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SYNTHESIS OF ISOXAZOLINE-FUSED CHLORINS BY 1,3-DIPOLAR CYCLOADDITION REACTION OF PORPHYRINS WITH ALKYL NITRILE OXIDES

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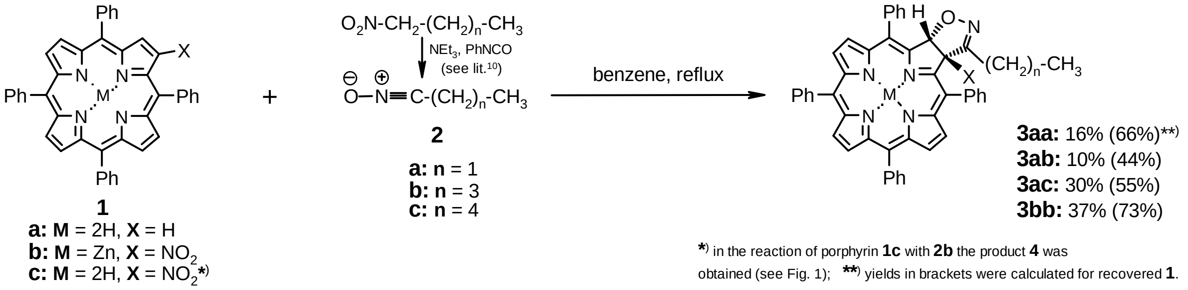
Abstract – *meso*-Tetraphenylporphyrin and its β-nitro zinc complex derivative react at higher temperature with unstable alkyl nitrile oxides affording isoxazoline-fused chlorins according to dipolar [3+2]-cycloaddition pathway. The respective nitrile oxides were *in situ* generated from the corresponding nitroalkanes in the presence of triethylamine and phenyl isocyanate. The products obtained are attractive intermediates for further functionalization of porphyrins and may be of potential use as sensitizers in photodynamic therapy.

Chlorins and bacteriochlorins may be considered as second generation photosensitizers in antitumor photodynamic therapy (PDT)[1] due to their characteristic strong absorption bands shifted to the red region of visible spectrum (630-780 nm). In the recent past numerous investigations oriented towards the synthesis and utilization of these compounds have been undertaken.

The attractive chlorin systems can be synthesized by various methods.[2] One of the approaches involves 1,3-dipolar cycloaddition reaction of peripheral β,β-double bonds of porphyrin moiety with some 1,3-dipoles (azomethine ylides,[3] diazomethane,[4] nitrones,[5] and carbonyl ylides[6]). Nitrile oxides could be also used for this purpose, thus leading to fused porphyrin-isoxazoline derivatives.[7] Subsequently, the isoxazoline moiety embedded in this system conceivably may be easily cleaved[8] to provide novel functionalized chlorins. In the case of relatively stable 2,6-disubstituted benzonitrile oxides the reaction, to be completed successfully, required long-time of heating with periodical addition of the respective oxide.[7a,b] Herein we report our preliminary studies concerning this type of cycloaddition with the use of alkyl nitrile oxides, generation of which is more difficult, and which are generally less stable as compared to the aryl ones. However, this is a challenging task because the chlorins prepared by the above method, bearing lipophilic alkyl chains, can be transformed into hydrophilic ketones, amines, alcohols, etc.,[8] and therefore may lead to very attractive amphiphilic systems,[9] which are sought in many fields of this chemistry. The precursors for the *in situ* generation of the nitrile oxides, in the reaction with triethylamine and phenyl isocyanate, were short-chain nitroalkanes. Thus, the additional problem in these transformations are the relatively low boiling points of the nitrocompounds used – as this type of cycloadditions are usually carried-out at higher temperature.



*) in the reaction of porphyrin **1c** with **2b** the product **4** was obtained (see Fig. 1); **) yields in brackets were calculated for recovered **1**.

Scheme 1

The reaction of *meso*-tetraphenylporphyrin (**1a**) with an excess of nitrocompounds (**2a-c**), in the presence of NEt_3 and PhNCO (in refluxing benzene or 1,2,4-trichlorobenzene), gave the corresponding isoxazoline–fused chlorins (**3aa-3ac**) (Scheme 1). To the substrates, heated in a light-shielded flask, the new portions of $R\text{-}NO_2$, NEt_3, and PhNCO were added every 3 hours to supplement the loss of the formed *in situ* nitrile oxide (because of its fast degradation). The reactions were continued for *ca* 50 hrs.[11] Due to the above mentioned difficulties the yields of the products are rather low or moderate.

