

Reductive Amination of Aldehydes with Sodium Borohydride and Lithium Aluminum Hydride in the Presence of Lithium Perchlorate

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A one-pot high yielding reductive amination of aldehydes with primary and secondary amines using LiClO₄/NaBH₄ and LiClO₄/LiAlH₄ as reducing agents in diethyl ether is described.

Keywords: Reductive amination, Sodium borohydride, Lithium aluminum hydride, Lithium perchlorate, Aldehyde

INTRODUCTION

Direct reductive amination of aldehydes is a convenient method for the preparation of amines. These compounds have wide applications in organic chemistry [1,2]. The reaction sequence proceeds through the formation of an imine or iminium ion intermediate upon reaction of an aldehyde with ammonia, a primary amine or a secondary amine followed by *in situ* reduction to form an amine of higher order. The Borch reduction using sodium cyanoborohydride, NaBH₃CN [3], and reductive amination by sodium triacetoxyborohydride, NaBH(OAc)₃ [4] are very popular methods to achieve these transformations. However, the use of expensive and highly toxic NaBH₃CN carries the risk of having residual cyanide formed during work-up in the isolated product and makes this procedure less attractive. Some limitations apply to sodium borohydride and even more to lithium aluminum hydride. Many other reagents, such as NaBH₄/CF₃COOH [4,5], NaBH₄/aqueous sulfuric acid [6], borane-pyridine [7], Ti(O*i*Pr)₄/NaBH₃CN [8], borohydride exchange resin [9],

Zn/AcOH [10], NaBH₄/Mg(ClO₄)₂ [11], Zn(BH₄)₂/ZnCl₂ [12], silica gel/Zn(BH₄)₂ [13], NiCl₂/NaBH₄ [14], Pd/HCOOH [15] and Ti(O*i*Pr)₄/NaBH₄ [16] for reductive amination of aldehydes and ketones have been reported in the literature. Alternative metal hydride reagents, such as Bu₃SnH [17], Bu₂SnClH [18], Bu₂SnIH [18], Et₃SiH-trifluoroacetic acid [19], Ti(O*i*Pr)₄-polymethylhydro-siloxane [20], PhSiH₃-Bu₂SnCl₂ [21], α-picoline-borane [22], NaBH(OAc)₃/microwave irradiation [23], dibutylchlorotin hydride complex [24], and electrochemical reductive amination reactions [25] have recently been developed in order to circumvent the drawbacks of the previous reagents. In addition, [Zr(BH₄)₂Cl₂(dabco)₂] has been successfully used for the reduction of imines and enamines, reductive amination of aldehydes and ketones, and reductive methylation of amines [26].

EXPERIMENTAL

General Procedure for Reduction of *in situ* Prepared Imine and Iminium Ion with NaBH₄/LiClO₄

Lithium perchlorate 0.3 g (3 mmol) for primary amines

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and 0.4 g (4 mmol) for secondary amines was dissolved in dry diethyl ether (1 ml) in a 15 ml test tube fitted with a magnetic bar and a rubber septum. An aldehyde (1 mmol) was added to the test tube. Then a primary or secondary amine (1.1 mmol) was added with a syringe. After stirring for 10 to 20 min, NaBH₄ (3 mmol) was added slowly and the mixture stirred for an hour. Then methanol (2 ml) was added and the mixture was heated at 60 °C for 10 min. Water (5 ml) was added and the product was extracted with ether (3 × 5 ml). After extraction with 10% HCl and basification of the aqueous layer with 10% NaOH, the corresponding amine was extracted with ether. The organic layer was dried over MgSO₄ and solvent was evaporated *in vacuo* to give the crude product. After purification by short column chromatography or by extraction with 5% HCl solution, all amine products were characterized on the basis of their spectroscopic data and by comparison with those reported in the literature [4-23,27].

