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A Novel Method for the Large Scale Synthesis of Cinacalcet Hydrochloride Using Iron Catalyzed C−C Coupling

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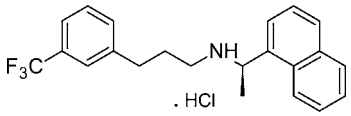
ABSTRACT: A novel synthetic route for commercial preparation of cinacalcet hydrochloride (**1**), a calcimimetic agent and calcium-sensing receptor antagonist, is described. Our synthetic approach involves the preparation of cinacalcet using C−C bond formation catalyzed by iron acetylacetonate/NMP complex with aryl Grignard reagent benzotrifluoride magnesium bromide (**8**) and alkenyl halide *N*-chloropropene naphthylethylamine (**6**).

INTRODUCTION

Cinacalcet belongs to the calcimimetics class of compounds.[1] Calcimimetics are ionomimetics which affect one or more calcium receptor activities by binding to a calcium receptor. This class of compounds is useful for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease and hypocalcaemia in patients with parathyroid carcinoma.[1,2]



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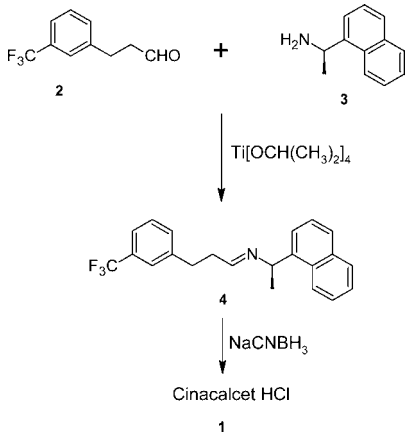
Several synthetic methods are reported for preparation of cinacalcet hydrochloride.[3−5] The reported synthesis as described in *Drugs of the Future* involves the condensation of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (**2**) with (1*R*)-(+)-1-naphthylethylamine (**3**) in the presence of titanium isopropoxide followed by reduction of imine using sodium cyanoborohydride[6,7] (Scheme 1).

In one of the recent publications,[3] industrial application of the Forster reaction for cinacalcet was reported. This article reports a novel method for the preparation of **1** involving iron catalyzed C−C bond formation by Kochi coupling[8,9] of aryl Grignard reagent with alkenyl halide.

Scheme 1



RESULTS AND DISCUSSION

The present method involves C−C bond formation by coupling *N*-chloropropene naphthylethylamine (**6**) and benzotrifluoro-3-magnesium bromide (**7**) in the presence of iron acetylacetonate/*N*-methyl-2-pyrrolidone (NMP) complex (Scheme 2). The preparation of **6** was carried out by phase transfer catalyzed *N*-alkylation of (1*R*)-(+)-1-naphthylethylamine (**3**) with 1,3-dichloropropene (**5**) and potassium carbonate in a biphasic mixture of toluene and water at 65−70 °C. In the reaction 8−10% *N*-dialkylated product **10** was formed and was eliminated during workup. The *N*-alkylated intermediate was isolated as HCl salt in acetone, and its treatment with aqueous sodium hydroxide gave free base **6** as oil. This intermediate **6** reacted with in situ prepared [3-(trifluoromethyl)phenyl]magnesium bromide (**8**) from 3-bromobenzotrifluoride (**7**) at −50 to 0 °C using catalytic quantity of iron acetylacetonate/*N*-methyl-2-pyrrolidone (NMP) to give a mixture of cis and trans unsaturated cinacalcet in the ratio 1:10. Product was isolated as trans unsaturated cinacalcet hydrochloride in 99% purity with ∼1% of cis isomer, and both the isomers on reduction afford cinacalcet hydrochloride. No other byproducts are formed during the reaction.

The product was isolated as unsaturated cinacalcet hydrochloride (**9**) from isopropyl acetate after usual work up. The catalytic hydrogenation of **9** with 2.5% palladium carbon resulted in cinacalcet hydrochloride (**1**) in 56% overall yield from **3** with HPLC purity above 99.5%. Only *N*-propyl naphthylethylamine impurity was observed in less than 0.1% in isolated product. Under this reduction condition no desfluorinated impurity was observed. Residual 1,3-dichloropropene was monitored at genotoxic level in the final product **1** and is not detected.

