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Efficient synthesis of α-glycosyl chlorides using 2-chloro-1,3-dimethylimidazolinium chloride: A convenient protocol for quick one-pot glycosylation

Madhu Babu Tatina,[a] Duc Thinh Khong,[a] Zaher M. A. Judeh*[a]

Abstract: A mild and convenient method for the synthesis of α-glycosyl chlorides in high 80-96% yields within 15-30 min using 2-chloro-1,3-dimethylimidazolinium chloride (DMC) is disclosed. The method has a wide substrate scope and is compatible with labile hydroxyl protecting groups including benzyl, acetyl, benzoyl, isopropylidene, benzylidene, TBDMS and TBDPS silyl ether. The excellent α selectivity obtained in this reaction is attributed to *in-situ* isomerization of β-glycosyl chlorides to the more stable α-glycosyl chlorides as proven ^{1}H NMR studies. Disarmed sugars with OBz or OAc at C2 were chlorinated at a faster rate but ismomerized (β → α) at a slower rate in comparison to armed sugars with OBz at C2. More important, the method enables the highly desired one-pot glycosylation thus allowing for the efficient syntheses of disaccharides and simple *O*-glycosylated sugars in high overall yields without the need for separation or purification of the α-glycosyl chloride donors. This method will be especially useful for the direct glycosylation using glycosyl chloride donors that are unstable upon separation and purification.

Introduction

Glycosyl halides (chlorides, bromides, iodides and fluorides) are important donors used for the synthesis of *O*-, *C*- and *N*-glycosides.[1] Excellent progress has been made in synthesizing α-glycosyl chlorides using several methods including metal halides ($SnCl_4$ and $TiCl_4$),[2] PPh_3/CCl_4,[3] DMF/trichlorotriazine,[4] oxalyl chloride,[5] triphosgene,[6] PPh_3/hexachloroacetone[7] and others.[8] Ideally, the chlorinating reagent should have wide substrate scope, show tolerance to labile sugar protecting groups, demonstrate convenience to avoid strict chlorination conditions, reduce reaction times and allow for easy separation of the products.

Over the past years, we have been interested in developing simple approaches for the synthesis of phenylethanoid glycosides.[9] Our strategy required us to *in-situ* generate glycosyl donors to undergo one-pot glycosylation without donors separation or switching of reaction solvents to avoid multistep reactions and tedious purifications. This became even more imperative since some α-glycosyl chlorides decompose during purification using silica gel column chromatography or during storage.[4,7] For this purpose, we re-investigated the synthesis of α-glycosyl chlorides anticipating developing a simple synthetic approach that tolerates typical sugar protecting groups and at the same time enables direct one-pot glycosylation. One-pot glycosylation[10] represents a quick and simple process for obtaining oligosaccharides and is therefore highly desirable. It reduces the number of synthetic steps, avoids tedious purification and solves potential degradation problems of some glycosyl chloride donors. For example, Mong and co-workers developed a two-step, one-pot chlorination-glycosylation protocol that required separation of the glycosyl chlorides and a solvent switch before the glycosylation reaction.[4] Nishida and co-workers reported successful one-pot bromination-glycosylation between the *in-situ* generated glycosyl bromides and various acceptors. However, the reaction required the use of 3 mol equiv. of both the acceptor as well as the catalyst with respect to the glycosyl bromide donors and also needed long times of 22-96 h for completion.[11]

Herein, we wish to report a simple method for the synthesis of a wide range of α-glycosyl chlorides using commercially available chlorinating agent 2-chloro-1,3-dimethylimidazolinium chloride (DMC) and demonstrate the practicality of this method in direct one-pot glycosylation of selected sugars.

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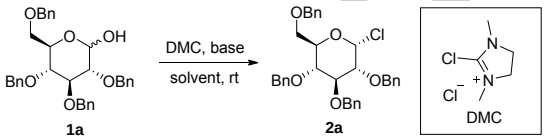
Results and Discussion

