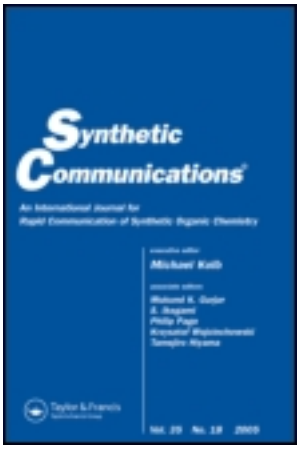

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Efficient Synthesis and Practical Resolution of 1-(Naphthalen-1-yl)ethanamine, a Key Intermediate for Cinacalcet

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EFFICIENT SYNTHESIS AND PRACTICAL RESOLUTION OF 1-(NAPHTHALEN-1-YL)ETHANAMINE, A KEY INTERMEDIATE FOR CINACALCET

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An efficient synthesis of 1-(naphthalen-1-yl)ethanamine (*RS-*2) and its practical resolution to optically pure (1*R*)-(naphthalen-1-yl)ethanamine (*R-(+)-*2), a key intermediate in the synthesis of cinacalcet hydrochloride (1), is described. The resolution of* RS-2 *using* R-*(−)-mandelic acid as a resolving agent in ethanol was established on an industrial scale to give pure* R-(+)-*2 with >99.8% ee after liberation of the amine from its mandelate salt. An efficient process for the racemization of undesired isomer* S-(−)-*2 is also provided to maximize the yield of desired enantiomer.

Keywords: Cinacalcet; industrially feasible; 1-(naphthalen-1-yl)ethanamine; *R*-(−)-mandelic acid; resolution

INTRODUCTION

More than half of the chiral drugs in the pharmaceutical market are produced by the diastereomeric salt-formation method using enantiopure resolving agents.[1] Resolution via diastereomeric salt formation is widely practiced because of the ease of operation and relative simplicity of producing laboratory-scale data efficiently on an industrial scale. Selection of resolving agents, through both rational concepts and practical experience, is an ongoing subject of research and development.[2] Herein, we report a practical synthesis of (1*R*)-1-(naphthlen-1-yl)ethanamine (***R*-(+)-2**), a crucial and cost-contributing intermediate for the preparation of cinacalcet via an efficient resolution process.

Cinacalcet hydrochloride (**1**), 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 (Fig. 1).[3] Different synthetic approaches reported for **1** by various research groups involve ***R*-(+)-2** as common chiral intermediate.[4,5]

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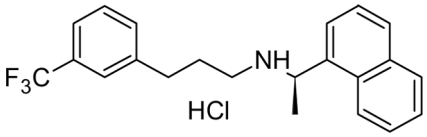
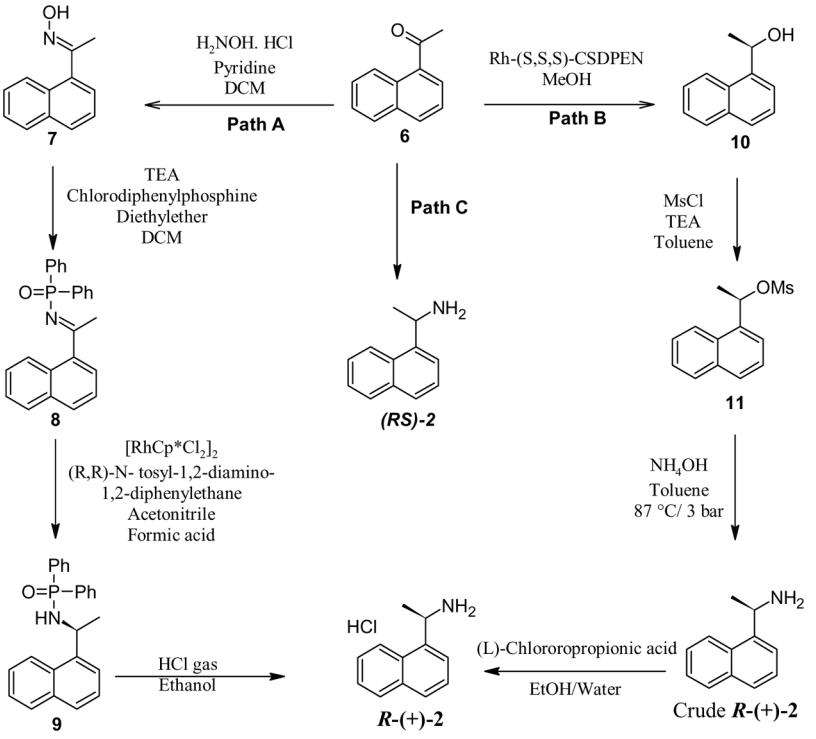


Figure 1. Cinacalcet hydrochloride (**1**).

