **19** were obtained in high yields. With these substrates, water was not added since a further halogenation is prevented by the lack of a H-atom at the C-2 position. 2-(1-Chloroalkyl)-1,3-dioxolanes afforded, instead, 2,2-dichloro acid esters as the main products.[9] On using 2-bromo aldehyde dimethyl acetals as substrates, 2-chloro acid esters were again isolated, owing to nucleophilic substitution by chloride ions on the intermediary 2-bromo derivatives (see Experimental).

We think that TCIA is the true oxidizing reagent. In a parallel experiment using 2-chlorohexanal dimethyl acetal and replacing TCIA with molecular chlorine, the reaction was slow, unclean, and unselective, affording methyl 2-chlorohexanoate in a 42% yield after 96 h. The need for an oxidant amount higher than the stoichiometric one may be rationalized by molecular chlorine formation, probably from the reaction of TCIA with HCl produced in the transformation. This oxidant excess may be lowered by starting from ethylene acetals **4** and **9**, since their conversion into 2-chloroethyl esters recovers some of the chloride ion delivered to the system, thereby reducing the HCl accumulation. With aldehyde dimethyl acetals, the absence of chloromethane among the reaction products agrees with a higher HCl concentration and the consequent overconsumption of TCIA.

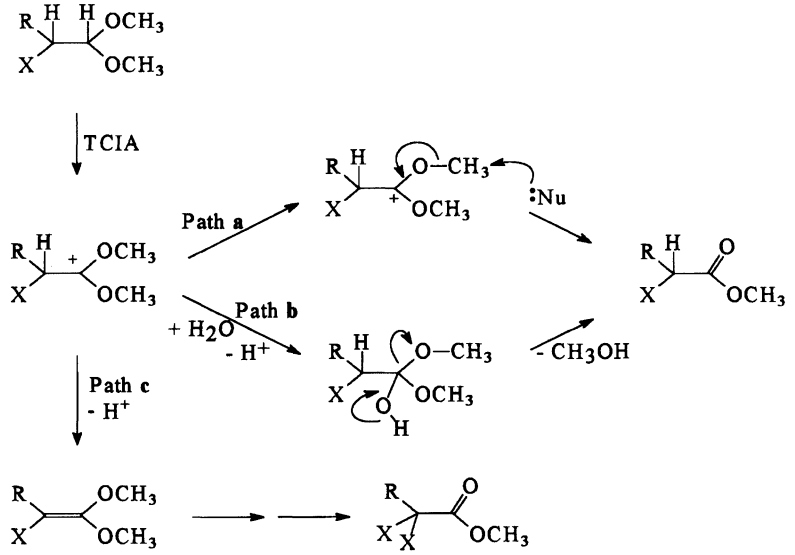
Since no free carboxylic acids are detected during the reaction, a pathway involving the oxidation of 2-chloro aldehydes, from 2-chloro aldehyde dimethyl acetal hydrolysis, is unlikely; moreover, a higher amount of water added to the reaction mixture dramatically reduces substrate conversion. The unsuccessful formation of chlorocyclohexane in a test using cyclohexane as a substrate rules out a radical reaction pathway. As reported for the heterolytic oxidation of ethers by reagents containing electropositive chlorine, in particular dibutyl ether oxidation with TCIA,[7c,10] the process, very likely, starts from hydride abstraction on the acetalic carbon (see Scheme 1).

The carbenium ion (path a) is then dealkylated by a nucleophile yielding the 2-chloro acid ester. In a parallel route (path b), this carbenium ion may very likely be quenched by water thus preventing proton elimination

Table 1. Effect of Additives on TCIA Oxidation of 2-Chlorohexanal Dimethyl Acetal[a)]

Entry	Additives			Esters (yields%)		Recovered
	H_2O	Cyanuric acid	LiCl	2-chloro	2,2-dichloro	2-chlorohexanal
	μl	mmol	mmol			
1[b)]	0	0	0	76	14	6
2[b)]	22	0	0	70	1	14
3[c)]	11	0	0	85	3	8
4[b)]	10	0	2.4	69	2	21
5[c)]	11	2	0	90	2	5
6[b)]	0	2	0	70	3	20

a) Substrate 2.5 mmol, TCIA 0.5 g, T=40° C, Time 22 h. b) DMF 1.25 ml. c) DMF 1.00 ml.



Scheme 1.

(path c) to an intermediary ketene acetal and therefore 2,2-dichloro acid ester formation.

