Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 2231–2234
Tetrahedron Letters

Selective synthesis of anomeric α-glycosyl acetamides via intramolecular Staudinger ligation of the α-azides ☆

Aldo Bianchi and Anna Bernardi*

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, via Venezian 21, 20133 Milano, Italy

Received 5 November 2003; revised 10 December 2003; accepted 19 December 2003

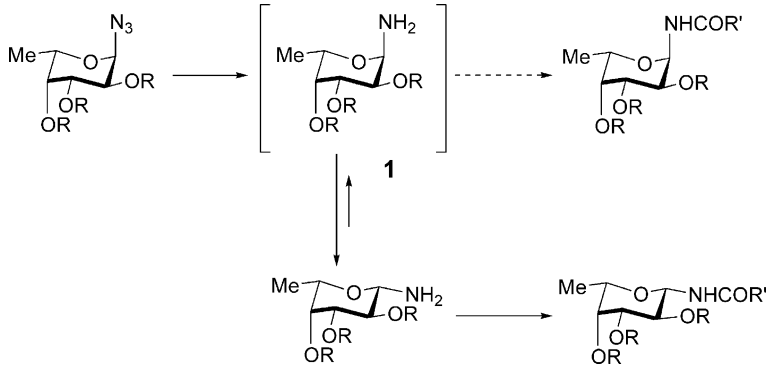
Abstract—α-Glycosyl azides can be transformed into the corresponding α-glycosyl acetamides with complete retention of configuration via reduction–acylation (Staudinger ligation) reactions using specifically functionalized phosphines. The α-acetamides of per-O-benzylated-fucose, per-O-benzylated-glucose and per-O-benzylated-galactose were selectively synthesized by this process.

The synthesis of glycosyl amides is receiving increasing attention because of the importance of glycopeptides and glycoproteins in many biological processes. In the course of our studies towards the design of glycomimetics we needed to evaluate whether α-fucosyl amides could be used as building blocks to allow an easy connection of the carbohydrate fragment to non-sugar scaffolds. However, the α-amino glycopyranoses such as **1** required to form the corresponding amides are not configurationally stable and immediately equilibrate to the β-anomer (Scheme 1).

Various schemes have been proposed to circumvent this process, which compromises the stereochemical integrity of the product amides, and to synthesize α-glycosyl amides avoiding intermediate formation of the free amines.[1–6] However, in most cases, and in particular for fucosyl derivatives (see below), anomerization remains a significant problem.[4]

In this paper we show that the Staudinger ligation of α-glycosyl azides[7,8] with specifically functionalized phosphines is an effective method for synthesizing α-fucosyl acetamides from α-fucosyl azide **4** and applies equally well to the synthesis of other α-glycosyl acetamides. In the process, we also introduce a new and effective method for the stereoselective synthesis of **4**.

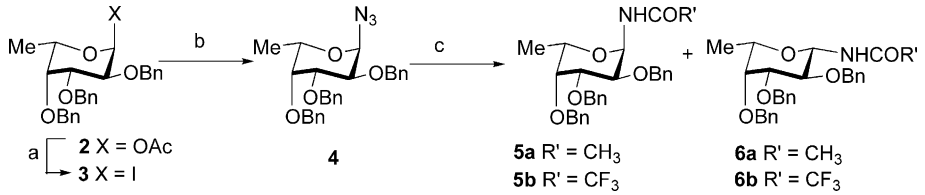
α-Glycosyl azides are generally synthesized via S_N2 azide displacement of anomeric halides[9,10] or by treating



Scheme 1. α → β isomerization of anomeric amines precludes their use for the stereoselective synthesis of α-glycosyl amides.

Keywords: Carbohydrates; Glycosyl amides; Ligation reactions; Stereoselective synthesis.
☆ Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.tetlet.2003.12.159
* Corresponding author. Tel.: +39-02-50314092; fax: +39-02-50314072; e-mail: anna.bernardi@unimi.it

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.159



Scheme 2. Stereoselective synthesis of the α-fucosyl azide **4**. Reagents and conditions: (a) TMSI, CH_2Cl_2, 0 °C, 1 h; (b) Bu_4NI, NaN_3, CH_2Cl_2, room temperature, 24 h (64% overall yield from **2**); (c) reduction–acetylation of **4** (see tables).

