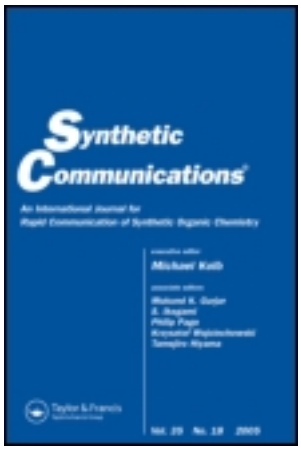

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One-Pot Reductive Amination of Acetals with Aromatic Amines Using Decaborane ($B_{10}H_{14}$) in Methanol

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One-Pot Reductive Amination of Acetals with Aromatic Amines Using Decaborane ($B_{10}H_{14}$) in Methanol

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ABSTRACT

Aldehyde acetals and ketone ketals were reductively aminated in one pot with aromatic amines to give the corresponding amines in methanol or aqueous methanol in good to high yields. This direct method might be important because acetals and ketals are used as a popular protecting group for aldehyde and ketones. The advantage of our method is effective even in an aqueous solution and in the application to selective reaction.

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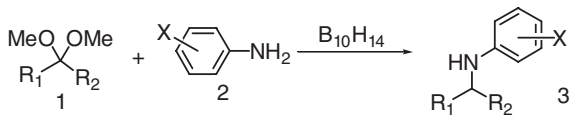
Key Words: One-pot reaction; Reductive amination; Decaborane; Acetals; Ketals.

The direct conversion of protected functional groups to other functional groups is very important since it provides time and cost savings by avoiding the deprotection step and tedious work-up.[1] Acetals and ketals are widely used as protecting groups for aldehydes and ketones due to their easy preparation, deprotection and stability in neutral and basic condition.[2] The reductive amination reaction is a popular method for the preparation of secondary amines from the primary amines and carbonyls.[3,4] A large number of reagents for the deprotection of acetals and for reductive amination have been developed. To the best of our knowledge, one pot reductive amination from acetals and amines to corresponding secondary amines has not been developed because two reagents for deprotection and reductive amination are not comaptible in the same solution. The other reason is the reaction condition. Efficient reductive amination needs an anhydrous condition, while generally deprotection needs aqueous conditions. The best way to carry out the direct reductive amination of acetals is development of the new reagent compatible for two consecutive reactions; deprotection and reductive amination.

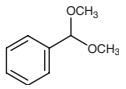
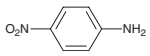
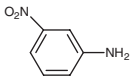
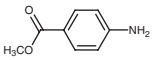
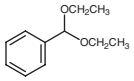
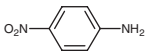
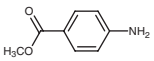
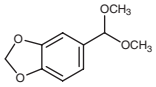
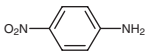
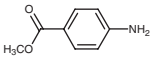
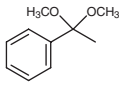
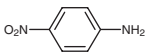
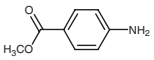
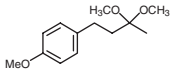
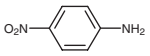
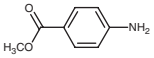
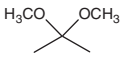
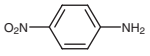
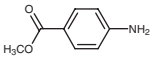
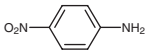
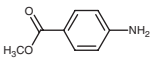
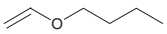
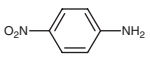
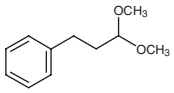
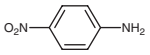
Recently, we reported reductive amination using decaborane having dual roles as a catalyst as well as a reducing agent, which can be easily removed by a simple work-up.[5,6] In connection with the studies on decaborane, we tried the direct reductive amination of acetals and ketals (and enol ethers) with aromatic amines in methanol as well as in aqueous methanol (Sch. 1) and the results are shown in Tables 1 and 2.

The reductive amination of various conjugated acetals, ketals and enol ethers with anilines having electron withdrawing groups (nitro or ester) in methanol using decaborane gave the corresponding products in high yields as shown in Table 1. The optimum amount of decaborane in the reaction was 30 mol%, the amount of which was determined by the reaction of benzaldehyde dimethy acetal with 4-nitroaniline as a model.



