Cyano-activated fluoro displacement reactions in the synthesis of cyanophenoxazines and related compounds†

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Cyano-activated fluoro displacement reactions between 2,3- and 3,4-difluorobenzonitriles and the nucleophiles catechol, 2-aminophenol, 2-aminobenzenethiol and benzene-1,2-dithiol either in DMF at 130 °C or in DMSO at rt, in the presence of potassium carbonate, lead to new substituted heterocycles or other species in high yield. Catechol at rt gives quantitative yields of cyanodibenzo[1,4]dioxines. 2-Aminophenol and 2-aminobenzenethiol at 130 °C give cyanophenoxazines and cyanophenothiazines, respectively, while at rt 2-aminophenol yields (aminophenoxy)cyanofluorobenzenes which can be converted into different cyanophenoxazines on heating in the presence or absence of base. The base-catalysed reactions involve a Smiles rearrangement. Benzene-1,2-dithiol yields cyanothianthrenes (130 °C) or a mixture of cyanothianthrene and bis(cyanofluorophenylsulfanyl)benzenes at rt.

Introduction

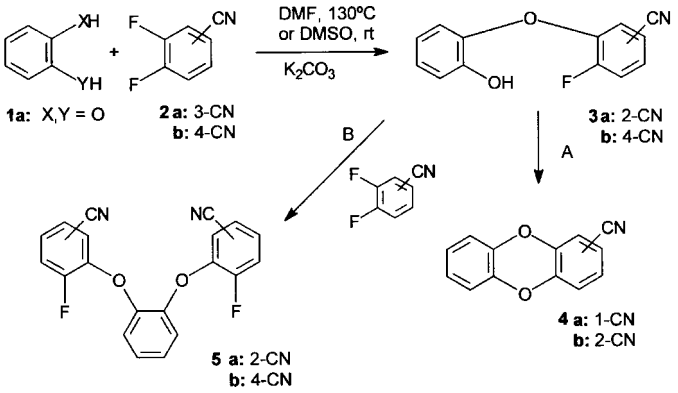
We recently reported a procedure for the simple and quantitative synthesis of a new family of cyano-substituted dibenzo[1,4]dioxines[1] involving a cyano-activated fluoro displacement reaction between catechol **1a**, or a catechol derivative, and either 2,3- or 3,4-difluorobenzonitrile **2a** or **2b** in an aprotic solvent, DMF, in the presence of potassium carbonate at 130 °C (Scheme 1). The reaction involved a combination of either a facile *ortho*- or *para*-fluoro displacement reaction and a, presumably, subsequent and less facile *meta*-fluoro displacement reaction; previous work demonstrated that cyano-activated fluoro displacement with 3-fluorobenzonitrile will proceed in *N*-methylpyrrolidinone (NMP) but only at the higher temperature of about 170 °C.[2] Following the initial displacement reaction, it is conceivable that reaction of the first-formed product **3a** or **3b** could follow either of two routes, an intramolecular cyclisation reaction (Scheme 1, path A) to form a cyanodibenzo[1,4]dioxine **4a** or **4b** or an intermolecular reaction with a second molecule of **2a** or **2b** to form a bis(ether nitrile) **5a** or **5b** (Scheme 1, path B). In fact the rate of the intramolecular *meta*-fluoro displacement reaction, involving cyclisation, was greatly accelerated relative to the previously described intermolecular *meta*-fluoro displacement[2] and cyanodibenzo[1,4]dioxines **4** were formed in quantitative yields.

Subsequently, as reported here, it was discovered that the same fluoro displacement reactions will also proceed at ambient temperatures if the solvent is changed to DMSO. Thus, even at room temperature, compound **3** will cyclise rather than the second hydroxyl group undergoing an intermolecular reaction to form a fluoro-substituted bis(ether dinitrile) **5a, 5b**, referred to here as an 'open product'.

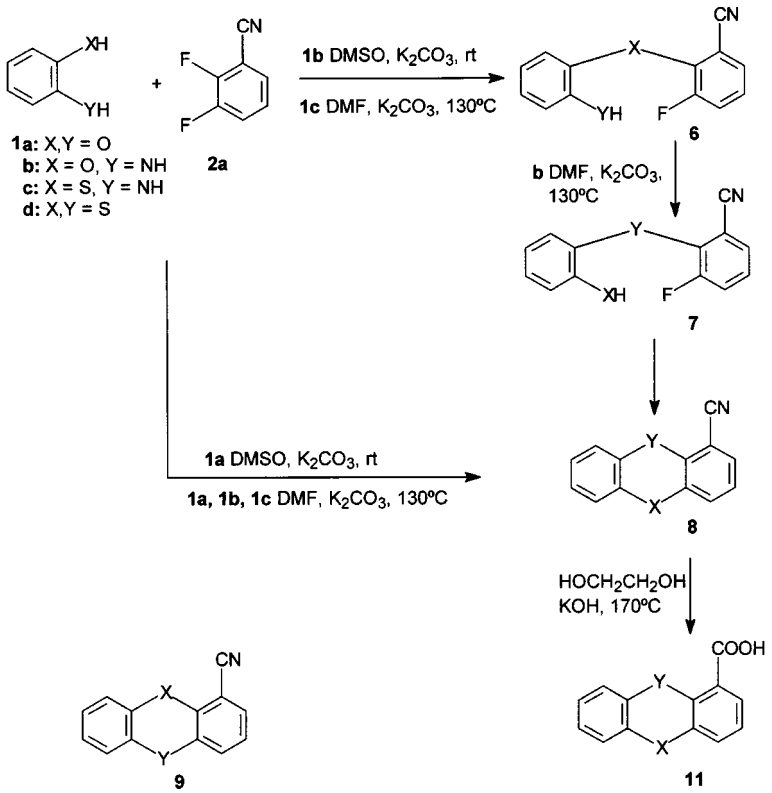
The potential of the cyano-activated fluoro displacement reactions in the synthesis of other heterocycles has also been explored. To this end, and to investigate the possibilities of synthesizing phenoxazines, phenothiazines and thianthrenes by fluoro displacement reactions, we treated 2,3- and 3,4-difluorobenzonitrile (**2a**, **2b**) with 2-aminophenol **1b**, 2-aminobenzenethiol **1c** and benzene-1,2-dithiol **1d** (Scheme 2).

