Nucleic Acid Related Compounds. 87. Nucleophilic Functionalization of Cytidine and 2′-Deoxycytidine Derivatives via Elaboration of the 4-Amino Group into a Readily Displaced 1,2,4-Triazol-4-yl Substituent[1]

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Introduction

Nucleosides which contain substituents on the heterocyclic base other than the natural oxo and amino functionalities are important compounds for medicinal chemistry and biological studies. A common methodology for synthesis of such compounds involves modification/displacement of a natural functional group by a nucleophile.[2] Established procedures are available for conversion of pyrimidine 4 and purine 6-oxo functionalities into alkoxy, chloro, pyridinium, silyloxy, and sulfur leaving groups.[3,4] However, few methods have been described for accomplishing analogous transformations beginning with an amino group, and these are generally inconvenient.[5,6]

Divakar and Reese developed a method utilized frequently for transformation of a pyrimidine 4-oxo functionality into a good leaving group by treatment of uracil nucleoside derivatives with phosphoryl chloride and 1,2,4-triazole.[3a] The 4-oxo group is transformed into a 4-(1,2,4-triazol-1-yl) substituent by nucleophilic replacement of 4-*O*-phosphorylated species. This 4-(triazol-1-yl) moiety undergoes nucleophilic replacement readily to provide a mild and efficient route to 4-substituted pyrimidin-2-one nucleosides. Recently, we have demonstrated elaboration of an isomeric 1,2,4-triazol-4-yl ring onto the amino group of purine, pyrrolo[2,3-*d*]pyrimidine, and pyrazolo[4,3-*d*]pyrimidine nucleosides. Triazole was displaced by several nucleophiles to give the substituted base analogues.[1,7] We now report new applications of this methodology for transformation of *unprotected* cytidine and 2′-deoxycytidine into 4-substituted pyrimidin-2-one nucleosides.

Results and Discussion

In situ displacement of the initially formed triazole moiety by dimethylamine liberated from the azine reagent occurred upon treatment of 2′,3′,5′-tri-*O*-acetylcytidine (**1b**, Scheme 1) with 1,2-bis[(dimethylamino)-methylene]hydrazine dihydrochloride[7] (**2′**). Analogous generation of a 7-(dimethylamino)pyrazolo[4,3-*d*]pyrimidine derivative was observed in reactions with formycin.[1] Thus, treatment of **1b** with **2′** in pyridine at 100 °C for 12 h gave quantitative conversion to the 4-(dimethylamino) product **5b**. In the less basic solvent *N,N*-dimethylformamide (DMF), mixtures of **5b**, 4-(1,2,4-triazol-4-yl) derivative **3b**, and its isomeric 4-(1,2,4-triazol-1-yl) derivative **4b**[3a] were obtained. The latter presumably was formed via nucleophilic replacement of the initial 4-(triazol-4-yl) moiety from **3b** by triazole generated in situ. NMR spectroscopy (Tables 1 and 2) provided ready differentiation of the symmetric (**3b**) and unsymmetric (**4b**) triazole substitution. Several attempts to trap/inactivate dimethylamine liberated during the cyclization reaction were unsuccessful, so alternative methods were evaluated for elaboration of a triazole ring onto an amino group.[8]

The chlorobenzylidene azine (PhClC=N–N=CClPh) is known to react with primary amines to give 4-substituted 3,5-diphenyl-1,2,4-triazoles.[9] Treatment of **1b** with this azine in pyridine at 100 °C for 5 h gave a product with ^{1}H NMR and mass spectral data consistent with the expected 4-(3,5-diphenyl-1,2,4-triazol-4-yl) derivative. However, treatment of this material with aqueous dimethylamine did not give the 4-(dimethylamino) compound. It is possible that the bulky phenyl rings on the triazole moiety are oriented orthogonally with respect to the pyrimidine ring and effectively block approach of a nucleophile. Since no displacement products were observed, this approach was abandoned.

