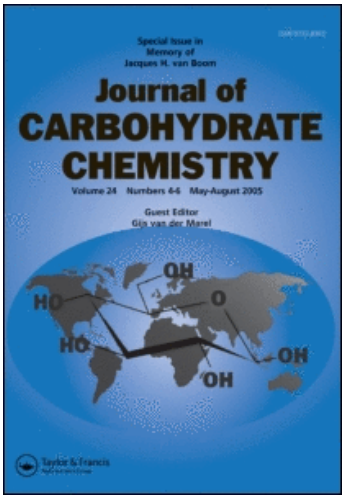

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REVIEW ARTICLE

SYNTHESIS, STRUCTURE AND REACTIONS OF GLYCOSYL AZIDES

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1. Introduction

Recent progress in synthetic methods and structure determination has resulted in several new developments in the chemistry of glycosyl azides. A review on these synthetically useful intermediates was published by Micheel and Klemer[1] more than 30

years ago but newer treatments[2,3] of related topics scarcely take notice of these compounds despite their definite importance as precursors to glycosyl amines and heterocyclic derivatives such as 1,2,3-triazoles.

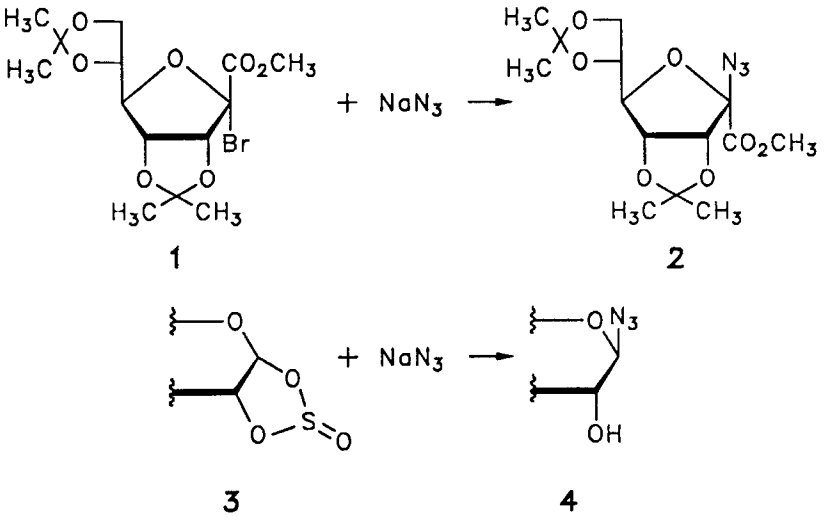
2. Syntheses of glycosyl azides

2.1. Syntheses of 1,2-*trans* glycosyl azides from halogenoses

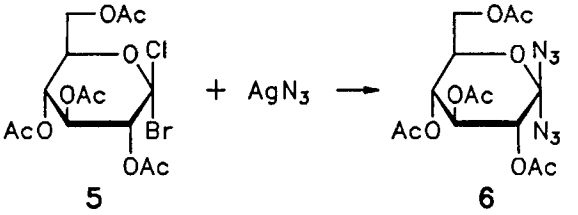
The single method known up to 1974 for preparing glycosyl azides was the conversion of acylated halogenoses by treatment with sodium or silver azide[1] in dilute solutions of acetonitrile which resulted in moderate product yields. Examples include the preparation of per-*O*-acetylglycobiosyl-,[4] 2,3,5-tri-*O*-benzoyl-α-D-lyxofuranosyl-,[5a] -ß-D-ribofuranosyl-[5b] and 2,3,4-tri-*O*-acetyl-ß-D-xylopyranosyl azides.[6] The explosive nature of silver azide makes this method dangerous (see, e. g. the synthesis of 2-acetamido-3,4,6-tri-*O*-acetyl-ß-D-glucopyranosyl azide).[7,8] Following a modification by Pfleiderer[9] the use of the dipolar aprotic DMF as a solvent makes the conversion faster by dissolving the sodium azide. In this way 2,3,4,6-tetra-*O*-acetyl-ß-D-galactopyranosyl azide and its *gluco*-analogue were obtained[9] in 68 and 75% yield, respectively. 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride or -bromide were transformed into azides with similar results.[8,10-13] The methyl 1-azido-1-deoxy-ß-D-glucopyranuronate[14,15] and the 4,6-di-*O*-acetyl-2,3-*O*-ethylene-ß-D-glucopyranosyl azide were obtained in a similar manner, the reaction proceeding at room temperature in the latter case.[16]

Mild conditions were also employed for synthesis, with inversion, of methyl 3,4-anhydro-5-azido-1,2-*O*-isopropylidene-ß-L-iduronate from methyl 3,5-anhydro-5-bromo-1,2-*O*-isopropylidene-α-D-glucuronate or methyl 2,5-anhydro-2-azido-3,4:6,7-di-*O*-isopropylidene-D-*glycero*-D-taloheptonate **1** from the highly hindered D-*galacto*-bromide **2**.[17] Treatment of protected, cyclic 1,2-sulfites of monosaccharides **3** with NaN_3 in DMF resulted in the formation of homogenous 1,2-*trans* azides **4** with a free OH-group in position 2.[18]

Reaction of 2-levulinoyl halogenoses with NaN_3 gave the corresponding azides which, in turn, were converted into 3,4,6-tri-*O*-acetyl-ß-D-gluco- and -galactopyranosyl azides.[19] It is known that phase-transfer catalysis can also be used for the synthesis of



1,2-*trans* pyranosyl azides. 2,3,4,6-Tetra-*O*-benzoyl-ß-D-glucopyranosyl azide[20] and 2-acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-ß-D-glucopyranosyl)-3,6-di-*O*-acetyl-2-deoxy-ß-D-glucopyranosyl azide[21] (heptaacetyl-chitobiosyl azide) were obtained from the corresponding bromides using benzyltriethylammonium chloride[20] or tri-*n*-caprylmethylammonium chloride[21] catalysis.

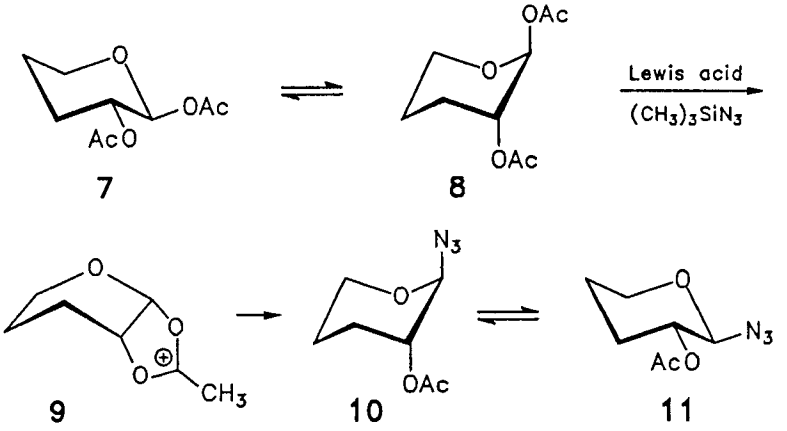


Treatment of unprotected α-D-glucopyranosyl fluoride with calcium azide in aqueous methanol yielded ß-D-glucopyranosyl azide.[1,22] A kinetic study has shown that the transformation proceeds through a concerted bimolecular S_N2 (or A_ND_N) mechanism.[23] Starting from 1,1-dihalogeno derivative **5**, 1,1-diazide **6** could be obtained in 40 % yield.[24]

2.2. Synthesis of 1,2-*trans* glycosyl azides using trimethylsilyl azide

Trimethylsilyl azide is an excellent azide donor and enables direct conversion, under Lewis acid catalysis, of acylated (mainly acetylated) mono- and reducing disaccharides into glycosyl azides, thus eliminating the halogenoses from the reaction sequence.[25] The high stereoselectivity observed in these reactions is due to intermediate formation of acyloxonium ions[26] whose ring opening by the azide reactant

yields 1,2-*trans* products. When the starting acylated saccharide has a 1,2-*cis*-configuration this process is presumably preceded by a Lewis-acid-promoted anomerization.[25] This is illustrated for **7** to **11** in the following scheme.

