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One-Pot Synthesis of Asymmetric Annulated Bis(pyrrole)s

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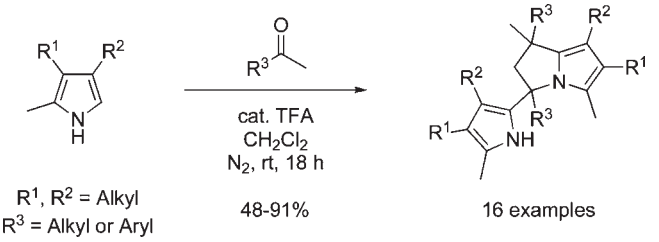
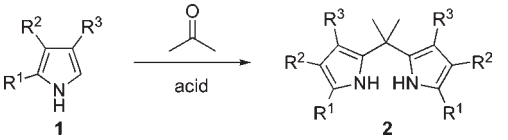
ABSTRACT



Condensation of activated functionalized pyrroles with acetone results in asymmetric bis(pyrrole)s, formed via ring annulation. The methodology is somewhat general and can be applied to a variety of ketones, as well as to a range of pyrrolic substrates that do not bear electron-withdrawing groups directly adjacent to the pyrrole ring.

Dipyrromethanes are well-known for their role in the synthesis of naturally occurring porphyrins and other polypyrrolic compounds. In recent years, meso- or 5-substituted dipyrromethanes have attracted much attention as precursors to synthetic porphyrins, as well as dipyrrins, chlorins, corroles, and calixpyrroles.[1] During the course of ongoing investigations into the synthesis and use of polypyrrolic compounds, we became interested in 5,5-dimethyldipyrromethanes (**2**, Scheme 1). Their synthesis generally involves the condensation of an excess of a pyrrole with acetone in the presence of catalytic TFA.[1] Although there are many reported conditions for this reaction, generally employing TFA or boron trifluoride diethyl etherate as the catalyst, the majority of literature examples focus on the reaction of pyrrole itself, with limited examples involving substituted pyrroles.[2−5]

Scheme 1. Synthesis of 5,5-Dimethyldipyrromethanes



Our initial work with reactions of this type focused on the use of pyrroles (**1**) bearing conjugated (and thereby deactivating) esters in the 2- or 3-positions and resulted in the corresponding dimethyldipyrromethanes as hoped. However, employing a pyrrole that is not deactivated by such conjugation (**3a**) (Scheme 2) gave an asymmetric material containing two unique pyrrolic rings. Although an azafulvene/pyrrole dimer was previously suggested as a minor byproduct in an analogous reaction,[5] the spectroscopic data did not support this assignment in our case.

Reaction of pyrrole **3a** with deuterated acetone generated the analogous deuterated product. Comparison of the ^{1}H NMR spectra obtained for both compounds (Figure 1) revealed the acetone-derived peaks for the two compounds.

Successful crystallization of the deuterated product enabled analysis of the new compound using X-ray crystallography (Figure 2). This revealed the structure of the

(1) Laha, J. K.; Dhanalekshmi, S.; Taniguchi, M.; Ambroise, A.; Lindsey, J. S. *Org. Process Res. Dev.* **2003**, *7*, 799–812.
(2) Boev, N. V.; Ustynyuk, Y. A. *Russ. J. Org. Chem.* **2007**, *43*, 297–304.
(3) Reisinger, A.; Bernhardt, P. V.; Wentrup, C. *Org. Biomol. Chem.* **2004**, *2*, 246–256.
(4) Swartz, D. L., II; Odom, A. L. *Organometallics* **2006**, *25*, 6125–6133.
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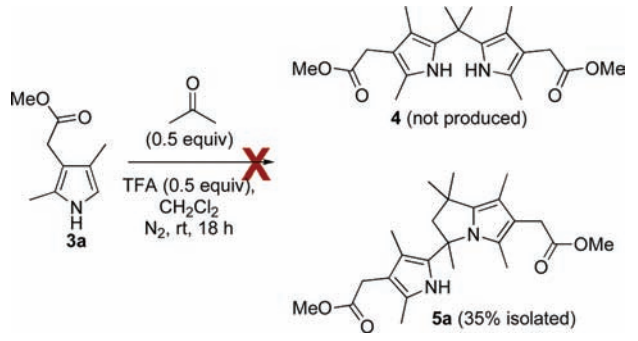
Scheme 2. Unexpected Formation of Annulated Product



