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Synthesis of polyfluorodibenz[*b*,*f*][1,4]oxazepines by the cyclization of 2-[(polyfluorobenzylidene)amino]phenols

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Abstract

Thermolysis of 2-[(polyfluorobenzylidene)amino]phenols in ethanol in the presence of triethylamine affords the corresponding fluorinated dibenz[*b*,*f*][1,4]oxazepines in moderate to high yields. The structures of 2-[(2,3,4,5,6-pentafluorobenzylidene)amino]phenol and 1,2,3,4-tetrafluorodibenzo[*b*,*f*][1,4]oxazepine have been determined by single-crystal X-ray diffraction.

Keywords: Dibenzoxazepine; Cyclisation; S_NAr; Crystal structure

1. Introduction

The pentafluorinated compound 2-[(2,3,4,5,6-pentafluorobenzylidene)amino]phenol, **1a**, has been reported to undergo cyclisation in DMF at 100 °C to afford in high yield 1,2,3,4-tetrafluorodibenzo[*b*,*f*][1,4]oxazepine, **2a** (Scheme 1) [1] by an intramolecular S_NAr reaction [2–4]. Similarly, 2-[(2,3,4,5,6-pentafluorophenylimino)methyl]phenol, **3**, cyclised to 6,7,8,9-tetrafluorodibenzo[*b*,*f*][1,4]oxazepine, **4**, in DMF at 100 °C in the presence of potassium fluoride [1].

Although this route might be expected to provide a convenient and high yield route to other fluorinated dibenz[*b*,*f*][1,4]oxazepines and related heterocylces, it has been limited to **1a**, **3** and its *para*-methoxy-substituted tetrafluoro analogue [5]. We are interested in fluorinated dibenz[*b*,*f*][1,4]oxazepines and related fluorinated heterocycles because of the well documented biological activity of dibenz[*b*,*f*][1,4]oxazepine [6–12], which might be expected to be enhanced by the presence of fluorine atoms [13–15], and also as precursors to more elaborate fluorinated compounds [16,17].

Here, we report the syntheses of fluorinated dibenzoxazepines by intramolecular cyclisation of 2-[(polyfluorobenzylidene)amino]phenols, attempts to prepare other fluorinated heterocycles by a similar route and the structures of **1a** and **2a**.

2. Results and discussion

The fluorinated aromatic imines **1a–d** were prepared readily in high yields from the respective fluorinated benzaldehyde and 2-aminophenol by Schiff base condensation in dichloromethane over anhydrous magnesium sulphate at room temperature (Scheme 2). Imines **1a–d** were characterised by mass spectrometry, NMR and IR spectroscopies, and elemental analysis. Imine **1a** was structurally characterised by single-crystal X-ray diffraction (Fig. 1). Crystallographic data are given in Table 1 and selected bond distances and angles are given in Table 2. The asymmetric unit of **1a** contains one molecule. The molecule is almost planar with torsion angles across C(6)–C(7), C(7)–N(8) and N(8)–C(9) of −172.9(2), 179.7(2) and −176.4(2)°, respectively. The molecule possesses an intramolecular O–H···N hydrogen bond between the hydroxyl and the imine moieties (H···N 2.10(3) Å, H···N 2.631(2) Å and an O–H···N angle of 122(2)°). The hydroxyl group also shows a weak secondary intramolecular interaction with the closest fluorine atom (H···F distance of 2.90 Å). The molecules of **1a** are arranged as dimeric columns via O–H···O (H···O 2.52(2) Å, O···O 2.865(3) Å and an O–H···O angle of 107(2)°) and π···π hydrogen bonding interactions with H···O and ring centre to ring centre distances of 2.51 and 3.64 Å, respectively. The columns are arranged such that the pentafluorophenyl and the phenyl moieties alternate within a column.

Thermolysis of **1a** in refluxing ethanol for 96 h. produced a mixture of products. The expected cyclic product 1,2,3,4-tetrafluorodibenzo[*b*,*f*][1,4]oxazepine, **2a**, was isolated as a

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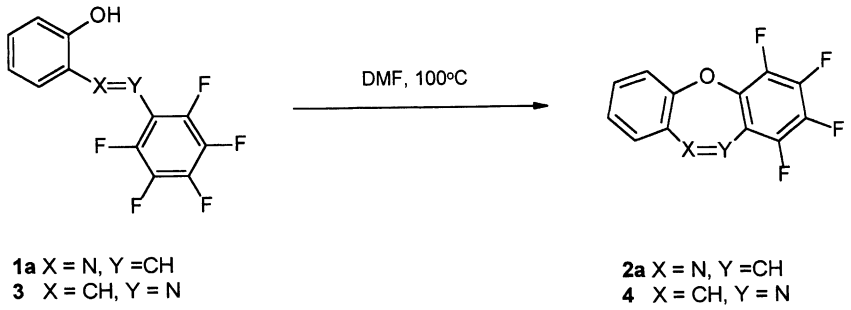
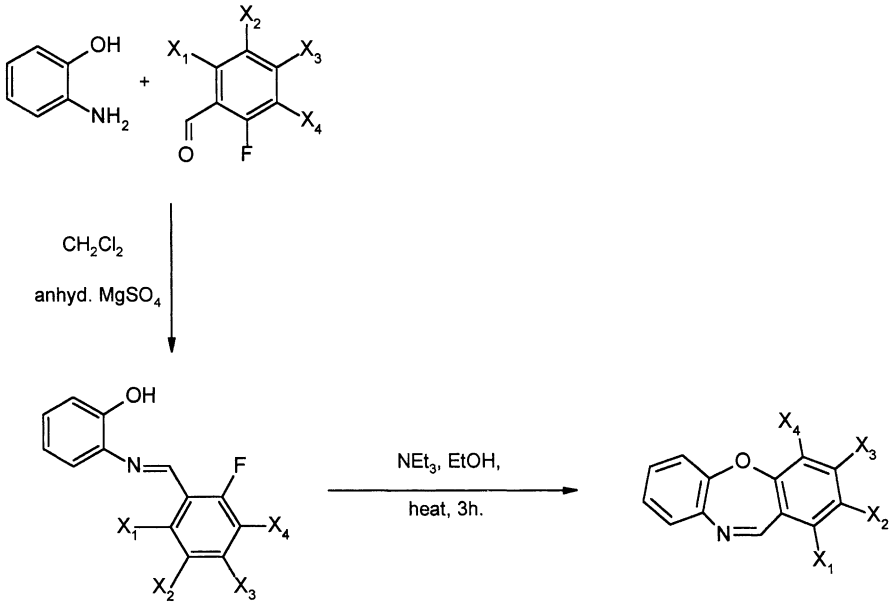


1a X = N, Y =CH
3 X = CH, Y = N

2a X = N, Y =CH
4 X = CH, Y = N

Scheme 1.