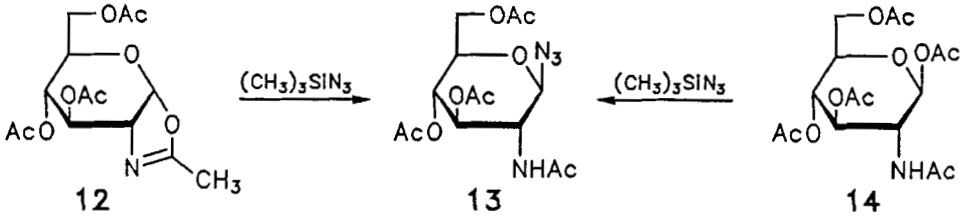


7 **8** **9** **10** **11**

Four pentopyranosyl derivatives, 2,3,4-tri-*O*-acetyl-ß-D-xylopyranosyl azide, seven of the eight hexopyranose derivatives,[25] three 6-deoxy compounds, the acetylated α-L-rhamno-, α-L-talo and ß-L-fucopyranosyl azides[27,28] and the 1,2-*trans* isomers of 4-deoxy-DL-*threo*- and -*erythro*-pentopyranosyl azide have all been synthesized using this method.[29] 6-Deoxy-6-halogeno- and 6-azido-6-deoxy-D-gluco- and galactopyranosyl azides could be advantageously prepared using $SnCl_4$ catalysis.[30] These azides can, of course, be obtained from the appropriate 6-tosyl esters *via* nucleophilic displacement, preferably using lithium halogenides.[30]

Benzoylated pyranoses also react smoothly with trimethylsilyl azide.[31,32] Penta-*O*-benzoyl-α-D-mannopyranose is converted, under $SnCl_4$ catalysis, into the 1,2-*trans* 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl azide[31] and not into the ß-anomer as claimed.[33] The easily accessible acetates of lactose, maltose and melibiose are readily converted, in good yields, into the appropriate 1,2-*trans* glycobiosyl azide hepta-*O*-acetates,[34] more conveniently than with the previously published procedure[35] for the preparation of hepta-*O*-acetyl-ß-cellobiosyl azide.

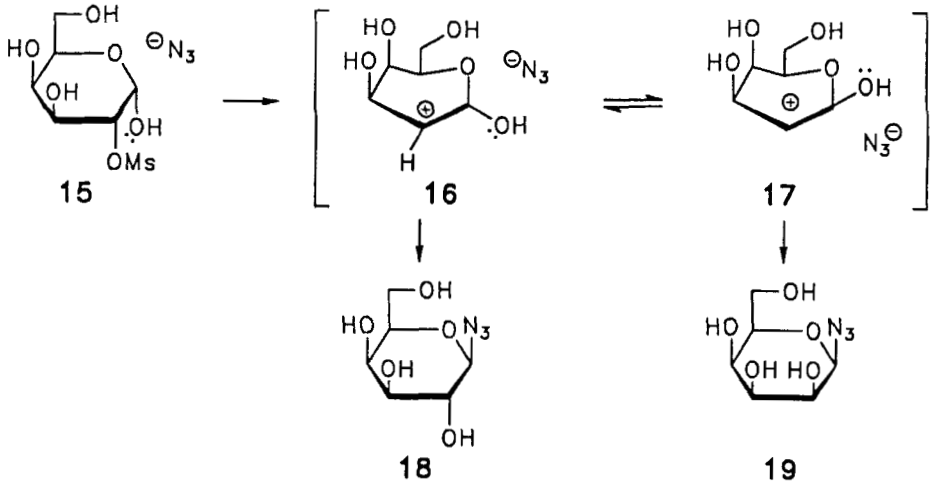
The known 2,3,5-tri-*O*-benzoyl-ß-D-ribopyranosyl azide[5b] and the tri-*O*-acetyl compound[36] were also synthesized by the trimethylsilyl method[37] and it was found that trimethylsilyl triflate is a good catalyst for this reaction. The influence of Lewis acids such as $AlCl_3$, $TiCl_4$ or $BF_3.Et_2O$ as well as the amount of excess Me_3SiN_3 on reaction rates has been investigated[38] (cf.[39]). The potential sialidase inhibitors, 2-azido-2-deoxy-neuraminic acid[39] and its 6-thio analogue have also been obtained[40] using this method.



Trimethylsilyl azide is useful for opening the oxazoline ring. 2-Methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-d]-2-oxazoline (**12**) gives the same 1,2-*trans*-azide **13** as that obtained[42] from 2-acetamido-1,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranose (**14**) (see also[43]). Opening of pyrano[2,1-d]oxazolines with trimethylsilyl azide proved to be applicable to higher oligosaccharides as well.[44]

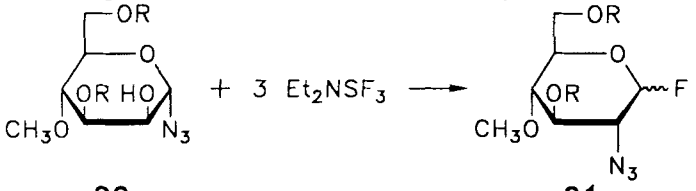
With some furanoses, no selectivity towards 1,2-*trans* products could be observed; examples include reaction of trimethylsilyl azide with 2-*O*-acetyl-1,3,4,6-tetra-*O*-benzoyl-D-fructofuranose (anomeric mixture).[45] In another case 6-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-ß-D-psicofuranose was converted into a 8:1 mixture of α:ß anomeric azides[46] (see also[29]). Glycosyl azides with pivaloyl protecting groups have also been obtained by this method.[28,47]

2.3. Syntheses of 1,2-*trans* glycopyranosyl azides through intramolecular rearrangement



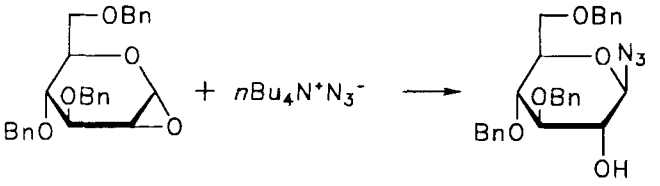
Attempts at displacing the mesyl group by azide in 2-*O*-methanesulphonyl-D-mannopyranose or -D-galactopyranose resulted in the formation of ß-D-glucopyranosyl azide or a mixture of β-D-galactopyranosyl- **18** and ß-D-talopyranosyl azides **19**, respectively.[48] Analogous nucleophilic substitution reaction (NaN_3 in 2-methoxy-

ethanol) with 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulphonyl-D-glucopyranose yielded 2,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranosyl azide.[49] It was suggested[49] that in an S_N1 reaction carbocations are generated first and then converted into the epimeric mixture of the products under nucleophilic attack by the azide ion.