In all cases the considerable amounts of the starting porphyrin were recovered. The prolonged reaction time did not give higher yields, because in these conditions the progressive degradation of the products was observed. The compounds **3aa-3ac** were separated easily by column chromatography[12] and identified by MS, ^1H NMR and UV-Vis methods (Table 1, Figure 2). In the mass spectrum the $(M+H)^+$ ion peaks were found at m/z = 686, 714, and 728, respectively. The observed isotope patterns of the peaks match the patterns expected for their respective compositions. The ^1H NMR spectra reveal characteristic broad singlets at *ca* –1.80 ppm originating from NH protons. In the region 6.45-6.70 ppm the signals of H^β-protons in reduced pyrrole ring (H^β-chlorin) were found. The products also exhibit typical electronic absorption spectra with maximum peaks at *ca* 415–420 nm (Soret) and 645–650 nm (Q-bands; one example is given on Figure 2, region 500–750 nm).

Table 1. Products and their characteristic and diagnostic data.

Product No	HR-MS (ESI; $[M+H]^+$) calcd. (found)	^1H NMR [ppm] (diagnostic signals)
3aa	686.2920 (686.2925) for $C_{47}H_{36}N_5O$	-1.79 (s, 2×NH), 6.49 & 6.72 (2×d, J = 8.7 Hz, H-2 & H-3)
3ab	714.3233 (714.3283) for $C_{49}H_{40}N_5O$	-1.77 (s, 2×NH), 6.47-6.60 (m, H-2 & H-3)
3ac	728.3389 (728.3397) for $C_{50}H_{42}N_5O$	-1.81 (s, 2×NH), 6.50-6.64 (m, H-2 & H-3)
3bb	803 (M^+ – OH) for $C_{49}H_{35}N_6O_2Zn$	5.72 (broad s, H-2)

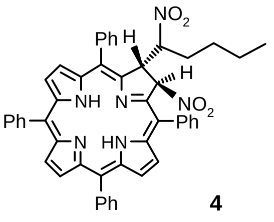


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Figure 1

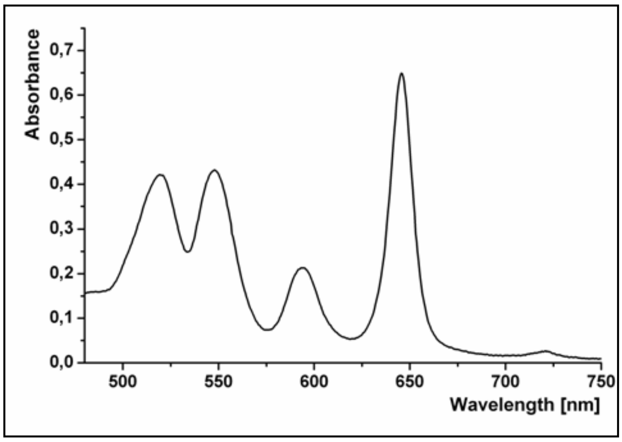

Figure 2. The UV-Vis spectrum of compound **3aa**.

Reaction of zinc-complex (**1b**) with 1-nitropentane gave regioselectively the product (**3bb**) in 37% yield (73% for recovered **1b**). Its structure was proposed on the basis of the regiochemistry observed in this type of [3+2]-cycloadditions.[4b,13] Finally the use of β-nitroporphyrin (**1c**), which was successfully applied in some Diels-Alder reactions,[14] did not give the [3+2]-cycloadduct, and the reaction took a different course. For the product obtained (with **2b**), on the basis of MS (ESI) and ^{1}H NMR investigations, the structure **4** was proposed (see Figure 1). In the mass spectrum small molecular ion peak was found at *m/z* = 776 and more intensive one at *m/z* = 713 (M – NO_2 – OH). The formation of this compound can be rationalized by the reaction of the carbanion which is formed in the first step of the reaction of nitropentane with triethylamine. It readily enter the Michael addition to activated by NO_2 group β,β-double bond, which exhibits considerable olefinic character.

The reactivity pattern of **1b** and **1c** is in accordance with the known observations that metalloporphyrins are less reactive towards nucleophiles, thus **1b** did not undergo Michael addition; however, it was reactive enough as dipolarophile in [3+2]-cycloaddition with nitrile oxides.

