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Invited Review

Conversions of Nitroalkyl to Carbonyl Groups in Carbohydrates

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Summary. Since the development of the *Sowden* methodology in the middle of the twentieth century, several other efficient and complementary methods for the transformation of sugar nitromethyl groups to aldehyde functionalities in their free, hemiacetal, or otherwise derivatized forms have been developed. Hydrogen peroxide oxidation as well as ozonolysis of 1-deoxyalditol-1-nitronates in aqueous solution provide free aldoses, thus presenting alternatives to the well-known *Nef* reaction. When applied to 2,5- or 2,6-anhydro-1-deoxy-1-nitroalditols, also known also as glycosylnitromethanes, the *Nef* reaction fails, and the hydrogen peroxide oxidation overoxidizes the expected products to 2,5- or 2,6-anhydroaldonic acids. On the other hand, the ozonolysis of such compounds under *pH*-controlled conditions results in up to 85% of the interesting glycosylformaldehydes. The *Nef* reaction carried out in anhydrous low alcohols, however, has revealed a new conversion of glycosylnitromethanes to glycosylmethanal dialkyl acetals, even more interesting C-glycoside synthons. A similar acid-catalyzed methanolysis of 1-deoxyalditol-1-nitronates leads to methyl furanosides. Finally, a treatment of per-O-substituted glycosylnitromethanes with tributyltin hydride in boiling benzene causes their radical reduction under a nearly quantitative formation of glycosylmethanal oximes.

Keywords. Nitroalditols; C-Glycosyl compounds; *Nef* reaction; Ozonolysis; Sugar oximes.

Introduction

The nitro group is a rather scarcely occurring functionality in natural compounds, and few such compounds are known among carbohydrates. The functional group has become more frequently employed in synthetic carbohydrate chemistry since the introduction of the nitromethane methodology for the carbon skeleton elongation of aldoses known as the *Sowden* method. By convenient modifications of the *Henry* and *Nef* reactions [1, 2], both known since about 1890, *J. C. Sowden* and *H. O. L. Fischer* have developed an efficient synthesis of aldoses *via* intermediate 1-deoxy-1-nitroalditols [3]. The addition of the methanenitronate nucleophile **2** to an aldose **1** results in the formation of a mixture of an epimeric pair of products in

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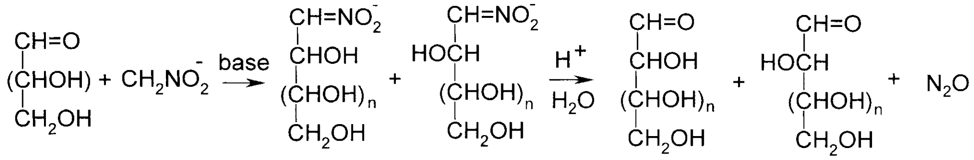

1 **2** **3a** **3b** **4a** **4b**

Scheme 1

their nitronate forms (**3a**,**b**). In a subsequent step these are subjected to a strong acid-catalyzed hydrolysis under the formation of two new aldoses by one carbon longer (**4a**,**b**) and nitrous oxide (Scheme 1).

Although the acid is used as a catalyst, an excess is necessary to quantitatively accomplish the hydrolysis of the alditolnitronates. The method has been shown to be universal for the synthesis of aldoses and, if coapplying formaldehyde in the addition step, *i.e.*, in the so-called nitroethanol synthesis, also for some 2-ketoses. A comprehensive review on the *Sowden* method has been published where details can be found [4]. Later, the methodology has been utilized also for syntheses of branched-chain aldoses [5] or keto derivatives of sugars [6]. However, 2,6-anhydro-1-deoxy-1-nitroalditols (and their less common 2,5-anhydro isomers) in their nitronate forms are resistant to the *Nef* reaction, and only the starting nitro compounds are recovered from the reaction mixtures [7].

The Hydrogen Peroxide Oxidation

In 1974, *V. Bílik* has introduced an alternative transformation of 1-deoxyalditol-1-nitronates to aldoses [8][1], showing that the treatment of an aqueous solution of a mixture of epimeric sodium 1-deoxyalditol-1-nitronates **3a**,**b** with hydrogen peroxide in the presence of molybdate, tungstate, or vanadate ions results in the formation of the corresponding aldoses **4a**,**b** and sodium nitrite (Scheme 2). The molybdate ions have been found to be the best catalyst for this transformation.

