Highly Efficient $AgNO_3$-Catalyzed Preparation of Substituted Furanopyrimidine Nucleosides

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Abstract: An efficient method for the synthesis of substituted furanopyrimidine nucleosides is described. Upon treatment with catalytic $AgNO_3$, 5-alkynyl uracil derivatives were almost quantitatively converted into their corresponding bicyclic nucleoside analogues.

Key words: $AgNO_3$, cyclization, furanopyrimidines

Various *C*-5-alkynyl nucleosides can be obtained in high yields (70–97%) by the cross-coupling of halogenated derivatives with terminal alkynes under Pd(0)-catalyzed Sonogashira coupling conditions.[1] In most cases, a strongly fluorescent furanopyrimidine derivative by-product could be isolated with a <7% yield, or just detected by TLC. Recently, McGuigan et al.[2] reported that compounds such as **1** displayed important potency and exclusive selectivity against varicella zoster virus (VZV). Structurally-related imidazo[*1,2-c*]pyrimidin-5(6*H*)-one heterosubstituted nucleoside analogs **2** were discovered by Mansour et al.[3] to have anti-HBV (hepatitis B virus) activity (Figure 1). Despite their biological importance, the synthetic methodology used for the O-hetero-annulation process is limited and suffers from poor to moderate yields (8–73%). A more versatile and efficient procedure remains a challenge.

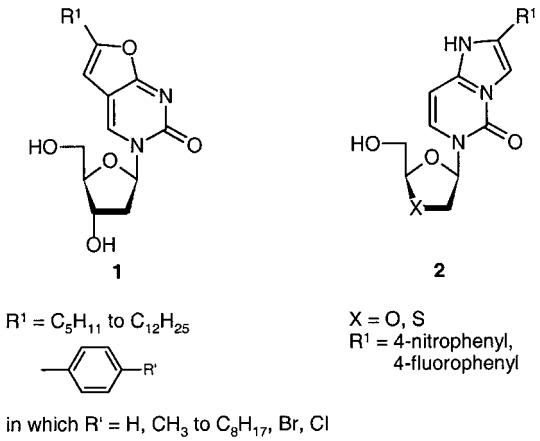
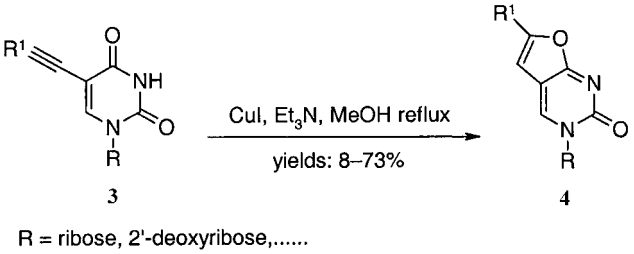


Figure 1 Structure of antiviral furano- (**1**) and imidazopyrimidine (**2**) nucleosides

The most common synthetic pathway for cyclization to the target bicyclic nucleosides **1**, as reported by Robins and Barr,[4] consists of the base and copper-catalyzed 5-*endo-dig* cyclization of alkynyluridines **3** with CuI in triethylamine/methanol at reflux, between the *C*-4 pyrimidine oxygen and acetylenic bond (Scheme 1). Similar cyclization was noted in Stephens–Castro couplings of *o*-iodoanilines with copper(I) acetylides[5] by Bleackley et al.[6] Considerable amounts of this cyclized by-product were isolated when longer reaction times were employed or when an electron-withdrawing group was present on the alkyne moiety. Homocoupling was found to compete with cross-coupling, depending upon the steric hindrance around the catalyst.



Scheme 1

Motivated by our recent work concerning the palladium-catalyzed synthesis of uridines on polystyrene based solid supports,[7] we explored a 5-*endo-dig* electrophilic cyclization catalyzed by $AgNO_3$.[8] The Lewis acid nature of $AgNO_3$ enables it to complex with alkynes and allenes, thus permitting an intramolecular cycloaddition to proceed. This procedure has already been used, for instance, on various phenolic keto-ynes[9] and α-hydroxyallenes.[10] Nevertheless, no systematic application to α-alkynyl carbonyl compounds, especially in the field of nucleosides, has been explored. We describe herein the use of $AgNO_3$, as a clean, efficient and improved method for the synthesis of known or new alkyl furanopyrimidine nucleosides (Figure 2). In all cases, the cyclization yields were >95%, with no need for purification.

