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AROMATIC POLYFLUORO- COMPOUNDS—XXXVIII[1]

1,2,3,4-TETRAFLUORODIBENZOFURAN AND SOME NUCLEOPHILIC REPLACEMENT REACTIONS

P. J. N. Brown, R. Stephens and J. C. Tatlow
Department of Chemistry, The University, Edgbaston, Birmingham, 15

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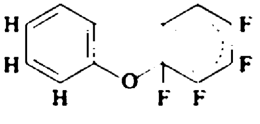
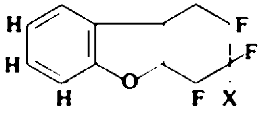
Abstract—1,2,3,4-Tetrafluorodibenzofuran has been prepared from hexafluorobenzene and *o*-lithioanisole *via* 2'-hydroxy-2,3,4,5,6-pentafluorobiphenyl which undergoes an intramolecular nucleophilic substitution reaction with potassium carbonate in dimethyl formamide. 1,2,3,4-Tetrafluorodibenzofuran undergoes nucleophilic substitution reactions with sodium hydrogen sulphide, sodium thiomethoxide and LAH involving replacement of the 3-fluorine atom; this was established by reference to an Ullmann reaction between *o*-bromo-anisole and bromo-2,3,5,6-tetrafluorobenzene.

HEXAFLUOROBENZENE is readily phenylated with phenyl-lithium in ether.[2] The general applicability of this process has now been indicated by its extension to a substituted phenyl-lithium, *viz.* 2-methoxyphenyl-lithium (I), which reacted vigorously with hexafluorobenzene in ether to give 2'-methoxy-2,3,4,5,6-pentafluorobiphenyl (II) and the suspected 2,2''-dimethoxy-2',3',5',6'-tetrafluoroterphenyl.

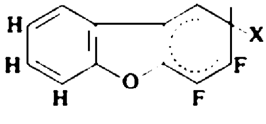
Demethylation of 2'-methoxy-2,3,4,5,6-pentafluorobiphenyl (II) with aluminium chloride gave the phenol III which was characterized as its benzoate. The phenol III underwent a facile intramolecular replacement reaction[3] of the 2-fluorine atom when heated under reflux in dimethylformamide (DMF) containing potassium carbonate to give 1,2,3,4-tetrafluorodibenzofuran (IV). Intermolecular replacement products[3] were not detected and the unrecrystallized dibenzofuran (85%) displayed an IR spectrum identical to that of an analytically pure specimen. This unusually high '*ortho*-substitution'[4] presumably results from the very favourable steric factor associated with the 5-membered ring of the Wheland-type intermediate V.



(V)



XIII



XIV

1,2,3,4-Tetrafluorodibenzofuran (IV) was characterized by elemental analysis, IR, UV and NMR spectroscopy and mass spectrometry. Some nucleophilic replacement reactions of IV were undertaken as part of our general study of such reactions;[4]

