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Direct alkylation of pyrrole with vinyl substituted aromatics: versatile precursors for the synthesis of porphyrinoid macrocycles

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ABSTRACT

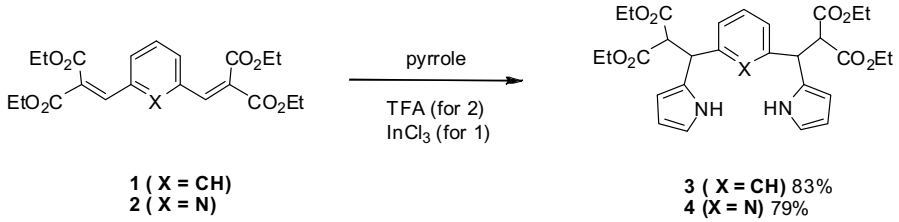
5-Substituted dipyrromethane analogues (**8**), (**23**) and (**25**) were synthesized by the reaction of 2-vinylpyrroles, 2-vinylthiophene or 2-vinylbenzenes with excess pyrrole in the presence of Lewis acids. Accordingly, tripyrromethane analogues could be obtained by starting with 2,5-divinyl thiophene or 2,6-divinylbenzenes. The reaction usually gave moderate yields and catalyst-dependent was seen in some cases. The reaction is compatible with other reported dipyrromethane syntheses and could be applied for the construction of unusual porphyrins.

Recent interests in porphyrinoids chemistry led to the extensive development of the synthesis of *meso*-substituted dipyrromethanes and 1,9-functionalized dipyrromethanes. 5-Substituted dipyrromethanes are the key building blocks for the construction of porphyrin-based model systems and related porphyrinoid macrocycles. Since the first one-flask synthesis of dipyrromethanes was reported in 1994,[1] a number of methods have then been developed for refine the synthesis and purification.[2–6] Several refined methods have been reported recently by various combinations of acids and solvents.[7,8] The reported methods utilize the one-flask reaction of aldehydes with pyrrole in the presence of various acid catalysts including Lewis acids and more-recently *N*-tosyl imines with excess pyrrole in the presence of metal triflates.[9] The reaction usually afforded good yields of dipyrromethanes regardless of the nature of the starting aldehydes. However, our recent results indicated that Lewis acids are excellent catalysts for the conjugate addition of pyrrole to α,β-unsaturated esters or ketones (Scheme 1).[10,11] With these regards, we sought the synthesis of monopyrrylmethyl- or bis-pyrrylmethyl-substituted aromatics such as benzene, pyridine or pyrrole. These building blocks can be used in the construction of novel porphyrinoid macrocycles. With these regards, we report the synthesis of dipyrromethanes from vinyl-substituted pyrroles.

2,6-Bis-vinyl benzene derivative (**1**) and the 2,6-bis-vinylpyridine derivative (**2**) were obtained readily via the Knoevenagel condensation of diethyl malonate with 2,6-pyridinedicaboxaldehyde or isophthalaldehyde, respectively. Acid-catalyzed addition of pyrrole served to convert (**1**) or (**2**) to the corresponding tripyrrane analogues (**3**) and (**4**) as reported earlier (Scheme 1).[10]

Interestingly, it was found that the yield of the desired product dramatically depends on the catalyst applied. For example, the best yield of (**3**) was obtained when $InCl_3$ was applied as the catalyst. On the other hand, the highest yield of 79% was obtained when trifluoroacetic acid was employed for the same purpose.[10,11]

This difference was rationalized in terms of pyridine being able to coordinate to the In(III) center, with the resulting complex presumably not being sufficiently activated to undergo electrophilic substitution at the methylene α-carbon. Metal coordination could



1 (X = CH)
2 (X = N)

3 (X = CH) 83%
4 (X = N) 79%

Scheme 1.

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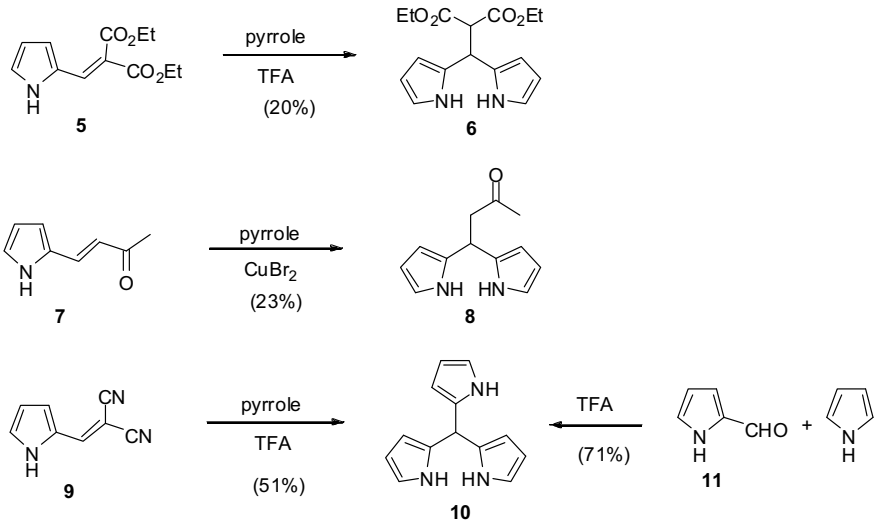


