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Zinc-Catalyzed Cycloisomerizations. Synthesis of Substituted Furans and Furopyrimidine Nucleosides

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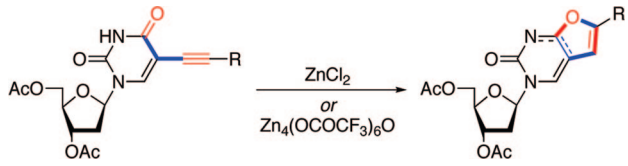

5-*Endo-dig* cycloisomerization of 1,4- and 1,2,4- mostly aryl-substituted but-3-yn-1-ones in the presence of a catalytic amount of zinc chloride etherate (10 mol %) in dichloromethane at room temperature gave 2,5-di- and 2,3,5-trisubstituted furans in high yields (85−97%). DSC studies confirmed that a solely thermal process does not take place. A relevant catalytic process, employing μ-oxo-tetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$, yielded bicyclic furopyrimidine nucleosides, when starting from acetyl-protected 5-alkynyl-2′-deoxyuridines (85−86%). Furopyrimidine was deprotected or simultaneously converted into pyrrolopyrimidine nucleoside. The time/concentration dependence for the reaction of 1-phenyl-4-(4-methylphenyl)butynone to 2-(4-methylphenyl)-5-phenylfuran displayed first-order kinetics with the rate dependent on catalyst concentration. The plot of ln k_{obs} versus ln[$ZnCl_2$] indicated first-order cycloisomerization, as referred to $ZnCl_2$ concentration, using both NMR and UV−vis reaction monitoring. The crystal structure of propyl furopyrimidine nucleoside (orthorhombic, $P2_12_12_1$, $a/b/c$ = 5.684(2)/6.682(2)/36.02(2) Å, Z = 4) shows C2′-*endo* deoxyribose puckering, and the base is found in the *anti* position in crystalline form.

Introduction

The furan unit can be found in biologically active compounds and natural products and is a useful synthetic intermediate. Thus, development of synthetic methods that provide access to highly substituted furans is an active area of investigation, despite existing significant achievements.[1,2]

Partly due to perfect atom economy, intramolecular cycloisomerization reactions involving unsaturated functional groups are at the frontiers of the synthetic schemes. Internal nucleophiles, containing oxygen, derived from alcohols, oxiranes, or carbonyl compounds have been successfully used for furan formation. A variety of catalysts have been applied for the cycloisomerization of oxo-alkynyl/allenyl compounds. Reactions of alkynyloxiranes,[3–6] (*Z*)-alk-2-en-4-yn-1-ols,[7–11] alka-2,3-dien-

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1-ones,[8,12–16] alk-2-yn-1-ones,[17–19] alk-4-yn-1-ones,[20–24] 2-(1-alkynyl)-2-alken-1-ones,[8,25,26] and alka-2,3,4-trien-1-ols[27] all furnished furans.

We have focused attention on starting materials containing but-3-yn-1-one (homopropargylic ketone) moiety.[28] Similarly, several catalysts have been used for the conversion of alk-3-yn-1-ones to furans. In addition to Brønstedt bases,[29] derivatives of metals such as silver,[12] palladium,[30] gold,[14,31] or mercury[32] have been applied for furans or related heterocycles[33] formation. Those methods offer useful routes, but moderate yields, elevated reaction temperatures, or costs are currently challenging some of these procedures. Also important, when considering potential biological activity, is the cytotoxicity of the metal and its residues in the final product. This concern requires the use of scavengers. Therefore, in an effort to continue method development, we have investigated easy-to-handle, inexpensive, and readily available zinc derivatives that also provide catalytic behavior similar to the currently available systems, without affecting the bioactivity of the products.[34]

Flexibility of coordination combined with soft Lewis acidity makes zinc centers useful for catalysis. However, the formation of ring systems with the use of zinc halides has not been extensively explored.[35] For example, ZnI_2-catalyzed cyclization of propargylic *N*-hydroxylamines to 2,3-dihydroisoxazoles has been observed in DMAP.[36] Synthesis of furans from alk-2-yn-1-ones in the presence of $ZnBr_2$ and *i*-Pr_2NEt (MeCN, 40−50 °C, 24 h) has also been reported.[19] Relatively few cyclization reactions have been pursued with the aid of $ZnCl_2$. The protocol usually includes stoichiometric use of the zinc reagent. For instance, 2-alkynylphenols are converted into benzofurans with the use of *n*-BuLi/$ZnCl_2$ in refluxing toluene.[37] Cyclocondensation of 1-hydroxy-2-methoxyalk-3-yne in the presence of $ZnCl_2$ in refluxing CCl_4 has produced furan ring.[38] Thus, we further explored the potential of Zn-catalyzed procedures.

Results and Discussion

In pursuit of an inexpensive, mild, and efficient synthesis of 2,5-di- and 2,3,5-trisubstituted furans, a variety of commercially available zinc salts was selected for examination (Table 1). In a glovebox, 0.1 M solutions of ZnI_2, $ZnBr_2$, or $ZnCl_2$ in ether

TABLE 1. Effect of Catalyst on the Cycloisomerization of 1a to 2a (R = Ph, R′ = H, R″ *p*-MeC$_6$H$_4$)[a]

catalyst	time (h)	yield (%)[b]
ZnI_2[c]	24	41
$ZnBr_2$[c]	24	54
$ZnCl_2$[c]	24[d]	>99
$ZnCl_2$[e]	1	>99
$Zn(OAc)_2$[f]	24	<2
$Zn(OTf)_2$[f]	24	7
Zn phthalocyanine	24	<2
$Zn_4(OCOCF_3)_6O$	2[g]	>99

[a] Reactions were carried out on a 0.213 mmol scale using 0.11 M solution of **1a** in CH_2Cl_2 in drybox with 10 mol % of Zn catalyst unless referenced otherwise. [b] As determined by ^{1}H NMR after quenching the reaction with water. [c] 0.1 M Et_2O solution (prepared). [d] Incomplete conversion after 20 h. [e] 1.0 M Et_2O solution (commercial). [f] Suspension. [g] 2.5 mol % (10 mol % based on atomic zinc); incomplete conversion after 1 h.

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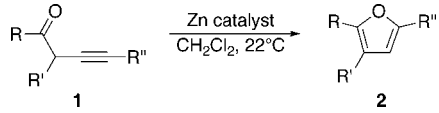
SCHEME 1. Synthesis of Furans 2[a]



[a] For catalyst and substrate structures, see Tables 1 and 2.

were added to ketone **1a** (R = Ph, R′ = H, R″ = *p*-MeC_6H_4; Scheme 1). Despite stirring at room temperature for 24 h, significant but not complete conversion to **2a** was observed with $ZnBr_2$ and ZnI_2. On the other hand quantitative formation of **2a** was achieved with $ZnCl_2$. Interestingly, the order of reactivity was $ZnCl_2$ > $ZnBr_2$ > ZnI_2 (Table 1).[39,40]

The catalytic properties of the $ZnCl_2$/ether combination have been investigated by Mayr's group for the addition of chlorodiphenylmethane to methylpentene.[41] The highest activity was observed at a $ZnCl_2$/ether ratio that optimized homogenity with a minimum amount of ether. An increased amount of ether resulted in slower conversion. Thus, following this lead, we turned our attention to 1.0 M $ZnCl_2$ etherate,[42] an inexpensive commercially available reagent that provided homogenity in the reactions and complete conversion within 1 h at a $ZnCl_2$/ether molar ratio of 1:9.6.