monosaccharides acylated at position 1 and bearing a non-participating group in position 2 with trimethylsilyl azide.[9] In the case of fucose, treatment of the acetate **2** with trimethylsilyl azide gave a 55:45 mixture of the desired α-anomer **4** and of the corresponding β-azide. The starting α-fucosyl azide **4** was synthesized with good yields and total stereocontrol using glycosyl iodide chemistry (Scheme 2).[11,12] Thus, starting from the acetate **2**, the α-iodide **3** was formed by reaction with TMSI. Treatment of **3** with an excess of NaN_3 in CH_2Cl_2 in the presence of Bu_4NI gave **4** in 64% overall yield and in a one-pot sequence, which does not require purification of the intermediate iodide. In the presence of Bu_4NI some β-iodide is presumably formed from **3**. It has been shown[12] that this more reactive anomer is selectively displaced in S_N2 reactions by weak nucleophiles, such as alcohols. The low solubility of NaN_3 in CH_2Cl_2 dampens its reactivity and allows selective formation of the α-azide, presumably by selective displacement of the more reactive β-anomer of **3**. Soluble azide salts (i.e., Bu_4NN_3) are too reactive to display α-selectivity in this reaction.[11]

As expected, catalytic hydrogenation of **4**, followed by acetylation of the intermediate amine, gave the β-fucosyl acetamide **6** (Scheme 2) in quantitative yield and with complete stereocontrol (Table 1, entry 1). Running the catalytic hydrogenation in Ac_2O as the solvent, the intermediate α-amine **1** (R = Bn) could be trapped and the fucosyl acetamide (Scheme 2) was formed in an 80:20 α/β ratio (Table 1, entry 2). In contrast, using THF in the presence of excess AcCl led to a 40:60 α/β mixture in modest yield (Table 1, entry 3).

Table 1. Reduction–acetylation of **4** under various reaction conditions

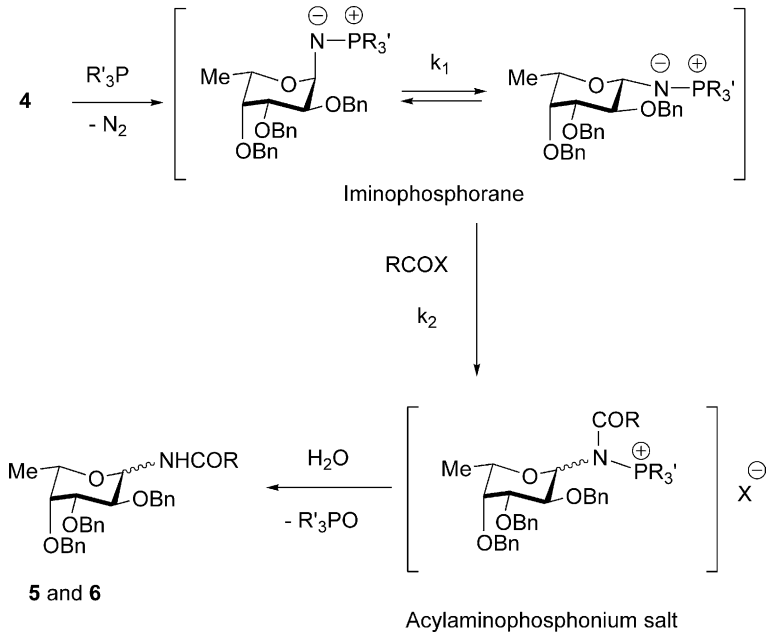
Entry	Reaction conditions	α/β **5**:**6** ratio[a]	Total Y (%)
1	(a) H_2/Pd in MeOH (b) Ac_2O, Et_3N, CH_2Cl_2	0:100	98
2	H_2/Pd, Ac_2O, AcONa[b]	80:20	80
3	H_2/Pd, THF, AcCl, AcONa[b]	40:60	50
4	AcSH, $CHCl_3$, 2,6-lutidine[c]	50:50	23
5	(a) Me_3P in CH_2Cl_2[d] (b) $(CF_3CO)_2O$, Et_3N[f]	100:0	76[e]
6	(a) Me_3P in CH_2Cl_2[d] (b) Ac_2O, Et_3N, DMAP[f]	0:100	94
7	(a) Me_3P in CH_2Cl_2[d] (b) PFPOAc[g]	20:80	67

[a] Determined by ^1H NMR of the crude products.
[b] 3 h at room temperature.
[c] 3 days at room temperature.
[d] 30 min at room temperature.
[e] Reaction product is **5b**.
[f] 3 h, −78 °C.
[g] 3 h, 0 °C.