The transformation is believed to proceed *via* intermediates **5a**,**b** which spontaneously eliminate the nitrite ions giving rise to aldoses **4a**,**b**. Being able to form their hemiacetals, the aldoses are resistant to a further oxidation to aldonic acids. However, this is not a case when 2,5- or 2,6-anhydro-1-deoxy-1-nitroalditols (glycosylnitromethanes) in their nitronate forms are subjected to the oxidation. The respective products, 2,5- or 2,6-anhydroaldoses, usually cannot form stable hemiacetals and undergo a further oxidation with hydrogen peroxide, even without the presence of transient metal anions, to the corresponding anhydroaldonic acids [11].

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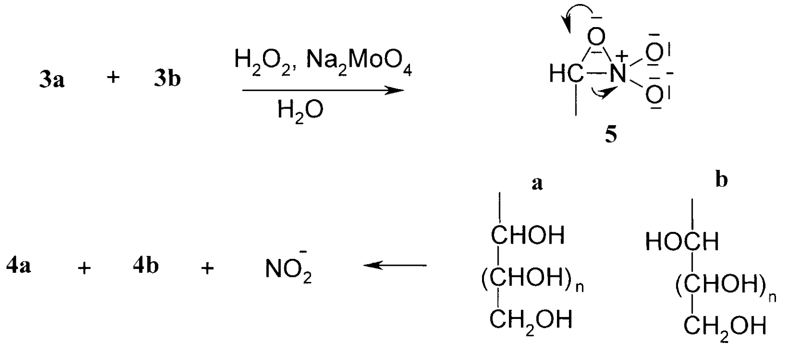
[1] The reaction has actually been developed in analogy to another carbohydrate reaction developed by *V. Bílik*, the stereoselective hydroxylation of glycals with peroxomolybdate or peroxotungstate ions providing *cis*-C-2-OH–C-3-OH aldoses [9]. However, the most famous carbohydrate reaction introduced by the same author in 1972 is a stereospecific, dimolybdate-catalyzed C-1-C-2-carbon skeleton rearrangement of aldoses which with isotopically uniform aldoses leads to their mutual C-2-epimerization and which has been coined the *Bílik* reaction [10].

