Improved Procedure for Borane-Dimethyl Sulfide Reduction of Primary Amides to Amines

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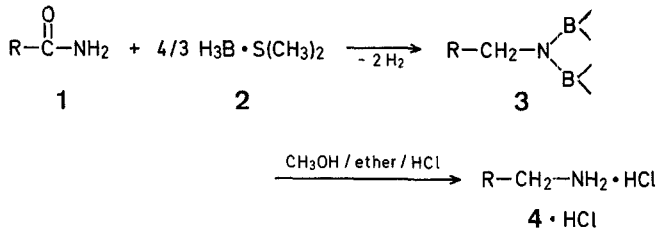
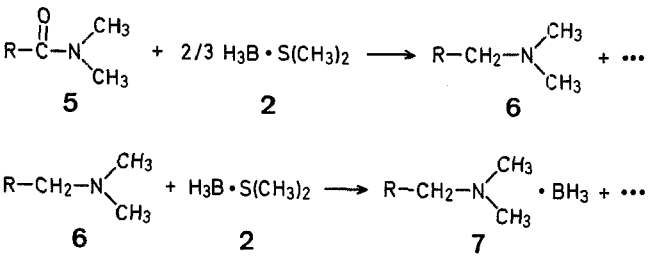
Primary amides **1** are rapidly and quantitatively reduced to primary amines **4** by borane-dimethyl sulfide (**2**) used in essentially theoretical amounts.



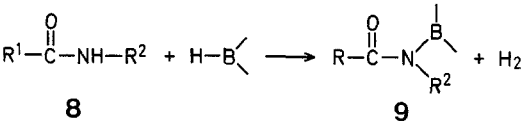
This procedure requires far less borane reagent than earlier methods[1,2]. Consequently, this improved procedure provides a more satisfactory route for the conversion of many carboxylic acids through the corresponding amides to the primary amines.

Borane-tetrahydrofuran and borane-dimethyl sulfide[2] (**2**) have proven to be reagents of choice over lithium aluminium hydride[3] for most reductions of carboxylic acid amides to amines. In the reduction of tertiary amides **5** to amines **6**, it was established that excess borane reagent is required to form the borane-amine adduct[1] (**7**).



Thus, instead of the two equivalents of hydride (H—B<) required for the reduction, five equivalents were used[1,2].

The reduction of secondary (**8**) and primary amides (**1**) involve hydrogen evolution to give **9** and **3**.



Consequently, six equivalents of hydride were recommended for the reduction of secondary amides and seven equivalents of hydride for the reduction of primary amides.

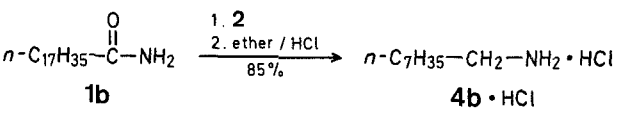
In the course of investigating the advantages of distilling dimethyl sulfide out of the reaction mixture[4], we discovered that reductions of primary amides do not require an additional mol of **2**. Apparently, the bis-borane derivative **3** does not coordinate strongly with borane in the way the tertiary amine does. A test of secondary amides revealed that this still requires a total of six equivalents of hydride. Nevertheless, the facile reduction of primary amides to primary amines is an important reaction of great promise in providing a simple route from carboxylic acids to primary amines through the intermediate amides. Consequently, we undertook a detailed study of this procedure.

The following experiment establishes the stoichiometry of the reaction and the requirement for considerably less borane reagent than previously recommended.

