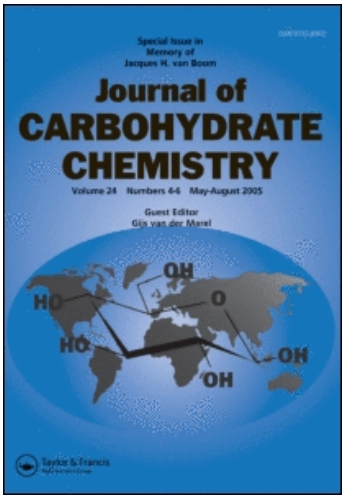

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Review Article Monosaccharide Isocyanides, Synthesis, Chemistry and Application

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REVIEW ARTICLE

MONOSACCHARIDE ISOCYANIDES, SYNTHESIS, CHEMISTRY AND APPLICATION.

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INTRODUCTION

Attention has been recently directed toward synthesis of various types of heterocyclic derivatives, among them nucleoside analogs with potential antibacterial and antitumor properties.[1] Although a number of synthetic approaches have been developed, there are a few methods that appear to have the versatility for

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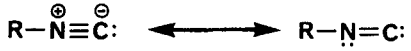
construction of a variety of heterocyclic systems. Among these are approaches that employ heterocyclic elaboration of glycosyl cyanides,[2] important C-glycosyl intermediates that have been used in the synthesis of a number of naturally occurring C-nucleoside antibiotics[3] as well as many analogs.[2,4]

While the glycosyl cyanides,[2] and other cyano sugars such as unsaturated cyanides,[5] are well known, the isomeric isocyanides are relatively unknown. Their potential applications include α-metalation,[6,7] which could give access to C-glycosides or C-nucleosides. The fact that the chemistry of carbohydrate isocyanides, in contrast to other monosaccharide derivatives such as thiocyanates[8] and isothiocyanates,[9] is relatively unexplored encouraged review of the literature in this field.

2. METHODS OF SYNTHESIS OF MONOSACCHARIDE ISOCYANIDES AND APPLICATIONS

Isocyanides can be considered as a semiionic structures[10] based mainly on their IR,[11-13] Raman,[11,12] and microwave spectral properties,[15] and dipole moment studies.[16]

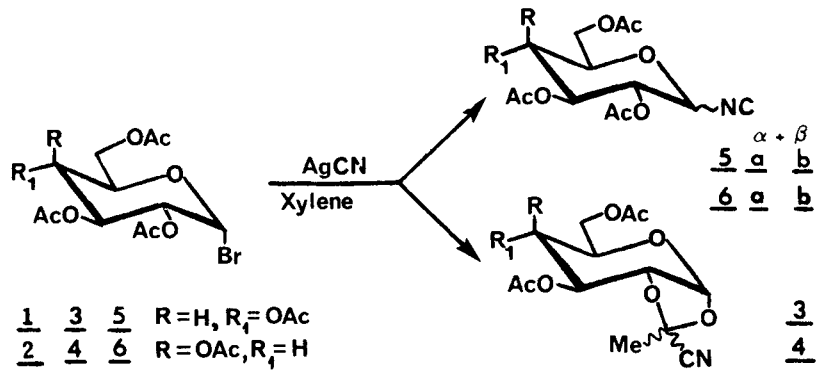


A particularly interesting property of isocyanides is their ability to accept protons to form hydrogen bonds.[17-18] These properties clearly explain the chemical character of this class of compounds and suggest the kinds of methods that can be used for their syntheses.[19]

Three classical isocyanide syntheses, the alkylation of silver cyanide, the reaction of primary amines with chloroform and alkali, and dehydration of formamides, remained until recently the only preparative routes to carbohydrate isocyanides.

The first method, based on the procedure of Gautier[20] has been applied in carbohydrate chemistry. Nucleophilic attack of the ambident cyanide ion[21] on glycosyl halides can lead either to cyanides or isomeric isocyanides.[22] The substitution of glycosyl halides with sodium or mercuric cyanide generally yields glycosyl cyanides.[23-28] The same substitution with silver cyanide lead to the corresponding isocyanides.[29-31]

When the substitution is carried out with silver cyanide and 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (1), a glycosyl halide having a participating group in the C-2 position, the reaction leads predominantly to the formation of 3,4,6-tri-O-acetyl-1,2-O-(1-cyanoethylidene)-α-D-glucopyranose (3), as has been shown by Coxon and Fletcher,[26] and not 2,3,4,6-tetra-O-acetyl-α-D-glycosyl cyanide (8) as had been previously stated.[32]

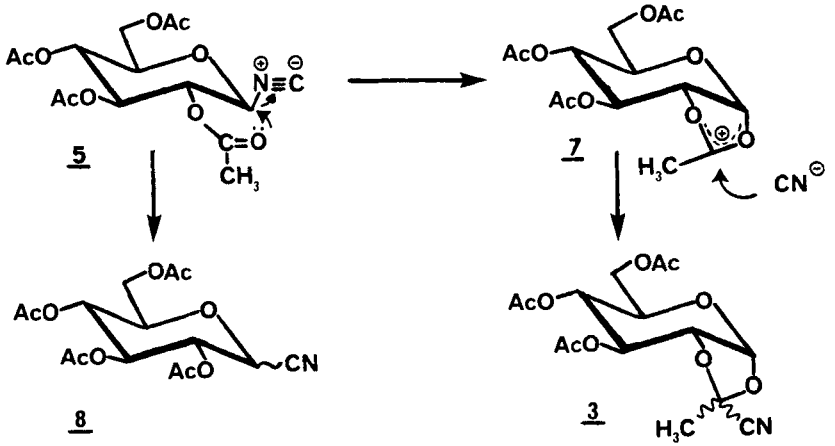


However, recently this reaction has been reinvestigated by Martin-Lomas and co-workers[30] who reported the formation of 3 as a main product and the anomeric isocyanides 5a in 10% and 5b in 12% yields as minor products.

