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A New Synthesis of 1,3-Aminols from Direct Double Reduction of β-Enamino Ketones Formed *in situ* by Reaction of β-Dicarbonyl Compounds with Anilines

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A new one-pot synthesis of 1,3-aminols by direct reduction of β-enamino ketones, formed *in situ* by reaction of easily available β-dicarbonyl compounds, with anilines were described. In the case of aliphatic amines such as benzyl amine, n-butyl amine and β-hydroxy ethyl amine, the corresponding 1,3-minols were not obtained. In fact, the β-enamino ketone formed was failed to accomplish further reduction to 1,3-aminol. This approach is the most direct available method for the synthesis of 1,3-aminols.

Keywords: 1,3-Aminols, β-Enamino ketones, β-Dicarbonyls, Anilines, $NaBH_4$

INTRODUCTION

1,3-Aminols are an important class of compounds that have been studied extensively due to their role in the field of pharmacological chemistry and biologically active natural products [1]. These compounds are prepared by direct reduction of 1,3-difunctioalized unsaturated compounds containing nitrogen and oxygen including β-amino ketones [2], β-hydroxy oximes [3], β-keto amides [4], and β-enamino ketones [5]. Among the traditional reductive methods for producing 1,3-aminols, the reduction of β-enamino ketones is one of the most attractive routes.

Recently, we became interested in the synthesis of β-aminols [6] and β-enamino ketones [7]. In continuation of these works, we now describe a new alternative approach in which β-dicarbonyl compound is converted directly to 1,3-aminols. This approach is more direct than the other available methods.

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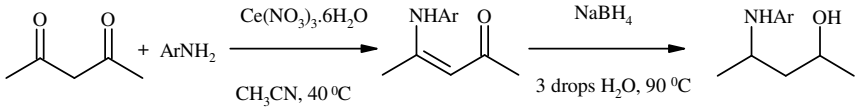
EXPERIMENTAL

All yields refer to isolated products. Most of the products are known compounds and were characterized by comparison of their spectral data (^{1}H NMR, ^{13}C NMR, IR) with those reported in the literature. Monitoring of the reactions was accomplished by TLC on sheets precoated with silica gel 60 F_{254}.

A Typical Procedure

In a round bottomed flask (25 ml), acetyl acetone (1 mmol), aniline (1 mmol) and $Ce(NO_3)_3.6H_2O$ (0.2 mmol) were added. The reaction mixture was stirred at 40 °C for 10 min. After completion of the reaction as monitored by TLC, $NaBH_4$ (4 mmol), 3 drops of water and acetonitrile (3 ml) were added to the mixture and the temperature was raised to 90 °C. The reaction mixture was stirred at 90 °C for 100 min. Again, the progress of the reaction was followed by TLC. After completion, the reaction was quenched by addition of water (5 ml). The product was extracted with diethyl ether (3 × 10 ml)

Table 1. Synthesis of 1,3-Aminols from Direct Reactions of Acetyl Acetone with Anilines



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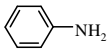
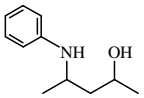
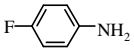
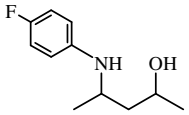
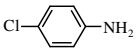
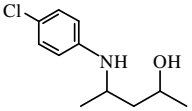
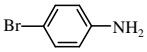
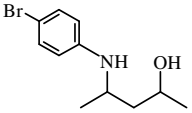
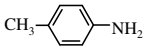
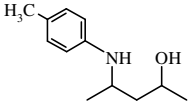
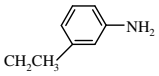
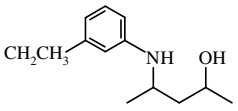
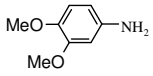
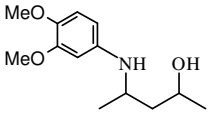
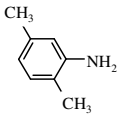
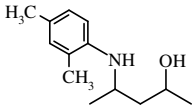
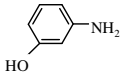
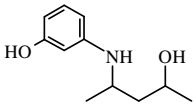
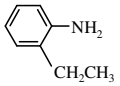
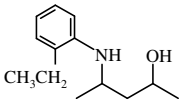
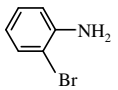
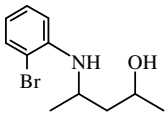
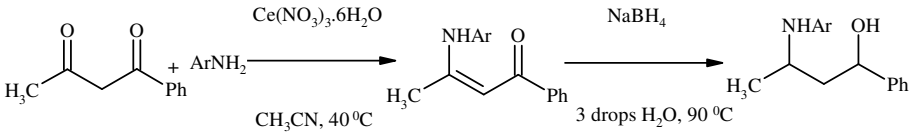
1		100	90	
2		85	90	
3		60	80	
4		65	90	
5		40	60	
6		95	90	
7		100	0	
8		40	95	
9		100	80	
10		45	90	
11		100	95	

