Intramolecular Friedel–Crafts Cyclization of Nitrogen Heterocycles. An Expeditious Approach to the Azaphenanthrene Skeleton

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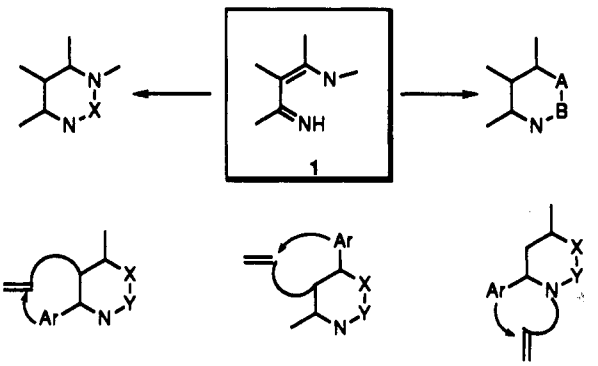
The intramolecular Friedel–Crafts type cyclization of several heterocycles prepared from 4-amino-1-azabutadienes leading to the preparation of several azaphenanthrene and azasteroid structures, using phosphoric or trifluoromethanesulfonic acid, is described. The reactions are carried out under mild conditions, and good yields are obtained. In some cases, such as the cyclization of thiazine **5**, the reaction is totally regioselective.

Azaphenanthrene derivatives are important systems, constituting the structure of many natural products[1] and having interesting pharmacological properties.[2] It is also known that heteroatoms have a key influence, specially when placed near the bay region, on the biological activity of azaphenantrenic systems.[3] Obviously, considerable efforts have been devoted to the study of developing new methodologies for ring construction. The most widely used strategies leading to polycyclic structures include cycloaddition reactions and intramolecular electrophile-induced carbocyclizations, especially the Friedel–Crafts type cyclization.[4]

Previously, we have demonstrated the 4-amino-1-azabutadienes **1** to be suitable starting materials for the synthesis of a high variety of heterocycles, particularly six-membered rings, in a regioselective manner.[5] The ease with which these rings were produced prompted us to explore the possibility of using heterocycles containing aryl and alkenyl substituents as appropriate precursors of complex heteropolycycles by intramolecular Friedel–Crafts alkylations (Scheme I).

In this paper, we detail the results of the acid-catalyzed intramolecular carbocyclization protocol of various six-membered nitrogen-containing heterocycles as applied to the synthesis of a number of aza- and diazaphenanthrene derivatives.[6]

Scheme I



Preparation of the Starting Heterocycles 2–6

These heterocycles were prepared in high yields (85–96%) starting from the appropriate C-allylated or propargylated azadienes **1**,[7] following well-established procedures (Scheme II). Thus, 5-allylpyridones **2a,b** were available by N-acetylation of **1a** and **1b**, respectively, followed by Dieckman-type condensation of the resulting acetamide derivative in the presence of LDA.[8] The formation of 1,2-dihydropyrimidine-2(1*H*)-one **3** involved simply the treatment of **1a** with ethyl chlorocarbonate in pyridine,[9] while 1,2-dihydropyrimidines with an allyl, **4a**, or a propargyl, **4b**, appendage were readily obtained by Lewis acid catalyzed cyclocondensation of **1a** or **1c** with acetaldehyde.[10] According to the methodology developed for pyridones **2**, the related thiazine **5** was synthesized in two steps by treating **1d** with methanesulfonyl chloride followed by LDA-promoted intramolecular heterocyclization.[11] 1,2,6-Thiadiazine dioxide **6** was prepared by *m*-CPBA oxidation of the thiazine *S*-oxide obtained by condensation of the aza diene **1a** with thionyl chloride in pyridine (Scheme II).[12]

Results and Discussion

Synthesis of Benz[*f*]isoquinolone and Benzo[*h*]-quinolones. We started our work studying the cyclization of the 2*H*-pyridone ring as the simplest model. Moreover, the 2-pyridone moiety is present in many natural products, such as the antitumor alkaloid camptothecin, and other compounds with interesting medicinal properties,[13] and

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(2) (a) Ishii, H.; Ichikawa, Y.; Kawanabe, E. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2283. (b) Hirota, T.; Sasaki, K.; Yamamoto, H.; Katsu, T. *Heterocycles* **1987**, *26*, 3211.
(3) (a) Lowe, J. P.; Silverman, B. D. *Acc. Chem. Res.* **1984**, *17*, 322. (b) Ramesh, D.; Kar, G. K.; Chatterjee, B. G.; Ray, J. K. *J. Org. Chem.* **1988**, *53*, 212. (c) Young, S. D.; Wiggings, J. M.; Huff, J. R. *J. Org. Chem.* **1988**, *53*, 1114. (d) Kumar, S.; Czech, A.; La Voie, E. *J. Org. Chem.* **1988**, *53*, 1329.
(4) Ho, T.-L. In *Carbocycle Construction in Terpene Synthesis*: VCH: New York, 1988.
(5) (a) Barluenga, J. *Bull. Chem. Soc.* Belg. **1988**, *97*, 545. (b) Barluenga, J.; Aznar, F.; Fustero, S.; Tomás, M. *Pure Appl. Chem.* **1990**, *62*, 1957.
(6) Preliminary account: Barluenga, J.; Tomás, M.; Suárez-Sobrino, A.; Rubio, E. *Tetrahedron Lett.* **1990**, *31*, 2189.
(7) Barluenga, J.; Jardón, J.; Gotor, V. *J. Org. Chem.* **1985**, *50*, 802.
(8) Barluenga, J.; Tomás, M.; Suárez-Sobrino, A.; Gotor, V. *Tetrahedron Lett.* **1988**, *29*, 4855.
(9) Barluenga, J.; Tomás, M.; Rubio, V.; Gotor, V. *J. Chem. Soc., Chem. Commun.* **1979**, 675.
(10) Barluenga, J.; Tomás, M.; Fustero, S.; Gotor, V. *Synthesis* **1979**, 346.
(11) Barluenga, J.; Tomás, M.; Suárez-Sobrino, A. *Tetrahedron Lett.* **1989**, *30*, 4705.
(12) Barluenga, J.; López-Ortiz, J. F.; Tomás, M.; Gotor, V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1891.
(13) (a) Lednicer, D.; Mitscher, L. A. In *The Organic Chemistry of Drug Synthesis*; Wiley & Sons: New York, 1980; Vol. 2. (b) Niromiya, I.; Naito, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. XXII, p 189.

