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NOTE

Synthesis of 3-[(*tert*-Butyldimethylsilyl)oxy]glutaric Anhydride from Citric Acid

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A new synthesis of 3-[(*tert*-butyldimethylsilyl)oxy]glutaric anhydride has been developed from citric acid, which is a commodity chemical and more than a million tons are produced every year by fermentation. The new synthetic approach demonstrated an efficient utilization of bioresource for the synthesis of intermediate of rosuvastatin.

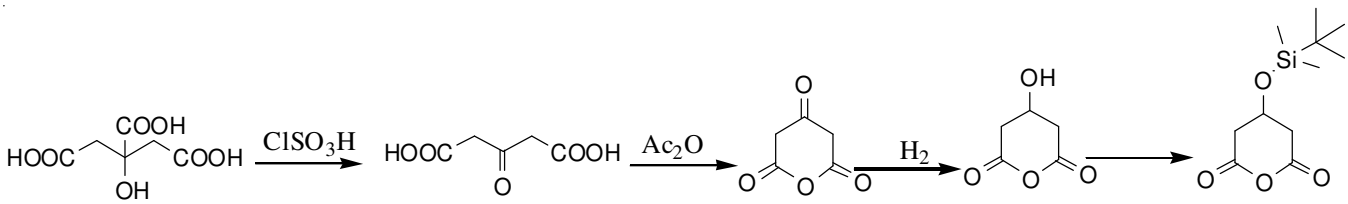
Keywords: Citric acid, 3-[(*tert*-butyldimethylsilyl)oxy]glutaric anhydride, Rosuvastatin.

Rosuvastatin (formerly known as ZD4522) is a new 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) with distinct pharmacologic properties. Compared to most other statins[1], it is relatively hydrophilic, similar in this respect to pravastatin. Rosuvastatin has been shown to be a comparatively potent inhibitor of HMG-CoA reductase activity in a purified preparation of the catalytic domain of the human enzyme, as well as in rat and human hepatic microsomes[2]. 3-[(*tert*-butyldimethylsilyl)oxy]glutaric anhydride is a key intermediate in the synthesis of rosuvastatin. The increasing requirement leads to the development of different procedures for the synthesis of 3-[(*tert*-butyldimethylsilyl)oxy]glutaric anhydride. The conventional synthesis process includes synthesis from, 3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-pentanedioic acid[3-5], or 3-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-pentane dioic acid-1,5-diethyl ester[6], but this process embodies a low atom-economy and is not good for environmentally friendly, only a few of such processes are practical. In this work, we investigate a new synthetic method of 3-[(*tert*-butyldimethylsilyl)oxy]glutaric anhydride from citric acid (**Scheme-I**).

All reagents and solvents were industrial grade and used without further purification. NMR spectra were recorded on a Bruker Avance DPX-250. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX. The purity of both starting materials as well as the reaction products were checked by TLC on silica-gel polygram SILG/ UV254 plates or by a Shimadzu Gas Chromatograph GC-10A instrument with a flame-ionization detector using a 15 % carbowax 20 M chromosorb-w acid washed 60-80 mesh column.

General procedure: Chlorosulfonic acid (12 g) was placed in a 100 mL round-bottomed flask with a drying tube. The flask was immediately cooled in an ice/salt bath on a stirring plate and fine citric acid powder (19.2 g) dissolve in 50 mL chloroform was gradually dropwise added. The reaction mixture was then extracted with pre-cooled ethyl acetate (100 mL × 3). Acetone dicarboxylic acid (14.6 g) was dehydrated with acetic anhydride (200 mL) for 3 h at 0 °C with stirring. The acetone dicarboxylic acid anhydride (11.5 g) just prepared was dissolved in chloroform (80 mL), then performed in a 100 mL stainless steel autoclave. The dihydro-4-hydroxy-2*H*-Pyran-2,6(3*H*)-dione in chloroform was directly used in next step, followed by charging of imidazole (6.5 g), *t*-butyldimethylsilyl chloride (13.5 g) under nitrogen atmosphere.

Several approaches have been reported for the synthesis of acetone dicarboxylic acid by fuming sulfuric acid[7,8].



