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A FACILE PORPHYRIN ESTERIFICATION / ETHERIFICATION PROCEDURE

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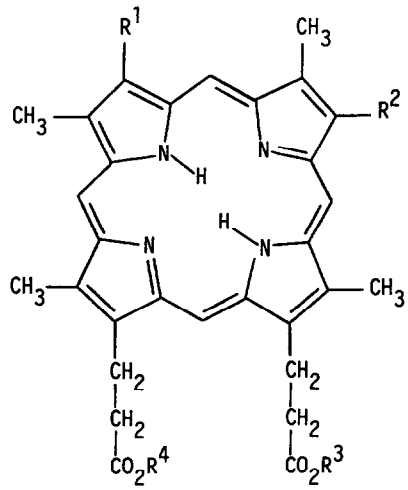
Abstract: Porphyrin carboxylic acids and 1-hydroxyethyl groups can be rapidly esterified and etherified using alcohol/trialkyl orthoformate/strong acid mixtures; addition of water to the reagent permits esterification only.

The esterification of many of the naturally occurring porphyrin carboxylic acids is often not a trivial process using common reagents. For example, diazomethane reacts with hemin at the metal atom as well as the carboxylic acid groups;[1,2] protoporphyrin may undergo acid catalysed additions to the vinyl groups with acidified alcohol reagents at room temperature[1] and hematoporphyrin can be etherified and/or dehydrated at the 1-hydroxyethyl side chains, as well as esterified, using acidified alcohol reagents.[1,2] For these reasons many of the esterification procedures for these compounds specify long reaction times (many hours to several days) at low temperatures (0° or below) to minimise side reactions.[1,2]

Because diazomethane can be inconvenient to prepare, particularly for small amounts of porphyrins, and since it is not suitable for the esterification of metalloporphyrins, we have been interested in finding alternative conditions for the esterification of porphyrin acids that are quick as well as quantitative. In addition, we required a procedure that would permit the esterification of aqueous solutions of porphyrin acids since the vacuum drying of some porphyrin acids, particularly those with 1-hydroxyethyl or related side chains, can lead to modification of the porphyrin periphery. A search of the literature revealed only a brief comment that aqueous solutions of porphyrin acids can be rapidly esterified by a reagent comprising trimethyl orthoformate, methanol and concentrated sulfuric acid.[3] Unfortunately, details of this procedure have not been published. We now report that a reagent consisting of a trialkyl orthoformate, the corresponding alcohol and a strong acid, rapidly esterifies porphyrin acids. The reaction can be controlled to permit both esterification and etherification, or esterification only, of hematoporphyrin related systems by the absence or addition of water.

Table 1 summarises the reactions of hematoporphyrin (**1**) with a variety of acid catalysed esterification procedures. Entry 1 clearly indicates that both esterification and etherification occur using the classical methanol/concentrated sulfuric acid procedure at room temperature for forty-five minutes. The esterification is much slower in methanol



	R^1	R^2	R^3	R^4
(1)	HE	HE	H	H
(2)	HE	HE	CH_3,H*	
(3)	HE	HE	CH_3	CH_3
(4)	HE,ME*		CH_3	CH_3
(5a)	ME	ME	CH_3	CH_3
(5b)	EE	EE	C_2H_5	C_2H_5
(6)	HE,V*		H	H
(7a)	ME,V*		CH_3	CH_3
(7b)	EE,V*		C_2H_5	C_2H_5
(8)	V	V	H	H
(9a)	V	V	CH_3	CH_3
(9b)	V	V	C_2H_5	C_2H_5
(10)	C_2H_5	C_2H_5	H	H
(11a)	C_2H_5	C_2H_5	CH_3	CH_3
(11b)	C_2H_5	C_2H_5	C_2H_5	C_2H_5

HE = $CH_3CH(OH)$— , ME = $CH_3CH(OCH_3)$— , EE = $CH_3CH(OC_2H_5)$— , V = CH_2=CH— .

