

Improved Process for the Preparation of Cetilistat from Isatoic Anhydride

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Abstract: 2-Amino,5-methyl benzoic acid on reaction with triposgene or phosgene gas in polar solvent or nonpolar solvent to produce isatoic anhydride. Isatoic anhydride on treating with Cetyl chloroformate to produce Cetilistat with good purity and yield.

Keywords: Cetilistat, triglycerides and synthetic lipase inhibitor

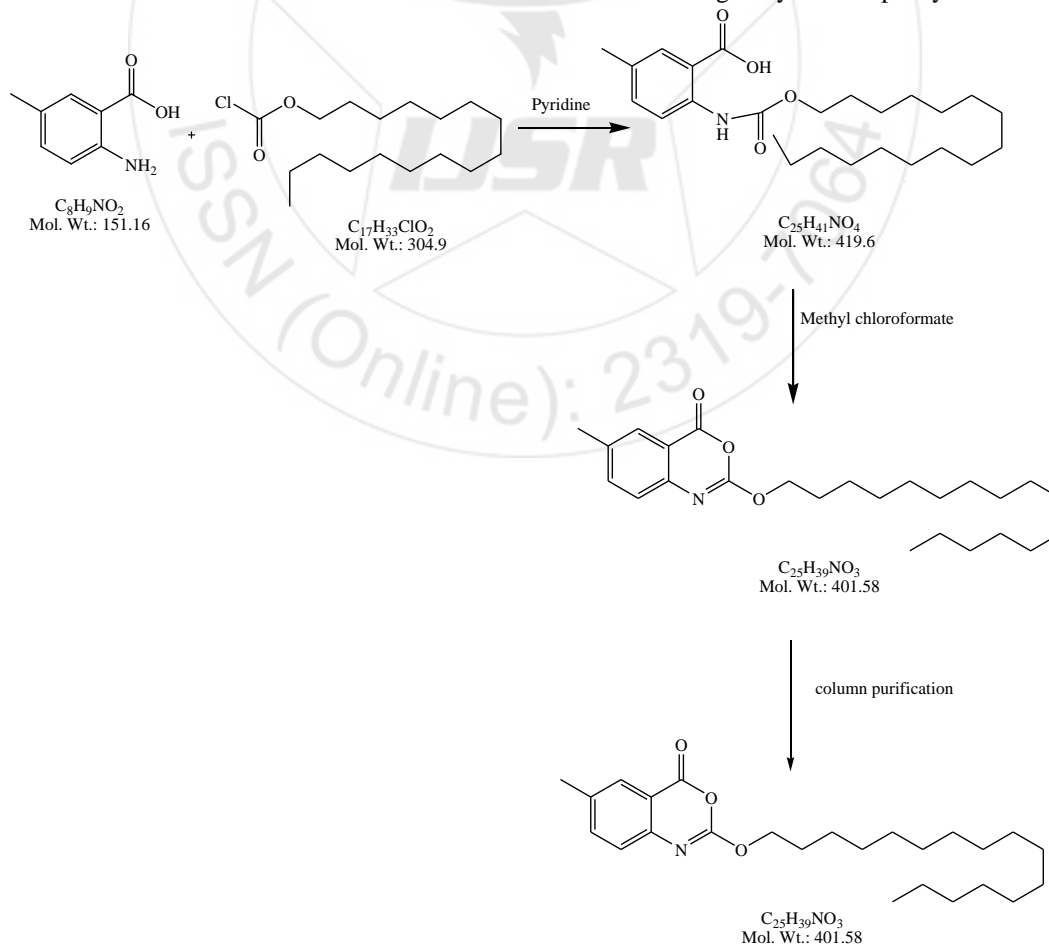
1. Introduction

Cetilistat is a drug designed to treat obesity. It acts in the same way as the older drug Orlistat (Xenical) by inhibiting pancreatic lipase, an enzyme that breaks down triglycerides in the intestine. Without this enzyme, triglycerides from the diet are prevented from being hydrolyzed into absorbable free fatty acids and are excreted undigested. In human trials, Cetilistat was shown to produce similar weight loss to Orlistat, but also produced similar side effects such as oily, loose stools, fecal incontinence, frequent bowel movements, and flatulence. It is likely that the same precautions would apply in that absorption of fat-soluble vitamins and other fat-soluble nutrients may be inhibited, requiring vitamin supplements to be used to avoid deficiencies.

