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Chlorotrimethylsilane: A Suitable Reagent for the Synthesis of Chlorohydrin Esters

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A new methodology for obtaining chlorohydrin esters using a one-pot esterification−chlorination reaction, in which one of the reagents, chlorotrimethylsilane, acts as solvent, is described. The reaction is stereospecific and its regioselectivity depends on the number of carbons between the hydroxyl groups present in the starting material. A mechanism is proposed.

Introduction

The selective transformation of diols is always a challenging task for a chemist, and many chemical and enzymatic methodologies have been developed to date.[1] For instance, their transformation to monoesters has been used as a strategy for preparing highly stereoisomerically pure compounds using lipase as a tool.[2] Considering that in this approach the ee of the desired stereoisomer is usually improved using long acyl chains,[3] we planned to expand our previously described chlorotrimethylsilane (CTMS) method[4] for the formation of fatty monoesters of diols, as a previous step to studying their lipase hydrolysis.

During our attempts using 2,3-butanediol and methyl palmitate, we found a secondary compound that was identified as 3-chloro-2-butyl palmitate. To the best of our knowledge, this type of combined reaction in the presence of CTMS, producing chlorohydrin esters is unprecedented. Chlorohydrin esters have been used in the preparation of drugs,[5] surfactants,[6] epoxides,[7] and epichlorohydrins.[8] Methodologies for preparing these esters include (a) esterification of either chloro alcohols with different acylating agents[6,9] or diols with acyl chlorides,[10] (b) reaction of diol monoesters with dry HCl,[11] (c) cleavage of ethers and epoxides using different reagents;[12] (d) cleavage of cyclic ketal acids with phosphorus pentachloride,[13] thionyl chloride[14] or pivaloyl chloride,[15] and (e) cleavage of cyclic ortho esters with either trityl chloride[16] or CTMS.[7] Whereas most of these methodologies are only applicable for preparing β- or γ-chlorohydrin esters, a few of them can be used to prepare δ- or ϵ-chlorohydrin esters.[17] Moreover, only one of these methodologies does not require a solvent to carry out the reaction.[12b]

All of the facts described above prompted us to investigate further the desymmetrization of 2,3-butanediol using CTMS as a reagent and the scope of this methodology for preparing different halohydrin esters (Scheme 1).

Results and Discussion

Initially, the influence of the amount of commercial diastereomeric mixture of 2,3-butanediol (**1a**−**c**) was studied. As expected, the increase of diol concentration from equimolar to 5-fold molar excess caused an increase in 3-chloro-2-butyl palmitate formation (diastereomeric

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SCHEME 1. Strategy for the Synthesis of Chlorohydrin Esters

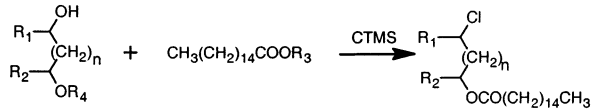
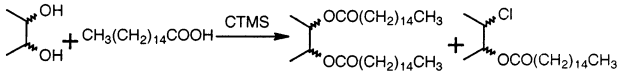


TABLE 1. Influence of the Amount of Commercial Diastereomeric Mixture of 2,3-Butanediol When Palmitic Acid Was Used



entry	1:3	**10a−d** (yield %)[a]
1	1	91 (71%)[b]
2	2	99
3	3	99 (51%)[c]
4	4	80
5	5	89

[a] Determined by GC. Mixture of diastereomers t_R = 24.18 and 24.03 min. [b] Isolated yield after column chromatography purification. [c] Isolated yield after crystallization, mp 29−34 °C.

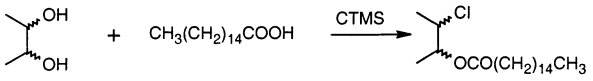
mixture, **10a−d**) from 55 to 99% yields. No differences were observed by GC between the area ratio of the two chromatographic peaks, each corresponding to the expected racemates (results not shown).

