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Glycerol as a starting material to prepare palmitate derivatives

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Glicerol com a material de partida per a la preparació de derivats de l'àcid palmític

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In memoriam of Professor J.J. Bonet

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RESUMEN

A partir de glicerol, y mediante un proceso en dos pasos, se ha sintetizado palmitato de glicidilo, intermedio empleado en la preparación de monoglicéridos de alta pureza. El primer paso de la síntesis consiste en una doble reacción esterificación-clorinación del glicerol. Mediante Cs_2CO_3 se produce una reacción de eliminación sobre el intermedio obtenido, de manera que se obtiene el correspondiente palmitato de glicidilo.

Key words: **Bioproceso. Biotecnología. Esteres de clorohidrinas. Esteres de glicidilo. Compuestos halogenados. Derivados de ácido. Química sostenible.**

SUMMARY

Glycidyl palmitate, used to obtain high purity monoglycerides and epoxy resins, can be obtained from glycerol using a two-step process. The first step of this new approach consists in a reaction of esterification-chlorination of glycerol. An elimination reaction using Cs_2CO_3 allows the corresponding glycidyl ester to be prepared from the chlorohydrin ester intermediate.

Key words: **Bioprocess. Biotechnology. Chlorohydrin esters. Glycidyl esters. Halogen compounds. Acid derivatives. Sustainable chemistry.**

RESUM

Emprant glicerol, i gràcies a un procés en dos passos, s'ha sintetitzat palmitat de glicidil, intermedi emprat en la preparació de monoglicèrids d'alta puresa. El primer pas de la síntesi consisteix en una doble reacció d'esterificación-clorinació del glicerol. Quan l'intermedi obtingut es tracta amb Cs_2CO_3 es provoca una reacció d'eliminació, de manera que s'obté el corresponent palmitat de glicidil.

Mots clau: **Bioprocés. Biotecnologia. Esters de clorohidrines. Esters de glicidil. Compostos halogenats. Derivats d'àcid. Química sostenible.**

INTRODUCTION

Rising petroleum prices and environmental considerations have restored interest in the use of biomass as a primary source for the chemical industry[(1)]. Oils and fats of vegetable and animal origin make up the greatest percentage of

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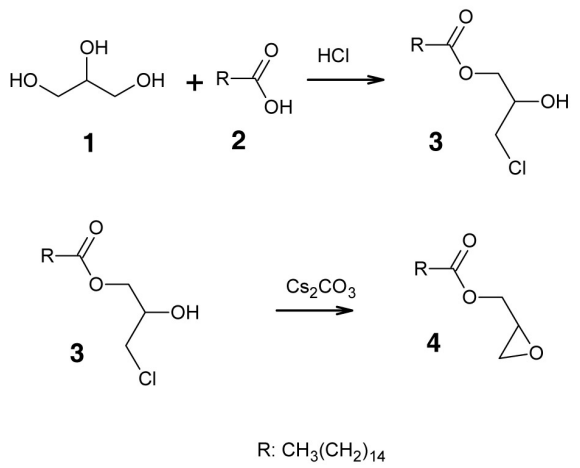
the current consumption of renewable raw materials in the chemical industry, since they offer a large number of possibilities for application[2]. Recently, interest in vegetable oils has increased because they constitute the raw material for the biodiesel industry. One of the by-products of this industry is glycerol, which already has many applications. However, the expected increase in biodiesel production is stimulating research to find new industrial applications for glycerol[3]. In this context, our group has adopted new approaches based on the transformation of this polyol into halohydrin esters. Synthetic methods for obtaining these products include chloroalcohol esterification with several different acylating agents[4] and ring opening of cyclic ortoesters with several reactants[5]. Most of these methods have only been used to prepare α,β– or α,γ-chlorohydrin esters, but α,δ or α,ε-chlorohydrin esters have also been prepared[6]. In turn, halohydrin esters can be transformed into medicines[7], food additives[8], surfactants[9], epichlorohydrins[10] and other epoxides[11]. Preparation of glycidyl esters is a central matter of interest in several industrial processes, such as the production of high-purity monoglycerides and epoxy resins[12]. However, direct synthesis of these esters from glycidol is under discussion due to the high toxicity of this compound. At present, this problem is avoided using Epikote 1004 , a epoxy resin produced from bisphenol A and epichlorohydrin, which is normally used in a 12:1 relationship to the acid[13].

