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Direct reductive amination of carbonyl compounds using sodium borohydride-silica chloride

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A simple and convenient procedure for reductive amination of aldehydes and ketones using sodium borohydride in the presence of silica chloride as an active, inexpensive, recoverable, and recyclable catalyst is described. The reactions were carried out with equimolar amounts of amine and carbonyl compound using silica chloride-sodium borohydride in THF at room temperature.

Key Words: Reductive amination, silica chloride, sodium borohydride, aldehyde, ketone.

Introduction

Reductive amination of carbonyl compounds is a very important methodology for chemists to target the synthesis of secondary or tertiary amines;[1] thus, there are many approaches to carry out this direct process. $NaBH_3CN$ is a representative reducing agent,[2] and various modified borohydride derivatives have been used that involve $NaBH(OAc)_3$,[3] $NaBH_4$-$Mg(ClO_4)_2$,[4] $NaBH_4$–wet clay,[5] $Ti(O^i\text{-}Pr)_4$-$NaBH_4$,[6] $NaBH_4$-$ZnCl_2$,[7] $NaBH_4$-$NiCl_2$,[8] silica gel–$Zn(BH_4)_2$,[9] $[Zr(BH_4)_2Cl_2(dabco)_2]$,[10] $NaBH_4$ in micellar media,[11] *N*-methylpiperidine zinc borohydride,[12] $NaBH_4$-$H_3PW_{12}O_{40}$,[13] $NaBH_4$-silica phosphoric acid,[14] and *N*-methylpyrrolidine zinc borohydride.[15] However, most of these reagents may have one drawback or another. For example, catalytic hydrogenation is incompatible with compounds containing carbon–carbon multiple bonds, nitro groups, and cyano groups.[16] Sodium cyanoborohydride and tin hydride[17] reagents are highly toxic and generate toxic by-products such as HCN, NaCN, or organotin compounds upon workup.

Sodium borohydride is an inexpensive, safe to handle, and environmental friendly reducing agent for the reductive amination of aldehydes and ketones.[18] Procedures for using this mild and selective reagent have been developed for a wide variety of substrates.

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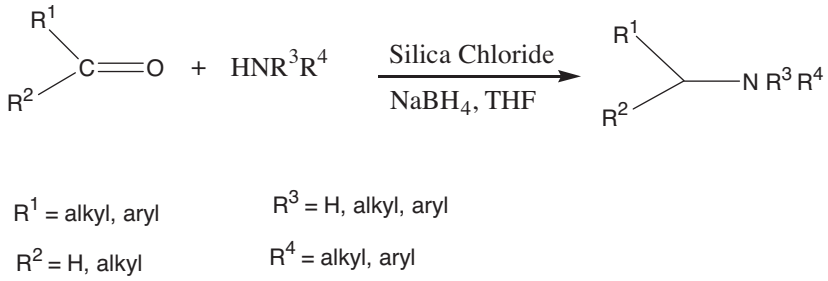
In recent years, heterogeneous catalysts have gained importance due to environmental and economic considerations. Among these, the application of silica chloride as a stable heterogeneous catalyst in organic synthesis has been widely studied. This catalyst is important from an environmental point of view, because it produces little waste. It also has excellent activity and selectivity even on an industrial scale and in most cases can be recovered from reaction mixtures and reused.[19]

Herein we report an efficient and convenient procedure for the reductive amination of a variety of carbonyl compounds using $NaBH_4$ in the presence of silica chloride at room temperature (Scheme).



Scheme. Reductive amination of carbonyl compounds using $NaBH_4$/silica chloride.

Experimental

Materials were purchased from Merck and Fluka companies. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230-400 mesh) and were identified by comparison of their spectra and physical data with those of the authentic samples. ^{1}H-NMR spectra were measured at 500 MHz on a JEOL spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent. IR spectra were recorded on Pye-unicam SP 1100 spectrophotometer.

