# Synthesis of *meso*-substituted porphyrins in room temparature ionic liquid

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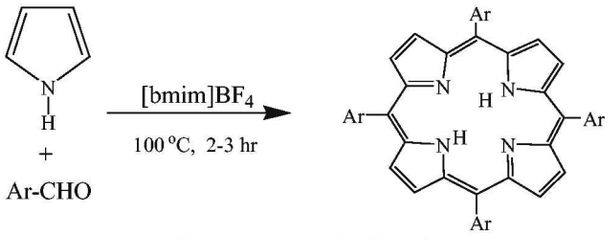
*meso*-Substituted porphyrins are synthesised from pyrrole and aryl, heteryl aldehydes cleanly and efficiently in one step by reactions at temperatures 100 °C in ionic liquid using air as oxidant.

**Keywords:** *meso*-substituted porphyrins, ionic liquid

Porphyrins are tetra pyrrolic compounds in which four pyrrole groups are interconnected four methane bridges between their α-carbon atoms.[1] The chemistry of porphyrins and their derivatives is relevant to applications such as biomimetic photosynthesis, molecular electronics, supramolecular catalysis, MRI, photodynamic therapy, cytochrome P-450 function, *etc.*[2-4] In order to exploit their chemistry, it is necessary to fine-tune their properties by introducing various functional groups at the periphery of the porphyrin macrocycle. A variety of substituted porphyrins have been reported[5-8] for various applications. Of these, the heteryl porphyrins with diverse substituents are important for the studies of biomimetic and molecular recognition properties. Nitrogen heterocyclic porphyrins are particularly interesting in this regard as they provide sites for metal coordination, hydrogen bonding, alkylation and modulating electronic properties.[9] Indeed, pyridine substituents had yielded a broad array of metal coordinated multi porphyrin architectures.[10,11] As the applications of porphyrins increase, it is necessary to develop alternative methods, which enable facile synthesis under mild conditions, with easy workup in moderate to good yields.

A variety of synthetic methods have been developed for non-natural porphyrins, especially meso tetra substituted porphyrins. Rothemund[12] first reported the synthesis of tetraphenyl porphyrin more than 50 years ago, by condensation of benzaldehyde and pyrrole in pyridine. The yields were low and the conditions so severe that few substituted benzaldehydes could be converted to the corresponding porphyrins. Adler–Longo[13] modified the Rothemund reaction by allowing benzaldehyde and pyrrole to react for 30 min *et al.* in refluxing propionic acid (141 °C) open to the air. This method using comparatively milder reaction conditions has allowed a wider selection of substituted benzaldehydes to be converted to the corresponding porphyrins in yields up to 20%. Instead of heating the solvents, Lindsey *et al.*[14-15] have selected dichloromethane with an appropriate acid as the reaction medium, and improved yield up to around 50%. Due to its mild conditions, good yield and convenience, the Lindsey method has come into widespread use for preparations of porphyrins. By the method of using dichloromethane, N-confused tetraphenyl porphyrin (NC-TPP) was first isolated in *ca.* 5% yield by Furuta *et al.*[16] and Latos Grazynski *et al.*[17] and later Lindsey *et al.*[18] again optimised the reaction condition to yield NC-TPP in 39%. Drain *et al.*[19] condensed pyrrole with aldehyde without solvent and acid catalyst for the synthesis of porphyrins.[19] All these methods involve the consumption of harmful acids and halogenated solvents which are not eco-friendly. There is an ecological need to reduce the use of the halogenated solvents and harmful acids, without any loss of the productivity, in the preparation of porphyrins.

In contrast, room temperature ionic liquids (IL) could be suitable and environmentally safer replacement for the volatile, toxic, and flammable organic solvents currently used in synthetic and catalytic reactions. For example, ILs are used for synthetic transformations, enzyme catalysed reactions, Heck reaction, Bischler–Napierlaski cyclisation, Beckmann rearrangement, addition of thiols to unsaturated ketones and 1-proline catalysed aldol reactions. However, the utilisation of ILs for porphyrin synthesis has been limited to tetraphenyl derivatives only. Ishikawa and co-workers[20-21] have used various ILs for the preparation of tetraphenyl porphyrin and NC-TPP in the presence of halogenated solvent and acid catalyst at room temperature. In the present study we have taken 1-butyl-3-methyl imidazolium tetrafluorborate ([bmim]$BF_4$) IL and various aromatic aldehydes for porphyrin synthesis.




