Dod-S-Me and Methyl 6-Morpholinohexyl Sulfide (MMS) as New Odorless Borane Carriers

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Dedicated to Professor H. Ila on the occasion of her 60th birthday

Abstract: Odorless Dod-S-Me (1) and MMS (3) are developed as efficient borane carriers. The yields of hydroborations and reductions with borane complex 2 of 1 are very high and the recovery of 1 after the reaction is quantitative. The borane complexes 4 and 5 of 3 are also useful. In the latter case chromatographic separation is unnecessary when excess oxidizing agent (alkaline H2O2) is used after hydroboration.

Key words: odorless, sulfides, borane, hydroborations, reductions

Chemistry of thiols and sulfides is very versatile and they are used extensively as reagents in industries and academic laboratories.1 Owing to their intrinsic toxicity and malodor, attempts have been made to prepare odorless derivatives.2 Our continuing efforts in this direction led us to develop odorless substitutes for the most commonly used malodorous thiols and sulfide species.3 Odoriferous dimethyl sulfide (DMS) forms a stable coordination complex with borane, which makes the otherwise pyrophoric borane easy to handle and store. BH3-DMS (BMS) is regularly used in hydroboration and various reductions and is considered to be superior over its THF counterpart (BH3-THF) in terms of stability and longevity.4 However, due to growing environmental concerns, there have been efforts to replace the toxic and volatile DMS as borane carrier.5 Recently, we reported Dod-S-Me (1) as a very effective and odorless alternative to DMS in Corey–Kim and Swern oxidations.3a,b Although the purification of the reagent 1 after the reaction was not difficult given its relatively non-polar character, we sought to improve upon this by an extractable morpholino linked methyl sulfide (MMS; 3), which did not require column chromatography for separation.6 We now report the suitability of our newly synthesized odorless sulfide derivatives as potential borane carriers.

Table 1. Hydroboration of Alkenes with 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (3 equiv)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Rec. (%) of 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>77</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
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<td>89</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>81</td>
<td>89</td>
</tr>
</tbody>
</table>

Ded-S-Me (1, n-C12H25-S-Me, available from Wako Pure Chemical Industries, Ltd.) was passed through the diborane gas (Scheme 1) generated from NaBH4 and BF3-diglyme7 for approximately 30 minutes to provide the DodSMe·BH3 (DodBMS; 2) in quantitative yield (1H NMR: δDdSMe = 0.12; 11B NMR: δ = –21.9). This compound is a colorless oil at room temperature that can be stored indefinitely under argon at 4 °C.

The results of hydroborations in Table 1 demonstrate that 2 is an effective borane carrier. The highly non-polar nature of the carrier (Dod-S-Me) enables easy separation from the products by passing through a short silica gel chromatographic column using hexane and EtOAc as the eluents. The yields of the alcohols were good to excellent.

Scheme 1

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and the recovery of 1 was generally quantitative (89–99%).

We next attempted to study our second odorless sulfide, which has a terminal morpholino group. This morpholino group has the potential to form the second more stable borane coordination. The tert-amine borane complex is considered more stable and thus not very reactive. In order to have both the amine- and sulfide-boranes in one carrier, the diborane gas was passed through a neat sample of MMS (3) at room temperature for 45 minutes (Scheme 2). A viscous colorless liquid was obtained and the NMR studies revealed the formation of two species as the expected diborane 4 (80%, 1H NMR: $\Delta\delta_{\text{SiMe}} = 0.13$; 11B NMR: $\delta = -14.1, -22.0$) and amine borane 5 (20%). The highly viscous nature of the products makes the introduction and absorption of borane difficult even after prolonged exposure (>1 h) to diborane gas resulting in incomplete transformation of 5 to 4. The mixture was used as such for hydroboration of several olefins as shown in Table 2.

