Pergamon

Tetrahedron Letters 40 (1999) 2925–2926

TETRAHEDRON
LETTERS

Synthesis of Porphyrin Dimers Using a Heck-Type Coupling Reaction with Bisacrylates

Nikolaus Risch*, Rainer Gauler, Ralf Keuper

Universität-GH Paderborn, Fachbereich für Chemie und Chemietechnik,
Warburger Str. 100, D-33098 Paderborn, Germany[a]

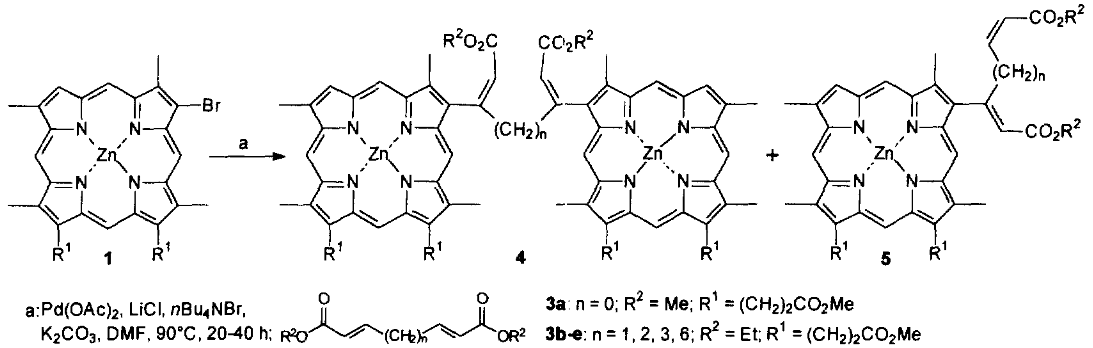
Received 12 January 1999; revised 18 February 1999; accepted 19 February 1999

Abstract:

The Heck-type crosscoupling reaction in DMF under phase-transfer conditions of zinc(II)-monobromo-deuteroporphyrin-dimethylester (**1**) and several bifunctional α,β-unsaturated carbonyl compounds **3a-e** provided C-C-linked dimeric porphyrins, an important class of photosensitizers.

Keywords: Heck reaction; dimeric porphyrins; photodynamic therapy; palladium(0)-catalyzed C-C coupling

The development of new strategies in the synthesis of C–C-linked di- and oligomeric porphyrins has attracted considerable interest [1-4]. An important application of these tetrapyrroles is their use as *in vivo* photosensitizers in photodynamic therapy (PDT) [5-7]. This is particularly true for those possessing a substitution pattern related to that of the natural tetrapyrrole derivatives (e.g. hemato- / protoporphyrin [6,7]).



Scheme 1: Synthesis of C-C-linked dimeric porphyrins.

The Heck crosscoupling is established as a powerful reaction in the functionalization and linking

---

[a] Fax: Int. code + 5251 60 3245; e-mail: nr@chemie.uni-paderborn.de

PII: S0040-4039(99)00418-9

of porphyrins [3,4,8-10]. As yet, derivatives of natural tetrapyrroles linked by acrylate units, have not been described. Such porphyrins are of interest as Michael acceptors and as monomers in polymerization reaction. Furthermore, an easy and stepwise modification of the hydrophobic properties (responsible for the enrichment of the photosensitizers in the tumor cells) of these systems is possible. We examine the Heck-type reaction of bifunctional α,β-unsaturated carbonyl compounds **3a-e** with derivatives of natural tetrapyrroles[11]. The metalloporphyrin **1** is used as starting material, which is easily obtained from heme [12,13]. Preparation of the bisacrylates **3a-e**: The ester **3a** is prepared by esterification of *t,t*-muconic acid (**2a**). **3b-e** are synthesized by a Wittig-Horner reaction [14-19]. The reaction of **3a** and **1** led to the formation of a mixture of regioisomers of **4a** and **5a** (19 / 17 %). The identification of the products takes place by their FAB-MS spectra. After chromatography, the dimeric porphyrins **4b** and **4c** can be detected by NMR and MS (17 / 29 %). The low yield of the monomers **5b** and **5c** (both 8 %) is significant; on increasing the length of the spacer, the yields decrease dramatically. In the case of **3e,** the formation of the dimer **4e** is not observed. Apparently the turnover rate of the Pd(0)-catalyzed reaction depends highly on the distance between the reaction centers of the diester. Porphyrins assume a cofacial arrangement with an interplanar distance of 3.4–3.6 Å [20]. It is reasonable to assume, that the oxidative addition with a parallel orientation of the neighbouring porphyrin occurs very fast after the initial Heck reaction of **1** and the diester **3**. In accordance with the calculated values [**3b**: 2.5 Å, **3c**: 3.8 Å], the dimeric porphyrins **4b** / **4c** can be obtained in acceptable yields [21], whereas the yield of the corresponding monomers **5b** / **5c** is very low (8 %). Decreasing and increasing numbers of methylene groups lead to the formation of a greater amount of monomeric porphyrins [**5a** (17 %); **5d** (18 %)] and simultaneous the yield of the dimer **4** decreases [**4a** (19 %); **4d** (10 %)].

