Tetrahedron Letters 51 (2010) 4505–4508

Contents lists available at ScienceDirect

Tetrahedron Letters

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

[2-Methylazeteochlorinato]Ni(II): a pyrrole ring-contracted chlorin analogue

Subhadeep Banerjee [†], Michael A. Hyland [†], Christian Brückner [*]

Department of Chemistry, University of Connecticut, Unit 3060, Storrs, CT 06269-3060, USA

ARTICLE INFO

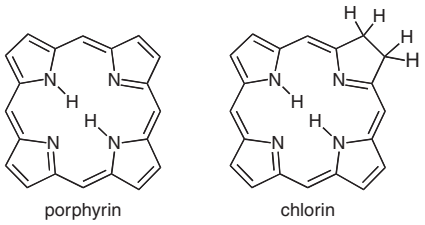
Article history:
Received 20 May 2010
Revised 16 June 2010
Accepted 17 June 2010
Available online 22 June 2010

Keywords:
Porphyrins
Porphyrinoids
Chlorins
Chlorin analogues
Pyrrole-modified porphyrins

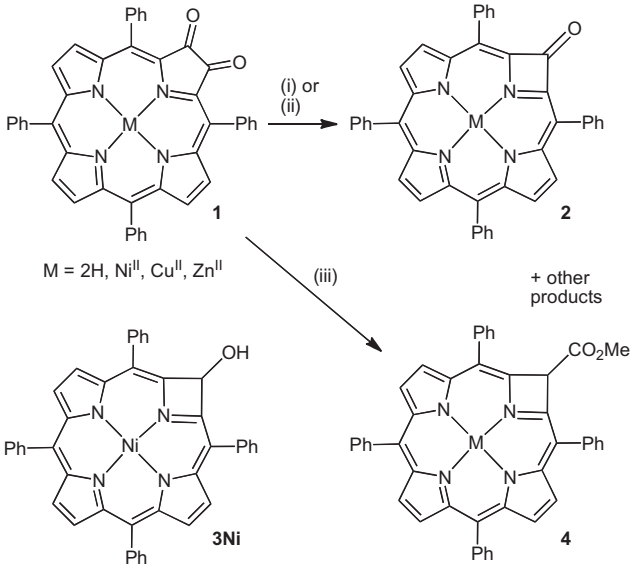
ABSTRACT

The formal replacement of one of the pyrrole rings in [*meso*-tetraphenylporphyrinato]Ni(II) (**5Ni**) by an azete moiety is reported. Thus, reaction of known chlorophin monoaldehyde **7Ni** (made in three steps from **5Ni**) with methyl-Grignard, followed by an acid-catalyzed ring-closure reaction, generates the title compound [*meso*-tetraphenyl-2-methylazeteochlorinato]Ni(II) (**10Ni**) in a rational and scalable process in good yields. The UV–vis spectroscopic properties of this chromophore are, as expected for this chlorin analogue, red-shifted when compared to the corresponding [porphyrinato]Ni(II) (**5Ni**) complex. A much improved synthesis of the starting material **7Ni** by Vilsmeier–Haack formylation of [*meso*-tetraphenylchlorophinato]Ni(II) (**8Ni**) is also reported.

The potential application of porphyrins and chlorins (dihydroporphyrins) as dyes in, for instance, light harvesting and photomedicine largely drives their study.[1] Particularly derivatives with modulated photophysical properties are of interest. Therefore, porphyrin isomers and porphyrin analogues containing non-pyrrolic heterocycles were synthesized.[2] In addition, a host of expanded porphyrins has become known.[3]



