Regioselective halogenation and palladium-catalysed couplings on 5,15-diphenylporphyrin

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Received 5 March 1999; Revised 30 April 1999
Accepted 5 May 1999

ABSTRACT: 5,15-Diphenylporphyrin was regiospecifically halogenated in high yield to give 5-iodo-15-bromo-10,20-diphenylporphyrin, which was then subjected to Heck and Stille-type coupling reactions to form unsymmetrically substituted porphyrins. The regioselectivity of the iodination of diphenylporphyrins and subsequent formation of amphiphilic porphyrins via palladium-based methodology was also studied. The utility of this method for the synthesis of photodynamic sensitisers has been demonstrated on AR4-2J rat pancreatic carcinoma cells. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: porphyrins; palladium; cross-coupling; amphiphiles; photodynamic therapy

INTRODUCTION

The introduction of substituents onto a preformed porphyrin macrocycle is usually performed by electrophilic substitution reactions; however, regioselectivity has been almost exclusively controlled by blocking one of the two differential sites of attack present on the porphyrin with other groups. This is exemplified by tetraphenylporphyrin [1], where the meso positions are blocked by phenyl groups, thereby directing substituents to the available β positions, and octaalkylporphyrin [2], where, conversely, the β positions are blocked by alkyl groups, leading to substitution at the meso positions. Even in these cases, introduction of more than one substituent can result in mixtures of regioisomers being formed.

Recently we have become interested in exploring the regioselectivity of substitution reactions on 5,15-diphenylporphyrin (1), which has both meso and β positions available on the same porphyrin molecule. We are also interested in developing synthetic methodology to allow the regioselective introduction of a variety of different groups using intermediate halogenodiphenylporphyrins and palladium(0)-catalysed coupling reactions. We present here methods for the regioselective halogenation of 5,15-diphenylporphyrin (1) and also the subsequent conversion of the products to a range of unsymmetrically substituted analogues using palladium(0)-catalysed coupling reactions.

RESULTS AND DISCUSSION

In a previous communication [3] we reported the first procedure for iodination of 5,15-diphenylporphyrin (1). The regioselectivity of this reaction was such that monosubstitution occurred selectively at one of the two available meso positions; however, if the same conditions were used for disubstitution, the second iodo group was introduced non-selectively at one of the eight available β positions, resulting in a mixture of regioisomers. We now report that diiodination of 5,15-diphenylporphyrin can be performed regioselectively at the two meso positions when methoxy groups are present at the 3’, 4’ and 5’ positions of the two phenyl rings (2); this is in accord with a recent report that sterically bulky substituents on the phenyl rings encourage meso, meso diiodination [4]. The ability to obtain 5,15-diido-10,20-di(3’,4’,5’-trimethoxyphenyl)porphyrin (3, M=H₂) in good yield (59%)}

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led us to explore the possibility of using palladium(0)-catalysed couplings [5, 6] to synthesise a series of amphiphilic porphyrins for studying structure–activity relationships of these molecules. Amphiphilic porphyrin photosensitisers have previously been shown to be amongst the most active compounds [7] for use in photodynamic therapy [8]. Coupling of [5,15-diodo-10,20-di(3′,4′,5′-trimethoxyphenyl)porphyrinato]zinc(II) (3, M=Zn) with 1-pentyne, 1-octyne, 1-dodecyne and 1-hexadecyne respectively gave the expected 10,20-dialkyne-substituted products (4a–4d) in good yields (Scheme 1). Preliminary biological testing of the ability of these compounds to photoinactivate AR4-2J rat pancreatic carcinoma cells [9] indicates an inverse relationship between photodynamic activity and alkyl chain length, with compound 4a (EC₅₀ = 9 μM) showing the highest activity.

