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Diethyl 2,7-Dibromo-4*H*,5*H*-thieno[3,2-*b*:4,5-*b*′]dipyrrole-3,6-dicarboxylate: A Key Intermediate for a Diversity Oriented Synthesis of 2,7,12,17-Tetraarylporphycenes

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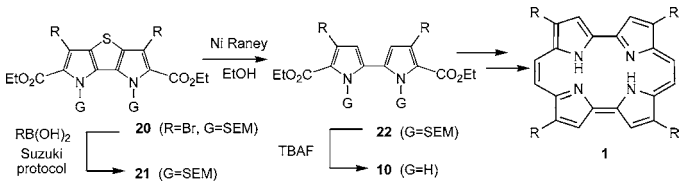
ABSTRACT



A new Suzuki-based strategy for the synthesis of 4,4′-diaryl (or heteroaryl)-substituted 2,2′-bipyrroles (10), precursors of 2,7,12,17-tetraaryl (or heteroaryl)-substituted porphycenes, is described. Bromination of the previously described diethyl 4*H*,5*H*-thieno[3,2-*b*:4,5-*b*′]dipyrrole-3,6-dicarboxylate afforded dibromo compound 19, which is the key intermediate of such strategy.

Porphycenes (**1**) are porphyrin isomers with much higher absorption coefficients above 630 nm, which is the spectral region of interest for photodynamic therapy of cancer (PDT). In fact, studies of cell photoinactivation have demonstrated their usefulness as PDT photosensitizers.[1] However, since the synthesis by Vogel and co-workers of the parent nonsubstituted compound **1**{*1*} in 1986,[2] only a few variants of the initial synthetic methodology have been described.[3−5] All of them are based on an Ullmann dimerization of a preformed pyrrole which carries the R susbstituent present in the resulting porphycene (Figure 1).

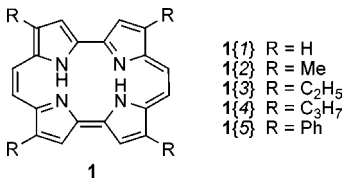


Figure 1. 2,7,12,17-Substituted porphycenes (**1**{*1*−*5*}).

Thus, the original methodology[3] starts from a diethyl 2-methylpyrrole-3,5-dicarboxylate (**2**, R^1 = Et) bearing the

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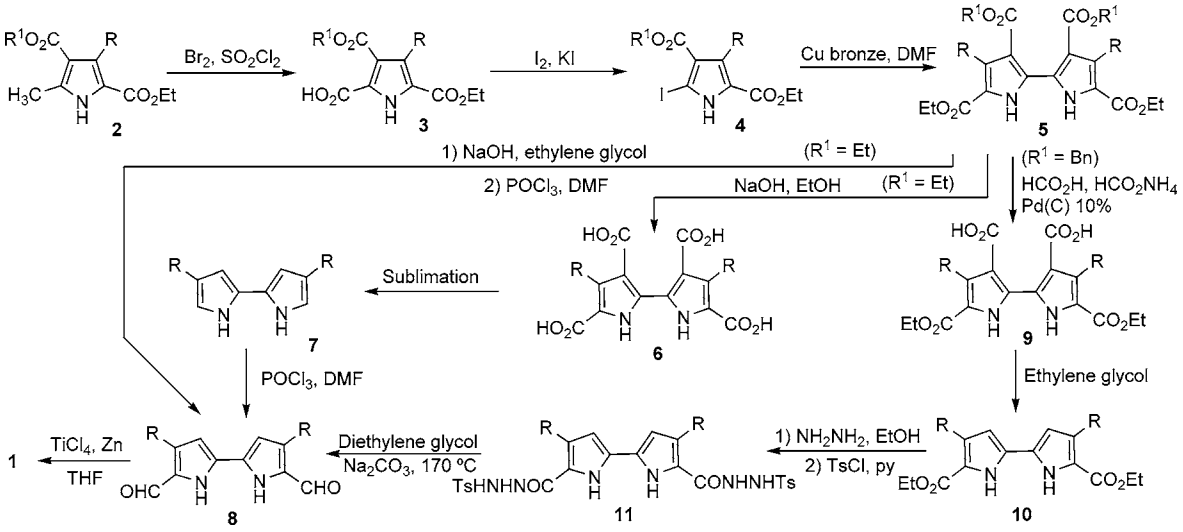
Scheme 1. Described Methodologies for the Synthesis of 2,7,12,17-Tetrasubstituted Porphycenes **1**



