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Simple and efficient protocol for synthesis of *N-Boc* protected oxazolidines via cyclization of chiral serine

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ABSTRACT

In present work we wish to report synthesis and characterization of (S)-tert-butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (5) derivatives from L-Serine as a chiral starting material. Amino terminal of L-serine was protected by $(Boc)_2O$ (ditertiary butyl dicarbonate); Cyclization of C- and N-terminal protected α-L amino acid is achieved by refluxing it with DMP (2, 2 dimethoxy propane) and PTSA (*para* toluene sulfonic acid) in benzene. Structure of the product was confirmed by FT-IR, LC-MS, ^{1}H NMR and ^{13}C NMR. Retention of stereochemistry was confirmed by optical rotation obtained on polarimeter. After hydrolysis of methyl ester of 2, 2-dimethyloxazolidine, alcohol as side chain obtained underwent for 'Swern Oxidation' using TFAA (Trifluoro acetic anhydride), TEA and DMSO to afford aldehyde.(S)-tert-butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate as final product, which is important synthetic precursor for synthesis of medicinally significant candidates.

KEYWORDS

Serine;
Oxazolidine;
Swern oxidation.

INTRODUCTION

Nitrogen-containing molecules are critical building blocks in pharmaceuticals, catalysts, and materials[1]. Among them, 1, 3-oxazolidine derivatives are of particular interest because of their wide applications in organic synthesis, chiral auxiliaries or ligands, and drug designing such as the anticancer prodrugs, doxoform, doxazolidine, and doxaz carbamate[2]. *N*-Boc protected 2-substituted-1, 3-oxazolidines are also vastly studied nitrogen-containing heterocycles due to their effective application in medicine, agriculture, and polymer and paint and varnish industry[3]. (S) - tert - butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (5) has been discovered to be a promising precursor to form analogs of sphingosine to inhibit the enzyme Protein Kinase C (PKC) that promotes cell growth and cell differentiation[4]. These analogs are believed to hinder tumor cells from spreading, which can be a useful tool in the steadfast discovery for a cure for cancer[5]. Substituted oxazolidines have been investigated extensively because of their importance as chiral auxiliaries in the synthesis of a variety of chiral compounds and as chain protecting groups for amino alcohols[6]. 1, 3-Oxazolidines are usually prepared by condensation of 1, 2- amino alcohols with aldehydes or ketones but these reactions are time consuming and less yielding[7]. Therefore, it is highly desirable to develop new method for the efficient construction of 1, 3-oxazolidine moieties. So looking to this context of amino alcohol herein,

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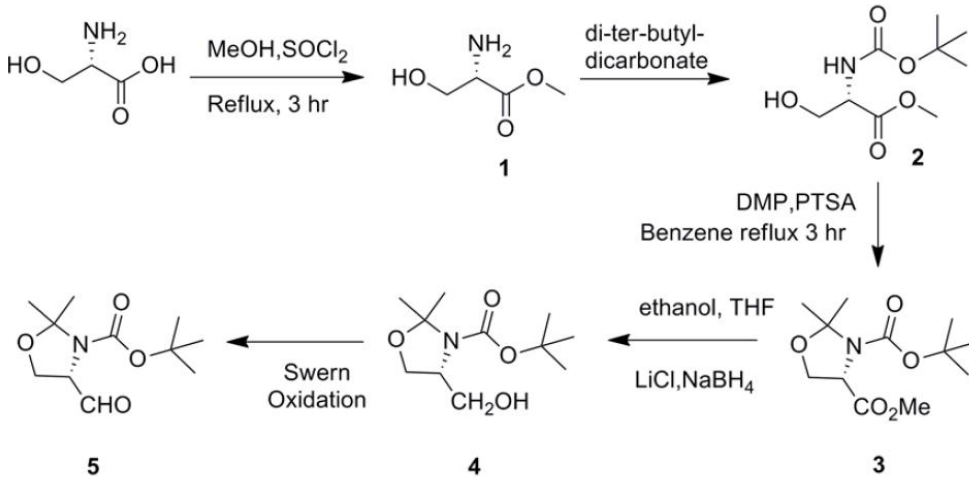

Scheme 1

we wish to report the synthesis of (S) N-*Boc* 4-(hydroxymethyl)-2, 2-dimethyloxazolidine, from reasonably cheap starting material chiral L-serine and then followed by swern oxidation to afford aldehyde at 4th position of oxazolidine.

