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Synthesis of Novel Heteroaromatics Structurally Related to Ellipticine Alkaloids via Thermolysis of Pyridannulated Enyne−Carbodiimides†

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

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

kwang@wvu.edu

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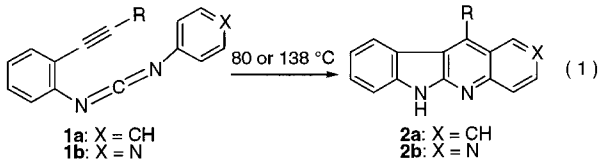
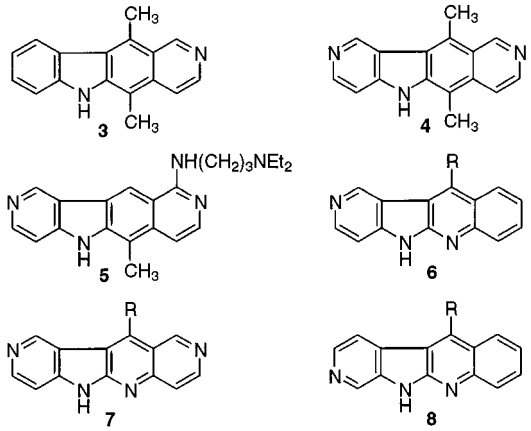
Abstract: New synthetic pathways to the 5*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*b*]quinolines **6**, the 6*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*b*][1,6]naphthyridines **7**, and the 11*H*-pyrido[4′,3′:4,5]pyrrolo[2,3-*b*]quinolines **8** via thermolysis of the pyridannulated enyne−carbodiimides **14**, **19**, and **23** were established. These novel heteroaromatic systems are structurally related to ellipticine alkaloids and could serve as DNA-intercalating agents.

Thermolysis of the benzannulated enyne−carbodiimides provides efficient synthetic pathways to novel heterocyclic aromatic compounds. With a phenyl substituent at the carbodiimide terminus in **1a**, a variety of the 6*H*-indolo[2,3-*b*]quinolines **2a** were readily obtained (eq 1).[1] Similarly, the presence of a 4-pyridyl substituent in **1b** led to the formation of the 6*H*-indolo[2,3-*b*][1,6]-naphthyridines **2b**,[2] which could be regarded as the 5-aza analogues of ellipticine (**3**), a naturally occurring alkaloid.[3a]



Ellipticine and many of its derivatives were found to exhibit potent antitumor activities.[3b−m] The azaellipticines **4** and **5** are active on topoisomerase II and initiate the cleavage of DNA,[3c,l,m] and **5** has undergone clinical trials.[3c,d] We envisioned that by replacing the central benzene ring in **1a** and **1b** with a pyridine ring, a simple synthetic pathway to a variety of new heteroaromatics having structures related to ellipticine alkaloids could thus be established. We now report our findings of using this strategy for the synthesis of the 5*H*-pyrido[3′,4′:4,5]-pyrrolo[2,3-*b*]quinolines **6**, the 6*H*-pyrido[3′,4′:4,5]pyrrolo-[2,3-*b*][1,6]naphthyridines **7**, and the 11*H*-pyrido[4′,3′:4,5]pyrrolo[2,3-*b*]quinolines **8**.



Results and Discussion

The synthetic sequence outlined in Scheme 1 involves the use of the Pd-catalyzed cross-coupling reaction between 4-amino-3-iodopyridine (**9**)[4] with terminal alkynes **10** to form **11**. Treatment of **11** with dibromotriphenylphosphorane gave the iminophosphoranes **12**[5] for the subsequent aza-Wittig reaction with phenyl isocyanate (**13**) to produce in situ the pyridannulated enyne−carbodiimides **14**. Thermolysis of **14** under refluxing *p*-xylene at 138 °C then afforded the 5*H*-pyrido[3′,4′:4,5]-pyrrolo[2,3-*b*]quinolines **6**. In the case of **6b**, a small amount (16%) of a urea derivative, derived from the reaction between the nitrogen of the pyrrole ring of **6b** and phenyl isocyanate (**13**), was also isolated. The structure of **6c** was established by the X-ray structure analysis.

The transformation from **14** to **6** could proceed either through a two-step biradical pathway as in the enyne−allene system[6] or through a concerted intramolecular

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

† Dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

‡ 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.

