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Rational Synthesis of Tripyrranes

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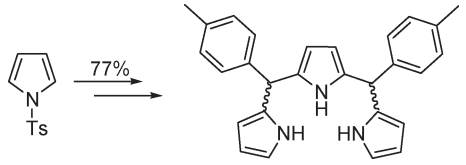

The rational, chromatography-free synthesis of two regioisomeric 5,10-diaryltripyrranes from pyrrole and aromatic acids has been developed. The strategy is general and should be applicable to a broad range of acids. This methodology was successfully applied to the synthesis of monoprotected dipyrrane. The oxidation of *N*,*N*′-bis-mesyltripyrrane under basic conditions led to the formation of both known tripyrrin-1-one and unknown 1-methoxytripyrrin—a fluorescent dye strongly absorbing green light.

Tripyrranes are popular building blocks in the construction of various porphyrinoids. They were used in the synthesis of porphyrins,[1] hexaphyrins,[2] sapphyrins,[3,4] rubyrins,[5] pentaphyrins,[6] *N*-fused [24]pentaphyrins,[7] and texaphyrins.[8] Recently, we employed them in the synthesis of chlorins.[9] The most obvious method for the synthesis of tripyrranes bearing *meso*-aryl substituents consists of an acid-catalyzed condensation of aldehydes with pyrrole described by Dolphin[4] and Lee.[10] Although one step, this procedure is associated with many problems such as undesired formation of various oligocondensates and the necessity for long chromatographical separation.[4,10] This prompted us to develop an alternative stepwise procedure but with easier overall purification.

The idea was to construct the tripyrrolic system via the reaction of *N*-protected pyrrole-derived alcohols with pyrrole. The sulfonyl group was chosen as a protecting group for the following reasons: (1) stability under acidic conditions; (2) easy removal under basic conditions; and (3) electron-withdrawing effect that deactivates the pyrrole ring against electrophilic aromatic substitution. Readily available *N*-mesylpyrrole (**1**)[11] was chosen as a building block, which was acylated with mixed anhydride,[12] formed in situ from 4-methylbenzoic acid and trifluoroacetic acid anhydride (TFAA), to afford ketone **2** (Scheme 1). Subsequent reduction with sodium borohydride gave alcohol **3**, which after condensation with pyrrole under acidic conditions afforded bis-protected tripyrrane **4** in 94% yield. The use of a standard concentration of KOH solution (1.5%)[13] as the deprotecting agent led only to the recovery of the starting material. Thus 20% KOH/MeOH was applied resulting in the formation of >50 colorful products and a substantial amount of very polar black tar (Scheme 2).

Small amounts of products were formed and due to the significant similarity of their chromatographical properties only two of them were successfully isolated in the pure state and analyzed. In addition one product that was not present in the crude reaction mixture (it formed on silica gel) was isolated. The strong absorption of visible light by these compounds suggested that they formed by oxidation during or after deprotection of tripyrrane **4**. Unsubstituted tripyrrane **5** was detected only in small amounts under these conditions. In light of this observation, the deprotection reaction was carried out under argon, affording tripyrrane **5** in 99% yield as a mixture of diastereomers (Scheme 2). The new method consists of five steps giving tripyrrane **5** with an overall yield of 34% (only one silica pad filtration was needed). The same synthesis was carried out starting from *N*-tosylpyrrole, which resulted in tripyrrane **5** in even higher overall yield (77%) (see the Supporting Information). Subsequently, the structures of the three dyes formed during deprotection under air were studied. On the basis of standard analyses, the red one was identified as tripyrrin-1-one **7**. Analogous compounds substituted at β positions were studied by Falk and von Dobeneck and prepared from pyrrole-2-carboxyaldehydes and dipyrrin-1(10*H*)-ones.[14]

