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A Simple Method for the Preparation of Dichlorocatechols.

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Abstract

Dichlorocatechols (DCC) are common metabolites in the aerobic degradation of dichlorobenzenes. Their synthesis is therefore possible either enzymatically, or chemically by several two-step-syntheses starting from cycloalkanones or suitable dichlorophenols. A modified ultrasonic Reimer/Tiemann reaction and subsequent Dakin oxidation was used to prepare 3,5-DCC and 4,5-DCC. A new UV-photoradical single step synthesis of 3,4-dichlorocatechol as well as 3,6-dichlorocatechol is described in detail. Mass spectral and ^{13}C-NMR spectral data of all four dichlorocatechol isomers are presented.

Introduction

Dichlorocatechols are common metabolites in the microbial aerobic degradation of dichlorobenzenes [1-6]; they are products of dihydroxy-dihydrobenzene-oxidoreductase and substrates for the following ring cleaving catechol 1,2-dioxygenase (ortho pathway) or catechol 2,3-dioxygenase (meta pathway).

In cooperation with other working groups of the Technical University of Berlin, the enzymes involved in the microbial degradation of mono- and dichloro-benzenes and the use of selected cultures of microorganism in bioreactors are currently under investigation. For this reason, DCC's are required for studying the enzymology of the catechol-dioxygenase, and also as standards for the optimization of the various analytical procedures. DCC's were not commercial available.

The previously published methods for synthesis of DCC's use enzymatic treatment [4,5] or two step synthesis starting from dichlorophenols (DCPh) [1,2,5] or cycloalkanones [6,13,14]. Firstly, the well known Reimer/Tiemann reaction [7,8,9] was chosen to insert a carbonyl in the ortho position to the hydroxy-group with unwanted by-products formed by para-introduction, leading to the corresponding dichlorosalicylic aldehyde. Subsequent oxidation [10,11,12] was required to yield the desired DCC.

We used a modified ultrasonic Reimer/Tiemann-reaction [8] and subsequent Dakin reaction [10] successfully to prepare 3,5-DCC from 2,4-DCPh and 4,5-DCC from 3,4-DCPh.

However, the Reimer/Tiemann-reaction failed with 2,5-DCPh (although reported [2]) and also with 2,3-DCPh. In both cases, and after various modifications of reaction conditions, the corresponding salicylic aldehyde could not be

isolated in acceptable amounts. In this paper we describe a UV-photoradical single step synthesis of 3,4-DCC and 3,6-DCC and their subsequent isolation as well as identification by mass spectrometry and ^{13}C-nuclear magnetic resonance measurements.

Materials and Instruments

Materials: 2,3-DCPh (98%), 2,4-DCPh (99%), 3,4-DCPh (99%) and 2,5-DCPh (98%) were purchased from ALDRICH, Steinheim, FRG and used without further purification. Acetontrile, methanol and formic acid were used as pure grade chemicals from MERCK, Darmstadt, FRG., while methyl-tert. butyl-ether and light petroleum (b.p. 30-60°C) were commercial grade and purchased from FLUKA, Buchs, Switzerland. Hydrogen peroxide (85%) was supplied by PEROXID-CHEMIE, Höllriegelskreuth, FRG. Thin layer chromatography (TLC) was performed with silica gel 60 $_F$ $_{254}$ from MERCK, (analytical: aluminum, 5 x 10 cm, 0.2 mm thickness; preparative: glass, 20 x 20 cm, 2 mm thickness). For flash-chromatography we used silica gel with particle size 40-63 µm from MERCK.

