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Application of combinatorial techniques in the synthesis of unsymmetrically substituted 5,15-diphenylporphyrins

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Abstract

Combinatorial techniques, both solid and solution phase, have been applied to the synthesis of unsymmetrically substituted 5,15-diphenylporphyrins. 5-(4-Hydroxyphenyl)-15-pentafluorophenylporphyrin can be loaded onto solid supports and substituted on the pentafluorophenyl ring with thiols. Diversity is then expanded by cleavage and solution phase substitution of the second phenyl ring using a solid supported base. © 2000 Elsevier Science Ltd. All rights reserved.

Porphyrins are molecules of considerable interest due to their ability to act as photosensitisers when irradiated with visible light.[1] Exploitation of this property has led to clinical approval of porphyrin based photodynamic therapy (PDT) for the treatment of certain cancers and, recently, age related macular degeneration of the retina.[2] It has been shown that the pharmacokinetics and biodistribution of porphyrins used for PDT is dependent on the nature and distribution of substituents around the photoactive macrocyclic core.[3] Structure–activity relationships (SARs) for photodynamic sensitisers have received relatively little attention, compared to other pharmaceuticals, partly due to the difficulty of synthesising porphyrins with a common core, but substituted with a wide diversity of substituents. We have recently become interested in developing synthetic methodologies that will allow libraries of PDT sensitisers to be generated, these can then be subjected to high throughput screening, thus allowing SARs to be defined more rigorously.

Combinatorial chemistry offers the ability, through the use of solid supports, to simplify the work up and purification steps of synthetic reactions and drive reactions to completion using large excesses of reagents.[4] We recognised that these steps are often the most time consuming and tedious stages of porphyrin substitution reactions, usually due to poor solubility and aggregation effects. Combinatorial techniques therefore seemed attractive for use in porphyrin synthetic chemistry. We wish to report here our first results in this area, in which we demonstrate that porphyrins are amenable to loading and

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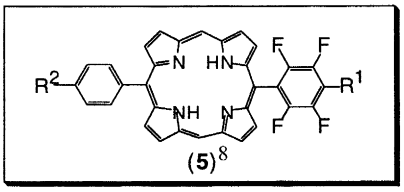
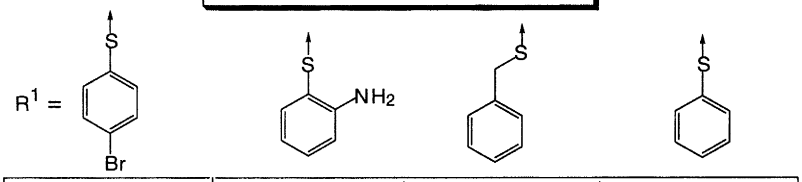
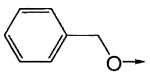
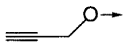
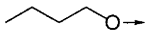
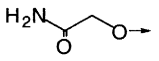
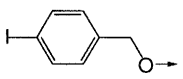
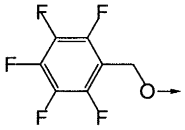
Table 1
Unsymmetrical 5,15-diphenylporphyrin library. HPLC: C_{18} gradient water/MeCN(1:1) 0.1% TFA to MeCN 0.1% TFA over 30 min; MS: MALDI-TOF



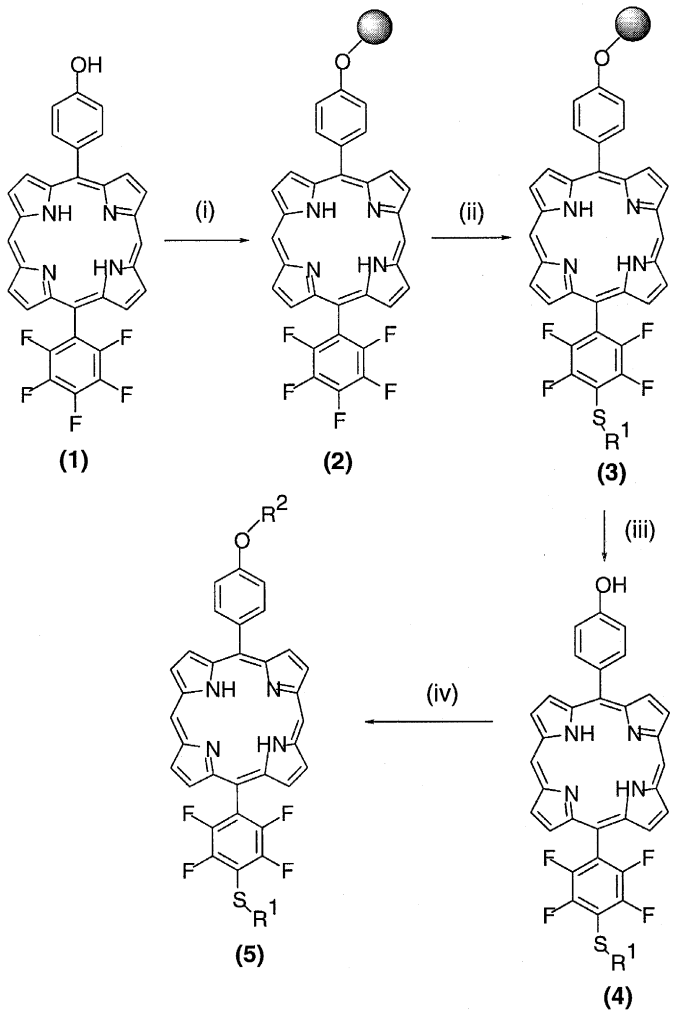
(**5**)[8]



