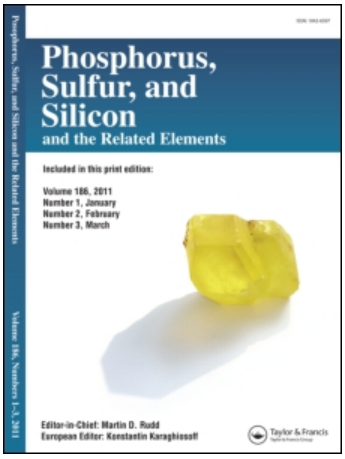


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# α-(METHYLTHIO) BENZYL SULFONES AS SYNTHETIC INTERMEDIATES. PART V. SYNTHESES OF SOME *o*- AND *m*-SUBSTITUTED 1-DEUTERIOBENZALDEHYDES

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# α-(METHYLTHIO) BENZYL SULFONES AS SYNTHETIC INTERMEDIATES. PART V. SYNTHESES OF SOME *o*- AND *m*-SUBSTITUTED 1-DEUTERIOBENZALDEHYDES

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*o*- and *m*-Substituted α-methylthiobenzyl sulfones incorporate deuterium when treated with a base and deuterium oxide. The resulting deuterated sulfones, by thermal decomposition, afford *o*- and *m*-substituted 1-deuteriobenzaldehydes in good yields and high isotopic purity.

*Key words:* Deuteriobenzaldehydes; *ortho*; *meta*; benzyl sulfones; deuterium oxide.



## INTRODUCTION

The utilization of the *p*-substituted α-sulfenylated benzyl sulfones as synthetic intermediates has been explored.[1–3] Their use as the precursors of the *p*-substituted 1-deuteriobenzaldehydes, through deuteration-thermal decomposition,[2] showed to be advantageous due to high yields, high isotopic purity of the products and inexpensive deuteration reagent-deuterium oxide.

In the previous communication[4] we examined the corresponding *o*- and *m*-substituted benzylic sulfones and reported a new sulfenylation method under the phase transfer condition to obtain the *o*-substituted α-methylthiobenzyl sulfones. It became of interest to extend the deuteriation-thermal decomposition method to these compounds to obtain the *o*- and *m*-substituted 1-deuteriobenzaldehydes, which may be useful after reduction to quiralic primary alcohols for mechanistic and biochemical studies.[5,6]

A survey of the literature surprisingly showed that no general method for the preparation of the *o*- and *m*-substituted 1-deuteriobenzaldehydes has been developed, but only some isolated representatives obtained by different procedures were reported.[7–11]

## RESULTS

Two series of the α-methylthiobenzyl sulfones, the *o*-substituted **1a–c** and the *m*-substituted **2a–c** isomers, were subjected to a two-step reaction: deuteration, employing base/$D_2O$ at room temperature to give the corresponding deuterated sulfones **3a–c** and **4a–c**, followed by thermal decomposition to yield the corresponding 1-deuteriobenzaldehydes **5a–c** and **6a–c** (Scheme).

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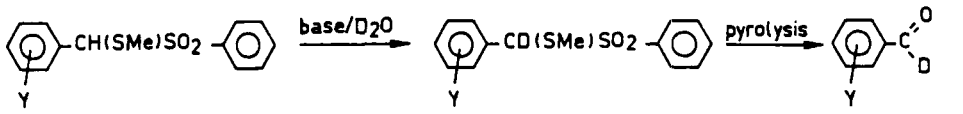


1(o-), 2(m-) 3(o-), 4(m-) 5(o-), 6(m-)

Y= a : $OCH_3$ ; b : $NO_2$ ; c : CN

SCHEME

The use of NaH/THF, which was successfully employed as base for the deuteriation of *p*-substituted α-methylthiobenzyl sulfones,[2] was also satisfactory for all *meta*- **2a–c**, *ortho*-nitro **1b** and *ortho*-cyano **1c** derivatives but failed for the *ortho* methoxy isomer **1a**. In the case of the latter, a stronger base, namely BuLi/THF, had to be used. All deuterated sulfones **3a–c** and **4a–c** were isolated in good yields (Table I) and showed, by mass spectral analysis, 100% deuterium incorporation.

