A Modified Vilsmeier–Haack Strategy to Construct β-Pyridine-Fused 5,10,15,20-Tetraarylporphyrins

Pargat Singh
Mahendra Nath *

Department of Chemistry, Faculty of Science, University of Delhi, Delhi-110 007, India
mnath@chemistry.du.ac.in

Abstract A modified Vilsmeier–Haack strategy has been developed to construct a novel series of π-extended nickel(II) or copper(II) complexes of 2-chloro-3-formyl- and 3-formylpyrido[2,3-b]porphyrins from 2-acetamido-meso-tetraarylporphyrins. After chromatographic purification and spectral characterization, nickel(II) complexes of 2-chloro-3-formyl- and 3-formylpyrido[2,3-b]porphyrins underwent reaction with malononitrile under Knoevenagel conditions to afford new porphyrins with extended π-conjugation in appreciable yields. On photophysical investigation, the newly prepared pyridoporphyrins displayed a significant redshift in their electronic absorption spectra as compared to simple meso-tetraarylporphyrin precursors.

Key words 2-chloro-3-formylpyrido[2,3-b]porphyrins, 3-formylpyrido[2,3-b]porphyrins, Knoevenagel condensation, redshift, synthesis, Vilsmeier–Haack reaction.

Porphyrin macromolecules are an important class of tetapyrrolic systems that play key roles in diverse processes including photosynthesis,1 oxygen transport,2 and solar energy conservation.3,4 Apart from naturally occurring porphyrins, a large number of artificial porphyrins have been constructed for various electronic applications due to their good thermal stabilities and π-electron conjugation.5–7 Furthermore, the incorporation of electron-rich aromatic and heteroaromatic systems at the porphyrin periphery have led to the generation of molecules with extended π-systems. These porphyrins display a wide range of applications in diverse areas including molecular devices,8–12 hybrid solar cells,13–17 light-emitting diodes18,19 and sensors.20–23 Efforts have also been made to synthesize a variety of β,β′-fused porphyrins decorated with different heterocyclic scaffolds24–29 including pyrrole, pyrazole, triazole, imidazole, BODIPY, and pyrrolo[1,2-a]pyrazine to develop conjugated structures that demonstrate intense electronic absorption and fluorescence properties.

To this end, Cavaleiro and co-workers synthesized various pyridine-appended porphyrins through hetero-Diels–Alder reaction of nickel(II) complexes of 2-imino-meso-tetraphenylporphyrins with electron-rich dienophiles or one-pot reaction of 2-amino-meso-tetraarylporphyrins with cyclic enol ethers.30–32 Recently, our group developed a simple one-pot strategy to generate densely π-conjugated coumarin-fused pyrido[2,3-b]porphyrins via a trichloroacetic acid accelerated reaction of 2-amino-5,10,15,20-tetraphenylporphyrins with aromatic aldehydes and 4-hydroxycoumarin.33 On photophysical investigation, these pyrido[2,3-b]porphyrinoids have shown a significant bathochromic shift in their UV/Vis and emission spectra. Prompted by these results and in the context of our interest in developing convenient and alternate synthetic methods for diverse β,β′-fused porphyrins from easily accessible meso-tetraarylporphyrin precursors,34–36 we report herein the synthesis of a new series of nickel(II) and copper(II) 2-chloro-3-formyl- and 3-formylpyrido[2,3-b]porphyrins by using a modified Vilsmeier–Haack strategy (Scheme 1). Although, the Vilsmeier–Haack protocol has been previously utilized to generate 2-formyl derivatives of meso-tetraarylporphyrins, this methodology has not been explored for the synthesis of β-pyridine-fused meso-tetraarylporphyrin systems. Hence, the current study further elaborates the scope of Vilsmeier–Haack reaction to generate conjugated porphyrin molecules.