Zinc acetate, triflate, and phthalocyanine all gave negligible conversion after 24 h. The zinc tetranuclear cluster $Zn_4(OCOCF_3)_6O$ (**3**, Figure 1; discussed below) yielded a homogeneous system and was very effective for conversion of **1a** to **2a** (Table 1). However, this reagent was not pursued for preparative scale reactions leading to furans **2** as it did not offer a distinctive advantage over the readily available $ZnCl_2$.

After catalyst selection, preparative reactions were attempted. Alk-3-yn-1-ones (**1a**−**h**) were prepared from the respective alk-3-yn-1-ols, which are available via alkynylation of oxiranes; procedures in DMSO,[43] or with BF_3 in THF[44] were both effective. The oxidation of alk-3-yn-1-ols was carried out with the Dess−Martin reagent[45] or with the Jones reagent,[46–48] at up to a 5 g scale (**1c**).[49] Alk-3-yn-1-ones are prone to isomerization to the corresponding allenes,[50,51] but this was not pertinent for the procedures for **1a**−**f**,**h**. In most cases triple bond stabilization by conjugation to an aromatic ring most likely precluded isomerization.[52] During attempted purification, contact with silica gel led to complex mixtures, which is most likely the reason that a silica-gel-supported Jones reagent[53] was not effective. Although the Dess−Martin procedure requires separate preparation of the oxidant, it offered milder conditions and was superior for the synthesis of labile methoxymethyl alkynone **1g**.

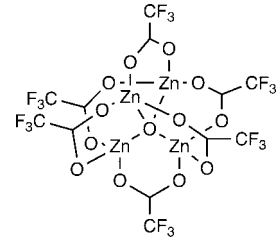


FIGURE 1. Molecular structure of μ-oxo-zinc tetranuclear cluster **3**.

Synthesis of furans **2a**−**h** was accomplished on a scale of 1−3 mmol. Examination of postreaction mixtures by ^{1}H NMR indicated quantitative conversions of **1** to the furans **2**. Compounds with combinations of substituents such as aryl (phenyl, *p*-alkylphenyls, *p*-halophenyls), alkyl (propyl), cycloalkyl (cyclopropyl, fused cyclohexyl), and ether (methoxymethyl) were produced with 85−97% yield (Table 2). Simple filtration through a silica gel pad allowed for the effective isolation of products. An $AgNO_3$ test of the filtrate showed no trace of chloride. Most of the furans gave highly accurate (±0.1%) elemental analyses. Compounds **2a**−**h** were characterized by NMR, IR, MS, and UV−vis spectroscopy. The data agreed with those previously reported for NMR[54] and UV[55] characterization of substituted furans. The molecular structure of furan **2d** was also confirmed by X-ray crystallography.[34]

The most straightforward mechanistic outline of the reaction includes activation of a triple bond by coordination with a Zn atom. However, in a related cycloisomerization of propargylic *N*-hydroxylamines to oxazoles (DMAP, CH_2Cl_2), the requirement for base was explained by the coordination of Zn to the oxygen atom of *N*-hydroxylamine.[36] In addition, coordination of zinc to oxygen is well documented in structurally characterized enolates.[56] Thus, we attempted to gain more information about mechanistic features of the reaction by kinetic measurements.

Kinetic Studies. The formation of **2a** was monitored by ^{1}H NMR to determine the effective reaction rate ($CDCl_3$, 22.0 °C). Yields were based upon spectra integration, since no byproduct formation was observed and chemical shifts of reactant and product are well separated.[57] Figure 2 top illustrates the progress of the reaction for a zinc chloride load of 3−7 mol %. The reaction was essentially completed after 40 min at higher $ZnCl_2$ concentrations. Thus, for preparative experiments, the reaction can likely be carried out with less than 10% catalyst load and shorter times than is reported. For example, full conversion was reached within 10 min in the NMR tube at a higher concentra-

(39) A similar trend was observed when finely ground solids of ZnI_2, $ZnBr_2$, or $ZnCl_2$ were added. Despite stirring at room temperature for 24 h, such systems remained heterogeneous.

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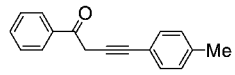
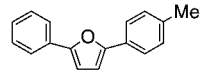
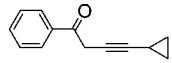
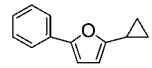
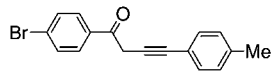
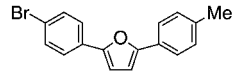
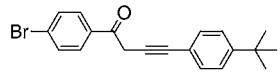
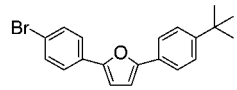
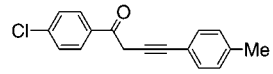
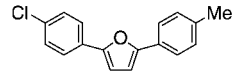
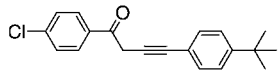
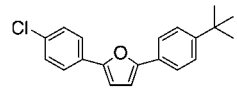
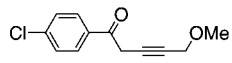
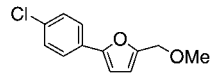
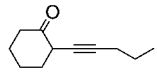
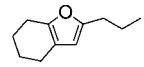
(57) See Supporting Information.

TABLE 2. Preparation of Furans 2 via Cycloisomerization of 1 with the Use of $ZnCl_2$

alkynone	number	furan	number	yield (%)[a]
	**1a**		**2a**[18]	97
	**1b**		**2b**	85
	**1c**		**2c**	90
	**1d**		**2d**	96
	**1e**		**2e**	89
	**1f**		**2f**	85
	**1g**		**2g**	65[b]
	**1h**		**2h**	89[c]

[a] Reactions were carried out on a 1.0 mmol scale with 10 mol % of $ZnCl_2$, in CH_2Cl_2 at room temperature for 2 h, unless referenced otherwise. Yields >99% as determined by ^1H NMR. [b] 0.18 mol % of $ZnCl_2$, crude **1g** was used as a substrate. [c] 3.2 mmol scale.

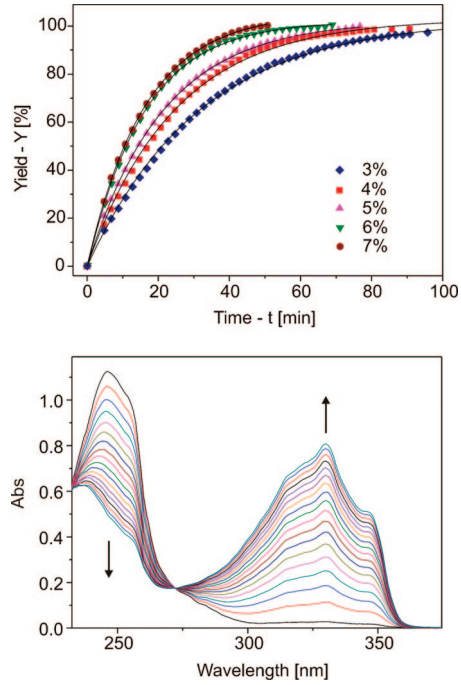


FIGURE 2. Progress of cycloisomerization of **1a** with $ZnCl_2$ in $CDCl_3$ (^1H NMR, 22.0 °C, [**1a**] = 0.0854 M) (top) and in CH_2Cl_2 (132 equiv, UV−vis, 24.0 °C, [**1a**] = 3.35 × 10^{-5} M) (bottom).

tion of **1a**. The aromatization reaction can also be readily monitored by UV−vis spectroscopy, due to the well-separated absorption maxima of the acyclic substrate **1a** and the aromatic product **2a**. This allowed the collection of additional data points at high catalyst load (12.5−170 equiv) by measuring the absorbance at 255/330 nm (decay/growth, CH_2Cl_2, 24 °C; Figure 2 bottom).