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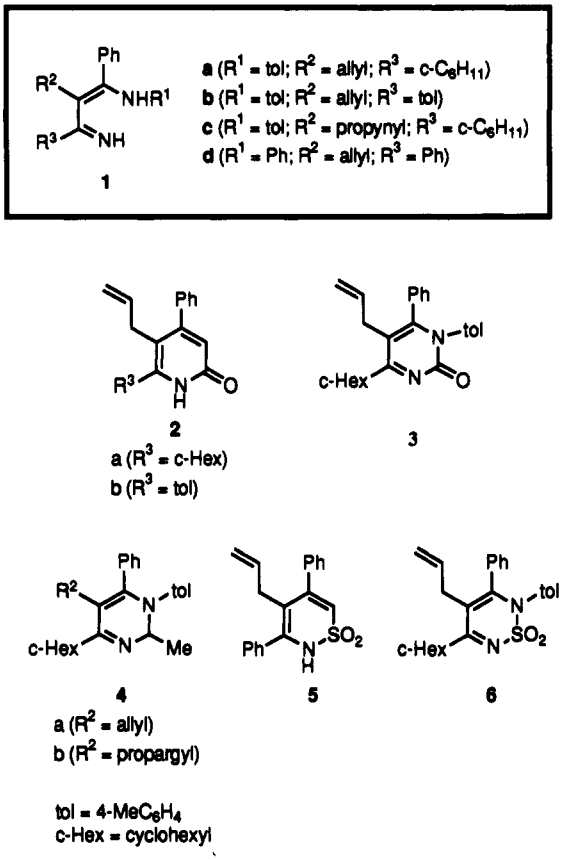
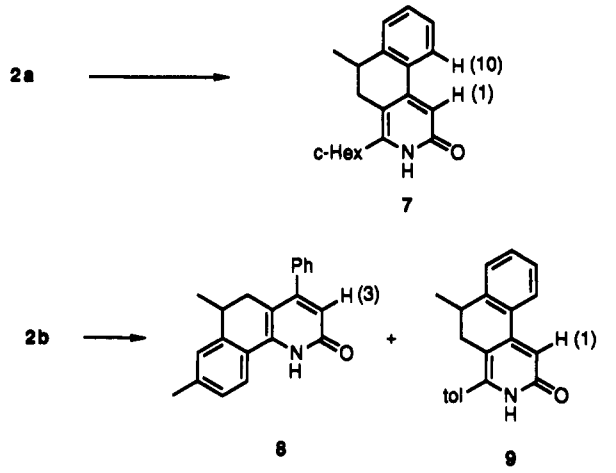
Scheme II



several approaches to this ring are known.[14] Polycyclic 2-pyridones have recently been synthesized in a nice convergent way through reaction of vinyl isocyanates with enamines.[15]

We carried out the carbocyclization reaction by heating **2** in the presence of acid. Thus, pyridone **2a** was heated at 60 °C with 85% H_3PO_4 to give **7** in 85% yield after aqueous workup and column chromatography purification. Although the spectroscopic data are fully consistent with the structure **7**, it must be noted in the ^1H NMR that the H-1 hydrogen of **7** (δ = 6.9 ppm) is significantly deshielded with respect to the starting pyridone **2a** (δ = 6.4 ppm); this is probably due to the steric interactions between H-1 and H-10 hydrogens as a consequence of the coplanarity of the rings.[16] As expected, when two competing aromatic rings (contiguous to the allyl moiety) were present in the molecule (R^3 = *p*-tolyl), no selectivity was observed and a 1:1 mixture of regioisomers **8** and **9** was isolated from aza diene **1b**. The separation of both compounds was easily achieved by column chromatography (silica gel; hexane/ether, 3:1), affording benz[*f*]isoquinolone **8** (40%) and benzo[*h*]quinolone **9** (45%) (Scheme III). The assignation of the structure for these compounds was made on the basis of their NMR spectra; thus, **8** presented the ^1H NMR signal for the H-3 hydrogen at 6.5 ppm, while the resonance of the H-1 hydrogen in **9**, placed in the bay region, shifted to 6.9 ppm, which is in agreement with the spectral data of **7** discussed above.

