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Facile Syntheses of Perfluoroalkylporphyrins. Electron Deficient Porphyrins II

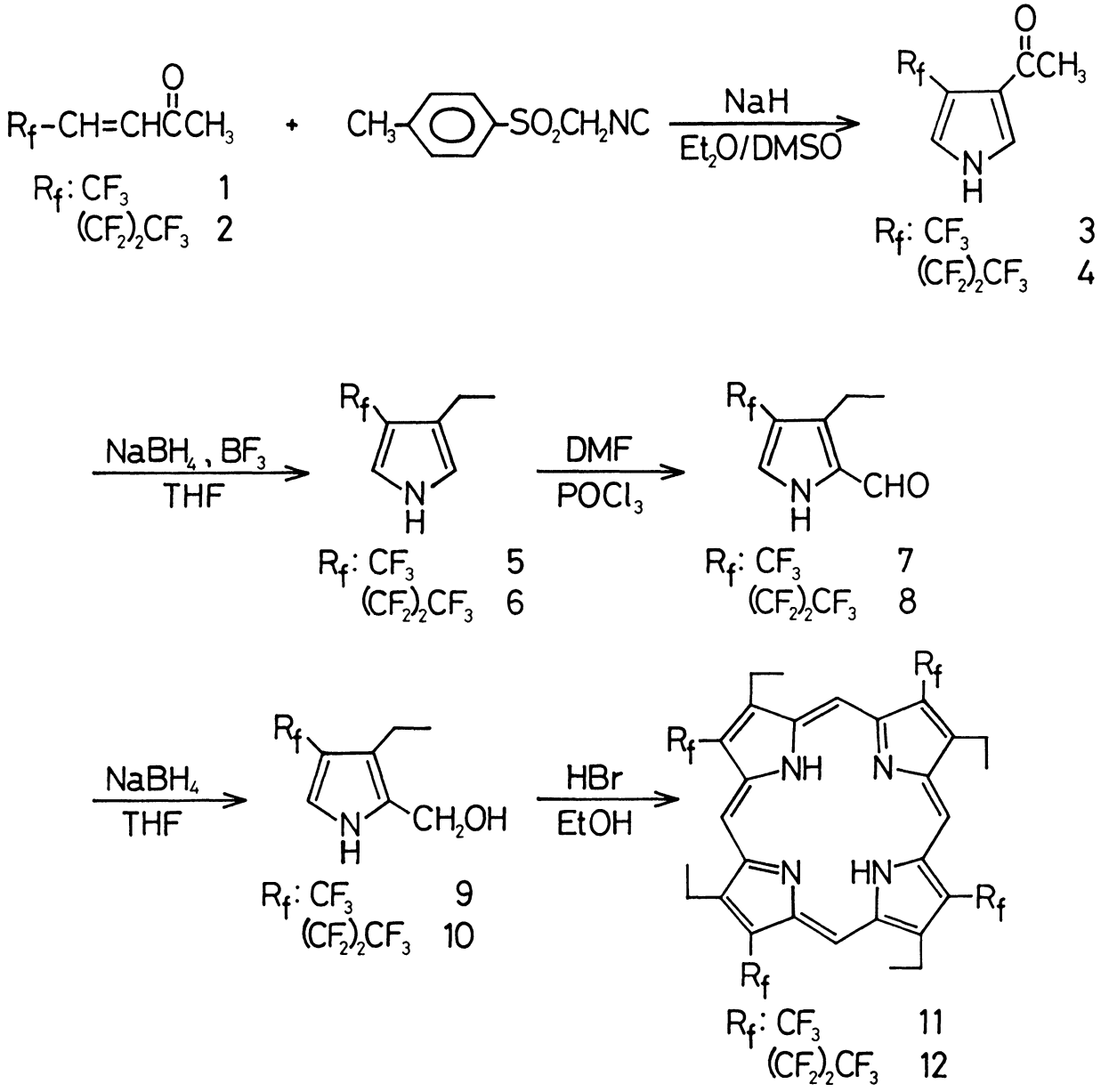
Katsuhiro AOYAGI,* Hiroo TOI,† Yasuhiro AOYAMA,† and Hisanobu OGOSHI*††
Department of Industrial Chemistry, Fukushima National College of Technology, Taira, Iwaki, Fukushima 970
†Department of Chemistry, Technological University of Nagaoka, Kamitomioka 1603-1, Nagaoka, Ni-igata 940-21
††Department of Synthetic Chemistry, Kyoto University, Yoshida-honmachi, Kyoto 606