1a $X_1 = X_2 = X_3 = X_4 = F$
1b $X_1 = X_2 = X_4 = F, X_3 = H$
1c $X_1 = F, X_2 = X_3 = X_4 = H$
1d $X_1 = X_2 = X_3 = X_4 = H$

2a $X_1 = X_2 = X_3 = X_4 = F$
2b $X_1 = X_2 = X_4 = F, X_3 = H$
2c $X_1 = F, X_2 = X_3 = X_4 = H$
2d $X_1 = X_2 = X_3 = X_4 = H$

Scheme 2.

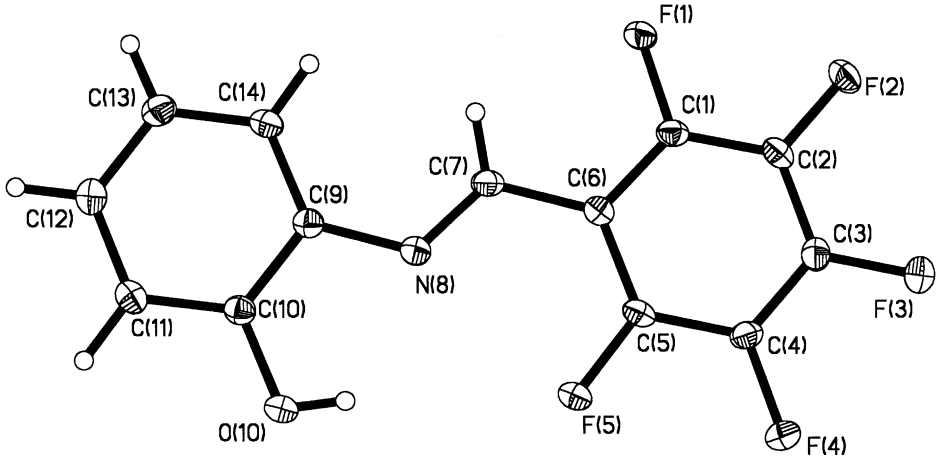


Fig. 1. Molecular structure of 2-[(2,3,4,5,6-pentafluorobenzylidene)amino]phenol **1a** with thermal ellipsoids at the 30% level.

Table 1
Crystallographic data for 2-[(2,3,4,5,6-pentafluorobenzylidene)amino]phenol, **1a**, and 1,2,3,4-tetrafluorodibenzo[*b*,*f*][1,4]oxazepine, **2a**

	1a	**2a**
Formula	$C_{13}H_6F_5NO$	$C_{13}H_5F_4NO$
Formula weight	287.19	267.18
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/n$
a (Å)	6.3133(9)	7.4091(6)
b (Å)	7.1840(10)	21.5604(16)
c (Å)	12.2583(17)	13.3325(10)
α (°)	81.888(2)	–
β (°)	86.162(3)	97.966(2)
γ (°)	86.896(3)	–
V (Å^3)	548.61(13)	2109.2(3)
Z	2	8
D_c (g cm^{-3})	1.739	1.683
Crystal size (mm)	0.43 × 0.32 × 0.11	0.42 × 0.24 × 0.19
μ (mm^{-1})	0.169	0.156
2θ range (°)	3 → 58	3 → 58
Total reflections	6390	24369
Unique reflections (R_{int})	2475 (0.0391)	4967 (0.0804)
Observed reflections ($I > 2\sigma(I)$)	1580	2501
Parameters	205	383
Final R indices ($I > 2\sigma(I)$)	R_1 0.0469, wR_2 0.1160	R_1 0.0503, wR_2 0.1048
R indices (all data)	R_1 0.0744, wR_2 0.1303	R_1 0.1145, wR_2 0.1254
Weighting scheme	$w = 1/[\sigma^2(F_0^2) + \{0.0784(F_0^2 + 2F_c^2)/3\}^3]$	$w = 1/[\sigma^2(F_0^2) + \{0.0572(F_0^2 + 2F_c^2)/3\}^3]$
Max., min. $\Delta\rho$ (eÅ^{-3})	0.32, −0.24	0.26, −0.27
Goodness of fit on F^2	0.940	0.881
Data completeness	0.87	0.92

Estimated standard deviations are given in parentheses. Data were collected at 153(2) K on a Bruker DXS SMART diffractometer with graphite monochromator and Mo Kα radiation ($\lambda = 0.71073$ Å).

Table 2
Selected distances (Å) and angles (°) for 2-[(2,3,4,5,6-pentafluorobenzylidene)amino]phenol, **1a**

N(8)–C(7)	1.261(3)
C(7)–C(6)	1.463(3)
N(8)–C(9)	1.412(2)
O(10)–C(10)	1.361(2)
Mean C–F	1.341(2)
Mean C–C (C_6F_5)	1.385(3)
Mean C–C (C_6H_4OH)	1.392(3)
C(7)–N(8)–C(9)	122.50(17)
N(8)–C(7)–C(6)	122.74(18)
C(7)–C(6)–C(1)	119.46(17)
C(7)–C(6)–C(5)	124.79(17)
C(1)–C(6)–C(5)	115.76(17)
N(8)–C(9)–C(10)	113.38(16)
N(8)–C(9)–C(14)	127.48(17)
C(10)–C(9)–C(14)	119.14(17)
O(10)–C(10)–C(9)	119.15(17)
F(1)–C(1)–C(6)	119.47(16)
F(5)–C(5)–C(6)	121.15(16)
C(1)–C(6)–C(7)–N(8)	−172.9(2)
C(6)–C(7)–N(8)–C(9)	179.7(2)
C(7)–C(8)–N(8)–C(10)	−176.4(2)

Estimated standard deviations are given in parentheses.

pale yellow solid in ca. 50% yield by extraction with hexane, leaving a red residue. Compound **2a** was fully characterised by elemental analysis, mass spectrometry and NMR and IR spectroscopies. The ^{19}F spectrum of **2a**, recorded in *d*-chloroform, shows four resonances of equal intensity indicative of four non-equivalent fluorine environments in the range δ −140 to −165, and the ^{1}H NMR spectrum shows the imine hydrogen atom resonance at δ 8.57. These spectral data are similar to those reported for **2a** in acetone and THF [1]. The identity of the red residue, which is insoluble in chloroform, but completely soluble in acetone is unknown. The ^{1}H and ^{19}F NMR spectra of the residue are simple and similar to those of **2a**, but slightly broadened in the ^{19}F NMR spectrum. Mass spectrometry revealed no simple low molecular mass compound and the analytical data revealed a significantly lower proportion of carbon than for **2a**. We tentatively suggest that the residue may be a polymeric compound formed by intermolecular reactions. The formation of compound **2a** is presumably by an intramolecular S_NAr reaction whereby the phenolic oxygen, probably as phenoxide, attacks an *ortho*-C–F bond, after isomerisation to the *cis*-isomer [2–4]. The byproduct of this reaction would be expected to be hydrogen fluoride. Although this was not observed directly, the ^{19}F NMR spectrum of the crude product showed characteristic resonances at ca. δ −136.8 and −150.0, which can be assigned to the anions SiF_6^{2-} and