Recently, Martinvingt-Mounir *et al.*[3] also reported the use of cyano-activated halogeno displacement reactions to form cyanophenothiazines at ambient and elevated temperatures and we take this opportunity to compare their observations with ours.

† Electronic supplementary information (ESI) available: ^{13}C NMR data for cyanophenoxazines and related compounds, crystal structures of compounds **17** and **18**. See http://www.rsc.org/suppdata/nj/b0/b008503k/



Scheme 1



Scheme 2

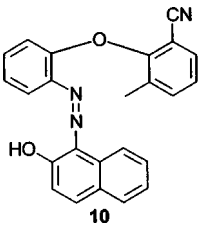
Results and discussion

Reactions were performed between equimolar quantities of nucleophile **1** and either 2,3- or 3,4-difluorobenzonitrile in the presence of potassium carbonate. Under one set of reaction conditions the reagents were allowed to react at room temperature in DMSO. Alternatively, reagents were treated under reflux in DMF–toluene at 130 °C.

Reactions were performed between 2,3-difluorobenzonitrile **2a** and all four nucleophiles **1a–1d** (Scheme 2). We had previously established that the "high-temperature" reaction at 130 °C between **1a** and **2a** in DMF gave 1-cyanodibenzo[1,4]-dioxine **8a** in 99% yield.[1] Reactions have now been carried out in DMSO at room temperature for periods of 24 h and 5 days. Again, only one crystalline product was isolated and, by comparison with previous results, this was confirmed as **8a**; the yield after 24 h was 44% and after 5 days was 96%. Thus, under both sets of reaction conditions only the cyclised product (the dioxine) was obtained. There was no evidence for the formation of the hydroxyphenyl ether **6a** as an isolatable intermediate; nor for a second intermolecular fluoro displacement to form **5** (Scheme 1).

Reactions with aminophenols

When 2-aminophenol **1b** was used as the nucleophile the results were more complex than those with catechol. Single products, identified by single peaks in GC, were isolated from reactions both at room temperature (20 °C) and at 130 °C, but, according to their retention times and the masses of their molecular ions, the products were different. Reaction for 1 h at 130 °C in DMF gave a yellow, fluorescent product (see ESI†) that analysed as cyanophenoxazine **8b** or **9b** (mp 182–184 °C; X-ray data on the *N*-acetyl derivative as described below confirm the product as **8b**, see ESI†) in high yield. In contrast, reaction for 67 h at room temperature in DMSO gave in 88.5% yield a product which analysed as an (aminophenoxy)fluorobenzonitrile **6b**; this was established by MS, FTIR and NMR. Further proof that the product was a primary aromatic amine was provided by its solubility in HCl. In addition, the product was diazotized with sodium nitrite and coupled with 2-naphthol to give a red dye, the azo compound **10**. Thus, it was concluded that the initial reaction at 20 °C



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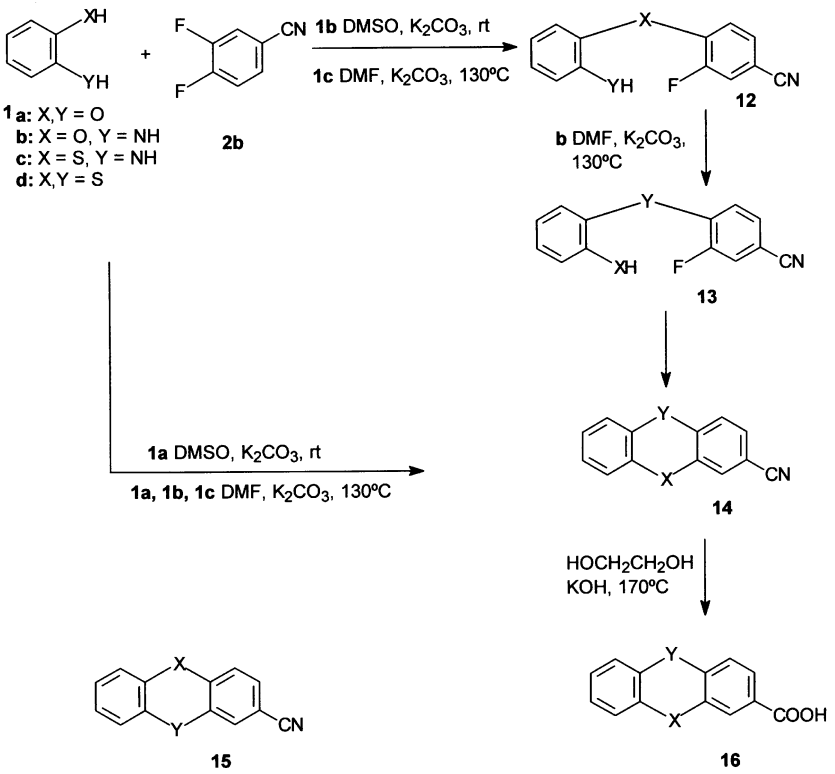
proceeded by nucleophilic displacement of fluoride *ortho* to the nitrile of **2a** to give 1-(2-aminophenoxy)-2-cyano-6-fluorobenzene **6b** as the initial product.

