JOC*Article*

Thermolysis of Benzannulated Enyne−Carbodiimides. Application in the Synthesis of Pyrido[1′,2′:1,2]pyrimido[4,5-*b*]indoles and Related Heteroaromatic Compounds

Xiaoling Lu, Jeffrey L. Petersen,† and Kung K. Wang*

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506-6045

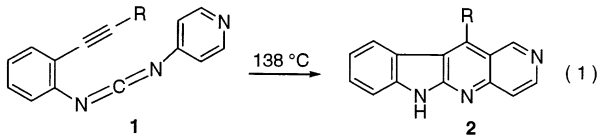
kwang@wvu.edu

Received June 13, 2002

Several derivatives of the pyrido[1′,2′:1,2]pyrimido[4,5-*b*]indoles **4** and the pyrazino[1′,2′:1,2]-pyrimido[4,5-*b*]indoles **14** were synthesized by treatment of the benzannulated enyne−isocyanates **8** with the iminophosphoranes **9** and **13**, respectively, for the aza-Wittig reaction followed by thermolysis. The reaction presumably proceeds through an initial formation of the corresponding benzannulated enyne−carbodiimides, such as **10**, followed by a formal intramolecular hetero Diels−Alder reaction. Surprisingly, when the iminophosphorane **17** was used for condensation with **8**, the expected pyrimido[1′,6′:1,2]pyrimido[4,5-*b*]indoles **16** were not obtained. Instead, the isomeric pyrimido[6′,1′:2,3]pyrimido[4,5-*b*]indoles **21** were isolated. Presumably, an alternative reaction pathway involving an initial [2 + 2] cycloaddition reaction to form **19** followed by ring opening could lead to **20** and, after an intramolecular radical−radical coupling, **21**. Treatment of the urea derivatives **24** with dibromotriphenylphosphorane also produced in situ the benzannulated enyne−carbodiimides **25**, which on thermolysis gave the isoquinolino[2′,1′:1,2]pyrimido[4,5-*b*]indoles **26**. Methylation of **4a**, **14a**, and **26a** with methyl iodide occurred exclusively at the site of the indolo nitrogen. The planar geometry of those novel heteroaromatic compounds, resembling many DNA-binding agents, makes them potential candidates as DNA intercalators.

Introduction

We recently reported a new synthetic procedure involving thermolysis of the benzannulated enyne−carbodiimides **1** to form the 6*H*-indolo[2,3-*b*][1,6]naphthyridines **2** (eq 1)[1a] as the 5-aza analogues of ellipticine (**3**),[2a] a naturally occurring alkaloid. Ellipticine and many of its



1 **2** (1)

derivatives were found to exhibit potent antitumor activities.[2b−m] Similarly, by placing a 3-pyridyl substituent at the carbodiimide terminus, 6*H*-indolo[2,3-*b*][1,5]-naphthyridines and 10*H*-indolo[2,3-*b*][1,7]naphthyridines were likewise synthesized.[1a] We now have successfully extended this strategy to the synthesis of the pyrido[1′,2′:1,2]pyrimido[4,5-*b*]indoles **4** and related heteroaromatic compounds using the systems having a 2-pyridyl, a pyrazinyl, a 4-pyrimidyl, or a 1-isoquinolinyl substituent.

It is worth noting that the core structure of **4** represents a new heteroaromatic system. The planar geometry of the indoles **4**, resembling those of indolo[2,3-*b*]quinolizinium bromide (**5**)[3] and the tetracyclic heteroaromatic salts **6**,[4] makes these compounds potential candidates as DNA intercalators. It was recently reported that **5** binds preferentially to GC base pairs.[3] Irradiation of DNA in the presence of **5** resulted in efficient single-strand cleavage of the nucleic acid. In addition, the indoles **4** can also be regarded as the pyridannulated derivatives of 9*H*-pyrimido[4,5-*b*]indole (**7**). Many derivatives of 9*H*-

* To whom correspondence should be addressed. Phone: (304) 293-3068, ext 6441. Fax: (304) 293-4904.

† To whom correspondence concerning the X-ray structure should be addressed. Phone: (304) 293-3435, ext 6423. Fax: (304) 293-4904. E-mail: jpeterse@wvu.edu.

(1) (a) Zhang, Q.; Shi, C.; Zhang, H.-R.; Wang, K. K. *J. Org. Chem.* **2000**, *65*, 7977−7983. For other similar studies, see: (b) Shi, C.; Zhang, Q.; Wang, K. K. *J. Org. Chem.* **1999**, *64*, 925−932. (c) Lu, X.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2002**, *67*, 5412−5415. (d) Schmittel, M.; Steffen, J.-P.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2371−2373. For a photochemically induced reaction, see: (e) Schmittel, M.; Rodríguez, D.; Steffen, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2152−2155.

