Chemoselective Staudinger Strategy in the Practical, Fit for Purpose, Gram-Scale Synthesis of an HCV RNA Polymerase Inhibitor

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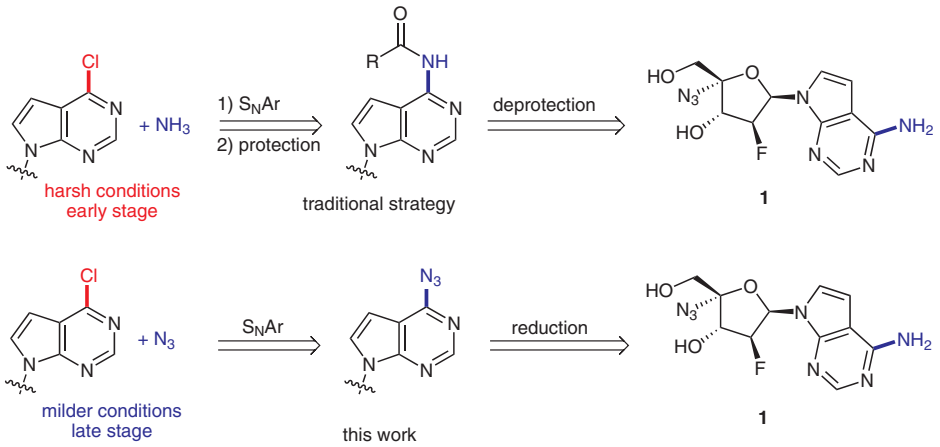
Abstract: The use of a late-stage selective Staudinger reaction in the preparation of the novel HCV RNA polymerase inhibitor is described.

Key words: Staudigner, nucleoside, 7-deaza-adenosine, azide, HCV NS5B

7-Deaza-adenosines are a unique class of nucleosides which have received considerable attention due to their interesting biological activity as inhibitors of HCV RNA polymerase (NS5B).[1,2] Inhibitors of this enzyme block HCV replication, making NS5B a crucial target in the development of novel anti-HCV therapies.[3] The main available building block to synthesize 7-deaza-adenosine are based on 6-chloro-7-deazapurine which can be conveniently appended onto any carbohydrate derivative using conventional anomeric center displacement chemistry. Traditional methodology used to introduce the required 6-amino functionality relies on S_NAr reaction with ammonia (Scheme 1). Because the reaction conditions required for this step are harsh (>85 ºC using a large excess of ammonia), this step is usually performed at an early stage of a synthetic sequence in order to minimize side reactions and starting material decomposition. It is therefore necessary to protect the amino functionality during the remaining steps of the sequence until it is to be unveiled, usually in the final step. Methods relying on milder reaction conditions would therefore allow for late-stage introduction of this amine and circumvention of problems often associated with a protecting group strategy.

In the context of our discovery colleagues' efforts in the development of an NS5B inhibitor,[4] we were faced with the problem of developing a practical and efficient synthesis of compound **1** which would allow for its preparation on gram-scale. The synthesis posed several synthetic challenges resulting from the use of a deaza-adenine base and a 4′-azido 2′-fluoroarabinose core. Herein we describe the multigram synthesis of **1** via late-stage introduction of the 4-amino group via a mild S_NAr reaction of NaN_3 followed by a chemoselective Staudinger reduction.[5]

Initially, **1** was prepared using the discovery route outlined in Scheme 2.[4] The key features of this route were the formation of vinyl ether **7** through a sequence of six transformations from the fluoro-arabinose derivative **2**. The 6-amino functionality was installed via an S_NAr reaction with ammonia on the sensitive vinyl ether precursor. Unavoidable substrate decomposition and the necessity for the use of a pivaloyl protecting group (which needed to be removed in the final step of the synthesis) resulted in poor overall yield (<0.1%). Installation of the key 4′-azido functionality was achieved using epoxidation with DMDO and Lewis acid enabled ring opening with $TMSN_3$.[6] Final deprotection and HPLC purification completed the end game.



