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Rapid Continuous Synthesis of 5′-Deoxyribonucleosides in Flow via Brønsted Acid Catalyzed Glycosylation

Bo Shen and Timothy F. Jamison*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

tfj@mit.edu

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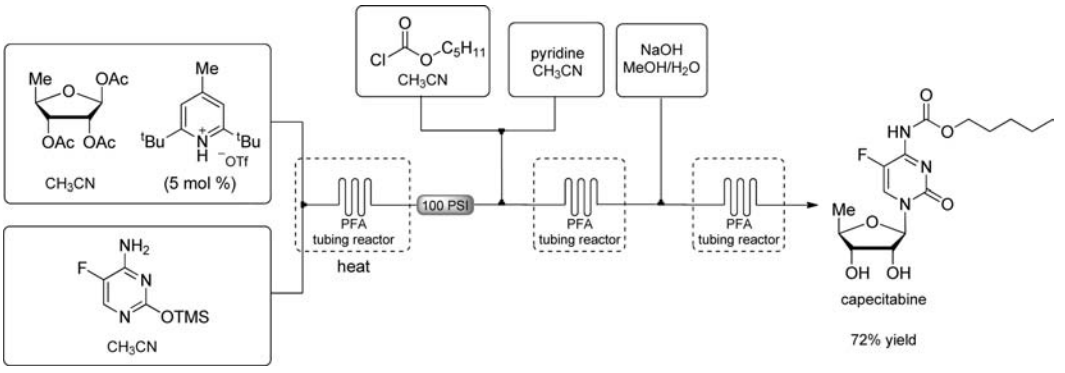
ABSTRACT



A general, green, and efficient Brønsted acid-catalyzed glycosylation serves as a key step in the one-flow, multistep syntheses of several important 5′-deoxyribonucleoside pharmaceuticals.

Compelling biological activities are associated with many deoxynucleosides.[1] Among them, 5′-deoxyribonucleosides, including doxifluridine (**1**), galocitabine (**2**), and capecitabine (**3**) (Figure 1), demonstrate potent antiviral and antitumor effects. In particular, capecitabine is an important drug used for the treatment of breast and colorectal cancers.[2] Syntheses of some specific 5′-deoxyribonucleoside targets have been reported,[3,4] and in all cases the key glycosylation step is effected using the Vorbrüggen modification of the silyl–Hilbert–Johnson reaction.[5,6] This method joins a protected sugar (e.g., **4**) with silylated nitrogenous bases in the presence of a Lewis acid. However, the reaction generally requires several hours and a stoichiometric amount or excess of a Lewis acid, with $SnCl_4$ being the most commonly used. Aqueous workup followed by extraction and separation is required, generating copious amounts of waste. A greener and more

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efficient process for the synthesis of 5′-deoxyribonucleosides is highly desired. Herein we report an efficient synthesis of these valuable 5′-deoxyribonucleosides, a one-flow method that combines two to three steps into a single, telescoped procedure and affords the desired compounds rapidly (typically < 10 min) and in high yields (typically $> 90\%$).

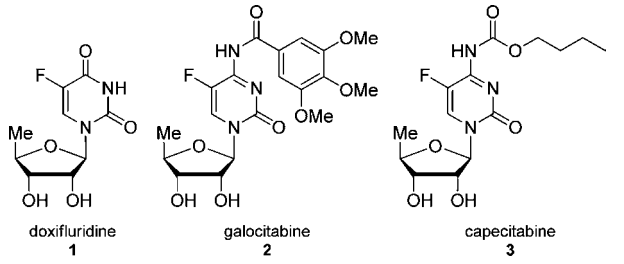
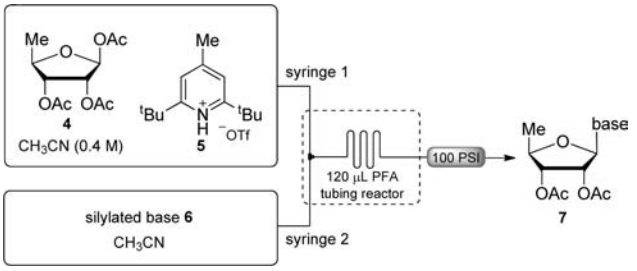