20 **21**

R = *t*BuSi(Me)$_2$-

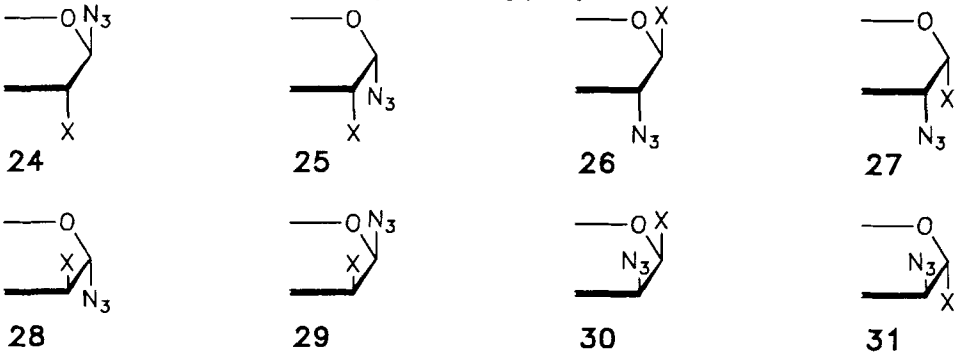


22 **23**

A similar transformation was observed when a mannosyl azide **20** unsubstituted in position 2 rearranged into 2-azido-2-deoxy-D-glucosyl fluoride **21** under the action of DAST.[50]

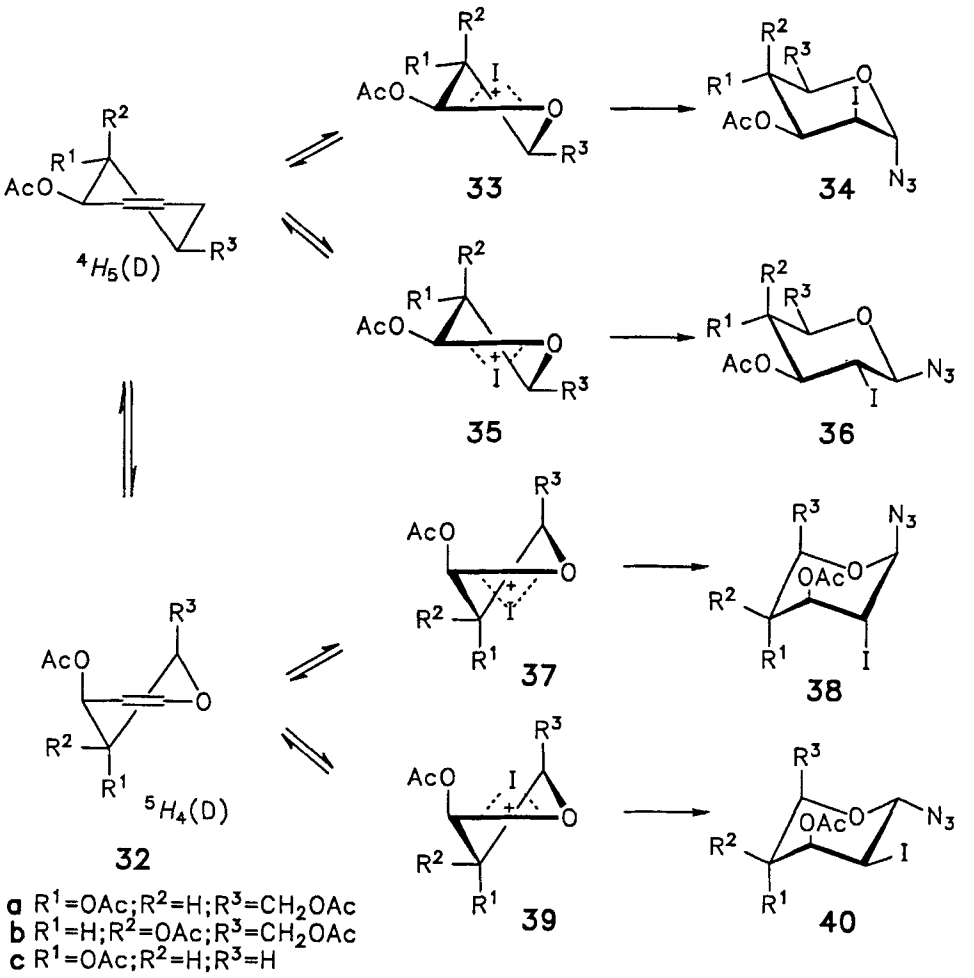
Epoxide ring opening of **22** with tetrabutylammonium azide yielded mainly a 1,2-*trans* product **23**.[51]

2.4. 2-Halogen-substituted 2-deoxy-1,2-*trans* glycosyl azides



These derivatives received considerable attention during studies of addition reactions of hex-/pent-1-enitols ("glycals") with halogeno azides[52] in a search for synthetic equivalents of 2-amino-hexoses. Reactions of a trisubstituted olefin (to which glycals are related) with unsymmetrical reagents, such as halogenoazide, may lead to a mixture of eight isomers **24-31**.

Nevertheless, a high regio- and stereoselectivity of these reactions may be expected if all the factors (steric and energetic) governing the additions are considered. Polarization of halogenoazide requires ionic conditions to yield glycosyl azides and radical conditions to yield 2-azido-2-deoxy sugars. Under the radical conditions employed by Khorlin[52] (2.0 - 2.5 equivalents of chloroazide, -20 °C, 3 h in

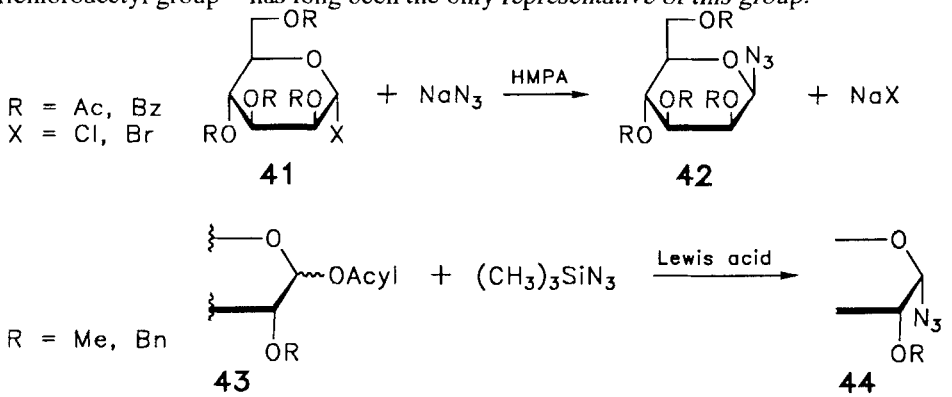


nitromethane), 1,2-*trans*-halogenoazides were obtained in moderate yields only; the 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-ß-D-glucopyranosyl azide and the 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl azide could be isolated in crystalline form from the same reaction mixture in yields of 17 % and 26 %, respectively. Higher regioselectivity could be achieved using iodoazide while ionic addition to **32** (0 °C, acetonitrile or ethyl acetate, 2 h) yielded 1,2-*trans*-2-deoxy-2-iodo-glycosyl azides **34**,

