Use of Hydrogen Bonds To Control Molecular Aggregation. Behavior of Dipyridones and Pyridone–Pyrimidones Designed To Form Cyclic Triplexes

Éric Boucher,[1] Michel Simard, and James D. Wuest*,[2]

Département de Chimie, Université de Montréal, Montréal, Québec, H3C 3J7 Canada

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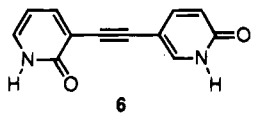
The tendency of 2-pyridones and related heterocycles to form cyclic hydrogen-bonded dimers allows them to be used as sticky sites that induce molecules in which they are incorporated to associate in particular ways. Compound **7**, which is constructed from pyridone and pyrimidone subunits linked to a rigid linear acetylenic spacer, incorporates an array of hydrogen-bonding sites designed to favor the formation of a cyclic triplex. Pyridone–pyrimidone **7** was synthesized and the structure of its DMSO solvate was determined by X-ray crystallography. Aggregation does not produce a cyclic triplex but rather gives chains in which adjacent molecules of compound **7** are linked by single hydrogen bonds.

The tendency of 2-pyridones and related heterocycles to form cyclic hydrogen-bonded dimers allows them to be used as sticky sites that induce molecules in which they are incorporated to associate in particular ways.[3] For example, linking two pyridones to linear spacers at the 3 and 6′ positions creates self-complementary molecules **1** that are able to form strong antiparallel duplexes **2** joined by four hydrogen bonds (Scheme 1, eq 1).[3g] In contrast, isomeric 6,6′-linked dipyridone **3** and the analogous 3,3′-linked structure are not fully self-complementary and must therefore form linear oligomers (Scheme 1, eq 2). These simple examples show that the systematic attachment of sticky heterocyclic subunits to well-chosen frameworks can be a powerful strategy for constructing molecules predisposed to associate in particular ways.[3] A notable advantage of this strategy is that it provides access to markedly different patterns of aggregation by the simple expedient of reorienting the sticky heterocyclic subunits, rather than by the more complex process of synthesizing entirely new types of associating molecules.

In principle, dipyridones **4** created by linking pyridones to rigid linear spacers at the 3 and 5′ positions contain arrays of hydrogen-bonding sites that are perfectly self-complementary in cyclic triplexes **5** (Scheme 1, eq 3).[3f,4] The rigidity of dipyridone **4** allows us to estimate that $\Delta H°$ for the trimerization of eq 3 will be approximately −17.7 kcal/mol in $CHCl_3$, three times $\Delta H°$ for the dimerization of 2-pyridone,[5,6] and that $\Delta S°$ will be approximately −21.4 eu, twice $\Delta S°$ for the dimerization of 2-pyridone.[5,8] As a result, $\Delta G°$ for the trimerization of eq 3 should be about −11 kcal/mol in $CHCl_3$ at 25 °C, making triplex **5** a potentially important species even in relatively dilute solutions. In this paper, we describe the synthesis and chemical behavior of two compounds, acetylenic dipyridone **6** and the closely related pyridone–pyrimidone **7**, that have been designed to form cyclic triplexes of this type.



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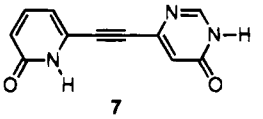

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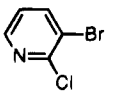
Acetylenic dipyridone **6** was prepared in the following way. An improved procedure was devised for converting 2-chloro-3-pyridinamine into 3-bromo-2-chloropyridine (**8**),[9] which was then used to make 3-ethynyl-2-(phenylmethoxy)pyridine (**9**) by the published method.[3g] In addition, the known 5-bromo-2-(phenylmethoxy)pyridine (**10**)[10] was prepared from 2,5-dibromopyridine by an improved method. Deprotonation of ethynylpyridine **9**



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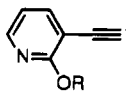
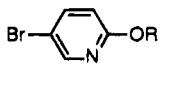
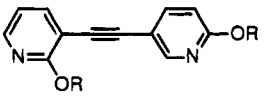


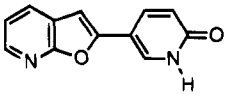
9 (R = CH_2Ph)



10 (R = CH_2Ph)



11 (R = CH_2Ph)



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(1) Fellow of the Ministère de l'Éducation du Québec (FCAR), 1990–1992.