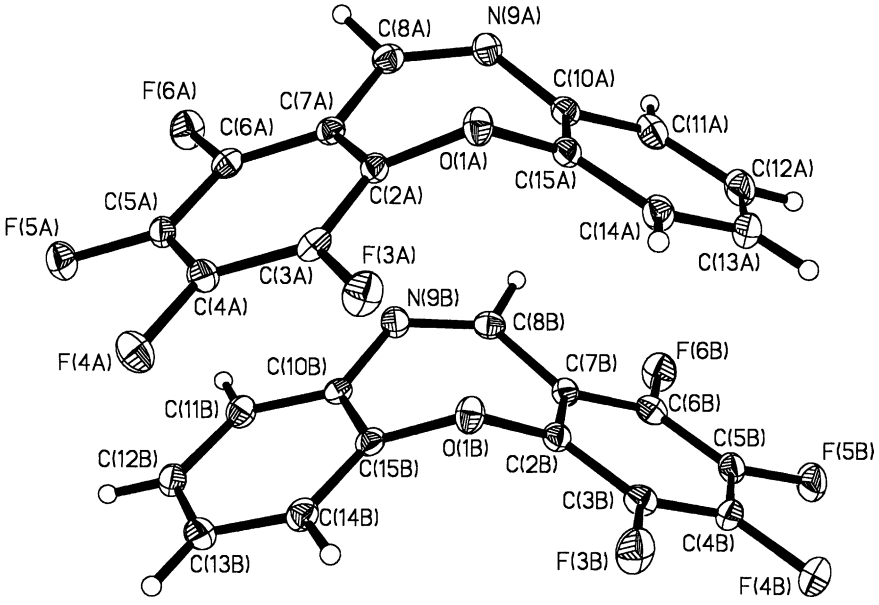


Fig. 2. Molecular structures of the two molecules in the asymmetric unit of 1,2,3,4-tetrafluorodibenzo[*b*,*f*][1,4]oxazepine **2a** with thermal ellipsoids at the 30% level.

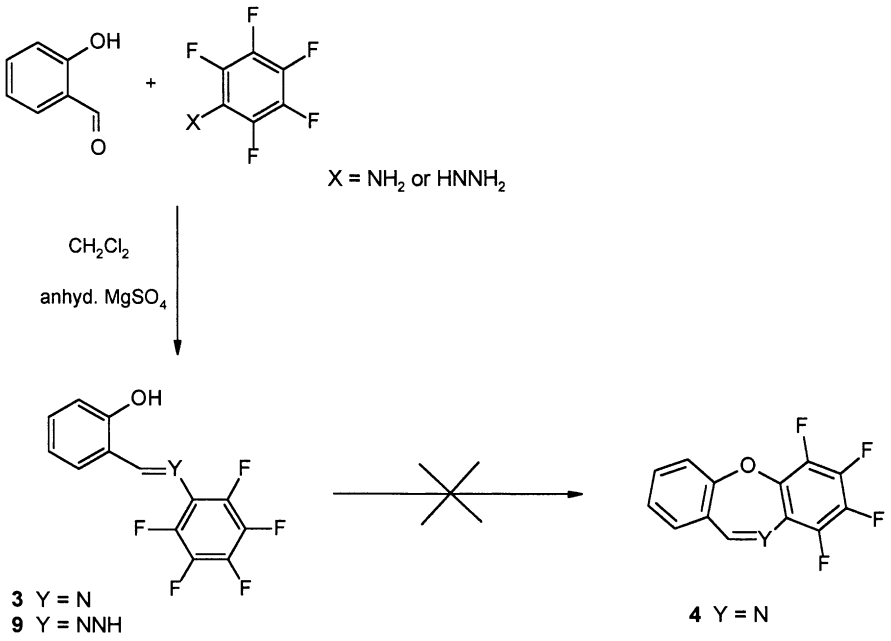
BF_4^-, respectively. These anions are formed by the reaction of HF with the borosilicate glass reaction vessel [18]. Further confirmation of the mechanism was obtained by addition of a slight excess of triethylamine to the reaction, which greatly reduced the time of the reaction to 3 h. and also the amount of red by-product, to give **2a** in ca. 80% yield.

The structure of **2a** has been determined by single-crystal X-ray diffraction (Fig. 2). Crystallographic data are given in Table 1 and selected bond distance and angles are given in Table 3. The asymmetric unit of **2a** contains two independent molecules **A** and **B**, which are enantiomers by virtue of the buckling of the seven-membered ring. The angles between the planes defined by C_6H_4 and C_6F_4, 145(1) and 147(1)° for **A** and **B**, respectively, are similar to that of 144° between the two C_6H_4 planes of the similar compound 2-chloro-11-(4-methylpiperazin-1-yl)dibenz[*b*,*f*][1,4]oxazepine (loxapine) [19]. Although not confirmed, the interconversion of the enantiomers of **2a** is presumably rapid in solution, since interconversions of enantiomers of similar compounds comprising seven-membered rings have been found to have low activation energies (ca. 40 kJ mol^{-1}) [20]. The bond distances and angles for **A** and **B** are identical within experimental error. The molecules are arranged into columns consisting of alternating **A** and **B** via $\pi\cdots\pi$ stacking (distances of 3.62 and 3.78 Å). These columns are arranged in pairs resulting from formation of C–H···N (bridging C–H to imine of an adjacent molecule) hydrogen bonded dimers (H···O 2.51(2) Å, C···N 3.504(3) Å and an C–H···N angle of 169(1)°). As in **1a** the columns are arranged such that the tetrafluorophenyl and the phenyl moieties alternate within a column. The bond distances of the seven-membered ring are identical within experimental error with those of related dibenz[*b*,*f*][1,4]oxazepines, such as loxapine, the structure of which has been determined for orthorhombic [19] and monoclinic polymorphs [21], and 2-chloro-11-(piperazin-1-yl)dibenz[*b*,*f*][1,4]oxazepine (amoxapine) [21]. The angles are however significantly different. In particular, the N=C–C and C–O–C angles are ca. 3 and 4° more obtuse, respectively, than for the loxapine and amoxapine. Presumably this is a consequence of the piperazinyl substituent at the imine carbon atom of loxapine and amoxapine.

