An Efficient Approach to Pyrroles and *N*-Bridgehead Pyrroles by Propargylation/Cycloamination of 4-Amino-1-azabutadiene Derivatives

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The thermal cycloamination of several propargyl-substituted 4-amino-1-azabutadienes **2** leading to 3-functionalized pyrroles **4**−**6** is described. Derivatives of pyrrolizidines **9** and indolizidines and azaazulenes **11**−**13** are synthesized directly from cyclic imines **7** and **10**, respectively, in a multistep process that involves metalation with LDA, addition of a nitrile, carbanion trapping with propargyl bromide, and cycloamination. In all cases the more substituted imine nitrogen is involved in the cyclization reaction; such an experimental finding is supported by theoretical calculations.

Pyrrole derivatives represent a class of heterocycles of great importance, as many reviews, monographs, and reports have been released. Compounds containing the pyrrole ring are widely spread in nature[1] and substituted pyrroles very frequently display biological activity;[2] moreover, polymers derived from pyrrole have found applications as conducting and nonlinear optics materials.[3] On the other hand, *N*-bridgehead pyrroles, for instance pyrrolizidines and indolizidines, encompass one of the most intriguing fused pyrrole derivatives; they constitute the basic skeleton of many alkaloids with well recognized pharmacological properties.[4]

Of the many efficient pyrrole synthesis reported to date,[5] the cyclization of aminoalkynes has not been extensively exploited.[6] Thus, functionalized amino and amido alkynes have been cyclized in the presence of palladium(II)[7] and silver(I)[8] salts, respectively. The intramolecular [2 + 2] cycloaddition between group IV metal−imido complexes and alkynes[9] and its application to the synthesis of (±)-monomorine[10] reported by Livinghouse is remarkable. Obviously, the potential of this simple cycloamination methodology would become greatly enhanced if its application to fused pyrroles would be feasible.

Continuing our interest in the regioselective preparation of heterocycles from readily available starting materials,[11] we report herein the synthesis of functionalized pyrroles, pyrrolizidines, indolizidines, and azaazulenes, which is based on the intramolecular amination of 3-propargyl-4-(alkyl(aryl)amino)-1-azabutadienes.[12]

Synthesis of Pyrroles 4−6. First, the required propargyl azadienes **2** were obtained in multigram quantities by metalation of azadienes **1**[13] with *n*-butyllithium followed by *C*-alkylation with propargyl bromide (R^4 = H) or 2-butynyl *p*-toluenesulfonate (R^4 = Me), as previously reported.[14] Then, heating compounds **2a-d** in toluene at 60 °C for 4 h followed by work-up with 1N HCl resulted in the formation of 3-acylpyrroles **4** in excellent yields after column chromatographic purification (Scheme 1; Table 1, compounds **4a-d**, entries 1−4). When using azadiene **2e** having a more nucleophilic, unhindered nitrogen (R^1 = *n*-Bu, entry 5, Table 1) the process was found to occur in 2 h at room temperature; conversely, the cyclization of the azadiene **2f** derived from an internal alkyne (R^4 = Me) into the pyrrole **4f** (entry 6, Table 1) required more drastic reaction conditions (120 °C, EtOH, sealed tube, 24 h).

Although the primary cycloamination products **3** were not isolated in pure form because of their easy hydrolysis when subjected to column chromatography purification, the imine function of **3** could be acylated or reduced *in situ* (Scheme 2, Table 1). Thus, azadiene **2a** was cyclized, and the resulting toluene solution was cooled back to room temperature and treated with benzoyl chloride in the presence of pyridine to furnish the 3-(benzoylimino)-

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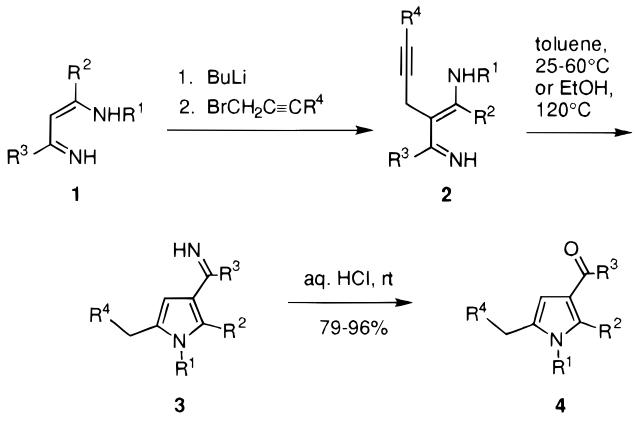
Table 1. Pyrrole Derivatives 4–6 Prepared from Azadienes 2

entry	azadienes **2**	R^1	R^2	R^3	R^4	compounds	yield (%)[a,b]
1	**2a**	*p*-Me-C_6H_4	Ph	Ph	H	**4a**	96
2	**2b**	Ph	Ph	Ph	H	**4b**	95
3	**2c**	c-C_6H_{11}	H	*p*-Me-C_6H_4	H	**4c**	80
4	**2d**	*p*-Me-C_6H_4	Ph	c-C_6H_{11}	H	**4d**	95
5	**2e**	*n*-Bu	Ph	Ph	H	**4e**	91
6	**2f**	*p*-Me-C_6H_4	Ph	Ph	Me	**4f**	79
7	**2a**	*p*-Me-C_6H_4	Ph	Ph	H	**5**	93
8	**2a**	*p*-Me-C_6H_4	Ph	Ph	H	**6a**	93
9	**2d**	*p*-Me-C_6H_4	Ph	c-C_6H_{11}	H	**6b**	91
10	**2e**	*n*-Bu	Ph	Ph	H	**6c**	91
11	**2g**	*p*-Me-C_6H_4	Ph	*p*-Me-C_6H_4	H	**6d**	96

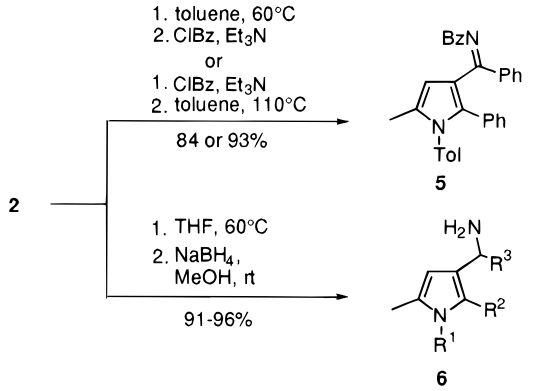
[a] Isolated yields from azadienes **2**. [b] Yields of purified compounds.