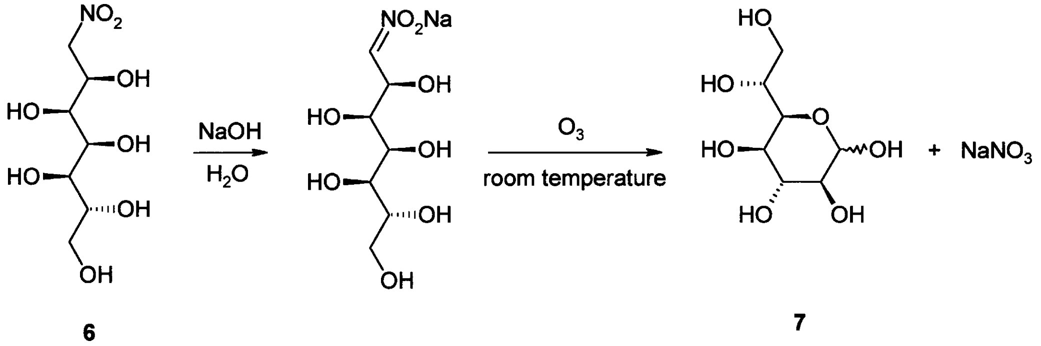


Scheme 2

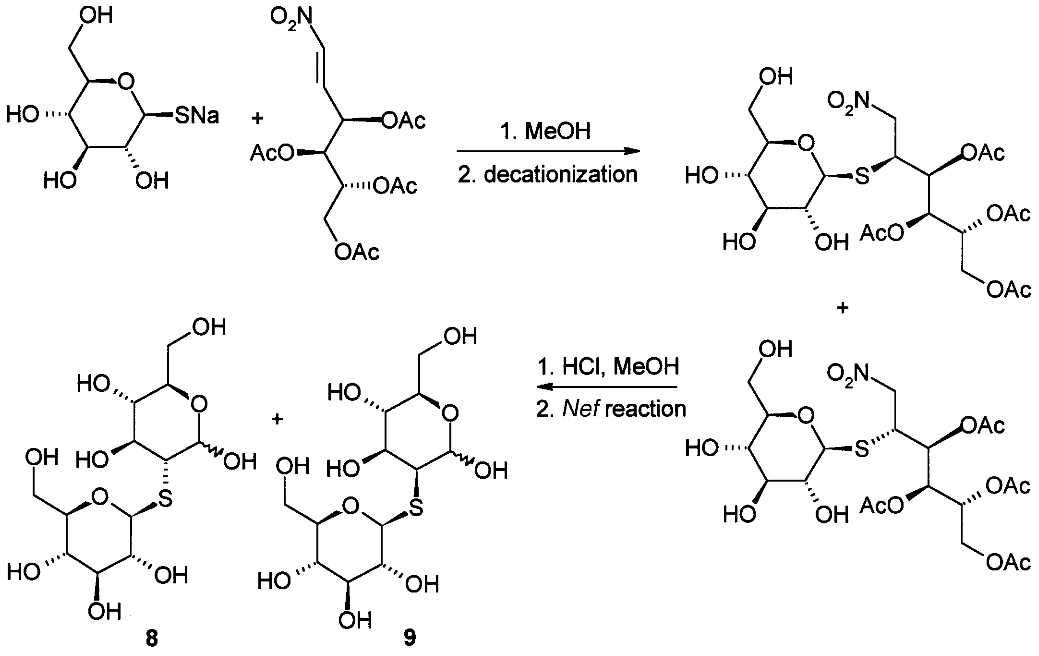
The hydrogen peroxide oxidation, preferentially called the oxidative decomposition of 1-deoxy-1-nitroalditols in the literature, has been applied for the preparation of monosaccharide hexoses [8, 12], heptoses [13–15], octoses [16, 17], and disaccharide 4-O-hexosylhexoses [18]. Also, some ω-deoxyhexoses and heptoses have been prepared by this route [19].

Ozonolysis

In the early 1990s the third simple and universal method for the transformation of 1-deoxy-1-nitroalditols to aldoses with the same number of carbon atoms has been introduced [20]. The method utilizes the treatment of an aqueous solution of the intermediate sodium 1-deoxyalditol-1-nitronates with ozone at room temperature. Scheme 3 represents such an ozonolysis on the example of 1-deoxy-*D*-glycero-*D*-ido-heptitol-1-nitronate (**6**), leading to *D*-glycero-*D*-ido-heptose (**7**) and sodium nitrate. The yields are comparable with those of the hydrogen peroxide oxidation as well as those of the acid-catalyzed hydrolysis of the same substrates; the isolated yield of heptose **7** in the conversion shown in Scheme 3 is 85% [20]. This summary follows also from a comparative study of the three nitromethane methods applied to the *D*-mannose to *D*-glycero-*D*-galacto- and -*D*-talo-heptose transformation [21].



Scheme 3



Scheme 4

Similarly as in the hydrogen peroxide oxidation, the hemiacetal functionality sufficiently protects the aldose from subsequent oxidation to the corresponding aldonic acid. Thus, no formation of acid derivatives of saccharides in ozonolysis of sodium 1-deoxyalditol-1-nitronates with ozone generated from pure oxygen has been observed[2].

Ozonolyzing alkaline alditolnitronates, monosaccharide hexoses and heptoses [20] as well as two disaccharidic 4-O-hexosyl-2-deoxy-2-acetamidohexoses have been prepared [22]. However, if electron-rich heteroatoms are present in the substrates a competitive oxidation occurs which is a significant limitation of the method. Thus, ozonolysis of the nitronate forms of the 1-thio-*D*-glucose-to-1,2-dideoxy-1-nitro-*D*-arabino-hex-1-enitol adducts failed, and neither 2-thiosophorose (**8**) nor its epimer **9** could be prepared (Scheme 4). A classical *Nef* reaction solved the problem, and high yields of the crystalline thiodisaccharides were obtained [23].