DMC is a versatile dehydrating reagent used in several organic transformations including esterification, amination, oxidation, reduction and conversion of alcohols to chlorides.[12] In carbohydrate chemistry, and specifically concerning the anomeric center, DMC was used for several selective transformations such as acetylation,[13] azidation,[14] synthesis of triazoles and oxazoline,[15] synthesis of 1,6-anhydro sugars[16] and thio glycosylation.[17] To examine the usefulness of DMC in the preparation of α-glycosyl chlorides from sugars, we initially screened the chlorination of 2,3,4,6-tetra-*O*-benzyl D-glucopyranose **1a** as a model substrate using *s*-collidine as a base in dichloromethane (DCM) (Table 1, entry 1). These reaction conditions were intentionally chosen to ensure compatibility with the planned one-pot glycosylation conditions to avoid isolation/purification of the α-glycosyl chlorides, solvent switching and interference of the by-products. However, under these conditions, the desired α-glycosyl chloride **2a** was not detected even after 24 h (Table 1, entry 1). We then screened several bases including Et_3N, DBU, pyridine and NaH (Table 1, entry 2-5). Et_3N gave the highest yield of 89% of α-glycosyl chloride **2a** in just 15 min while DBU gave **2a** in lower 70% yield after 30 min (Table 1, entries 2 and 3, respectively). However, the chlorination using pyridine was sluggish (40% yield after 24 h) and NaH failed to give any product possibly due to its insolubility in DCM (Table 1, entries 4 and 5, respectively). Attempts to further increase the yield of **2a** by replacing DCM with CH_3CN, THF or DMF were not fruitful since either lower yields or no products were obtained (Table 1, entries 6-8). The reason why no products were obtained with THF and DMF is not known. In fact, ^{1}H NMR spectra of the crude reaction mixture did not show any change in all the substrates used in the reaction. In all the cases, glycosyl chloride **2a** was obtained exclusively with α selectivity. With the optimized reaction conditions in our hands (Table 1, entry 2), we proceeded to examine the scope and limitation of this reaction. It is important to note that these conditions are classic for glycosylation reactions.

Table 1. Optimization of chlorination of per-*O*-benzylated glucose **1a** using DMC to synthesize α-glycosyl chloride **2a**.[a]



1a **2a**

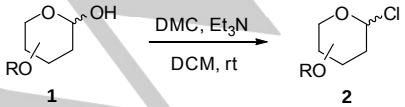
Entry	Solvent	Base	Time	Yield [%] (only α)[b]
1	DCM	*s*-Collidine	24 h	N.R.
2	DCM	Et_3N	15 min	89
3	DCM	DBU	30 min	70
4	DCM	Pyridine	24 h	40
5	DCM	NaH	24 h	N.R.
6	CH_3CN	Et_3N	24 h	65
7	THF	Et_3N	24 h	N.R.
8	DMF	Et_3N	24 h	N.R.

[a] DMC (0.1 mmol) was added to a solution of tetra-O-benzylated glucose **1a** (0.1 mmol) and base (0.1 mmol) in 1.5 ml of the solvent. [b] Isolated yields after column chromatography purification. [c] N.R. = no reaction.

