Synthesis of fluorinated fused benzofurans and benzothiophenes: smiles-type rearrangement and cyclisation of perfluoro(het)aryl ethers and sulfides

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Citation: GONZALEZ, J.P. ... et al., 2011. Synthesis of fluorinated fused benzofurans and benzothiophenes: smiles-type rearrangement and cyclisation of perfluoro(het)aryl ethers and sulfides. Organic and Biomolecular Chemistry, 9 (7), pp. 2294 - 2305.

Additional Information:

- This article was published in the journal, Organic and Biomolecular Chemistry [© Royal Society of Chemistry] and the definitive version is available at: http://dx.doi.org/10.1039/C0OB00790K

Metadata Record: https://dspace.lboro.ac.uk/2134/11881

Version: Accepted for publication

Publisher: © The Royal Society of Chemistry

Please cite the published version.
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Abstract
Lithium-bromine exchange in 2-bromophenyl perfluoroaryl ethers or sulfides affords fused fluorinated benzofurans or benzothiophenes respectively by SNAr substitution of the adjacent fluorine in the perfluoroaryl substituent. The structures of the new compounds were confirmed by NMR spectroscopy and single crystal X-ray diffraction analysis. In the case of 2-bromophenyl tetrafluoropyrid-4-yl ether, lithiation promoted a Smiles-type rearrangement which led to formation of 4-(2-hydroxyphenyl)tetrafluoropyridine, the structure of which confirmed by X-ray crystallography.

Aromatic nucleophilic substitution in per- and poly-fluorinated arenes is a valuable method for constructing highly functionalised heterocycles and aromatics. Such compounds have been widely investigated by Chambers and Sandford and have been used as scaffolds for drug discovery. The mechanistic and synthetic potential of fluorinated arenes has been reviewed. There is considerable interest in ring closing reactions of substituted polyfluoroarenes as a way of rapidly generating usefully functionalised polycyclic compounds. As part of our investigations in this area we have studied ring closure by lithiation of bromoaryl ethers and sulfides containing a perfluoroarene ring. Reaction of a lithiated binaphthyl with hexafluorobenzene has recently been used in an elegant synthesis of a fluorinated helicene by Piers. In our study lithiation of the easily prepared 2-bromophenyl tetrafluoropyrid-4-yl ether (Scheme 1) was expected to form the pyrido-fused benzofuran derivative by
Scheme 1  Formation and Smiles-type rearrangement of ether 2

lithium-bromine exchange and then intramolecular substitution of the fluorine at C-3 of the pyridine ring to close the furan ring. However treatment of the tetrafluoropyridyl ether 2 with n-butyllithium in THF at low temperature afforded a compound which was not the expected tricyclic furan 3. IR and $^1$H NMR spectroscopy indicated the presence of an alcohol group ($\delta_H 5.01$, exchangeable with D$_2$O) while the $^{19}$F NMR spectrum showed signals for two pairs of fluorine atoms indicating that the tetrafluoropyridine ring was intact. The product was identified as the 2-(tetrafluoropyrid-4-yl)phenol 4 and the structure was confirmed by X-ray crystallography (Figure 1, Table 1) indicating that the reaction had proceeded by a Smiles type$^{11,12}$ rearrangement rather than S$_{N}$Ar reaction at the 3-position of the pyridine ring. The structure of the biaryl 4 showed a unique hydrogen bond between the phenolic OH group and the weakly basic tetrafluoropyridine nitrogen, resulting in zig-zag chains of molecules. The torsion angle between the two aryl rings is 56.05(3)$^\circ$. Molecules $\pi\cdots\pi$ stack with centroid-centroid separations of 3.864 and 4.021 Å and a shortest contact of 3.620 Å for N(4)$\cdots$C(12$'$). Treatment of the phenol 4 with sodium hydride in DMF gave the fused benzofuran 5 quantitatively with the phenoxide oxygen effecting nucleophilic substitution of the fluorine atom at 3-position of the pyridine ring.
Figure 1. Crystal structure of 4 showing π···π stacking and H-bond intermolecular interactions. O(8)–H(8)···N(4') = 2.846 Å, angle at H(8) = 168 °.

Reaction of pentafluoropyridine and sodium 2-bromobenzenethiolate in DMF (Scheme 2) gave the corresponding sulfide 6 (50%) together with a small amount (17%) of the product of trisubstitution 7. The latter was identified as the 2,4,5-tri(2-bromophenylthio)-3,6-difluoropyridine, and the substitution pattern, which differs.

Scheme 2  Formation and cyclisation of sulfide 6
from that usually found\textsuperscript{14} for pentafluoropyridine, was shown by the \textsuperscript{19}F NMR spectrum ($\delta_F$ 45.6 and 99.0), and was confirmed by X-ray crystallography (Figure 2, Table 1). Compound 7 crystallised as the hemi-toluene solvate and exhibits no $\pi\cdots\pi$ stacking but two types of halogen···halogen interactions ($F(3)\cdots Br(3') = 3.248$; $Br(3)\cdots Br(3'') = 3.880$ Å). None of the 2,4-disubstituted product was isolated.

Lithiation of sulfide 6 (Scheme 2) gave a pyrido-fused benzothiophene in 79\% yield, which was shown by X-ray crystallography (Figure 3, Table 1) to be compound 8 rather than the alternatively fused tricycle 10. In this case direct intramolecular substitution of the C-3 fluorine in the pyridine ring occurred rather than Smiles rearrangement, which would have formed thiolate 9 that could have undergone ring closure to form isomer 10.

