Hindawi Publishing Corporation
Journal of Chemistry
Volume 2013, Article ID 183049, 10 pages
http://dx.doi.org/10.1155/2013/183049

Review Article

Diarylmethyl Ethers for the Protection of Polyols

Sigthor Petursson

Department of Natural Resource Sciences, University of Akureyri, 600 Akureyri, Iceland

Correspondence should be addressed to Sigthor Petursson; sigthor@unak.is

Received 13 June 2012; Accepted 2 August 2012

Academic Editor: Christophe Len

The paper discusses the use of diarylmethyl ethers for the protection of hydroxyl groups, in particular, carbohydrate hydroxyl groups. The formation of these ethers can be done nonselectively by the thermal reactions of diryldiazomethanes via a carbene mechanism or by tin(II) halide catalysis of the diazo compounds with diols. The catalyzed reactions give useful regioselectivities.

1. Introduction

Wöhler's synthesis of urea in 1828 is often taken to mark the beginning of organic chemistry [1]. Protecting groups play no role in this accidental discovery, but before the end of the 19th century organic chemistry had advanced considerably and the concept of protecting groups was developed by the pioneering work on carbohydrates by Emil Fischer and his students. Kunz points out in his essay on Fischer that he "was presumably the first to have undertaken protective group chemistry when he introduced the isopropylidene group into different carbohydrates…" [2–5]. With the benefit of modern understanding of chemistry it is easy to appreciate the need for protecting groups and in particular hydroxyl protecting groups when one contemplates specific reactions of the four hydroxyls of glucose and other hexoses or any manipulation of the anomeric center as is done in oligosaccharide synthesis [6–8].

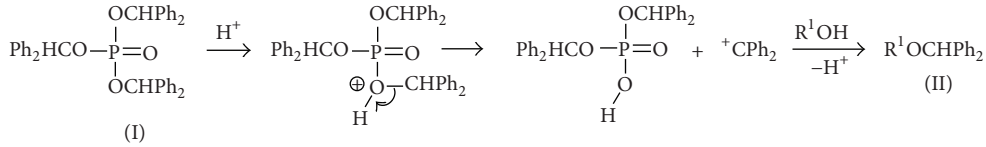
In their books on the chemistry of the carbohydrates, Ferrier and Collins have put forward the prerequisites for useful protecting agents by stating that

(i) they must be selective for the function to be protected,

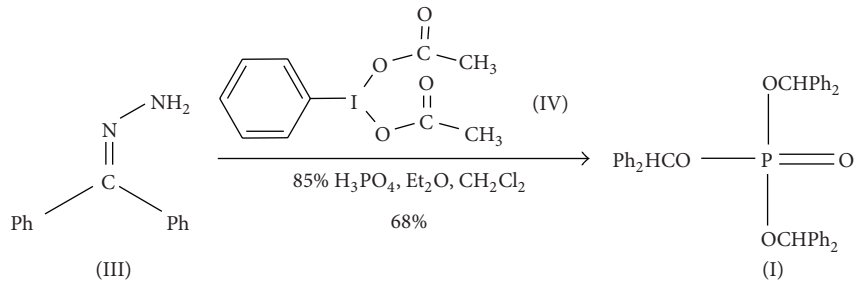
(ii) they must form derivatives that are stable under the conditions to be used subsequently,

(iii) the protecting group formed must be removable by methods which leave other substituents unaffected [9, 10].

Most protecting groups fall into one of three broad categories of compounds, namely, esters, acetals, and ethers. The esters, being base sensitive have a fairly limited scope in general synthetic work but they were used in early oligosaccharide synthesis. Acetals which Fischer introduced as already mentioned are on the other hand extremely useful being much more stable, especially under basic conditions. A glycoside is of course an acetal protection of the carbonyl group of a monosaccharide but in addition to that, the hydroxyl groups can be protected very effectively as cyclic acetals by the use of external aldehydes and ketones. These cyclic acetals/ketals give certain regioselectivities since the configuration of the monosaccharides and reaction conditions will determine which pairs of hydroxyl groups are engaged [11]. The acetals, as has been alluded to, have a special place in carbohydrate chemistry, but they do by no means fulfil all the needs for hydroxyl protection for modern synthetic chemistry. Ether protecting groups are in many respects complimentary to the acetals. Like the acetals they are stable to basic condition and most ethers are also much more acid stable. The most commonly used ethers for protecting purposes, the benzyl ethers, are in addition removable by catalytic hydrogenolysis under very mild, pH neutral, conditions. However, the strongly basic conditions most commonly used for the introduction of an ether protecting group and the lack of regioselectivity put certain restrictions on their use. The triphenylmethyl (trityl) ether group has also found use, especially in carbohydrate



Scheme 1: The benzhydrylation of an alcohol in the presence of strong acid.



Scheme 2: The preparation of tris(diphenylmethyl) phosphate.

chemistry. The bulk of this group gives it a strong preference for the primary hydroxyl group.

2. Preparation of Diphenylmethyl or Benzhydryl Ethers

Since both benzyl, $PhCH_2$-, and triphenylmethyl, Ph_3C-, ethers have been popular protecting groups, it is interesting that apparently little attention has been paid to the diphenylmethyl ethers, which can be looked on as structurally lying between these two groups. A reason for this may be that an obvious first choice method for the preparation of diarylmethyl ether is the reaction of the diarymethyl halide (chloride or bromide) under conditions similar to those used for the preparation of benzyl ethers or those used for the triphenylmethyl ether. Somewhat surprisingly no high yielding reports of this type of diphenylmethyl or benzhydryl ether synthesis have been found in the synthetic literature. This is consistent with unpublished results from the author's laboratory showing that in fact these supposedly simple reactions give very poor results. Benzhydryl ethers have therefore had to be made by other methods. The generally applicable methods reported for benzhydryl ether formation fall into one of the four following categories:

(i) the use of tribenzhydryl phosphate,

(ii) the use of the alcohol, benzhydrol, under dehydrating conditions,

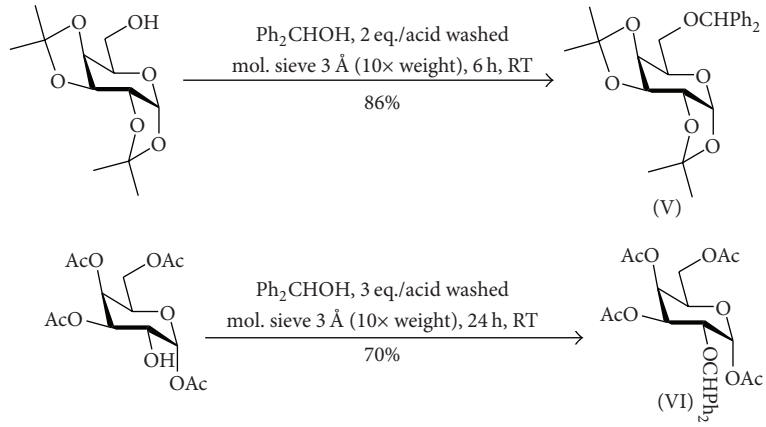
(iii) the use of diazo(diphenyl)methane in a refluxing nonprotic solvent, such as benzene, toluene or acetonitrile, which react by a carbene mechanism,

(iv) Tin halide catalyzed monoetherifications of diols with diaryldiazomethanes [12–17].

