Palladium-Catalyzed Allylic Coupling of 1,2,3-Triazolo[4,5-*d*]pyrimidines (8-Azapurines)

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Received May 3, 1996[⊗]

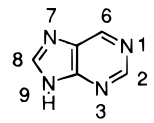
The palladium-catalyzed coupling of the sodium salt of 7-amino-1,2,3-triazolo[4,5-*d*]pyrimidine (8-azaadenine, **1**) with allylic phosphates or carbonates resulted in mixtures of 2- and 3-substituted 1,2,3-triazolopyrimidines, which were separated by chromatography. 1-Substituted triazolopyrimidines were not isolated from these reactions. Regioselectivity (and stereoselectivity) was also observed for substitution of the allylic moiety when more than one isomer is possible from the reaction. The use of 5-amino-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones (8-azaguanine, **2**), instead of 8-azaadenine, also resulted in mixtures. Alternate syntheses of the 3-allyl-1,2,3-triazolo[4,5-*d*]-pyrimidines confirmed the structures of these compounds.

Introduction

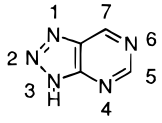
In the search for new lead compounds for a variety of medicinal uses such as antiviral or antitumor therapy, many syntheses of modified nucleosides have been reported.[1] The modifications include alterations to the ribose, the base (purine or pyrimidine), or both. Replacement of the C-8 of purines with a N gives 1,2,3-triazolo-[4,5-*d*]pyrimidines (8-azapurines). The numbering systems for purines and triazolopyrimidines are shown in Scheme 1. The triazolopyrimidines often display increased toxicity and improved antitumor properties when compared to those of the corresponding purines.[2] Reported methods of synthesizing substituted triazolopyrimidines, however, are limited.[3] The most common method, which proceeds through a condensation of nitrous acid with a 4,5-diaminopyrimidine (Traube synthesis), requires a number of steps to build an 8-azaadenine or an 8-azaguanine moiety from an appropriate amine.[3] Reported methods of directly replacing leaving groups (such as a halide) with triazolopyrimidines lead to mixtures of three or more isomers[4] with the N-2 substitution product often being the dominant isomer.[4e] Therefore, an improved short synthesis of N-3-substituted triazolopyrimidines is desirable.

Palladium-catalyzed coupling of purines with allylic carbonates or acetates has been reported recently as a method of directly placing a purine onto a modified sugar. Examples of this methodology include the key steps in the syntheses of the natural product aristeromycin[5] and the antiviral compound carbovir.[5b,6] The palladium-catalyzed coupling gives substitution of a purine for a carbonate or acetate. In addition to the predictable regiospecific 9-substitition of the purine, these reactions also give net stereochemical retention of configuration and a predictable regiochemistry for the allylic moiety. Thus, we decided to explore whether this chemistry could be useful in the synthesis of substituted triazolopyrimidines.

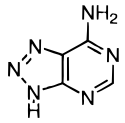
Scheme 1. Numbering Systems and Nomenclature for 8-Azapurines



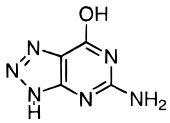
purine numbering



1,2,3-triazolo[4,5-*d*]pyrimidine (8-azapurine) numbering



1, 8-azaadenine



2, 8-azaguanine

Results and Discussion

We first examined the reactivity of the sodium salt of 7-amino-1,2,3-triazolo[4,5-*d*]pyrimidine (8-azaadenine, **1**) toward allyl phosphate **3** (Table 1) under palladium catalysis. Tetrakis(triphenylphosphine)palladium(0), palladium(II) acetate, and tris(dibenzylideneacetone)dipalladium(0)−chloroform adduct were examined as catalysts for this reaction. Of these, the first catalyst gave the best yield of triazolopyrimidine **4** and the cleanest product after chromatography. Thus, this catalyst was used in all subsequent palladium-catalyzed reactions that are

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1996.

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(3) Review of the chemistry of 8-azapurines, see: Albert, A. *Adv. Heterocycl. Chem.* **1986**, *39*, 117−180.

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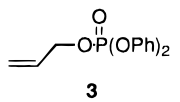
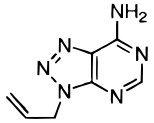
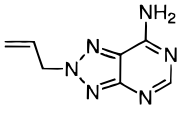
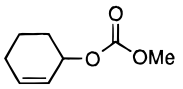
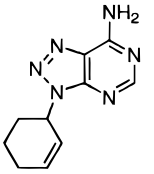
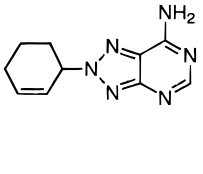
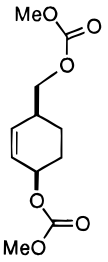
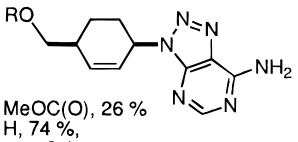
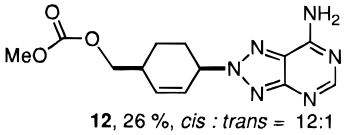
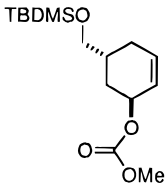
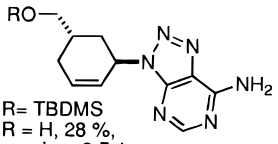
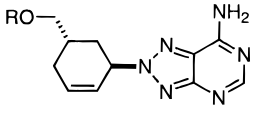
S0022-3263(96)00815-8 CCC: $12.00