When 1-octene (2.3 equiv, Table 2, entry 1) in CH₂Cl₂ or THF solution was reacted with a mixture of 4 and 5 (4:1, 1 equiv of 4: calculated as 80% from the total weight of the mixture 4 and 5), hydroboration was complete within 2 hours (11B NMR: $s, \delta = 86$ for trioctyl borane and $s, \delta = -14$ for unreacted 5). Standard oxidation using alkaline hydrogen peroxide followed by acidic work-up (1 N HCl) afforded 1-octanol (>98% pure based on NMR). There was no trace of reagent amine observed. Excess oxidizing agent (5 equiv) was required to oxidize also the tert-amine-borane moiety, which allowed easy and clean separation of the reagent from the product by simple extraction. However, when 4-octene (Table 2, entry 3) was hydroborated and oxidized using H₂O₂ (3 equiv) and 3 M NaOH (1.5 equiv), after similar work-up, we observed the product being contaminated with the amine-borane 5.

The amine-borane complex 5 was stable enough to be separated and purified by silica gel column chromatography. Upon long aerial standing (>3 d) gradual decomposition of it was observed by forming white insoluble boric acid. Hindered tert-amine-borane adducts have also been effective hydrobating agents. In one of our attempts to use the morpholine-borane in hydroboration, 1-octene (432 mg, 3.85 mmol, Table 2, entry 2) was reacted with the mixture of 4 and 5 (4:1, 156 mg, 0.64 mmol). The reaction mixture was initially stirred at room temperature (even after 24 h TLC showed the presence of 5, $R_f = 0.2$ in 4:1 hexane and EtOAc). Refluxing the reaction mixture for 2 days (monitored by TLC) ensured complete consumption of the reagent. Standard oxidation and work-up afforded 1-octanol (446 mg) in 89% yield.

We also used the newly prepared borane careers as reducing agents for the substrates shown in Table 3. DodBMS 2 was used in most cases to reduce various benzyl esters (Table 3, entries 1 and 3), lactones (Table 3, entries 5 and 6), 4-methoxyphenylacetonitrile (Table 3, entry 4) and an amide (Table 3, entry 7). The yields of the products are good to excellent and the recovery of the Dod-S-Me (1) was quantitative. In one example (Table 3, entry 2), the

![Scheme 2](image1)

Table 2 Hydroboration of Alkenes with 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (equiv)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₈H₁₇ (2.3)</td>
<td>HO-C₈H₁₇</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>C₈H₁₇ (6)</td>
<td>HO-C₈H₁₇</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₆</td>
<td>HO-C₆H₆</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
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</tr>
<tr>
<td>7</td>
<td>C₆H₆</td>
<td>HO-C₆H₆</td>
<td>81</td>
</tr>
</tbody>
</table>

*The reaction mixture was stirred at r.t. for 24 h, followed by reflux for 2 d before standard oxidation.

*a Reaction was carried in CH₂Cl₂, oxidized with H₂O₂ (3 equiv) and NaOH (1.5 equiv). Work-up and column chromatography afforded 4-octanol (90%) along with 5 (66%).
borane source was the mixture of 4 and 5. The decomposition of the unreactive 5 was conveniently carried out by refluxing in MeOH and 1 N HCl. Aqueous extractive work-up afforded the phenethyl alcohol (94%) devoid of the amine carrier.

Table 3. Reduction with New Odorless Borane Complexes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Rec. (%) of 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>81</td>
<td>95</td>
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<td>7</td>
<td></td>
<td></td>
<td>99</td>
<td>96</td>
</tr>
</tbody>
</table>

**a** The diborane complex mixture 4 and 5 was used as the borane source.

`b` Not determined.

`c` Refluxed for 5 h.

`d` Refluxed for 8 h.

In conclusion, we have demonstrated successful use of these new odorless borane carriers in reactions which are usually done by malodorous BMS. Moreover, the reagent 2 is recyclable in high yields. The diborane complex 4 is unique with two differentially reactive boranes and may be very useful. The starting materials are either available cheaply from commercial sources or can be prepared from cheap reagents in few simple steps. Given their odorlessness, stability and recyclability, these reagents could be the future choice of industries as well as academia.

