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Novel preparation of fluorinated isoindoles and their conversion to fluorinated benzoporphyrins

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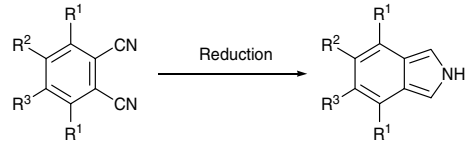
Abstract—4,5,6,7-Tetrafluoroisoindole and their related compounds were prepared directly from the corresponding phthalonitriles by reduction of a hydride reagent such as DIBAL or catalytic hydrogenation in the presence of an acid. 4,5,6,7-Tetrafluoroisoindole was converted to fluorinated benzoporphyrins.

Isoindole is a very important 10π aromatic heterocycle and has attracted much attention from synthetic and theoretical points of view.[1–3] Facile tautomerism of isoindole between 1*H*- and 2*H*-isomers is well known. The 1- and 3-positions of 2*H*-isoindole are very reactive toward electrophiles, while the 3-position of 1*H*-isoindole is highly electrophilic. Thus, self-condensation of isoindole between the tautomers easily occurs especially in solution. The parent isoindole was successfully prepared by flash vapor pyrolysis (600 °C) of the corresponding precursor.[4] Stabilization of isoindoles was effectively achieved by the introduction of substituents on the five-membered pyrrole moiety. Many successful methods for the preparation of such isoindole derivatives were reported and their strategies for the stabilization are as follows: fixation of the tautomerism to the 2*H*-isomer by N-substitution, substitution by bulky groups in order to protect these 1- and 3-positions sterically, and introduction of electron-withdrawing groups in order to lower the HOMO level.[5] Contrarily, successful preparations of 1,2,3-free isoindoles are limited to 5-pivaroyl-2*H*-isoindole[6] and 4,5,6,7-tetrahalo-2*H*-isoindoles.[4,7] In the former case, stabilization by hydrogen bonding in a solid state was suggested,[6] and HOMO levels of the latter were greatly lowered.[7]

During our continuous studies for the preparation and application of π-expanded porphyrins,[8] we became interested in the stable isoindoles especially 4,5,6,7-tetrafluoro-2*H*-isoindole[9] as a building block[10] for the preparation of polyfluorinated benzoporphyrins, because the polyfluorinated phthalocyanines can be applied to an n-type field effect transistor (FET).[11] Only one preparation method of 4,5,6,7-tetrafluoroisoindole based on the retro-Diels–Alder strategy has been reported so far.[4,8] This method, however, required multi-step conversion starting from the rather expensive materials such as bromopentafluorobenzene and *N*-benzylpyrrole. Since pyrroles were prepared by the reduction of malenonitrile derivative,[12] we thought this strategy might be applicable for the synthesis of 4,5,6,7-tetrafluoro-2*H*-isoindole from 3,4,5,6-tetrafluorophthalonitrile. This was really found to be the case. In this Letter, we report this new preparation method of 4,5,6,7-tetrafluoro-2*H*-isoindole.



(1)

1a: $R^1 = R^2 = R^3 = F$
1b: $R^1 = F$, $R^2 = R^3 = OC_6F_5$
1c: $R^1 = R^2 = F$, $R^3 = Cl$
1d: $R^1 = R^2 = R^3 = Cl$

2a: $R^1 = R^2 = R^3 = F$
2b: $R^1 = F$, $R^2 = R^3 = OC_6F_5$
2c: $R^1 = R^2 = F$, $R^3 = Cl$
2d: $R^1 = R^2 = R^3 = Cl$

Reduction of 3,4,5,6-tetrafluorophthalonitrile (**1a**) with DIBAL was conducted in toluene at 95 °C. After acidic

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quenching, a black reaction mixture was obtained. From the ^{19}F NMR, TLC [silica gel, $R_f = 0.45$ (30% EtOAc/hexane)] and GC analyses of the reaction mixture, formation of only one product was suggested (>98%). Chromatographic separation followed by sublimation, however, gave 4,5,6,7-tetrafluoro-2*H*-isoindole (**2a**) as colorless crystals in only 23% yield (Table 1, entry 1). From the sublimation residue, octafluoro-1,1′-biisoindole **3** was obtained in a small amount. In order to improve the yield, we tested other reduction conditions. The results are summarized in Table 1.