For the synthesis of the target pyridoporphyrins, nickel(II) and copper(II) 2-acetamido-5,10,15,20-tetraarylporphyrin precursors 2a–d were synthesized in 74–78% yields.
through acetylation of the corresponding 2-aminopyrro-
dins 1a–d using acetic anhydride at 60 °C (Scheme 2). Ini-
tially, nickel(II) 2-acetamido-5,10,15,20-tetraphenylpor-
phyrin (2a) was selected as a model substrate to optimize
the reaction conditions for the synthesis of the desired pyr-
idoporphyrins 3 and 4. In a typical experiment, 2a was al-
lowed to react with the Vilsmeier reagent (chloromethy-
leneiminium ion), generated in situ after mixing N,N-di-
methylformamide (DMF) with phosphorus oxychloride in
a ratio of 1:3 in 1,2-dichloroethane (DCE) at 80 °C (Table 1,
entry 1). As indicated by TLC, the starting material was
completely consumed within two hours and the reaction
mixture turned green in color. The solvent was then evapo-
rated under reduced pressure and the residue obtained was
loaded onto neutral alumina and the desired green product
was eluted using 40% chloroform in hexane to afford a mix-
ture. The desired porphyrins could be separated by silica gel
preparative TLC using 65% chloroform in hexane as an elu-
ent. The desired porphyrins 3 and 4 were obtained in mod-
erate (37%) and poor (11%) isolated yields, respectively, and
characterized by spectroscopic analysis. The proton NMR
spectrum of nickel(II) 3-formylpyrido[2,3-b]porphyrin (4)
showed two singlets for one proton each at δ = 9.14 and
9.00 ppm, corresponding to the two pyridine protons. In
addition, a singlet at δ = 9.22 ppm for one proton confirmed
the presence of an aldehydic proton in the molecule. Fur-
thermore, IR spectroscopic and mass spectrometric data
also support the formation of porphyrin 4.
To improve the yields of porphyrins 3 and 4, experiments were carried out by varying the ratio of DMF and POCl₃ in 1,2-dichloroethane (Table 1, entries 2–6). Increasing the ratio of POCl₃ to DMF to 5:1 caused complete decomposition of the starting material (entry 2). The yield of desired porphyrins (3; 42% and 4; 18%) increased when the reaction was carried out in an equimolar mixture of DMF and POCl₃ (entry 3), and use of a slight excess of POCl₃ in DMF further improved the yields of the desired porphyrin products (entry 5). The best results were obtained when DMF and POCl₃ were used in a 5:6 ratio to afford the desired porphyrins 3 and 4 in 51 and 22% isolated yields, respectively (entry 6). Carrying out the reaction in refluxing benzene did not provide any desired product and only decomposition of starting materials was observed (entry 7). The effect of temperature on the formation of porphyrins 3 and 4 was also studied by carrying out the reactions at 100 °C in 1,4-dioxane and at 60 °C in DCE or THF (entries 8–10). Increasing the reaction temperature from 80 to 100 °C afforded the desired porphyrins 3 and 4 in lower yields (entry 8); whereas decreasing the reaction temperature to 60 °C did not result in formation of the desired porphyrins, and unreacted starting material, 2-acetamidoporphyrin (2a) was recovered quantitatively. Hence, the use of DMF-POCl₃ (5:6) in DCE at 80 °C was considered to be the optimum condition for the synthesis of porphyrins 3 and 4.

After establishing the optimized conditions, the protocol was further extended to construct various nickel(II) and copper(II) 2-chloro-3-formylpyrido[2,3-b]porphyrins 5, 7, and 9, and 3-formylpyrido[2,3-b]porphyrins 6, 8, and 10 from the corresponding nickel(II) and copper(II) 2-acetamido-5,10,15,20-tetraphenylporphyrins 2b–d in moderate yields, as presented in Scheme 2.

Literature reports on the synthesis of 2-chloroquinoline-3-carbaldehydes from acetanilides provided an insight into a possible mechanistic pathway for the formation of nickel(II) or copper(II) complexes of 2-chloro-3-formylpyrido[2,3-b]porphyrins 3, 5, 7, and 9. The reaction may proceed via formation of the corresponding imidoyl chloride from the 2-acetamido-5,10,15,20-tetraphenylporphyrin in the presence of POCl₃. In the next step, an enameline intermediate is formed under the acidic conditions and this undergoes electrophilic addition twice by reacting with chloromethyleneiminium cation (generated in situ from the reaction of DMF and POCl₃). This will form methyleneiminium cation I, which, on aza-π-cyclization followed by elimination of dimethylamine and hydrolysis, affords the desired 2-chloro-3-formylpyrido[2,3-b]porphyrins (Scheme 3). Similarly, a possible mechanism

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>DMF-POCl₃</th>
<th>Yields (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCE</td>
<td>80</td>
<td>1:3</td>
<td>37</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>80</td>
<td>1:5</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>DCE</td>
<td>80</td>
<td>1:1</td>
<td>42</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>DCE</td>
<td>80</td>
<td>2:1</td>
<td>20</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>DCE</td>
<td>80</td>
<td>5:7</td>
<td>45</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>DCE</td>
<td>80</td>
<td>5:6</td>
<td>51</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>benzene</td>
<td>80</td>
<td>5:6</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>5:6</td>
<td>32</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>DCE</td>
<td>60</td>
<td>5:6</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>60</td>
<td>5:6</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: Nickel(II) 2-acetamido-5,10,15,20-tetraphenylporphyrin (2a; 0.14 mmol), DMF/POCl₃ (28 L), solvent (35 mL), heat, 2 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> Starting material was decomposed.

