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RESEARCH ARTICLE

Reductive Amination of Aldehydes with Sodium Borohydride-Silica Gel System†

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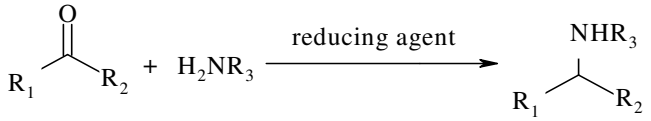
Abstract: A simple and convenient procedure for reductive amination of aldehydes using sodium borohydride in the presence of silica gel as an active and inexpensive catalyst is described. The reactions were carried out with equimolar amounts of amine and aldehyde using silica gel-sodium borohydride in THF at room temperature.

Keywords: Aldehydes, Reductive amination, Sodium borohydride, Silica gel

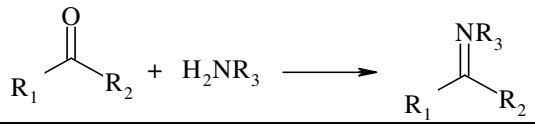
Introduction

The transformation of amines from carbonyl compounds is an important method in organic synthesis because of their versatile utility as intermediates for synthesis of pharmaceuticals[1] and agrochemicals[2]. Two synthetic methods are generally used to effect this transformation. One is the reductive amination, which is termed as a direct reaction. This allows the conversion of carbonyl functionality to an amine by directly treating a mixture of the carbonyl compound and the amine with suitable reducing agents in a single operation (Scheme 1). The other is a stepwise or indirect reaction, which involves the conversion of amine from the reduction of the imine derivatives isolated in a separate step (Scheme 2).



R_1, R_3 = alkyl, aryl or heterocyclic, R_2 = H, alkyl, aryl or heterocyclic

Scheme 1. Direct reductive amination



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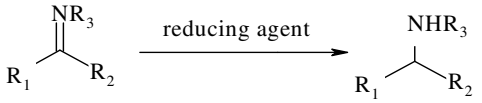
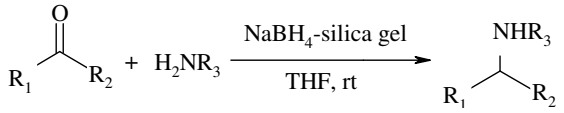


R_1, R_3 = alkyl, aryl or heterocyclic, R_2 = H, alkyl, aryl or heterocyclic

Scheme 2. Indirect reductive amination

As effective reducing methods for these conversions, catalytic hydrogenation[3], metal hydride reductions using $NaBH_3CN$,[4] $LiBH_3CN$,[5] $(n\text{-}Bu)_4NBH_3CN$,[6] $NaBH_3CN\text{-}ZnCl_2$,[7] $NaBH_3CN\text{-}Ti(O^iPr)_4$,[8] $NaBH_3CN\text{-}Mg(ClO_4)_2$,[9] $NaBH(OAc)_3$,[10] $NaBH_4\text{-}NiCl_2$,[11] $NaBH_4\text{-}ZrCl_4$,[12] $NaBH_4\text{-}Ti(O^iPr)_4$,[12] $NaBH_4\text{-}H_2SO_4$,[13] $NaBH_4$-wet clay-microwave,[14] borohydride exchange resin,[15] $NaBH_4\text{-}LiClO_4$,[16] $NaBH_4$-silica chloride,[17] $ZnBH_4$,[18] $ZnBH_4\text{-}ZnCl_2$,[19] $ZnBH_4\text{-}SiO_2$,[20] pyridine-borane,[21] picoline-borane,[22] diborane-MeOH,[23] Zn-AcOH,[24] polymethylhydrosiloxane(PMHS)-$Ti(O^iPr)_4$,[25] PMHS-$ZnCl_2$,[26] PMHS-BuSn$(OCOR)_3$,[27] $Et_3SiH\text{-}CF_3COOH$,[28] $PhMe_2SiH\text{-}(C_6F_6)_3$,[29] Cl_3SiH-DMF,[30] $PhSiH_3\text{-}Bu_2SnCl_2$,[31] Bu_3SnH-DMF,[32] $Bu_3SnH\text{-}SiO_2$[33] and BuSnClH[34] have been reported. However, most of these reagents may have one drawback or another. For examples, catalytic hydrogenation is incompatible with compounds containing a carbon-carbon double or triple bond and other reducible functional groups such as nitro, cyano and furyl groups[3]. Cyanoborohydride and tin hydride reagents are highly toxic and generate toxic by-products such as HCN, NaCN or organotin compounds[35] upon workup and may result in the contamination of the product with the toxic compounds. Other hydrides such as $ZnBH_4$,[36] nickel boride[35] and PHMS-$Ti(O^iPr)_4$[37] may be not suitable for use of chemoselective reduction of imines having ketone, ester, amide and nitro groups, since these reagents can reduce those functional groups.