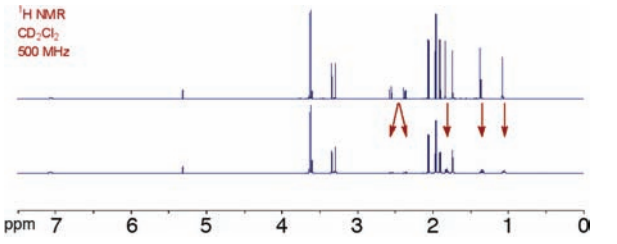


Figure 1. ^{1}H NMR spectra obtained from reaction of **3a** with acetone (top) and deuterated acetone (bottom).

asymmetric product to be that of **5a**; in essence, two equivalents of acetone had condensed with two equivalents of the pyrrole to generate an asymmetric bis(pyrrole) featuring a fused pyrrole−pyrrolidine ring system akin to that found in the naturally occurring antiparasitic bis(indolic) alkaloids isoborreverine and dimethylisoborreverine.[6]

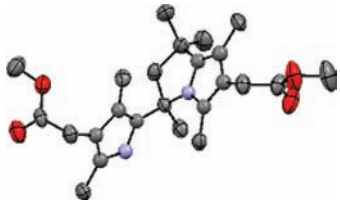
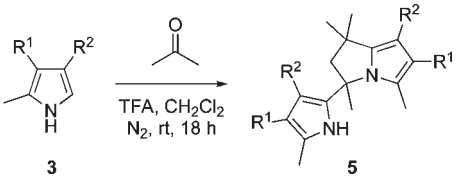


Figure 2. Confirmed structure of isolated compound (ellipsoid diagram, 50%; H/D atoms removed for clarity).

Confirmation of the structure allowed for the optimization of the reaction by using the necessary stoichiometry of reactants. Using a 1:1 ratio of pyrrole **3a** and acetone thus resulted in a significantly improved yield of **5a** (86%, Table 1, entry 1) after purification over neutral alumina as opposed to silica gel, as **5a** was observed to be acid-sensitive.

Table 1. Application of Annulation to Various Pyrroles[a]



entry	R^1	R^2	yield (%)[b]
1	CH_2CO_2Me	Me	86 (**5a**)
2	H	Me	85 (**5b**)
3	Me	Me	79 (**5c**)
4	Et	Me	85 (**5d**)
5	$(CH_2)_2CO_2Me$	Me	87 (**5e**)
6	$(CH_2)_4CH_3$	Me	56 (**5f**)
7	$(CH_2)_7CH_3$	Me	51 (**5g**)
8	$(CH_2)_7CO_2Me$	Me	65 (**5h**)
9	$(CH_2)_8OH$	Me	51 (**5i**)
10	Me	Et	83 (**5j**)
11	Et	Et	51 (**5k**)

[a] All reactions involve a 1:1 ratio of pyrrole/acetone, with 0.5 equiv TFA. [b] Isolated yield.

To examine the scope of this unusual annulation reaction, we examined a variety of activated α-free pyrroles. In all cases, the now expected annulation reaction successfully generated annulated bis(pyrrole)s in generally very good yields (**5a**−**k**, Table 1). However, it is important to note that these compounds are somewhat unstable and begin to show visible signs of degradation from a yellow to a brown oil within 24 h of purification unless dried thoroughly and stored at −20 °C under nitrogen. Our immediate purification of the crude products over neutral alumina ensured accurate yields.

