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A Direct Reductive Deamination of Amidines with Sodium Borohydride. Formation of Deaminated Compounds and Secondary Amines

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The reaction of 3-substituted-4-amino-1*H*-1,5-benzodiazepines (**1a**, **b**) with sodium borohydride afforded deaminated compounds (**4a**, **b** and **6a**, **b**). On the other hand, acyclic amidines were converted by treatment with sodium borohydride to the corresponding secondary amines (**13**) under the same conditions.

Keywords—1,5-benzodiazepines; deamination; amidines; mass analysis; IR absorption of cyano group; H-NMR; ¹³C-NMR

There is considerable interest in reductive deamination in connection with organic syntheses and biological reactions. The reaction involves net replacement of an amino group attached to carbon by hydrogen. Chemical procedures that accomplish this change for aromatic amines are well known^{1,2)} and in aliphatic series a direct method was reported by Nickon and co-workers.³⁾ Enzymatic and radiolytic deaminations have also been studied.^{4,5)}

In this report, we describe a simple direct method for reductive deamination of amidines using sodium borohydride. When sodium borohydride was added to an aqueous solution of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride (**1a**),⁶⁾ the deamination occurred rapidly in good yield (see Chart 1). Thin layer chromatographic (TLC) analysis revealed that the product consisted of two components, 3-cyano-4,5-dihydro-1*H*-1,5-benzodiazepine (**4a**) and 3-cyano-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**6a**). The later compound **6a** was isolated in 37% yield by means of column chromatography on aluminum oxide with chloroform as an eluant. However, **4a** was gradually decomposed during the column chromatography, and only a small amount of **4a** was isolated as needles. Similarly, the reaction of ethyl 4-amino-1*H*-1,5-benzodiazepine-3-carboxylate hydrochloride (**1b**)⁶⁾ with sodium borohydride was carried out. A deaminated compound, 3-ethoxycarbonyl-4,5-dihydro-1*H*-1,5-benzodiazepine (**4b**), was obtained, but the tetrahydro derivative (**6b**) could not be isolated. During purification by column chromatography on aluminum oxide with chloroform as an eluant, **4b** was also decomposed.

The structures of **6a**, **4b** and **4a** were determined on the basis of nuclear magnetic resonance (NMR), mass (MS) and infrared (IR) spectral data. The H-NMR spectrum of **6a** showed multiplet signals for four aromatic protons at 6.55—6.58 ppm, and multiplet signals for one methine and four methylene protons at 3.00—3.65 ppm where signals for two amino protons

Fig. 1. ^{13}C -NMR Spectra of Compound **6a** (MeOD Solution)

are included. It is interesting that the methine proton resonated in the field of the methylene protons. This unusual result was explained by both the shielding effect of the aromatic ring for the methine proton and the deshielding effect for the methylene protons. The CPK model of **6a** shows that the methine proton is over the aromatic ring. The ^{13}C -NMR spectral data of **6a** are entirely in accord with the proposed structure (see Fig. 1). In MS analysis of **6a**, two main fragment ion peaks were observed. Namely, $\text{N}_1\text{-C}_2$ bond cleavage of the parent ion (m/e 173, M^+ , 45.5%) followed by McLafferty rearrangement may produce a fragment ion (**7**) [m/e 119, ($\text{M}^+ - \text{CH}_3\dot{\text{C}}\text{HCN}$), 100%] which may be converted to a fragment ion (**8**) (m/e 92, $\text{C}_6\text{H}_4^+ - \text{NH}_2$, 10.9%) by elimination of hydrogen cyanide through the McLafferty rearrangement. Moreover, the absorption band of the cyano group of **6a** was observed at 2255 cm^{-1} in the IR spectrum.

In MS analysis of **4b**, the same fragment ions described above were observed at m/e (100%) and m/e 92 (11.8%) in addition to fragment ions at m/e 189 (37.3%) and m/e 145 (58.8%), which may be due to de-ethylation and decarboxylation of the parent ion (m/e 218, M^+ , 52.9%), respectively. On the basis of these data, we determined the structure **4a** by MS analysis. Namely, the parent ion at m/e 171 (M^+ , 50%) and two main fragment ions at m/e 119 (100%) and m/e 92 (12%) were recognized. These fragment ions may be the same as those of **6a** and **4b**. In the IR spectrum of **4a**, the absorption band of the cyano group was observed at 2200 cm^{-1} , which was at lower wave number than that of **6a**. The reason for this shift is the $\text{C}=\text{C}$ double bond conjugated to the cyano group.

