Synthetic Application of Monoprotected Hydrazines toward the Synthesis of 1-Aminopyrroles

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Although the first synthesis of 1-aminopyrroles was accomplished many years ago, it is only recently that these molecules were used as precursors in the synthesis of biologically active compounds such as analgesics[1] and NMDA receptor antagonists.[2] Only a few methods exist for their preparation and this may partly explain their limited presence of literature.[3]

The condensation of hydrazine with 1,4-dicarbonyl compounds is reported to provide 1-aminopyrroles in only low yields.[4] With this modified Paal−Knorr synthesis, dihydropyridazines and 1,1′-bispyrroles are also formed as byproducts. Monoprotected hydrazines were then employed in order to suppress the formation of these byproducts. The use of tosylhydrazine has not resolved this issue since pyridazine derivatives are still produced with this reagent.[5] *N*-Aminophthalimide,[4,6] thiosemicarbazide,[7] benzyl- and *tert*-butyl hydrazides[8,9] are known to condense on 1,4-diketones to provide the desired protected 1-aminopyrroles without the formation of side products. However, in these reports no general methods are presented.

In this paper we present our work on the synthetic application of monoprotected hydrazines toward the synthesis of both simple and sophisticated 1-aminopyrroles. In addition, these 1-aminopyrroles can be used for the synthesis of unsymmetrical 1,1′-bispyrroles and in reductive amination reactions.

In recent works from our research group it has been depicted that 2,2,2-trichloroethyl- (**1**) and 2-(trimethylsilyl)ethyl hydrazine (**2**) are readily available in large quantities from commercially available materials.[10,11] In principle these hydrazides should condense on 1,4-dicarbonyl compounds **3** to allow the preparation of protected 1-aminopyrroles **4** which in turn could be deprotected under very mild conditions to afford the corresponding free amines **5** (Scheme 1).

Results and Discussion

Condensation of 2,2,2-Trichloroethyl Hydrazide on 1,4-Diketones. 2,2,2-Trichloroethyl hydrazide (**1**) (1.2 equiv) was efficiently condensed with 1,4-diketones such as 2,5-hexanedione (**6**), dibenzoylethane (**7**), and 1-phenyl-1,4-pentanedione (**8**) under acidic conditions (Scheme 1). Generally, the reaction was conducted in toluene at 80 °C with pyridinium *p*-toluenesulfonate (PPTS) as a catalyst to provide the corresponding protected 1-aminopyrroles (**12**, **14**, **16**) in high yields. With highly reactive substrates such as 2,5-hexanedione (**6**), the reaction can be performed in AcOH[12] at 80 °C or with $Yb(OTf)_3$ in CH_2Cl_2 at reflux. Unfortunately, the removal of the trichloroethyl ester group under previously described conditions (Zn/AcOH)[10,13] led to the formation of pyrroles in addition to the desired 1-aminopyrroles **21**−**23**.

Condensation of 2-(Trimethylsilyl)ethyl Hydrazide on 1,4-Dicarbonyl Compounds. As for the trichloroethyl case, 2-(trimethylsilyl)ethyl hydrazide (**2**) was condensed with 1,4-diketones **6**−**8** to provide the pyrroles **13**, **15**, **17** in high yields. 2,3,5-Trisubstituted pyrrole derivatives **18** and **19** were obtained by using the diketones **9** and **10** as substrates which were prepared from the Stetter condensation.[14] 1,4-Keto aldehydes can be used as substrates to provide monosubstituted pyrroles, as exemplified by 4-oxopentanal (**11**).[15] The protected 1-aminopyrroles were then smoothly converted, in high yields, to the free 1-aminopyrroles **21**−**26** with nBu_4NF in THF.

With regard to the reaction pathway for the formation of the pyrrole ring system, in most cases several intermediates were detected by TLC during the course of the reaction. However, it has been observed that the bishydrazone **27** is an intermediate involved in the reaction when 2,5-hexanedione (**6**) is the substrate (Scheme 2). The bishydrazone **27** was formed very rapidly, as a single intermediate, by mixing the hydrazide **2** with the diketone **6** in toluene at room temperature. When this intermediate was resuspended in toluene in the presence of PPTS, the pyrrole **13** and hydrazide **2** were obtained. Similar intermediates were observed from the condensation of monoprotected hydrazine such as tosylhydrazine[5] and thiosemicarbazide,[7] with 1,4-dicarbonyl compounds.

