Synthesis of cyanodibenzo[1,4]dioxines and their derivatives by cyano-activated fluoro displacement reactions†

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Received (in Cambridge) 19th October 2000, Accepted 23rd December 2000
First published as an Advance Article on the web 21st February 2001

A new group of cyanodibenzo[1,4]dioxines have been synthesized by cyano-activated fluoro displacement reactions between cyanodifluorobenzenes and catechols in DMF at 130 °C in the presence of potassium carbonate. This route is exemplified by the synthesis of cyanodibenzo[1,4]dioxines from several substituted catechols. The reactions are virtually quantitative. Cyanodibenzo[1,4]dioxines were hydrolysed with potassium hydroxide in ethylene glycol or converted into amide derivatives to yield additional substituted dibenzo[1,4]dioxines. Cyanodibenzo[1,4]-dioxines are fluorescent and excitation and emission data are presented. Improved syntheses of 4,5-diphenyl-veratrole and 3,6-dimethylcatechol, the latter involving reduction of a phenolic Mannich base at atmospheric pressure, have been elaborated.

Introduction

Hazardous chlorine-substituted dibenzo[1,4]dioxines apart, there is current interest in the efficient synthesis of substituted dibenzo[1,4]dioxines, some derivatives of which, *e.g.* dibenzo[1,4]dioxine-1-carboxamide, have potentially useful biomedical properties, such as significant *in vivo* anti-tumor activity.[1] Dibenzo[1,4]dioxine-1- and -2-carboxylic acid were first prepared in 1943 and 1936,[2,3] respectively, but the biological activity of certain dibenzo[1,4]dioxines[1,4,5] has recently generated interest in an efficient synthetic route to the relatively unexplored substituted dibenzo[1,4]dioxines, especially dibenzo[1,4]dioxine-1-carboxylic acid, and their derivatives.[4,6,7]

Lee and Denny reviewed routes to substituted dibenzodioxines and favored reaction between catechol (or substituted catechols) and activated 1,2-dichlorobenzenes or 1-chloro-2-nitrobenzenes as the most useful route to provide the compounds in high overall yields.[6] Unsubstituted dibenzo[1,4]-dioxine was obtained in good yield by treating catechol with potassium metal in dry HMPA (a carcinogenic solvent), to form the dianion at 20 °C, and then with chloro-2-nitrobenzene at 110 °C (71% yield) or with 1,2-dinitrobenzene (87%) but in negligible yields on reaction with 1,2-difluoro- or 1,2-dichloro-benzene. Ester activation was used to produce substituted dioxines as precursors to dibenzo[1,4]dioxine-1- and -2-carboxylic acids, wherein isopropyl esters of 1- and 2-substituted acids were produced in 15–60% yields. More recently Hellberg and Pelcman employed copper-mediated aryl ether synthesis, with 2,3-dihydroxynaphthalene, to prepare dibenzo[1,4]dioxines having naphthalene substituents, in yields of about 20%.[8] Most previous syntheses of dibenzo[1,4]dioxines involving nucleophilic displacement reactions have employed nitro-activation and displacement of chloride or nitro groups and yields have generally been modest. Cyano-activation and fluoro displacement have not been used widely, if at all.

† Electronic supplementary information (ESI) available: NMR and fluorescence spectral data for compounds **6** and **7**, crystal structures of **6a**, **11** and **16**. See http://www.rsc.org/suppdata/nj/b0/b008508l/

It was against this background that we recently reported, briefly, the facile, quantitative synthesis of a new family of substituted dibenzo[1,4]dioxines, namely, cyanodibenzo[1,4]-dioxines,[9] which can be hydrolysed to carboxy-substituted dibenzo[1,4]dioxines and, subsequently, converted into other derivatives. The cyanodibenzo[1,4]-dioxines were prepared *via* a simple reaction (Scheme 1) between a catechol (**1**) and 2,3- or 3,4-difluorobenzonitrile (**2**, **3**) in DMF at 130 °C in the presence of potassium carbonate. This process involves both the facile cyano-activated *ortho*- or *para*-fluoro displacement reaction and then, presumably, the subsequent and less-facile *meta*-fluoro displacement reaction, accelerated as an intramolecular cyclization reaction. We had previously demonstrated that intermolecular cyano-activated *ortho*- and *para*-fluoro displacement reactions between catechol and 1-cyano-2-fluorobenzonitrile or 1-cyano-4-fluorobenzonitrile proceeded readily under the same reaction conditions at 130 °C but *meta*-fluoro displacement from 1-cyano-3-fluorobenzonitrile required an elevated temperature of 170 °C.[10,11]

In this paper we exemplify the procedure used and describe, in more detail, the synthesis and characterization of a larger family of cyanodibenzo[1,4]dioxines and carboxydibenzo-[1,4]dioxines derived therefrom. We also illustrate the further functionalization of the dibenzo[1,4]dioxines by conversion into other potentially useful derivatives. In addition, we make comparisons between the cyano-activated and related nitro-activated fluoro displacement reactions. Characterization data for the compounds, including fluorescence data, are reported as ESI.

