Refined Synthesis of 5-Substituted Dipyrromethanes

Benjamin J. Littler, Mark A. Miller,
Chen-Hsiung Hung,[†] Richard W. Wagner,
Donal F. O'Shea,[‡] Paul D. Boyle, and
Jonathan S. Lindsey*

*Department of Chemistry, North Carolina State University,
Raleigh, North Carolina 27695-8204*

Introduction

5-Substituted dipyrromethanes are important precursors for the synthesis of meso-substituted porphyrins,[1] expanded porphyrins, and porphyrin analogues.[2] Several one-flask methods have been reported for the synthesis of 5-substituted dipyrromethanes by the condensation of an aldehyde and pyrrole using various combinations of acids and solvents.[3–14] We previously reported a one-flask synthesis of dipyrromethanes in which an aldehyde is dissolved in a 40-fold excess of pyrrole with a catalytic amount of an acid at room temperature in the absence of any other solvent.[8] This method has afforded good yields of 5-substituted dipyrromethanes bearing many types of functional groups.[15] However, purification of the product is typically achieved by flash column chromatography, restricting application to the small-scale preparation of dipyrromethanes.

Our objective in this study was to eliminate the use of chromatography during purification, thereby removing the major bottleneck to the synthesis of multigram quantities of dipyrromethanes. Upon examining the crude reaction mixture from the acid-catalyzed condensation of benzaldehyde in excess pyrrole, we found that the principal reaction products consist of the dipyrromethane **(1)**, the N-confused dipyrromethane (2,3′-dipyrromethane) **(2)** and the tripyrrane **(3)** (Scheme 1). The presence of the N-confused dipyrromethane was surprising as this species had not been detected previously.[8] Using GC we have examined the distribution of these products as a function of the pyrrole:benzaldehyde ratio and the acid catalyst. We have developed a purification process based on bulb-to-bulb distillation followed by recrystallization that affords analytically pure dipyrromethanes in multigram quantities. The condensation of pyrrole and benzaldehyde upon heating without added acids has also been examined.

Results and Discussion

Investigation of Reaction Conditions. We first examined the crude product distribution formed under our previously reported conditions for the synthesis of 5-phenyldipyrromethane, which involve reaction of pyrrole and benzaldehyde (40:1) catalyzed by TFA (0.1 equiv) at room temperature for 15 min.[8] Analysis of the crude product by GC showed three major peaks which were assigned as 5-phenyldipyrromethane **(1)**, N-confused 5-phenyldipyrromethane **(2)**, and 5,10-diphenyltripyrrane **(3)**. Identification of **1** was made by comparison with pure material prepared by our previously reported method.[8] The N-confused dipyrromethane **2** was assigned by comparison with an authentic sample (vide infra). Assignment of tripyrrane **3** was based on GC-MS data which showed a molecular ion with $m/z = 377$ and by comparison with an impure sample of **3** (ca. 90% pure) prepared in a manner analogous to that described by Brückner et al.[16] Minor peaks (typically less than 5% of the total area) seen in the chromatogram could not be assigned by GC-MS and were easily removed in the purification procedure developed (vide infra). Benzaldehyde was not detected in any samples, even those removed 5 min after the addition of acid, hence the rate of reaction must be rapid.

To optimize the formation of the dipyrromethane, we initially examined the effect of changing the pyrrole:benzaldehyde ratio on the crude product distribution (Figure 1). The product distribution showed little change with time, indicating that the reaction is essentially complete within 5 min and that extended reaction did not lead to the formation of higher oligomers. As the pyrrole:benzaldehyde ratio increases the dipyrromethane:tripyrrane **(1:3)** ratio increased for both TFA and BF₃·Et₂O catalysis. The ratio was much higher under BF₃·Et₂O catalysis because little tripyrrane is formed under these conditions. TFA catalysis gave a lower **1:3** ratio, but also gave significantly lower amounts of the N-confused dipyrromethane **2**.

Next, we examined the effect of different concentrations of BF₃·Et₂O and TFA on the distribution of products for condensations performed at a 25:1 pyrrole:benzaldehyde ratio (Figure 2). With 0.316 equiv of acid (relative to benzaldehyde), the percentage of **3** declined markedly

† Present address: National Changhua University of Education, Changhua, Taiwan 50058.

‡ Present address: Eastman Kodak Company, 1999 Lake Avenue, Rochester, NY 14650.

(1) Lindsey, J. S. In *Metalloporphyrins Catalyzed Oxidations*; Kluwer Academic Publishers: The Netherlands, 1994; pp 49–86.

(2) Jasat, A.; Dolphin, D. *Chem. Rev.* **1997**, *22*, 677–2340.

(3) Nagarkatti, J. P.; Ashley, K. R. *Synthesis* **1974**, 186–187.

(4) Casiraghi, G.; Cornia, M.; Rassu, G.; Del Sante, C.; Spanu, P. *Tetrahedron* **1992**, *48*, 5619–5628.

(5) Hammel, D.; Erk, P.; Schuler, B.; Heinze, J.; Müllen, K. *Adv. Mater.* **1992**, *4*, 737–739. See also: Brückner, C.; Posakony, J. J.; Johnson, C. K.; Boyle, R. W.; James, B. R.; Dolphin, D. *J. Porphyrins Phthalocyanines* **1998**, *2*, 455–465.

(6) Boyle, R. W.; Xie, L. Y.; Dolphin, D. *Tetrahedron Lett.* **1994**, *35*, 5377–5380.

(7) Casiraghi, G.; Cornia, M.; Zanardi, F.; Rassu, G.; Ragg, E.; Bortolini, R. *J. Org. Chem.* **1994**, *59*, 1801–1808.

(8) Lee, C.-H.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427–11440.

(9) Mizutani, T.; Ema, T.; Tomita, T.; Kuroda, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1994**, *116*, 4240–4250.

(10) Staab, H. A.; Carell, T.; Döhling, A. *Chem. Ber.* **1994**, *127*, 223–229.

(11) Vigmond, S. J.; Chang, M. C.; Kallury, K. M. R.; Thompson, M. *Tetrahedron Lett.* **1994**, *35*, 2455–2458.

(12) Nishino, N.; Wagner, R. W.; Lindsey, J. S. *J. Org. Chem.* **1996**, *61*, 7534–7544.

(13) Wijesekera, T. P. *Can. J. Chem.* **1996**, *74*, 1868–1871.

(14) Setsune, J.; Hashimoto, M.; Shiozawa, K.; Hayakawa, J.; Ochi, T.; Masuda, R. *Tetrahedron* **1998**, *54*, 1407–1424.

