Universitat de Lleida

Glicerol en la preparació d'esters de clorohidrina i derivats

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Memòria presentada per Marc Escribà i Gelonch per optar al grau de Doctor per la Universitat de Lleida

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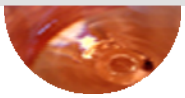


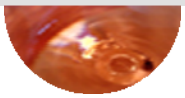
RESUM

Es presenten diferents reaccions de síntesi química, en les quals participa el glicerol com a reactiu, moltes d'elles amb rendiments elevats i bons percentatges de conversió. Un aspecte rellevant d'aquestes reaccions és l'obtenció de compostos o precursors sintètics de substàncies d'alt valor afegit.

Així, a partir de la síntesi d'esters de dicloropropil, usant glicerol i clorotrimetilsilà com a font de clor o amb clorur d'alumini usant un líquid iònic, s'han sintetitzat esters d'al·lil, alguns d'ells amb efecte ovicida en insectes. Un dels esters de dicloropropil sintetitzat a partir d'un àcid versàtic ha estat la referència per a la preparació d'esters dessimetritzats usant iodur, hidroxils o imidazoles com a nucleòfils.

Amb la finalitat de fer les reaccions més sostenibles, s'han usat reactius provinents de subproductes industrials, tant del sector d'olis i greixos, com de la indústria del biodiesel.

S'han emprat noves tècniques en síntesi orgànica, com els líquids iònics i les microones. L'ús de microreactors en una de les reaccions ha demostrat ser efectiu per a disminuir el temps de reacció, la qual cosa hauria de facilitar el seu escalat.



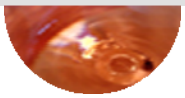
SUMMARY

Different synthetic reactions are shown, where glycerol is used as a starting material. High yields and conversions are reported in many of the described reactions. One relevant aspect is that compounds or synthetic precursors with high added value can be obtained.

Thus, starting from dichloropropyl esters, allyl esters can be obtained, some of them with ovicidal effects. These esters can be synthesised using glycerol and either chlorotrimetylsilane or aluminium chloride as chlorine source. In the later case an ionic liquid is needed. A versatic dichloropropyl ester has been the reference to prepare desymmetrized esters using iodine, hydroxy ion or imidazole derivatives as nucleophilic groups.

With the aim to develop sustainable reactions, industrial byproducts from the vegetable oil and fat industries, and from the biodiesel industries have been used as reagents.

New technologies, such as ionic liquids and microwaves have also been applied. A continuous process using a microreactor has been developed, which could allow the corresponding reaction to be scaled.



RESUMEN

Se presentan diferentes reacciones de síntesis química en las cuales participa el glicerol como reactivo. La mayoría de ellas presentan altos rendimientos y buenos porcentajes de conversión. Un aspecto relevante de estas reacciones es la obtención mediante síntesis química de compuestos o precursores sintéticos de sustancias de alto valor añadido.

Así, a partir de la síntesis de ésteres de dicloropropilo, usando glicerol y clorotrimetilsilano como fuente de cloro, o con cloruro de aluminio usando un líquido iónico, se han sintetizado ésteres de alilo, algunos de ellos con efecto ovicida. Una de los ésteres de dicloropropilo obtenido a partir de un ácido versático se ha usado como referencia para la preparación de ésteres desimetrizados usando ioduro, hidroxilo o imidazole como nucleófilos.

Con la finalidad de aumentar la sostenibilidad, se han usado reactivos procedentes de subproductos industriales, tanto del sector de aceites y grasas, como de la industria del biodiesel.

Las nuevas tecnologías, como los líquidos iónicos y las microondas, también han sido aplicadas en algunas de las reacciones estudiadas. Por otra parte, el uso de microreactores ha permitido mejorar el tiempo de reacción de uno de los procesos estudiados, hecho que debería facilitar su escalado.

ABREVIATURES

ADN: Àcid desoxiribonuclèic

[BMIM][$(CF_3SO_2)_2$N] Bis(trifluorometanosulfonat)amida d'1-butil-3-metilimidazolidini

[BMIM][HSO_4] Hidrogensulfat d'1-butil-3-metilimidazolidini

[OMIM][HSO_4] Hidrogensulfat d'1-octil-3-metilimidazolidini

[BMIM][PF_6]: Hexafluorofosfat d'1-butil-3-metilimidazolidini

[BMIM]$_2$[SO_4] Sulfat d'1-Butil-3-metilimidazolidini

CD_3COCD_3: Acetona deuterada

CTMS: Clorotrimetilsilà

DATEM: Esters diacetiltartàrics de monoglicèrids

DBO_5: Demanda biològica d'oxígen passats 5 dies

$DCCl_3$: Cloroform deuterat

DMSO: Dimetilsulfòxid

ee: Excés enentiomèric

EPA: Agència de Protecció Mediambiental (USA)

FAOSTAT: Servei d'estadístiques de la *Food and Agriculture Organization*

GC-FID: Cromatografia de gasos amb detector d'ionització de flama

GC-MS: Cromatografia de gasos amb espectrometria de masses

gCOSY: *Gradient Correlation Espectroscopy*

GSH : γ-Glutamilcisteinilglicina

HRMS: Espectre de masses d'alta ressolució

IFRA: *International Fragrance Association*

IGR: *Insect Grouth Regulator*

IL: Líquids iònics

IR: Espectre d'infraroig

LC_{50}: Dosi letal per al 50% de la població

LC_{90}: Dosi letal per al 90% de la població

LC-TOF-MS: *Liquid Chromatography – Time Of Flight – Mass spectroscopy*

FTIR: *Fourier Transform InfraRed spectroscopy*

HATR: *Horizontal Attenuated Total Reflection spectroscopy*

PTFE: Politetrafluoroetilè

MW: Microones

NMR: Ressonància magnètica nuclear

NREL: Laboratori Nacional d'Energia Renovable dels USA

PGR: Propilen glicol renovable

RH: Humitat relativa

SD: Desviació standard

TBME: t-Butil metil eter

UE: Unió Europea

UNCED: Conferència de les Nacions Unides sobre Medi Ambient i el Desenvolupament

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CAPÍTOL I: INTRODUCCIÓ

1.- Vers energies renovables

La societat del segle XXI afronta el repte de l'esgotament dels recursos naturals i de la contaminació que la pròpia civilització genera. L'increment progressiu del preu del petroli i l'augment de la sensibilitat ambiental ha provocat els darrers anys un replantejament dels mètodes de producció emprats per la indústria química. El repte consisteix en trobar materials adients, abundants i renovables, i formes de producció eficients i amb la suficient capacitat productiva, per tal de substituir les fonts no renovables de la natura per productes substitutius, que no generin contaminació ni per la seva obtenció ni pel seu ús. És el que es coneix com el paradigma de la Química Sostenible.

Considerant aquestes apreciacions, es fa necessari un esforç de canvi racional d'enfocament del concepte actual de producció. Aquest canvi podria venir donat a través de tres conceptes: El de consum sostenible, el de producció sostenible i el de reutilització de subproductes industrials.

El model de "consum sostenible" és molt variable, ja que depèn molt del grau de conscienciació de la població de cada país en aquest concepte. També depèn de les modes i corrents estilístics, com és el cas del corrent social actual d'ecologia i models "bio", i culturals: com la predisposició nord-europea a l'aprofitament, reciclatge i reutilització de productes i materials, contraposades a altres pràctiques no massa ecològiques d'altres països.

D'altra banda els conceptes de "producció sostenible" i "reutilització de subproductes", podrien anar d'alguna manera lligats. Així, una producció sostenible seria compatible amb una reutilització dels subproductes i a la inversa, no solament en termes productius, sinó també en relació a temes energètics i d'aprofitament. Així la reutilització dels residus ha experimentat un augment molt important en els darrers anys[1]. En particular, les indústries relacionades amb productes vegetals han esdevingut una de les principals fonts de subproductes per a l'obtenció d'energia[2]. Tot i així, en la literatura trobem que, en termes de producció, solament al voltant d'un 8% de l'energia renovable prové de la reutilització dels residus vegetals que s'usen en una gran proporció per a la indústria de biocombustibles[3,4]. És per això que la política de la reutilització de subproductes encara no ha arribat a desenvolupar-se amb totes les seves possibilitats.

Com a conseqüència de l'aprofundiment i la conscienciació que el model de producció sostenible ha tingut en la societat en general, han aparegut sectors industrials disposats a basar tota o part de la seva activitat en la reutilització de subproductes. Una de les conseqüències ha estat la necessitat d'adaptar la legislació a tots nivells, per aquests nous sectors. Històricament, trobem les primeres intencions normatives en els principis de la Conferència de les Nacions Unides sobre Medi Ambient i el Desenvolupament (UNCED), celebrada el juny de 1992 a Rio de Janeiro, la Cimera Mundial sobre el Desenvolupament Sostenible, celebrada a l'agost de 2002 a Johannesburg i l'Agenda 21, el pla integral d'acció per al segle 21, aprovada per més de 170 governs.

A Europa, també s'han anat introduint aquests principis. En l'actualitat aquests marquen com a objectiu que un 20% de la producció d'energia sigui renovable al 2020 (2009/28/EC), i en particular, que un 10% sigui en concepte de biofuel. Aquest ja s'ha anat introduint com a complement dels carburants habituals procedents del petroli. La figura 1 mostra l'evolució creixent de la producció anual dels dos biofuels majoritaris; el biodièsel i el bioetanol, enfront del grau d'incorporació d'aquests biocombustibles al mercat, i la tendència que s'estima que tindrà en un futur proper.

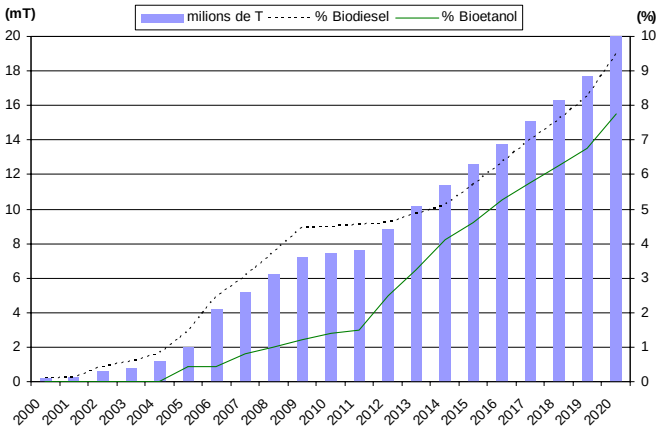


Figura 1: Evolució de la demanda de biocombustibles respecte del grau de incorporació al mercat, en la Europa dels 27 fins al 2020. Font: AGRI G-2/WM D(2007)

Com a conseqüència, un dels camps que més s'ha desenvolupat en els darrers anys en relació a les energies renovables és, precisament, el dels productes substitutius del petroli com a combustible; el bioetanol i el biodièsel. D'altres productes substitutius darrerament emergents, tot i que encara en un nivell de desenvolupament menor, presenten molta projecció i moltes oportunitats a nivell industrial: Són el bioquerosè[5] (a partir l'oli del pinyó de l'Índia, *Jatropha curcas,* cultivat fonamentalment en terrenys Africans per qüestions climàtiques) i fotobiofuel[6,7] (a partir d'algues adherides a fotobioreactors).

La figura 2 mostra esquemàticament la producció de biodièsel i bioetanol. Entenem el bioetanol com l'alcohol produït a partir de la fermentació dels sucres provinents de vegetals com la remolatxa (*Beta vulgaris*), el blat de moro (*Zea mays*), la civada (*Avena sativa*), el blat (*Triticum aestivum*), la canya de sucre (*Saccharum officinarum*), la melca (*Sorghum vulgare*) i altres cultius, que sol o mesclat amb la gasolina, produeix un combustible que pot ser usat en els motors de gasolina convencionals amb poques modificacions.

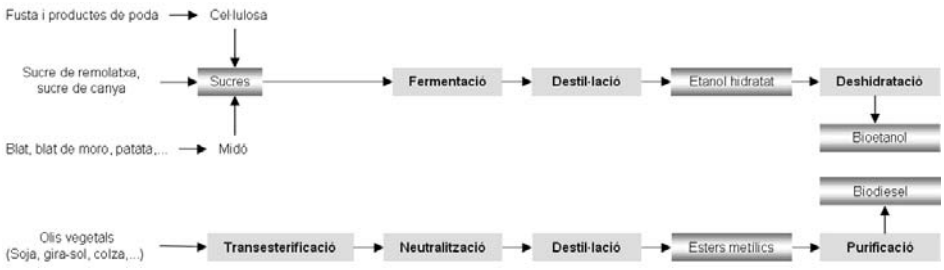


Figura 2: Diagrama de flux de la síntesi de bioetanol i biodièsel.

Paral·lelament, entenem el biodièsel bàsicament com aquella mescla d'esters metílics dels àcids grassos provinents de la transesterificació d'olis vegetals amb metanol en presència normalment d'una base. El resultat són els esters metílics i glicerol com a subproducte. Darrerament també s'ha obtingut biodièsel de la transesterificació d'olis d'origen animal pel mateix procediment, i també per catàlisi amb sulfats i òxids de titani en etanol[8].

Segons la font d'obtenció dels biocombustibles, i atenent a la cronologia des de l'inici de l'aplicació de la metodologia, es parla de generacions de biocarburants. Així, tant el bioetanol com el biodièsel obtinguts a partir de cultius extensius tradicionals, com els anteriorment esmentats, es consideren de primera generació, mentre que serien de segona l'etanol lignocel·lulòsic[9,10] obtingut de la fermentació de la fusta, i de tercera generació el biohidrogen de les algues[6,7]. Tanmateix, també s'ha proposat l'obtenció de biodièsel de segona generació que no generin glicerol[11,12].

Des d'un punt de vista tecnològic el bioetanol i el biodièsel es poden obtenir per diferents vies, la majoria de les quals encara es troben en fases de desenvolupament o d'optimització atès que, en alguns casos, l'enginyeria que es precisa els fa encara inviables econòmicament: Així, els productes es poden generar per catàlisi heterogènia o clàssica[13], sintetitzant esters metílics a partir de triglicèrids usant metanol, o per catàlisi enzimàtica[14], utilitzant enzims amb activitat lipàssica de *Pseudomonas fluorescens, Mucor miehei* i *Candida sp.*, amb l'avantatge que en aquest cas el glicerol format no necessita purificació. D'altra banda, a nivell funcional, alguns estudis amb caràcter més incipient proposen mecanismes per a l'estabilització oxidativa del biodièsel mitjançant processos que utilitzen el metanol en condicions supercrítiques i lignines[15].

Conceptualment aquests combustibles semblen *a priori* molt competitius, però enfront d'aquesta fortalesa existeixen també debilitats. Efectivament, la seva producció massiva podria suposar un perill ecològic de desforestació a causa de la basta extensió de conreus que serien necessaris per assolir la demanda del mercat. D'aquesta manera, si aquesta situació no es gestiona adequadament, es podrien veure alterades a més: la pluviometria, l'efecte hivernacle, la biodiversitat i el sòl des d'un vessant erosiu.

En aquesta mateixa línia, el glicerol subproducte industrial obtingut de la seva síntesi seria generat en grans quantitats, que sobrepassarien en molt l'actual demanda mundial.

2.- Cap a una química més sostenible

A finals de la dècada dels 60 i principis dels 70 s'inicia un corrent pro medi ambient que culmina amb la creació de l'Agència de Protecció Mediambiental (EPA) l'any 1970 als Estats Units d'Amèrica. A principis dels anys 90 la "Química Verda" o química no perjudicial pel medi ambient es converteix en un objecte formal de l'EPA, amb la finalitat de dissenyar productes o processos químics que redueixin o eliminin l'ús i producció de substancies perilloses i la gestió de residus. Per a tal finalitat es promouen 12 postulats[16] com a full de ruta per acomplir els objectius fixats, aquests principis es basen en els següents punts:

1. Prevenció: millor evitar el residu abans d'haver-lo d'eliminar.

2. Economia en les relacions molars de les reaccions.

3. Síntesis químiques menys perilloses amb productes innocus o poc contaminants.

4. Els productes químics han d'acomplir la seva funció amb la mínima toxicitat possible.

5. Ús de dissolvents no derivats del petroli, fluids supercrítics, aigua o reaccions sense dissolvents.

6. Eficiència energètica amb fons alternatives; microones, electroquímica...

7. Avaluació i re-aprofitament de residus.

8. Reduir la formació de derivats.

9. Catàlisi selectiva de reaccions.

10. Disseny de productes de fàcil degradació després de la vida útil per evitar acumulacions ambientals.

11. Monitorització de reaccions per assegurar que no hi ha intermediaris perillosos.

12. Les substàncies d'un procés s'han d'escollir amb l'objectiu de minimitzar els accidents.

3.- Residus industrials d'olis i greixos

3.1.- Residus del procés d'extracció

El sector productiu d'olis suposa, només en extensió de vegetació, poc més de 250 milions d'hectàrees a escala mundial, la major part concentrats en la zona d'Àsia. A la zona Mediterrània la producció d'olis i greixos (de gairebé 18 milions de tones) és un actiu important a nivell econòmic, patrimonial i ecològic. Així, no és d'estranyar que els principals productors de la zona europea de la Mediterrània siguin Espanya, Itàlia i Grècia[(*)].

Tanmateix, el procés productiu, per exemple per a l'oli d'oliva, té un rendiment del 20% en oli, 30% de residus semisòlids, i un 50% d'oliasses, que en termes absoluts suposen al voltant de 4 milions de tones de residus semisòlids anuals, considerant solament la producció europea (12 milions de tones). Aquests residus suposen un problema ambiental a resoldre. La producció d'olis a la UE es mostra en la figura següent.

[*] *Veure FAOSTAT, 2009. http://faostat.fao.org. (Darrer accés nov 2009)*

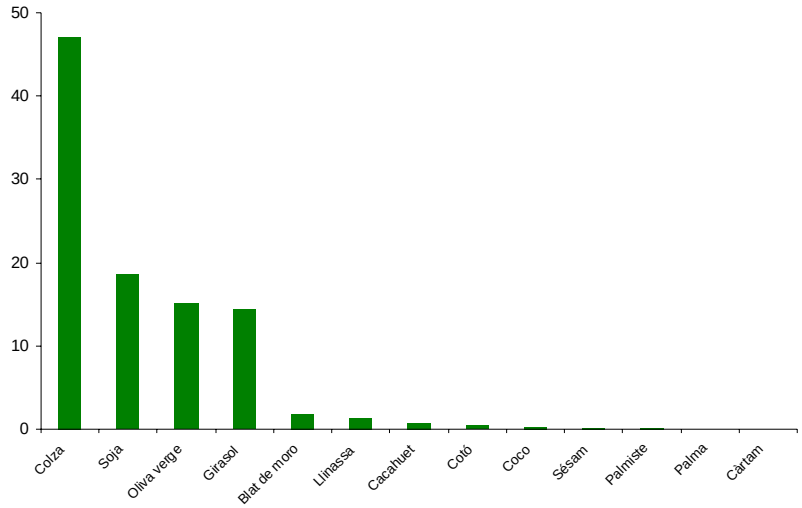


Figura 3: Producció d'olis a la UE l'any 2008. Font: Faostat (2009)

La composició d'aquests residus és molt variable, segons la varietat, les condicions climàtiques, edat de la planta o arbre i processos aplicats. Tot i això, els subproductes a nivell d'elements biogènics tenen unes característiques relativament homogènies. En quan al contingut en greix en particular, aquest és relativament baix com a conseqüència de les successives extraccions.

En el cas de l'oli d'oliva, la sansa obtinguda conté pedres triturades, polpa, pell, al voltant d'un 25% d'aigua i encara vora d'un 10% d'oli. La seva aparença no és massa agradable, ja que combina el color fosc quasi negre amb una olor que recorda al lleixiu. Aquest producte suposa un seriós problema per a la indústria, ja que no pot ser abocat a la xarxa ordinària

degut al seu alt contingut de DBO_5. Aquest fet s'accentua pel fet que els continguts en residus sòlids i sals corrosives es van acumulant. Per tant, es fa necessària la seva reutilització per evitar la contaminació ambiental que suposa amb efectes adversos sobre el sòl, la corrosió de conduccions, la contaminació d'aqüífers i la contaminació atmosfèrica.

Actualment els residus de la indústria oleícola es poden classificar en dues categories[1]: La part derivada de l'esporga i dels procediments propis de la collita, que va generalment cap a compostatge, i la part corresponent al procés post-collita que engloba fraccions de la sansa d'oliva, les salmorres, les aigües de rentat, l'oli llampant, gasos emesos i la fracció semisòlida.

3.2.- Residus industrials post-collita

L'agroindústria s'ha consolidat com un subsector industrial important en el conjunt de l'economia catalana, sobretot pel creixement que ha experimentat els darrers anys. La utilització d'olis, i per tant la generació de residus d'aquesta categoria, no és una característica pròpia exclusivament de la indústria productora d'olis. Així, sectors agroalimentaris com els precuinats, pastisseria i dolços usen olis per l'elaboració dels seus productes. El creixement del sector agroindustrial ha donat lloc també a un increment en la generació de residus.

Els olis usats en la majoria de casos no s'eliminen adequadament. Els olis i greixos com els obtinguts com a subproductes d'altres processos o els de baixa qualitat, poden ser utilitzats en l'obtenció de compostos químics, camp que actualment està en expansió, i obra el camí per evitar l'acumulació d'aquests olis i greixos. Així s'han desenvolupat diverses metodologies per a la preparació d'estabilitzants per a polímers[17], l'àcid azelàic[18], el 1-decè[19], els derivats de l'àcid ftàlic[20] o d'esters d'àcids[21] i carbohidrats entre altres[22].

A més, els mono i diglicèrids, i el glicerol[23-25] usats com additius alimentaris[26], poden ser també productes de partida per a la preparació de tensoactius usant aminoàcids[27], additius alimentaris tipus esters diacetiltartàrics de monoglicèrids (DATEM)[28], o additius en la fabricació de polímers[29] i tintes d'impressora[30]. En aquest sentit s'han desenvolupat 57 patents entre 2005 i 2009*(†)*.

Les llavors d'oleaginoses i els seus subproductes[31], a part de ser una font renovable d'àcids grassos i glicerol[32], també han estat usats per la obtenció de substàncies com l'escualè[33,34], el manitol[35], l'àcid oleànic[36], xantà[37], sulfactants[38], β-sitosterol[39],

† Segons cerca realitzada amb SciFinder (2010): Paraules clau: glicerol, additius, tensoactius. Filtrat segons tipus de publicació (Patent) i segons any de publicació (2005-2009)

biogàs[40], fertilitzants[41] i tocoferols[42]. L'obtenció de tocoferols a partir de residus de greixos com antioxidants naturals actualment està despertant també un gran interès[43].

Una de les utilitzacions d'aquests productes que ha suscitat interès mediàtic, ha estat la utilització dels greixos de fregir per a produir també biodièsel.

4.- Avantatges del Biodièsel

Els productes substitutius del petroli, com el bioetanol i el biodièsel, han suposat tota una novetat pel que fa al seu desenvolupament en els darrers anys.

La producció tradicional de biodièsel consisteix en el escalfament durant 2 h a 55 ºC dels olis amb un excés d'aproximadament el 30% de metanol amb hidròxid potàssic. L'excés de metanol es recupera amb una destil·lació posterior per a reutilitzar-lo. El biodièsel resultant s'asseca per eliminar l'aigua residual.

Els avantatges del producte resideixen en la seva condició de substitutiu del petroli i en altres avantatges mediambientals com:

1. Són biodegradables i no tòxics
2. Milloren la qualitat de l'aire en zones urbanes
3. No incrementen els nivell d'anhídrid carbònic a llarg termini.

Els desavantatges del procés consisteix en l'excés d'alcohol que es requereix, a més de la separació posterior obligada pels costos. A més, la formació de sabons afecta al rendiment global de la reacció, i l'extensió de conreus necessaris per a cobrir la demanda pot suposar una gran desforestació.

La producció de biodièsel amb un mecanisme optimitzat i amb una reutilització dels subproductes generats, pot crear noves oportunitats de desenvolupament rural sostenible en el marc d'una política agrícola més orientada al mercat, ja que pot fomentar el desenvolupament de cultius energètics i la creació d'agroindústries, contribuint a mantenir nivells de treball i renda en l'àmbit rural, en detriment d'una desforestació que s'hauria d'intentar pal·liar o ajustar en la seva sostenibilitat.

La tecnologia, tal com la coneixement en l'actualitat, data de finals del segle XX i va destinat fonamentalment per a motors de tipus Diesel. Atès que el biodièsel posseeix característiques semblants que el gasoli de petroli usat en els motors Diesel, s'ha observat que pot ser usat en qualsevol proporció juntament amb el mateix gasoli, sense necessitat de modificar la constitució bàsica dels motors o amb lleugeres modificacions. En aquest sentit, països com els Estats Units l'han catalogat com l'únic combustible alternatiu que respon a la directriu EPA: *Tier I Health Effects Section 211 (b) Clean Air Act*.

Aquest nou producte presenta algunes avantatges relatives a les seves emissions[44]. Així per exemple: respecte del monòxid de carboni, la seva producció és de l'ordre del 50% menor comparat amb les emissions del gasoli convencional normal, a més, el biodièsel no produeix diòxid de sofre, un dels causants de les pluges àcides, ni derivats orgànics aromàtics.

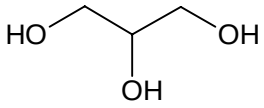
El subproducte principal de la seva obtenció per aquest procés és el glicerol, del qual s'intenta reduir l'impacte ambiental degut a la seva possible acumulació.

5.- El glicerol

El glicerol (1,2,3-propantriol), del grec *glykos* (dolç) també anomenat glicerina, és una substància coneguda químicament des de fa més de 200 anys. Fou descoberta pel suec Carl Wilhelm cap al 1783 quan tractava olis amb productes alcalins. El glicerol és una substància viscosa, incolora, inodora i amb gust dolç, obtinguda comercialment a partir de la hidròlisi dels greixos i de la indústria petroquímica. Generalment es presenta amb una riquesa del 95-99%, essent la resta principalment aigua. La seva solubilitat en aigua, en alcohols i en dissolvents com l'èter i el dioxà és alta, i baixa en substancies apolars i hidrocarburs. Els primers usos van ser en la preparació de la dinamita com a precursor del nitroglicerol[45].

Taula 1: Propietats del glicerol a 20 ºC[46]

Formula empírica	$C_2H_8O_3$
Massa molecular	92,09382 $g.mol^{-1}$
Densitat	1,261 $g.cm^{-3}$
Viscositat	1,5 Pa.s
Punt de fusió	18,2 ºC
Punt d'ebullició	290 ºC
Valor energètic	4,32 $kcal.g^{-1}$



El glicerol és una substància molt estable a temperatura ambient, i compatible amb la majoria de materials. No presenta irritabilitat i no se li coneix capacitat de causar efectes ambientals nocius. Arribat en aquest punt, el lector es

pot preguntar: on és doncs el problema? I la resposta és; que la qüestió no està en la substància, sinó en la enorme quantitat que se n'obté, i en la qualitat del mateix, que supera en escreix la demanda de les indústries transformadores actuals, creant un desequilibri oferta-demanda que requereix solucions. Alguns industrials (*Nexant ChemSystems*) proposen el propilèn glicol renovable (PGR) com una bona solució, tal com mostra la figura següent.

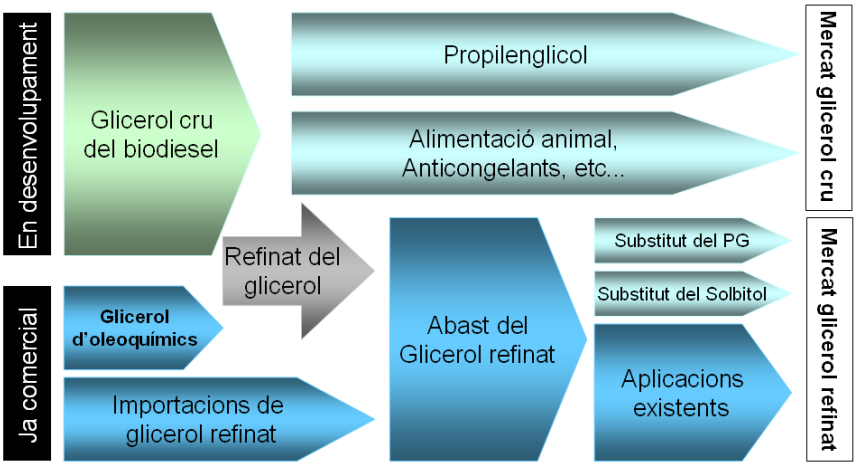


Figura 4: El propilenglicol (PG) renovable . Una sortida per a l'excés de glicerol. Font: Nexant ChemSystems.

El procés del glicerol cru a propilèn glicol ja és comercial i ja estan en funcionament diferents projectes en aquest sentit, entre ells: *Senergy Chemical*, *Cargill/Ashland*, *ADM*, a més de treballs d'investigació per part d'empreses i institucions com: *UOP (grup Honeywell)*, *Virent Energy Systems* i el Laboratori Nacional d'Energia Renovable dels EEUU (*NREL)*. D'altra

banda, segons fonts de la pròpia empresa, *Solvay* construirà una planta per a produir epiclorohidrina a partir de glicerol usant un procés propi que anomenen *Epicerol*.

El glicerol actua generalment en baixes concentracions com a humectant, si el producte ho requereix per les seves característiques, o com a protector d'aquest contra la dessecació. També s'explota el seu vessant lubricant aprofitant la seva reologia.

En aquest sentit, la quantitat de glicerol utilitzada, sigui com a additiu o com a reactiu, va ser d'uns 160.000.000 kg l'any 2006 segons J. Bonnardeaux[47]. D'aquestes quantitats se n'esperava un creixement del 2,8% anual, que suposant acurades les prediccions, suposaria 179.000.000 kg l'any 2010. Per a tenir idea de l'ordre de magnitud del tema que ens ocupa, solament dues de les empreses multinacionals productores de biodièsel(‡) l'any 2008 ja van produir uns 172.000.000 kg de glicerol residual, pràcticament tot el necessari actualment, i per tant, tota la resta del glicerol produït com a subproducte per les empreses a nivell mundial seria excedentari atesa la demanda, acumulant-se any rere any. Així doncs, el mercat actual no pot absorbir la gran quantitat de glicerol que prové i provindrà de les indústries del biodièsel.

‡ *Veure http://www.novaol.it/ilgruppo.html (Darrer accés, nov 2009)*

Tot i aquestes apreciacions, el vessant positiu resideix en el preu del glicerol el qual, en els darrers anys, ha anat baixant fent-lo encara més atractiu de cara a trobar-ne altres aplicacions. Així, si l'any 2000 cotitzava en un interval de 1 a 1,3€/kg, l'any 2006 ja ho va fer entre 0,5 i 0,7 €/kg[45]. De fet, ja ha substituït altres poliols en la producció a gran escala d'edulcorants, i reductors de calories en productes alimentaris[47].

El mercat del glicerol necessita experimentar canvis radicals per tal d'absorbir les tones excedentàries que del biodièsel se'n deriven. És per això que es fa necessari el desenvolupament de nous productes que l'usin com a matèria primera. La indústria dels biocombustibles, tal com la tenim plantejada, presenta la contradicció de l'intent de resoldre el problema de la mancança d'un recurs no renovable, usant un procés que genera un altre subproducte, l'ús o gestió del qual encara és motiu de recerca.

Autors com Pagliaro i Rossi[47] han fet un recull de les diferents utilitats d'aquest compost proposades per diferents autors: des de convertir-lo en un altre producte, fins a utilitzar-lo com a dissolvent, anticongelant, com a detergent, additiu tèxtil, en el món sanitari, farmacèutic i cosmètic entre d'altres[48].

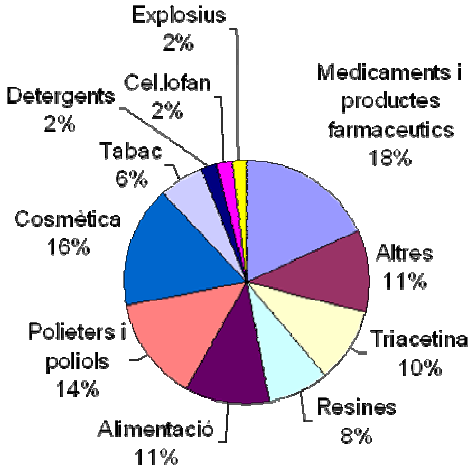


Figura 5: Usos del glicerol[47].

Totes questes aplicacions depenen molt de les característiques del producte, les propietats i el seu comportament. És per això que el món científic en general, i el grup de recerca de Metabolòmica Agroalimentària de la Universitat de Lleida en particular, hem dedicat els darrers anys esforços en investigar noves rutes de transformació del glicerol.

5.1.- Glicerol subproducte vs Glicerol comercial

L'esterificació del glicerol dóna lloc a una gran varietat de productes i en els darrers anys ha esdevingut una font de gran activitat en el camp industrial. Així per exemple[47] l'any 2006 es van sintetitzar 400.000.000 kg d'emulsificants, un 10% dels quals van ser monooleïnes. Els diglicèrids també suposen un motiu d'interès industrial[(§)], tant els d'origen vegetal com animal, són estables a les temperatures típiques de cocció dels aliments. De fet, els darrers estudis indiquen que limiten considerablement l'acumulació de greix en els humans. Aquest fet no queda exempt d'importància sanitària en la societat del segle XXI. [49]

El glicerol cru obtingut del biodièsel és una mescla de glicerol enfosquit degut a l'escalfament, amb restes de metanol, aigua, sals inorgàniques, i amb la presència d'àcids grassos lliures i esters metílics d'aquests. En aquestes condicions el glicerol té poques aplicacions directes i en la majoria de casos necessita d'un condicionament. Si es vol obtenir amb una puresa superior[47], el mitjà més econòmic passa per l'electrodiàlisi i la nanofiltració, seguida segons la puresa requerida, d'una destil·lació per tal d'eliminar l'aigua i el

§ *Veure http://www.kao.co.jp/rd/dag%5Fen (Darrer accés, nov 2009)*

metanol residual. Aquest darrer procediment fa que el producte final tingui un preu prou elevat.

Glicerol cru de la síntesi de biodièsel

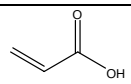
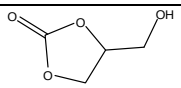
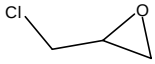
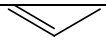
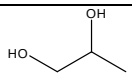
Glicerol cru neutralitzat, sense metanol ni aigua

Glicerol comercial

Figura 6: Diferents aspectes que ofereix el glicerol[47]

La situació ideal, doncs, passaria per a poder donar utilitat a aquest glicerol residual degudament condicionat, per tal d'aconseguir productes reutilitzables, tal com en els darrers anys ha suggerit l'anomenada "*Química verda*" o "*Green Chemistry*". Actualment alguns dels productes que es poden obtenir del glicerol, i les principals firmes comercials que les produeixen, es resumeixen en la taula2[50]. Molts d'aquests productes estan subjectes a patents:

Taula 2: Productes comercials obtinguts a partir del glicerol

Producte		Principal marca comercial
Àcid acrílic		Arkema
Carbonat de glicerina		Huntsman
Epiclorohidrina		Dow Solvay
Hidrogen	H_2	Linde
Metanol	CH_3OH	BioMCN
Propilè		Quattor
Propilenglicol		Cargill i Ashland

En aquest sentit, una de la vies d'aprofitament és la síntesi de les anomenades clorohidrines.

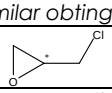
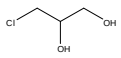
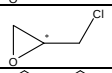
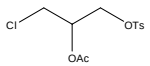
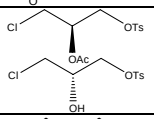
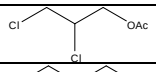
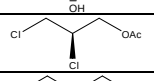
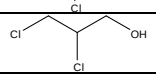
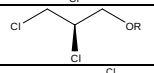
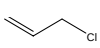
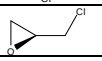
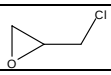
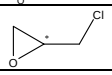
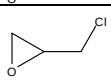
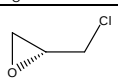
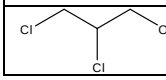
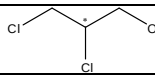
6.- Les clorohidrines

Amb el nom de clorohidrines s'engloben aquelles substàncies orgàniques alifàtiques derivades de polialcohols alquílics en els quals hi ha hagut una substitució d'un o més grups hidroxil per un àtom de clor. La majoria de clorohidrines dissoltes en aigua tenen un gust lleugerament dolç i un olor agradable, especialment el 3-cloro-1,2-propandiol, l'1,3-dicloro-2-propanol

i el 3-cloro-1-propanol. La majoria es caracteritzen pel seu alt potencial corrosiu.

La síntesi d'algunes clorohidrines es pot resumir en la taula següent:

Taula 3: Mètodes d'obtenció de la epiclorohidrina, del 2,3-dicloro-1-propanol i del tossilat de 3-cloro-2-hidroxi-1-propil.

Producte de partida	*Clorohidrina o similar obtingut*	*Mètode utilitzat en la síntesi*
D-Manitol		*Hidròlisi i reducció* [51]
		*Resolució de diols amb la D-camforquinona quinona* [52]
		*Hidròlisi estereoselectiva amb lipases*[53]
		*Hidròlisi asimètrica amb lipasses*[54]
		*Esterificació amb lipasses*[55]
		*Epoxidació assimètrica*[56]
		*Obertura enantioselectiva d'epòxids*[57]
		*Degradació enantioselectiva amb Nocardia sp.*[58]
		*Dissimetrització per enzims bacterians*[59-61]

Una substància molt propera, i molt usada industrialment, és la epiclorohidrina, estructuralment anàloga al glicidol *(figura 7)*. Les clorohidrines més usades són el 2,3-dicloro-1-propanol, el 3-cloro-1,2-propandiol i els seus derivats, els quals, per la seva

quiralitat esdevenen productes interessants, per a la indústria farmacèutica i química fonamentalment[62].

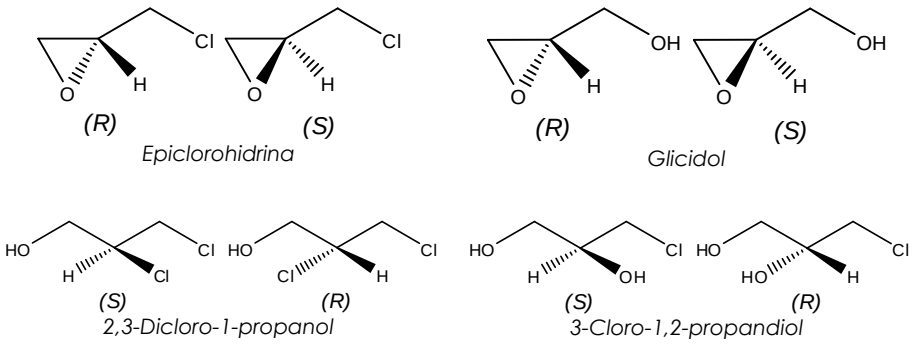
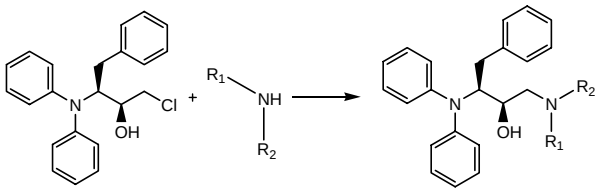


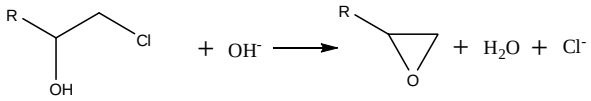
Figura 7: El glicidol, la epiclorohidrina i els principals tipus de clorohidrines

La seva reactivitat està descrita per diversos autors, i està basada en la versatilitat que els grups clor i hidroxil confereixen a la molècula, podent reaccionar de forma selectiva: així les clorohidrines poden donar lloc a èters[63] reaccionant amb alcohols o fenols en condicions bàsiques. També poden donar lloc a esters[64] amb àcids carboxílics en medi bàsic i β-cloroesters[65] amb clorurs d'àcid. També està documentada la formació de carbonats cíclics[66] amb diòxid de carboni en presència d'una amina. Altres aplicacions inclouen les clorohidrines i similars com a *building blocks*[67] en la síntesi química d'altres productes *(figura 8a)*. La conversió de les clorohidrines, per l'acció d'una base com una adaptació de la

síntesi de Williamson per a donar anells oxiràncics (epòxids), és una de les reaccions més comunes *(figura 8b)*[68].



(a)



(b)

Figura 8: (a) Exemple d'aplicació com a "building blocks" (b)La reacció més comuna de les clorohidrines és la deshidrocloració per a donar anells epòxid

Altres autors proposen l'aplicació de clorohidrines en la preparació de glicols *(figura 9)*[69] i en la formació de carbonats cíclics[70].

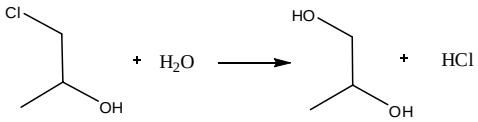


Figura 9: Exemple d'hidròlisi de clorohidrina

Moltes d'aquestes clorohidrines són quirals, i la seva versatilitat en reaccionar amb nucleòfils permet introduir quiralitat en substancies amb activitat fisiològica útil en farmacologia.

La producció de clorohidrines ja va superar les 740.000.000 kg l'any 1995, i la seva aplicació es focalitza en la síntesi de resines epoxi (especialment l'òxid de propilè i l'epiclorhidrina[71]) i de cautxú, materials adhesius, pintures i com a intermediaris de fàrmacs[72] i productes agroquímics[73]. Les clorohidrines també es poden trobar aplicades en additius en la fabricació del paper[74], en blanquejadors fluorescents i fotosensibilitzants[75] o en materials lubricants[76].

Les clorhidrines[77] poden ser usades en la preparació de medicaments *(figura 10-a)*[78,79], additius alimentaris[79-81], tensioactius[82], epiclorhidrines[53] i altres epòxids[83]. Les metodologies per a la seva preparació inclouen des de l'esterificació de cloroalcohols mitjançant diferents agents acidificants[84], fins al trencament de ortoésters cíclics mitjançant diferents reactius *(figura 10-b)*[85-87].

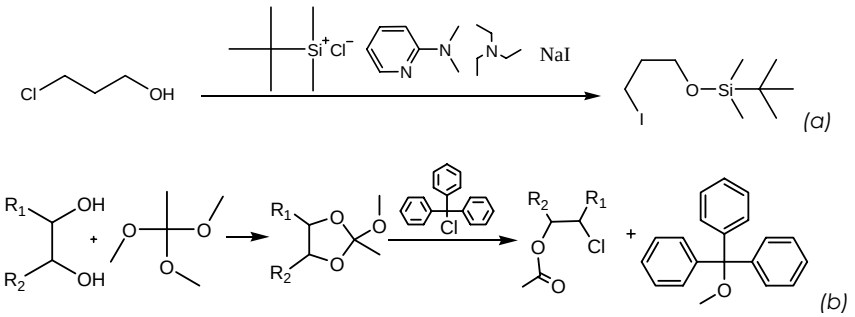


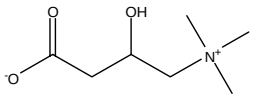
Figura 10: (a) Síntesi de $ICH_2CH_2CH_20Si$-t-$BuMe_2$ a partir del 3-cloro-1-propanol [78] (b) Conversió de 1,2-diols a acetats de clorohidrines(R_1= metil o fenil i R_2 = metil o hidrogen)[87]

6.1.- Els esters de clorohidrines

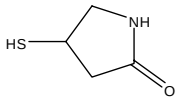
Les clorohidrines és poden trobar esterificades amb àcids carboxílics formant els esters de clorohidrines. S'han desenvolupat processos en els quals, partint de diferents poliols, s'obtenen esters de clorohidrines amb un alt rendiment[88,89]. Alguns d'aquests esters, o dels seus derivats immediats, constitueixen la principal via per la síntesi de substancies com: la carnitina[90], el 4-mercaptopirrolidin-2-ona[91], l'iodixanol[92], precursors de feromones[93], certs anticolestèmics[94] i certs antihipertensius[62]. Alguns esters de clorohidrina presenten centres quirals, com en el cas d'algunes clorohidrines provinents del glicerol. Així per exemple, quan es preparen derivats de clorohidrines a partir de glicerol esterificant en la posició 1, s'obtenen esters de 2,3-dicloropropanol, el qual conté un centre quiral.

Aquests productes han estat emprats tant en la indústria d'aromes[95], control de plagues forestals[96], i indústria agroalimentària[97-102] com en estudis de la indústria de biodièsel[103], i en la preparació de productes amb interès farmacèutic[104].

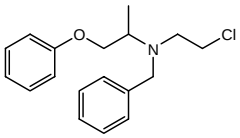
Taula 4: Substancies en la síntesi de les quals pot intervenir el glicerol



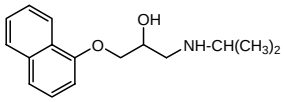
Carnitina



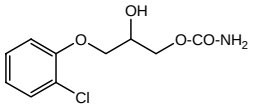
4-mercaptopirrolidin-2-ona



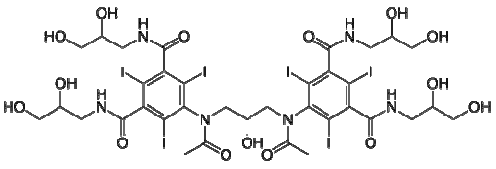
Fenoxibenzamina (antihipertensiu)



Propanolol (Antiarrítmic β-bloquejant)



Carbamat de guaifenesina



Iodixanol

Però l'interès d'aquestes substàncies com a productes intermedis d'altres reaccions, com la síntesi d'esters d'al·lil, fins al moment encara no ha estat avaluada. Aquesta possibilitat es contempla en aquesta tesi, i contribuiria a ampliar el seu ventall de possibilitats.