Results and discussion

In our preliminary study it was demonstrated that catechol (**1a**) and the catechol derivative 2,3-dihydroxynaphthalene (**1b**) will undergo a double fluoro displacement reaction with 2,3- or 3,4-difluorobenzonitrile (**2**, **3**) to yield a 1- or 2-cyanodibenzo[1,4]dioxine (**6**, **7**), respectively.[9] Equivalent reactions between a series of catechol derivatives and the same difluorobenzonitriles have now been investigated, *i.e.* in each reagent hydroxyl groups or fluoro substituents are *ortho* to each other. Substituted catechols were chosen such that, in most cases, only a single cyanodibenzo[1,4]dioxine regio-

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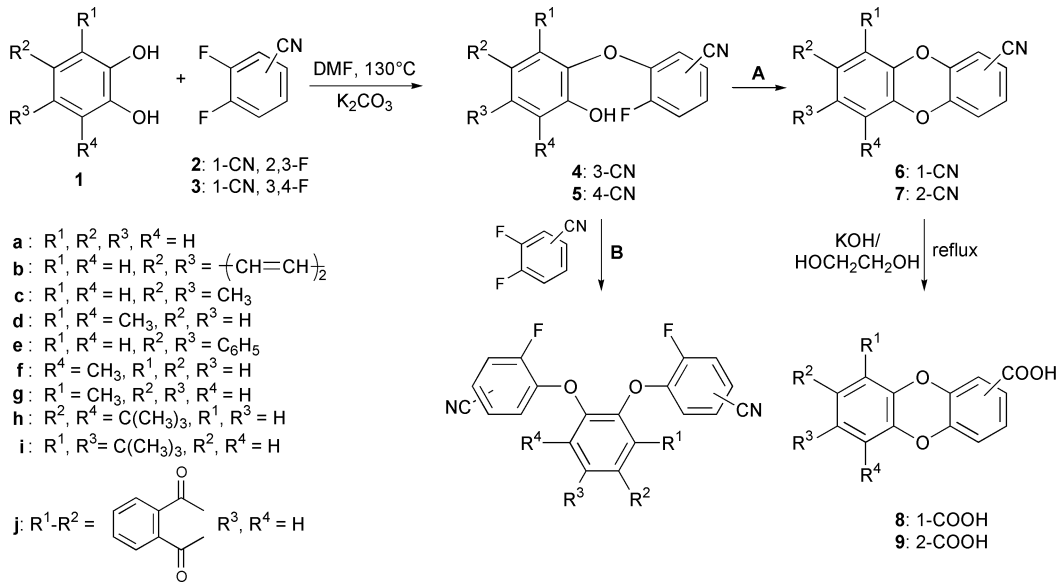
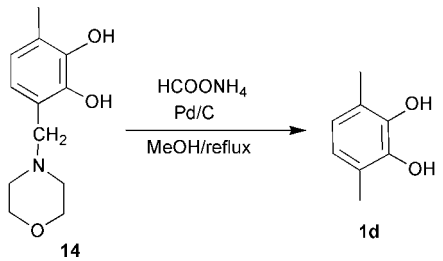


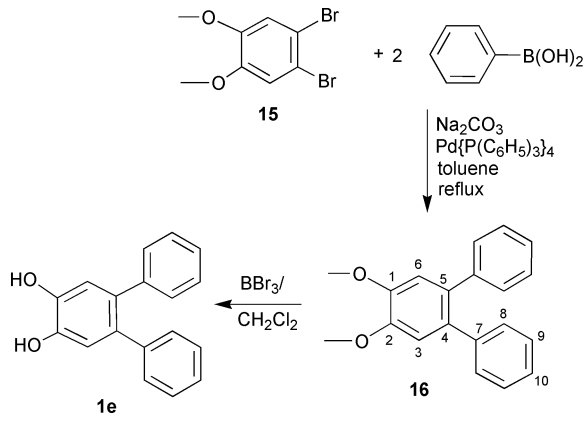
Scheme 1

isomer could be formed. 4,5-Dimethylcatechol (**1c**) was prepared according to a literature procedure.[12] In addition, 3,6-dimethylcatechol (**1d**) was synthesized by reduction of 3-methyl-6-morpholinomethylcatechol. The reduction of phenolic Mannich bases is usually performed under high pressures of hydrogen.[13] However, it was demonstrated that the bases can be reduced at atmospheric pressure in refluxing methanol by using ammonium formate with Pd/C catalysis (Scheme 2).

To extend the synthesis to other cyanodibenzo[1,4]dioxines for which only one regioisomer is possible, 4,5-diphenylcatechol (**1e**) was synthesized and an improved preparation of this substance was developed. Previous workers prepared 4,5-diphenylcatechol by a dienone–phenol rearrangement.[14] In contrast, the use of a Suzuki coupling reaction between 4,5-dibromoveratrole and phenylboronic acid was investigated (Scheme 3). This led to 4,5-diphenylveratrole in 85% yield and this was demethoxylated to 4,5-diphenylcatechol in 99% yield.



