Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8629–8630
Tetrahedron Letters

Convenient synthesis of porphine from β-tetra(*tert*-butyl)porphyrin

Saburo Neya,[a,*] Jingshun Quan,[a] Tyuji Hoshino,[a] Masayuki Hata[a] and Noriaki Funasaki[b]

[a]*Department of Physical Chemistry, Graduate School of Pharmaceutical Sciences, Chiba University, Chiba 263-8522, Japan*
[b]*Department of Physical Chemistry, Kyoto Pharmaceutical University, Yamashina, Kyoto 607-8414, Japan*

Received 31 August 2004; revised 22 September 2004; accepted 24 September 2004
Available online 8 October 2004

Abstract—β-Tetra(*tert*-butyl)porphyrin was prepared from 2-dimethylaminomethyl-4-*tert*-butylpyrrole and converted into porphine, the mother compound of porphyrins, in 64% yield. The dealkylation smoothly proceeded in aqueous sulfuric acid over 15 min at 190 °C under nitrogen.

1. Introduction

Porphyrin is the essential component of hemoproteins such as hemoglobin and cytochrome. The macrocycle is composed of four pyrrole rings connected with four *meso*-carbons, and variously substituted at the periphery. The parent nucleus without any substituents is called porphine (**1**). Despite the simple structure, the preparative difficulty of **1** has been well documented.[1] The commercial sample is fairly expensive.[2] The synthesis has been improved[3] step by step since the initial reports in 1936 by Rothemund[4] and Fischer and Gleim.[5] Neya et al.[6] in 1993 prepared more than 100 mg of **1** at one time from formalin and pyrrole. Taniguchi et al.[7] recently devised an elaborate porphine synthesis from tripyrrane and 2,5-bis(hydroxymethyl)-pyrrole with 30% yield.

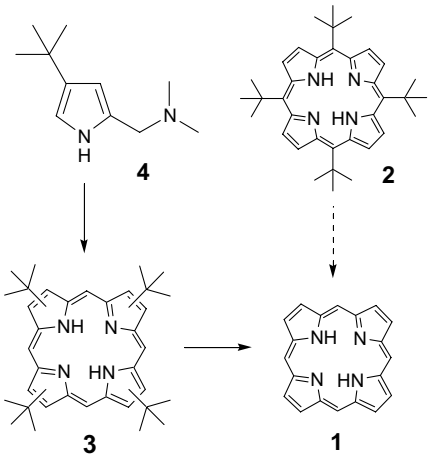
Owing to the fundamental importance, **1** takes up the central place in porphyrin chemistry just as benzene in aromatic organic chemistry. The free *meso*-bridges and pyrrole β-carbons in **1** suggest the potential utility of **1** as the staring material for various porphyrin derivatives[8] and building block of porphine oligomers. In addition, the iron complex has been employed as the smallest prosthetic group of hemoprotein to modify intensively the heme–globin interactions.[9,10] In view of the growing chemical and biological utility of **1**, the facile synthesis still remains as an attractive goal.

We have recently reported porphine formation[11] from *meso*-tetra(*tert*-butyl)porphyrin (**2**). The de-*tert*-butylation of **2** afforded **1** in 74% yield. Intensive literature survey shows that another tetra(*tert*-butyl)porphyrin, that is β-tetra(*tert*-butyl)porphyrin (**3**), was synthesized in 1974 by Whitlock et al.[12] Porphyrin **3** bears peripheral groups on the β-pyrrole carbons whereas compound **2** is substituted on the *meso*-carbons. Whole purpose of their synthesis[12] was to investigate the cyclization mechanism of the monomer, 2-dimethylaminomethyl-4-*tert*-butylpyrrole (**4**). The product **3** is actually a mixture of four isomers separable by chromatography. Since complete removal of the *tert*-butyl substituents in the four isomers results in the same product, porphyrin **3** will serve as a precursor for **1**. We accordingly undertook the de-*tert*-butylation of **3** to explore this possibility.

The synthetic route is outlined in Scheme 1. Pyrrole **4** was converted into porphyrin **3** in refluxing acetic acid.[12] The nominal yield of about 25% for **3**[12] was well reproducible in our hands. The proton NMR spectrum of **3** was in accordance with that reported,[12] indicating dominance of the isomers I and III. We attempted the dealkylation of **3** under various conditions. Several kinds of acid catalysts such as *p*-toluenesulfonic acid, sulfuric acid, and aluminum chloride[13,14] were examined over a 90–200 °C range. Satisfactory result was obtained with hydrated sulfuric acid[14] at 190 °C. Compound **3** was smoothly dealkylated in 15 min. The Soret band shifted from 400 to 394 nm and the characteristic phyllo-type of visible spectrum[11] appeared to reflect the formation of **1**.

Keywords: De-*tert*-butylation; Hydrated sulfuric acid; β-Tetra(*tert*-butyl)porphyrin; Porphine.
* Corresponding author. Tel.: +81 43 290 2927; fax: +81 43 290 2925; e-mail: sneya@p.chiba-u.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.09.154



Scheme 1. Synthesis of **1** from pyrrole **4**. Conversion of **2** to **1** has been already reported.[11]

The reaction temperature is much higher than 90 °C applied for the de-*tert*-butylation of **2**.[11] The higher temperature may arise from the flat macrocycle of **3** with the *tert*-butyl groups on the less crowded β-pyrrole carbons. It is notable that the carbon atom bearing *tert*-butyl group is constrained into an sp^3-carbon like conformation upon proton attachment.[15] In porphyrin **2**, the *meso*-carbons are inherently constrained[16] due to the *tert*-butyl substituents on the crowded *meso*-bridges. Thus, the de-*tert*-butylation for non-planar **2** is feasible at lower temperature.

