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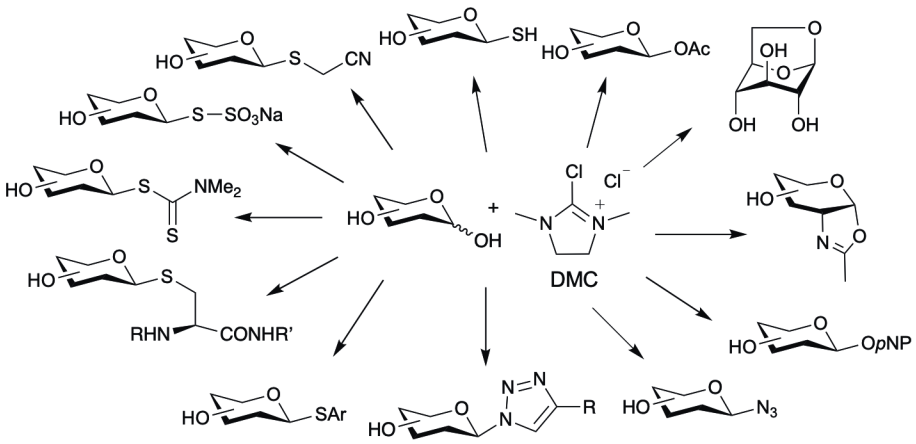

Applications of Shoda's reagent (DMC) and analogues for activation of the anomeric centre of unprotected carbohydrates

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Dedicated to Professor Shin-ichiro Shoda on the occasion of his 67th birthday

Abstract

2-Chloro-1,3-dimethylimidazolinium chloride (DMC, herein also referred to as Shoda's reagent) and its derivatives are useful for numerous synthetic transformations in which the anomeric centre of unprotected reducing sugars is selectively activated in aqueous solution. As such unprotected sugars can undergo anomeric substitution with a range of added nucleophiles, providing highly efficient routes to a range of glycosides and glycoconjugates without the need for traditional protecting group manipulations. This mini-review summarizes the development of DMC and some of its derivatives/analogues, and highlights recent applications for protecting group-free synthesis.

Keywords: carbohydrates, DMC, 2-chloro-1,3-dimethylimidazolinium chloride, ADMP, glycosylation, glycosides, protecting group free, aqueous solution, nucleophilic substitution

1. Introduction

Glycosylation is the chemical transformation most central to glycoscience. In biological systems glycosylation is achieved under aqueous conditions, usually by glycosyl transferases processing activated sugar donor substrates, and attaching them to a myriad of glycosyl acceptors with complete control of both regio- and stereochemistry. Glycosylation for the synthetic

carbohydrate chemist is usually much more difficult. The organic chemist must strive to define reaction outcome; achieving control of regiochemistry usually only after multiple protecting groups manipulations, and performing glycosylation reactions under strictly anhydrous conditions. Clearly such processes are logistically highly inefficient, both in terms of the lengths of reaction sequences, and also with respect to atom economy and the quantities of reagents, solvents, etc required.

Emulation of Nature's supreme efficiency, i.e. the direct chemical glycosylation of unprotected carbohydrates, particularly in an aqueous environment, has therefore become an area of significant interest. Fischer glycosylation, whist typically being performed in an alcohol as the solvent, is an almost ubiquitous reaction of unprotected monosaccharides, performed at some point in time by almost all synthetic carbohydrate chemists. However the harsh acidic conditions involved means that it cannot generally be applied to di- or oligosaccharides. A range of other chemoselective reactions of unprotected carbohydrates have therefore been developed, and the reader is refered to several excellent recent reviews for further details of these processes.[1,2]

This specific focus of the mini-review is the development and application of the dehydrating agent 2-chloro-1,3-dimethylimidazolinium chloride (DMC **1**, **'**Shoda's reagent', Fig. 1) for selective activation of the anomeric centre of unprotected carbohydrates in aqueous solution. Applications of the azido-derivative 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP **3**), and the benzimidazole analogue, 2-chloro-1,3-dimethyl-1H-benzimidazol-3-ium chloride (CDMBI **4**) will also be discussed (Fig. 1).

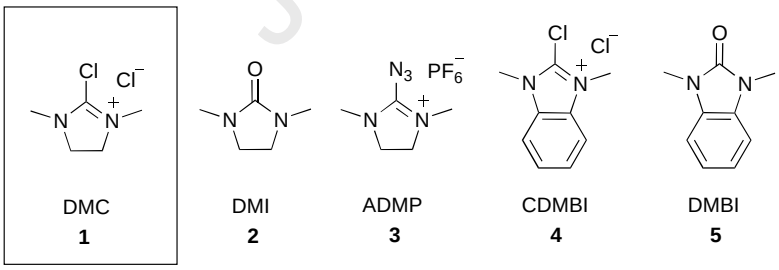
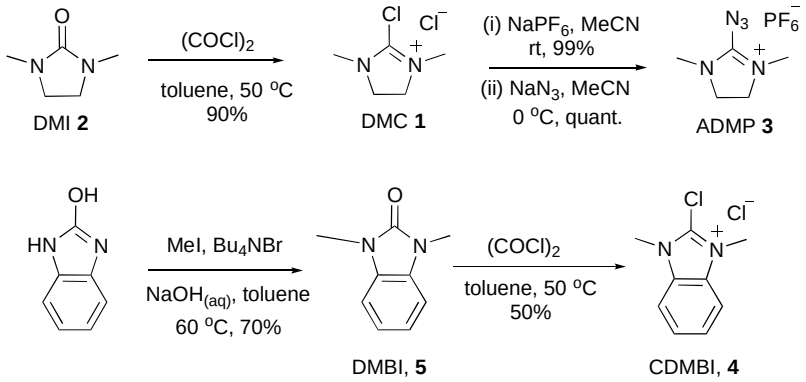


Figure 1. DMC and analogues

DMC **1**,[3] although first used as a reagent for organic synthesis as far back as the 1972 for the amidation of penicillanic acid,[4] only found intermittent application[5] until its development as a versatile dehydrating agent by Isobe and Ishikawa[6,7,8] the late 1990's in their search for a replacement for dicyclohexylcarbodiimide (DCC). However it was only some 10 years later that Shoda realised the potential utility of DMC in the carbohydrate field for reactions in an aqueous

environment. It is in the context of these significant applications in the carbohydrate field that the epithet 'Shoda's reagent' is applied to DMC. DMC **1** is a relatively cheap commercially available,[9] colourless odourless crystalline (m.p. 95-100 ^{o}C) though moderately hygroscopic solid, which is very soluble in protic (e.g. H_2O, EtOH etc), chlorinated (e.g. CH_2Cl_2, $CHCl_3$) and some polar aprotic (e.g. MeCN, DMF) solvents. It is insoluble in non-polar and ethereal solvents (e.g. Et_2O, THF). The azido-analogue of DMC, ADMP **3**, which is also commercially available[10] but considerably more expensive than DMC, can be made from DMC *via* firstly a counter-ion exchange to give the hexafluorophosphate salt (which reduces the hygroscopicity) and then reaction with sodium azide in acetonitrile (Scheme 1). ADMP **3** is a reagent that was originally developed and used extensively by Kitamura for diazo-transfers,[11,12] migratory aminations[13,14] and azide transfer reactions,[15] and despite first appearances is reportedly non-explosive.[16] Shoda has also synthesised and used the benzo- analogue of DMC, 2-chloro-1,3-dimethyl-1H-benzimidazol-3-ium chloride (CDMBI **4**, Fig 1).[17]

The electrophilic nature of DMC **1**, ADMP **3**, and CDMBI **4** is clear in that they should be readily attacked by nucleophiles at the carbon atom of the imidazolinium ring between the two nitrogens. Their hydrolysis products are the ureas 1,3-dimethylimidazolidin-2-one (DMI, **2**) and 1,3-dimethylbenzimidazol-2-one (DMBI, **5**) respectively, along with 2 equivalents of HCl. DMI **2** and DMBI **5** are therefore side-products formed in all DMC/ADMP or CDMBI mediated reactions. The corollary is that DMC **1** and CDMBI **4** can be made by chlorination of either DMI **2** or DMBI **5** respectively, and this can be achieved simply by heating with oxalyl chloride in toluene (Scheme 1). The urea DMBI **5** can in turn be made by methylation of 1H-benzimidazol-2-ol (itself readily available from benzene-1,2-diamine) under bi-phasic conditions (toluene/aqueous sodium hydroxide) with a phase transfer catalyst.[17]



Scheme 1. Preparation of DMC **1**, ADMP **3**, and CDMBI **4**.

2. Discussion

2.1 General considerations

2.1.1 Mechanistic pathways

The application of a known dehydrating agent, reportedly unstable in protic solvents, to reactions of unprotected sugars to be performed in aqueous solution at first seems somewhat counter-intuitive. However as direct reaction of DMC with solvent water proceeds at only a moderate rate, particularly at reduced temperature, then selective reaction with an unprotected carbohydrate substrate becomes a possibility. Crucially the key to selective activation of the anomeric centre by DMC is the enhanced acidity (pKa ~12.1-12.5)[18,19,20,21] of the anomeric hydroxyl group, which is presumably selectively de-protonated to a significant degree under the typically basic reaction conditions used for DMC mediated reactions (e.g. pKa of Et_3NH^+ ~10.75). As de-protonation increases nucleophilicity by several orders of magnitude, reaction can occur *via* this minor amount of the de-protonated form, with a corresponding shift in equilibrium. This key difference in pKa's, in combination with a base of appropriate strength (most commonly at least a two-fold excess of Et_3N), therefore allows the anomeric hydroxyl group the possibility of out-competing both solvent water and the other sugar hydroxyl groups for attack on DMC.

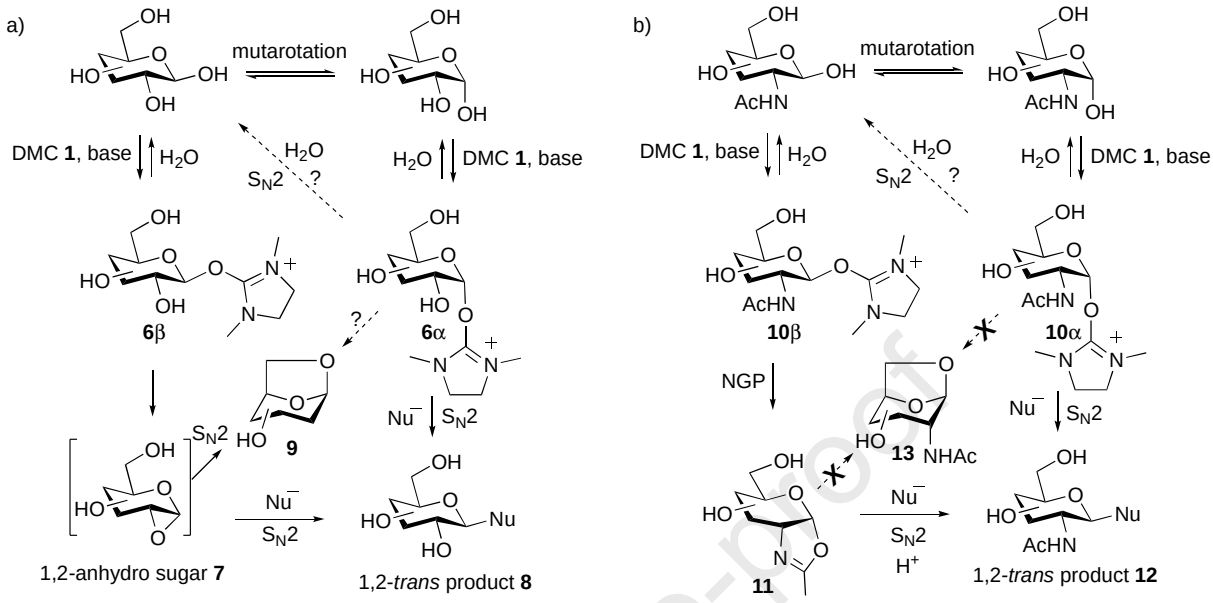


Figure 2. Plausible mechanistic rationalisations of the DMC activation of unprotected sugars for: a) 2-hydroxy sugars; b) 2-acetamido sugars.

