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Reaction of *sec*-Amides with Metal Hydrides. I.[1] A Combination of Sodium Borohydride with Anilides as a Novel Reducing Reagent for Carbonyl Compounds

Yasuo Kikugawa

Faculty of Pharmaceutical Sciences, Josai University[2]

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Sodium anilidoborohydrides were synthesized from sodium borohydride and anilides in pyridine or in α-picoline, and these compounds were found to be useful reagents for facile reduction of both esters in α-picoline and aldehydes or ketones in dichloromethane. The structure of sodium acetanilidoborohydride was discussed.

In comparing the reducing properties of sodium borohydride with those of lithium aluminum hydride and its derivatives, there is often a need for the enhancement of the reduciability of sodium borohydride. The combination of inorganic compounds such as magnesium oxide,[3] lithium bromide,[4] cobalt chloride,[5] and aluminum chloride[6] with sodium borohydride, which showed specific reducing characters, has been studied for this purpose. Recently, lithium alkylborohydrides[7a,b] were synthesized and found to have unique reducing properties.

On the other hand, combination of organic compounds with sodium borohydride has scarcely been investigated,[8] except alkoxy borohydrides[9] which had slightly stronger reducing ability[10] than sodium borohydride. During the investigation on the reaction of *sec*-amides with sodium borohydride we found that acetanilide or benzanilide reacted with sodium borohydride in pyridine with evolution of an equimolar amount of hydrogen[11] to form anilidoborohydride, which had a suitable reducing ability for ester groups. Sodium acetanilidoborohydride was especially easily soluble in common organic solvents (dichloromethane, benzene, *etc.*), which is practically useful in the reduction of the complicated compounds.

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1) Part of this report has been a subject of the preliminary communication: Y. Kikugawa, *Chem. Lett.*, **1975**, 1029.
2) Location: *1-1 Keyakidai, Sakadomachi, Irumagun, Saitama, 350-02, Japan.*
3) Y. Mima, Jpn. Patent 577765 [*C.A.*, **72**, 89764, (1970)].
4) H.C. Brown, E.J. Mead, and B.C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).
5) I. Satoh, S. Suzuki, Y. Miyaji, and Z. Imai, *Tetrahedron Letters*, **1969**, 4555.
6) H.J. Williams, *Tetrahedron Letters*, **1975**, 1271.
7) *a*) H.C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **95**, 1669 (1973); *b*) J. Hooz, S. Akiyama, F.J. Cedar, M.J. Bennett, and R.M. Tuggle, *J. Am. Chem. Soc.*, **96**, 274 (1974).
8) Recently it was reported that $NaBH_4$ in carboxylic acids was employed to reduce the indole double bond and to alkylate the nitrogen atom to give N-alkylindolines [G.W. Gribble, P.D. Lord, J. Skotnicki, S.E. Dietz, J.T. Eaton, and J.L. Johnson, *J. Am. Chem. Soc.*, **96**, 7812 (1974). G.W. Gribble and D.C. Ferguson, *Chem. Commun.*, **1975**, 535.
9) Strictly speaking, it is impossible to distinguish between $NaBH_4$ itself and $NaBH_n(OR)_{4-n}(n<4)$ as a reducing agent in alcohols, because $NaBH_4$ is partially transformed to $NaBH_n(OR)_{4-n}$ in ROH, especially in methanol and ethanol.
10) H.C. Brown and E.J. Mead, *J. Am. Chem. Soc.*, **75**, 6263 (1953).
11) Not only hydrogen but also diborane is evolved when the acidity of an amide is high enough to react with $NaBH_4$ to form insoluble sodium salt of the amide. The *sec*-amide, having not so strong acidic hydrogen such as acetanilide (p*K*a 17.59) or benzanilide (p*K*a 16.53), can form a complex with $NaBH_4$ generating an equimolar amount of hydrogen. Only a small amount of hydrogen was evolved in the case of N-methylbenzamide (p*K*a 19.0) under the same reaction conditions. p*K*a values are taken from "The Chemistry of Amides," ed. by J. Zabicky, Interscience Publishers p. 239, 1970.

Reduction of Esters

It is generally accepted that sodium borohydride does not reduce carboxylic esters except when the neighboring functional groups are participating.[12a-c] Some simple esters can be reduced with a 10-fold excess of sodium borohydride in refluxing methanol but aliphatic and α,β-unsaturated carboxylic acid esters cannot be reduced in practice.[13] The surest way to obtain alcohols from esters is to use lithium aluminum hydride or its derivatives. However, with these reagents solvents are usually limited to ethers and selective reduction of esters is rather difficult when other functional groups are also involved in the same molecule. We synthesized sodium anilidoborohydrides by mixing sodium borohydride and anilides in pyridine or in α-picoline and found that esters were preferentially reduced with these reagents in the presence of other functional groups which would be expected to be reduced with lithium aluminum hydride. The reducing agent was sensitive to the steric bulkiness of an ester. In the case of XII, preferential reduction of methyl ester over isopropyl ester was observed. The results are presented in Table I. Neither high temperature nor anhydrous condition are necessary for the reaction. Totally a 1.5-fold excess[14] of sodium borohydride to the ester is adequate for the reduction. The procedure is very simple because the liberated benzanilide is easily recovered by filtration due to its low solubility in water and cold organic solvents.