Scheme 2



Scheme 3

Fluoro displacement reactions between both compounds **2** and **3** and several catechol derivatives (**1a–1e**) were investigated. In all cases the reactions were performed in DMF at 130 °C in the presence of potassium carbonate; these reaction conditions were identical to those used previously in order to synthesize bis(ether dinitrile)s, such as 1,2-bis(4-aminophenoxy)benzene from **1a** and 4-fluorobenzonitrile.[11] As can be seen from the data presented, in all cases cyanodibenzo-[1,4]dioxines were formed in high yields, in almost all cases in excess of 90% and usually virtually quantitative; 2-cyano-7,8-dimethyldibenzo[1,4]dioxine was formed in 80% yield. The products were readily purified to yield materials with sharp melting points and further characterized by elemental analysis, FTIR and ^{1}H and ^{13}C NMR. In addition, the identity of 1-cyanodibenzo[1,4]dioxine (**6a**) was confirmed by single crystal X-ray diffraction (see ESI†). It crystallizes in monoclinic space group *C*2/*c* with two molecules in the asymmetric unit. Both crystallographically independent molecules are planar within a deviation of only 0.02 Å. The molecules are arranged in a herringbone pattern which is commonly observed in crystal structures of condensed aromatic systems.[15]

In addition to using symmetrical catechol derivatives, which can only lead to a single regioisomeric cyanodibenzo[1,4]-dioxine, reactions were also performed with a small number of unsymmetrical catechols which could lead to two regioisomers. Thus 3-methylcatechol (**1f**) and 3,5-di-*tert*-butylcatechol (**1h**) were treated with **3**, and alizarin (1,2-dihydroxyanthraquinone) (**1j**) with **2** to synthesize cyanodibenzo[1,4]dioxines.

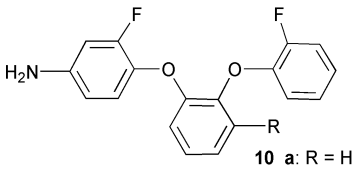
Compounds **1f** and **1h** both gave high yields of 2-cyanodibenzo[1,4]dioxines. Gas chromatography of the products demonstrated, in each case, the presence of two products, presumably the two possible regioisomers, 2-cyano-6-methyldibenzo[1,4]dioxine **7f** and 2-cyano-9-methyldibenzo[1,4]dioxine **7g** from the catechol **1f** and 2-cyano-6,8-di-*tert*-butyldibenzo[1,4]dioxine **7h** and 2-cyano-7,9-di-*tert*-butyldibenzo[1,4]dioxine **7i** from **1h**, in equal quantities. Thus the fluoro displacement reactions showed little or no regioselectivity due to the position of substituents on the catechol. No attempt was made to separate or characterize the individual isomers. A corresponding fluoro displacement reaction was performed with alizarin primarily to demonstrate the potential scope of the reaction; Sutherland *et al.*[16] described the synthesis of the corresponding unsubstituted benzo[*b*]anthracen-9,10-diono[1,2-*e*][1,4]dioxine and there is potentially greater interest in substituted dibenzo[1,4]dioxines. Reaction between compounds **1j** and **2** gave a violet powder, when dry,

from which only compound **6j** was isolated in modest yield (28%) as a bright yellow crystalline solid; no attempt was made to investigate the formation of regioisomers or to identify other products. Compound **6j** was fluorescent and its fluorescence could be switched on and off by reduction and oxidation, respectively.

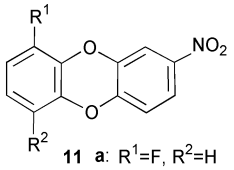
We presume that, in the first step of Scheme 1, the more-facile *ortho*- or *para*-cyano-activated fluorine is displaced first to form intermediates **4** and **5**, respectively. Then, rather than undergoing a second intermolecular fluoro displacement reaction between the remaining hydroxyl on the catechol and another molecule of difluorobenzonitrile (Scheme 1, path B), an accelerated rapid intramolecular fluoro displacement reaction involving ring closure proceeds preferentially to give the cyano-substituted dibenzo[1,4]dioxine (Scheme 1, path A).

In synthetic organic chemistry, nitro-activated nucleophilic displacement reactions are more widely used than their cyano-activated equivalents. It is therefore relevant to compare the two processes in the current context. While synthesizing bis(ether dinitrile)s by treating diols with fluorobenzonitriles we had demonstrated that, in addition to the *ortho*- and *para*-cyano-activated fluoro displacements, which proceed readily in DMF at 130 °C, it was also possible to perform *meta*-fluoro displacement at 170 °C.[11] In contrast, while nitro-activated *ortho*- and *para*-fluoro displacement reactions would also proceed readily at 130 °C the corresponding *meta*-fluoro displacement would not proceed even at 170 °C.[17] Thus it was possible to take advantage of this fact and to prepare 1,2-bis(4-amino-2-fluorophenoxy)benzene (**10a**) by treating two molar equivalents of compound **3** with 1 molar equivalent of catechol **1a** and reduction of the dinitro compound so formed; we did not attempt to prepare the equivalent bis(ether dinitrile) because of anticipated complications over competition between, say, *para*- and *meta*-fluoro displacement which could lead to a mixture of products.

In an attempt to increase the fluorine content of dinitro compounds, as precursors to bis(ether amine)s, by treating 2 molar equivalents of the nitrile **3** with 1 molar equivalent of 3-fluorocatechol (to form **10b**), it was found that the reaction was not clean but gave dark products. The only crystalline compound successfully isolated from the reaction mixture proved to be a fluoronitrodibenzo[1,4]dioxine (**11**). It was as a result of this finding that the reactions between catechols and difluorobenzonitriles were undertaken. Two fluoronitrodibenzo[1,4]dioxine isomers were possible from the above reaction, *viz*. 6-fluoro-2-nitrodibenzo[1,4]dioxine (**11b**) and 9-fluoro-2-nitrodibenzo[1,4]dioxine (**11a**). The overall product gave good elemental analysis for fluoronitrodibenzo[1,4]dioxine. GC/MS showed the presence of two products, in approximately equal proportions, both of which gave molecular ions corresponding to fluoronitrodibenzo[1,4]dioxines. Crystal structure analysis on the crystalline product obtained from MeCN also shows the existence of two isomers as indicated by statistical disorder of fluorine atoms at the 1 and 4 positions (see ESI†). Refinement of the occupancy factors of both domains gives a ratio of 85 : 15 for isomers 9-fluoro-2-nitro- and 6-fluoro-2-nitro-dibenzo[1,4]dioxine in the crystal. Although a value of 15% for one domain seems to be rather low to be accounted for in the refinement, the *R* value dropped from 0.071 to 0.037 by introducing split F and H positions in the refinement. In contrast to compound **6a** the dibenzodioxine core is slightly bent along the O–O vector to 175.7°.



