Preparation of 2,2-Dihalocarboxylic Acid Methyl Esters by Oxidation–Chlorination of 2-(1-Haloalkyl)-4-methyl-1,3-dioxolanes with Trichloroisocyanuric Acid

Monica BONI, Franco GHELFI,* Ugo Maria PAGNONI, and Claudia ZUCCHI
Dipartimento di Chimica dell' Università, Università Degli Studi di Modena, Via Campi 183, I-41100, Modena, Italy
(Received September 13, 1993)

Methyl 2,2-dichloro or 2-bromo-2-chloro carboxylates were obtained in excellent yields by oxidation–chlorination of 2-(1-haloalkyl)-4-methyl-1,3-dioxolanes with trichloroisocyanuric acid.

2,2-Dichloro carboxylic esters are useful intermediates in the preparation of 2-chloro esters[1] and of glycidic esters through the Darzens reaction.[2] They are generally prepared by alkylation of dichloroacetates[3] or by the Hell–Volhard–Zelinskii chlorination of carboxylic acids.[4] Recently we described a method for the preparation of 2-chloro carboxylic esters by oxidation of 2-chloro aldehyde dimethyl acetals with trichloroisocyanuric acid (TCIA);[5] however, when attempted with 2-(1-chloropentyl)-1,3-dioxolane, the same procedure afforded, regrettably, a 4:1 mixture of 2,2-dichloro ester and 2-chloro ester. It thus became intriguing to study which factors could drive the oxidative halogenation toward a completely selective production of dihalo esters.

Here we report that when 2-(1-haloalkyl)-4-methyl-1,3-dioxolanes, easily obtained by transacetalization from 2-halo aldehyde dimethyl acetals, are treated with TCIA in dimethylformamide (DMF), 2,2-dichloro esters are produced. As far as we know, minor amounts of 2-halo- and 2,2-dihalo carboxylic esters have been reported among the reaction products only in a few examples of cyclic acetal oxidation with NBS[6,7] or TCIA.[8]

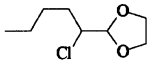
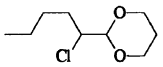
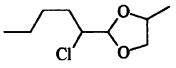
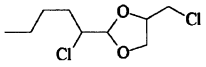
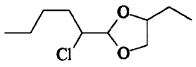
Results and Discussion

The oxidation–chlorination with TCIA was first applied to a number of cyclic acetals of 2-chlorohexanal in order to evaluate a possible steric effect on the reaction. Table 1 shows that 2,2-dichloro esters were specifically obtained on introducing an alkyl group at the C-4 position of the dioxolane ring (Entries 3, 4, and 5), whereas an electron-withdrawing group appeared to retard the reaction (Entry 4).

On attempting a larger scale preparation (10 mmol) thermostatted at 40 °C, an explosion was observed; however, at 5 °C and with a stoichiometric amount of TCIA the reactions were smooth and the yields were much improved.

Since a mixture of 2,2-dichloro carboxylic esters were produced in the reaction, the crude products were transesterified with methanol to isolate the methyl 2,2-dichloro carboxylates (Scheme 1). The oxidation–chlorination with TCIA was applied to a number of 2-(1-haloalkyl)-4-alkyl-1,3-dioxolanes, affording excellent yields of 2,2-dihalo methyl esters (Table 2); in the case of the 2-chloromethyl-4-ethyl-1,3-dioxolane (Entry 1), methyl trichloroacetate was isolated, by an exhaustive halogenation process.

Table 1. Acetal Group Effect on the Chlorination–Oxidation Reactions of 2-Chlorohexanal Cyclic Acetals with TCIA in DMF[a]

