Abstract: This invention relates to a process for the preparation of cinacalcet hydrochloride and its key intermediate 3-[3-(trifluoromethyl)phenyl]propionaldehyde, said process comprising reductive amination of 3-[3-(trifluoromethyl)phenyl]propionaldehyde and (R)-(1-naphthylethylamine) in presence of activated sodium borohydride by an acid; the invention also provides a process for preparing 3-[3-(trifluoromethyl)phenyl]propionaldehyde by reacting 3-[3-(trifluoromethyl)phenyl]propan-1-ol (IV) with dimethylsulfide and N-chlorosuccinimide; or dimethylsulfide and N-bromosuccinimide; or dimethylsulfide and chlorine gas; or thioanisole and N-chlorosuccinimide; or thioanisole and N-bromosuccinimide in a suitable organic solvent.
A PROCESS FOR THE PREPARATION OF CINACALCET HYDROCHLORIDE AND ITS INTERMEDIATE

FIELD OF THE INVENTION

This invention relates to the field of organic chemistry and more particularly to synthetic process for the preparation of cinacalcet hydrochloride and its intermediate 3-[3-(trifluoromethyl)phenyl]propionaldehyde(I).

BACKGROUND OF THE INVENTION

Cinacalcet hydrochloride (HI), 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. Process for the preparation of cinacalcet was reported in Drug of the future, 2002, 27(9), 831-836. According to the journal, cinacalcet can be prepared by reacting (R)-(1-naphthyl)ethylamine with 3-[3-(trifluoromethyl)phenyl]propionaldehyde in the presence of titanium tetraisopropoxide to give cinacalcet imine, which was then reduced with sodium cyanoborohydride in ethanol. The synthetic procedure was illustrated in scheme I below:

\[ \text{Scheme-1} \]
There are three approaches for the preparation of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I), the key intermediate for the synthesis of Cinacalcet hydrochloride (III). In route A, the preparation of 3-[3-(trifluoromethyl)phenyl]propan-1-ol (IV) has been reported in Tetrahedron Letters, (45), 8355-8358, (2004). In route B, the preparation of I by reacting 3-[3-(trifluoromethyl)phenyl]propan-1-ol (IV) 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 PCT publication WO 2008/035212. Route C, involves the oxidation of 3-[3-(trifluoromethyl)phenyl]propan-1-ol (IV) with dimethylsulfoxide and activated phosphrous pentaoxide to afford compound I has been reported in EP Patent No 2327684 (2011). All these methods commonly require expensive reagents, low temperatures and tedious procedures, thus we report here an improved reproducible process and is amenable to scale-up.

Hence, there is still a need for an improved process for preparing cinacalcet hydrochloride and its intermediate 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I) that can take care of prior art disadvantages. This invention provides a simple and industrially viable process for the synthesis of cinacalcet hydrochloride and its intermediate 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I) which may be more conveniently prepared and enables the synthesis of Cinacalcet hydrochloride to be carried out in a cost effect manner and avoiding unfavorable reaction.

SUMMARY OF THE INVENTION

In one aspect the invention provides a process for the synthesis of cinacalcet hydrochloride (III), by the reductive amination of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I) and (R)-(l-napthyl)ethylamine (II) using activated sodium borohydride by an acid.
In another aspect the invention provides a process for the synthesis of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I), a key intermediate used in the synthesis Cinacalcet. The said process comprises of decomposition of compound of formula VII in the presence of base.

In another aspect the invention provides a process for preparing a compound of formula VII, said method comprises of reacting 3-[3-(trifluoromethyl)phenyl]propan-1-ol (IV) with dimethylsulfide and N-chlorosuccinamide; or dimethylsulfide and N-bromosuccinamide; or dimethylsulfide and chlorine gas; orthioanisole and N-chlorosuccinamide; or thioanisole and N-bromosuccinamide in a suitable organic solvent or mixture thereof.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention provides a method for producing 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I), a key intermediate used in the synthesis Cinacalcet.

One embodiment of this invention is directed to a method of producing 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I). The said method comprises of decomposition of compound of formula VII in the presence of base. The base used in the reaction with the compound of formula (VII) is an alkali metal alkoxide, or an alkali metal hydroxide or alkylamines. The alkoxide is preferably a C1-C6 alkoxide, more preferably a C1-C4 alkoxide, and most preferably a methoxide or ethoxide. The alkali metal is preferably lithium, sodium or potassium. The reaction temperature is suitably in the range from about -25°C to about 10°C.