Scheme III



Synthesis of Benzo[*h*]quinazolines. Then, we envisaged the preparation of the related diaza derivatives using pyrimidine derivatives **3** and **4**. Benzo[*h*]quinazolines and benzo[*h*]quinazolones are systems with known pharmacological properties as antitumoral and antidepressive agents.[17] In addition, few methods have been described for their synthesis, almost all of them employing naphthylamines[18] or tetralones[19] as starting materials. Thus, pyrimidone **3**, when treated with phosphoric acid in toluene at 100 °C, afforded the expected 5,6-dihydro-2(1*H*)-benzo[*h*]quinazolone **10** in 85% yield. In the case of pyrimidine **4a** (R^2 = allyl), in which a second sterogenic center is created, it was observed the presence of a stereoisomeric mixture of 5,6-dihydrobenzo[*h*]quinazolines **11** in 81% yield in a 1:1 ratio according to the ^1H NMR of the reaction crude. The separation of both isomers was unsuccessful, and hence, the stereochemical assignation of each one was not made. Interestingly, the carbocyclization reaction was found to work fine when the allyl chain was replaced with a propargyl moiety. In this way, 1,2-dihydrobenzo[*h*]quinazoline **12** was obtained in almost quantitative yield (96%) upon heating **4b** in toluene with phosphoric acid at 60 °C (Scheme IV).[20]

Synthesis of Naphtho[2,1-*d*][1,2]thiazines and -[1,2,6]thiadiazines. Next, we have studied the cyclization of thiazine dioxide **5**. In this case, phosphoric acid failed to accomplish the desired carbocyclization, the starting material being recovered unaltered even after prolongated heating. Fortunately, triflic acid smoothly converted **5** into naphtho[2,1-*d*][1,2]thiazine **13** in 89% yield. Remarkably, this reaction proceeded with complete regioselectivity involving the phenyl group attached at C-5 of the thiazine ring, with no traces of the isomer resulting from cyclization toward the phenyl group at C-3 being detected by NMR in the reaction crude. ^1H NMR studies in acetone-d_6 showed that **13** is in equilibrium with its tautomer **13'** in a ratio of ca. 4:1. Heteropolycyclic **13** presents a characteristic singlet at δ 4.4 ppm assigned to

(14) (a) Overman, L. E.; Tsuboi, S.; Roos, J. P.; Taylor, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 747. (b) Overman, L. E.; Roos, J. P. *J. Org. Chem.* **1981**, *46*, 811. (c) Sainte, F.; Serckx-Ponzin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428. (d) Earl, R. A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6991.

(15) Rigby, J.; Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224.

(16) Gunther, H. In *NMR Spectroscopy*; J. Wiley & Sons: New York, 1980; p 88.

(17) Parrot-López, H.; Delacotte, J. M.; Renault, J. *J. Heterocycl. Chem.* **1986**, *23*, 1039.

(18) Robev, S. *Dokl. Bolg. Akad. Nauk* **1983**, *36*, 1551; *Chem. Abstr.* **1984**, *101*, 110858.

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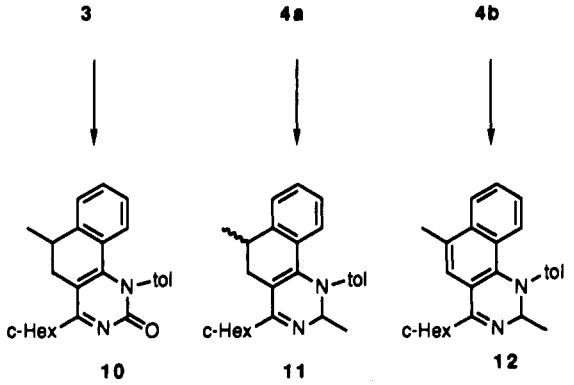
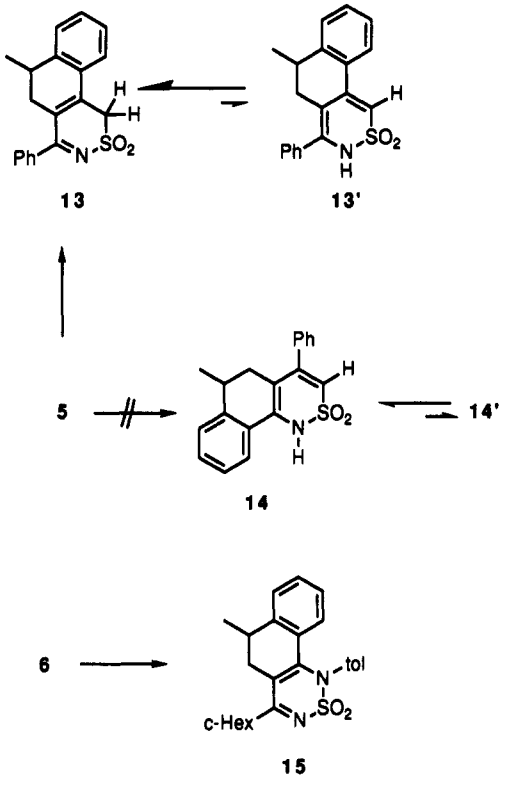
(20) This cyclization has the added interest of the participation of a triple bond in a Friedel–Crafts type reaction, a process much less reported in the literature. For an example of this cyclization, see: Brooks, J. R.; Harcourt, D. N.; Waigh, R. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2588.