Ar = aromatic or hetero aromatic aldehyde

[bmim]$BF_4$ = 1-butyl-3-methylimidazolium tetrafluoroborate

The IL was prepared as reported in the literature.[22] We have adopted Rothemund (aerobic) reaction conditions unlike Ishikawa and co-workers who used Lindsey (anaerobic) reaction conditions for porphyrin synthesis. Initially, we have taken benzaldehyde (1 mmol) to react with pyrrole (1 mmol) in [bmim]$BF_4$ (3 ml) at 100 °C for 2 h under aerobic conditions. Air is the oxidising agent for this reaction. The crude product was extracted with chloroform and purified by column chromatography to obtain 26% of product. The same reaction carried out using propionic acid method, gave a yield of only 20%. We have observed only simple porphyrin and no NC-TPP in this method unlike Ishikawa and co-workers who observed both simple porphyrin and NC-TPP under anaerobic conditions. We have extended this methodology to a variety of aryl and heteryl aldehydes and the results are presented in Table 1. The heteryl aldehydes (Entries **6** and **7**) were synthesised by a modified procedure reported in the literature. We have observed an overall yield of corresponding quinoline porphyrins at around 18% yield. Amaravathi *et al.*[23] have carried out the same reaction with the propionic acid method with only 12% yield. Similarly, with coumarin aldehydes (Entries **8** and **9**), we have observed an overall yield of porphyrin 24% with IL method. Whereas with the propionic acid method, it was only 20% yield.[24] Similarly, we have observed 28% yields in case of imidazole porphyrins (Entries **10–12**), which is a better yield than the propionic acid method.[25]

The major advantage of this method is that we have used no chlorinated solvent, no acid catalyst non oxidising agent

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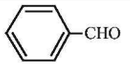
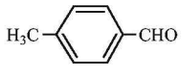
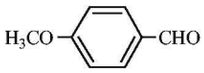
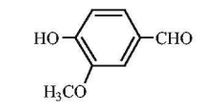
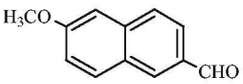
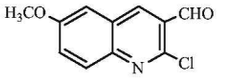
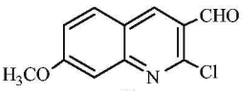
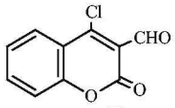
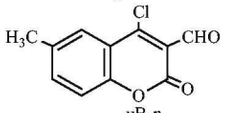
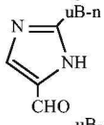
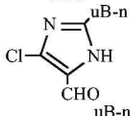
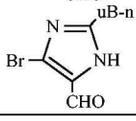
**Table 1**

| Entry | Ar | Product[a] | Yield/% |
|---|---|---|---|
| 1 |  | **2a** | 26 |
| 2 |  | **2b** | 28 |
| 3 |  | **2c** | 29 |
| 4 |  | **2d** | 33 |
| 5 |  | **2e** | 23 |
| 6 |  | **2f** | 18 |
| 7 |  | **2g** | 17 |
| 8 |  | **2h** | 24 |
| 9 |  | **2i** | 24 |
| 10 |  | **2j** | 26 |
| 11 |  | **2k** | 28 |
| 12 |  | **2l** | 22 |

unlike other porphyrin synthetic methods. The IL used in this method acts as solvent as well as Lewis acid catalyst providing a quick and efficient route to the synthesis of *meso*-substituted porphyrins with higher yields compared with Rothumand method for the synthesis of porphyrins. This method provides a facile and alternative method for the preparation of various *meso*-substituted porphyrins under eco-friendly conditions.

In conclusion we have developed an alternative method for meso-substituted porphyrins by using ILs under aerobic reaction conditions. The yields are better than the propionic acid method.

## Expermental

In a typical reaction, pyrrole (1 mmol) and bezalaldehyde (1 mmol) were placed in about 3 ml of IL. The reaction mixture was heated at 100 °C for about 2–3 h. The crude product was extracted with chloroform and subjected to alumina column and eluted with chloroform to get the desired product (**2a**) in 26% yield.