A novel process for the preparation of cinacalcet using C−C bond formation by iron catalyzed cross coupling of aryl Grignard reagent with alkenyl halide has been developed and

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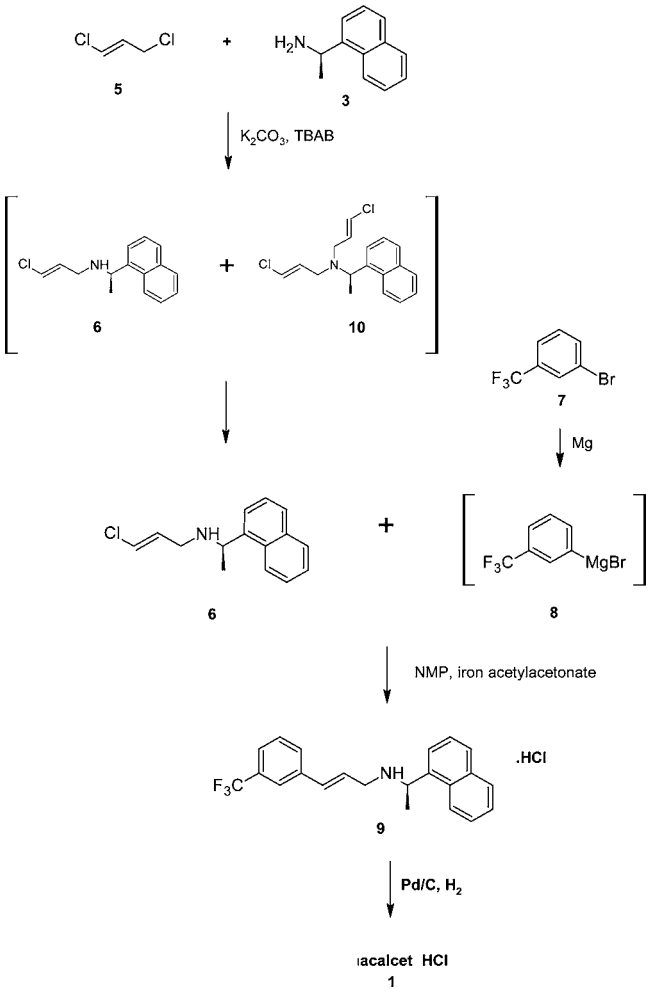
Scheme 2



scaled up at pilot plant using inexpensive and commercially available raw materials.

CONCLUSION

An efficient, scalable and inexpensive novel method for the preparation of cinacalcet hydrochloride in good yield and high purity is reported.

EXPERIMENTAL SECTION

General. Reagents were used as such without purification. 1,3-Dichloropropene is toxic and harmful by inhalation. Suitable personal protective equipment should be used while handling. Melting point points were determined on a Buchi B545 capillary melting point apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker spectrometer. The chemical shift data are reported as δ (ppm) using tetramethylsilane as internal standard. Mass spectra were recorded using an API 2000 (MPS SCIEX) instrument. Infrared spectra were recorded using Perkin-Elmer FTIR (Spectrum One) instrument. HPLC analysis was performed on a Waters instrument with a UV detector (223 nm) using a Inertsil ODS-4 (150 × 4.6 mm, 5 μm) column and mobile phase [buffer (prepared by dissolving 2.72 g of potassium dihydrogen phosphate in water (1 L) and adjusted pH to 6.0 ± 0.05 with dilute KOH solution):acetonitrile, gradient 65:35 (0−25 min), 25:75 (25−45 min) and 65:35 (45−55 min) with flow rate 0.8 mL/min]. The chiral HPLC analysis was performed using a CHIRALPAK IA, 5 μm (250 mm × 4.6 mm) column and mobile phase *n*-hexane, isopropyl alcohol and diethylamine in the ratio 980:20:04 (v/v/v) with flow rate 0.3 mL/min (UV detector at 223 nm).

Preparation of Unsaturated Cinacalcet Hydrochloride (9). *Part A: 3-Chloro-N-[(1R)-1-(naphthalen-1-yl)ethyl]prop-2-en-1-amine (**6**).* To a mixture of **3** (5.0 kg, 0.029 kmol), toluene (25 L), water (2.5 L) and TBAB (1.0 kg, 0.031 kmol) was added potassium carbonate (4.2 kg, 0.03 kmol) at room temperature. The mixture was heated to 60−70 °C. At this temperature 1,3-dichloropropene (4.2 kg, 0.038 kmol) was added and the resulting mixture was refluxed for 1−2 h and monitored by HPLC. After completion of the reaction, it was cooled to room temperature, water (15 L) was added, the mixture was stirred for 10−15 min and the layers were separated. The toluene layer was washed with water (15 L) and recovered under vacuum. The residue was dissolved in acetone (25 L) and water (5 L), and the pH was adjusted to 0.5−1.0 with 6 N hydrochloric acid (∼ 5.0 L) .The resulting slurry was stirred at 25−30 °C for 60 min, and the solid was filtered and washed with acetone (10 L) followed by water (15 L). The wet solid was suspended in a mixture of toluene (25 L), methanol (12.5 L) and water (12.5 L). The pH of the resulting mixture was adjusted to 11−12 with aqueous sodium hydroxide solution (20%, ∼5.0 L) and stirred for 10−15 min. The mixture was allowed to settle, the layers were separated and the organic layer was washed with water (10 L) .Concentration of the toluene layer under vacuum yielded **6** as an oil, which was used in the subsequent step of C−C coupling.

