Short Note

O6-[2′,3′-O-Isopropylidene-5′-O-′butyldimethylsilyl)penty]-5′-O-′butyldiphenylsilyl-2′,3′-O-isopropylideneinosine

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Abstract: Cyclic adenosine diphosphate ribose (cADPR) is a cyclic nucleotide involved in the Ca2+ homeostasis. In its structure, the northern ribose, bonded to adenosine through an N1 glycosidic bond, is connected to the southern ribose through a pyrophosphate bridge. Due to the chemical instability at the N1 glycosidic bond, new bioactive cADPR derivatives have been synthesized. One of the most interesting analogues is the cyclic inosine diphosphate ribose (cIDPR), in which the hypoxanthine replaced adenosine. The efforts for synthesizing new linear and cyclic northern ribose modified cIDPR analogues led us to study in detail the inosine N1 alkylation reaction. In the last few years, we have produced new flexible cIDPR analogues, where the northern ribose has been replaced by alkyl chains. With the aim to obtain the closest flexible cIDPR analogue, we have attached to the inosine N1 position a 2′,3′-dihydroxypentyl chain, possessing the two OH groups in a ribose-like fashion. The inosine alkylation reaction afforded also the O6-alkylated regiosomer, which could be a useful intermediate for the construction of new kinds of cADPR mimics.

Keywords: cADPR; nucleosides; nucleotides; inosine; alkylation; calcium mobilization; ryanodine receptor; primary cortical neurons

1. Introduction

The design and synthesis of new nucleoside and nucleotide analogues is a frontier theme in light of the current SARS-CoV-2 pandemic that the world is facing [1]. However, apart from being employed in medicinal chemistry both as antiviral [2] and antitumor drugs [3], nucleosides, nucleotides, and their analogues can be also used as probes in the signaling pathways [4–6]. Cyclic nucleotides are important second messengers involved in signal transduction [7,8]. Among them, cADPR (1, Figure 1), an 18-membered cyclic nucleotide firstly isolated from sea urchin egg extracts [9], elicits Ca2+ ions from the endoplasmic reticulum (ER) to cytosol through the ryanodine receptor (RyR) in several cellular systems [10]. Alterations in the cADPR biosynthesis and calcium homeostasis can play pathological roles in diabetes, airway hyper-responsiveness and autism [11]. Unfortunately, the chemical instability at the N1 glycosidic bond in physiological conditions...
hampered the definition of cADPR molecular mechanism of action [12]. In this frame, efforts have been devoted to the synthesis of stable cADPR analogues [13–16]. In particular, the replacement of the adenine with hypoxanthine generated the very stable cIDPR analogue 2, which retained the same Ca\(^{2+}\) mobilizing activity of the endogenous metabolite [17]. In the last few years, we have produced both in solution [18–21] and on solid phase [22,23] some cIDPR analogues with alkyl chains in the place of the northern ribose (3–7). As we have found a promising Ca\(^{2+}\) mobilizing activity in the derivative with a pentyl chain (6, \(n = 4\)) in a neuronal cellular model [18], we have recently prepared a new flexible cIDPR analogue (8), with a 2″,3″-dihydroxypentyl chain replacing the northern ribose [21].

![Diagram of cADPR and cIDPR analogues](image_url)

**Figure 1.** The structures of cADPR (1), cIDPR (2) and their analogues (3–8).

As the last mimic possesses the two OH groups in a ribose-like fashion, it may be considered the closest cIDPR flexible analogue. Interestingly, the cyclic compound 8 induced a concentration-dependent increase in [Ca\(^{2+}\)]\(_i\) when perfused to primary cortical neurons as efficiently as cADPR.

Since 6-substituted purine nucleosides displayed interesting biological activities [24–26], herein we report on the synthesis and characterization of the O6-alkylated compound 9, obtained as a side product during the coupling reaction of the protected inosine 10 and the tosylate 11 (Scheme 1). That reaction was revealed to be fundamental for the construction of the new cyclic analogue (8) scaffold.
Scheme 1. Reagents and conditions: (i) 11, DBU, DMF, 80 °C, 12 h (entry 6, Table 1).

Table 1. Optimization of the reaction between 10 and 11.¹

| Entry | Base           | Equivalents² | Temperature (°C) | Yield (%) | 9:12 |
|-------|----------------|--------------|------------------|-----------|------|
| 1     | K₂CO₃          | 1 or 3       | r.t.             | No reaction | -    |
| 2     | K₂CO₃          | 3            | 80               | 10        | 20:80|
| 3     | Triethylamine  | 1 or 3       | r.t.             | No reaction | -    |
| 4     | Triethylamine  | 3            | 80               | No reaction | -    |
| 5     | DBU            | 1 or 3       | r.t.             | No reaction | -    |
| 6     | DBU            | 3            | 80               | 70        | 30:70|
| 7     | DBU            | 3            | 120              | 30        | 60:40|

¹ All the reactions were carried out in anhydrous N,N-dimethylformamide (DMF) as solvent. ² Calculated from 10.

