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Tetrahedron Letters 46 (2005) 4731–4735
Tetrahedron Letters

Intramolecular metal-catalyzed amination of pseudo-anomeric C–H bonds

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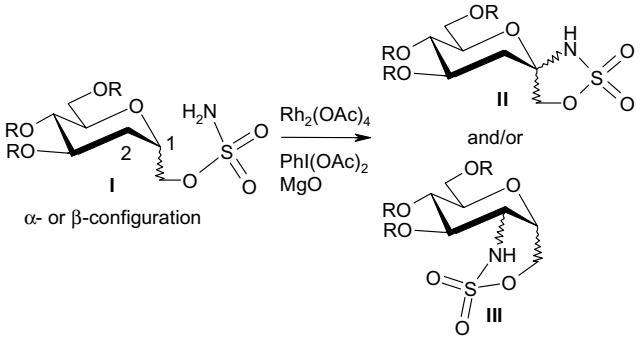
Received 12 April 2005; revised 11 May 2005; accepted 11 May 2005
Available online 31 May 2005

Abstract—Intramolecular metal-catalyzed amination of a pseudo-anomeric C–H bond in a *C*-glycoside is reported. Treatment of α,β-*C*-carbamoyloxymethyl- or β-*C*-sulfamoyloxymethyl glycosides with $Rh_2(OAc)_4$, $PhI(OAc)_2$, and MgO provided original spiro-oxazolidines or spirooxathiazolidines in reasonable yields. No correlation between 'anomeric' stereochemistry and insertion efficiency was found for the conversion of carbamate derivatives whereas amination reactions of the corresponding sulfamate esters were found to be strongly dependent on the anomeric configuration.

The catalytic selective functionalization of unactivated C–H bonds represents a major challenge in organic chemistry and provides chemists with fertile ground for the synthesis of complex molecules.[1] In this context, the latest work of Du Bois and co-workers[2] and Che and co-workers[3] on the intramolecular Rh-catalyzed amination reactions of sulfamates or carbamates is of particular interest for the efficient preparation of nitrogen-containing structures.[4] The elegant synthesis of (−)-tetrodotoxin has recently underscored the synthetic power of this methodology.[5] In connection with our studies on iminosugars and *C*-glycosides,[6] we were particularly interested in applying Rh-catalyzed amination reactions to carbohydrate frameworks. It has long been acknowledged that 'half of sugar chemistry resides at the anomeric carbon atom'.[7] We therefore designed *C*-glycosides **I** as test substrates to develop efficient access to original glycomimetics of biological interest and to study the regioselectivity and the mechanism of the intramolecular nitrogen atom transfer (Scheme 1). Amination of the C-2 position would open a general route to hexosamine *C*-glycosides[8] from **III** whereas nitrogen atom insertion into the C–H anomeric bond would yield glycomimetics **II** containing a *N*,*O*-acetal structure that could serve as surrogate iminium ions (Scheme 1).[9] To the best of our knowledge, there has been no reports of an intramolecular metal-catalyzed amination of 'anomeric' C–H bond of a carbohydrate.[10] The increased reactivity of axial anomeric C–H bonds, compared to equatorial C–H bonds, in a number of reactions such as radical H-abstraction, represents an attractive opportunity to get further insights into the mechanism of the intramolecular nitrogen atom transfer.[11] Sulfamate esters were firstly evaluated since they generally lead to the formation of the corresponding six-membered ring insertion products whereas carbamates afforded five-membered rings.



Scheme 1.

The synthesis of the test substrates **6** and **8** was performed from commercially available tri-*O*-benzyl-D-glucal **1** (Scheme 2). Heptenitol **2** was obtained in two steps by the conversion of **1** into the corresponding

