

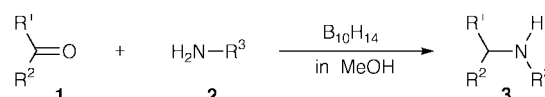
A reductive amination of carbonyls with amines using decaborane in methanol

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Aldehydes and ketones were easily converted to the corresponding amines by the reaction of amines in methanol using decaborane ($B_{10}H_{14}$) at room temperature under nitrogen. The reaction is simple and efficient.



Scheme 1

Reductive amination is an important synthetic method in organic synthesis, in which carbonyl compounds and amines are mixed with reducing agents. A variety of reducing agents are known to effect reductive amination of aldehydes and ketones. These are hydrogen in the presence of metal catalyst,¹ sodium borohydride,² borane–pyridine,³ borohydride exchange resin (BER),⁴ zinc–acetic acid,⁵ sodium borohydride–magnesium perchlorate,⁶ zinc borohydride–zinc chloride,⁷ sodium triacetoxyborohydride,⁸ silica gel–zinc borohydride⁹ and dibutyltin chloride hydride.¹⁰ Among these reagents, the most general and commonly used reagents are hydrogen in the presence of metal catalyst, sodium triacetoxyborohydride, and sodium cyanoborohydride. However, catalytic hydrogenation is incompatible with other functional groups such as carbon–carbon multiple bonds, nitro groups, and cyano groups. Sodium cyanoborohydride is highly toxic and may need a large excess of amine (5-fold excess).¹¹ Sodium triacetoxyborohydride has a limitation with aromatic and conjugated ketones.

During the study of decaborane as a mild hydride reagent,¹² we found that carbonyls and amines undergo reductive amination in the presence of decaborane (Scheme 1). The treatment of carbonyls with amines using decaborane in methanol at room temperature under nitrogen, gave the corresponding amines in excellent yields. The reaction is relatively fast, simple and efficient, even with a relatively poor nucleophilic amine

such as 4-nitroaniline. The effectiveness and fast rate of the reaction seems to result from the catalytic activity of decaborane for imine formation, which is known to be the rate limiting step in reductive aminations.¹³ Methanol was found to be the best solvent, the reaction occurred more slowly when ethanol was the solvent. The optimized amount of decaborane used for all these reactions was 30 mol%. The reactions proceed when using 20 mol% decaborane, but at a slower rate. The purification of the reaction mixture is simpler than that of other methods, simply requiring concentration of the reaction mixture, followed by column chromatography on silica gel using a solution of ethyl acetate and hexane.

Generally, products indicated in Table 1 were obtained in excellent isolated yields under the reaction conditions, even when we used poor nucleophile 4-nitroaniline (entries 1, 4–7, 10, 13 and 14) or poor electrophile acetophenone (entries 7 and 8). The poor electrophile acetophenone was reductively aminated in high yield by the reaction with poor nucleophilic amines in 12 hours (entries 7 and 8). This result is much better than that reported using a pyridine–borane system (10% isolated yield).^{3b} The reaction of benzaldehyde with 2,4,6-trichloroaniline under our conditions gave the amine **3o** in 39% yield (entry 15), a reaction known to fail using sodium triacetoxyborohydride.²

Table 1 Reductive amination of carbonyl compounds^a

Entry	Carbonyls	Amine (equiv.)	Time/h	Product ^c	Yield (%) ^b
1	Acetone	4-Nitroaniline (1)	1/2	3a	96
2	Acetone	<i>p</i> -Toluidine (1.2)	1/2	3b	95
3	Butan-2-one	<i>p</i> -Toluidine (1.2)	1	3c	97
4	Butan-2-one	4-Nitroaniline (1)	1/2	3d	94
5	Ethyl acetoacetate	4-Nitroaniline (1)	3	3e	93
6	(<i>E</i>)-4-Phenylbut-3-en-2-one	4-Nitroaniline (1.2)	1	3f	92
7	Acetophenone	4-Nitroaniline (1)	12	3g	97
8	Acetophenone	4-Aminobenzoic acid (1)	12	3h	98
9			1/2	3i	96
10	Propanol	4-Nitroaniline (1.2)	1/2	3g	92
11	Salicylaldehyde	Benzylamine (1.2)	1	3k	90
12	Salicylaldehyde	<i>n</i> -Butylamine (1.2)	2	3l	95
13	3-Bromobenzaldehyde	4-Nitroaniline (1.2)	1/2	3m	94
14	Benzaldehyde	4-Nitroaniline (1.2)	1/2	3n	96
15	Benzaldehyde	2,4,6-Trichloroaniline (1.2)	1	3o	39
16	Salicylaldehyde	Morpholine (1.2)	1	3p	92

^a Relative amount of reagents: carbonyls, amine (1 or 1.2 equiv.), decaborane (30 mol%). ^b Isolated yield. ^c All products gave spectra consistent with the assigned structures.

The low yield in the reaction of 2,4,6-trichloroaniline appears to be due to the low reactivity resulting from electronic and steric effects. The reaction of (*E*)-4-phenylbut-3-en-2-one, a conjugated ketone, with 4-nitroaniline gave the amine **3f** in 92% yield (entry 6). In some reactions with amines we observed the formation of side products: a decaborane-amine adduct¹⁴ in the reaction with good nucleophilic amines (entries 2, 3, 11 and 12); and a tertiary amine and a reductive etherification product¹² in the reaction of reactive benzaldehydes (entries 10 to 16). To overcome the lower yield resulting from the formation of side products, 1.2 equiv. of amine was used in these reactions. The reaction of salicylaldehyde with morpholine gave the tertiary amine **3p** in 92% yield (entry 16).

The presence of hydroxy groups did not reduce the effectiveness of the reactions (entries 9, 11, 12 and 16). These reduction conditions are compatible with the presence of other functional groups such as nitro groups (entries 1, 4–7, 10, 13 and 14), halo substituents (entries 9, 13 and 15), olefins (entries 6 and 9), an ester (entry 9) and a carboxylic acid (entry 8).

In conclusion, a new efficient reductive amination method was developed using decaborane as a mild reducing agent in methanol. This is an efficient reaction, and is compatible with other functional groups such as nitro groups, olefins and halogen groups.

Further work using decaborane for reductive amination is underway and will be reported in due course.

Experimental

A representative procedure (entry 1, Table 1)

To a solution of acetone (0.053 ml, 0.72 mmol) and *p*-nitroaniline (100 mg, 0.72 mmol) in 10 ml of methanol was added decaborane (26 mg, 0.21 mmol) at room temperature under nitrogen. The resulting solution was stirred at room temperature for ½ h. The reaction was followed by TLC using a solution of ethyl acetate and hexane (1:4). The reaction was concentrated under reduced pressure, chromatographed on a short pad of silica gel using a solution of ethyl acetate and hexane (1:8) to give the product amine **3a** as a yellow solid.

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- Decaborane in this reaction seems to have a dual action: a catalyst for the imine formation as well as a mild reducing agent for the reduction of the imine.
- We observed the formation of an adduct by stirring the mixture of decaborane and primary amine in methanol and using TLC: the R_f value of the adduct was higher than that of the corresponding amine when a mixture of ethyl acetate and *n*-hexane (1:4) was used as the developing solvent.

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