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Novel practical synthesis of D-cycloserine

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ABSTRACT

The synthesis of D-cycloserine has been successfully accomplished from the readily available D-serine through three simple and efficient routes. In each synthetic strategy, cyclization reactions are involved as the key step, and one-pot processes are employed. The simple treatment and mild reaction conditions are attractive features in this methodology.

The chemical structure of D-cycloserine, a natural product of *Streptomyces orchidaceus*, *Streptomyces garyphalus*, and *Streptomyces lavendulus*, has been observed to be D-4-amino-3-isoxazolidone.[1]

D-Cycloserine is recognized as the effective drug against a number of bacteria. It is an antibiotic with a broad spectrum of activity and clinically used against *Mycobacterium tuberculosis* and *Mycobacterium avium*.[2] As a competitive antagonist of D-alanine, D-cycloserine inhibits D-alanyl-D-alanine synthetase and D-alanine racemase.[3] This leads to the destruction of bacteria because inhibiting those two enzymes interrupts the bacterial cell wall synthesis. Increased interests in D-cycloserine also have stimulated the study of the synthesis and antibacterial activity of cycloserine derivatives for potential antibiotic.[3,4]

Another interesting use of D-cycloserine can be found in the treatment of psychotherapy. Studies have shown that D-cycloserine can facilitate the extinction learning by partially binding and activating *N*-methyl-D-aspartate (NMDA) receptor at the glycine recognition site.[5] D-Cycloserine enhances the outcomes of the treatment for anxiety disorders and obsessive–compulsive disorders when it is employed before exposure therapy.[6] Moreover, administration of D-cycloserine affects on memory consolidation, which can be used on negative symptoms and cognition in mental illnesses, such as Alzheimer's disease and schizophrenia.[7]

While various applications of D-cycloserine have been investigated, several efforts to optimize the production of the compound with shorter steps, stable intermediates, and satisfactory yields have been made.[8] Recently, we reported the synthesis of D-cycloserine.[9] Our previous routes to the D-cycloserine utilized Mitsunobu reaction of primary alcohol of D-serine with N-hydroxyphthalimide. The removal of phthalimide group of D-serine using hydrazine led to the cyclization and then deprotection of TFA with NaOH provided D-cycloserine. Although this synthesis has some advantages such as mild reaction conditions and easy manipulation, the synthetic route consists of four steps from starting material. Therefore, we were encouraged to exploit short and facile synthetic routes toward D-cycloserine by using cheap reagents. Herein, we describe three efficient synthetic methods for D-cycloserine.

In this Letter new research techniques for the synthesis of D-cycloserine from inexpensive and readily available D-serine are described in details. The first step of the synthesis involved the formation of methyl ester moiety from carboxyl acid of D-serine in the presence of acetyl chloride in methanol solution. This was achieved through reflux while the primary amine functional group of D-serine was protected with HCl.[10] The product of this step was D-serine methyl ester. The treatment of this compound **2** with trifluoroacetic anhydride and triethyl amine in CH_2Cl_2 successfully resulted in a high yield of the compound **3**, which was protected by TFA moiety, shown in Scheme 1.

Next, compound **3** was reacted with methanesulfonyl chloride and then trifluoroacetohydroxamic acid to finally yield D-cycloserine. This process utilizes a simplified technique where the intermediary compound **4** formed from compound **3** could further react with trifluoroacetohydroxamic acid followed by addition of NaOH in one-pot synthesis. This enabled the path to perform multiple transformations in a single reaction vessel. This technique is one