Keywords: *C*-Glycosides; Amination; C–H insertion; Rhodium; *N*,*O*-Acetals.
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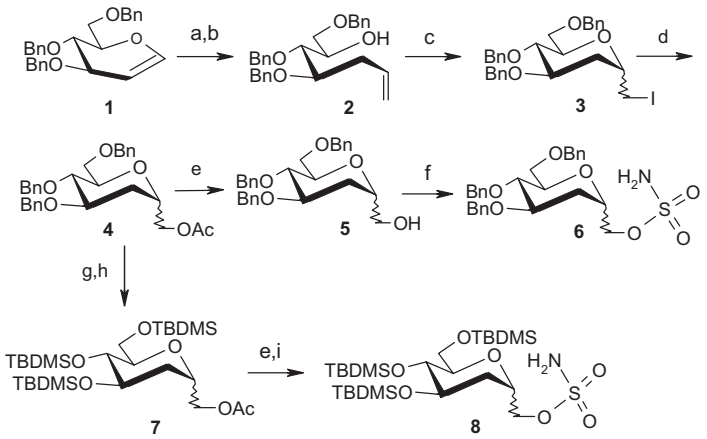
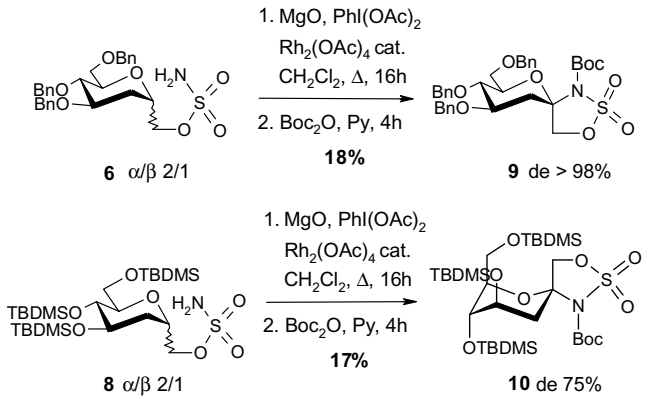
doi:10.1016/j.tetlet.2005.05.043



Scheme 2. Reagents and conditions: (a) (i) NIS (1.1 equiv), CH_3CN/H_2O (95:5), 0 to 20 °C, 15 min. (ii) $Na_2S_2O_4$ (4 equiv), $NaHCO_3$ (10 equiv), DMF/H_2O (1:1), 5 h, 98%. (b) $Ph_3P^+CH_3Br^-$ (3.5 equiv), *n*-BuLi (3.3 equiv), 0–20 °C, 16 h, 80%. (c) I_2 (1.7 equiv), $NaHCO_3$ (1.8 equiv), Et_2O/H_2O (5:2), 16 h, 72%. (d) *n*-Bu_4NOAc (1.5 equiv), toluene, 50 °C, 15 h, 55%. (e) NaOMe/MeOH, 3 h, 95% (Bn groups); 20% (TBDMS groups). (f) $ClSO_2NH_2$ (2 equiv), pyridine (2 equiv), CH_2Cl_2, 16 h, 90%. (g) H_2, Pd/C, MeOH, 16 h, quant. (h) TBDMSCl (5 equiv), imidazole (10 equiv), DMF, 0–60 °C, 16 h (97%). (i) $ClSO_2NH_2$ (2 equiv+2 equiv after 16 h), pyridine (2 equiv), CH_2Cl_2, 16 h at room temperature +1 h at 40 °C, 27%.

2-deoxysugar by a mild one-pot procedure,[12] followed by Wittig methylenation.[13] The I_2-promoted iodocyclization of the δ-hydroxy alkene **2** in the presence of $NaHCO_3$ afforded the *C*-iodomethyl glycosides **3** with a modest diastereoselectivity in favor of the α-anomer (α/β 2:1). In our hands, the two diastereoisomers could not been separated by flash chromatography. The rest of the synthetic sequence was thus performed using the mixture of the two diastereoisomers. After various attempts, introduction of a protected hydroxyl group in place of the iodine atom was efficiently achieved by way of a nucleophilic substitution using *n*-Bu_4NOAc in toluene to yield the key intermediates **4**.[14] After saponification of acetates **4**, the corresponding alcohols **5** were reacted with sulfamoyl chloride and pyridine to afford the benzylated test substrates **6** in high yield. To study the influence of protecting groups on the insertion reaction, we synthesized the corresponding TBDMS-protected analogs **7** from the common intermediate **4**. Quantitative hydrogenolysis of **4** afforded the corresponding triols, which were protected as silyl ethers to yield compounds **7**. Treatment with sodium methanolate, followed by condensation with sulfamoyl chloride afforded the desired substrates **8**.

