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Effect of the Temperature on the Stoichiometry of Borane Dimethyl Sulfide Reduction of Secondary and Tertiary Amides

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EFFECT OF THE TEMPERATURE ON THE STOICHIOMETRY OF BORANE DIMETHYL SULFIDE REDUCTION OF SECONDARY AND TERTIARY AMIDES

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Abstract : A simple procedure has been described for the reduction of secondary and tertiary amides to amines using borane-dimethyl sulfide in the pretical amounts.

Numerous chemicals of interest and importance in chemistry have been preparated through an amide reduction with a borane reagent (1).

Borane-tetrahydrofuran (2) and borane-dimethyl sulfide (3) have proven to be the reagents of choice for most reductions of carboxylic amides to amines.

Primary amides are reduced to primary amines by borane-dimethyl sulfide (BMS) used in theoretical amounts (3,4)

(1)
$$\operatorname{RCONH}_2$$
 + 4/3 BH₃. $\operatorname{S(CH}_3)_2 \xrightarrow{\text{THF}} \operatorname{R-CH}_2 \cdot \operatorname{N(B}_2)_2 \xrightarrow{\text{H}_2 \circ} \operatorname{R-CH}_2 \operatorname{NH}_2$
1 2 3 4

In the same conditions, the amine-borane adducts $\underline{7}$ and $\underline{11}$ corresponding to secondary and tertiary amides are inert towards further hydride transfer reaction. Hence for the complete reduction, six or five equiv. of hydride (H-B) was needed to reduce secondary or tertiary amides respectively (eq 2 and 3).

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(2)

$$RCONHR' \xrightarrow{H_{3}B-S(CH_{3})_{2}} R-CH_{2}-NR'-B \xrightarrow{H_{3}B-S(CH_{3})_{2}} 5$$

$$\frac{5}{6}$$

$$R-CH_{2}-NR'-B \xrightarrow{.BH_{3}} \xrightarrow{H_{2}O} R-CH_{2}NHR'$$

$$\frac{7}{2} \qquad \underline{8}$$

$$\begin{array}{c|c} \text{RCONR'R"} & \frac{2/3 \text{ H}_3\text{B-S(CH}_3)_2}{\text{M}_3\text{B-S(CH}_3)_2} \rightarrow \text{RCH}_2\text{-NR'R"} & \frac{\text{H}_3\text{B-S(CH}_3)_2}{\text{M}_3\text{B-S(CH}_3)_2} \rightarrow \\ \hline (3) & 9 & 10 \\ \text{R-CH}_2\text{NR'R"}.\text{BH}_3 & \frac{\text{H}_2\text{O}}{\text{M}_3\text{CH}_2\text{NR'R"}} \\ \hline 11 & 12 \end{array}$$

To use reduced amounts of BMS in the reduction of these amides, Brown et al. (3,5) described a method in which BMS is used for reduction purposes and boron trifluoride etherate for the complexation with <u>6</u> or <u>10</u>.

In the course of studying the stability of the amine-borane adduct, we discovered that the stoichiometry of the reduction of secondary and tertiary amides is largely dependent on the temperature.

In refluxing toluene we observe that amides do not require an additional mole of BMS for the complexation, thus :

- secondary amides are reduced with one mole of BMS,

- tertiary amides need only two equivalents of hydride (2/3 mole of BMS).

The above stoichiometry is dependent on the temperature and not the solvent. If we decrease the temperature of toluene to $65-70^\circ$, we observe only partial reduction of amides as in the case of reduction in THF. On the other hand the reduction in dibutyl ether at 115-120° gave a high yield of amine (90% for the transformation <u>9d-12d</u>).

Finally N - acetyl p - acetoxy aniline was examined to test the utility of this procedure for selective reduction. The amine - ester was obtained in 95 % yield, confirming the value of this procedure for selective reduction.

$$CH_3CO_2 \longrightarrow NHCOCH_3 \longrightarrow CH_3CO_2 \longrightarrow OHCH_2CH_3$$

From a practical point of view, our procedure offers two advantages : - distillation from the reaction mixture of dimethyl - sulfide is not necessary, - there is no need for final decomplexation of amine-borane complex.

The results are summarized in table :

Table - Reduction of secondary and tertiary amides with borane-dimethyl sulfide in toluene.

R-CONR'R" → R-CH₂NR'R"

Amide	R	R'	R"	Reaction time (h)	Yield ^a (%)
<u>5a</u>	CH3	C6H5	Н	2	87
b	C ₂ H ₅	C6H5	н	4	80
с	C6H5	C6H5	н	2	97
d	4-02N-C6H4	cyclohexyl	Н	2	82
e	2-Cl-C6H5	n-C4H9	Н	2	81
<u>9a</u>	CH3	C2H5	CH2-C6H5	4b	78
b	C ₂ H ₅	i-C3H7	i-C3H7	2	80 ^c
c	C ₆ H ₅	C ₂ H ₅	C ₂ H ₅	4b	85
d	C ₆ H ₅	C ₂ H ₅	CH2-C6H5	2	93
e	C6H5	CH2-C6H5	CH2-C6H5	2	83

a : yields represent pure isolated products. All of the products were fully characterised by ${}^{1}H$ NMR spectra and physical constants (bp/mp).

b: complete reduction (100%) required 12h.

c: this amine was isolated by extraction of the toluene solution with hydrochloric acid.

General Procedure :

Borane-dimethylsulfide (10,5 mM, 1,05 mL, 5% excess) was added dropwise under nitrogen at 0°C to a stirred suspension (or solution) of amide (10 mM for 5, 15 mM for 9) in toluene (10 mL).

The reaction mixture was stirred at 0°C for 15 min. and then was refluxed. After 2-4h, the flask was cooled at room temperature, 15mL of 10% aqueous sodium carbonate was added and the reaction mixture was stirred at 20°C (100°C in the case of compounds <u>9a</u> and <u>9c</u>) for 30 min. The toluene layer was separated and dried (sodium sulfate), and the solvent was evaporated. The crude amine was distilled with a Kugelrohr apparatus.

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