The above method has several advantages. Pyrrole **4** is easily derived from pyrrole.[12,17] Porphyrin **3** is available from pyrrole **4** in multi-gram quantities with 20–29% yield after brief reflux in a small volume of acetic acid.[12] Deaeration and dehydration are unnecessary for the acetic acid whereas a large amount of oxygen-free and dry dichloromethane is required to prepare **2**.[16] In addition, the expensive oxidizing agent 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, necessary for **2**,[16] is not used. The 64% yield of **1** from **3** is satisfactory and comparable with 74% reported for analogous reaction for **2**.[11] Easy de-*tert*-butylation of **3** makes this porphyrin a superior precursor for **1**. In conclusion, we developed a new route to **1**. The route as well as our previous methodology[11] facilitates the access to porphine.

2. Experimental

β-Tetra(*tert*-butyl)porphyrin[12] **3** (200 mg) was dissolved in sulfuric acid (14 mL), and water (6 mL) was added dropwise. Nitrogen was bubbled over 10 min through the solution for deaeration. The mixture was subsequently heated at 190–200 °C under nitrogen atmosphere for 15 min. 1-Butanol (40 mL) and chloroform (200 mL) were added to the cooled solution before being washed until neutrality with dilute aqueous sodium hydroxide and water. The chloroform layer containing crude **1** was evaporated to dryness. The residue, washed on a centrifuge with small portions of methanol until colorless, was purified by silica-gel column chromatography with chloroform. The fast-moving red band was collected and evaporated to dryness. Recrystallization from chloroform/methanol afforded 74 mg of **1** (64% yield). The visible absorption spectrum in dichloromethane was identical with that reported in the literature.[11] Anal. Calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.69; H, 4.61; N, 17.70. MS: *m*/*z* 310 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 10.37 (s, 4H, *meso*-H), 9.53 (s, 8H, pyrrole-H), −3.96 (br s, 2H, NH).

References and notes

1. (a) Kim, J. B.; Adler, A. D.; Longo, F. R. In *The Porphyrins*; Dolphin, Ed.; Academic Press: New York, 1978; Vol. 1, pp 85–100; (b) Frank, B.; Nonn, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1795–1811.
2. According to the Sigma catalogue in 2004, the price for 5 mg of porphine (product code, P7259) is 477 US dollars.
3. (a) Eisner, U.; Linstead, R. P. *J. Chem. Soc.* **1955**, 3742–3749; (b) Krol, S. *J. Org. Chem.* **1959**, *24*, 2065–2067; (c) Longo, F. R.; Throne, E. J.; Adler, A. D.; Dym, S. *J. Heterocycl. Chem.* **1975**, *12*, 1305–1309.
4. Rothemund, P. *J. Am. Chem. Soc.* **1936**, *58*, 625–628.
5. Fischer, H.; Gleim, W. *Liebigs Ann. Chem.* **1936**, *521*, 157–160.
6. Neya, S.; Yodo, H.; Funasaki, N. *J. Heterocycl. Chem.* **1993**, *30*, 549–550.
7. Taniguchi, S.; Hasegawa, H.; Nishimura, M.; Takahashi, M. *Synlett* **1999**, 73–74.
8. (a) Schlözer, R.; Fuhrhop, J.-H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 363; (b) Nudy, L. R.; Schieber, C.; Longo, F. R.; Agarwala, V. S. *Heterocycles* **1987**, *26*, 1797–1803; (c) Shi, D.-F.; Wheelhouse, R. T. *Tetrahedron Lett.* **2002**, *43*, 9341–9342; (d) Hatcher, S.; Senge, M. O. *Tetrahedron Lett.* **2003**, *44*, 157–160.
9. Sato, T.; Tanaka, N.; Neya, S.; Funasaki, N.; Iizuka, T.; Shiro, Y. *Biochim. Biophys. Acta* **1992**, *1121*, 1–7.
10. Neya, S.; Funasaki, N.; Sato, T.; Igarashi, N.; Tanaka, N. *J. Biol. Chem.* **1993**, *268*, 8935–8942.
11. Neya, S.; Funasaki, N. *Tetrahedron Lett.* **2002**, *43*, 1057–1058.
12. Whitlock, B. J.; Whitlock, H. W.; Alles, H. *J. Am. Chem. Soc.* **1974**, *96*, 3959–3965.
13. Saleh, S. A.; Tashtoush, H. I. *Tetrahedron* **1998**, *54*, 14157–14177.
14. Cerfontain, H.; Arends, J. M. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 358–366.
15. Hendrickson, J. B.; Cram, D. J.; Hammond, G. S. *Organic Chemistry*, 3rd ed.; McGraw-Hill: New York, 1970; pp 668–670.
16. Senge, M. O.; Bischoff, I.; Nelson, N. Y.; Smith, K. M. *J. Porphyrins Phthalocyanines* **1999**, *3*, 99–116.
17. (a) Anderson, H. J.; Loader, C. E.; Xu, R. X.; Lé, N.; Gogan, N. L.; McDonald, R.; Edwards, L. G. *Can. J. Chem.* **1985**, *63*, 896–902; (b) Müller-Westerhoff, U. T.; Swiegers, G. F. *Synth. Commun.* **1994**, *24*, 1389–1393; (c) Zelikin, A.; Shastri, V.; Langer, R. *J. Org. Chem.* **1999**, *64*, 3379–3380.