The deamination pathway is postulated to be as shown in Chart 2.⁷⁾ First, **1** is deaminated by a hydrogen anion to give **2** by nucleophilic substitution. Next, nucleophilic addition of a hydrogen anion to **2** affords **3** which withdraws a proton from water to give **4**. The C=C double bond of **4** is partially reduced to **6** via **5**. This reduction seems to be unusual, but it has already been reported that the C=C double bond of α,β -unsaturated carbonyl compounds is partially reduced to provide the saturated alcohols.⁸⁾

Chart 2

An attempt was made to react general amidines with sodium borohydride, and the results are listed in Table I. Benzamidine was converted to dibenzylamine and other amidines were also converted to the corresponding secondary amines. It is worth noting that this reaction only proceeds in water. When alcohol was employed as a solvent, the starting amidine was recovered. The formation pathway is shown in Chart 3, in which the amidine (**9**) may be deaminated to (**10**), followed by reduction to the amine (**11**) which reacts with **10** to afford **12**. The deamination of **12** affords the secondary amine, which was crystallized as the hydrochloride salt (**13**).

TABLE I. Secondary Amines

$$\text{R}-\text{C} \begin{array}{l} \nearrow \text{NH} \\ \searrow \text{NH}_2 \end{array} \cdot \text{HCl} \xrightarrow[\text{HOH}]{\text{NaBH}_4} \text{R}-\text{CH}_2-\text{CH}_2-\text{NH} \cdot \text{HCl}$$

No.	R	Recryst. solvent	Yield (%)	mp (°C)	Formula	M ⁺	Analysis					
							Calcd			Found		
							C	H	N	C	H	N
13 a		EtOH	23	253—256 ^{b)}	C ₁₄ H ₁₆ ClN	197	71.94	6.90	5.99	72.14	6.87	5.94
13 b	CH ₃ -	EtOH	21	263—266	C ₁₆ H ₂₀ ClN	225	73.41	7.70	5.35	73.39	7.83	5.41
13 c	CH ₃ - ^{a)}	EtOH + ether	11	hygroscopic	C ₄ H ₁₂ ClN	73	43.84	11.04	12.77	—	—	—
13 d	CH ₃ CH ₂ - ^{a)}	EtOH + ether	19	hygroscopic	C ₆ H ₁₆ ClN	101	52.35	11.72	10.17	—	—	—

^{a)} IR and MS spectra of these secondary amines coincided with those of authentic samples.

^{b)} lit. 9, mp 256—258°.

In conclusion, reductive deamination proceeds readily when amidine is reacted with sodium borohydride. In particular, acyclic amidines, both aromatic and aliphatic, were converted to the corresponding secondary amines.

Chart 3

Experimental

Elementary analysis was performed on a Perkin-Elmer 240 machine. Melting points were determined in a Yamato Scientific stirred liquid apparatus and are uncorrected. IR spectra were recorded on a Jasco IRA-1 (Japan Electron Optics Co., Ltd.). NMR and MS spectra were obtained on a JMS-PS-100 spectrometer with Me_4Si as an internal standard and on a JMS-D-100 spectrometer (Japan Electron Optics Laboratory Co., Ltd.), respectively.

3-Cyano-4,5-dihydro-1*H*-1,5-benzodiazepine (4a) and 3-Cyano-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride (1a) (1 g, 4.5 mmol) in 100 ml of water with stirring. The solution immediately decolorized. The mixture was stirred for 3 hr at room temperature to give crystals (0.71 g), which were recrystallized from water, mp 97–98° (TLC, two spots). The crystals were purified by column chromatography on aluminum oxide with chloroform as an eluant. The first eluate was evaporated to dryness under reduced pressure to give **6a** as a powder in 37% yield (0.29 g), mp 133°. *Anal.* Calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.51; H, 6.43; N, 24.31. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 2255 ($\text{C}\equiv\text{N}$). NMR solvent: $\text{CD}_3\text{-COCD}_3$.