RESULT AND DISCUSSION

Methyl esterification of L-Serine (1) was done by reported procedure[8], using methanol and thionyl chloride refluxed for 3 hr, followed by N-*Boc* protection, to afford carboxyl and amino terminal protected (*S*)-L-Serine (2). This isomer was confirmed by retention of configuration observed by optical rotation. This protection strategy facilitated us to afford cyclized product i.e. oxazolidines (3). Cyclization was achieved by refluxing (2) with DMP (2, 2 dimethoxy propane) and PTSA (*p*-toluenesulfonic acid) in benzene. Product (3) of this step was confirmed and characterized by spectral data. Next step was to prepare an aldehyde (5) from (3). A reaction was planned on the ground of analogous procedure reported[9] using DIBAL (Diisobutylaluminium hydride) (1 eq.) in toluene, but no (S)-tert-butyl 4-formyl-2, 2-dimethyloxazolidine-3-carboxylate (5) was formed. Large starting material was unconsumed, instead an alcohol (4) was formed in little amount. From this result, we decided to prepare an alcohol (4) and then it's oxidation to afford desired aldehyde (Scheme 1) rather than direct route[9].

So, synthesized oxazolidine (3) was treated for ester hydrolysis to afford alcohol functionality (4), a hydrolysis reaction was done successfully with good yield using LiCl & $NaBH_4$ in ethanol and THF. After workup and column purification, isolated product was confirmed by FT-IR spectra where apparently IR absorbance due to hydroxyl group was observed at cm^{-1}: 3582. Oxidation of alcohol functionality was achieved by modified 'Swern Oxidation' procedure to afford final compound (S)-tert-butyl 4-formyl-2, 2-dimethyloxazolidine-3-carboxylate (5), In this procedure TFAA (Trifluoro acetic anhydride) was used instead of oxalyl chloride as it leads to formation of number of byproducts[10]. After workup new non-polar spot was observed in TLC which was then purified by column chromatography and confirmed as desired product by FT-IR, LC-MS, ^{1}H NMR and ^{13}C NMR spectra.

EXPERIMENTAL

Commercial grade reagents were used without further purification. Solvents were dried and distilled following the usual protocols. Column chromatography was carried out using silica gel (100–200 mesh). TLC was performed on aluminium-backed plates coated with Silica Gel 60 with F_{254} indicator. The ^{1}H NMR spectra were recorded with a 400 MHz and ^{13}C NMR spectra were recorded with a 100 MHz using $CDCl_3$ and DMSO-d_6. ^{1}H NMR chemical shifts are expressed in parts per million (δ). ^{13}C NMR chemical shifts are expressed in parts per million (δ).

IR spectra are recorded on FT-IR (PERKIN ELMER) instrument. Mass of synthesized materials was determined on LC-MS (Q-trap): Triple quadrapole instrument (m/z values are given).

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(S)-methyl 2-amino-3-hydroxypropanoate (1)

In inert atmosphere, L-Serine (9.59 mmol) was dissolved in methanol (2 ml/mmol) and cooled to < 0° C (brine/ice). Thionyl chloride (56.69 mmol, 5.9eq.) was added slowly by syringe, reaction mixture was refluxed for 3 hr and then concentrated and co-evaporated with ether. TLC was monitored in BuOH: Acetic acid: Water (3:1:1) system. Product was confirmed by LC-Ms. m/z: 119.09 with yield 80 %. *White crystalline solid* M.P:- 162-166 °C.