Herein, we report the transformation of glycerol (**1**) to 3-chloro-2-hydroxypropyl palmitate (**3**). Chlorohydrin fatty ester formation has been identified in small amounts during the hydrochloric acid hydrolysis of acylglycerides[14]. Recently, we reported a similar reaction using different carboxylic acids, chlorotrimethylsilane and polyols[15, 16]. Compound **3** can subsequently be converted to glycidyl palmitate (**4**) using an appropriate basic reagent (Scheme 1).



Scheme 1. Transformation of glycerol into glycidyl esters.

MATERIAL AND METHODS

General. NMR spectra were recorded on a VARIAN 400 spectrometer (400 MHz for ^{1}H, and 100 MHz for ^{13}C). Chemical shifts are reported in delta units (δ), parts per million (ppm) relative to the singlet at 7.26 ppm of $CDCl_3$ for ^{1}H and to the center line of a triplet at 77.00 ppm for ^{13}C NMR. The following abbreviations are used: s: singlet, d: doublet, t: triplet, q: quartet, quin: quintuplet, m: multiplet. GC-MS were performed in an Agilent Technologies 6890N equipped with a DB5-MS column (J&W) (30m x 0.25 µm x 0.25 mm) coupled to an Agilent Technologies 5973 Network detector and He as a carrier gas. The following chromatographic conditions were used: constant flow 2 mL/min, split injection ratio 20:1 at 300 ºC. The oven started at 50 ºC for 5 min; temperature was increased at 5 ºC/min to 110 ºC, then increased at 10 ºC/min until the final temperature of 260 ºC for 15 min.

Materials. Palmitic acid 98% was purchased from Across Organics. Glycerol 99% and calcium hydride 95%were purchased from Sigma. Cesium carbonate 99% was purchased from Aldrich. Hydrochloric acid 37% PRS and anhydrous magnesium sulfate 97% were purchased from Panreac. Argon 99,995% was purchased from Carburos Metálicos and used as received. tertButyl methyl ether 99% was purchased from J. T. Baker and dried with molecular sieves (3 Å) by conventional method prior to use.

Synthesis of 3-chloro-2-hydroxypropyl palmitate (3). General procedure. A given ratio (see molar ratios in Table I) of palmitic acid (**2**), glycerol (**1**) and 12 M HCl was added to a reaction vial fitted with a PTFE-lined cap. The mixture was heated at 100 ºC for 24 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydrous magnesium sulfate and solvent was evaporated under vacuum to give the corresponding reaction crude. This was purified by column liquid chromatography to yield **3**[17].

^{1}HNMR ($CDCl_3$) δ: 0.90 (t, *J* = 6.3 Hz, 3H, -C<u>H</u>3), 1.20-1.40 (m, 24H, –(C<u>H</u>$_2$)$_{12}$–), 1.66 (m, 2H, C<u>H</u>$_2$CH$_2$COO), 2.30 (t, *J* = 7.5 Hz, 2H, C<u>H</u>$_2$COO), 3.59 and 3.65 (dd, *J* = 8.5 Hz, *J* = 5.2 Hz, 2H, C<u>H</u>$_2$Cl), 4.00 (quin, *J* = 5.2 Hz, 1H, C<u>H</u>OH), 4.15 (dd, *J* = 5.2 Hz, *J* = 1.7 Hz, 2H, OC<u>H</u>$_2$CH-). ^{13}C-NMR ($CDCl_3$) δ: 177 (<u>C</u>OO), 70 (<u>C</u>HOH), 66 (O<u>C</u>H$_2$CH), 45 (CH$_2$Cl), 34 (<u>C</u>H$_2$COO), 32-22 (13C, <u>C</u>H$_2$), 17 (<u>C</u>H$_3$), GC-MS *m/z*: 348 [M]$^+$, 299 [M-CH$_2$Cl]$^+$, 269 [M-C$_2$H$_2$ClO]$^+$, 255 [M-C$_3$H$_6$ClO]$^+$, 239 [M-C$_3$H$_6$ClO$_2$]$^+$, 152 [C$_5$H$_9$O$_3$Cl]$^+$ (McLafferty rearrangement).

