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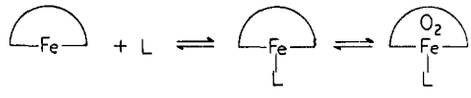
Efficient Peripheral Functionalization of Capped Porphyrins

Summary: An efficient method of functionalizing a capped porphyrin (**1**) is achieved by use of silver nitrite–iodine reagent. The nitro derivative is cleanly reducible to the amine, which may be further derivatized by standard procedures.

Sir: Previously we reported the synthesis of capped porphyrin **1** and the observation that its iron(II) complex exhibited reversible and stoichiometric binding of dioxygen at ambient temperature.[1,2] This reversible behavior was shown to be dependent on the concentration of apical ligand, L, e.g., *N*-methylimidazole, as a consequence of the equilibrium between irreversibly oxidized square planar form **2** and reversibly oxygenated pentacoordinate species **3**, eq 1. One obvious solution



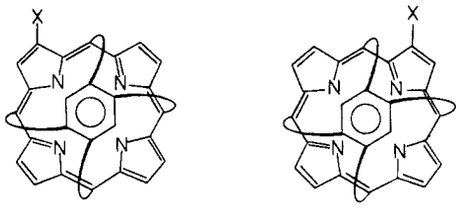
(1)

2 3 4

to the difficulties associated with working at high ligand concentrations was to attach the apical ligand L directly to the capped structure, schematically as **5**, thereby removing, at least in part, the preliminary equilibrium in eq 1. Similar reasoning has guided the experiments of others in this field.[3]

5

We now report an efficient direct peripheral functionalization of **1**, itself now available in quantity by a modification[4] of our original synthesis.[1] After many unsuccessful attempts at conventional electrophilic nitration procedures, we developed the following method. Thus the zinc-capped porphyrin, prepared by addition of anhydrous zinc chloride to a refluxing DMF solution of the free porphyrin[5] in CH_2Cl_2–CH_3CN (1:1), was treated sequentially with iodine (1.5 M, CH_2Cl_2) and silver nitrite (1.5 M, CH_3CN), stirred for 35 min at 25 °C, filtered, and evaporated to dryness.[6] Trituration with CH_2Cl_2 gave, after concentration, an approximately equal mixture of two isomeric zinc mononitroporphyrins as a purple solid (98%): M^+ 1143 ± 1; λ_{max} (CH_2Cl_2) 605, 558, 520 (sh), 431 nm; NMR ($CDCl_3$) δ 3.5–4.6 (m, 16 H), 5.03, 5.78 (d, 1 H), 5.43, 5.57 (d, 1 H), 7.17–8.0 (m, 16 H), 8.57–8.77 (m, 7 H).[7,8] Removal of the zinc (HBr gas, CH_2Cl_2, 5 min, 25 °C) gave the metal-free nitroporphyrin isomers **6** and **7**[8] as a crystalline solid (quantitatively) [M^+ 1143 ± 1; λ_{max} (CH_2Cl_2) 668, 605, 531, 425 nm; ν_{max} (KBr) 1723, 1510, 1342 cm^{-1}] which could be separated by preparative thin-layer chromatography over silica gel (C_6H_6–EtOAc, 7:3 v/v); however, for our present purposes, we have proceeded with this mixture.

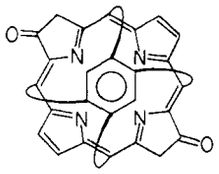


6 + 7, X = NO_2
8 + 9, X = NH_2
10 + 11, X = $NHCOCH_3$
12 + 13, X = NCO
14 + 15, X = $NHCO_2CH_2CH_3$

Reduction of the nitro group was achieved in a clean and reproducible manner by addition of sodium borohydride (50 equiv) to a suspension of 10% Pd/C in a solution of the nitro-capped porphyrin in dried ch_2Cl_2–CH_3OH (1:1 v/v) under argon. After stirring (30 min), filtration and evaporation gave the unstable aminoporphyrins **8** and **9** in quantitative yield: λ_{max} (CH_2Cl_2) 651, 595, 560 (sh), 522, 425, 418; ν_{max} (KBr) 3420, 3350, 1725 cm^{-1}; NMR ($CDCl_3$) δ −3.21 (1 H), −2.72 (1 H), 3.8–4.7 (m, 16 H), 5.5, 5.6, 5.8, 5.95 (4s, 2 H), 7.2–7.8 (m, 16 H), 8.3–8.8 (m, 7 H). This substance is unstable to chromatography and is readily acetylated (pyr, Ac_2O) to the *N*-

acetylporphyrins **10** and **11**: M^+ 1093 ± 1; λ_{max} 648, 595, 550 (sh), 519, 423 nm; ν_{max} (CH_2Cl_2) 3400, 1722, 1697 cm^{-1}; NMR ($CDCl_3$) δ 1.98 (s, 3 H), 3.8–4.7 (m, 16 H), 5.32, 5.45, 5.5, 5.55 (4s, 2 H), 7.3–8.0 (m, 16 H), 8.32–8.8 (m, 7 H). Similarly the isocyanates **12** and **13** could be prepared ($COCl_2$) and converted to stable ethylurethanes **14** and **15**: M^+ 1123 ± 1; λ_{max} (CH_2Cl_2) 658, 595, 550, 518, 423 nm; ν_{max} 3300 cm^{-1}; NMR ($CDCl_3$) δ 5.35 (d, 2 H), 1.15 (t, 3 H, J = 7 Hz, ethyl group).