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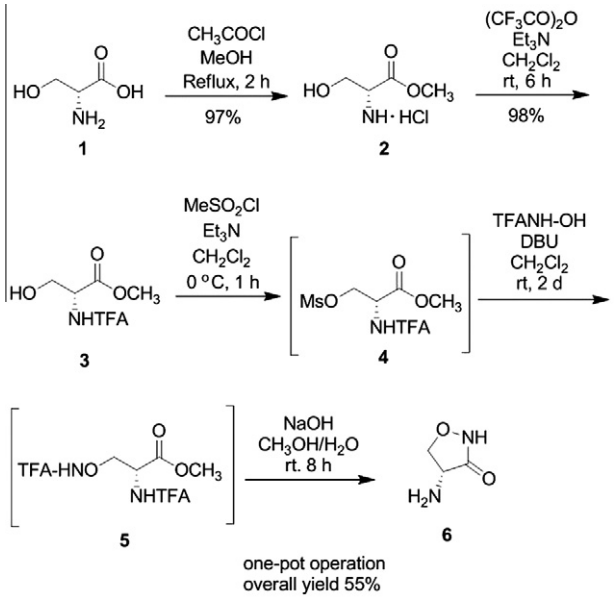
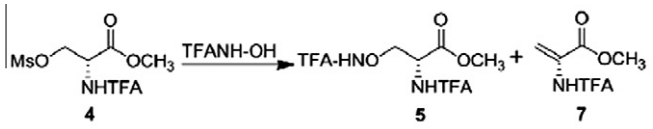


Scheme 1. Synthesis of D-cycloserine via mesylation (method A).

Table 1
O-Alkylation of compound **4** with the trifluoroacetohydroxamic acid



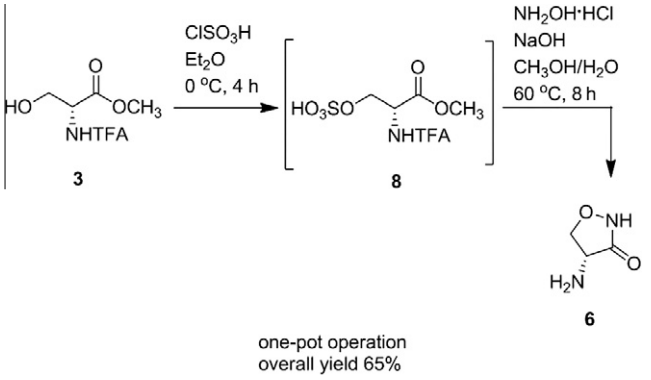
Entry	Reagent	Yield[c] (%) of **5**	Yield[c] (%) of **7**
1[a]	NaOH	5	82
2[a]	$NaOCH_3$	9	78
3[b]	DBU	72	11

[a] Reaction run at rt for 5 h.
[b] Reaction run at rt for 2 d.
[c] Isolation yield.

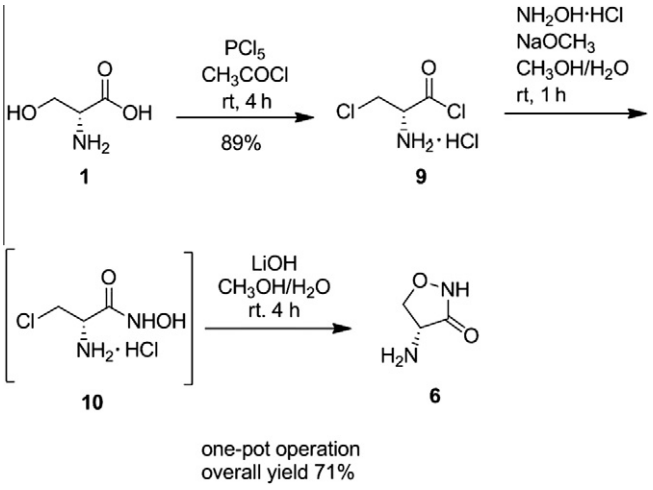
of the most efficient methods which would provide many advantages such as reduction of purification procedures, while reducing excessive chemical waste production. The one-pot synthesis of this study consisted of mesylation of primary alcohol, nucleophilic reaction with trifluoroaceto hydroxamic acid and addition of NaOH in methanol and H_2O.

For the transformation of primary alcohol into O-substituted hydroxylamines, the alcohol functional group was successfully converted into mesyl esters in a triethylamine solution, and subsequently a nucleophilic reaction was carried out in the presence of trifluoroacetohydroxamic acid to yield the final product.

Although methanesulfonyl functional group is a good leaving group for nucleophilic substitution reactions, it could also easily lead to side reactions such as elimination reactions. Therefore, several basic solutions of various bases were examined for the second step of the synthesis. When bases such as sodium hydroxide and sodium methoxide were treated with mesylate ester of compound **4**, the nucleophilic substitution reactions resulted in very low yields (5% and 9%, respectively), and the elimination product was the major product (82% and 78% yields, respectively). However, O-alkylation of trifluoroacetohydroxamic acid with the Ms-O functional group successfully accomplished the goal of the synthesis in



Scheme 2. Synthesis of D-cycloserine via sulfonic acid (method B).



