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The Chemistry of Diborane and Sodium Borohydride. XI.[1] The Reaction of Isoquinoline Reissert Compounds with Sodium Borohydride

Isao Saito, Yasuo Kikugawa[2] and Shun-ichi Yamada[2a]

Faculty of Pharmaceutical Sciences, University of Tokyo[2]

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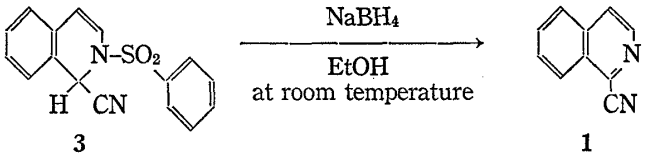
N-Benzenesulfonyl Reissert compound was converted to isoquinaldonitrile with sodium borohydride under very mild reaction conditions and also the N-benzoyl Reissert compound underwent the reductive fission with sodium borohydride. The latter was applied to the synthesis of 1-alkylisoquinolines.

A) The Reaction of N-Benzenesulfonyl-1,2-dihydroisoquinaldonitrile (3) with Sodium Borohydride

During our investigation of the reactions of heteroaromatic compounds with sodium borohydride, a large amount of quinaldonitrile (**1**) was needed and we examined the easy method to obtain it.

Wefer, *et al.* reported[3] that N-benzenesulfonyl-1,2-dihydroisoquinaldonitrile (**3**) was converted to the compound (**1**) with sodium hydride in good yield. According to this reaction procedure, the reaction conditions are vigorous (xylene is used for the solvent and refluxed, and the reaction mixture is colored considerably). When a diluted sodium hydroxide solution can be employed instead of sodium hydride, isoquinaldoamide was obtained as a by-product.

Table I. The Reaction of N-Benzenesulfonyl Reissert Compound with $NaBH_4$



3 1

Molar ratio $NaBH_4$/S.M.[a]	Reaction time (hr)	Yield (%) (isolated)
5	0.5	82
3	0.5	89
1	0.5	100

a) S.M.=starting material

We want to improve the preparation method and to use sodium borohydride instead of sodium hydride which is very troublesome to handle because of its sensitivity to moisture. The product, isoquinaldonitrile (**1**) was not reactive toward sodium borohydride in ethanol,[1] so the reaction of the compound (**3**) with sodium borohydride was examined in ethanol. Table I shows the result. The method is very simple. The equimolar ratio of sodium borohydride

1) Part X: Y. Kikugawa, I. Saito, M. Kuramoto and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 1927 (1973).
2) Location: *Hongo, Bunkyo-ku, Tokyo*; *a*) To whom inquires should be addressed.
3) J.M. Wefer, A. Catala and F.D. Popp, *J. Org. Chem.*, **30**, 3075 (1965).

to the starting compound is used and the reaction goes smoothly at room temperature in a clear solution evolving hydrogen gas. The yield is also very good when N-(*p*-toluenesulfonyl)-1,2-dihydroisoquinaldonitrile (**4**) was used as the starting compound.

In this reaction, sodium borohydride was behaving as a base like sodium hydride and not as a reducing agent. The mechanism was postulated in Fig. 1.

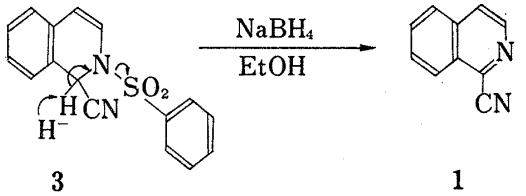


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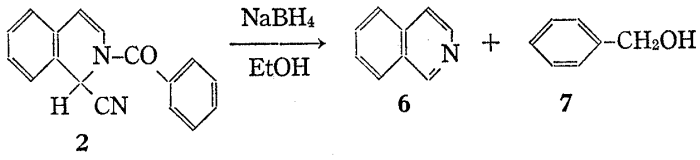
Fig. 1. Reaction Mechanism

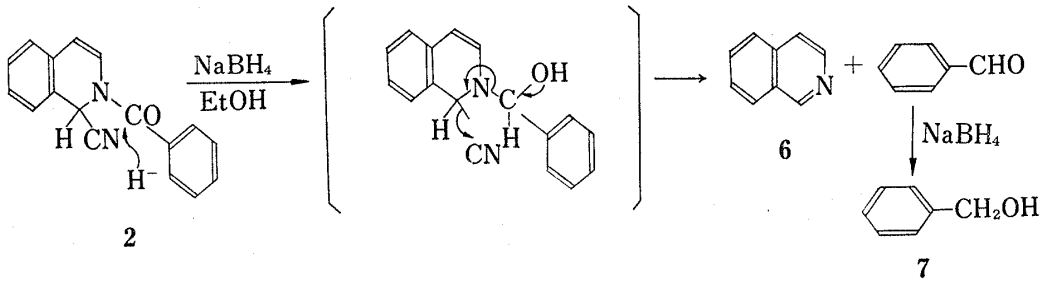


2 6 7

Fig. 2. The Reduction of N-Benzoyl Reissert Compound with $NaBH_4$

B) The Reaction of N-Benzoyl-1,2-dihydroisoquinaldonitrile (2) with Sodium Borohydride