Table 3
Selected bond distances (Å) and angles (°) for 1,2,3,4-tetrafluorodibenzo[*b*,*f*][1,4]oxazepine, **2a**

	Molecule **A**	Molecule **B**
N–C(8)	1.287(3)	1.276(3)
N–C(10)	1.405(3)	1.415(3)
C(7)–C(8)	1.472(3)	1.477(3)
O(1)–C(2)	1.378(3)	1.372(3)
O(1)–C(15)	1.398(3)	1.407(3)
Mean C–F	1.343(3)	1.345(3)
Mean C–C (C_6F_4)	1.379(3)	1.379(3)
Mean C–C (C_6H_4)	1.388(4)	1.385(4)
C(8)–N–C(10)	123.1(2)	123.3(2)
N–C(8)–C(7)	129.1(2)	129.6(2)
C(8)–C(7)–C(2)	122.7(2)	122.7(2)
C(8)–C(7)–C(6)	120.1(2)	119.6(2)
C(2)–C(7)–C(6)	117.2(2)	117.5(2)
N–C(10)–C(11)	117.0(2)	116.7(2)
N–C(10)–C(15)	126.0(2)	125.8(2)
C(11)–C(10)–C(15)	116.9(2)	117.4(2)
C(2)–O–C(15)	114.72(17)	115.60(17)
O–C(2)–C(7)	121.4(2)	121.7(2)
O–C(15)–C(10)	120.9(2)	121.1(2)

Estimated standard deviations are given in parentheses.



Scheme 3.

Using the same conditions as for the synthesis of **2a**, the fluorinated 2-[(benzylidene)amino]phenols, **1b** and **1c**, gave the respective polyfluorodibenz[*b*,*f*][1,4]oxazepines, **2b** and **2c**, in yields of ca. 65% (Scheme 2). The convenience of the two-step syntheses of fluorinated dibenz[*b*,*f*][1,4]oxazepines suggested that this route may also offer advantages over the four-step synthesis of the non-fluorinated dibenz-[*b*,*f*][1,4]oxazepine, **2d** which involves initial formation of the ether linkage by the reaction of phenol with 2-chloronitrobenzene, followed by reduction of the nitro group, conversion to the formamide, and cyclisation to form the seven-membered ring by a Bischler–Napieralski type reaction [22]. However, attempts to prepare **2d** by cyclisation of 2-[(2-fluorobenzylidene)amino]phenol, **1d**, in ethanol with excess triethylamine were unsuccessful, even after prolonged reflux.

2-[(2,3,4,5,6-Pentafluorophenylimino)methyl]phenol, **3** [1], was prepared similarly to **1a** from salicylaldehyde and pentafluoroaniline (Scheme 3). Consistent with the less nucleophilic nature of the nitrogen of pentafluoroaniline in comparison to aminophenol and the less electrophilic nature of the carbonyl carbon of salicylaldehyde in comparison to fluorinated benzaldehydes, the reaction was slower than for the formation of **1a**, and **3** was obtained in a relatively low yield even after heating for 14 h. Imine **3** was characterised by elemental analysis and NMR and IR spectroscopies. Crystals of **3** suitable for an X-ray diffraction study were obtained from dichloromethane, and since **3** has been reported to exhibit polymorphism [23], it was considered worthwhile to perform a cell parameter determination of the crystals we obtained. The crystallographic and structural data are entirely consistent with the α2 polymorph [23].

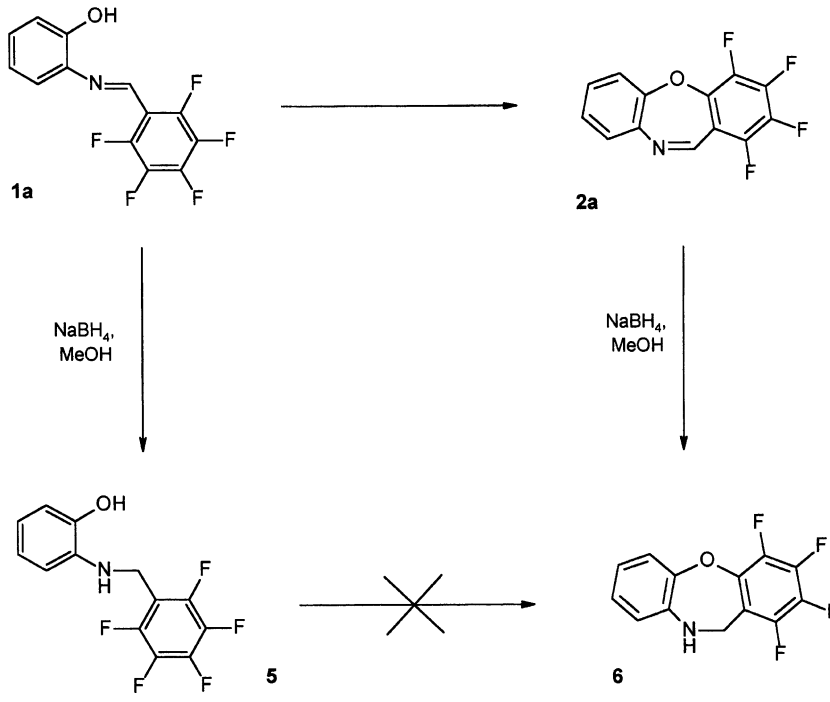
Attempts to prepare 6,7,8,9-tetrafluorodibenzo[*b*,*f*][1,4]-oxazepine, **4**, by cyclisation of **3** using the same conditions as for the formation of **2a** were unsuccessful, even after prolonged reflux. Evidently this reaction is dependent on the solvent. That **1a** reacts readily and **3** does not is consistent with an S_NAr reaction. As expected, the electron-withdrawing –CH=N substituent enhances the susceptibility of C_6F_5 to nucleophilic attack, whereas the electron-donating –N=CH substituent has the opposite effect.

We were interested in investigating whether similar fluorinated compounds would undergo similar cyclisations. Reduction of imine **1a** with sodium borohydride yielded