Hitherto, it has been shown that the monoprotected hydrazine **2** can be used, in a two-step sequence, to prepare 1-aminopyrroles under very mild conditions. The procedure makes it possible to synthesize simple and more sophisticated 1-aminopyrroles which can then serve as precursors for condensation with 1,4-dicarbonyl compounds to provide unsymmetrical 1,1′-bispyrroles. 1,1′-Bispyrroles **28**−**31** can be efficiently prepared from 1-aminopyrroles **22**−**24** and the 1,4-diketones **6**, **7**, and **10**. The reactions were performed in toluene with

(1) Effland, R. C.; Klein, J. T. U.S. Patent 4,546,105, 1985. Chem. Abstr. **1986**, *104*, 186307.
(2) Kulagowski, J.; Janusz, J.; Leeson, P. D. UK Patent 2,265,372, 1993. *Chem. Abstr.* **1993**, *120*, 134504.
(3) For review see: (a) Cirrincione, G.; Almerico, A. M.; Aiello, E. In Pyrroles. *The Chemistry of Heterocyclic Compounds*; Jones, R. A., Ed.; Wiley: New York, 1992; Vol. 48, Pt. 2, Chapter 3, pp 315−323. (b) Bean, G. P. Pyrroles. In *The Chemistry of Heterocyclic Compounds*; Jones, R. A., Ed.; Wiley: New York, 1990; Vol. 48, Pt. 1, Chapter 2, pp 208, 218−219. (c) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: New York, 1977; pp 384−387.
(4) Epton, R. *Chem. Ind.* **1965**, 425.
(5) Lemal, D. M.; Rave, T. W. *Tetrahedron* **1963**, *19*, 1119.
(6) Flitsch, W.; Krämer, U.; Zimmermann, H. *Chem. Ber.* **1969**, *102*, 3268.
(7) Beyer, H.; Pyl, T.; Völcker, C. E. *Justus Liebigs Ann. Chem.* **1960**, *638*, 150.
(8) Overberger, C. G.; Palmer, L. C.; Marks, B. S.; Byrd, N. R. *J. Am. Chem. Soc.* **1955**, *77*, 4100.
(9) Carpino, L. A. *J. Org. Chem.* **1964**, *30*, 736.
(10) (a) Boudreault, N.; Ball, R. G.; Bayly, C.; Bernstein, M. A.; Leblanc, Y. *Tetrahedron* **1994**, *50*, 7947. (b) Scartozzi, M.; Grondin, R.; Leblanc, Y. *Tetrahedron Lett.* **1992**, *33*, 5717.
(11) Mitchell, H.; Leblanc, Y. *J. Org. Chem.* **1994**, *59*, 682.
(12) With less reactive substrates there is a competitive reaction between the hydrazide and the AcOH to give the bishydrazide.
(13) (a) Leblanc, Y.; Boudreault, N. *J. Org. Chem.* **1995**, *60*, 4268. (b) Zaltsgendler, I.; Leblanc, Y.; Bernstein, M. A. *Tetrahedron Lett.* **1993**, *34*, 2441. (c) Grondin, R.; Leblanc, Y.; Hoogsteen, K. *Tetrahedron Lett.* **1991**, *32*, 5021. (d) Leblanc, Y.; Fitzsimmons, B. J. *Tetrahedron Lett.* **1989**, *30*, 2889.
(14) (a) Stetter, H.; Hilboll, G.; Kuhlmann, H. *Chem. Ber.* **1979**, *112*, 84. (b) Stetter, H.; Schreckenberg, M. *Chem. Ber.* **1974**, *107*, 2453. (c) Stetter, H.; Schreckenberg, M. *Angew. Chem.* **1973**, *85*, 89.
(15) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.
(16) Numbers in brackets represent the chemical yields for the deaminated pyrroles.

