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Mono-(pentafluorophenyl)porphyrins – Useful Intermediates in the Regioselective Synthesis of Multifunctionalised Porphyrins

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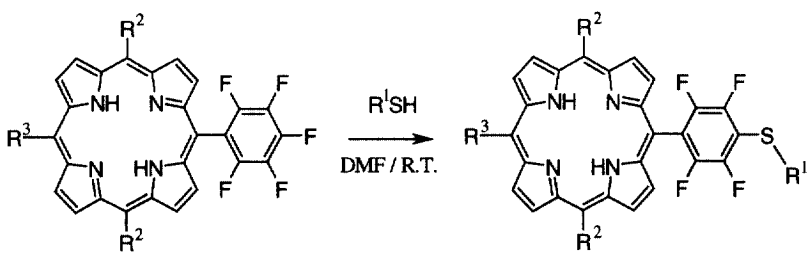
Abstract: A method is presented for coupling *meso*-phenylporphyrins bearing a single pentafluorophenyl ring to thiol substituted molecules. Mild reaction conditions are conducive to the employment of a wide range of thiols including biologically active moieties. Both diphenyl- and tetraphenylporphyrins bearing a variety of different substituents on the non-fluorinated rings have been used to demonstrate the wide applicability of the method.

The increasingly diverse applications of porphyrin analogues in fields ranging from catalysis [1] to biomedical science [2] frequently require modification of the porphyrin core to allow attachment of additional groups. Generally applicable procedures capable of introducing a single substituent to the porphyrin nucleus regioselectively are thus highly desirable. One such method is presented herein.

The selective nucleophilic substitution of the *p*-F atom in a mono-(pentafluorophenyl)porphyrin can be achieved in high yield (70-94%) using a range of thiols at room temperature in DMF solution (Scheme 1). The synthesis of the novel, monofunctionalised, pentafluorophenylporphyrin **1** ($R^2 = R^3 = p\text{-}MeOC_6H_4$) has been achieved by means of a mixed condensation of pentafluorobenzaldehyde with *p*-methoxybenzaldehyde and pyrrole according to the Adler Longo procedure [3].



1 **2 - 13**

Scheme 1

The suitability of the procedure to 5,15-diphenylporphyrins was initially investigated using the symmetrical *bis*-pentafluorophenylporphyrin **1** ($R^2 = H$, $R^3 = C_6F_5$). The successful application of the method to this compound prompted the synthesis of unsymmetric diphenylporphyrins such as **1** ($R^2 = H$, $R^3 = p\text{-}MeOC_6H_4$), which allow conjugation of the porphyrin macrocycle to a single thiol substrate. This may be accomplished using a procedure recently developed within our laboratory [4] which allows selective synthesis of mono-(pentafluorophenyl)-5,15-diphenylporphyrins and thus avoids the need for chromatographic separation of a mixture.

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The substitution of *p*-F atoms by a number of nucleophiles has been reported [5] using a refluxing solution of DMF/Et_3N (2:1). However, we have found that the *p*-F atom can be displaced efficiently at room temperature without requirement for Et_3N [6]. All compounds were characterised by ^1H and ^{13}C N.M.R. and MALDI mass spectrometry (Table 1).

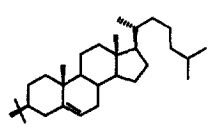
	R^1	R^2	R^3	% Yield	Time / h
2	*p*-HOC_6H_4	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	89	12
3	*p*-$H_2NC_6H_4$	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	73	12
4	Ph	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	94	12
5	Benzyl	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	72	12
6	CH_2CH_2OH	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	80	12
7	$CH_3(CH_2)_{17}$	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	82	36
8	*p*-Pyridyl	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	71	48
9		*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	70	168
10	*p*-HOC_6H_4	H	*p*-$MeOC_6H_4$	84	12
11	*p*-HOC_6H_4	H	3,4,5-$(MeO)_3C_6H_2$	89	12
12	*p*-HOC_6H_4	H	*p*-$MeO_2CC_6H_4$	77	
13	$CH_3(CH_2)_{17}$	H	*p*-$MeO_2CC_6H_4$	91	12

Table 1 Synthesis of thioether linked porphyrins

The range of thiols shown above demonstrates the flexibility of the reaction as well as illustrating its tolerance of additional functional groups. It was found that aromatic, aliphatic and heterocyclic groups were compatible with the reaction conditions. However, it is noteworthy that neither severely sterically hindered thiols e.g. Ph_3CSH nor thioesters e.g. HSCOMe underwent reaction. In summary, it should be emphasised that this method provides a single step, high yielding and regioselective route for conjugation of porphyrins to thiol substituted moieties which may be adapted to suit the demands of a wide range of applications.

References and Notes:

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

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[4] Clarke O, Boyle R. *Tetrahedron Lett.* 1998;39:7167-7168

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

[6] In a typical preparation porphyrin **1** ($R^2 = R^3$ = *p*-$MeOC_6H_4$), (20mg, 0.025mmol) was dissolved in DMF (5ml) and the required thiol (1.2 eq) 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** (20mg, 89% yield). ^1H NMR (270 MHz, $CDCl_3$) –2.72 (2H, s, NH), 4.09 (9H, s, CH_3), 6.90-6.92 (2H, m, *m*Ar-phenolic), 7.27-7.31 (6H, m, 10,15,20-*m*Ar), 7.68-7.71 (2H, m, *o*Ar-phenolic), 8.09-8.13 (6H, m, 10,15,20-*o*Ar), 8.75-8.77 (2H, m, βH), 8.87 (4H, br s, βH), 8.92-8.94 (2H, m, βH); MS (MALDI) m/e 901.5 (M^+).

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