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Research note

One-pot reductive amination of aldehydes by the dihydropyridine in water

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Abstract An efficient, highly chemoselective and simple synthesis of secondary amines via reductive amination of aldehydes, aromatic amines and inexpensive and easily accessible Diethyl 2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate (DHP) in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA) in water in good to excellent yields is reported.

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1. Introduction

Amines are ubiquitous functionalities in active pharmaceutical intermediates, dye and fine chemicals [1]. Furthermore, optically active secondary amines have important applications in organic asymmetric synthesis as chiral auxiliaries, catalysts, and resolving agents [2]. Consequently, synthesis of amines is an active field in medicinal chemistry and modern organic synthesis.

The synthesis of secondary and tertiary amines by the reductive amination of aldehydes and ketones is usually and relatively fast and efficient. A variety of methods are available for the direct reductive amination of aldehydes and ketones using sodium borohydride and sodium cyanoborohydride [3–7]. These reactions offer the advantages of simplicity, wide availability of substrates, mild reaction conditions, and tolerance to other functional groups. A further development has been described using sodium triacetoxyborohydride and borane–pyridine, silane [8,9], metal hydride reagents [10] and

dehydropyridine (Hantzsch) ester [11–13] in order to improve the selectivity and yield of the reaction.

However, most of these reagents may have some drawbacks; 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. Cyanoborohydride and tin hydride reagents generate toxic by-products such as HCN, NaCN or organotin compounds upon workup and may result in the contamination of the product with the toxic compounds. Furthermore, almost all the above reactions were performed in organic solvent. As literature survey shows, there are no reports concerning the selective synthesis of secondary amines via reductive amination of aldehydes and amines with inexpensive and easily accessible dihydropyridine in water. Thus, the development of novel and simple catalytic method for a mild direct reductive amination in water is an important research goal.

2. Results and discussion

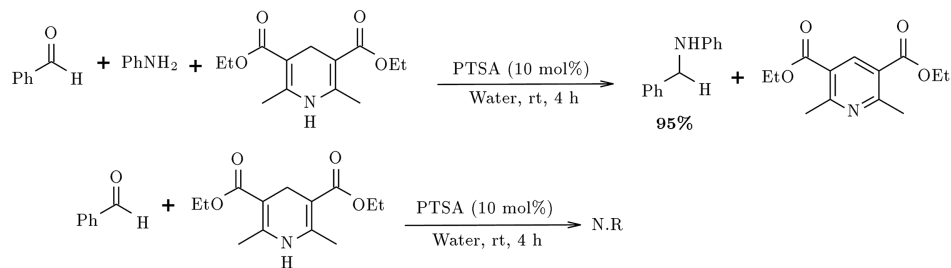
Water is an elegant solution with the ultimate goal of hazard-free, waste-free and energy efficient for the synthesis of biologically active compounds with potential application in the pharmaceutical or agrochemical industries. In the context of our ongoing investigations of the organic transformation under solvent free reaction conditions or in water, herein, we report that DHP is an efficient, safe and environmentally friendly reducing agent for the direct reduction of imines. This method

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Scheme 1: Optimization of reaction conditions.

Table 1: PTSA catalyzed reductive amination in water.

Entry	Aldehyde (Ar)	Amine (Ar')	Yield (%)	Entry	Aldehyde (Ar)	Amine (Ar')	Yield (%)
1	Ph	2a	90	13	2-NO ₂ C ₆ H ₄	2a	80
2	Ph	2b	92	14	2-NO ₂ C ₆ H ₄	2d	85
3	Ph	2e	72	15	3-NO ₂ C ₆ H ₄	2a	92
4	Ph	2d	80	16	3-NO ₂ C ₆ H ₄	2b	82
5	4-ClC ₆ H ₄	2a	95	17	3-NO ₂ C ₆ H ₄	2d	85
6	4-ClC ₆ H ₄	2b	84	18	4-NO ₂ C ₆ H ₄	2a	95
7	4-ClC ₆ H ₄	2d	78	19	4-NO ₂ C ₆ H ₄	2c	90
8	4-ClC ₆ H ₄	2e	70	20	4-NO ₂ C ₆ H ₄	2d	88
9	3-OMeC ₆ H ₄	2a	75	21	2-Furyl	2a	82
10	3-OMeC ₆ H ₄	2c	82	22	2-Furyl	2f	70
11	4-MeC ₆ H ₄	2a	88	23	2-Thienyl	2a	70

is not only of interest from ecological point of view, but also proves to be a clean, rapid and very simple procedure in large-scale production of secondary amines.

