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# 5-*Endo-Dig* Electrophilic Cyclization of α-Alkynyl Carbonyl Compounds: Synthesis of Novel Bicyclic 5-Iodo- and 5-Bromofuranopyrimidine Nucleosides

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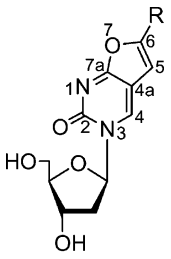
**Abstract:** 5-*Endo-dig* electrophilic cyclization of 5-alkynyl-2′-deoxyuridines with *N*-iodosuccinimide or *N*-bromosuccinimide in acetone at room temperature gives 3-(2′-deoxy-β-D-ribofuranosyl)-5-halo-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-ones that usually precipitate from the reaction mixture (86−74%).

Construction of the furan ring, which is found in many natural and biologically important molecules,[1−3] is attracting considerable attention.[4] Heteroannulation processes for the synthesis of substituted furans have been vigorously applied, in particular palladium-catalyzed annulation of alkynes,[5,6] which is also suited for combinatorial synthesis.[3] Electrophilic cyclization of unsaturated compounds has also proven to be an efficient method for one-step construction and functionalization of the furan unit.[7−10] This reaction is generally believed to proceed through an intramolecular, stepwise mechanism involving a cationic intermediate.[8,11] Although reactions of *o*-alkynyl phenols,[7] acetoxy- or benzyloxypyridines,[8] and thiophenols[12] have been investigated, the electrophilic halocyclization of α-alkynyl carbonyl compounds has not been synthetically explored.[6,13]




**2**

**FIGURE 1.** Structure of furanopyrimidine nucleoside **2**.

Elucidation of biological properties for 5-alkynyl uridines (**1**) has resulted in detailed synthetic studies.[14,15] When synthesis of **1** via palladium-catalyzed coupling is carried out at a higher temperature in the presence of a base, formation of bicyclic furanopyrimidine (**2**, Figure 1) is observed.[14c,d,16] The recent discovery of selective inhibition of varicella-zoster virus (VZV) replication[17,18] has revitalized interest in bicyclic structure **2**. In particular, the activity of furanopyrimidines substituted at C-6 with the 4-(*n*-alkyl)phenyl group surpasses ca. $10^4$ times the activity of acyclovir or (*E*)-5-(2-bromovinyl)-2′-deoxy-

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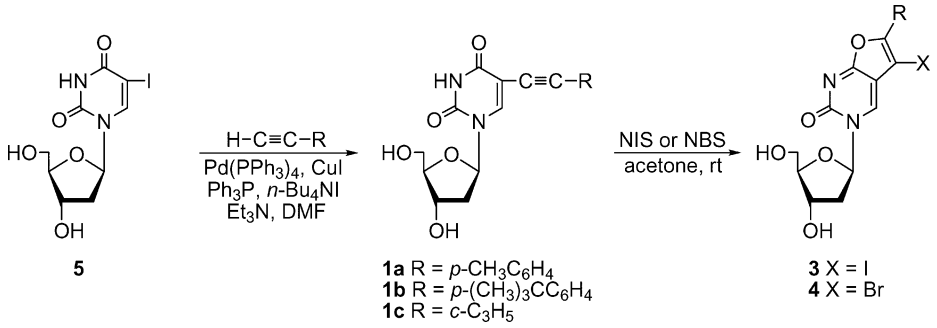
**SCHEME 1. Synthesis of Bicyclic Halofuranopyrimidine Nucleosides 3 and 4**




uridine (BVDU).[18a] It is likely that **2** will be further pursued for clinical development.[17a,b]

The synthetic methodology leading to bicyclic furanopyrimidine nucleosides **2** includes palladium- or coppercatalyzed 5-*endo-dig* cyclization of alkynyluridines **1**,[14c,18] involving the C-4 pyrimidine oxygen and acetylenic bond. This approach introduces hydrogen at C-5 of the furano pyrimidine (IUPAC nomenclature numbering of the bicyclic ring, Figure 1), limiting access to nucleoside analogues with different substitutents at this position.[19]

Here we report a type of new chemistry that opens a valuable route to a new series of iodo- and bromofuranopyrimidine nucleosides (**3**, **4**), with a potential for biological activity.[20] We have synthesized the halo-functionalized bicyclic structures for the following reasons: (i) vinyl halides **3** and **4** are key synthons; palladium-catalyzed reactions will allow for introduction of a variety of substituents at C-5 of the furanopyrimidine, thus providing access to a wide range of functionalized 5,6-disubstituted furano nucleosides;[7,21] (ii) nucleosides **3** or **4** combine halovinyl- and furanopyrimidine fragments,[22] both with well-documented high activity.[17,18,23]