Diformylhydrazine (**6**) is known to react with amines to give 4-substituted 1,2,4-triazoles.[10] However, literature methods employed high temperatures (180–250 °C),[11] and some also required Lewis acids. Such condi-

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Scheme 1

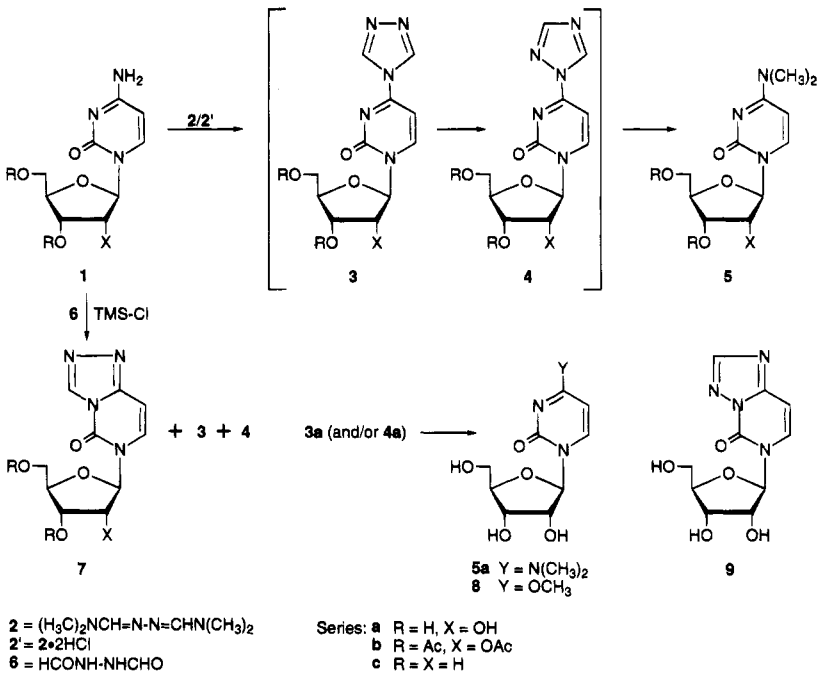


Table 1. ^{1}H NMR Spectral Data[a,b]

compd	H1′ [c] ($J_{1'-2'}$)	H2′/H2″ [d] ($J_{2'-3'}$)	H3′ [d] ($J_{3'-4'}$)	H4′ [d] ($J_{4'-5',5''}$)	H5′,5″ [e,f] ($J_{5'-5''}$)	H5 [c] (J_{5-6})	H6 [c]	H(Triaz) [g]	OH5′ [h] (J_{HO-CH_2})	OH3′ [c] (J_{HO-CH})	OH2′ [c] (J_{HO-CH})
3a	5.78 (1.4)	3.94–4.04	3.94–4.04	3.94–4.04 (1.8, 1.7)	3.85, 3.65 (12.3)	7.10 (7.3)	8.92	9.35	5.34 (4.7)	5.05 (5.8)	5.67 (4.6)
3c	6.10[h] (6.2), (5.6)[j]	2.39[e]/2.13[e] (4.9), (6.2),[i] (13.3)[m]	4.25 (3.1)	3.91[e] (3.3, 3.8)	3.55–3.76,[d] 3.71, 3.61[j,k] (12.1)	7.08 (7.3)	8.77	9.35	5.20 (5.0)	5.32 (4.4)	
4a	5.80 (2.1)	3.94–4.08	3.94–4.08	3.94–4.08 (1.7, 1.6)	3.82, 3.63 (11.9)	6.98 (7.2)	8.84	9.45,[n] 8.41[o]	5.26 (4.7)	5.06 (5.9)	5.64 (4.7)
7b	6.14 (4.9)	5.55[j] (6.2)	5.39[j] (5.2)	4.23–4.41	4.23–4.41[d]	6.97[p] (8.0)	7.61[q]	9.30[r]	*s*	*s*	*s*

[a] Chemical shifts (δ) at 200 MHz in Me_2SO-d_6 unless noted otherwise. [b] "Apparent" first-order coupling constants (Hz, in parentheses). [c] Doublet unless noted otherwise. [d] Multiplet unless noted otherwise. [e] Doublet of doublets of doublets unless noted otherwise. [f] Upfield resonance assigned to H5″ (*pro-R*). [g] Singlet. [h] Triplet. [i] ($J_{2''-3'}$). [j] Doublet of doublets. [k] After D_2O exchange. [l] ($J_{1'-2''}$). [m] ($J_{2'-2''}$). [n] Triazole-H5. [o] Triazole-H3. [p] H8 (J_{8-7}). [q] H7. [r] H3. [s] Singlets (OAc) at δ 2.06, 2.07, and 2.09.

