Tetrahedron Letters, Vol. 34, No. 18, pp. 2907-2910, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Glycoside Synthesis via Electrophile-Induced Activation of N-Allyl Carbamates

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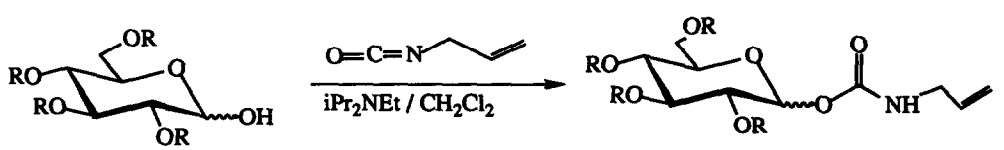
Abstract: *O-Benzyl-, O-acyl-, N-acyl- and isopropylidene-protected glycosyl N-allylcarbamates, obtained from anomerically unprotected monosaccharides and allyl isocyanate, are activated by an electrophile-induced cyclisation and react with hydroxyl compounds to form the corresponding glycosides.*

The key function of glycoconjugates in various biological recognition processes, e.g. in the uptake of serum components into cells, in antigen antibody interaction, in infectious processes or in cell-cell communications, is receiving increasing attention.The elucidation of these regulatory functions demands model glycoconjugates of exactly specified structure. Glycoconjugates isolated from biological sources often are microheterogeneous. Therefore the chemical synthesis of glycosides is a continuous task. A number of efficient glycosylation procedures have been developed in addition to the classical Koenigs-Knorr methodology .[1-5] However, further alternatives of glycosylations which start from stable educts and proceed under mild activation conditions are still required.

The observation of an unexpected instability of the N-allyloxycarbonyl group[6] towards soft electrophiles in glycosylations of serine peptides using thioglycosides as glycosyl donors stimulated the development of a glycosylation method which is based on an electrophile-induced lactonisation of anomeric alkenoic esters.[7-8] This activation results in the formation of lactones as the leaving groups at the anomeric center. The required soft electrophiles which produce the remote activation in the alkene side chain are analogous or similar to those used by Fraser-Reid et al.[9,10] for the activation of pentenyl glycosides. Recently, these researchers also reported on glycosylations via the electrophile-induced lactonisation. [11]

In order to achieve a more direct access to the glycosyl donors and to improve their reactivity, in particular for those which carry acyl protection at 2-position, we have now applied the anomeric N-allyl carbamates. These compounds are readily obtained from anomerically unprotected carbohydrates **1** (or their 1-O-acyl derivates after treatment with hydrazine acetate) by reaction with commercially available allyl isocyanate.



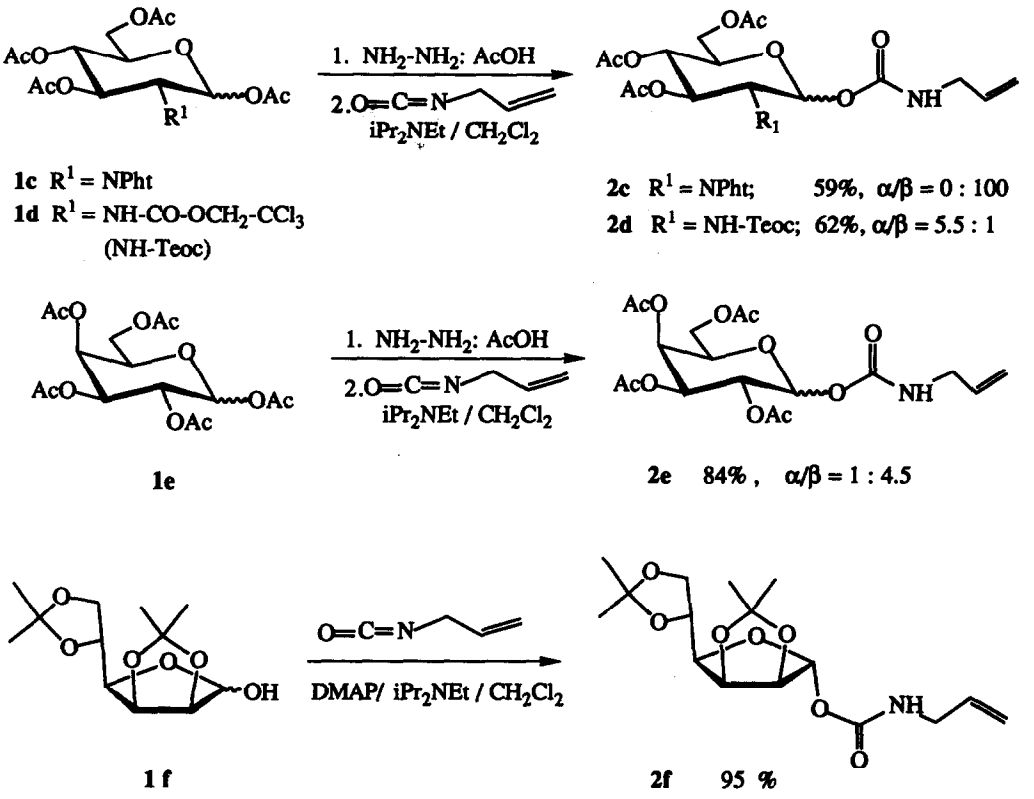
1a R = CH_2-C_6H_5 (Bzl)