36, **38** and **40**.[53] Although separation of the α- and ß-anomers of 1,2-*trans*-products form acetylated glycals (3,4,6-tri-*O*-acetyl-1,5-anhydro-D-*arabino* and D-*lyxo*-hex-1-enitol vs. 3,4-di-*O*-acetyl-1,5-anhydro-D-*threo*-pent-1-enitol) required an additional step[54] the benzylated and methoxy-methylated glycals, on the other hand, gave 1,2-*trans*-2-iodo azides in good overall yields. It was suggested[53] that the 2-iodoglycosyl azides are formed from glycals *via* cyclic iodonium intermediates **33**, **35**, **37** and **39**. Iodine azide can be conveniently generated by reacting iodine with sodium azide. Using this reagent 6-azido-6-deoxy-D-glucal was converted into a 20:1 mixture of 6-azido-2,6-dideoxy-2-iodo-α-D-mannopyranosyl- and ß-D-glucopyranosyl azides.[55]

2.5. 1,2-*cis* Glycopyranosyl azides

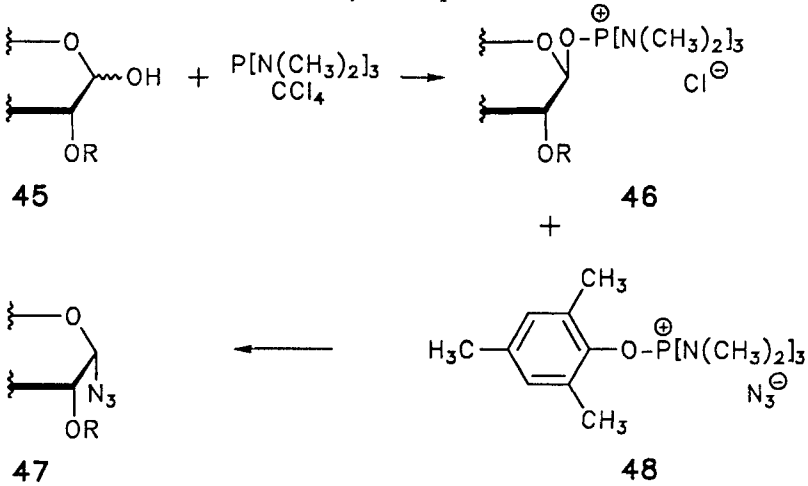
3,4,6-Tri-*O*-acetyl-α-D-glucopyranosyl azide, obtained from Brigl's 3,4,6-tri-*O*-acetyl-2-trichloroacetyl-ß-D-glucopyranosyl chloride by selective removal of the trichloroacetyl group[56] has long been the only representative of this group.



We have found that under certain conditions acylated halogenoses react with alkali azides with inversion by an S_N2 process. Thus, 1,2-*cis* azides can be prepared through reaction of the thermodynamically less stable 1,2-*trans* per-*O*-acyl-glycopyranosyl halides (preferably chlorides), e.g. **41** with NaN_3 in HMPA at room temperature. After a short time anomerically pure products can be isolated by dilution of the mixture with water. An example is provided by the synthesis of ß-mannopyranosyl derivatives **42**.[31]

It has been observed that the course of the reactions is not uniform in DMF and DMSO. This method proved to be useful for the syntheses of 1,2-*cis*-hexopyranosyl azides,[42,57,58] 6-deoxy-1,2-*cis*-hexopyranosyl azides,[27] 6-substituded-6-deoxy-1,2-*cis*-hexopyranosyl azides,[30] 2-acylamino-2-deoxy-1,2-*cis*-hexopyranosyl azides,[42] and 1,2-*cis*-glycobiosyl azides.[34] 1,2-*cis*-Pentopyranosyl azides have also been obtained this way.[59]

Monosaccharides acylated at position 1 and bearing a nonparticipating group in position 2 mainly give 1,2-*cis* azides in reactions with trimethylsilyl azide under Lewis acid-catalyzed conditions. According to the scheme 3,4,6-tri-*O*-acetyl-2-*O*-methyl-α-D-gluco- and -galactopyranosyl azides **44** are obtained[19] from 2-*O*-methyl-1,3,4,6-tetra-*O*-acetyl-α-D-gluco- and -galactopyranose (**43**), respectively and, similarly, an α-azide is obtained from 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose.[32] However, when 2,3,4,6-tetra-*O*-benzyl-α,ß-D-glucopyranosyl fluoride is employed as a starting material the product of the reaction is a 10:1 mixture of the α- and ß-azides[60] (see also [47b]). On the other hand, reaction of *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)trichloroacetimidate with azoimide yields a pure α-azide.[61]



An example from the pentose series is provided by the reaction of 2,3-*O*-isopropylidene-1,5-di-*O*-(*p*-nitrobenzoyl)-ß-D-ribofuranose with trimethylsilyl azide giving rise to the formation of the ß- and α-anomeric azides in yields of 51.5 % and 41.2 %, respectively[38] (compare with[36]). Sugars **45** with a free anomeric OH group **45** react with tris(dimethylamino)phosphine in CCl_4 to give alkoxy-tris(dimethylamino)-phosphonium chlorides **46** with 1,2-*trans* stereochemistry. These reactive oxy-phosphonium salts can be converted at -10 °C under kinetic control into 1,2-*cis* azides **47** using mesityloxytris-(dimethylamino)phosphonium azide (**48**).[62] In this reaction 2,3:5,6-di-*O*-isopropylidene-ß-D-mannofuranosyl azide was obtained in 65 % yield; starting from 2,3,5-tri-*O*-benzyl-D-arabinofuranose a 14:3 mixture of the *cis* and *trans* azides could be isolated.[62]

Partially protected monosaccharides bearing a free anomeric OH group can be conveniently converted into furanosyl or pyranosyl azides by taking advantage of the

Mukaiyama reaction[63] (azoimide, diethyl azodicarboxylate and triphenyl phosphine). In this way 2,3:5,6-di-*O*-isopropylidene-ß-D-mannopyranosyl azide could be obtained in 75 % yield in crystalline form[37a] while 5-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-α,ß-D-ribofuranose gave rise to the formation of a mixture of α- (70 %) and ß-azide (10 %) which were separated by column chromatography.

3. Structural studies of glycosyl azides

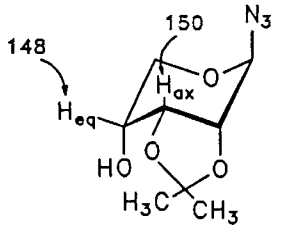
The solution conformations of pentopyranoses are mainly determined by the anomeric effect.[64] Studies of conformational equilibria by NMR can therefore provide important clues on a substituent group's capability to generate such an effect.[64,65] Relying on $J_{H4,H5}$ values we have compared the solution conformations of a series of 1,2-*trans* pentopyranoses carrying various substituents at C-1 and found that the azido group behaves like the *O*-acetyl group as far as the anomeric effect is concerned.[65] In view of the discussions, in terms of steric (or dipole-dipole or n-n-type) and electronic (or conjugative, back-donation or n→σ-type) interactions, about the origin of the anomeric effect[66,67] it is worth noting that the dipolar character of the azido group[68] correlates fairly well with this experimental result. Conformational equilibria of 1,2-*cis* pentopyranosyl azides, as determined by ^{1}H NMR, can also be rationalized[59] in terms of the anomeric effect of the N_3 group.

