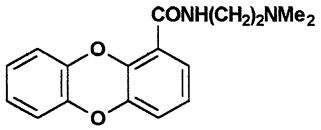
Cyanodibenzo[1,4]dioxines: A New Family of Synthons for Substituted Dibenzo[1,4]dioxines

Geoffrey C. Eastmond* and Jerzy Paprotny
Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK

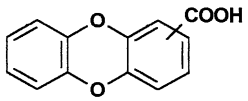
(Received January 11, 1999; CL-990028)

Cyanodibenzo[1,4]dioxines, previously unreported, are prepared quantitatively from catechols by nucleophilic fluorodisplacement from 2,3- and 3,4-difluorobenzonitriles, involving *meta*-fluorodisplacement, in DMF at 130 °C in the presence of potassium carbonate; the cyano-substituted dioxines can be transformed to other substituted dibenzo[1,4]dioxines.

Substituted dibenzodioxines may be highly toxic (2,3,7,8-tetrachlorodibenzo[1,4]dioxine) or have significant *in vivo* anti-tumour activity (dibenzo[1,4]-dioxin-1-carboxamide **1**).[1] The recently recognised biological activity of certain dibenzo[1,4]-dioxines[1-3] has generated interest in an efficient synthetic route to the relatively unexplored substituted dibenzo[1,4]dioxines, especially dibenzodioxine-1-carboxylic acid, and its derivatives.[2,4,5] Lee and Denny reviewed routes to substituted dibenzodioxines and favoured reaction between catechol (or substituted catechols) and activated 1,2-dichloro- or 1-chloro-2-nitrobenzenes as the most useful route to high overall yields.[4] Ester activation was used to produce substituted dioxines as precursors to dibenzo[1,4]dioxine-1- and 2-carboxylic acids **2a,b** when isopropyl esters of **2a** and **2b** were formed in 15-60% yields.[4] Here we report the quantitative syntheses of 1- and 2-cyanodibenzo[1,4]dioxines and their conversion to carboxy-dibenzo[1,4]dioxines.



1



2 a 1-COOH
b 2-COOH

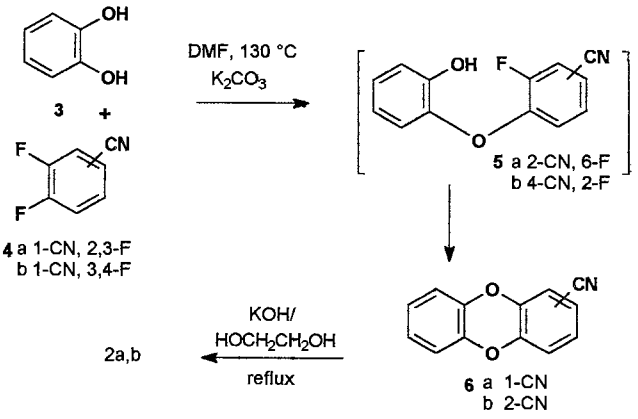
2-Cyanodibenzo[1,4]dioxine **6b** was synthesized by refluxing together (at 130-135 °C) equimolar quantities (0.01 mol) of catechol **3** and 3,4-difluorobenzonitrile **4b** in DMF-toluene (8:2) in the presence of anhydrous potassium carbonate under a nitrogen atmosphere in a reaction vessel equipped with a Dean-Stark trap, Scheme 1. Product **6b** was recovered by cooling the reaction mixture to 80 °C and pouring it into ice-water; the off-white crystalline 2-cyanodibenzo[1,4]dioxine **6b** so formed was washed with water and dried. The product could be recrystallized from methanol or, preferably, acetonitrile with 10% water; best analytical results were obtained from samples purified by vacuum sublimation. The synthesis of 1-cyanodibenzo[1,4]dioxine **6a** was identical to that for **6b** but made use of 2,3-difluorobenzonitrile **4a**. Yields for both of these previously unknown cyanodibenzo[1,4]dioxines were in excess of 98% based on **3**. Melting points of the products and results of elemental analyses are recorded in Table 1. Ir (selected absorptions (cm^{-1}) for **6a**: 2227 (C≡N), 1499 (aryl), 1452 (C=C), 1301 (C-O), 746 (aromatic); and for **6b**: 2220 (C≡N), 1494, 1417 (aryl C=C), 1311 (C-O), 746 (aromatic)) and nmr spectra of the compounds were consistent with the structures of the cyanodibenzo[1,4]dioxines; the structure of **6a** was confirmed by X-ray diffraction. Cyanobenzo[b]naphtho[2,3-e][1,4]dioxines **7a,b** were also prepared by the same procedure from 2,3-dihydroxynaphthalene and the characterization data are recorded in Table 1; yields of **7a** and **7b** were 91 and 97%, respectively. The identities of all products were further confirmed by mass spectrometry (molecular ion and accurate mass); data are presented in Table 1.

