Black Light Induced Radical Cyclization Approach to Cyclonucleosides: An Independent Approach

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Received April 23, 2010: Revised March 12, 2011: Accepted March 15, 2011

Abstract: The paper highlights an efficient methodology based on consecutive radical reaction for the preparation of cyclonucleoside derivatives. The reactions were performed in organic and aqueous media, using common and efficient free radical hydrogen donors in the range of innovative and conventional initiation conditions to afford good to excellent yields of corresponding cyclonucleosides. The mechanistic aspects of the transformations are also addressed.

Keywords: Cyclo-nucleosides, black light, aqueous media, free radical reactions.

Cyclopurine and cyclopyrimidine lesions are observed among the decomposition products of DNA, when exposed to ionizing radiation or to some antitumor agents [1]. Recently, several examples of independent formation of 5',6-cyclo-5,6-dihydrothymidine and 5',8-cyclo-2'-deoxyadenosine have been reported [2]. The unique structural features of the cyclo-nucleosides incorporate an additional base-sugar linkage between the C6 position of pyrimidine or C8 position of purine and the C5' position of the 2'-deoxyribose [3]. Conformationally fixed nucleosides analogues are a unique class of compounds that can be used as a tool for investigating steric interactions between nucleosides or nucleotides and the enzymes that utilize them [4] (Fig. **1**).

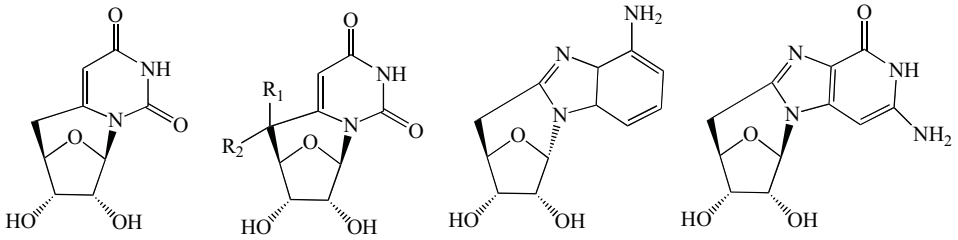

Fig. (1). Structure of C-Cyclonucleosides.

To date, various modified 2-deoxynucleosides containing specific DNA lesions and their incorporation into a defined sequence of oligonucleotides have been an outstanding approach to investigate the biological consequences. Synthetic oligonucleotides that contain the modified nucleosides [5-7] as well as similar cyclopurine [7] and cyclopyrimidine [8] moieties were also prepared. Recent studies have shown that the chemical synthesis of these lesions and their incorporation on specific sites of DNA are of considerable importance in order to investigate, in detail, the biochemical and biophysical features of the double helix damage [6, 9, 10].

Several key contributions in the area have recently reported synthetically usefull cascade methodologies for effective generation of the cyclonucleosides in order obtain a general procedure for the preparation of some of the diastereoisomers of the cyclonucleosides as well as try to overcome the limitations of the existing approaches, due to low yield multiple-step synthesis, problematic chromatographic and separation properties [6-10].

Photolysis is one of the most appropriate and widely used methods of generating nucleosidyl radicals, with numerous reports in the literature reported of sources and set-ups for the generation, however most of the methods require specialized experimental setups, glassware and rather expensive light sources for the desired transformations.

In order to overcome these problems, we decided to investigate the use of a black light, which has a maximum peak wavelength at 352nm, and performs effectively in a broad range of free radical transformations as reported by Ryu *et al.* [10] and is applicable to generation of C5' nucleosidyl purine and pyrimidyl radicals in organic and aqueous media in

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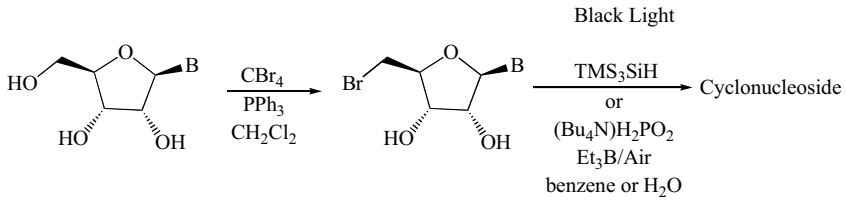


