

~~REDUCTION OF ORGANIC COMPOUNDS WITH SODIUM BOROHYDRIDE-TRANSITION~~

## METAL SALT SYSTEMS (1)

## REDUCTION OF ORGANIC NITRILE, NITRO AND AMIDE COMPOUNDS TO PRIMARY AMINES.

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Sodium borohydride is well known as one of the most excellent reducing agents for ketones, acid halogenides and some kinds of esters<sup>(1)</sup>. The reagent, however, has no ability to reduce nitriles, amides and nitro compounds to corresponding primary amines. To increase the reducing ability to these compounds, some mixed systems like sodium borohydride-aluminum chloride<sup>(2)</sup>, borontrifluoride or lithium chloride<sup>(2)</sup> have been successfully used. These reductions are commonly conducted in non-hydroxylic solvents, which losses the advantage of sodium borohydride reduction.

Authors found that nitrile, nitro and amide compounds can be easily reduced to primary amines with sodium borohydride-transition metal salts systems in a good yield even in hydroxylic solvents as well as in non-hydroxylic solvents.

The results are summarized in Table 1, 2 and 3.

Table 1 Reduction of Nitrile Compounds with NaBH<sub>4</sub>-CoCl<sub>2</sub> System\*

<u>Nitrile</u>	<u>Product</u>	<u>Temp.</u>	<u>Yield, %</u>
C <sub>6</sub> H <sub>5</sub> CN	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	20°	72
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	-10°	60
p-HOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN	p-HOC <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	20°	70

Continued from Table 1.

<u>Nitrile</u>	<u>Product</u>	<u>Temp.</u>	<u>Yield, %</u>
n-C <sub>7</sub> H <sub>15</sub> CN	n-C <sub>8</sub> H <sub>17</sub> NH <sub>2</sub>	20°	80
C <sub>6</sub> H <sub>5</sub> CH(OH)CN	C <sub>6</sub> H <sub>5</sub> CH(OH)CH <sub>2</sub> NH <sub>2</sub>	20°	80
$\beta$ -cyanopyridine	$\beta$ -aminomethylpyridine	40°	35
$\alpha$ -cyanofuran	$\alpha$ -aminomethylfuran	20°	75
CH <sub>2</sub> =CHCN	CH <sub>2</sub> =CHCH <sub>2</sub> NH <sub>2</sub>	20°	70

\* methanol was used as solvent

Table 2 Reduction of Nitro Compounds with NaBH<sub>4</sub>-CoCl<sub>2</sub> System

<u>Nitro Compound</u>	<u>Product</u>	<u>Solvent (Temp.)</u>	<u>Yield, %</u>
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN	p-NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	CH <sub>3</sub> OH (40°)	50
o-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COOH	o-NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COOH	Dioxane (bp)*	40
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OH	p-NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OH	Dioxane (bp)	35
p-HOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH(NO <sub>2</sub> )CH <sub>3</sub>	p-HOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH(NH <sub>2</sub> )CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OH (bp)	45
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>3</sub> H	p-NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>3</sub> H	C <sub>2</sub> H <sub>5</sub> OH (bp)	38

\* boiling point

Table 3 Reduction of Amide Compounds with NaBH<sub>4</sub>-CoCl<sub>2</sub> System

<u>Amide</u>	<u>Product</u>	<u>Solvent (Temp.)</u>	<u>Yield, %</u>
C <sub>6</sub> H <sub>5</sub> CONH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	CH <sub>3</sub> OH (30°)	60
n-C <sub>3</sub> H <sub>7</sub> CONH <sub>2</sub>	n-C <sub>4</sub> H <sub>9</sub> NH <sub>2</sub>	CH <sub>3</sub> OH (30°)	70
HSCH <sub>2</sub> CH(NH <sub>2</sub> )CONH <sub>2</sub>	HSCH <sub>2</sub> CH(NH <sub>2</sub> )CH <sub>2</sub> NH <sub>2</sub>	CH <sub>3</sub> OH (-10°)	40
C <sub>6</sub> H <sub>5</sub> CONHCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NHCH <sub>3</sub>	Dioxane (bp)	30

In a typical experiment, benzonitrile (5g, 0.05 mol) and cobaltous chloride hexahydrate (23.8g, 0.1 mol) were dissolved in 99% methanol (300 cc) and sodium borohydride (19g, 0.5 mol) was added in portions with stirring at 20°. Evolution of hydrogen gas was observed and then black precipitates appeared during the addition of sodium borohydride. When the addition was complete, stirring was continued for one hr. at 20°.

One hundred cc of 3 N hydrochloric acid was poured into the reaction mixture and that stirred till the black precipitate was dissolved. After removal of methanol by distillation and unreacted benzonitrile by extraction with ether, the aqueous layer was made alkaline with conc. ammonium hydroxyde solution and then extracted with 50 cc portion of ether three times. The combined extracts were washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated. The residue was distilled under reduced pressure to give 3.6g (72%) of gas chromatographically pure benzylamine bp 90° (11mm), hydrochloride mp 254°.

As shown in Table 1, nitrile compounds were readily reduced in considerable low temperature to give the corresponding primary amines. Slight amount of by-product was detected in gas chromatographic analysis.

Mandelonitrile, which is known to give  $\alpha$ -hydroxy- $\beta$ -phenethyl amine in low yield by lithium aluminum hydride reduction<sup>(3)</sup> because of the formation of insoluble intermediate in ether, was smoothly reduced with sodium borohydride-cobaltous chloride system in a good yield.

Reduction of nitro compounds required higher temperatures than in the case of nitrile compounds, which indicates the possibility of the selective reduction of nitrile group to primary amine of the compound having nitro group in a molecule. In fact, p-nitrobenzyl nitrile was easily reduced at -10° to p-nitrophenethyl amine, otherwise, at 40° it gave p-aminophenethyl amine and none of p-nitrophenethylamine was isolated.

Amide compounds are liable to reduce to the amine in order of primary, secondary and tertiary amides, especially tertiary amide substantially gave no reduction product even at 100° in dioxane.

Hydrogenation of C-C double bond and desulfurization of thiol compounds were not observed by treatment with this system.

Acrylonitrile and cysteinamide gave allylamine and 1,3 diamino 3-mercapto-propane respectively, and no propylamine or 1,3-diaminopropane were obtained.

As shown in Table 4, halogenides, sulfates and carboxylates of cobalt, nickel, iridium, rhodium, osmium and platinum could be advantageously used as metal salts of the reduction systems instead of cobaltous chloride.

Cupric salts were also effective as metal salts in the reduction system, 1,1-diphenyl-1-hydroxy-2-cyanobutane gave 1-1-diphenyl-1-hydroxy-2-aminomethyl-butane in 10% yield in the system of sodium borohydride-cupric chloride at 20°.

Table 4 Reduction of Benzonitrile with NaBH<sub>4</sub>-Transition Metal Systems

<u>Metal Salt</u>	<u>Yield of Benzylamine, %</u>
Nickel Chloride	75
Cobaltous Benzoate*	50
Osmium Tetrachloride	78
Iridium Trichloride	75
Platinous Chloride	80

\* benzene was used as solvent

#### References

- (1) H. Seki, K. Koga and S. Yamada, Chem. Pharm. Bull., 15, 1948 (1967).
- (2) R. L. Augustine, Reduction, Marcel Dekker, N. Y. (1968).
- (3) W. G. Brown, Org. Reactions, vol.6, p.480, J. Wiley, N. Y. (1952).