Tetrahedron Letters 55 (2014) 544–547

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new reagent for the synthesis of [26]hexaphyrin: *N*-sulfonyl aldimine

Seda Cinar, Baris Temelli, Canan Unaleroglu *

Hacettepe University, Department of Chemistry, 06800 Ankara, Turkey

ARTICLE INFO

Article history:
Received 31 May 2013
Revised 5 November 2013
Accepted 26 November 2013
Available online 1 December 2013

Keywords:
Expanded porphyrin
Hexaphyrin
Tripyrrane
N-sulfonyl aldimine

ABSTRACT

The selective synthesis of [26]hexaphyrin(1.1.1.1.1.1) has been achieved by the reaction of *meso*-substituted tripyrrane and *N*-sulfonyl aldimine. The protocol is simple and requires only a catalytic amount of copper(II) triflate under mild reaction conditions.

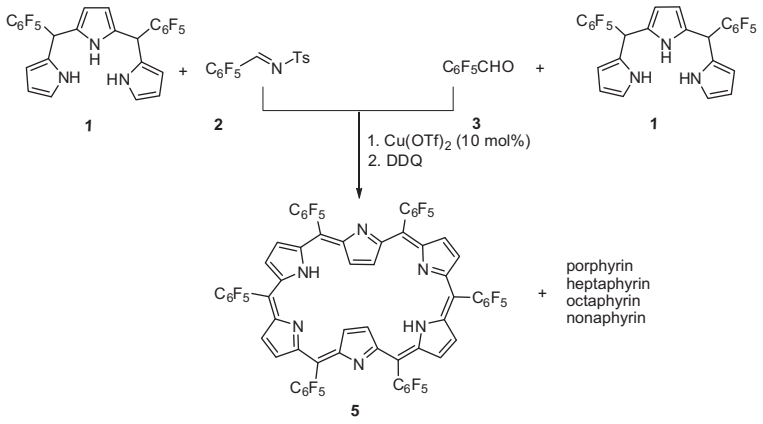
Expanded porphyrins as a class of macrocyclic molecules have attracted much attention because of their unique optical, electrochemical, and coordination properties.[1] The number of pyrrolic units and their linkages designate the structures of expanded porphyrins, the ring size of which and number of π electrons influence their properties. Their complexing ability with transition metals also makes them important precursors in the field of biomedical applications such as photodynamic therapy (PDT) and magnetic resonance imaging (MRI).[2] Among expanded porphyrins, hexapyrrolic systems have drawn attention due to their structural stability, flexibility, high molecular symmetry, and variable metallation behavior. The first *meso*-hexaphenylhexaphyrin was reported by Dolphin et al., but the poor stability of this compound prevented spectroscopic characterization.[3] Cavaleiro et al. obtained stable *meso*-hexa(pentafluorophenyl)hexaphyrin during Rothemund synthesis of *meso*-tetra(pentafluorophenyl)porphyrin.[4] They characterized the structure by using spectroscopic techniques and reported the X-ray structure. Osuka and co-workers have made significant contributions, especially on the synthesis and characterization of hexaphyrin and higher analogues.[5] Their pioneering work on the ring size selective synthesis of expanded porphyrins indicated that dipyrromethane or tripyrromethane in place of pyrrole was suitable starting material. The reaction conditions and catalyst are also very important in the synthesis of the target molecules.[6] It is still challenging for organic chemists to develop more convenient synthetic routes for ring size selective hexaphyrin synthesis. In this context, we have successfully developed the ring size selective synthesis of hexaphyrin by copper(II) triflate catalyzed [3+3] condensation of *meso*-pentafluorophenyl substituted tripyrrane **1** and *N*-sulfonyl aldimine **2**. Herein, we report our results in detail.

The reactivity of pyrroles with *N*-sulfonyl aldimines in the presence of metal triflate catalysts was first discovered during our previous studies on the synthesis of 2-substituted pyrrole sulfonamides, *meso*-substituted dipyrromethanes, and porphyrins.[6] These results prompted us to investigate further the synthesis of expanded porphyrins, especially *meso*-substituted hexaphyrins from *meso*-pentafluorophenyl substituted tripyrrane **1** and *N*-sulfonyl aldimine **2**. In initial experiments, we compared the reactivity of tripyrrane **1** toward aldehyde **3** and *N*-sulfonyl aldimine **2** (Scheme 1). Condensation reactions were carried out in the presence of 10 mol % of copper(II) triflate as the catalyst at room temperature in dichloromethane for two hours, and the condensation products were oxidized by adding DDQ. *N*-Sulfonyl aldimine **2** afforded *meso*-pentafluorophenyl substituted [26]hexaphyrin(1.1.1.1.1.1) **5** in a promising 19% yield and in 14% yield with pentafluorobenzaldehyde. The spectroscopic data of hexaphyrin were in agreement with the literature values. Both reactions gave porphyrin and some expanded porphyrins (heptaphyrin, octaphyrin, and nonaphyrin) as side products, and scrambling of expanded porphyrinogen precursors, which is typically encountered in porphyrin synthesis could be the main reason for the formation of these side products.[7] These compounds were separated by column chromatography and identified by MALDI-TOF-MS.

