Synthesis of Glycerol Monostearate with High Purity

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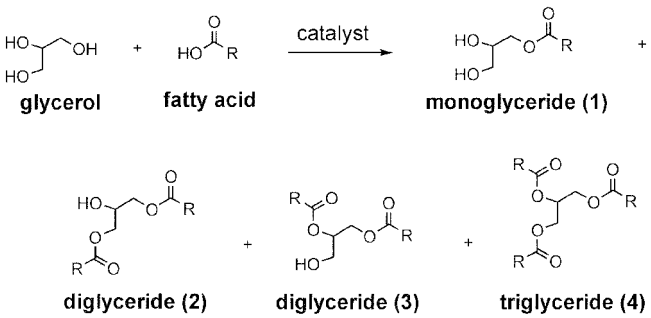
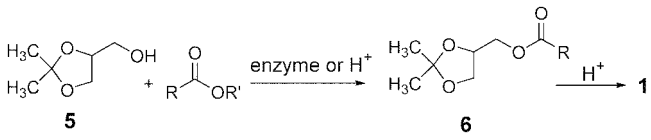
Glycerol monoesters synthesized from glycerol have many applications, such as emulsifying agents in food, pharmaceuticals, cosmetics, or in detergents.[1] Monoglycerides are generally obtained from the (i) glycerolysis or (ii) hydrolysis of triglycerides, or (iii) the direct esterification of glycerol with fatty acids.[2] The industrial processes involved generally use homogeneous acid or basic catalysts, which lead to a mixture of mono-, di-, and triglycerides in general (40 : 50 : 10) after direct esterification (Scheme 1).

Many different ways to improve the selectivity of the mono-esterification of glycerol have been attempted, including enzymatic methods,[3] guanidine,[4] solid acid catalysts, such as zeolites,[5] and basic catalysts, such as ZnO.[6] Since glycerol and fatty acids react spontaneously at 110 °C and the reaction is significant at higher temperatures, it is difficult to prevent the formation of the diglyceride (**2**, **3**) and triglyceride (**4**) completely during direct esterification at higher temperatures.[7]

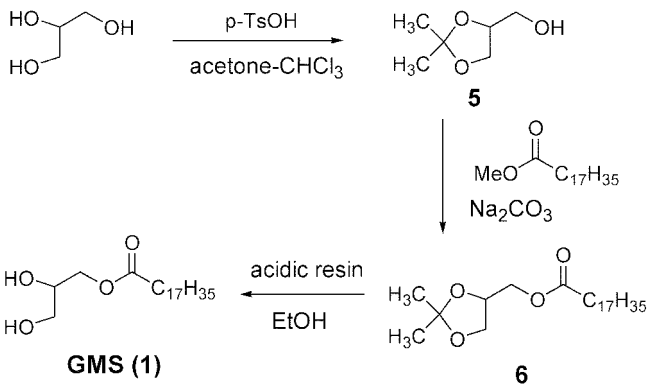
To overcome the subsequent acylation problem, several research groups employed protected glycerols. For example, using 1,2-*O*-isopropylidene glycerol (**5**)[8-12] instead of glycerol, highly pure GMS was synthesized, as shown in Scheme 2. Scheme 2 shows two different approaches using **5**; enzymatic and acid-catalyzed procedures. However, we found that the esterification of **5** with stearic acid in the presence of *p*-toluenesulfonic acid followed by acidic hydrolysis yielded less than 70% GMS (**1**) along with **2**-**4**, and several unidentified side products. The side products are thought to result



Scheme 1



Scheme 2



Scheme 3

from the instability of **6** in the presence of the acid.[6] Therefore, we studied the transesterification of **5** into **6** using a basic catalyst, followed by the efficient deprotection to obtain highly pure GMS (Scheme 3).

Experimental Section

Protection of glycerol with acetone. A mixture of acetone (36 g), $CHCl_3$ (156 g), glycerol (30 g) and *p*-toluenesulfonic acid (1.2 g) was refluxed for 6 h. Water formed during the reaction was removed continuously by Dean-Stark apparatus. After cooling the reaction mixture, Na_2CO_3 (1.3 g) was added and stirred for 30 min. The reaction mixture was vacuum distilled (10 mmHg) to obtain pure 1,2-*O*-isopropylidene glycerol (**5**). ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.42 (s, 3H), 3.60 (dd, 1H), 3.67 (dd, 1H), 3.80 (dd, 1H), 4.02 (dd, 1H), 4.22 (m, 1H). ^{13}C NMR (CDC_{l3}) δ 25.2, 26.6, 62.9, 65.6, 76.1, 109.3.