7.- Els esters d'al·lil

El grup al·lil es el nom comú del grup 2-propenil. L'alcohol al·lílic és el 2-propenol i la seva esterificació amb un àcid carboxílic dóna lloc als esters d'al·lil. Les seves propietats depenen de l'àcid carboxílic i del propi grup al·lil. Així els esters d'al·lil de cadena curta, com l'acetat d'al·lil i l'acrilat d'al·lil són líquids incolors de baixa viscositat que causen una severa irritabilitat en les membranes mucoses. Els de cadena llarga tenen viscositats i punts d'ebullició elevats, i desprenen poca olor[105].

D'entre les característiques químiques destaca la seva capacitat de polimerització en presència d'oxigen o peròxids, la facilitat d'hidrolitzar-se o transesterificar-se. Així per exemple, l'acetat d'al·lil en presència de pal·ladi, oxigen i àcid acètic s'oxida donant diacetat de 2-propen-1,1-diol o acetat d'al·lilidè[106], tal com mostra la *figura 11*.

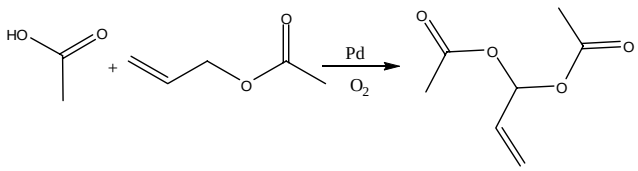


Figura 11: Obtenció del diacetat d'al·lilidè a partir d'un ester d'al·lil

Els esters d'al·lil tenen nombroses aplicacions industrials entre les que destaquen el seu ús en la fabricació d'aromes[107], resines[108] i diferents tipus de materials bioactius per a aplicacions en agricultura[109], alimentació[107], cosmètica[110], perfumeria[111], industries gràfiques[112] i farmàcia[113]. Igualment s'han usat com a producte de partida en la preparació d'altres productes químics tals com monoacilglicèrids i derivats de reaccions de Diels-Alder[114].

Fins avui, la seva obtenció s'ha portat a terme mitjançant mètodes químics basats en els següents processos:

a) Eliminació d'un residu ester d'alquil en diésters o monoésters de poliols[115,116]
b) Reacció entre sulfonats d'al·lil i el corresponent àcid o anhídrid d'àcid[117-119]
c) Esterificació d'anhídrid d'àcid, dels corresponents àcids o halurs d'acil, amb alcohol al·lílic[120,121]
d) Alcohòlisi amb alcohol al·lílic d'esters o amides[122,123]
e) Eliminació d'anells de 1*H*-pirazol de nitrosamides[124,125]
f) Reacció del corresponent àcid i les seves sals amb propè, aliltrialquilestannans, aliltrialquilsilans, alilalquilfosfines o halurs d'al·lil[126]
g) Reacció de mescles d'àcid carboxílic i les seves sals amb clorociclopropà o ciclopropanamina[127]

h) Desoxigenació d'esters de glicidol[128]

i) Transesterificació entre esters d'al·lil i halurs d'acil[120,129]

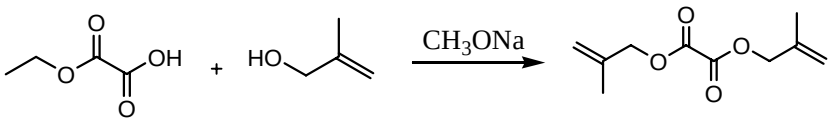


Figura 12: Exemple de síntesi d'esters d'al·lil, en particular, l'oxalat de dimetal·lil[130].

Alguns d'aquests processos usen alcohol al·lílic i halurs d'al·lil, reactius altament irritants. En moltes de les reaccions descrites fins avui els rendiments no superen el 80% i, en més d'un cas, s'obtenen mescles de substàncies difícils de separar.

Els esforços actuals s'encaminen a superar inconvenients com l'ús de reactius perillosos, la necessitat d'utilitzar fonts renovables de matèria prima i l'obtenció de productes finals amb un alt rendiment sense la presència de restes d'alcohol al·lílic, el qual per imperatiu de la reglamentació actual no pot estar en quantitats superiors al 0,1% en el cas que es desitgi preparar additius per a l'ús alimentari**.

Ni les publicacions sobre la preparació d'esters al·lílics ni les patents relacionades amb el tema, han desenvolupat fins el moment un procediment que superi els inconvenients abans esmentats.

** *The International Fragrance Association (IFRA), http://www.ifraorg.org/AboutIfra.asp.*

8.- La dissimetrització de compostos

W. Marckwald[131] l'any 1904 ja va definir la *síntesi asimètrica* com aquelles reaccions que produeixen substàncies òpticament actives a partir de compostos simètrics, usant compostos intermedis òpticament actius. Aquesta definició ha anat evolucionant amb els anys, fins i tot acceptant que el camí per arribar a un compost asimètric no passa sempre per sintetitzar-lo directament. Així apareix el concepte de *dissimetrització* en estereoquímica; entesa com el procés pel qual es produeix la modificació d'una estructura molecular de manera que perd un o més elements de simetria. Quan l'estructura no disposa de cap pla de simetria es diu que és quiral o asimètrica.

Durant les últimes dècades la preparació dels compostos enantiomèricament purs ha esdevingut motiu de forta atenció, ja que tenen un paper crucial en la naturalesa a l'estar relacionats amb propietats i funcions biològiques de gran importància. Així enantiòmers oposats interaccionen fisiològicament de manera diferent en els organismes i poden mostrar diferents funcionalitats. Algunes diferències són importants, distingint des d'olors i sabors a efectes teratogènics, com en el cas de la talidomida, que passa de comportar-se

com a sedant en el cas de l'enantiòmer *R* a fer-ho com a teratogènic per a l'*S*[132]. Casos com aquest han estimulat la legislació farmacològica, incloent directrius per a la regulació i comercialització de medicaments sintètics quirals molt restrictives[††]. La conseqüència és que actualment en molts casos està prohibida la comercialització de productes racèmics. Tot això dóna èmfasi en el desenvolupament dels estereoisòmers purs per a la comercialització de nous productes[133].

La dissimetrització es pot realitzar per diverses vies. Inicialment la utilització d'enzims específics era l'opció més estesa. Tanmateix, en els darrers anys han aparegut nombroses publicacions on es mostren dissimetritzacions amb catalitzadors[134] o biotransformacions emprant microorganismes amb gran especificitat[135,136].

Des d'un vessant catalític, la dissimetrització de substrats meso i aquirals mitjançant catalitzadors assimètrics és una de les eines més importants en la síntesi de compostos orgànics amb alta riquesa enantiomèrica[137]. En alguns casos, la seva viabilitat enfront de la utilització d'enzims es veu afavorida pel menor cost dels catalitzadors, i perquè les reaccions poden establir estereoquímica simultàniament en diversos centres, fins i tot si

[††] *Per exemple : B.O. 16/09/08 - Disp. 5260/2008-ANMAT*

estan lluny del punt de reacció, possibilitat que seria més difícil d'aconseguir per altres mètodes. En aquest cas, l'estratègia es basa generalment en la diferència de reactivitat dels àtoms enantiotòpics o dels grups funcionals del substrat amb el reactiu quiral o catalitzador.

Catalíticament, els substrats d'una dissimetrització poden classificar-se segons si poden resoldre en una sola transformació (con en el cas de l'obertura nucleofílica d'epòxids[138], aziridines[139,140] o l'acilació de diols[141]) o en dues reaccions (com la dissimetrització de diens aquirals per hidrosililació catalítica assimètrica[142]).

En alguns casos la dissimetrització es dóna gràcies a una resolució cinètica, on un catalitzador afavoreix la reacció sobre un dels grups enantiotòpics, donant lloc a un altre enantiòmer. Com a conseqüència, el catalitzador resol bé cinèticament, aconseguint eficientment la dissimetrització de compostos meso.

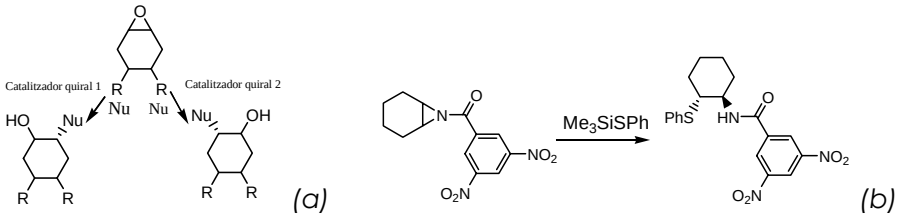


Figura 13: (a) Dissimetrització d'epòxids meso[138](b) Síntesi de β-amidofeniltioeters per dissimetrització de meso-aziridines[140]

D'aquesta manera la dissimetrització de compostos amb grups funcionals enantiotòpics esdevé sintèticament molt atractiva, ja que inicialment les reaccions comporten una dissimetrització que es pot basar en una resolució cinètica, permetent una alta riquesa enantiomèrica[143]. Un exemple seria la reacció en diols meso amb un catalitzador quiral amb anhídrid acètic[144] *(figura 14)*: en un estadi inicial es produeix una formació desigual de monoésters enantiomèrics (1 i 2). Per tal d'enriquir enantiomèricament 1, es practica una acilació posterior la qual està afavorida per a l'enantiòmer minoritari en la primera acilació (2), aconseguint així la resolució de forma cinètica, ja que aquest reacciona més ràpidament transformant-se en un diéster meso. Com a conseqüència, l'excés enantiomèric del monoéster (1) augmenta. D'aquesta manera quan més llarga és la reacció, més riquesa enantiomèrica en monoéster s'obté i més selectiva esdevé la reacció per al monoéster 1.

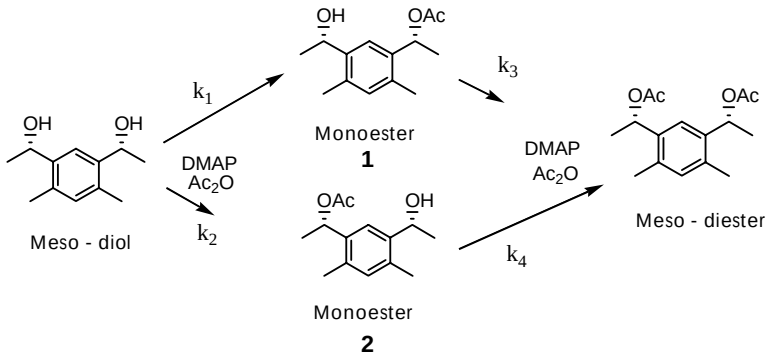


Figura 14: Resolució cinètica catalítica de diols (es representa el diol i l'ester presentant els dos hidroxils en una mateixa posició relativa). En ella: $k_1>k_2$ i $k_4>k_3$. [144]

La dissimetrització catalítica es pot dur a terme resolent al mateix temps dos grups enantiotòpics funcionals. És el cas de la hidrosililació asimètrica intramolecular de diens[142], tal com mostra la figura 15a, on la oxidació del producte proporciona 1,3-diols amb dos nous centres estereogènics simultàniament.

Altres reaccions catalítiques es basen en altres estratègies de síntesi:

- Per desprotonació enantioselectiva[145] *(figura 15b)*
- Per addició enantioselectiva[146,147] *(figura 15c)*
- Per incorporació no regioselectiva de grups funcionals[148] *(figura 15d)* o bé regioselectiva[88].

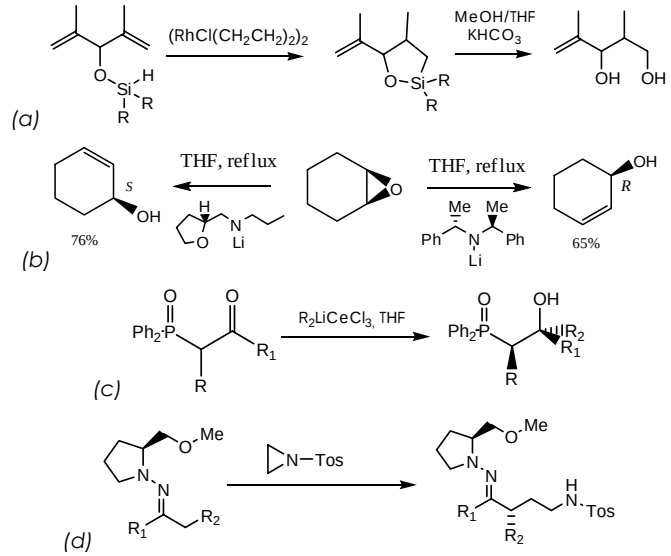


Figura 15 (a) Dissimetrització de diens per hidrosililació[142] (b) per desprotonació (c) per addició (d) per incorporació no regioselectiva de grups funcionals.

El vessant enzimàtic és el més tradicional, atesa la seva especificitat. Així, per al cas dels alcohols, el 1,3-propanodiol s'ha usat en la síntesi de compostos biològicament actius precursors d'antibiòtics antitumorals amb bons rendiments, usant una lipasa de *Pseudomonas sp.*[149].

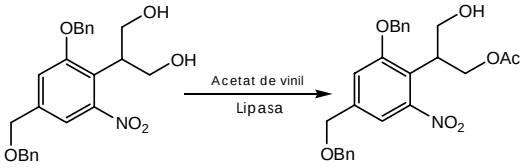
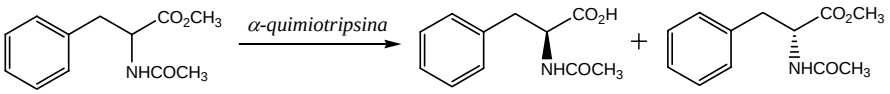


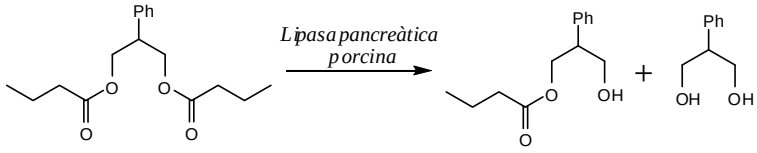
Figura 16: Dissimetrització de diols[149]

En el cas dels esters, algunes hidrolases han esdevingut molt eficients en la dissimetrització de compostos meso i proquirals d'interès farmacèutic, com és el cas de la α-quimotripsina[150]:

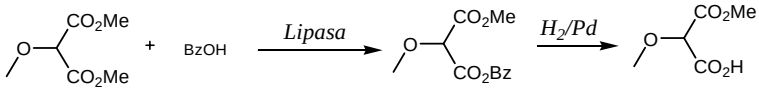


Altres recursos passen per usar agents biològics com *Rhodococcus sp.*, que s'ha mostrat efectiu per a la dissimetrització de nitrils amb bona resolució enantiomèrica.

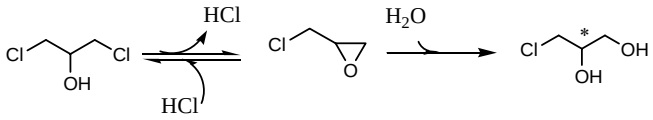
Així, també per via enzimàtica s'ha descrit la síntesi enantioselectiva dels derivats del 2-metil-1,3-propanodiol[151], així com la dissimetrització d'altres 2-(substituït)-1,3-propanodiols[152-155],



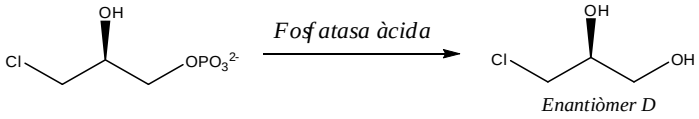
de malonats[156-159],



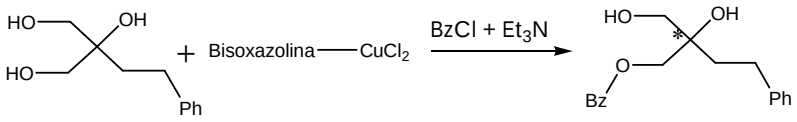
així com de 3-cloro-1,2-propanodiol[160-162] mitjançant *Corynebacterium sp.*:



En el cas de la dissimetrització de productes com el glicerol, la literatura fins al moment inclou majoritàriament la dissimetrització per via enzimàtica[163],



tot i que també es presenten algunes catàlisis químiques[164,165].



9.- Incorporació de noves tècniques en síntesi orgànica

L'estalvi d'energia no només és un postulat de la *Green Chemistry*, sinó que en un món superpoblat i amb recursos renovables limitats, l'aprofitament de l'energia esdevé molt important i necessari. En aquest sentit, la incorporació de la tecnologia de les microones com a font d'energia per escalfar, ha contribuït a optimitzar i reduir les necessitats energètiques dels sistemes d'escalfament clàssics de conducció i convecció. D'altra banda la robotització i els microreactors[166,167] han aportat una optimització dels processos, una automatització, i la capacitat de poder dissenyar instal·lacions de producció en continu. Altrament, els líquids iònics han aportat un nou ventall de possibilitats per a reaccions en un medi líquid iònic apròtic i amb la capacitat de recuperació i reutilització d'aquestes substàncies.

9.1.- L'escalfament per microones

L'increment que s'ha apreciat en els darrers anys en la literatura respecte a l'ús de microones, com alternativa a sistemes d'escalfament que es poden considerar tradicionals[168,169], suposa un exemple de la seva rellevància.

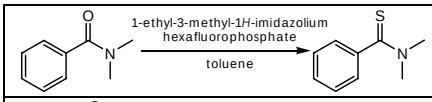
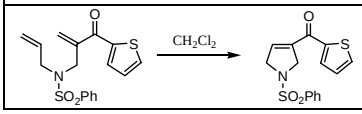
El sistema d'escalfament per microones es basa en l'aplicació d'energia de forma directa sobre les molècules[170]. Aquest fenomen difereix de forma clara amb la metodologia clàssica de transferència de calor per conducció i convecció. És per això que és necessari definir si les microones comporten millores sobre els mètodes considerats tradicionals de escalfament.

La introducció de la energia que aporten les microones en una reacció química, on hi ha d'haver un component capaç d'absorbir les microones, permet una velocitat d'escalfament superior a aquell que pot aportar el sistema convencional[171]. Per a molts dissolvents orgànics aquesta velocitat per assolir la temperatura de reacció desitjada és molt superior a la del sistema convencional. Aquest fenomen és degut a la diferència en la transmissió de l'energia. Així, en el mètode d'escalfament per convecció tradicional l'energia es transmet des de l'exterior a l'interior. En el cas de les microones, aquesta

s'aplica directament, gracies a les col·lisions que experimenten les molècules amb moment dipolar, per efecte de l'absorció del camp elèctric que la radiació de microones duu associat.

L'energia de la microona s'incorpora en el reactor per la radiació que produeix el magnetró, i això comporta que no es fa necessària una interacció directa entre la font d'energia i la mostra que està essent escalfada. Aquest fet, juntament amb el de la velocitat d'escalfament abans esmentat, permet obtenir uns perfils de temperatures més homogenis. L'escalfament per convecció va associat a un escalfament heterogeni, segons la penetració de l'energia de fora cap a dins, donant lloc moltes vegades a tractaments de llarga durada. En aquest sentit la *taula 5* mostra dades comparatives de reaccions dutes a terme en tots dos procediments. S'observa que els temps de reacció en els assajos amb microones són sensiblement més curts.

Taula 5: Exemples de reaccions amb tractaments convencionals i amb microones

	Microones	Convencional
	200 ºC 15 min[172]	90 ºC 30 h
	100 ºC 10 min[173]	20 ºC 24 h

L'escalfament per microones permet assolir la temperatura desitjada de forma quasi immediata, afavorint l'eficiència del tractament, enfront al mètode convencional, que requereix un temps d'acondicionament. El tractament per microones també és capaç d'aconseguir un refredament ràpid de la mostra. Així el tractament esdevé més curt, ja que l'energia s'aporta i es retira més ràpidament.

Els materials dels aparells de microones interaccionen de manera diferent segons la seva transparència a les microones. Així, és possible refredar el vial de reacció amb un component refrigerant transparent a les microones, com el nitrogen líquid, mantenint les parets del reactor fredes, mentre s'està tractant la mostra amb les microones, sense interferir en la reacció de l'interior del vial[168].

L'aplicabilitat ha quedat palesa en diferents camps de la síntesi química, com el de reaccions amb enzims[174] i, en general, amb productes termolàbils, com ara les proteïnes ja que l'escalfament per convecció tradicional les desnaturalitzava de forma que perdien la seva funcionalitat[169].

Quan en una reacció química s'usen mescles de substàncies de diferent capacitat d'absorció, la inducció calorífica d'una pot induir escalfament a l'altra tot i ser transparent a les

microones. Així per exemple, en la mescla del benzè (98%), que és quasi transparent a les microones, amb metanol (2%), també s'observa un escalfament ràpid de la mescla. El procés en microones comporta uns moviment de rotació i translació de les molècules, i encara que l'efecte pugui tenir els seus orígens en la rotació de les molècules veïnes, en aquest cas del metanol, les col·lisions provoquen l'escalfament del benzè[169].

Els aparells de microones que funcionen en el sistema monomodal focalitzen l'energia en una única regió, aquest fet permet un millor control de la pressió i la temperatura, i per tant, de les condicions de treball. D'aquesta manera es poden dur a terme reaccions a alta pressió i temperatura de fins a 100 ºC superior a la del seu punt d'ebullició, actuant el dissolvent en unes condicions, quasi supercrítiques, que s'assoleixen de forma molt ràpida. Així per exemple a l'augmentar la temperatura de l'aigua s'observa que es comporta com un dissolvent orgànic esdevenint fins i tot apolar fent que els compostos orgànics apolars esdevinguin solubles[168]. En condicions supercrítiques *(Tc=374 ºC i Pc=218 atm)*, l'aigua augmenta l'acidesa, i redueix la densitat i la constant dielèctrica[168].

En mostres solides, la transferència d'energia és menor i en conseqüència l'escalfor generada no es pot dissipar fàcilment

ocasionant sobreescalfament. Tot i així hi ha autors[175-177] que introdueixen amb èxit la possibilitat de fer les reaccions en fase solida sense dissolvent, com a mètode efectiu per a produir reaccions d'acord amb la *Green Chemistry*[171].

9.2.- Els líquids iònics

Els líquids iònics (IL) són aquelles substàncies salines que es mantenen líquides a temperatures inferiors a 100 ºC. Altres sals també esdevenen líquides a temperatures superiors, si bé en aquests casos es parla de sals foses, i no pas de líquids iònics.

La seva síntesi es remunta al 1914[178], quan es va sintetitzar el nitrat de trietilamoni addicionant àcid nítric a la trietilamina i evaporant la mescla fins a sequedat.

Per la seva naturalesa tenen una pressió de vapor molt baixa, això limita les seves emissions tòxiques o perilloses a l'atmosfera. Els conseqüents beneficis ambientals que comporta fa que algunes vegades siguin mal anomenats "*green solvents*"[179]. El cert és que alguns d'ells poden arribar a ser molt corrosius, inflamables, i fins i tot tòxics[180]. Amb tot, actualment són acceptats com a part de la "*Green Chemistry*", encara que la

seva possible solubilitat en aigua els faci perillosos a nivell aquàtic[179].

Els ions dels IL presenten una estructura relativament voluminosa. Les seves característiques físico-químiques en alguns casos encara estan per descobrir. Tot i això, les seves propietats més notables resideixen en la seva molt baixa pressió de vapor[181], baixa inflamabilitat[182], estabilitat tèrmica (alguns suporten temperatures per sobre de 500 ºC), el seu potencial de solvatació i l'elevat rang de potencial electroquímic[183].

La seva solubilitat pot ser variable: així, considerant sempre les sals amb imidazole i derivats, l'afinitat per l'aigua[184] és alta en les sals d'halur, acetat, nitrat o trifluoroacetat, i molt baixa en les sals amb $[PF_6]^-$ i $[(CF_3SO_2)_2N]^-$ [185].

Per tant, l'elecció de l'anió permet variar les característiques entre ILs amb el mateix catió. Així, segons les seves propietats seran adequats per una o una altra funció, essent així l'elecció dels ions l'estadi més crític quan es treballa amb IL.

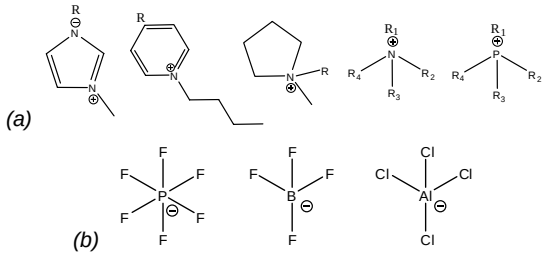


Figura 17: Exemples d'estructures de cations (a) de IL: 1-R-3-metilimidazola, 4-R-N-butilpiridina, N-metil-N-R-pirrolidina, i amoni i fósfor quaternaris. De anions (b): hexafluorofosfat, tetrafluoroborat i tetraclorur d'alumini.

El procés de producció d'un IL es divideix en dues parts[184]: la formació del catió i el bescanvi amb l'anió per formar el producte desitjat, que es pot subdividir en unes altres tres parts: Reacció entre halurs (com un halur d'amoni) i àcids de Lewis (*figura 18*), la formació del IL per metàtesi[186] o una reacció de neutralització àcid-base.

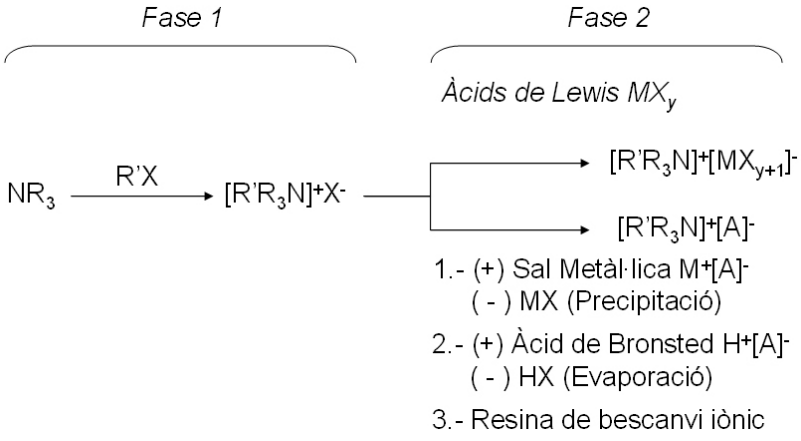


Figura 18: Exemple de passos per a la síntesi de IL

El seu potencial encara avui no està del tot definit. S'usen generalment com a dissolvents, electròlits electroquímics o catalitzadors, com a alternativa als dissolvents orgànics habituals.

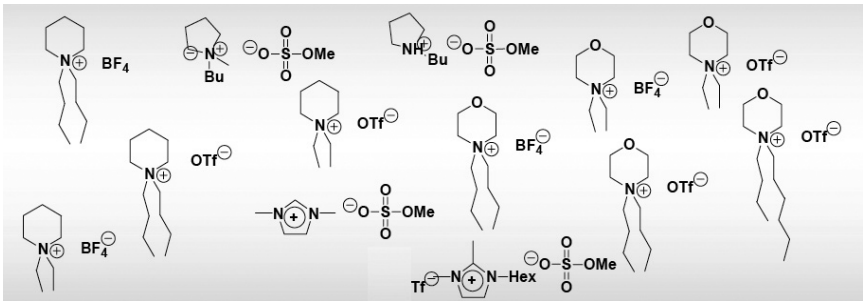


Figura 19: Exemples de IL

Les aplicacions dels IL's, es limiten fonamentalment a l'àmbit de laboratori, per això els principals productors són proveïdors de laboratoris, com Across, Cytec, Merk, Scionix o Sigma-Aldrich. Les seves aplicacions ofereixen multitud de possibilitats en el camp de la recerca. Les principals són:

1) En reaccions i catàlisi[187], per exemple:

Alquilació Friedel-Crafts[188-190]	*Sulfonació*
Acoblament de Heck i Suzuki[191]	*Nitració*
Oxidació (amb aire o oxigen)[192]	*Halogenació*
Reducció	*Diazotació*
Hidrogenació quiral[193]	*Diels-Alder*[195]
Oligomerització	*N-alquilació i O-alquilació*
Polimerització[184,194]	*Condensació aldòlica*

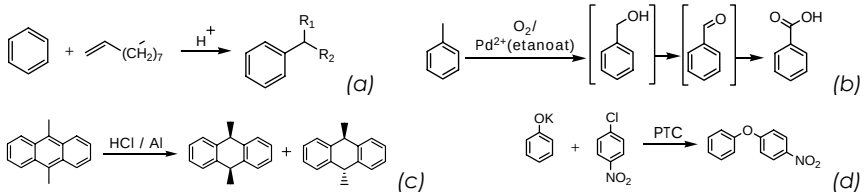
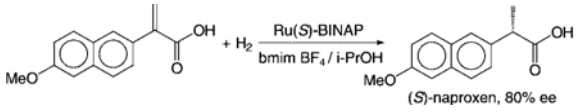


Figura 20: (a) Exemple d'alquilació de Friedel-Crafts amb líquids iònics[196]. com $[BMIM]_2[SO_4]$, $[BMIM][HSO_4]$, $[OMIM][HSO_4]$ i $[BMIM][(CF_3SO_2)_2N]$ Radicals aparellats en ordre: R_1(metil, etil, propil o butil) R_2 (octil, heptil, hexil o pentil) (b) Oxidació catalítica selectiva de toluè amb [C4dmim][BF4][192] (c) Hidrogenació estereoselectiva amb [emim]Cl–$AlCl_3$[193] (d) Síntesi del p-nitrofenil fenil èter amb CYPHOS IL® [197] (PTC = phase transfer catalysis)

2) Com a dissolvents per a catàlisi[198,199]
3) En síntesi de polímers[184]
4) En biocatàlisi, com en la síntesi de *(S)-naproxen*[200]



5) Aplicacions electroquímiques com a dissolvent[199]
6) Com a fases estacionàries en cromatografia[201]
7) En separacions líquides i gasoses[202,203]
8) Com a fluids tèrmics o lubricants[199]

A nivell industrial, el seu principal inconvenient resideix en el seu cost, avui en dia encara massa elevat per a que es pugui pensar en una aplicació en processos a gran escala. Aquest fet unit a la seva elevada viscositat, fa que encara no siguin molt utilitzats pel sector industrial.

La puresa dels IL es determina generalment per NMR[204] anàlisi elemental i espectroscòpia de masses per tal de caracteritzar-los. Les estructures cristal·lines es poden determinar per difracció monocristal·lina de raigs-X per comparar les similituds estructurals entre el microcristall i la composició global microcristal·lina. Les propietats tèrmiques es determinen per termogravimetria diferencial.[205].

9.3.- Els microreactors

La tecnologia de microreacció s'està desenvolupant amb força en els darrers temps com a complement o suport a altres tecnologies. La seva avantatge principal resideix en la possibilitat d'aplicar les condicions de reacció desitjades (generalment relatives a flux, que es tradueix en temps de residència, pressió i temperatura) amb una bona transferència de calor, conferint la possibilitat de reduir d'aquesta manera el temps de residència.

Al mateix temps, el fet d'optimitzar molt les proporcions, la precisió del sistema i l'energia, fa que presenti característiques molt d'acord amb els postulats de la *Green Chemistry*. En aquests termes, els microreactors també responen al concepte d'intensificació, entesa com: el desenvolupament de nous aparells i tècniques que, en comparació amb les usades

comunament, confereixen millores substancials en el procés i en la manufactura, reduint substancialment el tamany dels equips i el ràtio mida/producció d'aquests, el seu consum d'energia i la seva producció de residus, donant lloc a tecnologies més econòmiques i sostenibles[206]. L'adequació a aquest concepte també contribueix a aquesta idoneïtat amb la química verda.

Un microreactor *(figura 21)* consta generalment d'una matriu metàl·lica, de vidre borosilicat o de silice, microcanalitzada mitjançant làser o d'altres tècniques, de manera que el producte circula de forma contínua pels microcanals aconseguint una intensificació de les condicions que permeten de reduir el temps de reacció. La matriu es disposa dins d'una estructura metàl·lica calefactada i pressuritzada a la mateixa pressió del sistema.

Figura 21: Microreactor amb matriu microcanalitzada amb finestra[166]

Aquesta tecnologia facilita l'escalat amb poca infraestructura, lluny dels grans reactors discontinus, gràcies a la capacitat de producció en continu. D'aquesta manera, el control sobre el procés és superior i més eficient, ja que elimina els possibles gradients interns que són inevitables en els reactors discontinus. També optimitza la transferència de calor, i minimitza els riscos en reaccions agressives per acumulació d'agents perillosos en el temps[207,208]. Com a exemples de reaccions on s'han usat microreactors podem trobar la condensació de Knoevenagel[209] i la reacció de Suzuki[210].

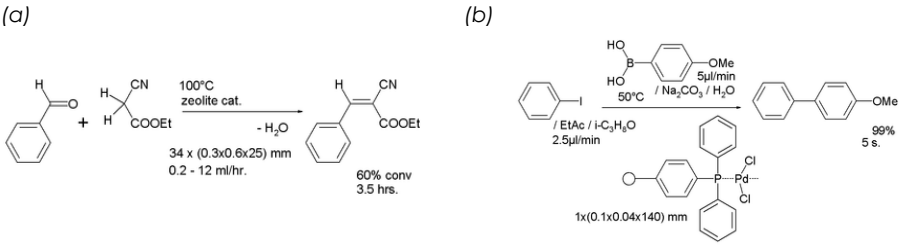


Figura 22: Exemples de reaccions realitzades amb microreactors: (a) Reacció de condensació de Knoevenagel (b) Reacció de Suzuki

Darrerament la mecanització de processos amb microreactors s'ha millorat gràcies a l'acoblament de micromescladors que permeten optimitzar el procés continu i la reacció, ja que els components poden ser mesclats *in situ*, de manera que tenen la possibilitat de ser pre-escalfats. Aquest fet permet escurçaments superiors de les reaccions.

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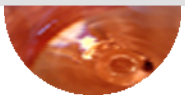


ELS OBJECTIUS

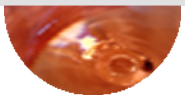
Després de tots els condicionants i motivacions descrits en el capítol anterior referents a la necessitat de trobar usos alternatius per a l'excedent de glicerol, l'objectiu general d'aquesta tesi és la preparació de derivats d'aquest producte, que tinguin un interès ja sigui com a productes finals o com a precursors sintètics d'altres productes.

Aquest objectiu principal, es particularitza en l'estudi d'una primera reacció que contempla de manera simultania un procés d'esterificació-substitució del glicerol amb un àcid carboxílic i font d'ions clorur, i que dóna lloc als esters de dicloropropil. Aquest estudi dóna lloc a altres objectius complementaris com són:

1. Estudiar el comportament, conversions i rendiments, de l'esterificació usant diferents àcids carboxílics.

2. Sintetitzar esters d'al·lil a partir dels esters de dicloropropil.

3. Fer substitucions selectives per dessimetritzar els esters de dicloropropil amb la finalitat d'obtenir compostos quirals.



4. Estudiar la viabilitat, i ajustar les condicions, de l'ús de subproductes industrials com a reactius per aquesta esterificació-substitució.

5. Optimitzar tant en despesa de reactius com d'energia la reacció, incorporant noves tècniques de síntesi orgànica.

6. Estudiar l'activitat ovicida que manifesten alguns esters d'al·lil.

CAPÍTOL III: SÍNTESI D'ESTERS DE DICLOROPROPIL

1.- Introducció

Aquest capítol està dedicat íntegrament a l'estudi de la reacció de síntesi dels esters de dicloropropil. L'esterificació-cloració de diols amb alts rendiments, ja va ser descrita amb anterioritat[1]. Es pretén doncs aplicar la mateixa reacció al glicerol i aprofundir en el seu estudi.

La reacció consisteix inicialment en una esterificació de l'alcohol en medi àcid a través d'intermediaris cíclics dioxolans. Aquests evolucionen degut a l'atac nucleofílic dels ions clorur aportats pel clorotrimetilsilà (CTMS) que condueixen a la substitució seqüencial dels dos hidroxils, tal com mostra la figura següent.

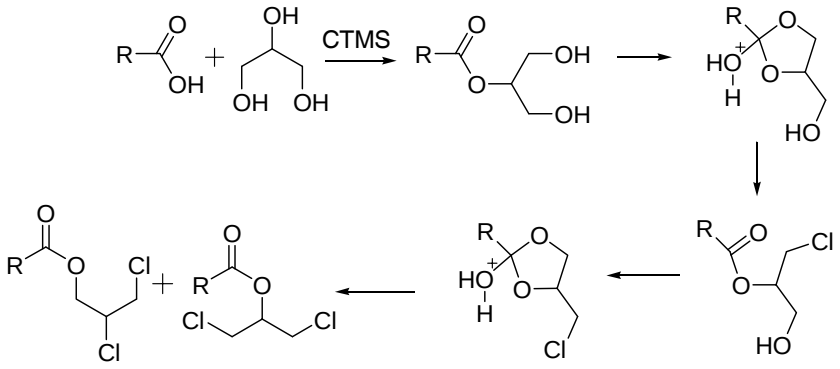


Figura 1: Exemple d'una de les vies d'esterificació i cloració simultànies del glicerol en la síntesi d'esters de dicloropropil

La reacció s'ha assajat amb èxit amb diferents tipus d'àcids: alifàtics saturats i insaturats, aromàtics, versàtics i heterocicles amb oxigen o sofre, aconseguint rendiments entre un 77 i un 95% en sistema *batch*.

Tanmateix, s'observa que la reacció pot donar lloc a dos regioisòmers: l'ester de 2-cloro-1-(clorometil)etil i l'ester de 2,3-dicloropropil. En aquest sentit s'han avaluat les diferències entre les proporcions regioisomèriques dels productes, atenent a la quantitat d'energia aportada, observant-se l'existència d'un control cinètic de la reacció a temperatura moderada. Així, s'ha l'aplicat el mètode d'escalfament clàssic o convencional, a temperatura inferior i temps més llarg, i l'escalfament per microones, a temperatura superior i temps més curt.

Per altra part, s'han ajustat les relacions molars de reactius, fent-les properes a la equivalència i sense fer ús de dissolvents pel que fa a la reacció química. D'aquesta manera s'ha optimitzat el procés des d'un punt de vista d'ecomonia molar de reactius.

L'explicació de la formació dels dos regioisòmers en diferents proporcions segons la temperatura de reacció emprada resideix en que, energèticament, l'ester de 2,3-dicloropropil, si bé més estable, requereix una energia d'activació superior.

En tots els assajos duts a terme es fa evident que per a l'obtenció de l'ester de 2-cloro-1-(clorometil)etil, no es necessita tanta temperatura, la qual cosa es pot explicar hipotitzant que l'energia d'activació del procés és menor. Tanmateix, els càlculs teòrics realitzats a l'Institut de Química Computacional de la Universitat de Girona, indiquen que no és un producte tant estable com el seu corresponen regioisòmer. Aquests càlculs B3LYP s'han realitzat amb el programa Gausian03 (2004) amb nivell 6-311++G(d,p). Així la síntesi de l'ester de 1,3-dicloropropil es duria a terme sota control cinètic. Tanmateix, si considerem que la diferència de nivells energètics entre els dos estats no és massa gran, sempre s'obté una mescla dels dos regioisòmers.

Efectivament, s'ha comprovat que simplement escalfant amb microones l'ester de 2-cloro-1-(clorometil)etil sense cap altre reactiu, es pot induir la regiomerització cap a proporcions majoritàries de l'ester de 2,3-dicloropropil.

L'energia s'aporta més ràpidament usant microones, el qual assoleix fàcilment i en poc temps temperatures que gairebé tripliquen la temperatura modelitzada per al tractament convencional. D'aquesta manera, es confirma que la formació de l'ester de 2,3-dicloropropil està sota control termodinàmic, ja que s'aprecia que usant la mateixa intensitat de radiació de microones, i mantenint, en aquest cas, el reactor fred (com a màxim 35 ºC), no hi ha la formació d'aquest producte i sí del regiosiòmer 2-cloro-1-(clorometil)etil.

Per a realitzar aquesta darrera comprovació, s'ha emprat un àcid de cadena curta per tal d'assegurar que, en les condicions en les que es duu a terme la reacció en el microones, la mescla es mantingui homogènia i en estat líquid.

Una altra de les noves tècniques en síntesi orgànica que s'aplica a aquesta reacció d'esterificació és l'ús de líquids iònics (*IL*) com a dissolvent. En quest cas, el *IL* fa de catalitzador y de dissolvent alhora amb la particularitat que aquest és recuperable. D'altra banda la substitució del CTMS per un halur

dóna la possibilitat d'abaratir els costos de la reacció. En aquest cas s'ha optat per a substituir el clorotrimetilsilà pel clorur d'alumini hexahidratat. El líquid iònic utilitzat ha estat l'hexafluorofosfat de 1-butil-3-metilimidazole *[BMIM-PF_6]*. En la bibliografia es pot trobar un mètode semblant desenvolupat pel mateix grup de recerca que usa l'èter *Corona-18* per obtenir un rendiment similar usant *KCl* [2]. En aquest cas, s'han obtingut rendiments molt satisfactoris per a la totalitat dels àcids assajats, llevat de l'àcid picolínic. En el nou procés descrit en aquesta tesi no es fa necessària la presència de l'esmentat èter *Corona-18* en la reacció.

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2. From Glycerol to Chlorohydrin Esters using a Solvent-free System. Microwave Irradiation versus Conventional Heating

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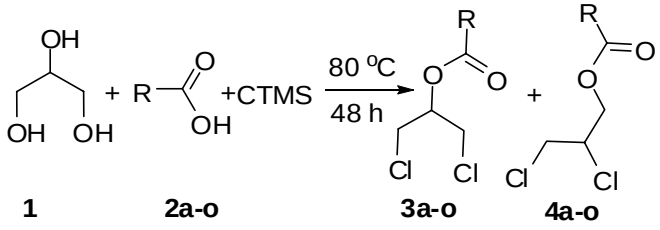
Abstract— Esterification–chlorination of glycerol provides chlorohydrin esters in high yields. A ratio of reagents close to equivalence can be used, so that atom economy of the reaction is optimized. The reaction can be carried out using either classical or microwave heating, and no solvent is required. 2-Chloro-1-(chloromethyl)ethyl esters can be obtained in high regioisomeric relationship when either low or moderate temperature is used. In contrast, microwave irradiation allows the use of higher reaction temperatures that render mixtures of both regioisomers in variable relationships. Kinetic control of the process is proposed for classical heating, and experimental results are analyzed with the aid of ab initio calculated values. Nonthermal phenomena can be used to explain the high efficiency of microwave irradiation at low temperature.

Keywords: Chlorohydrin esters, CTMS, glycerol, MW, nucleophilic substitution, rearrangement

1. Introduction

The interest in new industrial applications of glycerol is increasing parallel to the growth of biodiesel production. Recently, new procedures have been patented to convert this compound to a mixture of chlorohydrin esters and then to epichlorohydrin.[1] One of the main goals of these methods is to use a low-cost renewable feedstock such as glycerol.[2] The transformation of glycerol to dichloropropyl derivatives allows the preparation of several compounds with wide applications.[3]

We have already described how dichloropropyl esters can be obtained by an esterification–substitution reaction from both glycerol and 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (solketal), a monoketal from glycerol, using diverse reagents. Among them chlorotrimethylsilane (CTMS) has shown to be the more reliable one.[4] These results has prompted us to study deeply the use of CTMS for a direct esterification–substitution of glycerol to prepare dichloropropyl esters. The use of CTMS as an acidic catalyst in esterification is widely described, and its ability to produce chlorohydrin esters has been demonstrated using different diols[4a] and carboxylic acids.[5] Herein, we report the direct transformation of glycerol (**1**) into dichloropropyl esters (Scheme 1). No solvent is required for the reaction, and reagents can be used close to equivalence. The energy needed for the reaction can be provided using either classical heating or microwave systems. The mechanism proposed for this transformation is supported by the experimental results and a computational analysis approach. Moreover, the effect of microwave irradiation at low temperature could be explained by considering nonthermal microwave effects.[6]



Scheme 1. Simultaneous esterification and chlorination of glycerol using carboxylic acids, chlorotrimethylsilane (CTMS) and classical heating

2. Results and Discussion

First, a mixture of glycerol (**1**) with the corresponding carboxylic acid (**2a**–**o**) in a fivefold molar excess of CTMS was heated for 48 h at 80 ºC. All of the tested acids led to the formation of the corresponding 2-chloro-1-(chloromethyl)ethyl carboxylates (**3a–o**) as the main regioisomer (Table 1). To improve the atom economy (E) of the process, experiments were carried out using a mole ratio of 1.2:1:2.2 glycerol:carboxylic acid:CTMS. Crude yields and regioisomeric ratios were in most cases similar to those obtained with the 2:1:5 mole ratio (Table 1). Only dinitrobenzoic and linolenic acids exhibited lower yields. In these cases, the corresponding intermediate **15** (Scheme 2) was present in yields of around 30% (determined by 1H NMR). To shorten the reaction time, the same reactions were carried out using a mole ratio of 2:1:5 glycerol:carboxylic acid:CTMS and a pressurized monomode microwave oven at 2.45 GHz. The reaction for most of the compounds synthesized was carried out by programming the microwave oven temperature at 250 ºC for 20 min. The microwave reactor automatically controls the reaction pressure, the power irradiation, and the cooling time. Using these conditions, the reaction temperature was 243–247 ºC. Reactions using dinitrobenzoic acids (**2j** and **2k**) were carried out at 170–175 ºC (microwave oven temperature 175 ºC) for 20 min to avoid product decomposition. Although the yields after 20 min of reaction were similar to those obtained by conventional heating, the ratio of regioisomers (**3**:**4**) changed significantly (Table 1). Finally, equivalent experiments were carried out using a mole ratio of 1.2:1:2.2 glycerol:carboxylic acid:CTMS. Crude yields were in most cases lower to those obtained with the 2:1:5 mole ratio (Table 1). Nevertheless, regioisomeric ratios were similar (Table 1). The formation of insoluble materials was observed in these experiments. These materials could be produced from some of the intermediate compounds when temperature is high and CTMS is not present in enough molar excess.

