### REACTIONS ON SOLID SUPPORTS PART II: A CONVENIENT METHOD FOR SYNTHESIS OF PYRROMETHANES USING A MONTMORILLONITE CLAY AS CATALYST

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Alumina, silica gel, and other inorganic substrates, have been used successfully as catalysts in organic syntheses for several decades.<sup>1</sup> It is only recently that Montmorillonite clay has been used as catalyst but it has already proved to be of immense value in many organic reactions e.g. peptide synthesis,<sup>2</sup> acylation reactions,<sup>3</sup> esterifications,<sup>4</sup> aromatic chlorination and nitration reactions,<sup>5</sup> preparation of symmetric and unsymmetric ethers from alcohols,<sup>6</sup> Diels-Alder reactions,<sup>7</sup> polymerisation,<sup>8</sup> in the manufacture of methyl amines,<sup>9</sup> preparation of unsaturated aldehydes,<sup>10</sup> and acetal formation.<sup>11</sup> All these reactions take advantage of the highly acidic nature of the clay and in several instances the various ionic species present in it have been key factors. In view of the wide range of properties exhibited by the clay, we thought that it could be utilised in the synthesis of pyrromethanes.

Pyrromethanes are very important intermediates in the total synthesis of porphyrins and consequently many methods have been developed over the decades for their synthesis.<sup>12</sup> Condensation of an  $\alpha$ -acetoxymethylpyrrole (1) with an appropriately substituted  $\alpha$ -free pyrrole (2) appears by far the best method known to date, and the reactions are generally carried out in acetic acid<sup>13a</sup> or in pyridine<sup>13b</sup> or in the presence of catalysts such as toluene-p-sulphonic acid,<sup>13c</sup> or trifluoroacetic acid.<sup>13d</sup> However, isolation of the required pyrromethane (3) in some cases is tedious, and not only involves purification from tarry reaction by-products,<sup>13c</sup> but self-condensation of the acetoxymethylpyrrole (1) often also affords the symmetrical pyrromethane (4) as a by-product (cf. Scheme 1).

For these reasons we decided to investigate the use of Montmorillonite clay as a catalyst for pyrromethane preparations. In a typical procedure a solution of the acetoxymethylpyrrole<sup>10</sup> (1a) (0.5g; 1.4 mmol.) (cf. Scheme 1) and the  $\alpha$ -free pyrrole (2a) (0.37g; 1.4 mmol.) in dichloromethane (30 ml) was stirred with Montmorillonite clay (2g) and the colour of the solution turned reddish in 10 min. T.1.c. showed that a single pyrromethane had been formed and that reaction was complete. After filtration from the clay, and washing with dichloromethane, evaporation of the combined filtrates gave the unsymmetrical pyrromethane (3a) in 95% yield, after crystallisation from dichloromethane-hexane. T.1.c., h.p.1.c., n.m.r., and f.d. mass spectrometry confirmed that the product was homogeneous.



The absence of any symmetrical pyrromethane (4a) derived from self-condensation of the acetoxymethyl pyrrole (1a) was both surprising and gratifying, as such symmetrical pyrromethanes were contaminants in earlier syntheses.<sup>12</sup> On the other hand self-condensation of  $\alpha$ -halogenomethyl,  $\alpha$ -hydroxymethyl,  $\alpha$ -methoxymethyl and  $\alpha$ -alkylaminomethyl pyrroles is a well established method for symmetrical pyrromethane synthesis. We therefore studied the clay catalysed reactions of  $\alpha$ -acetoxymethyl pyrrole (1a) in dichloromethane in the absence of  $\alpha$ -free pyrrole and found that the symmetrical pyrromethane (4a) was indeed formed in virtually quantitative yield, but the reaction was appreciably slower than coupling with the  $\alpha$ -free pyrrole (2a).

We have now extended these observations to the synthesis of over twenty different unsymmetrical and symmetrical pyrromethanes and a representative series of examples is shown in Tables 1 and 2. In general unsymmetrical pyrromethane formation was complete in 5-10 mins. whereas the formation of the symmetrical pyrromethane took 1-5 hrs. To ensure that no symmetrical pyrromethanes are formed during the preparation of the unsymmetrical pyrromethanes we have found it convenient to use a slight excess of the  $\alpha$ -free pyrroles (especially as the latter are often oily or gummy materials prepared from the corresponding  $\alpha$ -t-butyloxy carbonyl or  $\alpha$ -benzyloxycarbonyl pyrroles).

The ease of carrying out these reactions, the high yields and the homogeneity of the products makes this catalytic method of synthesising pyrromethanes far superior to any of the existing procedures. Further studies on the generality of the reactions, effects of temperature, changes in the ionic characteristics of the clay, and of other types of pyrroles are in progress.

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Synthesis of Unsymmetrical Pyrromethanes								
(3)	R <sup>1</sup>	R <sup>2</sup>	$R^3$	R <sup>4</sup>	m.p.			
а	Me	CII2CO2Me	Me	CH2CH2CO2Me	gum +			
b	Me	Et	Et	Me	112-114 <sup>0</sup>			
с	Me	CII2CO2Me	Et	Me	ழு <b>m</b> +			
d	$\text{dl}_2\text{dl}_2\text{dl}_2\text{dl}_2\text{Me}$	CH2CO2Me	Et	Me	gum +			
e	Me	al <sub>2</sub> al <sub>2</sub> c1	Et	Me	gum <sup>+</sup>			
f	Н	Me	Et	Me	gum +			

# Table 1

+ As with many other pyrromethane t-butyl esters prepared in our laboratories, many of these could not be obtained in crystalline form, but their homogeneity was clearly evident from n.m.r. and mass spectral data, and t.l.c.

Synthesis of Symmetrical Pyrromethanes							
(4)	R <sup>1</sup>	R <sup>2</sup>	Yield	m.p.			
а	Me	CH2CO2Me	90	110-112 <sup>0</sup>			
b	Me	Et	95	Gum			
с	Me	a12a12c1	95	95-97 <sup>0</sup>			
d	Me	CH2CH2CO2Me	90	99-101 <sup>0</sup>			
e	$\mathrm{GH}_2\mathrm{GH}_2\mathrm{GO}_2\mathrm{Me}$	CH2CO2Me	90	143 <sup>0</sup>			
f	CH2CH2CO2Me	Me	90	89-91 <sup>0</sup>			

## Table 2

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