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The facile synthesis of 5-formylporphyrin

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Abstract

A facile synthetic route of 5-formylporphyrin (**2**) has been developed. Using pyrrole and pivaldehyde as the starting materials, **2** was obtained through several facile reactions. The synthetic route is easy to perform and can be scaled up, which gives the compound a better application perspective.

Keywords: 5-Formylporphyrin; Unsubstituted porphine; Vilsmeier reaction; Demetalation

As the core of the natural or synthetic porphyrins, porphine (**1**) has received much attention in recent years [1]. However, it was found that much effort has been focused on the theoretical calculations or deductions on porphine itself, or its metalized derivatives [2–3]; while their application in porphyrins' synthesis has been virtually ignored. This is partially due to the difficulties involved in the traditional synthetic routes in unsubstituted porphyrins and their derivatives [4–6]. For instance, 5-formylporphyrin (**2**), which can be the precursor for many other porphine's derivatives, has much potential in synthetic porphyrin chemistry. However, current synthetic route for **2** reported by Senge's group involves several expensive reagents (dithianyl group derivatives, bis(trifluoracetoxy)iodobenzene, *etc.*) and extreme reaction conditions (conditions to handle organic metal reagents, *etc.*) [7]. So there is a need for the facile synthesis of **2** (Fig. 1).

Inspired by the modified synthetic method of porphine synthesis introduced by Neya's group [8], we chose *meso*-tetra(*tert*-butyl)porphyrin (**3**) as the starting compound which was prepared using the classical Lindsey's method [9]. Then, porphine (**1**) was obtained as the intermediate through the de-*tert*-butylation of **3**. Porphine underwent metalation to give copper(II)porphine (**4**), which made the porphine ring reactive enough toward Vilsmeier reaction. The target molecule 5-formylporphyrin (**2**) was then obtained *via* Vilsmeier reaction. The synthetic route is shown in Scheme 1.

1. Experimental

Copper(II)porphine (**4**): compound **1** (45 mg, 0.145 mmol) was added into a mixture of 20 mL $CHCl_3$ and 6 mL CH_3OH. $Cu(OAc)_2{\cdot}H_2O$ (0.29 g, 1.45 mmol) was added into the solution and reaction proceeded under reflux for

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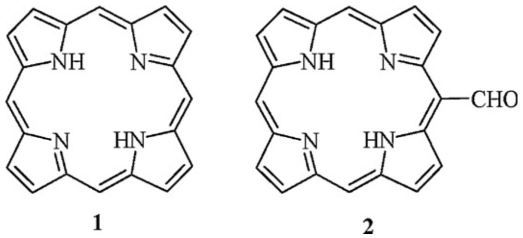


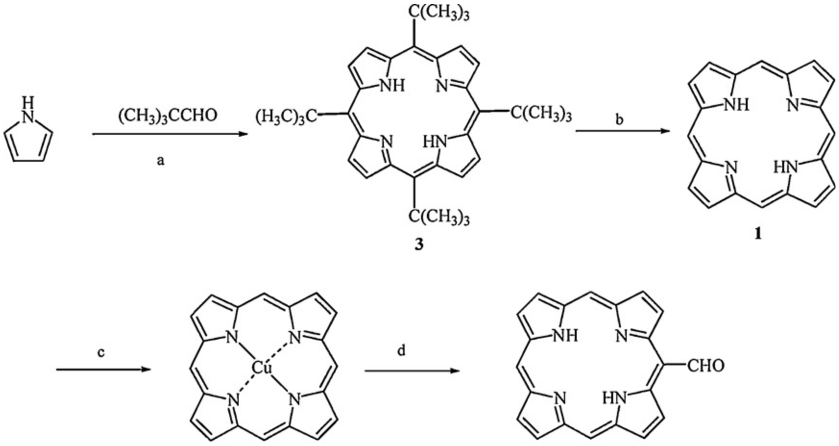
1 **2**

Fig. 1. The structures of unsubstituted porphine and 5-formylporphyrin.

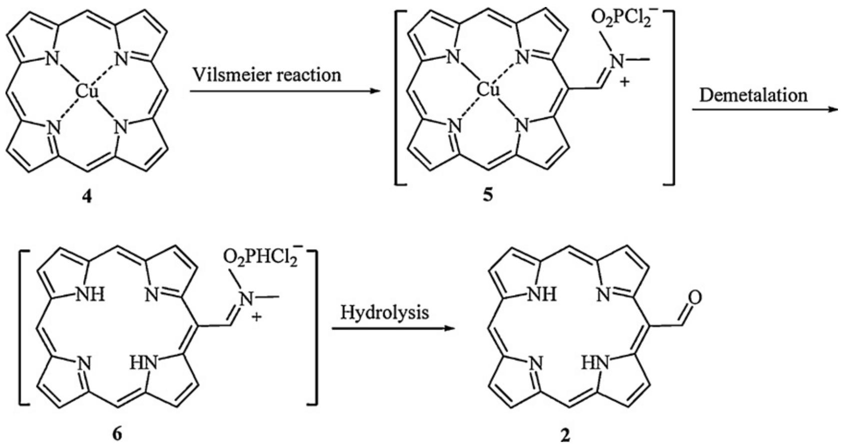
30 min. TLC analysis (1/1 v/v; CH_2Cl_2/hexane) showed exhaustion of the starting material. The reaction mixture was cooled off, washed with water and extracted with 25 mL CH_2Cl_2. The organic solvent was evaporated to dryness and the residue was recrystallized (CH_2Cl_2/CH_3OH). Compound **4** was obtained as a copper-colored powder. Yield 51 mg, 93%. UV/vis (CH_2Cl_2) λ_{max}, nm (ε): 391.5 (449200), 488.5 (16700), 520.5 (10000), 548.0 (8400).

