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2-Nitro Thioglycoside Donors: Versatile Precursors of β-D-Glycosides of Aminosugars

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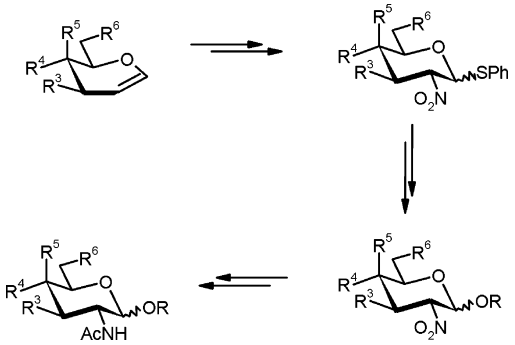
ABSTRACT



2-Nitro thioglycosides can be prepared by the Michael addition of thiophenol to 2-nitroglycal derivatives. NIS/TMSOTf activation of these 2-nitro thioglycosides, in the presence of alcohols, rapidly and cleanly led to the desired glycosides in good yield and β-selectivity. Reduction of the nitro group allowed generation of the corresponding 2-acetamido glycosides.

The application of 2-nitroglycals to the synthesis of mucin-type glycopeptides has recently attracted our attention[1] because of the fundamental role the latter play in biological processes such as cell−cell adhesion, cell growth, fertilization, parasitic infection, and inflammation.[2a,c] We previously demonstrated that 2-nitrogalactal concatenation is a useful tool for forming α-glycosidic bonds to L-serine or L-threonine. Via this methodology we synthesized all the members of the mucin family,[1,3] as well as many *O*-, *S*-, *P*-, and *C*-glycosides[4] and nucleosides.[5]

Although the synthesis of 2-nitro thioglycosides from 2-nitroglycals has already been reported by Holzapfel et al.,[6] the behavior of these compounds as glycosyl donors was never investigated. The synthesis of 2-nitro glycoside donors through Michael-type addition reactions and their use in glycosylation reactions is now reported here.

The 2-nitroglycals **1**, **2**,[3a], **3**,[6] and **4**[7] (Table 1), obtained by standard nitration conditions (addition of acetyl nitrate and elimination of acetic acid),[3a−c] were converted to the 2-nitro thioglycoside by base-catalyzed glycosylation with thiophenol and 0.1 equiv of potassium *tert*-butoxide. The 2-nitro thioglycosides (**5**−**8**) were obtained in excellent yield

(1) Winterfeld, G. A.; Schmidt, R. R. *Angew. Chem.* **2001**, *113*, 2718−2721; *Angew. Chem., Int. Ed.* **2001**, *40*, 2654−2657.

(2) (a) Varki, A. *Glycobiology* **1993**, *3*, 97−130. (b) Brockhausen, I. *Biochim. Biophys. Acta* **1999**, *1473*, 67−95. (c) Brocke, C.; Kunz, H. *Bioorg. Med. Chem.* **2002**, *10*, 3085−3112.

(3) (a) Das, J.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 1609−1613. (b) Winterfeld, G. A.; Ito, Y.; Ogawa, T.; Schmidt, R. R. *Eur. J. Org. Chem.* **1999**, 1167−1171. (c) Winterfeld, G. A.; Khodair, A. I.; Schmidt, R. R. *Eur. J. Org. Chem.* **2003**, 1009−1021.

(4) (a) Pachamuthu, K.; Gupta, A.; Das, J.; Schmidt, R. R.; Vankar, Y. D. *Eur. J. Org. Chem.* **2002**, 1479−1483. (b) Pachamuthu, K.; Schmidt, R. R. *Synlett* **2003**, 1355−1357. (c) Khodair, A. I.; Winterfeld, G. A.; Schmidt, R. R. *Eur. J. Org. Chem.* **2003**, 1847−1852. (d) Khodair, A. I.; Pachamuthu, K.; Schmidt, R. R. *Synthesis* **2004**, 53−58. (e) Geiger, J.; Barroca, N.; Schmidt, R. R. *Synlett* **2004**, accepted for publication.

(5) Winterfeld, G. A.; Das, J.; Schmidt, R. R. *Eur. J. Org. Chem.* **2000**, 3047−3050.

(6) Holzapfel, C. W.; Marais, C. F.; van Dyk, M. S. *Synth. Commun.* **1988**, *18*, 97−114.

(7) Pedretti, V.; Veyrières, A.; Sinaÿ, P. *Tetrahedron* **1990**, *46*, 77−88.