**2a**: M.p. >300 °C. Anal. Calcd for $C_{44}H_{30}N_4$: C, 85.99; H, 4.89; N, 9.02. Found: C, 85.86; H, 4.91; N, 8.94%. FAB-MS *m/z* 615 $(M + 1)^+$, requires 614. UV: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 420 (5.11), 510 (4.48), 555 (4.27), 595 (3.74), 650 (4.33). $^1$H NMR ($CDCl_3$ + $d_6$-DMSO) δ ppm: 8.82 (m, 8H, pyrrole β-protons), 7.54 (d, 8H, ArH), 7,58 (m, 12H, ArH), –2.62 (b, 2H, porphyrin NH).

**2b**: M.p. >300 °C. Anal. Calcd for $C_{48}H_{38}N_4$: C, 85.97; H, 5.67; N, 8.36. Found: C, 85.98; H, 5.66; N, 8.34%. FAB-MS *m/z* 671 $(M + 1)^+$, requires 670. UV: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 420 (5.20), 520 (4.44), 555 (4.27), 585 (3.74), 656 (4.23). $^1$H NMR ($CDCl_3$ + $d_6$-DMSO) δ ppm: 8.71 (m, 8H, pyrrole β-protons), 7.84 (d, 8H, ArH), 7,68 (s, 8H, ArH), 2.14 (s, 12H, 4x $CH_3$), –2.52 (b, 2H, porphyrin NH).

**2c**: M.p. >300 °C. Anal. Calcd for $C_{48}H_{38}N_4O_4$: C, 82.28; H, 5.36; N, 8.27. Found: C, 82.20; H, 5.31; N, 8.24%. FAB-MS *m/z* 735 $(M + 1)^+$, requires 734. UV: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 420 (5.21), 520 (4.42), 555 (4.21), 585 (3.54), 650 (4.13). $^1$H NMR ($CDCl_3$ + $d_6$-DMSO) δ ppm: 8.81 (m, 8H, pyrrole β-protons), 7.76 (d, 8H, ArH), 7,58 (d, 8H, ArH), 3.90 (s, 12H, 4x O–$CH_3$), –2.62 (b, 2H, porphyrin NH).

**2d**: M.p. >300 °C. Anal. Calcd for $C_{48}H_{38}N_40_8$: C, 72.18; H, 4.76; N, 7.17. Found: C, 72.26; H, 4.71; N, 6.94%. FAB-MS *m/z* 799 $(M + 1)^+$, requires 798. UV: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 420 (5.21), 520 (4.38), 555 (4.21), 595 (3.74), 650 (4.13). $^1$H NMR ($CDCl_3$ + $d_6$-DMSO) δ ppm: 8.91 (m, 8H, pyrrole β-protons), 7.74 (d, 4H, ArH), 7,58 (s, 4H, ArH), 7.25, 7.22 (d, 4H, ArH), 3.94 (s, 12H, 4x O–$CH_3$), –2.62 (b, 2H, porphyrin NH).

**2e**: M.p. >300 °C. Anal. Calcd for $C_{64}H_{46}N_40_4$: C, 82.22; H, 4.92; N, 5.99. Found: C, 82.34; H, 4.86; N, 5.90%. FAB-MS *m/z* 935 $(M + 1)^+$, requires 934. UV: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 431 (5.08), 520 (4.68), 557 (4.11), 595 (3.94), 651 (3.97). $^1$H NMR ($CDCl_3$ + $d_6$-DMSO) δ ppm: 8.85 (m, 8H, pyrrole β-protons), 8.58 (s, 4H, naphthyl –H), 8.35 (d, 4H, naphthyl –H), 7.94 (dd, 8H, naphthyl –H), 7,32 (m, 8H, naphthyl–H), 3.98 (s, 12H, 4x O-$CH_3$), –2.64 (b, 2H, porphyrin N–H).