Reductive amination of carbonyl compounds with sodium borohydride-silica chloride: a general procedure

Silica chloride was prepared according to the reported procedure.[20] Carbonyl compound (1 mmol) and amine (1 mmol) were mixed in THF (5 mL) and then treated with sodium borohydride (1 mmol) and silica chloride (0.5 g). The mixture was stirred at room temperature. After completion of the reaction, as indicated by TLC, the mixture was filtered and the residue was washed with CH_2Cl_2 (2×10 mL). Solvent was evaporated and the crude product was purified by column chromatography on silica gel (eluent: n-hexane/EtOAc) to afford the pure amine.

Some of the selected compounds' spectroscopic data

***N*-Benzyl-*N*-phenylamine. (entry 1)** IR (neat, cm^{-1}) 3384, 3003, 1600, 1498, 1321; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.42-7.20 (m, 5H, phenyl), 7.21 (t, 2H, phenyl), 6.77 (t, 1H, phenyl), 6.67 (d, 2H, phenyl), 4.35 (s, 2H, CH_2), 4.06 (br, 1H, NH).

***N*-(*p*-cyanobenzyl)-*N*-Phenylamine. (entry 2)** IR: 3330, 2940, 2850, 2210, 1610, 1530 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.60 (d, 2H, phenyl), 7.46 (d, 2H, phenyl), 7.15 (m, 2H, phenyl), 6.72 (t, 1H, phenyl), 6.56 (t, 2H, phenyl), 4.41 (s, 2H, CH_2), 4.20 (br, 1H, NH).

***N*-(*p*-methoxybenzyl)-*N*-Phenylamine. (entry 4)** ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24 (d, 2H, phenyl), 7.16 (t, 2H, phenyl), 6.88 (d, 2H, phenyl), 6.66 (m, 3H, phenyl), 4.25 (s, 2H, CH_2), 3.99 (br, 1H, NH), 3.79 (s, 3H, OMe).

***N*-Phenyl-*N*-(3-phenyl-2-propenyl)aniline. (entry 12)** IR: 3315, 3057, 3025, 2930, 2817, 1597, 1494, 1447, 967, 779, 692 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.17-7.38 (m, 5H), 6.73-6.61 (m, 7H), 3.94 (dd, 2H), 3.92 (br s, 1H).

***N*-methyl-*N*-phenyl benzylamine. (entry 8)** IR: 3411, 3055, 2926, 1602, 1503 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.19-7.31 (m, 7H), 6.70-6.75 (m, 3H), 4.52 (s, 2H), 3.00 (s, 3H).

Results and discussion

The reductive amination of a wide variety of aldehydes and ketones with primary and secondary amines in the presence of $NaBH_4$–silica chloride under neutral conditions was successful and gave the desired products in good to excellent yields (89%-97%) as summarized in the Table. Under such a condition, carbonyl compounds were not reduced in the reaction mixture, whereas the imine intermediates were converted easily to the corresponding amines. This reagent is suitable for use of chemoselective reduction of imines having nitro and cyano groups, since this reagent cannot reduce the nitro and cyano groups (entries 2, 3, and 6). 4-Nitroaniline under similar reaction conditions with 0.5 mmol excess of $NaBH_4$ afforded 97% of *N*-benzyl-4-nitroaniline within 20 min (entry 6). We found that 4-choloroanilines under optimal conditions efficiently react with benzaldehyde to produce the corresponding amine within 12 min (entry 7). In the case of α, β-unsaturated aldehydes and amines such as cinnamaldehyde and allyl amine, the reductive amination was successfully achieved without reduction of the C=C bond (entries 12, 13, and 16). Aliphatic aldehydes such as butanal underwent reductive amination successfully to give corresponding amines (entry 14). Reductive amination of cyclic and acyclic aliphatic ketones such as cyclohexanone and 2-heptanone with different aromatic and aliphatic amines such as aniline, allylamine, pipyridine, morpholine, and pyrrolidine also gave excellent yields of the corresponding amines (entries 15-20).