In our attempts to improve our yields for the diol, we planned to use palmitic acid instead of the corresponding methyl ester. Esterification of alcohols using carboxylic acids and CTMS had previously been described by Nakao et al.[18] Moreover, palmitic acid could easily be separated from the halohydrin ester by sodium bicarbonate washing. Table 1 shows the results obtained when palmitic acid and different amounts of the diol were used. In this case, a small spot was detected by TLC below the spot corresponding to **10a−d**. Its intensity decreases rapidly from the 1:3 ratio onward. This byproduct was identified by NMR as the diester, **11a−c**.

Our interest was then focused on studying the stereospecificity of this reaction. Thus, D-(−)-2,3-butanediol (**10b**) and *meso*-2,3-butanediol (**10c**) were treated with palmitic acid and CTMS (Table 2), and the corresponding chlorohydrin esters were analyzed by NMR and GC prior to SiO_2 column purification. Both techniques showed that each butanediol yielded one of the two possible racemates. Moreover, when the chlorohydrin ester from D-(−)-2,3-butanediol was injected into an optical rotation (OR) HPLC detector, the angle of rotation obtained was clockwise. Both results, one chromatographic peak and the presence of optical rotation, could indicate that D-(−)-2,3-butanediol (**10b**) produced a single compound. This result is in accordance with those described when either a corresponding cyclic α-ketal acid was opened using phosphorus pentachloride[13] or its cyclic orthoacetate was opened using trityl chloride.[14]

Finally, the developed methodology was applied to a set of different substrates to determine its regioselectivity and scope (Table 3). When 1,2-diols with a primary

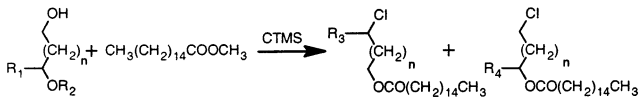
TABLE 2.



Compound	yield, % (Products)[a]
1b: 	87 (**10b**)
1c: 	81 (**10c+10d**)

[a] Isolated yields after column chromatography purification. Only one chromatographic peak was observed by GC in each experiment on the crude product. t_R = 24.02 min for **10b** and 24.16 min for **10c−d** racemate. Reactions were carried out using a 2.5 molar excess of the corresponding alcohol.

TABLE 3.



compd **4**			products				
4a−i	R_1	R_2	R_3	R_4	n	12:13[a]	yield (%)[b]
4a	H	H	H		0		60 (**12a**)
4b	H	H	H		2		60 (**12b**)
4c	H	H	H		4		88 (**12c**)
4d	CH_3	H	CH_3	H	0	0.10	92 (**12d** + **13d**)
4e	C_2H_5	H	C_2H_5	H	0	<0.04	94 (**12e** + **13e**)
4f	CH_3	H	CH_3	H	1	0.33	88 (**12f** + **13f**)
4g	CH_3	H	CH_3	H	2	1.08	69 (**12g** + **13g**)
4h	CH_3	H	CH_3	H	3	5.25	74 (**12h** + **13h**)
4i	$OC(CH_3)_2$			CH_2Cl	0		69 (**13i**)[c]

[a] Primary position versus secondary one. Determined by integration of the GC chromatogram of the crude products. [b] Isolated yields after column chromatography purification. Reactions were carried out using methyl palmitate and a 5-fold molar excess of the corresponding alcohol. [c] Yield after crystallization, mp 32−33 °C.

hydroxyl function were used (**4d** and **4e**), halohydrin esters with the chlorine atom in the primary position (**13d** and **13e**) were mainly obtained. The other regioisomers (**12d** and **12e**) were present in amounts below 10%. 1,3-Butanediol (**4f**) produced halohydrin ester with the chlorine atom in the primary position (**13f**) as the major compound. The other regioisomer (**12f**) was present now to the extent of about 25%. Subsequently, 1,4-pentanediol (**4g**) produced both chlorohydrin ester regioisomers (**12g** and **13g**) in a 1:1 proportion and 1,5-hexanediol (**4h**) produced mainly the ester presenting the chlorine atom in the secondary position (**12h**). 1,2-Ethanediol (**4a**), 1,4-butanediol (**4b**), and 1,6-hexanediol (**4c**) produced the corresponding halohydrin esters (**12a−c**). Finally, 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (**4i**) produced 1,3-dichloro-2-propyl palmitate (**13i**). In this case, neither the 2,3-dichloro isomer nor the dipalmitoyl chloropropanes were detected.[19]