[a] Isolated yields. [b] Products were characterized by comparison of their spectral data with those of authentic samples.

Table 2. Synthesis of 1,3-Aminols from Reactions of Benzoyl Acetone with Anilines



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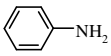
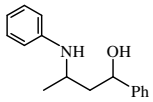
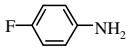
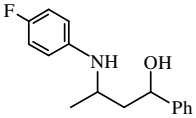
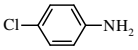
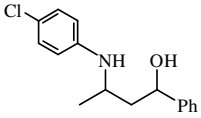
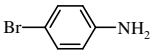
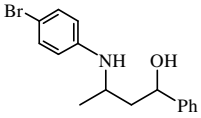
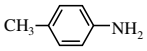
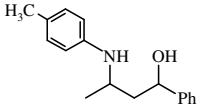
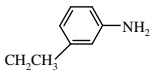
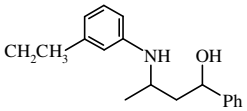
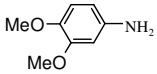
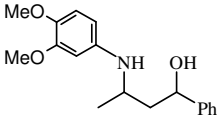
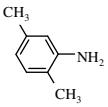
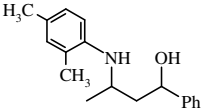
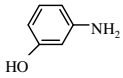
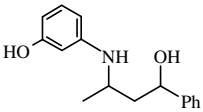
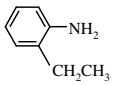
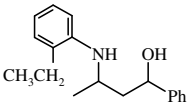
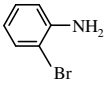
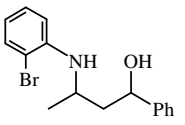
1		9	85	
2		8	87	
3		7.5	82	
4		9	82	
5		5	70	
6		8	78	
7		9	0	
8		6	80	
9		8	10	
10		6	80	
11		9	90	

[a] Isolated yields. [b] Products were characterized by comparison of their spectral data with those of authentic samples.

and then the organic layer was separated and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 4-anilino-butan-2-ol, in 90% yield after column chromatography on silica gel, using n-heptane/ethyl acetate (4/1) as the eluent. ^{1}H NMR (200 MHz, $CDCl_3$), δ, 1.59 (d, 6H, J = 6.4 Hz), 2.09 (t, 2H, J = 7 Hz), 3.9 (br s, 2H, NH, OH), 4.125 (m, lH), 4.35 (m, 1H), 7.03 - 7.75 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$), δ, 21.48, 22.72, 45.71, 50.32, 65.43, 114.21, 126.14, 129.56, 147.22; IR (neat): 3370, 2990, 1620 ,735, 690 cm^{-1}.

RESULTS AND DISCUSSION

We first synthesized the 1,3-aminol from acetyl acetone and aniline by reduction of the corresponding β-enamino ketone generated *in situ* using $NaBH_4$ and a few drops of water in acetonitrile. The reaction has been applied to a series of aniline derivatives and the desired products were obtained in good to excellent yields (Table 1).

