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

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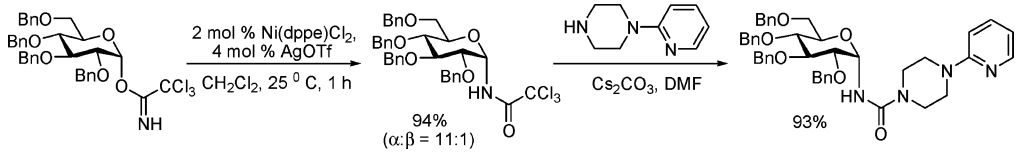
## ABSTRACT




**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

(1) (a) Chow, C. S.; Bogdan, F. M. *Chem. Rev.* **1997**, *97*, 1489–1513. (b) Busscher, G. F.; Rutjes, P. J. T.; van Delft, F. L. *Chem. Rev.* **2005**, *105*, 775–791. (c) Arya, D. P. *Top. Curr. Chem.* **2005**, *253*, 149–178. (d) Hainrichson, M.; Nudelman, I.; Baasov, T. *Org. Biomol. Chem.* **2008**, *6*, 227–239.

(2) Magnet, S.; Blanchard, J. S. *Chem. Rev.* **2005**, *105*, 477–497.

(3) Payne, D. J.; Wallis, N. G.; Gentry, D. R.; Rosenberg, M. *Curr. Opin. Drug. Discovery Dev.* **2003**, *3*, 177–190. (b) Haddad, J.; Kotra, L. P.; Llano-Sotelo, B.; Kim, C.; Azucena, E. F.; Lui, M.; Vakulenko, S. B.; Chow, C. S.; Mobashery, S *J. Am. Chem. Soc.* **2002**, *124*, 3229–3237. (c) Francois, B.; Szuchowski, J.; Adhikari, S. S.; Pachamuthu, K.; Swayze, E. E.; Griffey, R. H.; Migawa, M. T.; Westhof, E.; Hanessian, S. *Angew. Chem., Int. Ed* **2004**, *43*, 6735–6738. (d) Blout, K. F.; Zhao, F.; Hermann, T.; Tor, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9818–9829. (e) Kling, D.; Hesek, D.; Shi, Q.; Mobashery, S. *J. Org. Chem.* **2007**, *72*, 5450–5453.

(4) Kirst, H. A In *Burger's Medicinal Chemistry and Drug Discovery*; Wolff, M. E., Eds.; Wiley: New York, 1996; pp 463−525.

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(7) (a) Yang, J.; Mercer, G. J.; Nguyen, H. M. *Org. Lett.* **2007**, *9*, 4231–4234. (b) Mercer, G. J.; Yang, J.; McKay, M. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2008**, *130*, 11210–11218.

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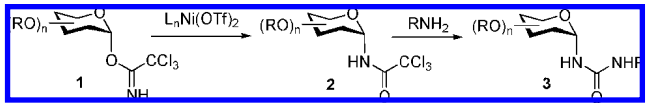
highly diastereoselective, its main drawbacks include the use of toxic $OsO_4$ to convert the resulting 2,3-unsaturated trichloroacetamides into the diol prior to transforming them into glycosyl ureas, the limited substrate scope (mannose residue only), and the overall moderate yields. In this paper, 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 trichloroacetimidate **1** to α- trichloroacetamide **2** (Scheme 1). The resulting

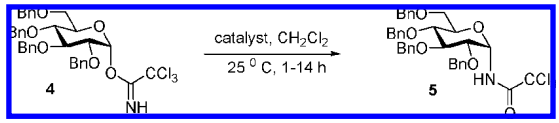
**Scheme 1.** Strategy for the Synthesis of α-Glycosyl Ureas




product **2** is then directly converted to glycosyl urea **3**, eliminating the need for using $OsO_4$.

In light of our previous success utilizing commercially available cationic palladium(II), $Pd(CH_3CN)_4(BF_4)_2$, for the [3,3]-sigmatropic rearrangement of glycal imidates,[7] we chose this catalyst system for our preliminary studies of the [1,3]-rearrangement of perbenzylated D-glucopyranosyl trichloroacetimidate **4** (Table 1).[8] The reaction did

