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Carbohydrate Research 328 (2000) 431–434

CARBOHYDRATE RESEARCH

Note

A convenient synthesis of glycosyl chlorides from sugar hemiacetals using triphosgene as the chlorine source

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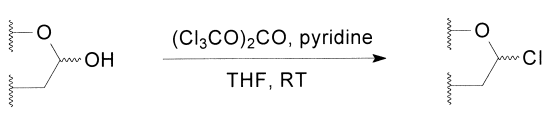
Received 19 January 2000; accepted 10 April 2000

Abstract

Treating partially protected sugar hemiacetals with triphosgene in THF results in the formation of glycosyl chlorides. The method is compatible with acid-sensitive isopropylidene protecting groups in the hemiacetal substrates.

Keywords: Glycosyl chloride; Sugar hemiacetal; Triphosgene

Glycosyl chlorides are important and versatile synthetic intermediates in carbohydrate chemistry, allowing for the ready introduction of further functionality at the anomeric carbon. These compounds are well known as glycosyl donors in the synthesis of *O*-glycosides [1], usually in the presence of a metal promotor. For the construction of *C*-glycosides, glycosyl chlorides are known to react with stabilized nucleophiles such as sodium diethylmalonate [2], and are convenient for the production of various glycosyl organometallic species [3]. The development of the glycal assembly method for oligosaccharide synthesis is dependant upon the availability of variously substituted glycals [4], which are in turn conveniently synthesized from glycosyl halides [5].



1 2

Scheme 1.

Methods for the synthesis of these important compounds include treatment of sugar peracetates with $AlCl_3$ or PCl_5 [6], or with $SOCl_2$–AcOH [7]; however, such conditions often preclude the use of acid-sensitive protecting groups. Generation of glycosyl chlorides under neutral conditions is possible using PPh_3–CCl_4 [8] or haloenamines [9] as the chlorine source. More recently, Wong and Hung [10] discovered that extended exposure of glycosyl hemiacetals to *n*-BuLi–$ClPO(OPh)_2$ afforded glycosyl chlorides in excellent yields, including several containing acid-sensitive protecting groups. Further, Peromo and Krepinsky have developed the chlorination of methyl glycosides using BCl_3 [11], and various groups have utilized dichloromethyl methyl ether in the synthesis of glycosyl chlorides [12]; however, this reagent is a powerful lachrymator and is

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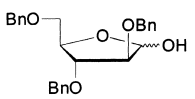
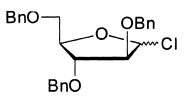
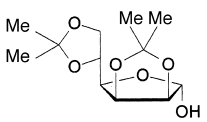
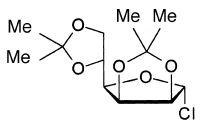
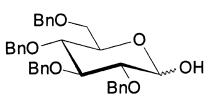
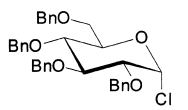
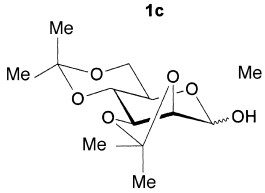
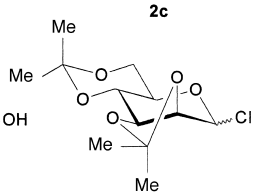
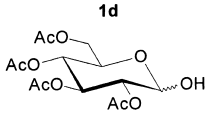
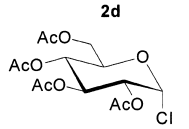
0008-6215/00/$ - see front matter
PII: S0008-6215(00)00115-4

Table 1
Yields and α:β ratios of glycosyl chlorides **2a–e**

Starting Hemiacetal	Glycosyl Chloride Product(s)	Yield, α/β Ratio
 **1a**	 **2a**	85%, 86:14
 **1b**	 **2b**	83%, α only
 **1c**	 **2c**	87%, α only
 **1d**	 **2d**	70%, 2:1
 **1e**	 **2e**	78%, α only

highly toxic. A method employing free sugars and *N*-(dichloromethylene)-*N*,*N*-dialkylammonium chlorides has also been described [13], as has the use of TsCl as the chlorinating agent [14].

We now report a simple synthesis of glycosyl chlorides **2**, which employs readily available sugar hemiacetals **1** and commercially available solid triphosgene as the chlorine source (Scheme 1). The method is compatible with acid-labile groups such as isopropylidene acetals, as well as benzyl groups; however, the reaction is less efficient with partially protected acetates.