General Procedure for the Reduction of *in situ* Prepared Imine and Iminium Ion with LiAlH₄/LiClO₄

Lithium perchlorate 0.3 g (3 mmol), for primary amines, or 0.4 g (4 mmol), for secondary amines, was dissolved in dry diethyl ether (1 ml) in a 15 ml test tube fitted with a magnetic bar and a rubber septum. An aldehyde (1 mmol) was added to the test tube. Then a primary or secondary amine (1.2 mmol) was added with a syringe. After stirring for 10 to 20 min, LiAlH₄ (2 mmol) was added gradually and the mixture stirred for 1 h. The reaction mixture was cooled to 0 °C and then methanol (2 ml) was added drop wise. After quenching LiAlH₄ with careful addition of water (5 ml), ether (5 ml) was added and the mixture was centrifuged. The organic layer was separated, washed with water and dried over MgSO₄ and the solvent was evaporated *in vacuo* to give the crude product. After purification by short column chromatography or by extraction with 5% HCl solution, all amine compounds were characterized on the basis of their spectroscopic data and by comparison with those reported in the literature [4-23,27].

Caution. Although we did not have any accident while using lithium perchlorate, it is advisable to dry LiClO₄ in a fume hood using a suitable lab-shield.

Selected Spectroscopic Data

***N,N*-Dimethyl-(4-bromophenyl)methaneamine.** (Table 2, Entry 14); ¹H NMR (400 MHz, CDCl₃): δ (ppm) 2.38 (s, 6H), 3.59 (s, 2H), 7.25 (d, *J* = 4.0 Hz, 2H), 7.48 (d, *J* = 4 Hz, 2H).

***N*-Benzyl-(4-bromophenyl)methaneamine.** (Table 1, Entry 10); ¹H NMR (400 MHz, CDCl₃): δ (ppm) 1.87 (s, 1H, NH), 3.78 (s, 2H), 3.85 (s, 2H), 7.29 (d, *J* = 4 Hz, 2H), 7.52 (d, *J* = 4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 52.4 (CH₂), 53.1 (CH₂), 120.8 (C), 127.2 (CH), 127.9 (CH), 128.4 (CH), 129.7 (CH), 131.3 (CH), 139.3 (C), 140.1 (C).

***N*-Benzyl crotylamine.** (Table 2, Entry 11); ¹H NMR (400 MHz, CDCl₃): δ (ppm) 1.76 (d, *J* = 4.1 Hz, 3H), 3.27 (d, *J* = 4.2 Hz, 2H), 3.83 (s, 2H), 5.68 (m, 2H), 7.36 (s, 5H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 27.1, 48.8, 53.9, 127.5, 127.9, 128.1, 128.4, 128.6, 140.4.

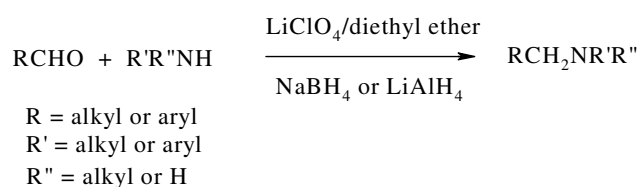
***N*-(2-phenylethyl)-*N*-(3-pyridylmethyl)amine.** (Table 1, Entry 13); ¹H NMR (400 MHz, CDCl₃): δ (ppm) 2.88 (m, 4H), 3.92 (s, 2H), 7.22 (m, 7H), 7.60 (m, 1H), 8.51 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 36.2, 50.9, 54.7, 121.9, 122.2, 126.4, 128.2, 128.7, 136.8, 139.7, 149.2, 159.3; MS for C₁₄H₁₆N₂, (M+1)⁺, m/z 213.22 (base peak).

RESULTS AND DISCUSSIONS

In recent years, concentrated solutions of lithium perchlorate in diethyl ether (LPDE) have been used in various organic transformations [27]. The LPDE is a convenient medium to carry out many different reactions under neutral conditions. We have shown that an aldehyde and a secondary or primary amine was produced an iminium salt or an imine in the concentrated ethereal solution of LiClO₄, which can be detected by ¹³C NMR and ¹H NMR spectroscopy, respectively (28 g, 28 h). In continuation of our interest in the applications of lithium perchlorate to various organic transformations [28], here we describe the scope of an efficient protocol for the reductive amination of aldehydes with primary and secondary amines using LiClO₄/NaBH₄ and LiClO₄/LiAlH₄ in diethyl ether in good to excellent yields (Scheme 1).