Instruments: Reactions were carried out in a 300 ml photoreactor, SCHOTT, Mainz, FRG, equipped with a submersible UV-lamp in a pure quartz cooling-finger, using a mercury-high-pressure-lamp TQ 150 from HERAEUS, Hanau, FRG, 47 W, 200-600 nm with maxima at 254/316/366 nm. The structural identification of the isolated compounds was first performed using mass spectrometric measurements with an MS VARIAN MAT 44 S (EI/70 eV) with direct probe inlet. Later measurements with underivatizated DCC's in methanolic solution were carried out by flow-injection into a particle beam interface HP 59980 B, connected with a MS HP 5989 A (EI/70 eV); for derivatizated DCC's we performed GC/MS with GC HP 5890 Series II (column HP 1, 25 m length, i.d. 0.2 mm, film thickness 0.17 µm) and the HP MS as mentioned above.
Conformation analysis by ^{13}C-nuclear-magnetic-resonance of all DCC-isomers was performed with a BRUKER AM 400, processed with ASPECT 3000, 100 MHz, DEPT and broad band proton decoupling.

Experimental Setup

30 mmol dichlorophenol diluted in 200 ml freshly distilled acetonitrile was poured into the photoreactor, followed by 300 mmol hydrogen peroxide solution. This reaction mixture was continuously stirred and heated, the bottom of the reactor being immersed in a silicone oil-bath of 120°C. This heating from the bottom with parallel cooling of the submersed UV-lamp resulted in a reaction mixture temperature of 50°C. Before starting the radiation, oxygen was removed from the reaction vessel by a stream of argon. The time of radiation was four hours.
After the reaction, the remaining hydrogen peroxide was decomposed with cold saturated aq. $NaHSO_3$-solution under further cooling in an ice-bath. After separation of the organic layer, the aqueous layer was extracted twice with methyl-tert.butyl-ether (mtb-ether). The combined organic layers were evaporated and the residue was purified by flash-chromatography on silica gel, using a mixture of light petroleum/mtb-ether/formic acid (65+30+5) as

eluent. Fractions of about 15 ml each were collected and checked for their composition by analysis on an analytical silica gel TLC plate using light petroleum/mtb-ether/formic acid (70+25+5) as solvent. Single spots were first detected under UV and then treated with an ethanolic solution of $FeCl_3$, the development of a blue colour being indicative of catechols. Impure catechol-containing fractions were combined, concentrated and cleaned up by flash-chromatography as described above, but using a column of smaller size. Further purification was carried out by preparative silica gel TLC, using the same solvents (60+40+7) as described for analytical TLC. The adsorbate was eluted with acetone/methanol (50+50), yielding >90% pure dichlorocatechols. The last purification step was vacuum sublimation at 50°C and 0.5 Torr; the sublimate was stored under nitrogen at -20°C until used.

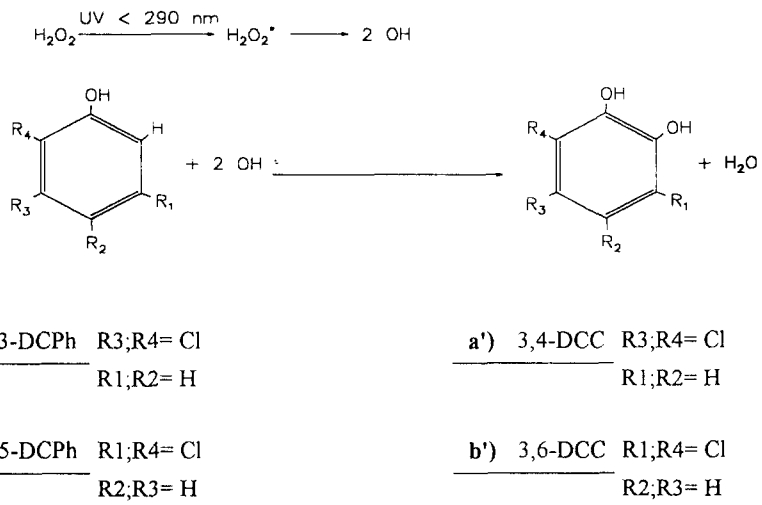

Fig.1 Reaction scheme of UV-photoradical synthesis of 3,4- and 3,6-DCC

The structural identification of the isolated compounds was performed using mass spectrometry with direct probe inlet and electron impact ionization under standard conditions (70 eV) and by direct flow-injection of methanolic solution of DCC into a particle-beam-interface connected with the mass spectrometer. Conformation analysis of all DCC-isomers, after dissolving them in $CDCl_3$, was performed by ^{13}-C NMR.