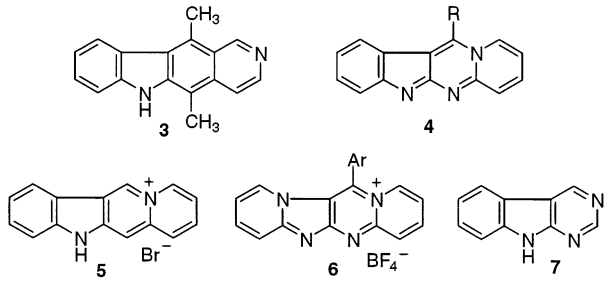
(2) (a) Goodwin S.; Smith, A. F.; Horning, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 1903−1908. (b) Dalton, L. K.; Demerac, S.; Elmes, B. C.; Loder, J. W.; Swan, J. M.; Teitei, T. *Aust. J. Chem.* **1967**, *20*, 2715−2727. (c) Gribble, G. W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1990; Vol. 39, p 239−351. (d) Suffness, M.; Cordell, G. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 25, pp 89−142. (e) Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389−2408. (f) Gribble, G. W.; Saulnier, M. G.; Obaza-Nutaitis, J. A.; Ketcha, D. M. *J. Org. Chem.* **1992**, *57*, 5891−5899. (g) Ishikura, M.; Yaginuma, T.; Agata, I.; Miwa, Y.; Yanada, R.; Taga, T. *Synlett* **1997**, 214−216. (h) Díaz, M. T.; Cobas, A.; Guitián, E.; Castedo, L. *Synlett* **1998**, 157−158. (i) Ergün, Y.; Patir, S.; Okay, G. *J. Heterocycl. Chem.* **1998**, *35*, 1445−1447. (j) Ishikura, M.; Hino, A.; Yaginuma, T.; Agata, I.; Katagiri, N. *Tetrahedron* **2000**, *56*, 193−207. (k) Anderson, W. K.; Gopalsamy, A.; Reddy, P. S. *J. Med. Chem.* **1994**, *37*, 1955−1963. (l) Pierson, V.; Pierre, A.; Pommier, Y.; Gros, P. *Cancer Res.* **1988**, *48*, 1404−1409. (m) Vilarem, M. J.; Riou, J. F.; Multon, E.; Gros, M. P.; Larsen, C. J. *Biochem. Pharmacol.* **1986**, *35*, 2087−2095.

(3) Ihmels, H.; Faulhaber, K.; Wissel, K.; Bringmann, G.; Messer, K.; Viola, G.; Vedaldi, D. *Eur. J. Org. Chem.* **2001**, 1157−1161.

(4) Barun, O.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2000**, *65*, 1583−1587.

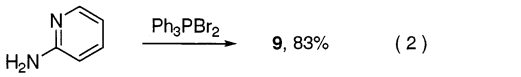
10.1021/jo0204092 CCC: $22.00
Published on Web 10/10/2002

pyrimido[4,5-*b*]indole have been found to exhibit potent biological activities,[5] and there are continuing interests in developing new synthetic methodologies for these derivatives.[5,6]

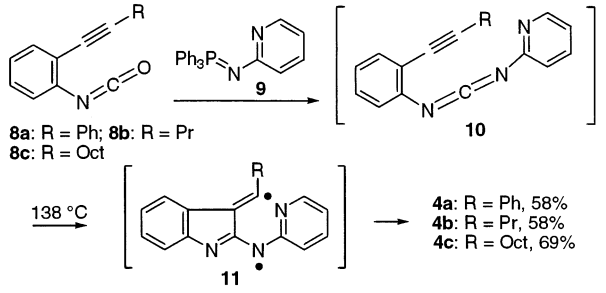


Results and Discussion

The aza-Wittig reaction between the benzannulated enyne−isocyanates **8**[1a] and the iminophosphorane **9**, derived from 2-aminopyridine and dibromotriphenylphosphorane in 83% yield (eq 2), produced in situ the benzannulated enyne−carbodiimides **10**, which on thermolysis under refluxing *p*-xylene at 138 °C gave the pyrido[1′,2′:1,2]pyrimido[4,5-*b*]indoles **4** (Scheme 1). The

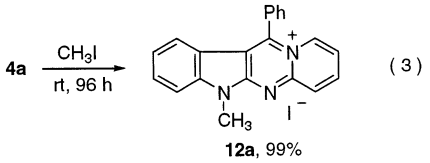


SCHEME 1



structures of **4b** and **4c** were established by the X-ray structure analysis. The transformation from **10** to **4** could proceed either through a two-step biradical pathway via the biradical **11** as in the enyne−allene system[7] or through a concerted intramolecular hetero-Diels−Alder reaction. It is interesting to note that the carbon−nitrogen double bond of the pyridyl ring is involved in the cyclization process to form **4** having an 18-π electron aromatic system. The alternative process involving a carbon−carbon double bond of the pyridyl ring did not appear to occur, presumably because such a reaction would disrupt the aromaticity of the pyridyl ring. A sample of **4b** was submitted to the National Cancer Institute for evaluation against human tumor cell lines, and it was found to exhibit activity against MCF7 (breast) in the primary anticancer assay.