Figure 2. Crystal structure of 7 showing halogen···halogen interactions. Toluene of crystallisation omitted for clarity.
Figure 3. Crystal structure of 8 showing fluorine···fluorine {F(3)···F(6') = 2.800 Å} and H-bond {C(12')–H(12')···N(5) = 2.54 Å; angle at H(12') = 157 °} intermolecular interactions. Not shown: π···π stacking interactions parallel to a with a spacing of a/2 = 3.61 Å.

In the case of the ether 2, reaction of the lithiated intermediate 11 (Scheme 3) must have proceeded with a Smiles-type rearrangement (path B) with attack at the ipso position occurring, even though this would involve the strained four-membered intermediate 13. Smiles rearrangements involving five-membered intermediates have been reported for perfluoroarene derivatives, and a radical Smiles rearrangement has
been described by Zard\textsuperscript{16} which proceeds through a four-membered cyclic intermediate. Dudley\textsuperscript{17} has recently reported a rearrangement of 2-benzylxopyridines to 2-pyridyl carbinols on treatment with LDA which involves a 3-membered intermediate. Attack at the ipso position in 11 must occur to avoid the unfavourable repulsion effect\textsuperscript{18,19,20} the 6-fluoro substituent would have on the pyridyl anion 12 if attack at C-3 occurred (path A). In the case of the lithiated thioether 15 (Scheme 4), the stabilising effect\textsuperscript{21} of the sulfur atom at C-4 must outweigh the destabilising influence of the fluorine at C-6 allowing attack at C-3 through a less strained five-membered intermediate (17 ↔ 18), rather than attack at C-4 forming 16. The longer C–S bonds in 15 may also make it harder to close the four-membered ring in 16. It is not clear why the initially formed phenoxide 14 (Scheme 3), generated in the lithiation promoted Smiles rearrangement of 2, did not cyclise to 5 under the reaction conditions, but complexation of the alkoxide by lithium in the relatively non-polar THF may have diminished its reactivity.

\textbf{Scheme 3} Possible reaction pathways for lithiated ether 11
We then investigated reaction of hexafluorobenzene 19 with 2-bromophenol or 2-bromobenzenethiol in the presence of sodium hydride. With the phenol it proved difficult to isolate the mono-substitution product 21 (Scheme 5). Replacement of the 4-fluorine atom in the first-formed product occurred, and the major product formed was the 1,4-bis ether 20. Only by using ten equivalents of hexafluorobenzene could we isolate the mono-ether 21 in a moderate 58% yield, and 20 was still formed in trace amount. Since bis-ether 20 could be readily formed in quantity, we decide to investigate lithiation of this substrate (Scheme 6). Treatment of 20 with two
Scheme 6  Cyclisation of bis-ether 20 to benzo[1,2-\textit{b}:4,5-\textit{b}']bis[\textit{b}]benzofuran 22

equivalents of \textit{n}-butyllithium in THF at -78 °C followed by warming to room
temperature gave, after aqueous work-up and crystallisation, a non-phenolic, high
melting (279-280 °C) crystalline product in low yield (19%). \textsuperscript{1}H and \textsuperscript{19}F NMR
spectroscopy showed the compound to be a symmetrical molecule with four proton
resonances and a single fluorine signal (δ\textsubscript{F} 14.7 ppm). X-ray crystallography showed
the product to be the centro-symmetric pentacyclic fused bis furan 22 (Figure 4, Table
1). The small, thin, weakly diffracting crystals required synchrotron radiation for data
collection. The molecules pack in a herring-bone fashion exhibiting both
halogen···halogen and π···π stacking interactions.
Figure 4. Crystal structure of 22 showing stepped chains via fluorine···fluorine 
\{F(1)···F(1') = 2.833 Å\} interactions and head-to-tail π···π interactions 
\{centroid···centroid = 3.902 Å, closest atom···atom separations ca. 3.42 Å\}.

It is not clear if this compound is formed by direct SNAr substitution of the adjacent 
fluorine atoms (20 → 22), or if Smiles rearrangement has taken place first at both 
ether linkages, forming the bis-phenoxide 26 which could have undergone ring 
closure to 22. None of the other possible products of cyclisation which could have 
shed light on to whether cyclisation occurred directly 23, with rearrangement 24, or 
with a combination of both 25, were isolated. An experiment to determine if 
rearrangement occurred during this reaction was carried out by treating bis-ether 20 
with a single equivalent of \(n\)-butyllithium with the expectation that isolation of 27 
would demonstrate direct cyclisation occurred, whereas formation of 28 would show 
that Smiles rearrangement had preceded cyclisation. Unfortunately this experiment 
was inconclusive with a complex mixture forming from which no identifiable 
products could be obtained. Treatment of the pentafluorophenyl ether 21 (Scheme 7) 
with \(n\)-butyllithium gave a fluorinated benzofuran in moderate yield (66% crude, 25% 
after crystallisation). Since excess \(n\)-butyllithium was employed in this reaction 
addition
of an \( n \)-butyl group to the fluorinated ring also occurred. The structure of the product was assigned as the 3-butyl derivative 29 (numbering shown) with the butyl group adding most likely \( \text{para} \) to carbon rather than oxygen (giving 30) assuming the addition occurred after ring closure. The low melting point (48 °C) of this compound precluded formation of suitable crystals for X-ray diffraction analysis, but detailed analysis of the long range carbon-fluorine coupling constants\(^{22} \) in the \(^{13}\text{C} \) NMR spectrum supported the assignment of the structure as 29. Calculation of the Mulliken charges in 1,2,3,4-tetrafluorodibenzofuran (structure optimised using Gaussian 03 at the B3LYP/6-31G* level\(^{23} \)) indicated C-3 (+0.261) to be more slightly electrophilic than C-4 (+0.258) also supporting assignment as 29. The values for C-1 and C-4 were +0.250 and +0.255 respectively.