Compound **6b**, on refluxing for 2 h in DMF in the presence of potassium carbonate, *i.e.* under similar reaction conditions as used for the "high-temperature" displacement reaction, gave 1-cyanophenoxazine **8b** (mp 186–187 °C), identical with the product of the "high-temperature" fluoro displacement reaction.

By analogy with the low-temperature reaction in DMSO, we presume that the initial displacement reaction at 130 °C is a fluoro displacement by the hydroxyl of compound **1b** to form the intermediate **6b** which is rapidly converted, by a Smiles rearrangement, into a phenol **7b** which then undergoes cyclisation to **8b** (Scheme 2).

The fact that the cyanophenoxazine produced was 1-cyanophenoxazine was confirmed by hydrolysing it to the corresponding acid **11b** and characterising that product. Cyanophenoxazine **8b** was hydrolysed by refluxing with potassium hydroxide in ethylene glycol at 170 °C to form a phenoxazine carboxylic acid. The designation of this carboxyphenoxazine as 1-carboxyphenoxazine, as opposed to the alternative 4-carboxyphenoxazine, and hence the designation of the new cyanophenoxazine produced here as 1-cyanophenoxazine, is based on earlier studies. The carboxyphenoxazine produced here had the same melting point as the carboxyphenoxazine produced by Gilman and Moore,[4] Blank and Baxter (247–248 °C),[5] Antonio *et al.* (244 °C)[6] and Katritzky *et al.* (247–249 °C),[7] the alternative 4-



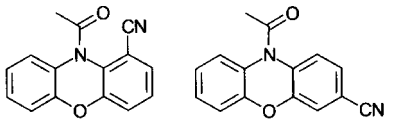
Scheme 3

carboxyphenoxazine is reported to have a melting point of 181–182 °C.[6] In addition, the product had the same ^{13}C NMR spectrum in $CDCl_3$ as obtained and assigned by Katritzky *et al*;[7] the ^{13}C NMR spectrum of the unsubstituted phenoxazine was assigned by Ragg *et al.*[8] (see ESI†). Although the carboxyphenoxazine produced by Gilman and Moore was originally claimed to be 4-carboxyphenoxazine, Blank and Baxter demonstrated the product was 1-carboxyphenoxazine.

This and later conversions of the cyanophenoxazines into the corresponding carboxylic acids were not clean reactions. Acid hydrolysis, with sulfuric acid at 140–150 °C, caused decomposition of the phenoxazines. Alkaline hydrolysis with KOH was slow and prolonged reaction gave black powders from which no useful products could be extracted by sublimation. The most satisfactory hydrolysis procedure was a rapid reaction with KOH in ethylene glycol at *ca.* 170 °C when after 15 min the acids could be extracted; crude yields were modest (*ca.* 70%) and attempts at further purification by sublimation reduced the overall yields as the products decomposed or oligomerised. Thus, hydrolysis of cyanophenoxazines was not found to be a good route to carboxyphenoxazines, in contrast to hydrolysis of cyanodibenzo[1,4]dioxines which gives good yields of carboxydibenzo[1,4]dioxines.

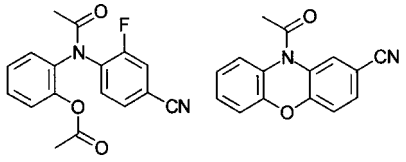
A corresponding series of reactions was carried out between compound **1b** and 3,4-difluorobenzonitrile **2b** (Scheme 3). The results were entirely consistent with those obtained for reaction with **2a**. Thus, fluoro displacement reaction at 130 °C yielded a cyanophenoxazine, while reaction at room temperature gave an amino ether. These results are consistent with reactions proceeding by nucleophilic displacement of fluoride *para* to the nitrile (in preference to that *meta* to the nitrile) of **2b** by the 2-aminophenoxide anion derived from **1b**. Thus, the cyanophenoxazine was assigned the structure **14b** (rather than **15b**) and the aminoether **12b**. The cyanophenoxazine was hydrolysed to the corresponding acid and assigned the structure **16b**; this acid is not known in the literature and independent confirmation of the structure was not possible.

Further proof that the cyanophenoxazines prepared directly at 130 °C or by heating compound **6b** or **12b** at 130 °C in the presence of base were **8b** and **14b**, respectively, was obtained by X-ray crystallography (see ESI†). In order to remove any possible ambiguity in the analysis of data from the cyanophenoxazines themselves, they were converted into their *N*-acetyl derivatives **17** and **18**.