Scheme 1 Strategies for the installation of the 6-amino functionality of 7-deaza-adenosine

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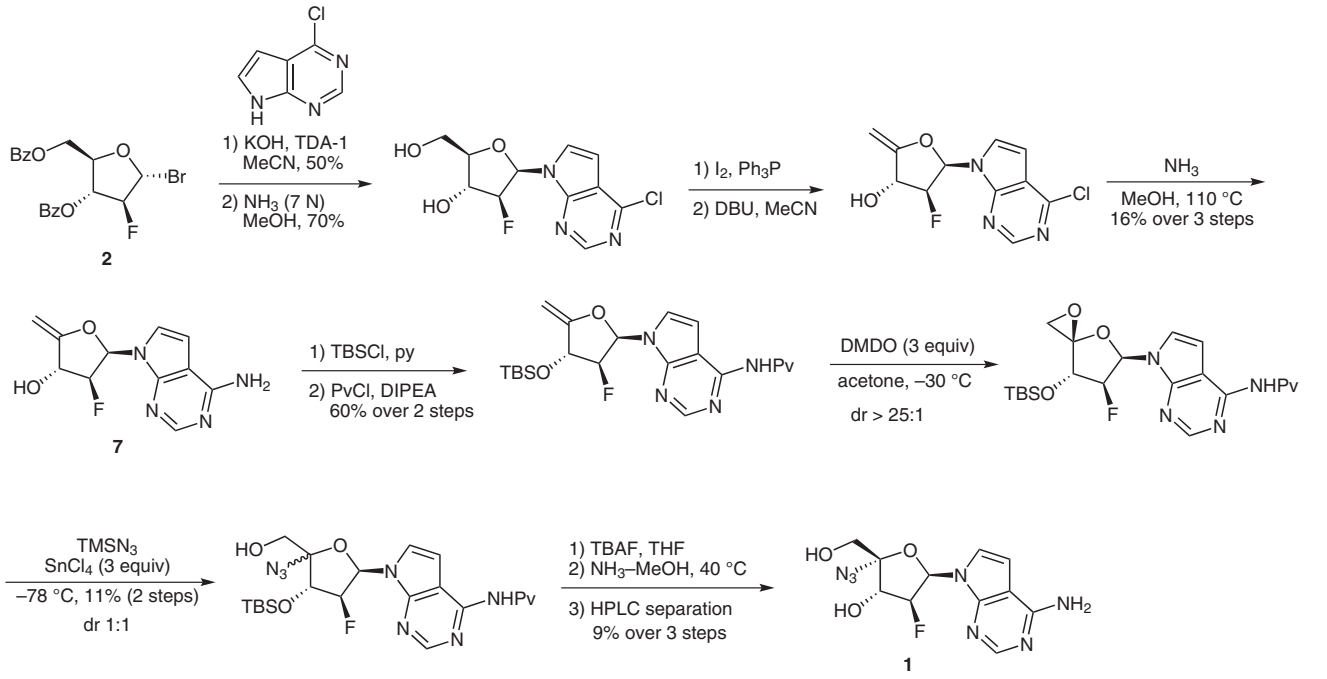
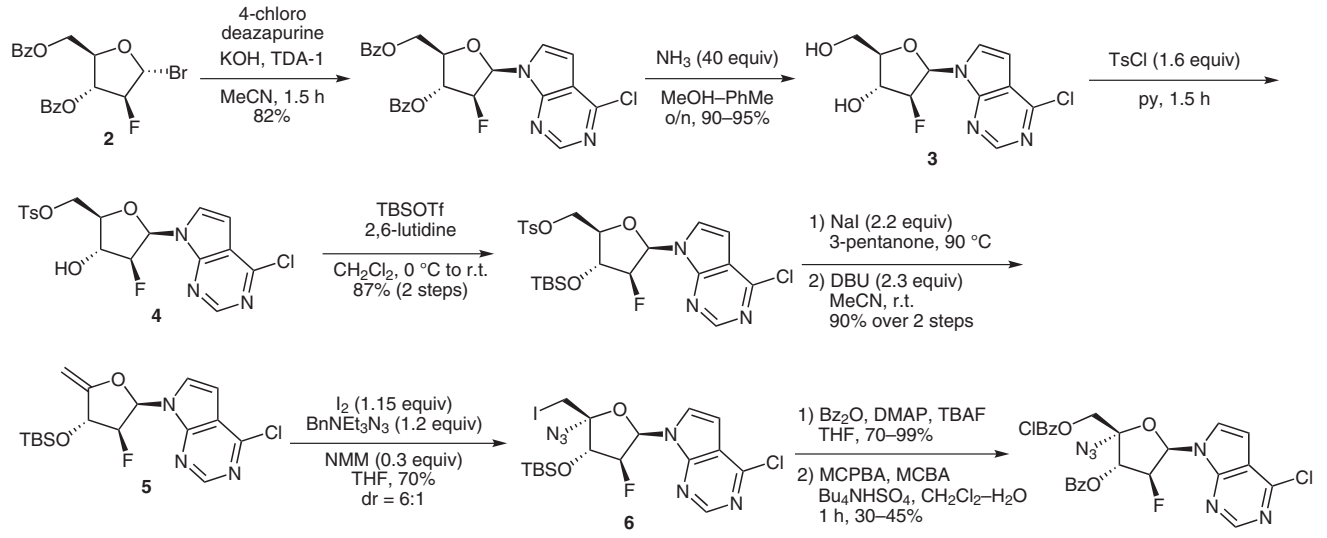