<sup>d</sup> Reaction did not proceed.

**Table 1** Optimization of Reaction Conditions for the Synthesis of Nickel(II) β-Pyridine-Fused Porphyrins 3 and 4

**Scheme 3** Plausible mechanism for the formation of Ni(II) and Cu(II) 2-chloro-3-formylpyrido[2,3-b]porphyrins 3, 5, 7, and 9
for the formation of nickel(II) and copper(II) complexes of 3-formylpyrido[2,3-b]porphyrins (4, 6, 8, and 10) is shown in the Supporting Information (Figure S32).

The structures of the newly synthesized porphyrins were established on the basis of spectroscopic analyses and their characterization data are presented in the experimental section as well as in the Supporting Information.

For comparative UV/Vis studies, the π-conjugation of newly prepared pyridoporphyrins was further extended through the functionalization of the aldehydic moiety of porphyrins 3 and 4 using a Knoevenagel condensation strategy. Under typical Knoevenagel conditions, nickel(II) 2-chloro-3-formylpyrido[2,3-b]porphyrin (3) and nickel(II) 3-formyl-pyrido[2,3-b]porphyrin (4) were reacted separately with malononitrile in the presence of triethylamine in dichloromethane at ambient temperature to produce highly conjugated nickel(II) porphyrins 11 and 12 in 81 and 83% yields, respectively (Scheme 4). The IR spectra of porphyrins 11 and 12 showed a new peak at ca. 2224 cm–1 due to the cyanide stretching and disappearance of the peak at ca. 1667 cm–1 due to the C=O bond stretching, confirming the formation of the expected porphyrin molecules. Furthermore, the absence of a signal for the CHO proton at ca. δ = 9.2 ppm and the appearance of a characteristic signal for a vinylic proton at δ = 7.13 ppm and δ = 7.08 ppm in the 1H NMR spectra of porphyrins 11 and 12, respectively, also supported the assigned structures of these porphyrin derivatives.

The electronic absorption spectra of the new porphyrins were recorded in CHCl₃ (1 × 10⁻⁶ M) at room temperature. The nickel(II) and copper(II) 2-acetamidoporphyrins 2a–d absorbed in a similar region to their precursors nickel(II) meso-tetraphenylporphyrin (NiTPP) and copper(II) mesotetraphenylporphyrin (CuTPP), and did not show any significant variation in their electronic absorption spectra, as presented in the Supporting Information Figure S33. However, UV/Vis studies of the newly formed nickel(II) and copper(II) pyridoporphyrin molecules did give very encouraging results. The electronic absorption spectra of nickel(II) 2-chloro-3-formylpyrido[2,3-b]porphyrin (3) and nickel(II) 3-formylpyrido[2,3-b]porphyrin (4) showed intense Soret bands at 439 and 442 nm, respectively, and two Q bands between 558 and 608 nm (Figure 1a). In contrast, nickel(II) porphyrins 11 and 12 displayed their Soret bands at 455 and 461 nm, respectively, and two Q bands between 552 and 632 nm (Figure 1a). However, the UV/Vis spectra of copper(II) 2-chloro-3-formylpyrido[2,3-b]porphyrin (7) and copper(II) 3-formylpyrido[2,3-b]porphyrin (8) exhibited Soret bands at 438 and 441 nm, respectively, and two Q bands between 559 and 610 nm (Figure 1b). The Soret and Q bands in all the newly prepared pyridoporphyrins are redshifted by ca. 20–45 nm compared to the simple meso-tetraphenylporphyrins such as NiTPP (Soret band at 417 nm and Q bands at 533 and 572 nm) and CuTPP (Soret band at 416 nm and Q bands at 540 and 569 nm).

In conclusion, Vilsmeier–Haack reaction conditions have been successfully applied to generate a novel series of π-extended nickel(II) and copper(II) 3-formylpyrido[2,3-b]porphyrin analogues from readily accessible 2-acetamido-meso-tetraarylporphyrins. In addition, the formyl moiety of two of these porphyrins has been functionalized by reaction with malononitrile under Knoevenagel reaction conditions.
conditions to form highly conjugated pyridoporphyrin molecules. Preliminary UV/Vis studies of these new porphyrins reveal significant bathochromic shifts in their electronic absorption spectra due to the extended π-conjugation. The new pyridoporphyrins contain a formyl functionality that is an excellent site for future modifications to develop highly conjugated aromatic superstructures for various medicinal and material applications.

