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Fluorous Dimethyl Sulfide: A Convenient, Odorless, Recyclable Borane Carrier

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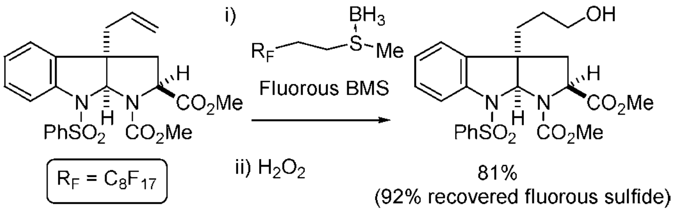
ABSTRACT



Borane gas and 2-(perfluorooctyl)ethyl methyl sulfide form a solid comprised of an approximately 1:1 mixture (fluorous BMS) of sulfide and the corresponding sulfide-borane. Fluorous BMS permits hydroboration of alkenes in a dichloromethane/perfluorinated hydrocarbon mixture with subsequent recycling of the fluorous sulfide by fluorous extraction. The use of fluorous BMS in the asymmetric reduction of ketones catalyzed by a chiral oxaborolidine catalyst, and in the reduction of other functional groups, is also reported.

Borane is one of the most useful and ubiquitous of organic reagents. It enables the hydroboration of alkenes and alkynes, and the myriad of transformations arising from the so-formed organoborane derivatives, and permits many other reductions to be carried out under mild conditions. Nevertheless, the pyrophoric nature of borane renders its use and transportation hazardous such that it is most commonly employed coordinated to either tetrahydrofuran ($BH_3{\cdot}THF$)[1] or dimethyl sulfide ($BH_3{\cdot}SMe_2$, BMS),[2] with the latter usually preferred because of its greater stability and longevity. BMS, while considerably more practical than borane itself, suffers from the disadvantage of liberating stoichiometric dimethyl sulfide in the course of its reactions, with all the adverse environmental problems contingent on the release of such a malodorous substance. This problem prompted Brown and co-workers to introduce 1,4-thioxane[3] as a less volatile carrier for borane and, more recently, bis(hydroxyethyl) sulfide,[4] which has the additional advantage of being water soluble and, so, conveniently removable by aqueous extraction following reductions by $BH_3{\cdot}S(CH_2CH_2OH)_2$.[5] In this paper we present 2-(perfluorooctyl)ethyl methyl sulfide (**1**) as a readily prepared, odorless sulfide for complexation and stablization of borane that is readily recycled by fluorous extraction and which additionally possesses the considerable advantage of not being pyrophoric.

Our interest in the development of recoverable, environmentally friendly fluorous[6] organoselenium[7] and organosulfur[8] reagents led us to consider the possibility of a nonvola-

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[1] (a) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 1637−1646. (b) Zaidlewicz, M.; Brown, H. C. In *EROS*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; Vol. 1, pp 638−644.

[2] (a) Braun, L. M.; Braun, R. A.; Crissman, H. R.; Opperman, M.; Adams, R. M. *J. Org. Chem.* **1971**, *36*, 2388−2389. (b) Lane, C. F. *J. Org. Chem.* **1974**, *39*, 1437−1438. (c) Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. *J. Org. Chem.* **1977**, *42*, 1392−1398. (d) Zaidlewicz, M. In *EROS*; Paquette, L. A., Ed.; Wiley: Chicester, UK, 1995; Vol. 1, pp 634−637.

[3] Brown, H. C.; Mandal, A. K. *J. Org. Chem.* **1992**, *57*, 4970−4976.

[4] Brown, H. C.; Zaidlewicz, M.; Dalvi, P. V.; Biswas, G. K. *J. Org. Chem.* **2001**, *66*, 4795−4798.

[5] Other sulfides that have been introduced as carriers for borane include 1,2-bis(*tert*-butylthio)ethane and 1,4-bis(benzylthio)butane: Follet, M. *Chem. Ind.* **1986**, 123−128.