The different regioisomeric ratios obtained for the various acids could be explained according to the charge density at the carboxylic carbon of the various acids.[5] Moreover, microwave irradiation usually tends to promote thermodynamically stable products.[6] This effect is enhanced when polar intermediates occur during the reaction process.[7] Nevertheless, some experiments show that microwave can also modify activation parameters.[14] Consequently, different compounds can be obtained.

Trying to determine the reason for the different results observed among both energy providing systems, a set of experiments were planned using a microwave reactor and palmitic acid as a model system (Table 2). First, the reaction was carried out at the same temperature as classical heating using palmitic acid as a model system. After 16 h, the reaction was almost completed, and the 2-chloro-1-(chloromethyl)ethyl

Table 1.

Percentage yields and regioisomeric ratio of chlorohydrin esters 3:4 obtained using different reaction conditions and heating systems

		Classical[a]		Classical[b]		Microwave[c]		Microwave[d]	
Eentry	R	Isolated yield %	ratio	Crude yield %[e]	Ratio	Isolated yield %	ratio	Crude yield %[e]	ratio
A	$CH_3(CH_2)_{14}$	91	98:2	110	97:3	86	37:63	70	38:62
B	$CH_3(CH_2)_6$	88	85:15	92	81:19	81	39:61	73	35:65
C	$(CH_3)_3C$	95	99:1	94	100:0	90	41:59	62	33:67
D	Linolenyl	86	99:1	63	81:19	74	30:70	79	30:70
E	C_6H_5	88	99:1	96	100:0	80	35:65	64	39:61
F	C_6H_5-CH=CH	80	100:0	83	99:1	73	41:59	64	44:56
G	o-Cl-C_6H_4	85	98:2	103	99:1	78	35:65	61	41:59
H	o-HO-C_6H_4	92	97:3	89	100:0	73	41:59	52	43:57
I	m-NO_2-C_6H_4	90	100:0	91	98:2	78	30:70	60	36:64
J	3,5-$(NO_2)_2$-C_6H_4	77	100:0	52	99:1	77[f]	54:46	57[g]	55:45
K	2,4-$(NO_2)_2$-C_6H_4	81	99:1	30	100:0	75[f]	59:41	65[g]	58:42
L	1-naphthyl	89	100:0	93	99:1	82	36:64	55	37:63
M	2-naphthyl	82	100:0	101	100:0	76	37:63	60	41:59
N	2-furyl	84	96:4	94	98:2	78	35:65	55	33:67
O	2-thiophencarboxyl	88	99:1	90	100:0	72	36:64	63	39:61

[a] Mole ratio 1:2:CTMS, 2:1:5, reaction temperature 80 ºC, reaction time 48 h

[b] Mole ratio 1:2:CTMS, 1.2:1:2.2, reaction temperature 80 ºC, reaction time 48 h

[c] Mole ratio 1:2:CTMS, 2:1:5, reaction temperature 243–247 ºC, reaction time 20 min

[d] Mole ratio 1:2:CTMS, 1.2:1:2.2, reaction temperature 243–247 ºC, reaction time 20 min

[e] Determined by GC using an internal standard

[f] Mole ratio 1:2:CTMS, 2:1:5, reaction temperature 170–175 ºC, reaction time 20 min

[g] Mole ratio 1:2:CTMS, 1.2:1:2.2, reaction temperature 170–175 ºC, reaction time 20 min

regioisomer was the main isomer synthesized. Classical heating provided 64% yield for the same temperature and reaction period. Once we had determined that classical and microwave heating gave similar regioisomeric ratios at 80 ºC, experiments at higher temperatures were carried out using microwave irradiation. The reaction period was progressively diminished to avoid product decomposition. Nevertheless, changes introduced in the reaction time were always tested, at the corresponding

temperature, to determine that the regioisomeric ratio was not strongly affected by the reaction time. Table 2 shows that 2,3-dichloropropyl ester **4a** increased parallel to temperature increase.

Consequently, regioisomeric ratio seems to be dependent of the temperature and independent of the heating system used. Nevertheless, considering that irradiation power in the experiments described above changed automatically to achieve the desired temperature and that non-thermal effects[7] have been adduced to explain some results in microwave irradiation studies, we decided to carry out a new set of experiments using the highest irradiation power yielded by the reactor (300 W) but maintaining the temperature at 30–35 ºC. These reactions were carried out in an open vessel provided with a low temperature accessory. Using this approach, we tried to determine if non-thermal microwave effects were able to promote the formation of the 2,3-dichloropropyl palmitate **4a**. When the reaction was carried at 30–35 ºC and 300 W for 2 h, dichloropropyl palmitates **3a** and **4a** were obtained with 32% yield and a 90:10 ratio. Consequently, a high ratio of the **3a** regioisomer was also observed using the highest irradiation power but maintaining low temperature. The same reaction was carried out at 30–31 ºC for 48 h without microwave irradiation. Although a Labroller rotator was used to improve reaction stirring, no reaction was observed in this case. As these results could stem from the lack of homogeneity, because palmitic acid is a solid at this temperature, an equivalent experiment was performed using caprylic acid (**2b**) to assure a liquid homogeneous system.

When the reaction was carried out at 30–35 ºC and 300 W for 2 h, dichloropropyl caprylates (**3b** and **4b**) were obtained with 95% yield. Similar yields were obtained carrying out the reaction for 48 h at 30–31 ºC without microwave irradiation. The **3b:4b** regioisomeric ratios, 85:15, were similar in both cases. In conclusion, high microwave irradiation power at low temperature did not produce the increase of 2,3-regioisomeric ester but significantly decreased the reaction time needed to obtain high conversion yields. This effect has been extensively described in the literature and is best observed when polar products such as glycerol are present in the reaction medium.

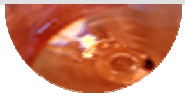


Table 2

Percentage yields and regioisomeric ratio of chlorohydrin palmitates **3a:4a** (in parentheses) obtained at different temperatures and reaction times.

Temp. °C (SD)[a]	Reaction Time (h)[b]				
	1/3	2	5	8	16
80.0 (0.5)[c]		52% (96:4)	72% (95:5)	85% (95:5)	96% (90:10)
99.9 (0.7)[c]		54% (92:8)			
149.8 (0.6)[c]	96% (85:15)	95% (84:16)			
199.4 (0.8)[c]	98% (40:60)				
234.1 (8.3)[c]	93% (32:68)				
80.0 (1.0)[d]		9% (94:6)		35% (97:3)	64% (98:2)

[a] Standard deviation

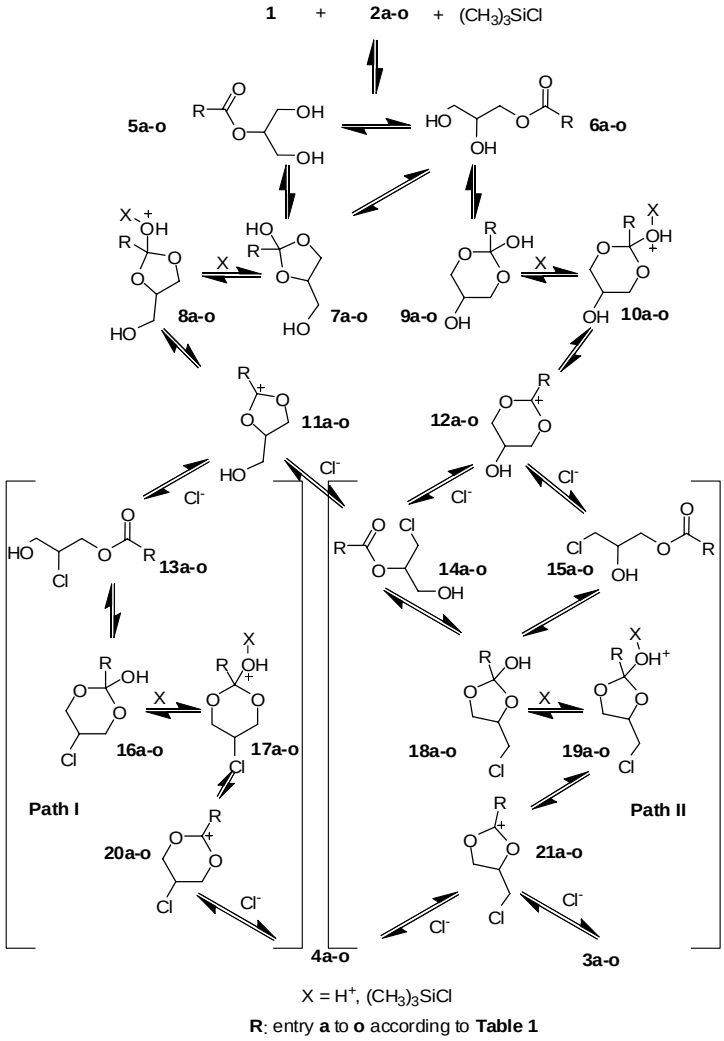
[b] Yields determined by GC using an internal standard

[c] Mole ratio 1:2:CTMS, 2:1:5, microwave irradiation

[d] Mole ratio 1:2:CTMS, 2:1:5, classical heating

Non-thermal processes have been proposed to explain such results.[6b] Glycerol, a highly polar molecule, will instantaneously absorb a high amount of microwave energy.[7] The rotational motion of such molecules is then increased. This causes a kinetic energy increase in the molecules that could drive the reaction to completion faster than using conventional heating. This effect could also be assumed to explain the results obtained using palmitic acid at low temperatures. Microwave irradiation could provoke hot spots on the solid; then the energy absorbed would be enough to carry out the reaction to some extent.[6b] However, the generated energy may not be enough to produce an increase of the 2,3-regioisomeric ester.

These results could be explained assuming the kinetic control of the reaction at low temperature. Reaction will be thermodynamic controlled as the temperature increases. Nevertheless, diverse pathways could be proposed to obtain these two regioisoemers (Scheme 2). Pathway II will allow a kinetic versus thermodynamic control of the reaction, whereas pathway I will allow a different way to obtain the 2,3-regiosomer. This pathway could be favored by using the microwave reactor.



Scheme 2. Putative mechanistic pathways to explain the formation of chlorohydrin esters using CTMS as reagent and catalyst

To propose a feasible mechanism for this one-pot esterification–chlorination reaction, an isomeration set of experiments and a computational analysis were carried out.

Table 3

Final regioisomeric ratio obtained after microwave irradiation (300 w max, 17 atm max, 243–247 ºc) of 2-chloro-1-(chloromethyl)ethyl palmitate **3a** in various solvents

Solvent	Reaction time[a]	
	1 h	2 h
None	3:7	---
Isooctane	6:4	3:7
Xylene	4:6	---
Chloroform	3:7	---
Chlorotrimethylsilane	4:6	4:6
Hexamethyldisiloxane	7:3	5:5
Butanone	3:7	---
tert-Butanol	3:7	---

[a] **3a:4a** ratio determined by GC using an internal standard

2-Chloro-1-(chloromethyl)ethyl palmitate **3a** was heated either in a solvent-free system or in the presence of several solvents to evaluate the putative isomerization of **3a** to **4a** (Scheme 2, Pathway II) in diverse conditions. Table 3 shows that in all cases **3a** led to a similar regioisomeric mixture whatever the reaction medium used. Similar results were described by Derbesy and Naudet[8] studying the isomerization of 1-chloro-2-propyl and 4-chloro-2-butyl esters and for the isomerization of dihalopropyl acetates.[9] In contrast, Nayler[10] described the isomerization of 2,3-dibromopropyl aryl esters to the corresponding 2-bromo-1-(bromomethyl)ethyl esters by classical heating. In this case, none of the 2,3-regioisomers remained at the end of the reaction. Nevertheless, the authors reported that 2,3-dibromopropyl alkyl esters did not isomerize to the 2-bromo-1-(bromomethyl)ethyl esters under the same reaction conditions.

Once the isomerization process was studied, a B3LYP[11] calculations at the 6-311++G(d,p)[12] level were carried out for the different species using the Gaussian03[13] package (see supplementary data).

Table 4

DFT B3LYP/6-311++G(d,p) electronic energies for the formation of dichloropropyl pivaloates and dichloropropyl benzoates (a.u.)

entry	**C**	**e**
3	-1384.317846	-1458.135040
4	-1384.322864	-1458.138310
5	-615.575979	-689.387273
6	-615.581423	-689.392973
7	-615.558250	-689.363810
8	-	-
9	-615.546909	-689.366530
10	-	-
11	-539.454866	-613.274373
12	-539.454574	-613.271013
13	-999.939768	-1073.756168
14	-999.962433	-1073.773905
15	-999.959785	-1073.771218
16	-999.940996	-1073.746778
17	-	-
18	-999.942836	-1073.748508
19	-	-
20	-923.831767	-997.64845
21	-923.832924	-997.650673

The calculation of harmonic frequencies was performed to confirm that they were minima. Table 4 shows electronic energies for each different intermediate and the final products for pivalic and benzoic acids as model compounds. Species **8**, **10**, **17** and **19** were not allocated because the protonation of **7**, **9**, **16** and **18** result into a spontaneous H_2O elimination. These data seem to confirm that the corresponding 2-chloro-1-(chloromethyl)ethyl esters (**3**) are less thermodynamically stable than the 2,3-dichloropropyl esters (**4**) (13.16 kJ mol^{-1} for R = $C(CH_3)_3$ and 8.58 kJ mol^{-1} for C_6H_5). Therefore, classical heating will drive the process to the kinetically controlled products, whereas high temperatures, reached with microwave heating, favor thermodynamic control of the reaction. Pews and Davis[9] have shown that the 2-

chloro-1-(chloromethyl)ethyl acetate can be partially isomerized to 2,3-dichloro-1-propyl acetate at 180 ºC, which confirms our hypothesis. Table 4 also shows that regioisomer **6** is more stable than **5** (14.28 kJ mol^{-1} and 14.95 kJ mol^{-1} for each substituent), confirming that α-monoacylglycerides are more stable than β-monoacylglycerides. However, intermediate **14** is more stable than **13** (59.49 kJ mol^{-1} for R = $C(CH_3)_3$ and 46.52 kJmol^{-1} for C_6H_5) and **15** (6.99 kJ mol^{-1} and 7.04 kJ mol^{-1}, respectively), both containing the carboxylic group in the α position. Moreover, 1,3-dioxolanic compounds **18** is more stable than the corresponding 1,3-dioxanic isomers **16** (4.83 kJ mol^{-1} and 4.54 kJ mol^{-1}). Protonation of **16** and **18** proceeds spontaneous to the loose of H_2O, giving **20** and **21**, being **21** the most stable compound for both substituients (3.03 kJ mol^{-1} and 5.83 kJ mol^{-1} for R = $C(CH_3)_3$ and C_6H_5) respectively.

These results prompted us to propose that glycerol is transformed to the 2,3-dichlorohydrin regioisomer by the 4-chloromethyldioxolanic (pathway II) rather than the 5-chlorodioxanic (pathway I) whatever the heating system used. Kinetic control will determine the final regioisomeric ratio of the reaction when low temperature is used. The rearrangement process from 1,3- to 2,3-regioisomers will involve a nucleophilic attack of the sp^2 oxygen present in the carboxylic group to form the 1,3-dioxolane cations (**21a**–**o**). A similar rearrangement process was proposed by Nayler[10] and Pews and Davis[9] during the studies described above, and Steblyanko et al.[141] in the polymerization of acyloxymethyl five-member cyclic dithiocarbonates. Non-purely thermal specific MW effects will be consistent with the solvent-free conditions and the polar mechanisms proposed (more polar transition states when compared to their ground states).[7]

3. Summary

Glycerol can be transformed into 2-chloro-1-(chloromethyl)ethyl alkyl and aryl esters through a kinetically controlled process. These esters could be partially transformed to the corresponding 2,3-dichloropropyl regioisomer using a monomode microwave oven and sufficiently high temperature. Microwave irradiation maintaining low temperature dramatically increases the reaction rate, maintaining kinetic control of the reaction. This effect can be explained by assuming non-thermal microwave effects. A plausible mechanism is proposed on the basis of computational and experimental studies.

4. Experimental section

4.1. Material and Methods

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a VARIAN 400 spectrometer. All 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 centre 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: quintet, m: multiplet.

GC-FID analyses were performed in an Agilent Technologies 6890N equipped with a DB5-MS column (J&W) (30m x 0.25 µm x 0.25 mm) and He as carrier gas. The following chromatographic conditions were used: constant flow 2mL/min, split injection ratio 20:1 at 300ºC. Oven started at 50ºC for 5 min, temperature was increased at 5ºC/min to 110ºC, then increased at 10ºC/min until final temperature of 260ºC for 15 min. Tridecane from Aldrich was used as internal standard to carry out GC quantification.

GC-MS analyses 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 carrier gas. The following chromatographic conditions were used: constant flow 2mL/min, split injection ratio 20:1 at 280ºC. Oven started at 50ºC for 5 min, temperature was increased at 5ºC/min to 110ºC, then increased at 10ºC/min until final temperature of 260ºC for 15 min.

IR spectra were recorded on a Magna IR 560 NicoleT FTIR spectrophotometer in the range 4000-600 cm^{-1} with KBr pellets or with diamond HATR from SpectraTech as specified. Spectra are reported in reciprocal centimeters (cm^{-1}).

High-resolution mass spectral (HRMS) data were obtained by direct infusion on LC-TOF-MS Waters LCT Premier XE using ESI or APCI or on Waters GCT Premier using EI as specified.

4.2. General Procedure for dichloropropyl ester synthesis. (3a-o, 4a-o)

The corresponding acid, glycerol, and CTMS (see Table 1) were added in a reaction vial fitted with a PTFE-lined cap. The mixture was either heated at 80 ºC for 48 h or irradiated to heat the reaction mixture at 250 ºC or 175 ºC (maximum power irradiation 300 W, maximum reaction pressure 17 atm, see Table 1) for 20 min using a Discover LabMate microwave reactor (CEM, Matthews, USA) equipped with magnetic stirring and an air cooling system. After cooling, an organic solvent was added, and the mixture was washed three times with water. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum. The crude product was purified by crystallization, distillation, or SiO_2 column chromatography.

4.3. General procedure for 2-chloro-1-(chloromethyl)ethyl palmitate (3a) synthesis studies.

Palmitic acid (256 mg, 1 mmol, **2a**), glycerol (184 mg, 2 mmol, **1**), and CTMS (540 mg, 5 mmol) were added to a reaction vial fitted with a PTFE-lined cap. The mixture was heated or irradiated using a Discover LabMate microwave reactor (CEM, Matthews, USA) equipped with magnetic stirring and an air cooling system to reach the corresponding temperature for 1/3, 2, 5, 8, or 16 h (see Table 3). After cooling, *t*-butyl methyl ether was added, and the mixture was washed three times with water. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum. The crude product was analyzed by GC/FID using tridecane as the internal standard.

4.4. General procedure for 2-chloro-1-(chloromethyl)ethyl palmitate (3a) isomerization studies.

Pure ester **3a** (366 mg, 1 mmol) and the corresponding solvent (5 mmol), when required (see Table 4), were added to a reaction vial fitted with a PTFE-lined cap. The mixture was heated at 250 ºC (300 W max, 17 atm max) for either 1 or 2 h using a Discover LabMate microwave reactor (CEM, Matthews, USA) equipped with magnetic stirring and an air cooling system. After cooling, *t*-butyl methyl ether was added, and the mixture was washed three times with water. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum. The crude product was analyzed by GC/FID to determine the final regioisomeric ratio.

4.5. General procedure for dichloropropyl ester (3-4a and 3-4b) synthesis at low temperature.

Palmitic acid (256 mg, 1 mmol, **2a**) or caprylic acid (144 mg, 1 mmol, **2b**), glycerol (184 mg, 2 mmol, **1**) and CTMS (540 mg, 5 mmol) were added to a reaction vial. The mixture was either classically heated at 30 ºC for 48 h or irradiated using the power–time mode of the Discover LabMate microwave reactor (CEM, Matthews, USA). Irradiation power was fixed at 300 W, and the temperature was maintained at 30–35 ºC for 2 h using the Cool Mate low temperature accessory (CEM, Matthews, USA). *t*-Butyl methyl ether was added, and the mixture was washed three times with water. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum. The crude product was analyzed by GC/FID using tridecane as the internal standard.

4.6. Analytical data

Spectroscopic data for **3a-o** and **4a-o** compounds is available in supplementary data.

Acknowledgments

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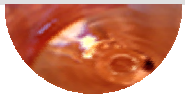

3. Combining $AlCl_3 \cdot 6H_2O$ and an ionic liquid to prepare chlorohydrin esters from glycerol

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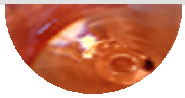
Abstract — We describe here the first example in which glycerol has been transformed into chlorohydrin esters using an ionic liquid and hydrated aluminium chloride. The method avoids using Crown-18 ether, which was needed to obtain a similar yield when KCl was used. Alkyl and aryl acids can be used, although yields are very dependent on the carboxylic acid used.

Keywords: chlorohydrin esters; glycerol; ionic liquids; substitution reactions



Glycerol is considered a low-cost, renewable feedstock that is a co-product of the biodiesel process.[1] Recently, new procedures have been patented to convert this compound to a mixture of chlorohydrin esters, commercial compounds with wide applications.[2]

We have already developed a direct methodology to prepare chlorohydrin esters from polyols. The method consists of a one-pot esterification–chlorination reaction, in which chlorotrimethylsilane acts as a solvent and reagent. Using this methodology, dichloropropyl esters can be obtained by an esterification–substitution reaction from either 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (solketal), a monoketal from glycerol.[3] Dichloropropyl palmitate could be also obtained in low yields from glycerol and hydrochloric acid.[4] To avoid the use of chlorotrimethylsilane, we have developed a new friendly one-pot halohydrin ester synthesis using potassium halides (KX) as the halogen source in ionic liquids ([BMIM][PF_6]) in the presence of Crown-18 ether.[5] Using this methodology, several diols and carboxylic acids were transformed to the corresponding halohydrin esters.

As a continuation of our work, we report here that glycerol undergoes an esterification–substitution reaction with a carboxylic acid to give the corresponding chlorohydrin ester in 48 h in [BMIM][PF_6] as a solvent and $AlCl_3 \cdot 6H_2O$ as a source of chlorine.[6] The corresponding 1,3-dichloro-2-propyl ester **3** (Fig. 1) is the main regioisomer. When palmitic acid is chosen as a model reagent, it is observed that yields can be maintained by using $AlCl_3 \cdot 6H_2O$ instead of KCl[7] (entry a), avoiding the use of crown ether as was proposed in our previous work (Table 1).

To the best of our knowledge, this reaction represents the first example of dichlorohydrin ester synthesis from glycerol using an ionic liquid and metal halide as chloride source. Hydrated aluminium chloride is much easier to handle than the corresponding anhydrous $AlCl_3$ and Friedel–Craft-like reactions are avoided.

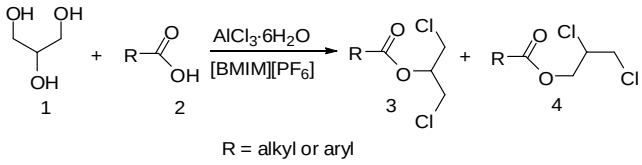


Figure 1. Preparation of dichloropropyl esters from glycerol and a carboxylic acid.

The importance of these results particularly relates to: (i) the transformation of a renewable material to valuable compounds, (ii) the use of a handy chloride salt as chloride source and (iii) the use of an ionic liquid (IL) as solvent.

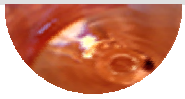


Table 1 shows the different regioisomeric ratios obtained depending on the carboxylic acid used. Nevertheless, regioisomer **3** is always the main compound obtained. Kinetic control is proposed to explain the predominance of this regioisomer. This hypothesis is in agreement with several similar reactions.[8] The ratio dependence upon the carboxylic acid used could be explained considering the charge density at the carbon of the carboxylic group.[9] Nevertheless, 3-nitrobenzoic acid and oleic acid gave the highest **3**:**4** ratio whereas 3,5-nitrobenzoic acid gave the lowest **3**:**4** ratio. Ionic liquids can produce different electrostatic environments, which can significantly affect a given reaction. Furthermore, ionic liquids are able to give π-π and π-cation interactions that in some cases may significantly affect the reactivity in these solvent media.[10] Bearing in mind the putative ionic intermediates present in these processes,[3] ions constituting ionic liquids could induce different effects depending on the starting carboxylic acid. Opposing effects on the rate of reaction of the substrate have been described for unimolecular substitution processes in presence of ionic liquids. Addition of different amounts of ionic liquid to the reaction mixture, favoured in different extents the reaction in terms of activation enthalpy whereas disfavoured it in terms of activation entropy.[11] These facts could explain that the regioisomeric ratios were very sensitive to the chemical structure of the reagents. Yields are also rather dependent on the carboxylic acid used. For aliphatic acids, the highest yield was obtained for palmitic acid. Acids with shorter chain lengths showed lower yields. For aromatic and heteroaromatic acids, yields range from high (benzoic and 3-nitrobenzoic acids) to low (salicylic, cinnamic and 1-naphthoic acids) (Table 1). The reaction is compatible with C=C double bounds, aromatic amino and hydroxyl groups. Only picolinic acid (**2q**) did not give the desired compounds in the described conditions.

These results are similar to those obtained in our previous work when several diols were assayed.[5] The fact that those reactions in ionic liquids are very sensitive to the chemical structure of the reagents can be used again to explain these results.[12] Consequently, large aliphatic acids (oleic, palmitic and pentadecanoic acids) and some small aromatic acids will be the best acids for carrying out this reaction in [BMIM][PF_6]. Moreover, the recovery of the resulting esters from the reaction mixture with solvents such as hexane seems more difficult when aromatic acids are used (Table 1). The addition of water at the end of the reaction, followed by extraction with ethyl acetate seems to overcome this second fact.

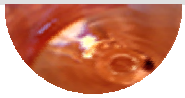


Table 1. Dichoropropyl esters **3a–p: 4a–p** produced from glycerol and carboxylic acid in [BMIM][PF_6]

Entry	R	Conditions	Ratio **3**:**4**[a]	Yield %[b]
a	$CH_3(CH_2)_{14}$	KCl (5 mequiv), 18-Crown ether[c]	94:6	83
a	$CH_3(CH_2)_{14}$	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	93:7	80
b	$CH_3(CH_2)_4CH{=}CH(CH_2)_{10}$	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	95:5	73
c	$CH_3(CH_2)_{13}$	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	95:5	76
d	$CH_3(CH_2)_{10}$	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	96:4	56
e	$CH_3(CH_2)_6$	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	70:30	28
f	2-furoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	68:32	8
f	2-furoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	68:32	48
g	2-thiophencarboxoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	81:19	13
g	2-thiophencarboxoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	81:19	50
h	benzoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	78:22	25
h	benzoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	78:22	87
i	cinnamyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	68:32	9
i	cinnamyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	68:32	36
j	salicyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	86:14	6
j	salicyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	86:14	21
k	2-chlorobenzoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	83:13	19
k	2-chlorobenzoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	83:13	64
l	3-aminobenzoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	--	--[e]
l	3-aminobenzoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	88:12	41[e]
m	3-nitrobenzoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	95:5	9
m	3-nitrobenzoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	95:5	88
n	3,5-dinitrobenzoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	--	--
n	3,5-dinitrobenzoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	55:45	56
o	1-naphthoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	72:28	16
o	1-naphthoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	72:28	24
p	2-naphthoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	75:25	30
p	2-naphthoyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	75:25	62
q	picolyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[c]	--	--[e]
q	picolyl	$AlCl_3{\cdot}6H_2O$ (2 mequiv)[d]	--	--[e]

[a]Calculated by ^{1}H NMR considering signals at δ = 5.19 ppm for **3** and δ = 4.22 ppm for **4**.

[b]Yield calculated by ^{1}H NMR using 1,4-dichlorobenzene for aliphatic acids and 1,4-dioxane for aromatic and heteroaromatic acids.

[c]Crude reaction mixture was extracted with hexane.

[d]Crude reaction mixture was dissolved in water and extracted with ethyl acetate.

[e]After careful neutralization with solid sodium bicarbonate.

In conclusion, we have described the first example in which glycerol has been transformed to chlorohydrin esters using an ionic liquid and hydrated aluminium chloride. The described method avoids using Crown-18 ether needed to obtain satisfactory yields when KCl is used. Alkyl and aryl acids can be used, although yields are very dependent on the carboxylic acid used. Aminoaromatic acids seem to be compatible with the reaction conditions used.

Acknowledgments

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6. ***Experimental procedure***:

A mixture of carboxylic acid (1 mequiv), glycerol (2 mequiv) and hydrated aluminium chloride (2 mequiv) and [BMIM][PF_6] (2.5 g) was stirred in a 10 mL reactor for 48 h at 100 °C. The crude reaction mixture was extracted with hexane (3 × 2 mL) while stirring in a circular shaker placed into an oven for 30 min at 40 °C. Crude reaction mixtures from aromatic and heteroaromatic acids were also dissolved in water and extracted with ethyl acetate (3 × 20 mL). The upper phase was recovered and dried over anhydrous sodium sulfate. The organic solutions were filtered and evaporated to dryness. The yield was determined using ^{1}H NMR and either 1,4-dichlorobenzene or 1,4-dioxane as internal standard (see Table 1).

1,3-Dichloro-2-propyl palmitate (**3a**): ^{1}H NMR ($CDCl_3$), δ: 5.18 (quin, *J*=5.2 Hz, 1H, O-C*H*), 3.73 (m, 4H, 2 CH_2-Cl), 2.37 (t, *J*=7 Hz, 2H, C$H_{2\ (\alpha)}$ (C=O)), 1.65 (m, 2H, C$H_{2\ (\beta)}$ (C=O)), 1.26 (m, 24H, CH_2), 0.88 (t, *J*=7 Hz, 3H, CH_3). ^{13}C RMN ($CDCl_3$), δ: 172.7 (*C*=O), 71.5 (O-*C*H), 42.5 (*C*H_2-Cl), 34.1 (*C*$H_{2\ (\alpha)}$ (C=O)), 31.9 (*C*H_2-CH_2-CH_3), 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0 (*C*H_2), 24.8 (*C*$H_{2\ (\beta)}$ (C=O)), 22.7 (*C*H_2-CH_3), 14.1 (*C*H_3).

1,3-Dichloro-2-propyl oleate (**3b**): ^{1}H NMR ($CDCl_3$), δ: 5.35 (m, 2H, C*H*=C*H*), 5.18 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.74 (dd, J_1=11.6 Hz, J_2=2 Hz , 4H, 2 CH_2-Cl), 2.36 (t, *J*=7.4 Hz, 2H, C$H_{2\ (\alpha)}$ (C=O)), 2.0 (m, 4H, CH_2-CH=), 1.68 (m, 2H, C$H_{2\ (\beta)}$ (C=O)), 1.26 (m, 18H, CH_2), 0.88 (t, *J*=7.0 Hz, 3H, CH_3). ^{13}C RMN ($CDCl_3$), δ: 172.9 (*C*=O), 130.2, 129.9 (*C*H=*C*H), 71.7 (O-*C*H), 42.7 (*C*H_2-Cl), 34.3 (*C*$H_{2\ (\alpha)}$ (C=O)), 32.1 (*C*H_2-CH_2-CH_3), 30.0, 29.9, 29.7, 29.5, 29.4, 29.3, (*C*H_2), 26.7 (*C*H_2-CH=CH-*C*H_2), 25.0 (*C*$H_{2\ (\beta)}$ (C=O)), 22.9 (*C*H_2-CH_3), 14.3 (*C*H_3). HRMS (EI+) calculated for $C_{11}H_{20}O_2Cl_2$: 392.2249. Found: 392.2247.

1,3-Dichloro-2-propyl pentadecanoate (**3c**): ^{1}H NMR ($CDCl_3$), δ: 5.18 (quin, *J*=5.2 Hz, 1H, O-C*H*), 3.74 (dd, J_1=5.4 Hz, J_2=2 Hz , 4H, 2 CH_2-Cl), 2.36 (t, *J*=7.4 Hz, 2H, C$H_{2\ (\alpha)}$ (C=O)), 1.64 (m, 2H, C$H_{2\ (\beta)}$ (C=O)), 1.25 (m, 22H, CH_2), 0.87 (t, *J*=6.9 Hz, 3H, CH_3). ^{13}C RMN ($CDCl_3$), δ: 173.0 (*C*=O), 71.7 (O-*C*H), 42.7 (*C*H_2-Cl), 34.4 (*C*$H_{2\ (\alpha)}$ (C=O)), 32.2 (*C*H_2-CH_2-CH_3), 29.9, 29.8, 29.7, 29.6, 29.4, 29.3 (*C*H_2), 25.1 (*C*$H_{2\ (\beta)}$ (C=O)), 22.9 (*C*H_2-CH_3), 14.4 (*C*H_3). HRMS (EI+) calculated for $C_{11}H_{20}O_2Cl_2$: 352.1936. Found: 352.1932.

1,3-Dichloro-2-propyl laureate (**3d**): ^{1}H NMR ($CDCl_3$), δ: 5.18 (quin, *J*=5.2 Hz, 1H, O-C*H*), 3.73 (dd, J_1=5.4 Hz, J_2=2 Hz , 4H, 2 CH_2-Cl), 2.37 (t, *J*=7 Hz, 2H, C$H_{2\ (\alpha)}$ (C=O)), 1.65 (m, 2H, C$H_{2\ (\beta)}$ (C=O)), 1.26 (m, 24H, CH_2), 0.88 (t, *J*=7 Hz, 3H, CH_3). ^{13}C RMN ($CDCl_3$), δ: 173.0 (*C*=O), 71.7 (O-*C*H), 42.7 (*C*H_2-Cl), 34.3 (*C*$H_{2\ (\alpha)}$ (C=O)), 32.1 (*C*H_2-CH_2-CH_3), 29.8, 29.6, 29.5, 29.4, 29.3, (*C*H_2), 25.1 (*C*$H_{2\ (\beta)}$ (C=O)), 22.9 (*C*H_2-CH_3), 14.3 (*C*H_3).

1,3-Dichloro-2-propyl caprylate (**3e**): ^{1}H NMR ($CDCl_3$), δ: 5.12 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.74 (dd, J_1=5.5 Hz, J_2=2.0 Hz, 4H, 2 CH_2-Cl), 2.34 (t, *J*=7.8 Hz, 2H, C$H_{2\ (\alpha)}$ (C=O)), 1.63 (quin, *J*=7.4 Hz, 2H, C$H_{2\ (\beta)}$ (C=O)), 1.29 (m, 8H, CH_2), 0.87 (t, *J*=7.0 Hz, 3H, CH_3). ^{13}C RMN ($CDCl_3$), δ: 173.0 (*C*=O), 72.0 (O-*C*H), 42.0 (*C*H_2-Cl), 34.4 (*C*$H_{2\ (\alpha)}$ (C=O)), 32.1 (*C*H_2-CH_2-CH_3), 29.5 (*C*H_2), 25.0 (*C*$H_{2\ (\beta)}$ (C=O)), 22.5 (*C*H_2-CH_3), 14.5 (*C*H_3).

1,3-Dichloro-2-propyl 2-furoate (**3f**): ^{1}H NMR ($CDCl_3$), δ: 7.62 (m, CH_{ar}), 7.26 (dt, J_1=3.5 Hz, J_2=0.8 Hz, 1H, CH_{ar}), 6.53 (m, 1H, CH_{ar}), 5.39 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.85 (d, *J*=5.6 Hz, 4H, CH_2-Cl). ^{13}C RMN ($CDCl_3$), δ: 156.9 (*C*=O), 146.5 (*C*H_{ar}), 143.7 (*C*H_{ar}-C=O), 119.8, 112.1 (*C*H_{ar}), 72.3 (O-*C*H), 43.1 (*C*H_2-Cl).

1,3-Dichloro-2-propyl 2-thiophencarboxylate (**3g**): ^{1}H NMR ($CDCl_3$), δ: 7.79 (dd, J_1=3.9 Hz, J_2=1.2 Hz, 1H, CH_{ar}), 7.55 (dd, J_1=5.1 Hz, J_2=1.2 Hz, 1H, CH_{ar}), 7.06 (dd, J_1=5.0 Hz, J_2=3.9 Hz, 1H, CH_{ar}), 5.31 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.80 (d, *J*=5.1 Hz, 4H, CH_2-Cl). ^{13}C RMN ($CDCl_3$), δ: 161.1 (*C*=O), 144.8 (*C*H_{ar}), 143.8 (*C*H_{ar}-C=O), 122.5, 118.1 (*C*H_{ar}), 72.2 (O-*C*H), 42.8 (*C*H_2-Cl).

1,3-Dichloro-2-propyl benzoate (**3h**): ^{1}H NMR ($CDCl_3$), δ: 8.00 (m, 1H, C$H_{ar\ (\alpha)}$ (C=O)), 7.53 (m, 1H, CH_{ar}), 7.39 (m, 2H, CH_{ar}), 5.36 (quin, *J*=5.3 Hz, 1H, O-C*H*), 3.82 (m, 4H, 2 CH_2-Cl). ^{13}C RMN ($CDCl_3$), δ: 163.4 (*C*=O), 131.7,127.9, 127.2, 126.6 (*C*$_{ar}$), 70.1 (O-*C*H), 40.5 (*C*H_2-Cl).

1,3-Dichloro-2-propyl cinnamate (**3i**): ^{1}H NMR ($CDCl_3$), δ: 7.73 (d, *J*=15.6 Hz, 1H, CH_{ar}), 7.48 (m, 2H, 2 CH_{ar}), 7.34 (m, 3H, 2 CH_{ar}, Ph-C*H*=CH), 6.41 (m, 1H, Ph-CH=C*H*), 5.25 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.76 (d, *J*=5.5 Hz, 4H, 2 CH_2-Cl). ^{13}C RMN ($CDCl_3$), δ: 165.9 (*C*=O), 146.7 (Ph-*C*H=CH), 134.2 (*C*$_{ar}$), 130.9, 129.2, 128.5 (*C*H_{ar}), 117.0 (Ph-CH=*C*H), 71.9 (O-*C*H), 42.7 (*C*H_2-Cl).
1,3-Dichloro-2-propyl salicylate (**3j**): ^{1}H NMR ($CDCl_3$), δ: 7.81 (dd, J_1=8.2 Hz, J_2=1.7 Hz, 1H, CH_{ar}), 7.50 (m, 1H, CH_{ar}), 6.95 (d, *J*=7.5 Hz, 1H, CH_{ar}), 6.80 (m, 1H, CH_{ar}), 5.39 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.82 (d, *J*=5.5 Hz, 4H, 2 CH_2-Cl). ^{13}C RMN ($CDCl_3$), δ: 169.1 (*C*=O), 162.1 (*C*$_{ar}$-OH), 136.7, 130.3, 119.7, 117.9, 111.8 (*C*H_{ar}), 72.7 (O-*C*H), 42.5 (*C*H_2-Cl).

1,3-Dichloro-2-propyl 2-chlorobenzoate (**3k**): ^{1}H NMR ($CDCl_3$), δ: 7.88 (m, 1H, CH_{ar}), 7.47 (td, J_1=7.8 Hz, J_2=1.6 Hz, 2H, CH_{ar}), 7.35 (m, 1H, CH_{ar}), 5.44 (quin, *J*=5.2 Hz, 1H, O-C*H*), 3.89 (d, *J*=5.5 Hz, 4H, 2 CH_2-Cl). ^{13}C RMN ($CDCl_3$), δ: 164.5 (*C*=O), 134.4 (*C*$_{ar}$-OH), 133.4, 131.9, 131.5, 129.1, 126.9 (*C*$_{ar}$), 72.9 (O-*C*H), 42.5 (*C*H_2-Cl).

1,3-Dichloro-2-propyl 3-aminobenzoate (**3l**): ^{1}H NMR ($CDCl_3$), δ: 5.38 (quin, *J*=5.0 Hz, 1H, O-C*H*), 3.90 (d, 4H, *J*=5.1 Hz, 2 CH_2-Cl). ^{13}C RMN (MeOD), δ: 166.1 (*C*=O), 148.4 (*C*$_{ar}$-NH_2), 130.1 (*C*$_{ar}$-C=O), 129.0, 119.9, 118.8, 115.7 (*C*H_{ar}), 72.6 (O-*C*H), 42.6 (*C*H_2-Cl). HRMS (EI+) calculated for $C_{11}H_{20}O_2Cl_2$: 247.0167. Found: 247.0162.

1,3-Dichloro-2-propyl 3-nitrobenzoate (**3m**): ^{1}H NMR ($CDCl_3$), δ: 8.87 (s, 1H, C*H*$_{ar}$), 8.42 (dd, J_1=25.0 Hz, J_2=8.2 Hz, 2H, C*H*$_{ar}$), 7.69 (t, *J*=8.2 Hz, 1H, C*H*$_{ar}$), 5.48 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.90 (d, *J*=5.5 Hz, 4H, 2 C*H*$_2$-Cl). ^{13}C RMN ($CDCl_3$), δ: 163.8 (*C*=O), 151.1 (*C*$_{ar}$-NO_2), 134.7 (*C*$_{ar}$-C=O), 130, 129.8, 122.7 (*C*H$_{ar}$), 73.3 (O-*C*H), 42.5 (*C*H$_2$-Cl).

1,3-Dichloro-2-propyl 3,5-dinitrobenzoate (**3n**): ^{1}H NMR ($COCD_6$), δ: 9.17 (t, *J*=2.1 Hz 1H, C*H*$_{ar}$), 9.10 (d, *J*=2.1 Hz, 2H, C*H*$_{ar}$), 5.67 (quin, *J*=5.1 Hz, 1H, O-C*H*), 4.11 (d, *J*=5.1 Hz, 4H, C*H*$_2$-Cl). ^{13}C RMN ($COCD_6$), δ: 164.4 (*C*=O), 149.1 (*C*$_{ar}$-NO_2), 134.3 (*C*$_{ar}$-C=O), 128.0, 122.8 (*C*H$_{ar}$), 76.3 (O-*C*H), 43.5 (*C*H$_2$-Cl).

1,3-Dichloro-2-propyl 1-naphthoate (**3o**): ^{1}H NMR ($CDCl_3$), δ: 8.93 (dd, J_1=8.8 Hz, J_2=0.8 Hz, 1H, C*H*$_{ar}$), 8.28 (dd, J_1=7.6 Hz, J_2=1.6 Hz, 1H, C*H*$_{ar}$), 8.07 (d, *J*=8.4 Hz, 1H, C*H*$_{ar}$), 7.91 (d, *J*=7.6 Hz, 1H, C*H*$_{ar}$), 7.65 (m, 1H, C*H*$_{ar}$), 7.54 (m, 2H, 2 C*H*$_{ar}$), 5.54 (quin, *J*=4.8 Hz, 1H, O-C*H*), 3.96 (d, *J*=4.8 Hz, 4H, 2 C*H*$_2$-Cl). ^{13}C RMN ($CDCl_3$), δ: 166.3 (*C*=O), 134.4, 134.1, 131.6, 131.2, 128.9, 128.4, 126.6, 125.9, 125.8, 124.8 (*C*H$_{ar}$), 72.4 (O-*C*H), 42.8 (*C*H$_2$-Cl).

1,3-Dichloro-2-propyl 2-naphthoate (**3p**): ^{1}H NMR ($CDCl_3$), δ: 8.58 (s, 1H, C*H*$_{ar}$), 8.01 (dd, J_1=8.8 Hz, J_2=1.6 Hz, 1H, C*H*$_{ar}$), 7.92 (d, *J*=8.4 Hz, 1H, C*H*$_{ar}$), 7.84 (d, *J*=8.8 Hz, 1H, C*H*$_{ar}$), 7.83 (d, *J*=8 Hz, 1H, C*H*$_{ar}$), 7.53 (m, 2H, 2 C*H*$_{ar}$), 5.44 (quin, *J*=4.8 Hz, 1H, O-C*H*), 3.88 (d, *J*=4.8 Hz, 4H, 2 C*H*$_2$-Cl). ^{13}C RMN ($CDCl_3$), δ: 165.8 (*C*=O), 136.0, 132.7, 131.9, 129.7, 128.9, 128.6, 128.0, 127.1, 126.6, 125.4 (*C*H$_{ar}$), 72.4 (O-*C*H), 42.7 (*C*H$_2$-Cl).

7. *Experimental procedure*. A mixture of palmitic acid (1 mequiv), glycerol (2 mequiv), Crown-18 ether (0.125 mequiv, 10% mol), potassium chloride (5 mequiv) and [BMIM][PF_6] (2.5 g) was stirred in a 10 mL reactor for 48 h at 100 °C. The crude reaction mixture was extracted with hexane (3 × 2 mL) while stirring in a circular shaker placed into an oven for 30 min at 40 °C. The upper phase was recovered and dried over anhydrous sodium sulfate. The organic solution was filtered and evaporated to dryness. The yield was determined using ^{1}H NMR and either 1,4-dichlorobenzene[10] as internal standard.

   1,3-Dichloro-2-propyl palmitate (**3a**): ^{1}H NMR ($CDCl_3$), δ: 5.18 (quin, *J*=5.2 Hz, 1H, O-C*H*), 3.73 (m, 4H, 2 C*H*$_2$-Cl), 2.37 (t, *J*=7 Hz, 2H, C*H*$_{2\ (\alpha)}$ (C=O)), 1.65 (m, 2H, C*H*$_{2\ (\beta)}$ (C=O)), 1.26 (m, 24H, C*H*$_2$), 0.88 (t, *J*=7 Hz, 3H, C*H*$_3$). ^{13}C RMN ($CDCl_3$), δ: 172.7 (*C*=O), 71.5 (O-*C*H), 42.5 (*C*H$_2$-Cl), 34.1 (*C*H$_{2\ (\alpha)}$ (C=O)), 31.9 (*C*H$_2$-CH$_2$-CH$_3$), 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0 (*C*H$_2$), 24.8 (*C*H$_{2\ (\beta)}$ (C=O)), 22.7 (*C*H$_2$-CH$_3$), 14.1 (*C*H$_3$).t

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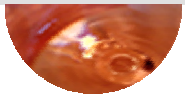

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CAPÍTOL IV: TRANSFORMACIONS SOBRE ELS ESTERS DE DICLOROPROPIL

1.- Introducció

Aquest capítol versa sobre la transformació dels esters de dicloropropil descrits en el capítol 3. El capítol està subdividit en dos parts; el primer sub-apartat fa referència a la síntesi d'esters d'al·lil a partir dels esters de dicloropropil, i a llur aplicació com a agent ovicida. Aquesta línia d'aplicació ha estat especialment desenvolupada en aquesta tesi i per això té un subapartat específic. Els articles presentats són un desenvolupament i aplicació de la patent (ES 2293836-A1-20080316) que ha estat registrada sobre aquest procediment, un resum de la qual figura als annexes.