Reduction with borane gave a similar result (entry 3). Catalytic hydrogenation in the presence of one molar equivalent of sulfuric acid gave a better yield (41%, entry 5). Pentafluorophenoxy- and chloro-substituted fluorophthalonitriles **1b**, **c** were also employed for this conversion, and the corresponding 2*H*-isoindoles **2b** and **2c** were obtained (entries 8 and 9), although the yield of **2c** was quite low (13%). In the case of tetrachlorophthalonitrile **1d**, isoindole **2d** was detected immediately after column chromatography but it deteriorated very rapidly.

Table 1. Preparation of fluorinated isoindoles

Entry	Phthalonitrile	Reagents and conditions	Yield (%)
1	**1a**	DIBAL, toluene, 95 °C[a]	23
2	**1a**	DIBAL, toluene, rt[b]	20
3	**1a**	BH_3·THF, toluene, 65 °C	37
4	**1a**	BH_3·THF, toluene, rt	35
5	**1a**	H_2, Pd/C, H_2SO_4, MeOH, rt	41
6	**1a**	H_2, Pd/C, MeOH, rt	—[c]
7	**1a**	H_2, Pd/C, TFA, EtOAc, rt	33
8	**1b**	DIBAL, toluene, 95 °C	34
9	**1c**	DIBAL, toluene, 95 °C	13
10	**1d**	H_2, Pd/C, H_2SO_4, MeOH, rt	—[d]

[a] Acidic work-up (1.0 M HCl).
[b] Basic work-up (1.0 M NaOH).
[c] A complex mixture was obtained.
[d] See text.

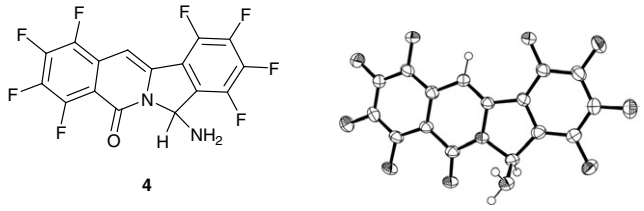
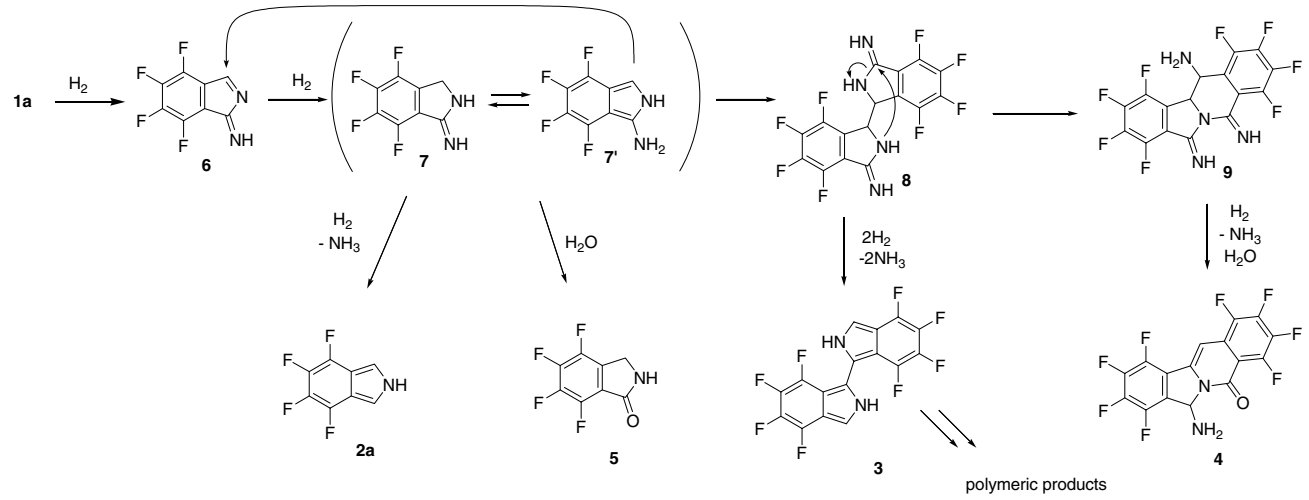


Figure 1. Chemical and Ortep drawings of by-product **4**.