To confirm the viability of our method we treated different substrates with a catalytic amount of $AgNO_3$: 2′-deoxyribosyl nucleosides (series 1) and acyclonucleosides (series 2 and 3), which were substituted at C-5 with either alkyl- or alkylphenyl alkynes (Table 1). Thus according to the literature, 5-alkynyluraciles derivatives were first prepared from known iodinated protected

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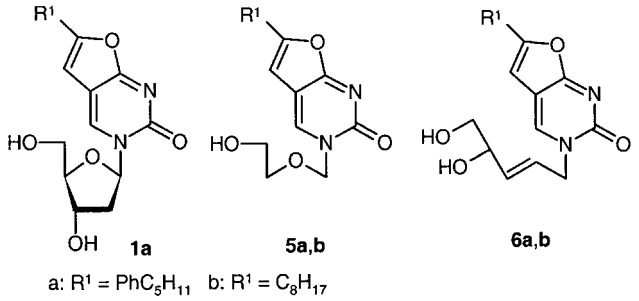
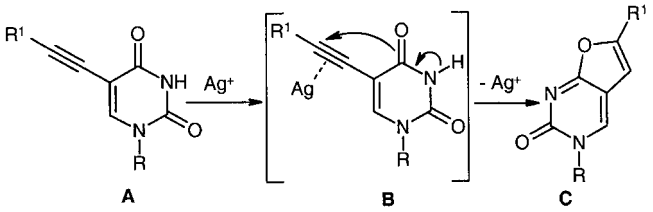


Figure 2 Structure of obtained furopyrimidines nucleosides

precursors **7**,[11] **8**,[12] **9**[13] under Sonogashira cross-coupling conditions[14] at room temperature.[15] The cyclization[16] occurred in the presence of a catalytic amount of $AgNO_3$ (Table 1), affording the desired bicyclic furanopyrimidine nucleosides **13**, **14a**,**b**, **15a**,**b**[17] with no purification necessary other than an extraction to remove the catalyst. In all cases, the isolated yields were >95%. After an appropriate deprotection step[18,19] (TFA–H_2O, 2:1, v/v or MeOH–pyridine–H_2O–NaOH), the unprotected bicyclic nucleosides **1**, **5a**,**b**, **6a,b**[20] were isolated in quantitative yields. This electrophilic 5-*endo-dig* cyclization with $AgNO_3$ is believed to proceed through a catalytic mechanism involving a cationic intermediate (Scheme 2).

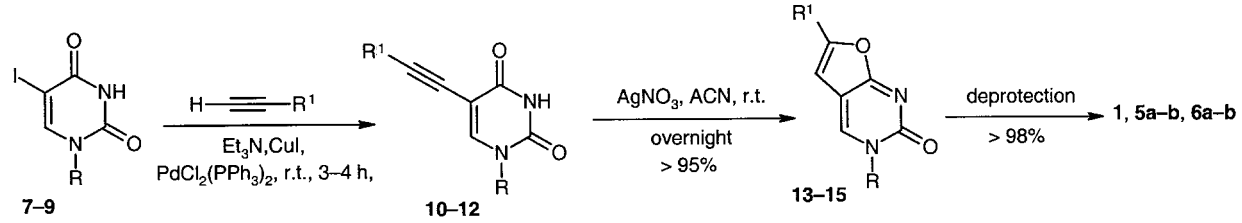


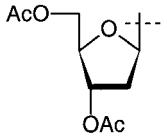
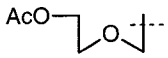
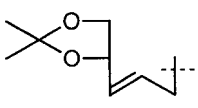
Scheme 2 Hypothesized mechanism for cyclization through $AgNO_3$

This hypothetical mechanism can be divided into two steps: (1) initial activation of the triple bond through its complexation with Ag^+ and (2) intramolecular attack of the oxygen across the activated carbon-carbon triple bond with subsequent proton transfer and release of Ag^+, to give the target furanopyrimidine product **C**.