A plausible mechanistic rationalisation for DMC activation of a reducing sugar in aqueous solution is illustrated in Fig 2. A caveat is that Fig. 2 is based largely on observed reaction outcomes rather than any detailed mechanistic studies. Different mechanistic pathways are followed depending on whether the substrate has either a hydroxyl (Fig 2a) or acetamido group (Fig 2b) at position-2 of the residue at the reducing terminus. For 2-hydroxy sugars, firstly the anomeric hydroxyl group attacks DMC **1**. In the case of the α-anomer this yields the 1,2-*cis* activated intermediate **6α**, while the β-anomer yields the 1,2-*trans* activated intermediate **6β**. Hydrolysis of either **6α** or **6β** by attack of water at the imidazolinium ring results in hydrolysis back to the starting anomer, without any change of anomeric configuration. In an early paper Shoda suggested that water could also perhaps cause hydrolysis of **6α** back to the β-anomer of the starting material (see: dotted arrow in Fig 2a), but there is no evidence of this pathway occurring, and given the relatively low nucleophilicity of water it seems perhaps unlikely. Intramolecular attack of the 2-hydroxyl of the β-activated intermediate **6β** can then result in the formation of the 1,2-anyhdro sugar **7**, which has been observed as an intermediate by NMR (*vide*

infra). Reaction of 1,2-anhydro sugar **7** with an external nucleophile attacking the anomeric centre in an S_N2 sense then produces the 1,2-*trans* substituted product **8**. Alternatively, an external nucleophile may also attack the anomeric centre of **6α** in an S_N2 sense, to again produce the 1,2-*trans* substituted product **8**. In the absence of external nucleophiles, or in competition with intermolecular processes, intramolecular attack of the 6-hydroxyl group of 1,2-anhydro sugar **7** results in formation of the corresponding 1,6-anhydro sugar **9**. Although it is possible that activated intermediate **6α** could also undergo this process directly (Fig. 2a dotted arrow), the report that a 2-hydroxyl group is essential for 1,6-anhydro sugar formation would seem to imply that this route is not generally followed.

For 2-acetamido sugars the pathways (Fig 2b) differ in so far as that neighbouring group participation (NGP) of the 2-acetamido group can occur. Again, activation of the α- and β-anomers of the starting material occurs by attack of the anomeric hydroxyl on DMC, yielding the reactive intermediates **10α** and **10β** (Fig. 2b). Intramolecular attack of the 2-acetamido group at the anomeric centre of the 1,2-*trans* configured **10β**, followed by proton removal by the base, then affords the oxazoline **11**. Under certain circumstances, notably in the presence of added acid, oxazoline **11** can be opened by attack of an external nucleophile to give the 1,2-*trans* substitution product **12**. In contrast the α-imidazolinium intermediate **10α** cannot directly form an oxazoline. In the presence of an external nucleophile **10α** can undergo an S_N2 type reaction to directly yield the 1,2-*trans* substitution product **12**. However, in the absence of external nucleophiles the oxazoline is the sole reaction product, so the question therefore arises is how precisely is **10α** converted into the oxazoline. Shoda has suggested (*vide supra*) that **10α** is probably hydrolysed to regenerate the β-anomer of the free sugar, but again the required S_N2 substitution by water has not been evidenced. Additionally Shoda has also stated that 'the intermediacy of glycosyl chlorides cannot be ruled out'. Indeed since glycosyl chlorides have now been isolated following reaction of protected reducing sugars with DMC and Et_3N in CH_2Cl_2, as recently reported by Judeh and co-workers,[22] their formation as transient intermediates in DMC-mediated reactions in aqueous solution seems distinctly possible. Therefore, plausibly S_N2 attack at the anomeric centre of α-activated intermediates such as **6α** and **10α** by chloride would give the corresponding β-chlorides as ephemeral species that could then undergo rapid conversion to either the 1,2-anhydro sugar **7** or oxazoline **11**. Finally in

studies performed to date using 2-acetamido sugars as substrates there has been no reported formation of the corresponding 1,6-anhydro sugar **13** under the reported reaction conditions (crossed dotted arrow in Fig. 2b)

Several aspects of these mechanistic rationalisations are worthy of comment. Firstly, it is not completely clear how fast mutarotation of the α- and β-anomers of the staring material is relative to other processes, particularly as mutarotation is both pH and temperature dependent. Importantly the reaction pH invariably changes with time as two equivalents of HCl are produced for each molecule of DMC that reacts: though precise values depend on the identity of the added nucleophile, the pH at the start of the reaction with Et_3N as the base is typically ~12,[23] and this decreases during the course of the reaction to ~11. Secondly, it should also be noted that although some reactions are possible with weaker bases, such as 2,6-lutidine (pKa of conjugate acid ~ 6.7), the required reaction times (36-48 h with lutidine vs 1 h with Et_3N) and temperatures (rt with lutidine vs 0 ^oC with Et_3N) indicate that such reactions are very much slower.[24] Thirdly, early in the development of DMC Shoda postulated the possible intermediacy of 1,2-anyhydro sugars,[25] such as **7**, in nucleophilic substitution processes involving DMC. Shoda actually confirmed this theory in 2017 when a low T NMR study[26] revealed that 1,2-anhydro glucose was indeed an intermediate in DMC reactions. At the approximately the same time Hoeck also provided NMR evidence[27] for the intermediacy of 1,2-anhydro sugars in a related study on nucleophilic substitution of 5-O-trityl ribofuranose. It can therefore be concluded that 1,2-anhydro sugars are indeed formed under a variety of aqueous reaction conditions. Fourthly, hydrolysis of intermediates such as **6a** and **10a** back to the starting material (as a mixture of anomers) could possibly occur by an S_N1 pathway. However, there is no direct evidence of unimolecular processes occurring under the quite strongly basic reaction conditions, and no E1 elimination products have been reported. Likewise, competing S_N1 processes may also be expected to lead to measurable amounts of stereochemical leakage. Finally in the presence of extremely good external nucleophiles, for example thiols, intermolecular substitution of intermediates such as **6β** or **10β** may compete with the stereocontrolling intramolecular processes, and so some amount of stereochemical leakage, namely the formation of minor amounts of 1,2-*cis* products, may be observed.

2.1.2 Side reactions, solvents and scope

In general, the objective of DMC activation is the introduction of an external nucleophile, though important examples of cyclisation reactions have been developed, pre-eminently oxazoline formation. The side reactions that generally compete with 'desired' nucleophilic substitution are: a) the hydrolysis of either DMC or activated intermediates (such as **6** and **10**) by solvent water; b) reaction of the added nucleophile directly with DMC; c) intramolecular nucleophilic substitution reactions to give 1,6-anhydro sugars or oxazolines.

Direct reaction of DMC with the added nucleophile may in some cases be avoided by the pre-activation process developed by Winssinger (see Section 2.2.3, Scheme 12).[28] Herein activation of the sugar can be undertaken at low temperature (e.g. -10 ^{o}C) by reaction of with DMC and Et_3N in a mixed aqueous solvent system, before the nucleophile is then added after a certain time period (e.g. 30 min).

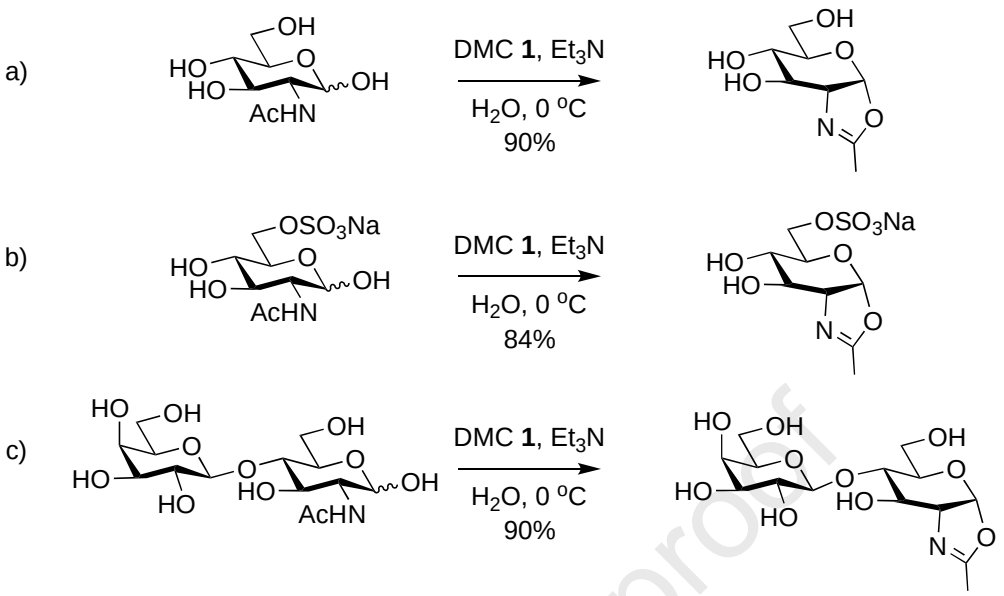
Oxazoline formation is invariably a significant competing process when 2-acetamido sugars are used as substrates, and it cannot be avoided altogether, though the use of a weaker base than Et_3N, for example 2,6-lutidine, has been reported to reduce competitive oxazoline formation during glycosyl azide formation.[24] In contrast 1,6-anhydro sugar formation can reportedly be reduced significantly either by the use of a bulkier base, such as Hunig's base (diisopropylamine, DIPEA), or by using MeCN as a co-solvent with water.[29] In some cases, particularly for the use of ADMP **3**, the use of an organic co-solvent such as MeCN is actually required in order to solubilise the activating reagent. When using ADMP typically the organic co-solvent is the minor component, e.g. water/MeCN ratios of 4:1 are used. Contrastingly the use of stronger bases such as DBU (pKa of the conjugate acid, ~13.5) has been reported to increase the amount of 1,6-anhydro sugar formation.[30] Hydrolysis of reactive intermediates by solvent water can be reduced by using D_2O as the solvent; in many cases the use of D_2O instead of H_2O results in an increase in product yield, typically in the order of ~5-10 percentage points (e.g. a 60% yield in water becomes ~65-70% in D_2O). This observation has been ascribed to the known solvent kinetic isotope effect of water in hydrolysis reactions.[31,32] Recent studies indicate that DMC activation is probably limited to aldoses, and that uronic acids are not suitable substrates, presumably as a result of the deactivating electronic withdrawing effect of the C-6 acid.[23] Furthermore, it is notable that where processes have occasionally been applied to 2-deoxy sugars, the product yields are invariably poorer, and the reaction outcome is invariably not stereocontrolled. Finally, a comment on product purification may be useful. Typically the

reaction products are highly polar, and the crude reaction mixture contains a very large excess of Et_3NH^+ salts, which are difficult to remove completely, either by ion exchange or by chromatography. A useful method for facilitating product purification is therefore to co-evaporate the crude reaction mixture twice with an added solution of ~35% w/w aqueous NH_4OH; this volatilises the Et_3N, and simplifies subsequent chromatography.

