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Optimizing the synthesis of 5,10-disubstituted tripyrromethanes

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Abstract

Condensation of aldehydes with pyrrole in the presence of acid catalyst gave the mixture of dipyrromethanes and tripyrromethanes. The major product was switched from dipyrromethanes to tripyrromethanes according to the sequence of adding the reactants and catalyst. Higher oligomers such as tetrapyrromethane and pentapyrromethane were isolated and characterized from the reaction of 4-methoxycarbonylbenzaldehyde with pyrrole.

Keywords: dipyrromethane; tripyrromethane; tetrapyrromethane; pentapyrromethane.

meso-Substituted dipyrromethanes and 5,10-disubstituted tripyrromethanes are important precursors for the synthesis of various *meso*-substituted porphyrins,[1,2] porphyrinoid macrocycles and expanded porphyrins.[3,4] Since the initial one-flask synthesis of dipyrromethanes reported in 1994,[5] several refinements have been made in the purification and isolation of these compounds.[6,7] The synthetic method involves the acid catalyzed condensation of an aldehyde with pyrrole, wherein the suppression of polymerization is achieved by using large excess of pyrrole without any other solvents. The method has afforded high yields of 5-substituted dipyrromethanes having a variety of functional groups,[8–11] in addition to the improved purification with the elimination of the use of column chromatography. Now it is possible to synthesize multigram quantities of dipyrromethanes. The tripyrromethanes have also been important in the synthesis of *cis*-substituted porphyrins and expanded porphyrin analogues.[3,12–14] The typical one-flask synthesis of dipyrromethanes mentioned above usually resulted in the formation of tripyrromethanes **2** as minor products (Scheme 1).

As part of our efforts on the selective synthesis of tripyrromethanes (**2**), we report herein some of the results obtained from the one-flask condensation of an aldehyde with pyrrole in the presence of catalytic amount of acid. Upon examining the sequence of addition of the reagents, we found significant difference in the product composition. We also have succeeded to synthesize

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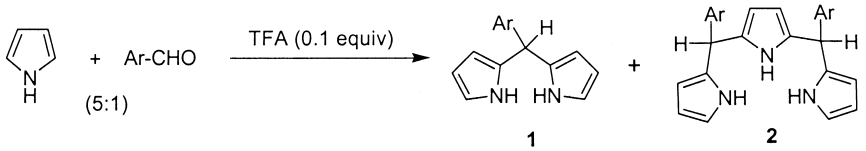


Scheme 1.

dipyrromethanes and tripyrromethanes bearing carboxylic acid or phenolic hydroxy group on the *meso*-positions.

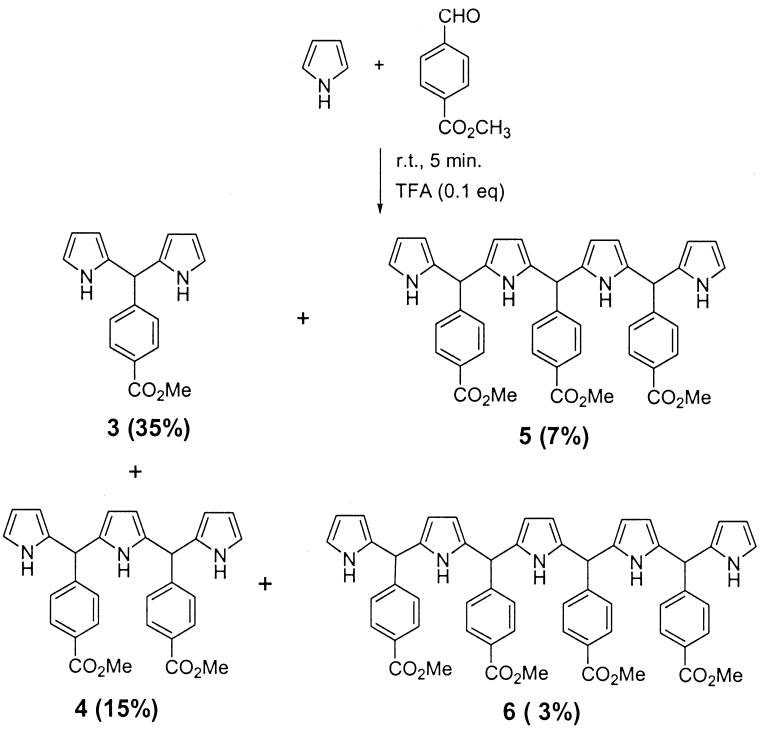
As shown in Scheme 1, we first examined the product distribution formed under the conditions involving different order of addition of starting material and catalyst: Pre-stirring of pyrrole and aldehyde (molar ratio, 5/1) for 5 min followed by addition of TFA (0.1 equiv.) at room temperature (method A) and pre-mixing of aldehydes and catalyst followed by addition of pyrrole at once (method B). The reaction was quenched with aqueous base after 5 min of the reaction. As reported by Lindsey et al.,[6] dipyrromethanes can be easily purified by vacuum distillation using Kugelrohr, we adopted the same procedure of Lindsey's and found that dipyrromethanes distilled out completely under this condition. The residual black solid remained after vacuum distillation exclusively contained tripyrromethanes and other oligomeric compounds from which the tripyrromethanes were cleanly separated by column chromatography on silica. The isolated yields of each components are listed in Table 1 and the data clearly indicated that method A gives dipyrromethanes (**1**) as the major product as usual. But method B gives tripyrromethanes (**2**) as the major