Martin and Campbell reported[6] the synthesis of ***R*-(+)-2** by reacting 1-acetylnaphthylene (**6**) with hydroxylamine hydrochloride to furnish oxime (**7**), which was further treated with chlorodiphenylphosphine to provide imine derivative (**8**). This was subjected to asymmetric transfer hydrogenation catalyzed by Rh complex, followed by treatment of the obtained protected amine (**9**) with hydrogen chloride gas in ethanol (Scheme 1, path A). This process appears to have limitations: use of expensive ruthenium, iridium, or rhodium complexes. An additional obstacle of this process is to show that the content of these metals in the final active pharmaceutical ingredient (API) is within the acceptable limits.[7]

Blacker and Martin[8] adopted a different strategy for the synthesis of ***R*-(+)-2**; stereoselective reduction of **6** using $[Rh(C_5Me_5)Cl_2]_2$ complex and (*S,S,S*)-Cs-DPEN as a chiral ligand followed by conversion of the obtained (1*R*)-1-naphthalen-1-ylethanol (**10**) to its mesylate derivative (**11**), which was then converted to ***R*-(+)-2**



Scheme 1. Reported synthetic approach of (1R)-1-(naphthalene-1-yl) ethanamine.

with 90–94% ee using aqueous ammonia under reduced pressure (Scheme 1, path B). Enantiopurity of the resulting amine was improved to >99% through diastereomeric salt resolution using optically pure (L)-chloropropionic acid. Notable drawbacks of this synthesis is usage of expensive rhodium complexes and the additional diastereomeric salt resolution step to achieve the desired chiral purity of ***R*-(+)-2**.

Synthetic procedures reported for racemic amine (***RS*-2**) from ketone **6** use carcinogenic pyridine, longer reaction period (5 days), high temperatures (190–200 °C), and high pressure (1000 lbs per inch), which make them not suitable for industrial use (Scheme 1, path C).[6,8,9] With these limitations, development of a practical synthetic method for ***R*-(+)-2** that can be carried out on a large scale with low cost is desirable.

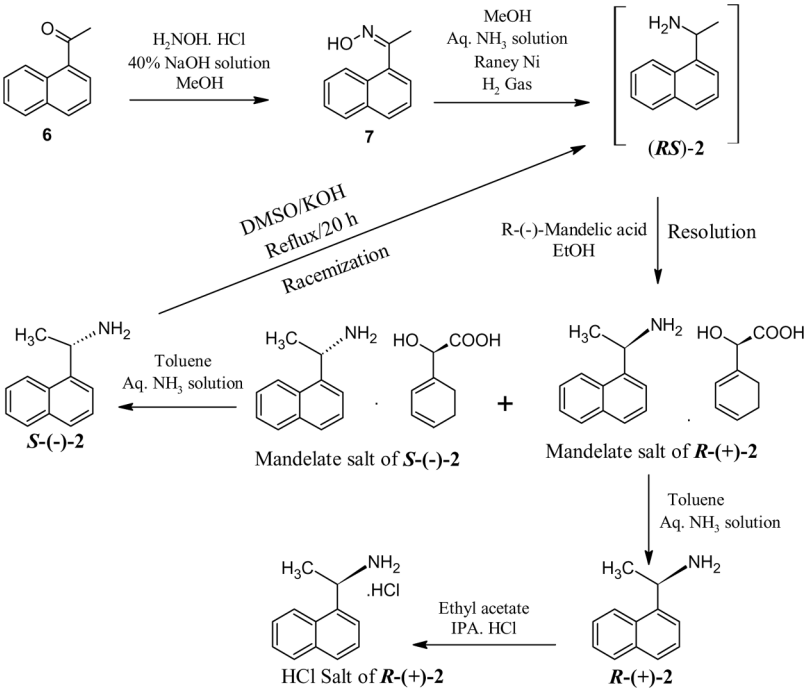
In this communication, we report a simple, efficient, economic, and single-pot synthesis for large-scale preparation of ***RS*-2** and its resolution through diastereomeric salt formation using a commercially available resolving agent, *R*-(−)-mandelic acid, to obtain ***R*-(+)-2** with an efficient turnaround time. The process is of significance because it does not require any enatioselective catalysts, expensive toxic reagents, or harsh reaction condition and is simpler than the other reported approaches.