Scheme IV



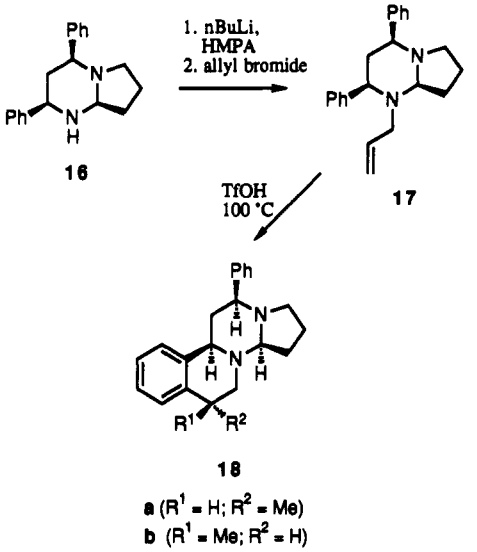
Scheme V



the methylenic hydrogens of the thiazine ring (CH_2SO_2), while the $CHSO_2$ grouping of 13′ appears at 6.9 ppm as a singlet. Moreover, the less stable cross-conjugated structure[21] 13′ was not detected in deuteriochloroform solution, and only single signals assigned to 13 were observed. The regioisomeric structure 14/14′ was ruled out on the basis of the chemical shift observed for the methine hydrogen (δ = 6.9 ppm) which is in much better agreement with structure 13′ than 14 (see spectroscopic discussion for compound 7). Similarly, thiadiazine dioxide 6 cyclized under the same reaction conditions (TfOH, 60 °C, toluene) to afford the tricyclic compound 15 in 90% yield (Scheme V). Both skeletons 13 and 15 display the interesting feature of being unknown in the literature to our knowledge.

Synthesis of Diazasteroid 18. Finally, the wide scope of this methodology for the the construction of polycyclic structures was proved by the short preparation of the target molecule 8,13-diazasteroid derivative 18 (Scheme VI).

Scheme VI



Systems of this sort have been in the last years the subject of different studies dealing with their synthesis and biological activity as well.[22] For this purpose, we have started with the bicyclic compound 16, which was prepared by intramolecular condensation of the corresponding 4-((4,4-diethoxybutyl)amino)-1-azabutadiene followed by diastereoselective sodium borohydride reduction to the fully saturated pyrrolopyrimidine 16.[23] The bicyclic system 16 was then allylated with *n*-BuLi and allyl bromide to yield 17 which was not purified but subjected to heating at 100 °C in the presence of triflic acid to yield a 6:1 mixture of C-6 diazasteroid epimers 18. The major isomer 18a with the methyl group placed in an equatorial orientation was easily separated by column chromatography in silica gel using a mixture of hexane/ether (10:1) and isolated as a yellow oil in 75% overall yield from 16.

Conclusions

In summary, the work described here represents a very easy, versatile entry into a high variety of heteropolycycles including diazasteroid systems by Friedel–Crafts annulations of a number of heterocycles of different nature, which are in turn readily available from aza dienes 1 containing allyl/propargyl chains and aryl groups. This strategy allows one to synthesize compounds with potential pharmacological interest, some of them with a nitrogen atom placed in the bay region, as well as structures hitherto unknown, namely naphtho[2,1-*d*]thiadiazines 13 and 15.

Experimental Section

General Methods. MP's are uncorrected. General spectroscopic techniques have been previously reported.[24] NMR experiments were run in $CDCl_3$. Column chromatography was

(21) (a) The cross conjugation as defined herein refers only to the whole tricyclic framework. (b) March, J. In *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1985; p 31.

(22) (a) Rasmusson, G. H.; Reynolds, G. F.; Steinberg, N. G.; Walton, E.; Patel, G. F.; Liang, T.; Cascieri, M. A.; Cheung, A. H.; Brooks, J. R.; Berman, C. *J. Med. Chem.* **1986**, *29*, 2298. (b) Brooks, J. R.; Berman, C.; Primka, R. L.; Reynolds, G. F.; Rasmusson, G. H. *Steroids* **1986**, *47*, 1. (c) Dolle, R. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1988**, 133. (d) Huisman, H. O.; Speckamp, W. N. In *MTP International Review of Science, Organic Chemistry, Series Two*; Johns, W. F., Ed.; Butterworths: London, 1976; Vol. 8, pp 207–236.

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(24) Barluenga, J.; Aguilar, E.; Olano, B.; Fustero, S. *J. Org. Chem.* **1988**, *53*, 1741.

performed with E. Merck silica gel (230–400 mesh) by standard flash chromatography techniques.[25]

Materials. Benzene and toluene were distilled from sodium benzophenone ketyl under nitrogen prior to use. Dichloromethane was previously treated with 0.05 N NaOH, dried over anhydrous sodium sulfate, and distilled under nitrogen from phosphorus pentoxide. Ether and THF were treated with sodium and distilled over sodium. *n*-BuLi was used in a 2.5 M solution in toluene. The starting heterocycles **2–6** were prepared following previously described procedures.[8-12] Compounds **2b**,[8] **5**,[11] and **16**[23] have been fully characterized before.

