Synthetic Utility of Amine–Cyanoborane Complexes as Reducing Agents

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Investigations with amine–cyanoborane complexes as new viable reducing agents have shown that the reactivity of amine–cyanoborane complexes is highly dependent on the nature of the component amine and on the solvent used, and that the amine–cyanoborane complexes derived from primary amines are highly efficient and chemoselective reducing agents compared to those derived from secondary and tertiary amines.

Reducing behavior of amine–borane complexes towards aldehydes and ketones has been widely investigated with mixed success.[1—3] However, in spite of possessing desirable properties such as thermal and hydrolytic stability and solubility in protic and aprotic solvents, the use of amine–borane complexes as viable reducing agents in synthetic organic chemistry is rather minimal. Apparently, one of the principal reasons for their disuse is the sluggish nature of their reaction in the absence of a Lewis acid catalyst. Although a number of amine–cyanoborane complexes have been known,[4—7] no investigation on their behavior as reducing agents has heretofore been reported. We, therefore, report here the results of investigations on some amine–cyanoborane complexes as viable reducing agents, vis-a-vis with those of an amine–borane complex analog and sodium cyanotrihydroborate[8] on a highly susceptible substrate, viz. 4-nitrobenzaldehyde.

Results and Discussion

The reaction occurs at pH ca. 3—4 in ethanol or THF medium, and the overall reaction which occurs in 1 : 1 mole ratio of the substrate and reagent, may be represented simply as,

$$> C{=}O \xrightarrow[(H^+)]{R_{3-n}H_nNBH_2CN\ (n = 1, 2)} > CHOH.$$

As the reactions in this study are carried out at room temperature the problem of polymerization as observed with amine–borane complexes in high boiling ethereal solvents[1a] can be avoided to a large extent. Also the liberated amine can be very easily removed due to its volatility. The reactivity of amine–cyanoborane complexes depends considerably on the nature of the component amine. For example, trimethylamine–cyanoborane complex,[4b] one of the earliest reported amine–cyanoborane complexes, is very stable in acid media, even at pH 2 or lower[9] and, therefore, is unsuitable for such purpose. In the course of our investigations with various amine–cyanoborane complexes, we have found butylamine–cyanoborane complex[6] to be a very satisfactory reagent, because of its high air, moisture and thermal stability and high solubility in protic and aprotic solvents. Moreover, the yield of butylamine–cyanoborane complex in its preparation is satisfactory. Propylamine–cyanoborane complex is also found to reduce the carbonyl compounds very satisfactorily, but it is less suitable as a reagent due to its less air and moisture stability and the poor yield in its synthesis. Propylamine–cyanoborane complex reduced the highly susceptible 4-nitrobenzaldehyde with the highest products yield (87%), while butylamine–cyanoborane complex reduces the same with 82% product yield which is quite comparable to the former. It is found that the reactivity of amine–cyanoborane complexes decreases in the order of primary, secondary, and tertiary amine in the reagent. Thus, dibutylamine–cyanoborane complex reduces 4-nitrobenzaldehyde with 16% yield of the product, and the corresponding tertiary amine complex, tributylamine–cyanoborane complex yields no detectable amount of the alcohol with the same substrate. The results thus indicate the importance of the steric factor rather than electronic factor.[10] The results are given in Table 1.

Reductions of several aldehydes and ketones, both aliphatic and aromatic, have, therefore, been investigated in acidic ethanol with two amine–cyanoborane complexes, viz. butylamine–cyanoborane complex and propylamine–cyanoborane complex. Reductions of 4-nitrobenzaldehyde, 2-nitrobenzaldehyde and 4-chlorobenzaldehyde with butylamine–cyanoborane complex in acidic tetrahydrofuran (THF) were also studied. The results indicate THF as an inferior solvent. Similarly, the results of reduction of 4-nitrobenzaldehyde and 2-nitrobenzaldehyde in acidic aqueous medium indicate that water is even more inferior than THF. For comparison, butylamine–borane complex and sodium cyanotrihydroborate have been investigated with the highly susceptible substrate, 4-nitrobenzaldehyde. The results indicate that they are somewhat inferior reagents under similar experimetal conditions for the substrate under question. All the results are shown in Table 1.