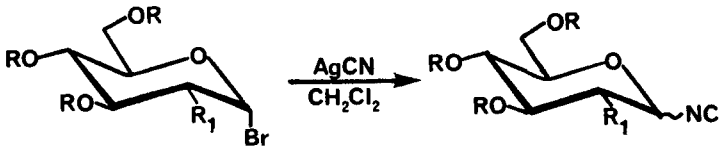
Interestingly, in the galactose series the 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl isocyanide (6b) has been separated as a crystalline derivative in 20% yield, whereas the α-anomer (6a) and cyanoethylidene compounds (4), were isolated in low yield after column chromatography.

According to the observation of Descotes and co-workers[31] the

cyanoethylidene derivative 3 was the main product in the reaction of 1 with silver cyanide in boiling xylene. However, the authors found that this reaction under the conditions given by Martin-Lomas[30] afforded a complicated reaction mixture containing isomeric cyanide 8, probably formed by the isomerization of isocyanide 5, and the cyanoethylidene derivative 3. This latter compound was the main product of the reaction and probably was formed via the 1,2-acetoxonium ion intermediate (7) as previously proposed by Coxon and Fletcher.[26]

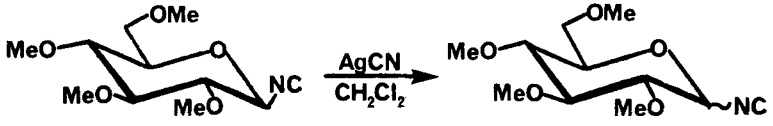


Boullanger and Descotes[29,31] have improved this method by using as a starting material benzylated halogeno sugars 9-13 and aprotic solvents, dichloromethane or toluene at room temperature, and have obtained anomeric mixtures (α+β) of the isocyanides in good yields. The formation of the corresponding cyanoethylidene derivatives has not been observed. It was found that the yields and the time of the above reaction are strongly dependent on the solvent used as well as on the reactivity of the glycosyl halides. Use of aprotic solvents of medium polarity such as dichloromethane gave a good yield of anomeric isocyanides, whereas in nonpolar solvents the reaction is slow and yields are lower. On the other hand in polar solvents such as nitromethane, the reaction is faster, but the yields are lower.[31]



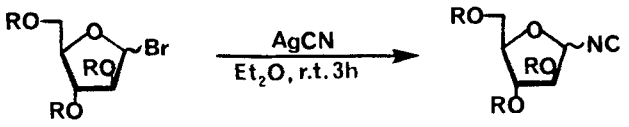
		α	+	β
1	R = Ac, R_1 = OAc	5	a	b
9	R = Bn, R_1 = OBn	14	a	b
10	R = Bn, R_1 = H	15	a	b
11	R = Bn, R_1 = Br	16	a	b
12	R = Bn, R_1 = Cl	17	a	b
13	R = Me, R_1 = OMe	18	a	b

It is noteworthy that under Walden inversion β-anomeric isocyanides are formed preferentially, probably due to the shielding effect of the leaving bromine atom on the α-side of the molecule. However, anomerization during the reaction has been observed, with the formation of α-isocyanides in 35% yield. Anomerization of pure β-anomer (18b) in dichloromethane and in the presence of silver cyanide has also been observed. The anomeric ratio at equilibrium α:β = 3:1 (after 7 days) did not support a reverse anomeric effect for these isomers.



18b 18a + 18b (3:1)

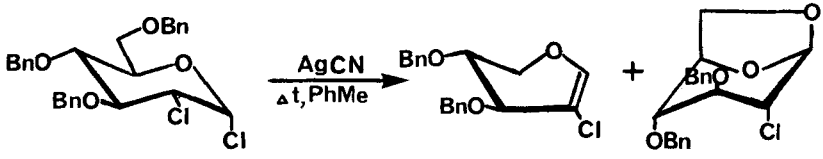
In the furanose series, the substitution of highly reactive furanosyl bromides (19) and (20) in ether as a solvent afforded an anomeric mixture of corresponding isocyanides 21-23 in the ratio α:β = 5:1. In this case fast anomerization of β-anomers causes preferential formation of the α-isocyanides 21 in 40% and 23 in 38% yield respectively.[31]



