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Synthesis and Structural Characterization of 5-Bromo-2,3-dimethylphenol

André J. Niestroj, Clemens Bruhn, [a]) and Martin E. Maier

Halle/S., Fachbereich Chemie, Institut für Organische Chemie, [a]) Institut für Anorganische Chemie, Martin-Luther-Universität Halle-Wittenberg

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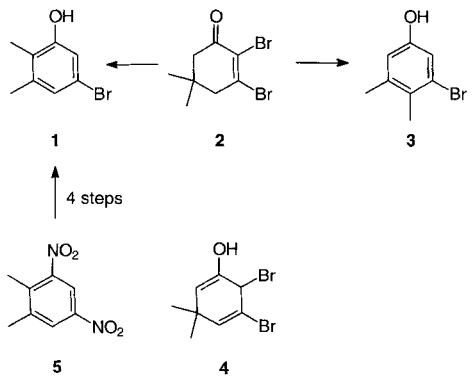
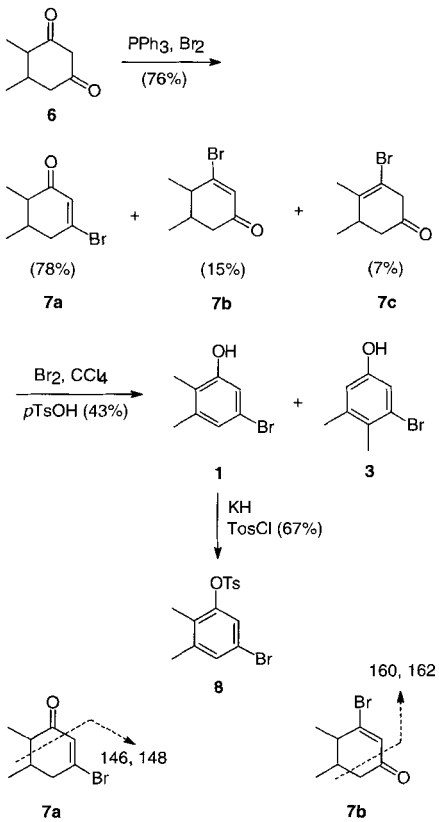
Abstract. Bromination of the disubstituted 4,5-dimethyl-1,3-cyclohexanedione (**6**) followed by oxidation of the resulting 3-bromo-5,6-dimethyl-2-cyclohexen-1-ones (**7**) gave 5-bromo-2,3-dimethylphenol (**1**) together with its constitutional isomer **3**. The structure of **1** was secured by a x-ray analysis of its tosyl derivative **8**.

In the context of the synthesis of dynemicin A analogs, [1, 2] which are of interest as antitumor compounds, 5-bromo-2,3-dimethylphenol (**1**) was needed as a building block. The literature reveals that this compound can be accessed through a rearrangement reaction from 2,3-dibromo-5,5-dimethyl-cyclohex-2-en-1-one **2** [3]. However, the yield for this route which involves the migration of a methyl group and concomitant loss of the 2-bromine is too low to be of practical value. In addition, the constitutional isomer **3** is also being formed [4]. Alternatively, the phenol **1** can be obtained from 1,2-dimethyl-3,5-dinitrobenzene **5** by sequential reductions of the nitro groups and replacement of the amino groups by a hydroxyl function and a bromine atom, respectively (Scheme 1) [5]. While the structural assignment for the two isomers **1** and **3** seems to be plausible, a definitive proof is lacking.