2.2 Applications for nucleophilic substitution at the anomeric centre

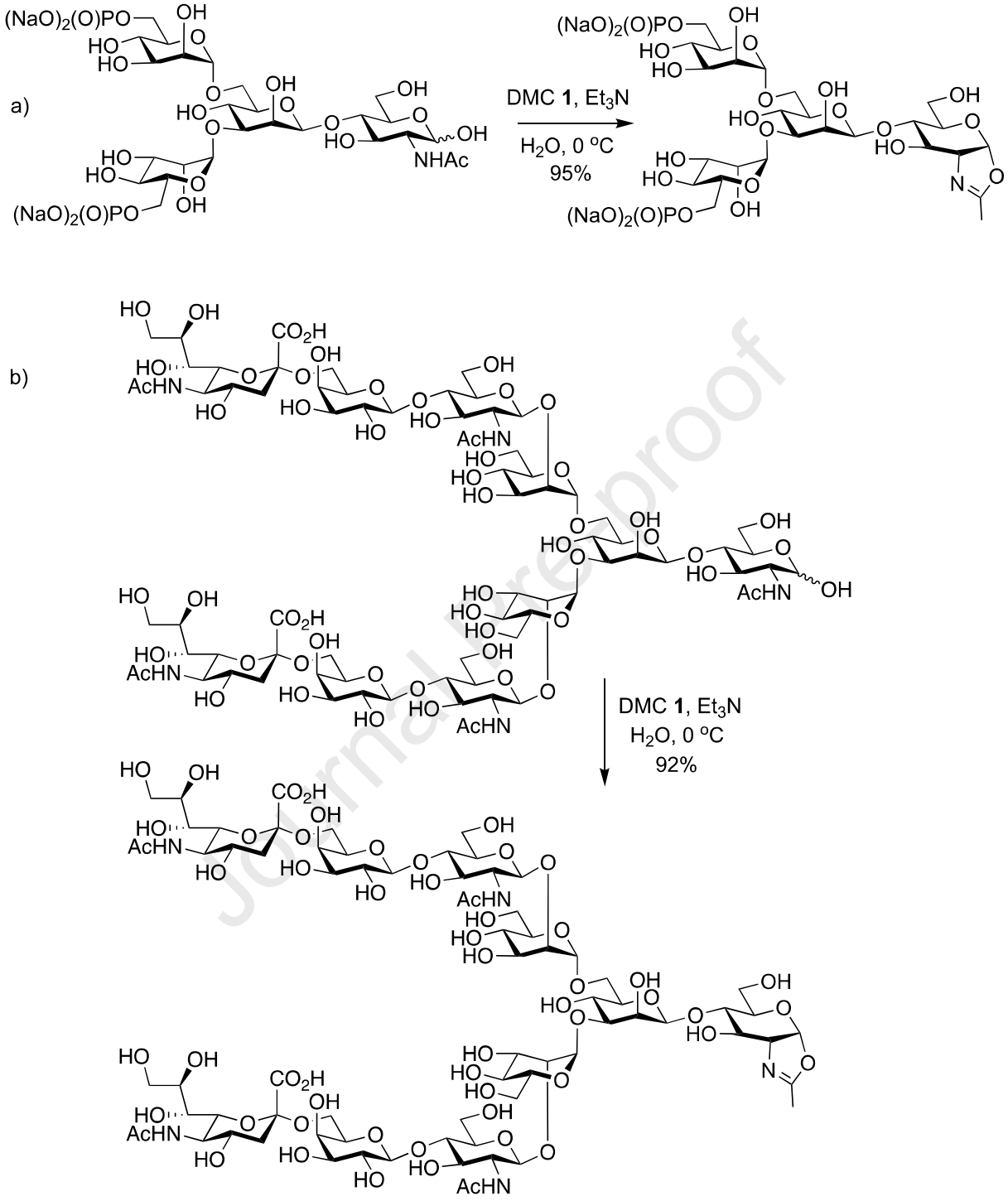
2.2.1 Oxygen nucleophiles

Since nucleophilic substitution processes must out-compete reaction with solvent water, all of the initial DMC-mediated processes that were developed involved intramolecular oxygen nucleophiles. Firstly, and perhaps most importantly, Shoda developed a reliable method for the production of glycosyl oxazolines from carbohydrates with a GlcNAc residue at the reducing terminus (Scheme 2).[33] The reaction was found to be compatible with either sulfation (Scheme 2b) or phosphorylation (Scheme 3a)[34,35] of sugar hydroxyl groups, and could be applied to oligosaccharides containing sialic acid.[36] The particular importance of this simple procedure arises since unprotected glycosyl oxazolines are important activated donor substrates for ENGase enzymes,[37] and can be used in the convergent enzymatic synthesis of glycopeptides and glycoproteins.[38,39] Shoda's seminal contribution in this context was the development of a very simple DMC mediated process for their direct synthesis in water, which has become the method of choice for their production,[40] superseding all previous methods.



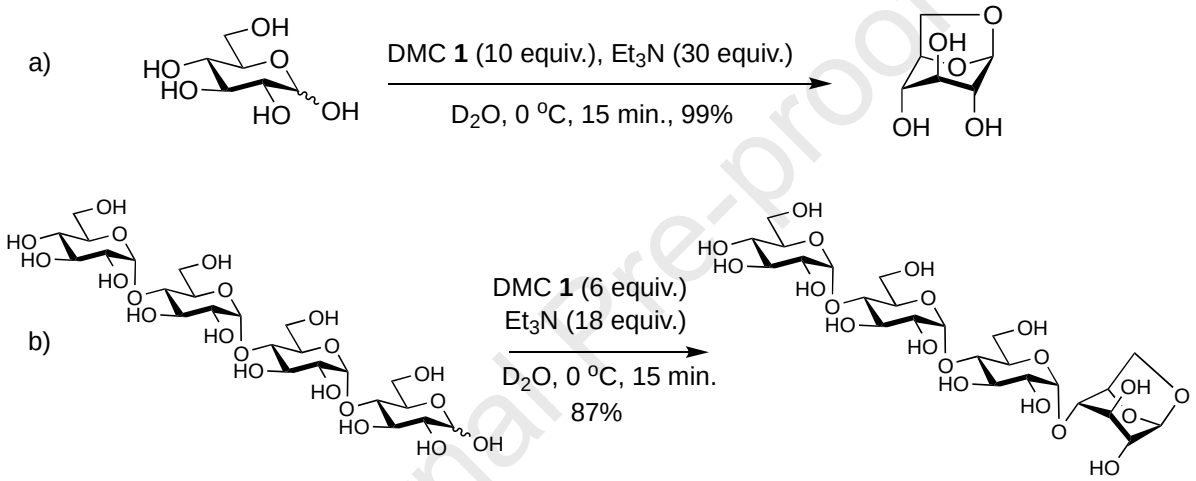
Scheme 2 Direct synthesis of glycosyl oxazolines from reducing sugars in water.

In particular the process can be readily applied to large *N*-glycan oligosaccharide structures, and since it can be readily performed on a small scale it is ideal for application to substrates isolated from natural sources (Scheme 3b).



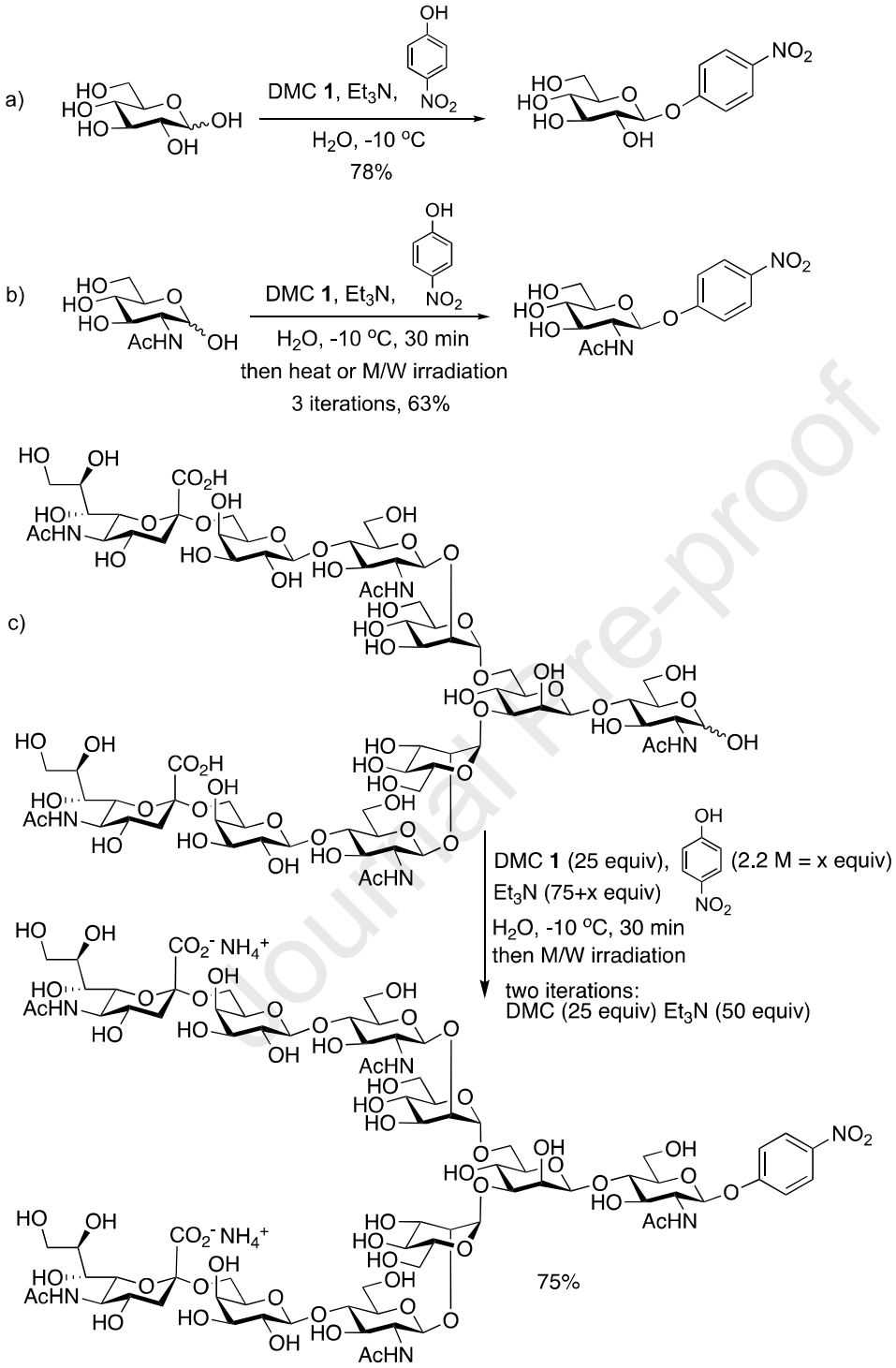
Scheme 3 The DMC-mediated production of *N*-glycan oxazolines using; a) synthetic oligosaccharides; b) *N*-glycans isolated from natural sources.

Shoda has reported that CDMBI **4** (Fig. 1) has advantages over DMC for oxazoline formation.[17] Firstly, it is less hygroscopic and therefore easier to handle. Secondly that replacement of the imidazolidine ring in DMC with the more electron-rich benzimidazole both reduces competitive hydrolysis by direct attack by water on CDMBI, and also makes the reactive glycosyl-imidazolidinium intermediate more stable. Finally, that the side product urea DMBI **5** (Fig. 1) is not aqueous soluble and so easier to remove. However, despite these apparent advantages almost all reports to date have used the more readily available DMC.



Scheme 4 DMC-mediated conversion of unprotected sugars directly into 1,6-anhydrosugars.

Following on from oxazoline formation, Shoda reported shortly afterwards[41] that for 2-hydroxy sugars (except mannose), activation with excess DMC in D_2O the presence of excess Et_3N led to good conversion directly to the corresponding 1,6-anhydro sugar (Scheme 4). The reaction was also applied to di- and oligosaccharides, but sugars with a substituent on the 3-hydroxyl group (e.g. 3-methyl glucose, nigerose [Glcα(1-3)Glc], and laminaribiose [Glcβ1-3Glc]) were not good substrates. DBU could be used as an alternative base to Et_3N, but all the other bases tested (Hunig's, lutidine, pyridine, N-methyl morpholine and sodium bicarbonate) did not give any 1,6-anhydro sugar. A mechanistic rationale was provided (see Fig 2a) which involved the intermediacy of the 1,2-anyhdro sugar **7** as 2-deoxy glucose and 2-fluoro-2-deoxy glucose did not react, highlighting the importance of the 2-hydroxyl group. No application of this process to 2-acetamido substrates was reported.

