Tetrahedron 71 (2015) 1095–1100

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Improved synthesis of mercapto C-nucleoside possessing *p*-phenyl thiol as base using a lithiated coupling reaction

Akihiko Hatano *, Munehiro Okada, Kentaro Dezaki, Seitaro Hirai

Department of Chemistry, Shibaura Institute of Technology, 307 Fukasaku, Minuma-ku, Saitama, 337-8570, Japan

ARTICLE INFO

Article history:
Received 24 October 2014
Received in revised form 21 December 2014
Accepted 23 December 2014
Available online 31 December 2014

Keywords:
C-nucleoside
Redox-active mercapto C-nucleoside
Stereoselective synthesis
Lithiation
Friedel–Crafts alkylation

ABSTRACT

We have developed a new route for synthesizing mercapto C-nucleoside possessing a phenyl thiol group, using organometallic reagents. Duplexes incorporating redox-active nucleobase analogues display a high melting temperature under oxidation condition. Originally, we had anticipated the production of mercapto C-nucleoside using a Friedel–Crafts coupling reaction via bis(toluoyl) protected ribose and *tert*-butyl phenyl sulfide in the presence of Lewis acid. However, an undesired coupling compound was formed by cleavage of the *S*-*tert*-butyl group of *S*-*tert*-butyl phenyl sulfide by Lewis acids (BF_3 Et_2O, $SnCl_4$). The highly stereoselective synthesis of mercapto C-nucleoside was, however, achieved by the addition of *p*-(*tert*-butyl)thiophenyllithium to a disiloxane-protected 2-deoxyribonolactone. This route showed moderately good yield at all steps. The *tert*-butyl moiety coupled to the sulfur atom at the phenyl group was converted to a 2-nitrophenylsulfenyl (Nps) group, and the Nps group was easily cleaved by ethanethiol to afford the desired compound and its disulfide dimer.

© 2015 Elsevier Ltd. All rights reserved.

1. Introduction

Recently, there has been considerable interest in the synthesis of nucleoside derivatives bearing a functionalized aromatic moiety at the anomeric position. C-nucleosides bearing aryl groups as an unnatural nucleobase are in high demand due to their use in several important applications such as extending the genetic alphabet,[1] formation of metal arrays[2] and construction of functionalized DNA.[3] Methods for the synthesis of C-nucleosides have been extensively studied. However, synthetic obstacles in terms of low yield and/or poor stereoselectivity have been frequently encountered. There are several synthetic approaches to generating C-nucleosides,[4] including Heck type coupling reaction of aryl iodides with glycals,[5] the addition of organometallic reagents to a protected lactone or ribose derivative[6] and electrophilic substitutions of electron-rich aromatics with ribose under Lewis acids.[7]

We had already carried out the synthesis and characterization of a mercapto C-nucleoside possessing a phenyl thiol group at an anomeric position.[8–10] A duplex containing the unnatural base under oxidizing conditions had a very high T_m. The observed high T_m is due to each unnatural *S*:*S* base pair forming a matching disulfide bond between complementary mercapto C-nucleosides under oxidizing conditions, which markedly stabilizes the resulting duplex by comparison to the control DNA. However, the coupling conversion of the β-anomer of mercapto C-nucleoside with Lewis acid (Friedel–Crafts reaction) had indicated a low yield of only 24% (β/α=2.8). It was therefore important to improve the conversion and stereoselectivity of the coupling reaction between the ribosyl moiety and protected thiophenyl derivatives at the anomeric position.

Herein, we describe an efficient alternative synthetic approach towards generating mercapto C-nucleosides possessing a thiophenyl group. This method utilizes the addition of a *p*-(*tert*-butylthio)phenyl lithium reagent to a disiloxane-protected lactone. We also attempted a Friedel–Crafts type coupling reaction of *tert*-butyl phenyl sulfide[11] and protected deoxyribose in the presence of Lewis acid.