17 **18**

When compound **12b**, produced by fluoro displacement in DMSO at 20 °C, was heated in NMP/toluene at 170–180 °C under nitrogen and in the absence of base in an attempt to induce a thermal Smiles rearrangement, it was slowly transformed into other products, including another cyanophenoxazine. Analysis of the reaction mixture, after 16 h, by GC-MS showed the presence of three products. There was a small amount of residual **12b** (*m/z* 228), a second peak (*m/z* 228) and a third peak (*m/z* 208) with intensity ratio 1 : 14 : 38; there was an extemely small fourth peak with *m/z* 208. The mixture of solids isolated was separated by treatment with sodium hydroxide (1 M) to extract any phenol. Another product was isolated from the residue by vacuum sublimation. The phenolic product analysed as **13b** and was found to have *m/z* 228 and a mp of 104–106 °C; the initial **12b** had a mp of 89–90 °C and was not alkali soluble. Thus the phenolic product was assigned the structure **13b**. Further evidence for the structure was obtained by acetylation with acetic anhydride in pyridine; this gave a diacetyl derivative that was assigned structure **19** on the basis of analytical and spectroscopic data.



19 **20**

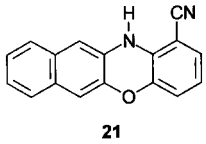
The product that was isolated by sublimation was found to have *m/z* 208; it analysed as a cyanophenoxazine and had a mp of 212–214 °C, compared with 198–199 °C for 3-cyanophenoxazine. The mixed melting point of the two cyanophenoxazines was 170 °C. The mixture of cyanophenoxazines gave two peaks when analysed by GC-MS, each having *m/z* 208. This confirmed that the species were isomers. The very small fourth peak present in the GC trace of the original reaction mixture had the same retention characterisitics as those of **14b**, indicating that this cyanophenoxazine was formed as a trace product in the absence of base. In view of the proof of identity of **14b**, it was concluded that the cyanophenoxazine produced by heating **12b** in the absence of base was 2-cyanophenoxazine **15b**. Acetylation of **15b** gave a monoacetyl derivative **20**, the melting point of which was different from that of 10-acetyl-3-cyanophenoxazine **18**.

GC analysis of samples taken during the course of the reaction demonstrated that compounds **13b** and **15b** were formed in a constant ratio, establishing that the species are formed independently and not sequentially. The minute amount of 3-cyanophenoxazine **14b** that was detected in the mixture indicates that cyclisation of the phenol **13b** to **14b** is a very minor reaction in the absence of base.

Similar results were obtained when compound **6b** was heated in the absence of base. A second cyanophenoxazine was produced with a melting point different to that of the cyanophenoxazine produced in the presence of base and shown to be **8b**. Thus this second cyanophenoxazine was assigned the structure 4-cyanophenoxazine, **9b**. Similarly, a phenolic product that was isolated in the absence of base was assigned structure **7b**.

In summary, the results obtained from fluoro displacement reactions between difluorobenzonitriles and 2-aminophenol demonstrate that, at 130 °C and in the presence of a base, cyanophenoxazines are formed readily. The structures of these compounds indicate that they result from a Smiles rearrangement in an intermediate. Reactions carried out at room temperature in the presence of a base yield 2-aminophenyl cyanofluorophenyl ethers. These ethers, on heating to 130 °C in the presence of a base, undergo Smiles rearrrangement and are converted into the same phenoxazines as are obtained by direct reaction of the two precursors. However when the ethers are heated in the absence of a base two different products are isolated from each: a phenoxazine that results from cyclisation without rearrangement and a 2-hydroxydiphenylamine that results from Smiles rearrangement. We conclude that in the absence of an added base. Smiles rearrangement is very slow and this allows a competing intramolecular displacement of the *meta* fluoro substituent by the amino group to take place, giving the cyanophenoxazines **9b** and **15b**. Thus, all four possible cyanophenoxazines can be produced by an appropriate choice of reagents and conditions. The 2-hydroxyphenyl ethers **7b** and **13b** apparently cyclise very slowly, if at all, in the absence of a base.

The synthesis of cyanophenoxazines was extended to 2-amino-3-hydroxynaphthalene *via* reactions at 130 °C. By analogy with 2-aminophenol, reaction with 2,3-difluorobenzonitrile gave a cyanophenoxazine which was assigned the structure **21**; the ^{13}C NMR spectrum consisted of 17 distinct lines, as expected. In contrast, when the reaction was performed with 3,4-difluorobenzonitrile a high melting point, single product, for which elemental analysis data were consistent with a cyanophenoxazine, was isolated in 96% yield. MS data, however, showed this product to have a mass of 514, corresponding to a dimeric species, such as **22**. The integrated intensity of the single NH peak in the ^1H NMR spectrum was approximately one nineteenth of the total integrated intensity. The ^{13}C spectrum showed 33 distinct lines as opposed to the 34 expected, one line however was of high intensity and we attributed that to two carbons; there were two distinct CN resonances at about δ 102, as expected for the structure **22**. There is precedence for the formation of dimeric species from naphthalene-based phenoxazines in the presence of catalysts such as copper(II) acetate[9] and we attribute the product obtained here to the analogous species **22**; steric restrictions may well preclude the formation of a dimer from **21**.