**2f**: M.p. >300 °C Anal. Calcd for $C_{60}H_{38}N_80_4Cl_4$: C, 66.92; H, 3.56; N, 10.41. Found: C, 66.86; H, 3.62; N, 10.50%: FAB-MS *m/z* 1077 $(M + 1)^+$, requires 1076. UV-Vis.: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 430 (5.53), 520(4.84), 600 (4.31), 661 (4.00). $^1$H NMR ($CDCl_3$ + DMSO-$d_6$) δ ppm: 9.06 (m, 8H, pyrrole β-protons), 8.66 (s, 4H, quinoline $C_4$–H), 7,94 (d, 4H, quinoline $C_8$–H), 7.52 (d, 4H, quinoline $C_7$–H), 7.18 (s, 4H, quinoline $C_5$–H), 3.96 (s, 12H, 4x O–$CH_3$), –2.60 (b, 2H, porphyrin N–H). IR (KBr) $cm^{-1}$: 3426 (w, porphyrin N–H stetch), 1622, 1588, 1494, 1462 (m, aromatic C=C, C=N ring stretch), 969, 959 (m, porphyrin macrocyclic bend), 831,797 (s, aromatic C=C–H out-of plane bend).

**2g**: M.p. > 300 °C Anal. Calcd for $C_{60}H_{38}N_80_4Cl_4$: C, 66.92; H, 3.56; N, 10.41. Found: C, 66.98; H, 3.64; N, 10.35%. FAB-MS *m/z* 1077 $(M + 1)^+$, requires 1076. UV-Vis.: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 430 (5.50), 520(4.41), 601 (4.21), 661 (4.00). $^1$H NMR ($CDCl_3$ + DMSO -$d_6$) δ ppm: 9.05 (m, 8H, pyrrole β-protons), 8.63 (s, 4H, quinoline $C_4$–H), 7,84 (d, 4H, quinoline $C_5$–H), 7.37 (s, 4H, quinoline $C_8$–H), 7.27 (d, 4H, quinoline $C_6$ –H), 3.98 (s, 12H, 4x O–$CH_3$), –2.60 (s, 2H, porphyrin N–H). IR (KBr) $cm^{-1}$: 3430 (w, pophyrin N–H stretch), 1620, 1585, 1492, 1464 (m, aromatic C=C, C=N ring stretch), 968, 958 (m, porphyrin macrocyclic bend), 832, 798 (s, aromatic C=C–H out-of plane bend).

**2h**: M.p. > 300 °C Anal. Calcd for $C_{56}H_{26}0_8N_4Cl_4$: C, 65.64; H, 2.56; N, 5.47. Found: C, 65.576; H, 2.56; N, 5.49%. FAB-MS *m/z* = 1025 ($M^+$ + 1) requires 1024. UV: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 426.5 (5.36), 514 (4.38), 589.5 (3.91). $^1$H NMR ($CDCl_3$ + $d_6$-DMSO) δ ppm: 9.02 (s, 8H, pyrrole C–*H*), 8.06, 8.02 (dd, 4H, coumarin $C_5$–*H*), 7.8–7.46 (m, 12H, coumarin $C_6$–*H*, $C_7$–*H* and C8–*H*), –2.56 (s, 2H, porphyrin N–H). IR (KBr) $cm^{-1}$: 3425 (broad, N–H str of porphyrin), 1727 (s, –C=O str of coumarin) 1602, 1550, 1454 (C=C, C=N in plane bend,) 966.6 (porphyrin microcyclic bend).

**2i**: M.p. > 300 °C. Anal. Calcd for $C_{60}H_{34}0_8N_4Cl_4$: C, 66.68; H, 3.17; N, 5.18. Found C, 66.589; H, 3.162; N, 5.178%. FAB-MS *m/z* = 1081 ($M^+$ + 1) requires 1080. UV-Vis.: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 427 (5.368), 515 (4.367), 591.5 (3.89). $^1$H NMR ($CDCl_3$ + $d_6$-DMSO) δ ppm: 9.02 (s, 8H, pyrrole C–*H*), 7.98, 7.94 (weak d, 4H, coumarin $C_5$–*H*), 7.64 (d, 4H, coumarin $C_8$–*H*), 7.57 (d, 4H, coumarin $C_7$–*H*), 2.6 (s, 12H, 4x$CH_3$), –2.56 (s, 2H, porphyrin N–H). IR (KBr) $cm^{-1}$: 3448 (broad, N–H str of porphyrin), 1726 (s, C=O str of coumarin) 1600, 1569, 1450 (C=C, C=N in plane bend), 966 (porphyrin microcyclic bend).