[6] (a) Horvath, I. T. *Acc. Chem. Res.* **1998**, *31*, 641−650. (b) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174−1196. (c) For a collection of articles on fluorous reagents and catalysts see: Curran, D. P.; Gladysz, J. A., Eds. *Tetrahedron* **2002**, *58*, issue 20.

[7] (a) Crich, D.; Hao, X.; Lucas, M. *Tetrahedron* **1999**, *55*, 14261−14268. (b) Crich, D.; Hao, X. *Org. Lett.* **1999**, *1*, 269−272. (c) Crich, D.; Barba, G. R. *Org. Lett.* **2000**, *2*, 989−991. (d) Crich, D.; Neelamkavil, S.; Sartillo-Piscil, F. *Org. Lett.* **2000**, *2*, 4029−4031.

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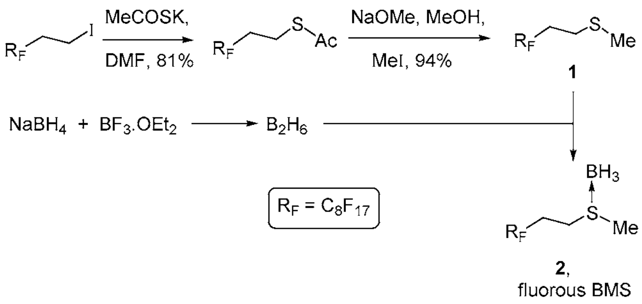
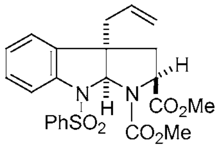
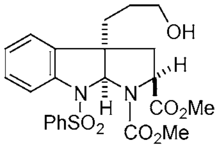
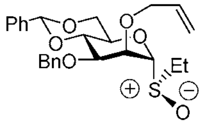
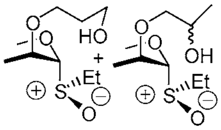
tile, recyclable fluorous analogue (**2**) of BMS. Contemplation of (i) the need for ≥60% F by weight to facilitate recycling by fluorous extraction, (ii) the need for an insulating spacer between the sulfide and the fluorous group to modulate the strongly electron-withdrawing ability of the latter, and (iii) economic considerations steered us toward 2-(perfluorooctyl)ethyl methyl sulfide (**1**, 65.4% F) and the corresponding borane adduct **2** (63.6% F). The synthesis of **1** was achieved in a straightforward manner, in 76% overall yield, by the displacement of iodide from 2-(perfluorooctyl)ethyl iodide with potassium thioacetate followed by saponification with concomitant alkylation of the thiolate with methyl iodide (Scheme 1).[9] The passage of borane gas, generated from BF_3•OEt_2 and $NaBH_4$,[10] through the neat, liquid sulfide then resulted in the formation of a white solid that was estimated by ^1H NMR spectroscopy to be an approximately 1:1 mixture of **1** and **2**.[11] The ^{11}B NMR spectrum of this mixture had a single resonance at δ −22 ppm consistent with the formation of **2**. Likewise the ESI mass spectrum of the mixture demonstrated a molecular ion at *m/z* 509 in full agreement with this proposition. As anticipated both **1** and the mixture of **1** and **2** were completely odorless. The solid mixture of **1** and **2** was only hydrolyzed slowly on standing in air at room temperature and additionally showed no tendency to ignite under those conditions; it was indefinitely stable under a nitrogen atmosphere in the refrigerator. The considerable stability of the solid mixture of **1** and **2** in air enables the reagent to be weighed on a simple laboratory balance. This, coupled with the ready determination of the stoichiometry of the mixture by integration of the ^1H NMR spectrum, affords a very ready, convenient method of adding precise amounts of reagent to a reaction and stands in contrast to the cumbersome determination of hydrogen released on hydrolysis usually recommended for the dosage of BMS and other boranes.[12] Interestingly, despite its high fluorine content, the solid mixture of **1** and **2** was only sparingly soluble in FC-72 with which it forms a fine suspension. The mixture is soluble in dichloromethane or benzotrifluoride[13] (trifluoromethylbenzene). In practice we have found it convenient to use either the solid mixture of **1** and **2** or a suspension in FC-72.