On replacing TCIA by *N*-bromosuccinimide (NBS),[11)] ICl,[11b)] Ph_3CBF_4,[12)] $RuCl_3$/*t*-butyl hydroperoxide,[13)] or O_3,[8b)] oxidants well-known for conversion of acetals into carboxylic esters, the yields of 2-chloroacid esters from 2-chloro aldehyde acetals are comparatively much poorer (Table 3).

Experimental

^{1}H NMR spectra were recorded on Bruker WP80 and Varian XL200 spectometers. Reagents and solvents were standard grade commercial products and were used without further purification. 2-Halo aldehyde dimethyl acetals were prepared according to the reported methods.[5,6)]

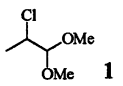
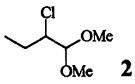
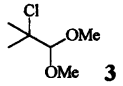
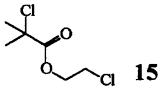
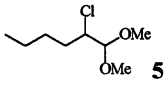
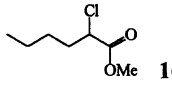
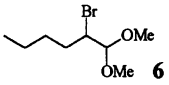
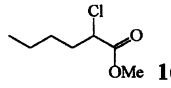
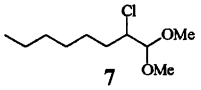
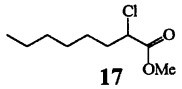
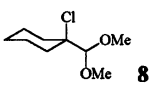
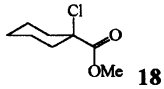
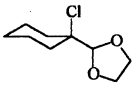
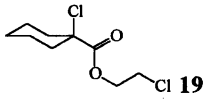
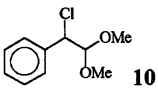
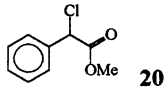
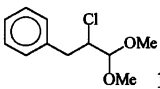
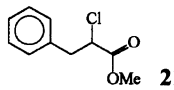
General Procedure for the Oxidation of 2-Chloro Aldehyde Dimethyl Acetals. In a two-necked round bottom flask (50 ml) fitted with a condenser, 2-chloro aldehyde dimethyl acetal (40 mmol), cyanuric acid (32 mmol), and H_2O (176 μl) were added to DMF (16 ml). The vigorously stirred mixture was thermostatted at 40 °C and TCIA (32 mmol) was added all at once. Owing to cyanuric acid precipitation, the mixture became slowly solid. After 18—24 h, the mixture was dispersed in 1 : 1 diethyl ether/petroleum ether (30—50 °C) (60 ml). The solid was filtered off and the organic solution was washed with aq 1 M $Na_2S_2O_5$ solution (1 M=1 mol dm^{-3}) (2×25 ml). The organic layer was dried over Na_2CO_3 and concentrated on a rotary evaporator. Products were isolated by distillation under reduced pressure.

Methyl 2-Chlorooctanoate. Yield 93%, bp 56—57 °C (0.1 mmHg, 1 mmHg=133.322 Pa). Found: C, 56.06; H, 8.92; Cl, 18.38%. Calcd for $C_9H_{17}ClO_2$: C, 56.10; H, 8.89; Cl, 18.40%. ^{1}H NMR ($CDCl_3$) δ=0.75—1.10 (3H, t, CH_3–C), 1.10—1.70 (8H, m, –$(CH_2)_4$–), 1.70—2.20 (2H, m, –CH_2–CCl–), 3.80 (3H, s, –CO–OCH_3), and 4.25 (1H, t, C–CHCl–CO_2). MS (EI) m/z 163 (11), 157 (11), 129 (7), 108 (100), 87 (13), 59 (21), and 55 (33).

Starting from 2-bromohexanal dimethylacetal **8**, the same procedure was followed; however, after 24 h, both the 2-bromo and 2-chloro carboxylic esters were present and an additional amount of DMF (16 ml) was added to make the mixture fluid. After a further 24 h, the replacement of bromide with chloride was complete and the reaction was worked up as reported above.

Preparation of 2-(1-Chloroalkyl)-1,3-dioxolanes. To a solution of 2-chloro aldehyde dimethyl acetal (200 mmol) in acetonitrile, ethylene glycol (400 mmol) and trimethylchlorosilane (200 mmol) were subsequently added.