desired R substituent (Scheme 1). Compound **2** is oxidized to the corresponding carboxylic acid **3** (R^1 = Et) which, in turn, is converted to the iodo derivative **4** (R^1 = Et). This later undergoes de-halogen coupling to the tetraester **5** (R^1 = Et), which is hydrolyzed to the tetraacid **6**. Sublimation of **6** yields the unstable bipyrroles **7** that underwent formylation to give the corresponding diformyl derivative **8**. This latter compound is transformed to the desired porphycene (**1**) by a McMurry coupling. Such a procedure has been used for the synthesis of several alkyl-substituted porphycenes such as **1**{*2*} (R = Me), **1**{*3*} (R = C_2H_5), and **1**{*4*} (R = C_3H_7).[6]

Our group described in 1995 the synthesis of 2,7,12,17-tetraphenylporphycene (**1**{*5*}, R = Ph) by a slight variation of the aforementioned methodology by which the tetraester **5**{*5*} (R^1 = Et, R = Ph) is directly transformed into the 5,5′-diformyl-2,2′-bipyrrole **8**{*5*} (R = Ph), avoiding the intermediate sublimation.[3]

More recently, we reported a non-tetradecarboxylative method to obtain **1**{*5*} (R = Ph) that avoids passing through the unstable intermediate **7**{*5*} (R = Ph).[4] We started from a pyrrole **2**{*5*} (R = Ph, R^1 = Bn) bearing two orthogonal ester groups, which was transformed to the corresponding bipyrrole **5**{*5*} (R = Ph, R^1 = Bn). The benzyl ester groups were selectively removed to afford diacid **9**{*5*} (R = Ph) that was subsequently decarboxylated to diester **10**{*5*} (R = Ph). **10**{*5*} was converted in dialdehyde **8**{*5*} (R = Ph), precursor of tetraphenyl porphycene **1**{*5*}, using the McFadyen−Stevens reaction. A similar concept has been used recently by Hayashi et al. to obtain the first fluorine-containing porphycenes.[5]

All of the preceding methods present two major drawbacks: (a) A change of substituent R, to improve the drugability and photochemical properties of the final porphycene, forces the development of a de novo synthesis, and (b) such methodologies are far from being of general applicability.

Thus, the nature of R greatly influences the performance of the reactions precluding the synthesis of some target compounds. This was the case, for instance, of the 2,7,12,17-tetra(pyridin-4-yl)porphycene **5**{*6*} (R = C_6H_4N), which failed in our hands in the steps previous to the Ullmann coupling.

All of these synthetic limitations combined with our interest in 2,7,12,17-tetraaryl-substituted porphycenes, due to the interesting photophysical properties[7] and biological activity[1e,i,j] found in 2,7,12,17-tetraphenylporphycene (**1**{*5*}, R = Ph), impelled us to develop a synthetic route for such porphycenes in which the aryl (or heteroaryl) R substituents will be introduced on a preformed 2,2′-bipyrrole in the later stages of the itinerary. Such a concept was used by our group in 2003 to obtain 2,7,12,17-tetraaryl-3,6,13,16-tetraazaporphycenes (**13**) from a dibromo-substituted biimidazole (**12**) (Figure 2).[8]

A literature search carried out revealed 4,4′-dibromo-1,1′-bis(trimethylsilyl)bipyrrole (**14**)[9] as a possible starting material for our purpose. However, the very low yield (10%) in the formation of the starting 1,1′-bis(trimethylsilyl)bipyrrole precluded its use.