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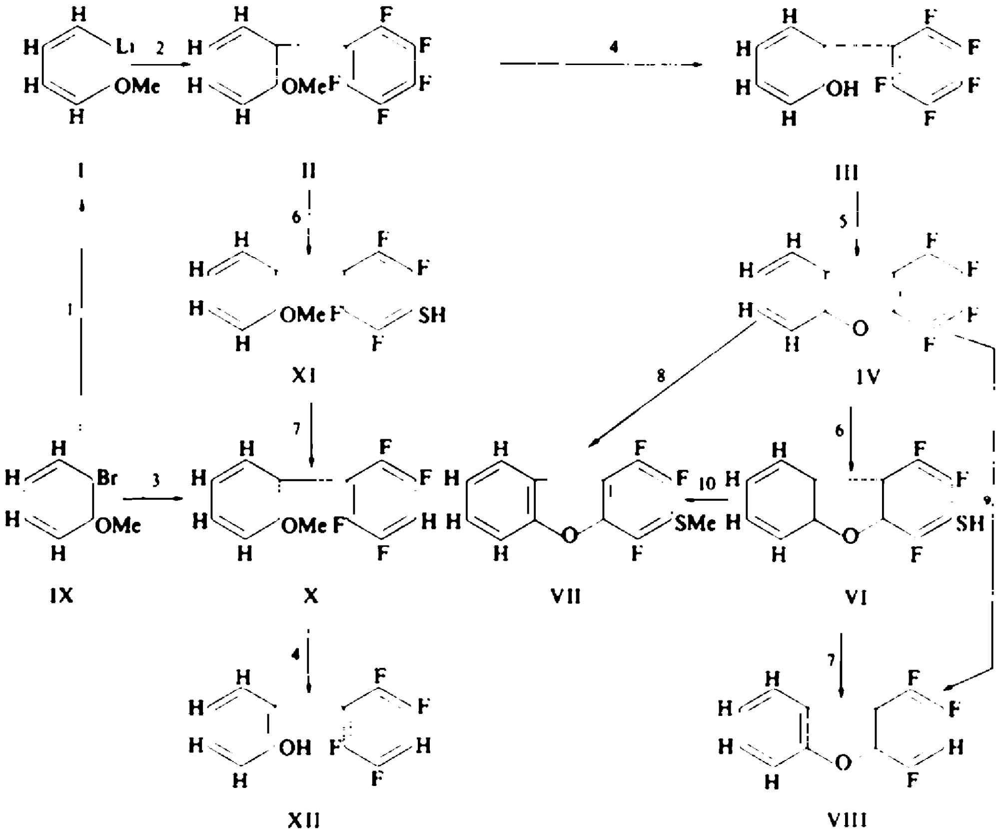
[1] Part XXXVII, P. L. Coe, A. E. Jukes and J. C. Tatlow, *J. Chem. Soc.* (C), 2323 (1966).

[2] M. T. Chaudhry and R. Stephens, *J. Chem. Soc.* 4281 (1963).

[3] J. Burdon, V. A. Damodaran and J. C. Tatlow, *J. Chem. Soc.* 763 (1964).

[4] J. C. Tatlow, *Endeavour* 22, 89 (1963).



Reagents: 1, Li in Et$_2$O; 2, C$_6$F$_6$ in Et$_2$O; 3, 4H-C$_6$F$_4$Br/Cu; 4, AlCl$_3$; 5, K$_2$CO$_3$ D.M.F.; 6, NaSH D.M.F.; 7, Ni; 8, MeSNa/MeOH; 9, LiAlH$_4$ in Et$_2$O; 10, CH$_2$N$_2$.

comparison with the recently reported[5] substitution reaction of octafluorodibenzothiophen is of interest.

1,2,3,4-Tetrafluorodibenzofuran (IV) and a large excess of sodium hydrogen sulphide in DMF gave 3-mercapto-1,2,4-trifluorodibenzofuran (VI) and its disulphide. The latter was prepared from VI with bromine in acetic acid and by aerial oxidation at 100°; it was readily reduced to the mercaptan VI with zinc dust in acetic acid. When the crude mixture of VI and its disulphide was treated with diazomethane in ether and the methylated product examined by ^{1}H NMR spectroscopy only a triplet centred at 7·44 τ was detected in the range associated with the $-SCH_3$ group. It was thus reasonable to assume that only one mercaptotrifluorodibenzofuran (VI) was formed. The same 3-methylthio-1,2,4-trifluorodibenzofuran (VII) was obtained also from 1,2,3,4-tetrafluorodibenzofuran (IV) and sodium thiomethoxide in methanol; the sulphide VII prepared by both routes gave a sulphone with hydrogen peroxide in acetic acid. The mercaptan VI was desulphurized by Raney nickel to give 1,2,4-trifluorodibenzofuran (VIII).

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[5] R. D. Chambers and J. A. Cunningham, *Chem. Comm.* 469 (1966).

