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Synthesis and role of glycosylthio heterocycles in carbohydrate chemistry

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Abbreviations: SPy, thiopyridyl; SQu, thioquinolinyl; SIm, thioimdazolyl; STh, thiothiazolyl; SBth, thiobenzothiazolyl; SBox, thiobenzoxazolyl; STr, thiotriazolyl; SOxd, thiooxadiazolyl; SThd, thiothiadiazolyl; STe, thiotetrazolyl; SPd, thiopyridazinyl; SPm, thiopyrimidinyl; SPz, thiopyrazinyl; SQz, thioquinazolinyl; SBtz, thiobenzothiazinyl; SQx, thioquinoxalinyl; STz, thiotriazinyl; HMDS, hexamethyldisilazane; TMSOTf, trimethylsilyltriflate; TBAHS, tetrabutylammonium hydrogen sulfate; TBAB, tetrabutylammonium bromide; $BnSOCl_2$, benzylsulfonyl chloride; BnBr, benzyl bromide; DMF, dimethyl formamide; MS, molecular sieves; NIS, *N*-iodosuccinimide; AgOTf, silver triflate; THOf, trifloromethane sulfonic acid; TBDMSOTf, *t*-butyldimethylsilyltriflate.

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1. Introduction

The majority of carbohydrates found in nature or biological systems exist as polysaccharides and/or glycoconjugates in which the monosaccharide units are joined via *O*- or *N*-glycosidic bonds. The necessity to form either a 1,2-*cis* or 1,2-*trans* glycosidic bond with complete stereoselectivity is the main concern during chemical *O*-glycosylations, which is one of the most challenging problems of modern synthetic chemistry. A strong demand still remains, however, to develop simple, mild and efficient methods for stereoselective glycosylations.

Thioglycosides have received considerable attention, because they are widely employed as biological inhibitors,[1–5] inducers[6–8] and ligands[9–12] for affinity chromatography of carbohydrate-processing enzymes and proteins. Moreover, they are promising candidates in synthetic carbohydrate chemistry as convenient and versatile glycosyl donors. Among these glycosyl donors are the thioglycosyl heterocycles that are sufficiently stable under a variety of reaction conditions and have the ability to be readily converted into a variety of other functionalities.[13–15] Most interesting is the divergent use of a number of thioglycosyl heterocycles as glycosyl acceptors and, subsequently, as donors which have been employed for the stereoselective synthesis of oligosaccharides.[13,14,16–20] There is, however, a lack of reviews in the literature on glycosylthio heterocycles, in spite of the fact that thioglycosides in general have been surveyed. Consequently, the present article reviews the literature on thioglycosyl heterocycles, particularly their synthesis and potential in carbohydrate chemistry, as well as their use as biological inhibitors.

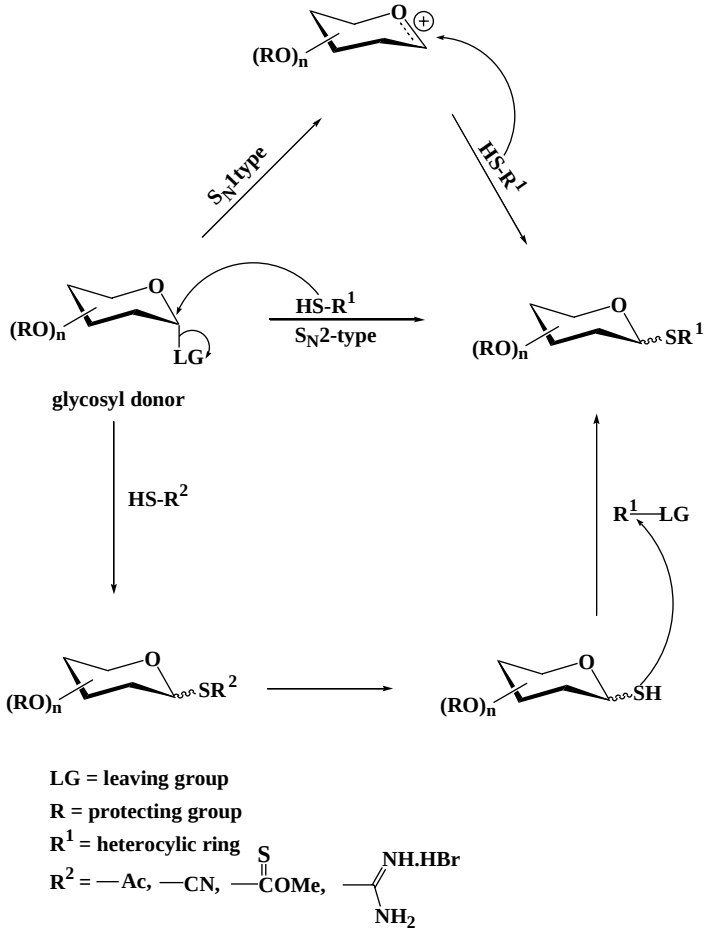
2. Synthesis of glycosylthio heterocycles

The general approaches to the synthesis of thioglycosides may proceed via the direct introduction of the heterocyclic thiol part, either by an S_N^1 or S_N^2 mechanism through a displacement reaction of an anomeric leaving group, sometimes aided by a promoter, in a manner similar to *O*-glycosylation reactions. Alternatively, a two- (or more) step procedure may be employed in which a thiol group is first introduced on the anomeric center, which is then reacted with an electrophile to give the target thioglycoside; the thiol functionality can be generated from the thioglycosyl derivatives having readily cleavable groups, in a selective manner, on the sulfur atom. The generation of α- and/or β-thioglycosyl heterocycles is dependent on all the factors involved in the reaction, particularly the protecting groups on the sugar portion of the glycosyl donor (Scheme 1). Consequently, the available synthetic approaches can be classified according to the structure of the glycosylating agent, and then according to the heterocycle and, in each case, according to the promoter or the catalyst.

2.1. Per-*O*-acylated sugars as glycosylating agents

The anomeric acetoxy group in a glycosyl donor can be efficiently displaced by a thiol group linked to a heterocycle under the influence of an acidic catalyst. The standard procedure is to react a per-*O*-acetylated aldose with a slight excess of thiol using a hard Lewis acid as promoter, which generally gives predominantly a high yield of the 1,2-*trans* product.[21] Various Lewis-acid catalysts have been employed, for example, $BF_3 \cdot Et_2O$, zinc chloride, stannic chloride and ferric chloride.[22–24] Thus, the reaction of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose **1** with 2-mercaptopyridine **2** in the presence of $BF_3 \cdot Et_2O$ in dichloroethane at 0 °C yielded the β-ribofuranoside **3** in 85% yield.[25] Using 4-mercaptopyridine **5** instead of **2**, however, under the same reaction conditions, a 2:1 mixture of the α- and β-anomers of thioribofuranoside **6** was obtained.[25] The trimethylsilyl derivatives of heterocyclic thiols were also used for generating the thioglycosyl heterocycles. Thus, the trimethylsilylated derivative **4** of 2-mercaptopyridine was reacted with **1** in the presence of TMSOTf to give **3**[26] (Scheme 2).

Stannic chloride in acetonitrile was used for the coupling of trimethylsilylated pyridine **9** with **7** or **8** to give the β-thioglycosides[27] **10** and **11**, respectively (Scheme 2).



Scheme 1.

The reaction of polyfunctionalized pyridine-2(1*H*)-thiones **12** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **13**, in the presence of hexamethyldisilazane (HMDS) and ammonium sulphate in methylene chloride containing a catalytic amount of TMSOTf, gave the β-thioribosides **14**.[28]

2-Pyridyl 1-thiogluco- and 1-thiogalacto-pyranosides **15** and **16** were also prepared in 79 and 73% yield, respectively, when glucose or galactose pentaacetates **7** and **8** were reacted with 2-mercaptopyridine **2** in the presence of $ZrCl_4$ in 1,2-dichloroethane[29] (Scheme 2). Deacetylation of **15** followed by tritylation and then benzylation gave **17**.

The reaction of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose **18** with 1-aminoimidazole 2(3*H*)-thione derivatives **19** was catalyzed by *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and TMSOTf at 40 °C to give **20**, exclusively in the β-anomeric configuration, in 66–84% yield.[30] Under the same conditions, D-glucose pentaacetate **7** was coupled with **19** to afford the β-thioglucoside **21** (65% yield).[30] The coupling of **19** (R=4-ClC_6H_4) with **13** was also carried out in the presence of NaH in DMF as a solvent to give **20** (R=4-ClC_6H_4) in low yield (38%)[31] (Scheme 3).

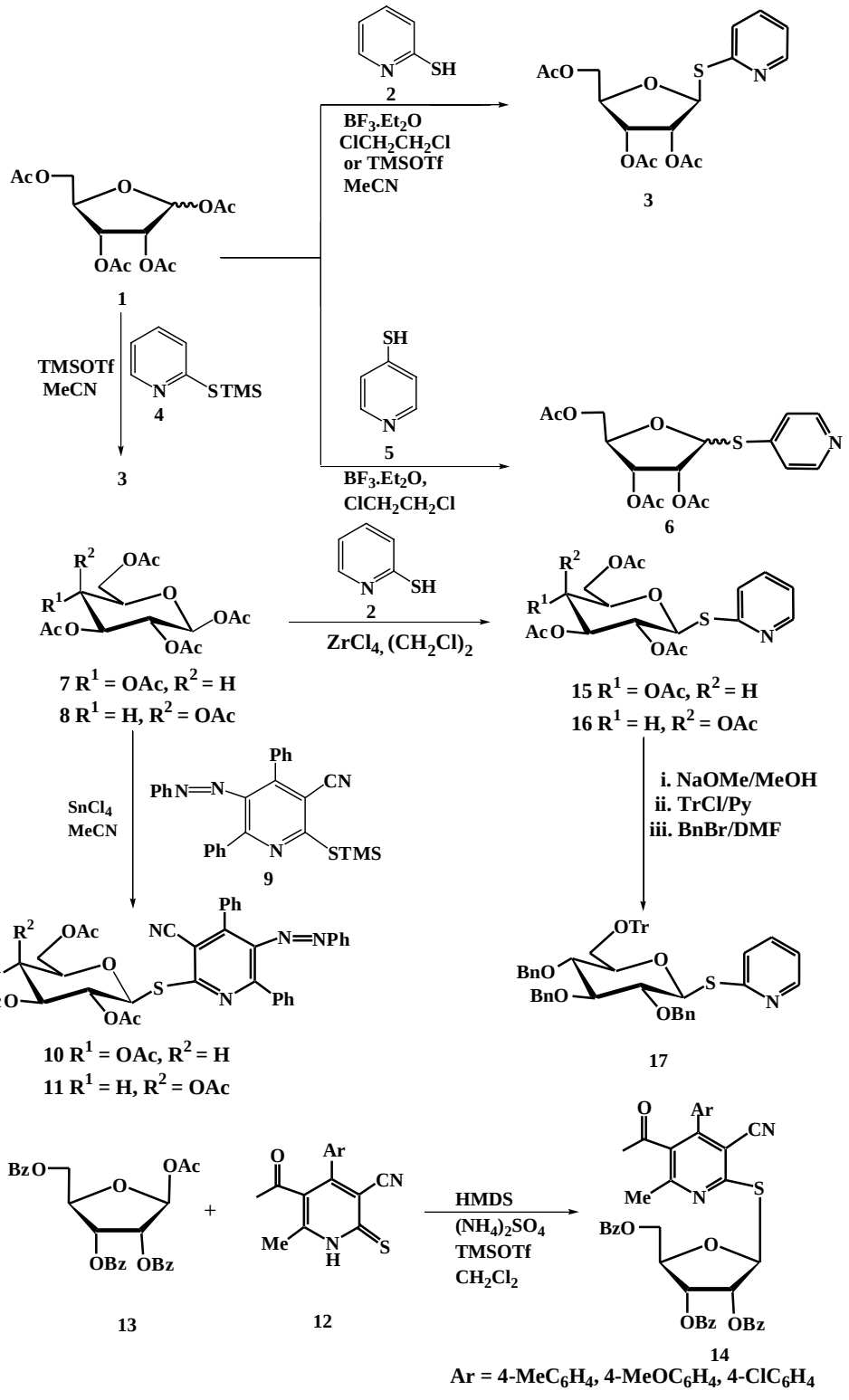
The coupling of **7** with a silylated benzylidene of the thiohydantoin **22** was catalyzed by TMSOTf to afford the β-thioglucoside **23** in 58% yield[32] (Scheme 4). Catalysis of the thioglycosylation with $BF_3\cdot Et_2O$ was used for reacting penta-*O*-acetyl-D-galactofuranose **24** with heterocyclic thiols **25** to give the β-thiofuranosides **26**[33] (Scheme 4).

Coupling of the β-anomer **13** with 5,6-dichloro-2-mercaptobenzimidazole **27** in the presence of TMSOTf at room temperature gave the β-thioriboside[34] **28**.

In the presence of $BF_3\cdot Et_2O$, D-glucose pentaacetate **7** was reacted with 2-mercaptobenzoxazole (**30**, HSBox) to afford **32** as an anomeric mixture (α:β=1:3.5) in 79% yield.[35] On the other hand, when 1,2,4,6-tetra-*O*-acetyl-3-*O*-methyl-D-glucopyranose **29** was coupled with 2-mercaptobenzothiazole **31** under the same reaction conditions, it afforded only the β-thioglucopyranoside derivative **33**.[36] Similarly, 1-thio D-galactofuranoside derivative **26** was obtained when penta-*O*-acetyl-D-galactofuranose **24** was reacted with **31**.[33]

The trimethylsilyl derivative **35** was reacted with **34**β in presence of TMSOTf to afford the β-thioriboside derivative **36** in 78% yield[26] (Scheme 5).

The β-thioglucuronopyranosides **40** and **41** were obtained from the coupling of methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucuronate **37** with 5-halogenated 2- and 4-mercaptouracils



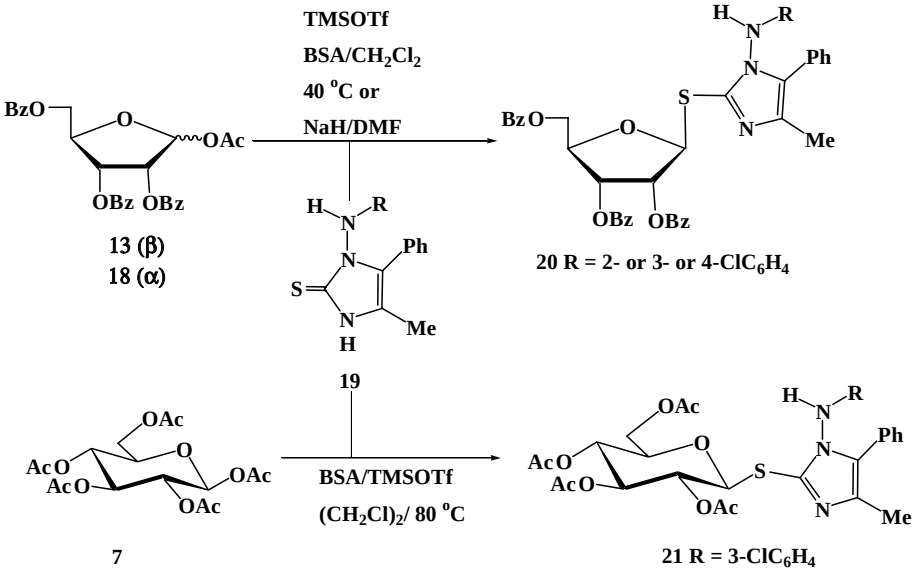
Scheme 2.

38 and **39**, respectively, in the presence of $SnCl_4$ in acetonitrile.[37]

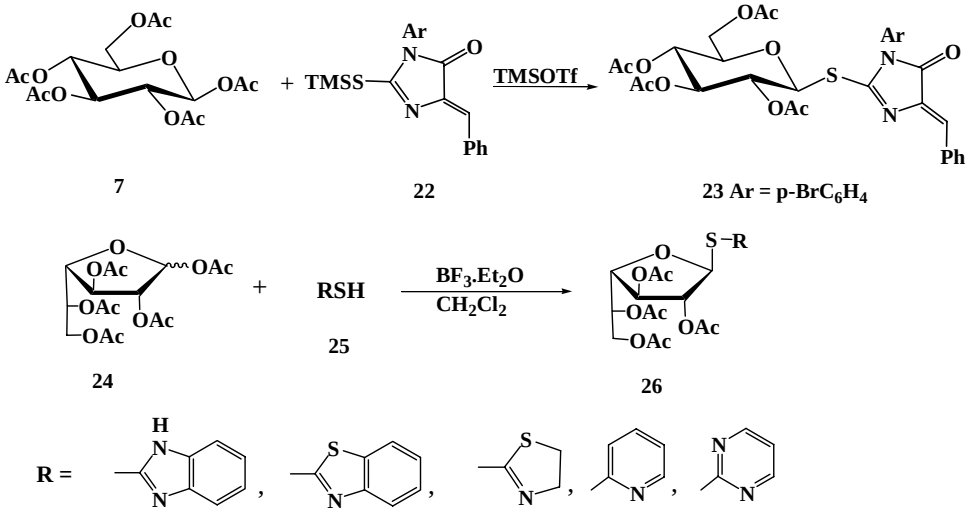
Similarly, 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose **1** was coupled with 4-mercapto-2-methylthiopyrimidine **42**, but in the presence of $BF_3 \cdot Et_2O$, to give the thio-β-D-ribofuranoside **43**[38] (Scheme 6).

2.2. Glycosyl halides as glycosylating agents

A classical route to thioglycosides is the reaction between an acetohalosugar and a thiolate anion. The high nucleophilicity of sulfur towards the anomeric position combined with its rather low basicity make it possible to perform the reaction in acetone or methanol or even in an acetone-water



Scheme 3.



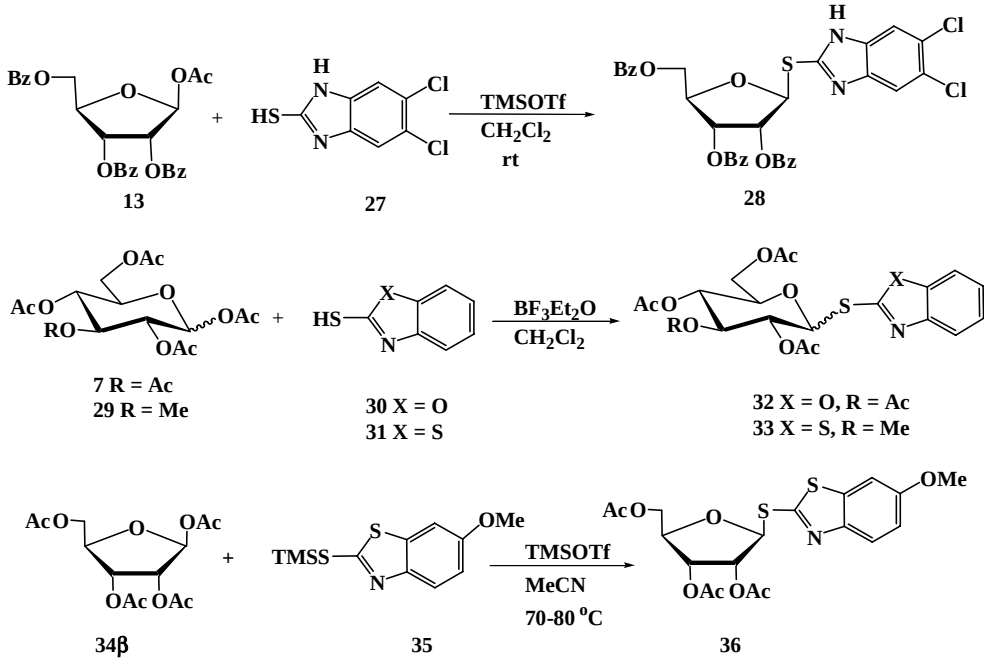
Scheme 4.

mixture. Usually, a 1,2-*trans* product is obtained, possibly through the participation of the 2-*O*-acetyl group, but, if the conditions are carefully selected, a direct S_N^2 displacement reaction can take place.[39] The thiolate anion can be generated from heterocyclic thiols in situ with the aid of bases such as sodium or potassium hydroxide, sodium hydride or potassium carbonate. There are many examples that can be included under this title. Consequently, herein they have been subdivided according to the heterocyclic ring system; heterocycles with one heteroatom come first, followed by those with increasing size and complexity of the ring. Each heterocycle has been denoted by an abbreviation, as reported in the literature, and others were developed for the purpose of this review.

2.2.1. Heterocycles with one heteroatom. Although, thioglycosides of the six-membered ring heterocycle, pyridine, were extensively reported, no examples have been given of the synthesis of the respective thioglycosides of five-membered ring heterocycles with one heteroatom.

2.2.1.1. Thiopyridyl (SPy) glycosides. Thiopyridyl glycosides are the most extensively studied thioglycosyl heterocycles, particularly because of their potential as glycosyl donors. Treatment of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and -α-D-galacto-pyranosyl bromide **44** and **45** or 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride **46** with 2-mercaptopyridine **2** in the presence of K_2CO_3 in acetone afforded the respective pyrid-2-yl 1-thio-β-D-glycopyranoside derivatives **15**, **16** and **47**, respectively, in 86 and 72% yield.[14,40,41] The thioglucoside **15** and the thiogalactoside **16** can be obtained in 77 and 86% yield when the coupling was carried out in the presence of NaH in acetonitrile.[26] In the presence of K_2CO_3 in hot toluene–acetone as the solvent, 2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl bromide was reacted with **2** to give the thioribofuranoside **48**, which, on debenzoylation and subsequent benzylation, afforded the benzylated derivative[42] **49**.

2-Mercaptopyridine **2** was coupled with α-acetobromo-rhamnose, α-acetobromomaltose and α-acetobromolactose



13 27 28

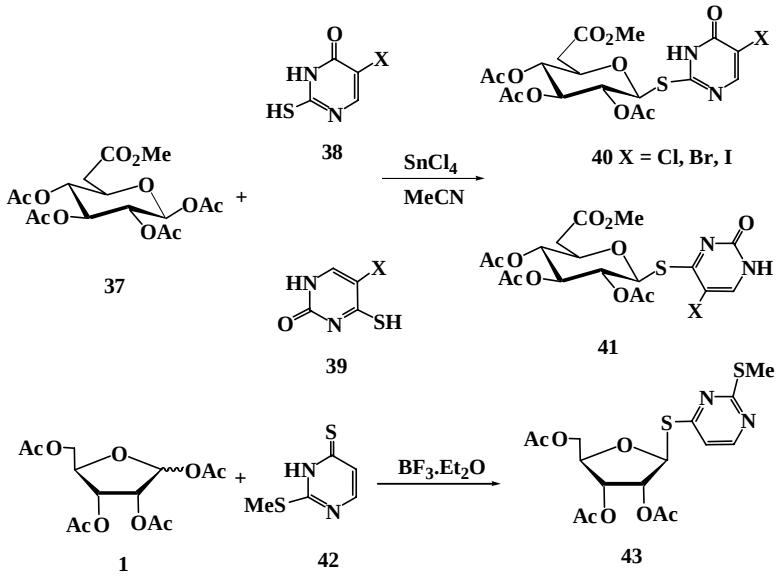
7 R = Ac
29 R = Me

30 X = O
31 X = S

32 X = O, R = Ac
33 X = S, R = Me

34β 35 36

Scheme 5.



37 38 39 40 X = Cl, Br, I 41 1 42 43

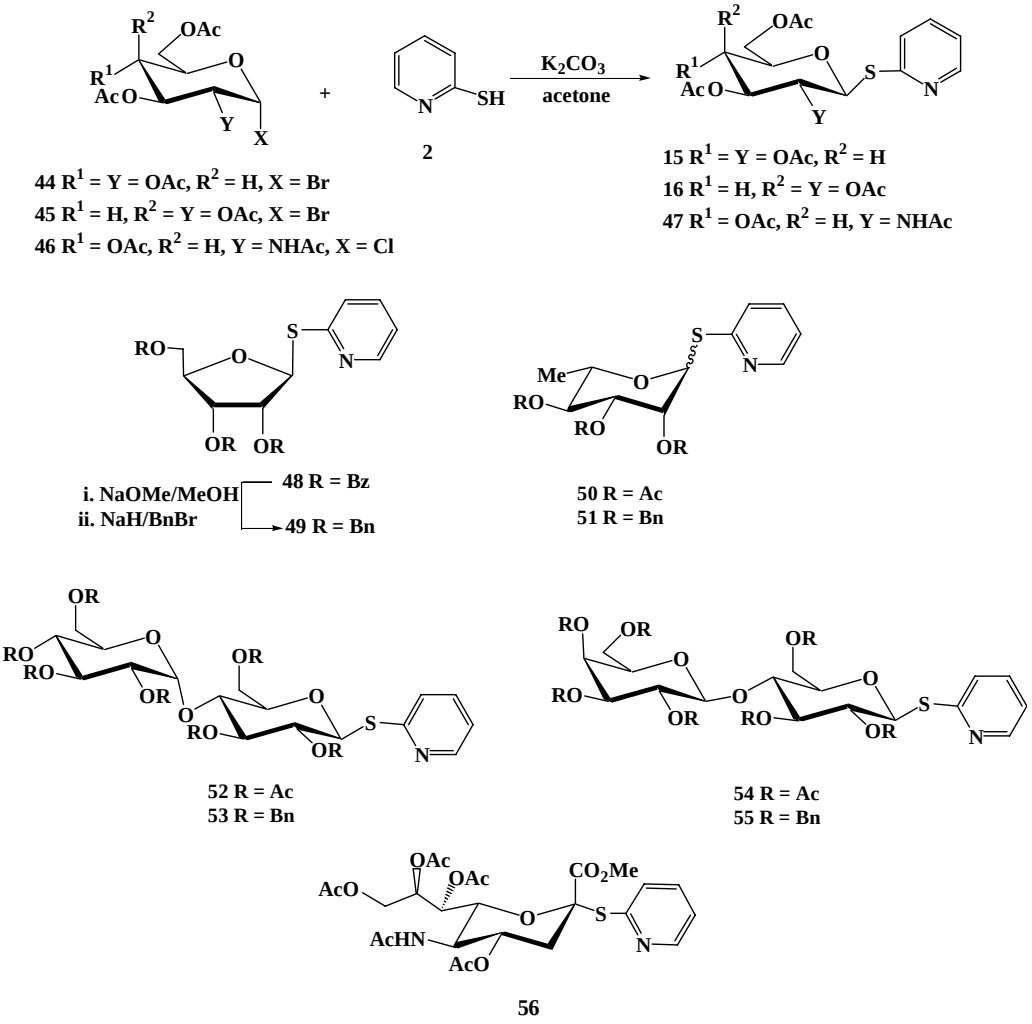
Scheme 6.

to give 1-thio-L-rhamnopyranoside **50**, in an α:β ratio of 1:1, 1-thio-β-maltoside **52** and 1-thio-β-lactoside **54**, respectively.[43,44] Deacetylation followed by benzylation of these thioglycosides gave the benzyl derivatives **51**, **53** and **55**, respectively.[43,44]

Coupling of per-*O*-acetyl β-acetochloroneuraminic ester with **2** at room temperature in the presence of tetra-*n*-butylammonium hydrogen sulfate (TBAHS) and a 1 M solution of sodium carbonate under phase-transfer conditions in either methylene chloride or ethyl acetate afforded the α-thiopyridyl derivative[45] **56** (Scheme 7).

The reaction of sodium salts of 5-arylazo-3-cyano-2-mercaptopyridines **58**, obtained from the reaction of cyanothioacetamide with 2-arylhydrazono-1,3-diphenyl-propane-1,3-diones in the presence of sodium ethoxide, with acetobromoglucose **44** or acetobromogalactose **45** in acetone gave the respective *S*-glycosylated pyridine derivatives **59** and **60** in 67–74% yield (Scheme 8).[27]

Piperidinium salts of dihydropyridine thiolates **61** were also coupled with glucosyl or galactosyl bromide **44** and **45** in dry acetone at 0 °C[46,47] to give the 1,4-dihydro-3-cyanopyridine thioglycosides **62** and **63**, respectively, in good yields. On the other hand, when the reaction was carried out at 30 °C in dry acetone, the corresponding aromatized pyridine thioglycosides **64** and **65**, respectively,[46] were obtained that alternatively resulted from heating **62** and **63** in ethanol (Scheme 8).[48]



Scheme 7.

The synthesis of (2-pyridyl *N*-oxide) thioglycosides **67** and **68** has been achieved by condensation of the sodium salt **66** of 2-pyridinethiol *N*-oxide with acetobromoglucose **44** or methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl bromide uronate **57**. The reaction was dependent on the solvent; when DMF was used, the reaction of **44** with **66** gave **67** in high yield and high purity, whereas the reaction of **57** with **66** in DMF gave **68** in high yields, but in low purity. In methanol, however, **68** was obtained in low yield, but in much higher purity[49] (Scheme 8).

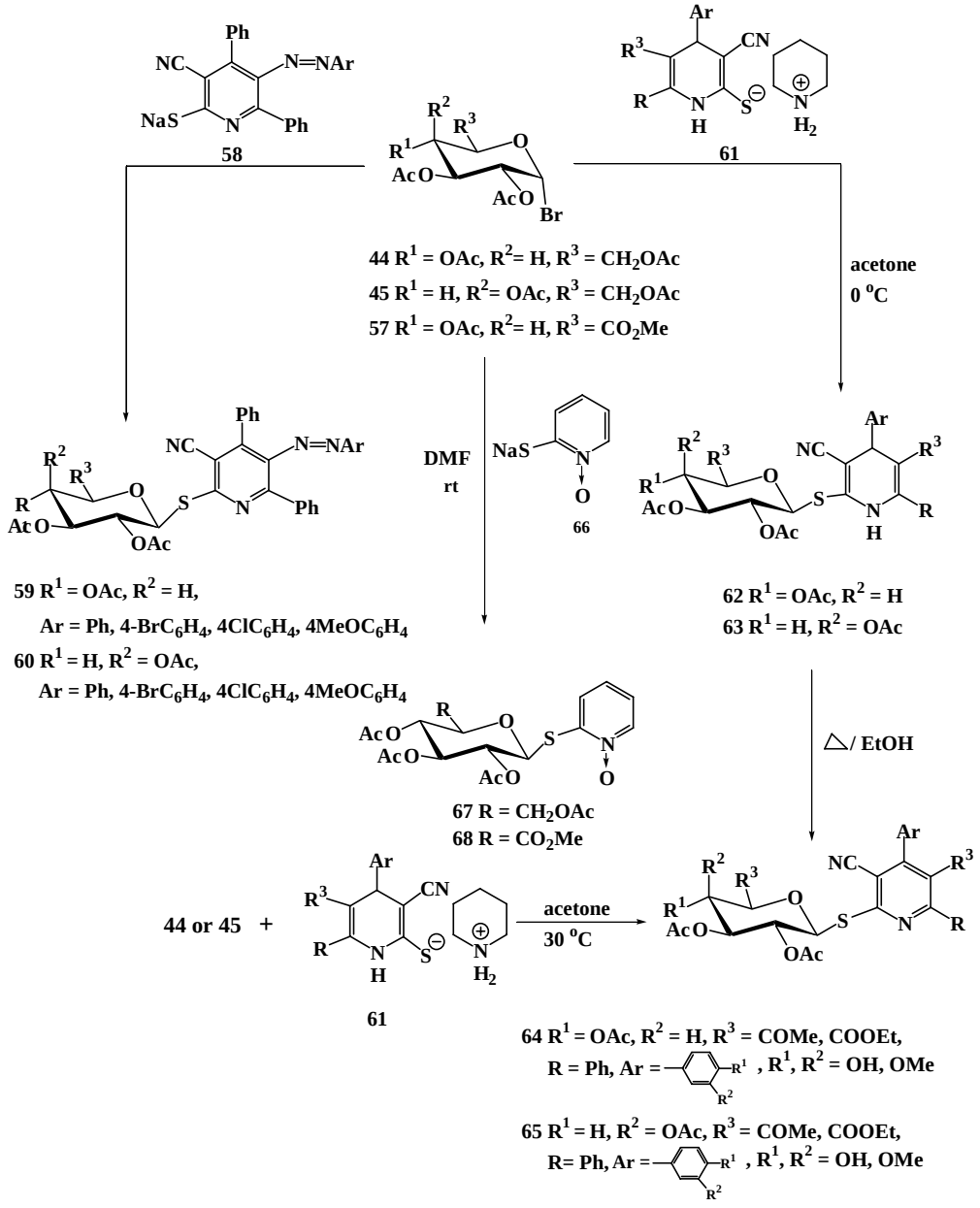
2.2.1.2. Thioquinolinyl (SQu) glycosides. 4-Quinolinyl thioglycosides **70** and **71** were obtained when an alcoholic potassium hydroxide solution of 4-mercaptoquinolines **69** was treated with acetobromoglucose or acetobromolactose.[50] Similarly, the thioglycosides **73** and **74** were obtained from cycloalkanopyridine thiones **72** in aqueous acetone[51,52] (Scheme 9).