19 R = Bn
20 R = Me

α + β
21 22 R = Bn
23 24 R = Me

The increasing electronegativity of the C-2 substituent (H>OBn>Br>Cl) in the above series of benzylated derivatives, probably causes resistance of 3,4,6-tri-O-benzyl-2-chloro-2-deoxy-α-D-glucopyranosyl chloride (25) towards substitution with silver cyanide. The formation of 1,6-anhydro-3,4-di-O-benzyl-2-chloro-2-deoxy-β-D-glucopyranose (26) and 1,5-anhydro-3,4,6-tri-O-benzyl-2-chloro-2-deoxy-D-arabino-hex-1-enitol (27) in 40% and 43% yield has been observed.[31]

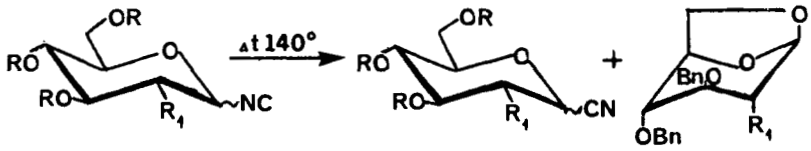


25 27 26

According to the authors[31] this lack of reactivity towards substitution with silver cyanide could be attributed to the strong inductive effect of the C-2 substituent, with concommitant destabilization of the ionic transition state.

3. TRANSFORMATION OF MONOSACCHARIDE ISOCYANIDES

The formation of derivatives (26) and (30) has been observed during the isomerization of isocyanides (14), (17), and (18) to the corresponding cyanides (28) and (29) at 140° in boiling xylene.[31] However, in the case of compound 17 no isomerization was observed and decomposition and elimination products only have been found in low yield.[31]

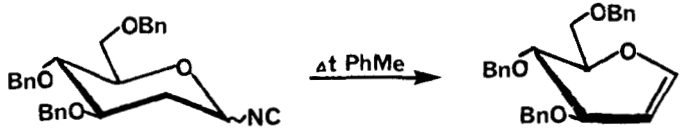


14 R=Bn, R_1=OBn
17 R=Bn, R_1=Cl
18 R=Me, R_1=OMe

28 R=Bn, R_1=OBn
29 R=Me, R_1=OMe

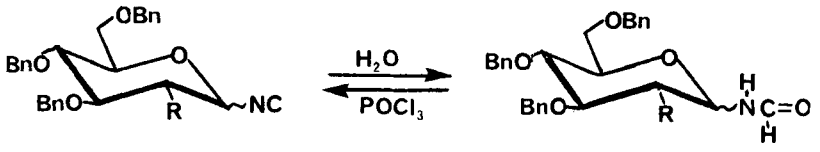
26 R_1=Cl
30 R_1=OBn

In the case of compound 15 the formation of 3,4,6-tri-O-benzyl-D-glucal (31) in 55% yield by an elimination reaction at 110° has been observed.



15 31

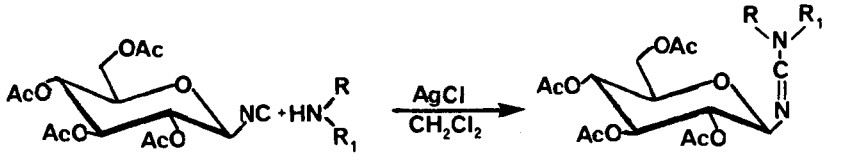
The hydrolysis of isocyanides (14)-(17) leads to the N-glycosylformamides 32 - 35 in almost quantitative yields with retention of the configuration at the anomeric center.



14 R = OBn	32 R = OBn
15 R = H	33 R = H
16 R = Br	34 R = Br
17 R = Cl	35 R = Cl

Dehydration of N-glycosyl formamides 32 - 35 with phosphorus oxychloride in pyridine solution produces isocyanides 14 - 17 in 60% yield.

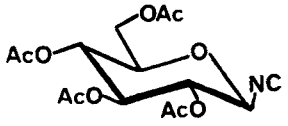
An interesting example of α-addition of various amines to glycosyl isocyanides with the formation of substituted glycosyl formamidines has been reported.[33,34]



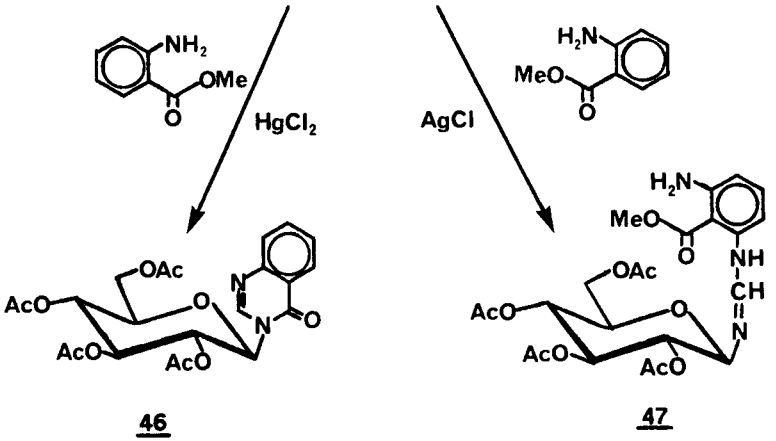
5b	36 R = R_1 = $CH_2(CH_2)_3CH_2$-	41
	37 R = R_1 = Et	42
	38 R = R_1 = n-Bu	43
	39 R = i-Bu, R_1 = H	44
	40 R = Ph, R_1 = H	45

This synthetic approach proceeds via a metal atom complex which readily reacts at room temperature with amines 36 - 40 with the formation of substituted formamidines 41 - 45 in almost quantitative yields. It is noteworthy that under the same conditions reaction with methyl anthranilate in the presence of mercuric chloride leads to the formation of a cyclization product, N-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl-3-quinazoline-4-one

(46), whereas the presence of silver chloride leads to the formation of formamidine 47. This example indicates that formamidines represent very good precursors for the synthesis of nucleoside analogs.

