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Direct reductive amination of aldehydes and selective reduction of α,β-unsaturated carbonyl compounds by $NaBH_4$ in the presence of guanidine hydrochloride in water

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This paper is dedicated to Professor Mehdi Golshani.

Abstract

A selective and direct access to secondary amines and a regioselective procedure for 1,2-reduction of α,β-unsaturated aldehydes and ketones with sodium borohydride activated by guanidine hydrochloride (5 mol%) in water is described.

Keywords: Direct reductive amination; Guanidine hydrochloride; Sodium borohydride; Imines; Secondary amines; α,β-unsaturated aldehydes and ketones; Allyl alcohols

1. Introduction

Reductive amination of carbonyl compounds, mostly aldehydes or ketones, is an important tool for the synthesis of amines [1]. The overall process involves the formation of an imine or iminium intermediate followed by reduction to an alkylated amine. The reductive amination is a stepwise, indirect or direct reaction. A stepwise or indirect reaction involves the formation of the intermediate imine followed by reduction in a separate step. When a mixture of carbonyl compound and the amine is treated with appropriate reducing agent in a single operation it is termed a direct reductive amination reaction. A variety of reducing agents, such as hydrogen in the presence of metal catalysts [2], Zn–AcOH [3], Et_3SiH–CF_3CO_2H [4], Bu_3SnH–DMF [5], $NaBH_3CN$ [6a], $NaBH(OAc)_3$ [6b], pyridine–BH_3 [6c], $ZnCl_2$–$NaBH_4$ [6d] silica gel–$Zn(BH_4)_2$ [6e], Ti(*O*-*i*-Pr)$_4$–$NaBH_4$ [6f] and $NiCl_2$–$NaBH_4$ [6g], $NaBH_4$–$ZrCl_4$ [6h], $NaBH_4$–H_2SO_4 [6i], $NaBH_4$-wet clay-microwave, [6j], $NaBH_4$–$H_3P_{12}O_{40}$ [6k], and borohydride exchange resin [6l] have been developed. However, in terms of functional group tolerance, side reactions and reaction conditions such reducing agents have many limitations. For example, catalytic hydrogenation is attractive from economical and ecological viewpoints, despite its incompatibility with compounds containing other reducible functional groups such as carbon–carbon double or triple bond, cyano and furyl groups [7]. Pyridine–BH_3 is unstable to heat and must be handled with extreme care. Nickel boride, $Zn(BH_4)_2$ is not suitable for reduction of imines having also ketone, ester, amide and nitro groups [8].

The direct reductive amination reaction (a one-pot three-component condensation reaction) is interesting and important, not only because two bonds are formed in one-pot, but in many cases, also offers considerable synthetic advantages in terms of broad variety of compounds and simplicity of the reaction procedure. Usually $NaBH_3CN$ and $NaBH(OAc)_3$ from commercial sources are utilized to carry out this transformation. It can be carried out under mild conditions, and is compatible, in some cases, with many functional groups. However, the processes based on such reducing agents have many limitations. $NaBH_3CN$ is expensive and highly toxic and it may contaminate the product with NaCN and generate toxic HCN upon work-up [9]. Furthermore, it is necessary to use excess amount of the amines (up to a fivefold) in order to limit or prevent the competitive reduction of the carbonyl groups. Clearly, the use of $NaBH_3CN$ is not environmentally friendly and is not accepted in industry. $NaBH(OAc)_3$ is flammable, water-reactive and poorly soluble

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in the most commonly organic solvents and has limitations with aromatic and unsaturated ketones. In addition, this reagent has only one available hydrogen and usually excess (1.5 equiv.) of the reagent are necessary for reaction. It is generally accepted that direct reductive amination is performed under anhydrous conditions in order to avoid the decomposition of the reducing agents or catalysts, and is favorable to generate the intermediate imines or imminium ions. Although many of the reported protocols for reductive aminations work well for the preparation of tertiary amines, in many cases the synthesis of secondary amines is compromised by over alkylation reactions [10]. Consequently, the selection of the reagents and conditions is very crucial [11]. If one can perform the direct reductive amination of carbonyl compounds in air and in the presence of moisture, it would be of considerable interest. Consequently, introduction of new procedure that alleviates or eliminates the abovementioned problems it should be a useful contribution in organic synthesis.

