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Cyclic sulfates as synthetic equivalents of α-epoxynucleosides

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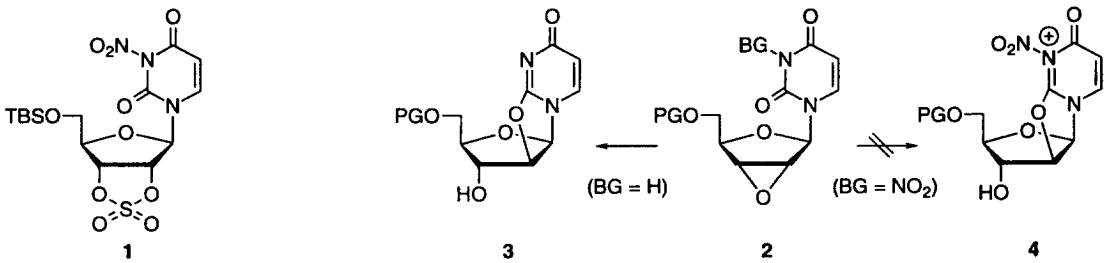
Abstract

A stable sulfate derivative of *N*-nitrouridine has been obtained for the first time; it shows synthetic advantages in relation to its α-epoxide counterpart. A new iodide-mediated denitration reaction is reported.

Keywords: epoxides; nitro compounds; nucleosides; sulfuric acid derivatives; uridines.

Modification of the ribose moiety of nucleosides is a powerful strategy to gain access to a variety of substances with interesting biological and pharmaceutical properties.[1] Although the preparation of modified pyrimidine nucleosides by means of S_N2-type reactions would seem an obvious approach to β-substituted nucleosides, such reactions usually provide *O*-anhydronucleosides, α-substituted nucleosides and/or base-modified nucleosides.[2] Recently, we have shown that *N*-nitronucleoside chemistry[3] can be used to control the stereochemistry of these reactions to give *arabino*- and *lyxo*-nucleosides.[4] In this paper we report on the preparation of *xylo*-nucleosides using a *N*-nitrouridine cyclic sulfate (**1**, Scheme 1) as a key intermediate.



1 **3** **2** **4**

Scheme 1.

Cyclic sulfates of type **1** can be envisaged as synthetic equivalents of α-epoxides (**2**). We should recall that the chemical behavior of α- and β-epoxide derivatives of uridine is very different. Whereas the latter are well known species that have been widely used in nucleoside chemistry, the former ones have been hardly mentioned as reaction intermediates;[5] in fact, the unblocked α-epoxide (**2**, BG=PG=H), could

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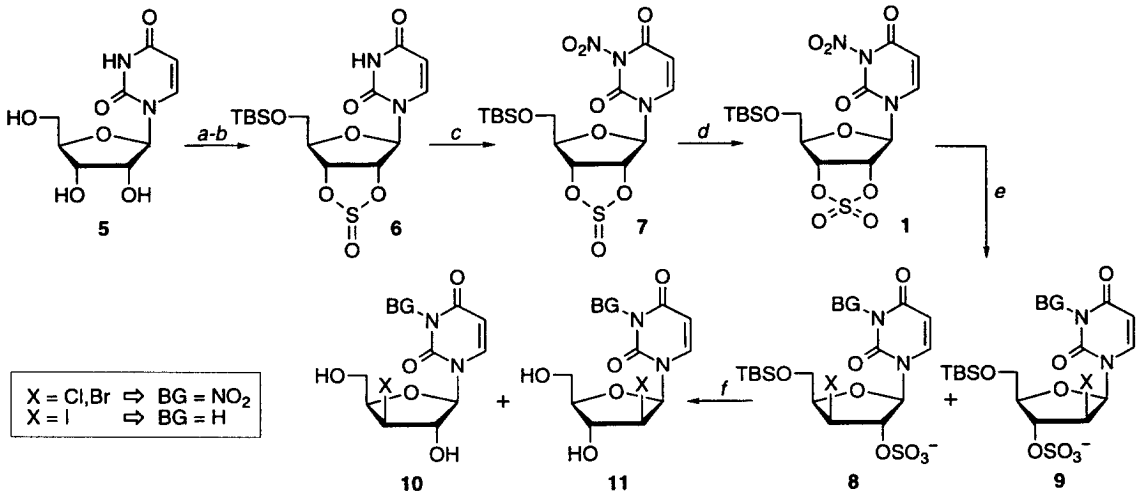
not be isolated until very recently, by Reese et al.[6] The elusive preparation of these oxirans relies upon their tendency to cyclize to 2,2′-*O*-anhydronucleosides (**3**, see Scheme 1), especially in basic media. *N*-Nitration may prevent such a transformation, so that the corresponding α-epoxides (**2**, BG=NO_2) may be isolated without difficulties.[4] Unfortunately, treatment of a *N*-nitroepoxide (PG=Tr) with nucleophiles lead to complex mixtures containing products arising from the initial attack at C4. It is likely that the *N*-nitro group actually avoids the formation of anhydronucleosides, but the oxiran ring is less reactive than the activated C4 carbonyl group. The lack of reactivity that the oxiran ring exhibits prompted us to use a cyclic sulfate as a synthetic equivalent of **2**. Although the reactivity of cyclic sulfates is well known,[7] their application to nucleoside chemistry has received little attention[8] and, to our knowledge, no cyclic sulfate of a pyrimidine nucleoside has been reported so far. Thus, to get a stable sulfate derivative of uridine (**5**), sulfite **6** was *N*-nitrated to **7**, which was oxidized to **1** (Scheme 2).

