Novel synthetic method for allylic amination of cyclic allylic ethers using chlorosulfonyl isocyanate

Sang Hwi Lee a, In Su Kim b, Qing Ri Li a, Guang Ri Dong a, Young Hoon Jung a,*

a School of Pharmacy, Sungkyunkwan University, Suwon 440-746, Republic of Korea
b Department of Chemistry, University of Ulsan, Ulsan 680-749, Republic of Korea

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Abstract
The introduction of amines to allylic or benzylic position of cyclic compounds with chlorosulfonyl isocyanate is developed in high to excellent yields. This method provides a novel access to biologically active compounds including the framework of 1-aminoindanes, 1-aminotetralines, and 1-amino-2-hydroxy cyclic compounds. Mechanistic evidence for the reaction pathway is also provided.

Considerable effort has been devoted in the last decades toward new methods for forming carbon–nitrogen bonds. Traditional methods can be divided into two large categories such as nucleophilic substitution and direct amination. Representative examples for nucleophilic substitution include metal-catalyzed nucleophilic substitutions, Mitsunobu reactions, Overmann rearrangement, and Gabriel amination. The direct amination methods involve the nitrene addition, [2,2]- or [2,3]-cycloaddition reactions, and reductive amination. In particular, cycloaddition reactions between alkenes and an imine moiety in chlorosulfonyl isocyanate have found great utility in synthetic chemistry and are now valuable tools that are employed routinely. As a result, carbon–nitrogen bond formation using chlorosulfonyl isocyanate can often be found as common synthetic steps in numerous total syntheses of biologically active natural and unnatural compounds, that is, rasagiline, sertraline, abacavir, and acarbose, as shown in Figure 1.

The initial study focused on the reaction of benzyl cyclohex-2-enyl ether (1a) with CSI by varying the solvent and temperature to optimize the yield, and the results are summarized in Table 1. The reaction in methylene chloride at 0 °C furnished the corresponding carbamate 2a in 78% and 85% yield, respectively (Table 1, entries 1 and 2). However, the reaction in a nonpolar solvent, such as toluene and hexanes, provided slightly lower reaction rates and chemical yields (Table 1, entries 3–5).

The optimal reaction conditions established for the allylic amination of cyclic benzylic ether 1a were applied to cyclic allylic ethers 1b–e and cyclic aliphatic ether 1f, as shown in Table 2.

Treatment of cyclopentenyl ether 1b with CSI in methylene chloride at 0 °C afforded the corresponding carbamate 2b in 81% yield (Table 2, entry 2). In the case of cyclohexenyl ethers 1c and 1d, the desired products 2c and 2d were generated in good yield, regardless of the hydroxyl protection groups (Table 2, entries 1, 3, and 4). The introduction of a methyl moiety at the 3-position decreased the reaction rate slightly (Table 2, entry 5). However, the reaction of cyclohexyl benzyl ether 1f was ineffective, even at an increased reaction temperature and time under otherwise identical conditions (Table 2, entry 6). This is presumably due to the formation of a relatively unstable secondary carbocation intermediate, compared to the allylic secondary one.
Next, the reaction of bicyclic benzylic ethers 3a with CSI was examined. After further optimization, 1-benzyloxy-1,2,3,4-tetrahydro-naphthalene (3a) was converted to the corresponding product 4a at −78 °C for 3 h under otherwise identical conditions. However, the reaction between compound 3a and CSI above 0 °C afforded compound 4a in low yield (50%) and 1,2-dihydronaphthalene as the eliminated byproduct in 43% yield. With the optimal reaction condition established, the substrate scope was explored, as shown in Table 3.

Treatment of 1-benzyloxy indane 3b and 1-methoxy indane 3c with CSI under these standard conditions gave the desired products 4b and 4c, respectively, in excellent yield (Table 3, entries 2 and 3). However, when the benzyloxy group was located at the C-2 position, the amination product 4d was not formed, even at an increased reaction temperature and time under otherwise identical conditions. This is presumably due to the formation of a relatively unstable secondary carbocation intermediate, compared to the benzylic secondary one. (Table 3, entry 4). In addition, 4-(benzyloxy)chroman 3e and 9-(benzyloxy)-9H-fluorene 3f were converted into compound 4e (59%) and compound 4f (70%), respectively, even though this required an increased reaction temperature and an extended reaction time, as shown in entries 5 and 6. In addition, 1,2-anti-dibenzyloxy tetraline 3g led to the formation of the C-1 adduct 4g with excellent regioselectivity and anti-diastereoselectivity of 99 > 1 (Table 3, entry 7).

To gain further insight into the reaction mechanism, additional experiments were performed using isotopically labeled allylic ether (deutério-1a) under different solvents. As shown in Table 4, the incorporation of deuterium is dependent on the dielectric constant of the solvent. In particular, the use of n-hexanes provided a mixture of deutério-product 5a and iso-deutério-product 5b at the interior allylic position (95%) and the exterior vinylic position (5%).