NMR spectra were recorded at 400 MHz (1H), 128.3 MHz (11B) and 50 MHz (13C) on a VARIAN INOVA 400 and GEMINI 200 MHz NMR spectrometer. The spectra were run in CDCl3 and chemical shifts are reported (δ) relative to TMS (1H) and CDCl3 (13C) as the internal standards. BF3·Et2O was used as the external standard for 11B. All the reagents are commercially available or were prepared by known methods and the products of hydroborations and reductions, identical to the literature data.

**DodBMS (2); Typical Procedure**

To a stirred suspension of NaBH4 (7.5 g, 0.20 M) in diglyme (25 mL) was added BF3·diglyme (30 mL, generated from 25 mL of BF3·Et2O and 40 mL of diglyme) dropwise with caution. The diborane gas thus generated was bubbled via a cannula through a stirring near sample of 1 (6.5 g, 0.03 M) for 30 min. 1H NMR of the sample after 30 min confirmed complete coordination.

1H NMR (400 MHz, CDCl3): δ = 2.55 (dt, J = 3.3, 7.6 Hz, 2 H, SCH3), 2.22 (s, 3 H, SCH3), 1.68 (quint, J = 7.7 Hz, 2 H, CH2), 1.38–1.21 (m, 18 H, 9 × CH3), 0.88 (t, J = 6.8 Hz, 3 H, CH3).

13C NMR (50 MHz, CDCl3): δ = 42.7, 31.9, 29.6, 29.5, 29.4, 29.3 (2), 29.0, 28.7, 25.9, 24.1, 22.7, 14.2.

11B NMR (128.3 MHz, CDCl3): δ = –21.91.

**Mixture of 4 and 5; Typical Procedure**

To a stirred suspension of NaBH4 (4.0 g, 0.10 M) in diglyme (12 mL) was added BF3·diglyme (15 mL, generated from 15 mL of BF3·Et2O and 20 mL of diglyme) dropwise with caution. The diborane gas thus generated was bubbled via a cannula through a stirring near sample of 3 (3.0 g, 13.80 mmol) for 45 min. 1H NMR of the sample showed a 4:1 relation of 4:5.

1H NMR (400 MHz, CDCl3): δ = 4.24–4.17 (m, 2 H, OCH2 of 4, 5), 3.74–3.69 (m, 2 H, OCH2 of 4, 5), 2.97 (br d, J = 12.4 Hz, 2 H, NCH3 of 4, 5), 2.78–2.69 (m, 4 H, NCH2 of 4, 5), 2.57 (t, J = 7.5 Hz, 2 H, SCH of 4), 2.50 (t, J = 7.3 Hz, 2 H, SCH of 5), 2.23 (s, 3 H, SCH3 of 4), 2.10 (s, 3 H, SCH3 of 5), 1.90–1.30 (m, 8 H, 4 × CH2 of 4, 5).

11B NMR (128.3 MHz, CDCl3): δ = –14.12, –22.00.

**Hydroboration Using 2; General Procedure**

To a solution of borane reagent 2 (0.24 mmol, 1 equiv) in anhyd THF (2 mL/mmol) at 0 °C was added dropwise a solution of olefin (0.72 mmol, 3 equiv) in THF (2 mL/mmol). The reaction mixture was stirred at r.t. for 2 h, cooled to 10 °C followed by slow addition of 30% H2O2 (3 equiv) and 3 M NaOH (1.5 equiv). The reaction mixture was stirred at ambient temperature for 8 h and diluted with water (5 mL). Stirred for 30 min and extracted with Et2O (3 × 50 mL). The Et2O extracts were washed with water and brine and dried (Na2SO4). Evaporation of the solvent afforded usually colorless residue, which upon silica gel column chromatography using hexane and EtOAc (10:1) as the eluents afforded pure products.