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(6) Separation of the pyridone subunits by a rigid linear spacer ensures that each subunit will make an approximately additive contribution to the overall enthalpy of association. Secondary electrostatic interactions in the aggregate will be similar to those in the dimer of 2-pyridone itself.[7]

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(8) (a) This is a very crude approximation that neglects the loss of entropy of rotation around the spacer as well as other factors. (b) For a discussion of $\Delta S°$ in the formation of hydrogen-bonded dimers, see: Doig, A. J.; Williams, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 338. Williams, D. H. *Aldrichim. Acta* **1992**, *25*, 9.

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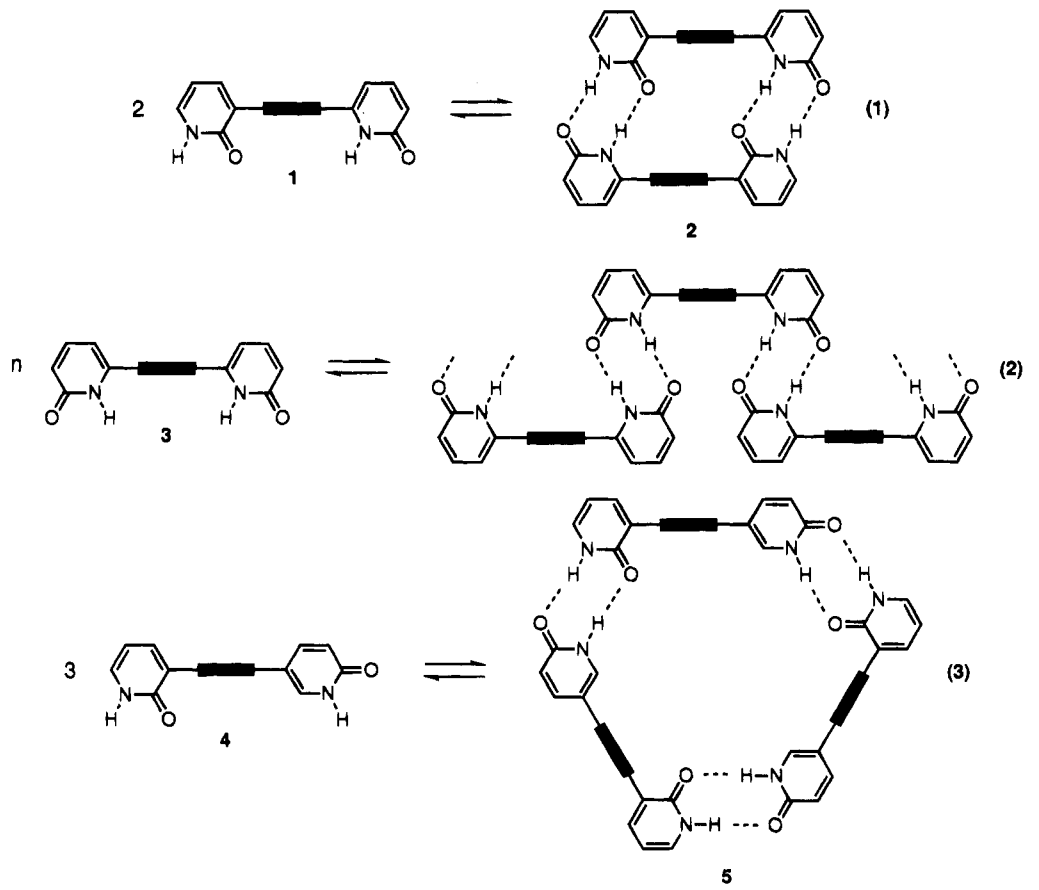
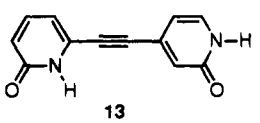
Scheme 1



(BuLi), followed by the addition of $ZnCl_2$, bromopyridine **10**, and a catalytic amount of $Pd(PPh_3)_4$, then provided the coupled product **11** in 74% yield.[11] Careful deprotection (CF_3COOH, 25 °C)[12] then gave the the corresponding 3,5′-dipyridone **6** in quantitative yield. Although compound **6** could be isolated and partially characterized, it proved to be unstable in solution and was transformed rapidly into furopyridine **12** by intramolecular addition to the triple bond.[3d,13] As a result, we were unable to crystallize dipyridone **6**, purify it, or study its aggregation in solution or in the solid state.