All kinetic curves showed a very good fit to the pseudo-first-order equation.[57] The kinetics are first-order, since $ZnCl_2$ acts as a catalyst and the concentration can be assumed constant over the course of the reaction. Thus, the rate of the reaction can be expressed as $V = k[ZnCl_2]^x$[**1a**], where x denotes an unknown order of the reaction relative to $ZnCl_2$, i.e., the number of zinc atoms participating in the reaction. Simplifying the reaction to pseudo-first-order gives $V = k_{obs}$[**1a**], where $k_{obs} = k[ZnCl_2]^x$ (k_{obs} is the observed first-order rate constant, and k is the rate of cycloisomerization in the presence of the catalyst). Therefore the relationship of ln k_{obs} versus ln[$ZnCl_2$] should be linear (ln k_{obs} = ln k + x ln[$ZnCl_2$]) and indeed, a good linear regression fit was found using $x = 0.84 \pm 0.10$ and ln $k = 1.58 \pm 0.54$ for NMR, $x = 0.85 \pm 0.10/0.95 \pm 0.13$ and ln $k = 1.43 \pm 0.59/1.94 \pm 0.79$ for UV−vis growth/decay (Figure 3). Thus, despite the widely different concentrations and substrate/catalyst ratios used, both NMR and UV−vis methods produced similar results. For combined all data points the best linear regression for the relationship of ln k_{obs} versus ln[$ZnCl_2$] was obtained with $x \approx 1$ (0.94 ± 0.07), which indicates a first-order reaction in $ZnCl_2$ and the participation of only one zinc atom in the reaction mechanism. Therefore, assuming $x = 1$, from the dependence $k_{obs} = k[ZnCl_2]$, a rate constant for catalytic cycloisomerization can be estimated as $k = (11.50 \pm 0.40)$ M^{-1} min^{-1}.[58] Supporting Information contains the results of the Levenberg−Marquardt fitting procedure for all concentrations of $ZnCl_2$ in the form of

(58) $k = (0.191 \pm 0.007)$ M^{-1} s^{-1}.

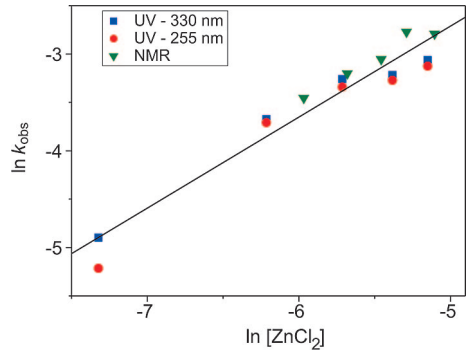


FIGURE 3. Plot of ln k_{obs} versus ln[$ZnCl_2$] for ^{1}H NMR and UV−vis growth/decay observations.

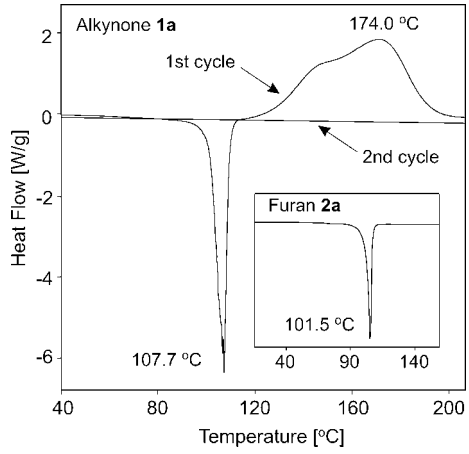


FIGURE 4. DSC traces for alkynone **1a** and (inset) for furan **2a**.

figures that include the calculated kinetic parameters (final yield, k_{obs}), errors, and R^2 values. The presence of an isosbestic point in the UV−vis spectra can be used to support the contention that the reaction proceeds with a limited number or no intermediates that occur within the UV−vis time frame.

The possible noncatalytic process of cycloisomerization of but-3-yn-1-ones[59] was investigated by differential scanning calorimetry (DSC), which has been shown to be helpful in analyzing thermolytic reactions.[60] The thermal cyclization of **1a** in the absence of solvent and catalyst was studied by DSC in the range between 0 and 250 °C. Figure 4 shows DSC data that exhibit a melting peak of the alkynone **1a** at 107.7 °C and an exothermic process starting at about 128 °C. No melting or recrystallization was observed when repeat scans were performed, regardless of the heating or cooling rate in the repeated runs. This included a melting point at 101.5 °C characteristic for **2a** (Figure 4 inset). In addition, weight loss was noticed above 128 °C with the aid of thermogravimetric analysis (TGA). Altogether, mass loss of 14% was observed in samples heated up to 254 °C. Furthermore, ^{1}H NMR monitoring of **1a** preheated in NMR tubes in the range of 140−180 °C confirmed the degradation of **1a** and did not indicate the formation of **2a**. Thus, it can be concluded that thermal cycloisomerization of but-3-yn-1-ones is not a viable alternative to the catalyzed reaction.

Furopyrimidine nucleosides are potent and selective antiviral agents with high specific activity against the varicella-zoster virus (VZV).[61] These bicyclic nucleosides are routinely produced via a cyclization of 5-alkynyl-2′-deoxyuridines.[62,63] Commonly, copper/amine and/or palladium are used to catalyze this reaction, frequently in a one-pot coupling/cyclization procedure. However, residual traces of these metals may affect biological activity determinations, and the reported yields are often moderate.[64] More recently, a silver catalyst was used effectively for the cyclization,[65] but difficulties in separating silver from the furopyrimidines were reported.[66] Considering the importance of these bicyclic nucleosides, we decided to examine the use of zinc catalysts to produce furopyrimidines. Derivatives containing 4-alkylphenyl and *n*-alkyl substituents are among the most active structures.[61] Accordingly, a representative nucleoside of each group was chosen to pursue (Scheme 2).

SCHEME 2. Synthesis of Furopyrimidine Nucleosides 5

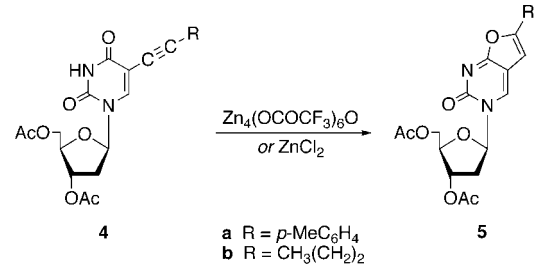


TABLE 3. Optimization of the Cycloisomerization of Nucleoside 4a to 5a

catalyst	amount	time (h)	solvent/temperature (°C)	yield (%)[a]
$ZnCl_2$	1.8 equiv	20	CH_2Cl_2/22	99 (89)
$ZnCl_2$	10 mol %	20	DCE/reflux	64
$ZnCl_2$	20 mol %	20	DCE/reflux	86
$ZnCl_2$	30 mol %	20	DCE/reflux	88
$ZnCl_2$	40 mol %	20	DCE/reflux	94
$Zn_4(OCOCF_3)_6O$	1 mol %	20	DCE/reflux	48
$Zn_4(OCOCF_3)_6O$	2 mol %	20	DCE/reflux	71
$Zn_4(OCOCF_3)_6O$	3 mol %	30	DCE/reflux	99 (86)

[a] ^{1}H NMR yield; yield of isolated product in parenthesis.