Table 2. ^{13}C NMR Spectral Data[a,b]

compd	C2	C4	C5[c]	C6[c]	C1′	C2′	C3′	C4′	C5′	C(Triaz)
3a	154.02	157.11	94.77	148.42	91.42	74.81	68.04	84.25	59.37	140.74
3c	153.87	157.04	94.73	148.17	87.35	41.23	69.44	88.38	60.63	140.74
4a[c]	154.00	158.84	93.91	148.63	91.41	74.84	68.36	84.41	59.69	143.95 (C5″) 154.37 (C3″)

compd	C5	C7	C8	C8a	C1′	C2′	C3′	C4′	C5′	C3
7b[d]	144.29[e]	131.87	96.30	148.70[e]	88.79	72.62	69.66	79.61	63.15	137.79

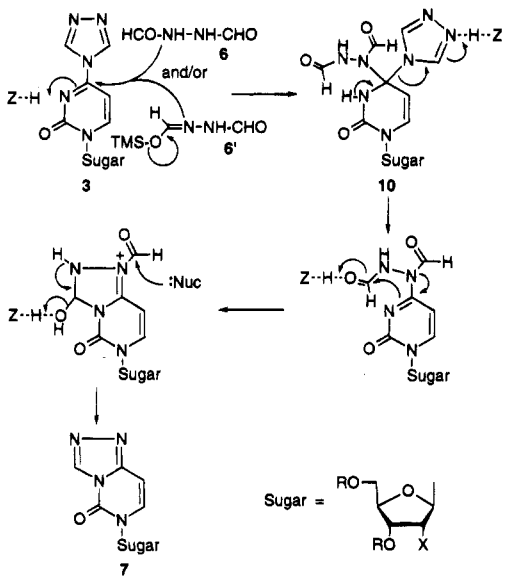
[a] Chemical shifts (δ) at 50.3 MHz in Me_2SO-d_6. [b] Proton-decoupled singlets. [c] Assignments verified by HETCOR. [d] Also peaks (OAc) at δ 20.53, 20.61, 20.84; 169.58 and 170.32. [e] Assignments might be reversed.

tions were expected to be too harsh for nucleoside substrates. We considered that TMS-Cl might be an effective Lewis acid which could bond preferentially with oxygen and activate diformylhydrazine in preference to protecting the 4-amino group. Its dehydrating ability should help drive the reaction, and both hydroxyl protection and reagent activation could be accomplished in situ. We had found that TMS-protected purine nucleosides were stable at 100 °C for 24 h with TMS-Cl, and the TMS group was removed readily by solvolysis.[1]

No reaction was observed upon treatment of 2′,3′,5′-tri-*O*-acetylcytidine (**1b**) with **6** in pyridine at 100 °C. However, analogous treatment of **1b** with **6** and TMS-Cl at 80 °C gave the 4-(1,2,4-triazol-4-yl) product **3b**, although considerable starting material remained. Enhanced formation of a byproduct [**7b**, UV (MeOH) λ_{max} 260 nm] and decreased levels of **3b** were observed at increased reaction temperatures. Similar results were obtained with cytidine (**1a**). Treatment of **1a** with **6** and TMS-Cl in pyridine gave **3a** (after workup) plus a significant quantity of byproduct **7a**. Treatment of purified **3a** with **6** and TMS-Cl in pyridine resulted in slow formation of **7a**, and similar results were observed upon heating **3a** and **6** in pyridine in the absence of TMS-Cl. This indicated that diformylhydrazine (**6**) can displace triazole during the cyclization reaction, and presumably silylated diformylhydrazine species also could participate.

A mechanistic process consistent with formation of the 6-glycosyl-1,2,4-triazolo[4,3-c]pyrimidin-5-one byproducts **7** is presented in Scheme 2. Nucleophilic addition of diformylhydrazine **6** or a trimethylsilylated derivative **6′**

Scheme 2



to the highly reactive 3–4 bond of the 4-(1,2,4-triazol-4-yl) intermediate **3** would give the tetrahedral addition complex **10**. Elimination of triazole, ring closure by nucleophilic attack of N3 at the formamidyl carbonyl group, and deformylation/dehydration would give byproduct **7**. This process is consistent with formation of **7** from **3**, but alternative mechanisms involving direct attack of diformylhydrazine (**6**) and/or silylated **6'** at C4 of cytidine derivatives followed by ring closure/deformylation/dehydration processes may also occur. Maeda and Kawazoe prepared isomer **9** (Scheme 1) of compound **7** by treatment of 3-aminocytidine with ethyl orthoformate/acetic acid at elevated temperature,[12] and a 3-methyl derivative of **7a** has been reported.[13]

