[Chem. Pharm. Bull. 26(1) 108—110 (1978)]

UDC 547.751.04 : 542.942.6.04

Reduction of Alkylindoles with Sodium Borohydride-Aluminium Chloride in Pyridine

YASUO KIKUGAWA

Faculty of Pharmaceutical Sciences, Josai University[1]

(Received May 23, 1977)

Several indole derivatives were reduced to the corresponding indolines in the combination of sodium borohydride with aluminium chloride in pyridine. N-Benzoyltryptamine (**1f**) was selectively reduced to the indoline derivative without reduction of the amide group.

Keywords——sodium borohydride; aluminium chloride; pyridine; reduction; pyridine-borane; alkylindoles; N-benzoyltryptamine

Reduction of the indole double bond is considered to be the most interesting area which is being actively studied[2] for many years because indole derivatives often have a potent biological activity. Of the several methods available for the reduction of indoles to indolines,[2] reduction of 3*H*-indolium ion[3] generated by protonation of indoles in strongly acidic media is the most widely applicable one. On the other hand it is generally accepted that the indole double bond resists reduction and lithium aluminium hydride, the strongest reducing agent in complex metal hydrides, cannot reduce indoles.[2a] For the enhancement of reducibility of sodium borohydride, the combination of aluminium chloride with sodium borohydride in diglyme was studied by Brown, *et al.*[4] and this reducing agent indiscriminately reduced various functional groups in good yields. Pyridine is an interesting solvent in the case of sodium borohydride reduction[5] and we used pyridine instead of diglyme as the solvent to find that carboxylic acids, *tert*-amides, esters, and cyano groups which were easily reduced in diglyme could not be reduced in pyridine. Therefore, selective reduction of some functional groups which are reducible by this reduction procedure may be anticipated. We have investigated reduction of the indole double bond with sodium borohydride-aluminium chloride in pyridine and found that it was reduced under the following conditions. After reduction of indole as described in the Experimental part, pyridine was removed over under a reduced pressure and cold water was added to the residue. The aqueous layer was extracted with benzene which was washed with saturated aqueous sodium chloride. After evaporation of benzene the residual oil was submitted to the thin-layer chromatography which showed the presence[6] of the starting material (32%), indoline (68%), and pyridine-borane. Pyridine-borane was decomposed completely by the addition of 10% aqueous hydrochloric acid and then residual starting material was reduced to give indoline.[7] Consequently indoline was the

1) Location: *1-1 Keyakidai, Sakado-shi, Saitama 350-02, Japan.*
2) *a*) B. Robinson, *Chem. Rev.*, **69**, 785 (1969); *b*) R.J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970, p. 129, and references contained therein.
3) *a*) 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); *b*) J.G. Berger, *Synthesis*, **1974**, 508; *c*) A. Smith and J.H.P. Utley, *J. Chem. Soc.* (*C*), **1970**, 1; *d*) *Idem*, *Chem. Commun.*, **1965**, 427.
4) H.C. Brown and B.C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 2582 (1956).
5) *a*) Y. Kikugawa, S. Ikegami, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 98 (1969); *b*) Y. Kikugawa, M. Kuramoto, I. Saito, and S. Yamada, *ibid.*, **21**, 1914 (1973).
6) Approximate yields were calculated from the gas chromatographic analysis (SE-30, 1.5×3 mm, i.d., column temperature 130°). Pyridine borane formed by $NaBH_4$ and $AlCl_3$ in pyridine colud not be detected under the same gas chromatographic conditions probably due to its decomposition by heat.
7) Reduction of indoles with pyridine-borane-HCl will be published. Y. Kikugawa, *J. Chem. Research* (*s*), **1977**, 212.

only isolable product in overall reduction as depicted in Chart 1. As the decomposition of pyridine borane is inevitable for isolation of indoline, this reduction can be recognized as apparent one step reduction and it is not necessary to distinguish between two kinds of reduction for a synthetic purpose. Table I shows its results.