A variety of β-perfluoroalkylpyrroles were prepared from reaction of β-perfluoroalkyl-α,β-unsaturated ketones with p-toluenesulfonylmethylisocyanide in moderate yields. Tetrakis-(perfluoroalkyl)porphyrins were readily obtained by oxidative cyclization of 2-hydroxymethyl-3-ethyl-4-perfluoroalkylpyrroles in acidic media.

Fluorine substitution of organic substrates, prosthetic groups, and enzymes has provided a useful tool in ^{19}F-NMR investigation on enzymes as a nuclear probe. Second interesting point is promising antitumor activity of the fluorininated heterocycles.[1] In previous communication, we have reported syntheses of novel electron deficient porphyrins from template reaction of β-trifluoromethylpyrrole derivatives with copper salt.[2] However, syntheses of precursory pyrroles required hazardous manipulation to use freshly generated HNO_2 and further steps to complete the Knorr condensation.[3] Present paper deals with more facile and general pathway to obtain electron deficient porphyrins in moderate yields.

The Wittig reaction with (acetylmethylene)triphenylphosphorane and perfluoroalkylaldehyde R_fCHO afforded β-R_f-α,β-unsaturated ketones 1 and 2 in 75% and 78% yields respectively.[4,5] A solution of 1 (550 mg, 4.0 mmol) and p-toluensulfonylmethylisocyanide (780 mg, 4.0 mmol) in ether-DMSO (2:1 vol., 20 ml) is added to an ether suspension of 50% NaH (400 mg, 8.3 mmol). After stirring reaction mixture for 30 min, a mixture was added water (80 ml) and extracted with ether. Ether solution was washed with water, dried over anhydrous $MgSO_4$, and condensed to dryness. Crystallization from $CHCl_3$/n-pentane gave 3-acetyl-4-trifluoromethylpyrrole 3 (310 mg) as white crystals in 44%.[6,7] Similar reaction for 2 gave 3-acetyl-4-heptafluoropropylpyrrole 4 in 39% as colorless crystals.[8] Reduction of 3 (2.0 g, 11.3 mmol) with $NaBH_4$ (2.1 g, 55.6 mmol) and 47% BF_3 etherate (10.5 g, 72.8 mmol) in THF at room temperature under nitrogen for 1 h afforded 3-ethyl-4-trifluoromethylpyrrole 5 (1.8 g) as colorless oil in 98% yield.[9] Acetylpyrrole 4 was likewisely reduced to give 3-ethyl-4-heptafluoropropylpyrrole 6 in 86%

yield.[10] Formylation of 5 (1.8 g, 11.0 mmol) was carried out with DMF (1.2 g, 16.4 mmol) and phosphorous oxychloride (2.6 g, 17.0 mmol) in ethylene dichloride at 100 °C for 15min. Reaction mixture was treated with saturated aqueous sodium acetate and further stirred at 100 °C for 15min. Ethylene dichloride layer was separated, washed with water, dried over anhydrous Na_2SO_4, and condensed to dryness. Recrystallization from $CHCl_3$/n-pentane gave 2-formyl-3-ethyl-4-trifluoromethylpyrrole 7 (1.8 g) as colorless crystals in 86% yield.[11] Heptafluoropropylpyrrole 6 was formylated to give 2-formyl-3-ethyl-4-heptafluoropropylpyrrole 8 in 70% yield.[12] Marked difference in electronic effect of β-alkyl and -perfluoro-



alkyl groups at the β-position brought about exclusive formylation of α-free pyrrole at the adjacent position of alkyl group, whereas Vilsmeier formylation of asymmetric 3,4-dialkylpyrroles gives rise to two isomers.