Scheme-I: Synthesis of 3-[(*tert*-butyldimethylsilyl)oxy]glutaric anhydride from citric acid

However, fuming sulfuric acid is a hazardous and corrosive solution. We use chlorosulfonic acid in place of the fuming sulfuric acid and use chloroform as the solvent, which can cut the cost of acid. In a typical experiment, chlorosulfonic acid (12 g) was placed in a 100 mL round-bottomed flask with a drying tube. The flask was immediately cooled in an ice/salt bath on a stirring plate and fine citric acid powder (19.2 g) dissolve in 50 mL chloroform was gradually dropwise added. The temperature was controlled to be less than 10 °C. The citric acid dissolved into a clear solution in 0.5 h, then the reaction temperature was gradually raised to room temperature to allow evolution of CO gas. Once the foaming ceased, the temperature of the reaction mixture was increased to 30 °C for another 20 min to complete the reaction and promptly returned to the ice/salt bath. When the bath temperature rises to 5 °C over time, finely cracked ice cubes should be intermittently added into the bath at around 5 °C for another 0.5 h. The reaction mixture was then extracted with pre-cooled ethyl acetate (100 mL × 3). The organic solution was dried over anhydrous Na_2SO_4 and subsequently subjected to a rota-vapor to remove organic solvent with a yield of 90.1 %. Pure acetone dicarboxylic acid obtained is unstable. Therefore, it was immediately used in the next step. Acetone dicarboxylic acid (14.6 g) was dehydrated with acetic anhydride (200 mL) for 3 h at 0 °C with stirring. The pale yellow precipitate was filtered, washed with glacial acetic acid (300 mL) and then with benzene (100 mL). The obtained white solid was characterized as acetone dicarboxylic anhydride with the yield of 95.3 %, m.p. 137-138 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.68 (s, 2H), 5.23 (s, 1H), 12.5 (br s, 1H). GC-MS calcd. For $C_5H_4O_4$ *m/z* 128.01, found 128.1. The acetone dicarboxylic acid anhydride (11.5 g) just prepared was dissolved in chloroform (80 mL), then performed in a 100 mL stainless steel autoclave. 0.1 g 3 wt. % Ru/C (50.2 % water content, surface area of 789 m^2/g) was transferred into the autoclave. After the necessary connection between the autoclave and hydrogen gas cylinder was duly made, H_2 gas passed into the autoclave until H_2 pressure reached 1.0 MPa. H_2 pressure was maintained for a few seconds to allow good mixing of H_2 and air in the autoclave. Then the gas mixture in the autoclave was allowed to expand. Pressurization and successive depressurization were repeated 10 times so as to completely replace the air in the autoclave. The autoclave filled with air-free H_2 gas was put in a water bath, the temperature of which was adjusted to the 30 °C. H_2 pressure was adjusted to 1 MPa, then reacted for three hours. After reaction, the product was filtered, analyzed by means of a Shimadzu GC-MS, GC-MS calcd. For $C_5H_6O_4$, *m/z* 130.03, found 130. The dihydro-4-hydroxy-2*H*-pyran-2,6(3*H*)-dione in chloroform was directly used in next step, followed by charging of imidazole (6.5g), *t*-butyldimethylsilyl chloride (13.5 g) under nitrogen atmosphere. Reaction mass was maintained at 20-30 °C for 24 h, followed by washing the reaction mass using water and brine. The product was extracted with *t*-butylmethyl ether and concentrated to precipitate 3-[(*tert*-butyldimethylsilyl)oxy]glutaric anhydride. The product was crystallized from cyclohexane and dried to obtain 89.7 % of a white crystalline solid with amp 80-81 °C, ^{1}H NMR($CDCl_3$) 0. 08 (s, 6H, CH_3), 1 (s, 9H, CH_3), 2. 26 (d, 4H, CH_2), 5 (m, H, CH). GC-MS calcd. For $C_{11}H_{20}O_4Si$ *m/z* 244.11, found 244.10.

Conclusion

In summary, we report a new synthetic method for 3-[(*tert*-butyldimethylsilyl)-oxy]glutaric anhydride utilizing a bioresource precursor with the total yield of 77 % by four steps. Each step is through crystallization or simple extraction and without column chromatography. Additionally, the new synthetic route also demonstrated a potential utilization of organic bioresource in the synthesis of intermediate of rosuvastatin.

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