There is also one report from 1964 of a small scale benzhydrylation of 1,2,3,4-tetra-*O*-acetyl-β-D-glucose using benzhydryl bromide in 2,6-lutidine giving 64% yield of 1,2,3,4-tetra-*O*-acetyl-6-*O*-benzhydryl-β-D-glucose. The preparation of this compound on a larger scale was also done by benzhydrylating glucose itself followed by the peracetylation giving a 20% yield of the crystallized product [18].

2.1. The Use of Tris(diphenylmethyl) Phosphate for the Formation of Benzhydryl Ethers. This method for the formation of benzhydryl ethers (II) was developed by Lapatsanis in 1978. The method uses tris(diphenylmethyl) phosphate (I) and a strong acid catalyst in refluxing dichloromethane or a mixture of dichloromethane and ethyl acetate. The acid used was trifluoroacetic acid. The acid protonates the phosphate ester oxygen creating a good leaving group which releases a relatively stable diphenylmethyl carbocation. This carbocation is a strong electrophile, which reacts with hydroxyl groups present as shown in Scheme 1. The yields for simple primary and secondary alcohols were 65–86% [13].

When the simultaneous protection of the carboxyl and the hydroxyl group of a hydroxyamino acids was performed, toluenesulfonic acid in refluxing toluene was used. The acid which was used in stoichiometric amounts simultaneously protects the α-amino group and prevents N-alkylation [19]. Froussios reported two convenient methods for the preparation of the alkylating agent, tris(diphenylmethyl) phosphate, which does not keep very well. The first method uses anhydrous phosphoric acid and diazo(diphenyl)methane but the second method uses commercially available reagents, namely, 85% phosphoric acid, benzophenone hydrazone (III), and (diacetoxy)iodobenzene (IV) (Scheme 2) [20].



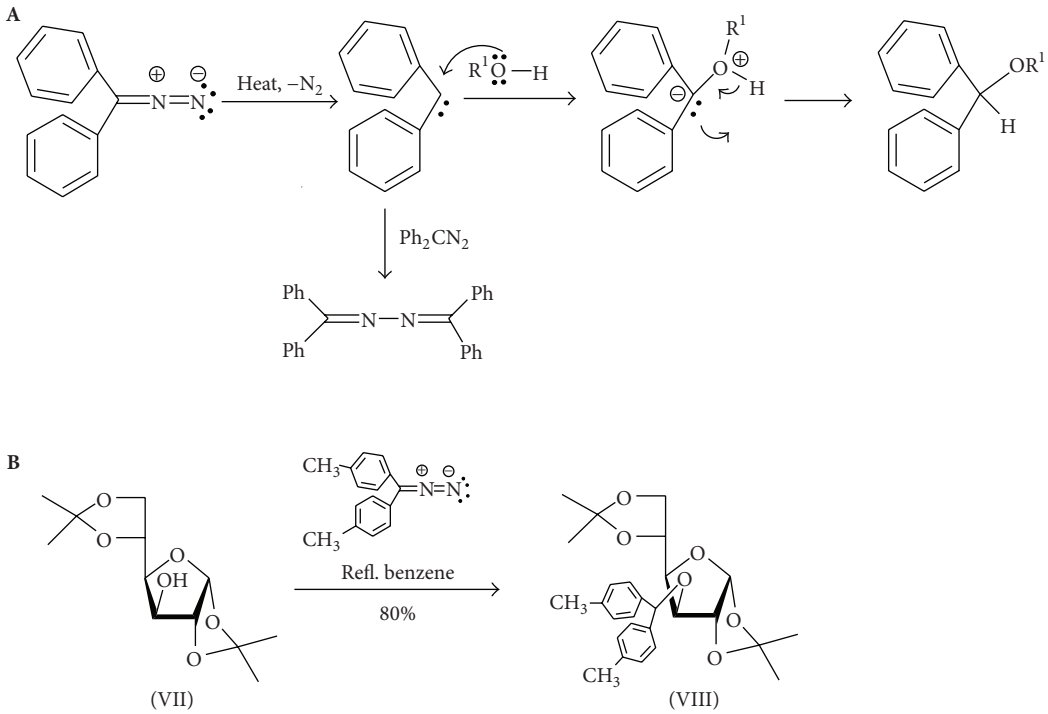
Scheme 3: Benzhydrylation using benzhydrol and strong acid catalyst.

2.2. The Use of Benzhydrol under Dehydrating Conditions. The stability of the diphenylmethyl carbocation and its ease of formation mentioned above, makes its direct formation possible by dehydration after protonation of benzhydrol itself. Two recent methods use immobilized acids. Firstly, use is made of the perfluorinated sulfonic acid resin *Nafion-H* to give the benzhydryl ether in excellent yield [14]. The second method uses acid washed molecular sieve 4 Å to tritylate and benzhydrylate a number of partly protected monosaccharides in good yield. It is noteworthy that these monosaccharide derivatives contain acid labile *O*-ketal (V) and *O*-acetyl (VI) protection [15]. Two examples of these benzhydrylations are shown in Scheme 3.

More recent use of benzhydrol for the benzhydrylation of simple alcohols in the presence of palladium(II) chloride have been reported by Pale and coworkers, but the poor yields for anything but the simplest of alcohols do not seem to justify the use of such an expensive catalyst [21]. The same authors reported the use of copper(II) bromide for the diarymethylation with the most reactive of the benzhydrol derivatives, namely, bis(4-methoxyphenyl)methanol. These reactions went smoothly in good yields for a number of alcohols including alcohols in compounds containing acid labile protecting groups [22].