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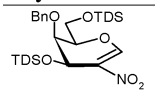
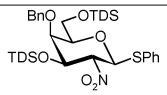
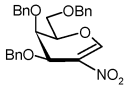
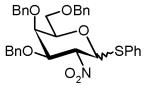
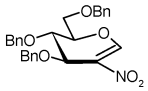
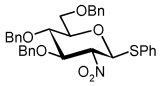
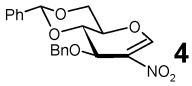
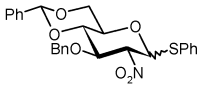
Table 1. Base-Catalyzed Addition of Thiophenol to Glycals **1**−**4**[a]

Glycal	Reaction time	Product	α:β selectivity	Yield
 **1**[b]	0.5 h	 **5**	0:1	88%
 **2**	1 h 0.3 h	 **6a:6b**	1:3 0:1	81% 80%
 **3**	0.3 h	 **7**	0:1	70%
 **4**	0.3 h	 **8a:8b**	1:2	70%

[a] Reactions were conducted at room temperature in toluene in the presence of 0.1 equiv of potassium *tert*-butoxide. [b] TDS = thexyldimethylsilyl.

Table 2. Coupling Reactions of 2-Nitrothioglycosides

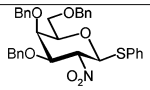
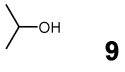
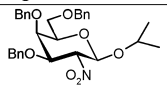
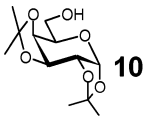
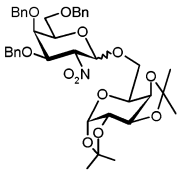
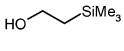
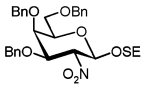
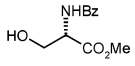
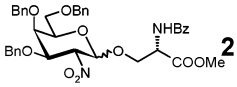
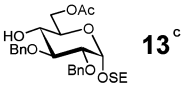
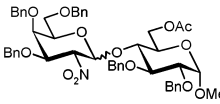
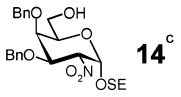
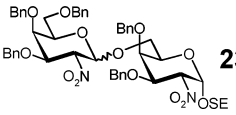
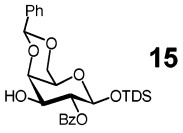
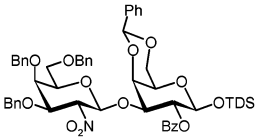
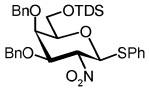
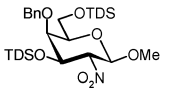
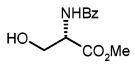
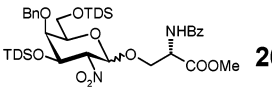
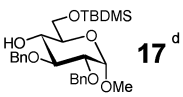
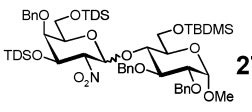
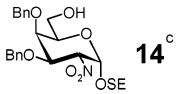
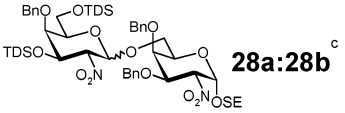
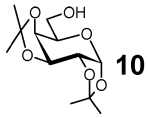
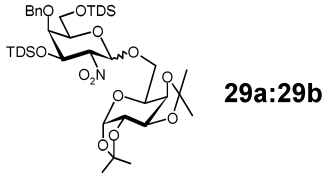
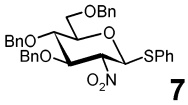
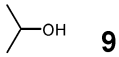
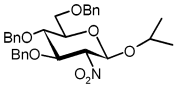
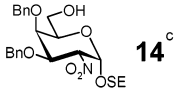
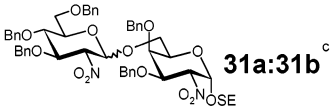
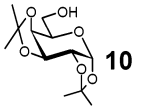
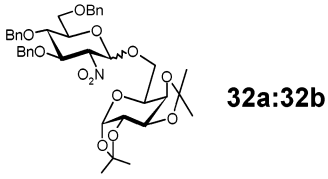
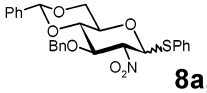
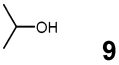
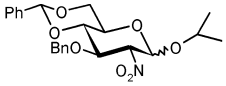
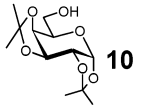
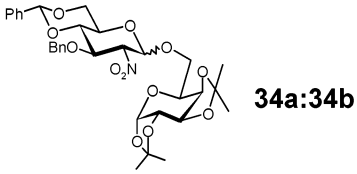
Entry	Donors	Acceptors	Major product	Yields, α:β selectivity
1	 **6b**	 **9**	 **18**	70% (0:1)[a]
2	"	 **10**	 **19a:19b**	90% (1:5)[a]
3	"	 **11**	 **20**[c]	70% (0:1)[a]
4	"	 **12**	 **21a:21b**	63% (1:4)[a]
5	"			90% (1:8)[b]
6	"	 **13**[c]	 **22a:22b**[c]	70% (1:1.1)[a]
7	"			77% (1:15)[b]
8	"	 **14**[c]	 **23a:23b**[c]	74% (1:8)[a]
9	"	 **15**	 **24**	60% (0 : 1)[b]
10	 **5**	Me—OH **16**	 **25**	68% (0:1)[a]
11	"	 **12**	 **26a:26b**	77% (1:1)[a]
12	"			68% (1:4)[b]
13	"	 **17**[d]	 **27a:27b**[d]	50% (1:1.5)[a]

