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Synthesis of 5′-functionalized adenosine: suppression of cyclonucleoside formation

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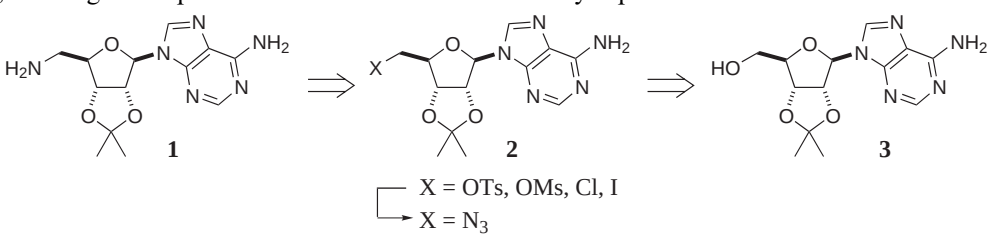
Abstract—A new method of preparation for 5′-amino-2′,3′-isopropylidene adenosine **1**, an important precursor to many adenosine derivatives, is described. This procedure suppresses the undesired intramolecular cyclization and does not require chemical protection of the exocyclic amino group of the adenine ring. The use of a 5′-phophate triester activating group is representative of natural biological substitution at this position, which likely contributes to its greater stability and selective reactivity. This sequence is efficient and should allow easy access to compounds of type **1** in high yield.

Functional group transformation at the 5′-carbon of nucleosides is an important aspect of nucleoside derivatizations for the study of biological systems. The need for efficient functionalization at this position is heightened by growing recognition that binding specificity for nucleotide binding pockets can be ascribed to binding interactions in the phosphate recognition site.[1]

Amine-nucleoside **1**, a 5′-transformed analogue of 2′,3′-isopropylidene adenosine **3**, is a useful precursor for many adenosine derivatives. Several syntheses of **1** have been described, most of which utilize a sulfonate or halide group to activate the 5′-position.[2–4] Subsequent substitution is usually conducted with an azide as the nucleophile, which is then reduced to give amine nucleoside **1**. The yields reported for this sequence are variable, ranging from 14%[2] to 50%,[4] mainly due to the formation of cycloadenosine **4**, which results from the intramolecular nucleophilic substitution by N^3 (Scheme 1). It was reported that, upon rotation of the adenine ring of 5′-activated adenosine, the N^3 of the base can readily displace the 5′-activation to give the ionic cycloadenosine, causing a steep decrease of the overall yield of **1**.[5] In fact, intramolecular displacement of sulfonate is so rapid that it interferes with product isolation and purification. Numerous reports have provided solutions to the problem of undesired cyclonucleoside formation, all of which involve electron-density reduction on the base by protecting either the N^6 (**5**)[6] or the N^1 (**6**)[7] with electron withdrawing groups. This unfortunately increases the synthesis of **1** to a five-step sequence. In the course of our investigation of the synthesis of 5′-functionalized adenosine derivatives we have found an alternative biomimetic approach that does not lead to intramolecular cyclization or require additional protection steps. Herein, we report a new and efficient preparation of **1**, via a phosphate triester intermediate, in a three-step sequence with 75% overall isolated yield.

In order to facilitate a more efficient strategy for the synthesis of amino-nucleoside **1**, we investigated 5′-modified nucleosides with various leaving groups. Phosphate triester modified 5′-diphenylphosphate-5′-deoxy-2′,3′-isopropylidene adenosine **7** has been previously reported.[8] Based on the described synthesis, using