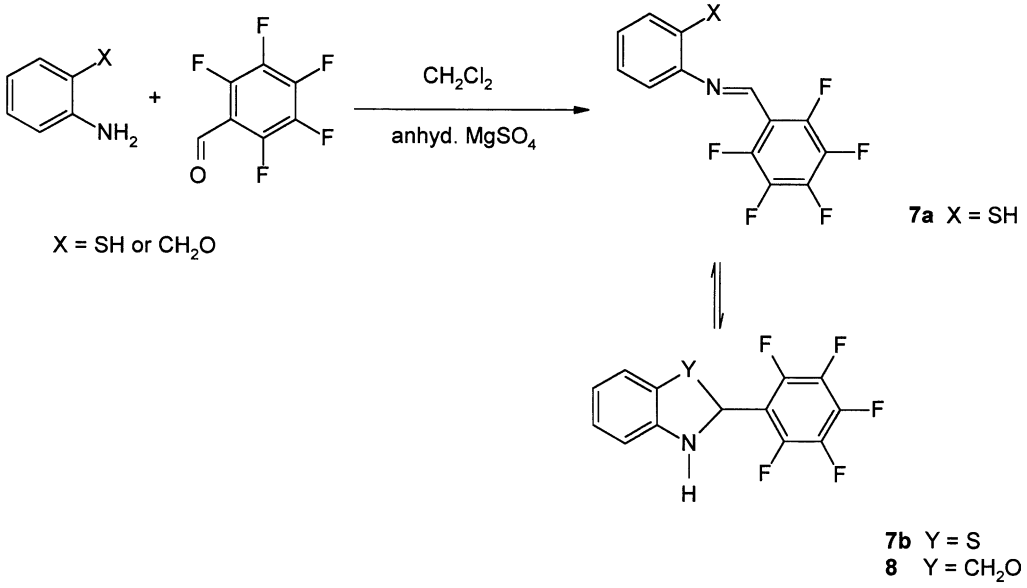
2-(2,3,4,5,6-Pentafluorobenzylamino)phenol, **5**, in 79% yield (Scheme 4). Attempts to prepare 1,2,3,4-tetrafluoro-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine, **6**, by cyclisation of **5** were unsuccessful. Compound **6** has previously been prepared by reduction of dibenz[*b*,*f*][1,4]oxapeine, **2a** [17].

In an attempt to prepare the thiophenol analogue of **1a**, pentafluorobenzaldehyde was treated with 2-aminothiophenol. The product, **7**, comprised a mixture of two isomers (Scheme 5). 2-[(2,3,4,5,6-Pentafluorobenzylidene)amino]-thiophenol, **7a**, is the minor isomer and 2-(2,3,4,5,6-pentafluorophenyl)-2,3-dihydrobenzothiazole, **7b**, is the major isomer as determined by ^{1}H NMR spectroscopy.

In an attempt to prepare a fluorinated aromatic imine containing a benzyl alcohol functionality, pentafluorobenzaldehyde was treated with 2-aminobenzyl alcohol (Scheme 5). The product **8** was characterised spectroscopically as 2-(2,3,4,5,6-pentafluorophenyl)-1,4-dihydro-2H-benzo[*d*][1,3]oxazine. The ^{1}H and ^{19}F NMR spectra also contained resonances which suggest that the imine isomer may also be present in small amounts (<5%). The pentafluorophenylhydrazone, **9**,



Scheme 4.



Scheme 5.

was prepared from 2-hydroxyphenylhydrazine and pentafluorobenzaldehyde as for the imine **1a** (Scheme 3). None of **7–9** underwent cyclisation on treatment with triethylamine in refluxing ethanol.

3. Conclusion

Cyclisation of 2-[(polyfluorobenzylidene)amino]phenols to give fluorinated dibenzo[*b*,*f*][1,4]oxazepines can be conveniently carried out in reluxing ethanol by the addition of triethylamine. The reaction occurs by an intramolecular S_NAr reaction and at least two fluorine atoms are necessary on the benzylidene arene. The difference in reactivity between **1a** and **3** indicates that under these conditions it is necessary for the electrophilic arene to be a benzylidene and not a phenylimine. The lack of reactivity of **9** further supports this conclusion. The lack of reactivity of **5**, **7** and **8** indicates also that the nucleophile must be a phenoxide.

4. Experimental

4.1. Instrumentation

The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded using Bruker DPX300 or DRX500 spectrometers in $CDCl_3$ unless stated otherwise. ^{1}H (300.01 or 500.13 MHz) were referenced internally, using the residual protio solvent resonance, relative to $SiMe_4$ (δ 0) and ^{19}F (282.26 MHz) externally to $CFCl_3$ (δ 0). All chemical shifts are quoted in δ (ppm), using the high frequency positive convention, and coupling constants in Hz. Unless stated otherwise, NMR spectra were recorded in $CDCl_3$. IR spectra were recorded as KBr dics. Mass spectra were recorded on a VG Autospec X-series mass spectrometer. Elemental analyses were carried out by A.S.E.P., The School of Chemistry, The Queen's University of Belfast.

4.2. Materials

The compounds $C_6H_4(OH)NH_2$-1,2, $C_6H_4(CH_2OH)NH_2$-1,2, $C_6H_4(SH)NH_2$-1,2, $C_6H_4(OH)CHO$-1,2, C_6F_5CHO, C_6HF_4CHO-2,3,5,6, $C_6H_3F_2CHO$-2,6, C_6H_3FCHO-2, $C_6F_5NH_2$ and $C_6F_5NHNH_2$ (Aldrich) were used as supplied.

4.3. Syntheses of 2-[(polyfluorobenzylidene)amino] phenols

A solution of the appropriate polyfluorobenzaldehyde and a stoichiometric quantity of 2-aminophenol in CH_2Cl_2 over anhydrous $MgSO_4$ was left at room temperature for 24 h. The solution was filtered and the solvent removed by rotary evaporation affording the product.

4.3.1. 2-[(2,3,4,5,6-Pentafluorobenzylidene)amino] phenol (**1a**)

Yellow crystals, yield 74%. Analysis: calc. for $C_{13}H_6F_5NO$: C, 54.4; H, 2.1; N, 4.9; found: C, 54.3; H, 2.1; N, 5.1%. HRMS: $C_{13}H_6F_5NO$ requires 287.03646; found: M^+ 287.03696. IR: ν_{max}(KBr) (cm^{-1}) 3368, 1650, 1619, 1597, 1584, 1525, 1495, 1481, 1420, 1387, 1369, 1291, 1247, 1212, 1176, 1150, 1130, 1027, 1013, 965, 953, 936, 819, 755, 745, 673, 653, 570 and 471. ^{1}H NMR: 8.82 (1H, s, HC=N), 7.35 (1H, dd, *J* 8.0, 1.3, C_6H_4), 7.28 (1H, m, C_6H_4), 7.04 (1H, dd, *J* 8.2, 1.2, C_6H_4), 6.93 (1H, m, C_6H_4). ^{19}F NMR: −142.25 (2F, dm, *J* 15.7, F_{ortho}), −149.76 (1F, t, *J* 20.8, F_{para}), −161.60 (2F, m, F_{meta}).

4.3.2. 2-[(2,3,5,6-Tetrafluorobenzylidene)amino] phenol (**1b**)

Yellow crystals, yield 77%. Analysis: calc. for $C_{13}H_7F_4NO$: C, 58.0; H, 2.6; N, 5.2; found: C, 57.3; H, 2.8; N, 5.1%. HRMS: $C_{13}H_7F_4NO$ requires 269.04638; found M^+ 269.04707. IR: ν_{max}(KBr) (cm^{-1}) 3358, 1645, 1626, 1595, 1495, 1483, 1390, 1378, 1286, 1273, 1249, 1205, 1178, 1145, 1047, 939, 845, 808, 753, 745, 699, 656, 579 and 458. ^{1}H NMR: 8.82 (1H, s, HC=N), 7.30 (1H, dd, *J* 8.1, 1.4), 7.19 (1H, m), 7.14 (1H, m), 6.97 (1H, dd, *J* 8.2, 1.3), 6.86 (1H, m). ^{19}F NMR: −138.91 (2F, m), −143.06 (2F, m).