Results and Discussion

The reaction of the photoradical synthesis of 3,4- and 3,6-DCC is presented schematically in figure 1. After extraction and purification as described, the two DCC's were found to appear at high purity as can be seen from the mass spectrum presented for 3,6-DCC in figure 2. All major ions in the spectrum can easily be assigned to fragments from 3,6-DCC.

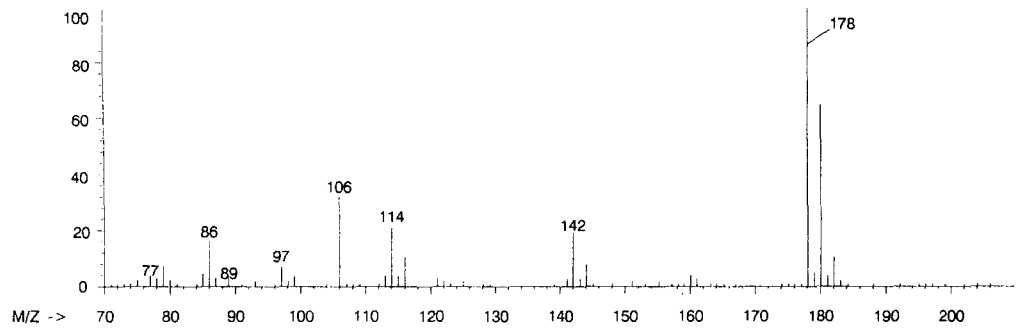

Fig.2 Mass spectrum of 3,6-DCC obtained after flow-injection of an methanolic solution into a particle-beam-interface/MS.

The mass spectral data show the molecular weight to be 178. The molecular ion represents the base peak in the spectrum, showing the typical chlorine-cluster for two chlorines in the ion. After loss of HCl the fragment ion at m/z 142 exhibits a typical single chlorine pattern. The ion with m/z 106, which exhibits the highest intensity after the base peak, arises by a further loss of HCl from fragment ion m/z 142 and consequently shows no longer the chlorine isotopic cluster. The ion at m/z 114 can be explained by ring fission and loss of CO from the ion with m/z 142, one chlorine is still present as indicated by the isotopic ion at m/z 116. The ion with m/z 97 represents a further fragment of of ion m/z 114 after fission of the last OH. Although the mass spectrum is indicative for a DCC of considerable purity, data were not able to prove structural confirmation of the measured compounds, because all substances show rather similar spectra with slight differences in the intensity of the above mentioned ions. Conformation analysis with ^{13}C-NMR provide data to prove the structural identity of the four possible isomers of DCC The NMR spectra also demonstrated the purity of the DCC isomers produced because no other signals at significant intensities were observed. The data and their interpretation are compiled in table 1. By this method it was possible to confirm the products postulated according to the photoreaction scheme in figure 1.

^{13}C-NMR was run at 100 MHz, DEPT and broad band proton decoupling.
NMR spectral data are given in ppm (δ), related to TMS

C-No.	C_1	C_2	C_3	C_4	C_5	C_6
3,4-dcc	$140,4^{s}$	$143,2^{s}$	$118,7^{s*}$	$118,3^{s*}$	$121,5^{d}$	$115,0^{d}$
3,5-dcc	$138,2^{s}$	$145,0^{s}$	$120,0^{s}$	$120,1^{d}$	$125,8^{s}$	$114,9^{d}$
3,6-dcc	$140,7^{s}$	$140,7^{s}$	$118,8^{s}$	$120,8^{d}$	$120,8^{d}$	$118,8^{s}$
4,5-dcc	$143,1^{s}$	$143,1^{s}$	$116,7^{d}$	$123,4^{s}$	$123,4^{s}$	$116,7^{d}$

(* = exchangable ; ^{s} = singlet ; ^{d} = doublet)

Table 1 ^{13}C-NMR spectral data of all dichlorocatechol isomers.

