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A mild and general method for preparation of α-glycosyl chlorides

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ABSTRACT

A mild and efficient chlorination method for production of glycosyl chlorides is first described which employs inexpensive trichlorotriazine (TCT) and DMF as a chlorination reagent and is compatible with typical acid-labile hydroxyl protecting functions. The scope and limitations, reaction mechanism and its application in the sequential glycosylations are discussed.

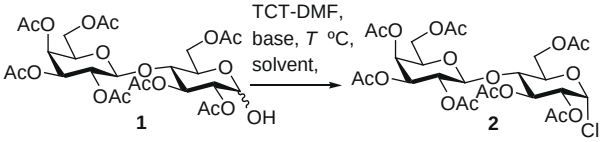
Developing inexpensive and operationally simple procedures for organic reactions is always attractive to chemists, which is illustrated by the application of trichlorotriazine (TCT) in functional group conversions.[1–7] As for example, TCT and DMF (TCT–DMF adduct) have been used for chlorination of aliphatic alcohols,[8] but there have not been any elaborative studies about using such TCT–DMF adduct for chlorination of glycosyl substrates.

Glycosyl chlorides constitute an important class of carbohydrate building blocks in oligosaccharide synthesis;[9] moreover, they are precursors for preparing O-glycosides,[10] C-glycosides,[11a] N-glycosides,[11b] and glycals.[12] Therefore, a facile production of glycosyl chlorides is highly desired. Typical preparation of glycosyl chlorides involves the treatment of peracyl glycosyl substrates with highly acidic reagents that renders them incompatible with acid-labile protecting functions.[13,14] Though milder reagents for chlorination of glycosyl hemiacetals have been developed including PPh_3–CCl_4,[15a] Viehe's salt,[15b] chloroenamine,[15c] chlorodiphenyl phosphate,[15d] and triphosgene,[15e] either such reagents are not commercially available or their efficiency is inadequate for disarmed glycosyl substrates.[15b,c] To pursue a milder and efficient method for glycosyl chloride production, we herein describe for the first time the use of inexpensive TCT and DMF for preparation of glycosyl chlorides, and its applications in sequential functional group transformations and glycosylations.

In the model study, peracetyl lactosyl hemiacetal **1** dissolving in CH_2Cl_2 was treated with pre-mixed TCT (1.1 equiv) and DMF (ca. 2.2 equiv) at room temperature based on literature procedure (Table 1, entry 1).[8d] Disappointingly, the expected lactosyl chloride **2** was furnished in moderate 58% yield after 48 h. Such a sluggish reaction is attributed to the highly disarmed nature of peracetyl-protected substrate and sub-optimal reaction conditions.[16] After some experimentations, several reaction parameters are found essential for TCT–DMF chlorination which include: (1) addition of proton scavenger to reaction mixture such as diazabicyclo-[5.4.0]-undec-7-ene (DBU), triethylamine or K_2CO_3; (2) application of higher reaction temperature (45–60 °C); and (3) optimization of TCT–DMF stoichiometric ratio to ca. 1:4. With all these parameters in hands, reaction times of chlorination were dramatically reduced to 1.5–4 h and yields were improved to 75–87% (Table 1, entries 2–6).

Based on the aforementioned parameters, we explored the scope and limitations of TCT–DMF chlorination (Table 2, entries a–r). Thus various glycosyl substrates **3a–20a** were prepared by standard methods and treated with either chlorination protocol A or chlorination protocol B.[17,18] Protocol A employs DBU (1 equiv) as the base and is performed in dichloroethane (DCE) at 60 °C. This protocol is presumably suitable for less reactive glycosyl substrates such as **3a–10a**, **14a,** and **20a** (Table 2, entries a–h, l, and r). While protocol B employs excess K_2CO_3 (5 equiv) and is conducted in CH_2Cl_2 at 45 °C (Table 2, entries i–k and m–q), both K_2CO_3- and TCT-derived byproduct of protocol B are readily precipitated in