The regios elective diiodination described above encouraged us to investigate the possibility of regioselectively introducing two different halogens onto 5,15-diphenylporphyrin (1). 5,15-Diphenylporphyrin (1) was first brominated regioslectively, using N-bromosuccinimide, at one meso position. Application of our iodination conditions to the 5-bromo-10,20-diphenylporphyrin resulted in conversion of this compound into 5-iodo-15-bromo-10,20-diphenylporphyrin (5, M=H₂) in quantitative yield. Interestingly, if the order of halogenations is reversed and 5-iodo-10,20-diphenylporphyrin is brominated, a complex mixture of products results. Regioselective control over the introduction of both a bromo and an iodo group onto 5,15-diphenylporphyrin (1) offered the possibility of utilising their differential reactivity in palladium(0)-catalysed coupling reactions. It has been demonstrated that an aromatic iodo group undergoes palladium(0)-catalysed coupling at a significantly greater rate compared with the aromatic bromo analogue [10]. We sought to exploit this difference to react the bromo and iodo groups on 5-iodo-10,20-diphenylporphyrin (5, M=H₂) independently with different substrates, thus providing a method for introduction of different substituents onto the porphyrin via similar methodology (Scheme 2).

[5-Iodo-15-bromo-10,20-diphenylporphyrinato]zinc(II) (5, M=Zn) was first reacted with 1-octyne to give [5-bromo-15-(1-octyne)-10,20-diphenylporphyrinato]zinc(II) in 78% yield. As the remaining bromo group on the porphyrin undergoes palladium(0)-catalysed coupling with terminal acetylenes at a very slow rate, it was decided to employ a more reactive trialkyltin-bearing substrate under Stille conditions [11] to complete our experiments. Thus [5-bromo-15-(1-octyne)-10,20-diphenylporphyrinato]zinc(II) was reacted with vinyltributyltin in the presence of tetrakis(triphenylphosphine)palladium(0) to give [5-ethenyl-15-(1-octyne)-10,20-diphenylporphyrinato]zinc(II) (6a).

In conclusion, we have developed novel methods for controlling the regioselectivity and nature of halogenation reactions on 5,15-diphenylporphyrins. In addition, we have developed a method for introducing a variety of different substituents regioselectively onto the 10 and 20 meso positions of the same molecules, independently, to yield unsymmetrically substituted porphyrins. Biological screenings of
unsymmetrically substituted porphyrins and steroidal porphyrins, to determine their potential as photodynamic sensitisers, are currently being performed in our laboratories.

EXPERIMENTAL

General

5,15-Diphenylporphyrin (1) and 5,15-di(3,4,5-trimethoxyphenyl)porphyrin (2) were synthesised as previously described [12]. Porphyrin metallations were performed using a literature procedure [13]. All reagents were purchased from Aldrich Chemical Company, Gillingham, UK and used as received. Chromatography was performed on Silica Gel 60 (200–400 mesh) from Prolabo, UK. NMR spectra were obtained using a Jeol EX270 FT-NMR. Mass spectra were obtained on a Kratos MALDI II mass spectrometer. UV-vis spectra were recorded on a Unicam UV4 spectrophotometer.

5,15-Diiodo-10,20-di(3,4,5-trimethoxyphenyl)porphyrin (3, M=H2)

To 2 (51 mg, 0.08 mmol) in CHCl3 (50 ml) was added I2 (30.5 mg, 0.12 mmol) in one portion. A solution of bis(trifluoroacetoxyl)iodobenzene (38.7 mg, 0.09 mmol) in CHCl3 (25 ml) was added dropwise, followed by pyridine (10 drops). The solution was stirred at room temperature, in the dark, for 20 min. The solvent was evaporated in vacuo and the crude mixture was chromatographed (silica gel, dichloromethane/ethyl acetate 7:1) to give 3, M=H2 as a purple solid (42 mg, 59%). 1H NMR (CDCl3): δ 2.60 (br s, 2H), 3.98 (s, 12H), 4.20 (s, 6H), 7.41 (s, 4H), 8.90 (d, J = 4.84 Hz, 4H), 9.61 (d, J = 5.64 Hz, 4H). MS (MALDI): m/z 894 (M+). UV-vis (EtOH): λmax (log ε) 422 (5.62), 514 (4.25), 554 (3.73), 592 (3.73), 638 (3.14) nm.