5-Formylporphyrin (**2**): compound **4** (140 mg, 0.377 mmol), dissolved in 60 mL 1, 2-dichloroethane, was added into the freshly obtained Vilsmeier reagent prepared by *N, N*-dimethylformamide (DMF, 1.2 mL, 15.5 mmol) and $POCl_3$ (9.6 mmol) under Ar protection. Reaction proceeded at 85 °C for 1 h. After cooling off, sulfuric acid (3 mL, 98%) was added and stir continued for 10 min. The reaction mixture was poured into aqueous NaOH and was stirred until no green color being observed. CH_2Cl_2 was added to extract the product and the organic phase was washed with water to neutrality. The organic solvent was evaporated to dryness and the residue was purified by silica-gel column chromatography using CH_2Cl_2 as the eluent. The major purple band was collected and recrystallized (CH_2Cl_2/CH_3OH). Compound **2** was obtained as a blue/violet powder. Yield 89 mg, 70%. UV/vis (CH_2Cl_2) λ_{max}, nm (ε): 407.0 (357300), 509.5 (17900), 548.0 (25000), 581.5 (15600), 635.0 (22600). ESI-HRMS calcd. for $[M+H]^+$ $C_{21}H_{15}N_4O$: 339.1246, found: 339.1225. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.52 (s, 1H, C*H*O), 10.27 (s, 2H, H_{meso}), 10.25 (s, 1H, H_{meso}), 10.17 (d, 2H, $J = 4.4$ Hz, H_β), 9.49 (d, 2H, $J = 4.4$ Hz, H_β), 9.39 (d, 2H, $J = 4.4$ Hz, H_β), 9.36 (d, 2H, $J = 4.0$ Hz, H_β), −3.05 (s, 2H, N*H*).

5-Formylnickel(II)porphyrin (**10**): compound **7** (37 mg, 0.101 mmol), dissolved in 60 mL 1, 2-dichloroethane, was added into the freshly obtained Vilsmeier reagent prepared by DMF (1.2 mL, 15.5 mmol) and $POCl_3$ (9.6 mmol) under Ar protection. Reaction proceeded at 85 °C for 1 h. The reaction mixture was cooled off to obtain dark green reaction mixture which majorly contained the iminium salt of **7**. Treatment of the dark green mixture with sulfuric acid (3 mL, 98%, stir at room temperature for 15 min) or with trifluoroacetic acid (4 mL, reflux at 80 °C for 2 h) did not obtain compound **6**, since no compound **2** was detected in the hydrolyzed product. The reaction mixture was poured into aqueous NaOH and was stirred until no green color being observed. CH_2Cl_2 was added to extract the product and the



Scheme 1. Synthetic route of 5-formylporphyrin. (a) (1) $BF_3{\cdot}Et_2O$, CH_2Cl_2 as solvent, argon protection, 4 h, (2) DDQ, reflux, 1 h; (b) H_2SO_4/*i*-PrOH (1/1, v/v), 90 °C, 1 h; (c) $Cu(OAc)_2{\cdot}H_2O$, $CHCl_3$-MeOH, reflux 30 min; (d) (1) Vilsmeier reagent, CH_2ClCH_2Cl, reflux, 1 h (2) H_2SO_4, 5 min (3) NaOH (aq).



Scheme 2. The proposed mechanism of the formation of 2.

