Unexpected Formation of Naphtyl 1,3-Diaminopropan-2-ol Derivative through Azetidinium Ion Intermediate

Minsoo Han†,‡ and Hoh-Gyu Hahn†,*

†Organic Chemistry Laboratory, Korea Institute of Science and Technology, Seoul 136-791, Korea. *E-mail: hghahn@kist.re.kr
‡Department of Chemistry, Korea University, Seoul 136-701, Korea
Received July 13, 2012, Accepted August 16, 2012

Key Words : Azetidinium ion, Azetidinium ylide, Rearrangement, Regioselectivity, 1,3-Diaminopropan-2-ol

The cause of depression is commonly associated with a deficiency of monoamine neurotransmitters such as serotonin, norepinephrine and dopamine in the brain. Inhibition of monoamine reuptake has been an effective pharmacological treatment of various CNS disorders. As a part of our continuing efforts to develop novel antidepressants for multiple therapeutic utilities, we designed diaminopropan-2-ol 1 through structure analysis and molecular modification and of currently marketed reuptake transporter based antidepressants.

The retrosynthetic route of the designed diaminopropan-2-ol 1 is illustrated in Scheme 1. The diaminopropan-2-ol 1 would be synthesized from oxirane 3 via a diol intermediate 2 by nucleophilic attack of the amine (HNR₁R₂) to epoxide moiety. The oxirane 3 is a key intermediate to accomplish the exploration of novel antidepressants. The epoxide is susceptible to the ring opening reaction with various nucleophiles, and the resulting hydroxy group would bear diverse substituents.

The overall synthetic route is summarized in Scheme 2. The Wittig reaction of aldehyde 5 with ethyl 2-(triphenylphosphoranylidene)acetate in methylene chloride at room temperature afforded the ester 6 in quantitative yield. The reduction of the ester 6 by the treatment with diisobutylaluminium hydride (DABAL-H) in methylene chloride under a nitrogen atmosphere at –78 ºC provided the corresponding alcohol 4. Epoxidation of the double bond in 4 by reaction with m-chloroperbenzoic acid (m-CPBA) in methylene chloride at room temperature proceeded smoothly, resulting in oxirane 3.

The initial attempt for the synthesis of our target compound

\[
\text{Scheme 1. Retrosynthetic analysis of the diaminopropan-2-ol 1.}
\]

\[
\text{Scheme 2. Reagents and conditions: i) Ph_3PCHCO_2Et, CH_2Cl_2, rt, 93%. ii) DIBAL-H, CH_2Cl_2, –78 ºC, 78%. iii) m-CPBA, CH_2Cl_2, rt, 89%. iv) pyrrolidine, 110 ºC, 89%. v) MsCl, TEA, CH_2Cl_2, 0 ºC. vi) CH_3NH_2, CH_2Cl_2, rt, 53%}
\]
involved the reaction of oxirane 3 with pyrrolidine. Regio-
specific nucleophilic attack of nitrogen on pyrrolidine of 3 afforded a diol 7a yield of 89% (see supporting information of X-ray crystallographic analysis). The diol 7a was treated with methanesulfonyl chloride (MsCl) in the presence of triethylamine in methylene chloride at 0 ºC, and was then reacted with excess methylamine dissolved in ethanol solution at room temperature. We expected that the nucleophilic conversion of nitrogen of the methylamine, to methylene carbon, neighboring the mesyl moiety would result in our target compound 10 through an intermediate 8a. Unexpectedly, the resulting product 9a was obtained with a 53% yield as a solid. From the 1H and 13C NMR spectroscopic analysis of the end product, it was not possible to structurally distinguish between 9a and 10. Hence, we elucidated the structure using X-ray crystallographic analysis (Figure 1), and surprisingly, it was clearly identified as 9a.

The proposed reaction mechanism for the formation of 9a is illustrated in Scheme 3.

It is most likely that the intermediate 8a was initially formed from the reaction of the diol 7a with MsCl. Internal nucleophilic attack of nitrogen to methylene carbon neighboring the mesyl moiety would result in azetidinium as an intermediate 11. The next reaction would then proceed through two possible routes, route a and route b, as depicted in Scheme 3. Nucleophilic attack of nitrogen of methylamine, to the carbon α, attached to nitrogen of the azetidinium skeleton would result in 9a (route a). In this case, the regioselectivity of the nucleophilic opening of azetidinium ions, in the presence of a naphthyl group substituted in carbon α, attached to nitrogen of the azetidinium skeleton, would dictate the nucleophilic attack to occur at the carbon bearing the substituent. Another possible process for the formation of 9a was the route through the azetidinium ylide 12, and following epoxide 13 (route b). The opening of the strained four-membered ring, by the internal addition of oxygen of the alkoxide to the neighboring carbon of the naphthyl group, would result in 13. Apparently, a positively charged nitrogen atom drove the internal nucleophilic attack of oxygen, of the alkoxide in the azetidinium ylide intermediate 12, of which the molecular entity is discussed below. Interestingly, the epoxide 13 was a transient intermediate in the reaction and hence, could not be isolated. However, we did successfully isolate 13, with a 47% yield, as a solid, from the independent reaction of the addition of triethylamine instead of methylamine, to the carbon of the epoxide 13.