Synthesis of glycidyl palmitate (4). General procedure. 3-chloro-2-hydroxypropyl palmitate (**3; 348** mg; 1 mmol) was dissolved in 5 mL *t*-butyl methyl ether under argon atmosphere in a reaction vial fitted with a PTFE-lined cap. Subsequently, either CaH_2 or Cs_2CO_3 (1,3 mmol) was added

TABLE I

Influence of different ratios of glycerol (1), palmitic acid (2) and HCl 12M and temperature on 3-chloro-2-hydroxypropyl palmitate (3) yield. The amount of several side-products found in the final reaction crude is also shown.

2:1:HCl 12M mM ratio	T(ºC)	% of 3	% of 1	% of 10	% of 5a-b
1,5 : 3 : 1,2	80	38,3	16,3	19,2	21,5
1,5 : 3 : 1,5	80	25,0	31,3	20,7	15,1
2 : 3 : 1,2	80	46,8	18,8	14,1	17,9
2 : 3 : 1,5	80	23,4	58,8	13,2	4,7
1,5 : 3 : 1,2	100	61,5	6,4	10,0	13,9
1,5 : 3 : 1,3	100	70,0	7,0	23,0	–
1,5 : 3 : 1,5	100	61,0	12,0	27,0	–
2 : 3 : 1,2	100	40,5	36,6	12,0	6,4

to the vial. The mixture was heated at the corresponding temperature for 24 h. Then, the mixture was centrifuged at 3000 rpm for 5 min, and the liquid phase was recovered and dried over anhydrous magnesium sulfate. The solvent was evaporated under vacuum to give the corresponding reaction crude. This was purified by column liquid chromatography to yield **4**[18].

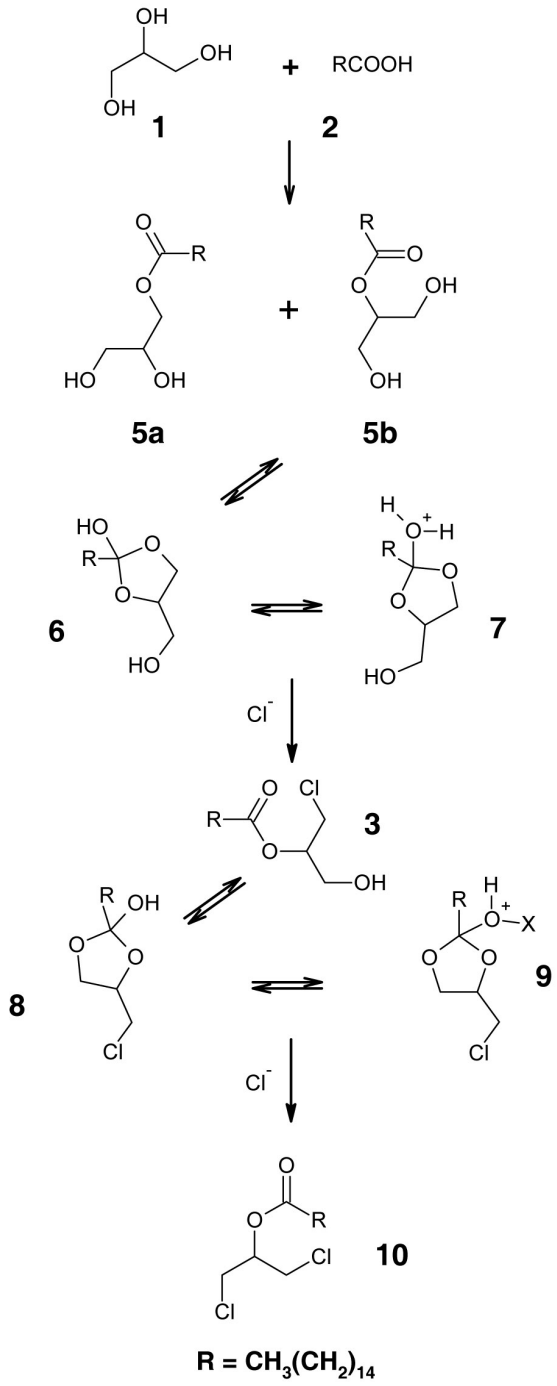
^{1}HNMR ($CDCl_3$) δ: 0.90 (t, *J* = 6.3 Hz, 3H, -C<u>H</u>$_3$), 1.20-1.40 (m, 24H, –(C<u>H</u>$_2$)$_{12}$-), 1.66 (m, 2H, C<u>H</u>$_2$CH$_2$COO), 2.30 (t, *J* = 7.5 Hz, 2H, C<u>H</u>$_2$COO), 2.65 (dd, *J* = 5.0 Hz, *J* = 2.7 Hz, 1H, oxyrane CH$_2$), 2.75 (dd, *J* = 5.0 Hz, *J* = 4.1 Hz, 1H, oxyrane C<u>H</u>$_2$), 3.20 (m, 1H, oxyrane C<u>H</u>), 3.90 (dd, *J* = 12.3 Hz, *J* = 6.4 Hz, 1H, OC<u>H</u>$_2$), 4.40 (dd, *J* = 12.3 Hz, *J* = 3.1 Hz, 1H, OC<u>H</u>2). . GC-MS *m/z:* 312 $[M]^+$, 297 $[M\text{-}O]^+$, 283 $[M\text{-}CH_2O]^+$, 269 $[M\text{-}C_2H_3O]^+$, 255 $[M\text{-}C_3H_5O]^+$, 239 $[M\text{-}C_3H_5O_2]^+$, 129 $[M\text{-}C_{13}H_{27}]^+$, 57 $[C_3H_5O]^+$.