Triphosgene [$(Cl_3CO)_2CO$] is a convenient, commercially available (e.g., from Aldrich Chemical Company, Milwaukee, WI) solid replacement for phosgene gas and is finding increased use within organic synthesis [15]. Of relevance to the present report is that Mobashery and colleagues have shown that triphosgene may be used for convenient chlorination of activated alcohols such as those of benzylic and allylic systems [16]. We reasoned that this reagent might be capable of producing glycosyl chlorides from the readily available hemiacetals of sugars, and that the conditions employed (triphosgene and pyridine in THF) should be compatible with a variety of protecting groups. This has now been shown to be the case as can be seen from the representative results in Table 1[1].

The method is adapted from the Mobashery work and involves treating the appropriate sugar in THF solution with 0.4 equivalents of triphosgene, followed by the addition of pyridine. Within seconds of the addition of pyridine, the byproduct, pyridinium hydrochloride, precipitates as a white solid and CO_2 gas is evolved. Generally, simply stirring the mixture at room temperature for 2–4 h causes conversion to the corresponding glycosyl chloride, reaction progress being conveniently monitored by TLC. After the appropriate time the solids are filtered, and the solution is evaporated to yield the glycosyl chloride in $>90\%$ purity in the yields detailed in Table 1. Appropriately stable chlorides may be further purified by flash chromatography on silica gel as needed. As previously [10], the composition of anomeric mixtures may be determined from ^{1}H NMR spectra. Unstable chlorides such as **2a** and **2d** decompose upon standing; however, filtration of the pyridinium hydrochloride from the reaction mixture yields a THF solution of glycosyl chloride that is suitable for further use.

The reaction of acetate protected hemiacetal **1e** is markedly slower than the formation of **2a–d**, and working up the reaction after 2 h yields a syrup that, from ^{1}H and ^{13}C NMR evidence, is considered to be the intermediate glycosyl chloroformate. Refluxing the reaction mixture overnight drives the reaction to the glycosyl chloride **2e**. Since formation of the starting tetraacetate **1e** requires selective deprotection of the anomeric acetate from a pentaacetate precursor [17], the classical method of Lemieux [18] which employs β-D-glucopyranose pentaacetate and $TiCl_4$, is far more convenient than the present route.

[1] The chlorides in Table 1 are known compounds, and the samples prepared by this method gave spectral data in agreement with literature values.

Insight into the mechanism of glycosyl chloride formation is gained by running the chlorinations in $CDCl_3$ solution and monitoring product formation by ^1H NMR spectroscopy. When configurationally pure α-D-*manno* hemiacetal **1b** is treated with triphosgene and pyridine in $CDCl_3$, the starting hemiacetal is consumed within 2 min and ^1H NMR spectroscopy at that time reveals a mixture of α- and β-glycosyl chlorides in a 3:2 ratio. This mixture then equilibrates to essentially all α anomer (**2b**) over a 2 h period.

This preliminary evidence favors an S_N1 mechanism for the formation of glycosyl chlorides by this method. If reaction of **1b** with triphosgene results in the formation of a configurationally pure α-glycosyl chloroformate **3**, rapid loss of CO_2 would generate the intermediate glycosyl cation **4**, which would subsequently be trapped by chloride to give an α/β mixture (Scheme 2). Direct displacement of an α-glycosyl chloroformate such as **3** by chloride would generate only the β-glycosyl chloride, and this outcome would not account for the observed 3:2 anomeric mixture observed after the 2 min period. Furthermore, the slow formation of chloride from peracetylated substrate **1e** is likely a consequence of cation formation being retarded by the acetoxy group at C-2.

The complete scope and mechanism of this reaction for the synthesis of glycosyl chlorides are presently under investigation.

1. Experimental

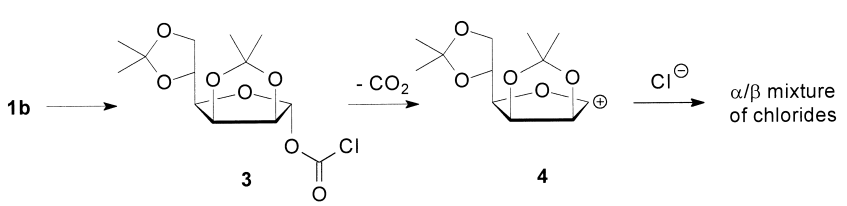
General.—TLC was performed on precoated aluminum-backed plates of Silica Gel 60 (E. Merck). ^1H NMR spectra were recorded on a Varian Gemini 2000 instrument at 400 MHz as solutions in $CDCl_3$ with Me_4Si as the internal standard.