El segon sub-apartat versa sobre la dissimetrització dels esters de dicloropropil i les diferents substitucions aplicades sobre els clorurs. Així mateix també es dissenya un sistema continu de producció d'un dels esters dissimetritzats aplicant microreactors. Aquesta part de la recerca ha estat realitzada als laboratoris de l'*Institut für Mikrotechnik GmbH* situat a la ciutat alemana de Mainz sota la supervisió del Prof. Dr. Volker Hessel.

La síntesi d'esters d'al·lil a partir dels corresponents esters de clorohidrina s'ha aconseguit a través d'una reacció semblant a la proposada per Hans Finkelstein[1], que consistia en un bescanvi S_N2 d'halògens entre el clorur o bromur d'alquil cap a el iodur d'alquil usant acetona com a dissolvent. La reacció estava basada en la diferent solubilitat de les sals d'halur en el medi. En el cas estudiat en la present tesi, l'aplicació de la reacció no s'atura en aquest estadi, sinó que evoluciona mitjançant una transposició i eliminació cap a l'ester d'al·lil.

Els esters d'al·lil s'obtenen amb bones conversions i bons rendiments a partir d'una reacció seqüencial duta a terme en un únic procés. En primer lloc una substitució d'un dels clorurs del grup dicloropropil de l'ester de partida, seguit d'una transposició en la cadena carbonada i finalment una eliminació. Durant la reacció, la presència de l'ester de

cloroiodopropil intermedi experimenta un augment fins a un màxim entre un 50-55% en massa (segons l'àcid de partida), que es manté mentre hi ha ester de dicloropropil en el medi de reacció. A la finalització d'aquest, la quantitat de l'ester de cloroiodopropil va disminuint, degut a la seva conversió a ester d'al·lil, fins a la finalització de la reacció. En aquest sentit, l'estudi acurat de la reacció ha permès definir el moment de màxima presència de l'ester dissimetritzat, fet que ha permès el seu aïllament i descripció en la segona part d'aquest capítol.

La reacció s'ha assajat usant com a substracte els esters de 1,3-dicloropropil degudament purificats que s'obtenien de la síntesi descrita en el capítol 3 d'aquesta tesi. Tots ells han donat lloc a conversions i rendiments elevats.

En la fase transposició de la reacció, la reestructuració a través del dioxolà duu a la eliminació successiva dels clors de la estructura, de manera que el clorur format queda en forma de clorur sòdic. L'eliminació final duu a la formació de l'ester d'al·lil i la formació de iode. La presència d'aquest darrer es pot controlar afegint un reductor (en aquesta tesi tiosulfat sòdic) que redueix altre cop el iode a iodur. Si el iode no es redueix un altre cop a iodur cal afegir un excés de iodur (NaI) perquè es completi la reacció, si no es així, s'ha observat que aquest iode pot donar lloc a la hidròlisi de l'ester d'al·lil

obtenint el conseqüent alcohol al·lílic i l'àcid corresponent. Així doncs, la possibilitat de regenerar el iodur, permet obtenir l'ester d'al·lil amb una menor necessitat de iodur sòdic com a reactiu, fent que la proporció molar requerida sigui menor a la estequiomètricament esperada.

Mitjançant aquest procediment o amb lleugeres modificacions, s'han obtingut també mescles d'esters d'al·lil a partir de esters de dicloropropil preparats a partir d'olis crus, residus rics en olis o greixos provinents de la indústria, i greixos animals. El glicerol que s'ha usat és glicerol recuperat de la indústria del biodiesel. Aquest glicerol cru s'ha sotmès a una etapa prèvia de purificació. Els rendiments i les conversions dels esters d'al·lil finals han estat elevats; d'entre 70 y 95%, segons les condicions assajades i el tipus de residus inicials.

En una altra aproximació en col·laboració amb el grup de entomologia de l'ETSEA liderat pel professor Jesús Avilla, i atenent a la capacitat insecticida que tenen alguns compostos amb el grup al·lil[2,3], s'ha comprovat l'eficiència dels esters d'al·lil dels àcids grassos com ovicides sobre l'insecte plaga de fruiters *Cydia pomonella (L.)*. Així els experiments s'han dissenyat de la següent manera: ous sense tractar solament per a comprovar la correcta eclosió en les condicions de conservació, ous tractats amb dissolvent o

població control, i ous tractats amb diferents concentracions per cada ester d'al·lil assajat.

A partir d'aquí s'ha avaluat la mortalitat corregida amb la formula d'Abbot:

$$\%Corregit = 100.\left(1 - \frac{Població\_tractada}{Població\_control}\right)$$

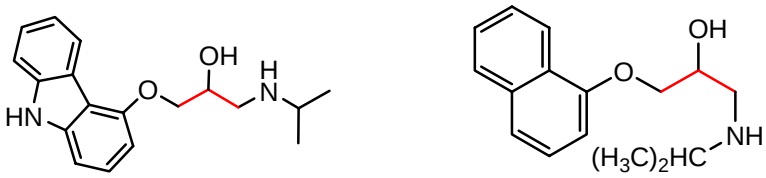
S'ha observat que el caprilat d'al·lil és el que presenta una activitat superior respecte dels altres. També s'observa una relació inversa entre la longitud de la cadena del residu d'àcid de l'ester d'al·lil i les concentracions letals. Així, s'observa una disminució en la dosi letal per als esters d'àcids de cadena intermitja, cas del caprilat i del caprat, i una major efectivitat al produir-se la mort en estadis més inicials de desenvolupament (fase de cap blanc). Tant pels esters d'àcids de cadena més llarga, com pels de cadena més curta, s'observen nivells de mortalitat inferior.

La segona part del capítol es centra en la dissimetrització de l'ester de 1,3-dicloro-2-propil. En aquest cas s'ha escollit un dels àcids estudiats per a dur a terme l'estudi. Aquesta elecció no s'ha deixat a l'atzar, ja que s'ha escollit l'àcid pivàlic (2,2-dimetilpropanoic) que és un àcid versàtic. Aquests àcids es

caracteritzen per la presència del carboni *alfa* del grup carboxil totalment substituït. Aquesta circumstància confereix a la mol·lècula una sèrie de característiques singulars: una estabilitat tèrmica excepcional, hidrofobicitat, estabilitat hidrolítica, resistència a l'oxidació, a les bases i a la radiació UV*. En aquest cas, atès que les substitucions es volien realitzar sobre el dicloropropil, s'ha preferit assegurar l'estabilitat estructural de la resta de la cadena.

D'aquesta manera s'ha dissimetritzat l'estructura mitjançant monosubstitucions d'un dels clorurs per un altre halogen (iodur), per un hidroxil en medi bàsic, o per heterocicles. Aquesta capacitat d'assumir monosubstitucions dóna a la mol·lècula molta versatilitat de cara a sintetitzar productes d'alt valor afegit *(Figura 1)*. Alguns amb activitat farmacològica com el propanolol (antiarrítmic), el carbazolol (β-adrenèrgic), el carbamat de guaifenesina (relaxant muscular). Altres productes com el fucunazol amb característiques antifúngiques, i altres productes d'interès químic com els líquids iònics.

* *Hexion Specialty Chemicals B.V. Versatics. Rotterdam, The Netherlands http://www.hexion.com/Products/ProductLiterature.aspx?id=733 (darrer accès: setembre de 2010)*

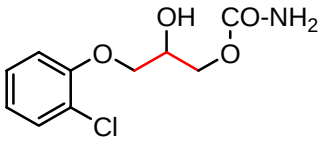


Carazolol

(Antagonista del receptor β-adrenèrgic)

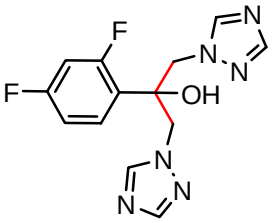
Propanolol

(β-blocant antiarrítmic)



Carbamat de guaifenessina

(Relaxant muscular)



Fluconazol

(Antifúngic)

Figura 1: Productes susceptibles de ser obtinguts mitjançant substitucions selectives sobre el pivaloat de 1,3-dicloro-2-propil. Es presenta marcada l'estructura corresponent al glicerol.

Totes les reaccions han estat estudiades cercant el rendiment màxim dels productes finals, els quals s'han identificat i caracteritzat. La reacció de síntesi del pivaloat de 3-cloro-2-hidroxi-1-propil s'ha escalat i aplicat en un sistema continu. El disseny, aplicat usant la tecnologia de microreactor, ha requerit una modificació de les condicions inicialment establertes per a la reacció per qüestions fluidomecàniques. Així, la reacció inicial es realitzava en fase heterogènia utilitzant carbonat sòdic com a base acceptora de clorurs, i usant dioxà com a dissolvent.

Aquestes condicions, incompatibles amb el sistema continu utilitzat, han requerit un estudi previ de bases alternatives solubles en el medi i un canvi de dissolvent atès a que el dioxà causava danys al sistema de bombeig *(Taula 1)*.

Taula 1: Estudi d'alternatives de bases receptores de clorurs en n-butanol

Base utilitzada	*Rendiment % massa*			
	Ester de dicloropropil	Ester de hidroxicloropropil	Ester de dihidroxipropil	Àcid
DMAP	2	54	41	3
Trietilamina	2	46	50	2
Butilimidazole	2	53	42	3
Carbonat sòdic	1	71	28	<1

Després d'un estudi d'alternatives la reacció es va modificar aplicant n-butanol com a dissolvent i usant n-butilimidazole com a base, al ser l'únic cas en el qual no es va trobar precipitat al refredar.

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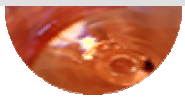


2.1. Process for the preparation of aliphatic acid allyl esters. ES 2293836 A1 20080316 (2008)

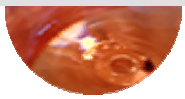
De totes les aplicacions dels esters de dicloropropanol tractades en aquesta tesi, la que ha estat estudiada amb més profunditat és la transformació d'aquests en esters d'al.lil. Algunes substancies que presenten aquest grup són conegudes per la seva activitat com a repelents d'insectes, insecticides i com acaricides. En particular, en la literatura es poden trobar referències a l'efecte pesticida dels esters d'al.lil provinents d'àcids grassos (Per exemple: JP-A 08133909, 2006).

La innovació que proposa aquesta patent és la possibilitat de sintetitzar aquests productes a partir d'una esterificació-cloració previa del glicerol. Al representar una nova via d'utilització del glicerol excedent de la industria del biodiesel per a generar altres productes d'alt valor afegit, s'ha considerat aconsellable protegir aquest procediment.

En aquest sentit, la metodologia general de síntesi d'aquests compostos s'ha descrit en la patent que es presenta (ES 2293836 A1 20080316) i que es transcriu en l'anex VIII-1.

El desenvolupament de les aplicacions d'aquests productes es descriu en els articles inclosos en el capitol IV-2: Per una part es presenta la optimització i estudi de la reacció *(Tetrahedron 2009, 65(25) 4866-4870)* on s'inclou la formació de l'ester d'al.lil amb excés de NaI. En el mateix article també es descriu com es pot economitzar el NaI fins a relacions equimol·leculars usant tiosulfat sòdic.

Per altra banda es presenta la síntesi d'esters d'al.lil a partir de materials greixosos, alguns d'ells subproductes industrials *(Bioresource Technology(Enviat))*, tant d'origen animal com vegetal, la qual cosa suposa l'aplicació de la reacció amb materials reals de rebutjos industrials. Finalment l'efecte ovicida dels compostos obtinguts a partir de l'aplicació d'aquesta patent es posen de manifest amb eficiència per a *Cydia pomonella (L.)*. *(Journal of Agricultural and Food Chemistry 2009, 57(11) 4849-4853)*.



2.2. A tandem Finkelstein-rearrangement-elimination reaction. A straightforward synthetic route to allyl esters

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Tetrahedron 65(25)4866-4870 (2009)

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Abstract — Allyl esters can be obtained by a Finkelstein-rearrangement-elimination reaction of 1,3-dichloro-2-propyl esters induced by NaI. Sodium iodide can be used below equivalence using a reductive agent as sodium thiosulfate. High yields are obtained with most of the diverse esters studied. The method described avoids the use of allyl alcohol as a reagent. 1,3-Dichloro-2-propyl esters are prepared from glycerol, the main by-product of biodiesel industry. The effectiveness of iodine as reagent to hydrolyse allyl esters is also confirmed.

Keywords: Allylic compounds, elimination, esters, nucleophilic substitution, rearrangement

1. Introduction

Agricultural raw materials have become a matter of interest in the 21st century in the search for new sources of chemicals to help sustainable development. Oils and fats of vegetable and animal origin make up the greatest proportion of the current consumption of renewable raw materials in the chemical industry because they offer a large number of possibilities for application.[1] Recently, the industrial 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.[2] Glycerol can be easily transformed into several 1,3-dichloropropyl esters directly[3-6] or through its transformation to different derivatives as 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (solketal) and a subsequent one-pot esterification-chlorination.[7] These esters are putative precursors of 1-chloro-3-iodo-2-propyl esters (**3a-j** in Scheme 1) which are versatile starting materials with a chiral centre.

While trying to induce desymmetrisation in the 1,3-dichloropropyl esters, we found that NaI was able to induce the formation of the corresponding allyl esters starting from **1a**.[8] Herein we report different parameters having an effect on the allyl esters formation by the Finkelstein-rearrangement-elimination reaction of 1,3-dichloro-2-propyl esters induced by NaI. To the best of our knowledge, this type of combined reaction in the presence of NaI is unprecedented.

2. Results and Discussion

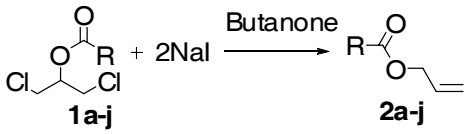
First, we studied the treatment of **1a** with NaI (2.0 equivalents) in acetone at 80ºC for 48 h. Ester **2a** was obtained in moderate yield. Nevertheless, considering that allyl esters have many applications in such wide-ranging fields as cosmetics,[9] aromas,[10] resins,[11] energy storage,[12] olefin metathesis[13] and precursors in allylation reactions[14-16] a set of experiments were carried out trying to improve the yield of this new reaction.

When the same reaction was carried out at 115ºC using butanone as solvent, the yield increased up to 93%.

To study the scope of this reaction, the same process was studied with several alkyl and aryl acids (Table 1). Yields varied from 61% (entry **h**) to 98% (entry **d**). Finally, the process was scaled up to thirty times using 1,3-dichloro-2-propyl esters **1a** and **1j**. The yields were 91% and 82% of purified allyl esters **2a** and **2j** respectively.

Table 1.

1,3-Dichloro-2-propyl ester (**1a-j**) dechlorination with sodium iodide in butanone.



Our approach differs from most of the methods described so far in that the use of allyl alcohol, undesired residue on some allylic ester preparations,[17] is avoided. These methods use catalysts such as hydrogen chloride[18-19] sulfuric acid,[20-21] and titanium sulfate,[22] or enzymes such as lipases.[22] Allyl acetate can also be prepared by acetoxylation of propylene[18] and pyrolysis of 1,3-diacetoxypropane[24] and 1,2-diacetoxypropane.[25]

1 entry	R	Isolate yield (%) **2**
a	$CH_3(CH_2)_{14}$	93
b	$CH_3(CH_2)_8$	91
c	$(CH_3)_3C$	84
d	C_6H_5-CH=CH	98
e	C_6H_5	97
f	*o*-Cl-C_6H_4	81
g	*p*-NO_2-C_6H_4	96
h	*o*-HO-C_6H_4	61
i	1-naphthyl	96
j	2-naphthyl	83

To study some aspects of the mechanism of this transformation, two different approaches were followed. First, the progress of the reaction between **1a** and sodium iodide in butanone at 115ºC was studied for 48 h. Besides the starting compound **1a** and the final allyl palmitate (**2a**), the formation of about 48% 1-chloro-3-iodo-2-propyl palmitate (**3a**) as an intermediate compound was observed (chromatographic peak at t_R = 34.7 min presenting ions $[M]^+$:458, 460; $[M\text{-}Cl]^+$: 423, 425; $[M\text{-}I]^+$: 331, 333; $[M\text{-}C_3H_5ICl]^+$: 255, 257 and $[C_3H_5ICl]^+$: 203, 205) after 6 h of reaction (see supplementary data).

Figure 1 shows the progress of the reaction. Whereas the starting ester **1a** had almost disappeared after 6 h, **3a** reached its maximum concentration between 3 and 6 h, and then a gradual decline was observed. Allyl palmitate (**2a**) and a dark colour,

considered to be due to free iodine, appeared as the reaction time increased. A dynamic NMR experiment carried out for 28 h using CD_3COCD_3 (see supplementary data) only permitted the detection of the compounds indicated in Figure 1.

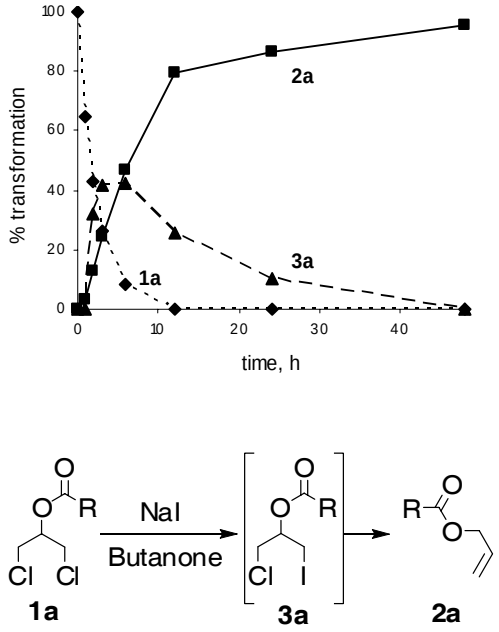
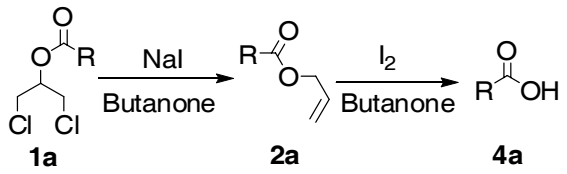


Figure 1. Evolution of the starting material (**1a**), the final product (**2a**) and an intermediate (**3a**) in presence of NaI at 115ºC (R= $CH_3(CH_2)_{14}$).

Second, the same reaction was studied using different ratios of **1a** to NaI. Figure 2 shows that when amounts of NaI are used under equivalence, the reaction is not complete and the formation of small amounts of **4a** is observed. When 1:1 molar ratio was used, only **4a** was recovered after 48 h of reaction. When using the 1:2 and 1:4 molar ratios the reaction progressed to **2a** without detecting the formation of **4a**.

Based on these results, the mechanism of the present reaction is proposed as shown in Scheme 1. Substitution of chlorine by iodine forms the compound **3a-j**. Nucleophilic attack of the sp^2 oxygen present in the carboxylic group could form the 1,3-dioxolane cations **5a-j** and **6a-j**, similar to the intermediates proposed by several authors.[3, 26] Intermediate **6a-j** could be transformed to **5a-j** by a new chlorine-iodine exchange. Compound **5a-j** could also be formed from 1,3-diiodo-2-propyl esters

(not shown in Scheme 1). However, these esters were not detected in the NMR experiment indicated above. Finally, **5a-j** could be transformed into the stable **2a-j** through the corresponding ring opening. This last step is very similar to that proposed by several authors for some dehalogenation reactions occurring in polar solvents. Barluenga et al.[27] proposed the formation of an allyl alcohol through an iodide-induced ß-elimination of an epiiodohydrin. Similar iodide-induced ß-elimination mechanism was proposed for the sodium iodide dehalogenation of *vic*-bromochlorides and *vic*-dichlorides.[28] Moreover, ionic mechanisms were proposed for some abnormal Finkelstein reactions[29] and the decomposition of ethylene diiodide in polar solvents.[30]



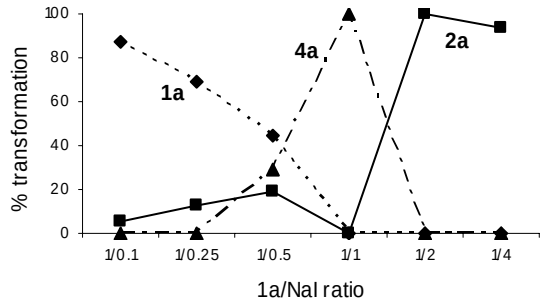
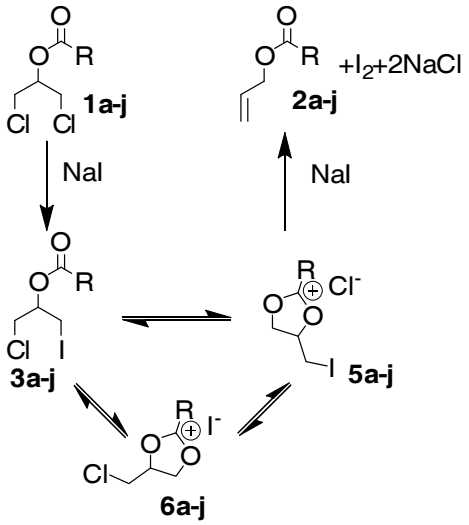


Figure 2. Effect of **1a**:NaI ratio in the products obtained from the transformation of **1a** after 48 h of reaction at 115ºC (R= $CH_3(CH_2)_{14}$).

When NaI was not in molar excess, the amount of iodide anion was not sufficient to bring the reaction to full completion. Moreover, the presence of some free iodine could cause the hydrolysis of a certain amount of **2a**.

Taksande et al.[31] have recently described iodine as a useful catalyst for hydrolyzing allyl esters in DMSO. As the amount of NaI increases, the amount of **4a** can also increase, as can the iodine present. This could explain why only **4a** is obtained when the 1:1 **1a**:NaI molar ratio was used. An extra increase in NaI could help the formation of I_3^-, which could stop the hydrolysis.



Scheme 1. Proposed mechanism for allyl ester formation (R = entries **a** to **j** according Table 1).

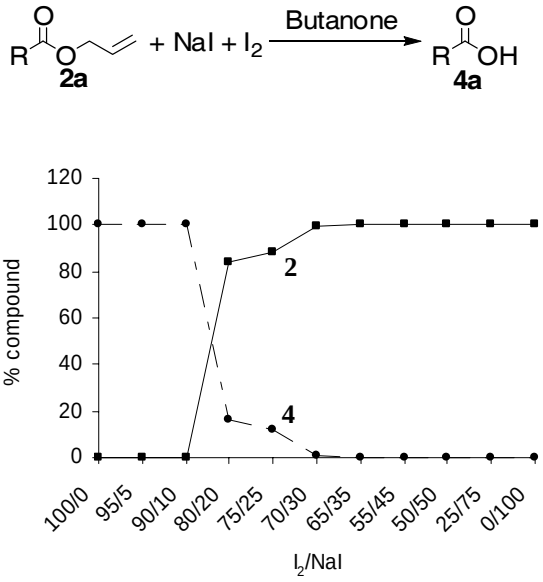


Figure 3. Evolution of the hydrolysis of **2a** in presence of different relative amounts of I_2 and NaI. The reaction was carried out at 110ºC for 24 h (R= $CH_3(CH_2)_{14}$).

To confirm this hypothesis **2a** was heated in the presence of different amounts of I_2:NaI mixture for 24 h. Figure 3 shows that when NaI was not present the compound **2a** was fully hydrolysed. This confirms that iodine is a suitable reagent for the hydrolysis of allyl esters even in butanone[31]. When the NaI amount increased, hydrolysis decreased. Finally, from a I_2:NaI ratio of 70:30 onward **2a** was not hydrolysed.

Considering these results a final set of experiments was planned using esters **1a** and **1j** again. They consisted on the introduction of sodium thiosulfate as an I_2 reducing agent in the reaction media. Using this approach, we tried to maintain the I_2 concentration below that which causes allyl esters hydrolysis while trying to diminish the amount of NaI, an expensive reagent. Moreover, iodide anion should always be present to catalyse the rearrangement-elimination reaction.

Table 2 shows that reaction can be carried out using amounts of NaI below the equivalence. Thus, 89% crude yield of **2a** is reached after 48 h using 0.5 mol of this salt. Yields are poorest for **2j**. However, 94% crude yield of **2j** could be obtained using 1 mmol NaI, half of the stechiometric equivalents needed This confirms that iodine concentration is maintained below the amount needed to cause the hydrolysis of allyl esters. No free acid was detected in any of these experiments. Nevertheless, the reaction time needed to reach similar yields depends on the amount of initial NaI used. This confirms that iodide anion should be present in the rate-determining step of this reaction. An increase of the amount of sodium thiosulfate does not cause an increase of the reaction rate nor the yield (results not shown). These results could be explained considering the low solubility of sodium thiosulfate in butanone.

3. Summary

1,3-Dichloro-2-propyl alkyl or aryl esters prepared from glycerol can be transformed to the corresponding allyl ester when two equivalents of NaI are used. Shorter reaction times yield noteworthy amounts (almost 50%) of 1-chloro-3-iodo-2-propyl esters, a potentially valuable compound to be obtained. Using less NaI leads to the formation of carboxylic acid unless a reducing agent like sodium thiosulfate is present in the reaction media. In this case, the reaction can be carried out to completion using 0.5 mmol (0.25 equivalents) of NaI during 48 h. Iodine in butanone is a suitable reagent to hydrolyse some allyl esters.

The application of this methodology to the synthesis of chiral halohydrin esters to be used as building-blocks is under study, as is the utilization of butanone:iodine mixture as hydrolyzing system for other allyl esters. Both studies will be reported in due course.

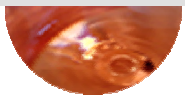
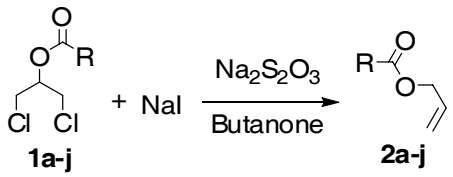


Table 2. 1,3-Dichloro-2-propyl ester (**1a-j**) dechlorination with sodium iodide/ sodium thiosulfate in butanone.



1 entry	NaI (mmol)	Crude yield (%) **2**	
		24h	48h
a	1.00	98	99
a	0.75	95	98
a	0.50	72	89
a	0.25	43	66
a	0.10	12	18
j	1.00	87	94
j	0.75	52	71
j	0.50	40	50
j	0.25	18	38
j	0.10	6	11

4. Experimental section

4.1. Material and Methods

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a VARIAN 400 spectrometer. All 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 centre 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: quintet, m: multiplet.

GC-FID analyses were performed in an Agilent Technologies 6890N equipped with a DB5-MS column (J&W) (30m x 0.25 µm x 0.25 mm) and He as carrier gas. The following chromatographic conditions were used: constant flow 2mL/min, split injection ratio 20:1 at 300ºC. Oven started at 50ºC for 5 min, temperature was increased at 5ºC/min to 110ºC, then increased at 10ºC/min until final temperature of 260ºC for 15 min. Tridecane from Aldrich was used as internal standard to carry out GC quantification.

GC-MS analyses 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 carrier gas. The following chromatographic conditions were used: constant flow 2mL/min, split injection ratio 20:1 at 280ºC. Oven started at 50ºC for 5 min, temperature was increased at 5ºC/min to 110ºC, then increased at 10ºC/min until final temperature of 260ºC for 15 min.

IR spectra were recorded on a Magna IR 560 NicoleT FTIR spectrophotometer in the range 4000-600 cm^{-1} with KBr pellets or with diamond HATR from SpectraTech as specified. Spectra are reported in reciprocal centimeters (cm^{-1}).

High-resolution mass spectral (HRMS) data were obtained by direct infusion on LC-TOF-MS Waters LCT Premier XE using ESI or APCI or on Waters GCT Premier using EI as specified.

4.2. General procedure for the preparation of allyl esters (2a-j)

A solution of 1,3-dichloro-2-propyl ester[5] (0.5 mmol) and sodium iodide (300 mg; 2 mmol) in dried butanone (1 mL) was heated for 48 h at 115ºC in a reaction vial. After cooling, *tert*-butyl methyl ether was added; the mixture was washed with saturated solution of $Na_2S_2O_3$ and water. The upper layer was recovered and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum to give the allyl derivate. The crude was purified by SiO_2 column chromatography to give the corresponding allyl ester.

4.3. General procedure for the preparation of allyl esters using $Na_2S_2O_3$ (2a-j)

A solution of 1,3-dichloro-2-propyl ester[5] (0.5 mmol), sodium iodide (150-15 mg; 1-0.1 mmol) and (158 mg, 1 mmol) in dried butanone (1 mL) was heated for 24-48 h at 115ºC in a reaction vial. After cooling, *tert*-butyl methyl ether was added; the mixture was washed with water. The upper layer was recovered and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum to give the allyl derivate. The crude was analysed by GC to determine the yield of the corresponding allyl ester.

4.4. Scaled up preparation of allyl palmitate (2a).

Prepared following the general procedure in a 125 mL reaction vial fitted with PFE-lined cap. A solution of 1,3-dichloro-2-propyl palmitate[5] **3a** (6.6 g, 18 mmol), and sodium iodide (10 g; 67 mmol) in dried butanone (25 mL) yielded the allyl palmitate **12a** (4.9 g, 91%).

4.5. Scaled up preparation of allyl 2-naphthoate (2j).

Prepared as described above. A solution of 1,3-dichloro-2-propyl naphthoate[5] The purified compound **3j** (7.1 g, 27 mmol), and sodium iodide (16,2 g; 108 mmol) in dried butanone (30 mL) yielded the allyl 2-naphthoate **(12j)** (4.3 g, 82%).

4.6. Study of the evolution of 1,3-dichloro-2-propyl palmitate (1a), 1-chloro-3-iodo-2-propyl palmitate (3a) and allyl palmitate using Dynamic ^{1}H-NMR spectra.

In a screw cap NMR tube were added 1,3-dichloro-2-propyl palmitate[5] (**1a**) (25,5 mg, 0.07 mmol), sodium iodide (42 mg, 0.28 mmol) and 1,5 mL acetone-*d6*. The mixture was introduced in NMR spectrometer at 80ºC for 30 h recording one spectrum every 2 h until the end of the experiment.

4.7. Reaction progress study (figure 1 main text)

1,3-Dichloro-2-propyl palmitate[5] (**1a**; 366 mg; 1 mmol) and sodium iodide (600 mg; 4 mmol) in dried butanone (1.5 mL) were heated at 115 ºC in a reaction vial. Samples were collected in triplicate at 2, 4, 8, 16, 24, 48 h and analyzed by GC and GC-MS in duplicated.

4.8. Influence of sodium iodide ratio (figure 2 main text)

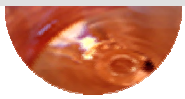
1,3-Dichloro-2-propyl palmitate[5] (**1a**; 366 mg; 1 mmol)**,** dried butanone (1.5 mL) and the amounts of sodium iodide as indicated in the following table:

mg NaI	1a:NaI molar ratio
15	1/0.1
37.5	1/0.25
75	1/0.5
150	1/1
300	1/2
600	1/4

were heated at 115ºC for 48 h in a reaction vial. Samples were collected and analyzed by GC and GC-MS in duplicated.

4.9. Stability in front NaI:I_2 ratio (figure 3 main text)

Allyl palmitate (**2a**; 50 mg; 0,17 mmol) was heated in presence of different I_2:NaI molar ratios (100:0; 95:5; 90:10; 80:20; 75:25; 70:30; 65:35; 55:45; 50:50; 25:75; 0:100) for 24 h at 110 ºC in a reaction vial. The samples were collected and analyzed by GC-MS in duplicate.



4.10. Analytical data

4.10.1. Allyl palmitate (2a)

[CAS: 43211-62-7]**:** **^{1}H-RMN** ($CDCl_3$) **δ**: 5.92 (m, 1H, CH_2-C*H*=CH_2), 5.31 (dq, J_{trans}=17.2 Hz, J_{gem}=1.6 Hz, 1H, CH=CH_2), 5.23 (dq, J_{cis}=10.2 Hz, J_{gem}=1.2 Hz, 1H, CH=CH_2), 4.57 (dt, J_1=5.5 Hz , J_2=1.5 Hz, 2H, CH_2-CH=CH_2), 2.33 (t, *J*=7 Hz, 2H, C$H_{2\ (\alpha)\ (C=O)}$), 1.63 (quin , *J*=7.5 Hz, 2H, C$H_{2\ (\beta)\ (C=O)}$), 1.25 (m, 24H, CH_2), 0.88 (t, *J*=7 Hz, 3H, CH_3). **^{13}C-RMN** ($CDCl_3$) **δ**: 173.7 (*C*=O), 132.6 (*C*H=), 118.3 (=CH_2), 65.1 (O-CH_2), 34.5 ($CH_{2\ (\alpha)\ (C=O)}$), 32.2 (CH_2-CH_2-CH_3), 29.9, 29.8, 29.7, 29.6, 29.5, 29.4 (CH_2), 25.2 ($CH_{2\ (\beta)\ (C=O)}$), 22.9 (CH_2-CH_3), 14.3 (CH_3). **GC-MS** *m/z*: 296 $[M]^+$; 267 $[M\text{-}C_2H_3]^+$; 253 $[M\text{-}C_3H_5]^+$; 239 $[M\text{-}OC_3H_5]^+$. **IR** ATR ν max.: 3075, 2924, 2853, 1740, 1592, 1437, 1245, 1115, 1051, 747 cm^{-1}.

4.10.2. Allyl caprate (2b)

[CAS: 57856-81-2]**:** **^{1}H-NMR** ($CDCl_3$) **δ**: 5.91 (m, 1H, CH_2-C*H*=CH_2), 5.26 (m, 2H, CH=CH_2), 4.56 (dd, J_1=5.6 Hz, J_2=1.2 Hz, 2H, CH_2-CH=CH_2), 2.33 (t, *J*=8 Hz, 2H, C$H_{2\ (\alpha)\ (C=O)}$), 1.62 (m, 2H, C$H_{2\ (\beta)\ (C=O)}$), 1.25 (m, 12H, CH_2), 0.87 (t, *J*=6.8 Hz, 3H, CH_3). **^{13}C-RMN** ($CDCl_3$) **δ**: 173.7 (*C*=O), 132.5 (*C*H=), 118.2 (=CH_2), 65.1 (O-CH_2), 34.5 ($CH_{2\ (\alpha)\ (C=O)}$), 32.1 (CH_2-CH_2-CH_3), 29.6, 29.5, 29.4 (CH_2), 25.2 ($CH_{2\ (\beta)\ (C=O)}$), 22.9 (CH_2-CH_3), 14.3 (CH_3). **GC-MS** *m/z*: 212 $[M]^+$; 183 $[M\text{-}C_2H_3]^+$; 169 $[M\text{-}C_3H_5]^+$; 155 $[M\text{-}OC_3H_5]^+$. **IR** KBr film ν max.: 3074, 2924, 2854, 1737, 1460, 1159, 989, 723 cm^{-1}.

4.10.3. Allyl pivaloate (2c)

[CAS: 15784-26-6]**:** **^{1}H-RMN** ($CDCl_3$) **δ**: 5.85 (m, 1H, CH_2-C*H*=CH_2), 5.24 (dq, J_{trans}=17.2 Hz, J_{gem}=1.6 Hz, 1H, CH=CH_2), 5.15 (dq, J_{cis}=10.8 Hz, J_{gem}=1.6 Hz, 1H, C*H*=CH_2), 4.50 (dt, J_1=5.2 Hz , J_2=1.2 Hz, 2H, CH_2-CH=CH_2), 1.16 (m, 9H, CH_3). **^{13}C-RMN** ($CDCl_3$) **δ**: 178.4 (*C*=O), 132.7 (*C*H=CH_2), 117.7 (CH=CH_2), 65.1 (O-CH_2), 38.9 (*C*-$(CH_3)_3$), 27.4 (3CH_3). **GC-MS** *m/z*: 142 $[M]^+$, 102 $[M\text{-}C_3H_5]^+$; 84 $[M\text{-}OC_3H_5]^+$; 57 $[M\text{-}CO_2C_3H_5]^+$. **IR** KBr film ν max.: 3094, 2975, 2966, 1730, 1481, 1280, 1146, 982, 771 cm^{-1}.

4.10.4. Allyl cinnamate (2d)

[CAS: 1866-31-5]**:** **^{1}H-RMN** ($CDCl_3$) **δ**: 7.66 (d, *J*=16 Hz, 1H, CH_{ar}), 7.47 (m, 2H, 2 CH_{ar}), 7.32 (m, 3H, 2 CH_{ar}; Ph-C*H*=CH), 6.41 (d, *J*=16.4 Hz, 1H, Ph-C*H*=CH), 5.94 (m, 1H, CH_2-C*H*=CH_2), 5.32 (dq, J_{trans}=17.2 Hz, J_{gem}=1.6 Hz, 1H, CH=CH_2), 5.21 (dq, J_{cis}=10 Hz, J_{gem}=1.6 Hz, 1H, CH=CH_2), 4.66 (dt, J_1=5.6 Hz , J_2=1.6 Hz, 2H, CH_2-CH=CH_2). **^{13}C-RMN** ($CDCl_3$) **δ**: 166.8 (*C*=O), 145.3 (Ph-*C*H=CH), 134.6 (*C*H_{ar}), 132.5 (*C*H=CH_2), 130.6, 129.1, 128.3 (CH_{ar}), 118.5, 118.1 (CH=*C*H_2, Ph-CH=*C*H), 65.4 (O-*C*H). **GC-MS** *m/z*: 188 $[M]^+$; 173 $[M\text{-}CH_3]^+$; 147 $[M\text{-}C_3H_5]^+$; 131 $[M\text{-}OC_3H_5]^+$; 103 $[M\text{-}CO_2C_3H_5]^+$; 91 $[M\text{-}CHCO_2C_3H_5]^+$; 77 $[M\text{-}C_2H_2CO_2C_3H_5]^+$. **IR** KBr film ν max.: 3084, 3062, 3029, 2965, 1709, 1636, 1450, 1308, 1162, 979, 766 cm^{-1}.

4.10.5. Allyl benzoate (2e)

[CAS: 583-04-0]**: ^{1}H-RMN** ($CDCl_3$) δ: 8.01 (m, 2H, C*H*$_{ar}$-C=O), 7.49 (m, 1H, C*H*$_{ar}$), 7.38 (m, 2H, 2 C*H*$_{ar}$), 5.98 (m, 1H, CH_2-C*H*=CH_2), 5.35 (dq, J_{trans}=17.2 Hz, J_{gem}=2 Hz, 1H, CH=C*H*$_2$), 5.23 (dq, J_{cis}=10.8 Hz, J_{gem}=1.2 Hz, 1H, CH=C*H*$_2$), 4.76 (dt, J_1=5.6 Hz , J_2=1.6 Hz, 2H, C*H*$_2$-CH=CH_2). **^{13}C-RMN** ($CDCl_3$) δ: 166.5 (*C*=O), 133.2 (*C*H=CH_2), 132.4, 130.4, 129.8, 128.6 (*C*H$_{ar}$), 118.5 (CH=*C*H$_2$), 65.8 (O-*C*H$_2$). **GC-MS** *m/z*: 162 $[M]^+$; 147 $[M\text{-}CH_3]^+$; 121 $[M\text{-}C_3H_5]^+$; 105 $[M\text{-}OC_3H_5]^+$; 77 $[M\text{-}CO_2C_3H_5]^+$. **IR** KBr film ν max.: 3063, 3033 2970, 1724, 1451, 1269, 1107, 1069, 709 cm^{-1}.

4.10.6. Allyl 2-chlorobenzoate (2f)

[CAS: 15721-27-4]**: ^{1}H-RMN** ($CDCl_3$) δ: 7.85 (m, 1H, C*H*$_{ar}$-C=O), 7.44 (m, 2H, 2 C*H*$_{ar}$), 7.32 (m, 1H, C*H*$_{ar}$-Cl), 6.04 (m, 1H, CH_2-C*H*=CH_2), 5.44 (dq, J_{trans}=17.2 Hz, J_{gem}=1.2 Hz, 1H, CH=C*H*$_2$), 5.31 (dq, J_{cis}=10.4 Hz, J_{gem}=1.6 Hz, 1H, CH=C*H*$_2$), 4.84 (dt, J_1=5.6 Hz , J_2=1.2 Hz, 2H, C*H*$_2$-CH=CH_2). **^{13}C-RMN** ($CDCl_3$) δ: 165.6 (*C*=O), 132.8 (*C*H=CH_2, *C*H$_{ar}$), 131.9, 131.7, 131.3, 130.3, 126.8 (*C*H$_{ar}$), 119.0 (CH=*C*H$_2$), 66.4 (O-*C*H$_2$). **GC-MS** *m/z*: 196 $[M]^+$; 139 $[M\text{-}OC_3H_5]^+$; 111 $[M\text{-}CO_2C_3H_5]^+$. **IR** KBr film ν max.: 3075 3050, 3032, 2947, 1734, 1593, 1437, 1296, 1249, 1119, 1050, 935, 748 cm^{-1}.

4.10.7. Allyl 4-nitrobenzoate (2g)

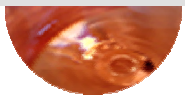
[CAS: 15757-80-7]**: ^{1}H-RMN** ($CDCl_3$) δ: 8.28 (m, 4H, CH_{ar}), 6.05 (m, 1H, CH_2-C*H*=CH_2), 5.43 (dq, J_{trans}=17.2 Hz, J_{gem}=1.6 Hz, 1H, CH=C*H*$_2$), 5.34 (dq, J_{cis}=10 Hz, J_{gem}=1.2 Hz, 1H, CH=C*H*$_2$), 4.87 (dt, J_1=6 Hz , J_2=1.6 Hz, 2H, C*H*$_2$-CH=CH_2). **^{13}C-RMN** ($CDCl_3$) δ: 164.6 (*C*=O), 150.8 (CH_{ar}-NO_2), 135.8 (*C*H=), 131.7, 131.1, 131.0, 123.9, 123.8 (*C*H$_{ar}$),119.4 (=CH_2), 66.7 (O-*C*H$_2$). **GC-MS** *m/z*: 207 $[M]^+$; 150 $[M\text{-}CO_2C_3H_5]^+$; 134 $[M\text{-}NO_2C_2H_3]^+$; 120 $[M\text{-}NO_2C_3H_5]^+$; 104 $[M\text{-}CO_2C_3H_5]^+$; 76 $[M\text{-}C_2H_2CO_2C_3H_5]^+$. **IR** KBr film ν max.: 3112, 3080, 2962, 1727, 1528, 1351, 1260, 1099, 1016, 872, 799, 719 cm^{-1}.

4.10.8. Allyl salicylate (2h)

[CAS: 10484-09-0]**: ^{1}H-RMN** ($CDCl_3$) δ: 7.90 (m, 1H, C*H*$_{ar}$), 7.48 (m, 1H, C*H*$_{ar}$), 6.99 (m, 1H, C*H*$_{ar}$), 6.90 (m, 1H, C*H*$_{ar}$), 6.04 (m, 1H, CH_2-C*H*=CH_2), 5.43 (dq, J_{trans}=17.2 Hz, J_{gem}=1.6 Hz, 1H, CH=C*H*$_2$), 5.33 (dq, J_{cis}=10.4 Hz, J_{gem}=1.6 Hz, 1H, CH=C*H*$_2$), 4.85 (dt, J_1=5.2 Hz , J_2=1.6 Hz, 2H, C*H*$_2$-CH=CH_2). **^{13}C-RMN** ($CDCl_3$) δ: 169.1 (*C*=O), 162.1 (*C*H$_{ar}$-OH), 136.7 (*C*H=CH_2), 130.4, 119.7 (*C*H$_{ar}$), 117.9 (CH=*C*H$_2$), 111.8 (*C*H$_{ar}$), 72.7 (O-*C*H$_2$). **GC-MS** *m/z*: 179 $[M]^+$; 137 $[M\text{-}C_3H_5]^+$; 120 $[M\text{-}HCO_2C_3H_5]^+$; 92 $[M\text{-}HCO_2C_3H_5]^+$. **IR** KBr film ν max.: 3294, 3025, 2975, 1673, 1613, 1484, 1298, 1247, 1209, 1156, 1084, 755, 698 cm^{-1}.

4.10.9. Allyl 1-naphthoate (2i)

[CAS: 53548-26-8]**: ^{1}H-RMN** ($CDCl_3$) δ: 8.92 (m, 1H, C*H*$_{ar}$), 8.23 (dd, J_1=7.2 Hz, J_2=1.2 Hz, 1H, C*H*$_{ar}$), 8.03 (d, *J*=8.4 Hz, 1H, C*H*$_{ar}$), 7.89 (m, 1H, C*H*$_{ar}$), 7.62 (m, 1H, C*H*$_{ar}$), 7.52 (m, 2H, 2 C*H*$_{ar}$), 6.11 (m, 1H, CH_2-C*H*=CH_2), 5.47 (dq, J_{trans}=17.6 Hz, J_{gem}=1.6 Hz, 1H, CH=C*H*$_2$), 5.33 (dq, J_{cis}=10.4 Hz, J_{gem}=1.6 Hz, 1H, CH=C*H*$_2$), 4.93 (dt, J_1=5.6 Hz , J_2=1.6 Hz, 2H, C*H*$_2$-CH=CH_2). **^{13}C-RMN** ($CDCl_3$) δ: 167.4 (*C*=O), 134.1, 133.7 (*C*H$_{ar}$), 132.5 (*C*H=CH_2), 131.6, 130.5, 128.8, 128.0, 127.3, 126.4, 126.0, 124.7 (*C*H$_{ar}$), 118.7 (CH=*C*H$_2$), 65.9 (O-*C*H$_2$). **GC-MS** *m/z*: 212



$[M]^+$; 155 $[M\text{-}OC_3H_5]^+$; 127 $[M\text{-}CO_2C_3H_5]^+$. **IR** ATR ν max.: 3087, 3052, 3017, 2984, 2944, 1716, 1510, 1275, 1243, 1196, 1133, 1013, 934, 814, 782 cm^{-1}.

