ORGANIC
LETTERS

2009
Vol. 11, No. 1
77−79

One-Pot Synthesis of Substituted 2,2′-Bipyrroles. A Straightforward Route to Aryl Porphycenes[†]

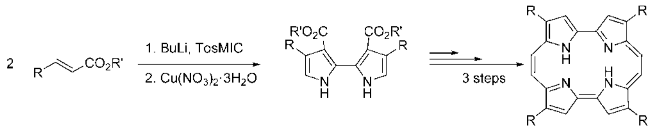
David Sánchez-García,* José I. Borrell, and Santi Nonell

Grup d'Enginyeria Molecular, Institut Químic de Sarrià, Universitat Ramon Llull,
Via Augusta, 390, E-08017 Barcelona, Spain

david.sanchez@iqs.edu

Received October 15, 2008

ABSTRACT



A one-pot reaction for the synthesis of 4,4′-diaryl- and 4,4′-diheteroaryl-substituted 2,2′-bipyrroles is described. The new methodology is based on the oxidative coupling of a 2-trimethylstannylated pyrrole and does not require chromatography. These 2,2′-bipyrroles can be used as precursors in a expeditious synthesis of 2,7,12,17-tetraaryl-porphycenes.

The first investigations devoted to 2,2′-bipyrroles[1] were motivated by their presence as structural subunits in important naturally occurring compounds such as prodigiosin[2] and vitamin B_{12}.[3] However, it is in the field of conducting polymers,[4] especially in the field of synthetic porphyrinoids,[5] where 2,2′-bipyrroles have found their main applications. The syntheses of isomeric and expanded forms of porphyins, such as porphycenes,[6] sapphyrins,[7] and cyclopyrroles,[8] are some remarkable achievements in this area based on the use of 2,2′-bipyrroles as starting materials.

These porphyrinoids are endowed with properties of great interest in a variety of fields ranging from sensors for explosives[9] to biomedicine.[10] Nevertheless, the practical application of these compounds is predicated on the easy availability of substituted 2,2′-bipyrroles bearing groups able to modify the behavior of the parent macrocycle, namely, solubility or optical properties.

Unfortunately, present general methods to obtain 2,2′-bipyrroles[1,11,12] are usually limited since long syntheses are involved. Besides, the introduction of diversity in positions 4 and 4′ is challenging.[13]

To reduce the number of synthetic steps, a strategy based on an oxidative dimerization is most convenient since the only requirement is one free α position in the starting pyrrole. This kind of coupling has been applied successfully in the construction of oligopyrroles[14] and macrocycles.[8]

However, in the case of 4,4′-disubstituted-2,2′-bipyrroles the application of this methodology is more complex because the coupling must be carried out in a regioselective fashion.[15−17] In this regard, Waluk and co-workers have recently prepared a tosyl-protected 4,4′-di-*tert*-butyl-2,2′-bipyrrole by metalation of 3-*tert*-butyl-1-tosyl-1*H*-pyrrole with BuLi followed by exposure to $CuCl_2$.[18]

Because the use of protecting groups implies the addition of two extra steps, using a less reactive metal could make

---

[†] Dedicated to Professor Emanuel Vogel on the occasion of his 80th birthday.

(1) Rapoport, H.; Castagnoli, N. *J. Am. Chem. Soc.* **1962**, *84*, 2178–2181.

(2) Rapoport, H.; Holden, K. G. *J. Am. Chem. Soc.* **1962**, *84*, 635–642.

(3) Bonnett, R.; Cannon, J. R.; Clark, V. M.; Johnson, A. W.; Parker, L. F. J.; Smith, E. L.; Todd, A. *J. Chem. Soc.* **1957**, 1158.

(4) Benincori, T.; Brenna, E.; Sannicolò, F.; Zotti, G.; Zecchin, S.; Schiavon, G.; Gatti, C.; Frigerio, G. *Chem. Mater.* **2000**, *12*, 1480–1489.

(5) Sessler, J. L.; Weghorn, S. J. *Expanded, Contracted, and Isomeric Porphyrins*; Elsevier: Oxford, 1997.

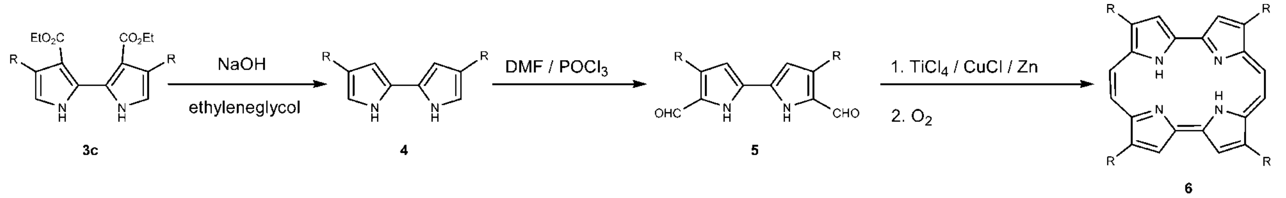
(6) Vogel, E.; Köcher, M.; Schmickler, H.; Lex, J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 257–259.

