Stereoselective Rearrangement of Trichloroacetimidates: Application to the Synthesis of α-Glycosyl Ureas

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ABSTRACT

A new method for the stereoselective synthesis of α-glycosyl ureas, via nickel-catalyzed [1,3]-rearrangement of glycosyl trichloroacetimidates, has been developed. The α-stereoselectivity at the anomeric carbon of the resulting trichloroacetamides depends on the nature of the cationic nickel catalyst. This method is applicable to a number of trichloroacetimidate substrates. The α-glycosyl trichloroacetamides can be directly converted into α-glycosyl ureas in the presence of amines. In all cases, the stereochemical integrity at the urea linkages remains intact.

Aminoglycosides are clinically important antibiotics with a broad antibacterial spectrum.1 They are used predominantly in the treatment of Gram-negative bacterial infections. However, bacterial resistance against aminoglycoside antibiotics has been increasing at an alarming rate.2 In response to this medical concern, the search for new classes of antibiotic has intensified.3 Research in the area of glycosyl ureas, in which the O- and N-glycosidic bonds are replaced with the urea linkage, has emerged due to their potential application in the field of aminoglycosides.4 Methods for synthesizing glycosyl ureas require many steps.5 In particular, general methods for the stereoselective synthesis of α-glycosyl ureas are still unavailable.6

A recent method developed in our group utilized Pd(II)–ligand complexes for the stereoselective [3,3]-sigmatropic rearrangement of glycal imidates to the corresponding α-and β-2,3-unsaturated trichloroacetamides, which are then converted into the glycosyl ureas.7 While this method is

highly diastereoselective, its main drawbacks include the use of toxic OsO₄ to convert the resulting 2,3-unsaturated trichloroacetamides into the diol prior to transforming them into glycosyl ureas, the limited substrate scope (mannose residue only), and the overall moderate yields. In this paper, we report a practical method for the stereoselective synthesis of α-glycosyl ureas that is applicable to an array of carbohydrate substrates. The method utilizes a cationic nickel(II) catalyst to rearrange glycosyl trichloroacetimdate 1 to α-trichloroacetamide 2 (Scheme 1). The resulting product 2 is then directly converted to glycosyl urea 3, eliminating the need for using OsO₄.

In light of our previous success utilizing commercially available cationic palladium(II), Pd(CH₃CN)₄(BF₄)₂, for the [3,3]-sigmatropic rearrangement of glycal imidates, we chose this catalyst system for our preliminary studies of the [1,3]-rearrangement of perbenzylated D-glucopyranosyl trichloroacetimdate 4 (Table 1). The reaction did not proceed even with 5 mol % of Pd(CH₃CN)₄(BF₄)₂ (entry 1). Changing to the more reactive cationic palladium(II) catalyst, Pd(PhCN)₂(OTf)₂, provided the desired glycosyl trichloroacetamide 5 in 86% yield with excellent α-selectivity (entry 2). Lowering the catalyst loading from 5 to 2 mol % still maintained the yield and anomer selectivity (entry 3). Our interest in nickel catalysis led us to consider Ni(PhCN)₄(Cl)₂, which was generated in situ from Ni(PhCN)₄Cl₂ and AgOTf (entry 4). Employing Ni(dppe)(OTf)₂ led to an improvement of the yield and maintained the α-selectivity (entry 7). Overall, with use of either palladium or nickel catalyst, the rearrangement proceeded smoothly within 1 h. In contrast, it took 14 h for the reaction to go to completion with use of 6 mol % of AgOTf, and trichloroacetamide 5 was isolated in 72% yield with α/β = 5:1 (entry 8). Employing BF₃·OEt₂ yielded 5 in 65% yield with α/β = 4:1 (entry 9).

With the optimal conditions at hand, we set out to define the substrate scope of this rearrangement. The cationic nickel-catalyzed reaction is effective for a variety of trichloroacetamide substrates (Figure 1). Specifically, D-glucose trichloroacetamidates with allyl and TIPS groups incorporated at the C(2)-positions afforded excellent yields and α-selectivity of glycosyl trichloroacetamides 6 and 7. Substrates such as D-xylene and D-quinovose that lacked the protected C(6)-hydroxyl functionality also provided the corresponding trichloroacetamides 8 and 9, respectively, in good yields and almost exclusively as α-rearrangement isomers. Furthermore, both D-mannose and D-galactose substrates were viable trichloroacetamidates for providing the desired products 10 and 11, respectively, with excellent α-selectivity.

We have established that the trichloroacetamide proton of a diol intermediate such as 13 can be deprotonated with Cs₂CO₃ to generate in situ an isocyanate 14, which participates in glycosyl urea formation in the presence of a nucleophilic nitrogen (Scheme 2). This approach requires three steps (dihydroxylation, coupling, and acylation) starting from 2,3-unsaturated trichloroacetamide 12.

