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ORIGINAL PAPER

Efficient Synthesis of α-Monoglycerides via Solventless Condensation of Fatty Acids with Glycerol Carbonate

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Abstract Highly pure α-monoglycerides (5a–e) were successfully prepared in high yields by the condensation of fatty acids such as lauric, myristic, palmitic, stearic and oleic (2a–e) with glycerol carbonate (4-hydroxymethyl-1,3-dioxolan-2-one) (1) in the presence of triethylamine as catalyst. Reaction conditions and spectroscopic identification of products will be presented in this article.

Keywords Monoglycerides · Glycerol carbonate · Fatty acids · Emulsifier

Introduction

Glycerol esters are the largest group of fatty acid partial esters of commercial significance. Due to the presence of specific hydrophilic and hydrophobic moieties in their structures, they act as important non-ionic surfactants of low HLB value, especially valuable as benign and environmentally friendly "water in oil" emulsifiers [1]. Glycerol monofatty esters (monoglycerides), are widely used in a variety of industries such as food and feed production [2], cosmetics [3], pharmaceutical formulations [4], topical drug delivery systems [5], oil well drilling [6], textile [7], packaging [8], plastic processing [9] and construction materials [10]. They act as emulsifiers, emollients, lubricants and dispersants.

Monoglycerides have traditionally been prepared by catalytic glycerolysis of fats and oil [11] or fatty acid methyl esters [12]. Direct esterification of glycerol with fatty acids in the presence of homogeneous or heterogeneous catalysts have also been carried out [13]. The main drawback of these processes is that a mixture of mono-, di- and triglycerides is obtained as products. To improve the selectivity of monoglyceride, alternative processes such as esterification of fatty acids with glycidol [14], and reaction of acetone protected glycerol (glycerol acetonide) with fatty acid ester [15] have been examined. Although utilization of glycidol yields the relevant pure monoglyceride, but glycidol, in addition to being an unstable precursor is a suspected human carcinogen and expensive to handle [16]. On the other hand, use of glycerol acetonide for monoglycerides production entails a tedious hydrolytic acetone removal process of the intermediate " ester-ketal ", making the process viability doubtful. Two- step lipase- assisted enzymatic esterification process of a number of fatty acids with glycerol in a molar ratio of 1:4 in acetone has been reported to yield the relevant monoglycerides [17]. Although the procedure is benign and environmentally friendly, the overall yield is 66.8% and the process suffers from difficulties related to enzyme deactivation and use of acetone as solvent.

In this article, we are pleased to report an efficient method for selective synthesis of industrially important highly pure α- monoglycerides 5a–e (Scheme 1) in excellent yields through condensation of glycerol carbonate with technically pure fatty acids in the presence of triethylamine as catalyst.

Experimental Procedures

Chemicals and Measurements

All chemicals and reagents including fatty acids (lauric, 99%, myristic, 98%, palmitic, 98%, stearic, 97%, and oleic,

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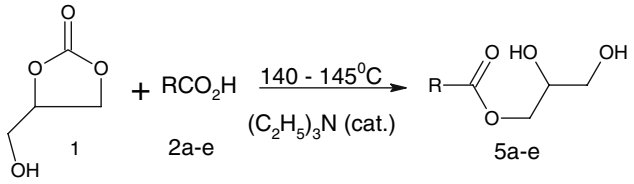


RCO_2H : Lauric, Myristic, Palmitic, Stearic, Oleic

Scheme 1 Reaction of fatty acids with glycerol carbonate in the presence of triethylamine catalyst

extra pure) were purchased from Merck and used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 AVANCE spectrometer. Mass spectra of the products were obtained on a Agilent Technology (HP), 5937 Mass Selective Detector, with Electron Impact (EI) 70 eV, and Quadrupole Analyzer.

