Improved Procedure for Borane-Dimethyl Sulfide Reduction of Tertiary and Secondary Amides in the Presence of Boron Trifluoride Etherate

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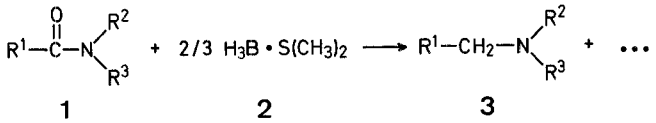
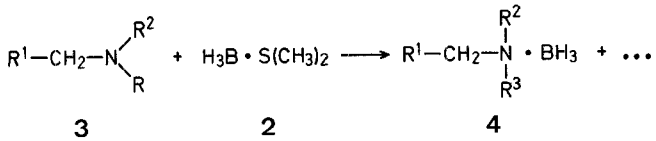
Previously we reported that the reduction of primary amides to the corresponding amines by borane-dimethyl sulfide requires no more than the calculated quantity of the reagent[1]. This is far less than that specified in earlier procedures where sufficient borane reagent was utilized to form the amine-borane adduct[2,3]. However, the reduction of tertiary amides **1** does require additional borane reagent to coordinate with the amine **3**, forming as product the inert borane-amine adduct **4**.



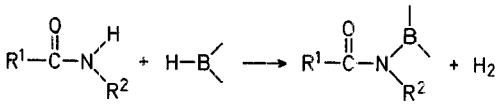
1 **2** **3**



3 **2** **4**

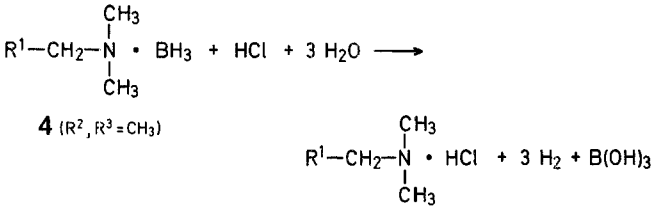
Thus, instead of two equivalents of hydride (H—B<) required for the actual reaction, a total of five equivalents must be used to achieve complete reduction[2,3].

The reduction of secondary amides **5** involves hydrogen evolution together with formation of **6**. Consequently, a total of six equivalents of hydride were recommended for the reduction of secondary amines[2,3], one equivalent for the evolution of hydrogen, two equivalents for the reduction, and three equivalents to form the amine-borane adduct.



5 **6**

The complexed borane is wasted during the isolation of the amine products, making such reduction procedures relatively wasteful of hydride reagent.

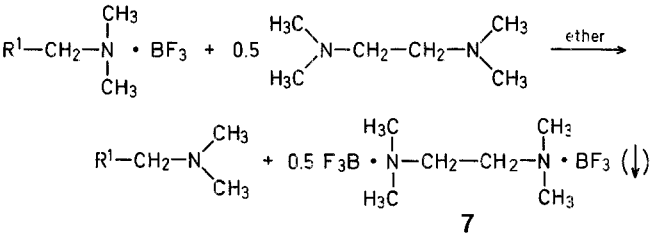


4 ($R^2, R^3 = CH_3$)

In the case of primary amides, we established that the use of excess **2** was not essential[1]. However, we confirmed that the reduction of secondary and tertiary amides require such excess reagent, forming the stable amine-borane adducts as the products. Fortunately, this problem could be easily circumvented by carrying out the reduction in the presence of a molar equivalent of boron trifluoride etherate. Under these conditions, the boron trifluoride combines preferentially with the amine, eliminating the need for excess borane-dimethyl sulfide reagent (**2**).

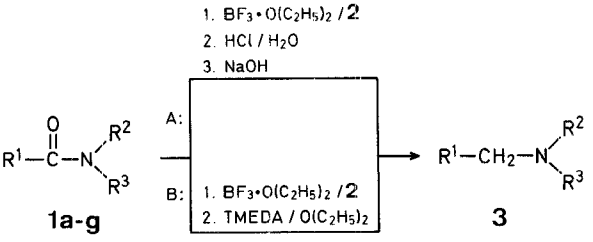
The preferential formation of the amine-boron trifluoride complex in the presence of **2** was confirmed experimentally as was the revised stoichiometric requirement for borane-dimethyl sulfide (**2**).