1b R = CO-tBu (Piv)

2a R = Bzl; 93%, α/β = 1 : 3

2b R = Piv; 94%, α/β = 1 : 9

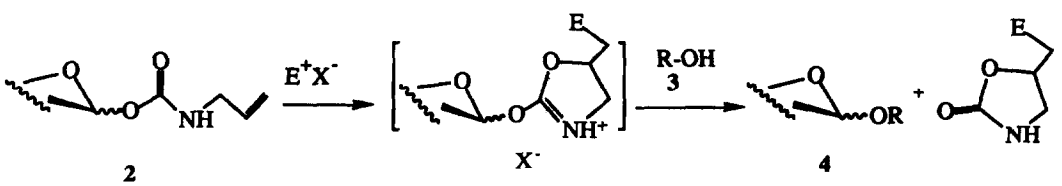
Scheme 1



Scheme 2

The formation of the O-glycosyl N-allyl carbamates **2**[12] is carried out in dichloromethane and requires catalysis by bases, such as dimethylaminopyridine or ethyldiisopropylamine. Starting from anomerically unprotected carbohydrates, e.g. **1a**, **1b**, **1f**, the the carbamates **2** are obtained in almost quantitative yield.

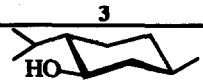
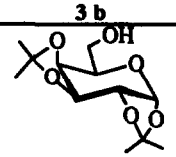
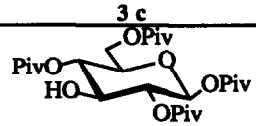
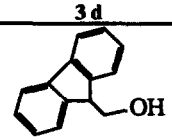
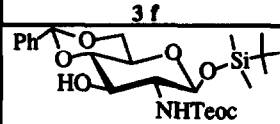
While the carbamates **2** are stable compounds, they can be efficiently activated by electrophiles which attack the allylic double bond. In the presence of glycosyl acceptors R-OH **3** the corresponding glycosides are furnished (Scheme 3, Table 1).



Scheme 3

The glycosylations (Scheme 3) are usually carried out by using an excess of the acceptor **3** (1.1 to 2 equivalents) in the presence of molecular sieves 4Å at room temperature under exclusion of light. The conversion can be monitored by t. l. c., and the obtained glycosides **4** are purified by flash chromatography (Table 1).

Table 1: Synthesis of Glycosides and Saccharides 4 via Electrophile-Induced Activation of O-Glycosyl N-Allyl Carbamates 2 (Scheme 3)

Donor 2[12]	ROH 3	$E^+ X^-$ [a]	Solvent Time	Product 4[17]	Yield (%)[c]	α:β [d]
2 a	 3 a	DMTST	CH_2Cl_2 2.5 h	4 a	60	1:1
	Z-Ser-Ala-OtBu 3 b	DMTST	CH_2Cl_2 2.5h	4 b	79	2:1
	 3 c	$Coll_2$ I ClO_4	CH_2Cl_2 16h	4 c	81	1:1
	 3 d	$Coll_2$ I ClO_4	CH_2Cl_2 16h	4 d	33	3:1
	 3 e	$Coll_2$ I ClO_4	CH_2Cl_2 CH_3CN THF 16h	4 e 4 e 4 e	91 65 56	1.1:1 1:3.5 2:1
2 b	3 c	TMTSB[16]	CH_2Cl_2 45′	4 f	66	0:100
	3 e	TMTSB[16]	CH_2Cl_2 45′	4 g	90	0:100
2 c	3 c	TMTSB[16]	CH_2Cl_2 30′	4 h	73	0:100
2 d	Fmoc-Ser-OBzl 3 f	TMTSB[16]	CH_2Cl_2 45′	4 i	77	0:100
2 e	 3 g	TMTSB[16]	CH_2Cl_2 1h 45′	4 j	55	0:100
2 f	3 a	$Coll_2$ I ClO_4	CH_2Cl_2 16 h	4 k	95	2.5:1