The *exo*-anomeric effect is another manifestation of the stereoelectronic interactions mentioned. We have employed circular dichroism to study this effect in glycopyranosyl azides. Application of the azide octant rule[69] predicted a negative Cotton effect for α-glycosyl azides no matter whether the conformation of the pyranose ring is $^1C_4$ or $^4C_1$.[25] For ß-anomers a positive Cotton effect was predicted; both were confirmed by experiment.[25] Uncertainties occur when the Cotton effect is small as in the case of ß-D-mannopyranosyl azide.[31] Solvent effects also have to be taken into account when evaluating CD measurements on pyranosyl azides.[70]

X-ray structure determinations[71a,c] and semiempirical PCILO calculations[71b] of 2,3,4-tri-*O*-acetyl-α- and ß-D-arabinopyranosyl azides provided evidence for the operation of the *exo*-anomeric effect in the crystalline state. In hexopyranoses interactions other than the anomeric effect are contributing to the conformational behavior. Using straightforward ^{1}H NMR analysis it has been established[27] that 6-deoxy-L-hexopyranosyl azides with *manno*-, *galacto*- or *talo*-configurations assume $^1C_4$(L) conformations in D_2O (unprotected sugars) or $CDCl_3$ (per-*O*-acetyl derivatives)

irrespective of the anomeric configuration. The latter is most easily determined, as in other pyranose derivatives, from δ_{H-1} and $J_{H1,H2}$-values. A notable exception is the *talo* configuration where it may not be possible to deduce the configuration at C-1 if only one of the anomers is available. For example, an equatorial H-1 (from δ_H) combined with a small $J_{H1,H2}$ is equally compatible with either an α-$^1C_4$(L) or ß-$^4C_1$(L) conformation.[27]

The measurement of $^1J_{C1,H1}$ values has long been established as a tool for the determination of the anomeric configuration.[72] We have shown[42] that the general rule, $^1J_{C1,Heq} \approx {}^1J_{C1,Hax} + 10$ Hz applies to glycosyl azides too. It is worth noting, however, that in some cases, it might be misleading to deduce the anomeric configuration from $J_{C1,H1}$ values alone since the electronic and/or steric influences of substituents at non-anomeric carbons may alter them to such an extent that the difference between $J_{C1,H1e}$ and $J_{C1,H1a}$ may become negligible especially when only one of the anomers is available. For instance, $^1J_{C1,H1eq} = 167.5$ Hz in 4-*O*-acetyl-2,3-*O*-isopropylidene-α-L-rhamnopyranosyl azide and this value is only 2.7 Hz larger than $^1J_{C1,H1ax}$ in 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-ß-D-glucopyranosyl azide. We have also pointed out that one-bond C-H coupling constants for H_{eq} are, as a general rule, larger than for H_{ax}



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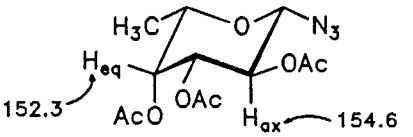


50

$^1J_{C,H}$-Coupling

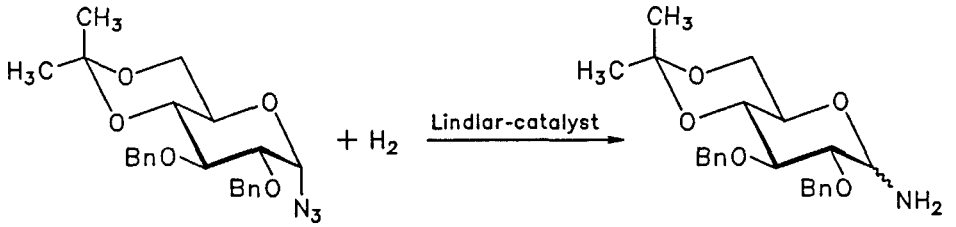
(ΔJ≈4-9 Hz) for *non-anomeric* C-H bonds as well. However, a substituent (hydroxyl, acetoxyl, alkoxyl, azido, etc.) in 1,3-diaxial relationship with H_a significantly increases the value of $^1J_{C,Ha}$. Furthermore, bond-angle distortions in the fused-ring bicyclic systems of some isopropylidene derivatives result in $^1J_{C,Ha}$ values being larger than the $^1J_{C,He}$ values. These interesting trends are illustrated by compounds **49** and **50**.

^{13}C Chemical shifts for C-1 of hexopyranosyl azides fall in the range of 85-90 ppm[34,57] but Δ(C-1) values for the anomeric pairs cannot be relied upon for establishing the anomeric configuration.[42] However, in accordance with earlier findings on other derivatives[73] a significant γ-*gauche* upfield shift is observed[42] for the signals of C-3 and especially at C-5 in the α-anomers (N_3 axial) relative to the ß- ones.

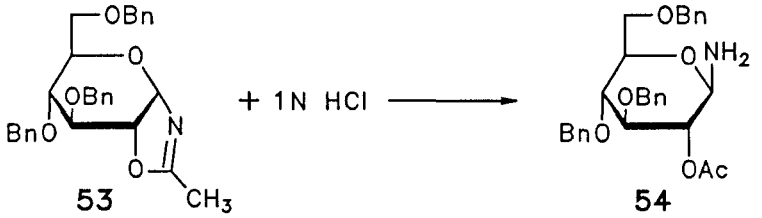
4. Reactions of glycosyl azides

4.1. Reduction of glycosyl azides

Reduction of glycosyl azides under mild conditions (hydrogenation at atmospheric pressure and room temperature using PtO_2[1] or Raney Ni[9,74] catalysts) leads to the formation of glycosylamines.[75] The direct syntheses from aldoses, such as treatment with NH_3 in methanol[76] or using a large excess of NH_4HCO_3 in water[77] (for another method, see ref. 78) rarely yields pure anomers. Up to present no rule has emerged which would be generally applicable to the reduction of glycosyl azides. Preference for ß-amine formation is illustrated by reduction of 2,3,4,6-tetra-*O*-acetyl-ß-D-



51 52 α:β=1:3

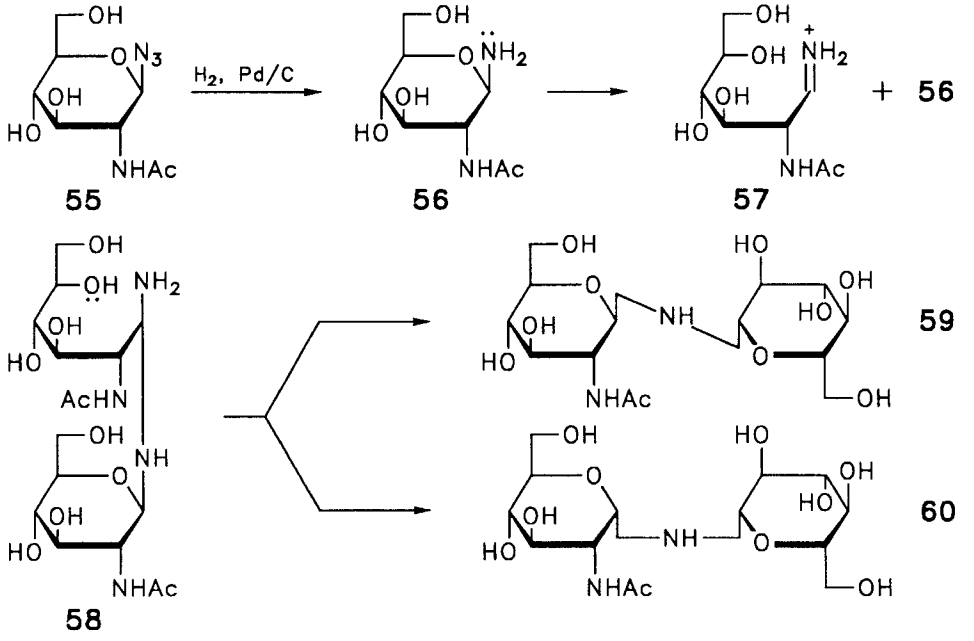


53 54

xylopyranosyl azide,[65] 2-acetamido-6-*O*-acetyl-2-deoxy-ß-D-glucopyranosyl azide[79] (see, also[80]), various *O*-pivaloyl azides[28,47], hepta-*O*-acetyl-chitobiosyl azide,[21] and 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl azide. The α-mannopyranosyl azide is accompanied by anomerization.[15,68,81] Such anomerizations can be misleading if one attempts to deduce the configuration of the azide from that of the reduction product.[33a,c]

