An Improved Synthesis of Substituted Dibenzo[1,4]dioxines

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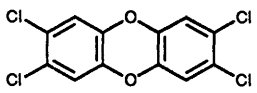
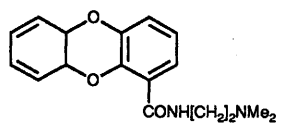
An improved general synthesis of substituted dibenzo[1,4]dioxines by reaction of catechol and substituted 1,2-dichloro- or 2-chloronitro-benzenes with metallic potassium in hexamethylphosphoramide is reported. The yields are generally superior to those in published methods, and in particular the reaction appears the one of choice for the synthesis of both the parent dibenzodioxine and the 1-carboxy derivative.

In spite of the large literature on the environmental toxin 2,3,7,8-tetrachlorodibenzo[1,4]dioxine (**1**, TCDD), there has been relatively little work on general synthetic routes to substituted dibenzodioxines. Our recent discovery[1] of the potent *in vitro* cytotoxicity and significant *in vivo* antitumour activity of the dibenzodioxine-4-carboxamide derivative (**2**) has prompted us to explore methods for the synthesis of asymmetrically disubstituted dibenzodioxines, particularly substituted dibenzodioxine-1-carboxylic acids.



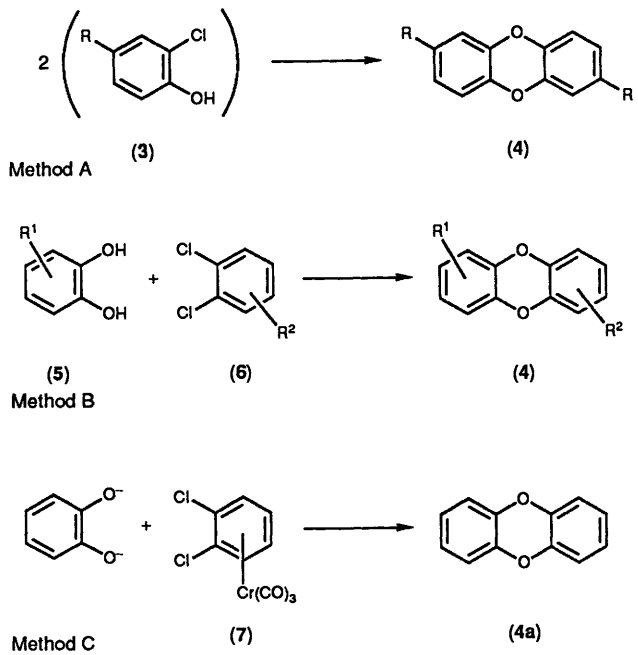
(1) TCDD



(2)

Two main routes to the dibenzodioxine chromophore are known. Self-condensation of 2-halogenophenols (**3**) with base (method A, Scheme) has been used to prepare the unsubstituted compound (**4a**; R = H) in moderate yields (10–20%).[2,3] The reaction is usually regiospecific, although products of unusual rearrangements have been noted.[4] However, the method is essentially limited to the synthesis of symmetrically substituted compounds, and the yields are low to moderate.[5] Two different 2-halogenophenols can be used, but complex mixtures of products resulting from self-condensation of each reactant as well as the desired cross-condensation product are usually obtained.[6]

Dibenzodioxines have also been prepared by condensation of catechols (**5**) with activated chlorobenzenes (**6**) (method B, Scheme). This reaction can be used to prepare asymmetrically substituted compounds, but has the disadvantage of generally not being regiospecific.[7,8] Reaction of substituted catechols with nitro-activated chlorobenzenes in the absence of base has been used to prepare asymmetrically substituted dibenzodioxines in low to moderate yields (10–25%), where the starting materials were selected in order to avoid regioisomeric mixtures.[9] In these reaction the nitro group serves to promote chlorine substitution and also acts as a preferential leaving group, since nitro-containing dibenzodioxines were not obtained.[9] However, activation by additional chloro groups is sufficient, since polychlorobenzenes react to form dibenzodioxines in a base-catalysed reaction.[10] An alternative halogen activation (method C, Scheme) is by complexation with the tricarbonylchromium unit.[11] However, although the complex (**7**) reacts readily with catechol dianion in hexamethylphosphoramide (HMPA) to give a good yield (80%) of



Scheme.