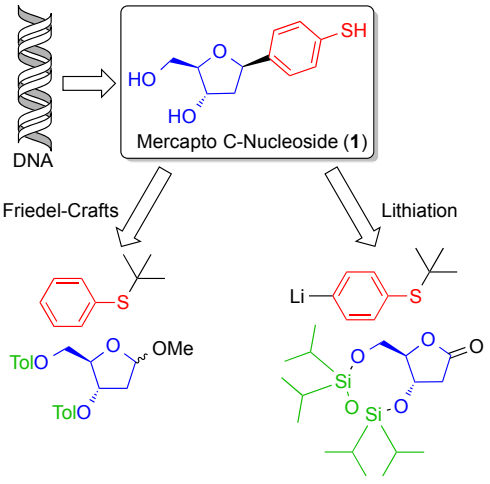
1.1. Synthetic strategy

The synthetic strategy was as follows. Route 1 was a Friedel–Crafts coupling reaction between the oxonium intermediate derived from the bis(toluoyl)-protected deoxyribose and protected thiophenol with Lewis acid (Scheme 1, left). Although this reaction was very convenient and easily performed, the resulting products were a mixture of α- and β-forms at the anomeric position of C-deoxyribose. Because the coupling efficiency was low, we attempted to couple several combinations of protected thiophenol

* Corresponding author. Tel.: +81 48 687 5035; fax: +81 48 687 5013; e-mail address: a-hatano@sic.shibaura-it.ac.jp (A. Hatano).

http://dx.doi.org/10.1016/j.tet.2014.12.085
0040-4020/© 2015 Elsevier Ltd. All rights reserved.

component and 3,5-ditoluoyl-1-α/β-methoxy-2-deoxy-D-ribose.[8] Most of the protected thiophenols did not react with 3,5-ditoluoyl-1-α/β-methoxy-2-deoxy-D-ribose using a variety of Lewis acids. However, benzyl phenyl sulfide did produce the desired Bn protected C-nucleoside in high yield (65%).[8,9] The *S*-benzyl group of benzylthiophenyl C-nucleoside remained uncleaved in the presence of many different reagents, suggesting the *S*-benzyl group was very stable. The tertiary butyl group is a simple hydrocarbon that allows facile deprotection of *tert*-butyl protected compounds. We also anticipated *tert*-butyl phenyl sulfide to be a good starting material for Friedel–Crafts coupling.



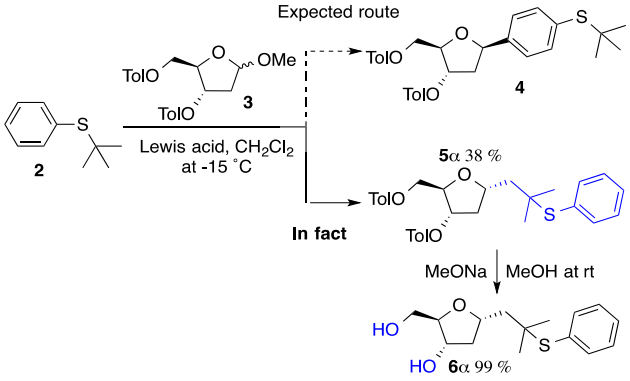
Scheme 1. Synthetic strategy of mercapto C-nucleoside (**1**) possessing a phenyl thiol group as base.

Route 2 involved an organometallic coupling reaction between disiloxane–protected deoxyribonolactone and *tert*-butyl 4-bromophenyl sulfide with *n*-butyllithium at −78 °C (Scheme 1, right).[12] There are several reagents that can be used to protect a thiol group in the presence of *n*-butyllithium.[13] The reduction of the hemiketal coupling product with an excess of Et_3SiH/BF_3 Et_2O provided only the β-epimer C-nucleoside.[6c,12] This route is superior in configuration control at the anomeric position to the route using Friedel–Crafts coupling. However, using this route, available sulfur protective groups for *p*-bromobenzenethiol were somewhat limited due to resistance of the *n*-BuLi to deprotection. As mentioned earlier, we selected the *S*-*tert*-butyl group for protection of *p*-bromobenzenethiol.