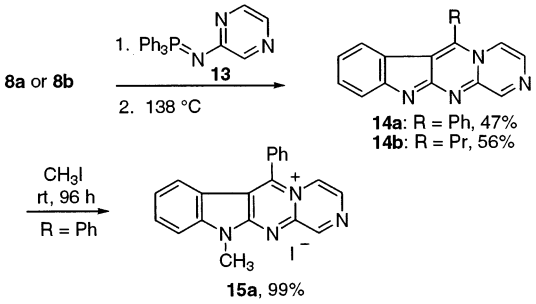
Alkylation of **4a** with methyl iodide occurred exclusively at the site of the indolo nitrogen, producing the indolium iodide **12a** in quantitative yield (eq 3). The



structure of **12a** was unequivocally established by the X-ray structure analysis. The close resemblance between the core structure of **12a** and **5** makes **12a** a potential DNA-binding agent. A sample of **12a** was also submitted to the National Cancer Institute for screening against human tumor cell lines, and it was found to exhibit activities against the three-cell line panel in the primary anticancer assay.

The iminophosphorane **13**, prepared from aminopyrazine in 80% yield, was also found to react with **8a** and **8b**, leading to the pyrazino[1′,2′:1,2]pyrimido[4,5-*b*]indoles **14a** and **14b**,[8] respectively (Scheme 2). The core

SCHEME 2



structure of **14** also represents a new heteroaromatic system. Again, alkylation of **14a** with methyl iodide occurred exclusively at the site of the indolo nitrogen to furnish **15a**[8] in quantitative yield.

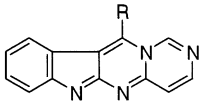
We have also attempted to prepare the pyrimido[1′,6′:1,2]pyrimido[4,5-*b*]indoles **16** by treatment of **8a** and **8b** with the iminophosphorane **17**, which was prepared in 96% yield from 4-aminopyrimidine. However, we were surprised to observe that the isomeric pyrimido[6′,1′:2,3]-pyrimido[4,5-*b*]indoles **21** were obtained instead (Scheme 3). The structure of **21a** was unequivocally established by the X-ray structure analysis, and the structure of **21b** was assigned on the basis of NMR chemical shift cor-

(5) (a) Showalter, H. D. H.; Bridges, A. J.; Zhou, H.; Sercel, A. D.; McMichael, A.; Fry, D. W. *J. Med. Chem.* **1999**, *42*, 5464−5474. (b) Traxler, P. M.; Furet, P.; Mett, H.; Buchdunger, E.; Meyer, T.; Lydon, N. *J. Med. Chem.* **1996**, *39*, 2285−2292.

(6) (a) Gangjee, A.; Chen, L. *J. Heterocycl. Chem.* **1999**, *36*, 441−444. (b) Plé, N.; Turck, A.; Heynderickx, A.; Quéguiner, G. *J. Heterocycl. Chem.* **1994**, *31*, 1311−1315. (c) Molina, P.; Arques, A.; Alías, A.; Vinader, M. L. *Tetrahedron Lett.* **1991**, *32*, 4401−4404. (d) Edstrom, E. D.; Yuan, W. *Tetrahedron Lett.* **1991**, *32*, 323−326. (e) Kondo, Y.; Watanabe, R.; Sakamoto, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1989**, *37*, 2933−2936. (f) Venugopalan B.; Desai, P. D.; de Souza, N. J. *J. Heterocycl. Chem.* **1988**, *25*, 1633−1639. (g) Bernier, J.-L.; Hénichart, J.-P. *J. Org. Chem.* **1981**, *46*, 4197−4198. (h) Higashino, T.; Hayashi, E.; Matsuda, H.; Katori, T. *Heterocycles* **1981**, *15*, 483−487. (i) Wright, G. E. *J. Heterocycl. Chem.* **1976**, *13*, 539−544. (j) Senda, S.; Hirota, K.; Takahashi, M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 503−507. (k) Wamhoff, H.; Wehling, B. *Chem. Ber.* **1975**, *108*, 2107−2114. (l) Hyatt, J. A.; Swenton, J. S. *J. Org. Chem.* **1972**, *37*, 3216−3220. (m) Hyatt, J. A.; Swenton, J. S. *J. Heterocycl. Chem.* **1972**, *9*, 409−410. (n) Schulte, K. E.; Reisch, J.; Stoess, U. *Arch. Pharm.* (*Weinheim, Ger.*) **1972**, *305*, 523−533.

(7) (a) Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1843−1845. (b) Schmittel, M.; Maywald, M.; Strittmatter, M. *Synlett* **1997**, 165−166. (c) Musch, P. W.; Engels, B. *J. Am. Chem. Soc.* **2001**, *123*, 5557−5562.