Table 1
Isolated yields of the dipyrromethanes (**1**) and tripyrromethanes (**2**). (a) Method A: aldehyde and pyrrole were mixed first and stirred for 5 min then added TFA (0.1 equiv.) at room temperature. Method B: aldehyde was mixed with acid first and stirred for 5 min then added pyrrole at once. The reaction time was 5 min in all occasions. (b) Since aldehydes were solid, method B was not tried. (c) Reaction temperature was 50°C. (d) Higher oligomeric compounds (**5**) and (**6**) were cleanly isolated as minor products (Scheme 2)

Aldehydes	Pyrrole (equiv)	Method[a]	Yield (%)	
			1	**2**
p-Anisaldehyde	5	A	42	23
	5	B	22	27
p-Tolualdehyde	5	A	42	34
	5	B	11	40
	20	A	47	36
	20	B	16	28
3-Bromobenzaldehyde	5	A	35	24
	5	B	24	48
Pentafluorobenzaldehyde	5	A	41	13
	5	B	16	44
p-Carboxybenzaldehyde	5	A[b]	18	74
4-Pyridinecarboxaldehyde	5	A	35	11
Formaldehyde (37 % aq)	5	A[c]	62	16
p-Methoxycarbonyl benzaldehyde[d]	5	A[b]	35	15

product in all the attempted cases. The reaction carried out with varying ratio of pyrrole:aldehyde from 5:1 to 20:1 gave almost identical product distribution.[15] Pre-equilibrium protonation of aldehyde before the addition of pyrrole somehow resulted in higher yields of tripyrromethane. The results of method A indicate that the protonated aldehyde may react with one molecule of pyrrole to give 2-α-hydroxypyrrole which upon dehydrative condensation with another pyrrole lead to dipyrromethane. This step must be comparably fast and thus the amount of dipyrromethane is not negligible at the early stage of the reaction. Further reaction of the dipyrromethane with aldehyde and pyrrole successively would give rise to tripyrromethane. On the other hand, if the catalyst was introduced after the aldehyde and pyrrole were combined, the predominant protonation would occur at pyrrole due to its higher basicity. Once pyrrole is protonated, it is not nucleophilic anymore. Therefore, effective concentration of acid is reduced at the early stage of the reaction.

The formation of *N*-confused dipyrromethanes and tripyrromethanes were negligible in the above reaction conditions. The reaction of *p*-carboxybenzaldehyde with pyrrole gave the highest yield of tripyrromethane. The water soluble *meso*-(4-carboxyphenyl)dipyrromethane and 5,10-di(4-carboxyphenyl)tripyrromethane were also synthesized and easily separated by adjustment of pH of the reaction mixture: The excess pyrrole was removed in vacuo then the remaining solid were combined with aqueous NaOH solution (pH 8). Then the mixture was extracted with ethyl acetate until the extract did not contain any organic material. The organic phase exclusively contained dipyrromethane and no tripyrromethane was extracted at this pH. Evaporation of the solvent afforded pure *meso*-(4-carboxyphenyl)dipyrromethane. Then, the pH of the mother liquor was adjusted to ~6 by adding dilute HCl and extracted with ethyl acetate resulting in exclusive extraction of tripyrromethane. Aqueous formaldehyde solution is not miscible well with pyrrole



Scheme 2.

at room temperature causing slower reaction. The reaction was carried out at slightly elevated temperature (50°C). Dipyrromethane was the major product in both methods and the yield was higher than the one obtained from the reaction of paraformaldehyde and pyrrole.[6] In the case of solid state aldehydes such as *p*-methoxycarbonylbenzaldehyde and 4-carboxybenzaldehyde, only method A was applicable and it was found that *meso*-substituted dipyrromethanes were formed as the major products in all cases. In some cases, the higher oligomers (**5**) and (**6**) were cleanly isolated from the residual dark brown solid left over after vacuum distillation (Scheme 2). A large difference in molecular weight and relatively stable nature enabled the isolation of higher oligomers. The ^{1}H NMR spectra of (**4**), (**5**) and (**6**) showed almost identical resonance of all the pyrrolic protons[16] whereas the presence of increased number of pyrrole rings caused broadening of the resonance lines.

