Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 637–639

TETRAHEDRON LETTERS

Anomeric activation of thioglycosides and preparation of deoxyglycosides using polymer-bound iodate(I) complexes

Janis Jaunzems, Georgia Sourkouni-Argirusi, Martin Jesberger and Andreas Kirschning*

Institut für Organische Chemie der Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany

Received 29 October 2002; revised 27 November 2002; accepted 28 November 2002

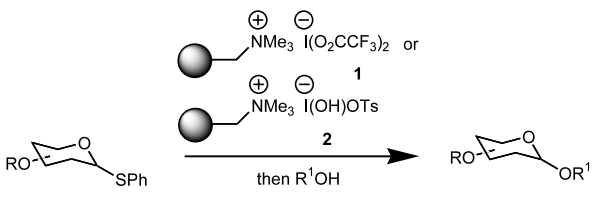
Abstract—New thiophilic polymer-bound haloate(I) complexes are presented which are well suited for the polymer-assisted solution-phase activation of 2-deoxythioglycosides. In the presence of alcohols 2-deoxyglycosides are obtained in yields between 60 and 95%. Isolation of the target glycosides is further simplified by removing the byproduct diphenyldisulfide by reductive work-up. Here also a polymer-bound reagent, namely borohydride exchange resin, served as a tool for sequestering the sulfur-containing impurities.

The efficient preparation of oligosaccharides and glycoconjugates in solution is still a challenging topic and various new solution phase techniques have been developed recently. These include the use of fluorous phases,[1] functionalized polymers,[2] scavenging protocols based on 'capping and tagging' protecting groups,[3] multienzyme loaded beads for sugar nucleotide regeneration[4] and computer-assisted planning of solution syntheses.[5]

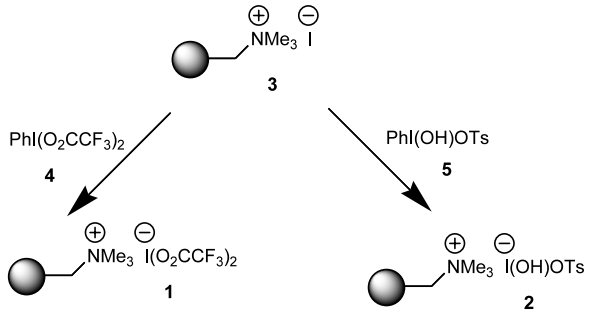
A solution-phase technique of general importance is the utilization of polymer-supported reagents and catalysts[6] because work-up is minimized to the point that only filtration is necessary. The activation of glycosyl bromides with silver ions that are immobilized on a solid-phase was first studied by Paulsen and Lockhoff[7] and later by Capillon et al.[8] Recently, we disclosed the preparation of 2-deoxyglycosides by employing polymer-attached silyltriflate as activating agent for the corresponding 2-deoxygenated glycosyl acetates.[3] In this communication, we describe the facile preparation of oligodeoxysaccharides and therefrom derived glycoconjugates using thioglycosides and polymer-supported haloate(I) complexes **1** and **2** (Scheme 1). As is shown, these new polymer-supported reagents are highly thiophilic. They are prepared in analogy to related reagents[9] as is described in Scheme 2 by oxidative ligand transfer of the mobile ligands in [bis(trifluoroacetoxy)iodo]benzene **4** or [hydroxy(tosyloxy)iodo]benzene **5**,[10] often referred to as the Koser reagent, onto polymer-bound iodide **3**.

After washing with dry dichloromethane, these new functionalized polymers can be stored at −20°C for weeks. Polymer-bound iodide **3** is obtained by treatment of anionic exchange resin IRA-400 or IRA-900 (chloride form) with an excess of an aqueous solution of HI (3N).

The key step of this project is the glycosidation step. We employed thioglycosides **6** and **7** as glycosyl donors which were activated by functionalized polymers **1** and



Scheme 1.



Scheme 2.

* Corresponding author. Tel.: +49(0)511/762-4613; fax: +49(0)511/762-3011; e-mail: andreas.kirschning@oci.uni-hannover.de

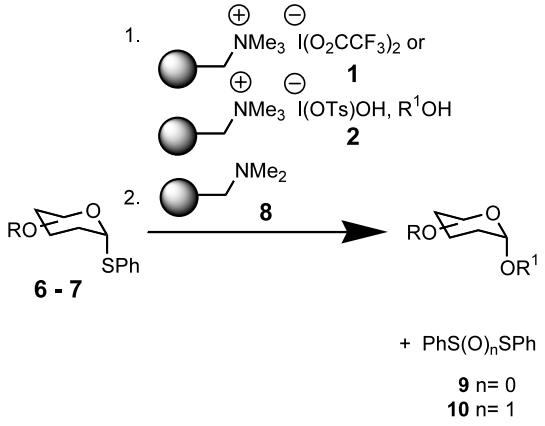
0040-4039/03/$ - see front matter
PII: S0040-4039(02)02708-9

2 in the presence of various alcohols (Scheme 3 and Table 1). The two iodate(I)-complexes **1** and **2** show differences in reactivity towards thioglycosides.[11] While in the presence of bis-trifluoroacetate **1** thioglycosides are instantaneously consumed in dichloromethane, reagent **2** reacts substantially slower (40°C, 24 h). With both reagents the glycosidation products are not formed immediately. TLC-analysis revealed rapid formation of a new more polar compound which vanished as time proceeded while the glycosidation products appeared. Early work-up allowed us to isolate the corresponding pyranoses which presumably are the hydrolysis products of the glycosyl trifluoracetates and glycosyl tosylates, respectively, or the corresponding iodine (III) species arising from the reaction of the iodate(I)-anion and the oxonium cation.