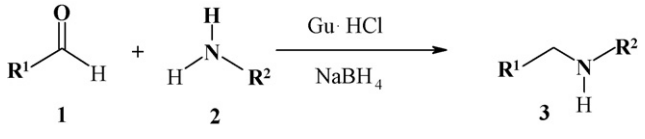
2. Results and discussion

We have approached this challenge to discover a new reagent from the viewpoint of both process and green chemistry. After surveying many of commercially available hydride reagents, we selected sodium borohydride as the least expensive, safe to handle, and environmentally friendly reducing agent, which can particularly be used for large-scale reductions. It is also particularly a current challenges to develop environmentally benign synthetic systems in water [12].

In continuation of our interest in the application of guanidine hydrochloride in water for organic transformation [13], we report the results of our investigations for direct reductive amination of aldehydes and ketones with a variety of primary amines by sodium borohydride/guanidine hydrochloride (5 mol%) in water. Water is the cheapest and nontoxic, nonflammable and environmentally benign solvent. In addition, reactions in aqueous medium eliminate the additional efforts of preparing anhydrous substrates and reagents before use, and the unique properties of water can be utilized to realize reactivity and selectivity that cannot be attained in organic solvents.

At first, we carried out the reductive amination of benzaldehyde with aniline using guanidine hydrochloride GuHCl (5 mol%)/$NaBH_4$ in H_2O at room temperature and after the usual work up benzylphenylamine was obtained in 95% isolated yield. Under this standard conditions, direct reductive amination of *p*-cyano benzaldehydes with a primary amine proceeded smoothly with full conversion of the aldehyde and good yields of the desired alkylated amine. The results in Scheme 1 show that the reductive amination of a wide variety of aldehydes with aniline has been successful under this condition and gives the desired products in good to excellent yields.

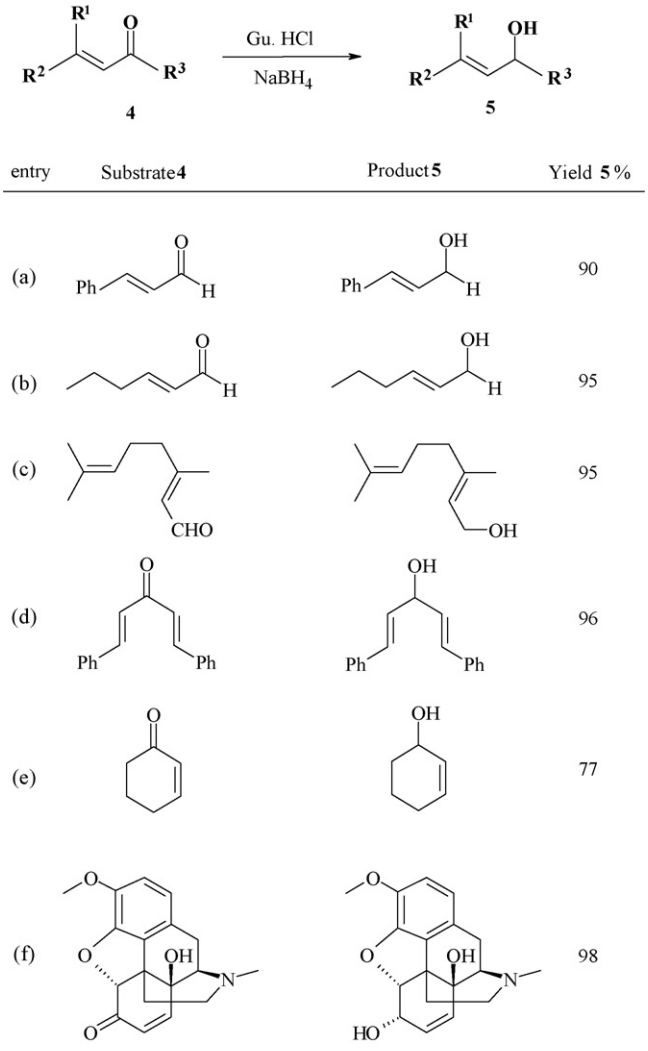
These encouraging results prompted us to further investigate the use of GuHCl/$NaBH_4$ as reducing agent. We have been studying the use of α,β-unsaturated aldehydes and ketones for the synthesis of the corresponding allyl alcohols. Allyl alcohols are important intermediates in the production of pharmaceuticals, agrochemicals and fragrances. Chemoselective reduction of conjugated carbonyl compounds is a common reaction extensively used in synthetic chemistry and industry.