Table 1. Isolated Products from the Palladium-Catalyzed Coupling of 8-Azaadenine to an Allylic Phosphate and Allylic Carbonates[a]

phosphate or carbonate	products, yields
 **3**	 **4**, 29 %  **5**, 14 %
 **6**	 **7**, 23 %  **8**, 43 %
 **9**	 **10**, R = MeOC(O), 26 % **11**, R = H, 74 %, *cis* : *trans* = 9:1  **12**, 26 %, *cis* : *trans* = 12:1
 **13**	 **14**, R= TBDMS **15**, R = H, 28 %, *trans* : *cis* = 3.5:1  **16**, R = TBDMS **17**, R = H, 15 %, *trans* : *cis* = 5.5:1

[a] See Experimental Section for conditions. All yields are isolated yields of purified products, except for **10** which was contaminated with triphenylphosphine oxide. The yield of **10** was calculated, on the basis of purity as determined by ^{1}H NMR. Compound **10** was hydrolyzed to **11** which was separated from the impurity. The amount of the impurity isolated corresponded to the amount calculated on the basis of the ^{1}H NMR of **10**. The TBDMS groups were removed from **14** and **16** with TBAF and HOAc, giving **15** and **17**.

reported in this study. The palladium-catalyzed reaction of 8-azaadenine with allyl phosphate **3** gave a mixture of two compounds which were separated by column chromatography. The faster eluting compound was identified as the 3-substituted triazolopyrimidine **4** (29%), and the slower eluting compound was identified as the 2-substituted triazolopyrimidine **5** (14%) (Table 1).

The palladium-catalyzed reactions of **1** with three allylic carbonates (**6**, **9**, and **13**) were studied, and the results are shown in Table 1. In each case, 3-substituted triazolopyrimidines (**7**, **10**, and **14**, 23−28%) and 2-substituted triazolopyrimidines (**8**, **11**, and **15**, 11−43%) were isolated. Triazolopyrimidine **10** could not be obtained as a pure product due to contamination with triphenylphosphine oxide (a reproducible observation). The route by which the triphenylphosphine is oxidized is not clear. The amounts of triazolopyrimidine **10** and triphenylphosphine oxide were calculated, based on the ^{1}H NMR areas. The triazolopyrimidine **10** was, subsequently, hydrolyzed, and the triphenylphosphine oxide was separated from triazolopyrimidine **11**. The amount of triphenylphosphine oxide found closely agreed with the amount calculated to be contaminating triazolopyrimidine **10**, and its identity was verified by comparison (including mixed melting point) to an authentic sample. Triazolopyrimidines **14** and **16** were separated, but they were also contaminated with impurities. These were each deprotected under conditions that we have previously described,[7] giving triazolopyrimidines **15** and **17** in yields of 28 and 15%, respectively, from carbonate **13**.

Triazolopyrimidines **11**, **12**, **15**, and **17** were each isolated and found to be mixtures of major and minor stereoisomers that were inseparable by chromatography. Since the purine analogs of triazolopyrimidines **11** and **15** that were synthesized by palladium coupling were accompanied by minor amounts of *trans* and *cis* isomers, respectively,[7,8a] the appearance of the minor isomers of triazolopyrimidines **11**, **12**, **15**, and **17** was not surprising.

The regiochemistry of triazolopyrimidines **11** and **12** and the minor isomer of triazolopyrimidines **12**, with respect to the cyclohexyl ring, was determined by examination of COSY spectra of triazolopyrimidines **11** and **12**. Carbonate **9** did not give any detectable allylic rearrangement product even though the allylpalladium intermediate would allow such a formation. Only the less sterically hindered products **10** and **12** and their minor *trans* isomers were isolated. This is analogous to what has been observed with purines in palladium-catalyzed couplings.[5−8] Determination of which is the major stereoisomer and which is the minor stereoisomer for triazolopyrimidines **11** and **12** was made by a comparison of their ^{1}H NMR spectra to the spectra of their purine analogs which were assigned structures on the basis of NOE experiments.[8a] Several features were noticed in the ^{1}H NMR spectra of the purine analogs of **11** that were useful in determination of the stereochemistry. The chemical shift of the H-2 of the cyclohexyl ring is upfield and the chemical shift of the H-3 is downfield for the *cis* isomers when compared to those of the *trans* isomers. In addition, the coupling between H-1 and the H-2 is significantly larger for the *trans* isomers. Application of these features gave the expected *cis* assignment to the major isomers of triazolopyrimidines **11** and **12**.

The symmetric nature of the allylpalladium intermediate formed from carbonate **13** allows for only one regioisomer, with respect to the cyclohexyl ring, for triazolopyrimidines **15** and **17**. The stereochemistry of triazolopyrimidine **15** was determined by comparison of its ^{1}H NMR spectrum to the spectrum of its *cis* analog that was made by an unambiguous route.[9] The ^{1}H NMR spectrum of the *cis* analogs matched the signals of the minor isomer, leaving the *trans* stereochemistry for assignment to the major isomer (as is shown in structure **15**). In addition, the chemical shifts of the H-4 and H-5 of the cyclohexyl ring are consistently further downfield

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(8) (a) Konkel, M. J.; Vince, R. *Tetrahedron* **1996**, *52*, 799−808. (b) Akella, L. B.; Vince, R. *Tetrahedron* **1996**, *52*, 2789−2794.
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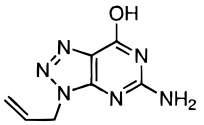
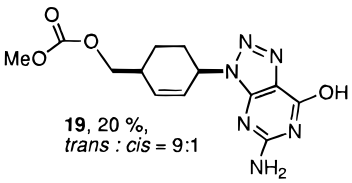
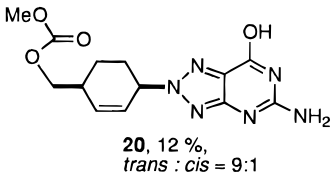
Table 2. Isolated Products from the Palladium-Catalyzed Coupling of 8-Azaguanine to an Allylic Phosphate and an Allylic Carbonate[a]

phosphate or carbonate	products, yields
3	 **18**, 7 %
9	 **19**, 20 %, *trans* : *cis* = 9:1  **20**, 12 %, *trans* : *cis* = 9:1

[a] See Experimental Section for conditions. All yields are isolated yields after chromatography.

for the *trans* isomers than for the *cis* isomers of purine analogs of **15**.[7,9] In the ^{1}H NMR spectra of both triazolopyrimidines **15** and **17**, the chemical shifts for the major isomers of the H-4 and H-5 are further downfield than those for the minor isomers. Application of these features gave the expected *trans* assignment to the major isomers of triazolopyrimidines **15** and **17**.