2. Results and Discussion

Scheme 1 shows the convergent synthetic approach that we have used for the preparation of the cyclic compound 8. The ribose-protected inosine 10, after reaction with the tosylate 11, afforded as the main product the N1-alkylated derivative 12. The electrophile 11 was prepared as a racemic mixture starting from the commercially available propargyl alcohol 13 with an overall 63% yield [21].

To obtain the target compound 8, we used the well-known Hata protocol, which required an I₂ mediated cyclopyrophosphorylation reaction among a phosphomonoester and a phosphorothioate [14]. As a TBDMS group could be selectively removed in the presence of a TBDPS group [27], we followed the synthetic sequence reported in Scheme 1,
and compound 14 was readily obtained. The two phosphates in 14 were then deprotected to give the key intermediate 17. The pyrophosphate bond formation was carried out by adding compound 17 through a syringe pump to a very diluted solution of Li2. The cyclic compound was isolated from a complex reaction mixture and finally deprotected from both the acetondes, affording the new cADPR analogue 8 with an overall 1% yield.

The reaction between the protected inosine 10 with the electrophile 11 has been studied in detail. In principle, as hypoxanthine is an ambident nucleophile [28] at the N1 and O6 purine positions [29,30], the two regioisomers 12 and 9 could be expected. In our studies focused on the inosine N1 functionalization, we discovered that the Mitsunobu reaction was not a good method to regioselectivity obtain the N1-alkylated isomer. In fact, the reaction of inosine with di-tert-butyl (5-hydroxypentyl)phosphonate in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh3) afforded mainly the O6-alkylated regioisomer. We attributed the observed regioselectivity to the hard–hard interaction between the alkoxy-phosphonium cation intermediate and the nucleobase O6 atom [19]. On the other hand, previous findings demonstrated that inosine could be efficiently alkylated at the N1 purine position at room temperature (r.t.) when a soft electrophile was used [31]. Unfortunately, all the attempts to transform both the tosylate 11 and its primary alcohol precursor into the iodide derivative proceeded with very unsatisfactory yields [21]. As literature data reported on the efficient nucleophilic mediated displacement of a tosylate flanked by an isopropylidene under mild conditions [32,33], we reacted the inosine derivative 10 with the electrophile 11 at r.t. in the presence of some bases (Table 1); unfortunately, no reaction took place. By increasing the temperature, we noted on TLC (petroleum ether/AcOEt, 6:4) the formation of two spots. 1D/2D NMR analyses of the purified compounds (see Supplementary Materials) allowed to assign the N1-alkylated inosine 12 to the spot with Rf = 0.10, whereas the O6-alkylated inosine 9 to that with Rf = 0.50. In detail, in the 1H NMR spectrum of compound 12 the two 1”-H protons resonated as two doublets of doublets centered at 4.70 and 4.66 ppm and correlated with their carbon atom resonating around 47.7 ppm. The HMBC correlation between the purine 2-H and the C1” carbon atom supported the structure 12 [21]. Conversely, in the 1H NMR spectrum of compound 9 (Figure S1, Supplementary Materials) the 1”-H protons resonated in the range 4.68–4.54 ppm and correlated with their carbon atom resonating at 65.6 ppm (Figure S4). The HMBC correlation between the two 1”-H protons and the C6 purine carbon atom resonating at 160.3 ppm and the absence of HMBC correlation between the purine 2-H (8.43 ppm) and the C1” carbon atom supported the structure 9 (Figure S5).

Careful tuning of the reaction conditions allowed to recover the N1-alkylated regioisomer 12 as the main product. In particular, 3.0 equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 80 °C for 12 h were the best conditions to recover the N1 and O6 regioisomers with a good 70% yield in a 7:3 ratio. (Scheme 2 and Table 1) Higher temperatures were detrimental to the reaction yield and increased the ratio 9:12. The last experimental evidence could be explained assuming that compound 9 is the thermodynamic regioisomer.