Scheme 1



1 **2** **3** **4**

Scheme 2



5 **6**

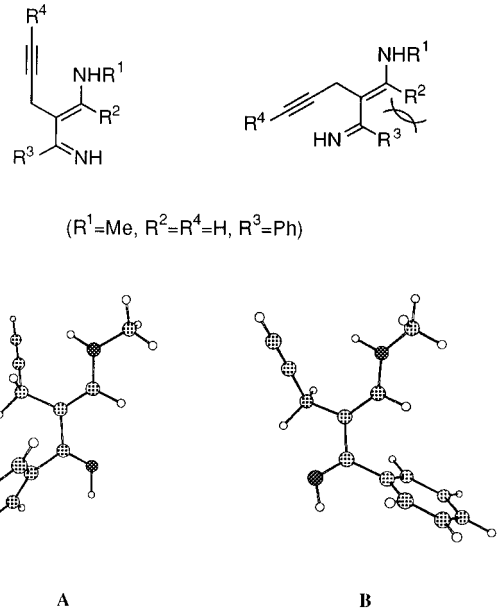


Figure 1.

pyrrole **5** (entry 7, Table 1). Alternatively, this benzoylated derivative **5** is readily available in two steps by *N*-benzoylation of azadiene **2a** (benzoyl chloride, toluene–Et_3N, 25 °C)[14] followed by heating in toluene at 110 °C. Similarly, the preparation of 3-(α-aminoalkyl)pyrrole derivatives **6** (entries 8–11) could be achieved in high yields in a one-pot procedure that involves heating of azadienes **2** in THF and treatment of the resulting 3-iminopyrrole intermediates **3** with $NaBH_4$ (molar ratio 1:1) in THF/MeOH at room temperature.

The process shown is an example of a favorable exo-dig cyclization,[15] in which two unexpected features have to be mentioned. Firstly, the reaction takes place with complete chemoselectivity, and secondly, the more substituted nitrogen is surprisingly involved in the cyclization.[16] In order to gain some evidence regarding these results, semiempirical calculations using the Gaussian 92 series of programs[17] and the AM1 hamiltonian[18] were performed. All the structures located were fully optimized and characterized by the corresponding frequency calculations. On the basis of these calculations we can infer that the *s-cis* conformer **A**, wherein the carbon–carbon triple bond was found to be nearly coplanar with the substituted nitrogen, is responsible for the cyclization rather than the *s-trans* conformer **B** (Figure 1).

The most stable conformations located for a simple 4-amino-1-azabutadiene **2** (R^1 = Me, R^2 = R^4 = H, R^3 = Ph) are shown in Figure 1. The AM1 calculations indicate that the *s-cis* conformer **A** ($\Delta H_f°$ = 107.2 kcal mol^{-1}) is more stable than the *s-trans* conformer **B** ($\Delta H_f°$ = 108.4 kcal mol^{-1}) by 1.2 kcal mol^{-1}. This result is consistent with the steric requirements of the phenyl group. Accordingly, it can reasonably be expected that the cycloamination reaction proceeds through the substituted nitrogen (conformation **A**). We have not found any stationary point corresponding to a conformation having the alkyne function close to the unsubstituted imine nitrogen. In addition, the analysis of the Mulliken

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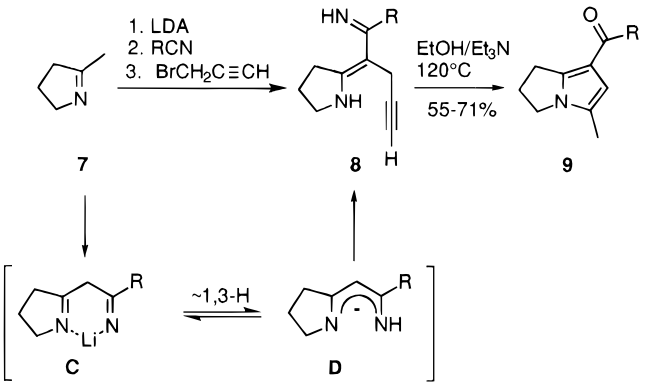
Scheme 3



charges shows that the nitrogen actually involved in the cyclization is the most negatively charged (0.16 e *vs* 0.12 e).

The process shown here provides access to 3-functionalized pyrroles, e.g. 3-acylpyrroles, in a simple and efficient fashion. While the synthesis of 2-acylpyrroles is easily achieved by direct acylation of pyrroles, the approaches to 3-acylpyrroles are relatively few in number. For instance, the directed electrophilic acylation of the pyrrole ring has been achieved by the introduction of appropriate, removable substituents either at nitrogen[19] or at C-2 positions;[20] the [4 + 1] annulation of 2-acyl-3-sulfonylbutadienes with primary aliphatic amines[21] also gives access to some pyrroles of this type.