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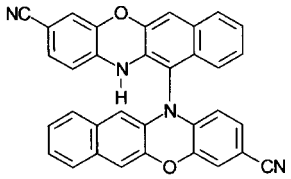

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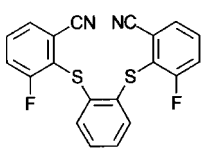
Reactions with 2-aminobenzenethiol

A fluoro displacement reaction between 2,3-difluorobenzonitrile **2a** and 2-aminobenzenethiol **1c** in the presence of potassium carbonate at room temperature gave 2-aminophenyl 2-cyano-6-fluorophenyl sulfide **6c** in high yield. Displacement at 125 °C gave a mixture of two products: the aminophenyl cyanophenyl sulfide **6c** and a cyanophenothiazine that was tentatively assigned structure **8c** by analogy with the literature report.[3] This reaction sequence would also be analogous to that observed with 2-aminophenol. Martinvingt-Mounir *et al.* performed similar displacement reactions with both 2,3- and 3,4-difluorobenzonitrile and 2-aminophenol but in the presence of sodium hydride.[3] Our observations correspond to theirs and when the results are taken together they indicate that there is a very similar pattern of reactions between these nitriles and either 2-aminophenol or 2-aminobenzenethiol.

Reactions with benzene-1,2-dithiol

Benzene-1,2-dithiol **1d** was allowed to react with the difluorobenzonitriles **2a** and **2b** in DMSO at room temperature in the presence of potassium carbonate. The product mixtures were analysed by GS-MS but neither showed the presence of a thioether corresponding to a single displacement of fluoride (*m/z* 261). The mixture obtained from the reaction with 2,3-difluorobenzonitrile **2a** contained a component with *m/z* 241, consistent with 1-cyanothianthrene **8d**. A pure specimen of the compound was isolated by vacuum distillation as a colorless crystalline solid with a strong yellow fluorescence. A second component was isolated that showed *m/z* 380; this was tentatively assigned the structure **23**. This is the product that would result from double intramolecular displacement of the *ortho* fluoride by the dithiol, a reaction that corresponds to path B in Scheme 1 but which was not observed with catechol. A very similar reaction pattern was found with 3,4-difluorobenzonitrile **2b**. Although 2-cyanothianthrene **14d** was detected in the reaction mixture by GC-MS and by its strong fluorescence it was not isolated pure. Again, a 2 : 1 adduct, which was assigned structure **24**, was also formed.



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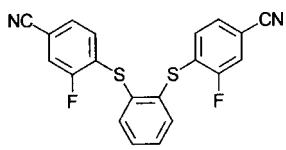

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In contrast, each reaction gave a single substance in high yield when they were carried out in DMF under reflux. These substances were identified as 1-cyanothianthrene **8d** and 2-cyanothianthrene **14d**, respectively. Thus, the reactions take a different course from those with catechol at room temperature but the same course at higher temperature, the double displacement of fluoride providing an efficient route to these new thianthrene derivatives.

Experimental

For General Methods see the preceding paper.[10]

Crystallography

Crystal data were collected on a Stoe-IPDS diffractometer at 213 K using Mo-Kα radiation ($\lambda = 0.710\,73$ Å). Full-matrix least squares refinements on F^2 using all data (SHELX 97).[11] **17**: $C_{15}H_{10}N_2O_2$, $M = 250.27$, monoclinic, space group $P2_1/c$, $a = 8.010(2)$, $b = 17.598(3)$, $c = 8.826(2)$ Å, $\beta = 105.42(3)$, $V = 1199.4(5)$ Å^3, $Z = 4$, μ(Mo-Kα) = 0.094 mm^{-1}, $R1[I > 2\sigma(I)] = 0.065$, $wR2$ (all data) = 0.194, 4437 measured and 1630 independent reflections, $R_{int} = 0.115$. **18**: $C_{15}H_{10}N_2O_2$, $M = 250.27$, monoclinic, space group $P2_1/n$, $a = 11.872(2)$, $b = 7.8232(12)$, $c = 12.943(2)$ Å, $\beta = 99.18(2)°$, $V = 1186.7(3)$ Å^3, $Z = 4$, μ(Mo-Kα) = 0.095 mm^{-1}, $R1[I > 2\sigma(I)] = 0.113$, $wR2$ (all data) = 0.297, 6426 measured and 1642 independent reflections, $R_{int} = 0.102$. The crystals of compound **18** were of poor quality leading to a rather high R factor. While the overall connectivity is not in doubt, the quality of the refinement does not allow a detailed discussion of structural parameters.

CCDC reference number 440/254. See http://www.rsc.org/suppdata/nj/b0/b008503k/ for crystallographic files in .cif format.

1-Cyanophenoxazine 8b. 2-Aminophenol **1b** (1.09 g, 10 mmol) was dissolved in DMF (20 mL) with potassium carbonate (3 g) and toluene (12 mL) and the mixture heated under reflux for 0.5 h under a flow of nitrogen to remove water with the aid of a Dean–Stark trap. The flask was cooled to about 80 °C when 2,3-difluorobenzonitrile **2a** (1.39 g, 10 mmol) was added and the mixture heated under reflux for 4 h after which the toluene was distilled off and replaced with DMF. The mixture was heated at 150 °C for 4.5 h to give 1-cyanophenoxazine **8b** (1.98 g, 95%) as a bright yellow, highly fluorescent, crystalline solid, mp 182–184 °C; IR (KBr): 3310, 2223, 1510, 1473, 1300 and 732 cm^{-1}; ^{1}H NMR (d$_6$-DMSO): δ 5.86 (s, 1 H), 6.50 (d, 1 H, $J = 7.5$), 6.62 (dd, 1 H), 6.66 (d, 1 H), 6.76 (d, 1 H), 6.80 (dd, 1 H), 6.91 (d, 1 H, $J = 7.1$ Hz) and 7.74 (dd, 1 H); for ^{13}C NMR see ESI.† Calc. for $C_{13}H_8N_2O$: C, 74.98; H, 3.87; N, 13.45%. Found: C, 75.04; H, 3.83; N, 13.38%. HRMS: calc. for $C_{13}H_8N_2O$ m/z 208.063 65, found 208.063 65.

