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A practical synthesis of archaeosine and its base

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ABSTRACT

A practical synthetic route to 7-formamidino-7-deazaguanosine (archaeosine), a hypermodified nucleoside observed in archaeal tRNA, has been developed, which involves the addition of hydroxylamine to the cyano group of 7-cyano-7-deazaguanosine ($preQ_0$-nucleoside) and a subsequent Pd-catalyzed hydrogenation. $PreQ_0$-nucleoside was obtained from an optimized β-selective glycosylation developed by Hocek et al. The corresponding archaeosine base was subsequently synthesized in high yield from its precursor 7-cyano-7-deazaguanine ($preQ_0$).

1. Introduction

7-Formamidino-7-deazaguanosine (archaeosine or G^+; Fig. 1) is a hypermodified nucleoside located at position 15 of archaeal tRNA [1,2]. Since its first appearance in the literature in 1982 [1a], this unique nucleoside has been extensively studied, and its biosynthetic pathways and functions have been gradually uncovered [3]. However, there are still many aspects that remain to be elucidated. For example, G^+ is considered to stabilize the three-dimensional structure of tRNA, but the mechanism of stabilization has not yet been fully clarified [3b]. Chemically synthesized G^+ and oligonucleotides that contain G^+ should thus represent useful tools to investigate its functions in detail.

To date, three reports on the chemical synthesis of G^+ have been published [1b,4]. McCloskey et al. have synthesized G^+ in 31% yield from 7-cyano-7-deazaguanosine ($preQ_0$-nucleoside) by the addition of NH_3 to the 7-cyano group in the presence of a catalytic amount of NH_4Cl in liquid NH_3 at ~100 °C. The total synthesis was achieved in seven steps from 7-cyano-7-deazaadenosine (toyocamycin) to G^+ with an overall yield of 0.7% [1b]. Carell et al. have reported the synthesis of G^+ via the addition of MeOH to the 7-cyano group of $preQ_0$-nucleoside under acidic conditions and subsequent nucleophilic substitution by methanolic ammonia (Pinner reaction [5]) in 30% yield (eight steps from 2,6-diaminopyrimidin-4-one; 0.8% overall yield) [4a]. These authors have also reported another synthesis of G^+, in which a protected $preQ_0$-nucleoside was subjected to Pinner conditions for the simultaneous formation of the 7-formamidine group and the global deprotection to generate G^+ in 40% yield (eight steps from 2,6-diaminopyrimidin-4-one; 2.4% overall yield) [4b].

Despite their success, these studies also show two challenges that remain to be resolved for a more efficient total synthesis of G^+: i) the inefficient generation of the 7-formamidine group, for which neither the direct addition of NH_3 [1b] nor the Pinner reaction is effective [4]; ii) the low yield of the glycosylation for the preparation of $preQ_0$-nucleoside, which is the synthetic precursor of G^+. $PreQ_0$-nucleoside has been synthesized in low to modest yields by Lewis-acid- or Brønsted-base-promoted glycosylations between the corresponding ribose moiety and $preQ_0$ or some other 7-deazaguanine derivatives with appropriate protecting groups

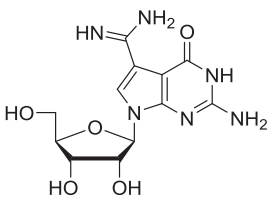

Fig. 1. Chemical structure of archaeosine.

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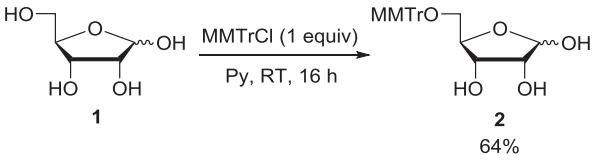


Scheme 1. Synthesis of glycosyl donor **2**.

[4,6]. Although the glycosylation step can be circumvented by using toyocamycin as the starting material, the latter is an expensive natural product and its conversion to preQ$_0$-nucleoside requires multiple steps [1b,7].

We anticipated that the conversion of the 7-cyano group into the 7-formamidine group could possibly be carried out more smoothly via an *N*-hydroxyformamidino intermediate, which can be obtained from the addition of hydroxylamine. This strategy has previously been applied to the synthesis of 7-formamidino-7-deazaadenosine and 7-formamidino-7-deazainosine [8], but not to the synthesis of G$^+$ [9]. We also considered that the synthesis of preQ$_0$-nucleoside should be achieved more efficiently by applying a modified Mitsunobu reaction, which has recently been reported by Hocek et al. [10] This reaction is completely β-selective and proceeds under nearly neutral conditions so that any potential undesired acid- or base-promoted side reactions can be suppressed.