In summary, we have demonstrated that the electrophilic cyclization using $AgNO_3$ at room temperature is an improved and useful alternative pathway for the cyclization of α-alkynyl carbonyl compounds giving access to alkyl furano pyrimidine in quantitative yields (>95%). Further work is in progress to extend the present methodology to the preparation of more complex molecular structures and to its application to the synthesis of furanopyrimidine nucleosides on solid support.

Table 1 Cyclization of Alkynylpyrimidines Derivatives Using Catalytic $AgNO_3$



Entry	R	Iodo compound	R^1	Alkynes Product (Yield, %)	Cyclized Product (Yield, %)
1		**7**	PhC_5H_{11}	**10**	**13** (>98%)[a,b]
2		**8**	PhC_5H_{11}	**11a**	**14a** (98%)[a]
3			C_8H_{17}	**11b**	**14b** (98%)[a]
4		**9**	PhC_5H_{11}	**12a** (78%)	**15a** (95%)[c]
5			C_8H_{17}	**12b** (61%)	**15b** (98%)

[a] Yield calculated over 2 steps.
[b] <20% Cyclization yield using CuI–Et_3N–MeOH.
[c] <50% Yield with CuI, Et_3N, MeOH.

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(14) **Typical Procedure for Sonogashira Cross-Coupling.** Under dry nitrogen, the iodo derivatives (0.026 mmol) were dissolved in DMF (0.5 mL), then alkyne (0.079 mmol), Et_3N (0.079 mmol), CuI (0.005 mmol), $PdCl_2(PPh_3)_2$ (0.003 mmol) were added. The reaction was stirred at r.t. until complete conversion was reached. After evaporation of volatiles the crude residue was purified by flash chromatography.

(15) **5-(1-decynyl)-1-[(*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-2,4 (1*H*,3*H*)-pyrimidinedione (12b):** ^{1}H NMR ($CDCl_3$): δ = 0.86 (t, 3 H, *J* = 6.9 Hz), 1.15–1.48 (m, 16 H), 1.50–1.63 (m, 1 H), 2.36 (t, 2 H, *J* = 6.9 Hz), 3.58 (dd, 1 H, *J* = 8.0 Hz), 4.10 (dd, 1 H, *J* = 6.3 Hz, *J* = 8.0 Hz), 4.22–4.41 (m, 2 H), 4.48–4.61 (m, 1 H), 5.72 (dd, 1 H, *J* = 6.0 Hz, *J* = 15.4 Hz), 5.83 (dt, 1 H, *J* = 5.7 Hz, *J* = 15.4 Hz), 7.31 (s, 1 H), 9.17 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 19.7 (CH_2), 22.7 (CH_2), 25.8 (CH_3), 26.7 (CH_3), 28.6 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.9 (CH_2), 49.3 (CH_2), 69.3 (CH_2), 70.8, 75.9 (CH), 95.9, 101.3, 109.8, 126.6 (CH), 133.4 (CH), 145.4 (CH), 149.8, 162.2. HRMS (ESI): *m/z* calcd for $C_{22}H_{32}N_2O_4Na$: 411.2260 $[M + Na]^+$. Found: 411.2259.

(16) **General Procedure for Alkyne Cyclization Reactions:** Under dry nitrogen, the alkyne derivatives (0.047 mmol) were dissolved in acetone (1 mL), then $AgNO_3$ (0.009 mmol) was added. The reaction was stirred at r.t. until complete conversion was reached. After evaporation of volatiles, the crude residue was dissolved in EtOAc, washed 3 times with H_2O, dried over $MgSO_4$, filtered and concentred in vacuo. The cyclized compound was pure enough (purity determined by proton-decoupled ^{13}C NMR) to be subjected to the next reaction without further purification.

