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

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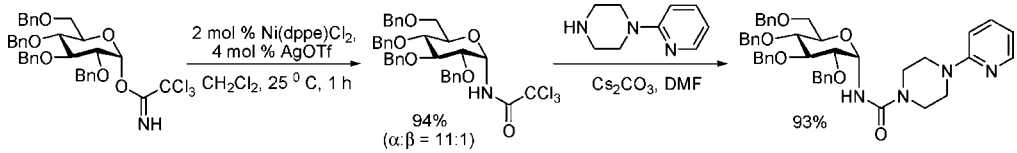
ABSTRACT



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

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

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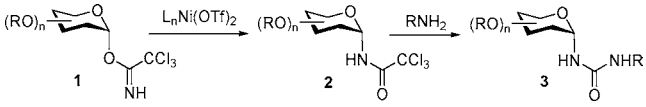
highly diastereoselective, its main drawbacks include the use of toxic OsO_4 to convert the resulting 2,3-unsaturated trichloroacetamides into the diol prior to transforming them into glycosyl ureas, the limited substrate scope (mannose residue only), and the overall moderate yields. In this paper, we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

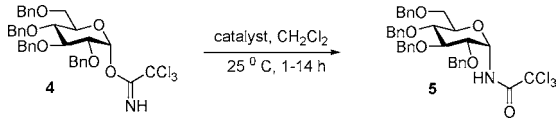
Scheme 1. Strategy for the Synthesis of α-Glycosyl Ureas



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,

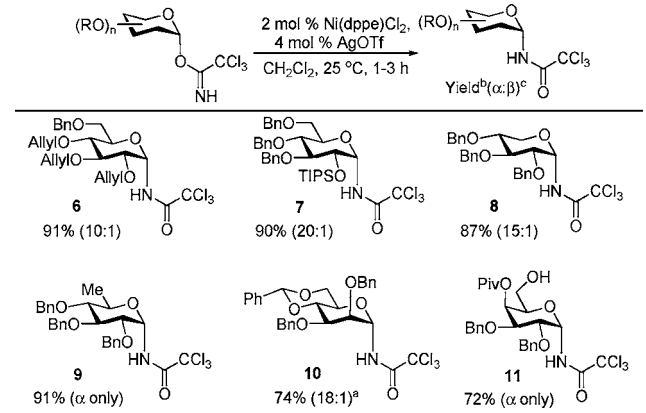


Figure 1. Cationic nickel-catalyzed 1,3-rearrangement of glycosyl trichloroacetimidate substrates: (a) compound **10** was peformed with 4 mol % of $Ni(dppe)Cl_2$ and 8 mol % of AgOTf; (b) isolated yield; (c) ^1H NMR ratio.

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.

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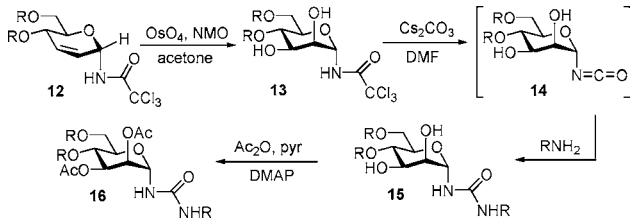
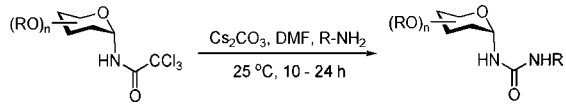
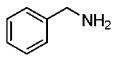
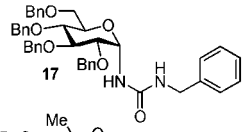
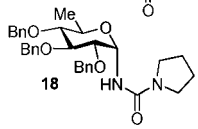
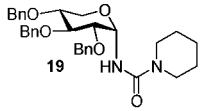
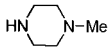
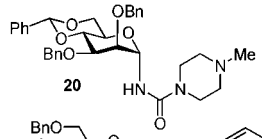
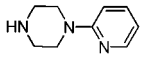
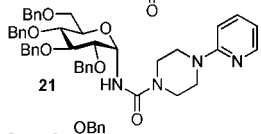
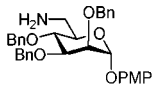
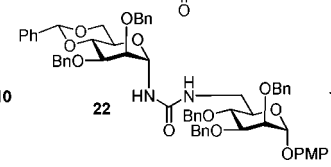
Scheme 2. Transformation of α-Glycal Trichloroacetamides into α-Glycosyl Ureas



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 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).

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

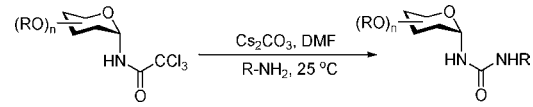


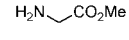
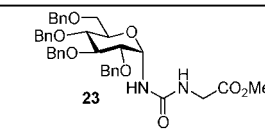
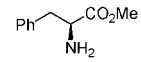
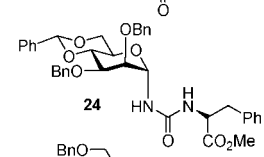
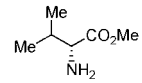
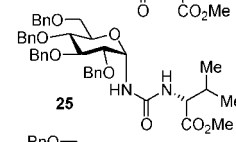
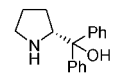
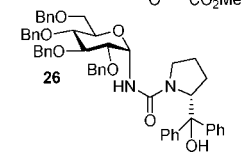
Entry	R-NH_2	Trichloroacetamides	Glycosyl Ureas	Yield[b]
1		**5**	 **17**	80%
2		**9**	 **18**	88%
3		**8**	 **19**	94%
4		**10**	 **20**	75%
5		**5**	 **21**	93%
6		**10**	 **22**	76%

[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.

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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