A similar cyclization cannot occur in isomeric dipyridone **13**. Unfortunately, however, its synthesis would require coupling an acetylene with suitable 4-substituted derivatives of 2-pyridone, which are not readily available.



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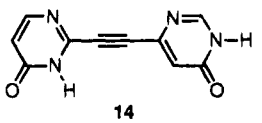

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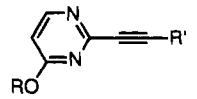
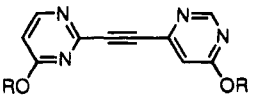


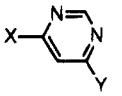
15 (R = CH_3, R' = $Si(CH_3)_3$)

16 (R = CH_3, R' = H)



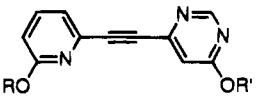
17 (R = CH_3)

We expected the related dipyrimidone **14** and the pyridone-pyrimidone **7** to be more accessible, and we were able to synthesize protected derivatives by the following procedures. Coupling of (trimethylsilyl)acetylene with 2-chloro-4-methoxypyrimidine,[14] carried out in $N(C_2H_5)_3$ containing catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI,[15] gave an 89% yield of compound **15**, which was converted by treatment with tetrabutylammonium fluoride into ethynylpyrimidine **16** in 70% yield. Compound **16** was then converted into the protected derivative **17** of dipyrimidone **14** in 69% yield by a similar coupling with 4-iodo-6-methoxypyrimidine (**18**), which was prepared in



18 (X = OCH_3, Y = I)

19 (X = Y = I)



20 (R = CH_2Ph, R' = CH_3)

69% overall yield by using aqueous HI to convert 4,6-dichloropyrimidine into 4,6-diiodopyrimidine (**19**),[16] followed by the addition of an equimolar amount of sodium methoxide. Unfortunately, all attempts to deprotect compound **17** led only to products of degradation, and the desired dipyrimidone **14** could not be isolated. Standard coupling[15] of 2-ethynyl-6-(phenylmethoxy)-pyridine[3g] with 4-iodo-6-methoxypyrimidine (**18**) provided an 80% yield of pyridopyrimidine **20**, which could be

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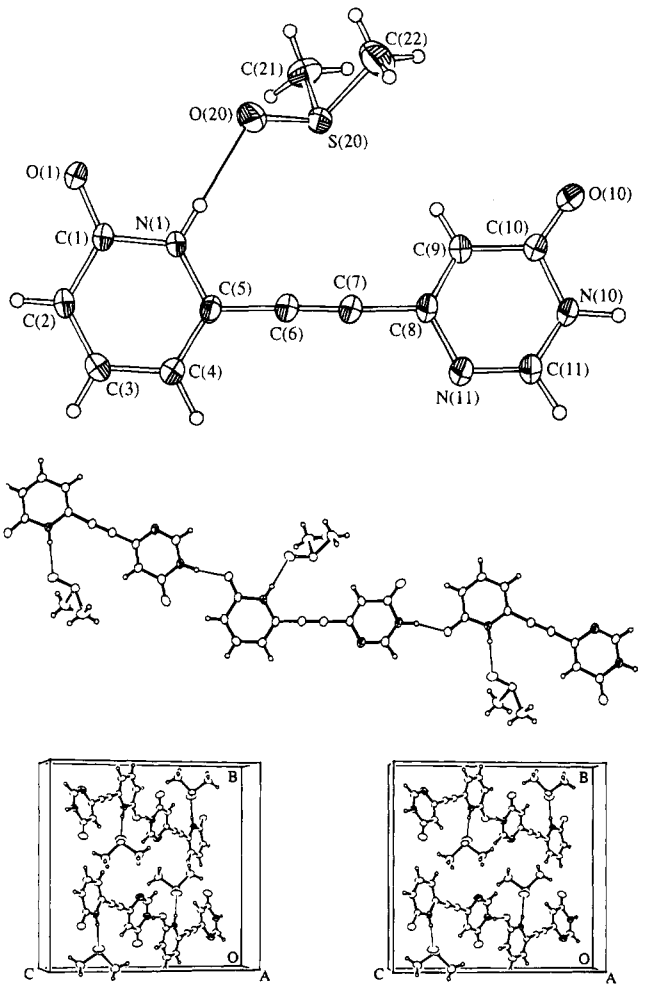

