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A convenient preparation of 2,3,5,6-tetrafluoro-4-iodo-benzaldehyde and its application in porphyrin synthesis

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Abstract

An efficient synthesis of 2,3,5,6-tetrafluoro-4-iodo-benzaldehyde (**1**) is presented. This new compound was readily obtained via iodination at low temperature of the lithio derivative of 2-(2,3,5,6-tetrafluoro-phenyl)-[1,3]dioxolane (**4**). The crystal structure of **1** consists of linear polymeric chains, with non-covalent O $\cdots$ I bonding as the directing interaction, responsible for the observed assembly. Aldehyde **1** is further employed in the synthesis of 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (**6**), a potential precursor of supramolecular assemblies.

Keywords: Iodo-perfluorocarbons; Porphyrins; Self assembly; Halogen bonds

1. Introduction

Iodoperfluorocarbons have been successfully used in the synthesis of intermolecular aggregates by self-assembly with N- or O-containing electron donor molecules via the formation of relatively strong donor $\cdots$ iodine non-covalent bonds [1]. From this viewpoint, 5,10,15,20-tetrakis(2,3,5,6-tetrafluoro-4-iodo-phenyl)porphyrin (**6**) appeared to be particularly attractive as a precursor to multiporphyrin arrays. For the preparation of this porphyrin using classic procedures, we needed 2,3,5,6-tetrafluoro-4-iodo-benzaldehyde (**1**).

Unlike pentafluorobenzaldehyde, which has been widely used for the synthesis of *meso*-pentafluorophenyl-substituted porphyrins (see for example: [2]) and various porphyrinoids (see for example: [3]), aldehyde **1** was hitherto unreported. In this paper, we describe an efficient route to this new compound and its use in the preparation of porphyrin **6**.

2. Results and discussion

2.1. Aldehyde synthesis

Examination of the literature indicated that very few potential precursors of the target compound **6**, for example acid derivatives potentially reducible to aldehyde [4], were available. However, a recent paper on the synthesis of tetrafluorobenzene derivatives designed for the preparation of conducting polymers [5] gave us a valuable starting point for the synthesis of **1**. The short route developed is outlined in Scheme 1. The commercially available starting material 1,2,4,5-tetrafluorobenzene (**2**) was lithiated using *n*-BuLi in THF at dry ice temperatures. Efficient formylation was performed with excess of ethyl formate, leading to 2,3,5,6-tetrafluorobenzaldehyde (**3**) which was subsequently protected by forming the acetal **4** [6]. Lithiation of compound **4** in the same conditions as for **2** and subsequent iodination of the lithio derivative at ca. −70 °C led to the 4-iodo acetal **5**. The cleavage of the protecting group was performed in warm aqueous acidic medium (mixture of trifluoroacetic and hydrochloric acids), affording the desired aldehyde **1** which was recrystallized from chloroform.

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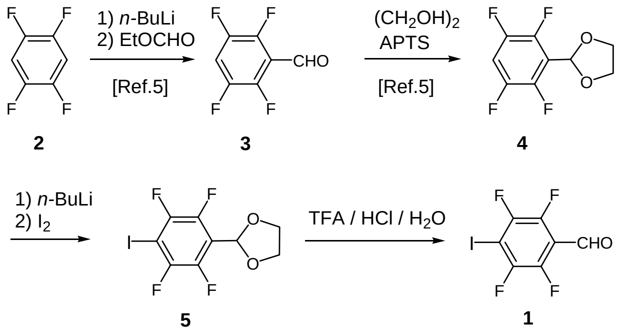
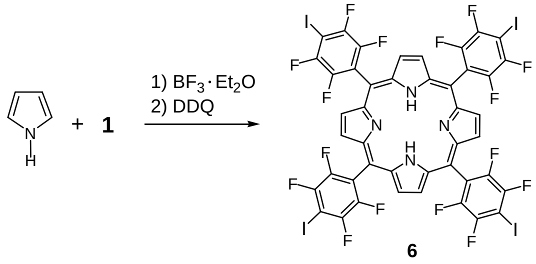


Scheme 1.

