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Industrially viable synthesis of 3-[3-(trifluoromethyl)phenyl]propionaldehyde. A key intermediate of cinacalcet

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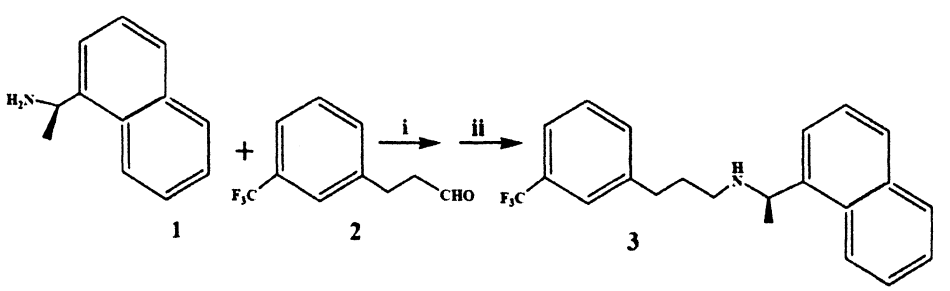
Abstract : An improved synthesis of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (2), a key intermediate of cinacalcet hydrochloride ((*R*)-alpha-methyl-*N*-[3-[3-(triflouoromethyl)phenyl]propyl]-1-naphthalene methane amine hydrochloride) has been described. The key step include the Corey-Kim oxidation under normal conditions.

Keywords : Calcimimetics, cinacalcet, Corey-Kim oxidation, NCS, dimethyl sulfide.

Introduction

Cinacalcet hydrochloride (**3**), an optically active calcimimetic drug, has been approved by the U.S. Food and Drug Administration as Sensiper for the treatment of secondary hyperparathyroidism. A condition characterized by the oversecretion of parathyroid hormone in patients with chronic kidney disease on dialysis[1], has been synthesized[2] by the reductive amination of (*R*)-(1-naphthyl)ethylamine (**1**) with 3-[3-(trifluoromethyl)-phenyl]propionaldehyde (**2**), followed by reduction of the double bond (Scheme 1).



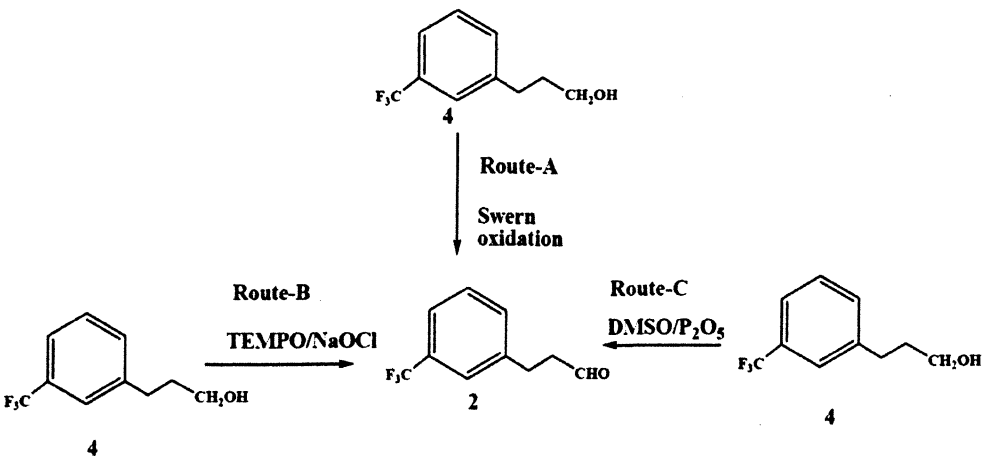
(i) $Ti(O\text{-}i\text{-}Pr)_4$, (ii) $NaCNBH_3$, methanol

Scheme 1

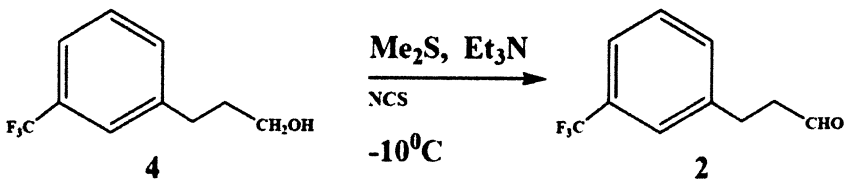
There are three approaches for the preparation of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (**2**), the key intermediate for the synthesis of cinacalcet hydrochloride (**3**). In route A, the preparation of **2** by Swern oxidation of 3-[3-(trifluoromethyl)phenyl]propan-1-ol has been reported[3]. In route B, the preparation of **2** by reacting 3-[3-(trifluoromethyl)phenyl]propan-1-ol with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and sodium hypochlorite in the presence of potassium bromide in methylene chloride has been reported in patent[4]. Route C, involves the oxidation of 3-[3-(trifluoromethyl)phenyl]-propan-1-ol with dimethylsulfoxide and activated by phosphorous pentaoxide[5] to afford compound **2**.

However, all these methods require expensive reagents, low temperature and tedious procedures and thus we set out to find a more economical and efficient method for the preparation of bulk quantities of **2**.

We now report the operationally simple, highly selective and efficient preparation of **2** from 3-[3-(trifluoro-



Scheme 2. Reported synthetic approach of **2**.



Scheme 3

methyl)phenyl]propan-1-ol by the Corey-Kim oxidation[6] (Scheme 3). It is commercially available, easy to handle even at the production scale, and the reaction temperature reported was mild (e.g. brine-cooling). Overall, we optimized the reaction conditions and manufactured the key intermediate aldehyde **2** up to a 250 kg scale.

Experimental

General : Solvents were dried over sodium sulfate and freshly distilled prior to use. ^{1}H NMR spectra were recorded on a Brucker ADVANCE-400 MHz, using $CDCl_3$ as solvent and TMS as internal standard. Infrared spectra were obtained on a Perkin-Elmer spectrum 100 FT-IR spectrophotometer. Electrospray ionization mass spectroscopy was performed using an ion trap mass spectrometer (Model 6310 agilent).

Synthesis of 3-[3-(trifluoromethyl)phenyl]-propionaldehyde (**2**) :

To a solution of 3-[3-(trifluoromethyl)phenyl]propan-1-ol (**4**), (100 g, 0.49 mol) in toluene (2000 ml) at -10 °C to -15 °C, dimethyl sulfide (30 g, 0.48 mol) and triethylamine (62 g, 0.61 mol) were added in a single lot under argon and stirred for 15-30 min. Then *N*-chlorosuccinimide (180 g, 1.35 mol) was added portionwise over 1 h while the internal temperature was maintained at -5 °C to -10 °C. The reaction mixture was stirred for 3 h at -5 °C to -10 °C. Completion of reaction was monitored by gas chromatography (GC). The reaction mixture was diluted with aqueous sodium hydroxide solution (40 g in 1200 ml of water) at -5 °C to -10 °C. After the addition, the mixture was allowed to warm to 20 °C and stirred for 1 h at 20 °C. The aqueous and organic layers were separated and the organic layer was extracted with aqueous sodium bisulfite solution (140 g in 1100 ml of water). Sodium carbonate solution (25% in water) was added to aqueous layer to adjust the pH to 9.5-9.8 and it was extracted with toluene (600 ml). The solvent was removed under reduced pressure to give the pure product 87.0 g (88.0%), as a yellowish oil. ^{1}H NMR ($CDCl_3$, δ ppm) : 9.83 (1H, t, *J* 0.9 Hz), 7.48-7.38 (4H, m), 3.02 (2H, t, *J* 7.2 Hz), 2.82 (2H, m).

Acknowledgement

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