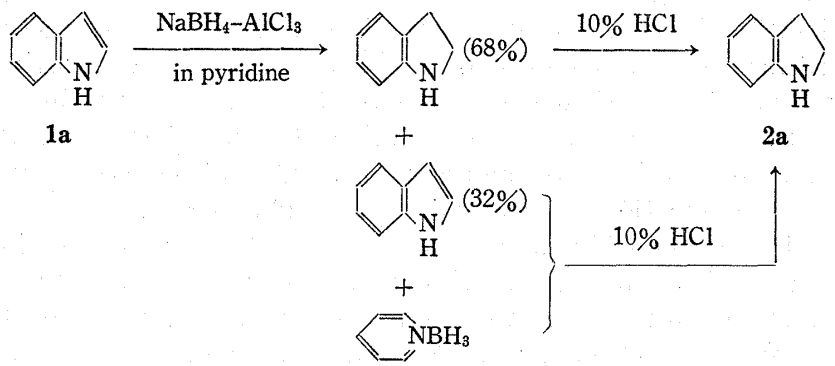
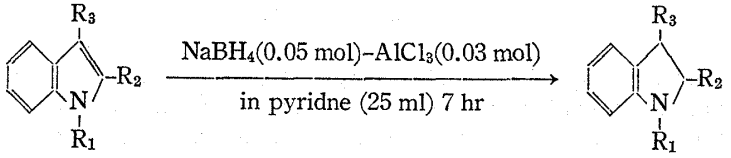


Chart 1

TABLE I. Reduction of Indoles with $NaBH_4$–$AlCl_3$ in Pyridine at Room Temp.



1 (0.01 mol) 2

1	Compound	Yields of 2 (%)[b]	Physical constants of 2[a]
a	$R_1=R_2=R_3=H$	76	bp 120—122°/33 Torr (bp 113—116°/20 Torr)[c]
b	$R_1=R_2=H$, $R_3=CH_3$	75(7)	bp 122—125°/29 Torr (bp 231—232°/744 Torr)[d]
c	$R_1=R_3=H$, $R_2=CH_3$	80	bp 116—118°/25 Torr (bp 269—271°)[e]
d	$R_1=CH_3$, $R_2=R_3=H$	56(10)	bp 109°/30 Torr (bp 90—95°/10 Torr)[f]
e	$R_1=R_3=H$, $R_2=C_6H_5$	15(75)	Benzoate, mp 131—133° (benzene–hexane), *Anal.* Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68; Found: C, 84.08; H, 5.61; N, 4.91
f	$R_1=R_2=H$ $R_3=CH_2CH_2NHCOC_6H_5$	42(45) 56(42)	mp 135—137° (benzene–hexane), *Anal.* Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52; Found: C, 76.91; H, 6.79; N, 10.30

a) All **2** showed reasonable IR and NMR spectra.
b) Figures in parentheses indicate recovery of **1** in percentage.
c) H. Plieninger, H. Bauer, W. Bühler, J. Kurze, and U. Lerch, *Ann. Chem.*, **680**, 80 (1964).
d) M. Wenzing, *Ann. Chem.*, **239**, 242 (1887).
e) H. Adkins and H. L. Coonradt, *J. Am. Chem. Soc.*, **63**, 1567 (1941).
f) *Chem. Abstr.*, **66**, 115538 (1967).

The combination of sodium borohydride with aluminium chloride in pyridine showed a specific reducing ability for the indole double bond. N-Benzoyltryptamine (**1f**) was reduced to the corresponding indoline derivative (**2f**) in a moderate yield without reduction of the amide group, while reduction of **1f** with lithium aluminium hydride[8] or with sodium borohydride-aluminium chloride in refluxing ether (2 hr) and in diglyme (3 hr) at room temperature did not give indoline derivative (**2f**) and only the starting material was recovered. Ethyl indole-3-butyrate and indole-3-acetonitrile were submitted to reduction of the indole double bond without affecting other functional groups to give trace amounts of the desired indoline derivatives and the recovery of the starting materials.

8) No reduction of the secondary amide (**1f**) will be mainly due to poor solubility of **1f** in ether.