Table 2 (Continued)

Entry	Donors	Acceptors	Major product	Yields, α:β selectivity
14	"	 **14**[c]	 **28a:28b**[c]	63% (1:4)[a]
15	"	 **10**	 **29a:29b**	50% (1:4)[a]
16	 **7**	 **9**	 **30**	63% (0:1)[a]
17	"	 **14**[c]	 **31a:31b**[c]	63% (1:8)[a]
18	"	 **10**	 **32a:32b**	80% (1:2)[a]
19	 **8a, b**	 **9**	 **33a:33b**	35% (1:1)[a]
20	"	 **10**	 **34a:34b**	30% (1:1)[b]

[a] Reactions, unless stated otherwise, were conducted in CH_2Cl_2. Anomeric ratios were determined by isolated products. [b] Reactions were conducted in propionitrile at −15 °C. [c] SE = trimethylsilylethyl. [d] TBDMS = *tert*-butyldimethylsilyl.

(70−88%). As previously reported,[8] concatenation with soft nucleophiles such as thiophenol yields mainly the β-anomer in a time-dependent manner. The β-linkage was confirmed by ^{1}H NMR studies, which showed a coupling constant $J_{1,2}$ = 6 Hz, which contrasted with a $J_{1,2}$ of 4 Hz for the α-anomer.

With the requisite thiophenylglycosides in hand, a series of coupling reactions with different acceptors **9**, **10**,[9] **11**, **12**, **13**,[10] **14**,[11] **15**,[10] **16**, and **17**[12] (Table 2) were carried out. Activation simply involved cooling a 1:1.2:1.5 mixture of the thioglycoside, the acceptor, and NIS in CH_2Cl_2 at 0 °C and then adding 0.15 equiv of TMSOTf (Method A). Alternatively, the same protocol could be carried out at −15 °C in propionitrile (Method B). Workup thereafter afforded the desired glycosides.

A series of compounds, selected to illustrate the wide range of possible coupling types, was prepared. The results are presented in Table 2. In the case of highly reactive acceptor alcohols (entries 1, 3, 10, and 16) only the β anomers were detected. For less reactive primary and secondary hydroxy acceptors, β-selectivity was conserved but was not exclusive. To improve selectivity, propionitrile was used as solvent, and with the help of the nitrile effect,[13] the β-selectivity was further increased (entries 5, 7, and 12). The presence of a nitro group at position 2 seemed to allow anchimeric assistance and consequently orientated the glycosylations in the direction of the β-anomer as the major product.

To investigate the influence of a 4,6-*O*-benzylidene acetal protecting group on the outcome of the glycosidation,[14a−d] nitro thioglucoside donor **8a**, **b** was tested under the same reaction conditions. Unfortunately, in this case, activation

(8) Winterfeld, G. A., Dissertation, University of Konstanz, 2000.
(9) Liu, H. W.; Nakanishi K. *J. Am. Chem. Soc*. **1982**, *104*, 1178−1185.
(10) Borén, H. B.; Garegg, P. J.; Kenne, L.; Pilotti, A.; Svensson, S.; Swahn, C. G. *Acta Chem. Scand*. **1973**, *27*, 2740−2748.
(11) See Experimental Section.
(12) Klaffke, W.; Warren, C. D.; Jeanloz, R. W. *Carbohydr. Res*. **1993**, *244*, 171−179.
(13) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694−697.
(14) (a) Crich, D.; Sun, S. *J. Org. Chem*. **1996**, *61*, 4506−4507. (b) Crich, D.; Cai, W. *J. Org. Chem*. **1999**, *64*, 4926−4930. (c) Crich, D.; Smith, M. *Org Lett*. **2000**, *2*, 4067−4069. (d) Crich, D.; Smith, M. *J. Am. Chem. Soc*. **2001**, *123*, 9015−9020.

