Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5083–5086

TETRAHEDRON LETTERS

Parallel synthesis of unsymmetrically substituted tetraphenyl porphyrins on Wang resin

Baolu Shi,[a] Martin Scobie[b] and Ross W. Boyle[a,*]

[a]*Department of Chemistry, University of Hull, Cottingham Road, Hull, East Yorkshire HU6 7RX, UK*
[b]*Department of Chemical Technologies, Biovitrum AB, Rapsgatan 7, SE-751 82, Uppsala, Sweden*

Received 1 April 2003; revised 22 April 2003; accepted 2 May 2003

Abstract—A method for synthesizing combinatorial libraries of unsymmetrically substituted tetra-*meso*-phenyl porphyrins on polystyrene based resin is described. Attachment of 5,15-dibromo-10-(4-hydroxyphenyl)-20-(4-nitrophenyl)porphyrin onto brominated Wang resin gave a convenient scaffold for the synthesis of photoactive porphyrin libraries with three points for generating diversity. An array of nine TPP derivatives was prepared by sequential Suzuki coupling/nitro-reduction and acylation protocols.

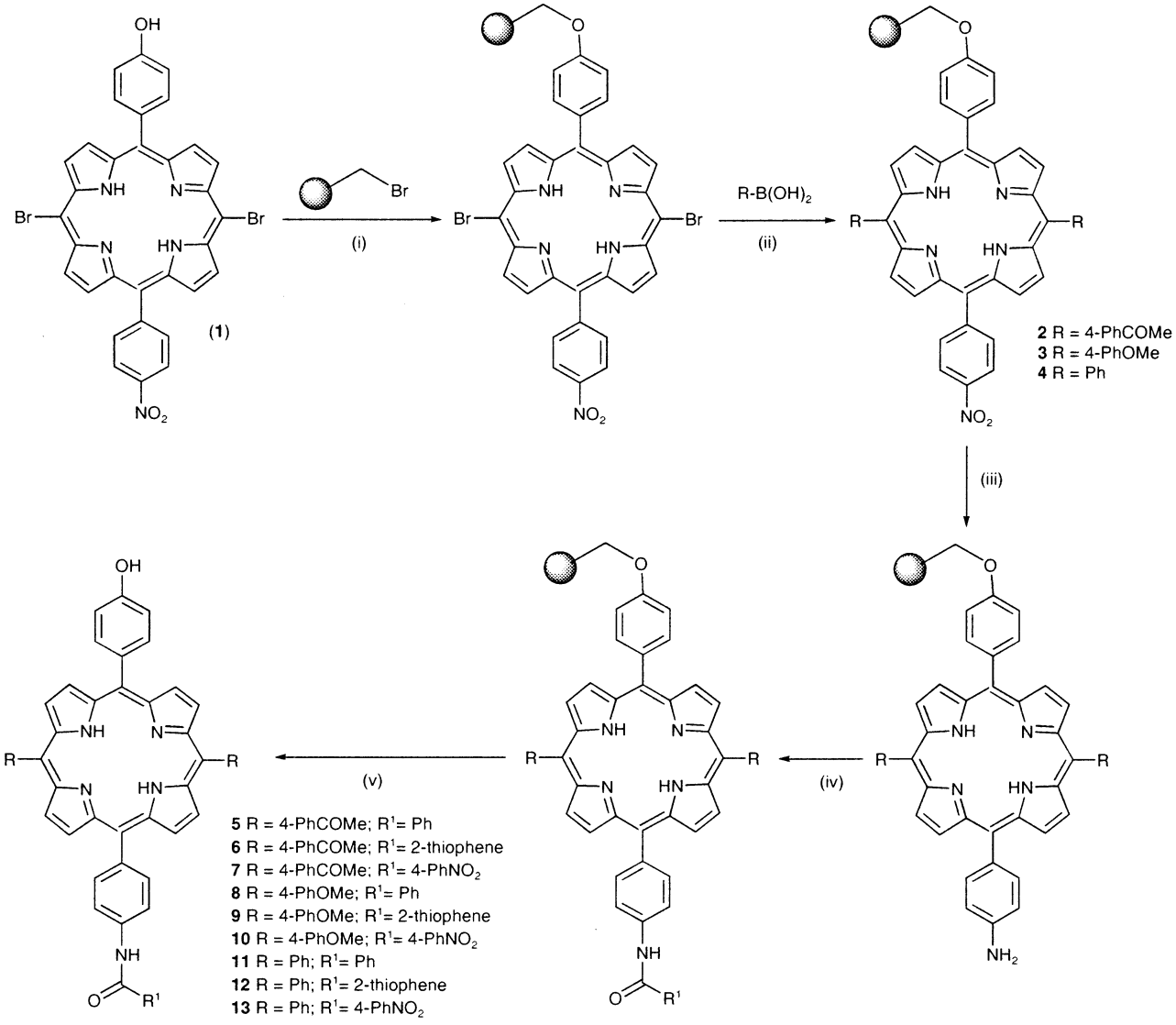
Tetra-*meso*-phenyl porphyrins (TPPs) are the most readily available synthetic porphyrins, and symmetrically substituted derivatives can be produced easily and in reasonable quantities by the well established procedures of Adler[1] and Lindsey.[2] Unsymmetrically substituted TPPs are, however, much more complicated to access by these routes, and often involve condensation of mixtures of differently substituted benzaldehydes with pyrrole, to generate statistical mixtures of differently substituted TPPs and isomers, which must then be separated by extensive and laborious chromatography. Indeed, some substituent combinations defy synthesis by this methodology due to close similarities in R_f values, which make chromatographic separations impossible. It has been demonstrated that many 'high tech' applications of porphyrins such as optoelectronics[3] and photodynamic therapy[4] require unsymmetrically substituted TPPs. Unsymmetrical substituent patterns and specific isomers allow incorporation of porphyrins into polymeric matrices in a controlled manner and the majority of most active photodynamic sensitisers used for photodynamic therapy have unsymmetrical patterns of substituents around the photoactive porphyrin core.[5] Previously we have developed a variety of solution phase methods for synthesis of unsymmetrically substituted tetra- and di-*meso*-phenyl porphyrins,[6–8] and recently we have extended this to allow a 5,15-di-*meso*-phenyl porphyrin (DPP) attached to a solid support to be used as a scaffold for the synthesis of an unsymmetrically substituted DPP library.[9] In the latter case one point of diversity was available for elaboration on the solid support, while the second point of diversity was functionalised after cleavage, in solution using a resin bound reagent. We now wish to report methodology which allows a DPP scaffold to be attached to resin and converted to unsymmetrically substituted TPPs by independent reactions at two points of diversity on the porphyrin core.