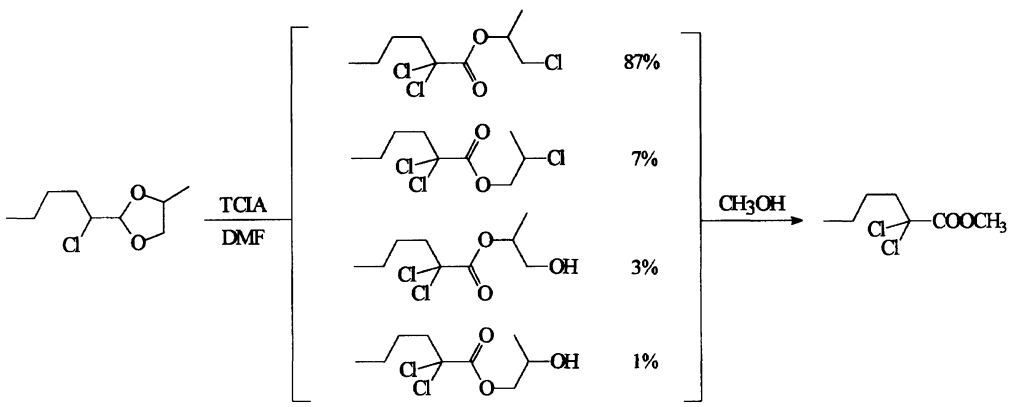
Entry	Substrate	Yield%	
		2,2-Dichloroester	2-Chloroester
1		74	18
2		63	23
3		95	<1
4		86	0[b]
5		93	<1

a) Substrate 2.5 mmol; TCIA 0.5 g; DMF 1 ml; T 40 °C; reaction time 40 h. b) 11% recovered starting material.

Though cyclic acetals are more easily oxidized with respect to open ones,[5] free chlorine was not able to transform 2-(1-chloropentyl)-4-methyl-1,3-dioxolane (see Experimental) in DMF at 5 °C. Since the addition of pyridine (0.5 mmol/mmol of substrate) lowered the conversion to only 5%, and the oxidation–chlorination of 2-(1-chloropentyl)-4-methyl-1,3-dioxolane (Entry 7) showed an induction period of about 15 min,[9] we think that a protonated TCIA is the real oxidizing agent.

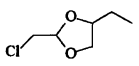
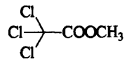
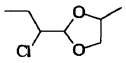
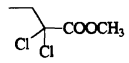
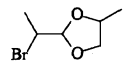
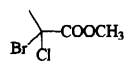
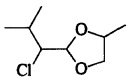
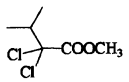
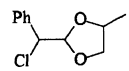
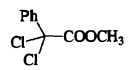
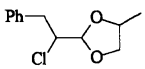
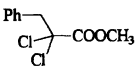
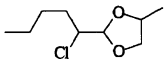
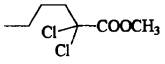
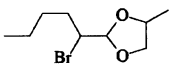
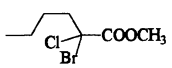
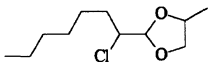
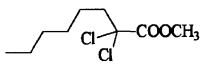
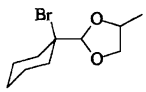
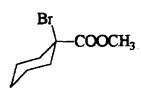
In contrast to 2-chloro aldehyde dimethyl acetals which require a large excess of TCIA,[5] a stoichiometric amount of the reagent was sufficient for these cyclic acetals. According to Scheme 1, all the chlorine atoms of TCIA were recovered in the reaction products, and very small amounts of HCl and Cl_2 developed.[5] Two other features differentiate the behavior of cyclic acetals from open ones: No benzylic chlorination was observed on starting from aromatic substrates (Entry 6), and 2-(1-bromoalkyl)-4-methyl-1,3-dioxolanes (Entries 3, 8, and 10) selectively gave the 2-bromo-2-chloro esters without bromine substitution.

The key step in the process is the formation of 1,3-



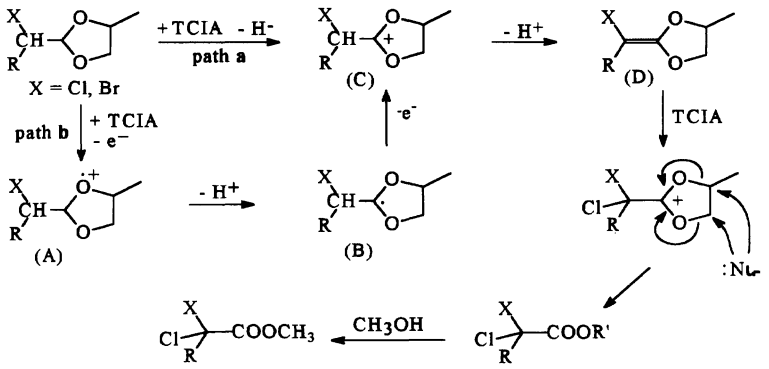
Scheme 1.