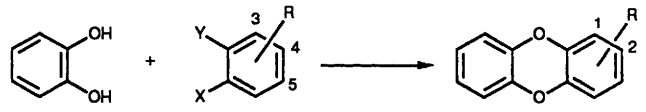
dibenzodioxine (**4a**), the preparative usefulness of this reaction is limited by a low yield (15%) in the formation of the complex itself.[11] A recent paper[12] also reported the use of cyclopentadienyliron complexes for halogen activation in the synthesis of dibenzodioxines.

Method B is clearly the most flexible, in spite of the potential problem of regioisomer formation, and we explore it in this paper.

Results and Discussion

The dianion of catechol (**8**) was prepared from equimolar amounts of catechol and metallic potassium in dry HMPA at 20 °C. Reaction of the unactivated 1,2-dichlorobenzene (**9a**) with this anion in HMPA gave only trace amounts (< 1%) of the parent dibenzodioxine (**4a**), even after 25 h at 110 °C, and 1,2-difluorobenzene (**9b**) gave a yield of only 3% under the same conditions. However, 2-chloronitrobenzene (**9c**) gave a 71% yield, and 1,2-dinitrobenzene (**9d**) an 87% yield of (**4a**) under the same conditions. HMPA was clearly the solvent of choice for

Table. Synthesis of substituted dibenzodioxines.



(8) (9) (4)

(9)				Ratio	Reaction	(4)		
	X	Y	R	(8):(9)	time/h[a]		R	% Yield[b] (eluting solvent)[c]
a	Cl	Cl	H	2:1	4	**a**	H	0[d]
				2:1	25	**a**	H	<1[e]
b	F	F	H	2:1	4	**a**	H	3 (hexane)
c	Cl	NO_2	H	2:1	4	**a**	H	71 (hexane)
d	NO_2	NO_2	H	2:1	4	**a**	H	87 (hexane)
e	Cl	Cl	3-Cl	2:1	4	**b**	1-Cl	27 (hexane)
f	Cl	Cl	3-NO_2	2:1	4	**b**	1-Cl	96 (hexane)
g	NO_2	Cl	3-NO	2:1	4	**c**	1-NO_2	57 (EtOAc–hexane, 1:100)
h	Cl	Cl	3-CO_2H	2:1	4	**d**	1-CO_2H	0[d]
i	Cl	Cl	3-CO_2Me	2:1	4	**e**	1-CO_2Me	15
j	Cl	Cl	3-CO_2Pr^i	1:2	5	**f**	1-CO_2Pr^i	35 (EtOAc–hexane, 1:50)
k	NO_2	Cl	3-CO_2H	1:2	4	**d**	1-CO_2H	<1[e]
				2:1	4	**d**	1-CO_2H	17 (EtOAc–MeOH, 10:1)
l	NO_2	Cl	3-CO_2Pr^i	1:2	4	**f**	1-CO_2Pr^i	59 (hexane)
m	Cl	NO_2	3-CO_2Pr^i	1:2	4	**f**	1-CO_2Pr^i	48 (Me_2CO–hexane, 1:100)
n	Cl	Cl	4-Cl	2:1	4	**g**	2-Cl	9 (hexane)
o	Cl	Cl	4,5-Cl_2	2:1	4	**h**	2,3-Cl_2	100 hexane)
p	Cl	Cl	4-CO_2Pr^i	1:1	0.33[f]	**i**	2-CO_2Pr^i	<15[e]
				1:1	4[f]	**i**	2-CO_2Pr^i	15 (CH_2Cl_2–hexane, 1:5)
q	Cl	Cl	4-NO_2	2:1	4	**j**	2-NO_2	74 (hexane)
r	Cl	NO_2	4-Cl	2:1	4	**g**	2-Cl	100 (hexane)
s	Cl	NO_2	4-CO_2Pr^i	1:2	0.33	**i**	2-CO_2Pr^i	22 (Me_2CO–hexane, 1:50)
				2:1	0.33[f]	**i**	2-CO_2Pr^i	63 (Me_2CO–hexane, 1:50)
t	Cl	NO_2	4-NO_2	2:1	4	**j**	2-NO_2	66 (hexane)
(10)				2:1	4	**(11)**		76 (EtOAc–hexane, 1:20)
(12)				1:1	0.33	**(13)**		61 Recryst. from EtOAc
(14)				1:1	0.33	**(15)**		85 Recryst. from acetone