RESULTS AND DISCUSSION

In our approach, commercially available 1-acetylnaphthalene (**6**) is treated with hydroxylamine hydrochloride in methanol for 4–5 h in the presence of sodium hydroxide to afford an oxime (**7**) in 95% yield. Oxime (7) is then reduced to racemic amine ***RS*-2** by catalytic hydrogenation using Raney-Ni at 55–60 °C for 3–4 h under the hydrogen pressure of 4–5 Kg/cm^2 in a mixture of methanol and aqueous ammonia in the ratio of 3:1 to obtain ***RS*-2** with 97% yield and 97% purity by high performance liquid chromatography (HPLC). The resulting ***RS*-2** obtained after usual workup (as thick syrup) is then subjected to diastereomeric salt resolution in the same pot by adding *R*-(−)-mandelic acid as a resolving agent and ethanol as solvent to furnish mandelate salt of ***R*-(+)-2** in 62–64% yield and >99.5% chiral purity by HPLC and >99.8% chemical purity. The mandelate salt of ***R*-(+)-2** is hydrolyzed with aqueous ammonia in toluene to get ***R*-(+)-2**, which can be converted to HCl salt in ethyl acetate using hydrochloric acid in isopropyl alcohol (IPA-HCl). The mandelate salt of ***S*-(−)-2** present in the mother liquor is hydrolyzed, racemized, and resolved (Scheme 2) to obtain the additional quantity of ***R*-(+)-2**, and the details are furnished here.

Resolution of *RS*-2

To find a suitable resolving agent, commercially available optically pure chiral acids such as mandelic acid, tartaric acid, dibenzoyl tartaric acid, and di-*p*-toluoyl tartaric acid were screened in various solvents such as methanol, ethanol, acetonitrile, ethyl acetate, and acetone for their ability to resolve ***RS*-2**. Among those tested, both the antipodes of mandelic acid are excellent choices for diastereomeric salt formation in ethanol. It is common to apply the opposite enantiomer[10] of the target substrate and hence we opted *R*-(−)-mandelic acid as a resolving agent. The optimized experimental procedure involves heating a mixture of ***RS*-2** and *R*-(−)-mandelic acid in ethanol (six times) to 55–60 °C until a clear solution is



Scheme 2. Synthesis and resolution of **RS-2** and racemization of *S*-(−)2.

obtained. The mixture is gradually cooled to 25–30 °C, and the solid obtained is stirred at 15–20 °C for 50–60 min and then filtered to get crude mandelate salt of ***R*-(+)-2** in 72% yield with enantiomeric purity of >95% by chiral HPLC. The ee of the obtained solid has been improved to >99.5% by HPLC by recrystallizing the crude at 55–60 °C in ethanol. In this process, maintaining the reaction mass below 15 °C for a longer period resulted in coprecipitation of the undesired S-isomer ***S*-(−)-2** as evidenced by the drop in an enantiomeric purity.

Racemization of *S*-(−)-2

The undesired isomer ***S*-(−)-2** recovered from the mother liquor after liberating it from its mandelate salt is heated in dimethylsulfoxide in the presence of potassium hydroxide for 20 h to obtain ***RS*-2** in quantitative yield. The racemate so obtained is then subjected to resolution using aforementioned process to maximize the yield of desired enantiomer ***R*-(+)-2** via another cycle of resolution.

EXPERIMENTAL

1-(1-Naphthyl)ethanone Oxime (7)

A mixture of 1-acetylnaphthalene (**6**, 100 g) and hydroxylamine hydrochloride (123 g) was stirred in methanol (500 mL) at 25–35 °C. The pH of the reaction mass was adjusted 6.0 to 6.5 using 40% solution of sodium hydroxide. The resulting

mixture was then stirred at ambient temperature for 2–3 h. After completion of the reaction as monitored by thin-layer chromatography (TLC), the reaction mass was quenched slowly over water (800 mL), and the obtained suspension was stirred at 25–35 °C for 3–4 h. The slurry was filtered, and the wet cake was washed with cold water (2 × 100 mL) and dried under vacuum to afford compound **7** as a white solid. Yield: 100 g (92%). IR (cm^{-1}): 3280, 3105, 3055, 2358, 2329, 1504, 1307, 1272. MS: m/z 186.5 ($M^+ + 1$). ^1H NMR (CD_3OD, δ ppm): 8.04 (s, 1H), 7.87–7.90 (dd, 2H), 7.84–7.78 (m, 2H), 7.48–7.49 (m, 2H), 2.34 (s, 3H).