Table 1
Elucidation of essential reaction conditions of TCT–DMF chlorination



Entry	Base	Solvent	T (C)	Time (h)	Yield[a] (%)
1	None	CH_2Cl_2	25	48	58
2	None	DCE	60	4	85
3	DBU	DCE	60	1.5	87
4	DBU	DCE	50	2.5	83
5	Et_3N	DCE	50	4	81
6	K_2CO_3	CH_2Cl_2	45	4	75[b]

[a] Isolated yield via brief chromatography purification.
[b] 5.0 equiv of K_2CO_3 was used.

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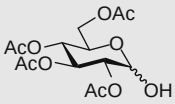
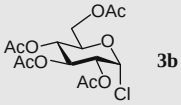
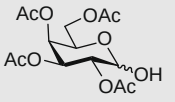
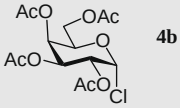
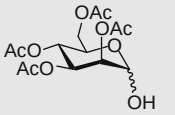
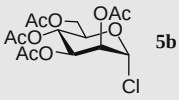
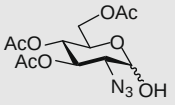
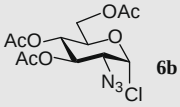
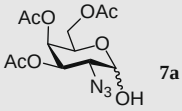
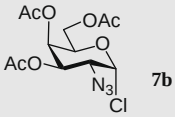
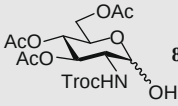
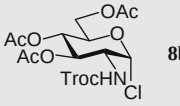
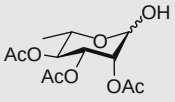
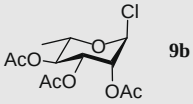
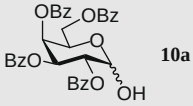
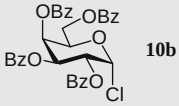
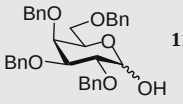
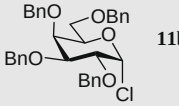
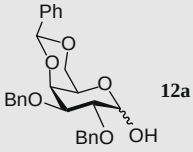
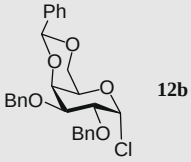
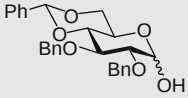
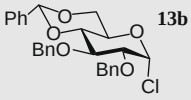
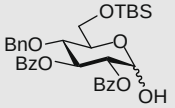
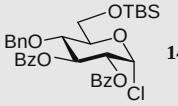
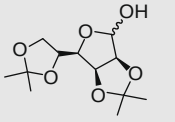
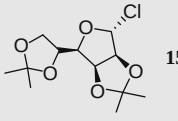
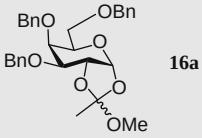
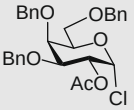
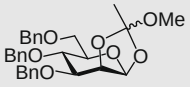
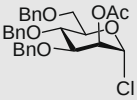
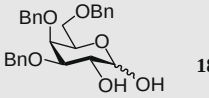
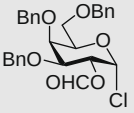
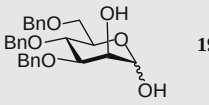
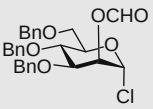
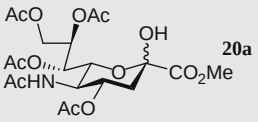
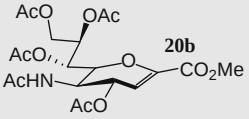
Table 2
Examination of TCT–DMF chlorination of glycosyl hemiacetals **3a–20a**