Consequently, we focused on structure **15**, described by Farnier et al. in 1976,[10] as a possible precursor of 2,7,12,17-

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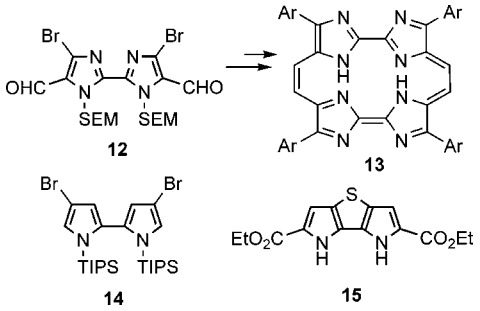


Figure 2.

tetraarylporphycenes. This compound fulfills the requirements needed for our synthetic approach: (i) The pyrrole rings of **15** only present free those positions in which we want to introduce the bromine atoms; (ii) the sulfur bridge, easily removable with Raney nickel according to Farnier,[11] blocks the two inner positions of the bipyrrolic system present in **15** avoiding further substitution there, which would compromise planarity of the resulting porphycene;[5] and (iii) **15** contains two ester groups easily transformable into the required aldehydes by using the aforesaid McFadyen−Stevens protocol.[4]

The thieno[3,2-*b*:4,5-*b*′]dipyrrole (**15**) is obtained (Scheme 2) starting from the commercially available thiophene-2,5-dicarboxaldehyde (**16**), also accessible from thiophene,[12] by treatment with ethyl azidoacetate (**17**) in NaOEt/EtOH to afford bis(azido-2′-ethoxycarbonyl-2′-vinyl)-2,5-thiophene (**18**) in 54% yield. Compound **18** is transformed in the desired thienodipyrrole **15** by heating in xylene at reflux (85% yield). This optimized procedure allows us to obtain **15** in 100 g scale.[13]

Bromination of **15** was first assayed by using *N*-bromosuccinimide or 1,3-dibromo-5,5-dimethylhydantoin, typical brominating agents for pyrroles, in a wide range of organic solvents, but in no case was compound **19** even detected. Thus, we treated **15** with Br_2 in a 2:5 AcOH/AcOEt mixture to yield the desired dibromo derivative **19** in 89% yield as a white precipitate of high purity that can be directly used for the next steps without further purification. Once the dibromo compound was obtained, we faced the key step of our synthetic strategy: the introduction of the R-substituent by a Suzuki reaction.

We treated **19** with phenylboronic acid ($RB(OH)_2$, R = Ph) using a wide range of reaction conditions which include the following: $Pd(PPh_3)_4$, $PdCl_2(dppf)$ or $Pd(OAc)_2$ and Buchwald ligand[14] as catalysts; Na_2CO_3, K_3PO_4 or CsF as bases; DMF, dimethoxyethane, or 1,4-dioxane as solvents; the use of conventional or microwave heating. However, the desired diphenyl-substituted derivative was not formed in any case. These results are in agreement with literature reports, indicating that, in some cases, the Suzuki coupling does not proceed on unprotected pyrroles.[15]

Consequently, we decided to protect both nitrogen atoms of dibromothienodipyrrole **19**. Treatment with methyl chloroformate using NaH as base and anhydrous THF as solvent afforded the monoprotected derivative **23** in 60% yield. All efforts carried out to achieve diprotection failed. Thus, when **19** was treated with $MeOCOCl/K_2CO_3$/TBAI (tetrabutylammonium iodide) in DMF,[16] the *N*,*N*′-dimethyl-substituted thienodipyrrole **24** was surprisingly obtained (Figure 3).