Preparation of 6-Cyclohexyl-4-phenyl-5-propenyl-2(1*H*)-pyridone (2a).[8] Reaction of aza diene **1a** (20 mM) with acetyl chloride (20 mM) in pyridine, and then with LDA (20 mM) in THF, afforded **2a** in 92% yield after aqueous workup (2 M H_2SO_4, ether): mp 234–235 °C after recrystallization from hexane–chloroform; IR (KBr) 1665 cm^{-1}; ^1H NMR δ 1.2–2.0 (m, 10 H), 2.7 (m, 1 H), 3.0 (m, 1 H), 4.8 (m, 1 H), 5.0 (m, 1 H), 5.8 (m, 1 H), 6.3 (s, 1 H), 7.2–7.5 (m, 5 H), and 11.0 (broad s, NH); ^{13}C NMR δ 163.7 (s), 157.6 (s), 151.5 (s), 139.8 (s), 137.4 (d), 128.1 (d), 127.9 (d), 127.8 (d), 117.7 (d), 115.4 (t), 111.4 (s), 39.6 (d), 31.5 (t), 30.7 (t), 26.6 (t), and 25.4 (t); MS *m/e* 293 (M^+, 97), 238 (74), 210 (89), 41 (100). Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.91; H, 7.85; N, 4.73.

Preparation of 4-Cyclohexyl-1-(4-methylphenyl)-6-phenyl-5-propenyl-2(1*H*)-pyrimidone (3).[9] Reaction of aza diene **1a** (20 mM) with ethyl chlorocarbonate (75 mM) in pyridine afforded **3** in 96% yield after aqueous workup (3 N NaOH, ether): mp 220–222 °C after recrystallization from hexane–ether; IR (KBr) 1660 cm^{-1}; ^1H NMR δ 1.2–2.0 (m, 10 H), 2.2 (s, 3 H), 2.8 (m, 1 H), 2.9 (m, 2 H), 4.8 (dd, J = 17.1, 1.4 Hz, 1 H), 5.0 (dd, J = 10.2, 1.4 Hz, 1 H), 5.8 (m, 1 H), and 6.9–7.2 (m, 9 H); ^{13}C NMR δ 183.4 (s), 156.9 (s), 156.4 (s), 137.5 (s), 136.1 (d), 135.7 (s), 132.2 (s), 129.2 (d), 128.6 (d), 128.2 (d), 127.9 (d), 127.7 (d), 115.6 (t), 111.4 (s), 42.8 (d), 31.4 (t), 30.9 (t), 25.9 (t), 25.3 (t), and 20.7 (q); MS *m/e* 384 (M^+, 38), 329 (50), 301 (65), 194 (45), 91 (100). Anal. Calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.28. Found: C, 81.33; H, 7.28; N, 7.37.

Preparation of 1,2-Dihydropyrimidines (4).[10] **4-Cyclohexyl-2-methyl-1-(4-methylphenyl)-6-phenyl-5-(3-propenyl)-1,2-dihydropyrimidine (4a).** Reaction of aza diene **1a** (15 mM) with acetaldehyde (75 mM) and $AlCl_3$ (15 mM) afforded **4a** in 87% yield after aqueous workup (3 N NaOH, ether) and was used without further purification: oil; ^1H NMR δ 1.1–2.0 (m, 10 H), 1.4 (d, J = 12.5 Hz, 3 H), 2.1 (s, 3 H), 2.2 (m, 1 H), 3.0 (m, 2 H), 4.7 (m, 1 H), 5.3 (q, J = 12.5 Hz, 1 H), 5.6 (m, 1 H), and 6.7–7.4 (m, 9 H); ^{13}C NMR δ 166.2 (s), 141.9 (s), 141.2 (s), 136.3 (d), 134.2 (s), 130.4 (s), 128.8 (d), 127.3 (d), 126.8 (d), 126.5 (d), 126.2 (d), 122.2 (d), 113.4 (t), 112.9 (s), 71.55 (d), 40.0 (d), 31.1 (t), 30.1 (t), 29.1 (t), 25.4 (t), 25.0 (t), 24.8 (t), 19.1 (q), and 16.6 (q); MS *m/e* 384 (M^+, 7), 369 (100). Anal. Calcd for $C_{27}H_{32}N_2$: C, 84.33; H, 8.39; N, 7.29. Found: C, 84.32; H, 8.44; N, 7.37.

4-Cyclohexyl-2-methyl-1-(4-methylphenyl)-6-phenyl-5-(3-propynyl)-1,2-dihydropyrimidine (4b). In the same way, **4b** was obtained in 89% yield from **1c**: oil; IR (neat) 2110 cm^{-1}; ^1H NMR δ 1.1–2.0 (m, 10 H), 1.4 (d, J = 12.2 Hz, 3 H), 2.0 (t, J = 1.5 Hz, 1 H), 2.1 (s, 3 H), 2.2 (m, 1 H), 3.2 (m, 2 H), 5.3 (q, J = 12.2 Hz, 1 H), and 6.3–7.2 (m, 9 H); ^{13}C NMR δ 168.2 (s), 143.3 (s), 142.7 (s), 134.5 (s), 132.2 (s), 129.8 (d), 128.2 (d), 127.8 (d), 127.6 (d), 123.2 (d), 111.2 (s), 82.8 (d), 72.7 (s), 68.5 (d), 40.9 (d), 30.5 (t), 30.4 (t), 26.3 (t), 26.0 (t), 25.7 (t), 20.1 (q), 17.6 (q), and 17.4 (t); MS *m/e* 382 (M^+, 11), 367 (100). Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.90; N, 7.32. Found: C, 84.88; H, 7.87; N, 7.41.