Scheme 2. The reaction of the nucleoside 10 with the tosylate 11.
3. Materials and Methods

All the reagents and solvents were commercially available and used without further purification. 1H- and 13C-NMR spectra were acquired on the Bruker Avance 600 MHz spectrometer (Bruker-Biospin, Billerica, MA, USA) using CDCl3 as solvent. NMR chemical shifts are reported in parts per million (δ) relative to residual solvents signals: CHCl3 7.26 for 1H-NMR and CDCl3 77.0, for 13C-NMR. The 1H NMR chemical shifts were assigned through 2D NMR experiments. The NMR spectra were processed with the MestReNova (Mestrelab Research, Santiago de Campostela, Spain) suite. The HRESI-MS spectra were acquired on a Thermo Orbitrap XL mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). Column chromatography was carried out on silica gel-60 (Merck, Readington Township, NJ, USA, 0.063–0.200 mm). TLC analyses were carried out on F254 silica gel plates (0.2 mm thick, Merck). TLC spots were detected under UV light (254 nm).

The crude product was purified over a silica gel column eluted with increasing amounts of AcOEt/ether/AcOEt, 6:4). The mixture was cooled, and the solvents removed under reduced pressure. The product was purified over a silica gel column eluted with increasing amounts of AcOEt in petroleum ether (up to 20%), giving the pure 9 as a 1:1 mixture of diastereomers (RF = 0.50). Colorless syrup (21% yield). 1H NMR (600 MHz, CD3OD) δ 8.43 (s, 1H, 2-H), 8.42 (s, 1H, 2-H), 8.07 (s, 1H, 8-H), 7.62–7.54 (complex signal, 8H, arom.), 7.43–7.25 (complex signal, 12H, arom.), 6.15 (d, J = 1.7 Hz, 2H, 2 × 1'H), 5.32–5.28 (m, 2H, 2 × 2'-H), 4.98–4.95 (m, 2H, 2 × 3'-H), 4.68–4.62 (m, 2H, 2 × 1''H), 4.61–4.54 (complex signal, 4H, 2 × 1''H, and 2 × 2''H), 4.49–4.43 (m, 2H, 2 × 3''-H), 4.42–4.38 (m, 2H, 2 × 4'-H), 3.92–3.85 (m, 2H, 2 × 5'-H), 3.83–3.74 (complex signal, 6H, 2 × 5''-H, and 2 × 5''-H), 1.97–1.89 (m, 2H, 2 × 4''-H), 1.85–1.75 (m, 2H, 2 × 4''-H), 1.62 (s, 6H, 2 × CH3 acetone), 1.48 (s, 6H, 2 × CH3 acetone), 1.37 (t, two overlapped singlets, 12H, 4 × CH3 acetone), 1.01 (two overlapped singlets, 18H, 2 × t-Bu), 0.88 (s, 18H, 2 × t-Bu), 0.04 (s, 6H, 2 × SiCH3), 0.05 (s, 6H, 2 × SiCH3). 13C NMR (151 MHz, CDCl3) δ 16032 (2 × C6), 15210 (C2), 15208 (C2), 15145 (C4), 15144 (C4), 15141 (C8), 14098 (C8), 13549, 13547, 13282, 13280, 13269, 12985, 12774, 12769, 12762, 12205 (2 × C5), 11434 (Cq ribose acetonide) 11433 (Cq ribose acetonide), 10837 (2 × Cq acetonide), 9119 (C1), 9117 (C1), 8702 (C4), 8697 (C4), 8440 (C2), 8436 (C2), 8136 (C3), 8135 (C3), 7514 (C2), 7512 (C2), 7371 (C3), 7370 (C3), 6560 (2 × C1”), 6385 (2 × C5”), 6002 (C5”), 6000 (C5”), 3216 (C4”), 3214 (C4”), 2966, 2819, 2817, 2719, 2681, 2591, 2586, 2558, 2535, 1915, 1830, –539, –544. HRESI-MS m/z 819.4184, ([M + H]+) calcd. for C45H63N3O9Si2 819.4191.

4. Conclusions

Purine bases and nucleosides carrying O-, N- and C-substituents at the C6 position represent an important class of compounds endowed with important biological activities. These compounds are generally prepared by nucleophilic aromatic (SNAr) substitutions, [34] metal-mediated cross-coupling reactions [35,36] and by Grignard’s reagents addition [26] to 6-halopurine ribosides. In our search of new cADPR analogues, we have obtained the O6-alkylated inosine 9 as a side product during the S2O2 reaction between the nucleoside 10 and the tosylate 11. The O6 reactivity of the ambient nucleophile hypoxanthine in 10 was a consequence of the high temperature necessary to perform the coupling reaction. Product 9 is an interesting intermediate that will be exploited for the synthesis of unprecedented O6-substituted cADPR derivatives.

Supplementary Materials: The following are available online. Figures S1–S6: copies of 1H-, 13C-NMR, COSY, HSQC, HMBC and HRESI-MS spectra of compound 9.

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