^{19}F NMR spectroscopy on the above products,[6] VI, VII and VIII, confirmed that one fluorine had been replaced but the position of replacement could not be determined conclusively. Instead the orientations given were established by reference to the product of an Ullmann reaction between *o*-bromoanisole (IX) and bromo-2,3,5,6-tetrafluorobenzene, which gave 2′-methoxy-2,3,5,6-tetrafluorobiphenyl (X) as well as 2,2′-dimethoxybiphenyl. The former compound X was obtained in better yield from the desulphurization of 2′-methoxy-4-mercapto-2,3,5,6-tetrafluorobiphenyl (XI) which was produced from II and sodium hydrogen sulphide in DMF. Demethylation of X with aluminium chloride gave 2′-hydroxy-2,3,5,6-tetrafluorobiphenyl (XII) which underwent an intramolecular replacement reaction with potassium carbonate in DMF to give 1,2,4-trifluorodibenzofuran (VIII).

A very sluggish reaction was observed between 1,2,3,4-tetrafluorodibenzofuran (IV) and LAH in ether heated under reflux. However, after 156 hr, it was approximately half-converted into the expected 1,2,4-trifluorodibenzofuran (VIII).

The nucleophilic replacement of the 3-fluorine atom in 1,2,3,4-tetrafluorodibenzofuran is consistent with general orientation effects observed previously in polyfluoroaromatic compounds.[4] Thus, the Wheland-type intermediate XIII should be preferred to XIV, since the former has the greater degree of delocalization and none of the destabilization associated with an oxygen-substituted carbanion as in XIV.

In view of the bactericidal activity of some substituted dibenzofurans, 1,2,4-trifluoro- and 1,2,3,4-tetrafluoro-dibenzofuran were tested for antibacterial activity, but both compounds were inactive against *Staphylococcus aureus*, *Streptococcus faecalis*, *Klebsiella aerogenes* and *Escherichia coli* in tests made on serial two fold dilutions in a range 1000 µg/ml to 0·121 µg/ml.

EXPERIMENTAL

2′-Methoxy-2,3,4,5,6-pentafluorobiphenyl (II) *and 2,2″-dimethoxy-2′,3′,5′,6′-tetrafluoroterphenyl*

o-Bromoanisole (20·01 g) in diethyl ether (30 ml) was added to Li metal (2·29 g) in ether (20 ml) under N_2 at such a rate that a moderate reflux was maintained. When reaction was complete the mixture was filtered through glass wool and the filtrate diluted with ether (350 ml) and then added dropwise during 100 min to a stirred soln of hexafluorobenzene (20·03 g) in ether (300 ml) under N_2. When the exothermic reaction had subsided stirring was continued for 1 hr and the mixture then poured into water (700 ml). The dried ($MgSO_4$) ether soln was filtered and evaporated to give a liquid which was shown by GPC (silicone gum/celite, 150°, N_2 1 l./hr) to contain *o*-bromoanisole, anisole and one other component which was separated by distillation to give *2′-methoxy-2,3,4,5,6-pentafluorobiphenyl* (19·18 g) m.p. 46–47·5° from perfluoro-1,3-dimethylcyclohexane. (Found: C, 56·9; H, 2·5. $C_{13}H_7F_5O$ requires: C, 56·9; H, 2·6%.) Ether was added to the solid residue from the latter distillation and the insoluble material (0·25 g) m.p. 192–193·5 was recrystallized from a MeOH–acetone mixture to give *2,2″-dimethoxy 2′,3′,5′,6′-tetrafluoroterphenyl* (0·15 g) m.p. 198–199°. (Found: C, 66·6; H, 4·1. $C_{20}H_{14}F_4O_2$ requires: C, 66·3; H, 3·9%.)

2′-Hydroxy-2,3,4,5,6-pentafluorobiphenyl

An intimate mixture of $AlCl_3$ (7·40 g) and II (5·05 g) was kept at 120° for 1 hr. The cooled mixture was added to water (100 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The extracts were dried ($MgSO_4$), filtered and evaporated to leave a solid which was sublimed at a reduced press (15 mm) to give *2′-hydroxy-2,3,4,5,6-pentafluorobiphenyl* (3·94 g) m.p. 94·5–95·5°. (Found: C, 55·4; H, 2·1. $C_{12}H_5F_5O$ requires: C, 55·4; H, 1·9%.) ν_{max} 3603 cm^{-1} (—OH) in CCl_4. The phenol (0·50 g), in acetone (2 ml) benzoyl chloride (1 ml) and 10% NaOHaq (25 ml) were shaken together to give the *benzoate* m.p. 57–59°. (Found: C, 62·4; H, 2·5. $C_{19}H_9F_5O_2$ requires: C, 62·6; H, 2·5%.)