During reduction of 2,3,4-tri-*O*-acetyl-ß-D-ribopyranosyl azide *O*→*N* acyl migration and epimerization yielded a mixture of products from which the 1,2,3,4-tetra-*O*,*N*-acetyl-ß-D-ribopyranosylamine was isolated.[65] Acyl migration without epimerization was observed upon hydrogenation of 2,3-di-*O*-acetyl-4-deoxy-α-DL-*threo*-hexopyranosyl azide over Pd/C catalyst.[29] On the other hand, no acyl migration was detected when 2,3,4,6-tetra-*O*-benzoyl-ß-D-glucopyranosyl azide was subjected to

reduction using either Pd/C[20] or Raney Ni.[82] Reduction of 2,3,5-tri-*O*-benzoyl-ß-D-ribofuranosyl azide with PtO_2 catalyst gave ß-amine as the main product.[1,39] Anomerization occurs during the synthesis of α-D-glucopyranosylamine and its 6-*O*-glycosides *via* hydrogenation of the appropriate azides;[57,83] formation of the ß-anomers (e.g. **52**) are favored[84] no matter what protecting groups and catalysts are used.[83]

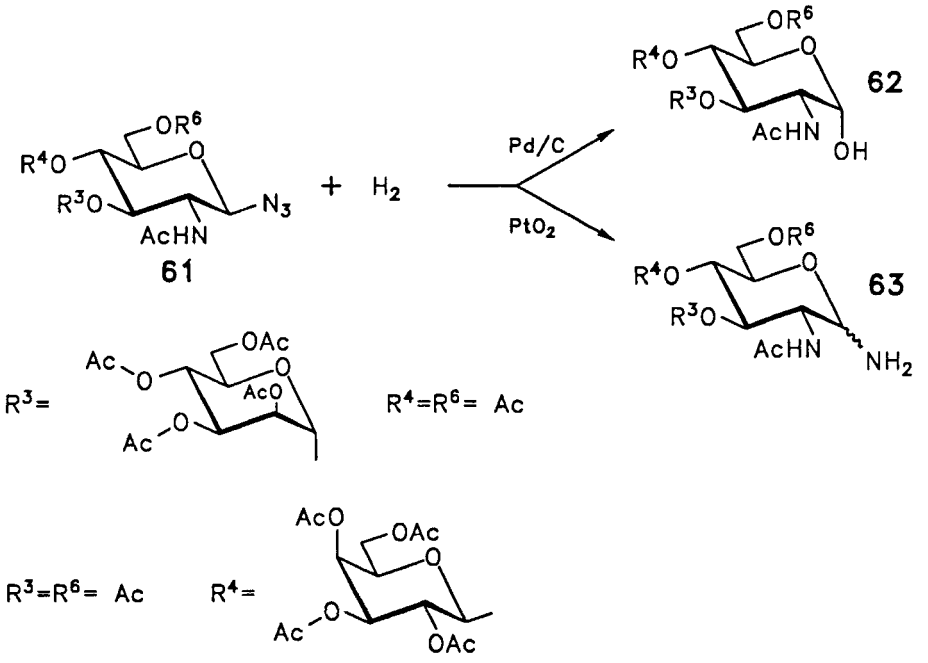


The preference of the anomeric amine group for equatorial orientation indicates operation of the inverse anomeric effect[65] in these cases (see also[86] for 2-methylamino-tetrahydropyran). It is worth noting in this respect that the formation of a ß-anomeric product[87] **54** in the reaction of oxazoline **53** can be attributed to the stronger inverse anomeric effect of a protonated amino group.[65,66]

In addition to anomerization dimer formation with elimination of ammonia is frequently observed in these reactions. For instance, formation of diglycosylamines **59** and **60** were observed[7,11,12,88-90] during the synthesis of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-ß-D-glucopyranosylamine **56** which is an important intermediate in the synthesis of glycopeptides. A probable mechanism of dimer formation is shown in scheme **55** to **60**.[8] Initially, the resulting amine **56** in methanol is converted into the acyclic immonium intermediate **57** which then reacts with a second molecule of **56** to give the intermediate **58**. The latter undergoes ring closure, with elimination of the amino group at the anomeric carbon atom as ammonia, giving the ß,ß- and α,ß-dimers

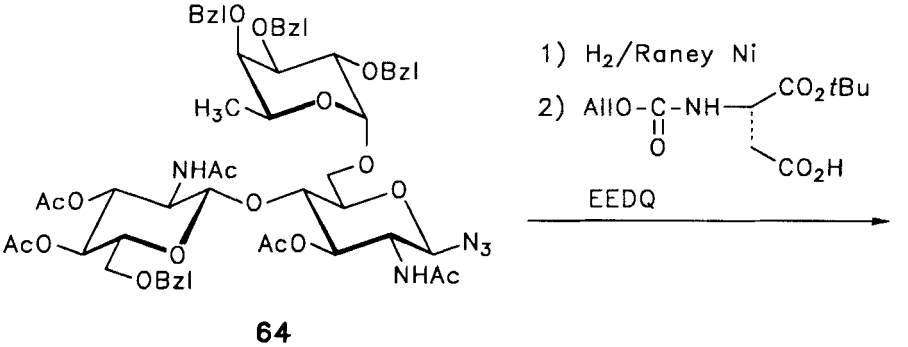
59 and **60**. Formation of dimers was also described from D-ribopyranosyl amine[91] and D-glucopyranosyl amine.[92]

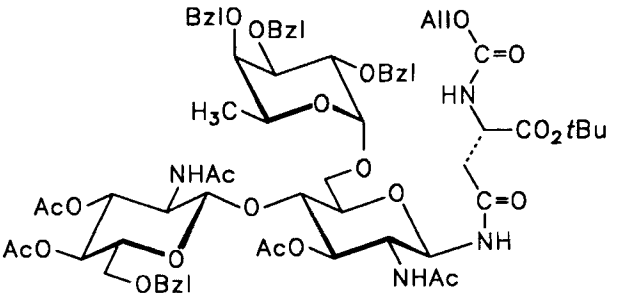
It is to be noticed that in the following examples[93,94] the use of Pd/C catalyst results in the loss of the nitrogen function and formation of disaccharides **62** with free



anomeric hydroxyls. Reduction to amines **63**, albeit in the form of anomeric mixtures can be effected by employing Adam's catalyst.