of the thiophenyl group by NIS was found to be difficult, the α/β-ratios and the yields often being poor. The rigidity induced by the 4,6-*O*-benzylidene ring could explain this result.

Also the use of 1-benzenesulfinyl piperidine (BSP)/trifluoromethanesulfonic anhydride in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP) was investigated for thioglycoside activation.[14a−d] Unfortunately, however, the 2-nitrothiophenyl donors were not activated under these conditions. Only low yields of the desired compounds were usually obtained; side products from elimination of the intermediate triflate[14a−d] typically predominated (Figure 1).

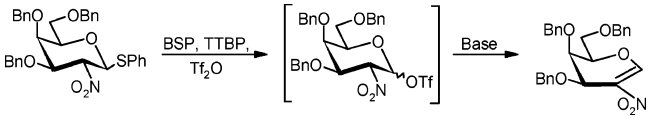
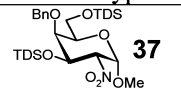
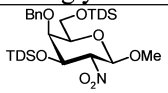
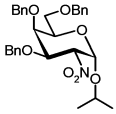
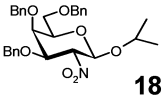
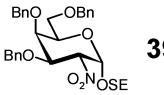
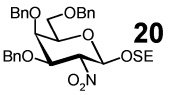
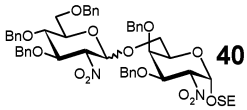
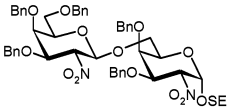


Figure 1. Activation with BSP, Tf_2O, and TTBP.

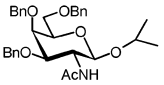
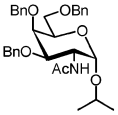
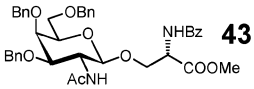
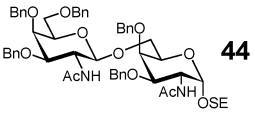
Overall, our studies have demonstrated that glycosidations with 2-nitro thiophenylglycosides generate β-anomers with high yield and selectivity. These results, along with Michael-type additions of alcohols to 2-nitrogalactals,[3a−d] thus allow access to both types of glycoside, as described in Table 3.

Table 3. Comparison between Glycosidation and Michael Addition

Michael-type addition		Thioglycoside glycosylation	
 **37**	92%	 **25**	68%
 **38**	75%	 **18**	70%
 **39**	70%	 **20**	70%
 **40**	80%	 **23b**	66%

Because in nature most amino sugars are mainly *N*-acetamido glycosides, some of our nitroglycoside compounds were submitted to reduction of the nitro group, as depicted in Table 4. A method using an excess of zinc dust[15] and

Table 4. Reduction of the 2-Nitro Group

Entry	Compounds	Products	Yields
1	**18**	 **41**	81%
2	**38**	 **42**	75%
5	**21b**	 **43**	76%
6	**23b**	 **44**	60%

aqueous 1 N HCl in aqueous AcOH was employed and then followed by acetylation. This method gave access to the desired acetamido derivatives **41**−**44**.[4c,11] A one-pot reaction, using acetic anhydride instead of acetic acid, was also explored. Unfortunately, although reduction of the nitro group occurred without hitch, the one-pot acetylation was never observed and only the free amine could ever be isolated at the end of reaction. An additional step of acetylation was necessary.

In summary, 2-nitro thioglycoside donors can be successfully activated in the presence of NIS/TMSOTf to allow the preparation of β-glycosides in good yield and selectivity. The nitro group could then be reduced to afford the corresponding acetamido glycosides. Starting from 2-nitroglycals, both α or β selectivity can now be attained using Michael-type addition or thioglycoside coupling, respectively. This demonstrates the versatility of 2-nitro sugars as glycosyl donors in glycoside synthesis. Applications of these donors are currently underway in the synthesis of core 3 and 6 mucin types; the results of these studies will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral/analytical data for key intermediates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049729T

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