Functionalized aromatic aldehydes and ketones have been used for the purpose of studying selective reduction. Reductions were carried out in ethanol, water, and THF (all at pH ca. 3.1—4.4) using Methyl Orange indicator. It has been observed that in acidic ethanol medium 4-nitrobenzaldehyde was reduced to the greatest extent producing 82% (after purification) of the corresponding alcohol. These are followed by 2-nitrobenzaldehyde (70%) and 3-nitrobenzaldehyde (56%) in

Table 1. Comparative Reducing Behavior of Amine–Cyanoborane Complexes, Butylamine–Borane Complex, and $NaBH_3CN$

Amine–cyanoborane (Amine=) /other borane reagents	Carbonyl compound	Solvent	Product alcohol	Mp °C	Yield[a] %
Propylamine	4-Nitrobenzaldehyde	Ethanol	4-Nitrobenzyl alcohol	92	87
Propylamine	4-Chlorobenzaldehyde	Ethanol	4-Chlorobenzyl alcohol	70	80
Butylamine	4-Nitrobenzaldehyde	Ethanol	4-Nitrobenzyl alcohol	92	82
Butylamine	4-Chlorobenzaldehyde	Ethanol	4-Chlorobenzyl alcohol	70	70
Dibutylamine	4-Nitrobenzaldehyde	Ethanol	4-Nitrobenzyl alcohol	92	16
Dibutylamine	4-Chlorobenzaldehyde	Ethanol	4-Chlorobenzyl alcohol	70	12
Tributylamine	4-Nitrobenzaldehyde	Ethanol	No reaction	—	—
Butylamine	4-Nitrobenzaldehyde	THF	4-Nitrobenzyl alcohol	92	72
Butylamine	4-Nitrobenzaldehyde	Water	4-Nitrobenzyl alcohol	92	40
Butylamine	2-Nitrobenzaldehyde	THF	2-Nitrobenzyl alcohol	72	50
Butylamine	2-Nitrobenzaldehyde	Water	2-Nitrobenzyl alcohol	72	30
Butylamine	4-Chlorobenzaldehyde [b]	THF	4-Chlorobenzyl alcohol	70	52
Butylamine–Borane	4-Nitrobenzaldehyde	Ethanol	4-Nitrobenzyl alcohol	92	77
$NaBH_3CN$	4-Nitrobenzaldehyde	Ethanol	4-Nitrobenzyl alcohol	92	80

a) Yields reported here are after purification and separation by chromatography. b) Cannot be done in water due to immiscibility of the aldehyde with water.

terms of yields of the corresponding alcohol (purified and separated by chromatography) when the reactions were carried out under similar experimental conditions. This is, of course, what is expected from their steric and –I effect. The NO_2 group was not reduced as was evident from their melting points and infrared and ^1H NMR spectra of the products. Other functional groups such as phenolic –OH and $-OCH_3$, aryl halides, olefinic double bonds remained unaffected by the reagents. 2-Furaldehyde, a heterocyclic aromatic carbonyl compound, was found to polymerize under the experimental conditions studied here. It has also been found that amides and esters were not reduced by butylamine–cyanoborane complex or propylamine–cyanoborane complex. The ν(OH) modes in the products appear in the region 3520—3180 cm^{-1} with concurrent absence of the carbonyl bands appearing in the region 1730—1620 cm^{-1} for the parent compounds. For the nitro compounds no amine group was detected either in the infrared or in the ^1H NMR spectra. The results are summarized in Table 2.