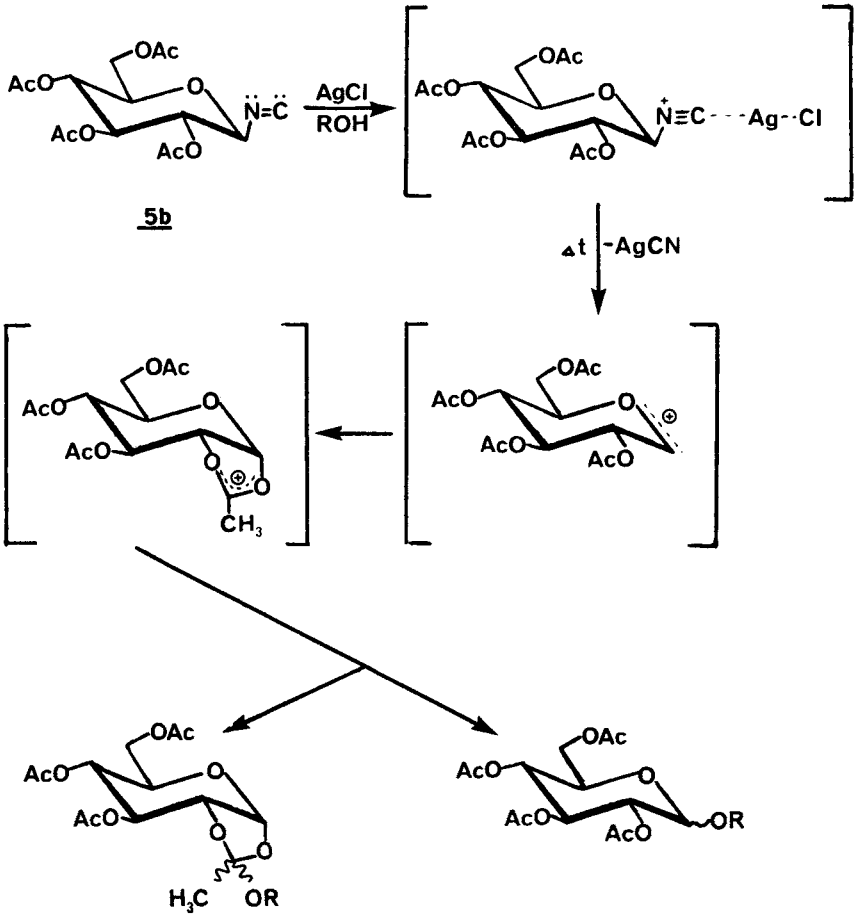


5b



46 47

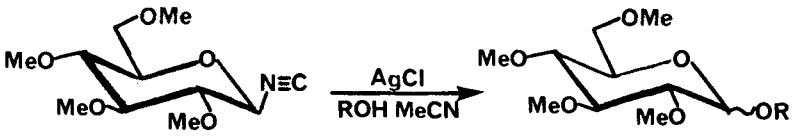
The (Z) or (E) configuration of formamidines 41-45 as well as 47 has been determined by ^{13}C NMR.[34] The reaction of glycosyl isocyanides with alcohols has been also reported.[34] The proposed mechanism of this reaction proceeds via a complex with silver chloride, which in the presence of alcohols in acetonitrile solution decompose with the formation of an intermediate oxonium ion, when a participating group such as acetyl is present at C-2. Under these conditions the formation of the endo and exo orthoesters 48a-48d as major products, and glycosides 49a-49d as coproducts has been observed.



48a R = Me
48b R = s-Bu
48c R = n-Bu
48d R = 4-heptyl

49a R = Me
49b R = s-Bu
49c R = n-Bu
49d R = 4-heptyl

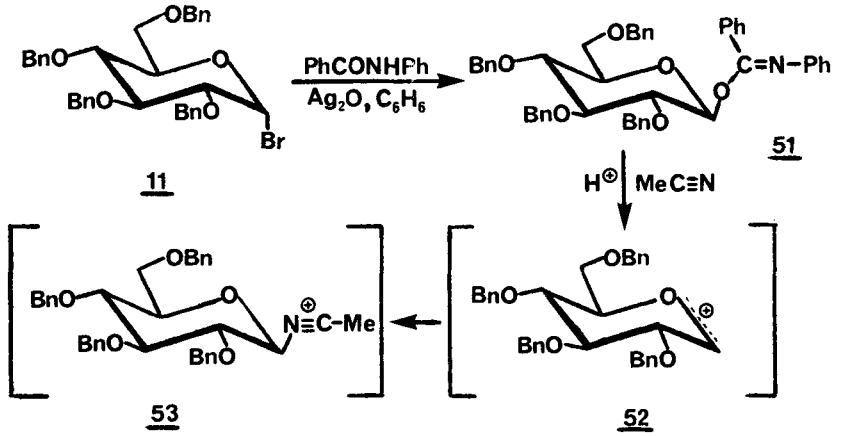
In the case of non-participating neighboring groups at C-2, such as O-methyl in (18b), the formation of only the anomeric mixture of glycosides 50a and 50b has been observed.[34]