What was formed from the rest of **1a** under the reduction conditions? In order to find other products, the silica gel used for the separation was thoroughly extracted with EtOAc and the extracted material was subject to MALDI-TOF MS. Peaks ($m/z > 500$) due to oligomeric products were found from $m/z = 561$ (corresponding to trimer) to ca. 2000 with intervals of 187 due to the tetrafluoroisoindole part. By the preparative GPC separation, one by-product was isolated, the structure of which was assigned as **4** by spectroscopic and finally X-ray analyses (Fig. 1).[21] When the reaction mixture was treated with acetic anhydride, 3-acetoxy-4,5,6,7-tetrafluoro-1*H*-isoindole was obtained in 4% yield. This by-product was thought to be formed by acetylation of 4,5,6,7-tetrafluorophthalide (**5**). The possible reaction routes to isoindole **2** and the by-products are illustrated in Scheme 1.

Although 4,5,6,7-tetrafluoro-2*H*-isoindole (**2a**) was stable and stored in the dark without any further precaution, it deteriorated during the work-up manipulation. We decided to carry out X-ray analysis of the sublimed sample of **2a**. The crystal packing diagram of **2a** is shown in Figure 2. The double NH–F interaction between NH proton and fluorine atoms at 5- and 6-positions [2.444(4) Å] connected 2*H*-isoindole molecules linearly, and a sheet formation was observed by additional similar interactions between proton and fluorine atoms at 1-, 3-, 4-, and 7-positions [2.524(4) Å]. Moreover, the molecules stacked in an anti-parallel fashion, and the distance of the mean planes was 3.421(5) Å. This crystal packing fixes the tautomers to 2*H*-isoindole and also prevents the attack of oxygen. Distinctive bond



Scheme 1. Possible reaction routes.

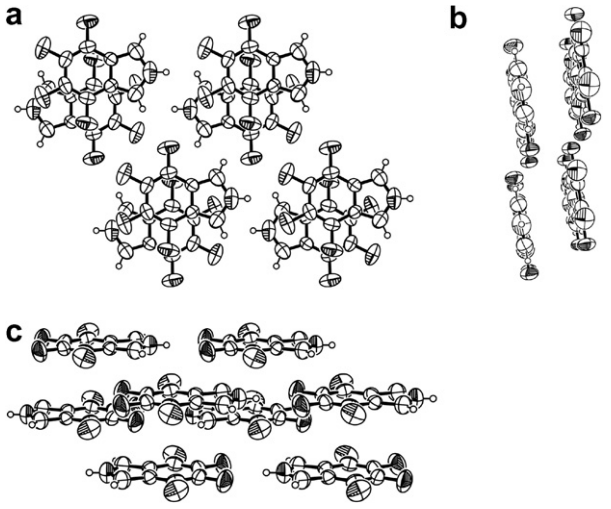
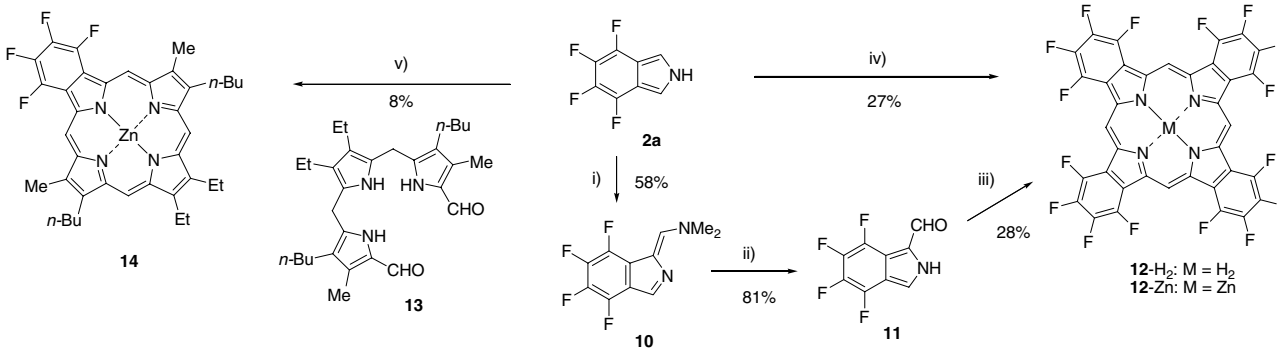