(15) For some highly functionalized examples; see: (a) Cornia, M.; Binacchi, S.; Del Soldato, T.; Zanardi, F.; Casiraghi, G. *J. Org. Chem.* **1995**, *60*, 4964–4965. (b) Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6585–6587. (c) Halterman, R. L.; Mei, X. *Tetrahedron Lett.* **1996**, *37*, 6291–6294. (d) Milgrom, L. R.; Yahioglu, G. *Tetrahedron Lett.* **1996**, *37*, 4069–4072.

(16) Brückner, C.; Sternberg, E. D.; Boyle, R. W.; Dolphin, D. *J. Chem. Soc., Chem. Commun.* **1997**, 1689–1690.
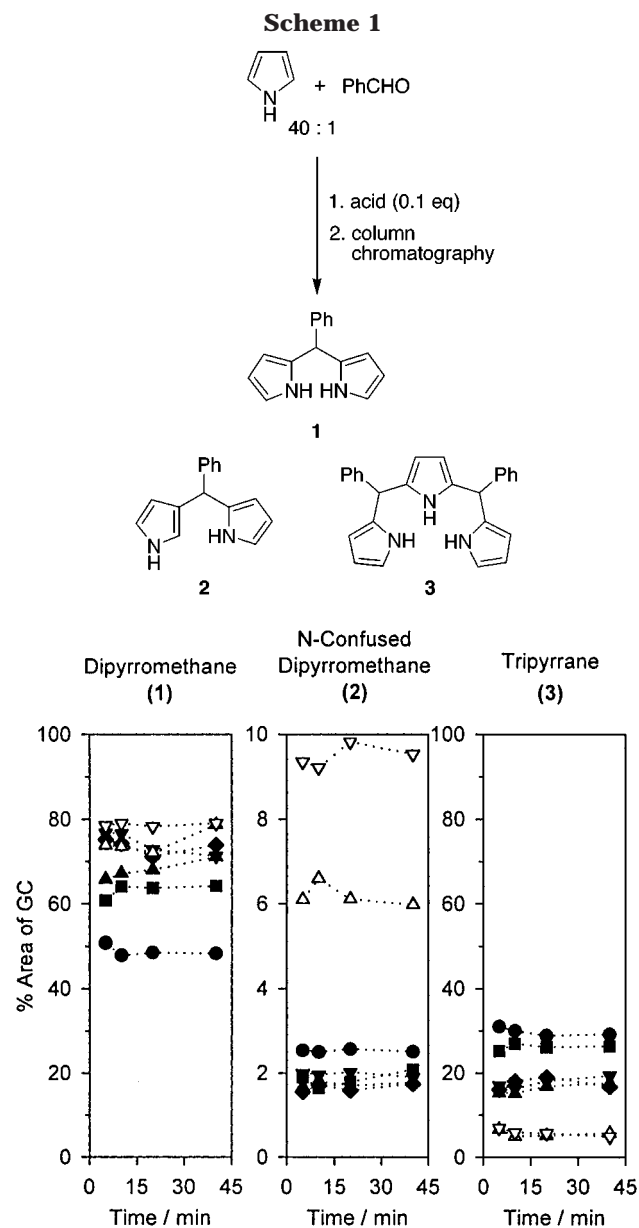
Scheme 1

Figure 1. Percentage of the total area of the gas chromatogram occupied by **1**–**3** for the condensation of pyrrole and benzaldehyde catalyzed by 0.1 equiv of TFA (filled symbols) or BF$_3$·Et$_2$O (open symbols) over a range of pyrrole:benzaldehyde ratios (5:1, ●; 10:1, ■; 25:1, ▲; 40:1, ▼; 80:1, ◆). The reaction mixture was sampled at 5, 10, 20, and 40 min. Note that the scale extends only to 10% for **2**.

and a number of broad new peaks appeared in the chromatogram, making accurate integration difficult. Reducing the amount of acid from 0.1 to 0.0316 equiv had little change on the percentage of **1**, but the percentage of **2** and **3** showed a small increase at the lower acid concentration. Therefore, all further reactions were run with 0.1 equiv of acid.

Synthesis and Identification of N-Confused Dipyrromethanes. Identification of the N-confused dipyrromethane **2** is noteworthy because such species have not been previously identified in dipyrromethane condensations involving unsubstituted pyrrole,[17] though acid-catalyzed acylation of pyrrole is known to give 2-substitution accompanied by some 3-substitution.[18] We were unable to separate a sample of pure **2** from the crude reaction mixture using chromatography, so confirmation
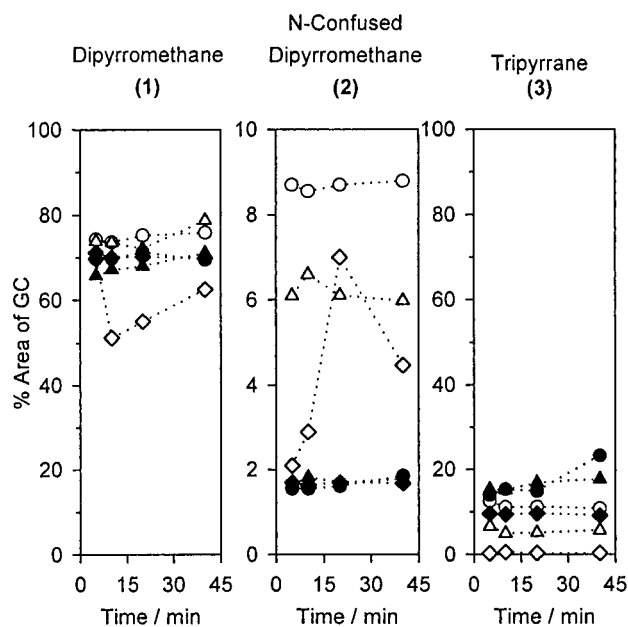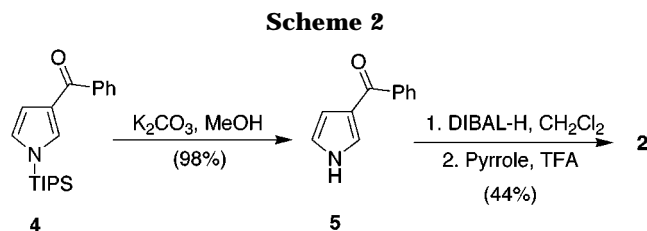