Synthesis of Monoglycerides 5a–e: General Procedure

Fatty acid (2a–e) (0.100 mol) was placed in a 100 mL, three neck, round bottom flask, equipped with a thermometer, dropping funnel, mechanical stirrer (200 revolutions/min.) and a condenser connected to a gas bubbler. Temperature was then raised to 80 °C, and triethylamine (0.008 mol) was added. The temperature was raised again to 143–145 °C and glycerol carbonate (1) (95%, 0.107 mol) was added drop-wise within 1 h. The mixture was then kept at this temperature for an appropriate time (see Table 1). With the exception of glycerol monooleate, 100 mL of petroleum ether (55–70 °C) was added to the reaction mixture precooled to around 60 °C. The mixture was refluxed for 15–20 min and allowed to stand for 15 min at 40–45 °C without stirring. Then, the viscous liquid film was deposited at the bottom of the flask, it was very difficult to analyze, but was assumed to consist of polyglycerol derivatives. The upper petroleum ether layer was then separated by decantation. The monoglycerides 5a–d were obtained as white crystalline materials upon cooling the petroleum ether solutions. Pure products were obtained in high yields by recrystallization from petroleum ether (55–70 °C). In the case of monoglyceride 5e, the prepurification step was carried out in hexane and the decanted hexane solution was kept in a refrigerator for 24 h, due to its low melting point (see Table 1). The crystalline product was immediately filtered under reduced pressure. Acid numbers (see Table 1) were determined by titrating the pure monoglycerides dissolved in ethanol with a 0.01 M KOH solution. In the case of glycerol monooleate 5e, the iodine number was found to be 72.8.

Table 1 Reaction conditions and results obtained for monoglycerides 5a–e prepared from condensation of fatty acids 2a–e with glycerol carbonate 1 in the presence of triethylamine

Fatty acid	Time (h)	Temperature (°C)	MP (°C)	Acid number	Yield (%)
Lauric (1a)	8	143–145	63	1.4	91(3a)
Myristic (1b)	9	143–145	70	2.2	90(3b)
Palmitic (1c)	9.5	143–145	73	2	93(3c)
Stearic (1d)	10	143–145	77	0.74	90(3d)
Oleic (1e)	9.0	140	25	1.8	91.5(3e)

Glycerol Monolaurate 5a:

(25.0 g, 91%), White solid (from petroleum ether 55–70 °C), MP 63 °C. IR (KBr) υ_{max} 3400(OH), 2920(CH), 2850(CH), 1737(CO), 1459(CH_3). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J 6.9 Hz, 3H, CH_3), 1.29(m, 16H, 8CH_2), 1.65(m, 2H, CH_2), 2.17(m, 1H, OH), 2.37(t, J 7.5, 2H, CH_2CO), 2.61(s, 1H, OH), 3.62(m, 1H, CHOH), 3.72(m, 1H, CHOH), 3.96(m, 1H, CHOH), 4.17(dd, J 4.6, 11.6 Hz, 1H, CHOCO), 4.23(dd, J 4.6, 11.6 Hz, 1H, CHOCO). ^{13}C NMR ($CDCl_3$) δ 14.46(1C, CH_3), 23.05(1C, CH_2), 25.30(1C, CH_2), 2954-29.99(6C, 6CH_2), 32.29(1C, CH_2), 34.56(1C, CH_2CO), 63.82(1C, CH_2OH), 65.48(1C, CHOH), 70.68(1CH_2OCO), 174.75(1C, CO). MS calculated for $C_{15}H_{30}O_4^+$ = 274; found: 275.

Glycerol Monomyristate 5b:

(27.2 g, 90%), White solid (from petroleum ether 55–70), MP 70 °C. IR (KBr) υ_{max} 3400 (OH), 2914 (CH), 2852(CH), 1734(CO), 1454 (CH_3). ^{1}H NMR ($CDCl_3$) δ 0.90(t, J 7.1 Hz, 3H, CH_3), 1.29(m, 20H, 10 CH_2), 1.65(m, 2H, CH_2), 2.35(bs, 1H,OH), 2.37(t, J 7.5 Hz, 2H, CH_2CO), 2.70(bs, 1H,OH), 3.62(dd, J 5.9, 11.4 Hz, 1H, CHOH), 3.72(dd, J 5.9, 11.4 Hz, 1H, CHOH), 3.94(m, 1H, CHOH), 4.16 (dd, J 5.9, 11.7 Hz, 2H, CHOCO), 4.23(dd, J 5.9, 11.7 Hz,1H, CHOCO). ^{13}C NMR ($CDCl_3$) δ14.47(1C, CH_3), 23.08(1C, CH_2), 25.29(1C, CH_2), 29.56-30.08(8C, 8CH_2), 32.32(1C, CH_2), 34.55(1C, CH_2CO), 63.81(1C, CH_2OH), 65.44(1C, CHOH), 70.65(1C, CH_2OCO), 174.77 (1C, CO), MS calculated for $C_{17}H_{34}O_4^+$ = 302; found: 302.