Figure 2. Crystal packing of 4,5,6,7-tetrafluoro-2*H*-isoindole **2a**. (a) View normal to (001); (b) view normal to (010); (c) view normal to (100).

alteration is observed even in the benzene ring; C^4–C^5(C^6–C^7) bonds [1.331(3) Å] are shorter than C^5–C^6 [1.411(4) Å] and C^{3a}–C^4 (C^7–C^{7a}) bonds [1.401(3) Å], and the inner bond (C^{3a}–C^{7a}) is extremely elongated to be 1.436(3) Å. A similar bond alteration was reported for 2*H*-isoindoles.[13–16]

Next, we aimed to prepare fluorinated benzoporphyrins. Remy reported the efficient preparation (57%) of hexadecafluorotetrabenzoporphyrin zinc complex **12**-Zn by condensation of **2a** and formaldehyde in the presence of zinc acetate at a high temperature (375 °C).[17] However, he just reported the UV data, and failed to provide any NMR data and correct MS spectra. He ascribed the failure to the formation of paramagnetic species during the reaction. Therefore, we investigated milder reaction conditions for the preparation of **12** (Scheme 2). The Vilsmeier reaction of **2a** gave 1-(*N*,*N*-dimethylaminomethylene)-1*H*-isoindole **10** in 58% yield. The isoindolenine structure (1*H*-isoindole) of **10** was unambiguously confirmed by the X-ray analysis.[21] Small bond alteration was observed in the benzo moiety [1.369(2)–1.415(2) Å]. Hydrolysis of **10** gave 2*H*-isoindole-1-carbaldehyde **11** in 81% yield. Reduction of **11** with DIBAL followed by acid treatment and oxidation afforded hexadecafluorotetrabenzoporphyrin **12**-H_2 in 28% yield. When isoindole **2a** was treated successively with the Eschenmoser reagent, zinc acetate, and DDQ, hexadecafluorotetrabenzoporphyrin zinc complex **12**-Zn were obtained in 27% yield. We also encountered the difficulty in the purification and identification of hexadecafluorotetrabenzoporphyrins **12** due to their highly stacking nature and easy colloidal formation. Purification of **12** was performed by washing with ethyl acetate, chloroform, methanol, and water. In C_5D_5N, on NMR spectra of **12**-Zn could be taken due to the colloidal



Scheme 2. Preparation of F_{16}-porphyrins. Reagents and conditions: (i) DMF, $POCl_3$; CH_2Cl_2, rt; aq-NaOAc; (ii) NaOH, EtOH, refl.; (iii) DIBAL, THF; HCl; AcOH, EtOH; Et_3N; DDQ; (iv) $Me_2N^+{=}CH_2{\cdot}I^-$, CH_3CN; $Zn(OAc)_2$, air; (v) **13**, TFA, CH_2Cl_2; $Zn(OAc)_2$; air.

