



One pot conversion of carbohydrates alcohol into chloride via benzotriazole sulfonate



Chandra S. Azad, Anil K. Saxena*

Division of Medicinal and Process Chemistry Division, Central Drug Research Institute (CDRI), CSIR, Chattar Manzil Palace, MG Road, Lucknow 226001, Uttar Pradesh, India

ARTICLE INFO

Article history:

Received 8 November 2012
Received in revised form 8 January 2013
Accepted 15 January 2013
Available online 24 January 2013

Dedicated to Professor Richard R. Schmidt on the occasion of his 78th birthday.

Keywords:

Deoxyhalogeno-carbohydrate
Benzotriazole-1-sulfonate
Alcohols to chloride
Appel reaction

ABSTRACT

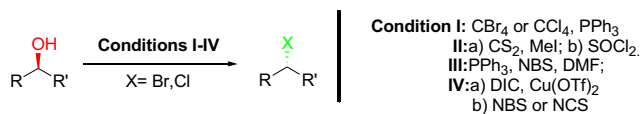
A one pot method for chloro-dehydroxylation of carbohydrates alcohol including sterically and electrically hindered ones in excellent yield was developed. The benzotriazole-1-sulfonate proposed to play a crucial role in the reaction medium, which undergoes substitution by chloride ion in the reaction medium to give only desired chloride derivative without the formation of side product. The optimized methodology can be used in the synthesis of number of biologically active compounds or chiral syntheses.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

Deoxyhalogeno-carbohydrates are of key importance to carbohydrate and medicinal chemists as they are used as potent artificial sweeteners,¹ male antifertility agents,² hepatocyte cellular glycosaminoglycan inhibitors³ and major scaffolds in antibiotics.⁴ Recently halogenated carbohydrates have been shown to be a part of pharmacophores.⁵ The 2-deoxy-D-glucose known for its medicinal utility,⁶ can be easily synthesized from the corresponding 2-halo derivatives of glucose via free radical elimination.⁷ In general, the conversion of alcohol functionality of carbohydrate into halide involves first the conversion of alcohol into nucleofugal group e.g., mesylate, tosylate, triflate and imidazylate etc., followed by its substitution with an appropriate nucleophile.⁸ In general mesylates and tosylates are considered as good leaving groups but not in the field of the carbohydrate chemistry because their substitution involves drastic reaction conditions, such as heating at 130 °C for 80 h in DMF and that too provide nominal amount of the desired product.⁹ Though the replacement of mesylates and tosylates by triflates, substantially extended the scope of reactivity¹⁰ of these sulfonic esters towards nucleophilic substitution reaction, but the major limitations of some triflate esters are their inadequate self

life, high cost and cumbersome application in large scale synthesis. Appel reaction, a milestone in this direction where triphenylphosphine (PPh₃) and carbon tetrachloride or bromide are used in the conversion of alcohols into halides (**I**, Scheme 1).¹¹ The major disadvantage associated with the Appel reaction is the formation of triphenylphosphine oxide and its removal from the reaction mixture. Further attempts have been made by different research groups, which include (**II**) conversion of alcohol into chloride with the retention of configuration treating its xanthates with thionyl chloride,¹² (**III**) conversion of alcohols into halide with the aid of the Vilsmeier-type reagent (PPh₃, *N*-bromosuccinimide and DMF)¹³ and (**IV**) conversion of hydroxyl into halides by treating its *O*-alkyl isoureas derivatives with *N*-halosuccinimide (Scheme 1).¹⁴



Scheme 1. Various protocol for simple conversion of alcohol to halide (Br or Cl).

All these methods involve harsh reaction conditions and expensive reagents. Furthermore, the formation of halides from nucleofugal groups leads in the formation of unsaturated products due to competitive elimination reaction. Therefore, investigations

* Corresponding author. Tel.: +91 522 2612411 8x4268, +91 522 2624273; fax: +91 522 2623405/2623938; e-mail addresses: anilsak@gmail.com, ak_saxena@cdri.nic.in (A.K. Saxena).

were made to find a new, simple, cost effective and one pot method for the synthesis of deoxy-halogenated carbohydrate.

We describe herein one pot conversion of sterically and electronically hindered alcohol of carbohydrates to their respective chlorides via benzotriazole sulfonate (Btz), which was designed on the basis of imidazole-1-sulfonate (Imz, Fig. 1). The Imz is known for its cost effectiveness and good nucleofugal properties.¹⁵ Unlike Imz, which is used after isolation and purification from the reaction mixture, the Btz synthesized from sulfuryl chloride and 1,2,3-benzotriazole (BtH) was used as such without isolation (in situ) for converting the alcohol of carbohydrates to their respective chloride derivative (**1b–7b**, Fig. 2). The in situ generated Btz possibly fragments into BtH and SO₃, may be due to the remote activation of carbon bearing –OH group by the benzotriazolium salt (BtH⁺Cl⁻) during the reaction, which leads to the displacement of nucleofuge (sulfonic ester). This has been exemplified in the conversion of carbohydrates alcohol (carb-OH) to their corresponding chloride in excellent yield. These chlorides may be useful synthons for the synthesis of bioactive molecules.

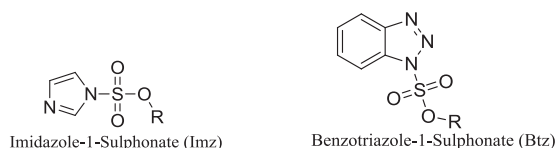


Fig. 1. Schematic representation of Imz and Btz.