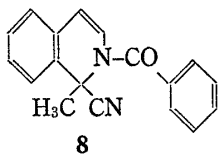
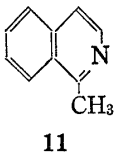
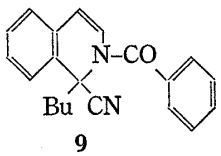
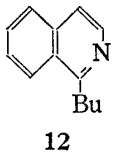
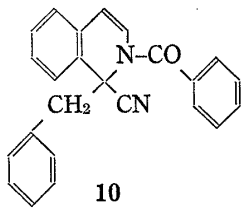
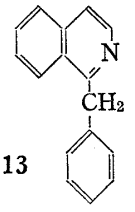
The same reaction as (A) was examined by changing the benzenesulfonyl group to the benzoyl group. The reaction proceeded as described in Fig. 2 to give the products, isoquinoline (**6**) and benzyl alcohol (**7**). A hydride ion should attack the carbonyl group to give isoquinoline (**6**) and benzaldehyde which was reduced to the alcohol (**7**) with excess hydride ions as assumed



2 6 7

Fig. 3. Reduction Mechanism

TABLE II. The Reduction of 1-Alkyl-N-benzoyl Reissert Compounds with $NaBH_4$

Starting materials	Products	Yield % (isolated)
 **8**	 **11**	75
 **9**	 **12**	72 Bu=*n*-Butyl
 **10**	 **13**	42

in Fig. 3. Usually tert. amides cannot be reduced with sodium borohydride in ethanol,[4a-c] but the benzamide was reduced to the alcohol in the case of the compound (**2**). In this instance, the benzamide (**2**) is not the normal amide but has a nitrogen atom conjugated with the aromatic system. N-Benzoylcarbazole (**5**) is almost analogous to the amide (**2**) from this standpoint, so it was subjected to the same reaction, and carbazole and benzyl alcohol were obtained as expected. There are some examples[5a-d] belonging to this type of reaction. This reaction would be applied to the synthesis of 1-alkylisoquinoline,[6] when 1-alkylisoquinoline Reissert compounds were used as the starting compounds. Three Reissert compounds (**8**), (**9**) and (**10**) were prepared as described in the literature[7] and the corresponding 1-alkylisoquinolines were obtained as listed in Table II. This is the new application of sodium borohydride for the synthesis of 1-alkylisoquinolines.

Experimental[8]

Material——Sodium borohydride was purchased from Kawaken Fine Chemicals Co., Ltd., and used without further purification. Starting materials (**2**), (**3**), (**6**), (**7**) and (**8**) were prepared by the methods described in the literatures listed in Table III.

Isoquinaldonitrile (**1**) **from N-Benzenesulfonyl-1,2-dihydroisoquinaldonitrile** (**3**)——To the mixture of the compound (**3**) (1.49 g, 0.005 moles) and ethanol (50 ml), $NaBH_4$ (190 mg, 0.005 moles) was added under stirring. After 30 min at room temperature, ethanol was removed under the reduced pressure and to the residue H_2O (20 ml) was added. The aqueous layer was extracted with $CHCl_3$ (three times, 40, 30 and 30 ml) which was washed with satd. NaCl and dried over anhyd. Na_2SO_4.

After the evaporation of the solvent, the nitrile (**1**) was obtained as a solid. 770 mg, Y. 100% mp 86—87° (*n*-hexane). It was identified by the mixture melting point measurement with the authentic sample (mp 87—88°).[9]

Isoquinaldonitrile (**1**) **from N-(*p*-Toluenesulfonyl)-1,2-dihydroisoquinaldonitrile** (**4**)——The compound (**4**) (1.50 g, 0.005 moles), $NaBH_4$ (190 mg, 0.005 moles) and ethanol (50 ml) were mixed and the reaction procedure was the same to the method just mentioned above.

The nitrile (**1**) was obtained as a solid. 730 g, yield 95%.