18b 50a + 50b

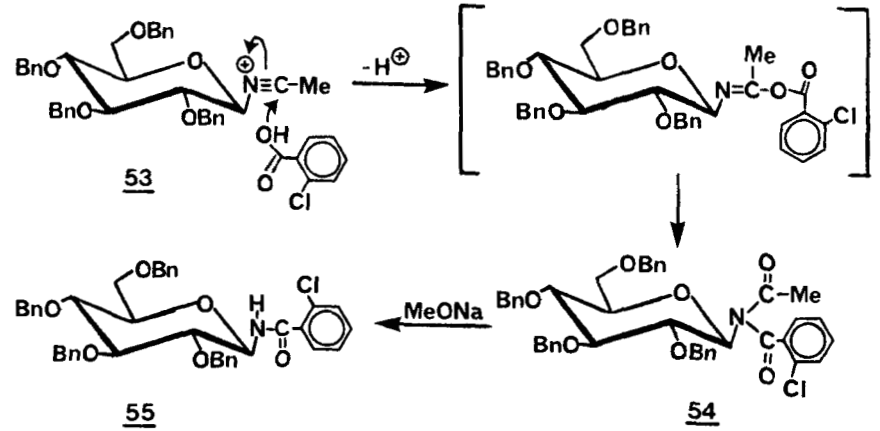
R = Me, sec-Bu, n-Bu, 4-heptyl

An interesting approach (via nitrilium salt) to the preparation of substituted glycosyl amides has been reported by Pougny and Sinaÿ.[35] This approach starts from the corresponding imidate (51) prepared by glycosylation of benzanilide in the presence of silver oxide. Treatment of 51 with acetonitrile in the presence of mild acids produces the intermediate nitrilium derivative 53 probably via an oxocarbenium ion 52.

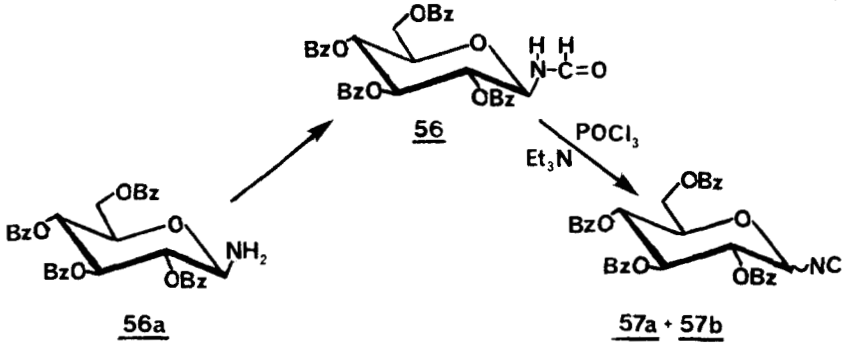


11 51 53 52

The very reactive nitrilium derivative 53 reacts rapidly with 2-chlorobenzoic acid to form quantitatively imide 54, which on treatment with sodium methoxide affords 2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl-N-2-chlorobenzamide (55).



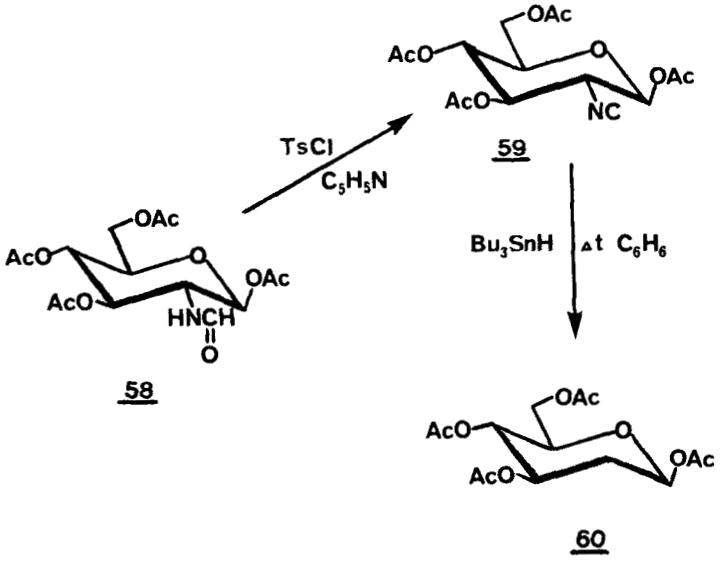
A very similar mechanism of formation of the intermediate salt by nucleophilic attack on an electrophilic carbon by a nitrile has been reported.[36,37] Another convenient approach to monosaccharide isocyanides is dehydration of the corresponding N-formylglucopyranosylamine derivative 56 as mentioned previously,[31] using phosphorus oxychloride and triethylamine[38] or p-toluenesulphonyl chloride in pyridine[39] as the dehydrating agents. Nolte and co-workers[38] reported this method for preparation of benzoylated isocyanides 57a and 57b in 86% yield.



