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단 신

1,3-Oxazolidin-2-ones와 1,3-Thiazolidin-2-ones의 부분 입체 이성질체 선택적환원법

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Diastereoselective Reduction of 1,3-Oxazolidin-2-ones and 1,3-Thiazolidin-2-ones

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주제어: 1,3-Oxazolidin-2-one, 부분 입체 이성질체 선택적 환원법, Lithium triethylborohydride, 수소화붕소나트륨
Keywords: 1,3-Oxazolidin-2-one, Diastereoselective reduction, Lithium triethylborohydride, Sodium borohydride

L-Nucleosides, as well as analogues have been explored as potential antitumour and antiviral agents. Primarily as a result of the utility and efficacy of certain 2,3′-dideoxy nucleosides e.g. 3-thiacytidine, 3′-azido-2′,3′-dideoxy thymidine (AZT) in combating acquired immuno deficiency syndrome (AIDS). Therefore numerous synthetic efforts have been undertaken that were directed at modifying these structures to provide compounds that retain inhibitory activity without detrimental side effects.[1]

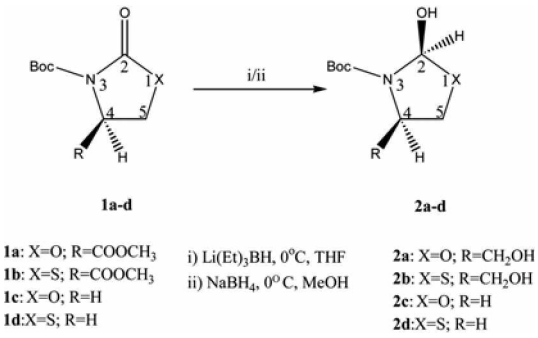
N-Boc-1,3-oxazolidin-2-ones and *N*-Boc-1,3-thiazolidin-2-ones (**1a-d**), the precursors for the synthesis of L-Nucleosides are used as chiral inductors.[2] *N-tert*-butoxy carbonyl protecting group is very popular protecting group since it can be easily introduced and removed.[3,4] Its use in the present case has required the development of a method in order to control creation of the C-2 oxazolidine stereogenic center.[5] In order to get oxazolidine and thiazolidine in a diasteremerically pure form, it was necessary to add di-*tert*-butyl-dicarbonate in a slower rate.

RESULT AND DISCUSSION

The di-*tert*-butyl-dicarbonate and dimethylaminopyridine (DMAP) were found to be useful for the synthesis of cyclic carbonates. Compound **1a** has been prepared by condensing di-*tert*-butyl-dicarbonate with L-serine methyl ester hydrochloride in the presence of DMAP and triethylamine. Similarly **1b** was prepared by condensing L-cysteine methyl ester hydrochloride with di-*tert*-butyl dicarbonate.[6]

Encouraged by these findings this communication illustrates about the reduced products 1,3-oxazolidin-2-ols and 1,3-thiazolidin-2-ols, (*Scheme* 1) which are the intermediates in the synthesis of L-oxazolidinyl and L-thiazolidinyl purine and pyrimidine nucleosides in our protocol.[7]

Unfortunately reduction of ester and lactone to the alcohol with variety of reagents such as diisobutylaluminium hydride, lithium borohydride and calcium borohydride was complicated.[8] In the best case based on Brown *et al.*[9] procedure, when both



Scheme 1.

1,3-oxazolidin-2-one and 1,3-thiazolidin-2-one were reduced using stereoselective reducing agent lithium triethylborohydride at -78 °C in tetrahydofuran, a mixture of primary and secondary alcohols were obtained and it was difficult to separate using column chromatography. Later we tried to reduce the same using lithium triethylborohydride at 0 °C in THF. Surprisingly reduction of lactone ring was achieved, but a trace amount of ester has been remained. Similarly we have carried out the reduction of both 1,3-oxazolidin-2-ones and 1,3-thiazolidin-2-ones (**1a-d**) using sodium borohydride in methanol at 0C, which afforded complete reduction of both lactone and ester functional groups with moderate yield compared to lithium triethylboro hydride.[10]

In addition, the reduction of *N-tert*-butoxy carbonyl 1,3-oxazolidine-2-one (**1c**) and *N-tert*-butoxycarbonyl-1,3-thiazolidine-2-one (**1d**) was carried out. Compound **1c** was prepared by the condensation of 2-aminoethanol hydrochloride with di-*tert*-butyldicarbonate in the presence of DMAP and triethylamine and **1d** was prepared by the condensation of 2-aminoethanethiol hydrochloride with di-*tert*-butyl-dicarbonate.[11,12] We carried out the reduction of both **1c** and **1d** using both sodium borohydride and lithium triethylborohydride at 0C which afforded reduced products **2c** and **2d** respectively.[13] The yield of lactol was good in lithium triethylborohydride compared to sodium borohydride and the spectroscopic data of the reduced products **2a-d** are mentioned.[14] All the synthesized compounds were purified by silica gel chromatography using chloroform : ethyl acetate (7:2) as the eluting solvents.