2.2.2. Five-membered heterocycles with two heteroatoms.

2.2.2.1. Thioimidazolyl (SIm) glycosides. Glycosylation of 2-mercapto-4,5-diphenylimidazole **75** or 2-mercapto-1,4,5-triphenylimidazole **76** with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and -α-D-galacto-pyranosyl bromides or 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride in acetone–DMF in the presence of triethylamine at room temperature gave the β-thioglycosides **77**, **78** and **79**, respectively, in 74–86% yield.[53] The reaction has been accelerated by microwave irradiation to give higher yields (88–94%) within 2–4 min.[53]

Ribosylation of 1-(4-chlorophenyl)amino-2,3,-dihydro-4-methyl-5-phenyl-1*H*-imidazole-2-thione with 2-deoxyribofuranosyl chloride **80** in the presence of NaH in DMF afforded only the β-anomer thioglycoside[31] **82**.

5-Alkylidenes and 5-arylidenes of 3-aryl-2-thiohydantoins have been glycosylated with glycosyl halides in the presence of NaH in acetonitrile to give the *S*-glycosylated hydantoins of the gluco-, galacto- and ribo- analogues.[32,54,55] Similarly, compounds **84** (R^3=H, R^4=naphthyl) were also obtained when **44** or **45** were coupled with the hydantoin derivatives in aqueous potassium hydroxide or potassium carbonate in acetone.[55] When **44** was reacted with the *N*-3-unsubstituted hydantoin derivative under the same conditions, it gave the thioglycoside **84** (R=H) and the thio and *N*-3 diglycosyl derivative **85**.[54] The reaction has been explained to take place at the sulfur followed by further reaction at the nitrogen, when available, to give the diglycosylated derivative that could



Scheme 8.

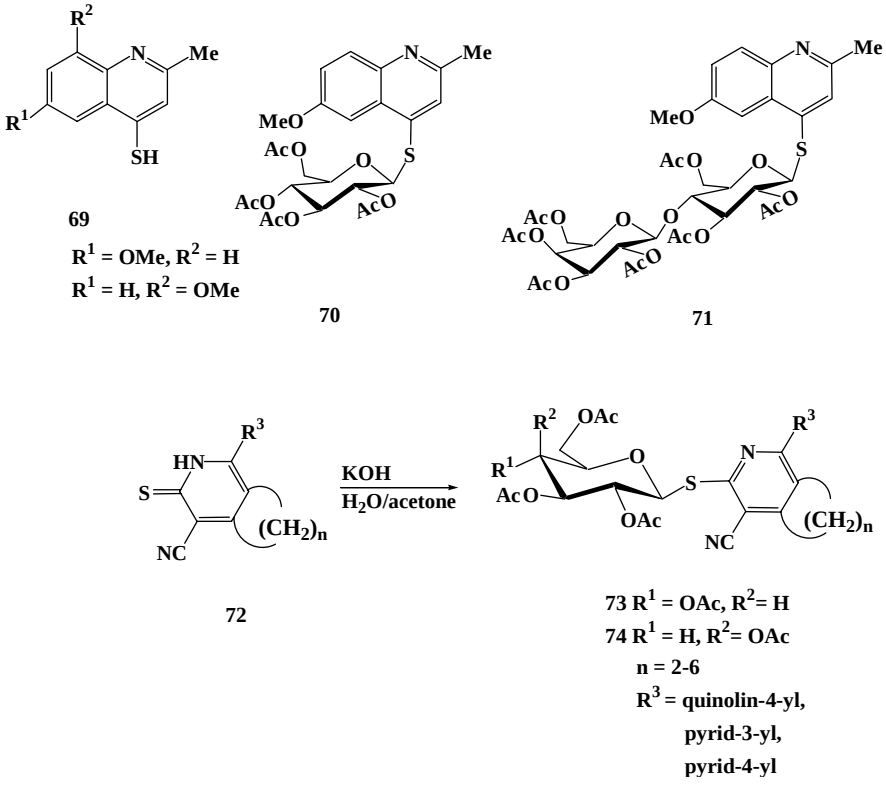
be the only product in the presence of an excess of the glycosylating agent.[55] In one pot, **84** was prepared by coupling 3-aryl-2-thiohydantoin with benzaldehyde in the presence of ethanolic potassium hydroxide followed by subsequent reaction with acetobromoglucose in aqueous acetone.[32]

Under phase-transfer catalysis, imidazolyl-2-α-thio-neura minic ester **87** was obtained in 68% yield when β-aceto-chloroneuraminic ester **86** was reacted with 1-methyl-2-mercaptoimidazole in the presence of TBAHS and a 1 M solution of sodium carbonate in either methylene chloride or ethyl acetate[45] (Scheme 10).

2.2.2.2. Thiobenzimidazolyl (SBim) glycosides. Potassium 1-methylbenzimidazole-2-thiolate **88** gave, upon glucosylation with acetobromoglucose **44** in acetone, 1-methyl-2-(tetra-*O*-acetyl-β-D-glucopyranosylthio)benzimidazole **90** and a small amount of the respective β-*N*-benzimidazole glucoside analogue **92**.[56] Using 5-nitrobenzimidazole **89** in the coupling with **44**, however, afforded only the 5-nitrobenzimidazolyl thioglucoside derivative **91** in 74% yield[41] (Scheme 11).

2.2.2.3. Thiothiazolyl (STh) glycosides. Thiazolin-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **93** has been prepared by the reaction of acetobromoglucose with 2-mercaptothiazoline (**25**, R=thiazolinyl) in the presence of NaH in acetonitrile followed by deacetylation and benzylation[57] to give **94** (Scheme 12).

2.2.2.4. Thiobenzothiazolyl (SBth) glycosides. Conversion of 2-mercaptobenzothiazole **31** into the respective sodium salt with sodium hydride in dry acetonitrile, followed by reaction with acetobromoglucose **44** afforded the β-thioglucoside **96** as the major product (84%) and the β-nucleoside **100** as the minor product (4%).[26] Under the



Scheme 9.

same conditions, the coupling of **44** with 5-methoxy-2-mercaptobenzothiazole **95** gave only the β-thioglucoside **97** in 83% yield.[26] On the other hand, only the thiogalactoside **98** was obtained in 90% yield by reacting the acetylated galactopyranosyl bromide **45** with **31**, whereas, with **95**, the thiogalactoside **99** resulted as the major isomer (60%) and nucleoside **101** as the minor isomer (22%).[26]

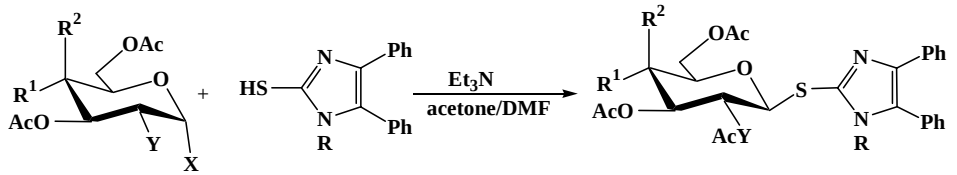
Thiobenzothiazolyl glycoside derivative **102** has been prepared by glycosidation of 2-mercaptobenzothiazole **31** with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride in the presence of 1,8-bis-(dimethylamino)naphthalene in dichloromethane[58] (Scheme 12).

2.2.2.5. Thiobenzoxazolyl (SBox) glycosides. The reaction of 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl bromide **103** with 2-mercaptobenzoxazole (**30**, HSBox) in the presence of potassium carbonate in acetone afforded the β-anomer, benzoxazolyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside **108** in high yield.[57] Similarly, the D-galactoside derivative **109** was prepared from **104**. Under the same reaction conditions, **30** was coupled with acetobromoglucose to give the benzoxazolyl thio-β-glucoside **32**.[35,41,57] Prolonged reaction times were required for the transformation of the less reactive benzoyl D-gluco- **105**, D-galacto- **106** and D-manno- **107** bromide derivatives into the respective thioglycosides[35] **110**, **111** and **112**. The synthesis of an SBox glycoside having nonparticipating groups was achieved by deacetylation and subsequent benzylation of **32** to afford the respective thioglucoside **113**.[57] Alternatively, compound **113** was obtained in 75% yield when 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucpyranosyl bromide was treated with HSBox **30** in CH_2Cl_2 in the presence of 1,8-bis(dimethylamino)naphthalene.[41] An alternative method for the synthesis of the thioglycosides **110**, **111** and **112** in 90–97% yields was developed by reacting KSBox with benzoylated glycosyl bromides **105**, **106** and **107**, respectively, in the presence of 18-crown-6 in acetone; the mannoside **112** was accompanied by its α-anomer as an α,β-anomeric mixture (1:1).[35] The glucoside benzoate **110** was also obtained when **30** was treated with NaH followed by **105** in acetonitrile,[26] whereas the galactopyranosyl bromide derivative **45**, under the same reaction conditions, gave the thiogalactoside, 2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-thiobenzoxazole, in addition to the respective galactonucleoside derivative, in 45 and 38% yield, respectively[26] (Scheme 13).

2.2.3. Five-membered heterocycles with three heteroatoms.

2.2.3.1. Thiotriazolyl (STr) glycosides. The coupling of a 3-mercapto-5-substituted-1*H*-1,2,4-triazole **114** with acetohalosugars was studied under various reaction conditions. Thus, the reaction of **114** with **44**–**46** in the presence of K_2CO_3 in DMF at room temperature overnight followed by heating for 2–4 h afforded the *N*,*S*-di-β-glycosides **115**–**117** in 72–75% yields. On the other hand, a regioselective formation of the respective β-thioglycosides **118**–**120** was achieved in 73–78% yields by performing the reaction in the presence of triethylamine.[59] Alternatively, compounds **115**–**117** and **118**–**120** were obtained under microwave irradiation within 3–5 min in better yields[59] than using conventional heating (Scheme 14).

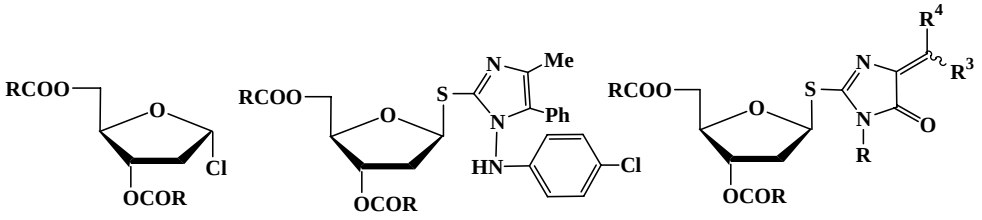
3-Phenyl-1,2,4-triazolin-5-thione **122** was reacted with acetobromoglucose **44** or acetobromoxylose **121** in the presence of sodium hydroxide to give the thioglucopyranoside



44 R^1 = Y = OAc, R^2 = H, X = Br
45 R^1 = H, R^2 = Y = OAc, X = Br
46 R^1 = OAc, R^2 = H, Y = NHAc, X = Cl

75 R = H
76 R = Ph

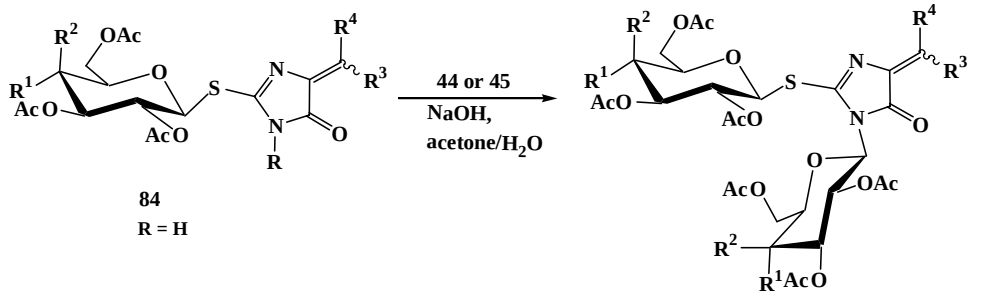
77 R^1 = OAc, R^2 = H, Y = O, R = H or Ph
78 R^1 = H, R^2 = OAc, Y = O, R = H or Ph
79 R^1 = H, R^2 = OAc, Y = NH, R = H or Ph



80 R = 4-ClC_6H_4
81 R = 4-MeC_6H_4

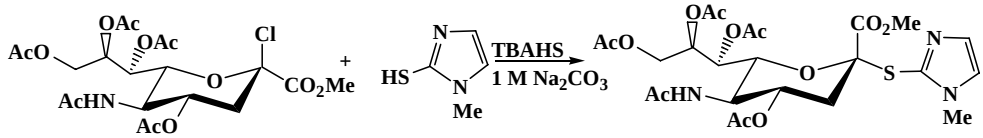
82 R = 4-ClC_6H_4

83 R = 4-MeC_6H_4
R^3 = H, R^4 = Ph, 2-thienyl, 3-indolyl



84
R = H

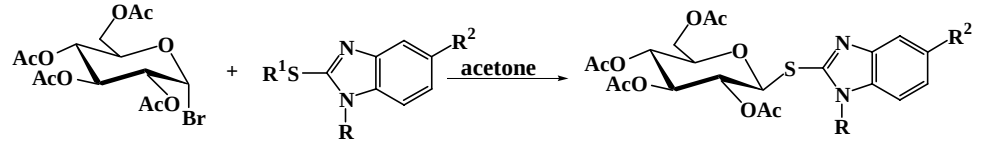
85
R^1 = OAc, R^2 = H



86

87

Scheme 10.

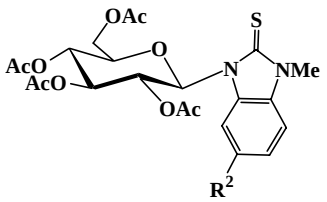


44

88 R = Me, R^1 = K, R^2 = H
89 R = R^1 = H, R^2 = NO_2

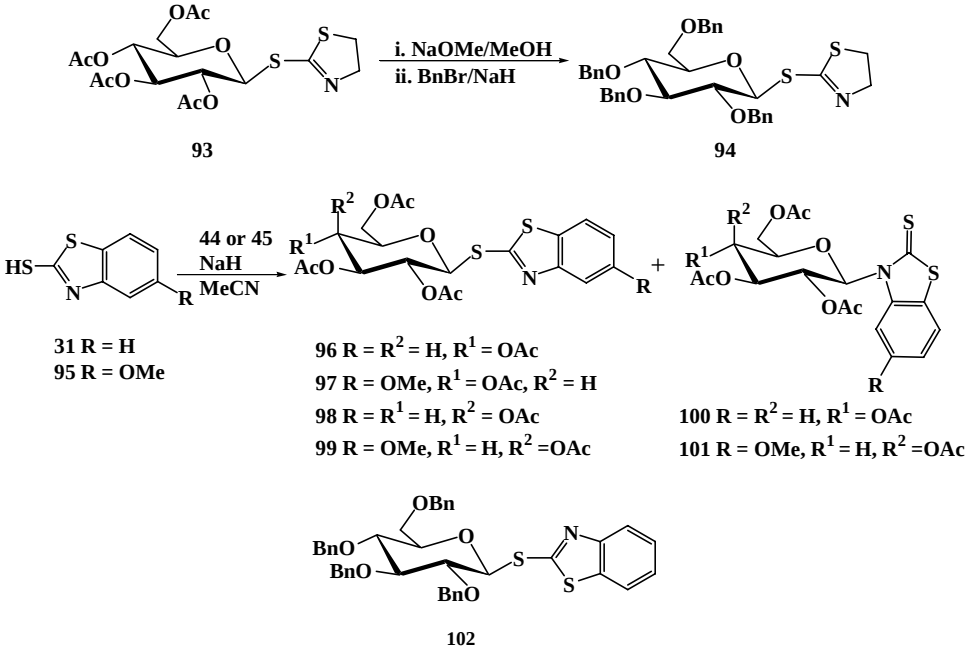
90 R = Me, R^2 = H
91 R = H, R^2 = NO_2

+



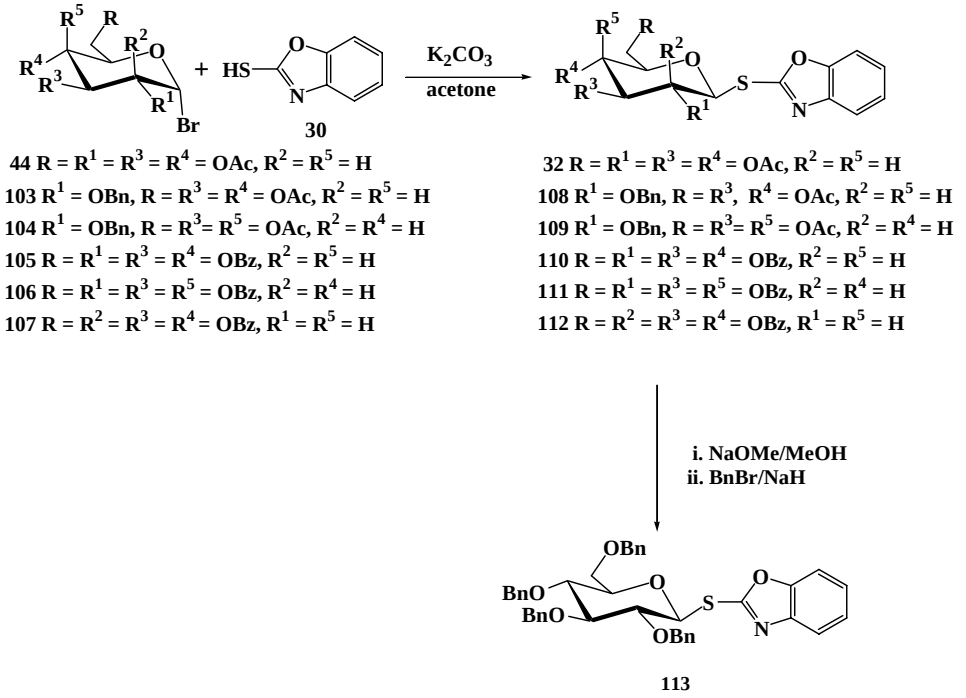
92 R^2 = H

Scheme 11.



93 94 102

Scheme 12.

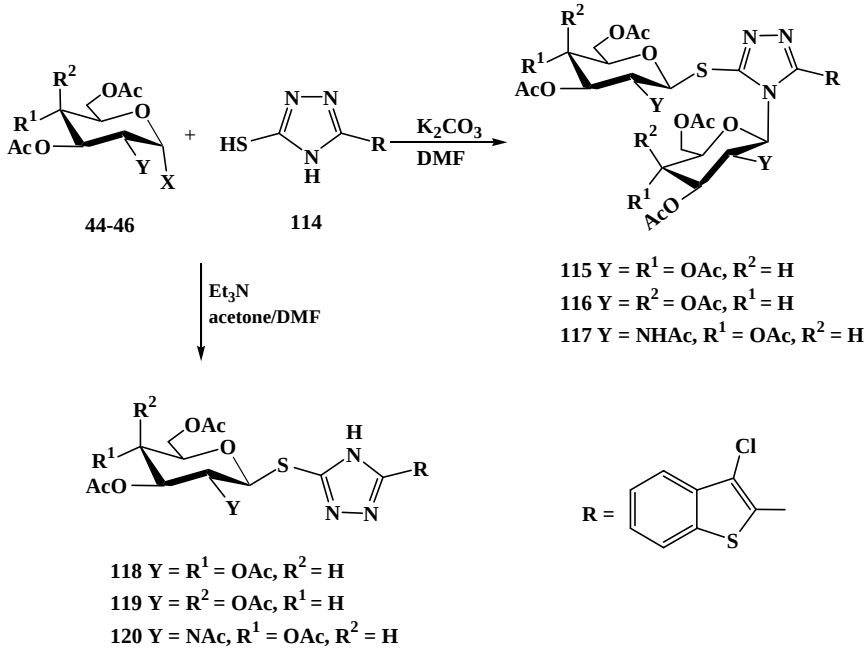


30 113

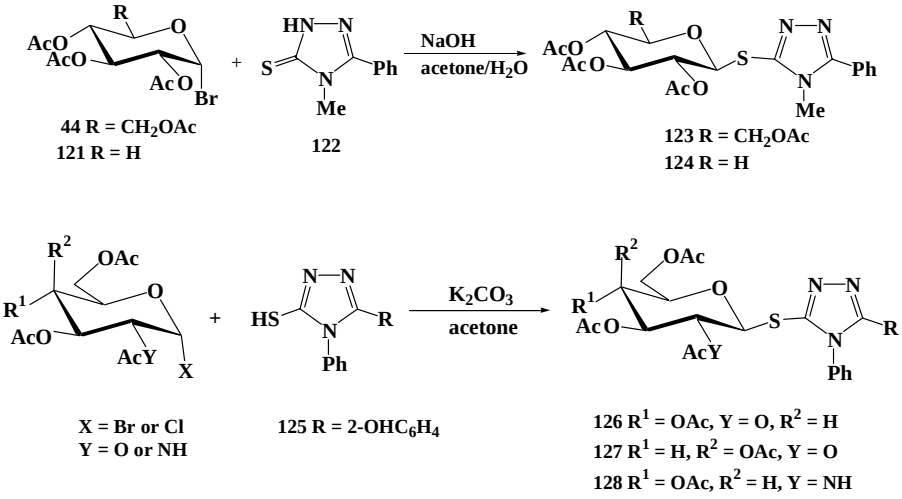
Scheme 13.

123 and thioxylopyranoside **124**, respectively.[60] Reaction of 3-(2-hydroxyphenyl)-5-mercapto-4-phenyl-1,2,4-triazole **125** with acetohalosugars in acetone in the presence of potassium carbonate at room temperature afforded the respective β-thioglycosides **126**–**128**[53] (Scheme 15). Better yields were obtained in shorter reaction times when the microwave technique was applied to these reactions.[53]

2.2.3.2. Thiooxadiazolyl (SOxd) and thiothiadiazolyl (SThd) glycosides. Condensation of acetobromoglucose **44** with 5-aryl-1,3,4-oxadiazoline- or thiadiazolin-2-thiones in the presence of potassium hydroxide in acetone gave the thioglucosides **129**, and the *N*-glucosyl derivatives **130** in poor yield.[61] When 5-phenyl-1,3,4-oxa or thiadiazolin-2-thione was, however, coupled with **44** or acetobromoxylose **121** in the presence of sodium hydroxide in acetone, they gave only the *S*-glycoside derivatives **129** or **131** (Ar=Ph).[60,62] Treatment of **129** or **131** with mercuric bromide in toluene afforded the *N*-nucleosides **130** and **132**, respectively.[61,62]



Scheme 14.



Scheme 15.

Reaction of 1,3,4-thiadiazolidine-2,5-dithione **133** with acetobromoglucose **44** gave a mixture of the dithioglucoside **134** and the *N*,*S*-diglucoside **135**, whereas, when **133** was used in excess, the product was the monothioglucoside **139**. Similarly, the methylthio analogue **136** gave the respective thioglucoside **137** and the *N*-glucoside **138**.[63]

The potassium salts of 2-mercapto-4-methyl- or 2-mercapto-4-phenyl-5-thiono-1,3,4-thiadiazoline were reacted with acetobromoglucose **44** under various conditions to give 4-methyl- or 4-phenyl-5-thiono-1,3,4-thiadiazolinyl-2-(tetra-*O*-acetyl-β-D-thioglucopyranoside) **140** or **141**, respectively.[64] The acetyl–thioglucoside **141** has been oxidized to the corresponding sulphone **142**, either by hydrogen peroxide or potassium permanganate[64] (Scheme 16).

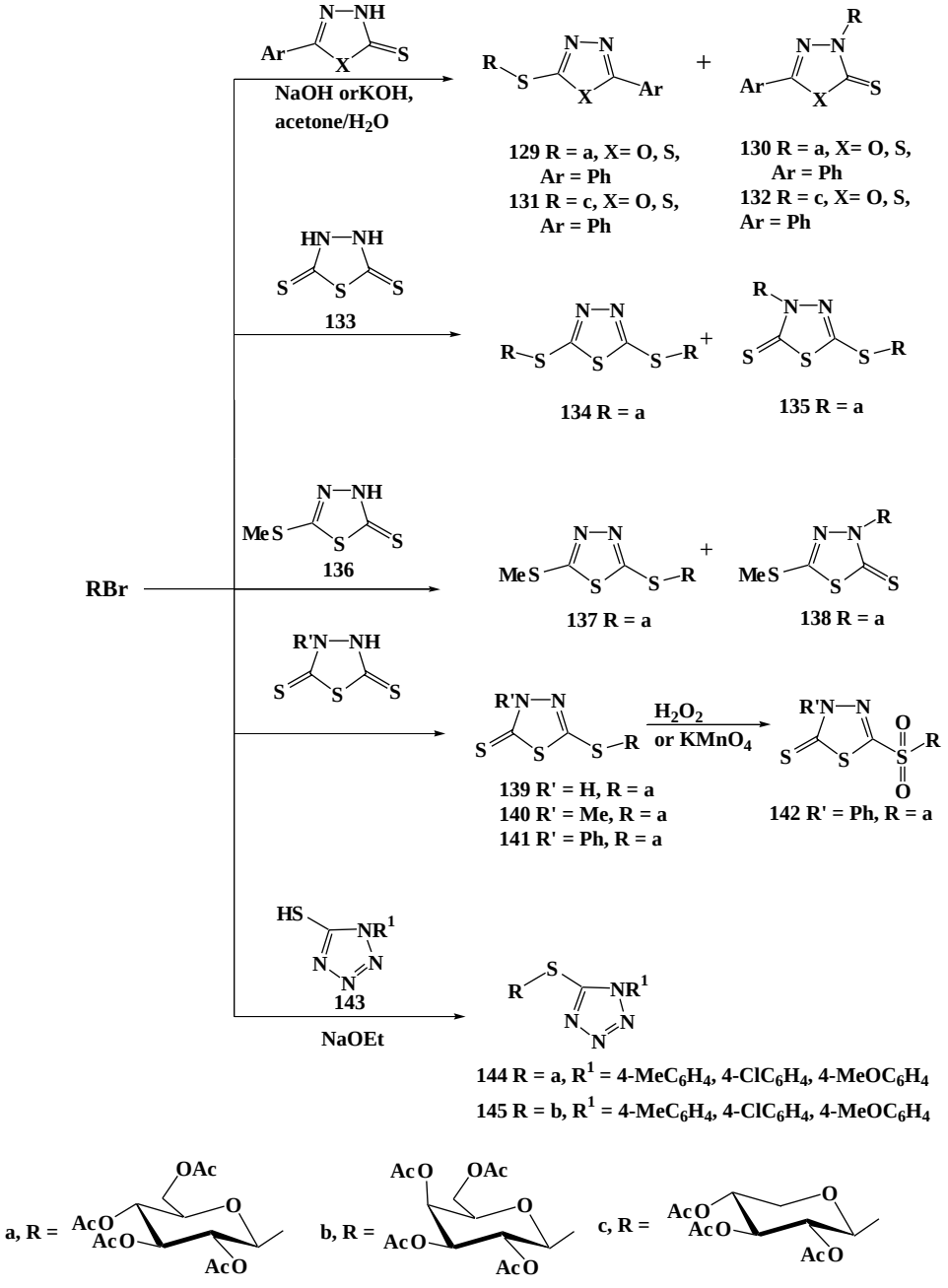
2.2.4. Five-membered heterocycles with four heteroatoms.

2.2.4.1. Thiotetrazolyl (STe) glycosides. The (tetrazol-5-yl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucosides **144** and -galactosides **145** were obtained by the reaction of 1-substituted-5-mercaptotetrazoles **143** with acetobromoglucose **44** or acetobromogalactose **45**, respectively, in the presence of sodium ethoxide[65] (Scheme 16).

2.2.5. Six-membered heterocycles with two heteroatoms.

2.2.5.1. Thiopyridazinyl (SPd) glycosides. Condensation of 4-mercaptopyridazine with acetobromoglucose **44** in the presence of potassium hydroxide in acetone afforded a mixture of *S*- and *N*-glycosides **146** and **147**, respectively.[66]

When ribofuranosyl chloride **81** was reacted with thiopyridazine derivatives **148** in the presence of pyridine, the



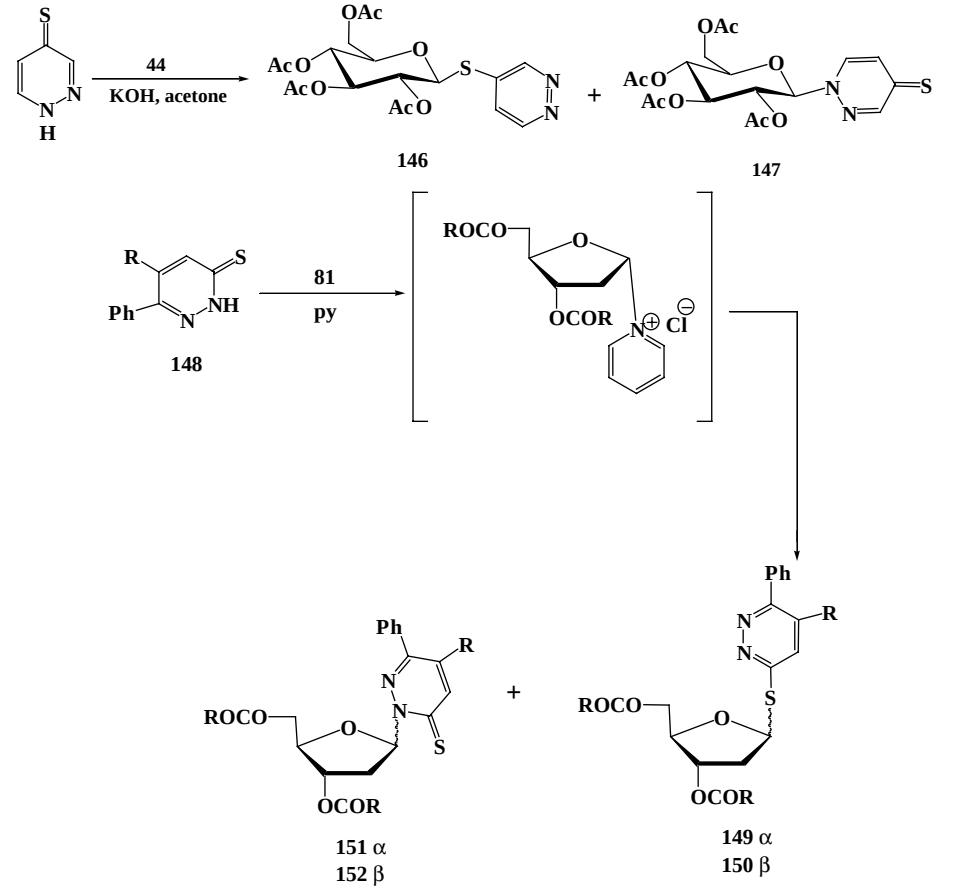
Scheme 16.

simultaneous formation of a pyridinium chloride as an intermediate was formed, which coupled with **148** to give a mixture of the α and β *S*- and *N*-glycosides **149–152**[67,68] (Scheme 17).

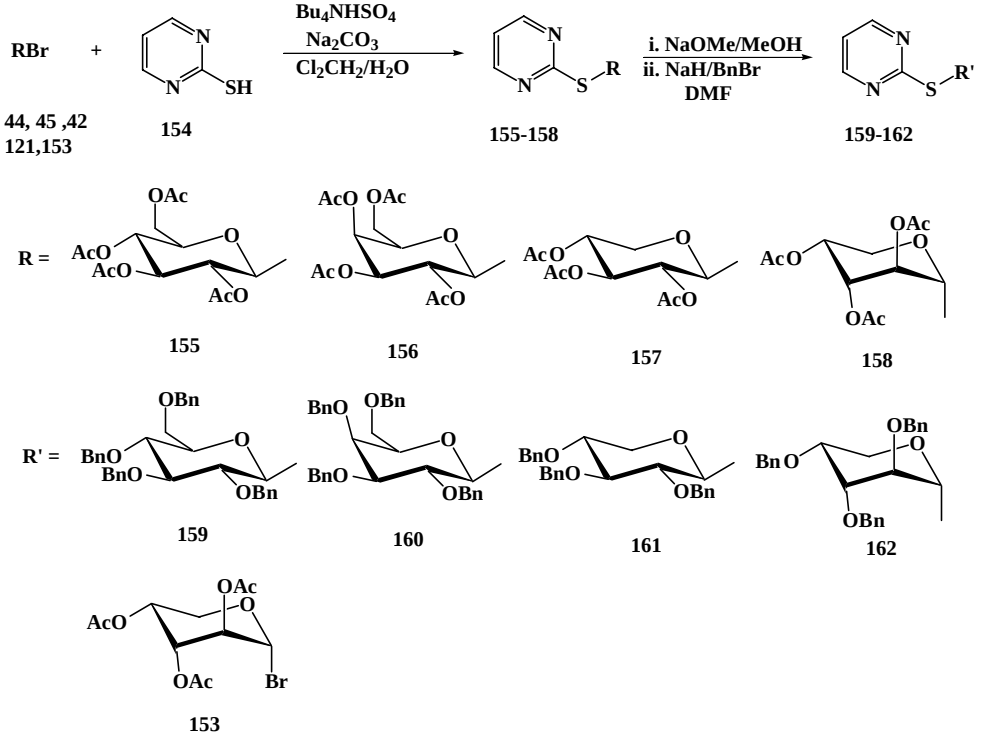
2.2.5.2. Thiopyrimidinyl (SPm) glycosides. Phase-transfer reaction conditions allowed the use of the free thiol and non-polar solvents[69–71] to give high yields of the corresponding 1,2-*trans*-thioglycosides from acetylated bromosugars. Thus, treatment of acetobromosugars **44**, **45**, **121** and **153** with 2-mercaptopyrimidine **154** in the presence of tetrabutylammonium hydrogen sulfate and sodium carbonate in a mixture of dichloromethane and water afforded the corresponding thioglycopyranosides **155–158**. Increasing the molar ratio of **154** to 3 mol equiv gave an almost quantitative yield of **155** and **156**.[13] Deacetylation followed by benzylation with benzyl bromide afforded the respective benzyl derivatives **159–162**[13] (Scheme 18).