Synthesis of *N*-Bridgehead Pyrroles. Next, this methodology was extended to the synthesis of *N*-bridgehead heterocycles containing a pyrrole unit, including not only the classical pyrrolizidine[22] and indolizidine[23] systems, but also the quite rare azaazulene derivatives.[24]

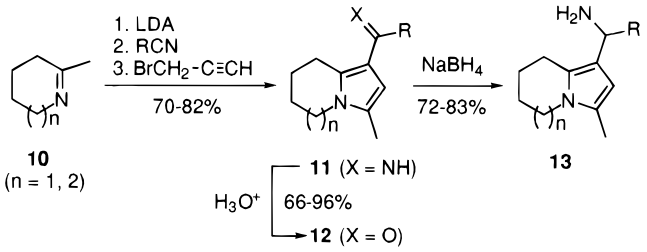
First, the monocyclic azadienes **8** required for the preparation of pyrrolizidines **9** were generated in one-pot from the corresponding 2-methyl-1-pyrroline **7**[25] following the procedure for acyclic azadienes **2**[14] (Scheme 3). To this end, azadienes **8** were formed by successive treatment of imines **7** in THF with one equiv of LDA (-78 °C), an aliphatic or aromatic nitrile (1 equiv, −78 °C), and propargyl bromide (1 equiv, −78 °C to 25 °C).[26] The use of equimolecular amounts of base implies that the addition of the azaenolate to the nitrile function giving the species **C** is followed by tautomerization to form the 1,5-diazapentadienyl anion **D**, which finally undergoes C-propargylation (Scheme 3). The corresponding aminoazabutadienes **8** were isolated after aqueous workup of the reaction mixture and used without purification. Furthermore, heating a solution of **8** in a mixture of EtOH−Et_3N (100 °C, sealed tube, 6 h) resulted in pyrrole annulation and hydrolysis of the imine group affording didehydropyrrolizidines **9** in moderate yields after column chromatographic purification (Table 2).

Table 2. *N*-Bridgehead Pyrroles 9−13

cmpd	*n*	R	yield[a] (%)
9a	–	Ph	55
9b	–	c-C_6H_{11}	71
11a	1	Ph	82
11b	1	c-C_3H_5	75
11c	1	2-thienyl	71
11d	2	2-furyl	78
11e	2	Ph	70
11f	2	2-thienyl	77
12a	1	c-C_3H_5	88[b]
12b	1	2-thienyl	92[b]
12c	1	2-furyl	87[b]
12d	2	Ph	96[b]
12e	2	2-thienyl	82[b]
12f	2	3,4-dimethoxyphenyl	76[b]
13a	1	2-thienyl	83
13b	2	2-furyl	72

[a] Yields of purified products. [b] Overall yields from imine **10**.

Scheme 4



On the other hand, when six- and seven-membered cyclic imines **10** (n = 1,2) were subjected to the same protocol as described above for five-membered imines **7**, the corresponding azadiene derivatives could not be isolated. Gratifyingly, the cyclization of the latter occurred at room temperature, giving rise directly to indolizidine and azaazulene derivatives **11** (n = 1,2) in good yields (70−82% from imine **10**) (Scheme 4, Table 2). Unlike their monocyclic analogues **3**, compounds **11** could be easily purified by column chromatography without observed hydrolysis of the unsubstituted imine function. Heterocycles **11** were further hydrolyzed with dilute HCl giving **12** or reduced with $NaBH_4$/MeOH to yield α-aminoalkyl derivatives **13**.

It should be noted that this cycloamination process works well for alkyl, aryl, and heteroaryl nitriles, providing potentially useful compounds. For instance, derivatives **13a** and **13b** can be envisaged as masked non-natural α-amino acids,[27] whereas the incorporation of the synthetically useful cyclopropyl group (compounds **11b** and **12a**) should permit further manipulations.[28] On the other hand, these fused aromatic pyrroles are a highly uncommon type of *N*-bridgehead heterocycles. Besides, the biological activity of compounds of this sort, e.g. didehydropyrrolizidines, is well recognized.[29]

Conclusions

The work described here represents an efficient and simple entry into 3-functionalized pyrroles. The method is based on the uncatalyzed cyclization of propargyl-substituted 4-amino-1-azabutadienes and is applied to

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both monocyclic and *N*-bridgehead pyrroles; in the case of the latter, the process starts from conventional cyclic imines and is run in one-pot in most instances, though it comprises as many as four steps (metalation of an imine, addition to a nitrile, propynylation, and cycloamination).

Experimental Section

General Methods. Mp's are uncorrected. General spectroscopic techniques have been previously reported.[30] NMR experiments were run in $CDCl_3$. Column chromatography was performed with silica gel (230−400 mesh) and florisil (100−200 mesh) by standard flash chromatographic techniques.[31]

Materials. Toluene was distilled from sodium benzophenone ketyl under nitrogen prior to use. Ether and THF were treated with sodium and distilled over sodium. Triethylamine was distilled from KOH pellets. Ethanol was distilled from calcium hydride. *n*-BuLi was used as a 2.5 M solution in hexane. The preparations of the starting azadienes **1**,[13] their alkylated derivatives **2**,[14] and imines **7** and **10**[25] have been previously described.

General Procedure for the Preparation of Pyrroles 4a−e. Azadienes **2** (5 mM) were dissolved in 15 mL of toluene and stirred (60 °C, 4 h for **4a−d**; 25 °C, 2 h for **4e**). The solution was then cooled to rt and treated with 1 N HCl (25 mL). After extraction with ether (3 × 20 mL), the combined organic layers were washed with water and dried over anhydrous sodium sulfate and the solvents removed at vacuum. The residue was then subjected to column chromatography (SiO_2, hexane/ether, 2:1) to yield compounds **4a−e** which were recrystallized from hexane−$CHCl_3$.

3-Benzoyl-5-methyl-2-phenyl-1-(*p*-tolyl)pyrrole (4a): mp 152−153 °C; ^{1}H NMR δ 2.1 (s, 3H), 2.3 (s, 3H), 6.4 (s, 1H), 6.9−7.4 (m, 12H), 7.7 (d, J = 7.1Hz, 2H); ^{13}C NMR δ 12.8 (CH_3), 20.9 (CH_3), 110.12 (CH), 121.3 (C), 126.9 (CH), 127.2 (CH), 127.4 (CH), 127.9 (CH), 129.2 (CH), 129.3 (CH), 130.2 (C), 130.7 (CH), 130.9 (CH), 131.6 (C), 135.0 (C), 137.6 (C), 138.6 (C), 139.5 (C), 192.0 (C); MS *m*/*e* 351 (M^+, 100), 274 (87), 105 (48), 77 (65). Anal. Calcd for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.98. Found: C, 85.28; H, 5.89; N, 4.21.