Further proof that the proposed mechanism involving the azetidinium ion intermediate was correct, was provided by an isolation of an azetidine derivative 14 from the reaction of a methylenedioil 7b with MsCl in the presence of an excess amount (2 molar equivalent) of triethylamine at room temperature (Scheme 4). The reaction was quenched at 30 min (approximately halfway) to give a 79:21 mixture of 8b and 14. The mesylate 8b was a transient intermediate in the reaction, and transformed slowly to form 14, which was identified using TLC. Careful isolation of the mixture through flash chromatography on silica gel provided mesylate 8b as a fomy solid, and azetidine derivative 14 as a white solid. Their structures were confirmed by respective 1H NMR spectra.

![Figure 1. ORTEP plots of the prepared naphtyl 1,3-diamino-propan-2-ol 9a.](image-url)

![Scheme 3. Proposed reaction mechanism for the formation of 9a.](image-url)
naphtyl 1,3-diaminopropan-2-ol derivatives

Table 1. Physical properties and isolated yields of the prepared naphtyl 1,3-diaminopropan-2-ol derivatives 9a-g

<table>
<thead>
<tr>
<th>No</th>
<th>Compound</th>
<th>NR,R₂</th>
<th>R₃</th>
<th>mp (°C)</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9a</td>
<td>NH-CH₃</td>
<td></td>
<td>100</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>9b</td>
<td>NH-CH₃</td>
<td></td>
<td>109</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>9c</td>
<td>NH-CH₃</td>
<td></td>
<td>110</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>9d</td>
<td>NH-CH₃</td>
<td></td>
<td>105</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>9e</td>
<td>NH-CH₃</td>
<td></td>
<td>141</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>9f</td>
<td>S-C₆H₄(4-Cl)</td>
<td></td>
<td>133</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>9g</td>
<td>S-C₆H₄(4-Cl)</td>
<td></td>
<td>125</td>
<td>53</td>
</tr>
</tbody>
</table>

*Yields: isolated yields

Similar reactions, using 4-chlorobenzenethiol instead of methylamine, resulted in the corresponding thio analogues (see entries 6 and 7 in Table 1). We prepared several naphtyl 1,3-diaminopropan-2-ol analogues 9 through a similar manner, achieving moderate yields (42-71%) (Table 1).

In summary, 3-amino-1,2-diol derivatives 7 were converted to the corresponding diaminopropan-2-ol derivatives 9 by the reaction with MsCl in the presence of triethylamine followed by the treatment of either amine or thiol. We prepared azetidinium ion 11 or azetidinium ylide 12 as an intermediate in the reaction, and prepared 7 analogues by similar manner.

**Experimental Section**

**Synthesis of (E)-3-(naphthalen-2-yl)prop-2-en-1-ol (4).** To a solution of 6 (6.0 g, 26 mmol) in methylene chloride (170 mL) at −78 °C cooled under dry ice/acetone cooling bath was added dropwise diisopropylaluminum hydride (1.0 M solution in methylene chloride, 94 mL, 93 mmol) under N₂ atmosphere. The reaction mixture was stirred at the same temperature for 3 h. Na₂SO₄, 10H₂O (15 g, 47 mol) was added to destroy excess diisopropylaluminum hydride while stirring over 1 h at room temperature. The precipitates were removed by filtration through celite. The solvent was removed by evaporation to afford 4.

*Yield 78%, mp 94 °C; ¹H NMR (300 MHz, CDCl₃) δ 6.24 (s, 1H, OH), 4.36 (dd, 2H, J = 5.7 Hz, CH₂), 6.48 (dt, 1H, J = 15.9 Hz, J = 5.7 Hz, vinyl-H) 6.76 (d, 1H, J = 15.9 Hz, vinyl-H) 7.42-7.80 (m, 7H, ArH); ¹³C NMR (400 MHz, CDCl₃) δ 63.81, 123.58, 125.94, 126.30, 126.48, 127.69, 128.01, 128.26, 128.56, 129.87, 131.99, 133.31, 134.22, 144.63, 167.06.