2.3. Reaction with Diazo(diphenyl)methane in Nonprotic Solvents under Reflux. Diazo compounds are highly reactive towards hydroxyl groups. Alkyl diazo compounds (R_2CN_2, where R = alkyl group) where delocalisation is restricted to the diazo system itself are unstable and cannot be isolated [23]. Diazomethane itself is an explosive gas (b.p. −23°C) which is normally generated as required from *N*-methyl-*N*-tolylsulfonyl nitrosamide in basic solution [24]. Phenyldiazomethane is a liquid which can be isolated but is generally made as required by for example the thermal decomposition of benzaldehyde tosylhydrazone in the presence of a strong base [25]. This is not a convenient compound to use. The diaryldiazomethanes are much more manageable crystalline compounds. The parent compound, diazodiphenylmethane, is low melting (m.p. 32°C) but the *para* dimethoxy-, dimethyl- and dichloro-derivatives, and diazofluorene all have melting points over 100°C. Explosion hazard is not an issue with these compounds but all diazo compounds should be assumed to be carcinogenic and handled accordingly. Diazo(diphenyl)methane is easily produced by oxidation of the commercially available benzophenone hydrazine [26]. This compound can therefore be made in convenient laboratory quantities and stored for years at low temperature.

Most diaryldiazomethanes react spontaneously with carboxylic acids at room temperature forming esters by a mechanism which is thought to involve a simultaneous attack by the carboxyl proton and the oxygen on the diazo carbon [27, 28]. Alcohols are on the other hand not acidic enough by themselves to protonate the diazo-carbon causing the loss of nitrogen and the formation of a carbocation. The use of tin(II) halides for the catalysis of the reaction of diols with the diaryldiasomethanes will be dealt with later, but the formation of the carbocation by the catalysis with strong acids in the presence of an alcohol causes the diazo compound to decompose but does not result in the formation of an ether. Diaryldiazomethanes react however with alcohols in refluxing nonprotic solvents such as benzene (b.p. 80°C), acetonitrile (b.p. 82°C), or toluene (b.p. 111°C) [16]. This reaction takes place via the formation of a reactive carbene which reacts indiscriminately with hydroxyl groups. These conditions are mild enough to leave most other common protecting groups, including esters and acetals, unaffected. Sensitive and synthetically important γ- and δ-lactones have also been protected by this method [29, 30]. Diazofluorene requires higher temperatures for decomposition. These reactions of diazo(diphenyl)methane are extremely easy to perform but the products have been usually isolated by column chromatography because of the formation of a substantial amount of a yellow byproduct, benzophenone azine. The mechanism of the benzydrylation in refluxing benzene involves the creation of an intermediate carbene as already mentioned. Scheme 4 shows the steps involved and the formation of the benzophenone azine byproduct (**A**) as well as the reaction of diazo [bis(4-methylphenyl)]methane with 1,2 : 5,6-di-O-isopropylidene-α-D-glucofuranose (VII) in refluxing benzene (**B**), which



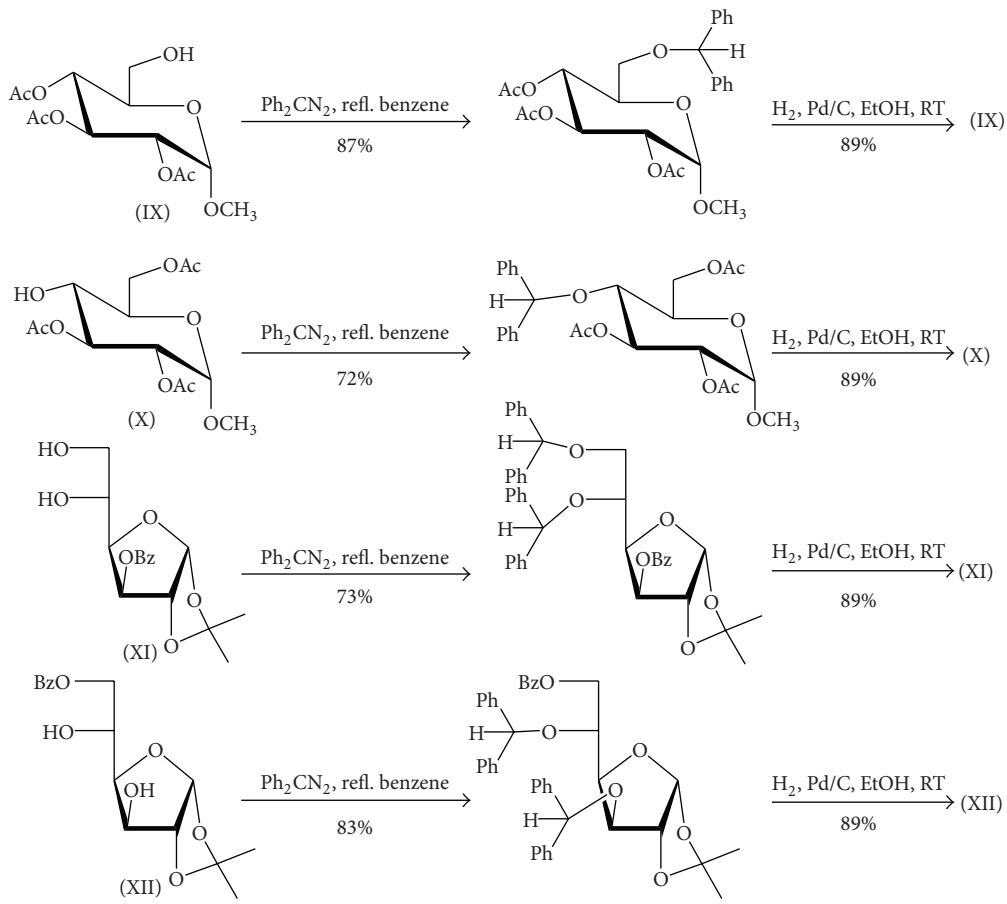
Scheme 4: Diaryldiazomethane reactions via thermal decomposition and the formation of a carbene.

gives the 3-(4,4-dimethylbenzhydryl)-ether (VIII) in good yield.

The early investigations of the uncatalyzed benzhydrylation method by Webber and coworkers in Birmingham illustrate the mildness of this method (Scheme 5). Thus, methyl 2,3,4-tri-O-acetyl-α-D-glucopyranoside (IX), methyl 2,3,6-tri-O-acetyl-α-D-glucopyranoside (X), 3-O-benzoyl-1,2-O-isopropylidene-α-D-glucofuranose (XI), and 6-O-benzoyl-1,2-O-isopropylidene-α-D-glucofuranose (XII) could all be benzhydrylated in good to excellent yields and the benzhydryl group removed by catalytic hydrogenolysis over palladium-on-carbon. The protection-deprotection of IX and XI are particularly noteworthy since acyl migration is known to happen particularly readily on these compounds [16].