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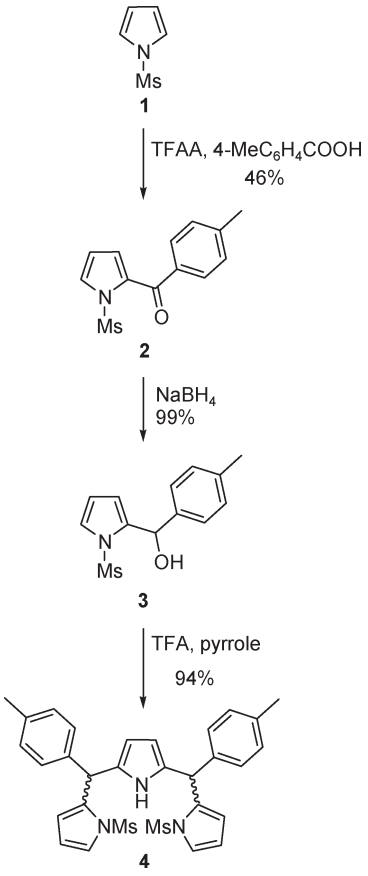
SCHEME 1

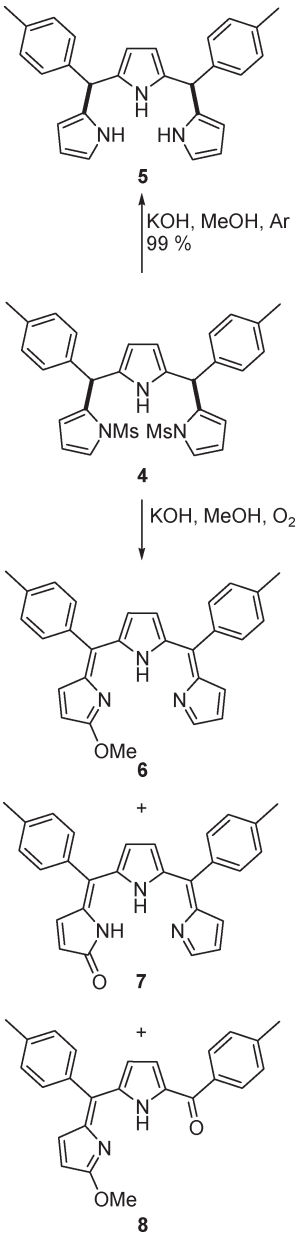


Sessler and co-workers revealed that subjecting β-substituted tripyrranes to $Cu(OAc)_2$ resulted in the formation of tripyrrin-1,5-dione copper complex.[15] Recently Osuka and Furuta have reported the formation of 14-benzoyltripyrrin-1-one as copper complexes via oxidation of *N*-confused porphyrins.[16] Furthermore, in 2003 Anderson found that the tripyrrin-1-one forms during the oxidation step, which follows the condensation reaction of TIPS-propynal with 3,4-diethylpyrrole.[17]

The second isolated product was not present in the original reaction mixture; however, it was observed as a strong yellow unpolar band during chromatography. This compound was isolated in 13% yield. NMR data clearly confirmed its structure as methoxydipyrrin **8** (Scheme 2). This compound is probably formed from some unidentifiable precursor during silica-catalyzed scrambling. The lack of stability of dipyrranes on silica is well documented.[18]

At this point the structure of the third product remained unclear. Taking the synthetic route employed into account, together with using standard analytical methods two possibilities (**6** and **6′**) for the structure were identified (Figure 1). Formation of compound **6′** can be considered because, although Friedel−Crafts reaction of pyrrole with aldehydes

SCHEME 2



mainly occurs at position 2, compounds substituted at position 3 are also formed as minor products.[19]

Structure identification and signal assignments were achieved by the use of ^1H and ^{13}C 1D NMR, 1D NOE experiments, and 2D NMR techniques: COSY, LR-COSY (long-range COSY, the measurement of which was optimized for small coupling constants), ^{13}C,^1H-gHSQC, and ^{13}C,^1H-gHMBC. Initially, three pairs of ^1H signals (two doublets and two broad peaks) within the range of 6 to 7 ppm were identified by the use of the COSY spectrum. The LR-COSY spectrum revealed the week coupling of the signal at 7.87 ppm with the signal at 6.47 ppm. The ^1H NMR spectrum with resolution enhancement (by Lorentzian-to-Gauss transformation) allowed the detection of small splittings of the signals at 6.75 and 6.46 ppm (1.0 and 0.4 Hz, respectively). These signals together with a signal at 7.87 ppm were identified as being part of the same AMX spin system.