Preparation of 5-Cyclohexyl-2-(4-methylphenyl)-3-phenyl-4-propenyl-2*H*-1,2,6-thiadiazine 1,1-Dioxide (6).[12] Reaction of aza diene **1a** (20 mM) with thionyl chloride (25 mM) and oxidation with *m*-CPBA (40 mM) afforded **6** in 91% overall yield after aqueous workup (5% HCO_3Na, ether): mp 145–146 °C after recrystallization from hexane–chloroform; IR (KBr) 1345, 1120 cm^{-1}; ^1H NMR δ 1.2–1.9 (m, 10 H), 2.2 (s, 3 H), 2.7 (m, 1 H), 3.0 (m, 2 H), 4.9 (dd, J = 17.2, 1.2 Hz, 1 H), 5.0 (dd, J = 10.2, 1.2 Hz, 1 H), 5.7 (m, 1 H), and 6.9–7.3 (m, 9 H); ^{13}C NMR δ 183.3 (s), 154.6 (s), 138.4 (s), 136.3 (d), 133.1 (s), 132.5 (s), 129.4 (d), 129.2 (d), 128.8 (d), 128.5 (d), 128.0 (d), 116.1 (t), 112.5 (s), 43.5 (d), 31.9 (t), 31.1 (t), 25.9 (t), 25.3 (t), and 20.9 (q); MS *m/e* 420 (M^+, 32), 356 (21), 337 (93), 91 (100). Anal. Calcd for $C_{25}H_{28}N_2O_2S$: C, 71.40; H, 6.71; N, 6.66. Found: C, 71.49; H, 6.46; N, 6.86.

Preparation of 2,4-Diphenyl-4-propenyl-1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-*a*]pyrimidine (17). To a solution of **16**[23] (3 mM) in THF (20 mL) was added *n*-BuLi (4.5 mM) at −20 °C, and after the mixture was stirred for 1 h, HMPA (6 mM) was added. The reaction mixture was allowed to warm to room temperature, and allyl bromide (9 mM) in THF (15 mL) was then added. Stirring was continued for 12 h at room temperature, and then the reaction crude was treated with ice–water and extracted with dichloromethane (3 × 30 mL). The combined organic layers were concentrated at reduced pressure to give **17** as an oily residue in 94%, which was used without purification in the carbocyclization process: ^{13}C NMR δ 141.9 (s), 141.6 (s), 132.3 (d), 127.6 (d), 127.3 (d), 127.2 (d), 126.7 (d), 126.1 (d), 126.1 (d), 116.6 (t), 82.7 (d), 67.2 (d), 65.1 (d), 51.8 (t), 49.4 (t), 34.7 (t), 28.3 (t), and 18.4 (t).

Carbocyclization Reactions of 2–4. Method A. To the corresponding heterocycles **2–4** (3 mM) in toluene (25 mL) was added 85% H_3PO_4 (5 mL). The solution was heated (at 60 °C for **2**, **4** and 100 °C for **3**) for 12 h, and then the crude was cooled and treated with 5 M NaOH (50 mL), extracted with dichloromethane, and dried over anhydrous sodium sulfate. The organic layer was concentrated and purified by flash column chromatography (hexane/ether, 10:1). By using this procedure the following compounds were prepared.

4-Cyclohexyl-6-methyl-5,6-dihydro-2(3*H*)-benz[*f*]isoquinolone (7). Reaction of **2a** (3 mM) gave **7** in 85% yield: mp 239–241 °C; IR (KBr) 1651, 1605 cm^{-1}; ^1H NMR δ 1.1 (d, J = 6.5 Hz, 3 H), 1.2–1.9 (m, 10 H), 2.5 (dd, J = 14.6, 6.1 Hz, 1 H), 2.6 (dd, J = 14.6, 4.8 Hz, 1 H), 2.8 (m, 1 H), 2.9 (m, 1 H), 6.9 (s, 1 H), 7.1–7.4 (m, 3 H), 7.7 (d, J = 7.0 Hz, 1 H), and 10.8 (broad s, NH); ^{13}C NMR δ 164.7 (s), 149.1 (s), 148.0 (s), 143.6 (s), 131.7 (s), 129.9 (d), 127.0 (d), 126.8 (d), 125.6 (d), 111.1 (d), 110.2 (s), 39.2 (d), 33.1 (d), 30.8 (t), 30.3 (t), 30.2 (t), 26.8 (t), 26.7 (t), 25.6 (t), and 20.1 (q); MS *m/e* 293 (M^+, 28), 278 (100), 238 (42). Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 82.00; H, 7.86; N, 4.47.

Reaction of **2b** (3 mM) gave a 1:1 mixture of **8** and **9** with a global yield of 91%. Both compounds were separated (40% for **8**; 45% for **9**, isolated yields) by column chromatography (silica gel; hexane/ether, 3:1).

6,8-Dimethyl-4-phenyl-5,6-dihydro-2(1*H*)-benzo[*h*]quinolone (8): mp 268–269 °C; IR (KBr) 1655 cm^{-1}; ^1H NMR δ 1.1 (d, J = 6.9 Hz, 3 H), 2.3 (s, 3 H), 2.4 (dd, J = 15.6, 6.7 Hz, 1 H), 2.6 (dd, J = 15.6, 5.5 Hz, 1 H), 2.9 (m, 1 H), 6.5 (s, 1 H), 7.1–8.0 (m, 8 H), and 10.9 (broad s, NH); ^{13}C NMR δ 163.9 (s), 155.9 (s), 142.7 (s), 140.2 (s), 139.8 (s), 138.5 (s), 128.3 (d), 128.2 (d), 128.1 (d), 127.9 (d), 127.2 (d), 125.1 (s), 123.5 (d), 118.0 (d), 112.1 (s), 32.4 (d), 31.3 (t), 21.4 (q), and 19.2 (q); MS *m/e* 301 (M^+, 100), 286 (60). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.55; H, 6.42; N, 4.83.