The second eluate turned brown during the chromatography, and some needles of **4a** were precipitated on the glass wall of the flask. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 2200 ($\text{C}\equiv\text{N}$).

3-Ethoxycarbonyl-4,5-dihydro-1*H*-1,5-benzodiazepine (4b)—Sodium borohydride (0.08 g, 2.1 mmol) was added to a solution of ethyl 4-amino-1*H*-1,5-benzodiazepine-3-carboxylate (**1b**) (0.5 g, 1.9 mmol) in 50 ml of water with stirring. Decolorization of the solution occurred immediately, and after 10 min, a powder was precipitated. The powder (0.06 g) was collected by filtration and purified by chromatography (aluminum oxide, CHCl_3) to give **4b** as a powder in 5% yield (0.02 g), mp 143°. *Anal.* Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$: C, 66.04; H, 6.47; N, 12.83. Found: C, 66.22; H, 6.45; N, 12.88. NMR ($\text{DMSO}-d_6$) δ : 1.23 (3H, t, $J=7$ Hz, CH_3), 3.80 (4H, m, cyclic- CH_2), 4.08 (2H, q, $J=7$ Hz, CH_2CH_3), 5.60 (1H, b, NH), 6.77 (4H, s, aromatic), 7.38 (1H, d, $J=7.5$ Hz, olefinic), 8.93 (1H, d, $J=7.5$ Hz, NH).

General Procedure for Synthesis of Secondary Amines—Sodium borohydride (1.0 g) was added to a solution of an equimolar amount of benzamidinium hydrochloride, and the mixture was stirred for 3 hr at room temperature. The solution was extracted with chloroform and the extract was acidified with ethanolic hydrogen chloride. The solvent was evaporated off under reduced pressure to give crystals. Recrystallization from ethanol gave plates of dibenzylamine in 23% yield.

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Convenient Procedure for the Preparation of α -Amino Alcohols¹⁾

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Various N^α -protected amino acid active esters used in peptide chemistry were found to be excellent source materials for the preparation of the corresponding amino alcohols by reduction with sodium borohydride. The validity of this procedure for the convenient preparation of aliphatic alcohols was demonstrated by taking stearyl alcohol as an example.

Keywords—sodium borohydride reduction; N^α -protected L-amino alcohols; N^α -protected amino acid active esters; stearyl alcohol; stearic acid

Sodium borohydride is one of the most useful reducing agents for aldehydes and ketones, but not generally for carboxylic acid esters. Yamada *et al.*²⁻⁴⁾ reported that the facile reduction of optically active α -amino acid esters and their hydrochlorides with sodium borohydride took place to give the corresponding optically active α -amino alcohols in fairly good yields, and in better yields when the carboxylic acids were converted to the corresponding mixed anhydrides with ethyl chloroformate. Chaikin *et al.*⁵⁾ reported that acid chlorides were effectively reduced to alcohols by sodium borohydride.

Information now available indicates that carboxylic acids in activated forms with increased electrophilicity are more susceptible to sodium borohydride reduction. We found that a number of N^α -protected L-amino acid active esters, more stable activated derivatives than mixed anhydrides and acid chlorides, could be smoothly converted, under cooling with ice, to the corresponding N^α -protected amino alcohols with retention of the configuration.

In order to determine optimum reaction conditions, reduction of four active esters of Z(OMe)-Met-OH ; Z(OMe)-Met-OPCP , Z(OMe)-Met-OTCP ,⁶⁾ Z(OMe)-Met-OSu and Z(OMe)-Met-ONB , with sodium borohydride was performed in comparison with that of Z(OMe)-Met-OMe .

TABLE I. Preparation of Z(OMe)-Met-ol from the Various Active Esters

Z(OMe)-Met-OR	NaBH_4 (eq.)	Temp. (°C)	Time (min)	Yield (%)	$[\alpha]_D^{25}$ (MeOH)
TCP	10	10	15	87	-24.2
TCP	5	10	15	85	-24.2
PCP	5	10	15	88	-23.8
Su	5	10	15	93	-23.9
NB	5	10	15	75	-24.1
Me	5	25	120	92	-24.1