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One-pot α-glycosylation pathway via the generation in situ of α-glycopyranosyl imidates in *N*,*N*-dimethylformamide

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Abstract—Divergent pathways are disclosed in the activation of 2-*O*-benzyl-1-hydroxy sugars by a reagent combination of CBr_4 and Ph_3P, all of which afford one-pot α-glycosylation methods. When this reagent is used in CH_2Cl_2, the 1-hydroxy sugar is converted to the α-glycosyl bromide in a conventional way and leads to the one-pot α-glycosylation method based on a halide ion-catalytic mechanism. In either DMF or a mixture of DMF and $CHCl_3$, however, alternative α-glycosyl species are generated. From the ^1H and ^{13}C NMR study of the products, as well as the reactions using Vilsmeier reagents $[(CH_3)_2N^+{=}CHX]X^-$ (X = Br and Cl), these were identified as cationic α-glycopyranosyl imidates having either Br^- or Cl^- counter ion. The cationic α-glycosyl imidate (Br^-), derived specifically in the presence of DMF, is more reactive than the α-glycosyl bromide and thus is responsible for the accelerated one-pot α-glycosylation. The one-pot α-glycosylation methodology performed in DMF was assessed also with different types of acceptor substrates including tertiary alcohols and an anomeric mixture of 1-OH sugars.

Keywords: α-Glycoside epitopes; Imidates; Solvent effects; Glycosylation; Trehalose; Glycolipids

1. Introduction

The development of practical α-glycosylation reactions is one of the meaningful challenges in organic chemistry.[1] This is mainly because a large part of mammalian oligosaccharides carry the corresponding α-glycoside epitope such as α-L-fucopyranoside and α-D-galactopyranoside in Lewis^X and globosyl antigens, respectively.[2] Also for the developing glycosylation methodologies, such as those based on semi-automatic,[3] solid-phase,[4] fluorous,[5] and modular syntheses,[6] simple and practical α-glycosylation reactions are essential. Among the popular α-glycosylation reactions hitherto reported,[7] the halide-ion catalytic α-glycosylation reaction established by Lemieux and his co-workers[8] seems to provide one of the most definitive pathways. A typical reaction utilizes a 2-*O*-benzyl-α-glycopyranosyl bromide as the glycosyl donor and *N*-tetraethylammonium bromide ($Et_4N^+Br^-$) as the catalyst. The α-glycosylation involves an in situ anomerization of the donor in the presence of the catalyst as the key step to give the β-glycosyl bromide in equilibrium. The β-species is more reactive than the α-glycosyl bromide, and therefore, it is able to serve as an actual donor in the α-glycosylation reaction. Moreover, it is notable from a practical viewpoint that this methodology requires none of the heavy metals and strong Lewis acids often seen in this type of reaction.

Also in our synthetic studies on the cell-membrane glycolipids (GGPLs)[9] of *Mycoplasma fermentans*,[10] we have applied the halide-ion catalytic method effectively. This method can be carried out under neutral conditions and is applicable to α-glycosylation with chiral epoxy alcohols [(*S*)- and (*R*)-glycidols] required for constructing the α-glycosyl-*sn*-glycerol skeleton. Along these lines, we have attempted to make the overall synthetic

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process simpler. In preceding papers,[11,12] we reported that the halide-ion catalytic α-glycosylation reaction could be conducted in a one-pot manner starting from a 2-*O*-benzyl-1-hydroxy sugar. For the one-pot α-glycosylation, the reagent combination of CBr_4 and Ph_3P, called the Appel–Lee reagent[13–15] in this paper, plays multiple roles such as conversion of the 1-hydroxy sugar into an α-glycosyl bromide, in situ anomerization, and dehydration of the reaction system. More recently, we found that an alternative α-glycosyl species was derived when the Appel–Lee reagent was used in DMF for the activation of the 1-hydroxy sugar.[16] The α-glycosyl species is labile to water and any isolation process, giving a mixture of the known α-glycosyl bromide and 1-hydroxy sugar. Moreover, the subsequent one-pot α-glycosylation was accelerated in comparison with the reactions conducted in CH_2Cl_2. These results have suggested that there may be an alternative α-glycosylation pathway in which the reactive α-glycosyl species serve as the glycosyl donor. In the present study, we examined the activation of the 1-hydroxy sugar by the Appel–Lee reagent in more detail, as well as the structure and possible role of the α-glycosyl species in the one-pot α-glycosylation conducted in DMF.