6-Methyl-4-(4-methylphenyl)-5,6-dihydro-2(3*H*)-benz[*f*]isoquinolone (9): mp 237–239 °C; IR (KBr) 1650 cm^{-1}; ^1H NMR δ 1.1 (d, J = 6.9 Hz, 3 H), 2.4 (s, 3 H), 2.5 (dd, J = 14.8, 6.3 Hz, 1 H), 2.7 (dd, J = 14.8, 4.7 Hz, 1 H), 2.9 (m, 1 H), 6.9 (s, 1 H), 7.2–7.8 (m, 8 H), and 11.0 (broad s, NH); ^{13}C NMR δ 164.3 (s), 148.0 (s), 143.5 (s), 143.4 (s), 139.3 (s), 131.4 (s), 130.7 (s), 129.9 (d), 129.2 (d), 128.9 (d), 126.9 (d), 126.5 (d), 125.4 (d), 112.3 (s), 112.0 (d), 33.0 (d), 31.4 (t), 21.3 (q), and 19.6 (q); MS *m/e* 301 (M^+, 100), 286 (91), 91 (31). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.71; H, 6.29; N, 4.70.

4-Cyclohexyl-6-methyl-1-(4-methylphenyl)-5,6-dihydro-2(1*H*)-benzo[*h*]quinazolone (10). Reaction of **3** (3 mM) gave **10** in 85% yield: mp 205–207 °C; IR (KBr) 1668 cm^{-1}; ^1H NMR δ 1.3 (d, J = 6.9 Hz, 3 H), 1.2–1.9 (m, 10 H), 2.3 (s, 3 H), 2.5 (dd, J = 15.6, 7.8 Hz, 1 H), 2.7 (dd, J = 15.6, 5.0 Hz, 1 H), 2.8 (m, 1 H), 2.9 (m, 1 H), and 6.7–7.2 (m, 8 H); ^{13}C NMR δ 181.0 (s), 157.0 (s), 149.8 (s), 144.8 (s), 137.9 (s), 137.2 (s), 129.8 (d), 129.7 (d), 128.3 (d), 128.1 (d), 127.0 (s), 125.6 (d), 125.4 (d), 112.0 (s), 42.5 (d), 32.5 (d), 30.5 (t), 30.2 (t), 30.0 (t), 26.1 (t), 26.0 (t), 25.6 (t), 21.0 (q), and 18.3 (q); MS *m/e* 384 (M^+, 41), 369 (100), 329 (92),

(25) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

316 (73). Anal. Calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.28. Found: C, 81.01; H, 7.36; N, 7.37.

4-Cyclohexyl-2,6-dimethyl-1-(4-methylphenyl)-1,2,5,6-tetrahydrobenzo[*h*]quinazoline (11). Reaction of **4a** (3 mM) gave **11** as a mixture of isomers in 81% yield: ^{1}H NMR δ 1.1–1.9 (m, 10 H), 1.2 (d, J = 6.4 Hz, 3 H), 1.3 (d, J = 7.1 Hz, 3 H), 2.2 (s, 3 H), 2.5 (m, 1 H), 2.6 (dd, J = 16.0, 7.8 Hz, 1 H), 2.7 (dd, J = 16.0, 5.3 Hz, 1 H), 3.0 (m, 1 H), 5.6 (m, 1 H), and 6.6–7.2 (m, 8 H); ^{13}C NMR δ 166.6 (s), 166.2 (s), 145.0 (s), 144.8 (s), 143.0 (s), 142.3 (s), 139.5 (s), 139.1 (s), 132.0 (s), 131.9 (s), 129.3–121.9 (m, C Ar), 115.5 (s), 113.7 (s), 73.5 (d), 41.9 (d), 41.7 (d), 32.4 (d), 32.3 (d), 31.4 (t), 31.0 (t), 30.6 (t), 30.5 (t), 30.4 (t), 28.3 (t), 26.6 (t), 26.5 (t), 26.4 (t), 26.3 (t), 26.1 (t), 26.0 (t), 20.7 (q), 20.5 (q), 18.5 (q), 18.1 (q); MS m/e 384 (M^+, 6), 369 (100). Anal. Calcd for $C_{27}H_{32}N_2$: C, 84.33; H, 8.39; N, 7.28. Found: C, 84.11; H, 8.36; N, 7.37.