Even with 2-acetamido-1,2-dideoxyaditol-1-nitronates treated with ozone a partial degradation occurs, decreasing the yields of the corresponding 2-acetamidosugars by 10–15% compared with an analog conversion leading to unsubstituted aldoses. However, things do not improve using either *Nef* hydrolysis or hydrogen peroxide oxidation. The conditions of the former reaction bring about a significant acid-catalyzed N-deacetylation, whereas under those of the latter a

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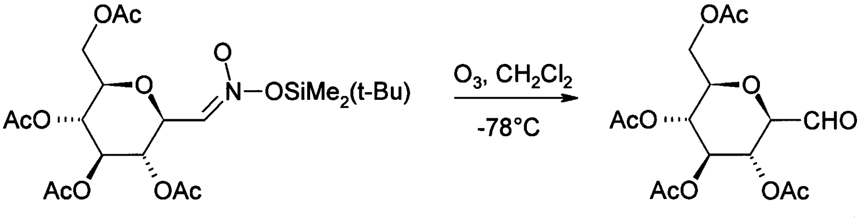
[2] When insufficiently pure oxygen is used for ozone generation, significant amounts of acidic byproducts are formed, apparently from oxidation by cogenerated oxides of nitrogen.



10 **11**

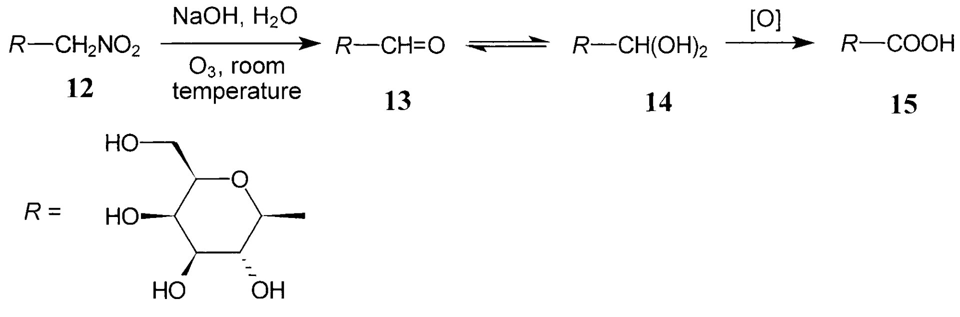
Scheme 5

competitive degradation of the 2-acetamidosugars to the corresponding one-carbon shorter aldose occurs [24].

Anyway, the ozonolysis of the 1-deoxy-1-nitroalditol-1-nitronates to aldoses is a side product of another endeavor. The challenge was a good access to glycopyranosylnitromethanes [25], despite of their known resistance to the *Nef* reaction. Thus, *O. Martin et al.* for the first time have introduced the ozonolysis of nitromethane derivatives of sugars already in 1989 [26], and the per-O-acetylated silylnitronate **10** was used for the conversion to the corresponding aldehyde **11** (Scheme 5).

Although the authors have claimed a practically quantitative yield, the method has still limitations due to a low stability of the silylnitronates (*e.g.*, trimethylsilylnitronates are too unstable to be prepared). A little later, a significant simplification of the method, the ozonolysis of the sodium nitronate forms of *β*-glycopyranosylnitromethanes at room temperature, has been introduced [27]. Thus, the ozonolysis of the sodium *β*-*D*-galactopyranosylmethanenitronate gives rise to the expected aldehyde **13** (Scheme 6). The compound, unable to be stabilized *via* a hemiacetal due to stereochemical reasons, is present in reaction mixture in an equilibrium with its aldehydrol form (**14**) in ratio of 1:4 (hydrate predominates) and is consecutively oxidized to the corresponding 2,6-anhydroaldonic acid **15**.