[a] Reaction in HMPA at 110 °C, as detailed in the Experimental section. [b] Isolated yields, based on the limiting component in the reaction mixture. Yields have not been optimised. [c] Purification by silica gel chromatography. [d] No product could be detected by TLC. [e] Yield estimated from TLC. [f] Modification of the reaction conditions for unstable compounds (**9**). See Experimental section.

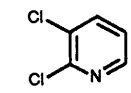
these reactions, since the use of tetrahydrofuran (THF), dimethylformamide (DMF), or sulpholane gave virtually no (**4a**). This synthesis of dibenzodioxine from the readily available 2-chloronitrobenzene is clearly superior to the existing methods, which require severe conditions and result in only moderate yields.

Even mild activation of the halogens of 1,2-dichlorobenzene results in improved yields of ring-closed products, the yield increasing with the degree of activation. Thus, 1,2,3-trichlorobenzene (**9e**) gave a 27% yield of 1-chlorobenzodioxine (**4b**). 1,2-Dichloro-3-nitrobenzene (**9f**) gave no 1-nitro compound, but instead a virtually quantitative yield of the chloro compound (**4b**), resulting from preferential displacement of the nitro group. However, 2,6-dinitrochlorobenzene (**9g**) did give a 57% yield of 1-nitrodibenzodioxine (**4c**). Although the anion of the benzoic acid (**9h**) did not react to give the dibenzodioxine-1-carboxylic acid (**4d**) directly, the methyl ester (**9i**) gave a 15% yield of methyl dibenzodioxine-1-carboxylate (**4e**), and the more base-stable isopropyl ester (**9j**) a 35% yield of the corresponding 1-isopropyl ester (**4f**). This ester could be quantitatively hydrolysed to the acid (**4d**) by aqueous KOH in MeOH at room temperature. This method constitutes a more convenient synthesis of this compound than the previous routes *via* metallation of dibenzodioxine.[1,13]

The chloronitrobenzoic acid (**9k**) gave a 17% yield of (**4d**) directly, while use of the two isomeric isopropyl chloronitrobenzoates (**9l**) and (**9m**) gave the ester (**4f**) in much better yield (50—60%) than that obtained using the dichloro ester (**9j**).

The reaction was also extended to the synthesis of 2-substituted dibenzodioxines. 1,2,4-Trichlorobenzene (**9n**) gave only a 9% yield of the 2-chloro derivative (**4g**), while 1,2,4,5-tetrachlorobenzene (**9o**) gave a quantitative yield of 2,3-dichlorodibenzodioxine (**4h**). This compound has been synthesized previously[10] in 80% yield, using considerably more severe conditions (refluxing Me_2SO). The 4-isopropyl ester (**9p**) gave a 15% yield of the 2-ester (**4i**), and 1,2-dichloro-4-nitrobenzene (**9q**) a 74% yield of 2-nitrodibenzodioxine (**4j**). In view of the known[14] toxicity of HMPA, this reaction was also carried out using 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) as solvent. DMPU has been suggested[14] as a relatively non-toxic replacement for HMPA, but proved inferior, giving only a 22% yield of (**4j**). A series of 4-substituted chloronitro starting materials (**9r**)–(**9t**) gave similar yields of the 2-substituted dibenzodioxines (**4h**)–(**4j**) to those obtained with the corresponding dichloro starting materials.