Figure 1. ORTEP drawings of the structure of the 1:1 solvate of pyridone–pyrimidone **7** with DMSO. The upper figure shows the atomic numbering, the middle figure shows the hydrogen-bonded chains present in the structure, and the lower figure provides a stereoview of the unit cell along the *a* axis. Hydrogen atoms appear as spheres of arbitrary size, while other atoms are represented by ellipsoids corresponding to 40% probability. Atoms of nitrogen are distinguished by shading, and hydrogen bonds are indicated by narrow lines. Important bond lengths include O(1)–C(1) = 1.246(2), O(10)–C(10) = 1.223(2), C(2)–C(3) = 1.341(3), C(3)–C(4) = 1.406(3), C(4)–C(5) = 1.356(3), N(10)–C(11) = 1.344(3), N(11)–C(11) = 1.298-(2), C(5)–C(6) = 1.433(2), C(6)–C(7) = 1.192(3), and C(7)–C(8) = 1.445(2) Å.

converted into the desired pyridone–pyrimidone **7** in 82% yield by a two-step deprotection using KOH in dioxane followed by CF_3COOH.

The solubility of pyridone–pyrimidone **7** proved to be too low to allow study of its aggregation in solution, so we examined its association in the solid state. The preparation of crystals suitable for X-ray diffraction was difficult but could finally be achieved by adding benzene to a solution of compound **7** in DMSO. The structure was solved and is shown in Figure 1, along with selected bond lengths. The short O(1)–C(1) and O(10)–C(10) distances, the observed alternation in the C(2)–C(3), C(3)–C(4), and C(4)–C(5) distances, and the short N(11)–C(11) distance indicate that the pyridone–pyrimidone adopts tautomeric structure **7** in the solid state rather than one of the five alternatives. Moreover, the pyridone and pyrimidone rings are approximately coplanar, and rotation around the acetylenic spacer has yielded the particular conformer required for formation of a cyclic triplex. Nevertheless, the expected association does not occur. Instead, the pyridone subunit of each molecule of compound **7** donates a hydrogen bond to the oxygen atom of DMSO and accepts a hydrogen bond from the pyrimidone subunit in a second molecule, creating chains in which adjacent molecules of compound **7** are linked by single hydrogen bonds (Figure 1). The origins of the failure of compound **7** to produce a cyclic triplex under these conditions are undoubtedly complex; however, it is tempting to attribute the failure to the presence of DMSO, which is presumably a stronger acceptor of hydrogen bonds than the oxygen atom of pyrimidone.

Experimental Section

$N(C_2H_5)_3$ was dried by distillation from CaH_2, and tetrahydrofuran (THF) was dried by distillation from the sodium ketyl of benzophenone. $Pd(PPh_3)_4$[17] and $PdCl_2(PPh_3)_2$[18] were prepared by known methods, $ZnCl_2$ was dried in an oven before use, and CuI was purified by a standard procedure.[19] Other commercial reagents were used without further purification. Flash chromatography was performed in the normal way.[20]

3-Bromo-2-chloropyridine (8).[9] A solution prepared by dissolving 2-chloro-3-pyridinamine (12.3 g, 95.7 mmol) in 48% aqueous HBr (30 mL) was stirred at 0 °C and treated with a cold solution of $NaNO_2$ (7.08 g, 103 mmol) in water (20 mL), added at a rate that kept the temperature of the mixture from exceeding 10 °C. CuBr (7.08 g, 49.4 mmol) was then added, the mixture was heated at reflux, and the organic product was removed by steam distillation. The distillate was extracted with CH_2Cl_2, and volatiles were removed by evaporation under reduced pressure. This left a white solid residue of 3-bromo-2-chloropyridine (**8**; 16.7 g, 86.8 mmol, 91%),[9] which could be used for the preparation of 3-ethynyl-2-(phenylmethoxy)-pyridine (**9**) without further purification.

