ORGANIC LETTERS

2007
Vol. 9, No. 12
2305−2308

An Easy Synthetic Approach to Pyridoporphyrins by Domino Reactions§

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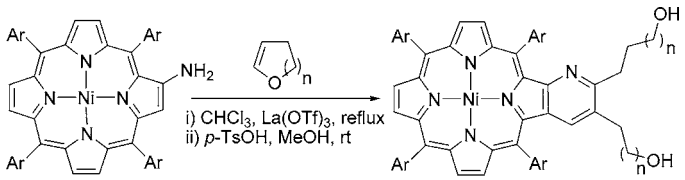
Received March 12, 2007

ABSTRACT



***β*-Amino-*meso*-tetraarylporphyrins react with cyclic enol ethers to yield pyrido[2,3-*b*]porphyrins bearing two vicinal hydroxyalkyl groups. These reactions are catalyzed by lanthanum triflate and occur under mild conditions. Esterification of the hydroxyalkyl groups with succinic anhydride and dodecanoyl chloride afforded the corresponding esters in almost quantitative yields. The crystal structure of the most hydrophobic derivative 7 was determined, and it shows that these porphyrinic macrocycles form one-dimensional supramolecular tapes in the solid state.**

The key roles played by porphyrins in nature have been established for decades, as well as their applications in several fields such as medicine and catalysis and as components of new electronic materials.[1] Therefore, several research groups have been focused on the synthesis and chemical transformation of porphyrins into new derivatives with improved features that may turn them into possible candidates to be used in different applications.

Among all the available synthetic tools for porphyrin functionalization, those considering pericyclic reactions are being increasingly exploited.[2] Despite the large number of reports in which porphyrins are used as dienes[2,3] or as dienophiles[4,5] in Diels−Alder reactions, the use of porphyrins as heterodienes has received scarce attention. In fact, as far as we are aware, only our research group has reported the use of porphyrin derivatives as heterodienes in Diels−Alder reactions. In that work, pyrido[2,3-*b*]porphyrins and *β*-tetrahydroquinoline-substituted porphyrins were prepared by a three-component reaction of aromatic amines, aromatic aldehydes, and cyclic enol ethers using lanthanum triflate as the catalyst.[6]

Lately, the synthesis of 1,2,3,4-tetrahydroquinoline derivatives by domino reactions has attracted increasing attention. Two different strategies have been used: the three-component reaction (involving aromatic aldehydes, anilines,

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§ Dedicated to Prof. Miguel Yus, University of Alicante, Spain, on the occasion of his 60th anniversary.

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10.1021/ol070601w CCC: $37.00
Published on Web 05/17/2007

and enol ethers)[6−10] and the two-component reaction (involving anilines and enol ethers). Concerning the latter strategy, a number of different catalysts have been employed in these reactions, mainly, Lewis acids,[11−13] montmorillonite clays,[14] cation-exchange resins,[15] and molecular iodine.[16] Some interesting variations of this reaction have been also reported. In one of them, the use of a catalyst is not required,[17] and in others, certain nitroarenes[18] or aryl azides[19] are used as starting materials.

As an extension of our previous work,[6] we report herein the synthesis of new pyrido[2,3-*b*]porphyrin derivatives bearing two vicinal hydroxyalkyl groups from the reaction between *β*-amino-*meso*-tetraarylporphyrins (**1a**−**d**) and 3,4-dihydro-*2H*-pyran or 2,3-dihydrofuran.

A model reaction was carried out with *β*-amino-*meso*-tetraphenylporphyrin **1a** and 3,4-dihydro-*2H*-pyran in refluxing chloroform, using lanthanum triflate as the catalyst. After 1 day of reaction time, it was observed by TLC that the starting porphyrin was consumed. The workup was carried out by washing with water and drying over Na_2SO_4, and then the reaction mixture was separated by preparative TLC affording **2a** (13% yield) and **3a** (38% yield) as the main products[20] (Figure 1), along with several other minor compounds which were identified as analogues[21] of **2a** and **3a** but containing monoprotected or unprotected hydroxyl groups. These compounds were also obtained when the reaction was carried out at room temperature, but in this case, 4 days are required for completion.