10 **a**: R = H
b: R = F

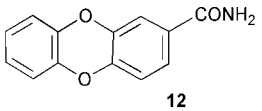


11 **a**: R^1=F, R^2=H
b: R^1=H, R^2=F

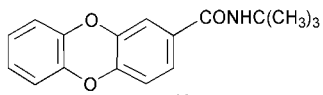
In general, the nitro-activated nucleophilic displacement reactions are not as clean as the nitrile activated processes and we have not pursued these reactions further.

In view of the interest in functionalized dibenzo[1,4]-dioxines, we converted the cyanodibenzo[1,4]dioxines into a variety of other dibenzo[1,4]dioxine derivatives. We investigated the hydrolysis of the cyanodibenzo[1,4]dioxines. Previously we had demonstrated that nitrile groups in bis(cyanophenoxy)benzenes are readily hydrolysed by refluxing with methanolic potassium hydroxide.[11] Cyanodibenzo-[1,4]dioxines proved to be more resistant to hydrolysis but we demonstrated that they could be hydrolysed readily at higher temperatures. Thus, on refluxing with potassium hydroxide in ethylene glycol complete hydrolysis (evolution of ammonia) was achieved in about 15 min. High yields (in excess of 95%) of the corresponding carboxydibenzo[1,4]dioxines **8** and **9** were obtained in this way (Scheme 1).

Interest has been expressed in amides of dibenzo[1,4]-dioxines.[1] We therefore considered the direct conversion of cyanodibenzo[1,4]dioxines into amides; indirect conversion *via* the carboxydibenzo[1,4]dioxine should be trivial. Despite the relative difficulty in hydrolysing cyanodibenzo[1,4]-dioxines to carboxydibenzo[1,4]dioxines, partial hydrolysis to the dibenzo[1,4]dioxinecarboxylic acid amides proved easy. Radziszewski, in 1885, first described the conversion of a nitrile into an amide by reaction with hydrogen peroxide under alkaline conditions;[18] this reaction became a standard route for synthesis of amides from nitriles and subsequently many variations of this procedure have been reported.[19] We adapted the Radziszewski reaction to cyanodibenzo[1,4]-dioxines. For the conversion of compound **7a** a 1 : 1 acetone–ethanol mixture was found to be a suitable solvent system. Reaction was performed in sodium hydroxide solution (6 M). Hydrogen peroxide (30%) was added to the reaction mixture which was heated to 60 °C for 4 h. The product, dibenzo[1,4]-dioxine-2-carboxamide (**12**), was isolated by acidifying the reaction mixture with hydrochloric acid. Volatiles were then removed and the product was diluted with acetonitrile, warmed to about 80 °C and filtered while warm. The yield of the crude product, which was readily purified by recrystallization from acetonitrile, was 93%.



12



13

For a second example we adapted the Ritter reaction which can be used to convert nitriles into alkyl-substituted secondary amides with olefins, or olefins generated *in situ*, in the presence of sulfuric acid.[20] To demonstrate the applicability of the Ritter reaction to cyanodibenzo[1,4]dioxines, compound **7a** was suspended in acetic acid and Bu^{t}OH added at 40–50 °C. This was followed by a small amount of concentrated sulfuric acid which caused the reaction mixture to become clear. The solution was stirred at 40 °C for 2 h. On cooling to about 0 °C the crystalline product dibenzo[1,4]dioxine-2-(*N*-*tert*-butyl)carboxamide (**13**) was then isolated in 80% yield.

Experimental

General

IR spectra were determined from KBr discs on a Perkin-Elmer FT-IR spectrometer Paragon 1000, NMR spectra on a Bruker AMX-400 spectrometer. Accurate masses were measured using a VG analytical 7070E spectrometer and masses of molecular ions on a TR10 spectrometer. Melting points were determined with a Mettler hot stage attached to a polarizing microscope, using a heating rate of 1 °C min^{-1}. ^{13}C NMR assignments and crystal structures of compounds **6a**, **11** and **16** are in the ESI†.

