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Reductive Amination of Aldehydes by $NaBH_4$ in the Presence of $NaH_2PO_4.H_2O$

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ABSTRACT

Thereductive aminationofa varietyof aldehydes withanilines has been carried out by $NaBH_4$/ $NaH_2PO_4.H_2O$as new reducing systemswithin 55-100 min in THFunder reflux conditionsin high to excellent yields of products (85-92%).

Key words: $NaBH_4$, $NaH_2PO_4.H_2O$, Reductive amination, Aldehydes, Amines.

INTRODUCTION

The reduction of nitro, cyano, azide, carboxamide compounds is common routes for the synthesis of amines. Also, this goal has been achieved by the alkylation of amines. These methods for the preparation of secondary amines are often problemssuch as harsh reaction conditions, overalkylation, low chemical selectivity and generally poor yields. Other approach is reductive amination reaction in a single operation*i.e*reductive amination. The reductive aminationhas been carried out by sodium borohydride under different reducing system such as: $NaBH_4$/cellulose sulfuric Acid/ EtOH[1], $NaBH_4$-amberlyst15 [2], $NaBH_4$-silica chloride[3], $NaBH_4$-silica-gel-supported sulfuric acid [4], $NaBH_4$-$H_3PW_{12}O_{40}$ [5], $NaBH_4$/guanidine hydrochloride /H_2O [6], $NaBH_4$/Bronsted acidic ionic liquid (1-butyl-3-methyl imidazoliumtetrafluoroborate [(BMIm)BF_4]) [7], $NaBH_4$ or $LiAlH_4$/$LiClO_4$/diethyl ether [8] $NaBH_4$-$PhCO_2H$ [9], $NaBH_4$-$NiCl_2$[10], Ti(O-*i*-Pr)$_4$-$NaBH_4$[11], $NaBH_4$-wet-clay-microwave [12], $NaBH_4$/Mg$(ClO_4)_2$[13], $NaBH_4$/B$(OH)_3$ or Al$(OH)_3$ [14] $NaBH_4$/Ga$(OH)_3$[15].In continuing our efforts for the development of new reducing systems [16-26],in this context, we have carried outthe reductive amination reaction of aldehydes with anilinesby $NaBH_4$/$NaH_2PO_4.H_2O$ system in THF.

Table 1. Reductive Amination of Aldehydes (1 mmol) with Anlines (1 mmol) by $NaBH_4$ (1 mmol) in the presence of $NaH_2PO_4.H_2O$(1 mmol) in THF (3 mL) under reflux conditions

Entry	Aldehydes	Anilines	Products	Time/min	Yield[a]/%
1	benzaldehyde	aniline	*N*-benzylaniline	55	92
2	benzaldehyde	4-bromoaniline	*N*-benzyl-4-bromoaniline	65	87
3	benzaldehyde	4-methylaniline	*N*-benzyl-4-methylaniline	60	89
4	benzaldehyde	4-nitroaniline	*N*-benzyl-4-nitroaniline	65	88
5	4-bromobenzaldehyde	aniline	*N*-(4-bromobenzyl)aniline	60	88
6	4-bromobenzaldehyde	4-methoxyaniline	*N*-(4-bromobenzyl)-4-methoxyaniline	85	90
7	4-methoxybenzaldehyde	4-bromoaniline	*N*-(4-methoxybenzyl)-4-bromoaniline	100	85
8	4-methylbenzaldehyde	aniline	*N*-(4-methylbenzyl)aniline	100	87
9	2-methoxybenzaldehyde	aniline	*N*-(2-methoxybenzyl)aniline	100	85
10	4-methylbenzaldehyde	4-methoxyaniline	*N*-(4-methylbenzyl)-4-methoxyaniline	90	89
11	4-bromobenzaldehyde	4-bromoaniline	*N*-(4-bromobenzyl)-4-bromoaniline	60	90
12	4-methoxybenzaldehyde	aniline	*N*-(4-methoxybenzyl)aniline	80	92
13	4-nitrobenzaldehyde	4-bromoaniline	*N*-(4-nitrobenzyl)-4-bromoaniline	70	90
14	2-methoxybenzaldehyde	4-methylaniline	*N*-(2-methoxybenzyl)-4-methylaniline	100	91

[a] Yields refer to isolated pure products (±5%).

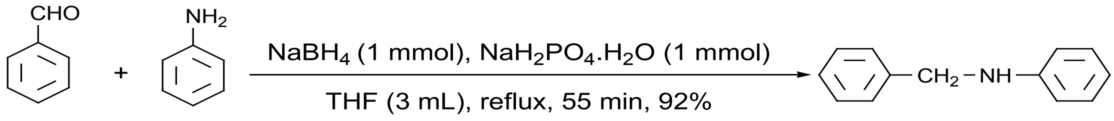
RESULTS AND DISCUSSIONS

The model reaction has been selected by reductive amination of benzaldehyde with aniline. This reaction was performedwith different molar ratio of the benzaldehyde/aniline/$NaH_2PO_4.H_2O$/$NaBH_4$in different solvents for the selection of appropriate conditions. Experiments have been shown that using 1eq. of $NaH_2PO_4.H_2O$in THF (3 mL) under reflux conditionsis the best conditions to complete the reductive amination of benzaldehye (1 mmol) and aniline (1 mmol) to *N*-benzylaniline. The reductive amination completes within 55 min with 92% yields of product as shown in scheme 1.

By using the various structurally different aldehydes and anilines, the efficiency of this protocol was further examined. Experiments have been shown the correspondingsecondary amines were obtained in excellent yields (85-92%) within 55-100 min as shown in Table 1. The influence of $NaH_2PO_4.H_2O$ is not clear but we observed sodium borohydride slowly is liberated hydrogen gas *in situ* in the presence of $NaH_2PO_4.H_2O$. Consequently, the generated molecular hydrogen combines with more easily hydride attack, thus accelerates the rate of reduction reaction.

EXPERIMENTAL

IR and ^{1}H NMR spectra were recorded on PerkinElmer FT-IR RXI and 400 MHz Bruker spectrometers, respectively. The products were characterized by their ^{1}H NMR or IR spectra and comparison with authentic samples (melting or boiling points). TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 F_{254} aluminum sheet.



Scheme 1:

Reductive amination of banzaldehyde and aniline with $NaBH_4$/$NaH_2PO_4.H_2O$ system (typical procedure)

In a round-bottomed flask (10 mL) equipped with a magnetic stirrer, a solution of benzaldehyde (0.106 g, 1 mmol), aniline (0.093 g, 1 mmol) and $NaH_2PO_4.H_2O$(0.14, 1 mmol) was preparedin THF (3 mL). Then the $NaBH_4$ (0.036 g, 1 mmol) was added to the reaction mixture and stirred under reflux conditions. TLC monitored the progress of the reaction (eluent, CCl_4/Ether: 5/2). The reaction was filtered after completion within 55 min. Evaporation of the solvent and short column chromatography of the resulting crude material over silica gel (eluent, CCl_4/Ether: 5/2) afforded the *N*-benzylaniline (0.l66 g, 92% yield, Table 1, entry 1).

CONCLUSION

In this context, we have shown that the $NaBH_4$/$NaH_2PO_4.H_2O_3$ as reducing system is efficient for the reductive amination of a variety of aldehydes and anilines to their corresponding secondary amineas. Reduction reactions were carried out with $NaBH_4$ (1 mmol) and $NaH_2PO_4.H_2O$(1 mmol) in THFunder reflux conditions.Highefficiency of the reduction reactions and easy work-up procedure makes as an attractive new protocol for reductive amination of aldehydes.

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