Notes

Convenient Synthesis of Dipyrromethanes Containing Heteroatoms Other than Nitrogen

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Advances in porphyrin-based model systems are closely tied to the development of synthetic methods of porphyrins. We have sought to develop a synthetic method for asymmetric porphyrins with different meso-substituents. As a part of these efforts, we recently have reported the synthesis of meso-substituted, 1,9-unsubstituted dipyrromethanes in a single step.[1] A few reports have emerged[2] for the direct synthesis of dipyrromethanes thereafter. But the direct synthesis of 1,14-unsubstituted tetrahydrotripyrrins containing heteroatoms other than nitrogen have not developed. The tetrahydrotripyrrins containing heteroatoms other than nitrogen could be obtained by condensing 2,5-bis(α-hydroxymethyl)pyrrole, furan and thiophene in excess pyrrole in the presence of acid catalyst. The easy availability of dipyrromethanes or tetrahydrotripyrrins could play a key role in the regioisomerically pure synthesis of porphyrins and related macrocyclic systems. Although porphyrin is easily obtainable from pyrroles and an aldehydes, generic methods are still limited to symmetric porphyrins because the mixed condensations usually resulted in many mixture of isomeric porphyrins and consequent difficulties in separation and identification. Methods currently available have major limitation in placing different substituents selectively at four meso-positions or in placing different ligand-containing unit selectively at the core of the porphyrins. Thus, methods for the synthesis of meso-substituted porphyrins with predesignated orientation of core-ligand or meso-substituents still need to be developed, especially in creating sophisticated models of porphyrin-based enzymes as well as medicinal applications.
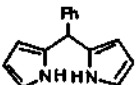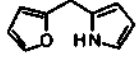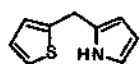
In spite of increasing attentions toward the chemistry of ligand-modified porphyrins, the synthetic methods for those porphyrins have not well established. Currently available synthetic approaches are only applicable in the symmetric modification of the two among the four nitrogen ligands.[3] Since easy access to 1,9-unsubstituted dipyrromethanes containing heteroatoms other than nitrogen is crucial in the synthesis of custom-made porphyrins, we pursued a synthesis of ligand modified dipyrromethanes and tetrahydrotripyrrins. Development of the convenient synthetic method of these unit will be able to synthesize porphyrins with predesignated orientation of different heterocycles. We hereby report a selective synthesis of dipyrromethanes containing heteroatoms other than nitrogen and modified tetrahydrotripyrrins by the reaction of pyrrole and α-hydroxymethylated aromatics in the presence of acid catalysts.
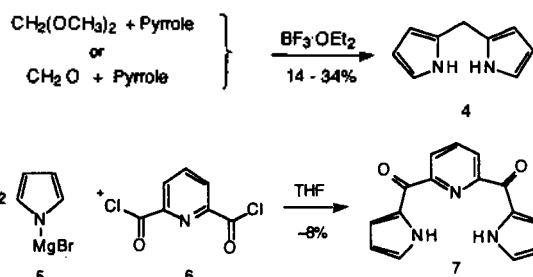
Results and Discussion

It has been well known that aldehydes and pyrrole readily undergo acid-catalyzed condensation.[4] Due to the high reactivity of pyrrole toward nucleophilic addition, the normal condensation usually gave the mixture of oligomeric or polymeric condensation products instead of dipyrromethane. But 1,9-unsubstituted, meso-substituted dipyrromethanes was obtained by performing the condensation in pyrrole in the presence of Lewis acid catalyst.[1] Easy availability of dipyrromethanes enabled the regioselective synthesis of transsubstituted porphyrins and porphyrins bearing four different meso-substituents.[5] The fact that dipyrromethanes could be obtained from the reaction of 2-(α-hydroxymethyl)pyrrole in the presence of excess pyrrole[4] indicates that the condensation of aldehydes and pyrrole must proceed *via* 2-(α-hydroxymethyl)pyrrole as an intermediate. Thus, the same analogy can be applied to the synthesis of dipyrromethanes containing heteroatoms other than nitrogen. If 2-α-Hydroxymethylfuran, 2-α-hydroxymethylthiophene and 2-α-hydroxymethylbenzene condense with pyrrole in the presence of acid catalyst, the products will be the corresponding dipyrromethanes. The same methodology has been applied for the synthesis of tetrahydrotripyrrins.[6] Indeed, this was the case. Stirring a solution of 2-(a-hydroxymethyl)furan in 20 times excess pyrrole with $BF_3 \cdot OEt_2$ for 45 min at 10 °C afforded dipyrromethane **2** in 21% yield. Washing the reaction mixture with base (0.1 M aqueous NaOH) immediate after the reaction seemed to be critical. Otherwise extensive decomposition was observed. The crude product was obtained by removing excess pyrrole under vacuum after washing the reaction mixture with 0.1 M NaOH solution. Then column chromatography on silica usually afforded the pure product. This method has been applied to the synthesis of a variety of dipyrromethanes as shown in Table 1 and Scheme 1.

