Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5593–5595

TETRAHEDRON LETTERS

Hydroformylation: a versatile tool for the synthesis of new β-formyl-metalloporphyrins

Andreia Peixoto,[a] Mariette M. Pereira,[a,*] M. Graça P. M. S. Neves,[b] Artur M. S. Silva[b] and José A. S. Cavaleiro[b]

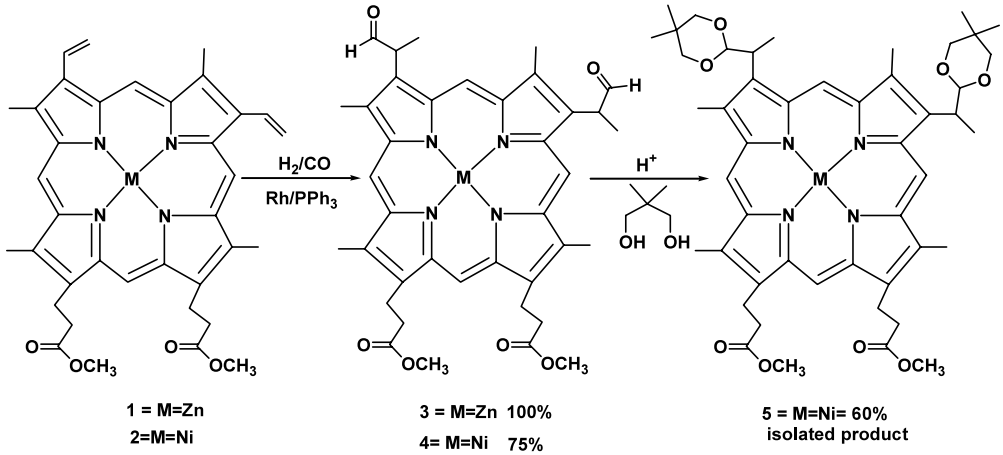
[a]*Departamento de Química, Universidade de Coimbra, Rua Larga, 3004-535 Coimbra, Portugal*
[b]*Departamento de Química, Universidade de Aveiro, 3810-193 Aveiro, Portugal*

Received 12 March 2003; revised 28 May 2003; accepted 3 June 2003

Abstract—Formyl derivatives of protoporphyrin-IX dimethyl ester metal complexes were obtained via hydroformylation reactions, catalysed by rhodium–triphenylphosphine complexes. The regioselectivity of the reaction is remarkably dependent on the metal centre of the porphyrin, yielding 100% of the branched aldehyde with zinc(II) complexes and 75% with the nickel(II). The NMR characterisation of the new compounds was carried out after their derivatisation into acetals.

Aldehydes are important building blocks for pharmaceuticals and performance materials and currently the hydroformylation reaction is an atom-efficient route to promote the one-step transformation of olefins to aldehydes. The discovery of new catalytic systems in the last decade brought a special significance to the hydroformylation reaction as an important tool for the production of fine chemicals.[1–4]

The derivatisation of the vinyl groups of β-substituted porphyrins is a topic of great interest due to the important applications of β-substituted porphyrins in tumour and virus necrosis[5–10] and for the preparation of new materials.[11] The classic methods for promoting the transformations of vinylporphyrins into aldehydes require in general several steps[12–14] and the direct introduction of the formyl group into a porphyrin macrocy-



Scheme 1. Hydroformylation reaction of metal complexes of protoporphyrin-IX and derivatisation to the corresponding acetals.

Keywords: formylporphyrin; protoporphyrin-IX; rhodium; hydroformylation.
* Corresponding author. Tel.: 351239852080; fax: 351239827703; e-mail: mmp@ci.uc.pt

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01379-0

cle is usually achieved via the Vilsmeier reaction, but in this case a free *meso*- or β-position should be present in the macrocycle.[15]

In this publication we present the first direct introduction of formyl groups into β-vinyl-metalloporphyrins via a hydroformylation reaction. The remarkable synergetic effect of the influence of the metal centre on the regioselectivity of the reaction is disclosed for the first time.