Both formyl groups of 7 and 8 were reduced by $NaBH_4$ in THF to yield 2-hydroxymethylpyrrole 9 and 10 in 81% and 92% respectively.[13,14] The 2-hydroxymethylpyrrole 9 is sensitive to air. When the $CHCl_3$ solution of 9 was exposed to air, its color gradually turned to red due to spontaneous formation of porphyrin. A mixture of 9 (145 mg, 0.75 mmol) and several drops of 48% hydrobromic acid in ethanol was stirred at room temperature for 2 days. The reaction mixture was poured into cold water and extracted with $CHCl_3$. After evaporation of $CHCl_3$ residual solid was chromatographed on alumina gel with $CHCl_3$. Red colored eluant was condensed into dryness. Crystallization from $CHCl_3$/MeOH gave 1,3,5,7-tetrakis(trifluoromethyl)-2,4,6,8-tetraethylporphyrin 11 (39 mg, 30%) as red crystals, which is confirmed by comparing with physical property and prominent spectroscopic data of authentic porphyrin.[2] In similar manner, 1,3,5,7-tetrakis-(heptafluoropropyl)-2,4,6,8-tetraethylporphyrin 12 was obtainable in 11% yield.[15] Highly symmetric frameworks of two porphyrins 11 and 12 are verified by their simple spectral patterns of ^{1}H-NMR and ^{19}F-NMR. No asymmetric porphyrin isomers were detected.[16]

The β-perfluoroalkyl-α,β-unsaturated ketones can be utilized as building block element for direct syntheses of a variety of α-free-β-perfluoroalkyl-pyrroles. Present synthetic pathway to electron deficient porphyrins is much more convenient than templete synthesis with pyrroles derived from modified Knorr condensation. Furthermore, it provides method for facile replacement of the CH_3 group at peripheral positions of naturally occuring porphyrins with the CF_3 group. Total syntheses of hemes substituted with the CF_3 group and paramagnetic ^{19}F-NMR investigation on heme enzymes with new hemes are currently underway.

References

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7) Compound 3: Mp 175-177 °C; Mass spectrum m/e 177 (M^+); IR (KBr) 3140 (ν(NH)), 1650 (ν(C=O)), and 1238, 1175, 1125 and 1097 cm^{-1} (ν(CF_3)); ^{1}H-NMR ($CDCl_3$, TMS, 270 MHz) δ 9.14 (broad s, 1H, NH), 7.46 and 7.22 (m, 1H, 1H, 2 and 5-H), and 2.47 (s, 3H, $COCH_3$); ^{19}F-NMR (CD_3OD, $CFCl_3$) δ -58.4 (s, CF_3).

8) Compound 4: Mp 176-179 °C; Mass spectrum m/e 277 (M^+); IR (KBr) 3175 (ν(NH)), 1652 (ν(C=O)), and 1235, 1189, 1179, and 1108 cm^{-1} (ν($CF_2CF_2CF_3$)); ^{1}H-NMR ($CDCl_3$) δ 9.00 (broad s, 1H, NH), 7.46 and 7.20 (m, 1H, 1H, 2 and 5-H), and 2.45 (s, 3H, $COC\underline{H}_3$); ^{19}F-NMR (CD_3OD) δ -81.0 (t, 3F, CF_3), -102.2, -124.7 (m, 2F, 2F, $C\underline{F}_2CF_2CF_3$ or $CF_2C\underline{F}_2CF_3$).

9) Compound 5: Bp 43-44 °C (5 mmHg); Mass spectrum m/e 163 (M^+); IR (liquid film) 3425 (ν(NH)), and 1256, 1208, 1127, and 1107 cm^{-1} (ν(CF_3)); ^{1}H-NMR ($CDCl_3$) δ 8.12 (broad s, 1H, NH), 7.02 and 6.57 (m, 1H, 1H, 2 and 5-H), 2.16 (q, 2H, $C\underline{H}_2CH_3$), and 1.21 (t, 3H, $CH_2C\underline{H}_3$); ^{19}F-NMR ($CDCl_3$) δ -55.8 (s, CF_3).