The 1- and 2-cyanodibenzo[1,4]dioxines **6a,b** were hydrolysed to dibenzo[1,4]dioxine carboxylic acids **2a,b** by refluxing with potassium hydroxide in ethylene glycol, Scheme 1. Hydrolyses were complete (evolution of ammonia ceased) in about 15 min. After 30 min heating the mixture was cooled and acidified with hydrochloric acid. Products **2a,b** were isolated by filtration, washed until neutral and, while wet, were recrystallized

Table 1. Characterization data for cyano- and carboxydibenzo[1,4]dioxines

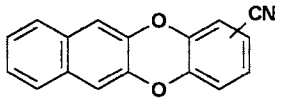
Substance		6a	6b	7a	7b	2a	2b	7c
Melting point/°C		91.7-92.0	158-159	195.7-196.0	240.2-240.4	211-213 205-207[a] 212-215[b]	245-247 245.5-247[b] 239-241[c]	270.8-271.3
Elemental analysis								
Calc.	C		74.63		78.75		68.42	73.37
	H		3.37		3.49		3.53	3.62
	N		6.69		5.40			
Found	C	74.63	74.41	78.76	78.68	68.33	68.35	73.40
	H	3.35	3.24	3.43	3.46	3.34	3.38	3.58
	N	6.72	6.61	5.39	5.42			
Accurate masses/Da								
Calc.		209.04767	209.04767	259.06332	259.06332	228.04227	228.042272	278.05792
Found		209.04780	209.04760	259.06387	259.06387	228.04244	228.04222	278.05815

[a]Ref. 1. [b]Ref. 6. [c]Ref. 7.



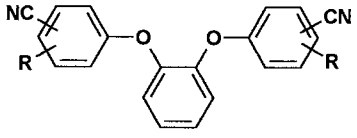
Scheme 1.

from acetic acid; very pure acids were obtained by sublimation under vacuum (0.5 torr) above 150 °C. Yields of dibenzodioxine carboxylic acids were in excess of 95%. Similarly, the cyanobenzonaphtho[1,4]dioxine **7a** was hydrolysed to the corresponding acid **7c**. Characterization data for the diacids are presented in Table 1. Ir and nmr data for the two known carboxydioxines **2a,b** are identical with literature data and melting points are similar to published data.[1,6,7]



7 X = a 1-CN c 1-COOH
b 2-CN

We recently used of nitrile- and nitro-activated fluoro-displacement reactions with dihydroxyphenylenes in aprotic solvents in the presence of potassium carbonate to produce bis(cyanophenoxy)arylenes and bis(nitrophenoxy)arylenes, as precursors to bis(ether acid)s and bis(ether amine)s, with various substitution patterns and substituents (alkyl and fluoro) on the several aromatic rings.[8,9] *Para-* and *ortho*-fluorobenzonitrile undergo reaction with **3** in almost quantitative yield (130 °C, DMF) to produce **8a** and **8b**, respectively. However, we demonstrated, unexpectedly, that *meta*-fluorobenzonitrile also undergoes reaction, but at higher temperatures (170 °C, NMP), to form **8c** in good yield (50-80%, depending on substituents on the catechol).[10] There are a few previous examples of *meta*-activated nucleophilic displacements, primarily involving nitro-displacements in hexa-methylphosphoramide,[11] although some other reaction conditions have been used but not with catechol as nucleophile.[12] Fluorodisplacement from 3-fluoronitrobenzene by



8 a 4-CN, R = H d 4-CN, R = 2-F
b 2-CN, R = H e 2-CN, R = 6-F
c 3-CN, R = H

methoxide at 100 °C is reported to be 10^3 slower than from 4-fluoronitrobenzene.[13]

