# Reductive Aminations of Ketones and Aldehydes using Borane–Pyridine

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Borane–pyridine is introduced as a cheap and readily available alternative to sodium cyanotrihydroborate for the purpose of the reductive amination of a wide variety of carbonyl compounds. It does not suffer from the severe toxicity associated with sodium cyanotrihydroborate.

In both biological and chemical systems the reductive amination of aldehydes and ketones is an important transformation which allows the direct conversion of carbonyl compounds into amines. Ignoring possible protonated forms of the intermediates the reaction proceeds as in equations (1)—(3).

$$R^1R^2CO + R^3NH_2 \rightleftharpoons R^1R^2C(OH)\cdot NHR^3 \quad (1)$$

$$R^1R^2C(OH)NHR^3 \rightleftharpoons R^1R^2C{:}NR^3 + H_2O \quad (2)$$

$$R^1R^2C{:}NR^3 \xrightleftharpoons{\text{reductant}} R^1R^2CHNHR^3 \quad (3)$$

$$R^1R^2CO \xrightarrow{\text{reductant}} R^1R^2CHOH \quad (4)$$

For the overall process to succeed there should, at equilibrium, be a reasonable concentration of imine and conditions should be such that there is excellent discrimination between reduction of the intermediate imine [equation (3)] and reduction of the initial carbonyl compound [equation (4)]. The reductant used must, of course, be stable to the optimal conditions for imine formation and reduction.

In general the formation of imines and enamines is aided by acid catalysis[1,2] and such conditions hold out the prospect that equation (3) will be superseded by the very ready nucleophilic reduction of protonated imine. Imines are considerably more basic than carbonyl compounds and hence should protonate preferentially, thus directing reduction mainly to the nitrogeneous species at the expense of the starting carbonyl compound.[3] Such an analysis demands nucleophilic reductants that are acid stable, a rather difficult condition to meet. In addition, for biological systems in general, a reactant compatible with hydroxylic solvents is required.

Sodium tetrahydroborate readily reduces imines and ketones in neutral conditions but in acid media decomposition of the reductant is rapid and therefore reductive amination is difficult. Nevertheless, reductive aminations involving *aromatic* amines and aldehydes have been carried out by use of sodium tetrahydroborate in the presence of a carboxylic acid at room temperature.[4] Raising the temperature causes acylation of the product amine followed by reduction.[4]

Due to the electron-withdrawing cyanide group attached to boron, cyanotrihydroborates are milder and more selective reductants than tetrahydroborates. They are relatively stable under mildly acid conditions, in which they readily reduce enamines[5] and imines[6] and this has made them the reductants of choice for reductive aminations.[7,8] However, for industrial usage and for *N*-alkylation in biological systems the use of poisonous sodium cyanotrihydroborate is unattractive as is the work-up, in which great care must be exercised with respect to sodium cyanide and hydrogen cyanide.

Borane–amine complexes exhibit a graded range of reactivity dependent on the stereoelectronic requirements of the complexing amine.[9,10] Thus complexes of borane with weakly basic amines of medium to large steric requirements behave, like borane–tetrahydrofuran (THF), as electrophilic reagents. However, borane complexes of strong bases of little steric demand have a 'hydroborate-like' character. Thus borane–trimethylamine has been reported to be completely hydrolysed by 1M-hydrochloric acid in water–ethylene glycol (1:1) at 25 °C in 1 000 min compared with complete hydrolysis of borane–*N*,*N*-diethylaniline in 2 min under the same conditions. Similarly borane–trimethylamine is a very poor hydroborating agent compared with borane–*N*,*N*-diethylaniline.[11] Borane–t-amine complexes reduce ketones and aldehydes rather slowly, although there is a striking rate enhancement in the presence of mineral or Lewis acids.[12] Borane–ammonia and borane–t-butylamine are excellent reductants for imines, enamines, and iminium salts[13,14] but are also very useful reagents for the chemo- and stereo-selective reductions of aldehydes and ketones under *neutral* conditions in both aqueous and organic media.[15] Hence they are unlikely to possess the necessary selectivity for reductive amination.