Similarly, 2,3,4,6-tetra-*O*-acetyl-β-L-fucopyranosyl bromide **163** under phase-transfer conditions afforded the β-L-fucothiopyranoside derivative **164**, which, upon deacetylation followed by isopropylidenation, formed **165** that benzylated and hydrolyzed to give **166**. Selective benzylation of **166** with benzyl bromide via its dibutyltin complex gave **167**. Acylation of **167** by acetic anhydride or stearoyl chloride gave the respective 4-*O*-acetyl **168** or 4-*O*-stearoyl **169** derivatives[72] (Scheme 19).

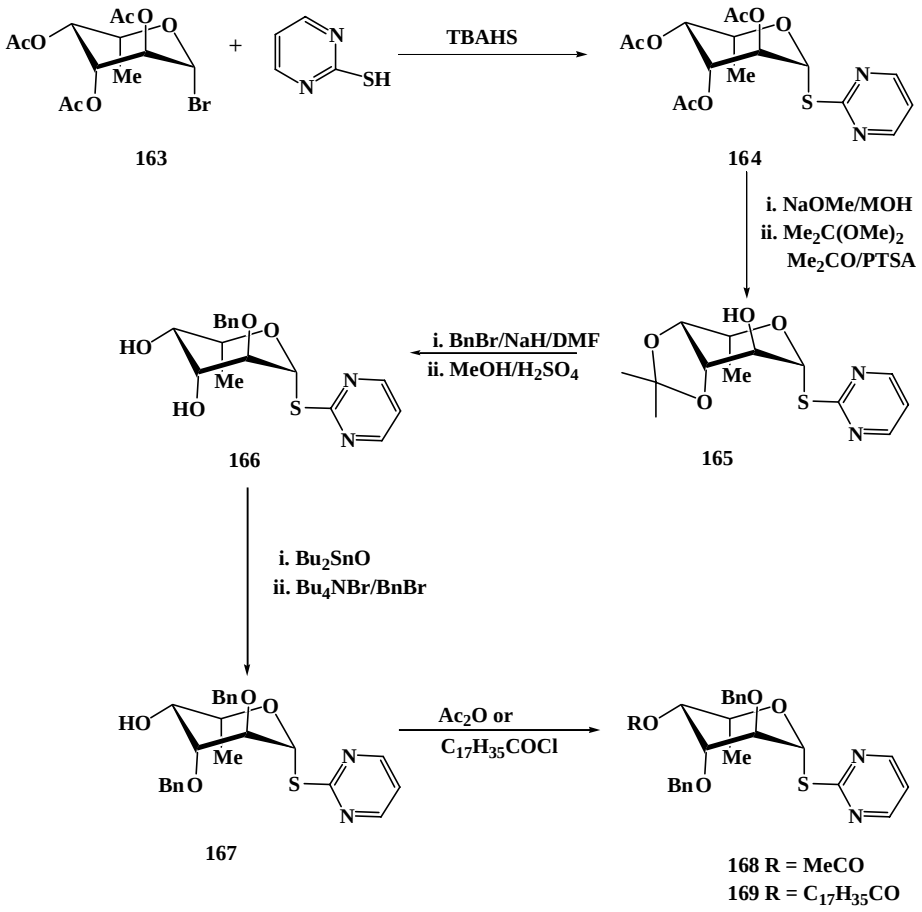
Reaction of 2-deoxy-ribofuranosyl chloride **81** with bis(trimethysilyl)-2-thiouracil **170** in 1,2-dichloroethane at room temperature afforded the respective



Scheme 17.



Scheme 18.



Scheme 19.

β-thioribfuranoside **171**. When the reaction was catalyzed with $SnCl_4$ in CH_2Cl_2 at −78 °C, it afforded the α-anomer **172** in 90% purity (remainder **171**).[73] Thioglycosides **43** and **174** were prepared by reacting 4-mercapto-2-methylthiopyrimidine with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide **173** (R=Ac, X=Br) and acetobromoglucose **44**, respectively, in the presence of K_2CO_3 in acetone.[38]

Reaction of acetobromoglucose with 6-mercaptouracil took place in aqueous acetone in the presence of sodium hydroxide to give **175** and with 6-mercaptocytosine in the presence of potassium carbonate to give **176**.[74]

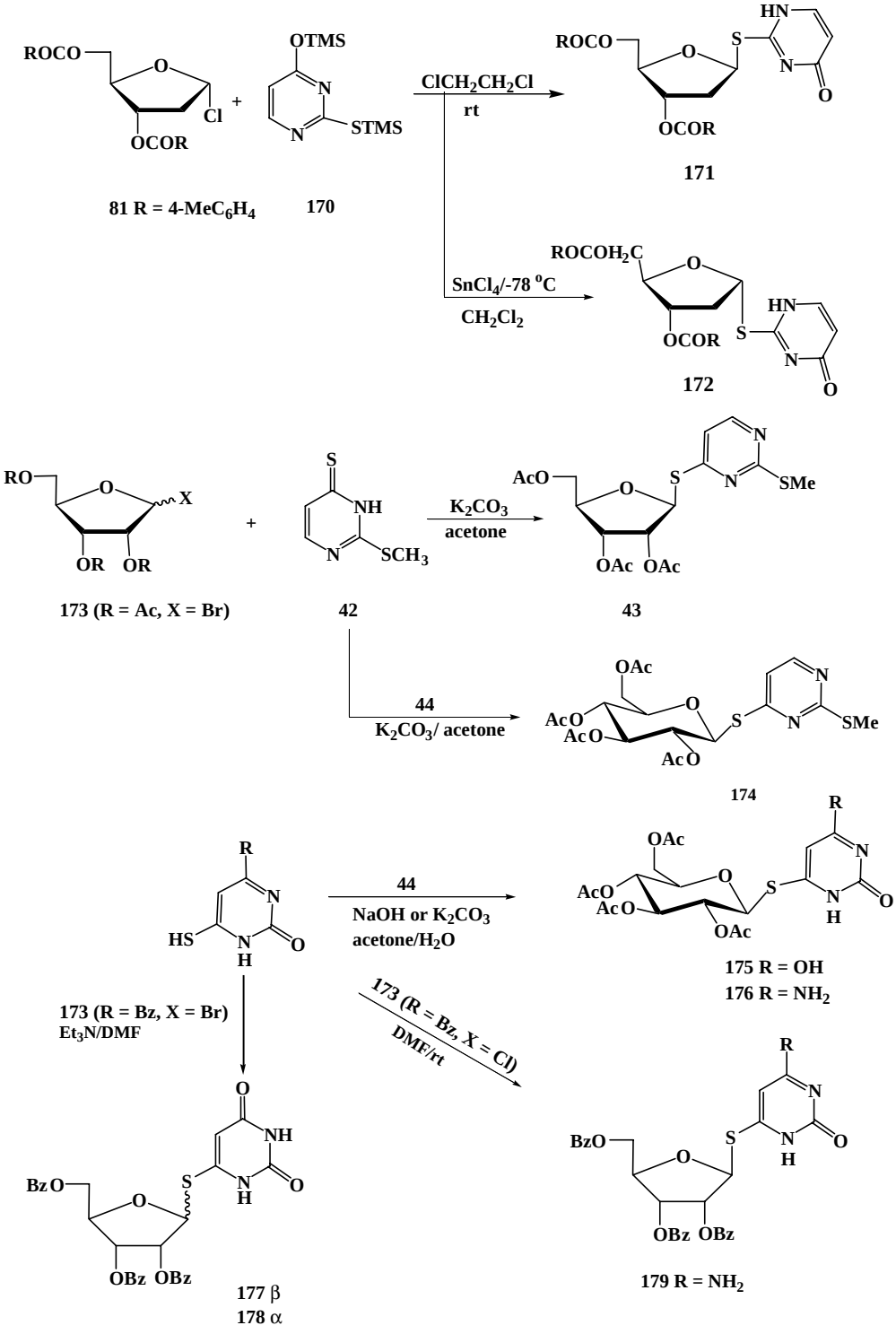
The reaction of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide **173** (R=Bz, X=Br) with 5-mercaptouracil in DMF in the presence of Et_3N as a catalyst yielded a mixture of the β-anomer **177** as a major product (31.5%) and the α-anomer **178** as a minor product (14.6%).[75] When 2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl chloride **173** (R=Bz, X=Cl) was coupled with the sodium salt of 6-mercaptouracil in DMF at room temperature, it gave the β-thioriboside[74] **179** (Scheme 20).

Reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or -α-D-galacto-pyranosyl bromides (**44** and **45**) with thiopyrimidin-4-one derivatives **180** in the presence of aqueous KOH in acetone or with the sodium salts of **180** in DMSO gave the corresponding bisglycosides **181**. Deacetylation of **181** with ammonia in methanol cleaved the *S*-glycosyl residue to give the N^3-glycosylated analogues[76a] **182**. When the piperidinium salts of **183** were coupled with **44** or **45** in aqueous acetone,[76b] gave a mixture of nucleosides **184** and **185**, resulted.

Coupling of the potassium salts of 4-aryl-7-(substituted benzylidene)-tetrahydrocyclopentapyrimidine-2(3*H*)-thiones **186** with acetobromoglucose **44** or acetobromogalactose **45** in aqueous potassium hydroxide afforded the thioglucosides **187** and thiogalactosides **188**, respectively[77] (Scheme 21).

2.2.5.3. Thiopyrazinyl (SPz) glycosides. Reaction of the sodium salts of mercaptopyrazine derivatives **189** with acetobromoglucose **44** in the presence of sodium hydroxide in acetone gave the corresponding *S*- and *N*-glucosides[78] **190** and **191** (Scheme 22).

2.2.5.4. Thioquinazolinlyl (SQz) glycosides. A series of acetylated glycosides of 2-thio-4(3*H*)-quinazolinones and their thiono analogues, including D-glucose, D-galactose, D-xylose and L-arabinose derivatives, have been synthesized by the reaction of 6,8-disubstituted 3-aryl-2-thio-4(*H*)-quinazolinones and quinazolinethiones **192** with tetra-*O*-acetylglycopyranosyl bromides in the presence of potassium hydroxide or potassium carbonate in acetone to yield the corresponding *S*-glycosides **193**.[79] 3-Phenylamino-2-thioxo-3*H*-quinazolin-4-ones were also reacted with acetylglycosyl bromides in the presence of NaH in DMF at room temperature to yield the *S*-glycoside derivatives **194**[80]



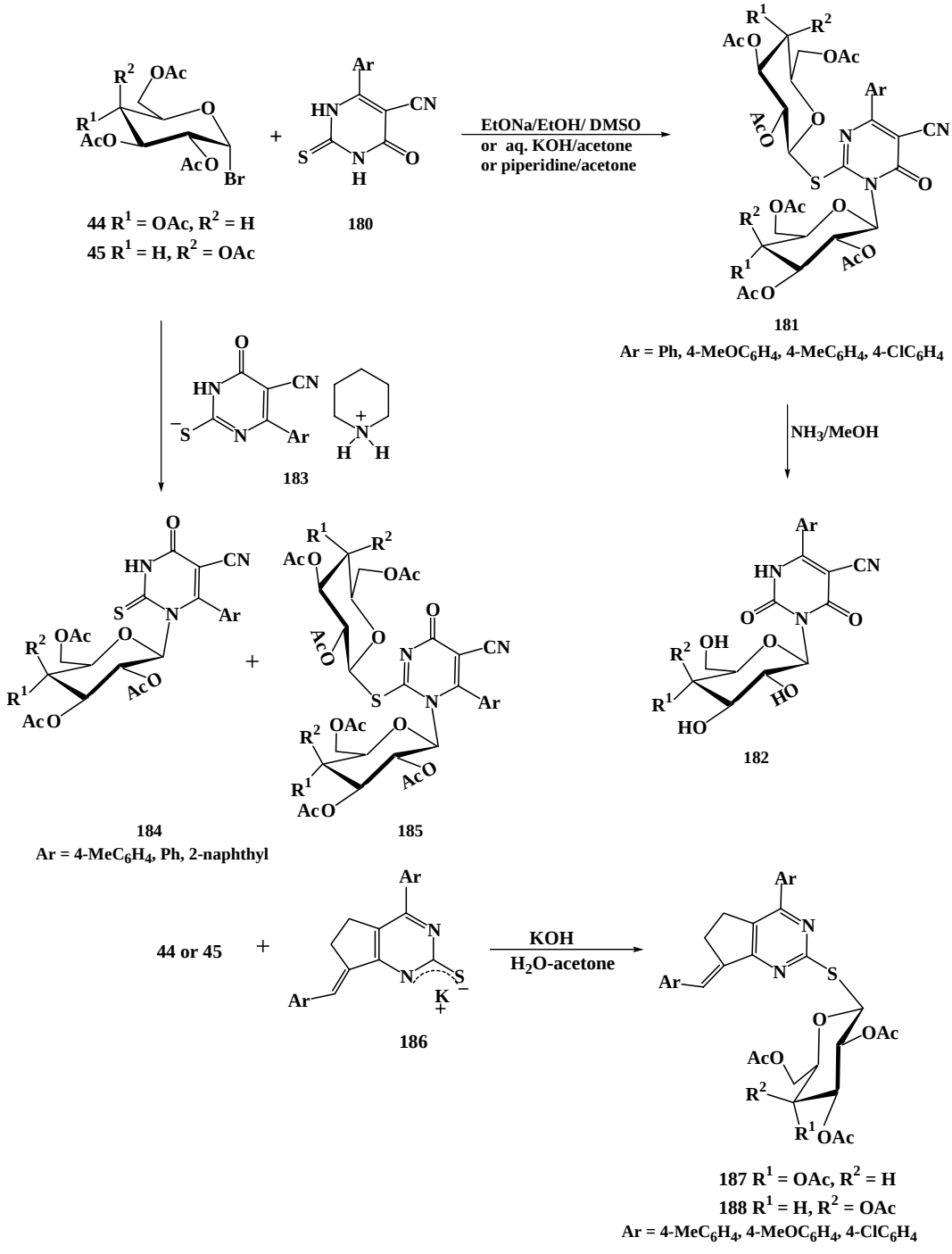
Scheme 20.

(Scheme 23). Oxidation of **193** and **194** with potassium permanganate or hydrogen peroxide in acetic acid gave the respective sulphones **195**.[80]

On the other hand, 6-substituted-2-aryl-4(3*H*)-quinazolinethiones **196** were coupled with acetobromoglucose **44** in the presence of potassium hydroxide in aqueous acetone to give the *N*- and *S*-glucosides **197** and **198** in poor yield[81] (Scheme 24). Oxidation of the thioglucosides **198** with potassium permanganate in acetic acid afforded the sulphones **199**.[79–81]

Treatment of 3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acrylic acid with glucopyranosyl bromide in an alkaline medium afforded the respective *S*- and *N*-glucosides.[82]

2.2.5.5. Thiobenzothiazinyl (SBtz) glycosides. When **44** or **45** were reacted with 3,1-benzothiazin-2,4-dithione



44 R^1 = OAc, R^2 = H
45 R^1 = H, R^2 = OAc

180

181
Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4

183

182

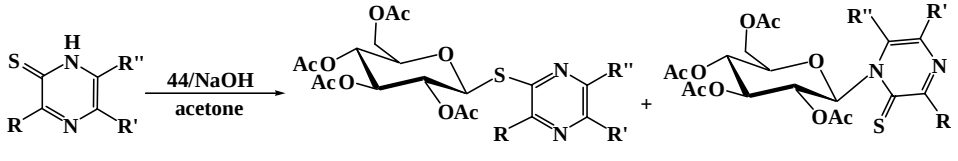
184
Ar = 4-MeC_6H_4, Ph, 2-naphthyl

185

186

187 R^1 = OAc, R^2 = H
188 R^1 = H, R^2 = OAc
Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

Scheme 21.

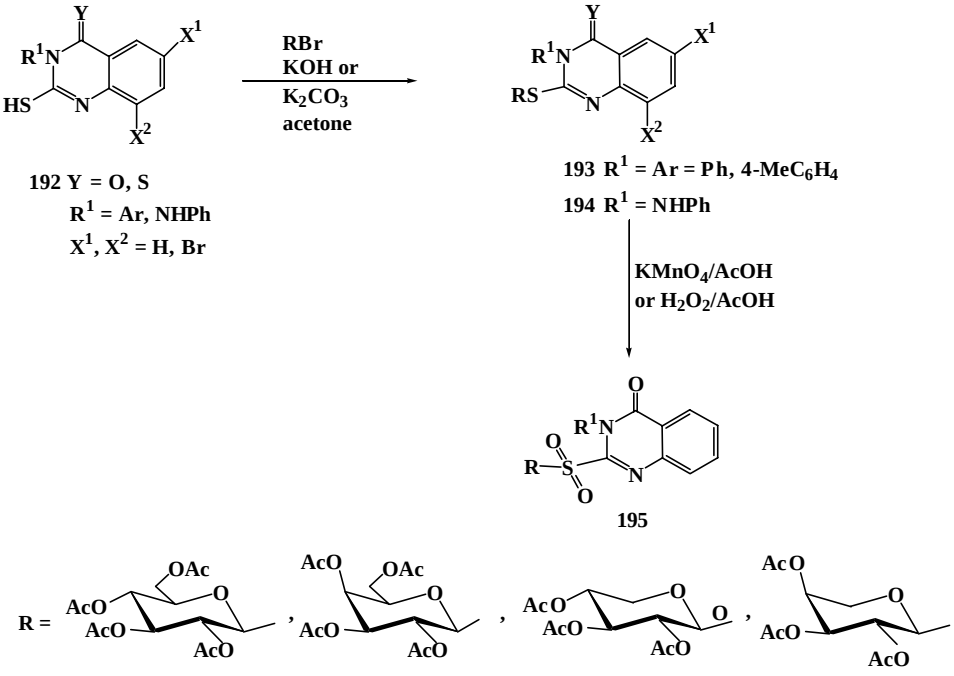


189

190

191
R = H, Ph
R` = H, Ph
R`` = H, Ph

Scheme 22.



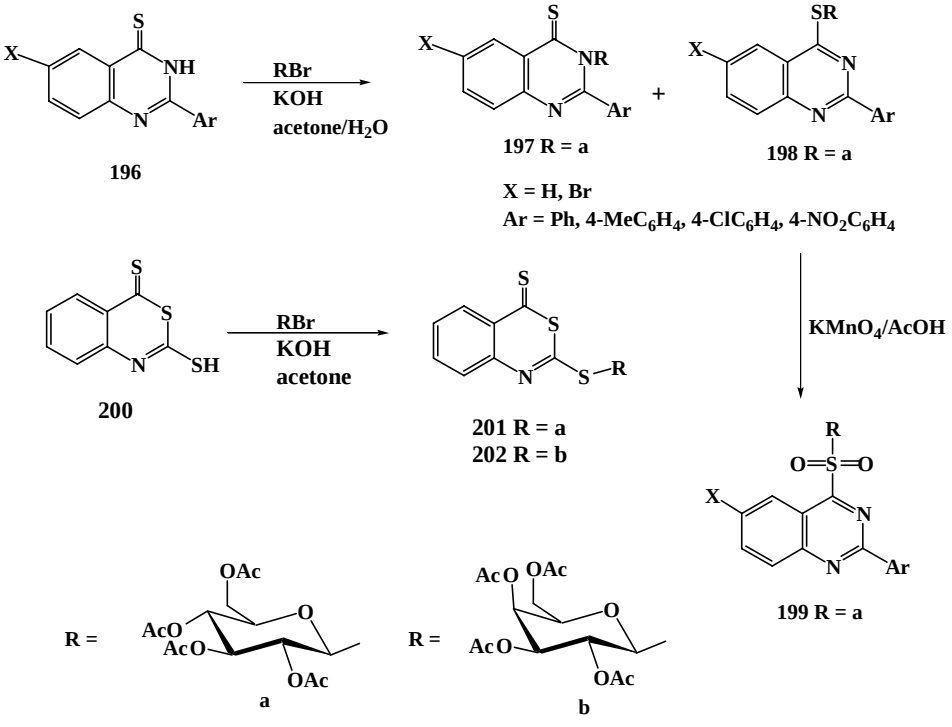
Scheme 23.

200, (tetra-*O*-acetyl-β-D-gluco- or -β-D-galacto-pyranosyl)-thio-3,1-benzothiazine-4-thione[79] **201** and **202**, respectively, were obtained (Scheme 24).

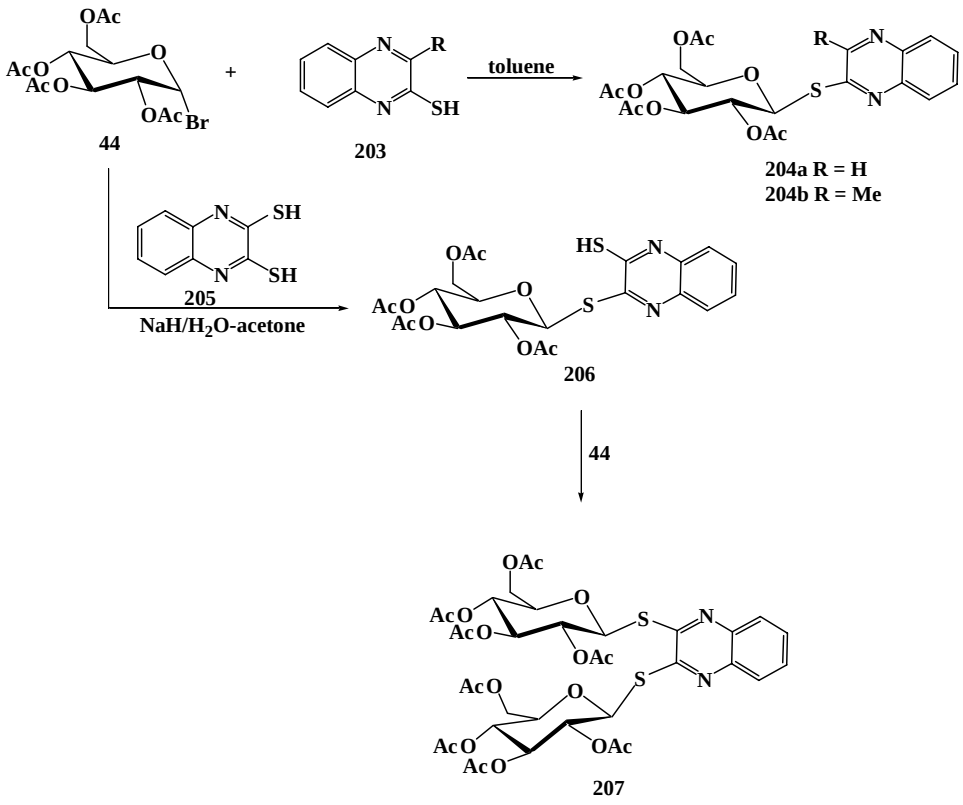
2.2.5.6. Thioquinoxalinyl (SQx) glycosides. Reaction of 2-mercaptoquinoxaline derivatives **203** with acetobromoglucose **44** in toluene afforded the quinoxaline β-thioglucosides **204**. Coupling of equimolar amounts of 2,3-dimercaptoquinoxaline **205** and **44** in the presence of sodium hydride in aqueous acetone gave the β-monothioglucoside **206**, while the bisthioglucoside **207** was obtained when **205** was reacted with two molar equivalents of **44** under the same reaction conditions[83] (Scheme 25).

2.2.6. Six-membered heterocycles with three heteroatoms.

2.2.6.1. Thiotriazinyl (STz) glycosides. Glycosylation of 3-mercapto-1,2,4-triazine **208** with **44** was achieved in aqueous acetone containing sodium hydroxide to give **209** in 98% yield.[84]



Scheme 24.

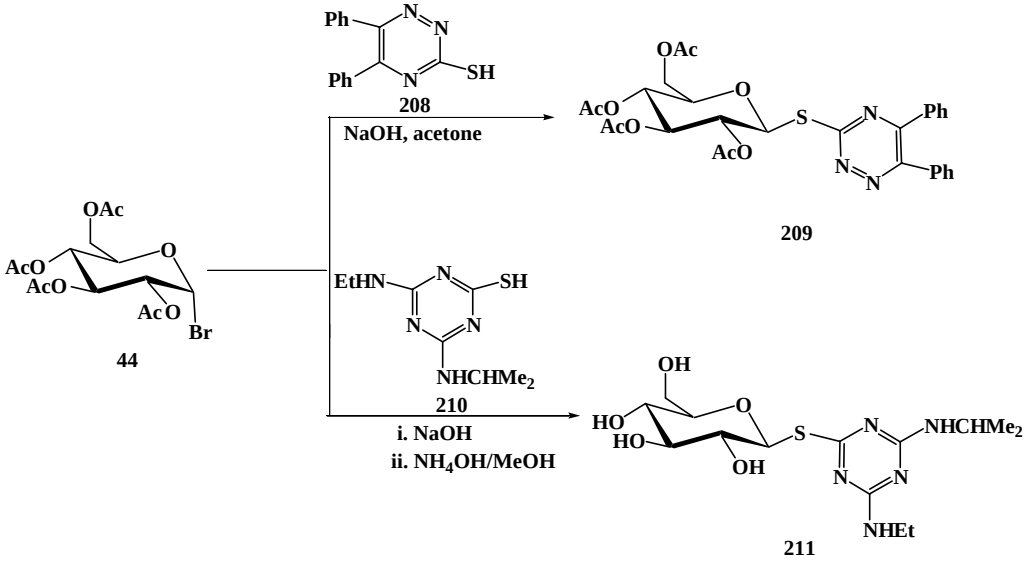


Scheme 25.

Acetobromoglucose **44** was also reacted with 2-mercaptotriazine **210** in the presence of sodium hydroxide in acetone at reflux, followed by deacetylation using ammonium hydroxide, to give the thioglucoside **211**[85] (Scheme 26).

2.2.7. Biheterocycles. Simultaneous glycosylation and deacetylation have taken place when 6-mercaptopurine **212** was condensed with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or -α-D-galacto-pyranosyl chloride in the presence of ammonium hydroxide to give 6-purinyl β-D-gluco or β-D-galactopyranoside[86,87] **213** and **214**, respectively. Similarly, 1-chloro-2,3,4-tri-*O*-acetyl-L-rhamnopyranose **215** gave 6-purinyl thiorhamnopyranoside **216**,[87] and **217** gave the ammonium salt of 6-purinyl thioglucofuranuronide **218**.[87]

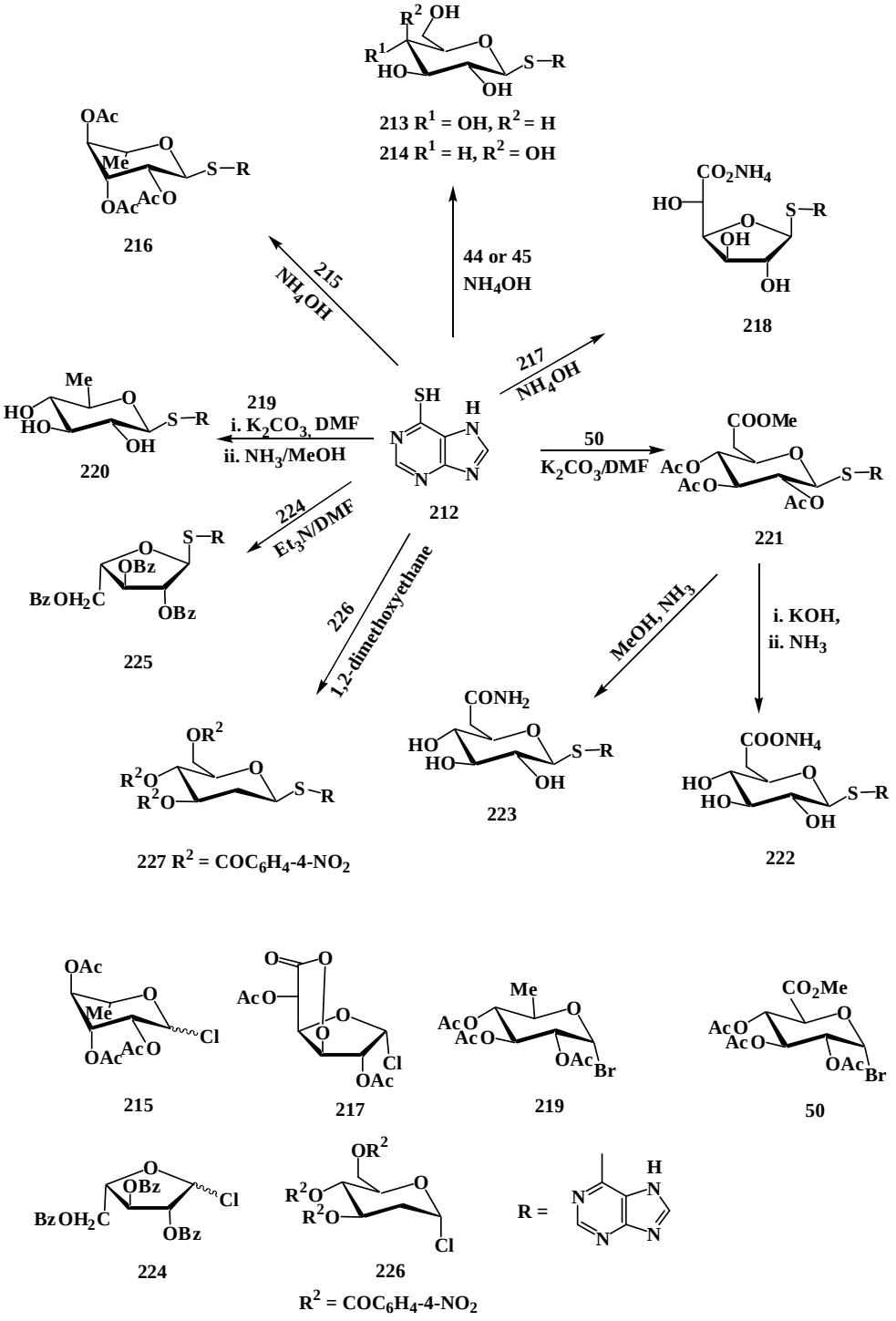
Purin-6-yl 6-deoxy-1-thio-β-D-glucopyranoside **220** was obtained from the reaction of **212** with 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranosyl bromide **219** in the presence of potassium carbonate, followed by deacetylation using ammonia in methanol.[88] Similarly, treatment of **212** with



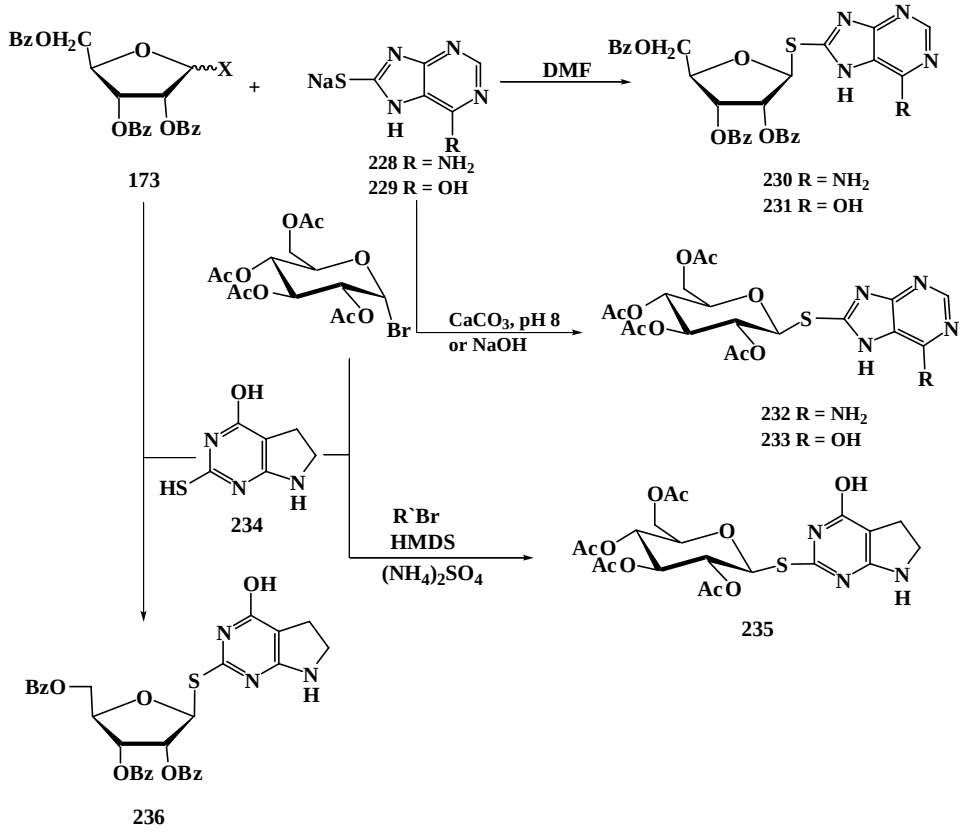
Scheme 26.

methyl 1-deoxy-1-bromo-2,3,4-tri-*O*-acetyl-α-glucopyranosyluronate (**50**), yielded the corresponding purine thioglucoside **221**, which in turn, was transformed into the ammonium salt **222** and the amide **223**.[89] Base-catalyzed glycosylation of **212** with tri-*O*-benzoyl-L-arabinofuranosyl chloride **224** was carried out in the presence of triethylamine in DMF to afford α-L-arabinothiofuranoside **225** in 28% yield.[90] The sodium salt of 6-mercaptopurine was coupled with 2-deoxy-3,4,6-tri-*O*-(*p*-nitrobenzoyl)-α-D-arabinohexopyranosyl chloride **226** in 1,2-dimethoxyethane to give **227**[91] (Scheme 27).

