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Synthesis of Glycosyl Chlorides and Bromides by Chelation Assisted Activation of Picolinic Esters under Mild Neutral Conditions

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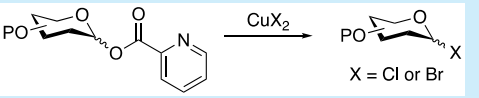
ABSTRACT: A general method has been developed for the formation of glycosyl chlorides and bromides from picolinic esters under mild and neutral conditions. Benchtop stable picolinic esters are activated by a copper(II) halide species to afford the corresponding products in high yields with a traceless leaving group. Rare β glycosyl chlorides are accessible via this route through neighboring group participation. Additionally, glycosyl chlorides with labile protecting groups previously not easily accessible can be prepared.

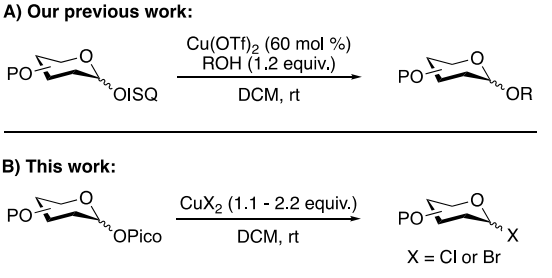


Carbohydrates have garnered significant interest from the scientific community due to their heavy prevalence in biological systems and indispensable functionality as mediators of intra- and intercellular interactions.[1] Given the heterogeneous nature of carbohydrates in biological sources, the structurally defined synthetic glycans have proved as invaluable tools for studies in glycobiology.[2] In synthetic carbohydrate chemistry, glycosylation is arguably one of the most important and challenging reactions,[3] and the need for a more efficient and general glycosylation method has stimulated tremendous efforts to develop glycosyl donors with novel anomeric leaving groups.[4] Interestingly, glycosyl halides, which are among the earliest known activated glycosyl donors, have always been one of the most versatile glycosyl donors for complex carbohydrate synthesis since its discovery over a century ago.[5] On the basis of Koenigs' and Knorr's conditions for activating glycosyl bromides with silver salt, a wide variety of methods have been developed by employing different silver or mercury salts, or even metal-free reagents.[6] Meanwhile, the toolbox of glycosyl halides as glycosyl donors has expanded from traditionally used glycosyl bromides and chlorides to include more stable glycosyl fluorides[7] and more reactive glycosyl iodides,[8] rendering the opportunity of fine-tuning the reactivities of glycosyl donors for particular circumstances. Glycosyl halides also display unique properties in controlling the anomeric stereochemistry of glycosylation products by invoking classical neighboring group participation,[9] halide exchange,[10] or invertive S_N2 mechanisms, making 1,2-*trans*-, 1,2-*cis*-, and 2-deoxy-β-glycosides[11] accessible from one set of glycosyl donors.

Glycosyl halides, particularly acetohalogenoses, have been prepared from their anomeric acetate or hemiacetal precursors under strong Lewis or Brønsted acidic conditions.[12] However, toxic halogenating reagents are frequently employed, and these forcing conditions are usually incompatible with acid-labile protecting groups or interglycosydic linkages and only allow the preparation of glycosyl halides with a limited level of structural diversity.[13] Therefore, methods that can expand the functional group compatibility of halogenation have been developed over the past several years.[14] Nevertheless, in view of the increasing popularity of glycosyl halides in carbohydrate synthesis, a set of general, mild, and neutral conditions for their preparation from readily available benchtop stable precursors is still highly demanded.

Glycosyl picolinic esters (Pico) have been developed as stable and easily accessible glycosyl donors, which can be activated by nontoxic copper(II) salts under mild conditions,[15] through remote activation.[16] In response to the potential transesterification side reactions, we recently reported isoquinoline-1-carboxylate (ISQ) as a readily available, traceless, and bulkier anomeric leaving group, which successfully blocks the attack of hydroxylic acceptors on the carbonyl carbon center (Scheme 1).[17] While screening potential copper(II) sources for the activation of isoquinolinic esters,