The diastereoselective reduction of these ester and lactum functional groups yields cis and trans diols using inexpensive sodium borohydrides and stereselective lithium triethylborohydrides.

EXPERIMENTAL

General procedure for the reduction of compounds 1a-d using Lithium triethylborohydride

To a cooled solution of (0C) of **1a-d** (1.0 g, 4.92mmol) in THF (20 ml), 2 equivalent of 1 M solution of lithium triethylborohydride (1.04g, 9.85 mmol) in THF was added and stirred for 1 h. After completion of the reaction, excess reagent was destroyed by the addition of saturated solution of NH_4Cl at 0C, exctracted with dichloromethane (45 ml), dried over anhydrous $MgSO_4$ and evaporated to dryness and purified by flash chromatography hexane ethylacetate (7:2) to afford the compounds **2a-d.**

General procedure for the reduction of compounds 1a-d using Sodiumborohydride

To a cooled solution of (0 °C) of **1a-d** (1.0 g, 4.92

Table 1.

Compound	Reduced product	Reducing agent and conditions	Status	Yield
1a	2a	i)	Light yellow oil	65.8%
		ii)		45.2%
1b	2b	i)	Yellow oil	67.8%
		ii)		51.1%
1c	2c	i)	Colorless oil	69.8%
		ii)		56.8%
1d	2d	i)	Light yellow oil	64.3%
		ii)		49.9%

mmol) in methanol (20 ml), 2 equivalent of 1M solution of Sodiumborohydride (1.04g, 3.05 mmol) in methanol was added and stirred for 1 h. After completion of the reaction, excess reagent was destroyed by the addition of 10% HCl at 0 °C, exctracted with ethylacetate (45 ml), dried over anhydrous $MgSO_4$ and evaporated to dryness and purified by flash chromatography hexane: ethylacetate (7:2) to afford the compounds **2a-d.**

In summary, 1,3-oxazolidine-2-ones and 1,3-thiazolidine-2-ones (**1a-d**) were reduced using both sodium borohydride and lithium triethylborohydride. Sodium borohydride reduces both lactone and ester functional groups successfully with moderate yield. Where as lithium triethylborohydride selectively reduces lactone with good yield but reduction of ester will be difficult. Efforts were pursued in our laboratory towards the reduction of other diastereoselective 1,3-oxazolidin-2-ones and 1,3-thiazolidin-2-ones following this methodology and will be reported in due time.

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14. **2a**: IR (nujol) 1710-1720 cm^{-1} (CO of Boc-ester group), 3200-3220 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 400 MHz) d 4.30 (dd, *J*=6.2, 3.2 Hz, 1H), 3.71 (dd, *J*=16.0, 9.2 Hz, 1H), 3.46 (dd, *J*=16.0, 12.0 Hz, 1H), 3.88 (t, *J*=0 Hz, 2H), 1.51 (s, 9H), 6.68 (s, 1H), 2.00 (s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) 28.5, 58.9, 59.9, 64.5, 111.1, 154.1; Anal Calcd for $C_9H_{17}NO_5$; C, 49.31; H, 7.76; N, 6.30. Found: C, 49.27; H, 7.70; N, 6.26. **2b**: IR (nujol) 1720-1725 cm^{-1} (CO of Boc-ester group), 3200-3220 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 400 MHz) d 3.95 (dd, *J*=6.5, 2.8 Hz, 1H), 2.79 (dd, *J*=17.0, 10.0 Hz, 1H), 2.54 (dd, *J*=17.0, 5.5 Hz, 1H), 3.88 (t, *J*=0 Hz, 2H), 6.37 (s, 1H), 1.50 (s, 9H), 2.00 (s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) 28.5, 30.6, 60.2, 62.5, 79.8, 88.8, 154.1; Anal Calcd for $C_9H_{17}NO_4S$; C, 45.95; H, 7.23; N, 5.95; S, 13.67. Found: C, 45.91; H, 7.19; N, 5.95; S, 13.61. **2c**: IR (nujol) 1710-1720 cm^{-1} (CO of Boc-ester group), 3000-3200 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 400 MHz) d 3.18 (t, *J*=0 Hz, 2H), 3.6 (t, J=0 Hz, 2H), 6.60 (s, 1H), 2.00 (s, 1H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 400 MHz) 28.5, 48.5, 62.2, 79.8, 113.3, 154.4; Anal Calcd for $C_8H_{15}NO_4$; C, 50.79; H, 7.93; N, 7.40; S. Found: C, 50.75; H, 7.88; N, 7.35. **2d**: IR (nujol) 1720-1730 cm^{-1} (CO of Boc-ester group), 3400-3410 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 400 MHz) d 3.10 (dd, *J*=0 Hz, 2H), 3.60 (t, *J*=0 Hz, 2H), 6.60 (s, 1H), 2.00 (s, 1H), 1.50 (s, 9H), 2.00 (s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) 25.6, 28.5, 47.5, 79.8, 91.0, 154.4; Anal Calcd for $C_8H_{15}NO_2S$; C, 50.26; H, 7.85; N, 7.32; S, 16.75. Found: C, 50.20; H, 7.79; N, 7.30; S, 16.70.