The Du Bois reaction was first investigated with the epimeric mixture of the benzyl-protected derivatives **6**. Following a standard protocol using $PhI(OAc)_2$ (1.1 equiv), MgO (2.3 equiv) and 5 mol % of $Rh(OAc)_4$, a sluggish conversion of the sulfamate esters was observed (Scheme 3). ^1H and ^{13}C NMR spectra of the crude product proved quite complex and appeared to indicate the presence of a spirooxathiazolidine[15] in equilibrium with the corresponding open-chain imine form (ratio 2:1 in favor of the oxathiazolidine). In particular, the carbon resonance observed at δ 183.6 in ^{13}C NMR is consistent with a sulfonimine ester structure.[16] Since purification proved difficult, the crude product was treated directly with Boc_2O in pyridine to afford, after a simple filtration on silica gel, compound **9** in 18% yield from **6** and as a single diastereoisomer. No other identifiable products were



Scheme 3.

isolated from this reaction. The structure of **9** was determined on the basis of mass and NMR spectral data (^1H, COSY, NOESY, and ^{13}C).[17]

The configuration of the newly created stereogenic center was unambiguously determined by the definite NOE interactions between H'_a and H-2_{eq} and between H'_a and H-3 (Fig. 1). The regioselectivity of the reaction may be rationalized by the fact that electron-donating groups generally activate the α-C–H bond toward insertion.[16b] In addition, insertion into tertiary C–H bonds is generally preferred to secondary C–H bonds.

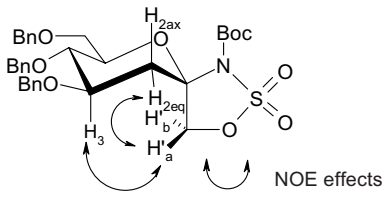
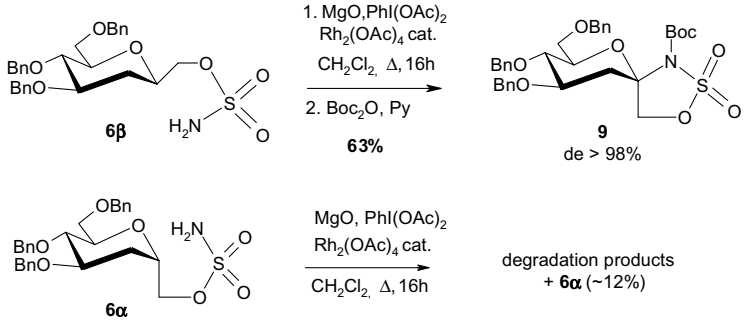


Figure 1.

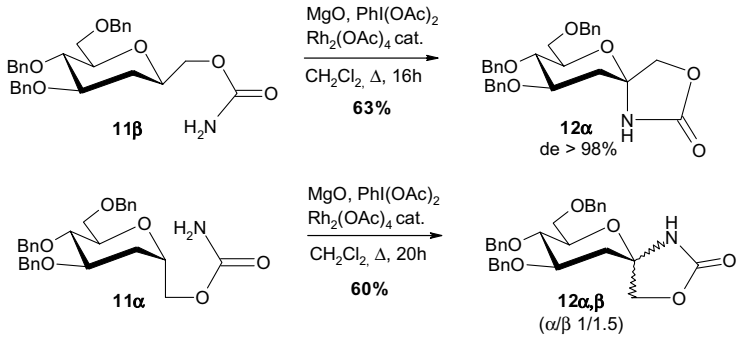
As the low yield observed may be due to undesirable side reactions generated by the presence of benzylic methylenes in **6**, we performed the intramolecular C–H insertion from TBDMS-protected sulfamate esters **8**. After treatment of the crude product with Boc_2O in pyridine,[18] we isolated spirooxathiazolidines **10** as a mixture of two diatereoisomers (de 75%) in a yield similar to the one obtained from **6** (17% from **8**). Extensive NMR analysis indicated that the major epimer exists predominantly in a $^1C_4$ chair conformation in which all the *O*-silyloxy groups are in an axial position, the C–N bond being equatorial.[19] In this case, the normal steric preference for the equatorial position due to the bulky Boc group outweighs the small anomeric effect of nitrogen substituents.[20]