Since the detection of DCC's as metabolites in aerobic degradation of dichlorobenzenes should be carried out by GC/MS, derivatization of the hydroxyl-groups is necessary to obtain volatile compounds amenable to gas chromatography. In addition to methylation with diazomethane, esterification with phenyl- or butyl-boronic acid was studied because of their selective reactions with cis-diols. These boronic acid esters of DCC's demonstrate excellent chromatographic properties and provide definite mass spectra as shown with butyl-boronic acid ester of 3,6-DCC in figure 3. The mass spectrum shows the molecular ion at m/z 244 and the base peak at m/z 188, which represents the main fragment originating from the molecular ion by loss of the butyl-group.

The spectra of phenyl-boronic acid esters of DCC's in contrast show the molecular ion with m/z 264 as base peak and no fragment ion at m/z 188 (data not shown).

Although spectra of the boronic acid esters of DCC isomers are similar to each other, distinction is possible by their different peak retention times. (to be published elsewhere)

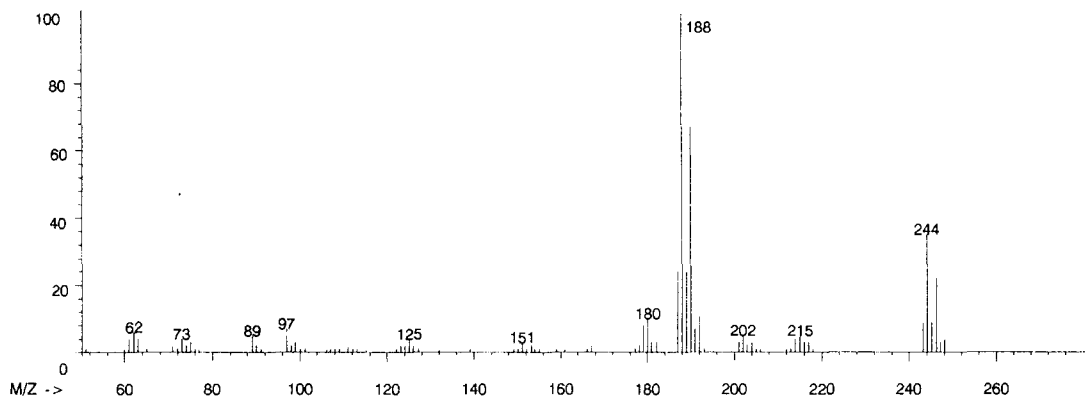

Fig.3 Mass spectral data of butyl-boronic acid ester of 3,6-dichlorocatechol

Photoradical hydroxylation with hydrogen peroxide in aprotic organic solvent was proposed by Omura and Matsuura [15,16] as a general procedure. They worked with various substituted phenols. However, the only halogenated compound in their study was p-chlorophenol, which underwent C-Cl cleavage in part. Omura and Matsuura reported decreasing reactivity towards di- and trisubstituted phenols, mainly caused by steric and electronic effects of the substituents. Phenols with electron withdrawing groups gave better results than those with electron donating groups like chlorine.

With the drastic conditions used in our procedure the corresponding dichlorohydroquinones and other polar products had obviously been generated in considerable amounts, making more cleaning steps necessary to isolate the DCC's.

The yield of UV-photoradical-reaction of 2,3-DCPh was about 0.7 mmol 3,4-DCC (2.3% theor. yield) whereas that of 2,5-DCPh reaction was 1.1 mmol 3,6-DCC (3.7%). This result is in accordance with the observations of Omura and Matsuura.