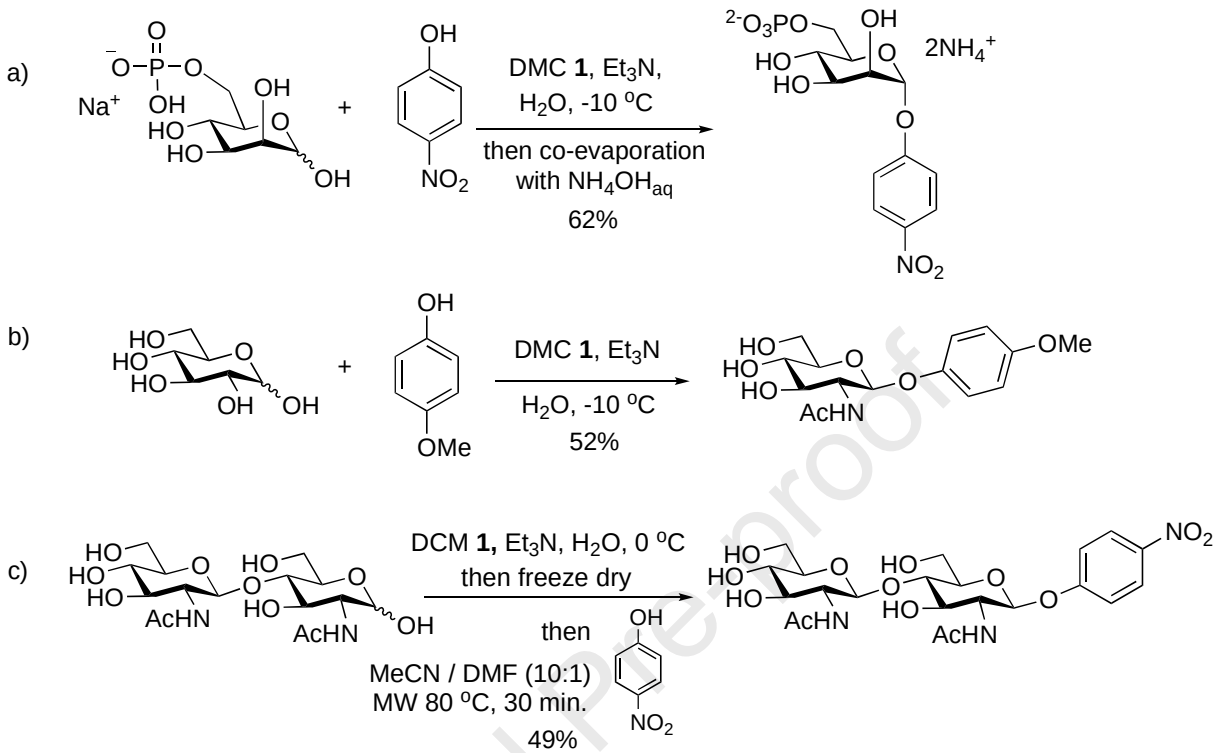


Scheme 5 DMC-mediated production of *p*NP glycosides from unprotected sugars.

It was not until recently that good yields of reaction products were obtained using DMC activation of unprotected sugars in the presence of intermolecular oxygen nucleophiles. In a

recent study Fairbanks and Qiu reported[42] that the activation of sugars at -10 ^{o}C, in either D_2O or water, in the presence of *para*-nitrophenol (*p*NPOH) and excess Et_3N gave the corresponding *p*NP-glycosides (Scheme 5). This one step method of the production of these very useful and widely used enzyme substrates is significantly more efficient than traditional multi-step syntheses. The process worked well for 2-hydroxy sugars (Scheme 5a), but for 2-acetamido substrates oxazoline formation out-competed *p*NP-glycoside formation. Therefore, for 2-acetamido substrates a two-step one-pot process was developed in which the oxazoline was firstly formed deliberately by DMC activation at low T, and then converted to the desired *p*NP-glycoside by microwave irradiation. Iterations of DMC activation/oxazoline formation and then microwave irradiation gave the *p*NP-glycoside in good yield (typically 60-70%, Scheme 5b). The process was equally applicable to a complex biantennary *N*-glycan isolated from natural sources (Scheme 5c).

In a follow-up study[23] the scope of the reaction was investigated, and the authors found that the process was applicable to both sulfated and phosphorylated sugars (Scheme 6a), but that it was not applicable to either ketoses or uronic acids. They also reported that whilst the process worked with other phenols, the product yield depended markedly on the phenol pKa (Scheme 6b). The process for 2-acetamido sugars was simplified to a single operation involving a change of solvent; thus in the first step the oxazoline was made by treatment of the reducing sugar with DMC and Et_3N in water, the whole reaction mixture was then freeze dried, the residue dissolved in a 10:1 mixture of MeCN and DMF before the *para*-nitrophenol was added, and finally the mixture irradiated (Scheme 6c). This process was advantageous in that no iteration was required, saving time and meaning that considerably lower quantities of reagents were needed.

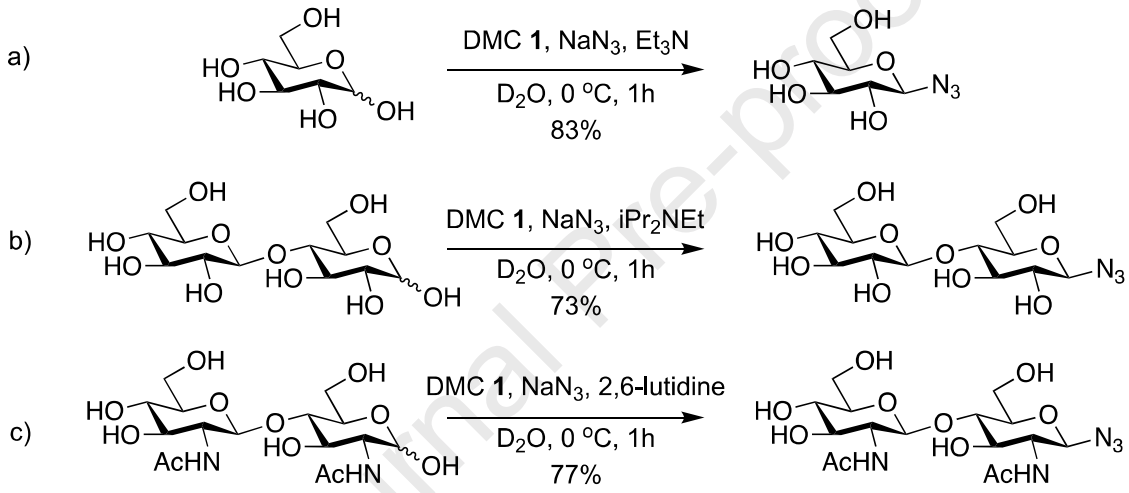


Scheme 6 DMC-mediated production of phenyl *g*lycosides from unprotected sugars.

2.2.2 Nitrogen nucleophiles

Glycosyl azides are highly versatile synthetic intermediates,[43] but their synthesis by traditional methods requires multiple steps. Shoda was quick to realise the potential of DMC for intermolecular nucleophilic substitution reactions of unprotected sugars with good nucleophiles, such as azide, which should outcompete side reactions. In the first report DMC activation of unprotected sugars in the presence of a large excess of azide and Et_3N (typically 10 equiv. of each) produced the corresponding 1,2-*trans* glycosyl azides directly using D_2O as the solvent (Scheme 7).[24] However, significant side reactions were also discovered. Firstly, when the reaction was applied to disaccharides with Et_3N as the base, considerable amounts of 1,6-anhydro sugars were formed as by-products. It was suggested that the amount of 1,6-anyhdro sugar formation depended on the identity of the added base and a screen of alternatives revealed that 1,6-anhydro sugar formation was reduced using Hunig's base (diisopropylethylamine, DIPEA). It was tentatively suggested that this bulkier base resulted in less intramolecular reaction. Secondly for 2-acetamido substrates, oxazoline formation competed significantly with

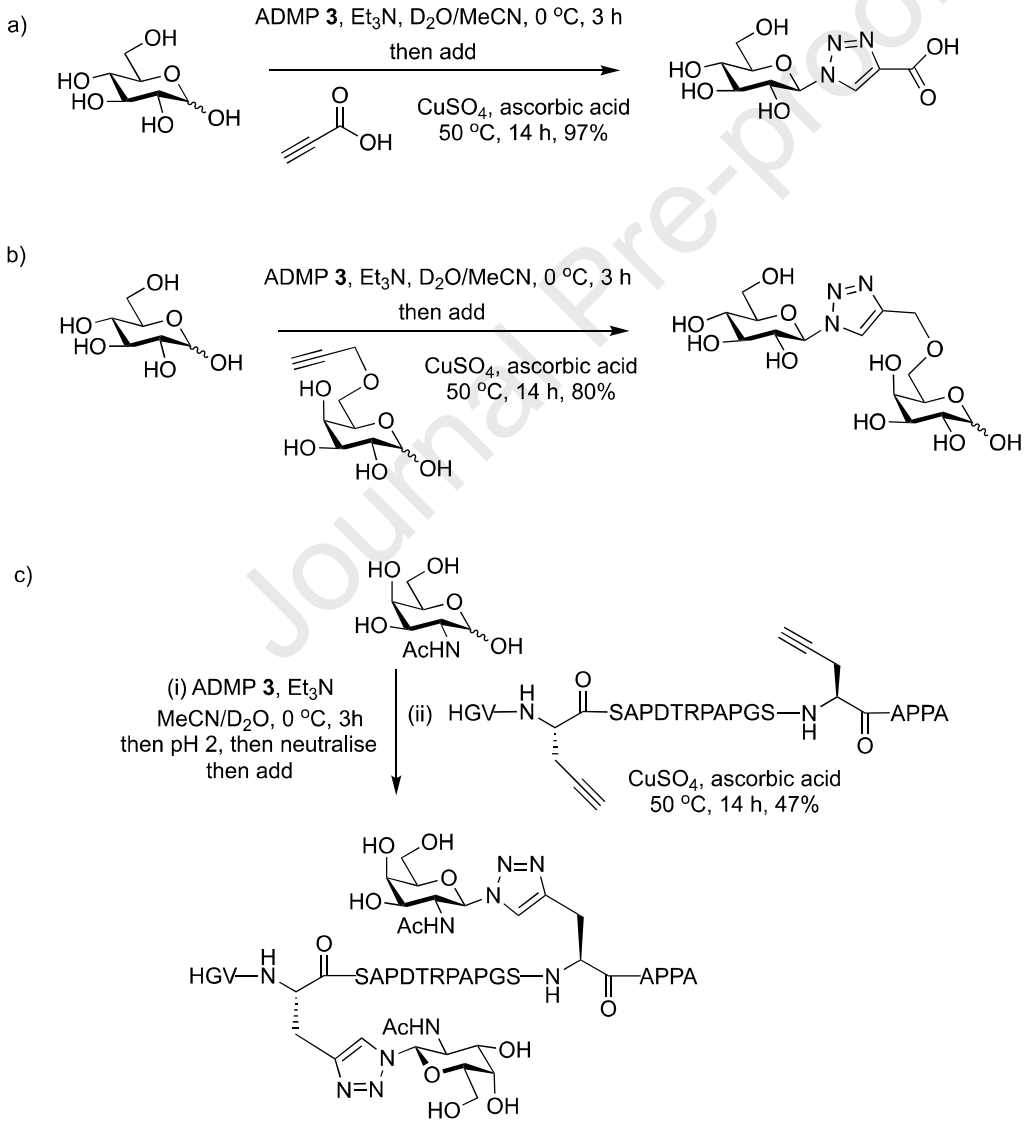
glycosyl azide formation. In these cases it was found that the use of the weaker base 2,6-lutidine (pKa of the conjugate acid ~6.7) reduced oxazoline formation. Interestingly it was reported that reaction also worked on a 2-deoxy sugar (yield not given), but in this case the transformation was not stereoselective, highlighting the importance of 1,2-anhydro sugar intermediates for stereocontrolled reactions, but also revealing that the 2-hydroxyl group is not absolutely required. Glycosyl azides formed in this way were used as substrates for subsequent click reactions with acetylene terminated polylactides for the formation of 70-200 nm diameter nanoparticles.[44]



Scheme 7 DMC-mediated protecting group free production of glycosyl azides.