[5,15-Dialkynyl-10,20-di(3,4,5-trimethoxyphenyl)]porphyrinato]zinc(II) (4a–4d)

A standard method was employed for the synthesis of 4a–4d which differed only in the weight of alkyl acetylene used.

3, M=Zn (15 mg, 0.016 mmol) in dry THF was added to a flask containing bis(triphenylphosphine)palladium(II) chloride (3 mg, 4.28 μmol) and copper(I) iodide (3 mg, 16 μmol), followed by triethylamine (0.04 ml, 0.28 mmol) and the alkyl acetylene (0.16 mmol). The mixture was stirred under argon at room temperature for 16 h. The solvent was evaporated in vacuo and the crude mixture was chromatographed (silica gel, chloroform) to give 4a (9.3 mg, 70%). 1H NMR (CDCl3): δ 1.00 (m, 6H), 2.04 (m, 4H), 3.00 (m, 4H), 3.98 (s, 12H), 4.18 (s, 6H), 7.44 (s, 4H), 8.99 (d, J = 4.03 Hz, 4H), 9.68 (d, J = 4.03 Hz, 4H). MS (MALDI): m/z 838 (M+). UV-vis (EtOH): λmax (log ε) 434 (5.55), 572 (4.41), 622 (4.06) nm. 4b (10.4 mg, 72%). 1H NMR (CDCl3): δ 1.00 (m, 6H), 1.37 (m, 8H), 1.84 (m, 4H), 2.03 (m, 4H), 3.01 (m, 4H), 3.96 (s, 12H), 4.15 (s, 6H), 7.43 (s, 4H), 8.98 (d, J = 4.83 Hz, 4H), 9.67 (d, J = 4.83 Hz, 4H). MS (MALDI): m/z 922 (M+). UV-vis (EtOH): λmax (log ε)
5-Bromo-10,20-diphenylporphyrin

5,15-Diphenyolphyrin (1) (135 mg, 0.29 mmol) was dissolved in chloroform (150 ml). To this was added N-bromosuccinimide (39 mg, 0.22 mmol). The mixture was stirred for 30 min, then the solvent was evaporated in vacuo and the residue was purified by column chromatography (silica, hexane/toluene 3:1) to yield 105 mg (66%) of 5-bromo-10,20-diphenylporphyrin as a purple solid. $^1$H NMR (CDCl$_3$): $\delta$ –3.01 (br s, 2H), 7.72–7.86 (m, 6H), 8.14–8.26 (m, 4H), 8.95–8.97 (m, 4H), 9.28 (d, $J$ = 4.5 Hz, 2H), 9.74 (d, $J$ = 4.5 Hz, 2H), 10.16 (s, 1H). MS (El): $m/z$ 540/542 (M$^+$). UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$) 414 (5.54), 512 (4.21), 544 (4.01), 588 (3.65), 644 (3.62) nm.

5-Lodo-15-bromo-10,20-diphenylporphyrin (5, M=H$_2$) Bromo-10,20-diphenyolphyrin (54 mg, 0.10 mmol) was dissolved in chloroform (80 ml). Iodine (36 mg, 0.14 mmol) was added, followed by pyridine (four drops) and bis(trifluoroacetoxy)iodobenzene (42 mg, 0.10 mmol). The mixture was stirred for 48 h at room temperature in the dark. After removal of the solvent and purification by chromatography (silica, dichloromethane), 5, M=H$_2$ was obtained as a purple solid in quantitative yield. $^1$H NMR (CDCl$_3$): $\delta$ –2.68 (br s, 2H), 7.71–7.83 (m, 6H), 8.11–8.20 (m, 4H), 8.76–8.86 (m, 4H), 9.54–9.63 (m, 4H). MS (El): $m/z$ 668 (M$^+$). UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$) 424 (5.47), 560 (4.06), 604 (3.61) nm.