In our search for alternatives to the cyanohydroborates as reductants for reductive aminations we chose to concentrate on borane–pyridine (BAP) rather than say borane–dimethylamine[16] or borane–trimethylamine[17] for the following reasons. (1) BAP is a cheap chemical, produced commercially on a large scale. (2) The borane is reasonably strongly complexed and has hydroborate character. (3) In neutral media, BAP is a particularly poor reductant for ketones and aldehydes.[15,18] Thus 4-t-butylcyclohexanone is completely reduced by borane–ammonia or borane–t-butylamine in 15 min, whereas after 18 h reduction with BAP is only 29% complete.[15] Benzaldehyde in refluxing diethyl ether is not reduced after 3 h.[18] Thus selectivity should be possible with BAP. In the presence of trifluoracetic acid, BAP reacts with aldehydes to give ethers, with aliphatic ketones to give alcohols, and with aromatic ketones to give alkanes.[19] (4) The pyridine released during the reaction cannot compete with a secondary or primary amine for the carbonyl component.

## Results

We first studied the decomposition of BAP under acid conditions as compared with sodium cyanotrihydroborate (Figure). In 5M-HCl, BAP rapidly decomposes to a greater extent than sodium cyanotrihydroborate. However, in acetic acid, sodium cyanotrihydroborate loses one of its hydrogen atoms in 5 min, *whereas BAP is not decomposed even after* 60 min. Thus it is safe to use BAP as a reductant in the presence of a carboxylic acid, without the need for excess of reagent to allow for decomposition.

With this assurance we studied the interaction of benzaldehyde and acetophenone with substituted anilines at 25 °C in the presence of equimolar quantities of BAP [equation (5)].

In neutral media no reductive amination is observed. However, in glacial acetic acid, benzaldehyde condenses in a

**Table 1.** Reductive amination of benzaldehyde and acetophenone with anilines using BAP [a]

| Carbonyl compd. | 1° Amine | Solvent | BAP | % Yield of 2° amine |
|---|---|---|---|---|
| PhCHO | $PhNH_2$ | AcOH | 1M in $CH_2Cl_2$ | (**3a**) 93 [b] |
| PhCHO | $p$-$MeOC_5H_4NH_2$ | AcOH–$CH_2Cl_2$ (1:1) | 1M in $CH_2Cl_2$ | (**3b**) 94 [b] |
| PhCHO | $p$-$NO_2C_6H_4NH_2$ | AcOH–THF (1:1) | 1M in $CH_2Cl_2$ | (**3c**) 76 [b] |
| Acetophenone | $PhNH_2$ | AcOH | neat | (**3d**) 69 [b] |
| Acetophenone | $p$-$MeOC_6H_4NH_2$ | AcOH–$CH_2Cl_2$ (1:1) | neat | (**3e**) 72 [b] |
| Acetophenone | $p$-$MeOC_6H_4NH_2$ | AcOH–$CH_2Cl_2$ (1:1) | 1M in $CH_2Cl_2$ | (**3e**) 60 [b] |
| Acetophenone | $p$-$NO_2C_6H_4NH_2$ | AcOH–THF (1:1) | neat | (**3f**) <10 [c] |

[a] Equimolar proportions of reactants. [b] Isolated yields. [c] Estimated by g.c.