Substitution of pyridine for triethylamine as the base lowered the yield of isocyanides to 15%. It is noteworthy that other dehydrating agents such as thionyl chloride in N,N-dimethyl-

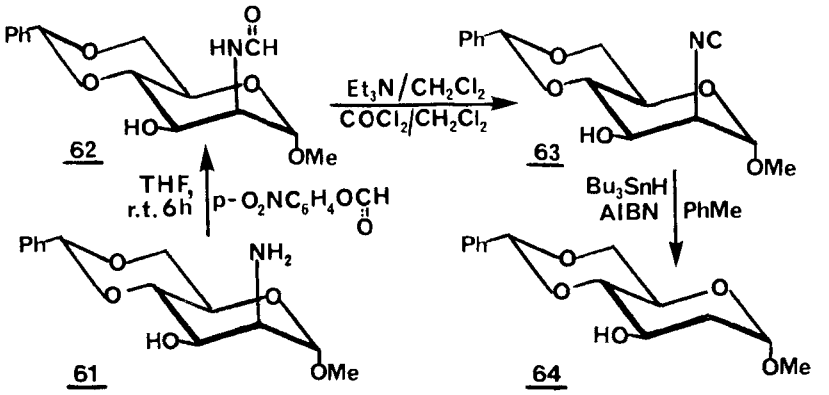
formanide and triphenylphosphine-carbon tetrachloride gave little or no isocyanides.[38]

A similar dehydration of N-formylglucosamine derivative (58) by p-toluenesulphonyl chloride in pyridine has been reported.[39] The intermediate isocyanide (59) was readily reduced with tri-n-butyltin hydride to the 2-deoxyglucopyranose derivative (60) in 72% yield.

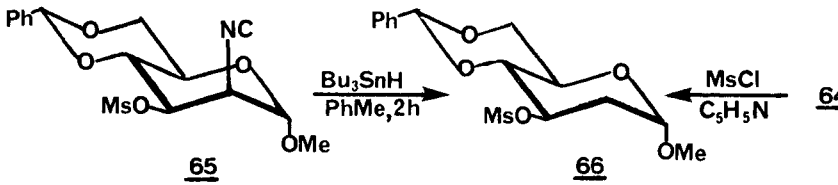


The above deamination reaction probably proceeds via a radical type intermediate as has been reported.[39]

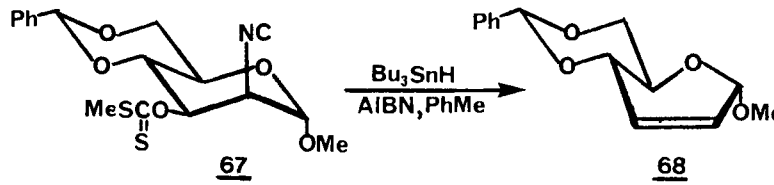
An interesting formylation-dehydration sequence has been reported by Barton and coworkers.[40] In this approach to formamide (62), the formylation agent, p-nitrophenylformate, has been applied. The dehydration of (62) by phosgene/triethylamine produced isocyanide (63) in 60% yield. Reduction of (63) with tri-n-butyltin hydride in the presence of azoisobutyronitrile (AIBN) as a radical initiator afforded the corresponding deoxyalcohol (64) in excellent yield (92%).



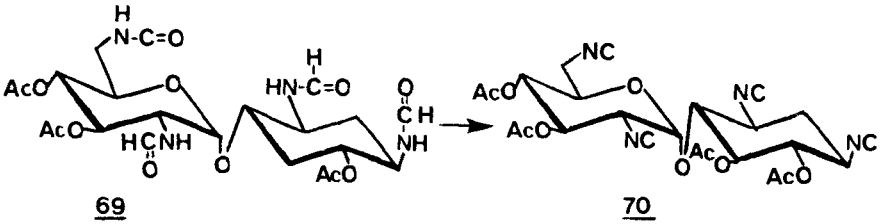
It is noteworthy that the course of the above radical-induced deamination reaction is not affected by the presence of a neighboring mesyl group in mesylate (65). The resulting mesylate (66) obtained in 77% yield has been independently prepared by mesylation of deoxyalcohol 64.



In the case of dithiocarbonate 67, treatment with tri-n-butyltin hydride led to a virtually quantitative yield (90%) of the unsaturated derivative (68).