The pyrolysis of the deuterated sulfones **3a–c** and **4a–c** was performed by heating under a nitrogen atmosphere at 100–135°C to give the corresponding 1-deuteriobenzaldehydes **5a–c** and **6a–c** in good yields with isotopic purity of ca 98% as shown by $^1H$ NMR and mass spectral analysis (Table I).

We can conclude that our method is of general application to the preparation of the 1-deuteriobenzaldehydes containing substituents in the ring, independent either on their electronic effect or position. This originates from the availability of the starting benzyl alcohols for the preparation of the benzylic sulfones, the success of the sulfenylation reaction and no restriction for the deuteration and final decomposition.

## EXPERIMENTAL

The IR spectra were run on a Perkin Elmer 1750FT instrument. $^1H$ NMR spectra were recorded on a Varian T-60 or on a Bruker AC-80 spectrometer. Mass spectra were obtained with a HP5988A spectrometer. Compounds **1a–c** and **2a–c** were prepared as previously reported.[4]

TABLE I

Yields of the deuterated α-methylthiobenzyl sulfones and yields and deuterium incorporation of the corresponding 1-deuteriobenzaldehydes

| Deuterated sulfones | | 1-Deuteriobenzaldehydes | | |
|---|---|---|---|---|
| No. | Yields % | No. | Yields %[a] | % Deuter.incorp.[b] |
| 3a | 92 | 5a | 70 | 96.2 |
| 3b | 95 | 5b | 75 | 98.5 |
| 3c | 96 | 5c | 46 | 98.0 |
| 4a | 76 | 6a | 88 | 98.3 |
| 4b | 76 | 6b | 84 | 98.2 |
| 4c | 82 | 6c | 81 | 98.9 |

[a] Yields of pure compounds

[b] Determined by $^1H$ NMR and mass spectrometry

*General procedure for deuteration of o- and m-substituted α-methylthiobenzyl phenyl sulfones:* To a suspension of 9.0 mmol of sodium hydride (70% in mineral oil, previously washed with dry THF) in dry THF (20 ml) were added 3.0 mmol of sulfone **1a–c** or **2a–c**. After stirring at room temperature for 30 minutes, 0.75 ml of $D_2O$ and 0.60 ml of acetic anhydride were added, and the reaction mixture was stirred for 30 minutes. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform. After washing the organic extract with water (3 × 50 ml) and drying with ($MgSO_4$), the solvent was removed under reduced pressure, and the residue was washed with dry hexane (3 × 5.0 ml). The resulting solid was pure 100% deuterated sulfone **3a–c** or **4a–c**. For spectroscopic and mass spectra data see Table II.

*General procedure for thermal decomposition of o- and m-substituted α-deuterio, α'-methylthiobenzyl phenyl sulfones:* Sulfones **3a–c** or **4a–c** (0.70 mmol) were heated under $N_2$ atmosphere at temperatures and for the times reported in Table III. 1-Deuteriobenzaldehydes **6a** and **6c** were isolated by column chromatography (silica-gel 70–230 mesh, $CCl_4/CHCl_3$ 7:3 as eluent). Crude **5c** was purified by recrystallization from $CCl_4$. Compounds **5a**, **5b** and **6b** were isolated by the following procedure: the crude product was dissolved in chloroform (10 ml). After extraction using a 20% aqueous bissulfite solution

TABLE II

Deuterated α-methylthiobenzyl phenyl sulfones

| Product | $^1$H NMR ($CDCl_3$/TMS) δ (ppm) | IR(film/cm$^{-1}$) $\nu_{SO_2}$; $\nu_{CD}$; $\nu_{CN}$ | MS m/z(relative abundance) |
|---|---|---|---|
| 3a | 2.50(s,3 H),3.43(s,3 H) 6.47-7.78(m,9 H) | 1145, 2204 - 1295 | 168(100),138(11),77(16), 61(52) |
| 3b | 2.40(s,3 H),7.33-8.00(m,9 H) | 1147, 2232 - 1310 | 183(100),153(11),136(24), 92(28),77(27),51(14) |
| 3c | 2.42(s,3 H),7.27-7.80(m,9 H) | 1147, 2231 2231 1306 | 163(100),77(13),51(13 |
| 4a | 2.45(s,3 H), 3.69(s,3 H), 6.63-7.60(m,9 H) | 1150, 2194 - 1304 | 168(100),151(6),77(7), 51(3) |
| 4b | 2.44(s,3 H),7.37-8.23(m,9 H) | 1145, 2184 - 1302 | 183(100),166(2),137(23), 77(6),51(3) |
| 4c | 2.44(s,3 H),7.30-7.80(m,9 H) | 1147, 2197 2232 1302 | 163(100),146(12),117(6), 77(8),51(3) |