Conclusion

We described an efficient and chemoselective method for the synthesis of amines by reductive amination of carbonyl compounds with various amines in the presence of sodium borohydride and silica chloride. The scope of the reaction was demonstrated with aliphatic, aromatic, cyclic, and acyclic carbonyl compounds with primary and secondary amines. This method afforded amines as the only isolated products at room temperature. The neutral non-aqueous reaction conditions, simple workup, isolation of pure products, high yields, very short reaction time, and the use of safe and inexpensive reagent with no special handling technique are the notable advantages of the present method.

Table. Reductive amination of aldehydes and ketones using sodium borohydride-silica chloride at room temperature.[a]

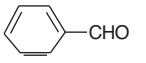
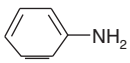
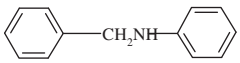
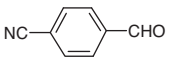
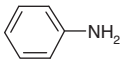
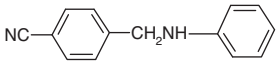
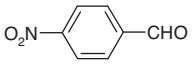
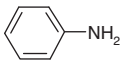
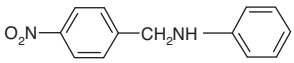
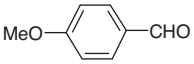
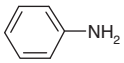
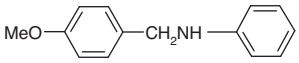
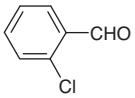
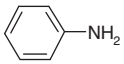
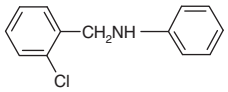
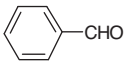
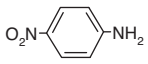
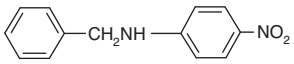
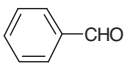
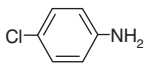
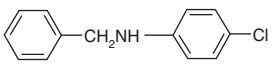
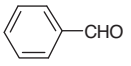
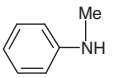
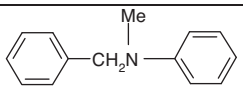
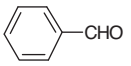
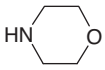
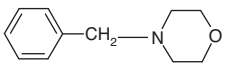
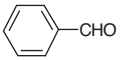
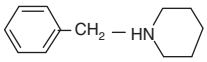
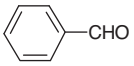
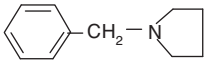
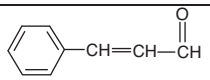
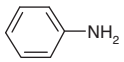
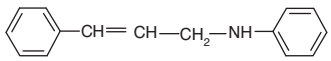
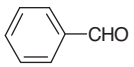
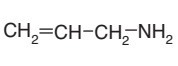
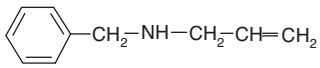
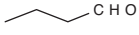
Entry	Compound	Amine	Product[b]	Time (min)	Yield (%)[c]
1				5	95[21]
2				9	96[22]
3				5	89[22]
4				10	95[5]
5				7	96[5]
6				20	97[23]
7				12	95[24]
8				6	90[25]
9				5	95[21]
10				Immediately	95[21]
11				Immediately	95[26]
12				Immediately	89[22]
13				Immediately	95[27]
14				Immediately	96[21]
15				Immediately	95[28]
16				Immediately	94[21]

Table. Contunied.

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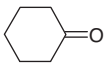
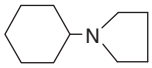
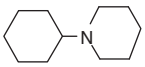
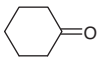
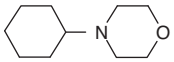
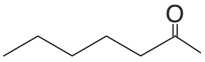
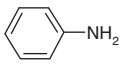
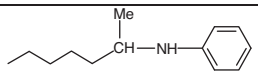
17				Immediately	90[26]
18				Immediately	92[21]
19				5	94[22]
20				5	95[29]

[a] All reactions were carried out at r.t. and molar ratio of reagent/carbonyl compound/amine was 1/1/1.
[b] All products were characterized spectroscopically (^{1}H-NMR, IR) and showed physical and spectral data in accordance with their expected structure and by comparison with authentic samples.
[c] Yields refer to pure isolated products.

Acknowledgements

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