Reaction of 2-bromobenzenethiol (two equivalents), sodium hydride and hexafluorobenzene in DMF gave the 1,4-disubstitution product 31 (Scheme 8) in 81% crude yield (70% after crystallisation). The monosubstitution product could not be formed even when a large excess of hexafluorobenzene was employed. Treatment of 31 with a single equivalent of \( n \)-butyllithium afforded the 2-(bromophenylthio)-1,3,4-
trifluorodibenzothiophene 32 showing that cyclisation had occurred without initial

\[
\begin{align*}
&\begin{array}{c}
\text{19} \\
\text{F} & \text{F} & \text{F} & \text{F} \\
\end{array} & \xrightarrow{\text{NaH}} & \begin{array}{c}
\text{1 eq. BuLi} \\
\text{Br} & \text{Br} \\
\end{array} & \begin{array}{c}
\text{31} \\
\text{S} & \text{Br} \\
\end{array} & \xrightarrow{\text{DMF}} & \begin{array}{c}
\text{32} \\
\text{F} & \text{Br} \\
\end{array} & \xrightarrow{\text{33}} & \begin{array}{c}
\text{33} \\
\text{S} & \text{Br} \\
\end{array}
\end{align*}
\]

Scheme 8  Direct cyclisation of bis-sulfide 31 with 1 equivalent of \(n\)-BuLi

Smiles rearrangement as was observed for the pyridyl ether. None of the isomer 33 was detected. The structure of the dibenzothiophene 32 was confirmed by X-ray crystallography which showed that the sulfur atoms retained their original 1,4-relationship. The compound crystallised as two monoclinic polymorphs (32A – rod-shaped crystals and 32B – plate-shaped) (Figures 5 and 6, Table 1). Both polymorphs have 3D supramolecular structures, but the balance of \(\pi\)····\(\pi\) and halogen····halogen interactions differs. In 32A there are both types: \(\text{Br}(1)\cdots\text{Br}(1'') = 3.268, \text{F}(3)\cdots\text{F}(3''') = 2.879 \text{ Å}\) and centroid····centroid separations of 3.688 and 3.547 Å for ring C(15)–C(20) with its symmetry equivalent and ring C(8)–C(13) with ring C(2')–C(7') respectively. In 32B there are no halogen····halogen interactions, although there is an \(\text{F}(6)\cdots\text{S}(1') = 3.260 \text{ Å}\) short contact; however there are more \(\pi\)····\(\pi\) interactions: ring C(15)–C(20) with its symmetry equivalent (centroid····centroid = 3.716 Å) and head-to-tail interactions between the three fused rings and their symmetry equivalents (centroid····centroid = 3.586 Å).
When the bis-sulfide 31 was treated with two equivalents of n-butyllithium (Scheme 9) cyclisation occurred between both bromophenyl groups and the central fluorinated benzene ring to give the pentacyclic 6,12-difluorobenzo[1,2-\(b\):4,5-\(b\)]bis[\(b\)]benzothiophene 34 in high yield (95\%). No evidence for formation of any of the other possible cyclisation products (35, 36 or 37) was obtained. The benzo[1,2-\(b\):4,5-\(b\')]bis[\(b\)]benzothiophene ring system has recently been synthesised by acid catalysed ring closure of a methylsulfinyl group onto an adjacent benzene ring.\(^{24}\) The structure of 34 was confirmed by X-ray crystallography (Figure 7, Table 1) supporting ring closure by direct S\(_{N}\)Ar reaction at C-2 and C-5 without initial
rearrangement. The crystals of 34 were very thin and flexible and the crystal structure showed π···π stacking parallel to $b$ with the closest atom···atom contact being 3.50 Å.

Figure 7 Crystal structure of 7 showing π···π stacking parallel to $b$.

![Chemical structures and reactions](image)

isomers not observed
In conclusion we have shown that lithiation of arylthio-substituents on perfluorinated arenes can be used to rapidly build up useful functionalised polycyclic structures. Cyclisation can occur by direct attack of the initially formed carbanion on the neighbouring position by $S_NAr$ reaction, and this seems to be the norm for groups attached through a sulfur atom. In the case of fluoroaryl ethers Smiles-type rearrangement of the initially formed carbanion can occur, although the scope of this process needs to be investigated further. The crystal structures of key examples reveal a fine balance between halogen···halogen and π···π stacking interactions and polymorphism in one case. Further work on the mechanistic aspects of these reactions, and results on the cyclisation of corresponding perfluoroaryl amines will be reported in due course.