Glycerol Monopalmitate 5c:

(30.7 g, 93%), White solid (from petroleum ether 55–70 °C), MP 73 °C. IR(KBr) υ_{max} 3350(OH), 2928(CH), 2852(CH),1739(CO),1470(CH_3). ^{1}H NMR ($CDCl_3$) δ 0.89(t, J 7.1 Hz, 3H, CH_3), 1.29(m, 24H, 12CH_2), 1.65(m, 2H, CH_2), 2.36(t, J 7.6 Hz, 2H, CH_2CO), 2.70(bs, 1H, OH), 3.20(bs, 1H, OH), 3.61(dd, J 5.9, 11.5 Hz, 1H, CHOH), 3.72(dd, J 5.9, 11.5 Hz, 1H, CHOH), 3.95(m, 1H, CHOH),

4.18(dd, J 5.5, 11.3 Hz, 1H, CHOCO), 4.20(dd, J 5.5, 11.3, 1H, CHOCO). ^{13}C NMR $CDCl_3$, δ 14.53(1C, CH_3), 23.11(1C, CH_2), 25.32(1C, CH_2), 29.56-30.11(10C, $10CH_2$), 32.34(1C, CH_2), 34.58(1C, CH_2CO), 63.79(1C, CH_2OH), 65.53(1C,CHOH), 70.69(1C, CH_2OCO), 174.81 (1C, CO), MS calculated for $C_{19}H_{38}O_4^+$ = 330; found: 331.

Glycerol Monostearate 5d:

(32.2 g, 90%), White solid (from normal hexane), MP 77 °C, IR (KBr) υ_{max} 3400(OH), 2928(CH), 2852(CH), 1735(CO), 1463(CH_3). ^{1}H NMR ($CDCl_3$) δ 0.90(t, J 7.1 Hz, 3H, CH_3), 1.29(m, 28H, $14CH_2$), 1.63(m, 2H, CH_2), 2.37(t, J 7.5 Hz, 2H, CH_2), 2.60(bs, 2H, OH), 3.61(dd, J 5.9, 11.4 Hz, 1H, CHOH), 3.70(dd, J 5.9, 11.4 Hz, 1H, CHOH), 3.95(m, 1H, CHOH), 4.16(dd, J 6.1, 11.7 Hz, 1H, CHOCO), 4.22(dd, J 6.1, 11.7 Hz, 1H, CHOCO). ^{13}C NMR ($CDCl_3$) δ 14.54(1C, CH_3), 23.11(1C, CH_2), 25.34(1C, CH_2), 29.56–30.12(12C, $12CH_2$), 32.35(1C, CH_2), 34.59(1C, CH_2CO), 63.77(1C, CH_2OH), 65.56(1C, CHOH), 70.69(1C, CH_2OCO), 174.81(1C, CO), MS calculated for $C_{21}H_{42}O_4^+$ = 358; found: 359.

Glycerolmonooleate 5e:

(32.5 g, 91.5%), Colorless liquid, MP 25 °C(from normal hexane), IR(neat) υ_{mav} 3402(OH), 2922(CH),2853(CH), 1739(CO), 1458(CH3). ^{1}H NMR ($CDCl_3$) δ0.91(t, J 7.0 Hz, 3H, CH_3), 1.28(m,22H, $11CH_2$), 1.65(m, 2H, CH_2), 2.05(m, 4H, 2 CH_2-C = C), 2.38(t, J 6.0 Hz, 2H, CH_2CO), 3.59(dd, J 5.5, 8.9 Hz,1H, CHOH), 3.68(dd, J 5.5, 8.9 Hz,1H, CHOH), 3.90(m,1H, CHOH), 4.16–4.18 (d, J 5.0 Hz, 2H, CH_2OCO). ^{13}C NMR ($CDCl_3$) δ14.50(1C, CH_3), 23.09(1C, CH_2), 25.30(1C, CH_2), 27.57(1C, CH_2), 27.63(1C, CH_2), 29.51–30.17(8C, $8CH_2$), 32.31(1C, CH_2), 34.56(1C, CH_2CO), 63.79(1C, CH_2OH), 65.44(1C, CHOH), 70.68(1C, CH_2OCO), 130.11(1C, 1C =), 130.44(1C, 1C=), 174.78(1C, CO), MS calculated for $C_{21}H_{40}O_4^+$ = 356; found: 357.