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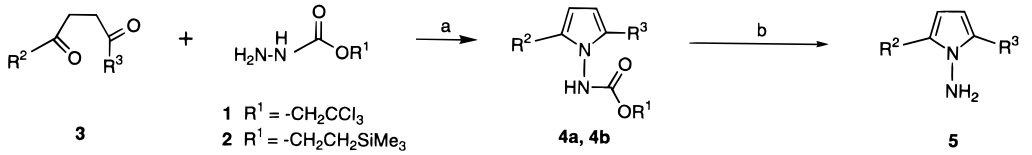
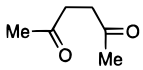
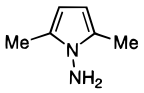
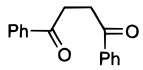
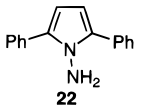
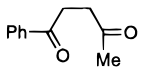
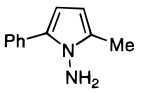
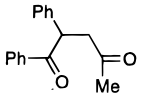
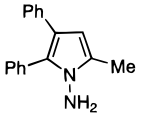
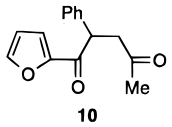
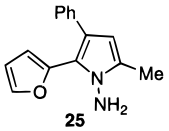
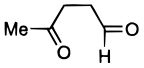
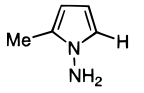
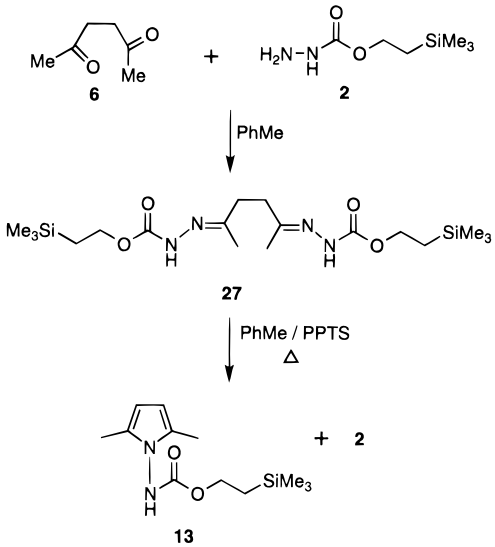
Scheme 1[a]



1,4-DICARBONYL COMPOUND	PROTECTED N-AMINOPYRROLE			N-AMINOPYRROLE [16]	
	REAGENT	METHOD	YIELD	METHOD	YIELD
 6	1	A	96%		
	1	B	12 90%	D[10,13] 0% (46%)	 21
	2	B	86%		
	2	C 50°C	13 90%	E 81%	
	2	A	94%		
 7	1	C 80°C	14 93%	D[10,13] 60% (7%)	 22
	2	C 80°C	15 86%	E 83%	
 8	1	C 80°C	16 94%	D[10,13] 30% (59%)	 23
	2	C 60°C	17 90%	E 62%	
 9	2	C 50°C	18 72%	E 71%	 24
 10	2	C 60°C	19 60%	E 74%	 25
 11	2	C 80°C	20 30%	E 80%	 26

[a] Method A: AcOH; 80 °C, method B; $Yb(OTf)_3$, CH_2Cl_2, reflux; method C: PPTS, PhMe, Δ; (b) method D: Zn/HOAc;[10,13] method E: nBu_4NF, THF, rt.

Scheme 2



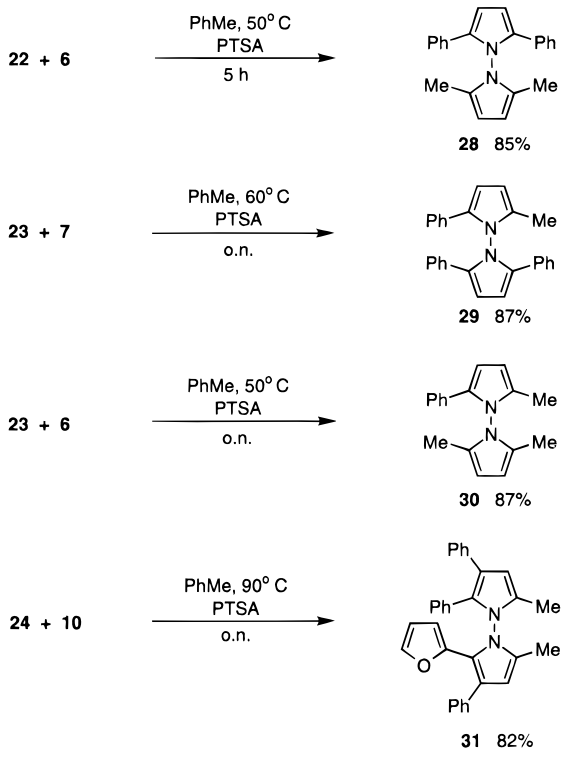
p-toluenesulfonic acid (PTSA) as a catalyst (Scheme 3). Furthermore, the 1-aminopyrrole compounds can be potentially used for the preparation of a large variety of (pyrrolylamino)piperidines. For example, the aminopyrrole **25** was condensed with *N*-methylpiperidone **32** in benzene with PTSA to afford the hydrazone **33** in 84% yield (Scheme 4). The hydrazone was then reduced with $NaBH_4$ in 2-propanol to provide the aminopiperidine **34** in 70% yield. These (pyrrolylamino)piperidines have been claimed to possess analgesic properties.[1]