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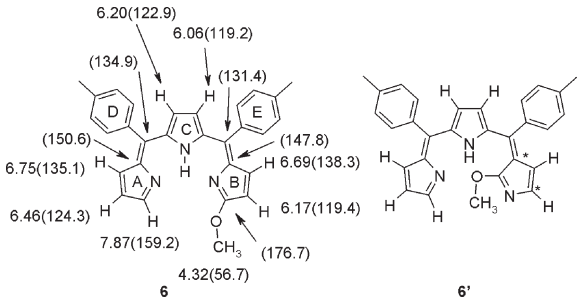

FIGURE 1. ^{1}H and ^{13}C NMR chemical shifts of **6** ($CDCl_3$ solution) as well as an alternative structure **6′** (atoms marked by asterisks in the figure—see the explanation in the text).

This was confirmed by the $^{13}C,^{1}H$-gHMBC technique. By carrying out NOE experiments, the signals of two Ar rings (D and E) as well as the pyrrolic signals at 6.06, 6.20, 6.69, and 6.75 ppm were identified. Hence, the presence of the AMX and two AX systems in the spectrum together with NOE findings argued the presence of A, B, and C rings in the structure (Figure 1).

The signals of ring B bearing the methoxy group were identified initially by $^{13}C,^{1}H$-gHMBC experiment taking into account the correlation between the methyl group and the signal at 176.7 ppm. Then, the remaining assignments were easily made by using $^{13}C,^{1}H$-gHSQC and COSY data. The positions of the methoxy group and both CH atoms in ring B were established by a NOE experiment, in which a NOE interaction between the signals 6.69 and 7.22 ppm (Ar), and CH_3 and 7.87 ppm, respectively, was observed. An alternative structure of ring B (**6′**) was excluded on the basis of ^{13}C chemical shifts of the quaternary and CH carbon atoms (marked by asterisks in Figure 1). The first value (147.8 ppm) suggests the vicinity of the N atom, whereas the latter (119.4 ppm) indicates a larger distance from the nitrogen.

Since all ^{1}H signals were identified either by COSY or LR-COSY techniques, the assignment of the ^{13}C signals by using $^{13}C,^{1}H$-gHSQC and gHMBC data was straightforward. Only the assignment of two quaternary carbon atoms of the C ring, at 137.1 and 141.4 ppm, was ambiguous.

$^{15}N,^{1}H$-gHSQC measurement revealed one ^{15}N signal at −90.2 ppm (assuming $CH_3NO_2 = 0$ ppm), assigned to the A ring. Such a chemical shift value suggests a pyridine-type nitrogen atom. The signals of the remaining nitrogen atoms were not detected, probably due to signal broadening.

All attempts to improve the yields of compounds **6** and **7** by using various oxidants like DDQ, *p*-chloranil, [bis(trifluoroacetoxy)iodo]benzene (PIFA), CAN, and O_2/Pd/C failed. In all cases dyes **6** and **7** were formed in lower yields or were not formed at all. Tripyrrins bearing substituents at β-positions were intensively investigated by Bröring.[20,21] He proved that the presence of *tert*-butyl groups at flanked positions allows the stability of the free bases to match that

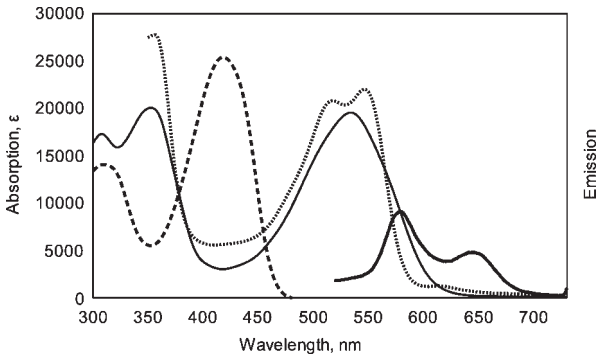

FIGURE 2. Absorption of **6** (dotted line), **7** (solid line), and **8** (dashed line) as well as emission of **6** (bold line) in THF.

of the chelated compound. Otherwise tripyrrins can only be obtained as metal complexes. Our 1-methoxytripyrrin is the first example of a nonsterically hindered tripyrrin stable as a free base.