Acknowledgment. We thank the *Fonds der Chemischen Industrie* and the *Deutsche Forschungsgemeinschaft* for financial support.

References and Notes

[1] S. G. DiMagno, V. S.-Y. Lin, M. J. Therien, *J. Am. Chem. Soc.* **1993**, *115*, 2513-2515. [2] S. G. DiMagno, V. S.-Y. Lin, M. J. Therien, *J. Org. Chem.* **1993**, *58*, 5983-5993. [3] H. Ali, J. E. van Lier, *Tetrahedron* **1994**, *50*, 11933-11944. [4] K. S. Chang, B. Luo, T. C. Mak, *J. Chem. Soc., Chem. Commun.* **1994**, 271-272. [5] R. K. Pandey, K. M. Smith, T. J. Dougherty, *J. Med. Chem.* **1990**, *33*, 2032-2038. [6] R. K. Pandey, T. P. Forsyth, K. M. Smith, *Tetrahedron Lett.*, **1992**, *33*, 5315-5318. [7] R. K. Pandey, G. Zheng, D. A. Lee, T. J. Dougherty, K. M. Smith, *J. Mol. Recog.* **1996**, *9*, 118-122. [8] R. W. Boyle, C. K. Johnson, D. Dolphin, *J. Chem. Soc., Chem. Commun.* **1995**, 527-528. [9] D. P. Arnold, L. J. Nitschinsk, *Tetrahedron Lett.* **1993**, *34*, 693-696. [10] A. de Meijere, F. E. Meyer, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379-2411. [11] I. K. Morris, K. M. Snow, K. M. Smith, *J. Org. Chem.* **1990**, *55*, 1231-1236. [12] R. Gauler, N. Risch, *Tetrahedron Lett.* **1997**, *38*, 223-224. [13] R. Gauler, N. Risch, *Eur. J. Org. Chem.* **1998**, 1193-1200. [14] M. Stark, G. Kaupp, *Chem. Ber.* **1977**, *110*, 3084-3110. [15] P. G. Klimko, D. A. Singleton, *J. Org. Chem.* **1992**, *57*, 1733-1740. [16] H. O. House, T. H. Cronin, *J. Org. Chem.* **1965**, *30*, 1061-1070. [17] J. Villieras, M. Rambaud, M. Graff, *Synth. Commun.* **1986**, *16*, 149-156. [18] With exception of glutaraldehyde (**2d**) the dialdehydes **2b,c,e** have to be prepared from available compounds [15-17, 19]. [19] J. J. Pappas, W. P. Keaveney, M. Berger, *Tetrahedron Lett.* **1966**, *7*, 4273-4278. [20] C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112*, 5525-5534. [21] Dimer **4c**: mp.: > 280 °C. – ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.03 (t, 6H, J =7.11 Hz, CH_3), 3.23-3.45 (m, 8H, $13^2/17^2$-CH_2, CH_3), 3.23-4.02 (m, 42H, CH_3), 4.40-4.58 (m, 8H, $13^1/17^1$-CH_2) 6.32 (s, 2H, CH_{vinyl}), 9.10-9.18 (m, 2H, 3(8)-$CH_{\beta\text{-pyr}}$), 9.98-10.03 (m, 2H, CH_{meso}), 10.11-10.25 (m, 6H, CH_{meso}). – UV/VIS (CH_2Cl_2): λ_{max} (lg ε)= 404 (5.649), 535 (4.342), 573 (4.440). – FAB-MS (NBA): *m/z* (%): 1426.11 (89) [M$^+$]. – $C_{76}H_{78}N_8O_{12}Zn_2$ (1426.26): calc. C 64.00, H 5.51, N 7.86; found C 63.57 , H 5.31, N 7.73.