In order to obtain crystals suitable for X-ray analysis (see ESI†) the compound was further characterised as its 10-acetyl derivative **17** by acetylation with acetic anhydride in pyridine with 4-dimethylaminopyridine as catalyst; mp 188–189 °C. Calc. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.02; N, 11.19%. Found: C, 71.74; H, 3.99; N, 11.13%.

3-Cyanophenoxazine 14b. Reaction between 2-aminophenol **1b** and 3,4-difluorobenzonitrile **2b** was conducted as for the synthesis of 1-cyanophenoxazine. This gave 3-cyanophenoxazine **14b** (1.98 g, 95%) as a yellow highly fluorescent crystalline solid, mp 198–199 °C; IR (KBr): 3314, 2220, 1525, 1499, 1320 and 740 cm^{-1}; ^{1}H NMR (d$_6$-DMSO): δ 6.49 (m, 2 H), 6.64 (m, 2 H), 6.77 (ddd, 1 H, $J = 7.8$, 7.6, 2.2), 6.97 (d, 1 H, $J = 1.7$), 7.16 (dd, 1 H, $J = 8.2$, 1.8 Hz) and 8.90 (s, 1 H); for ^{13}C NMR see ESI.† Calc. for $C_{13}H_8N_2O$: C, 74.98; H, 3.87; N, 13.45%. Found: C, 74.83; H, 3.87; N, 13.52%. HRMS: calc. for $C_{13}H_8N_2O$ m/z 208.063 65, Found 208.06365.

The 10-acetyl derivative **18** had mp 147–148.5 °C and was characterised by X-ray diffraction (see ESI†). Calc. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.02; N, 11.19%. Found: C, 71.68; H, 4.03; N, 11.25%.

1-Cyanobenzo[*b*]phenoxazine 21. Reaction between 3-amino-2-naphthol and 2,3-difluorobenzonitrile **2a**, conducted as for the synthesis of 1-cyanophenoxazine, gave 1-cyanobenzo[b]phenoxazine **21** (2.27 g, 88%). A portion was sublimed to give an analytical specimen as a pale green crystalline solid, mp 299–300 °C (decomp.); IR (KBr): 3314, 2220, 1525, 1499, 1320 and 740 cm^{-1}; ^{1}H NMR (d$_6$-DMSO): δ 6.71 (dd, 1 H, $J = 8.0$, 7.9), 7.00 (dd, 1 H, $J = 7.9$, 1.3), 7.14 (dd, 1 H, $J = 7.8$, 1.8), 7.15 (s, 1 H), 7.21 (s, 1 H), 7.27 (m, 3 H), 7.54 (d, 1 H, $J = 7.5$), 7.58 (d, 1 H, $J = 7.8$ Hz) and 9.31 (s, 1 H); for ^{13}C NMR see ESI.† Calc. for $C_{17}H_{10}N_2O$: C, 79.06; H, 3.90; N, 10.85%. Found: C, 78.79; H, 3.86; N, 10.92%. HRMS: calc. for $C_{17}H_{10}N_2O$ m/z 258.079 32, found 258.078 86.

3-Cyano-12-(3-cyanobenzo[*b*]phenoxazin-11-yl)benzo[*b*]phenoxazine 22. Reaction between 3-amino-2-naphthol and 3,4-difluorobenzonitrile **2b**, conducted as for the synthesis of 1-cyanophenoxazine, gave a crude product (96%) as a colourless crystalline solid, mp >300 °C. A pure sample was obtained by slow vacuum sublimation at 250 °C and 0.5 mmHg; some decomposition was found when attempts were made to recrystallise the product from THF. GC-MS showed the presence of only one component with m/z 514; ^{1}H NMR (d$_6$-DMSO): δ 6.15 (d, 1 H, $J = 8.3$), 6.44 (s, 1 H), 6.86 (d, 1 H, $J = 8.3$), 7.18–7.55 (m, 12 H), 7.73 (d, 1 H, $J = 7.8$), 7.86 (d, 1 H, $J = 8.3$ Hz) and 9.57 (s, 1 H); ^{13}C NMR (d$_6$-DMSO): δ 102.22, 102.76, 108.46, 111.21, 111.52, 112.22, 113.30, 114.44, 118.18, 118.26, 118.74, 118.84, 120.63, 124.77, 124.98, 125.30, 126.42 (2C), 126.78, 126.94, 127.97, 129.15, 129.25, 130.06, 130.17, 130.24, 130.45, 130.95, 134.48, 135.42, 142.04, 143.19, 143.33 and 143.37. Calc. for $C_{34}H_{18}N_4O_2$: C, 79.37; H, 3.53; N, 10.89%. Found: C, 78.79; H, 3.86; N, 10.92%.