In another embodiment this invention provides a process of synthesis of compound d of formula VII (sulfoxonium complex) said method comprises of
reacting 3-[3-(trifluoromethyl)phenyl]propan-l-ol (IV) with dimethylsulfide and N-chlorosuccinamide; or dimethylsulfide and N-bromosuccinamide; or dimethylsulfide and chlorine gas; or thioanisole and N-chlorosuccinamide; or thioanisole and N-bromosuccinamide in a suitable organic solvent. The solvent used in the reaction of compound of formula VII is benzene, toluene, xylene, dioxane, tetrahydrofuran, chlorinated solvents or a mixture thereof. The reaction temperature is suitably in the range from about -25°C to about 10°C.

This invention provides a process for the oxidation of 3-[3-(trifluoromethyl)phenyl]propan-l-ol (IV) to 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I), which is operationally simple, highly selective, and efficient. This process would effectively allow an overall transformation such as: RR'CHOH + C12 ----→ RR'CO + 2HCl, which is mediated by a sulfide. The operability of this scheme has now been demonstrated.

For example, treatment of dimethyl sulfide in carbon tetrachloride at 0°C with 1 equiv of chlorine or N-Chlorosuccinamide in carbon tetrachloride at 0°C results in rapid formation of the partially insoluble complex V or VI which when cooled to -20°C and treated with 3-[3-(trifluoromethyl)phenyl]propan-l-ol (IV) for 2 hr at -20°C with stirring is converted to the sulfoxonium complex VII. Addition of 2 equiv of triethylamine removal of the cooling bath, and isolation after 5 min afford pure 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I) in ca.85% yield.
The oxidation of 3-[3-(trifluoromethyl)phenyl]propan-1-ol (IV) can be effected even more cleanly and efficiently (85 % yield) using the reported complex V or VI from dimethyl sulfide and chlorine or N-chlorosuccinimide under carefully controlled conditions.
According to another aspect of the present invention there is provided an improved process for the preparation of cinacalcet hydrochloride in high yield, which comprises
a) Adding 3-[3-(trifluoromethyl)phenyl]propionaldehyde to (R)-(1-
napthyl)ethylamine at room temperature.,
b) Reacting activated sodium borohydride by an acid with the reaction mass obtained in step a.,
c) Quenching the step b reaction mass in aqueous base.,
d) Adding organic solvent and dilute HCl to the reaction mass obtained in step c,
e) Isolating cinacalcet hydrochloride.

Hereinafter the invention is explained more specifically referring to the working examples, it being understood that the examples incur no restricting effect on the invention.

Example 1

Preparation of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I)

To a solution of 3-[3-(trifluoromethyl)phenyl]propan-l-ol (IV) (100g, 0.49 mol) in toluene (2 L) at -10°C to -15°C, dimethyl sulfide (30 g, 0.4828 mol) and triethyl amine (62g, 0.6127mol) were added in a single lot under argon and stirred for 15-30 min. N-Chlorosuccinimide (180 g, 1.3480mol) was added lot wise over 1hr while maintaining the internal temperature at -10°Cto -15°C. The reaction mixture was stirred for 3hr at -10°C to -15°C. Completion of reaction was monitored by Gas Chromatography(GC) or Thin layer chromatography (TLC). After completion of reaction, dilute Sodium hydroxide solution (40 g in 1200mL of water) was added slowly at temperature less than -5°C. After the addition, the mixture was warmed to 20°Cand stirred for 1 hr at 20°C. The aqueous and organic layers were separated and the product from organic layer was extracted with sodium bisulphate solution(140 g in 1100mL of water). The product layer was washed
with dichloromethane (200mL). Sodium carbonate solution (25% in water) was added to product aqueous layer to adjust pH to 9.5 to 9.8. The product was extracted with dichloromethane and concentrated under vacuum to give 3-[3-(trifluoromethyl)phenyl]propionaldehyde as yellow oil (84 g, 85% yield).