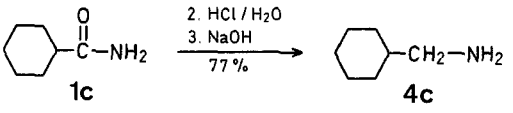
n-Hexanamide (5 mmol) in tetrahydrofuran (1.0 ml) is heated to reflux and borane-dimethyl sulfide (**2**; 0.74 ml, 7.3 mmol) is added. The hydrogen evolved is collected and measured: 230 ml, 9 mmol, 90% theoretical[5]. The dimethyl sulfide liberated in the course of the reaction is allowed to distill off. After 4 h, the product is analyzed. An aliquot (0.1 ml) is diluted five-fold and examined by ^{11}B-N.M.R. spectrometry (Varian FT 80). The decoupled spectrum indicates two peaks at $\delta = -19.9$ (**2**) and -23.3 ppm (**3**). The remaining reaction mixture is treated with 6 molar hydrochloric acid (0.83 ml, 5.0 mmol) at 25 °C. Hydrolysis is facile under these conditions (in contrast to the behavior of the amine-borane complex). Excess (50%) sodium hydroxide (pellets) is added to neutralize the solution and separate the tetrahydrofuran layer. This layer is dried and analyzed by G.L.C. The starting amide is absent; an essentially quantitative yield of *n*-hexylamine (**4a**) is present.

An alternative procedure for isolating the product is to treat the reaction mixture with methanol, followed by a 1.15 molar solution of hydrogen chloride in diethyl ether. The amine hydrochloride (**4a**·HCl) usually precipitates cleanly and can be recovered by filtration.

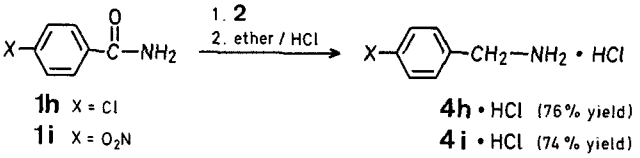
In this way *n*-octadecanamide (**1b**) was reduced to *n*-octadecanamine hydrochloride (**4b**·HCl).



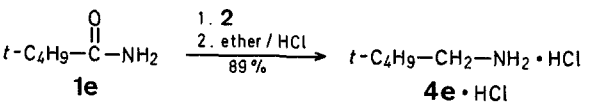
Similarly, cyclohexanecarboxamide (**1c**) was reduced to aminomethylcyclohexane (**4c**).



Aromatic amides **1h, i** are readily reduced to the benzylamine hydrochlorides **4h, i**·HCl. A considerable number of substituents are readily tolerated.



No difficulty was encountered in reducing the hindered 2,2-dimethylpropanamide (**1e**) to the corresponding amine hydrochloride **4e**·HCl.



Finally, the procedure proved satisfactory for the reduction of dimethylmalonamide (**1j**) to 2,2-dimethyl-1,3-propanediamine dihydrochloride (**4j**·HCl).

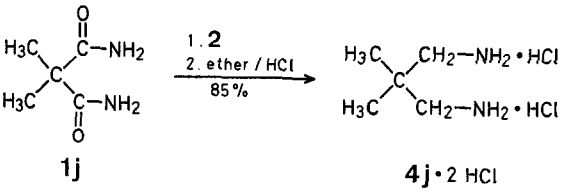


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Table. Reduction of Primary Amides **1** with Borane-Dimethyl Sulfide (**2**)

Amide No.	R	Product No.	Reaction time [h]	Procedure	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr	
						found	reported
1a	n-C_5H_{11}	**4a**·HCl	1.0	A	75	217–219°	219°[6]
1b	n-$C_{17}H_{35}$	**4b**·HCl	1.0	A	85	158–160°	162–163°[7]
1c	c-C_6H_{11}	**4c**	1.0	B	77	70–72°/30	163–165°/760[8]
1d	C_6H_5	**4d**	1.0	B	78	96–97°/15	182–185°/760[9]
1e	t-C_4H_9	**4e**·HCl	1.0	A	89	299°	275°[10]
1f	2-H_3C—C_6H_4	**4f**·HCl	2.0	A	81	218–220°	219–220°[11]
1g	2-H_3CO—C_6H_4	**4g**	2.0	B	73	125–127°/30	224°/724[12]
1h	4-Cl—C_6H_4	**4h**·HCl	1.0	A	76	256–258°	259°[13]
1i	4-O_2N—C_6H_4	**4i**·HCl	1.0	A	74	258–260° (dec)	250°[9]; >260° (dec)[2]
1j	—CO—$C(CH_3)_2$—CO—	**4j**·2HCl	2.0	A	85	260–262° (dec)	259°[14]

[a] Yield of pure, isolated product.