Table 2. Preparation of 2,2-Dihalo Carboxylic Acid Methyl Esters by Reaction of 2-(1-Haloalkyl)-4-methyl-1,3-dioxolanes with TCIA

Entry	Substrate	Product	Transesterification method[19]	Yield/%
1			A	90[a]
2			A	92
3			A	93
4			B	89
5			B	93
6			A	90
7			A	95[b]
8			A	95
9			A	93
10			B	94[c]

a) Bp 153—154 °C (Lit, 152 °C, Beil. **2 III**, 469). b) Bp 78—79 °C/0.1 mmHg (Lit, 91 °C/18 mmHg, Synthesis, **1975**, 524). c) Bp 63 °C/0.1 mmHg (Lit, 115—116 °C/19 mmHg, Beil. **9 IV**, 31).

dioxolan-2-ylium cation intermediate **C**. Since no chlorocyclohexane was obtained on using cyclohexane as a substrate, a radical mechanism can be ruled out. Formation of cation **C** may occur according to path **a**, a hydride ion being removed by the reagent, or according to path **b**, where radical cation intermediate **A** is originated through a single electron-transfer mechanism[10] (Scheme 2). Since 2-(1-chloropentyl)-4-methyl-1,3-dioxolane was not transformed by electrochemical oxidation in DMF at 25 °C, and radical cations from acetals are subject to cleavage of the carbon–carbon bond adjacent to the acetal group exclusively,[11] path **a** better rationalizes the results and agrees with the mechanism suggested in ether oxidation by TCIA.[12] 1,3-Dioxolan-



Scheme 2.

2-ylium cation **C**[13] may be immediately attacked at the C-4 or C-5 position by a nucleophile yielding the 2-chloro esters; owing to the steric hindrance of the C-4 methyl group, however, this attack is slow and β-proton elimination occurs giving rise to ketene acetal **D**.[14] Its subsequent chlorination affords a new dioxolanylium ion that eventually produces the 2,2-dihalo esters (Scheme 2).

With respect to the Hell–Volhard–Zelinskii and the 2,2-dichloroacetates alkylation procedures, the reaction described here provides higher yields of 2,2-dichloro carboxylic esters under milder and easier conditions. It is also useful in the preparation of methyl 2-bromo-2-chloro carboxylates. Owing to the low amount of solvent used, the procedure is suitable for large scale preparations.

Experimental

The ^{1}H NMR spectra were recorded on Bruker WP80 and Varian XL200 spectrometers and the MS-Spectra on a GC-MS HP Engine. Substrates, reagents, and solvents were standard grade commercial products, and were used without further purification. The 2-chloro[15] and 2-bromo[16] aldehyde dimethyl acetals were prepared according to well-known procedures.

Preparation of 2-(1-Haloalkyl)-4-methyl-1,3-dioxolane. To a vigorously stirred mixture of $CoCl_2$ (150 mmol) in acetonitrile (300 ml), 2-chloro aldehyde dimethyl acetal (300 mmol), 1,2-propanediol (450 mmol), and chlorotrimethylsilane (300 mmol) were successively added. After 24 h the mixture was diluted with $CHCl_3$ (100 ml) and poured into H_2O (300 ml). The organic phase was separated, and the aqueous layer washed with $CHCl_3$ (2×30 ml). The combined organic phase was dried and neutralized over solid Na_2CO_3, then evaporated at 20—40 mmHg. (1 mmHg=133.322 Pa) Yields were 90—98%. Crude products were purified by distillation.

General Procedure for the Oxidation–Chlorination of 2-(1-Haloalkyl)-4-methyl-1,3-dioxolanes. The reaction must be performed under a hood and behind a safety shield. In a three-necked round bottom flask (50 ml) fitted with a condenser and a thermometer, TCIA (28 mmol) was dissolved in DMF (16 ml). The stirred solution was thermostatted at 5 °C and 2-(1-chloroalkyl)-4-methyl-1,3-dioxolane (40 mmol) was added all at once.[17] Owing to the precipitation of cyanuric acid, the mixture slowly solidified. After 18—24 h it was diluted with 1:1 diethyl ether/petroleum ether (30—50 °C) (25 ml) and water (5 ml), and $Na_2S_2O_5$ was added to reduce the excess oxidant. The solid was filtered off and washed with 1:1 diethyl ether/petroleum ether (2×25 ml). The combined organic phase was washed with H_2O (2×20 ml), dried and neutralized over Na_2CO_3, and concentrated on a rotary evaporator.