Table 1 shows the results of reductive amination of different aldehydes (aliphatics and aromatics) in the presence of primary amines (aliphatics and aromatics) with NaBH₄ and LiAlH₄ in concentrated solution of LiClO₄ in diethyl ether. Reduction of imines, prepared *in situ* in the ethereal solution

Reductive Amination of Aldehydes



Scheme 1

Table 1. Reductive Amination of Aldehydes with Primary Amines

Entry	Aldehyde	Amine	Product	NaBH ₄ (yield %) ^a	LiAlH ₄ (yield %) ^a
1	PhCHO	PhNH ₂		100	97
2	PhCHO			97	98
3	PhCHO			98	97
4				98	99
5				99	100
6				99	96
7				98	-
8				98	-
9				96	-
10		PhCH ₂ NH ₂		-	98
11		PhCH ₂ NH ₂		62	52
12		PhCH ₂ NH ₂		94	-
13		PhCH ₂ CH ₂ NH ₂		90	-

Table 1. Continued

14				78	-
15				95	-
16				90	-
17				88	-

^aConversion yields.


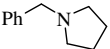

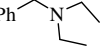

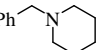
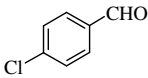

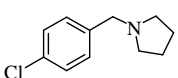
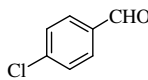

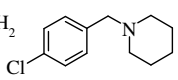
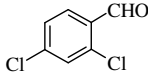

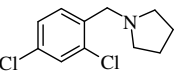
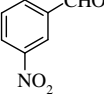

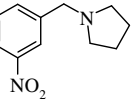

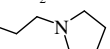

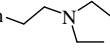
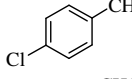

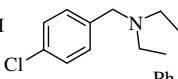
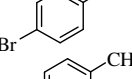
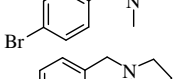
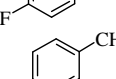

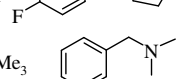

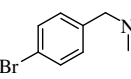


of LiClO₄ [28], with NaBH₄ or LiAlH₄ gives excellent yields of different secondary amines. Both reagents give similar yields, although the use of LiAlH₄ has some disadvantages such as reducing other functional groups (nitro, esters, epoxides, etc.) and a more difficult work up procedure.

On the other hand, reduction of *in situ*-prepared iminium ions in the concentrated solution of LiClO₄, gives lower yields compared to imines (Table 2). In this case, despite the fact that using NaBH₄ as a reducing agent requires an easier work-up procedure, the use of LiAlH₄ as reducing agent will result in yields 10-20% higher than those with NaBH₄.

As is shown in Tables 1 and 2, in some cases, only one reducing agent was tested. Reductive amination of α,β -unsaturated aldehydes produced unsaturated amines (Table 1, Entries 11 and 13), while in the case of crotonaldehyde, some polymeric material was also formed. When LiAlH₄ was used as the reducing agent for reductive amination of 2-pyridinecarboxaldehyde, a mixture of products was formed. While, by using NaBH₄, a clean reductive amination takes place in a good yield.

In general, 1.0 equivalent of aldehyde, 1.1 equivalent of amine and an excess of reducing agent were used for these reactions. In the case of crotonaldehyde, the reaction was carried out in an ice-bath. In all cases, the reaction time was short and better results were obtained with primary amines compared to the secondary ones. The reductive amination of aldehydes with secondary amines gives the corresponding alcohol as a side product. The direct reductive amination reactions were carried out in a 3 or 4 M solution of LiClO₄ in

Table 1. Reductive Amination of Aldehydes with Secondary Amines

Entry	Aldehyde	Amine	Product	NaBH ₄ (yield %)	LiAlH ₄ (yield %)
1	PhCHO			78	86
2	PhCHO			45	63
3	PhCHO			66	83
4				72	82
5				60	75
6				79	91
7				78	
8	Ph-CH ₂ -CHO			76	88
9	Ph-CH ₂ -CHO			65	75
10					58
11		PhNHMe		62	
12				70	78
13		Me ₂ NSiMe ₃			82
14		Me ₂ NSiMe ₃		81	95

diethyl ether. Lithium perchlorate can be recovered, dried at 160 °C and reused as the stock reagent.

In summary, we have developed a complementary method for the synthesis of secondary and tertiary amines through a one-pot reaction of aldehydes, amines, LiClO₄ and NaBH₄ or LiAlH₄ in ether. These reducing agents are highly efficient

reductive amination reagents, which are applicable to the reductive amination of aldehydes with primary and secondary amines. In particular, NaBH₄ is a very common and safe reducing agent for this reaction, especially for reductive amination with primary amine.

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