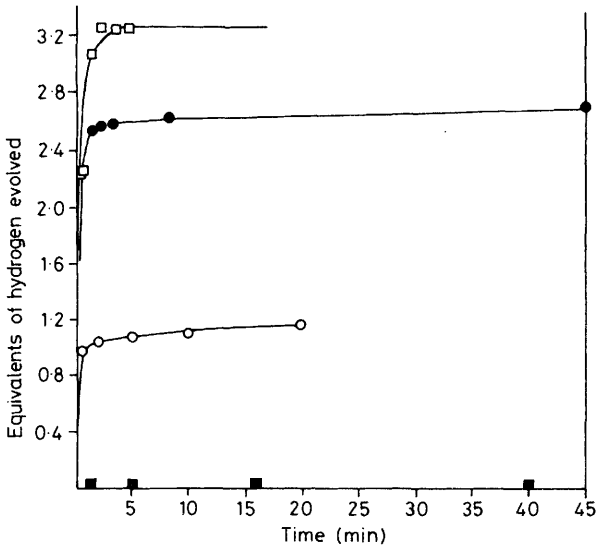
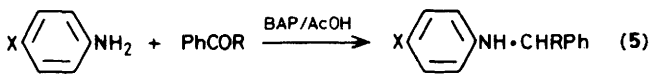



**Figure.** Hydrolysis of borane–pyridine and sodium cyanotrihydroborate in 5M-HCl solution and in glacial acetic acid (AcOH) at 25 °C: □ = pyridine–borane in 5M-HCl; ● = $NaBH_3CN$ in 5M-HCl; ■ = pyridine–borane in AcOH; ○ = $NaBH_3CN$ in AcOH




(1) (2) (3)

**a**; X = H, R = H
**b**; X = OMe, R = H
**c**; X = $NO_2$, R = H
**d**; X = H, R = Me
**e**; X = OMe, R = Me
**f**; X = $NO_2$, R = Me

satisfactory fashion with the anilines tried (Table 1), it being particularly noteworthy that even the weakly basic *para*-nitroaniline could be successfully utilised. Optimal conditions (*e.g.* increase in the excess of reductant) were not sought for these reactions. From acetophenone satisfactory yields of (**3d**) and (**3e**) were obtained but (**3f**) could not be produced in good yield in this fashion.

Presumably the equilibrium in equation (1) is displaced to the left and possibly also protonation and reduction of any imine present is less favoured.

The reaction of acetophenone with *p*-methoxyaniline to give (**3e**) was then used for a rough assessment of the effectiveness of BAP for reductive amination as compared with other reductants (Table 2). The conditions could not be exactly standardised owing to the instability of some of the reagents in acids, and therefore conditions as near optimal as possible were chosen. For sodium cyanotrihydroborate, standard conditions for reductive amination were used.[5,6] It is clear that for this particular reaction BAP would be the reagent of choice.

**Table 2.** Use of reductants other than BAP for the reductive amination of acetophenone with *p*-methoxyaniline [a]

| Reductant | Solvent | % Yield of (**3e**) |
|---|---|---|
| $NaBH_4$ | 95% EtOH, two drops of AcOH | 0 [a] |
| $NaBH_3CN$ | MeOH–AcOH (1:1) | 55 [b] |
| $BH_3{\cdot}SMe_2$ | $CH_2Cl_2$, two drops of AcOH | 11 [b] |

[a] All acetophenone reduced to alcohol. [b] Remaining acetophenone reduced to alcohol.

The same reductive amination was systematically studied in an effort to define optimal yield conditions. When co-solvents were used (ratio of glacial acetic acid to co-solvent was 2:7) the yields of (**3e**) were for toluene 77%, dichloromethane 63%, and tetrahydrofuran 41%. Thus either reductive amination is favoured or carbonyl reduction is suppressed in less polar media.

In the glacial acetic acid–dichloromethane system, reductive amination is favoured at higher temperatures. Thus at 0 °C the yield was 41%, at 22 °C it was 63%, and at 35—40 °C it was 81%. Hence heating equimolar quantities of carbonyl compound, amine, and BAP in a glacial acetic acid–nonpolar solvent system should be favourable.