2-Aminophenyl 2-cyano-6-fluorophenyl ether 6b. 2-Aminophenol **1b** (2.18 g, 20 mmol) was dissolved in anhydrous DMSO (20 mL) and the solution deoxygenated by blowing nitrogen through for 5 min. Then 2,3-difluorobenzonitrile **2a** (2.78 g, 20 mmol) was added followed by anhydrous potassium carbonate (5 g). The reaction mixture was stirred in a closed vessel for 72 h; then poured into ice–water when the solid product that precipitated was filtered off and thoroughly washed with water and dried. This gave the ether **6b** (4.33 g, 95%) as the only product. An analytical specimen was obtained by vacuum distillation as a pale pink solid, mp 95–96 °C; IR (KBr): 3430, 3351, 2233, 1623, 1505 and 753 cm^{-1}; ^{1}H NMR (d$_6$-DMSO): δ 5.20 (s, 2 H), 6.44–6.47 (m, 2 H), 6.80 (ddd, 1 H, $J = 8.6$, 1.5, 0.5 Hz), 6.84–6.89 (m, 1 H), 7.42–7.47 (m, 1 H) and 7.73–7.80 (m, 2 H); ^{13}C NMR (d$_6$-DMSO): δ 107.86, 114.16, 114.64, 115.60, 122.77, 124.19, 126.53, 129.71, 138.27, 144.17, 144.94, 152.60 and 155.09. Calc. for $C_{13}H_9FN_2O$: C, 68.41; H, 3.97; N, 12.27%. Found: C, 68.35; H, 3.92; N, 12.33%. HRMS: calc. for $C_{13}H_9FN_2O$ m/z 228.069 89, found 228.069 59.

2-Aminophenyl 4-cyano-2-fluorophenyl ether 12b. Reaction between 2-aminophenol (20 mmol) and 3,4-difluorobenzonitrile **2b** (20 mmol) as described above gave the ether **12b** (95%) as a pink–white solid. An analytical sample, obtained by vacuum distillation, had mp 89–90 °C; IR (KBr): 3479, 3377, 2235, 1504, 1314 and 741 cm^{-1}; ^{1}H NMR (d$_6$-DMSO): δ 5.20 (s, 2 H), 6.44–6.47 (m, 2 H), 6.60 (td, 1 H, $J = 8.5$, 1.6), 6.78 (t, 1 H, $J = 8.5$), 6.89 (dd, 1 H, $J = 8.0$, 1.5), 6.91 (1 H, dd, $J = 8.0$, 1.4), 7.03 (td, 1 H, $J = 7.6$, 1.4), 7.59 (ddd, 1 H, $J = 8.5$, 2.01, 1.1) and 7.960 (dd, 1 H, $J = 11.0$, 2.0 Hz); ^{13}C NMR (d$_6$-DMSO): δ 104.43, 116.39, 117.36, 117.83, 120.51, 120.84, 126.51, 130.09, 139.24, 140.65, 149.67, 150.22 and 152.69. Calc. for $C_{13}H_9FN_2O$: C, 68.41; H, 3.97; N, 12.27%. Found: C, 68.52; H, 3.95; N, 12.35%. HRMS: calc. for $C_{13}H_9FN_2O$ m/z 228.069 89, found 228.070 03.

Thermal reaction of 2-aminophenyl 4-cyano-2-fluorophenyl ether 12b in the absence of base. The ether **12b** (0.5 g) was

heated under reflux in NMP (10 mL) and toluene (5 mL) under N_2 at 170–180 °C for 16 h. The solution was poured into ice–water; the solid was filtered off, washed three times with water and dried (0.45 g). GC-MS showed the presence of three components in the ratio 1 : 14 : 38. The first (*m*/*z* 228) was identified as the starting ether **12b**, the second also had *m*/*z* 228 and the third *m*/*z* 208. The components were separated, first by extracting the product with 1 M NaOH, then with 5 M HCl. The residue (fraction 3) was purified by sublimation. The acid soluble fraction (9 mg) was identified as the starting ether **12b**. The alkaline-soluble fraction (*m*/*z* 228) had mp 104–106 °C; IR (KBr): 3336, 3300–3200br, 1619 and 1525 cm^{-1}; this was tentatively identified as the phenol **13b**. This was characterized as its diacetyl derivative **19**, mp 117–118 °C. Calc. for $C_{17}H_{13}FN_2O_3$: C, 65.38; H, 4.19; N, 8.97%. Found: C, 65.18; H, 4.19; N, 9.08%. The third fraction (*m*/*z* 208) was identified as 2-cyanophenoxazine **15b**, mp 212–214 °C, mixed mp with 3-cyanophenoxazine **14b** 170 °C; IR (KBr): 3352, 2219, 1582, 1494, 1313 and 733 cm^{-1}. Calc. for $C_{13}H_8N_2O$: C, 74.98; H, 3.87; N, 13.45%. Found: C, 74.80; H, 3.84; N, 13.39%. The 10-acetyl derivative **20** had mp 106–108 °C. Calc. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.02; N, 11.19%. Found: C, 71.71; H, 4.03; N, 11.26%.

Thermal reaction of 2-aminophenyl 2-cyano-6-fluorophenyl ether 6b in the absence of base. The ether **6b** (1.0 g) was heated under reflux in NMP (10 mL) and toluene (5 mL) under N_2 at 170–180 °C for 30 h. The solution was poured into ice–water; the solid was filtered off, washed three times with water and dried. GC-MS showed the presence of three components. These were separated by extracting the mixture with 1 M NaOH, then with 5 M HCl. The acid soluble fraction (9 mg) was identified as the starting amine **6b**. The alkali soluble fraction (9 mg) was assigned the structure **7b**; IR (KBr): 3372, 3300–3000br, 2230, 1654, 1599, 1515 and 1426 cm^{-1}; *m*/*z* 228. The residue (0.5 g) was purified by vacuum sublimation to give 4-cyanophenoxazine **9b**, mp 148–150 °C; IR (KBr): 3332, 2230, 1581, 1490, 1311 and 712 cm^{-1}. Calc. for $C_{13}H_8N_2O$: C, 74.98; H, 3.87; N, 13.45%. Found: C, 74.93; H, 3.83; N, 13.40%.