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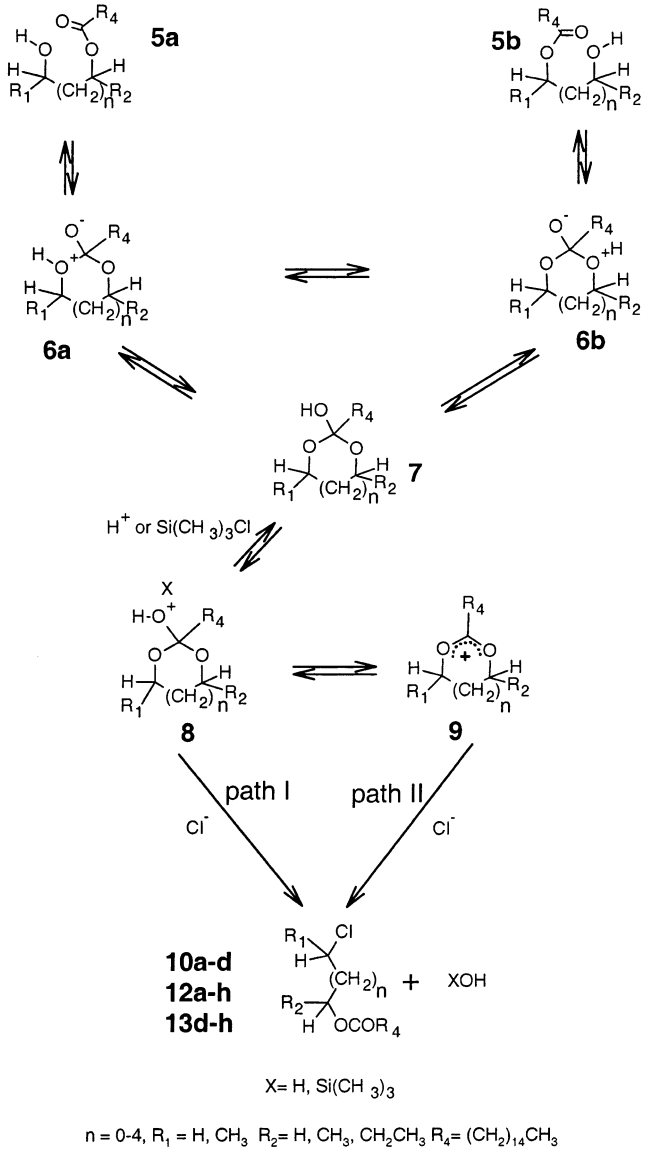
To study some aspects of the mechanism of this transformation, two different reactions were carried out using methyl palmitate and either 2,3-butanediol or 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane as reagents. Their progress was followed by GC/MS. The formation and then the gradual decline of the two chromatographic peaks were observed in each case. These chromatographic peaks were different from the ones corresponding to the putative halohydrin esters, which arose as the reaction time increased. When 2,3-butanediol was used, the two chromatographic peaks produced an *m*/*z* of 284, corresponding to the M^+ of each diastereomeric monoester. Two chromatographic peaks were also detected when 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane was used. Both showed an *m*/*z* of 355, which can be assigned to the $[M - 15]^+$ of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl palmitate or 2,2-dimethyl-1,3-dioxan-5-yl palmitate. The identity of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl palmitate was confirmed by comparison with a sample obtained by a literature method.[20] Finally, 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane was treated with CTMS without the presence of either palmitic acid or methyl palmitate. After 72 h, the alcohol was recovered almost unaltered. The putative chloro derivatives were only detected in a very small amount by GC/MS, showing that CTMS alone can only cause hydroxyl substitution and ring opening to a very slight extent. Snyder[21] has already demonstrated that CTMS can only result in substitution of primary and tertiary hydroxyls if DMSO is present. Secondary alcohols were not transformed to secondary chloro derivatives under the same conditions. Thus, the assistance of the ester seems necessary to produce the chlorohydrin esters. The need for similar assistance has already been proposed by several authors to explain similar processes.[11,17,22]