Example - 2

Preparation of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I)

To a stirred solution of 3-[3-(trifluoromethyl)phenyl]propan-1-ol (IV) (10 g, 0.049 mol) in dichloromethane, thioanisole (1.3 g, 0.09 mol) and triethylamine (18.5 g, 0.09 mol) were added at 0°C in a single lot under argon. The solution was cooled to -10°C to -15°C. N-Chlorosuccinamide (12.2 g, 0.091 mol) was added lot wise over 1 hr to the reaction mixture while maintaining the internal temperature at -10°C to -15°C. The reaction mixture was stirred for 3 hr at -10°C to -15°C. Completion of reaction was monitored by Gas Chromatography (GC) or thin layer chromatography (TLC). After completion of reaction, dilute sodium hydroxide solution (4 g in 120 mL of water) was slowly added below -5°C. After the addition, the reaction mixture was warmed to 20°C and stirred for 1 hr. The aqueous and organic layers were separated. The product from organic layer was extracted with sodium bisulphitesolution (14 g in 110 mL of water). The aqueous product layer was washed with dichloromethane. The aqueous layer was collected and pH was adjusted to 9.5 to 9.8 with sodium carbonate solution (25% in water). The product was extracted with dichloromethane. Organic layer was concentrated under vacuum to give 3-[3-(trifluoromethyl)phenyl]propionaldehyde as a yellow oil (6.9 g, 70% yield).

Example - 3

Preparation of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I)
To a solution of 3-[3-(trifluoromethyl)phenyl]propan-l-ol (IV) (100g, 0.49 mol) in dichloromethane (2 L) at -10°C to -15°C, dimethyl sulfide (30 g, 0.4828 mol) and triethyl amine (62 g, 0.6127 mol) were added in a single lot under argon and stirred for 15-30 min. N-Chlorosuccinamide (180 g, 1.3480 mol) was added lot wise over 1 hr while maintaining the internal temperature at -10°C to -15°C. The reaction mixture was stirred for 3 hr at -10°C to -15°C. Completion of reaction was monitored by Gas Chromatography (GC) or Thin layer chromatography (TLC). After completion of reaction, dilute Sodium hydroxide solution (40 g in 1200 mL of water) was added slowly at temperature less than -5°C. After the addition, the mixture was warmed to 20°C and stirred for 1 hr at 20°C. The aqueous and organic layers were separated and the product from organic layer was extracted with sodium bisulphate solution (140 g in HOOML of water). The product layer was washed with dichloromethane (200 mL). Sodium carbonate solution (25% in water) was added to product aqueous layer to adjust pH to 9.5 to 9.8. Then the product was extracted with dichloromethane and concentrated under vacumm to give 3-[3-(trifluoromethyl)phenyl]propionaldehyde as a yellow oil (80 g, 81% yield).

Example -4

Preparation of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (I)

To a solution of chlorine (3.2 g, 0.045 mol) in carbon tetrachloride at -10°C, a solution of thioanisole (5.6 g, 0.045 mol) of in dichloromethane was added under argon. A white precipitate appeared immediately after addition of the sulfide. The mixture was cooled to -20°C, and a solution of 3-[3-(trifluoromethyl)phenyl]propan-l-ol (IV) (5g, 0.025 mol) in dichloromethane was added dropwise. Stirring was continued for 90 min at -20°C, and then a solution of triethylamine (4.9 g, 0.05 mol) in dichloromethane was added dropwise. The cooling bath was removed, and after 5 min ether was added. The product from organic layer was extracted with sodium bisulphate solution (7 g in 60 mL of...
water). The product layer was washed with dichloromethane. To the aqueous layer pH was adjusted to 9.5 to 9.8 with sodium carbonate solution (20% in water) and then extracted with dichloromethane. The organic layer was concentrated under vaccum to give 3-[3-(trifluoromethyl)phenyl]propionaldehyde as a yellow oil (2.75 gr, 55% yield).

Example -5

Preparation of Cinacalcet Hydrochloride (III)