In all these cases, BAP was added immediately after mixing the components as was done with sodium cyanotrihydroborate.[5] We wondered whether a pre-reduction equilibration period would be beneficial. On mixing the components at 22 °C imine formation was immediate but the imine was present in only *ca.* 10% molar ratio (g.c.). No increase in imine concentration was noted over a 2 h period. Despite this, in glacial acetic acid alone at 22 °C a 2 h equilibration period before adding BAP increased the yield of (**3e**) from 40 to 69%. However, when glacial acetic acid–light petroleum (b.p. 40—60 °C) was used, no difference in isolated yield (82%) was observed with or without a pre-reduction period. The glacial acetic acid–light petroleum system is of particular interest since it was the only two-phase system used. It is possible that there is an advantageous partitioning occurring here—the protonated imine and reductant being present mainly in the polar phase whilst acetophenone is largely present in the light petroleum.

The production of (**3e**) was followed under identical conditions of concentration and time in (i) glacial acetic acid, (ii) dichloromethane with a catalytic quantity of glacial acetic acid, (iii) dichloromethane, and (iv) a two-phase system involving dichloromethane and an aqueous acetic acid–sodium acetate buffer at pH 4.6. The corresponding yields (g.c.) were 79%, 6%, trace, and trace. In glacial acetic acid, the only usable system, the acetophenone was quantitatively accounted for as (**3e**) or as 1-phenylethanol.

We then attempted to extend the BAP reductive amination process to a wider variety of substrates. A standard procedure

**Table 3.** Reductive amination of ketones by primary amines

| Ketone | 1° Amine | % Yield of 2° amine |
|---|---|---|
| Cyclohexanone | Aniline | 93[a] |
| Cyclohexanone | Cyclohexylamine | 63[b] |
| 2-Methylcyclohexanone | Aniline | 83[a] |
| Camphor | Aniline | < 5%[c] |
| Acetophenone | Octylamine | Trace[d] |
| Acetophenone | Cyclohexylamine | < 10%[d] |

[a] Isolated yield of amine. [b] Yield is of recrystallised hydrochloride. [c] Incomplete reduction of camphor. [d] Acetophone is reduced to 1-phenylethanol.

was adopted with no attempt being made to optimise any single reaction. In general, the carbonyl compound was mixed with a solvent system consisting of glacial acetic acid and light petroleum (2:7) and an equimolar quantity of amine was added. The mixture was stirred at room temperature for 2 h, after which an equimolar quantity of neat BAP was added and the reaction stirred for a further 2 h prior to work-up. This procedure had to be modified for the reactions of aldehydes where over-reaction was observed when equimolar quantities of reactants were used (*vide infra*).

Cyclohexanone or 2-methylcyclohexanone react satisfactorily with either aniline or cyclohexylamine (chosen as the aliphatic analogue of aniline). However, as with similar reactions using sodium cyanotrihydroborate, more hindered or less reactive ketones were simply reduced to the corresponding alcohol (Table 3).

From 2-methylcyclohexanone the *cis*- and *trans*-phenylamines were produced in a ratio of 66:34. The assignments were made on the basis of the peak areas of the peaks (CH–N) at δ 3.4 and 2.8 respectively, in the $^1$H n.m.r. spectra, in accord with the chemical shifts[14] and coupling patterns. The preponderance of equatorial attack by BAP is similar to the results obtained by attack of hydride reagents on the imine derived from 2-methylcyclohexanone and benzylamine.[13,14] In that case reduction by sodium cyanotrihydroborate gave a *cis*:*trans* ratio of 64:36[14] or 76:24.[13] More bulky and faster acting reductants give *cis*-product almost completely.[14]

1-Phenylethanol is the only isolable product from the reactions of cyclohexylamine and n-octylamine with acetophenone in the presence of BAP and acetic acid. This failure to give secondary amines is thought to be due to an extremely low standing concentration of imine in these cases. This arises from two factors. The first is that the more basic aliphatic amines will be more readily protonated than aromatic amines in acetic acid and hence the concentration of free aliphatic amine, the active nucleophile in equation (1), will be low.* This will be of particular importance in the case of a slow interaction with ketones as compared with a rapid reaction with aldehydes. The second factor is that equation (2) proceeds less readily to the right to give imines in the case of aliphatic amines as compared with aromatic amines. This, in turn, is due to the lower degree of conjugation of the derived imine in the case of aliphatic amines.