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[6] P. J. N. Brown and E. F. Mooney, *Tetrahedron* 23, 4047 (1967).

1,2,3,4-*Tetrafluorodibenzofuran* (IV)

Potassium carbonate (1·00 g), 2′-hydroxy-2,3,4,5,6-pentafluorobiphenyl (1·00 g) and DMF (50 ml) were heated under reflux for 4½ hr and then water (400 ml) was added. The ppt (0·78 g), m.p. 96–98°, was washed with water (400 ml) dried and a portion (0·50 g) recrystallized from MeOH to give the furan (0·27 g) m.p. 98·5–99·5° and then a portion (0·16 g) of this was recrystallized from petrol (b.p. 60–80°) to give 1,2,3,4-*tetrafluorodibenzofuran* (0·04 g) m.p. 100–101°. (Found C, 60·0; H, 1·6. $C_{12}H_4F_4O$ requires: C, 60·0; H, 1·7%.) ν_{max} 1530 and 1492 cm^{-1} (fluorinated aromatic ring), λ_{max} 2510, 2740, 2880, and 3000 Å (ε, 6·6, 7·6, 4·2, and 4·4 × 10^3, respectively; in hexane), mass spectrometry gave a large peak at 240 ($C_{12}H_4F_4O$).

3-*Mercaptor*-1,2,4-*trifluorodibenzofuran* (VI)

A soln of IV (4·72 g) in DMF (80 ml) was added dropwise during 100 min to a vigorously stirred suspension of NaHS (6·50 g) in DMF (240 ml) at room temp. After 35 min stirring and 20 hr at room temp, the mixture was poured into 1·3N HCl (750 ml) and extracted with ether (3 × 100 ml). The combined extracts were evaporated and the residue was added to 1·3N HCl (300 ml) and extracted with ether (3 × 100 ml), dried ($MgSO_4$), filtered and evaporated to give a yellow solid (5·02 g). After 48 hr at room temp the latter solid was shaken with ether (100 ml) and filtered to give the *disulphide* of VI (0·41 g) m.p. 191–201°. (Found: C, 56·6; H, 1·7. $C_{24}H_8F_6O_2S_2$ requires: C, 56·9; H, 1·6%.) The filtrate was evaporated and a portion (1·22 g) of the residue was sublimed at a reduced press (15 mm) to give 3-*mercapto*-1,2,4-*trifluorodibenzofuran* (0·40 g) m.p. 71–73°. (Found: C, 56·4; H, 1·9. $C_{12}H_5F_3OS$ requires: C, 56·7; H, 2·0%.) ν_{max} 2600 (–SH) and 1500 cm^{-1} (fluorinated aromatic ring). The residue from the sublimation gave the disulphide (0·13 g) m.p. 200·5–203·5° from acetone. (Found: C, 56·8; H, 1·6%.)

Compound VI (0·10 g) and Br_2 (0·32 g) in glacial AcOH (5 ml) at room temp immediately gave a ppt which was collected after 1 hr and shown by IR spectroscopy to be the disulphide (0·10 g).

When kept for 48 hr at 100° in an open tube VI (0·02 g) was partly converted into the disulphide (50%) as shown by IR spectroscopy.

The above disulphide (0·10 g), Zn powder (5·0 g) and glacial AcOH (50 ml) were kept at 118° for 3 hr and the mixture extracted with ether in the presence of conc. HCl (50 ml) to afford VI (0·10 g) containing a small amount of the disulphide, as shown by IR spectroscopy.