TABLE III

Thermal decomposition of compounds **3a–c** and **4a–c**

| Compound | Temperature (°C) | Time (min.) |
|---|---|---|
| 3a | 135 | 60 |
| 3b | 100 | 180 |
| 3c | 125[a] | 10 |
| 4a | 118 | 105 |
| 4b | 135 | 45 |
| 4c | 120 | 150 |

[a]Under reduced pressure (2 mm Hg)

(5 ml), unreacted organic material was removed by extraction of the aqueous adduct solution with chloroform (3 × 10 ml). To the aqueous layer were added 10 ml of concentrated hydrochloric acid, and the reaction mixture was refluxed for 5 minutes, cooled to room temperature, and extracted with chloroform (3 × 10 ml). After drying with ($MgSO_4$), the solvent was removed under reduced pressure to yield a product that did not need further purification.

*2-Methoxy-1-deuteriobenzaldehyde* (**5a**). Mp of 2,4-dinitrophenylhydrazone: 247–9°C (Lit[12] mp 249–250°C). IR (neat): 1664 ($\nu_{CO}$), 2156, 2130 ($\nu_{CD}$); $^1$H NMR ($CDCl_3$/TMS, $\delta$ ppm): 3.92 (s, 3 H), 6.80–7.97 (m, 4 H). MS (m/z, relative abundance): 138(9), 137(100), 136(7), 135(31), 104(27), 92(36), 77(42), 66(23).

*2-Nitro-1-deuteriobenzaldehyde* (**5b**). Mp (Lit[13] mp 43.5–44.5°C). IR (neat): 1674 ($\nu_{CO}$), 2173 ($\nu_{CD}$). $^1$H NMR ($CDCl_3$/TMS, $\delta$ ppm): 7.68–8.34 (m, 4 H). MS (m/z, relative abundance): 123(7), 122(83), 121(1), 104(21), 94(54), 76(26), 66(100), 52(14).

*2-Cyano-1-deuteriobenzaldehyde* (**5c**). Mp 102–3°C (Lit[14] mp 103–4°C). IR (neat): 1679 ($\nu_{CO}$), 2142 ($\nu_{CD}$), 2225 ($\nu_{CN}$). $^1$H NMR ($CDCl_3$/TMS), $\delta$ ppm: 7.70–8.13 (m, 4 H). MS (m/z, relative abundance): 133(0.6), 132(7), 131(1), 130(11), 104(100), 76(22), 50(2).

*3-Methoxy-1-deuteriobenzaldehyde* (**6a**). Mp of 2,4-dinitrophenylhydrazone: 218–220°C (Lit[15] mp 219–220°C). IR (neat): 1680 ($\nu_{CO}$), 2109 ($\nu_{CD}$). $^1$H NMR ($CDCl_3$/TMS, $\delta$ ppm): 3.86 (s, 3 H), 7.08–7.97 (m, 4 H). MS (m/z, relative abundance: 138(8), 137(97), 136(10), 135(100), 107(44), 92(21), 77(40), 66(27), 51(8).

*3-Nitro-1-deuteriobenzaldehyde* (**6b**). Mp 58°C (Lit[10] mp 55–7°C. IR (neat): 1689 ($\nu_{CO}$), 2157 ($\nu_{CD}$). $^1$H NMR ($CDCl_3$/TMS, $\delta$ ppm): 7.63–8.83 (m, 4 H). MS (m/z, relative abundance): 153(9), 152(100), 151(8), 150(68), 122(5), 106(44), 78(64), 52(15).

*3-Cyano-1-deuteriobenzaldehyde* (**6c**). Mp 79–80°C (Lit[16] mp 79–81°C. IR (neat): 1683 ($\nu_{CO}$), 2135 ($\nu_{CD}$), 2234 ($\nu_{CN}$). $^1$H NMR ($CDCl_3$/TMS, $\delta$ ppm): 7.29–8.37 (m, 4 H). MS (m/z, relative abundance): 133(7), 132(77), 131(10), 130(100), 102(43), 77(13), 51(3).



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