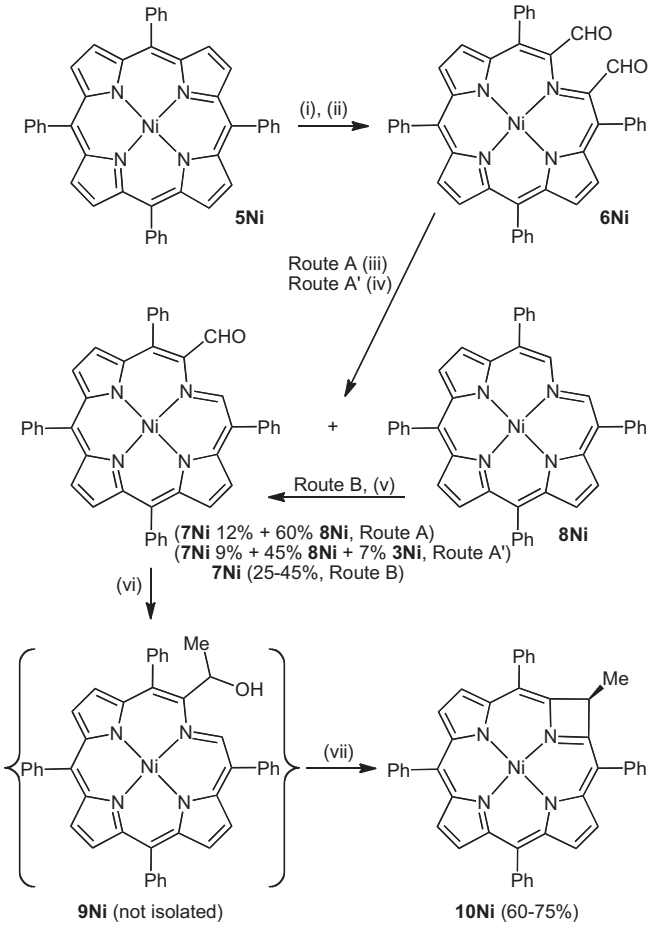
Only most recently, however, a contracted porphyrin analogue containing only three conjugated pyrroles was reported.[4] Similarly, very little has become known about pyrrole-ring-contracted porphyrinoids, that is, products in which a pyrrolic moiety in a porphyrin is replaced by a four-membered ring, although Crossley and King showed as early as 1984 that the oxidation of porphyrin dione **1** leads to the formation of free base azeteoporphyrin ketone **2** (Scheme 1) as a minor product (4%).[5] In 2005, we indicated the existence of azeteochlorin alcohol **3Ni** which formed as a side product of the Vilsmeier–Haack formylation of chlorophin (for more details of this reaction, see below).[6] Though its formation could be rationalized, no realistic synthesis could be presented.



Scheme 1. Reaction and conditions: (i) (1) NaH, O_2, CH_2Cl_2; (2) 3 M aq HCl. (ii) Excess BSA, chlorobenzene, reflux. (iii) (1) NH_2NH-Ts, CH_2Cl_2; (2) 200 W HgXe lamp (λ >300 nm), CH_2Cl_2/MeOH.

* Corresponding author. Tel.: +1 860 486 2743; fax: +1 860 486 2981.
E-mail address: c.bruckner@uconn.edu (C. Brückner).
† Contributed equally.

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.06.096



Scheme 2. Reaction and conditions: (i) (1) OsO_4, pyridine, $CHCl_3$; (2) H_2S, $CHCl_3$/MeOH. (ii) Pb^{IV}(acetate)$_4$, THF. (iii) 2–3 equiv $(Ph_3P)_3RhCl$, PhCN, reflux. (iv) 2 equiv $(Ph_3P)_3RhCl$ added in portions over 2–3 days, PhMe/PhCN, reflux. (v) (1) DMF–$POCl_3$, $CHCl_3$, reflux, 5 min; (2) aq $NaHCO_3$. (vi) MeMgBr, dry THF. (vii) (1) TMSOTf, CH_2Cl_2; (2) aq $NaHCO_3$.

