THIONYL CHLORIDE–MEDIATED SYNTHESIS OF TERT-BUTYL ((S)-1-((R)-OXIRAN-2-YL)-2-PHENYLETHYL)CARBAMATE WITH BOC-INVOLVED NEIGHBORING GROUP PARTICIPATION

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GRAPHICAL ABSTRACT

Abstract A convenient, high-yielding preparation of tert-butyl ((S)-1-((R)-oxiran-2-yl)-2-phenylethyl)carbamate is described. An efficient chiral inversion as the key step is furnished via Boc-involved neighboring group participation mediated by thionyl chloride. This preparation has significant advantages over the previously reported methods with respect to simplicity, cost efficiency, yield, and purification procedure as well as industry reliability.

Keywords Chiral inversion; chiral retention; neighboring group participation; thionyl chloride

INTRODUCTION

Chiral N-protected α-amino epoxides or their derivatives are key building blocks or essential starting materials for a series of HIV protease inhibitors, including atazanavir,[1,2] ritonavir,[3] fosamprenavir,[4] darunavir,[5] saquinavir,[6] amprenavir,[7] and nelfanavir.[8] As a result, the synthesis of related compounds has attracted considerable attention from both academia and the pharmaceutical industry in recent years.

The optically active tert-butyl ((S)-1-((R)-oxiran-2-yl)-2-phenylethyl)carbamate (1)[9] is one of the most important examples. Carbamate 1 can be prepared by epoxidation of the related alkenes, which are usually synthesized via aldehydes by

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Wittig reactions (route 1). It can also be obtained via an intramolecular Mitsunobu reaction \((4, Y=\text{OH})\) or via a direct intramolecular nucleophilic cyclization \((4, Y=\text{halogen}, \text{etc.})\) (route 2). An intramolecular SN2 nucleophilic substitution leads to \(1\) with a configuration inversion on the 2-positioned carbon atom when the sec-hydroxyl group of tert-butyl \((2S,3S)-3,4\)-dihydroxy-1-phenylbutan-2-yl)carbamate \((5)\) is protected with methylsulfonyl chloride (route 3). In addition, the sec-OH group of tert-butyl \((2S,3S)-4\)-chloro-3-hydroxy-1-phenylbutan-2-yl)carbamate \((7)\) can be inversed via an intermolecular Mitsunobu reaction or SN2 nucleophilic substitution with CsOAc, followed by hydrolysis and cyclization to furnish \(1\) (route 4). It is also intriguing to find a recently reported transformation from carbamate \(7\) via an in situ-formed oxazolidinone \(10\) (route 5). (See Scheme 1.)

From the perspective of pharmaceutical production, routes 4 and 5 are highly appreciated because of their high efficiency and convenience, since these routes start from commercially available L-phenylalanine or tert-butyl \((2S,3S)-4\)-chloro-3-hydroxy-1-phenylbutan-2-yl)carbamate \((7)\). However, it is regretful to find that the generation of triphenylphosphine oxide as the major by-product is always troublesome and cannot be removed easily (route 4). In addition, methylsulfonyl esters from methylsulfonyl chloride and alcohols show obvious structural alerts for genotoxicity so that methylsulfonyl chloride and its ester derivatives are now not recommended to be involved in the drug production. Thus it is highly desirable to further improve route 4 and 5 in order to develop a more industrially economical, convenient, and reliable process.

Scheme 1. Reported synthetic routes of \(1\).
RESULTS AND DISCUSSION

Thionyl chloride was reported to react with various alcohols to form chlorosulfite esters.[19] When tert-butyl ((2S,3S)-4-chloro-3-hydroxy-1-phenylbutan-2-yl)carbamate (7) was treated with excess thionyl chloride in methyl tert-butyl ether (MTBE) followed by heating to 55 °C, it was surprising to find the formation of (4S,5R)-4-benzyl-5-(chloromethyl)oxazolidin-2-one (10),[17] which was clean enough for the next step after a usual workup. Protection with Boc$_2$O could furnish (4S,5R)-tert-butyl 4-benzyl-5-(chloromethyl)-2-oxooxazolidine-3-carboxylate (11) in overall 70–75% yield for two steps, followed by hydrolysis under strongly basic conditions to give the target compound tert-butyl ((S)-1-((R)-oxiran-2-yl)-2-phenylethyl)carbamate (1) with more than 92% yield and 99.3% purity. With this process, the target product 1 could be easily obtained through usual workups and crystallizations, making it highly suitable for large-scale production[20] (Scheme 2).

