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Regioselective synthesis of 5-trifluoromethyl-1,2,3-triazole nucleoside analogues via TBS-directed 1,3-dipolar cycloaddition reaction

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ABSTRACT

Herein described was a straightforward method for the highly regioselective synthesis of 5-trifluoromethyl-1,2,3-triazole nucleoside analogues, which featured the utilization of tert-butyldimethylsilyl (TBDMS) group as the directing group in the 1,3-dipolar cycloaddition reactions. 4-tert-Butyldimethylsilyl-5-trifluoromethyl-1,2,3-triazole nucleoside analogues were generated as the only cycloaddition products in moderate yields (15–79%) via the treatment of glycosyl azides with 3,3,3-trifluoro-1-tert-butyldimethylsilylpropyne **1** in toluene at 85 °C. Removal of TBS groups in these triazole cycloadducts with tetrabutylammonium fluoride (TBAF) smoothly afforded the various 5-trifluoromethyl-1,5-disubstituted 1,2,3-triazole nucleoside analogues in good yields (40–88%).

1. Introduction

Naturally occurring nucleosides and their synthetic analogues have been the intensive research interest due to their highly potential biological activity as antitumor and antiviral agents [1]. Among them nucleosides bearing a five-member ring nucleobase are of great interest due the fact that they have exhibited unique biological activities [2]. In the past years, many highly bioactive triazole nucleosides have been synthesized and biologically evaluated for virus and hepatitis therapies [3–6]. For example, 1,2,3-triazole TSAO analogue displayed very strong bioactivity for inhibition of HIV-1 in CEM and MT-4 cells [4a] and 1,2,4-triazole ribavirin derivative has been reported to be very potent for treatment of drug-resistant pancreatic cancer [6a] (Fig. 1).

On the other hand, introduction of a trifluoromethyl group into some nucleosides has drawn considerable attention in view of the remarkable changes in the bioactivity and stability of the corresponding compounds [7]. Thus, development of methodology for synthesizing trifluoromethylated triazolo nucleoside analogues has been of interest of organic chemists, medicinal chemists and pharmacologists. So far, the most versatile method to access triazole-based nucleoside analogues has been the Huisgen 1,3-dipolar cycloaddition of glycosyl azides with alkynes [8]. This classic thermal cycloaddition, however, usually suffers from the formation of regioisomeric mixture of products when azides were treated with unsymmetrical acetylene [9]. Although the regioselective synthesis of the 4-trifluoromethyl-substituted 1,2,3-triazoles has been made by several groups [10], to the best of our knowledge the regioselective incorporation of a CF_3 group into 5-position of 1,2,3-triazolo moiety of nucleosides has never been explored [11]. Indeed, the strong electron-withdrawing property of trifluoromethyl group makes it more accessible to 4-position of triazole ring. Recently, Hlasta et al. [12] reported the use of trimethylsilyl group as regiodirecting group to control the regioselectivity in synthesizing 1,5-disubstituted 4-trimethylsilyl 1,2,3-triazoles via the cycloaddition reaction of 1-trimethylsilylacetylenes and organoazides. Inspired by Hlasta's work, we were interested to investigate the viability of utilizing the trifluoromethylated acetylene as an efficient building block to regioselective preparation of 5-trifluoromethylated 1,2,3-triazoles. Herein described was our methodology of practically constructing 5-trifluoromethyl 1,5-disubstituted 1,2,3-triazole nucleoside analogues via tert-butyldimethylsilyl(TBS)-directed 1,3-dipolar cycloaddition reaction.

2. Results and discussion

We first prepared the 3,3,3-trifluoro-1-tert-butyldimethylsilylpropyne **1** as the dipolarophile for cycloaddition reaction. According to a modified procedure reported by Hanamoto and

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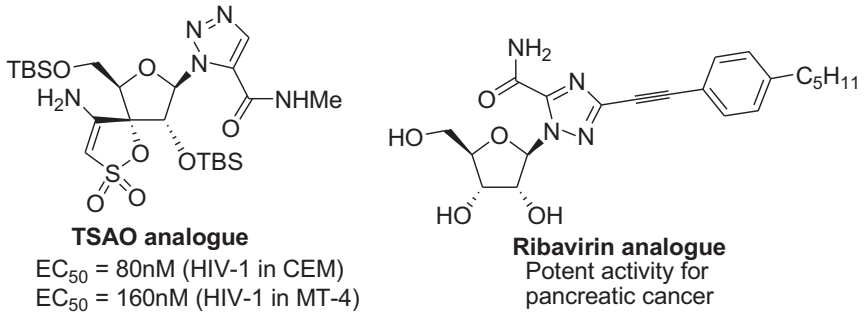
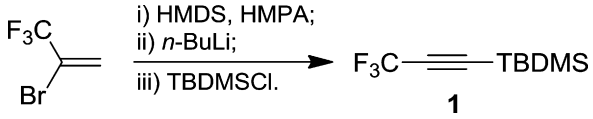


Fig. 1. Highly bioactive triazolo nucleoside analogues.



Scheme 1. Synthesis of **1** from 2-bromo-3,3,3-trifluoropropene.