TLC analysis of each reaction mixture showed corresponding dipyrromethanes and tar-like material in origin which turns dark red or dark brown upon exposure to bromine vapor. The product **2** was clearly seen as purple spot upon exposure to bromine vapor. Compound **3** on the other hand turned red upon exposure to bromine vapor. Treatment of formaldehyde diethyl acetal with excess pyrrole in the presence of $BF_3 \cdot OEt_2$ also gave meso-unsubstituted dipyrromethane **4** in 38% yield. 10-Thiadipyrromethane **3** was obtained in 21% yield by reaction of 2-(α-hydroxymethyl)

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Table 1. Yields of dipyrromethanes in the presence of various catalysts

R₁	R₂	Catalyst	Yield (%)	Product
(pyrrole)	Ph	BF₃·OEt₂	95	1
		CF₃COOH	44	
		TiCl₄	39	
(furan)	H	BF₃·OEt₂	21	2
		CF₃COOH	trace	
		TiCl₄	5	
(thiophene)	H	BF₃·OEt₂	21	3
		CF₃COOH	trace	
		TiCl₄	17	

Table 2. Effect of molar ratios of starting materials and catalysts on pyrromethane yields

Compounds	Molar ratio of Ar/catalyst	Catalyst	Yield**	Product
R₁ = (furan) R₂ = H	1/0.5	BF₃·OEt₂	12	
	1/1.5	BF₃·OEt₂	21	
	1/3.0	BF₃·OEt₂	5	2
	1/0.5	*TiCl₄	5	
	1/1.5	*TiCl₄	5	
R₁ = (thiophene) R₂ = H	1/0.5	*TiCl₄	17	3
	1/1.5	*TiCl₄	5	

*Most of the product. was polymeric material and no starting material was observed. **After chromatographic separation of crude reaction mixture.
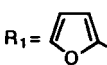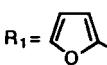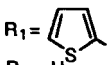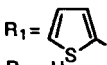

Scheme 1.

thiophene with excess pyrrole in the presence of BF₃·OEt₂. The proton nmr spectra of **1-4** showed a few distinctive feature. The meso-proton appeared at δ 3.92 ppm for **4**, at 3.98 ppm for **2** and 4.17 ppm for **3**. Six different sets of multiplet for aromatic protons were shown in **2** and **3**. Similar reaction condensing 2,6-pyridinedicarbonyl dichloride **6** with pyrrole-Grignard **5** in THF gave 2,6-bispyrrocarbonylpyridine **7** in 8% yield (Scheme 1).

As shown in Table 2, a few experiments were performed to determine the appropriate ratios of reactants to catalysts and to see any improvement in the yields. Only small amount of product is observed with 0.5 to 3.0 mole of catalyst per furfuryl alcohol. In the case of the reaction with 2-thiophenemethanol, best yield was obtained when 1.5 equivalent of acid is used. But most of the starting alcohol was recovered when trifluoroacetic acid was used as catalyst. Condensation of 2-thiophenemethanol with pyrrole in the presence of titanium(IV) chloride (0.5 mole) results in low yield of desired dipyrromethane.

The best condition we found with this limited study was using 1.5 mole of acid per reactant. Increasing the reaction temperature did not give improvement in yields. The advantages of above synthesis obviously lie in the easy access to asymmetric dipyrromethanes that could be applied to the synthesis of core-modified asymmetric porphyrins. Although the yields are not practically high, the mild reaction condition would allow us to prepare a building unit of porphyrin with various meso-substituents. The functionalization of 1,9-position of **1-4** make the customized core-mod-

ification possible in less than three steps. In order to establish synthetic generality for the preparation of porphyrin building blocks, extensive adjustment is under investigation.

Experimental

The synthesis of meso-phenyldipyrromethane **1** from the condensation of benzaldehyde and excess pyrrole was reported previously.[1] The spectroscopic data for the compound **1** synthesized in this study was identical with the authentic sample.

11-oxodipyrromethane (2). To a mixture of furanmethanol (0.98g, 10 mmol) and pyrrole (13.4 g) was added BF₃·OEt₂ (2.13 g, 15 mmol) under nitrogen atmosphere. The mixture was stirred for 45 min at 10 °C then diluted with methylene chloride (100 mL). The dark red mixture was washed with aqueous sodium hydroxide (0.1 N, 100 mL), water and dried (anhydrous Na₂SO₄). Evaporation of the solvent to dryness and column chromatographic separation on silica afforded pure product. Yield 0.31 g (21%); ¹H NMR (CDCl₃) δ 8.07 (bs, 1H, N-H), 7.33 (s, 1H, furan-9-H), 6.68 (m, 1H, pyrrole-H), 6.30 (m, 1H, pyrrole-H), 6.14 (m, 1H, furan-H), 6.05(m, 1H, furan-H), 6.02 (m, 1H, pyrrole-H), 3.97 (s, 2H, meso-H).