Scheme 1

For these reasons we developed an independent synthesis for **1** and proved its structure by x-ray analysis of its tosyl derivative **8** (Scheme 2). The synthesis commenced with the condensation of (*E*)-3-methyl-pent-3-en-2-one and diethyl malonate followed by decarboxylation. [6] The resulting mixture of the *cis*, *trans*-disubstituted 1,3-cyclohexanediones **6** was brominated to give a mixture of the bromocyclohexenones **7a–c**.[7] The ratios were determined by GC-MS. The fragmentation patterns of **7a** and **7b** differ significantly, allowing a tentative structural assignment. For example, **7a** is characterized by strong peaks at m/z = 146 and 148 due to

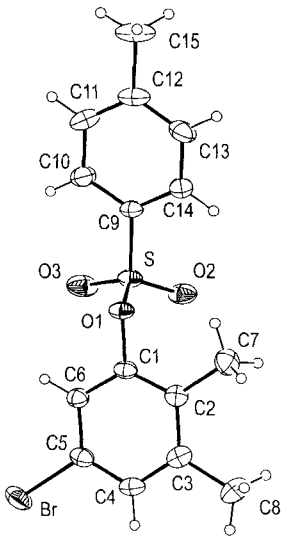


Scheme 2

the extrusion of C_3H_4O. This indicates that the carbonyl group is located next to a methyl group. In contrast, the corresponding peaks of **7b** are at *m/z* = 160 and 162 [loss of C_2H_2O].

Subsequent oxidation of the mixture of the bromocyclohexenones **7a–c** with bromine in tetrachloromethane gave a mixture of aromatized compounds from which the desired bromophenol **1** could be isolated by distillation and chromatography. The oxidation reaction works less reliable on a larger scale. Other oxidants were examined but they turned out to be less efficient.

In order to prove the constitution of **1**, it was converted to the tosylate **8** with tosyl chloride and potassium hydride as base in THF. Chromatographic purification gave crystals of **8** suitable for x-ray analysis. As indicated in Figure 1, this x-ray analysis ultimately proves the structure of **1** and thereby also that of **3**. In addition, it confirms the structural assignment that was made on the basis of the mass spectra of the congeners **7a** and **7b**. It can be seeen that the bond lengths and angles are in the usual range.



Scheme 3

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Experimental

^{1}H NMR: GEMINI 2000 (400 MHz). – ^{13}C NMR: GEMINI 2000 (100 MHz); all spectra were recorded in $CDCl_3$ as solvent. – The signal multiplicity's were determined by means of the APT technique; + for CH or CH_3, – for CH_2, × for C. IR: Perkin–Elmer FT-IR Spectrometer SPECTRUM 1000. – Melting points: Dr. Tottoli melting point apparatus. – EI-MS: AMD Intectra GmbH AMD 402. – GC-MS: HP 5972A (quadrupol, 70 eV), gas chromatograph HP5890 II (capillary column HP-5MS: 30 m × 0.25 mm), program: 70 °C injection, 1 min at 70 °C, then 10 degrees/min to 250 °C. – Flash chromatography: J. T. Baker silica gel 30–60 µm. – TLC: Merck Si 60 F_{254}. – Solvents were distilled prior to use; petroleum ether with a boiling range of 35–65 °C was used; THF was distilled from sodium diphenyl ketyl immediately before use. – All reactions were carried out under an atmosphere of argon. – The compound 4,5-dimethyl-1,3-cyclohexane- dione was prepared according to the literature [6].

*5-Bromo-2,3-dimethylphenol (**1**) and 3-Bromo-4,5-dimethylphenol* (**3**)

To a solution of 3-bromo-5,6-dimethyl-hex-2-en-1-one (**6**) (mixture of isomers) (1.76 g, 8.66 mmol) in dry CCl_4 (12 ml) was added a solution of bromine (1.38 g, 8.66 mmol) in dry CCl_4 (10 ml). After 15 min *p*-toluenesulfonic acid monohydrate (0.20 g, 1.05 mmol) was added and the mixture was stirred for 48 h at room temperature. The solution was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting oil was purified by distillation (91–98 °C/1 mbar) and subsequently by chromatography (petroleum ether/ethyl acetate, 10:1) to give the phenol **1** (0.80 g, 46%) as a white solid of *m.p.* 76–79 °C and the isomer **3** (0.12 g, 7%) as white solid of *m.p.* 95–99 °C. Performing the reaction on a larger scale gave a somewhat lower yield of **1**.