Figure 2. Percentage of the total area of the gas chromatogram occupied by **1**–**3** for the condensation of pyrrole and benzaldehyde (25:1) catalyzed by a range of TFA (filled symbols) or BF$_3$·Et$_2$O (open symbols) equivalents (0.0316 equiv, ●; 0.100 equiv, ▲; 0.316 equiv, ◆). Note that the scale extends only to 10% for **2**.
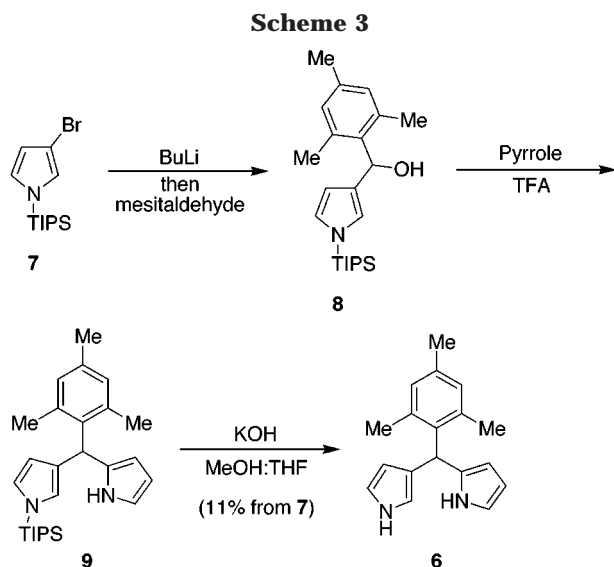
Scheme 2

of the assignment of **2** was provided by an authentic sample prepared by the synthetic route shown in Scheme 2. This sample gave GC-MS data identical to the peak observed by GC-MS of the crude reaction mixture produced by condensation of benzaldehyde with pyrrole and gave a ^{1}H NMR spectrum consistent with peaks observed in a partially purified sample.

We also prepared N-confused 5-mesityldipyrromethane (**6**) as shown in Scheme 3 from mesitaldehyde and the anion derived from 3-bromo-1-(triisopropylsilyl)pyrrole (**7**).[19] The authentic sample of **6** obtained in this manner gave GC-MS and ^{1}H NMR data identical to that of a byproduct formed in the condensation of mesitaldehyde with neat excess pyrrole. These two routes provide access to N-confused dipyrromethanes from either the aldehyde or the acid chloride.

Investigation of Isolation Procedures. The major limitation of our previous method for the preparation of dipyrromethanes was the requirement to purify the

(17) Production of a 2,3′-dipyrrylmethane from the condensation between ethyl pyrrole 2-carboxylate and *o*-nitrobenzaldehyde catalyzed by TiCl$_4$ in CH$_2$Cl$_2$ has been recently reported in ref 14. However, it should be noted that the introduction of an electron-withdrawing group onto the 2-position pyrrole ring is known to promote substitution at both the 4- and 5-position; see: Jackson, A. H. In *Pyrroles, Part One*; Jones, R. A., Ed.; Wiley-Interscience: New York, 1990; Vol. 48, The Chemistry of Heterocyclic Compounds, pp 295–303.

(18) Anderson, H. J.; Loader, C. E. In *Pyrroles, Part One*; Jones, R. A., Ed.; Wiley-Interscience: New York, 1990; Vol. 48, The Chemistry of Heterocyclic Compounds, pp 397–497.

Scheme 3

Scheme 4

Pyrrole + Aldehyde
  25   1

TFA (0.1 eq),
5 min, 25 °C | *Condensation*

↓

Dipyrromethane   N-Confused Dipyrromethane

Tripyrrane   Oligomers

| *Bulb-to-Bulb Distillation*

↓

Dipyrromethane   N-Confused Dipyrromethane

| *Recrystallization*

↓

Dipyrromethane

Figure 3. Isolated yields of dipyrromethanes (**1** and **2**) prepared by the refined procedure (pyrrole and benzaldehyde, TFA 0.1 equiv, 5 min, followed by distillation) over a range of pyrrole:benzaldehyde ratios from 5:1 to 80:1.

product by column chromatography. In this study we sought to extend the work of Hammel et al. who first demonstrated that dipyrromethanes could be purified by distillation at reduced pressure.[5] We found that tripyrrane **3** and higher oligomers were easily removed by distillation, but that removal of the N-confused dipyrromethane **2** required recrystallization after distillation (Scheme 4). This result is relevant to the choice of acid catalyst because significant amounts of **2** were formed by reactions catalyzed by $BF_3 \cdot Et_2O$ (Figure 1) and many recrystallizations were required for complete removal of **2** (as judged by GC). In contrast, reactions catalyzed by TFA afforded trace amounts of **2**, which were typically removed by two recrystallizations. Therefore, TFA is the acid catalyst of choice for the preparation of dipyrromethanes. This refined process enabled straightforward preparation of multigram batches of 5-phenyldipyrromethane (**1**) that are analytically pure and contain none of the undesired N-confused dipyrromethane **2**. A complete description of studies performed to optimize the purification procedure is provided in the Supporting Information.

To examine how the isolated yields of dipyrromethane prepared by this refined procedure varied with the pyrrole:benzaldehyde ratio, we performed a series of condensations catalyzed by TFA (0.1 equiv) over a range
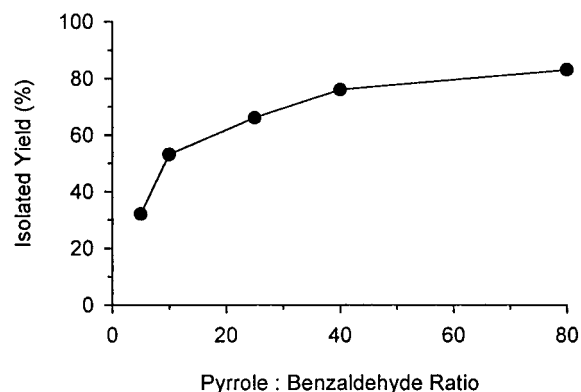
of ratios from 5:1 to 80:1. Figure 3 shows that the isolated yields of dipyrromethanes after distillation increased with the pyrrole:benzaldehyde ratio in a manner consistent with the GC data (Figure 1) but that the isolated yields showed a greater range than the GC data. This result is consistent with the hypothesis that a high pyrrole:benzaldehyde ratio prevents polymerization and therefore reduces the amount of nonvolatile material that cannot be examined by GC. As a compromise between the increased isolated yield of dipyrromethane at high pyrrole:benzaldehyde ratios and the requirement for excessive volumes of pyrrole,[20] we prefer to use a pyrrole:benzaldehyde ratio of 25:1 in the condensations.