Crystallography

Crystal data were collected on a Stoe-IPDS diffractometer at 293 K using Mo-Kα radiation ($\lambda = 0.710\,73$ Å). Full-matrix least square refinements on F^2 using all data (SHELX 97).[21] **6a**: $C_{13}H_7NO_2$, $M = 209.20$, monoclinic, space group $C2/c$, $a = 27.732(6)$, $b = 7.833(2)$, $c = 19.416(4)$ Å, $\beta = 106.80(3)°$, $V = 4038(2)$ Å^3, $Z = 16$, μ(Mo-Kα) = 0.094 mm^{-1}, $R1[I > 2\sigma(I)] = 0.046$, $wR2$ (all data) = 0.112, 10 366 measured and 2555 independent reflections, $R_{int} = 0.136$. **11**: $C_{12}H_6FNO_4$, $M = 247.18$, monoclinic, space group $P2_1/c$, $a = 10.641(2)$, $b = 5.9763(7)$, $c = 16.382(2)$ Å, $\beta = 102.50(2)°$, $V = 1017.1(2)$ Å^3, $Z = 4$, μ(Mo-Kα) = 0.135 mm^{-1}, $R1[I > 2\sigma(I)] = 0.037$, $wR2$ (all data) = 0.109, 7413 measured and 1919 independent reflections, $R_{int} = 0.027$. The F atom in **11** is disordered on two positions (see Discussion for details). **16**: $C_{20}H_{18}O_2$, $M = 290.38$, orthorhombic, space group $P2_12_12_1$, $a = 8.6688(13)$, $b = 9.4019(10)$, $c = 19.222(2)$ Å, $V = 1566.7(3)$ Å^3, $Z = 4$, μ(Mo-Kα) = 0.078 mm^{-1}, $R1[I > 2\sigma(I)] = 0.041$, $wR2$ (all data) = 0.074, 8441 measured and 1981 independent reflections, $R_{int} = 0.038$.

CCDC reference number 440/255. See http://www.rsc.org/suppdata/nj/b0/b008508l/ for crystallographic files in .cif format.

Preparation of catechols

3,4-Dimethylphenol, 3,5-di-*tert*-butylcatechol, 3-methylcatechol, 2,3-dihydroxynaphthalene and alizarin were available from commercial sources and used as supplied.

4,5-Dimethylcatechol (1c). This compound was prepared (67.5%) from 3,4-dimethylphenol by oxidation with Fremy's salt in buffered (KH_2PO_4), according to the procedure of Teuber and co-workers.[12] The intermediate *ortho*-quinone was not isolated but taken into chloroform and reduced with sodium dithionite. The compound had mp 86–87 °C (lit.[12] 87–88 °C).

3,6-Dimethylcatechol (1d). (i) 3-Methyl-6-morpholinomethylcatechol (**14**) was synthesized (71%) from 3-methylcatechol according to the procedure of Cram and co-workers.[13] (ii) To the catechol **14** (2.23 g, 10 mmol) in MeOH (25 mL), 10% Pd/C (2.4 g) wetted with methanol was added, followed by powdered ammonium formate (2.6 g). The mixture was heated under reflux for 30 h then the catalyst was filtered off and washed twice with warm MeOH. The MeOH was removed on a rotary evaporator and the residue dissolved in CH_2Cl_2 (50 mL). The solution was washed with HCl (1 M) then with a saturated aq. solution of NaCl. The product was isolated by evaporation of the solvent to yield the catechol **1d** (1.01 g, 73%) which readily sublimed under vacuum to give snow-white needles, mp 99.8 °C (lit.[22] 98.5–99.5 °C). Calc. for $C_8H_{10}O_2$: C, 69.54; H, 7.29. Found: C, 69.38; H, 7.32%.

4,5-Diphenylcatechol (1e). (i) To 4,5-dibromoveratrole (**15**) (2.96 g, 10 mmol) in toluene (20 mL) under N_2 was added 2 M aq. sodium carbonate (15 mL), followed by phenylboronic acid (2.6 g, 21.4 mmol) and tetrakis(triphenylphosphine)-palladium(0) (0.43 mmol). The reaction mixture was heated under reflux for 13 h then cooled to rt, 30% aq. H_2O_2 (0.7 mL) added and the product extracted with diethyl ether (120 mL). The ether layer was washed with water, saturated aq. sodium hydrogencarbonate and water and then dried and evaporated to give 4,5-diphenylveratrole (**16**) (2.45 g, 85%). Analytical samples were obtained by crystallization from any of cyclohexane, MeOH, EtOH or CH_2Cl_2 or by sublimation under high vacuum; mp 145.5–146.5 °C (lit.[23] 140–142 °C); ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 6H), 6.94 (s, 2H), 7.13 (dd, 4H, $J = 9.0$, 2.0 Hz) and 7.16–7.21 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 56.05, 113.67, 126.25, 127.87, 129.95, 133.03, 141.43 and 148.19. Calc. for $C_{20}H_{18}O_2$: C, 82.73, H, 6.24. Found: C, 82.73; H, 6.30%. The crystal structure was determined (see ESI†).

(ii) To 4,5-diphenylveratrole (1.75 g, 6 mmol) in CH_2Cl_2 (100 mL) under N_2 at −78 °C boron tribromide (6 mL) in CH_2Cl_2 (60 mL) was added dropwise. The reaction mixture was then added gradually in small portions to water (15 mL). The water was changed four times when its pH reached 6.5–7.0. The CH_2Cl_2 layer was dried and solvent removed to yield the crude catechol (**1e**) (1.57 g, 99%). The product was purified either by sublimation (250 °C, 0.5 Torr) or by recrystallization from acetone–hexane (35 : 65) to give a sample of mp 146–146.8 °C (lit.[14] 142–143 °C). Calc. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.37. Found: C, 81.97, H, 5.34%. HRMS: calc. for $C_{18}H_{14}O_2$ m/z 262.099 37, found 262.099 22.