Special Cases. *a*) In Entry 1, 41 mmol of TCIA were used; *b*) in the case of 2-(1-bromoalkyl)-4-methyl-1,3-dioxolane, 27 mmol of TCIA for Entries 3 and 8, and 13.5 mmol for entry 10 were used; *c*) with 2-(α-chlorobenzyl)-4-methyl-1,3-dioxolane (Entry 5) the reaction time was 48 h.

General Procedures for Transesterification to Methyl 2,2-Dihalo Carboxylate. Method A. In a 50 ml round bottom flask a mixture of 2,2-dihalo esters (40 mmol) was dissolved in methanol (40 ml) and $ZnCl_2$ (Carlo Erba RPE) (20 mmol)[18] was added. The solution was thermostatted at 40 °C and the reaction monitored by GC. After 24—48 h the mixture was diluted with water (40 ml) and extracted with CH_2Cl_2 (4×20 ml). The organic combined extracts were dried and neutralized over Na_2CO_3 and concentrated on a rotary evaporator. The products were isolated and purified by distillation under reduced pressure.

Method B. In a 50 ml round bottom flask, $LiOCH_3$[19] was prepared by cautious addition of LiH (12 mmol) to CH_3OH (40 ml). When the sparkling stopped, the mixture was thermostatted at 5 °C and the 2,2-dichloro esters (40 mmol) were added all at once. The solution was stirred for 3 h, diluted with CH_2Cl_2 (20 ml), and washed with 2.5% aq HCl solution (40 ml). The aqueous phase was extracted again with CH_2Cl_2 (2×20 ml). The organic extracts were collected, and dried and neutralized over Na_2CO_3. After solvent evaporation, the reaction products were isolated and purified by distillation under reduced pressure.

Special Cases. For a fast reaction time (30—60 min) and high yield transesterification of 2-bromo-2-chloro esters a catalytic amount of $LiOCH_3$ (3 mmol) is needed, otherwise a somewhat unclean reaction take place.

Methyl 2,2-Dichlorobutanoate; bp 73—74 °C (14—15 mmHg). Found: C, 35.10; H, 4.72%. Calcd for $C_5H_8Cl_2O_2$: C, 35.12; H, 4.71%. ^{1}H NMR ($CDCl_3$) δ=1.15 (3H, t, J=8 Hz, $-CH_3$), 2.45 (2H, q, $-CH_2-CCl_2$), and 3.90 (3H, s, $-COOCH_3$). IR (neat) 1750 and 1765 (CO) cm^{-1}. MS (EI, 70 eV) m/z (%) 142/144/146 (11/7/1) [$M^+-C_2H_4$];

111/113/115 (68/46/7) [$M^+-COOCH_3$]; 59 (100).

Methyl 2-Bromo-2-chloropropanoate; bp 69—71 °C (14—15 mmHg). Found: C, 23.84; H, 3.02%. Calcd for $C_4H_6BrClO_2$: C, 23.85; H, 3.00%. ^1H NMR ($CDCl_3$) $\delta=$ 2.48 (3H, s, CH_3–CClBr), and 3.90 (3H, s, –$COOCH_3$). IR (neat) 1750 and 1760 (CO) cm^{-1}. MS (EI, 70 eV) m/z (%) 141/143/145 (48/64/16) [$M^+-COOCH_3$]; 121/123 (100/30) [M^+-Br].

Methyl 2,2-Dichloro-3-methylbutanoate; bp 39—41 °C (0.1 mmHg). Found: C, 38.92; H, 5.48%. Calcd for $C_6H_{10}Cl_2O_2$: C, 38.94; H, 5.45%. ^1H NMR ($CDCl_3$) δ=1.15 (6H, d, J=7 Hz, 2×–CH_3), 2.45—3.00 (1H, m, –CH–CCl_2), and 3.90 (3H, s, –$COOCH_3$). IR (neat) 1755 and 1770 (CO) cm^{-1}. MS (EI, 70 eV) m/z (%) 142/144/146 (100/64/10) [$M^+-C_3H_6$]; 125/127/129 (22/18/5) [$M^+-COOCH_3$].

