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ORIGINAL PAPER

Synthesis and Structure of 1-Chlorosulfonyl-2-(4′-Nitrophenoxy)-5-Methylbenzene

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Abstract Diphenyl ethers are structural elements found in medicinally useful antibiotics such as vancomycin as well as in biological toxins in the environment such as dioxins. The purpose of this paper is to report the synthesis and characterization of the previously unreported 1-chlorosulfonyl-2-(4′-nitrophenoxy)-5-methylbenzene, a trisubstituted diphenyl ether derivative. ^{1}H NMR ($CDCl_3$) δ 2.45 (3H, methyl$_5$, s), 7.07 (1H, H$_4$, d, J ~8.27 Hz), 7.13 (2H, H$_{2'}$, H$_{6'}$, d, J ~9.0 Hz), 7.54 (1H, H$_3$, d, J ~8.28 Hz), 7.87 (1H, H$_6$, s), 8.22 (2H, H$_{3'}$, H$_{5'}$, J ~9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.7, 118.2, 121.9, 126.0, 129.8, 135.2, 135.8, 137.8, 143.8, 150.3, 161.4. An X-ray analysis has provided valuable insight into the effect of steric factors on the three dimensional shape of this compound which serves as a useful advanced intermediate in the synthesis of these biologically active molecules. A multistep synthesis of this molecule has been designed by retrosynthetic analysis as part of an ongoing program aimed at a function-oriented, multistep economical synthesis of vancomycin lead antibiotics. Crystals are triclinic, space group P-1, $a = 7.6537(15)$, $b = 8.976(2)$, $c = 11.050(2)$ Å, $\alpha = 67.645(11)$, $\beta = 79.735(11)$, $\gamma = 87.798(10)°$, $V = 690.5(2)$ Å^3, $Z = 2$.

Keywords Natural products · Spectroscopy · Synthesis · Diphenyl ether · Forensic chemistry

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Introduction

Diphenyl ethers are structural elements found in biological toxins in the environment such as dioxins as well as in medicinally useful antibiotics such as vancomycin. The latter is a front line antibiotic for the treatment of life-threatening gram-positive bacterial infections and many clinical isolates have become resistant to it, focusing interest on sucessors to vancomycin.

Dioxins are some of the most toxic chemicals known to science. There are no "safe" levels of exposure to dioxin. Dioxins are cancer hazards. They are fat-soluble, they bioaccumulate and they are mainly found in meat and dairy products. Dioxin exposure has been linked to birth defects, inability to maintain pregnancy, decreased fertility, reduced sperm counts, endometriosis, diabetes, learning disabilities, immune system suppression, lung problems, skin disorders, and lowered testosterone levels [1–4]. Derivatives of substituted diphenyl ether have been found to show considerable anaesthetic action but were too toxic to be of practical value. They are useful herbicides and intermediates for textile protective agents [5]. More recently, derivatives of diphenyl ethers have been used as advanced intermediates in the total synthesis of glycopeptide antibiotics which includes telcoplanin and vancomycin. The members of the vancomycin class of glycopeptide antibiotics are important agents for the treatment of severe bacterial infections, particularly those caused by methicillin-resistant *Staphylococcus aureus*, and the basis of their activity has been of interest for some time [6–11].

The purpose of this paper is to report a multi-step synthesis and characterization of a trisubstituted derivative of diphenyl ether, 1-chlorosulfonyl-2-(4′-nitrophenoxy)-5-methylbenzene (**5**). The X-ray structure of the compound (**5**) is previously unreported and it serves as a useful

advanced intermediate in the synthesis of these biologically active molecules.

Materials and Methods

Chemicals and Materials

Glacial acetic acid (CH_3COOH), Chlorosulfonic acid ($ClSO_3H$), Benzene (C_6H_6), and activated charcoal were obtained from Sigma–Aldrich Corp. (St Louis, MO).

Instruments

^1H NMR and ^{13}C NMR were recorded on a Bruker Inova spectrometer (AM-500) instrument; X-ray data were collected using a Nonius Kappa CCD diffractometer.