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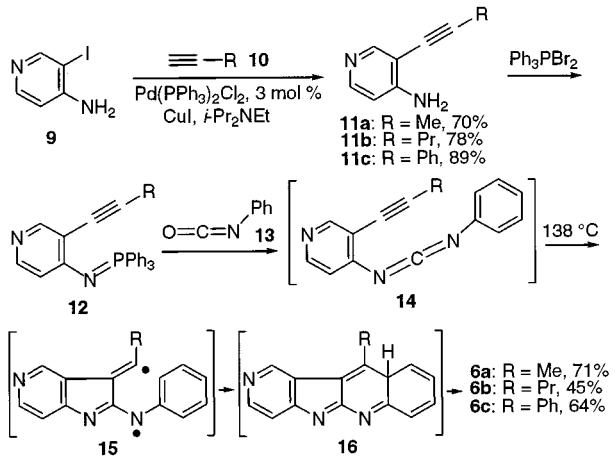
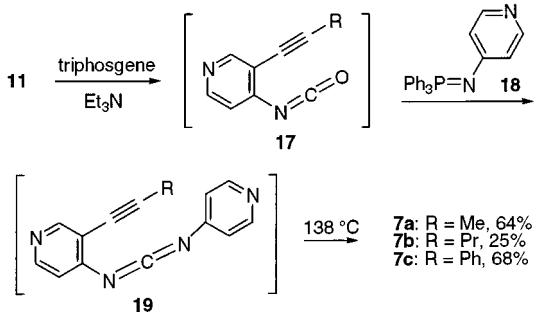
SCHEME 1



SCHEME 2

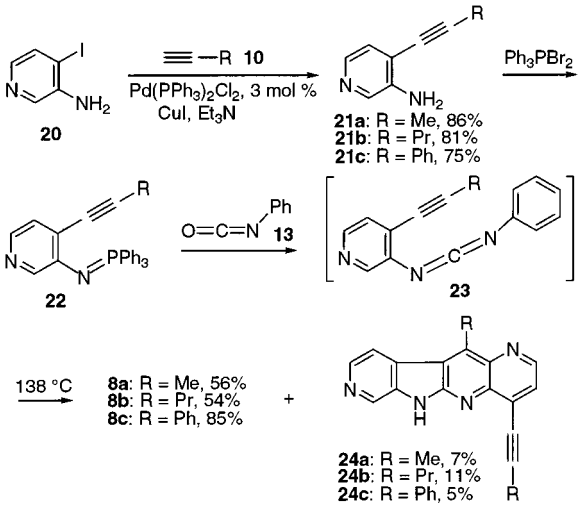


Diels−Alder reaction. It is worth noting that the core structure of **6** represents a new heterocyclic aromatic system. A sample of **6a** was submitted to the National Cancer Institute for evaluation against human tumor cell lines, and it was found to exhibit activity against MCF7 (breast) in the primary anticancer assay.

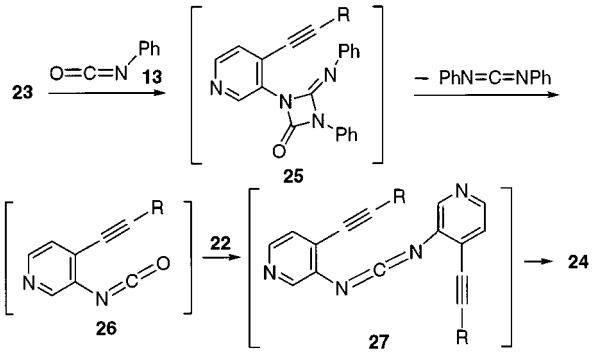
Treatment of **11** with triphosgene produced in situ the 4-pyridyl isocyanates **17** (Scheme 2). It was reported that the parent 4-pyridyl isocyanate is very reactive and presumably undergoes spontaneous trimerization to form an isocyanurate.[7] Fortunately, with an adjacent alkynyl substituent in the cases of **17**, the 4-pyridyl isocyanates **17** were relatively stable to allow the subsequent aza-Wittig reaction with the iminophosphorane **18**[2] to furnish in situ the pyridannulated enyne−carbodiimides **19**. Thermolysis of **19** under refluxing *p*-xylene at 138 °C then afforded the 6*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*b*][1,6]-naphthyridines **7** having a nitrogen in each of the four rings of the novel heterocyclic system. A sample of **7a** 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.