The reaction is terminated after 2–3 h by addition of Amberlyst A-21 **8** which scavenged trifluoroacetic acid and toluenesulfonic acid, respectively. After filtration and concentration the crude product was treated with polymer-bound borohydride (BER) **11** in *iso*-propanol at rt for 12 h. We found that these conditions efficiently scavenge thiophenol and diphenyldisulfide **9** (Scheme 4).

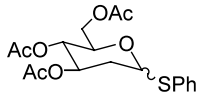
Thus, the target glycosides were isolated as mixtures of α/β-anomers and free of disulfide **9**[12] if reagent **1** served as activating agent (Schemes 3 and 4). This scavenging system is so effective because *iso*-propanol is a solvent which reacts only very sluggishly with borohydride exchange resin **11**.[13] Therefore, it is able to reduce diphenyldisulfide **9** which is followed by the scavenging of the nucleophilic thiophenol which presumably results in the formation of resin **12** (Scheme 4). In contrast to this observation, polymer-bound haloate(I) complex **2** yielded sulfoxide **10**[14] as byproduct which could not efficiently be removed by this procedure.

The glycosidation protocol favours α-glycosides when *arabino*-configured 2-deoxythioglycosides are employed. However, the stereoselectivity of the process is moderate when *arabino*-configured 2-deoxythioglycosides are employed. In close proximity, this result is independent of the α/β-ratio of the thioglycoside **6** employed. In contrast, *ribo*-configured thioglycosides

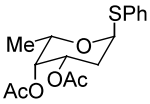


Scheme 3.

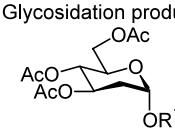
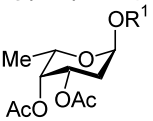
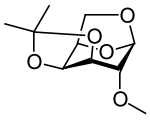
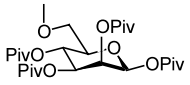
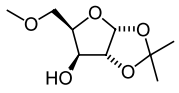
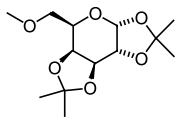
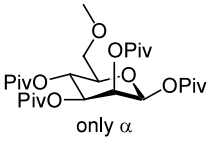
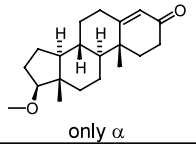
Table 1. Polymer-assisted glycosidation of 2-deoxythioglycosides



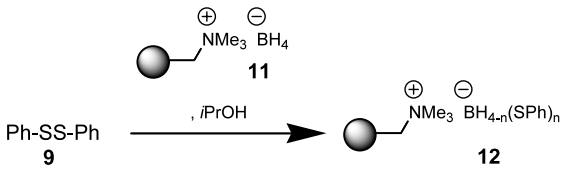
6
(α/β= 3.3:1 employed)



7
(only α employed)

Glycosidation products[a] (R^1 refers to glycosyl acceptors R^1OH)			
	% Yield		% Yield
R^1= Me α/β= 4:1	95[b]	R^1= Me only α	84[b] 90[d]
R^1= Et α/β= 3 : 1	95[b]		
R^1= Bn α/β= 1.4 : 1	60[b]	R^1= C_6H_{11} only α	82[d]
R^1= C_6H_{11} α/β= 1.5 : 1	94[b]	 only α	77[c]
 α/β= 1.6 : 1	76[b]	 only α	84[c]
		 only α	63[c]
		 only α	72[c]
		 only α	81[b]

[a] Only α-isomers are depicted; product ratios were determined from the ^1H NMR spectra of the crude products; yields refer to isolated yields of pure products. Thioglycoside **6** was employed as anomeric mixture. Scavenging protocol according to scheme 4. [b]Reaction condition with reagent **1**: CH_2Cl_2, rt, 4h. [c]Reaction condition with reagent **2**: CH_2Cl_2, 40°C, 24h. [d]Rt instead of 40°C.



Scheme 4.

only furnish α-configured glycosidation products in good to excellent yield. These observations are in accordance with conventional solution-phase glycosidations of 2-deoxythioglycosides when no stereodirecting group is present at C-2.[15,16]

In conclusion, we developed a polymer-assisted solution-phase approach to 2-deoxyoligosaccharides and glycoconjugates which uses thioglycosides as glycosyl donors. For this purpose we developed a new set of thiophilic reagents and a scavenging protocol which can be utilized to quantitatively remove disulfides from solution. Tedious work-up and product isolation are reduced to a minimum. Hence, this synthetic strategy has the potential for the automated synthesis of oligosaccharides in solution.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 416) and the Fonds der Chemischen Industrie. This project is part of the joint initiative 'Biologisch aktive Naturstoffe-Chemische Diversität' at the University of Hannover. We thank Dr. G. Jas (CHELONA GmbH, Potsdam) for helpful discussions.