Apparently, protonation of cytidine (pK_a ~4.2)[14] retards conversion of starting material into the 4-(1,2,4-triazol-4-yl) product **3**. Conditions that produced high concentrations of pyridinium acids also resulted in no observed **3**, but formation of **7** occurred. Conditions that produced intermediate levels of pyridinium acids also favored formation of **7**. Addition of certain bases prevented formation of **3**. However, the use of triethylamine allowed adequate activation of **6** with neutralization of excess acid and minimal formation of **7**. Treatment of **1a** with **6**/TMS-Cl/Et_3N/pyridine at 80 °C for 2 days gave 1-(β-D-ribofuranosyl)-4-(1,2,4-triazol-4-yl)pyrimidin-2-one (**3a**, 71%).

Divakar and Reese obtained the 4-(1,2,4-triazol-1-yl) compounds via nucleophilic attack by triazole on 4-*O*-phosphorylated intermediates.[3a] We confirmed that our 4-(1,2,4-triazol-4-yl) isomer **3a** is thermodynamically less stable than its 4-(1,2,4-triazol-1-yl) counterpart **4a**. Treatment of **3a** with ~5 equiv of 1,2,4-triazole in pyridine at 100 °C resulted in its conversion into **4a**. We then attempted to exploit this enhanced stability in an in situ cyclization process with cytidine (**1a**). Treatment of **1a** with **6**/TMS-Cl/Et_3N/1,2,4-triazole/pyridine at 80 °C for 24 h gave 1-(β-D-ribofuranosyl)-4-(1,2,4-triazol-1-yl)pyrimidin-2-one (**4a**, 75%). Thus, addition of triazole resulted in reduction of the reaction time by about half. However, significant formation of **7a** occurred, and the yield of **4a** (75%) was not improved significantly relative to formation of isomer **3a** (71%) in the absence of exogenous triazole.

Application of this diformylhydrazine/triazole procedure to 2'-deoxycytidine (**1c**) resulted in glycosyl cleavage, and attempts to reduce cleavage by moderating the acidity of the reaction mixture favored formation of **7c**. We then employed a procedure that was successful for the preparation of an analogously reactive triazole derivative from formycin.[1] Treatment of **1c** with 1,2-bis-[(dimethylamino)methylene]hydrazine[1,15] (**2**) and TMS-Cl in toluene at 70 °C for 17 h gave 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-4-(1,2,4-triazol-4-yl)pyrimidin-2-one (**3c**, 80%). The structure of a minor byproduct in this reaction was consistent with **7c**. Apparently, azine **2** can displace triazole from **3** and form a fused-ring system by a process similar to that illustrated in Scheme 2. The **2**/TMS-Cl/toluene procedure was applied to cytidine to give **3a** (81%) after 12.5 h. This is more convenient and also gives a higher yield than the diformylhydrazine method.

Treatment of **3a** with 40% $HNMe_2/H_2O$ at ambient temperature gave 4-(dimethylamino)-1-(β-D-ribofuranosyl)pyrimidin-2-one (**5a**, 86%). Treatment of **3a** in methanol on a column of Dowex 1 × 2 (OH^-) resin (soaked in MeOH) gave 4-methoxy-1-(β-D-ribofuranosyl)pyrimidin-2-one (**8**, 99.7%).

In summary, we have shown that the synthetically useful 4-(1,2,4-triazol-4-yl) substituent can be constructed onto the 4-amino group of *unprotected* cytidine and 2'-deoxycytidine in high yields without chromatography. These compounds are less thermodynamically stable than their 4-(1,2,4-triazol-1-yl) isomers synthesized by the Divakar–Reese procedure from uracil nucleosides[3a] and undergo smooth nucleophilic displacement of the triazole moiety to give 4-substituted pyrimidin-2-one nucleosides. This further demonstrates the scope and utility of the triazole-elaboration methodology developed in this laboratory with aminopurine derivatives and analogues.[1,7] Cytosine nucleosides can now be utilized as convenient starting materials for the preparation of 4-substituted pyrimidin-2-one products for the first time.