Table 2. Products and Yields of TCIA Oxidation of 2-Chloro Aldehydes Acetals

Substrates	Products	Yields[a] (%)	Bp/mmHg (Lit)	Recovered substrate (%)	Time (h)
 **1**	 **12**	90 (2)	131—132/760 (130.9—131.5/760)[c]	6	18
 **2**	 **13**	93 (1)	144—147/760 (145—146/756)[d]	3	18
 **3**	 **14**	11	132—134/760 (133—135/760)[e]	86	18
 **4**	 **15**	99	42—43/0.1	—	17
 **5**	 **16**	92 (2)	71—73/5 (68—73/5)[f]	3	20
 **6**	 **16**	92	71—73/5 (68—73/5)[f]	—	18
 **7**	 **17**	93 (2)	56—57/0.1	3	18
 **8**	 **18**	20	52—54/0.2	75	17
 **9**	 **19**	92	82—83/0.1	—	17
 **10**	 **20**	42 (18)	85—87/1.5 (92—93/2.5)[g]	33	18
 **11**	 **21**	16[b]	115—118/5 (110-111/4)[h]	—	18

a) Yields of 2,2-dichloro esters in parentheses. b) 2,3-dichloro ester 41%, 2,3-dichloro acetal 36%.
c) Beil. **2** III 554. d) Beil. **2** 227. e) Beil. **2** III 657. f) Beil. **2** III 735. g) Beil. **9** IV 1676.
h) Beil. **9** III 2399.

Then, under vigorous stirring, $CoCl_2$ (100 mmol) was introduced. After 24 h, the mixture was diluted with CH_2Cl_2 (100 ml) and poured into H_2O (300 ml). The organic phase was separated and the aqueous layer was washed with CH_2Cl_2 (2×30 ml). The organic phases were collected, dried, and neutralized with solid Na_2CO_3, and then evaporated at 20—40 mmHg. Yields were >90%. Crude products were purified by distillation.

General Procedure for the Oxidation of 2-(1-Chloroalkyl)-1,3-dioxolanes. In a two-necked round bottom flask fitted with a condenser, 2-(1-chloroalkyl)-1,3-dioxolanes (40 mmol) and cyanuric acid (32 mmol) were added to DMF (16 ml). The vigorously stirred mixture was thermostatted at 40 °C and TCIA (19 mmol) was introduced. After 18 h, the mixture was diluted with 1:1 diethyl ether/petroleum ether (30—50 °C) (60 ml). The solid was filtered off and the organic solution was washed with aq 1 M $Na_2S_2O_5$ solution (2×10 ml). The organic layer was dried over Na_2CO_3 and concentrated. Products were isolated and purified by distillation.

2-Chloroethyl 1-Chlorocyclohexane-1-carboxylate. Yield 92%; bp 82—83 °C (0.1 mmHg). Found: C, 47.98;

Table 3. Comparation of 2-Chlorohexanal Dimethyl Acetal Oxidation by TCIA and Other Reagents

Entry	Oxidant	Yields (%)[a] of 2-chloro ester	Conversion %
1	TCIA	95	97
2	NBS[11a]	53	58
3	NBS[b]	21	19
4	NCS[b]	72	47
5	$RuCl_3/Me_3COOH$[13]	0	10
6	ICl[11b]	11	54
7	Ph_3CBF_4 [12]	0	14
8	O_3[8b]	18	29

a) Yields are calculated on coverted substrates. b) 2-Chloro hexanal dimethyl acetal 2.5 mM, DMF 1.25 ml, *N*-halo succinimide 6 mM, *T* 40 °C, Time 20 h.

H, 6.30; Cl, 31.51%. Calcd for $C_9H_{14}Cl_2O_2$: C, 48.02; H, 6.27; Cl, 31.50%. ^{1}H NMR ($CDCl_3$) δ=1.20—2.40 (10H, m, $-C_6H_{10}$), 3.75 (2H, t, C–CH_2Cl), and 4.45 (2H, t, CO–O–CH_2–). MS (EI) *m/z* 224 (M^+, 3), 189 (14), 169 (16), 145 (6), 117 (21), 81 (100), and 63 (15).

2- Chloroethyl 2- Chloro- 2- methyl- propionate. Yield 99%, bp. 42—43 °C (0.1 mmHg). Found: C, 38.98; H, 5.41; Cl, 38.36%. Calcd for $C_6H_{10}Cl_2O_2$: C, 38.94; H, 5.45; Cl, 38.32%. ^{1}H NMR ($CDCl_3$) δ=1.85 (6H, s, 2×CH_3), 3.72 (2H, t, C–CH_2Cl), and 4.45 (2H, t, –CH_2–O–CO). MS (EI) *m/z* 149 (6), 135 (6), 121 (3), 105 (12), 77 (100), 63 (34), and 41 (71).

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9) Starting from 2-(1-chlorophentyl)-1,3-dioxolane, 2-chloroethyl 2,2-dichlorohexanoate and 2-chloroethyl 2-chlorohexanoate were obtained in 66 and 28% yields, respectively.

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