In order to optimize this procedure, a variety of catalysts were screened (Table 1). Among the triflates, only $Cu(OTf)_2$ showed catalytic activity by producing hexaphyrin **5** with high selectivity (19% yield) (Table 1, entries 1–4). $BF_3{\cdot}OEt_2$ and TfOH gave porphyrin

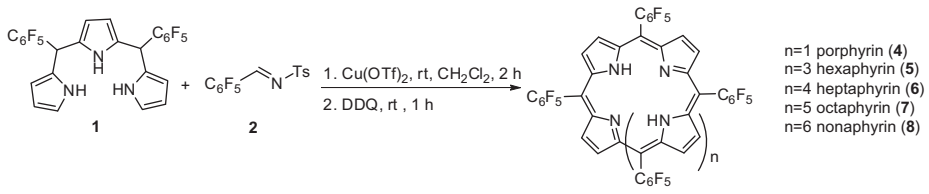
* Corresponding author. Tel.: +90 312 297 7962; fax: +90 312 299 2163.
E-mail address: canan@hacettepe.edu.tr (C. Unaleroglu).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.11.101



Scheme 1. Synthesis of expanded porphyrins.

Table 1
Effect of the catalyst on the reaction of tripyrrane **1** and *N*-sulfonyl aldimine **2**



Entry[b]	Catalyst	Yield[a] (%)				
		4	**5**	**6**	**7**	**8**
1	$Y(OTf)_3$	–	–	–	–	–
2	$Yb(OTf)_3$	–	–	–	–	–
3	$Sc(OTf)_3$	–	–	–	–	–
4	$Cu(OTf)_2$	12	19	1	5	4
5	TFA	8	15	5	–	–
6	$BF_3{\cdot}OEt_2$	21	–	–	–	–
7	TfOH	35	–	–	–	–

[a] Isolated yield after column chromatography.
[b] Reactions were carried out at 45 mM concentration.

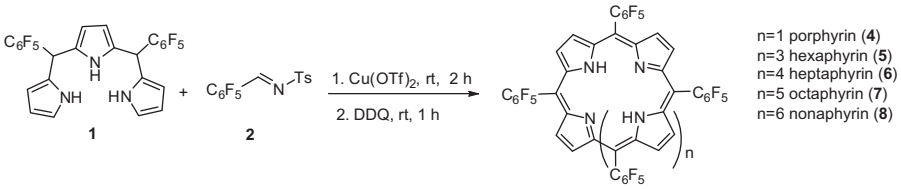
4 as the sole product in 21% and 35% yields, respectively (Table 1, entries 5 and 6). Only TFA which is a commonly used catalyst in the synthesis of porphyrins and expanded porphyrins afforded hexaphyrin (**5**) (15%) in a comparable yield to $Cu(OTf)_2$.

Next, we investigated the effect of the solvent on the reaction (Table 2, entries 1–5). Among the examined solvents, the best result was obtained in dichloromethane. While porphyrins were formed in chloroform with comparable yields to dichloromethane, no products were obtained in acetonitrile or toluene. The effect of catalyst loading on the reaction was also tested (Table 2, entries 6–8). When 1% of the catalyst was used, no products were obtained; 5% and 20% catalyst loadings led to a decrease in the yield of hexaphyrin (**5**). However, there was a significant increase in the yield of heptaphyrin (**6**) (9%) with a high $Cu(OTf)_2$ loading (Table 2, entry 6).

Using our optimized conditions, we further examined the effect of concentration, temperature and time on the reaction. The substrate concentration has a profound effect on the formation of porphyrins.[7a] For this reason, the reaction was performed at different concentrations (Table 3, entries 1–4). The highest yield of hexaphyrin **5** was obtained at 45 mM. When the concentration was decreased to 30 mM, or increased to 60 mM or 90 mM, formation of hexaphyrin **5** in high yields was no longer selective. Porphyrin **4**, hexaphyrin **5**, heptaphyrin **6**, and nonaphyrin **8** products were obtained in almost the same yields (~2–5%) at 30 mM. The reaction showed similar behavior at 60 mM and 90 mM for all the products and the yield of hexaphyrin **5** was reduced to 9%. The tendency for the polymerization of oligopyrroles at higher concentrations caused a decrease in the yield of hexaphyrin.