* refers to the mixture of the two possible regioisomers.

saturated with anhydrous hydrogen chloride and requires six hours at room temperature to complete the reaction. Entry 2 shows that etherification is enhanced by the addition of trimethyl orthoformate. This synthesis of the dimethyl ether (**5a**) of hematoporphyrin dimethyl ester in one step from hematoporphyrin (**1**) is a much more convenient procedure than those currently in the literature.[4,5,6] Addition of a small amount of water to the mixture has no significant effect on the esterification process but severely retards the etherification reaction (entry 3). Thus by a suitable choice of reaction condition (the presence or absence of water) the methanol/trimethyl orthoformate mixture can be used to prepare methyl ethers and methyl esters from hematoporphyrin or methyl esters only. The addition of a similar amount of water to the methanol/concentrated sulfuric acid reaction retards both the esterification and etherification processes (entry 4). Basic hydrolysis of the diester/diether material (**5a**) cleanly provides the corresponding diether diacid.[7]

By suitably altering the time of the reaction or the relative amounts of water, the methanol/trimethyl orthoformate reagent can be used to provide acceptable yields of either the monoester (**2**), (entry 5) or the monoether (**4**). In the latter case it is preferable to start with the diester (**3**) and use a short reaction time. The extent of the reactions can easily be followed by silica TLC or by HPLC.[7]

Very similar results are obtained using ethanol/triethyl orthoformate/concentrated sulfuric acid mixtures although the reaction times are slightly longer. These reactions

TABLE 1 - Esterification and Etherification of Hematoporphyrin [a]

Entry	Reagent (ml)			Yield (%) [b]				
	CH_3OH	$(CH_3O)_3CH$	H_2O	(1)	(2)	(3)	(4)	(5a)
1	1.0	-	-	-	-	67	14	9
2	0.5	0.5	-	-	-	-	-	81
3	0.5	0.5	0.1	-	-	71	-	-
4	1.0	-	0.1	-	3	71	-	-
5	0.25	0.25	0.5	27	42	19	-	-

a) Concentrated sulfuric acid (0.1 ml) was added to each mixture containing 10 mg of hematoporphyrin (commercial material, approximately 90% pure by HPLC) for a reaction time of forty-five minutes.[9]

b) Determined by HPLC, using previously described conditions.[7]

TABLE 2 - Esterification / Etherification of Porphyrins [a]

Acid [b]	Product	Yield (%) [c]
(1)	(5a)	81
(1)	(5b)	70 [d]
(6)	(7a)	96
(6)	(7b)	81
(8)	(9a)	71
(8)	(9b)	80
(10)	(11a)	82
(10)	(11b)	81

a) Reagent: alcohol/trialkyl orthoformate/concentrated sulfuric acid (1.0:1.0:0.1 ml) at room temperature for forty-five minutes.[9]

b) 10 mg in each case.

c) Determined by HPLC.

d) Product also contained the corresponding monoether/monoalcohol diester and the dialcohol diester (total 15%).

also proceed with benzyl alcohol/tribenzyl orthoformate, but since tribenzyl orthoformate cannot be prepared pure[8] the products are contaminated with ethylated material from the triethyl orthoformate presumably still present. The anhydrous conditions also provide a convenient method for trans-esterification but not trans-etherification; thus the dibenzyl ether of hematoporphyrin dibenzyl ester is converted to the dibenzyl ether of the dimethyl ester with methanol/trimethyl orthoformate/concentrated sulfuric acid.

Table 2 shows that the reaction can be used to prepare, in good yield, the dimethyl or diethyl esters of a variety of other porphyrin diacids. By using anhydrous conditions the benzylic type alcohols (1) and (6) can also be alkylated. Additions to the vinyl groups of (6), (8) and (12) were not observed using either aqueous or anhydrous conditions.

The procedure also provides an efficient esterification method for hemin, however the reaction times for hemin are somewhat variable due to the difficulty in dissolving hemin in the reaction mixture. Thus the dimethyl ester (91%) and diethyl ester (66%, with 26% of hemin recovered) of hemin could be prepared using extended reaction times.

Acknowledgements

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9. A typical reaction procedure is as follows. The porphyrin (10 mg) was added to a stirred solution of the orthoformate (0.5 ml) and the corresponding alcohol (0.5 ml). Concentrated sulfuric acid (0.1 ml) was then added slowly, with cooling to room temperature, and the solution was stirred at room temperature for 45 minutes. The mixture was then diluted with water, the pH was adjusted to 4.5 by the addition of dilute sodium hydroxide and the mixture was extracted with dichloromethane. The organic extracts were washed with water and the solvent was removed under reduced pressure.

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