Given the relative rates of reactions observed, it might have been expected that fluorodisplacement reactions between **3** and **4a,b** carried out at ~130 °C would proceed, at least initially, to yield intermediates **5a,b** (Scheme 1), as precursors to **8d** or **8e**, respectively. It might then be expected that, in competition with formation of **8d,e**, through further reaction with **4**, a proportion of the fluoro-substituent *meta* to CN in **5** (or **8**) might react slowly with **3** to yield a mixture of non-cyclic products, or the initially-formed intermediate **5** might react slowly and intramolecularly to produce a cyano-dibenzo[1,4]dioxine in low yield. In fact, we unexpectedly found the reaction produced exclusively cyanodibenzo[1,4]dioxines in 100% yield, approximately, based on **3**. That is, the reaction proceeded according to Scheme 1. Normally, to prepare 1,2-bis(cyano-phenoxy)phenylenes **8a-c** fluorobenzo-nitrile was reacted with **3** in the molar ratio 2:1, but in these reactions of **4** with **3**, whether a 1:1 or a 3:1 molar ratio was used, yields of dioxine were close to 100% based on **3**. Thus, the intramolecular, cyano-activated *meta*-fluorodisplacement reactions in Scheme 1 are highly efficient.

This observation contrasts dramatically with the results obtained with the nitro-activated 1,2-difluoro-4-nitrobenzene when reaction with **3** (mole ratio 2:1) produced 1,2-bis(2'-fluoro-4'-nitrophenoxy)benzene in 90% yield.[9] While cyano-activation in **5** gives 100% intramolecular ring closure, the stronger nitro-activation results in the first-formed product reacting intermolecularly with difluoronitrobenzene in preference to intramolecular cyclization.

This new, efficient synthesis of cyano- and carboxy-dibenzo-[1,4]dioxines provides potential routes to other functionalized dibenzo-[1,4]dioxines and, by using catechol derivatives, to other substituted dibenzo-[1,4]dioxines.

The authors thank EPSRC for financial support.

References

1 B. D. Palmer, G. W. Rewcastle, G. J. Atwell, B. C. Baguley, and W. A. Denny, *J. Med. Chem.*, **31**, 707 (1988).
2 N. Ruiz, C. Boun, M. D. Pukol, G. Guillaumet, and G. Coudert, *Synth. Commun.*, **26**, 2057 (1996).
3 H. H. Lee, B. D. Palmer, M. Boyd, B. C. Baguley, and W. A. Denny, *J. Med. Chem.*, **35**, 258 (1992).
4 H. H. Lee and W. A. Denny, *J. Chem. Soc., Perkin Trans.*1, **1990** 1071.
5 C. Chowdhury, G. Chowdhury, S. Guha, A. K. Mukherjee, and N. G. Kunda, *J. Org. Chem.*, **63**, 1863 (1998).
6 R. C. Cambie, S. J. Janssen, P. S. Rutledge, and P. D. Woodgate, *J. Organomet. Chem.*, **420**, 387 (1991).
7 G. Vasilescu and I. Baciu, *An. Univ. Bucuresti Ser. Stiint. Natur.*, **15**, 125 (1996).
8 G. C. Eastmond and J. Paprotny, *Polymer*, **40**, 469 (1999); WO 97/00903(1997); U. S. Patent 5834620 (1998).
9 G. C. Eastmond and J. Paprotny, *Synthesis*, **1998**, 894.
10 G. C. Eastmond and J. Paprotny, *J. Mater. Chem.*, 7, 1321 (1997).
11 N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith, and P. A. Wade, *J. Org. Chem.*, **41**, 1560 (1976); G. Bartoli, A. La Trofa, F. Naso, and P. F. Todesco, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2671.
12 J. P. Idoux, M. L. Madenwald, B. S. Garcia, and D-L, Chu, *J. Org. Chem.*, **50**, 1876 (1985); Y. Yoshikawa, K. Yamaguchi, K. Sugimoto, Y. Tanabe, and A. Yamaguchi, Eur. Pat. Appl., Al 0192480 (1986); *Chem. Abstr.*, **105** 208599 (1986). S. Tamai, A. Yamaguchi and M. Ohta, *Polymer*, **37**, 3683 (1996).
13 J. Hirst and S. J. Una, *J. Chem. Soc., Sect. B*, **1971**, 2221.