Experimental Section

Uncorrected melting points were determined with a capillary melting point apparatus. UV spectra were determined with solutions in MeOH. NMR spectra were obtained with solutions in Me_2SO-d_6 with Me_4Si as internal standard [^1H (200 MHz); ^{13}C (50.3 MHz)]. Mass spectra were determined at 20 eV by direct sample introduction. TLC was performed using Whatman Al Sil G/UV 254 plates. Reagent grade chemicals were used, and reaction solvents except toluene were distilled before use. Pyridine was dried by reflux over and distillation from CaH_2. TMS-Cl was distilled before use. All cyclization reactions were conducted under N_2 or Ar with a leak-proof Teflon sleeve on the ground-glass joint of the condenser. Volatiles were flash evaporated at ≤35 °C under water aspirator or mechanical oil pump vacuum. Solid products were dried in vacuo over P_4O_{10} at elevated temperatures, except **7b**. Optimization of conditions for individual nucleoside precursors has been pursued. Yields can suffer markedly by alteration of described concentrations for triazole cyclization reactions, cold workup conditions, etc.

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1-(β-D-Ribofuranosyl)-4-(1,2,4-triazol-4-yl)pyrimidin-2-one (3a). Method A. A mixture of cytidine (**1a**; 568 mg, 2.34 mmol) and **6** (720 mg, 8.18 mmol) was suspended in dry pyridine and evaporated (3×). Pyridine (5 mL), TMS-Cl (4.44 mL, 35 mmol), and Et_3N (2.17 mL, 15.6 mmol) were added, and the mixture was heated at 80 °C for 48 h (the thick suspension was initially fractured with a Teflon rod to allow magnetic stirring). Volatiles were evaporated, and the residue was dissolved in ice-cold CH_2Cl_2 (85 mL). The solution was washed with [brine (34 mL) + satd $NaHCO_3/H_2O$ (17 mL)] and [brine (34 mL) + 2 M HCl/H_2O (17 mL)] and filtered through Na_2SO_4. Volatiles were evaporated, and the residue was stirred in acetone (30 mL)/H_2O (5 mL) for 2 h. The suspension was filtered, and the solid was dried in vacuo to give **3a** (490 mg, 71%): mp 206.5–208 °C dec; UV max 311, 237 nm (ε 7300, 9500), min 267, 233 nm (ε 1200, 9500); MS *m/z* 296 (0.6, M + H), 163 (57, B + H), 164 (62, B + 2H). Anal. Calcd for $C_{11}H_{13}N_5O_5$ (295.3): C, 44.75; H, 4.44; N, 23.72. Found: C, 44.59; H, 4.50; N, 23.52.

Method B. TMS-Cl (0.33 mL, 2.6 mmol) was added to a suspension of **1a** (206 mg, 0.847 mmol) and **2**[1,15] (337 mg, 2.37 mmol) in toluene (13 mL), the mixture was heated at 70 °C for 12.5 h, and volatiles were evaporated. The residue was dissolved in CH_2Cl_2 (50 mL, at 5 °C) and washed with 1 M HCl/H_2O (12 mL), and the solution was filtered through Na_2SO_4. Volatiles were evaporated, and the residue was stirred with [MeOH (30 mL) + H_2O (5 mL) + "1 drop" of 5% $HOAc/H_2O$] at ambient temperature for 24 h. Volatiles were evaporated, and the residue was suspended in MeOH and filtered. The white solid was dried in vacuo to give **3a** (203 mg, 81%): mp 201.5–203.5 °C dec. NMR spectra were identical with those obtained with a sample from method A.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-4-(1,2,4-triazol-4-yl)pyrimidin-2-one (3c). A suspension of 2′-deoxycytidine (**1c**; 219 mg, 0.964 mmol) and **2**[1,15] (332 mg, 2.33 mmol) in toluene (13 mL) was treated with TMS-Cl (0.260 mL, 2.05 mmol) was stirred at ambient temperature (0.5 h) and then 70 °C (17 h), and volatiles were evaporated. The residue was dissolved in CH_2Cl_2 (50 mL at 5 °C), washed with cold 1 M HCl/H_2O (12 mL), and filtered through Na_2SO_4. Volatiles were evaporated, the residue was stirred with MeOH at ambient temperature for 10 h, volatiles were evaporated, the residue was suspended in MeOH, and the suspension was filtered. The white solid was dried to give **3c** (216 mg, 80%): mp 175–176 °C softening, 217–220 °C dec; UV max 311 nm (ε 7900), min 266 nm (ε 1200) shoulder 233 nm; MS *m/z* 163 (100, B + H), 164 (18, B + 2H). Anal. Calcd for $C_{11}H_{13}N_5O_4$ (279.3): C, 47.31; H, 4.69; N, 25.08. Found: C, 47.45; H, 4.76; N, 25.20.