Other activated dichloro compounds also gave good yield of dioxines under these conditions. 2,3-Dichloropyridine (**10**) gave a 76% yield of [1,4]benzodioxino[2,3-*b*]pyridine (**11**),[12] while 2,3-dichloronaphthoquinone (**12**) gave a 61% yield of benzo[*b*]-naphtho[2,3-*e*]dioxine-6,11-dione (**13**). This compound has also been prepared in similar yield (54%) by refluxing the two components in excess of diethylamine.[15] 2,3-Dichloroquin-



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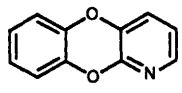

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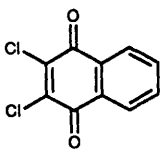

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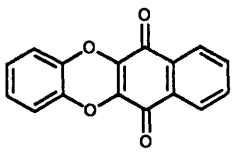

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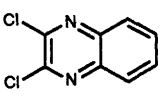

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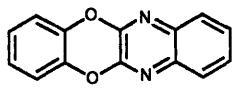

(15)

oxaline (**14**) gave an 85% yield of [1,4]benzodioxino[2,3-*b*]quinoxaline (**15**), which has been prepared previously using Na_2CO_3 in diethyl ketone as solvent.[16]

All the dibenzodioxines were characterized by ^1H and ^{13}C NMR spectroscopy. In the ^{13}C spectra of the substituted compounds, the signals of the four carbons attached to oxygen and forming the central dioxine ring are readily recognized, occurring in the region δ 137.0–146.0 and of relatively low peak height (*ca.* 20% of that of the other carbons).

In summary, the reaction of catechol (**8**) and a variety of 1,2-dichloro- and 1,2-chloronitrobenzenes (**9**) with metallic potassium in HMPA constitutes an efficient and general synthesis of substituted dibenzo[1,4]dioxines (**4**). Yields are generally superior to those in published methods, and the reaction is the one of choice for the synthesis of both the unsubstituted dibenzodioxine (**4a**) and the 1-carboxy derivative (**4d**). Extensions of the synthesis to asymmetrically disubstituted dibenzodioxines are obvious.

Experimental

Analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin. M.p.s were determined on an Electrothermal apparatus with the supplied stem-corrected thermometer, and are as read. NMR spectra were obtained on a Bruker AM-400 spectrometer (Me_4Si). **Warning:** Hexamethylphosphoramide (HMPA) is listed by the International Agency for Research on Cancer (IARC) as a possible human carcinogen. **Warning:** Some substituted dibenzo[1,4]dioxines are potent skin irritants and teratogens. In the absence of such information about the compounds described here, particular precautions to avoid exposure should be taken.

2-*Nitrodibenzo*[1,4]*dioxine* (**4j**). *Example of General Method.*—A mixture of catechol (**8**) (0.22 g, 2.0 mmol) and metallic potassium (0.14 g, 3.6 mmol) was stirred at 20 °C in dry hexamethylphosphoramide (HMPA; purified by distillation under reduced pressure followed by prolonged storage over 4A molecular sieve; 3 ml) under a slow stream of dry N_2 until all the potassium metal had been consumed. Solid 1,2-dichloro-4-nitrobenzene (**9q**) (0.19 g, 1.0 mmol) was then added, and the mixture was stirred at 110 °C (bath temperature) for 4 h. The cooled mixture was diluted with EtOAc (50 ml), and the organic layer was washed sequentially with 0.5M HCl and water. The residue was chromatographed on silica gel with hexane as eluant to give 2-nitrodibenzo[1,4]dioxine (**4j**) (0.17 g, 74%), m.p. 140–142 °C (from EtOAc) (lit.,[17] m.p. 141 °C); $\delta_H(CDCl_3)$ 7.83 (1 H, dd, *J* 8.9 and 2.6 Hz, 3-H), 7.73 (1 H, d, *J* 2.6 Hz, 1-H), and 7.00–6.86 (5 H, m, ArH); δ_C 147.6, 143.6, 142.1, 140.9, 140.8, 125.1, 124.7, 120.1, 116.7, 116.6, 116.4, and 112.4.