R^2 =	R^1 =			
H–O–	R_t = 15.4 (86%) m/z = 738 λ_{max} = 408	R_t = 13.8 (85%) m/z = 674 λ_{max} = 404	R_t = 14.3 (65%) m/z = 672 λ_{max} = 408	R_t = 13.7 (83%) m/z = 658 λ_{max} = 408
	R_t = 16.1 (76%) m/z = 829 λ_{max} = 408	R_t = 15.1 (69%) m/z = 764 λ_{max} = 404	R_t = 15.9 (69%) m/z = 764 λ_{max} = 408	R_t = 15.8 (83%) m/z = 750 λ_{max} = 408
	R_t = 15.5 (69%) m/z = 775 λ_{max} = 408	R_t = 13.8 (87%) m/z = 712 λ_{max} = 404	R_t = 14.6 (55%) m/z = 711 λ_{max} = 404	R_t = 13.8 (60%) m/z = 699 λ_{max} = 408
	R_t = 18.5 (75%) m/z = 793 λ_{max} = 408	R_t = 15.5 (60%) m/z = 730 λ_{max} = 408	R_t = 15.5 (66%) m/z = 729 λ_{max} = 408	R_t = 14.5 (81%) m/z = 714 λ_{max} = 408
	R_t = 13.2 (69%) m/z = 795 λ_{max} = 408	R_t = 11.9 (66%) m/z = 730 λ_{max} = 404	R_t = 14.3 (58%) m/z = 731 λ_{max} = 404	R_t = 14.6 (66%) m/z = 716 λ_{max} = 408
	R_t = 17.1 (81%) m/z = 953 λ_{max} = 408	R_t = 16.2(63%) m/z = 889 λ_{max} = 408	R_t = 16.5 (43%) m/z = 889 λ_{max} = 408	R_t = 16.8 (80%) m/z = 875 λ_{max} = 408
	R_t = 16.7 (89%) m/z = 917 λ_{max} = 408	R_t = 15.7(62%) m/z = 853 λ_{max} = 408	R_t = 16.3 (64%) m/z = 852 λ_{max} = 408	R_t = 16.3 (96%) m/z = 838 λ_{max} = 408

substitution reactions on polystyrene resin, and further extend this using resin bound reagents to generate a two dimensional library of unsymmetrically *trans* substituted 5,15-diphenylporphyrins.

In order to exploit the advantages of solid phase synthetic techniques it was first necessary to identify a resin/porphyrin pair suitable for this purpose. Several combinations were explored, however our best results were obtained using 2-chlorotrityl chloride resin and porphyrins bearing a 4-hydroxyphenyl moiety. We found that good loading could be obtained with this system under essentially ambient conditions,



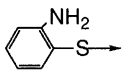
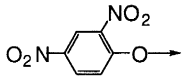
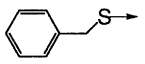
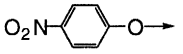
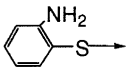
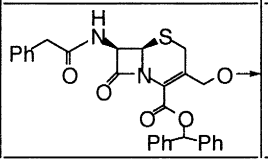
Scheme 1. (i) 2-Chlorotrityl chloride resin 0.5 equiv., DIPEA 1.5 equiv., CH_2Cl_2 25°C, 17 h; (ii) R^1SH 100 equiv., DMF 25°C, 96 h; (iii) 2% TFA in CH_2Cl_2 25°C, 2 h; (iv) R^2X 0.8 equiv., TBD resin 6 equiv., CH_2Cl_2, 25°C, 96 h