Later Fairbanks and co-workers[45] revisited glycosyl azide formation with the intention of developing a one-pot method for glycosyl azide formation and subsequent click reaction by Huisgen cycloaddition,[46,47] to give a wide variety of glycosyl triazoles.[48] However, the very large excesses of azide and base required for the Shoda procedure made this difficult. Several improvements were made. Firstly, realising that doubtless azide itself actually reacted with DMC during the transformation, producing one equivalent of HCl in the process, an equivalent compound to the product of that reaction (e.g. 2-azido-1,3-dimethylimidazolinium hexafluorophosphate, ADMP **3**, Fig. 1) was used as the activator instead of DMC. It should be noted that a mixed solvent system of water and MeCN (4:1, v/v) is required to completely solubilise the ADMP for its use as an activator. Unlike DMC **1**, ADMP **3** is a non-hydroscopic

stable crystalline solid and is easily handled, and can easily be made from DMC as shown previously (Scheme 1). Secondly in order to overcome any competitive oxazoline formation a procedure first developed by Shoda for the synthesis of thiopyridyl glycosides (*vide infra*, was applied to 2-acetamido substrates. Thus, following the completion of the reaction, 1 M aqueous HCl was added to the crude reaction mixture until pH 2 was reached; this was followed by immediate neutralisation by the addition of aqueous $NaHCO_3$. This process resulted in oxazoline ring opening by azide in solution, and the production of desired glycosyl azides as the sole reaction products.



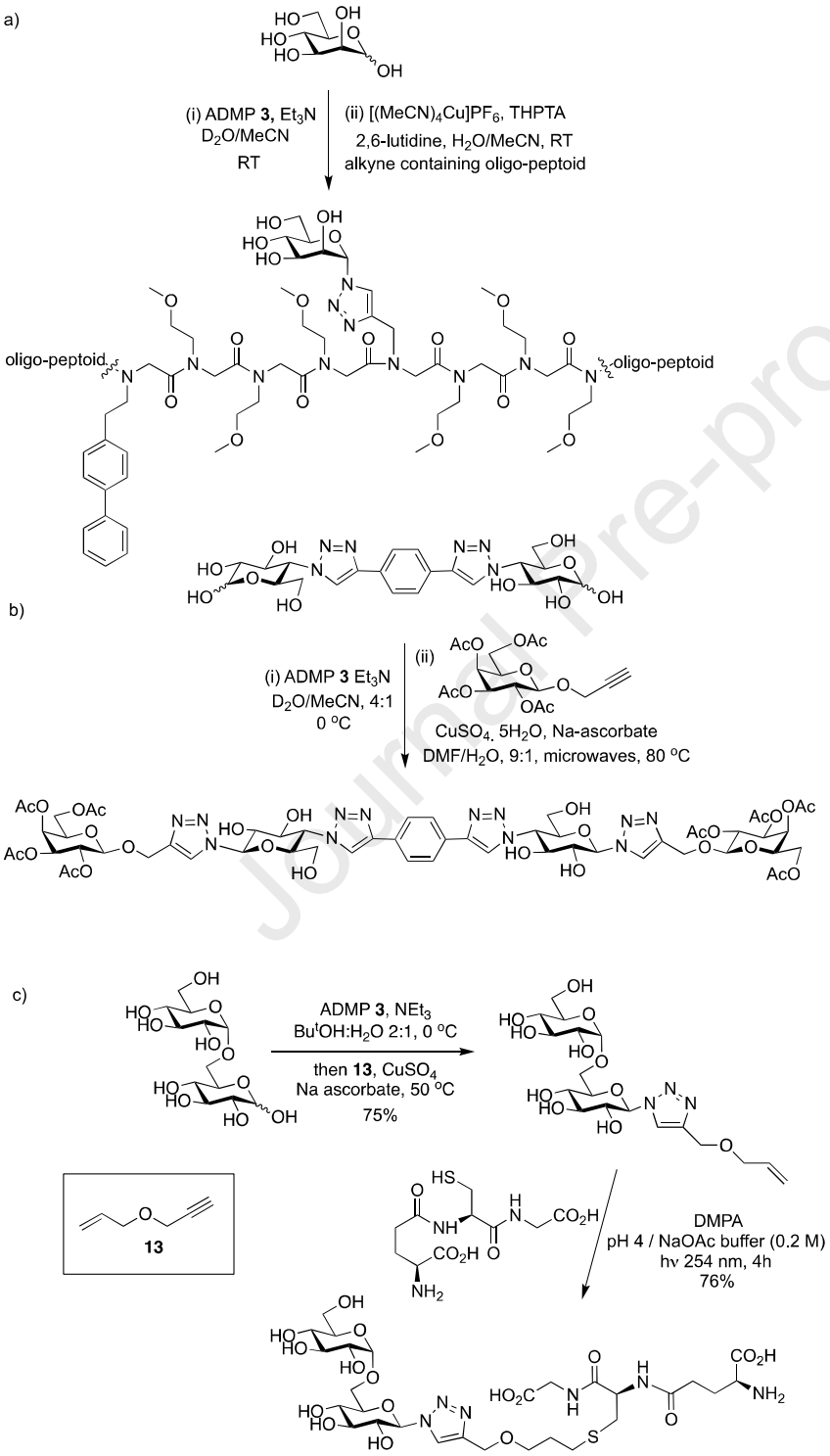
Scheme 8 ADMP mediated production of glycosyl triazoles.

Using ADMP **3** activation (typically only 3 equivalents are required) a one-pot conversion of the glycosyl azide formed *in situ* to a wide variety of functionalised glycosyl triazoles was possible, simply by the addition of an alkyne, $CuSO_4$, and L-ascorbic acid, and then heating at 50 °C. The process could not only be used to make glycosyl triazoles in a single step (Scheme 8a), but also as a ligation method by which sugars could be linked together (Scheme 8b), or by which sugars could be linked to peptides *via* triazole rings. The process was applicable to both large oligosaccharides and for peptides up to 20 amino acids long (Scheme 8c). It should be noted that the use of D_2O as the reaction solvent leads to some deuterium incorporation into the triazole product.

This type of ADMP-mediated click chemistry has found useful application, particularly in the glyco/biomaterials field. For example recently Zuckermann and co-workers used it for the production of glycosylated peptoid nanosheets.[49] In this work (Scheme 9a) mannose was converted to the corresponding glycosyl azide using ADMP **3**, and then immediately clicked to a variety of peptoids (typically ~30 units long) containing alkynes by the addition of copper (I) hexafluorophosphate (TACP) as the copper catalyst, 2,6-lutidine as the base, and tris(hydroxypropyltriazolylmethyl)amine (THPTA) as stabilising agent. In another recent report Pieters[50] used ADMP/click chemistry for the assembly of divalent ligands for the adhesion protein of *Peudomonas aeruginosa* (Scheme 9b). ADMP **3** has also been recently been used by Pei and co-workers[51] for the direct production of unprotected glycosyl azides and their attachment to alkyne-functionalised surfaces by click chemistry, to make branched chain carbohydrate chips for the study of protein/carbohydrate interactions. Godula and co-workers[52] used ADMP **3** for the direct production of the glycosyl azide of the trisaccharide 6'-sialylactose and its conjugation to a dibenzocyclooctyne containing lipid using a strain-promoted click reaction, as part of the *de novo* assembly of a synthetic glycocalyx.

Fairbanks has demonstrated that ADMP **3** can be used for the protecting group free synthesis of glycoconjugates by a double click approach, which involves the use of a bifunctional linker such as allyl propargyl ether **13** (Scheme 9c). In the first step this is conjugated to the sugar, *via* ADMP-mediated glycosyl azide formation in a ^{t}BuOH/water solvent mixture (2:1, required because of the low aqueous solubility of **13)** and azide-alkyne click. Then in the second step the

product is attached to a thiol *via* a photochemical thiol-ene click reaction using 2,2-dimethoxy-2-phenyl acetophenone (DMPA) as the initiator (Scheme 9c).[53]



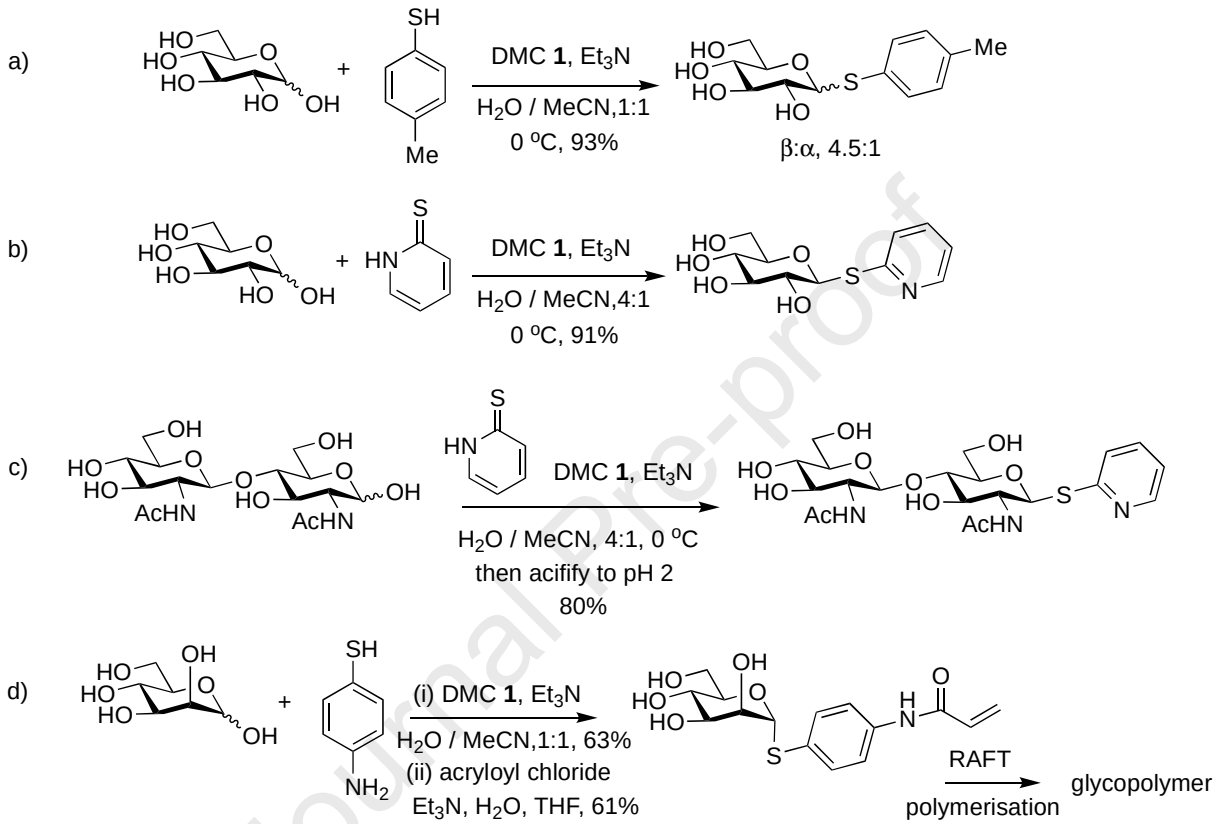
Scheme 9 Some recent applications of ADMP/click chemistry.

2.2.3 Sulfur nucleophiles

Since sulfur is highly nucleophilic is may be expected that DMC activation of reducing sugars in the presence of S-nucleophiles should result in efficient intermolecular substitution. However with 2-acetamido sugars some oxazoline formation is also to be expected. Thioglycosides are commonly used glycosyl donors for chemical oligosaccharide synthesis, but are normally required in protected form, so there is perhaps only a limited advantage to be gained in their direct production in aqueous solution. On the other hand glycosyl thiols find direct use in unprotected form, particularly for their chemoselective attachment to peptides and proteins. Therefore there are significant advantages in routes by which they are directly accessible from unprotected sugars.