Temperature is known to be an important parameter in the synthesis of expanded porphyrins and reactions in the literature are generally carried out at low temperatures such as 0 °C.[5b,8] Taking into account this importance, the reaction was repeated at 0 and 50 °C (Table 3, entries 5 and 6). The reaction at 0 °C gave hexaphyrin **5** in 7% yield with the same yield of porphyrin **4**. At 50 °C, the amount of hexaphyrin **5** was reduced dramatically to 5% and a large increase in the amount of porphyrin **4** resulted (20% yield). Interestingly, no other expanded products (heptaphyrin, octaphyrin, or nonaphyrin) were observed at lower or higher temperatures. We finally examined the effect of the reaction time before DDQ addition using the optimized conditions (Table 3, entries 7–11). When the reaction time was reduced to one hour, the yield of hexaphyrin **5** decreased to 10%. However, when the reaction time was extended to eight hours, size selective hexaphyrin formation was successfully achieved raising the yield to 25%. In the literature, hexaphyrin is known to be synthesized in up to 30% yield along

Table 2
Effect of the solvent and catalyst loading on the reaction of tripyrrane **1** and *N*-sulfonyl aldimine **2**



Entry[b]	Solvent	Catalyst (%)	Yield[a] (%)				
			4	**5**	**6**	**7**	**8**
1	CH_2Cl_2	10	12	19	1	5	4
2	$CHCl_3$	10	12	18	5	6	2
3	THF	10	2	9	14	2	3
4	Toluene	10	—	—	—	—	—
5	CH_3CN	10	—	—	—	—	—
6	CH_2Cl_2	20	7	14	9	—	—
7	CH_2Cl_2	5	4	4	1	5	—
8	CH_2Cl_2	1	—	—	—	—	—

[a] Isolated yield after column chromatography.
[b] Reactions were carried out at 45 mM concentration.

Table 3
Effect of the concentration, temperature and reaction time on the $Cu(OTf)_2$-catalyzed reaction of tripyrrane **1** and *N*-sulfonyl aldimine **2** in CH_2Cl_2

Entry	**1** (mM)	Temp (°C)	Time[b] (h)	Yield[a] (%)				
				4	**5**	**6**	**7**	**8**
1	30	rt	2	4	4	2	4	5
2	45	rt	2	12	19	1	5	4
3	60	rt	2	5	9	3	5	4
4	90	rt	2	3	9	3	5	5
5	45	0	2	7	7	—	—	—
6	45	50	2	20	5	—	—	—
7	45	rt	1	8	10	14	—	—
8	45	rt	4	9	21	11	2	5
9	45	rt	8	11	25	1	3	7
10	45	rt	16	12	22	4	5	5
11	45	rt	24	12	22	5	7	4

[a] Isolated yield after column chromatography.
[b] The reaction time before addition of DDQ.

with high yields of other expanded porphyrins.[9] A suggested reaction pathway for hexaphyrin synthesis is shown in Scheme 2.

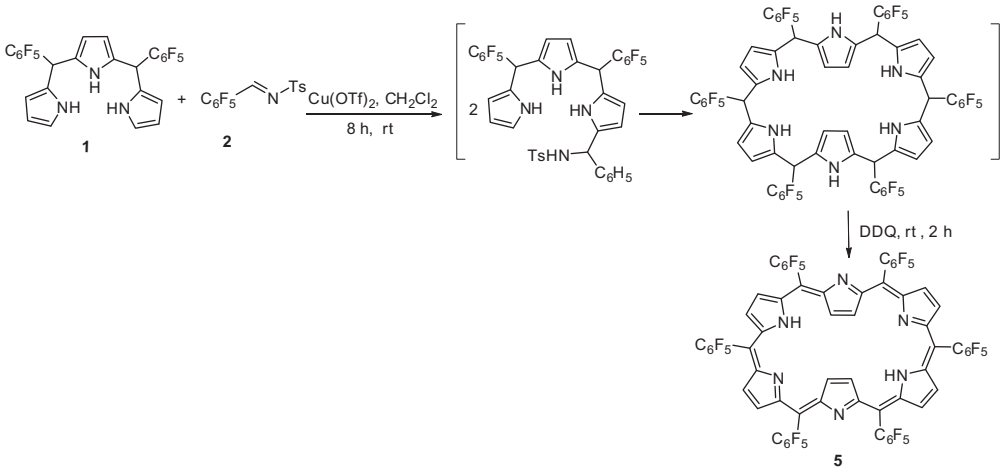
In summary, we have developed an efficient reaction protocol for the synthesis of hexaphyrin based on the $Cu(OTf)_2$-catalyzed reaction of tripyrrane with *N*-sulfonyl aldimine. The reaction conditions were optimized to give the highest yield of hexaphyrin with high selectivity. The method requires a catalytic amount of $Cu(OTf)_2$ as a water-stable catalyst, which is reusable and inexpensive.

