COMMUNICATIONS

- New or improved synthetic methods
- Key intermediates
- with full experimental and analytical data

Improved Procedure for Borane-Dimethyl Sulfide Reduction of Nitriles

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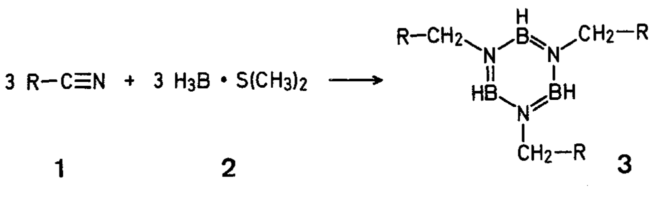
Borane reagents [diborane[1], borane-tetrahydrofuran ($BH_3 \cdot THF$)[2], and borane-dimethyl sulfide (BMS)[3]] are known to be very effective for the conversion of nitriles **1** to amines **4**. However, the reactions are often quite slow[4], especially with BMS[3]. Since borane-dimethyl sulfide **(2)** has a number of advantages over diborane and $BH_3 \cdot THF$, it is the preferred reagent[3]. We wish to describe here a simple procedure which makes it possible to reduce nitriles **1** to amines **4** with **2** rapidly, in essentially quantitative yields.

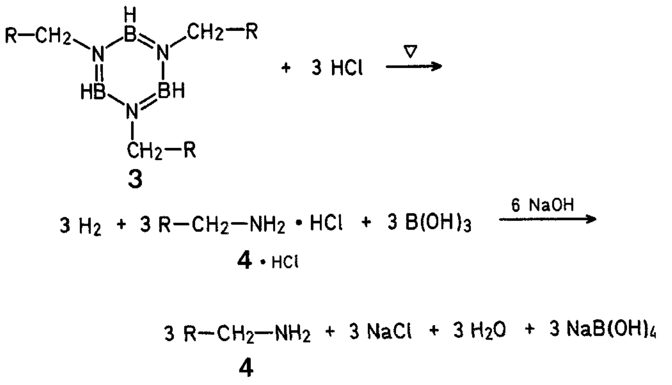
We earlier demonstrated that the distillation of dimethyl sulfide out of the reaction mixture greatly increases the rate of reduction of esters[5] and amides[6]. We examined the same procedure for the reduction of nitriles. Indeed, under these conditions, **2** rapidly reduces nitriles **1** to an intermediate, presumably the borazine derivative **3**[7].



Although nitriles should require only two hydrides for complete reduction to amines, experimentally we found that three hydrides are required, apparently because of the utilization of one hydride per nitrile in the formation of 3. This stoichiometry was established by the following experiment in which we attempted to use only two hydrides per nitrile.

Benzonitrile (**1c**; 30 mmol) in tetrahydrofuran (4.7 ml) is heated to reflux and a 10% excess of reagent **2** (2.3 ml, 22 mmol) is added. The dimethyl sulfide liberated in the course of the reaction is allowed to distill off (a total of 2.4 ml is recovered within 15 min, a quantitative recovery). The heating is continued for 5 h to insure completion of the reduction. Then a 0.5-ml aliquot is hydrolyzed with 6 normal hydrochloric acid (0.5 ml, 3 mmol), the product is neutralized with sodium hydroxide (0.25 g), and the aqueous layer is saturated with anhydrous potassium carbonate (Method A). The dry tetrahydrofuran layer, on analysis by G.L.C. (6′ × 1/8″ Carbowax-20M; Varian 1200 Chromatograph) using dodecane as the internal standard, indicates the presence of 7.0 mmol of benzonitrile. The same quantity is present when the reaction mixture is analyzed after a total of 8 h heating. However, the use of 33 mmol of **2** causes the reduction to be complete in 0.25 h, producing an essentially quantitative yield of benzylamine **(4c)**.

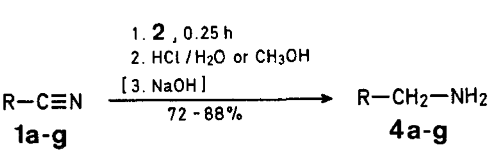
Hence, the stoichiometry of three mol of hydride per nitrile group was employed in the subsequent reduction of a variety of organic nitriles. Hydrolysis of the borazine **3** with hydrochloric acid, followed by neutralization with sodium hydroxide, produces the amine **4** in essentially quantitative yield.



An alternative procedure (Method B) for isolating the product is to treat the reaction mixture with 1 molar methanolic hydrogen chloride, reflux for 4 h, allowing methyl borate to distill off as the azeotrope (1:1) with methanol[8]. The pure amine hydrochloride is readily isolated as the product. This can be purified by recrystallization from absolute ethanol.

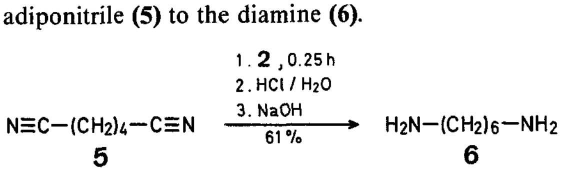
The yields of the initial products appear to be essentially quantitative by G.L.C. analysis or by weighing the initial hydrochloride. Following isolation by distillation or recrystallization, the yields of product isolated were in the range of 70 to 80%.

A number of nitriles were reduced following this general procedure. Thus, capronitrile (**1a**; $R = n\text{-}C_5H_{11}$) was reduced to *n*-hexylamine **(4a)** (Method A).