11-thiadipyrromethane (3). To a mixture of thiophenemethanol (1.14 g, 10 mmol) and pyrrole (13.4 g) was added BF₃·OEt₂ (2.13 g, 15 mmol) under nitrogen atmosphere. The mixture was stirred for 45 min at 10 °C then diluted with methylene chloride (100 mL). The dark brown mixture was washed with aqueous sodium hydroxide (0.1 N, 100 mL), water and dried (anhydrous Na₂SO₄). Evaporation of the solvent to dryness and column chromatographic

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separation on silica afforded pure product. Yield 0.32 g (20%); ^{1}H NMR (CDCl$_3$) δ 7.99 (bs, 1H, N-H), 7.18-7.15 (m, 1H, thiophene-H), 6.96-6.91 (m, 1H, thiophene-H), 6.85-6.83 (m, 1H, thiophene-H), 6.74-6.72 (m, 1H, pyrrole-H), 6.16-6.15 (m, 1H, pyrrole-H), 6.05 (m, 1H, pyrrole-H), 4.17 (s, 2H, meso-H).

Dipyrromethane (4). To a mixture of thiophene-methanol (0.26 g, 3.4 mmol) and pyrrole (0.46 g) was added BF$_3$·OEt$_2$ (0.48g, 3.4 mmol) under nitrogen atmosphere. The mixture was stirred for 60 min at 10 °C then diluted with methylene chloride (100 mL). The dark brown mixture was washed with aqueous sodium hydroxide (0.1 N, 100 mL), water and dried (anhydrous Na$_2$SO$_4$). Evaporation of the solvent to dryness and column chromatographic separation on silica afforded pure product. Yield 0.073 g (15%); ^{1}H NMR (CDCl$_3$) δ 7.70 (bs, 2H, N-H), 6.60-6.58 (m, 2H, pyrrole-H), 6.02 (m, 2H, pyrrole-H), 3.92 (s, 2H, meso-H).

2,6-pyrrocarbonylpyrridine (7). To a solution of pyrrole (1.32 mL, 19.6 mmol) in 15 mL THF was added a solution of ethyl magnesium bromide (3.0 M in diethyl ether solution, ~8.5 mL) until gas evolution was ceased. The mixture was stirred for 30 min at room temperature then a solution of pyridine dicarbonyl dichloride (1.0 g, 4.9 mmol) in 20 mL THF was added dropwise. The solution was stirred an additional 1 h and then diluted with 50 mL THF. The mixture was washed with 100 mL 25% NaOH, H$_2$O and dried (Na$_2$SO$_4$). The solvent was evaporated to dryness and the resulting brown solid was chromatographied on silica (ethyl acetate/hexane=5/5). Yield 0.11g (8%); ^{1}H NMR (CDCl$_3$) δ 10.65 (bs, 2H, N-H), 8.36 (d, 2H, J=8.0 Hz, Ar-3,5-H), 8.12 (t, 1H, J=8.0 Hz, Ar-4-H), 7.49-7.46 (m, 2H, pyrrole-H), 7.13-7.12 (m, 2H, pyrrole-H), 6.42-6.37 (m, 2H, pyrrole-H).

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Activated Zirconium Metal Powder Prepared by Reduction of Zirconium(IV) chloride with Lithium Promoted Coupling of Aldehydes, Ketones and Organic Halides

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Within the area of metal catalyzed or promoted organic reactions, an increasing interest is centered to the use of highly reactive metal powders which are prepared simply by the treatment of metal halides with a group I or group II elements.[1]

Although activated metal powders (Ni,[2] Zn,[1a,3] W,[4] U,[5] Th,[6] Ce,[7] Tl,[8] Cu,[9] Ti,[10] Mn[11]) prepared by this method have been employed for the reductive coupling of ketones,[10] benzoyl chloride,[12] aldehydes[13] and organic halides,[2,3,5,8,9,11] no successful examples for the use of zirconium metal to reductive coupling of carbonyls and organic halides have been reported so far. In a previous communication, we reported that activated nickel catalyzed hydrosilylation of olefin with chlorosilane[14,15] and activated metal reduced nitroarenes.[16] In this paper we describe in detail the preparation of activated zirconium slurries by the reduction of zirconium tetrachloride with lithium and the reaction of the resulting metal slurries with a aldehydes, ketones and alkyl halides.

The results of coupling reaction using activated zirconium metal powders are summarized in the Table 1. High yields and mild reaction conditions are the obvious advantage of this method. Interestingly, commercially available zirconium powder was inert for the coupling reaction (run 2). Aryl and benzyl halides coupled to give the corresponding coupling products in high yields with stirring at room temperature (run 6-9). These results show that yields are comparable to or greater than those from the cases using ordinary metals.[17] Coupling reaction of benzal chloride with activated zirconium proceeded smoothly at room temperature to give only *trans*-stilbene in 85% yield (run 10). Benzaldehyde also coupled to give only *trans*-stilbene (run 1) and *p*-anisaldehyde coupled to give only *trans*-1,2-bis(4-methoxyphenyl)ethylene (run 3). Acetophenone coupled to give a mixture of *cis* and *trans*-2,3-diphenyl-2-butene along