Transesterification. A mixture of methyl stearate (43 g, 0.15 mole) and 1,2-*O*-isopropylidene glycerol (**5**) (30 g, 0.23 mole) was stirred at 140 °C in the presence of Na_2CO_3 (0.5

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g) for 6 h. Methanol formed during the reaction was removed continuously by evaporation under atmosphere. After the reaction was completed, excess of 1,2-*O*-isopropylidene glycerol was recovered under vacuum (10 mmHg) and the residue was dissolved in ether, washed with water to remove Na_2CO_3 and concentrated to give 1,2-*O*-isopropylidene glycerol stearate (**6**) (56 g, 97%) which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 3H), 1.25 (s, 28H), 1.36 (s, 3H), 1.43 (s, 1H), 1.62 (m, 2H), 2.33 (t, J = 7.8 Hz, 2H), 3.72 (dd, J = 8.7, 6.4, 1H), 4.08 (m, 2H), 4.15 (dd, J = 11.5, 5.1 Hz, 2H), 4.32 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 24.9, 25.4, 26.7, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 29.7, 31.9, 34.1, 64.5, 66.3, 73.7.

Deprotection. Compound **6** (10 g) in ethanol (95%, 40 mL) was refluxed for 3 h in the presence of Amberlyst 15 (wet) ion-exchange resin (1.0 g). The reaction mixture was filtered and the filtrate was concentrated to give GMS (**1**) (8.8 g, 99% yield, 97% purity). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H), 1.24-1.28 (m, 28H), 1.62 (m, 2H), 2.34 (t, 3H), 3.59 (dd, 2H), 3.69 (dd, 2H), 3.92 (dd, 2H), 4.13 (dd, 2H), 4.19 (dd, 2H). ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 24.6, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7, 29.7, 31.9, 34.2, 63.3, 65.2, 70.3.

Analysis of GMS purities. Purity of GMS was analyzed by gel permeation chromatography (GPC) equipped with a RI detector (Younglin 750F, Korea) and styragel HR 0.5 column (Waters, 7.8 × 300 mm × 2). Using THF as eluent with 0.8 mL/min of flow rate, retention times for GMS, stearic acid, ethyl stearate and glycerol were 14.39, 14.99, 15.27 and 16.84 min respectively.

Results and Discussion

1,2-*O*-Isopropylidene glycerol is a well-known protected glycerol, which can be obtained by refluxing glycerol with excess (>20 eq) of acetone in the presence of an acid catalyst. On a large scale, however, the amount of acetone can be reduced drastically by using chloroform as a solvent, considering complete conversion, reactor capacity and the energy required to remove acetone. A mixture of glycerol, acetone, chloroform, and *p*-toluenesulfonic acid in a 1 : 1.2 : 5.2 : 0.04 ratio was refluxed.[9] During the reaction, the resulting water was removed continuously using the Dean-Stark apparatus. After neutralizing *p*-toluenesulfonic acid with Na_2CO_3, the reaction mixture was distilled to obtain pure 1,2-*O*-isopropylidene glycerol (94% yield).

For transesterification of **5** with methyl stearate, we used Na_2CO_3, a basic catalyst instead of the acidic catalyst in the reference[9] in order to prevent several side reactions. A mixture of methyl stearate and 1,2-*O*-isopropylidene glycerol (1.3 eq) was stirred at 140 °C in the presence of Na_2CO_3 (0.1 eq). During the reaction, the resulting methanol was removed continuously by evaporation. After the reaction was completed, excess 1,2-*O*-isopropylidene glycerol was recovered under vacuum (10 mmHg) and the resulting solid was dissolved in ether, washed with water to remove Na_2CO_3, and concentrated to give sufficiently pure 1,2-*O*-isopropylidene glycerol stearate (99% purity, containing less than 1% 1,2-*O*-isopropylidene glycerol, stearic acid, and its methyl ester) by GPC analysis. In this step, all the Na_2CO_3 must be removed, otherwise a large amount of acidic catalyst is needed in the subsequent deprotection step.