(17) **3-[(*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-6-(4-pentylphenyl)furo[2,3-*d*]pyrimidin-2-(3*H*)-one (15a):** ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, 3 H, *J* = 6.7 Hz), 1.21–1.41 (m, 4 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 1.55–1.71 (m, 2 H), 2.64 (t, 2 H, *J* = 7.3 Hz), 3.61 (dd, 1 H, *J* = 8.0 Hz), 4.11 (dd, 1 H, *J* = 6.1 Hz, *J* = 8.0 Hz), 4.50–4.76 (m, 3 H), 5.77 (dd, 1 H, *J* = 7.0 Hz, *J* = 15.5 Hz), 6.01 (dt, 1 H, *J* = 6.0 Hz, *J* = 15.5 Hz), 6.64 (s, 1 H), 7.25 (d, 2 H, *J* = 8.1 Hz), 7.66 (d, 2 H, *J* = 8.1 Hz), 7.89 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 22.6 (CH_2), 25.9 (CH_3), 26.7 (CH_3), 31.0 (CH_2), 31.5 (CH_2), 35.9 (CH_2), 52.4 (CH_2), 69.3 (CH_2), 76.1 (CH), 96.4 (CH), 108.9, 109.8, 125.1 (CH × 2), 125.7, 127.5 (CH), 129.2 (CH × 2), 133.4 (CH), 138.9 (CH), 145.4, 155.2, 156.4, 171.9. HRMS (ESI): *m/z* calcd for $C_{25}H_{30}N_2O_4Na$: 445.5186 $[M + Na]^+$. Found: 445.5182.

(18) **General Procedure for Deprotection of Acetalic Derivatives:** The protected derivative (acetal, 0.22 mmol) was stirred at r.t. for 3 h in a mixture of TFA–H_2O (10 mL/5 mL). After evaporation of volatiles the crude residue was purified by flash chromatography.

(19) **General Procedure for Deacetylation:** Acetylated nucleoside analogue (1 mmol) was dissolved in pyridine (10 mL) and EtOH (5 mL). The reaction mixture was cooled to –10 °C and 5 mL of 1 M NaOH aq solution was added. The resulting solution was stirred at this temperature until completion (typically 1–4 h, followed by TLC). The reaction mixture was neutralized with Dowex (H^+ form) then filtered through a fritted glass funnel. Solvents were evaporated in vacuo and the oily residue was submitted to a flash column chromatography using an appropriate eluent (typically hexanes–EtOAc 25:75, EtOAc, and MeOH–EtOAc 1%) to furnish the desired nucleosides.

(20) **1-[(*E*)-4,5-dihydroxy-2-pentenyl]-5-[2-(4-pentylphenyl)ethynyl]-2,4 (1*H*,3*H*)-pyrimidinedione (6a):** ^{1}H NMR (DMSO-d_6): δ = 0.73–0.91 (m, 3 H), 1.18–1.37 (m, 4 H), 1.49–1.68 (m, 2 H), 2.57 (t, 2 H, *J* = 7.5 Hz), 3.22–3.33 (m, 2 H), 3.91–4.03 (m, 1 H), 4.25–4.39 (m, 2 H), 4.51–4.61 (m, OH), 4.86 (d, OH, *J* = 4.5 Hz), 5.69–5.85 (m, 2 H), 7.22 (d, 2 H, *J* = 8.0 Hz), 7.36 (d, 2 H, *J* = 8.0 Hz), 8.10 (s, 1 H) 11.64 (s, NH). ^{13}C NMR (DMSO-d_6): δ = 13.9 (CH_3), 21.9 (CH_2), 30.3 (CH_2), 30.8 (CH_2), 34.9 (CH_2), 48.9 (CH_2), 65.7 (CH_2), 71.4 (CH), 81.6, 92.0, 97.7, 119.6, 123.7 (CH), 128.7 (CH × 2), 131.0 (CH × 2), 135.8 (CH), 143.2, 148.3 (CH), 149.8, 161.9. HRMS (ESI): *m/z* calcd for $C_{22}H_{26}N_2O_4Na$: 405.1790 $[M + Na]^+$. Found: 405.1791.