5-Bromo-2-(phenylmethoxy)pyridine (10).[10] A mixture of 2,5-dibromopyridine (1.00 g, 4.22 mmol), dibenzo-18-crown-6 (0.0814 g, 0.226 mmol), benzyl alcohol (0.598 g, 5.53 mmol), and KOH (0.571 g, 10.2 mmol) in toluene (15 mL) was heated at reflux for 3 h in an apparatus fitted with a Dean-Stark trap. Toluene was then removed by evaporation under reduced pressure, water was added to the residue, and the resulting mixture was extracted with $CHCl_3$. Volatiles were removed from the organic extracts by evaporation under reduced pressure. Kugelrohr distillation of the residue then provided 5-bromo-2-(phenylmethoxy)pyridine (**10**; 1.10 g, 4.16 mmol, 99%)[10] as a colorless liquid: bp 110–120 °C/0.15 Torr (lit.[10] bp 178–185 °C/14 Torr); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, 2H), 6.73 (d, ^3J = 8.8 Hz, 1H), 7.30–7.50 (m, 5H), 7.66 (dd, ^3J = 8.8 Hz, ^4J = 2.6 Hz, 1H), 8.21 (d, ^4J = 2.6 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 67.8, 111.7, 112.7, 127.8, 127.8, 128.3, 136.7, 141.0, 147.2, 162.2; MS (FAB) *m/e* 264; HRMS (EI) calcd for $C_{12}H_{10}$ ^{79}BrNO 262.9946, found 262.9952.

2-(Phenylmethoxy)-3-[2-[2-(phenylmethoxy)-5-pyridinyl]ethynyl]pyridine (11). A solution of 3-ethynyl-2-(phenylmethoxy)pyridine (**9**; 205 mg, 0.980 mmol)[3g] in THF (1 mL) was stirred at 0 °C under dry N_2 and treated dropwise with a solution of BuLi (0.70 mL, 1.48 M in hexane, 1.0 mmol). The resulting deep red solution was kept at 0 °C for 30 min, and then a solution of $ZnCl_2$ (157 mg, 1.15 mmol) in THF (1 mL) was added. The mixture was kept at 25 °C for 90 min and was then transferred to a stirred solution of 5-bromo-2-(phenylmethoxy)pyridine (**10**; 278 mg, 1.05 mmol) and $Pd(PPh_3)_4$ (19.9 mg, 0.0172 mmol) in THF (6 mL). The mixture was heated at reflux for 12 h, volatiles were removed by evaporation under reduced pressure, the residue was partitioned between water and $CHCl_3$, and solvent was removed from the organic phase by evaporation under reduced pressure.

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Crystallization of the residue from ethanol provided analytically pure 2-(phenylmethoxy)-3-[2-[2-(phenylmethoxy)-5-pyridinyl]ethynyl]pyridine (**11**; 281 mg, 0.716 mmol, 73%) as a beige solid: mp 108.5–109.5 °C; IR (KBr) 2210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (s, 2H) 5.51 (s, 2H), 6.79 (d, ^3J = 8.6 Hz, 1H), 6.91 (dd, ^3J = 7.4 Hz, ^3J = 5.1 Hz, 1H), 7.31–7.55 (m, 10H), 7.69 (dd, ^3J = 8.6 Hz, ^4J = 2.4 Hz, 1H), 7.76 (dd, ^3J = 7.4 Hz, ^4J = 1.9 Hz, 1H), 8.13 (dd, ^3J = 5.1 Hz, ^4J = 1.9 Hz, 1H), 8.36 (d, ^4J = 2.4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 67.7, 67.9, 85.6, 91.7, 107.6, 111.0, 113.3, 116.6, 127.2, 127.6, 127.9, 128.0, 128.3, 128.4, 131.6, 136.9, 137.3, 141.2, 146.2, 150.0, 162.9, 163.0; MS (FAB) *m/e* 393, 301; HRMS (FAB) calcd for $C_{26}H_{20}N_2O_2$ + H 393.1603, found 393.1615. Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14. Found: C, 79.37; H, 5.36.

2-(1,2-Dihydro-2-oxo-5-pyridinyl)furo[2,3-*b*]pyridine (12). A suspension of 2-(phenylmethoxy)-3-[2-[2-(phenylmethoxy)-5-pyridinyl]ethynyl]pyridine (**11**; 605 mg, 1.54 mmol) in CF_3COOH (6 mL) was heated at reflux for 2 h. Volatiles were then removed by evaporation under reduced pressure, toluene was added, and volatiles were again removed by evaporation under reduced pressure. The residual solid was triturated with $N(C_2H_5)_3$ (1 mL) and acetone (3 mL), the supernatant liquid was decanted after centrifugation, and the solid was washed with additional acetone and dried. Recrystallization from 1-butanol provided analytically pure 2-(1,2-dihydro-2-oxo-5-pyridinyl)furo[2,3-*b*]pyridine (**12**; 182 mg, 0.858 mmol, 56%) as fine yellow needles: mp 260–262 °C; IR (KBr) 3200–2300, 1666, 1632 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.49 (d, ^3J = 10.4 Hz, 1H), 7.17 (s, 1H), 7.28 (dd, ^3J = 7.6 Hz, ^3J = 4.9 Hz, 1H), 7.95 (m, 2H), 8.00 (dd, ^3J = 7.6 Hz, ^4J = 1.7 Hz, 1H), 8.19 (dd, ^3J = 4.9 Hz, ^4J = 1.7 Hz, 1H), 12.03 (s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 98.9, 108.3, 120.1, 120.7, 121.2, 129.7, 131.3, 137.5, 143.1, 152.4, 161.1, 162.0; MS (EI) *m/e* 212; HRMS (EI) calcd for $C_{12}H_8N_2O_2$ 212.0586, found 212.0594.