*Part B: Preparation of Grignard Reagent (**8**).* To a suspension of magnesium turnings (1.92 kg, 0.079 kmol) in THF (15 L) was added iodine (10 g), and the mixture was heated to reflux. To this, a solution of 3-bromobenzotrifluoride (7.5 kg, 0.033 kmol) in THF (10 L) was added in portions under reflux conditions and stirred for 60 min. The resulting suspension was cooled to −50 to −55 °C.

*Part C: Preparation of Unsaturated Cinacalcet Hydrochloride (**9**).* Intermediate **6** (from part A) was dissolved in THF (18 L) and cooled to −5 to 0 °C. NMP (50 g, 0.5 mol) and iron acetyl acetonate (180 g, 0.5 mol) were added at −5 to 0 °C and stirred for 5−10 min. This solution was added to the above Grignard reagent (part B) maintained at −50 to −55 °C over a period of 20−30 min keeping the temperature below 0 °C (reaction is exothermic). The reaction mixture was stirred for an additional 20−30 min, and after completion of the reaction, it was quenched with water (7.5 L) followed by addition of 6 N hydrochloric acid solution (25 L) at 25−35 °C and stirred for 60 min. Toluene (25 L) was added, the mixture was stirred for 10−15 min and the layers were separated. The toluene layer was washed with dilute HCl (2 × 2.5 L) and concentrated under reduced pressure. The residue obtained was dissolved in isopropyl acetate (25 L) and stirred for 6−8 h at 15−25 °C. The resultant solid was filtered, washed with isopropyl acetate (10 L) and dried at 45−50 °C under vacuum for 8 h to give unsaturated cinacalcet hydrochloride (**9**) (6.92 kg, 61% yield). HPLC purity: 98.85%. MS (*m*/*z*): 356.2 [M + H]$^+$. Mp: 176−178 °C. ^{1}H NMR ($CDCl_3$): δ 1.97 (d, J = 6.76 Hz, 3H), 3.37−3.39 (m, 1H), 3.68 −3.71 (m, 1H), 5.23−5.27 (m, 1H), 6.12−6.16 (d, J = 15.88 Hz, 1H), 6.44−6.50 (m, 1H), 7.26−7.95 (m, 10H), 8.28 (d, 1H), 10.34 (br, H), 10.83 (br, 1H).

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Preparation of Cinacalcet Hydrochloride (1). To a solution of unsaturated cinacalcet hydrochloride (**9**, 5.0 kg) in ethyl acetate (25 L) and water (1 L) was added 2.5% palladium/carbon (250 g, ∼50% wet) at 25−30 °C. The resulting suspension was hydrogenated at 3−4 kg pressure for 2−3 h, and the reaction was monitored by HPLC. The reaction mixture was filtered, and the bed was washed with a mixture of ethyl acetate (10 L) and DI water (1 L). To the combined filtrate was added water (10 L), and the mixture was stirred for 10−15 min. The ethyl acetate layer was separated and concentrated under reduced pressure. The residue was diluted with fresh ethyl acetate (40 L), and the resulting solution was concentrated under reduced pressure to 20−22 L. The resulting slurry was stirred for 60 min at 25−30 °C, cooled to 0−5 °C, filtered and washed with ethyl acetate (10 L). The wet material was dried under vacuum at 50−55 °C to afford **1** as a white solid (4.55 kg, 91% yield). HPLC purity: 99.86%. S isomer content (chiral HPLC): not detected. Mp: 181−183 °C (lit.[3] mp 178−182 °C). IR (KBr) (cm^{-1}): 3447, 2964, 1587, 800, 776. MS: m/z = 358.3 $[M + H]^+$. ^1H NMR ($CDCl_3$): δ 1.98 (d, J = 6.7 Hz, 3H), 2.2−2.35 (m, 2H), 2.46−2.60 (m, 2H), 2.55−2.85 (m, 2H), 5.10−5.25 (m, 1H), 7.16−7.26 (m, 3H), 7.31−7.33 (d, J = 7.4 Hz 1H), 7.54−7.65 (m, 3H), 7.88−7.97 (m, 3H), 8.23 (d, J = 7.2 Hz,1H). ^{13}C NMR (DMSO-d_6): δ 19.99 (CH_3), 27.01 (CH_2), 31.50 (CH_2), 44.65 (CH_2), 52.05 (CH), 122.58, 122.69, 122.73, 124.42, 124.74, 124.67, 125.50, 126.10, 126.88, 128.83, 128.89, 129.32, 130.28, 132.39, 133.32, 134.10, 142.25.

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Notes

The authors declare no competing financial interest.

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