A series of 8-adenine thioglycosides were obtained from condensation of the sodium salt of 8-mercapto-adenine **228** and -hypoxanthine **229** with glycosyl halides. Thus, the reaction of **228** or **229** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride **173** (R=Bz, X=Cl) in DMF afforded the β-thioribfuranosides **230** and **231**, respectively. Reaction of acetobromoglucose with **228** was carried out in the presence of $CaCO_3$ at pH 8 to give **232**, whereas 8-mercaptohypoxanthine **229** was coupled with acetobromoglucose in the presence of NaOH to give the β-thioglucopyranoside **233**[74] (Scheme 28).



Scheme 27.



Scheme 28.

Glycosylation of mercaptopyrrolopyrimidine **234** with either tetra-*O*-acetyl-α-D-glucopyranosyl bromide or tri-*O*-benzoyl-D-ribofuranosyl bromide in the presence of $(Me_3Si)_2NH$ containing $(NH_4)_2SO_4$ gave the β-glycosides **235** and **236**, in 62 and 73% yield,[92] respectively, (Scheme 28).

The reaction of 4-aryl-1-thioxo[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones (**237**) with acetylated glycosyl bromides (D-gluco-, D-galacto- and D-xylo-) in the presence of potassium carbonate in acetone at room temperature afforded a mixture of the corresponding β-*S*-glycoside derivatives **238** and β-*N*-glycoside derivatives **239**. Oxidation with *m*-chloroperbenzoic acid (CPBA) of **238** yielded the corresponding sulphones **240**, whereas the *N*-glycosyl derivatives **239** yielded the 1-oxo-derivatives **241**[93] (Scheme 29).

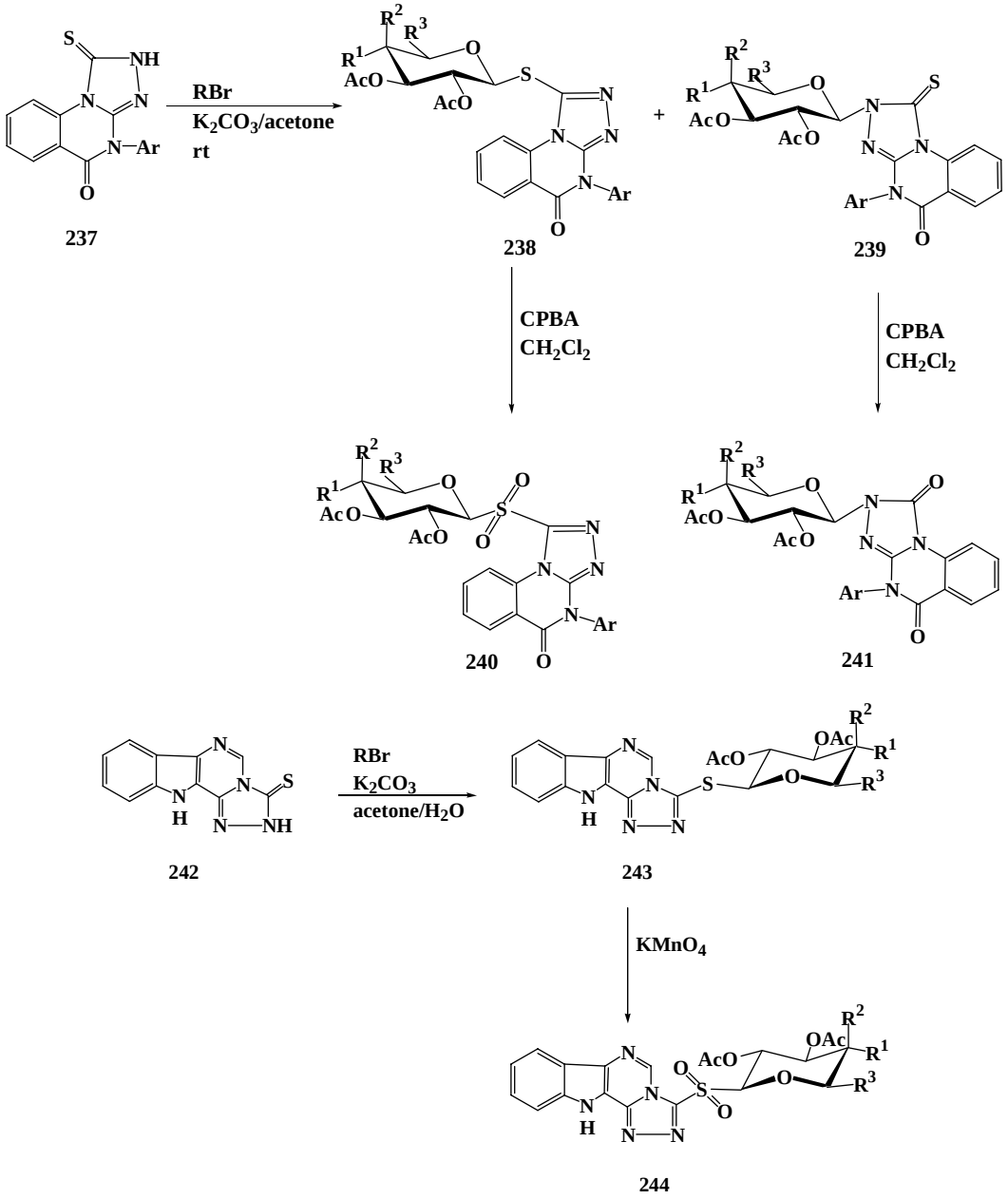
Similarly, reaction of 3-thioxo-11*H*-1,2,4-triazolo[4,3-*c*]-pyrimido[5,4-*b*]indole **242** with per-*O*-acetylglycopyranosyl halides gave the respective β-thioglycosides **243**, oxidation of which with potassium permanganate yielded the corresponding sulfones **244**[94] (Scheme 29).

2.3. 1-*O*-Trichloroacetimidates as glycosylating agents

Thioglycosides can be effectively synthesized from trichloroacetamidates as glycosyl donors using hard Lewis acids such as $BF_3 \cdot Et_2O$ or TMSOTf as promoters.[95] The α-anomer thioglucoside **248** was synthesized from 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose **245** by transformation into the β-trichloroacetimidate **246**, which, upon treatment with 2-mercaptopyridine **2** in the presence of $BF_3 \cdot Et_2O$, gave the α-2-pyridyl thioglucoside **247**. Subsequent reduction of the azide and acetylation gave **248**, oxidation of which with MCPBA led to the glycosyl 2-pyridyl sulfone **249**[96] (Scheme 30).

2.4. Hemiacetals as glycosylation agents

In recent years, a number of methods to synthesize thioglycosides from hemiacetals have been reported. Hence, the 2-pyridyl 2,3,4-tri-*O*-benzyl-α,β-L-rhamnopyranoside **51** and α,β-L-fucopyranoside **253**[97] were synthesized from **250** and **252**, respectively, using bis(2-pyridyl)disulfide (**251**) in the presence of Bu_3P. Treatment of a fully protected hemiacetal monosaccharide such as 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **254** with **251** in the presence of triethylphosphine in acetonitrile gave an α:β mixture of 2′-pyridyl 2,3:5,6-di-*O*-isopropylidene-1-thio-D-mannofuranoside **255** in 8 and 79% yield, respectively. Under the same reaction conditions, 2,3-*O*-isopropylidene-D-ribofuranose **256** afforded only the α-anomer **257**.[98] On the other hand, the thioriboside derivatives **259** and **261** were obtained as α:β mixtures (1:1 and 3:1) when **258** and **260** were reacted under the same conditions,[99] and for the reaction of **259** in the presence of *p*-toluenesulfonic acid.[99] The 2-pyridyl 2,3:5,6-di-*O*-isopropylidene-1-thio-β-mannofuranoside **255**, 2-pyridyl-3,5-di-*O*-benzoyl-2-deoxy-1-thio-D-ribofuranoside **263** and 2-pyridyl 2,6-dideoxy-3-methoxy-4-*O*-acetyl-1-thio-L-arabinopyranoside **265** were also synthesized from **262**

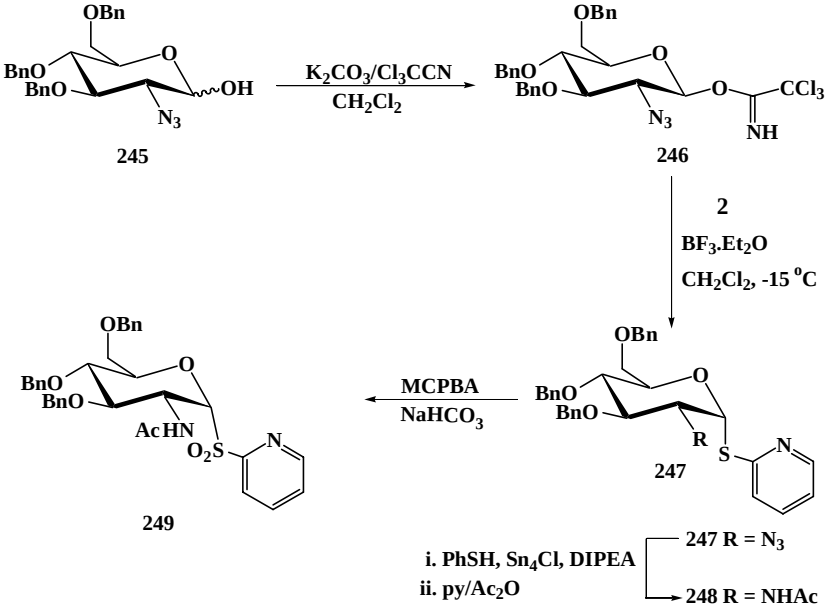


Scheme 29.

and **264**, respectively.[42] Per-*O*-benzylated 2-pyridyl 1-thio-α/β-D-gluco- **269**, galacto- **270** and manno- **271** pyranosides were prepared from the corresponding 2,3,4,6-tetra-*O*-benzyl-D-glycopyranose derivatives **266–268** with 2,2′-dipyridyl disulfide **251** in the presence of a trialkylphosphine. Thus, 2-pyridyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α/β-D-glucopyranoside **269** was obtained in a 1:3 α:β mixture when triethylphosphine was used,[98] whereas, with tri-*n*-butylphosphine in methylene chloride, a 2:3 α:β mixture was obtained.[43,97] It was reported,[99] however that, under the same reaction conditions, only the β-isomer was isolated. Using $^{n}Bu_3P$ in the coupling of benzylated galactopyranose **267** and mannopyranose **268** with **251**, afforded the thiopyridyl derivatives **270–271** in 1:1 α:β mixtures.[43]

Alternatively, compounds **269** and **270** were obtained by deacetylation of the corresponding per-*O*-acetyl derivatives followed by benzylation.[43]

2-Pyridyl 1-thio-α/β-L-arabinopyranoside **273** was obtained by acid hydrolysis of methyl β-L-arabinoside **272** followed by treatment with dipyridyl disulfide in the presence of Bu_3P in CH_2Cl_2[100] (Scheme 31).



Scheme 30.

2′-Benzothiazolyl 2,3:5,6-di-*O*-isopropylidene-1-thio-β-D-mannofuranoside **275** was obtained in good yield when 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **254** was treated with bis(2-benzothiazolyl)disulfide **274** and Et_3P in acetonitrile.[98] On the other hand, under the same reaction conditions 3,4-*O*-isopropylidene-L-arabinose **276** afforded a mixture of the α,β anomers of **277**[98] (Scheme 32).

Under phase-transfer conditions, an α,β mixture (1:3) of thioglucoside **278** was obtained when 2-mercaptobenzothiazole was reacted with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **266** in the presence of tosyl chloride and tetrabutylammonium chloride (TBAC) in benzene and 50% aqueous sodium hydroxide.[101] In this method, a good leaving group was generated from the anomeric hydroxyl group by reaction with TsCl. Under the same reaction conditions, the α,β mixture of 2-benzothiazolyl-1-thio-xyloside **279** was prepared from the respective sugar[101] (Scheme 32).

Treatment of **266** with 5,5′-bis(1-phenyl-1*H*-tetrazol-5′-yl)dithiocarbonate in the presence of triethylamine or 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in acetonitrile afforded the *S*-glucosides **280** and **281** as the main products and a trace of **282**. DMAP was superior to triethylamine as a catalyst (Scheme 33).[102]

2.5. 1-Thiosugars as glycosylating agents

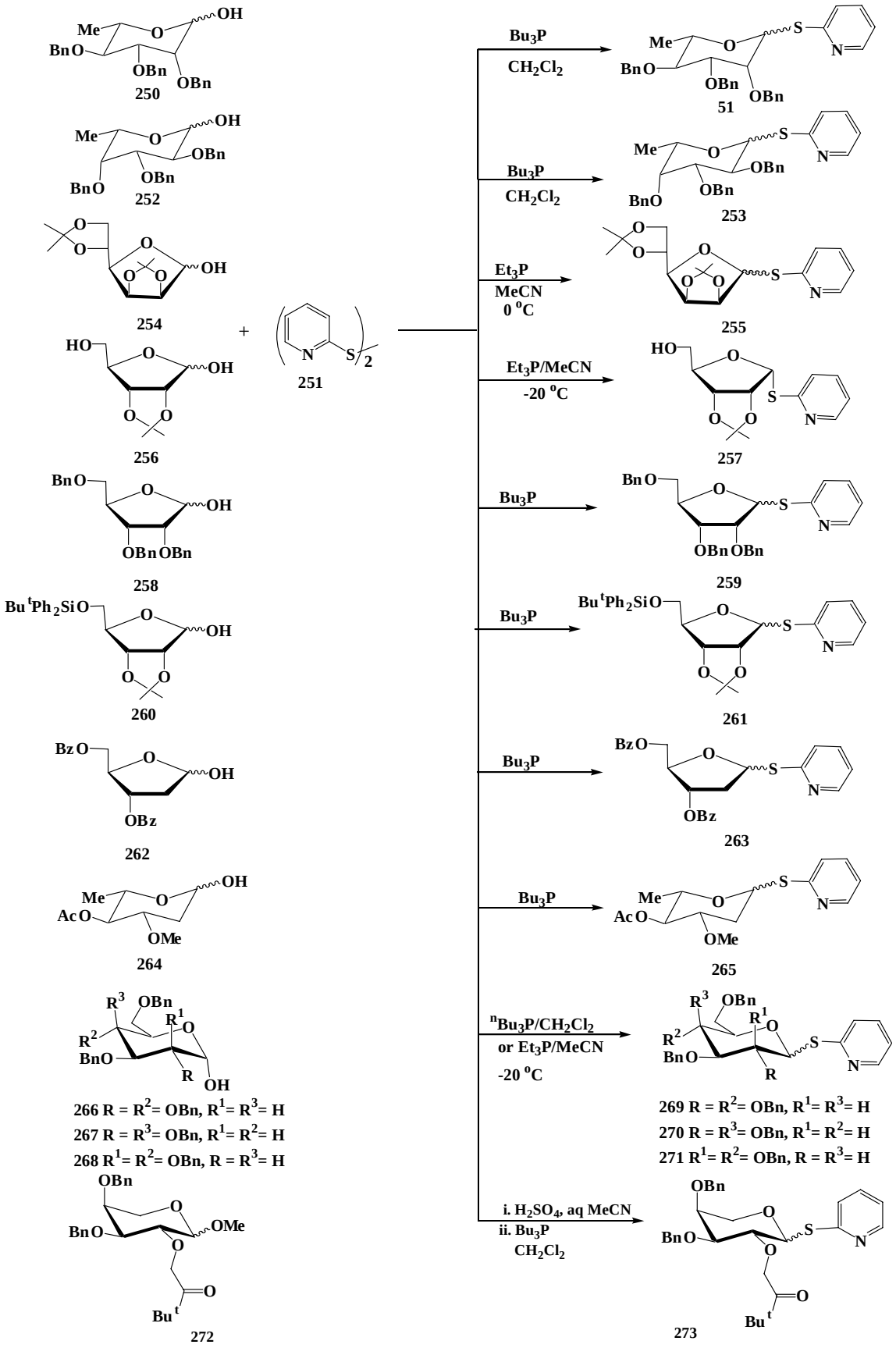
A method for the synthesis of thioglycosides has been based on the reaction of 1-thiosugars with halogenated heterocyclic compounds. Thus, direct displacement of one or two chloro atoms in halogenated maleimides **284** or **285**, by reaction with 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **283** in the presence of triethylamine in anhydrous dioxane at room temperature, gave **286** and **287**, respectively[103] (Scheme 34).

Similarly, nitroimidazolyl 1-thioglycosides were obtained in good yield from per-*O*-acetyl 1-thiosugars and bromonitroimidazole derivatives.[104] An efficient synthesis of 2-pyridyl thioglycoside derivatives has been achieved by the reaction of 1-thiosugar derivatives with either 2-bromopyridine *N*-oxide[105] or 2-chloro-nitropyridine.[106]

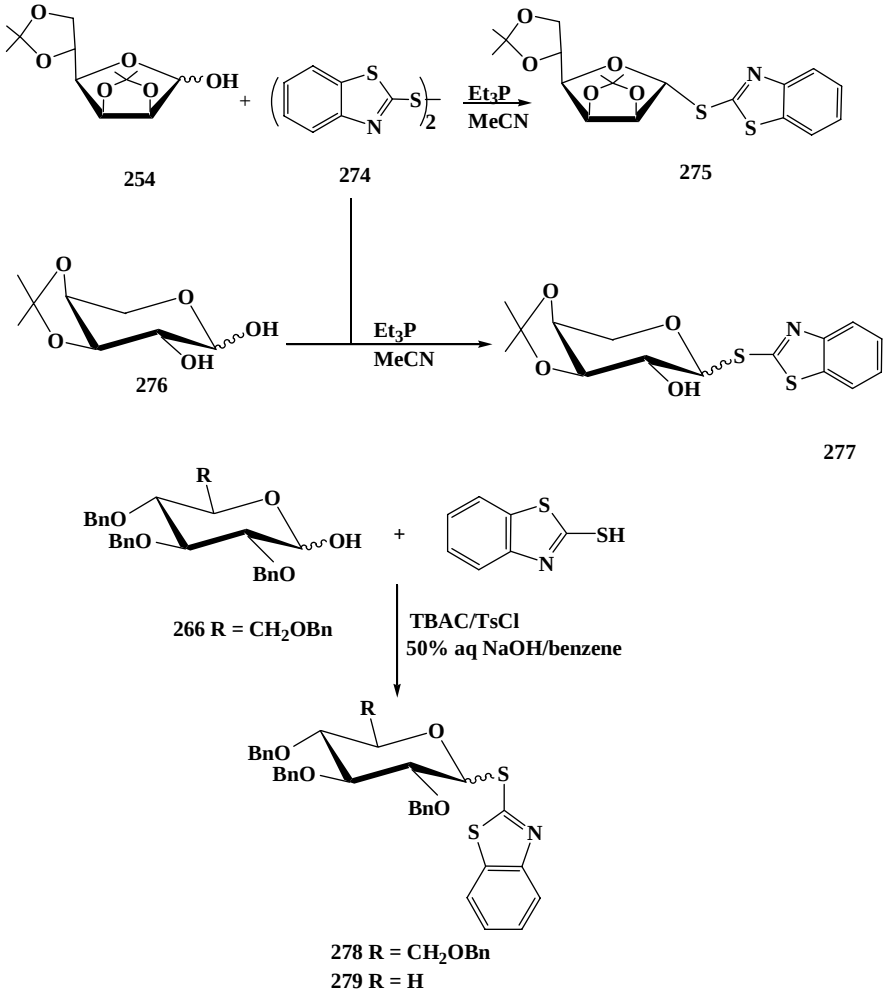
2,4,6-Trichloro-1,3,5-triazine **288** showed a high reactivity towards reaction with three equivalents of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **283** in the presence of Et_3N in acetonirile to give the tris-thioglucoside **289**.[107] On the other hand, reaction of **288** with 1 equiv of **283** to form the corresponding monoglycosylated derivative was unsuccessful, owing to the high reactivity of the product and its decomposition.[107] 1-Thio-D-glucose **283** was also treated with the nitrogen- and oxygen-linked spin-labeled triazine compounds **290** and **291** in acetone in the presence of $NaHCO_3$ at room temperature to form, respectively, the mono- **292** and **293** as well as the bis-thiosugar **294** and **295** derivatives[107] (Scheme 35).

Condensation of 5-chloro-3-methylmercapto-1,2,4-thiadiazole **296** with **283** in the presence of sodium hydroxide in acetone gave the thioglucoside **297**.[108] The 6-purinyl β-D-glucothiopyranoside **300** was synthesized from the sodium thiolate resulting from acetylthio 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose **298** by deacetylation upon reaction with 6-chloropurine **299**.[86] Similarly, coupling of 6-chloropurine with 1-acetylthiohepta-*O*-acetyl lactose **301** in the presence of sodium in methanol afforded the respective thiolactoside **302**[87] (Scheme 36).

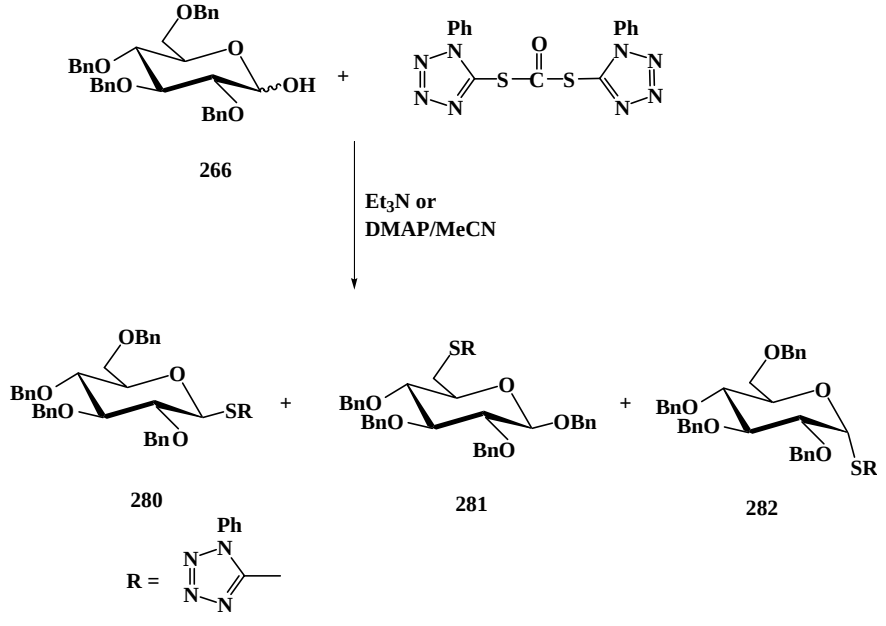
An alternative approach to the synthesis of thioglycosyl heterocycles was attempted by constructing the heterocycle in functionalized thiosugar hydrazones. Thus, 1,5-diarylpyrazol-3-yl 1-thioglycosides were synthesized by the reaction of miscellaneous per-*O*-acetylated glycosylmercaptans **303** with cinnamohydrazonoyl bromides in the presence of Et_3N and methylene chloride–ether as the solvent to afford styryl-type 1-*S*-glycopyranosyl thiohydrazonates **304** in high yield, cyclization of which with iodine or *N*-bromosuccinimide in methylene chloride gave the pyrazol-3-yl-thioglycosides **305**[109] (Scheme 37).


250
252
254
256
258
260
262
264
266 R = R2= OBn, R1= R3= H
267 R = R3= OBn, R1= R2= H
268 R1= R2= OBn, R = R3= H
272
251
Bu3P
CH2Cl2
51
253
Et3P
MeCN
0 °C
255
Et3P/MeCN
-20 °C
257
259
261
263
265
nBu3P/CH2Cl2
or Et3P/MeCN
-20 °C
269 R = R2= OBn, R1= R3= H
270 R = R3= OBn, R1= R2= H
271 R1= R2= OBn, R = R3= H
i. H2SO4, aq MeCN
ii. Bu3P
CH2Cl2
273

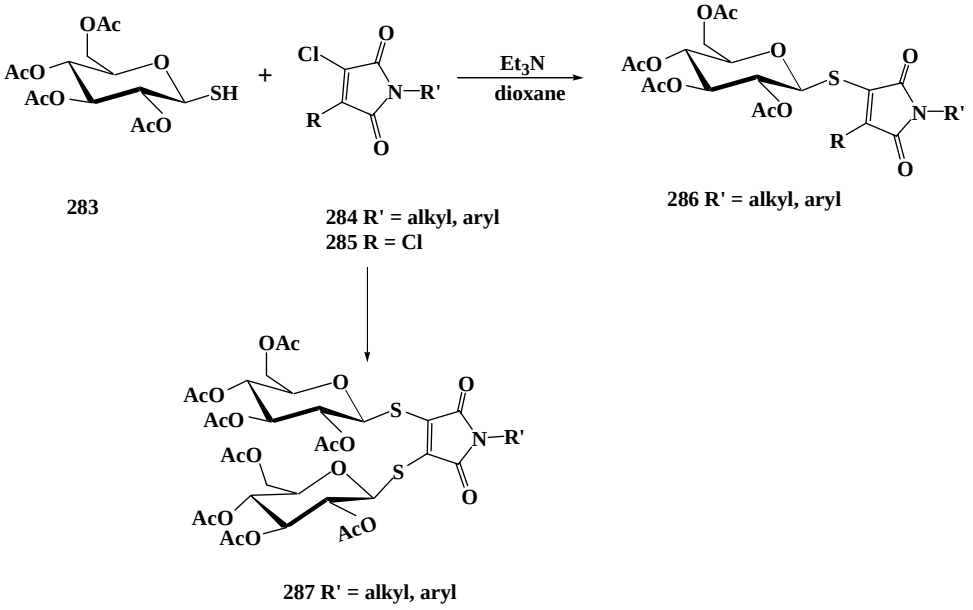
Scheme 31.



Scheme 32.



Scheme 33.



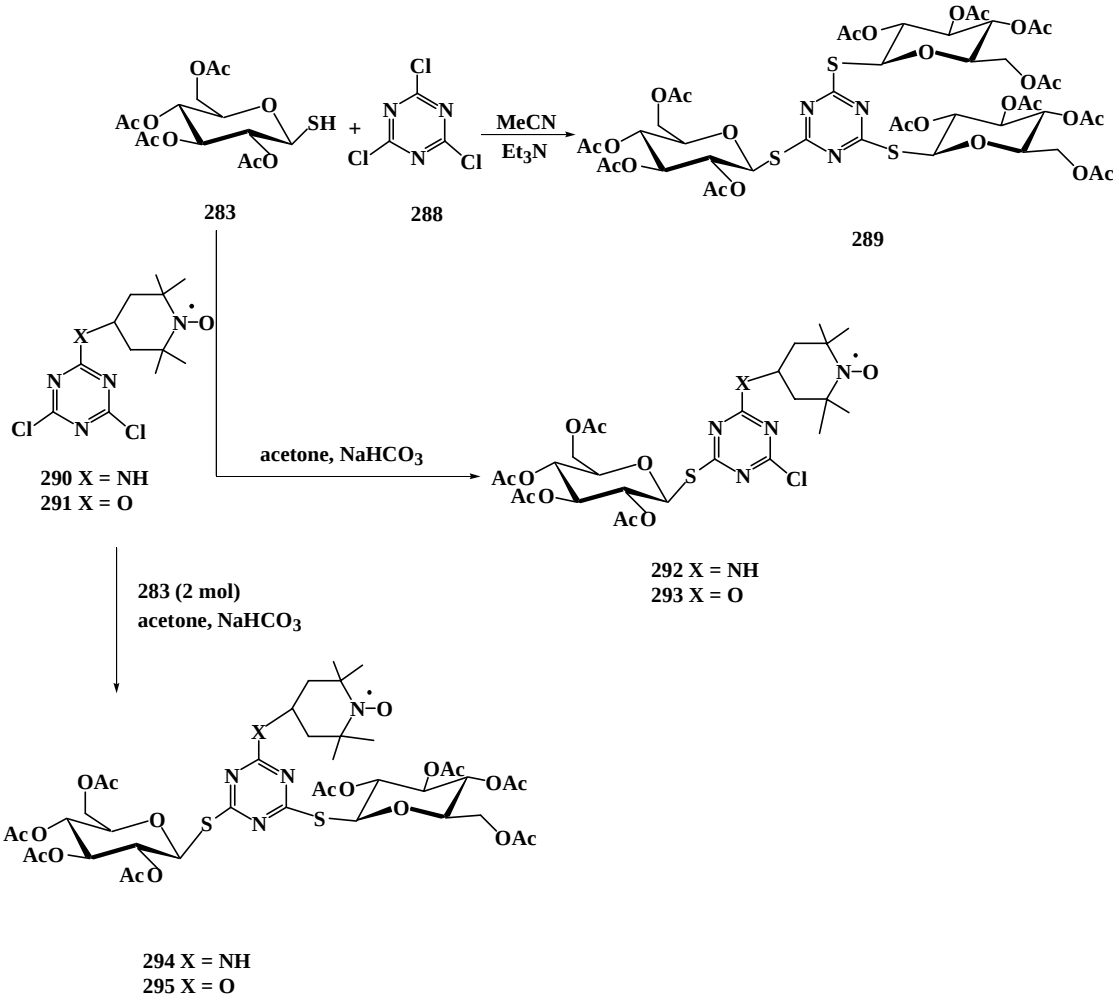
283

284 R' = alkyl, aryl
285 R = Cl

286 R' = alkyl, aryl

287 R' = alkyl, aryl

Scheme 34.



283

288

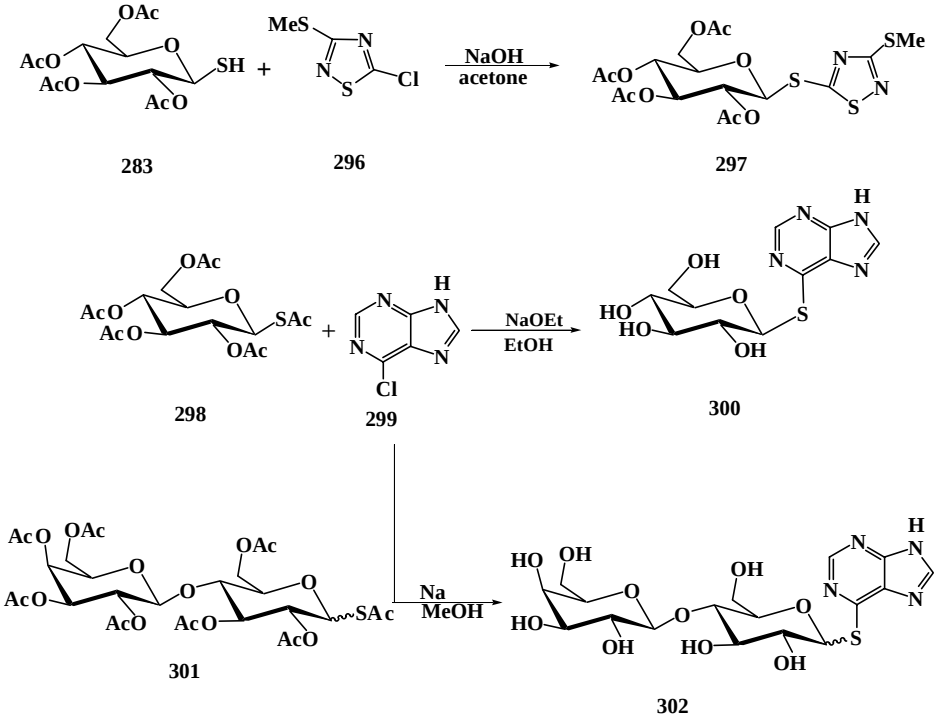
289

290 X = NH
291 X = O

292 X = NH
293 X = O

294 X = NH
295 X = O

Scheme 35.