Entry	Glycosyl substrate	Product	Protocol,[a] time	Yield[b] (%)
a	 **3a**	 **3b**	A, 4 h	89
b	 **4a**	 **4b**	A, 2 h	90
c	 **5a**	 **5b**	A, 2 h	92
d	 **6a**	 **6b**	A, 1.5 h	76
e	 **7a**	 **7b**	A, 2 h	88
f	 **8a**	 **8b**	A, 3 h	75
g	 **9a**	 **9b**	A, 1 h	79
h	 **10a**	 **10b**	A, 1 h	80
i	 **11a**	 **11b**	B, 4 h	82
J	 **12a**	 **12b**	B, 4 h	85
k	 **13a**	 **13b**	B, 3 h	82
l	 **14a**	 **14b**	A, 2 h	67
m	 **15a**	 **15b**	B, 2 h	89

(*continued on next page*)

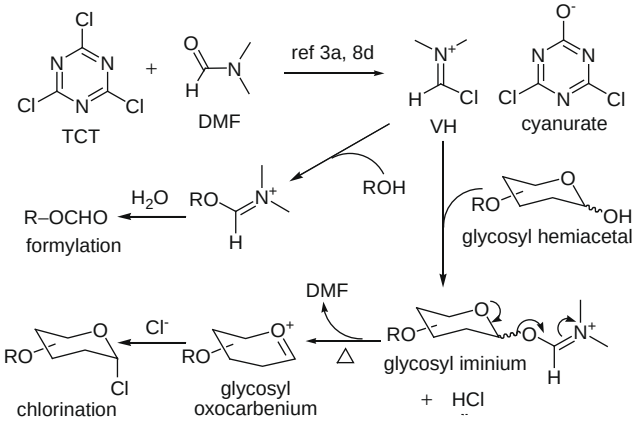
Table 1 (*continued*)

Entry	Glycosyl substrate	Product	Protocol,[a] time	Yield[b] (%)
n	 **16a**	 **16b**	B,[c] 2 h	85
o	 **17a**	 **17b**	B,[c] 2 h	92
p	 **18a**	 **18b**	B, 3 h	70
q	 **19a**	 **19b**	B, 2 h	95
r	 **20a**	 **20b**	A,[d] 3 h	85

[a] Protocol A = TCT (1.1 equiv), DMF (4 equiv), DBU (1.0 equiv) in DCE at 60 °C. Protocol B = TCT (1.1 equiv), DMF (4 equiv), K_2CO_3 (5 equiv) in CH_2Cl_2 at 45 °C.
[b] Isolated yield after brief chromatography purification.
[c] Base was omitted.
[d] 65 °C was applied.

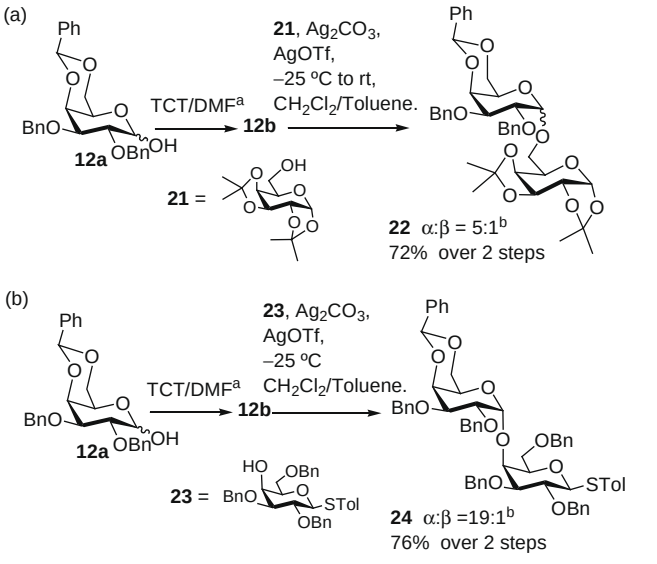
Et_2O and thus they can be removed by simple filtration. Such physical features render protocol B particularly suitable for incorporation to sequential functional group transformations.

