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Reductive Amination of Aldehydes and Ketones to Their Corresponding Amines with $NaBH_4$ in Micellar Media

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Summary. A variety of aliphatic and aromatic aldehydes and ketones were efficiently reduced to their corresponding amines when treated with primary and secondary amines and $NaBH_4$ in micellar media at room temperature under neutral conditions.

Keywords. Reductive amination; Aldehydes; Ketones; Amines; $NaBH_4$; Micellar media.

Introduction

In biological and chemical systems, the reductive amination of aldehydes and ketones is an important transformation which allows the direct conversion of carbonyl compounds into amines [1]. Reports describing the synthesis of amines using reductive amination procedures include tetrahydroborate exchange resin [2a], borane-pyridine in *Ac*OH [2b], $Ti(i\text{-}PrO)_4/NaBH_4$ [3], $Na[BH(OAc)_3]$ [4], $Li[BH_3CN]$ [5], $Na[BH_3CN]$ [6], $Na[BH_3CN]$ in combination with $TiCl_4$ [7a] and $ZnCl_2$ [7b], and $NaBH_4$/wet clay/microwave irradiation [8]. The most widely used reagents are: a) Using the highly toxic $Na[BH_3CN]$; these reactions should be conducted in highly acidic conditions (5 *M* HCl/CH_3OH) and suffers from low to moderate yields and sometimes from long reaction times [6a]. This reagent is also sluggish for the reductive amination of aldehydes with anilines bearing electron-withdrawing groups [9]. b) Using $Na[BH(OAc)_3]$ in the presence of acetic acid, which is corrosive. This method also suffers from moderate yields and long reaction times [4].

The generally accepted reaction steps for reductive amination of carbonyl compounds are shown by Eqs. (1)–(3). Equations (3) and (4) show that two competitive

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reductive reactions (C=N *vs.* C=O) are inevitable and occur in the reductive amination of carbonyl compounds [2b].

$$R^1R^2CO + R^3NH_2 \rightleftharpoons R^1R^2C(OH)NHR^3 \quad (1)$$

$$R^1R^2C(OH)NHR^3 \rightleftharpoons R^1R^2C{=}NR^3 + H_2O \quad (2)$$

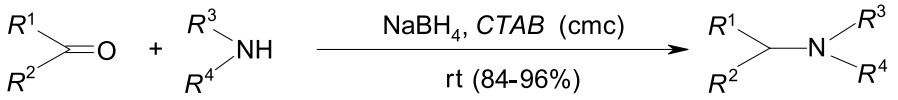
$$R^1R^2C{=}NR^3 + {''}H{''} \rightleftharpoons R^1R^2CHNHR^3 \quad (3)$$

$$R^1R^2C{=}O + {''}H{''} \rightleftharpoons R^1R^2CHOH \quad (4)$$

The use of water as reaction medium is advantageous not only from an economical and environmental point, but also frequently from a chemical view. It is well established that, in many cases, rates and pathways of all kinds of chemical reactions can be altered by performing the reactions in micellar media instead of pure bulk solvents. Micelles are able to concentrate the reactants within their small volumes [10], stabilize substrates, intermediates, or products [11], and orient substrates [12] so that, ionization potentials and oxidation-reduction properties [13], dissociation constants [14], physical properties, and quantum efficiencies and reactivities [15] are changed. Thus, they can alter the reaction rate, mechanism, and regio and stereochemistry [16]. For some reactions rate enhancement in the order of 10^6-fold has been noted [17]. One of the most important aspects leading to micellar effects on reaction is the solubilization of substrates in micellar interiors [18]. Another way by which micelles can catalyze a reaction is the stabilization of intermediates or substrates as bound counterions [19, 20]. Counterions interact with the head groups not only electrostatically, but also hydrophobically. $NaBH_4$ in the presence of a cationic surfactant such as cetyl trimethylammonium bromide (*CTAB*) has already been used in the reduction of enones and gave mostly 1,4-reduction products [21]. Therefore, we decided to study reductive transformations in micellar solutions using $NaBH_4$ as reducing agent.

Results and Discussion

We here report that in the presence of $NaBH_4$, an efficient and smooth reductive amination of a variety of carbonyl compounds proceeded well under neutral conditions. Under this condition carbonyl compounds were not reduced in the reaction mixture, whereas the imine intermediates were converted easily to the corresponding amines. However, the absence of formation of any hydroxyl compound in these reductions suggests that the overall process would proceed successfully if a reasonable concentration of imines is available and the reaction conditions could discriminate between the reduction of the imine intermediate (Eq. (3)) and the carbonyl compound present in the reaction mixture (Eq. (4)). In general, the reactions were carried out with 4 equivalents of the primary amine and 2 equivalents of secondary amine per 1 equivalent of the carbonyl compound using appropriate amounts of $NaBH_4$ as reducing agent in *CTAB* aqueous solution of critical micellar concentration at room temperature (Scheme 1).



R^1, R^4 = H, alkyl
R^2, R^3 = alkyl, aryl

Scheme 1

In order to show the general applicability of this method, we have applied this system for the reductive amination of structurally different carbonyl compounds with amines.