We thank Loughborough University for support, the Socrates Programme which allowed JPG to study in Loughborough and the EPSRC National Mass Spectrometry service at the University of Swansea, and John Kershaw and Sheena Grainger (Loughborough University) for recording mass spectra. We also thank STFC for beam time at Daresbury Laboratory where Dr. S.J.E. Warren and P.J. Rizkallah provided scientific support.

Experimental

General

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate which were distilled from CaCl$_2$, dichloromethane which was distilled from CaH$_2$, and THF which was distilled from sodium and benzophenone. Light petroleum refers to the fraction boiling between 40-60 °C fraction. Sodium hydride was a 60% dispersion in mineral oil. A 1.6 or 2.5 M solution of $n$-butyllithium in hexane was used. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Infrared spectra...
were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. $^1$H (400 MHz), $^{13}$C (100 Hz) and $^{19}$F (376 MHz) NMR spectra were recorded on a Bruker DPX-400 instrument. $^{19}$F NMR spectra are referenced to hexafluorobenzene as internal standard. Spectra were obtained from solutions in CDCl$_3$ unless otherwise specified. Chemical shifts are given in parts per million (ppm) and $J$ values in hertz (Hz). Assignments were made using a combination of COSY, HMQC and HMBC analysis. Mass spectra were recorded on a Jeol SX102 high resolution mass spectrometer, a ThermoFisher Exactive™ Orbitrap instrument equipped with an Advion TriVersa NanoMate®, or were run by the EPSRC MS Service at the University of Wales, Swansea. TLC using silica as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F$_{254}$), and TLC using alumina as absorbent was carried out with aluminium backed plates coated with neutral aluminium oxide (Merck 150 F$_{254}$,TypeT). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography.

4-(2-Bromophenoxy)tetrafluoropyridine 2

2-Bromophenol (3.46 g, 0.02 mol) was added dropwise to a stirred suspension of sodium hydride (1.0 g, 0.025 mol) in DMF (40 mL) at ice-bath temperature. When gas evolution had stopped pentafluoropyridine (3.38 g, 0.02 mol) was added dropwise and the resulting turbid yellow solution stirred at room temperature overnight for 19 h. Water (100 mL) was added and the mixture extracted with ether (250 mL). The organic layer was dried over MgSO$_4$, filtered and evaporated to give the title compound as a yellow oil (5.96 g, 92%).

$\nu_{\text{max}}$/cm$^{-1}$ (film) 3069, 2925, 2853, 2565, 2033, 1842, 1641, 1576, 1473, 1443, 1259, 1214, 1073.

$\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 6.99 (1H, dd, $J$ 1.2 and 8), 7.08, (1H, dt, $J$ 1.2 and 7.6), 7.26 (1H, dt, $J$ 1.6 and 7.6), 7.58 (1H, dd, $J$ 1.6 and 8)

$\delta_{\text{F}}$ (376 MHz, CDCl$_3$) 6.5-6.9 (2F, m), 73.5-73.7 (2F, m)

$m/z$ (FAB) 321/323 (MH$^+$)

Found 320.9420, C$_{11}$H$_5^{18}$BrF$_4$NO requires 320.9412
4-(2-Hydroxyphenyl)tetrafluoropyridine 4

A solution of 4-(2-bromophenoxy)tetrafluoropyridine 2 (1.05 g, 0.0033 mol) in anhydrous THF (7 mL) was stirred at -78 °C and treated dropwise with a solution of \( n \)-butyllithium in hexanes (2.5 M, 1.5 mL, 0.0037 mol). The solution turned orange and then faded to yellow over 50 min. The mixture was stirred and allowed to warm to room temperature overnight. Water (10 mL) was added and the mixture extracted with ether (3 x 20 mL). Brine was added to break up the emulsion which formed during extraction. The combined ether layers were dried over MgSO\(_4\), filtered and evaporated to give a yellow oil (0.9 g) which crystallised on standing. Recrystallisation from dichloromethane and light petroleum gave off-white crystals of the title compound (0.25 g, 31%).

m.p. 138-141 °C

\( \nu_{\text{max}}/\text{cm}^{-1} \) (film) 3380 br. (OH), 3070, 2957, 2927, 2567, 1915, 1842, 1790, 1642, 1590, 1472, 1291, 1263, 1214, 1073, 888, 752.

\( \delta_H \) (400 MHz, CDCl\(_3\)) 5.02 (1H, bs, exch., OH) 6.90 (1H, dd, \( J \) 0.8 and 8.4), 7.12, (1H, dt, \( J \) 0.8 and 7.6), 7.22 (1H, d, \( J \) 7.6), 7.35 (1H, dt, \( J \) 1.6 and 8.4)

\( \delta_F \) (376 MHz, CDCl\(_3\)) 20.7-20.9 (2F, m), 70.7-70.9 (2F, m)

\( m/z \) (FAB) 244 (MH\(^+\))

Found 244.0328, C\(_{11}\)H\(_6\)F\(_4\)NO requires 244.0307

1,3,4-Trifluorobenzo[b]furo[2,3-c]pyridine 5

4-(2-Hydroxyphenyl)tetrafluoropyridine 4 (0.23 g, 0.95 mmol) was added to a stirred suspension of sodium hydride (0.04 g, 1.0 mmol) in anhydrous DMF (10 mL). The mixture was heated at 100 °C for 3 h. After cooling water (25 mL) was added, and the mixture was extracted with ether (50 mL). The organic extract was dried over MgSO\(_4\), filtered and evaporated to give 5 as a pale yellow solid (0.2 g, quant.), m.p. 136-137 °C (from dichloromethane/light petroleum).