The crystal structure of **1** consists of linear polymeric chains, seemingly suggesting the O···I intermolecular bonding as the directing interaction (Fig. 1). To our knowledge, it is the first time that such a interaction between an aldehyde function and a iodoperfluorocarbon has been reported. Both the carbonyl oxygen and the iodine are involved in the halogen bonding as terminal lone pair donor and the most exposed electron acceptor site, respectively. This conclusion can be drawn from the O···I distance (2.95 Å) which is significantly shorter (by ca. 17%) than the sum of the van der Waals radii of oxygen and iodine [7]. The nearly linear arrangement of O···I–C (O–I–C angle = 175.9°) is consistent with the $n \rightarrow \sigma^*$ character of the halogen bonding [8]. The observed values are within the range of the values reported in the literature for non-covalent O···I–C bonds [9]. 4-Iodobenzaldehyde, the hydrogen analogue of **5**, shows also non-covalent halogen bonding with only a slightly longer O···I distance (3.07 Å) [10].

2.2. Porphyrin synthesis

The porphyrin **6** was prepared readily by the acid-catalyzed condensation of aldehyde **1** with pyrrole following the synthetic procedure developed by Lindsey et al. [11], except that the ‘‘catalyst’’ BF_3 etherate was used in more than the stoichiometric amount (Scheme 2). Oxidation of the porphyrinogen was performed after 1 h with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Porphyrin **6** was isolated after flash column chromatography as a dark-brown solid in 17% yield [12]. Its structure has been confirmed by ^{1}H and ^{19}F NMR, UV-Vis and high resolution mass spectroscopy. The porphyrin **6** bearing four tetrafluoro-monoiodo phenyl groups, represents a two-dimensional building block with electron acceptor sites in the four directions of the macrocycle plane, well suited for the elaboration of multiporphyrin arrays via self assembly. In this light, the spontaneous formation of non-covalent halogen bonds within the crystal structure of the aldehyde **1** is an encouraging observation (Scheme 2).



Scheme 2.

3. Conclusion

We have presented a short organometallic route to the previously unknown 2,3,5,6-tetrafluoro-4-iodo-benzaldehyde (**1**), starting from 1,2,4,5-tetrafluorobenzene (**2**). This new, polyfunctional compound, has been successfully used in the synthesis of the new porphyrin **6**, a potential precursor of supramolecular assemblies. Additionally, both derivatives **1** and **6** are potentially usable for further applications, e.g. palladium-catalyzed coupling reactions such as Sonogashira (see for example: [13]) or Heck (see for example: [14]), which makes them valuable precursors for the synthesis of fluorinated derivatives.

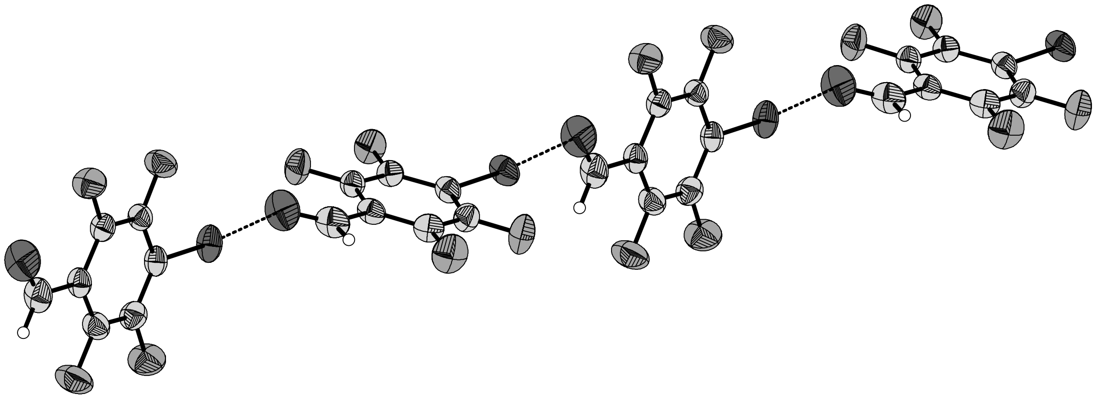


Fig. 1. One-dimensional chain fragment of aldehyde **1** with non-covalent O···I bonds as the directing interaction.