All the chemicals were purchased from Sigma–Aldrich and used without further purification. The progress of the reactions was monitored by thin-layer chromatography (TLC) using silica gel 60 F254 precoated aluminium sheets) from Merck. The synthesized products were purified by column as well as preparative thin-layer chromatography using neutral aluminum oxide (Brokmann grade I–II, Merck) and silica gel grade G. NMR spectra were obtained in CDCl3 with a JEOl EAX 400P (400 MHz) NMR spectrometer using TMS as an internal standard. Chemical shifts are expressed in parts per million (ppm) relative to residual CHCl3 (δ = 7.26 ppm for 1H NMR and δ = 77.00 ppm for 13C NMR) and coupling constants (J) are reported in hertz (Hz). Infrared spectra were recorded with a Bruker FTIR spectrometer and absorption maxima (υmax) are given in cm–1. Electronic absorption spectra were measured in CHCl3 with an Analytik Jena Spectord 200 UV/Vis spectrophotometer. Mass spectra (ESI-HRMS) were recorded with an ESI-HRMS as eluents to afford the desired 2-chloro-3-formylpyri-

Nickel(II) or Copper(II) 2-Chloro-3-formylpyrido[2,3-b]porphyrins 4, 6, 8, and 10; General Procedure

To a solution of DMF (0.14 mmol) in 1,2-dichloroethane (5 mL), POCl3 (0.17 mmol) was added dropwise and the reaction mixture was stirred at r.t. for 5–10 minutes. A solution of nickel(II) or copper(II) 2-acetamido-5,10,15,20-tetraarylporphyrin 2a–d (0.14 mmol) in 1,2-dichloroethane (30 mL) was then added and the reaction mixture was stirred at 80 °C for 2 hours. Upon completion of reaction, the solvent was evaporated under reduced pressure. The solid residue was dissolved in chloroform (30 mL) and the resulting solution was washed twice with water (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude products were purified over neutral alumina column using 40–50% chloroform in hexane. The two porphyrin analogues were separated on silica gel preparative TLC using 65% chloroform in hexane (for compounds 5–9 and 7–8) and chloroform (for compounds 5–6 and 9–10) as eluents to afford the desired 2-chloro-3-formylpyrido[2,3-b]porphyrins 4, 6, 8, and 10 in 18–54% isolated yields. Characterization data of representative porphyrins 3 and 4 are given below.

Nickel(II) Pyrido[2,3-b]porphyrin (3)

Yield: 65 mg (51%); purple solid; mp >300 °C.


IR (CHCl3): 3058, 2922, 2853, 1666, 1574, 1540, 1451, 1395, 1360, 1300, 1246, 1187, 1152, 1076, 1011, 964, 835, 770, 755, 707, 667 cm–1.

1H NMR (400 MHz, CDCl3): δ = 9.23 (s, 1 H, CHO), 8.95 (s, 1 H, pyridine H), 8.73–8.65 (m, 5 H, β-pyrrolic H), 8.60 (d, J = 5.08 Hz, 1 H, β-pyrrolic H), 8.00–7.88 (m, 7 H, meso-ArH), 7.80–6.74 (m, 14 H, meso-ArH), 7.21 (d, J = 8.52 Hz, 1 H, meso-ArH), 7.07 (d, J = 8.52 Hz, 1 H, meso-ArH).

13C NMR (100 MHz, CDCl3): δ = 188.13, 156.79, 149.32, 144.42, 143.96, 142.47, 142.22, 141.78, 139.91, 139.58, 139.29, 137.98, 137.23, 136.67, 134.87, 133.74, 133.52, 133.45, 133.25, 133.08, 132.66, 132.27, 131.98, 131.38, 128.87, 128.31, 128.14, 127.50, 127.18, 126.99, 123.05, 121.05, 120.39, 116.52, 115.94.


Nickel(II) Pyrido[2,3-b]porphyrin (4)

Yield: 23 mg (22%); purple solid; mp >300 °C.

UV: υmax (ε × 10–4, M–1cm–1): 442 (29.84), 559 (1.95), 608 (3.49) nm.

IR (CHCl3): 3058, 2922, 2853, 1666, 1574, 1521, 1451, 1395, 1355, 1273, 1075, 1013, 941, 859, 789, 753, 704 cm–1.

1H NMR (400 MHz, CDCl3): δ = 9.23 (s, 1 H, CHO), 9.11 (s, 1 H, pyridine H), 9.01 (s, 1 H, pyridine H), 8.72–8.58 (m, 5 H, β-pyrrolic H), 8.60 (d, J = 5.08 Hz, 1 H, β-pyrrolic H), 8.00–7.88 (m, 7 H, meso-ArH), 7.80–6.74 (m, 14 H, meso-ArH), 7.21–7.18 (m, 13 H, meso-ArH), 6.96–6.99 (m, 1 H, meso-ArH).