(S)-methyl 2-((tert-butoxycarbonyl) amino)-3-hydroxypropanoate (2)

(S)-methyl 2-amino-3-hydroxypropanoate (1) (3.22mmol) was reconstituted in CH_2Cl_2 and triethylamine (8.06 mmol, 2.5 eq) was added drop wise at 0°C in presence of nitrogen. To this stirring solution, was added di-tertbutyl dicarbonate (3.86mmol, 1.2eq.) in one portion. The reaction mixture was stirred until the starting material was consumed, as determined by TLC (1:1 EtOAc/ hexane) & observed in Ninhydrin stain. The reaction mixture was concentrated and dissolved in EtOAc (15 ml) and then washed with saturated $NaHCO_3$ (aq) (3ml) followed by brine. Organic part was dried over sodium sulphate and evaporated under reduced pressure. Purification was done by column chromatography (silica G 100-200), product was eluted using 10, 15, 20, 25, 30% ethyl acetate/ hexane as mobile phase. Isolated as *yellow oil*, with yield 75%. Product was confirmed by LC-Ms m/z: 219.11, Optical rotation $[\alpha]_{27D}$ 27D -18.7º (*c* 6.16, MeOH) which is very close to that of reported value[11], {Lit[11] [α]27D 27D -18.9º (*c* 5.00, MeOH)}, ^{1}H NMR, 400 MHz, $CDCl_3$: 9H (s, δ=1.44), 1H (s, δ=2.1) 3H (s, δ=3.78), 2H (m, *J*=6.664, δ=3092), 1H (s, δ=4.38), 1H (s, δ=5.40). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ: 28.4 (3 x -*C*H_{3Boc}), 51.8 (-*C*H_3), 59.6(-*C*-NH_2), 62.4 (*C*-OH), 79.6 (-*C*-CH_3*Boc*), 156.0(-*C*O_{2Boc}), 171.4 (-*C*O_2-).

(S)-3-tert-butyl 4-methyl 2, 2-dimethyloxazolidine-3, 4-dicarboxylate (3)

(S)-methyl 2-((tert-butoxycarbonyl) amino)-3-hydroxypropanoate (2) (2.28 mmol), 2, 2-dimethoxypropane (4.56 mmol, 2eq), and PTSA monohydrate (0.228 mmol, 0.1eq) in benzene (8mL) was heated at reflux for 30 min and slowly distilled until a volume of 6 ml of solvent had been collected. Additional DMP (0.1mL) and benzene (3 ml) were added, and the procedure was repeated to collect 3 ml of distillate. The cooled solution was diluted with diethyl ether (15 ml) and washed with saturated $NaHCO_3$ solution (2 x 5 ml), and saturated NaCl solution (5 ml). The organic layer was dried over Na_2SO_4 and concentrated. Purification was done by column chromatography (silica G 100-200); product was eluted using 10-12% ethyl acetate/ hexane as mobile phase. Compound isolated as *brown oil*, with 62 % yield. Product was confirmed by LC-MS m/z : 259.14, Optical rotation $[\alpha]_{27D}$ 27D -54.3º (*c* 1.16, $CHCl_3$) which is very close to that of reported value[11], {Lit[11] [α]27D 27D -54.0º (*c* 1.07, $CHCl_3$)} ^{1}H NMR, 400 MHz, $CDCl_3$, 9H (m, δ=1.46), 3H (d, δ=1.53), 3H (d, δ=1.64), 3H (s, δ=3.74), 1H (m, *J*=2.6, δ=4.03), 1H (m, *J*=7.32, δ=4.13), 1H (m, *J*=2.88, δ=4.40). IR (film) cm^{-1}: 3130, 2951, 2761, 2258, 1755, 1598, 1373, 1189, 1076, 736, 594. ^{13}C NMR ($CDCl_3$) δ: 24.7 (*dimethyl*), δ: 28.4 (3 x -*C*H_{3Boc}), 51.8 (*C*H_3), 63.3 (-*C*H_2-O $_{oxazolidine}$), 69.6 (-*C*-N- $_{oxazolidine}$), 79.8 (-*C*-CH_3*Boc*), 106.7 (-*C*-$_{dimethyl}$) 151.7 (-*C*O_{2Boc}), 171.4 (-CO_2-).

