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COMMUNICATION

Continuous Flow Photocatalysis Enhanced Using an Aluminum Mirror: Rapid and Selective Synthesis of 2'-Deoxy and 2',3'-Dideoxynucleosides

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A unique photochemical flow reactor featuring quartz tubing, an aluminum mirror and temperature control has been developed for the photo-induced electron-transfer deoxygenation reaction to produce 2'-deoxy and 2',3'-dideoxynucleosides. The continuous flow format significantly increased the efficiency and selectivity of the reaction.

Many deoxynucleosides have potent effects against viruses and tumors.¹ Several have been approved as antiviral and/or anti-cancer drugs, including zidovudine, stavudine, trifluridine, idoxuridine, cladribine and didanosine (Figure 1). Extraction from natural sources and fermentation processes provide only a limited number of naturally occurring 2'-deoxynucleosides; therefore, chemical approaches for the general synthesis of deoxynucleosides are highly desired.² A common strategy is the direct S_N2 reaction between a 1-chloro-2-deoxyribose derivative and a metalated or silylated nitrogenous base. Drawbacks of this strategy are the costs and stereochemical lability of 1-chloro sugars. Furthermore, the substitution reaction tends to generate a mixture of anomers that are difficult to separate.^{2a,3}

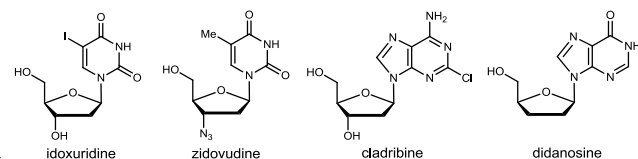
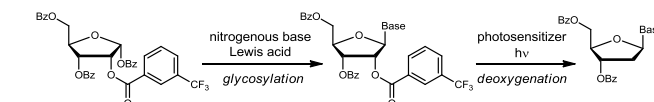


Fig. 1 Selected Deoxynucleoside Drugs

Herein, we report the efficient photochemical synthesis of two important classes of deoxynucleosides in continuous flow. We also introduce a novel photochemical reactor design in which an aluminum mirror enhances the reactivity and efficiency by reflection of UV light. Other features of this method include high selectivity, high chemical yield, and short reaction (residence) times (≤ 10 min for 2'-deoxynucleosides; ≤ 20 min for 2',3'-dideoxynucleosides).

Rizzo and co-workers reported the synthesis of 2'-deoxynucleosides involving Lewis acid mediated Vorbrüggen glycosylation⁴ followed by selective C2'-deoxygenation (Scheme 1).⁵ The C2'-hydroxyl group was derivatized as *m*-CF₃-benzoate

which served as the directing group for Vorbrüggen glycosylation, allowing the installation of both natural and non-natural nitrogenous bases with high diastereoselectivity while favoring the β -anomer. The 2'-*m*-CF₃-benzoate was then selectively removed (deoxygenated) under photo-induced electron-transfer (PET) conditions.⁶ Nevertheless, the synthesis of 2'-deoxynucleosides required relatively long irradiation time (1.5-2.0 h), and over-deoxygenation (3'-position) was often observed, leading to diminished yields of the desired 2'-deoxynucleosides.^{5c,d}



Scheme 1 Synthesis of 2'-Deoxynucleosides via Photo-induced Deoxygenation

Photochemical reactions are commonly performed in immersion well reactors with fixed volume; therefore, the reactions are often troublesome to scale up. Additionally, poor reproducibility is often encountered given the fact that photochemical efficiency depends directly upon the pathlength of the incident light (Beer-Lambert Law). Continuous flow synthetic chemistry has recently emerged as a promising technology,⁷ and demonstrated to be an efficient tool for circumventing many of the limitations of traditional batch photochemistry.⁸ Larger scales can be achieved by allowing more material to flow for longer periods of time (scale out). The thin channel within the photochemical reactor allows maximal light transmission and thus significantly increases reactivity. In addition, since the product is continuously removed from irradiation, over reaction and/or detrimental side-reactions can be minimized.

For our studies we used a 450 W medium pressure Hg lamp with a Pyrex sleeve (280 nm cutoff) that was positioned in the center of a quartz jacketed immersion well with tap water running through to prevent overheating. Customized coils of quartz tubing (1 mm i.d., 1.84 mL total volume) were placed around the immersion well approximately 2 cm from the surface of the lamp (Figure 2a). The quartz tubing was extended with PFA tubing, with the entry connected to a peristaltic pump, and the exit connected to a 20 psi back pressure regulator and then a collection vial. The apparatus described above was placed in a Pyrex cylinder through which water was circulated with the aid of a water pump immersed in a temperature controlled bath. The photoreactor (quartz tubing loops) was submerged in the water

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flowing through the cylinder (Figure 2b), allowing the reaction temperature to be controlled from 0 to 50 °C by the bath.