(7) Bauer, V. J.; Clive, D. R.; Dolphin, D.; Paine, J. B.; Harris, F. L.; King, M. M.; Loder, J.; Wang, S.-W. C.; Woodward, R. B. *J. Am. Chem. Soc.* **1983**, *105*, 6429–6436.

(8) Seidel, D.; Lynch, V.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 1422–1425.

10.1021/ol802380g CCC: $40.75

Scheme 1. Synthetic Pathway of Porphycene **6**



R = -$C_6H_4CH_2OMe$

protecting groups unnecessary. Our first choice was tin, because stannanes have been used in C−C bound formation and oxidative dimerizations. In fact, phenyl-2-trimethylstannyl-pyrroles were obtained in 1998 by van Leusen and coworkers in a single reaction.[19]

According to that report, when tosylmethyl isocyanide (TosMIC) is reacted with 2 equiv of BuLi, a dilithiated species is formed. It is now found that the sequential exposure of this intermediate to an excess of Me_3SnCl and then to a variety of Michael acceptors provides selectively 2-(trimethylstannyl)pyrroles **2** with yields ranging from 40% to 90% (Figure 1).

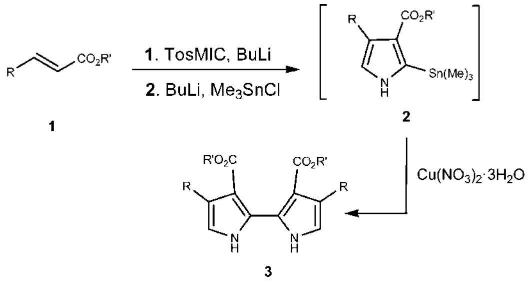
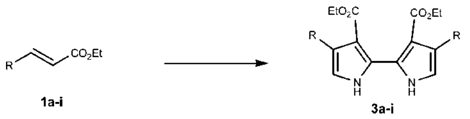


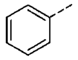
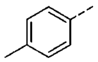
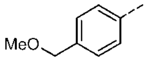
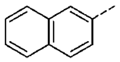
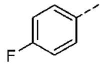
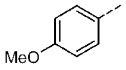
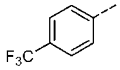
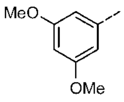
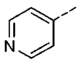
Figure 1. One-pot synthesis of 2,2′-bypirroles.

For preliminary studies, commercially available ethyl cinnamate (**1a**, R = Ph) was used, and the reaction was conducted following the original procedure. Remarkably, the crude material, after extraction and filtration through a short pad of alumina, provided an almost pure pyrrole **2a** (R = Ph). This result prompted us to attempt the oxidative dimerization without further purification of the starting pyrrole. For this propose and following the methodology reported by Quayle and co-workers,[20] 1 equiv of pyrrole **2a** was treated with an excess of $Cu(NO_3)_2{\cdot}3H_2O$ in THF at room temperature. To our delight, the starting material was consumed in 30 min, and a bright fluorescent nonpolar spot appeared on TLC, which was identified as the corresponding 2,2′-bipyrrole **3a**.

At this juncture we decided to investigate the possibility to combine these two separate processes into a one-pot reaction. As expected, the reaction proceeded similarly and gave bipyrrole **3a** without significant losses of yield. To assess the substrate scope of this one-pot-two-process reaction, a variety of cinnamic esters were tested (Table 1). Substituted bipyrroles were obtained with yields consistent to those reported for the two processes (roughly 70−50% for pyrrole formation and 50% for oxidative coupling of related heterocycles).[19,20]

Table 1. Substrate Scope of the Synthesis of 2,2′-Bipyrroles



entry	R	product	yield
1		3a	42%
2		3b	39%
3		3c	48%
4		3d	32%
5		3e	23%
6		3f	25%
7		3g	21%
8		3h	27%
9		3i	53%

It is noteworthy that although the crude reaction gave a complex mixture, bipyrroles could be easily isolated without chromatography by elimination of the copper salts with diluted ammonia and subsequent precipitation with ethyl acetate. In all of the studied examples the precipitate gave satisfactory analytical data. Additional structural evidence for bypyrrole **3h** was provided by X-ray diffraction (Figure 2).