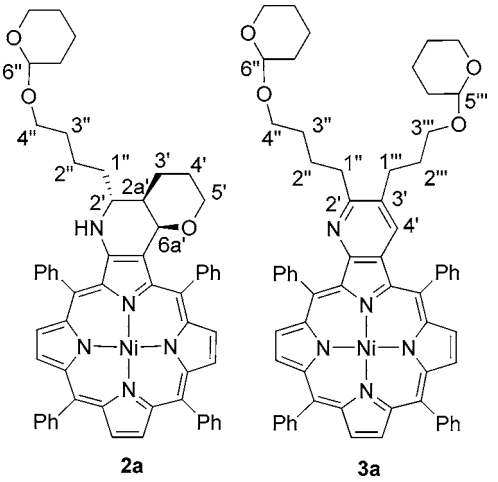
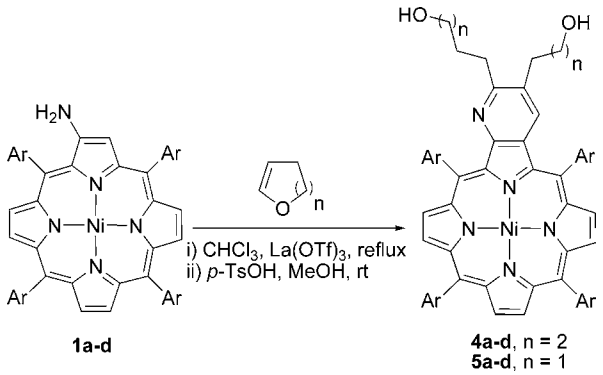


Figure 1. Structures of derivatives **2a** and **3a**.

Hoping to improve the reaction outcome (by decreasing the number of reaction products and increasing the reaction yield), we introduced several modifications in the synthetic procedure, namely, longer reaction times, use of a larger excess of 3,4-dihydro-*2H*-pyran, and use of different solvents at higher temperatures. However, these modifications were unfruitful. A different approach was then considered: the crude reaction mixture was treated with a methanolic solution of *p*-toluenesulfonic acid for 4 h at room temperature. With this procedure, the initial mixture of products was converted into a single compound, **4a** (Table 1). This simple modification also had a positive outcome in the purification process allowing us to use column chromatography as the purification technique.

Table 1. Synthesis of Pyrido[2,3-*b*]porphyrins **4** and **5**



1	Ar	yield of **4** (%)	yield of **5** (%)
a	C_6H_5	69	68
b	*m*-$MeOC_6H_4$	46	48
c	*p*-BrC_6H_4	31	62
d	*p*-$MeCO_2C_6H_4$	33	50

To evaluate the scope of this methodology, our studies were extended to porphyrins **1b**−**d** and to 2,3-dihydrofuran.

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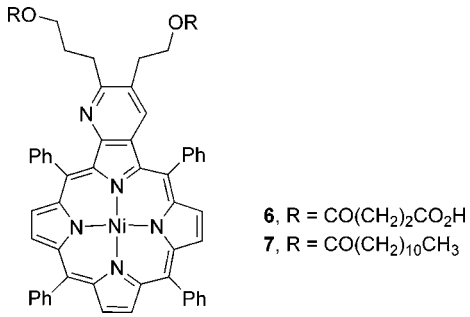
(20) The structures of **2a** and **3a** were established from a careful analysis of their NMR (^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY), MS, and UV−vis spectra (see Supporting Information). The ^{1}H NMR spectra of both compounds display signals corresponding to the resonances of only six *β*-pyrrolic protons, which is indicative of *β*,*β*-fusion. In the NOESY spectrum of compound **2a**, there are NOE cross peaks between the NH and H-2′ and also between H-2a′ and H-6a′; there is no NOE cross peak between H-2′ and H-6a′. These findings allowed the establishment of the configuration of **2a** as depicted in Figure 1. The ^{13}C NMR spectrum shows that the signals of some carbons are split, which is probably due to the presence of a mixture of diastereomers (C-6″ is a chirality center). The ^{1}H NMR spectrum of **3a** shows a singlet at *δ* 6.90 ppm corresponding to H-4′, indicating that, in this case, we are in the presence of a pyridine-fused derivative. The presence of the two tetrahydropyranyl groups was established by the mass spectrum, which shows a peak at *m*/*z* 1019 $(M)^{\bullet+}$, and by the ^{1}H NMR spectrum, which shows the diagnostic signals corresponding to H-6″ and H-5‴ as multiplets at *δ* 4.59−4.61 and *δ* 4.63−4.65 ppm.
(21) Confirmed by mass spectrometry.



6, R = $CO(CH_2)_2CO_2H$
7, R = $CO(CH_2)_{10}CH_3$

Figure 2. Structures of derivatives **6** and **7**.