Zaleski and co-workers achieved a breakthrough, in that they were able to provide two examples of azeteoporphyrins/chlorins:[7–10] the synthesis of ketone **2** (as its Ni(II) and Cu(II) complexes) using a benzeneseleninic anhydride oxidation of **1** and preparation of ester **4** (as its Ni(II), Cu(II), and Zn(II) complexes) using a photochemically induced Wolff rearrangement of diazo derivative **3** (Scheme 1). Importantly, their methods are relatively high yielding and the first proof of the structures of **2Ni**, **2Cu**, and **4Ni** by X-ray diffractometry was provided by this group.

Mirroring the differences of the oxidation states of porphyrins and chlorins, we like to refer **2** as an azeteoporphyrin, but like to name **4** and other derivatives containing sp^3-carbon in the azete moiety as azeteochlorins.

We present herein the expansion of the class of azeteochlorins by a member that is available through a rational and stepwise synthesis. Their formation highlight a unique reactivity of chlorophins, and points toward a generalized strategy for the conversion of a porphyrin to pyrrole ring-contracted derivatives.

We have previously shown the synthetic utility of secochlorin bisaldehyde **6Ni** (and its free base analogue) for the formation of pyrrole-modified porphyrins,[11–13] including its step-wise deformylation to form chlorophin monoaldehyde **7Ni** and chlorophin **8Ni** (Scheme 2).[6,14] Our earlier observation of (fortuitously formed) azeteochlorin alcohol derivative **3** could be rationalized by an intramolecular Friedel–Crafts-type reaction of chlorophin monoaldehyde derivative **7Ni**.[6] This suggested to us the exploitation of the seemingly high reactivity of the α-position of the chlorophin framework toward the synthesis of azeteochlorins.

To this end, we reacted brown-green monoaldehyde **7Ni** with a stoichiometric excess of methyl-Grignard (Scheme 2; for details, see Supplementary data). The rapid formation of a more polar (R_f = 0.42 vs the R_f of **7Ni** of 0.50, silica-CH_2Cl_2/petroleum ether 30-60, 1:1) green product suggested the formation of secondary alcohol **9Ni**. The ^{1}H NMR spectrum of a crude sample of **9Ni** showed the presence of a major product lacking axial symmetry (e.g., six β-protons signals could be identified), and displaying a signal corresponding to a single α-position (10.3 ppm; for details, see Supplementary data). This indicated that no ring closure had taken place. A broad signal at 5.15 ppm was indicative of an alcohol moiety. Attempted purification of this compound resulted in its decomposition. Thus, this product was reacted in crude form with a stoichiometric excess of TMSOTf to induce an intramolecular Friedel–Crafts reaction by removal of the alcohol and generation of the corresponding carbocation. As the starting material was consumed, a new green low polarity (R_f = 0.70, silica-CH_2Cl_2/petroleum ether 30–60, 1:1) product was formed. It was isolated by preparative plate chromatography in, after crystallization by solvent exchange, up to 75% yields.

The molecular formula of this product was shown by HR-MS (FAB) to be $C_{44}H_{30}N_4Ni$.[15] The composition is commensurate with an intramolecular electrophilic substitution of the presumably formed secondary carbocation with the *ortho*-position of a flanking phenyl group, forming a fused dehydroindane moiety, or the desired α-substitution product **10Ni**.[12,16] The ^{1}H and ^{13}C NMR spectra of **10Ni** are characteristic for a twofold symmetric product (e.g., two d at 8.70 and 8.67 ppm, ^3J = 4 Hz, and a s at 8.52 ppm, all 2H ea, assigned to the β-protons) (Fig. 1). This immediately excludes the possibility of the phenyl-fused product. Diagnostic peaks for