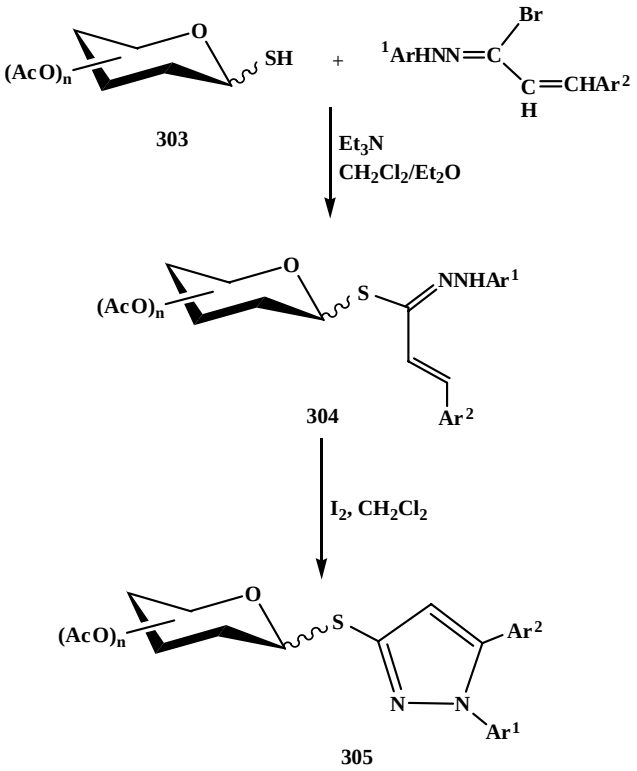


283 296 297 298 299 300 301 302

Scheme 36.

2.6. Isothiouronium salts as glycosylating agents

One of the most convenient and simple methods for the preparation of thioglycosides has utilized isothiourea derivatives of sugars as the starting materials, which are readily available from the reaction of glycosyl halides with thiourea.[63,110] With this method, thioglycosides can be synthesized under very mild reaction conditions. The



303 304 305

n = 3-4

Ar^1, Ar^2 = Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$

Scheme 37.

synthetic procedure involved cleavage of a glycosyl isothiouronium salt by treatment with potassium carbonate, sodium hydrogen sulfide or metabisulfite in water/acetone media, followed by reaction of the resulting 1-thioglycopyranose with alkyl or aryl and glycosyl halides. Triethylamine has been found to react readily with isothiouronium salts to form 1-thioglycoses and can successfully be used for the activation of the resulting 1-thioglycosides by converting them into the more nucleophilic thiolate anions.[110]

Thus, thioglycosides **309–312** with a nitropyridyl moiety at position 3 or 5 have been synthesized when the isothiouronium salts **306** and **307** were treated with 2-chloro-3-nitropyridine **308** ($R^1=H$, $R=NO_2$) or 2-chloro-5-nitropyridine **308** ($R^1=NO_2$, $R=H$) in acetonitrile and in the presence of triethylamine under MWI for 2–3 min in 60, 85, 80 and 88% yield, respectively. On the other hand, compounds **309–312** were traditionally obtained within 6–8 h in 40, 60, 68 and 68% yield, respectively.[111]

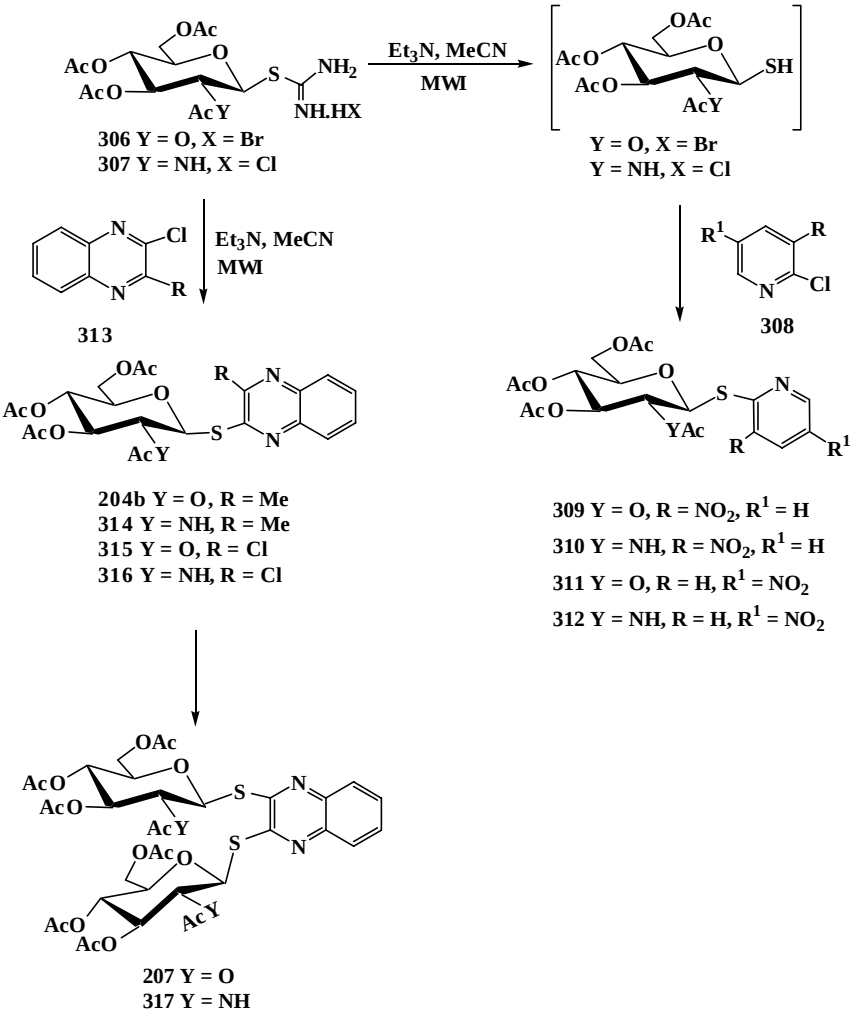
Under the same conditions, the isothiouronium salts **306** and **307** were coupled with 2-chloro-3-methylquinoxaline **313** ($R=Me$) to give the thioglycosides **204** and **314**, respectively, in 60 and 66% yield within 3 min under MWI. Similarly, 2,3-dichloroquinoxaline **313** ($R=Cl$) was reacted with 1 mol equiv of **306** and **307** to afford the monothioglycosides **315** and **316** in 48–50% yield, whereas, with 2 equiv, the bis analogues **207** and **317** were obtained. Conventionally, compounds **314–316** were obtained in 40–48% yield within 10 h[111] (Scheme 38).

2.7. Glycals as glycosylating agents

Acid-catalyzed addition of thiols to glycals gave the 2-deoxythioglycosides. Thus, 3,4,6-tri-*O*-acetyl-D-glucal **318**, -D-galactal **319**, and 3,4-di-*O*-acetyl-L-rhamanal **322**, were reacted with 2-mercaptopyridine (**2**), either with or without anhydrous *p*-toluenesulfonic acid (PTSA) in dichloromethane, to afford α,β mixtures of the 1,2-addition products **320**, **321** and **323**, respectively.[112,113] Similarly, glycal disaccharides **324** and **325** were treated with **2** in the presence of PTSA in CH_2Cl_2 at 5 °C to afford α/β mixtures of 2-deoxy-thioglycosides **326** and **327**, respectively.[113]

When the reaction of **318** was carried out in the presence of $BF_3\cdot Et_2O$ as a catalyst, an allylic displacement took place, with the formation of the 2,3-dideoxy-1-thioglycoside **328**.[112]

On the other hand, when the reaction of **318** or **319** with **2** was carried out in the presence of $SnCl_4$ as a catalyst, it was found to be dependent on the molar ratio of the thiol and



Scheme 38.

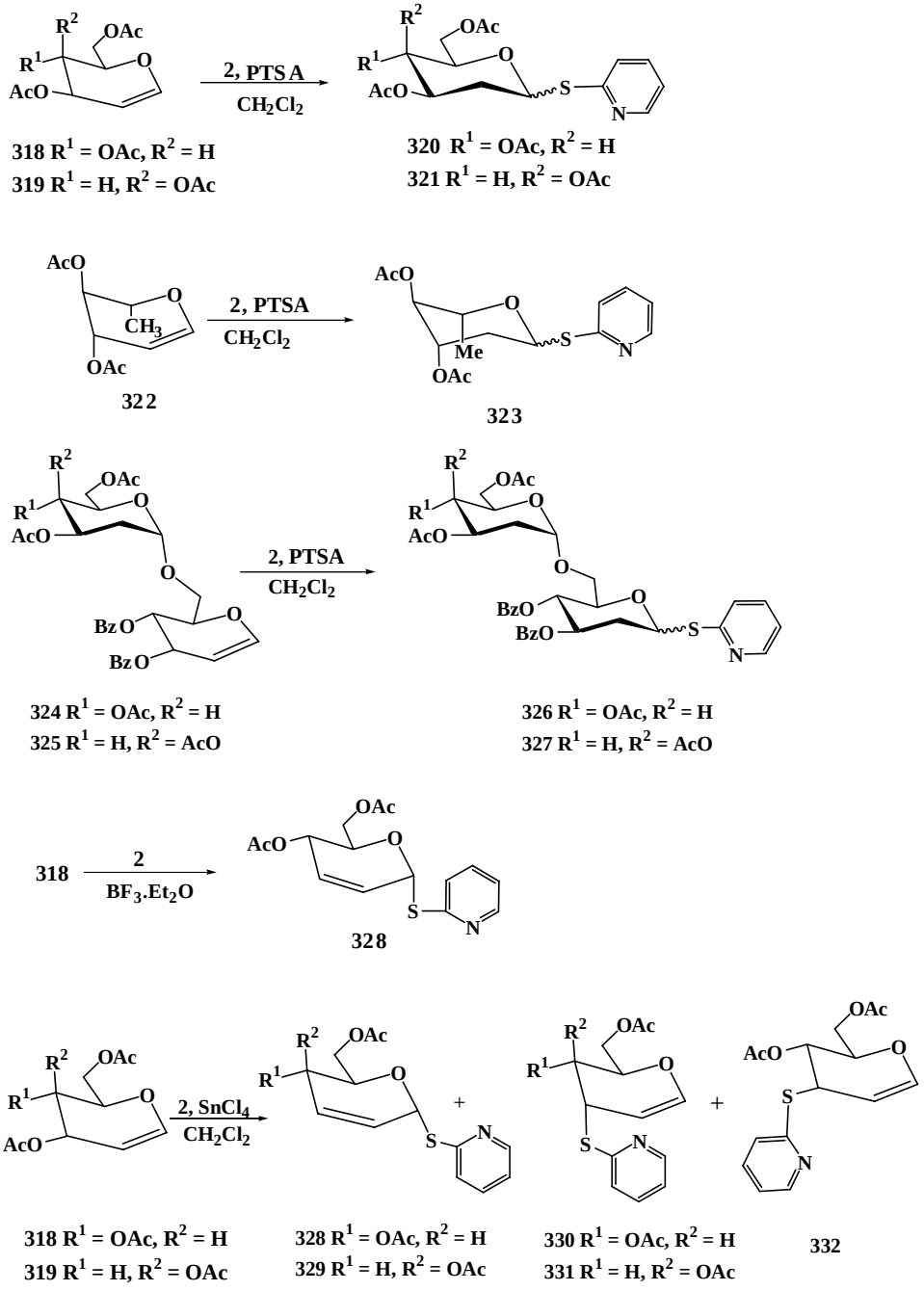
catalyst as well as the temperature.[114] Thus, when **318** was reacted with 1.1 mol equiv of **2** and $SnCl_4$ in dichloromethane at room temperature for 20 min, it gave a mixture of the allylic displacement products **328** (25%), **330** (37%) and **332** (29%), whereas, with 1.5 mol equiv of **2** at −20 °C for 3 h, **328** (69%) was only obtained. When 3,4,6-tri-*O*-acetyl-D-galactal **319** was reacted with 1.1 mol equiv of **2** and 1.0 mol equiv of $SnCl_4$ at −20 °C, a minor product **329** (24%) and traces of **331** were obtained, with the recovery of the starting product **319**. Increasing the molar equivalents of **2** to 1.2 and $SnCl_4$ to 1.5 and the reaction time to 24 h at 0 °C to room temperature afforded **331** as the major product (65%) and **329** as the minor product (15%) with recovered starting material **319** (6%)[114] (Scheme 39).

2.8. Glycosides as glycosylating agents

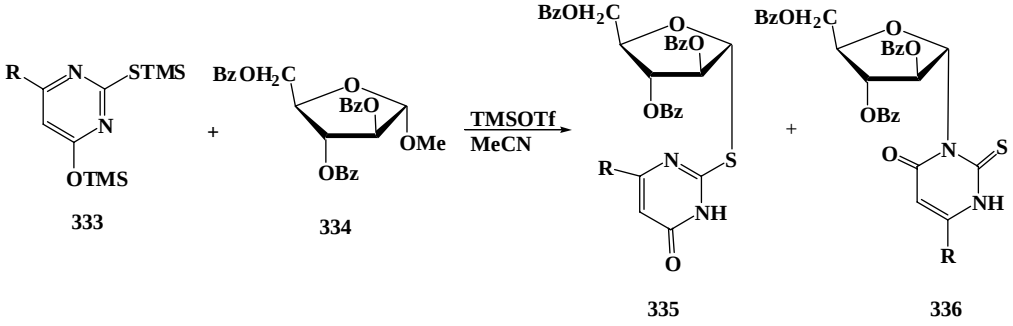
O-Glycosides can be converted into *S*-glycosides in quite acceptable yields by treatment with a thiol or a thiotrimethylsilane and a Lewis acid. The silylated 6-substituted thiouracil **333** was readily reacted with methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside **334** in acetonitrile in the presence of trimethylsilyl triflate (TMSOTf) to give the thioglycoside **335** as a minor product while the nucleoside **336** was the major product[115] (Scheme 40).

2.9. Orthoesters as glycosylating agents

Protected 1,2-*O*-methoxyethylidene β-D-mannopyranose **337** (R′=OAc, OBn) were coupled with 2-mercaptopyrimidine in



Scheme 39.



Scheme 40.

dry acetonitrile in presence of mercuric bromide to give the respective 1,2-*trans* thioglycosides, pyrimidin-2-yl 1-thio-α-D-mannopyranosides **338** and **339** in excellent yields.[116] Selective 6-*O*-debenzylation of **339** with trimethylsilyl triflate in acetic anhydride at −50 °C afforded the pyrimidin-2-yl 2,6-di-*O*-acetyl-3,4-di-*O*-benzyl-1-thio-α-D-mannopyranoside.[116] On the other hand, the fully benzylated thiopyrimidinyl derivative **340** was obtained by deacetylation of **338a** followed by benzylation.[116]

Treatment of 3,4,6-tri-*O*-benzyl-β-D-mannopyranose orthoacetate **337** ($R'=Bn$) with 2-mercaptopyridine, 2-mercaptopyrimidine, 2-mercaptobenzoxazole, or 2-mercaptobenzothiazole in acetonitrile in the presence of $HgBr_2$ afforded the 1-thio-α-mannopyranosides **339a–d** in 87–93% yield,[117] deacetylation of which gave **340a–d**. Treatment of **340b** with benzylsulfonyl chloride in pyridine afforded the 2-pyridyl 3,4,6-tri-*O*-benzyl-2-*O*-benzylsulfonyl-α-D-mannopyranoside **341**.[118]

Under the same reaction conditions, compound **337** was coupled with 2,5-dimercapto-1,3,4-thiadiazole to give the bis-thiomannoside **342** in 88% yield.[117] The reaction of 1,2-*O*-methoxyethylidene β-L-rhamnopyranose **343** with 2-mercaptopyrimidine under similar conditions as above gave **344** or **345**.[116] Deacetylation of **345** followed by benzylation gave **345a** (Scheme 41).

Treatment of **340b** with isophthaloyl chloride in dry toluene and in the presence of a catalytic amount of dry pyridine afforded **346**, which, on treatment with methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **347** in the presence of dibutyltin oxide and tetrabutylammonium iodide (TBAI), afforded **348**.[117] Under the same reaction conditions, the thioglycosides **340a–d** were treated with α,α′-dibromo-*m*-xylene (**349**) followed by coupling with **347** to give the respective mannosides **350a–d** (Scheme 42).[117]

3. Role of thioglycosyl heterocycles in *O*-glycoside synthesis

One of the hot topics in organic synthesis and, in particular, carbohydrate chemistry is the exploration of methods for the synthesis of glycosides. Their formation normally requires a glycosyl donor and an acceptor, which may proceed in an intermolecular or intramolecular fashion, as shown in Scheme 43.

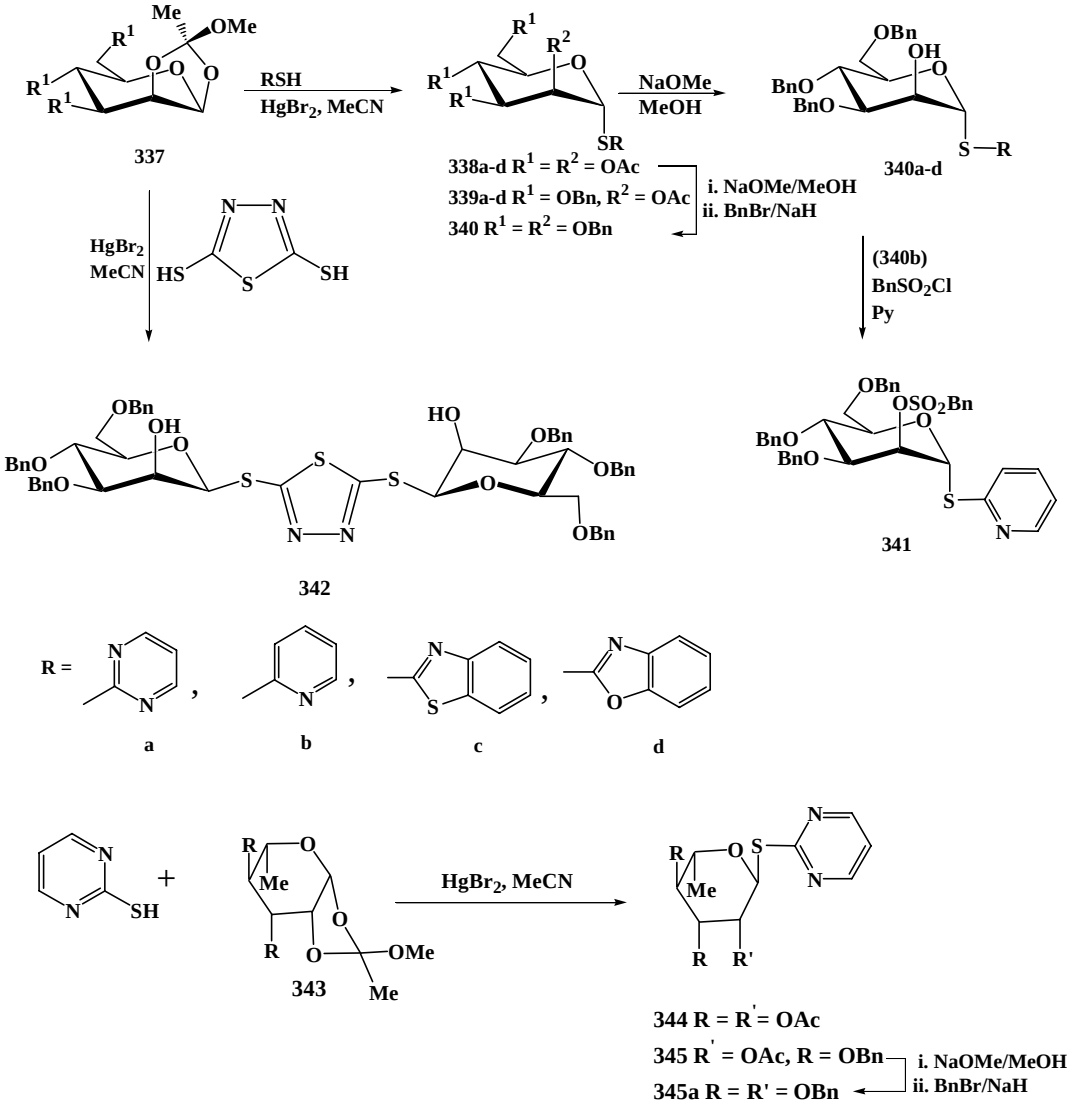
Thioglycosides and, more recently, thioglycosyl heterocycles have become promising candidates as glycosyl donors, which sometimes provide an interesting entry for complex oligosaccharides. Since the thioglycosyl heterocycles are stable towards replacement with alcohols, it has been found that, upon activation, they provide excellent glycosyl donors. This activation of the anomeric center, usually carried out with a promoter, has attracted much attention and, consequently, much research has become available in the literature. In order to review work, it is convenient to classify according to the promoter utilized in the glycosidation step.

3.1. Methyl iodide as promoter

In addition to the selection of a promoter for activating the anomeric center, the protection on the hydroxyl groups has frequently played an important and/or decisive role on the diastereoselectivity of the glycosidation process. This has been exemplified by using participating groups such as acetyl groups and nonparticipating groups such benzyl groups.

Glycosidation reactions of 2-pyridyl 2,3,4,6-tetra-*O*-benzyl-β-D-gluco- **269** and -β-D-galacto-pyranosides **270** were investigated with different alcohols in different solvents using alkyl halides as activators to give the alkyl glycosides **351a** and **352a**, respectively.[43,118] As expected, methanol was more reactive than isopropyl and *t*-butyl alcohols, but *t*-butyl alcohol showed a higher α-diastereoselectivity. The α-distereoselectivity was higher for galactosides **352**, compared to glucosides **351**. Methyl iodide was found to be the ideal activator in terms of the rate of reaction and distereoselectivity. Using *n*-butyl iodide resulted in the recovery of 55% of the glycosyl donor **269** with 30% yield of **351** ($R={}^{i}Pr$), whereas, using *n*-butyl bromide, **269** was completely recovered. Dichloromethane was found to be a suitable solvent in terms of solubility and providing good yields as well as stereoselectivity[43] (Table 1).

With 2-azidoethanol, **17**, **269** and **270** under the same reaction conditions afforded only the α-glycosides **351**, **352** and **353** in 68–72% yield.[44] 2-Pyridyl thioglycosides **49**, **51** and **55** gave the α-*O*-glycosides **354–356** in 70, 56 and 66% yield, respectively. Stereoselective α-glycosylation was also observed when an anomeric mixture of 2-pyridyl thioglycosides **269–271**, **51**, **253** and **53** was used in the glycosylation with various acceptors in the presence of methyl iodide as an activator and 4 Å molecular sieves in CH_2Cl_2 to



Scheme 41.

afford the α-glycosides **351** (R=c,d,e,f), **352** (R=c,e), **357** (R=c), **358** and **359**, respectively[43,97] (Scheme 44).

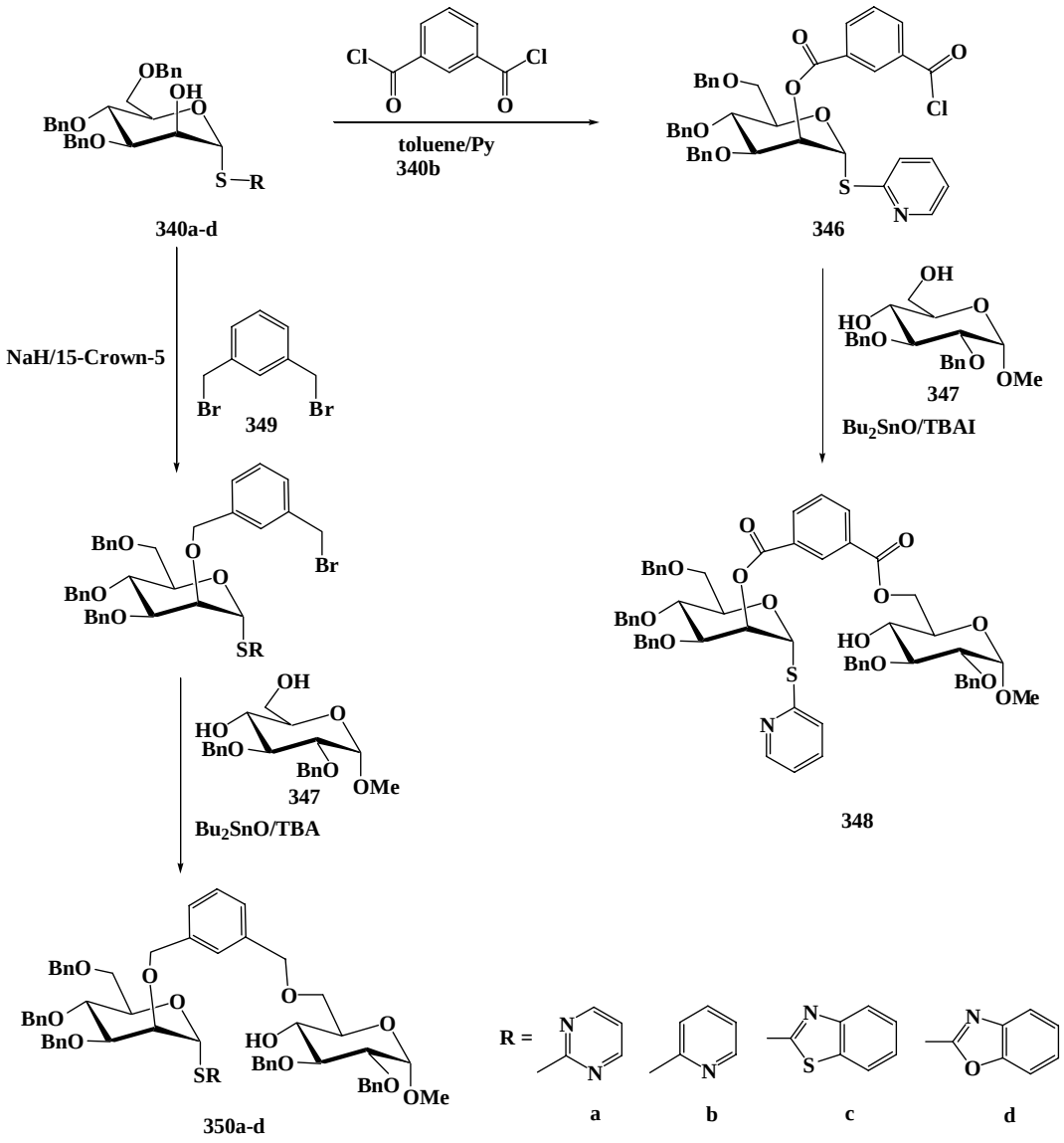
The reaction of per-*O*-benzyl 2-pyridyl-1-thio-β-D-ribofuranoside **49** and 2-pyridyl 2,3:5,6-di-*O*-isopropylidene-1-thio-β-D-mannofuranoside **255** with the acceptors, 1,2:5,6-di-*O*-isopropylidene-D-glucopyranose and methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside, using methyl iodide as an activator afforded the respective α-disaccharides **354** and **360** in 67–81% yield[42] (Scheme 44).

The thiopyridyl sialoside **56** and its thio-*N*-methylimidazolyl analogue, however, failed to react with glycosyl acceptors when either MeI or NBS were used as promoters.[45]

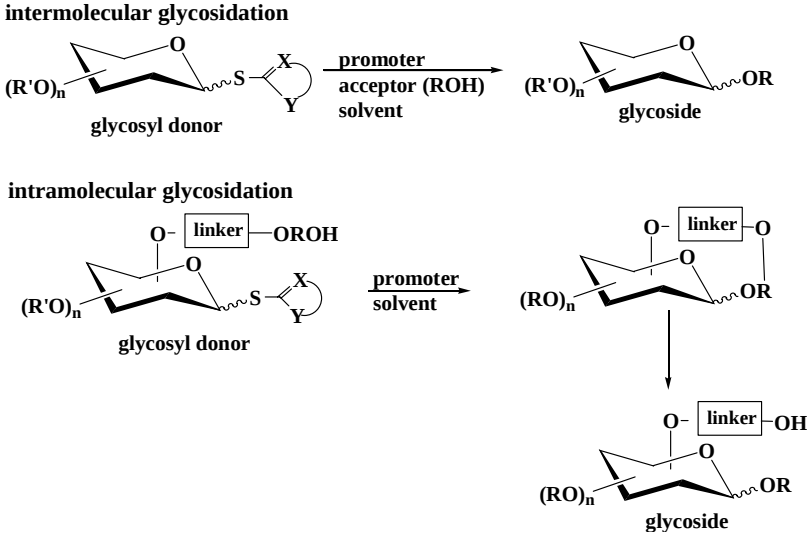
On the other hand, only a few examples were reported on thioglycosyl donors with acetyl groups. This can be attributed to the high success in achieving high diastereoselectivies encountered using acetyl derivatives and different leaving groups at the anomeric center. Under the same reaction conditions, the acetylated derivative, 2-pyridyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **15**, with methanol or ethanol resulted in the recovery of 90% of **15**,[119] whereas 2-pyridyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside **47** afforded the β-glucosides **363**, **364**, **365** and **366** in 72–81% yield, respectively.[40,119] Similarly, the benzoylated derivative **361** afforded the β-glucoside **362** (Scheme 45).[119] With the glycosyl acceptors, 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose and 4-*O*-(2,3-di-*O*-acetyl-α-D-glucopyranosyl)-1,2,3,6-tetra-*O*-acetyl-β-D-glucopyranose, the thiopyridyl donor **47** afforded the β-glucosides **367** and **368**, respectively, (Scheme 45).[40]

Methyl iodide as a promoter was used for the synthesis of complex oligosaccharides. Thus, the glycosyl donor **369** was coupled with 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose to give the tetrasaccharide[119] **370** (Scheme 46).

Methyl iodide was evaluated as a promoter for the coupling of 2-pyridyl 2-deoxy-1-thio-α/β-D-glycopyranosides with several acceptors in CH_2Cl_2 to give the α-linked disaccharides[42,113] **371** and **372**, respectively, in 65–87% yield, except for the disaccharide **371** (R=**a**), which was obtained as an α:β mixture with a ratio of 85:15.[42] The reaction was



Scheme 42.



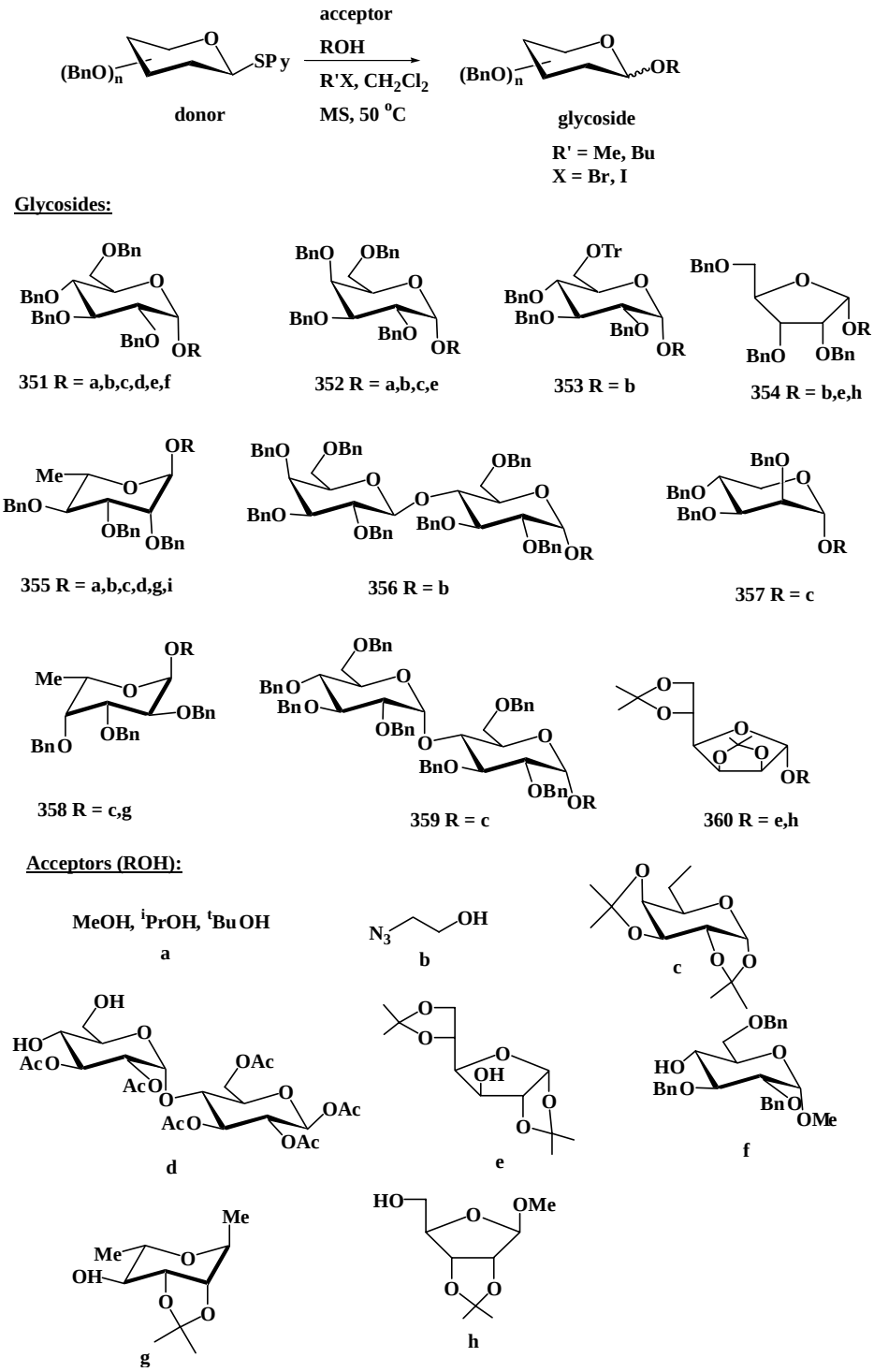
Scheme 43.