The palladium coupling chemistry of triazolopyrimidines resembles the palladium coupling chemistry of purines in some respects. The *cis*:*trans* ratios for **10**, **12**, **15**, and **17** were 9:1, 10:1, 1:3.5, 1:5.5, respectively. These ratios are similar to the ratios that have been previously observed for the purine analogs which were synthesized by the allylic palladium-catalyzed coupling chemistry.[7,8] A 1-substituted triazolopyrimidine was not isolated from any of these reactions. This result is analogous to the allylic palladium-catalyzed coupling reactions of purines in which 7-substituted products are generally not observed.[5−8]

The use of the sodium salt of 5-amino-1,2,3-triazolo-[4,5-*d*]pyrimidin-7-one (8-azaguanine, **2**) as the nucleophile in allylic palladium-catalyzed coupling reactions was tested with one phosphate and one carbonate (Table 2). Phosphate **3** gave the 3-substituted triazolopyrimidine **18** in only 8% yield. The major component isolated (35%) was an inseparable mixture of two isomers in a 55:45 ratio. The isomers are tentatively assigned to be the 1- and 2-substituted triazolopyrimidines, based on UV, ^{1}H NMR, and MS data. Carbonate **9** gave the 3-substituted triazolopyrimidine **19** in 20% yield, along with the 2-substituted triazolopyrimidine **20** in 12% yield. The regiochemistry and stereochemistry for triazolopyrimidines **19** and **20** were determined as described above for triazolopyrimidines **11** and **12**. Both of the 3-substituted triazolopyrimidines **18** and **19**, however, proved to be difficult to purify. We have not been successful in obtaining an acceptable elemental analysis for either of these compounds when they are purified by chromatography and recrystallization.

Table 3. UV Spectra of Substituted 8-Azaadenines

8-azaadenines[a]	λ_{max}, nm ($\epsilon \times 10^{-3}$) pH 1	pH 7
1-(β-D-2-deoxyribofuranosyl)-[b]	262 (11.7)	287 (8.4)
2-(β-D-2-deoxyribofuranosyl)-[b]	285 (11.2)	254 (4.3), 297 (10.2)
3-(β-D-2-deoxyribofuranosyl)-[b]	263 (10.9)	278 (11.8)
4	263	278
5	282	255, 292
7	262	276
8	282	256, 290
11	263	278
12	283	255, 291
15	262	276
17	282	256, 290

[a] 1,2,3-Triazolo[4,5-*d*]pyrimidine numbering. [b] Reference 4d.

The position of the substitution on the triazolopyrimidines was determined by the comparison of the UV data to that of other literature triazolopyrimidines (Tables 3 and 4).[4c−d,10] In addition to the λ_{max} value, the relative size of the absorbencies and the shape of the peaks was also taken into account when determining the position of the substitutions of the 5-amino-1,2,3-triazolo[4,5-*d*]-pyrimidin-7-ones.

The novel triazolopyrimidines **4** and **18** were also synthesized using conventional chemistry[3] to confirm the structural assignments. This synthetic route is shown in Scheme 2. Triazolopyrimidines **4** and **18**, synthesized by these routes, were identical in all respects (except for a higher mp for **18**) to the triazolopyrimidines **4** and **18** synthesized by the palladium-catalyzed coupling. In addition, mixed melting points were not depressed.

Conclusions

In this study, we used commercially available 8-azaadenine (**1**) and 8-azaguanine (**2**) as the triazolopyrimidine nucleophiles, since our desire was to find a short route to triazolopyrimidine nucleosides. Although the 5-amino-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one derivatives were difficult to purify, the 2- and 3-substituted 7-amino-1,2,3-triazolo[4,5-*d*]pyrimidine derivatives were synthesized by palladium-catalyzed coupling in moderate yields in one to two steps from easily prepared carbonates or phosphates.

Experimental Section

General. ^{1}H NMR spectra were recorded on 500 or 300 MHz spectrometers and referenced to the solvent. Chemical shifts are expressed in ppm, and coupling constants are in hertz. Melting points were measured in open capillary tubes and are uncorrected. Column chromatography was performed with Whatman 60 Å 230−400 mesh ASTM silica gel, and thin-layer chromatography was performed with Whatman 60 Å K6F 250 μm silica gel. Elemental analysis were performed by M-H-W Laboratories, Phoenix, AZ. Methyl 2-cyclohexenyl carbonate (**6**),[11] methyl *cis*-[4-[(methoxycarbonyl)oxy]-2-cyclohexen-1-yl]methyl carbonate (**9**),[8a] and methyl [*cis*-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-cyclohexen-1-yl]carbonate (**13**)[7] were prepared by reported procedures. Anhydrous DMF and THF were obtained from Aldrich Chemical Co. All other solvents and chemicals were reagent grade. All glassware was oven-dried.