4.10.10. Allyl 2-naphthoate (2j)

[CAS: 53409-01-1]**:** **^{1}H-RMN** ($CDCl_3$) δ: 8.64 (s, 1H, CH_{ar}), 8.08 (dd, J_1=8.4 Hz, J_2=1.2 Hz, 1H, CH_{ar}), 7.96 (d, J=8 Hz, 1H, CH_{ar}), 7.89 (d, J=8.8 Hz, 2H, 2 CH_{ar}), 7.57 (m, 2H, 2 CH_{ar}), 6.10 (m, 1H, CH_2-C*H*=CH_2), 5.46 (dq, J_{trans}=16.8 Hz, J_{gem}=1.6 Hz, 1H, CH=CH_2), 5.34 (dq, J_{cis}=10.4 Hz, J_{gem}=1.2 Hz, 1H, CH=CH_2), 4.89 (dt, J_1=5.6 Hz , J_2=1.2 Hz, 2H, CH_2-CH=CH_2). **^{13}C-RMN** ($CDCl_3$) δ: 166.6 (*C*=O), 135.8, 132.7 (*C*H_{ar}), 132.5 (*C*H=CH_2), 131.4, 129.6, 128.5, 128.4, 128.0, 127.6, 126.8, 125.4 (*C*H_{ar}), 118.6 (CH=*C*H_2), 65.9 (O-*C*H_2). **GC-MS** *m/z*: 212 $[M]^+$; 155 $[M\text{-}OC_3H_5]^+$; 127 $[M\text{-}CO_2C_3H_5]^+$. **IR** ATR ν max.: 3060, 3022, 2942, 1719, 1631, 1469, 1355, 1281, 1227, 1196, 1130, 1093, 980, 778, 762 cm^{-1}.

4.11. Determination of 1-chloro-3-iodo-2-propyl palmitate (3a)

During the GC-MS analysis of the samples obtained in the reaction of **1a** with NaI a chromatographic peak at t_R = 34.7 min was detected. Its MS presented characteristic ions of **3a** ($[M]^+$:458, 460; $[M\text{-}Cl]^+$: 423, 425; $[M\text{-}I]^+$: 331, 333; $[M\text{-}C_3H_5ICl]^+$: 255, 257 and $[C_3H_5ICl]^+$: 203, 205). To confirm the presence of this intermediate compound, these samples were analyzed by ^{1}H-NMR. The formation of **3a** was evidenced by the presence of a characteristic quintuplet at 4.93 and a multiplet at 3.42 ppm of the O-C*H* and CH_2-I groups respectively.

Acknowledgments

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References and notes

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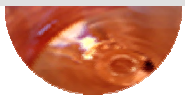

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2.3. Aplicació de la síntesi d'esters d'al·lil a materials greixosos *(en preparació)*

Crude glycerol and fatty materials for the synthesis of allyl esters

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Vegetable oils and fats are important renewable raw materials for use by the chemical industry. Biodiesel industries use them to prepare methyl esters to produce large amounts of glycerol. Consequently, crude glycerol is moving from a by-product to a residue. New industrial applications for this substance are required. A conversion of this by-product to allyl esters using various fatty materials in a two-step process is reported: After a simultaneous transesterification–chlorination reaction of vegetable oils and fats without a solvent, allyl esters were synthesized in a high yield by a rearrangement–elimination reaction using n-butanol as a solvent. All the reactions could be carried out using conventional heating or microwave irradiation with comparable results. Microwave irradiation allows for an important reduction in the reaction time.

1. Introduction

Nowadays, environmental renewable strategy is gaining the political and economic emphasis required to make a meaningful contribution to reducing waste. Vegetable oils and fats, as renewable raw materials, can play an important role in the chemical industry, since they offer a large number of possibilities for applications (Little, 2004 and Niederl 2006). Crude vegetable oils from different seeds (e.g., soy, palm, sunflower, and rape) can be processed to manufacture soaps, distilled fatty acids, and oil-seed cake (Abouelwafa et al., 2008). Overall, these operations lead to the production of significant quantities of very diverse liquid waste (Abouelwafa et al., 2008), often amounting to 0.15 l/kg of oil material produced.

In many countries today, owing to the obligatory requirement for biodiesel production, an application of these oil materials is in the biodiesel industry. Moreover, as a result of the large volume of biodiesel produced from diverse sources, there is an excess of crude glycerol, which is mainly treated as industrial waste (Mu et al., 2008). Consequently, the need for new industrial applications for crude glycerol has stimulated research in this field. Nevertheless, the literature still shows that the composition of crude biodiesel glycerol varies widely (Slinn et al., 2008; Valliyappan et al., 2008; Dou et al., 2009; Hansen et al., 2009). This is why it is difficult to predict its industrial usage. In addition, the presence of other matrix components, such as nonreacted and partially reacted fats, free fatty acids, methanol, esters, and salts makes crude glycerol difficult to handle. Purifying this glycerol for use in cosmetic and pharmaceutical purposes does not justify the high cost of the refining process. This cost, principally borne by the medium-sized biodiesel producers, requires a special effort from these companies (Liang et al. 2010).

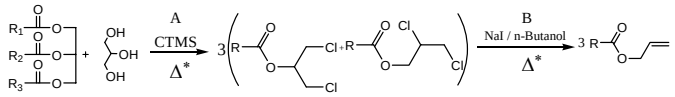
Recently, our research group has described an easy process to obtain allyl esters (Eras et al. 2009). These esters were prepared in butanone using a simultaneous Finkelstein rearrangement–elimination reaction of dichloropropyl esters. These dichloropropyl esters had been synthesized using carboxylic acids, glycerol, and a source of chlorine (Escribà et al. 2009*a* and Villorbina et al. 2009).

Several compounds containing an allyl group exhibit a high activity as insecticides, acaricides, and insect repellents (Ojimelukwe et al. 1999, Takahashi et al. 2007, Iwasaki et al. 2000). Allyl esters of fatty acids have been proposed as wood preservatives against termites (Yoshida et al. 2006). In addition, an ovicidal effect against *Cydia pomonella (L.)* has been described on using allyl alkylcarboxylates (Escribà et al. 2009*b*).

Another application of allyl ester mixtures of higher fatty acids is in polymeric synthesis. In this sense, highly effective and generally useful copolymers have been prepared from allyl esters (Gan et al. 1992, Van Horne et al. 1952).

Herein, we describe a new approach to the synthesis of allyl fatty esters using various fatty materials and crude glycerol obtained from the biodiesel industry, using both conventional and microwave heating (Scheme 1).

Scheme 1. A two-step synthesis of allyl esters.



(*) Conventional or microwave heating

Chlorotrimethylsilane (CTMS) was used as a source of chlorine to prepare the corresponding dichloropropyl esters from the fatty material and crude glycerol. Using this process, we addressed both the use of acylglycerides and glycerol by-products. The reaction could be carried out using either classical heating or microwave irradiation.

2. Material and methods

2.1. *Characterization and purification of the glycerol by-product.*

Three crude glycerol samples were obtained from a biodiesel industrial supplier that used an alkali-catalyzed transesterification procedure (Raluy S.L., Spain). Crude glycerol is an inhomogeneous material with a gel-like appearance and a dark reddish color (Fig. 1). First, crude glycerol was homogenized using mechanical shaking to analyze its composition. Next, the water content was measured using the Karl–Fisher method and the ash content by oven calcination at 520 °C until white ash was produced. The alkalinity of the ash was measured using volumetry. High temperature gas chromatography (HT-GC) (Tomas et al. 2009) of the product revealed the presence of methanol, nonreacted acylglycerides, and free fatty acids. Crude glycerol was neutralized using sulfuric acid, and the residual methanol was removed by distillation under vacuum. Finally, glycerol was centrifuged at 2600 g and decanted to remove any solids in the suspension. The final product was analyzed using ^{1}H-NMR in deuterated dimethylsulfoxide using N,N-dimethylformamide as an internal standard. The final substrate was glycerol rich to approx. 90% for the three samples studied.

Fig 1. Crude glycerol

2.2. *Characterization of the fatty material.*

Animal fat, vegetable oils, and industrial waste oil were collected from different Spanish food industries (Table 1). For each sample, the acylglyceride content, the free glycerol and fatty acid profiles were determined. The composition of the acylglycerides was analyzed using HT-GC (Tomas et al. 2009). The free glycerol content was measured using gas chromatography (GC) after previous silylation with bis(trimethylsilyl)acetamide (EN-14105). The fatty acid profile was determined using GC according to Eras et al. (2004). An extraction with dichloromethane was carried out to characterize the oily waste from an industrial producing olive pomace oil sample.

The organic solvent layer was filtered to remove any solids in the suspension. The solvent was evaporated, and the residue was weighted and analyzed, as described above for the other fatty materials. According to the acid profiles, an average molar weight (AMW) and acylglyceride content (AG) were determined for each fatty material. Table 1 shows the AMW and AG values found for each material used.

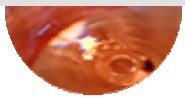


Table 1. Average molar weight and acylglyceride content of the fatty material samples.

Entry	Fat	AMW (g/mol)	AG(%, w/w)
1	Refined soy oil	277	99
2	Mixture of frying oils	279	80
3	Crude palm oil	272	99
4	Frying palm oil from the donut industry	270	92
5	Chicken fat	274	99
6	Rape seed crude oil	280	97
7	Waste fatty material from the olive pomace oil industry	279	77

2.3. *Transesterification–chlorination reaction (A)*

Each fatty material (1–7) was mixed with pretreated crude glycerol and chlorotrimethylsilane (CTMS), and was added to a reaction vial fitted with a PTFE-lined cap. The molar ratio of each reagent was 1:8:14, respectively, considering the average molar weight of each material and the amount of residual acylglycerides present in the glycerol. The mixture was heated in a silicon oil bath or irradiated in a monomode microwave oven. The conditions used for the silicon oil bath were 115 °C for 48 h, and for the microwave oven, the conditions used were 225 °C (300 W, 17 atm) for 3 h using a Discover LabMate microwave reactor (CEM, Matthews, USA) equipped with magnetic stirring and an air cooling system. After cooling, *t*-butyl methyl ether was added, and the mixture was washed three times with water. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum. All the assays were carried out in duplicate.

The dichloropropyl ester mixture content was determined using an Agilent (Barcelona, Spain) HP6890 series GC coupled to a FID detector. The analytical column used was a 15 m × 0.32 mm fused silica capillary coated with a 0.1 μm film equivalent to 100% dimethylpolysiloxane (TRB-1HT; Teknokroma). The temperature program used was 50 °C for 1 min, then the temperature was increased to 180 °C at a heating rate of 15 °C/min, then to 230 °C at a heating rate of 7 °C/min, and then to 370 °C at a heating rate of 10 °C/min. The sample was then held

at 370 °C for a period of 10 min. An on-column injection system was used, employing hydrogen as the carrier gas at a flow rate of 4 mL/min.

The identification of dichloropropyl esters mixture was carried out using a GLC–MS Agilent 6890N GC coupled to a 5973 mass selective detector (Agilent Technologies España S.L., Las Rozas, Spain). The analytical column used was a 30 m × 0.25 mm fused silica capillary coated with a 0.25 μm film equivalent to 5% (phenyl)methylpolysiloxane (DB-5MS; Agilent). Detection was carried out using a 5973 mass selective single quadrupole detector (Agilent).

2.4. *Rearrangement–elimination reaction (B)*

A mixture of the dichloropropyl esters, previously dried sodium iodine and sodium thiosulfate (2:0.5:1 molar ratio) in a solvent of n-butanol (6 ml) was added to the reaction vial fitted with a PTFE-lined cap. The mixture was heated to 115 °C for 48 h in a silicon oil bath, or irradiated to a temperature of 150 °C for 25 min in the microwave oven. After cooling, *t*-butyl methyl ether was added, and the mixture was washed three times with water. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under vacuum.

Both the quantitative and qualitative analyses of the allyl esters were carried out using the same GC-FID Agilent HP6890 series GC and GLC–MS Agilent 6890N GC coupled to a 5973 mass selective detector, as described above.

3. Results and discussion

3.1. *Transesterification-chlorination reaction (A)*

The selected molar ratio of the reagents of 1:8:14 (fatty material: glycerol: CTMS) was obtained after the study on the reaction using refined soy oil, pure glycerol, and CTMS in a conventional heating system. Various molar ratios of reagents were studied to optimize the conversion and yield. When the molar ratio of glycerol was < 4, diacylglycerides were present at a percentage > 10% and triacylglycerides were present at a percentage 1%–10% (w/w). When the molar ratio of CTMS was < 12, the percentage of diacylglycerides increased to > 10%. We found that the best molar ratios were 1: 6: 12 and 1: 8: 14 (fatty material: glycerol: CTMS). The first ratio allowed a conversion of 96% (w/w) of soy oil in dichloropropyl fatty esters with 4% of diacylglycerides present. The second ratio allowed a conversion of 97% (w/w) of dichloropropyl esters with only 3% of diacylglycerides.

Subsequently, the reactions using the fatty materials and crude glycerol were assayed using a molar ratio of 1: 8: 14. In all the fatty acid samples, the amount of free glycerol was < 1%, and so was not taken into account. The amount of fatty material and crude glycerol used in the reaction was established considering the acylglyceride richness of each starting material (Table 1).

Once the reaction was finished, the reaction yields were determined according to the average molar weight of both the initial acylglycerides and the final dichloropropyl esters. The yield was determined with reference to the amount of acylglyceride present in each assay.

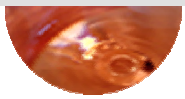
In all cases (Table 2), the yield obtained using a conventional heated reactor was > 90%, except in the case of using the industrial waste from the olive oil producer (yield = 85%). Microwave irradiation led to similar yields. Nevertheless, the dark color of the crude product suggests some product degradation occurred as a consequence of the high temperature used.

Table 2. Average yield (%) for the transesterification–chlorination reaction using diverse fatty materials.

Entry	Conventional reactor	Microwave irradiation
1	99	95
2	97	98
3	97	97
4	97	97
5	97	97
6	99	99
7	85	86

3.2. *Rearrangement–elimination reaction (B)*

The crude products obtained in the reaction described in the previous subsection were mainly a mixture of dichloropropyl esters, and these can be used directly as a starting material to prepare allyl esters. GC-MS analysis could identify the allyl esters present. Sodium thiosulfate allowed us to use a 0.5 molar ratio of sodium iodine to maintain high



yields (Table 3). In this case, n-butanol was used as a solvent instead of butanone. (Eras et al. 2009).

Microwave heating had a lower conversion rate than conventional heating did, in five samples being < 90%. Nevertheless, the reaction was complete in a period of only 25 min, whereas conventional heating required a period of 48 h.

Table 3. Average yield (%) for the rearrangement–elimination reaction using various crude dichloropropyl fatty esters prepared from fatty materials.

Entry	Conventional reactor	Microwave irradiation
1	99	92
2	99	94
3	98	96
4	99	98
5	99	95
6	97	93
7	95	92

According to our results, the global yield for the allyl ester synthesis under conventional heating conditions was > 95% in all the samples, except for the waste material from the olive oil industry, where the final yield was 80%. Using microwave irradiation, the yield was comparable, but was slightly lower than the conventional heating yield. A partial decomposition on microwave irradiation could contribute to the lower yield obtained. Nevertheless, all the final yields determined with reference to the amount of acylglyceride present in each assay were > 90%, except for the industrial olive oil waste material, which had a yield of 79%. The most important difference between the two heating methods was the reaction time: a total of 96 h was required for the conventional heating conditions, and 3.5 h was required for microwave irradiation.

4. Conclusions

It is possible to prepare mixtures of allyl esters with high overall yields from various fatty materials using crude glycerol from the biodiesel industry. The reactions can be carried out under conventional heating conditions or using microwave irradiation with comparable global yields. Microwave irradiation reduces the reaction time from 96 h to 3.5 h. The first step of the reaction is carried out without the use of a solvent, rendering dichloropropyl fatty esters as the starting materials for several possible applications. The second step can be carried out using an environmentally friendly solvent. The use of a reducing reagent permits the use of NaI below the equivalence level. This process allows the reuse of waste from vegetable oil and fat industries, and, even more importantly, the reuse of crude glycerol produced by the biodiesel industry.

Acknowledgments

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2.4. Synthesis of Allyl Esters of Fatty Acids and their Ovicidal Effect on *Cydia pomonella (L.)*

Escribà, M; Barbut, M.; Eras, J., Canela, R.; Avilla, J., Balcells, M.*

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Abstract - Eight allyl esters of fatty acids were synthesized in moderate to high yields with a novel two-step procedure using glycerol as a starting material. The two-step methodology avoids the use of allyl alcohol. The first step consisted of heating at 80 °C for 48 h a 2:1:5 mmol mixture of glycerol, a fatty acid and chlorotrimethylsilane in a solvent-free medium. The crude compound was then dissolved in butanone and heated at 115 °C in the presence of NaI. A tandem Finkelstein-rearrangement–elimination reaction occurs producing the corresponding allyl ester. The activity of these esters against *Cydia pomonella* (L.) (Lepidoptera: Tortricidae) eggs was tested in the laboratory by topical application of one 0.1 μL drop. All of the compounds showed a concentration–mortality response and caused 100% mortality at the highest concentration tested (10 mg/mL). There was an inverse relationship between the alkyl chain length and the ovicidal activity of the allyl ester; the LC_{50} and the LC_{90} of the two compounds that have the longer alkyl chains were significantly higher than those of the rest of the compounds. To the best of our knowledge, the ovicidal and IGR activity of this kind of compound are unprecedented.

keywords: allyl esters; codling moth; *cydia pomonella*; insecticide; ovicide

1. Introduction

Economic losses caused by codling moth [*Cydia pomonella* (L.), Lepidoptera: Tortricidae], a major pest of apple, pear and walnut crops, demand effective control methods against it. Damage is caused by the larvae, which enter into the fruits, feed on them, and cause their fall and depreciation. Of Euroasiatic origin, it is nowadays a key pest almost everywhere that apple and pear trees are grown (*1*); therefore, many control methods have been developed to reduce its population, chemical control and mating disruption being the most important methods. Many synthetic and natural chemicals show insecticidal activity against this pest, although resistant populations against different chemical pesticides have been reported in many countries (*2*, *3*). It is necessary, then, to find compounds with new modes of action, such as moulting accelerator compounds (e.g., methoxyfenozide) or activators of insect ryanodine receptors (e.g., chlorantranilipole) (*4*) and to restrict their use to those modes that are more environmentally friendly.

The search for new compounds active against *C. pomonella* eggs began in our laboratory with the synthesis of the *N*-(4-phenoxyphenyl)-2-pyridinecarboxamide, designed with reference to the phenoxyphenyl moiety, which is supposed to be responsible for juvenilizing activity in insects, and adding a pyridine ring to it. This compound showed ovicidal activity on codling moth and juvelinization effects on *Tribolium confusum* duVal (Coleoptera: Tenebrionidae) (*5*). The activity of 13 phenoxyphenyl pyridine and pyrazine carboxamides on eggs of *C. pomonella* was tested afterwards. Six compounds showed ovicidal activity (their efficacy ranged from 26 to 50%), and they also produced a significant increase in the length of the development period of the eggs (from one to two days) (*6*). Moreover, the insecticidal activity of extracts of *Maytenus* species against the same pest has also been studied (*7*).

It is also well known that diverse compounds containing the allyl group, such as the pyrethroid allethrin, 4-allyl anisol or allyl isothiocyanate, have a high activity as insecticides, acaridides and insect repellents (*12–14*). Allyl esters of fatty acids have been proposed as wood preservatives, allyl pentanoate having the highest activity on termites (*15*). Moreover, allyl formate has been tested against several pest species (*16*), and allyl alcohol itself is used as a herbicide manufactured by the Shell Chemical Company, 1025 Connecticut Avenue, Suite 200, Washington, DC 20036, and Haco, Inc., PO Box 7190, Madison, WI 53707. According to these references and our previous experience, we hypothesize that allyl esters could have ovicidal activity. Furthermore, many of these esters have been used as aromas and in cosmetic formulations for a long time (*8–11*), so low or no human toxicity is expected, which is a desirable characteristic of new insecticidal compounds.

With this aim, we have developed an easy synthesis of allyl esters of fatty acids. Starting from glycerol, a fatty acid and chlorotrimethylsilane (CTMS) 1,3-

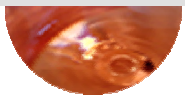
dichloropropyl esters are obtained. 1,3-Dichloropropyl esters lead to allyl esters in high yields in a tandem Finkelstein-transposition–elimination reaction promoted by NaI in a further step. This process allows the use of glycerol as a starting material, avoiding the use of reagents such as allylic alcohol, an irritant compound, and fatty acid acyl chlorides. The synthesis of the intermediate compounds can also be carried out by an alternative synthesis. Researchers from Dow Global Technologies recently described its synthesis starting from glycerol, carboxylic acids and hydrogen chloride with a partial pressure greater than 15 psi (*17*). A mixture of glycerol, carboxylic acid and metal halide in an ionic liquid leads also to the same intermediates (*18*). Nevertheless, using CTMS results in obtaining the allyl ester precursors in high purity. Yields were also high in most of the reactions assayed. Once the allyl esters of medium and long chain fatty acids were obtained, their ovicidal activity against eggs of *C. pomonella* was tested. A set of experiments using different concentrations of each allyl ester was carried out to evaluate the efficacy and the growth regulator activity on *C. pomonella* eggs.

2.- Materials and Methods

Chemicals. Butanone was purchased from Across and dried over molecular sieves (3 Å) by the conventional method prior to use. Sodium iodide was purchased from Riedel-deHaën and dried by heating at 110 ºC for 24 h. Chlorotrimethylsilane (CTMS), glycerol and the other fatty acids were purchased from Fluka (Sigma-Aldrich Química, S.A.**,** Madrid, Spain) and used as received. *t*-Butyl methyl ether was purchased from J. T. Baker (Quimega, Lleida, Spain). Anhydrous magnesium sulfate ($MgSO_4$) was purchased from Panreac (Panreac, Barcelona, Spain).

Apparatus. NMR spectra were recorded on a VARIAN 400 spectrometer (400 MHz for ^1H, 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 ^1H and the center line of the triplet at 77.00 ppm for ^{13}C NMR: The following abbreviations are used; s: singlet, d: doublet, t: triplet, q: quartet, quin: quintet, m: multiplet. GC–MS was performed in an Agilent 6890N GC coupled to a 5973 Mass Selective Detector (Agilent Technologies España, S.L., Las Rozas, Spain), and equipped with a DB5-MS column (J&W, Anorsa, Barcelona, Spain) (30 m × 0.25 mm × 0.25 μm). The following chromatographic conditions were used: injection volume was 1 μL, constant flow 2 mL/min with He as the carrier gas, split injection ratio 20:1 at 280 ºC. The oven temperature program started at 50 ºC for 5 min, and the temperature was increased at 5 ºC/min to 110 ºC, then increased at 10 ºC/min until holding at the final temperature of 260 ºC for 15 min. MS acquisition parameters were scan mode from 50 to 600 *m*/*z*, 280 ºC interface temperature and 1200 V resulting EM voltage.

Synthesis of allyl esters (general procedure). Carboxylic acid (1 mmol) **2a**–**h**, glycerol (2 mmol) and CTMS (5 mmol) were mixed in a 15 mL reaction vial fitted with a PTFE-lined cap. The mixture was heated at 80 ºC for 48 h in a digestion



stirrer block. After cooling, *t*-butyl methyl ether was added, and the mixture was washed three times with water. The organic layer was dried ($MgSO_4$), filtered and evaporated under vacuum to give the corresponding crude compound. The crude product was used in the next step without further purification. A solution of that 1,3-dichloro-2-propyl ester (1 mmol) and sodium iodide (4 mmol) in dried butanone was heated at 115 ºC for 48 h in a capped reaction vial. After cooling, *t*-butyl methyl ether was added, and the mixture was filtered and then washed with a saturated solution of sodium thiosulfate and water. The upper layer was recovered and dried over anhydrous magnesium sulfate. The solvent was evaporated under vacuum to give the corresponding crude compound. The crude compound, in the case of allyl decanoate, allyl dodecanoate, allyl tetradecanoate, allyl hexadecanoate and allyl octadecanoate was purified by silica column chromatography (45 μm particle size) and eluted with *n*-hexane to produce the corresponding allyl ester in solid form after solvent evaporation. Liquid allyl esters, such as allyl butanoate, allyl hexanoate and allyl octanoate were purified by distillation under vacuum, with a Büchi Kugelrohr apparatus (Massó Analítica S.A., Barcelona, Spain).

Allyl butanoate [CAS: 2051-78-7] **4a:** Prepared following the general procedure from butanoic acid **2a** (1.76 g, 20 mmol), glycerol (5.52 g, 60 mmol) and CTMS (25 mL, 200 mmol) to give 1,3-dichloro-2-propyl butanoate **3a** (2.59 g, yield 67%). Compound **3a** (0.52 g, 2.6 mmol) and sodium iodide (11.55 g; 77 mmol) in dried butanone (7.6 mL) gave allyl butanoate **4a** (288 mg, yield 86%) (Distillation at 50–71 ºC, 20 mbar).

Allyl hexanoate 4b [CAS: 123-68-2]**:** Prepared following the general procedure from hexanoic acid **2b** (2.32 g, 20 mmol), glycerol (5.50 g, 60 mmol) and CTMS (25 mL, 200 mmol) to give 1,3-dichloro-2-propyl hexanoate **6** (4.35 g, yield 96%). Compound **6** (0.51 g, 2.2 mmol) and sodium iodide (1.33 g; 9 mmol) in dried butanone (6.6 mL) gave allyl hexanoate **4b** (189 mg, yield 54%) (Distillation at 75–98 ºC, 20 mbar).

Allyl octanoate 4c [CAS: 4230-97-1]**:** Prepared following the general procedure from octanoic acid **2c** (2.88 g, 20 mmol), glycerol (5.61 g, 60 mmol) and CTMS (25 mL, 200 mmol) to give 1,3-dichloro-2-propyl octanoate **3c** (4.26 g, yield 84%). Compound **3c** (380 mg, 1.5 mmol) and sodium iodide (0.6 g; 4 mmol) in dried butanone (3 mL) gave allyl octanoate **4c** (257 mg, yield 94%) (Distillation at 90–105 ºC, 7 mbar).

Allyl decanoate 4d [CAS: 57856-81-2]**:** Prepared following the general procedure from decanoic acid **2d** (1.72 g, 10 mmol), glycerol (1.85 g, 20 mmol) and CTMS (6.35 mL, 50 mmol) to give 1,3-dichloro-2-propyl decanoate **3d** (2.75 g yield 97%). The crude compound (0.28 g, 1 mmol) and sodium iodide (0.6 g; 4 mmol) in dried butanone (3 mL) gave allyl decanoate **4d** (177 mg, 84%).

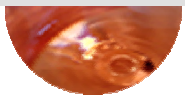
Allyl dodecanoate 4e [CAS: 7003-75-0]**:** Prepared following the general procedure from dodecanoic acid **20** (4.1 g, 20 mmol), glycerol (5.53 g, 60 mmol) and CTMS (25 mL, 200 mmol) to give 1,3-dichloro-2-propyl dodecanoate **3e** (6.19 g, yield 96%). The crude compound (6.2 g, 20 mmol) and sodium iodide (11.9 g; 80 mmol) in dried butanone (30 mL) gave allyl dodecanoate **4e** (4.08 g, 89%).

Allyl tetradecanoate 4f [CAS: 45236-96-2]**:** Prepared following the general procedure from tetradecanoic acid **2f** (4.58 g, 20 mmol), glycerol (5.69 g, 62 mmol) and CTMS (25 mL, 200 mmol) to give 1,3-dichloro-2-propyl tetradecanoate **3f** (6.79 g, yield 98%). The crude compound (6.62 g, 20 mmol) and sodium iodide (11.64 g; 78 mmol) in dried butanone (30 mL) gave allyl tetradecanoate **4f** (5.01 g, 99%).

Allyl hexadecanoate 4g [CAS: 43211-62-7]**:** Prepared following the general procedure from hexadecanoic acid **2g** (3.04 g, 12 mmol), glycerol (2.86 mg, 31 mmol) and CTMS (7.5 mL, 60 mmol) to give 1,3-dichloro-2-propyl hexadecanoate **3g** (3.43 g, yield 77%). The crude compound (0.37 g, 1 mmol) and sodium iodide (0.6 g; 4 mmol) in dried butanone (3 mL) gave allyl hexadecanoate **4g** (287 mg, 100%).

Allyl octadecanoate 4h [CAS: 6289-31-2]**:** Prepared following the general procedure from octadecanoic acid **2h** (5.65 g, 20 mmol), glycerol (5.57 g, 60 mmol) and CTMS (25 mL, 200 mmol) to give 1,3-dichloro-2-propyl octadecanoate **3h** (7.85 g, yield 97%). The crude compound (7.85 g, 20 mmol) and sodium iodide (11.8 g; 79 mmol) in dried butanone (30 mL) gave allyl octadecanoate **4h** (6.11 mg, 99%).

Activity on *C. pomonella* Eggs. The *Cydia pomonella* population was collected from an unsprayed apple tree orchard in 1993 at Lleida (northeastern Spain), and it has been reared since then on an agar-based semisynthetic diet at room temperature under long-day conditions (*19*). The adults were kept in cylindrical rearing cages, where the substrate for egg laying was wax paper (Reynolds® Cut-Rite wax paper). Because codling moth adult females have a crepuscular activity, the wax paper was changed in the evening, and the eggs were collected the following morning. This procedure provided eggs that were less than 24 h old. The eggs were individually and topically treated with a 0.1 μL drop of the compound to be tested dissolved in pure acetone to the appropriate concentration, using a Harvard Apparatus Pump 11 Injector (Harvard Apparatus, Inc., Holliston, USA). Preliminary experiments showed that a bigger size of the drop caused greater than 20% mortality in the acetone-treated controls, because of the small size of codling moth eggs. Three replicates of 30 eggs each were carried out per chemical compound and concentration tested. The syringe was washed 10 times with pure acetone between two different compounds. After evaporation of the solvent, the eggs of each replicate were confined in a plastic Petri dish (9 cm diameter) lined on its bottom with slightly wetted filter paper and sealed with parafilm. Petri dishes were kept in a



climatic chamber at 22 ± 2 ºC, 60 ± 10% RH and 16:8 h (Light:Darkness) photoperiod. The eggs were checked daily for larval emergence, until no more larvae emerged on three consecutive days. Because codling moth larval emergence takes place mostly between 10:00 and 12:00 in the morning, the emergence was checked always at the same time of the day: between 12:00 and 14:00. Untreated eggs and eggs treated with 0.1 μL of pure acetone were used as controls every time a set of treatments was carried out. The tested concentrations were 10; 7.5; 5; 2.5; 1.75; 1; 0.5 and 0.1 mg/mL.

The following variables were recorded: egg mortality (%), duration of the development (d), and egg developmental stage at death (White Egg, Red Ring and Black Head) (*20*).

Statistical Analyses. The mortality of the treated eggs was corrected with the mortality of the pure acetone-treated eggs (*21*). The mortality of the untreated eggs was only used as a check on the validity of the replicate. The whole replicate was discarded when the mortality of the untreated eggs was higher than 20%. The corrected mortality was analyzed using the routine ANOVA of the statistical package SAS, followed by Duncan's Multiple Range Test ($P < 0.05$).

For each compound, a probit analysis of the mortality vs the concentration was carried out with the program Polo Plus (*22*). Only the concentrations that produced mortality between 5 and 95% were used. Tests of equality and parallelism of the lines were carried out. The comparison of the LC_{50} (concentration that kills 50% of the treated individuals) and LC_{90} (concentration that kills 90% of the treated individuals) of the different compounds was carried out using the overlapping of the confidence intervals as the criterion.

3. Results and Discussion

The chemical reaction used to prepare the bioactive compounds is shown in Figure 1. The synthetic method is very simple. The first step consisted of heating at 80 °C for 48 h a 2:1:5 mmol mixture of glycerol, a fatty acid and chlorotrimethylsilane in a solvent-free medium. The formation of the 1,3-dichloro-2-propyl ester was confirmed by GC/MS and the following ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (100 MHz, $CDCl_3$ signals at δ: 5.2 (quin, 1, J = 5.2 Hz, O–C<u>H</u>), 3.7 (m, 4, C<u>H$_2$</u>–Cl), 2.3 (t, 2, J = 7.5 Hz, C<u>H$_2$</u>–C=O); and δ: 173 (<u>C</u>O–O), 71 (O–<u>C</u>H), 42 (<u>C</u>H$_2$–Cl), 34 (<u>C</u>H$_2$–C=O)). The crude compound was then dissolved in butanone and heated at 115 °C in the presence of NaI producing the corresponding allyl ester. Formation of allyl esters is easy to monitor by NMR. Characteristic signals appear at δ: 2.3 (t, 2, J = 7.5 Hz, –C<u>H$_2$</u>–COO), 4.6 (dt, 2, J = 5.7, 1.5 Hz, –O–C<u>H$_2$</u>–CH–), 5.2 (ddt, 1, J = 10.5, 1.6, 1.6 Hz, C<u>H$_2$</u>=CH–), 5.3 (ddt, 1, J = 17.2, 1.6, 1.6 Hz, C<u>H$_2$</u>=CH–), 5.9 (ddt, 1, J = 17.2, 10.5, 5.7 Hz, CH_2=C<u>H</u>–) in ^{1}H-NMR (400 MHz, $CDCl_3$); and δ: 34 (–<u>C</u>H$_2$–CO–), 65 (–O–<u>C</u>H$_2$–), 118 (<u>C</u>H$_2$=CH–), 132 (CH_2=<u>C</u>H–), 173 (<u>C</u>O–O–) in ^{13}C-

NMR (100 MHz, $CDCl_3$). This description is in accordance with data found in the literature.

Fig. 1. General scheme of the reaction process

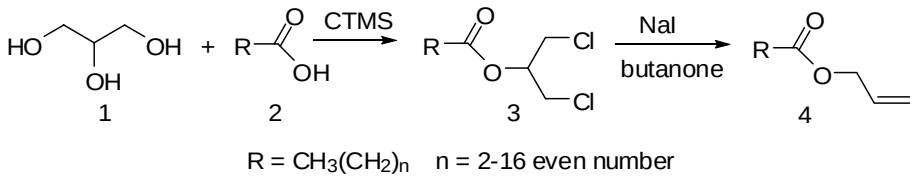


Table 1. Fatty Acids Used and Yields of Crude 1,3-Dichloropropen-2-yl Carboxylate (**3**) and Purified Allyl Carboxylate (**4**)

Entry	R (Figure 1)	Crude 3 (%)	4 (%)
a	$CH_3(CH_2)_2$	67	86
b	$CH_3(CH_2)_4$	96	54
c	$CH_3(CH_2)_6$	84	94
d	$CH_3(CH_2)_8$	97	84
e	$CH_3(CH_2)_{10}$	96	89
f	$CH_3(CH_2)_{12}$	98	99
g	$CH_3(CH_2)_{14}$	77	100
h	$CH_3(CH_2)_{16}$	97	99

Yield values are rounded to integer figures.

Furthermore, the MS spectrum shows a fragment ion of *m*/*z* 100, formed by a McLafferty rearrangement, which is a key fragment for allyl esters of straight chain acids with a chain length greater than three carbon atoms.

The two steps, synthesis of 1,3-dichloropropyl ester and synthesis of allyl esters run, in general, with very high yields. All of the allyl esters used in the assays were prepared according to the general procedure. Purification of the reaction crude product yielded pure allyl esters (Table 1).

The mean mortality of the controls (untreated and acetone-treated) was always smaller than 20% (data not shown), which validates all the replicates and permits the use of the Abbot formula to calculate the corrected mortality. The corrected mortality ranged from 0 to 100 in the range of concentrations tested. All of the compounds showed a concentration–mortality response and caused 100% mortality at the highest concentration tested, 10 mg/mL (Table 2). However, no compound was as effective as fenoxycarb proved to be in previous experiments carried out using the same codling moth population and the same methodology. Fenoxycarb caused 100% mortality when eggs were treated with 0.1 μL at a concentration of 0.5 mg/mL (unpublished data), in contrast to a maximum of 30% achieved with the tested compounds (Table 2).

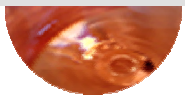


Table 2. Corrected Mortality (%) of Less-than-24-hour-old *C. pomonella* Eggs Treated with 0.1 µL of Allyl Esters Solution at Different Concentrations

Entry [1]	Concentration (mg/mL)							
	10	7.5	5	2.5	1.75	1	0.5	0.1
4a	100 ± 0	100 ± 0 [a]	98.7 ± 0.6 [a]	83.3 ± 2.6 [d]	72.0 ± 3.0 [bc]	42.7 ± 2.0 [c]	20.5 ± 1.3 [b]	6.0 ± 2.0 [bc]
4b	100 ± 0	100 ± 0 [a]	98.7 ± 0.6 [a]	95.8 ± 0.8 [b]	83.8 ± 2.1 [a]	51.2 ± 1.7 [b]	22.4 ± 1.6 [b]	8.4 ± 1.0 [ab]
4c	100 ± 0	98.8 ± 0.4 [b]	97.7 ± 0.5 [b]	95.9 ± 0.9 [b]	83.8 ± 1.3 [a]	59.2 ± 0.8 [a]	29.9 ± 2.0 [a]	9.7 ± 0.6 [a]
4d	100 ± 0	100 ± 0 [a]	98.7 ± 0.5 [a]	97.2 ± 0.6 [a]	76.3 ± 1.3 [b]	30.5 ± 1.3 [e]	12.4 ± 1.4 [c]	7.4 ± 0.03 [bc]
4e	100 ± 0	98.8 ± 0.4 [b]	96.5 ± 0.7 [c]	95.9 ± 0.6 [b]	71.7 ± 1.6 [c]	36.4 ± 0.7 [d]	10.0 ± 0.4 [d]	0 ± 1.3 [e]
4f	100 ± 0	97.7 ± 0.5 [b]	97.2 ± 0.6 [bc]	87.5 ± 1.8 [c]	49.5 ± 4.0 [d]	19.8 ± 1.6 [f]	7.5 ± 1.4 [e]	4.6 ± 0.2 [d]
4g	100 ± 0	87.2 ± 0.4 [c]	72.2 ± 3.2 [e]	66.6 ± 1.8 [e]	32.6 ± 3.3 [e]	6.0 ± 1.03 [g]	0 ± 0.5 [f]	0 ± 0.1 [e]
4h	100 ± 0	87.2 ± 0.5 [c]	82.2 ± 3.4 [d]	41.6 ± 3.7 [f]	32.1 ± 4.4 [e]	17.3 ± 1.0 [f]	11.9 ± 2.0 [cd]	0 ± 1.4 [e]

Mean and standard error of three replicates of 30 eggs each. Values followed by the same letter in the same column are not significantly different (Duncan's Multiple Range Test, $P < 0.05$).
[1] See Table 1 for compound identification.

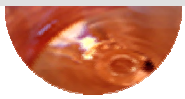
A probit regression line could be adjusted for all of the compounds (values of the heterogeneity index sufficiently low (*22*), Table 3). The regression lines were not equal (chi-square: 408, degrees of freedom: 14, tail probability: 0.000), nor parallel (chi-square: 29.23, degrees of freedom: 7, tail probability: 0.000). Table 4 shows the values and the confidence intervals of the LC_{50} and the LC_{90}. There was an inverse relationship between the alkyl chain length and the lethal concentrations. The two compounds bearing the longest chains (**4g** and **4h**) were the least effective, as both their LC_{50} and LC_{90} were significantly higher than the LC_{50} and LC_{90} of the rest of the compounds. The separation of the LC_{50} is clearer than the separation of the LC_{90} because of the higher values of the confidence intervals of the LC_{90}. Probably, the greater length of the alkyl chain hampers the penetration of the compound through the egg chorion.

Table 3. Results of the Probit Regression Analysis for Less-than-24-hour-old *C. pomonella* Eggs Topically Treated with 0.1 µL of Allyl Esters Solution

Entry [1]	*n*	Slope ± sd	Intercept	*t*-ratio	chi-square	heterogeneity
4a	270 (28)	2.66 ± 0.29	4.93	4.23	15.53	0.97
4b	270 (29)	3.36 ± 0.40	5.18	1.82	13.50	1.03
4c	300 (29)	2.64 ± 0.43	5.39	–0.63	16.82	1.01
4d	270 (29)	6.14 ± 1.03	4.10	–3.60	28.59	1.78
4e	270 (31)	4.11 ± 0.53	4.76	–1.78	5.51	0.42
4f	300 (29)	3.53 ± 0.39	4.47	–3.83	22.85	1.42
4g	300 (29)	2.51 ± 0.22	4.01	–7.93	40.38	2.12
4h	300 (29)	2.94 ± 0.32	3.73	–6.93	40.23	1.82

n: Total number of eggs in the acetone-treated control (number of dead eggs in the acetone-treated control). Regression lines not equal (chi-square: 408, df: 14, $P > 0.001$), nor parallel (chi-square: 29.23, df: 7, $P < 0.001$).
[1] See Table 1 for compound identification.

The vast majority of the eggs from the untreated control and from the acetone control died at the last egg developmental stage (Black Head), when the larva is fully developed inside the egg (data for the highest concentration shown in Table 5; rest of the data not shown). This fact confirms that the observed mortality at the



White Egg stage was not due to a lack of egg fertilization. The stage of development at which the eggs treated with 10 mg/mL died depended on the compound; the eggs treated with the longest chain compounds (**4g** and **4h**) died at the Black Head stage, while the eggs treated with the rest of the compounds mostly died at the White Egg stage (Table 5). Therefore, the less active materials (**4g** and **4h**) also took longer to kill the eggs.

In general, the duration of the development of the eggs treated with any compound was higher than the duration of the development of the acetone-treated eggs (data not shown because the increase was always smaller than one day, which has no consequences in the field populations).

Table 4. Values and confidence intervals of the LC_{50} and LC_{90} (mg/mL) of Less-than-24-hour-old *C. pomonella* Eggs Topically Treated with 0.1 μL of Solution of Allyl Esters

Entry [1]	*n* (Control)	LC_{50}		LC_{90}	
4a	270 (29)	1.06 [bc]	0.86–1.25	3.20 [a]	2.62–4.29
4b	270 (28)	0.88 [ab]	0.73–1.02	2.13 [a]	1.79–2.75
4c	300 (29)	0.71 [a]	0.53–0.85	2.18 [a]	1.78–3.06
4d	270 (29)	1.40 [c]	1.13–1.56	2.26 [a]	1.98–3.09
4e	270 (31)	1.14 [bc]	0.98–1.28	2.34 [a]	2.04–2.86
4f	300 (29)	1.41 [c]	1.16–1.64	3.24 [a]	2.69–4.33
4g	300 (29)	2.46 [d]	1.96–3.03	7.97 [b]	5.93–12.77
4h	300 (29)	2.69 [d]	2.19–3.16	7.33 [b]	5.80–10.88

n: Total number of eggs in the acetone-treated control (number of dead eggs in the acetone-treated control). Values followed by the same letter in the same column are not significantly different because of the overlapping of the confidence intervals ($P < 0.05$).

[1] See Table 1 for compound identification.

Some of the most active allyl esters studied are present in many foods and have been used as flavoring compounds for a long time (*23*). Consequently, they are putative candidates to be considered Generally Recognized as Safe (**GRAS**) substances. This, and also the fact that they can be easily synthesized from a renewable resource obtained in large scale as a byproduct of biodiesel production, makes those active esters interesting candidates to be used to control coddling moth. Furthermore, these compounds add a new class of products that will help to diversify alternatives for pest management.

In conclusion, a set of allyl alkylcarboxylic esters has been obtained from glycerol, a by-product of the biodiesel industry. These compounds show ovicidal activity on codling moth eggs. This activity is related to the length of the alkyl chain.

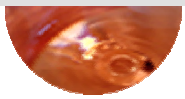


Table 5. Distribution (%) by Developmental Stages of the Mortality of Less-than-24-hour-old *C. pomonella* Eggs Treated with 0.1 μL of 10 mg/mL Solution of Allyl Esters

Entry [1]	Egg developmental stage at death		
	White Head	Red Ring	Black Head
Untreated control	0.00 ± 0.00	0.00 ± 0.00	100 ± 0.00
Acetone control	1.1 ± 0.44	4.4 ± 0.22	94.4 ± 0.1
4a	75.6 ± 2.96	14.4 ± 1.48	10.0 ± 2.2
4b	67.8 ± 5.19	13.3 ± 2.22	18.9 ± 7.4
4c	80.0 ± 2.22	13.3 ± 2.22	6.7 ± 0.0
4d	68.9 ± 5.19	16.7 ± 0.00	14.4 ± 5.2
4e	68.9 ± 1.48	12.2 ± 3.70	18.9 ± 3.0
4f	54.4 ± 3.70	17.8 ± 5.93	27.8 ± 3.0
4g	28.9 ± 3.70	24.4 ± 5.93	46.7 ± 2.2
4h	43.3 ± 2.22	13.3 ± 2.22	43.3 ± 4.4

Mean and SE of three replicates of initially 30 eggs each.
[1] See Table 1 for compound identification.

Acknowledgment.