Table 1. Results of glycosidation of **269** and **270** with various alcohols in CH_2Cl_2 using MeI

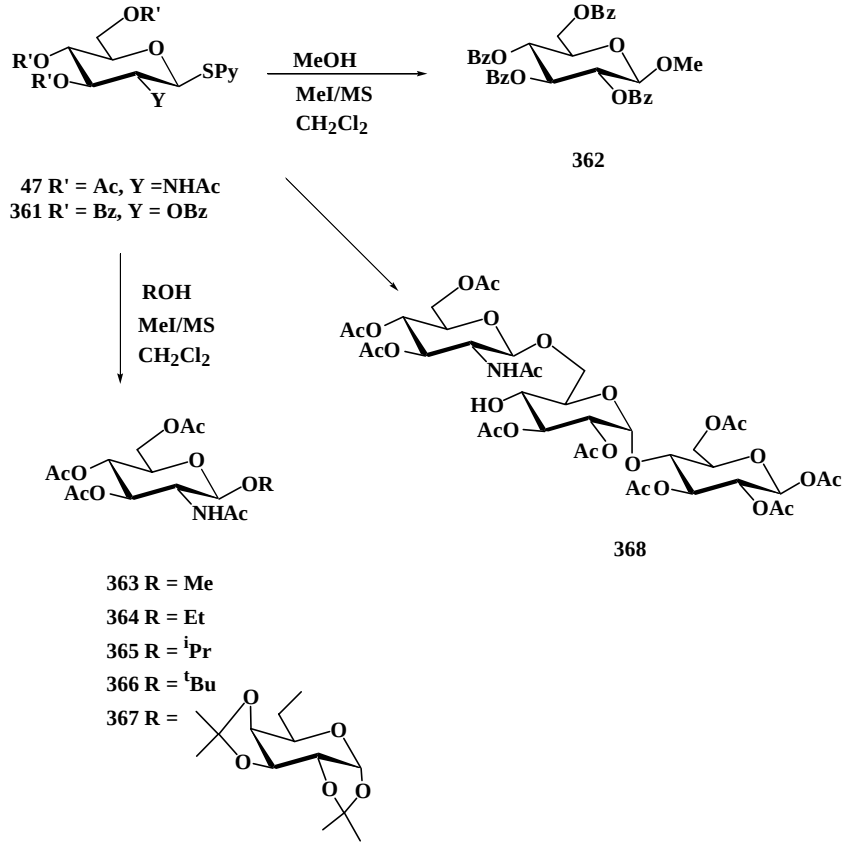
Acceptor	Glycosyl donor	Yield (%)	α:β
MeOH	**269**	95	65:35
^{i}PrOH	**269**	85	82:18
^{t}BuOH	**269**	82	89:11
MeOH	**270**	96	72:28
^{i}PrOH	**270**	87	87:13
^{t}BuOH	**270**	80	91:9

extended to the 2-deoxyrhamnopyranosides to give also the corresponding α-disaccharides **373** and **374**, whereas an α,β mixture of **373** (R=**a**, 86% yield, 85:15 α:β) and 1,2-elimination products were isolated.[42]

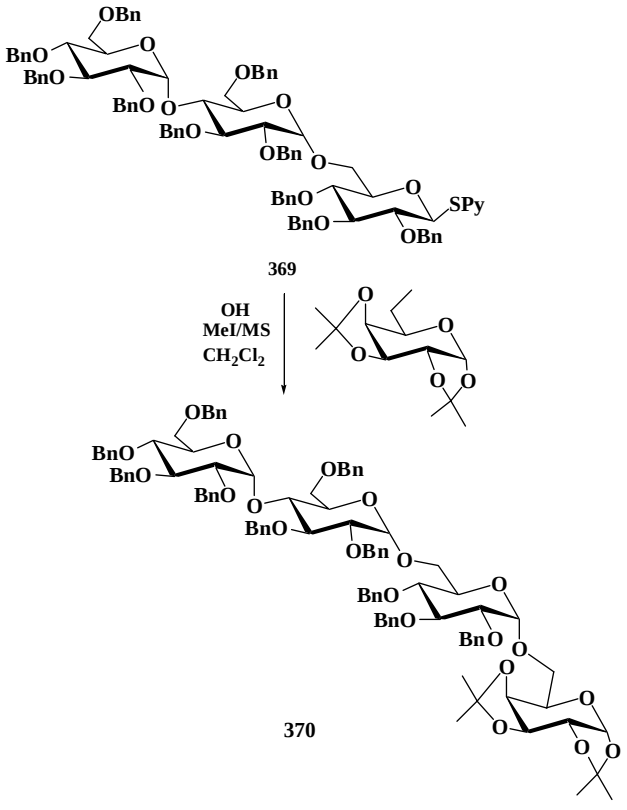
2-Pyridyl 3,5-di-*O*-benzoyl-2-deoxy-1-thio-α/β-D-ribofuranoside **263** was coupled with various acceptors to give only the α-2-deoxy disaccharides **375** (R=**a**,**b**,**c**,**i**) in 72–85% yield, along with 1,4-anhydro-2-deoxy-3,5-di-*O*-benzoyl-D-erythro-pent-1-enilol.[42]



Scheme 44.



Scheme 45.



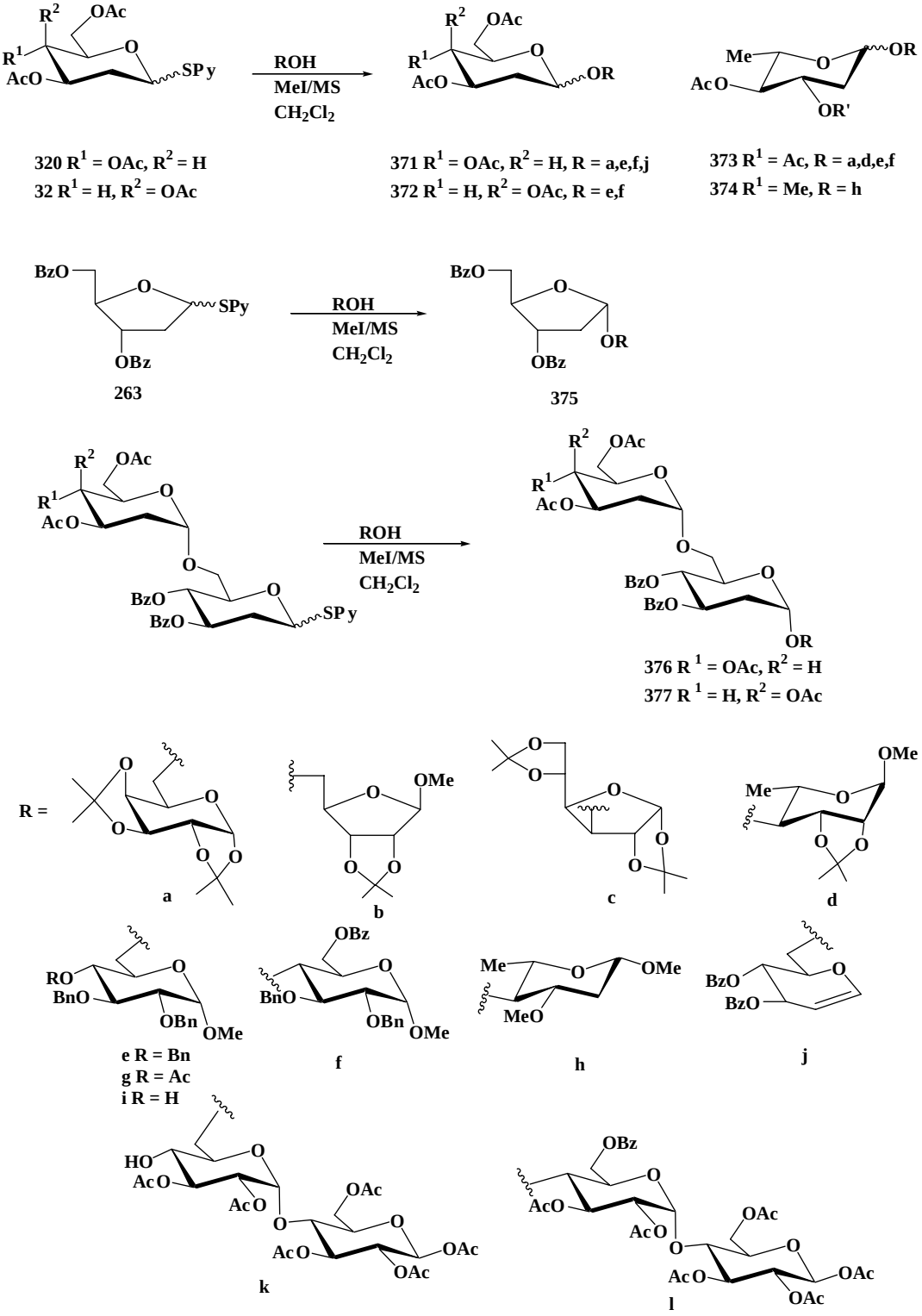
Scheme 46.

Similarly, the α-trisaccharides **372k**, **373k** and **373l** were obtained in 63, 71 and 66% yield, respectively,[42] and the α-anomer trisaccharides **376a**,**c** and **377a** in 73–81% yield[113] (Scheme 47).

The selectivity of coupling has been investigated using the acceptor, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside α-**378** (R^1 = Me), which has two sites for reaction, the coupling of which with the donor **269** in the presence of methyl iodide in dichloromethane under reflux afforded the 1→2 disaccharide **379**, 1→3 disaccharide **380**, together with the trisaccharide **381**, in 20, 48 and 10% yield, respectively.[120] Under the same reaction conditions, an α-stereoselectivity was observed upon using the β-anomer **378** as acceptor, to give only the respective 1→2 and 1→3 disaccharides in 23.5 and 46% yield.[120] On the other hand, using long-chain alkyl groups such as *n*-octyl at the anomeric carbon of the glycosyl acceptor **378** (R = nC_8H_{17}) in the coupling reaction with **269** resulted in a high regioselectivity, with the formation of 2-*O*-β-glycosylated **379** (OR^1 = β-$nC_8H_{17}O$) in 77% yield and 3-*O*-α-**380** (OR^1 = α-$nC_8H_{17}O$, 58% yield).[120]

Glycosylation of (±)1-hydroxy-*trans*-2-(hydroxymethyl)cyclohexane **382** with 2-thiopyridyl glucoside **269**, in the presence of methyl iodide, gave four α-glucosides **383**, **384**, **385** and **386** in a ratio of 3:3:1:1 and a combined yield of 47% and, whereas **384** and **385** could be separated by chromatographic means, **383** and **386** were inseparable[121] (Scheme 48).

A high-pressure-assisted glycosylation reaction with the glycosyl donor, 2-benzothiazolyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **102**, for the acceptors,



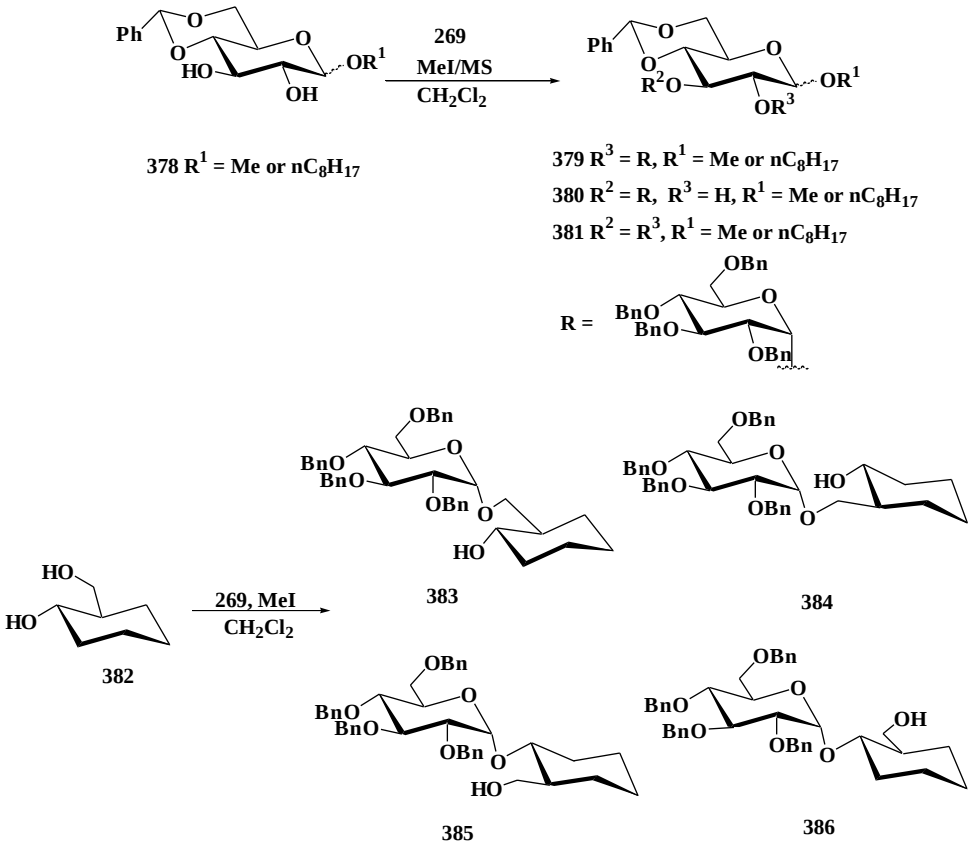
Scheme 47.

t-butanol, *n*-octanol, and cholesterol, using methyl iodide as an activator, gave the 1,2-*cis* glucosides **351** as the major products in good yield and high α-selectivity[122] (Table 2).

3.2. *N*-Halosuccinimides as promoters

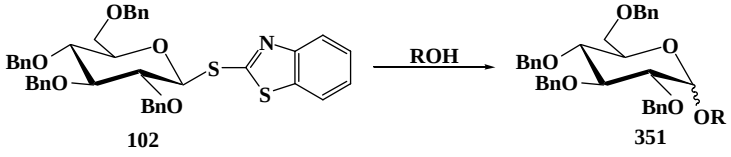
NBS in acetonitrile has been used for activating the thioglucosyl pyridine **387** towards glycosylation with methanol to give a 4:1 mixture of methyl α- and β-D-glucopyranosides[14] (Scheme 49).

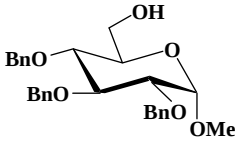
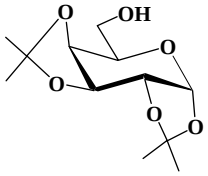
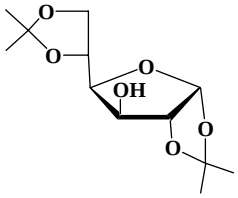
Glycosylation of pyrazol-3-yl per-*O*-acetyl-1-thio-β-D-glucopyranoside **305** with alcohol in the presence of NBS did not take place to give **390**. The per-*O*-benzylated derivative **388** could, however, be *O*-glycosylated[109] to give **389** (Scheme 49).

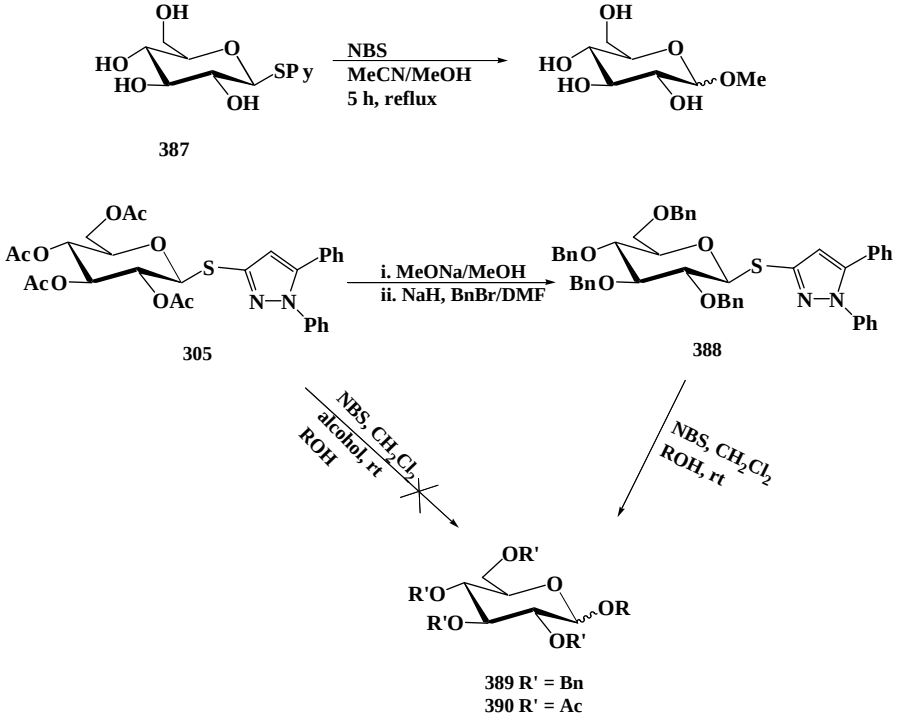


Scheme 48.

Table 2. Yields and anomeric ratios for coupling of **102** with different acceptors



Acceptor ROH	Yield (%)	α:β
$Me(CH_2)_6CH_2OH$	85	89:11
$(Me)_3COH$	65	89:11
	71	88:12
	71	90:10
	40	90:10
Cholesterol	80	90:10



Scheme 49.

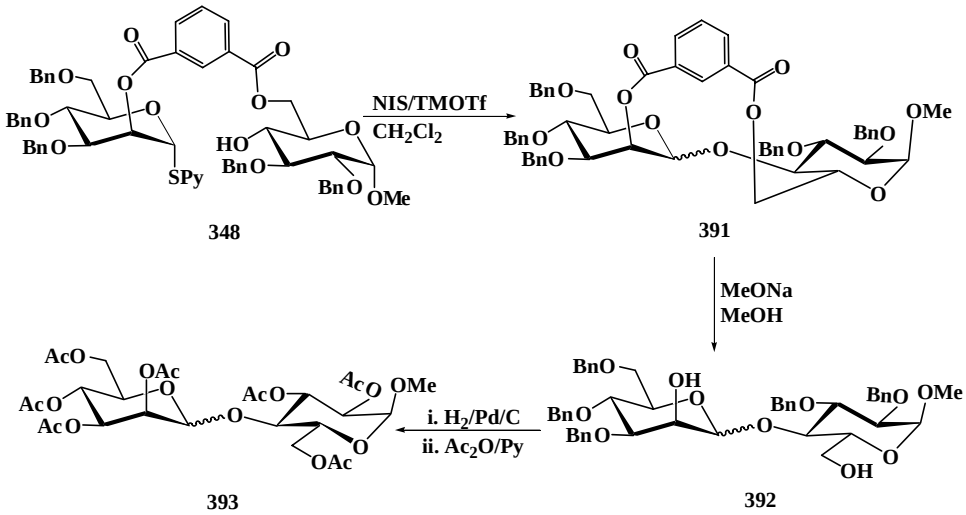
An efficient and highly region- and stereoselective protocol for intramolecular β-mannopyranoside synthesis was developed using 2-thio derivatives of nitrogen heterocycles as leaving groups at the anomeric position and isophthaloyl and *m*-xylenyl derivatives as rigid spacers linked to the 2-hydroxy group of the mannose residue.[117] Thus, *N*-iodosuccinimide (NIS, 1.3 equiv) and TMSOTf (0.1 equiv) in CH_2Cl_2 were used for the activation of intramolecular glycosylation in the isophthaloyl derivative **348** to give the 1→4 linked disaccharide **391** in an α:β ratio of 1:6 (70% yield).[117] Treatment of **391** with sodium methoxide in methanol afforded **392**, the debenzylation and subsequent acetylation of which gave **393** (Scheme 50).

Under the same reaction conditions, the *m*-xylenyl thiomannopyranosides **350a**,**c**,**d** were intramolecularly glycosylated to give the disaccharide **394** in an α,β ratio of 1:9–10, which, upon deprotection and subsequent acetylation, gave **393**, which was similarly obtained from **392**.[117] The disaccharide **394** was also obtained (72% yield, α:β 1:6) when the mannosyl donor **395** was activated with NIS–TMSOTf in CH_2Cl_2[117] (Scheme 51).

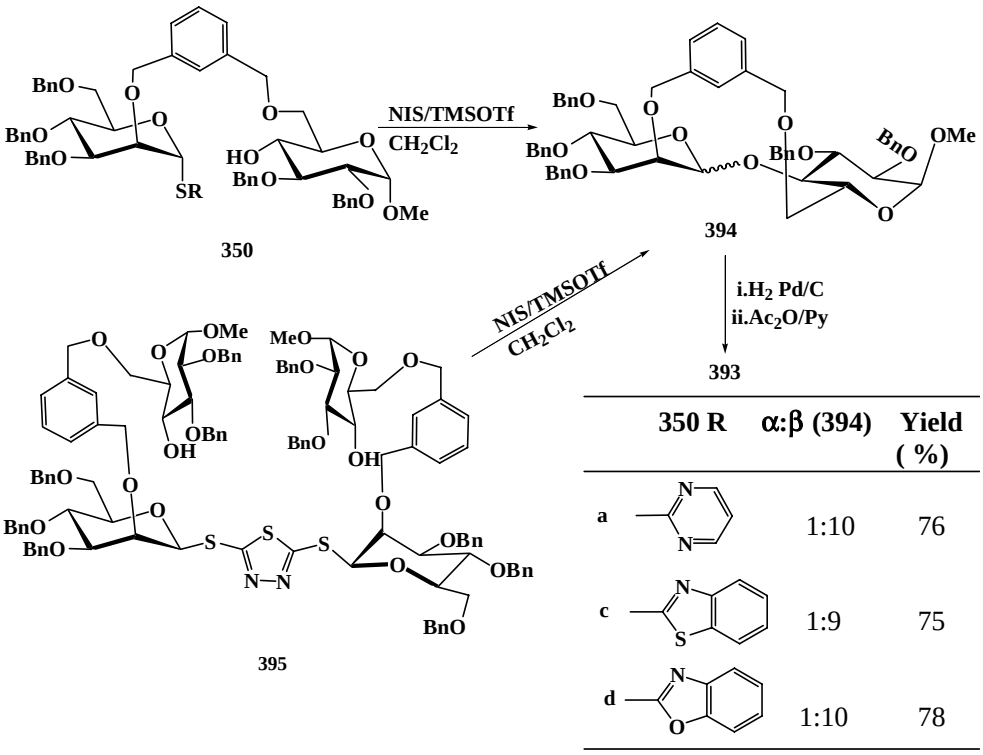
NIS has been used in combination with TfOH to activate the glycosylation of 2-benzoxazolyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside,[35] (see Section 3.5).

3.3. Metal salts as promoters

Some salts of mercury, zinc and silver have been used for the activation of anomeric centers, and consequently, have promoted the glycosylation of glycosylthio heterocycles.



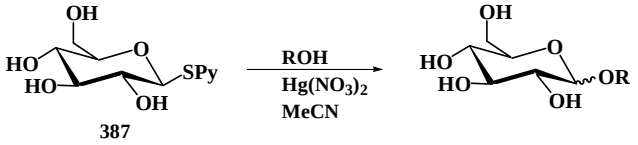
Scheme 50.



Scheme 51.

Thus, mercuric nitrate promoted the reaction of **387**, obtained by deacetylation of **15**, with various alcohols and monosaccharides in acetonitrile within a few minutes, to give the α-anomeric glucosides as the major products,[14] regardless of the structural complexity of the alcohol (Table 3). The 6-*O*-*tert*-butyldiphenylsilyl derivative of **387** glycosylated isopropanol in CH_2Cl_2 under the same reaction conditions, to give the same α:β ratio of isopropyl D-glucopyranoside. Similarly, using the 4,6-*O*-benzylidene derivative of **387** did not alter the α:β ratio of the resulting glucoside.[14] The low polarity of the solvent also did not alter the α:β ratio.

Table 3. Yields and anomeric ratios for glucosides resulting from **385** by activation with mercuric nitrate



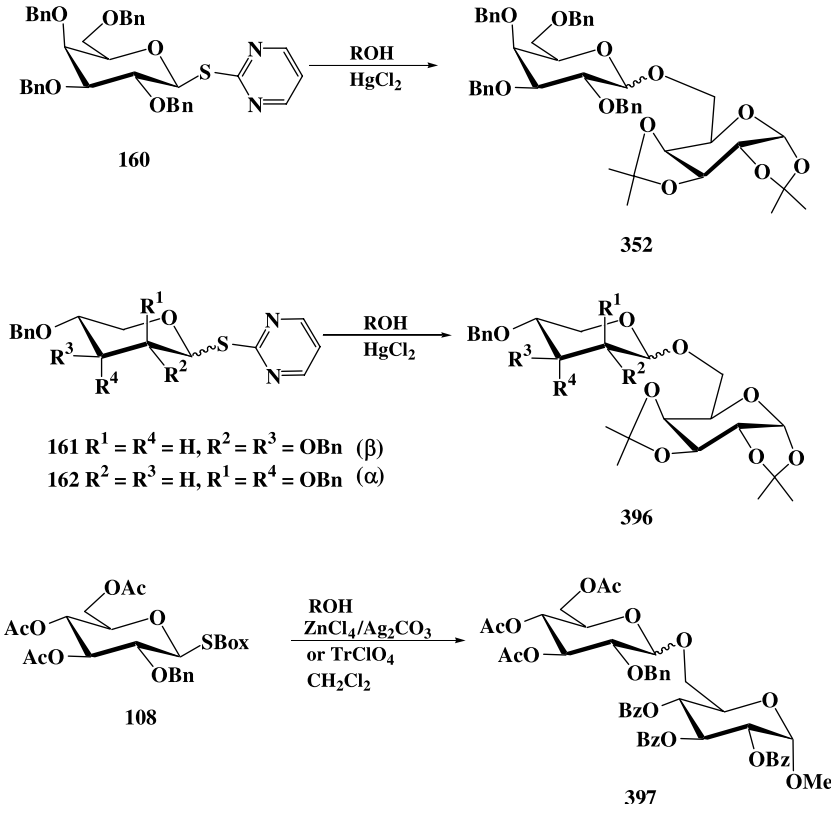
ROH	Solvent	Yield (%)	α:β
MeOH	MeCN	95	70:30
EtOH	MeCN	85	68:32
2-Propanol	MeCN	77	62:38
Cyclohexanol	MeCN	75	51:49
2,2-Dimethyl-1-propanol	MeCN	47	58:42
1,2:3,4-Di-*O*-isopropylidene-α-D-Galactopyranose	MeCN	35	55:45
2-Chloroethanol	-	80	α Only
2-Propanol	1-Chloro-pentane	70	1:1

The reaction of pyrimidinyl thioglycosides **160–162** with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in the presence of mercuric chloride as activator gave an α:β mixture of the disaccharides **352** and **396**, respectively, in 60% yield; the 1,2-*cis*(α)-glycosides were the major products.[13]

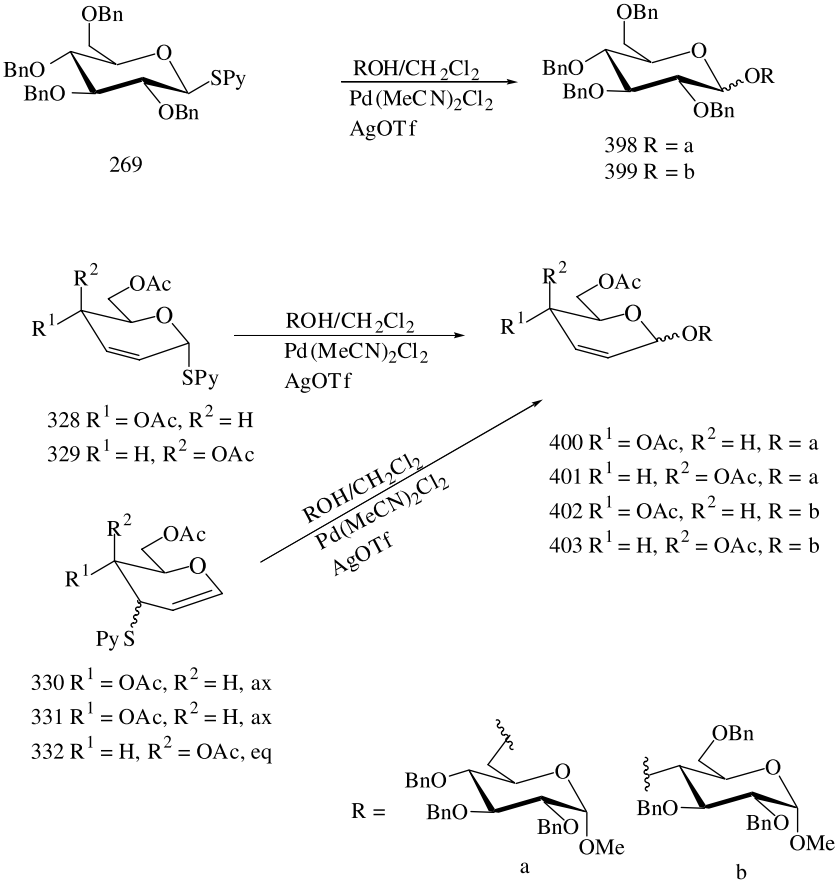
A high stereoselectivity was reported,[57] when the SBox-glucoside **108** was coupled with methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside in the presence of $ZnCl_4$/Ag_2CO_3, in CH_2Cl_2 to afford within 2 h the disaccharide **397** in 70% yield with high stereoselectivity (α:β 10:1). Moreover, compound **397** was obtained in 88% yield in higher α-stereoselectivity (α:β 15:1) upon using $TrClO_4$ as an activator[57] (Scheme 52).

A combination of silver triflate with bis(acetonitrile)dichloropalladium(II) activated the glycosidation reaction of β-**269** with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside in CH_2Cl_2; a molar ratio of **269**:ROH(**a**):$Pd(MeCN)_2Cl_2$:AgOTf of 2:1:2:2 gave an α:β (60:40) mixture of the disaccharide **398** in 80% yield. An increase in the molar ratio of AgOTf to 4 equiv increased the yield and α-ratio (93% yield, α:β 65:35) of **398**. On the other hand, coupling of **269** with the acceptors to give **398** and **399** was affected by the solvents; a mixture of acetonitrile and dichloromethane of molar equivalents 2:1:3:6 exhibited a marked β-favored solvent effect, compared to a dichloromethane solution.[114]

Glycosidation with 1-thio-2-enosides **328** and **329** or 3-thio-1-enosides **330**, **331** and **332** of the acceptors in the presence of $Pd(MeCN)_2Cl_2$-AgOTf as activator in CH_2Cl_2 in a molar ratio of donor:acceptor:Pd(II) and AgOTf of 2:1:2:2 afforded preferentially the α-2-enosides **400–403**, respectively, in 55–94% yield (Scheme 53). Increasing the molar ratio of **329** to 4 equiv or using an equivalent ratio of **332** and other reagents gave only the α-anomer **403**[114] (Table 4).



Scheme 52.



Scheme 53.

Table 4. Effect of molar ratio of reactants, promoters and solvents on stereoselectivity of disaccharides in Scheme 53

Donor	Acceptor ROH	Molar ratio	Solvent	Product	Yield (%)	α:β
269	a-OH	2:1:2:2	CH_2Cl_2	**398**	**80**	60:40
269	a-OH	2:1:2:4	CH_2Cl_2	**398**	**93**	65:35
269	a-OH	2:1:3:6	CH_2Cl_2–MeCN	**398**	**88**	13:87
269	b-OH	2:1:3:6	CH_2Cl_2–MeCN	**399**	**93**	42:58
328	a-OH	2:1:2:2	CH_2Cl_2	**400**	**94**	83:17
329	a-OH	2:1:2:2	CH_2Cl_2	**401**	**81**	94:6
329	b-OH	1:1:1:1	CH_2Cl_2	**403**	**68**	α Only
330	b-OH	2:1:2:2	CH_2Cl_2	**401**	**68**	96:4
330	b-OH	2:1:2:2	CH_2Cl_2	**403**	**72**	96:4
331	a-OH	2:1:2:2	CH_2Cl_2	**400**	**55**	α Only
331	b-OH	4:1:2:2	CH_2Cl_2	**402**	**87**	α Only
332	b-OH	2:1:2:2	CH_2Cl_2	**402**	**62**	90:10

3.4. Triflates as promoters

Glycosylation of 1-(1-phenyl-1*H*-tetrazol-5-yl)-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **280** with a variety of glycosyl acceptors using silver triflate as a promoter afforded an α/β mixture of glucopyranosides **351**. The α:β anomeric ratio ratio was found to be dependent on the type of alcohol[102] (Table 5).

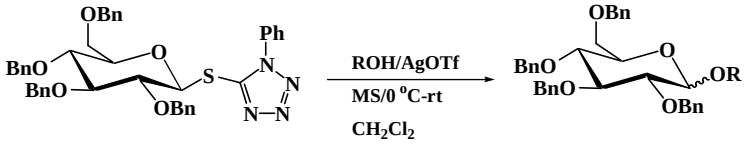
The S-Box-glycosides **110–112** were reacted with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**h**) in the presence of AgOTf or MeOTf and molecular sieves in 1,2-dichloroethane to give the 1,2-*trans* disaccharides **404–406** in 76–95% yield.[35] Similarly, the disaccharides **404a–g** were obtained when **110** was coupled with various acceptors using AgOTf or MeOTf.[35] NIS/TfOH promoted the glycosylation of **110** and **h**, in the absence of molecular sieves, to give **404**[35] (Scheme 54).