Shoda and co-workers reported[29] that DMC-mediated activation of reducing sugars in aqueous solution in the presence of Et_3N and a range of aryl and pyridyl thiols led to the direct synthesis of range of the corresponding aryl thioglycosides (Scheme 10). Two points are worthy of note. Firstly in some cases when electron rich aryl thiols were used the process was not completely stereoselective (Scheme 10a). This was presumably as a result of the high nucleophilicity of the aryl thiol, which was able to compete with 1,2-anyhydro sugar formation as an intermolecular nucleophile, leading to the formation of minor amounts of 1,2-*cis* thioglycoside product. Secondly when water alone was used as the solvent some 1,6-anhydro sugar formation was observed, but it was stated that this was suppressed when MeCN was used as a co-solvent (>35% by volume of MeCN required). However, in contrast to this statement, the most commonly used reaction conditions used a 4:1 (v/v) mixture of water and MeCN as the solvent at 0 ^{o}C. The reaction was extended to the production of more pyridyl thioglycosides using a range of mono-, di-, and oligosaccharide substrates.[30] Using this approach 2-deoxy glucose could be converted to the corresponding pyridyl thioglycoside by the use of large excesses of reagents (6 equiv. of DMC, and 16 equiv. of thiol and base), but the reaction was not stereoselective (β:α, 1.6:1). Interestingly it was found that when GlcNAc was used as a substrate a considerable amount of oxazoline was also formed (as observed by NMR), but this could be converted to the desired product *in situ* simply by treating the crude reaction mixture with 1M HCl. This acidic treatment

method allowed the procedure to be applied to a range of oligosaccharides with a GlcNAc residue at the reducing terminus (Scheme 10c).

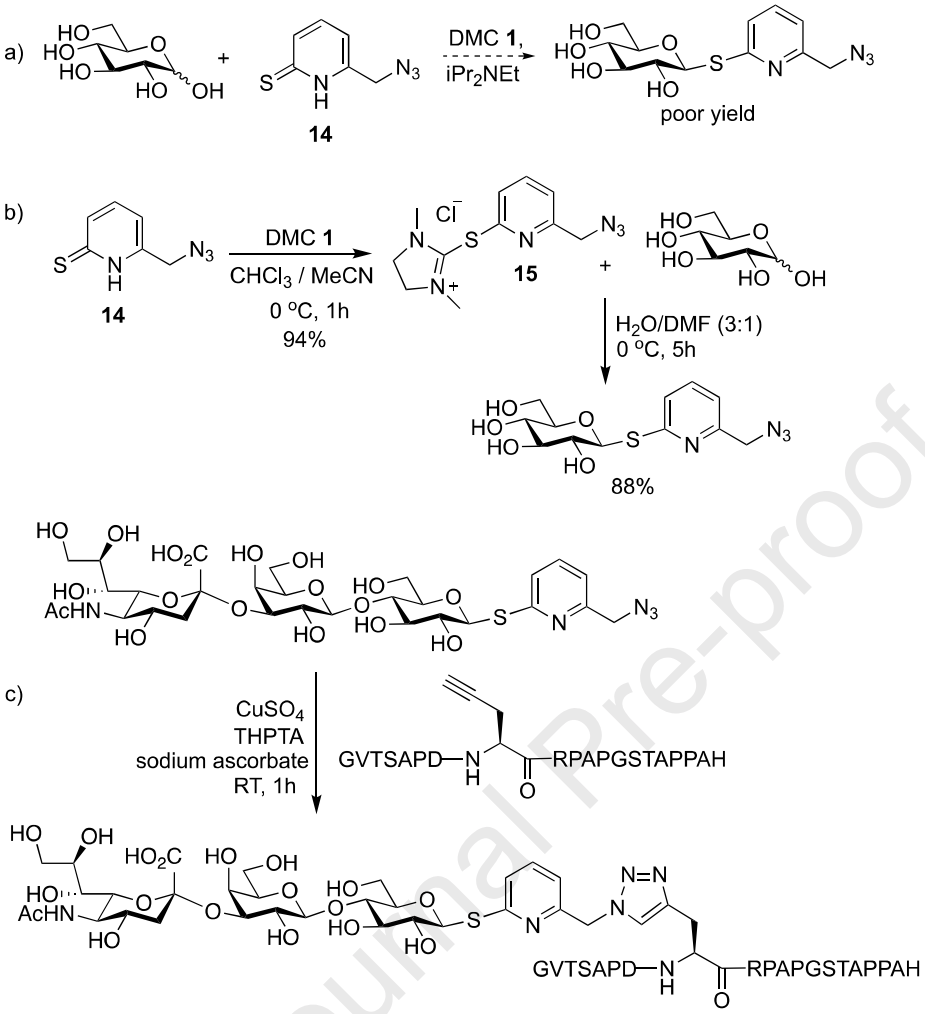


Scheme 10 Direct synthesis of aryl and pyridyl thioglycosides using DMC.

Shoda and co-workers went on to apply this basic transformation to the synthesis[54] of a range 4-methyl-7-thioumbelliferone (MUS) glycosides of mono- and oligosaccharides, which comprised a carbohydrate attached to a fluorescent label. Another interesting application by Shoda was the direct DMC-mediated synthesis of 4-aminophenyl 1-thio-glycosides in water, and their subsequent acrylamidation (Scheme 10d).[55] The acylamide containing 'glycomonomers' then underwent reversible addition-fragmentation chain transfer (RAFT) living radical polymerisation, to give glycopolymers which were finally conjugated to gold nanoparticles to investigate glycocluster effects.

In related work Winssinger[56] used DMC activation and substitution with a thiopicolyl azide **14** to access azide-containing thioglycosides (Scheme 11). Interestingly when direct DMC mediated of

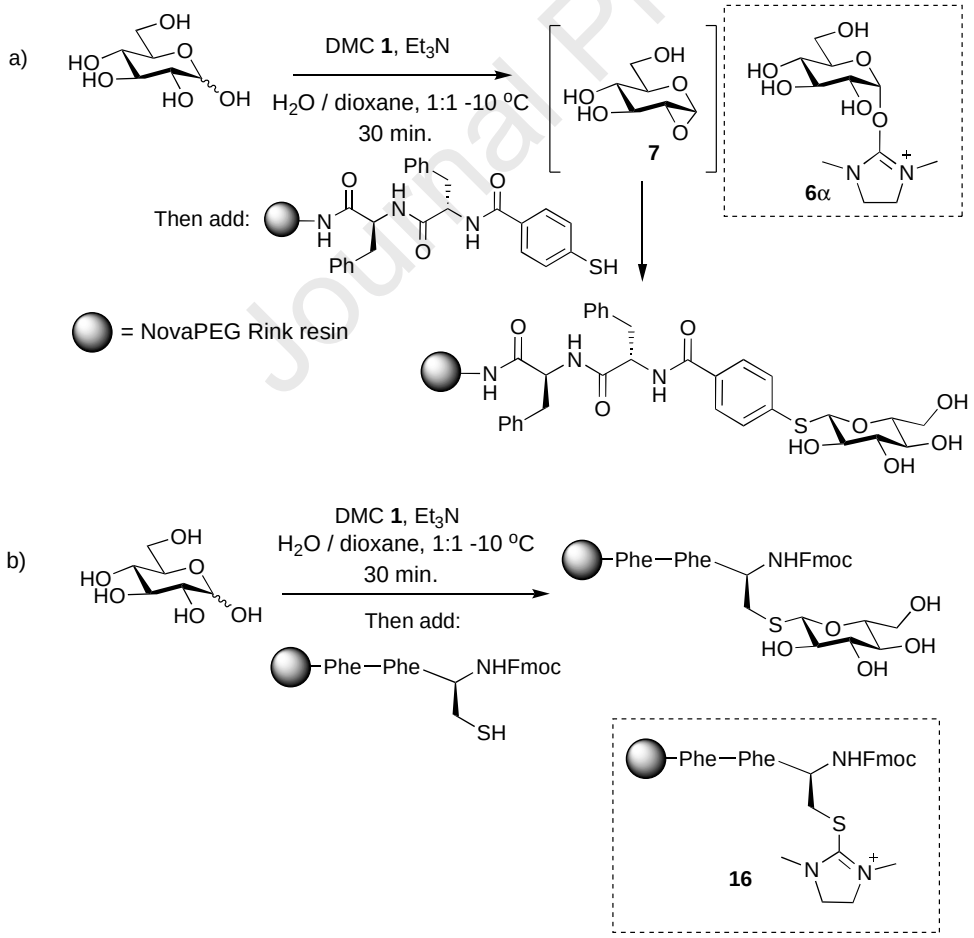
glucose was attempted with **14** only poor product yields were obtained because of azide reduction by the thiol under the basic reaction conditions (Scheme 11a). Thiol **14** was therefore deliberately reacted with DMC first, to produce imidazolinium species **15** as a stable crystalline solid (Scheme 11b). Reaction of **15** with a range of mono-, and small oligosaccharides in the presence of Hunig's base in a water / DMF (3:1) solvent mixture then proceeded smoothly to give the corresponding thioglycosides. The reactions were completely 1,2-*trans* stereoselective except in the cases of galactose and fucose where some of the α-anomers (10-16%) were also isolated. The presence of azide in the products then allowed chelation-assisted Cu-catalysed click reactions in the presence of the ligand tris-hydroxypropyltriazolylmethylamine (THPTA) for the attachment of sugars to either peptides (Scheme 11c) or oligonucleotides containing alkyne side chains. The approach was also extended to HeLa cells that had been incubated with homopropargylglycine to incorporate an alkyne into protein biosynthesis; herein a fluorescent labelled sugar could be conjugated to live cells and subsequently visualised by fluorescence microscopy.[56]



Scheme 11 Synthesis of azido-picolyl thioglycosides for chelation-assisted click chemistry.

