Synthesis of 2,3,9,10,16,17,23,24-Octasubstituted Phthalocyaninatozinc(II) Complexes Mediated by Reductive Agents

Gabriela A. Gauna, Ana Clara Monsalvo, Josefina Awruch*
Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, 1113 Buenos Aires, Argentina
Fax 54(11)45083645; E-mail: jawruch@ffyb.uba.ar
Received 7 January 2009; revised 25 February 2009

Abstract: N-Butyl-N-(4,5-dicyano-2-methylbenzyl)butanamide (6) was synthesized in 69% yield from the corresponding 4,5-dibromo derivative 5. Treatment of 6 with zinc acetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene gave the octasubstituted zinc(II) phthalocyanine 7, which was reduced with diborane to give phthalocyanine 8. Quaternization of 8 with iodomethane gave the cationic dye 9.

Key words: octasubstituted phthalocyaninatozinc, reduction, nucleophilic aromatic substitution, phthalocyanine, zinc complexes

Phthalocyanines play a major role in modern technology, including medicine. Because phthalocyanines are barely soluble, considerable efforts have been made to prepare lipophilic derivatives by the introduction of peripheral alkyl chains. Most octasubstituted phthalocyanines are symmetrical compounds and contain two substituents on each of the benzene rings. As single symmetrical compounds, octasubstituted phthalocyanines are generally less soluble in organic solvents than are the corresponding tetrasubstituted phthalocyanines. Because synthesis of octasubstituted zinc(II) phthalocyanines that have four identical substituents in the 2-, 9-, 16-, and 23-positions, and a different group of identical substituents at the 3-, 10-, 17-, and 24-positions affords a mixture of positional isomers, these compounds could be expected to have a greater solubility than those with eight identical substituents. However, 2,3,9,10,16,17,23,24-octasubstituted phthalocyanines prepared from phthalonitriles with two different substituents in the 4- and 5-positions have received relatively little study, and only few derivatives have been reported. Similar metallophthalocyanines octasubstituted in the 1-, 3-, 8-, 10-, 15-, 17-, 22-, and 24-positions have, however, been described more extensively in the literature.

A few years ago, we showed that zinc phthalocyanine derivatives functionalized with both methyl and phthalimidomethyl or methyl and aminomethyl units on the benzenoid rings are moderately soluble in organic solvents but insoluble in water. To improve the amphiplicity of these compounds, we incorporated substituents derived from the (dibutylamino)methyl group, instead of a phthalimidomethyl or aminomethyl group, in the peripheral positions of the phthalocyanines. We report the synthesis and spectroscopic properties of three novel 2,3,9,10,16,17,23,24-octasubstituted phthalocyaninatozinc(II) complexes that are highly soluble in polar organic solvents.

As shown in Scheme 1, the sequence began with the reaction of 2-(4,5-dibromo-2-methylbenzyl)-1H-isoisindole-1,3(2H)-dione (1) with hydrazine in refluxing ethanol to give 1-(4,5-dibromo-2-methylphenyl)ethanamine (2) quantitatively. Treatment of amine 2 with butanoyl chloride gave the amide 3, which was reduced with diborane in tetrahydrofuran at room temperature to give N-(4,5-dibromo-2-methylbenzyl)butan-1-amine (4). Acylation of this compound with butanoyl chloride gave the corresponding amide 5, treatment of which with copper(I) cyanide in 1-methylpyrrolidin-2-one (NMP) as a solvent gave the phthalonitrile 6 in 69% yield; the use of a 5:1 molar excess of copper(I) cyanide gave the best yield.

We recently showed that zinc(II) phthalocyanine derivatives carrying amido substituents on the macrocycle can be effectively reduced by diborane under relatively mild conditions to give the corresponding amino phthalocyanines in good yields. Phthalocyanine 7 was readily prepared by cyclotetramerization of phthalonitrile 6 in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and zinc(II) acetate in 36% yield; lower yields were obtained when hexan-1-ol was used as the solvent, and the use of butan-1-ol as the solvent failed to give the desired dye 7. Also, the reaction time was reduced from 30 min to 5 min when the reaction was carried out in the absence of a solvent. Phthalocyanine 8 was synthesized in 38% yield by the reduction of phthalocyanine 7 with diborane. Treatment of phthalocyanine 8 with iodomethane at 60 °C gave cationic phthalocyanine 9 in 81% yield.

Dyes 7–9 were characterized by means of electrospray ionization time-of-flight (ESI-TOF) mass spectrometry, and intermediates 2–5 were characterized by means of electron ionization (EI) mass spectrometry at 70 eV. The ion–molecule signal of phthalonitrile 6 was not observed by EI mass spectrometry, but could be observed by ESI-TOF mass spectrometry. The UV-visible absorption spectra of phthalocyanines 7–9 showed Soret and Q band at around 360 and 677 nm, respectively. The molar absorption coefficients for the monomeric forms of 7–9 in N,N-dimethylformamide are 87890 M⁻¹ cm⁻¹ (λ_max = 678 nm), 84660 M⁻¹ cm⁻¹ (λ_max = 678 nm), and 66290 M⁻¹ cm⁻¹.
A mixture of isonindolinedione 1 (1.0 g, 2.45 mmol) and NH₄H₂O (0.5 mL) in EtOH (50 mL) was stirred and refluxed for 6 h, then cooled. 1 M HCl (5 mL) was added and the mixture was heated at 100 °C for 8 h, then cooled. The precipitate was filtered off and washed with H₂O. The filtrate was evaporated in vacuo to eliminate the solvent, and the residue was dissolved in 10% aq NaOH (20 mL), filtered, and extracted with Et₂O (4 × 20 mL). The extracts were washed with Na₂SO₄ and then evaporated to dryness in vacuo to give a highly viscous oil; yield: 0.682 g (quant).