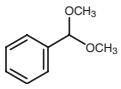
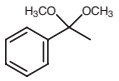
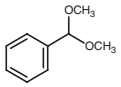
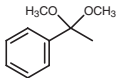
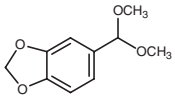
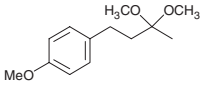
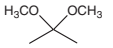
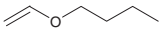
Scheme 1.

Table 1. Direct reductive alkylation of aromatic amines.

Entry	Cabonyl	Amine	Yield (%)[a]	Time (h)
1			96	1
2			91	2
3			90	1.5
4			96	1
5			86	8
6			95	1/6
7			94	1
8			93	0.5
9			97	1.5
10			100	1
11			93	1
12			99	0.5
13			96	1
14			99	1
15			95	1
16			56	12
17			No rex	24

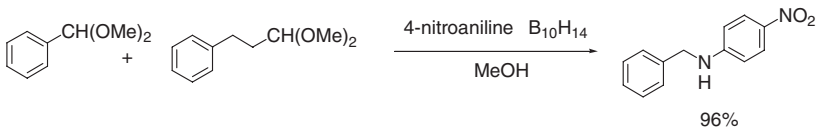
[a]Isolated yield and products were characterized by spectroscopic methods.

Table 2. Direct reductive alkylation of 3-toluidine with various acetals and ketals.

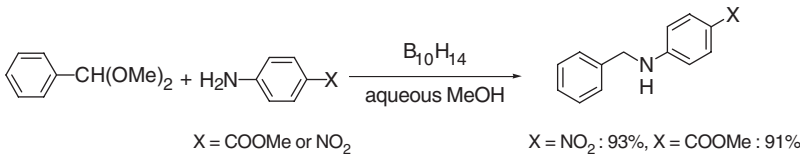
Entry	Acetal (1.1 equiv.)	Solvent	Reaction time (h)[b]	Yield[a] (%)
1		THF:H_2O = 4:1	1 (1)	83
2		THF:H_2O = 4:1	1 (12)	40
3		MeOH:H_2O = 10:1	1 (1)	84
4		MeOH:H_2O = 10:1	1 (12)	80
5		MeOH:H_2O = 10:1	1 (1)	95
6		MeOH:H_2O = 10:1	1 (4)	90
7		MeOH:H_2O = 10:1	1 (4)	88
8		MeOH:H_2O = 10:1	1 (4)	85
9		MeOH:H_2O = 10:1	1 (12)	20

[a]Isolated yield.
[b]The reaction time for acetal hydrolysis and the reaction time in parenthesis for reductive amination.

The imine intermediate in the reaction seemed to be formed after hydrolysis of acetals (or ketals) to aldehyde (or ketones). Decaborane in the reaction seemed to act as a catalyst in the hydrolysis of acetals and the imine formation as well as a reducing agent of imine. One point one equivalent of acetals and ketals was used in the reaction due to possible side reactions such as reduction of carbonyls[7] and reductive etherification.[8] The reaction of 4-nitroaniline and methyl 4-aminobenzoate with acetals and ketals was complete within 1h to give the corresponding products in high yields (Entries 1–13). Whereas the reaction of 2-methoxypropene with 4-nitroaniline (Entry 14) and methyl 4-aminobenzoate (Entry 15) gave the corresponding products within 1 h in almost quanti-



Scheme 2.



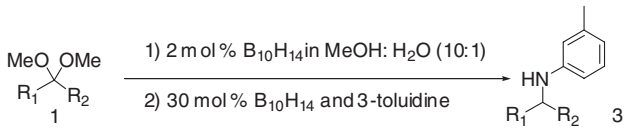
Scheme 3.

tative yield, the reaction of *n*-butyl vinyl ether with 4-nitroaniline gave the product in 56% yield due to its slow hydrolysis rate to aldehyde (Entry 16). The reductive amination of dihydrocinnamaldehyde acetal with 4-nitroaniline (Entry 17) did not proceed at all even in extended reaction time due to its stability against hydrolysis to carbonyl under the reaction condition.