(10) (a) Noell, C. W.; Townsend, L. B.; Robins, R. K. *Synth. Proced. Nucleic Acid Chem.* **1968**, *1*, 44−46. (b) Townsend, L. B.; Robins, R. K. *Synth. Proced. Nucleic Acid Chem.* **1968**, *1*, 18−21. (c) Albert, A.; Taguchi, H. *J. Chem. Soc., Perkin Trans. 1* **1972**, 449−456.

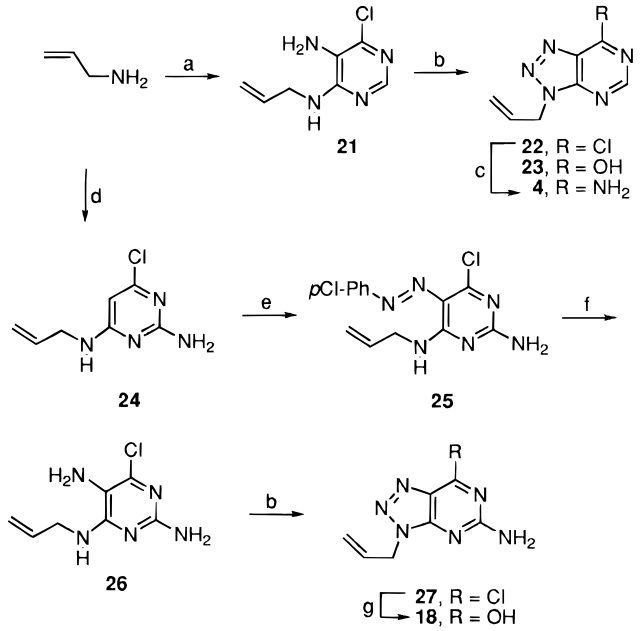
(11) Brettle, R.; Sutton, J. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1947−1954.

Table 4. UV Spectra of Substituted 8-Azaguanines

8-azaguanines[a]	λ_{max}, nm (ϵ X 10^{-3})		
	0.1 N HCl	pH 7	0.1 N NaOH
4-methyl-[b]	205 (25.7), 264 (7.39)	213 (7.56), 249 (9.85), 267 (11.2)	249 (9.76), 267 (11.2)
6-methyl-[c]	252 (5.65), 264 (sh, 4.16)		
1-methyl-[d]	210 (23.5), 270 (5.37)	210 (25.7), 240 (7.12), 296 (5.23)	219 (20.1), 245 (sh, 5.46), 297 (5.89)
2-methyl-[d]	206 (26.8), 269 (8.84)	211 (28.7), 241 (6.69), 292 (6.32)	218 (22.7), 250 (4.97), 296 (7.98)
9-β-D-ribofuranosyl-[e]	255 (13.4), 275 (sh, 9.34)	256 (12.9), 275 (sh, 9.00)	221 (23.3), 278 (11.7)
18	251,[f] 270 (sh)	252,[f] 270	215,[f] 280
19	252,[f] 271 (sh)	252,[f] 271	219,[f] 278
20	212 (sh),[f] 267	209 (sh),[f] 243,[g] 297[h]	217,[f] 248,[g] 297[h]

[a] 1,2,3-Triazolo[4,5-*d*]pyrimidine numbering. [b] Reference 10a. [c] Reference 10b. [d] Reference 10c. [e] Reference 4c. [f] Major relative intensity. [g] Minor relative intensity. [h] Medium relative intensity.

Scheme 2. Alternate Syntheses of 3-Allyltriazolo[4,5-*d*]pyrimidines[a]



[a] Reagents and conditions: (a) 5-amino-4,6-dichloropyrimidine, Et_3N, BuOH; 94%; (b) $NaNO_2$, HCl; **22**, 74%, **23**, 15%; **27**, 53%; (c) NH_3, MeOH; 76%; (d) 2-amino-4,6-dichloropyrimidine, Et_3N, BuOH; 99%; (e) *p*-chlorophenyldiazonium chloride, H_2O−HOAc, NaOAc; 94%; (f) Zn, HOAc, H_2O−EtOH; 56%; (g) 0.25 N NaOH; 88%.

Allyl diphenyl phosphate (3) was prepared by a literature method[12] and by using Mitsunobu conditions.[13] The latter method was carried out as follows: DEAD (1.81 g, 10.4 mmol) in THF (15 mL) were added over 20 min to a stirring solution of allyl alcohol (300 mg, 5.17 mmol), triphenylphosphine (2.71 g, 10.3 mmol), and diphenyl phosphate (2.61 g, 10.5 mmol) in THF (35 mL). After 21 h, the solvent was removed under reduced pressure and the residue was purified by flash chromatography, eluting with a gradient of hexane to hexane:EtOAc (3:1). The solvent was removed from the first fraction that was UV-active, leaving phosphate **3** as a clear oil (1.20 g, 4.14 mmol, 80%) that was identical in all respects to the phosphate **3** prepared by the literature method.[12]

General Procedure for Palladium-Catalyzed Couplings. 8-Azapurine (**1** or **2**, 1 equiv, 0.66−1.40 mmol) was added to a stirring solution of NaH (95%, 0.95 equiv) in DMF (15 mL) and heated in a 60 °C oil bath for 0.5−2 h. Then the solution was cooled to rt and the allylic phosphate or allylic carbonate (1 equivalent) in DMF (3 mL) and tetrakis(triphenylphosphine)palladium(0) (0.15 equivalent) were added. The solution was protected from light, put under N_2, and stirred at 60 °C for 2−3 h. The solution was then cooled and filtered, and the solvent was removed *in vacuo*. The resulting solid was dissolved in EtOAc or EtOAc:MeOH, and any undissolved material was filtered. The solvent was removed from the filtrate under reduced pressure, and the residue was purified by flash chromatography. The products were eluted with one of the following solvent systems: (A) EtOAc; (B) a gradient of hexane:PhH (3:1) to hexane:PhH:2-propanol (2:1:1) with a constant PhH concentration; or (C) a gradient of PhH to PhH:2-propanol (1:1).