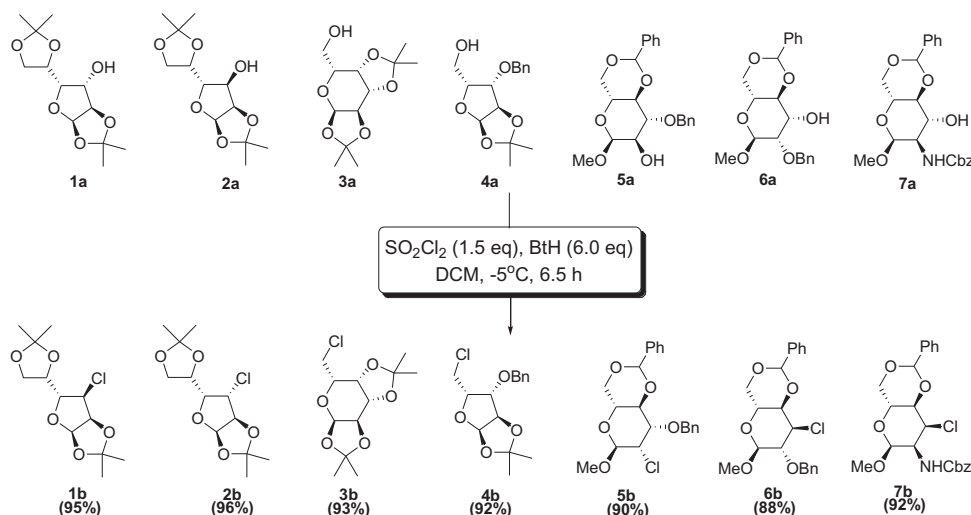
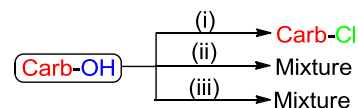


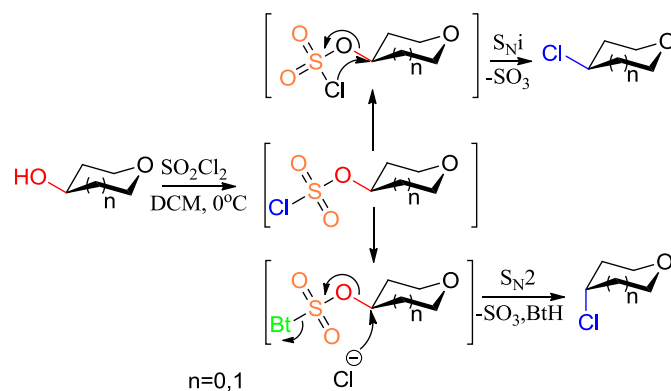
Fig. 2. One pot conversion of alcohols into chlorides.

In view of several successful attempts in increasing the stability and reactivity of benzotriazole derived reagents over the corresponding imidazole derivatives,¹⁶ possibly due to the increase in their electron withdrawing nature as compared to corresponding imidazole derivatives, the Btz analogue of Imz was synthesized. Three approaches were adopted for the synthesis of Btz. In the first approach the carb-OH was reacted with sulfuryl chloride at –40 °C in DMF in the presence of BtH. In the second approach, the carb-OH was converted to its sodium salt with NaH at 0 °C, which was reacted with BtSO₂Bt at –40 °C. The BtSO₂Bt was prepared by the action of sulfuryl chloride with 1-(trimethylsilyl)-benzotriazole according to the reported procedure.¹⁷ In the third approach, carb-OH was converted into its silyl ether with the HMDS in pyridine. The silyl ether was then reacted with BtSO₂Bt in presence of Bu₄NF under reflux (Scheme 2).



Scheme 2. (i) First approach: SO₂Cl₂, BtH, DMF, –40 °C. (ii) Second approach: NaH, DMF, BtSO₂Bt, –40 °C. (iii) Third approach: (a) NH(SiMe₃)₂, Py; (b) Bu₄NF, DCM, BtSO₂Bt.

In the first approach the isolated product was the chloride derivative of the corresponding carb-OH instead of the expected Btz, while in the second and third approach a complex nonseparable mixture was obtained. Thus the unusual formation of chloride derivative in 88–96% yield with complete inversion of configuration in the first approach is only possible through Btz. Although, Btz was not isolated from the reaction mixture, but its formation can be explained on the basis of the product obtained. In order to identify the role of BtH, the reaction was performed between carb-OH (**1a**) and sulfuryl chloride without BtH under the similar reaction conditions *viz.* temperature –40 °C, time 24 h to yield the chloride derivative (**2b**) in less than 10% yield with retention of configuration. This reaction may involve the chlorosulfonate ester, which might have been substituted by the chloride ion through S_Ni Mechanism (Scheme 3). However the formation of the product in presence of BtH suggests that Btz is formed in the reaction and gets substituted by the chloride ion due to its high nucleofugal property to give an excellent yield of the chloride derivatives **1b–7b**. These derivatives were characterized by the state of art techniques like



Scheme 3. Plausible reaction mechanism.

Download English Version:

<https://daneshyari.com/en/article/5218196>

Download Persian Version:

<https://daneshyari.com/article/5218196>

[Daneshyari.com](https://daneshyari.com)