3-Benzoyl-5-methyl-1,2-diphenylpyrrole (4b): mp 136−137 °C; ^{1}H NMR δ 2.1 (s, 3H), 6.4 (s, 1H), 6.9−7.7 (m, 15H); ^{13}C NMR δ 12.8 (CH_3), 110.2 (CH), 121.4 (C), 127.0 (CH), 127.1 (CH), 127.4 (CH), 127.8 (CH), 128.3 (CH), 128.7 (CH), 129.3 (CH), 130.1 (C), 130.7 (CH), 131.0 (CH), 131.5 (C), 137.7 (C), 138.2 (C), 139.5(C), 192.0 (C); MS *m*/*e* 337 (M^+, 100), 260 (83), 105 (30), 77 (92). Anal. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.67; N, 4.15. Found: C, 85.49; H, 5.47; N, 4.31.

1-Cyclohexyl-5-methyl-3-(*p*-tolylcarbonyl)pyrrole (4c): oil; ^{1}H NMR δ 1.2−2.1 (m, 10H), 2.3 (s, 3H), 2.4 (s, 3H), 3.8 (m, 1H), 6.4 (s, 1H), 7.2 (s, 1H), 7.3 (d, J = 7.6 Hz, 2H), 7.7 (d, J = 7.6 Hz, 2H); ^{13}C NMR δ 11.9 (CH_3), 21.4 (CH_3), 25.2 (CH_2), 25.7 (CH_2), 35.1 (CH_2), 55.6 (CH), 108.6 (CH), 123.0 (C), 124.1 (CH), 128.6 (CH), 128.9 (CH), 129.7 (C), 137.5 (C), 141.3 (C), 190.3 (C); MS *m*/*e* 281 (M^+, 100), 119 (100). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.21; H, 8.28; N, 4.87.

3-(Cyclohexylcarbonyl)-2-phenyl-5-methyl-1-(*p*-tolyl)-pyrrole (4d): mp 148−149 °C; ^{1}H NMR δ 1.0−1.7 (m, 10H), 2.1 (s, 3H), 2.3 (s, 3H), 2.6 (m, 1H), 6.5 (s, 1H), 6.9 (d, J = 8.4 Hz, 2H), 7.1 (d, J = 8.4 Hz, 2H), 7.2 (m, 5H); ^{13}C NMR δ 12.8 (CH_3), 21.0 (CH_3), 25.8 (CH_2), 29.3 (CH_2), 47.4 (CH), 107.9 (CH), 121.5 (C), 127.4 (CH), 127.5 (CH), 128.0 (CH), 129.2 (CH), 130.2 (C), 130.9 (CH), 132.6 (C), 135.0 (C), 137.6 (C), 200.4 (C); MS *m*/*e* 357 (M^+, 13), 274 (100). Anal. Calcd for $C_{25}H_{27}NO$: C, 83.99; H, 7.61; N, 3.92. Found: C, 83.98; H, 7.67; N, 3.85.

3-Benzoyl-1-butyl-5-methyl-2-phenylpyrrole (4e): oil; ^{1}H NMR δ 0.6 (t, J = 7.3 Hz, 3H), 1.1 (m, 2H), 1.4 (m, 2H), 2.2 (s, 3H), 3.7 (m, 2H), 6.3 (s, 1H), 7.1−7.3 (m, 8H), 7.6 (d, J = 7.6 Hz, 2H); ^{13}C NMR δ 12.3 (CH_3), 13.4 (CH_3), 19.6 (CH_2), 32.7 (CH_2), 43.8 (CH_2), 110.2 (CH), 120.9 (C), 127.4 (CH), 127.7 (CH), 127.8 (CH), 128.4 (C), 129.1 (CH), 130.6 (CH), 130.7 (CH), 132.4 (C), 140.0 (C), 141.0 (C), 191.6 (C); MS *m*/*e* 317 (M^+, 79), 105 (100). Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.58; H, 7.67; N, 4.15.

Preparation of 3-Benzoyl-5-ethyl-2-phenyl-1-(*p*-tolyl)-pyrrole (4f). Azadiene **2f** (5 mM, 1.8 g) was dissolved in 10 mL of EtOH and heated in a sealed tube at 120 °C for 12 h. The mixture was cooled back to rt, treated with 1 N HCl (20 mL), extracted with ether (3 × 10 mL), washed with brine, and dried over anhydrous sodium sulfate. Removal of solvents under vacuum and purification as above resulted in pyrrole **4f** (1.4 g, 79%): mp 135−136 °C; ^{1}H NMR δ 1.0 (t, J = 7.4 Hz, 3H), 2.3 (s, 3H), 2.4 (q, J = 7.4 Hz, 2H), 6.4 (s, 1H), 6.9−7.4 (m, 12H), 7.7 (d, J = 7.9 Hz, 2H); ^{13}C NMR δ 12.6 (CH_3), 20.2 (CH_3), 21.0 (CH_2), 108.3 (CH), 121.4 (C), 127.0 (CH), 127.2 (CH), 127.4 (CH), 128.2 (CH), 129.3 (CH), 129.4 (CH), 130.9 (CH), 131.0 (CH), 131.6 (C), 135.0 (C), 136.8 (C), 137.8 (C), 138.6 (C), 139.6 (C), 192.3 (C); MS *m*/*e* 365 (M^+, 40), 105 (100), 77 (56). Anal. Calcd for $C_{26}H_{23}NO$: C, 85.45; H, 6.34; N, 3.83. Found: C, 85.26; H, 6.47; N, 3.76.

