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The Use of 4,6-Disubstituted Pyrimidine-5-aldehydes in the Synthesis of *meso*-Tetraarylporphyrins

Filip Motmans, Erik Ceulemans, Stefan Smeets and Wim Dehaen*

Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, B- 3001 Heverlee (Belgium)

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Abstract : A new type of double picket-fence porphyrin, bearing pyrimidine rings at the *meso*-positions was prepared from the corresponding pyrimidine-5-aldehydes using either Rothemund or McDonald condensation reactions.
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The metallated derivatives of 5,10,15,20-tetrakis(2',6'-dichlorophenyl)porphyrin **1** (TDCPP) or other *ortho, ortho'*-substituted tetraarylporphyrins **1** such as TMP and TPFPP (see Figure 1) have been used extensively in so-called second-generation oxidation catalysts,[1] displaying increased stability as compared to the first generation catalysts derived from tetraphenylporphyrin (TPP). The synthesis of the porphyrins **1** is generally rather simple, using the Lindsey modification ($BF_3.Et_2O$ as catalyst, dichloromethane, oxidation with *p*-chloranil) of the Rothemund condensation of a 2,6-disubstituted benzaldehyde and pyrrole.[2] The stability can be further increased by substitution (mostly halogenation) at the β-positions, affording a third generation of very robust metalloporphyrin catalysts.[1] Other functionalizations of TDCPP generally are difficult, although some efforts have been made by Pozzi et al.,[3] using nitro substituted 2,6-dichlorobenzaldehydes which are not easy to prepare. The *ortho, ortho'*-hydroxy and amino substituted tetraarylporphyrins are rather easily functionalized with electrophiles but the catalysts derived from them may suffer from low stabilities.[4,5]

In this study we use a heterocyclic analog of 2,6-dichlorobenzaldehyde, namely the 4,6-dichloropyrimidine-5-aldehyde **2a** in the synthesis of porphyrins **3**. The chlorine functionalities on the pyrimidine ring are highly activated towards nucleophilic substitution, allowing us to prepare a very broad substitution pattern of porphyrins. We wanted to investigate the effectiveness of this substitution reaction either at the pyrimidine or porphyrin stage.

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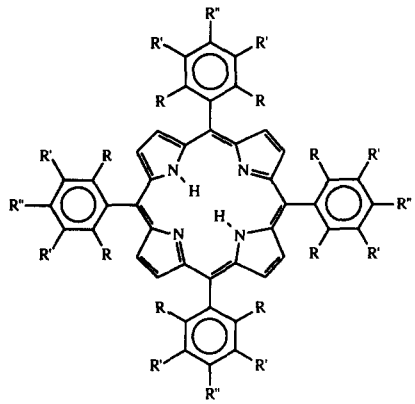
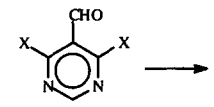
RESULTS AND DISCUSSION

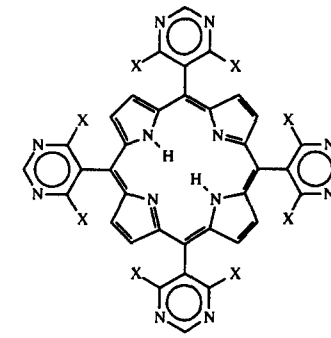
The aldehyde **2a** was prepared using the reported Vilsmeier conditions ($DMF/POCl_3$) for chloroformylation of 4,6-dihydroxypyrimidine.[6] Functionalization of the two chlorine atoms was possible with a range of nucleophiles including methoxide, substituted phenolates, and thiolates. This afforded the 4,6-disubstituted pyrimidine-5-aldehydes **2b-f** in good to excellent yields (respectively 46, 91, 91, 88, 42%, Figure 1).



1 R=R'=R''=H (TPP)
1 R=Cl, R'=R''=H (TDCPP)
1 R=R''=Me, R'=H (TMP)
1 R=R'=R''=F (TPFPP)
4 R'= *t*-Bu, R=R''=H



2a X = Cl
2b X = MeO
2c X = 4-*t*-BuC_6H_4O
2d X = 3,5-(*t*-$Bu)_2C_6H_3O$
2e X = 4-$(MeOOC)C_6H_4O$
2f X = $SCH_2CH{=}C(CH_3)_2$