5-Bromo-2,3-dimethylphenol (**1**)

TLC (petroleum ether/ethyl acetate, 8:1): R_f = 0.44. – IR (KBr) ν/cm^{-1} = 3312, 1573, 1448, 840. – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 2.08 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.76 (s, 1H, OH), 6.78 (d, *J* = 1.7 Hz, 1H, aryl-H), 6.89 (d, *J* = 1.7 Hz, 1H, aryl-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 11.1, 19.8 (+, aryl-CH_3), 115.9 (+, CH), 118.6 (×, $\underline{C}CH_3$), 121.7 (×, CBr), 125.3 (+, CH), 140.1 (×, $\underline{C}CH_3$), 154.3 (×, COH). – MS (EI), *m/z* (%): 202 (100) [M^+, ^{81}Br], 121 (60) [M^+– Br].

3-Bromo-4,5-dimethylphenol (**3**)

TLC (petroleum ether/ethyl acetate; 8:1): R_f = 0.35. – IR (KBr) ν/cm^{-1} = 3269, 1611, 1477, 839. – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 2.25 (s, 6H, $2CH_3$), 4.70 (s, 1H, OH), 6.59 (d, *J* = 2.5 Hz, 1H, aryl-H), 6.91 (d, *J* = 2.5 Hz, 1H, aryl-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 18.2, 21.3 (2 +, aryl-CH_3), 116.4 (+, CH), 117.0 (+, CH), 125.3 (×, CBr), 128.4 (×, $\underline{C}CH_3$), 139.4 (×, $\underline{C}CH_3$), 153.4 (×, COH). – MS (EI), *m/z* (%): 202 (100) [M^+, ^{81}Br], 121 (70) [M^+– Br].

3-Bromo-5,6-dimethyl-cyclohex-2-en-1-one (**7**)

To an ice-cold, stirred solution of recrystallized triphenylphosphine (29.5 g, 112 mmol) in dry benzene (500 ml) were added dropwise 112 ml of a 1M solution (112 mmol) of bromine in benzene. To the resulting suspension were then added triethylamine (11.3 g, 15.6 ml, 112 mmol) and 4,5-dimethyl-1,3-cyclohexanedione (**6**) (14.3 g, 102 mmol) in dry benzene (100 ml). After being stirred overnight at room temperature, the mixture was filtered through a short pad of celite and the solvent was removed under reduced pressure. The residue was purified using a dry column (diethylether) to give **7** as a mixture of five isomers as detected by GC-MS (15.72 g, 76%). Because of the unstable nature no elemental analysis was performed. – TLC (petroleum ether/ethyl acetate, 8:1): R_f = 0.63, 0.53, 0.47. – IR (film) ν/cm^{-1} = 1678, 1610. – ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm = 0.97 (d, *J* = 7.0 Hz, CH_3, minor isomer), 1.03 (d, *J* = 7.0 Hz, CH_3, minor isomer), 1.08 (d, *J* = 6.5 Hz,

CH_3, major isomer), 1.12 (d, J = 6.7 Hz, CH_3, major isomer), 1.62–2.14 (m, 2H, CH_2), 2.32–2.90 (m, 2H, $CHCH_3$), 6.37–6.41 (m, 1H, olefinic H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 11.5, 13.0, 16.2, 20.3 (+, CH_3), 35.1, 37.7, 46.0, 48.2 (+, $CHCH_3$), 43.5, 45.3, 46.4, 46.7 (–, CH_2), 132.3, 132.7 (+, CH), 148.7, 148.9 (×, CBr), 199.7 (×, C=O). – GC-MS: t_{ret} = 8.56 min, 8.67 min; 204 [M^+, ^{81}Br], 148 [$M^+ - C_3H_4O$ (**7a**, *cis* and *trans*)], Σ = 78.4%; 8.62 min, 8.73 min, 9.00 min; 204 [M^+, ^{81}Br], 160 [$M^+ - C_2H_2O$ (**7b,c**)], Σ = 21.6%.