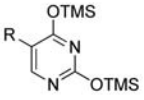
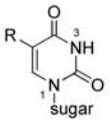
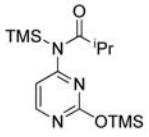
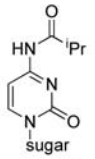
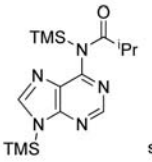
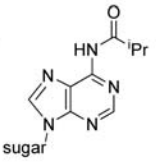
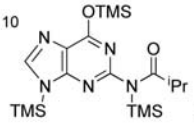
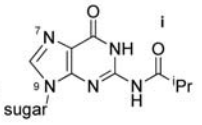
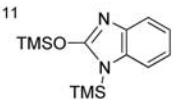
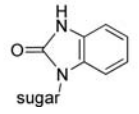
Figure 1. 5′-Deoxyribonucleoside drugs.

Continuous flow synthetic chemistry has emerged as a promising technology in the past decade, offering several advantages over traditional batch processes.[7,8] We recently reported the first organocatalytic method for nucleobase glycosylation, a Brønsted acid-catalyzed C−N bond-forming reaction in flow that provides ribonucleosides in high yields.[9] Pyridinium triflates, e.g., **5**, were found to be the superior catalysts.

We thus began our present study with the glycosylation of silylated thymine **6a** by 5-deoxyribose donor **4**. A syringe pump was used to deliver the solution of the base and the sugar with the catalyst in two syringes. They were mixed in a T-mixer and reacted at an elevated temperature in PFA tubing coils (120 μL) as they flowed. A back pressure regulator (100 psi) was employed to allow reaction temperatures above the boiling point of solvent CH_3CN. We quickly identified that in the presence of 5 mol % of catalyst **5**, the glycosylation of **6a** with 5-deoxyribose **4** was complete at 120 °C in only 5 min, affording 5′-deoxyribonucleoside **7a** in 99% yield and $> 98{:}2$ dr (limit of detection) after purification via column chromatography (Table 1, entry 1). It is worth noting that no

Table 1. Brønsted Acid Catalyzed Glycosylation Reaction in Flow



entry[a]	silylated base **6**	product **7**	R	temp (°C)	t_r (min)	yield (%)[b]
1			**a** CH_3	120	5	99 (0)
2			**b** F	100	5	55 (20)
3			**b** F	80	8	92 (6)
4[c]			**c** H	80	12	89 (5)
5			**d** I	100	1	96 (0)
6			**e** NO_2	100	3	92 (3)
7			**f** CF_3	100	1	96 (0)
8[c]			**g**	90	20	86 (5)
9			**h**	120	5	94 (0)
10			**i**	120	5	96 (0)[d]
11			**j**	100	4	88 (0)

[a] All reactions were performed using 1 equiv of sugar **4**, 1.1−2 equiv of silylated base **6**, and 5 mol % of catalyst **5**, unless otherwise noted. See the Supporting Information for complete details. [b] Isolated yields. Bisglycosylation product yields in parentheses. [c] 10 mol % of catalyst **5** was used. [d] Mixture of isomers $N9/N7 = 5{:}1$.

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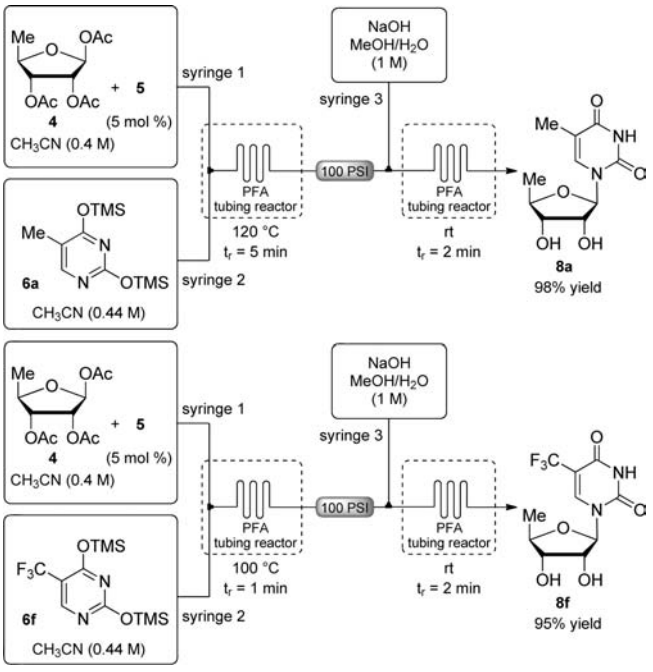
Scheme 1. One-Flow, Two-Step Synthesis of 5′-Deoxyribonucleosides



aqueous workup was necessary, reducing labor, cost, and waste.