Acyl protection of the ribose hydroxyl groups prevented interaction of hydroxyl groups with the catalyst and afforded greater solubility of the nucleosides in the reaction solvent. Although preparative conversion of acetylated 5-*p*-tolylethynyl-2′-deoxyuridine **4a** (R = *p*-MeC_6H_4)[62,67] to furopyrimidine nucleoside **5a** was accomplished (89% yield), 1.8 equiv of $ZnCl_2$ at room temperature (dichloromethane) or 0.4 equiv of $ZnCl_2$ in refluxing DCE for **4a** were required (20 h, Table 3). Thus, we turned our attention to the μ-oxo-tetranuclear zinc cluster **3**.[68] This compound effectively catalyzes the direct conversion

(59) Flash vacuum thermolysis reactions of allenyl ketones are known: (a) Jullien, J.; Pechine, J. M.; Perez, F.; Piade, J. J. *Tetrahedron* **1982**, *38*, 1413–1416. (b) Huntsman, W. D.; Yin, T.-K. *J. Org. Chem.* **1983**, *48*, 3813–3814.

(60) Kappe, T.; Stadlbauer, W. *Molecules* **1996**, *1*, 255–263, and references therein.

(61) (a) McGuigan, C.; Balzarini, J. *Antiviral Res.* **2006**, *71*, 149–153. (b) De Clercq, E. D. *Med. Res. Rev.* **2003**, *23*, 253–274.

(62) Robins, M. J.; Barr, P. J. *J. Org. Chem.* **1983**, *48*, 1854–1862.

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(64) McGuigan, C.; Barucki, H.; Blewett, S.; Carangio, A.; Erichsen, J. T.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2000**, *43*, 4993–4997.

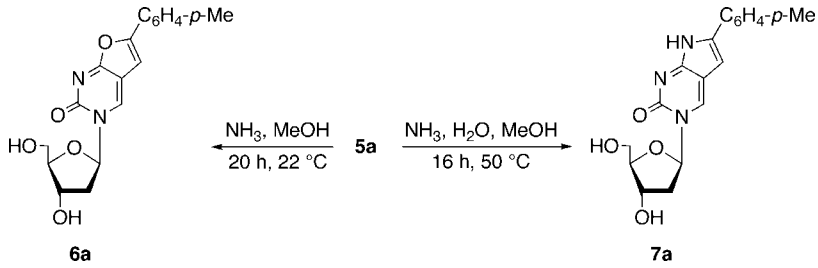
(65) (a) Amblard, F.; Aucagne, V.; Guenot, P.; Schinazi, R. F.; Agrofoglio, L. A. *Bioorg. Med. Chem.* **2005**, *13*, 1239–1248. (b) Aucagne, V.; Amblard, F.; Agrofoglio, L. A. *Synlett* **2006**, 2406–2408.

(66) Hudson, R. H. E.; Moszynski, J. M. *Synlett* **2006**, 2997–3000.

(67) Esho, N.; Davies, B.; Lee, J.; Dembinski, R. *Chem. Commun.* **2002**, 332–333.

(68) Ohshima, T.; Iwasaki, T.; Mashima, K. *Chem. Commun.* **2006**, 2711–2713.

SCHEME 3. Deprotection of Furopyrimidine Nucleoside 5a and Its Conversion to Pyrrolopyrimidine 7a



of esters, lactones, and carboxylic acids to oxazolines in high yield.[68] It has also been found to be highly effective in a transesterification reaction.[69,70] Previously the cluster **3** was shown to be highly effective for cyclization of butynone **1a**. Only 3 mol % of $Zn_4(OCOCF_3)_6O$ with the alkynyluridines **4a/b** in refluxing DCE for 30 h was needed to produce furopyrimidine nucleosides **5a/b** in 86%/85% yields. Purification was achieved with column chromatography with the use of a low polarity eluent, as a result of acetylated hydroxyl groups. Atomic absorption spectrometry confirmed the absence of significant amounts of Zn in the products **5a**,**b**.

Ammonia is the commonly used reagent for the deprotection of acyl groups from the ribose hydroxyl function.[71] It is also known that at elevated temperatures ammonia converts furopyrimidines into pyrrolopyrimidines,[72,73] which may form unusual base pairs.[74] This transformation is also observed during classical deprotection of synthetic oligonucleotides, in which incorporated furopyrimidines are quantitatively converted into pyrrolopyrimidines.[75] These observations prompted us to take advantage of different reaction conditions. Accordingly, combination of two reactions in a one-pot procedure gave unprotected pyrrolopyrimidine **7a** in 57% yield (50 °C, 16 h, Scheme 3). Although almost quantitative conversion was observed by TLC, the presence of acetamide in the post reaction mixture required careful chromatography for effective isolation of pyrrolo nucleoside **7a**. Alternatively, protected nucleoside **5a**[76] was deacetylated to yield furanopyrimidine **6a** in 91% yield when treated with ammonia/methanol at room temperature for 20 h (Scheme 3).[77]

The structure of nucleosides **5**, **6**, and **7** was confirmed by NMR, IR, MS, and UV−vis spectroscopy. In addition, the molecular structure of nucleoside **6b** that was obtained in a similar manner as **6a** (87% yield) was confirmed by X-ray crystallography (Figure 5).[78] In solid state, the ribose adopted a C2′-*endo* conformation and the ribose−base distance, C1′−N3, is 1.4850(19) Å. The C2 carbonyl group of **6b** adopted an *anti* orientation toward the ribose ring: the glycosidic bond torsion angle χ (O4′−C1′−N3−C2) is −153.26(13)°. The C5′−O5′ bond is +*sc* to the C4′−C3′ bond, which can be visualized by the O5′−C5′−C4′−C3′ torsion angle γ = 48.48(18)°. Packing diagrams and a crystallographical table are available.[57]

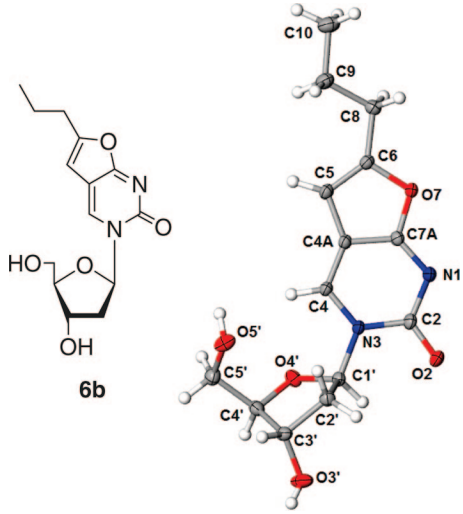


FIGURE 5. ORTEP view and a molecular structure of **6b** with the atom-labeling scheme. Thermal ellipsoids at the 50% probability level.

