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Facile Synthesis of Unsubstituted β,β'-Linked Diformyldipyrromethanes

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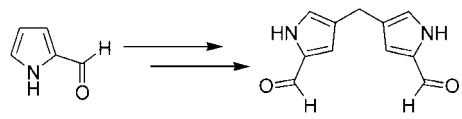

Unsubstituted β,β'-linked diformyldipyrromethanes are promising precursors for the synthesis of novel poly dipyrromethene ligands and N-confused porphyrins. A strategy has been developed to selectively synthesize unsubstituted β,β'-linked diformyldipyrromethanes in moderate yields starting from 2-formylpyrrole.

It is well-known in pyrrole chemistry that the α position dominates in most electrophilic reactions. As a result, the synthesis of α,α′-linked species such as dipyrromethanes[1] is rather facile, while selectively setting up a linker at a β position has remained a synthetic challenge. Exploration into the synthesis of novel β,β'-linked synthons increases the structural variety and thus the number of applications in porphyrin and other chemistries. For example, unsubstituted β,β'-linked diformyldipyrromethanes are precursors of interesting α-free bis(dipyrromethene) ligands[2] for supra-molecular chemistry.[3] They are also potential precursors of N-confused porphyrins (NCPs)[4] (Figure 1), which have attracted increasing attention due to their unique properties.[5] For these reasons, we have investigated methods of selectively preparing unsubstituted β,β'-linked diformyldipyrromethanes.

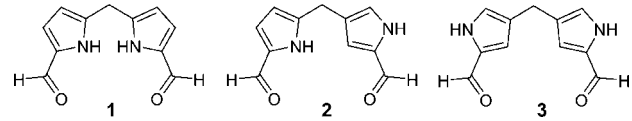

FIGURE 1. Unsubstituted β,β'-linked diformyldipyrromethane **3** and its configurational isomers.

To direct a linker to the β position, β,β'-linked dipyrromethanes are normally prepared using α-blocked pyrroles as starting materials.[6] However, α-substituted dipyrromethanes are usually not suitable for NCP synthesis because the crowding caused by substituents discourages formation of conjugated macrocycles.[7] Since removing α-substituents can present a significant challenge, this route is limited to the synthesis of unsubstituted β,β'-linked dipyrromethanes. The isolation of β,β'-linked *meso*-substituted dipyrromethanes was reported by Sessler and his colleagues,[8] but these compounds only occur as minor byproduct in the condensation reactions of aldehyde and pyrrole. As a result, efficient synthetic pathways to unsubstituted β,β'-linked dipyrromethanes and related derivatives have not been well developed.

To circumvent both the pitfalls of α-blocked starting materials and the reactive α-position, we chose a strategy of reducing the reactivity of the α-position, which eventually led us to using protected 2-formylpyrrole as a precursor. 1-(Pyrrol-2-ylmethylene) pyrrolidinium perchlorate **5**,[9] an iminium salt of 2-formylpyrrole **4**, was an attractive candidate. It was previously used to prepare β-halogenated compounds[10] and the positively charged α-group exhibited an exclusively β-directing effect in halogenation reactions. Furthermore, using **5** as substrate also has advantages such as quantitative conversion from commercially available **4**, protection of the reactive formyl group, and facile regeneration of the formyl group.[10]

The β,β'-linked diformyldipyrromethane **3** was initially synthesized from iminium salt **5** and dimethoxymethane at room temperature following a modified procedure for acid-catalyzed condensation of aldehyde and pyrrole[1]a (Scheme 1). After column chromatography, β,β'-linked **3** was obtained as a white powder with a 25% yield, while 50−60% of 2-formylpyrrole was recovered. Although the yield was not high, this reaction was highly regioselective with no undesired α,α′-linked or α,β'-linked products being produced.

The β,β'-linked structure of compound **3** was characterized by ^{1}H NMR spectroscopy. Both the chemical shifts and coupling pattern of **3** exhibited characteristics distinct from authentic α,α′-

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(8) Dolenský, B.; Kroulík, J.; Král, V.; Sessler, J. L.; Dvoøáková, H.; Bouø, P.; Bernátková, M.; Bucher, C.; Lynch, V. *J. Am. Chem. Soc.* **2004**, *126*, 13714–13722.

(9) Perchlorates are known as oxidizers and explosives. Although the authors found **5** is safe under the reaction conditions, safety precautions are necessary.