Reductive aminations of all aldehydes with primary amines show a tendency to over-reaction (Table 4) due to competition for the aldehyde between the primary amine and the product secondary amine. This is also a feature of reductive aminations using sodium cyanotrihydroborate and, in that case, was solved by use of a six-fold excess of primary amine.[5] Using such conditions it was clear (g.c.) that reactions between

* We thank a referee for pointing out this factor.

**Table 4.** Reductive aminations of aldehydes with equimolar quantities of primary amines

| Aldehyde | 1° Amine | 2° Amine | 3° Amine[a] |
|---|---|---|---|
| Benzaldehyde | Cyclohexylamine | 93 | 7 |
| Benzaldehyde | Octylamine | 74 | 26 |
| Octanal | Cyclohexylamine | 82 | 18 |
| Octanal | Octylamine | 54 | 46 |

[a] Estimated from g.c. peak areas.

benzaldehyde and cyclohexylamine and n-octylamine give excellent yields of the desired secondary amine with little, if any, of contaminant tertiary amine. Separation of the product however from the excess of primary amines was a little difficult and the yield of isolated cyclohexylbenzylamine (as the recrystallised hydrochloride) was 69% and of octylbenzylamine (as the recrystallised hydrochloride) was 67%.

A few general comments on the separation of the products are in order. (i) Aniline derivatives are readily separated by flash chromatography on silica gel. (ii) Products derived from aliphatic amines do not give such clean separations. Distillation is therefore the best method of isolation, particularly when a large excess of primary amine is used. (iii) In the quenching of reaction mixtures there is occasionally a precipitate of amine hydrochloride (*e.g.* in the reactions between cyclohexylamine and benzaldehyde and cyclohexanone). The precipitated salt is derived almost exclusively from the desired secondary amine and is readily isolated and recrystallised.

It is clear that borane–pyridine is a cheap, clean reducing reagent, highly suitable for a wide variety of reductive amination reactions for which it should always be considered.

## Experimental

I.r. spectra were recorded on a Pye Unicam SP1050 spectrophotometer, $^1$H n.m.r. on a Hitachi-Perkin-Elmer R24B at 60 MHz and a Varian HA100 spectrometer at 100 MHz. Mass spectra and accurate mass measurements were taken on an A.E.I. MS9 mass spectrometer. Gas–liquid chromatograms were run on a Pye 104 programmed chromatograph fitted with a 6 ft × 0.25 in glass column packed with 4% Dexsil on Chrom 9 AW/OMCS, 100—120 mesh.

Borane–pyridine (Aldrich) was used as obtained. Ethers and hydrocarbons were pre-dried and finally distilled from lithium aluminium hydride under nitrogen. Dichloromethane and acetic acid were distilled under nitrogen from phosphorus pentaoxide. Aldehydes and ketones were dried over and distilled from calcium sulphate. Amines were distilled from calcium hydride or recrystallised and stirred over phosphorus pentaoxide.

*Reductive Aminations.*—All products were characterised by i.r., $^1$H n.m.r., and mass spectrometry and compared directly with authentic samples. Details of exploratory experiments are given in the text and therefore only one example of each of the three general methods used is given here.

