Pergamon

Tetrahedron Letters, Vol. 35, No. 26, pp. 4497-4500, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00877-9

Use of Montmorillonite Clay for the Synthesis of Linear Tetrapyrroles and their Cyclization to Uroporphyrinogens.

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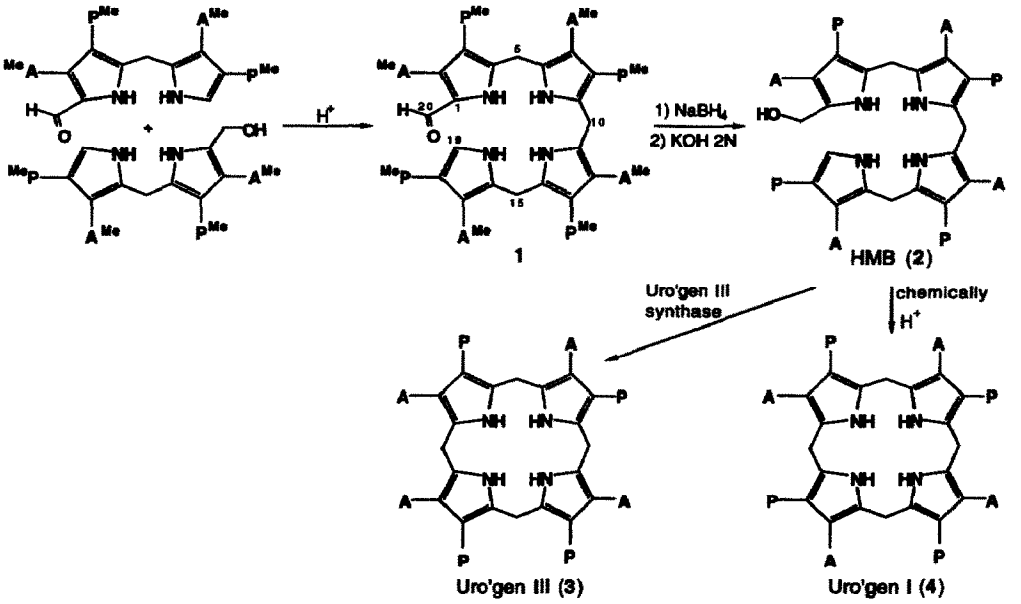
Abstract: Linear tetrapyrroles, such as the formylbilane (**1**), were obtained by condensation of α-hydroxymethyldipyrromethanes with α-free dipyrromethanes using Montmorillonite clay as acid catalyst. After reduction of the formyl group, hydroxymethylbilanes were cyclized to Uroporphyrinogens in presence of the clay.

Over the years, a number of inorganic solids, such as silica gel or alumina, have been used as catalyst in organic synthesis.[1] More recently, Montmorillonite clay has been successfully applied as initiator for a wide range of organic reactions.[2] In pyrrole chemistry, the oxidation of α-methylpyrroles to α-formylpyrroles by treatment with a thallium (III) nitrate/Montmorillonite clay system has been reported.[3] The same authors have also found that unsymmetrical dipyrromethanes were obtained very cleanly by coupling α-acetoxymethylpyrroles with α-free pyrroles in presence of clay and symmetrical dipyrromethanes by self-condensation of α-acetoxymethylpyrroles.[4]

Our laboratory has been interested for some time in Uroporphyrinogen III synthase, the enzyme in the porphyrinoid pathway, which cyclizes the linear tetrapyrrole hydroxymethylbilane (HMB, **2**) to Uroporphyrinogen III (Uro'gen III, **3**), a key precursor of many vital pigments present in living system (vitamin B_{12}, chlorophyll). In the absence of the enzyme, HMB ring-closes chemically to form Uro'gen I (**4**)(scheme 1). In order to perform mechanistic studies on this enzyme, it was necessary to prepare different HMB analogs.[5] Particularly, the 19-bromo-HMB was selected as potential inhibitor of the enzyme, but could not be obtained following the method

developed for the preparation of HMB [condensation of the hydroxymethyldipyrromethane with the formyldipyrromethane in acetic acid-dichloromethane system (scheme 1)].[6] For this reason, we decided to investigate the use of Montmorillonite clay as acid catalyst for the preparation of bilanes.

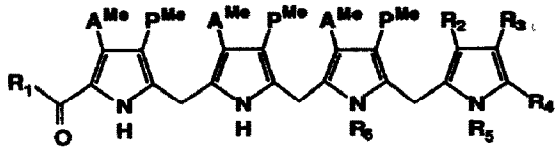


A^{Me}=CH_2CO_2Me; A=CH_2CO_2H; P^{Me}=$CH_2CH_2CO_2Me$; P=$CH_2CH_2CO_2H$.