The porphyrin scaffold, 5,15-dibromo-10-(4-hydroxyphenyl)-20-(4-nitrophenyl)porphyrin, **1** was prepared in 6% overall yield by condensation of 5-(4-*t*-butyldiphenylsiloxyphenyl)dipyrromethane[10] with 5-(4-nitrophenyl)dipyrromethane[10] using a previously reported procedure[11] followed by bis-*meso*-bromination of the resulting DPP[12] and finally deprotection of the silyl protected hydroxyl group with tetrabutylammonium fluoride.[10] In previous work involving attachment of porphyrins to solid supports[9] it has been demonstrated that 2-chlorotrityl chloride resin reacts well with hydroxy substituted porphyrins, immobilising them for further reactions, however this resin is highly sensitive to acidic conditions, limiting the on-resin reactions which can be performed without cleavage of the porphyrin. Alternative resins, compatible with a wider range of reaction conditions were therefore investigated. Wang resin is one of the most common and cheapest resins used in combinatorial chemistry, and typically is much less sensitive towards acid induced cleavage of attached substrates. Initially attachment to Wang resin was attempted by utilising 5,15-dibromo-

* Corresponding author. Tel.: (01482) 466353; fax: (01482) 466410; e-mail: r.w.boyle@hull.ac.uk

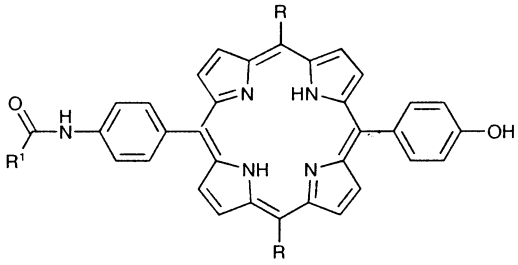
0040-4039/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4039(03)01142-0