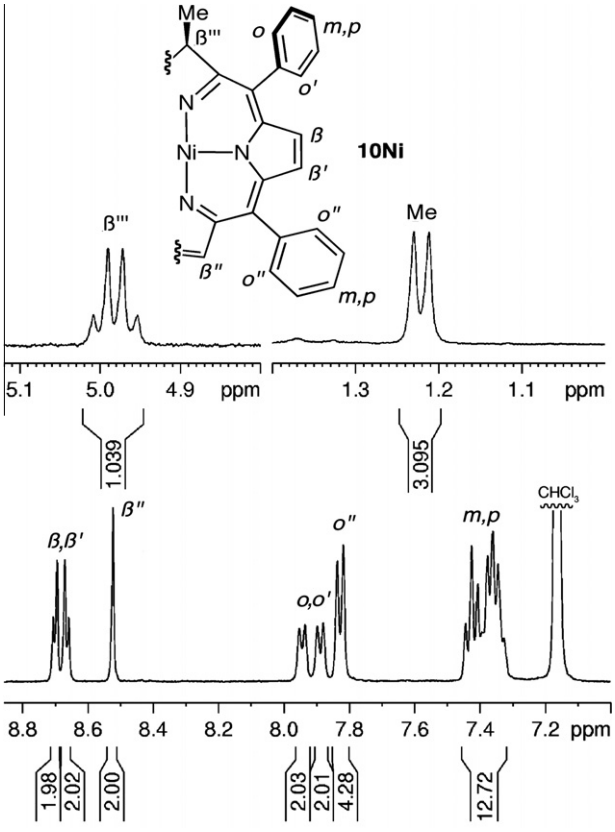


Figure 1. ^{1}H NMR spectrum (400 MHz, C_6D_6, 25 °C) of **10Ni**.

azeteochlorin **10Ni** are the signals for the methyl group (d, 1.23, 3H and 30.0 ppm, respectively) and the sp^3-azete position (q, 4.99, 1H and 45.0 ppm, respectively; see also Supplementary data). The methyl group located on one face of the porphyrin causes a face differentiation at the *ortho*-positions of the flanking phenyl groups. Evidently, phenyl rotation is slow on the NMR time scale.

Although the two-step conversion of monoaldehyde **7Ni** to **10Ni** is high yielding and straightforward, the preparation of **7Ni** is fraught with problems: it cannot be prepared efficiently by mono-deformylation of secochlorin bisaldehyde **6Ni** (itself readily available from the corresponding diol chlorin,[6] which itself is available in gram-scales from the corresponding porphyrin by an OsO_4-mediated dihydroxylation reaction).[13] This is because the reaction of bisaldehyde **6Ni** with excess Wilkinson's catalyst in refluxing PhCN generates chlorophin **8Ni** in 60% isolated yields, but monoaldehyde **7Ni** in only about 12% yields.[6] In other words, the first deformylation is much slower than the second, greatly inhibiting the generation of larger quantities (e.g., 25 mg batches) of **7Ni**. In the attempts to optimize the reaction conditions, we varied the solvents (using mixtures of varying ratios of dry PhCN and $PhCH_3$) and reduced the stoichiometric ratio of Wilkinson's catalyst initially used (down to 1.0 equiv with a batch-wise addition of further 1.0 equiv over the course of 3 days at reflux temperatures; for details, see Supplementary data). In the best of circumstances, this allowed the isolation of 9% of **7Ni**, with up to 30% recovery of the starting material **6Ni**. The extended reaction times also led to the loss of the brown-green **7Ni** as it is converted to the turquoise alcohol **3Ni** in ~7% yield (this represents an improvement over the previously described formation,[6] but still does not constitute a practical synthesis).

Since we failed to skew the product ratios of the deformylation reaction toward the monoformyl product **7Ni**, we revisited the Vilsmeier–Haack formylation of **8Ni** that, in an earlier report,[6] did not proceed satisfactorily (Scheme 2). When we used a much lower ratio of Vilsmeier reagent (chloroiminium formed from DMF and $POCl_3$) to substrate than that previously described and switched the solvent to $CHCl_3$ under reflux conditions for short periods of time (5–10 min),[17] we were able to obtain the monoformylated product in up to 45% isolated yields (for details, see Supplementary data). Despite no **8Ni** can be recovered from the reaction and two minor unidentified side products formed, the reaction has the advantage of allowing the preparation of 10 mg batches of **7Ni** (using 20 × 20 cm, 500 μm silica gel preparative chromatography plates for the isolation of the product). The selectivity of the formylation reaction provides another indication for the high reactivity of the chlorphin α-position when compared to its β- or the phenyl positions, particularly as the method used was firstly reported for the β-formylation of **5Ni**.