Benzene, which was mainly used as solvent during the early research on the reactions of diazodiphenylmethane with carbohydrate hydroxyl groups, is a known carcinogen and therefore unpopular as a routine solvent in research laboratories today. A recent investigation, which has shown that benzene can be replaced by toluene giving excellent yields and order of magnitude shorter reaction times, is therefore significant [29]. This method has proved particularly suitable for the the synthetically useful lactones. Thus, the free hydroxyl group of 2,3-O-isopropylidene-D-ribono-γ-lactone (XIII) and its 2-C-methyl derivative (XIV) were both benzhydrylated in over 90% yield by diazodiphenylmethane in refluxing toluene. The other solvent investigated, acetonitrile was used for the benzhydrylation the 3,5-O-benzylidene-L-lyxonolactone (XV) which gave the ether (XVI) in 88% yield after refluxing for 18 h. Removal of the benzylidene in 87% yield by refluxing in 80% acetic acid demonstrated the stability of the benzhydryl group under these relatively mild acidic conditions (see formation of XVII). This gives a simpler access to the 2-O-ether protected 1,4-lactone than previously available (see Scheme 6).

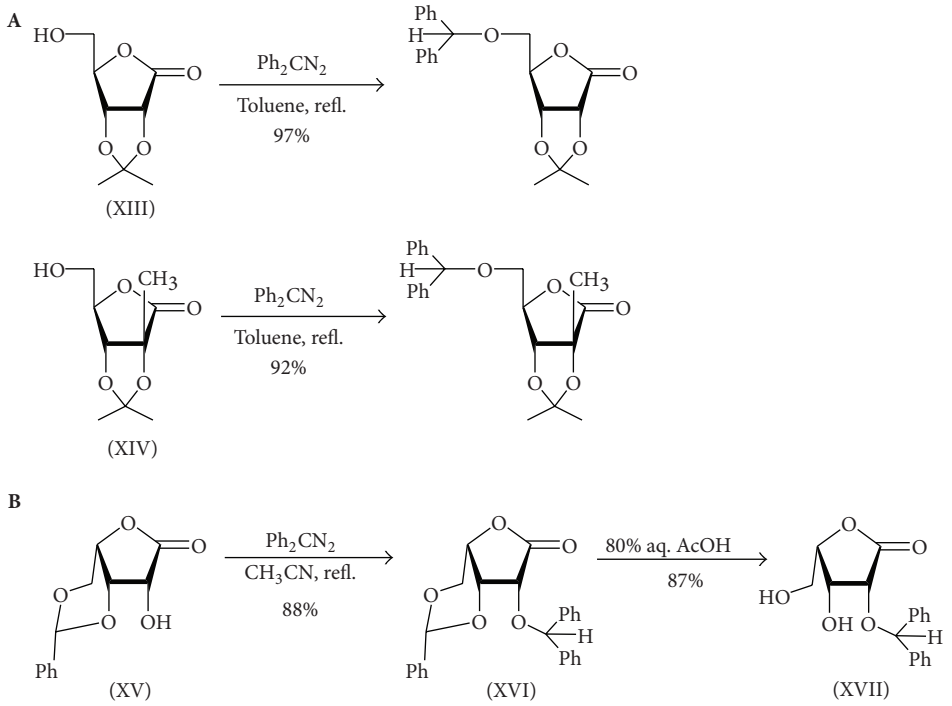
2.4. Reactions of Diols with Diazo(diphenyl)methane and Tin(II) Halides. The introduction of the diphenylmethyl group, just described, by the thermal decomposition of diazo(diphenyl)methane method, where peralkylation of all hydroxyl groups is intended and is straight forward as already pointed out. The reagent itself is easily made but its low melting point makes it fairly inconvenient to handle. Like all alkylating agents it is also a compound with undesirable biological properties. The formation of substantial amount of an azine byproduct makes column purification necessary in practically all cases and has to be balanced against its positive characteristics. Catalysts have therefore been sought for the reactions of diazodiphenylmethane with hydroxyl groups. This has included Lewis acids like BF_3, copper and cuprous salts, and protic acids like toluene-p-sulphonic acid. All these catalysts cause increased rate of decomposition of the diazo compound but little or no ether formation [16, 31]. In spite of this apparent lack of effective catalysts for the benzhydrylation of single hydroxyl groups, there are reports that go back to the 1970's of tin(II) chlorides and later tin(II) bromides being effective and regioselective catalysts for the reactions of diazomethane [32–36], diazophenylmethane [37–40] and aryldiazomethanes [41–45]. These reactions are characterized by the need for at least a diol, most commonly a vicinal



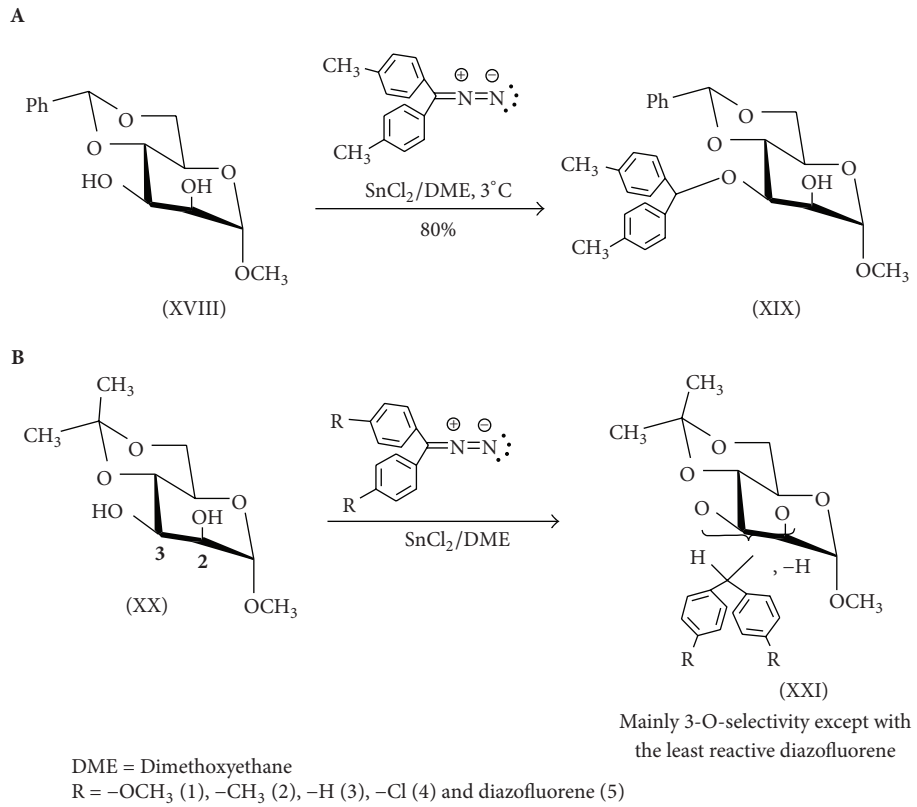
Scheme 5: Benzhydrylations in refluxing benzene of glucose derivatives illustrating the mildness of this ether forming method and the benzhydryl removal by catalytic hydrogenolysis.