(10) (a) Sonnet, P. E. *J. Org. Chem.* **1971**, *36*, 1005–1007. (b) Mitsui, T.; Kimoto, M.; Sato, A.; Yokoyama, S.; Hirao, I. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4515–4518.

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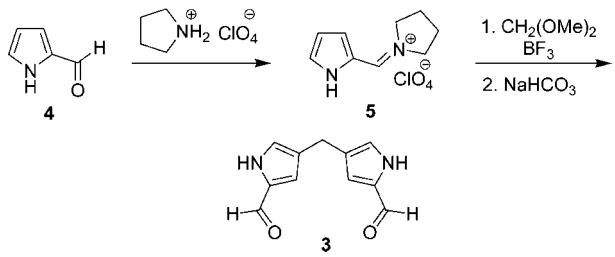
SCHEME 1. Synthesis of *β*,*β*′-Linked Diformyldipyrromethane 3



linked **1**.[11] In d_6-DMSO, two broad singlets (7.04 and 6.82 ppm) were observed for **3** in the aromatic region (Figure 2) and thus the linker must be located at the β positions.[12] To confirm its structure, a single crystal of **3** was grown by vapor diffusion of hexane into a THF solution. X-ray diffraction analysis confirmed a β,β'-linked structure as expected.[13]

To optimize the formation of **3**, reaction conditions such as acid catalysts, reaction temperature and solvents were surveyed. It was found that other Lewis acids including tin(IV) chloride, titanium(IV) chloride, indium(III) chloride and ytterbium(III) triflate were not able to facilitate the formation of **3**; aluminum chloride did catalyze the reaction, to produce **3**, but in much lower yield (<2%). Brønsted acids such as trifluoroacetic acid, methanesulfonic acid, *p*-toluenesulfonic acid and sulfuric acid could not replace $BF_3 \cdot OEt_2$. Increasing the reaction temperature from 25 to 80 °C increased the yield of β,β'-linked product (**3**). Unfortunately, undesired α,α′-linked or α,β'-linked side-products (**1** or **2**) were observed when the temperature was higher than 65 °C. The reactions could be carried out in either methylene chloride, chloroform or acetonitrile, but solubility was better in acetonitrile, which was deemed the preferred solvent. Acetone, however, is to be avoided for the reaction since it was found that **5** reacted with acetone to form a new species **6**,[14] similar to a reaction reported by Johnson and his colleagues[15] using dipyrromethenes. Under the optimal conditions for the reaction, **3** could be obtained in a 30% yield and over 60% of **4** was recovered. Attempts to increase the yields by using microwave irradiation or other protecting groups were also made. Unfortunately, microwave irradiation didn't improve the yields and less electron-withdrawing protecting groups such as cyanovinyl always led to the formation of α,α′-linked products. The advantage of the iminium group is its strong electron-withdrawing character which results in the high regioselectivity but also accounts for the low reactivity.

This method for the synthesis of unsubstituted β,β'-linked diformyldipyrromethanes is applicable to a wide range of aryl acetals and aliphatic acetals (Table 1). Several interesting phenomena were observed in the experiments:

(1) The relative reactivities of reactants toward **5** followed the sequence: aromatic acetals > aliphatic acetals ≫ aldehydes.[16] Additionally, aromatic acetals with electron-withdrawing group(s) were relatively more productive than those with electron-donating group(s).

(2) Ketals were unreactive with **5** under the same conditions.

(3) The formation of **10** was retarded and the yield was low probably due to steric hindrance (entry 4 in Table 1).

(4) Preparation of **15** should not be performed in acetonitrile. For some unknown reason, the expected product was not obtained in acetonitrile while a good yield was achieved in chloroform (entry 9 in Table 1).

The mechanism of Lewis-acid-promoted nucleophilic substitution reactions of acetals can be either S_N1 or S_N2 depending on reaction conditions and substrates.[17] The reactions discussed here were performed in polar solvents and thus likely occurred via an S_N1 mechanism.[18] The high reactivities of acetals over corresponding aldehydes are in accordance with the studies made by Mayr et al.[19]

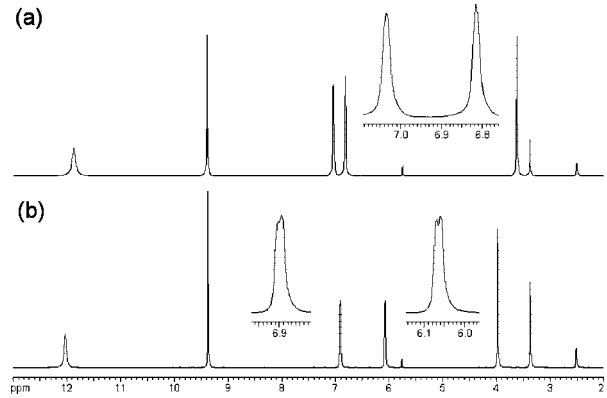
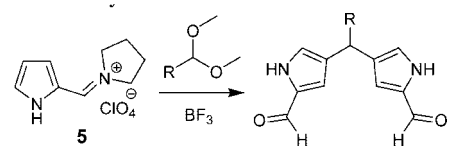


FIGURE 2. ^{1}H NMR spectra of (a) **3** and (b) **1** in d_6-DMSO.