Scheme 3. Synthesis of D-cycloserine via halogenation (method C).

the presence of DBU at room temperature and resulted in much higher yield, 72% for nucleophilic substitution (see Table 1).

Then, TFA group of O-substituted hydroxylamine was deprotected to give the corresponding aminoxy group, followed by cyclization by the treatment with sodium hydroxide. Meanwhile, deprotection of another TFA group of primary amine afforded to free amine moiety of D-cycloserine. The pure target product was obtained via precipitation.

The second synthesis described in Scheme 2 also used one-pot operation to generate D-cycloserine. After preparation of compound **3**, the primary alcohol was converted into the corresponding sulfate by the treatment of 1.2 equiv of chlorosulfonic acid in diethyl ether at room temperature for 4 h. Transformation of methyl carboxylic esters into hydroxamine acids was accomplished in the presence of hydroxylamine hydrochloride and sodium hydroxide. Addition of 5 equiv of sodium hydroxide provided cyclization through nucleophilic reaction as well as deprotection of TFA group of primary amine to give the desired product. This one-pot sequent operation using sulfate moiety afforded the D-cycloserine in a 65% yield, and using the second synthetic method proceeded in a 62% yield of D-cycloserine from D-serine. [11]

We also tried to do halogenation of primary alcohol, which would allow cyclization to generate the target molecule, shown in Scheme 3. The reaction of D-serine with phosphorus pentachloride in the acetyl chloride at room temperature for 4 h afforded D-2-amino-3-chloropropionic acid chloride as an HCl ammonium salt form. In this reaction, both of the chlorination of the primary alcohol and chloroformylation of D-serine were successfully achieved

at the same time and compound **9** was easily isolated from the impurity by a simple filtration after the reaction. Next, one-pot operation was employed to perform the cyclization step of the compound **9** for the completion of D-cycloserine. The one-pot cyclization in Scheme 3 consisted of three steps: formation of hydroxamic acids, cyclization through nucleophilic reaction, and removal of HCl from nitrogen. After the treatment of hydroxylamine hydrochloride with sodium methoxide in MeOH, transformation of acid chloride of the compound **9** into hydroxamine acids was achieved by addition of hydroxylamine. Then, the cyclization reaction between alcohol and chlorine was carried out in the presence of LiOH in methanol and H_2O. Meanwhile, deprotection of the HCl synchronously took place to produce D-cycloserine.

In summary, three simple and practical processes for the synthesis of D-cycloserine from D-serine were developed. In our synthesis, cyclization reaction was the key step for each synthetic route, and multi-step one-pot operations provided novel efficient and short synthetic methods for the completion of synthesis of target molecule. The main advantages of the present synthesis are the mild reaction conditions, easy treatment, and fair yields. These efficient synthetic routes can be amenable to the synthesis of D-cycloserine for the industrial process.