Our reaction condition can be applied to selective reductive amination between hydrolyzable acetal and nonhydrolyzable acetal. One example is shown in Sch. 2. When a solution of benzaldehyde dimethyl acetal and dihydrocinnamaldehyde acetal in the presence of 1 equiv. of 4-nitroaniline in methanol was exposed to our reaction condition, benzaldehyde acetal underwent the selective reductive amination to give benzyl 4-nitrophenylamine within 1 h in 96% yield. However, dihydrocinnam aldehyde dimethyl acetal was recovered quantitatively (Sch. 2).

One pot reductive amination also was tried in aqueous methanol. The reaction of benzaldehyde acetal with methyl 4-aminobenzoate and 4-nitroaniline in a solution of MeOH and water (10:1) gave the corresponding amines within 1 h in 91% and 93% isolated yields respectively (Sch. 3). These results are similar to those of reductive aminations in anhydrous methanol (Entries 1 and 3 of Table 1).

The reductive amination of benzaldehyde acetal with 3-toluidine in MeOH using decaborane was failed in one-pot, because 3-toluidine is too basic for decaborane to act as a Lewis acid catalyst in the hydrolysis of acetals. Therefore, the consecutive procedure was employed. Acetals (or ketals or enol ethers) were hydrolyzed to aldehydes (or ketones) in the presence of catalytic amount of decaborane (2 mol%) followed by addition of 3-toluidine and 30% decaborane. While the reductive



Scheme 4.

amination of benzaldehyde acetal and acetophenone acetal with 3-toluidine in an aqueous THF (THF:water = 4:1) gave the products within 1 h in 83% and 40% yield (Entries 1 and 2) respectively under the consecutive reaction condition, that of benzaldehyde acetal and acetophenone acetal with 3-toluidine in aqueous methanol (methanol: water = 10:1) gave the corresponding amines in 84% and 80% yields (Entries 3 and 4). Therefore, aqueous methanol was a choice solution for the reaction. When water ratio was increased, the reaction became inefficient because of the low solubility of decaborane. The reductive amination of various acetals with 3-toluidine in aqueous methanol gave the corresponding amines in high yield (Entries 3–8). The reductive amination of *n*-butyl vinyl ether gave secondary amine in 20% yield due to the stability against its hydrolysis to aldehyde under the reaction condition (Entry 9).

In conclusion, acetals and ketals were reductively aminated with anilines using decaborane as a catalyst and a reagent in methanol or in aqueous methanol in high yield in one pot way. However, direct reductive amination of some enol ethers with aniline having electron withdrawing groups was not efficient and gave the reductive amination product in low yield. For basic 3-toluidine, the reductive amination reaction with various acetals in aqueous methanol (methanol:water = 10:1) in consecutive way gave the corresponding amines generally in high yield.

EXPERIMENTAL

All solvents and reagents were used as purchased. Silica gel 60 (230–400 mesh, Merck) was used for column chromatography, and silica gel $60F_{254}$ plates (0.25 mm, Merck) were used for TLC. ^{1}H NMR spectra were recorded on a VARIAN at 300 MHz.

Two typical procedures depending on the basicity of anilines are as follows:

Method 1 (Table 1). To a homogeneous solution of 4-nitroaniline (92 mg, 0.67 mmol) and acetals (112 mg, 0.74 mmol, 1.1 equiv.) in metha-

nol (5 mL, HPLC grade), decaborane (24 mg, 0.2 mmol, 30 mol%) was added at rt under nitrogen. The resulting solution was stirred until the amine disappeared on TLC using a solution of ethyl acetate and hexane (1:4). During the reaction, a yellow solid was formed. After 1 h, the reaction was cooled, filtered, washed with ice cold methanol and dried to give a yellow crystalline solid in 96% yield (147 mg).