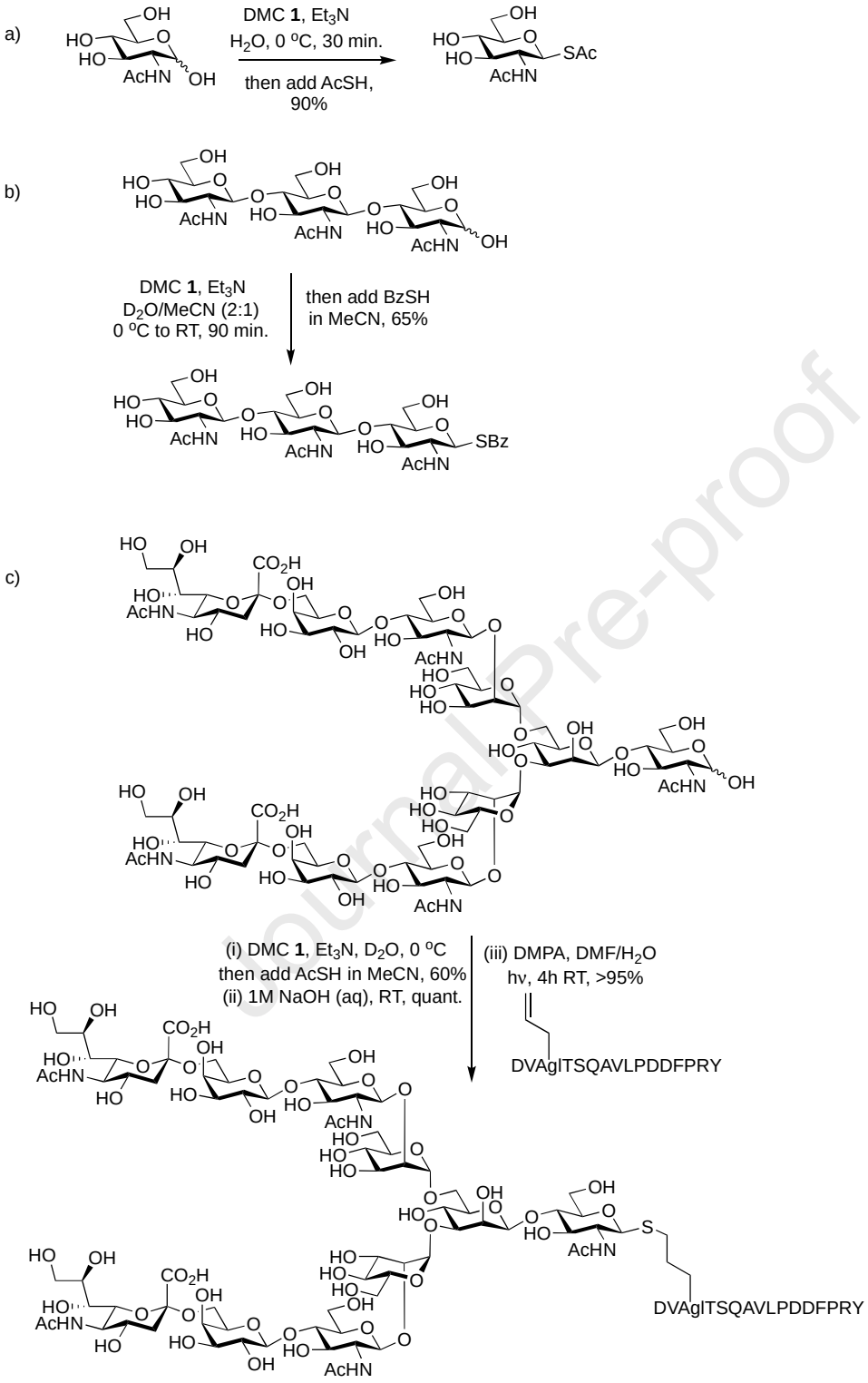
Winssinger was the first to investigate DMC-activation as a means of linking sugars to peptides by reaction of activated intermediates with cysteine residues (Scheme 12).[28] Key to the development of a successful reaction here was pre-activation of the sugar by DMC, by stirring the sugar and Et_3N at -10 ˚C in a H_2O/dioxane solvent mixture and adding the DMC, before then adding a cysteine containing amino acid or peptide 30 min. later. An NMR study indicated the stability of an intermediate species at this temperature ($T_{1/2}$ >100 min. at -10 ^oC), and so provided a window of opportunity for activation before addition of the nucleophile. Although this intermediate was originally assigned as the oxazolinium ion **6α**,[28] with hindsight and comparison with the subsequent work of Shoda, this species is probably the 1,2-anhydrosugar **7**. Regardless of the identity of the intermediate, the use of a pre-activation step is required to avoid direct reaction of the thiol with DMC, which is a major side reaction, and in the case of a non-aromatic

thiol is irreversible. Using this low T pre-activation method Winssinger and co-workers firstly glycosylated a polymer-linked peptide containing an aryl thiol (Scheme 12a). Subsequently they obtained moderate to good yields (30%-95%) of glycosylation of the cysteine residue in a polymer bound PhePheCys tripeptide (Scheme 12b) with a range of mono- and disaccharides. Importantly direct reaction of the cysteine containing peptide with the sugar and DMC led only to formation of the side product **16** resulting from direct reaction of the thiol with DMC. Finally by using three iterations of sugar pre-activation and then reaction with the peptide, conversions could be increased to >99%. This high yielding iterative approach allowed application of the methodology to the glycosylation of two cysteine residues in a 20-mer peptide, which was synthesised as a MUC1 analogue. Glycosylation could be performed either during the solid-supported peptide synthesis, allowing the attachment of different mono- or disaccharides to the two cysteines, of following completion of the peptide allowing installation of the same sugar at both positions.

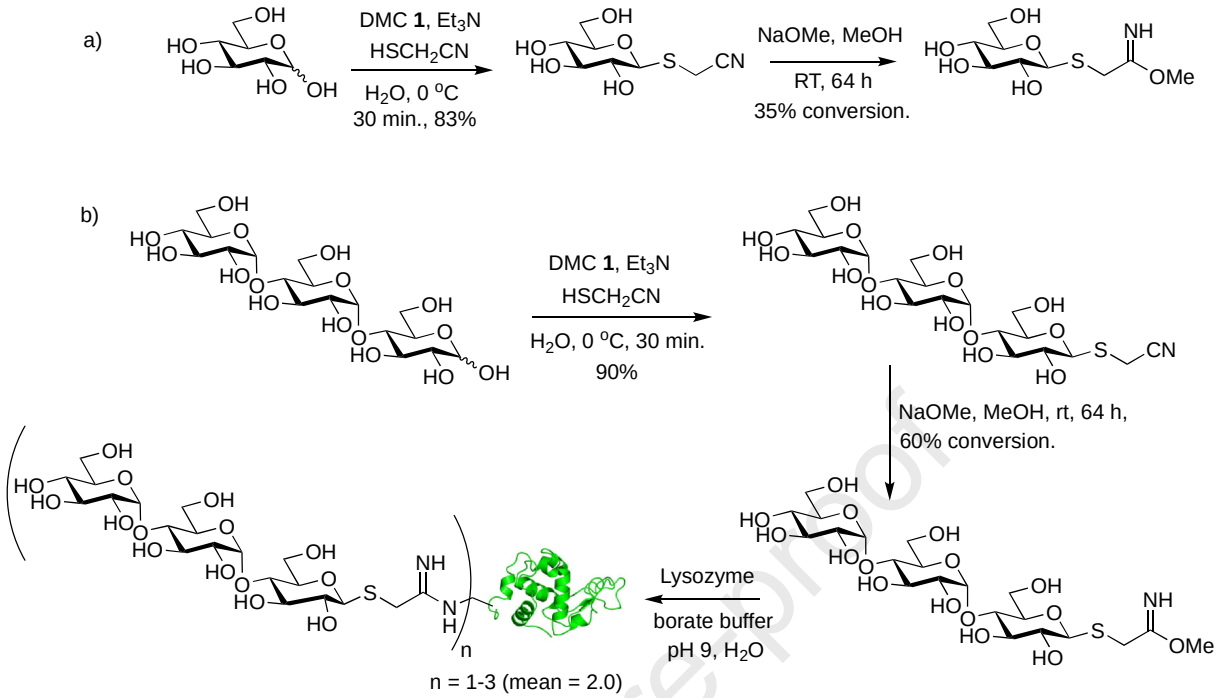


Scheme 12 The Winssinger pre-activation method with DMC at -10 ^{o}C allows: a) glycosylation of a polymer bound thiol; b) glycosylation of cysteine containing peptides on the solid phase.

Glycosyl thiols have proven to be extremely useful species for the production of neo-glyconjugates, using a variety of strategies to link the thiol to peptides or proteins.[57,58] However, typically their synthesis has required multistep reaction sequences and protecting group manipulations. Rademann[59] and Fairbanks[60] both reported the use of DMC for the protecting group free synthesis of glycosyl thiols (Scheme 13). The method, which is limited in application to substrates (mono-, di-, or oligosaccharides) with a 2-acetamido residue at the reducing terminus, involves DMC mediated formation of an oxazoline, which is then opened *in situ* by the addition of a thiocarboxylic (e.g. thioacetic or thiobenzoic) acid to the reaction mixture once oxazoline formation is complete. The anomeric thioester is then hydrolysed in a subsequent step. The presence of a thiol and DMC together in the reaction mixture simply leads to reaction between the two (*vide supra*), whilst attempted application of the method to 2-hydroxy sugars led to extensive competitive 1,6-anhydro sugar formation. Rademann used this approach for the production of glycosyl thiols *via* both glycosyl thioacetates and thiobenzoates (Scheme 13b), and exemplified their application in numerous derivatisation reactions.[59] Impressively this included the conjugation of a hexasaccharide fragment of hyaluronic acid to an engineered lipase *Thermoanaerobacter thermohydrosulfuricus*, which contains an N-pentenoyl lysine residue at position 221, *via* thiol-ene click chemistry. Fairbanks demonstrated application of the method for the protecting group free conjugation of a naturally derived oligosaccharide to a synthetic 16-mer peptide containing an allyl glycine (Agl) residue *via* thiol-ene click chemistry (Scheme 13c).[60]



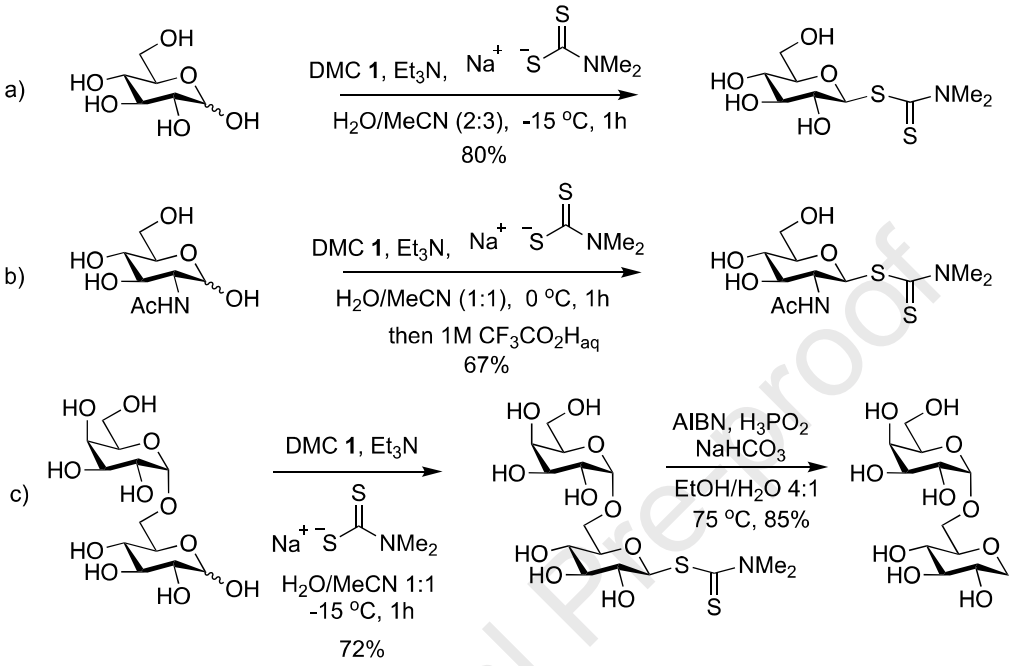
Scheme 13 Protecting group free synthesis of glycosyl thiols of 2-acetamido sugars using DMC and application for thiol-ene click chemistry.