In summary, 1-aminopyrroles can be easily prepared by the condensation of 2-(trimethylsilyl)ethyl hydrazide with 1,4-dicarbonyl compounds followed by deprotection under mild conditions. These 1-aminopyrroles can then serve as precursors for the preparation of a large variety of molecules containing N−N bond that could be useful in the synthesis of biologically active compounds. Presently, other synthetic applications of these monoprotected hydrazides are being studied and results will be reported in due course.

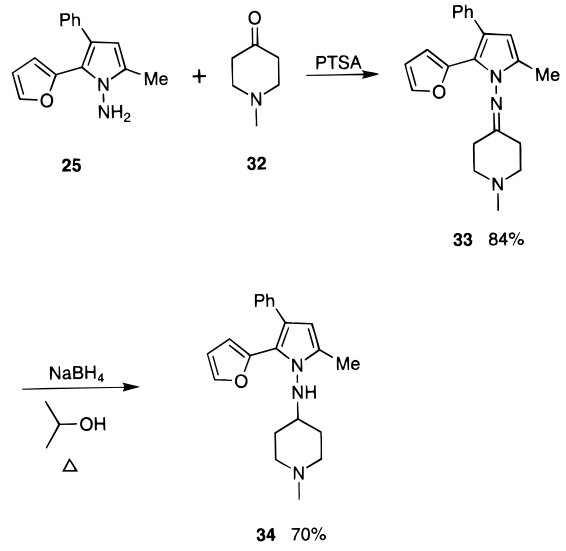
Experimental Section

Typical Procedures for the Condensation of Hydrazides on 1,4-Dicarbonyl Compounds with AcOH (Method A). 2,5-Dimethyl-1-[[[[2-(trimethylsilyl)ethyl]oxy]carbonyl]amino]-pyrrole (13). To a solution of 2,5-hexanedione (500 mg, 4.38 mmol) in AcOH (4.05 mL) was added the hydrazide **2** (926 mg, 5.26 mmol). The resulting mixture was heated at 80 °C for 30 min. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (20% EtOAc in hexane). The title compound was obtained as white solid (1.05

Scheme 3



Scheme 4



g, 94%): mp 89.5 °C (ether/hexane); ^{1}H NMR (200 MHz, acetone-d_6) δ 0.06 (s, 9H), 1.06 (t, 2H), 2.04 (s, 6H), 4.26 (t, 2H), 5.60 (s, 2H), 9.04 (bs, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ −1.4, 11.2, 18.2, 64.3, 103.9, 128.4, 156.5. Anal. Calcd for $C_{12}H_{22}N_2O_2Si$: C, 56.65; H, 8.70; N, 11.00. Found: C, 56.81; H, 8.72; N, 11.05.

With Yb (OTf)$_3$ (Method B). 2,5-Dimethyl-1-[[[(2,2,2-trichloroethyl)oxy]carbonyl]amino]pyrrole (12). To a solution of 2,5-hexanedione (231 mg, 2.02 mmol) in CH_2Cl_2 (5.0 mL) were added the hydrazide **1** (500 mg, 2.43 mmol) and Yb (OTf)$_3$ (63 mg, 0.10 mmol). After a period of 18 h at 50 °C, the resulting mixture was washed with 25% aqueous NH_4OAc solution. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography (7.5% EtOAc in hexane) to provide 532 mg of a white solid (92%): mp 114−115 °C (Et_2O/hexane); IR (cm^{-1}) 3325, 2960, 1738; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.10 (s, 6H), 4.99 (s, 2H), 5.67 (s, 2H), 9.75 (bs, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 11.2, 75.1, 96.6, 104.2, 128.4, 155.0. Anal. Calcd for $C_9H_{11}Cl_3N_2O_2$: C, 38.02; H, 3.87; N, 9.85. Found: C, 37.85; H, 3.86; N, 9.72.