**N-(4,5-Dibromo-2-methylbenzyl)butanamide (3)**

A solution of PrCOCl (0.6 mL, 5.78 mmol) and NH₄H₂O (0.5 mL) in EtOH (50 mL) was stirred and refluxed for 6 h, then cooled. 2 M HCl (5 mL) was added and the mixture was heated at 100 °C for 8 h, then cooled. The precipitate was filtered off and washed with H₂O. The filtrate was evaporated in vacuo to eliminate the solvent, and the residue was dissolved in 10% aq NaOH (20 mL), filtered, and extracted with Et₂O (4 × 20 mL). The extracts were washed with Na₂SO₄ and then evaporated to dryness in vacuo to give a highly viscous oil; yield: 0.682 g (quant).

**N-(4,5-Dibromo-2-methylbenzyl)butan-1-amine (4)**

A solution of PrCOCl (0.6 mL, 5.78 mmol) and NH₄H₂O (0.5 mL) in EtOH (50 mL) was stirred and refluxed for 6 h, then cooled. 2 M HCl (5 mL) was added and the mixture was heated at 100 °C for 8 h, then cooled. The precipitate was filtered off and washed with H₂O. The filtrate was evaporated in vacuo to eliminate the solvent, and the residue was dissolved in 10% aq NaOH (20 mL), filtered, and extracted with Et₂O (4 × 20 mL). The extracts were washed with Na₂SO₄ and then evaporated to dryness in vacuo to give a highly viscous oil; yield: 0.682 g (quant).

**Melt points** were determined on an Electrothermal 9100 capillary melting-point apparatus. 1H NMR spectra were recorded on a Bruker MSL 300 spectrometer. The 1H NMR of phthalocyanines 7, 8, and 9 were recorded on a Bruker AM 500. Mass spectra were obtained with a TRIO 2 (El, 70 eV) spectrometer. ESI-TOF mass spectrometry was used to characterize phthalocyanines 7–9. Electronic absorption spectra were recorded on a Shimadzu UV-3101 PC spectrophotometer. Fluorescence spectra were recorded on a QuantMaster Model QM-1 PTI spectrophotometer. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Microanalyses were carried out by using a Carlo Erba EA 1108 elemental analyzer. Chromatography columns were prepared with TLC Kieselgel (Merck), and aluminium oxide 90 standardized (Merck). DMF was dried over 3–A molecular sieves for 72 h, then filtered and freshly distilled before use.3

**Scheme 1 Reagents and conditions:** (a) H₄NNH₂, EtOH, reflux, 6 h, quant; (b) PrCOCl, py, r.t., 12 h, 55% (c) B₂H₆, THF, r.t., 72 h, 51%; (d) PrCOCl, i-Pr₂NEt, r.t., 48 h, 75%; (e) CuCN, NMP, 200 °C, 6 h, 69%; (f) Zn(OAc)₂, DBU, 158 °C, 5 min, 36%; (g) B₂H₆, THF, reflux, 48 h, 38%; (h) MeI, 60 °C, 48 h, 81%.

(λmax = 676 nm) respectively. When excited at 610 nm, compounds 7–9 showed fluorescence emission spectra typical of zinc phthalocyanines; at a concentration of 10–6 M in N,N-dimethylformamide the emission maxima occurred at 683, 686 and 682 nm for 7–9, respectively.

With regard to solubility, note that 7 and 8 are soluble in most organic solvents. Quaternization of 8 gave compound 9, which was partially soluble in dichloromethane, methanol, and water.

To summarize, we prepared and characterized three novel octasubstituted zinc(II) phthalocyanines. We are currently attempting to improve the yields of the syntheses and conducting photobiological studies on 7–9.
at 158 °C for 5 min under argon, then cooled. CH2Cl2 (15 mL) was then added dropwise to a stirred cold soln of amide 4 (0.010 g, 0.30 mmol) in CH2Cl2 (1.5 mL) containing i-Pr2NEt (0.1 mL). The mixture was stirred for 48 h at r.t., then CH2Cl2 (40 mL) was added and the mixture was washed with H2O (2 × 30 mL). The organic phase was dried (Na2SO4) and evaporated to dryness in vacuo. The residue was dissolved in a small volume of CH2Cl2–MeOH (9:1) and filtered through a silica gel column that had been packed and washed with CH2Cl2–hexane (9:1). Past crystallization (CH2Cl2–hexane); yield: 0.015 g (69%).

A soln of PrCOCl (0.1 mL, 0.96 mmol) in anhyd CH2Cl2 (1.5 mL) was added to a soln of amide 5 (0.037 g, 0.12 mmol), anhyd Zn(OAc)2 (0.037 g, 0.20 mmol), and DBU (0.4 mL, 2.68 mmol) was stirred and heated until 30 mL). The mixture was refluxed for 48 h, cooled, and poured into 25% aq NH4OH (3 mL), and stirred for 24 h. The mixture was evaporated in vacuo to give a blue-green solid that was dissolved in CH2Cl2–MeOH (5:1) and filtered through an Al2O3 column that had been packed and washed with the same solvent. Evaporation of the solvent gave a solid residue that was crystallized (CH2Cl2–hexane); yield: 0.014 g (36%).

IR (KBr): 3437, 2959, 2930, 2872, 1647, 1466, 1379, 1305, 1281, 1172, 1098, 977, 801, 729, 571 cm–1.


Acknowledgment

This work was supported by grants from the Universidad de Buenos Aires, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), and the Agencia Nacional de Promoción Científica y Tecnológica. We wish to thank Ms. Juana Alcira Valdez for technical assistance with chromatography. Mr. Diego Cobice for assistance with the ESI-TOF mass spectrometry, and Prof. Rex Davis for help with the English language.

References


