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Use of orthoesters in the synthesis of *meso*-substituted porphyrins

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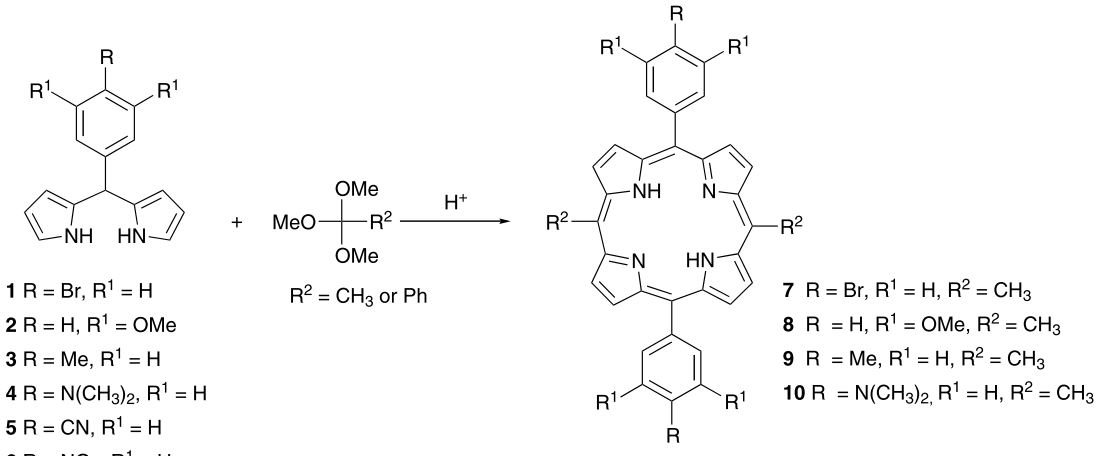
Abstract—The use of two orthoesters, trimethyl orthoacetate and trimethyl orthobenzoate, in the synthesis of porphyrins from 5-phenyldipyrromethanes is described. Previously unreported 5,15-diphenyl-10,20-dimethyl porphyrins can be accessed conveniently by this route. A relationship between the steric bulk of the orthoester and the amount of scrambling of the porphyrin products has been found. Strong electron-withdrawing substituents on the phenyl ring of the dipyrromethane also enhance scrambling. © 2003 Elsevier Science Ltd. All rights reserved.

The condensation of 5-phenyldipyrromethanes with reagents which are capable of supplying the two bridging *meso* positions, to form porphyrins, is an established, and often convenient, synthetic method. Typically this strategy gives access to 5,15-diphenyl porphyrins (DPPs),[1] when 5-phenyldipyrromethanes are condensed under acidic conditions with trimethyl orthoformate, and 5,10,15,20-tetraphenyl porphyrins (TPPs),[2] when the same pyrrolic precursors are condensed with benzaldehydes. Two restrictions limit the versatility of this methodology however, firstly the use of trimethyl orthoformate prevents the introduction of substituents at the 10 and 20 *meso* positions during the condensation, and secondly condensation with benzaldehydes often leads to scrambling of products resulting in complex mixtures of TPPs, which require chromatographic separation.[3–5] Other than the restriction on the 10,20 substituents mentioned above, the condensation of 5-phenyldipyrromethanes with trimethyl orthoformate is versatile and routinely used within our laboratories to produce a wide range of 5,15-diphenyl porphyrins,[6–8] which are used as starting materials in further syntheses. Due to our familiarity with this synthesis we became interested in exploring



1 R = Br, R^1 = H
2 R = H, R^1 = OMe
3 R = Me, R^1 = H
4 R = $N(CH_3)_2$, R^1 = H
5 R = CN, R^1 = H
6 R = NO_2, R^1 = H

7 R = Br, R^1 = H, R^2 = CH_3
8 R = H, R^1 = OMe, R^2 = CH_3
9 R = Me, R^1 = H, R^2 = CH_3
10 R = $N(CH_3)_2$, R^1 = H, R^2 = CH_3

Scheme 1.