Preparation of 3-[(Benzoylimino)phenylmethyl]-2-phenyl-5-methyl-1-(*p*-tolyl)pyrrole (5). Method A. A solution of azadiene **2a** (5 mM, 1.75 g) in 15 mL of toluene was heated at 60 °C for 4 h under N_2; after cooling the solution to rt, Et_3N (5 mM, 0.7 mL) and benzoyl chloride (5 mM, 700 mg) were added. The mixture was stirred for 6 h at rt and then treated with 1 N HCl (20 mL) and extracted with ether (3 × 20 mL). The combined organic layers were washed with aqueous saturated solution of $NaHCO_3$ (2 × 20 mL) and water (2 × 20 mL) and dried over anhydrous sodium sulfate. After removal of solvents at vacuum, the residue was subjected to column chromatography (SiO_2, hexane/ether, 2:1) to yield compound **5** (1.9 g, 84%) which was further recrystallized from hexane−$CHCl_3$.

Method B. Azadiene **2a** was acylated following the method described.[14] The resulting acylazadiene was heated at 110 °C in toluene for 12 h. Removal of toluene gave a residue which was purified as above to afford **5** in 93% yield: mp 192−193 °C; ^{1}H NMR δ 2.0 (s, 3H), 2.3 (s, 3H), 6.2 (s, 1H), 6.8−7.5 (m, 15H), 7.6 (d, J = 9.2 Hz, 2H), 7.9 (d, J = 9.2 Hz, 2H); ^{13}C NMR δ 12.9 (CH_3), 20.9 (CH_3), 109.3 (CH), 118.7 (C), 126.5 (CH), 127.2 (CH), 127.4 (CH), 128.0 (CH), 128.1 (CH), 129.1 (CH), 129.3 (CH), 129.4 (CH), 130.1 (CH), 130.5 (CH), 131.5 (C), 132.0 (CH), 134.3 (C), 135.4 (C), 135.9 (C), 137.5 (C), 137.8 (C), 164.9 (C), 179.4 (C); MS *m*/*e* 454 (M^+, 20), 349 (32), 105 (100), 77 (95). Anal. Calcd for $C_{32}H_{26}N_2O$: C, 84.55; H, 5.76; N, 6.16. Found: C, 84.80; H, 5.67; N, 6.31.

General Procedure for the Preparation of Pyrroles 6. Azadienes **2** (5 mM) were disolved in 15 mL of THF and heated at 60 °C under N_2 for 6 h. After cooling to 0 °C, MeOH (7 mL) and portionwise sodium borohydride (15 mM) were added and the mixture was stirred for 12 h at rt. Conventional aqueous workup gave a residue which was subjected to column chromatography (SiO_2, hexane/ether/diethylamine, 4:4:1) to yield the pure compounds **6**.

3-(α-Aminobenzyl)-5-methyl-2-phenyl-1-(*p*-tolyl)pyrrole (6a): oil; ^{1}H NMR δ 2.1 (s, 3H), 2.4 (s, 3H), 5.2 (s, 1H), 6.1 (s, 1H), 7.0−7.6 (m, 16H); ^{13}C NMR δ 13.1 (CH_3), 20.8 (CH_3), 52.0 (CH), 105.4 (CH), 126.2 (CH), 126.6 (CH), 127.2

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(C), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.5 (C), 129.6 (CH), 130.0 (CH), 130.2 (C), 130.3 (CH), 130.5 (C), 132.6 (C), 136.1 (C), 136.4 (C); MS *m/e* 352 (M^+, 58), 275 (100). Anal. Calcd for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95. Found: C, 85.32; H, 6.67; N, 7.84.

3-(Aminocyclohexylmethyl)-5-methyl-2-phenyl-1-(*p*-tolyl)pyrrole (6b): oil; ^{1}H NMR δ 0.8−2.1 (m, 11H), 2.2 (s, 3H), 2.3 (s, 3H), 3.5 (d, J = 8.1 Hz, 1H), 6.1 (s, 1H), 6.9−7.3 (m, 11H); ^{13}C NMR δ 13.1 (CH_3), 20.8 (CH_3), 26.1 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 29.8 (CH_2), 30.2 (CH_2), 45.1 (CH), 53.1 (CH), 104.7 (CH), 125.9 (CH), 127.4 (CH), 127.9 (CH), 128.9 (CH), 129.7 (C), 130.5 (CH), 130.8 (C), 130.9 (C), 132.9 (C), 136.2(C), 136.8 (C); MS *m/e* 358 (M^+, 26), 275 (100). Anal. Calcd for $C_{25}H_{30}N_2$: C, 83.75; H, 8.43; N, 7.81. Found: C, 83.98; H, 8.47; N, 7.61.

3-(α-Aminobenzyl)-1-butyl-5-methyl-2-phenylpyrrole (6c): oil; ^{1}H NMR δ 0.7 (t, J = 7.5 Hz, 3H), 1.2 (m, 2H), 1.5 (m, 2H), 2.3 (s, 3H), 3.7 (m, 2H), 4.9 (s, 1H), 5.9 (s, 1H), 7.1−7.6 (m, 12H); ^{13}C NMR δ 12.4 (CH_3), 13.4 (CH_3), 19.6 (CH_2), 33.0 (CH_2), 43.5 (CH_2), 52.0 (CH), 104.4 (CH), 125.2 (C), 126.0 (CH), 126.4 (CH), 127.2 (CH), 127.9 (CH), 128.0 (CH), 128.6 (C), 129.5 (C), 130.9 (CH), 133.0 (C), 146.8 (C); MS *m/e* 318 (M^+, 48), 241 (100), 104(15). Anal. Calcd for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80. Found: C, 83.00; H, 8.27; N, 8.71.