By starting from 3-amino-4-iodopyridine (**20**),[8] the synthetic sequence outlined in Scheme 3 led to the

SCHEME 3



SCHEME 4



formation of the 11*H*-pyrido[4′,3′:4,5]pyrrolo[2,3-*b*]quinolines **8**. The structures of **8b** and **8c** were established by the X-ray structure analysis. Again the core structure of **8** represents a new heterocyclic aromatic system. Interestingly, in addition to **8**, minor amounts of **24** were also isolated with the structure of **24b** being established by the X-ray structure analysis. Presumably, cycloaddition between **23** and phenyl isocyanate (**13**) produced **25**, which then eliminated a molecule of diphenylcarbodiimide to form the 4-pyridyl isocyanates **26** (Scheme 4).[9] A subsequent aza-Wittig reaction with **22** then produced the pyridannulated enyne−carbodiimides **27** as the precursors of **24**.

Experimental Section

All reactions were conducted in oven-dried (120 °C) glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from benzophenone ketyl, and triethylamine was distilled from calcium hydride prior to use. 1-Alkynes were obtained from chemical suppliers and were used without further purification. Dibromotriphenylphosphorane (Ph_3PBr_2), $Pd(PPh_3)_2Cl_2$, copper(I) iodide, *p*-xylene (anhydrous), *N*,*N*-dimethylformamide (DMF), *N*,*N*-diisopropylethylamine, phenyl isocyanate (**13**), and triphosgene were used as received. 4-Amino-3-iodopyridine (**9**) was prepared in 98% yield by treatment of the corresponding trimethylacetamide[4] with 4.5 M sulfuric acidic under refluxing water for 2 h. 3-Amino-4-iodopyridine (**20**)[8] and the iminophosphorane **18**[2] were prepared according to the reported procedures.

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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.

4-Amino-3-(2-phenylethynyl)pyridine (11c). The following procedure for the preparation of **11c** is representative. The flask containing 0.051 g (0.072 mmol) of $Pd(PPh_3)_2Cl_2$ and 0.023 g (0.120 mmol) of copper(I) iodide was evacuated and then filled with nitrogen. To the flask were added in sequence via cannula 5 mL of degassed DMF, a degassed solution of 1.34 mL (7.65 mmol) of *N*,*N*-diisopropylethylamine and 0.525 g (2.39 mmol) of 4-amino-3-iodopyridine (**9**) in 5 mL of DMF, and a degassed solution of 0.510 g (5.00 mmol) of phenylacetylene (**10c**) in 10 mL of DMF. After 12 h at rt, the reaction mixture was poured into a flask containing 20 mL of dichloromethane and 20 mL of a saturated NH_4Cl solution. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate/95% ethanol = 5:5:1) to afford **11c** (0.412 g, 2.12 mmol, 89%) as a white solid: mp 97−98 °C; IR (KBr) 3454, 3298, 1643, 757, 689 cm^{-1}; ^{1}H δ 8.45 (1 H, s), 8.16 (1 H, d, J = 3.4 Hz), 7.55−7.51 (2 H, m), 7.38−7.35 (3 H, m), 6.57 (1 H, d, J = 5.8 Hz), 4.79 (2 H, br); ^{13}C δ 153.0, 152.6, 149.2, 131.5, 128.6, 128.4, 122.6, 108.2, 105.0, 97.1, 82.5; MS *m*/*z* 194 (M^+), 166, 139.

11-Phenyl-5*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*b*]quinoline (6c). The following procedure for the preparation of **6c** is representative. To a solution of 1.020 g (2.420 mmol) of Ph_3PBr_2 and 2.79 mL (20.00 mmol) of anhydrous triethylamine in 20 mL of anhydrous *p*-xylene was introduced via cannula a solution of 0.215 g (1.11 mmol) of 4-amino-3-(2-phenylethynyl)pyridine (**11c**) in 20 mL of anhydrous *p*-xylene. The reaction mixture was kept at 80−90 °C for 12 h before it was allowed to cool to rt. The triethylammonium bromide precipitate was removed by filtration under a nitrogen atmosphere and was washed twice with 10 mL of anhydrous *p*-xylene. To the combined yellow-brown filtrate and the *p*-xylene solutions was added via cannula a solution of 0.118 g (0.990 mmol) of phenyl isocyanate (**13**) in 10 mL of anhydrous *p*-xylene. After 5 h at rt, the reaction mixture was heated under reflux at 138 °C for 12 h and then was allowed to cool to rt and concentrated. The residue was purified by column chromatography (silica gel/10% absolute ethanol in chloroform) to afford 0.188 g (0.064 mmol, 64%) of **6c** as a yellow powder. Recrystallization from chloroform and absolute ethanol (100:5) afforded yellow crystals: mp 297−298 °C; IR (KBr) 3426, 1605, 759, 699 cm^{-1}; ^{1}H δ 12.35 (1 H, br), 8.45 (1 H, d, J = 5.3 Hz), 8.30 (1 H, s), 8.20 (1 H, d, J = 8.4 Hz), 7.86−7.74 (2 H, m), 7.72−7.64 (3 H, m), 7.56−7.42 (3 H, m), 7.35 (1 H, d, J = 5.3 Hz); ^{13}C δ 152.6, 147.2, 146.6, 146.2, 144.5, 144.0, 135.8, 129.7, 129.3, 129.1, 126.8, 126.4, 124.1, 123.9, 118.1, 115.1, 106.1. Anal. Calcd for $C_{20}H_{13}N_3$: C, 81.34; H, 4.44; N, 14.23. Found: C, 81.42; H, 4.45; N, 14.37. The structure of **6c** was established by the X-ray analysis.