Experimental Procedure

1-chlorosulfonyl-2-(4′-nitrophenoxy)-5-methylbenzene **(5)**. A cold (0 °C) stirred solution of chlorosulfonic acid (7.0 mL, 0.1 mol) was treated with small amounts of crystalline 1-(4′-nitrophenoxy)-4-methylbenzene (2.29 g, 0.01 mol) (**4**). The addition of the solid was completed in 0.5 h. The reaction flask was then stoppered and kept overnight in a refrigerator at a temperature of 0–5 °C. Finally, the reaction mixture was poured over crushed ice with stirring. The precipitated solid was filtered and washed with cold water till free of acid. The sticky solid obtained was dissolved in hot benzene and then boiled with a little activated charcoal. The solution was filtered and evaporated to give the sulfonyl chloride **5** (70%) after recrystallization from glacial acetic acid (M. pt., 147 °C). ^1H NMR ($CDCl_3$) δ 2.45 (3H, methyl$_5$, s), 7.07 (1H, H_4, d, J ~8.27 Hz), 7.13 (2H, $H_{2'}$, $H_{6'}$, d, J ~9.0 Hz), 7.54 (1H, H_3, d, J ~8.28 Hz), 7.87 (1H, H_6, s), 8.22 (2H, $H_{3'}$, $H_{5'}$, d, J ~9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.7, 118.2, 121.9, 126.0, 129.8, 135.2, 135.8, 137.8, 143.8, 150.3, 161.4.

X-ray Crystallography

Diffraction data for **5** were collected at 90 K on a Nonius Kappa CCD diffractometer fitted with an Oxford Cryostream sample chiller and graphite-monochromated MoKα ($\alpha = 0.71073$ Å) radiation, using a colorless plate crystal. Data reduction and scaling were carried out using HKL SCALEPACK [12]. The structure was solved by direct methods and refined by full-matrix least squares techniques using SHELXL97 [13]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were visible in difference maps, but were placed in idealized positions with C–H distance 0.95 Å for sp^2 C atoms and 0.98 Å for the methyl group. Displacement parameters for H were assigned as $U_{iso} = 1.2\ U_{eq}$ for the bonded atom (1.5 for methyl). Crystal data and details of the data collection and refinement are given in Table 1.

Results and Discussion

Retrosynthetic Analysis

A retrosynthetic analysis (Fig. 1) approach has been employed in designing a multistep synthesis of the target molecule (**5**). The trifunctionalized derivative of diphenyl ether contains an aryl chlorosulfonyl element which is the required retron for an aromatic chlorosulfonation transform on target (**5**) to produce the synthetic precursor (**4**). Thus, a disconnection of the carbon–sulfur bond on compound (**5**) at the C-1 atom bearing a chlorosulfonyl group produces compound (**4**) which is a disubstituted diphenyl ether

Table 1 Crystal data and structure refinement

Empirical formula	$C_{13}H_{10}ClNO_5S$	Z	2
CCDC deposition no.	CCDC 698480	crystal size (mm)	0.07 × 0.30 × 0.32
fw	327.73	ρ_{calc} (g cm^{-3})	1.576
Crystal system	Triclinic	μ (mm^{-1})	0.448
Space group	P-1	Radiation	MoKα
Cell dimensions		θ_{max} (°)	30.1
a (Å)	7.6537(15)	Data collected	15,885
b (Å)	8.976(2)	Independent data	4,036
c (Å)	11.050(2)	Observed ($I > 2\sigma(I)$)	3,415
α (°)	67.645(11)	R_{int}	0.023
β (°)	79.735(11)	R	0.031
γ (°)	87.798(10)	wR2 [$I > 2\sigma(I)$]	0.077
V (Å^3)	690.5(2)	Data/param	4,036/192
T (K)	90	Resistant density (eÅ^{-3})	0.43, −0.46