3-[Amino(*p*-tolyl)methyl]-5-methyl-2-phenyl-1-(*p*-tolyl)-pyrrole (6d): oil; ^{1}H NMR δ 2.1 (s, 3H), 2.2 (s, 3H), 2.3 (s, 3H), 5.1 (s, 1H), 6.1 (s, 1H), 6.8−7.3 (m, 15H); ^{13}C NMR δ 13.1 (CH_3), 20.8 ($2CH_3$), 51.7 (CH), 105.4 (CH), 115.0 (C), 126.1 (CH), 126.4 (CH), 127.6 (CH), 128.0 (CH), 128.7 (CH), 129.0 (CH), 130.0 (C), 130.1 (C), 130.3 (CH), 132.6 (C), 135.6 (C), 136.2 (C), 136.4 (C), 143.7 (C); MS *m/e* 366 (M^+, 55), 275(83), 91(100). Anal. Calcd for $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.28; H, 7.27; N, 7.71.

Preparation of Azadienes 8. To a freshly prepared solution of LDA (10 mM) in THF (20 mL) was slowly added at −78 °C a solution of imine **7** (10 mM) in THF (25 mL). The mixture was stirred for 1 h at the same temperature, and then a solution of the corresponding nitrile (10 mM) in THF (10 mL) was added. After stirring at this temperature for 1 h the mixture was quenched with water, extracted with ether (3 × 10 mL), and dried over anhydrous sodium sulfate. Removal of solvents under vacuum resulted in azadienes **8** which were used without further purification. **8a**: ^{1}H NMR δ 1.7−1.9 (m, 4H), 2.7−2.9 (m, 3H), 3.9 (t, J = 6.5 Hz, 2H), 7.4−7.7 (m, 6H).

Preparation of Pyrrolizidines 9. A solution of freshly prepared azadiene **8** (5 mM) in a 1:1 mixture of EtOH/Et_3N (20 mL) was heated at 100 °C in a sealed tube for 6 h. After cooling to rt, the mixture was treated with 1 N HCl and extracted with ether (3 × 10 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, and the solvents were removed under vacuum. The oily residue thus obtained was subjected to column chromatography (florisil, CH_2Cl_2/MeOH, 5:1) to yield pure pyrrolizidine derivatives **9**.

7-Benzoyl-5-methyl-2,3-dihydro-1*H*-pyrrolizine (9a): oil; ^{1}H NMR δ 2.1 (s, 3H), 2.4 (m, 2H), 2.9 (t, J = 7.5 Hz, 2H), 3.8 (t, J = 6.5 Hz, 2H), 6.2 (s, 1H), 7.3−7.7 (m, 5H); ^{13}C NMR δ 11.3 (CH_3), 26.3 (CH_2), 26.5 (CH_2), 44.5 (CH_2), 111.5 (CH), 116.0 (C), 128.6 (CH), 129.0 (CH), 129.3 (CH), 131.3 (C), 141.4 (C), 144.5 (C), 191.6 (C). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.72; H, 6.63; N, 6.39.

7-(Cyclohexylcarbonyl)-5-methyl-2,3-dihydro-1*H*-pyrrolizine (9b): oil; ^{1}H NMR δ 1.1−1.8 (m, 10H), 2.1 (s, 3H), 2.5 (m, 2H), 2.9 (m, 1H), 3.0 (t, J = 7.4 Hz, 2H), 3.8 (t, J = 6.5 Hz, 2H), 6.2 (s, 1H); ^{13}C NMR δ 12.5, 22.3, 24.2, 26.3, 26.9, 27.4, 27.8, 30.2, 45.5, 48.0, 110.5, 125.0, 131.5, 143.1, 200.3. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.06. Found: C, 77.70; H, 9.23; N, 5.98.

General Procedure for the Preparation of Imine Derivatives 11. To a freshly prepared solution of LDA (10 mM) in THF (20 mL) was slowly added at −78 °C a solution of imine **10** (n = 1, 2) (10 mM) in THF (25 mL). The mixture was stirred for 1 h at the same temperature, and then a solution of the corresponding nitrile (10 mM) in THF (10 mL) was added. After stirring at this temperature for 1 h, a solution of propargyl bromide (10 mM) in THF (10 mL) was added. The reaction mixture was then allowed to slowly reach rt, treated with H_2O (50 mL), and extracted with ether (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvents removed at vacuum. The oily residue was then subjected to column chromatography (florisil, CH_2Cl_2/MeOH, 5:1) to yield pure compounds **11**.

1-(Iminophenylmethyl)-3-methyl-5,6,7,8-tetrahydroindolizine (11a): oil; ^{1}H NMR δ 1.8−2.0 (m, 4H), 2.2 (s, 3H), 2.8 (t, 2H), 3.8 (t, 2H), 6.0 (s, 1H), 7.4−7.7 (m, 5H); ^{13}C NMR δ: 11.5 (CH_3), 20.0 (CH_2), 22.8 (CH_2), 24.5 (CH_2), 42.9 (CH_2), 107.8 (CH), 127.4 (C), 128.0 (CH), 128.6 (CH), 129.6 (CH), 130.4 (C), 132.5 (C), 140.8 (C), 174.2 (C); MS *m/e* 238 (M^+, 12), 162 (7), 134 (15), 104 (21), 77 (100). Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.77; H, 7.88; N, 11.65.

1-(Iminocyclopropylmethyl)-3-methyl-5,6,7,8-tetrahydroindolizine (11b): oil; ^{1}H NMR δ 0.8−1.0 (m, 4H), 1.5−2.1 (m, 5H), 2.1 (s, 3H), 3.0 (t, J = 7.5 Hz, 2H), 3.7 (t, J = 6.6 Hz, 2H), 6.1 (s, 1H); ^{13}C NMR δ 7.9 (CH_2), 11.6 (CH), 14.0 (CH_3), 20.3 (CH_2), 22.8 (CH_2), 24.6 (CH_2), 42.8 (CH_2), 106.9 (CH), 119.0 (C), 128.1 (C), 130.2 (C), 176.0 (C). Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.19; H, 9.04; N, 13.77.