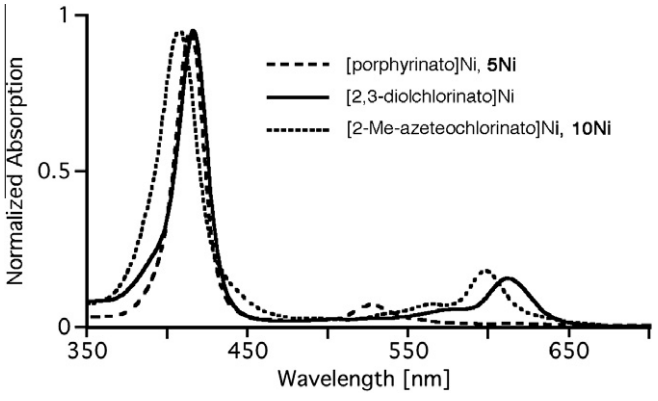


Figure 2. UV–vis spectral comparison of [tetraphenylporphyrinato]Ni(II) **5Ni** (dashed trace), [tetraphenyl-2,3-diolchlorininato]Ni(II) (solid trace), and [tetraphenylazeteochlorinato]Ni(II) **10Ni** (dotted trace), all in CH_2Cl_2.

A comparison of the Electronic absorption spectrum of **10Ni** to that of a typical Ni(II) chlorin [tetraphenyl-2,3-dihydroxychlorinato]Ni(II) and that of the metalloporphyrin **5Ni** clearly demonstrates that it is based on the relative intensity of the Q-band with respect to the Soret band and the Q-band shapes and positions, metallochlorin-like (Fig. 2). However, the Soret band is ~10 nm hypsochromically shifted as compared to the corresponding band of the chlorin and Ni(II) porphyrin **5Ni**. We interpret this blue-shift as a spectroscopic signature for the (projected)[18] planarity of the system compared to the ruffled conformation of the chlorin and the porphyrin.[19] As expected, the spectral features of Zaleski's azeteochlorin ester **4Ni** ($\Delta_{Soret} = -2$ nm, $\Delta_{\lambda max} = -3$ nm)[7,9] and alcohol **3Ni** ($\Delta_{Soret} = 2$ nm, $\Delta_{\lambda max} = 9$ nm) are overall similar compared to those of **10Ni**.

In summary, an improved Vilsmeier–Haack formylation of chlorophin results in the efficient formation of monoformyl chlorophin **7Ni**. This aldehyde is susceptible to a ring-closing reaction using the addition of methyl-Grignard, followed by an acid-catalyzed ring-closing step to form azeteochlorin **10Ni**. This reaction explores the high reactivity of the α-position of the chlorophin toward electrophilic substitution. This work points toward a novel strategy for the construction of novel pyrrole-contracted porphyrinoids. The optical properties of **10Ni** are suggestive of the presence of a planar macrocycle, providing an additional evidence for an increased rigidity of the azeteoporphyrin/chlorin chromophore when compared to the corresponding porphyrins/chlorins.

Acknowledgments

This work was supported by the NSF (CHE-0517782 and CMMI-0730826) and the US Air Force (through a stipend to M.A.H.).

Supplementary data

Supplementary data (procedure for the conversion of **7Ni** to **10Ni** via **9Ni** and for the optimized Vilsmeier–Haak mono-formylation of **8Ni** to provide **7Ni**, including corresponding spectroscopic data of the novel compounds and reproductions of key spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.096.