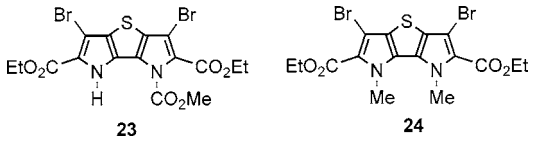
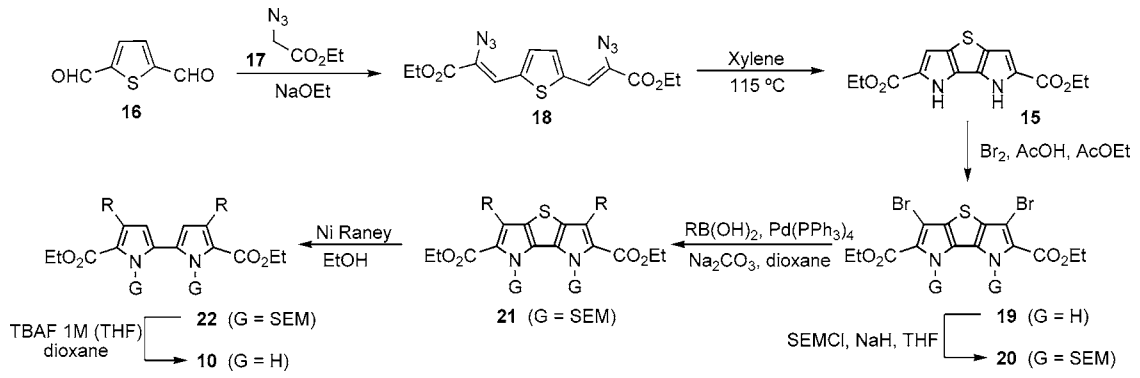


Figure 3.

Fortunately, treatment of **19** with trimethylsilylethoxymethyl chloride (SEM-Cl) with NaH in THF yielded the *N*,*N*′-di(SEM) protected thienodipirrole **20** (G = SEM) in 94% yield (Scheme 2).[17]

The Suzuki coupling between **20** and $RB(OH)_2$ (R = Ph) in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 in 1,4-dioxane gave the diphenyl-substituted thienodipyrrole **21**{*5*} (R = Ph) in quantitative yield. Similarly obtained were the di(pyridin-4-yl)-substituted derivative **21**{*6*} (R = C_6H_4N) and the di-

Scheme 2



(*p*-methoxyphenyl)-substituted one **21**{*7*} (R = *p*-MeOC$_6$H$_4$), in 95% and 100% yield, respectively, upon treatment of **20** with the corresponding boronic acids.

Desulfurization of **21**{*5*}, **21**{*6*}, and **21**{*7*} was carried out by treatment with Raney Ni in ethanol to afford bipyrroles **22**{*5*} (R = Ph) and **22**{*6*} (R = C$_6$H$_4$N) in quantitative yield, while bipyrrole **22**{*7*} (R = *p*-MeOC$_6$H$_4$) was obtained in 94% yield (Scheme 2).

During the removal of the SEM protecting groups of **22**{*5*}, **22**{*6*}, and **22**{*7*}, we found problems similar to those described by Rawal and Cava.[18] Finally, the reaction was achieved by using TBAF in 1,4-dioxane at reflux to yield **10**{*5*} (R = Ph), **10**{*6*} (R = C$_6$H$_4$N), and **10**{*7*} (R = *p*-MeOC$_6$H$_4$) in 93%, 89%, and 91% yield, respectively (Scheme 2), proving the general applicability of this synthetic approach.

The preparation of **10**{*5*} (R = Ph), **10**{*6*} (R = C$_6$H$_4$N), and **10**{*7*} (R = *p*-MeOC$_6$H$_4$) completes, in one side, a new synthesis of 2,7,12,17-tetraphenylporphycene (**1**{*5*}, R = Ph) (see Scheme 1) and, on the other, opens a new general route for the synthesis of 2,7,12,17-tetraaryl (or heteroaryl)-substituted porphycenes.

An application of such methodology to the production of porphycene libraries is currently underway.