The Reaction of N-Benzoyl-1,2-dihydroisoquinaldonitrile (**2**) **and $NaBH_4$**——The ethanol suspension (50 ml) of the compound (**2**) (1.30 g, 0.005 moles) and $NaBH_4$ (0.95 g, 0.025 moles) was refluxed for 15 hr under stirring. After the reaction, ethanol was removed under the reduced pressure and the residue H_2O (20 ml) was added. The aqueous layer was extracted with $CHCl_3$ (three times, 40, 30 and 30 ml) which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. After the evaporation of the solvent, the residual oil was dissolved in benzene which was extracted with 10% HCl. From the benzene layer benzyl alcohol was obtained 269 mg, yield 50%. It was identified with the gas chromatography[10] and the comparison of the IR of the authentic sample.

10% HCl layer was made alkaline by adding 10% NaOH and it was extracted with $CHCl_3$ which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. After the evaporation of the solvent isoquinoline was obtained 470 mg, yield 73%. It was identified by the gas chromatography[10] and the comparison of the IR of the authentic sample.

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4) *a*) N.G. Gaylord, "Reduction with Complex Metal Hydride," Interscience Publ. 1956. Tert. amides can be reduced to the amines with sodium borohydride when pyridine is used for the solvent; *b*) Y. Kikugawa, S. Ikegami and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 98 (1969); *c*) I. Saito, Y. Kikugawa and S. Yamada, *ibid.*, **18**, 1731 (1970).

5) *a*) P. Cerutti, Y. Kondo, W.R. Landis and B. Witkop, *J. Am. Chem. Soc.*, **90**, 771 (1968); *b*) Z. Pravda and J. Rudinger, *Coll. Czechoslow. Chem. Comm.*, **20**, 1 (1955); *c*) K. Banholzer, T.W. Campbell and H. Schmid, *Helv. Chim. Acta*, **35**, 1577 (1952); *d*) V.M. Micovic and M.Lj. Mihailovic, *J.O.C.*, **18**, 1190 (1953).

6) The common method to obtain 1-alkylisoquinolines is to boil the mixture of the Reissert compound and conc. sodium hydroxide solution. J. Weinstock and V. Boekelheide, "Org. Synth., Coll." Vol. **4**, 641 (1962).

7) B.C. Uff and J.R. Kershaw, *J. Chem. Soc.*, **1969**, 666.

8) All melting points and boiling points were uncorrected. Infrared (IR) spectra measurements were performed with a Spectrometer, Model DS-402. Japan Spectroscopic Co., Ltd.

9) J.M. Wefer, A. Catala and F.D. Popp, *Chem. Ind.*, **1965**, 140.

10) The gas chromatographic conditions: Carbowax, Temperature 200°, Flow Rate 1.0 kg/cm^2, Carrier Gas He.

The Reaction of N-Benzoylcarbazole (5) and $NaBH_4$——The compound (5) (0.54 g, 0.002 moles), $NaBH_4$ (380 mg, 0.01 mole) and ethanol (20 ml) were mixed and the reaction procedure was the same to the method just mentioned above.

The products were carbazole (265 mg, yield 79%) and benzyl alcohol (110 mg, yield 51%). They were identified by the comparison of the IR of the authentic samples.

The Reaction of 1-Alkyl-N-benzoyl-1,2-dihydroisoquinolines (8), (9) and (10) with $NaBH_4$——The starting material (0.0025 moles) and $NaBH_4$ (0.0125 mloes) were mixed in ethanol (25 ml) and it was refluxed for 15 hr. After the reaction the product was isolated by the same treatment as described in the case of the compound (2). The yields are listed in Table II. The physical constants of the products are as follows: 1-Methylisoquinoline(11)Hydrochloride mp 200—205° (mp 200—205°),[11] 1-Butylisoquinoline(12)Picrate mp 189—191° (mp 185.5°),[12] 1-Benzylisoquinoline(13)Hydrochloride mp 170—172° (mp 172—173°).[7]

Table III. Physical Constants of the Starting Compounds

Numbers	mp °C	Literature mp °C
2	127	125—127[a]
3	110—112	109—112[b]
4	98—100	101—103[b]
5	98— 99	98.5[c]
8	118—120	120—122[a]
9	107—109	107[d]
10	127—128	129[d]

a) J. Weinstock and V. Bockelheide, "Org. Synth. Coll," Vol. 4, 1962, p. 641
b) J.M. Wefer, A. Catala and F.D. Dopp, *J. Org. Chem.*, **30**, 3075 (1965)
c) G. Mazzara, *Chem. Ber.*, **24**, 278 (1891)
d) M. Mieczyslaw, *Tetrahedron Letters*, **1969**, 677

11) E. Späth, F. Berger and W. Kuntara, *Chem. Ber.*, **63**, 134 (1930).
12) K. Ziegler and H. Zeiser, *Ann.*, **485**, 174 (1931).