*Reductive Amination of Acetophenone with* p-*Methoxyaniline to give* 4-*Methoxy*-N-(1-*phenylethyl*)*aniline.*—A dry round-bottomed flask (50 ml) fitted with a magnetic follower and protected by a serum cap was flushed with argon and charged with dry light petroleum (b.p. 40—60 °C) (7 ml) and dry, glacial acetic acid (2 ml). Acetophenone (1.17 ml, 10 mmol) and 4-methoxyaniline (1.23 g, 10 mmol) were added by syringe after which the solution was stirred whilst BAP (1.20 ml, 10 mmol) was added dropwise over 15 min; the mixture was then

stirred at room temperature for 2 h. The serum cap was removed and 5M-hydrochloric acid (6 ml) added dropwise. After 15 min, when gas evolution had ceased, the mixture was diluted with water (20 ml) and extracted with diethyl ether (2 × 25 ml). The acid aqueous phase was made strongly basic with 5M-NaOH solution, and re-extracted with ether (3 × 25 ml). The combined ether extracts after basification were washed with saturated aqueous sodium chloride (1 × 25 ml), dried ($MgSO_4$), filtered, and concentrated to give an oil (2.53 g). Flash chromatography on Kieselgel 60 (45 g, 34—60 μm, dichloromethane as eluant) gave 4-methoxy-*N*-(1-phenylethyl)-aniline, m.p. 64.5—65.6 °C (lit.,[20] m.p. 64—65 °C).

*Reductive Amination of Cyclohexanone with Cyclohexylamine to give Dicyclohexylamine.*—Using the apparatus described above, cyclohexanone (1.04 ml, 10 mmol) and cyclohexylamine (1.14 ml, 10 mmol) were added to light petroleum (b.p. 40—60 °C) (7 ml) and dry glacial acetic acid (2 ml). The solution was then allowed to stand for 2 h at room temperature after which BAP (1.2 ml, 10 mmol) was added dropwise with stirring over 10 min. The reaction was stirred for 2 h after which the serum cap was removed and 5M-hydrochloric acid (6 ml) added. During addition of the acid, the secondary amine hydrochloride was precipitated and this was collected on a sinter. The precipitate was washed with a solution of sodium chloride (10 g) in 3M-hydrochloric acid (100 ml) and then with light petroleum (b.p. 30—40 °C; 3 × 30 ml); it was then dissolved in chloroform. The chloroform solution was dried ($MgSO_4$), filtered, and concentrated to give the dicyclohexylamine hydrochloride (1.58 g). Recrystallisation from methanol–ethyl acetate gave dicyclohexylamine hydrochloride (1.37 g, 63%) identical in all respects with an authentic sample.

*Reductive Amination of Benzaldehyde with Octylamine to give N-Benzyloctylamine.*—To a dry, argon-filled round-bottomed flask (100 ml) containing a magnetic stirrer bar and protected by a serum cap were added n-octylamine (9.9 ml, 60 mmol), benzaldehyde (1.02 ml, 10 mmol), light petroleum (b.p. 40—60 °C) (17.5 ml), and dry glacial acetic acid (5 ml). The addition of glacial acetic acid led to an exothermic reaction and resulted in a one-phase reaction mixture which was allowed to stand for 2 h. BAP (1.20 ml, 10 mmol) was then added dropwise with stirring over 10 min after which the mixture was stirred for 2 h. The serum cap was removed and 5M-hydrochloric acid (12 ml) added. After gas evolution has ceased the solution was basified with 5M-sodium hydroxide solution and extracted with diethyl ether (3 × 25 ml). The combined ethereal extracts were dried ($MgSO_4$), filtered, and concentrated to give an oil which was distilled at reduced pressure. Octylamine distils at 40—45 °C/3 mmHg and the desired *N*-benzyloctylamine (1.85 g, 84%) at 115—120 °C/0.3 mmHg. Analysis by g.c. showed the product to be >95% pure. It was further purified as the hydrochloride salt prepared by the action of anhydrous hydrogen chloride in ether on the product. Recrystallisation from a mixture of light petroleum (b.p. 80—100 °C)–ethyl acetate–ethanol gave the pure hydrochloride[21] (1.72 g, 67%, m.p. 199—202 °C).

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