Zn(II) protoporphyrin-IX dimethyl ester **1** was synthesised from protoporphyrin-IX dimethyl ester by chloroform/methanol/metal salt method[16] yielding 90% of isolated product and Ni(II) protoporphyrin-IX dimethyl ester **2** was prepared from protoporphyrin-IX dimethyl ester by dimethylformamide/metal salt method[17] yielding 80% of isolated product.

In a typical hydroformylation reaction, $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ (7.8×10^{-5} mmol), triphenylphosphine (3.73×10^{-7}) and the Zn(II) complex, **1** (1.56×10^{-5} mmol), were dissolved in toluene (6 mL). The solution was transferred into an autoclave, which was then pressurised with the *syn*-gas until the pressure reached 20 bar (10 bar CO–10 bar H_2) and the temperature raised to 80°C. The reaction was then maintained for 14 h. After evaporation of the toluene, the reaction mixture showed a typical metalloporphyrin UV–vis absorption spectrum with bands at λ_{max} 414.0, 538.0 and 574 nm. The same mixture was analysed by ^{1}H NMR and total conversion with 100% of chemo and regioselectivity for 3^1,8^1-diformyl Zn(II) protoporphyrin-IX dimethyl ester **3**[†] was observed (Scheme 1). The proton resonance of the *CHO* appears at $\delta=10.47$ (doublet) and the four *meso* protons (singlets) at $\delta=$ 9.17, 9.63, 9.80 and 9.97.

In all attempts of aldehyde purification by preparative thin-layer silica-gel chromatography, enolisation with partial degradation of the product and also partial decomplexation has been observed. To avoid decomplexation, the Ni(II) complex **2** was submitted to the hydroformylation reaction conditions as described above. After 14 h the solvent was evaporated and surprisingly only 75% of the branched dialdehyde **4**, 3^1,8^1-diformyl Ni(II)-protoporphyrin-IX dimethyl ester,[‡] was obtained concomitantly with 25% of a mixture of compounds with linear-branched and linear-linear aldehydes, which have been identified by NMR.[§] The reaction was repeated several times and is fully reproducible. This is an interesting new observation, since by changing the metal centre of the porphyrin it is possible to modulate the regioselectivity of the hydroformylation reaction.

To avoid the enolisation, the derivatisation of the reaction mixture to the corresponding acetals was carried out. After evaporation of the solvent from the hydroformylation reaction mixture, which revealed the presence of a major product identified as dialdehyde **4**, the residue was taken in toluene (60 ml) and neopentanediol (1.41×10^{-3} mmol) and *p*-toluenesulfonic acid monohydrate (1.98×10^{-2} mmol) were added. This solution was refluxed during 5 h in a system equipped with Dean–Stark apparatus. After work-up the mixture was purified by preparative thin-layer chromatography using dichloromethane as eluent. The product corresponding to the first spot was isolated with 60% yield. The compound presents a FAB mass spectrum with a molecular ion at m/z 879 and it was fully characterised as the 3^1,8^1-di(5,5′-dimethyl-1,3-dioxan-2-yl) Ni(II)-protoporphyrin-IX dimethyl ester[¶] **5**, using ^{1}H, ^{13}C, COSY, HMBC, HSQC NMR spectra. The NMR data seems to indicate the presence of a diastereomeric mixture of two esters (1:1), since some signals are duplicated. Three of the *meso* protons of the two diastereomers appear as singlets at δ 9.72, 9.77, 10.01 ppm while the remaining *meso* protons appear as two singlets at δ 10.02 and 10.03 ($1H_{meso}$). A similar situation was observed in ^{13}C NMR with five signals at δ 96.2, 97.0, 98.30, 98.34 and 98.4 ppm attributed to the *meso*-carbons.