Reductive acylation of azides with thioacids has recently been suggested for the conversion of glycosyl azides into amides with no epimerization.[6] However, treatment of **4** with excess AcSH in the presence of 2,6-lutidine gave a 1:1 mixture of anomers **5a** and **6** in poor yield (Table 1, entry 4).

One-pot reduction–acylation of α-anomeric azides using phosphines as the reducing agent (the Staudinger reaction[13]) in the presence of acylating reagents has been used to prevent anomerization with some success.[2,4] Under these conditions an intermediate iminophosphorane is initially formed (Scheme 3). This species is also subject to anomeric isomerization, but it can be trapped by acylating agents to give a configurationally stable acylamino phosphonium salt. This in turn, upon quenching, yields the corresponding amide. Thus, starting from an α-azide, the anomeric ratio of the final amide product depends on the relative ratio of the iminophosphorane anomeric equilibration (k_1 in Scheme 3) and of its acylation (k_2).[14] In practice, the group of Györgydeák has reported that α → β epimerization can only be avoided by using very potent acylating agents, such as trifluoroacetic anhydride,[4] and the range of α-glycosyl amides that are readily available through this procedure appears to be rather limited. Indeed, reaction of **4** with Me_3P followed by the in situ addition of trifluoroacetic anhydride afforded only the α-amide **5b** (Table 1, entry 5), whereas addition of acetic anhydride afforded exclusively the β-amide **6** (Table 1, entry 6). Similar results were obtained using other acetylating agents. Under these conditions, the most α-selective acetylating agent appeared to be pentafluorophenol acetate (PFPOAc), which afforded a 20:80 α/β ratio of anomers (Table 1, entry 7).

Recently, so-called 'Staudinger ligation' reactions have been introduced to couple peptides to azido groups.[7,8] These reactions use specifically functionalized phosphines to trap the Staudinger aza-ylide intermediates in an intramolecular fashion, resulting in the direct formation of an amide link. Fast, intramolecular acylation of the anomeric nitrogen should prevent epimerization of the anomeric carbon, therefore we examined the reaction of **4** with two of the reported[8] phosphine reagents **7**[15] and **8**.[16]



Scheme 3. The mechanism of the Staudinger reduction–acylation of azides.

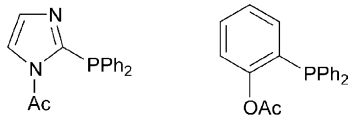
The 2-diphenylphosphino-*N*-acetylimidazole **7** reacts very slowly with **4** at room temperature, but clean ligation can be obtained at 70 °C. Both yields and α/β-selectivity displayed a marked solvent effect, going from 10:90 α/β and 70% yield in THF (Table 2, entry 1) to 50:50 α/β and 68% yield in CCl_4 (Table 2, entry 3).

Better results were obtained using phosphine **8**, which displayed α-selectivity in all the solvents examined (Table 2, entries 4–7). Running the reactions at 70 °C overnight in CCl_4 (entry 6) the acetamide was formed in 77% yield and in an 80:20 α/β ratio. In toluene (entry 5), a 75% yield and 85:15 α/β anomer ratio were obtained. TLC inspection of the reaction course showed that at 70 °C in both solvents, consumption of the azide **4** was complete in 3 h. At this stage an intermediate was formed, which is slowly converted to **5a**. When the temperature was reduced to 40 °C following the disappearance of the azide spot from the TLC plate, the process became more selective, and the α/β ratio was improved to synthetically useful levels (Table 2, entry 7).

This reaction can be extended to other glycosyl azides. For instance the α-glucosyl azide **9**[9] and the α-galactosyl azide **10**[9] (Scheme 4) were both reduced with complete α-selectivity by treatment with **8** at 70 °C in CCl_4 for 24 h.[17]

In conclusion, we have described here the first general methodology for reductive acetylation (Staudinger ligation) of α-glycosyl azides that proceeds with retention of configuration at the anomeric carbon. The reagent employed, the functionalized phosphine **8**,[16] can be easily synthesized and handled, and can be stored

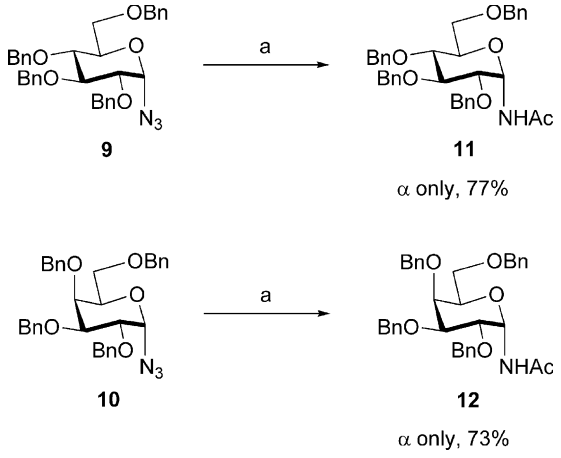
Table 2. Reduction–acetylation of **4** with functionalized phosphines **7** and **8**