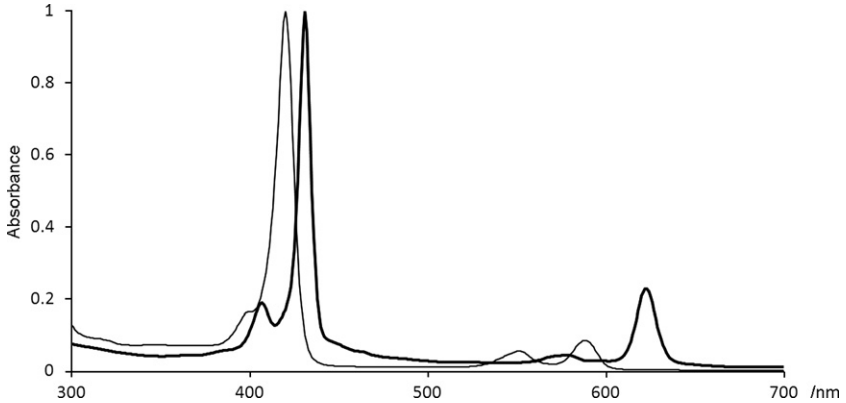


Figure 3. UV–vis spectra of **12**-Zn (bold line) in THF and **14** (solid line) in chloroform.

formation. Finally, fine ^{19}F NMR spectra of **12**-Zn was obtained in THF-d_8 [$\delta = -143.6$ (8F, m) and -154.8 (8F, m)]. The inverse [3+1] porphyrin synthesis[18] of **2a** with tripyrranedicarbaldehyde **13**[19] afforded tetrafluorobenzoporphyrin **14** in 8% yield. The UV–vis spectra of fluorinated benzoporphyrin zinc complexes **12**-Zn and **14** are shown in Figure 3. The Soret bands of **12**-Zn and **14** showed bathochromical shifts (5 nm for **12**-Zn and 12 nm for **14**) compared to the corresponding non-fluorinated benzoporphyrins.[20] Similar shifts were also observed in Q band absorptions.

In conclusion, we achieved the facile preparation of benzene-ring-fluorinated 2*H*-isoindoles by reduction of the corresponding phthalonitriles in one step, although the yields were rather low. Distinctive stability of 4,5,6,7-tetrafluoro-2*H*-isoindole in solid was rationalized by X-ray analysis. Utilization of 4,5,6,7-tetrafluoro-2*H*-isoindole for benzoporphyrin synthesis was done, and fluorinated benzoporphyrins were prepared.