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**Scheme 1. Strategy for the Synthesis of α-Glycosyl Ureas**

![Scheme 1](image)

**Table 1. Optimization of Nickel-Catalyzed Rearrangement of Glycosyl Trichloroacetimdate 4**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>loading (mol %)</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>α/β</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(CH₃CN)₄(BF₄)₂</td>
<td>5</td>
<td>5</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pd(PhCN)₂(OTf)₂</td>
<td>5</td>
<td>1</td>
<td>86</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PhCN)₂(OTf)₂</td>
<td>2</td>
<td>1</td>
<td>85</td>
<td>1:1</td>
</tr>
<tr>
<td>4</td>
<td>Ni(PhCN)₄(OTf)₂</td>
<td>2</td>
<td>1</td>
<td>84</td>
<td>1:1</td>
</tr>
<tr>
<td>5</td>
<td>Ni(dppe)(OTf)₂</td>
<td>2</td>
<td>1</td>
<td>88</td>
<td>1:1</td>
</tr>
<tr>
<td>6</td>
<td>Ni(μ-PhCN)₄(OTf)₂</td>
<td>2</td>
<td>1</td>
<td>90</td>
<td>1:1</td>
</tr>
<tr>
<td>7</td>
<td>Ni(dppe)(OTf)₂</td>
<td>2</td>
<td>1</td>
<td>94</td>
<td>1:1</td>
</tr>
<tr>
<td>8</td>
<td>AgOTf</td>
<td>6</td>
<td>14</td>
<td>72</td>
<td>5:1</td>
</tr>
<tr>
<td>9</td>
<td>BF₃·OEt₂</td>
<td>4</td>
<td>6</td>
<td>65</td>
<td>1:4</td>
</tr>
<tr>
<td>10</td>
<td>Ni(dppe)(OTf)₂</td>
<td>4</td>
<td>6</td>
<td>81</td>
<td>4:1</td>
</tr>
<tr>
<td>11</td>
<td>AgOTf</td>
<td>6</td>
<td>14</td>
<td>72</td>
<td>5:1</td>
</tr>
</tbody>
</table>

*The reactions were performed with Pd(CH₃CN)₄(BF₄)₂ or Pd(PhCN)₂(OTf)₂ or Ni(OTf)₂, generated in situ from Pd(PhCN)₄Cl₂ or NiCl₂ and AgOTf. Isolated yield. "H NMR ratio.*

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**Figure 1. Cationic nickel-catalyzed 1,3-rearrangement of glycosyl trichloroacetimdate substrates:**


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**Notes:**

In this new strategy, the α-glycosyl ureas can be directly obtained from the resulting α-trichloroacetamides in a single step with much higher yields (Table 2). Our previous work has shown that both primary and secondary nitrogen nucleophiles gave the desired α-glycosyl ureas in overall 51–61% yield.7 Our new method, however, provided the corresponding α-glycosyl ureas 17–21 in 75–94% yield (entries 1–5). Similarly, the urea-linked disaccharide 22 was also obtained in higher yield (entry 6).

Carbohydrates linked to the amino acid backbone of protein have received considerable attention due to their involvement in a variety of biochemical processes.10 Although the synthesis of β-urea-linked glycopeptides has been documented,11 there is no method available for the stereoselective preparation of α-urea-linked glycopeptides. To determine if both D- and L-amino acids are viable nucleophiles, α-glycosyl trichloroacetamides 5 and 10 were coupled with four different amino acids. It was found that α-urea-linked glycopeptides 23–26 were formed in good yield (Table 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino Acids</th>
<th>Trichloroacetamides</th>
<th>Urea-Linked Glycopeptides</th>
<th>Yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂N-CO₂Me</td>
<td>5</td>
<td>23</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>Ph-CO₂Me</td>
<td>10</td>
<td>24</td>
<td>88%</td>
</tr>
<tr>
<td>3</td>
<td>Me-CO₂Me</td>
<td>5</td>
<td>25</td>
<td>80%</td>
</tr>
<tr>
<td>4</td>
<td>Ph-OH</td>
<td>5</td>
<td>26</td>
<td>90%</td>
</tr>
</tbody>
</table>

*The reactions were performed with 3 equiv of Cs₂CO₃ and 2 equiv of amine in DMF (0.2 M) at 25 °C. b Isolated yield.

In summary, a novel method for the stereoselective synthesis of α-glycosyl ureas, via cationic nickel-catalyzed 1,3-rearrangement of glycosyl trichloroacetimidates, has been developed. The α-selectivity at the anomeric carbon of the resulting glycosyl trichloroacetimidates depends on the nature of the nickel catalyst. This new method is applicable to a number of glycosyl trichloroacetamide substrates which cannot be easily accessed by our previous method. The α-glycosyl trichloroacetamides are then directly converted into the corresponding α-glycosyl ureas.
in the presence of amine nucleophiles. In all cases, the stereochemical integrity at the C(1)-carbon of the newly formed glycosyl ureas remains intact.

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**Supporting Information Available:** Experimental procedure and compound characterization data. This material is available free of charge via the internet at http://pubs.acs.org.

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