From results obtained with sulfamate esters **6** and **8**, we postulated that only the minor β-epimer was a substrate for the cyclization reaction. This working hypothesis was mainly based on two observations. According to TLC, the conversion of **6** or **8** proceeded smoothly before slowing down significantly after a few hours. After difficult purification of the reaction mixture, the starting material recovered was isolated as a single diastereoisomer having the α-anomeric configuration. No trace of the β-epimer was detected. Our hypothesis prompted us to find practical means to obtained diastereomerically pure samples of the α- and β-epimers of sulfamate esters **6**. Eventually, the mixture of diastereoisomers **6** could be separated after careful purification on silica gel. The intramolecular C–H insertion reaction was first investigated with the sulfamate ester **6β**. We were pleased to find that oxathiazolidine **9** was obtained in 63% yield from **6β** after treatment with Boc_2O in pyridine (Scheme 4). In sharp contrast, exposure of the α-epimer to $PhI(OAc)_2$, MgO and catalytic $Rh(OAc)_4$ led to a mixture of unidentifiable products. The starting material **6α** was the only compound that could be isolated by chromatography on silica gel after 16 h (~12% yield). Longer reaction times led to the complete degradation of compound **6α**. These results are consistent with those obtained for the diastereoisomeric mixture of **6** (Scheme 3).

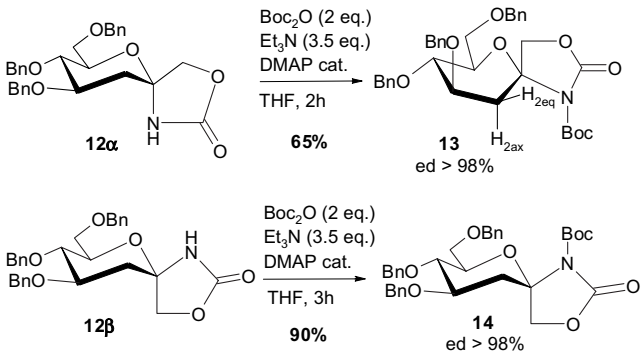
The results observed for the sulfamate esters **6** and **8** prompted us to explore the reactivity of the corresponding carbamates. The test substrates **11** were obtained in 79% yield from the epimeric mixture of alcohols **5** by treatment with $CCl_3C(O)NCO$ followed by NH_3/H_2O.[21] Difficult separation of the mixture of diastereoisomers on silica gel afforded pure samples of the α- and β-epimers of carbamates **11**. In sharp contrast with findings for sulfamates **6**, both epimers of carbamates **11** provided the expected insertion products in similar yields (60–63%) (Scheme 5). In addition, no trace of the corresponding open-chain imine form of **12** was detected by NMR analysis of the crude product. Conversion of **11β** afforded the spirooxazolidine **12α** having an anomeric α-configuration whereas the corresponding epimer **11α** led to a mixture of the two diastereoisomers **12α** and **12β** (α/β 1:2.2 after work-up; α/β 1:1.5 after flash chromatography). In this latter reaction, due to a small anomeric effect expected for nitrogen substituents, the carbamate **12α** was probably generated via



Scheme 4.



Scheme 5.



Scheme 6.

equilibration of the initially formed epimer **12β**.[22] This claim is supported by an equilibration experiment performed from a pure sample of **12β**. Under typical amination conditions, epimerization occurred and ^{1}H NMR analysis of the crude product indicated the following ratio: **12α/12β** 1:2.2 after 16 h. These results confirm that the amination reaction proceed either via a direct insertion mechanism or by H-abstraction/radical recombination where the second step is extremely fast,[11] thus preventing the formation of a planar π-type anomeric radical intermediate.[23]

The cyclic carbamates **12** were protected with a Boc group (Scheme 6). Interestingly, extensive NMR analysis indicated that compound **13**[24] exists predominantly in a $B_{2,5}$ conformation in which the *N*-Boc and benzyloxymethyl substituents adopted a pseudo-equatorial position that minimizes steric interactions. Coupling constants[24] are in good agreement with the proposed structure as well as NOE effects observed between H-5 and H-2_{ax}, and between H′a and H-2_{eq}. As a general rule, C–N bond of the *N*-Boc spiranic derivatives **9**, **10**, **13**, or **14** always adopt an equatorial position via epimerization or conformational interconversion.

