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An Improved New Path to Synthesize Gemfibrozil

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A new route has been developed for synthesis of gemfibrozil in good yield with high purity. The obtained gemfibrozil was characterized by using IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies. According to Biopharmaceutical Classification System, gemfibrozil is classified under class-II drugs (low solubility-high permeability) and an antihyperlipidimic. So it's admirable to synthesize the intention molecule in easy and economical way.

Keywords: Gemfibrozil, Antihypolipidimic, Lopid.

INTRODUCTION

Gemfibrozil, 2,2-dimethyl-5-(2,5-dimethylphenoxy)-pentanoic acid, is an pharmaceutical drug used for prevention and treatment of atherosclerosis. It was developed by Parke-Davis & Co. (USA)[1]. Gemfibrozil is used for the treatment of adult patients with very high elevations of serium triglyceride levels (types IV and V hyperlipidemia) who are at risk of developing pancreatitis (inflammation of pancreas) and who do not respond adequately to a strict diet. Gemfibrozil, a fibric acid antilipemic agent similar to clofibrate, is used to treat hyperlipoproteinemia and as a second line therapy for type IIb hypercholesterolemia. It reduces triglyceride levels, low density lipoprotien (LDL), very low density lipoprotien (VLDL) levels and increase high density lipoprotien (HDL) levels[2,3]. Gemfibrozil increase the activity of extra hepatic lipoprotein lipase (LL), thereby increasing lipoprotein triglyceride lipolysis. Chylomicrons are degraded, very low density lipoprotiens are converted to low density lipoprotiens and low density lipoprotiens are converted to high density lipoprotiens[4-6]. Gemfibrozil also inhibits the synthesis and increases the clearance of apolipoprotein B, a carrier molecule for very low density lipoprotien.

Reports are available in the literature related to the various synthetic routes for the preparation of gemfibrozil. These processes[7] reported have restricted application in the industry because of less overall yield, number of purifications and the stringent regulatory requirement to meet the quality of a finished drug substance. To minimize the cost constraints and number of purifications, we avoided tedious work-up processes. In view of the high-volume requirement, huge revenues associated with this molecule and disadvantages from the reported processes, there arises a need to develop an alternative process for gemfibrozil, meeting with all regulatory aspects.

EXPERIMENTAL

Melting points were recorded on electro-thermal melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300 MHz spectrometer in IISc, Bangalore, India. The chemical shifts are shown in δ values (ppm) with tetramethylsilane as an internal standard. LC-MS were obtained using C 18 column on Shimadzu, LCMS 2010A, Japan. The FT-IR spectra of the compounds were taken in ABB FTLA spectrometer in the range between 4000 to 500 cm^{-1}. The column chromatography was performed using silica gel (230-400 mesh). Silica gel GF254 plates from Merck were used for TLC and spots located either by UV or dipping in potassium permanganate solution. The chemicals were purchased from Sigma-Aldrich Co and from SD Fine chemicals. The solvents for column chromatography were of reagent grade and were purchased from commercial source.

General procedure

Preparation of allyl isobutyrate)1): Conc.H_2SO_4 (3.33 g, 0.033 mol) was added drop wise to a flask containing isobutyric acid (100 g, 1.135 mol) and allyl alcohol (79.11 g 1.362 mol) at room temperature under N_2 atmosphere. The reaction mixture was heated to reflux at 95 ºC for 5 h. The completion of reaction was monitored by TLC. After completion the

reaction, mixture was cooled to room temperature and was added saturated solution of sodium bicarbonate. Organic layer was separated. Aqueous layer was extracted with Hexane (2 × 50 mL) and dried with sodium sulphate. Hexane was distilled off at atmospheric pressure to get 113.32 g (78.15 %) of allyl isobutyrate as a yellow liquid with GC purity 96.76 %.

Preparation of 2,2-dimethy1-4-pentanoic acid (DMP) (2): To a four necked flask equipped with condenser and nitrogen inlet, added sodium hydride (27.12 g, 1.13 mol) and toluene (340 mL, 3 vol). The resulting mixture was heated to 110 ºC with stirring. Thereafter, allyl isobutyrate (113 g, 0.88 mol) was added drop wise over period of 5 h. After the addition, stirring was continued at 110 ºC for further 3 h. The completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature and 20 mL of methanol was added to decompose unreacted sodium hydride. After dissolving insoluble matters with addition of 226 mL of water, toluene and aqueous layer were separated from each other. Aqueous layer was washed with 100 mL of toluene and separated from each other. Aqueous layer was acidified to a pH-1 with conc. HCl (36 mL). The formed oil layer was recovered and the aqueous layer was extracted with hexane (100 mL). Combined organic layer was dried with sodium sulphate. Hexane was distilled off at atmospheric pressure to get 92.3 g (82 %) of 2,2-dimethyl-4-pentenoic acid as a brown liquid with GC purity 99.23 %.