We initially examined a direct reductive amination reaction of benzaldehyde with aniline using *p*-toluenesulfonic acid monohydrate (PTSA)-activated DHP. The reaction was carried out by directly mixing a 1:1:1:0.1 mixture of benzaldehyde, aniline, DHP and PTSA in 5 mL of water at room temperature in air until TLC showed complete disappearance of benzaldehyde (Scheme 1). It was interestingly found that quantitative yields of *N*-benzylaniline obtained without reduction of benzaldehyde. Moreover, the reductant was found to be inactive toward aldehydes or ketones in the absence of amines (Scheme 1).

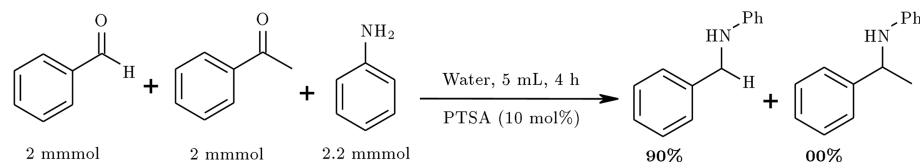
After optimization of reaction condition, we then studied the general applicability of this procedure for the synthesis of sterically, electronically, and functionally diverse amines and aldehydes (Table 1). The data in Table 1 shows that different aromatic aldehydes are successfully converted to the corresponding amines in high yields at room temperature in water. The presence of electron-withdrawing or electron-donating substituents on the aromatic ring did not affect the course of the reaction. Sensitive functionalities such as OMe and NO₂ were tolerated under the mild reaction conditions. Furthermore, selective reductions of carbonyl compounds

in the presence of double bond were performed in the cinnamaldehyde exactly without reduction of double bonds. However, aliphatic aldehyde and aliphatic amine did not give any products in this reaction condition.

The reactions are clean and highly selective for affording desired amines in high yields and short times. The reaction conditions are mild enough to perform either in the presence of acid or base and also sensitive functional groups. Furthermore, this method is as well effective for the aromatic, hindered or unhindered amines. The reported method is highly selective for the preparation of amines from aldehydes, and the reductive amination of aldehydes in the presence of ketones, by this method, gives only secondary amines of the aldehydes (Scheme 2).

3. Conclusions

In conclusion, we have developed a mild, general, and efficient method for reductive amination aromatic aldehydes and amines under mild conditions, mediated by PTSA in water. Furthermore, this method has the advantages of inexpensive reagents, simple operation, improved yields, enhanced rates, simple experimental work up, stability, and non-toxicity. The



absence of side-reactions such as aldehyde reduction products in this procedure clearly indicates that a selective reductive amination operates in this reaction medium.

4. Experimental

4.1. General

^1H NMR spectra were recorded on a 500 MHz Bruker NMR spectrometer and ^{13}C NMR spectra were recorded on a 125 MHz NMR spectrometer, respectively, using CDCl_3 as solvent and TMS as internal standard. Chemical shifts are reported in ppm. Melting points are measured on a Buchi Melting Point B-545 apparatus and are not corrected. All amines, aldehydes and solvent are commercially available and were purchased and used without further purification; water and other solvent were distilled before being used.

4.2. Preparation of diethyl 2, 6-dimethyl-1, 4-dihydro-3, 5-pyridinedicarboxylate (DHP)

A mixture of ethyl acetoacetate (100 mmol), formaldehyde (70 mmol) and ammonium acetate (90 mmol) were added together and stirred at $80\text{ }^\circ\text{C}$ for 5 h. After the reaction was completed (TLC checked), the crude product was isolated by precipitation upon addition of cold water to the reaction mixture followed by vigorous shaking and decanting of the aqueous layer. The precipitate was then filtered off, washed with water and was then recrystallized from ethanol to give the pure products [14].

4.3. General procedure for reductive amination in water

To a stirred solution of aldehydes (3 mmol) and aromatic amines (3 mmol) in 5 mL of water in a test tube, dihydropyridine (3 mmol) and PTSA (10 mol%) were added and the resulting mixture was stirred at room temperature for 4–8 h. The reaction mixture was extracted by ethyl acetate and dried over anhydrous Na_2SO_4 . Evaporation of the solvent afforded the desired crude products. The crude product was further purified by flash column chromatography on silica gel afforded the pure amine. All compounds were characterized on the basis of their spectroscopic data (IR, NMR).

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