

# Preparation of 4-(2-Deuterio-2-propyl)anisole Through Cathodic Cleavage of a Sulfone in the Presence of Deuterium Oxide

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In connection with other work, the title compound was needed. Several attempts to prepare this acid-sensitive,  $\alpha$ -deuterated isopropyl compound from 2-(4-methoxyphenyl)-2-propanol failed, except for reduction with a mixture of aluminium chloride and lithium tetra-deuterido-aluminate, which gave a mediocre yield of the desired material.

It occurred to us that cathodic cleavage of a sulfone in a deuterium oxide-containing solvent might be a feasible procedure, since acidic conditions are avoided. The route illustrated in Scheme 1 was devised and found to furnish the title compound in an isotopic purity of 98.5 %.

Dialkylation of the known<sup>1</sup> *p*-methoxybenzyl *p*-tolyl sulfone with butyllithium and iodomethane was straightforward. Upon cathodic reduction of the dimethyl compound, a radical anion is initially formed. The latter undergoes

fragmentation to a benzylic radical and a sulfinate anion. A second electron transfer to the radical yields a carbanion, which is rapidly protonated by the strongest acid present in the medium. We used a solution of 4 % deuterium oxide in anhydrous DMF (*N,N*-dimethylformamide), containing tetraethylammonium perchlorate (0.25 M).

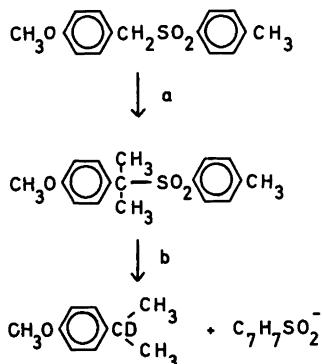
The possibility that tetraethylammonium ion from the supporting electrolyte might compete as the proton donor was a matter of concern, since it would lead to inferior isotopic purity. A small but measurable participation by tetraethylammonium bromide has been reported<sup>2</sup> in the cathodic cleavage of iodobenzene in DMF solution containing ordinary or heavy water. It was suggested<sup>2</sup> that hydroxide (or deuterioxide) ions, formed in the catholyte upon electrolysis, cause Hofmann elimination, whereby protons are formed. In order to avoid this possibility, we performed the electrolysis at ice-bath temperature (5 °C) and interrupted it after 35 % extent of reaction, before too much base had accumulated. In this way, a material of sufficient isotopic purity was secured.

*Experimental.* GLC analyses were performed on a Perkin Elmer Model 900 instrument, NMR spectra on a Bruker WH 270 instrument, MS either on a GC-MS Finnigan 4021 or a VG analytical ZAB instrument. Voltammetry and preparative electrolyses were carried out as described previously.<sup>3</sup>

The reaction between sodium *p*-toluenesulfinate and *p*-anisyl alcohol in formic acid solution gave a quantitative yield of *p*-methoxybenzyl *p*-tolyl sulfone as reported.<sup>1</sup> A solution of 4 g (14.5 mmol) of this material in 25 ml of dry THF was added to 14.5 mmol of butyl lithium (15 % solution in hexane) in 20 ml of dry THF at -10 °C during 15 min. After another 15 min at -10 °C, 0.95 ml (15 mmol) of iodomethane was added, and the mixture was allowed to attain room temperature. After 30 min, it was again cooled to -10 °C, and the treatment with butyl lithium and iodomethane was repeated. After evaporation of the solvent, the lithium iodide was removed by washing with water, and the residue was recrystallized from ethanol. The yield was 3.7 g (85 %), m.p. 120–121 °C, <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta$  1.76 (6 H, s), 2.37 (3 H, s), 3.80 (3 H, s), 6.79 (2 H, d, *J* 9 Hz), 7.13 (2 H, d, *J* 8 Hz), 7.24–7.28 (4 H, m). Anal.: C, H, S.

In order to determine a suitable electrolysis potential, a cyclic voltammogram at a hanging mercury drop electrode was recorded. At a sweep speed of 25 mV s<sup>-1</sup>, an irreversible peak was obtained at -2.18 V (vs. SCE) in 0.1 M tetraethylammonium perchlorate in DMF. The

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*Scheme 1.* Synthesis and cathodic cleavage of 2-(4-methoxyphenyl)-2-propyl 4-tolyl sulfone. Conditions: a. C<sub>4</sub>H<sub>9</sub>Li, CH<sub>3</sub>I, then repeat; b. Hg cathode at -2.3 V vs. SCE, 0.25 M (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NClO<sub>4</sub> in DMF, 4 % D<sub>2</sub>O.

preparative electrolysis was performed at the cathode potential  $-2.3$  V vs. SCE in an H-cell with  $20$  cm<sup>2</sup> mercury cathode surface. The catholyte was  $100$  ml  $0.25$  M tetraethylammonium perchlorate in DMF, containing  $4$  ml of deuterium oxide (Ciba-Geigy,  $99.7$  atom % D), and  $3$  g ( $10$  mmol) of 2-(4-methoxyphenyl)-2-propyl 4-tolyl sulfone. The anolyte, separated by a Nafion® 125 cation exchange membrane, contained  $0.25$  M tetraethylammonium bromide so as to avoid formation of protons at the carbon anode. The cell was cooled in an ice-bath. After introduction of  $700$  As (the amount of charge necessary for cleavage of  $35$  % of the substrate), the run was interrupted ( $6$  h). The catholyte was diluted with  $300$  ml of water and extracted with ether. The organic layer was dried over sodium sulfate, and the solvent was evaporated. A residue of  $2.5$  g, consisting of product and starting material in the approximate ratio  $1:2$ , was obtained. Chromatography on a column of alumina with hexane as the eluent yielded  $0.45$  g ( $30$  %) of 4-(2-deuterio-2-propyl)anisole, pure according to GLC. <sup>1</sup>H NMR ( $270$  MHz, CDCl<sub>3</sub>):  $\delta$  1.21 (6 H, t,  $J$  0.9 Hz), 3.78 (3 H, s), 6.85 (2 H, d,  $J$  9 Hz), 7.14 (2 H, d,  $J$  9 Hz). MS [IP 70 eV;  $m/e$  (% rel. int.)]: 151 (27.4), 136 (100), 106 (21.1), 92 (18.3), 78 (11.4), 51 (10). Mol. wt. obs. 151.10806, calc. for C<sub>10</sub>H<sub>13</sub>DO 151.11074.

Through quantitative analysis the isotopic purity was determined at  $98.5$  %. The signal for the residual  $\alpha$  protons was measured at high amplification.

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