In aprotic solvents such as THF or glyme, the amine–borane complexes were reported to follow a dissociative mechanism for the reduction.[3] But in the case of amine–cyanoborane complexes, as the reactions are performed in acidic medium, the potential carbocation character of carbonyl carbon atom is enhanced by the protonation of the carbonyl oxygen. This may, then, be attacked by the reagent in a nucleophilic path as follows (Eqs. 1 and 2):

$$>\overset{\delta+}{C}=\overset{\delta-}{O}\xrightarrow{H^+}>C=\overset{+}{O}-H, \quad (1)$$

$$>C=\overset{+}{O}-H+R_{3-n}H_nN\underset{H}{B}HCN\xrightarrow{\text{r.d.s.}}>CHOH. \quad (2)$$

This is also supported by the mechanism of acid hydrolysis of amine–cyanoborane complexes which undergo stepwise hydride liberation[9] during hydrolysis. The second step i.e. the hydride transfer may be the rate determining step. If this be the path followed, there should be an effect of the bulkiness of the reagent on the rate of the reaction which is also found to be true for acid hydrolysis.[9] A primary amine being least bulky, the nucleophilic attack by a primary amine–cyanoborane complex in the rate determining step will be most facilitated. The nature of the alkyl of aryl groups attached to carbonyl group also affects the yield of the product.[10] Thus aromatic aldehydes having –I groups, viz. $-NO_2$, –Cl, –Br in the 2- and 4-positions give better yields of alcohols compared to those having +R groups, as in the cases 4-hydroxybenzaldehyde and cinnamaldehyde. 4-Nitrobenzaldehyde gives better yield than 2-nitrobenzaldehyde due to steric factor. Butylamine–cyanoborane complex chemoselectively reduces an aldehyde in presence of an active ketone. For example, benzaldehyde and 4-nitrobenzaldehyde are reduced selectively in the presence of cyclohexanone. Also benzaldehyde is selectively reduced to benzyl alcohol in the presence of acetophenone. No measurable amounts of cyclohexanol in the first case and 1-phenylethanol in the second case are detected, when one molar proportion of the reducing agent is used. Cyclopentanone yields 42% of cyclopentanol when one molar proportion of the reducing agent is used, while 20% conversion of 2-cyclohexenone to 2-cyclohexenol without affecting the unsaturation has been achieved under similar conditions. Even with excess of reducing agent the unsaturation remains unaffected. The results are given in Table 2.

Experimental

All chemicals and reagents were of reagent grade quality. The solvents were dried by standard methods[11] and the amine–cyanoborane complexes were prepared by literature method.[6] While butylamine–borane complex was prepared

Table 2. Reduction of Carbonyl Compounds with Butylamine–Cyanoborane Complex in Ethanol

Carbonyl compound	Product alcohol	Mp/°C (lit)	Yield %	ν(OH) cm^{-1}	ν(C=O) cm^{-1}
Benzaldehyde	Benzyl alcohol	Liq	70	3400	1707
4-Nitrobenzaldehyde	4-Nitrobenzyl alcohol	92(93)	82	3520	1707
2-Nitrobenzaldehyde	2-Nitrobenzyl alcohol	72(74)	70	3320	1700
3-Nitrobenzaldehyde	3-Nitrobenzyl alcohol	25(27)	56	3440	1730
4-Chlorobenzaldehyde	4-Chlorobenzyl alcohol	70(71—72)	70	3380	1690
4-Bromobenzaldehyde	4-Bromobenzyl alcohol	76(77)	70	3480	1660
2-Hydroxybenzaldehyde	2-Hydroxybenzyl alcohol	86(87)	47	3440 3180	1650
4-Methoxybenzaldehyde	4-Methoxybenzyl alcohol	Liq	68	3518	1624
Cinnamaldehyde	Cinnamyl alcohol	Liq	40	3412	1682
Acetone	2-Propanol[a)]	Liq	41	3355	1725
Acetophenone	1-Phenylethanol	Liq	45	3362	1689
Benzophenone	Diphenylmethanol	66(68)	40	3380	1660
Cyclopentanone	Cyclopentanol	Liq	42	3440	1740
Cyclohexanone	Cyclohexanol	Liq	53	3358	1715
2-Cyclohexen-1-one	2-Cyclohexen-1-ol	Liq	20	3480	1720
4-Nitrobenzaldehyde+ cyclohexanone (1 : 1)[b)]	4-Nitrobenzyl alcohol (No cyclohexanol)	92	80	3520	1707
4-Nitrobenzaldehyde+ cyclohexanone (1 : 1)[c)]	4-Nitrobenzyl alcohol and cyclohexanol		81 46	3520 3358	1707 1715
Benzaldehyde+ cyclohexanone (1 : 1)[b)]	Benzyl alcohol (No cyclohexanol)		67	3400	1707
Benzaldehyde+ cyclohexanone (1 : 1)[c)]	Benzyl alcohol and cyclohexanol		68 51	3400 3358	1707 1715
Benzaldehyde+ acetophenone (1 : 1)[b)]	Benzyl alcohol (No 1-phenylethanol)		67	3400	1707
Benzaldehyde+ acetophenone (1 : 1)[c)]	Benzyl alcohol and 1-phenylethanol		62 46	3400 3362	1707 1689