diol, and the formation of mono-ethers only. Regioselectivity is sometimes good but usually it is not complete and both mono-ethers are obtained. Useful regioselectivities have, however, been obtained in these tin(II) halide catalyzed reactions and one study explored the effect of 4,4′-substitutions of diaryl(diazo)methanes [17]. Scheme 7 shows the results from the tin(II) chloride catalyzed reactions of diazo [bis(4-methylphenyl)]methane with methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (XVIII) (A). This reaction gave the 3-ether (XIX) in 80% yield and no 2-ether. This was also the case for the reactions of diazodiphenylmethane itself and for the dichloro derivative. Below (B) the results from similar reactions of these three diazo compounds, namely, diazo [bis(4-methylphenyl)]methane (**2**), diazo(diphenyl)methane (**3**), and diazo [bis(4-chlorophenyl)]methane (**4**) and in addition the most reactive in this series, diazo [bis(4-methoxyphenyl)]methane (**1**), and the least reactive, 9-diazofluorene (**5**), with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside (XX). As expected no diether was formed in these reactions. The results showed mainly 3-O-selectivity, which decreased with increasing stability of the diazo compound (XXI). The diminished 3-O-selectivity was small except for the most stable compound of the series, namely, 9-diazofluorine.

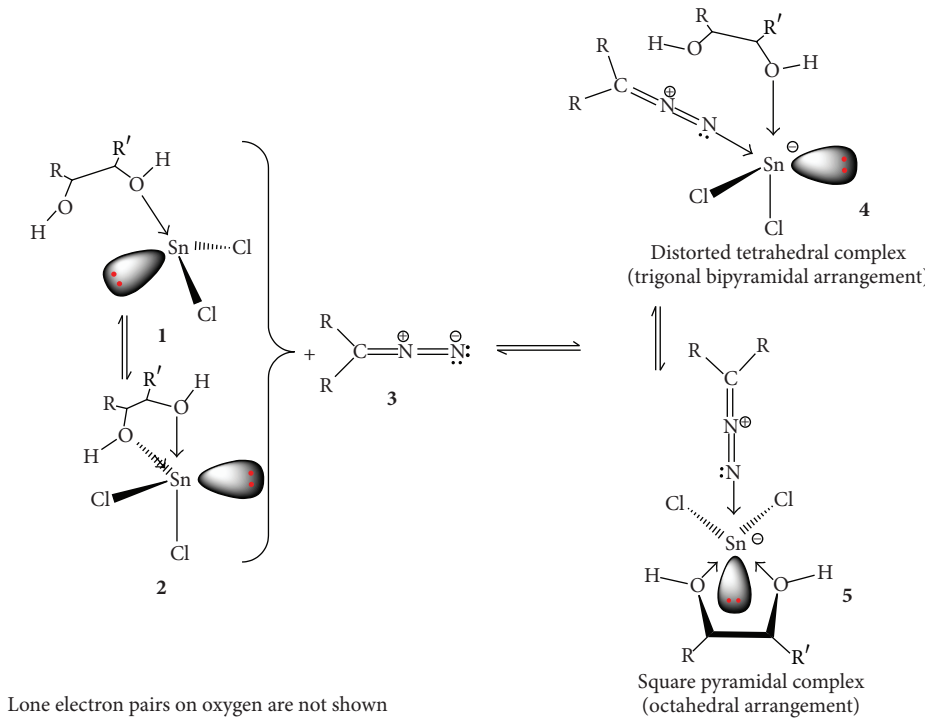
The results shown in Scheme 7 raise interesting mechanistic questions, which have not been answered, but it is likely that the complexes shown in Scheme 8 are involved. This model is based on the fact that tin(II) chloride dihydrate, which is normally formulated as $SnCl_2{\cdot}2H_2O$, but has been shown to be $[SnCl_2(H_2O)]{\cdot}H_2O$ consisting of pyramidal $SnCl_2(H_2O)$ groups (Sn–Cl, 259; Sn–O, 216 pm) with the mean bond angle of 85° [46]. A pyramidal structure such as 1 in Scheme 8 must therefore be considered a possible intermediate formed initially on mixing the tin(II) chloride with a diol in an inert solvent. A diol would also be more likely to form a second coordinate bond to the tin atom than another H_2O molecule, which does not happen in the case of $[SnCl_2(H_2O)]{\cdot}H_2O$. If that were to happen we have the trigonal bipyramidal structure 2 in Scheme 8, with the lone pair in the equatorial position. On addition of the diazo compound with the terminal nitrogen as a powerful ligand, complexes 4 and 5 could be formed. It is fairly obvious that complex 4 would lead to alkylation of the hydroxyl group not liganded to the tin atom, therefore, if one of the hydroxyl



Scheme 6: Benzhydrylation with diazodiphenylmethane in refluxing toluene (A) and acetonitril (B).



Scheme 7: Tin(II) chloride catalyzed reactions of diazo [bis(4-methoxyphenyl)]methane with methyl 4,6-*O*-benzylidene-α-D-mannopyranoside and the reactions of five diaryldiazomethanes with methyl 4,6-O-isopropylidene-α-D-mannopyranoside.



Scheme 8: Likely tin(II) chloride complex intermediates.

groups on mannose is more likely to form this complex bond, either for reasons of acidity or for steric reasons, this would lead to alkylation of the other hydroxyl group. This could explain the exclusive regioselectivity for the 3-OH in the case of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside. The formation of the square pyramidal complex 5 seems more likely to give reaction of either hydroxyl group, and a trend towards the more acidic hydroxyl group as the acid stability of the diazo compound increases also seems likely. This could explain what is happening during the reactions of the five diazo compounds with methyl 4,6-O-isopropylidene-α-D-mannopyranoside. It seems reasonable to assume that the two mannose derivatives could show different ligand arrangements around the divalent tin but evidence is not yet available that shows that only the 4,6-O-isopropylidene forms the square pyramidal complex.