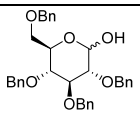
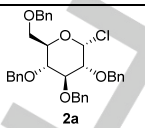
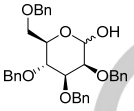
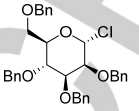
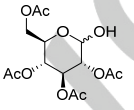
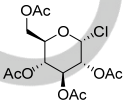
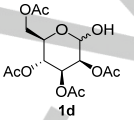
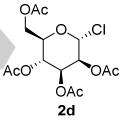
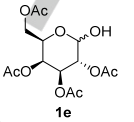
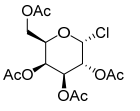
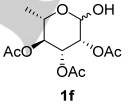
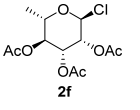
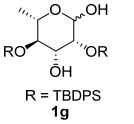
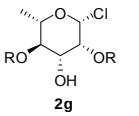
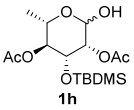
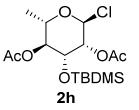
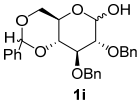
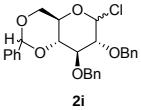
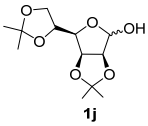
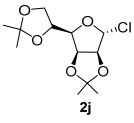
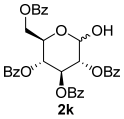
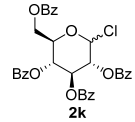
To examine the scope of this chlorination reaction, we prepared various substrates including tetra-*O*-benzylated **1b**, tetra-*O*-acetylated **1c**-**1f**, partially silylated 2,4-*O*-TBDPS (*t*-butyl diphenylsilyl ether) **1g**, 2,4-*O*-acetylated-3-*O*-TBDMS *(t*-butyl dimethylsilyl ether) **1h**, 4,6-*O*-benzylidene-2,3-di-*O*-benzylated **1i**, diisopropylidene **1j** and tetra-*O*-benzoylated **1k** sugars (Table 2). In all the cases, the chlorination reactions of **1a**-**j** proceeded successfully to give high 80-96% yield of glycosyl chlorides **2a**-**k** within 15-30 min at room temperature without special precautions (Table 2). In the case of tetra-*O*-benzylated glucose **1a** and tetra-*O*-benzylated mannose **1b** (armed sugars), the glycosyl chlorides **2a** and **2b** were obtained in *ca* 90% yield in just 15 min with complete α selectivity (Table 2, entries 1-2). Tetra-*O*-acylated glucose, mannose, galactose and rhamnose **1c**-**1f** (disarmed sugars) took double the reaction time (30 min) to give the corresponding glycosyl chlorides **2c**-**2f** in slightly lower 82-85% yields and with complete α selectivity with the exception of **1e** which gave **2e** in α:β ratio of 3:1 (Table 2, entry 3-6).[18a] We noted that reaction of **1c**-**1f** with DMC was very quick as indicated by TLC (within 5 minutes) but longer reaction times of 30 minutes were employed to convert the β-anomers to their corresponding α-anomers (see discussion under mechanism later). Effectively, the reaction can be stopped at 5 minutes to

obtain the β-glycosyl chlorides. Chlorination of sugars containing acid-labile protecting groups such as TBDPS **1g,** TBDMS **1h** and cyclic acetals **1i** and **1j** also proceeded smoothly to give the corresponding glycosyl chlorides **2g**-**j**, respectively, in good to excellent yields (Table 2, entries 7-10). In the case of the partially silylated 2,4-di-*O*-TBDPS rhamnose **1g**, we obtained excellent 88% yield of **2g** with exclusive α selectivity (Table 2, entry 7). Rhamnose sugar with TBDMS and Ac moieties reacted smothly under to yield the correspong glycosyl chloride **2h** (Table 2, entry 8). α-Glycosyl chloride **2g** was unstable during column chromatography purification using silica gel and quickly hydrolysed to give back the starting material **1g** whereas compound **2h** exhibits good stability during purification. On the other hand, 4,6-*O*-benzylidene-2,3-di-*O*-benzylated glucose **1i** gave the glycosyl chloride **2h** in 80% yield within 20 min with α:β selectivity ratio of 3:1 (Table 2, entry 9). The exact reason for the formation of the β-isomer is not very clear and may be due to the disarming nature of benzylidenes moiety.[18b] Diisopropylidene mannofuranose **1j** gave 95% yield of α-glycosyl chloride **2j** with complete α selectivity within 30 min (Table 2, entry 9). Interestingly, tetra-*O*-benzoylated glucose **1k** gave 96% of glycosyl chloride **2k** with α:β ratio of 1:10. From TLC, we noted that formation of the glycosyl chloride was very quick (5-10 min) but the reaction was continued for 30 minutes to attempt to convert β-glycosyl chloride **2k** to its α-anomer. This did not happen to a great extent as in the cases of **2c**-**2f** because OBz is less electron withdrawing group than OAc. Longer reaction times and purification over silica gel increased the ratio of α-glycosyl chlorides on the account of their β-anomers. The α:β selectivity ratios will be reasoned during our discussion on the mechanism of the DMC-mediated chlorination below.

Table 2. Scope of the DMC-mediated chlorination of glycosyl substrates **1** to give glycosyl chlorides **2**.[a]



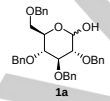
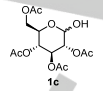
1 **2**

Entry	Glycosyl substrate **1**[a]	Glycosyl chloride **2**	Time (min)	Yield [%] (α:β)[b]
1	 **1a**	 **2a**	15	89 (α only)
2	 **1b**	 **2b**	15	90 (α only)
3	 **1c**	 **2c**	30	85 (α only)
4	 **1d**	 **2d**	30	85 (α only)
5	 **1e**	 **2e**	30	82 (3:1)
6	 **1f**	 **2f**	30	85 (α only)
7	 R = TBDPS **1g**	 **2g**	20	88[c] (α only)
8	 **1h**	 **2h**	30	80 (α only)
9	 **1i**	 **2i**	20	80 (3:1)
10	 **1j**	 **2j**	30	95 (α only)
11	 **2k**	 **2k**	30	96 (1:10)