TABLE 1. Acid-Catalyzed Condensations of Acetals and Iminium Salt 5



entry	R	*T* (°C)	time (h)	product	yield (%)
1	Ph_5	60	10	**7**	45.7
2	C_6F_5	60	10	**8**	40.8
3	4-MeOPh	60	10	**9**	37.6
4	2,4,6-Me_3Ph	60	48	**10**	16.9
5	4-(NO_2)Ph	60	10	**11**	68.1
6	4-$(MeCO_2)$Ph	60	10	**12**	55.1
7	4-ClPh	60	10	**13**	39.1
8	4-MePh	60	10	**14**	34.9
9[a]	2,6-Cl_2Ph	60	10	**15**	35.3
10	Me	60	10	**16**	25.0
11	H	60	10	**3**	29.7
12	H	20	10	**3**	25.0

[a] Acetonitrile was used as solvent except for entry 9 where chloroform was used.

(11) Taniguchi, M.; Balakumar, A.; Fan, D.; McDowell, B. E.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2005**, *9*, 554–574.

(12) Interestingly, split peaks were observed for **3** in d_3-acetonitrile which might be attributed to intramolecular hydrogen bonding; nevertheless, the chemical shifts still showed an obvious difference from those of authentic **1**. Peak-assignments for α and β-Hs were based on the HH COSY NMR data. See Figure S30 in the Suppporting Information.

(13) See the Supporting Information.

(14) The structure of **6** was confirmed by X-ray crystallography. See the Supporting Information.

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(16) Aldehydes give less than 10% yields of products.

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In conclusion, we have established an efficient method of preparing novel unsubstituted β,β'-linked diformyldipyrromethanes. Although the yields are not outstanding, considering the high selectivity, recoverability of unconverted reactants and the fact that there is no other known method to make such compounds, this method represents a promising route to the preparation of various synthons for N-confused porphyrins and novel polydipyrromethene ligands. Studies on the application to porphyrin and supramolecular chemistry are currently underway.

Experimental Section

General Procedure for Synthesis of β,β'-Linked Diformyl-Dipyrromethanes: Synthesis of 4,4′-Methylenebis(1H-pyrrole-2-carbaldehyde) (3). A solution of **5** (2.48 g, 10 mmol) and dimethoxymethane (5 mmol) in anhydrous acetonitrile (50 mL) was treated with boron trifluoride diethyl etherate (1 mL, 1.2 equiv) and heated at 60 °C for 10 h. The reaction was quenched with aqueous $NaHCO_3$ and the solution was extracted with ethyl acetate (2×100 mL). After drying over anhydrous Na_2SO_4 and evaporation, the reaction mixture was separated by column chromatography on silica gel. Using CH_2Cl_2 initially as eluent, unreacted pyrrole-2-carboxaldehyde **4** was recovered. Further elution with ethyl acetate/methylene chloride (1:4 v:v) provided **3** as white crystals: mp 153−154 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 11.87 (br s, 2H, NH), 9.39 (s, 2H, CHO), 7.04 (s, 2H, β-H), 6.82 (s, 2H, α-H), 3.62 (s, 2H, *meso*-CH_2); ^{1}H NMR (300 MHz, CD_3CN) δ 9.93 (br s, 2H, NH), 9.42 (d, $J = 0.7$ Hz, 2H, CHO), 6.97 (m, 2H, β-H), 6.82 (m, 2H, α-H), 3.69 (s, 2H, *meso*-CH_2); ^{13}C NMR (75 MHz, d_6-DMSO) δ 178.9, 132.6, 125.7, 125.3, 119.9, 23.5. MS (EI) *m*/*z* 202 (M^+). Elemental Anal. calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.53; H, 5.15; N, 14.00.

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Supporting Information Available: Experimental procedures, spectroscopic data, and data for the X-ray diffraction analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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