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References and notes

1. For reviews, see: *'Comprehensive Heterocyclic Chemistry'*, *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2.
2. Bird, C. W. *Tetrahedron* **1992**, *58*, 335.
3. Chacko, E.; Bornstein, J.; Sadella, D. J. *Tetrahedron* **1979**, *35*, 1055.
4. Bornstein, J.; Remy, D. E.; Shield, J. E. *J. Chem. Soc., Chem. Commun.* **1972**, 1149; Bornstein, J.; Remy, D. E.; Shields, J. E. *Tetrahedron Lett.* **1974**, 4247.
5. Donohoe, T. J. 1*H*- and 2*H*-isoindoles. In *Hetarenes and Related Ring Systems, Fused Five-Membered Hetarenes with One Heteroatom*; Thomas, E. J., Ed.; Science of Synthesis; George Thieme Verlag: Stuttgart, 2000; Vol. 10.14, p 654.
6. Kreher, R.; Kohl, N.; Use, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 621.
7. Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003, From our simple calculation (MOPAC PM3), the HOMO levels of indole and tetrafluoroisoindole **1a** were -8.02 and -8.75 eV, respectively.
8. Anderson, P. S.; Christy, M. E.; Engelhardt, E. L.; Lundell, G. F.; Ponticello, G. S. *J. Heterocycl. Chem.* **1977**, *14*, 213.
9. For a recent example, see: Uno, H.; Nakamoto, K.; Kuroki, K.; Fujimoto, A.; Ono, N. *Chem. Eur. J.* **2007**, *13*, 5773–5784.
10. Warrener, R. N.; Butler, D. N. *Aldrichim. Acta* **1997**, *30*, 119.
11. Huang, C.; Katz, H.; West, J. E. *J. Appl. Phys.* **2006**, *100*, 114512/1–114512/9; de Oteyza, D. G.; Barrena, E.; Osso, J. O.; Dossch, H.; Meyer, S.; Pflaum, J. *Appl. Phys. Lett.* **2005**, *87*, 183504/1–183504/3.
12. Schwenninger, R.; Ramondenc, V.; Wurst, K.; Schlöl, J.; Kräutler, B. *Chem. Eur. J.* **2000**, *6*, 1214.
13. Bonnett, R.; Hursthouse, M. B.; North, S. A.; Trotter, J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 833.
14. Bonnett, R.; Hursthouse, M. B.; North, S. A.; Trotter, J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 293.
15. Murashima, T.; Tamai, R.; Nishi, K.; Nomura, K.; Fujita, K.; Uno, H.; Ono, N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 995.
16. Takahashi, I.; Tsuzuki, M.; Keumi, T.; Kitajima, H.; Isa, K.; Hosoi, S.; Tsuda, Y. *Chem. Pharm. Bull.* **1994**, *42*, 947.
17. Remy, D. E. *Tetrahedron Lett.* **1983**, *24*, 1451.
18. Uno, H.; Masumoto, A.; Ono, N. *J. Am. Chem. Soc.* **2003**, *125*, 12082; Sessler, J. L.; Johnson, M. R.; Lynch, V. *J. Org. Chem.* **1987**, *52*, 4394; Shevchuk, S. V.; Davis, J. M.; Sessler, J. L. *Tetrahedron Lett.* **2001**, *42*, 2447.
19. Uno, H.; Nakamoto, K.; Kuroki, K.; Fujimoto, A.; Ono, N. *Chem. Eur. J.* **2007**, *13*, 5773.
20. Ito, S.; Ochi, N.; Murashima, T.; Uno, H.; Ono, N. *Heterocycles* **2000**, *52*, 399; Itoh, T.; Murashima, T.; Uno, H.; Ono, N. *J. Chem. Soc., Chem. Commun.* **1998**, 1661.
21. *Crystallographical data for* **4**: $C_{16}H_4F_8N_2O$; FW = 392.21, colorless prisms, $0.20 \times 0.15 \times 0.05$ mm, monoclinic, $P2_1/c$ (#14), $Z = 4$ in a cell of dimensions $a = 4.6394(17)$ Å, $b = 24.603(8)$ Å, $c = 11.746(4)$ Å, $\beta = 98.349(3)°$, $V = 1326.5(8)$ Å^3, $D_{calc} = 1.964$ g cm^{-3}, Mo Kα, $F(000) = 776$, $T = 150$, 2997 unique reflections, 2342 with $F^2 > 2\sigma(F^2)$. The final $R_1 = 0.084$, $wR_2(\text{all}) = 0.211$, goodness-of-fit = 1.013 for 259 parameters refined on F^2, CCDC No. 635797. **2a**: $C_8H_3F_4N$; FW = 189.11, colorless blocks, $0.50 \times 0.16 \times 0.16$ mm, monoclinic, $C2/c$ (#15), $Z = 4$ in a cell of dimensions $a = 13.297(10)$ Å, $b = 8.546(6)$ Å, $c = 7.204(5)$ Å, $\beta = 117.305(4)°$, $V = 727.4(9)$ Å^3, $D_{calc} = 1.727$ g cm^{-3}, Mo Kα, $F(000) = 376$, $T = 298$, 832 unique reflections, 341 with $F^2 > 2\sigma(F^2)$. The final $R_1 = 0.062$, $wR_2(\text{all}) = 0.143$, goodness-of-fit = 1.00 for 67 parameters refined on F^2, CCDC No. 635798. **10**: $C_{11}H_8F_4N_2$; FW = 244.19, grey platelet, $0.50 \times 0.50 \times 0.20$ mm, monoclinic, $P2_1/c$ (#14), $Z = 4$ in a cell of dimensions $a = 6.681(2)$ Å, $b = 19.699(7)$ Å, $c = 7.723(3)$ Å, $\beta = 101.598(2)°$, $V = 995.6(6)$ Å^3, $D_{calc} = 1.629$ g cm^{-3}, Mo Kα, $F(000) = 376$, $T = 150$, 2280 unique reflections, 2073 with $F^2 > 2\sigma(F^2)$. The final $R_1 = 0.038$, $wR_2(\text{all}) = 0.103$, goodness-of-fit = 1.05 for 155 parameters refined on F^2, CCDC No. 652719.