RESULTS AND DISCUSSION

A mixture of glycerol (**1**) and palmitic acid (**2**) in presence of the appropriate ratio of concentrated hydrochloric acid (Table 1) without the addition of any organic solvent leads to the formation of the corresponding 3-chloro-2-hydroxypropyl palmitate (**3**) in a satisfactory yield. The best yield was obtained by carrying out the reaction for 24 h at 100 ºC using a 1,5 : 3 : 1,3 (**2:1**:HCl 12M) molar ratio. Lower temperature always yields a lower percentage of 3-chloro-2-hydroxypropyl palmitate (**3**). In addition, the formation of some amounts of monopalmitines **(5a-b)** and of 1,3-dichloro-2-propyl palmitate (**10**) as side-products was observed.

This one-pot esterification-chlorination reaction of glycerol can be described by a mechanism (Scheme 2) similar to that proposed for the synthesis of chlorohydrin esters from diols[15]. After glycerol esterification, the compounds obtained (**5a** and **5b**) can be transformed into the 1,3-dioxolane derivative **(6)**[19-22]. Compound **6** could produce **7**, favored by the presence in the medium of protons. These intermediates **(6, 7)** could react with chloride ions in the medium through a nucleophylic ring opening process[15, 16] rendering the corresponding chlorohydrin ester **(3)**. Considering this mechanism, the presence of monopalmitines **(5a-b)** and the 1,3-dichloro-2-propyl palmitate **(10)** is also substantiated.

Transformation of **3** into the glycidyl derivative **4** was studied using two basic reagents with poor nucleophylic capability to avoid ester hydrolysis. Table II shows the results obtained using CaH_2 and Cs_2CO_3. The best yield was obtained by carrying out the reaction with Cs_2CO_3 for 24 h at 60 ºC. Reactions carried out using H_2Ca always gave the lowest yield.



Scheme 2. Mechanism proposed to describe the one-pot esterification-chlorination of glycerol.

TABLE II

Influence of basic reagent and temperature on glycidyl palmitate (4) formation.

Basic Reagent	T (°C)	% yield of 4
CaH_2	22	–
CaH_2	60	37
Cs_2CO_3	22	80
Cs_2CO_3	60	87

CONCLUSION

Glycerol can be converted into 3-chloro-2-hydroxypropyl palmitate (**3**) using concentrated hydrochloric acid without adding any organic solvent. Subsequently, this ester could be converted to the corresponding glycidyl palmitate using Cs_2CO_3 and *tert*-butyl ethyl ether. Both esters are potentially valuable compounds. The application of this new methodology to the synthesis of other 3-chloro-2-hydroxypropyl and glycidyl esters from glycerol is under study and will be reported in due course.

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