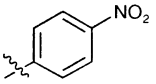
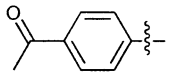
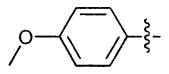
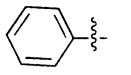
10-(4-nitrophenyl)-20-(4-carboxyphenyl)porphyrin via a carbodiimide coupling reaction; however, this resulted in poor loading values and excess porphyrin was transformed by the reaction conditions and could not be recycled. In order to overcome these unfavourable conditions, and yet still take advantage of the acid tolerance associated with Wang resin, commercially available brominated Wang resin was used, which resulted in good loading values and quantitative recovery of excess porphyrin which could be recycled (Scheme 1). The loaded batch of resin was split into portions in preparation for parallel combinatorial synthesis. Diversity was first introduced at the 5,15-*meso* positions by adapting synthetic conditions previously developed in our laboratory for Suzuki coupling of brominated porphyrins and aryl boronic acids in solution.[13] Three aryl boronic acids, benzene boronic acid, 4-acetylbenzene boronic acid and 4-methoxybenzene boronic acid, were selected to represent a range of functionalities. Resin bound porphyrin was stirred under reflux with boronic acid (10 equiv.), tetrakis(triphenylphosphine) palladium(0) (0.1 equiv.) and potassium phosphate (20 equiv.) in anhydrous THF for 16 h. A sample of one batch of resin was then cleaved with 50% trifluoroacetic acid in dichloromethane and the resulting porphyrin product checked. Analytical results indicated efficient on-resin conversion of the DPP scaffold to the corresponding TPPs (**2**–**4**). Due to the large number of aryl boronic acids available commercially large one-dimensional libraries can be produced by on-resin Suzuki coupling of brominated porphyrins; however, the scale of these libraries would be greatly increased by introduction of a second point of diversity. Porphyrins bearing nitro groups are well known to undergo reduction to amino groups by treatment with tin(II) chloride in aqueous HCl.[14] Although Wang resin is not compatible with the fully aqueous reaction conditions, it was possible to perform the



Scheme 1. *Reagents and conditions*: (i) Na_2CO_3, DMF, rt, 1 day; (ii) tetrakis(triphenylphosphine) palladium(0), K_3PO_4, THF, reflux overnight; (iii) tin(II) chloride dihydrate, DMF/H_2O, rt, 1 day; (iv) R^1COCl, DIPEA, DCM, rt, overnight; (10) 50% TFA/DCM, rt, 2 h.

Table 1. Library of unsymmetrically substituted $AA'B_2$ porphyrins. *Conditions*: HPLC: Luna 5μ C_{18} 250×4.6 mm, 1 ml/min, isocratic 20% MeCN/H_2O (containing 0.1% TFA) for 2 min, then gradient elution to 100% MeCN over 30 min; MS: MALDI-TOF (no matrix)



R \ R1			
	**5** 77% R_t = 26.0 *m/z* = 834.7	**6** 85% R_t = 25.6 *m/z* = 840.8	**7** 79% R_t = 27.3 *m/z* = 879.8
	**8** 73% R_t = 19.2 *m/z* = 810.8	**9** 80% R_t = 19.0 *m/z* = 816.8	**10** 64% R_t = 23.7 *m/z* = 855.8
	**11** 85% R_t = 23.7 *m/z* = 750.8	**12** 86% R_t = 23.3 *m/z* = 756.7	**13** 69% R_t = 24.5 *m/z* = 795.7

reduction in aqueous dimethylformamide, resulting in efficient conversion of the resin bound nitro porphyrin to the corresponding amine. Sequential Suzuki coupling/tin(II) reduction potentially allowed a second dimension to be added to the combinatorial library by reaction of the amino group with alkylating reagents. The three resin bound TPPs generated by the on-resin Suzuki couplings (**2**–**4**) were subjected, in parallel, to tin(II) reduction followed by reaction with three representative acid chlorides with the aim of generating a small (3×3) library of TPP amides. Cleavage of products and analysis by coupled HPLC/UV–vis diode array/MS gave information regarding the nature and purity of each member of the library (Table 1). Analysis confirmed the presence of the expected TPP amides (**5**–**13**) in all cases.[15] Purity values ranged from 64% to 86%, however it is worth noting that six of the nine members of the library gave purity values greater than 75% for this three-step on-resin reaction sequence. Considering that many three-step reaction sequences for porphyrins in solution would fail to achieve this level of purity without extensive chromatographic purification between each step, the value of this type of procedure for the synthesis of multifunctionalised porphyrins is clear.

In conclusion, a method has been developed which allows unsymmetrical TPPs of the $AA'B_2$ type to be synthesised from a DPP precursor tethered to a solid support. A small library has been constructed to demonstrate the applicability of this procedure in the combinatorial synthesis of multiply substituted porphyrins. It is believed that this type of synthetic strategy will be particularly valuable where large numbers of porphyrins are required to screen for activity in high value applications such as photodynamic therapy.