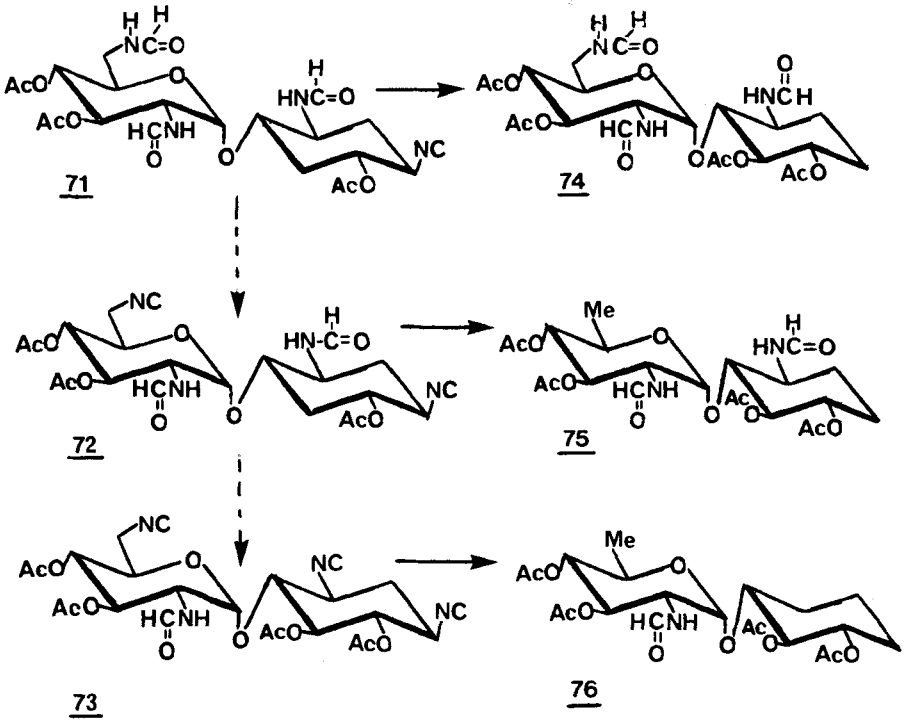


Performylation of the pseudodisaccharide neamine with p-nitrophenyl formate followed by peracetylation with acetic anhydride in pyridine afforded the corresponding tri-O-acetyl tetraformamide (69), a starting material for the radical-induced deamination reaction.[41]



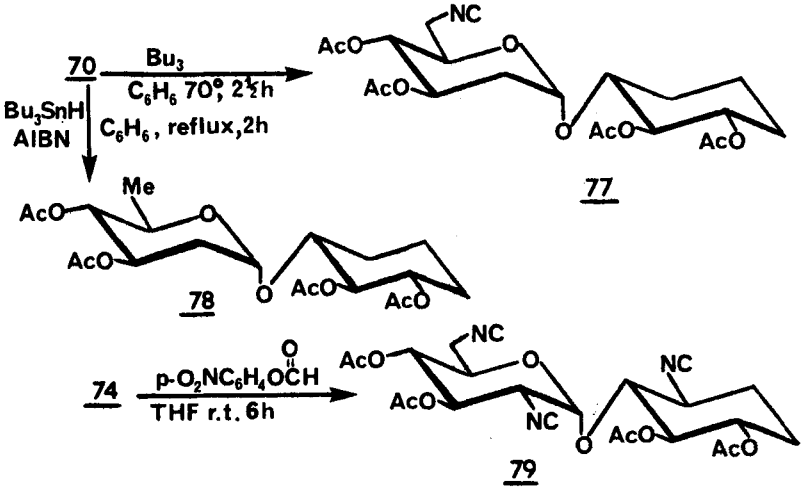
69 70

Dehydration of 69 with phosphorus oxychloride and triethylamine in dichloromethane afforded a mixture of four isocyanides (70), (71), (72) and (73). The yields of these products are strongly dependent on the time and temperature of the reaction. At a temperature of 8° for 24h the main product, isocyanide 70 , was formed in 59% yield, whereas at temperature -38° to 0° the formation of intermediate isocyanides 71 - 73 has been observed. Treatment of 71 - 73 with tri-n-butyltin hydride under the same conditions as for compounds 63 - 65 afforded the corresponding deoxy derivatives (74)-(76) in high yields.



71 74 72 75 73 76

It is noteworthy that selective removal of secondary isocyanide groupings in the isocyanide 70 was accomplished by performing the reaction in benzene at 70- 72°C and afforded the partially deaminated isocyanide 77 in 63% yield,[41] whereas, under reflux temperature the formation of deamination product (78) was observed. Dehydration of 74 in the same manner as for 69 afforded isocyanide 79 in 76% yield.



4. SPECTROSCOPIC PROPERTIES OF MONOSACCHARIDE ISOCYANIDES

The C≡N stretching bands in the IR spectra of alkyl nitriles and isocyanides are typically around 2250 and 2150 cm^{-1}, respectively.[32] Interestingly, in the case of glycosyl cyanides the C≡N stretching signals are not detectable. This phenomenon, noted previously,[24-26] is not uncommon in unconjugated systems. On the other hand a sharp, intensive band in the region 2120-2150 cm^{-1} is observed in the spectra on glycosyl isocyanides.[31] It is noteworthy that the precise frequency of this band is directly

related to the appropriate anomeric configuration of the isocyanide; for α-anomer (N≡C) is 2123-2129cm^{-1} whereas for the β-anomer (N≡C) is 2141-2146 cm^{-1}.[30,31,38] These stretching frequencies could be used for the easy determination of the anomeric configurations of glycosyl isocyanides.[31,38]

The ^{13}C NMR chemical shifts for the sp carbon of alkyl cyanides appear at 112-126 ppm, whereas for isocyanides they occur at 156-158 ppm.[43,44] In the glycosyl cyanides the chemical shifts are in the same range 114.5-117 ppm, as in the alkyl series.[45]

The signal of the isocyanide carbon has been observed at 163.8 ppm for the α-anomer, and at 162.3 ppm for the β-anomer.[31] Martin-Lomas and coworkers[30] observed this signal at 164.4 ppm, and Nolte and coworkers[38] at 166.1 ppm for α-anomer and 165.1 ppm for β-anomer.