7-Amino-3-(2-ethenyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (4) and 7-Amino-2-(2-ethenyl)-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (5). Reaction of **1** with **3** following the general procedure (eluted with B) gave **4** as a white powder (71.9 mg, 0.41 mmol, 29%): mp 203.5−204 °C; R_f = 0.32 (hexane:PhH:2-propanol, 2:1:1); ^{1}H NMR (DMSO-d_6, 300 MHz) 8.42 (br s, 1 H, D_2O exchangeable), 8.28 (s, 1 H), 8.09 (br s, 1 H, D_2O exchangeable), 6.07 (dddt, 1 H, J = 17.1, 10.5, 1.5, 5.4), 5.22 (d q, 1 H, J = 10.5, 1.5), 5.14 (d t, 1 H, J = 5.4, 1.5), 5.07 (d q, 1 H, J = 17.1, 1.5); MS (EI) *m*/*z* (intensity) 176 (M^+, 31), 148 (100). Anal. Calcd for $C_7H_8N_6$: C, 47.72; H, 4.58; N, 47.70. Found: C, 47.49; H, 4.80; N, 47.49.

Further elution gave a pink sticky material (42.3 mg) which was further purified on a preparative TLC plate, giving **5** as a white powder (34.6 mg, 0.20 mmol, 14%): mp 156−157 °C; R_f = 0.19 (hexane:PhH:2-propanol, 2:1:1); ^{1}H NMR (DMSO-d_6, 300 MHz) 8.27 (s with br base, 2 H, br base is D_2O exchangeable), 8.04 (br s, 1 H, D_2O exchangeable), 6.13 (m, 1 H), 5.33 (m with d in center, 4 H, J = 7.8); MS (EI) *m*/*z* (intensity) 176 (M^+, 100). Anal. Calcd for $C_7H_8N_6$: C, 47.72; H, 4.58; N, 47.70. Found: C, 47.73; H, 4.67; N, 47.51.

7-Amino-3-(2-cyclohexenyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (7) and 7-Amino-2-(2-cyclohexenyl)-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (8). Reaction of **1** with **6** following the general procedure (eluted with B) gave **7** as white flakes (88.7 mg, 0.41 mmol, 23%): mp 233−234 °C; R_f = 0.43 (hexane:PhH:2-propanol, 2:1:1); ^{1}H NMR (DMSO-d_6, 300 MHz) 8.40 (br s, 1 H, D_2O exchangeable), 8.27 (s, 1 H), 8.06 (br s, 1 H, D_2O exchangeable), 6.05 (m, 1 H), 5.80 (m, 1 H), 5.46 (m, 1 H), 2.12 (m, 4 H), 1.85 (m, 1 H), 1.75 (m, 1 H); MS (CI) *m*/*z* (intensity) 217 (MH^+, 100). Anal. Calcd for $C_{10}H_{12}N_6$: C, 55.54; H, 5.59; N, 38.86. Found: C, 55.50; H, 5.77; N, 38.62.

Further elution gave **8** as a white powder (165.3 mg, 0.76 mmol, 43%): mp 202−202.5 °C; R_f = 0.24 (hexane:PhH:2-propanol, 2:1:1); ^{1}H NMR (DMSO-d_6, 300 MHz) 8.26 (s, 1 H), 8.21 (br s, 1 H, D_2O exchangeable), 7.98 (br s, 1 H, D_2O exchangeable), 6.08 (d m, 1 H, J = 9.5), 5.89 (dm, 1 H, J = 9.5), 5.50 (m, 1 H), 2.20 (m, 1 H), 2.11 (m, 3 H), 1.82 (m, 1 H), 1.72 (m, 1 H); MS (CI) *m*/*z* (intensity) 217 (MH^+, 100). Anal. Calcd for $C_{10}H_{12}N_6$: C, 55.54; H, 5.59; N, 38.86. Found: C, 55.61; H, 5.49; N, 38.94.

***cis*-4-(7-Amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-2-cyclohexenylmethanol (11) and Methyl *cis*-[4-(7-Amino-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-2-yl)-2-cyclohexen-1-yl]methyl Carbonate (12).** Reaction of **1** with **9** following the general procedure (eluted with A) gave a mixture of **10** and triphenylphosphine oxide as a white solid [262.1 mg, R_f = 0.37 (EtOAc)]. ^{1}H NMR areas indicate that **10** is ~60% of the mixture by weight.

Further elution gave **12** as a white powder (104.2 mg, 0.34 mmol, 26%): mp 118−124 °C; R_f = 0.20 (EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) 8.42 (br s, 1 H, D_2O exchangeable), 8.28

(12) Miller, J. A.; Wood, H. C. S. *J. Chem. Soc. C* **1968**, 1837−1843.
(13) Review, see: Mitsunobu, O. *Synthesis* **1981**, 1−28.

(s, 1 H), 8.07 (br s, 1 H, D_2O exchangeable), 5.99 (dm, 1 H, J = 10.0), 5.95 (dm, 1 H, J = 10.0), 5.43 (m, 1 H), 4.12 (dd, 1 H, J = 10.5, 6.0), 4.07 (dd, 1 H, J = 10.5, 8.0), 3.70 (s, 3 H), 2.57 (m, 1 H), 2.13 (m, 1 H), 1.90 (m, 1 H), 1.83 (m, 1 H), 1.69 (m, 1 H); MS (CI) m/z (intensity) 305 (MH^+, 100). Anal. Calcd for $C_{13}H_{16}N_6O_3$: C, 51.31; H, 5.30; N, 27.62. Found: C, 51.51; H, 5.46; N, 27.39.