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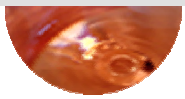

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3.1. Dissimetrització del pivalat de 1,3-dicloro-2-propil *(en preparació)*

Moving toward desymmetrization of a glycerol derivative

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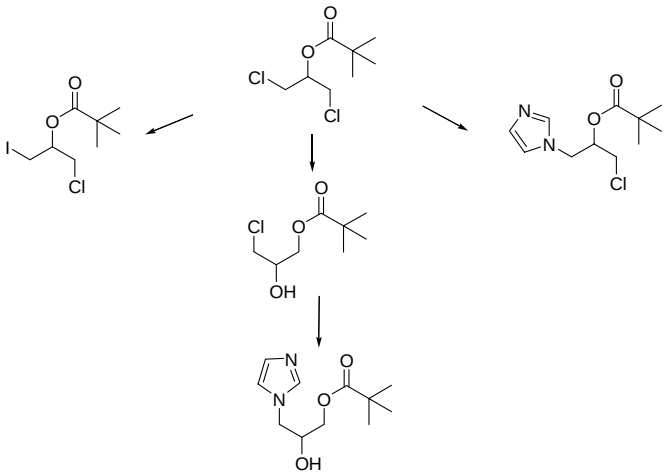
Abstract - Putative approaches to the desymmetrization of 1,3-dichloro-2-propyl pivalate have been evaluated. This ester can be obtained from crude glycerol provided from a biodiesel industry. Most of the assayed reactions are highly regioselectives. Moreover, the dissymmetric compounds prepared are putative precursors of medicaments and chiral ionic liquids.



Nowadays, the interest for glycerol as starting material to prepare useful chemical compounds is increasing together with biodiesel industry development and the interest in disposing renewable materials. Glycerol is present in a huge number of natural products integrating part of their structure. Moreover, it presents great synthetic potential for creation of stereogenic centers since it functionalization in its three carbons.

In last years different ways for 1,2-diols nonenzimatic desymmetrization have been described.[1] Nevertheless only few examples of nonenzimatic asymmetric catalysis for 1,3 and 1,4 diols have been reported.[2] In particular, the interest for 2-substituted-1,3-propanediols has been risen up.[3]

Otherwise, imidazole ring is a common heterocyclic fragment of many biologically important small molecules, such as histidine, histamine, adenine, etc. There are also many effective pharmaceutical compounds and drugs containing the imidazole residue. Finally, it is one of the more used reagents in the preparation of ionic liquids.

We report herein a study on the desymmetrization of a glycerol derivative based on the regioselective substitution of one of the chlorine present in both the 1,3-dichloro-2-propyl pivalate and the 3-chloro-2-hydroxy-1-propyl pivalate. Pivalate (trimethylacetate) esters can be considered a versatic compounds. The special characteristics of these esters increase their stabilty in front of weak bases as the ones used in the experiments described below. Moreover, pivalate ester has been used to generate prodrugs to increase oral bioavailability.[4]

The initial product, 1,3-dichloro-2-propyl pivalate (**1**) was obtained as described by an sterification-chlorination of glycerol with pivalic acid[5,6]. Also, this compound was partially desymmetrizated to 2,3-dichloropropyl pivalate with thermal microwave irradiation without any other reactant.[5]

Both 1,3 and 2,3-dichloropropyl esters were described as precursors of allyl esters throw a rearrangement–elimination reaction.[7] Herein, the formation of 1-chloro-3-iodo-2-propyl pivalate (**2**), an intermediate of this reaction, has been studied and the compound isolated (Scheme 1).

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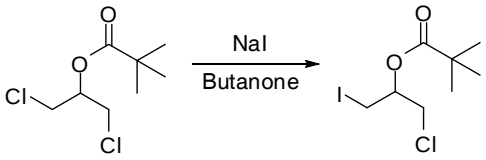
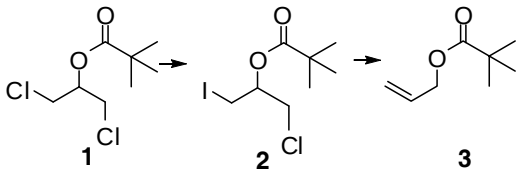
Scheme 1. Synthesis of 1-chloro-3-iodo-2-propyl pivalate



1 **2**

Initially, a set of reaction were carried out at 115 ºC during different periods to optimize the formation of **2** (Table 1). The percentatge of each chemical compound was determined by ^{1}HNMR. Although the amount of iodochloroalkyl esters was almost constant during all the study, 3 h was considered the optimal time. At this time, the highest amount of this compound (61%) is formed and the steady state of this intermediate product seems to be reached. Moreover, the amount of allyl ester (**3**) is still low. The three compounds can be isolated by distillation from the crude of reaction. The final yield of the distilled product was 55%.

Table 1. Influence of the reaction period in the percentatge of reagents and products during the preparation of **2** .



1 **2** **3**

t (h)	**1** (%)	**2** (%)	**3** (%)
2	38	55	8
3	29	61	11
3,5	27	58	15
4	20	57	22
5	11	58	31

[a] All ratios were determined by comparing ^{1}HNMR signals of **1**, **2** and **3**.

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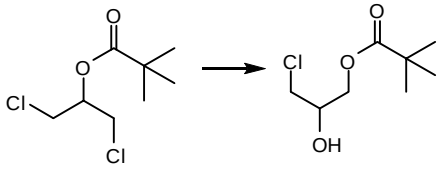
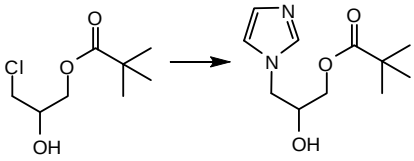
The preparation of 3-chloro-2-hydroxy-1-propyl pivalate (**4**) has previously been described for our group[8] (Scheme 2). Now, a reaction with this already dessymmetrizated compound and imidazole was carried out at 115 ºC for 48 h using 1-propanol as solvent. This reaction gave a 74% yield of 2-hydroxy-3-(1*H*-imidazol-1-yl)-1-propyl pivalate (**5**). Herein, chloride was substituted by imidazole (Scheme 3), which acts as nucleophile and proton scavenger.



1 **4**

Scheme 2. Synthesis of **4** using 1,3-dichloro-2-propyl pivalate.

A new study was carried out adding NaI to the reaction mixture in a 0,2 molar ratio. The substutution was successful and the final reaction conversion was improved from 74% to 84%. This results suggest that the presence of NaI could help to the nucleophilic substitution through the formation of **2** reaction. However, we were not able to isolate this intermediate.

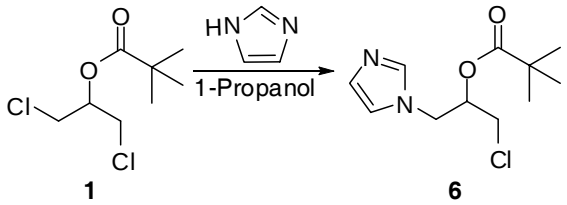


4 **5**

Scheme 3: Synthesis of **5** using **4** as intermediate product.

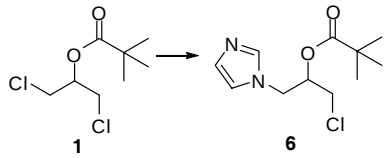
Subsequently, a nucleophyllic substitution of one of the chlorides of the **1** with imidazole was carried out using 1-propanol as solvent (Scheme 4). Initially, the reaction was carried out at different times using imidazole as both reagent and proton scavenger (Table 2). The reaction was carried out at 110 ºC and 75% yield was reached after 48 h reaction. The crude of reaction was submitted to a chromatographic purification using silica H-60. 1-Chloro-3-(1*H*-imidazol-1-yl)-2-propyl pivalate (**6**) was isolated with a yield of 70 %. When the reaction temperature was increased at 115 ºC some isomerization was observed (results not showed). The presence of NaI do not increase the yield of the reaction in this case (results not showed).

Scheme 4. Synthesis of 1-chloro-3-(1*H*-imidazol-1-yl)-2-propyl pivalate (**6**)



To avoid the use of excess of imidazole a study was carried out using either triethylamine, 1-buthylimidazole or sodium carbonate as proton escavengers (Table 2). The reaction was carried out at 110 ºC for 48 h. Both triethylamine and 1-buthylimidazole gave worse conversion than imidazole alone. Whereas, sodium carbonate allowed to increase the crude yield of the reaction to 83% despite that the reaction was carried out under heterogeneous phase.

Table 2. Influence of time and the proton scavenger in the preparation of **6**



time	Proton scavenger			
[h]	Imidazole	Triethylamine	1-Buthylimidazole	Na_2CO_3
6	28			
12	40			
24	53			
36	64			
48	75	64	49	83

[a] All conversions [%] were determined by comparing ^{1}HNMR signals of **1** and **6**.

In summary, we have described different aproaches to glycerol derivative desymmetrization using 1,3-dichloro-2-propyl pivalate as starting material. Also we have obtained new versatile and valuable compounds which can be used as synthetic intermediate, since most of them are pupative precursors of medicaments and chiral ionic liquids.

Acknowledgment. This work was supported in part by a Grant-in-Aid for the Secretaría de Estado de Política Científica y Tecnológica of the Spanish Ministry of Education and Culture (Contract grant number: CTQ2009-14699-C02-01). The authors are grateful to the Comissionat per a Universitats i Recerca del Departament d'Innovació, Universitats i Empresa de la Generalitat de Catalunya and to the the European Social Fund (ESF) for the FI grant of Marc Escribà Gelonch.

Supporting Information Available: Experimental procedures and product characterization data for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

3.2. Applying a continuous capillary-based process to the synthesis of 3-chloro-2-hydroxypropyl pivaloate

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Nowadays, continuous chemical processes ('flow chemistry') using micro process technology are becoming highly competitive, both for cost (better selectivity, higher productivity) and sustainability (low environmental impact) reasons. The first needs true process intensification and the second, among others, new eco-efficient starting and product materials. In this context, a new application for glycerol is reported with increasing industrial interest and tested here under highly intensified conditions. Starting from prior batch processing experience, it is reported about the transfer to a continuous process to transform dichloropropyl pivaloate, prepared from glycerol, into 3-chloro-2-hydroxypropyl ester. The continuous microreactor based process has up to two orders-of-magnitude reduced reaction times (240x) by virtue of exploiting unusual experimental conditions in organic chemistry (Novel Process Windows), i.e. superheated pressurised processing much above the boiling point. The yields are fully comparable with the ones obtained under batch conditions. This principally enables the new continuous process to target much higher productivities. After an upheavalled reporting on capillary- or microreactor-based superheated processing within the last two years, this is among the very first reports about a superheated reaction with a distinct selectivity issue with two known byproduct pathways, one of which (follow-product formation) is investigated in detail.

1. Introduction

Organic chemistry synthesis in the laboratories has been carried out traditionally in flasks since this discipline started. Processes at industrial scale used and uses batch vessels in most cases. The scale-up from laboratory to production is affected by this approach since mixing and mass transfer as well as heating and cooling rates are rather slow if big batch reactors are used. The full potential of chemistry, i.e. intrinsic kinetics without mass and heat transfer hindrance and fast kinetics through harsh process conditions, cannot be exploited in this way. Flow processing[1] offers here opportunities, but was industrially used mainly for gas-phase processes of bulk industry and rarely applied to fine-chemical organic reactions in the past. Recently, so called "Flow Chemistry" entered the organic chemists' laboratories and started changing the way reactions are processed here.[2-5]

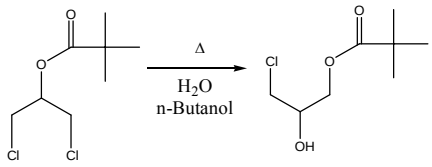
Flow chemistry, while being practiced for organic chemistry here and there already since the 80ies, was strongly pushed since the mid90ies by the emerging continuous micro process technologies to overpass the limits of batch processing mentioned above. Besides their kinetic enabling function through elimination of mass and heat transfer hindrances in the chemical engineering context, these methodologies allow a further chemistry-related usage by virtue of highly exothermic, high temperature or high pressure routes (superheated processing[6-12]), and the governing concept here is "Novel Process Windows".[6-9] In this way, fast intrinsic kinetics are exploited which can speed up chemical processes by an order of magnitude.

Micro process technology[6-8,13-16], flow chemistry[2-5], and process intensification[17-20] are at the edge of being used in industry and are available for the user at the market.[21] The net result typically is a faster and more selective reaction, besides several other advantages[6-8,13-16], thus overall a more cost efficient process with a lower environmental impact.[15] These better developed processes lead to higher competitiveness of chemical industry.[22] The synthetic chemist in the lab can have benefits as well. As examples, micro- and flow reactors facilitate automated multistep synthesis[4,23-27] and processes based on precise in line analytics.[28,29] The goal of an *integrated design* in chemical synthesis can be achieved only if a large flexibility in measuring, controlling and interacting of the operational conditions is provided for the chemical process.[26,30,31] Actually, process control has been forecasted as open and leading-edge future research topic in micro process engineering.[32]

Chemical processes based on renewable materials are of utmost current interest and, not surprisingly, microreactor investigations have started here as well. For biodiesel formation, a two-phase process with mass limitation, order-of-magnitude increases of reaction speed were found.[33] Parallel to the growth of biodiesel research and production, the interest in new industrial applications of glycerol is increasing. Recently, new procedures have been patented to convert this compound to a mixture of chlorohydrin esters and then to epichlorohydrin. One of the main goals of these methods is to use a low-cost renewable feedstock such as glycerol.[34]

We have already described how 3-chloro-2-hydroxypropyl esters can be prepared from dichloropropyl esters by single chlorine substitution.[35] Dichloropropyl esters can be synthesized from glycerol by a esterification–substitution reaction.[36] 2,3- and 1,3-dichloropropyl pivaloates are formed together with different ratios depending on the reaction conditions; the pure 1,3-dichloropropyl pivaloate used in this study was obtained by distillation.

Herein, we report the direct transformation of 1,3-dichloropropyl pivaloate into 3-chloro-2-hydroxypropyl pivaloate (Scheme 1). The reaction can be carried out using a traditional batch reactor and using a continuous capillary reactor. The results of both systems are compared.



Scheme 1. Chlorine substitution in 1,3-dichloropropyl pivaloate using water as a reagent, 4-buthylimidazole as a base and n-butanol as a solvent

Besides such chemical resource-based motivation, the main challenge of the paper is a chemical engineering and enabling technology rooted one, namely to add a detailed selectivity study for superheated continuous capillary processing with generic insights. In our previous research, we investigated in detail the impact of superheated capillary processing on the reactivity the aqueous Kolbe-Schmitt reaction[37-39]; in the same sense as many dozens of other investigations.[6-12] We observed a speed-up of reaction time from 2 hours to a very few seconds by transfer from batch to continuous processing and correspondingly a space-time yield increase from 0.02 t/(h m^3) in a 1 l-flask up to 64.23 t/(h m^3) in a capillary setup. The impact on and benefits for process costs and environment (life cycle analysis) were discussed in[40-41]. In this paper we would like to go beyond such analysis and to investigate the synthesis of 3-chloro-2-hydroxypropyl pivaloate, to our best knowledge, as first example in superheated capillary processing with dominant distinct selectivity issue, while still being largely accelerated by virtue of using Novel Process Windows conditions.[7-12]

Two selectivity issues exist for the synthesis of 3-chloro-2-hydroxypropyl pivaloate.

- *Regio isomerism*

Both 3-chloro-2-hydroxypropyl and 1-chloro-3-hydroxypropyl pivaloate are formed as main and side product, respectively, the latter in amounts of no more than 2-3%. It is known that the pure side product (no solvent) can be transformed in the main product by

increasing the temperature beyond 115ºC; it is assumed that in solution this takes place as well. Since side product contribution is small and difficult to resolve analytically the region isomerism selectivity analysis is not part of this paper, but may be investigated in future.

- *Mono- versus di-substitution*

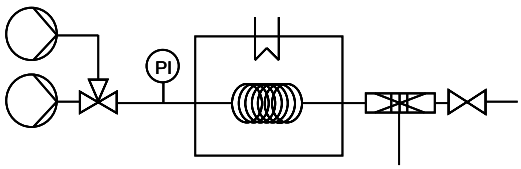
3-chloro-2-hydroxypropyl ester is an intermediate of the dechlorination reaction. That's why dihydrixypropyl ester is also synthetized. In the following referred to as 'monoproduct' and 'diproduct', respectively. The diproduct formation is substantial (up to about 30%), as shown below, process-parameter dependent and analytically measurable. Thus, this selectivity issue was followed in this paper to collect new generic information about the selectivity potential of superheated processing in microreactors or capillaries.

2. Material and methods

The reaction mixture consists of 1,3-dichloropropyl pivaloate (1) 4-butylimidazole (2) water and dry n-butanol in an 1:1:1.6:35 molar ratio.

The batch reaction was carried out in a reaction vial fitted with PTFE-lined cap, and submerged in silicon oil bath. The mixture was heated at 115 ºC for 48 h.[35] After cooling, the mixture was dried over anhydrous $MgSO_4$. 3-Chloro-2-hydroxypropyl pivaloate was isolated by distillation and characterized using ^{1}HNMR, ^{13}CNMR, FTIR, GC-MS and LC/ESI-MS.

The continuous capillary setup is shown in scheme 2. The reaction mixture was pumped through a pressurized reaction system consisting of a capillary 1/8" (1,395 mm internal diameter) tube submerged in a heated thermostat bath. Both synthetic and silicon oil were used depending on the required temperature. A six plates heat exchanger was used to cool down as fast as possible using nitrogen gas as a cooler agent. Both ISCO and Chemyx Nexus pumps were used. For each assay the temperature was risen up at the same time that the system was filled and pressurized. After stabilization of the pressure, probes were taken at two different sampling times. Three samples were collected each time and each assay. Fifteen microliters of n-tridecane were added to each vial as internal standard using a Hamilton high precision syringe. All samples were injected in a GC/FID chromatograph Varian 3900, using Varian Factor Four VF-1ms CP-8907 column 15m x 0,25mm x 0,25mm.

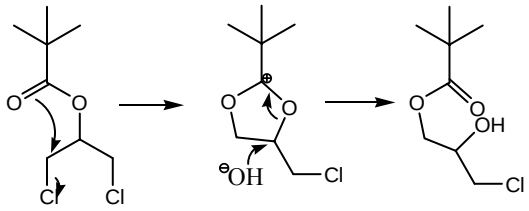


Scheme 2. Scheme of the continuous system applied

In order to maintain the hydrodynamics of the reacting flow, responsible for the residence time distribution and thus the temperature exposure time as well as for the convective heating in general, the flowrate was 4.5 mL/h, constant in most of assays. The residence time was varied by shortening the lengh of the submerged tube; the only exception being one experimental assay, the very fast 30 s processing (18.2 mL/h), which otherwise would have resulted in a much too short capillary length.

3. Results and discussion

The putative reaction mechanism is similar to another already proposed[36], with cyclic intermediates formed to give compound 3 (Scheme 3).



Scheme 3. The proposed reaction mechanism

First, assays at different temperatures were carried out with a residence time of 2 h. The conversion, yield and selectivity are given in Figure 1. Here and in the following Figures and the summarising Tables 1 and 2, the yield is referred to both 3-chloro-2-hydroxypropyl and 1-chloro-3-hydroxypropyl pivaloate; however assuming that the side product is only marginally present with no more than 2-3%, thus attributing the yield largely to 3-chloro-2-hydroxypropyl pivaloate. The selectivities are referred to the amount of product formed normalised by the amount of starting material reacted. The latter includes the two monoproducts and the diproduct.

The yield of the mono- and diproduct increase almost linearly and with almost same gradient (but at different overall level) until 160ºC is reached, where the conversion becomes >95%. Then the monoproduct reaches a maximum and decreases, whereas the diproduct formation keeps its linear gradient. The conversion increases until at almost quantitative level a maximum is reached.

The maximum monoproduct yield as well as the corresponding diproduct yield in this very first continuous processing assay almost perfectly match the batch performance which amounts to a monoproduct yield of 63% and diproduct yield of 27%.

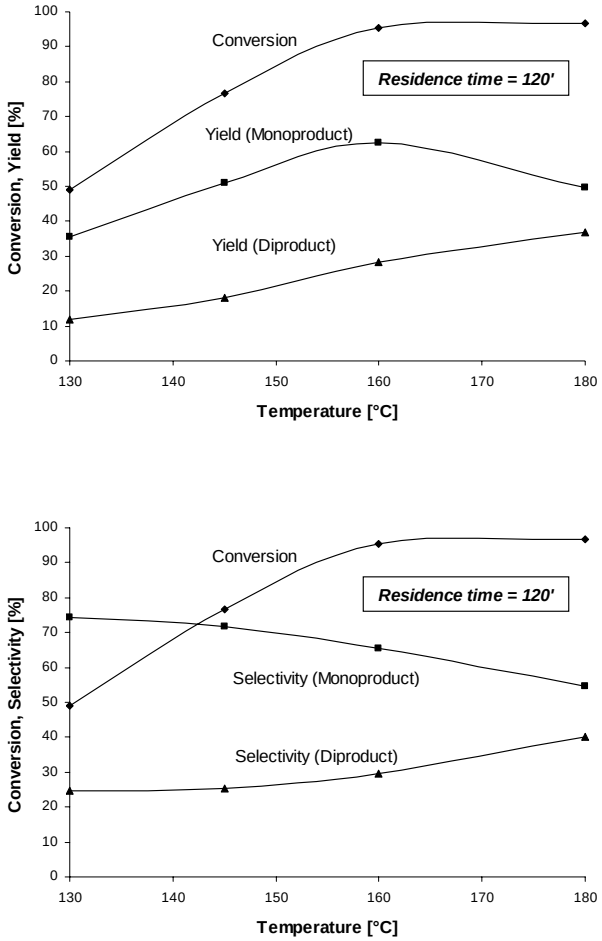


Figure 1. Effect of temperature at 2 h residence time.
Top: yield, conversion; bottom: selectivity, conversion.

As the follow-up reaction discussed here is characterised by a temporal evolution with the start of the diproduct formation only after first monoproduct formation, which then passes maximum, the shortening of the residence time is a general means to possibly reduce the content of diproduct formation and increase the monoproduct yield. Such study was carried out at the highest temperature investigated in Figure 1, which is 180 ºC, in order to compensate for the time reduction by increased reactivity. Figure 2 shows an antagonistic behaviour. A maximal yield over 60% is achieved at a residence time of 5 min, being almost constant until 20 min; thus, the initial assumption of the positive residence time effect is confirmed – yield (180 °C) monoproduct (120 min: 50%; 20 min: 60%) and yield (180°C) diproduct (120 min: 38%; 20 min: 33%). A steep decrease by about 10% is observed when reducing the residence time further to 2 min. The maximum yield at 160°C and 2 h is similar to that obtained under batch conditions[35], but now using 180ºC for just 5-20 min. Thus, at best a 24 fold reduction in reaction time was achieved, similar to other results reported for superheated organic reactions[7-12], but now for a reaction with large selectivity issue. The transformation of mono- to diproduct is evident when being decoupled from conversion effects, i.e. when conversion is high and constant (< 62 min) and exhibits a slow respective decrease and increase with increasing residence time.

Considering these motivating results, a set of new assays were carried out under more extreme conditions using temperatures up to 260 ºC and shortening the residence time in three steps further down – first to 20 min, then 10 min, and finally to 30 s.

The results at 20 min residence time given in Figure 3 were not encouraging, rather a more pronounced decrease in the monoproduct yield for the full temperature range investigated was observed. The diproduct yield is almost constant for the lower temperatures, but decreases with almost similar gradient at the highest temperature investigated. The very low mono- and diproduct yields show a high contribution of an unknown decomposition reaction at 240°C (about half of the overall amount of converted molecules). Some blackened precipitates were also observed, indicative for unselective reactions at such high temperature (e.g. oxidations, hydrolysis, polymerisations, decomposition).

The results at 10 min residence time given in Figure 4 were a bit more encouraging, as the rapid decrease in monoproduct yield and selectivity set in only for temperatures beyond about 210°C (and not beyond 180°C already as in Figure 3). Other findings are the same as for the 20 min processing.

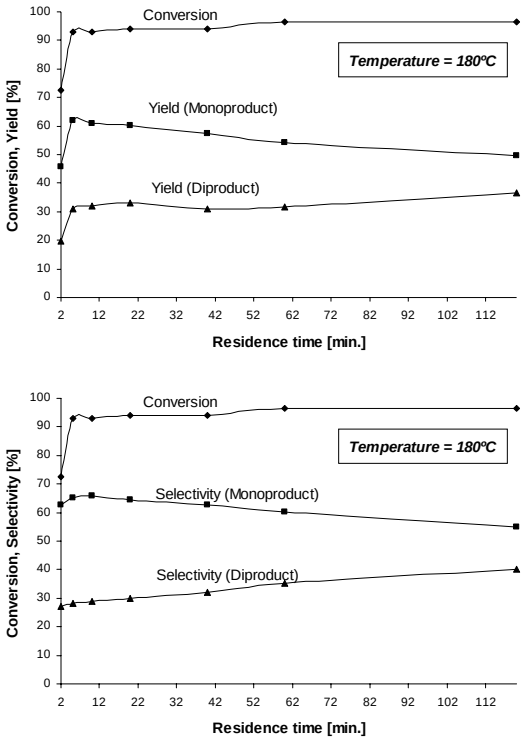


Figure 2. Effect of residence time at 180ºC.
Top: yield, conversion; bottom: selectivity, conversion.

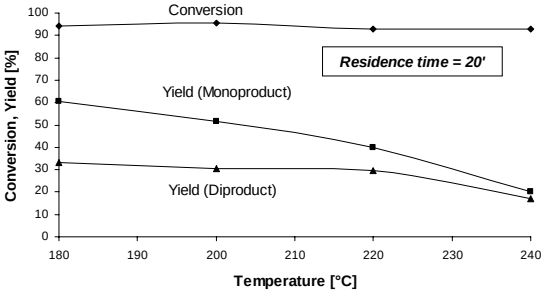


Figure 3. Effect of elevated temperature at 20 min residence time. Only "yield, conversion" is given; the "selectivity, conversion" contains no further relevant information, but resembles the "yield, conversion" dependencies.

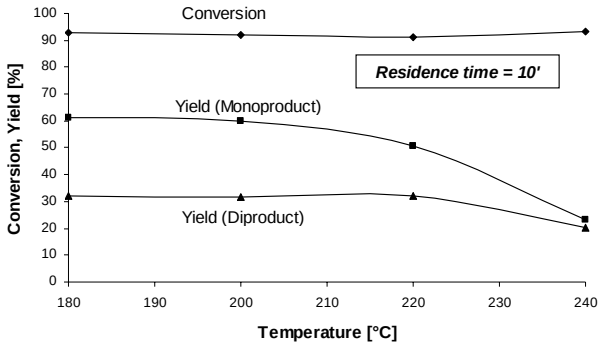


Figure 4. Effect of elevated temperature at 10 min residence time; the "selectivity, conversion" contains no further relevant information, but resembles the "yield, conversion" dependencies.

This indicated that a rather radical further reduction in residence time is required – thus, a 30 s-processing was chosen. This time frame setting is in line with the best performance achieved for the aqueous superheated Kolbe-Schmitt synthesis and many other investigated superheated organic reactions, being in the seconds' range up to one minute. Flowrate, oil-bath and pump were changed in 260 ºC assay because, under these extreme conditions, the pressure was too high for the pump used prior and the temperature used could cause oil decomposition. Also, the flowrate was increased to 18.24 mL/h in the 30 s assay, because the equivalent tube length was too short to be coupled to the system.

Under such extreme conditions and despite the short residence times, a yield close to 60 % was obtained at 260 ºC, see Figure 5. As indicated by the results given in Figure 2, the diproduct yield is further lowered below 20 %. Conversion, however, cannot reach quantitative level anymore, but only approaches at best 90% - in line with similar findings for the aqueous Kolbe-Schmitt synthesis.[37-39] This in consequence leads to a lower target monoproduct yield, which sets intrinsic limits to the performance of superheated processing. While the monoproduct yield increases with temperature, diproduct yield and selectivity are almost constant. The yield of diproduct formation is actually low (<20 %) throughout the whole temperature range and correspondingly the ratio of mono- to diproduct formation is improved for the best performance in Figure 5 as compared to all previous Figures. Figure 5 shows in addition that the mono- and diproduct selectivies are almost constant for the whole temperature range investigated, again different from the other investigations.

Neglecting the small decrease in yield as compared to optimum, now a 240 fold reduction in reaction time was achieved by using extreme temperature conditions. In view of the 4.05 fold increase in flow rate and considering the somewhat smaller yield, an increase in space-time yield of a factor of about 900 was reached as opposed to the initial experiments at 2 h residence time. Concerning the flow rate of 18.24 mL/h used, this still cannot compete, however, with batch processing (e.g. a 200 mL/h vessel), but this was not the objective of the investigation in this paper and certainly can be made competitive by means of further increases in flow rate and numbering-up, as many microreactor investigations have shown in the past.

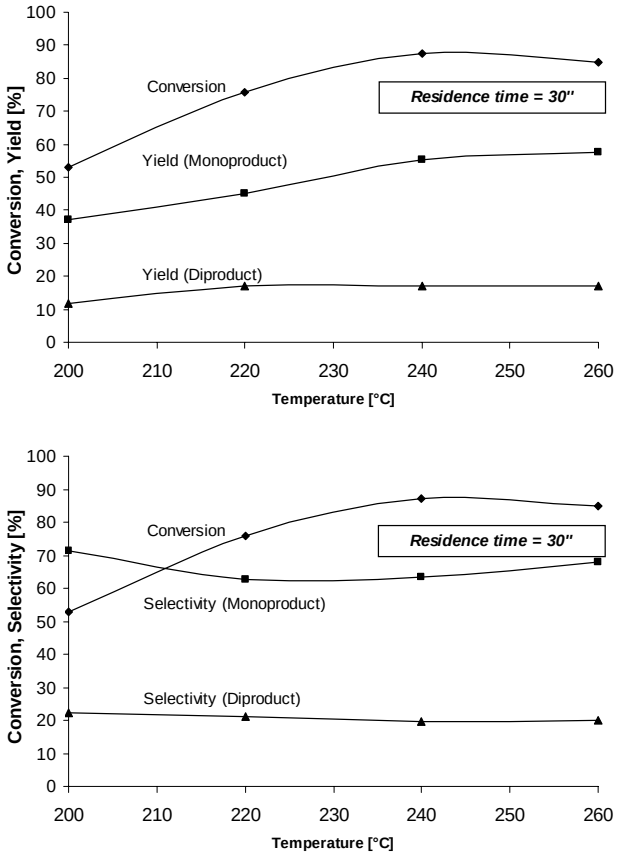


Figure 5. Effect of elevated temperature at 30 s residence time. Top: yield, conversion; bottom: selectivity, conversion.

All results shown are summarised in Table 1.

Residence time(min)	Temp. (°C)	Conversion (%)	Monoprod. Yield(%)	Diproduct Yield (%)
120	130	49	35	12
120	145	77	51	18
120	160	95	63	28
120	180	97	50	37
60	180	96	54	32
40	180	94	58	31
20	180	94	60	33
20	200	96	52	31
20	220	93	40	30
20	240	93	20	17
10	180	93	61	32
10	200	92	60	32
10	220	91	50	32
10	240	93	23	20
5	180	93	62	31
2	180	73	46	20
0,5	200	53	37	12
0,5	220	76	45	17
0,5	240	87	55	17
0,5	260	85	58	17

Table 1. Compilation of process parameters and yield-conversion results used for the Figures 1-5.

Conclusions

Capillary-based continuous-flow processing at high pressure, and high temperature reduced considerably the reaction time of the synthesis of 3-chloro-2-hydroxypropyl pivaloate compared with the batch system, giving similar final yields. Whereas 48 h are needed in the batch system to reach high conversions and 60% yields, similar yields are obtained at 180– 200ºC for 5 – 10 min by superheated capillary continuous processing, amounting to a 24-fold reduction. Even residence times can be shortened to 30 s without observing a dramatic yield decrease, amounting to a 24-fold reduction.

Such order-of-magnitude decreases in reaction time by superheated processing were observed earlier,[6-12] but in this study for the first time a distinct selectivity issue is put in

the focus of the investigation. The synthesis involves one known side-product and one follow-up product reaction path. This is a first step towards some generic information about possibilities and limits in superheated microreactor- or capillary-based processing with regard to the kinetics of the different reaction paths. So far "robust" reactions with thermally stable molecules, and most often with a preferred high-temperature path already for the batch processing, were investigated at even higher temperatures. In our case, a much more "sensitive" reaction was investigated with pronounced diproduct formation path. The possibilities and limits of operation up to 260°C were shown.

Residence time(min)	Temp. (°C)	Conversion (%)	Monoprod. Selectivity (%)	Diproduct Selectivity (%)
120	130	49	74	25
120	145	77	72	25
120	160	95	66	30
120	180	97	55	40
60	180	96	60	35
40	180	94	63	32
20	180	94	65	30
20	200	96	54	32
20	220	93	43	32
20	240	93	32	20
10	180	93	66	29
10	200	92	65	34
10	220	91	55	35
10	240	93	25	20
5	180	93	65	28
2	180	73	63	27
0,5	200	53	71	22
0,5	220	76	63	21
0,5	240	87	64	20
0,5	260	85	68	20

Table 2. Compilation of process parameters and selectivity-conversion results used for the Figures 1-5.

Acknowledgements

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CAPÍTOL V: DISCUSSIÓ GENERAL

L'aprofitament del glicerol excedentari en els diferents processos industrials, no solament pot fer sostenibles els sistemes productius industrials, sinó que obre una nova via per a la síntesi de nous compostos i obre unes noves rutes per a la fabricació de productes ja coneguts usant el glicerol com a producte de partida.

Síntesi dels esters de dicloropropil

Així, la síntesi dels esters de clorohidrina usant clorotrimetilsilà com a catalitzador i font de clorur, si bé és una reacció lenta, aconsegueix en tots els casos estudiats molt bones conversions i rendiments. S'ha assajat amb èxit amb diferents tipologies d'àcids: alifàtics saturats i insaturats, aromàtics monocíclics, aromàtics bicíclics, alifàtics amb anell terminal, versàtics, aromàtics nitrogenats i heterocicles amb oxigen o sofre. Tots ells s'han avaluat sense usar dissolvent i usant líquids iònics, i usant un reactor tipus *batch* amb escalfament convencional o usant microones. En tots els casos s'han obtingut conversions i

rendiments molt satisfactoris, si bé en microones s'ha apreciat un rendiment lleugerament menor degut a les pèrdues que, per descomposició a altes temperatures, es produeixen. Aquestes pèrdues són degudes a les condicions a les que es sotmet la reacció, i queden justificades per la reducció del temps de reacció i l'estalvi d'energia. S'han descrit degudament tots els productes de nova síntesi incorporant dades d'espectrometria de masses, infraroig, *^{1}H-RMN*, *^{13}C-RMN*, massa exacta (LC-TOF-HRMS) o anàlisi elemental, i punts de fusió en el cas dels productes sòlids. La descripció ha anat precedida de la purificació de cada producte: Els que són sòlids, s'han cristal·litzat amb etanol. Els líquids s'han purificat usant una columna de sílica H60, essent necessària únicament l'elució amb hexà per a la obtenció de la majoria de compostos. Per als més volàtils, la purificació s'ha realitzat mitjançant destil·lació al buit emprant una columna de destil·lació.

Els estudis de reaccions químiques dutes a terme usant microones com a font energètica han estat i són font de debat entre el món científic. Per una part, autors com Beyer[1], Hickenboth[2], Shazman[3] i Rosen[4] es posicionen a favor de la teoria de l'anomenada mecanoquímica. Aquesta es basa en la hipòtesi de que es pot induir energia cinètica a les mol·lècules sensibles a les microones, de manera que en un

moment determinat la energia pot ser suficient com per activar la reacció química. D'aquesta manera, si la energia cinètica és superior a la energia d'activació, la reacció es pot dur a terme sense necessitat d'escalfament. Aquest principi podria ser realment útil en reaccions on algun dels components fos termosensible estructuralment (proteïnes, enzims...), o per a reaccions on la temperatura de treball s'hagués de mantenir per sota del punt de descomposició per l'acció tèrmica (com en els compostos amb sofre).

Malauradament aquest principi sembla ser molt selectiu amb les reaccions on es pot aplicar, ja que en altres casos, el fenomen mecanoquímic es redueix a una simple acceleració de la reacció per una combinació de fenòmens cinètics i tèrmics. En aquest sentit, s'ha tractat de comprovar la teoria mecanoquímica en la síntesi dels esters de dicloropropil aprofitant la presència del glicerol (gran captador d'energia provinent de les microones) entre els reactius. L'assaig s'ha realitzat aplicant microones (300 W) a baixa temperatura (com a màxim 35 ºC) fent us d'us sistema de refrigeració extern del vas de reacció. En aquest cas les diferències trobades no han estat significatives en els resultats d'aplicar microones o escalfament convencional. Fruit d'aquest assaig s'ha conclòs que la reacció no té idoneïtat amb la teoria mecanoquímica.

Per tant, les microones contribueixen a escurçar el temps de reacció atès a que donen la possibilitat de treballar en condicions més extremes.

L'aparició del segon regioisòmer en la síntesi dels esters de dicloropropil es deu a una qüestió energètica i d'estabilitat, no mecanoquímica. Així, el regioisòmer 1,3-dicloropropílic si bé és menys estable, requereix una menor energia d'activació per a la seva síntesi que el 2,3-dicloropropílic, tot i que la estabilitat d'aquest darrer és superior.

Finalitzada la part de posada punt, s'ha ampliat l'estudi d'aquesta reacció aplicant-la a greixos i olis de procedència industrial: tant crus com refinats, o subproductes com un oli de sansa, producte residual de la indústria oleícola. En aquests casos les proporcions de reactius i condicions de la reacció s'han hagut d'adaptar, tant per al mètode d'escalfament mitjançant reactor convencional, com per al de microones. Aquest canvi queda justificat atès que la natura de la reacció ja no és una esterificació, sinó una transesterificació, i que les proporcions s'han de ajustar en funció dels continguts d'àcids i de glicerol que la pròpia matriu ja pugui contenir. Per tal de ser acurats en aquest aspecte, s'ha procedit a la caracterització prèvia del glicerol provinent de la indústria del biodiesel emprat per a l'assaig, i l'anàlisi del perfil acídic, del contingut en

acilglicèrids, en àcids grassos lliures, i en glicerol de cadascun dels olis i greixos emprats. El seguiment s'ha realitzat mitjançant CG-FID amb columna d'alta temperatura. Les conversions dels triacilglicèrids a esters de dicloropropil han estat elevades, i si bé s'ha apreciat una lleugera diferència entre el comportament del glicerol comercial, i el provinent de la indústria de biodiesel, els rendiments han estat molt alts en tots els casos.

L'ús d'un subproducte industrial, la doble funció (reactiu i dissolvent) que fa el clorotrimetilsilà, el fet que la reacció sigui complerta, que s'hagi aconseguit de dur a terme la reacció amb microones, optimitzant així el temps i la energia, i el fet que s'hagi aconseguit ajustar les proporcions molars dels reactius, fa que la reacció acompleixi molts dels principis de la *Green Chemistry*.

La seva aplicabilitat

Una vegada realitzat l'estudi de la síntesi d'esters de dicloropropil, els esforços s'han centrat en avaluar la seva aplicabilitat.

Síntesi dels esters d'al·lil

L'aplicació més immediata s'ha trobat realitzant una reacció de mono-substitució a mode de Finkelstein[5] i posterior eliminació-transposició sobre el grup dicloropropil, donant lloc a esters d'al·lil en un sol pas. La reacció s'ha estudiant usant diferents proporcions de iodur sòdic. La introducció de iodurs a l'estructura enlloc de clors, facilitarà les reaccions d'eliminació al ser un millor grup sortint.

Aquesta reacció es duu a terme en fase heterogènia en agitació constant, tant per al cas d'usar un reactor convencional, com en el vial de reacció en el microones. Els esters de partida han estat els de dicloropropil, degudament purificats, que s'havien obtingut de la fase anterior. En aquest cas les conversions han estat igualment elevades, i s'han obtingut uns rendiments, en molts casos propers al 100%. Tots els productes nous han estat degudament descrits, i per tal de seguir l'evolució de la reacció, s'ha realitzat un experiment mitjançant ^{1}*H-RMN (Figura 23)*. Aquest seguiment ha portat a la

identificació d'un producte intermedi dissimetritzat que es forma: l'ester de cloroiodopropil.

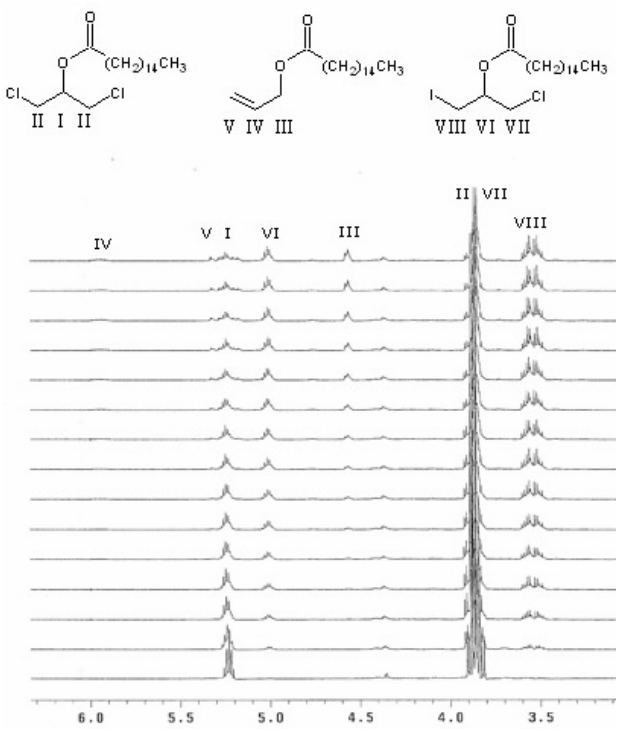

Figura 23: Seguiment per ¹HNMR de la reacció de síntesi de l'ester d'al·lil, les primeres 7 h de reacció en intervals de 30 min. Secció corresponent als desplaçaments químics de 3,5 a 6.

La darrera fase de la reacció consisteix en una deshalogenació que s'ha hagut d'estudiar amb cura ja que, tal com va descriure Taksande[6], el iode pot induir la deal·lilació dels esters d'al·lil, donant lloc a la formació d'alcohol al·lílic. Efectivament s'ha observat que a una concentració

determinada de iode s'indueix el trencament de l'ester donant l'àcid inicial. Aquesta situació no s'ha donat quan la concentració de iodur ha estat superior a la de iode. Una manera d'aconseguir de no sobrepassar aquest llindar ha estat regenerar *in situ,* mitjançant un reductor, el iodur a partir del iode format.

Anàlogament, com en el cas dels esters de dicloropropil, s'ha estudiat la reacció de preparació dels esters d'al·lil fent ús dels esters de dicloropropil provinents dels greixos, olis crus o refinats i residus de procedència industrial. En aquest cas no ha estat necessari cap adaptació significativa de les condicions de reacció, atès que els productes de partida ja són monoésters de dicloropropil. L'aplicació directa doncs de la reacció, s'ha portat a terme igualment usant el mètode d'escalfament mitjançant reactor convencional, i l'escalfament per microones, obtenint en tots dos casos alts rendiments i conversions, cap als esters d'al·lil.

Per altra part s'ha avaluat la capacitat ovicida dels esters d'al·lil obtinguts sobre ous de *Cydia pomonella,* una plaga que suposa un problema en la producció de poma. En aquest cas l'estudi s'ha fet únicament per als esters d'àcids grassos alifàtics saturats de diferents longituds de cadena. Assajant diferents concentracions s'ha constatat de que els esters d'al·lil

obtinguts per aquesta via sintètica tenen efectes ovicides a partir de dosis de 10 mg/ml per als ous d'aquesta espècie.

Dissimetrització i substitucions sobre el grup dicloropropil

S'han estudiat condicions per tal d'aconseguir dissimetritzar amb una bona conversió els esters de dicloropropil, usant microones en elevades condicions de pressió i temperatura. La dissimetrització cap el regioisòmer *(2,3)*, amb un carboni quiral, confereix a la molècula la possibilitat d'experimentar substitucions en posicions diferents.

La dissimetrització s'ha aplicat a l'àcid piválic. Efectivament, s'ha aconseguit fer substitucions sobre un dels clorurs de l'ester de dicloropropil, aconseguint dues noves substàncies: el pivaloat de 3-cloro-2-hidroxiprop-1-il, i el pivaloat de 2-cloro-3-(1*H*-imidazol-1-il)prop-1-il, totes dues amb un carboni quiral.

S'ha estudiat també la reacció del pivaloat de 3-cloro-2-hidroxiprop-1-il amb imidazole, aconseguint la corresponent mono-substitució del clorur terminal. La reacció ha portat a la síntesi i, conseqüent descripció, d'un nou producte: el pivaloat de 2-hidroxi-3-(1*H*-imidazol-1-il)prop-1-il. Aquest producte de nova síntesi és susceptible de ser un precursor de líquids iònics.

Pel que fa a l'aplicació de microreactors a la dissimetrització, s'ha realitzat un estudi en tub capilar, equivalent a un dels canals que el microreactor té en la matriu interna. La extrapolació s'esperaria comparable. La reacció estudiada ha estat la dissimetrització del pivaloat de dicloropropil a pivaloat de 3-cloro-2-hidroxipropil. En aquest sentit s'ha hagut de modificar la reacció per tal de fer-la idònia amb un sistema fluid, ja que tal com inicialment s'havia posat a punt no era aplicable atès a que es realitzava en fase heterogènia.

A tal finalitat s'han realitzat estudis previs relatius a variacions del dissolvent i de la base receptora dels clorurs sortints: el dissolvent no pot ser dioxà ja que causa danys als anells del pistó de la bomba. La base, inicialment carbonat sòdic, tampoc és adequada per microreactor al no ser soluble en els dissolvents assajats. Finalment l'estudi ha donat com a satisfactori amb resultats comparables la combinació: n-butanol com a dissolvent, i 1-butilimidazole com a base.