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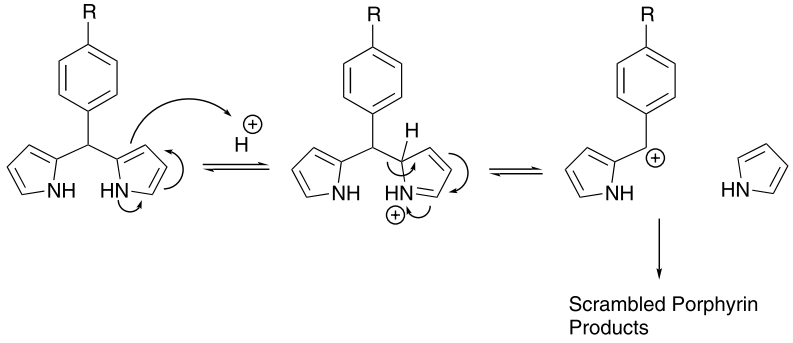
the possibility of using alternative orthoesters, in place of orthoformate, to allow groups other than hydrogen to be introduced into the 10 and 20 positions of the 5,15-diphenyl porphyrin core.

Initially three 5-phenyldipyrromethanes were selected, which were known to react cleanly with trimethyl orthoformate giving the corresponding 5,15-DPPs, these were 5-(4-bromophenyl)dipyrromethane **1**, 5-(3,5-dimethoxyphenyl)dipyrromethane **2** and 5-(4-methylphenyl)dipyrromethane **3**, which were all prepared by condensation of the appropriate benzaldehyde with excess pyrrole.[1] The dipyrromethanes were condensed separately with trimethyl orthoacetate in the presence of trichloroacetic acid (Scheme 1). Subsequent air oxidation of the crude product gave single porphyrin products by TLC, which analysis by NMR, mass spectrometry and UV–vis spectroscopy proved to be 5,15-di(4-bromophenyl)-10,20-dimethyl porphyrin **7**, 5,15-di(3,5-dimethoxyphenyl)-10,20-dimethyl porphyrin **8** and 5,15-di(4-methylphenyl)-10,20-dimethyl porphyrin **9** respectively.[9] To our knowledge this is the first reported synthesis of 5,15-diphenyl-10,20-dimethyl porphyrins, which represent an interesting, and now easily accessible, class of porphyrins for further study. In order to further explore the versatility of the method several more 5-phenyldipyrromethanes were investigated, 5-(4-dimethylaminophenyl)dipyrromethane **4** was again condensed with trimethyl orthoacetate to give one porphyrin product by TLC, however, although mass spectrometry indicated the correct mass ion for the expected product, 5,15-di(4-dimethylaminophenyl)-10,20-dimethyl porphyrin **10**, NMR data suggested the presence of several products. Two more dipyrromethanes were condensed with trimethyl orthoacetate under similar conditions, however, both 5-(4-cyanophenyl)dipyrromethane **5** and 5-(4-nitrophenyl)dipyrromethane **6** gave complex mixtures of porphyrin products by TLC. Mass spectrometric examination of the product mixtures indicated the presence of 'scrambled' porphyrins, resulting from acidic cleavage of the dipyrromethanes (Scheme 2).

Results from condensation of 5-phenyldipyrromethanes with trimethyl orthoacetate suggest that the presence of strongly electron-withdrawing substituents on the phenyl ring encourage the acid driven cleavage of the dipyrromethanes, subsequent reaction of fragments from this cleavage can then give rise to the scrambled products detected by TLC and mass spectrometry. A relationship between phenyl substituents and dipyrromethane acidolysis has recently been reported by Lindsey et al.,[5] who noted that acidolysis, and hence scrambling, was more pronounced for 5-phenyldipyrromethane than 5-(2,4,6-trimethylphenyl)dipyrromethane. Lindsey et al. ascribed this effect to steric factors involving the two methyl groups flanking the carbon joining the two pyrrole rings, however, the results reported here suggest that there may also be significant electronic factors involved in this process.