Whereas at the beginning of the reaction the *pH* is strongly alkaline at the end it is close to 7, and it is easy to control the ozonolysis and thus to prevent undesirable further oxidation. As part of the starting alkalinity necessary for generation of the nitronate form is consumed by acid **15**, the optimum conditions for the conversion



Scheme 6

Table 1. Ozonolysis of **12** in its sodium nitronate form

Reactants (mmol)[a]		Reaction products (%)[b]		
12	NaOH	**13** (+**14**)	**15**	**12**
1.0	1.0	80	10	10
1.0	1.1	85	10	5
1.0	1.2	75	25	0
1.0	1.3	65	35	0
1.0	1.4	55	45	0
1.0	1.5	40	60	0

[a] Total volume of reaction mixture: 4 cm^3; [b] values estimated from the ^{13}C NMR spectra

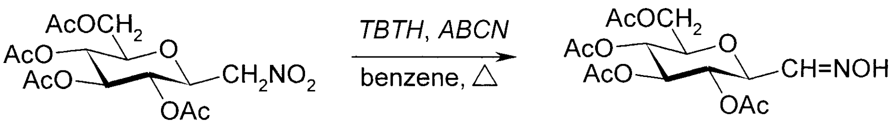
of **12** to **13** employ a 10% molar excess of sodium hydroxide based on **12** (Table 1). In addition to about 85% of aldehyde, including its hydrate, the final reaction mixture contains about 10% of aldonic acid **15** and about 5% of glycopyranosylnitromethane **12**. For a complete disappearance of the starting compound, a 20% excess of sodium hydroxide has to be used. In spite of a decreased yield of the aldehyde derivative (to about 75%) it is rather a practical step to avoid a contamination of the product with the starting glycopyranosylnitromethane as the aldonic acid is more easily separable later on. Thus, such raw aldehydes can be used for the preparation of homologous 2-(glycopyranosyl)-nitroethanes [27b].

A very efficient reaction, the ozonolysis of the secondary nitronate group, has been performed with an epimeric mixture of the 1:1-adducts of β-*D*-galactopyranosylnitromethane to formaldehyde [28]. The product obtained is 3,7-anhydro-*D*-glycero-*L*-manno-oct-2-ulose, a potential precursor of the 3-deoxy-*D*-galacto-oct-2-ulosonic acid *via* an intramolecular elimination which remains to be investigated.

The Radical Reduction

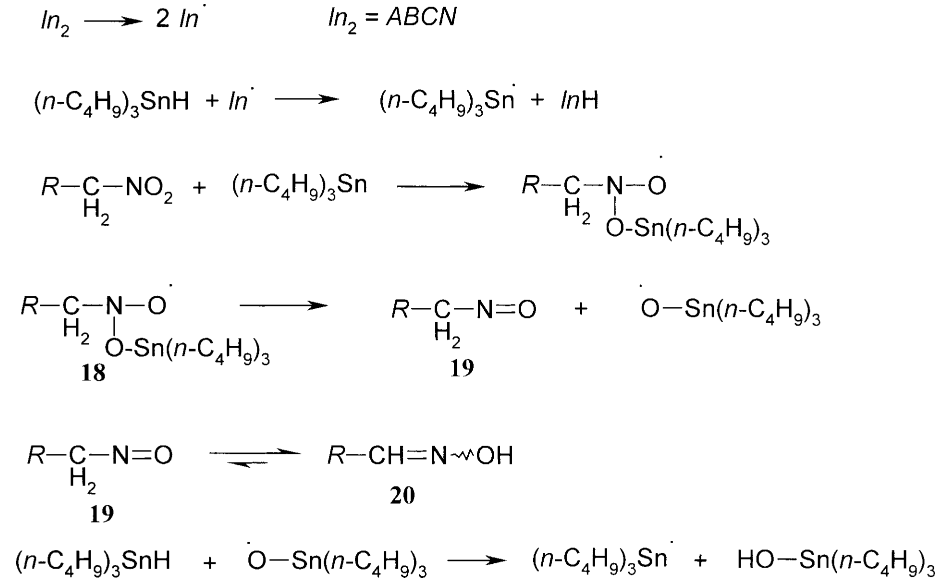
The primary nitro group originally considered to be inert with respect to the *TBTH/AIBN* radical denitration conditions [29, 30] has later been reported to undergo such a reaction with *TBTH/ABCN* [31]. Attempts to accomplish the denitration of per-O-acetylated β-*D*-glucopyranosylnitromethane (**16**, Scheme 7) with *TBTH* in boiling benzene in the presence of *ABCN* did not lead to the expected replacement of the nitro group by hydrogen but to its reduction to β-*D*-glucopyranosylmethanal oxime (**17**) in 90% yield [32].