Methyl 2,2-Dichloro-2-phenylacetate; bp 97—98 °C (0.1 mmHg). Found: C, 49.39; H, 3.70%. Calcd for $C_9H_8Cl_2O_2$: C, 49.35; H, 3.68%. ^1H NMR ($CDCl_3$) $\delta=3.90$ (3H, s, $-COOCH_3$), and 7.30—7.90 (5H, m, $-C_6H_5$). IR (neat) 1765 (CO) cm^{-1}. MS (EI, 70 eV) m/z (%) 218/220/222 (17/11/2) [M^+]; 159/161/163 (100/64/10) [$M^+-COOCH_3$].

Methyl 2,2-Dichloro-3-phenylpropanoate; bp 104—105 °C (0.1 mmHg). Found: C, 51.51; H, 4.35%. Calcd for $C_{10}H_{10}Cl_2O_2$: C, 51.53; H, 4.32%. ^1H NMR ($CDCl_3$) $\delta=3.75$ (2H, s, $-CH_2-CCl_2$), 3.90 (3H, s, –$COOCH_3$), and 7.35 (5H, bs, $-C_6H_5$). IR (neat) 1750 and 1770 (CO) cm^{-1}. MS (EI, 70 eV) m/z (%) 197/199 (12/4) [M^+-Cl]; 91 (100).

Methyl 2-Bromo-2-chlorohexanoate; bp 61—62 °C (0.1 mmHg). Found: C, 34.50; H, 5.01%. Calcd for $C_7H_{12}BrClO_2$: C, 34.52; H, 4.97%. ^1H NMR ($CDCl_3$) δ=0.80—1.10 (3H, t, J=6 Hz, CH_3–C), 1.20—1.80 (4H, m, C–$(CH_2)_2$–C), 2.40—2.65 (2H, m, –CH_2–CClBr–), and 3.90 (3H, s, –$COOCH_3$). IR (neat) 1750 and 1760 (CO) cm^{-1}. MS (EI, 70 eV) m/z (%) 186/188/190 (31/41/10) [$M^+-C_4H_8$]; 127 (100) [$M^+-Br-HCl$].

Methyl 2,2-Dichlorooctanoate; bp 78—79 °C (14—15 mmHg). Found: C, 47.62; H, 7.11%. Calcd for $C_9H_{16}Cl_2O_2$: C, 47.59; H, 7.10%. ^1H NMR ($CDCl_3$) $\delta=$ 0.75—1.10 (3H, t, J=5 Hz, CH_3–C), 1.10—1.75 (8H, m, –C–$(CH_2)_4$–C), 2.30—2.60 (2H, m, –CH_2–CCl_2), and 3.90 (3H, s, –$COOCH_3$). IR (neat) 1755 and 1770 (CO) cm^{-1}. MS (EI, 70 eV) m/z (%) 142/144/146 (100/63/10) [$M^+-C_6H_{12}$].

Reaction of 2-(1-Chloropentyl)-4-methyl-1,3-dioxolane with Cl_2. In a 50 ml two-necked round bottom flask fitted with a thermometer, 2-(1-chloropentyl)-4-methyl-1,3-dioxolane (20 mmol) was dissolved in DMF. The stirred solution was thermostatted at 5 °C and bubbled with Cl_2 until a yellow color developed. After 20 h Cl_2 was added again and, after other 4 h, the reaction was worked up. Conversion was very low, ca. 5%, and a small amount of 2,2-dichloro esters (2%) was accompanied by an unidentified product (3%).