Table I. Reduction of Esters with Sodium Anilidoborohydrides in α-Picoline (10—12 ml) at 100°

Compd.	Ester	Ester mmol	R.A.[a] mmol	Reaction time (hr)	No. of product	Alcohols isolated (%)
I	$C_6H_5CO_2CH_3$	5	10	2	XIII	71
I	$C_6H_5CO_2CH_3$	5	15[b]	2	XIII	6(69)[c]
I	$C_6H_5CO_2CH_3$	10	10	5	XIII	85
II	$C_6H_5CH_2CH_2CO_2CH_3$	10	10	5	XIV	97
III	$CH_3(CH_2)_7CO_2CH_3$	10	10	5	XV	87
IV	$C_6H_5CH=CHCO_2CH_3$	7	10	5	XIV:XVI	71(9:1)[d]
V	o-$CH_3OC_6H_4CO_2CH_3$	5	5[e]	6	XVII	93
VI	p-$CH_3OC_6H_4CO_2CH_3$	5	5[e]	6	XVIII	75
VII	 -CO_2CH_3	10	10[e]	6	XIX	64
III	$CH_3(CH_2)_7CO_2CH_3$	5	5[e]	5	XV	87
VIII	$CH_3(CH_2)_6CO_2CH_3$	30	30[e]	5	XX	74[f]
IX	methyl 2-furoate	5	5[e]	6	XXI	71
X	p-$NCC_6H_4CO_2CH_3$	5	5[e]	3	XXII	89
XI	p-$(CH_3)_2NCC_6H_4COCH_3$ (O, O)	5	5[e]	3.5	XXIII	78
XII	p-$CH_3OCC_6H_4COC(CH_3)_2$ (O, O, H)	5	5[e]	4	XXIV:XXV	73(90:10)[g]

a) reducing agent
b) $NaBH_4$ was employed instead of anilidoborohydrides for comparison.
c) recovery of the starting ester, 69%
d) Isolated alcohols consisted of 10% of unsaturated (XVI) and 90% of saturated (XIV) alcohols.
e) mmoles of benzanilidoborohydride. Acetanilidoborohydride was used in others.
f) yields after distillation (bp 104—105°/28 Torr)
g) XXIV and XXV represent the alcohols obtained by the reduction of methyl ester and *tert*-butyl ester, respectively. The ratio was calculated from the integrations of methyl and isodropyl signals in a NMR spectrum.

12) a) J.E.G. Barnet and P.W. Kent, *J. Chem. Soc.*, **1963**, 2743; b) E.C. Pesterfield and D.M.S. Wheeler, *J. Org. Chem.* **30**, 1513 (1965); c) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 995 (1963).
13) M.S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 1963, 3261.
14) Longer reaction time was necessary for the formation of anilidoborohydride when an equimolar amount of $NaBH_4$ to anilide (or ester) was employed.

Considering these advantages, this reduction procedure may be available for not only a laboratory scale but also a large scale reduction.

Reduction of Aldehydes and Ketones

After sodium acetanilidoborohydride was synthesized from acetanilide and sodium borohydride in pyridine at 100°, pyridine was evaporated *in vacuo* (70°/30 Torr) and dichloromethane was added to the residue and the whole was well triturated. Insoluble excess sodium borohydride was removed by filtration. It is very interesting that sodium anilidoborohydride was soluble in benzene, chloroform, and other common organic solvents.[15] As Table II shows, aldehydes and ketones were reduced in dichloromethane which could not be used for sodium borohydride reduction owing to the poor solubility of the metal hydride.