A solution of impure **10** (100 mg) in THF (10 mL) and 0.20 N NaOH (5 mL) was stirred for 3 h at rt. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography. Elution with a gradient of hexane to EtOAc gave triphenylphosphine oxide (60.9 mg). Elution was continued with EtOAc:MeOH (9:1), giving **11** as a white solid (23.5 mg, 0.096 mmol, 74% from calcd amount of **10**): mp 229−230 °C; R_f = 0.53 (EtOAc:MeOH, 4:1); ^{1}H NMR (DMSO-d_6, 500 MHz) 8.39 (br s, 1 H, D_2O exchangeable), 8.27 (s, 1 H), 8.05 (br s, 1 H, D_2O exchangeable), 6.04 (d m, 1 H, J = 9.9), 5.85 (d m, 1 H, J = 9.9), 5.41 (m, 1 H), 4.74 (t, 1 H, J = 5.3, D_2O exchangeable), 3.42 (m, 2 H), 2.28 (m, 1 H), 2.11 (m, 1 H), 2.03 (m, 1 H), 1.77 (m, 1 H), 1.69 (m, 1 H); MS (CI) m/z (intensity) 247 (MH^+, 100). Anal. Calcd for $C_{11}H_{14}N_6O$: C, 53.65; H, 5.73; N, 34.13. Found: C, 53.80; H, 5.90; N, 34.01.

***trans*-3-(7-Amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-4-cyclohexenylmethanol (15) and *trans*-3-(7-Amino-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-2-yl)-4-cyclohexenylmethanol (17).** Reaction of **1** with **13** following the general procedure (eluted with B) gave **14** [177.1 mg, R_f = 0.54 (hexane:PhH:2-propanol, 2:1:1)] as an impure white solid and **16** [96.6 mg, R_f = 0.36 (hexane:PhH:2-propanol, 2:1:1)] as an impure white tacky solid.

Tetrabutylammonium fluoride (1 M in THF, 1.00 mL) was added to a solution of **14** in THF (4 mL) and HOAc (0.12 mL) and stirred for 20 h at rt. Silica gel was added, and the solvent was removed under reduced pressure. The silica gel was placed on a column of silica gel, and the contents were eluted with hexane:PhH:2-propanol (2:1:1) until the first band was removed from the column. Then the column was eluted with THF, giving a white solid (105.4 mg) which slowly turned pale yellow. The solid was triturated with a small amount of MeOH and filtered, giving **15** as a pale yellow powder (45.8 mg, 0.19 mmol, 28% from **13**): mp 226.5−227.5 °C; ^{1}H NMR (DMSO-d_6, 300 MHz, major isomer) 8.40 (br s, 1 H, D_2O exchangeable), 8.28 (s, 1 H), 8.06 (br s, 1 H, D_2O exchangeable), 6.13 (m, 1 H), 5.81 (m, 1 H), 5.44 (m, 1 H), 4.52 (t, 1 H, J = 5.0, D_2O exchangeable), 3.32 (m, 2 H), 2.22 (m, 1 H), 2.05 (m, 2 H), 1.87 (m, 1 H), 1.84 (m, 1 H); MS (CI) m/z (intensity) 247 (MH^+, 100). Anal. Calcd for $C_{11}H_{14}N_6O$: C, 53.65; H, 5.73; N, 34.13. Found: C, 53.80; H, 5.90; N, 34.01.

16 was treated and purified by chromatography as described above for **14**, giving a yellow paste. The paste was dissolved in hot EtOAc with the aid of a small amount of MeOH, hexane was added until cloudy, and the solution was placed in a freezer for several hours. The solution was filtered, giving **17** as an off-white powder (25.5 mg, 0.10 mmol, 15% from **13**): mp 193.5−195 °C; ^{1}H NMR (DMSO-d_6, 300 MHz, major isomer) 8.27 (s, 1 H), 8.20 (br s, 1 H, D_2O exchangeable), 7.98 (br s, 1 H, D_2O exchangeable), 6.16 (m, 1 H), 5.95 (m, 1 H), 5.50 (m, 1 H), 4.55 (m, 1 H, D_2O exchangeable), 3.27 (m, 2 H), 2.19 (m, 2 H), 1.90 (m, 3 H); MS (CI) m/z (intensity) 247 (MH^+, 100). Anal. Calcd for $C_{11}H_{14}N_6O \cdot {}^2/_5MeOH$: C, 52.85; H, 6.07; N, 32.44. Found: C, 52.82; H, 5.96; N, 32.53.

5-Amino-3-(2-ethenyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (18). Reaction of **2** with **3** following the general procedure (eluted with C) gave **18** as a white powder (19.1 mg, 0.10 mmol, 7%, mp 228−231 °C. This sample was identical in all respects, except for a few minor peaks in the ^{1}H NMR and a lower mp, to the sample of **18** obtained from **27**. A mixed melting point was not depressed (238−250 °C).

The filtered undissolved solid was adsorbed to silica gel and eluted with C, giving a pale yellow powder (72.5 mg) which ^{1}H NMR showed to be a 55:45 mixture of isomers. Neither isomer was **18**.

Methyl *cis*-[4-(5-Amino-7-oxo-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl)-2-cyclohexen-1-yl]methyl Carbonate (19) and Methyl *cis*-[4-(5-Amino-7-oxo-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-2-yl)-2-cyclohexen-1-yl]methyl Carbonate (20). Reaction of **2** with **9** following the general procedure [neutralized with NH_4Cl, resolved twice with hexane:PhH:2-propanol (3:1:1) on a preparative TLC plate] gave **20** as an off-white solid (25.6 mg, 0.08 mmol, 12%): mp 294−296 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 10.90 (br s, 1 H, D_2O exchangeable), 6.49 (br s, 2 H, D_2O exchangeable), 5.95 (m, 2 H), 5.24 (m, 1 H), 4.08 (m, 2 H), 3.69 (s, 3 H), 2.49 (m, 1 H + DMSO), 2.09 (m, 2 H), 1.76 (m, 1 H), 1.59 (m, 1 H); MS (FAB) 321 (MH^+). Anal. Calcd for $C_{13}H_{16}N_6O_4$: C, 48.75; H, 5.03; N, 26.24. Found: C, 49.00; H, 5.20; N, 26.35.