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11. Procedures and selected data
(a) *Synthesis of compound* ***3***. Et_3N (2.97 mL, 21.29 mmol) was added to a solution of serine methyl ester hydrochloride (1.1 g, 7.09 mmol) in CH_2Cl_2 (20 mL). After the mixture solution was cooled to 0 °C, trifluoroacetic anhydride (2.17 ml, 15.62 mmol) was added over 10 min. The mixture was stirred for 6 h at room temperature and then concentrated under reduced pressure. The residue was extracted with ethyl acetate and washed with aqueous $NaHCO_3$, 0.1 M HCl and brine, followed by the drying step under $MgSO_4$. The residue was purified by flash chromatography on silica gel (eluent: AcOEt/hexane, 1:1) to give compound **3** (1.49 g, 98%) as a colorless oil. $[\alpha]_D^{20} = -34.7$ ($c = 4.4$, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52 (s, 1H), 4.45–4.56 (m, 1H), 3.95 (dd, $J = 6.8$ Hz, $J = 18.8$ Hz, 1H), 3.89 (dd, $J = 5.2$ Hz, $J = 17.8$ Hz, 1H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 156.1, 115.5, 62.6, 55.5, 52.2; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_6H_8F_3NO_4 = 215.1272$, found 215.1263.
(b) *Synthesis of compound* ***6*** *from compound* ***3*** *(method A).* Et_3N (0.79 mL, 5.65 mmol) was added to a solution of compound **3** (0.9 g, 4.19 mmol) in CH_2Cl_2 (20 mL) and stirred at 0 °C for 10 min. Methanesulfonyl chloride (0.55 g, 4.81 mmol) was added and the mixture was stirred at 0 °C for 1 h and warmed to room temperature with stirring for 1 h. After stirring the solution of DBU (0.94 mL, 6.28 mmol) and trifluoroacetohydroxamic acid (0.76 g, 5.86 mmol) in CH_2Cl_2 (30 mL) to 0 °C for 30 min, the mixture of DBU and trifluoroacetohydroxamic acid was added to crude mesylate solution at 0 °C. The mixture was stirred at 0 °C for 1 h and warmed to room temperature with stirring for 2 d. After the addition of NaOH (1.12 g, 27 mmol) in water (40 mL) and MeOH (40 mL), the mixture was stirred at room temperature for 6 h. 50 mL of ethanol/isopropyl alcohol was added. The precipitated salts were filtered, and the filtrate was cooled to 0 °C in an ice bath. Glacial acetic acid was added dropwise to the well-stirred mixture to reach pH of 6.0 and then gave a colorless solid. The crystalline precipitates were filtered and washed twice with 1:1 ethanol/isopropyl alcohol and diethyl ether to give D-4-amino-3-isoxazolidone (233 mg, 55%). m.p. 146–148 °C; $[\alpha]_D^{25} = +110$ (c 1.0, H_2O); ^1H NMR (DMSO-d_6, 300 MHz) δ 4.38 (t, 1H), 3.51 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 174.5, 75.1, 53.6; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_3H_6N_2O_2 = 102.0919$, found 102.0927.
(c) *Synthesis of compound* ***6*** *from compound* ***3*** *(method B).* Chlorosulfonic acid (0.72 g, 6.14 mmol) was added to a solution of compound **3** (1.1 g, 5.12 mmol) in Et_2O (40 mL) at 0 °C. The mixture was stirred at 0 °C for 4 h. After sodium hydroxide (1.02 g, 25.57 mmol) was added to hydroxylamine hydrochloride (0.49 g, 7.16 mmol) in H_2O (50 mL) and MeOH (50 mL) and stirred at room temperature for 5 min, the mixture of hydroxylamine was added to the solution of sulfonic acid compound. The mixture was stirred at 0 °C for 2 h and then stirred at 60 °C for 8 h. The reaction mixture was neutralized with AcOH and concentrated under reduced pressure. 60 mL of ethanol/isopropyl alcohol was added. The precipitated salts were filtered, and the filtrate was cooled to 0 °C in an ice bath. Glacial acetic acid was added dropwise to the well-stirred mixture to reach pH of 6.0, giving a colorless solid. The crystalline precipitates were filtered and washed twice with 1:1 ethanol/isopropyl alcohol and diethyl ether to give D-4-amino-3-isoxazolidone 341 mg, 65%).
(d) *Synthesis of compound* ***6*** *from compound* ***9*** *(method C).* Sodium methoxide (0.806 g, 14.92 mmol) was added to hydroxylamine hydrochloride (0.57 g, 8.14 mmol) in H_2O (50 mL) and MeOH (50 mL) and stirred for 5 min. The solution of hydroxylamine was added to the compound **9** (1.2 g, 6.78 mmol) and stirred at room temperature for 10 min. Lithium hydroxide (0.65 g, 27.13 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 5 h. The reaction mixture was neutralized with AcOH and then concentrated under reduced pressure. 60 mL of ethanol/isopropyl alcohol was added. The precipitated salts were filtered, and the filtrate was cooled to 0 °C in an ice bath. Glacial acetic acid was added dropwise to the well-stirred mixture to reach pH of 6.0 and gave a colorless solid. The crystalline precipitates were filtered and washed twice with 1:1 ethanol/isopropyl alcohol and diethyl ether to give D-4-amino-3-isoxazolidone (494 mg, 71%).