The NMR studies of the second spot revealed the presence of two other metalloporphyrins with linear-linear and linear-branched acetals. The main NMR features of the major product with linear-branched acetals are: (i) linear part, δ 4.06 (t, $J=7.2$ Hz, 2H), 2.49 (dt, $J=5.3$ and 7.2 Hz, 2H), 4.42 (t, $J=5.3$ Hz, $1H_{acetal}$); (ii)

[†] The spectral data of this reaction mixture indicate the presence of 100% of 3^1,8^1-diformyl Zn(II) protoporphyrin-IX dimethyl ester, **3**. MS (FAB) m/z: 714 (M^+). NMR ^{1}H (300 MHz, ppm) δ 2.22 (d, $J=6.9$ Hz, 6H, CH_3-3^2), 2.93 and 3.03 (2t, $J=7.6$ and $J=7.8$ Hz, 4H, CH_2-13^2 and 17^2), 3.51 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 3.61 (s, 9H, CH_3), 3.66 (s, 3H, CH_3), 3.81 and 4.16 (2t, $J=7.7$ Hz, 4H, CH_2-13^1 and 17^1), 5.31–5.35 (m, 2H, CH_2-3^1), 9.16 (s, $1H_{meso}$), 9.63 (s, $1H_{meso}$), 9.80 (s, $1H_{meso}$), 9.97 (s, $1H_{meso}$), 10.47 (d, $J=2.4$ Hz, 2H, *CH*O).

[‡] In the ^{1}H NMR spectrum, the signal of C*H*O appears as a broad singlet at δ 10.35 ppm and is correlated in the COSY spectrum with that at δ 5.11–5.13 ppm (1H). This signal is also correlated with the one assigned to a methyl group which appear as a doublet at δ 2.08 ppm.

[§] In the ^{1}H NMR spectrum of these compounds the major fraction (branched-linear) showed the signal of C*H*O, as a broad singlet, at δ 10.04 ppm which is correlated in the COSY spectrum with that at δ 3.24–3.29 ppm.

[¶] **5** UV–vis. λ_{max} (nm) (ε): 395.0, (8.7×10^4), 518.0, (2.669×10^3), 553.5, (7.521×10^3). MS (FAB) m/z: 879 (M^+). ^{1}H NMR (500 MHz, ppm) δ 0.74 and 0.75 (2s, 6H, $CH_{3acetal}$), 1.31 (s, 6H, $CH_{3acetal}$), 2.02 (d, $J=7.3$ Hz, 3H, CH_3-$H3^2$ or $H8^2$), 2.02 (d, $J=9.0$ Hz, 3H, CH_3-$H8^2$ or $H3^2$), 3.16 and 3.18 (2t, $J=7.6$ Hz, 4H, CH_2-13^2 or 17^2), 3.47–3.50 (m, 2H, $CH_{2acetal}$), 3.48 (s, 3H, CH_3), 3.49 (s, 6H, CH_3), 3.55 (s, 3H, CH_3), 3.60–3.66 (m, 4H, $CH_{2acetal}$), 3.68 and 3.69 (2s, 2×3H, 2×OCH_3), 3.86 (dt, $J=2.3$ and 11.1 Hz, 2H, $CH_{2acetal}$), 4.25 (t, $J=7.8$ Hz, 4H, CH_2-13^1 and 17^1), 4.65–4.68 (m, 2H, $H3^1$ and $H8^1$), 5.34–5.36 (m, 2H, $H3^3$ and $H8^3$), 9.72 (s, $1H_{meso}$), 9.77 (s, $1H_{meso}$), 10.01 (s, $1H_{meso}$), 10.02 and 10.03 (s, $1H_{meso}$). ^{13}C NMR: δ 11.6, 11.7 and 12.7 (2,7,12,18-CH_3), 17.0 (C-3^2 and C-8^2), 21.8 and 23.2 (4×$CH_{3acetal}$), 36.8 (C-13^2 and C-17^2), 38.5 (C-3^1 and C-8^1), 77.48, 77.51, 77.56 and 77.62 (4×$CH_{2acetal}$), 96.2, 97.0, 98.30, 98.34 and 98.4 (C-5, C-10, C-15 and C-20), 104.9 (C-3^3 and C-8^3); 137.3, 137.43, 137.45, 137.65, 137.9, 139.0, 139.1, 140.26, 140.31, 140.9, 141.1, 141.2, 141.3, 141.48, 141.54 and 141.6.