Preparation of cyanodibenzo[1,4]dioxines: general procedure

In a three-necked flask equipped with a magnetic stirring bar, N_2 inlet, Dean–Stark trap and thermometer were placed the catechol (10 mmol) (or as detailed below), the difluoronitrile (**2** or **3**) (10 mmol), DMF (30 mL) and toluene (10 mL, or sufficient to achieve a reflux temperature of 125–130 °C). Under a stream of N_2 anhydrous potassium carbonate (30 mmol) was added. The mixture was refluxed under N_2 for 4–5 h (not optimized). Some toluene was distilled off and the reaction mixture cooled to about 80 °C and poured with vigorous stirring into an ice–water mixture. The white, or off-white, product was filtered off, washed thoroughly with water and air dried. The cyanodibenzo[1,4]dioxines could be purified by recrystallization from MeOH or, better, from MeCN–water (9 : 1). Analytical samples were best produced by sublimation at 200 °C and 0.5 Torr.

1-Cyanodibenzo[1,4]dioxine (6a). This compound was prepared (99%) according to the general procedure from catechol (**1a**) (20 mmol) and the nitrile **2**; mp 91.7–92.0 °C (after sublimation); IR (KBr): 2227, 1499, 1452, 1301 and 746 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.81 (m, 1H), 6.92 (dd, 1H, $J = 8.1$, 7.7), 6.93 (m, 3H), 7.00 (dd, 1H, $J = 8.1$, 1.6) and 7.11 (dd, 1H, $J = 7.7$, 1.6 Hz). Calc. for $C_{13}H_7NO_2$: C, 74.64; H, 3.37; N, 6.69%. Found: C, 74.63; H, 3.35; N, 6.72%. HRMS: calc. for $C_{13}H_7NO_2$ m/z 209.047 67, found 209.047 80.

2-Cyanodibenzo[1,4]dioxine (7a). This compound was prepared (quant.) from catechol (**1a**) (20 mmol) and the nitrile **3**; mp 159–159 °C (after sublimation); IR (KBr): 2220, 1494, 1417, 1311 and 760 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.82 (m, 2H), 6.84 (d, 1H, $J = 8.35$), 6.92 (m, 2H), 7.03 (d, 1H, $J = 1.9$) and 7.16 (dd, 1H, $J = 8.35$, 1.9 Hz). Calc. for $C_{13}H_7NO_2$: C, 74.64; H, 3.37; N, 6.69%. Found: C, 74.41; H, 3.24; N, 6.61%. HRMS: calc. for $C_{13}H_7NO_2$ m/z 209.047 67, found 209.047 60.

1-Cyanobenzo[*b*]naphtho[2,3-*e*][1,4]dioxine (6b). This was prepared (91%) from 2,3-dihydroxynaphthalene (**1b**) (10 mmol) and the nitrile **2**; mp 195.7–196.0 °C (from MeCN); IR (KBr): 2229, 1513, 1461, 1292 and 750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.98 (dd, 1H, $J = 8.2$, 7.7), 7.11 (dd, 1H, $J = 8.2$, 1.5), 7.18 (dd, 1H, $J = 7.7$, 1.5 Hz), 7.23 (s, 1H), 7.36 (m, 2H), 7.37 (s, 1H) and 7.64 (m, 2H). Calc. for $C_{17}H_9NO_2$: C, 78.75; H, 3.49; N, 5.40%. Found: C, 78.76; H, 3.43; N, 5.39%. HRMS: calc. for $C_{17}H_9NO_2$ m/z 259.063 32, found: 259.063 87.

2-Cyanobenzo[*b*]naphtho[2,3-*e*][1,4]dioxine (7b). This was prepared (97%) from 2,3-dihydroxynaphthalene (**1b**) (10 mmol) and the nitrile **3**; mp 240.2–240.4 °C (from MeCN); IR: 2224, 1504, 1469, 1301 and 753 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.99 (dd, 1H, $J = 8.35$, 0.3), 7.20 (dd, 1H, $J = 1.9$, 0.3), 7.25 (dd, 1H, $J = 8.35$, 1.9 Hz), 7.27 (m, 2H), 7.37 (m, 2H) and 7.55 (m, 2H). Calc. for $C_{17}H_9NO_2$: C, 78.75; H, 3.49; N, 5.40%.

Found: C, 78.68; H, 3.46; N, 5.42%. HRMS: calc. for $C_{17}H_9NO_2$ *m/z* 259.063 32, found 259.063 87.

1-Cyano-7,8-dimethyldibenzo[1,4]dioxine (6c). This was prepared (80%) from 4,5-dimethylcatechol (**1c**) (10 mmol) and the nitrile **2**; mp 178–179 °C (after sublimation); IR (KBr): 2229, 1507, 1472, 1322 and 719 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.15 (s, 6H), 6.62 (m, 1H), 6.75 (m, 2H), 6.91 (dd, 1H, $J = 8.2$, 7.8), 7.00 (dd, 1H, $J = 8.2$, 1.6) and 7.12 (dd, 1H, $J = 7.8$, 1.6 Hz). Calc. for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90%. Found: C, 75.98; H, 4.65; N, 5.91%. HMRS: calc. for $C_{15}H_{11}NO_2$ *m/z* 237.078 98, found: 237.079 03.