In summary, we have demonstrated that $ZnCl_2$ and the $Zn_4(OCOCF_3)_6O$ cluster **3** are efficient, metallic catalysts for quantitative cycloisomerization of the but-3-yn-1-ones **1** at room temperature in the absence of base to furans **2** and also for conversion of acylated 5-alkynyl-2′-deoxyuridines **4** to furanopyrimidines **5**. The kinetics for $ZnCl_2$-catalyzed conversion of **1a** to **2a** was shown to be pseudo-first-order. It was also determined that the reaction could not be carried out in a thermal, noncatalytic mode. The cluster **3** exceeds the reactivity of $ZnCl_2$ for nucleosides and equals its reactivity observed during the synthesis of the furans. A relatively short reaction time and inexpensive, easy to handle catalysts provide an appealing alternative to currently available methods. Our approach allows for the facile and effective preparation of substituted furans and biologically active furopyrimidine nucleosides. This method, with excellent atom economy, facilitates the introduction of furans substituents, such as cyclopropyl, that are not easily carried out by other methods[79] and tolerates most functional groups present in nucleosides.

Experimental Section

General Procedure for Alk-3-yn-1-ones (1) with the Use of Dess−Martin Periodinane.[52,80] A round-bottom flask was charged with Dess−Martin periodinane (3.54 mmol) and CH_2Cl_2 (22 mL).

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(71) See for example: Neilson, T.; Werstiuk, E. S. *Can. J. Chem.* **1971**, *49*, 493–499.
(72) (a) Woo, J.; Meyer, R. B.; Gamper, H. B. *Nucleic Acids Res.* **1996**, *24*, 2470–2475. (b) Hudson, R. H. E.; Ghorbani-Choghamarani, A. *Synlett* **2007**, 870–873.
(73) MeONa can be used for deacylation of furanopyrimidines in solution.[65b]
(74) (a) Dash, C.; Rausch, J. W.; Le Grice, S. F. J. *Nucleic Acids Res.* **2004**, *32*, 1539–1547. (b) Liu, C.; Martin, C. T. *J. Biol. Chem.* **2002**, *277*, 2725–2731.
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(77) For deacetylation at 0 °C see: Robins, M. J.; Nowak, I.; Rajwanshi, V. K.; Miranda, K.; Cannon, J. F.; Peterson, M. A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2007**, *50*, 3897–3905.

A solution of alk-3-yn-1-ol (2.95 mmol) in CH_2Cl_2 (14 mL) was added dropwise via syringe. The solution was stirred under nitrogen atmosphere at room temperature. After 1 h TLC showed complete conversion of the substrate. Sodium thiosulfate aqueous solution (1.5 g) in saturated $NaHCO_3$ (60 mL) was added to reaction mixture, which was then stirred until two clear phases were formed. The aqueous phase was extracted with ether (3 × 50 mL). The combined organic layers were washed with saturated solution of $NaHCO_3$ (30 mL). The organic phase was dried over Na_2SO_4, and solvent was removed by rotary evaporation. The resulting solid was dried for 6 h under oil pump vacuum (volatile liquid samples were treated carefully at room temperature by rotary evaporator equipped with a water pump) to give **1**, which was used in the next step without further purification.

General Procedure for Synthesis of Furans (2). A round-bottom flask was charged with **1** (1.00 mmol) and CH_2Cl_2 (10 mL). Zinc chloride (1.0 M in ether, 0.10 mL, 0.10 mmol) was added dropwise via syringe. The solution was stirred at room temperature for 2 h. ^{1}H NMR/TLC showed complete conversion of the substrate. Reaction mixture was passed through a silica gel column (2.5 cm × 15 cm; CH_2Cl_2). The solvent was removed by rotary evaporation, and the residue was dried by oil pump vacuum for 3 h to give **2**. Volatile liquid samples were treated carefully at room temperature by a rotary evaporator equipped with a water pump.

2-(4-Methylphenyl)-5-phenylfuran (2a).[18] From 4-(4-methylphenyl)-1-phenylbut-3-yn-1-one (**1a**) (0.234 g, 1.00 mmol), CH_2Cl_2 (10 mL), and $ZnCl_2$ (1.0 M in ether; 0.10 mL, 0.10 mmol). White solid of **2a** (0.227 g, 0.970 mmol, 97%). DSC (T_p) 101.5 °C. Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.05; H, 6.03. UV−vis (ε, M^{-1} cm^{-1}; ether; 4.7 × 10^{-5} M) 227 (11000), 326 (28000). MS 234 (M^+, 100%); no other peaks of >20%. Other spectral data matched those reported earlier.[81]

2-Cyclopropyl-5-phenylfuran (2b). From 4-cyclopropyl-1-phenylbut-3-yn-1-one (**1b**) (0.184 g, 1.00 mmol), CH_2Cl_2 (10 mL), and $ZnCl_2$ (1.0 M in ether; 0.10 mL, 0.10 mmol). Colorless oil of **2b** (0.156 g, 0.846 mmol, 85%). Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.63; 6.79. IR (cm^{-1}, neat) 1487 s, 1448 s, 781 s, 757 s, 690 s. UV−vis (ε, M^{-1} cm^{-1}; ether; 7.6 × 10^{-5} M) 223 (14000), 291 (34000). MS 184 (M^+, 100%), 157 (40%), 128 (22%), 115 (30%), 105 (34%); no other peaks above 100 of >20%. NMR ($CDCl_3$):[82] ^{1}H 7.72−7.62 (m, 2H), 7.47−7.20 (m, 3H), 6.50 (d, 1H, J = 3.3), 6.00 (d, 1H, J = 3.4), 2.10−1.94 (m, 1H), 1.06−0.86 (m, 4H); ^{13}C 157.3, 151.8, 131.3, 128.7, 126.8, 123.4, 105.9, 105.7, 9.2, 7.1.

2-(4-Bromophenyl)-5-(4-methylphenyl)furan (2c). From 1-(4-bromophenyl)-4-(4-methylphenyl)but-3-yn-1-one (**1c**) (0.313 g, 1.00 mmol), CH_2Cl_2 (10 mL), and $ZnCl_2$ (1.0 M in ether; 0.10 mL, 0.10 mmol). White solid of **2c** (0.283 g, 0.904 mmol, 90%), mp 202−204 °C. Anal. Calcd for $C_{17}H_{13}BrO$: C, 65.19; H, 4.18. Found: C, 64.96; H, 4.17. IR (cm^{-1}, KBr) 1496 s, 1475 s, 826 s, 793 s. UV−vis (ε, M^{-1} cm^{-1}; ether; 3.5 × 10^{-5} M) 230 (13000), 332 (36000). MS 312 (M^+, 100%); no other peaks above 150 of >20%. NMR ($CDCl_3$): ^{1}H 7.63 (d, 2H, J = 8.1), 7.60 (d, 2H, J = 8.6), 7.51 (d, 2H, J = 8.6), 7.22 (d, 2H, J = 8.1), 6.73 (d, 1H, J = 3.3), 6.68 (d, 1H, J = 3.3), 2.38 (s, 3H); ^{13}C 154.1, 152.0, 137.6, 132.0, 129.9, 129.6, 128.0, 125.2, 123.9, 121.0, 107.9, 106.7, 21.5.