Synthesis of 5-bromo-2-,2-dimethyl-pentanoic acid (3): 2,2-Dimethyl-1,4-pentanoic acid (92 g, 0.718 mol) was added to a flask containing hexane (644 mL, 7 vol) and benzoyl peroxide (0.92,1 %). 64 g of HBr gas was bubbled into the reaction solution at 0-5 °C over period of 3 h. After completion of bubbling stirring continued for further 2 h. Completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was washed with 100 mL water. The hexane layer was separated, dried with sodium sulphate. Hexane was distilled off at atmospheric pressure to get 112.6 g (75 %) of 5-bromo-2,2-dimethyl-pentanoic acid as a brown liquid.

Synthesis of 5-bromo-2,2-dimethyl-pentanoic acid methyl ester (4): 4.48 mL of conc. H_2SO_4 was added drop wise to a flask containing methanol (224 mL, 2 vol) and 5-bromo-2,2-dimethyl-pentanoic acid (112 g, 0.535 mol) at room temperature. The resulting mixture was heated to reflux at 60-70° C for 16 h. The completion of reaction was monitored by TLC. After completion of reaction methanol was distilled of at atmospheric pressure. Reaction mass was cooled to room temperature, followed by addition of saturated sodium bicarbonate solution. Organic layer was separated, aqueous layer was extracted with hexane (2 × 50 mL). The combined organic layer was washed with water (100 mL), dried with sodium sulphate. Hexane was distilled off at atmospheric pressure to get 113.52 g (95 %) of 5-bromo-2,2-dimethyl-pentanoic acid methyl ester as a brown liquid with GC purity 75.6 %. The crude ester was distilled under reduced pressure (vacuum = 1.3 mm).

Synthesis of *gem*-methyl ester 5: To a flask containing toluene (125 mL, 2.5 v) and xylenol (27.39 g, 0.224 mol), potassium carbonate (34.65 g, 0.251 mol) and TBAB (5 g, 10 %) were added at room temperature under N_2 atmosphere. The resulting mixture was heated to reflux at 110 °C with stirring. Thereafter, bromoester (50 g, 0.224 mol) was added drop wise at 110 °C over period of 2 h. After completion of addition stirring was continued at 110 °C for further 16 h. Completion of reaction was monitored by TLC. After completion of reaction, reaction mass was cooled to room temperature. Organic layer was separated, aqueous layer was extracted with toluene (2 × 50 mL). The combined organic layer was washed with 10 % sodium hydroxide solution (2 × 50 mL), dried with sodium sulphate. Toluene was distilled off using line vacuum to get 56.8 g (96.1 %) of *gem*-methyl ester as a brown liquid with GC purity 90 %. The crude ester was distilled under reduced pressure (vacuum = 1.3 mm).