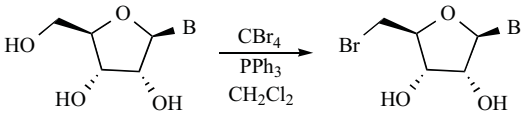
Scheme 1. General synthetic approaches and methodology.

the presence of derivatives of hypophosphorous acids in organic and aqueous media.

In this paper we report an independent generation of C5' radical precursor of 5'-bromouridine as radical precursors for C5' radical generation under black light initiation (Scheme **1**).

RESULTS AND DISCUSSION

Commercially available nucleosides such as uridine, adenosine and quanosine were reacted with freshly prepared Appel bromide in CH_2Cl_2 in order to prepare corresponding 5'-Bromonucleosides derivatives. The compounds were prepared in moderate to good yields. The 5'- bromonucleoside derivatives were purified on the C18 HPLC chromatography column and identified through comparison of spectral data reported in the literature.



where B=Ur 54%
=Ad 42%
=Gua 46%

Scheme 2. Preparation of 5'bromonucleosides.

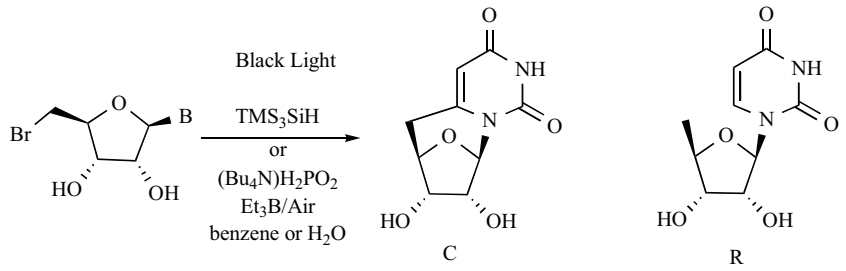
Following our initial plan, we examined tandem radical 1,6-HAT-cyclization of 5'-bromouridine in the presence of a. TMS_3SiH, b. $H_3PO_2/Bu_4N^+Cl^-$ c. Bu_3SnH and in benzene and water under black light initiation, Et_3B/air and AIBN/80°C conditions and the results are summarized in Scheme **3** and Table **1**.

Major reaction products of all the transformations summarized in the table are indicative of the intra-molecular radical 6-*exo*-trig reaction being predominant, suggesting that intermolecular hydrogen transfer reaction is a much slower process in comparison to intra-molecular radical 6- *exo*-trig cascade reaction. However in the case of Bu_3SnH, the yield of product R (minor product) accounts for 30% in the final product mixture, which is consistent with the difference in the hydrogen donor ability of Bu_3SnH vs TMS_3SiH vs $H_3PO_2/Bu_4N^+Cl^-$, highlighting the potential for further development of the methodology. This observation is consistent with the previous reports by Navacchia, Chatgilialoglu and Cadet in there pioneering work on the understanding of the mechanistic aspects of C5' radicals.[11, 12]

The proposed mechanism for the transformation in question is represented in Scheme **4**. Initiator decomposes to abstract a hydrogen atom from the radical mediator such as ($(TMS)_3SiH$, H_3PO_2 or Bu_3SnH), which generates a corresponding silyl, phosphorous centered or stannyl radical. The latter abstracts the halogen atom to form a C5' radical. In the case of ($(TMS)_3SiH$, H_3PO_2 or Bu_3SnH) as hydrogen donors, C5'radical undergoes a 6-*exo*-trig cyclization adding to the double bond of the base. The resulting C5-radical abstracts hydrogen from the hydrogen donor, yielding a *cyclo*-compound, while completing the radical chain. The minor product, which is the product of the direct reduction is also formed due to much less but still competitive H-abstraction reaction and is observed in all transformations in different amounts as pointed out in Table **1**.

