

Novel Borane–Selenium Complex: Highly Selective Reduction of Tertiary Amides and Nitriles to the Corresponding Amines with Sodium Borohydride–Dialkylselenium Dibromide

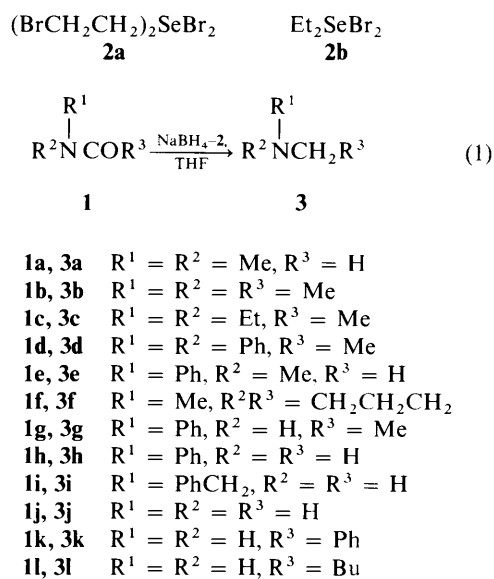
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The reaction of sodium borohydride with bis(2-bromoethyl)selenium dibromide and/or diethylselenium dibromide in tetrahydrofuran (THF) gave borane. Treatment of tertiary amides with mixtures of sodium borohydride and either of the dibromides in THF gave the corresponding amines. Similar reactions with secondary and primary amides did not proceed. Furthermore, under similar reduction conditions, the reaction of nitriles with the above reagents also gave the corresponding primary amines.

The preparation of amines from amides is one of the most important reactions in medicinal and industrial chemistry, and the reduction of amides with borane reagents has been widely studied.¹ Primary, secondary and tertiary amides are reduced rapidly with BH_3 –THF reagent.² Various other metal hydride reagents are known³ to reduce amides to amines, but lithium aluminium hydride is probably the most widely used alternative to the borane reagents. For example, the reduction of tertiary amides with LiAlH_4 under ordinary conditions, *i.e.*, with an excess of the reducing agent present, usually produces the corresponding tertiary amines.⁴ However, in some cases reductive cleavage to an alcohol and a secondary amine has been observed.^{5,6} The reduction of secondary amides⁶ with LiAlH_4 gives the corresponding amines, while primary amides⁷ are reduced to the corresponding amines *via* the nitriles in moderate to high yield. Furthermore, the reduction of tertiary amides with LiAlH_4 in the presence of a phase-transfer catalyst in non-polar solvents gives the corresponding amines.⁸ Although the amides are not generally reduced with sodium borohydride which is a mild reducing agent,⁹ they are reduced with a combination of NaBH_4 and pyridine.^{9,10} In this reaction the tertiary and primary amides are smoothly converted into the corresponding amines and nitriles, respectively, while the secondary amides are not affected. In addition, the combination of NaBH_4 with TiCl_4 ,¹¹ CoCl_2 ,¹² or SnCl_4 ¹³ has been successfully applied to the conversion of amides into the corresponding amines. Furthermore, the Vilsmeier complexes of tertiary and secondary amides can be reduced with NaBH_4 in high yield.^{14,15} As described above, many reagents can reduce tertiary, secondary, and primary amides without selectivity. Borane reagents (borane–diethyl ether,¹⁶ borane–THF,¹⁶ borane–dimethyl sulphide,¹⁷ and tetrabutylammonium borohydride¹⁸) are known to be very effective in converting nitriles into amines. Furthermore, it is also reported that the reaction of nitriles with NaBH_4 –transition metal halides gave the corresponding amines.¹⁹ We report here a new procedure for the highly selective reduction of tertiary amides to amines with NaBH_4 –bis(2-bromoethyl)selenium dibromide **2a** and/or NaBH_4 –diethylselenium dibromide **2b** as the reducing agent in THF.²⁰

The reaction was carried out as follows. Treatment of a suspension of NaBH_4 (5 mmol) in THF (50 cm^3) with tertiary amides **1a–1f** (1 mmol) and reagent **2a**²¹ (1 mmol) at room temperature afforded the corresponding amines **3a–3f** in moderate to high yield [equation (1)] (Table 1). At higher temperatures (reflux in THF), this reaction proceeded more smoothly and was complete in a short time. However, reduction of secondary and primary amides (**1g–1i** and **1j–1l**) with