4.3.3. 2-[(2,6-Difluorobenzylidene)amino]phenol (**1c**)

Yield 46%. Analysis: calc. for $C_{13}H_9F_2NO$: C, 66.95; H, 3.9; N, 6.0; found: C, 66.4; H, 3.55; N, 5.6%. HRMS: $C_{13}H_9F_2NO$ requires 233.06522; found: M^+ 233.06434. IR: ν_{max}(KBr) (cm^{-1}) 3323, 1623, 1603, 1588, 1565, 1470, 1382, 1291, 1249, 1197, 1149, 1009, 966, 927, 856, 793, 782, 739, 711, 645, 580, 530, 519, 506, 468 and 458. ^{1}H NMR: 8.86 (1H, s, HC=N), 7.33 (2H, m), 7.16 (1H, t, *J* 7.2), 6.95 (3H, m), 6.87 (1H, m). ^{19}F NMR: −112.57 (2F, dm, *J* 7.0).

4.3.4. 2-[(2-Fluorobenzylidene)amino]phenol (**1d**)

Yield 71%. Analysis: calc. for $C_{13}H_{10}FNO$: C, 72.55; H, 4.5; N, 6.4; found: C, 72.2; H, 4.5; N, 6.4%. HRMS: $C_{13}H_{10}FNO$ requires 215.07464; found: M^+ 215.07416. IR: ν_{max}(KBr) (cm^{-1}) 3426, 1619, 1586, 1573, 1488, 1455, 1384, 1361, 1280, 1249, 1215, 1202, 1174, 1152, 1091, 1030, 974, 934, 859, 851, 820, 776, 764, 754, 600, 575, 482 and 472. ^{1}H NMR: 8.95 (1H, s, HC=N), 8.10 (1H, td, *J* 7.6, 1.6), 7.41 (1H, m), 7.27 (1H, dd, *J* 8.0, 1.4), 7.13 (3H, m), 6.95 (1H, dd, *J* 8.2, 1.2), 6.85 (1H, m). ^{19}F NMR: −120.96 (1F, m).

4.4. Syntheses of dibenzo[b,f][1,4]oxazepines

4.4.1. 1,2,3,4-Tetrafluorodibenzo[b,f][1,4]oxazepine (**2a**)

A solution of **1a** (0.152 g, 0.52 m mol) in ethanol (50 cm^3) was treated with an excess of NEt_3 (ca. 1 cm^3) at reflux. After 3 h the solvent was removed by rotary evaporation to yield an orange oil, which was extracted several times with hexane. The extracts were combined and the solvent removed by rotary evaporation to give **2a** as a yellow solid (0.108 g, 78%). Analysis: calc. for $C_{13}H_5F_4NO$: C, 58.4; H, 1.9; N, 5.2; found: C, 57.9; H, 2.3; N, 5.0%. HRMS: $C_{13}H_5F_4NO$ requires 267.03073; found: M^+ 267.02969. IR ν_{max}(KBr) (cm^{-1}) 2965, 1644, 1608, 1517, 1494, 1473, 1449, 1400, 1305, 1263, 1216, 1180, 1127, 1032, 1012, 963, 921, 875, 852, 826, 770, 738, 683, 668, 642, 615, 575, 549 and 462. ^{1}H NMR: 8.67 (1H, s, HC=N), 7.39 (1H, m), 7.28 (2H, m), 7.20 (1H, m). ^{19}F NMR: −144.30 (1F, m), −149.31 (1F, dd, $J \approx 19.5$, 19.5), −1565.94 (1F, m), −160.91 (1F, m).

4.4.2. 1,2,4-Trifluorodibenzo[b,f][1,4]oxazepine (**2b**)

Yield 67%. HRMS: $C_{13}H_6F_3NO$ requires 249.04015; found: M^+ 249.04098. IR: ν_{max}(KBr) (cm^{-1}) 1627, 1606, 1591, 1495, 1473, 1441, 1372, 1287, 1265, 1253, 1214, 1177, 1120, 1099, 1031, 960, 924, 853, 804, 768, 739, 722, 649 and 555. ^{1}H NMR [$(CD_3)_2CO$]: 8.66 (1H, s, HC=N), 7.51 (1H, m), 7.24 (3H, m), 7.11 (1H, m). ^{19}F NMR [$(CD_3)_2CO$]: −135.58 (1F, dm, *J* 13.9), −140.37 (1F, dm, *J* 20.8), −147.28 (1F, m).

*4.4.3. 1-Fluorodibenzo[b,f][1,4]oxazepine (**2c**)*

Yield 66%. HRMS: $C_{13}H_8FNO$ requires 213.05899; found: M^+ 213.05788. IR: ν_{max}(KBr) (cm^{-1}) 1674, 1622, 1585, 1484, 1379, 1270, 1222, 1102, 1065, 1031, 980, 885, 828, 737, 707, 612 and 543. ^1H NMR: 8.55 (1H, s, HC=N), 7.32 (2H, m), 7.15 (2H, m), 7.04 (1H, m), 6.86 (2H, m). ^{19}F NMR: −115.81 (s).

*4.5. Thermolysis of 2-[(2,3,4,5,6-pentafluorobenzylidene)amino]phenol (**1a**)*

A solution of **1** (0.350 g, 1.20 m mol) in ethanol (70 cm^3) was heated under reflux for 96 h. After cooling, the solvent was removed by rotary evaporation to give a red solid, which was extracted with hexane. Removal of the solvent from the hexane extract yielded **2a** as yellow crystals. Yield 0.160 g (50%). The residue was obtained as 0.135 g of red solid, which was washed with a small amount of chloroform and dried in vacuo. (Found: C, 44.0; H, 2.20; N, 5.15); ν_{max}(KBr) (cm^{-1}) 3254, 1636, 1580, 1535, 1497, 1473, 1449, 1395, 1315, 1293, 1262, 1225, 1156, 1105, 1019, 758, 599 and 473. ^1H NMR [$(CD_3)_2CO$]: 8.93 (1H, s, HC=N), 7.60 (3H, m, C_6H_4), 7.43 (1H, m, C_6H_4). ^{19}F NMR [$(CD_3)_2CO$)]: −144.70 (1F, m, C_6F_4-terminal), −151.08 (1F, dd, $J \approx$ 23.4, 23.4, C_6F_4), −158.20 (1F, dd, J 20.7, 10.4, C_6F_4-terminal), −162.20 (1F, dd, $J \approx$ 20.7, 20.7, C_6F_4).