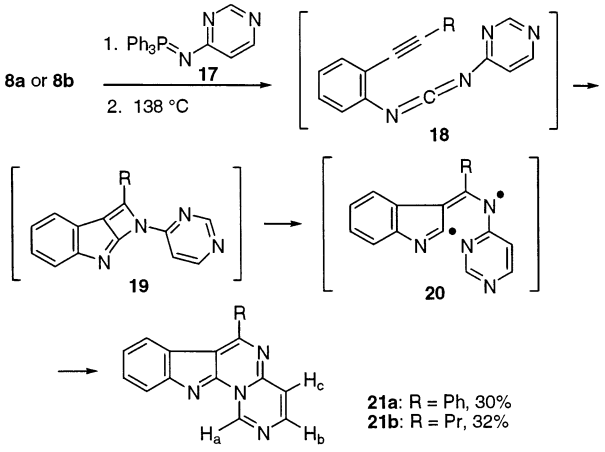
(8) The structure was established by the X-ray structure analysis.



16a: R = Ph; **16b**: R = Pr

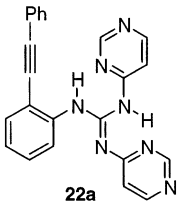
relations with those of **21a**. The indoles **21a** and **21b** exhibited essentially identical ^{1}H NMR chemical shifts for H_a, H_b, and H_c. Because **16** and **21** could be expected to exhibit identical number and multiplicity of NMR signals, it was only after the X-ray structure of **21a** had been obtained that we realized that the isolated products were not the expected indoles **16**.

SCHEME 3



Presumably, an alternative reaction mechanism involving an initial [2 + 2] cycloaddition reaction to form **19** became the preferred pathway. An analogous [2 + 2] cycloaddition reaction of the benzannulated enyne−allene system was reported previously.[9] Ring opening of **19** could lead to **20**, which could then undergo an intramolecular radical−radical coupling to produce **21**. It is worth mentioning that the alkenyl radical center in **20** is perhaps stabilized by the adjacent electron lone pair on the indolo nitrogen, facilitating the ring opening of **19**. The analogous α-aminoalkyl radicals are stabilized radicals having large stabilization energies due to conjugative delocalization.[10] The reason for the change of the reaction pathway in favor of **21** over **16** is not clear at this time.

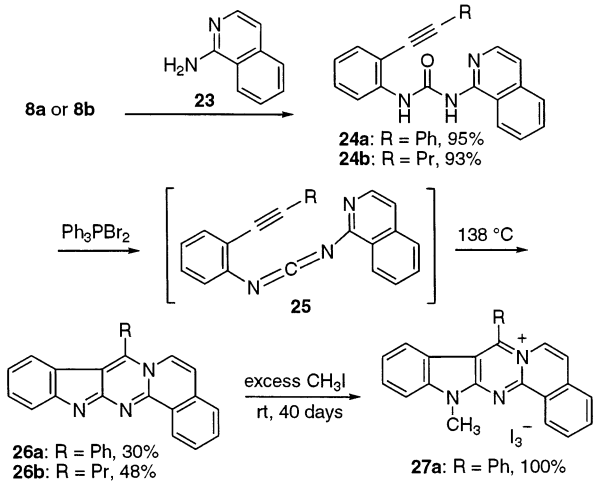
In the case of **21a**, a small amount (10%) of the guanidine derivative **22a** was also isolated. Two intramolecular hydrogen bondings are present in **22a** as indicated by the X-ray crystallographic structure. Unlike **4a** and **14a**, compound **21a** did not exhibit any reactivity toward methyl iodide at room temperature for several days.



22a

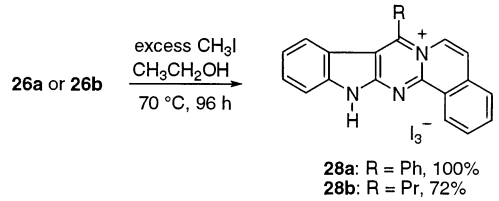
Attempts to synthesize the benzannulated enyne−carbodiimides **25** by the aza-Wittig reaction between **8** and the iminophosphorane derived from 1-aminoisoquinoline (**23**) were unsuccessful. Fortunately, an alternative route involving condensation between **8** and **23** was successful in producing the corresponding urea derivatives **24** as the precursors of **25** (Scheme 4).

SCHEME 4



Subsequent treatment of **24a** with dibromotriphenylphosphorane[11] produced in situ **25a**, which on heating under refluxing *p*-xylene furnished 8-phenylisoquinolino[2′,1′:1,2]pyrimido[4,5-*b*]indole (**26a**) in 30% yield. The structure of **26a** was established by the X-ray structure analysis. In addition to **26a**, a second product (24% yield) exhibiting NMR signals very similar to those of **26a** was also isolated. Unfortunately, we were unable to obtain a single-crystal suitable for the X-ray analysis to establish its structure. In the case of **24b**, the same reaction condition produced **26b** as the only isolated product in 48% yield.

