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Methyl α,α-Dichloro-Esters by Oxidation-Chlorination of Cyclic Acetals with Trichloroisocyanuric Acid.

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Abstract: Methyl α-chloro- or α,α-dichloro-esters are obtained in excellent yields by oxidation chlorination of 2-alkyl-4,5-dimethyl-1,3-dioxolanes with trichloroisocyanuric acid.

Esters of α,α-dichloro-carboxylic acids are useful intermediates in the preparation of α-chloro-esters[1] and of glycidic esters,[2,3] through the Darzens reaction. General procedures for the synthesis of these dihaloesters have been till now limited to the alkylation of dichloroacetates[3] and to the Hell-Volhard-Zelinskii chlorination of carboxylic acids.[5] However, the former method, though being more versatile, follows a very complicated procedure and the second one uses drastic reaction conditions. A preparation of α,α-dihaloesters by halogenation of ketene thioacetals has been also reported, but without experimental details and yields.[5]

Recently, we set up an effective and practical synthetic route to methyl α,α-dihaloesters through a simultaneous oxidation-chlorination of 2-(1-chloroalkyl)-4-methyl-1,3-dioxolanes with trichloroisocyanuric acid (TCIA) in dimethylformamide (DMF) under mild conditions.[6]

Though α-chloro-acetals are easily prepared,[7] a more straight and appealing procedure to methyl α-chloro- or α,α-dichloro-esters would start from simple acetals, by-passing the α-chloro-acetals preparation step. As far as we know, the formation of small amounts of α-halo- and α,α-dihalo-esters has been observed only in a few examples of cyclic acetal oxidation with NBS[8] or TCIA,[9] the simple esters being the main products. Now we report that excellent yields of α,α-dichloro-esters can be easily obtained on treating 2-alkyl-4,5-dimethyl-1,3-dioxolanes with TCIA in DMF.

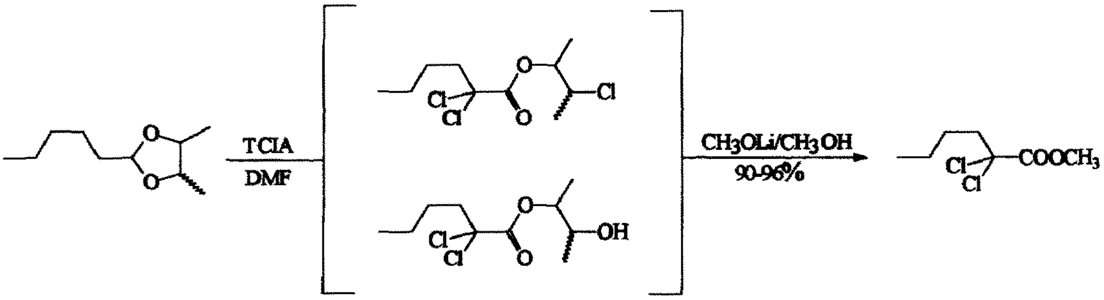
Since a mixture of α,α-dichloro-esters is generated in these transformations (see figure), we preferred to proceed by a transesterification with methanol, to isolate the α,α-dichloro-carboxylic acids as methylesters.

Early trials of oxidation-chlorination with TCIA on some hexanal cyclic acetals showed a marked steric effect on the course of the reaction.[10] When just one alkyl group at the C-4 position of the dioxolane ring (entries 1 and 2) is indeed present, the formation of the α,α-dichloro-ester occurs together with a small amount of simple ester; when instead both C-4 and C-5 positions are alkylated, the transformation to α,α-dichloro-ester is complete (entries 3, 4, 5 and 6.).

The reaction is strongly exothermic and a temperature control is strictly required to avoid a violent and dangerous overheating. The best procedure is to drop the acetal in the reaction flask thermostatted at -10 °C, so that the internal temperature does not exceed +5 °C.

A number of acetals afford very excellent yields of methyl α,α-dihalo-esters (Table) by this oxidation-chlorination procedure. Substrates carrying only one hydrogen atom at the carbon adjacent to the acetalic function (entries 8 and 9) give α-chloro-esters.

Being not attacked by TCIA under the reaction conditions, both esters and α-chloro-esters are ruled out as intermediates in these cyclic acetal transformations.[8]



Figure

As already suggested in our previous work,[6] the key step in the process is the formation of a fleeting dioxenium ion by hydride abstraction promoted by the protonated TCIA.[11] The ring of the 1,3-dioxolan-2-ylium cation[12] is usually opened by a nucleophile at C-4 or C-5 position; however, when these positions are sterically hindered,[10] the life of the cation becomes so long that a β-proton elimination to ketene acetal[13] is preferred. This latter compound may be readily chlorinated giving rise to a new dioxenium ion which, by a β-hydrogen elimination and a subsequent chlorination, affords the α,α-dichloro-ester.

