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A green process for demethylation reaction in synthesis of raloxifene hydrochloride

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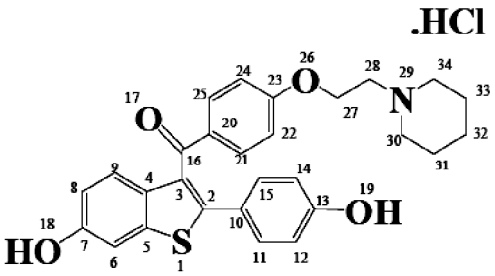
A green process for demethylation reaction in synthesis of raloxifene hydrochloride by using aluminium chloride and odorless decanethiol as demethylation agent instead of aluminium chloride and ethanethiol (foul smell) under normal conditions is described.

Keywords: Estrogen agonist/antagonist, raloxifene, odorless thio, demethylation reaction, aluminium chloride, decanethiol.

Introduction

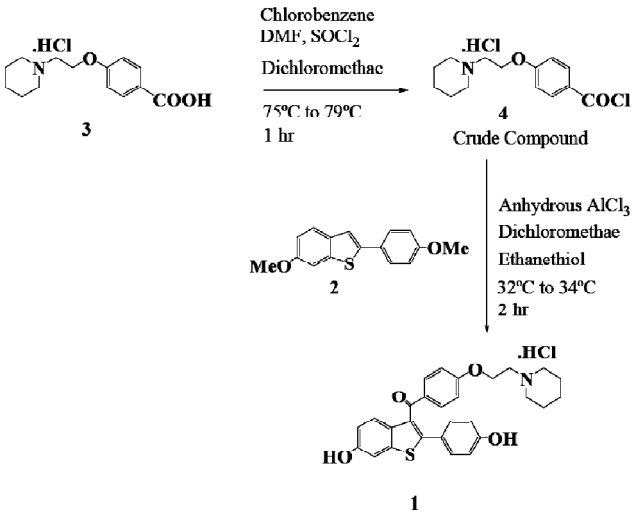
Raloxifene hydrochloride (**1**), is an estrogen agonist/antagonist, commonly referred to as a selective estrogen receptor modulator (SERM)[1,2] that belongs to the benzothiophene class of compounds. Raloxifene decreases the resorption of bone and reduces the biochemical markers of bone turnover to the premenopausal range[3–5]. Raloxifene hydrochloride may also lower the chance of developing a certain type of breast cancer (invasive breast cancer) in postmenopausal women[6,7].



1

Raloxifene hydrochloride

It can be synthesized[3] directly from aroylation of 6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (**2**) by the acid chloride (**4**) of 4-[2-(1-piperidinyl)ethoxy]benzoic acid hydrochloride (**3**) in the presence of $AlCl_3$ followed by addition of ethanethiol (Scheme 1).

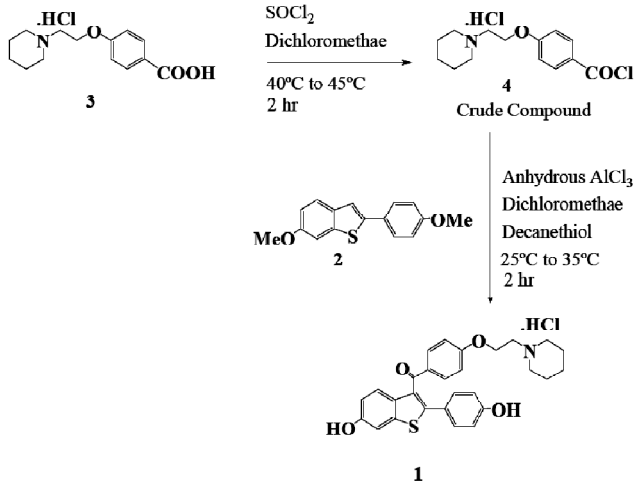


Scheme 1

Results and discussion

Commonly used thiols like ethanethiol and benzyl mercaptan in demethylation reactions have a foul smell making them difficult and unpleasant to use in the laboratory without

fume hoods. The problem becomes even worse in industry on a large scale. Odorless substitutes are therefore always required. Few papers[8,9] discuss the use of long chain thiols to minimize odor, so we used this work as a basis for choosing a long chain thiol for our demethylation reaction. We now report a new, highly active demethylation reagent, an aluminum chloride and decanethiol, characterized by rapid action under mild conditions, easy workup of the reaction product, and high yield (Scheme 2).