Both methoxytripyrrin **6** and tripyrrin-1-one **7** are red-violet in solution. The most notable feature of their UV−vis spectra is strong absorption of green light (Figure 2, λ_{max} (**6**) = 545 nm, λ_{max} (**7**) = 534 nm). The visible band of methoxytripyrrin **6** is both bathochromically and hyperchromically shifted when compared to that of tripyrrin-1-one **7**. Weak absorption of lower energy light reported by Osuka for 14-benzoyltipyrrin-ones[16] is absent in the spectrum of **7**. In contrast to compound **7**, dye **6** is weakly fluorescent in solution (λ_{em} (**6**) = 579 nm) (Figure 2). The Stokes shift for compound **6** is 1080 cm^{-1} (Figure 2).

Encouraged by the overall efficiency of the preparation of tripyrrane **5**, we decided to synthesize *N*-monoprotected dipyrrane and regioisomeric tripyrrane in which one terminal pyrrole ring is linked at position 3 by the same methodology. These types of tipyrranes (the potential building block in the synthesis of porphyrinoids) was unknown until now. *N*-Phenylsulfonylpyrrole **9**[22] was acylated in position 3 (Scheme 3) to give ketone **10**.[23] Subsequent reduction gave the corresponding alcohol, which was reacted with *N*-tosyldipyrrane **11** (prepared via reaction of alcohol **S3** with an excess of pyrrole under acidic conditions, see the Supporting Information) to give doubly protected "*N*-confused tripyrrane" **12** in 60% yield. Finally deprotection under basic conditions gave tripyrrane **13** in 83% yield (Scheme 3).

In summary, we have developed a new rational procedure toward tripyrranes via a five-step sequence of reactions from *N*-mesylpyrrole or *N*-tosylpyrrole and carboxylic acids. Our studies have clearly documented that [*N*-(mesyl)pyrrol-2-yl]-(4-aryl)methanols are stable under acidic reaction conditions and can selectively react with unsubstituted pyrrole. The extraordinary ease with which all intermediates can be prepared makes this protocol ideal for the generation of a range of 5,10-diaryldipyrranes. This procedure offers several advantages where the classical method cannot be used or gives rise to an inseparable mixture of oligocondensates. The same strategy was used in the synthesis of "confused tripyrrane". Our results underline the instability

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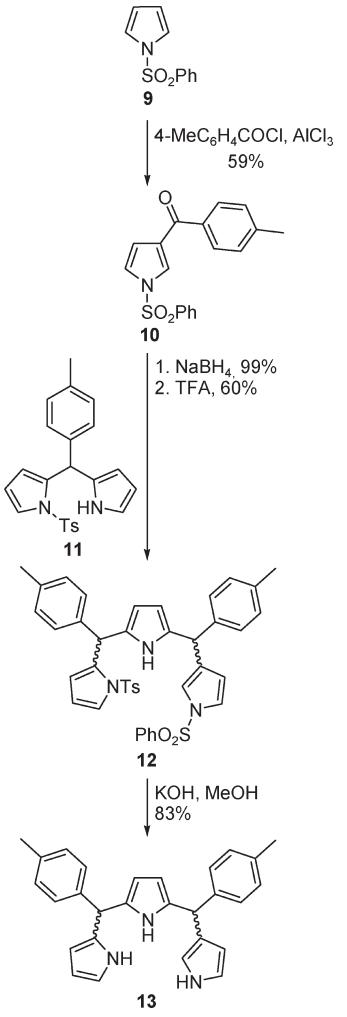
SCHEME 3



of tripyrranes toward even mild oxidants. Oxidation of *meso*-substituted tripyrranes leads to their two oxidation products—tripyrrin-1-ones and 1-methoxytripyrrins. 1-Methoxytripyrrins strongly absorb green light and they display fluorescence.

