Pergamon

Tetrahedron Letters 43 (2002) 9341–9342

TETRAHEDRON LETTERS

A novel, high-yielding synthesis of *meso*-substituted porphyrins via the direct arylation of porphine

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Received 29 August 2002; accepted 18 October 2002

Abstract—A new method for the synthesis of *meso*-substituted porphyrins is described: reaction of 5,10,15,20-tetrabromoporphine magnesium complex with aryl or heteroaryl boronic acids in the presence of $Pd(PPh_3)_4$ gave *meso*-substituted porphyrins in yields up to 70%. © 2002 Elsevier Science Ltd. All rights reserved.

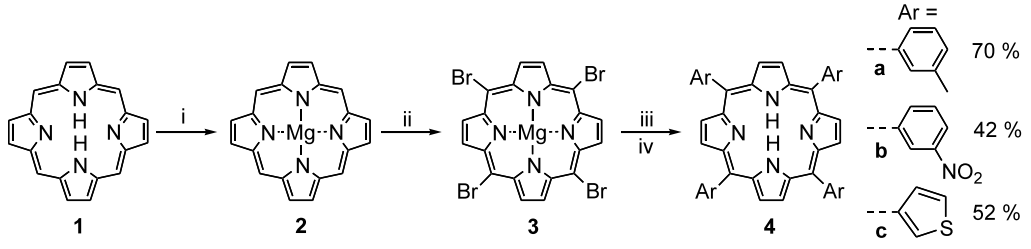
1. Introduction

Interest in cationic porphyrins that modify gene expression or inhibit human telomerase has led us to design a number of novel porphyrins that might interact selectively with tetraplex DNA and thereby modify the growth of tumour cells.[1–5] Whilst synthesis by the conventional condensation of pyrrole with aryl and heteroaryl aldehydes proved adequate where the aldehydes were readily available, the poor yields encountered in the porphyrin-forming step (typically in the range 1–17%) meant that this approach was unsuitable for the preparation of substituted porphyrins where the corresponding aldehyde was only available after several synthetic steps; yields were particularly low in the case of aldehydes bearing heterocylic groups.[1]

The observation that the *meso* positions of unsubstituted porphine **1** show more aromatic than olefinic character in their reactions[6] led us to investigate the direct substitution of porphine. Thus, we envisaged that *meso*-tetrabromoporphine, **3**, could undergo a Suzuki cross-coupling[7] reaction with arylboronic acids in the presence of a palladium(0) catalyst to yield 5,10,15,20-tetra aryl—or tetra heteroaryl—porphines, **4** (Scheme 1).

2. Results and discussion

The selective bromination of porphine at the *meso* positions is known but experimental details have not been reported. Crucially, bromination with *N*-bromoacetamide was directed to the *meso* positions when porphine was present as the magnesium complex, whilst in the absence of magnesium, bromination was observed solely at the pyrrole β-positions.[8] Magnesium·porphine complex **2**[9] was prepared by an adaptation of the method of Lindsey and Woodford;[10] it was



Scheme 1. *Reagents and conditions*: (i) $MgBr_2{\cdot}OEt_2$, Et_3N, CH_2Cl_2, 60°C; (ii) $CH_3CONHBr$, $CHCl_3$, 0°C; (iii) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, $PhCH_3$, MeOH, 70°C; (iv) HCl.

Keywords: porphyrin; Suzuki coupling reactions; palladium.

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PII: S0040-4039(02)02339-0

extremely acid labile so was purified by careful chromatography on basic alumina. Subsequent bromination with a small excess of *N*-bromoacetamide yielded the desired 5,10,15,20-tetrabromoporhine **3**[11] in 97% isolated yield. Coupling with aryl boronic acids using standard Suzuki conditions, followed by a final acid wash to remove the magnesium ion, furnished the desired *meso*-aryl products, **4**, in up to 70% yields.[12]

The Suzuki coupling reaction has seen wide application in the preparation of biaryl compounds and its versatility has resulted in its use in the construction of combinatorial libraries, adaptation to solid phase technologies and a rapid increase in the range of commercially available boronic acids. Herein, its value in the preparation of substituted porphyrins has been demonstrated. In the course of this work, conceptually similar investigations were reported[13,14] using palladium-catalysed reactions to arylate *meso*-halogenated porphyrins; none the less, the current report shows the generality of the method and extends it to the introduction of heterocyclic substituents.