(S)-tert-butyl 4-(hydroxymethyl)-2,2-dimethyloxazolidine-3-carboxylate (4)

To a suspension of lithium chloride (1.54 mmol, 2eq.) and sodium borohydride (1.54 mmol, 2eq.) in ethanol (1.5 ml), at 0 °C under nitrogen, a solution of *ter*-butyl 4-(hydroxymethyl)-2, 2-dimethyloxazolidine-3-carboxylate (3) (0.771) in dry THF (0.8 ml) was added dropwise. The mixture was stirred at room temperature for 4 hr and the precipitate formed was removed by filtration and washed with ethanol (4 ml). The filtrate and washings were then concentrated to a white residue which was extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution (250 ml) and dried over Na_2SO_4. The product was purified by column chromatography (silica G 100-200) and eluted using 17-19 % ethyl acetate/ hexane as mobile phase. Product obtained was *yellow oil*, with 88 % yield and confirmed by LC-MS m/z: 231.12, ^{1}H NMR 400 MHz in $CDCl_3$, 9H (s, δ=1.48), 4H (m, δ=3.70), 1H (s, δ=4.01), 1H (s, δ=4.10). IR (film) cm^{-1}: 3582, 3030, 2958, 2258, 1598, 1435, 1373, 1326, 1189, 1076, 736, 594. ^{13}C NMR, 100 MHz,

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($CDCl_3$) δ: 25.4 (*dimethyl*), δ: 28.4 (3 x -CH_{3Boc}), 60.1 (-CH_2-OH), 65.3 (-CH_2-O $_{oxazolidine}$), 67.6 (-*C*-N- $_{oxazolidine}$), 79.8 (-*C*-CH_{3Boc}), 106.7 (-*C*-$_{dimethyl}$) 153.4 (-CO_{2Boc}).

(S) *ter*-butyl 4-formyl-2, 2- dimethyloxazolidine-3-carboxylate (5)(Modified Swern oxidation)

To a pre-cooled solution of methylene chloride (1.5ml/mmol) and DMSO (.05mmol, 2eq) at-78°C TFAA Trifluro acetic anhydride (0.38mmol, 1.5eq) was added dropwise. After1hr, (S)-tert-butyl 4-(hydroxymethyl)-2,2-dimethyloxazolidine-3-carboxylate (4) (0.259mmol) in methylene chloride was added over a period of 15 min. The reaction mixture was stirred at -78 °C for 1 hr, at this time triethylamine (0.108ml) was added. The resulting solution was warmed to 25 °C, quenched with saturated aqueous NaCl solution (2 ml) and extracted with diethyl ether (2 x 8 ml). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford a crude oil. The product was purified by column chromatography (silica G 100-200) and eluted using 12-14 % ethyl acetate/ hexane as mobile phase. Compound obtained as *brown oil* with 84 % yieldand confirmed by LC-MS m/z: 229.17, ^{1}H NMR, 400 MHz, $CDCl_3$, 15 H (m, δ=1.42-1.48), 2H (m, δ=4.13), 1H (s, δ=4.32), 1H (s, δ=9.54). IR (film) cm^{-1}: 3028, 2967, 2234, 1737, 1598, 1435, 1373, 1326, 1189, 1076, 736, 594. ^{13}C NMR, 100 MHz, ($CDCl_3$) δ: 24.4 (*dimethyl*), δ: 28.2 (3 x -CH_{3Boc}), 60.3 (-CH_2-O $_{oxazolidine}$), 79.6 (-*C*-N- $_{oxazolidine}$), 79.8 (-*C*-CH_{3Boc}), 106.7 (-*C*-$_{dimethyl}$) 151.8 (-CO_{2Boc}).

CONCLUSION

We have synthesized N-Boc protected 4-formyl-2,2-dimethyloxazolidine by using simple cheap starting material L-serine involving minimum and novel steps. Application of swern oxidation using, TFFA (Trifluro acetic anhydride) is well explored to afford final desired aldehyde compound.

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