Raney Ni was found[74b,95] to be a very efficient agent for reducing *O*-glycosylated 2-acetamido-2-deoxy-D-glucopyranosyl azide and the trisaccharide **64** was converted to ß-glycosylamine in quantitative yield. The EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) mediated coupling of the product with α-*t*-butyl-*N*-allyloxycarbonylaspartate resulted in the formation of the *N*-glycosylic conjugate of

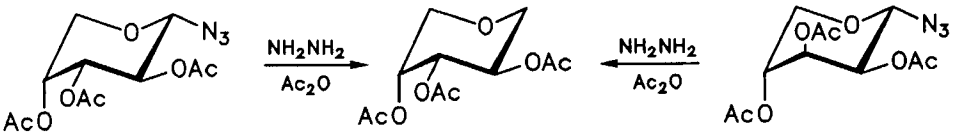




65

asparagine **65** in pure anomeric form.[95] Compound **65** is a useful building block for glycopeptide synthesis.

Different products are obtained from pyranosyl azides by reduction with hydrazine. We have shown[96] that under such conditions (neat hydrazine, 2 h, 60 °C)



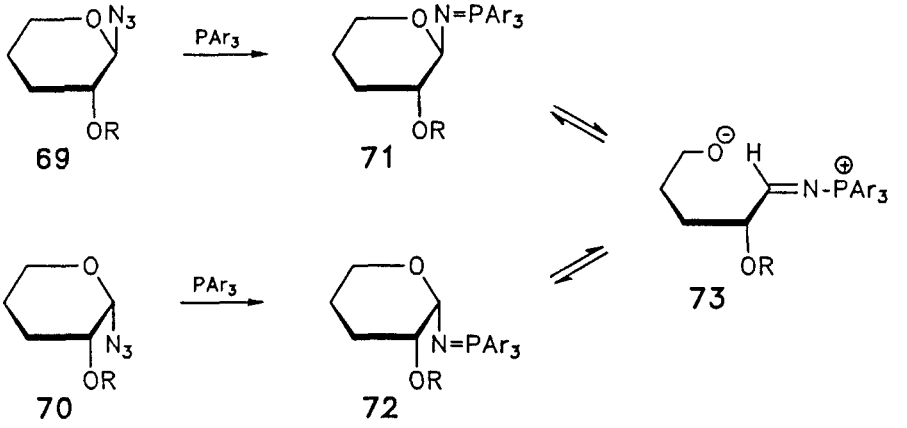
66 **67** **68**

1,5-anhydro alditols are the reaction products. The chirality of one carbon atom is destroyed in this reaction so that 2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl azide **66** and α-D-lyxopyranosyl azide **68** yield the same 2,3,4-tri-*O*-acetyl-1,5-anhydro-D-arabitol **67** upon treatment with hydrazine and followed by acetylation.

4.2. Phosphinimines from glycosyl azides

The Staudinger reaction[97] of protected glycosyl azides **69** and **70** with triarylphosphines leading to glycosyl phosphinimines (iminophosphoranes) **71** and **72** has found widespread use.[1,65,98,99] In some cases unprotected glycosyl azides also proved to be suitable[100] for obtaining phosphinimines which, in contrast to vicinal azidohydrins,[101] do not cyclize to oxazaphospholidines but are converted into glycosylamines by treatment according to Zemplén.[99] The HCl salts of phosphinimines are sensitive to moisture but their methiodides, on the other hand, are stable.[99] Due to their ylid structure, in which the nitrogen bears a negative charge, the phosphinimines show a marked anomeric effect as demonstrated[65] with appropriate acetylated pentopyranosyl derivatives. The reaction products from the Staudinger reaction are useful intermediates for the syntheses of symmetric or mixed carbodiimides.[98,102] As a consequence of their ylid character, reactions of phosphinimines often result in the

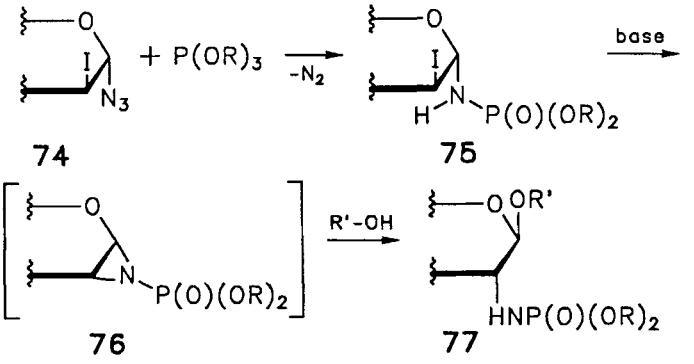
formation of anomeric mixtures and/or isomerized products[102,103] cf. also[104], (see reaction **71** to **73**).



Reaction of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-ß-D-glucopyranosyl phosphinimine with carbon dioxide yielded bis(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-ß-D-glucopyranosyl)carbodiimide[105] (see[98] for analogous transformations); unprotected sugar phosphinimines, on the other hand, gave rise to the formation of cyclic carbamates.[100]

Formamido derivatives were obtained[37b] from several furanosyl azides (ß-D-*allo*-, α- and ß-D-*ribo*-, ß-D-*xylo*- and α-L-*talo*-) by reaction with acetic formic acid anhydride.

Azides **74** easily react with trimethyl phosphite to give glycosylaminophosphorimidates.[65] The mild conditions used in these reactions have

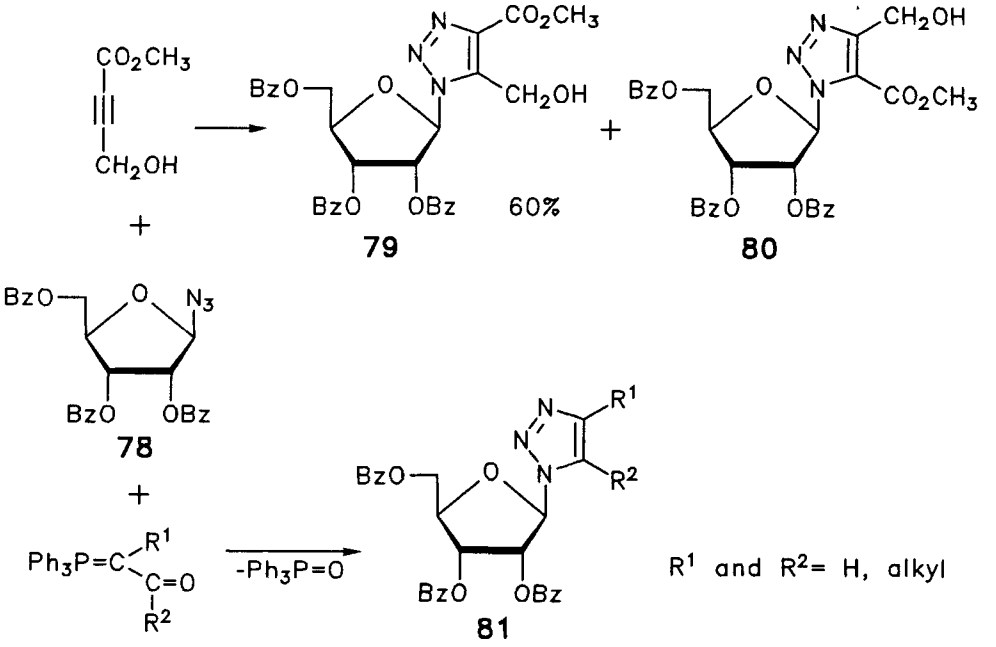


been applied to the 2-deoxy-2-halogeno-azides **74** mentioned earlier (section 2.4) and it was found[53] that the 2-iodo phosphoramidates **75** obtained can be readily isolated as well characterized compounds. These proved to be useful starting materials since