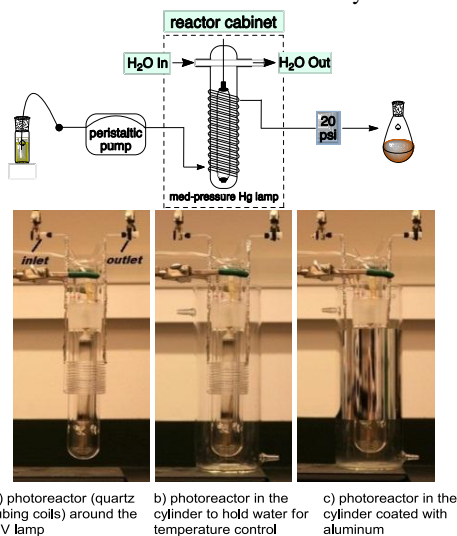


Fig. 2 Photochemical Flow Reactor Featuring Quartz Tubing and an Aluminum Mirror

Using our flow system, we found that 20 mol% photosensitizer carbazole **2a**⁹ catalyzed the PET deoxygenation reaction of *m*-CF₃-benzoate **1a** to deliver protected thymidine **3a** in 41% yield in only 10 min at 30 °C. We hypothesized that a UV-reflecting mirror would increase the effective light intensity and thus enhance the efficiency and throughput of photochemical reactions in flow. Therefore, the cylinder was coated with aluminum (mirror diameter = 11 cm, Figure 2c), which is best for UV reflection (>80%). Gratifyingly, this improved set-up increased the yield of **3a** to 66% under the aforementioned conditions.

Table 1 Screening of the Photosensitizers^a

entry	photosensitizer	yield [%] ^b
1	2a	41
2 ^c	2a	66
3 ^c	2b	49
4 ^c	2c	73
5 ^c	2d	0 ^d
6 ^c	2e	0 ^d
7 ^{c,e}	2c	84

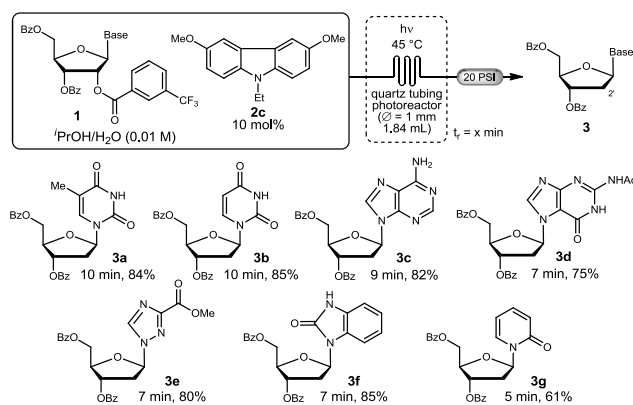
^a All reactions were carried out at 30 °C using 20 mol% photosensitizers unless otherwise noted. ^b Isolated yield. ^c Aluminum mirror was used. ^d Carbazole decomposed. ^e Reaction was carried out at 45 °C using 10 mol% photosensitizer.

We next investigated the effect of structure of the carbazoles photosensitizer (Table 1), and 3,6-dimethoxy-9-ethylcarbazole (**2c**) proved to be the best, affording **3a** in 73% yield (Table 1, entry 4). This improvement is attributable to the electron-rich substituents on 3- and 6- positions of the carbazole, which stabilize the proposed radical cation intermediate better than the H atoms at the same positions in **2a**.¹⁰ Unfortunately, more electron-rich carbazoles **2d** and **2e** bearing the amino substituents decomposed when subjected to UV light (Table 1, entries 5 & 6). When the reaction temperature was raised to 45 °C, only 10

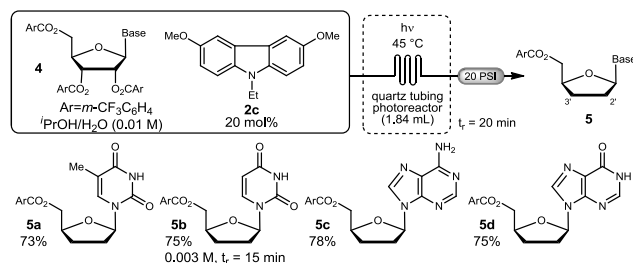
mol% carbazole **2c** was needed to provide **3a** in 84% yield (Table 1, entry 7). The additive Mg(ClO₄)₂ used in other reports^{5,6} was not necessary in our system.