Scheme 2 Discovery route for the synthesis of **1**

To realize our objective, several key areas for optimization were identified. First, we envisioned the replacement of the early stage introduction of the 6-amino functionality to the 7-deazapurine ring with a later stage alternative using milder conditions. This would preclude the need for a protection–deprotection strategy for the 6-amino group. Second, DMDO oxidation would need to be replaced with a more scalable alternative. Finally, the introduction of the azide at C4′ led to 50% loss of this advanced intermediate due to the lack of selectivity observed for this transformation. A more diastereoselective approach would therefore be desirable.

We began our investigation with the S_N2 reaction of 4-chloro deazapurine with bromide **2** (Scheme 3). We found that the low yield in the discovery route was a result of competing saponification of the benzoyl protecting groups. With careful monitoring of the reaction, we were able to achieve high conversion to the desired product with minimal attendant hydrolysis. The crude product could then be deprotected using ammonia in methanol. Activation of the primary alcohol with MsCl–Et_3N resulted in the formation of a significant amount of bismesylate. On the other hand, diol **3** could be selectively activated with TsCl at the primary position. This simple alternative allowed us to avoid the use of Ph_3P/I_2 which complicated purification of the activated species. We sought to use tosylate **4** directly in the elimination reaction but were surprised to find it was quite stable and no conversion to the vinyl ether was observed. Finkelstein displacement of the tosylate group with NaI also proved difficult with only



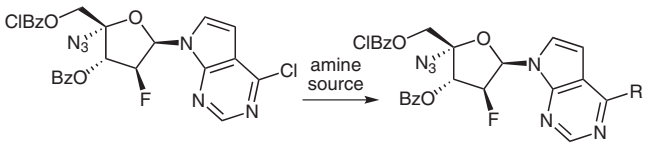
Scheme 3 Elaboration of 4′-azido core

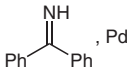
85% conversion achieved after several days at 40 °C in acetone.[7] Conversely, we investigated the option of installing the TBS protecting group prior to the activation/elimination sequence. The TBS group could be easily installed on tosylate **4** and Finkelstein displacement of this intermediate proceeded cleanly without decomposition in 3-pentanone. The iodide could then be eliminated in two hours to afford vinyl ether **5** in high yield.[8] Overall this key intermediate was prepared in seven steps and 63% yield on 100-g scale (Scheme 3).

Having established a robust and scalable route to vinyl ether **5**, we sought an alternative to the DMDO epoxidation–ring-opening sequence used for the azide installation given the risks associated with synthesizing and using DMDO on scale,[9] as well as the low diastereomeric ratio (dr) observed for the epoxide opening.[10] Inspired by recent patent literature,[11] we investigated the use of an azido-iodination reaction of the electron-rich alkene. Gratifyingly, this provided the expected iodoazide **6** in 70% yield with 6:1 dr in favor of the desired diastereoisomer. Displacement of the iodide using MCPBA was attempted on **6** but resulted in starting material decomposition. A protecting group swap for a benzoyl allowed for the reaction to proceed in modest yield.[11] At this point the diastereoisomers were separated via reverse-phase chromatography.