Acknowledgements

The authors would like to associate this communication with Professor Laurence Hurley in whose laboratory this project was initiated. We thank Alvin Carter of Mid-Century Chemicals, Chicago IL, for many helpful discussions. Mass spectra were obtained from the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, UK.

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9. **Porphine magnesium complex (2)**. A mixture of porphine (99 mg, 0.32 mmol) and $MgBr_2{\cdot}OEt_2$ (2 g, 7.75 mmol) in 800 ml of CH_2Cl_2 in the presence of Et_3N (1.5 ml) was stirred at 60°C overnight. The reaction mixture was washed with 5% aqueous $NaHCO_3$ (3×150 ml) and water, then dried over K_2CO_3. The product was purified by chromatography on alumina eluting with CH_2Cl_2–MeOH (50:1) to give red crystals (105 mg, 97%) δ_H ($CDCl_3$, 250 MHz) 10.25 (s, 4H), 9.47 (s, 8H); MS (CI) m/z 333 (M+1).
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11. **5,10,15,20-Tetrabromoporphine magnesium complex (2)**. To a solution of compound **2** (60 mg, 0.18 mmol) in 120 ml of $CHCl_3$ was added dropwise a solution of *N*-bromoacetamide (116 mg, 0.846 mmol) in 20 ml of $CHCl_3$ at 0°C over 5 min. The reaction mixture was then stirred at room temperature for further 10 min, then 20 ml of acetone and 20 ml of water were added to quench the reaction. The organic phase was separated and the aqueous phase was extracted with $CHCl_3$ until no product was detected by TLC. The combined organic phases were dried over K_2CO_3. The product was purified by chromatography on alumina using CH_2Cl_2–MeOH (200:3) as eluent to give a green-purple powder (94.7 mg, 81%) δ_H ($CDCl_3$, 250 MHz) 9.51 (s, 8H); MS (CI) 649 m/z (M+1).
12. **General procedure for preparation of 5,10,15,20-tetra-substituted porphines (4)**. Magnesium complex **3** (20 mg, 30.8 μmol), aryl or heteroaryl boronic acid (140 μmol) and $Pd(Ph_3P)_4$ (1 mg, 0.8 μmol) were dissolved in a mixture of toluene (2.5 ml) and methanol (0.6 ml) under N_2. Aqueous sodium carbonate (2 M, 0.5 ml) was added via a syringe and the reaction mixture was stirred at 70°C for 20 h. The mixture was poured into 40 ml of water and extracted with chloroform (4×30 ml). The combined chloroform extracts were shaken with 1 M HCl (to disrupt the magnesium complex), washed with 1 M ammonia solution, dried over Na_2SO_4, concentrated to a small volume and purified by chromatography on silica gel eluting with appropriate mixtures of dichloromethane with methanol or hexane. **5,10,15,20-Tetra(3-methylphenyl)porphine (4a)**. Yield 70%; δ_H ($CDCl_3$, 250 MHz) 8.85 (s, 8H), 8.02–8.00 (m, 4H), 7.64–7.55 (m, 4H), 2.63 (s, 12H, CH_3), −2.92 (br, 2H, NH); MS (FAB) 671.3174 (M+H), $C_{48}H_{39}N_4$ requires 671.3183. **5,10,15,20-Tetra(3-nitrophenyl)porphine (4b)**. Yield 42%; δ_H ($CDCl_3$, 250 MHz) 9.18 (d, 4H), 8.72 (s, 8H), 8.56 (br d, 4H), 8.10–7.94 (m, 8H), −2.98 (br, 2H, NH); MS (FAB) 795.1945 (M+H), $C_{44}H_{27}N_8O_8$ requires 795.1953. **5,10,15,20-Tetra(thiophen-3-yl)porphine (4c)**. Yield 52%; δ_H ($CDCl_3$, 270 MHz) 8.91 (s, 8H), 7.96 (dd, 4H), 7.93 (dd, 4H), 7.67 (dd, 4H), −2.80 (br, 2H, NH); MS (FAB) 639.0801 (M+H); $C_{63}H_{23}N_4S_4$ requires 639.0806.
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