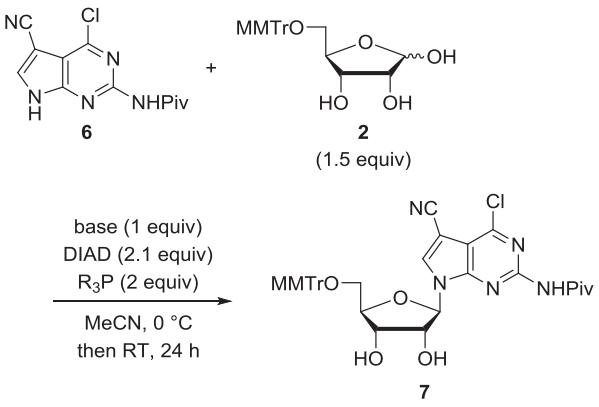
2. Results and discussion

2.1. Synthesis of preQ$_0$-nucleoside and archaeosine

Initially, we investigated the synthesis of preQ$_0$-nucleoside. The corresponding glycosyl donor and acceptor for the glycosylation were synthesized according to Schemes 1 and 2, respectively. The primary hydroxy group of ribose **1** was selectively protected with a monomethoxytrityl (MMTr) group to give **2** (Scheme 1) [10]. PreQ$_0$ **4** [11] was synthesized from 2,6-diaminopyrimidin-4-one and converted into an appropriately protected derivative (**6**) [10a] according to a literature procedure [4a] (Scheme 2).

Then, we studied the glycosylation between **2** and **6** (Table 1). A direct application of the reaction conditions reported by Hocek *at al.* using DBU, DIAD, and Bu$_3$P[10a] afforded the desired product (**7**) in 50% yield (entry 1). Upon screening phosphines and tertiary amines, we discovered that the yield of **7** significantly improved (89%) when DBU was replaced with *N*,*N*-diisopropylethylamine

Table 1
Synthesis of **7** via a Mitsunobu reaction.



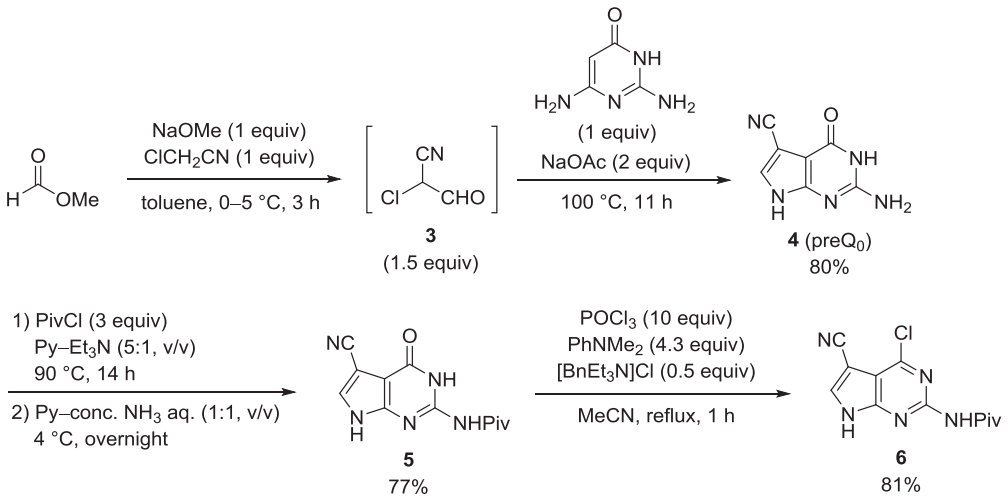
entry	base	R_3P	yield (%)
1	DBU	Bu_3P	50
2	*i*-Pr_2NEt	Bu_3P	89
3[a]	*i*-Pr_2NEt	Bu_3P	78
4	Et_3N	Bu_3P	85
5	2,6-lutidine	Bu_3P	76
6	*i*-Pr_2NEt	$MePPh_2$	66
7	*i*-Pr_2NEt	$Ph_2PCH_2CH_2PPh_2$[b]	51
8	*i*-Pr_2NEt	Ph_3P	55

[a] **2** (1.2 equiv), DIAD (1.5 equiv), and Bu_3P (1.5 equiv).
[b] 1 equiv.

(entry 2). Reducing the amount of **2** from 1.5 equiv to 1.2 equiv decreased the yield of **7** from 89% to 78% (entry 3). Bases weaker than *N*,*N*-diisopropylethylamine, such as triethylamine and 2,6-lutidine, furnished **7** in lower yield (76%–85%, entries 4 and 5). More electron-deficient phosphines than Bu_3P also resulted in the less efficient formation of **7** (51%–66%, entries 6–8).

As the protected preQ$_0$-nucleoside **7** was obtained in high yield, we attempted to deprotect **7** to obtain preQ$_0$-nucleoside. For that purpose, we tried to hydrolyze the 6-chloro group by applying the conditions of a DABCO-promoted [4a,12] hydrolysis (Scheme 3). However, the desired product (**8**) was not produced, presumably due to the robustness of the 6-chloro group.

Therefore, we synthesized the preQ$_0$ derivative **10**, which



Scheme 2. Synthesis of glycosyl acceptor **6**.