**Synthesis of (E)-3-(naphthalen-2-yl)oxiran-2-yl)methan-1-ol (3).** To a solution of 4 (1.0 g, 5.4 mmol) in methylene chloride (25 mL) at 0 °C under N₂ atmosphere was added a solution of m-chloroperbenzoic acid (1.4 g, 6.2 mmol) dissolved in methylene chloride (20 mL). The reaction mixture was stirred at the same temperature for 3 h. The resulting reaction mixture was added saturated aqueous NaHCO₃ solution while stirring. This mixture was stirred at room temperature for 1 h and then extracted with diisopropylaluminum hydride while stirring over 3 h. The precipitates were removed by filtration through celite. The solvent was removed by evaporation to afford 3.

*Yield 89%, mp 107 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.86 (br.s, 1H, OH), 3.38 (dt, 1H, J = 3.6 Hz, J = 2.1Hz, CH), 3.92 (dd, 1H, J = 12.9 Hz, J = 3.6 Hz, CH), 4.13 (dd, 1H, J = 12.6 Hz, J = 2.1 Hz, CH), 4.16 (d, 1H, J = 2.1 Hz, CH) 7.31-7.90 (m, 7H, ArH); ¹³C NMR (400 MHz, CDCl₃) δ 55.86, 61.29, 62.53, 122.89, 125.44, 126.20, 126.44, 127.79, 127.81, 128.45, 133.15, 133.36, 134.11.

**Synthesis of the Naphtyl 3-aminopropane-1,2-diol (7)** (General Procedure). A mixture of 3 (0.50 mmol) and...
amine (0.50 mmol) was heated at 110 °C for 5 h and then cooled to room temperature. The reaction mixture was purified by flash chromatography on silica gel (methanol: chloroform = 4:1) to obtain the corresponding diol 7 (36-89% yields).

**Typical Compound, For 3-(Naphthalen-2-yl)-3-(pyrrolidin-1-yl)propane-1,2-diol (7a):** Yield 89%, mp 127 °C; 1H NMR (300 MHz, CDCl3) δ 1.83 (s, 4H, pyrrolidine-H), 2.61-2.73 (m, 4H, pyrrolidine-H), 3.01 (br.s, 1H, OH), 3.49 (dd, 1H, J = 10.8 Hz, J = 6.9 Hz, CH) 3.53 (dd, 1H, J = 10.8 Hz, J = 5.1 Hz, CH), 3.67 (d, 1H, J = 5.4 Hz, CH), 4.32 (m, 1H, CH), 7.55-7.93 (m, 7H, ArH); 13C NMR (400 MHz, CDCl3) δ 23.04, 51.82, 65.86, 71.32, 72.13, 125.94, 126.08, 127.20, 127.61, 127.73, 127.94, 128.26, 133.05, 134.82.

**Synthesis of the Naphtyl 1,3-diamino-propan-2-ol (9)** (General Procedure). To a solution of 7 (1.4 mmol) in methylene chloride (10 mL) at 0 °C under N2 atmosphere was added sequentially triethylamine (2.8 mmol) and methanesulfonyl chloride (1.7 mmol). The reaction mixture was stirred at the same temperature for 3 h. Methylamine (33 wt% solution in ethanol, 1 mL, 10 mmol) or 4-chlorobenzylamine (0.50 mmol) was heated at 110 °C for 5 h and then cooled to room temperature. The reaction mixture was washed with saturated aqueous NaHCO3 solution and then dried over anhydrous MgSO4. The solvent was removed by evaporation and the crude product was purified by flash chromatography on silica gel (methanol:chloroform = 4:1) to obtain 9 (42-71% yields).

**Typical Compound, For 1-(Methylamino)-1-(naphthalen-2-yl)-3-(pyrrolidin-1-yl)propan-2-ol (9a):** Yield 53%, mp 100 °C; 1H NMR (300 MHz, CDCl3) δ 1.67 (m, 4H, pyrrolidine-H), 1.95 (dd, 1H, J = 12.3 Hz, J = 3.3 Hz, CH), 2.26 (s, 3H, NCH3), 2.29-2.57 (m, 5H, pyrrolidine-H, CH), 3.48 (d, 1H, J = 8.1 Hz, CH), 3.82 (m, 1H, CH), 7.44-7.84 (m, 7H, ArH), 13C NMR (400 MHz, CDCl3) δ 23.57, 34.29, 53.97, 58.89, 70.33, 72.05, 125.72, 125.79, 126.01, 127.43, 127.69, 127.82, 128.27, 133.18, 133.36, 137.92.

**Acknowledgments.** This work was financially supported by the Korea Institute of Science and Technology. We thanks Prof. Mah, H. and Dr. Nam, K. D. for assistance of the experimental work.

**Supporting Information.** The yields, melting point, 1H NMR data for all the compounds and X-ray crystallographic data for 7a and 9a.

**References and Notes**