This method was used to prepare the majority of the derivatives listed in the Table. Non-crystalline acceptors (**9**) were added as solutions in dry HMPA. In this way were prepared the following. Dibenzo[1,4]dioxine (**4a**), m.p. 119–120 °C (from hexane) (lit.,[18] m.p. 119 °C); $\delta_H(CDCl_3)$ 6.88 (4 H, m, 1-, 4-, 6-, and 9-H) and 6.83 (4 H, m, 2-, 3-, 7-, and 8-H); δ_C 142.2, 123.8, and 116.3.

1-*Chlorodibenzo*[1,4]*dioxine* (**4b**), m.p. 96–98 °C (from hexane) (Found: C, 66.0; H, 3.25; Cl, 16.3. $C_{12}H_7ClO_2$ requires C, 65.9; H, 3.2; Cl, 16.2%); $\delta_H(CDCl_3)$ 6.97–6.83 (5 H, m, ArH), 6.81 (1 H, t, *J* 8.1 Hz, 3-H) and 6.74 (1 H, dd, *J* 8.1 and 1.7 Hz, 2-H); δ_C 142.3, 141.7, 141.6, 138.9, 124.7, 124.4, 124.1, 123.3, 121.3, 116.7, 116.3, and 114.8.

1-*Nitrodibenzo*[1,4]*dioxine* (**4c**), m.p. 124–126 °C (from EtOAc–hexane) (Found: C, 62.6; H, 2.9; N, 6.2. $C_{12}H_7NO_4$ requires C, 62.9; H, 3.1; N, 6.1%); $\delta_H(CDCl_3)$ 7.50 (1 H, dd, *J* 8.3 and 1.6 Hz, 2-H), 7.06 (1 H, dd, *J* 8.2 and 1.6 Hz, 4-H), and 6.99–6.83 (5 H, m, ArH); δ_C 143.5, 141.2, 140.7, 138.1, 137.5, 125.2, 124.6, 122.6, 120.8, 119.8, 117.0, and 116.4.

Isopropyl dibenzo[1,4]*dioxine-1-carboxylate* (**4f**), oil; $\delta_H(CDCl_3)$ 7.39 (1 H, dd, *J* 7.8 and 1.8 Hz, 2-H), 6.96 (1 H, dd, *J* 8.0 and 1.8 Hz, 4-H), 6.92–6.80 (5 H, m, ArH), 5.28 (1 H, septet, *J* 6.2 Hz, C*H*Me_2), and 1.39 (6 H, d, *J* 6.2 Hz, Me); δ_C 164.4, 142.8, 142.4, 141.9, 141.7, 125.6, 124.3, 124.0, 122.8, 120.3, 119.8, 116.7, 116.1, 68.8, and 21.9.

2-*Chlorodibenzo*[1,4]*dioxine* (**4g**), m.p. 87–89 °C (from hexane) (lit.,[3] m.p. 87–90 °C); $\delta_H(CDCl_3)$ 6.89 (2 H, m), 6.83 (4 H, m), and 6.75 (1 H, m), unable to assign; δ_C 142.6, 141.8, 141.5, 140.9, 128.2, 124.2, 124.0, 123.6, 117.1, 116.7, 116.43, and 116.41.

2,3-*Dichloro*[1,4]*dibenzodioxine* (**4h**), m.p. 157–159 °C (from EtOAc) (lit.,[10] m.p. 159–160 °C); $\delta_H(CDCl_3)$ 6.94 (2 H, s, 1- and 4-H), 6.92 (2 H, m, 6- and 9-H), and 6.84 (2 H, m, 7- and 8-H); δ_C 141.3, 141.2, 126.5, 124.4, 117.6, and 116.5.