Methylation of **26a** with large excess of methyl iodide was very sluggish at room temperature, producing only ca. 10% of a methylated adduct after several days. It was only after 40 days that **27a**[8] was obtained in essentially quantitative yield. Interestingly, an attempt to increase the rate of methylation by treatment of **26a** with large excess of methyl iodide in a mixture of solvents, including ethanol, in a sealed tube at 70 °C for 96 h afforded the corresponding isoquinolinium triiodide **28a** (eq 4). The



(4)

structure of **28a** was unequivocally established by the X-ray structure analysis. Apparently, under the elevated reaction temperature, hydrogen iodide was generated from the reaction between methyl iodide and ethanol.[12]

(9) (a) Li, H.; Zhang, H.-R.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2001**, *66*, 6662−6668. (b) Gillmann, T.; Hulsen, T.; Massa, W.; Wocadlo, S. *Synlett* **1995**, 1257−1259.

(10) Griller, D.; Lossing, F. P. *J. Am. Chem. Soc.* **1981**, *103*, 1586−1587.

(11) Palomo, C.; Mestres, R. *Synthesis* **1981**, 373−374.

(12) Ogg, R. A., Jr. *J. Am. Chem. Soc.* **1938**, *60*, 2000−2001.

As in methylation, protonation occurred exclusively at the site of the indolo nitrogen of **26a**. Similarly, with **26b** the same reaction condition produced the isoquinolinium triiodide **28b**.[8]

Conclusions

Thermolysis of the benzannulated enyne−carbodiimides provides easy access to a variety of the pyrido[1′,2′:1,2]pyrimido[4,5-*b*]indoles **4** and related heteroaromatic compounds. The simplicity of the reaction sequence makes the process especially attractive for the synthesis of novel heteroaromatic compounds as potential DNA-intercalating agents. The formation of the pyrimido[6′,1′:2,3]pyrimido[4,5-*b*]indoles **21** was unexpected and likely involved a novel [2 + 2] cycloaddition pathway of the benzannulated enyne−carbodiimides.

Experimental Section

All reactions were conducted in oven-dried (120 °C) glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) and diethyl ether were distilled from benzophenone ketyl. Triethylamine and benzene were distilled from calcium hydride prior to use. The isocyanates **8** were prepared as described previously.[1a] 1-Alkynes, dibromotriphenylphosphorane (Ph_3PBr_2), *p*-xylene (anhydrous), 2-aminopyridine, aminopyrazine, 4-aminopyrimidine, and 1-aminoisoquinoline (**23**) were purchased from chemical suppliers and were used as received. Melting points were uncorrected. ^{1}H (270 MHz) and ^{13}C (67.9 MHz) NMR spectra were recorded in $CDCl_3$ using $CHCl_3$ (^{1}H δ 7.26) and $CDCl_3$ (^{13}C δ 77.00) as internal standards unless otherwise indicated.

Iminophosphorane 9. The following procedure for the preparation of the iminophosphorane **9** is representative. A reaction mixture of 0.487 g (5.18 mmol) of 2-aminopyridine, 2.900 g (6.87 mmol) of Ph_3PBr_2, and 1.74 mL (12.5 mmol) of anhydrous triethylamine in 40 mL of anhydrous benzene was heated under reflux for 12 h. The triethylammonium bromide precipitate was removed by filtration, and the filtrate was concentrated. To the resulting viscous residue was added 30 mL of diethyl ether followed by filtration to afford **9** (1.517 g, 4.28 mmol, 83%) as a white solid: mp 140−141 °C; IR (KBr) 1584, 718, 692 cm^{-1}; ^{1}H δ 7.9−7.8 (7 H, m), 7.54−7.30 (10 H, m), 6.92 (1 H, dt, J = 8.4, 0.8 Hz), 6.44 (1 H, ddd, J = 6.1, 5.0, 1.1 Hz); ^{13}C δ 163.7 (d, J = 6.2 Hz), 147.0, 136.5 (d, J = 4.7 Hz), 133.1 (d, J = 9.8 Hz), 131.4 (d, J = 2.6 Hz), 130.4 (d, J = 99.4 Hz), 128.2 (d, J = 11.9 Hz), 117.2 (d, J = 24.3 Hz), 112.2.

