SODIUM BOROHYDRIDE IN REDUCTIVE AMINATION REACTIONS

A. V. Panfilov,¹ Yu. D. Markovich,¹ I. P. Ivashev,¹ A. A. Zhirov,¹ A. F. Eleev,¹ V. K. Kurochkin,¹ A. T. Kirsanov,¹ and G. V. Nazarov¹

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 34, No. 2, pp. 32 - 33, February, 2000.

Original article submitted June 25, 1998.

Among a variety of methods developed for the synthesis of substituted amines from carbonyl-containing compounds, a promising approach is that based on the reductive amination (hydroamination) reaction. The set of available complex borohydrides used in this process is restricted to several compounds such as sodium cyanoborohydride and sodium or lithium triacetoxyborohydrides [1-3]. It was established that reactions involving these compounds include several stages. A Schiff base, formed from a carbonyl compound and amine in the first stage, is subsequently reduced under the action of sodium triacetoxy- or cyanoborohydride.

The maximum yields of target amines were observed in the reaction media with pH 3 - 4, under which conditions the carbonyl group is not reduced, whereas the azomethine bond is reduced at a sufficiently high rate [2].

In this work, we have established that the salts of primary or secondary amines and inorganic acids react with aldehydes and ketones in the presence of sodium borohydride to form the corresponding secondary and tertiary amines with a 10 - 80% yield.

As is known, the interaction of equimolar amounts of the ammonium salts of inorganic acids with sodium or lithium borohydrides leads to the formation of borane – amine complexes used as reducing agents in the synthesis of alcohols from carbonyl compounds [2]. The borane – amine complexation is a two-stage process, including the stage of ammonium borohydride formation [2, 4] followed by their decomposition to borane amines.

$$R - NH_2 \cdot HX + NaBH_4 - (R - NH_3)BH_4 + NaX$$
$$R - NH_3)BH_4 - R - NH_2 : BH_3 + H_2$$
$$X = F_2 \cdot CI_2 \cdot HSO_4^2.$$

In our opinion, it is this ammonium borohydride formed *in situ* in the first stage that enters the reductive amination reaction

$$R^{1} = O + (R - NH_{3})BH_{4} \xrightarrow{R^{1}} CH - NH - R$$

This conclusion is confirmed by the fact that adding phenylammonium borohydride solution (prepared preliminarily from aniline hydrochloride and sodium borohydride in isopropyl alcohol) in portions at equal time intervals to cyclohexanone leads to a decrease in the amount of cyclohexylaniline and an increase in the proportion of cyclohexanol (due to the borane aniline accumulation in solution). Another experimental fact is that borane bubbling through a mixture of cyclohexanone and aniline in isopropanol leads to the formation of cyclohexanol.

We have studied the reactions of reductive amination in the following media: waster, methanol, ethanol, 2-propanol, and DMF. The yields of substituted amines were 50 - 80%for the reactions in DMF and isopropanol, and 10 - 30% for methanol and ethanol. In water, the amination reaction does not proceed and the carbonyl compounds are reduced to alcohols. Other reagents were ammonium iodide, sulfates and hydrochlorides of primary and secondary amines, and aliphatic, cyclic, and aromatic aldehydes and ketones. The results of our experiments are summarized in Table 1. As seen from the data presented, the maximum yields of substituted amines were obtained using cyclic and heterocyclic ketones and aniline salts.

Table 2 illustrates the effect of the amount of acid and sodium borohydride on the yield of cyclohexanone and aniline reaction products for the equimolar reagent ratio in isopropyl alcohol. As seen from these data, the reaction involves 1 mole of sodium borohydride per mole aniline. The amount of mineral acid necessary to provide for the maximum yield is about 1 - 3 g-eq.

Thus, we have demonstrated that the interaction of carbonyl compounds, inorganic salts of primary and secondary amines, and sodium borohydride yields the corresponding substituted amines.

¹ State Institute of Organic Chemistry and Technology, Federal Scientific Center, Moscow, Russia.