1 2 3

	R^1	R^2	3%
a	Phenyl	Phenyl	93
b	4-Cl-Phenyl	Phenyl	95
c	4-NC-Phenyl	Phenyl	90
d	4-Pyridyl	Phenyl	94
e	*2*-Furyl	Phenyl	98
f	*tert*-Butyl	Phenyl	81
g	*n*-Hexyl	Phenyl	88
h	PhenylCH_2CH_2	Phenyl	93
i	2-Furyl	4-Me-Phenyl	93
j	2-Furyl	2-HO-Phenyl	89
k	2-Furyl	4-MeO-Phenyl	91
l	Phenyl	PhenylCHCH_2OH	92

Scheme 1.



Scheme 2. 1,2-Selective reduction of unsaturated aldehydes and ketones.

Many useful methodologies for selective 1,2-reduction of α,β-unsaturated carbonyl compounds have been developed through metal hydride mediated reductions [14]. The most widely accepted of these involves sodium borohydride in the presence of cerium chloride. This has been optimized to give excellent selectivity under mild condition [15].

We now report that GuHCl (5 mol%)/$NaBH_4$ in water effects a facile and smooth reduction of α,β-unsaturated aldehydes and ketones (r.t., <15 min) to produced exclusively the corresponding allylic alcohols. It is interesting to note that in the reduction of 14-hydroxycodeninone (**4f**) only the 6α-allyl alcohol (**5f**) is obtained in very good yield [16]. The results of this remarkably reduction are summarized in Scheme 2 [17].

3. Conclusion

In summary, we have described methodologies which enable the mono *N*-alkylation of primary amines with various aldehydes covering a wide range of steric and electronic characteristics and also is generally applicable to the selective 1,2-reduction of α,β-unsaturated aldehydes and ketones. This should find widespread use in organic synthesis.

4. Experimental

All products were identified by comparing their ^{1}H NMR, ^{13}C NMR and IR values and physical properties with those of authentic samples. All yields refer to isolated products.

4.1. General procedure I: N-monoalkylation of primary amines

To a solution containing GuHCl (10 mg, 5 mol%) in H_2O (4 mL), was added the carbonyl compound (2 mmol) and aniline (2.2 mmol) and the mixture vigorously stirred for 15 min at room temperature. After, $NaBH_4$ (20 mg, 2.1 mmol) was added, the mixture was stirred for additional 10 min. The reaction mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated under vacuum and the crude mixture was purified by column chromatography on silica gel (hexane:ethylacetate, 2:1) to afford the pure products.