With the exception of Neu5Ac hemiacetal **20a** (Table 2, entry r), TCT–DMF chlorination of **3a–19a** produced the corresponding α-glycosyl chlorides **3b–19b** as the single anomers in 67–95% yields at 1–4 h time frames; the observed α-selectivities can be partially attributed to anomeric effect and thermodynamic reaction conditions.[19] Though β-glycosyl chloride formation was reported in previous study, however no such β-glycosyl chlorides were isolated in present chlorination experiments.[20] This may be ascribed to the decomposition of the unstable β-glycosyl anomers during chromatography purification.



Scheme 1. Plausible mechanism of TCT–DMF chlorination of glycosyl hemiacetals.

The TCT–DMF chlorination is compatible with different acid-labile hydroxyl protecting functions such as alkylidene acetals and silyl ether functions (Table 2, entries j–m). Consequently with the current method, glycosyl chlorides in different protecting group settings are easily prepared. In addition, we envisaged that omitting the base in TCT–DMF chlorination can effect a one-pot conversion of glycosyl orthoester to glycosyl chloride. It should



Scheme 2. Sequential chlorination–glycosylation. [a] Protocol B: TCT (1 equiv), DMF (4 equiv), K_2CO_3 (5 equiv) in CH_2Cl_2 at 45 °C. [b] α-/β-Anomer ratio was determined by ^1H NMR analysis.

be mentioned that similar conversion explained in previous study requires four reaction steps.[21] Thus treatment of glycosyl orthoesters **16a**, **17a** with the modified procedure of protocol B resulted in the formation of glycosyl chlorides **16b**, **17b** in high yields (Table 2, entries n and o).[22]

Particularly intriguing is the chlorination of glycosyl hemiacetals **18a** and **19a**; each of these substrates contains non-anomeric and anomeric hydroxyl functions. Applying TCT–DMF chlorination protocol B resulted in chemoselective anomeric hydroxyl chlorination and C-2 hydroxyl formylation. No traces of crossly functionalized products were detected. (Table 2, entries p and q).

Although TCT–DMF chlorination is useful for a wide range of glycosyl substrates, its application to Neu5Ac hemiacetal **20a** gave rise to elimination product, Neu5Ac glycal **20b** (Table 2, entry r). This result may be explained by the high propensity of Neu5Ac glycosyl chloride for elimination. Nevertheless, Neu5Ac glycal **20b** is the valuable precursor for preparing sialidase inhibitors;[23] thus by serendipity, our method provides an easy entry to Neu5Ac glycal derivative.

It is worth mentioning that armed glycosyl chlorides (**11b–13b** and **16b–19b**) are prone to decomposition; nevertheless, brief chromatography purification over short pad of silica gel is tolerable. However, a prolonged contact would lead to substantial decomposition of both armed and disarmed glycosyl chlorides; while the extent of decomposition is much greater for the armed chlorides than for the disarmed chlorides.[24] Noted that TCT–DMF chlorination method is amenable to larger scale preparation (5–10 g of glycosyl hemiacetal), for which a slightly longer reaction time is required.

Based on the literature review and experimental observations, a plausible mechanism of TCT–DMF chlorination is outlined in Scheme 1.[8a,d] At first, TCT was reacted with DMF giving Vilsmeier–Haack (VH) adduct and cyanurate; VH-adduct was then coupled to glycosyl hemiacetal furnishing glycosyl iminium. The presence of glycosyl iminium was supported by isolation of its hydrolyzed product, glycosyl formate (data not shown). Subsequent cleavage of the 'exo' anomeric C–O bond in glycosyl iminium was promoted by the 'push and pull' stereoelectronic feature of substrate, which generated glycosyl oxocarbenium. Note that the absence of such a stereoelectronic feature as is the case in aliphatic alcohol results in hydroxyl formylation. Final coupling of oxocarbenium intermediate with chloride ion furnished α-glycosyl chloride.