With PPTS (Method C). 2,5-Diphenyl-1-[[[[2-(trimethylsilyl)ethyl]oxy]carbonyl]amino]pyrrole (15). To a solution of the hydrazide **2** (1.24 g, 7.02 mmol) in toluene (30 mL) were added 1,2-dibenzoylethane (1.40 g, 5.85 mmol) and PPTS (70 mg, 0.30 mmol). The mixture was stirred under a nitrogen atmosphere at 80 °C. After a period of 10 h, the solvent was removed under reduced pressure and the crude product purified by flash chromatography (30% EtOAc in hexane) to yield 1.90 g (86%) of material: mp 136−137 °C (EtOAc/hexane); ^{1}H NMR (200 MHz, acetone-d_6) δ 0.05 (s, 9H), 0.65 and 0.85 (2 bt, 2H), 3.90 and 4.05 (2 bt, 2H), 6.35 (s, 2H), 7.45 (m, 10H), 9.25 and 9.45 (2bs, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ −1.5, 18.2, 64.3, 108.1, 127.7, 128.7, 129.2, 133.3, 137.2, 156.4. Anal. Calcd for $C_{22}H_{26}N_2O_2Si$: C, 69.80; H, 6.92; N, 7.40. Found: C, 69.51; H, 6.95; N, 7.35.

2,5-Diphenyl-1-[[[(2,2,2-trichloroethyl)oxy]carbonyl]amino]pyrrole (14): yield 298 mg (93%) from 0.777 mmol of 7; mp 168−169 °C (EtOAc/hexane); ^{1}H NMR (200 MHz, acetone-d_6) δ 4.75 (s, 2H), 6.40 (s, 2H), 7.45 (m, 10H), 10.25 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 75.0, 96.2, 108.4, 127.9, 128.8, 129.2, 132.8, 137.4, 154.7; Anal. Calcd for $C_{19}H_{15}Cl_3N_2O_2$: C, 55.70; H, 3.69; N, 6.84. Found: C, 55.95; H, 3.83; N, 6.86.

5-Methyl-2-phenyl-1-[[[(2,2,2-trichloroethyl)oxy]carbonyl]amino]pyrrole (16): yield 1.86 g (94%) from 5.67 mmol of **8**; mp 100−103 °C (EtOAc/hexane): ^{1}H NMR (400 MHz, acetone-d_6) δ 2.15 (s, 3H), 4.90 (s, 2H), 5.90 (d, 1H), 6.20 (d, 1H), 7.30 (m, 5H), 9.98 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 11.3, 75.1, 96.3, 106.0, 107.0, 127.3, 128.2, 129.1, 131.9, 133.2, 134.0, 155.0. Anal. Calcd for $C_{14}H_{13}Cl_3N_2O_2$: C, 48.37; H, 3.77; N, 8.06. Found: C, 48.28; H, 3.67; N, 8.10.

5-Methyl-2-phenyl-1-[[[[(2-(trimethylsilyl)ethyl]oxy]carbonyl]amino]pyrrole (17): yield 1.62 g (90%) from 5.67 mmol of **8**; mp 68−70 °C (EtOAc/hexane); ^{1}H NMR (400 MHz, acetone-d_6) δ 0.05 (s, 9H), 1.05 (t, 2H), 2.18 (s, 3H), 4.25 (t, 2H), 5.85 (d, 1H), 6.10 (d, 1H), 7.30 (m, 5H), 9.30 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ −1.4, 11.3, 18.2, 64.4, 105.6, 106.7, 127.1, 128.0, 129.0, 132.0, 133.5, 133.9, 156.5. Anal. Calcd for $C_{17}H_{24}N_2O_2Si$: C, 64.52; H, 7.65; N, 8.86. Found: C, 64.57; H, 7.60; N, 8.86.

2,3-Diphenyl-5-methyl-1-[[[[2-(trimethylsilyl)ethyl]oxy]carbonyl]amino]pyrrole (18): yield 578 mg (72%) from 2.46 mmol of **9**; mp 107−110 °C (EtOAc/hexane); ^{1}H NMR (200 MHz, acetone-d_6) δ 0.05 (s, 9H), 0.95 (t, 2H), 2.21 (s, 3H), 4.20 (t, 2H), 6.15 (s, 1H), 7.20 (m, 10H), 9.21 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ −1.5, 11.2, 18.1, 64.3, 105.6, 120.7, 126.0, 128.1, 128.4, 128.8, 129.0, 130.9, 131.4, 133.0, 137.4, 156.0. Anal. Calcd for $C_{13}H_{28}N_2O_2Si$: C, 70.37; H, 7.19; N, 7.14. Found: C, 70.39; H, 7.04; N, 7.10.