Acknowledgements

The authors wish to thank the Wellcome Trust (059572, 066948) and BBSRC (21/E12509) for financial support. B.S. thanks the Department of Chemistry, University of Hull for a studentship. The authors also thank Dr. K. Welham and Mrs. B. Worthington for mass spectrometry and NMR analyses.

References

1. Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.
2. Linsdey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827–836.
3. Taylor, P. N.; Huuskonen, J.; Rumbles, G.; Aplin, R. T.; Williams, E.; Anderson, H. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 986–989.
4. MacDonald, I. J.; Dougherty, T. J. *J. Porphyrins Phthalocyanines* **2001**, *5*, 105–129.

5. Boyle, R. W.; Dolphin, D. *Photochem. Photobiol.* **1996**, *63*, 469–485.
6. Clarke, O. J.; Boyle, R. W. *Tetrahedron Lett.* **1998**, *39*, 7167–7168.
7. Shaw, S. J.; Elgie, K. J.; Edwards, C.; Boyle, R. W. *Tetrahedron Lett.* **1999**, *40*, 1595–1596.
8. Shaw, S. J.; Edwards, C.; Boyle, R. W. *Tetrahedron Lett.* **1999**, *40*, 7585–7586.
9. Elgie, K. J.; Scobie, M.; Boyle, R. W. *Tetrahedron Lett.* **2000**, *41*, 2753–2757.
10. Sutton, J. M.; Clarke, O. J.; Fernandez, N.; Boyle, R. W. *Bioconjugate Chem.* **2002**, *13*, 249–263.
11. Boyle, R. W.; Bruckner, C.; Posakony, J.; James, B. R.; Dolphin, D. *Org. Synth.* **1998**, *76*, 287–293.
12. DiMagno, S. G.; Lin, V. S.-Y.; Therien, M. J. *J. Org. Chem.* **1993**, *58*, 5983–5993.
13. Shi, B.; Boyle, R. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, *11*, 1397–1400.
14. Frixa, C.; Mahon, M. F.; Thompson, A. S.; Threadgill, M. D. *Org. Biomol. Chem.* **2003**, *1*, 306–317.
15. In a typical preparation brominated Wang resin (4-(bromomethyl)phenoxymethyl polystyrene, 1.40 mmol/g) (1 equiv.) and Na_2CO_3 (3 equiv.) was added to a solution of 5,15-dibromo-10-(4-hydroxyphenyl)-20-(4-nitrophenyl)-porphyrin (**1**) (2 equiv.) in anhydrous DMF. The mixture was stirred under nitrogen and protected from light at rt for 1 day. The resin was filtered, washed with DMF, DMF/H_2O, MeOH, DCM and MeOH and dried in vacuo. Porphyrin loaded resin was treated with K_3PO_4 (20 equiv.), benzene boronic acid (10 equiv.) and tetrakis(triphenylphosphine) palladium(0) (0.1 equiv.) in anhydrous THF. The mixture was stirred under reflux and protected from light for 16 h. The resin was filtered, washed with THF, THF/H_2O, MeOH, DCM, and MeOH and dried in vacuo. Tin(II) chloride dihydrate (20 equiv.) in DMF/H_2O was added to resin and the reaction was shaken at rt in darkness for 1 day. The resin was then filtered, washed with DMF, MeOH, DCM, MeOH and dried in vacuo. Benzoyl chloride (50 equiv.) and *N*-ethyldiisopropylamine (DIPEA) (50 equiv.) were added to a suspension of resin in DCM. The reaction was shaken at rt and protected from light for 1 day, filtered, washed with DCM and MeOH and dried in vacuo. Finally, the resin was treated with 50% TFA/DCM solution and allowed to react for 2 h at rt. The resin was filtered and washed with DCM (2 ml). The filtrate was collected, diluted further with DCM and washed with saturated aqueous Na_2CO_3 and H_2O. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in vacuo to recover the porphyrin product **11**. UV–vis λ_{max} (CH_2Cl_2) 420, 517, 554, 593, 649 nm; ^1H NMR δ (400MHz, $CDCl_3$), −2.77 (2H, s, NH), 7.20–7.22 (2H, m, 5-Ar-3,5H), 7.60–7.62 (2H, m, 15-Ar-3,5H), 7.75–7.77 (6H, m, 10,20-Ar-3,4,5H), 8.05–8.09 (5H, m, benzamide H), 8.17–8.25 (8H, m, 5,10,15,20-Ar-2,6H) and 8.84–8.89 (8H, m, β-pyrrole H); MS (MALDI-TOF) $m/z = 750.8$ ($[M+H]^+$)