3-[2-(1,2-Dihydro-2-oxo-5-pyridinyl)ethynyl]-2(1*H*)-pyridinone (6). A similar procedure in which 2-(phenylmethoxy)-3-[2-[2-(phenylmethoxy)-5-pyridinyl]ethynyl]pyridine (**11**) was stirred in CF_3COOH under milder conditions (25 °C, 2 h) produced 3-[2-(1,2-dihydro-2-oxo-5-pyridinyl)ethynyl]-2(1*H*)-pyridinone (**6**) as an unstable yellow solid: ^1H NMR (300 MHz, DMSO-d_6) δ 6.20 (t, ^3J = 6.7 Hz, 1H), 6.35 (d, ^3J = 9.5 Hz, 1H), 7.43 (m, 1H), 7.46 (m, 1H), 7.67 (m, 2H), 11.9 (bs, 2H).

4-Methoxy-2-[(trimethylsilyl)ethynyl]pyrimidine (15). A mixture of 2-chloro-4-methoxypyrimidine (1.87 g, 12.9 mmol),[14] $PdCl_2(PPh_3)_2$ (0.282 g, 0.402 mmol), CuI (0.129 g, 0.677 mmol), and (trimethylsilyl)ethyne (1.56 g, 15.9 mmol) in $N(C_2H_5)_3$ (10 mL) was degassed and sealed under vacuum in a glass tube. The tube was heated at 100 °C for 12 h, its contents were poured into water, the mixture was extracted with $CHCl_3$, and volatiles were removed from the combined extracts by evaporation under reduced pressure. Kugelrohr distillation of the residue provided analytically pure 4-methoxy-2-[(trimethylsilyl)ethynyl]pyrimidine (**15**; 2.37 g, 11.5 mmol, 89%) as a colorless liquid: bp 120 °C/1 Torr; ^1H NMR (300 MHz, $CDCl_3$) δ 0.30 (s, 9 H), 4.01 (s, 3H), 6.67 (d, ^3J = 5.8 Hz, 1H), 8.38 (d, ^3J = 5.8 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ −0.6, 53.9, 93.0, 102.3, 107.8, 151.5, 156.9, 169.0; MS (EI) *m/e* 206; HRMS (EI) calcd for $C_{10}H_{14}N_2OSi$ 206.0875, found 206.0876.

2-Ethynyl-4-methoxypyrimidine (16). A stirred solution of 4-methoxy-2-[(trimethylsilyl)ethynyl]pyrimidine (**15**; 3.64 g, 17.6 mmol) and CH_3COOH (1.05 g, 17.5 mmol) in THF (25 mL) was treated with a solution of tetrabutylammonium fluoride (17.7 mL, 1.0 M in THF, 17.7 mmol). After 5 min, 10% aqueous K_2CO_3 (50 mL) was added, volatiles were removed by evaporation under reduced pressure, the residue was extracted with $CHCl_3$, and volatiles were removed from the organic extracts by evaporation under reduced pressure. Sublimation (50 °C/0.5 Torr) of the residue provided analytically pure 2-ethynyl-4-methoxypyrimidine (**16**; 1.65 g, 12.3 mmol, 70%) as a white solid: mp 88.0–89.5 °C; IR (melt) 2118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 1H), 4.00 (s, 3H), 6.71 (d, ^3J = 5.8 Hz, 1H), 8.38 (d, ^3J = 5.8 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 54.0, 74.9, 81.8, 108.4, 151.2, 157.0, 169.2; MS (EI) *m/e* 134; HRMS (EI) calcd for $C_7H_6N_2O$ 134.0480, found 134.0480. Anal. Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.78; H, 4.71; N, 21.20.