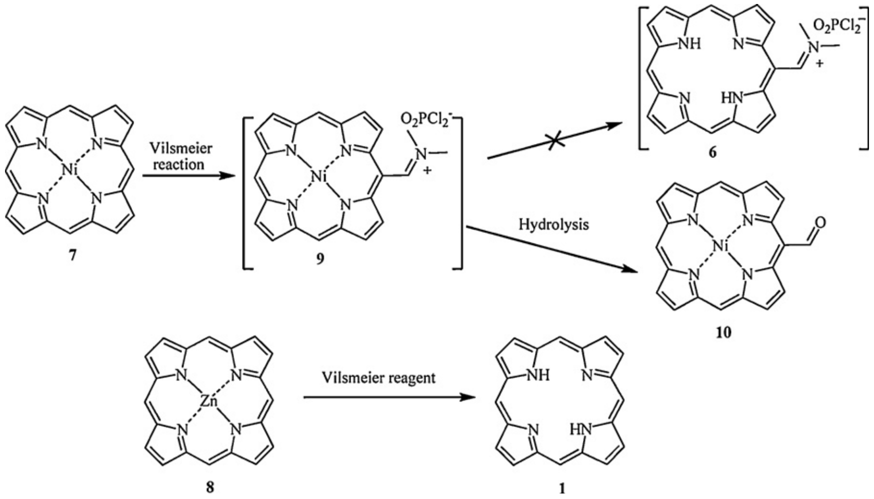
organic phase was washed with water to neutrality. The organic solvent was evaporated to dryness and the residue was purified by silica-gel column chromatography using CH_2Cl_2 as the eluent. The major dark red band was collected and recrystallized (CH_2Cl_2/CH_3OH). Compound **10** was obtained as a reddish-brown powder. Yield 29 mg (from the mixture treated by sulfuric acid), 72%. UV/vis (CH_2Cl_2) λ_{max}, nm (ε): 401.5 (417800), 535 (br, 20000), 576 (37100). ESI-HRMS calcd for $[M+H]^+$ $C_{21}H_{13}N_4NiO$: 395.0443, found: 395.0484. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 12.22 (s, 1H, C*H*O), 10.00 (d, 2H, $J = 4.5$ Hz, H_β), 9.85 (s, 1H, H_{meso}), 9.82 (s, 2H, H_{meso}), 9.25 (d, 2H, $J = 5.0$ Hz, H_β), 9.20 (d, 2H, $J = 4.0$ Hz, H_β), 9.14 (d, 2H, $J = 3.6$ Hz, H_β).

2. Results and discussion

Compounds **3** and **1** were prepared according to the method reported in literature [8–9]. Compound **4** was prepared using $CHCl_3$–CH_3OH co-solvent system with high yield. The crucial step of the whole route lies in the Vilsmeier reaction of **4**. There has been literature reporting that in Vilsmeier reaction, the active site of porphine's copper complex is exclusively at the *meso*-position [10]. But the literature did not explore the accessibility to the metal-free 5-formylporphyrin from the iminium salt stage. We made a difference in the reaction by demetalizing the intermediate iminium salt and successfully obtained the target compound with moderate yield (70%). The mechanism of the formation of **2** is proposed in Scheme 2. Demetalation of the iminium salt **5** and subsequent hydrolysis guaranteed the ideal yield of **2** [11]. However, the porphine core has no steric hinderance compared to phenylporphyrins. Unlike the Vilsmeier reaction of phenylporphyrin's metal complexes, whose products stay mainly at the *mono*-formylation stage [12], the reaction of porphine's metal complex could have multi-formyl porphines as by-products. Therefore, the reaction should last for no longer than 1 h and the temperature should be carefully controlled. It is also noteworthy that the pure compound **2** is quite susceptible to degradation, as we have discovered in the purification process. So it is highly recommended that **2** should avoid refined purification process and be directly used for following-up reactions.

The possibility of other metal complexes of porphine to prepare compound **2** was examined. Nickel(II)porphine (**7**) and zinc(II)porphine (**8**), which had been prepared using the same method of preparing copper(II)porphine, respectively reacted with the Vilsmeier reagent. It was found that **8** did not undergo Vilsmeier reaction because the zinc atom in the porphine ring was dissociated by the acid in the reaction mixture. The intermediate iminium salt of **7** was successfully prepared. However, demetalation of the iminium salt by adding sulfuric acid or by refluxing with trifluoroacetic acid failed since the nickel(II) complex of porphine lacked reactivity and 5-formylnickel(II)porphyrin (**10**) was obtained as the alternative formylation product of porphine. Stronger demetalation conditions caused the rupture of the porphine ring. The results indicate that copper(II)porphine was the only compound suitable to prepare **2** in the method introduced.

Compared to the method reported by Senge's group, the synthetic route has several advantages. The overall yield of Senge's method is 62.5% from the porphyrin precursor. It is noteworthy that they used several hard-to-obtain reagents in the route, which substantially lowered the productivity. In their synthetic route, the reagent dipyrromethane was relatively difficult to obtain, thereby lowering the scale of the reactions; handling organic metal reagents caused



Scheme 3. Insufficient reactivity of the intermediate iminium salt of nickel(II)porphine and unstableness of zinc(II)porphine.

stricter reaction conditions; reagents such as bis(trifluoracetoxy)iodobenzene made the method more expensive. Plus, the total reaction time exceeded 30 h. The overall yield of our method is 65.1% from porphine. The starting materials and the reagents involved in the route are all commercially available and are relatively low in cost; so the scale of the reactions can be elevated (which has been proved by the result that compound **2** could be obtained on the scale of 100 mg). The reaction conditions were less strict, making the experiments easier to proceed. The total reaction time was lower than 15 h and the production cycle was shortened (Scheme 3).

3. Conclusion

A synthetic route to **2** with relatively lower cost, shorter production cycle, milder reaction conditions and higher productivity than the route reported in the existing literature has been developed. The modification in the synthetic route of **2** gives the compound a wider range of application perspective in porphyrin's synthetic chemistry.

Acknowledgments

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