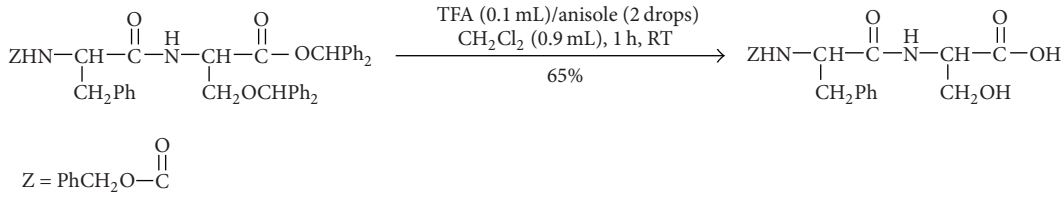
The alkylating properties of the substituted diazo-(diphenyl)methanes are similar to the parent compound. The dimethoxy compound is so reactive and unstable that more care is needed in its handling than the other compounds, but it is an easily made crystalline compound. The 4,4′-dimethyl derivative, which is more reactive than the parent compound, and the 4,4′-dichloro derivative are useful alternatives since both are easier to handle, being well crystalline with a melting points above 100°C [31, 47].

Diazo [bis(4-nitrophenyl)]methane has also been shown to be a useful ether forming compound. Boron trifluoride etherate catalyzes the reaction of this diazo compound with alcohols at −20 to 25°C in dichloromethane to give the 4,4′-dinitrobenzhydryl ethers in over 90% to near quantitative yields. A notable complication in the use of this protecting strategy arose in the attempted 3-*O*- protection of 1,2 : 5,6-di-O-isopropylidene-α-D-glucofuranose which resulted in 1,2 : 3,5-di-O-isopropylidene-6-*O*-[bis(4-nitrophenyl)]methyl-α-D-glucofuranose in 94% yield after acetal migration [48].

3. Deprotection of Diarylmethyl Ethers

The diphenylmethyl group is acid-labile, but it is sufficiently stable to allow selective removal of acetal groups by acid hydrolysis. For example, mild hydrolysis (0.2 M hydrochloric acid, 35°C, 18 h) of methyl 4,6-*O*-benzylidene-2,3-di-*O*-diphenylmethyl-α-D-glucopyranoside gave methyl 2,3-di-*O*-diphenylmethyl-α-D-glucopyranoside in 80% yield. More drastic condition like those used by Freudenberg in the preparation of 3-*O*-benzylglucose, that is, 0.3 M sulfuric acid in methanol/water (2 : 1) at 70°C for 4 h, did remove the diphenylmethyl group as well as the acetal protection [16, 49]. All the methods used for the removal of benzyl protection which rely on the relative stability of a benzyl carbocation intermediate or a benzyl radical will remove the diphenylmethyl group more readily. This includes both acid hydrolysis and catalytic hydrogenolysis. This would also include acetolysis, which replaces benzyl ethers with acetyl groups. The selectivity in the debenzylation of a perbenzylated methyl glucoside has recently been discussed [50].

3.1. Hydrogenolysis Using a Palladium Catalyst. Hydrogenolysis and hydrogen transfer methods are well-known debenzyl- and debenzylidenation reactions [51, 52]. These methods can also be applied to debenzhydrylations keeping



Scheme 9: Simultaneous benzhydryl ester and ether deprotection in the presence of *n*-benzyloxycarbonyl protection.

in mind that debenzhydrylation happens more readily than the removal of a benzyl or benzylidene protection. Selective debenzhydrylation was for example done on methyl 4,6-*O*-benzylidene-3-*O*-diphenylmethyl-2-*O*-methyl-α-D-mannopyranoside in 55% yield without resorting to less active forms of the palladium catalyst [16]. Olah has also reported a method for a hydrogen transfer reaction using aluminium trichloride/palladium catalyst, which cleaved a simple diphenylmethyl ether in over 90% yield [53].

3.2. Electrolytic Reduction. Mairanovski has shown that a number of different protecting groups common in synthetic chemistry, including the diphenylmethyl group, can be removed selectively by electrolytic reduction. The method requires equipment that the average synthetic chemist is not so familiar with and, in the case of selectivity between protecting groups, needs fine tuning which may make unnecessary demand on time for an incidental deprotection. For industrial applications and routine operations the method which can be represented by the following equation, seems very attractive: [54, 55]

$$\mathrm{Ph_2CH{-}O{-}R} \xrightarrow{2e^-,\,2H^+} \mathrm{Ph_2CH_2} + \mathrm{HO{-}R} \qquad (1)$$

3.3. Simultaneous Deprotection of Diphenylmethyl Ester and Ether in the Presence of an N-benzyloxycarbonyl Group. A noteworthy method for the removal of an *O*-diphenylmethyl ether, especially in applications to peptide synthesis, is Froussios's use of trifluoroacetic acid and anisole in dichloromethane. This method removed both a diphenylmethyl ester and a diphenylmethyl ether protection but left a terminal *N*-benzyloxycarbonyl (Z) group as illustrated in Scheme 9 [20].

3.4. Palladium(II) Chloride and Copper(II) Bromide Catalyzed Deprotections. Pale and coworkers used $PdCl_2$ and later $CuBr_2$ for the formation of diarylmethyl ethers as discussed in [21, 22]. These catalysts could also be used for the deprotection of the alcohols [56].

3.5. Removal of the 4,4′-dinitrobenzhydryl Group. Removal of the [bis(4-nitrophenyl)]methyl ether group can be effected by hydrogen reduction of the nitro group to an amino group followed by mild acid hydrolysis. The reducing systems used were H_2/PtO_2, H_2/Ni_2B (from $NaBH_4$ and $Ni(OAc)_2$) and $Fe_2(CO)_{12}$ [48].

References

[1] W. Friedrich, "Sur la Formation artificielle de l'Urée," *Annales de Chimie et de Physique*, vol. 37, pp. 330–334, 1828.

[2] H. Kunz, "Emil Fischer: unerreichter Klassiker, Meister der organisch-chemischen Forschung und genialer Wegbereiter der biologischen Chemie," *Angewandte Chemie*, vol. 114, pp. 4619–4632, 2002.

[3] H. Kunz, "Emil Fischer—unequalled classicist, master of organic chemistry research, and inspired trailblazer of biological chemistry," *Angewandte Chemie International Edition*, vol. 41, no. 23, pp. 4439–4451, 2002.

[4] E. Fischer, "Ueber die Verbindungen der Zucker mit den Alkoholen und Ketonen," *Berichte der deutschen chemischen Gesellschaft*, vol. 28, no. 1, pp. 1145–1167, 1895.