Nickel(II) Pyrido[2,3-b]porphyrins 11 and 12

To a solution of nickel(II) 2-chloro-3-formylpyrido[2,3-b]porphyrin or nickel(II) 3-formylpyrido[2,3-b]porphyrin 3 or 4 (0.05 mmol) in dichloromethane (20 mL), malononitrile (0.4 mmol) and triethylamine (0.15 mmol) were added and the reaction mixture was stirred at r.t.
for 30 minutes. Upon completion of reaction, the mixture was diluted with chloroform (20 mL) and washed twice with water (2 × 40 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude porphyrin 11 was purified on neutral alumina column using 40% chloroform in hexane as eluent. However, porphyrin 12 was obtained in a sufficiently pure form by titration of the crude solid with methanol. Characterization data of title porphyrins are given below.

**Nickel(II) Pyrido[2,3-b]porphyrin (11)**

Yield: 34 mg (81%); greenish-purple solid; mp >300 °C.

UV: $\lambda_{\text{max}}$ (e × 10$^{-6}$, M$^{-1}$cm$^{-1}$): 455 (29.84), 552 (2.15), 632 (4.62) nm.

IR (CHCl$_3$): 3057, 3020, 2919, 2852, 2224, 1567, 1528, 1448, 1356, 1300, 1190, 1133, 1009, 922, 847, 792, 752, 705, 670 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): 8.71–8.65 (m, 1 H, meso-$\text{ArH}$), 7.89–7.79 (m, 5 H, meso-$\text{ArH}$), 7.97–7.93 (m, 4 H, meso-$\text{ArH}$), 7.24–7.20 (m, 1 H, meso-$\text{ArH}$), 7.13 (s, 1 H, vinylic H), 7.06–7.02 (m, 1 H, meso-$\text{ArH}$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 156.92, 155.23, 149.49, 144.75, 144.51, 142.66, 141.92, 141.10, 139.35, 138.87, 138.38, 138.06, 135.60, 134.73, 133.99, 133.81, 133.43, 133.26, 132.80, 132.69, 132.53, 132.33, 131.32, 129.48, 128.97, 128.60, 128.22, 128.00, 127.81, 127.36, 127.24, 127.08, 123.18, 121.33, 120.60, 116.15, 114.08, 113.38.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{51}$H$_{29}$ClN$_7$Ni$: 832.1521; found: 832.1548.

**Nickel(II) Pyrido[2,3-b]porphyrin (12)**

Yield: 33 mg (83%); greenish-purple solid; mp >300 °C.

UV: $\lambda_{\text{max}}$ (e × 10$^{-6}$, M$^{-1}$cm$^{-1}$): 461 (22.56), 564 (2.05), 632 (3.73) nm.

IR (CHCl$_3$): 3057, 3020, 2919, 2852, 2224, 1567, 1528, 1448, 1356, 1300, 1190, 1133, 1009, 922, 847, 792, 752, 705, 670 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): 8.71–8.65 (m, 1 H, pyridine H), 8.71–8.65 (m, 1 H, pyridine H), 7.89–7.79 (m, 5 H, meso-$\text{ArH}$), 7.97–7.93 (m, 4 H, meso-$\text{ArH}$), 7.24–7.20 (m, 1 H, meso-$\text{ArH}$), 7.13 (s, 1 H, vinylic H), 7.06–7.02 (m, 1 H, meso-$\text{ArH}$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 156.92, 155.23, 149.49, 144.75, 144.51, 142.66, 141.92, 141.10, 139.35, 138.87, 138.38, 138.06, 135.60, 134.73, 133.99, 133.81, 133.43, 133.26, 132.80, 132.69, 132.53, 132.33, 131.32, 129.48, 128.97, 128.60, 128.22, 128.00, 127.81, 127.36, 127.24, 127.08, 123.18, 121.33, 120.60, 116.15, 114.08, 113.38.

HRMS (ESI): m/z [M + K]$^+$ calcd for C$_{51}$H$_{29}$N$_7$KNi$: 836.1469; found: 836.1548.

**Funding Information**

The authors are grateful to the University of Delhi for providing a DST PURSE grant. P.S. is grateful to UGC, New Delhi, India for the award of a Senior Research Fellowship.

**Acknowledgment**

We are grateful to the Central Instrumentation Facility, University of Delhi, India and AIRF, Jawaharlal Nehru University, New Delhi, India for providing the NMR and mass spectrometric data, respectively.

**Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707519.