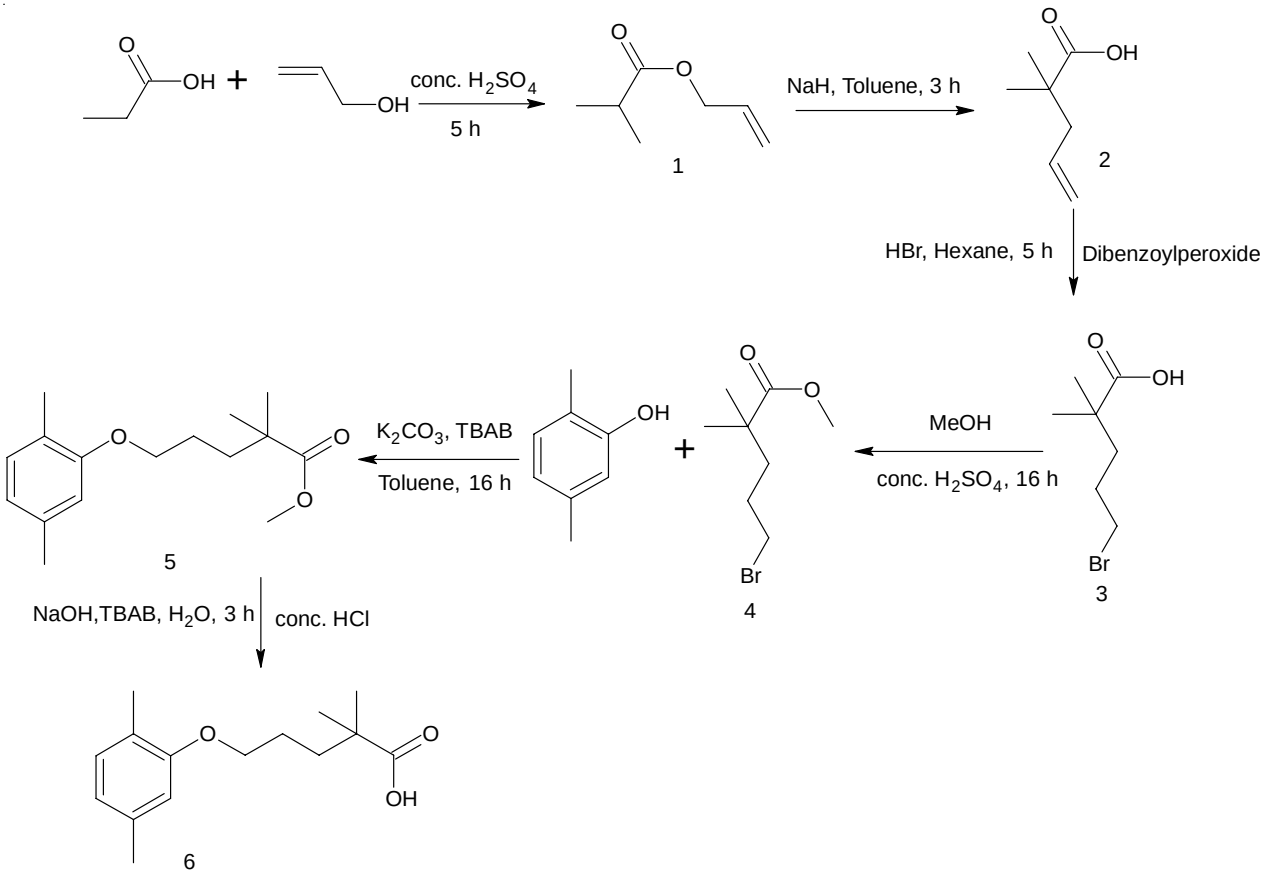
Anal. Calcd for (%) $C_{16}H_{23}O_3$ (264.3 g/ mol): C 72.69, H 9.15, Found: C 72.65, H 9.13,; IR (KBr, ν_{max}, cm^{-1}): 3030 (C-H aromatic stretching), 2870 (C-H methylene stretching), 1732 (ester stretching), 1585 (C=C); ^{1}H NMR ($CDCl_3$) ppm: δ 1.2 (s, 3H), δ 1.3 (s, 3H), δ 1.7 (m, 2H), δ 1.8 (m, 2H), δ 2.2 (s, 3H, 6C), δ 2.3 (s, 3H, 1C), δ 3.7 (s, 3H, methoxy), δ 4.0 (s, 2H), δ 6.7-7.0 (3H, Ar H); ^{13}C NMR ($CDCl_3$) ppm): 164.10, 158.49, 149.05, 142.32, 136.41, 135.0, 130.96, 128.47, 128.26, 128.04, 126.99, 125.56, 122.93, 121.20, 119.93, 110.61, 107.02 (17 Ar-C), 55.90 (methoxy); M 276.1.

General procedure for the synthesis of gemfibrozil (6): To a flask containing water (9.97 mL), NaOH (9.97 g, 0.25 mol) and TBAB (4.3 g, 10 %), *gem*-methyl ester (43 g, 0.162 mol) was added at room temperature under N_2 atmosphere. The resulting mixture was heated to reflux at 73-75 °C with stirring for 2-3 h. Completion of reaction was monitored by TLC. After completion of reaction, methanol was distilled off. Reaction mass was cooled to room temperature, followed by addition of water. Again mass was cooled to 0-5 °C. The resulting sodium salt of gemfibrozil was filtered, washed with toluene. The salt was dissolved in water taken in another flask, added charcoal and heated to reflux for 0.5 h. Hot reaction mass was filtered through hyflo and washed with hot water. Filtrate was cooled to 5-10 °C and acidified with conc. HCl (22 mL) and resulting solid was filtered suck dried. The solid was dissolved in methanol taken in another flask, added charcoal and heated to reflux for 0.5 h. Hot reaction mass was filtered through hyflo and washed with hot methanol. Filtrate was cooled to 5-10 °C. Resulting solid was filtered, suck dried. Dried under vacuum at 50 °C to get 31.6 g (77.6 %) of gemfibrozil as a white solid with LC purity 99.5 %. m.p. 59-61 °C.