2-(2-Furanyl)-5-methyl-3-phenyl-1-[[[2-(trimethylsilyl)-oxy]carbonyl]amino]pyrrole (19): yield 2.02 g (60%) from 8.81 mmol of **10**; ^{1}H NMR (200 MHz, acetone-d_6) δ 0.05 (s, 9H), 1.05 (t, 2H), 2.25 (s, 3H), 4.25 (t, 2H), 6.15 (d, 1H), 6.38 (d, 1H), 6.50 (d of d, 1H), 7.25 (m, 5H), 7.55 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ −1.5, 11.2, 18.2, 64.5, 105.7, 110.8, 111.7, 123.6, 126.5, 128.1, 128.4, 128.9, 132.4, 136.9, 143.1, 146.2, 156.3; HRMS m/z calcd for $C_{21}H_{27}N_2O_3Si$: $(M + H)^+$ 383.1791, found 383.1791. Anal. Calcd for $C_{21}H_{26}N_2O_3Si$: C, 65.94; H, 6.85; N, 7.32. Found: C, 65.92; H, 6.69; N, 7.38.

2-Methyl-1-[[[[2-(trimethylsilyl)ethyl]oxy]carbonyl]-amino]pyrrole (20): yield 180 mg (30%) from 2.50 mmol of **11**. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.06 (s, 9H), 1.06 (bt, 2H), 2.07 (s, 3H), 4.25 (t, 2H), 5.70 (m, 1H), 5.85 (t, 1H), 6.55 (m, 1H), 9.20 (bs, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ −1.5, 10.7, 18.2, 64.2, 105.3, 106.1, 121.4, 129.6, 150.5. Anal. Calcd for $C_{11}H_{20}N_2O_2Si$: C, 55.00; H, 8.33; N, 11.66. Found: C, 54.45; H, 8.56; N, 11.58.

Typical Procedure for the Deprotection with nBu$_4$NF (Method E). 1-Amino-2,5-diphenylpyrrole (22). To a solution of the protected 1-aminopyrrole **15** (433 mg, 1.14 mmol) in THF (6.0 mL) at 0 °C was added a 1 M THF solution of nBu$_4$NF (2.28 mL). The reaction was warmed to rt and after a period of 5 h, and the reaction mixture was poured into a saturated solution of $NaHCO_3$. The resulting mixture was extracted with EtOAc, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography (3% EtOAc in toluene) to yield 221 mg of the title compound (83%): mp 215−216 °C (DMF); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.38 (s, 2H), 6.23 (s, 2H), 7.50 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.6, 127.0, 128.4, 128.6, 132.5, 135.2. Anal. Calcd

for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.63; H, 6.27; N, 11.76.

1-Amino-2,5-dimethylpyrrole (21): yield 174 mg (81%) from 1.96 mmol of **13**: mp 48−50 °C (benzene); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.13 (bs, 6H), 4.84 (bs, 2H), 5.49 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.51, 102.21, 127.86; HRMS calcd for $C_6H_{11}N_2$ $(M + H)^+$ 110.0844, found 110.0844.

1-Amino-2-methyl-5-phenylpyrrole (23): yield 337 mg (62%) from 3.17 mmol of **17**; mp 102−103 °C (EtOAc/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.09 (bs, 2H), 5.90 (d, 1H), 6.15 (d, 1H), 7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 103.9, 105.3, 126.4, 128.2, 128.3, 130.8, 132.9. Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.55; H, 6.90; N, 16.20.

1-Amino-2,3-diphenyl-5-methylpyrrole (24): yield 221 mg (71%) from 1.25 mmol of **18**: mp 134−135 °C (EtOAc/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.50 (bs, 2H), 6.10 (s, 1H), 7.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 103.7, 119.8, 125.1, 127.5, 127.6, 128.1, 128.6, 129.1, 130.1, 131.0, 132.3, 136.5. Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 81.89; H, 6.62; N, 11.19.

1-Amino-2-(2-furanyl)-5-methyl-3-phenylpyrrole (25): yield 505 mg (74%) from 2.86 mmol of **19**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3H), 4.55 (s, 2H), 6.02 (s, 1H), 6.29 (d, 1H), 6.45 (d of d, 1H), 7.20 (m, 5H), 7.50 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2, 104.2, 110.3, 111.0, 119.0, 123.0, 125.8, 127.6, 128.2, 131.8, 136.2, 142.3, 146.0; HRMS *m/z* calcd for $C_{15}H_{15}N_2O$ $(M + H)^+$ 239.1185, found 239.1184. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.40; H, 6.02; N, 11.32.