1-(β-D-Ribofuranosyl)-4-(1,2,4-triazol-1-yl)pyrimidin-2-one (4a). A suspension of cytidine (**1a**; 713 mg, 2.93 mmol), diformylhydrazine (**6**; 644 mg, 7.31 mmol), and 1,2,4-triazole (1.01 g, 14.6 mmol) in pyridine (5 mL) was treated with TMS-Cl (4.46 mL, 35.1 mmol) and Et_3N (2.18 mL, 15.6 mmol) and heated (80 °C, 24 h). Volatiles were evaporated, and the residue was partitioned [ice-cold CH_2Cl_2 (85 mL) and ice-cold brine (34 mL) + satd $NaHCO_3/H_2O$ (17 mL)]. The organic layer was washed [ice-cold brine (64 mL) + 2 M HCl/H_2O (34 mL)], filtered through Na_2SO_4, and evaporated. The residue was stirred (4 °C, 24 h) in CH_2Cl_2/MeOH (4:1, 45 mL), and the suspension was filtered to give a fluffy white solid which was dried in vacuo to give **4a** (653 mg, 75%): mp 208.5–210 °C; UV max 313, 249 nm (ε 8000, 12 700), min 277, 232 nm (ε 2200, 6900); MS *m/z* 295 (2, M^+), 164 (100, B + 2H). Anal. Calcd for $C_{11}H_{13}N_5O_5$ (295.3): C, 44.75; H, 4.44; N, 23.72. Found: C, 44.81; H, 4.56; N, 23.62.

6-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-4*H*-1,2,4-triazolo-[4,3-*c*]pyrimidin-5-one (7b). TMS-Cl (0.16 mL, 1.3 mmol) was added to 2′,3′,5′-tri-*O*-acetylcytidine (**1b**; 45.5 mg, 0.123 mmol) and diformylhydrazine (**6**; 38 mg, 0.43 mmol) in pyridine (1 mL), and the mixture was heated at 100 °C for 2 days. Volatiles were evaporated and the residue was flash chromatographed (CH_2Cl_2/MeOH, 97:3) to give analytically pure **7b** (6.1 mg, 13%) as a glassy solid: UV max 258 nm (ε 13 000), min 217 nm (ε 1900); MS *m/z* 394 (11, M^+). Anal. Calcd for $C_{16}H_{18}N_4O_8$ (394.3): C, 48.73; H, 4.60; N, 14.21. Found: C, 48.90; H, 4.73; N, 14.09. Bordering chromatographic fractions with trace impurities gave an additional 8.1 mg of **7b** (total: 14.2 mg, 29%).

4-(Dimethylamino)-1-(β-D-ribofuranosyl)pyrimidin-2-one (5a). Treatment of **3a** (39 mg, 0.13 mmol) with 40% $HNMe_2/H_2O$ (1 mL) at ambient temperature for 15 min, evaporation of volatiles, and passage of the residue through a column of Dowex 1 × 2 (OH^-) [H_2O; H_2O/MeOH (1:1); MeOH] gave a product that was heated with acetonitrile and evaporated (2×) to give white solid **5a** (30.9 mg, 86%): mp 158–161 °C (lit.[16] mp 158–160 °C); UV max 279 nm (ε 13 100), min 237 nm (ε 5700); MS *m/z* 271 (2, M^+), 272 (6, M + 1). Anal. Calcd for $C_{11}H_{17}N_3O_5$ (271.3): C, 48.70; H, 6.32; N, 15.49. Found: C, 48.63; H, 6.38; N, 15.40.

4-Methoxy-1-(β-D-ribofuranosyl)pyrimidin-2-one (8). A sample of **3a** (45.2 mg, 0.153 mmol) was mixed with the surface of a column of Dowex 1 × 2 (OH^-) resin (soaked in MeOH) and allowed to stand for 2–3 days. The product was eluted with MeOH, volatiles were evaporated, and the residue was heated with acetonitrile and evaporated (3×). The white solid was dried to give **8** (39.4 mg, 99.7%): mp 137.5–139 °C (lit.[3i] mp 141–142 °C); UV max 276 nm (ε 6100), min 238 nm (ε 1100); MS *m/z* 258 (2, M^+), 259 (6, M + 1). Anal. Calcd for $C_{10}H_{14}N_2O_6$ (258.2): C, 46.51; H, 5.46; N, 10.85. Found: C, 46.56; H, 5.31; N, 10.96.

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