4,6-Diiodopyrimidine (19).[16] A solution prepared by dissolving 4,6-dichloropyrimidine (14.9 g, 100 mmol) in 48% aqueous HI (200 mL) was stirred at 25 °C in the dark for 72 h. The precipitated solid was then removed by filtration and added to a mixture of 10% aqueous K_2CO_3 (200 mL) and 10% aqueous $Na_2S_2O_3$ (10 mL). The mixture was extracted with $CHCl_3$, and volatiles were removed from the combined extracts by evaporation under reduced pressure. Crystallization of the residue from hexane provided 4,6-diiodopyrimidine (**19**; 27.0 g, 81.4 mmol, 81%)[16] as a white solid: mp 107–109 °C (lit.[16] mp 107.5–108.5 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, ^5J = 1.0 Hz, 1H), 8.55 (d, ^5J = 1.0 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 128.5, 142.8, 157.7.

4-Iodo-6-methoxypyrimidine (18). At 0 °C under dry N_2, a solution of $NaOCH_3$ (9.3 mL, 4.4 M in CH_3OH, 41 mmol) was added slowly by syringe pump to a stirred solution of 4,6-diiodopyrimidine (**19**; 13.8 g, 41.6 mmol) in CH_3OH (250 mL). The mixture was kept at 25 °C for 2 h, and volatiles were then removed by evaporation under reduced pressure. The residue was treated with $CHCl_3$, the resulting mixture was filtered, and volatiles were removed from the organic phase by evaporation under reduced pressure. Kugelrohr distillation of the residue provided analytically pure 4-iodo-6-methoxypyrimidine (**18**; 8.36 g, 35.4 mmol, 85%) as a white solid: mp 68.0–69.5 0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.23 (s, 1H), 8.45 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 54.2, 119.1, 127.3, 157.5, 168.6; MS (EI) 236, 109; HRMS (EI) calcd for $C_5H_5IN_2O$ 235.9447, found 235.9443. Anal. Calcd for $C_5H_5IN_2O$: C, 25.45; H, 2.14; N, 11.87. Found: C, 25.36; H, 2.14; N, 11.78.

4-Methoxy-2-[2-(6-methoxy-4-pyrimidinyl)ethynyl]pyrimidine (17). A stirred mixture of 2-ethynyl-4-methoxypyrimidine (**16**; 136 mg, 1.01 mmol), 4-iodo-6-methoxypyrimidine (**18**; 204 mg, 0.864 mmol), $PdCl_2(PPh_3)_2$ (35.0 mg, 0.0499 mmol), and CuI (18.0 mg, 0.0945 mmol) in $N(C_2H_5)_3$ (6 mL) was heated at reflux under N_2 for 12 h. Volatiles were removed by evaporation under reduced pressure, the residue was extracted with $CHCl_3$, and volatiles were removed from the extracts by evaporation under reduced pressure. The residue was purified by flash chromatography (silica, hexane (50%)/ethyl acetate (50%)), and recrystallization from acetone provided analytically pure 4-methoxy-2-[2-(6-methoxy-4-pyrimidinyl)ethynyl]pyrimidine (**17**; 145 mg, 0.599 mmol, 69%) as a white solid: mp 184–186 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 6H), 6.74 (d, ^3J = 5.9 Hz, 1H), 7.03 (d, ^5J = 1.1 Hz, 1H), 8.45 (d, ^3J = 5.9 Hz, 1H), 8.80 (d, ^5J = 1.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 54.0, 54.1, 82.3, 89.3, 108.5, 111.7, 149.1, 151.2, 157.0, 158.5, 169.1, 169.4; MS (EI) *m/e* 242; HRMS (EI) calcd for $C_{12}H_{10}N_4O_2$ 242.0804, found 242.0805.