An alternative procedure for isolating the product is to take advantage of the insolubility of the addition compound of boron trifluoride with *N,N,N',N'*-tetramethylethylenediamine[4] (TMEDA). The reaction mixture is treated with TMEDA and stirred for ~30 min. Exchange occurs and the insoluble adduct **7** precipitates (Method **B**).



7

A number of representative tertiary amides **1a-g** were reduced following this procedure and a number of functional groups are easily tolerated. Also no difficulty was encountered in the reduction of sterically hindered amides **1e,f** to the corresponding amines **3e,f** (Table).



1a-g **3**

Secondary amides **5a-c** are also easily reduced to the corresponding amines **8a-c** (Table). However, in this case three

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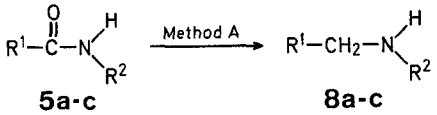
equivalents of hydride (H—B<) are necessary for the reduction.



5a-c **8a-c**

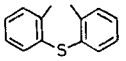
Unlike lactones[5], the lactam **5c** undergoes selective reduction of the carbonyl group with **2** forming the cyclic amine **8c**.

With the usual limitations of employing borane-dimethyl sulfide **(2)**, this procedure affords a convenient method for the rapid and selective reduction of tertiary **(1)** and secondary **(5)** amides utilizing stoichiometric quantities of the reagents.

Preferential Formation of Amine-Boron Trifluoride Complex:
A mixture (0.5 mmol each) of *N,N*-dimethylbenzylamine, boron trifluoride etherate, and borane-dimethyl sulfide in tetrahydrofuran (1.0 ml) is examined by ^{11}B-N.M.R., spectrometry and the chemical shifts compared with those for standard samples: δ (amine · BF_3) = −0.13 ppm, δ (amine · BH_3) = −7.8 ppm, δ (borane · dimethyl sulfide) = −19.8 ppm. The decoupled spectrum shows signals with chemical shifts of δ = −0.13 and −19.8 ppm, corresponding to the presence of the amine-boron trifluoride and the borane-dimethyl sulfide adducts. Clearly, the amine-borane adduct does not form in the presence of an equivalent of boron trifluoride.

Stoichiometric Requirement for Borane-Dimethyl Sulfide (2):
A solution of *N,N*-dimethylbenzamide (**1c**; 4.48 g, 30 mmol) and boron trifluoride etherate (3.69 ml, 30 mmol) in tetrahydrofuran (3.91 ml) is heated under reflux. To the clear solution is added dropwise borane-dimethyl sulfide (**2**; 2.32 ml, 22 mmol; 10% excess) over a period of 10 min. Dimethyl sulfide and ether are distilled off and collected as the reaction proceeds (3.6 ml). After 0.25 h, a 0.5 ml aliquot is hydrolyzed with 6 molar hydrochloric acid (0.5 ml) and neutralized with 3 molar sodium hydroxide solution (1.5 ml; 50% excess). The product is extracted with ether (1 ml), the extract dried with anhydrous potassium carbonate, and analyzed by G.L.C. (6′ × 1/8″ Carbowax-20M; Varian 1200 chromatograph). The starting amide is absent; a quantitative yield of *N,N*-dimethylbenzylamine **(3c)** is present.