Scheme 2.

also be inhibitory as the result of steric hinderance. Such limitations would not be operative in the case of TFA-mediated catalysis, even under conditions where the pyridine nitrogen atom is protonated. 2-Vinyl substituted pyrrole (**5**), (**7**) and (**9**) were also examined for regioselective addition of pyrrole by employing various catalysts (Scheme 2). Although the isolated yield was comparably low, the reaction gave desired products in all attempted cases. The reaction of (**5**) with pyrrole provided dipyrromethane (**6**) in 20% yield. TFA was found to be the only catalyst producing the desired product. The vinyl ketone (**7**) which reacted with neat pyrrole afforded corresponding dipyrromethane (**8**) in low yield (23%). The most of the un-reacted starting material was recovered even after prolonged reaction time. $CuBr_2$ seemed to be the only catalyst giving the desired product.[12] Other catalysts examined including TFA and $InCl_3$ did not give the desired product.

The reaction of compound (**9**), which was obtained from the condensation of 2-pyrrolecarboxaldehyde with malononitrile under typical condition, with pyrrole unexpectedly resulted in the formation of tripyrrylmethane (**10**) in 51% yield.[13] Formation of (**10**) is easily explained by elimination–addition reaction. The malononitrile group is eliminated from the initially formed dipyrromethane product to form dipyrryl methyl cation followed by nucleophilic attack of pyrrole. Compound (**10**) can be obtained by simple acid-catalyzed condensation of 2-pyrrolecarboxaldehyde (**11**) with pyrrole.[14]

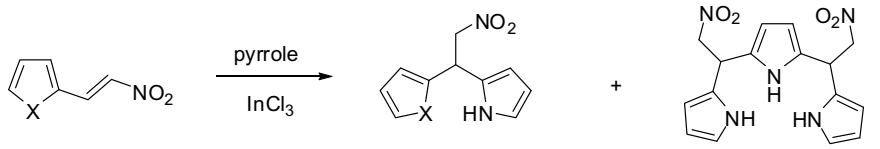
Nitrovinyl-substituted pyrrole (**12**), thiophene (**13**) and furan (**14**) also underwent regioselective addition of pyrrole in the presence of $InCl_3$ in neat pyrrole solvent (Scheme 3). Superior yields were obtained when the pyrrole N–H was protected with Boc group (**15**). Small amount of (**20**) was also isolated from the reaction mixture. The formation of (**20**) can be easily explained by regioselective addition of more nucleophilic primary product (**16**) to starting material (**12**).

Interestingly, attempted addition of pyrrole to (**21**) was not successful in spite of extensive screening of many different Lewis acids including TFA, $InCl_3$, $InBr_3$, $In(OTf)_3$, $NiCl_2$ and $Pd(OAc)_2$. This is probably because the α-position of (**21**) is not activated enough to be attacked by nucleophilic pyrrole. On the other hand, we found that the dipyrromethane bearing mono-ethyl acetate group at *meso*-position can be synthesized from acetal (**22**). As shown in Scheme 4, In(III)-catalyzed condensation of (**22**) with pyrrole afforded dipyrromethane (**23**) in 31% yield.[15]

Unlike bis-vinyl benzene (**1**) or bis-vinyl pyridine (**2**), acid-catalyzed condensation of bis-vinyl pyrrole (**24**) resulted in the formation of (**25**) as sole product in 61% yield. Rapid reversible cleavage of initially formed product must be involved in this reaction. The structural characterization of all the reaction products was straight forward. The identity of the compounds (**6**), (**16**)–(**18**) has been reported previously.[13] The new compounds (**8**), (**19**), (**23**), (**25**) and (**26**) were characterized by HRMS and ^1H NMR spectroscopy.[16]

Attempted porphyrin synthesis by '2+2' condensation from the dipyrromethane (**23**) and *p*-(*t*-butyl)benzaldehyde afforded 25% of porphyrin (**26**) without observable scrambling (Scheme 5). The amount of acid catalyst (TFA) seems to be critical in preventing the scrambling. Attempted reaction with valeraldehyde under the same condition resulted in extensive scrambling on the other hand.[15]