Electrochemical Oxidation of 2-(1-Chloropentyl)-4-methyl-1,3-dioxolane. Cyclic voltammetry was performed using a Potentiostat Galvanostat PAR 270 A. Electrochemical measurements, at scan rates of between 0.02—20 V/s, were carried out at room temperature in DMF containing 0.002 M (1 M=1 mol dm^{-3}) 2-(1-chloropentyl)-4-methyl-1,3-dioxolane, and 0.1 M tetrabutylammonium perchlorate as the supporting electrolyte. Hanging mercury, platinum ring, and Ag/AgCl/$NaCl_{sat}$ electrodes were used as work, counter, and reference electrodes respectively. While the potential was increased until solvent discharge, no acetal oxidation was observed.

We thank the C.N.R. (Rome) and the Ministero della Università e della Ricerca Scientifica e Tecnologica for financial assistance.

References

1) J. Villieras, P. Perriot, M. Bourgain, and J.-F. Normant, *Synthesis*, **1975**, 533.

2) G. Darzens and G. Levy, *Compt. Rend.*, **24**, 272 (1937); J. Villieras, B. Castro, and M. N. N. Ferracutti, *Bull. Soc. Chim. Fr.*, **1970**, 1450.

3) J. Villieras, J. R. Disnar, P. Perriot, and J.-F. Normant, *Synthesis*, **1975**, 524.

4) R. Stroh, in "Houben-Weil," Georg Thieme Verlag, Stuttgart (1962), Vol. V/3, p. 624.

5) F. Bellesia, M. Boni, F. Ghelfi, and U. M. Pagnoni, *Bull. Chem. Soc. Jpn.*, **67**, 136 (1994).

6) J. Gelas and S. Michaud, *Bull. Soc. Chim. Fr.*, **1972**, 2444.

7) S. D. Venkataramu, J. H. Cleveland, and D. E. Pearson, *J. Org. Chem.*, **44**, 3082 (1979).

8) J. Gelas and D. Petrequin, *Carbohydr. Res.*, **36**, 227 (1974).

9) The monitoring of the 2-(1-chloropentyl)-4-methyl-1,3-dioxolane transformation also showed that the conversion was at 85% after about 6 h, and suggested that the substrate is directly transformed into the final products, as no intermediate was detected.

10) An article appeared recently about the use of *N*-bromosuccinimide as an electrontransfer oxidant: E. Lennart, *Pure Appl. Chem.*, **63**, 205 (1991).

11) S. Steenken and R. A McClelland, *J. Am. Chem. Soc.*, **111**, 4967 (1989); M. Mella, E. Fasani, and A. Albini, *J. Org. Chem.*, **57**, 3051 (1992).

12) L. S. Boguslavskaya, A. V. Kartashov, and N. N. Chuvatkin, *Russ. Chem. Rev.*, **59**, 501 (1990).

13) For a review on the chemistry of 1,3-dioxolan-2-ylium cations see: C. U. Pittman, S. P. McManus, and J. W. Larsen, *Chem. Rev.*, **72**, 357 (1972). See also: S. Hünig, *Angew. Chem., Int. Ed. Engl.*, **3**, 548 (1964).

14) S. M. McElvain and W. R. Davie, *J. Am. Chem. Soc.*, **74**, 1816 (1952); H. Gross, J. Freiberg, and B. Costisella, *Chem. Ber.*, **101**, 1250 (1968).

15) F. Bellesia, M. Boni, F. Ghelfi, R. Grandi, U. M. Pagnoni, and A. Pinetti, *Tetrahedron*, **48**, 4579 (1992); M. Boni, F. Ghelfi, U. M. Pagnoni, and A. Pinetti, *Synth. Commun.*, **1993**, 1915.

16) F. Bellesia, M. Boni, F. Ghelfi, and U. M. Pagnoni, *Gazz. Chim. Ital.*, **123**, 629 (1993).

17) If reaction mixture thermostatting is not efficient enough, the temperature rises and an extremely exothermic and dangerous reaction takes place at 35—40 °C. For larger scale preparations (40—300 mmol), thermostatting at −10 °C and drop by drop substrate addition are required to ensure that the temperature does not exceed 5 °C.

18) The transesterification under acid catalysis gave good

results only with $ZnCl_2$; other catalysts such as HBr, chlorotrimethylsilane, *p*-toluenesulfonic acid, $FeCl_3$, BF_3, and $TiCl_4$ gave poor conversions.

19) For Entries, 4, 5, and 10, transesterification with method B was preferable, since unsatisfactory results were obtained with method A.