Scheme 14 Protecting group free synthesis of cyanoethyl thioglycosides of 2-hydroxy sugars using DMC, and applications for neoglycoprotein synthesis

Fairbanks reported the protecting group free production[61] of cyanoethyl thioglycosides by reaction of unprotected sugars with DMC and mercaptoacetonitrile ($HSCH_2CN$) in the presence of Et_3N (Scheme 14). Since direct reaction of a thiol with DMC is a competing side reaction, this must be reversible in this case, in line with the low pKa of $HSCH_2CN$ (pKa ~6), meaning that pre-activation is not required. However the correct order of the addition of reagents was important to maximise product yield, and reduce the amount of 1,6-anhydro sugar by-product formed. The reaction was applicable to a range of mono-, di- and oligosaccharides with a 2-hydroxy sugar at the reducing terminus, but the instability of both the cyanoethyl glycoside product and mercaptoacetonitrile towards acid meant that good yields could not be obtained from 2-acetamido sugars because of competing oxazoline formation. Cyanoethyl thioglycosides can be readily converted into the corresponding imidates (2-imino-2-methoxyethyl-1-thioglycosides, or IME-thioglycosides), by reaction with methoxide as first reported by Lee;[62] this equilibrium activation process typically produces the corresponding imidate with ~50% conversion. These imidates are useful reagents for the conjugation of carbohydrates to other entities,[63] and in particular for protein modification by selective reaction with surface exposed lysines, for

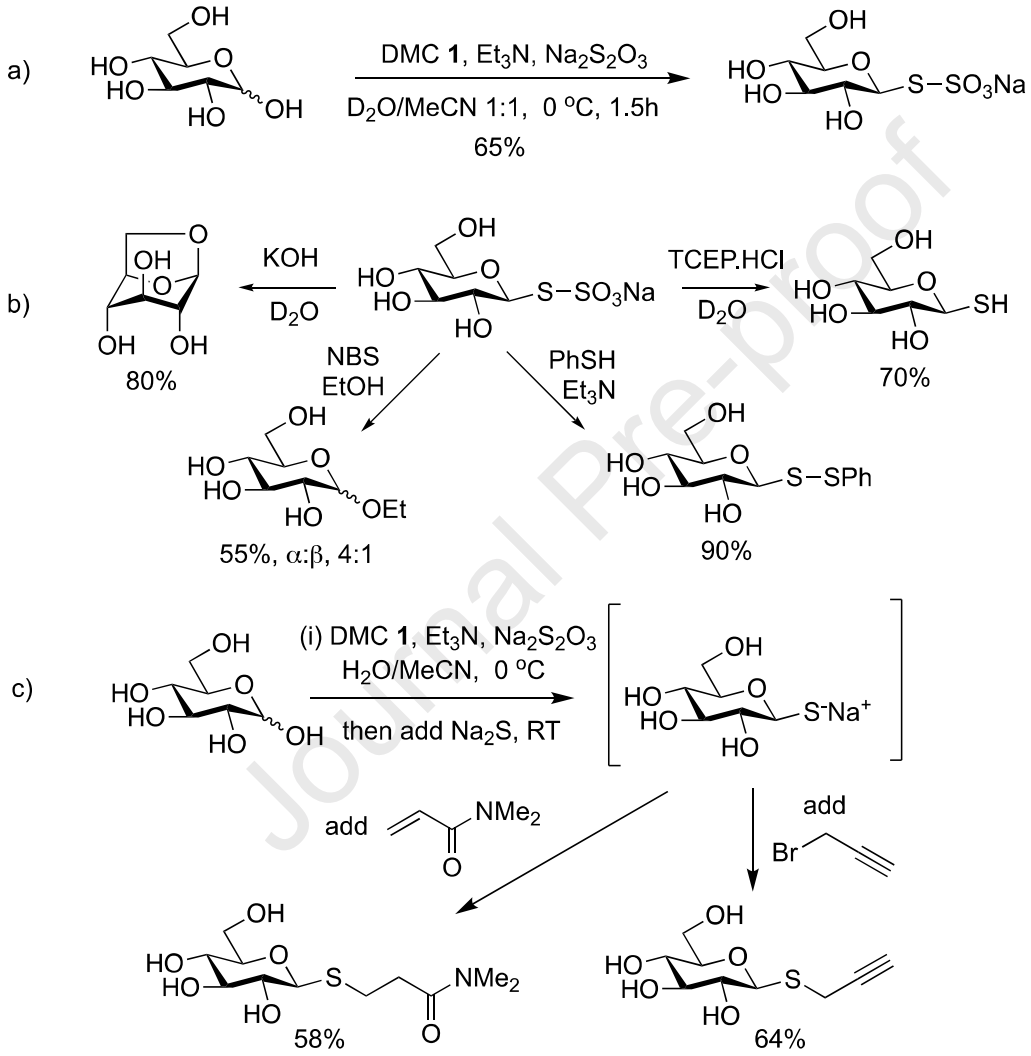
example with lysozyme (Scheme 14b).[64] Access to them without recourse to any protecting group manipulations opens up the production of diverse new IME-thioglycosides using small quantities of oligosaccharides derived from natural sources.



Scheme 15 Protecting group free synthesis of glycosyl dithiocarbamates and their conversion to 1-deoxy sugars.

In 2016 Shoda first reported the DMC mediated production of a range of glycosyl dithiocarbamates (glycosyl DTCs, Scheme 15), by reaction of unprotected sugars with DMC, Et_3N and several different DTC salts in a water/MeCN solvent mixture (usually 1:1) at low temperature (ranging from -15 to 0 °C).[65] The process could be applied to a range of mono-, di- and oligosaccharides. When GlcNAc was used as a substrate more that 40% of the oxazoline was formed as a side-product, but the yield of the desired product was significantly increased by the addition of 1M aqueous trifluoracetic acid, which caused oxazoline opening by the remaining dithiocarbamate in solution (Scheme 15b). Interestingly 2-deoxy glucose could be converted to the corresponding glycosyl dithiocarbamate, but the yield was poor (42%) and the reaction was not stereoselective (α:β, 45:55). The reaction was expanded to a one-pot three-component process involving the *in situ* synthesis of the DTC salt by reaction of CS_2 with a dialkylamine in the presence of the Et_3N, before the addition of an aqueous solution of the sugar, and finally the

DMC, avoiding the need for the isolation of the DTC salts. Usefully these glycosyl dithiocarbamates could be directly converted into 1-deoxy sugars by free radical reduction,[66] thus providing the first completely protecting group free synthesis of 1-deoxy sugars (Scheme 15c).



Scheme 16 Protecting group free synthesis and uses of glycosyl thiosulfates (Bunte salts).

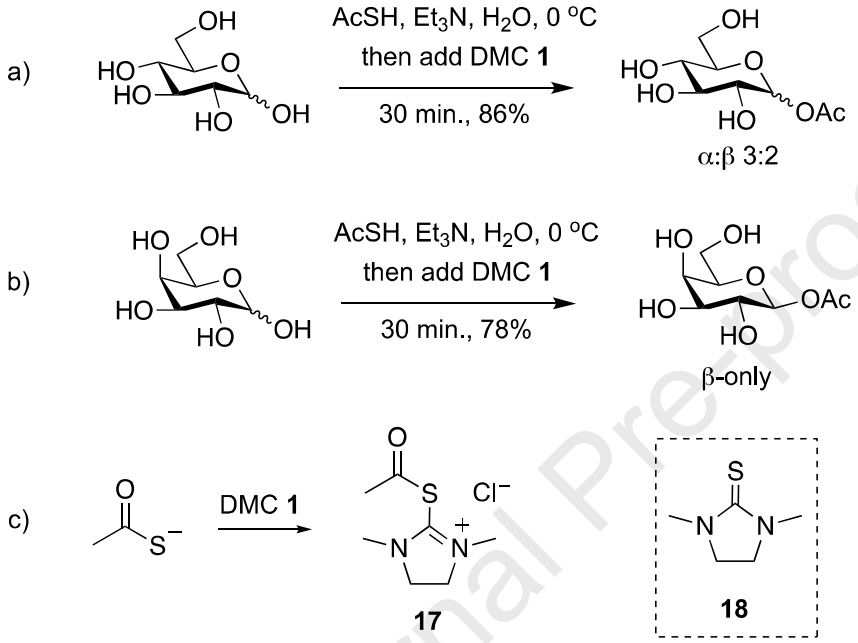
Shoda recently reported[67] the DMC-mediated synthesis of glycosyl thiosulfates, also called Bunte salts, by DMC activation in the presence of sodium thiosulfate and Et_3N in a D_2O/MeCN mixed solvent system. The reaction was applicable to a range of mono-, di-, and

oligosaccharides. For 2-acetamido sugars again oxazoline formation was a significant competing process, but this could be overcome by treatment of the crude reaction mixture with 1M aqueous HCl, which caused oxazoline opening and conversion to the 1,2-*trans* glycosyl thiosulfate. The Bunte salts could be readily converted into a range of other functionalised glycosides (Scheme 16b), including glycosyl thiols, glycosyl di-sulfides, 1,6-anhydro sugars and *O*-glycosides, though the latter transformation was not completely stereoselective. One pot conversion of unprotected sugars to the corresponding glycosyl thiolate could be achieved by treatment of the Bunte salts with excess Na_2S, and this immediately followed by other reactions such as conjugate addition or nucleophilic substitution (note: the glycosl thiolates oxidised rapidly to di-sufides during attempted purification by chromatography), leading to a variety of functionalised S-glycosides directly from the unprotected reducing sugar in a one-pot three step process (Scheme 16c).[68]

2.2.4 Other applications

Occasionally side reactions, for example direct reaction of DMC with added nucleophiles, can find useful application. In 2017 Fairbanks and Lim reported a method for the selective acetylation of the anomeric hydroxyl group of unprotected sugars in aqueous solution, so providing a direct one-step synthesis of glycosyl acetates.[69] The reaction involved the addition of DMC to a solution of the sugar, thioacetic acid and Et_3N in water at 0 ^oC (Scheme 17). Under these conditions, rather than the formation of a glycosyl thioacetate, the reaction products were glycosyl acetates in which only the anomeric hydroxyl group had been acetylated. The order of addition of the reagents was important (DMC must be added last) to avoid competing reactions, such as oxazoline or 1,6-anhydro sugar formation. Although Et_3N could be replaced by using Na_2CO_3 as the base, this change meant that multiple additions of reagents were required to ensure complete conversion to the product. Whilst the transformation was not stereoselective for 2-acetamido sugars (Scheme 17a), interestingly acetylation was found to be completely stereoselective for 2-hydroxy sugars, yielding the 1,2-*trans* glycosyl acetates only (Scheme 17b). The reasons for this difference are not yet clear. Mechanistically the process is thought to proceed by initial reaction of thioacetate with DMC **1** to produce an activated ester **17** (Scheme 17c), which then acts as a selective acylating agent, reacting only with the anomeric hydroxyl group which is selectively deprotonated at the reaction pH. Support for this hypothesis was

isolation of the thiourea **18** as a side-product at the end of the reaction. The process could also be applied to di- and oligosaccharides, and when Na_2CO_3 was used as the base, the glycosyl acetate product could then be used for glycosidase catalysed synthesis simply by adding an appropriate enzyme to the crude reaction mixture.



Scheme 17 Selective acetylation of the anomeric hydroxyl group of unprotected sugars by reaction with Et_3N, thioacetic acid, and DMC.

3. Conclusions

The original development of DMC by Professor Shoda and co-workers as a remarkable reagent capable of selective activation of the anomeric hydroxyl group of unprotected sugars in aqueous solution represents a significant advance in the synthetic chemistry of carbohydrates. This work has subsequently inspired numerous others to further this line of research, and now, some 11 years after the first seminal papers from the Shoda group appeared, a whole range of transformations that previously could only be achieved using numerous protecting group manipulations can now be performed in a single step using unprotected sugars in aqueous solvent systems. These include the synthesis of highly useful enzyme substrates such as glycosyl oxazolines and *p*NP-glycosides, and the one step production of 1,6-anhydro sugars, glycosyl azides, pyridyl, aryl, and cyanoethyl thioglycosides, glycosyl thiols, glycosyl thiosulfates and

glycosyl thiocarbamates. DMC even allows the selective acetylation of the anomeric hydroxyl group of unprotected sugars in aqueous solution. Additionally, the DMC derivative ADMP is an excellent reagent for the formation of glycosyl azides *in situ* and subsequent click chemistry with added alkynes, which allows the facile synthesis of glycoconjugates in which sugars are linked to other species *via* triazoles. All of these processes are valuable additions to the expanding toolbox of the carbohydrate chemist. Although the list of transformations that can be achieved using DMC already seems quite extensive, given the diversity of carbohydrate chemistry it seems certain that there are still further useful developments yet to come.

Acknowledgements

The author thanks his co-workers, Dr David Lim, Dr Stewart Alexander and Xin Qiu, and his numerous collaborators, all of whom have contributed so fruitfully to the further development of novel protecting group free transformations in his group. The author also thanks Professor Shin-ichiro Shoda for his inspirational developments, and wishes him an extremely happy retirement.

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[10] Current price of ADMP from Sigma-Aldrich is US$220 for 5g.

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- protecting group free activation of unprotected sugars under aqueous conditions
- single step stereoselective synthesis of a wide variety of glycosides
- direct formation of glycosyl oxazolines as donor substrates for enzyme catalysed reactions
- applications to oligosaccharides isolated from natural sources
- one-pot tandem processes, such as glycosyl azide or thiol formation, and Click chemistry

No conflicts to declare