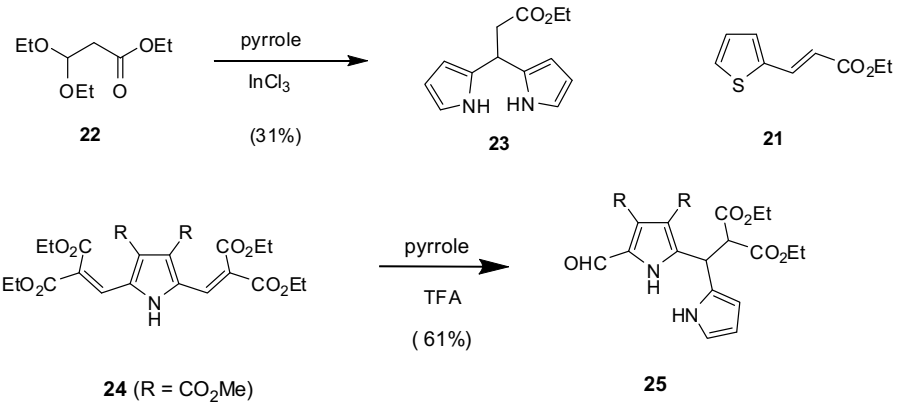
In summary, we report that regioselective addition of pyrrole to vinyl substituted aromatics bearing electron-withdrawing groups. The reaction afforded novel dipyrromethanes analogues, which



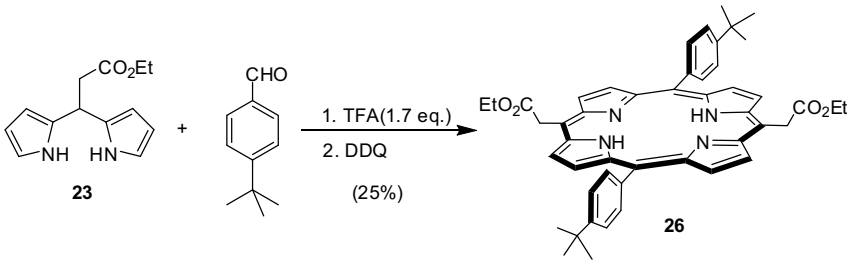
12 X = NH
13 X = S
14 X = O
15 X = N-Boc

16 X = NH (60%)
17 X = S (32%)
18 X = O (27%)
19 X = N-Boc (82%)

Scheme 3.



Scheme 4.



Scheme 5.

can be applied to the synthesis of various porphyrins and core-modified porphyrins. The reaction and yields are very sensitive with catalysts applied and highly dependent on the substituents on the vinyl function. The application to the synthesis of porphyrins is under study.

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16. *Typical experimental procedure and spectroscopic data for 5-(acetylmethyl)dipyrromethane* (**8**): Compound (**7**) (106 mg, 0.78 mmol) and $CuBr_2$ (38 mg, 0.17 mmol) were dissolved in neat pyrrole (2 mL). The resulting mixture was stirred at room temperature for 4 h. Then, the solution was diluted with CH_2Cl_2 and washed with water (50 mL). The organic layer was dried (anhyd Na_2SO_4) and the solvent was evaporated under reduced pressure. The remaining solid was purified by solvent-gradient column chromatography on silica (from CH_2Cl_2/EtOAc = 95/5 to CH_2Cl_2/EtOAc = 3/1) to afford (**8**) (36 mg, 23%) as yellowish oil; ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 3.16 (d, J = 6.63 Hz, 2H), 4.61 (t, J = 6.64 Hz, 1H), 5.91–5.92 (m, 2H), 6.37 (dd, 2H), 6.68–6.66 (m, 2H), 8.27 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 30.57, 32.57, 49.45, 105.31, 108.11, 117.18, 132.62, 208.42; EI-MS calcd for $C_{12}H_{14}N_2O$ 202.11, found 202.07.
10-(tert-Butoxycarbonyl)-5-(nitromethyl)dipyrromethane (**19**): Compound (**15**) (505 mg, 2.12 mmol) and $InCl_3$ (52 mg, 0.24 mmol) were dissolved in neat pyrrole (8 mL) and the resulting mixture was stirred at room temperature for 1 h. Then, aqueous NaOH solution (0.1 N, 50 mL) was added in order to quench the reaction. The solution was diluted with CH_2Cl_2 and washed with water (50 mL). The organic layer was evaporated under reduced pressure. The residue was purified by column chromatography on silica (CH_2Cl_2) to give (**19**) (534 mg, 82%) as yellowish oil; ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 9H), 4.80–4.98 (m, 2H), 5.71 (t, J = 7.9 Hz, 1H), 5.98–5.99 (m, 1H), 6.06–6.12 (m, 3H), 6.64–6.66 (m, 1H), 7.18–7.19 (m, 1H), 8.41 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.94, 35.50, 77.86, 84.67, 105.47, 108.58, 110.34, 112.09, 117.34, 122.34, 128.83, 131,96, 149.46; EI-MS calcd for $C_{15}H_{19}N_3O_4$ 305.14, found 305.13.
5-(Ethoxycarbonylmethyl)dipyrromethane (**23**): Compound (**22**) (0.5 mL, 2.55 mmol), $InCl_3$ (59 mg, 0.26 mmol) and pyrrole (2 mL) were treated identically as for the synthesis of (**19**) (60 °C for 2 h under nitrogen atmosphere). The desired product (**23**) (182 mg, 31%) was obtained by column chromatography on silica (from CH_2Cl_2 to hexanes/EtOAc = 1/1) as yellowish oil; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7.12 Hz, 3H), 2.98 (d, J = 7.00 Hz, 2H), 4.12 (t, J = 7.12 Hz,2H), 4.57 (t, J = 6.98 Hz, 1H), 5.98–6.00 (m, 2H), 6.11–