4-Cyclohexyl-2,6-dimethyl-1-(4-methylphenyl)-1,2-dihydrobenzo[*h*]quinazoline (12). Reaction of **4b** (4 mM) gave **12** in 96% yield: mp 154–156 °C; ^{1}H NMR δ 1.1–2.0 (m, 10 H), 1.2 (d, J = 6.5 Hz, 3 H), 2.1 (s, 3 H), 2.6 (s, 3 H), 2.9 (m, 1 H), 5.7 (q, J = 6.5 Hz, 1 H), and 6.6–7.9 (m, 9 H); ^{13}C NMR δ 166.4 (s), 147.9 (s), 138.1 (s), 134.5 (s), 131.8 (s), 129.5 (d), 129.3 (s), 128.6 (s), 126.8 (d), 126.0 (d), 125.4 (d), 124.4 (d), 121.8 (d), 121.7 (d), 121.0 (s), 74.7 (d), 41.3 (d), 32.1 (t), 30.5 (t), 26.6 (t), 26.3 (t), 26.1 (t), 20.6 (q), 19.6 (q), and 18.6 (q); MS m/e 382 (M^+, 14), 367 (100). Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.90; N, 7.32. Found: C, 84.91; H, 7.95; N, 7.43.

Method B. To the corresponding heterocycle **5** or **6** (3 mM) in dry toluene (25 mL) was added trifluoromethanesulfonic acid (3 mM) at 0 °C under nitrogen. The reaction was stirred for 15 h at 60 °C and then cooled and treated with ice–water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residues were purified by recrystallization from hexane/ether (compound **13**) or by column chromatography in silica gel (hexane/ether, 10:1) (compound **15**).

6-Methyl-4-phenyl-5,6-dihydro-1*H*-naphtho[2,1-*d*][1,2]thiazine 2,2-Dioxide (13). Reaction of **5** (3 mM) gave **13** in 89% yield: mp 205–206 °C; IR (KBr) 1360, 1180 cm^{-1}; ^{1}H NMR δ 1.2 (d, J = 6.9 Hz, 3 H), 2.3 (dd, J = 16.5, 8.6 Hz, 1 H), 2.6 (dd, J = 16.5, 5.7 Hz, 1 H), 3.0 (m, 1 H), 4.4 (s, 2 H), and 7.3–7.7 (m, 9 H); ^{13}C NMR δ 178.6 (s), 142.3 (s), 140.1 (s), 135.8 (s), 131.8 (d), 131.6 (s), 131.4 (d), 128.5 (d), 128.4 (d), 127.1 (d), 126.2 (d), 124.4 (s), 124.0 (d), 44.8 (t), 34.7 (t), 32.0 (d), and 18.7 (q); MS m/e 323 (M^+, 80), 259 (27), 244 (100), 141 (36), 115 (34). Anal. Calcd for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33. Found: C, 70.40; H, 5.37; N, 4.40.

4-Cyclohexyl-6-methyl-1-(4-methylphenyl)-5,6-dihydro-1*H*-naphtho[1,2-*c*][1,2,6]thiadiazine 2,2-Dioxide (15). Reaction of **6** (3 mM) gave **15** in 90% yield: mp 205–207 °C; IR (KBr) 1505, 1482, 1361, 1179 cm^{-1}; ^{1}H NMR δ 1.2–2.0 (m, 10 H), 1.4 (d, J = 6.8 Hz, 3 H), 2.3 (s, 3 H), 2.6 (dd, J = 15.9, 7.2 Hz, 1 H), 2.8 (dd, J = 15.9, 5.3 Hz, 1 H), 2.9 (m, 1 H), 3.1 (m, 1 H), and 7.1–7.4 (m, 8 H); ^{13}C NMR δ 182.2 (s), 147.3 (s), 144.0 (s), 137.8 (s), 135.9 (s), 130.8 (d), 129.7 (d), 128.7 (d), 127.9 (s), 126.8 (d), 126.5 (d), 126.1 (d), 116.6 (s), 43.9 (d), 31.9 (d), 30.6 (t), 30.1 (t), 29.8 (t), 25.9 (t), 25.6 (t), 20.9 (q), and 19.0 (q); MS m/e 420 (M^+, 15), 365 (49), 356 (68), 341 (100), 184 (43). Anal. Calcd for $C_{25}H_{28}N_2O_2S$: C, 71.40; H, 6.71; N, 6.66. Found: C, 71.43; H, 6.68; N, 6.56.

Preparation of 6-Methyl-12-phenyl-1,2,3,3a,5,6,11,12-octahydro-5*H*-pyrrolo[2′,1′:2,3]pyrimido[6,1-*a*]isoquinoline (18). To a solution of **17** (3 mM) in 25 mL of toluene was added trifluoromethane sulfonic acid (3 mM) at 0 °C under nitrogen. The reaction was stirred for 15 h at 100 °C and then cooled and treated with ice–water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to afford **18** as a 6:1 mixture of epimers from which **18a** was isolated by column chromatography in silica gel (hexane/ether, 10:1) in 75% yield: oil; ^{1}H NMR δ 1.2 (d, J = 6.8 Hz, 3 H), 1.5–2.3 (m, 8 H), 2.7 (t, J = 8.6 Hz, 1 H), 2.8 (t, J = 8.2 Hz, 1 H), 3.1–3.5 (m, 4 H), and 7.0–7.5 (m, 9 H); ^{13}C NMR δ 143.2 (s), 139.5 (s), 136.8 (s), 128.2 (d), 127.3 (d), 127.1 (d), 126.6 (d), 126.2 (d), 125.2 (d), 124.3 (d), 84.9 (d), 67.7 (d), 63.5 (d), 55.0 (t), 50.3 (t), 40.1 (t), 32.4 (d), 28.7 (t), 19.4 (t), and 19.0 (q); MS m/e 318 (M^+, 55), 104 (100). Anal. Calcd for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.45; H, 8.38; N, 6.60.

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