In all of the reaction mixtures we were unable to identify bacteriochlorins or isobacteriochlorins that usually accompany the main products.

We presented herein an approach to fused isoxazoline-type chlorins by dipolar [3+2]-cycloaddition of unstable alkyl nitrile oxides to *meso*-tetraphenylporphyrin derivatives. This reaction may well receive future attention in the area of porphyrin skeleton modifications. Studies on the scope and limitations of this derivatization method are in progress. Currently, we are in the midst of exploring other possibilities of generation this type of nitrile oxides and their applications in the above cycloaddition. The products obtained are potentially attractive and versatile intermediates for the further derivatization of *meso*-arylchlorins designed as photosensitizers in PDT.

REFERENCES AND NOTES

1. (a) E. D. Sternberg, D. Dolphin, and Ch. Brückner, *Tetrahedron*, 1998, **54**, 4151. (b) L. Bourre, G. Simonneaux, Y. Ferrand, S. Thibaut, Y. Lajat, and T. Patrice, *J. Photochem. Photobiol. B*, 2003, **69**, 179. (c) E. S. Nyman and P. H. Hynninen, *J. Photochem. Photobiol. B*, 2004, **73**, 1.
2. For example: (a) reduction: H. W. Whitlock Jr., R. Hanauer, M. Y. Oester, and B. K. Bower, *J. Am. Chem. Soc.*, 1969, **91**, 7485. (b) oxidation by OsO_4: A. N. Kozyrev, T. J. Dougherty, and R. K. Pandey, *Tetrahedron Lett.*, 1996, **37**, 3781. Ch. Brückner, S. J. Rettig, and D. Dolphin, *J. Org. Chem.*, 1998, **63**, 2094; and refs. cited therein. (c) addition of Br_2: M. K. Tse, Z.-Y. Zhou, T. C. W. Mak, and K. S. Chan, *Tetrahedron*, 2000, **56**, 7779. (d) Diels-Alder reaction: A. C. Tomé, P. S. S. Lacerda, M. G. P. M. S. Neves, and J. A. S. Cavaleiro, *Chem. Commun.*, **1997**, 1199. M. G. H. Vicente, M. T. Cancilla, C. B. Lebrilla, and K. M. Smith, *Chem. Commun.*, **1998**, 2355. S. Zhao, M. G. P. M. S.

Neves, A. C. Tomé, A. M. S. Silva, J. A. S. Cavaleiro, M. R. M. Domingues, and A. J. F. Correia, *Tetrahedron Lett.*, 2005, **46**, 2189. A. M. G. Silva, A. C. Tomé, M. G. P. M. S. Neves, and J. A. S. Cavaleiro, *Tetrahedron Lett.*, 2000, **41**, 3065. (e) 1,3-dipolar cycloaddition: J. A. S. Cavaleiro, M. G. P. M. S. Neves, and A. C. Tomé, *Arkivoc*, **2003** (*xiv*), 107. (f) cyclopropanation *via* carbene addition: H. J. Callot, F. Metz, and C. Piechocki, *Tetrahedron*, 1982, **38**, 2365; and refs. cited therein.