11-Methyl-6*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*b*][1,6]naphthyridine (7a). The following procedure for the preparation of **7a** is representative. To a solution of 0.0594 g (0.200 mmol) of triphosgene in 20 mL of anhydrous *p*-xylene was added dropwise using a pressure-equalizing addition funnel over 2 h a solution of 0.28 mL (2.00 mmol) of anhydrous triethylamine and 0.066 g (0.500 mmol) of 4-amino-3-(1-propynyl)pyridine (**11a**) in 10 mL of anhydrous *p*-xylene. The reaction mixture was heated to 70 °C for 12 h before it was allowed to cool to rt. The triethylammonium chloride precipitate was removed by filtration under a nitrogen atmosphere and was washed twice with 10 mL of anhydrous *p*-xylene. To the combined pale yellow filtrate and the *p*-xylene solutions was added via cannula a solution of 0.177 g (0.500 mmol) of the iminophosphorane **18** in 20 mL of anhydrous *p*-xylene. After the reaction mixture was kept at 50 °C for 6 h, it was heated under reflux at 138 °C for 12 h before it was allowed to cool to rt. The solution was concentrated, and the residue was purified by column chromatography (neutral alumina/5% absolute ethanol in dichloromethane) to afford 0.075 g (0.321 mmol, 64%) of **7a** as a pale yellow solid: mp >360 °C; IR (KBr) 3447, 1605, 736 cm^{-1}; ^{1}H (6% CD_3OD in $CDCl_3$) δ 9.54 (1 H, s), 9.30 (1 H, s), 8.58 (1 H, d, J = 5.3 Hz), 8.50 (1 H, d, J = 5.0 Hz), 7.77 (1 H, d, J = 6.1 Hz), 7.42 (1 H, d, J = 5.5 Hz), 3.24 (1 H, s); ^{13}C (6% CD_3OD in $CDCl_3$) δ 154.3, 149.3, 149.0, 146.7, 145.4, 143.8, 142.1, 120.4, 120.1, 118.7, 116.7, 106.9, 15.2.

3-Amino-4-(1-pentynyl)pyridine (21b). The following procedure for the preparation of **21b** is representative**.** The flask containing 0.031 g (0.044 mmol) of $Pd(PPh_3)_2Cl_2$ and 0.014 g (0.074 mmol) of copper(I) iodide was evacuated and then filled with nitrogen. To the flask were added in sequence via cannula 15 mL of degassed triethylamine, a degassed solution of 0.323 g (1.47 mmol) of 3-amino-4-iodopyridine (**20**) in 5 mL of anhydrous THF, and a degassed solution of 0.250 g (3.68 mmol) of 1-pentyne (**10b**) in 5 mL of triethylamine. After 12 h at rt, the reaction mixture was poured into a flask containing 20 mL of dichloromethane and 20 mL of a saturated NH_4Cl solution. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (neutral alumina/50% ethyl acetate in hexanes) to afford **21b** (0.190 g, 1.19 mmol, 81%) as a brown yellow liquid: IR (neat) 3456, 3314, 2218, 821 cm^{-1}; ^{1}H δ 7.99 (1 H, s), 7.77 (1 H, d, J = 5.0 Hz), 6.96 (1 H, d, J = 5.0 Hz), 4.41 (2 H, br), 2.31 (2 H, t, J = 7.2 Hz), 1.51 (2 H, sextet, J = 7.2 Hz), 0.92 (3 H, t, J = 7.2 Hz); ^{13}C δ 143.3, 138.1, 136.2, 124.9, 115.1, 99.6, 74.8, 21.7, 21.2, 13.2; MS *m*/*z* 160 (M^+), 145, 131.