Two limitations should be pointed out. The presence of carbon-carbon unsaturation will lead to hydroboration. Consequently, such unsaturated derivatives cannot be reduced. The presence of readily reducible groups, such as aldehyde, ketones, carboxylic acids and esters, will involve competitive reduction. Such derivatives cannot be converted to amines without concurrent reduction. On the other hand, the presence of substituents which are not readily reduced, such as halogen, alkoxy, nitro, and sulfone, do not interfere.

2,2-Dimethylpropanamine Hydrochloride (4e·HCl) by Procedure 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 distillation head is connected to the top of the Vigreux column. A measuring cylinder is fitted to the receiver end. The outlet is connected to a gas measuring buret through a Dry Ice/acetone trap. The whole system is assembled under nitrogen. The flask is charged with 2,2-dimethylpropanamide (**1e**; 3.03 g, 30 mmol) and tetrahydrofuran (5.54 ml) and heated to reflux. Borane-dimethyl sulfide (**2**; 4.46 ml, 44 mmol) is added dropwise over a period of 20 min. Hydrogen evolved is collected and measured (49 mmol, 82% of the theoretical value). Meanwhile, the dimethyl sulfide distills off and is collected in the receiver (3.5 ml). The amount collected can be used as a convenient means of following the reaction. The reaction is also followed by hydrolyzing small aliquots (0.1 ml) using 6 normal hydrochloric acid, neutralizing with sodium hydroxide, extracting with tetrahydrofuran, and analyzing the dry organic layer by G.L.C. (8′ × 1/8″, 5% SE-30 on Varaport using a Varian 1200 chromatograph). Standard samples are used for identification by coinjection with the organic layer. The absence of any peak corresponding to the amide indicates completion of the reaction.

The reaction is complete in 1.0 h. A duplicate experiment is carried out to isolate the product. After an appropriate time interval, the flask is cooled to room temperature and methanol (5.3 ml, 132 mmol) is added dropwise. Hydrogen evolved is collected; the volume corresponds to 12.6 mmol, indicating the reaction to be almost complete. A 1.15 molar solution of dry hydrogen chloride in ether is prepared and added (26 ml, 30 mmol) dropwise. A white precipitate forms immediately. The reaction mixture is stirred for 30 min at 25 °C and 15 min at 0 °C, then filtered. The residue is washed with ether (3 × 10 ml) and dried. The crude product **4e**·HCl weighs 3.49 g: 95% yield. It is recrystallized from ethanol/ether mixture, providing the amine hydrochloride; yield: 3.30 g (89%); m.p. 299 °C [Lit.[10], m.p. 275 °C]. A small portion is neutralized with sodium hydroxide. The liberated amine is isolated and found to be identical with the standard sample: b.p. 80–82 °C [Lit.[10], b.p. 81–82 °C].

Aminomethylcyclohexane (4c) by Procedure B:
Following the above procedure, **1c** (3.81 g, 30 mmol) is reduced with borane-dimethyl sulfide (**2**; 44 mmol). After 1.0 h, 6 normal hydrochloric acid (5 ml, 30 mmol) is added dropwise and the mixture is refluxed for 15 min. The clear solution is cooled to 0 °C and sodium hydroxide (1.8 g, 45 mmol) is added. The liberated amine is extracted with ether (3 × 10 ml) and dried with anhydrous potassium carbonate. Fractional distillation gives the amine **4c**; yield: 2.61 g (77%); b.p. 70–72 °C/30 torr [Lit.[8], b.p. 163–165 °C].

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