Sodium borohydride is an inexpensive, safe to handle and environmental friendly reducing agent for the reductive amination of carbonyl compounds[38]. Procedures for using this mild and selective reagent have been developed for a wide variety of substrates. We report herein the details of direct reductive amination of aldehydes and ketones using sodium borohydride-silica gel (Scheme 3).



R_1, R_3 = alkyl, aryl or heterocyclic, R_2 = H, alkyl, aryl or heterocyclic

Scheme 3. Direct reductive amination

Experimental

The reactions were monitored by TLC using silica gel plates and the products were purified by column chromatography on silica gel. ^1H NMR spectra were recorded at 200 MHz. The chemical shifts are expressed as δ units with Me_4Si as the internal standard in $CDCl_3$. Sodium borohydride, silica gel and THF were purchased from Qualigens and used without further purification.

General procedure

An aldehyde (2 mmol) was added to the amine (2 mmol) in THF (5 mL) and was stirred for 15 min at room temperature. To the resulting mixture sodium borohydride (2.5 mmol) and silica gel (200 mg) was added and then the mixture was stirred under room temperature until TLC showed complete disappearance of the starting aldehyde or ketone. The reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined extract was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude products obtained were further purified by a column chromatography on silica gel using a suitable eluent.

Results and Discussion

To explore the possibility of the reductive amination of amines and carbonyl compounds, a model reaction, between benzaldehyde and aniline was performed. By optimizing the solvent, reaction temperature and the amount of the reagents, the conditions shown in Scheme 3 were found to be suitable. Using the same methodology, the reductive aminations of structurally different aldehydes with various amines were examined (Table 1). Reductive amination of benzaldehyde with other aromatic and aliphatic primary amines proceeded smoothly to give the corresponding secondary amines (entries 1-5). The reactions with aliphatic and heterocyclic aldehydes, such as cyclohexanecarboxaldehyde and furfural, with various primary amines gave the respective secondary amines in good yields (entries 6).

Table 1. Reductive amination of aldehyde and ketone with $NaBH_4$-silica gel

Entry No.	Aldehyde	Amine	Yield[a]
1.	PhCHO	$PhNH_2$	95
2.	PhCHO	*p*-$OMeC_6H_4NH_2$	96
3.	PhCHO	$PhCH_2NH_2$	90
4.	PhCHO	*n*-$C_7H_{15}NH_2$	89
5.	PhCHO	*c*-$C_6H_{11}NH_2$	70
6.	Furfural	$PhNH_2$	92

*N-Phenylbenzylamine (**1**)*

Yield: 95%; ^{1}H NMR δ 3.90 (br s, 1H, NH), 4.30 (s, 2H, CH_2), 6.60 (d, 2H, Ar-H), 6.70 (t, 1H, Ar-H), 7.10 (t, 2H, Ar-H), 7.20-7.38 (m, 5H, Ar-H)

*N-(p-Methoxyphenyl)benzylamine (**2**)*

Yield: 96%; ^{1}H NMR δ 3.60 (br s, 1H, NH), 3.71 (s, 3H, OCH_3), 4.25 (s, 2H, CH_2), 6.60 (d, 2H, Ar-H), 6.75 (d, 2H, Ar-H), 7.20-7.38 (m, 5H, Ar-H).

*Dibenzylamine (**3**)*

Yield: 90%; ^{1}H NMR δ 2.00 (br s, 1H, NH), 3.81 (s, 4H, $2CH_2$), 7.20-7.35 (m, 10H, Ar-H).

N-Benzyl-1-heptylamine (4)

Yield: 89%; ^{1}H NMR δ 0.90 (t, 3H, CH_3), 1.08-1.26 (m, 6H, CH_2), 1.52-1.74 (m, 4H, CH_2), 2.58-2.69 (m, 2H, CH_2), 3.60 (d, 1H, CH), 3.80 (br s, 1H, NH), 4.18 (d, 1H, CH), 7.25-7.40 (m, 5H, Ar-H).

N-Benzylcyclohexylamine (5)

Yield: 70%; ^{1}H NMR δ 0.70-2.10 (m, 10H, cyclohexyl), 2.71 (m, 1H, cyclohexyl), 3.39 (br s, 1H, NH), 3.80 (d, 1H, CH), 4.04 (d, 1H, CH), 7.220-7.41 (m, 5H, Ar-H).

N-Phenylfurfurylamine (6)

Yield: 92%; ^{1}H NMR δ 3.95 (br s, 1H, NH), 4.30 (s, 2H, CH_2), 6.22 (m, 1H, CH), 6.30 (m, 1H, CH), 6.72 (t, 1H, CH), 7.16-7.34 (m, 5H, Ar-H).

Conclusion

An efficient method for the synthesis of amines by direct reductive amination of carbonyl compounds with various amines in the presence of sodium borohydride and silica gel is described. This method afforded amines as the only isolated products at room temperature. The neutral reaction conditions, simple workup, isolation of pure products, high yields and the use of safe and inexpensive reagent are notable advantages of the present method.

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