2-(4-Bromophenyl)-5-(4-*tert*-butylphenyl)furan (2d). From 1-(4-bromophenyl)-4-(4-*tert*-butylphenyl)but-3-yn-1-one (**1d**) (0.355 g, 1.00 mmol), CH_2Cl_2 (10 mL), and $ZnCl_2$ (1.0 M in ether; 0.10 mL, 0.10 mmol). White solid of **2d** (0.340 g, 0.957 mmol, 96%), mp 152−154 °C. Anal. Calcd for $C_{20}H_{19}BrO$: C, 67.61; H, 5.39. Found: C, 67.60; H, 5.41. IR (cm^{-1}, KBr) 1494 s, 1474 s, 834 s, 821 s, 792 s. UV−vis (ε, M^{-1} cm^{-1}; ether, 3.1 × 10^{-5} M) 230 (12000), 332 (34000). MS 354 (M^+, 87%), 339 ($(M\text{-}Me)^+$, 100%); no other peaks above 200 of >20%. NMR ($CDCl_3$): ^{1}H 7.67 (d, 2H, J = 8.5), 7.60 (d, 2H, J = 8.7), 7.51 (d, 2H, J = 8.7), 7.43 (d, 2H, J = 8.5), 6.73 (d, 1H, J = 3.5), 6.69 (d, 1H, J = 3.5), 1.36 (s, 9H); ^{13}C 154.1, 152.1, 150.9, 132.0, 129.9, 128.0, 125.8, 125.2, 123.8, 121.0, 107.9, 106.9, 34.8, 31.4.

2-(4-Chlorophenyl)-5-(4-methylphenyl)furan (2e). From 1-(4-chlorophenyl)-4-(4-methylphenyl)but-3-yn-1-one (**1e**) (0.269 g, 1.00 mmol), CH_2Cl_2 (10 mL), and $ZnCl_2$ (1.0 M in ether; 0.10 mL, 0.10 mmol). White solid of **2e** (0.240 g, 0.893 mmol, 89%), mp 188−190 °C. Anal. Calcd for $C_{17}H_{13}ClO$: C, 75.98; H, 4.88. Found: C, 75.98; H, 4.86. IR (cm^{-1}, KBr) 1497 s, 1479 s, 827 s, 793 s. UV−vis (ε, M^{-1} cm^{-1}; ether; 4.1 × 10^{-5} M) 229 (11000), 330 (28000). MS 268 (M^+, 100%); no other peaks above of >20%. NMR ($CDCl_3$): ^{1}H 7.66 (d, 2H, J = 8.6), 7.63 (d, 2H, J = 8.1), 7.36 (d, 2H, J = 8.6), 7.22 (d, 2H, J = 8.1), 6.72 (d, 1H, J = 3.5), 6.68 (d, 1H, J = 3.5), 2.38 (s, 3H); ^{13}C 154.1, 152.0, 137.6, 132.9, 129.6, 129.0, 128.0, 125.0, 123.9, 107.8, 106.7, 21.5.

2-(4-Chlorophenyl)-5-(*tert*-butylphenyl)furan (2f). From 1-(4-chlorophenyl)-4-(4-*tert*-butylphenyl)but-3-yn-1-one (**1f**) (0.311 g, 1.00 mmol), CH_2Cl_2 (10 mL), and $ZnCl_2$ (1.0 M in ether; 0.10 mL, 0.10 mmol). White solid of **2f** (0.263 g, 0.846 mmol, 85%), mp 141−143 °C. Anal. Calcd for $C_{20}H_{19}ClO$: C, 77.28; H, 6.16. Found: C, 77.07; H, 6.21. IR (cm^{-1}, KBr) 1494 s, 1477 s, 835 s, 824 s, 791 s. UV−vis (ε, M^{-1} cm^{-1}; ether; 3.5 × 10^{-5} M) 229 (10000), 331 (26000). MS 310 (M^+, 73%), 295 ($(M\text{-}Me)^+$, 100%); no other peaks above 150 of >20%. NMR ($CDCl_3$): ^{1}H 7.69 (d, 2H, J = 8.5), 7.66 (d, 2H, J = 8.6), 7.43 (d, 2H, J = 8.5), 7.37 (d, 2H, J = 8.6), 6.72 (d, 1H, J = 3.4), 6.69 (d, 1H, J = 3.4), 1.35 (s, 9H); ^{13}C 154.0, 152.1, 150.9, 132.9, 129.6, 129.0, 128.0, 125.8, 125.0, 123.7, 107.8, 106.9, 34.8, 31.4.

2-(4-Chlorophenyl)-5-(methoxymethyl)furan (2g). From crude 1-(4-chlorophenyl)-5-methoxypent-3-yn-1-one (**1g**) (0.223 g, 1.00 mmol), CH_2Cl_2 (10 mL), and $ZnCl_2$ (1.0 M in ether; 0.10 mL, 0.10 mmol). Yellow oil of **2g** (0.145 g, 0.651 mmol, 65%). Anal. Calcd for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.98. Found: C, 64.67; 4.92. IR (cm^{-1}, neat) 2927 s, 2821 s, 1482 s, 1205 s, 830 s, 789 s. UV−vis (ε, M^{-1} cm^{-1}; ether; 8.1 × 10^{-5} M) 221 (8000), 289 (27000). MS 222 (M^+, 31%), 191 ($(M - OMe)^+$, 100%); no other peaks above 150 of >20%. NMR ($CDCl_3$): ^{1}H 7.60 (d, 2H, J = 8.6), 7.33 (d, 2H, J = 8.6), 6.58 (d, 1H, J = 3.3), 6.40 (d, 1H, J = 3.3), 4.44 (s, 2H), 3.40 (s, 3H); ^{13}C 153.2, 151.6, 133.1, 129.2, 128.9, 125.1, 111.7, 106.1, 66.5, 57.9.

2-Propyl-4,5,6,7-tetrahydro-1-benzofuran (2h). From 2-(pent-1-yn-1-yl)cyclohexanone (**1h**) (0.527 g, 3.21 mmol), CH_2Cl_2 (15 mL), and $ZnCl_2$ (1.0 M in ether; 0.32 mL, 0.32 mmol). Colorless oil of **2h** (0.468 g, 2.85 mmol, 89%). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.27; H, 9.96. IR (cm^{-1}, neat) 1573 s, 1445 s. UV−vis (ε, M^{-1} cm^{-1}; ether; 1.3 × 10^{-4} M) 224 (10000). MS 164 (M^+, 77%), 135 (M − Et, 100%); no other peaks above 100 of >20%. NMR ($CDCl_3$): ^{1}H 5.76 (s, 1H), 2.52 (t, 4H, J = 7.3), 2.40−2.32 (m, 2H), 1.82−1.56 (m, 4H), 1.65 (p, 2H, J = 7.4), 0.95 (t, 3H, J = 7.4); ^{13}C 154.1, 148.7, 117.2, 105.7, 30.3, 23.4 (2C), 23.4, 22.3, 21.7, 13.9.

3-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(4-methylphenyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (5a).[76] *Method A* ($ZnCl_2$, CH_2Cl_2, room temperature). A round-bottom flask was charged with 3′,5′-di-*O*-acetyl-2′-deoxy-5-*p*-tolylethynyluridine (**4a**) (0.380 g, 0.891 mmol) and CH_2Cl_2 (8 mL). $ZnCl_2$ (1.0 M in ether; 1.60 mL, 1.60 mmol) was added dropwise via syringe in three equal parts every 1 h. The solution was stirred at room temperature for 20 h. ^{1}H NMR showed complete conversion of the substrate. Silica gel

(78) Crystallographic data (excluding structural factors) for the structure reported in this paper were also deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-683563. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223−336033.

(79) Donohoe, T. J.; Fishlock, L. P.; Lacy, A. R.; Procopiou, P. A. *Org. Lett.* **2007**, *9*, 953–956.

(80) Freshly prepared Dess−Martin periodinane reagent was used at 1.2 equiv stoichiometry. Prolonged storage of the reagent required the use of additional amounts, up to 1.5 equiv.

(81) Koga, Y.; Kusama, H.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 475–482.