5-Propyl-11*H*-pyrido[4′,3′:4,5]pyrrolo[2,3-*b*]quinoline (8b) and 4-(1-Pentynyl)-11-propyl-6*H*-pyrido[4′,3′:4,5]pyrrolo[2,3-*b*][1,5]naphthyridine (24b). The following procedure for the preparation of **8b** is representative. To a solution of 0.464 g (1.100 mmol) of Ph_3PBr_2 and 1.39 mL of anhydrous triethylamine (10.00 mmol) in 10 mL of anhydrous *p*-xylene was introduced via cannula a solution of 0.080 g (0.500 mmol) of 3-amino-4-(1-pentynyl)pyridine (**21b**) in 10 mL of anhydrous *p*-xylene. The reaction solution was kept at 80−90 °C for 12 h before it was allowed to cool to rt. The triethylammonium bromide precipitate was removed by filtration under a nitrogen atmosphere and was washed twice with 10 mL of anhydrous *p*-xylene. To the combined yellow-brown filtrate and the *p*-xylene solutions was then added via cannula a solution of 0.054 g (0.450 mmol) of phenyl isocyanate (**13**) in 10 mL of anhydrous *p*-xylene. After 5 h of stirring at rt followed by heating under reflux at 138 °C for 12 h, the reaction mixture was allowed to cool to rt. The solution was concentrated, and the residue was purified by column chromatography (neutral alumina/chloroform) to afford 0.063 g (0.241 mmol, 54%) of **8b** as a pale yellow powder and 0.016 g (0.049 mmol, 11%) of **24b** as a light yellow solid. Compound **8b**: mp 253−254 °C (sample recrystallized from 5% absolute ethanol in chloroform); IR (KBr) 3448, 1625, 757 cm^{-1}; ^{1}H δ 11.34 (1 H, br), 9.06 (1 H, s), 8.60 (1 H, d, J = 5.3 Hz), 8.32 (1 H, d, J = 8.7 Hz), 8.21 (1 H, d, J = 7.9 Hz), 8.04 (1 H, d, J = 5.3 Hz), 7.83 (1 H, ddd, J = 8.2, 6.9, 1.3 Hz), 7.57 (1 H, ddd, J = 8.2, 6.9, 1.1 Hz), 3.68 (2 H, d, J = 8.0 Hz), 1.99 (2 H, sextet, J = 7.6 Hz), 1.23 (3 H, t, J = 7.4 Hz); ^{13}C δ 153.0, 147.9, 147.8, 140.8, 136.9, 133.7, 130.2, 127.5, 127.4, 124.5, 123.51, 123.47, 117.2, 114.9, 31.2, 23.3, 14.7; Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.41; H, 5.71; N, 16.00. The structure of **8b** was established by the X-ray analysis. Compound **24b**: compound turns dark at 185 °C and becomes black at 215 °C (sample recrystallized from chloroform); IR (KBr) 1626, 1394, 1257, 822 cm^{-1}; ^{1}H δ 10.63 (1 H, br), 9.01 (1 H, s), 8.91 (1 H, d, J = 4.2 Hz), 8.61 (1 H, d, J = 5.0 Hz), 8.08 (1 H, d, J = 5.3 Hz), 7.80 (1 H, d, J = 4.2 Hz), 3.90 (2 H, t, J = 7.9 Hz), 2.38 (2 H, t, J = 7.1 Hz), 1.96 (2 H, sextet, J = 7.7 Hz), 1.62−1.54 (2 H, m), 1.19 (3 H, t, J = 7.4 Hz), 1.00 (3 H, t, J = 7.4 Hz); ^{13}C δ 153.0, 150.5, 146.4, 142.9, 140.8, 139.1, 137.3, 135.0, 129.6, 127.6, 126.9, 117.7, 117.3, 102.0, 78.0, 30.1, 23.2, 21.9, 21.5, 14.7, 13.5. The structure of **24b** was established by the X-ray analysis.

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dation 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 **6a**,**b**, a urea derivative of **6b**, **7b**,**c**, **8a**,**c**, **11a**,**b**, **21a**,**c**, and **24a**,**c**; ^{1}H and ^{13}C NMR spectra for **6a**−**c**, a urea derivative of **6b**, **7a**−**c**, **8a**−**c**, **11a**−**c**, **21a**−**c**, and **24a**−**c**; and ORTEP drawings and tables of crystallographic data for the X-ray diffraction analyses of **6c**, **8b**,**c**, and **24b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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