6.13 (m, 2H), 6.65–6,66 (m, 2H), 8.22 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.54, 34.14, 40.50, 61.24, 105.94, 108.56, 117.73, 132.51; EI-MS calcd for $C_{13}H_{16}N_2O_2$ 232.12, found 232.05.

*2,5-Bis[(α-diethoxycarbonylmethyl-α-(pyrrol-2-yl))methyl]-3,5-dimethoxycarbonylpyrrole (***25** *)*: Compound (**24**) (0.082 g, 0.16 mmol) was dissolved in neat pyrrole (2 mL, 28 mmol) and then TFA (0.05 mL, 0.65 mmol) was added. The mixture was stirred for 24 h at room temperature. The reaction was quenched by addition of aqueous NaOH (0.1 N) and extracted with CH_2Cl_2. The organic layer was washed with water and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting solid was purified by column chromatography on silica ($CHCl_3$/EtOAc/hexanes = 7/2/1). Yield 0.043 g (61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (br s, 1H, NH), 10.39 (br s, 1H, NH), 9.65 (s, 1H, CHO), 6.61–6.59 (m, 1H, pyrrole-H), 6.01 (m, 1H, pyrrole-H), 5.88–5.86 (m, 1H, pyrrole-H), 5.38 (d, *J* = 12.47, 1H, *meso*-H), 4.82 (d, *J* = 12.47, 1H, CH), 4.02–3.39 (m, 4H, CH_2CH_3), 3.80 (s, 3H, CO_2CH_3), 3.79 (s, 3H, CO_2CH_3), 1.01 (t, *J* = 7.09, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.85, 166.61, 166.59, 163.60, 163.47, 141.64, 130.17, 127.13, 123.94, 117.79, 113.27, 107.28, 106.09, 61.129, 61.018, 54.307, 52.265, 51.710, 35.162, 13.568, 13.424; EI-MS calcd for $C_{21}H_{24}NO_9$ 448.15, found 448.06.

5,15-Bis(p-tert-butylphenyl)-10,20-(ethoxycarbonylmethyl)porphyrin (**26**): Compound (**23**) (230 mg, 0.99 mmol) and 4-*tert*-butylbenzaldehyde (166 μL, 0.99 mmol) were dissolved in CH_2Cl_2 (100 mL) with stirring and then TFA (136 μL, 1.77 mmol) was added. The solution was stirred for 40 min at room temperature. Then, DDQ (675 mg, 2.98 mmol) was added and the mixture was stirred for 1 h. The reaction mixture was washed with aqueous saturated $NaHCO_3$ (50 mL), water and dried with anhydrous sodium sulfate. After the drying agent was filtered off, the solvent was evaporated under reduced pressure. The residual solid was purified by column chromatography on silica (CH_2Cl_2) to give desired porphyrin. Yield 93 mg (25%); ^{1}H NMR ($CDCl_3$) δ −2.73 (s, 2H), 1.12 (t, *J* = 7.11 Hz, 6H), 1.63 (s, 18H), 4.16 (q, *J* = 7.11 Hz, 4H), 5.97 (s, 4H), 7.77 (d, *J* = 8.24 Hz, 4H), 8.11 (d, *J* = 8.22 Hz, 4H), 8.94 (d, *J* = 4.86 Hz, 4H), 9.47 (d, *J* = 4.91 Hz, 4H); UV–vis ($CHCl_3$, 2.1×10^{-6} M) $\lambda_{max}(\varepsilon)$ 420 (384000), 517 (16900), 552 (5000), 595 (3800), 651 (2000); MALDI-TOF MS calcd for $C_{48}H_{50}N_4O_4$ *m*/*z* 746.38, found 746.33.