Halogens were introduced via electrophilic 5-*endo-dig* cyclization of 5-alkynyluridines. 4-Alkylphenyls[17,18a] and cyclopropyl[24] were selected as model R substituents. Iodination using elemental iodine was approached; a base was not included as it may affect the *N*-glycosidic bond. Although successful $I_2$ electrophilic cyclizations have been described,[7−9] attempts to effect iodocyclization of homopropargylic alcohols have led to vinyl diiodides.[9e] However, a cyclization reaction was observed when cyclopropyl-substituted ethynyluridine (**1c**, R = *c*-$C_3H_5$) was treated with $I_2$ in $CH_2Cl_2$. Two products were isolated in poor yield; the structures were assigned as the iodocyclized nucleoside **3c** and its base. Therefore, we have turned our attention to *N*-halosuccinimides, which have precedence in the synthesis of bromobenzo[*b*]thiophene.[11,25,26]

5-Alkynyluridines **1b**,**c** were prepared by Sonogashira coupling at room temperature,[14c,27] similar to **1a**.[28] 5-Iodo-2′-deoxyuridine (**5**) (1.0 equiv) was combined with terminal alkyne HC≡CR (R = $C_6H_4$-*p*-$C(CH_3)_3$, *c*-$C_3H_5$) (1.8−2.0 equiv) in the presence of $Pd(PPh_3)_4$ (0.11 equiv), CuI (0.3−1.0 equiv), $Ph_3P$ (1.0 equiv), *n*-$Bu_4NI$ (1.0 equiv), and $Et_3N$ (2.0 equiv) in DMF (Scheme 1). Alkynyl nucleosides **1b**/**c** were obtained in 84/76% yield. The isolated nucleosides **1a**−**c** were treated with *N*-iodosuccinimide (NIS) (1.5 equiv) in acetone at room temperature, as visualized in Scheme 1. Formation of precipitate was observed after 2 h or more for aryl-substituted compounds **1a**,**b**. The solid was isolated by filtration, giving usually analytically pure bicyclic 5-iodofuranopyrimidines **3a**/**b** in 86/74% yield. Short column silica gel chromatography was applied as needed. The cyclopropyl derivative **3c** is more soluble in acetone; therefore, it was isolated by column chromatography in 80% yield. The results are summarized in Table 1.

A *p*-tolyl derivative **1a** was treated with *N*-bromosuccinimide (NBS) (1.9 equiv) in a similar manner to access a bromoderivative **4** and compare reactivity of an analogous reagent. Reaction time was prolonged compared to iodination; full conversion and precipitation occurred after 5 h. Although it is known that substituted furans undergo oxidative ring opening with NBS in acetone,[29] bicyclic 5-bromofuranopyrimidine **4a** was isolated, after workup, in 79% yield. However, the bromocyclization is sensitive to the quality of the reagents.

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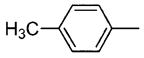
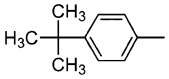
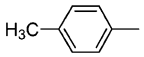
**TABLE 1. Preparation of Halofuranopyrimidines 3 and 4 via Cyclization of 1**

| compound | R | reagents and conditions | yield (%) |
|---|---|---|---|
| **3a** |  | NIS 1.5 equiv 2 h, rt | 86 |
| **3b** |  | NIS 1.5 equiv 2 h, rt | 74 |
| **3c** |  | NIS 1.5 equiv 3 h, rt | 80 |
| **4a** |  | NBS 1.9 equiv 5 h, rt | 79 |

Sometimes cleavage of the *N*-glycosidic bond was observed in repeated experiments, especially when acetone was not of high purity. In that case the bromocyclized nucleoside base was isolated, as determined by $^1$H and $^{13}$C NMR.

