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AN IMPROVED SYNTHESIS OF RALOXIFENE HYDROCHORIDE: A SELECTIVE ESTROGEN RECEPTOR MODULATOR

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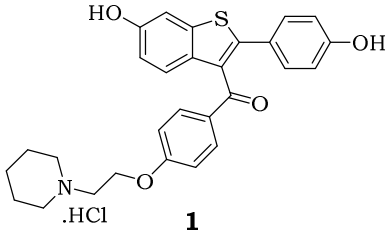
ABSTRACT:
Raloxifene hydrochloride (**1**) is a selective estrogen receptor modulator (SERM), belongs to the family of benzothiophene class of compounds. The present work details the journey towards development of a simple, cost effective, environmentally friendly synthesis of raloxifene hydrochloride (**1**). The key feature of the improved process is one pot high yielding de-protection of sulfonyl group in water.

KEYWORDS: Raloxifene hydrochloride, SERM, Friedel-Crafts acylation, Hydrolysis.

INTRODUCTION:

Raloxifene hydrochloride (**1**) having the structure formula-**1** is a selective estrogen receptor modulator (SERM) used for the treatment and prevention of postmenopausal disorder inwomen [i].



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Literature precedents reveal that various methods [ii] has been reported for the synthesis of raloxifene hydrochloride (**1**), includes, methods used hazardous chemicals and large amount of flammable, volatile and toxic organic solvents. The general method for the preparation of raloxifene involves friedal crafts acylation of peperidinyl)ethoxy]benzoyl chloride hydrochloride, followed by de-protection of methane sulfonyl group of 6-methylsulfonyloxy-2-[4-methylsulfonyloxy) phenyl] benzothiophene. Where in the de-protection of methane sulfonyl group attracted most of the researchers owing to its criticality [iii-viii]. However, all these reported processes has several disadvantages, such as 1) Mixture of solvents were used for the hydrolysis

2) Multiple impurities **(figure-1)** formation with low purity of the product (**1**) to purify impurities multiple crystallizations are required 3) Column chromatography is often used for purification of product which is commercially not viable. Keeping in view the criticality of de-protection of methane sulfonyl group and low yield we have started for development of a relatively superior process.

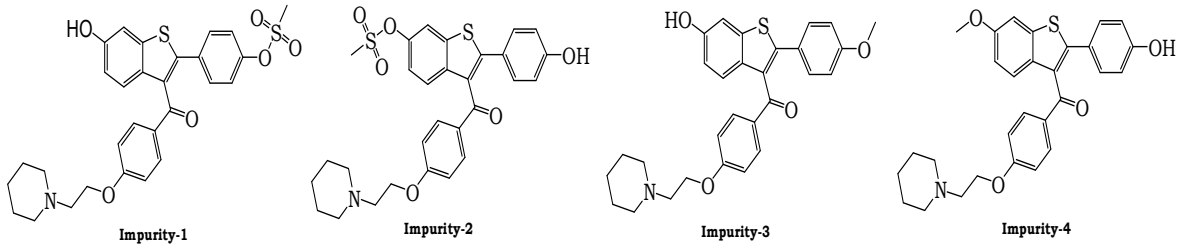
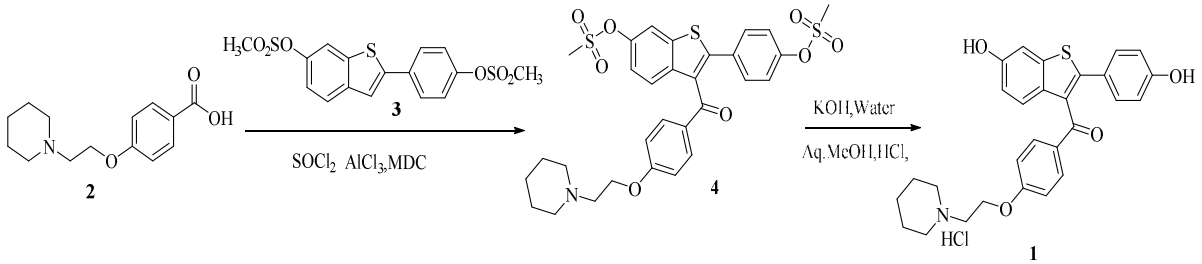


Figure: 1 Reported impurities during the hydrolysis of sulfonyl groups

The development of economic and eco-friendly process is the central focus of green and sustainable chemistry in order to that we have developed a superior process for de-protection of sulfonyl group under base condition in water without using any organic solvent. This is the first of its kind of sulfonyl group de-protection in water for the manufacture of raloxifene.

RESULTS AND DISCUSSION:

The process as described in scheme-1, involves reacting 4-[2-(piperidinyl) ethoxy] benzoic acid hydrochloride **(2)** with thionyl chloride, in dichloromethane, to form 4-[2-(piperidinyl) ethoxy]benzoyl chloride hydrochloride. Acylating 6-methylsulfonyloxy-2-[4-methysulfonyloxy) phenyl] benzothiophene (**3**) with 4-[2-(piperidinyl)ethoxy]benzoyl chloride hydrochloride in presence of aluminum chloride and dichloromethane, to give 6-methylsulfonyloxy-2-[4-methylsulfonyloxy)phenyl]-3-[4-(2-(piperidinyl) ethoxy] benzoyl] benzothiophene hydrochloride(**4**) followed b**y** hydrolysis in aqueous medium under basic conditions at reflux temperature gives desired raloxifene hydrochloride (**1**). Initially various bases were screened and found that KOH is the best for achieving good conversion and yield. After reaction, raloxifene free base was isolated from water and then converted to hydrochloride in aqueous methanol. High yield, cost effectiveness of the process made this water medium de-protection of sulfonyl group an attractive alternative. Since, the process involves de-sulfonylation at two phenolic groups; partial de-sulfonylation at either of the groups was envisaged. The optimization of various parameters involved in the de-sulfonylation step resulted in a dramatic improvement in the purity and yield of raloxifene hydrochloride.