Coupling of the glycosyl donor **32** with cyclohexanol in CH_2Cl_2 at 0 °C in the presence of AgOTf gave cyclohexyl β-D-glucopyranoside **407**[41] in 68% yield. Similarly, nitrobenzimidazolyl **89** and pyridyl **15** thioglucosides gave **407** in 38 and 66% yields, respectively.[41]

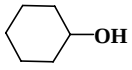
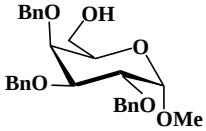
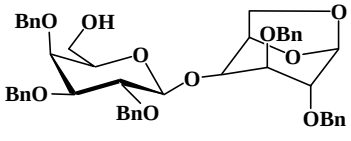
Under the same reaction conditions **32** coupled with thexyldimethylsilyl 3,6-di-*O*-benzyl-2-deoxy-2-*N*-dimethylmaleimido-β-D-glucopyranoside **408** to give the β-disaccharide **409** in 46% yield. On the other hand, the benzyl derivative **113**, under the same reaction conditions, gave the disaccharide **410** also in 46% yield, but in an α:β ratio of 1:3.[41] Similarly, **113** coupled with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside in the presence of AgOTf or TMSOTf to afford the disaccharide **398** in 44% yield and in an α:β ratio of 1:4[41] (Scheme 55).

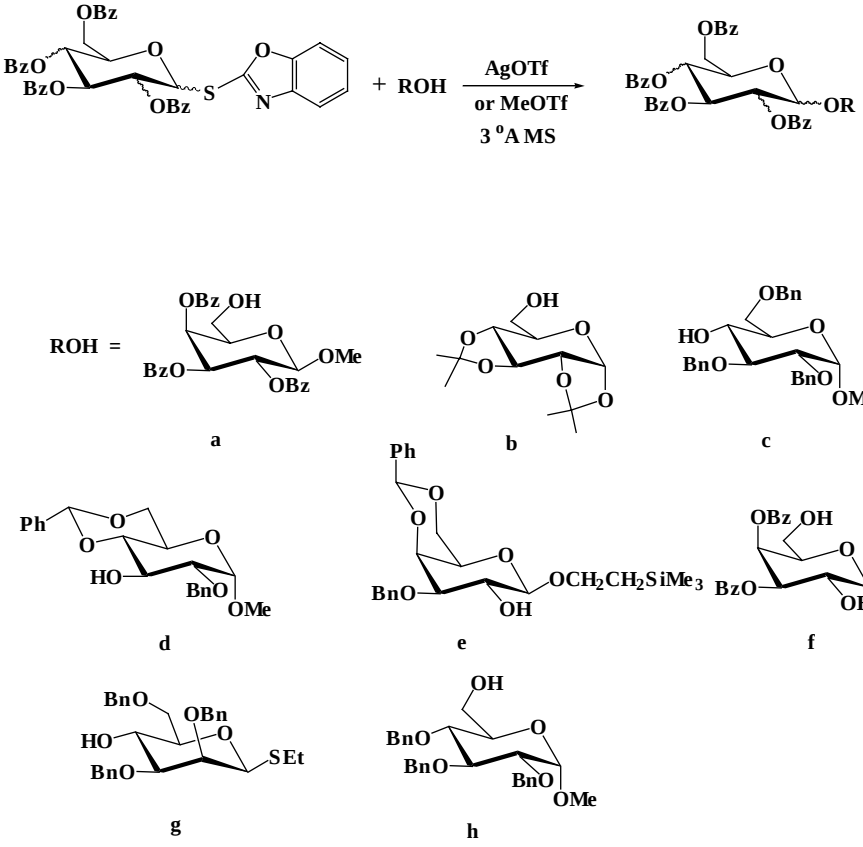
The presence of only one nonparticipating group on O-2 in the thioglycosides, 2-benzoxazolyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-1-thio-β-D-glycopyranoside **108** and **109**, resulted in the formation of α-linked disaccharides **411** and **412**, respectively, in comparable yield when AgOTf/MS or MeOTf/MS were used as promoters for their coupling with **a**. In addition, **108** gave only the α-disaccharide **411** when coupled with **c** or **g** using AgOTf or MeOTf as a promoter. When TMSOTf was used as activator in the coupling of **108** with acceptor **a**, a sluggish reaction occurred (incomplete within 24–48 h) and, although a high or complete anomeric selectivity was found, a low isolated yield was obtained.[57] When NIS–TMSOTf was used as a promoter, however, an α:β mixture of **411** was obtained in a ratio of 15:1. On the

Table 5. Yields and α/β ratios of products from glycosylation of **280**

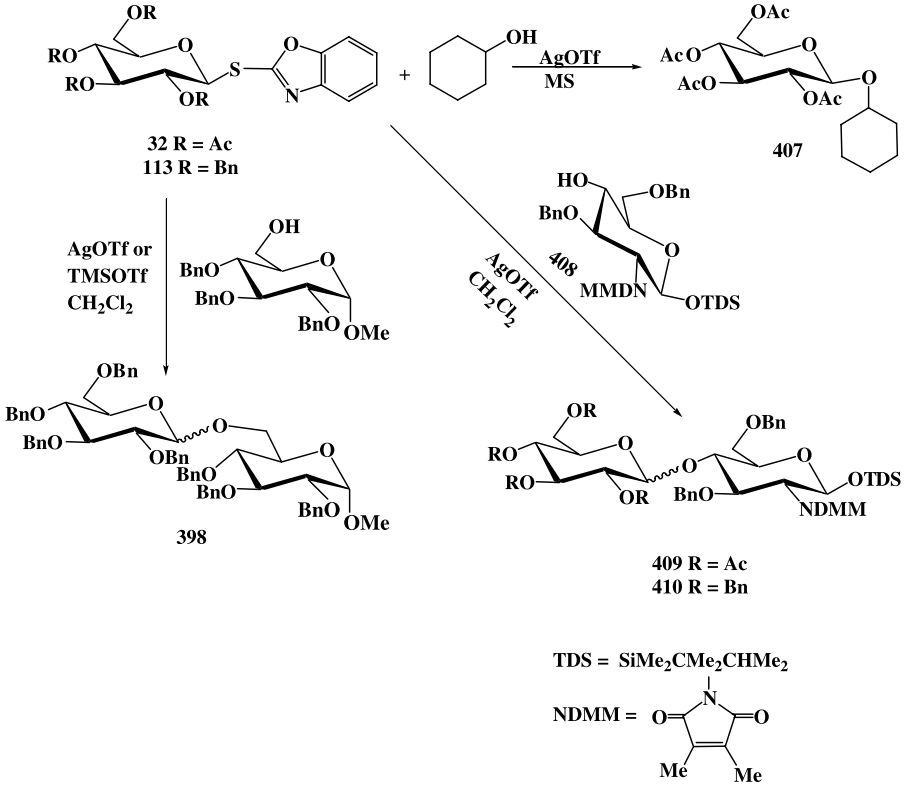


280 **351**

ROH	Yield (%)	α:β
MeOH	87	771:29
Cholesterol	95	50:50
	95	33:67
	48	66:34
	71	66:34

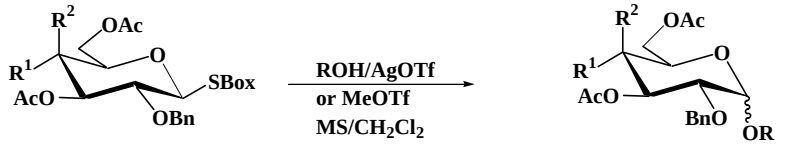


Scheme 54.



Scheme 55.

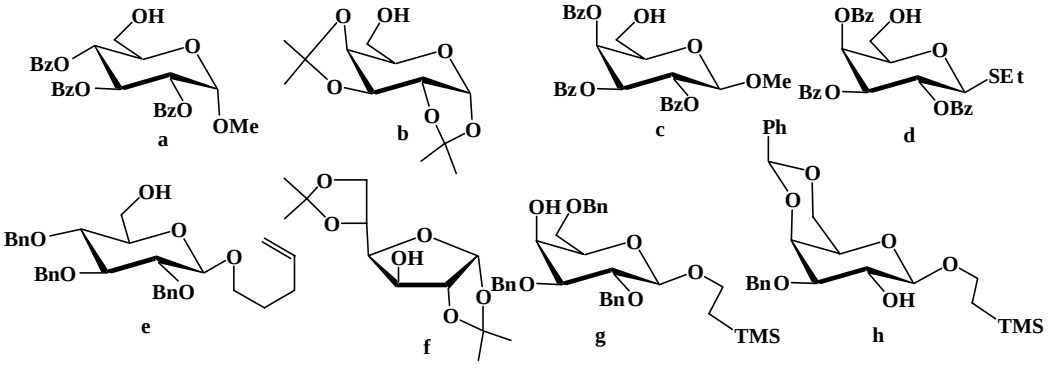
Table 6. Results of coupling of **108** or **109** with acceptors in presence of AgOTf or MeOTf



108 R^1 = OAc, R^2 = H
109 R^1 = H, R^2 = OAc

411 R^1 = OAc, R^2 = H
412 R^1 = H, R^2 = OAc

Donor	Acceptor	Promoter	Yield (%)	α:β
108	**a**	MeOTf/MS	**89**	α Only
108	**a**	AgOTf/MS	**92**	α Only
108	**b**	AgOTf	**99**	**11**:**1**
108	**c**	AgOTf/MS	**85**	**15**:**1**
108	**c**	AgOTf	**97**	α Only
108	**d**	AgOTf	**98**	α Only
108	**e**	AgOTf	**99**	**8**:**1**
108	**f**	MeOTf	**88**	**8**:**1**
108	**g**	MeOTf	**88**	**A** Only
108	**h**	MeOTf	**78**	**3**:**1**
109	**b**	AgOTf	**90**	**10**:**1**
109	**c**	AgOTf	**80**	α Only



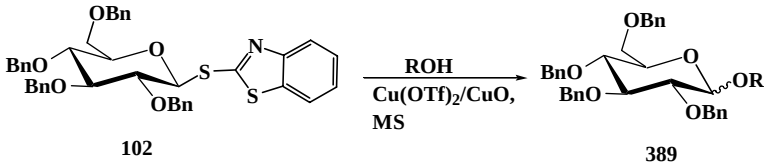
other hand, when an Ag_2CO_3/AgOTf promoter was used for the same reaction, the α-linked disaccharide **411** was obtained.[57] Glycosidation reactions of **108** and **109** with various acceptors in the presence of AgOTf or MeOTf are summarized in Table 6.

Cupric triflate activated the glycosidation of 2-benzothiazolyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **102** with the acceptors in the presence of cupric oxide and 4 Å MS to give an α,β-mixture of glucosides **389**, with the α-glucoside as the major isomer[58] (Table 7).

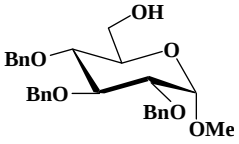
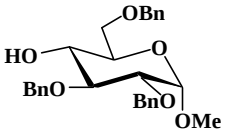
Pyrimidin-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-manno pyranoside **339a** and pyrimidin-2-yl 2,3,4-tri-*O*-benzyl- and 2-*O*-acetyl-3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyrano sides (**345a**,**345**) were coupled with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose using 2 mol equiv of AgOTf as activator to give only the respective 1,2-*trans* disaccharides **413** (R=**a**,**b**,**c**) in 93–95% yield.[116] Reducing the molar ratio of AgOTf in the coupling with **345a** lowered the yield (65%) of **411** (R=**c**), with the formation of benzyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rahmnopyranoside,[116] which became the main product upon decreasing AgOTf to 0.4 equiv. The thioglycosides, pyrimidin-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside **160** and pyrimidin-2-yl 2,3,4-tri-*O*-benzyl-1-thio-β-D-xylo- and -β-D-arabino-pyranosides **161**,**162** were coupled with the same acceptor, in the presence of two equivalents of AgOTf, to give high yields of the 1→6 disaccharides **413**, where the 1,2-*cis* anomer was the major isomer; the α:β ratios were 1.6:1 for **413d**, 1.2:1 for **413i** and 1:2.3 for **413e**[13] (Scheme 56). The reaction was extended to the donors **339a**, and **340**, pyrimidin-2-yl 2,6-di-*O*-acetyl-3,4-di-*O*-benzyl-1-thio-α-D-mannopyranoside **339b** with the acceptor **x** to give the α-linked disaccharides **414** (R=**a**,**f**,**g**).[116] The use of TMSOTf as a promoter gave similar results. Longer reaction times led to poorer selectivity, whereas a shorter reaction time did not change the selectivity, but decreased the yield.[13]

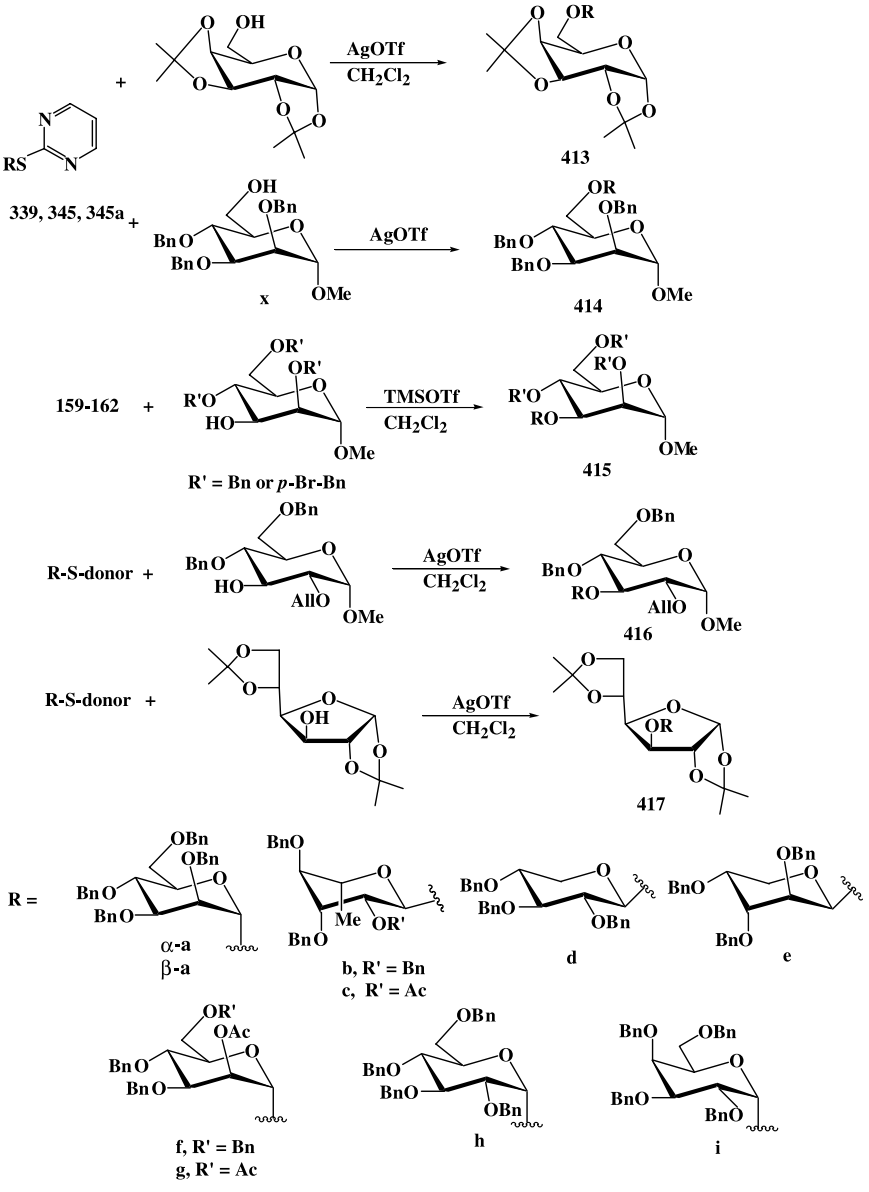
Reaction of fully benzylated pyrimidin-2-yl-1-thio-β-D-gluco- **159**, β-D-galacto- **160**, β-D-xylo- **161** and α-D-arabino-pyranosides **162** with methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside in CH_2Cl_2 at room temperature in the presence of TMSOTf as activator afforded the 1,2-*cis* disaccharides **415**, respectively, in good to excellent yields.[13] The use of AgOTf as a promoter also gave exclusive 1,2-*cis* selectivity, but in lower yield (no data).[13] If methyl 2,4,6-tri-*O*-*p*-bromobenzyl-α-D-mannopyranoside was, however, used as acceptor for coupling with **160** in the presence of TMSOTf, conversion took place into the respective α-linked disaccharide in 96% yield within 1 h.[13]

Table 7. Results of glycosylation with **102** in presence of $Cu(OTf)_2/CuO$ to give **389**

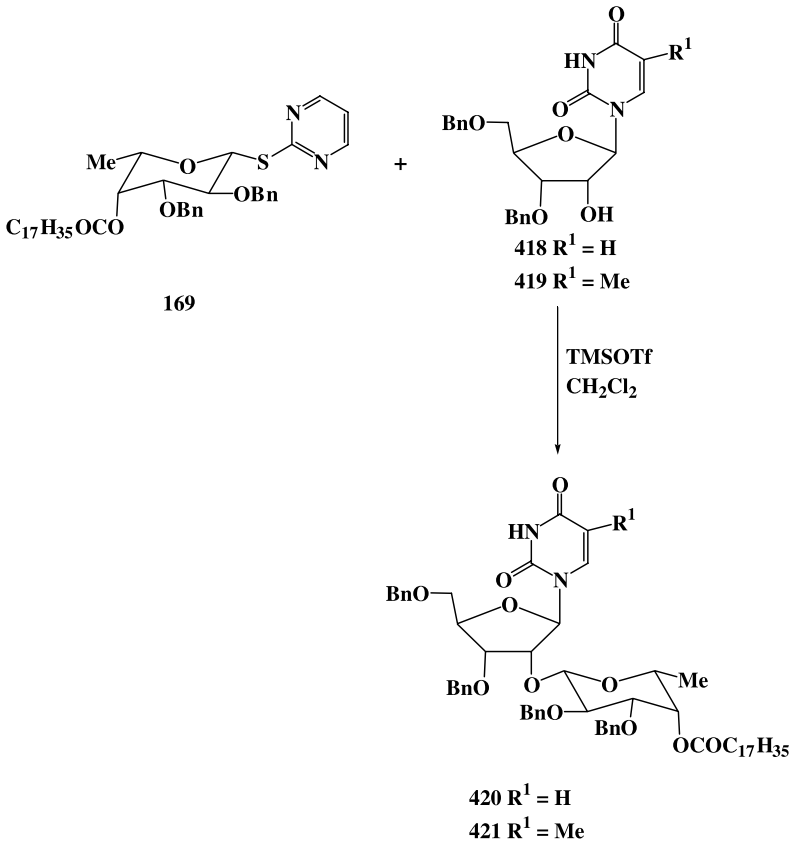


102 **389**

R	Yield (%)	α:β in **389**
MeOH	93	70:30
	92	80:12
	73	67:33
Cholesterol	79	83:17



Scheme 56.



Scheme 57.

Coupling of thiorhamnoside **345a** with methyl 2-*O*-allyl-4,6-di-*O*-benzyl-α-D-glucopyranoside afforded only the α-linked disaccharide **416** in high yield (87%). Under the same reaction conditions, however, the thioglycosides **339a** or **345a** were coupled with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, to give a nonseparable α,β anomeric mixture, 4:1 of **417** (R=**a**) and 1:1 of **417** (R=**b**) in 64–75% yield[116] (Scheme 56).

Pyrimidin-2-yl thiopyranoside **169** was coupled with the nucleoside acceptors **418** and **419** in the presence of TMSOTf (0.5 equiv) to give only the respective α-linked disaccharides **420** and **421** in 90–93% yield[72] (Scheme 57).

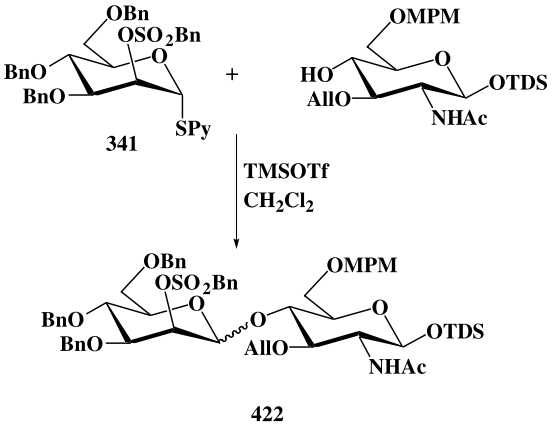
Stereoselective β-mannoside formation was achieved when 2-pyridyl 3,4,6-tri-*O*-benzyl-2-*O*-benzylsulfonyl-1-thio-α-D-mannopyranoside **341** was coupled with the acceptor, thexyldimethylsilyl-2-acetamido-3-*O*-allyl-6-*O*-(*p*-methoxybenzyl)-2-deoxy-β-D-glucopyranoside, in the presence of TMSOTf to give the respective disaccharide **422** in 82% yield with an α:β ratio of 1:7.4 (Scheme 58).[118]

Selective glycosylation of a hydroxyl group in the macrocyclic lactone **423** with D-desosaminide **424** in methylene chloride–toluene at room temperature in the presence of silver triflate afforded the β-glycoside **425**, the methanolysis of which gave **426** in 36% yield.[123] Further, glycosidation of **426** with L-cladinoside **427** in acetonitrile at room temperature in the presence of $Pd(ClO_4)_2$ gave, after methanolysis, the respective α-linked glycoside **428**[123] (Scheme 59).

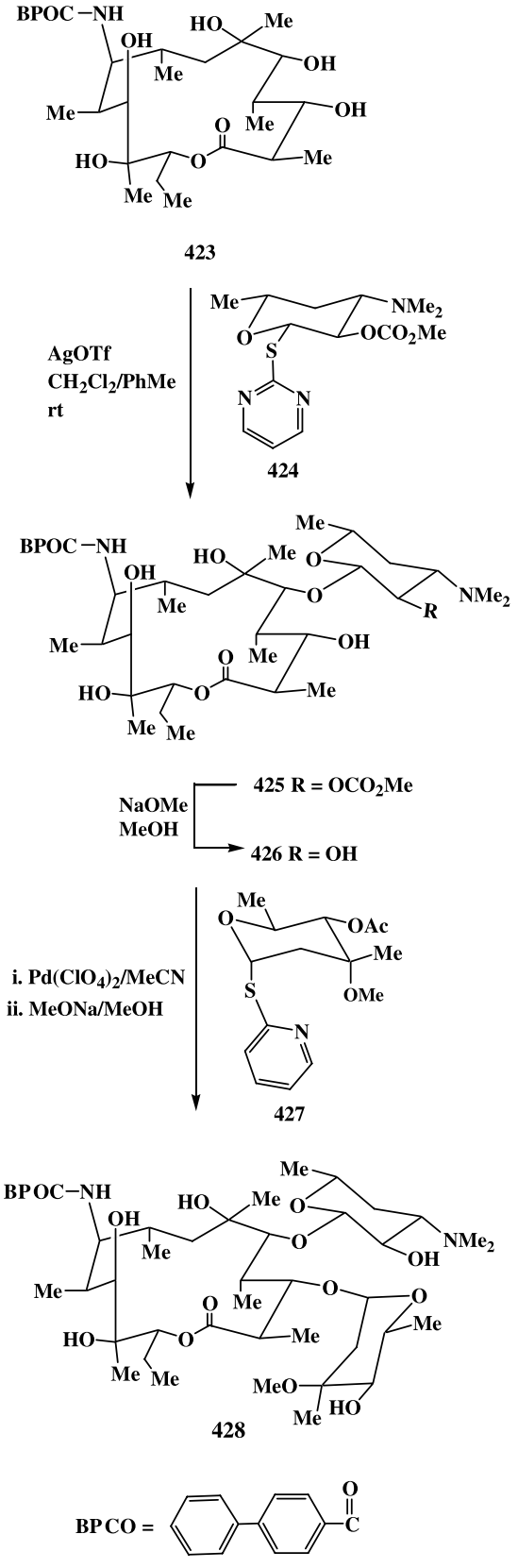
3.5. Sulphonic acids as promoters

Boiling of 2-pyridyl-1-thio-β-D-glucopyranoside **387** with methanol in the presence of one equivalent of methanesulfonic acid gave methyl α-D-glucopyranoside.[14] When isopropanol was the acceptor in acetonitrile containing *p*-toluenesulfonic acid (1.2 equiv) under reflux, however, it gave, after acetylation, a 3:2 α:β mixture of 2-propyl D-glucopyranoside.[14]

An NIS/TfOH-promoted glycosylation reaction of 2-benzoxazolyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside **110** with the acceptor, methyl 2,3,4-tri-



Scheme 58.



Scheme 59.

O-benzyl-α-D-glucopyranoside, afforded the β-disaccharide **404h** in 86% yield, within 30 min, which is a somewhat lower yield than those obtained from AgOTf or MeOTf (94–95%)[35] (Scheme 60).

4. Role of glycosylthio heterocycles in *C*-glycoside synthesis

The reaction of 2-pyridyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **269** with trimethylsilyl enol ethers or electron-rich aromatics at room temperature in the presence of AgOTf afforded the respective *C*-glycosides **429** and **430**.[99] In this case an α-mode of attack was the general trend with moderately nucleophilic species.[99] The reaction presumably involved the rapid formation of an oxonium ion **A**, which could exist in CH_2Cl_2 as a solvent separated ion pair of α/β-triflates **B** and **C**, in which the β-triflate **C** would be the reactive species and, consequently, gave the α selectivity. With 1,3,5-trimethoxybenezene in CH_2Cl_2, however, the β-anomer only was obtained, which could be due to the high reactivity of the nucleophile that intercepts the oxonium ion **A** from the less hindered β face before the equilibrium between the triflates can be established, as was found to have occurred with the less nucleophilic species[99] (Scheme 61).

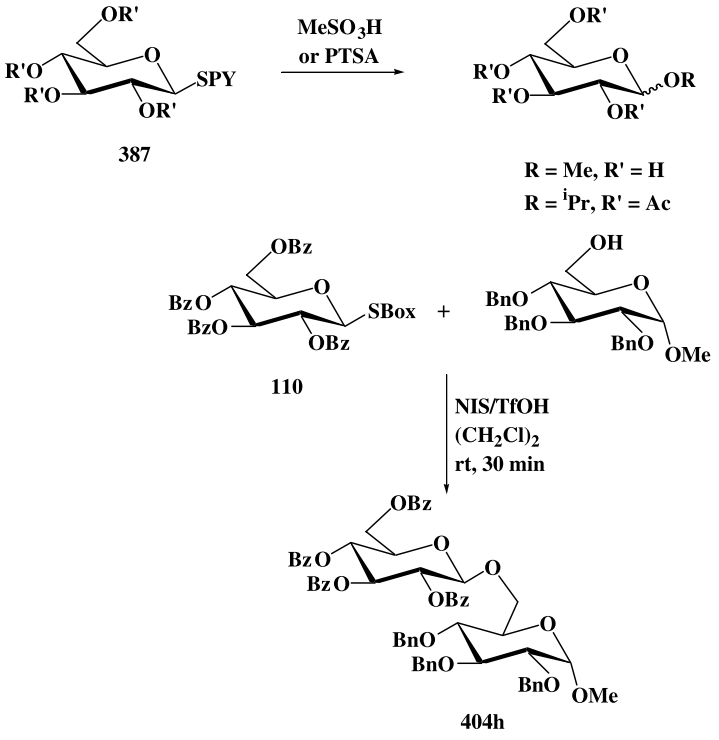
In more polar solvents such as diethyl ether, the α selectivity was observed exclusively.[99] Highly polar solvents such as acetonitrile or tetrahydrofuran were unsuccessful for C-glycosidation. Ribose substrates **259** and **261** exhibited high degrees of α/β stereocontrol,[99] to favor the formation of **431** and **432**. Glycosidation with **259** and **261** of 1,3,5-trimethoxybenzene, however, afforded the respective β-*C*-glycosides[99] (Table 8) (Scheme 62).

Treatment of the thiopyridyl derivative of L-arabino-pyranoside **273** with TBDMSOTf in the presence of triethylamine in ether at room temperature gave the silylated derivative **433**, which, upon treatment with AgOTf, underwent intramolecular cyclization to give **434**[100] (Scheme 63).

5. Role of glycosylthio heterocycles as acceptors

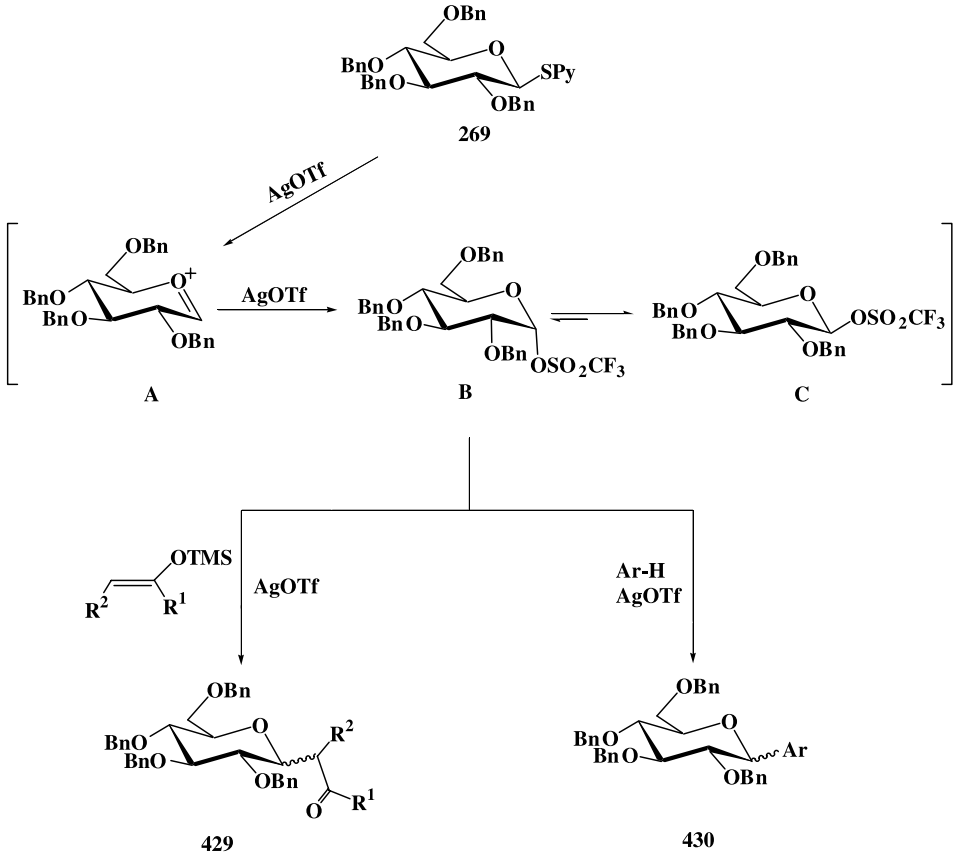
Heteroaryl thioglycosides with electron-withdrawing groups in the ring are very stable donors under most glycosylation conditions.[124] 5-Nitro-2-pyridyl β-D-thio-glucoside **435** was found to be an inert donor towards methanol and di-isopropylidene α-D-galactopyranose as glycosyl acceptors by using different promoters.[124] Coupling of **435** with several glycosyl donors **436** using a variety of promoters, however, took place smoothly to afford the disaccharides **437** in good yields with moderate to high stereoselectivity[124] (Scheme 64) (Table 9).

Glycosidation of *N*,*N*-diethyl *S*-(2,3,5-tri-*O*-benzyl-D-ribo-furanosyl) dithiocarbamate **436g** with the glycosyl acceptor **435** using NIS/TfOH as an activator in toluene afforded the 1→6 disaccharide **437g** with high α selectivity.[124,125] Under the same reaction conditions, D-xylo- **436f** and L-arabino-furanoside **436h** coupled with **435** to afford the disaccharides **437f** and **437h** in high yield, but in moderate 1,2-*cis* seteroselectivity.[124] The use of AgOTf and TMSOTf as catalysts was less successful. In the presence of $BF_3 \cdot Et_2O$, however, the coupling of **435** with **436g** took place within 48 h, with the formation of the respective α:β mixture of **437** in a ratio of 1:5[124,125] (Scheme 64).



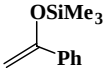
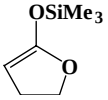
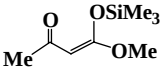
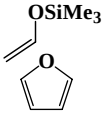
Scheme 60.