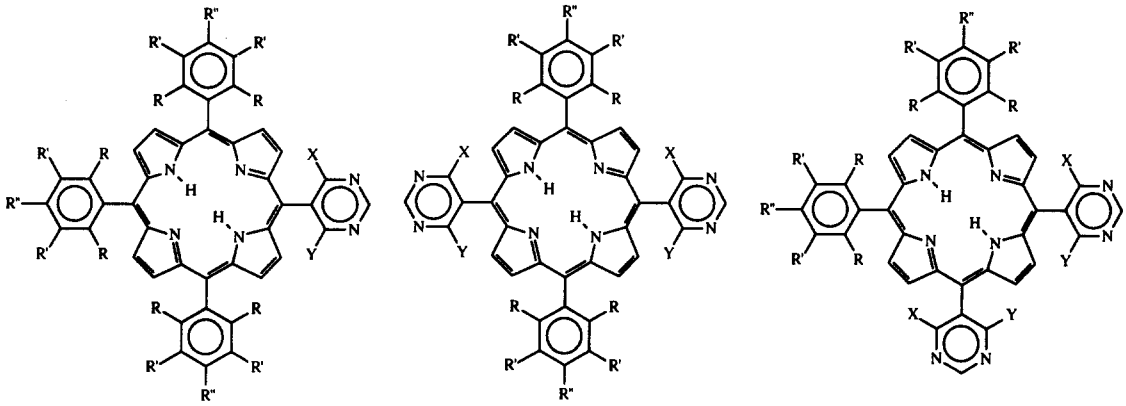


3a
3b
3c
3d
3e
3f

Figure 1

To our disappointment we were not able to isolate **3a**, the octaaza analogue of TDCPP **1** from the condensation reaction of aldehyde **2a** with pyrrole, using either Adler-Longo (refluxing propionic acid) or Lindsey conditions, although according to the UV spectra of the reaction mixture some porphyrin was formed. The dimethoxy substituted aldehyde **2b** also gave no porphyrin **3b**. One of the reasons of these failures might be the unstability and low solubility of the intermediates in the reaction mixture. On the other hand, it was gratifying to see that aldehydes **2c-g**, which have higher stability and solubility, gave acceptable isolated yields of octasubstituted porphyrins **3c** (40 %), **3d** (13 %), **3e** (73 %) and **3f** (13 %) when reacted with pyrrole under Lindsey conditions. Derivative **3d** is extremely sterically hindered and is a true "double picket fence" porphyrin.

To increase the solubilities of the oligopyrrole intermediates leading to the desired porphyrins, we undertook a mixed condensation of aldehyde **2a** with 3,5-bis(*t*-butyl)benzaldehyde and pyrrole (1:3:4 ratio). The resulting reaction mixture contained a statistical mixture of porphyrins **4** (4 %), **5a** (27 %), **6a** (19 %) and **7a** (2 %), which could be separated by column chromatography (eluting in this order) without problem. In the same way, aldehyde **2b** was converted into porphyrins **4** (23 %), **5b** (12 %), **6b** (7 %) and **7b** (7 %).



5a X=Y= Cl, R=R''=H, R'= *t*-Bu
5b X=Y= MeO, R=R''=H, R'= *t*-Bu
9a X= Cl, Y= MeO, R=R''=H, R'=*t*-Bu
9b X= Cl, Y= SCH_2COOMe, R=R''=H, R'=*t*-Bu

6a X=Y= Cl, R=R''=H, R'= *t*-Bu
6b X=Y= MeO, R=R''=H, R'= *t*-Bu
8 X=Y= Cl, R=R''= Me, R'=H
10 X= Cl, Y= MeO, R=R''=Me, R'=H

7a X=Y= Cl, R=R''=H, R'= *t*-Bu
7b X=Y= MeO, R=R''=H, R'= *t*-Bu

Figure 2

A 5,15-bis(pyrimidyl)porphyrin **8** could be prepared selectively in acceptable yield (53 %) by condensing the mesityl dipyrromethane[7] with aldehyde **2a** and pyrrole under Lindsey conditions. No scrambling of the *meso*-functions of the porphyrin was observed.

The 5-(4,6-dichloropyrimidin-5-yl)porphyrin **5a** was reacted with methoxide and thiolate nucleophiles. It was found that the substitution reaction generally was much slower than for the corresponding aldehyde **2a**. This is probably due to a combination of steric and electronic factors. In fact, only monosubstition was possible, even after prolonged heating of the reaction mixtures, leading to the monofunctionalized porphyrins **9a** (51 %) and **9b** (40 %). Substitution of the tetrachloroporphyrin **8** with methoxide gave a inseparable mixture of disubstituted atropoisomers **10** (50 %, ratio 1:1). The isomers do not equilibrate at room temperature.

Conclusions

Octasubstituted tetrakis(pyrimidinyl)porphyrins **3c-f** , a new type of double picket fence porphyrins, are easily accessible (with the exception of the octachloro and the octamethoxy derivatives **3a** and **3b**), starting from the corresponding pyrimidine-5-aldehydes **2b-f**. Mixed condensations and [2+2] (McDonald) reactions are also possible, giving porphyrins **5a-b**, **6a-b**, **7a-b, 8** and **10**, having either one or two *meso* pyrimidinyl substituents. Only one of the two chlorine functions of each pyrimidine ring of the porphyrins **5a**, **6a** and **8** could be substituted by nucleophiles. The structures of all new products were confirmed by the ^{1}H and ^{13}C-NMR, UV and electrospray MS spectra.[8]

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8. For instance : **3f** : m.p.>300°C, ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ = -2.25 (2H, s, NH), 1.43 and 1.47 (2s, each 24 H, Me), 3.75 (d, ^{3}J = 7.8 Hz, 16H, CH_2S), 5.09 (t, 3J = 7.8 Hz, 8H, olefin H), 8.64 (s, 8H, porphyrin β H), 9.14 (s, 4H, pyrimidine H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ = 17.8 and 25.5 (Me), 29.2 (CH_2S), 110.5 (meso C), 118.3 (olefin CH), 129.3 (pyrimidine C-5), 136.8 (olefin C), 156.7 (pyrimidine CH-4) and 170.7 (pyrimidine C-4,6). The pyrrole carbons were too broad to be detected. ESMS 1424 (M^{+}); UV-Vis (CH_2Cl_2) 435 , 527, 561, 598, 670 nm