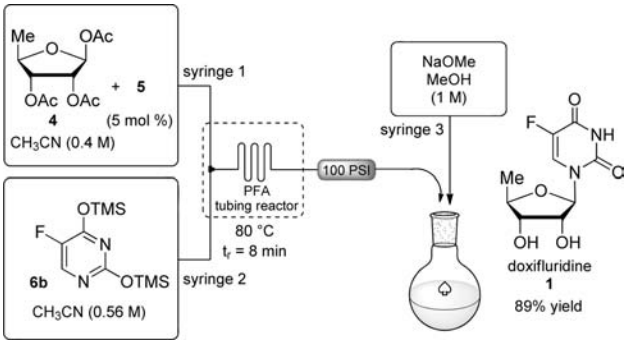
Other pyrimidine derivatives were examined and individually optimized, rapidly (1−12 min) affording desired 5′-deoxynucleosides **7** in high yields (Table 1, entries 3−7). An important trend was observed that merits discussion: nucleophiles bearing electron-withdrawing groups were more reactive, requiring less time and lower temperature (cf. entries 1 vs 7 and 3 vs 4), consistent with our previous study wherein a ribose derivative was used as the glycosyl donor.[9] Smaller nucleophiles tended to give small amounts of *N*1,*N*3-bisglycosylation products (entries 3, 4, 6, and 8). Nevertheless, the formation of the desired monosubstitution product was favored at a lower temperature with extended reaction time (cf. entries 2 vs 3, 55% vs 92% yield, respectively).

This glycosylation method encompasses other silylated bases, such as derivatives of naturally occurring cytosine (**6g**), adenosine (**6h**) and guanine (**6i**), as well as the nonnatural imidazole derivative **6j** (entries 8−11). All were smoothly converted to the corresponding deoxynucleosides in high yield and, as above, > 98:2 dr. In the case of guanine derivative **6i**, a mixture of regioisomers (*N*9/*N*7 = 5:1) was obtained, similar to our previous observations.[9]

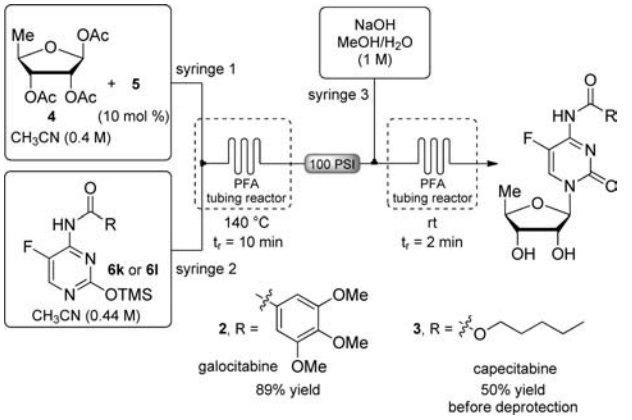
For a reaction with 0.4 M in sugar **4** and residence time of 5 min, using a 120 uL tubing reactor, a throughput of 0.288 mmol/h was obtained (115 mg/h for MW of 400 based on 100% yield). Higher through-put can generally be achieved using reactors with a larger volume and faster flow rate under the same reaction conditions.

Multistep synthesis in flow has emerged as a very effective strategy as it circumvents the need for purifying