3. A. M. G. Silva, A. C. Tomé, M. G. P. M. S. Neves, A. M. S. Silva, and J. A. S. Cavaleiro, *Chem. Commun.*, **1999**, 1767.
4. (a) A. Desjardins, J. Flemming, E. D. Sternberg, and D. Dolphin, *Chem. Commun.*, **2002**, 2622. (b) A. M. G. Silva, A. C. Tomé, M. G. P. M. S. Neves, and J. A. S. Cavaleiro, *Synlett*, **2002**, 1155.
5. A. M. G. Silva, A. C. Tomé, M. G. P. M. S. Neves, A. M. S. Silva, J. A. S. Cavaleiro, D. Perrone, and A. Dondoni, *Tetrahedron Lett.*, 2002, **43**, 603.
6. J. Flemming and D. Dolphin, *Tetrahedron Lett.*, 2002, **43**, 7281.
7. During our investigations involved in this project two independent papers were published by the groups of Li, Zhu, and Feng, respectively, describing 1,3-dipolar cycloaddition of aryl nitrile oxides to *meso*-tetraphenylporphyrin derivatives: (a) X. Li, J. Zhuang, Y. Li, H. Liu, S. Wang, and D. Zhu, *Tetrahedron Lett.*, 2005, **46**, 1555. (b) X. Liu, Y. Feng, X. Chen, F. Li, and X. Li, *Synlett*, **2005**, 1030. However, the 2,6-dichlorobenzonitrile oxide used in the above mentioned papers is relatively stable. We present herein the preliminary results in this type of cycloaddition with the use of unstable alkyl nitrile oxides.
8. For example: (a) reaction with HI: G. W. Perold and F. V. K. von Reiche, *J. Am. Chem. Soc.*, 1957, **79**, 465. (b) transformation to oximes: V. Jäger and H. Grund, *Angew. Chem.*, 1976, **88**, 27. (c) reduction: A. P. Kozikowsky and M. Adamczyk, *Tetrahedron Lett.*, 1982, **23**, 3123. (d) thermal cleavage: R. G. Shotter, D. Sesardic, and P. H. Wright, *Tetrahedron*, 1975, **31**, 3069. (e) *via* quarternization: S. Shatzmiller, E. Shalom, R. Lidor, and E. Tartkovski, *Liebigs Ann. Chem.*, 1983, **6**, 897; S. Kwiatkowski and S. Ostrowski, *Bull. Soc. Chim. Belg.*, 1993, **102**, 259. For review see: R. Gandolfig and P. Grünanger, In *The Chemistry of Heterocyclic Compounds*; Part 2: "Isoxazoles"; P. Grünanger and P. Vita-Finzi, Eds.; An Interscience, John Wiley & Sons, Inc.: New York – Chichester – Weinheim – Brisbane – Singapore – Toronto, **1999**; pp 671-739.
9. (a) T. Peters Jr., *All about albumin*, Academic Press: San Diego, CA, 1992. (b) D.-K. Han, G. Jin, B. Y. Chung, and Y. K. Shim, *Bull. Korean Chem. Soc.*, 1999, **20**, 137.
10. R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. France*, 1962, **7**, 2215.
11. **Typical Procedure:** To a stirred solution of porphyin (**1a-c**; 0.035 mmol) and nitrocompound (**2a-c**; 0.90 mmol) in anhydrous benzene (1 mL), triethylamine (0.070 mL, 0.50 mmol) was added, and the mixture was stirred for 15 min. at room temperature in a light-shielded flask. Then, the reaction mixture was heated to reflux, and a solution of phenyl isocyanate (85 mg, 0.71 mmol) in benzene (0.5 mL) was added dropwise *via* syringe over a period of *ca* 15 min. The new portions of nitroalkane, NEt_3, and PhNCO were added every 3 hrs. After 50 hrs the reaction mixture was cooled to room temperature, the precipitate was filtered off, and the residue was chromatographed (SiO_2, 230-400 mesh; eluent: *n*-hexane to $CHCl_3$ / *n*-hexane (2:1), then $CHCl_3$) to give the desired product.

    Data for product 3ab: Mp >300 °C. ^1H NMR (200 MHz; $CDCl_3$): δ_H = 8.63 (d, J = 4.8 Hz, 1 H, H^β-pyrrole), 8.59-8.50 (m, 1 H, H^β-pyrrole), 8.48 (s, 2 H, H^β-pyrrole), 8.35 (d, J = 4.6 Hz, 1 H, H^β-pyrrole), 8.30-7.12 (m, 22 H; 2 H of H^β-pyrrole and 20 H of H-Ph), 6.60-6.47 (m, 2 H, H-2 & H-3), 2.69-2.46 (m, CH_2), 1.80-1.17 (m, 2 × CH_2), 0.97 (t, J = 7.2 Hz, CH_3), -1.77 (broad s, 2 H, 2 × NH). UV-Vis ($CHCl_3$): λ_{max} (log ε) = 645.5 (4.20), 593.5 (3.69), 547.5 (4.00), 519.5 (3.98), 416.0 nm (5.10, Soret). MS (ESI): *m/z* (% rel. int.) = 716 (5), 715 (37), and 714 (100) [isotope $(M+H)^+$]; HR-MS (ESI) – see Table 1. The molecular formula was also confirmed by comparing the theoretical and experimental isotope patterns for the $[M + H]^+$ ion ($C_{49}H_{40}N_5O$) – found to be identical within the experimental error limits.
12. The products have lower R_f values as compared to the starting porphyrin **1a** (TLC: $CHCl_3$).
13. N. Barbulescu and P. Grünanger, *Gazz. Chim. Ital.*, 1962, **92**, 138.
14. S. Ostrowski and P. Wyrębek (in preparation).