10) Compound 6: Bp 40-43 °C (4 mmHg); Mass spectrum m/e 263 (M^+); IR (liquid film) 3495 (ν(NH)), and 1229, 1212, 1178, and 1110 cm^{-1} (ν($CF_2CF_2CF_3$)); ^{1}H-NMR ($CDCl_3$) δ 8.28 (broad s, 1H, NH), 6.98 and 6.61 (m, 1H, 1H, 2 and 5-H), 2.58 (q, 2H, $C\underline{H}_2CH_3$), and 1.20 (t, 3H, $CH_2C\underline{H}_3$); ^{19}F-NMR ($CDCl_3$) δ -78.9 (s, 3F, CF_3), -103.2, -124.9 (m, 2F, 2F, $C\underline{F}_2CF_2CF_3$ or $CF_2C\underline{F}_2CF_3$).

11) Compound 7: Mp 90-92 °C; Mass spectrum m/e 191 (M^+); IR (KBr) 3250 (ν(NH)), 1655 (ν(C=O)), and 1288, 1219, 1126, and 1090 cm^{-1} (ν(CF_3)); ^{1}H-NMR ($CDCl_3$) δ 10.89 (broad s, 1H, NH), 9.70 (s, 1H, CHO), 7.39 (m, 1H, α-H), 2.91 (q, 2H, $C\underline{H}_2CH_3$), and 1.30 (t, 3H, $CH_2C\underline{H}_3$); ^{19}F-NMR ($CDCl_3$) δ -56.0 (s, CF_3).

12) Compound 8: Bp 165-167 °C (2 mmHg); Mass spectrum m/e 291 (M^+); IR (liquid film) 3270 (ν(NH)), 1659 (ν(C=O)), and 1281, 1215, 1180, and 1114 cm^{-1} (ν($CF_2CF_2CF_3$)); ^{1}H-NMR ($CDCl_3$) δ 10.96 (broad s, 1H, NH), 9.71 (s, 1H, CHO), 7.32 (m, 1H, α-H), 2.88 (q, 2H, $C\underline{H}_2CH_3$), and 1.27 (t, 3H, $CH_2C\underline{H}_3$); ^{19}F-NMR ($CDCl_3$) δ -78.8 (s, 3F, CF_3), -103.9, -125.0 (m, 2F, 2F, $C\underline{F}_2CF_2CF_3$ or $CF_2C\underline{F}_2CF_3$).

13) Compound 9: ^{1}H-NMR ($CDCl_3$) δ 8.87 (broad s, 1H, NH), 6.85 (m, 1H, α-H), 4.47 (s, 2H, $C\underline{H}_2OH$), 2.37 (q, 2H, $C\underline{H}_2CH_3$), and 1.10 (t, 3H, $CH_2C\underline{H}_3$).

14) Compound 10: ^{1}H-NMR ($CDCl_3$) δ 8.80 (broad s, 1H, NH), 6.93 (m, 1H, α-H), 4.63 (s, 2H, $C\underline{H}_2OH$), 2.43 (q, 2H, $C\underline{H}_2CH_3$), and 1.13 (t, 3H, $CH_2C\underline{H}_3$).

15) Compound 12: Mass spectrum m/e 1094 (M^+); IR (KBr) 3315 (ν(NH)), and 1232 and 1115 cm^{-1} (ν($CF_2CF_2CF_3$)); ^{1}H-NMR ($CDCl_3$) δ 10.47 (s, 4H, meso-H), 4.25 (q, 8H, $C\underline{H}_2CH_3$), 1.99 (t, 12H, $CH_2C\underline{H}_3$), -3.33 (s, 2H, NH); ^{19}F-NMR ($CDCl_3$) δ -78.2 (t, 12F, CF_3), -99.1, -122.8 (m, 8F, 8F, $C\underline{F}_2CF_2CF_3$ or $CF_2C\underline{F}_2CF_3$); Vis ($CHCl_3$) λ_{max} (ratios) 409 (17.0), 505 (1.0), 539 (0.39), 580 (0.36), 635 (0.14) nm.

16) It has been reported that four types of porphyrin isomers (Type I - IV) are formed in the cyclization reaction of α-hydroxymethylpyrrole in the presence of formic acid and formaldehyde dimethylacetal,[17] however, the reaction condition and electronic effect of the β-substituents are different from our case. No asymmetric porphyrin isomers have been found in our case under mild condition.

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