The reaction mechanism of the key step was proposed as follows: Thionyl chloride reacted with 7 to give chlorosulfite esters 12. Probably the newly formed chlorosulfite ester bond was repelled by intramolecular C=O bond of Boc group followed by further rearrangement to form (4S,5R)-4-benzyl-5-(chloromethyl)oxazolidin-2-one (10) with highly efficient chiral inversion. The high efficiency of this SN2 reaction was proved by spiking high-performance liquid chromatography (HPLC) study of compound 10 (crude) and its diastereoisomer (4S,5S)-4-benzyl-5-(chloromethyl)oxazolidin-2-one (14),[21] which indicated that the diastereoselectivity was as high as 297:1 in this key step. Further, the quality of tert-butyl ((S)-1-((R)-oxiran-2-yl)-2-phenylethyl)carbamate (1) was considered to be a key factor to evaluate this route. On the one hand, the diastereoisomer tert-butyl ((S)-1-((S)-oxiran-2-yl)-2-phenylethyl)carbamate (15)[22] was easily prepared from compound 7 by a cyclization in the basic condition. Spiking HPLC analysis shown that there were no obvious diastereoisomer (15) and enantiomer tert-butyl ((R)-1-((S)-oxiran-2-yl)-2-phenylethyl)carbamate (16)[23] found in the crude product of 1, which also meant the complete chiral inversion of SN2 conversion in the first step and the complete retention of the other chiral center in the whole process. On the other hand,
Further verification in the plant confirmed that the quality of compound 1 could completely meet the quality specification set before.

**CONCLUSION**

A new industrially reliable process was developed for the manufacturing of tert-butyl ((S)-1-((R)-oxiran-2-yl)-2-phenylethyl)carbamate (1). Two important intermediates were isolated and characterized, and the reaction mechanism was elucidated. With this process route, product 1 could be conveniently manufactured with good quality. By preliminary estimate, the manufacture cost could be reduced at least 20–30% with the current process compared to the early routes. Further study on the mechanism, process optimization, and process development are still in progress.

**EXPERIMENTAL**

**{(4S,5R)}-4-Benzyl-5-(chloromethyl)oxazolidin-2-one (10)** [20,24]

tert-Butyl ((2S,3S)-4-chloro-3-hydroxy-1-phenylbutan-2-yl)carbamate (7) (10.00 g, 33.4 mmol) was dissolved in 100 mL dry MTBE and stirred, followed by addition of SOCl₂ (14.6 mL, 200.4 mmol) at 10–20 °C within about 20 min. The mixture was heated to 55 °C, kept at this temperature for 8 h, and cooled to 0 °C. Then 50 mL saturated aqueous NaHCO₃ was charged slowly to quench the excess SOCl₂. The mixture was separated and the aqueous layer was extracted with MTBE (2 × 30 mL). The organic layer was combined, washed with saturated aqueous NaHCO₃ (30 mL) and then brine (30 mL), dried over Na₂SO₄, filtered, concentrated to ca. 100 mL, and then used directly for the next step. NMR spectra were recorded after drying in a vacuum for 5 h at room temperature. ¹H NMR (400 MHz, TMS, CDCl₃) δ (ppm) 2.86 (dd, J = 6.8, 13.6 Hz, 1H), 2.96 (dd, J = 7.2, 13.6 Hz, 1H), 3.41 (dd, J = 4.4, 12.0 Hz, 1H), 3.52 (dd, J = 6.0, 11.6 Hz, 1H), 3.96 (dd, J = 6.8, 12.0 Hz, 1H), 4.46 (dd, J = 4.8, 10.0 Hz, 1H), 6.58 (s, 1H), 7.18–7.35 (m, 5H). ¹³C NMR (CDCl₃) δ (ppm) 41.5, 44.4, 56.7, 79.4, 127.4, 129.0, 129.3, 135.4, 158.3. ESI-MS: C₁₁H₁₃ClNO₂ [M+H]⁺ calculated 226.0629, found 226.0633.