[1,4]-*Benzodioxino*[2,3-b]*pyridine* (**11**), m.p. 95–96 °C (from EtOAc–hexane) (lit.,[12] m.p. 94–95 °C) (Found: C, 71.3; H, 3.9; N, 7.3. Calc. for $C_{11}H_7NO_2$: C, 71.3; H, 3.8; N, 7.6%); $\delta_H(CDCl_3)$ 7.81 (1 H, dd, *J* 4.9 and 1.5 Hz, 2-H), 7.15 (1 H, dd, *J* 7.8 and 1.5 Hz, 4-H), and 6.99–6.84 (5 H, m, ArH); δ_C 149.6, 141.9, 141.6, 141.2, 138.2, 124.5, 123.9, 120.7, 117.2, and 116.2.

Benzo[b]*naphtho*[2,3-e]*dioxine-6,11-dione* (**13**), m.p. 282–284 °C (red-brown crystals from EtOAc) (lit.,[15] m.p. 280 °C); $\delta_H(CDCl_3)$ 8.12 (2 H, m, 7- and 10-H), 7.75 (2 H, m, 8- and 9-H), and 7.01 (4 H, m, 1-, 2-, 3-, and 4-H); δ_C 177.5, 140.7, 139.7, 134.2, 129.9, 126.5, 126.0, and 117.4.

A slightly modified version of the above method (dilution of the reaction mixture with water, collection of the precipitate, and washing with water followed by crystallization from Me_2CO) gave [1,4]benzodioxino[2,3-*b*]quinoxaline (**15**), m.p. 265–267 °C (lit.,[16] m.p. 264–265 °C); $\delta_H(CDCl_3)$ 7.81 (2 H, m, 7- and 10-H), 7.58 (2 H, m, 8- and 9-H), 7.12 (2 H, m, 1- and 4-H), and 7.08 (2 H, m, 2- and 3-H); δ_C 144.7, 140.4, 139.1, 128.9, 127.3, 125.2, and 117.2.

Isopropyl Dibenzo[1,4]*dioxine-2-carboxylate* (**4i**). *Modification of General Method for Reactive Substrates.*—A mixture of catechol (0.11 g, 1.0 mmol) and metallic potassium (0.08 g, 2.0 mmol) in HMPA was stirred under N_2 at 20 °C until all the metal had been consumed. The mixture was then heated to 80–90 °C, and a dilute solution of isopropyl 4-chloro-3-nitrobenzoate (**9p**) (0.25 g, 1.0 mmol) in HMPA (3 ml) was added dropwise over 5 min. At the end of the addition, the mixture was stirred at 110 °C for a further 20 min, then worked up as above to give *isopropyl dibenzo*[1,4]*dioxine-2-carboxylate* (**4j**) (0.17 g, 63%), which crystallized from EtOAc–hexane as needles,

m.p. 68–69 °C (Found: C, 71.1; H, 5.4. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%); $\delta_H(CDCl_3)$ 7.61 (1 H, dd, *J* 8.3 and 2.0 Hz, 3-H), 7.52 (1 H, d, *J* 2.0 Hz, 1-H), 6.95–6.84 (5 H, m, ArH), 5.22 (1 H, septet, *J* 6.2 Hz, C*H*Me$_2$), and 1.26 (6 H, d, *J* 6.2 Hz, Me); δ_C 164.9, 145.9, 141.8, 141.5, 126.7, 125.8, 124.4, 124.1, 117.7, 116.5, 68.5, and 21.9.

Hydrolysis of Isopropyl Dibenzo[1,4]*dioxine-1-carboxylate* (**4f**).—To a solution of the ester (**4f**) (47 mg, 0.174 mmol) in MeOH (2 ml), 2M aqueous KOH (0.5 ml) was added and the mixture was stirred at 20 °C for 10 h. Most of the MeOH was removed under reduced pressure at 20 °C, and the residue was partitioned between acidic water and EtOAc. Work-up of the organic layer gave dibenzo[1,4]dioxine-1-carboxylic acid (**4d**) (40 mg, 100%) m.p. and mixed m.p. with sample obtained from (**9k**) 203–205 °C.

Acknowledgements

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