3-[3-(trifluoromethyl)phenyl]propionaldehyde (5.9 g, 0.029 mol) was added to (R)-(1-naphthyle)ethylamine (5 g, 0.029 mol) for 30 min at room temperature and stirred for 1 hour. Mixture of boric acid (1.81 g, 0.029 mol) and sodium borohydride (1.08 g, 0.029 mol) was slowly added lot wise for 1 hour at room temperature. Stirred for 12 hours at room temperature, Completion of reaction was monitored by TLC. After the completion of reaction slowly added aqueous sodium bicarbonate (6 g in 100 ml water) for 30 min. Extract the reaction mass with ethylacetate (70 ml). Wash the ethylacetate layer with water (20 ml). Distill of ethyl acetate under vaccum and charged hexane (100 ml) and water (20 ml). Slowly added con. HCl for 30 min to get pH 1 to 3. Stir for 3 hours at room temperature and filter followed by washing with mixture of hexane and water. Crude product is dissolved in acetonitrile (30 ml) and heat to 50-60°C. The clear solution was cooled to 0-5°C and stir for 2 hours. Filter the reaction mass followed by washing with chilled acetonitrile (10 ml). The wet product was dried under vaccum at 50°C to yield Cinacalcet Hydrochloride as a white solid, (9.2 g, 80%).
We Claim

1. A process for preparing a compound of formula (I):

\[
\begin{align*}
\text{CF}_3 \\
\text{I} \\
\text{CHO}
\end{align*}
\]

comprising of decomposition of compound of formula VII in the presence of a base.

2. The process according to claim 1, wherein compound of formula VII is formed by reacting 3-[3-(trifluoromethyl)phenyl]propan-1-ol (IV) with

- dimethylsulfide and N-chlorosuccinamide; or
- dimethylsulfide and N-bromosuccinamide; or
- dimethylsulfide and chlorine gas; or
- thioanisole and N-chlorosuccinamide; or
- thioanisole and N-bromosuccinamide; or
- thioanisole and chlorine gas

3. The process according to claim 2, wherein said reaction is carried out in the presence of a solvent.

4. The process according to claim 3, wherein said solvent is benzene, toluene, xylene, dioxene, THF, chlorinated solvents or a mixture thereof.

5. The process according to claim 2, wherein the reaction is carried out at a temperature in the range from about -25°C to about 10°C.
6. The process according to claim 1, wherein the said base is an alkali metal alkoxide, or an alkali metal hydroxide or alkylamines.

7. The process according to claim 6, wherein said alkali metal is Lithium, Sodium or Potassium.

8. The process according to claim 1, wherein the reaction with the compound of formula VII is carried out at a temperature in the range from about -25°C to about 20°C.

9. A process for the preparation of Cinacalcet hydrochloride (III) in high yield which comprises

\[
\text{III}
\]

a) Adding 3-[3-(trifluoromethyl)phenyl]propionaldehyde to (R)-(1-naphthyle)ethylamine at room temperature,
b) Reacting activated sodium borohydride by an acid with the reaction mass obtained in step a,
c) Quenching the step b reaction mass in aqueous dilute base,
d) Adding organic solvent and dilute HCL to the reaction mass obtained in step c,
e) Isolating cinacalcet hydrochloride.

10. The process according to claim 9, in step a wherein the reaction is carried out at room temperature.
11. The process according to claim 10, wherein the reaction is carried out at about -10 to 50°C.

12. A process according to claim 9 in step b, wherein the suitable acids are boric acid, benzoic acid and para toluene sulfonic acid.

13. The process according to claim 9, wherein the aqueous inorganic base used in step c is carried out aqueous sodium hydroxide, aqueous sodium carbonate, aqueous potassium carbonate and potassium hydroxide.

14. The process according to claim 9, wherein the organic solvent used in step c is carried out tetrahydrofuran, diisopropyl ether, diethyl ether, di-tert-butyl ether, diglyme, dimethoxythane, dimethoxymethane or methoxyethane.
A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C45/30  C07C47/24  C07C209/28  C07C211/30

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>Footnote 12 on p. 8358</td>
<td>2-8</td>
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<td>EP 2 327 684 AI (DI PHARMA FRANCIS SRL [IT]) 1 June 2011 (2011-06-01), cited in the application on the whole document</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search: 11 April 2013

Date of mailing of the international search report: 03/07/2013

Name and mailing address of the ISA/Authorized officer

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
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Mooren, Nicolai
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INTERNATIONAL SEARCH REPORT

**DOCUMENTS CONSIDERED TO BE RELEVANT**

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This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. □ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. □ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8

Remark on Protest

□ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

□ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

□ □ No protest accompanied the payment of additional search fees.
This International Search Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8

   A process for preparing 3-[(trifluoromethyl)phenyl]propionaldehyde

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2. claims: 9-14

   A process for preparing cinacalcet hydrochloride from 3-[(trifluoromethyl)phenyl]propionaldehyde

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<td>US 2011124917 A1</td>
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