\( \nu_{\text{max}}/\text{cm}^{-1} \) (film) 1657, 1492, 1474, 1444, 1415, 1252, 1165, 1098, 973.

\( \delta_H \) (400 MHz, CDCl\(_3\)) 7.45 (1H, m), 7.62-7.68, (2H, m), 8.07 (1H, d, \( J \) 8)
\[ \delta_F (376 \text{ MHz, CDCl}_3) \] 6.7 (1F, dd, \( J = 21.6 \) and 33.5), 60.1 (1F, dd, \( J = 12.4 \) and 19.9), 69.0 (1F, dd, \( J = 12.8 \) and 33.5).

\[ m/z \ (\text{EI}) \] 223 (M\(^+\))

Found 223.0242, \( \text{C}_{11}\text{H}_4\text{F}_3\text{NO} \) requires 223.0245

Reaction of pentafluoropyridine with 2-bromobenzenethiol

2-Bromobenzenethiol (0.27 g, 2.1 mmol) was added dropwise to a stirred suspension of sodium hydride (0.1 g, 2.5 mmol) in DMF (4 mL) at ice-bath temperature. When gas evolution had stopped pentafluoropyridine (0.34 g, 2 mmol) was added dropwise. The mixture turned momentarily bright yellow and then faded to colourless. The solution was stirred at room temperature for 24 h. Water (15 mL) was added and the mixture extracted with ether (3 \times 15 \text{ mL}). The organic layers were dried over MgSO\(_4\), filtered and evaporated to give a pale yellow malodorous oil (0.76 g). The oil was dissolved in dichloromethane and the solution washed with saturated Na\(_2\)CO\(_3\) (aq) and then 5\% HCl(aq). Evaporation of the organic layer gave a less odorous brown oil (0.62 g) which was chromatographed over silica. Elution with light petroleum-dichloromethane (5:1) gave 4-(2-bromobenzenethio)tetrafluoropyridine \( \text{6} \) as a colourless crystalline solid (0.34 g, 50\%).

m.p. 47-48 °C

\( \nu_{\text{max}}/\text{cm}^{-1} \) 1699, 1682, 1652, 1627, 1558, 1463, 1235.

\( \delta_H (400 \text{ MHz, CDCl}_3) \) 7.23 (2H, m), 7.47 (1H, dd, \( J = 1.5, 7.6 \)), 7.59 (1H, dd, \( J = 1.5, 7.6 \)).

\( \delta_F (376 \text{ MHz, CDCl}_3) \) 25.4-25.6 (2F, m), 71.9-72.0 (2F, m).

\[ m/z \ (\text{EI}) \] 337/339 (M\(^+\))

Found 339.9177, \( \text{C}_{11}\text{H}_4\text{F}_7\text{Br} \) requires 336.9184

Further elution gave 2,4,5-tri(2-bromobenzenethio)difluoropyridine \( \text{7} \) as a pale yellow solid (0.24 g, 17\%).

m.p. 97-98 °C

\( \nu_{\text{max}}/\text{cm}^{-1} \) 1652, 1635, 1557, 1505, 1471, 1387.
$\delta_H$ (400 MHz, CDCl$_3$) 6.77 (1H, dd, $J$ 0.8, 8.0), 6.97 (1H, dt, $J$ 1.6, 7.2), 7.09 (2H, m), 7.17 (1H, m), 7.23 (1H, dt, $J$ 2.0, 8.0), 7.31 (2H, m), 7.45 (1H, dd, $J$ 1.2, 8.0), 7.51 (1H, dd, $J$ 1.2, 7.6), 7.58 (1H, dd, $J$ 1.6, 7.6), 7.63 (1H, dd, $J$ 1.2, 8.0).

$\delta_F$ (376 MHz, CDCl$_3$) 45.6 (1F, d, $J$ 21.1 Hz), 99.0 (1F, d, $J$ 21.1 Hz).

$m/z$ (FAB) (MNa$^+$) 696-703

Found 697.7512, C$_{23}$H$_{12}$Br$_2$F$_2$NNa$_3$S$_3$ requires 697.7522

1,3,4-trifluorobenzo[b]thieno[3,2-c]pyridine 8

A stirred solution of 4-(2-bromobenzenethio)tetrafluoropyridine 6 (0.31 g, 0.9 mmol) in anhydrous THF (3 mL) was cooled to -78 ºC and treated dropwise with $n$-butyllithium in hexanes (2.5 M, 0.4 mL, 1.0 mmol). The solution turned maroon in colour and then brown. The mixture was allowed to warm to room temperature overnight with stirring during which time it changed to yellow in colour. Water was added, precipitating a solid, and the mixture exhaustively extracted with ether redissolving the solid material. Evaporation of the ether afforded a solid (0.2 g) which was dissolved in dichloromethane, and the solution washed with saturated aqueous sodium carbonate to remove acidic material. Evaporation of the organic phase gave the benzothienopyridine 8 as a yellow solid (0.17 g, 79%).

m.p. 151-153 ºC (from dichloromethane-light petroleum)

$\nu_{max}$/cm$^{-1}$ 1656, 1618, 1547, 1479, 1439, 1253, 1026, 913.