4. Experimental

NMR spectra were recorded on a Bruker AC 250 spectrometer. ^{1}H NMR chemical shifts are reported using the residual protiochloroform as reference (7.24 ppm). ^{19}F NMR chemical shifts are given relative to internal $CFCl_3$ as reference. ^{13}C NMR chemical shifts are reported using $^{13}CDCl_3$ as reference (77.0 ppm). Mass spectra were recorded on a Jeol JMS-700 spectrometer. IR spectra were recorded on a Tensor 27 (Miracle Ge) spectrometer and the UV-Vis spectra on a Beckmann DU 7400 spectrophotometer. Elemental analyses were conducted by the Service de Microanalyse, CNRS (Gif-sur-Yvette and Lyon).

*4.1. 2-(2,3,5,6-Tetrafluoro-4-iodo-phenyl)-[1,3]dioxolane (**5**)*

A dry 100 mL four-necked flask under argon, equipped with a magnetic stir bar and a dropping funnel, was charged with dry THF (22 mL) and acetal **4** [5] (1.50 g, 6.75 mmol). The solution was cooled to ca. -72 °C and *n*-BuLi (4.25 mL, 1.75 M, 7.44 mmol) was added via syringe in ca. 10 min (temperature was kept below -60 °C) giving a yellow gold solution. After 1 h at -72 °C, a solution of iodine (1.88 g, 7.41 mmol) in dry THF (6 mL) was added dropwise via the funnel. Concomitant rapid fading of the brown solution occurred while keeping the temperature below ca. -65 °C. At the end of the addition the light yellow solution was allowed to reach rt then washed with saturated aqueous $NaHCO_3$ (5 mL). After separation, THF (10–20 mL) was added to the organic phase which was washed with 0.5 M aqueous $Na_2S_2O_3$ (5 mL). Brine (10 mL) was added to the mixture making decantation easier. After drying over $MgSO_4$, evaporation of the solvent afforded an off white solid (2.21 g) which was recrystallized at -20 °C from boiling *n*-pentane (40 mL) to yield **5** as colourless small plates (1.54 g, 4.42 mmol, 66%), m.p. 106.5–107 °C. A second crop was obtained from the mother liquor (0.2 g, total isolated yield 74%): ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 3.97–4.09 (m, 2H, CH_2), 4.13–4.25 (m, 2H, CH_2), 6.21 (s, 1H, CH); ^{19}F NMR (235 MHz, $CDCl_3$): δ -120.9 (m, 2F), -142.9 (m, 2F); ^{13}C NMR (63 MHz, $CDCl_3$): δ 66.1 (s, CH_2), 73.7 (t, $J = 28$ Hz, C-3), 96.8 (m, CH), 117.9 (t, $J = 13$ Hz, C-6), 144.6 (dm, $J = 256$ Hz, C-2), 147.2 (dm, $J = 245$ Hz, C-3); MS ($CI + NH_3$): *m/z* 348 $[M]^+$. Anal. calcd. for $C_9H_5IF_4O_2$: C, 31.1; H, 1.45; F, 21.9; I, 36.5. Found: C, 31.1; H, 1.45; F, 21.8; I, 36.0.