The final challenge we faced was installation of the 6-amino group (Table 1). As expected S_NAr reactions of amine nucleophiles resulted in significant decomposition of the starting material (entries 1–3). Looking for a milder alternative, Pd-catalyzed cross-coupling using the Buchwald[12] and Hartwig[13] protocols for aniline synthesis resulted in low yield or significant decomposition. The benzoyl protecting groups were, for the most part, unstable to these reactions. However, we found that azide was a good nucleophile in the S_NAr reaction and that this reaction could occur without decomposition affording the bisazide in 83% yield. We envisioned that a selective azide reduction would result in the desired amino group.

Table 1 Strategies for Introduction of 6-Amino Group

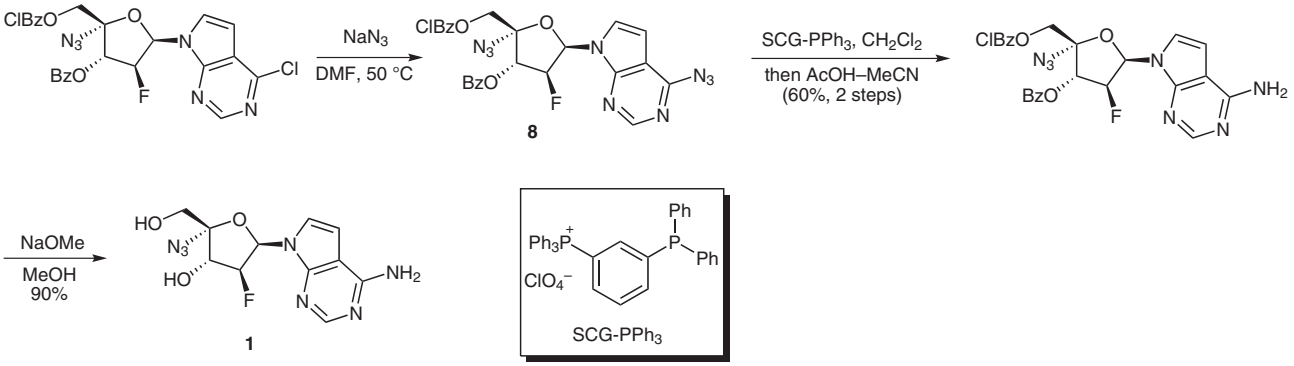


Entry	Amine Source	R	Yield
1	NH_3 in MeOH	NH_2	–
2	NH_3 in dioxane	NH_2	–
3	$BnNH_2$	BnNH	<10%
4	LiHMDS, Pd	NH_2	<10%
5		NH_2	23%
6	NaN_3	N_3	83%

Bisazido **8** was treated under a variety of reduction conditions (Scheme 4).[14] We were gratified to see that Staudinger reaction with PPh_3 occurred at the desired azide.[15,16] The intermediate aminophosphorane was stable and could be observed by HPLC. After complete formation of aminophosphorane was observed, the solvent was then switched to MeCN and treatment with aq 1 M AcOH at 60 °C delivered the free amine.

To simplify the purification process, we opted for the use of the SCG-PPh_3 reagent (Scheme 4) developed by the Charette group.[17] This allowed for easy purification of the penultimate intermediate.[18] Final global deprotection was achieved using sodium methoxide affording **1** in high yield.

Overall, the preparation of **1** was achieved in 12 steps in 9% yield allowing for gram-quantities to be prepared. The present late-stage S_NAr reaction of NaN_3 followed by the selective azide reduction offers a convenient procedure for the installation of the 6-amino group in the presence of the 4′-azido group. The use of this S_NAr–reduction strategy constitutes a powerful alternative to traditional meth-



Scheme 4 4-Amino group installation and end game

ods for the installation of the 6-amino group in 7-deaza-adenosine derivatives. To our knowledge, this is the first example of a selective Staudinger reaction on a nucleoside bearing multiple azido groups.

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(7) At higher temperatures, aromatic Finkelstein displacement of the Cl group was observed and elimination of the alkyl iodide proved sluggish requiring 2 d to proceed to 100% conversion. Increased heating resulted in decomposition of the sensitive vinyl ether product.

(8) The beneficial effect of the large TBS protecting group on reactions at C4′ might result from a preferred conformation alignment. Further mechanistic investigation is ongoing and will be reported in due course.

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