Table. Borane-Dimethyl Sulfide **(2)** Reduction of Amides in the Presence of Boron Trifluoride Etherate

Amide No	R_1	R^2	R^3	Product No.	Reaction time [h]	Method	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr	
								found	reported
1a	*n*-C_5H_{11}	CH_3	CH_3	**3a**	0.25	A	80	46°/15	146°/760[8]
1b	*c*-C_6H_{11}	CH_3	CH_3	**3b**	0.25	B	78	78-79°/30	76°/29[9]
1c	C_6H_5	CH_3	CH_3	**3c**	0.25	B	82	81-82°/30	73-74°/15[6]
1d	4-O_2N—C_6H_4	CH_3	CH_3	**3d**	0.25	B	86	79-80°/0.2	140-146°/13[10]
1e	*c*-C_6H_{11}	*i*-C_3H_7	*i*-C_3H_7	**3e**	0.50	B	83	110-112°/15[b]	—
1f	C_6H_5	*i*-C_3H_7	*i*-C_3H_7	**3f**	1.0	B	87	136-137°/15[c]	—
1g	CH_3			**3g**	0.25	B	89	102-103°	102[7]
5a	*c*-C_6H_{11}	CH_3	H	**8a**	0.25	A	77	144°/760	149°/760[11]
5b	C_6H_5	CH_3	H	**8b**	0.75	A	80	100-101°/17	184-189°/760[12]
5c	—$(CH_2)_5$—		H	**8c**	1.0	A	72	134°/740	138°/749[13]

[a] All of the products were fully characterized by ^{1}H-N.M.R. spectra. Unless otherwise stated, yields are of pure, isolated products.
[b] Mass spectral data (*m/e* = 197.215) is consistent with the molecular weight (197) and hence the molecular formula, $C_{13}H_{27}N$, of the product.
[c] BF_3 · etherate was added following the addition of **2**, since the normal addition results in the termination of a precipitate and retards the reaction rate (4 h). The product was characterized as the picrate derivative, m.p. 133-135°C [Lit.[2], m.p. 134-135°C].

***N,N*-Dimethylbenzylamine (3c); Typical Procedure for Method A:**
An oven-dried, 50-ml flask with a septum capped inlet and a magnetic stirring bar is equipped with a 12″ Vigreux column, wound by a heating band. A measuring cylinder is fitted to the receiver end. The outlet is connected to a source of nitrogen atmosphere through a mercury bubbler. The whole system is assembled under nitrogen. The flask is charged with *N,N*-dimethylbenzamide (**1c**; 4.48 g, 30 mmol) and tetrahydrofuran (3.91 ml). Then boron trifluoride etherate (3.67 ml, 30 mmol) is added and the mixture is heated under reflux. To the clear solution, borane-dimethyl sulfide (**2**; 2.32 ml, 22 mmol) is added dropwise over a period of 10 min. The liberated dimethyl sulfide and ether are distilled off as formed and collected (3.6 ml). After 0.25 h, the solvent is removed under suction and the residue heated at 100°C. To the amine-BF_3 complex (30 mmol) is added 6 normal hydrochloric acid (5 ml, 30 mmol) and the mixture is refluxed for 0.5-1 h to insure complete hydrolysis. The clear solution is cooled to 0°C and 6 normal sodium hydroxide solution (7.5 ml, 45 mmol) is added. The aqueous layer is saturated with anhydrous potassium carbonate, extracted with ether (3 × 10 ml), and dried. Fractional distillation provides the pure amine **3c**; yield: 3.32 g (82%); b.p. 81-82°C/30 torr (Lit.[6], b.p. 73-74°C/15 torr).

***N*-Ethylphenothiazine (3 g); Typical Procedure for Method B:**
Following the above procedure, *N*-acetylphenothiazine (**1 g**; 7.24 g, 30 mmol) is reduced with borane-dimethyl sulfide (**2**; 2.32 ml, 22 mmol) in the presence of boron trifluoride etherate (3.69 ml, 30 mmol). After 0.25 h, the solvent is removed under suction and ether (10 ml) added, followed by tetramethylethylenediamine (2.25 ml, 15 mmol). The reaction mixture is stirred for 30 min and centrifuged. The centrifugate is separated. The solid is washed with ether (3 × 10 ml) and the washings combined after centrifugation. Removal of ether gives the amine **3g**; yield: 6.05 g (89%); m.p. 102-103°C (Lit.[7], m.p. 102°C).

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