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Supporting Information Available: Detailed synthetic procedures and spectroscopic characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) **Diethyl 2,7-Dibromo-4*H*,5*H*-thieno[3,2-*b*:4,5-*b*′]dipyrrole-3,6-dicarboxylate (19).** A solution of 3 mL of Br$_2$ in 45 mL of AcOH was added dropwise to a suspension of 3.0 g (9.7 mmol) of **15** in a mixture of 250 mL of AcOEt and 100 mL of AcOH. The resulting mixture was stirred for 8 h at room temperature. The resulting precipitate was filtered, washed with 3 × 50 mL of an aqueous NaHCO$_3$ solution, and dried over P$_2$O$_5$ in vacuo (50 °C) to yield 4.1 g (8.7 mmol, 89%) of **19** as a white solid: mp > 290 °C dec; IR (KBr) ν_{max} 3417, 3327, 2924, 2853, 1686, 1649, 1375, 1230 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.52 (s, 2H, NH), 4.34 (q, 4H, J = 7.2 Hz, O-C*H*$_2$CH$_3$), 1.35 (t, 6H, J = 7.2 Hz, O-CH$_2$C*H*$_3$); ^{13}C NMR (DMSO-d_6) δ 158.9, 127.7, 125.2, 121.9, 96, 1, 60, 6, 14.3; MS (70 eV) *m*/*z* 463.6 ([M + 2H]$^+$), 419.6, 371.6, 264.7; HRMS calcd for C$_{14}$H$_{12}$Br$_2$N$_2$O$_4$S 461.8884, found 461.8892. Anal. Calcd for C$_{14}$H$_{12}$Br$_2$N$_2$O$_4$S: C, 36.23; H, 2.61; N, 6.04; S, 6.91. Found: C, 36.11; H, 2.54; N, 5.98; S, 6.59.
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(17) **Diethyl 2,7-Dibromo-4*H*,5*H*-bis(trimethylsilylethoxymethyl)-thieno[3,2-*b*:4,5-*b*′]dipyrrole-3,6-dicarboxylate (20).** NaH (2.1 g, 60% in mineral oil) was added portionwise to a suspension of 11 g (24 mmol) of **19** in 50 mL of anhydrous THF under Ar atmosphere. The resulting mixture was stirred for 15 min at room temperature. Then, 15 mL of trimethylsilylethoxymethyl chloride (SEM-Cl) was added dropwise, and the resulting solution was stirred for 1 h at room temperature. Crushed ice (100g) was added, and the resulting mixture was stirred until a precipitate appeared. The solid was filtered, washed with MeOH until it became white, and dried over P$_2$O$_5$ in vacuo (50 °C) to yield 13.4 g (18 mmol, 77%) of **20**. The mother liquor was extracted with hexane, washed (MgSO$_4$), and concentrated in vacuo to yield an extra crop of 3.0 g (4 mmol, 17%) of **20**: mp 127−129 °C; IR (KBr) ν_{max} 2952, 2902, 1705, 1382, 1319, 1228, 1088, 920, 859, 835 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.27 (s, 4H, N.-CH$_2$), 4.41 (q, 4H, J = 7.2 Hz, O-C*H*$_2$CH$_3$), 3.51 (t, 4H, J = 8.4 Hz, O-CH$_2$), 1.45 (t, 6H, J = 7.2 Hz, O-CH$_2$C*H*$_3$), 0.83 (t, 4H, J = 8.4 Hz, Si-CH$_2$), −0.07 (s, 18H, Si-(CH$_3$)$_3$); ^{13}C NMR (CDCl$_3$) δ 160.5, 130.7, 128.5, 123.9, 99.6, 75.0, 65.9, 61.1, 17.9, 14.4, −1.4; MS (ESI-TOF) *m*/*z* = 747.0 ([M + Na + 2H]$^+$), 337.3, 236.1, 218.2, 163.0; HRMS (MALDI-TOF) calcd for C$_{26}$H$_{40}$Br$_2$N$_2$O$_6$SSi$_2$ + Na 745.041, found 745.040. Anal. Calcd for C$_{26}$H$_{40}$Br$_2$N$_2$O$_6$SSi$_2$: C, 43.09; H, 5.56; N, 3.87; S, 4.42. Found: C, 43.25; H, 5.37; N, 3.64; S, 4.21.
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