Scheme: 1 an improved synthesis of raloxifene hydrochloride.

EXPERIMENTAL SECTION

^{1}HNMR spectra were recorded on a 200-MHz Varian Gemini FT NMR spectrometer, and ^{13}CNMR spectra were recorded using a 50-MHz Varian Gemini FT NMR spectrometer. The Chemical shifts are reported in ð ppm relative to TMS. Mass spectra (70 eV) were recorded on a HP-5989A LC-MS spectrometer. The melting points were determined using the capillary method on a Polmon (model MP-96) melting-point apparatus and are uncorrected. The solvents and reagents were used without further purification. Samples were analyzed by HPLC Waters Model Alliance 2695-separation module equipped with a waters 2998-photo diode array UV detector. The analysis was carried out on Inertsil C8 column, 250 x 4.6mm id., 5µ particle size (GL sciences Inc., Japan) with a mobile phase consisting of A = Dissolve 9.0g of monobasic potassium phosphate in 1000 ml of water, and mix. Add 0.6ml of phosphoric acid, further adjust with phosphoric acid or potassium hydroxide solution to a pH of 3.0 ±0.1 and B = Acetonitrile. Program gradient elution (T/%B =0/25, 9/25, 40.25/50, 42.25/25, 49/25) was used with UV detection at 280 nm at a flow rate of 1.0 ml /min. The column temperature was maintained at 35°C and the injection volume was 10 µl. The data was recorded using Waters Empower software.

Preparation of 6-Methylsulfonyloxy-2[(4-methyl Sulphonyloxy) phenyl]-3-[4(2-(piperidinyl) ethoxy] benzoyl] benzothiophene hydrochloride (4)

4-[2-(Piperidinyl)Ethoxy]benzoic acid hydrochloride 55g was taken dichloromethane 200 mL and 56 g of thionyl chloride was added under nitrogen atmosphere at 25-35 °C. The mixture was heated to 40 °C for 3 hours. After completing the reaction, solvent was evaporated under vacuum at below 40°C and chased-off with petroleum ether to remove excess thionyl chloride. Residue was dissolved in 250 mL of dichloromethane followed by added 6-methylsulfonyloxy-2-[4-methylsu4lfonyloxy) phenyl] benzothiophene(**3**) 50g to this mixture aluminum chloride (137.5 g) was added at 10-15°C and maintained for 4 hours at 25-35°C After completion of the reaction, it was quenched with water at 0-5 °C. After separating the layers, organic layer was washed with water and diluted HCl solution. Final organic layer was distilled under vacuum at below 40°C and isolated from isopropanol and dried at 70°Cunder vacuum for 5 hrs to afford 65g (82%) of the **4** with a purity of 97 % y HPLC.

(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(piperidin-1-yl)ethoxy)phenyl)methanone hydrochloride(1)

6-Methylsulfonyloxy-2[(4-methylsulphonyloxy)phenyl]-3-[4(2-(piperidinyl)ethoxy]benzoyl] benzothiophene hydrochloride (50 g) was taken in 2 volumes of water. To this mixture 5 molar 250 mL of KOH solution was added and heated to 102-105 °C and maintained for 60 minutes. After reaction completion, reaction mass was cooled to 25-35°C and added 250 mL of water. P^{H} of the reaction mass was adjusted to 10-11 and precipitated solid was filtered and washed with 50 mL of water. Wet material was taken in methanol (340 ml) and water (68 ml) mixture and heated to 70°C and maintained for 45 minutes. After attaining the clear solution charcoal was added and filtered through filter paper after 10 minutes at 70°Cand pH of the clear filtrate was adjusted to 2 with aqueous hydrochloric acid at 65-70 °C for 3 hours. To this reaction mass 300 mL of water was added and slowly cooled to 0-5°C for 60 minutes. Precipitated material was filtered and washed with methanol 34 mL and dried at 70°C to obtain 34g, 88% raloxifene hydrochloride with purity 99.9% by HPLC.Melting range 258-260°C; MS (m/z): 474.6 (M+H). ^{1}H NMR (200 MHz, $CDCl_3$) 1.19-1.63 (m, 6H) 2.31-2.40 (m, 4H), 2.62 (t, *J* = 6 Hz, 2H),

4.10(t, *J* = 6 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 6.89 (q, *J* = 8.6Hz, 2 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz,2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H) 9.75(br, 2H).^{13}C NMR (50 MHz, $CDCl_3$)24.8, 25.5, 54.5, 54.8, 66.4, 107.5, 113.6, 115.1, 116.3, 124.4, 125.4, 126.6, 129.3, 131.5, 133.4, 136.5, 143.6, 154.5, 158.5, 160.2, 163.5, 194.6.Analysis: Calcd for $C_{28}H_{27}NO_4S$: C, 71.01; H, 5.75; N, 2.96; S, 6.77. Found: C, 70.75; H, 5.65; N, 2. 93; S, 6.92.

CONCLUSION

In summary, a simple, convenient one pot synthetic method has been developed for the preparation of Raloxifene by utilizing easily accessible and inexpensive starting materials. This synthetic approach includes some important aspects such as high yields de-protection of sulfonyl group in aqueous media, which make this synthetic protocol useful and an attractive procedure for the industrial synthesis of Raloxifene.

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