Under the conditions indicated above, the expected pyrido-[2,3-*b*]porphyrin[22] derivatives **4** and **5** were obtained in moderate to good yields (Table 1). The obtained results illustrate the different reactivity profiles of the starting porphyrins. Although **1a**,**b** (bearing neutral and electron-donating substituents) react similarly with both cyclic enol ethers (yields and reaction times are identical in each case), porphyrins **1c**,**d** (bearing electron-withdrawing groups) give higher yields with 2,3-dihydrofuran.

The domino reactions of anilines with cyclic enol ethers are described as hetero-Diels−Alder reactions between an imine generated in situ and the cyclic enol ether. These reactions are completely regioselective, affording exclusively quinoline derivatives with the alkoxy group in position 4. A stepwise reaction mechanism has also been proposed for such reactions catalyzed by lanthanide triflates.[23] There are two different proposed mechanisms to explain the formation of the intermediate imine. The imine may result directly from the reaction between the cyclic enol ether and the aromatic amine[12] or from the initial addition of water to the cyclic enol ether, converting it into a hemiacetal. This hemiacetal, being in equilibrium with the corresponding aldehyde, in the presence of the aromatic amine affords the intermediate imine.[13a] This latter mechanism is supported by the observation that tetrahydroquinoline derivatives can be efficiently prepared from the reaction of aromatic amines and cyclic hemiacetals.[13b] Our own observations show that, irrespective of the role of the water in the reaction mechanism, its presence is indubitably important, at least for a better reaction rate. We observed that the reaction of **1a** with 3,4-dihydro-2*H*-pyran is complete in 1 day of reaction time when it is carried out in an open atmosphere, but it requires 2 days when it is carried out under a moisture-protected environment.

In the reported publications on the synthesis of tetrahydroquinolines from anilines and cyclic enol ethers, the products are pyrano- or furoquinoline derivatives with an unprotected hydroxyalkyl group. In our reactions, the alcohol

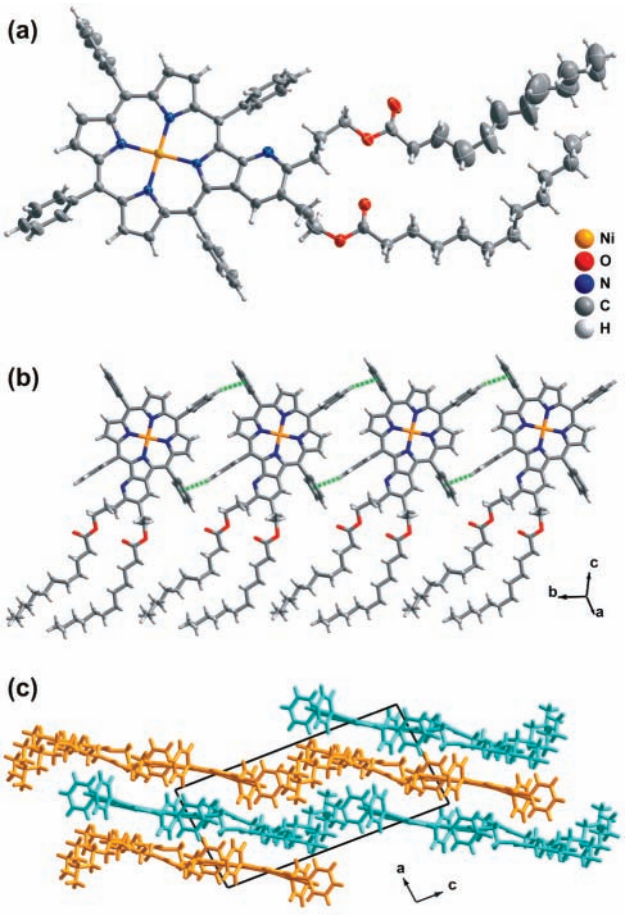


Figure 3. (a) Molecular unit of the crystal structure of porphyrin **7**. Non-hydrogen atoms are represented as thermal ellipsoids drawn at the 50% probability level, and hydrogen atoms are represented as small spheres with arbitrary radius (see Supporting Information for detailed atom labeling and tabulated bond lengths and angles). (b) Parallel packing of individual porphyrins along the [010] crystallographic direction, emphasizing the C−H···π interactions (dashed green lines) between phenyl rings (belonging to neighboring molecules) leading to the formation of supramolecular tapes. Geometry of represented hydrogen bonding interactions: C(56)−H(56)···C_g with $d_{C\cdots C_g}$ = 3.652(1) Å and ∠(DHA) = 162(1); C(68)−H(68)···C_g with $d_{C\cdots C_g}$ = 3.792(1) Å and ∠(DHA) = 153(1) (C_g stands for the center of gravity of the phenyl ring). (c) Crystal packing of **7** viewed along the [010] direction of the unit cell, showing the ABAB alternation of supramolecular tapes (represented in light blue and orange).