The most important step in the reaction employing protected glycerols is the cleavage of the protecting group. Various methods have been investigated, ranging from mild hydrolysis employing boric acid[7,14] to strong acidic conditions using concentrated HCl or trifluoroacetic acid.[10,15] However, in case of boric acid, a large amount of the acid (10 eq) is required, necessitating extraction and recrystallization to purify the GMS. The strong acidic condition resulted in the interesterification between two protected monoglycerol molecules, leading to the formation of diglyceride and glycerol as by-products.[15] Although enzymetic hydrolysis of 1,3-dioxolane-4-methanol butanoate yielded glycerol monobutanoate, hydrolysis of longer-chain fatty acid derivatives gave no reaction.[16]

To improve the selectivity and efficiency of the hydrolysis of acetonide, we have tested several acids (acetic acid, HCl, CF_3COOH, H_2SO_4, *p*-toluenesulfonic acid, and acidic resins) and solvents (methanol, ethanol, *i*-PrOH, *t*-BuOH, water, THF, hexane, and their co-solvents). Using HCl, CF_3COOH, H_2SO_4 and *p*-toluenesulfonic acid, the yield of **1** was low (31-68%) due to hydrolysis of ester group. We found that a resin with sulfonic acid functionality (Amberlyst 15, wet) – ethanol (95%) system was the most efficient in the selective hydrolysis of the acetonide group of **6** to give **1** in 97% yield. It should be noted that the selectivity of the hydrolysis of the acetonide/ester group was not high (68/32) when *p*-toluenesulfonic acid was used instead of Amberlyst 15. Compared with *p*-toluenesulfonic acid, the very high selectivity of the resin seems to originate from the steric hindrance of the resin; the approach of the bulky stearate to acidic sites on the resin might be hampered by the bulkiness of the resin.

In attempt of the selective ethanolysis of acetonide, a dry Amberlyst 15 - anhydrous ethanol system gave a significant amount (45%) of ethanolysis product of stearate. Although the presence of some water (5-10%) is crucial in the selective hydrolysis of acetonide, increase of water content slow down the reaction rate and the hydrolysis product of ester group was increased. In the replacement of solvent from EtOH-H_2O (95 : 5) to EtOH-H_2O (80 : 20), the reaction time prolonged from 6 h to 13 h and yield of **1** was dropped from 97% to 90%. This phenomenon is thought to be due to the low solubility of **6** in the solvent and serious in ethanol containing more than 25% water. The lower yield (83%) of **1** in methanol -H_2O (95 : 5) also can be accounted by the low solubility of **6**.

In THF-H_2O (10 : 1) or *n*-hexane-H_2O (10 : 1), about 40% of diglyseride (**2**, **3**) was formed. Although replacement of EtOH-H_2O (95 : 5) to *i*-PrOH-H_2O (95 : 5) or *t*-BuOH-H_2O (95 : 5) repressed the alcoholysis of ester group, longer reaction time (9 h) was required and the yield (less than 92 %) of **1** was lower than in EtOH-H_2O (95 : 5).

We concluded that appropriate solubility of **6** was prerequisite for high selectivity and the best solvent was 95%

(v/v) EtOH for the selective deprotection of **6**. The use of ion exchange resin to deprotect an acetonide is a well-known reaction. However, drastic solvent effect on the selective deprotection of acetonide in the presence of ester group using resin was not described previously as far as we know.

After the reaction was completed, the GMS was purified using a very simple procedure; filtration and concentration. Any further purification procedure was not required. GPC analysis revealed that the purity of the GMS exceeded 97% and the impurities identified were ethyl stearate, stearic acid, and glycerol. The Amberlite 15 catalyst was fully recovered by simple filtration and reusable because its activity was not changed.

Conclusions

In this three-step process, each purification procedure is very simple and the yield and purity are very high (overall yield: 92%). The selective and efficient deprotection of the acetonide was accomplished using the strongly acidic wet resin (Amberlyst-15)-ethanol (95%) system in which the purification procedure was very simple (filtration and concentration). This procedure can be applied to the production of monoglycerides of other fatty acids in industry.

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