With this success, we investigated whether the presence of an acyl stabilizing group would allow for this unusual annulation to take place or whether a *meso*-dimethyldipyrromethane would result. We also investigated the effectiveness of indole in this reaction. In both cases, the corresponding dipyrromethane (**6** and **7**) was found to result in yields of 75 and 68%, respectively (Figure 3). This was surprising in the case of indole, because substituted indoles have been reported to undergo a similar type of annulation to that described here, under conditions of excess HCl in isopropyl alcohol,[7] with there being no previous reports of the dipyrromethane analog **7** (i.e., indole itself has not previously been employed as a substrate). The indole-based substrates in the literature examples possess several electron-donating groups. It is thus logical to conclude that the electron-rich nature of the

(6) Fernandez, L. S.; Sykes, M. L.; Andrews, K. T.; Avery, V. M. *Int. J. Antimicrob. Agents* **2010**, *36*, 275–279.

(7) Wood, K.; Black, D. S.; Kumar, N. *Aust. J. Chem.* **2010**, *63*, 761–770.

starting material is imperative for a substrate to undergo this annulation reaction.

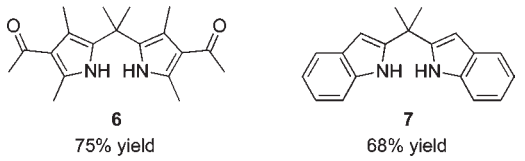
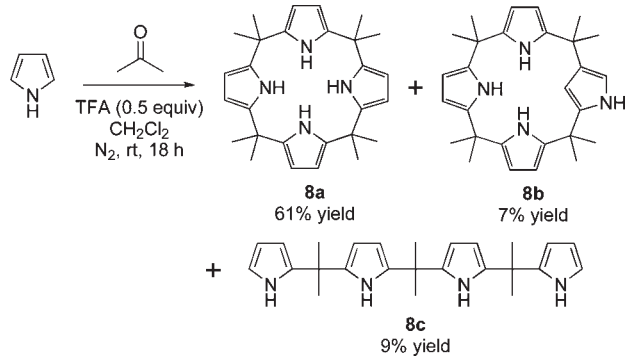


Figure 3. Dipyrromethanes resulting from use of a stabilized pyrrole and indole.

The final substrate examined was pyrrole itself, which was of interest after reading a report that an unusual annulation reaction was observed following reaction with acetylacetone.[8] However, we found that reaction with acetone gave the calix[4]pyrrole (**8a**) in a 61% yield along with the confused calix[4]pyrrole (**8b**)[9] and a linear tetrapyrrole (**8c**)[10] as minor products (Scheme 3).

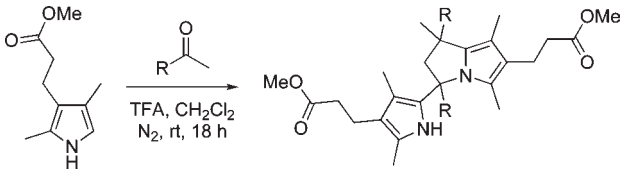
Scheme 3. Reaction of Pyrrole with Acetone



We next turned our attention to the nature of the carbonyl compound (Table 2). We chose to use pyrrole **3e** as our model substrate, as this had given the best yield in earlier studies (Table 1, entry 5), and it also appeared to be among the most stable, being one of the few α-free pyrroles examined that existed in the solid state at room temperature.

This study established the scope of carbonyl compounds able to bring about this unusual type of pyrrole annulation. Following our previous success with acetone (Table 2, entry 2) and cognizant that a methyl group was required to install the pyrrolidine-type ring, we examined acetyl-based carbonyl compounds. The simplest of these was acetaldehyde (Table 2, entry 1), which did not react in a similar manner. This was not surprising, as under acidic

Table 2. Reaction of **3e** with Various Carbonyl Compounds



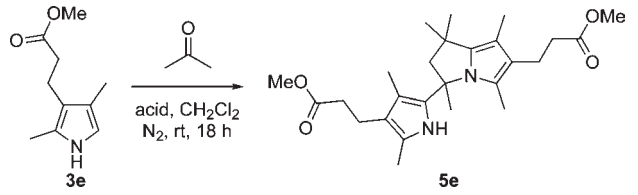
entry	R	product yield (%)[a]	recovered starting material (%)
1	H	0	0[b]
2	CH_3	87 (**5e**)	0
3	CF_3	48[c,d] (**9**, 1.0:0.7)	0
4	Et	60[d] (**10**)	0
5	^{t}Bu	0	19[b,e]
6	NMeOMe	0	34[b,e]
7	NMePy	0	91[b,f]
8	C_6H_5	91[d] (**11**, 1.0:0.8)	0
9	4-OMe-C_6H_4	87[d] (**12**, 1.0:0.9)	0
10	4-Cl-C_6H_4	76[d] (**13**, 1.0:0.6)	0