reagents **2** and NaBH_4 in THF did not proceed and the starting amides were recovered quantitatively. Furthermore, under similar reaction conditions, the reduction of tertiary, secondary, and primary amides (**1a–1f**, **1g–1i**, and **1j–1l**) with NaBH_4 in the absence of reagent **2a** did not proceed and the starting materials (**1a–1l** excepting **1e**) were recovered as described below. Furthermore, under similar reaction conditions, the reduction of tertiary amides **1a–1f** with NaBH_4 in the presence of diethylselenium dibromide **2b** in THF gave the corresponding amines **3a–3f** in moderate to high yield, while primary and secondary amides were not reduced and the starting materials were recovered quantitatively. The results were very similar to those in the case of reduction using NaBH_4 –**2a** as the reducing agent. These previous results suggested that the combination of NaBH_4 with the dibromides **2a** and/or **2b** can be used as a highly selective reducing agent for reduction of tertiary amides to the corresponding amines. The reduction of amides with NaBH_4 in refluxing pyridine²² and with borohydride anion in acidic dimethyl sulphoxide²³ proceeded more rapidly than with our method. This may be attributed to the low solubility of NaBH_4 in THF.³ Therefore, we have applied the NaBH_4 –**2a** reduction method in the presence of 18-crown-6 as a phase-transfer catalyst to the tertiary amides **1a** and **1e**. However, the results were similar to those already described. In order to obtain good reaction conditions we attempted the reduction of

Table 1 Reduction of amides with NaBH₄-bis-(2-bromoethyl)selenium dibromide **2a** and/or diethylselenium dibromide **2b** in THF^a

Compd.	Method ^a	Reaction temp (T/°C)	Reaction time (t/h)	Product yield(%)	M.p. or B.p. (°C) (lit./°C)
1a	A	65	4	3a 82 ^c	79.0–80.0 (82–84) ^{f,31}
	B	65	4	3a 82 ^c	
	A	25	50	3a 72 ^c	
1b	B	25	50	3a 70 ^c	215–217 (221–222) ³²
	A	65	50	3b 90 ^c	
	B	65	50	3b 92 ^c	
1c	A	25	50	3b 65 ^c	249–251 (253–254) ³²
	B	25	50	3b 65 ^c	
	A	65	50	3c 40 ^c	
1d	B	65	50	3c 75 ^c	150–152/14 mmHg ^g (295–297) ³²
	A	25	50	3c 5 ^c	
	B	25	50	3c 19 ^c	
1e	A	65	8	3d 89 ^d	80–83/14 mmHg ^g (192–194) ³⁰
	B	65	8	3d 90 ^d	
	A	25	4	3d 0 ^d	
1f	B	25	80	3d 59 ^d	76–79 (80–81) ³²
	A	65	12	3e 90 ^d	
	B	65	20	3e 91 ^d	
1e	A	25	80	3e 88 ^d	76–79 (80–81) ³²
	B	25	80	3e 73 ^d	
	A	65	50	3f 73 ^c	
1f	B	65	50	3f 70 ^c	76–79 (80–81) ³²
	A	25	50	3f 0 ^c	
	B	25	50	3f 3 ^c	

^a Amide (1.0 mol equiv.), NaBH₄ (5.0 mol equiv.), and reagent **2** (1.0 mol equiv.) (Method A: **2a**, Method B: **2b**) were used. ^b Products were identified by: (i) comparison of spectral data (IR, ¹H NMR, mass) with literature data, and (ii) in most cases, by the addition of authentic material upon HPLC analysis. ^c Isolated yield. ^d Determined by HPLC. ^e Determined by GLC. ^f As BH₃ complex. ^g Boiling points.

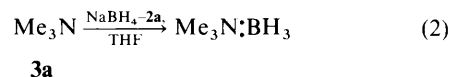
Table 2 Reduction of *N*-methylformanilide **1e** with NaBH₄ and/or NaBH₄-**2a** in THF^a

Reagents	Products and recovered starting materials (%) ^b		
	3e	3h	1e (recovered)
1e :NaBH ₄ : 2a			
1:5:0	0	79	21
1:5: $\frac{1}{8}$	66	15	17
1:5: $\frac{1}{2}$	90	3	1
1:5:1	91	7	1

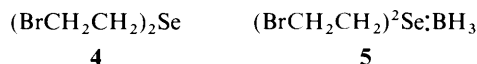
^a Reaction was carried out at 65 °C for 20 h in THF. ^b Determined by HPLC.