General procedure for synthesis of glycosyl chlorides **2a**–**e**.—The relevant hemiacetal (**1a**–**e**, 1 mmol) was dissolved in dry THF (5 mL), triphosgene (120 mg, 0.4 mmol) was added, and the mixture was stirred at rt with exclusion of moisture. Pyridine (0.1 mL) was added in three portions, and the mixture was allowed to stir at rt for 2–4 h (18 h at reflux for peracetate **2e**) while being monitored by TLC. After the reaction was complete, pyridinium hydrochloride was filtered, the solid was washed with THF (3 mL), and the filtrate was evaporated in vacuo below 40 °C. The resultant syrup contained glycosyl chloride of $>90\%$ purity as seen from NMR spectra, which were in agreement with reported literature values. Further purification was possible by extracting the syrups with ethyl acetate and evaporating, or by flash column chromatography.

Scaled-up procedure for **2a**–**d**.—The above procedure was followed except that external cooling with an ice-water bath was employed during the addition of pyridine since the reaction is exothermic. Yields of scaled-up syntheses (1 g of hemiacetal) are comparable with smaller scale reactions.

*Data for 2,3,5-tri-*O*-benzyl-α- and β-*D*-arabinofuranosyl chlorides* (**2a**) *[19].*—^1H NMR: δ 3.62 (m, 1 H, H-3), 3.96 (m, 1 H, H-4), 4.36–4.70 (m, 9 H, H-2, H-5, H-5′, CH_2Ph), 6.17 (s, H-1α), 6.21 (d, *J* 4.2 Hz, H-1β), 7.20–7.41 (m, 15 H, Ar-H).

*Data for 2,3,5,6-di-*O*-isopropylidene-α-*D*-mannofuranosyl chloride* (**2b**) *[9].*—^1H NMR: δ 1.33 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.46 (s, 6 H, 2 × CH_3), 4.01 (dd, 1 H, *J* 4.2, 8.8 Hz, H-6), 4.08 (dd, 1 H, *J* 6.2, 8.8 Hz, H-6′), 4.19 (dd, 1 H, *J* 3.5, 7.7 Hz, H-4), 4.42 (m, 1 H, H-5), 4.88 (dd, 1 H, *J* 3.5, 5.7 Hz, H-3), 4.95 (d, 1 H, *J* 5.8, H-2), 6.07 (s, 1 H, H-1).



Scheme 2.

Data for 2,3,4,6-tetra-O-*benzyl*-α-D-*glucopyranosyl chloride* (**2c**) *[9].*—^{1}H NMR: δ 3.63 (dd, 1 H, H-6, *J* 2.0, 11.0 Hz), 3.82 (m, 2 H, H-2, H-4), 3.86 (dd, 1 H, H-6′, *J* 2.7, 11.0 Hz), 4.11–4.20 (m, 2 H, H-5, H-3), 4.44–4.99 (m, 8 H, 4 × CH_2Ph), 6.05 (d, 1 H, H-1, *J* 3.7 Hz), 7.12–7.38 (m, 20 H, Ar-H).

Data for 2,3,4,6-di-O-*isopropylidene*-α- *and* β-D-*mannopyranosyl chlorides* (**2d**) *[20].*—^{1}H NMR: δ 1.33–1.55 (8s, 24 H, 8 × CH_3), 3.68–4.31 (m, 6 H, H-2, H-3, H-4, H-5, H-6, H-6′), 6.07 (d, 1 H, H-1β, *J* 0.6 Hz), 6.26 (s, 1-H, H-1α).

Data for 2,3,4,6-tetra-O-*acetyl*-α-D-*glucopyranosyl chloride* (**2e**) *[9].*—^{1}H NMR: δ 2.01, 2.03, 2.08, 2.09 (4 s, 12 H, 4 × $COCH_3$), 4.10–4.33 (m, 3 H, H-5, H-6, H-6′), 4.99–5.58 (m, 3 H, H-2, H-3, H-4), 6.28 (d, 1 H, H-1, *J* 3.8 Hz).

Acknowledgements

The Graduate School and the College of Arts and Sciences at Youngstown State University are gratefully acknowledged for their support during this work, as are the donors of the Petroleum Research Fund of the American Chemical Society.

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