Carbonul compound	A	Yield, %	
Carbonyi compound	Ammonum sait	substituted amine	alcohol
CH ₃ (CH ₂) ₃ C(O)H	$PhNH_2 \cdot (1/2)H_2SO_4$	CH ₃ (CH ₂) ₃ CH ₂ NH-Ph, 30	
(CH ₃) ₂ C=O	$PhNH_2 \cdot (1/2)H_2SO_4$	(CH ₃) ₂ CHNH-Ph, 50	
CH ₃ N =0	$PhNH_2 \cdot (1/2)H_2SO_4$	CH ₃ NNH-Ph, 80	10
	$PhNH_2 \cdot H_2SO_4$	NH-Ph, 80	10
────────────────────────────────────	$Ph_2NH \cdot (1/2)H_2SO_4$	_	80
C ₆ H ₅ C(O)CH ₃	PhNH ₂ · HCl	С ₆ H ₅ СНNH—Рh, 55 СН ₃	35
○ =0	CH ₃ NH ₂ · HCl	NHCH ₃ , 45	40
	$(C_2H_5)_2$ NH · HCl	\bigvee N(C ₂ H ₅) ₂ , 40	50
C ₆ H ₅ C(O)CH ₃	NH ₃ · HI	C_6H_5 CHNH ₂ , 20 CH ₃	70
C ₆ H ₅ C(O)CH ₃	CH ₃ NH ₂ · HCl	C ₆ H ₅ CHNHCH ₃ , 45	40
(CH ₃) ₂ C=O	$(C_2H_5)_2NH \cdot H_2SO_4$	(CH ₃) ₂ CHN(C ₂ H ₅) ₂ , 20	•••
C ₆ H ₅ C(O)H	$PhNH_2 \cdot H_2SO_4$	C ₆ H ₅ CH ₂ NH-Ph, 50	40

TABLE 1. Yields of Substituted Amines and Alcohols upon Interaction of Carbonyl Compounds, Ammonium Salts, and Sodium Borohydride in Equimolar Amounts in Isopropyl Alcohol

The experimental data indicate that the reaction of reductive amination involves substituted ammonium borohydrides formed *in situ*, such as $RNH_3 \cdot BH_4$ and $R_2NH_2 \cdot BH_4$.

EXPERIMENTAL PART

Data on the proposed structures of the target amines are presented in Table 1. The purity of reaction products was checked and the course of reactions was monitored by TLC on a CAMAG TLC-Scanner chromatograph system using Merck Kieselgel 60 F_{254} plates. The IR absorption spectra were measured on a Perkin-Elmer Model 577 spectrophotometer using thin-film samples. The IR spectra of secondary amines showed an absorption band in the region of 3300 – 3500 cm⁻¹.

Typical synthesis of substituted amines from carbonyl compounds and inorganic salts of ammonium and primary or secondary amines. To a solution of amine (1 mole) in anhydrous isopropyl alcohol was added with stirring and

TABLE 2. Yields of Cyclohexylaniline and Cyclohexanol Depending on the Amount of Mineral Acid

cooling 2 g-eq. of a mineral acid (or an equivalent amount of

preliminarily synthesized ammonium salt) and 1 mole of a carbonyl compound. To this mixture was added in portions at

Acid, g-eq. per mole aniline	Sodium borohydride, mole per mole aniline	Yield, %	
		cyclohexyl- aniline	cyclohexanol
HCI, 1	0.5	35	2
HCl, I	1.0	70	10
HCI, 1	1.5	70	10
HC1, 8	1.2	50	15
H ₂ SO ₄ , 0.2	1.0	20	80
H ₂ SO ₄ , 0.3	1.0	25	75
H ₂ SO ₄ , 1	1.0	75	14
H ₂ SO ₄ , 2	1.5	80	10
H ₂ SO ₄ , 5	1.0	60	10

 $20-30^{\circ}$ C sodium borohydride (1.0-1.1 mole), and the mixture was stirred until complete dissolution of borohydride. Then 2/3 of the solvent was distilled off, a 10% aqueous hydrochloric acid solution was added to acid reaction, and the impurities were extracted with benzene. The aqueous layer was alkalized to pH 10-12 with a 40% aqueous sodium hydroxide solution and the product was extracted with benzene. Finally, the extract was dried with sodium sulfate, the solvent was distilled off, and the target amine is isolated by the usual methods at a 10-80% yield.

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