The bicyclic nucleosides were characterized by $^1$H and $^{13}$C NMR, IR, MS, UV−vis, and fluorescence spectroscopy. The $^1$H and $^{13}$C NMR spectra supported the structural assignment for **3a**−**c** and **4a**. First, the furanopyrimidine H-4 signal exhibited a downfield shift by comparison to its alkynyl precursor (9.00−8.63 vs 8.35−8.11 (H-6) ppm, DMSO-$d_6$). Second, the furan C=C signals showed a chemical shift (157.8−154.2 and 59.0−58.4 (I), 90.3 (Br) ppm, DMSO-$d_6$) characteristic for O-vinyl and I/Br-vinyl carbons.[8] Distinctive changes occur as compared to the parent alkynes **1a**−**c** (96.9−91.8 and 82.1−68.6 ppm, DMSO-$d_6$) or nonhalogenated bicyclic furano pyrimidines **2** (100.2−99.5 (C-5) ppm, DMSO-$d_6$).[18a] Third, the $^{13}$C NMR coupled (gated decoupling) experiment showed an absence of hydrogen at C-5 for **3a**. In addition, this experiment allowed assignment of the $^{13}$C signals based upon the $^1J_{C-H}$ coupling constants pattern, which was extrapolated for other analogues.

Mass spectra of **3a**−**c** and **4a** exhibited intense molecular ions. The IR $\nu_{CO}$ values clustered in a narrow range (1663−1670 cm$^{-1}$). The representative UV−vis spectrum for **3a** is shown in Figure 2. As expected, absorptions shift to longer wavelengths for the fused cyclic system, as compared to the parent alkynyl uridines **1a**−**c**. The first two bands usually appear at 248−257 and 282−285 nm for aryl-substituted compounds, but a single band was observed at 248 nm for the cyclopropyl derivative **3c**. The position of the last well-pronounced band (longest wavelength), shifts slightly from cyclopropyl substituted **3c** (341 nm) to the aryl derivatives **3a**,**b** and **4a** (357/356/356 nm) and does not depend on the halogen. The molar absorptivities reach nearly to 18 000 M$^{-1}$ cm$^{-1}$.

Both iodo- and bromofurano pyrimidines **3** and **4** exhibited a strong purple luminescence on TLC plates under a UV lamp (254 nm); more detailed characterization was also undertaken as fluorescent nucleosides find practical applications.[30] We found optimal excitations between 320 and 350 nm. Wavelengths of the observed emissions do not vary much, and are between 430 and 450 nm, slightly shifted to the red by comparison to the alkynyl precursor **1a**.[28] A representative emission curve for **3a** is shown in Figure 2. All iodobicyclic nucleosides **3** gave the correct elemental analyses.

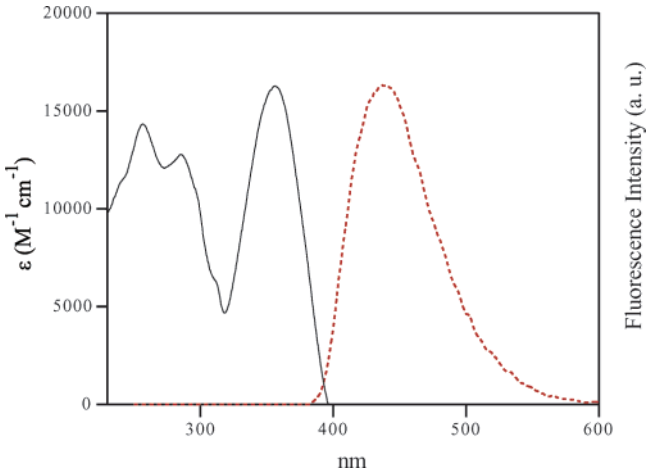



**FIGURE 2.** UV−vis (—) and fluorescence ($\lambda_{ex}$ = 340) (- - -) spectra for **3a** (methanol).

In summary, we have demonstrated that electrophilic cyclization of α-alkynyl carbonyl compounds leads to halofurans in mild conditions, and we have synthesized a new class of modified nucleosides containing biologically active substructures. The resulting bicyclic nucleoside iodides or bromides should be particularly useful as substrates in a variety of palladium-catalyzed reactions such as Heck, Suzuki, Sonogashira, or amination, and should thus provide material for a broad range of modified nucleosides for drug discovery. Corresponding synthetic studies are currently underway in our laboratory. Our protocol also offers a potential for iodine isotope labeling.

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**Supporting Information Available:** Synthetic procedures and analytical and spectral characterization data for all new compounds, and $^1$H and $^{13}$C NMR and MS spectra for **1b**,**c**, **3a**−**c**, and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) See, for example: Okamoto, A.; Tainaka, K.; Saito, I. *J. Am. Chem. Soc.* **2003**, *125*, 4972−4973.