[a] DMC (0.1 mmol) was added to a solution of glycosyl substrate **1** (0.1 mmol) and Et_3N (0.1 mmol) in 1.5 ml of the DCM. [b] Isolated yields after column chromatography purification. [c] Estimated using ^1H NMR spectrum of the crude product.

To gain an understanding of the mechanism of the DMC-mediated chlorination, we used ^{1}H NMR to monitor the progress of chlorination of tetra-*O*-benzylated glucose **1a** (having no neighbouring group participation (NGP)) and tetra-*O*-acetylated glucose **1c** (showing NGP) as model substrates (Table 3, Figure. 1). When DMC was mixed with a solution of **1a** and Et_3N in $CDCl_3$ and the ^{1}H NMR spectrum quickly measured (*Ca* after 5 min), two new sets of signals in *ca* 1.1:1 ratio corresponding to α-glycosyl chloride **2a** (δ = 6.01, d, *J* = 7.8 Hz, H-1) and β-glycosyl chloride **2a** (δ = 5.13, d, *J* = 3.6 Hz, H-1) were identified at 59% overall conversion (Figure. 1, Table 3, entry 1. Scheme 1).[18a] When the spectrum of the same sample was measured after 30 min and then 45 min, the α:β selectivity ratios were found to be 1:0.2 and 1:0.08, respectively, at ~95% conversion. However, when we repeated the same ^{1}H NMR study with **1c**, the ratio of α-glycosyl chloride to β-glycosyl chlorides after 5 min was found to be 1:10.4 after ~96% conversion while the ratio after 30 min and then 45 min was 1:8.4 and 1:7, respectively (Table 3, entry 2). Even after 15 h, the ratio was found to be 1:4.4 (Scheme 1). However, as indicated in Table 2, entry 3, when **2c** was isolated after 30 min, it was found to be pure α-glycosyl chloride with no sign of its β-anomer indicating quicker isomerization on silica gel during purification. Based on these observations and the literature reports,[14-17] a plausible mechanism for DMC chlorination is shown in scheme 1 for substrates without (e.g. **1a**) and with (e.g. **1c**) NGP. Abstraction of the OH protons of the substrates using Et_3N is followed by nucleophilic attack on the chloro imine carbon of DMC (Scheme 1). In the case where there is no NGP (R'= CH_2, Bn, TBDPS), intermediate β-**II** which is formed from β-**I** anomer undergoes S_N2 attack by Cl^- to form the α-glycosyl chlorides. Similarly, the α-**I** anomer should give the β-glycosyl chlorides through S_N2 attack on intermediate α-**II** (Scheme 1). Based on the anomeric effect concept, α-glycosyl chlorides are more stable than β-glycosyl chlorides.[19] Therefore, the initially formed β-glycosyl chlorides will isomerize through S_N2 attack by Cl^- (possibly from Et_3N.HCl) to α-glycosyl chlorides.[11,20] The presence of Et_3N.HCl was confirmed from the ^{1}H NMR studies since the signal at δ 11.26 ppm corresponded to the proton of Et_3N.HCl. Where there is NGP (R' = Ac or Bz) at C2, intramolecular attack of the carbonyl group of intermediate β-**III**, which is obtained from β-**I** anomer, gives β-**IV** which upon S_N2 attack by Cl^- gives the β-glycosyl chlorides that isomerize to the more stable α-glycosyl chlorides (Scheme 1). The α-**I** anomer with NGP is predicted to show similar mechanism to the α-**I** anomer with no NGP and give β-glycosyl chlorides through intermediates α-**VI** and α-**VII**. This is because attack from the α position is blocked due to steric effects.

Table 3. ^{1}H NMR study of the formation of α- and β-glycosyl chlorides.[a]

Entry	Reactant	Product	(α:β) Conv. ~ 5 min	(α:β) Conv. 30 min	(α:β) Conv. 45 min
1			(1.1:1) ~ 59%	(1:0.2) ~ 95%	(1:0.08) ~ 95%
2			(1:10.4) ~ 96%	(1:8.4) ~ 96%	(1:7) ~ 96%

[a] Measured using ^{1}H NMR after reaction for a specific time.