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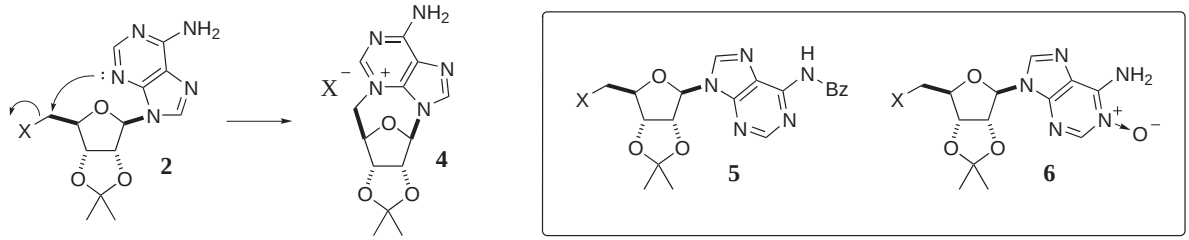
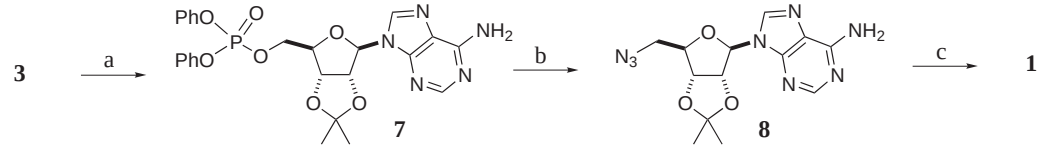


Scheme 1. Mechanism of cyclonucleoside formation and suppression strategies.



Scheme 2. Reagents and conditions: (a) DPPA, DBU, *p*-dioxane, rt, quantitative; (b) NaN_3, cat. tetrabutylammonium iodide, cat. 15-crown-5, refluxing *p*-dioxane, 90%; (c) triphenylphosphine, pyridine/NH_4OH, 1:1, rt, 84%.

phosphonic acid under Mitsunobu-like conditions, we found that **3** was sufficiently reactive toward diphenyl phosphoryl azide (DPPA) in the presence of DBU,[9] to give **8** in excellent yield (Scheme 2).[6] Surprisingly, the phosphate triester **7** was not sufficiently reactive, even in refluxing THF, to facilitate any intramolecular substitution at the 5′-position. After investigating a variety of reaction conditions, it was found that using *p*-dioxane under refluxing conditions (110°C), with the addition of excess sodium azide, 15-crown-5 and a catalytic amount (10 mol%) of tetrabutylammonium chloride, **8** could be formed in nearly quantitative yield.

To further simplify the synthetic sequence, formation of phosphate triester **7** was examined in *p*-dioxane and found to be a suitable solvent for the Mitsunobu-like reaction. This modification allows the synthesis of **8** in a two-step, one-pot procedure without the need to isolate intermediate **7**.[10] Staudinger reduction[11] of azide **8** proceeds efficiently to give **1**, which can be readily purified by flash chromatography on a silica gel column.

The enhanced selectivity of **7** for intermolecular azide displacement over intramolecular cyclonucleoside formation is intriguing and may be due to the relative leaving group abilities of sulfonates and phosphates. While the phosphate triester does exhibit a lower reactivity toward nucleophilic substitution than the sulfonate, presumably due to electronic differences, the resistance toward intramolecular reactivity could also be due to a steric or stereoelectronic conformational restriction. We are currently investigating the generality of this approach for the synthesis of additional 5′-modified nucleosides of both natural and unnatural origin.

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10. In a typical experiment, **3** (307 mg, 1 mmol) was suspended, with magnetic agitation, in dry *p*-dioxane (0.2 M) at room temperature under a nitrogen atmosphere. DPPA (0.43 mL, 2 mmol) and DBU (0.45 mL, 3 mmol) were then added in a dropwise fashion and stirring was continued for 3 h. After addition of sodium azide (325 mg, 5 mmol), tetrabutylammonium iodide (37 mg, 0.1 mmol) and 15-crown-5 (20 μL, 0.1 mmol), the reaction mixture was refluxed for 3–5 h. Purification by flash chromatography gave **8** as a white solid (300 mg, 90% yield).
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