Further elution with EtOAc:MeOH (4:1) brought a band off the baseline. The band was extracted with EtOAc:MeOH (4:1), giving **19** as a pale yellow powder (42.8 mg, 0.13 mmol, 20%): mp 199.5−200.5 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 11.10 (br s, 1 H, D_2O exchangeable), 6.96 (br s, 2 H, D_2O exchangeable), 5.93 (d, 1 H, J = 10.3), 5.87 (d, 1 H, J = 10.3), 5.06 (m, 1 H), 4.09 (m, 2 H), 3.68 (s, 3 H), 2.47 (m, 1 H + DMSO), 1.98 (m, 2 H), 1.75 (m, 1 H), 1.65 (m, 1 H); MS (FAB) 321 (MH^+).

5-Amino-6-chloro-4-(2-ethenylamino)pyrimidine (21). A solution of 5-amino-4,6-dichloropyrimidine (0.25 g, 1.52 mmol) in allylamine (10 mL) and triethylamine (3 mL) was stirred for 21 h at rt. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography (eluting with a gradient of hexane to EtOAc), giving **21** as a tan solid (265.5 mg, 1.44 mmol, 94%): mp 88−89 °C; R_f = 0.61 (EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz) 7.70 (s, 1 H), 6.96 (t, 1 H, J = 5.4, D_2O exchangeable), 5.90 (dddt, 1 H, J = 17.4, 10.5, 1.5, 5.4), 5.22 (dq, 1 H, J = 10.2, 1.5), 5.07 (dq, 1 H, J = 10.2, 1.5), 5.04 (s, 2 H, D_2O exchangeable), 5.07 (tt, 2 H, J = 5.4, 1.5); MS (EI) m/z (intensity) 186 (M^+ + 2, 15), 184 (M^+, 43), 169 (100). Anal. Calcd for $C_7H_9N_4Cl$: C, 45.54; H, 4.91; N, 30.35. Found: C, 45.55; H, 5.07; N, 30.50.

7-Chloro-3-(2-ethenyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (22) and 3-(2-Ethenyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (23). A cooled solution of $NaNO_2$ (92 mg, 1.33 mmol) in H_2O (2 mL) was added over 3 min to a solution of **21** (190 mg, 1.03 mmol) in H_2O (15 mL) and HOAc (5 mL) at 0 °C. The resulting solution was stirred for 2 h and then brought to rt and stirred for an additional 1 h. The solvent was removed, and the residue was purified by flash chromatography (eluting with a gradient of hexane to EtOAc), giving **22** as a pale yellow oil which slowly solidified (149.0 mg, 0.76 mmol, 74%): mp 39.5−41.5 °C; R_f = 0.74 (EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) 8.89 (s, 1 H), 6.09 (dddt, 1 H, J = 17.0, 10.0, 1.5, 6.0), 5.35 (dq, 1 H, J = 10.0, 1.5), 5.33−5.30 (m, 3 H); MS (EI) m/z (intensity) 197 (M^+ + 2, 1), 195 (M^+, 2), 41 (100).

Further elution with EtOAc gave **23** as a white solid (27.3 mg, 0.15 mmol, 15%) which was recrystallyzed from MeOH, giving clear crystals (26.5 mg, 0.15 mmol, 15%): mp 164−164.5 °C; R_f = 0.26 (EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) 12.69 (br s, 1 H, D_2O exchangeable), 8.23 (s, 1 H), 6.07 (dddt, 1 H, J = 17.0, 10.5, 1.5, 5.5), 5.24 (dq, 1 H, J = 10.5, 1.5), 5.15 (dt, 2 H, J = 5.5, 1.5), 5.35 (dm, 1 H, J = 17.5); MS (EI) m/z (intensity) 177 (M^+, 43), 120 (100). Anal. Calcd for $C_7H_7N_5O$: C, 47.45; H, 3.98; N, 39.53. Found: C, 47.50; H, 4.06; N, 39.41.

7-Amino-3-(2-ethenyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (4). A solution of **22** (94.4 mg, 0.483 mmol) in MeOH (10 mL) and NH_3 (~50 mL) was stirred in a bomb at 60 °C for 42 h and then cooled to rt. The NH_3 was carefully vented. The residue was triturated in H_2O and filtered, giving **4** as a light tan solid (64.4 mg, 0.366 mmol, 76%, mp 203.5−204.5 °C). This sample was identical in all respects to the **4** obtained through the palladium-catalyzed coupling route and a mixed melting point was not depressed (203−203.5 °C).

2-Amino-6-chloro-4-(2-ethenylamino)pyrimidine (24) was prepared as described for **21**, except 2-amino-4,6-dichloropyrimidine (1.00 g, 6.10 mmol) was used as the pyrimidine and 20 mL of allylamine was used, giving **24** as a white solid (1.11 g, 6.01 mmol, 99%): mp 116.5−117 °C; R_f = 0.63 (EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz) two isomers (2:1 ratio), peaks for major isomer 7.25 (br s, 1 H, J = 5.4, D_2O exchangeable), 6.40 (br s, 2 H, D_2O exchangeable), 5.89−5.67 (m, 2 H), 5.19−4.98 (m, 2 H), 3.80 (m, 2 H); MS (EI) m/z (intensity) 186 (M^+

+ 2, 10), 184 (M^+, 31), 169 (100). Anal. Calcd for $C_7H_9N_4Cl$: C, 45.54; H, 4.91; N, 30.35. Found: C, 45.41; H, 4.98; N, 30.20.