**Hydroboration Using the Mixture of 4 and 5; General Procedure**

To a solution of borane reagents 4 and 5 (0.30 mmol, 1 equiv of 4) in anhyd THF (2 mL/mmol) at 0 °C was added dropwise a solution of olefin (0.70 mmol, 2.3 equiv) in THF (2 mL/mmol). The reaction mixture was stirred at r.t. for 2–2.5 h. The solvent was removed in vacuo. The residue was diluted with MeOH (2 mL/mmol), cooled to 10 °C followed by slow addition of 30% H2O2 (5 equiv) and 3 M NaOH (3 equiv). The reaction mixture was stirred at ambient temperature for 8 h and the solvent was removed in vacuo, diluted with water (5 mL) and stirred for 30 min and then extracted with Et2O (3 × 50 mL). The Et2O extracts were washed with 1 N HCl (2 × 50 mL), brine (50 mL) and dried (Na2SO4). Evaporation of the solvent afforded the alcohol as a colorless oil (>98% pure in NMR).

**Reduction of Benzyl Esters and Lactones Using 2; General Procedure**

To a solution of ester or lactone (1 equiv) in THF (2 mL) was added a solution of 2 (1.5 equiv) in THF (2 mL) and the mixture was stirred for 18 h (lactone) or 24 h (ester). After completion of the reaction, MeOH (1 mL) was added to quench the excess borane. The mixture was diluted with water (50 mL) and extracted with Et2O (3 × 50 mL). The Et2O extracts were washed with brine (50 mL) and dried (Na2SO4). Upon concentration, the products were purified by silica gel column chromatography using hexane and EtOAc (10:1–2:1) as the eluents.
Reduction of Methyl Phenylacetate Using the Mixture of 4 and 5; Typical Procedure
To a solution of methyl phenylacetate (100 mg, 0.67 mmol) in THF (2 mL) was added a solution of the mixture of 4 and 5 (4:1, 377 mg, 0.99 mmol of 4) in THF (2 mL) and the mixture was stirred for 24 h. After completion of the reaction (TLC), MeOH (2 mL) and 1 N HCl (2 mL) were added and the mixture was refluxed for 6 h to quench the amine-borane. After cooling the mixture, the solvent was removed. The residue was taken up in Et₂O (75 mL) and quenched with 1 N HCl (2 × 30 mL). The ethereal layer was washed with 1 N HCl (2 × 30 mL) and dried (Na₂SO₄) and concentrated to afford phenethyl alcohol as a colorless oil (76.7 mg, 94%, >98% pure in NMR).

Reduction of 4-Methoxyphenylacetonitrile Using 2; Typical Procedure
To a solution of 4-methoxyphenylacetonitrile (100 mg, 0.68 mmol) in THF (2 mL) was added a solution of 2 (233.6 mg, 1.02 mmol) in THF (2 mL). The reaction mixture was refluxed for 5 h and cooled to r.t. To the reaction mixture, was added slowly 6 N HCl (1 mL) and then poured into water and basified (pH 9) using 3 M NaOH, extracted with Et₂O (3 × 30 mL) followed by a short column chromatography using hexane and EtOAc (10:1) to CHCl₃ and MeOH (20:1) as the eluents to afford 4-benzyl-2-(4-methoxyphenyl)acetamide (87 mg, 79%) and 1 (216 mg, 98%).

Reduction of N-Benzyl-2-(4-methoxyphenyl)acetamide Using 2; Typical Procedure
To a solution of N-benzyl-2-(4-methoxyphenyl) acetamide (85.9 mg, 0.34 mmol) in THF (2 mL) was added a solution of 2 (232 mg, 1.01 mmol) in THF (2 mL). The reaction mixture was refluxed for 8 h and cooled to r.t. The solvent was evaporated in vacuo and the residue was taken up in MeOH (2 mL) followed by the addition of 6 N HCl (1 mL). The reaction mixture was refluxed for 30 min and then poured into water and basified (pH 9) using 3 M NaOH, extracted with Et₂O (3 × 30 mL), dried (Na₂SO₄). Purification by a short column chromatography using hexane and EtOAc (10:1) to CHCl₃ and MeOH (20:1) as the eluents afforded benzyl-4-methoxyphenethyl amine (80 mg, 99%) and 1 (209 mg, 96%).

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