12-Propylpyrido[1′,2′:1,2]pyrimido[4,5-*b*]indole (4b). The following procedure for the synthesis of **4b** is representative. To a solution of 0.344 g (0.971 mmol) of the iminophosphorane **9** in 10 mL of anhydrous *p*-xylene was introduced via cannula a solution of 0.185 g (0.100 mmol) of the isocyanate **8b** in 10 mL of anhydrous *p*-xylene under a nitrogen atmosphere at rt. After 5 h, the reaction mixture was heated under reflux for 12 h before it was allowed to cool to rt. The mixture was then concentrated to yield a solid residue. After three cycles of washing the residue with 40 mL of diethyl ether followed by centrifugation and decanting the supernatant liquid, the remaining solid was pumped to dryness in vacuo to afford **4b** (0.147 g, 0.563 mmol, 58%) as an orange solid. Recrystallization from methylene chloride afforded orange flakes: compound turns black without melting at 222 °C; IR (KBr) 1557, 1420, 734 cm^{-1}; ^{1}H δ 8.29 (1 H, d, J = 7.4 Hz), 8.03 (1 H, d, J = 7.9 Hz), 7.93 (1 H, d, J = 7.9 Hz), 7.81 (1 H, dm, J = 9.2, 0.7 Hz), 7.62 (1 H, td, J = 7.7, 1.2 Hz), 7.53 (1 H, ddd, J = 9.2, 6.7, 1.2 Hz), 7.28 (1 H, td, J = 7.9, 1.0 Hz), 7.01 (1 H, ddd, J = 8.9, 7.4, 1.5 Hz), 3.62 (2 H, t, J = 7.9 Hz), 1.95 (2 H, sextet, J = 7.9 Hz), 1.22 (3 H, t, J = 7.4 Hz); ^{13}C δ 159.3, 158.0, 146.1, 141.4, 131.2, 129.4, 127.7, 127.0, 122.7, 121.8, 120.0, 119.3, 117.7, 113.6, 30.8, 20.1, 14.2; Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 77.95; H, 5.84; N, 16.03. The structure of **4b** was established by the X-ray structure analysis.

5-Methyl-12-phenyl-5*H*-pyrido[1′,2′:1,2]pyrimido[4,5-*b*]indol-11-ium Iodide (12a). To a solution of 0.0195 g (0.066 mmol) of **4a** in 15 mL of chloroform was added 13.2 mL of a 0.05 M solution of methyl iodide (0.660 mmol) in chloroform. The reaction mixture was stirred at rt for 96 h. The organic solvent was removed, and the remaining solid was washed with 1 mL of chloroform (chilled at 0 °C) to afford **12a** (0.0285 g, 0.065 mmol, 99%) as a yellow solid. Recrystallization from dichloromethane afforded yellow needles: mp 312−313 °C; IR (KBr) 3402, 1592, 758, 710 cm^{-1}; ^{1}H δ 8.58 (1 H, d, J = 7.4 Hz), 8.33 (1 H, dm, J = 9.0, 1.1 Hz), 8.26 (1 H, td, J = 9.0, 1.3 Hz), 7.98−7.94 (2 H, m), 7.86−7.81 (3 H, m), 7.73 (1 H, t, J = 7.4 Hz), 7.68 (1 H, td, J = 6.8, 1.6 Hz), 7.62 (1 H, d, J = 8.2 Hz), 7.24 (1 H, t, J = 7.9 Hz), 6.91 (1 H, d, J = 7.9 Hz), 4.12 (3 H, s); ^{13}C δ 153.0, 148.2, 145.2, 143.8, 138.2, 132.5, 131.8, 131.5, 130.9, 129.5, 127.6, 127.1, 124.0, 123.9, 119.9, 118.2, 115.8, 111.0, 28.9. The structure of **12a** was established by X-ray structure analysis.

6-Propylpyrazino[1′,2′:1,2]pyrimido[4,5-*b*]indole (14b). The following procedure for the synthesis of **14b** is representative. To a solution of 0.185 g (0.521 mmol) of the iminophosphorane **13** in 15 mL of anhydrous *p*-xylene was introduced via cannula a solution of 0.096 g (0.520 mmol) of the isocyanate **8b** in 10 mL of anhydrous *p*-xylene under a nitrogen atmosphere at rt. The reaction mixture was kept at 45 °C for 12 h and then was heated under reflux at 138 °C for an additional 12 h before it was allowed to cool to rt. The mixture was concentrated to yield a solid residue. After three cycles of washing the residue with 40 mL of diethyl ether followed by centrifugation and decanting the supernatant liquid, the remaining solid was pumped to dryness in vacuo to afford **14b** (0.076 g, 0.290 mmol, 56%) as an orange solid. Recrystallization from chloroform afforded dark red needles: compound turns black without melting at 170 °C; IR (KBr) 1639, 1414, 751 cm^{-1}; ^{1}H δ 9.19 (1 H, s), 8.03−7.93 (4 H, m), 7.63 (1 H, td, J = 7.9, 0.7 Hz), 7.31 (1 H, t, J = 7.9 Hz), 3.58 (2 H, t, J = 8.0 Hz), 1.91 (2 H, sextet, J = 7.4 Hz), 1.20 (3 H, t, J = 7.4 Hz); ^{13}C δ 158.2, 154.7, 140.6, 138.6, 130.0, 129.2, 122.9, 121.3, 121.0, 119.8, 118.5, 117.6, 30.0, 20.1, 14.1. The structure of **14b** was established by X-ray structure analysis.

