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A Novel Highly Selective Reduction of Tertiary Amides to Amines with Sodium Borohydride-Bis(2-bromoethyl)selenium Dibromide

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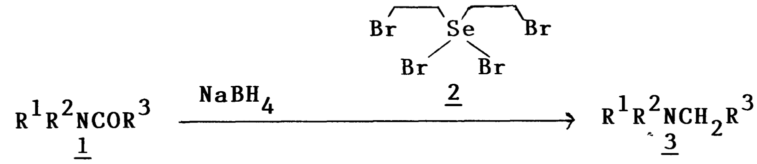
Treatment of tertiary amides with sodium borohydride-bis(2--bromoethyl)selenium dibromide in THF gave the corresponding amines, although the similar reactions of secondary and primary amides could not proceeded.

Numerous chemicals of interest and importance in medicinal chemistry have been prepared through an amide reduction with borane reagent.[1] Primary, secondary and tertiary amides are reduced rapidly with BH_3-tetrahydrofuran (THF) reagents[2]. Various other metal hydride reagents are known[3] to reduce amides to amines, but lithium aluminum hydride ($LiAlH_4$) is probably the most widely used alternative to the borane reagents. Although the amides are not generally reduced with sodium borohydride which is a mild reducing agent,[4] they are reduced to the corresponding amines using a combination of sodium borohydride and pyridine as the reducing agent.[4,5] As described above many reagents can reduce the tert-, sec-, and primary amides without selectivity. We report here a new procedure for the highly selective reduction of tertiary amides to amines with sodium borohydride-bis(2-bromoethyl)selenium dibromide (**2**) as the reducing agent.

The reaction was carried out as follows. Treatment of a suspension of sodium borohydride (5 mmol) in THF (50 ml) with tertiary amides (**1a**-**1f**) (1 mmol) and **2**[6] (1 mmol) at room temperature afforded the corresponding amines (**3a**-**3f**) in moderate to high yields (Table 1). At a higher temperature (reflux in THF), this reaction proceeded more smoothly and was completed in a short period.



$$\underset{\underline{1}}{R^1R^2NCOR^3} \xrightarrow[]{NaBH_4 \quad \underline{2}} \underset{\underline{3}}{R^1R^2NCH_2R^3}$$

However, reduction of secondary and primary amides with **2** and $NaBH_4$ in THF did not proceed and the starting amides were recovered in quantitative yields, respectively. Furthermore, under similar reaction conditions, the reduction of tertiary amides with $NaBH_4$ in the absence of **2** did not proceed and the starting materials were recovered. These results suggest that the combination of $NaBH_4$ and **2** can be used as a highly selective reducing agent for reduction of tertiary amides to the corresponding amines.

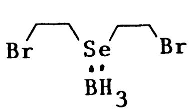
To examine the active species of this reduction, we investigated the

Table 1. Reduction of amides with $NaBH_4$-bis(2-bromoethyl)selenium dibromide in THF a)

Compd	R^1	R^2	R^3	Reaction temp/°C	Reaction time/h	Products b) Yields/% c)
1a	Me	Me	H	65	4	(3a) 82
				25	50	(3a) 73
1b	Et	Et	Me	65	50	(3b) 70
				25	50	(3b) 68
1c	Me	Me	Me	65	50	(3c) 35
1d	Ph	Ph	Me	65	8	(3d) 89 d)
1e	Ph	Me	H	65	12	(3e) 90 d)
				25	80	(3e) 88 d)
1f	Me	$-CH_2CH_2CH_2-$		65	50	(3f) 69

a) Amides(1.0 equiv.), $NaBH_4$(5.0 equiv.), and 2(1.0 equiv.) were used.
b) Products were identified by: (1) comparison of spectral data [ir,^{1}H nmr, mass] with literature data and (2) in most cases, by the addition of authentic materials upon HPLC analysis. c) Isolated yields. d) Determined by HPLC.

reaction of $NaBH_4$ (30 mmol) with **2** (6 mmol) in the presence of trimethylamine in THF (50 ml) at room temperature. The above reaction gave a complex (**4**) of trimethylamine with borane in 70% yield. The reaction of $NaBH_4$ with **2** may produce borane and bis(2-bromoethyl)selenide (**5**). Then the borane complex (**6**) would probably be formed, because it has previously been reported7) that the reaction of dimethyl sulfide with borane gives the 1:1 complex (CH_3SCH_3-BH_3) (**7**) which can reduce uniformly the primary, secondary, and tertiary amides to the corresponding amines. Such a selective reduction of tertiary amides to amines may be due to the difference in the reducing factor between **6** and **7**7) and/or BH_3-THF,2,8) because the combination of $NaBH_4$ with **2** can reduce the tertiary amines selectively.



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Furthermore, under similar reaction conditions the reaction of **1a** and **1e** with $NaBH_4$ in the presence of diethyl selenium dibromide ($(CH_3CH_2)_2SeBr_2$) in THF also give the corresponding amines (**3a** and **3e**) in 70 and 91% yields, respectively. Therefore, in the present reduction the part of dialkyl selenium dibromide of **2** probably plays an important role.

References

1) C. F. Lane, Chem Rev., 76, 773 (1976).
2) H. C. Brown and P. Heim, J. Am. Chem. Soc., 86, 3566 (1964).
3) A. Pelter, K. Smith, and H. C. Brown, "Boron Reagents," Academic Press, London (1988).
4) Y. Kikugawa, S. Ikegami, and S. Yamada, Chem. Pharm. Bull., 17, 98.(1969).
5) S. Yamada, Y. Kikugawa, and S. Ikegami, Chem. Pharm. Bull., 13, 394 (1965).
6) H. C. Bell and C. S. Gibson, J. Chem. Soc., 127, 1877 (1925).
7) H. C. Brown, S. Narasimhan, and M. Choi, Synthesis, 1981, 441, 996.
8) R. C. Northrop and P. L. Russ, J. Org. Chem., 42, 4148 (1977).

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