For the improvement of the reduction conditions, the reaction temperature was raised to refluxing for the reduction of 2-methylindole (**1c**) but the starting material was recovered quantitatively. The reducing species which is unknown[9] might be unstable to high temperature or be consumed for the reduction of pyridine.

When pyridine was replaced with α-picoline, which is a suitable solvent for anilidoborohydride reduction,[10] indole was not reduced at all. Pyridine-borane synthesized from another route[11] was used for the reduction of indole in pyridine as a control experiment but indoline was not obtained at all even when stirred at room temperature for 24 hr. Not only aluminium chloride but also zinc chloride, cobalt chloride, stannic chloride, and titanium chloride were examined for combination with sodium borohydride and these combinations were found to be effective for the reduction of 2-methylindole (Yield 60—80%).

To confirm the position of indole ring to be attacked by the hydride ion, a deuteration experiment was carried out by the use of sodium ^{2}H-borohydride. Deuteride attacked the 2-position of 2-methylindole, which was determined by the measurement of NMR spectrum showing a singlet peak of methyl signal. As oxidation from indolines to indoles was established,[12] this procedure will offer a route for the synthesis of 2-tritiated 3-substituted indoles by the replacement of sodium borohydride with sodium ^{3}H-borohydride.

Experimental

All melting points are uncorrected. The following instruments were used for obtaining the physical data. Infrared (IR) spectra, Shimadzu IR-400; NMR spectra (tetramethylsilane as an internal standard), JNM-C-60HL; gas chromatography, Shimadzu GC-4BM. Column chromatography was carried out on silica gel (Merck, Art. 7734) using benzene: acetone (6: 1) for elution.

Materials——$NaBH_4$, reagent grade pyridine, aluminium chloride, and **1a** were purchased from Wako Chemical Industries Ltd., Tokyo. The starting material **1b—e** were purchased from Tokyo Kasei Kogyo Co. **1f** (mp 139—140° (AcOEt)) was prepared by benzoylation of tryptamine, purchased from Tokyo Kasei Kogyo Co., by the usual method.

Reduction of Indoles to Indolines——To a chilled solution of the indole (0.01 mol) and $NaBH_4$ (0.05 mol) in 25 ml of pyridine finely crushed $AlCl_3$ (0.03 mol) was added. After 7 hr stirring, the solvent was evaporated under a reduced pressure. To the residue was added H_2O (50 ml) and the aq. layer was extracted with benzene which was washed with sat. NaCl and dried over anhyd. Na_2SO_4. After evaporation of benzene 10% HCl (15—20 ml) was added to the residue with cooling to decompose pyridine borane. 10% Na_2CO_3 and Na_2CO_3 powder were added to make the solution alkaline and the aq. layer was extracted with benzene which was washed with sat. NaCl and dried over anhyd. Na_2SO_4. After evaporation of benzene, the residue was purified most readily by chromatography on a short silica gel column, using benzene: acetone (6: 1) for elution. In the reduction of **1e**, **2e** was not isolated in a pure form because *Rf* value of **2e** was very close to that of **1e**. Approximate yield was calculated from the gas chromatographic analysis.

Reduction of If——Half of the reducing agent ($NaBH_4$ and $AlCl_3$) was added first to the reaction mixture and another half was added 4 hr later, and the solution was stirred for 7 hr in total. Yield of **2f** was raised to 56%.[13]

Acknowledgement We thank Professor S. Yamada, of this University, for his encouragement.

9) H.C. Brown, *et al.*[4] suggested the presence of $Al(BH_4)_3$ in the combination of $NaBH_4$–$AlCl_3$ in diglyme but the exact structure is still ambiguous as they reported no recovery of NaCl from the reaction mixture.
10) Y. Kikugawa, *Chem. Pharm. Bull.* (Tokyo), **24**, 1059 (1976).
11) M.D. Taylor, L.R. Grant, and C.A. Sands, *J. Am. Chem. Soc.*, **77**, 1506 (1955).
12) R.J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970, p. 132.
13) Improvement of the yield of **2f** may suggest that indoles were reduced rapidly only when $AlCl_3$ was added.