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Unprecedented formation of 8(*R*),5′-*O*-cycloribonucleosides through a triflation reaction of purine ribonucleosides

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ABSTRACT

The present paper describes the formation of *N*-triflyl-7,8-dihydro-8(*R*),5′-*O*-cyclonucleosides during our efforts to introduce the triflate leaving group at the 5′-position of purine ribonucleoside derivatives. The chemical structure of these original cyclonucleosides, including the absolute configuration at C-8, was unambiguously elucidated by elemental analysis, high-resolution mass spectrometry, NMR analysis and X-ray crystallography. Our results bring new insights into the reactivity of the 5′-*O*-triflate derivatives of purine ribonucleosides while providing an efficient access to original cyclonucleosides.

1. Introduction

Bioisosteric replacement of the phosphate moiety in biomolecules remains extremely challenging for medicinal chemists and chemical biologists.[1] Over the past decades, several classes of phosphate ester mimics have been developed, especially in the field of nucleic acids and their components (e.g., phosphonates,[1d,2] boranophosphates,[3] sulfonates and sulfonamides,[4] dicarboxylates,[5] squarates,[6] and cyclic mimics[7]) to confer membrane permeability and resistance to catabolic enzymes. The simplest and most investigated phosphate bioisostere is the methylene phosphonate, in which the hydrolyzable C–O–P bonding arrangement is replaced with the non-hydrolyzable C–C–P bonding arrangement. Fluorination at the α-carbon of phosphonates has been suggested to result in superior bioisosteres with reduced second pK_a values compared with those of the non-fluorinated congeners.[8] Indeed, α,α-difluoromethylphosphonates have been reported to be effective steric and electronic isosteres of the phosphate group in several active sites.[8e,9]

As part of our research program targeting the human 2′-deoxynucleoside 5′-phosphate *N*-hydrolase 1 (DNPH1),[10] we were interested in developing stable phosphate mimics of purine ribonucleotide analogues and investigated the potential use of α,α-difluoromethylphosphonate in the design of potent DNPH1 inhibitors. Earlier attempts by Matulic-Adamic et al.[11] to synthesize nucleoside 5′-deoxy-5′-difluoromethylphosphonates from 5′-deoxy-5′-iodonucleosides or from 5′-aldehyde derivatives were disappointing, leading to the recovery of starting compounds or to a complex mixture of products, respectively. Therefore, the common synthetic approach to ribonucleoside α,α-difluoromethylphosphonates is based on the condensation of ribose 5′-phosphonate derivatives with persilylated nucleobases under Vorbrüggen conditions.[8c,11,12] The required sugar α,α-difluoromethylphosphonates are readily obtained from the 5′-aldehyde[13] or the 5′-triflate derivative.[14] The use of the extremely reactive triflate leaving group has also been reported in nucleoside chemistry, mainly in S_N2 reactions at the 2′- or 3′-position of nucleosides. To our knowledge, the literature contain few reports of the use of triflate as a 5′-activating group. Herdewijn and co-workers[15] described the synthesis of double-headed pyrimidine nucleosides via the conversion of the primary hydroxyl groups into the corresponding triflates with trifluoromethanesulfonic chloride (TfCl) in the presence of pyridine in dry dichloromethane. More recently, two patents reported similar reactions on pyrimidine and purine ribonucleoside derivatives, where trifluoromethanesulfonic anhydride (Tf_2O) or TfCl was used as a triflating reagent.[16] Notably, in the case of the 2-chloroadenosine 5′-triflate derivative obtained by reaction of TfCl in pyridine,[16a] the molecular ion peak of the isolated

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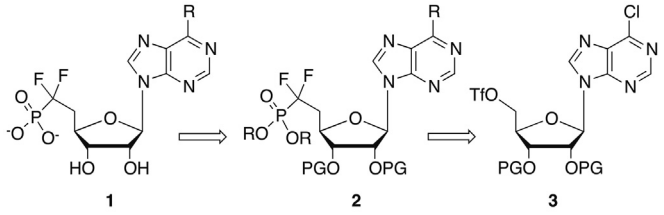
product is not in agreement with the chemical structure of the expected triflate. The formation of a pyridinium salt (see discussion later) could explain the reactivity of this intermediate towards further nucleophilic substitution.

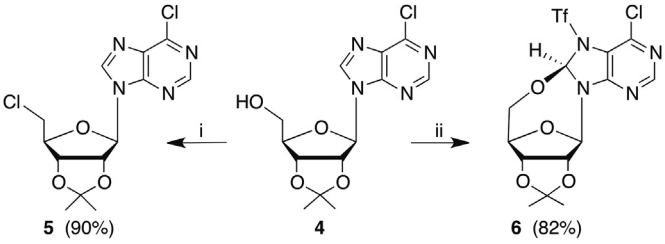
These literature data prompted us to investigate a more direct path to the target nucleoside 5′-α,α-difluoromethylphosphonates **1** from a 5′-*O*-triflate intermediate (as illustrated in Scheme 1). The 6-substituted purine derivatives **1** could be generated from a common precursor, the 6-chloropurine phosphonate derivative **2**, according to known procedures.[10c,d] By analogy with ribose α,α-difluoromethylphosphonate, this intermediate could be obtained by direct displacement of 5′-triflate group of **3** with the lithium salt of diethyl α,α-difluoromethylphosphonate. In this paper, we report the unexpected formation of 8(*R*),5′-*O*-cyclopurine derivatives during our efforts to prepare the target 5′-*O*-triflate ribonucleosides.