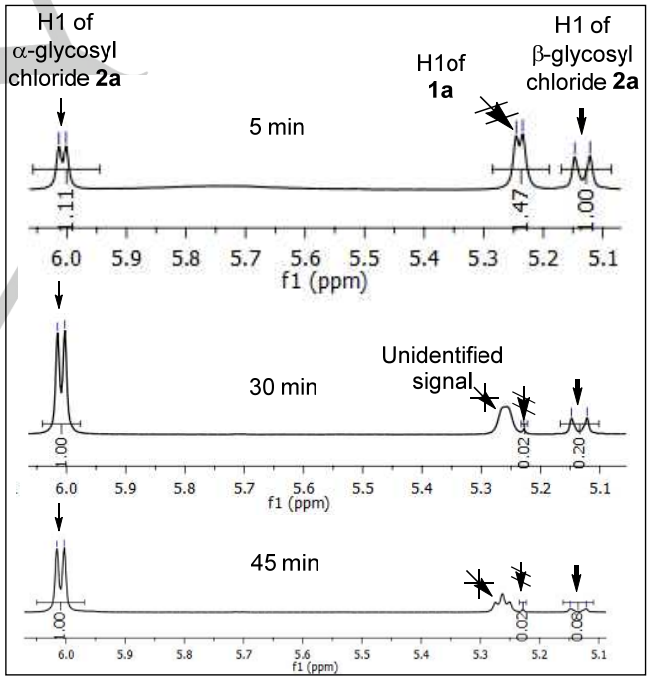
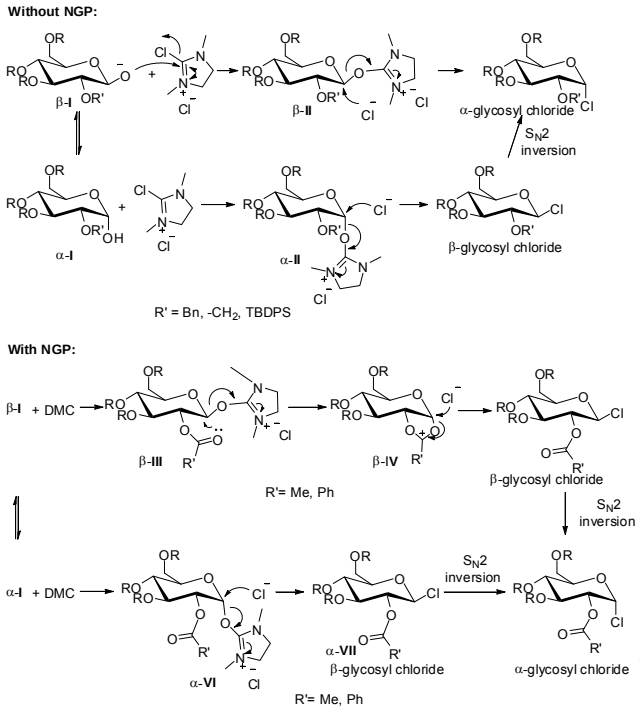


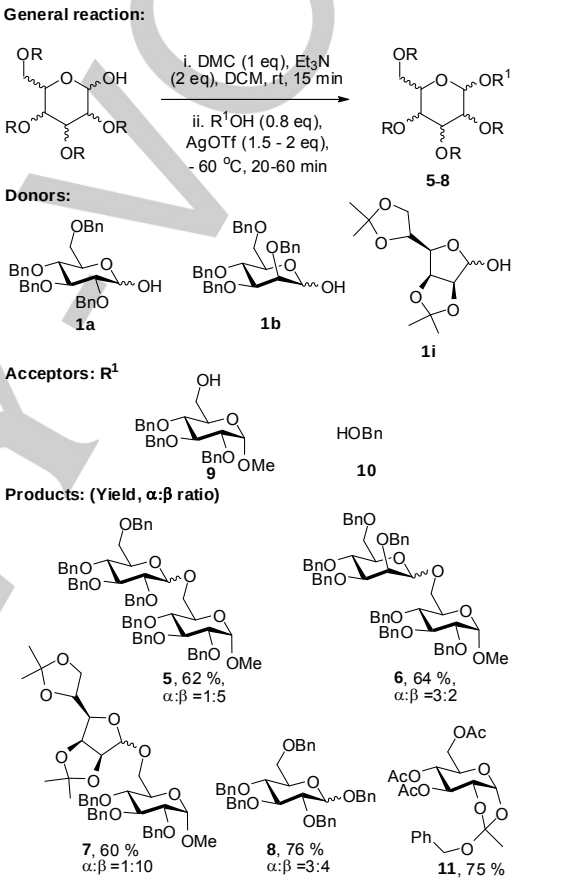
Figure 1. Progress of chlorination of tetra-*O*-benzyl-α-D-glucopyranosyl hemiacetal **1a** at different time interval using ^{1}H NMR.