Scheme 2

Experimental

4-[2-(1-Piperidinyl)ethoxy]benzoic acid hydrochloride (**3**) and 6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (**2**) were prepared by procedures reported previously[3]. Decanethiol was from commercial source. All melting points are uncorrected and were determined in capillary tubes on a Electothermal melting point apparatus. ^{1}H NMR spectra were recorded on a Brucker ADVANCE 400 MHz spectrometer, using DMSO-d_6 as solvent and TMS as internal standard. Electrospray ionization mass spectroscopy was performed using an ion trap mass spectrometer (Model 6310 Agilent). All reactions were monitored and checked by thin layer chromatography (TLC) using methanol and spots examined by a UV lamp.

*Preparation of [6-hydroxy-2-(4-hydroxyphenyl)benzo-[b]thiophen-3-yl] [4-[2-(1-piperidyl)ethoxy]phenyl]methanone hydrochloride (Raloxifene hydrochloride) (**1**):*

To a solution of 4-[2-(1-piperidinyl)ethoxy]benzoic acid hydrochloride (**3**) (14.3 g, 0.05 mol) in methylene dichloride (400 mL) at 25°C to 35°C, thionyl chloride (23.8 g, 0.20 mol) was added in a dropwise under argon for 15–30 min. The reaction mixture was stirred for 2 h at 40°C to 45°C. Excess thionyl chloride and solvent were removed in vacuo at 40°C to afford 15.0 g of the crude acid chloride hydrochloride salt (**4**). The crude solid acid chloride hydrochloride (**4**) was dissolved in methylene dichloride (150 mL), cooled to 0°C to 10°C, 6-methoxy-2-(4-methoxyphenyl)benzo[*b*] thiophene (**2**) (10.8 g, 0.04 mol) was added. Then, anhydrous aluminium chloride (37.0 g, 0.28 mol) was added portionwise over a period of 30 min and then the mixture was allowed to warm to 30°C and stirred for 2 h at 25–35°C. Then decanethiol (28.0 g, 0.16 mol) was added and stirred for 2 h at 25–35°C. The reaction mixture was quenched with mixture of methanol (100 mL), ice (200 g) and conc. HCl (15 mL) and stirred for 1 h at 25–35°C. The precipitated solid was collected, washed with water (100 mL×2) and dried at 65°C for 4 h to afford 20.0 g of crude compound **1**, which was crystallized from methanol/water (23/1, vol/vol) to yield 13.6 g of compound **1** (53.3%yield) as a white solid, m.p. 258–260°C. lit.[3] 258°C; ^{1}H NMR δ: 1.34, 1.72 (2H, m, $(CH_2CH_2)_2CH_2$), 1.76 (4H, m, $N(CH_2CH_2)_2$), 2.96 (2H, m, N-CH_2), 3.43 (4H, m, $N(CH_2CH_2)_2$), 4.44 (2H, m, O-CH_2), 6.67 (2H, d, Ar), 6.85 (1H, d, Ar), 6.95 (2H, d, Ar), 7.18 (2H, d, Ar), 7.25 (1H, d, Ar), 7.35 (1H, s, Ar), 7.70 (2H, d, Ar), 9.77 (1H, s, OH), 9.82 (1H, s, OH), 10.16 (1H, brs, NH); ^{13}C NMR (70 MHz, DMSO-d_6) δ: 192.7 (C-16), 161.6 (C-23), 158.0 (C-13), 155.7 (C-7), 140.8 (C-5), 139.3 (C-3), 132.3 (C-4), 131.9 (C-21,25), 130.4 (C-10), 129.8 (C-11,15), 129.6 (C-2), 123.8 (C-20), 123.3 (C-9), 115.8 (C-12,14), 115.4 (C-8), 114.6 (C-22,24), 107.3 (C-6), 62.6 (C-27), 54.6 (C-28), 52.7 (C-30,34), 22.3 (C-31,33), 21.1 (C-27); MS (ESI): *m/z* 474.6 (M +H). "This procedure has been scaled up using 250 g of compound **1**".

Conclusion

In conclusion, we have found that decanethiol is odorless thiol compared to ethanethiol. We believe that removing the foul-smelling thiols and use of these odorless thiols will greatly improve the green chemistry.

Acknowledgement

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