***N*-Benzyl-4-nitroaniline.** ^{1}H NMR ($CDCl_3$, 300 MHz): 8.09 (d, $J=$ 5.1 Hz, aromatic 2H), 7.32–7.38 (m, aromatic 5H), 6.58 (d, $J=5.1$ Hz, aromatic 2H), 4.85 (s, 1H), 4.43 (d, $J=3.9$ Hz, 2H).

***N*-Benzyl-3-nitroaniline.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.52–7.65 (m, aromatic 1H), 7.45 (t, $J=2.1$ Hz, aromatic 1H), 7.29–7.38 (m, aromatic 6H), 6.86–6.9 (m, aromatic 1H), 4.39 (s, 3H).

Methyl 4-*N*-benzylaminobenzoate. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.86 (d, $J=8.7$ Hz, aromatic 2H), 7.29–7.36 (m, aromatic 5H), 6.59 (d, $J=$ 8.7 Hz, aromatic 2H), 4.49 (s, 1H), 4.39 (s, 2H), 3.85 (s, 3H).

***N*-Piperonyl-4-nitroaniline**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09 (d, $J=$ 9.3 Hz, aromatic 2H), 6.81 (d, $J=2.4$ Hz, aromatic 3H), 6.56 (d, $J=$ 9.3 Hz, aromatic 2H), 5.97 (s, 1H), 4.79 (s, 1H), 4.33 (d, $J=5.4$ Hz, 2H).

Methyl 4-*N*-piperonylaminobenzoate. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (d, $J=8.7$ Hz, aromatic 2H), 6.79–6.83 (m, aromatic 3H), 6.58 (d, $J=$ 8.7 Hz aromatic 2H), 5.95 (s, 2H), 4.29 (s, 2H), 3.85 (s, 3H).

***N*-(4-Nitrophenyl)-1-phenethylamine.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (d, $J=9.3$ Hz, aromatic 2H), 7.24–7.37 (m, aromatic 5H), 6.46 (d, $J=9.3$ Hz, aromatic 2H), 4.88 (s, 1H), 4.60 (d, $J=6.3$ Hz, 1H), 1.58 (d, $J=6.6$ Hz, 3H).

Methyl 4-(*N*-1-phenethylamino)-benzoate. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.78 (d, $J=8.7$ Hz, aromatic 2H), 7.23–7.34 (m, aromatic 5H), 6.47 (d, $J=9$ Hz, aromatic 2H), 4.55–4.57 (m, 1H), 4.48 (s, 1H), 3.81 (s, 3H), 1.55 (d, $J=9.0$ Hz, 3H).

***N*-[4-(4-Methoxyphenyl)-2-butyl]-4-nitroaniline.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, $J=9.3$Hz, aromatic 2H), 7.17 (d, $J=8.7$ Hz, aromatic 2H), 6.83 (d, $J=8.7$ Hz, aromatic 2H), 6.41 (d, $J=9.3$ Hz, aromatic 2H), 4.29 (d, $J=8.1$ Hz, 1H), 3.8 (s, 1H), 3.53–3.58 (m, 1H), 2.66 (t, $J=6.6$ Hz, 2H), 1.79–1.89 (m, 2H), 1.26 (d, $J=6.6$ Hz, 3H).

Methyl *N*-4-[4-(4-methoxyphenyl)-2-butylamino]-benzoate. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.83 (d, $J=8.7$ Hz, aromatic 2H), 7.08 (d, $J=$ 8.4 Hz, aromatic 2H), 6.83 (d, $J=8.4$ Hz, aromatic 2H), 6.46 (d, $J=$ 8.7 Hz, aromatic 2H), 3.94 (d, $J=6.9$ Hz, 1H), 3.85 (d, 3H), 3.79 (s, 3H), 3.54 (m, 1H), 2.66 (t, $J=7.8$ Hz, 2H), 1.82 (m, 2H), 1.23 (d, $J=6.3$ Hz, 3H).

***N*-Isopropyl-4-nitroaniline.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08 (d, $J=9.3$ Hz, aromatic 2H), 6.49 (d, $J=9.3$ Hz, aromatic 2H), 4.35 (s, 1H), 3.7–3.77 (m, 1H), 1.27 (d, $J=6.3$ Hz, 6H).