Scope of Refined Procedure. We examined the scope of the refined procedure developed for **1** by application to a range of aldehydes. Examination of the crude reaction product for each reaction by GC produced a trace very similar to that seen for the condensation of pyrrole and benzaldehyde. For every case examined by GC-MS in this study, a distinct byproduct with a molecular ion mass identical to the dipyrromethane was observed, suggesting that the formation of N-confused dipyrromethane as a reaction byproduct is universal. We therefore followed the same purification procedure, involving distillation followed by recrystallization, to prepare analytically pure, multigram batches of 12 dipyrromethanes (Table 1). The dipyrromethanes are sufficiently pure to enable the acquisition of X-ray structures (see the Supporting Information for structures of **1** and **10**). Minor modifications to the procedure were required in four cases:

(1) Mesitaldehyde reacted more slowly with pyrrole than the other aldehydes examined in this study, requiring 1 h to proceed to completion. (For an assessment of other methods for preparation and isolation of **10**, see the Supporting Information.)

(2) Paraformaldehyde is relatively insoluble in neat pyrrole at room temperature, leading to a slow reaction and poor yields of dipyrromethane.[21] Heating the reaction mixture to 50 °C increased the solubility of the paraformaldehyde sufficiently to enable rapid condensation, providing an expedient synthesis of unsubstituted dipyrromethane **22**.

(19) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317−6328.
(20) Cost of pyrrole ∼$20/100 cm³ (Aldrich and Acros, 1998).
(21) Wang, Q. M.; Bruce, D. W. *Synlett* **1995**, 1267−1268.

Table 1. Isolated Yield and Distillation Conditions of the 5-Substituted Dipyrromethanes[a]

aldehyde/ketone	dipyrromethane	yield[b] (%)	distillation conditions (°C, mmHg)
benzaldehyde	**1**	53	130, 0.03
mesitaldehyde[c]	**10**	27	160–180, 0.03
p-tolualdehyde	**11**	33	180, 0.10
o-tolualdehyde	**12**	41	180–190, 0.20
p-anisaldehyde	**13**	68	200, 0.03
o-anisaldehyde	**14**	61	190–210, 0.50
4-iodobenzaldehyde	**15**	57	170–180, 0.03
3-iodobenzaldehyde	**16**	40	170–180, 0.03
4-fluorobenzaldehyde	**17**	28	190, 0.08
pentafluorobenzaldehyde	**18**	65	150–160, 0.03
2,6-dichlorobenzaldehyde	**19**	39	175–190, 0.03
4-nitrobenzaldehyde	**20**	56	not distilled
acetone	**21**	53	120–130, 0.03
paraformaldehyde	**22**	41	110, 0.04

[a] All reactions were performed using a pyrrole:aldehyde ratio of 25:1 with catalysis by TFA (0.1 equiv) for 5 min at room temperature. [b] Overall yields upon recrystallization of the distilled product. [c] Reaction was performed for 1 h.

(3) *p*-Nitrophenyldipyrromethane **20** decomposed on attempted distillation, but was easily isolated by precipitation from the crude reaction mixture as described by Brückner et al.[22]

(4) 5-(4-Pyridyl)dipyrromethane[3] was formed in only trace amounts using the refined procedure, and no improvement was achieved with 1.1 equiv of TFA.

The improvement in the synthetic methodology for the preparation of dipyrromethanes is exemplified by considering the reported syntheses of 5-(4-methylphenyl)-dipyrromethane **(11)**: (1) A 6-step synthesis from pyrrole afforded a brown oil.[23] (2) Direct condensation of *p*-tolualdehyde and pyrrole in dilute solution gave a solid (mp 75 °C) after chromatography.[11] (3) Direct condensation in excess pyrrole as the solvent gave a tan solid (mp 110–111 °C)[8] or a green solid (mp 114 °C),[24] but column chromatography was required to purify the product, and in each case less than a gram of material was prepared. Using the refined procedure described herein we prepared an analytically pure 2.22-g batch of **11** as a colorless crystalline solid (mp 114 °C) within 4 h without chromatography.

Thermal Condensation of Pyrrole and Benzaldehyde. During the course of this work, a photochemical synthesis of 5-phenyldipyrromethane **(1)** was reported by D'Auria et al.[25] In this procedure a mixture of pyrrole and benzaldehyde (694:1) was irradiated by a water-jacketed high-pressure Hg lamp for 3 h to give **1** in 50% yield. However, the ^{1}H NMR spectroscopic data given for the photochemical product are not consistent with ^{1}H NMR data for pure **1** or **2** prepared in this study.

While reexamining whether a purely photochemical process could yield dipyrromethanes, we discovered that a mixture of pyrrole and benzaldehyde (25:1) stirred under Ar for 24 h at room temperature (ca. 22 °C) in the absence of light gave **1** in 3% yield, despite no acid being deliberately added. An identical reaction mixture stirred at 40 °C for 24 h gave a GC trace analogous to that obtained from the deliberately acid-catalyzed process. Distillation of the crude reaction product afforded **1** in 56% yield. Reaction at 90 °C was complete within 90 min,

but the isolated yield of **1** fell to 42%. The mechanism of the thermal reaction was not examined in detail, but catalysis by trace amounts of residual benzoic acid or adventitious acids cannot be excluded.

The experimental information given by D'Auria et al. is insufficient to assess the radiation absorbed by the reaction mixture as well as the reaction temperature.[25] However, given that (1) pyrrole and benzaldehyde readily form **1** upon heating and (2) illumination by a high-pressure Hg lamp produces a significant amount of heat, formation of **1** by a purely photochemical process remains to be conclusively demonstrated.

Conclusion

We have developed a refined synthesis of 5-substituted dipyrromethanes. The procedure is based on condensation of an aldehyde with neat excess pyrrole catalyzed by TFA, followed by bulb-to-bulb distillation to remove oligomeric material and recrystallization to remove the N-confused dipyrromethane. The production of N-confused dipyrromethane in the one-flask synthesis appears to be universal. The procedure requires no chromatography, has wide scope, and allows synthesis of pure, multigram batches of 5-substituted dipyrromethanes.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra and absorption spectra were collected routinely. Elemental analyses were performed by Atlantic MicroLab, Inc. Melting points are uncorrected. A standard-size Kugelrohr short-path distillation apparatus was purchased from Aldrich. For reactions of 50 mmol of aldehyde, the distilling bulb was typically 250 mL, and the collection bulb was typically 100 mL. Column chromatography was performed on silica (Baker, 40-*μ*m average particle size) and alumina (Fisher, 80–200 mesh). Pyrrole was distilled from CaH$_2$ under Ar at atmospheric pressure. CH$_2$Cl$_2$ was distilled from K$_2$CO$_3$. THF was distilled from sodium chips under argon with benzophenone/ketyl as indicator. Benzaldehyde was freshly distilled before use. All other chemicals are reagent grade and were used as obtained. The dipyrromethanes are easily visualized upon exposure of thin-layer chromatography plates to Br$_2$ vapor.