1-[Imino(2-thienyl)methyl]-3-methyl-5,6,7,8-tetrahydroindolizine (11c): oil; ^{1}H NMR δ 1.6−1.9 (m, 4H), 2.0 (s, 3H), 2.6 (t, J = 7.6 Hz, 2H), 3.7 (t, J = 6.6 Hz, 2H), 6.1 (s, 1H), 7.2−7.6 (m, 3H); ^{13}C NMR δ 12.3 (CH_3), 20.9 (CH_2), 23.6 (CH_2), 24.6 (CH_2), 43.6 (CH_2), 107.7 (CH), 117.6 (C), 127.8 (C), 127.9 (CH), 129.6 (CH), 131.1 (CH), 131.4 (C), 146.0 (C) 167.3 (C). Anal. Calcd for $C_{14}H_{16}N_2S$: C, 68.82; H, 6.60; N, 11.46. Found: C, 68.74; H, 6.78; N, 11.42.

1-[Imino(2-furyl)methyl]-3-methylpyrrolo[1,2-*a*]azepane (11d): oil; ^{1}H NMR δ 1.5−1.8 (m, 6H), 2.2 (s, 3H), 2.9 (t, J = 7.6 Hz, 2H), 3.9 (t, J = 6.6 Hz, 2H), 6.0 (s, 1H), 6.5 (m, 1H), 6.9 (m, 1H), 7.6 (m, 1H); ^{13}C NMR δ 11.7 (CH_3), 25.2 (CH_2), 26.8 (CH_2), 28.0 (CH_2), 30.3 (CH_2), 44.8 (CH_2), 106.0 (CH), 111.3 (C), 114.7 (CH), 115.3 (CH), 126.6 (CH), 136.3 (C), 144.4 (C), 151.0 (C), 161.5 (C); MS *m/e* 242 (M^+, 100), 213 (82), 199 (90), 95 (25). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.41; H, 7.55; N, 11.67.

1-(Iminophenylmethyl)-3-methylpyrrolo[1,2-*a*]azepane (11e): oil; ^{1}H NMR δ 1.5−1.7 (m, 6H), 2.1 (s, 3H), 2.6 (t, J = 7.6 Hz, 2H), 3.8 (t, J = 6.7 Hz, 2H), 5.8 (s, 1H), 7.2−7.6 (m, 5H); ^{13}C NMR δ 12.1 (CH_3), 25.8 (CH_2), 27.1 (CH_2), 28.6 (CH_2), 30.8 (CH_2), 45.2 (CH_2), 106.5 (CH), 118.5 (C), 127.7 (CH), 128.0 (CH), 129.5 (CH), 132.2 (C), 135.8 (C), 141.1 (C), 174.7 (C); MS *m/e* 252 (M^+, 18), 199 (90), 105 (24), 95 (25), 77 (100). Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 81.08; H, 7.92; N, 11.23.

1-[Imino(2-thienyl)methyl]-3-methylpyrrolo[1,2-*a*]-azepane (11f): oil; ^{1}H NMR δ 1.5−1.8 (m, 6H), 2.0 (s, 3H), 2.7 (t, J = 7.4 Hz, 2H), 3.9 (t, J = 6.7 Hz, 2H), 5.9 (s, 1H), 7.0−7.6 (m, 3H); ^{13}C NMR δ 12.2 (CH_3), 25.9 (CH_2), 27.6 (CH_2), 28.6 (CH_2), 30.8 (CH_2), 45.3 (CH_2), 106.0 (CH), 118.7 (C), 126.8 (CH), 129.0 (CH), 130.7 (CH), 132.4 (C), 137.2 (C), 145.3 (C), 167.7 (C). Anal. Calcd for $C_{15}H_{18}N_2S$: C, 69.73; H, 7.02; N, 10.84. Found: C, 69.84; H, 7.09; N, 10.52.

Hydrolysis of Imine Derivatives 11. A solution of heterocycle **11** (5 mM) in THF (20 mL) was treated with 1 N HCl (10 mL) at rt for 2 h. The mixture was then extracted with ether (2 × 15 mL); the combined organic layers were washed with water and dried over anhydrous sodium sulfate and the solvents eliminated under vacuum. The oily residue thus obtained was subjected to column chromatography (florisil, CH_2Cl_2/MeOH, 9:1) to yield pure carbonyl derivatives **12**.

1-(Cyclopropylcarbonyl)-3-methyl-5,6,7,8-tetrahydroindolizine (12a): oil; ^{1}H NMR δ 0.8 (m, 2H), 1.2 (m, 2H), 1.7−2.1 (m, 4H), 2.2 (s, 3H), 2.4 (m, 1H), 3.1 (t, J = 7.5 Hz, 2H), 3.8 (t, J = 6.6 Hz, 2H), 6.4 (s, 1H); ^{13}C NMR δ 9.4 (CH_2), 11.4 (CH_3), 17.7 (CH_2), 19.5 (CH), 22.6 (CH_2), 24.4 (CH_2), 42.6 (CH_2), 106.7 (CH), 119.0 (C), 127.0 (C), 136.6 (C), 195.8 (C); MS *m/e* 203 (M^+, 100), 188 (91), 162 (80). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.73; H, 8.55; N, 6.69.

3-Methyl-1-(2-thienylcarbonyl)-5,6,7,8-tetrahydroindolizine (12b): oil; ^{1}H NMR δ 1.8 (m, 2H), 2.0 (m, 2H), 2.2 (s, 3H), 3.1 (t, J = 7.6 Hz, 2H), 3.8 (t, J = 6.6 Hz, 2H), 6.4 (s,

1H), 7.0 (m, 1H), 7.5 (m, 1H), 7.7 (m, 1H); ^{13}C NMR δ 11.4 (CH_3), 19.5 (CH_2), 22.6 (CH_2), 24.4 (CH_2), 42.7 (CH_2), 107.9 (CH), 117.0 (C), 127.1 (CH), 130.7 (CH), 131.0 (CH), 138.1 (C), 146.0 (C), 181.6 (C); MS *m/e* 245 (M^+, 100), 134 (90), 111 (78). Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.33; H, 5.95; N, 5.90.