amides, which show high polarity, using them as both substrates and solvents. The reduction of substrates **1a**, **1b**, and **1e** with NaBH₄-**2a** at room temperature for 4 h gave the corresponding tertiary amines (**3a**, **3b**, and **3e**) in 55, 36, and 87% yield, respectively. The above reaction proceeded more quickly compared with those in THF as solvent. This suggested that the solubility of NaBH₄ in solvent plays an important role. It is well known that sodium borohydride cannot reduce an amide group³ to the corresponding amino group, although a tertiary amide can be reduced with borane to the corresponding tertiary amine more easily than to secondary and primary amines.²⁴ Therefore, in order to compare the reduction ability of sodium borohydride with that of our reducing agents, the reactivities of amide, reagent **2a**, and sodium borohydride at various molar proportions were investigated. As shown in Table 2, the reduction of *N*-methylformanilide **1e** with sodium borohydride gave the reductive cleavage product, *N*-methylaniline **3h**, in 79% yield together with 21% of the recovered starting material. However, use of 1:5:1 molar proportions (amide:NaBH₄:**2a**) afforded the highest yield of the corresponding amine (**3e**) together with a small amount (7%) of *N*-methylaniline **3h**. These results suggested that the combination of NaBH₄-**2a** generates a new type of reducing agent. To examine the active species of this reduction, we investigated the reaction of NaBH₄ (30

mmol) with the dibromide **2a** (6 mmol) in the presence of trimethylamine in THF (50 cm³) at room temperature [equation (2)]. This reaction gave a complex (**3a**-BH₃) of



trimethylamine with borane in 70% yield. Freeguard *et al.*²⁵ reported that the reaction of NaBH₄ with iodine in diglyme gives diborane in excellent yield. Therefore, we attempted the reaction of NaBH₄ with bromine. The reaction of NaBH₄ with bromine in the presence of trimethylamine gave a borane complex (**3a**-BH₃) of trimethylamine in 30% yield. Therefore, the reaction of NaBH₄ with reagent **2a** may produce borane and bis(2-bromoethyl) selenide **4**. The borane complex **5** would



probably then be formed in an analogous way to the reaction between borane and dimethyl sulphide (Me₂S) **6**.¹⁷ The formation of complex **5** as a reducing agent was confirmed by the reduction of the amides with borane in the presence of diethyl selenide. For example, reduction of the tertiary amide **1e** with borane in the presence of diethyl selenide **6** in THF produced the corresponding tertiary amine **3e** in 86% yield, although similar reductions of secondary and primary amides (**1i** and **1k**) gave no products and the starting materials were recovered. Our selective reduction of tertiary amides to amines may be due to the difference in the reducing ability of compounds **5** and **6**-BH₃²⁶ which can reduce the amides with no selectivity, and/or BH₃-THF,^{2,27} because the combination of NaBH₄ with reagents **2a** and/or **2b** can selectively reduce tertiary amides. Furthermore, the reaction of tertiary, secondary, and primary amides with a combination of NaBH₄ and diethyl selenide gave no products and the starting materials were quantitatively recovered. In the present reduction, part or

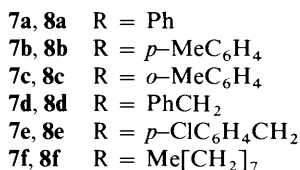
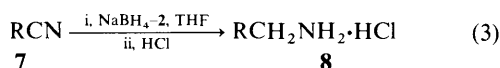
Table 3 Reduction of nitriles to amines with NaBH₄-bis(2-bromoethyl)selenium dibromide **2a** and/or NaBH₄-diethylselenium dibromide **2b** in THF^a

Compd.	Method ^a	Reaction time (t/h)	Product and yield (%) ^b	M.p. or B.p. (°C) (lit./°C)
7a	A	16	8a 72 ^c	246–248 (253) ³⁰
	B	16	8a 60 ^c	
7b	A	16	8b 53 ^c	232–234 (234.5–235.0) ³²
	B	16	8b 55 ^c	
7c	A	16	8c 35 ^c	219–220 (219–220) ³²
	B	16	8c 23 ^c	
7d	A	16	8d 42 ^c	216–218 (217) ³⁰
	B	16	8d 50 ^c	
7e	A	100	8e 44 ^c	258–260 (261–263) ³³
	B	100	8e 42 ^c	
7f	A	84	8f 60	100–103/15 mmHg ^d (201) ³²
	B	84	8f 31	

^a Nitrile (1.0 mol equiv.), NaBH₄ (5.0 mol equiv.), and reagent **2** (1.0 mol equiv.) (Method A: **2a**, Method B: **2b**) were used. ^b Isolated yield. ^c The amines were isolated as their HCl salts. ^d Boiling point.

all of the dialkylselenium dibromide of type **2** probably plays an important role, although the mechanism of the reaction is not yet fully understood. Although attempted isolation of the complex **5** was carried out, we were unfortunately not able to obtain any of this complex despite much effort.