2-Cyano-7,8-dimethyldibenzo[1,4]dioxine (7c). This was prepared (67%) from 4,5-dimethylcatechol (**1c**) (10 mmol) and the nitrile **3**; mp 215.8–216.4 °C (after sublimation); IR (KBr): 2224, 1504, 1460, 1327 and 796 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.15 (s, 6H), 6.62 (s, 1H), 6.63 (s, 1H), 6.86 (d, 1H, $J = 8.3$), 7.07 (d, 1H, $J = 1.9$) and 7.18 (dd 1H, $J = 8.3$, 1.9 Hz). Calc. for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N 5.90%. Found: C, 75.80; H, 4.67; N, 5.90%. HRMS: calc. for $C_{15}H_{11}NO_2$ *m/z* 237.078 98, found: 237.079 03.

1-Cyano-6,9-dimethyldibenzo[1,4]dioxine (6d). This was prepared (93%) from 3,6-dimethylcatechol (**1d**) (5 mmol) and the nitrile **2**; mp 185–186 °C (after sublimation); IR (KBr): 2214, 1464, 1425, 1302 and 777 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.17 (s, 3H), 2.23 (s, 3H), 6.66 (s, 2H), 6.90 (dd, 1H, $J = 8.1$, 7.8), 7.02 (dd, 1H, $J = 8.1$, 1.5) and 7.10 (dd, 1H, $J = 7.8$, 1.5 Hz). Calc. for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90%. Found: C, 75.88; H, 4.67; N, 5.95%. HRMS: calc. for $C_{15}H_{11}NO_2$ *m/z* 237.078 98, found: 237.079 03.

2-Cyano-6,9-dimethyldibenzo[1,4]dioxine (7d). This was prepared (92%) from 3,6-dimethylcatechol (**1d**) (5 mmol) and the nitrile **3**; mp 174–176 °C (after sublimation); IR (KBr): 2224, 1504, 1464, 1307 and 792 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H), 2.16 (s, 3H), 6.64 (s, 2H), 6.86 (d, H(1)), 7.07 (d, $J_{1,3} = 1.93$, H(3)) and 7.16 (dd, $J_{3,4} = 8.35$ Hz, H(4)). Calc. for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90%. Found: C, 75.84; H, 4.67; N, 5.90%. HRMS: calc. for $C_{15}H_{11}NO_2$ *m/z* 237.078 98, found 237.079 03. A violet dye was also isolated but not identified.

1-Cyano-7,8-diphenyldibenzo[1,4]dioxine (6e). This was prepared (99%) from 4,5-diphenylcatechol (**1e**) (1 mmol) and the nitrile **2**; mp 179–180 °C (after sublimation); IR (KBr): 2234, 1499, 1400, 1278 and 772 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.91 (s, 1H), 6.95 (dd, 1H, $J = 8.1$, 7.8), 7.02 (dd, 1H, $J = 8.1$, 1.6), 7.06 (s, 1H), 7.07 (m, 4H), 7.16 (dd, 1H, $J = 7.8$, 1.6 Hz) and 7.19 (m, 6H). Calc. for $C_{25}H_{15}NO_2$: C, 83.08; H, 4.18; N, 3.87%. Found: C, 82.97; H, 4.15; N, 3.86%. HRMS: calc. for $C_{25}H_{15}NO_2$ *m/z* 361.110 29, found 361.110 07.

2-Cyano-7,8-diphenyldibenzo[1,4]dioxine (7e). This was prepared (94%) from 4,5-diphenylcatechol (**1e**) (1 mmol) and the nitrile **3**; mp 249–249.6 °C (from toluene). IR (KBr): 2214, 1499, 1479, 1332 and 750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.94 (d, 1H, $J = 7.4$), 6.94 (s, 1H), 6.95 (s, 1H), 7.07 (m, 4H), 7.15 (d, 1H, $J = 1.8$), 7.20 (m, 6H) and 7.24 (dd, 1H, $J = 7.4$, 1.8 Hz). Calc. for $C_{25}H_{15}NO_2$: C, 83.08; H, 4.18; N, 3.87%. Found: C, 82.85; H, 4.15; N, 3.87%. HRMS: calc. for $C_{25}H_{15}NO_2$ *m/z* 361.110 29, found 361.109 36.

2-Cyano-6-methyldibenzo[1,4]dioxine (7f) and 2-cyano-9-methyldibenzo[1.4]dioxine (7g). These compounds were prepared (99%) as a 1 : 1 mixture (by GC/MS) from 3-methylcatechol (**1f**) (20 mmol) and the nitrile **3**; mp 130–138 °C (from MeOH); IR (KBr): 2222, 1505, 1471 and 1301 cm^{-1}. Calc. for $C_{14}H_9NO_2$: C, 75.32, H, 4.06, N, 6.27%. Found: C, 75.48; H, 4.07; N, 6.33%. The mixture was not characterized further.

2-Cyano-6,8-di-*tert*-butyldibenzo[1,4]dioxine (7h) and 2-cyano-7,9-di-*tert*-butyldibenzo[1,4]dioxine (7i). These compounds were prepared (quant.) as a 1 : 1 mixture (by GC/MS) from 3,5-di-*tert*-butylcatechol (**1h**) (10 mmol) and the nitrile **3**; mp 92–104 °C (after distillation). Calc. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.35%. Found: C, 78.80; H, 7.24; N, 4.37%. The compounds were not characterized further.

1-Cyanonaphtho[2,3,-*a*]dibenzo[1,4]dioxine-8,13-dione (6j). This was prepared (28%) from alizarine (**1j**) (6 mmol) and the nitrile **2** at 130 °C (from toluene); mp above 300 °C. IR (KBr): 2237, 1673 and 1467 cm^{-1}. Calc. for $C_{21}H_9NO_4$: C, 74.33; H, 2.67; N, 4.12%. Found: C, 74.52; H, 2.66; N, 4.09%. HRMS: calc. for $C_{21}H_9NO_4$ *m/z* 339.053 16, found 339.053 13.