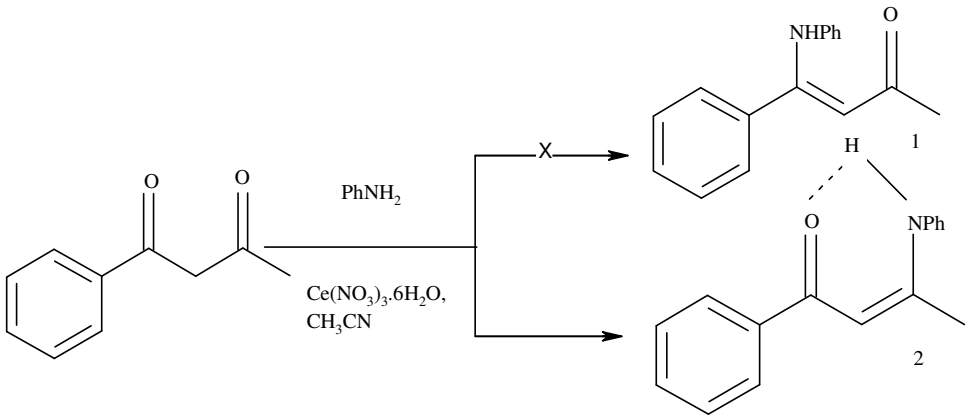
It is interesting to note that the reduction of β-enamino ketones with $NaBH_4$ was unsuccessful, but the reactions proceeded well when a few drops of water was added to the reaction mixture. The reactions work fine when the N-substituent is a phenyl group or its derivatives. However, when the substituent is, for example, a benzyl group the corresponding β-enamino ketone was obtained as a sole product and the formation of the corresponding 1,3-aminol was not observed. In fact, the β-enamino ketone failed to accomplish further reduction to 1,3-aminol. In the case of 3,4-$(CH_3O)_2C_6H_3NH_2$, the corresponding 1,3-aminol was not obtained and the only product was β-enamino ketone (Table 1, entry 7).

In order to show the general applicability and limitation of this method, the reaction of benzoyl acetone with various anilines were examined and their respective 1,3-aminols were obtained (Table 2). These reactions show lower yields and longer reaction times when compared with acetyl acetone reactions as mentioned above. Once again, the corresponding 1,3-aminols were not obtained when benzyl amine, n-butyl amine and β-hydroxy ethyl amine were used in the reactions. However, in these reactions, the corresponding β-enamino ketones were obtained as the sole products. Intermediate 1 cannot be prepared by direct condensation of benzoyl acetone with the appropriate amines because of the poor reactivity of the benzoyl group towards nucleophilic reaction with amines in comparison with the acetyl group. In this case, the only intermediate obtained is enamino ketone 2 which can be reduced to the corresponding 1,3-aminols (Scheme 1).

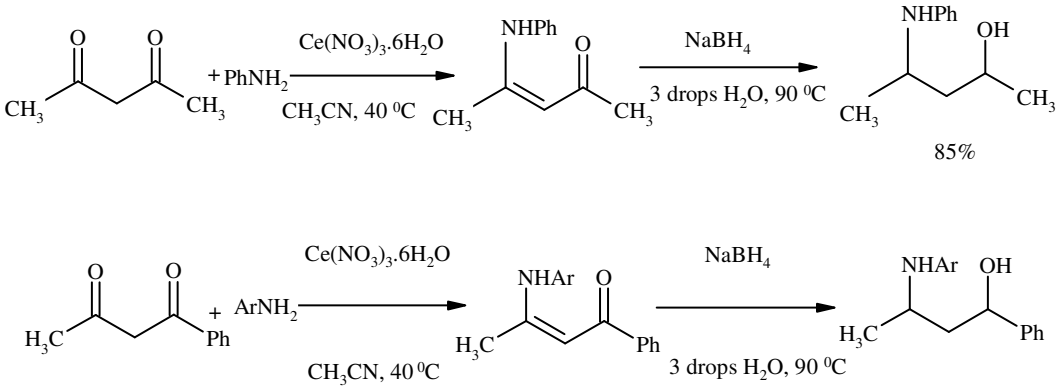
It was observed that, when acetyl acetone was used in the presence of benzoyl acetone in a binary mixture with a molar ratio of 1:1 under the same stoichiometry of the reagents to the substrate, the corresponding 1,3-aminol of acetyl acetone was obtained in 85% yield, while the corresponding β-enamino ketone of benzoyl acetone remained intact (Scheme 2).

CONCLUSIONS

A simple and efficient method for the preparation of 1,3-aminols has been introduced from readily available starting



Scheme 1



Scheme 2

materials including β-dicarbonyl compounds and a common reducing agent such as $NaBH_4$. In addition, this method is more direct than other available methods.

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