6-Phenylpyrimido[6′,1′:2,3]pyrimido[4,5-*b*]indole (21a) and the Guanidine Derivative 22a. The following procedure for the synthesis of **21a** is representative. To a solution of 0.177 g (0.499 mmol) of the iminophosphorane **17** in 10 mL of anhydrous *p*-xylene was introduced via cannula a solution of 0.109 g (0.498 mmol) of the isocyanate **8a** in 10 mL of anhydrous *p*-xylene under a nitrogen atmosphere at rt. The reaction mixture was kept at 50 °C for 12 h and then was heated under reflux at 138 °C for an additional 24 h before it was allowed to cool to rt. The mixture was then concentrated to yield a solid residue. After three cycles of washing the residue with 40 mL of diethyl ether followed by centrifugation and decanting the supernatant liquid, the remaining solid was pumped to dryness in vacuo to afford a golden yellow solid. The solid was again washed three times with 1 mL of dichloromethane and one time with 1 mL of diethyl ether to afford **21a** as a yellow solid (0.045 g, 0.152 mmol, 30%). Recrystallization from chloroform afforded bright yellow crystals. The combined solution of 3 mL of dichloromethane and 1 mL of diethyl ether was concentrated, and the residue was purified by column chromatography (neutral alumina, 2% absolute ethanol in dichloromethane) to yield the guanidine derivative **22a** (0.019 g, 0.049 mmol, 10%) as a pale yellow solid. Recrystallization from chloroform afforded pale yellow crystals. Compound **21a**: compound turns brown at 265 °C and melts at 270 °C; IR (KBr) 1556, 1199, 761, 702 cm^{-1}; ^{1}H δ 10.37 (1 H, d, J = 1.1 Hz), 8.46 (1 H, d, J = 6.3 Hz), 8.11−8.04 (2 H, m), 8.00 (1 H, d, J = 7.9 Hz), 7.93 (1 H, d, J = 7.9

Hz), 7.79 (1 H, dd, J = 6.3, 1.1 Hz), 7.67−7.64 (3 H, m), 7.58 (1 H, td, J = 7.6, 1.3 Hz), 7.25 (1 H, td, J = 7.6, 1.1 Hz); ^{13}C δ 157.6, 152.2, 148.2, 147.4, 143.5, 141.4, 137.6, 130.9, 129.3, 128.9, 128.2, 122.8, 121.9, 121.7, 119.6, 119.3, 115.5. The structure of **21a** was established by X-ray structure analysis. Compound **22a**: ^{1}H δ 14.13 (1 H, br, s), 12.28 (1 H, s), 8.81 (1 H, s), 8.62 (1 H, d, J = 8.2 Hz), 8.48 (1 H, d, J = 5.5 Hz), 8.42 (1 H, d, J = 5.5 Hz), 8.30 (1 H, s), 7.57 (1 H, d, J = 7.7 Hz), 7.51−7.48 (2 H, m), 7.41−7.30 (4 H, m), 7.12 (1 H, t, J = 7.4 Hz), 6.95 (1 H, d, J = 5.5 Hz), 6.86 (1 H, d, J = 5.0 Hz). The structure of **22a** was established by X-ray structure analysis.

Urea 24a. The following procedure for the preparation of the urea **24a** is representative. To a solution of 0.140 g (0.972 mmol) of 1-aminoisoquinoline (**23**) in 5 mL of anhydrous dichloromethane was added a solution of 0.213 g (0.973 mmol) of the isocyanate **8a** in 10 mL of anhydrous dichloromethane via cannula under a nitrogen atmosphere at rt. After 12 h, 15 mL of hexanes was added to the reaction mixture. Filtration of the mixture afforded 0.336 g (0.926 mmol, 95%) of **24a** as a white solid: mp 234−235 °C; IR (KBr) 3250, 3128, 1673, 758 cm^{-1}; ^{1}H δ 12.95 (1 H, s), 8.44 (1 H, d, J = 8.2 Hz), 8.11 (1 H, br), 8.07 (1 H, d, J = 8.4 Hz), 7.77−7.53 (7 H, m), 7.43−7.30 (4 H, m), 7.12−7.06 (2 H, m).