Results and Discussion

Various processes have been reported for the production of glycerol carbonate, such as the reaction of glycerol with phosgene [18], cyclization of 1,2-dihydroxypropyl carbamate [19], catalytic reaction of glycerol and CO_2 [20], transesterification of glycerol with ethylene carbonate [21] or dimethyl carbonate [22] and finally use of urea for the conversion of glycerol into its carbonate derivative [23]. Only the last two processes are technically and economically feasible for industrial and laboratory preparation. The urea process is particularly attractive because of its simplicity, use of readily available low-priced urea and low equipment costs. Therefore, glycerol carbonate was prepared by calcined zinc sulfate-catalyzed condensation of glycerol with urea [24] in 96% yield over 2 h. The ^{1}H-NMR (DMSO-d6) spectrum of the product was similar to that reported very recently [25]. Since it was decided that the experiments to be carried out with an equimolar amount of fatty acid with glycerol carbonate, it was found that partial excess of the latter had to be added in order to obtain optimized yields of monoglycerides. Compared to dimethyl carbonate, which yields 97% of glycerol carbonate in the reaction with glycerol in the ratio of 3/1 in the presence of potassium carbonate in 3 h [25], the formation of glycerol carbonate with an identical yield in 2 h starting with cheaper urea in equimolar amount with glycerol is an advantage.

Condensation of lauric acid 2a as the representative fatty acid with glycerol carbonate was examined in the presence of triethylamine as catalyst. The progress of reaction was followed by observing the liberation of carbon dioxide. By withdrawing reaction samples periodically and taking their IR spectra, the formation of the product was monitored by the disappearance of carbonyl peaks for fatty acid and glycerol carbonate at 1,700 and 1,785 cm^{-1} respectively, and the appearance of a carbonyl peak for the ester at 1737 cm^{-1}. The monoglyceride 5a was obtained as a white solid, which after recrystalization from petroleum ether (55–70 °C) afforded the pure product in 91% yield (see Table 1).

Based on the result obtained for glycerol monolaurate, the reactions of other fatty acids such as myristic, palmitic, stearic, and oleic 2b–e with glycerol carbonate were carried out in the presence of the same catalyst. The results are presented in Table 1.

Identification of 5a–e as the pure α-monoglycerides were carried out on the basis of their spectroscopic information. With the exception of glycerol monomyristate (5b), which showed the M^+ peak at 302, glycerol monolaurate (5a), glycerol monopalmitate (5c), glycerol monostearate (5d) and glycerol monooleate (5e) showed the molecular masses of 275, 331, 359 and 357 respectively, consistent with M + 1 ion peaks. It is known that the molecular ion abundance of alcohols decreases and is often not observable. Offsetting the parent ion peak, alcohols do undergo ion-molecule reactions to give a pressure-dependent (M + H) ion peak, which is useful for molecular weight determination [26]. It is worth mentioning that the mass of α-glycerol monolaurate previously prepared by Brunel and co-workers via catalytic condensation of lauric acid with glycidol has been reported as 257 [13].