Scheme 1. Copper(II) Activated Leaving Groups for Glycosylations of Sugars



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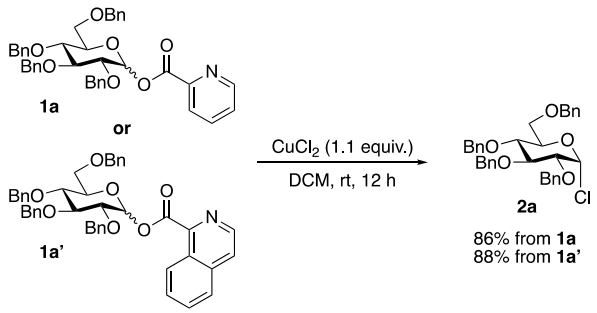
we discovered that using $CuCl_2$ produced no *O*-glycosides but instead led to the formation of the corresponding glycosyl chloride in high yield. The glycosyl halide was formed under conditions that were mild enough to facilitate inclusion of previously unavailable protecting groups that have low stability in acidic solutions. No strong Lewis acid is required for the reaction to proceed, and the pH of the solution remains neutral. Herein we report the formation of a range of glycosyl chlorides and bromides in high yields under mild and neutral conditions using copper(II) salts as both the activator and halogen source. The picolinic ester acts as a traceless leaving group and facilitates quick separation of the products from the reaction mixtures with no workup required.

The isoquinolinic ester was advantageous over the picolinic ester for the glycosylation reaction, because the carbonyl group in the latter could be attacked by the OH group in the glycosyl acceptor to form a transesterification product while no transesterification was observed for the former.[17] We began our investigation by comparing the isoquinolinic esters and picolinic esters and their ability to produce the corresponding glycosyl chloride in order to examine potential differences in reactivity. We determined that both carboxylate species produced the desired products in essentially the same yield with similar rates of reaction (Scheme 2). While both picolinic

Scheme 2. Comparison of Picolinic and Isoquinolinic Esters for the Formations of Glycosyl Halides[a]

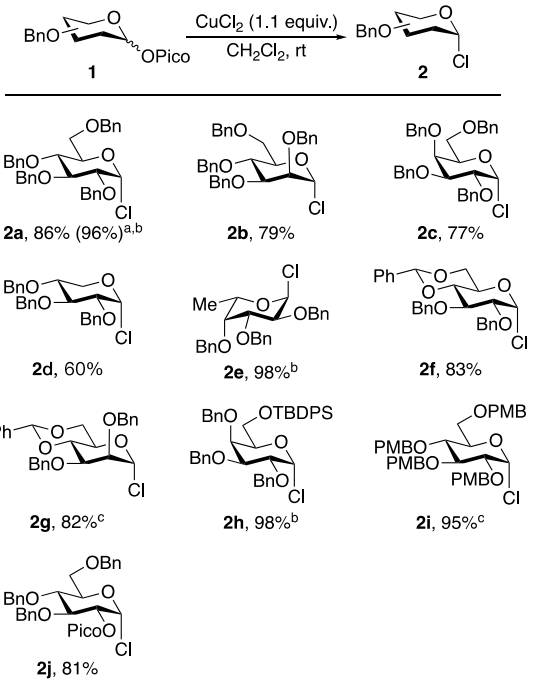


[a]Reactions run on 0.1 mmol scale with 0.3 mL of solvent and 150 mg of molecular sieves.

acid and isoquinolinic acid are commercially available and can be easily coupled to a pyranose moiety, the lower cost of the picolinic acid made it the preferred candidate for further study. Thus, we carried forward using picolinic esters as substrates for further examination of the reaction potential and scope.

An array of carbohydrate picolinic esters with armed ether-type protecting groups were synthesized and treated with $CuCl_2$ in dichloromethane in the presence of 4 Å molecular sieves as the only additive (Scheme 3). The reactions proceeded smoothly at room temperature with good yields and high α-selectivity observed for all of the per-benzylated monosaccharides screened (**2a**–**2e**). While most of the glycosyl chloride products were isolable by flash column chromatography, the crude reaction products were generally pure for further use without purification, as determined by NMR of the crude products. With the mild and neutral reaction conditions, the benzylidene protected glycosyl chlorides (**2f** and **2g**) and silyl ether protected glycosyl chloride (**2h**) were prepared in good yields with no degradation of the protecting groups observed. The PMB group, which can be more readily cleaved oxidatively than its