Experimental Section

1,17-Bis-*N*,*N*-methylosulfonylo-5,10-bis(4-methylphenyl)tripyrrane (4). To a solution of **3** (20 mmol, 5.25 g) and pyrrole (9.5 mmol, 660 μL) in CH_2Cl_2 (100 mL) was added TFA (1.5 mmol, 115 μL). The reaction mixture was stirred at room temperature for 72 h and washed with water. The organic layer was dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was filtered through a silica pad affording the pure product as a yellow-orange solid (5.0 g, 94%): ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si, ppm) δ 2.28 (s, 6H), 2.32 (s, 3H), 2.41 (s, 3H), 5.69 (dd, 2H, $J_1 = 2.6$ Hz, $J_2 = 10.2$ Hz), 5.82 (d, 2H, $J = 8.6$ Hz), 5.91 (d, 2H, $J = 3.3$ Hz), 6.16−6.18 (m, 2H), 7.10 (s, br, 8H), 7.28 (d, br, 1H, $J = 8.7$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 21.0, 41.7, 41.9, 108.2, 110.4, 114.2, 122.5, 128.7, 129.2, 131.5,136.9, 137.1, 137.7; HRMS (EI) calcd for $C_{30}H_{31}N_3O_4S_2$ [M^+] 561.1756, found 561.1740.

5,10-Bis(4-methylphenyl)tripyrrane (5). Method A: KOH (179 mmol, 10 g) was added to a solution of tripyrrane **4** (8.0 mmol, 4.5 g) in dry methanol (50 mL) under argon. The reaction mixture was stirred overnight and washed with water. The organic layer was dried (Na_2SO_4) and evaporated affording the pure product as a foamy orange solid (3.21 g, 99%). **Method B:** KOH (179 mmol, 10 g) was added to a solution of tripyrrane **S4** (6.4 mmol, 4.6 g) in dry methanol (50 mL) under argon. The reaction mixture was stirred for 20 h and water was added. After extraction with CH_2Cl_2 the organic layer was dried (Na_2SO_4) and evaporated affording the pure product as a foamy orange solid (2.55 g, 99%). IR (KBr, ν_{max}/cm^{-1}) 510, 718, 760, 1027, 1090, 1424, 1511, 1560, 1700 (br), 2920, 3411; HRMS (EI) calcd for $C_{28}H_{27}N_3$ [M^+] 405.2205, found 405.2219. Anal. Calcd for $C_{28}H_{27}N_3$: C, 82.93; H, 6.71; N, 10.36. Found: C, 82.69; H, 6.49; N, 10.26. Other analytical data are consistent with literature values.[24]

Tripyrrane 13. Tripyrrane **12** (2.71 mmol, 1.9 g) was dissolved in dry methanol (100 mL), then KOH (0.36 mol, 20 g) was added and the solution was stirred for 72 h under argon atmosphere. Subsequently, the reaction mixture was evaporated, dissolved in CH_2Cl_2, and washed with water. The organic layer was dried and evaporated affording pure product as a pale pink solid (906 mg, 83%): IR (KBr, ν_{max}/cm) 511, 717, 756, 1027, 1058, 1423, 1511, 2919, 3410 (br); ^{1}H NMR (200 MHz, $CDCl_3$, Me_4Si, ppm) δ 2.31 (s, 3H), 2.32 (s, 3H), 5.22 (s, 1H), 5.31 (s, 1H), 5.71(s, 1H), 5.72 (s, 1H), 5.83−5.86 (m, 1H), 6.04 (dd, 1H, $J_1 = 2.4$ Hz, $J_2 = 4.2$ Hz), 6.11 (m, 1H), 6.39−6.40 (m, 1H), 6.64 (dd, 1H, $J_1 = 2.6$ Hz, $J_2 = 4.2$ Hz), 6.68 (dd, 1H, $J_1 = 2.6$ Hz, $J_2 = 4.8$ Hz), 7.03−7.13 (m, 8H), 7.69 (s, br, 1H), 7.89 (s, br, 1H), 7.97 (s, br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 21.4, 43.3, 44.0, 106.9, 107.2, 107.4, 108.6, 109.0, 116.6, 117.2, 118.4, 126.4, 128.6 (2), 129.2 (2), 129.5, 131.8, 133.4, 135.2, 136.0, 136.6, 139.6, 141.7; HRMS (EI) *m*/*z* calcd for $C_{28}H_{27}N_3$ $(M)^+$ 405.2205. Found: 405.2223. Anal. Calcd for $C_{28}H27N_3$: C, 82.93; H, 6.71; N, 10.36. Found: C, 82.63; H, 6.57; N, 10.16.

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Supporting Information Available: Full description of experimental procedures and analyses of compounds **2**, **3**, **6**−**12**, and **S2**−**S4** and ^{1}H NMR and ^{13}C NMR spectra for compounds **2**−**13** and **S2**−**S4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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