residue usually appears in the acetal-protected form (**2a**).[24] Furthermore, the tetrahydropyran ring opens easily leading to the fully aromatic pyridoporphyrin derivative **3a**. As already mentioned, treatment of the reaction mixture with *p*-toluenesulfonic acid is important to reduce the number of products because it induces the opening of the tetrahydrofuran- or tetrahydropyran-fused rings and the deprotection of the hydroxyl groups. Consequently, it improves the reaction yields and facilitates the purification step.

(22) Careful structural characterization of the new compounds (based on NMR studies: ^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY) has shown that they are all aromatic pyridoporphyrin derivatives. Full spectroscopic data for all new compounds are available in the Supporting Information.

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The two vicinal hydroxyalkyl groups present in the new porphyrin derivatives are potential sites for further modifications. They can be used for the introduction of hydrophobic/hydrophilic groups or carrier molecules (for medicinal applications) or to link the porphyrins to polymers, etc. To confirm the viability of such methodology, porphyrin **5a** was reacted with succinic anhydride and dodecanoyl chloride. These reactions afforded the expected esters **6** and **7** in almost quantitative yields (Figure 2).

We were able to crystallize the derivative **7** from layered methanol over dichloromethane at room temperature during a period of 3 days and determine its crystal structure by means of single-crystal X-ray diffraction (Figure 3a).[25] The observed geometrical details, along with the remaining structural aspects of the derivatized tetraphenylporphyrin ("head"), are typical, as revealed by a search in the Cambridge Structural Database.[26,27] The substituent alkyl chains ("tail") composing the two hydroxyalkyl groups show significant conformational flexibility and are affected by thermal disorder. This is particularly evident for the C(41) → C(52) chain for which the carbon atoms could only be modeled with large anisotropic thermal displacement ellipsoids (Figure 3a, alkyl chain in the top). Individual molecules closely pack in a parallel fashion, mediated by weak C−H···π interactions between neighboring phenyl substituent aromatic rings. These robust cooperative interactions lead to the formation of intriguing one-dimensional supramolecular tapes as depicted in Figure 3b. Individual tapes pack into layers via typical "head-to-tail" interactions between molecules of **7** belonging to adjacent tapes (Figure 3c).

In summary, novel pyrido[2,3-*b*]porphyrins were obtained in moderate to good yields by a new synthetic approach. The methodology involves the reaction of a β-aminoporphyrin with a cyclic enol ether catalyzed by lanthanum triflate. Treatment of the crude reaction mixture with a methanolic solution of *p*-toluenesulfonic acid allowed the conversion of a complex mixture into a single compound, improving the reaction yield and facilitating the purification process. The new porphyrin derivatives bear two vicinal hydroxyalkyl groups which are excellent sites for further modification.

Acknowledgment. Thanks are due to Fundação para a Ciência e a Tecnologia (FCT, Portugal) and POCI 2010 (FEDER) for funding the Organic Chemistry Research Unit and the purchase of the single-crystal diffractometer. C. M. A. Alonso and V. I. V. Serra also thank FCT for postdoctoral (SFRH/BPD/8375/2002) and PhD grants (SFRH/BD/28122/2006), respectively.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. Details on the crystal data collection, solution and refinement for porphyrin **7**, along with bond lengths and angles for the central Ni^{2+} coordination environment, and additional structural drawings. Crystal structure in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Crystal data: $C_{76}H_{83}N_5NiO_4$, $M = 1189.18$, triclinic, space group $P\bar{1}$, $Z = 2$, $a = 11.2502(3)$ Å, $b = 13.2372(3)$ Å, $c = 23.0320(7)$ Å, $\alpha = 98.059(2)°$, $\beta = 94.078(2)°$, $\gamma = 106.160(2)°$, $V = 3239.94(15)$ Å^3, red plate with crystal size of $0.18 \times 0.16 \times 0.04$ mm^3. Of a total of 18 447 reflections collected, 7128 were independent ($R_{int} = 0.0422$). Final R1 = 0.0671 [$I > 2\sigma(I)$] and wR2 = 0.2096 (all data). CCDC 633482. See Supporting Information for further details on the crystal solution and refinement.

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