**Table 1.** Optimization of Nickel-Catalyzed Rearrangement of Glycosyl Trichloroacetimidate **4**[a]




| entry | catalyst | loading (mol %) | time (h) | yield[b] (%) | α:β[c] |
|---|---|---|---|---|---|
| 1 | $Pd(CH_3CN)_4(BF_4)_2$ | 5 | 5 | NR | |
| 2 | $Pd(PhCN)_2(OTf)_2$ | 5 | 1 | 86 | 10:1 |
| 3 | $Pd(PhCN)_2(OTf)_2$ | 2 | 1 | 85 | 10:1 |
| 4 | $Ni(PhCN)_4(OTf)_2$ | 2 | 1 | 84 | 11:1 |
| 5 | Ni(*p*-FPhCN)$_4$(OTf)$_2$ | 2 | 1 | 88 | 10:1 |
| 6 | Ni(*p*-MeOPhCN)$_4$(OTf)$_2$ | 2 | 1 | 90 | 10:1 |
| 7 | $Ni(dppe)(OTf)_2$ | 2 | 1 | 94 | 11:1 |
| 8 | AgOTf | 6 | 14 | 72 | 5:1 |
| 9 | $BF_3{\cdot}OEt_2$ | 4 | 6 | 65 | 4:1 |

[a] The reactions were performed with $Pd(CH_3CN)_4(BF_4)_2$ or $Pd(PhCN)_2(OTf)_2$ or $L_nNi(OTf)_2$, generated in situ from $Pd(PhCN)_2Cl_2$ or $L_nNiCl_2$ and AgOTf. [b] Isolated yield. [c] $^1H$ NMR ratio.

not proceed even with 5 mol % of $Pd(CH_3CN)_4(BF_4)_2$ (entry 1). Changing to the more reactive cationic palladium(II) catalyst, $Pd(PhCN)_2(OTf)_2$,[9] 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 anomeric selectivity (entry 3). Our interest in nickel catalysis led us to consider $Ni(PhCN)_4(OTf)_2$, which was generated in situ from $Ni(PhCN)_4Cl_2$ 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 $\alpha/\beta = 5{:}1$ (entry 8). Employing $BF_3{\cdot}OEt_2$ yielded **5** in 65% yield with $\alpha/\beta = 4{:}1$ (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 trichloroacetimidate substrates (Figure 1). Specifically,

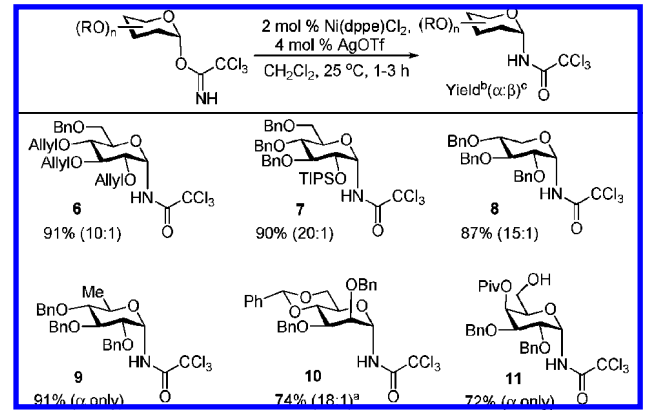



**Figure 1.** Cationic nickel-catalyzed 1,3-rearrangement of glycosyl trichloroacetimidate substrates: (a) compound **10** was peformed with 4 mol % of $Ni(dppe)Cl_2$ and 8 mol % of AgOTf; (b) isolated yield; (c) $^1H$ NMR ratio.

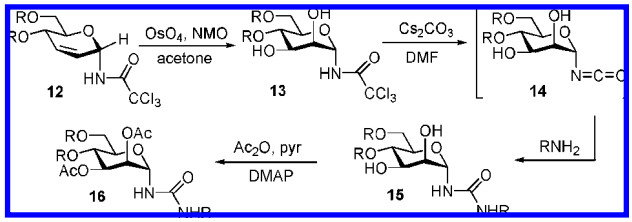
D-glucose trichloroacetimidates with allyl and TIPS groups incorporated at the C(2)-positions afforded excellent yields and α-selectivity of glycosyl trichloroacetamides **6** and **7**. Substrates such as D-xylose and D-quinovose that lacked the protected C(6)-hydroxyl functionality also provided the 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 trichloroacetimidates 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 $Cs_2CO_3$ to generate in situ an isocyanate **14**, which participates in glycosyl urea formation in the presence of a nucleophilic nitrogen (Scheme 2).[7] This approach requires three steps (dihydroxylation, coupling, and acylation) starting from 2,3-unsaturated trichloroacetamide **12**.

(8) (a) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed.* **1980**, *19*, 731–732. (b) Schmidt, R. R.; Hoffmann, M. *Angew. Chem.* **1983**, *95*, 417–418. (c) Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, *7*, 1249–1256. (d) Schmidt, R. R.; Michel, J. *Tetrahedron Lett.* **1984**, *25*, 821–824.