Els resultats han estat molt positius ja que, a més d'adaptar perfectament la reacció al sistema, s'ha aconseguit una reducció dràstica del temps de residència, i per tant, del temps de reacció amb uns rendiments globals del 60% de pivaloat de 3-cloro-2-hidroxiprop-1-il. La utilització d'aquest mètode no

suggereix variacions significatives en terme de rendiment respecte a la reacció realitzada en *batch*[†], si bé la millora en temps de reacció és important. Així de les 48 h que calien en reactors discontinus, en microreactor es poden realitzar en 30 s.

El flux ha estat de 18 mL/h, que considerant que en una matriu de microreactor poden haver-hi centenars de tubs capilars en paral·lel fa que la reacció pugui dur-se a terme a nivell industrial. A més, la possibilitat de reaprofitar per destil·lació la part d'ester de dicloropropil no reaccionat, i també tornar a preparar el ester de dicloropropil a partir del monoglicèrid, que es forma com a subproducte, fa que la reacció sigui més optimitzable.

[†] *C. Solarte, M. Escribà, J. Eras, G. Villorbina, R. Canela, and M. Balcells. Molecules, 2010 (Enviat)*

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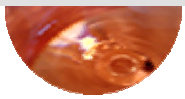


LES CONCLUSIONS

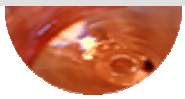
Atenent als objectius establerts, i considerant els resultats i les argumentacions que s'han elaborat, es poden establir les següents conclusions:

1. S'ha estudiat la reacció d'esterificació-substitució del glicerol amb CTMS usant diferents àcids carboxílics, obtenint els esters de dicloropropil amb rendiments entre un 77 i un 92%. S'han optimitzat les proporcions molars dels reactius i l'aport energètic mitjançant l'ús de microones. Així mateix, s'ha demostrat que es pot substituir el CTMS per $AlCl_3 \cdot 6H_2O$ en presència de [BMIM][PF_6].

2. S'han sintetitzat esters de dicloropropil a partir de subproductes industrials (glicerol subproducte provinent de la indústria de biodièsel, i greixos animals, olis crus, refinats i de sansa, provinents de la indústria d'olis i greixos) amb rendiments entre el 85 i 99%.

3. S'ha analitzat la regioselectivitat segons la quantitat d'energia aplicada, la qual afecta la proporció de regioisòmers obtinguda, tot establint els controls: cinètic per a la formació del regioisòmer 1,3-dicloropropil, i termodinàmic per a la formació del regioisòmer 2,3-dicloropropil.

4. S'ha estudiat la síntesi d'esters d'al·lil a partir dels esters de dicloropropil, amb rendiments entre el 61 i 98%, mitjançant un nou procés descrit per primera de substitució-eliminació-transposició en una sola etapa. S'ha identificat i aïllat també l'ester de 1-cloro-3-iodo-2-propil que es forma com a intermedi de la reacció.



5. S'ha fet un estudi d'aplicació dels esters d'al·lil com a ovicida en ous de *Cydia pomonella (L.)*. De tots els productes assajats, el caprilat d'al·lil s'ha mostrat com el producte més actiu. En aquest cas, les mortalitats han estat del 80% a concentracions de 10 mg/mL. Així mateix també s'ha observat un alentiment en el creixement dels adults.

6. S'ha estudiat la dissimetrització del pivalat de 1,3-dicloro-2-propil, obtenint esters amb centres quirals, mitjançant bescanvi S_N2 sobre un dels clorurs per: iodur, hidroxil o imidazole, amb rendiments entre el 60 i el 84 %. Aquests productes poden ser utilitzats com a tals o com a possibles precursors d'altres productes de valor afegit.

7. S'ha escalat, modelitzat i optimitzat la reacció de dissimetrització del pivalat de clorohidroxipropil en continu, usant sistemes pressuritzats en condicions d'alta temperatura (fins a 260 ºC), aconseguint rendiments al voltant del 55-65% amb un temps de residència de fins a 30 s.

7.1. ES 2293836 A1 20080316.

Procedimiento para la obtención de esters de alilo

UNIVERSITAT DE LLEIDA. REF: P167766/RM

17 de Julio de 2006

CAMPO DE LA INVENCIÓN.

La presente invención se refiere al campo de los ésteres de alilo. En particular, la presente invención se refiere a un procedimiento para la obtención de ésteres de alilo a partir de polioles o dihaloalcoholes y ácidos alquilcarboxílicos de origen natural o sintético en dos etapas.

El procedimiento de la presente invención se desarrolla con unas características, tales como la utilización de fuentes renovables de materia prima, ausencia de reactivos irritantes o gases, un menor consumo de energía, que permite la obtención de ésteres alílicos con características y especificaciones adecuadas, tales como la ausencia de alcohol alílico en el producto final, facilidad de recuperación del medio de reacción y altos rendimientos, para su utilización en diferentes aplicaciones industriales.

ANTECEDENTES DE LA INVENCIÓN.

Los ésteres alílicos tienen numerosas aplicaciones industriales entre las que cabe citar su empleo en la fabricación de aromas, resinas y varios materiales bioactivos para aplicaciones en agricultura, alimentación, cosmética, perfumería, industrias gráficas y medicina. Igualmente se han empleado como producto de partida en la preparación de otros productos químicos tales como monoacilglicéridos y derivados de reacciones de Diels-Alder.

Hasta la fecha, su obtención se ha llevado a cabo mediante métodos químicos basados en los siguientes procesos:

a) Eliminación de un resto alquilcarboxílico en diésteres o monoesteres de polioles;
b) Reacción entre sulfonatos de alilo y el correspondiente ácido o anhídrido de ácido;
c) Esterificación de anhídrido de ácido, o de los correspondientes ácidos o haluros de acilo, con alcohol alílico;
d) Alcohólisis con alcohol alílico de ésteres o amidas;
e) Eliminación de anillos de 1H-pirazol de nitrosoamidas;
f) Reacción del correspondiente ácido y sus sales con propeno, aliltrialquilestannanos, aliltrialiguilsilanos, alilalquilfosfinas o haluros de alilo;
g) Reacción de mezclas de ácido carboxílico y sus sales con clorociclopropano o ciclopropanoamina;
h) Desoxigenación de ésteres de glicidol; y
i) Reacción de éteres de alilo con haluros de acilo.

Sin embargo, el uso de alcohol alílico o de haluros de alilo, los reactivos más empleados, implica la utilización, en alguna de las etapas del proceso, de reactivos altamente irritantes. Por otra parte, la eliminación de alquilcarboxilos, en algunos casos obtenidos a partir de glicerol, requiere de altas temperaturas. En muchas de las reacciones descritas hasta la fecha los rendimientos no superan el 80% y, en más de un caso, se obtienen mezclas de sustancias difíciles de separar.

La presente invención tiene como finalidad superar inconvenientes tales como el empleo de reactivos peligrosos, la necesidad de utilizar fuentes no renovables de materia prima y la obtención de productos finales con alto rendimiento y sin la presencia de restos de alcohol alílico, el cual no puede estar en cantidades superiores al 0,1% en el supuesto de querer preparar aditivos para uso alimentario.

Si bien son numerosas las publicaciones sobre la preparación de ésteres alílicos ninguna de ellas, ni tampoco las patentes encontradas, desarrollan el procedimiento descrito en la presente invención que supera los inconvenientes indicados anteriormente.

DESCRIPCIÓN RESUMIDA DE LA INVENCIÓN.

Los presentes inventores han desarrollado un procedimiento de obtención de ésteres alílicos partiendo de un ácido alquilcarboxílico y un poliol o, alternativamente, de un dihaloalcohol, para obtener el correspondiente éster de α,γ-dihaloalquilo o β,γ-dihaloalquilo, donde dicho éster, al ser tratado con una sal neutra de tipo yoduro metálico o con amonio cuaternario, en presencia o no de disolvente, da lugar al correspondiente éster de alilo.

Sorprendentemente, los presentes inventores han observado que utilizando un agente de esterificación o transesterificación y un yoduro metálico o yoduro de amonio cuaternario en el procedimiento descrito posteriormente se consiguen una serie de ventajas con respecto a lo descrito en la técnica anterior:

1. Se utilizan fuentes renovables de materia prima (obtención del glicerol a partir de diferentes plantas) respecto a la utilización de productos de origen fósil.
2. Se evita el empleo de reactivos irritantes como son el alcohol alílico o los haloalquenilos.
3. Se evita el empleo de gases como es el propeno.
4. El consumo de energía es mucho menor respecto a aquellos métodos en los que se opta por un proceso de descarboxilación, ya que en la presente invención el proceso de eliminación es consecuencia del tamaño del yodo y al hecho de que los diyoduros geminales son muy poco estables y, por tanto, el proceso de eliminación necesario para la formación del doble enlace alílico puede tener lugar a una temperatura inferior a la descarboxilación.
5. El producto final, éster alílico, presenta espectros de resonancia magnética nuclear, de masas y un perfil cromatográfico que indican que posee una pureza adecuada para su utilización a escala industrial. Más aún, al no emplearse el alcohol alílico como reactivo para la preparación del éster correspondiente, en ningún caso se ha observado su presencia en el producto final.
6. El producto obtenido es fácilmente recuperable del medio de reacción.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN.

La presente invención se refiere a un procedimiento para la obtención de ésteres de alilo que comprende las etapas de:

a) mezclar, a una temperatura adecuada, un ácido alquilcarboxílico, de origen natural o sintético, o un derivado del mismo seleccionado entre anhídrido de ácido, haluro de acilo, éster, amida, amida sustituida, y ácido activado; un iniciador de la reacción; y un poliol alifático o, alternativamente, un α,γ-dihaloalcohol o β,γ-dihaloalcohol para obtener un éster de α,γ-dihaloalquilo o β,γ-dihaloalquilo, o mezcla de ambos;
b) hacer reaccionar el compuesto obtenido en la etapa (a), a una temperatura adecuada, con una sal neutra de tipo yoduro metálico o de yoduro de amonio cuaternario, para obtener el éster alílico correspondiente; y
c) aislar dicho éster alílico mediante un proceso de purificación.

En la presente invención, por "ácido alquilcarboxílico" se entiende cualquier sustancia que presenta una cadena hidrocarbonada de 2 a 18 átomos de carbono, lineal o ramificada, sustituida total o parcialmente por grupos alquilo, y, como mínimo, un grupo COOH en su estructura molecular.

Por "agente de esterificación o transesterificación" se entiende una sustancia catalizadora que aumenta la velocidad y posibilita la reacción entre un ácido y un

alcohol para obtener un éster en el caso de la esterificación o bien entre un éster y un alcohol para obtener otro éster en el caso de la transesterificación. Entre dichos agentes de esterificación o transesterificación se incluyen los polioles alifáticos, en particular el glicerol.

Por "éster" se entiende cualquier sustancia con una cadena hidrocarbonada lineal o ramificada, sustituida total o parcialmente por grupos alquilo y, como mínimo, un grupo COOX, siendo X un grupo alquilo o arilo.

Por "amida sustituida" se entiende una amida del tipo COONXY, siendo X e Y, independientemente, un grupo alquilo o arilo.

Por "poliol alifático" se entiende cualquier sustancia con una estructura de tipo XCH(OH)CH(OH)CH(OH)Y, siendo X e Y, independientemente, igual a H, un grupo alquilo o arilo.

Por "α,γ-dihaloalcohol" o "β,γ-dihaloalcohol" se entiende cualquier sustancia con una estructura de tipo XCH(Z)CH(Z)CH(Z)Y, siendo X e Y seleccionados, independientemente, de entre H, un grupo alquilo y un grupo arilo, una de las Z es OH y el resto de Z un halógeno seleccionado entre Cl, Br y I.

Por "sal neutra de tipo yoduro metálico o yoduro de amonio cuaternario" se entiende un compuesto del tipo MI, donde M puede ser cualquier catión metálico o bien un grupo NZ1Z2Z3Z4, donde Z1, Z2, Z3 y Z4 son, independientemente, H, un grupo alquilo o arilo.

En las definiciones de la presente invención, por “grupo alquilo” se entiende una cadena hidrocarbonada de 2 a 18 átomos de carbono, lineal o ramificada, sustituida total o parcialmente por grupos alquilo, y por “grupo arilo” se entiende un radical de un hidrocarburo aromático monocíclico o policíclico condensado, sustituido total o parcialmente por grupos alquilo.

En una realización de la presente invención, la mezcla se prepara adicionando un disolvente polar con un punto de ebullición comprendido entre 60 y 120ºC, donde el disolvente sirve de vehículo de contacto entre los reactivos y el iniciador.

En otra realización, el procedimiento se puede llevar a cabo sin la adición de un disolvente. En este caso, en la primera etapa de la reacción el iniciador puede hacer a su vez de disolvente, mientras que la segundo etapa del procedimiento puede desarrollarse en ausencia del mismo.

En una realización adicional de la presente invención, la sal neutra de tipo yoduro o yoduro de amonio cuaternario de la etapa (b) en encuentra mezclada con otros materiales sólidos.

Por “materiales sólidos” se entiende cualquier sal con capacidad reductora, tal como tiosulfato sódico, o un material inerte que se introduzca en el medio de la reacción.

En otra realización de la presente invención, el proceso de purificación de la etapa (c) se selecciona entre destilación, cristalización y cromatografía.

En una realización preferida de la presente invención, el poliol alifático es glicerol, el iniciador se selecciona entre clorotrimetilsilano (CTMS), ácido clorhídrico concentrado y una mezcla de ácido clorhídrico concentrado y cloruro de aluminio y el ácido se selecciona entre ácido palmítico, ácido caproico y ácido butírico.

La mezcla de todos ellos, calentada mediante métodos convencionales o empleando microondas, da lugar a la formación de una mezcla de alquilésteres de 1,3- y 2,3 dicloropilo.

Dichos ésteres igualmente se pueden obtener a partir de los correspondientes 1,3 y 2,3 dicloropronanoles, empleando un ácido alquilcarboxílico o un derivado del mismo.

Cuando se calientan entre 60 y 120ºC los correspondientes alquilésteres de 1,3 y 2,3 dicloropilo en presencia de NaI empleando o no butanona como disolvente se obtienen los correspondientes ésteres de alilo.

A modo ilustrativo y no limitativo, se describen, a continuación, los siguientes ejemplos de realización de la presente invención.

EJEMPLOS.

Ejemplo 1.

El procedimiento se llevó a cabo en un reactor tanque agitado de 100 ml de capacidad. Se introdujo en el mismo ácido palmítico (5,12 g), glicerol (5,34 g) y clorotrimetilsilano (10,85 g). El sistema se agitó durante 48 horas a 80oC y 200 rpm y, a continuación, se añadieron 6 g de bicarbonato sódico, (de una vez o de manera fraccionada), 25 ml de una solución acuosa saturada de bicarbonato sódico (de una vez o de manera fraccionada) y una vez acabada la efervescencia se añadieron 25 ml de hexano o t-butil metil éter (de una vez o de manera fraccionada).
Se recuperó la disolución orgánica, se secó y se evaporó recuperándose una fracción sólida.

Dicha fracción se disolvió en un reactor tanque agitado de 100 ml de capacidad, con 30 ml de butanona. Se añadieron 12 g de NaI y el sistema se agitó durante 48 horas a 115oC y 200 rpm. A continuación, se transfirió la mezcla a un embudo de decantación y se añadieron 50 ml de éter etílico, se lavó sucesivamente con agua, solución saturada de tiosulfato sódico y nuevamente otras tres veces con agua. Finalmente se recuperó la fracción orgánica que después de secada, se llevó a sequedad por evaporación del disolvente. El crudo recuperado se caracterizó como palmitato de alilo con una riqueza superior al 99 %. El rendimiento global de la reacción fue superior al 90%.

Ejemplo 2.

En este ejemplo se muestra la posibilidad de emplear microondas como fuente de energía, aspecto que permite una disminución ostensible de los tiempos de reacción.

El procedimiento se llevó a cabo en un reactor de PTFE de 50 ml de capacidad. Se introdujo en el mismo, ácido palmítico (0,51 g), glicerol (0,54 g) y clorotrimetilsilano (1,1 g). El sistema se introdujo en un reactor microondas y se agitó durante 3 min a 250 W y 15 min a una potencia nominal de 650 W y 200 rpm. A continuación, se añadieron 0,6 g de bicarbonato sódico, (de una vez o de manera fraccionada), 5 ml de una solución acuosa saturada de bicarbonato sódico (de una vez o de manera fraccionada) y hexano (de una vez o de manera fraccionada).

Se recuperó la disolución orgánica, se secó y se evaporó recuperándose una fracción sólida.

Dicha fracción se disolvió en un reactor de PTFE de 50 ml de capacidad, con 3 ml de butanona y se añadieron 1,2 g de NaI. El sistema se introdujo en un reactor microondas y se agitó durante 3 min a una potencia nominal de 250 W y 20 min a 450 W y 200 rpm. A continuación, se añadieron 10 ml de éter etílico. Finalmente, mediante un procedimiento de extracción, se recuperó la fracción orgánica. Dicha fracción se caracterizó como palmitato de alilo con una riqueza superior al 80%. El rendimiento global de la reacción fue superior al 70%.

Ejemplo 3.

En este ejemplo se muestra la posibilidad de emplear primero microondas como fuente de energía y seguidamente emplear una fuente de energía convencional, aspecto que también permite una disminución ostensible de los tiempos de reacción.

El procedimiento se llevó a cabo en un reactor de PTFE de 50 ml de capacidad. Se introdujo en el mismo ácido palmítico (0,51 g) glicerol (0,54 g) y clorotrimetilsilano (1,1 g). El sistema se introdujo en un reactor microondas y se agitó durante 3 min a 250 W y 15 min a una potencia nominal de 650 W y 200 rpm. A continuación, se añadieron 0,6 g de bicarbonato sódico, (de una vez o de manera fraccionada), 5 ml de una solución acuosa saturada de bicarbonato sódico (de una vez o de manera fraccionada) y hexano (de una vez o de manera fraccionada).

A continuación, se recuperó la disolución orgánica, se secó y se evaporó recuperándose una fracción sólida.

Dicha fracción se disolvió en un reactor tanque agitado de 10 ml de capacidad, con 3 ml de butanona. Se añadieron 1,2 g de NaI y el sistema se agitó durante 48 horas a 115oC y 200 rpm. A continuación, se añadieron 5 ml de éter etílico. Finalmente, mediante un procedimiento de extracción, se recuperó la fracción orgánica. Dicha fracción se caracterizó como palmitato de alilo con una riqueza superior al 90%. El rendimiento global de la reacción fue superior al 85%.

Ejemplo 4.

En este ejemplo se muestra la posibilidad de emplear microondas como fuente de energía tanto en la primera como en la segunda etapa de la reacción y sin utilizar disolventes en ninguna de las dos etapas.

El procedimiento se llevó a cabo en un reactor de PTFE de 50 ml de capacidad. Se introdujo en el mismo ácido palmítico (0,51 g), glicerol (0,54 g) y clorotrimetilsilano (1,1 g). El sistema se introdujo en un reactor microondas y se agitó durante 3 min a 250 W y 15 min a una potencia nominal de 650 W y 200 rpm. A continuación, se añadieron 0,6 g de bicarbonato sódico, (de una vez o de manera fraccionada), 5 ml de una solución acuosa saturada de bicarbonato sódico (de una vez o de manera fraccionada) y hexano (de una vez o de manera fraccionada).

A continuación, se recuperó la disolución orgánica, se secó y se evaporó recuperándose una fracción sólida.

Dicha fracción introdujo en un reactor de PTFE de 50ml. Se añadieron 1,2 g de NaI y el sistema se agitó durante 20 min y 200 rpm a una potencia nominal de 650 W. A continuación, se añadieron 5 ml de éter etílico. Finalmente, mediante un procedimiento de extracción, se recuperó la fracción orgánica. Dicha fracción se caracterizó como palmitato de alilo con una riqueza superior al 85%. El rendimiento global de la reacción fue superior al 80%.

Ejemplo 5.

En este ejemplo se muestra la posibilidad de realizar la primera reacción empleando ácido clorhídrico en sustitución de clorotrimetilsilano.

El procedimiento se llevó a cabo en un reactor tanque agitado de 50 ml de capacidad. Se introdujo en el mismo ácido palmítico (2,6 g), glicerol (2,7 g) y ácido clorhídrico concentrado (20 ml). El sistema se agitó durante 48 horas a 80oC y 200 rpm y, a continuación, se añadieron 0,5 g de bicarbonato sódico, (de una vez o de manera fraccionada), 5 ml de una solución acuosa saturada de bicarbonato sódico (de una vez o de manera fraccionada) y hexano (de una vez o de manera fraccionada).
A continuación se recuperó la disolución orgánica, se secó y se evaporó recuperándose una fracción sólida.

La transformación de la fracción sólida se llevó a cabo tal y como se ha descrito en los ejemplos 1 ó 2. El rendimiento global de la reacción fue superior al 50%.

Ejemplo 6.

En este ejemplo se muestra la posibilidad de emplear en primer lugar microondas como fuente de aporte de energía y una mezcla de ácido clorhídrico concentrado y un cloruro metálico en sustitución del clorotrimetilsilano en la primera etapa.

El procedimiento se llevó a cabo en un reactor de PTFE de 50 ml de capacidad. Se introdujo en el mismo ácido

palmítico (0,256 g), glicerol (0,18 g) y una mezcla de acido clorhídrico concentrado (20 l) y cloruro de aluminio anhidro (0,66 g). El sistema se introdujo en un reactor microondas y se agitó durante 3 min a 250 W y 15 min a una potencia nominal de 650 W y 200 rpm. A continuación, se añadieron 0,6 g de bicarbonato sódico, (de una vez o de manera fraccionada), 5 ml de una solución acuosa saturada de bicarbonato sódico (de una vez o de manera fraccionada) y 25 ml de hexano (de una vez o de manera fraccionada).

A continuación, se recuperó la disolución orgánica, se secó y se evaporó recuperándose una fracción sólida.

El rendimiento global de la reacción fue superior al 70%.

Ejemplo 7.

En este ejemplo se muestra la posibilidad de emplear el 1,3-dicloropropanol y un derivado de ácido, concretamente el palmitato de metilo.

El procedimiento se llevó a cabo en un reactor tanque agitado de 50 ml de capacidad. Se introdujo en el mismo palmitato de metilo (5,4 g), 1,3-dicloropropanol (2 g) y clorotrimetilsilano (1 ml). El sistema se agitó durante 48 horas a 80oC y 200 rpm, y a continuación, se añadieron 0,6 g de bicarbonato sódico, (de una vez o de manera fraccionada), 5 ml de una solución acuosa saturada de bicarbonato sódico (de una vez o de manera fraccionada) y hexano (de una vez o de manera fraccionada).

A continuación se recuperó la disolución orgánica, se secó y se evaporó recuperándose una fracción sólida.

La transformación de la fracción sólida se llevó a cabo tal y como se ha descrito en los ejemplos 1 ó 2. El rendimiento global de la reacción fue superior al 90%.

Ejemplo 8.

En este ejemplo se muestra la posibilidad de emplear un disolvente distinto a la butanona en la segunda etapa de la reacción.

La primera etapa se llevó a cabo tal y como se ha descrito en los ejemplos 1 ó 2. La fracción sólida recuperada después de evaporar el disolvente orgánico se disolvió, empleando un reactor tanque agitado de 50 ml de capacidad, con 15 ml de tetrahidrofurano. Se añadieron 12 g de NaI y el sistema se agitó durante 48 horas a 115oC y 200 rpm. A continuación se añadieron 20 ml de hexano. Finalmente, mediante un procedimiento de extracción, se recuperó la fracción orgánica. En dicha fracción se caracterizó el palmitato de alilo con una riqueza superior al 30%. El rendimiento global de la reacción fue superior al 25%.

Ejemplo 9.

En este ejemplo se muestra la posibilidad de emplear un disolvente como la acetona en la segunda etapa de la reacción.

La primera etapa se llevó a cabo tal y como se ha descrito en los ejemplos 1 ó 2. La fracción sólida recuperada después de evaporar el disolvente orgánico se disolvió, empleando un reactor tanque agitado de 50 ml de capacidad, con 15 ml de acetona previamente desecada. Se añadieron 12 g de NaI y el sistema se agitó durante 48 horas a 80oC y 200 rpm. A continuación se añadieron 20 ml de hexano. Finalmente, mediante un procedimiento de extracción, se recuperó la fracción orgánica. En dicha fracción se caracterizó el palmitato de alilo con una riqueza superior al 84%. El rendimiento global de la reacción fue superior al 75%.

Ejemplo 10.

En este ejemplo se muestra la posibilidad de llevar a cabo la segunda etapa de la reacción sin disolvente.
La primera etapa se llevó a cabo tal y como se ha descrito en los ejemplos 1 ó 2. La fracción sólida recuperada después de evaporar el disolvente orgánico se mezcló, empleando un reactor tanque agitado de 50 ml de capacidad, con 12 g de NaI y el sistema se agitó durante 48 horas a 115oC y 200 rpm. A continuación, se añadieron 20 ml de hexano. Finalmente, mediante un procedimiento de extracción, se recuperó la fracción orgánica. En dicha fracción se caracterizó el palmitato de alilo con una riqueza superior al 35%. El rendimiento global de la reacción fue superior al 30%.

Ejemplo 11.

En este ejemplo se muestra la posibilidad de realizar la reacción empleando otro ácido carboxílico en sustitución del ácido palmítico.

El procedimiento se llevó a cabo en un reactor tanque agitado de 50 ml de capacidad. Se introdujo en el mismo ácido cáprico (3,44 g), glicerol (5,34 g) y clorotrimetilsilano (10,85 g). El sistema se agitó durante 48 horas a 80oC y 200 rpm, y a continuación, se añadieron 6 g de bicarbonato sódico, (de una vez o de manera fraccionada), 25 ml de una solución acuosa saturada de bicarbonato sódico (de una vez o de manera fraccionada) y acabada la efervescencia se añadieron 20 ml de hexano o t-butil metil éter (de una vez o de manera fraccionada).

Se recuperó la disolución orgánica, se secó y se evaporó recuperándose un residuo.

La transformación de la fracción sólida se llevó a cabo tal y como se ha descrito en los ejemplos 1 ó 2. El producto final se caracterizó como caproato de alilo con una riqueza superior al 70%. El rendimiento global de la reacción fue superior al 70%.

Ejemplo 12.

En este ejemplo se muestra la posibilidad de realizar la reacción empleando otro ácido carboxílico de cadena corta en sustitución del ácido palmítico.

El procedimiento se llevó a cabo en un reactor tanque agitado de 50 ml de capacidad. Se introdujo en el mismo ácido butírico (1,75 g), glicerol (5,34 g) y clorotrimetilsilano (10,85 g). El sistema se agitó durante 48 horas a 80oC y 200 rpm, y a continuación, se añadieron 6 g de bicarbonato sódico, (de una vez o de manera

fraccionada), 25 ml de una solución acuosa saturada de bicarbonato sódico (de una vez o de manera fraccionada) y acabada la efervescencia se añadió 20 ml de hexano o t-butil metil éter (de una vez o de manera fraccionada).

Se recuperó la disolución orgánica, se secó y se evaporó recuperándose un residuo.

La transformación de la fracción sólida se llevó a cabo tal y como se ha descrito en los ejemplos 1 ó 2. El producto final se caracterizó como butirato de alilo con una riqueza superior al 85%. El rendimiento global de la reacción fue superior al 60%.

REIVINDICACIONES.

1.- Procedimiento para la obtención de ésteres de alilo caracterizado por el hecho de que comprende las etapas de:

a) mezclar, a una temperatura adecuada, un ácido alquilcarboxílico, de origen natural o sintético, o un derivado del mismo seleccionado entre anhídrido de ácido, haluro de acilo, éster, amida, amida sustituida, y ácido activado; un iniciador de la reacción; y un poliol alifático o, alternativamente, un α,γ-dihaloalcohol o β,γ-dihaloalcohol para obtener un éster de α,γ-dihaloalquilo o β,γ-dihaloalquilo, o mezcla de ambos;
b) hacer reaccionar el compuesto obtenido en la etapa (a), a una temperatura adecuada, con

una sal neutra de tipo yoduro metálico o de yoduro de amonio cuaternario, para obtener el éster alílico correspondiente; y

c) aislar dicho éster alílico mediante un proceso de purificación.

2.- Procedimiento según la reivindicación 1, caracterizado por el hecho de que la etapa (b) de la reacción puede llevarse a cabo adicionando un disolvente polar con un punto de ebullición comprendido entre 60 y 120ºC.

3.- Procedimiento según la reivindicación 2, caracterizado por el hecho de que el disolvente polar utilizado se selecciona entre acetona, butanona y tetrahidrofurano.

4.- Procedimiento según la reivindicación 1, caracterizado por el hecho de que la temperatura en las etapas (a) y (b) es inferior a 120ºC.

5.- Procedimiento según la reivindicación 1 y/o 4 caracterizado por el hecho de que se alcanza la temperatura adecuada en las etapas (a) y (b) utilizando microondas como sistema de aporte de energía.

6.- Procedimiento según cualquiera de las reivindicaciones anteriores, caracterizado por el hecho de que el poliol alifático es cualquier sustancia con una estructura de tipo XCH(OH)CH(OH)CH(OH)Y, siendo X e Y, independientemente, igual a H, un grupo alquilo o arilo.

7.- Procedimiento según la reivindicación 6 caracterizado por el hecho de que el poliol alifático es glicerol.

8.- Procedimiento según cualquiera de las reivindicaciones anteriores caracterizado por el hecho de que la sal neutra utilizada en la etapa (b) es un compuesto del tipo MI, donde M puede ser cualquier

catión metálico o bien un grupo NZ1Z2Z3Z4, donde Z1, Z2, Z3 y Z4 son, independientemente, H, un grupo alquilo o arilo.

9.- Procedimiento según la reivindicación 8, caracterizado por el hecho de que la sal neutra se selecciona entre NaI, LiI y yoduro de tetrametilamonio.

10.- Procedimiento según la reivindicación 1, caracterizado por el hecho de que la sal neutra de tipo yoduro o yoduro de amonio cuaternario de la etapa (b) se encuentra mezclada con otros materiales sólidos.

11.- Procedimiento según la reivindicación 10, caracterizado por el hecho de que dichos otros materiales sólidos es tiosulfato sódico.

12.- Procedimiento según cualquiera de las reivindicaciones anteriores, caracterizado por el hecho de que el iniciador se selecciona entre clorotrimetilsilano, ácido clorhídrico o una mezcla de ácido clorhídrico y cloruro de aluminio.

13. Procedimiento según cualquiera de las reivindicaciones anteriores, caracterizado por el hecho de que el ácido alquilcarboxílico se selecciona entre ácido palmítico, ácido caproico y ácido butírico.

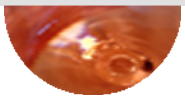
14.- Procedimiento según cualquiera de las reivindicaciones anteriores caracterizado por el hecho de que el éster obtenido en la etapa (a) es un alquilcarboxilato de 1,3-dicloropropilo, 1,2-dicloropropilo, o mezcla de ambos.

15.- Procedimiento según la reivindicación 1 caracterizado por el hecho el proceso de purificación de la etapa (c) se selecciona entre destilación, cristalización y cromatografía.

RESUMEN.

La presente invención describe un procedimiento para la obtención de ésteres de alilo, con ventajas en cuanto a utilización de reactivos, consumo de energía, rendimientos, pureza, que comprende las etapas de:

a) mezclar, a una temperatura adecuada, un ácido alquilcarboxílico, de origen natural o sintético, o un derivado del mismo seleccionado entre anhídrido de ácido, haluro de acilo, éster, amida, amida sustituida, y ácido activado; un iniciador de la reacción; y un poliol alifático o, alternativamente, un α,γ-dihaloalcohol o β,γ-dihaloalcohol para obtener un éster de α,γ-dihaloalquilo o β,γ-dihaloalquilo, o mezcla de ambos;
b) hacer reaccionar el compuesto obtenido en la etapa (a), a una temperatura adecuada, con una sal neutra de tipo yoduro metálico o de yoduro de amonio cuaternario, para obtener el éster alílico correspondiente; y
c) aislar dicho éster alílico mediante un proceso de purificación.



Supplementary data

From Glycerol to Chlorohydrin Esters using a Solvent-free System. Microwave Irradiation versus Conventional Heating

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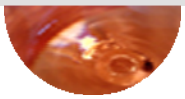
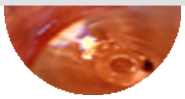


Materials and Methods. Silica gel was purchased from Merck and used as received.

NMR spectra were recorded on a 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 $CDCl_3$ or at 2.21 ppm of $COCD_6$ for ^{1}H NMR and centre line of a triplet at 77.00 ppm and at 29.8 ppm of $COCD_6$ for ^{13}C NMR: The following abbreviations are used; s: singlet, d: doublet, t: triplet, q: quartet, quin: quintet, m: multiplet. GC-MS were performed in a GC equipped with a DB5-MS column (J&W) (30m x 0.25 µm x 0.25 mm) coupled to an MS detector and He as carrier gas. The following chromatographic conditions were used: constant flow 2mL/min, split injection ratio 20:1 at 280 ºC. 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 final temperature of 260 ºC for 15 min. IR spectra were recorded on a FTIR spectrophotometer in the range 4000-600 cm^{-1}, with KBr pellets or with diamond HATR as specified. Spectra are reported in reciprocal centimeters (cm^{-1}). High resolution mass spectral data were obtained by direct infusion on LC-TOF-MS ESI or APCI as specified. Melting points were measured on a capillary melting point apparatus.



Experimental procedures

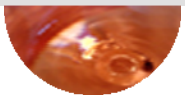
Synthesis of dichloropropyl esters using 2.5 equivalents of CTMS and conventional heating

1,3-Dichloro-2-propyl palmitate (3a) synthesis. [CAS: 72165-62-9]
Palmitic acid (256 mg; 1 mmol, **2a**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC/FID to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl palmitate **(3a)** was obtained by crystallization (333 mg, 91%).

1,3-Dichloro-2-propyl caprylate (3b) synthesis.
Caprylic acid (144 mg; 1 mmol, **2b**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl caprylate (**3b**) was obtained using silica column chromatography (224 mg, 88%).

1,3-Dichloro-2-propyl pivaloate (3c) synthesis.
Pivalic acid (102 mg; 1 mmol, **2c**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, pentane was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl pivaloate (**3c**) was obtained by distillation (202 mg, 95%).

1,3-Dichloro-2-propyl linolenate (3d) synthesis.
Technical linolenic acid (278 mg; 1 mmol, **2d**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was



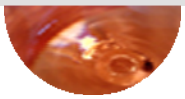
evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl linolenate (**3d**) was obtained using silica column chromatography (335 mg, 86%).

1,3-Dichloro-2-propyl benzoate (3e) synthesis.
Benzoic acid (122 mg; 1 mmol, **2e**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, pentane was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl benzoate (**3e**) was obtained by distillation (205 mg, 88%).

1,3-Dichloro-2-propyl cinnamate (3f) synthesis.
Cinnamic acid (148 mg; 1 mmol, **2f**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl cinnamate (**3f**) was obtained by silica column chromatography (207 mg, 80%).

1,3-Dichloro-2-propyl *o*-chlorobenzoate (3g) synthesis.
o-Chlorobenzoic acid (156 mg; 1 mmol, **2g**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl *o*-chlorobenzoate (**3g**) was obtained using silica column chromatography (227 mg, 85%).

1,3-Dichloro-2-propyl salicylate (3h) synthesis.
Salicylic acid (138 mg; 1 mmol, **2h**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl salicylate (**3h**) was obtained by crystallization (229 mg, 92%).



1,3-Dichloro-2-propyl *m*-nitrobenzoate (3i) synthesis.

m-Nitrobenzoic acid (167 mg; 1 mmol, **2i**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl *m*-nitrobenzoate (**3i**) was obtained by crystallization (250 mg, 90%).

1,3-Dichloro-2-propyl 3,5-dinitrobenzoate (3j) synthesis.

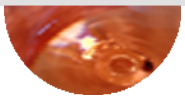
3,5-Dinitrobenzoic acid (212 mg; 1 mmol, **2j**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, CTMS was separated and ethyl acetate was added under low heat conditions. Then, glycerol was also separated, and the organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl 3,5-dinitrobenzoate (**3j**) was obtained by crystallization (248 mg, 77%).

1,3-Dichloro-2-propyl 2,4-dinitrobenzoate (3k) synthesis.

2,4-Dinitrobenzoic acid (212 mg; 1 mmol, **2k**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl 2,4-dinitrobenzoate (**3k**) was obtained using silica column chromatography (262 mg, 81%).

1,3-Dichloro-2-propyl 1-naphthoate (3l) synthesis.

1-Naphthoic acid (172 mg; 1 mmol, **2l**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl 1-naphthoate (**3l**) was obtained by crystallization (252 mg, 89%).



1,3-Dichloro-2-propyl 2-naphthoate (3m) synthesis.

2-Naphthoic acid (172 mg; 1 mmol, **2m**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl 2-naphthoate (**3m**) was obtained by crystallization (232 mg, 82%).

1,3-Dichloro-2-propyl 2-furoate (3n) synthesis.

2-Furoic acid (112 mg; 1 mmol, **2n**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl 2-furoate (**3n**) was obtained using silica column chromatography (187 mg, 84%).

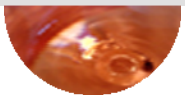
1,3-Dichloro-2-propyl 2-thiophencarboxylate (3o) synthesis.

2-Thiophencarboxylic acid (128 mg; 1 mmol, **2o**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. Pure 1,3-dichloro-2-propyl 2-thiophencarboxylate (**3o**) was obtained using silica column chromatography (210 mg, 88%).

Synthesis of dichloropropyl esters using 1.1 equivalents of CTMS and conventional heating

1,3-Dichloro-2-propyl palmitate (3a) synthesis.

Palmitic acid (256 mg; 1 mmol, **2a**), glycerol (110.5 mg; 1,2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3a** (403 mg, 110%). The crude was analyzed by GC using tridecane as internal standard.



1,3-Dichloro-2-propyl caprylate (3b) synthesis.

Caprylic acid (144 mg; 1 mmol, **2b**), glycerol (110.5 mg; 1,2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3b** (235 mg, 92%). The crude was analyzed by GC using tridecane as internal standard.

1,3-Dichloro-2-propyl pivaloate (3c) synthesis.

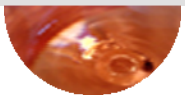
Pivalic acid (102 mg; 1 mmol, **2c**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, pentane was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3c** (200 mg, 94%). The crude was analyzed by GC using tridecane as internal standard.

1,3-Dichloro-2-propyl linolenate (3d) synthesis.

Technical linolenic acid (278 mg; 1 mmol, **2d**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give 1,3-Dichloro-2-propyl ester (245 mg, 63%). The crude was analyzed by GC using tridecane as internal standard.

1,3-Dichloro-2-propyl benzoate (3e) synthesis.

Benzoic acid (122 mg; 1 mmol, **2e**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, pentane was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3e** (224 mg, 96%). The crude was analyzed by GC using tridecane as internal standard.



1,3-Dichloro-2-propyl cinnamate (3f) synthesis.

Cinnamic acid (148 mg; 1 mmol, **2f**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3f** (215 mg, 83%). The crude was analyzed by GC using tridecane as internal standard.

1,3-Dichloro-2-propyl *o*-chlorobenzoate (3g) synthesis.

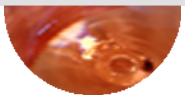
o-Chlorobenzoic acid (156 mg; 1 mmol, **2g**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3g** (275 mg, 103%). The crude was analyzed by GC using tridecane as internal standard.

1,3-Dichloro-2-propyl salicylate (3h) synthesis.

Salicylic acid (138 mg; 1 mmol, **2h**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3h** (222 mg, 89%). The crude was analyzed by GC using tridecane as internal standard.

1,3-Dichloro-2-propyl *m*-nitrobenzoate (3i) synthesis.

m-Nitrobenzoic acid (167 mg; 1 mmol, **2i**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3i** (253 mg, 91%). The crude was analyzed by GC using tridecane as internal standard.



1,3-Dichloro-2-propyl 3,5-dinitrobenzoate (3j) synthesis.

3,5-Dinitrobenzoic acid (212 mg; 1 mmol, **2j**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, CTMS was separated and ethyl acetate was added under low heat conditions. After cooling, glycerol was also separated, and the organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3j** (168 mg, 52%). The crude was analyzed by GC using tridecane as internal standard.

1,3-Dichloro-2-propyl 2,4-dinitrobenzoate (3k) synthesis.

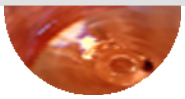
2,4-Dinitrobenzoic acid (212 mg; 1 mmol, **2k**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3k** (97 mg, 30%). The crude was analyzed by GC using tridecane as internal standard.

1,3-Dichloro-2-propyl 1-naphthoate (3l) synthesis.

1-Naphthoic acid (172 mg; 1 mmol), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol, **2l**) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3l** (263 mg, 93%). The crude was analyzed by GC using tridecane as internal standard.

1,3-Dichloro-2-propyl 2-naphthoate (3m) synthesis.

2-Naphthoic acid (172 mg; 1 mmol, **2m**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3m** (286 mg, 101%). The crude was analyzed by GC using tridecane as internal standard.



1,3-Dichloro-2-propyl 2-furoate (3n) synthesis.

2-Furoic acid (112 mg; 1 mmol, **2n**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3n** (210 mg, 94%). The crude was analyzed by GC using tridecane as internal standard.

1,3-Dichloro-2-propyl 2-thiophencarboxylate (3o) synthesis.

2-Thiophencarboxylic acid (128 mg; 1 mmol, **2o**), glycerol (110.5 mg; 1.2 mmol, **1**) and CTMS (238 mg; 2.2 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was heated at 80 ºC for 48 h. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum to give **3o** (215 mg, 90%). The crude was analyzed by GC using tridecane as internal standard.

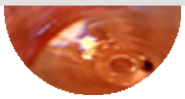
Synthesis of dichloropropyl esters using 2.5 equivalents of CTMS and microwave irradiation

1,3-Dichloro-2-propyl palmitate (3a) and 2,3-dichloro-1-propyl palmitate (4a) synthesis.

Palmitic acid (256 mg; 1 mmol, **2a**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300 W 250 ºC 250 psi during 20 min. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (315 mg, 86%).

1,3-Dichloro-2-propyl caprylate (3b) and 2,3-dichloro-1-propyl caprylate (4b) synthesis.

Caprylic acid (144 mg; 1 mmol, **2b**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300 W 250 ºC 250 psi during 20 min. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (206 mg, 81%).



1,3-Dichloro-2-propyl pivaloate (3c) and 2,3-dichloro-1-propyl pivaloate (4c) synthesis.

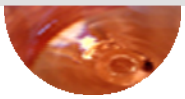
Pivalic acid (102 mg; 1 mmol, **2c**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300W, 250 psi (reaction temperature 230 ºC) for 20 min. After cooling, pentane was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained by Kugelrohr distillation (192 mg, 90%).

1,3-Dichloro-2-propyl linolenate (3d) and 2,3-dichloro-1-propyl linolenate (4d) synthesis.

Technical linolenic acid (278 mg; 1 mmol, **2d**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300W, 250 psi (reaction temperature 230 ºC) for 20 min. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (288 mg, 74%).

1,3-Dichloro-2-propyl benzoate (3e) and 2,3-dichloro-1-propyl benzoate (4e) synthesis.

Benzoic acid (122 mg; 1 mmol, **2e**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300W, 250 psi (reaction temperature 230 ºC) for 20 min. After cooling, pentane was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained by Kugelrohr distillation (186 mg, 80%).



1,3-Dichloro-2-propyl cinnamate (3f) and 2,3-dichloro-1-propyl cinnamate (3f) synthesis.

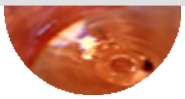
Cinnamic acid (148 mg; 1 mmol, **2f**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300W, 250 psi (reaction temperature 230 ºC) for 20 min. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (189 mg, 73 %).

1,3-Dichloro-2-propyl *o*-chlorobenzoate (3g) and 2,3-dichloro-1-propyl *o*-chlorobenzoate (4g) synthesis.

o-Chlorobenzoic acid (156 mg; 1 mmol, **2g**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300W, 250 psi (reaction temperature 230 ºC) for 20 min. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (208 mg, 78 %).

1,3-Dichloro-2-propyl salicylate (3h) and 2,3-dichloro-1-propyl salicylate (4o) synthesis.

Salicylic acid (138 mg; 1 mmol, **2h**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300W, 250 psi (reaction temperature 230 ºC) for 20 min. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (182 mg, 73 %).



1,3-Dichloro-2-propyl *m*-nitrobenzoate (3i) and 2,3-dichloro-1-propyl *m*-nitrobenzoate (4i) synthesis.

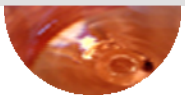
m-Nitrobenzoic acid (167 mg; 1 mmol, **2i**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300W, 250 psi (reaction temperature 230 ºC) for 20 min. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (217 mg, 78 %).

1,3-Dichloro-2-propyl 3,5-dinitrobenzoate (3j) and 2,3-dichloro-1-propyl 3,5-dinitrobenzoate (4j) synthesis.

3,5-Dinitrobenzoic acid (212 mg; 1 mmol, **2j**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300 W, 250 psi (reaction temperature 175 ºC) for 20 min. After cooling, CTMS was separated and ethyl acetate was added under low heat conditions. After cooling, glycerol was also separated, and the organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (249 mg, 77 %).

1,3-Dichloro-2-propyl 2,4-dinitrobenzoate (3k) and 2,3-dichloro-1-propyl 2,4-dinitrobenzoate (4k) synthesis.

2,4-Dinitrobenzoic acid (212 mg; 1 mmol, **2k**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300 W, 250 psi (reaction temperature 175 ºC) for 20 min. After cooling, CTMS was separated and ethyl acetate was added under low heat conditions. After cooling, glycerol was also separated, and the organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (242 mg, 75 %).



1,3-Dichloro-2-propyl 1-naphthoate (3l) and 2,3-dichloro-1-propyl 1-naphthoate (4l) synthesis.