We examined the utility of the direct condensation of aldehydes with pyrrole in the presence of acid catalyst. Examination of the sequence of adding reactants and catalyst showed dramatic influence in the product distribution. We therefore were able to establish the conditions affording tripyrromethanes as the major products. To the best of our knowledge, dipyrromethanes and tripyrromethanes bearing *meso*-pyridyl or *meso*-carboxyphenyl or *meso*-(methoxycarbonyl)-phenyl groups have been synthesized for the first time by acid-catalyzed, one-flask condensation. The improvement in the synthetic methodology for the preparation of tripyrromethanes will enable the rapid development of the porphyrin building blocks which have polar groups in *trans*- or *cis*-fashion at the porphyrin periphery. The predominant formation of tripyrromethanes from the one-flask synthesis will also be beneficial for the development of various porphyrin-based model systems.

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15. Typical procedure of method A: the solution of aldehyde (1 equiv.) and pyrrole (5 equiv.) was stirred for 5 min at room temperature under nitrogen atmosphere then added TFA (0.1 equiv.). The whole mixture was stirred for 5 min and then combined with aqueous NaOH (0.1N, 10 mL) in order to quench the reaction. The mixture was extracted with CH_2Cl_2 and the organic layer was dried ($NaHCO_3$). The solvent was removed in vacuo and resulting dark brown oil was distilled under vacuum. Dipyrromethanes were distilled off at 180–200°C (0.05 mmHg) and recrystallized from EtOH/water. The remained black solid contains the most of tripyrranes and other higher oligomers. Tripyrranes were cleanly separated by column chromatography on silica (CH_2Cl_2). Method B: the procedure was the same as method A except the mixing sequence of the reactants. Aldehydes and catalyst were mixed first and stirred for 5 min at room temperature, then pyrrole was introduced at once.
16. Pyrrole (4.1 g, 60.9 mmole) and 4-methoxycarbonyl benzaldehyde (2 g, 12.2 mmole) were reacted by the typical procedure (distilled at 200°C, 0.1 mmHg; recrystallized from ethanol/water) giving (**3**) as a pale green solid. Compound (**4**) and higher oligomers (**5**), (**6**) were separated by column chromatography on silica (CH_2Cl_2/EtOAc = 9/1). For (**3**) mp 160°C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, CH_3), 5.25 (s, 1H, *meso*-H), 5.89 (s, 2H, pyrrole-H), 6.16 (q, 2H, pyrrole-H), 6.71 (q, 2H, pyrrole-H), 7.28 (d, 2H, Ar-H), 7.96 (m, 4H, Ar-H and NH). For (**4**) mp 67°C; ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 6H, CH_3), 5.37 (s, 2H, *meso*-H), 5.71 (d, 2H, pyrrole-H), 5.81 (s, 2H, pyrrole-H), 6.09 (q, 2H, pyrrole-H), 6.64 (q, 2H, pyrrole-H), 7.18 and 7.85 (two doublet, 8H, Ar-H), 8.10 (br s, 1H, NH), 8.15 (br s, 2H, NH). For (**5**) mp 108°C; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 9H, CH_3), 5.31 to 5.37 (t, 3H, *meso*-H), 5.67 (m, 4H, pyrrole-H), 5.81 (s, 2H, pyrrole-H), 6.11 (q, 2H, pyrrole-H), 6.67 (m, 2H, pyrrole-H), 7.16 and 7.84 (m, 12H, Ar-H), 8.01 (m, 2H, NH), 8.10 (br s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ 166.92, 147.28, 147.18, 131.86, 131.82, 131.70, 131.48, 129.86, 129.66, 128.71, 128.50, 128.35, 128.29, 117.61, 108.47, 107.76, 107.44, 52.14, 44.11, 44.03. FAB-MS calcd for $C_{43}H_{38}N_4O_6$ 706.28, found 706.09 (M^+). For (**6**) mp 152°C; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 12H, CH_3), 5.27 to 5.37 (m, 4H, *meso*-H), 5.66 (m, 6H, pyrrole-H), 5.81 (s, 2H, pyrrole-H), 6.11 (m, 2H, pyrrole-H), 6.67 (m, 2H, pyrrole-H), 7.17 (m, 8H, Ar-H), 7.84 to 8.06 (m, 13H, Ar-H and NH). ^{13}C NMR ($CDCl_3$) δ 166.94, 147.37, 147.29, 147.24, 131.91, 131.79, 131.75, 131.70, 131.67, 131.49, 129.84, 128.63, 128.32, 128.27, 117.61, 108.43, 107.72, 107.43, 52.13, 44.08, 44.02. FAB-MS calcd for $C_{56}H_{49}N_5O_8$ 919.36, found 919.24 (M^+).