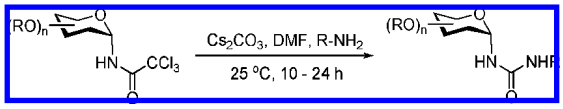
(9) Mensah, E. A.; Azzarelli, J. M.; Nguyen, H. M. *J. Org. Chem.* **2009**, *74*, 1650–1657.

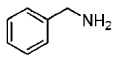
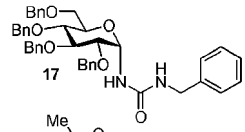
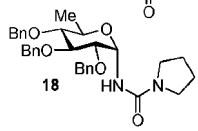
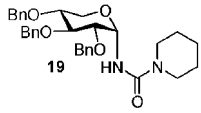
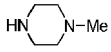
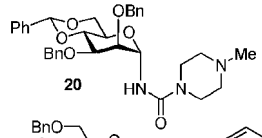
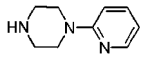
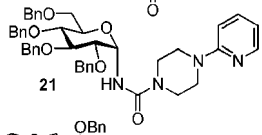
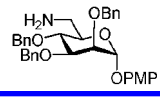
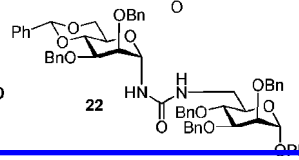
**Scheme 2.** Transformation of α-Glycal Trichloroacetamides into α-Glycosyl Ureas




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

**Table 2.** Coupling of Amines with α-Trichloroacetamides[a]



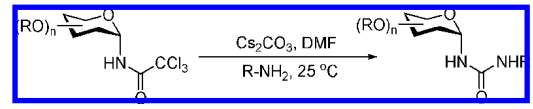

| Entry | R-NH$_2$ | Trichloroacetamides | Glycosyl Ureas | Yield[b] |
|---|---|---|---|---|
| 1 |  | **5** |  **17** | 80% |
| 2 |  | **9** |  **18** | 88% |
| 3 |  | **8** |  **19** | 94% |
| 4 |  | **10** |  **20** | 75% |
| 5 |  | **5** |  **21** | 93% |
| 6 |  | **10** |  **22** | 76% |

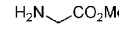
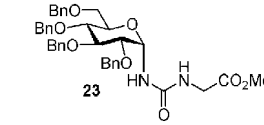
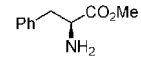
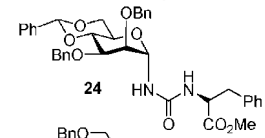
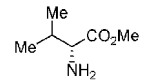
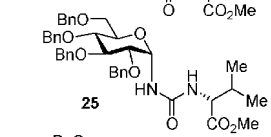
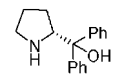
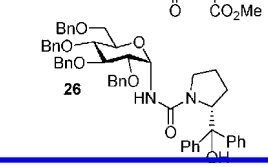
[a] The reactions were performed with 3−4 equiv of $Cs_2CO_3$ and 2−3 equiv of amine in DMF (0.2 M) at 25 °C. [b] Isolated yield.

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 3.** Coupling of Both D- and L-Amino Acids with α-Trichloroacetamides[a]




| Entry | Amino Acids | Trichloroacetamides | Urea-Linked Glycopeptides | Yield[b] |
|---|---|---|---|---|
| 1 |  | **5** |  **23** | 85% |
| 2 |  | **10** |  **24** | 88% |
| 3 |  | **5** |  **25** | 80% |
| 4 |  | **5** |  **26** | 90% |

[a] The reactions were performed with 3 equiv of $Cs_2CO_3$ 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 trichloroacetamides depends on the nature of the nickel catalyst. This new method is applicable to a number of glycosyl trichloroacetimidate substrates which cannot be easily accessed by our previous method. The α-glycosyl trichloroacetamides are then directly converted into the corresponding α-glycosyl ureas

(10) (a) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720. (b) Varki, A. *Glycobiology* **1993**, *3*, 97–130.

(11) (a) Ichikawa, Y.; Ohara, F.; Kotsuki, H.; Nakano, K. *Org. Lett.* **2006**, *8*, 5009–5012. (b) Christiansen-Brams, I.; Meldal, M.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1461–1471. (c) van Ameijde, J.; Albada, H. B.; Liskamp, R. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1042–1049.

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 Iinternet at http://pubs.acs.org.

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