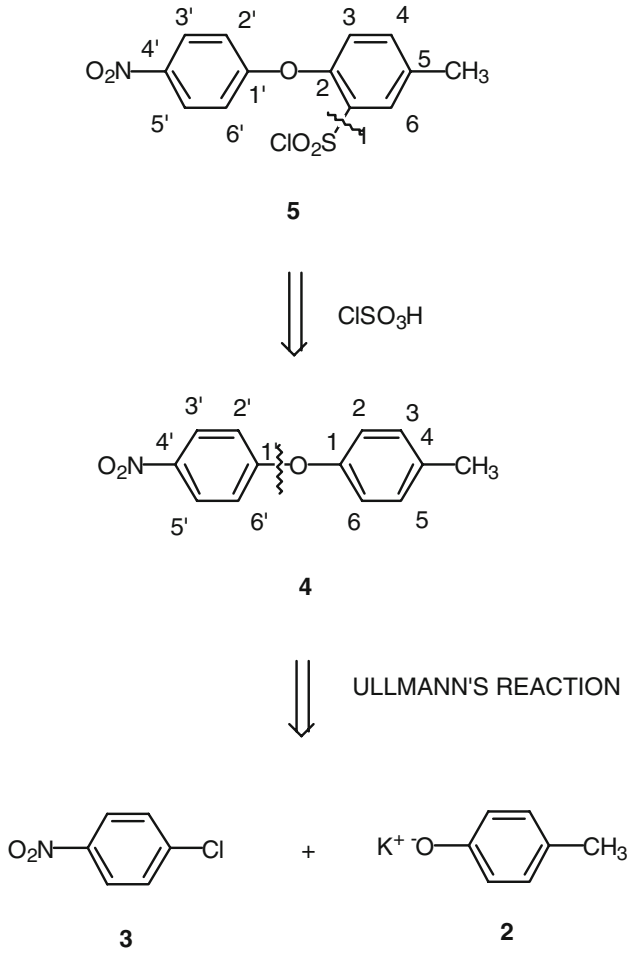

Fig. 1 Retrosynthetic analysis. Structures of compounds **2**–**5**

derivative bearing a methyl group on C-4 and a nitro substituent on C-4′. It is a target molecule containing a retron for a Ullmann coupling transform to give the synthetic precursors p-cresol (**1**) and p-chloronitrobenzene (**3**). A cleavage of the carbon-oxygen bond at the C-1′ atom of the compound (**4**) yields p-cresol and p-chloronitrobenzene which serve as synthons in a multistep synthesis of the advanced intermediate (**5**) [14, 15].

Synthetic Methodology

A function-oriented, multi-step economical synthesis of vancomycin lead antibiotics designed by antithetic analysis has created a need for the synthesis and characterization of the previously unreported compound (**5**) [15–18]. Commercially available p-cresol (**1**) was converted into its potassium salt (**2**) by heating it with potassium hydroxide pellets and then reacting it with p-chloronitrobenzene (**3**) in the presence of copper and potassuim iodide as catalysts and DMF as a solvent under refluxing conditions to yield 4-methyl-4′-nitrodiphenyl ether (**4**) as a product of Ullmann's coupling reaction [19–22]. The compound (**4**) was chlorosulfonated regioselectively in the presence of excess chlorosulfonic acid at 0 °C to yield the corresponding sulfonyl chloride derivative (**5**). The product obtained (Fig. 2) was found to be hydrophobic and it has been analyzed by ^{1}H NMR, and ^{13}C NMR spectroscopy. The compound's single crystal structure has been obtained by X-ray analysis. The sulfonyl chloride (**5**) was dissolved in boiling glacial acetic acid and then slowly allowed to cool to room temperature on its own. The crystals obtained from the supersaturated solution were filtered, dried under high vacuum and analyzed by X-ray crystallography.

^{1}H NMR Analysis

Nuclear Magnetic Resonance Spectroscopy (NMR) has been used to determine the structure of compound (**5**) [23]. Six different types of magnetically unequivalent protons were identified in the molecule due to the presence of proton peaks with six different chemical shifts in the ^{1}H