3-*Methylthio*-1,2,4-*trifluorodibenzofuran* (VII)

(a) A portion (1·01 g) of the crude reaction product from IV and NaHS was dissolved in ether and added at 0° to ethereal diazomethane prepared from methyl nitrosourea (3·0 g). After 1 hr at 15° the mixture was diluted with ether, dried ($MgSO_4$), filtered and evaporated to a solid (1·01 g) which displayed a ^{1}H NMR spectrum consisting of a triplet (J_{HF} 0·7 c/s) centred at 7·44 τ. A portion (0·41 g) of the latter solid was sublimed at a reduced press (15 mm) to give 3-*methylthio*-1,2,4-*trifluorodibenzofuran* (0·24 g) m.p. 79–81° from petrol b.p. 60–80°. (Found: C, 58·0; H, 2·6. $C_{13}H_7F_3OS$ requires: C, 58·2; H, 2·6%.) A second portion (0·25 g), H_2O_2 (1·25 ml; 30% w/w) and glacial AcOH (2·5 ml) were kept at 100° for 3 hr to give the *sulphone* (0·17 g) m.p. 187–190°. (Found: C, 51·7; H, 2·4. $C_{13}H_7F_3O_3S$ requires: C, 52·0; H, 2·4%.)

(b) Sodium (0·03 g) was added to dry MeOH (15 ml) and an excess of methanethiol passed through the soln. The latter soln was added to IV (0·30 g) in dry MeOH (15 ml) and the mixture heated under reflux for 22½ hr, poured into 1·3N HCl (300 ml) and extracted with ether (3 × 100 ml). The combined ether extracts were dried ($MgSO_4$), filtered and evaporated to give the crude methyl sulphide (0·33 g), its ^{1}H NMR spectrum consisted of a triplet centred at 7·44 τ. The crude sulphide was then passed down a column (1 × 48 cm) of commercial chromatography-grade alumina, which had been deactivated with $\frac{1}{10}$th by weight of water, in petrol (b.p. 40–60°) to give IV (0·08 g) and VII (0·30 g) m.p. 79–81°, both alone and in admixture with the previously described material, from petrol (b.p 60–80°); both with correct IR spectra; this sulphide (0·08 g) and H_2O_2 (0·6 ml; 30% w/w) in AcOH (1 ml) at 100° for 2 hr gave the *sulphone* (0·06 g) with a correct IR spectrum.

1,2,4-*Trifluorodibenzofuran* (VIII)

(a) Compound VI (0·22 g) in dry MeOH (20 ml) was added to a vigorously stirred suspension of Raney Ni (10 g) in dry MeOH (25 ml). After 2 hr at 65° the mixture was filtered, evaporated and the residue extracted with ether (200 ml). The dried ($MgSO_4$) extract was filtered, evaporated and the residue (0·13 g) sublimed at a diminished press (15 mm) to give 1,2,4-*trifluorodibenzofuran* m.p. 81·5–83°, from petrol (b.p. 60–80°). Found: C, 65·0; H, 2·3. $C_{12}H_5F_3O$ requires: C, 64·9; H, 2·3%.) ν_{max} 1528 cm^{-1} (broad) (fluorinated aromatic ring). λ_{max} 2490, 2540, 2710, 2760, 2960, and 3080 Å (ε, 13·6, 21·5, 11·4, 21·5, 4·4 and 5·7 × 10^3, respectively; in hexane) its IR spectrum was identical with the crude ether extract.

(b) Compound IV (0·25 g) in diethyl ether (20 ml) was added to a suspension of LAH (0·10 g) in ether (10 ml) and refluxed for 156 hr. The mixture was then poured into 4N HCl (100 ml) and extracted with ether (3 × 50 ml). The dried ($MgSO_4$) ether extract was filtered and evaporated to leave a solid (0·22 g) which was passed down a column (1 × 56 cm) packed with alumina (commercial chromatography-grade alumina deactivated with $\frac{1}{10}$th by weight of water) using petrol (b.p. 40–60°) as eluent. Only one band was detected and evaporation of the eluate gave a mixture of starting material and VIII (ca. 1:1) as shown by IR spectroscopy.