7 **8**

Entry	Reagent	Solvent	*T* (°C)	*t* (h)	α/β ratio[a]	Yield (%)
1	**7**	THF	70	2	10:90	70
2	**7**	Toluene	70	6	30:70	25
3	**7**	CCl_4	70	18	50:50	68
4	**8**	THF	70	18	75:25	50
5	**8**	Toluene	70	18	85:15	75
6	**8**	CCl_4	70	18	80:20	77
7	**8**	CCl_4	[b]	[b]	94:6	84

[a] Determined by ^{1}H NMR of the crude products.
[b] 3 h at 70 °C, followed by 24 h at 40 °C.



Scheme 4. Reduction–acetylation of α-glucosyl and α-galactosyl azides **9** and **10**. Reagents and conditions: (a) 1.2 equiv of **8**, 24 h at 70 °C in CCl_4.

under Ar as a 1 M toluene solution at 4 °C for several weeks. The reaction could be applied to per-O-benzylated-glycosyl azides in the fuco-, gluco- and galacto-series with good yields and selectivity. Further studies are in progress to extend the scope of this reaction to other acylating agents and to investigate the reaction mechanism.

Acknowledgements

We thank Andrea Colombo for suggestions in the initial phases of this project, and Andrea Russo for preparing the azides **9** and **10**. Funding was provided in part by the European Community's Human Potential Programme under contract HPRN-CT-2002-00173.

References and notes

1. Nair, L. G.; Fraser-Reid, B.; Szardenings, A. K. *Org. Lett.* **2001**, *3*, 317–319, and references cited therein.
2. Mizuno, M.; Muramoto, I.; Kobayashi, K.; Yaginuma, H.; Inazu, T. *Synthesis* **1999**, 162–165, and references cited therein.
3. Boullanger, P.; Maunier, V.; Lafont, D. V. *Carbohydr. Res.* **2000**, *324*, 97–106.
4. Kovács, L.; Ösz, E.; Domokos, V.; Holzer, W.; Györgydeák, Z. *Tetrahedron* **2001**, *57*, 4609–4621, and references cited therein.
5. Damkaci, F.; DeShong, P. *J. Am. Chem. Soc.* **2003**, *125*, 4408–4409.
6. Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754–7755.
7. Nillson, B. L.; Kiessling, L. K.; Raines, R. T. *Org. Lett.* **2000**, *2*, 1939–1941.
8. Saxon, E.; Armstrong, J. I.; Bertozzi, C. R. *Org. Lett.* **2000**, *2*, 2141–2143.
9. Györgydeák, Z.; Szitagyi, L.; Paulsen, H. *J. Carbohydr. Chem.* **1993**, *12*, 139–163, and references cited therein.
10. Soli, E. D.; Manoso, A. S.; Patterson, M. C.; DeShong, P.; Favor, D. A.; Hirshmann, R.; Smith, A. B., III. *J. Org. Chem.* **1999**, *64*, 3171–3177.
11. Gervay, J.; Nguyen, T. N.; Hadd, M. J. *Carbohydr. Res.* **1997**, *300*, 119–125.
12. Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 161–169.
13. Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 351–368.
14. A phosphotriazene is the first intermediate of the Staudinger azide reduction. Acylation of this intermediate, followed by elimination of N_2 and Ph_3PO could also occur (see Ref. 2).
15. Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038–4046.
16. Rauchfuss, T. B. *Inorg. Chem.* **1977**, *16*, 2966–2968.
17. All new compounds were fully characterized by ^{1}H and ^{13}C NMR and by MS spectrometry (FAB). General procedure for the Staudinger reduction–acylation: To a solution of the α-azide (1 equiv) in CCl_4 (0.1 M) at room temperature under Ar, was added the phosphine **8** (1.2 equiv) (1 M solution in dry toluene). The reaction mixture was stirred for the time and at the temperature indicated in Table 2. The solvent was then evaporated under reduced pressure. The residue was dissolved in AcOEt and extracted with water: the organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography using 6:4 toluene/AcOEt as the eluent.