$\delta_H$ (400 MHz, CDCl$_3$) 7.52-7.56 (2H, m), 7.883-7.85 (1H, m) 8.26-8.28 (1H, m)

$\delta_F$ (376 MHz, CDCl$_3$) 8.0 (1F, dd, $J$ 20.3 and 29.0), 62.4 (1F, dd, $J$ 11.3 and 20.3), 84.8 (1F, dd, $J$ 11.3 and 29.0)

$m/z$ (EI) 239 (M$^+$)

Found 239.0017, C$_{11}$H$_4$F$_3$NS requires 239.0016

Reaction of 2-bromophenol with hexafluorobenzene

2-Bromophenol (0.75 g, 4.3 mmol) was added dropwise to a suspension of sodium hydride (0.20 g, 5 mmol) in anhydrous DMF (8 mL) at 0 ºC. Hexafluorobenzene (0.040 g, 2.2 mmol) was added dropwise and the resulting mixture stirred at 50 ºC
overnight. The cooled mixture was diluted with water (20 mL) and extracted with ether (3 x 40 mL). Evaporation of the organic extracts gave a yellow oil (1.2 g) which was treated with light petroleum. On cooling afforded colourless crystals of 1,4-di(2-bromophenoxy)tetrafluorobenzene 20 (0.3 g, 31%) were formed.

m.p. 113-115 ºC

ν<sub>max</sub>/cm<sup>-1</sup> 1576, 1510, 1471, 1444, 1313, 1264, 1218.

δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 6.75 (2H, dd, J 1.4, 8.0), 6.97 (2H, dt, J 1.4, 7.6), 7.19 (2H, dt, J 1.6, 7.6), and 7.58 (2H, dd, J 1.6, 8.0).

δ<sub>F</sub> (376 MHz, CDCl<sub>3</sub>) 8.3 (4F, apparent t)

m/z (FAB) 490/492/494 (M<sup>+</sup>)

Found 489.8834, C<sub>18</sub>H<sub>8</sub>Br<sub>2</sub>F<sub>4</sub>O<sub>2</sub> requires 489.8827

When the above reaction was conducted using 10 equivalents of hexafluorobenzene 2-bromophenyl pentafluorophenyl ether 21 was obtained in 58% yield as a colourless oil (0.40 g from a 2 mmol scale reaction) after chromatography over silica using light petroleum as eluent.

ν<sub>max</sub>/cm<sup>-1</sup> 1733, 1717, 1699, 1683, 1653, 1576, 1558, 1516, 1474, 1319, 1265, 1221.

δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 6.74 (1H, dd, J 1.2, 8.0), 7.05 (1H, dt, J 1.2, 8.0), 7.26 (1H, dt, J 1.6, 8.0), and 7.66 (1H, dd, J 1.6, 8.0).

δ<sub>F</sub> (376 MHz, CDCl<sub>3</sub>) 0.42-0.56 (2F, m), 2.83 (1F, tt, J 1.5, 22.2), 8.37-8.46 (2F, m).

m/z (EI) 338/340 (M<sup>+</sup>)

Found 337.9370, C<sub>12</sub>H<sub>4</sub>Br<sub>5</sub>F<sub>5</sub>O requires 337.9366

The disubstituted product 20 was also isolated (0.005 g, 1%) on further elution.

6,12-difluorobenzo[1,2-b:4,5-b']bis[b]benzofuran 22

A solution of the bis ether 20 (0.3 g, 0.6 mmol) in anhydrous THF (2 mL) was stirred at -84 ºC and treated with n-butyllithium in hexanes (2.5 M, 0.5 mL, 1.25 mmol). The solution turned brown in colour and then faded to yellow after 1 h. After 2 h the
mixture was warmed to room temperature and treated with water (2 mL). Extraction with dichloromethane (x 3) and evaporation of the organic phases gave a pale brown solid (0.2 g). Recrystallisation from dichloromethane - light petroleum gave colourless needles of the benzo-bis-benzofuran 22 (0.033 g, 19%).

m.p. 279-280 °C

$\nu_{\text{max}}$ (cm$^{-1}$) 1652, 1557, 1539, 1436, 1418, 1306, 1246.

$\delta$ H (400 MHz, CD$_2$Cl$_2$) 7.39 (1H, dt, $J$ 0.8, 8.0), 7.51 (1H, dt, $J$ 1.2, 8.4), 7.59 (1H, d, $J$ 8.4), and 8.09 (1H, dd, $J$ 0.8, 8.0).

$\delta$ C (100 MHz, CD$_2$Cl$_2$) 111.81 (C-4,10), 114.48 (dd, $J$ 8, 12, C-6a,12a), 121.86 (C-6b,12b), 122.86 (t, $J$ 7, C-1,7), 123.71 (C-2,8), 128.39 (C-3,9), 137.90 (dd, $J$ 7, 25 Hz, C-6,12), 138.81 (dd, $J$ 8, 10, C-5a,11a), 156.69 (C-4a,10a)

$\delta$ F (376 MHz, DMSO-d$_6$) 14.7 (2F, s)

m/z (EI) 294 (M$^+$)

