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 effi-
cacy of certain 2,3'-dideoxy nucleosides e.g. 3-thia-
cytidine, 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-thi-
azolidin-2-ones (1a-d), the precursors for the
synthesis of L-Nucleosides are used as chiral inductors.7
N-tert-butoxy carbonyl protecting group is very
popular protecting group since it can be easily
introduced and removed.1,4 Its use in the present
case has required the development of a method in
order to control creation of the C-2 oxazolidine ste-
reogenic center.7 In order to get oxazolidine and thi-
azolidine 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 dimethylami-
nopyridine (DMAP) were found to be useful for
the synthesis of cyclic carbonates. Compound 1a
has been prepared by condensing di-tert-butyl-dicar-
bonate with L-serine methyl ester hydrochloride in
the presence of DMAP and triethylamine. Simi-
larly 1b was prepared by condensing L-cysteine
methyl ester hydrochloride with di-tert-butyl dicar-
bonate.6

Encouraged by these findings this communica-
tion 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 pyrimi-
dine nucleosides in our protocol.7

Unfortunately reduction of ester and lactone to
the alcohol with variety of reagents such as diisobu-
tylaluminium hydride, lithium borohydride and cal-
cium borohydride was complicated.8 In the best
case based on Brown et al.9 procedure, when both
1,3-Oxazolidin-2-ones and 1,3-Thiazolidin-2-ones were reduced using stereoselective reducing agent lithium triethylborohydride at -78 °C in tetrahydrofuran, 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 0°C, which afforded complete reduction of both lactone and ester functional groups with moderate yield compared to lithium triethylborohydride.

In addition, the reduction of N-tert-butoxycarbonyl 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-butyl-dicarbonate in the presence of DMAP and triethylamine and 1d was prepared by the condensation of 2-aminoethanethiol hydrochloride with di-tert-butyl-dicarbonate. We carried out the reduction of both 1c and 1d using both sodium borohydride and lithium triethylborohydride at 0°C which afforded reduced products 2c and 2d respectively. 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. 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 stereoselective lithium triethylborohydrides.

**EXPERIMENTAL**

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

To a cooled solution of (0°C) 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 NH₄Cl at 0°C, extracted with dichloromethane (45 ml), dried over anhydrous MgSO₄, 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 mmol) in methanol (20 ml), 2 equivalent of a 1 M solution of sodium borohydride (1.04g, 9.85 mmol) was added and stirred for 1 h. After completion of the reaction, excess reagent was destroyed by the addition of saturated solution of NH₄Cl at 0°C, extracted with dichloromethane (45 ml), dried over anhydrous MgSO₄, and evaporated to dryness and purified by flash chromatography hexane ethylacetate (7:2) to afford the compounds 2a-d.

**Table 1.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reduced product</th>
<th>Reducing agent and conditions</th>
<th>Status</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>i) Light yellow oil</td>
<td>65.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>i) Yellow oil</td>
<td>67.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>i) Colorless oil</td>
<td>69.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>i) Light yellow oil</td>
<td>64.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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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, extracted with ethylacetate (45 ml), dried over anhydrous MgSO₄ 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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REFERENCES

14. 2a: IR (nujol) 1710-1720 cm⁻¹ (CO of Boc-ester group), 3200-3220 cm⁻¹ (OH); ¹H NMR (CDCl₃, 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), 2.00 (s, 2H); ¹³C NMR (CDCl₃, 400 MHz) 28.5, 58.9, 59.9, 64.5, 111.1, 154.1; Anal Calcd for C₁₇H₂₃NO₅; 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, 400 MHz) 28.5, 30.6, 62.5, 79.8, 88.8, 154.1; Anal Calcd for C₁₇H₂₃NO₅S; 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, 400 MHz) 28.5, 48.5, 62.2, 79.8, 88.8, 154.4; Anal Calcd for C₁₇H₂₃NO₅S; C, 50.79; H, 7.93; N, 7.40. 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, 400 MHz) 25.6, 28.5, 47.5, 79.8, 91.0, 154.4; Anal Calcd for C₁₇H₂₃NO₅S; 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.