1-Amino-2-methylpyrrole (26): yield 204 mg (80%) from 2.66 mmol of **20**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H), 4.50 (bs, 2H), 5.75 (m, 1H), 5.95 (m, 1H), 6.63 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 104.2, 104.6, 121.0, 129.0; HRMS *m/z* calcd for $C_5H_8N_2$ $(M + H)^+$ 97.0766, found 97.0766.

1-(2-Furanyl)-2-phenyl-1,5-pentanedione (10). The title compound was obtained in 30% yield using the Stetter condensation: ^{1}H NMR (200 MHz, acetone-d_6) δ 2.15 (s, 3H), 2.85 (d of d, 1H), 3.55 (d of d, 1H), 4.90 (d of d, 1H), 6.60 (d, 1H), 7.30 (m, 6H), 7.88 (d, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 29.3, 47.1, 49.0, 112.8, 118.6, 127.8, 128.8, 129.4, 129.8, 139.3, 147.6, 152.9, 187.6; HRMS *m/z* calcd for $C_{18}H_{15}O_3$ $(M + H)^+$ 243.1022, found 243.1021.

Bishydrazone 27. To a stirred solution of 2,5-hexanedione (200 mg, 1.75 mmol) in toluene (10.0 mL) at room temperature was added the hydrazide **2** (678 mg, 3.86 mmol). After a period of 1 h, the white precipitate was filtered to provide 599 mg (80%) of the title compound: mp 147−149 °C; ^{1}H NMR (200 MHz, acetone-d_6) 0.05 (s, 18H), 0.95 (t, 4H), 1.80 (s, 6H), 2.35 (s, 4H), 4.15 (t, 4H), 9.59 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ −1.4, 16.1, 17.4, 35.2, 62.2, 153.3, 154.3; HRMS *m/z* calcd for $C_{18}H_{39}N_4O_4Si_2$ $(M + H)^+$ 431.2510, found 431.2510. Anal. Calcd for $C_{18}H_{38}N_4O_4Si_2$: C, 50.20; H, 8.89; N, 13.01. Found: C, 50.22; H, 8.60; N, 13.07.

Typical Procedure for the Preparation of 1,1′-Bispyrroles. 1-(5-Methyl-2-phenyl-1-pyrrolyl)-2,5-diphenylpyrrole (29). To a solution of 1-aminopyrrole **23** (108 mg, 0.625 mmol) in toluene (8.0 mL) was added, 1,2-dibenzoylethane (164 mg, 0.688 mmol) and PTSA (6 mg, 0.03 mmol). After a period of 5 h at 60 °C, the reaction mixture was quenched by the addition of saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting crude 1,1′-bispyrrole was purified by flash chromatography (5% EtOAc in hexane, to yield 205 mg (88%) of the title compound: mp 122−123 °C (DMF); ^{1}H NMR (200 MHz, acetone-d_6) δ 1.85 (s, 3H), 6.08 (d, 1H), 6.48 (d, 1H), 6.70 (s, 2H), 7.05 (m, 15H); ^{13}C NMR (100 MHz, acetone-d_6) δ 11.2, 107.3, 107.8, 108.9, 126.0, 126.9, 127.2, 127.8, 129.2, 129.3, 131.5, 131.8, 132.2, 133.0, 135.10. Anal. Calcd for $C_{27}H_{22}N_2$: C, 86.59; H, 5.93; N, 7.48. Found: C, 86.55; H, 5.84; N, 7.50.

1-(2,5-Dimethyl-1-pyrrolyl)-2,5-diphenylpyrrole (28): yield 60 mg (85%) from 0.223 mmol of **22**; mp 119−120 °C (EtOAc/hexane); ^{1}H NMR (400 MHz, acetone-d_6) δ 1.80 (s, 6H), 5.85 (s, 2H), 6.70 (s, 2H), 7.15 (m, 10H); ^{13}C NMR (100 MHz, acetone-d_6) δ 11.2, 106.0, 126.7, 127.6, 128.4, 129.5, 131.9, 135.1. Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.57; H, 6.46; N, 8.97. Found: C, 84.55; H, 6.37; N, 9.00.