CONCLUSION

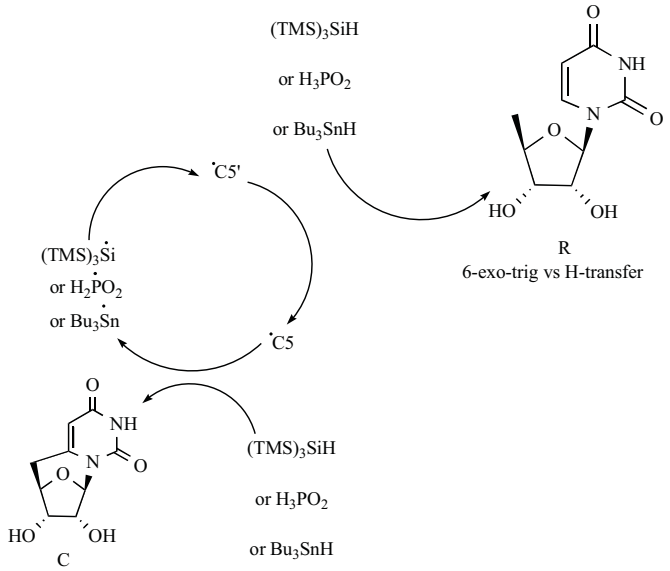
We have disclosed a short and efficient synthetic sequence, based on consecutive radical reactions in aqueous media, for the preparation of cyclonucleosides. The C5' radicals, generated by tandem homolytic bond cleavage followed by carbon-carbon bond formation are the key intermediates in these transformations. The chemical biology approach used for studying purine 5',8- cyclonucleoside lesions has brought significant achievements so far [13]. The site-specific generation of sugar radicals has been the key approach for a better understanding of chemical molecular mechanisms



Scheme 3. Radical cyclization reaction of C5'-BromoUridine in benzene and water under various initiation conditions and in the presence of free radical hydrogen donors.

Table 1. Radical Cyclization Reactions of C5'-BromoUridine under Black light, Et_3B/air(rt) and AIBN/80°C Initiation Conditions with Various free Radical Hydrogen Donors

Entry	H-Donor	Initiation	Solvent	% yield C:R
1	TMS_3SiH	Black light	Benzene	78:5
2		Et_3B/air(rt)	Benzene	72:5
3		AIBN/80°C	Benzene	78:4
4		Black light	H_2O	72:6
5		Et_3B/air(rt)	H_2O	70:4
6		AIBN/80°C	H_2O	79:4
7	$H_3PO_2/Bu_4N^+Cl^-$	Black light	Benzene	73:5
8		Et_3B/air(rt)	Benzene	70:6
9		AIBN/80°C	Benzene	67:3
10		Black light	H_2O	72:4
11		Et_3B/air(rt)	H_2O	70:6
12		AIBN/80°C	H_2O	71:5
13	Bu_3SnH	Black light	Benzene	60:30
14		Et_3B/air(rt)	Benzene	58:25
15		AIBN/80°C	Benzene	50:30
16		Black light	H_2O	50:30
17		Et_3B/air(rt)	H_2O	55:35
18		AIBN/80°C	H_2O	54:30



Scheme 4. Proposed Radical Chain Mechanism for the formation of the cyclised product (major product) and product of direct reduction (minor product).

occurring at the biological level. The chemistry of the C5' radicals in the purine nucleosides is fairly well understood and it is now clear that the fate of the C5' radicals is partitioned between uni-molecular processes (cyclizations) and bimolecular processes (reactions with oxygen, thiols, or oxidants) [13]. Therefore, the local concentration of these components and pH are extremely important in selecting the preferred pathway. Work is currently on the way to gain further insight into these important transformations at a molecular level under aerobic and anaerobic conditions.

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