**{(4S,5R)}-tert-Butyl 4-Benzyl-5-(chloromethyl)-2-oxooxazolidine-3-carboxylate (11)** [20]

To this solution, trimethylamine (TEA; 8.0 mL, 55.4 mmol), Boc₂O (8.01 g, 36.7 mmol), and dimethylaminopyridine (DMAP; 0.20 g, 0.165 mmol) were added. The reaction was kept at 10–20 °C for about 8 h. The mixture was then filtered and the cake was washed with cold MTBE to collect the solid. The mother liquor was washed with water (30 mL) and brine (30 mL), dried over Na₂SO₄, filtered, and concentrated in a vacuum to give a solid. The solid was combined and recrystallized in EtOH to afford 11 as a white solid (8.10 g, 74% for 2 steps). ¹H NMR (400 MHz, TMS, CDCl₃) δ (ppm) 1.60 (s, 9H), 2.86 (dd, J = 9.6, 13.6 Hz, 1H), 3.28–3.36 (m, 2H), 3.50 (dd, J = 5.6, 12.0 Hz, 1H), 4.36–4.42 (m, 2H), 7.18–7.20 (m, 2H), 7.28–7.36 (m, 3H). ¹³C NMR (CDCl₃) δ (ppm) 28.0, 38.9, 44.5, 58.6, 75.0, 84.4, 127.6, 129.1, 129.4, 134.5, 149.0, 151.0. ESI-MS: C₁₆H₂₀ClINaO₄ [M+Na]⁺ calculated: 348.0979, found 348.0983.
**TERT-BUTYL ((S)-1-((R)-OXIRAN-2-YL)-2-PHENYLETHYL)CARBAMATE**

**Tert-Butyl ((S)-1-((R)-Oxiran-2-yl)-2-phenylethyl)carbamate (1)**[10,12h,14b,14g,20]

Compound 11 (10.0 g, 31.0 mmol) and KOH (5.25 g, 93.0 mmol) were added respectively to 25 mL ethanol and cooled to ca. 5 °C. With stirring, KOH in ethanol was gradually added to the mixture. Then after 30 min the reaction mixture was concentrated in a vacuum, dissolved in 100 mL ethyl acetate, and washed with water (30 mL) and brine (30 mL). The organic layer was collected, dried over Na₂SO₄, filtered, and concentrated in a vacuum to give a colorless liquid (7.75 g, 95%), which could also be solidified at -20 °C to afford the title product as a white solid.

1H NMR (400 MHz, TMS, CDCl₃) δ (ppm) 1.39 (s, 9H), 2.58 (s, 1H), 2.70 (dd, J = 4.4, 4.4 Hz, 1H), 2.85–3.01 (m, 3H), 4.11 (s, br, 1H), 4.53 (s, br, 1H), 7.24–7.30 (m, 5H). 13C NMR (CDCl₃) δ (ppm) 28.3, 39.8, 44.5, 50.4, 52.6, 79.6, 126.6, 128.5, 129.4, 137.4, 155.5. ESI-MS: C₁₅H₂₁NNaO₃ [M+Na]⁺, calculated 286.1414, found 286.1423.

**Acetonyl chloride (14)**[21]

Acetonitrile (15 mL), and boron trifluoride–THF complex (1.0 equiv., 0.70 g) were added to compound tert-butyl ((S)-1-((R)-oxiran-2-yl)-2-phenylethyl) carbamate (1) (1.31 g, 5 mmol). The mixture was stirred at 60 °C for ca. 5 h. This reaction mixture was quenched with water and extracted with dichloromethane (DCM). The organic layer was combined, dried over Na₂SO₄, and purified by flash column chromatography on silica gel (hexane:ethyl acetate = 1:2) to furnish (4S,5S)-4-benzyl-5-(hydroxymethyl)oxazolidin-2-one as a white solid (0.74 g, 71%). 1H NMR (400 MHz, TMS, DMSO-d₆) δ (ppm) 2.69 (dd, J = 8.8, 14.0 Hz, 1H), 2.93 (dd, J = 5.2, 14.0 Hz, 1H), 3.63–3.64 (m, 2H), 4.12–4.17 (m, 1H), 4.51–4.55 (m, 1H), 5.03–5.04 (m, 1H), 7.20–7.32 (m, 5H), 7.54 (s, 1H). 13C NMR (DMSO-d₆) δ (ppm) 35.7, 54.7, 59.5, 79.0, 126.4, 128.6, 129.1, 138.1, 158.2. ESI-MS: C₁₁H₁₄NO₃[M+H]⁺, calculated 208.0968, found 208.0975.