Scheme 1. Preparation of Fluorous BMS



A series of five hydroborations were conducted with a FC-72 suspension of the mixture of **1** and **2** (1.7 M in **2**) with the results set out in Table 1. These reactions were conducted under nitrogen in a biphasic mixture of FC-72 and dichloromethane. On consumption of the olefin, the spent fluorous phase was removed ready for recycling and the organic phase was subjected to oxidative workup in the normal manner with alkaline hydrogen peroxide. The majority (~80%) of **1** and **2**, depleted in **2**, was recovered from the fluorous phase, while a further 10% was recovered from the organic phase following the oxidative workup and chromatography; interestingly no oxidation of the sulfide to the sulfoxide or sulfone was observed under the oxidative workup conditions. The fluorous solution of **1** and **2** was then re-subjected to treatment with borane following which it performed exactly as the original sample. Of the five examples presented, the first is straightforward and requires no comment. The second example is the hydroboration of *β*-pinene and performs exactly as expected from the precedent with BMS[2] and with

Table 1. Hydroboration with Fluorous BMS (**2**)

substrate	molar equiv of **2**	products (% yield)	rec'd **1** (%)[a]
trans-2-octene (**3**)	0.35	3-octanol (**4**) + 2-octanol (**5**) (1:1.2, 90%)	92
β-pinene (**6**)	0.35	*cis*-myrtanol (**7**) (93%)	91
1-methylcyclohexene (**8**)	0.35	*trans*-2-methylcyclohexanol (**9**) (91%)	90
 **10**	0.35	 **11** (81%)	92
 **12**	0.35	 **13** + **14** (3:1, 78%)	92

[a] The bulk of the reagent is recovered in its spent form, namely **1**; however, this is contaminated by small amounts of unreacted **2**. As the mixture is simply recycled by passage of borane gas, the small amount of **2** present was neither quantified nor separated.

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(8) (a) Crich, D.; Neelamkavil, S. *J. Am. Chem. Soc.* **2001**, *123*, 7449−7450. (b) Crich, D.; Neelamkavil, S. *Tetrahedron* **2002**, *58*, 3865−3870.

(9) We prefer this synthesis of fluorous BMS over the ones previously described for the lower homologues as it avoids the need to work with dimethyl disulfide.[8a,b]

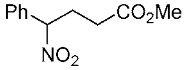
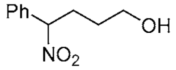
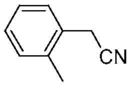
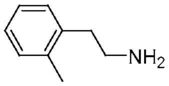
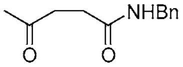
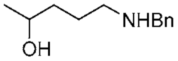
(10) Zweifel, G.; Brown, H. C. *Org. React.* **1963**, *13*, 1−54.

(11) Interestingly, the 1:1 mixture of **1** and **2** is formed both when borane is passed through neat **1** and when it is bubbled through solutions of **1** in FC-72. In the former case the reaction mixture solidifies at this stoichiometry whereas in the latter precipitation of the 1:1 mixture of **1** and **2** takes place.

(12) Brown, H. C. *Organic Synthesis via Boranes*; Wiley: New York, 1975.

(13) Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450−451.