(c) Anhyd K_2CO_3 (1·00 g), XII (1·00 g) and DMF (50 ml) were kept at 153° for 4 hr and then water (400 ml) was added. The ppt so obtained was washed with water (400 ml) and dried to give VIII (0·73 g) m.p. 80–82°, alone, and in admixture with the material obtained as described earlier, with a correct IR spectrum.

2′-*Methoxy-4-mercapto-2,3,5,6-tetrafluorobiphenyl* (XI)

Compound II (1·10 g) in DMF (10 ml) was added dropwise during 70 min to a vigorously stirred suspension of NaHS (1·25 g) in DMF (50 ml) at room temp. The mixture was then poured into 1·3N HCl (300 ml) and the resulting white ppt extracted with ether (3 × 50 ml). The combined ether extracts were washed with water (6 × 100 ml), dried ($MgSO_4$), filtered and evaporated under diminished press at a temp not greater than room temp (ca. 16°) to leave a semi-solid residue (1·21 g). Part (0·50 g) of the latter material was distilled under reduced press (0·2 mm) in an atmosphere of N_2 to give a distillate (0·25 g) which solidified when kept. Most (0·23 g) of the latter solid, m.p. 67–70°, was sublimed (0·5 mm) to give 2′-*methoxy-4-mercapto-2,3,5,6-tetrafluorobiphenyl* (0·21 g) m.p. 69·5–70·5°. (Found: C, 54·1; H, 2·7. $C_{13}H_8F_4OS$ requires: C, 54·2; H, 2·8%.) ν_{max} 2600 cm^{-1} (–SH).

2′-*Methoxy-2,3,5,6-tetrafluorobiphenyl*

(a) Compound XI (1·06 g) and Raney Ni (10 g) in MeOH (25 ml) treated in the usual way, gave a white crystalline solid (0·71 g), a portion (0·62 g) of which was recrystallized from petrol (b.p. 60–80°) to give the slightly impure methoxytetrafluorobiphenyl (0·39 g) m.p. 66–67·5° from which (0·20 g) a further recrystallization gave 2′-*methoxy-2,3,5,6-tetrafluorobiphenyl* (0·07 g) m.p. 66–67°. (Found: C, 60·7; H, 3·4. $C_{13}H_8F_4O$ requires: C, 60·9; H, 3·2%.)

(b) *o*-Bromoanisole (1·24 g), bromo-2,3,5,6-tetrafluorobenzene (1·50 g) and copper bronze (4·20 g) were kept together in a sealed Pyrex glass tube (2 × 15 cm) at 252° for 24 hr. The cold tube was opened and the contents heated under reflux with ether (200 ml) for 2 hr, filtered, dried ($MgSO_4$), filtered and evaporated to leave a semi-solid (1·31 g). A portion (0·63 g) of the latter solid was fractionally sublimed and the second fraction (0·14 g) was chromatographed on a column of alumina using petrol (b.p. 40–60°) as eluent. The second fraction gave X (0·07 g) m.p. 66–67° alone and in admixture with the compound obtained in (a) above; it displayed a correct IR spectrum.

2′-*Hydroxy-2,3,5,6-tetrafluorobiphenyl*

Compound X (1·00 g) and $AlCl_3$ (1·4 g) were kept together at 120° for 1 hr. Water (30 ml) was then added and the mixture extracted with ether (3 × 50 ml), the extract dried ($MgSO_4$), filtered and evaporated. The black residue (0·98 g) so obtained was sublimed at a reduced press (0·1 mm) to give a white solid (0·78 g) m.p. 58–77° of which a part (0·50 g) was crystallized from petrol (b.p. 60–80°) to give a white crystalline solid (0·29 g) m.p. 77–81°. Two further recrystallizations from petrol (b.p. 40–60°) gave 2′-*hydroxy-2,3,5,6-tetrafluorobiphenyl* m.p. 82–82·5°. (Found: C, 59·7; H, 2·5. $C_{12}H_6F_4O$ requires: C, 59·5; H, 2·5%.) ν_{max} 3603 (—OH) cm^{-1} in CCl_4 and 1508 and 1496 cm^{-1} (fluorinated aromatic ring) in Nujol.

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