4.2. General procedure II: selective 1,2-reduction of α,β-unsaturated aldehydes and ketones

To a solution containing GuHCl (10 mg, 5 mol%) in H_2O (4 mL), was added the carbonyl compound (2 mmol) and the mixture vigorously stirred for 10 min at room temperature. After, $NaBH_4$ (20 mg, 2 mmol, 1 equiv.) was added, the mixture was stirred for additional 10 min. The reaction mixture extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated under vacuum and the crude mixture was purified by column chromatography on silica gel (hexane:ethyl acetate, 2:1) to afford pure products. Spectroscopic data for selected examples follow: **3b**: ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 3.62$ (bs, 1H), 4.33 (s, 2H), 6.54–6.85 (m, 5H), 7.13–7.82 (m, 4H); ^{13}C NMR (22.5 MHz, $CDCl_3$): $\delta = 47.3$ (CH_2), 113.0 (CH), 117.9 (CH), 128.9 (CH), 129.3 (CH), 130.2 (CH), 131.1 (CH), 132.2 (C), 138.4 (C), 148.1 (C); **3i**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.2$ (s, 3H), 3.3 (bs, 1H), 4.3 (s, 2H), 6.27 (d, $J = 2.5$ Hz, 1H), 6.36 (m, 1H), 6.66 (d, $J = 8.5$ Hz, 2H), 7.05 (d, $J = 8.5$ Hz, 2H), 7.4 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.8$ (CH_3), 42.2 (CH_2), 107.3 (CH), 110.7 (CH), 113.8 (CH), 127.7 (C), 130.1 (CH), 142.2 (CH), 145.8 (C), 153.4 (C); **3k**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.65$ (bs, NH), 3.79 (s, 3H), 4.31 (s, 2H), 6.27 (d, $J = 2.7$ Hz, 1H), 6.37 (d, $J = 1.71$ Hz, 1H), 6.70 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.78$ Hz, 2H), 7.4 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 42.8$ (CH_2), 56.1 (OCH_3), 107.3 (CH), 110.8 (CH), 115.1 (CH), 115.2 (CH), 142.2 (CH), 142.3 (C), 152.9 (C), 153.5 (C); **3l**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.15$ (bs, OH), 3.60 (m, 1H), 3.65 (d, $J = 13$ Hz, 1H), 3.76 (dd, $J = 10.17$, 4.0 Hz, 1H), 3.81 (d, $J = 13$ Hz, 1H), 3.86 (dd, $J = 10.17$ Hz, 4.0 Hz, 1H), 4.7 (s, 1H), 7.38 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 51.6$ (CH), 64.1 (CH_2), 67.1 (CH_2), 127.5 (CH), 127.7 (CH), 127.9 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 140.4 (C), 140.9 (C); **5d**: ^{1}H NMR (500 MHz, $CDCl_3$): 2.7 (bs, OH), 5.07 (t, $J = 6.0$ Hz, 1H), 6.43 (dd, $J = 6.0$ Hz, 2H), 6.76 (d, $J = 16.0$ Hz, 2H), 7.33 (t, $J = 7.5$ Hz, 2H), 7.42 (t, $J = 6.19$ Hz, 4H), 7.48 (d, $J = 7.45$ Hz, 4H); ^{13}C NMR: (125 MHz, $CDCl_3$): $\delta = 74.0$ (CH), 127.13 (CH), 128.3 (CH), 129.1 (CH), 131.0 (CH), 131.2 (CH), 137.1 (C); **5f**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.81$ (d, $J = 9.65$ Hz, 1H), 2.44 (d, $J = 8.0$ Hz, 2H), 2.74 (s, 3H), 2.56 (dd, $J = 7.0$, 6.5 Hz, 2H), 2.9 (d, $J = 10$ Hz, 1H), 3.2 (bs, OH), 3.23 (d, $J = 8.5$ Hz, 1H), 3.88 (s, OMe), 4.67 (m, 1H), 4.93 (d, $J = 6.6$ Hz, 1H), 4.95 (s, OH), 5.54 (dd, $J = 10$ Hz, 2.75 Hz, 1H), 5.96 (d, $J = 10$ Hz, 1H), 6.63 (d, $J = 8.7$ Hz, 1H), 6.70 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 22.6$ (CH_2), 32.0 (CH_2), 43.2 (NCH_3), 45.6 (CH_2), 47.1 (C), 56.7 (OCH_3), 64.4 (CH), 65.6 (C), 69.1 (C), 90.3 (CH), 113.6 (CH), 119.7 (CH), 126.0 (C), 129.1 (CH), 132.6 (C), 138.4 (C), 143.0 (CH), 145.9 (C).

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