Product Quantitation by GC. Studies on the effect of the pyrrole:benzaldehyde ratio and the amount of added acid on the product distribution were performed by removing 250-*μ*L aliquots from the reaction mixture which were immediately quenched by injecting into a solution of ethyl acetate (240 *μ*L) containing excess triethylamine (10 *μ*L). These were then examined using a GC system equipped with a FID detector [temperature gradient temp 1, 35 °C (5 min); temp 2, 270 °C (10 min); rate 20 °C/min, total runtime 26.75 min]. [GC-MS was performed using a temperature gradient of temp 1, 100 °C (3 min); temp 2, 270 °C (10 min); rate 10 °C/min, total runtime 30

(22) Brückner, C.; Karunaratne, V.; Rettig, S. J.; Dolphin, D. *Can. J. Chem.* **1996**, *74*, 2182–2193.

(23) Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1993**, *58*, 7245–7257.

(24) Gaud, O.; Granet, R.; Kaouadji, M.; Krausz, P.; Blais, J. C.; Bolbach, G. *Can. J. Chem.* **1996**, *74*, 481–499.

(25) D'Auria, M.; De Luca, E.; Esposito, V.; Mauriello, G.; Racioppi, R. *Tetrahedron* **1997**, *53*, 1157–1166.

min.] We initially attempted to use GC to quantify the yields of **1**–**3** by constructing calibration curves for the FID detector using standard solutions of purified material. These studies demonstrated that the detector had an approximately linear response to the amount of **1**, **2**, or **3** present, but the quantitative results showed too much variance (up to 10%) to be reliable. Therefore, we present the percentages of the total area of the chromatogram with no correction for the differential response of the FID detector to **1**, **2**, or **3**.

Preparation of N-Confused 5-Phenyldipyrromethane (2). A solution of 3-benzoyl-1-(triisopropylsilyl)pyrrole[19] **(4)** (1.01 g, 3.10 mmol) and K_2CO_3 (71.1 mg, 0.50 mmol) in methanol (15 mL) was stirred under Ar for 3 h.[26] The solvent was removed under vacuum, and then the crude solid product was dissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$, and then dried ($MgSO_4$). Removal of the solvent under vacuum gave 3-benzoylpyrrole[19] **(5)** (520 mg, 98%) as a colorless solid.

A solution of **5** (456 mg, 2.20 mmol) in CH_2Cl_2 (2 mL) was added to a solution of DIBAL-H (1.0 M in CH_2Cl_2, 4.0 mL, 4.0 mmol) cooled to 0 °C under Ar. After 30 min TLC showed incomplete reduction, so an additional aliquot of DIBAL-H (1.0 M in CH_2Cl_2, 0.5 mL, 0.5 mmol) was added. After a further 10 min, no starting material remained. The reaction was quenched with H_2O and diluted with CH_2Cl_2. The organic phase was washed with H_2O and dried ($MgSO_4$), and the solvent was removed under vacuum. On the basis of a route for the directed synthesis of dipyrromethanes,[8] the crude reaction product was immediately dissolved in pyrrole (30 mL, 432 mmol) and degassed by a stream of Ar for 5 min. TFA (39 μL, 0.51 mmol) was added, and the reaction mixture was stirred for 10 min; then 0.1 M aqueous NaOH and CH_2Cl_2 were added. The organic phase was dried ($MgSO_4$), concentrated under vacuum, and then purified by flash column chromatography [Al_2O_3; hexanes:ethyl acetate (5:1)], giving **2** (260 mg, 44%) as a brown oil: ^1H NMR ($CDCl_3$) δ 5.34 (s, 1 H), 5.87 (s, 1 H), 6.07 (m, 1 H), 6.13 (q, J = 2.9 Hz, 1 H), 6.39 (m, 1 H), 6.63 (m, 1 H), 6.68 (m, 1 H), 7.23 (m, 5 H), 7.91 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 43.2, 106.5, 108.0, 108.7, 116.3, 116.5, 118.2, 125.7, 126.3, 128.3, 128.5, 134.9, 144.5; MS (EI$^+$) m/z 222 (M$^+$, 86%), 145 (100) [found (HRMS) m/z 222.1159, $C_{15}H_{14}N_2$ requires 222.1157].

Preparation of N-Confused 5-Mesityldipyrromethane (6). On the basis of a procedure described by Bray et al.,[19] a sample of 3-bromo-1-(triisopropylsilyl)pyrrole[19] **(7)** (3.50 g, 11.6 mmol) was dissolved in THF (50 mL) at room temperature under Ar and then cooled to −78 °C in a dry ice−acetone bath. *n*-Butyllithium (1.6 M in hexanes, 11.6 mmol, 7.25 mL) was added dropwise via a syringe. After 15 min mesitaldehyde (1.70 mL, 11.6 mmol) was added dropwise via syringe. Upon the final addition of mesitaldehyde the reaction mixture was allowed to warm to room temperature, and then H_2O was added. The aqueous layer was extracted with diethyl ether. The combined extracts were washed with brine and then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a dark yellow oil (4 g). Flash column chromatography [SiO_2; CH_2Cl_2:hexanes (1:1)] gave crude 3-[α-hydroxy-2,4,6-trimethylbenzyl]-1-(triisopropylsilyl)pyrrole **(8)** as the third major product eluted. TLC [CH_2Cl_2:hexanes (1:1); I_2 chamber detection] showed several minor impurities, and GC-MS showed a mixture of **8** (t_R = 20.5 min, m/z = 371) and an uncharacterized material (t_R = 11.7 min, m/z = 206). The clear yellow oil was used in the next step without further purification.

