Regioselective and Diastereoselective Amination with Use of Chlorosulfonyl Isocyanate: A Short and Efficient Synthesis of (−)-Cytoxazone

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ABSTRACT

The total synthesis of (−)-cytoxazone 1 was achieved in six linear steps (34% overall yield) from p-anisaldehyde. The key steps in this route are the regioselective and stereoselective introduction of a N-protected amine group, using the CSI reaction of the anti-1,2-dimethyl ether 3, and the subsequent regioselective cyclization of the N-protected amino diol 13 to give the 2-oxazolidinone unit of (−)-cytoxazone 1.

Cytoxazone 1 is a novel cytokine modulator that was isolated from Streptomyces sp., and interferes with cytokine IL4, IL10, and IgG production via the selective inhibition of the signaling pathway in Th2 cells. Its structure was determined to be (4R,5R)-5-hydroxymethyl-4-p-methoxyphenyl-1,3-oxazolidin-2-one based on the NMR, CD, and X-ray data.1

Due to its potent bioactivity and relatively simple structure, several methods of synthesizing (−)-cytoxazone and its trans-diastereoisomer (4-epicytoxazone) have recently been reported. These include Sharpless asymmetric dihydroxylation and the introduction of amine,2 Sharpless asymmetric aminohydroxylation,3 an asymmetric epoxidation and the regioselective introduction of azide,4 the Petasis reaction,5 an asymmetric aldol reaction,6 an imino-1,2-Wittig rearrangement,7 the addition of Grignard reagents to the protected imines,8 and the conjugated addition of chiral lithium amide.9 This paper presents our synthetic approach to (−)-cytoxazone, based on the regioselective and diastereoselective chlorosulfonyl isocyanate (CSI) reaction.10

The retrosynthetic scheme is shown below (Scheme 1) and the key steps are the regioselective and diastereoselective chlorosulfonyl isocyanate (CSI) reaction.10

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alcohol 2, using the CSI reaction and the regioselective intramolecular cyclization. Compound 3 could be easily prepared from p-anisaldehyde by using the chiral reagent, \((-\rangle-B\text{-methoxydiisopinocamphyl}-\text{borane})\).\(^\text{11}\)

First, the regioselectivity and the diastereoselectivity of the CSI reaction was investigated with \textit{anti}-1,2-dimethyl ether 3 prior to the approach to the total synthesis of \((-\rangle\text{-cytoxazone}).

The initial studies examined the diastereoselectivity of the reaction of the \textit{anti}-1,2-dimethyl ether 3 with CSI. The treatment of \textit{anti}-1,2-dimethyl ether with CSI afforded the \textit{anti}-1,2-amino alcohol 2 as the major product. The ratio of \textit{anti}-1,2-amino alcohol 2 and \textit{syn}-1,2-amino alcohol 4 depended on the solvent and temperature, as shown in Table 1.

<table>
<thead>
<tr>
<th>solvent</th>
<th>temp (°C)</th>
<th>ratio ((2:4)^a)</th>
<th>yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_2)Cl(_2)</td>
<td>0</td>
<td>5.7:1</td>
</tr>
<tr>
<td>2</td>
<td>CHCl(_3)</td>
<td>-78</td>
<td>7.0:1</td>
</tr>
<tr>
<td>3</td>
<td>CHCl(_3)</td>
<td>0</td>
<td>7.6:1</td>
</tr>
<tr>
<td>4</td>
<td>Et(_2)O</td>
<td>0</td>
<td>12:1</td>
</tr>
<tr>
<td>5</td>
<td>toluene</td>
<td>0</td>
<td>16:1</td>
</tr>
<tr>
<td>6</td>
<td>CCl(_4)</td>
<td>-78</td>
<td>27:1</td>
</tr>
<tr>
<td>7</td>
<td>hexane</td>
<td>0</td>
<td>13:1</td>
</tr>
<tr>
<td>8</td>
<td>-78</td>
<td></td>
<td>15:1</td>
</tr>
</tbody>
</table>

\(^a\) Isomer ratio determined from the \(^1\)H NMR spectrum. \(^b\) Isolated yield of pure material.

The reaction in methylene chloride at 0 °C gave a 5.7:1 inseparable mixture of diastereoisomers in 94% yield, and at -78 °C furnished a 7.0:1 ratio (entries 1 and 2). In particular, in toluene at -78 °C (entry 6), the highest diastereoselectivity (27:1) was obtained in 95% chemical yield. Table 1 showed a tendency to increase the formation of the \textit{anti}-stereoisomer of the 1,2-amino alcohol as the polarity of the solvent decreased.

From the reaction of the \textit{anti}-1,2-dimethyl ethers with CSI, it was found that the stereochemistry of the major product was the same as that of the starting material, even though the CSI reaction of \(p\)-methoxybenzyl methyl ether progresses via a carbocation intermediate through a \(S_N\text{1}\) mechanism.

The results of these reactions can be explained as follows:

First, the regioselective substitution at the \(p\)-methoxybenzyl position is expected. This is because the regioselectivity was controlled by the stability of the carbocation intermediate. Namely, the \(p\)-methoxybenzyl carbocation is more stable than the allyl one.\(^\text{12}\)

Second, the formation of the \textit{anti}-1,2-amino alcohol 2 from the \textit{anti}-1,2-dimethyl ether 3 can be explained by the Cieplak electronic model,\(^\text{9c,13}\) via a \(S_N\text{1}\) mechanism. In this model, the vinyl group takes up an anti position to nucleophile attack and the methoxy group orients inside (Figure 1).