Found 294.0495, C$_{18}$H$_8$F$_2$O$_2$ requires 294.0492

Reaction of 2-bromophenyl pentafluorophenyl ether 21 with $n$-butyllithium

A solution of 2-bromophenyl pentafluorophenyl ether 21 (1.1 g, 3 mmol) in dry THF (15 mL) was stirred at -78 °C and treated with $n$-butyllithium in hexanes (2.5 M, 3.1 mL, 7.8 mmol). The solution turned dark red in colour and then faded to orange after 30 min. The mixture was allowed to warm to room temperature over night and was then treated with water (10 mL). Extraction with ether (3 x 40 mL) and evaporation of the organic phases gave a yellow oil (0.52 g) which was chromatographed over silica. Elution with light petroleum gave colourless crystals of 3-$n$-butyl-1,2,4-trifluorodibenzofuran 29 (0.20 g, 24%).

m.p. 48-49 °C

$\nu_{\text{max}}$ (cm$^{-1}$) (film) 3739, 3628, 2958, 2928, 2863, 1708, 1690, 1676, 1648, 1551, 1534, 1479, 1449, 1300, 1262.

$\delta$ H (400 MHz, CDCl$_3$) 0.98 (3H, t, $J$ 7.6, CH$_3$), 1.44 (2H, sext., $J$ 7.6, CH$_2$), 1.68 (2H, quin., $J$ 7.6, CH$_2$), 2.89 (2H, tt, $J$ 2.0, 7.6, CH$_2$), 7.41 (1H, dt, $J$ 0.8, 7.6), 7.53 (1H, dt, $J$ 1.2, 8.4), 7.60 (1H, td, $J$ 1.0, 8.4), and 8.03 (1H, ddd, $J$ 0.8, 1.2, 7.6).

$\delta$ C (100 MHz, CDCl$_3$) 13.76 (CH$_3$), 22.34 (CH$_2$-3), 22.96 (CH$_2$-1), 31.82 (CH$_2$-2), 111.87 (C-6), 113.46 (td, $J$ 3.5, 6.3, C-9b), 118.54 (dd, $J$ 18.2, 19.6, C-3), 121.67 (td, $J$ 2.3, 4.6, C-9a), 122.65 (C-9), 123.64 (C-8), 128.13 (C-7), 139.18 (ddd, $J$ 2.0, 7.8,
14.1, C-4a), 140.96 (ddd, J 4.0, 16.1, 248.7, C-1), 141.57 (ddd, J 3.7, 7.1, 244.7, C-4), 144.19 (ddd, J 6.3, 12.0, 240.3, C-2), 156.22 (C-5a).

 δF (376 MHz, DMSO-d6) 13.6 (1F, t, J 19.5), 14.5 (1F, d, J 21.1), 18.6 (1F, d, J 19.2).

m/z (EI) 278 (M+)  
Found 278.0915, C16H13F3O requires 278.0919

1,4-di(2-bromobenzenethio)tetrafluorobenzene 31

2-Bromobenzenethiol (0.78 g, 4 mmol) was added dropwise to a stirred suspension of sodium hydride (0.20 g, 5 mmol) in anhydrous DMF (8 mL). Hexafluorobenzene (0.38 g, 2 mmol) was added dropwise and the resulting yellow mixture stirred at room temperature overnight. The cooled mixture was diluted with water (25 mL) and extracted with ether (3 x 50 mL). Evaporation of the organic extracts gave a yellow solid (0.85 g) with a pungent odour. Crystallisation from dichloromethane - light petroleum afforded pale yellow crystals of the title compound 31 (0.74 g, 70%).

m.p. 138 ºC

νmax/cm-1 (film) 1686, 1652, 1639, 1558, 1464, 1446, 1259.

δH (400 MHz, CDCl3) 7.15-7.19 (2H, m), 7.24-7.27 (1H, m), 7.62 (1H, dd, J 1.2, 8.4).

δF (376 MHz, CDCl3) 31.1 (4F, s)

m/z (EI) 522/524/526 (M+  
Found 523.8343, C18H879Br2F4S2 requires 523.8350

Reactions of bis-sulfide 31 with n-buthyllithium

A solution of bis-sulfide 31 (1.18 g, 2.2 mmol) in dry THF (6 mL) was stirred at -78 C and treated dropwise with n-buthyllithium in hexanes (2.5 M, 1.8 mL, 2.5 mmol). The solution turned dark brown in colour. The mixture was allowed to warm to room temperature over 48 h and was then treated with water (10 mL). Extraction with ether (x 3) and evaporation of the organic phases gave a brown solid (0.91 g) which was crystallised from dichloromethane - light petroleum to give colourless crystals of 2-(2-bromobenzenethio)-1,3,4-trifluorodibenzothiophene 32 (0.17 g, 23%).
m.p. 172-173 °C

$\nu_{\text{max}}$ cm$^{-1}$ (film) 1558, 1481, 1440, 1250.

$\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 6.83 (1H, d, $J$ 8.0), 7.05 (1H, dt, $J$ 1.2, 8.0), 7.14 (1H, dt, $J$ 1.2, 8.0), 7.52-7.60 (3H, m), 7.89-7.92 (1H, m), 8.34-8.38 (1H, m).