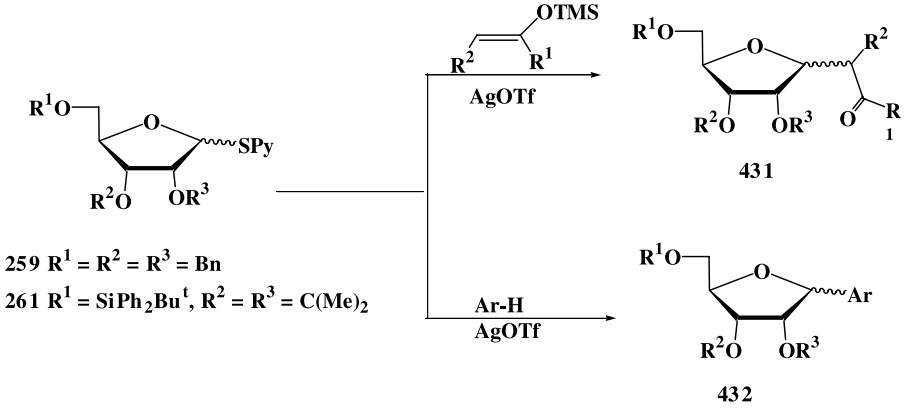
Thioglycosyl pyridines have been used for making more complex sequences of oligosaccharides by utilization of them as acceptors and donors, based on selecting the activation conditions and the more reactive thioglycosyl heterocycle to be the donor in the first sequence of the scheme protocol. Thus, the glycosyl acceptor, 2-pyridyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranoside, required for the glycosidation reaction, was synthesized from **15** by



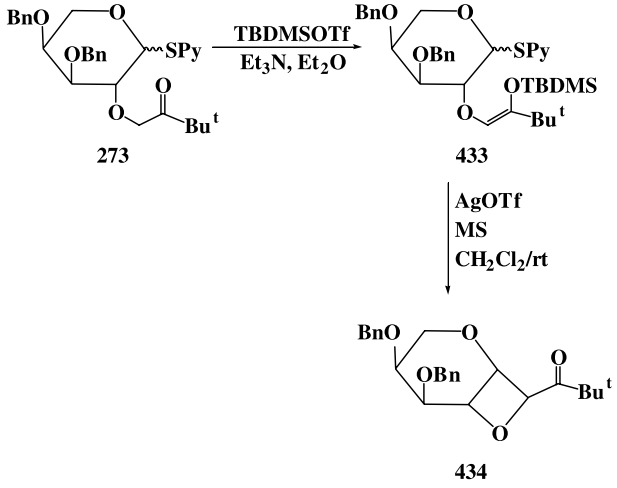
Scheme 61.

Table 8. Results of C-glycosidation of **259**, **261** and **269**

Nucleophile	Substrate	Solvent	Product α:β	Yield (%)
1,3,5-Trimethoxybenzene	**269**	CH_2Cl_2	β Only	63
1,3,5-Trimethoxybenzene	**259**	CH_2Cl_2	β	49
1,3,5-Trimethoxybenzene	**261**	CH_2Cl_2	β	61
1,3-Dimethoxybenzene	**261**	CH_2Cl_2	α	48
	**269**	CH_2Cl_2	α	81
	269	CH_2Cl_2	4:1	60
	**259**	CH_2Cl_2	α	70
	261	CH_2Cl_2	α	56
	**269**	CH_2Cl_2	α	43
	259	CH_2Cl_2	β	72
	**269**	CH_2Cl_2	α	35
	269	Furan, CH_2Cl_2	5:1	65



Scheme 62.

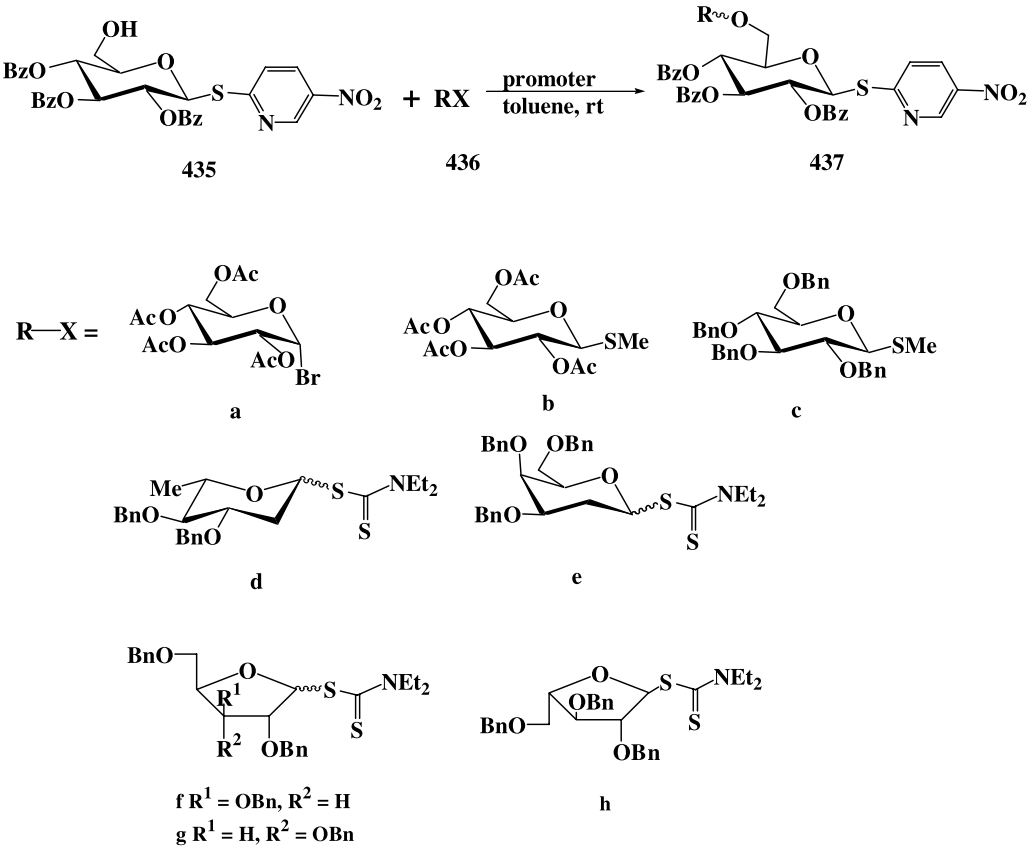


Scheme 63.

deacetylation to give **387** with subsequent selective 6-*O*-silylation to give **438**, that upon acetylation, gave **439** and desilylation gave **440**.[119] Coupling of **440** with **269** in CH_2Cl_2 in the presence of MeI/MS as a promoter afforded the α-disaccharide **441** in 66% yield. Replacement of the acetyl groups with benzyl groups gave **442**, which, upon coupling with 1,2:3,4-di-*O*-isopropylidine-D-galacto-pyranose, gave the α-1,6-linked trisaccharide **443** in 64% yield[119] (Scheme 64). Similarly, the glycosyl donor, 2-pyridyl-1-thio-β-maltoside **53**, was coupled with **440** to give the trisaccharide glycosyl donor **444**, which, on deacetylation and subsequent benzylation, gave **445** that, upon reaction with the acceptor **a**, gave the tetrasaccharide[119] **446** (Scheme 65).

6. Biological activity of glycosylthio heterocycles

The 5,6-dichlorobenzimidazol-2-yl β-D-thioribofuranoside derivative **28** was tested for its in vitro inhibitory effects on the replication of a number of DNA viruses, that is, human cytomegalovirus (CMV), herpes simplex virus types 1 and 2, vaccinia virus and RNA viruses (parainfluenza virus type

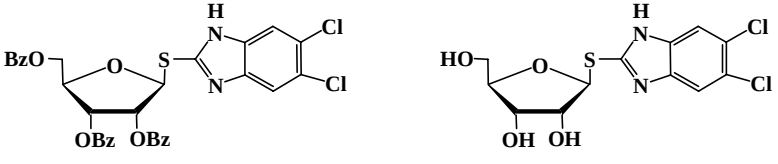


Scheme 64.

Table 9. Reaction of **435** as acceptor with different donors in Scheme 64

Donor	Reaction time	Promoter	α:β	Yield (%)
436a	24 h	Ag_2O	β Only	62
436b	24 h	NIS/TfOH	β Only	82
436c	1 h	NIS/TfOH	2:1	85
436d	5 min	AgOTf	4:1	67
436d	15 min	AgOTf	9:2	81
436d	15 min	TMSOTf	5:1	78
436d	1 h	$BF_3.Et_2O$	6:1	94
436d	25 min	NIS/TfOH	9:2	93
436d	50 min	IDCP	3:2	92
436e	25 min	AgOTf	15:1	71
436e	25 min	TMSOTf	15:1	95
436e	45 min	$BF_3.Et_2O$	16.5:1	92

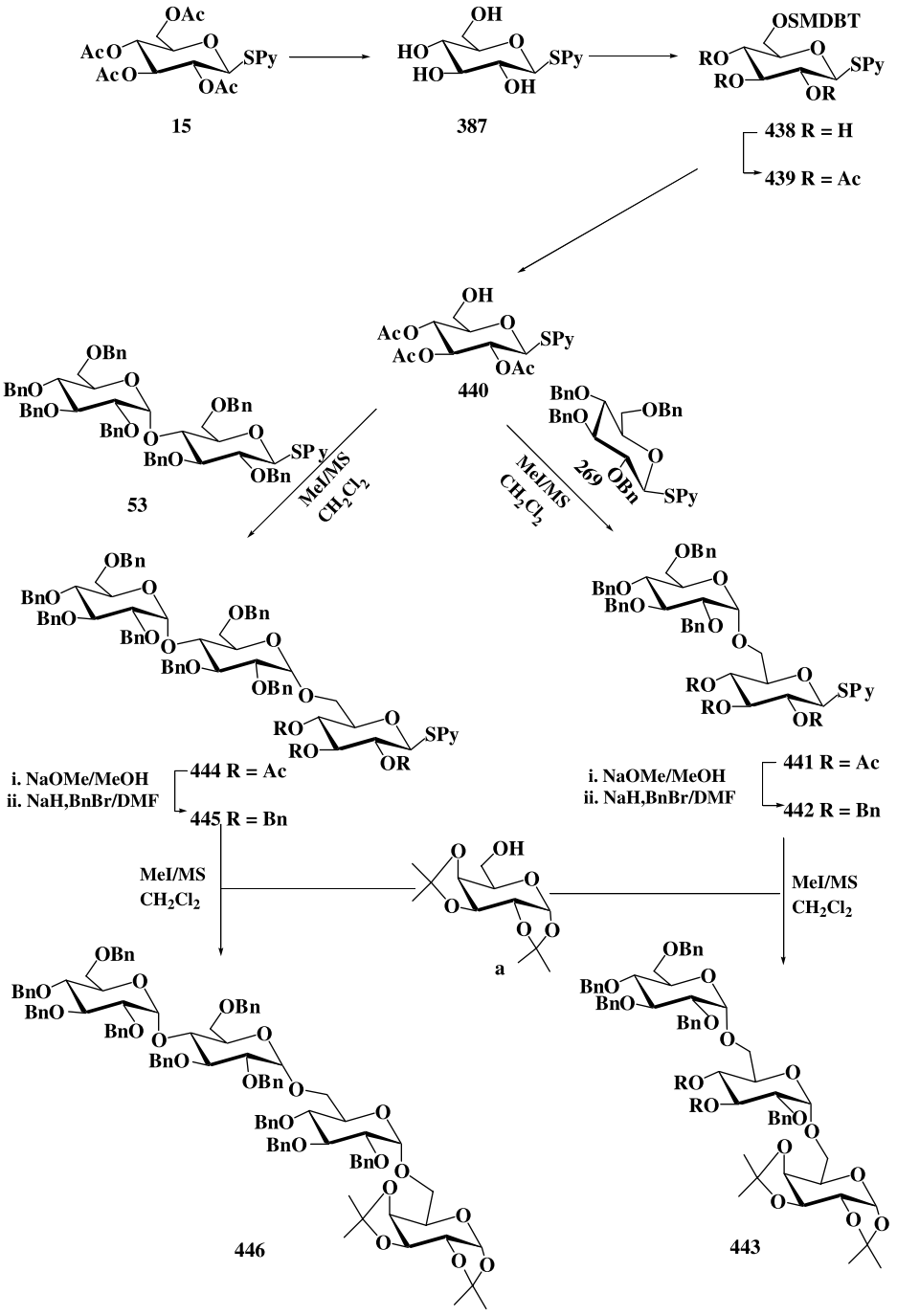
III, respiratory syncytial virus-1) in three cell systems (MRC-5, Vero and KB cells). Only the unprotected S-riboside **28a** showed an antiviral effect against CMV in MRC-5 cells without toxicity at 10^{-4} or 10^{-3} M with an ED_{50} value of 10^{-4} M.[34]



28 **28a**

The enzyme, β-glucuronidase, exists in human cancer tissues at a higher concentration than the normal level, which may be used in devising prodrugs. The activity of the β-glucuronidase was enhanced when the cell become more acidic. The cancer cells are already known to be more acidic than the normal cells and can specifically be increased by glucose.[126,127] Therefore, glucuronides of known anticancer compounds can selectively deliver these drugs to cancer tissues. Thus, ammonium 7*H*-purin-6-yl 1-thio-β-glucopyranosiduronate **447** and 7*H*-purin-6-yl 1-thio-β-glucopyranosiduronamide **448** were tested as substrates for the β-glucuronidase enzyme.[89] It was believed that the substrate behavior of **448** is not due to a nonspecific protein effect and that hydrolysis of **448** occurs at the enzyme active site.[128]

Glucopyranosiduronamide **448** has no effect on the growth of either the Chinese hamster lung fibroblast V79 line (a cell line not of tumor origin) or L1210 cells (a line of tumor origin).[89] In addition, **447** (10^{-5}–10^{-3} M) has no effect on the growth of the V79 line.[89] Compound **447**, however, at a concentration 10^{-4} M, showed 22% inhibition of the L1210 cells in 48 h, whereas, at lower concentrations (10^{-7}–10^{-5} M), no inhibition of cell growth was observed within 48 h.[89]

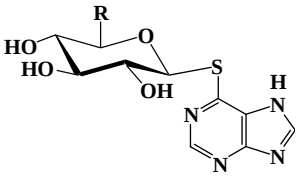


Scheme 65.

These results showed that **447** and **448** possess selectivity and that β-glucuronidase is most likely an obligate partner in the drug delivery.[89] Consequently, **448** is not cytotoxic, probably because it is too a poor substrate of glucuronidase to release an adequate amount of 6-mercaptopurine to inhibit L1210 cell growth.[89] On the other hand, **447** was virtually inactive towards the L1210 mouse screen employed by National Cancer Institute (NCI). The more lipophilic methyl ester **450** was, however, scarcely more active,[88] but not as active as 6-mercaptopurine.[88] No information is available concerning whether **450** penetrates cancer cells or is hydrolyzed in situ, either chemically or enzymatically, and it may be active in its own right.[88] Compound **447** was found to be of moderate selectivity for leukemic cells,[129] and both **447** and **450** appear to be less toxic than 6-mercaptopurine.[88]

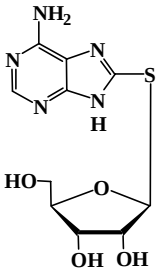
Purin-6-yl 6′-deoxy-1′-thio-β-D-glucopyranoside **450**, a substrate for almond β-glucosidase, was found to be a weak competitive inhibitor of bovine liver

β-D-glucuronidase ($K_i \sim 20$ mM). Purin-6-yl 1′-thio-β-D-glucopyranoside **449** was found to be active against sarcoma 180 and adenocarcinoma 755 and had relatively little toxicity, compared to 6-mercaptopurine.[88]

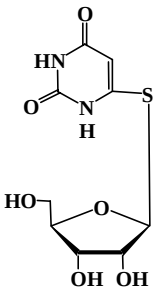


447 R = CO_2NH_4
448 R = $CONH_2$
449 R = CH_2OH
450 R = Me

6-Amino-8-(β-D-ribofuranosyl)thiopurine **451** and 6-(β-D-ribofuranosyl)thiouracil **452** were tested for the inhibition of cell growth of *Escherichia coli*, leukemia K1210 and Ehrlich ascites. The thioriboside **451** showed quite effective inhibition of 50% of *Escherichia coli* and *Ehrlich ascites* at concentrations of 5×10^{-6} and 3×10^{-4} M, respectively, whereas **452** was essentially inactive. In the tumor systems, **451** was moderately active, whereas **452** was inhibitory only at relatively high concentrations of $1\text{–}2\times10^{-3}$ M.[74]

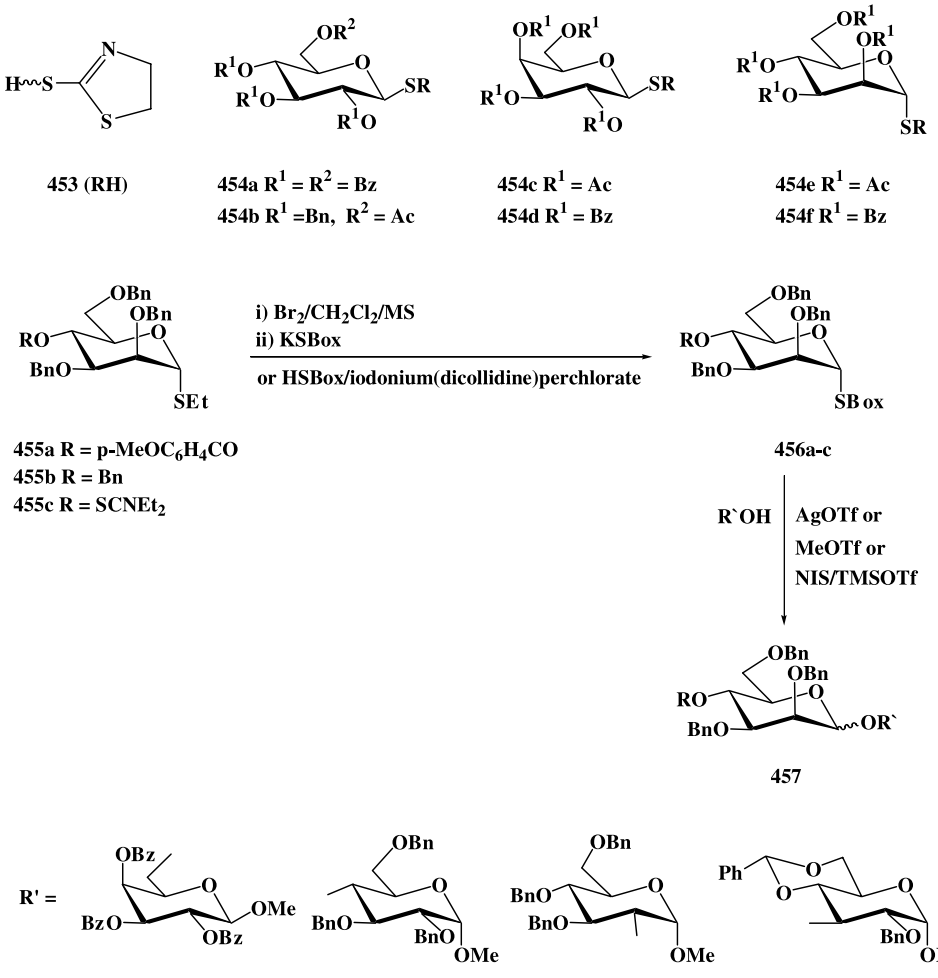


451



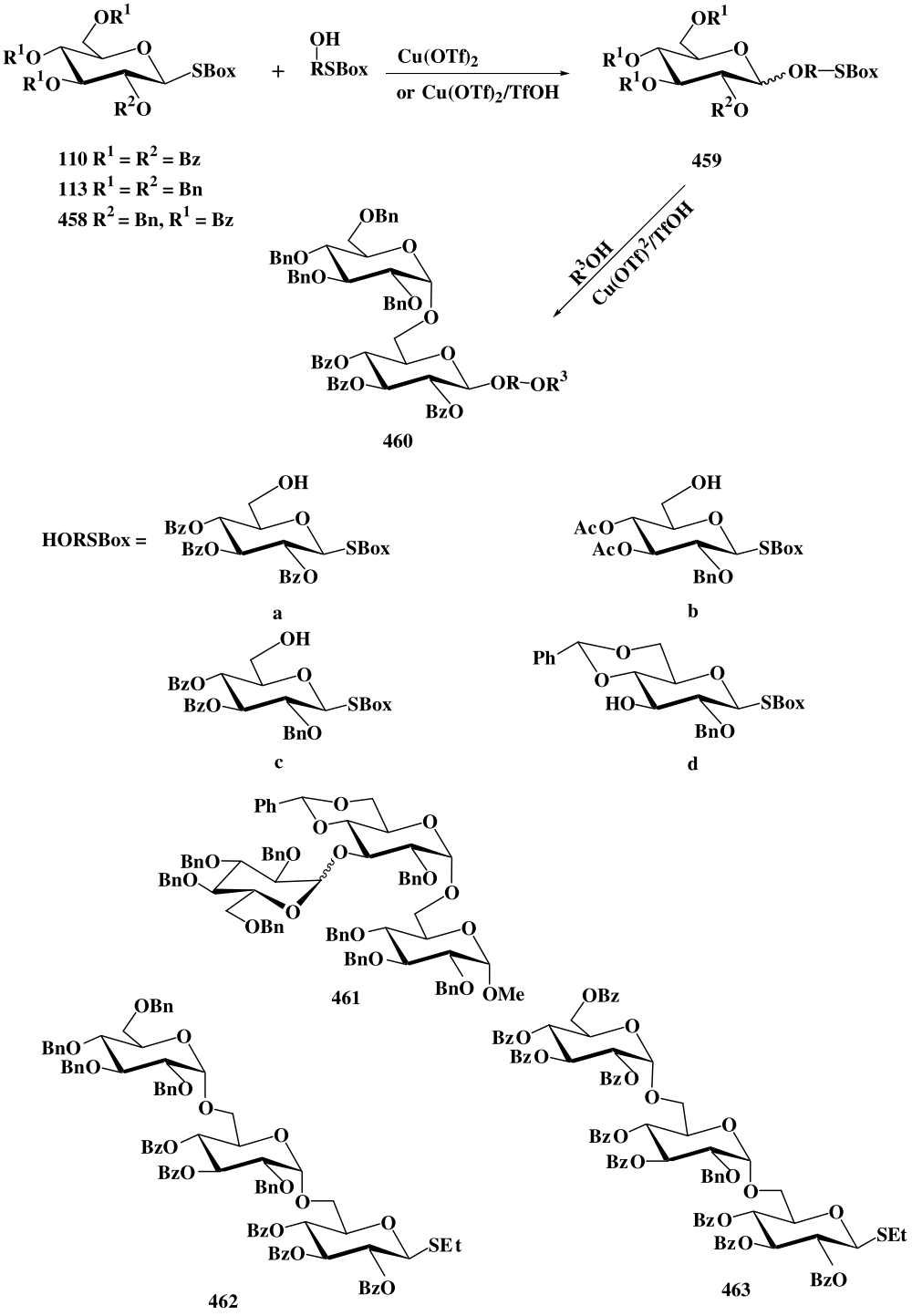
452

A low concentration of the thioglucoside **139** had no significant effect in vitro on the activity of α-glucosidase in liver homogenates of mice and the SBox **32** caused no detectable change in the activity of the enzyme.[130] The kinetics of inhibition of the lysosomal α-glucosidase fraction in vitro by compound **139** showed 23.2% competitive inhibition, with K_i 9×10^{-3} M, whereas **32** showed no detectable change in the enzyme activity.[130] Using *p*-nitrophenyl β-D-glucopyranoside as the substrate, compound **139** showed competitive inhibition of liver homogenate β-glucosidase in vitro.



Scheme 66.

The relative specific inhibition of β-glucosidase in vivo by compound **139** was found to be 60%.[130] The effect of compound **139** on blood sugar levels was studied to determine the relation between its inhibitory actions on the glucosidases and the antihyperglycemic behavior. Compound **139**, in low doses, did not cause a change in the blood sugar levels, whereas higher doses (0.74 mg/gm body weight) reduced the level to 56.6%, but a complete depression of the animal took place as a side effect.[130]



Scheme 67.

Acknowledgements

The partial support from AvH and BFG in Germany are highly appreciated. Thanks are due to N. Rezki and M.R. Aouad for their valuable help in preparing this manuscript.

Appendix A

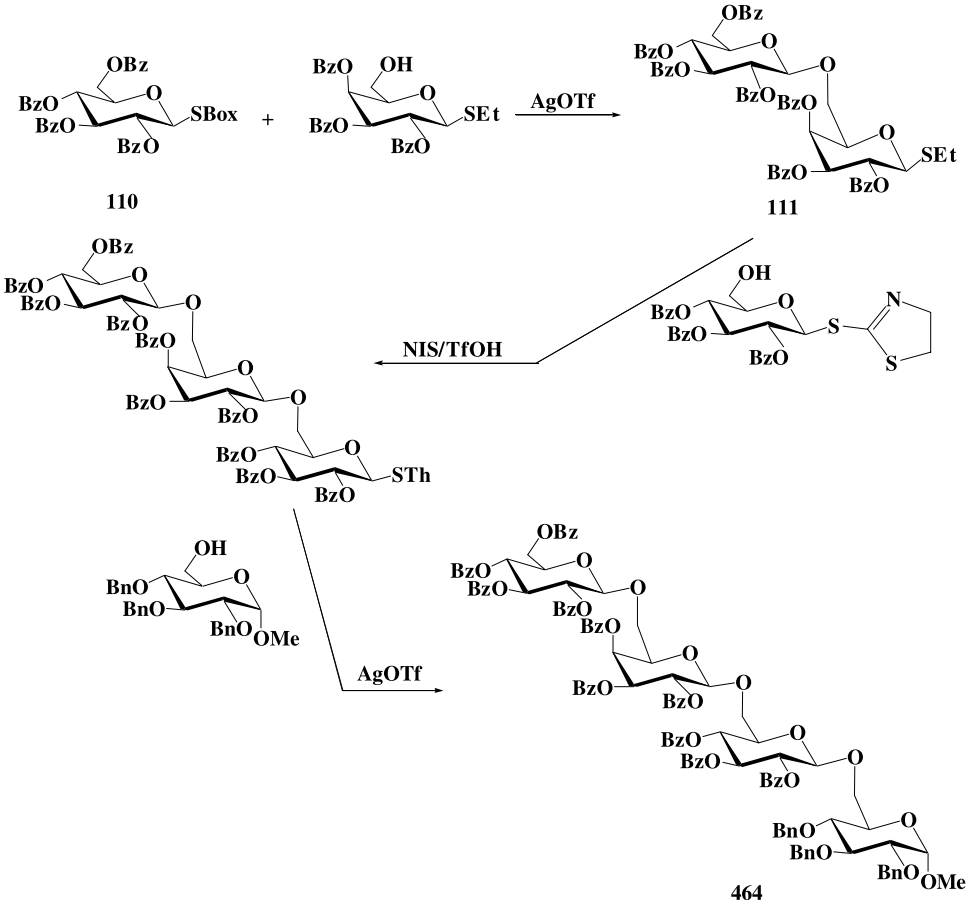
After this review was written, we found interesting and recent publications related to the topic which is worth being introduced under this appendix.

Thiothiazolin-2-yl thioglycosides **93** and **454** have been synthesized in complete stereoselectivity (1,2-*trans*) and in high yield from the reaction of per-*O*-acetylated D-glycopyranose and thiazoline-2-thiol **453** in the presence of $BF_3 \cdot Et_2O$ and 3 Å molecular sieves in methylene chloride.[131] Reaction of 3,4,6-tri-*O*-acetyl-1,2-anhydro-D-glucopyranose with **453** gave thiazolin-2-yl 3,4,6-tri-*O*-acetyl-1-thio-β-D-glucopyranoside by using $ZnCl_2$ as catalyst.[131] On the other hand, when **453** or its potassium or sodium salts were reacted with glycosyl halides in the presence of sodium hydride or crown ether, the 1,2-*trans* thioglycosides **94**, **454** in addition to the isomeric *N*-thiazolinylglycosides were obtained.[131]

Bromination of ethyl-1-thio-α-D-mannopyranosides **455a**,**b** with bromine followed by treatment with KSBox in presence of 18-crown-6 afforded 2-benzoxazolyl-1-thio-α-D-mannopyranosides **456a**,**b** in 58 and 79% yields, respectively. The 4-*O*-(*N*,*N*-diethylthiocarbamoyl)-derivative **456c** was obtained in 49% yield when **455c** was reacted with HSBox in CH_2Cl_2 followed by iodonium(dicollidine) perchlorate.[132] (Scheme 66)

Stereoselective β-mannosylation was improved by the use of electron-withdrawing substituent at C-4 and a bulky SBox leaving group at the anomeric center of the glycosyl donor. Thus, 2-benzoxazolyl 1-thio-α-D-mannopyranosides **456a**,**c** were coupled with the acceptor methyl 2,3,4-tri-*O*-benzoyl- β-D-galactopyranoside using AgOTf, MeOTf or NIS/TMSOTf to give the disaccharide **457** with α:β 1:3–5. The presence of 4-*O*-nonparticipating benzyl substituent as in **456b** resulted in a lower β-selectivity using AgOTf or MeOTf as promoters.[132] A slightly more β-selectivity was observed when a secondary glycosyl acceptors were coupled with **456a** rather than **456b**, although such selectivity was dependent on the position of the hydroxyl group (α:β 1:2.3–7.0) (Scheme 66).

Activation of fully benzylated 2-benzoxazolyl 1-thio-β-D-glucopyranoside **113** with $Cu(OTf)_2$ then coupling with 1,2,3,4-diisopropylidene galacose afforded the disaccharide **351c** in an α:β ratio 5.4:1 (89% yield).[133] On the other hand, no reaction has taken place when **108** or 2-benzoxazolyl 2-*O*-benzyl-3,4,6-tri-*O*-benzoyl-1-thio-β-D-glucopyranosides **458** were used as donors. This can be due to the electronically activated, armed benzyl groups in the



Scheme 68.

glycosyl donors. Chemoselective activation of armed **113** or moderately disarmed **110** glycosyl donors over the partially protected SBox glycoside acceptors (HORSBox) was achieved using $Cu(OTf)_2$ or $Cu(OTf)_2$/TfOH to give the disaccharides **459** together with the corresponding NBox disaccharides and the isomerized NBox glycosides.[133] (Scheme 67). Furthermore, reaction of the disaccharide **459** with R′OH gave the respective glycoside **460**.

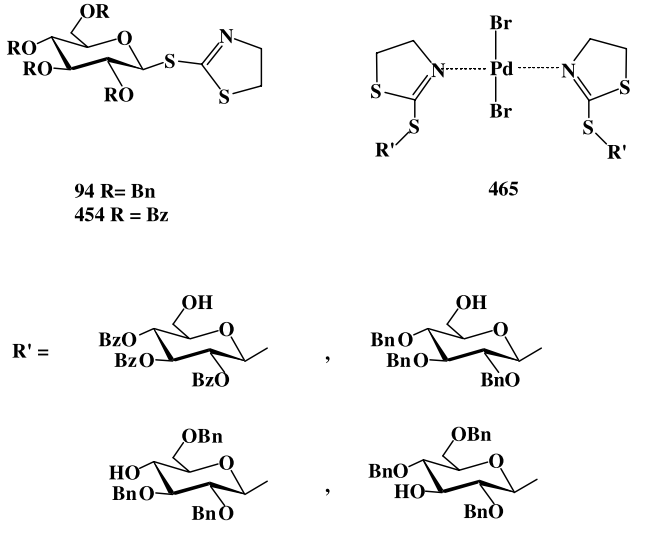
Coupling of fully benzoylated thiazolin-2-yl thioglycosides **454a**,**d**,**f** with various glycosyl acceptors using AgOTf, MeOTf, NIS/TfOH or $Cu(OTf)_2$ as promoters took place with complete stereoselectivity forming the 1,2-*trans* disaccharides in high yield (84–99%). On the other hand, 1,2-*cis* disaccharides were obtained when the thiazolinyl thioglycosides **94** or **454b** having 2-*O*-benzyl group were coupled with various acceptors using AgOTf as promoter. The α:β ratio of the disaccharide formed was dependent on the solvent used.[131]

Selective activation by using AgOTf of the thiazolinyl thioglycosides donors **454a**,**d** over partially protected ethyl 1-thio-β-D-glycopyranosides led to use the latter as acceptors.

Similarly, Silvertriflate activated the 2-benzoxazolyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside **110** over ethylthioglycosides to give β-disaccharides in high yields. The α-disaccharide were obtained when a non participating 2-*O*-benzylglycosyl donors were used.

On the other hand, when NIS/TfOH was used as a promoter, the ethyl or phenyl thioglycosides have been activated over the thiazolin-2-yl thioglycosides.[134] Thus allowed the synthesis disaccharides and tri-saccharides such as **461–463**[131,133] (Scheme 68). Also, the tetra-saccharide **464** was synthesized with complete 1,2-*trans* stereoselectivity[134] following the activation sequence as shown in Scheme 68.

Partially protected thiazolinyl thioglucoside acceptors can be deactivated by forming stable palladium II complexes by their reaction with $PdBr_2$ in 1,2-dichloroethane in the presence of 3 Å molecular sieve to give **465**. The coupling of which with thiazolinyl glycosyl donors such **94** and **454** using MeOTf, Cu(OTf) or NIS/TfOH gave the corresponding disaccharide (Scheme 69). Thus, this strategy provides a novel approach for oligosaccharides synthesis.[135]



Scheme 69.

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