Table 2. Further Reductions with Fluorous BMS

substrate	molar equiv of **2**	products (% yield)	rec'd **1** (%)[a]
 **15**	1.2	 **16** (83%)	95
 **17**	1.2	 **18** (81%)	88
 **19**	3	 **20** (79%)	86

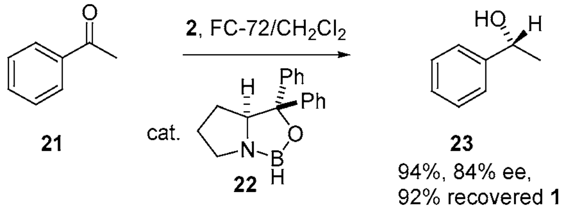
[a] The bulk of the reagent is recovered in its spent form, namely **1**; however, this is contaminated by small amounts of unreacted **2**. As the mixture is simply recycled by passage of borane gas, the small amount of **2** present was neither quantified nor separated.

borane.[14] The third example, the hydroboration of a trisubstituted alkene, proceeds with high yield and regio- and stereoselectivity exactly as anticipated.[15] The fourth example illustrates the compatibility with functionality[16] such as might be found in a typical pharmaceutical. The final example is a relatively unusual example of hydroboration in the presence of a sulfoxide;[17] the reduced regioselectivity observed in this example is typical of that seen in BMS hydroborations of other allyl ethers[18] and alkenes substituted with electron-withdrawing groups in general.[19] Fluorous BMS (**2**) therefore functions in hydroboration exactly as BMS itself but with the considerable advantage that the reaction is odor-free and may be conducted in an organic/fluorous biphasic mixture with straightforward recycling of the fluorous solution.

We subsequently used the fluorous suspension of **2**, typically in a biphasic manner with ready recycling, to conduct a number of other reductions (Table 2). Thus, treatment of nitroester **15** with the FC-72 solution of **2** enabled clean reduction of the ester without complications from the nitro group. This result compares well to that previously obtained with BH_3·THF.[20] A nitrile was reduced to a primary amine in a straightforward manner and *N*-benzyl levulinamide was converted to *N*-benzyl 4-hydroxypentylamine thereby demonstrating the ability of fluorous BMS to reduce both amides and ketones.

Finally, we investigated the ability of fluorous BMS (**2**) to regenerate the Corey-type oxaborolidine catalysts[21] in an asymmetric reduction (Scheme 2). In the event, reduction of acetophenone in THF by an FC-72 solution of **2** catalyzed by 10 mol % of **22** resulted in the formation of (*R*)-1-hydroxyethylbenzene in 94% yield and 84% ee as determined by chromatography over a Chircel OD column.

Scheme 2. Oxaborolidine-Catalyzed Reduction with Fluorous BMS



In conclusion, solutions of fluorous BMS (**2**) perform in a manner exactly analogous to BMS itself. The new reagent possesses, however, several considerable advantages over its well-established counterpart. First, it and the reduction product **1** are completely odorless. Second, the spent fluorous solution, enriched in **1**, is readily regenerated by the passage of borane gas. Third, both the solid mixture of **1** and **2**, and its suspension in FC-72 are quite stable under a nitrogen atmosphere and show no tendency toward ignition in air. Finally, the solid mixture of **1** and **2** may be readily weighed in air and the stoichiometry determined by standard ^1H NMR spectroscopy, thereby permitting facile dispensation of precise quantities of borane. These attributes combine to suggest that fluorous suspensions of **1** and **2** might well be suitable for large-scale industrial applications with simple regeneration at a remote borane generation facility.

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Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Zweifel, G. W.; Brown, H. C. *J. Am. Chem. Soc.* **1964**, *86*, 393–397.

(15) Brown, H. C.; Zweifel, G. W. *J. Am. Chem. Soc.* **1961**, *83*, 2544–2551.

(16) Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543–5549.

(17) Crich, D.; Dai, Z. *Tetrahedron* **1999**, *55*, 1569–1580.

(18) Corrie, J. E. T.; Papergeorgiou, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1583–1592.

(19) Smith, K.; Pelter, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, pp 703–731.

(20) Crich, D.; Neelamkavil, S. *Org. Lett.* **2002**, *4*, 2573–2575.

(21) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987–2012.