Methyl 4-*N*-isopropylamino-benzoate. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84 (d, $J = 9.0$ Hz, aromatic 2H), 6.52 (d, $J = 9.0$ Hz, aromatic 2H), 3.84 (s, 3H), 3.69 (m, 1H), 1.23 (d, $J = 6$ Hz, 6H).

***N*-Ethyl-4-nitroaniline.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09 (d, $J = 9.3$ Hz, aromatic 2H), 6.52 (d, $J = 9.3$ Hz, aromatic 2H), 4.40 (s, 1H), 3.22–3.31 (m, 2H), 1.31 (t, $J = 8.7$ Hz, 3H).

Method 2 (Table 2). To acetal (112 mg, 0.74 mmol, 1.1 equiv.) in 5 mL of a solution of MeOH and water (10:1) we added a catalytic amount of decaborane (1.6 mg, 2 mol%) and the resulting solution was sirred for 1 h at rt. And then, amine (74 mg, 0.67 mmol) and decaborane (22.8 mg, 28 mol%) was added and the resulting solution was stirred for 1 h. The reaction was monitored on TLC using a solution of ethyl acetate and hexane (1:4). After concentration, the concentrated stuff was chromatographed on silica gel using a solution of ethyl acetate and hexane (1:4 to 1:10). The concentration gave the expected reductive amination product as syrup in 73% yield (96 mg).

***N*-Benzyl-*m*-toluidine.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.18–7.27 (m, aromatic 5H), 6.98 (t, $J = 7.5$ Hz, aromatic 1H), 6.46 (d, $J = 7.5$ Hz, aromatic 1H), 6.36 (d, $J = 10.2$ Hz, aromatic 2H), 4.21 (s, 2H), 3.85 (s, 1H), 2.81 (s, 3H).

***N*-(1-Phenethyl)-*m*-toluidine.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23–7.40 (m, aromatic 5H), 6.99 (t, $J = 7.8$ Hz, aromatic 1H), 6.49 (d, $J = 7.8$ Hz, aromatic 1H), 6.38 (s, aromatic 1H), 6.32 (d, $J = 8.4$ Hz, aromatic 1H), 4.50 (m, 1H), 3.97 (s, 1H), 2.22 (s, 3H), 1.52 (d, $J = 6.6$ Hz, 3H).

***N*-Piperonyl-*m*-toluidine.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.06 (t, $J =$ 7.5 Hz, aromatic 1H), 6.67–6.86 (m, aromatic 3H), 6.54 (d, $J = 7.2$ Hz, aromatic 2H), 6.44 (d, $J = 8.4$ Hz, aromatic 1H), 5.94 (s, 2H), 4.22 (s, 2H), 2.27 (s, 3H).

***N*-[4-(4-Methoxy-phenyl)-2-butyl]-*m*-toluidine.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.11 (d, $J = 8.7$ Hz, aromatic 2H), 7.04 (t, $J = 7.5$ Hz, aromatic 1H), 6.84 (d, $J = 8.7$ Hz, aromatic 2H), 6.50 (d, $J = 7.5$ Hz, aromatic 1H), 6.36 (d, $J = 5.7$ Hz, aromatic 2H), 3.80 (s, 3H), 3.44–3.50 (m, 1H), 2.67 (t, $J = 7.8$ Hz, 2H), 2.26 (s, 3H), 1.71–1.86 (m, 2H), 1.21 (d, $J = 6.3$ Hz, 3H).

***N*-Isopropyl-*m*-toluidine.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.04–7.09 (m, aromatic 1H), 6.51 (d, $J = 3.6$ Hz, aromatic 2H), 6.41 (d, $J = 6.9$ Hz, aromatic 2H), 3.61–3.65 (m, 1H), 2.28 (s, 3H), 1.21 (d, $J = 6.3$ Hz, 6H).

***N*-Ethyl-*m*-toluidine.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.08 (t, $J =$ 8.7 Hz, aromatic 1H), 6.53 (d, $J = 7.8$ Hz, aromatic 1H), 6.44 (d, $J =$ 7.2 Hz, aromatic 2H), 3.09–3.20 (m, 2H), 1.26 (m, 3H).

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