*4.2. 2,3,5,6-Tetrafluoro-4-iodo-benzaldehyde (**1**)*

The acetal **5** (0.80 g, 2.3 mmol) was dissolved under stirring in trifluoroacetic acid (2.5 mL). To the solution, water (7 mL) was added, followed by hydrochloric acid (1.5 mL, 37%), giving a white precipitate. The mixture was heated at 65–70 °C for 90 min. After cooling, the suspension was extracted with chloroform (3×10 mL) and the organic phase washed with water (10 mL) then brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent furnished aldehyde **1** as an off-white powder (0.62 g, 2.04 mmol, 89%). Sublimation of the product at 70–80 °C under 1 mmHg gave slightly more pure compound **1** (0.56 g): m.p. 130.5–131.5 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.28 (s); ^{19}F NMR (235 MHz, $CDCl_3$): δ -117.8 (m, 2F), -143.2 (m, 2F); ^{13}C NMR (63 MHz, $CDCl_3$): δ 80.7 (t, $J = 27.7$ Hz, C-4), 115.3 (t, $J = 10$ Hz, C-1), 145.5 (dm, $J = 266$ Hz, C-2), 147.2 (dm, $J = 248$ Hz, C-3), 181.9 (quint, $J = 3$ Hz, CHO); IR (neat): ν 1693(s), 1655(m), 1630(w), 1472(s), 1440(m), 1415(m), 1284(w), 1266(m), 1032(m), 962(m), 768(w) cm^{-1}; MS (EI) *m/z* (rel. int.): 304 $[M]^+$ (100), 303 $[M–H]^+$ (48), 275 $[M–H–CO]^+$ (5), 148 $[M–H–CO–I]^+$ (9). Anal. calcd. for C_7HIF_4O: C, 27.7; H, 0.3; F, 25.0; I, 41.7. Found: C, 27.8; H, 0.4; F, 24.95; I, 41.7.

*4.3. 5,10,15,20-Tetrakis(2,3,5,6-tetrafluoro-4-iodo-phenyl)porphyrin (**6**)*

The aldehyde **1** (0.354 g, 1.16 mmol), pyrrole (0.081 mL, 1.16 mmol) and dichloromethane (125 mL) were placed under argon in a 250 mL round-bottom flask equipped with a magnetic stirring bar. The mixture was stirred while BF_3 etherate (0.5 mL, 3.95 mmol) was added at once via a syringe. After 1 h, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.55 g) then pyridine (1.6 mL) were added. The reaction mixture was stirred overnight (12–15 h) then filtered through a short silica gel column using dichloromethane as eluent. After evaporation of the solvent, the resulting brown solid was purified by flash column chromatography (50 mm × 200 mm column, Merck 9385 silica gel, 40–63 μm) with chloroform as eluent. The head fraction ($R_f \approx 0.90$ by TLC) was collected and evaporated affording porphyrin **6** as a dark-brown solid (0.070 g, 0.050 mmol, 17%): ^{1}H NMR (250 MHz, $CDCl_3$): δ -2.92 (s, 2H, NH), 8.91 (s, 8H, β-H); ^{19}F NMR (235 MHz, $CDCl_3$): δ -120.3 ($\approx$q, 2F, $J = 12$ Hz), -135.6 ($\approx$q, 2F, $J = 12$ Hz); UV-Vis (CH_2Cl_2): λ_{max} (nm) 415, 508, 584. HRMS ($CI + NH_3$) calcd. for $C_{44}H_{11}F_{16}I_4N_4$ ($M + H$) 1406.6900. Found 1406.6896.

*4.4. Crystal data for compound **1***

On cooling at -20 °C, a chloroform solution of aldehyde **1** afforded tabular single crystals. Crystal data were collected on an Enraf Nonius Kappa CCD diffractometer at 293 K using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å, and ω scans). The structure was solved by direct methods and refined by full-matrix least-squares refinement on F^2 using the program SHELX-97 [15]. Non-hydrogen atoms were refined anisotropically. The hydrogen atom, observed via the difference Fourier map, was placed in geometrically calculated positions and included in the final refinement using the “riding” model with isotropic temperature factors fixed at 1.2-times that of the parent atom.

Crystallographic data for compound **1**: emp. formula C_7HF_4IO; $M = 303.98$; monoclinic; space group $P21/c$; $a = 5.9517(12)$, $b = 8.5832(17)$, $15.831(3)$ Å; $\beta = 91.44(3)$; $V = 808.5(1)$; $Z = 4$; $\rho_{calc} = 2.497$ g cm^{-3}; 9218 collected reflections; 3667 unique reflections. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-229878. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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