Crude **8** (1.00 g, 2.70 mmol) was dissolved in pyrrole (4.7 mL, 67 mmol) at room temperature, and then TFA (21 μL, 0.27 mmol) was added. After 5 min GC-MS analysis showed complete consumption of **8**. After 30 min of stirring the pyrrole was removed under vacuum. Flash column chromatography [SiO_2; hexanes:CH_2Cl_2 (2:1)] gave **9** (500 mg) as the first major band eluted. GC-MS analysis showed the product to be >98% pure [t_R (product) = 23.5 min, m/z = 420]. The TIPS group was removed by treatment of **9** with powdered KOH (1.2 g) in methanol/THF (10:1, 11 mL). After the reaction was stirred at room-temperature overnight, no starting material was detected

by TLC [SiO_2; CH_2Cl_2:hexanes (1:1); I_2 chamber detection]. The reaction mixture was diluted with water, and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum giving a light yellow oil. Column chromatography [Al_2O_3; CH_2Cl_2:hexanes (1:1, then steadily enriched with CH_2Cl_2)] gave **6** (320 mg, overall yield 11% from **7**) as an oil that solidified upon standing in the freezer: mp 106−107 °C; ^1H NMR ($CDCl_3$) δ 2.08 (s, 6 H), 2.26 (s, 3 H), 5.81 (s, 1 H), 5.95 (m, 1 H), 6.18 (m, 1 H), 6.14 (m, 1 H), 6.50 (s, 1 H), 6.61 (m, 1 H), 6.75 (m, 1 H), 6.76 (s, 2 H), 7.91 (br s, 1 H), 8.02 (br s, 1 H); found (HRMS) m/z 264.1623, $C_{18}H_{20}N_2$ requires 264.1626.

Preparation of the Dipyrromethanes. General Procedure for the Preparation of 5-Substituted Dipyrromethanes. Pyrrole (25 equiv) and the aldehyde (1.0 equiv) were added to a dry round-bottomed flask and degassed with a stream of Ar for 5 min. TFA (0.10 equiv) was then added, and the solution was stirred under Ar at room temperature for 5 min and then quenched with 0.1 M NaOH. Ethyl acetate was then added. The organic phase was washed with water and dried (Na_2SO_4), and the solvent removed under vacuum to afford an orange oil. Bulb-to-bulb distillation typically gave an oil which crystallized upon standing. Crystallization of the oil was slow, so the oil was washed into a round-bottomed flask with ethyl acetate. Removal of the solvent under vacuum gave a solid that was recrystallized two times from ethanol or ethanol/water to give pure dipyrromethane as a crystalline solid.

5-Phenyldipyrromethane (1). Pyrrole (87.0 mL, 1.25 mol) and benzaldehyde (5.00 mL, 50.0 mmol) were reacted by the general procedure (distilled at 130 °C (0.03 mmHg); recrystallized from ethanol) giving **1** (5.93 g, 53%) as pale yellow crystals: mp 100−101 °C; ^1H NMR ($CDCl_3$) δ 5.48 (s, 1 H), 5.92 (s, 2 H), 6.15−6.18 (m, 2 H), 6.70 (m, 2 H), 7.21−7.33 (m, 5 H), 7.92 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 44.6, 107.9, 109.3, 117.8, 127.6, 128.9, 129.3, 133.2, 142.7; MS (EI$^+$) m/z 222 (M$^+$, 100%), 156 (42), 145 (89). Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.6. Found: C, 80.8; H, 6.3; N, 12.6.

5-Mesityldipyrromethane (10). Pyrrole (50.0 mL, 720 mmol) and mesitaldehyde (4.27 g, 28.8 mmol) were added to a dry 250-mL round-bottomed flask and degassed with a stream of Ar for 5 min. TFA (222 μL, 5.00 mmol) was then added, and the solution was stirred under Ar at room temperature for 1 h and then quenched with triethylamine (1.00 mL). Toluene (200 mL) was then added, and the organic phase was washed with brine (2 × 150 mL) and dried (Na_2SO_4). The solvent was removed under vacuum to give a black oil.[27] Bulb-to-bulb distillation at 160−180 °C (0.03 mmHg) gave a highly colored solid that was washed into a round-bottomed flask with ethyl acetate. The solvent was evaporated under vacuum until a solid began to form, and then cyclohexanes (100 mL) were added to precipitate a yellow solid that was filtered and recrystallized from ethanol/water (10:1) giving **10** (2.04 g, 27%) as pale yellow crystals: mp 170−171 °C; ^1H NMR ($CDCl_3$) δ 2.06 (s, 6 H), 2.28 (s, 3 H), 5.93 (s, 1 H), 6.01 (m, 2 H) 6.17−6.19 (m, 2 H), 6.67 (m, 2 H), 6.87 (s, 1 H), 7.97 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.6, 20.8, 38.3, 106.5, 108.7, 116.2, 130.4, 131.3, 134.6, 136.6, 137.6; MS (EI$^+$) m/z 264 (M$^+$, 100%), 196 (42), 145 (53). Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.8; H, 7.6; N, 10.6. Found: C, 81.7; H, 7.7; N, 10.6.

5-(4-Methylphenyl)dipyrromethane (11). Pyrrole (50.0 mL, 720 mmol) and *p*-tolualdehyde (3.46 g, 28.8 mmol) were reacted by the general procedure (distilled at 180 °C (0.1 mmHg); crystallized from ethyl acetate:hexanes; recrystallized from ethanol:water 4:1) giving **11** (2.22 g, 33%) as colorless crystals: mp 114 °C; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3 H), 5.44 (s, 1 H), 5.92 (m, 2 H), 6.15 (q, J = 2.9 Hz, 2 H), 6.68 (m, 2 H), 7.08−7.14 (m, 4 H), 7.91 (br s, 2 H); ^{13}C ($CDCl_3$) δ 21.0, 43.6, 107.1, 108.4, 117.1, 128.2, 129.3, 132.7, 136.5, 139.1; MS (EI$^+$) m/z 236 (M$^+$, 100%), 170 (42), 145 (83). Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.3; H, 6.8; N, 11.85. Found: C, 81.25; H, 6.8; N, 11.8.

(26) Attempted removal of the TIPS group with tetrabutylammonium fluoride as described in ref 19 failed, so K_2CO_3 in methanol was used instead, see: Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280−2286.

(27) The isolation of **10** on a larger scale (4−10 g) is most effective with the following modifications: (1) The black oil produced on removal of pyrrole is filtered through a short pad of silica (eluted with CH_2Cl_2), affording a brown oil upon removal of CH_2Cl_2 via rotary evaporation. (2) The bulb-to-bulb distillation is performed with a dry ice-cooled bulb inserted between the collection bulb and the Kugelrohr motor to collect a yellow oil that distills prior to **10**.