This method has not been further optimized, nor did we investigate by-products. We aimed at developing a quick and simple synthesis of small amounts of test substances, using quite common and cheap starting materials. Since the reaction proceeds in a non-alkali-medium at low temperature, the generation of polychlorodibenzo-p-dioxins even in small amounts is most improbable.

Our aim was to synthesize all four isomeric dichlorocatechols that can arise from the aerobic microbial degradation of the three isomeric dichlorobenzenes. We started using a modified Reimer/Tiemann reaction, which makes use of ultrasonic treatment of the reaction mixture to accelerate the generation of dichlorocarbene, leading to higher reaction rates. Subsequently a Dakin oxidation leads to a substitution of the carbonyl group by a hydroxy group. Both reactions are shown in the scheme of figure 4.

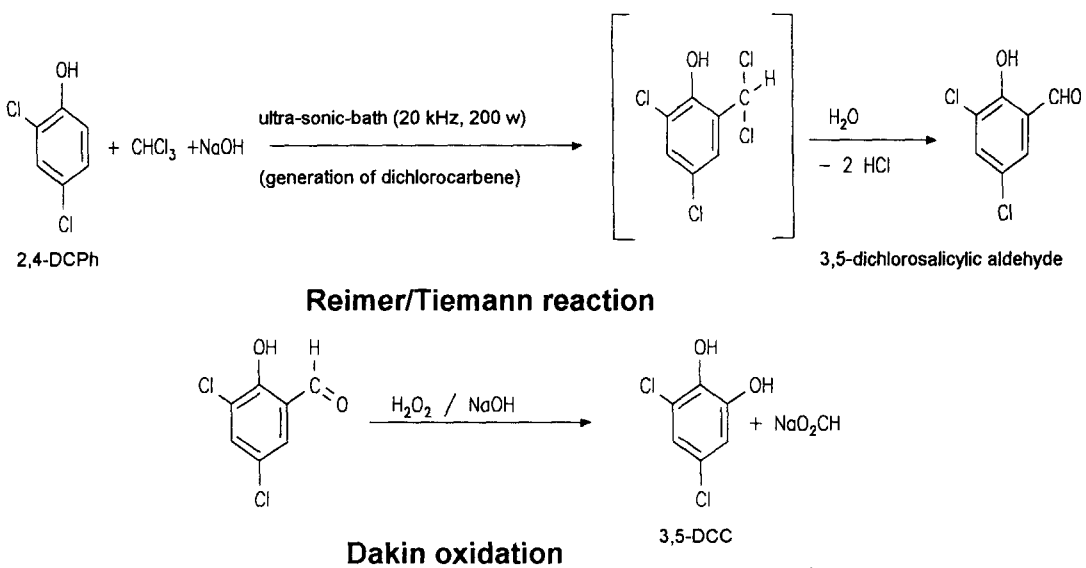

Fig.4 Reaction scheme of Reimer/Tiemann reaction of 2,4-Dichlorophenol and subsequent Dakin oxidation leading to 3,5-Dichlorocatechol.

With this synthesis we prepared successfully 3,5-DCC and 4,5-DCC, which were confirmed by mass spectral and nuclear magnetic resonance data (see table 1).

The application of the modified Reimer/Tiemann reaction failed with 2,3-DCPh and also with 2,5-DCPh, although the latter reported by Schraa et al. [2]. The reaction of 2,5-DCPh gave no corresponding salicylic aldehyde, presumable because of steric hindrance of the reactant dichlorocarbene. In the case of 2,3-DCPh we detected only traces of the salicylic aldehyde after Reimer/Tiemann reaction. Prolonging the reaction time, and increasing the temperature, gave no better results. Therefore, a completely different approach was chosen to synthesize these two compounds. Photoreaction applying UV-light (<290 nm) and hydrogen peroxide according to the general method of Omura and Matsuura [15,16] is a practible method for the synthesis of smaller amounts of 3,4-DCC from 2,3-DCPh and 3,6-DCC from 2,5-DCPh.

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