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$NaBH_4/Ga(OH)_3$: An Efficient Reducing System for Reductive Amination of Aldehydes

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ABSTRACT

Structurally different secondary amineshave been synthesized byreductive aminationofavarietyof aldehydes and anilines with $NaBH_4/Ga(OH)_3$ as new reducing systems in CH_3CN at room temperature in high to excellent yields of products (88-95%).

Key words: $NaBH_4$, $Ga(OH)_3$, Reductive amination, Carbonyl compounds, Amines

INTRODUCTION

Amines are important functionalities in active pharmaceutical intermediates and drugs.The reduction of nitro, cyano, azide, carboxamide compounds and alkylation of amines are common routes for the synthesis of amines. These methodologies for secondary amines are often problematic because of harsh reaction conditions, overalkylation, low chemical selectivity and generally poor yields. Therefore, there is a specific interest in developing controlled synthesis of secondary amines due to its vast applications. Other approach is reductive amination reaction in a single operation*i.e* direct reductive amination (DRA). Reductive aminationcan be carried out by amination of carbonyl compounds with sodiumborohydride 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 imidazoliumtetra fluoroborate [(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] and $NaBH_4/B(OH)_3$ or $Al(OH)_3$[14].In this context and in continuing our efforts for the development of new reducing systems[15-20],we have carried outre-examination of reductive aminationreaction.We now wish to report an efficient reductive aminationof aldehydes by $NaBH_4/Ga(OH)_3$ as new reducing system in CH_3CN at room temperature.

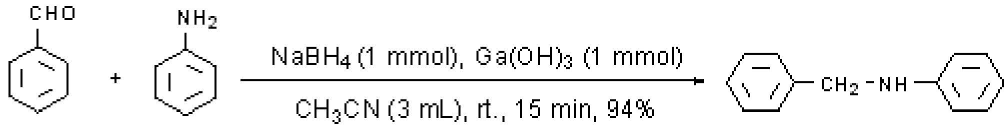
Table 1: Reductive Amination of Aldehydes (1 mmol) with Anlines (1 mmol) by $NaBH_4$ (1 mmol) in The presence of $Ga(OH)_3$) in CH_3CN (3 mL) at Room Temperature

Entry	Substrates		Products	Time	Yields[a]
	Aldehydes	Anilines		(min)	(%)
1	benzaldehyde	aniline	N-benzyl aniline	15	94
2	benzaldehyde	4-bromoaniline	N-benzyl-4-bromoaniline	15	90
3	benzaldehyde	4-methoxyaniline	N-benzyl-4-methoxyaniline	30	90
4	benzaldehyde	4-methylaniline	N-benzyl-4-methylaniline	30	88
5	4-bromobenzaldehyde	aniline	N-(4-bromobenzyl)aniline	15	94
6	4-bromobenzaldehyde	4-methoxyaniline	N-(4-bromobenzyl)-4-methoxyaniline	25	95
7	4-methylbenzaldehyde	4-bromoaniline	N-(4-methylbenzyl)-4-bromoaniline	35	95
8	4-methylbenzaldehyde	aniline	N-(4-methylbenzyl)aniline	30	90
9	4-methylbenzaldehyde	4-methylaniline	N-(4-methylbenzyl)- 4-methylaniline	35	91
10	4-methylbenzaldehyde	4-methoxyaniline	N-(4-methylbenzyl)-4-methoxyaniline	35	88
11	4-methoxybenzaldehyde	4-methylaniline	N-(4-methoxybenzyl)-4-methylaniline	40	89
12	4-methoxybenzaldehyde	aniline	N-(4-methoxybenzyl)aniline	40	92
13	4-nitrobenzaldehyde	aniline	N-(4-nitrobenzyl)aniline	15	93
14	2-methoxybenzaldehyde	4-bromoaniline	N-(2-methoxybenzyl)-4-bromoaniline	30	92
15	4-methoxybenzaldehyde	4-methylaniline	N-(4-methoxybenzyl)-4-methylaniline	40	94
16	4-bromobenzaldehyde	4-methylaniline	N-(4-bromobenzyl)-4-methylaniline	15	95

[a]Yields refer to isolated pure products.

RESULTS AND DISCUSSIONS

We performed the reductive amination reaction in the presence of $Ga(OH)_3$ asco-reactantsand using $NaBH_4$ as the reducing reagent in CH_3CN. It is notable, in the absence of co-reactants, imine formation does not occur and the aldehyde is reduced to benzyl alcohol. The model reaction has been selected by reductive amination of benzaldehyde with aniline. This reaction was carried out in different solvents, different molar ratio of the benzaldehyde/aniline/$Ga(OH)_3$/$NaBH_4$ for the selection of appropriate conditions at room temperature. Among the tested different solvents, the reaction was most facile and proceeded to give the highest yield in CH_3CN. The optimization reaction conditions showed that using 1 molar equivalents of $NaBH_4$ and 1 molar equivalents of $Ga(OH)_3$ in CH_3CN were the best conditions to complete the reductive amination of benzaldehye (1 mmol) and aniline (1 mmol) to N-benzylaniline. Our observation reveals that reductive amination completes within 15 min with 94% yields of product as shown in scheme 1.



Scheme 1

The efficiency of this protocol was further examined byusing various structurally different aldehydes and anilines. In this approach, the correspondingsecondary amines were obtained in excellent yields (88-95%) and within appropriate times (15-40 min) as shown in Table 1. The mechanism for the influence of$Ga(OH)_3$ is not clear, but we think that $Ga(OH)_3$able to helpfor Imine formation.Also, we observed sodium borohydride slowly is liberated hydrogen gas *in situ* in the presence of $Ga(OH)_3$. Consequently, the synergistically generated molecular hydrogen combines with more easily hydride attack to imine intermediate, thus accelerates the rate of reduction reaction.

EXPERIMENTAL

IR and ^1H NMR spectra were recorded on PerkinElmer FT-IR RXI and 400 MHz Bruker spectrometers, respectively. The products were characterized by their ^1H 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. Reductive amination of banzaldehyde and aniline with $NaBH_4$/$Ga(OH)_3$, A 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 $Ga(OH)_3$ (0.12, 1 mmol) in CH_3CN (3 mL) was prepared. The resulting mixture was stirred for 5 min at room temperature. Then the $NaBH_4$ (0.036 g, 1 mmol) was added to the reaction mixture and stirred at room temperature. TLC monitored the progress of the reaction (eluent; CCl_4/Ether: 5/2). The reaction was filtered after completion within 15 min. Evaporation of the solvent and short column chromatography of the resulting crude material over sil-ica gel (eluent; CCl_4/Ether: 5/2) afforded the N-benzylaniline (0.l72 g, 94% yield, Table 1, entry 1).

CONCLUSION

In this context, we have shown that the $NaBH_4$/$Ga(OH)_3$as new reducing system isconvenient 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$Ga(OH)_3$ (1 mmol)in CH_3CN at room temperature. Short reaction times, high efficiency of the reduction reactions and easy work-up procedure makes as an attractive new protocol for reductive amination of aldehydes.

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