2. Result and discussion

2.1. Synthetic approach using Friedel–Crafts alkylation

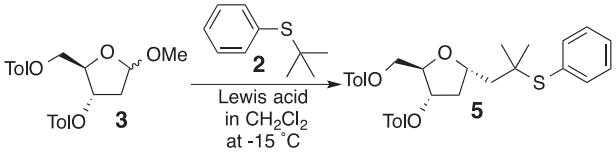
A first approach involved the Friedel–Crafts reaction between 3,5-ditoluoyl-1-α/β-methoxy-2-deoxy-D-ribose **3** and *tert*-butyl phenyl sulfide **2** to give coupling compound **4** (Scheme 2). A new spot corresponding to the coupling product was observed by TLC analysis. The chemical structure of this coupling product was then analyzed using NMR, which indicated the main species to be **5** rather than the anticipated **4**. The chemical structure of the new compound in which the bis(toluoyl)-protective groups had been cleaved by MeONa was investigated by NMR. The ^{1}H NMR spectrum of this deprotected compound **6** showed two features of interest. Firstly, two signals at 1.28 and 1.30 ppm integrated six protons instead of the nine protons one would expect for a *tert*-butyl group (Supplementary data 2, ^{1}H NMR). Secondly, two multiple signals at 1.71 and 1.95 ppm were observed in which each signal showed one proton as an integrated value (Supplementary data 2, ^{1}H NMR, COSY). The signal at 1.71 ppm overlapped with the proton signals of 2′Hα corresponding to the ribosyl moiety and hydroxyl group (HO-). Assuming the new spot obtained by TLC indicated the formation of compound **4** by Friedel–Crafts coupling, we would expect to observe a strong singlet signal derived from the *tert*-butyl group for nine protons at high magnetic field. A COSY spectrum revealed that the 1′H had the new cross-peaks for two protons at 1.71 and 1.95 ppm (Supplementary data 2, COSY). Moreover, these two signals at 1.71 and 1.95 ppm were associated with the same carbon by DEPT135 and HMQC. Therefore, we determined the chemical structure of the new spot as compound **5**. It was clarified that the configuration of the 1′ anomeric position of compound **6** was the α-form by NOESY (Scheme 4; Supplementary data 2, NOESY). NOE of 1′H indicated a cross-peak for the 2″β-proton (at 2.45 ppm), and the 2″β-proton revealed the NOE for the 3′ proton. Therefore, the anomeric proton at the 1′ position faces the β-configuration, and the coupled group faces the α-configuration.



Scheme 2. Anticipated (top) and actual (bottom) synthetic route towards mercapto C-nucleoside (**1**).

We carried out the Friedel–Crafts coupling reaction on compounds **2** and **3** with three different Lewis acids at −15 °C (Table 1). In all cases, we obtained only **5**α, rather than the desired 4-*S*-protected aryl C-nucleoside **4**. BF_3 and $SnCl_4$ as Lewis acids afforded compound **5**, but we could not generate both **4** and **5** in the presence of TMSOTf as Lewis acid.

Table 1
Effect of different Lewis acids on Friedel–Crafts coupling between compound **2** and **3**



Lewis acid	Equivalent	Time/h	Isolated yield of **5**α/%
BF_3	2	24	20
	4	6	11
	4	4	18
$SnCl_4$	4	4	38
	4	16	31
TMSOTf	4	24	0 (No reaction)

2.2. Synthetic approach using a lithiated coupling reaction

Next, our efforts were devoted to the synthesis of the mercapto C-nucleoside (**1**) by a lithiated route. The coupling reaction by lithiation essentially followed the syntheses of *C*-glycosides by Woski et al.[6c,12,14] As starting material for the synthesis of mercapto C-nucleoside (**1**), the readily available 3,5-*O*-[(1,1,3,3,-

Download English Version:

https://daneshyari.com/en/article/5215396

Download Persian Version:

https://daneshyari.com/article/5215396

Daneshyari.com