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Regioselective Synthesis of Multifunctionalised Porphyrins – Coupling of Mono-(pentafluorophenyl)porphyrins to Electrophiles

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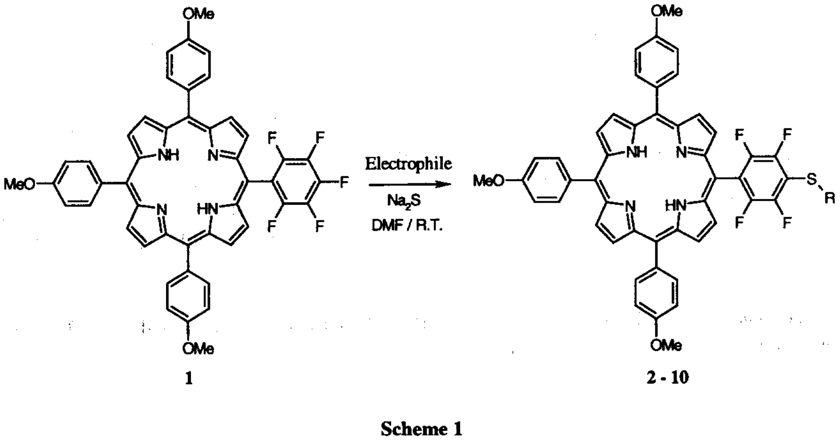
Abstract: A method is presented for the coupling of *meso*-phenylporphyrins, bearing a single pentafluorophenyl ring, to electrophilic moieties. Selective displacement of the *para* fluorine atom, using sodium sulphide, results in a transient thiolate species capable of reacting with electrophiles to give a thioether link. A wide range of electrophiles can be used including alkyl iodides, epoxides and activated aromatic systems. © 1999 Elsevier Science Ltd. All rights reserved.

The rapidly increasing diversity of applications for porphyrin analogues [1,2] makes the regioselective coupling of the porphyrin macrocycle to a wide range of substrates a frequent necessity. In addition, to accommodate sensitive moieties, it is especially desirable that these reactions proceed under mild conditions. We recently reported [3] a generally applicable method by which nucleophilic thiol moieties can be selectively coupled to a mono-(pentafluorophenyl)porphyrin **1**. Further investigations have led to the extension of this methodology allowing the efficient coupling of electrophiles to the same porphyrin nucleus *via* an intermediate porphyrin thiolate.

The nucleophilic substitution of the *p*-F atom of porphyrin **1**, using a range of thiols, was shown to be an efficient reaction [3]. It therefore seemed probable that the sulphide anion would react similarly to produce a thiolate species *in situ*, which could then be trapped by suitable electrophiles. This was an attractive possibility since the inherent instability of porphyin thiolates [4,5] had previously hindered their utility as porphyrin synthons. Weaker nucleophiles such as amino and hydroxy bearing porphyrins have often been found, in our laboratory, to be unreactive in the presence of electrophiles such as alkyl iodides. The greater nucleophilicity of a porphyrin thiolate thus represented a desirable synthetic intermediate.

Treatment of porphyrin **1** at room temperature, with sodium sulphide in the presence of an electrophile, yielded the desired thioether (**2-10**, Scheme 1). This suggested the transient existence of the thiolate anion since no thiol product or dimer could be detected when the electrophile and sodium sulphide were reacted in the absence of porphyrin.



Scheme 1

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The electrophiles investigated included alkyl iodides, epoxides and activated aromatic systems (Table 1). All reacted in good yield (57-92%) using an excess of electrophile and a typical reaction time of 12 h [6]. All compounds were characterised by ^{1}H and ^{13}C NMR, UV-vis and MALDI mass spectrometry.

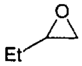
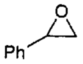
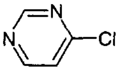
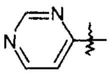
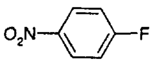
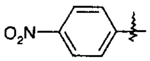
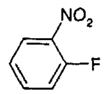
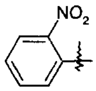
	Electrophile	R	% Yield	Time / h
2	$(CH_3)_3CCH_2I$	$(CH_3)_3CCH_2$	82	12
3	$CH_3(CH_2)_3I$	$CH_3(CH_2)_3$	80	12
4	$HOCH_2CH_2I$	$HOCH_2CH_2$	82	12
5	$CH_3(CH_2)_9I$	$CH_3(CH_2)_9$	74	48
6	H_2NCOCH_2I	H_2NCOCH_2	92	12
7		$CH_3CH_2CH(OH)CH_2$	57	12
8		$PhCH(OH)CH_2$	75	48
9			68	12
10			85	12
11			80	12

Table 1 Synthesis of thioether linked porphyrins

The range of electrophiles shown above demonstrates the flexibility of the reaction, which was found to be quite tolerant of steric hindrance, as illustrated by the reactions with neopentyl iodide (**2**) and 2-nitrofluorobenzene (**11**). The reaction also worked well in the presence of additional functional groups, including hydroxy, amido and nitro substituents. In summary, this method provides a simple, one pot, regioselective route for conjugation of porphyrins to electrophilic moieties, which may be adapted to suit the demands of a wide range of applications.

References and Notes:

[1] Teddy G T, Andrew R M. *J. Am. Chem. Soc.* 1989;111:7443.

[2] Bonnet R. *Chem Soc Reviews.* 1995;19.

[3] Shaw S, Elgie K, Edwards C, Boyle R. *Tetrahedron. Lett.* 1999;40:1595-1596.

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[5] Battioni P, Brigaud O, Desvaux H, Mansuy D, Traylor T. *Tetrahedron Lett.* 1991;32:2893-2896.

[6] In a typical preparation porphyrin 1 (20mg, 0.025mmol) and sodium sulphide (12mg, 0.050mmol) were dissolved in DMF (5ml) and neopentyl iodide (30μl, 0.100mmol) added. The solution was stirred at room temperature and the reaction monitored by T.L.C. After completion of the reaction, the solution was diluted with dichloromethane (20ml) and washed with saturated aqueous sodium hydrogen carbonate. Concentration of the organic layer *in vacuo*, followed by chromatographic purification, yielded the desired thioether linked porphyrin **2** (18mg, 82% yield). ^{1}H NMR (270 MHz, $CDCl_3$) -2.72 (2H, s, NH), 1.21 (9H, s, CH_3), 3.22 (2H, s, CH_2), 4.09 (9H, s, OCH_3), 7.25-7.30 (6H, m, 10,15,20-*m*Ar), 8.09-8.14 (6H, m, 10,15,20-*o*Ar), 8.77-8.79 (2H, m, βH), 8.87 (4H, br s, βH), 8.94-8.96 (2H, m, βH); MS (MALDI) m/e 879.3 (M^{+}).

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