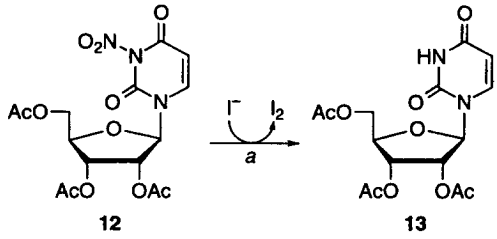


Scheme 2. (*a*) TBSCl, py/CH_2Cl_2, rt, 16 h, 91%. (*b*) $SOCl_2$ (1.8 equiv.), py (3.6 equiv.), CH_2Cl_2, rt, 15 h, 92%. (*c*) $CF_3CO_2NO_2$ (4 equiv.), CH_2Cl_2, 0°C, 30 min, 98%. (*d*) Oxone® (1.1 equiv.), $RuCl_3 \cdot xH_2O$ (0.1 equiv.), rt, 39 h, 63% (+29% s. m.). (*e*) X=Cl: Bu_4NCl (1.2 equiv.), CH_2Cl_2, rt, 2 days, 90% (**8**:**9**=8:1); X=Br:Bu_4NBr (1.2 equiv.), CH_2Cl_2, rt, 3 days, 95% (**8**:**9**=5:1); X=I: NaI (5 equiv.), acetone, rt, 7 days, 90% of **8**. (*f*) H_2SO_4 (5 equiv.), H_2O (5 equiv.), THF, rt, 2–3 h, 95% (X=Cl), 85% (X=Br), 60% (X=I)

As expected, *N*-nitration was required to avoid the formation of anhydronucleosides and to obtain stable sulfates (the direct oxidation of **6** yielded complex mixtures; attempts aimed at preparing a denitrated sulfate by removal of the NO_2 group of **1** by catalytic hydrogenation failed as well). It is worth mentioning that oxidation of **7** with $NaIO_4/RuCl_3$ under Sharpless conditions[7a] provided only a trace amount of sulfate **1**. Fortunately, **1** could be obtained in good yield on a multi gram scale by increasing the amount of $RuCl_3$ to 10% and using Oxone® instead of $NaIO_4$. Sulfate **1** is a stable solid that can be stored for months in the refrigerator and, as desired, it is more reactive than the corresponding α-nitroepoxide. It reacted readily with halide ions at rt to give excellent yields of the corresponding halo-salts **8/9** in which the *xylo* regioisomers largely predominate. Final hydrolyses of these mixtures provide the desired halo-alcohols **10/11**, which could be readily separated by flash chromatography (silica gel, CH_2Cl_2–MeOH).

It is noteworthy that a concomitant denitration process was observed during the treatment of **1** with NaI/acetone. In this case, the nucleophilic attack on the sulfate ring was complete in 2 days at rt to yield a mixture of nitrated and denitrated iodo derivatives (**8**, BG=NO_2, H). The denitration reaction required 7 days to achieve a 90% yield of **8** (BG=H) and a significant amount of iodine could be detected in the final reaction mixture. To establish the scope of the reaction, tri-*O*-acetylnitrouridine **12** was treated with

a large excess (15 equiv.) of NaI in acetone (see Scheme 3) at rt. Under these conditions, denitration was accomplished in 24 h to yield 80% of **13** after purification by flash chromatography. Thus, this iodide-mediated denitration process may be of general application in *N*-nitronucleoside chemistry.



12 **13**

Scheme 3. (*a*) NaI (15 equiv.), acetone, rt, 24 h, 80%

In spite of these good results, we should mention that reaction of **1** with Bu_4NN_3 afforded a complex mixture arising from the initial attack of the azide ion to C4; thus, competition of the carbonyl group at C4 may limit the synthetic utility of uridine sulfates, specially in processes involving strong nucleophiles.

In summary, a stable sulfate derivative of *N*-nitrouridine has been synthesized for the first time, which is equivalent to an α-epoxide derivative. Its reactivity, together with that of *N*-nitrouridine triflates, stress the synthetic utility of *N*-nitronucleosides to gain access to modified nucleosides of unusual stereochemistry.

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