2. Results and discussion

2.1. Divergent activation pathways of a 2-*O*-benzyl-1-hydroxy sugar by the Appel–Lee reagent

The combination of CBr_4 and Ph_3P used in CH_2Cl_2 or $CHCl_3$ converts 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranose (**1**) to the α-glycosyl bromide (α-**2-Br**, Fig. 1a) giving $Ph_3P{=}O$ as a side product.[11,12] A similar conversion was reported also by Khatuntseva et al.[15] When this reagent was used in DMF-d_7, an alternative α-glycopyranosyl species α-**2-X** was derived (Fig. 1b). This species was highly sensitive to water and intolerable to isolation processes, being decomposed simultaneously to a mixture of α-**2-Br** and **1**. In a solvent mixture of 1:1 DMF-d_7 and $CDCl_3$, a third α-glycosyl species α-**2-Y** was derived (Fig. 1c), which is obviously different from the 2-*O*-benzyl-α-glycosyl chloride (α-**2-Cl**) reported in the literature.[17]

In ^{1}H NMR spectroscopy, the unknown α-glycosyl species (α-**2-X** and α-**2-Y**) gave H-1 signals at a remarkably low field (δ 7.12 and δ 6.72 ppm) (Table 1). The ^{1}H chemical shifts are unusual for the D-hexopyranosyl $^4C_1$ (ring) conformation. This indicates that these products carry a highly electron-withdrawing group at the anomeric position. From their ^{1}H and ^{13}C NMR data and chemical properties we have observed, we assigned them tentatively as cationic α-glycopyranosyl imidates, possessing bromide and chloride counter ions, respectively (Scheme 1).

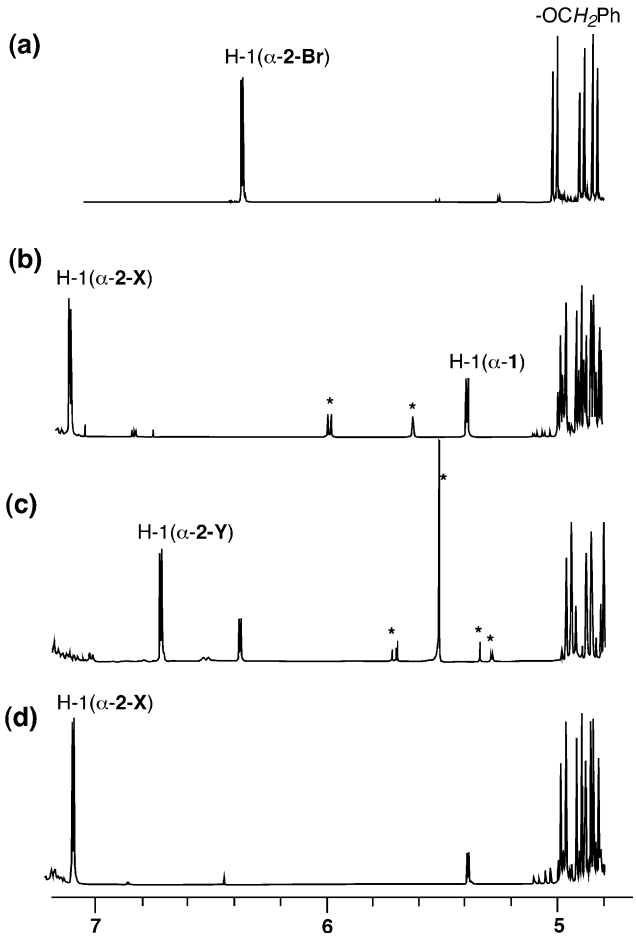

Figure 1. ^{1}H NMR spectra (500 MHz) of a mixture of **1** and (a) Appel–Lee reagent in $CDCl_3$, (b) Appel–Lee reagent in DMF-d_7, (c) Appel–Lee reagent in a mixture of 1:1 DMF-d_7 and $CDCl_3$, (d) Vilsmeier reagent (Br^--type) in DMF-d_7 solution. An asterisk (∗) denotes the signal of unidentified non-sugar products.

The assigned imidate structure is a kind of Vilsmeier–Haack intermediate having $[(CH_3)_2N^+{=}CH\text{-}OR]X^-$ as the general structure.[18] This intermediate is derived in reactions between an alkyl alcohol (R-OH) and a Vilsmeier reagent $[(CH_3)_2N^+{=}CHX]X^-$ (X = Cl or Br) on the way to forming alkyl halides (R-X).[19] Sugar OH groups are also known to give these intermediates including the anomeric imidate of 2,3:4,5-di-*O*-isopropylidene-D-mannofuranosyl imidates (Cl^- and *p*-TsO^- salts) derived with phosgene in DMF.[20]

To confirm the structures of α-**2-X** and α-**2-X**, we treated **1** with each of the bromide and the chloride types of Vilsmeier reagents (Aldrich). ^{1}H and ^{13}C NMR spectra of the main products accorded with the products derived with the Appel–Lee reagent. That is, the Br^- type of Vilsmeier reagent afforded α-**2-X** exclusively in DMF-d_7 (Fig. 1d), while it gave α-**2-Br** in $CDCl_3$. The Cl^- type of reagent gave α-**2-Y** in DMF-d_7 and α-**2-Cl** in $CDCl_3$. This means that the Appel–Lee reagent used in DMF generates the Vilsmeier reagents to afford the cationic