Base induced cyclisation of ether 6b. The ether **6b** (0.1 g) was heated under reflux in DMF with K_2CO_3 (0.9 g) for 2 h. The product was precipitated into water, filtered off and dried to give 1-cyanophenoxazine **8b**, mp 186–187 °C.

Phenoxazine-1-carboxylic acid 11b. 1-Cyanophenoxazine **8b** (50 mg) was heated under reflux in ethane-1,2-diol with KOH for 15 min. The crude acid was isolated (70%) after an acidic work-up. A pure sample was obtained by vacuum sublimation at 250 °C and had mp 243–245 °C (lit.[4,5,7] 247–248 °C); IR (KBr): 3353, 1665, 1498 and 1278 cm^{-1}; ^1H NMR (d_6-DMSO): δ 6.61 (dd, 1 H, J = 8.1, 7.9), 6.64–6.72 (m, 2 H), 6.73–6.80 (m, 2 H), 6.82 (dd, 1 H, J = 7.8, 1.4), 7.32 (dd, 1 H, J = 8.1, 1.4 Hz), 8.95 (s, 1 H) and 13.22 (s, 1 H); for ^{13}C NMR see ESI.† Calc. for $C_{13}H_9NO_3$: C, 68.71; H, 3.99; N, 6.16%. Found: C, 68.30; H, 3.87; N, 5.95%. HRMS: calc. for $C_{13}H_9NO_3$ *m*/*z* 227.058 23, found 227.058 32.

Phenoxazine-3-carboxylic acid 16b. Hydrolysis of 3-cyanophenoxazine **14b** as in the preceding preparation gave phenoxazine-3-carboxylic acid **16b**, mp 254–256 °C after vacuum sublimation; IR (KBr): 3419, 1671, 1583, 1457 and 1310 cm^{-1}. Calc. for $C_{13}H_9NO_3$: C, 68.71; H, 3.99; N, 6.16%. Found: C, 68.74; H, 3.97; N, 6.17%. HRMS: calc. for $C_{13}H_9NO_3$ *m*/*z* 227.058 23, found 227.057 88.

2-Aminophenyl 2-cyano-6-fluorophenyl sulfide 6c. A solution of 2-aminobenzenethiol **1c** (0.37 g, 3.0 mmol) and 2,3-difluorobenzonitrile **2a** (0.42 g, 3.1 mmol) in DMSO (20 mL) was stirred at rt with K_2CO_3 (3.0 g) for 67 h to give the sulfide **8c** (0.61 g, 84%), mp 96–97 °C (lit.,[3] 98 °C); IR (KBr): 3415 and 3339 cm^{-1}. Calc. for $C_{13}H_9FN_2S$: C, 63.91; H, 3.71; N, 11.46%. Found: C, 63.83; H, 3.69; N, 11.50%.

Reaction of 2-aminobenzenethiol and 2,3-difluorobenzonitrile on heating with base. The preceding reaction was repeated but with DMF as the solvent at 125 °C for 50 min. This gave a solid (0.64 g). GC-MS showed the presence of two components in a ratio of 1 : 5.5: (i) the sulfide **6c** (*m*/*z* 244) identified by comparison with an authentic specimen and (ii) a substance (*m*/*z* 224) tentatively identified as 1-cyanophenothiazine **8c**. The reaction mixture was not investigated further.

1-Cyanothianthrene 8d. A solution of benzene-1,2-dithiol **1d** (0.50 g, 3.5 mmol) in DMF (15 mL) containing K_2CO_3 (1.3 g) was heated under reflux under N_2 and 2,3-difluorobenzonitrile **2a** (0.48 g, 3.5 mmol) in DMF (5 mL) added dropwise during 1.5 h. After a further 0.5 h the reaction mixture was poured into ice to give a colourless precipitate (0.81 g, 95%). This was purified by sublimation at 0.5 mmHg to yield 1-cyanothianthrene **8d** (0.68 g, 81%), mp 128–129 °C; IR (KBr): 2228, 1442, 1402 and 747 cm^{-1}. Calc. for $C_{13}H_7NS_2$: C, 64.69; H, 2.92; N, 5.80%. Found: C, 64.88; H, 2.91; N, 5.87%. GC-MS: *m*/*z* 241 (M^+).

2-Cyanothianthrene 14d. A solution of benzene-1,2-dithiol **1d** (0.45 g, 3.1 mmol) and 3,4-difluorobenzonitrile **2b** (0.45 g, 3.2 mmol) in DMF (15 mL) containing K_2CO_3 (1.0 g) was heated under reflux under N_2 for 1.5 h. The reaction mixture was poured into ice to give a colourless precipitate (0.70 g, 92%). This was purified by sublimation at 0.5 mmHg to yield 2-cyanothianthrene **14d** (0.62 g, 83%), mp 133–134 °C; IR (KBr): 2230, 1446, 820 and 735 cm^{-1}. Calc. for $C_{13}H_7NS_2$: C, 64.69; H, 2.92; N, 5.80%. Found: C, 64.75; H, 2.88; N, 5.83%. GC-MS: *m*/*z* 241 (M^+).

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