Yamada [13], **1** could be provided by addition of commercially available 2-bromo-3,3,3-trifluoropropene to a solution of in situ generated lithium hexamethyldisilazide (LiHMDS) in THF using hexamethylphosphoramide (HMPA) as additive, followed by addition of tert-butyldimethylsilyl chloride(TBDMSCl). ^{19}F NMR spectroscopy of the reaction mixture illustrated that the reaction proceeded smoothly. However, it was unexpectedly difficult to isolate **1** from other components by fractional distillation due to their close boiling points. ^{1}H, ^{13}C and ^{19}F NMR showed that **1** was contaminated by the hexamethyldisilazane (HMDS) and other unknown compounds, which were also confirmed by the GC–MS analysis (Scheme 1) [14].

Although the purification of the compound **1** was unsuccessful, we believed that the cycloaddition between organic azides and the crude compound **1** should be chemospecific, thus purification of **1** was not necessary [15]. To investigate the reactivity of **1** for 1,3-dipolar cycloaddition, readily available benzyl azide **2** was chosen as the model substrate. We were pleased to find that the cycloaddition, when performed in toluene at 85 °C for 30 h, provided the desired triazole cycloadduct **3** as the single regioisomer product (Scheme 2). The regiochemistry assignment of the compound **3** was determined by HMBC experiment [16]. Increasing reaction temperature from 85 °C to reflux temperature or performing the reaction in THF provided the product in very low yield along with some complicated byproducts.

The promising result obtained from the cycloaddition of benzyl azide **2** with **1** stimulated us to extend the reaction to glycosyl azide substrates. Thus, a series of O-protected glycosyl azides **6a–6c** [17], **6d** [18], **6e–6g** [19] and **6h** [20] were prepared according to the reported procedures and used for cycloaddition reaction. It should be pointed out that for non-participating benzyl group protected glycosyl azide **6c**, anomeric mixture (α/β 1:1) was obtained. O-Acyl glycosyl azide **6e** was also contaminated by about 10% of 1,2-cis anomer [19b]. ^{n}-Octyl azide **4** was used as a control and the results were summarized in Table 1. We were pleased to find that all the glycosyl azides provided the desired cycloadducts

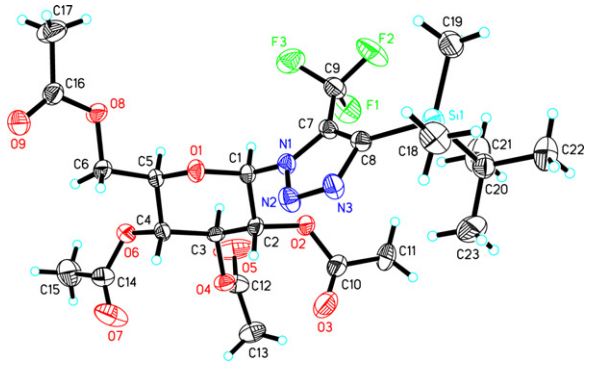
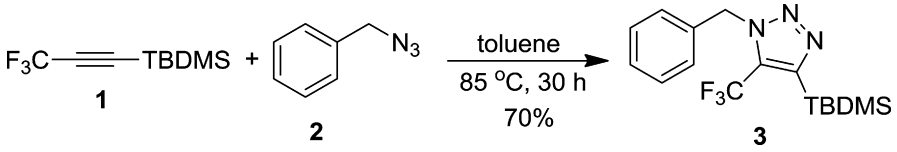


Fig. 2. ORTEP drawing of the X-ray crystallographic structure of **7a**.

in moderate yields (Table 1, entries 2–9), albeit lower yields compared to **4** (Table 1, entry 1). Of all the O-protected glycosyl azides, glycopyranosyl azides **6a** and **6b** (Table 1, entries 2 and 3) were more reactive in the cycloaddition reaction than glycofuranosyl azides **6e** and **6f** (Table 1, entries 6–8), although higher potential bioactivity should be expected from the latter ones. The lower reactivity of **6e** and **6f** was ascribed to the larger steric hindrance of furanose ring in the transition state of cycloaddition than that of their pyranose counterparts. Additionally, it was found that all the O-acyl glycosyl azides reacted smoothly to afford the corresponding cycloadducts with retention of configuration at the anomeric carbon (Table 1, entries 2 and 3 and entries 5–8). Lower yield (37%) was resulted for O-benzyl glucosyl azide **6c** (anomeric mixture 1:1) to afford the corresponding mixture **7c** of two α/β anomers (Table 1, entry 4) which may due to more crowded steric environment of azido group caused by benzyl group in **6c** than that caused by acetyl group in **6a** or **6b** [21]. It should be noted that cycloaddition reaction also proceeded well for the azides **6d** and **6h**, where azido groups were not attached to anomeric carbon (Table 1, entries 5 and 9), and the corresponding 1,2,3-triazole nucleosides **7d** and **7h** were provided in 70% and 54% yield, respectively. Most importantly, all the cycloaddition reactions exhibited very excellent regioselectivity and exclusively delivered the 5-trifluoromethyl-1,4,5-trisubstituted 1,2,3-triazoles. The absolute structure of compound **7a** was confirmed by X-ray diffraction analysis (Fig. 2) [22]. The excellent regioselectivities undoubtedly illustrated that the transition state of herein described 1,3-dipolar cycloaddition was mainly directed by TBS



Scheme 2. Model cycloaddition reaction between **1** and benzyl azide **2**.