5-Bromo-2,3-dimethylphenol-1-(4-methylphenylsulphonyl-oxy)benzene (**8**)

To a solution of the phenol **1** (380 mg, 1.89 mmol) in THF (10 ml) was added potassium hydride (83 mg, 2.07 mmol) in one portion at room temperature. After stirring for 30 min, 4-methyl-1-benzenesulfonyl chloride (720 mg, 3.76 mmol) was added. The mixture was stirred overnight before being quenched with 5 ml of water and diluted with 10 ml of ethyl acetate. After separation of the layers the organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 25:1) to give the compound **8** (450 mg, 67%) as a white solid, *m.p.* 98–100 °C (recrystallized from EtOH). – TLC (petroleum ether/ethyl acetate, 25:1): R_f = 0.2. – IR (KBr) ν/cm^{-1} = 3051, 1599, 1473, 1345. – ^1H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.93 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 6.95 (d, J = 1.5 Hz, 1H, bromoaryl-H), 7.18 (d, J = 1.5 Hz, 1H, bromoaryl-H), 7.33 (d, J = 8.0 Hz, 1H, tosylaryl-H), 7.75 (d, J = 8.0 Hz, 1H, tosylaryl-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 12.5, (+, bromoaryl-CH_3), 19.8, (+, tosylaryl-CH_3), 21.6 (+, bromoaryl-CH_3), 118.3 (×, CBr), 123.1 (+, bromoaryl-CH), 128.5, 129.9 (+, tosylaryl-CH), 131.3 (+, bromoaryl-CH), 129.7, 133.0, 140.7 (×, CCH_3), 145.7 (×, C–S), 148.4 (×, C–O). – MS (EI), *m/z* (%): 356 (15) [M^+, ^{81}Br], 155 (95) [$MeArSO_2$], 91 (100), [CH_3–Ar].

$C_{15}H_{15}BrSO_3$	calcd.:	C 50.72	H 4.26	S 9.02
(355.2)	found:	C 50.84	H 4.47	S 9.21.

Structure determination of 5-Bromo-2,3-dimethylphenol-1-(4-methylphenylsulphonyloxy)benzene

$C_{15}H_{15}BrSO_3$ (**8**); M_r = 355.24, triclinic, space group $\bar{P}$, a = 8.899 (3), b = 9.292 (2), c = 9.347 (3) Å, α = 78.63 (2), β = 89.35 (3), γ = 85.28 (2)°, V = 755.1 (4) Å^3, Z = 2, D_x = 1.562 g/cm^3, μ = 2.864 mm^{-1}, θ_{min} = 2.22, θ_{max} = 24.94°, refl. coll.: 3526, indep. refl.: 2634 (R_{int} = 0.0676), Semi-empirical absorption correction *via* Ψ-scans, T_{min}/T_{max} = 0.08/0.20, crystal size: 0.6 × 0.5 × 0.4 mm^3, T = 298 K. The structure was solved using direct routines (SHELXS-86) and refined using full matrix least squares methods against F^2 (SHELXL-93)[8]. All non H-atoms were refined anisotropically, H-atoms were placed in calculated positions and refined according to the "riding" model with free displacement parameters. 197 parameters were refined against 2632 reflections to final R values of: wR2 (all data): 0.0826 and R1 [$I > 2\sigma(I)$]: 0.0298. The largest residual electron density is max/min 0.389/ –0.428eÅ^{-3}.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data centre as supplementary publication no. CCDC-100962. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax. Int. code +(1223) 336-033; e-mail: deposit@chemcrys.cam.ac.uk).

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Address for correspondence:
Prof. Dr. Martin E. Maier
Institut für Organische Chemie
Universität Tübingen
Auf der Morgenstelle 18
D-72076 Tübingen