Scheme 3. Scope of Benzylated Glycosyl Chlorides



[a]Yield of reaction run on 1 mmol scale. [b]Yield of crude product. [c]2.2 equiv of $CuCl_2$ was used.

unsubstituted counterpart, was also well tolerated with **2i** isolated in 95% yield. A second picolinic ester at the C2-position did not change the stereochemical outcome of the reaction, and the α-chloride **2j** was isolated in 81% yield. A satisfactory result was also obtained when the reaction was run on the 1 mmol scale, as exemplified by the isolation of **2a** in essentially quantitative yield.

The high α-selectivity in all cases, which was independent of the anomeric configurations of the starting picolinic esters, suggests that an oxocarbenium intermediate is involved, and the thermodynamic products are likely formed through halide exchange via an S_N1 pathway. Although the current methodology is applicable to the synthesis of a wide variety of α-glycosyl chlorides with different configurations and deoxygenation patterns, it is worthwhile to mention that the preparation of the per-benzylated 2-deoxy glucopyranosyl chloride was hampered by the concomitant formation of a significant amount of glucal byproduct due to the elimination side reaction.

Carbohydrate picolinic esters with electron-withdrawing protecting groups were then examined for the preparation of disarmed glycosyl chlorides (Scheme 4). In the presence of ester-type protecting groups, the reactions required increased amounts of $CuCl_2$ (2.2 equiv) and longer reaction times (48–72 h) to ensure the completion of the reaction. Nevertheless, the corresponding glycosyl chlorides were isolated in good to excellent yields. Carbohydrate picolinic esters with *gluco*-configurations led to the formation of thermodynamically unstable β-glucosyl chlorides[18] as exclusive products (**2k**–**2m**). This revealed that the neighboring group participation from the ester at the C2-position was the major contributor to the stereoselectivity at the anomeric position during the chlorination. The low isolation yield of **2m** was a result of the low conversion of the α-glycosyl picolinic ester. With a strong electron-withdrawing carboxylate group at the 6-position, the

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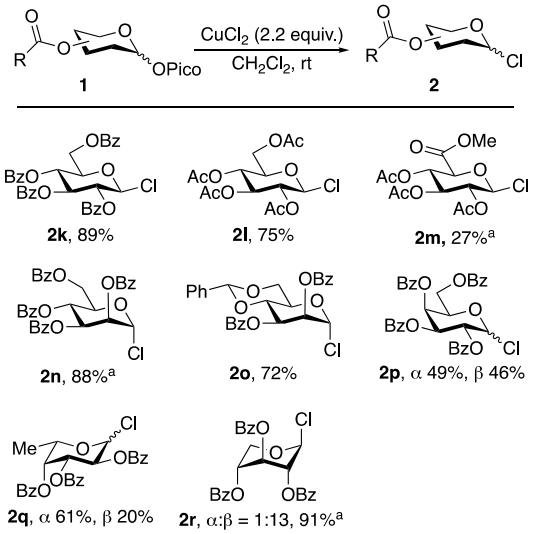
Scheme 4. Scope of Benzoylated and Acetylated Glycosyl Chlorides



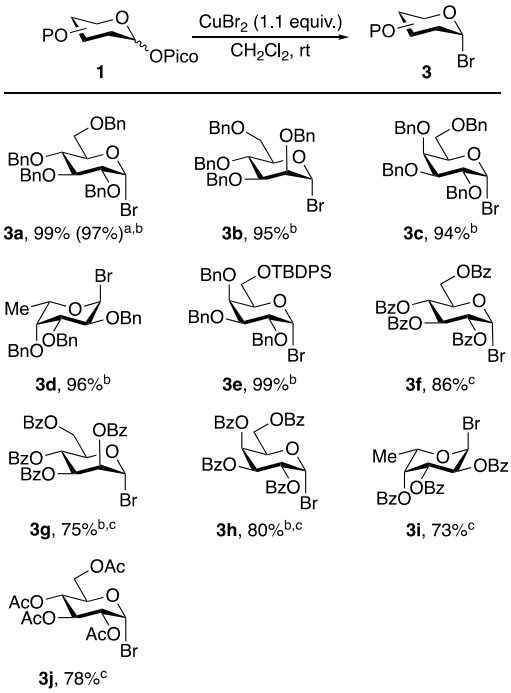
[a]Yield of crude product.

departure of the picolinate from the α-anomer is reduced without the anchimeric assistance of a *trans*-ester group at the C2-position.