Scheme 1. Plausible mechanism for DMC-mediated chlorination for the formation of α- and β-glycosyl chlorides.

This isomerization process and conversion of β-glycosyl chlorides to α-glycosyl chlorides are clearly supported by our ^{1}H NMR studies (Figure 1, Scheme 1). As mentioned before, the α:β ratio and the rate of isomerization depended on the reaction time and purification process. As time progress, β-glycosyl chlorides are converted to their α-anomers during the reaction and this process seems to be faster during purification over silica gel column. It is also obvious that the rate of isomerization is substrate dependant as demonstrated by ^{1}H NMR studies and when comparing the α:β selectivity ratios in Table 1).

We attempted a simple one-pot glycosylation protocol by *in-situ* generating the glycosyl chloride donors according to the optimum conditions in Table 2, cooling the reaction mixture to -60 °C followed by addition of sugar acceptors and AgOTf (Scheme 2). Consequently, one-pot glycosylation between glycosyl chloride **2a** (generated *in-situ* from tetra-*O*-benzylated glucose **1a**) and α-1-methoxy-2,3,4-*O*-tribenzyl glucose acceptor **9** gave disaccharide **5** in 62% yield in α:β ratio of 1:5 within 1 h (Scheme 2). Similarly, one-pot glycosylation between per-*O*-benzylated glucose **1a**, per-*O*-benzylated mannose **1b** and diisopropylidene mannofuranose **1i** as glycosyl chloride donors with α-1-methoxy-2,3,4-*O*-tribenzyl glucose **9** and benzyl alcohol **10** as acceptors gave disaccharides **6**-**7** and simple *O*-glycosylated product **8** in 60-72% overall yield with α:β selectivity as shown in Scheme 2. The glycosylation products seem to favours β selectivity as judged from their α:β ratios.[21] We noted that one-pot reaction between **1c** and **10** did not proceed probably due to the disarming effect of the OAc moieties. However, when AgOTf was replaced by Ag_2O, the orthoester **11** was obtained in % yield.



Scheme 2. Direct one-pot chlorination-glycosylation reaction.

Conclusions

We have developed a simple and highly efficient method for the synthesis of α-glycosyl chlorides in very high 80-96% yields and short 15-30 min reaction times using commercially available DMC. Under the reaction conditions employed, β-glycosyl chlorides isomerized to the more stable α-glycosyl chlorides as proven by the ^{1}H NMR studies. Disarmed sugars were chlorinated at a faster rate but isomerized at a slower rate in comparison to armed sugars. The method conveniently enabled

efficient one-pot glycosylation to give the products in high overall yields within 1 h. Attempts at one-pot *N*- and *S*-glycosylation using this protocol are under examination in our laboratory.

Experimental Section

1. General experimental methods

Chemical reagents were purchased from Sigma-Aldrich or Alfa Aesar and used as received without further purification. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance DPX 300. Unless stated otherwise, data refer to solutions in $CDCl_3$ with TMS as an internal reference. ^{13}C NMR spectra were recorded at 75.47 MHz on a Bruker Avance DPX 300. IR spectra were recorded using Bruker MPA FT-NIR. HRMS were recorded using a Qstar XL MS/MS system. Analytical TLC was performed using Merck 60 F_{254} precoated silica gel plates (0.2 mm thickness) and visualized using UV radiation (254 nm) or stained ceric ammonium nitrate in 30% H_2SO_4 solution. Flash chromatography was performed using Merck silica gel 60 (60-120 mesh).

