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RESEARCH ARTICLE

First Efficient, Facile Synthesis of β-aminoketones through the Nucleophilic Addition of Acetophenones to Imines Using Baker's Yeast as a Catalyst

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ABSTRACT

The present study describes the development of an efficient and facile synthesis of β-aminoketones **(3a-k)** through the nucleophilic addition of acetophenones to imines in the presence of Baker's yeast (BY) as a bio-catalyst. The present method is very facile and works under a mild and eco-friendly environment using ethyl alcohol (C_2H_5OH) as a green solvent and BY as a biocatalyst. The reaction follows the simple workup which gives the products in good to excellent yields. Thus, it is presumed that this newly developed protocol will open a new gateway for the chemist in the area of organic synthesis, particularly for the preparation of β-aminoketones through the nucleophilic addition of acetophenones to imines in facile and green environmental conditions.

Keywords: Baker's yeast, Bio-catalyst, Green chemistry, Imines, Nucleophilic addition, β-aminoketones

1. INTRODUCTION

Multicomponent reactions (MCRs) are considered to be an important methodological boost for synthetic and medicinal chemists to apply for various synthetic transformations, where classical methods usually involve multi-steps and required tedious work p. The MCR methodology is an important tool for the generation of a library of new chemical entities, especially in the drug discovery process [1]. Multicomponent Mannich reaction has received more attention, as they solve both the diversity and convolution problems in organic synthesis [2-4].

Multi-component Mannich reaction is one of the most significant carbon-carbon bond formation reactions in organic synthesis to product β-aminocarbonyl compounds [5-10]. Several commercially available drugs as shown in Figure 1 are containing the β-amino carbonyl compounds [11-17].

At present, β-aminoketones are prepared with advance methods which give products with (i) higher yields, (ii) improved reaction rates, and (iii) cost-effective [18]. Several strategies have been adopted for the synthesis of compounds that fulfill these conditions. There are mainly three main routes adopted, as represented in Figure 2.

(1) Mannich reaction [19-21], (2) from the accessible enolates and imines with the formation of a C–C bond [22,23], and (3) in another route, β-aminoketones were prepared through an Aza-Michael reaction involving the addition of amines to α, β-Unsaturated ketones [24-26].

Michael reactions generally take place in basic medium [27,28]. Sometimes, these reactions were also catalyzed in presence of Lewis acids such as bismuth nitrate ($Bi(NO_3)_3$ [29], hydrated cerium (III) chloride ($CeCl_3 \cdot 7H_2O$) [30], $SmI_2(THF)_2$ [31], and micellar solutions or by fixing stoichiometric ratio as reported in the literature [32]. Literature survey also reveals that β-aminoketones were prepared directly through reductive hydroamination of carbonyl alkynes through the chemo and region-selective synthesis of enamines with the hydroamination of terminal alkynes under catalytic conditions and also by the reduction of enaminones [33-40] under mild, eco-friendly catalyzed conditions [41-43]. β-aminoketones were also synthesized through the nucleophilic addition of acetophenones to imines as appeared in the literature [44-51] [Figure 3]. Unfortunately, the mostly reported methods were facing one or other short coming such as use of ionic liquid with co-catalyst, time taking, use of toxic solvents, and the use of metal supported catalysts and tedious recovery of catalyst process in work up. Thus, in view of the above said limitations, there is an immense need for the development of facile and effective eco-friendly method for the synthesis of Mannich bases. In this endeavors, we anticipated that the reactions mediated by Baker's Yeast (BY) as biocatalyst will be perfect solution for the same.

BY is a eukaryotic single whole-cell micro-organism and belongs to the Fungi (*Saccharomyces cerevisiae*) family. BY requires either slightly acidic or neutral pH for the growth [52]. BY was first used in ancient Egypt for the fermentation of sugar in bread dough, and thereafter, it has been widely used as a household and commercial substrate for food processing. Moreover, BY has become a useful catalyst to the organic chemists for bio-transformations of organic reactions due to the ease of culturing and availability. The enzymes present in BY also have the ability to reduce carbonyl compounds into corresponding optically active alcohol with high re-selectivity and in good yields [53]. BY has also been used in various transformations, which include reduction of nitro group, C-C bond formation, lactonization and de-chlorination, and hydrolysis of esters [54-60]. The application of BY in various MCRs is comprehensively reviewed by Soumava [61]. The MCRs such as Biginelli reaction [62], Hantzsch reaction [63,64], Knoevenagel-Michael reaction