*4.6. 2-[(2,3,4,5,6-Pentafluorophenylimino)methyl]phenol (**3**)*

A solution of pentafluoroaniline (1.00 g, 5.46 m mol) and salicylaldehyde (0.75 g, 6.14 m mol) in CH_2Cl_2 (100 cm^3) was refluxed over anhydrous $MgSO_4$ (ca. 1 g) for 14 h. The solution was filtered and the solvent removed by rotary evaporation affording a yellow solid, which was washed with hexane (100 cm^3) to remove unreacted starting materials and dried in vacuo to yield pale yellow crystals of **3**. Yield 0.335 g, 21%. Analysis: calc. for $C_{13}H_6F_5NO$: 54.4; H, 2.1; N, 4.9; found: C, 54.1; H, 2.2; N, 4.9%. IR: ν_{max}(KBr) (cm^{-1}) 1652, 1614, 1577, 1510, 1488, 1463, 1432, 1392, 1367, 1278, 1236, 1217, 1205, 1156, 1033, 979, 902, 790, 763, 722 and 468. ^1H NMR: 8.75 (1H, s, HC=N), 7.37 (2H, m, C_6H_4), 6.98 (1H, d, J 8.4, C_6H_4), 6.91 (1H, dd, $J \approx$ 7.5, 7.5, C_6H_4). ^{19}F NMR: −152.36 (2F, dd, J 20.7, 6.1, F_{ortho}), −158.58 (1F, t, J 20.9, F_{para}), −162.75 (2F, m, F_{meta}).

*4.7. Synthesis of 2-(2,3,4,5,6-pentafluorobenzylamino)phenol (**5**)*

Sodium borohydride (0.66 g, 17.5 m mol) was added in small portions to **1a** (0.62 g, 2.16 m mol) in methanol (80 cm^3) and the mixture left for 12 h. Water (10 cm^3) was added and the methanol removed by rotary evaporation. The product was extracted into dichloromethane (2 × 50 cm^3). The combined extracts were dried over magnesium sulphate and filtered. The solvent was removed by rotary evaporation to give **5** as a yellow-brown crystalline solid. Yield 0.49 g, 79%. Analysis: calc. for $C_{13}H_8F_5NO$: C, 54.1; H, 2.35; N, 4.9; found: C, 54.0; H, 2.8; N, 4.8%. HRMS: $C_{13}H_8F_5NO$ requires 289.05261; found: M^+ 289.05298. IR: ν_{max}(KBr) (cm^{-1}) 3328, 2708, 1658, 1602, 1522, 1504, 1460, 1447, 1417, 1356, 1325, 1300, 1278, 1247, 1185, 1157, 1120, 1113, 1060, 1043, 1021, 950, 929, 871, 854, 830, 764, 747, 731, 685, 600, 583, 562 and 462. ^1H NMR: 6.86 (1H, m, C_6H_4), 6.78 (1H, m, C_6H_4), 6.69 (2H, m, C_6H_4), 4.93 (1H, br s, NH), 4.47 (2H, s, CH_2). ^{19}F NMR: −144.10 (2F, m, F_{ortho}), −155.43 (1F, t, J 20.7, F_{para}), −162.28 (2F, m, F_{meta}).

*4.8. 2-[(2,3,4,5,6-Pentafluorobenzylidene)amino]-thiophenol (**7a**) and 2-(2,3,4,5,6-pentafluorophenyl)-2,3-dihydrobenzothiazole (**7b**)*

A solution of 2-aminothiophenol (1.40 g, 0.011 mol) and pentafluorobenzaldehyde (2.27 g, 0.012 mol) in CH_2Cl_2 (70 cm^3) over anhydrous $MgSO_4$ (ca. 2 g) was left at room temperature for 24 h. The solution was filtered and the solvent removed by rotary evaporation affording 2.77 g of a mixture of **7a** and **7b**.

Yield 83%. Analysis: calc. for $C_{13}H_6F_5NS$: C, 51.5; H, 2.0; N, 4.6; found: C, 51.3; H, 1.9; N, 4.6%. HRMS: $C_{13}H_6F_5NS$ requires 303.14112; found: M^+ 303.01405. IR: ν_{max}(KBr) (cm^{-1}) 3402, 2963, 1652, 1618, 1572, 1523, 1498, 1462, 1419, 1378, 1316, 1262, 1153, 1137, 1054, 1014, 966, 861, 799, 760, 732, 697, 663, 563, 474 and 458. **7a** ^1H NMR: 8.53 (1H, s, HC=N), 8.11 (1H, dd, J 8.4, 0.7, C_6H_4), 7.90 (1H, dd, J 8.5, 1.1, C_6H_4), 7.45 (2H, m). ^{19}F NMR: −138.82 (2F, m, F_{ortho}), −150.56 (1F, t, J 20.5, F_{para}), −161.08 (2F, m, F_{meta}). **7b** ^1H NMR: 6.97 (1H, dd, J 7.5, 2.3, C_6H_4), 6.89 (1H, m, C_6H_4), 6.71 (1H, m, C_6H_4), 6.62 (1H, s, NCHS), 6.59 (1H, dd, J 7.8, 0.8, C_6H_4), 4.23 (1H, br s, NH). ^{19}F NMR: −142.21 (2F, dd, J 22.0, 7.0, F_{ortho}), −154.49 (1F, t, J 21.0, F_{para}), −161.85 (2F, m, F_{meta}).

*4.9. 2-(2,3,4,5,6-Pentafluorophenyl)-1,4-dihydro-2H-benzo[d][1,3]oxazine (**8**)*

A solution of 2-aminobenzyl alcohol (0.58 g, 4.7 m mol) and pentafluorobenzaldehyde (0.93 g, 4.7 m mol) in CH_2Cl_2 (100 cm^3) over anhydrous $MgSO_4$ (ca. 2 g) was left at room temperature for 24 h. The solution was filtered and the concentrated to 20 cm^3 by rotary evaporation. Addition of hexane (20 cm^3) gave cream crystals of **8**, which were washed with hexane and dried in vacuo. Yield 53%. Analysis: calc. for $C_{14}H_8F_5NO$: C, 55.8; H, 2.7; N, 4.65; found: C, 56.0; H, 2.6; N, 4.8%. HRMS: $C_{14}H_8F_5NO$ + H requires 302.06043; found: M^+ 302.06091. IR: ν_{max}(KBr) (cm^{-1}) 3368, 1650, 1619, 1597, 1585, 1526, 1496, 1481, 1420, 1388, 1369, 1292, 1316, 1247, 1212, 1176, 1150, 1130, 1028, 1013, 965, 954, 937, 875, 819, 755, 745, 673, 653, 635, 570 and 471. ^1H NMR: 7.08 (1H, m, C_6H_4), 6.90 (2H, m, C_6H_4), 6.73 (1H, d, J 7.9, C_6H_4), 5.84 (1H, s, NCHO), 5.11, 5.02 (2H, AB quartet, J 14.0, $C_6H_4CH_2O$). ^{19}F NMR:

−142.18 (2F, d, *J* 6.0, F_{ortho}), −152.77 (1F, t, *J* 20.5, F_{para}), −161.40 (2F, m, F_{meta}).