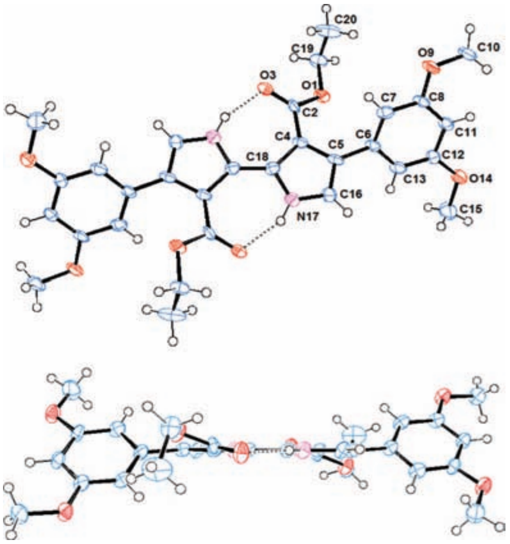


Figure 2. X-ray structure of bipyrrole **3h**.

With these bipyrroles in hand we devised a new shortened synthesis of porphycenes.[21,22] With this aim, **6** was selected as a target porphycene. As anticipated the saponification and decarboxylation of bipyrrole **3c** proceeded smoothly and provided the required free bipyrrole. Vilsmeier−Haack formylation followed by McMurry coupling furnished porphycene **6** (R = $C_6H_4CH_2OMe$) in only four steps from starting materials.[21] This new synthesis of bipyrroles thus gives access to 2,7,12,17-tetraaryl-porphycenes with a remarkable reduction in the number of steps (8 steps are necessary to prepare 2,7,12,17-tetraphenyl-porphycene by earlier methods).[23]

To conclude, a concise one-pot method to obtain 4,4′-substituted bipyrroles has been developed. This procedure provides aryl- and heteroaryl-2,2′-bipyrroles with no need of chromatographic purification on a multigram scale. These compounds are the most suitable starting materials for the synthesis of porphycenes.

Acknowledgment. We thank Dr. Brice Kauffmann (IECB, France) for obtaining X-ray crystallographic data. Financial support by the Spanish MCyT is gratefully acknowledged (grant no. CTQ2007-67763-C03-01/BQU).

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.

OL802380G

---

(9) Stepien, M.; Donnio, B.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 1431–1435.

(10) Stockert, J. C.; Cañete, M.; Juarranz, A.; Villanueva, A.; Horobin, R. W.; Borrell, J. I.; Teixidó, J.; Nonell, S. *Curr. Med. Chem.* **2007**, *14*, 997–1026.

(11) Merrill, B. A.; LeGoff, E. J. *J. Org. Chem.* **1990**, *55*, 2904–2908.

(12) (a) Grigg, R.; Johnson, A. W.; Wasley, J. W. F. *J. Chem. Soc.* **1963**, 359–366. (b) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80–87. (c) Groenendaal, L.; Peerlings, H. W. I.; Havinga, E. E.; Vekemans, J. A. J. M.; Meijer, E. W. *Synth. Met.* **1995**, *69*, 467–470.

(13) Arad, O.; Morros, J.; Batllori, X.; Teixidó, J.; Nonell, S.; Borrell, J. I. *Org. Lett.* **2006**, *8*, 847–850.

(14) (a) Falk, H.; Flodl, H. *Monatsh. Chem.* **1988**, *119*, 247–252. (b) Sessler, J. L.; Aguilar, A.; Sánchez-García, D.; Seidel, D.; Köhler, Th.; Arp, F.; Lynch, V. M. *Org. Lett.* **2005**, *7*, 1887–1890.

(15) Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405–1415.

(16) Gribble, G. W.; Blank, D. H.; Jasinski, J. P. *Chem. Commun.* **1999**, 2195–2196.

(17) Dohi, T.; Morimoto, K.; Ito, M.; Kita, Y. *Synthesis* **2007**, *18*, 2913–2919.

(18) Urbanska, N.; Pietraszkiewicz, M.; Waluk, J. *J. Porphyrins Phthalocyanines* **2007**, *11*, 596–600.

(19) Dijkstra, H. P.; ten Have, R.; van Leusen, A. M. *J. Org. Chem.* **1998**, *63*, 5332–5338.

(20) Beddoes, R. L.; Cheeseright, T.; Wang, J.; Quayle, P. *Tetrahedron Lett.* **1995**, *36*, 283–286.

(21) Sánchez-García, D.; Sessler, J. L. *Chem. Soc. Rev.* **2008**, *37*, 215–232.

(22) Jiao, L.; Hao, E.; Vicente, M. G. H.; Smith, K. M. *J. Org. Chem.* **2007**, *72*, 8119–8122.

(23) Nonell, S.; Bou, N.; Borrell, J. I.; Teixidó, J.; Villanueva, A.; Juarranz, A.; Cañete, M. *Tetrahedron Lett.* **1995**, *36*, 3405–3408.