Other β-glycopyranosylnitromethanes derived from common hexoses also gave high yields (85–97%) of the respective reduction products. The same products



16 **17**

Scheme 7



Scheme 8

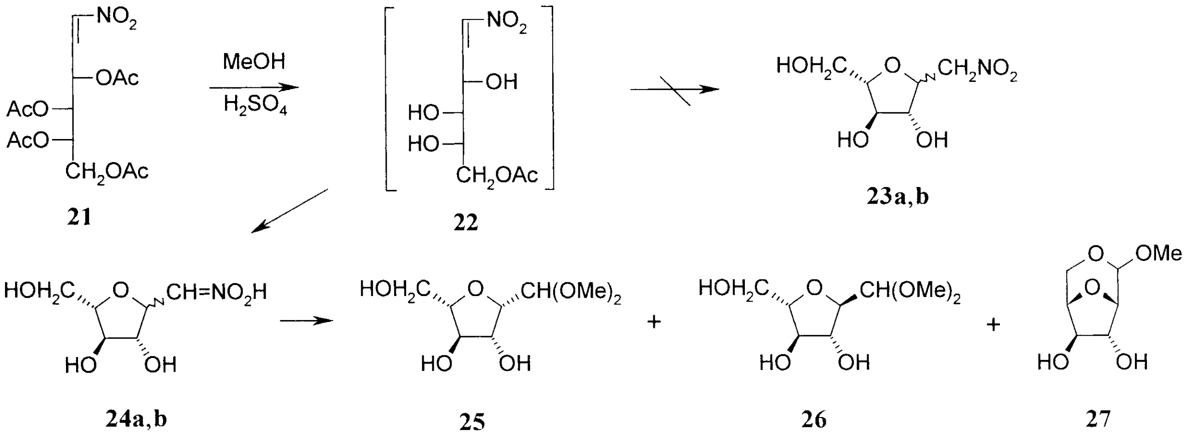
were formed when *AIBN* instead of *ABCN* was used. High yields of the analog reduction products were obtained from per-O-acetylated β-glycopyranosylnitromethanes derived of *L*-rhamnose and N-acetyl-*D*-glucosamine as well as from α-*D*-ribofuranosylnitromethane peracetate or 2,3:4,6-di-O-isopropylidene-β-*D*-mannopyranosylnitromethane [33].

The resistance of the primary nitro group to the denitration reaction is apparently a result of a stronger carbon-nitrogen bond than in tertiary or activated secondary nitro compounds. As a consequence, the SnO–N linkage in the key intermediate **18** (Scheme 8) is preferentially split, giving rise to the nitrosomethyl compound **19** which is a less populated tautomeric form of the final product **20**. The glycosylmethanal oximes thus obtained are good starting materials for the synthesis of some glycopyranosyl cyanides with complementary anomeric configuration to those obtainable from glycosyl halides [34].

Acid-Catalyzed Methanolysis

A surprising transformation of glycosylnitromethanes to very conveniently protected corresponding aldehyde derivatives by a modified *Nef* reaction was even more serendipitous than in the foregoing case. The idea was to prepare anomeric *L*-arabinofuranosylnitromethanes **23a**,**b** by a preferred five-member ring closure of 1,2-dideoxy-1-nitro-*L*-arabino-hex-1-enitol (**22**) under kinetic conditions, *i.e.* by acid-catalyzed methanolysis of its per-O-acetate **21** (Scheme 9). The proposed reaction, however, did not stop at the stage expected but afforded a mixture of the corresponding *L*-arabinofuranosylmethanal dimethyl acetals **25** and **26** and a mixed internal methyl acetal **27** [35].