Scheme 2. Synthesis of Doxifluridine



Scheme 3. Synthesis of Galocitabine and Capecitabine

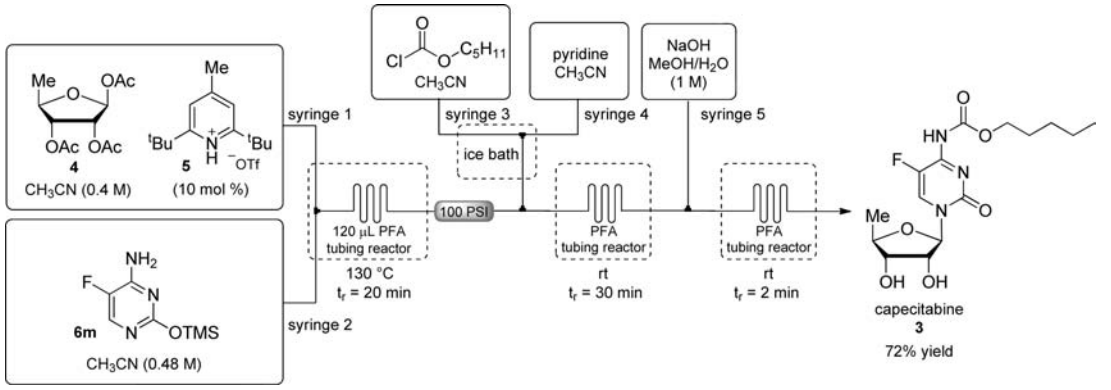


and isolating intermediate products.[10] The very efficient heat transfer of the continuous flow format also allows drastic changes in reaction conditions from one step to the next; very rapid heating/cooling of the small reaction volumes is easily accomplished. We examined the one-flow, two-step synthesis of fully deprotected 5′-deoxyribonucleosides by introducing a solution of NaOH in methanol and water to the exiting stream of the glycosylation reaction (Scheme 1). The deprotection was complete in only 2 min at room temperature, affording **8a** and **8f** in excellent yields.[11] The use of methanol/water mixture as the solvent is critical as it maintains the homogeneity of the reaction mixture. When only methanol was used, the product precipitated and clogged the tubing; when only water was used, the reaction mixture became biphasic, significantly slowing the reaction. Deprotection using methanolic ammonia (7 N) was also examined but in comparison was much more sluggish at room temperature.

(10) For reviews, see: (a) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675. (b) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17.

(11) The product crude mixture was neutralized, concentrated, and purified using column chromatography. See the Supporting Information for experimental details.

Scheme 4. One-Flow, Three-Step Synthesis of Capecitabine



We then investigated the one-flow, two-step synthesis of doxifluridine. Because of its poor solubility in methanol (even the presence of water could not prevent precipitation in this case), the streams of the glycosylation reaction and NaOMe were simultaneously introduced to a round-bottom flask, where the deprotection occurred (Scheme 2). We used NaOMe instead of NaOH for deprotection because the byproduct (methyl acetate) was easier to remove than acetic acid. Thus, doxifluridine (**1**) was obtained in 89% yield in only 10 min.

In order to synthesize galocitabine and capecitabine, silylated 5-fluorocytosine derivatives **6k** and **6l** were prepared and immediately used. Being much less reactive, these substrates required higher reaction temperature and 10 mol % catalyst **5**. The glycosylation of **6k** occurred smoothly at 140 °C and upon deprotection provided galocitabine (**2**) in 89% yield (Scheme 3).

However, the glycosylation of **6l** was accompanied with significant decomposition, resulting in only 50% yield of the corresponding product. An alternative sequence that began with glycosylation of **6m** instead of carbamate **6l** provided a solution to this problem (Scheme 4). The more electron-rich and thus less reactive **6m** was glycosylated in 20 min at 130 °C. The subsequent carbamate formation required 30 min at ambient temperature. Attempts to heat this stage in order to improve efficiency proved unfruitful. Critical are both mixing the chloroformate and pyridine at 0 °C and using the resulting mixture immediately; otherwise, decomposition occurred. With 10 mol % of pyridinium triflate **5**, this three-step-in-one-flow protocol (glycosylation–carbamate formation–deprotection) afforded capecitabine (**3**) in 72% yield in less than 1 h and is clearly greener and more efficient than any other previously reported processes.[3a–j]

In summary, we have developed a general synthesis of 5′-deoxyribonucleosides by way of an organocatalytic glycosylation reaction in continuous flow. The use of a Brønsted acid as a catalyst renders this method greener and more efficient than those requiring stoichiometric amounts (or more) of Lewis acids. The one-flow, multistep sequence circumvents purification of the intermediate products and produces unprotected 5′-deoxyribonucleosides in a streamlined manner, as demonstrated by the syntheses of the important compounds doxifluridine, galocitabine, and capecitabine.

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Supporting Information Available. Complete experimental procedures and characterization data of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.