we also determined that the porphyrin could be recovered quantitatively from the resin by cleavage with TFA in CH_2Cl_2. Recently, we have reported on a facile reaction which allows porphyrins bearing one pentafluorophenyl ring to undergo nucleophilic displacement of the fluorine *para* to the porphyrin when reacted with thiols.[5] In order to determine if this reaction could be successfully transferred to the solid phase it was first necessary to synthesise a porphyrin bearing the two functionalities mentioned above, 4-hydroxyphenyl and pentafluorophenyl respectively. Utilising methodology developed in our laboratory for the synthesis of unsymmetrically substituted 5,15-diphenylporphyrins,[6] 5-(4-hydroxyphenyl)-15-pentafluorophenylporphyrin (**1**) was synthesised in 16% yield and loaded onto 2-chlorotrityl chloride resin (**2**). The batch of loaded resin was then split and subjected to reaction with a number of different thiols, finally the resins were washed and products (**3**) were cleaved using 2% TFA in CH_2Cl_2. HPLC, MALDI-MS and UV–vis spectroscopy confirmed the identities and purities of products (Table 1). Now that optimised conditions had been established for functionalising one position of the porphyrin on the solid phase, we turned our attention to a second point at which diversity could be generated. We became interested in utilising the phenolic OH group, unmasked by cleavage (**4**), as a second point of diversity.

Xu et al. reported recently on the use of a resin bound guanidine (TBD resin) as combined base/scavenger for the solution phase alkylation of phenols.[7] Treatment of monofunctionalised porphyrins generated by cleavage from the solid phase with excess TBD resin, followed by a variety of alkylating agents (Scheme 1) gave 5,15-diphenylporphyrins unsymmetrically functionalised with ethers on one phenyl ring and thioethers on the opposing ring (**5**) (Table 1).

Having demonstrated the applicability of solid phase techniques for functionalisation of porphyrins, we became interested in expanding the range of reactions and substrates which could be used. We therefore investigated, firstly, the possibility of utilising the TBD resin/phenolic porphyrin to perform SNAr reactions and, secondly, the ability of this system to conjugate porphyrins to sensitive, biologically active substrates. Fluoro-2,4-dinitrobenzene and fluoro-4-nitrobenzene were successfully reacted with TBD resin/phenolic porphyrins as in Scheme 1, resulting in displacement of the *para* fluorine in both cases to give the corresponding unsymmetric 5,15-diphenyl porphyrins (Table 2). Finally, we wished to determine if our reactions were compatible with sensitive biologically active substrates. A protected derivative of the antibiotic 7-aminocephalosporanic acid was selected as a substrate for this purpose. Once again conditions were as shown in Scheme 1 and initial solid phase substitution was performed with 2-aminothiophenol. Subsequent reaction of the cleavage product (**5**, R^1=2-aminothiophenyl, R^2=OH) with the cephalosporin resulted in the ether linked porphyrin–cephalosporin dimer (Table 2).

Table 2

(**5**) R^1=	R^2 =	
		R_t = 14.8 (87%) m/z = 840 λ_{max} = 404
		R_t = 13.7 (72%) m/z = 796 λ_{max} = 408
		R_t = 10.4 (47%) m/z = 1169 λ_{max} = 408

In conclusion, we have demonstrated the applicability and flexibility of combinatorial methods in porphyrin chemistry. Several different classes of reactions were found to be possible using both solid and solution phase techniques, and relatively sensitive biologically active substrates could be used. We believe that the use of such techniques will help in generating porphyrin libraries for determining structure–activity relationships, and also provide a novel and convenient method for conjugating porphyrins to biomolecules.

Acknowledgements

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6. Clarke, O. J.; Boyle, R. W. *Tetrahedron Lett.* **1998**, *39*, 7167–7168.
7. Xu, W.; Mohan, R.; Morrisey, M. M. *Tetrahedron Lett*. **1997**, *38*, 7337–7340.
8. Analytical data for compound (**5**) R^1=2-aminothiophenyl, R^2=propargyloxy yield=48% ^{1}H NMR (270 MHz, $CDCl_3$) δ −3.33 (2H, s, NH), 1.21 (2H, s, NH_2), 2.64 (1H, s, CCH), 5.21 (2H, s, CH_2), 7.32–7.36 (2H, m, ArH), 7.39–7.63 (4H, m, ArH), 8.08–8.12 (2H, m, ArH), 9.03–9.04 (2H, m, βH), 9.28–9.31 (4H, m, βH), 9.35–9.37 (2H, m, βH), 10.23 (2H, s, *meso*); UV–vis (CH_2Cl_2) 404, 504, 536, 576, 628 nm; MS(MALDI) 712.