When the reduction of the zinc nitroporphyrin was carried out with $SnCl_2$–HCl in CH_2Cl_2 as cosolvent there was obtained after chromatography on silica gel (EtOAc–C_6H_6, 1:9 v/v) a 50% yield of the metal-free substance, tentatively suggested to be dione **16** [M^+ 1067 ± 1; ν_{max} 1720, 1601 cm^{-1}; λ_{max} (CH_2Cl_2) 655, 605, 578, 470 (sh), 412 nm; NMR ($CDCl_3$) δ −3.7 (1 H), 3.6–4.8 (m, 16 H), 5.26, 5.51, 5.55, 5.95 (4s, 2 H), 7.05–7.75 (m, 16 H), 8.34–8.72 (m, 6 H)], although the alternative isomeric possibilities are not excluded at this time.[9]



16

Presently we are attempting to elaborate these accessible functionalized capped porphyrins into species **5**.

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(8) The presence and ratio of isomers is clearly defined by the NMR signals from the capping protons, which appear, with equal weight, as four singlets at δ 5.03, 5.78, 5.43, and 5.57, two for each isomer.
(9) Repetition of this reduction on a mononitrotetraphenylporphine, prepared essentially as above, cf. ref 6 above, gave a carbonyl frequency on the infrared, ν_{max} 1720 cm^{-1}, which is characteristic of an unsaturated five-ring ketone and is, in this case, not obscured by the ester functions implicit in **16**.

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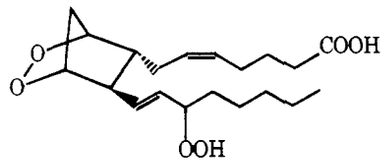
Prostanoid Endoperoxide Model Compounds: 2,3-Dioxabicyclo[2.2.1]heptane via Selective Diimide Reduction[1]

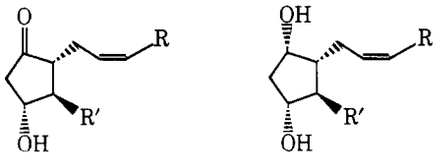
Summary: A convenient synthesis of 2,3-dioxabicyclo[2.2.1]-heptane (**2**) has been achieved in ~30% yield by photosensitized singlet oxygenation of cyclopentadiene, followed by carefully controlled diimide reduction in nonpolar and nonprotic media at dry ice temperature.

Sir: The importance of prostaglandin endoperoxide (**1**) as precursor to the physiologically potent prostaglandins thromboxane and prostacyclin in the oxygenation of arachidonic acid has been well documented.[2] These pharmacologically significant substances originate from **1** by skeletal transformations of the 2,3-dioxabicyclo[2.2.1]heptane ring system (**2**); the prostaglandins PGE and PGF enzymatically

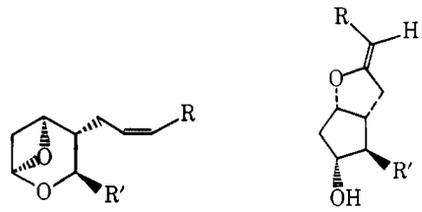


1 2

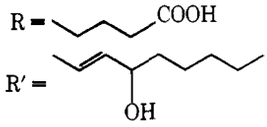
by base-catalyzed rearrangement and reduction,[3] the thromboxane A_2[4] and prostacyclin[5] presumably by enzymatic acid-catalyzed rearrangement. Thus, the synthesis of the parent endoperoxide skeleton **2** seemed timely and urgent in order to explore its chemistry in the interest of designing biologically active substitutes.



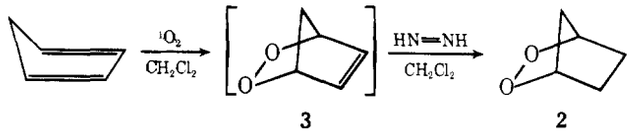
PGE PGF



Thromboxane A_2 Prostacyclin



The endoperoxide **2** has been prepared by silver oxide reaction with 3-bromocyclopentyl hydroperoxide.[6,7] Simultaneously, an alternative synthetic method was reported which shows great promise for the preparation of the natural prostaglandin peroxide from PGF.[8] These successes urge us to communicate our results on the preparation of 2,3-dioxabicyclo[2.2.1]heptane (**2**) from cyclopentadiene (eq 1).



3 2 (1)

When cyclopentadiene is photooxygenated in methanol at −78 °C with rose bengal as sensitizer[9] and the resulting thermally labile cyclopentadiene endoperoxide (**3**) solution treated directly with tenfold excess of diimide, generated in situ from potassium azodicarboxylate and acetic acid[10] at dry ice temperature, only reduced decomposition and rearrangement products could be isolated. It was clear that the labile endoperoxide **2** had been formed, but it did not survive the polar and protic reduction conditions in methanol. Since these reduction conditions proved successful in the preparation of bridgehead-substituted derivatives of **2**,[11] it was important to persist in this synthetic route for the parent endoperoxide.