A plausible reaction mechanism appears based on isotopically labeled experiments, as outlined in Figure 2. The initial attack by the oxygen of benzylic ether to CSI delivers an oxonium ion (I),
which can be converted to the deuterio-product 5a as a major compound through a 4-centered transition structure (IIa) according to a Sn1 mechanism. This is consistent with the results of isotopic labeling under nonpolar n-hexanes solvent, compared to relatively polar nitromethane and dichloromethane solvents. Another plausible SN1 mechanism can be in competition with the SNi mechanism. However, this reaction may be partially proceed via SN1 mechanism due to the incomplete orbital overlap between p orbital of the double bond and p orbital of cyclic allylic sp2 carbocation in the reaction intermediate (IIb).

In conclusion, we have reported the introduction of protected amines to the ring system by a treatment of various alkyl ethers at the allylic and benzylic positions with chlorosulfonyl isocyanate in high yield. These aminations are believed to proceed through a Sn1 mechanism. This synthetic methodology can be applied easily to the preparation of various biologically active natural products and drugs containing a cyclic amine moiety.

Acknowledgments

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**Table 3**

Reaction of bicyclic benzylic ethers 3a–g with CSI

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic ether</th>
<th>Product</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O\text{Bn} 3a</td>
<td>NH\text{COOBn} 4a</td>
<td>−78</td>
<td>3</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>O\text{Bn} 3b</td>
<td>NH\text{COOBn} 4b</td>
<td>−78</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>O\text{Me} 3c</td>
<td>NH\text{COOMe} 4c</td>
<td>−78</td>
<td>1</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>O\text{Bn} 3d</td>
<td>NH\text{COOBn} 4d</td>
<td>rt</td>
<td>24</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>O\text{Me} 3e</td>
<td>NH\text{COOBn} 4e</td>
<td>rt</td>
<td>12</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>O\text{Bn} 3f</td>
<td>NH\text{COOMe} 4f</td>
<td>rt</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>O\text{Bn} 3g</td>
<td>NH\text{COOBn} 4g</td>
<td>−40</td>
<td>24</td>
<td>68</td>
</tr>
</tbody>
</table>

* Isolated yield of pure materials.

**Table 4**

Isotopically labeled experiments

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Dielectric constant (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratiob (5a:5b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH\text{3}NO2</td>
<td>35.87 (30)</td>
<td>1</td>
<td>80</td>
<td>81:19</td>
</tr>
<tr>
<td>2</td>
<td>CH\text{3}Cl2</td>
<td>9.14 (20)</td>
<td>1</td>
<td>79</td>
<td>91:9</td>
</tr>
<tr>
<td>3</td>
<td>n-Hexanes</td>
<td>1.90 (20)</td>
<td>10</td>
<td>80</td>
<td>95:5</td>
</tr>
</tbody>
</table>

* Isolated yield of pure materials.

* Ratio was determined by 1H NMR and 2H NMR analysis.
Figure 2. Proposed reaction pathway (S_{n1} vs S_{n1}).

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tetlet.2011.02.036.

References and notes

11. General procedure for the reaction of cyclic allylic ether with chlorosulfonyl isocyanate (CSI): To a mixture of cyclic allylic ether (0.53 mmol) in anhydrous CH2Cl2 (2 mL, 0.27 M), Na2CO3 (1.59 mmol, 300 mol%) at 0 °C under N2. After being stirred for 20 min, CSI (0.80 mmol, 150 mol%) was slowly added at 0 °C. After the reaction was completed (TLC monitoring), and then extracted with CH2Cl2 (2 mL, 0.27 M). When the reaction mixture was stirred at indicated temperature for reaction time (see Tables 1–4), quenched with H2O (10 mL) when the reaction was completed (TLC monitoring), and then extracted with CH2Cl2 (2 mL, 0.27 M). When the reaction mixture was stirred at indicated temperature for reaction time (see Tables 1–4), quenched with H2O (10 mL) when the reaction was completed (TLC monitoring), and then extracted with CH2Cl2 (2 mL, 0.27 M). When the reaction mixture was stirred at indicated temperature for reaction time (see Tables 1–4), quenched with H2O (10 mL) when the reaction was completed (TLC monitoring), and then extracted with CH2Cl2 (2 mL, 0.27 M).
12. Selected characterization (2a): Rf = 0.14 (n-hexanes/EtOAc = 10/1); m p 66.2 °C. IR (KBr) ν 3313, 3034, 2936, 1685, 1531, 1306, 1241, 1036 cm31; 1H NMR (300 MHz, CDCl3) 1 1.49–1.68 (m, 3H), 1.88–2.02 (m, 3H), 4.21–4.23 (m, 3H), 4.70–4.72 (m, 3H), 5.10 (s, 2H), 5.59–5.64 (m, 1H), 5.80–5.86 (m, 1H), 7.28–7.43 (m, 5H), 13C NMR (75 MHz, CDCl3) 1 15.91, 24.67, 29.64, 46.27, 66.49, 127.64, 127.99, 128.05, 128.43, 130.74, 136.54, 155.57; HRMS (EI) Calcd for C176H17NO2 [M]+ 231.1259, found 231.1259.

Figure 2. Proposed reaction pathway (S_{n1} vs S_{n1}).