In conclusion, we have reported the first examples of intramolecular metal-catalyzed amination of a pseudo-anomeric C–H bonds in a *C*-glycoside. The oxidative conversion of sulfamate esters **6β** and carbamates **11** provides bicyclic glycomimetics[25] containing a functionalizable *N*,*O*-acetal structure. No correlation between anomeric stereochemistry and insertion efficiency was found for the conversion of carbamates **11**. In contrast, amination reactions of the corresponding sulfamate esters **6** were found to be strongly dependent on the 'anomeric' configuration. Exploration of the chemical reactivity of the oxathiazolidines or oxazolidines synthesized as well as further applications of Rh-catalyzed amination reactions to carbohydrates are currently under investigations in our laboratory.

Acknowledgements

Financial support of this study by grants from CNRS is gratefully acknowledged. S.T. thanks the French Department of Research for a fellowship (MENRT).

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17. Selected data for **9**: ^{1}H (500 MHz, $CDCl_3$): δ (ppm) 7.32 (m, 15H, $3C_6H_5$); 4.91 (d, 1H, CH_2Bn, J = 10.7 Hz); 4.71–4.64 (m, 4H, CH_2Bn); 4.61 (d, 1H, H′$_b$ J = 9.8 Hz); 4.57 (d, 1H, CH_2Bn, J = 12.1 Hz); 4.21 (d, 1H, H′$_a$, J = 9.8 Hz); 3.84 (dd, 1H, H_{6b}, J = 7.8, 11.6 Hz); 3.76–3.70 (m, 2H, H_4, H_{6a}), 3.59–3.50 (m, 2H, H_3, H_5); 3.02 (t, 1H, H_{2ax}, J = 12.8 Hz); 2.23 (dd, H_{2eq}, J = 4.7, 13.1 Hz);

1.54 (s, 9H, Boc). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 147.3, 138.4, 138.1, 137.8, 128.7–127.7, 89.8, 86.3, 77.1, 76.8, 75.9, 75.4, 73.6, 72.1, 70.9, 68.3, 35.2, 28.0; HRMS (ES) *m/z* 648.2241 $[M+Na]^+$ ($C_{33}H_{39}NO_9NaS$ requires 648.2243).

18. As it was observed for the reaction performed with **6**, ^{1}H NMR analysis of the crude product seemed to indicate the presence of the expected spirooxathiazolidine in equilibrium with the corresponding open-chain imine form (ratio 1:1).
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24. Selected data for **13**: ^{1}H (500 MHz, $CDCl_3$): δ (ppm) 7.40–7.19 (m, 15H, $3C_6H_5$); 4.60–4.51 (m, 4H, CH_2Bn); 4.49 (d, 1H, CH_2Bn, J = 12 Hz); 4.42 (d, 1H, CH_2Bn, J = 11.5 Hz); 4.36 (ddd, 1H, H_5, $J \sim 3.0$, 3.5, 9.5 Hz); 4.25 (d, 1H, H'_b J = 10.0 Hz); 4.20 (d, 1H, H'_a J = 10.0 Hz); 4.07 (m, 1H, H_3); 3.65 (d, 2H, H_6, J = 3.0 Hz); 3.62 (dd, 1H, H_4, $J \sim 2.5$, 9.5); 3.04 (dd, 1H, H_{2ax}, J = 4.0, 14.5 Hz); 2.07 (dd, 1H, H_{eq}, J = 4.0, 14.5 Hz); 1.55 (s, 9H, Boc). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 151.9, 150.2, 138.4, 137.9, 137.8, 128.7–127.7, 89.8, 84.6, 76.7, 76.4, 74.6, 73.3, 72.4, 71.3, 69.5, 32.4, 28.1; HRMS (ES) *m/z* 612.2570 $[M+Na]^+$ ($C_{34}H_{39}NO_8Na$ requires 612.2573).
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