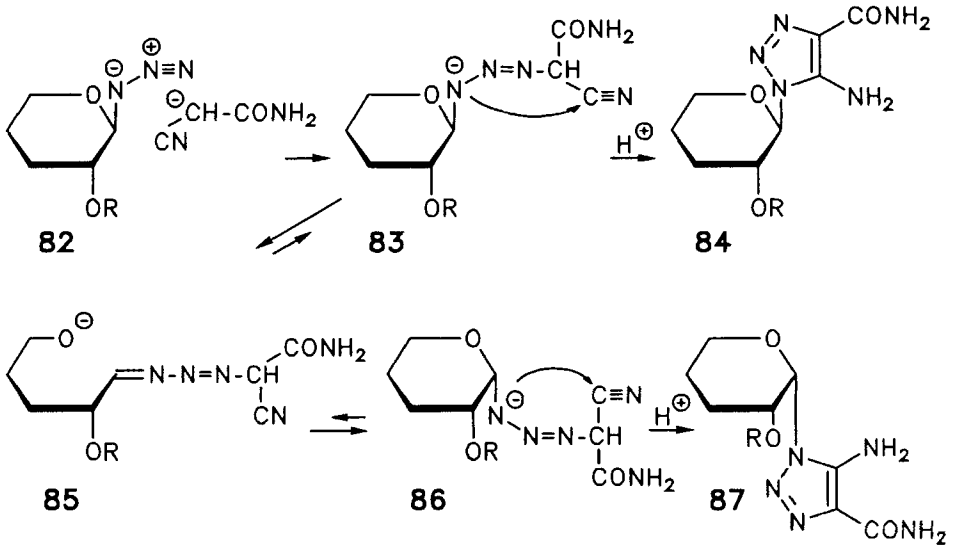
reacting them with alcohols in the presence of base leads, *via* *N*-aziridinophosphonic esters **76**, to the formation of 1,2-*trans* 2-deoxy-2-phosphoramido-glycopyranosides **77**.[106,107]

4.3. 1,3-Cycloaddition reactions of glycosyl azides

The 1,3-dipole character of the azido group has been previously exploited[1] for 1,3-dipolar cycloaddition reactions of glycosyl azides with compounds containing triple bonds. It is known that formation of 1,4-disubstituted 1,2,3-(*vic*,v-)triazoles is favored over the 1,5-disubstituted ones. Motivated mainly by pharmacological considerations (in order to obtain compounds with cytostatic, alkylating properties) syntheses of a great number of *N*-1 pyranosyl- and furanosyl-1,2,3-triazole derivatives have been reported.[35,37,59,65,108-120] These reactions are carried out simply by heating the azide in excess dipolarophile (or in toluene) as exemplified by the syntheses of methyl 5-hydroxymethyl-1-(2,3,5-tri-*O*-benzoyl-ß-D-ribofuranosyl)-v-triazole-4-carboxylate **79** and methyl 1-(2,3,5-tri-*O*-benzoyl-ß-D-ribofuranosyl)-5-carbomethoxy-4-hydroxy-methyl-v-triazole (**80**) from **78**.[119]

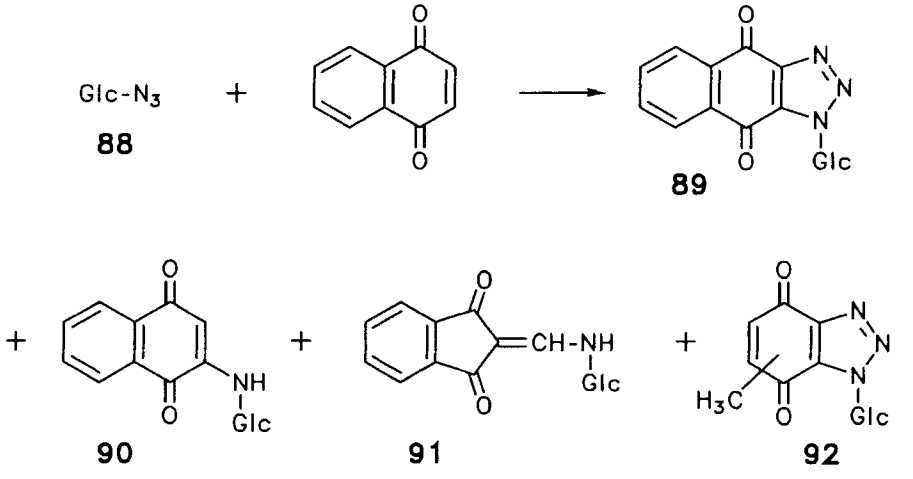


The same azide **78** reacts with ß-oxoalkylidene phosphoranes to give regioisomeric v-triazoles **81** in moderate yields.[37a,118] Cycloaddition reactions of



glycosyl azides can also be employed to the syntheses of v-triazole nucleosides functionalized in a different way. Starting from azides **82** equipped with base stable protecting groups, 5-amino-4-carbamoyl-1-α,ß-glycosyl-v-triazoles[104,120,121] **84** and **87** can be obtained by reaction with cyanoacetamide in the presence of bases. Anomeric mixtures are, in general, obtained under these conditions (KOH, DMF, 5 °C).

Dipolar cycloaddition of glycosyl azides **88** to 1,4-naphthoquinones has also been observed. At room temperature 1-glycosyl-naphtho[2,3-d]triazole-4,9-dione **89** was formed selectively in poor yield; at elevated temperatures decomposition of the cycloadduct took place[122] and further products such as **90**, **91** and **92** were identified.

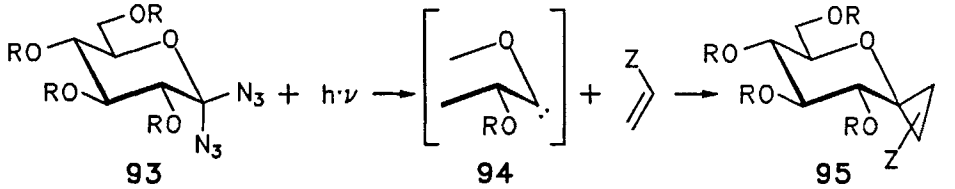


4.4. Transformations of OH groups of glycosyl azides

Glycosyl azides can, in general, be subjected to standard protection-deprotections operations commonly used in carbohydrate chemistry. Unprotected, free OH-containing glycosyl azides are most often obtained from acylated derivatives through Zemplén deacylation;[1,27,28,30,31,19,42,57,93,123] in some cases ammonia[13] or triethylamine[8] is used in methanolic solution. Stronger base can effect loss of the azido function as shown by the formation of 1,6-anhydro-β-D-glucopyranose from ß-D-glucopyranosyl azide under the action of $Ba(OH)_2$.[124]

Various protected derivatives, such as benzylidene,[4,93,98] isopropylidene,[19,27,85] 6-*O*-trityl,[94,125] partially acylated,[79,98,123] partially[84,126] or fully benzylated[33,126-128] glycosyl azides have been synthesized for use in the synthesis of disaccharides.

According to a recent report[24] derivatives of glycopyranosylidene 1,1-diazide **93** are used to generate glycosyl carbenes **94** which, in turn, can be trapped with suitable alkenes to obtain spirocyclopropyl saccharides **95**.[129]



93 **94** **95**

R = acetyl or benzyl

5. Acknowledgement

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