2-Amino-6-chloro-5-[(4-chlorophenyl)azo]-4-(2-ethenylamino)pyrimidine (25). A solution of $NaNO_2$ (451 mg, 6.54 mmol) in H_2O (10 mL) was added dropwise to a solution of 4-chloroaniline (777 mg, 6.09 mmol) in H_2O (10 mL) and concd HCl (4 mL) at 0 °C and stirred for 45 min. The resulting solution was stirred for 2 h, brought to rt, and stirred for an additional 1 h. The resulting solution was added over 10 min to a solution of **24** (850 mg, 4.61 mmol) in H_2O (100 mL) and HOAc (100 mL) at 0 °C. The solution was allowed to reach rt, stirred for 2 d, and then set in a refrigerator for 2 d. The solution was filtered, giving **25** as a bright yellow solid (752.8 mg, mp 195−198 °C). Several additional crops were obtained over several days after the volume of the filtrate was reduced to 50 mL, and the solution was set in a refrigerator. An analytical sample (mp 217−218 °C) was obtained by recrystallization from EtOAc:hexane, but the crude material was sufficiently pure for use in the next step: total 1.40 g, 4.33 mmol, 94%; $R_f = 0.59$ (hexane:EtOAc, 1:1); ^{1}H NMR (DMSO-d_6, 500 MHz) two isomers (7:3 ratio), peaks for major isomer 10.36 (br s, 1 H), 7.76 (d d, 2 H, $J = 7.0, 2.0$), 7.63−7.53 (m, 4 H), 5.99 (ddt, 1 H, $J = 17.0, 10.5,, 5.5$), 5.16 (m, 2 H), 4.16 (m, 2 H); MS (EI) m/z (intensity) 326 ($M^+ + 4$, 3), 324 ($M^+ + 2$, 19), 322 (M^+, 28), 196 (100). Anal. Calcd for $C_{13}H_{12}N_6Cl_2$: C, 48.31; H, 3.74; N, 26.00. Found: C, 48.21; H, 3.85; N, 25.87.

6-Chloro-2,5-diamino-3-(2-ethenylamino)pyrimidine (26). HOAc (1.6 mL) was added to a stirring solution of **25** (1.22 g, 3.77 mmol) and Zn dust (2.52 g) in H_2O (40 mL) and EtOH (40 mL) under N_2 at rt and then brought to reflux. After 3 h, the solution was cooled back to rt and rapidly filtered through sintered glass, and the residue was rinsed with a small portion of EtOH. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography [eluting with a gradient of $CHCl_3$ to $CHCl_3$:MeOH (30:1)], giving **26** as a white flakes (421.4 mg, 2.11 mmol, 56%): mp 120.5−121 °C; $R_f = 0.24$ ($CHCl_3$:EtOAc, 1:1); ^{1}H NMR (DMSO-d_6, 300 MHz) 6.64 (br s, 1 H, D_2O exchangeable), 5.89 (m, 1 H), 5.62 (br s, 2 H, D_2O exchangeable), 5.16 (d m, 1 H, $J = 17.4$), 5.07 (d m, 1 H, $J = 9.6$), 3.95 (m, 4 H, 2 H are D_2O exchangeable); MS (EI) m/z (intensity) 201 ($M^+ + 2$, 28), 199 (M^+, 100). Anal. Calcd for $C_7H_{10}N_5Cl$: C, 42.11; H, 5.05; N, 35.08. Found: C, 42.16; H, 5.17; N, 35.19.

5-Amino-7-chloro-3-(2-ethenyl)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidine (27) was prepared as described for **22**, except **26** (273.7 mg, 1.37 mmol) was used as the pyrimidine. The crude product was recrystallyzed from H_2O, giving **27** as pale yellow needles (152.4 mg, 0.72 mmol, 53%): mp 141−142 °C; $R_f = 0.76$ (EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz) 7.69 (br s, 2 H, D_2O exchangeable), 6.05 (ddt, 1 H, $J = 17.4, 10.5, 5.4$), 5.22 (d, 1 H, $J = 10.2$), 5.04 (m, 3 H); MS (EI) m/z (intensity) 210 (M^+, 35), 181 (100). Anal. Calcd for $C_7H_7N_6Cl$: C, 39.92; H, 3.35; N, 39.90. Found: C, 40.10; H, 3.17; N, 39.70.

5-Amino-3-(2-ethenyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (18). A solution of **27** (110 mg, 0.52 mmol) in 0.25 N NaOH was warmed at ∼80 °C. After 90 min, the solution was cooled to 0 °C and 1 N HCl was added to pH 3. The resulting solid was filtered and rinsed with H_2O, giving **18** as an off-white solid (88.7 mg, 0.46 mmol, 88%): mp 275.5−277 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 10.94 (s, 1 H, D_2O exchangeable), 6.93 (br s, 2 H, D_2O exchangeable), 6.01 (dddt, 1 H, $J = 17.1, 10.2, 1.3, 5.4$), 5.20 (dq, 1 H, $J = 10.2, 1.2$), 4.99 (dq, 1 H, $J = 17.1, 1.2$), 4.89 (dt, 1 H, $J = 5.4, 1.5$); MS (EI) m/z intensity 192 (M^+, 56), 43 (100). Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.20; N, 43.73. Found: C, 44.00; H, 4.03; N, 43.46.

Acknowledgment. This work was supported by Public Health Service Grant CA23263 from the National Cancer Institute.

JO960815J