The compounds thus obtained are formally the products of the methanolysis of the anomeric *L*-arabinofuranosylmethylnitronic acids **24a**,**b**, a reaction analogous

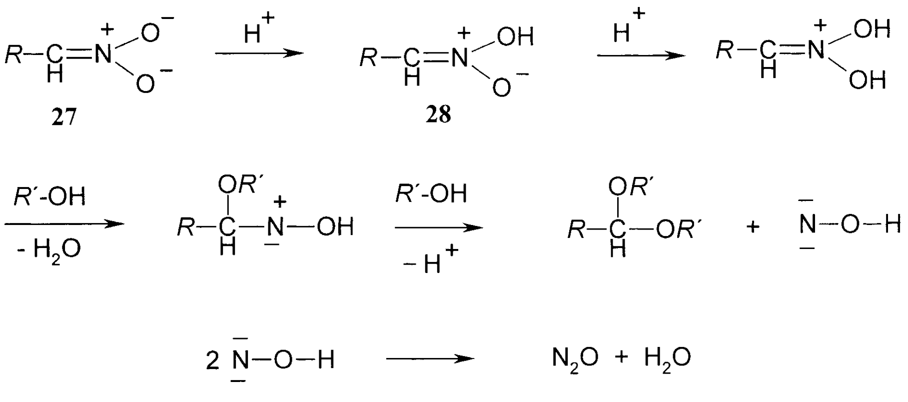


Scheme 9

to their hypothetic (not proceeding) hydrolysis, generally known as the *Nef* reaction. This means that the ring closure of 1,2-dideoxy-1-nitro-L-arabino-hex-1-enitol does not proceed as 1,2-addition but as 1,4-addition, giving rise to nitronic acids ready for the next step of the reaction. The switch from water to anhydrous methanol enabled to successfully transform common glycosylnitromethanes as β-*D*-glucopyranosylnitromethane, β-*D*-galactopyranosylnitromethane, or β-*D*-mannopyranosylnitromethane by the modified *Nef* reaction to the corresponding β-*D*-glycopyranosylmethanal dimethyl acetals in 80–94% yields [36]. Similar conversions were observed also in anhydrous ethanol, and the corresponding diethyl acetals were prepared.

A return to the acyclic 1-deoxy-1-nitroalditols and the application of *Nef* reaction under the new conditions has proposed a new method of preparation of low alkyl glycofuranosides, sometimes with very surprising results. For example, the only product from such a methanolysis of sodium 1-deoxy-*D*-mannitol-1-nitronate at −30°C isolated in 30% yield was methyl-β-*D*-mannofuranoside [36].

In summary, the extension of the *Nef* reaction to acidified lower alcohols turns the very easily available glycosylnitromethanes, since recently also as



Scheme 10

per-O-protected acetals [37], into a role of quite attractive C-glycosyl synthons. Moreover, the structures of the reaction products also provide an unambiguous evidence of the mechanism of the *Nef* reaction that can be generally described as a solvolysis of the (substituted) methanenitronate anion **27** catalyzed by an excess of a strong acid (Scheme 10). This is necessary to further protonize the methanenitronic acid **28** to increase the electron deficit at its carbon atom to facilitate the addition of the neutral nucleophiles. Finally, being stronger nucleophiles than the water molecules, the aliphatic alcohols are expected to be more reactive under such an arrangement.

The fine differences in reactivity of acyclic and cyclic 1-deoxyalditol-1-nitronates under the conditions of the classic *Nef* reaction apparently go to the account of an electronic effect similar to the anomeric one. Whereas acyclic species can avoid such an unfavourable interaction by a simple rotation of a bond, the effect in cyclic glycosylnitromethanes can represent a serious obstacle of their reactivity and remains to be further studied and quantified.

Perspectives

The developments introduced for the transformation of the nitroalkyl to carbonyl functionality imply some other possible transformations and their synthetic applications. In addition to the proton and the electrophilic oxygen species exploited until now for the decomposition of the electron-abundant nitronate group, several other possibilities still await their chances. Very interesting synthetic applications can be expected *e.g.* from applications of carbenes or nitrenes. Especially, a rapidly developing field of syntheses of glycomimetics based on the C-glycosyl compounds can efficiently benefit from these new developments. Finally, the better availability of the nitroalkyl to carbonyl group transformation methods should also lead to a broader exploitation of the acyclic species in oligosaccharide synthesis.

Acknowledgements

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