branched part, δ 2.03 (d, $J=7.3$ Hz, 3H), 4.68–4.70 (m, 1H), 5.35 (d, $J=5.4$ Hz, $1H_{acetal}$); *meso*-protons at δ 10.04, 9.88, 9.77 and 9.75 ppm.

In conclusion, a new versatile method has been developed for the synthesis of branched β-formyl porphyrins and an important effect on the regioselectivity of the reaction, due to the presence of different metal centres was observed.

The hydroformylation reaction is currently being extended to other vinylporphyrins. Also different reaction conditions in order to modulate the regioselectivity exclusively for branched or linear aldehydes and semiempirical PM3 calculations with different metal centres to explain this singular observation are currently being carried out.

Acknowledgements

The authors thank FCT, POCTI/QUI/42536/2001; POCTI/QUI/32851/1999; CYTED V.9102, for financial support.

References

1. Frohning, C. D.; Kohlpainter, C. W. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B.; Herrmann, W. A., Eds.; VCH: Weinheim, 1996; Vol. 1, Chapter 2.1.
2. Castillon, S.; Fernandez, E. In *Rhodium Catalyzed Hydroformylation*; van Leeuwen, P. W. N. M; Claver, C., Eds.; Kluwer Academic: Dordrecht, 2000; p. 145.
3. Siegel, H.; Himmele, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 178.
4. Freixa, Z.; Pereira, M. M.; Bayón, J. C.; Silva, A. M. S.; Salvador, J. A. R.; Beja, A. R.; Paixão, J. A.; Ramos, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1083.
5. Barth, R. F.; SoloWay, A. H.; Brugger, R. M. *Cancer Invest*. **1996**, *14*, 534.
6. *Chemical Aspects of Photodynamic Therapy*; Bonnet, R., Eds. Advanced Chemistry Texts, Gordon and Breach Publishers: London, 2000.
7. *The Fundamental Bases of Phototherapy*; Hönigsmann, H.; Jori, G.; Young, A. R., Eds.; OEMFspa: Milano, 1996.
8. Pandey, R. K.; Zheng, G. In *The Porphyrins Handbook Applications*: *Past*, *Present and Future*; Kadish, K. M.; Smith, K. M.; Guilard, R., Eds.; Academic Press: New York, 2000; p. 157.
9. Faustino, M. A. F.; Neves, M. G. P. M. S.; Vicente, M. G. H.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron Lett*. **1996**, *37*, 3569.
10. Cavaleiro, J. A. S.; Neves, M. G. P. M. S.; Augusto, C.; Tomé, A. M. S.; Silva, M.; Faustino, A. F.; Lacerda, P. S.; Silva, A. M. G. *J. Heterocyclic Chem*. **2000**, *37*, 527.
11. Alonso, C. M. A.; Neves, M. G. P. M. S.; Tomé, A. C.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron Lett*. **2000**, *41*, 5679.
12. Clesy, P. S.; Barret, J. *Biochem. J*. **1961**, *78*, 798.
13. Lemberg, R.; Parker, J. *Aust. J. Exp. Biol. Med. Sci*. **1952**, *30*, 163.
14. Sparatore, F.; Mauzerall, D. *J. Org. Chem*. **1960**, *25*, 1073.
15. Silva, A. M. G.; Faustino, M. A.; Silva, T. M. P. C.; Tomé, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1774.
16. Smith, K. M. *Porphyrins and Metalloporphyrins*; Elsevier Scientific: Amsterdam, 1975; p. 207.
17. Adler, A. D.; Longo, F. R.; Kampas, F.; Kim, J. *Inorg. Nucl. Chem*. **1970**, *32*, 2443.