1-(5-Methyl-2-phenyl-1-pyrrolyl)-2,5-dimethylpyrrole (30): yield 205 mg (87%) from 0.625 mmol of **23**. ^{1}H NMR (200 MHz, acetone-d_6) δ 1.85 (s, 6H), 1.95 (s, 3H), 5.85 (s, 2H), 6.05 (d, 1H), 6.50 (d, 1H), 7.10 (m, 5H); ^{13}C NMR (100 MHz, acetone-d_6) δ 10.8, 11.0, 105.5, 106.6, 107.2, 125.5, 126.9, 128.3, 129.3, 132.0, 132.3, 132.7; HRMS *m/z* calcd for $C_{17}H_{19}N_2$ $(M + H)^+$ 251.1548, found 251.1548. Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.71; H, 7.37; N, 11.16.

1-(2,3-Diphenyl-5-methylpyrrolyl)-2-(2-furanyl)-5-methyl-3-phenylpyrrole (31): yield 90 mg (82%) from 0.248 mmol of **24**; mp 194−195 °C (EtOAc/hexane); ^{1}H NMR (200 MHz, acetone-d_6) δ 1.95 (s, 3H), 2.38 (s, 3H), 5.87 (d, 1H), 6.12 (s, 1H), 6.35 (d, 1H), 6.41 (d, 1H), 6.51 (s, 1H), 7.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 11.0, 105.9, 106.6, 107.2, 111.0, 120.2, 121.1, 122.6, 125.6, 126.1, 127.3, 127.9, 128.0, 128.2, 128.3, 129.2, 129.8, 130.1, 131.2, 135.8, 135.9, 141.5, 145.3. Anal. Calcd for $C_{31}H_{26}N_2O$: C, 84.13; H, 5.92; N, 6.33. Found: C, 84.30; H, 5.87; N, 6.02.

Preparation of Hydrazone (33). To a solution of the 1-aminopyrrole (**25**) (280 mg, 1.17 mmol) in benzene (5.6 mL) at rt was added 1-methyl-4-piperidone (173 μL, 1.40 mmol) followed by PTSA (23 mg, 0.01 mmol). The reaction mixture was brought to reflux under a nitrogen atmosphere with magnetic stirring. After 36 h the reaction was quenched by a saturated aqueous solution of $NaHCO_3$, and extracted into ethyl acetate. The combined organic layers were dried over Na_2SO_4, and the solvent was removed by rotary evaporation. The crude hydrazone **33** was purified by flash chromatography (5% methanol in CH_2Cl_2), to give 0.313 g (84%) of **33** as a brown oil: ^{1}H NMR (200 MHz, acetone-d_6) δ 2.15 (m, 8H), 2.31 (s, 3H), 2.65 (bs, 3H), 6.11 (s, 1H), 6.20 (d, 1H), 6.39 (d of d, 1H), 7.25 (m, 5H), 7.39 (d, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 11.6, 30.6, 35.1, 55.2, 56.2, 105.6, 110.7, 111.7, 116.0, 123.3, 126.1, 127.2, 128.1, 128.8, 137.4, 142.7, 147.0; HRMS *m/z* calcd for $C_{21}H_{24}N_3O$ $(M + H)^+$ 334.1919, found 334.1919.

1-Methyl-4-(2-(2-furanyl)-5-methyl-3-phenyl-1-pyrrolyl)-aminopiperidine (34). To a solution of the hydrazone (**33**) (0.250 mg, 0.783 mmol), in isopropyl alcohol (15 mL) was added $NaBH_4$ (400 mg, 10 mmol). The reaction mixture was brought to reflux under a nitrogen atmosphere with magnetic stirring. After 72 h, the solvent was removed by rotary evaporation, and the residue was stirred in H_2O and then extracted with ethyl acetate. The organic layers were combined and dried over Na_2SO_4. Solvent was removed by rotary evaporation, and the crude (pyrrolylamino)piperidine **34** was purified by flash chromatography (25% methanol in acetone) to give 0.174 g (69%) of **33** as a white solid: ^{1}H NMR (200 MHz, acetone-d_6) δ 1.55 (bs, 4H), 2.35 (s, 3H), 2.37 (s, 3H), 2.80 (bs, 4H), 5.57 (s, 1H), 6.02 (s, 1H), 6.48 (d, 1H), 6.52 (d, 1H), 71.20 (m, 5H), 7.61 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 28.9, 45.0, 52.5, 56.0, 104.3, 104.5, 111.2, 117.6, 123.3, 125.7, 127.5, 128.1, 132.0, 135.9, 141.8; HRMS *m/z* calcd for $C_{21}H_{26}N_{30}$ $(M + H)^+$ 336.2076, found 336.2075.

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Supporting Information Available: Copies of ^{1}H NMR spectra are available for compounds **10**, **26**, **33**, and **34** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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