$\delta_{\text{F}}$ (376 MHz, CDCl$_3$) 17.6 (1F, dd, $J$ 17.6, 24, F-3), 27.3 (1F, d, $J$ 24, F-4), 45.8 (1F, d, $J$ 17.6, F-1),

$m/z$ (EI) 424/426 (M$^+$)

Found 423.9211, C$_{18}$H$_8$BrF$_3$S$_2$ requires 423.9203

Reaction with 2.2 equivalents of $n$-butyllithium

The above reaction using bis-sulfide (0.957 g, 0.0018 mmol) and 2.2 equivalents of $n$-butyllithium (2.5 M, 1.6 mL), and extraction with dichloromethane instead of ether afforded 6,12-difluorobenzo[1,2-b:4,5-b']bis[b]benzothiophene 34 as an orange brown solid (0.6 g, 95%). Recrystallisation from dichloromethane - light petroleum gave fine pale yellow needles m.p. 287 °C.

$\nu_{\text{max}}$ cm$^{-1}$ (film) 3318, 3105, 3039, 1649, 1608, 1560, 1503, 1433, 1468, 1325, 1252, 1222.

$\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.46-7.51 (2H, m), 7.82-7.84 (1H, m), 8.40-8.43 (1H, m).

$\delta_{\text{F}}$ (376 MHz, CDCl$_3$) 37.9 (2F, s).

$m/z$ (EI) 326 (M$^+$)

Found 326.0036, C$_{18}$H$_8$F$_2$S$_2$ requires 326.0036

Crystallography

For each sample, a crystal was mounted in oil on a glass fibre and fixed in the cold nitrogen stream on a Bruker APEX 2 CCD diffractometer equipped with MoK$\alpha$ radiation and a graphite monochromator, except for 22 which was measured at Daresbury Laboratory SRS, Station 9.8 due to tiny crystal size and weak diffraction$^{25}$. Intensity data were measured by thin-slice $\omega$-scans and corrected for Lp and absorption effects. Data were reduced using the SAINT$^{25}$ program. The structures were determined by the direct methods routine in the SHELXS-97 program and refined by full-matrix least-squares methods, on $F^2$, in SHELXL-97$^{26}$. The non-
hydrogen atoms were refined with anisotropic thermal parameters. H atoms were constrained.

For 4 the absolute structure could not be reliably determined due to the lack of anomalous scatters, so Friedel pairs were merged. Crystals of 7 were non-merohedrally twinned into two domains related by a 180° rotation about real axis [1 0 0] \(^{27}\). The occupancies of the two domains refined to 0.8744:0.1256(6). Crystals of 8 were non-merohedrally twinned into two domains related by a 180° rotation about reciprocal axis [0 0 1] \(^{27}\). The occupancies of the two domains refined to 0.6215:0.3785(8). Compound 32 grows as either rods (32A) or plates (32B) which are polymorphic. Although both crystallise in space group \(P_{2_1}/c\), the unit cell shapes are entirely different and the \(\pi\cdots\pi\) and halogen-halogen interactions are also different (see discussion). Crystals of 34 were extremely thin and flexible which led to some absorption correction difficulties and less than ideal anisotropic displacement parameters. Crystal data and refinement results are collated in Table 1.
Table 1. Crystallographic data for compounds 4, 7·½C₇H₈, 8, 22, 32A, 32B, and 34.

<table>
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<th>Compound</th>
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<th>7·½C₇H₈</th>
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<td>Formula</td>
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<td>C₂₁H₁₂Br₃F₂NS₃·½C₇H₈</td>
<td>C₁₁H₄F₃NS</td>
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<td>P ̅ 1</td>
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<td>150(2)</td>
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<td>Radiation, λ (Å)</td>
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<td>Unique reflections, R&lt;sub&gt;int&lt;/sub&gt;</td>
<td>1268, 0.0208</td>
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<td>354</td>
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<tr>
<td>R₁ [F² &gt; 2σ(F²)]</td>
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<td>1.03 and −0.88</td>
<td>0.37 and −0.19</td>
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Table 1 Continued.

<table>
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<tr>
<th>Compound</th>
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<td>Formula</td>
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<td>C_{18}H_{8}BrF_{3}S_{2}</td>
<td>C_{18}H_{8}F_{2}S_{2}</td>
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Unit cell dimensions

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Temp. (K) | 150(2) | 150(2) | 150(2) |

Radiation, λ (Å) | 0.71073 | 0.71073 | 0.71073 |

D_{calcd} (g cm⁻³) | 1.760   | 1.805   | 1.640   |

Absorption coefficient (mm⁻¹) | 2.848   | 2.921   | 0.417   |

Crystal size (mm) | 0.84 × 0.13 × 0.10 | 0.70 × 0.29 × 0.03 | 0.56 × 0.12 × 0.02 |

2θ_{max} (°) | 56.66 | 61.14 | 52.86 |

Reflections measured | 16379 | 18058 | 4059 |

Unique reflections, R_{int} | 3987, 0.0336 | 4770, 0.0410 | 1347, 0.0623 |

Reflections with F^2 > 2σ(F^2) | 3119 | 3675 | 1022 |

Transmission factors | 0.196 to 0.756 | 0.234 to 0.918 | 0.800 to 0.992 |

Number of parameters | 217 | 217 | 100 |

R₁ [F^2 > 2σ(F^2)] | 0.0378 | 0.0355 | 0.0559 |

wR₂ (all data) | 0.0976 | 0.1012 | 0.1366 |

Largest difference peak and hole (e Å⁻³) | 1.02 and −0.68 | 0.56 and −0.40 | 0.50 and −0.31 |
References