In order to further explore the practicality of using orthoesters in the synthesis of porphyrins from dipyrromethanes, 5-(4-bromophenyl)dipyrromethane **1** was condensed with trimethyl orthobenzoate. Interestingly, this dipyrromethane, which gives 5,15-di(4-bromophenyl) porphyrin and 5,15-di(4-bromophenyl)-10,20-dimethyl porphyrin as the sole porphyrin products, when condensed with trimethyl orthoformate and trimethyl orthoacetate, respectively; resulted in this case in the formation of a mixture of scrambled products as detected by TLC and mass spectrometry. This result was confirmed by repeating the procedure several times, in all cases scrambling resulted. As steric hindrance clearly increases from orthoformate to orthoacetate to orthobenzoate, the attack of the pyrrolic rings on the orthobenzoate seems to have been slowed enough to allow acidolysis to become a significant competing reaction. It is apparent then, that several sets of kinetics control the degree of scrambling observed for porphyrins formed from dipyrromethanes. Firstly, if reaction of the dipyrromethane with the species contributing the *meso* carbons to the incipient 10 and 20 positions is rapid enough, little or no scrambling is seen, however as this slows, due to factors such as steric hindrance of the orthoesters, scrambling occurs. Clearly a second set of parameters, associated with phenyl substitution, is also operating, as demonstrated by scrambling for strongly electron-withdrawing substituents on 5-phenyldipyrromethanes when condensed with trimethyl orthoacetate. Interestingly, no scrambling is observed for condensation of 5-(4-cyanophenyl)dipyrromethane **5** or 5-(4-nitrophenyl)-dipyrromethane **6** with trimethyl orthoformate, indicat-



Scheme 2.

ing that a fine balance between these factors determines whether scrambling occurs or not.

In conclusion, orthoesters are of use in the synthesis of *meso* aryl porphyrins, and can give access to a previously unreported class of porphyrins, the 5,15-diphenyl-10,20-dimethyl porphyrins. The methodology is limited, however, by: (a) steric hindrance of the orthoester and (b) electron-withdrawing substituents on the phenyl ring of the 5-phenyldipyrromethane, which can lead to scrambled products.

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9. *Selected spectroscopic data*:
   Compound **7**: 6% yield, $R_f = 0.54$ (silica, CH_2Cl_2/hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ −2.61 (2H, br, s, NH), 4.62 (6H, s, 10,20-CH_3), 7.91 (4H, m, $J^* = 5.16$ Hz, Ar-2,6-H), 8.05 (4H, m, $J^* = 5.16$ Hz, Ar-3,5-H), 8.83 (4H, m, β-H), 9.47 (4H, m, β-H); UV–vis (CH_2Cl_2): λ_{max} 419, 517, 552, 654 nm; HRMS (MALDI): m/z 648.0343 (M+, 100%).
   Compound **8**: 7% yield, $R_f = 0.47$ (silica, CH_2Cl_2/ethyl acetate, 9.8:0.2); ^{1}H NMR (400 MHz, $CDCl_3$): δ −2.59 (2H, br, s, NH), 3.97 (12H, s, OMe), 4.61 (6H, s, 10,20-CH_3), 6.90 (2H, m, $J^* = 19.2$ Hz, Ar-4-H), 7.38 (4H, d, $J^* = 19.2$ Hz, Ar-2,6-H), 8.95 (4H, d, $J^* = 18.7$ Hz, β-H), 9.43 (4H, d, $J^* = 18.7$ Hz, β-H); UV–vis (CH_2Cl_2): λ_{max} 428, 524, 564, 611, 641 nm; HRMS (MALDI): m/z 610.2575 (M+ 100%).
   Compound **9**: 4% yield, $R_f = 0.63$ (silica, CH_2Cl_2/hexane, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ −2.57 (2H, br, NH), 2.72 (6H, s, CH_3), 4.60 (6H, s, 10,20-CH_3), 7.57 (4H, m, $J^* = 19.6$ Hz, Ar-2,6-H), 8.05 (4H, m, $J^* = 19.6$ Hz, Ar-3,5-H), 8.87 (4H, d, $J^* = 21.7$ Hz, β-H), 9.42 (4H, d, $J^* = 21.7$ Hz, β-H); UV–vis (CH_2Cl_2): λ_{max} 419, 517, 553, 599, 655 nm; HRMS (EI): m/z 519.2548 ($M+H^+$ 100%).