Scheme 1: Synthesis of Uro'gen.

As shown in table 1, a variety of tetrapyrroles were prepared in reasonable yield in this way.[7] Yields of several runs to **1** were observed to be extremely variable. Comparative experiments were carried out with different samples of clay washed prior to the reaction with buffer at various pH (4 to 8), thus altering the acidity of the clay. The best results (35-50%) were obtained by simply washing with distilled water. This was particularly important in case of compound **9** (the precursor of 19-bromo-HMB), which proved to be more acid sensitive than the parent bilane **1**.

Table 1: Synthesis of Linear Tetrapyrroles.[7,8]



bilane	R_1	R_2	R_3	R_4	R_5	R_6	yield (%)
1	H	A^{Me}	P^{Me}	H	H	H	45
5	*CH_3*	A^{Me}	P^{Me}	H	H	H	17
6	*CF_3*	A^{Me}	P^{Me}	H	H	H	8
7	H	A^{TMSE}	P^{Me}	H	H	H	50
8	H	A^{Me}	B^{Me}	H	H	H	19
9	H	A^{Me}	P^{Me}	*Br*	H	H	30
10	H	A^{Me}	P^{Me}	*Me*	H	H	43
11	H	A^{Me}	P^{Me}	*CBZ*	H	H	39
12	H	A^{Me}	P^{Me}	H	*Me*	H	37
13	H	A^{Me}	P^{Me}	H	H	*Me*	23

A^{Me}=CH_2CO_2Me; A^{TMSE}=$CH_2CO_2CH_2CH_2SiMe_3$; P^{Me}=$CH_2CH_2CO_2Me$; B^{Me}=$CH_2CH_2CH_2CO_2Me$; CBZ=CO_2CH_2PH.

After reduction of the formyl (**1**, **8**, **12** and **13**) or the acetyl (**5**) groups with sodium borohydride, the α-free bilanes (R_4=H) were cyclized to Uro'gen I analogs (scheme 1) using again the clay as acid catalyst (table 2).[9]

Table 2: Cyclization of Hydroxymethylbilanes to Uro'gens.[8,9]

bilane	% Uro'gen
1	45
5	6
8	34
12	51
13	47

In conclusion, an alternative method using Montmorillonite clay as mild acid catalyst for the synthesis of tetrapyrroles and the preparation of

Uro'gen I analogs from hydroxymethylbilanes was developed to allow the obtention of acid sensitive products.

Acknowledgment: We thank the National Institutes of Health (N.I.D.D.K.) for financial support of this work.

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7. General procedure for the preparation of bilanes: The clay was washed with distilled H_2O (30 mL), then with MeOH (5 mL) and dried at 150 °C for 2 hrs prior to use. A solution of the α-hydroxymethyldipyrromethane (0.1 mmol) and α-formyldipyrromethane (0.2 mmol) in CH_2Cl_2 (2 mL) was stirred over clay (500 mg) at RT under N_2 in the dark for 2 days. The solution was filtered and the clay washed with CH_2Cl_2 containing 5% MeOH. After evaporation of the solvent, MeOH (2 mL) was added to the solid residue. The solid, containing mainly the bilane, was separated by centrifugation from the solution, which contained mainly the excess of α-formyl-dipyrromethane. The bilane was further purified by preparative TLC, eluting with CH_2Cl_2/MeOH (95/5) under N_2 in the dark.

8. The yields reported have been optimized only in case of **1**, **7** and **9**. All compounds gave satisfactory ^{1}H- and ^{13}C-NMR and mass spectra.

9. General procedure for the cyclization of formylbilane to Uro'gen I: The formylbilane (0.02 mmol) in MeOH/CH_2Cl_2 (1/1, 1mL) was reduced with $NaBH_4$ (20 mg) in presence of NH_4Cl (15 mg) at RT under N_2 in the dark. The reaction was quenched with H_2O and the hydroxymethylbilane extracted into CH_2Cl_2. The solution was dried over $MgSO_4$, filtered and the volume reduced to *ca.* 2 mL. Clay (150 mg) was added and the reaction stirred under N_2 for 2 days. The solution was filtered, the clay washed with CH_2Cl_2/MeOH (95/5) and the Uro'gen product was purified by preparative TLC, eluting with CH_2Cl_2/MeOH (95/5) under N_2.

(*Received in USA* 29 *March* 1994; *revised* 26 *April* 1994; *accepted* 4 *May* 1994)