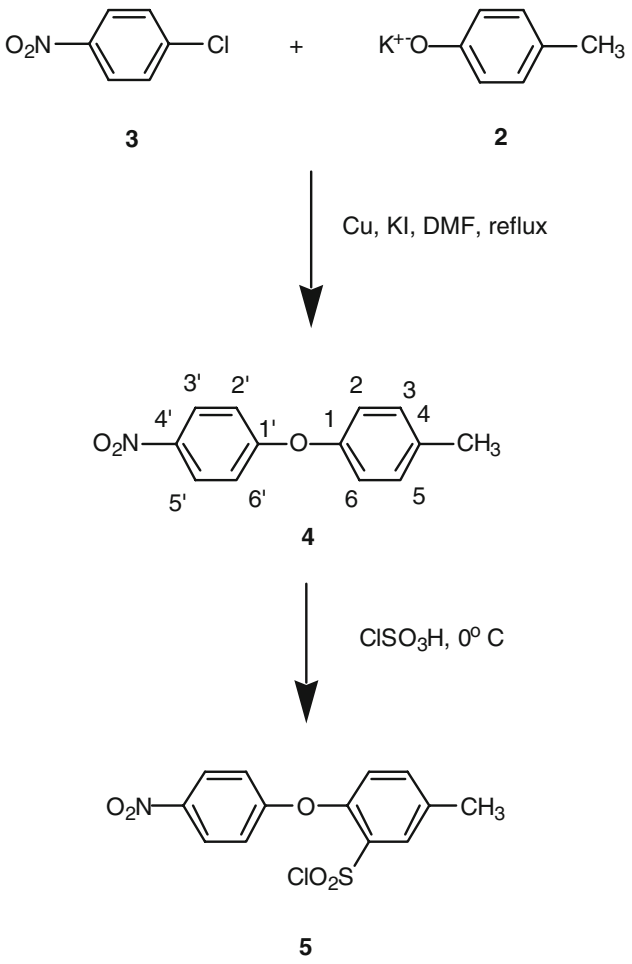

Fig. 2 Synthetic scheme

NMR spectrum. Integration of these proton peaks in the spectrum indicates the presence of seven aromatic protons and three protons belonging to a methyl group in the molecule. Information on the connectivity of protons in the trisubstituted diphenyl ether derivative was obtained from the coupling constant in order to assign protons to the four doublets seen in the spectrum. A singlet present upfield at δ (ppm) 2.45 (3H, methyl, s) corresponds to the three methyl protons. Two doublets present downfield at δ 7.07 (1H, H_4, d, J ~8.27 Hz) and δ 7.54 (1H, H_3, d, J ~8.28 Hz) have similar J values showing that the aromatic protons H_3 and H_4 are coupled to each other. Another singlet present downfield at δ 7.87 (1H, H_6, s) corresponds to the aromatic proton H_6 which is deshielded by the strongly electron withdrawing chlorosulfonyl group. The presence of two doublets downfield at δ 7.13 (2H, $H_{2'}$, $H_{6'}$, d, J ~9.0 Hz), and δ 8.22 (2H, $H_{3'}$, $H_{5'}$, J ~9 Hz) with identical J values indicates that a set of magnetically equivalent aromatic protons $H_{2'}$, $H_{6'}$ is coupled to another set of magnetically equivalent aromatic protons $H_{3'}$ and $H_{5'}$. These two sets of protons are deshielded by the strongly electron withdrawing nitro substituent present in the aryl moiety.

^{13}C NMR Analysis

Carbon spectral analysis of compound (**5**) confirms the presence of eleven types of magnetically nonequivalent carbon atoms [23]. A peak at δ (ppm) 20.7 corresponds to the sp^3 hybridized carbon atom in the methyl substituent. All other peaks correspond to sp^2 hybridized carbon atoms present in the aromatic rings. The peak at δ 161.4 corresponds to $C_{4'}$. It is deshielded by a strongly electron withdrawing nitro group. The peak at δ 150.3 corresponds to C_1 which is also deshielded by another strongly electron withdrawing chlorosulfonyl group. The peak at δ 143.8 corresponds to C_6. It is deshielded by the methyl group and also by the strongly electron withdrawing chlorosulfonyl group. The peaks at δ 137.8 and δ 135.8 correspond to C_2 and $C_{1'}$. They are deshielded by the oxygen atom of the diaryl ether functionality and the former is also deshielded by the chlorosulfonyl group. In addition, the ^{13}C NMR spectrum shows the presence of $C_{2'}$ and $C_{6'}$ as a set of magnetically equivalent carbon atoms and $C_{3'}$ and $C_{5'}$ as the other set of magnetically equivalent carbon atoms. Several other peaks at δ 118.2, 121.9, 126.0, 129.8, 135.2 correspond to the other remaining sp^2 hybridized carbon atoms present in the diaryl rings.

X-ray Analysis

The crystal structure of the molecule, (**5**) shown in Fig. 3, has provided valuable insight into the effect of steric factors such as ring strain, torsional strain and steric strain on its three dimensional shape. Geometric parameters are given in Table 2. The dihedral angle formed by the two phenyl planes is 64.49(4)°. There is a good deal of variability in the phenyl-phenyl dihedral angle in diphenyl ethers in the Cambridge Structural Database (CSD, version 5.29, Nov. 2007), but angles slightly less than 90° appear most common [24]. The two polymorphs of unsubstituted diphenyl ether have dihedral angles of 87.60(4) and 88.39(2)°. There are no other diphenyl ether structures having a chlorosulfonyl substituent ortho to the ether O in the CSD, thus standards for comparison of our dihedral angle are scarce [25]. However, the structure of 2-phenoxybenzenesulfonamide has been reported, and the dihedral angle formed by its phenyl groups varies from 66.2(1) to 74.3(1)° over four independent molecules, only slightly larger than that found in (**5**) [26]. The nitro group is nearly coplanar with the phenyl ring to which it is attached, with torsion angle O4-N1-C10-C9-9.52(18)°.