(82) The ^{1}H and ^{13}C NMR chemical shifts are in ppm, and J values are in Hz.

column chromatography (2.5 cm × 15 cm; $CHCl_3 \rightarrow CHCl_3$/MeOH, 99:1) gave a colorless fraction. The solvent was removed by rotary evaporation, and the residue was dried by oil pump vacuum to give **5a** as a white solid (0.340 g, 0.797 mmol, 89%). *Method B* ($Zn_4(OCOCF_3)_6O$,[68] DCE, reflux). A round-bottom flask was charged with $Zn_4(OCOCF_3)_6O$ (0.0185 g, 0.0194 mmol), 3′,5′-di-*O*-acetyl-2′-deoxy-5-*p*-tolylethynyluridine (**4a**) (0.275 g, 0.645 mmol), and DCE (5 mL). The solution was stirred and refluxed for 30 h. ^{1}H NMR showed complete conversion of the substrate. Silica gel column chromatography (2.5 cm × 15 cm; $CHCl_3 \rightarrow CHCl_3$/MeOH, 99:1) gave a colorless fraction. The solvent was removed by rotary evaporation and the residue was dried by oil pump vacuum to give **5a** as a white solid (0.237 g, 0.556 mmol, 86%). Anal. Calcd for $C_{22}H_{22}N_2O_7$: C, 61.97; H, 5.20. Found: C, 62.02; H, 5.26. NMR ($CDCl_3$): ^{1}H 8.28 (s, 1H, H4), 7.61 (d, J = 8.2, 2H, *o*-$C_6H_4CH_3$), 7.21 (d, J = 8.2, 2H, *m*-$C_6H_4CH_3$), 6.67 (s, 1H, H5), 6.31 (dd, J = 7.6, 5.6, 1H, H1′), 5.22 (d, J = 6.4, 1H, H3′), 4.39 (s, 3H, H4′, H5′), 2.92 (ddd, J = 14.6, 5.6, 2.2, 1H, H2′), 2.36 (s, 3H, $C_6H_4CH_3$), 2.08 (s, 3H, $COCH_3$), 2.11−2.03 (m, 1H, H2′), 2.05 (s, 3H, $COCH_3$); ^{13}C 171.8 (m, C7a), 170.4 and 170.3 (2m, 2 $COCH_3$), 156.2 (t, J = 4.2, C6), 154.5 (br s, C2), 140.1 (q, J = 6.9, *p*-$C_6H_4CH_3$), 134.5 (d, J = 184.9, C4), 129.7 (d, J = 158.2, *m*-$C_6H_4CH_3$), 125.6 (t, J = 7.5, *i*-$C_6H_4CH_3$), 124.9 (br d, J = 156.4, *o*-$C_6H_4CH_3$), 108.4 (m, C4a), 96.7 (d, J = 180.2, C5), 88.5 (d, J = 175.3, C1′), 83.3 (d, J = 152.1, C4′), 74.2 (d, J = 158.2, C3′), 63.7 (t, J = 148.7, C5′), 39.3 (dd, J = 139.7, 132.8, C2′), 21.5 (q, J = 126.8, $C_6H_4CH_3$), 20.9 (q, J = 130.0, 2 $COCH_3$).

3-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-propylfuro[2,3-*d*]pyrimidin-2(3*H*)-one (5b). *Method A*: from 3′,5′-di-*O*-acetyl-2′-deoxy-5-pent-1-yn-1-yluridine (**4b**) (0.247 g, 0.653 mmol), CH_2Cl_2 (6 mL), and $ZnCl_2$ (1.0 M in ether; 1.20 mL, 1.20 mmol). White oil/foam of **5b** (0.210 g, 0.555 mmol, 85%). *Method B*: from 3′,5′-di-*O*-acetyl-2′-deoxy-5-pent-1-yn-1-yluridine (**4b**) (0.530 g, 1.40 mmol), $Zn_4(OCOCF_3)_6O$ (0.040 g, 0.042 mmol), and DCE (10 mL). White oil/foam of **5b** (0.450 g, 1.19 mmol, 85%). Anal. Calcd for $C_{18}H_{22}N_2O_7$: C, 57.14; H, 5.86. Found: C, 52.24; H, 5.45. IR (cm^{-1}, CH_2Cl_2) 1745 s, 1675 s, 1577 m, 1382 m, 1234 m. UV−vis (ε, M^{-1} cm^{-1}; MeOH; 3.7 × 10^{-5} M) 244 (5400), 331 (10000). MS 379 ($(M+H)^+$, 40%), 179 ($(B+H)^+$, 100%). NMR ($CDCl_3$):[83] ^{1}H 8.16 (s, 1H, H4), 6.33 (dd, J = 7.6, 5.6, 1H, H1′), 6.12 (s, 1H, H5), 5.22 (d, J = 6.6, 1H, H3′), 4.39 (s, 3H, H4′, H5′), 2.94 (ddd, J = 14.4, 5.6, 2.3, 1H, H2′), 2.63 (t, J = 7.5, 2H, H1″), 2.11 (s, 3H, $COCH_3$), 2.14−2.00 (m, 1H, H2′), 2.06 (s, 3H, $COCH_3$), 1.72 (sextet, J = 7.5, 2H, H2″), 0.99 (t, J = 7.5, 3H, H3″); ^{13}C 171.9 (dd, J = 9.4, 6.9, C7a), 170.4 and 170.2 (br s, 2 $COCH_3$), 160.0 (br s, C6), 154.5 (d, J = 5.5, C2), 133.8 (d, J = 184.7, C4), 107.9 (s, C4a), 98.9 (d, J = 180.2, C5), 88.3 (d, J = 173.9, C1′), 83.1 (d, J = 152.2, C4′), 74.0 (d, J = 137.6, C3′), 63.7 (t, J = 148.7, C5′), 39.1 (dd, J = 140.0, 133.1, C2′), 30.1 (t, J = 126.0, C1″), 20.8 (q, J = 130.1, 2 $COCH_3$), 20.1 (t, J = 128.0, C2″), 13.5 (q, J = 125.5, C3″).

3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-(4-methylphenyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (6a).[64] A round-bottom flask was charged with **5a** (0.106 g, 0.248 mmol), MeOH (5 mL), and ammonia (7.0 M in MeOH; 1.2 mL, 8.4 mmol). The solution was stirred at room temperature for 20 h. TLC showed complete conversion of the substrate. The reaction mixture was filtered, and the solid was dried by oil pump vacuum to give **6a** (0.064 g, 0.19 mmol, 75%). The solvent was removed from the filtrate by rotary evaporation, and the remaining product was suspended in $CHCl_3$ and sonicated. Filtration and drying by oil pump vacuum gave an additional amount of **6a** as a white solid (0.014 g, 0.041 mmol, 16%; total 0.078 g, 0.23 mmol, 91%). The spectral data matched those reported earlier.[64]