Similarly, cyclopropyl cyanide (**1b**; $R = c\text{-}C_3H_5$) was reduced to cyclopropylmethylamine hydrochloride ($\mathbf{4b} \cdot HCl$) using Method B. Aromatic nitriles **1c, h** are easily reduced to **4c, h** using Method A. Substituents on the aromatic ring, such as nitro **(1g)** and chloro **(1f)** groups are readily tolerated. Even the reduction of the relatively hindered pivalonitrile (**1d**; $R = t\text{-}C_4H_9$) was very facile (Table).

Finally, the procedure proved satisfactory for the reduction of adiponitrile **(5)** to the diamine **(6)**.



The limitations of using **2** were pointed out elsewhere[6]. Nevertheless, the present procedure affords a highly convenient method for the rapid reduction of many nitriles in the presence of relatively inert substituents, such as halogen, alkoxy, nitro, and others.

o-Xylylamine (4h; $R = 2\text{-}H_3C—C_6H_4$); Typical Procedure for Method A:

An oven-dried, 50-ml flask containing a septum capped inlet and a magnetic stirring bar is equipped with a 12″ Vigreux column. A measuring cylinder is fitted to the end of the receiver. The outlet is connected through a mercury bubbler to a source of nitrogen to maintain an inert atmosphere. The whole system is assembled under nitrogen. The flask is charged with *o*-tolunitrile (**1h**; 3.64 g, 3.55 ml, 30 mmol) and tetrahydrofuran (2.90 ml), and brought to reflux. Then borane-di-

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Table. Reduction[a] of Nitriles with Borane-Dimethyl Sulfide (**2**)

Nitrile No.	R	Product	Method	Yield [%][b]	m.p. [°C] or b.p. [°C]/torr	
					found	reported
1a	n-C_5H_{11}	**4a**	A	72	128–130°/740	128–130°/760[11]
1b	c-C_3H_5	**4b**·HCl	B	76	193–195°	200°[12,18]
1c	C_6H_5	**4c**	A	76	82–84°/17	84°/24[13]
1d	t-C_4H_9	**4d**·HCl	B	88 (98)[c]	294–296°	275°[10], 299°[6]
1e	$(C_6H_5)_2CH$	**4e**	A	(93)[c]	47–49°	39–40°[14], 48–49°[18]
1f	4-Cl—C_6H_4	**4f**	A	78	102–104°/15–20	215°/760[15]
1g	3-O_2N—C_6H_4	**4g**·HCl	B	85	220–222°	221–223°[15]
1h	2-H_3C—C_6H_4	**4h**	A	79 (96)[d]	116–117°/15–17	201°/718[9]
1i	4-H_3CO—C_6H_4	**4i**	A	61	129–130°/15–17	234–235°/724[16]
5	—	**6**	A[e]	61	37–39°	40°[17]

[a] Reaction time 0.25 h.

[b] All the products were fully characterized by ^{1}H-N.M.R. spectra. Unless otherwise stated, yields are of pure, isolated products.

[c] Crude yield.

[d] G.L.C. yield.

[e] 30 mmol of **5**, 66 mmol of **2** used.

methyl sulfide (3.55 ml, 33 mmol) is added dropwise over a period of 10 min. The dimethyl sulfide distills off and is collected in the receiver (2.4 ml, 100%). After 0.25 h, the reaction mixture is cooled to room temperature and 6 normal hydrochloric acid (18 ml, 108 mmol) is added dropwise. (Hydrogen evolved essentially immediately following each addition of acid.) The reaction mixture is then heated under reflux for 0.5 h. The clear solution is cooled to 0 °C and sodium hydroxide (4.05 g, 162 mmol) is added. (In the case of water soluble amines, the aqueous phase should be saturated with potassium carbonate.) The liberated amine is extracted with ether (3 x 10 ml) and the extract dried with anhydrous potassium carbonate. Analysis of the ether extract by G.L.C. (6′ x 1/8″, Carbowax-20M; Varian 1200 Chromatograph) using undecane as the internal standard indicates the presence of a 96% yield of o-xylylamine. In a duplicate experiment, without the internal standard, fractional distillation of the ether extract provides o-xylylamine (**4h**); yield: 2.87 g (79%); b.p. 116–117 °C/15–17 torr [Lit.[9], 201 °C/718 torr].

Neopentylamine Hydrochloride (4d·HCl); Typical Procedure for Method B:

Following the above procedure, pivalonitrile (**1d**; 2.46 g, 3.32 ml, 30 mmol) is reduced with borane-dimethyl sulfide (**2**; 3.55 ml, 33 mmol). After 0.25 h, the flask is cooled to room temperature and 1.0 molar methanolic hydrogen chloride (31 ml, 31 mmol) is carefully added over 10 min. Vigorous evolution of hydrogen occurs. The solution is heated to reflux, allowing the methyl borate to distill off as a 1 : 1 azeotrope with methanol. After 4 h, when all of the solvent has distilled off, methanol (10 ml) is added and removed under suction to insure complete removal of boric acid residues. The resulting solid weighs 3.675 g, a 98% yield of amine hydrochloride: m.p. 289–291 °C [Lit.[10], 275 °C; Lit.[6], 299 °C]. The solid is dissolved in absolute ethanol (10 ml), cooled to 0 °C, and ether (50 ml) added. The precipitate is filtered, dried and weighed to give pure neopentylamine hydrochloride (**4d**·HCl); yield: 3.32 g (88%); m.p. 294–296 °C.

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