5-Bromo-15-(1-octyn-1-yl)-10,20-diphenyolphyrinato]zinc(II) (6a) The zinc chelate of 5 (M=Zn) (24 mg, 33 mmol) was dissolved in dry THF (15 ml) to which copper(I) iodide (3 mg, 16 µmol), bis(triphenylphosphine)palladium(II) chloride (1.5 mg, 2.1 µmol), triethylamine (50 µl, 0.36 mmol) and 1-octyne (24 µl, 0.16 µmol) had been added. The mixture was stirred under nitrogen for 1.5 h, then the solvent was evaporated in vacuo and the residue was purified by chromatography (silica, hexane/dichloromethane 1:1) to give 6a (18 mg, 78%). $^1$H NMR (DMSO-d$_6$): $\delta$ 0.95 (m, 3H), 1.41–1.59 (m, 4H), 1.75–1.92 (m, 2H), 1.97–2.05 (m, 2H), 3.03 (m, 2H), 7.79–7.86 (m, 6H), 8.13–8.20 (m, 4H), 8.77 (m, 4H), 9.58 (m, 4H). MS (El): $m/z$ 712 (M$^+$). UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$) 428 (5.59), 528 (3.56), 564 (4.15), 604 (3.85) nm.

5-Bromo-15-(1-butyn-4-ol)-10,20-diphenyolphyrinato]zinc(II) (6b) 5, M=Zn (4 mg, 5.5 µmol) was dissolved in dry THF (5 ml) to which copper(I) iodide (1 mg, 6 µmol), bis(triphenylphosphine)palladium chloride (0.5 mg, 0.7 µmol), triethylamine (0.02 ml, 0.14 mmol) and 3-butyln-1-ol (0.05 ml, 0.66 mmol) had been added. The mixture was stirred under nitrogen for 16 h, then the solvent was evaporated in vacuo and the residue was purified by chromatography (silica gel, ethyl acetate/dichloromethane 1:9) to give 6b (2 mg, 54%). $^1$H NMR (CDCl$_3$-d$_6$): $\delta$ 3.15 (m, 2H), 4.06 (m, 2H), 7.84 (m, 6H), 8.17 (m, 4H), 8.73 (m, 4H), 9.61 (m, 4H). MS (El): $m/z$ 672 (M$^+$). UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$) 428 (5.61), 526 (3.48), 562 (4.10), 602 (3.78) nm.

5-Bromo-15-ethynylestradiol-10,20-diphenyolphyrinato]zinc(II) (6c) 5, M=Zn (11 mg, 15 µmol) was dissolved in dry THF (10 ml) to which copper(I) iodide (1 mg, 6 µmol), bis(triphenylphosphine)palladium chloride (0.5 mg, 0.7 µmol), triethylamine (0.02 ml, 0.14 mmol) and 17-ethynylestradiol (10 mg, 0.034 mmol) had been added. The mixture was stirred under nitrogen for 16 h, then the solvent was evaporated in vacuo and the residue was purified by chromatography (silica gel, ethyl acetate/dichloromethane 1:9) to give 6c (6 mg, 45%). $^1$H NMR (CDCl$_3$): $\delta$ 1.09 (s, 3H), 4.47 (br s, 1H), 6.41–6.57 (m, 2H), 7.12 (d, $J$ = 8.8 Hz, 1H), 7.69–7.84 (m, 6H), 8.06–8.22 (m, 4H), 8.83–8.95 (m, 4H), 9.56–9.71 (m, 4H). MS (FAB (thioglycerol + CHCl$_3$ matrix)): $m/z$ 899 (M$^+$). UV-vis (CH$_2$Cl$_2$): $\lambda_{\text{max}}$ (log $\varepsilon$) 430 (5.57), 572 (4.16), 616 (3.94) nm.
[Ethenyl-15-(1-octyne)-10,20-diphenylporphyrinato]zinc(II) (7a)