**Acetonyl chloride (14)**[22]

Compound 7 (3.0 g, 10.0 mmol) and KOH (1.68 g, 30.0 mmol) was added respectively to 20 mL ethanol and cooled to ca. 5 °C. With stirring, KOH in ethanol was gradually added to the mixture. Then after 30 min the reaction mixture was concentrated in a vacuum, dissolved in 100 mL ethyl acetate, and washed with water (30 mL) and brine (30 mL). The organic layer was collected, dried over Na₂SO₄, filtered, and concentrated in a vacuum to give a colorless liquid (7.75 g, 95%), which could also be solidified at -20 °C to afford the title product as a white solid.

1H NMR (400 MHz, TMS, CDCl₃) δ (ppm) 1.39 (s, 9H), 2.58 (s, 1H), 2.70 (dd, J = 4.4, 4.4 Hz, 1H), 2.85–3.01 (m, 3H), 4.11 (s, br, 1H), 4.53 (s, br, 1H), 7.24–7.30 (m, 5H). 13C NMR (CDCl₃) δ (ppm) 28.3, 39.8, 44.5, 50.4, 52.6, 79.6, 126.6, 128.5, 129.4, 137.4, 155.5. ESI-MS: C₁₅H₂₁NNaO₃ [M+Na]⁺, calculated 286.1414, found 286.1423.

1H NMR (400 MHz, TMS, CDCl₃) δ (ppm) 2.69 (dd, J = 8.8, 14.0 Hz, 1H), 2.93 (dd, J = 5.2, 14.0 Hz, 1H), 3.63–3.64 (m, 2H), 4.12–4.17 (m, 1H), 4.51–4.55 (m, 1H), 5.03–5.04 (m, 1H), 7.20–7.32 (m, 5H), 7.54 (s, 1H). 13C NMR (DMSO-d₆) δ (ppm) 35.7, 54.7, 59.5, 79.0, 126.4, 128.6, 129.1, 138.1, 158.2. ESI-MS: C₁₁H₁₄NO₃[M+H]⁺, calculated 208.0968, found 208.0975.

1H NMR (400 MHz, TMS, CDCl₃) δ (ppm) 2.71 (dd, J = 12.8, 11.6 Hz, 1H), 3.10 (dd, J = 3.2, 13.2 Hz, 1H), 3.77 (dd, J = 8.0, 11.6 Hz, 1H), 3.85 (dd, J = 5.6, 11.6 Hz, 1H), 4.10–4.16 (m, 1H), 4.84–4.89 (m, 1H), 5.12 (br, 1H), 7.19 (d, J = 7.2 Hz, 2H), 7.26–7.38 (m, 3H); 13C NMR (CDCl₃) δ (ppm) 35.5, 40.0, 56.0, 77.7, 127.5, 129.0, 129.3, 136.0, 157.3. ESI-MS: C₁₁H₁₃ClNO₂ [M+H]⁺, calculated 226.0629, found 226.0635.

**Tert-Butyl ((S)-1-((S)-Oxiran-2-yl)-2-phenylethyl)carbamate (15)**[22]

Compound 7 (3.0 g, 10.0 mmol) and KOH (1.68 g, 30.0 mmol) was added respectively to 20 mL ethanol and cooled to ca. 5 °C. With stirring, KOH in ethanol
was gradually added to the mixture. The reaction was stirred for another 1 h and then concentrated in a vacuum. The crude mixture was dissolved in 40 mL ethyl acetate, washed with water (30 mL) and brine (30 mL), dried over Na₂SO₄, filtered, and concentrated in a vacuum to give a white solid (2.42 g, 92%). ¹H NMR (400 MHz, TMS, CDCl₃) δ (ppm) 1.38 (s, 9H), 2.76 (br, 1H), 2.78–2.81 (m, 1H), 2.87–2.99 (m, 3H), 3.70 (s, br, 1H), 4.49 (s, br, 1H), 7.21–7.31 (m, 5H). ¹³C NMR (CDCl₃) δ (ppm) 28.3, 37.6, 46.9, 52.6, 53.2, 79.6, 126.7, 128.6, 129.5, 136.8, 155.3. ESI-MS: C₁₅H₂₁NNaO₃ [M+Na]⁺, calculated 286.1414, found 286.1418.

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SUPPORTING INFORMATION

Full experimental detail, ¹H and ¹³C NMR spectra, HPLC conditions, and charts for this article can be accessed on the publisher’s website.

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