a) DMTST = dimethyl methylthiosulfonium trifluoromethanesulfonate;[13] $Coll_2$ I ClO_4 = bis-(sym-collidine) iodonium perchlorate;[14] TMTSB= methyl bis-methylthiosulfonium hexachloroantimonate;[15]

b) Teoc = Cl_3C-CH_2O-CO- ;

c) Purification by flash chromatography;

d) Determined by ^{1}H-NMR spectroscopy of the isolated products.

The stereochemical course of the glycosylations (Scheme 3) have not been optimized so far. The reactions were usually carried out in dichloromethane. For reactions of the O-benzyl protected glycosylcarbamate **2a** with 9-fluorenylmethanol **3e**, an expected influence of the solvent on the prevailing anomeric configuration of the product **4 e** is observed. The glycosylcarbamates **2b - 2e** carrying neighbouring-group active protection in the 2-position react under completely stereoselective formation of β-glycosides. As the reaction conditions are mild, sensitive structures and protecting groups remain unaffected during these glycosyation processes, e.g. tert-butyl ester, (**4b**) isopropylidene (**4c,4f,4h**,and **4k**) and benzylidene groups (**4j**), urethane-type protections in the peptide (**4b,4i**) or in the carbohydrate portion (**4i,4j**) and silyl ether groups (in **4j**).
The efficiency of the electrophile-induced activation of the O-glycosyl N-allyl carbamates, even in the cases of less reactive 2-acyl protected donors, together with the mild reaction conditions make this method an interesting tool in the synthesis of glycosides, saccharides and glycopeptides. As no protonic or other hard acids are required, acceptors of low reactivity, e.g. **3 d** and **3 g**, can be successfully converted to the corresponding glycosides or saccharides.

Acknowledgements: This work was supported by the *Deutsche Forschungsgemeinschaft* and by the *Fonds der Chemischen Industrie.*

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12. ^{13}C-NMR ($CDCl_3$): **2a:** $C_1\alpha$= 90.8, $C_1\beta$ = 95.2; **2b:** $C_1\beta$ = 93.1; **2c:** $C_1\beta$ = 90.3; **2d:** $C_1\alpha$ = 91.4, $C_1\beta$ = 93.5; **2e:** $C_1\alpha$= 89.1, $C_1\beta$ = 93.2 ; **2f:** $C_1\alpha$ = 101.2.
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16. Glycosylations using TMTSB are preferably conducted between -15°C and 0°C.
17. ^{13}C-NMR ($CDCl_3$): **4a:** $C_1\alpha$= 98.6, $C_1\beta$ = 100.7; **4b:** $C_1\alpha$ = 98.0, $C_1\beta$ = 104.4 ; **4c:** $C_1\alpha$ = 96.2, $C_1\beta$ = 104.3; **4d:** $C_1\alpha$ =97.6, $C_1\beta$ =102; **4e:** $C_1\alpha$ = 97.1, $C_1\beta$ =103.6; **4f:** $C_1\beta$ = 101.1; **4g:** $C_1\beta$ = 101.2; **4h:** $C_1\beta$ = 99.4; **4i:** $C_1\beta$ = 100.5; **4j:** $C_1\beta$ = 100.7; **4k** $C_1\alpha$ = 108.1, $C_1\beta$ = 99.9; **4f:** $[\alpha]_D^{22}$ = -33.0° (c = 1, $CHCl_3$); **4g:** $[\alpha]_D^{22}$ = -19.15° (c=1, $CHCl_3$); **4h:** $[\alpha]_D^{22}$ = -17.66° (c = 1, $CHCl_3$); **4i:** $[\alpha]_D^{22}$ = 3.94° (c = 1, $CHCl_3$); **4j:** $[\alpha]_D^{22}$ = 12.75° (c = 0.55, $CHCl_3$).

(Received in Germany 25 January 1993)