The here described procedure from cyclic acetals provides α,α-dichloro-esters easily and with significantly higher yields than any previously reported method;[3,5] owing to the low amounts of solvent used, it is also suitable to be scaled up to large preparations.

EXPERIMENTAL

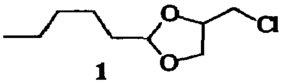
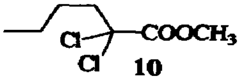
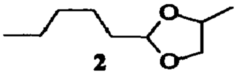
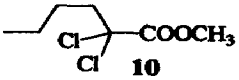
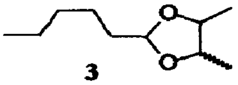
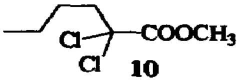
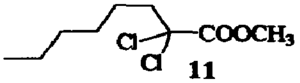
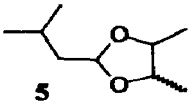
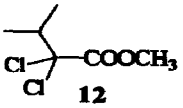
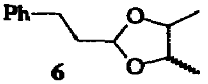
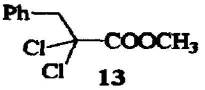
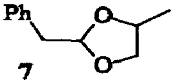
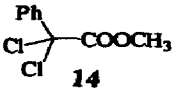
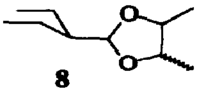
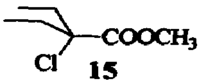
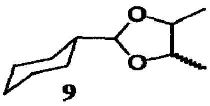
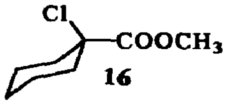
Substrates, reagents and solvents are standard grade commercial products, and were used without further purification. The dimethylacetals were prepared according to reported procedures.[6]

General procedure for the oxidation-chlorination of 2-alkyl-4,5-dimethyl-1,3-dioxolanes with TCIA.- *The reaction must be performed under a hood and behind a safety shield.* In a three-necked round bottom flask (100 mL) fitted with a condenser, a dropping funnel and a thermometer, TCIA (97%, 20,12g, 84 mmol) was dissolved in DMF (40 mL). The stirred solution was thermostatted at -10 °C and the 2-alkyl-4,5-dimethyl-1,3-dioxolane (80 mmol) added dropwise so that temperature did not exceeded +5 °C. Owing to cyanuric acid precipitation, the mixture slowly became semi-solid. The mixture was left at +5 °C for 18-24 h and then diluted with 1:1 diethyl ether/petroleum ether (30-50 °C) (25 mL) and H_2O (5 mL); $Na_2S_2O_5$ was slowly added till complete depletion of the oxidizing power. The solid was filtered off and washed with 1:1 diethyl ether/petroleum ether (30-50 °C) (2 x 35 mL). The collected organic phases were washed with H_2O (2 x 20 mL), dried and neutralized over solid Na_2CO_3, and concentrated on a rotary evaporator.

Special cases.- a) in the case of 2-benzyl-4-methyl-1,3-dioxolane (entry 7) the reaction time was 48 h; b) in the case of 2-(pent-3-yl)-4,5-dimethyl-1,3-dioxolane (entry 8) and 2-cyclohexan-4,5-dimethyl-1,3-dioxolane (entry 9) 56 mmoles of TCIA were used.

General procedure for the transesterification to methyl α,α-dichloro-esters.- In a 100 mL round bottom flask, $LiOCH_3$ was prepared by cautiously adding LiH (24 mmol) to CH_3OH (80 mL). When effervescence ended, the mixture was thermostatted at +5 °C and the α,α-dihalo-esters (80 mmol) were added all at once. The solution was stirred for 3 h and then diluted with CH_2Cl_2 (40 mL) and washed with aq. 2.5 % HCl solution (80 mL). The aqueous phase was extracted again with CH_2Cl_2 (2 x 20 mL). The organic extracts were collected, dried and neutralized over solid Na_2CO_3. After solvent evaporation, the reaction products

TABLE: Preparation of α-Chloro- or α,α-Dichloro-Methyl-Esters by Reaction of Cyclic Acetals with TCIA

Entry	Substrate	Product	Yield[a] %
1	 1	 10	84 (7)
2	 2	 10	88 (7)
3	 3	 10	96
4	 4	 11	94
5	 5	 12	90
6	 6	 13	94
7	 7	 14	95
8	 8	 15	76[b]
9	 9	 16	95

a) In parenthesis the yields of unchlorinated ester are reported.
b) 17% of recovered untransesterified 3-chloro-(but-2-yl) 2-chloro-2-ethylbutanoate.

were isolated and purified by distillation under reduced pressure. They were compared by GC-MS with authentic samples prepared by a different route.[6]

Special case.- For the transesterification to methyl 2-chloro-2-ethylbutanoate a stoichiometric amount of $LiOCH_3$ was used and the reaction worked-up after 36 h.

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