Another plausible mechanism for the diastereoselectivity is the neighboring group effect, as shown in Figure 2. This neighboring group (OMe) can use its electron pair to interact with the backside of the carbon atom undergoing substitution, and then nucleophilic attack can take place only from the front side, leading to the retention of the configuration.\(^\text{14}\)

The initial attack by the oxygen of \(p\)-methoxybenzyl methyl ether to CSI yields a \(p\)-methoxybenzyl carbocation, which is following an internal attack by the vicinal OMe that yields the oxiranium with an inversion of configuration at the \(p\)-methoxybenzyl carbocation. This \(p\)-methoxybenzyl carbon atom, in turn, undergoes an ordinary \(S_N\text{2}\) attack by \(\text{CISO}_2\text{N}^-\text{CO}_2\text{Me}\), with a second inversion of configuration. In this result, the configuration of the product is the same as that of the starting material. As the polarity of the solvent decreases, the attack of the vicinal OMe (the neighboring

group effect) becomes faster than the nucleophile attack and the diastereoselectivity of 1,2-amino alcohol increases. Therefore, this reaction is more efficient in nonpolar solvents.

A methyl moiety instead of a methoxy group was introduced at the allylic position to confirm the neighboring group effect. (Scheme 2).

The treatment of threo-ether 5 with CSI in methylene chloride at −78 °C furnished a 1:1.8 mixture of the threo-stereoisomer 6 and the erythro-stereoisomer 7 in 91% chemical yield (entry 1). The other results are summarized in Table 2.

The CSI reaction of compound 5 in toluene and hexane afforded a ratio similar to the case of methylene chloride (entries 2 and 3). The results shown in Table 2 reveal that the reaction of the β-methyl homoallyl ether with CSI is not affected by the solvent, and progresses through a free carbocation intermediate.

Therefore, it is clear that the diastereoselectivity of the CSI reaction of the 1,2-dimethyl ether 3 can be explained by the neighboring group effect and a partial S_{N}1 mechanism.

On the basis of the above results, the total synthesis of (−)-cytoxazone 1 was achieved from p-anisaldehyde as a starting material (Scheme 3).

The CSI reaction of compound 5 in toluene and hexane afforded a ratio similar to the case of methylene chloride (entries 2 and 3). The results shown in Table 2 reveal that the reaction of the β-methyl homoallyl ether with CSI is not affected by the solvent, and progresses through a free carbocation intermediate.

Figure 2. Neighboring group effect of nucleophilic attack on the p-methoxybenzylc carbocation.

Scheme 2. CSI Reactions of β-Methyl Homoallyl Ether 5 with Various Solvents

Table 2. CSI Reactions of β-Methyl Homoallyl Ether 5 with Various Solvents (at −78 °C)

<table>
<thead>
<tr>
<th>solvent</th>
<th>ratio (6:7)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CH_{2}Cl_{2}</td>
<td>1:1.8</td>
<td>91</td>
</tr>
<tr>
<td>2 toluene</td>
<td>1:1.7</td>
<td>83</td>
</tr>
<tr>
<td>3 hexane</td>
<td>1:1.6</td>
<td>81</td>
</tr>
</tbody>
</table>

*a Isomer ratio determined from the ^{1}H NMR spectrum. *b Isolated yield of pure material.

Scheme 3. Total Synthesis of (−)-Cytoxazone

p-Anisaldehyde was treated at −78 °C with B-[3-((diisopropylamino)dimethylsilyl)allyl]diisopinocampheyl-borane (8), prepared from (−)-B-methoxydiisopinocampheyl-borane and allyl(diisopropylamino)dimethylsilane,^{10} using n-butyl-lithium in N,N,N′,N′-tetramethylethylenediamine (TMEDA) in ether (Et_{2}O) at 0 °C, to provide an optically pure (1R,2S)-anti-diol 9 with a high enantioselectivity (95% ee via the Mosher ester) and diastereoselectivity (> 99%) in 52% chemical yield after recrystallization (toluene). The dimethylation of compound 9 with sodium hydride and iodomethane in tetrahydrofuran at 0 °C furnished the anti-1,2-dimethyl ether 3 in 96% yield.

The key reaction is the regioselective and diastereoselective introduction of a N-protected amine group of compound 3 with CSI. The treatment of compound 3 with CSI in the presence of sodium carbonate in anhydrous toluene at −78 °C, followed by the reduction of the N-chlorosulfonyl group with an aqueous potassium hydroxide and sodium thiosulfate solution furnished the desired anti-1,2-amino alcohol 4 with a high diastereoselectivity (27:1) in 95% yield. The conversion of compound 2 into the terminal primary alcohol 10
was achieved by ozonolysis of the double bond followed by sodium borohydride reduction\(^{15}\) in 94% chemical yield.

The regioselective deprotection of the methyl ether of compound 10 with boron tribromide\(^{16}\) in methylene chloride at 0 °C gave the desired diol 11 in 80% yield without affecting the methoxy group of the phenyl ring.

Finally, the regioselective intramolecular cyclization of compound 11, using sodium hydride\(^7\) in tetrahydrofuran at 0 °C, led to the (−)-cytoxazole 1 \{mp 118–120 °C; [α]\(^{24}\)_D −70.9 (c 0.1, MeOH); lit.\(^1\) mp 118–120 °C; [α]\(^{25}\)_D −71 (c 0.1, MeOH)\} in 95% yield.

In conclusion, the total synthesis of (−)-cytoxazole 1 was achieved in six linear steps (34% overall yield) from