1.1 General procedure for chlorination using DMC: DMC (1 eq.) was added to a stirred solution of sugars (**1a**-**k**, 0.5 mmol) and triethylamine (1 eq.) in DCM (3 mL) in glass vials at room temperature and the mixture was stirred for 15-30 min (TLC). After complete consumption of the sugar, the reaction mixture was diluted with DCM (10 mL) and washed with water (3 X 15 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under vacuum to give the crude glycosyl chlorides. Purification of the crude glycosyl chlorides using silica gel column chromatography using hexane:ethyl acetate (75:25) as eluent provided the pure glycosyl chlorides **2a**-**k**. Note that **2g** was unstable on silica gel.

1.2 General procedure for one-pot glycosylation with armed sugars: DMC (0.2 mmol) was added to a stirred solution of sugars **1a**, **1b**, **1i** (0.2 mmol) and triethylamine (0.4 mmol) in dichloromethane (3 mL) at room temperature and the mixture stirred for 15-30 min (TLC). After complete consumption of the sugars **1a**, **1b**, **1i**, the reaction mixture was cooled to -60 ^{o}C then the acceptors **9** or **10** (0.8 eq.) were added followed by addition of silver triflate (0.4 mmol). After complete consumption of the glycosyl chloride (TLC), the reaction mixture was quenched with Et_3N (0.4 mmol), diluted with DCM (15 mL) and filtered through a small pad of celite. The filtrates were then concentrated to give the crude glycosylated products which upon purification using column chromatography hexane:ethyl acetate gradient gave the pure glycosylated product **5**-**8**.

1.3 One-pot glycosylation using disarmed sugar 1c: DMC (0.2 mmol, 34 mg) was added to a stirred solution of **1c** (0.2 mmol, 70 mg) and triethylamine (0.4 mmol, 56 µl) in dichloromethane (3 mL) at room temperature and the mixture stirred for 15-30 min (TLC). After complete consumption of the **1c**, benzyl alcohol (0.8 eq. 0.16 mmol, 17 µl) and silver oxide (1 eq., 0.2 mmol, 47 mg) were added and the reaction mixture was stirred for another 8h at 40 ^{o}C. The reaction mixture was then diluted with DCM (15 mL) and filtered through a small pad of celite. The filtrates were then concentrated to give the crude product which upon purification using column chromatography 4:1 hexane:ethyl acetate gave the orthoester **11** as syrup (66 mg. 75% Yield).

1.4 NMR studies

In a NMR tube, sugar **1c** or **1i** (0.1 mmol) was dissolved in $CDCl_3$ (540 µl) and Et_3N (16 µl, 0.1 mmol) was added. The solution was shaken by inverting the NMR tube several times and then the ^{1}H NMR spectrum was recorded. DMC (17 mg, 0.1 mmol) was then added to the reaction mixture, the tube shaken by inverting it several times and both the ^{1}H and ^{13}C NMR spectra were recorded (*ca* 5 min). The spectra were recorded few times after a specific time (See Table 3). The α:β ratios were calculated from the integral values of the anomeric protons (H1) of the α- and β-glycosyl chlorides. Please see the complete ^{1}H NMR and ^{13}C NMR spectra of this experiment in the SI.

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Keywords: glycosyl chlorides • 2-Chloro-1,3-dimethylimidazolinium chloride • one pot glycosylation • Koenigs-knorr glycosylation • Armed/disarmed sugars

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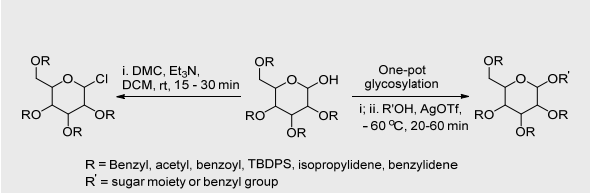

A convenient method for the synthesis of α-glycosyl chloride donors in high 80-96% yields within 15-30 min using 2-chloro-1,3-dimethylimidazolinium chloride has been developed. The method enables quick and direct one-pot glycosylation in high overall yields.

Glycosyl chlorides; glycosylation

Madhu Babu Tatina,[a] Duc Thinh Khong,[a] Zaher M. A. Judeh[a]*

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Efficient synthesis of α-glycosyl chlorides using 2-chloro-1,3-dimethylimidazolinium chloride: A convenient protocol for quick one-pot glycosylation