5. CONCLUSION

The preceding is a brief review of the preparative chemistry of glucosyl isocyanides. The use of monosaccharide isocyanides as intermediates in the preparation of various classes of heterocyclic carbohydrate derivatives such as N-glycosides and other nucleoside analogs *via* intermediate formamidines was noted. Similarly complexation of isocyanides with metals, and reaction with various alcohols gives access to orthoesters as well as O-glycosides. Glycosyl cyanides, important precursors in the synthesis of C-glycosides or C-nucleosides, can be prepared by thermal isomerization of glycosyl isocyanides. A new method of synthesis of deoxy sugars from monosaccharide isocyanides represents a potential application of reactive isocyanides in carbohydrate chemistry. The utility of isocyanides as synthetic intermediates represents a subject of several papers and the search for new and interesting applications is continuing. For these reasons the field of carbohydrate isocyanides will remain a rich area of investigation for many years to come.

TABLE 1

MONOSACCHARIDE ISOCYANIDES

Compound	M.p. °C	$[\alpha]_{20}^{D}$	Ref.
2,3,4,6-Tetra-O-acetyl-α-D-galactopyranosyl isocyanide	164-165°	+32°(C 1.5 $CHCl_3$)	30
2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl isocyanide	-	-	30
2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl isocyanide	107-109°	+99°(C 1.2 $CHCl_3$)	30
2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl isocyanide	102-104°	+4°(C 0.11 $CHCl_3$)	30
2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl isocyanide	-	+52.4°(C 3.6 $CHCl_3$)	29,31
2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl isocyanide	-	+22.5°(C 2.5 $CHCl_3$)	29,31
3,4,6-Tri-O-benzyl-2-deoxy-α-D-arabinohexopyranosyl isocyanide[a]	-	+64°(C 1.4 $CHCl_3$)	29,31
3,4,6-Tri-O-benzyl-2-bromo-2-deoxy-D-glucopyranosyl isocyanide[b]	-	-	29,31
3,4,6-Tri-O-benzyl-2-chloro-2-deoxy-D-glucopyranosyl isocyanide[b]	-	-	29,31
2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl isocyanide[c]	-	+28.1°(C 1.8 $CHCl_3$)	31
2,3,4,6-Tetra-O-methyl-β-D-glucopyranosyl isocyanide[c]	85-86°	+28.1°(C 1.8 $CHCl_3$)	31
2,3,5-Tri-O-benzyl-α-D-arabinofuranosyl isocyanide[d]	-	+49°(C 0.1 $CHCl_3$)	31
2,3,5-Tri-O-methyl-α-D-arabinofuranosyl isocyanide[d]	-	+73°(C 0.5 $CHCl_3$)	31
2,3,4,6-Tetra-O-benzoyl-α-D-glucopyranosyl isocyanide	54-56°	+70.4°(C 1.5 $CHCl_3$)	35
2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl isocyanide	88-90°	+44.7°(C 2.5 $CHCl_3$)	35
1,3,4,6-Tetra-O-acetyl-2-deoxy-2-isocyano-α-D-glucopyranose	131-132°	+48.7°(C 2.5 $CHCl_3$)	39,40

Methyl 4,6-O-Benzylidene-2-deoxy-2-isocyano-α-D-altropyranoside	159-159°	+66.6°(C 0.6 $CHCl_3$)	40
Methyl 4,6-O-Benzylidine-2-deoxy-2-isocyano-3-O-mesyl-α-D-altropyranoside	-	+31.5°(C 0.41 $CHCl_3$)	40
Methyl 4,6-O-Benzylidine-2-deoxy-2-isocyano-3-O-[(methylthio)thiocarbonyl]-α-D-altropyranoside	-	+31.2°(C 0.97 $CHCl_3$)	40
5,6,3,4-Tetra-O-acetyl-1,2,3,6-tetradeamino-1,3,2,6-tetraisocyano neamine	223-224°	+83.4°(C 1.2 $CHCl_3$)	41
5,6,3,4-Tetra-O-acetyl-1,2,3,6-tetradeamino-2-formamido-1,3,6-triisocyano neamine	140-150°	+48.0°(C 1.0 $CHCl_3$)	41
5,6,3,4-Tetra-O-acetyl-1,2,3,6-tetradeamino-3,2-diformamido-1,6-diisocyano neamine	165-170°	+31.3°(C 1.0 $CHCl_3$)	41
5,6,3,4-Tetra-O-acetyl-1,2,3,6-tetradeamino-3,2,6-triformamido-1-isocyano neamine	150-160°	+74.7°(C 1.0 $CHCl_3$)	41
5,6,3,4-Tetra-O-acetyl-1,2,3,6-tetradeamino-3,2,6-triisocyano neamine	113-115°	+105.6°(C 0.7 $CHCl_3$)	41

[a] β anomer has not been prepared.

[b] Syrup, α and β anomers are not separated.

[c] Literature[31] reported identical optical rotation for both anomers.

[d] Syrup contaminated by β-anomer (<5%).

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