**2j**: M.p. > 300 °C. Anal. Calcd for $C_{48}H_{54}N_{12}$: C, 72.18; H, 6.76; N, 21.05. Found C, 72.21; H, 6.77; N, 21.048%. FAB-MS *m/z* = 799 ($M^+$ + 1) requires 798. UV-Vis.: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 432.5 (5.09), 519 (4.22), 561 (4.08), 591 (3.94), 657.5 (3.86). $^1$H NMR ($CDCl_3$ + $d_6$-DMSO) δ ppm:13.12 (s, broad, 4H, imidazole N–H) 9.12 (s, 8H, pyrrole C–*H*), 7.65 (s, 4H, imidazole C–H), 2.8–2.9 (m, 8H, $–CH_2$), 2.05 (m, 8H, $CH_2$–$CH_2$–$CH_3$), 1.6 (m, 8H, $CH_2$–$CH_3$), 1.05 (m, 12H, *n*-butyl $CH_3$), –2.49 (s, 2H, porphyrin N–H): IR (KBr) $cm^{-1}$: 3400–3000 (broad, N–H str), 2950, 2830 (ω-aliphatic str), 1612, 1600, 1560, 1450 (m imidazole and C=C, C=N in plane bend), 940 (porphyrin microcyclic bend).

**2k**: M.p. > 300°C. Anal. Calcd for $C_{48}H_{50}Cl_4N_{12}$: C, 61.53; H, 5.34; N, 17.94. Found C, 61.48; H, 5.44; N, 17.90%. FAB-MS *m/z* = 937 ($M^+ + 1$) requires 936. UV-Vis.: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 433 (5.096), 519.5 (3.84), 559 (4.03), 599 (3.62), 657 (3.16). $^1$H NMR ($CDCl_3$ + $d_6$-DMSO) δ ppm:13.2 (s, 4H, imidazole N–H) 9.12 (s, 8H, pyrrole C–*H*), 2.8–2.95 (m, 8H, $-CH_2$), 2.05 (m, 8H, $CH_2$–$CH_2$–$CH_3$), 1.65 (m, 8H, $CH_2$–$CH_3$), 1.05 (m, 12H, *n*-butyl $CH_3$), –2.6 (s, 2H, porphyrin N–H): IR (KBr) cm$^{-1}$: 3350 (m, broad, imidazole (H–bonded) N–H str), 2920, 2900, 2850 (*m*-aliphatic str), 1600, 1510, 1400 (m imidazole and C=C, C=N in plane bend), 940 (porphyrin microcyclic bend).

**2l**: M.p. > 300°C. Anal. Calcd for $C_{48}H_{50}Br_4N_{12}$: C, 51.80; H, 4.50; N, 15.15. Found C, 51.83; H, 4.56; N, 15.12%. FAB-MS *m/z* = 1111 ($M^+ + 1$) requires 1110. UV-Vis.: $\lambda_{max}$ nm ($CHCl_3$) (log ε): 431 (5.096), 518 (4.18), 559 (4.02), 593.5 (3.88), 657.5 (3.96). $^1$H NMR ($CDCl_3$ + $d_6$-DMSO) δ ppm:13.25 (s, 4H, imidazole N–H) 9.1 (s, 8H, pyrrole C–*H*), 2.85–2.95 (m, 8H, $-CH_2$), 2.05 (m, 8H, $CH_2$–$CH_2$–$CH_3$), 1.65 (m, 8H, $CH_2$–$CH_3$), 1.02 (m, 12H, *n*-butyl $CH_3$), –2.62 (s, 2H, porphyrin N–H): IR (KBr) cm$^{-1}$: 3400 (s, broad, imidazole (H–bonded) N–H str), 2920, 2900, 2830 (*m*-aliphatic str), 1560, 1510, 1440 (m imidazole and C=C, C=N in plane bend), 945 (porphyrin microcyclic bend).

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