4-Methoxy-6-[2-[6-(phenylmethoxy)-2-pyridinyl]ethynyl]pyrimidine (20). A stirred mixture of 2-ethynyl-6-(phenylmethoxy)pyridine (3.90 g, 18.6 mmol),[3g] 4-iodo-6-methoxypyrimidine (**18**; 4.27 g, 18.1 mmol), $PdCl_2(PPh_3)_2$ (0.307 g, 0.437 mmol), and CuI (0.172 g, 0.903 mmol) in $N(C_2H_5)_3$ (200 mL) was heated at reflux under N_2 for 12 h. The crude product was isolated by the procedure described for compound **17** and purified by flash chromatography (silica, hexane (60%)/ethyl acetate (40%)) to give 4-methoxy-6-[2-[6-(phenylmethoxy)-2-pyridinyl]ethynyl]pyrimidine (**20**; 4.59 g, 14.5 mmol, 80%) as a yellow solid. Recrystallization from cyclohexane provided analytically pure yellow needles: mp 109.5–110.5 °C; IR (melt) 2225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 3H), 5.42 (s, 2H), 6.85 (dd, ^3J = 8.4 Hz, ^4J = 0.8 Hz, 1H), 7.00 (d, ^5J = 1.1 Hz, 1H), 7.25 (dd, ^3J = 7.3 Hz, ^4J = 0.8 Hz, 1H), 7.27–7.42 (m, 3H), 7.47–7.51 (m, 2H), 7.60 (dd, ^3J = 8.4 Hz, ^3J = 7.3 Hz, 1H), 8.79 (d, ^5J = 1.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 54.0, 67.9, 85.0, 91.1, 111.2, 112.8, 121.9, 127.9, 128.1, 128.4, 136.9, 138.5, 138.6, 149.9, 158.5, 163.4, 169.6; MS (EI) 317; HRMS (EI) calcd for $C_{19}H_{15}N_3O_2$ 317.1164, found 317.1161. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76. Found: C, 71.15; H, 4.99.

6-[2-(1,6-Dihydro-6-oxo-2-pyridinyl)ethynyl]-4(3*H*)-pyrimidinone (7). A suspension of 4-methoxy-6-[2-[6-(phenylmethoxy)-2-pyridinyl]ethynyl]pyrimidine (**20**; 3.37 g, 10.6

mmol) in a mixture of dioxane (25 mL) and 1 N aqueous KOH (35 mL) was heated at reflux for 4 h. When the solid had dissolved, volatiles were partially removed by evaporation under reduced pressure, and the pH of the residual solution was lowered to 7 by the addition of 3 N aqueous HCl. The precipitated solid was separated by centrifugation, washed with water, and dried. It was then heated for 2 h in boiling CF_3COOH (100 mL). Volatiles were removed by evaporation under reduced pressure, water (50 mL) was added, and the pH was raised to 7 by the addition of $N(C_2H_5)_3$. The precipitated solid was separated by centrifugation, washed with water and acetone, dried, and crystallized from 1-butanol. This provided analytically pure 6-[2-(1,6-dihydro-6-oxo-2-pyridinyl)-ethynyl]-4(3*H*)-pyrimidinone (**7**; 1.86 g, 8.72 mmol, 82%) as fine yellow needles: mp 250 °C dec; IR (KBr) 3500–2500, 2220, 1686, 1654 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.53 (dd, ^3J = 9.1 Hz, ^4J = 0.8 Hz, 1H), 6.63 (d, ^5J = 1.0 Hz, 1H), 6.73 (dd, ^3J = 6.9 Hz, ^4J = 0.8 Hz, 1H), 7.50 (dd, ^3J = 9.1 Hz, ^3J = 6.9 Hz, 1H), 8.20 (d, ^5J = 1.0 Hz, 1H), 12.3 (bs, 2H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 86.6, 88.6, 114.2, 119.7, 120.1, 130.0, 140.3, 146.0, 151.0, 160.3, 162.6.

X-ray Crystallographic Study of the 1:1 DMSO Solvate of 6-[2-(1,6-Dihydro-6-oxo-2-pyridinyl)ethynyl]-4(3*H*)-pyrimidinone (7).[21] Crystals of solvate **7**·DMSO belong to the monoclinic space group $P2_1/c$ with a = 4.7695(8) Å, b = 16.7966(18) Å, c = 17.0526(17) Å, β = 94.067(12)°, V = 1362.7-(3)Å^3, D_{calcd} = 1.420 g cm^{-3}, and Z = 4. Data were collected at 295 K, and the structure was refined to R_f = 0.040, R_w = 0.044 for 2259 reflections with $I > 1.96\sigma(I)$.

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Supplementary Material Available: ^1H NMR spectra of compounds **12**, **15**, **17**, and **20** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(21) The authors have deposited X-ray crystallographic data, a description of the structure determination, and tables of atomic coordinates and isotropic thermal parameters, bond lengths and angles, anisotropic thermal parameters, and refined and calculated hydrogen atom coordinates with the Cambridge Crystallographic Data Centre. The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ UK.