1-(2-Furylcarbonyl)-3-methyl-5,6,7,8-tetrahydroindolizine (12c): oil; ^{1}H NMR δ 1.8 (m, 2H), 1.9 (m, 2H), 2.2 (s, 3H), 3.2 (t, J = 7.5 Hz, 2H), 3.8 (t, J = 6.7 Hz, 2H), 6.5 (m, 1H), 6.6 (s, 1H), 7.2 (m, 1H), 7.6 (m, 1H); ^{13}C NMR δ 11.6 (CH_3), 19.6 (CH_2), 22.7 (CH_2), 24.7 (CH_2), 42.8 (CH_2), 107.8 (CH), 111.5 (CH), 116.1 (CH), 116.4 (C), 127.4 (C), 139.0 (C), 144.7 (CH), 154.5 (C), 176.9 (C); MS *m/e* 229 (M^+, 100), 214 (19), 134 (92). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.25; H, 6.61; N, 6.05.

1-Benzoyl-3-methylpyrrolo[1,2-*a*]azepane (12d): oil; ^{1}H NMR δ 1.4−1.7 (m, 6H), 2.1 (s, 3H), 3.1 (t, J = 7.5 Hz, 2H), 3.8 (t, J = 6.7 Hz, 2H), 5.9 (s, 1H), 7.2−7.8 (m, 5H); ^{13}C NMR δ 11.7 (CH_3), 25.0 (CH_2), 26.2 (CH_2), 27.6 (CH_2), 30.5 (CH_2), 44.8 (CH_2), 108.9 (CH), 117.4 (C), 126.3 (C), 127.2 (CH), 130.3 (CH), 131.4 (CH), 140.4 (C), 142.0 (C), 191.9 (C); MS *m/e* 253 (M^+, 100), 238 (38), 195 (42), 148 (45), 105 (40). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.47; H, 6.52; N, 5.49.

3-Methyl-1-(2-thienylcarbonyl)pyrrolo[1,2-*a*]azepane (12e): oil; ^{1}H NMR δ 1.7−1.9 (m, 6H), 2.2 (s, 3H), 3.2 (t, J = 7.4 Hz, 2H), 3.9 (t, J = 6.7 Hz, 2H), 6.3 (s, 1H), 7.1−7.9 (m, 3H); ^{13}C NMR δ 12.3 (CH_3), 25.5 (CH_2), 26.7 (CH_2), 28.4 (CH_2), 31.1 (CH_2), 45.4 (CH_2), 108.3 (CH), 115.6 (C), 127.0 (C), 127.9 (CH), 129.6 (CH), 131.1 (CH), 131.4 (C), 146.0 (C) 183.1 (C); MS *m/e* 259 (M^+, 85), 111 (100). Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.31; H, 6.44; N, 5.52.

1-[(3,4-Dimethoxyphenyl)carbonyl]-3-methylpyrrolo[1,2-*a*]azepane (12f): oil; ^{1}H NMR δ 1.6−1.8 (m, 6H), 2.1 (s, 3H), 3.1 (t, J = 7.5 Hz, 2H), 3.8 (s, 3H), 3.9 (s, 3H), 3.9 (t, J = 6.7 Hz, 2H), 5.9 (s, 1H), 6.8 (m, 1H), 7.2 (m, 1H), 7.4 (m, 1H); ^{13}C NMR δ 12.0 (CH_3), 25.4 (CH_2), 26.6 (CH_2), 28.2 (CH_2), 30.8 (CH_2), 45.1 (CH_2), 55.6 (CH_3), 55.7 (CH_3), 108.8 (CH), 109.3 (CH), 111.5 (CH), 118.9 (C), 123.4 (CH), 133.2 (C), 141.8 (C), 148.1 (C), 148.7 (C), 152.5 (C), 190.9 (C); MS *m/e* 313 (M^+, 100), 298 (32), 165 (70). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.99; H, 7.31; N, 4.69.

Reduction of Imine Derivatives 11. To a solution of heterocycle **11** (5 mM) in MeOH (20 mL) at 0 °C was carefully added $NaBH_4$ (10 mM) in small portions. The mixture was then stirred at room temperature for 6 h, treated with water (20 mL), and extracted with ether (3 × 10 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate and the solvents removed under vacuum. The oily residue thus obtained was subjected to column chromatography (florisil, CH_2Cl_2/MeOH, 9:1) to yield pure amino derivatives **13**.

1-[Amino(2-thienyl)methyl]-3-methyl-5,6,7,8-tetrahydroindolizine (13a): oil; ^{1}H NMR δ 1.7−1.9 (m, 4H), 2.1 (s, 3H), 2.7 (m, 2H), 3.7 (m, 2H), 5.5 (s, 1H), 5.8 (s, 1H), 6.8−7.5 (m, 3H); ^{13}C NMR δ 11.4, 20.3, 21.8, 23.2, 42.2, 55.8, 104.1, 105.5, 115.5, 123.4, 127.3, 132.4, 136.5, 144.2. Anal. Calcd for $C_{14}H_{18}N_2S$: C, 68.25; H, 7.36; N, 11.37. Found: C, 68.34; H, 7.31; N, 11.49.

1-[Amino(2-furyl)methyl]-3-methylpyrrolo[1,2-*a*]azepane (13b): oil; ^{1}H NMR δ 1.5−1.8 (m, 6H), 2.1 (s, 3H), 2.7 (m, 2H), 3.8 (m, 2H), 5.1 (s, 1H), 5.7 (s, 1H), 6.1 (m, 1H), 6.3 (m, 1H), 7.3 (m, 1H); ^{13}C NMR δ 12.3 (CH_3), 25.3 (CH_2), 28.5 (CH_2), 29.5 (CH_2), 31.6 (CH_2), 45.1 (CH_2), 47.6 (CH), 103.4 (CH), 104.8 (CH), 110.0 (CH), 119.3 (C), 126.6 (C), 131.3 (C), 141.4 (CH), 160.5 (C); MS *m/e* 244 (M^+, 12), 227 (100), 198 (29). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.46. Found: C, 73.77; H, 8.31; N, 11.69.

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