8-Phenylisoquinolino[2′,1′:1,2]pyrimido[4,5-*b*]indole (26a) and a Related Compound. To a solution of 0.278 g (0.660 mmol) of Ph_3PBr_2 and 0.83 mL (6.000 mmol) of anhydrous triethylamine in 25 mL of anhydrous dichloromethane was added dropwise, using a pressure equalizing addition funnel over 3 h, a solution of 0.109 g (0.300 mmol) of the urea **24a** in 50 mL of anhydrous dichloromethane. After 12 h of stirring at rt, 50 mL of anhydrous *p*-xylene was introduced and dichloromethane was removed by distillation under reduced pressure. The triethylammonium bromide precipitate was removed by filtration under a nitrogen atmosphere and washed twice with 5 mL of anhydrous *p*-xylene. The combined filtrate was heated under reflux for 15 h before it was allowed to cool to rt and concentrated to yield a solid residue. After three cycles of washing the residue with 40 mL of ethyl acetate followed by centrifugation and decanting the supernatant liquid, the remaining solid was pumped to dryness in vacuo. The solid was washed three times with 1 mL of dichloromethane and one time with 1 mL of diethyl ether and then pumped to dryness to yield **26a** (0.031 g, 0.090 mmol, 30%) as a brown solid. The combined solution of 3 mL of dichloromethane and 1 mL of diethyl ether was also concentrated to yield a second product (0.025 g, 24%) as a pale yellow solid. Compound **26a**: mp >360 °C; IR (KBr) 1599, 778, 750, 696 cm^{-1}; ^{1}H (6% CD_3OD in $CDCl_3$) δ 9.46 (1 H, m), 8.11 (1 H, d, J = 7.7 Hz), 7.99−7.84 (7 H, m), 7.68−7.62 (3 H, m), 7.59 (1 H, d, J = 7.7 Hz), 7.17 (1 H, t, J = 7.5 Hz), 6.84 (1 H, d, J = 7.9 Hz); ^{13}C δ 153.1, 147.5, 146.3, 142.2, 134.5, 132.5, 132.1, 131.5, 130.9, 130.6, 128.6, 127.9, 127.8, 127.1, 125.6, 124.3, 123.6, 122.8, 119.2, 118.2, 114.6, 113.9. The structure of **26a** was established by the X-ray structure analysis. However, during the course of refining the X-ray structure, it was apparent that there were solvent molecules intercalated in the crystal lattice that could not be identified. Second product: mp >360 °C; IR (KBr) 1585, 755, 708 cm^{-1}; ^{1}H (6% CD_3OD in $CDCl_3$) δ 8.92 (1 H, d, J = 8.4 Hz), 8.70 (1 H, d, J = 8.4 Hz), 8.18 (1 H, d, J = 7.7 Hz), 7.97−7.94 (3 H, m), 7.89 (1 H, t, J = 8.7 Hz), 7.84−7.74 (4 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.64 (1 H, tt, J = 8.4, 4.2 Hz), 7.33 (1 H, t, J = 7.7 Hz), 6.89 (1 H, d, J = 7.9 Hz); ^{13}C δ 153.3, 148.0, 147.7, 142.8, 134.7, 132.8, 132.5, 131.9, 130.9, 130.4, 129.0, 128.0, 127.9, 127.3, 125.8, 125.0, 124.6, 123.7, 120.1, 118.7, 115.5, 113.2.

8-Phenyl-13*H*-isoquinolino[2′,1′:1,2]pyrimido[4,5-*b*]indol-7-ium Triiodide (28a). To a tube were loaded 8 mg (0.023 mmol) of **26a**, 1 mL of acetonitrile, 0.5 mL of chloroform, 0.5 mL of absolute ethanol, and 0.2 mL of methyl iodide. The tube was flushed with nitrogen for 1 min and then sealed. It was heated to 70 °C for 96 h before it was allowed to cool to rt. The solution was concentrated to yield a solid residue. The solid residue was washed twice with 1 mL of ethyl acetate and then twice with 1 mL of chloroform to afford **28a** as a brown powder in quantitative yield. Recrystallization from dichloromethane afforded reddish brown crystals: mp 235−236 °C; ^{1}H (CD_2Cl_2) δ 10.37 (br), 9.51 (1 H, dm, J = 8.1, 2.4 Hz), 8.25 (1 H, d, J = 7.7 Hz), 8.15−8.03 (3 H, m), 7.98−7.86 (4 H, m), 7.80−7.70 (4 H, m), 7.32 (1 H, t, J = 7.7 Hz), 7.00 (1 H, d, J = 8.2 Hz). The structure of **28a** was established by X-ray structure analysis.

Acknowledgment. The financial support of the National Science Foundation (CHE-9618676) to K.K.W. is gratefully acknowledged. J.L.P. acknowledges the support (CHE-9120098) provided by the Chemical Instrumentation Program of the National Science Foundation for the acquisition of a Siemens P4 X-ray diffractometer in the Department of Chemistry at West Virginia University.

Supporting Information Available: Experimental procedures and spectroscopic data for **4a**,**c**, **13**, **14a**, **15a**, **17**, **21b**, **24b**, **26b**, **27a**, and **28b**; ^{1}H and/or ^{13}C NMR spectra for **4a**−**c**, **9**, **12a**, **13**, **14a**,**b**, **15a**, **17**, **21a**,**b**, **22a**, **24a**,**b**, **26a**,**b**, a compound related to **26a**, **27a**, and **28a**,**b**; and ORTEP drawings and/or tables of crystallographic data for the X-ray diffraction analyses of **4b**,**c**, **12a**, **14b**, **15a**, **21a**, **22a**, **27a**, and **28a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0204092