Preparation of dibenzo[1,4]dioxinecarboxylic acids: general procedure (5 mmol scale)

Potassium hydroxide (1.5 g) was dissolved in water (1.5 mL) and 1,2-ethanediol (10 mL). The cyanodibenzo[1,4]dioxine (5 mmol) was added and the reaction mixture heated under reflux for 30 min (ammonia evolution ceased after 15 min), cooled and diluted with water followed by acidification with hydrochloric acid. The carboxylic acid was filtered off, washed with water until neutral and, while wet, crystallized from acetic acid. With smaller quantities the product is more efficiently obtained by extraction of the acidified mixture with Et_2O. Analytical samples were obtained by sublimation at 150 °C and 0.5 Torr.

Dibenzo[1,4]dioxine-1-carboxylic acid (8a). This acid was prepared (quant.) from 1-cyanodibenzo[1,4]dioxine (**6a**) (0.7 g, 3.35 mmol); mp 212–213 °C (after sublimation) (lit.[1] 205–207 °C;[24] 212–215 °C). Calc. for $C_{13}H_8O_4$: C, 68.42; H, 3.53%. Found: C, 68.33; H, 3.34%. HRMS: calc. *m/z* 228.042 27, found 228.042 44.

Dibenzo[1,4]dioxine-2-carboxylic acid (9a). This acid was prepared (96%) from 2-cyanodibenzo[1,4]dioxine (**7a**) (5 mmol); mp 245–247 °C (from HOAc), 240 °C when sealed in a capillary (lit.[24] 245.5–247 °C;[25] 239–241 °C). Calc. for $C_{13}H_8O_4$: C, 68.42; H, 3.53%. Found: C, 68.35; H, 3.38%. HRMS: calc. *m/z* 228.042 27, found: 228.042 22.

Benzo[*b*]naphtho[2,3-*e*][1,4]dioxine-1-carboxylic acid (8b). The acid was prepared (78%) from 1-cyanobenzo[*b*]-naphtho[2,3-*e*][1,4]dioxine (**6b**) (2 mmol); mp 270.8–271.3 °C (after sublimation). Calc. for $C_{17}H_{10}O_4$: C, 73.37; H, 3.62%. Found: C, 73.40; H, 3.58%. HRMS: calc. for $C_{17}H_{10}O_4$ *m/z* 278.057 92, found 278.058 15.

Preparation of dibenzo[1,4]dioxinecarboxamides

Dibenzo[1,4]dioxine-2-carboxamide (12). 2-Cyanodibenzo-[1,4]dioxine (**7a**) (1.04 g, 5 mmol) was dissolved in 1 : 1 acetone–EtOH (50 mL). Aq. NaOH (6 M, 0.6 mL) was added followed by aq. H_2O_2 (30%, 3 mL) and the reaction mixture heated to 60 °C for 4 h. The mixture was then acidified (HCl) and the volatiles were removed by evaporation. The residue was diluted with MeCN (100 mL), warmed to about 80 °C and filtered while warm. The amide (**12**) crystallized from the filtrate as fine needles (0.73 g) after which further solvent evaporation yielded an additional 0.20 g. The filtrate from the first hot filtration was washed with water and dried to yield a further 0.12 g of less pure amide, giving a total of 1.05 g (93%). Analytical samples were obtained by recrystallization from

MeCN; mp 231.7–232.5 °C; IR (KBr): 3416, 3188, 1659, 1496, 1314 and 730 cm^{-1}. Calc. for $C_{13}H_9NO_3$: C, 68.71; H, 3.99; N, 6.16%. Found: C, 69.00; H, 3.96; N, 6.18%. HRMS: calc. for $C_{13}H_9NO_3$ *m/z* 227.058 23, found: 227.058 32.

Dibenzo[1,4]dioxine-2-(*N-tert*-butyl)carboxamide (13). 2-Cyanodibenzo[1,4]dioxine (**7a**) (0.152 g, 0.727 mmol) was suspended in HOAc (5 mL) at 40–50 °C and Bu^{t}OH (1 g) added, then conc. H_2SO_4 (1 g) when the suspension became clear. The solution was stirred at 40 °C for 2 h. After cooling to room temperature, no crystals formed until ice was added when the solid product was filtered off, washed with water, saturated aq. $NaHCO_3$ and water. The wet product was recrystallized to give dibenzo[1,4]dioxine-2-(*N-tert*-butyl)carboxamide (**13**) (0.16 g, 80%), mp 201.6–202.6 °C (from MeOH); IR (KBr): 1639, 1494, 1362, 1212, 1311 and 741 cm^{-1}. Calc. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.04; N, 4.94%. Found: C, 71.80; H, 6.14; N, 4.80%. HRMS: calc. for $C_{17}H_{17}NO_3$ *m/z* 283.120 85, found 283.121 25.

Acknowledgements

The authors wish to thank the EPSRC for financial support and acknowledge the help given by Mr S. Apter (elemental analysis, FTIR), Mr A. Mills and Ms M. McCarron (GC and MS), Dr P. Leonard who recorded NMR spectra and assigned the ^1H spectra and Mr J. Bickley (X-ray diffraction).

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