References and notes

1. Representative reviews of porphyrins in photomedicine: (a) Sternberg, E. D.; Dolphin, D.; Brückner, C. *Tetrahedron* **1998**, *54*, 4151–4202; (b) O'Connor, A. E.; Gallagher, W. M.; Byrne, A. T. *Photochem. Photobiol.* **2009**, *85*, 1053–1074; Light harvesting: (c) Aratani, N.; Kim, D.; Osuka, A. *Acc. Chem. Res.* **2009**, *42*, 1922–1934; (d) Gust, D.; Moore, T. A.; Moore, A. L. *Acc. Chem. Res.* **2009**, *42*, 1890–1898.
2. (a) Lash, T. D.. In Kadish, K. M., Smith, K. M., Guilard, R., Eds.; The Porphyrin Handbook; Academic Press: San Diego, 2000; pp 125–200; (b) Latos-Grazynski, L.. In Kadish, K. M., Smith, K. M., Guilard, R., Eds.; The Porphyrin Handbook; Academic Press: San Diego, 2000; pp 361–416.
3. Sessler, J. L.; Weghorn, S. *Expanded, Contracted & Isomeric Porphyrins*; Pergamon Press: New York, NY, 1997.
4. The much longer and well known corroles might also be considered ring-contracted porphyrins: Nardis, S.; Monti, D.; Paolesse, R. *Mini-Rev. Org. Chem.* **2005**, *2*, 355–374.
5. Crossley, M. J.; King, L. G. *J. Chem. Soc., Chem. Commun.* **1984**, 920–922.
6. Brückner, C.; Hyland, M. A.; Sternberg, E. D.; MacAlpine, J.; Rettig, S. J.; Patrick, B. O.; Dolphin, D. *Inorg. Chim. Acta* **2005**, *358*, 2943–2953.
7. Köpke, T.; Pink, M.; Zaleski, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 15864–15871.
8. Köpke, T.; Pink, M.; Zaleski, J. M. *Chem. Commun.* **2006**, 4940–4942.
9. Köpke, T.; Pink, M.; Zaleski, J. M. *Org. Biomol. Chem.* **2006**, *4*, 4059–4062.
10. Köpke, T. Ph.D. Thesis, Department of Chemistry, Indiana University, 2008.
11. (a) Campbell, C. J.; Rusling, J. F.; Brückner, C. *J. Am. Chem. Soc.* **2000**, *122*, 6679–6685; (b) McCarthy, J. R.; Melfi, P. J.; Capetta, S. H.; Brückner, C. *Tetrahedron* **2003**, *59*, 9137–9146; (c) Daniell, H. W.; Brückner, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1688–1691; (d) Akhigbe, J.; Ryppa, C.; Zeller, M.; Brückner, C. *J. Org. Chem.* **2009**, *74*, 4927–4933.

12. McCarthy, J. R.; Hyland, M. A.; Brückner, C. *Org. Biomol. Chem.* **2004**, *2*, 1484–1491.
13. Brückner, C.; Rettig, S. J.; Dolphin, D. *J. Org. Chem.* **1998**, *63*, 2094–2098.
14. Brückner, C.; Sternberg, E. D.; MacAlpine, J. K.; Rettig, S. J.; Dolphin, D. *J. Am. Chem. Soc.* **1999**, *121*, 2609–2610.
15. In fact, the composition of the product is identical with the composition of [*meso*-tetraphenylchlorinato]Ni(II). Thus, **10Ni** is formally a chlorin isomer.
16. Fox, S.; Boyle, R. W. *Tetrahedron* **2006**, *62*, 10039–10054.
17. Mironov, A. F.; Moskalchuk, T. V.; Shashkov, A. S. *Russ. J. Bioorg. Chem.* **2004**, *30*, 261–267.
18. This projection is based on the known crystal structures for **2Ni** and **4Ni**, Refs. 7–10.
19. Wondimagegn, T.; Ghosh, A. *J. Phys. Chem. B* **2000**, *104*, 10858–10862.