A feasible mechanism for this one-pot esterification−chlorination is outlined in Scheme 2. Although we have already noted that the esterification rate of primary alcohols was higher than that of the secondary ones under these conditions,[4] diols could be transformed into both monoesters (**5a** and **5b**) followed by the formation of a dioxygenated ring (**6a** and **6b**), similar to those proposed by several authors.[7,14,16,17] These intermediates, in equilibrium with the open hydroxyesters, can tautomerize to **7**. Compound **7** could produce **8**, favored by the presence in the medium of protons or CTMS. Then, either the intermediate **8** (path I) or the resulting 1,3-dioxo-2-ylium cation **9** (path II) could react with chloride ions present in the medium through a nucleophilic opening process similar to the one proposed by several authors.[7,14,16] This chloride attack would produce the corresponding chlorohydrin ester (**10**, **12**, or **13**) bringing the reaction to completion. This mechanism could explain why an epimerization process was not observed when D-(−)-2,3-butanediol (**10b**) was used as the substrate for this reaction.

Kolb and Sharpless[7] have already shown that when 1,3-dioxolan-2-ylium intermediates are formed, chloride ions will prefer primary carbons if they are present. Indeed, 1,2-propanediol and 1,2-butanediol form mainly

SCHEME 2



1-chloro-2-alkyl palmitates. However, 1,3-butanediol produced a 3:1 mixture of 4-chloro-2-butyl and 3-chlorobutyl palmitate isomers. As the ring size increases, chloride preference for the primary position decreases and, finally, for 1,5-diols, chloride shows a clear preference for the secondary position. Although steric hindrance phenomena could be invoked to explain the differences observed between 1,2-propanediol and 1,2-butanediol, this explanation does not seem conceivable for the progressive change found in the regioselectivity. We assume that inductive and conformational effects are likely to be present. Thus, the charge density of carbons supporting oxygen atoms could hardly be influenced by the alkyl group in 1,2-diols. This effect would tend to equalize as the separation between the two hydroxyls increases.[23] Moreover, as the ring size increases, both intermediates **8** and **9** become more flexible, so more conformational states with similar energy could be present. Then, the probability of the chloride ion approaching correctly to

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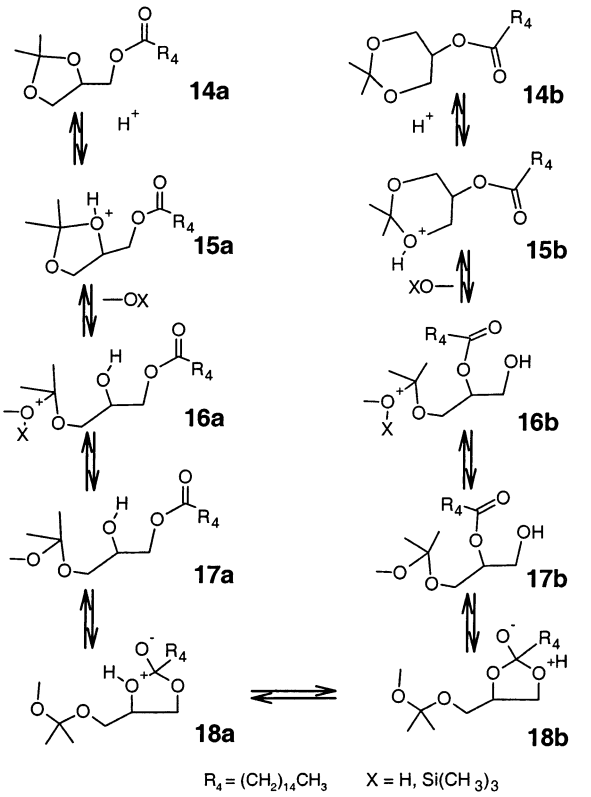
SCHEME 3



the secondary position could increase. Consequently, the primary ester would be predominant for 1,5-diols. In our opinion, the alternative direct palmitoyloxy substitution by chloride ion[24] does not seem conceivable. If it were so, the excess of CTMS should always cause equivalent substitutions whatever the initial substrate was.