References

1. Curran, D. P.; Ferritto, R.; Hua, Y. *Tetrahedron Lett.* **1998**, *39*, 4937–4940.
2. Kirschning, A.; Jesberger, M.; Schönberger, A. *Org. Lett.* **2001**, *3*, 3623–3626.
3. (a) Palmacci, E. R.; Hewitt, M. C.; Seeberger, P. H. *Angew. Chem.* **2001**, *113*, 4565–4568; *Angew. Chem., Int. Ed.* **2001**, *40*, 4433–4437; (b) Pozgay, V. *Org. Lett.* **1999**, *2*, 477–479.
4. Chen, X.; Fang, J.; Zhang, J.; Liu, Z.; Shao, J.; Kowal, P.; Andreana, P.; Wang, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 2081–2082.
5. (a) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753; (b) Burkhart, F.; Zhang, Z.; Wacowich-Sgarbi, S.; Wong, C.-H. *Angew. Chem.* **2001**, *113*, 1314–1317; *Angew. Chem., Int. Ed.* **2001**, *40*, 1274–1277.
6. For recent reviews on polymer-supported reagents, see: (a) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650–679; (b) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, I. R.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195; (c) Drewry, D. H.; Coe, D. M.; Poon, S. *Med. Res. Rev.* **1999**, *19*, 97–148.
7. Paulsen, H.; Lockhoff, O. *Ber.* **1981**, *114*, 3102–3114.
8. Capillon, J.; Richard, A.; Audebert, R.; Quivoron, C. *Polym. Bull.* **1985**, *13*, 185–192.
9. (a) Sourkouni-Argirusi, G.; Kirschning, A. *Org. Lett.* **2000**, *2*, 3781–3784; (b) Monenschein, H.; Sourkouni-Argirusi, G.; Schubothe, K. M.; O'Hare, T.; Kirschning, A. *Org. Lett.* **1999**, *1*, 2101–2104; (c) Kirschning, A.; Monenschein, H.; Schmeck, C. *Angew. Chem.* **1999**, *111*, 2720–2722; *Angew. Chem., Int. Ed.* **1999**, *38*, 2594–2596.
10. Koser, G. F. *Aldrichim. Acta* **2001**, *34*, 89–102.
11. We screened for thiophilicity among a wide range of polymer-bound haloate(I) complexes such as $I(OAc)_2^-$, $Br(OAc)_2^-$, $Br(O_2CCF_3)_2^-$, as well reagent mixtures like $Br(OAc)_2^-$/TMSOTf, and $I(OAc)_2^-$/TMSOTf which failed to promote glycosidation.
12. *General procedure for the glycosidation of thioglycosides using polymer-bound reagents* ***1*** *and* ***2*** *followed by sequestration of diphenyldisulfides*: To a solution of thioglycoside (1 equiv.) in absolute dichloromethane (50 $mL \times mmol^{-1}$) at rt were added the glycosyl acceptor (1.0 equiv.) and resins **1** or **2** (1–3 equiv.; 2.5 $mmol \times g^{-1}$ based on original loading of commercial resin). The reaction mixture was shaken at rt or at 40°C (refer to Table 1) 2–4 h at 300 rpm under light protection. The reaction was monitored by tlc and was terminated by addition of Amberlyst A-21 **8** (3 equiv.; 11 $mequiv. \times g^{-1}$ for dry resin). Shaking was continued for 30 minutes. After filtration, the resins were washed with CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure to yield the desired glycoside along with diphenyldisulfide. The crude material was taken up in *i*PrOH (30 $mL \times mmol^{-1}$) and borohydride exchange resin (1 $g \times mmol^{-1}$; 3 $mmol \times g^{-1}$ loading) was added. The reaction mixture was shaken overnight at rt, filtered and concentrated under reduced pressure to yield the pure glycosides. Isolation of each anomeric isomer requires column chromatography on silica gel.
13. (a) Kirschning, A. *J. Prakt. Chem.* **2000**, *342*, 508–511; (b) Ault-Justus, S. E.; Hodges, J. C.; Wilson, M. W. *Biotechnol. Bioeng.* **1998**, *61*, 17–22.
14. Non symmetric sulfoxide **10** was purified by chromatography and characterized by NMR and MS.
15. (a) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430–2434; (b) Roush, W. R.; Lin, X.; Straub, J. A. *J. Org. Chem.* **1991**, *56*, 1649–1655; (c) Fukase, K.; Hasuoka, A.; Kusumoto, S. *Tetrahedron Lett.* **1993**, *34*, 2187–2190.
16. Preliminary experiments indicate that fully oxidized thioglycosides, derived from D-glucose or D-galactose can not be employed in glycosidations with polymer-bound reagents **1** or **2**. The activation of the phenylthio group is inefficient.