5-(2-Methylphenyl)dipyrromethane (12). Pyrrole (50.0 mL, 720 mmol) and *o*-tolualdehyde (3.46 g, 28.8 mmol) were reacted by the general procedure (distilled at 180–190 °C (0.2 mmHg); crystallized from CH$_2$Cl$_2$:hexanes; recrystallized from ethanol:water) giving **12** (2.77 g, 41%) as colorless crystals: mp 118 °C; ^{1}H NMR (CDCl$_3$) δ 2.27 (s, 3 H), 5.62 (s, 1 H), 5.88 (m, 2 H), 6.15 (q, 2 H, J = 2.9 Hz), 6.66 (m, 2 H), 6.94 (m, 1 H), 7.11–7.17 (m, 3 H), 7.83 (br s, 2 H); ^{13}C NMR (CDCl$_3$) δ 19.3, 40.3, 107.2, 108.3, 117.0, 126.2, 126.9, 127.9, 130.5, 131.9, 136.3, 140.5; MS (EI$^+$) *m/z* 236 (M$^+$, 100%), 168 (54), 145 (85). Anal. Calcd. for C$_{16}$H$_{16}$N$_2$: C, 81.3; H, 6.8; N, 11.85. Found: C, 81.3; H, 6.8; N, 11.8.

5-(4-Methoxyphenyl)dipyrromethane (13). Pyrrole (50.0 mL, 720 mmol) and *p*-anisaldehyde (3.92 g, 28.8 mmol) were reacted by the general procedure (distilled at 200 °C (0.3 mmHg); recrystallized from diethyl ether:hexanes) giving **13** (4.96 g, 68%) as a colorless powder: mp 99 °C; ^{1}H NMR (CDCl$_3$) δ 3.79 (s, 3 H), 5.42 (s, 1 H), 5.91 (m, 2 H), 6.15 (q, J = 2.9 Hz, 2 H), 6.68 (m, 2 H), 6.85 (AA′BB′m, 2 H), 7.12 (AA′BB′m, 2 H), 7.91 (br s, 2 H); ^{13}C NMR (CDCl$_3$) δ 43.0, 55.2, 107.0, 108.3, 113.9, 117.1, 129.3, 132.8, 134.1, 158.4; MS (EI$^+$) *m/z* 252 (M$^+$, 100%), 186 (33), 170 (27), 145 (74). Anal. Calcd. for C$_{16}$H$_{16}$N$_2$O: C, 76.2; H, 6.4; N, 11.1. Found: C, 75.9; H, 6.35; N, 11.1.

5-(2-Methoxyphenyl)dipyrromethane (14). Pyrrole (50.0 mL, 720 mmol) and *o*-anisaldehyde (3.92 g, 28.8 mmol) were reacted by the general procedure (distilled at 190–210 °C (0.5 mmHg); recrystallized from CH$_2$Cl$_2$:hexanes) giving **14** (4.40 g, 61%) as a colorless powder: mp 115 °C; ^{1}H NMR (CDCl$_3$) δ 3.77 (s, 3 H), 5.81 (s, 1 H), 5.89 (m, 2 H), 6.13 (q, J = 2.9 Hz, 2 H), 6.65 (m, 2 H), 6.88–6.92 (m, 2 H), 7.09 (m, 1 H), 7.23 (m, 1 H), 8.06 (br s, 2 H); ^{13}C NMR (CDCl$_3$) δ 37.5, 55.7, 106.6, 108.1, 111.2, 116.7, 120.8, 128.0, 129.4, 130.8, 132.5, 156.6; MS (EI$^+$) *m/z* 252 (M$^+$, 100%), 145 (67). Anal. Calcd. for C$_{16}$H$_{16}$N$_2$O: C, 76.2; H, 6.4; N, 11.1. Found: C, 76.0; H, 6.35; N, 10.9.

5-(4-Iodophenyl)dipyrromethane (15). Pyrrole (25.0 mL, 360 mmol) and 4-iodobenzaldehyde (3.30 g, 14.4 mmol) were reacted by the general procedure (distilled at 170–180 °C (0.03 mmHg)) giving **15** (2.86 g, 57%) as colorless crystals: mp 145–146 °C; ^{1}H NMR (CDCl$_3$) δ 5.42 (s, 1 H), 5.89 (m, 2 H), 6.16 (q, J = 3.0 Hz, 2 H), 6.70–6.72 (m, 2 H), 6.95–6.98 (AA′BB′m, 2 H), 7.62–7.65 (AA′BB′m, 2 H), 8.65 (br s, 2 H); ^{13}C NMR (CDCl$_3$) δ 43.5, 92.3, 107.4, 108.5, 117.5, 130.4, 131.8, 137.7, 141.9; MS (EI$^+$) *m/z* 348 (M$^+$, 100%), 282 (36), 145 (93). Anal. Calcd. for C$_{15}$H$_{13}$N$_2$I: C, 51.7; H, 3.8; N, 8.05. Found: C, 51.7; H, 3.8; N, 8.1.

5-(3-Iodophenyl)dipyrromethane (16). Pyrrole (25.0 mL, 360 mmol) and 3-iodobenzaldehyde (3.30 g, 14.4 mmol) were reacted by the general procedure (distilled at 170–180 °C (0.03 mmHg); crystallized from ethyl acetate/hexanes; recrystallized from ethanol) giving **16** (1.97 g, 40%) as yellow crystals: mp 102–103 °C; ^{1}H NMR (CDCl$_3$) δ 5.41 (s, 1 H), 5.90 (m, 2 H), 6.16 (m, 2 H), 6.71 (m, 2 H), 7.02–7.07 (m, 1 H), 7.17 (m, 1 H), 7.58–7.61 (m, 2 H), 7.93 (br s, 2 H); ^{13}C NMR (CDCl$_3$) δ 43.4, 94.5, 107.4, 108.4, 117.5, 127.6, 130.3, 131.6, 136.0, 137.2, 144.4; MS (EI$^+$) *m/z* 348 (M$^+$, 68%), 282 (24), 145 (100). Anal. Calcd. for C$_{15}$H$_{13}$N$_2$I: C, 51.7; H, 3.8; N, 8.05. Found: C, 51.7; H, 3.6; N, 7.9.

5-(4-Fluorophenyl)dipyrromethane (17). Pyrrole (50.0 mL, 720 mmol) and 4-fluorobenzaldehyde (3.57 g, 28.8 mmol) were reacted by the general procedure (distilled at 190 °C (0.08 mmHg); recrystallized from ethanol) giving **17** (1.93 g, 28%) as colorless crystals: mp 81 °C; ^{1}H NMR (CDCl$_3$) δ 5.44 (s, 1 H), 5.88 (m, 2 H), 6.15 (q, J = 2.8 Hz, 2 H), 6.67 (m, 2 H), 6.98 (m, 2 H), 7.17 (m, 2 H), 7.90 (br s, 2 H); ^{13}C NMR (CDCl$_3$) δ 43.1, 107.2, 108.4, 115.1, 115.4, 117.4, 129.7, 129.8, 132.3, 137.7, 160.1, 163.3; MS (EI$^+$) *m/z* 240 (M$^+$, 100%), 174 (54), 145 (87). Anal. Calcd. for C$_{15}$H$_{13}$FN$_2$ C, 75.0; H, 5.45; N, 11.7. Found: C, 74.8; H, 5.55; N, 11.6.