Acknowledgment

This work was supported by the Scientific and Technological Research Council of Turkey (TUBITAK), under Grant 110T777.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.101.



Scheme 2. Suggested reaction pathway.

References and notes

1. (a) Jasat, A.; Dolphin, D. *Chem. Rev.* **1997**, *97*, 2267–2340; (b) Saito, S.; Osuka, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 4342–4373; (c) Rath, H.; Sankar, J.; PrabhuRaja, V.; Chandrashekar, T. K.; Nag, A.; Goswami, D. *J. Am. Chem. Soc.* **2005**, *127*, 11608–11609; (d) Yoon, Z. S.; Kwon, J. H.; Yoon, M. C.; Koh, M. K.; Noh, S. B.; Sessler, J. L.; Lee, J. T.; Seidel, D.; Aguilar, A.; Shimizu, S.; Suzuki, M.; Osuka, A.; Kim, D. *J. Am. Chem. Soc.* **2006**, *128*, 14128–14134; (e) Kang, S.; Hayashi, H.; Umeyama, T.; Matano, Y.; Tkavhenko, N. V.; Lemmetyinen, H.; Imahori, H. *Chem. Asian J.* **2008**, *3*, 2065–2074.
2. (a) Sessler, J. L.; Miller, R. A. *Biochem. Pharmacol.* **2000**, *59*, 733–739; (b) Sessler, J. L.; Tvermoes, N. A.; Davis, J.; Anzenbacher, P., Jr.; Jursikova, K.; Sato, W.; Seidel, D.; Lynch, V.; Black, C. B.; Try, A.; Andrioletti, B.; Hemmi, G.; Mody, T. D.; Magda, D. J.; Kral, V. *Pure Appl. Chem.* **1999**, *71*, 2009–2018; (c) Young, S. W.; Qing, F.; Harriman, A.; Sessler, J. L.; Dow, W. C.; Mody, T. D.; Hemmi, G. W.; Hao, Y.; Miller, R. A. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 6610–6615.
3. Brückner, C.; Sternberg, E. D.; Boyle, R. W.; Dolphin, D. *Chem. Commun.* **1997**, 1689–1690.
4. Neves, M. G. M. S.; Martins, R. M.; Tome, A. C.; Silvestre, A. J. D.; Silva, A. M. S.; Felix, V.; Drew, M. G. B.; Cavalerio, J. A. S. *Chem. Commun.* **1999**, 385–386.
5. (a) Shin, J. Y.; Furuta, H.; Yoza, K.; Igarashi, S.; Osuka, A. *J. Am. Chem. Soc.* **2001**, *123*, 7190–7191; (b) Taniguchi, R.; Shimizu, S.; Suzuki, M.; Shin, J.-Y.; Furuta, H.; Osuka, A. *Tetrahedron Lett.* **2003**, *44*, 2505–2507; (c) Suzuki, M.; Osuka, A. *Org. Lett.* **2003**, *5*, 3943–3946; (d) Shimizu, S.; Taniguchi, R.; Osuka, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2225–2229.
6. (a) Temelli, B.; Unaleroglu, C. *Tetrahedron Lett.* **2005**, *46*, 7941–7943; (b) Temelli, B.; Unaleroglu, C. *Tetrahedron* **2006**, *62*, 10130–10135; (c) Temelli, B.; Unaleroglu, C. *Tetrahedron* **2009**, *65*, 2043–2050.
7. (a) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827–836; (b) Littler, B. J.; Ciringh, Y.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 2864–2872.
8. (a) Tanaka, Y.; Shin, J. Y.; Osuka, A. *Eur. J. Org. Chem.* **2008**, 1341–1349; (b) Lim, J. M.; Shin, J. Y.; Tanaka, Y.; Saito, S.; Osuka, A.; Kim, D. *J. Am. Chem. Soc.* **2010**, *132*, 3105–3114.
9. Kamimura, Y.; Shimizu, S.; Osuka, A. *Chem. Eur. J.* **2007**, *13*, 1620–1628.