3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-propylfuro[2,3-*d*]pyrimidin-2(3*H*)-one (6b).[84] A round-bottom flask was charged with **5b** (0.270 g, 0.714 mmol), MeOH (10 mL), and ammonia (7.0 M in MeOH; 3.0 mL, 21 mmol). The solution was stirred at room temperature for 20 h. TLC showed complete conversion of the substrate. The solvent was removed by rotary evaporation and the residue was suspended in $CHCl_3$ and sonicated; MeOH (0.20 mL) was added (to dissolve acetamide, a byproduct). The solid was filtered off and dried by oil pump vacuum to give **6b** (0.128 g, 0.435 mmol, 61%). The solvent was removed from filtrate by rotary evaporation and the solid residue was suspended in $CHCl_3$ and sonicated. Filtration and drying by oil pump vacuum gave additional amount of white solid of **6b** (0.055 g, 0.19 mmol, 26%; total 0.183 g, 0.622 mmol, 87%). Anal. Calcd for $C_{14}H_{18}N_2O_5 \cdot {}^1/_2H_2O$: C, 55.44; H, 6.31. Found: C, 55.46; H, 6.13. IR (cm^{-1}, KBr) 3371 br, 3263 br, 1672 s, 1624 s, 1578 s, 1385 s, 1104 s, 784 s. UV−vis (ε, M^{-1} cm^{-1}; MeOH; 3.7 × 10^{-5} M) 225 (9800), 244 (8900), 331 (5200). MS 317 ($(M + Na)^+$, 27%), 295 (M^+, 24%), 179 ($(B + H)^+$, 100%). NMR (DMSO-d_6): ^{1}H 8.67 (s, 1H, H4), 6.43 (s, 1H, H5), 6.16 (t, J = 6.1, 1H, H1′), 5.28 (d, J = 4.2, 1H, OH3′), 5.12 (t, J = 5.1, 1H, OH5′), 4.36−4.16 (m, 1H, H3′), 3.99−3.82 (m, 1H, H4′), 3.78−3.51 (m, 2H, H5′), 2.62 (t, J = 7.3, 2H, H1″), 2.47−2.29 (m, 1H, H2′), 2.14−1.95 (m, 1H, H2′), 1.64 (sextet, J = 7.3, 2H, H2″), 0.93 (t, J = 7.3, 3H, H3″); ^{13}C 171.2 (m, C7a), 158.1 (br s, C6), 153.8 (d, J = 5.6, C2), 136.8 (d, J = 187.0, C4), 106.4 (s, C4a), 99.9 (d, J = 182.1, C5), 88.1 (d, J = 149.7, C4′), 87.4 (d, J = 173.4, C1′), 69.7 (d, J = 148.7, C3′), 60.8 (t, J = 139.9, C5′), 41.3 (C2′),[85] 29.3 (t, J = 130.3, C1″), 19.86 (t, J = 125.8, C2″), 13.4 (q, J = 121.5, C3″).

3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-(4-methylphenyl)-3,7-dihydro-2*H*-pyrrolo[2,3-*d*]pyrimidin-2-one (7a). A pressure vial was charged with **6a** (0.106 g, 0.248 mmol), MeOH (4 mL), and ammonia (30% aqueous solution; 4 mL). The vial was sealed, and the mixture was stirred at 50 °C for 16 h. ^{1}H NMR/TLC showed a complete conversion of the substrate. The solvent was removed by rotary evaporation. The residue was mixed with minimum amount of $CHCl_3$/MeOH and silica gel and, after evaporation, was charged on column (5 cm × 30 cm; $CHCl_3 \rightarrow CHCl_3$/MeOH, 92:8) gave a colorless fraction. The solvent was removed by rotary evaporation and the residue was dried by oil pump vacuum. The solid was dissolved in the minimum amount of MeOH and precipitated with excess of ether. Sonication of mixture for 10 min followed by filtration gave, after drying by oil pump vacuum, **7a** as a pale-yellow solid (0.048 g, 0.14 mmol, 57%). Anal. Calcd for $C_{18}H_{19}N_3O_4 \cdot 1.5\ H_2O$: C, 58.69; H, 6.02. Found: C, 58.70; H, 5.73. IR (cm^{-1}, KBr) 3344 br, 1656 s, 1570 s, 1452 m, 1096 m, 776 m. UV−vis (ε, M^{-1} cm^{-1}; MeOH; 3.2 × 10^{-5} M) 268 (22000), 367 (6600). MS 381 ($(M + K)^+$, 89%), 364 ($(M + Na)^+$, 100%), 342 (M^+, 6%). NMR (DMSO-d_6):[83] ^{1}H 11.72 (s, 1H, N7), 8.67 (s, 1H, H4), 7.72 and 7.27 (2d, J = 8.1, 2 × 2H, *o*- and *m*-$C_6H_4CH_3$), 6.66 (s, 1H, H5), 6.27 (t, J = 6.2, 1H, H1′), 5.27 (d, J = 4.1, 1H, OH3′), 5.14 (t, J = 5.0, 1H, OH5′), 4.38−4.19 (m, 1H, H3′), 3.90 (q, J = 3.4, 1H, H4′), 3.85−3.55 (m, 2H, H5′), 2.45−2.20 (m, 1H, H2′), 2.33 (s, CH_3), 2.17−1.96 (m, 1H, H2′); ^{13}C 159.9 (t, J = 7.1, C6), 153.8 (d, J = 4.8, C2), 139.5 and 137.9 (2s, *p*-$C_6H_4CH_3$ and C7a), 136.0 (d, J = 184.1, C4), 129.5 (d, J = 160.3, *m*- or *o*-$C_6H_4CH_3$), 127.8 (s, *p*-$C_6H_4CH_3$), 125.0 (d, J = 159.2, *o*- or *m*-$C_6H_4CH_3$), 109.2 (s, C4a), 96.2 (d, J = 178.7, C5), 87.9 and 87.0 (d, J = 149.5 and d, J = 174.0, C1′ and C4′), 69.9 (d, J = 145.9, C3′), 61.0 (t, J = 140.9, C5′), 41.5 (t, J = 133.5, C2′), 20.9 (q, J = 126.7, $C_6H_4CH_3$).

Kinetic Analysis was carried out using the Levenberg−Marquardt algorithm implemented into the OriginPro 7.5 software. The first-order rate constant values (k_{obs}) were evaluated from the fitting procedure of product build-up versus time to the first-order exponential growth with two unknown parameters ($[X]_\infty$ and k_{obs}):

(83) The *i*/*o*/*m*/*p* positions were designated with respect to the pyrimidine group.

(84) Compound **6b** has been reported but no spectral data were given: Rai, D.; Johar, M.; Manning, T.; Agrawal, B.; Kunimoto, D. Y.; Kumar, R. *J. Med. Chem.* **2005**, *48*, 7012–7017.

(85) Multiplicity was not determined in the ^{13}C NMR spectrum (peaks were obscured).

$[X]_t = [X]_\infty \cdot (1 - \exp(-k_{obs} \cdot t))$, where $[X]_t$ is concentration of the product at time t, $[X]_\infty$ is final concentration of the product, and k_{obs} is first-order rate constant of the product build-up; or if presented as a yield of the product: $[Y]_t = [Y]_\infty \cdot (1 - \exp(-k_{obs} \cdot t))$, where $[Y]_t$ is yield of the product at time t, $[Y]_\infty$ is final yield of the product, and k_{obs} is first-order rate constant of the product build-up. The substrate decay (UV−vis measurements, absorption at 255 nm) followed the first-order exponential decay: $[A]_t = [A]_0 \cdot \exp(-k_{obs} \cdot t) + y_0$, where $[A]_t$ is absorbance of the substrate at 255 nm at time t, $[A]_0$ is initial absorption of the substrate, y_0 is baseline absorbance and k_{obs} is the first-order rate constant of the substrate decay.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1** and **4**; kinetic studies data; NMR spectra for compounds **1**, **4b**, **5**, **6b**, and **7a**; X-ray table and packing diagrams; and a separate cif file for compound **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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