5-(Pentafluorophenyl)dipyrromethane (18). Pyrrole (25.0 mL, 360 mmol) and pentafluorobenzaldehyde (1.76 mL, 14.4 mmol) were reacted by the general procedure (distilled at 150–160 °C (0.03 mmHg)) giving **18** (2.92 g, 65%) as colorless crystals: mp 131–132 °C; ^{1}H NMR (CDCl$_3$) δ 5.90 (s, 1 H), 6.02 (m, 2 H), 6.16 (q, J = 2.9 Hz, 2 H), 6.72–6.75 (m, 2 H), 8.15 (br s, 2 H); ^{13}C NMR (CDCl$_3$) δ 33.0, 107.6, 108.6, 118.1, 128.1; MS

(EI$^+$) *m/z* 312 (M$^+$, 100%), 246 (53), 145 (79), 67 (32). Anal. Calcd. for C$_{15}$H$_9$N$_2$F$_5$: C, 57.7; H, 2.9; N, 9.0. Found: C, 57.45; H, 2.7; N, 8.9.

5-(2,6-Dichlorophenyl)dipyrromethane (19). Pyrrole (25.0 mL, 360 mmol) and 2,6-dichlorobenzaldehyde (2.58 g, 14.4 mmol) were reacted by the general procedure (distilled at 175–190 °C (0.03 mmHg)) giving **19** (1.63 g, 39%) as yellow crystals: mp 102–103 °C; ^{1}H NMR (CDCl$_3$) δ 6.06 (m, 2 H), 6.19 (q, J = 3.0 Hz, 2 H), 6.49 (s, 1 H), 6.72–6.73 (m, 2 H), 7.11–7.16 (t, J = 7.9 Hz, 1 H), 7.31–7.34 (d, J = 7.9 Hz, 2 H), 8.28 (br s, 2 H); ^{13}C NMR (CDCl$_3$) δ 40.0, 107.4, 108.6, 116.9, 128.5, 129.3, 129.6, 135.8, 137.1; MS (EI$^+$) *m/z* 290 (M$^+$, 68%), 188 (29), 145 (100). Anal. Calcd. for C$_{15}$H$_{12}$N$_2$Cl$_2$: C, 61.9; H, 4.15; N, 9.6. Found: C, 61.7; H, 4.1; N, 9.6.

5-(4-Nitrophenyl)dipyrromethane (20). Pyrrole (25.0 mL, 360 mmol) and 4-nitrobenzaldehyde (2.23 g, 14.4 mmol) were reacted by the general procedure. However, the crude product was not distilled but was crystallized from ethyl acetate–hexanes and then recrystallized from ethanol giving **20** (2.16 g, 56%) as green crystals: mp 159–160 °C; ^{1}H NMR (CDCl$_3$) δ 5.58 (s, 1 H), 5.87 (s, 2 H), 6.17 (q, J = 2.9 Hz, 2 H), 6.74 (m, 2 H), 7.36 (AA′BB′m, 2 H), 8.01 (br s, 2 H), 8.15 (AA′BB′m, 2 H); ^{13}C NMR (CDCl$_3$) δ 43.7, 107.8, 108.7, 117.9, 123.8, 129.2, 130.8, 146.9, 149.6; MS (EI$^+$) *m/z* 267 (M$^+$, 89%), 201 (34), 145 (100), 67 (31). Anal. Calcd. for C$_{15}$H$_{13}$N$_3$O$_2$: C, 67.4; H, 4.9; N, 15.7. Found: C, 67.1; H, 4.95; N, 15.5.

5,5-Dimethyldipyrromethane (21). Pyrrole (87.0 mL, 1.25 mol) and acetone (3.70 mL, 50.0 mmol) were reacted by the general procedure (distilled at 120–130 °C (0.03 mmHg)) giving **21** (4.57 g, 53%) as colorless crystals: mp 56 °C; ^{1}H NMR (CDCl$_3$) δ 1.65 (s, 6 H), 6.10 (m, 2 H), 6.14 (m, 2 H), 7.78 (br s, 2 H); ^{13}C NMR (CDCl$_3$) δ 29.3, 35.3, 103.7, 107.7, 117.1, and 139.1; MS (EI$^+$) *m/z* 174 (M$^+$, 41%), 159 (100), 92 (47). Anal. Calcd. for C$_{11}$H$_{14}$N$_2$: C, 75.8; H, 8.1; N, 16.1. Found: C, 75.5; H, 8.1; N, 15.9.

Dipyrromethane (22). A suspension of paraformaldehyde (1.73 g, 57.7 mmol) in pyrrole (100 mL, 1.44 mol) was placed in a 250-mL two-necked round-bottomed flask equipped with an internal thermometer and a water condenser in the reflux position. The solution was heated to 50 °C, and then the heat source was removed and TFA (444 μL, 5.77 mmol) was added immediately. A sharp increase in the temperature of the solution was observed (to ca. 70 °C), and the solution rapidly became clear and dark. After 5 min the reaction was quenched and the product was purified following the general procedure (distilled at 110 °C (0.04 mmHg); recrystallized from ethanol:water 1:1) giving **22** (3.48 g, 41%) as colorless crystals: mp 75 °C; ^{1}H NMR (CDCl$_3$) δ 3.96 (s, 2 H), 6.03 (m, 2 H), 6.15 (q, J = 2.9 Hz, 2 H), 6.64 (m, 2 H), 7.81 (br s, 2 H); ^{13}C NMR (CDCl$_3$) δ 26.1, 106.4, 108.1, 117.3, 129.1; MS (EI$^+$) *m/z* 146 (M$^+$, 100%), 80 (40), 67 (27). Anal. Calcd. For C$_9$H$_{10}$N$_2$ C, 73.9; H, 6.9; N, 19.2. Found: C, 73.6; H, 6.9; N, 19.1.

Supporting Information Available: A gas chromatogram of the crude reaction mixture from the condensation of pyrrole and benzaldehyde; a full description of the study into factors affecting the purification procedure; X-ray structural data for **1** and **10** including complete atomic coordinates and thermal parameters, bond distances and angles. This material is available free of charge via the Internet at http://pubs.acs.org.