[5] E. Fischer, "Ueber ein neues dem Amygdalin ähnliches Glucosid," *Berichte der deutschen chemischen Gesellschaft*, vol. 28, no. 2, pp. 1508–1511, 1895.

[6] T. W. Greene and P. G. M. Wutz, *Protective Groups in Organic Synthesis*, John Wiley and Sons, New York, NY, USA, 4th edition, 2008.

[7] P. J. Kocieński, *Protecting Groups*, Georg Thieme, Stuttgart, Germany, 3rd edition, 2004.

[8] S Petursson, in *Houben-Weyl Methods of Molecular Transformations, Science of Synthesis*, E. N. Jacobsen and C. J. Forsyth, Eds., vol. 37, pp. 847–892, Thieme Verlag, Stuttgart, Germany, 2008.

[9] R. Ferrier and P. Collins, *Monosaccharide Chemistry*, Penguin, London, UK, 1972.

[10] P. Collins and R. Ferrier, *Monosaccharides*, John Wiley & Sons, London, UK, 1995.

[11] E. G. V. Percival, *Structural Carbohydrate Chemistry*, J. Garnet Miller, London, UK, 1955.

[12] C. E. Dreef, R. J. Tuinman, A. W. M. Lefeber, C. J. J. Elie, G. A. Van Der Marel, and J. H. Van Boom, "Synthesis of racemic 3-methylphosphonate analogues of myo-inositol 3,4-bis- and 1,3,4-trisphosphate," *Tetrahedron*, vol. 47, no. 26, pp. 4709–4722, 1991.

[13] L. Lapatsanis, "A new method for the preparation of diphenylmethyl ethers," *Tetrahedron Letters*, vol. 19, no. 41, pp. 3943–3944, 1978.

[14] M. A. Stanescu and R. S. Varma, "Nafion-catalyzed preparation of benzhydryl ethers," *Tetrahedron Letters*, vol. 43, no. 41, pp. 7307–7309, 2002.

[15] M. Adinolfi, G. Barone, A. Iadonisi, and M. Schiattarella, "Mild benzhydrylation and tritylation of saccharidic hydroxyls promoted by acid washed molecular sieves," *Tetrahedron Letters*, vol. 44, no. 19, pp. 3733–3735, 2003.

[16] G. Jackson, H. F. Jones, S. Petursson, and J. M. Webber, "Diphenylmethylation of carbohydrate hydroxyl groups

by the reaction with diazo(diphenyl)methane," *Carbohydrate Research*, vol. 102, no. 1, pp. 147–157, 1982.

[17] S. Petursson and J. M. Webber, "Regioselective monoalkylations of the vicinal cis-diol group in mannopyranosides using diaryldiazoalkanes-tin(II) chloride," *Carbohydrate Research*, vol. 103, no. 1, pp. 41–52, 1982.

[18] D. J. Stanonis and W. D. King, "Syntheses of 1,2,3,4-tetra-O-acetyl-6-O-benzhydryl-β-D-glucose," *Journal of Chemical and Engineering Data*, vol. 9, no. 2, pp. 238–239, 1964.

[19] M. Kolovos and C. Froussios, "O-diphenylmethylation of alcohols and carboxylic acids using diphenylmethyl diphenyl phosphate as alkylating agent," *Tetrahedron Letters*, vol. 25, no. 35, pp. 3909–3912, 1984.

[20] C. Froussios and M. Kolovos, "Preparation of diphenylmethyl esters and ethers of unprotected amino acids and β-hydroxy-α-amino acids," *Synthesis*, no. 12, pp. 1106–1108, 1987.

[21] Y. Bikard, R. Mezaache, J. M. Weibel, A. Benkouider, C. Sirlin, and P. Pale, "Diarylmethyl ethers and Pd salts or complexes: a perfect combination for the protection and deprotection of alcohols," *Tetrahedron*, vol. 64, no. 44, pp. 10224–10232, 2008.

[22] R. Mezaache, Y. A. Dembelé, Y. Bikard, J. M. Weibel, A. Blanc, and P. Pale, "Copper(II) bromide as an efficient catalyst for the selective protection and deprotection of alcohols as bis(4-methoxyphenyl)methyl ethers," *Tetrahedron Letters*, vol. 50, no. 52, pp. 7322–7326, 2009.

[23] G. W. Cowell and A. Ledwith, "Developments in the chemistry of diazo-alkanes," *Quarterly Reviews, Chemical Society*, vol. 24, no. 1, pp. 119–167, 1970.

[24] *Organic Synthesis Collective*, vol. 4, p. 250, http://www.orgsyn.org/.

[25] *Organic Synthesis Collective*, vol. 7, p. 250, 1990, http://www.orgsyn.org/.

[26] J. B. Miller, "Notes-preparation of crystalline diphenyldiazomethane," *Journal of Organic Chemistry*, vol. 24, pp. 560–561, 1959.

[27] C. K. Hancock, R. F. Gilby, and J. S. Westmoreland, "The kinetics and mechanism of the reaction of benzoic acid and substituted diphenyldiazomethanes in toluene," *Journal of the American Chemical Society*, vol. 79, no. 8, pp. 1917–1920, 1957.

[28] B. Z. Jovanocic, F. H Assaleh, and A. D. Marinkovic, "Kinetics of the reaction of 5-substituted orotic acids with diazodiphenylmethane," *Journal of the Serbian Chemical Society*, vol. 69, no. 11, pp. 949–953, 2004.

[29] D. Best, S. F. Jenkinson, S. D. Rule et al., "High yield protection of alcohols, including tertiary and base sensitive alcohols, as benzhydryl ethers by heating with diphenyldiazomethane in the absence of any other reagent," *Tetrahedron Letters*, vol. 49, no. 14, pp. 2196–2199, 2008.

[30] P. J. Davis, L. Harris, A. Karim et al., "Substituted diaryldiazomethanes and diazofluorenes: structure, reactivity and stability," *Tetrahedron Letters*, vol. 52, no. 14, pp. 1553–1556, 2011.

[31] S. Petursson, *The use of some diphenyldiazo-compounds for the protection of carbohydrate hydroxyl groups [Ph.D. thesis]*, University of Birmingham, 1978.

[32] M. Aritomi and T. Kawasaki, "Partial methylation with diazomethane of the sugar moiety of some C- and O-D-glucopyranosides," *Chemical & Pharmaceutical Bulletin*, vol. 18, pp. 677–686, 1970.

[33] G. J. F. Chittenden, "Reaction of benzyl 4,6-O-benzylidene-β-D-galactopyranoside with diazomethane: synthesis of 2-O-methy]-D-galactose and some derivatives," vol. 43, no. 2, pp. 366–370, 1975.