Anal. Calcd for (%) $C_{16}H_{23}O_3$ (264.3 g/mol): C 71.97, H 8.86, Found: C 71.93, H 8.81; IR (KBr, ν_{max}, cm^{-1}): 2917 (broad band centering due to OH stretching vibrations of carboxylic acid, along with weaker C-H stretching bands), 1703 (C=O stretching); ^{1}H NMR ($CDCl_3$) ppm: δ 1.25 (s, 6H), δ 1.76 (m, 4H), δ 2.17 (s, 3H), δ 2.3 (s, 3H), δ 6.6 (s, 1H, Ar H), δ 6.67 (d, 1H, Ar H), δ 7.0 (d, 1H, Ar H); ^{13}C NMR ($CDCl_3$) ppm: 184.81, 156.99, 136.45, 130.33, 123.65, 120.77, 112.05, 67.97, 42.0, 36.91, 25.17, 24.98, 21.40, 15.74; M^{+1} 251.0.

RESULTS AND DISCUSSION

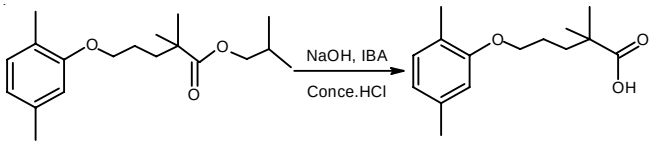
The present improved method is start with synthesis of allyl butyrate followed by rearrangement reaction to form compound **2**. The addition of hydrogen bromide to the com-



Scheme-I

pound resulted in the formation of compound **3**, followed by the esterification reaction. The compound **4** on treating with xylenol to form *gem*-methyl ester. The formation of compound confirmed by the spectral analysis. The alkali hydrolysis of *gem*-methyl ester yield the final compound gemfibrozil (**5**) (**Scheme-I**).

The final step of synthesis of **5** using this proposed scheme involves specific production difficulties. As follows from the literature, the yields are 55-60 %[8] at the step of *O*-alkylation with 1,3-dibromopropane and 70-76 %[9]. Thus, by this technique the total yield of gemfibrozil is 39-46 %. There are several techniques of synthesis of gemfibrozil and its derivatives reported with some modifications in the patent literature. Spanish patent[10] describes synthesis **5** by alkylation of corresponding potassium salt with 5-bromo-2,2-dimethylpentanamide, followed by the alkaline hydrolysis of the intermediate amide to **5**. A method for obtaining **5** by oxidation of respective aldehyde; other method reported that, N-isobutylidene-dicyclohexylamine followed by the hydrolysis of the imine formed[11]. The Warner-Lambert Company has improved the method developed by Parke Davis for obtaining 5[12]. In this patent, isobutyl isobutyrate undergoes the reaction with lithium diisopropylamide in THF in the presence of styrene. The resulting anion reacts with 1-bromo-3-chloropro-pane to yield isobutyl 5-chloro-2,2-dimethylpentanoate, which was treated with sodium 2,5-dimethylphenolate in a DMF/toluene mixture in the presence of NaI and the ester formed was hydrolyzed to **5**. The total yield (for two steps) of gemfibrozil is 80 %. Malonic acid derivatives also used for synthesis of gemfibrozil[13,14]. Spanish authors used the Hailer-Bauer reaction of ketone cleavage to synthesize **5**[15]. The Grignard reactions have been patented by other Spanish authors[16] in fewer yields (70 %). Apart from these reports, gemfibrinozil (**5**) has been synthesized by the hydrolysis of *gem*-ester (**Scheme-II**). But, preparation of *gem*-ester leads to more cycle time and more volume, Higher effluent generations and low output of gemfibrozil. Considering the literature data and the results, we proposed a novel scheme for synthesis of gemfibrozil (**5**) for less in economically and improve with respect to cycle time, reaction volume and energy cost and effluent reductions. The mass analysis of gemfibrozil (**5**) and synthesized intermediate compounds showed exact molecular ion peak of corresponding molecular weights. The characterizations of the final molecule gemfibrozil (**5**) based on the careful comparison of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.



Scheme-II

Conclusion

The formation of gemfibrozil moiety with the ease and procedural simplicity are the key aspects of the synthesis. An improved process has been developed for synthesis of gemfibrozil with an overall yield of 80 and 99.9 % purity. The

process described in this article has certain advantages over the reported processes, with the use of low cost starting material and avoided the multisteps.

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