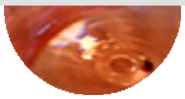
1-Naphthoic acid (172 mg; 1 mmol, **2l**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300 W, 250 psi (reaction temperature 250 ºC) for 20 min. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (232 mg, 82 %).

1,3-Dichloro-2-propyl 2-naphthoate (3m) and 2,3-dichloro-1-propyl 2-naphthoate (4m) synthesis.

2-Naphthoic acid (172 mg; 1 mmol, **2m**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300W, 250 psi (reaction temperature 230 ºC) for 20 min. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (215 mg, 76 %).

1,3-Dichloro-2-propyl 2-furoate (3n) and 2,3-dichloro-1-propyl 2-furoate (4n) synthesis.

2-Furoic acid (112 mg; 1 mmol, **2n**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300W, 250 psi (reaction temperature 230 ºC) for 20 min. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (174 mg, 78 %).



1,3-Dichloro-2-propyl 2-thiophencarboxylate (3o) and 2,3-dichloro-1-propyl 2-thiophencarboxylate (4o) synthesis.

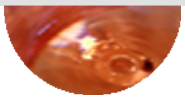
2-Thiophencarboxylic acid (128 mg; 1 mmol, **2o**), glycerol (184 mg; 2 mmol, **1**) and CTMS (540 mg; 5 mmol) were added in a reaction vial fitted with PTFE-lined cap. The mixture was irradiated at maximum 300W, 250 psi (reaction temperature 230 ºC) for 20 min. After cooling, *t*-butyl methyl ether was added and the mixture was washed three times with water. The organic layer was dried over anhydride $MgSO_4$ and solvent was evaporated under vacuum. The crude was analyzed by GC to determine the regioisomeric ratio. A purified regioisomeric mixture was obtained using silica column chromatography (172 mg, 72 %).

Analytical data:

1,3-Dichloro-2-propyl palmitate (**3a**) [CAS: 72165-62-9]: ^{1}H NMR ($CDCl_3$), δ: 5.18 (quin, *J*=5.2 Hz, 1H, O-C*H*), 3.73 (m, 4H, 2 CH_2-Cl), 2.37 (t, *J*=7 Hz, 2H, C$H_{2\ (\alpha)}$ (C=O)), 1.65 (m, 2H, C$H_{2\ (\beta)}$ (C=O)), 1.26 (m, 24H, CH_2), 0.88 (t, *J*=7 Hz, 3H, CH_3). ^{13}C RMN ($CDCl_3$), δ: 172.7 (*C*=O), 71.5 (O-*C*H), 42.5 (*C*H_2-Cl), 34.1 (*C*$H_{2\ (\alpha)}$ (C=O)), 31.9 (*C*H_2-CH_2-CH_3), 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0 (*C*H_2), 24.8 (*C*$H_{2\ (\beta)}$ (C=O)), 22.7 (*C*H_2-CH_3), 14.1 (*C*H_3). GC-MS, *m/z*: 366 $[M]^+$, 295 $[M\text{-}2Cl]^+$, 257 $[M\text{-}C_3H_5Cl_2]^+$, 239 $[M\text{-}OC_3H_5Cl_2]^+$. IR (ATR), ν max.: 2921, 2852, 1746, 1466, 1153, 764 cm^{-1}. m.p.: 30.1-30.6 ºC.[1]

1,3-Dichloro-2-propyl caprylate (**3b**): ^{1}H NMR ($CDCl_3$), δ: 5.12 (quin, *J*=5.2 Hz, 1H, O-C*H*), 3.68 (dd, J_1=5.7 Hz, J_2=2.2 Hz, 4H, 2 CH_2-Cl), 2.31 (t, *J*=7.6 Hz, 2H, C$H_{2\ (\alpha)}$ (C=O)), 1.58 (quin, *J*=7.4 Hz, 2H, C$H_{2\ (\beta)}$ (C=O)), 1.24 (m, 8H, CH_2), 0.82 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C RMN ($CDCl_3$), δ: 173 (*C*=O), 72 (O-*C*H), 42 (*C*H_2-Cl), 34.4 (*C*$H_{2\ (\alpha)}$ (C=O)), 32.1 (*C*H_2-CH_2-CH_3), 29.5 (*C*H_2), 25 (*C*$H_{2\ (\beta)}$ (C=O)), 22.5 (*C*H_2-CH_3), 14.5 (*C*H_3). GC-MS, *m/z*: 254.1 $[M]^+$, 183 $[M\text{-}2Cl]^+$, 143 $[M\text{-}C_3H_5Cl_2]^+$, 127 $[M\text{-}OC_3H_5Cl_2]^+$, 111 $[C_3H_5Cl_2]^+$. IR (ATR), ν max.: 2957, 2927, 2856, 1742, 1154, 1102, 1050, 846, 769 cm^{-1}. HRMS (EI+) calculated for $C_{11}H_{20}O_2Cl_2$: 254.0840, found: 254.0836.

[1] Eras, J.; Méndez, J. J.; Balcells, M.; Canela, R. *J. Org. Chem.* **2002**, *67*, 8631-9634



1,3-Dichloro-2-propyl pivaloate (**3c**) [CAS: 220499-01-4]: ^{1}H NMR ($CDCl_3$), δ: 5.14 (quin, *J*=5.2 Hz, 1H, O-C*H*), 3.76 (m, 4H, 2 CH_2-Cl), 1.24 (m, 9H, CH_3). ^{13}C RMN ($CDCl_3$), δ: 177.9 (*C*=O), 71.6 (O-*C*H), 42.7 (*C*H_2-Cl), 39.2 (*C*-$(CH_3)_3$), 27.3 (3*C*H_3). GC-MS, *m/z*: 212 $[M]^+$, 168 $[M\text{-}C_3H_9]^+$; 156 $[M\text{-}C_4H_9]^+$; 85 $[M\text{-}C_4H_9Cl_2]^+$; 57 $[M\text{-}C_6H_{13}Cl_2]^+$. IR (ATR), ν max.:2962, 1733 1253, 1140, 1050, 844, 756, 685 cm^{-1}. b.p.: 100ºC/130Torr (glass oven B-585 Kugelrohr) (271.7±20.0 °C/760Torr).[2]

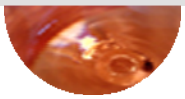
1,3-Dichloro-2-propyl linolenate (**3d**): ^{1}H NMR ($CDCl_3$), δ: 5.39 (m, 6H, C*H*=C*H*), 5.18 (quin, *J*=5.4 Hz, 1H, O-C*H*), 3.70 (d, *J*=2.0 Hz, 4H, CH_2-Cl), 2.36 (t, *J*=7.4 Hz, 4H, C=C-CH_2-C=C-CH_2-C=C), 2.00 (q, *J*=6.2 Hz, 2H, C$H_{2\ (\alpha)}$ (C=O)), 1.66 (m, 4H, 2 CH_3-CH_2-CH=C), 1.50 (m, 2H, C$H_{2\ (\beta)}$ (C=O)), 1.29 (m, 8H, CH_2), 0.87 (t, *J*=6.6 Hz, 3H, CH_3). ^{13}C RMN ($CDCl_3$), δ: 173 (*C*=O), 133.7,131.1, 129.2, 128.6, 127 (*C*=C_{chain}), 72.1 (O-*C*H), 42.5 (*C*H_2-Cl), 34.6 (*C*$H_{2\ (\alpha)}$ (C=O)), 41.9, 39.6, 39.2, 37.1, 25.1, 23.2, 20.8 (*C*H_2), 24.8 (*C*$H_{2\ (\beta)}$ (C=O)), 20.7 (*C*H_2-CH_3), 14.3 (*C*H_3). GC-MS, *m/z*: 388 $[M]^+$, 318 $[M\text{-}2Cl]^+$, 261 $[M\text{-}OC_3H_5Cl_2]^+$. IR (ATR), ν max.: 3010, 2926, 2954, 1743, 1156, 768, 706 cm^{-1}.

1,3-Dichloro-2-propyl benzoate (**3e**) [CAS: 36847-76-4]: ^{1}H NMR ($CDCl_3$), δ: 8.00 (m, 1H, C$H_{ar\ (\alpha)}$ (C=O)), 7.53 (m, 1H, CH_{ar}), 7.39 (m, 2H, CH_{ar}), 5.36 (quin, *J*=5.3 Hz, 1H, O-C*H*), 3.82 (m, 4H, 2 CH_2-Cl). ^{13}C RMN ($CDCl_3$), δ: 163.4 (*C*=O), 131.7, 127.9, 127.2, 126.6 (*C*$_{ar}$), 70.1 (O-*C*H), 40.5 (*C*H_2-Cl). GC-MS, *m/z*: 232 $[M]^+$, 122 $[M\text{-}C_3H_5Cl_2]^+$; 105 $[M\text{-}OC_3H_5Cl_2]^+$; 77 $[M\text{-}CO_2C_3H_5Cl_2]^+$. IR (KBr), ν max.: 3078, 2966, 1720, 1249, 1095, 705, 685 cm^{-1}. b.p.: 100ºC/130Torr (glass oven B-585 Kugelrohr) (271.7±20.0 °C/760Torr).[2]

1,3-Dichloro-2-propyl cinnamate (**3f**) [CAS: 157140-94-8]: ^{1}H NMR ($CDCl_3$), δ: 7.71 (d, *J*=16 Hz, 1H, CH_{ar}), 7.48 (t, *J*=3.5 Hz, 2H, 2 CH_{ar}), 7.34 (m, 3H, 2 CH_{ar}), 6.45 (dd, J_1=15.8 Hz, J_2=0.9 Hz, 2H, Ph-C*H*=C*H*), 5.26 (quin, *J*=5.2 Hz, 1H, O-C*H*), 3.81 (dd, J_1=5.2 Hz , J_2=0.8 Hz, 4H, 2 CH_2-Cl). ^{13}C RMN ($CDCl_3$), δ: 165.9 (*C*=O), 146.7 (Ph-*C*H=CH), 134.2 (*C*$_{ar}$), 130.9, 129.2, 128.5 (*CH*$_{ar}$), 117.0 (Ph-CH=*C*H), 71.9 (O-*C*H), 42.7 (*C*H_2-Cl). GC-MS, *m/z*: 258 $[M]^+$; 147 $[M\text{-}C_3H_5Cl_2]^+$; 131 $[M\text{-}COC_3H_5Cl_2]^+$; 103 $[M\text{-}CO_2C_3H_5Cl_2]^+$; 77 $[M\text{-}C_2H_2CO_2C_3H_5Cl_2]^+$. IR (KBr), ν max.: 3057, 3029, 2960, 1713, 1635, 1152, 765, 780, 682 cm^{-1}.[3]

[2] ZIC/VINITI data file. InfoChem Gesellschaft für chemische Information mbH. Landsberger Straße 408/V D-81241. München. Germany.

[3] Villorbina, G.; Tomàs, A.; Escribà, M.; Oromí-Farrús, M.; Eras J., Balcells, M.; Canela,R. *Tetrahedron Lett.* **2009**, *50*, 2828–2830.

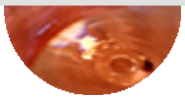


1,3-Dichloro-2-propyl 2-chlorobenzoate (**3g**): ^{1}H NMR ($CDCl_3$), δ: 7.83 (m, 1H, C*H*$_{ar}$-C=O), 7.40 (m, 2H, C*H*$_{ar}$), 7.28 (m, 1H, C*H*$_{ar}$-Cl), 5.38 (quin, *J*=5.3 Hz, 1H, O-C*H*), 3.83 (d, *J*=5.0 Hz, 4H, 2 C*H*$_2$-Cl). ^{13}C RMN ($CDCl_3$), δ: 164.5 (*C*=O), 134.4 (*C*$_{ar}$-Cl), 133.4, 131.9, 131.5, 129.1, 126.9 (*C*$_{ar}$), 72.9 (O-*C*H), 42.5 (*C*H$_2$-Cl). GC-MS, *m/z*: 266 $[M]^+$, 156 $[M\text{-}C_3H_5Cl_2]^+$; 139 $[M\text{-}OC_3H_5Cl_2]^+$; 111 $[M\text{-}CO_2C_3H_5Cl_2]^+$. IR (KBr), ν max.: 3072, 3030, 2968, 1736, 1591, 1436, 1287, 1246, 1115, 1051, 747, 689 cm^{-1}. HRMS (ES+) calculated for $C_{10}H_9Cl_3O_2Na$ adduct: 288.9566, found: 288.9575. Elem. Anal. calculated for $C_{10}H_9Cl_3O_2$: C, 44.89; H, 3.39; Cl, 39.75; O, 11.96. Found: C, 45.04; H 3.40; Cl, 40.86; O, 10.70.[3]

1,3-Dichloro-2-propyl salicylate (**3h**) [CAS: 64496-72-6]: ^{1}H NMR ($CDCl_3$), δ: 7.89 (dd, J_1=8.2 Hz, J_2=1.6 Hz, 1H, C*H*$_{ar}$), 7.49 (m, 1H, C*H*$_{ar}$), 7.01 (dd, J_1=8.6 Hz, J_2=0.8 Hz,1H, C*H*$_{ar}$), 6.92 (m, 1H, C*H*$_{ar}$), 5.46 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.89 (d, *J*=5.1 Hz, 4H, 2 C*H*$_2$-Cl). ^{13}C RMN ($CDCl_3$), δ: 169.1 (*C*=O), 162.1 (*C*$_{ar}$-OH), 136.7, 130.3, 119.7, 117.9, 111.8 (*C*$_{ar}$), 72.7 (O-*C*H), 42.5 (*C*H$_2$-Cl). GC-MS, *m/z*: 248 $[M]^+$, 137 $[M\text{-}C_3H_5Cl_2]^+$; 120 $[M\text{-}HOC_3H_5Cl_2]^+$; 93 $[M\text{-}HCO_2C_3H_5Cl_2]^+$. IR (ATR), ν max.: 3248, 3079, 2962, 1677 1613, 1484, 1289, 1156, 1085, 755, 698 cm^{-1}. m.p.:44.3-44.7 ºC. [3]

1,3-Dichloro-2-propyl *m*-nitrobenzoate (**3i**) [CAS: 68081-66-3]: ^{1}H NMR ($CDCl_3$), δ: 8.81 (t, *J*=2.0 Hz, 1H, C*H*$_{ar}$), 8.37 (m, 2H, C*H*$_{ar}$), 7.64 (t, *J*=8.2 Hz, 1H, C*H*$_{ar}$), 5.43 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.85 (d, *J*=5.1 Hz, 4H, 2 C*H*$_2$-Cl). ^{13}C RMN ($CDCl_3$), δ: 163.8 (*C*=O), 151.1 (*C*$_{ar}$-NO_2), 134.7 (*C*$_{ar}$-C=O), 130, 129.8, 122.7 (*C*H$_{ar}$), 73.3 (O-*C*H), 42.5 (*C*H$_2$-Cl). GC-MS, *m/z*: 278 $[M]^+$, 231 $[M\text{-}NO_2]^+$; 150 $[M\text{-}OC_3H_5Cl_2]^+$; 122 $[M\text{-}CO_2C_3H_5Cl_2]^+$; 104 $[M\text{-}NO_2OC_3H_5Cl_2]^+$; 76 $[M\text{-}NO_2CO_2C_3H_5Cl_2]^+$. IR (ATR), ν max.: 3111, 2966, 1726, 1525, 1343, 1262, 1100, 1014, 872, 716, 670 cm^{-1}. Elem. Anal. calculated for $C_{10}H_9Cl_2NO_4$: C, 43.19; H, 3.26; Cl, 25.50; N, 5.04; O, 23.01. Found: C, 43.48; H, 3.28; Cl, 24.50; N, 5.08; O, 23.66. m.p.: 56.5-56.7 ºC.

1,3-Dichloro-2-propyl 3,5-dinitrobenzoate (**3j**): ^{1}H NMR ($COCD_6$), δ: 9.21 (t, *J*=2.3 Hz 1H, C*H*$_{ar}$), 9.13 (d, *J*=2.4 Hz, 2H, C*H*$_{ar}$), 5.67 (quin, *J*=5.1 Hz, 1H, O-C*H*), 4.12 (d, *J*=4.9 Hz, 4H, C*H*$_2$-Cl). ^{13}C RMN ($COCD_6$), δ: 164.4 (*C*=O), 149.1 (*C*$_{ar}$-NO_2), 134.3 (*C*$_{ar}$-C=O), 128, 122.8 (*C*H$_{ar}$), 76.3 (O-*C*H), 43.5 (*C*H$_2$-Cl). GC-MS, *m/z*: 323 $[M]^+$, 275 $[M\text{-}NO_2]^+$; 229 $[M\text{-}2NO_2]^+$; 252 $[M\text{-}2Cl]^+$; 195 $[M\text{-}OC_3H_5Cl_2]^+$. IR (KBr), ν max.: 3099, 2963, 2884, 1735, 1544, 1346, 1275, 1165, 720 cm^{-1}. Elem. Anal. calculated for $C_{10}H_8Cl_2N_2O_6$: C, 37.17; H, 2.50; Cl, 21.95; N, 8.67; O, 29.71. Found: C, 37.23; H, 2.51; Cl, 21.82; N, 8.61; O, 29.83. m.p.: 131.6-131.8 ºC. [3]

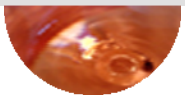


1,3-Dichloro-2-propyl 2,4-dinitrobenzoate (**3k**): ^{1}H NMR ($CDCl_3$), δ: 8.87 (d, *J*=2.0 Hz, 1H, C*H*$_{ar}$), 8.58 (dd, *J*=8.2, *J*=2.0 Hz, 1H, C*H*$_{ar}$), 7.96 (d, *J*=8.2 Hz, 1H, C*H*$_{ar}$), 5.50 (quin, *J*=5.1 Hz, 1H, O-*CH*), 3.88 (d, *J*=4.7 Hz, 4H, C*H*$_2$-Cl). ^{13}C RMN ($CDCl_3$), δ: 163.2 (*C*=O), 149.8, 147.9 (*C*$_{ar}$-NO_2), 132.7 (*C*$_{ar}$-C=O), 131.6, 129.1, 120.2 (*C*H$_{ar}$), 74.3 (O-*C*H), 42.1 (*C*H$_2$-Cl). GC-MS, *m/z*: 323 $[M]^+$, 275 $[M\text{-}NO_2]^+$; 230 $[M\text{-}2NO_2]^+$; 252 $[M\text{-}2Cl]^+$; 195 $[M\text{-}OC_3H_5Cl_2]^+$. IR (KBr), ν max.: 3107, 3058, 2960, 2885, 1743, 1541, 1349, 1283, 1110, 834 cm^{-1}. Elem. Anal. calculated for $C_{10}H_8Cl_2N_2O_6$: C, 37.17; H, 2.50; Cl, 21.95; N, 8.67; O, 29.71. Found: C, 37.67; H, 2.50; Cl, 21.90; N, 8.57; O, 29.36.

1,3-Dichloro-2-propyl 1-naphthoate (**3l**): ^{1}H NMR ($CDCl_3$), δ: 8.93 (dd, J_1=8.8 Hz, J_2=0.8 Hz, 1H, C*H*$_{ar}$), 8.28 (dd, J_1=7.6 Hz, J_2=1.6 Hz, 1H, C*H*$_{ar}$), 8.07 (d, *J*=8.4 Hz, 1H, C*H*$_{ar}$), 7.91 (d, *J*=7.6 Hz, 1H, C*H*$_{ar}$), 7.65 (m, 1H, C*H*$_{ar}$), 7.54 (m, 2H, 2 C*H*$_{ar}$), 5.54 (quin, *J*=4.8 Hz, 1H, O-C*H*), 3.96 (d, *J*=4.8 Hz, 4H, 2 C*H*$_2$-Cl). ^{13}C RMN ($CDCl_3$), δ: 166.3 (*C*=O), 134.4, 134.1, 131.6, 131.2, 128.9, 128.4, 126.6, 125.9, 125.8, 124.8 (*C*H$_{ar}$), 72.4 (O-*C*H), 42.8 (*C*H$_2$-Cl). GC-MS, *m/z*: 282 $[M]^+$, 212 $[M\text{-}Cl_2]^+$; 172 $[M\text{-}C_3H_5Cl_2]^+$; 155 $[M\text{-}OC_3H_5Cl_2]^+$; 127 $[M\text{-}CO_2C_3H_5Cl_2]^+$. IR (ATR), ν max.: 3051, 2964, 1716, 1509, 1236, 1191, 1126, 1036, 776, 752, 655 cm^{-1}. m.p.: 65.4-65.8 ºC. HRMS (EI+) calculated for $C_{14}H_{12}Cl_2O_2$: 282.0214, found: 282.0208. Elem. Anal. calculated for $C_{14}H_{12}Cl_2O_2$: C, 59.39; H, 4.27; Cl, 25.04; O, 11.30. Found: C, 59.41; H, 4.28; Cl, 24.93; O, 11.38. [3]

1,3-Dichloro-2-propyl 2-naphthoate (**3m**): ^{1}H NMR ($CDCl_3$), δ: 8.58 (s, 1H, C*H*$_{ar}$), 8.01 (dd, J_1=8.8 Hz, J_2=1.6 Hz, 1H, C*H*$_{ar}$), 7.92 (d, *J*=8.4 Hz, 1H, C*H*$_{ar}$), 7.84 (d, *J*=8.8 Hz, 1H, C*H*$_{ar}$), 7.83 (d, *J*=8 Hz, 1H, C*H*$_{ar}$), 7.53 (m, 2H, 2 C*H*$_{ar}$), 5.44 (quin, *J*=4.8 Hz, 1H, O-C*H*), 3.88 (d, *J*=4.8 Hz, 4H, 2 C*H*$_2$-Cl). ^{13}C RMN ($CDCl_3$), δ: 165.8 (*C*=O), 136.0, 132.7, 131.9, 129.7, 128.9, 128.6, 128.0, 127.1, 126.6, 125.4 (*C*H$_{ar}$), 72.4 (O-*C*H), 42.7 (*C*H$_2$-Cl). GC-MS, *m/z*: 282 $[M]^+$, 212 $[M\text{-}Cl_2]^+$; 172 $[M\text{-}C_3H_5Cl_2]^+$; 155 $[M\text{-}OC_3H_5Cl_2]^+$; 127 $[M\text{-}CO_2C_3H_5Cl_2]^+$. IR (ATR), ν max.: 3061, 2968, 1717, 1630, 1276, 1192, 1088, 775, 760, 703 cm^{-1}. m.p.: 62.5-65.9 ºC. HRMS (EI+) calculated for $C_{14}H_{12}Cl_2O_2$: 282.0219, found: 282.0208. Elem. Anal. calculated for $C_{14}H_{12}Cl_2O_2$: C, 59.39; H, 4.27; Cl, 25.04; O, 11.30. Found: C, 59.38; H, 4.29; Cl, 24.83; O, 11.50. [3]

1,3-Dichloro-2-propyl 2-furoate (**3n**): ^{1}H NMR ($CDCl_3$), δ: 7.57 (m, C*H*$_{ar}$), 7.21 (dt, J_1=3.5 Hz, J_2=0.8 Hz, 1H, C*H*$_{ar}$), 6.48 (m, 1H, C*H*$_{ar}$), 5.33 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.80 (d, *J*=5.1 Hz, 4H, C*H*$_2$-Cl). ^{13}C RMN ($CDCl_3$), δ: 156.9 (*C*=O), 146.5 (*C*H$_{ar}$), 143.7 (*C*$_{ar}$-C=O), 119.8, 112.1 (*C*H$_{ar}$), 72.3 (O-*C*H), 43.1 (*C*H$_2$-Cl). GC-MS, *m/z*: 222 $[M]^+$, 187 $[M\text{-}Cl]^+$; 112 $[M\text{-}C_3H_5Cl_2]^+$; 95 $[M\text{-}OC_3H_5Cl_2]^+$. IR (ATR), ν max.: 3180, 3175, 2960, 1705, 1410, 1261, 1122, 1045, 750, 660 cm^{-1}. HRMS (EI+) calculated for $C_8H_8Cl_2O_3$: 221.9850, found: 221.9840. [3]



1,3-Dichloro-2-propyl 2-thiophencarboxylate (3o): ^{1}H NMR ($CDCl_3$), δ: 7.79 (dd, , J_1=3.9 Hz, J_2=1.2 Hz, 1H, CH_{ar}), 7.61 (dd, J_1=5.1 Hz, J_2=1.2 Hz, 1H, CH_{ar}), 7.05 (dd, J_1=5.1 Hz, J_2=3.9 Hz, 1H, CH_{ar}), 5.31 (quin, J=5.1 Hz, 1H, O-C*H*), 3.79 (d, J=5.1 Hz, 4H, CH_2-Cl). ^{13}C RMN ($CDCl_3$), δ: 161.1 (*C*=O), 144.8 (*C*H$_{ar}$), 143.8 (*C*$_{ar}$-C=O), 122.5, 118.1 (*C*H$_{ar}$), 72.2 (O-*C*H), 42.8 (*C*H$_2$-Cl). GC-MS, *m/z*: 238 $[M]^+$, 202 $[M\text{-}Cl]^+$; 128 $[M\text{-}C_3H_5Cl_2]^+$; 111 $[M\text{-}OC_3H_5Cl_2]^+$. IR (ATR), ν max.: 3170, 2988, 1710, 1430, 1251, 1152, 1145, 760, 640 cm^{-1}. HRMS (EI+) calculated for $C_8H_8Cl_2O_2S$: 237.9622, found: 237.9611. [3]

1,3-Dichloro-2-propyl palmitate (3a) and 2,3-dichloro-1-propyl palmitate (4a). ***3a*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.18 (quin, J=5.2 Hz, 1H, O-C*H*) . All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 4.45 (m, 2H, O-CH_2), *4.18(m.* 1H, C*H*-Cl), 3.75 (m, 2H, CH_2-Cl), 2.37 (t, J=7 Hz, 2H, C$H_{2\,(\alpha)}$ (C=O)), 1.65 (m, 2H, C$H_{2\,(\beta)}$ (C=O)), 1.26 (m, 24H, CH_2), 0.88 (t, J=7 Hz, 3H, CH_3).

1,3-Dichloro-2-propyl caprylate (3b) and 2,3-dichloro-1-propyl caprylate (4b). ***3b*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.12 (quin, J=5.2 Hz, 1H, O-C*H*), 3.80 (dd, J_1=5.7 Hz, J_2=2.2 Hz, 4H, 2 CH_2-Cl),. All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 4.40 (m, 2H, O-CH_2), *4,25 (m,* 1H, C*H*-Cl), 3.75 (m, 2H, CH_2-Cl), 2.37 (t, J=7 Hz, 2H, C$H_{2\,(\alpha)}$ (C=O)), 1.65 (m, 2H, C$H_{2\,(\beta)}$ (C=O)), 1.26 (m, 24H, CH_2), 0.88 (t, J=7 Hz, 3H, CH_3).

1,3-Dichloro-2-propyl pivaloate (3c) and 2,3-dichloro-1-propyl pivaloate (3c). ***3c*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.14 (quin, J=5.2 Hz, 1H, O-C*H*), 3.76 (m, 4H, 2 CH_2-Cl). All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 4.38 (m, 2H, O-CH_2), *4.230 (m,* 1H, C*H*-Cl), 3.66 (m, 2H, CH_2-Cl), 2.37 (t, J=7 Hz, 2H, C$H_{2\,(\alpha)}$ (C=O)), 1.65 (m, 2H, C$H_{2\,(\beta)}$ (C=O)), 1.26 (m, 24H, CH_2), 0.88 (t, J=7 Hz, 3H, CH_3).

1,3-Dichloro-2-propyl linolenate (3d) and 2,3-dichloro-1-propyl linolenate (3d). ***3d*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.18 (quin, J=5.4 Hz, 1H, O-C*H*). All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.39 (m, 6H, C*H*=C*H*), 4.42 (m, 2H, O-CH_2), *4.21 (m,* 1H, C*H*-Cl), 3.70 (m, 2H, CH_2-Cl), 2.36 (t, J=7.4 Hz, 4H, C=C-CH_2-C=C-CH_2-C=C), 2.00 (q, J=6.2 Hz, 2H, C$H_{2\,(\alpha)}$ (C=O)), 1.66 (m, 4H, 2 CH$_3$-*C*H_2-CH=C), 1.50 (m, 2H, C$H_{2\,(\square)}$ (C=O)), 1.29 (m, 8H, CH_2), 0.87 (t, J=6.6 Hz, 3H, CH_3).

1,3-Dichloro-2-propyl benzoate (3e) and 2,3-dichloro-1-propyl benzoate (4e). ***3e*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.36 (quin, *J*=5.3 Hz, 1H, O-C*H*). All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 8.00 (m, 1H, C$H_{ar\ (\alpha)}$ (C=O)), 7.53 (m, 1H, CH_{ar}), 7.39 (m, 2H, CH_{ar}), 4.58 (m, 2H, O-CH_2), *4.35 (m,* 1H, C*H*-Cl), 3.82 (m, 2H, CH_2-Cl).

1,3-Dichloro-2-propyl cinnamate (3f) and 2,3-dichloro-1-propyl cinnamate (4f). ***3f*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.26 (quin, *J*=5.2 Hz, 1H, O-C*H*), 3.81 (dd, J_1=5.2 Hz , J_2=0.8 Hz, 4H, 2 CH_2-Cl). All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), 7.71 (d, *J*=16 Hz, 1H, CH_{ar}), 7.48 (t, *J*=3.5 Hz, 2H, 2 CH_{ar}), 7.34 (m, 3H, 2 CH_{ar}), 6.45 (dd, J_1=15.8 Hz, J_2=0.9 Hz, 2H, Ph-C*H*=C*H*), 4.47 (m, 2H, O-CH_2), *4.31(m,* 1H, C*H*-Cl), 3.65 (d, J_1=5.1 Hz, 2H, CH_2-Cl).

1,3-Dichloro-2-propyl 2-chlorobenzoate (3g) and 2,3-dichloro-1-propyl 2-chlorobenzoate (4g). ***3g*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.38 (quin, *J*=5.3 Hz, 1H, O-C*H*). All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 7.83 (m, 1H, CH_{ar}-C=O), 7.40 (m, 2H, CH_{ar}), 7.28 (m, 1H, CH_{ar}-Cl), 4.60 (m, 2H, O-CH_2, *4.35 (m,* 1H, C*H*-Cl), 3.81 (m, 2H, CH_2-Cl).

1,3-Dichloro-2-propyl salicylate (3h) and 2,3-dichloro-1-propyl salicylate (4h). ***3h*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.46 (quin, *J*=5.1 Hz, 1H, O-C*H*). All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 7.89 (dd, J_1=8.2 Hz, J_2=1.6 Hz, 1H, CH_{ar}), 7.49 (m, 1H, CH_{ar}), 7.01 (dd, J_1=8.6 Hz, J_2=0.8 Hz,1H, CH_{ar}), 6.92 (m, 1H, CH_{ar}), 4.55 (m, 2H, O-CH_2, 1H, C*H*-Cl), 3.91 (m, 2H, CH_2-Cl).

1,3-Dichloro-2-propyl *m*-nitrobenzoate (3i) and 2,3-dichloro-1-propyl *m*-nitrobenzoate (4i). ***3i*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.48 (quin, *J*=5.1 Hz, 1H, O-C*H*). All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 8.81 (t, *J*=2.0 Hz, 1H, CH_{ar}), 8.37 (m, 2H, CH_{ar}), 7.64 (t, *J*=8.2 Hz, 1H, CH_{ar}), 4.71 (m, 2H, O-CH_2), 4.39 (m, 1H, C*H*-Cl), 3.95 (m, 2H, CH_2-Cl).

1,3-Dichloro-2-propyl 3,5-dinitrobenzoate (3j) and 2,3-dichloro-1-propyl 3,5-dinitrobenzoate (4j). ***3j*** *Regioisomer*: ^{1}H NMR ($COCD_6$), δ: 9.21 (t, *J*=2.3 Hz 1H, CH_{ar}), 9.13 (d, *J*=2.4 Hz, 2H, CH_{ar}), 5.67 (quin, *J*=5.1 Hz, 1H, O-C*H*), 4.12 (d, *J*=4.9 Hz, 4H, CH_2-Cl). **4a** *Regioisomer*: All other NMR signals are hidden by the signals of the **3** regioisomer. ^{1}H NMR ($CDCl_3$), δ: 4.65 (m, 2H, O-CH_2) *4,43 (m,* 1H, C*H*-Cl).

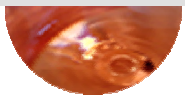
1,3-Dichloro-2-propyl 2,4-dinitrobenzoate (3k) and 2,3-dichloro-1-propyl 2,4-dinitrobenzoate (4k). ***3k*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 8.87 (d, *J*=2.0 Hz, 1H, C*H*$_{ar}$), 8.58 (dd, *J*=8.2, *J*=2.0 Hz, 1H, C*H*$_{ar}$), 7.96 (d, *J*=8.2 Hz, 1H, C*H*$_{ar}$), 5.50 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.88 (d, *J*=4.7 Hz, 4H, CH_2-Cl). **4a** *Regioisomer*: All other NMR signals are hidden by the signals of the **3** regioisomer. ^{1}H NMR ($CDCl_3$), δ: 4.67 (m, 2H, O-CH_2), 4.45 (m 1H, C*H*-Cl).

1,3-Dichloro-2-propyl 1-naphthoate (3l) and 2,3-dichloro-1-propyl 1-naphthoate (4l). ***3l*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.54 (quin, *J*=4.8 Hz, 1H, O-C*H*), 3.96 (d, *J*=4.8 Hz, 4H, 2 CH_2-Cl). All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 8.93 (dd, J_1=8.8 Hz, J_2=0.8 Hz, 1H, C*H*$_{ar}$), 8.28 (dd, J_1=7.6 Hz, J_2=1.6 Hz, 1H, C*H*$_{ar}$), 8.07 (d, *J*=8.4 Hz, 1H, C*H*$_{ar}$), 7.91 (d, *J*=7.6 Hz, 1H, C*H*$_{ar}$), 7.65 (m, 1H, C*H*$_{ar}$), 7.54 (m, 2H, 2 C*H*$_{ar}$), 4.62 (m, 2H, O-CH_2), 4.40 (m, 1H, C*H*-Cl), 3.81 (d, *J*=4.9 Hz, 2H, CH_2-Cl).

1,3-Dichloro-2-propyl 2-naphthoate (3m) and 2,3-dichloro-1-propyl 2-naphthoate (4m). ***3m*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.44 (quin, *J*=4.8 Hz, 1H, O-C*H*), 3.88 (d, *J*=4.8 Hz, 4H, 2 CH_2-Cl). All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 8.58 (s, 1H, C*H*$_{ar}$), 8.01 (dd, J_1=8.8 Hz, J_2=1.6 Hz, 1H, C*H*$_{ar}$), 7.92 (d, *J*=8.4 Hz, 1H, C*H*$_{ar}$), 7.84 (d, *J*=8.8 Hz, 1H, C*H*$_{ar}$), 7.83 (d, *J*=8 Hz, 1H, C*H*$_{ar}$), 7.53 (m, 2H, 2 C*H*$_{ar}$), 4.65 (m, 2H, O-CH_2), 4.38 (m, 1H, C*H*-Cl), 3.76 (d, *J*=4.9 Hz, 2H, CH_2-Cl).

1,3-Dichloro-2-propyl 2-furoate (3n) and 2,3-dichloro-1-propyl 2-furoate (4n). ***3n*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.41 (quin, *J*=5.1 Hz, 1H, O-C*H*), 3.90 (d, *J*=5.1 Hz, 4H, CH_2-Cl). All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 7.57 (m, C*H*$_{ar}$), 7.21 (dt, J_1=3.5 Hz, J_2=0.8 Hz, 1H, C*H*$_{ar}$), 6.48 (m, 1H, C*H*$_{ar}$), 4.62 (m, 2H, O-CH_2) 4.38 (m, 1H, C*H*-Cl), 3.80 (d, *J*=5.3 Hz, 2H, CH_2-Cl).

1,3-Dichloro-2-propyl 2-thiophencarboxylate (3o) and 2,3-dichloro-1-propyl 2-thiophencarboxylate (4o). ***3o*** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 5.31 (quin, *J*=5.1 Hz, 1H, O-C*H*). All other NMR signals are hidden by the signals of the **4** regioisomer. **4a** *Regioisomer*: ^{1}H NMR ($CDCl_3$), δ: 7.79 (dd, , J_1=3.9 Hz, J_2=1.2 Hz, 1H, C*H*$_{ar}$), 7.61 (dd, J_1=5.1 Hz, J_2=1.2 Hz, 1H, C*H*$_{ar}$), 7.05 (dd, J_1=5.1 Hz, J_2=3.9 Hz, 1H, C*H*$_{ar}$), 4.62 (m, 2H, O-CH_2) 4.38 (m, 1H, C*H*-Cl), 3.79 (m, 2H, CH_2-Cl).



Moving toward desymmetrization of a glycerol derivative

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SUPPORTING INFORMATION

Instrumental data.

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 $CDCl_3$ or at 2.21 ppm of $COCD_6$ for ^{1}H NMR and centre line of a triplet at 77.00 ppm and at 29.8 ppm of $COCD_6$ for ^{13}C NMR: The following abbreviations are used; s: singlet, d: doublet, t: triplet, q: quartet, quin: quintet, m: multiplet.

GC-MS were performed in an GC equipped with a DB5-MS column (J&W) (30m x 0.25 μm x 0.25 mm) coupled to an MS detector and He as carrier gas. The following chromatographic conditions were used: constant flow 2mL/min, split injection ratio 20:1 at 280 ºC. 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 final temperature of 260 ºC for 15 min.

IR spectra were recorded on a FTIR spectrophotometer in the range 4000-600 cm^{-1}. KBr pellets or with diamond HATR were required as specified. Spectra are reported in reciprocal centimeters (cm^{-1}).

High resolution mass spectral (HRMS) data were obtained by direct infusion on LC-TOF-MS ESI or APCI as specified.

Materials and Methods.

Silica gel H60 was purchased from Merck and used as received.

Initial 1,3-Dichloro-2-propyl pivalate synthesis. (1)

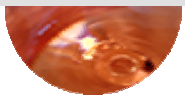
This compound was prepared according to the method of Escriba, et al. (Escriba, M.; Eras, J.; Duran, M.; Simon, S.; Butchosa, C.; Villorbina, G.; Balcells, M.; Canela, R. Tetrahedron 2009, 65 (50), 10370-10376.)

1-chloro-3-iodo-2-propyl pivalate synthesis. (2)

A solution of 1,3-dichloro-2-propyl pivalate (212mg, 1 mmol), dried sodium iodide (101ºC, 600mg, 4 mmol) and in dried butanone (3Å molecular sieves, 3 mL) was heated for different times, according to table 1 in main text, at 115 ºC in a reaction vial fitted with a PTFE-lined cap. After cooling, n-pentane was added, and the mixture was washed three times with water. The organic layer was dried over anhydrous $MgSO_4$. The final product was distilled under vacuum (75ºC under 0.3mmHg).

3-chloro-2-hydroxy-1-propyl pivalate synthesis. (4)

This compound was prepared according to the method of Solarte, et al. (Solarte, C.; Escribà, M.; Eras, J.; Villorbina, G.; Canela, R.; Balcells, M. *Organic Letters* 2010, *(sent)*)



2-hydroxy-3-(1*H*-imidazol-1-yl)-1-propyl pivalate synthesis. (5)

A solution of 3-chloro-2-hydroxy-1-propyl pivalate (194mg, 1 mmol), dried imidazole (vacuum, 109mg, 1.6 mmol), dried sodium iodide (101ºC, 30mg, 0.2 mmol), and in dried 1-propanol (Mg metallic, 2.25 mL) was heated 48H at 115ºC in a reaction vial fitted with a PTFE-lined cap. After cooling, 1-propanol was distilled under soft vacuum (70ºC under 100mmHg) and crude product that was purified by silica H-60 column chromatography using 6:4 ethyl acetate:acetone as eluant to 74% final yield.

1-chloro-3-(1*H*-imidazol-1-yl)-2-propyl pivalate synthesis. (6)

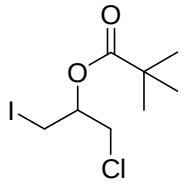
A solution of 1,3-dichloro-2-propyl pivalate (212mg, 1 mmol), dried imidazole (vacuum, 82mg, 2.4 mmol), and in dried 1-propanol (Mg metallic, 2.25 mL) was heated 48H at 110 ºC in a reaction vial fitted with a PTFE-lined cap. After cooling, 1-propanol was distilled under soft vacuum (70ºC under 100mmHg) and crude product that was purified by silica H-60 column chromatography using ethyl acetate as eluant to 70% final yield.

Analytical data.

1,3-Dichloro-2-propyl pivalate (1). [CAS: 220499-01-4]

The analytical and spectroscopic data are in accordance with the literature. (Mormann, W.; Demeter, J.; Wagner, T. Acta Polym. 1999, 50, 20–27)

1-chloro-3-iodo-2-propyl pivalate (2).



^{1}H NMR ($CDCl_3$) δ: 4.85 (quin, J_1=10.55 Hz, J_2=5.47 Hz, 1H, O-C*H*), 3.70 (m, 2H, 2 CH_2-Cl), 3.40 (m, 2H, 2 CH_2-I), 1.24 (s, 9H, 3CH_3).
^{13}C-RMN ($CDCl_3$), δ: 174 (*C*=O), 67.5 (O-*C*H), 41 (*C*H_2-Cl), 35 (*C*-(CH_3)$_3$), 23.3 (3*C*H_3), 0.2 (*C*H_2-I).
GC-MS m/z: 304 $[M]^+$; 202 $[M\text{-}C_5H_9O_2]^+$; 177 $[M\text{-}I]^+$; 141 $[CH_2I]^+$; 85 $[M\text{-}C_4H_9ClI]^+$; 57 $[M\text{-}C_6H_{13}ClI]^+$.

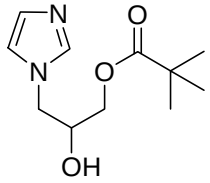
IR ATR ν max.: 2962, 1733, 1500, 1263, 1170, 1050, 804, 756, 685 cm^{-1}.

b.p.: (320±10.0 °C/1Atm).

3-chloro-2-hydroxy-1-propyl pivalate (4). [CAS: 52562-21-7]

The analytical and spectroscopic data are in accordance with the literature. (Solarte, C.; Escribà, M.; Eras, J.; Villorbina, G.; Canela, R.; Balcells, M. *Organic Letters* 2010, *(sent)*)

2-hydroxy-3-(1*H*-imidazol-1-yl)-1-propyl pivalate (5).



^{1}H NMR (C_3D_6O) δ: 9.42 (s, 1H, N=C*H*-N), 7.82 (d, 1H, J_1=3.71, C=C*H*-N), 7.22 (d, 1H, J_1=2.18 Hz, C=C*H*-N), 4.71(m, 1H, HO-C*H*), 4.38 (dd, 2H, J_1=4.96 Hz, J_2=13.23 Hz, O-CH_2), 4.04 (m, 2H, C-CH_2-N), 1.20 (s, 9H, 3CH_3).

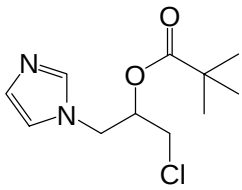
^{13}C-RMN (C_3D_6O), δ: 178 (*C*=O), 138 (N=*C*H-N), 134 (C=*C*H-N), 123 (C=*C*H-N), 73 (O-*C*H_2), 68.5 (*C*H-OH), 65.1 (*C*H_2-N), 39.2 (*C*-$(CH_3)_3$), 26.5 (3*C*H_3).

GC-MS m/z: 226 $[M]^+$; 211 $[M\text{-}CH_3]^+$; 141 $[M\text{-}C_5H_9O]^+$; 125 $[M\text{-}C_6H_9N_2O]^+$; 111 $[M\text{-}C_6H_{11}O_2]^+$; 85 $[M\text{-}C_6H_9N_2O_2]^+$; 57 $[M\text{-}C_7H_9N_2O_3]^+$.

IR KBr ν max.:3254, 3160, 2982, 1733, 1552, 1258, 1140 cm^{-1}.

HRMS (EI+) calculated for $C_{11}H_{18}O_3N_2$: 226.2761, found: 226.2432.

1-chloro-3-(1*H*-imidazol-1-yl)-2-propyl pivalate (6).



^{1}H NMR (C_3D_6O) δ: 7.52 (s, 1H, N=C*H*-N), 7.12 (s, 1H, C=C*H*-N), 6.92 (s, 1H, C=C*H*-N), 5.35 (quin, J_1=11.40 Hz, J_2=10.17 Hz, J_3=6.78 Hz, J_4=4.62 Hz, 1H, O-C*H*), 4.41 (m, 2H, CH_2-N), 3.76 (m, 2H, CH_2-Cl), 1.18 (s, 9H, 3CH_3).

^{13}C-RMN (C_3D_6O), δ: 176 (*C*=O), 138 (N=*C*H-N), 129 (C=*C*H-N), 119 (C=*C*H-N), 71.6 (O-*C*H), 47 (*C*H_2-N), 43 (*C*H_2-Cl), 39.2 (*C*-$(CH_3)_3$), 26.5 (3*C*H_3).

GC-MS m/z: 244 $[M]^+$, 229 $[M\text{-}CH_3]^+$; 209 $[M\text{-}Cl]^+$; 177 $[M\text{-}C_3H_3N_2]^+$; 107 $[M\text{-}C_4H_5N_2\text{-}C_4H_9]^+$; 143 $[M\text{-}C_6H_8N_2Cl]^+$; 81 $[M\text{-}C_7H_{12}ClO_2]^+$; 57 $[M\text{-}C_7H_8ClN_2O_2]^+$.

IR KBr ν max.: 3250, 2962, 1743, 1534, 1263, 1160, 1050, 844, 755, 680cm^{-1}.

HRMS (EI+) calculated for $C_{11}H_{17}ClN_2O_2$: 244.7217, found: 244.4061.