[34] G. J. F. Chittenden, "Syntheses of 2-O-methyl-, 3-O-methyl-, and 2,3-di-O-methyl-d-talose and some derivatives thereof," *Carbohydrate Research*, vol. 52, no. 1, pp. 23–29, 1976.

[35] G. J. F. Chittenden, "Reaction of 1,2-O-isopropylidene-α-d-glucofuranose and some of its derivatives with diazomethane-stannous chloride: synthesis of 3,5-di-O-methyl- and 5-O-methyl-d-glucose derivatives," *Carbohydrate Research*, vol. 74, no. 1, pp. 333–336, 1979.

[36] M. J. Robins and S. R. Naik, "Nucleic acid related compounds. II. A rapid and quantitative preparation of $2'$-0- and $3'$-0-methyl nucleosides," *Biochimica et Biophysica Acta*, vol. 246, pp. 341–343, 1971.

[37] M. J. Robins, S. R. Naik, and A. S. K. Lee, "Nucleic acid related compounds. 12. The facile and high-yield stannous chloride catalyzed monomethylation of the cis-glycol system of nucleosides by diazomethane," *Journal of Organic Chemistry*, vol. 39, no. 13, pp. 1891–1899, 1974.

[38] M. J. Robins, A. S. K. Lee, and F. A. Norris, "Catalytic monomethylation of the cis-glycol system by diazomethane. Effects of novel inorganic catalysts on isomer ratios," *Carbohydrate Research*, vol. 41, no. 1, pp. 304–307, 1975.

[39] L. F. Christensen and A. D. Broom, "Specific chemical synthesis of ribonucleoside O-benzyl ethers," *Journal of Organic Chemistry*, vol. 37, no. 22, pp. 3398–3401, 1972.

[40] G. J. F. Chittenden, "Selective alkylation of glycerol: direct synthesis of 2-O-benzylglycerol and 2-O-methylglycerol," *Carbohydrate Research*, vol. 91, no. 1, pp. 85–88, 1981.

[41] D. G. Bartholomew and A. D. Broom, "One-step chemical synthesis of ribonucleosides bearing a photolabile ether protecting group," *Chemical Communications*, no. 2, p. 38, 1975.

[42] Y. Mizuno, T. Endo, and K. Ikeda, "Nucleotides. V. Syntheses of $2'$ O and $3'$ O (3 methyl 2 picolyl 1 oxide) ribonucleosides and diribonucleoside monophosphates by application of 3 methyl 2 picolyl 1 oxide protection," *Journal of Organic Chemistry*, vol. 40, no. 10, pp. 1385–1390, 1975.

[43] S. F. Jenkinson, S. D. Rule, K. V. Booth, G. W. J. Fleet, D. J. Watkin, and S. Petursson, "2-O-Benzhydryl-3,4-(S)-O-benzylidene-d-xylono-1,4-lactone," *Acta Crystallographica E*, vol. 64, no. 6, p. o1012, 2008.

[44] S. Petursson, "Highly regioselective primary etherification of racemic propane-1,2-diol by the tin(II) bromide-catalyzed reaction with diazo[bis(4-methoxyphenyl)]methane and the resolution of enantiomers with the help of Pseudomonas cepacia lipase," *Tetrahedron Asymmetry*, vol. 20, no. 6–8, pp. 887–891, 2009.

[45] S. Petursson and S. Jonsdottir, "Resolution of a racemic 1,2-diol using triphenylmethyl protection of the primary hydroxyl group and Mucor miehei lipase (Lipozyme) for the kinetic resolution," *Tetrahedron Asymmetry*, vol. 22, no. 18-19, pp. 1809–1812, 2011.

[46] A. F. Wells, *Structural Inorganic Chemistry*, Oxford University Press, 5th edition, 1984.

[47] N. V. Sidgwick, L. E. Sutton, and W. Thomas, "107. Dipole moments and structures of the organic azides and aliphatic diazo-compounds," *Journal of the Chemical Society*, pp. 406–412, 1933.

[48] G. Just, Z. Y. Wang, and L. Chan, "p,p$'$-Dinitrobenzhydryl ethers, acid and base stable protecting groups, which are readily

removable in the presence of benzyl and monomethoxytrityl functions," *Journal of Organic Chemistry*, vol. 53, no. 5, pp. 1030–1033, 1988.

[49] K. Freudenberg, H. V. Hochstetter, and H. Engels, "Einige Derivate der Maltose und Glucose," *Berichte der deutschen chemischen Gesellschaft*, vol. 58, pp. 666–671, 1925.

[50] Y. Cao and H. Yamada, "Corrected order in the simultaneous debenzylation-acetolysis of methyl 2,3,4,6-tetra-O-benzyl-α-d-glucopyranoside," *Carbohydrate Research*, vol. 341, no. 7, pp. 909–911, 2006.

[51] S. Sato, K. Hiroe, T. Kumazawa, and O. Jun-ichi, "Total synthesis of two isoflavone C-glycosides: genistein and orobol 8-C-β-d-glucopyranosides," *Carbohydrate Research*, vol. 341, no. 9, pp. 1091–1095, 2006.

[52] C. H. Heathcock and R. Ratcliffe, "A stereoselective total synthesis of the guaiazulenic sesquiterpenoids α-bulnesene and bulnesol," *Journal of the American Chemical Society*, vol. 93, no. 7, pp. 1746–1757, 1971.

[53] G. A. Olah, G. K. S. Prakash, and S. C. Narang, "Synthetic methods and reactions; 53. Convenient reductive cleavage of benzylic (Benzhydrilic) ethers and acetals using $AlCl_3$/Pd-catalyzed hydrogen transfer from cyclohexene," *Synthesis*, no. 11, p. 825, 1978.

[54] V. G. Mairanovsky, "Elektro-Deblockierung—Elektrochemische Abspaltung von Schutzgruppen," *Angewandte Chemie*, vol. 88, no. 9, pp. 283–294, 1976.

[55] V. G. Mairanovsky, "Electro-deprotection—electrochemical removal of protecting groups," *Angewandte Chemie International Edition*, vol. 15, no. 5, pp. 281–292, 1976.

[56] Y. Bikard, J. M. Weibel, C. Sirlin, L. Dupuis, J. P. Loeffler, and P. Pale, "PdCl2, a useful catalyst for protection of alcohols as diphenylmethyl (DPM) ethers," *Tetrahedron Letters*, vol. 48, no. 50, pp. 8895–8899, 2007.