First we studied the reductive anilation of benzaldehyde with $NaBH_4$ in micellar solution of sodium dodecyl sulfonate as an anionic micelle and in solution of *CTAB* as a cationic micelle at their critical micellar concentrations (cmc). The best result for reductive anilation of benzaldehyde was obtained in *CTAB* solution. Under these conditions, carbonyl compounds or amines carrying both electron-donating and electron-withdrawing substituents produced the corresponding amines with high regioselectivity. As indicated in Table 1, a variety of aldehydes and ketones when treated with primary and secondary amines in the presence of $NaBH_4$ in *CTAB* solution, afforded the corresponding amines in high yields at room temperature. It is noteworthy that α,β-unsaturated aldehydes were chemoselectively reduced to the corresponding amine without reduction of the carbon–carbon double bond (Table 1; Entry 10). This method can be used for anilines

Table 1. Reductive Amination of Aldehydes and Ketones Using $NaBH_4$ in *CTAB* (cmc)[a]

Entry	Carbonyl compound	Amine	Product[b]	Portions of reagent	Time h	Yield[c] %
1	*Ph*–CHO	*Ph*–NH_2	*Ph*–CH_2–NH–*Ph*	3	9	92
2	3-NO_2–*Ph*–CHO	*Ph*–NH_2	3-NO_2–*Ph*–CH_2–NH–*Ph*	2	5	96
3	4-CN–*Ph*–CHO	*Ph*–NH_2	4-CN–*Ph*–CH_2–NH–*Ph*	2	6	92
4	4-Br–*Ph*–CHO	*Ph*–NH_2	4-Br–*Ph*–CH_2–NH–*Ph*	3	6.5	85
5	4-*Me*O–*Ph*–CHO	*Ph*–NH_2	4-*Me*O–*Ph*–CH_2–NH–*Ph*	4	12	94
6	2-*Et*–*Ph*–CHO	*Ph*–NH_2	2-*Et*–*Ph*–CH_2–NH–*Ph*	3	7	89
7	4-*Me*–*Ph*–CHO	*Ph*–NH_2	4-*Me*–*Ph*–CH_2–NH–*Ph*	3	8.5	91
8	*Ph*–CH_2–CH_2–CHO	*Ph*–NH_2	*Ph*–CH_2–CH_2–CH_2–NH–*Ph*	3	8	84
9	CH_3–CH_2–CH_2–CHO	*Ph*–NH_2	CH_2–CH_2–CH_2–CH_2–NH–*Ph*	5	12.5	89
10	*Ph*–CH=CH–CHO	*Ph*–NH_2	*Ph*–CH=CH–CH_2–NH–*Ph*	2	6	97
11	*Ph*–CO–*Me*	*Ph*–NH_2	*Ph*–CH(*Me*)–NH–*Ph*	4	10	90
12	3-Pyridyl–CO–*Me*	*Ph*–NH_2	3-Pyridyl–CH(*Me*)–NH–*Ph*	2	5	90
13	*Ph*–CHO	3-Cl–*Ph*–NH_2	3-Cl–*Ph*–NH–CH_2–*Ph*	5	13	95
14	*Ph*–CHO	4-NO_2–*Ph*–NH_2	4-NO_2–*Ph*–NH–CH_2–*Ph*	5	14	91
15	*Ph*–CHO	*Ph*–NH–*Me*	*Ph*–CH_2–N(*Me*)–*Ph*	4	12	94
16	*Ph*–CHO	Piperidine	4-Benzylpiperidine	5	14	96
17	*Ph*–CHO	Morpholine	4-Benzylmorpholine	4	9.5	92

[a] All reactions were carried out at room temperature; [b] all products are known compounds and gave satisfactory spectral analysis; [c] yields refer to pure isolated products

with electron-withdrawing groups which is not possible with [$NaBH_3CN$] [6] and [$NaBH(OAc)_3$] [4], the most often used reagents for this purpose (Table 1; Entries 13, 14).

It is also interesting to mention that in other methods [3–5], a strong acidic medium is applied whereas in our procedure we do not use any acid, and the reaction conditions are very mild. Thus, it can be used for acid sensitive substrates. The reducing agent is also a good substitute for $Na[BH(OAc)_3]$ and $Na[BH_3CN]$ for the preparation of amines by reductive amination of carbonyl compounds under neutral conditions. The use of $NaBH_4$ eliminates the problems encountered by $Na[BH_3CN]$, such as residual cyanide in the product and in the waste stream, and by using $Na[BH(OAc)_3]$ in the presence of acetic acid, which is corrosive and also suffers from moderate yields of the amine products and long reaction times [4, 6].

In conclusion, although there are several methods available for this transformation, we believe that the present method offers considerable advantages in terms of simplicity, commercially available reagents, mildness of the reaction medium, easy reaction work up, efficiency, chemoselectivity, high reaction rates and yields, low toxicity of the reagent, and no *pH* adjustment.

Experimental

$NaBH_4$ and carbonyl compounds were purchased from Merck. All products were identified by comparison of their spectra (^{1}H NMR, IR) and physical data with those of authentic samples. Yields refer to isolated products. IR spectra were determined on a Shimadzu instrument. ^{1}H NMR spectra were recorded with Bruker DRX500 AVANCE (500 MHz) and GNM-Ex90A (90 MHz) spectrometers, using $CDCl_3$ as solvent.

General Procedure for the Amination of Aldehydes and Ketones to their Corresponding Amines with $NaBH_4$ in Micellar Media

To a stirred solution of 1 mmol carbonyl compound and 4 mmol primary amine or 2 mmol secondary amine in 7 cm^3 aqueous *CTAB* solution (cmc), $NaBH_4$ was added in 0.5 mmol portions (0.019 g) every 3 h until the reaction showed by TLC (eluent: *n*-hexane/*Et*OAc = 8/1–10/1) to be complete. The mixture was stirred for the time specified in Table 1 and was extracted with 3×20 cm^3 Et_2O. The organic layers were combined and washed with H_2O, brine, dried ($MgSO_4$), and then the solvent was evaporated. The resulting mass was applied to a silica gel column and eluted with *n*-hexane/*Et*OAc (10/1–16/1). Evaporation of the solvent afforded the pure amines in 84–96% yields (Table 1).

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