When 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane is used, the formation of 1,3-dichloro-2-propyl palmitate (**13i**) could be explained by a similar mechanism involving a double dioxolane formation. Ketal opening would be favored by the presence of protons in the medium and the methoxide group, either free or bonded to trimethylsilane (Scheme 3). The presence of **14b** detected by GC/MS could be due to the tautomerization of **18a** to **18b**. Then, **18b** could produce **14b** through successive equilibria (Scheme 3).

In summary, we have developed a promising methodology for obtaining chlorohydrin esters from commercial substances using a one-pot esterification−chlorination reaction, in which one of the reagents, chlorotrimethylsilane, acts as a solvent. The reaction is stereospecific and its regioselectivity depends on the distance between the two hydroxyl groups. We have shown that the described reaction can be carried out with diols separated by up to six carbons. The influence of the alcohol concentration has also been studied. The application of this methodology as the starting step in the synthesis of chiral chlorohydrins to be used as building blocks is underway. The usefulness of other trimethylsilane derivatives in similar reactions is also underway. Both studies will be reported in due course.

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Experimental Section

General Methods. All reactions were carried out in screw cap vials with a Teflon-faced rubber liner under the pressure generated by the system. The vials were heated using an aluminum block. A 12-place carousel aluminum reaction station with reflux head and a syringe pump were used when CTMS was continuously added. All reagents were commercially available and were used as received. Chromatographic analyses (GLC) were carried out with a capillary column (30 m × 0.25 mm diameter, 0.25 μm film thickness) unless otherwise noted. Hydrogen (0.5 mL/min) was used as carrier gas. $T_{injector}$ = 275 °C, $T_{detector}$ = 300 °C, T_{column} = 50 °C (1 min), 50−250 °C (10 °C/min), and 250 °C (10 min); t_R values are given in min under these conditions, unless otherwise noted.

General Procedure Using Methyl Palmitate. Chlorotrimethylsilane (1.5 mL, 13.2 mmol) was continuously added for 2 h to a stirred solution of methyl palmitate (420 mg, 1.56 mmol) and the corresponding alcohol (1.56 to 7.78 mmol) at 80 °C. The reaction mixture was stirred at 80 °C for 48 h, quenched with saturated sodium bicarbonate solution, and then extracted with hexane. The combined organic extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo to give the chlorohydrin ester product. When indicated, the residue was purified by column chromatography (silica gel H60, hexane/ethyl acetate) or by crystallization (hot ethanol 200 mg/mL) to yield the expected compounds. Yields corresponding to compounds are included in Tables 1 and 4. Spectroscopic and analytical data are included as Supporting Information.

General Procedure Using Palmitic Acid. Chlorotrimethylsilane (1.5 mL, 13.2 mmol) was added by aliquots to a stirred solution of palmitic acid (400 mg, 1.56 mmol) and the corresponding alcohol (1.56 to 7.78 mmol). First, 100 μL of CTMS was added in four equivalent portions over a 2-h period. During this period the reaction mixture was stirred at 80 °C, and cooled each time CTMS was added. The remaining CTMS was then added as a single aliquot. The reaction mixture was stirred at 80 °C for 24 h, quenched with saturated sodium bicarbonate solution, and then extracted with hexane. The organic extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo to give the chlorohydrin ester product. When indicated, the residue was purified either by column chromatography (silica gel H60, hexane/ethyl acetate) or by crystallization (hot ethanol 200 mg/mL) to yield the expected compounds. Yields corresponding to compounds are shown in Tables 2 and 3. Spectroscopic and analytical data are included as Supporting Information.

Procedure for Determining the Capability of CTMS To React with Alcohols. Chlorotrimethylsilane (2 mL, 17.6 mmol) was added by aliquots to the 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (264 mg, 2.0 mmol). First, 100 μL of CTMS was added in four equivalent portions over 2 h. During this period, the reaction mixture was stirred at 80 °C and cooled each time CTMS was added. The remaining CTMS was then added as a single aliquot. The reaction mixture was stirred at 80 °C for 72 h, quenched with saturated sodium bicarbonate solution, and then extracted with ethyl acetate. The organic extract was dried over $MgSO_4$ and analyzed by GC/MS.

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Supporting Information Available: Analytical and spectroscopic data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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