Scheme 1. Retrosynthesis of nucleoside 5′-α,α-difluoromethylenephosphonates **1**.

2. Results and discussion

Our attempts to synthesize **3** from 6-chloro-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (**4**) with TfCl following reported protocols failed.[15,16] Indeed, when **4** was reacted with TfCl (1.2 equiv) in the presence of DMAP (3 equiv) in dichloromethane at −30 °C, TLC and LC–MS monitoring revealed the formation, within 10 min, of a unique compound that did not correspond to the desired triflate. After work-up and purification, the 5′-chloro derivative **5** was isolated in 90% yield (Scheme 2).



Scheme 2. Formation of **5** and **6** during triflation reactions.

We then examined the use of Tf_2O as the triflating reagent. The hindered base, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), was preferred to pyridine to avoid displacement of the primary triflates, a reaction previously reported in the glucopyranose series.[17] Thus, **4** was treated with a slight excess of Tf_2O (1.2 equiv) in the presence of DTBMP (1.3 equiv) in dichloromethane at −40 °C. TLC and LC–MS monitoring of the reaction showed that **4** was completely consumed within 10 min, leading to the formation of a unique compound with the expected mass. This compound was readily purified by silica-gel column chromatography and was isolated in 82% yield. On the basis of elemental analysis, NMR spectroscopy (^1H, ^{13}C and ^{19}F) and X-ray crystallography, the chemical structure of the latter was unambiguously assigned as the 8(*R*),5′-*O*-cyclonucleoside derivative **6** (Scheme 2). Indeed, the NMR spectra of **6** indicated a singlet at 6.67 ppm for H-8 in the ^1H spectrum and a signal at 100.1 ppm for C-8 in the ^{13}C spectrum, which is consistent with loss of aromaticity in the imidazole ring.[18] The 5′-protons are non-equivalent and appear as ABX patterns at 3.92 and 4.03 ppm, in agreement with a C–O linkage. The 8(*R*) stereochemistry was established on the basis of the NOE spectrum and by X-ray crystallography. An ORTEP diagram of the X-ray crystal structure of 6 is shown in Fig. 1.

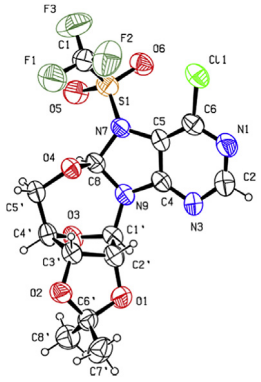


Fig. 1. ORTEP drawing of **6**.

Increasing the amounts of Tf_2O and DTBMP (up to 3.6 and 3.9 equiv, respectively) or changing the reaction temperature (−70 °C, -40 °C and room temperature) did not change the product distribution, and only **6** was isolated in excellent yield, regardless of the work-up (careful removal of the solvent by evaporation of the crude mixture or aqueous bicarbonate quenching followed by extraction[19]). Changes in the nature of the base (such as Et_3N or DIEA) or solvent (THF) resulted in a complex mixture of products. When pyridine was used in place of DTBMP in CH_2Cl_2, the pyridinium salt **7** was formed as a major compound along with **6** (determined by high-resolution mass spectrometry and NMR analysis of the crude mixture). Attempts to carry out in situ displacement in the crude triflation reaction with the lithium salt of diethyl difluoromethylphosphonate[14] failed.

On the basis on the product distribution that we obtained depending on triflation conditions, a plausible reaction mechanism for the formation of **6** is proposed (Scheme 3). After the 5′-*O*-triflate (intermediate A) is formed, it might be converted to the N-7 isomer (intermediate B) by an intermolecular reaction. This N-adduct results in the decrease of π-electron density at C-8,[18d] thus allowing attack of the 5′-oxygen to provide the cyclonucleoside **6**. Another possibility is the direct N-triflation of **4** into intermediate B; however, the formation of the 5′-chloride **5** and 5′-pyridinium salt **7** cannot be explained on the basis of intermediate B alone. The observed stereoselectivity of the cyclization can be explained by electronic repulsion between the 5′-oxygen and the 4′-oxygen of the furanose ring, which drives the nucleophilic attack at the C8-position exclusively in the (*R*) configuration.

To further study the cyclonucleoside formation, we next considered alternative protecting groups for the ribose moiety. The N-3 of purine nucleosides is well known to readily displace 5′-activating groups (e.g., tosyl, mesyl, iodo, *O*-sulfonamide), yielding N^3,5′-anhydronucleoside salts.[20] We assumed that the presence in **4** of a chlorine atom at the 6-position of the purine contributed to the reduction in nucleophilicity of N-3 and prevented N^3,5′-O-cyclization, as previously reported for acylation of the N6 amino group in adenosine derivatives.[21] Additionally, the replacement of 2′,3′-*O*-