As glycosyl chlorides are versatile donors for Koenigs–Knorr glycosylation,[25] it is reasonable to streamline TCT–DMF chlorination and Koenigs–Knorr glycosylation to a sequential process such that apparently glycosyl hemiacetals act as donors for glycosylations. Kobayashi reported for direct activation of glycosyl hemiacetals with the Appel-Lee (PPh_3–CBr_4) reagent and DMF, though the glycosylations were slow (required 1–3 days).[26] In present context, D-galactopyranosyl hemiacetal **12a** was first treated with TCT–DMF protocol B giving galactopyranosyl chloride **12b** (Scheme 2a). Crude galactopyranosyl chloride **12b** obtained after simple filtration and solvent removal was used directly as a donor for glycosylation of acceptor **21** without tedious chromatography isolation of glycosyl chloride. Desired disaccharide **22** was obtained in 72% overall yield as a 5:1 α:β-anomeric mixture. Such sequential chlorination–glycosylation also works well for thioglycoside acceptor rendering an orthogonal glycosylation possible (Scheme 2b). Thus **12a** was chlorinated and thereof glycosylated with thiogalactopyranoside **23** furnishing thioglycoside **24** in 76% overall yield and excellent α-selectivity.

In summary, we report for the first time a mild and efficient TCT–DMF chlorination method for different carbohydrate substrates including glycosyl hemiacetals and glycosyl orthoesters. Based on this new chlorination method, glycosyl chlorides in different protecting group settings become easily available, which in turn enables the development of sequential chlorination–glycosylation. Such a mild chlorination method should find useful for oligosaccharide synthesis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.077.

References and notes

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17. Preparation of glycosyl hemiacetals **3a–20a** were detailed in the Supplementary data.
18. TCT–DMF chlorination protocol A: DMF (1.55 mL, 20.0 mmol) was added to 2,4,6-trichloro-[1,3,5]-triazine (TCT) (1.0 g, 5.5 mmol) and the resulting suspension was stirred at rt for 15 min under N_2. Glycosyl hemiacetal (5.0 mmol) (**1**, **3a**, **4a**, **5a**, **6a**, **7a**, **8a**, **9a**, **10a,** or **14a**) in dichloroethane solution (DCE) was added to the TCT–DMF suspension followed by addition of DBU (0.8 mL, 5.5 mmol). The reaction mixture was stirred at 60 °C and progress of reaction was monitored by TLC (ca. 1–4 h). Upon completion of chlorination, the temperature was brought to rt and Et_2O was added to the mixture for the precipitation of cyanuric salt. After removal of cyanuric salt by filtration, the combined filtrate was concentrated to yield the crude glycosyl chloride. Further purification was performed by brief chromatography elution over a short pad of silica gel to furnish the respective α-glycosyl chloride **2**, **3b**, **4b**, **5b**, **6b**, **7b**, **8b**, **9b**, **10b,** or **14b**. TCT–DMF chlorination protocol B (**11a**, **12a**, **13a**, **15a**, **16a**, **17a**, **18a**, **19a**): Similar to protocol A except that CH_2Cl_2 and 5 mol equiv of K_2CO_3, were used as solvent and proton scavenger, respectively, to replace DCE and DBU in protocol A. The reaction was conducted at 45 °C and for glycosyl orthoesters **16a** and **17a**, K_2CO_3 was omitted. Subsequent workup followed the same procedure as described in protocol A above and the respective α-glycosyl chloride **11b**, **12b**, **13b**, **15b**, **16b**, **17b**, **18b,** or **19b** was obtained.
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22. During the revision of this manuscript, we prepared 2-*O*-acetyl-4,5,6-tri-*O*-benyzl-α-D-glucopyranosyl chloride from the corresponding D-glucopyranosyl orthoester in high yield with the same one-pot procedure.
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