TABLE II. Reduction of Aldehydes and Ketones with Sodium Anilidoborohydride in CH_2Cl_2 (25 ml) at Room Temp. (Reaction time, 30 min)

Compd.	S.M.[a]	S.M. mmol	R.A.[b] mmol	No. of product	Alcohols isolated (%)
XXVI	C_6H_5CHO	9.4	10	XIII	78
XXVII	$CH_3(CH_2)_6CHO$	7.8	10	XX	98
XXVIII	$C_6H_5COCH_2CH_3$	3.7	10	XXXI	78
XXIX	$C_6H_5CH_2CH_2COCH_3$	7.4	10	XXXII	92
XXX	$C_6H_5COC_6H_5$	8.2	10	XXXIII	99

a) starting materials
b) sodium anilidoborohydride

Structure of Sodium Acetanilidoborohydride

After the crude sodium acetanilidoborohydride was triturated with dichloromethane and the insoluble materials were filtered off as mentioned above,[16] the solvent was evaporated *in vacuo*. The glassy residue, contained acetanilide (*ca.* 10%) and a small amount of α-picoline in addition to sodium acetanilidoborohydride. Spectral data which excluded the absorption bands of acetanilide and α-picoline were as follows: NMR ($CDCl_3$) δ: 1.75 (3H, s, CH_3), 6.48—6.62 (2H, m, aromatic), 7.05—7.12 (3H, m, aromatic), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250—2400 (B–H), 1604 (N–Ph), 1560—1580 (–O–C=N–). The signal of two aromatic protons shifted to a higher field[17] and the methyl signal also shifted to a higher field by 0.36 ppm than the signal of acetanilide (2.11 ppm) and infrared (IR) absorption bands lie in the C=N region in place of the typical carbonyl region. Tani[18] synthesized the reaction product between trimethylaluminum and acetanilide, and elucidated its structure as Me_2Al-O-C(CH_3)=N-Ph from its spectral data. The structure of the present complex is also assumed to be an enol form on the basis of the spectral data.

$$NaBH_4 + CH_3CONHPh \longrightarrow \underset{\text{assumed structure}}{CH_3-\overset{OBH_3^-\ Na^+}{\overset{|}{C}}=N-Ph} + H_2 \xrightarrow{H^-} CH_3CH_2NHPh$$

Chart 1

15) Quaternary ammonium borohydride was reported to be soluble in hydrocarbons. A.L. Tengzelius, Fr. Patent, 1325439 [*C.A.*, **59**, 4820 (1963)].
16) In this case sodium acetanilidoborohydride was synthesized by the use of α-picoline as a solvent because the yield of the hydride was better in α-picoline (*ca.* 90%) than in pyridine (*ca.* 75%). Yields were calculated by the comparison of methyl signals of acetanilide and of anilidoborohydride in the NMR spectrum.
17) The signal of aromatic protons (δ: 6.48—6.62) was attributable to that of phenyl protons, because it did not vanish in the case of d_5-pyridine used as a solvent instead of pyridine, though the reason why the signal shifted to a higher field was not solved.
18) H. Tani, T. Araki, and H. Yasuda, *Polymer Lett.*, **4**, 727 (1966).

In the reaction of sodium borohydride and acetanilide, about equimolar hydrogen to the acetanilide was evolved. When heating was continued for 20 hr without adding other reducible substances, N-ethylaniline[19] (reduction product of acetanilide) was obtained in 37% yield. As *sec*-amides generally cannot be reduced with sodium borohydride except an unusual case,[20] it is easier to consider that acetanilide was transformed into more reducible form (enol form) with the evolution of hydrogen, though more prolonged heating or a rise in reaction temperature did not bring better yield.

Experimental

All melting points are uncorrected. The following instruments were used for obtaining the physical data. IR spectra: Shimadzu IR-400; nuclear magnetic resonance (NMR) spectra (tetramethylsilane as an internal standard), Hitachi R-20; gas chromatography: Schimadzu GC-4BM. Column chromatography was carried out on silica gel (Merck, Art. 7734) using benzene: acetone (6: 1) for a elution.

Materials——$NaBH_4$, pyridine (reagent-grade), and α-picoline (reagent grade) were purchased from Wako Chemical Industries, Ltd. The starting materials I, III—IX, XXVI—XXX and the authentic samples were purchased from Tokyo Kasei Kogyo Co., Ltd., and they were used without further purification. The esters X (mp 64—66°, lit.,[21] mp 61—63°) and II (bp 130—131°/29 Torr, lit.,[22] bp 82—86°/0.3 Torr) were synthesized from the corresponding carboxylic acid chlorides with methanol and gave the satisfactory spectral data. The esters XI (mp 106—107°, recryst. from benzene–hexane, IR ν_{max}^{Nujol} cm^{-1}: 1723 (C=O), 1620 (O=C–N); NMR ($CDCl_3$) δ: 3.02 (6H, s, dimethyl), 3.88 (3H, s, CH_3), 7.42 (2H, d, J=8 Hz, aromatic) 7.98 (2H, d, J=8 Hz, aromatic) and XII (bp 119—121°/4 Torr). IR ν_{max}^{oil} cm^{-1}: 1710 (C=O), 1260, 1090 (C–O); NMR ($CDCl_3$) δ: 1.35 (6H, d, J=6 Hz, $C(CH_3)_2$), 3.93 (3H, s, CH_3), 5.20 (1H, h, J=6 Hz, C–H), 8.12 (4H, s, aromatic)) were synthesized from *p*-methoxycarbonylbenzoic acid chloride with aq. dimethylamine and isopropyl alcohol, respectively.