4.10. 2-[N′-(2,3,4,5,6-pentafluorobenzylidene)hydrazino]phenol (**9**)

Salicylaldehyde (0.21 g, 1.72 m mol) and pentafluorohydrazine (0.35 g, 0.177 m mol) were treated as in 4.6 yielding 0.34 g of cream solid. Yield 66%. Analysis: calc. $C_{14}H_8F_5N_2O$ requires C, 51.7; H, 2.3; N, 9.3; found: C, 51.5; H, 1.9; N, 9.1%. HRMS: $C_{13}H_8F_5N_2O$ requires 302.04785; found: M^+ 302.04781. IR: ν_{max}(KBr) (cm^{-1}) 3304, 1660, 1622, 1601, 1571, 1545, 1532, 1501, 1459, 1388, 1263, 1218, 1202, 1170, 1143, 1130, 1104, 1023, 972, 950, 801, 786, 759, 670, 575 and 472. ^{1}H NMR: 10.35 (1H, s), 7.97 (1H, s), 7.28 (1H, m, C_6H_4), 7.17 (1H, dd, *J* 7.7, 1.6, C_6H_4), 6.99 (1H, d, *J* 8.2, C_6H_4), 6.91 (1H, m, C_6H_4). ^{19}F NMR: −157.51 (2F, d, *J* 20.0, F_{ortho}), −162.82 (2F, dd, *J* 22.5, 20.0, F_{meta}), −166.67 (1F, tm, *J* 22.5, F_{para}).

4.11. X-ray crystal structure determinations

Crystals of **1a**, **2a** and **3** were grown from dichloromethane. Data for **1a** and **2a** (Table 1) were collected using the SAINT-NT [24] software using φ/ω scans. Cell parameters for **3** were determined on a Siemens P3 diffractometer with graphite monochromated Cu Kα radiation at room temperature. Crystal stabilities for **1a** and **2a** were monitored via recollection of the first set of frames. There were no significant variations (<±1%). Cell parameters were obtained from 1959 and 3183 accurately centred reflections in the θ range 2–28° for **1a** and **2a**, respectively.

The structures were solved using direct methods and refined with the SHELXTL program package [25] and the non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen-atom positions were located from difference Fourier maps and then fully refined for **1a** and **2a**. The function minimised was $\sum[w(|F_0| - |F_c|^2)]$ with reflection weights $w^{-1} = [\sigma^2|F_0|^2 + (g_1P)^2 + (g_2P)]$ where $P = [\max|F_0|^2 + 2|F_c|^2]/3$. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 174440 and 174441. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

The cell parameters for **3** (monoclinic, $P2_1/c$, $a = 12.104(13)$, $b = 7.413(8)$, $c = 12.861(19)$ Å and $\beta = 95.91(10)°$) are entirely consistent with the α2 polymorph (monoclinic, $P2_1/c$, $a = 12.101$, $b = 7.373$, $c = 12.890$ Å and $\beta = 95.89°$) [25].

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References

[1] N.I. Petrenko, M.M. Kozlova, T.N. Gerasimova, J. Fluor. Chem. 36 (1987) 53.
[2] R.D. Chambers, Fluorine in Organic Chemistry, Wiley, New York, 1973 (Chapter 9).
[3] L.S. Kobrina, Fluor. Chem. Rev. 7 (1974) 1.
[4] G.M. Brooke, J. Fluor. Chem. 86 (1997) 1.
[5] A.V. Konstantinova, M.M. Kozlova, T.N. Gerasimova, Khim. Geterotsikl. Soedin. (1989) 668.
[6] R. Higginbottom, H. Suschitzky, J. Chem. Soc. (1962) 2367.
[7] F. Hunziker, F. Kunzle, O. Schindler, J. Schnutz, Helv. Chim. Acta 47 (1964) 1163.
[8] B. Ballantyne, F.W. Beswick, D.P. Thomas, Med. Sci. Law 13 (1973) 265.
[9] B. Ballantyne, D.W. Swanston, Acta Pharmacol. Toxicol. 35 (1974) 412.
[10] P. Holland, Br. J. Dermatol. 90 (1974) 657.
[11] D.G. Upshall, Tox. Appl. Pharmacol. 29 (1974) 30.
[12] R.E. Pattle, C. Schock, P. Dirnhuber, J.M. Creasey, Br. J. Exp. Path. 55 (1974) 213.
[13] J.W. Clayton Jr., Fluor. Chem. Rev. 1 (1967) 197.
[14] J.T. Welch, Bioorganic Chemistry of Fluorine, Wiley, New York, 1991.
[15] J.T.G. Hamilton, C.D. Murphy, M.R. Amin, D. O'Hagan, D.B. Harper, J. Chem. Soc., Perkin Trans. I (1998) 759.
[16] A.V. Konstantinova, T.N. Gerasimova, M.M. Kozlova, N.I. Petrenko, Khim. Geterotsikl. Soedin. (1989) 539.
[17] A.V. Konstantinova, O.D. Zborovskaya, T.N. Gerasimova, Khim. Geterotsikl. Soedin. (1990) 1679.
[18] M.J. Atherton, J. Fawcett, J.H. Holloway, E.G. Hope, A. Karaçar, D.R. Russell, G.C. Saunders, J. Chem. Soc., Dalton Trans. (1996) 3215.
[19] T.J. Petcher, H.-P. Weber, J. Chem. Soc., Perkin Trans. II (1976) 1415.
[20] M. Nógrádi, W.D. Ollis, I.O. Sutherland, J. Chem. Soc., Chem. Commun. (1970) 158.
[21] D.B. Cosulich, F.M. Lovell, Acta Cryst. B33 (1977) 1147.
[22] A.W.H. Wardrop, G.L. Sainsbury, J.M. Harrison, T.D. Inch, J. Chem. Soc., Perkin Trans. I (1976) 1279.
[23] S.V. Lindeman, V.G. Adrianov, S.G. Kravcheni, V.M. Potapov, K.A. Potekhin, Y.T. Struchkov, Zh. Strukt. Khim. 22 (1981) 123. (CSD code BANGOM02).
[24] SAINT-NT, Program for Data Collection and Data Reduction, Bruker-AXS, Madison, WI, 1998.
[25] G.M. Sheldrick, SHELXTL Version 5.0, A System for Structure Solution and Refinement, Bruker-AXS, Madison, WI, 1998.