Successive treatment of several kinds of nitrile **7** with a mixture of NaBH₄-**2a** in boiling THF leads to the corresponding primary amines **8** [equation (3)] (Table 3). For



example, treatment of benzonitrile **7a** with a mixture of NaBH₄-**2a** in THF for 16 h affords benzylamine **8a** in 72% yield. NaBH₄-**2a** was a satisfactory reducing agent for nitriles though the yields were not quite as high as those obtained with the zirconium tetrachloride-NaBH₄ reagent.²⁸ The utility of NaBH₄-**2a** for reduction of nitriles was further evidenced by the successful selective reduction of the nitrile function in the presence of nitro and ester groups. The reaction of benzonitrile **7a** with NaBH₄-**2a** in the presence of nitrobenzene in THF gave benzylamine **8a** in 70% yield, and 98% of the unchanged nitrobenzene was recovered. Similar reaction of benzonitrile **7a** in the presence of ethyl benzoate gave benzylamine **8a** in 68% yield together with 100% recovery of the unchanged ethyl benzoate. These results suggested that use of reagents NaBH₄-**2** which, unlike NaBH₄-CoCl₂¹² and BH₃-THF,²⁹ are mild and selective reducing agents, permits the presence of many other substituents which are less susceptible to its reducing action compared with the use of the other two reagents.

Experimental

M.p.s were recorded with a Yazawa micro m.p. apparatus and are uncorrected. ¹H NMR spectra were determined with a Hitachi R-60 spectrometer for solutions in CDCl₃ with tetramethylsilane as internal standard. High-performance liquid chromatography (HPLC) was carried out on a JASCO HPLC system with a Sil.C18-5 column monitored by UV absorption measurements. Gas chromatography was performed on a

Shimadzu G.C-8APF gas chromatograph with a PEG20M (2.0%) 2 m stainless steel column. All compounds purchased from commercial sources were used without further purification, and all solvents were purified by distillation in the usual manner.

General Procedure for the Reduction of Amides.—A suspension of *N*-methylformanilide **1e** (1.62 g, 12 mmol), the dibromide **2a** (5.4 g, 12 mmol), and sodium borohydride (2.28 g, 60 mmol) in THF (50 cm³) was stirred at room temperature for 80 h, and diluted with water (30 cm³). The aq. solution was extracted with diethyl ether. The extract was dried (MgSO₄) and concentrated. The resulting residue was distilled at reduced pressure to afford the corresponding amine **3e** in 83% yield. B.p. 80–83 °C/14 mmHg (lit.,³⁰ m.p. 192–194 °C).

Reduction of Amides 1e, 1i and 1k with a Mixture of Diethyl Selenide and Borane in THF.—To a solution of diethyl selenide (2.06 g, 15 mmol) in THF (20 cm³) was added a THF solution (7.5 cm³) of borane (103.8 mg, 7.5 mmol). After the mixture had been stirred under reflux for 2 h, *N*-methylformanilide **1e** (676 mg, 5 mmol) was quickly added and the mixture was refluxed and stirred for an additional 20 h. The yield of the product was determined by HPLC with an internal standard. The yield of product **3e** was 86%.

The reduction of compounds **1i** and **1k** was carried out similarly (reaction time 80 h). However, the reduction products (**3i** and **3k**) could not be obtained and the starting materials were recovered in quantitative yield.

General Procedure for the Reduction of Nitriles.—A suspension of benzonitrile **7a** (2.0 g, 20 mmol), the dibromide **2a** (9.0 g, 20 mmol), and sodium borohydride (3.8 g, 100 mmol) in THF (50 cm³) was refluxed for 16 h, and then diluted with water (50 cm³). The aq. solution was extracted with diethyl ether. The extract was concentrated and the resulting residue was acidified with 6 mol dm⁻³ HCl (20 cm³) and then stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure and the resulting precipitate was recrystallized from ethanol to give the corresponding amine **8a** as the HCl salt in 72% yield, m.p. 246–248 °C (lit.,³⁰ 253 °C).

Reduction of N-Methylformanilide 1e with Sodium Borohydride.—A suspension of *N*-methylformanilide **1e** (1.35 g, 10 mmol) and sodium borohydride (1.92 g, 50 mmol) in THF (50 cm³) was heated under reflux for 10 h. The reaction mixture was then cooled to room temperature and diluted with water (20 cm³). The aq. solution was extracted with diethyl ether and the extract was dried (MgSO₄), and then concentrated under

reduced pressure to afford *N*-methylaniline **3h** in 79% yield, b.p. 87–90 °C/14 mmHg (lit.,³⁰ m.p. 196 °C).

General Procedure for Selective Reduction of Nitriles with Reagent NaBH₄-2a.—A suspension of benzonitrile **7a** (516 mg, 5 mmol), nitrobenzene (615 mg, 5 mmol) and/or ethyl benzoate (750 mg, 5 mmol), the dibromide **2a** (2.25 mg, 5 mmol), and sodium borohydride (945 mg, 25 mmol) in THF (50 cm³) was refluxed for 20 h, and diluted with water (20 cm³). The aq. solution was extracted with diethyl ether. The yields of the products and recovered starting materials were determined by HPLC with the appropriate internal standards. The products and recovered starting materials were isolated from the reaction mixture by distillation.

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