Typical Procedure for Reduction of Ester——A mixture of $NaBH_4$ (7.5 mmol, 285 mg) and benzanilide (5 mmol, 990 mg) in α-picoline (9 ml) was maintained at 100° for about 40 min.[23] After about 5 mmolar hydrogen had evolved, methyl nonanoate (III) (5 mmol, 860 mg) was added and the solution was kept at 100°

Table III. Spectral Data of the Products

Compd.	IR $\nu_{max}^{cap.}$ cm^{-1}	NMR δ ($CDCl_3$)[a]
XXII	3450—3250(OH) 2230(C≡N) 1010—1030(C–O)	2.60(1H, br, OH) 4.68(2H, s, CH_2) 7.25—7.64(4H, m, aromatic)
XXIII	3425—3325(OH) 1610—1630(O=C–N) 1060(C–O)	3.01(6H, s, $N(CH_3)_2$) 3.35(1H, br, OH) 4.58(2H, s, CH_2) 7.22(4H, s, aromatic)
XXIV	3500—3300(OH) 1700—1710(C=O) 1270, 1120(C–O)	1.37(1H, d, J=7 Hz, $C(CH_3)_2$) 2.65(1H, br, OH) 4.75(2H, s, CH_2) 5.26(1H, h, J=7 Hz, CH)
XXV		3.90(3H, s, CH_3)[b]
XXXII	3400—3300(OH) 2975—2925(CH_2) 1605(Ph) 1115, 1030(C–O)	1.16(3H, d, J=7 Hz, CH_3) 1.65—1.90(3H, m, CH_2+OH) 2.55—2.85(2H, m, CH_2) 3.73(1H, m, CH) 7.15(5H, s, aromatic)

a) All OH was detected by deuteration with D_2O.
b) The presence of XXV and the ratio of XXIV to XXV were confirmed by gas chromatographic analysis.

19) It was identified by the comparison of spectral data with those of the authentic specimen and from gas chromatographic analysis.
20) K. Masuzawa, M. Kitagawa, and H. Uchida, *Bull. Chem. Soc. Japan*, **40**, 244 (1967).
21) L. Freedman and H. Shechter, *J. Org. Chem.*, **26**, 2523 (1961).
22) A.L. Wilds and R.E. Sutton, *J. Org. Chem.*, **16**, 1378 (1951).
23) More prolonged reaction time (about 90 min) was necessary in the case of acetanilide.

for 5 hr. The solvent was distilled off at 70° (25—30 Torr), and 5% HCl was added to the residue with cooling. Benzanilide liberated (about 85% recovery) was collected by filtration and washed with cold $CHCl_3$. The filtrate was extracted with $CHCl_3$ and the combined $CHCl_3$ layer was dried over anhyd. Na_2SO_4. After evaporation of $CHCl_3$, the residual oil was purified by column chromatography or by distillation.

General Procedure for Reduction of Aldehydes and Ketones——After sodium acetanilidoborohydride was synthesized from acetanilide (0.01 mol, 1.35 g) and $NaBH_4$ (0.015 mol, 570 mg) in pyridine (10 ml) as described above, the solvent was distilled off at 70° (25—30 Torr). To the residue CH_2Cl_2 (25 ml) was added and the insoluble materials were collected by filtration.[24] The starting aldehyde or ketone (see Table II) was added to the CH_2Cl_2 solution and it was stirred for 30 min. After the solvent was distilled off, 10% HCl was added to the residue with cooling. The aq. layer was extracted with $CHCl_3$ and combined $CHCl_3$ layer was dried over anhyd. Na_2SO_4. After evaporation of $CHCl_3$, the solidified residue was washed with cold benzene. Acetanilide was collected by filtration and the filtrate was distilled off *in vacuo*. The residual oil was purified by column chromatography.

Identification of Products——For the alcohols, XIII—XXI, XXXI and XXXIII, identity was established by the comparison of spectral data and/or the retention times in gas chromatographic analysis[25] of the authentic samples purchased from the commercial source. Other compounds gave satisfactory spectral data listed in the Table III.

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24) The filtrate (CH_2Cl_2) contains sodium acetanilidoborohydride.
25) The temperature of glass column (1.5 m × 3 mm, i.d.) packed with 10% SE-30 on Chromosorb W (60—80 mesh) and injection chamber were kept at 150° (110° for XXI) and 200°, respectively. N_2 was used as a carrier gas at the flow rate of 70 ml/min.