[a] Isolated yield. [b] Decomposition observed. [c] Reaction carried out at −10 °C. [d] Mixture of isomers. [e] Pyrrole **3e** recovered. [f] Ketone recovered.

conditions aldehydes and activated α-free pyrroles have the propensity to polymerize. Maintaining the acetone skeleton but varying one of the methyl groups to a trifluoromethyl group was successful (Table 2, entry 3). Slightly increasing the steric bulk on one side of the ketone to an ethyl group met with a lack of regioselectivity (Table 2, entry 4), with two products isolated in a combined yield of 43%; the complexity of the ^{1}H NMR spectra prevented assignment of the respective structures. Further increasing the size of the substituent group was not successful (Table 2, entries 5−7), with the starting material recovered in all cases. We then examined the use of acetophenone (Table 2, entry 8), which has been reported to be successful in the annulation of electron-rich indoles.[7] Pleasingly, we obtained the desired fused bis(pyrrole) (**11**), isolated in a 91% yield. Analysis of this arylated analogue (**11**) using ^{1}H NMR spectroscopy revealed the presence of two diastereoisomers (see the Supporting Information), and these were not separable using column chromatography. Further aryl substituents were examined, bearing electron-donating (Table 2, entry 9) and electron-withdrawing (Table 2, entry 10) groups. In both cases, the expected annulation gave good yields, with the products again appearing to be a mixture of stereoisomers. It was also noted that while the presence of an electron-withdrawing group seemed to enhance the stability of the product (**13**), electron-rich substituents greatly reduced the stability of the products (**11** and **12**), resulting in visible degradation beginning within an hour of purification: this observation is consistent with the nature of α-free pyrroles, because electron-withdrawing groups provide significantly enhanced stability.

(8) Mahanta, S. P.; Panda, P. K. *Tetrahedron Lett.* **2009**, *50*, 890–892.
(9) Nishiyabu, R.; Palacios, M. A.; Dehaen, W.; Anzenbacher, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11496–11504.
(10) Raghavan, K. V.; Kulkarni, S. J.; Kishan, M. R.; Srinivas, N.; (Council of Scientific and Industrial Research, India). Preparation of substituted calyx[4]pyrroles over molecular sieve catalysts. WO 2002068426 A1 20020906, 2002.

Table 3. Variation of Acid Catalyst



entry	acid	equiv	yield (%)[a]
1	TFA	0.5	87
2	TFA	0.1	85
3	MsOH	0.5	48
4	Conc. HCl	0.5	52
5[b]	$BF_3 \cdot OEt_2$	0.5	81

[a] Isolated yield. [b] Anhydrous reaction conditions employed.

Our final study concerned the nature of the acid used to catalyze the reaction. We examined the reaction of pyrrole **3e** with acetone in the presence of various acids (Table 3). In all four cases, the annulated bis(pyrrole) (**5a**) was the major isolated product in reasonable yield. However, TFA remained optimal with regard to this transformation. The effect of reducing the amount of TFA to just 0.1 equiv was also examined (Table 3, entry 2), whereby the desired product was still obtained in high yield. In summary, an unusual annulation of a range of activated pyrroles with acetone has been observed. The resulting asymmetric annulated bis(pyrrole)s, not previously described, were obtained in good to excellent yield and the reaction was found to be applicable to various ketones. The core structure of these compounds is similar to that of the naturally occurring indolic alkaloids isoborreverine and dimethylisoborreverine, recently shown to have antiparasitic activity.[6] Mechanistic studies are underway.

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Supporting Information Available. Experimental procedures, NMR characterization data for all previously unpublished compounds, and crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.