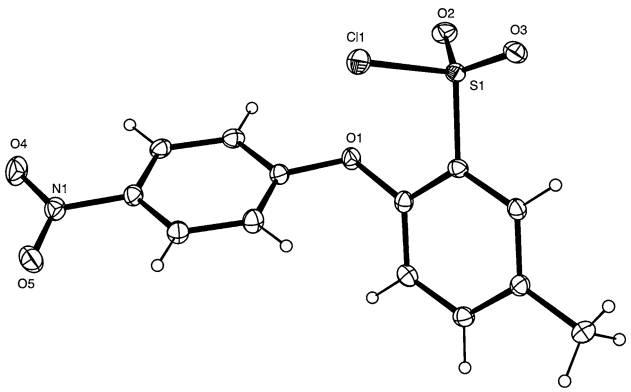

Fig. 3 ORTEP representation of the trisubstituted diphenyl ether **5** with non-hydrogen atoms shown as anisotropic displacement at the 50% probability level and hydrogen atoms (unlabeled) shown as *small circles* of an arbitrary radius

The chlorosulfonyl group in (**5**) has normal dimensions, but its conformation appears slightly unusual. The CSD contains nine structures containing benzenesulfonyl chloride moieties determined at low temperature: FAQJOW,

Table 2 Selected bond lengths (Å), angles (°) and torsion angles (°)

Cl1–S1	2.0398(6)	O3–S1–Cl1	106.17(5)
S1–O2	1.4264(10)	C1–S1–Cl1	101.69(5)
S1–O3	1.4275(10)	O2–S1–C1	112.05(6)
S1–C1	1.7592(13)	C7–O1–C2	119.43(10)
O1–C2	1.3851(15)	O4–N1–O5	123.27(12)
O1–C7	1.3808(15)	O4–N1–C10	118.48(12)
O4–N1	1.2316(15)	O5–N1–C10	118.24(11)
O5–N1	1.2317(16)	Cl1–S1–C1–C2	62.95(11)
N1–C10	1.4614(17)	C7–O1–C2–C1	−125.62(12)
O2–S1–O3	119.69(6)	C2–O1–C7–C12	15.29(18)
O2–S1–Cl1	106.33(5)	O4–N1–C10–C9	−9.52(18)

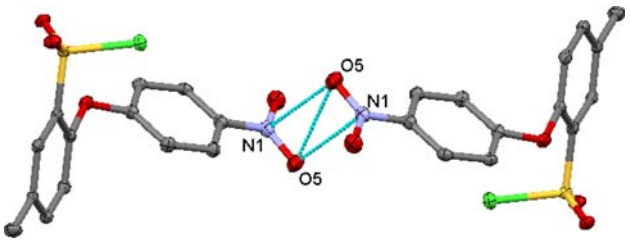

Fig. 4 Short contacts between nitro groups about the inversion center at 0, 0, 1

IJEMEP, JAGLIM, NAQLIM, NBZSOC01, OLAVAY, QQQHJA02, SUTYAH, and TECLUJ. The mean S–Cl distance is 2.032 Å in that set, and the mean S=O distance is 1.423 Å, both similar to values in (**5**). However, the S–Cl bond in those structures tends to be rotated by nearly the maximum value out of the phenyl plane, with C–C–S–Cl torsion angle magnitudes in the range 68.2–89.5°, and average value 80.6°. The value in (**5**) is 62.95(11)°, smaller than in any of the literature structures. This conformation forms intramolecular distances to the ether O atom O1···O2 2.930(1) and O1···Cl1 3.231(1) Å. There are no previous examples of phenylsulfonyl chlorides with O-containing substituents ortho to SO_2Cl in the CSD for comparison purposes.

The most notable intermolecular interaction is between nitro groups related by inversion (symmetry operation $i = -x, -y, 2-z$), illustrated in Fig. 4. It is similar to antiparallel carbonyl-carbonyl contacts described by Allen et al. [27] with O5···$O5^i$ 2.952(1), O5···$N1^i$ 2.994(1) Å, 0.09 and 0.08 Å less than van der Waals sums, respectively.

In conclusion, a multistep synthesis of 1-chlorosulfonyl-2-(4′-nitrophenoxy)-5-methylbenzene, a trisubstituted derivative of diphenyl ether has been accomplished. The synthetic method converts a disubstituted derivative of diphenyl ether (**4**) into a trisubstituted (**5**) chlorosulfonated one in a chemoselective and regioselective manner. A single crystal X-ray structure has provided valuable insight into the effect of steric factors such as ring strain, torsional strain and steric strain on the three dimensional shape of this molecule (**5**). In addition, it has been characterized spectroscopically by ^{1}H NMR, and ^{13}C NMR. The function-oriented, multi-step economical synthesis of vancomycin lead antibiotics has been designed by retro synthetic analysis. The synthesized molecule (**5**) is a useful advanced intermediate in the total synthesis of these biologically active molecules.

Supporting Information Available

Magnetic measurements for the trisubstituted diphenyl ether (**5**). This material is available in online for downloading. CCDC-698480 contains the CIF for this paper, which can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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