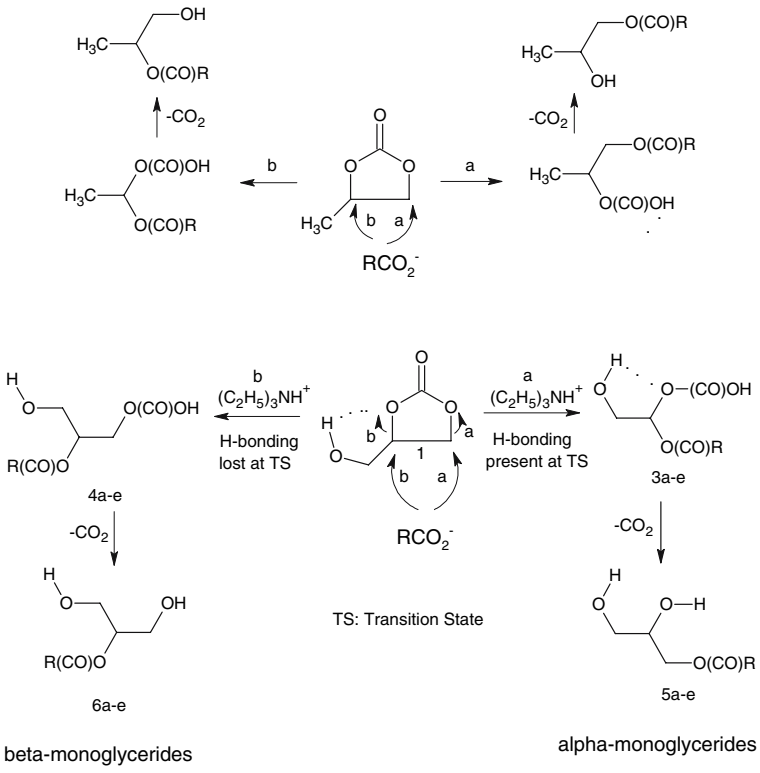
It should be remembered that β-glycerol monofatty acid esters can be easily identified on the basis of their ^{1}H and ^{13}C NMR due to the identical C1 and C3 protons and

carbons chemical shifts in their symmetric structures. On the other hand, we identified our products as α-monoglycerides both by comparison of their ^{1}H NMR with those prepared previously via other methods (vide infra) or from their ^{1}H and ^{13}C NMR spectra, which showed inequality of C1, C2 and C3 protons and carbons chemical shifts consistent with asymmetric structures. α-Glycerol monolaurate and monostearate were identified by comparison of their ^{1}H NMR spectra with those prepared previously [13, 14, 27]. The ^{1}H NMR spectra of α-glycerol monomyristate and α-glycerol monopalmitate exhibited the similar proton patterns of acyl and glycerol moieties in the ranges of 0.9–2.4 and 3.6–4.3 ppm respectively with appropriate intensity integrals. In the case of α-glycerol monooleate, the ester and glycerol part protons in ^{1}H NMR spectrum are similar to other monoglycerides containing saturated fatty acids except for olefinic and allylic protons, which appear at 5.36–5.38 and 2.03 ppm respectively. Details of spectroscopic analyses are presented in experimental procedures.

Based on the recent article of Clements on reactions of different nucleophiles with propylene carbonate [28], our proposed mechanism for reaction of fatty acids with glycerol carbonate is depicted in Scheme 2. Similar to propylene carbonate, the fatty acid salt might be expected to attack at the alkylene carbon (paths a or b), leading to a mixture of α (5a–e) and β-monoglycerides (6a–e). In contrast to the reaction of carboxylic acid salts with propylene carbonate, which yielded a mixture of two isomers [28], our reaction system afforded the α-monoglycerides (5a–e) as the sole products. As seen in Scheme 2, neither route a nor route b is preferred in the case of propylene carbonate. Therefore, one expects to obtain a mixture of two products whose ratio depends only on the different rates of nucleophile attack on primary and secondary carbons (routes a and b, respectively). On the other hand, the regiospecific formation of α-monoglycerides 5a–e as the sole products may not be surprising since similar nucleophile attacks on glycerol carbonate via route a is not only more favored with respect to route b due to reaction at primary alkylene carbon, but also maintains the internal hydrogen bonding through reactant, and transition state (TS). Therefore, a faster process (path a) is likely to be anticipated due to the lower activation energy of path a (see Scheme 2).

At the beginning of this study, it was not obvious whether or not we would obtain the intermediates 3a–e as primary products or the final products 5a–e (Scheme 2). Based on the mechanism presented in Scheme 2, the direct formation of the monoglycerides 5a–e under the reaction conditions is remarkable.

In summary, we have described an easy and benign solventless method for the synthesis of highly purified α-monoglycerides of lauric, myristic, palmitic, stearic and oleic acids. The simplicity of procedure as well as obtaining



Scheme 2 Reaction of carboxylic acid salt with propylene carbonate (top) and glycerol carbonate (bottom)

the products in high yields shows that our method is wothy of being scaled up for industrial applications.

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