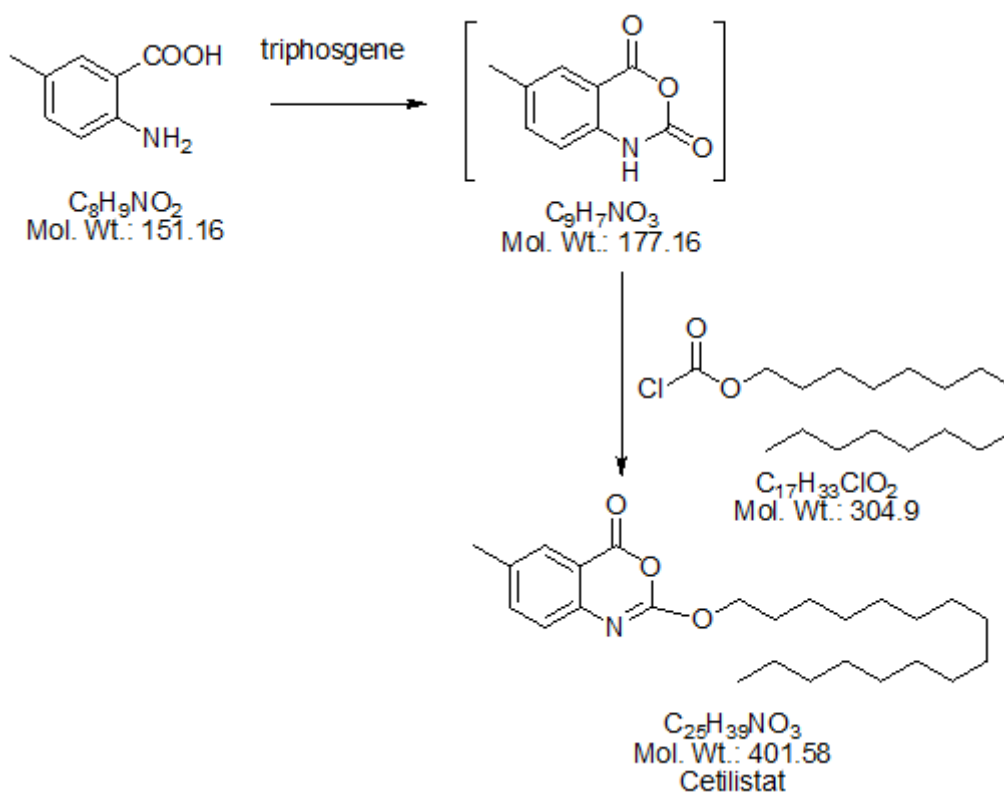
Takeda, under license from Norgina, is developing Cetilistat (ATL-962), an oral non-absorbed synthetic lipase inhibitor for the potential treatment of obesity in patients with or without diabetes

2. Detailed Description

As shown in literature ¹ Cetilistat can be prepared by reacting 2-amino-5-methyl benzoic acid with cetyl chloroformate (Hexadecyl chloroformate) in a ²suitable solvent like DMF, DMAC, pyridine etc. To get carbamate intermediate. Which on cyclizing in presence of cyclizing agent like methyl chloroformate, CDI or BOC to get Cetilistat with good yield and purity.



We prepared the same material by ⁴ using isatoic anhydride and cetyl chloroformate in a suitable solvent with high yield and purity which shown in figure -1.



3. Experimental

All the Chemical and reagents used were purchased from Aldrich. All the solvents were of analytical grade. Thin-layer chromatography (TLC) was checked by Merck AL silica gel 60 F₂₅₄ plates and visualized under UV light. IR spectra were recorded in KBr pellet with a shimadzu spectrum gx FTIR instrument and all the diagnostic, intense peaks are reported. ¹H NMR and ¹³C NMR spectra were recorded in DMSO- *d*₆ with a Varian Mercury plus 400 MHz and 100 MHz instruments respectively. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The ¹H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ABq (AB quartet); the list of coupling constants (*J*) corresponds to the order of multiplicity assignment. Mass spectra were recorded on a Shimadzu LCMS-QP 1000 mass spectrometer. Melting points were determined in open glass capillaries on a Stuart SMP30 apparatus and are uncorrected. All the reactions were performed under inert atmosphere.

4. Preparation of Cetilistat Isatoic Anhydride

Example: 1

Aminomethylbenzoic acid (100 g, 0.661 moles) is treated with triphosgene (30 g) in dichloromethane (500 ml) at 0-5°C, the reaction mass is heated to reflux and maintained for 3-4 hours under reflux. After reaction completion, the mass is washed with sodium bicarbonate solution and water, the

resulting Methelenedichloride solvent is evaporated under reduced pressure, the resulting residue is diluted in dimethyl acetamide (500 ml) and added cetyl chloroformate(0.73 moles) the resulting reaction mass is stirred for 2-3 hours, after reaction completion, water is added to reaction mass, filtered, washed with water. The wet crude material is purified in ethyl acetate to give cetilistat as white solid (185 g 70% yield)

Example: 2

Aminomethylbenzoic acid (100 g, 0.661 moles) is treated with triphosgene (30 g) in THF (300 ml) at 0-5°C, the reaction mass is heated to reflux and maintained for 3-4 hours under reflux. After reaction completion, the mass is washed with sodium bicarbonate solution and water, the resulting THF solvent is evaporated under reduced pressure, the resulting residue is diluted in dimethyl acetamide (500 ml) and added cetyl chloroformate(0.73 moles) the resulting reaction mass is stirred for 2-3 hours, after reaction completion, water is added to reaction mass, filtered, washed with water. The wet crude material is purified in isopropyl ether to give cetilistat as white solid (185 g 70% yield)

Example: 3

Aminomethylbenzoic acid (100 g, 0.661 moles) is treated with triphosgene (30 g) in ethyl acetate (400 ml) at 0-5°C, the reaction mass is heated to reflux and maintained for 3-4 hours under reflux. After reaction completion, the mass is washed with sodium bicarbonate solution and water, the resulting ethyl acetate solvent is evaporated under reduced pressure, the resulting residue is diluted in dimethyl acetamide (500 ml) and added cetyl chloroformate(0.73 moles) the resulting reaction mass is stirred for 2-3 hours,

after reaction completion, water is added to reaction mass, filtered, washed with water. The wet crude material is purified in isopropyl alcohol to give cetilistat as white solid (185 g 70% yield)

References

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