a) Yield determined by quantitative programme of IR spectrophotometer model PE 883. b) With 1 molar proportion of reducing agent. c) With 2 molar proportion of reducing agent.

by the $NaBH_4$ and butylamine hydrochloride following literature methods,[12] $NaBH_3CN$ was a Sigma (U.S.A) product. ^1H NMR spectra were recorded on a JEOL JNM-FX-100 spectrometer and IR spectra on a Perkin–Elmer 883 spectrophotometer using NaCl cells.

Method I : The following general procedure, applicable to both butylamine–cyanoborane complex and propylamine–cyanoborane complex as reducing agents, has been used. A mixture of an amine–cyanoborane complex (3.5 mmol) and a carbonyl compound (3.5 mmol, 1 : 1 mole ratio) and a trace amount of Methyl Orange in absolute ethanol (50 ml) was stirred along with a dropwise addition of ethanolic HCl till the color changed to red. The acidity was then maintained by continuing the addition of ethanolic HCl in the same fashion until the color persisted for 30 min. The stirring was continued for another 30 min. Solvent was then removed on a rotary evaporator (or on a water bath) and the residue was then extracted with peroxide free dry ether except for 2-cyclohexenone where dry chloroform was used as extractor. On removal of solvent the desired alcohol was obtained as a crude product. This was finally purified by column chromatography on silica gel using ethyl acetate–petroleum ether (40—60°C) mixture (10 : 1 v/v) as eluent.

In case of reductions of mixtures, the products were separated by column chromatography using the same eluent as noted before.

Method II : General Procedure in Water Medium. An amine–cyanoborane complex (3.5 mmol) and a carbonyl compound (3.5 mmol) were taken in a 100 ml round-bottom flask containing a magnetic stirring bar. To this 50 ml of water and a trace amount of Methyl Orange indicator were added, and the mixture was stirred with dropwise addition of dil HCl till the color changed to red. The mixture was then stirred at room temperature for 24 h and filtered. The filtrate on evaporation gave a residue from which a crude alcohol was obtained by treating with ice. This was separated by filtration and purified by column chromatography as described under Method I.

Reduction of 4-Nitrobenzaldehyde by $NaBH_3CN$. This reaction was carried out using 4-nitrobenzaldehyde (3.5 mmol) and $NaBH_3CN$ (3.5 mmol) in acidic ethanol following Method I up to the removal of the solvent. The residue thus left was taken with 5 ml water, saturated with sodium chloride and was extracted with four 5 ml portions of peroxide free ether. The combined ether extract yielded crude 4-nitrobenzyl alcohol on removal of the solvent. This was finally purified by column chromatography as described under Method I. Yield 80%.

Reduction of 4-Nitrobenzaldehyde with Butylamine–Borane Complex. The method was the same as in Method I up to the removal of the solvent. The residue thus obtained was stirred with crushed ice when 4-nitroben-

zyl alcohol precipitated. This was separated by filtration and finally purified by column chromatography as described under Method I. Yield 77%.

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