(1*R*)-1-(Naphthalen-1-yl)ethanamine Mandelate [Mandelate Salt of *R*-(+)-2]

A mixture of oxime **7** (100 g), Raney nickel (25 g, 25% loading with respect to oxime **7**), methanol (1 L), and aqueous ammonia (300 mL) was stirred under hydrogen pressure at 3.5–4.0 Kg/cm^2 at 58–62 °C for 3–4 h. The catalyst was removed by filtration and washed with methanol (400 mL), and the filtrate was concentrated in vacuo to obtain the thick residue. The residue was dissolved in dichloromethane (400 mL), water (1200 mL) was added, the pH was adjusted between 1 and 2 using conc. hydrochloric acid, the mixture was stirred for 15–20 min, and the organic layer was separated and discarded. The aqueous layer was further washed with dichloromethane (2 × 300 mL) and separated. The pH of the aqueous layer was adjusted to 10–11 using aqueous ammonia, and the desired compound was extracted in toluene (2 × 500 mL). The organic layer was washed with water and brine and distilled to get the residue. The residue containing ***RS*-2** was dissolved in ethanol (425 mL), and a solution of *R*-(−)-mandelic acid (76 g) in ethanol (255 mL) was added over 10 min. The mixture was maintained at 60–65 °C for 45 min. The resulting clear solution was slowly cooled to 25–35 °C and stirred for 2–3 h. The separated solid was filtered, washed with ethanol (40 mL), and dried under vacuum to afford the crude product, which was recrystallized from ethanol (396 mL) to furnish mandelate salt of ***R*-(+)-2** as a white crystalline solid. Yield: 56 g (64%). IR (cm^{-1}): 3415, 3190, 1712, 1180. MS: m/z 172 ($M^+ + 1$). ^1H NMR (DMSO-d_6, δ ppm): 7.47 (ddd, 1H), 7.49 (ddd, 1H), 7.80 (dd, 1H), 7.82 (dd, 1H), 7.87 (dd, 1H), 7.90 (dd, 1H), 8.04 (d, 1H).

(1*R*)-1-(Naphthalen-1-yl)ethanamine Hydrochloride [HCl Salt of *R*-(+)-2]

A mixture of (1*R*)-1-(napthyalene-1-yl) ethanamine mandelate (75 g) and aqueous ammonia (~40 mL) in toluene (750 mL) were stirred, and the organic layer containing the free base was separated and concentrated under vacuum to get a thick residue. The residue was dissolved in ethyl acetate (200 mL), and the pH of the solution was adjusted to 3–4 using IPA-HCl. The resulting solution was cooled to 10–15 °C and stirred for 40–50 min. The solid separated was filtered, washed with ethyl acetate (20 mL), and dried under vacuum to furnish HCl salt of ***R*-(+)-2** as a white solid. Yield: 40 g (84%). IR (cm^{-1}): 3415, 3190, 2983, 2839, 1610, 11.80. MS: m/z 172.6 ($M^+ + 1$). ^1H NMR (DMSO-d_6, δ ppm): 1.60 (dd, 3H), 5.22–5.30 (m, 1H), 7.52–7.62 (m, 3H), 7.80 (dd, 1H), 7.93–8.10 (dd, 2H), 8.13–8.18 (d, 1H), 8.80 (s, 2H).

Racemization of (1*S*)-1-(Naphthalen-1-yl)ethanamine

A mixture of (1*S*)-1-(naphthalen-1-yl)ethanamine (***S*-(−)-2**), free base liberated from the mother liquors containing ~15% of *R*-enantiomer, 10.0 g), dimethylsulfoxide (100 mL), and potassium hydroxide (13.1 g) was heated at 150–160 °C for 20 h. The reaction mixture was cooled to ambient temperature; water (100 mL) was added and stirred for 15 min. The product was extracted into toluene (50 mL × 2), washed with water, and concentrated under vacuum gave the ***RS*-2** as a thick residue. Yield: 9.5 g (95%); chiral HPLC: R-isomer, 44%, and S-isomer, 56%.

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