The use of our unique photochemical set-up substantially reduced the reaction time from 2 h in batch to 10 min in flow. More significantly, performing the reaction in the continuous flow fashion suppressed over reaction, namely, the 2',3'-dideoxy derivative was limited to only 2%, while it has been reported as 16% in batch.^{5c}

We investigated the scope of the deoxygenation reaction by surveying a collection of ribonucleosides (Scheme 2). Taking the advantage of the short reaction time under the flow conditions, we were able to rapidly optimize the residence time for each substrate by changing flow rates to maximize yields. Benzoyl-protected uridine (**1b**), adenosine (**1c**), *N*7-guanosine (**1d**) all generated the corresponding 2'-deoxynucleosides (**3b-3d**) in high yields in no more than 10 min.¹¹ Notably, compound **3b** is the precursor to the antiviral drug idoxuridine. Non-natural nucleosides containing the triazole (**1e**), imidazolone (**1f**) and pyridinone (**1g**) moieties were readily prepared by glycosylation reaction of the protected ribose with corresponding nitrogenous bases, and they were also successfully deoxygenated with high efficiency. Over 80% yields were obtained in most cases, and the dideoxylation products were barely detectable. The relatively low yield in the case of **3g** was due to partial decomposition, which was limited to the minimal extent by reducing the residence time to 5 min. Reactions in flow were found to be highly reproducible regardless of the scale in all cases.



Scheme 2 Synthesis of 2'-Deoxynucleosides in Flow

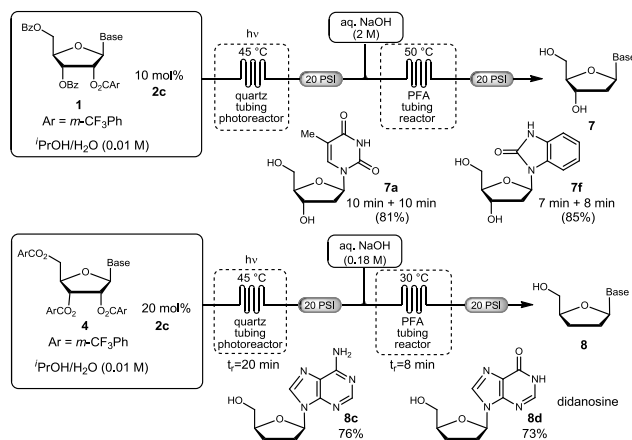


Scheme 3 Synthesis of 2',3'-Dideoxynucleosides in Flow

We also examined the double deoxygenation reaction of triesters **4**, prepared directly from the corresponding nucleosides. That is, differentiation of the 2'- and 3'-positions is unnecessary in these cases. By increasing the catalyst (**2c**) loading to 20 mol% and extending the residence time to 20 min, the deoxygenation

reaction afforded 2',3'-dideoxynucleosides **5a-d** selectively in high yields (Scheme 3). No 5'-deoxy derivative was observed in any case examined. Compound **5d** is of particular interest, as it is the precursor to the anti-HIV drug didanosine.

Deuterium-labeled deoxynucleosides are useful for the investigation of intermolecular interaction of a sugar moiety in a DNA complex with a protein or a drug by NMR spectroscopy.¹² When we used ¹PrOD (*d*-8) as the solvent, 2'-deoxy-[2'-D]ribonucleoside (**6**) was isolated in 84% yield with about 5:1 dr at C-2', favoring the C1'-C2' *trans* diastereomer.



Scheme 5 One-flow Two-step Synthesis of Deoxynucleosides

We then turned our attention to the preparation of unprotected deoxynucleosides. Multi-step synthesis in flow has emerged as a very effective strategy that saves cost and labor by circumventing the need for purifying and isolating intermediate products.¹³ Thus, a continuous one-flow, two-step setup was assembled as depicted in Scheme 5. An aqueous solution of NaOH was introduced via a T-mixer to the exiting stream from the PET deoxygenation reaction, and the deprotection occurred in 8-10 min to furnish the fully unprotected 2'-deoxynucleosides. The photosensitizer and the acid by-product from the first step did not affect the second step. Thymidine (**7a**) was produced in high yield in no more than 20 min in total, as well as the non-natural nucleoside **7f**. In a similar fashion, the two-step sequence also smoothly delivered 2',3'-dideoxynucleosides efficiently, including 2',3'-dideoxyadenosine (**8c**) and the anti-HIV drug didanosine (**8d**).

In conclusion, we have developed a unique flow photochemical reactor featuring quartz tubing, an aluminum mirror, and temperature control. With this setup, PET deoxygenation reactions were performed for the first time in flow and afforded protected deoxynucleosides in high yields and selectivity, in a short residence time. The new electron-rich carbazole **2c** further improves reactivity. Both natural and non-natural deoxynucleosides were prepared with high efficiency and reproducibility. The continuous two-step, one-flow sequence circumvented the need of purifying and isolating the intermediate product and produced unprotected 2'-deoxy and 2',3'-dideoxy ribonucleosides in a streamlined manner. We believe that this contribution not only improves the synthesis of deoxynucleosides, but will also incite further interest and development of other photochemical transformations in flow.

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the Novartis team for stimulating discussions and Edward Mitchell (James Glass, Inc.) for making the quartz tubing coils.

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