6a (5 mg, 7 μmol) was dissolved in dry THF (10 ml) to which had been added tetrakis(triphenylphosphine)палладий(0) (0.5 mg) and vinyltributyltin (10 μl, 0.034 mmol). The mixture was refluxed under nitrogen for 48 h. The solvent was evaporated and the residue was chromatographed (silica, dichloromethane) to give 7a (1 mg, 20%). 1 H NMR (CDCl3): δ 0.95 (m, 3H), 1.18–1.55 (m, 4H), 1.78 (m, 2H), 1.98 (m, 2H), 2.96 (m, 2H), 6.03 (m, 1H), 6.42 (m, 1H), 7.55–7.74 (m, 6H), 8.01–8.17 (m, 4H), 8.78–8.94 (m, 4H), 9.10 (m, 1H), 9.45 (m, 2H), 9.61 (m, 2H). MS (EI): m/z 658 (M+). UV-vis (CH2Cl2): λmax (log ε) 428 (5.50), 528 (3.51), 564 (4.12), 606 (3.92) nm.

[5-(1-Butyn-4-ol)-15-ethynyl-10,20-diphenylporphyrinato]zinc(II) (7b)

6b (20 mg, 30 μmol) was dissolved in dry THF (10 ml) to which tetrakis(triphenylphosphine)palladium(0) (2.5 mg, 2.2 μmol) and vinyltributyltin (50 μl, 0.17 μmol) had been added. The mixture was refluxed under nitrogen in the dark for 45 h. The solvent was evaporated and the residue was purified by chromatography (silica, THF/toluene 1:9) to give 7b as a green solid (10 mg, 54%). 1 H NMR (CDCl3): δ 3.15 (t, J = 6.1 Hz, 2H), 4.05 (br s, 2H), 6.05 (dd, J = 17.3, 1.5 Hz, 1H), 6.48 (dd, J = 11.2, 1.5 Hz, 1H), 7.72–7.78 (m, 6H), 8.17 (m, 4H), 8.90 (d, J = 1.4 Hz, 2H), 8.91 (d, J = 1.4 Hz, 2H), 9.18 (dd, J = 17.3, 11.2 Hz, 1H), 9.50 (d, J = 4.5 Hz, 2H), 9.61 (d, J = 4.5 Hz, 2H). MS (EI): m/z 618 (M+). UV-vis (CH2Cl2): λmax (log ε) 430 (5.51), 562 (4.15), 606 (3.94) nm.

[5-Ethenyl-15-ethynylestradiol-10,20-diphenylporphyrinato]zinc(II) (7c)

6c (6 mg, 6.7 μmol) was dissolved in dry THF (4 ml) to which had been added tetrakis(triphenylphosphine)palladium(0) (0.5 mg) and vinyltributyltin (50 μl, 0.17 μmol). The mixture was refluxed under nitrogen for 48 h, then the solvent was evaporated and the residue was purified by chromatography (silica gel, ethyl acetate/dichloromethane 1:9) to give 7c (4 mg, 50%). 1H NMR (CDCl3): δ 1.14 (s, 3H), 4.47 (br s, 1H), 6.05 (d, J = 17.6 Hz), 6.42–6.61 (m, 3H), 7.13 (d, J = 8.8 Hz), 7.65–7.83 (m, 6H), 8.05–8.24 (m, 4H), 8.82–8.99 (m, 4H), 9.18 (dd, J = 17.6, 6.4 Hz), 9.48 (d, J = 4.8 Hz, 2H), 9.65 (d, J = 4.8 Hz, 2H). MS (FAB (thioglycerol/TFA matrix)): m/z 845 (M+). UV-vis (CH2Cl2): λmax (log ε) 430 (5.51), 562 (4.15), 606 (3.94) nm.

Acknowledgements

This work was supported by the Wellcome Trust (049704) and the Natural Sciences and Engineering Council of Canada. We also thank the EPSRC Mass Spectrometry Service, Swansea for analyses.

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