In comparison, per-benzoylated galactopyranosyl, fucopyranosyl, and xylopyranosyl picolinic esters afforded glycosyl chlorides as mixtures of anomers (**2p**−**2r**), as indicated by NMR of the crude products. Such a deviation in anomeric selectivity can be interpreted as a function of the stabilization (or destabilization) effect of substituents on sugar rings on the putative glycosyl oxocarbenium ion. With all electron-withdrawing substituents on equatorial position, or an axial electron-withdrawing group at the C2-position, their destabilization effect on the electron-deficient oxocarbenium ion intermediate was maximized.[19] This resulted in the attack of a chloride ion on the relatively more stable dioxalenium ion formed by neighboring group participation, leading to the formation of 1,2-*trans* glycosyl chloride products **2k**−**2o**. Conversely, an axially oriented substituent further away from the oxocarbenium carbon center, or a deoxygenation modification, reduces the inductive effect,[20] therefore, shifting the reaction toward a mechanism involving a more stabilized oxocarbenium ion intermediate.

Not only were we successful in obtaining glycosyl chlorides, but using copper(II) bromide as the activator we could also obtain glycosyl bromides in high yields (Scheme 5). While both armed and disarmed glycosyl bromides were obtained in high yields, unlike the previous examples where a β-glycosyl chlorides could be obtained from neighboring group participation from a C2 ester, using copper(II) bromide with a C2-benzoylated or acetylated monosaccharide only gave the α-glycosyl bromide products (**3f**−**3j**). These results are in accordance with bromide ion's better leaving group ability and the high reactivity of β-glycosyl bromides. Again, the reaction can be scaled up to 1 mmol without any loss of reaction efficiency (**3a**). Attempts to prepare glycosyl fluorides using copper(II) fluoride salt under the same conditions were not successful. Because copper(II) oxidizes iodide to iodine, we tried to prepare glycosyl iodides using copper(I) iodide salt under the same conditions, but no reaction occurred.

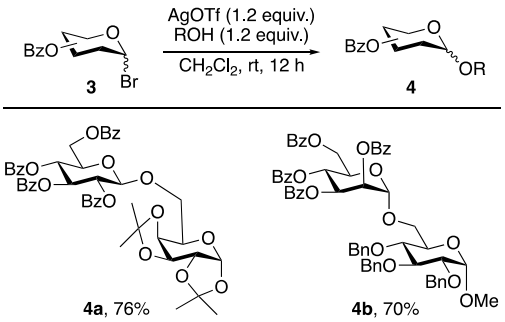
Scheme 5. Scope of Glycosyl Bromides[a]



[a]Yield of reaction run on 1 mmol scale. [b]Yield of crude product. [c]2.2 equiv of $CuBr_2$ was used.

To further demonstrate the utility of glycosyl halides obtained from this method, we synthesized two disaccharides from benzoylated glycosyl bromides (Scheme 6). Using silver

Scheme 6. Glycosylations of Glycosyl Bromides[a]



[a]Reactions run on 0.05 mmol scale with 0.3 mL of solvent and 180 mg of molecular sieves.

triflate as the activator and taking advantage of neighboring group participation of a C2 ester, we obtained the disaccharides (**4a** and **4b**) in good yields with high stereoselectivity.

In summary, we have successfully developed a new method to obtain glycosyl chlorides and bromides without the use of strong Brønsted or Lewis acids and thus can accommodate a wider variety of protecting groups in target compounds. This method utilizes readily available benchtop stable precursors and can access various β-glycosyl chlorides through neighboring group participation using benzoyl and acetyl protected sugars.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00078.

Detailed experimental procedures, characterization data (IR, ^{1}H, ^{13}C NMR, and HRMS), and spectra (^{1}H and ^{13}C NMR) (PDF)

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Notes

The authors declare no competing financial interest.

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