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[65,66], Kabachnik-Field reaction [67], and other MCRs reactions were also reported in the presence of BY [68]. In recent years, the use of biocatalysts for the synthesis of active pharmaceutical ingredients (APIs) and drug development through sustainable processes facilitates encouragement and creating interest among the scientific community in industry and academia. To our surprise, there is no report that appeared in the literature for the synthesis of β-aminoketones using BY through the nucleophilic addition of

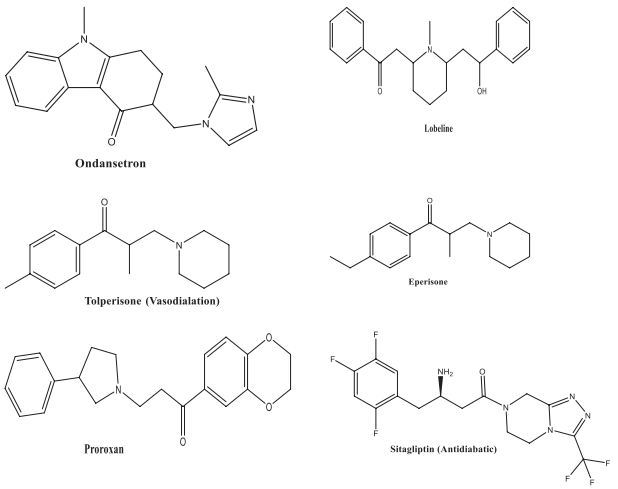


Figure 1: Representative β-aminocarbonyl derivatives as marketed drugs.

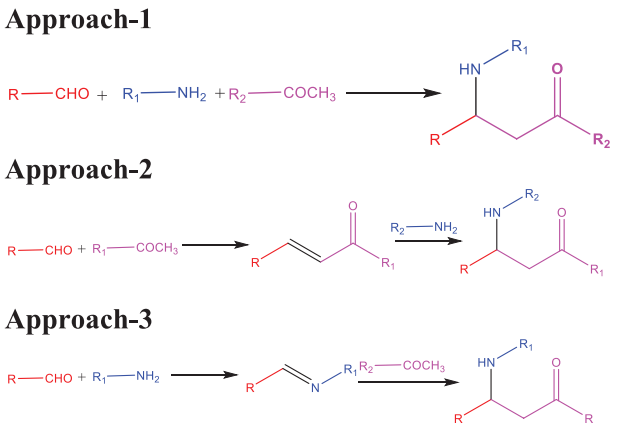


Figure 2: Different approaches for the synthesis of β-aminocarbonyl compounds (Mannich bases).

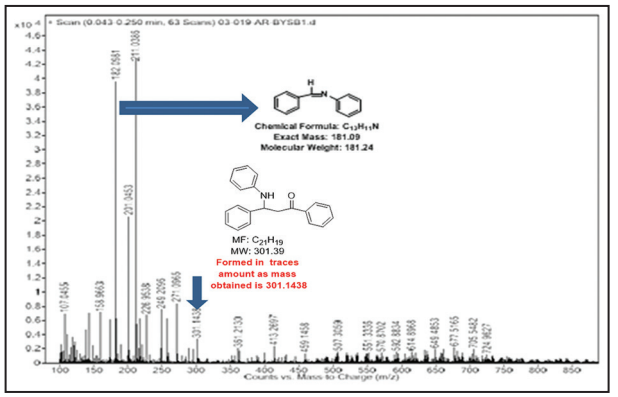


Figure 3: Mass spectra of Mannich reaction: m/z: 182.24 (M^{+1}); 211.03 (M^{+} MeOH adduct) and 301.14 (traces of β-aminoketone).

acetophenones to imines whereas other catalyzed methods have been reported as given in Figure 3.

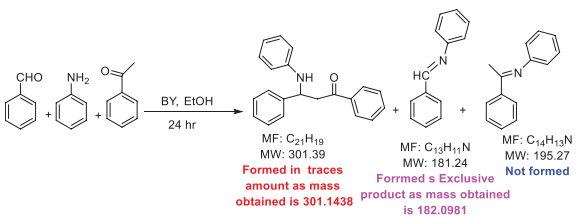
In continuation of our thrust to develop novel environmentally eco-friendly synthetic protocols for the various organic functional group transformations, we identified that *S. cerevisiae* (BY) catalyzed efficiently and chemo-selectively the synthesis of aldimines [69] and other reactions [70-72]. In-fact, this was the result we obtained when we tried to synthesize the β-aminoketones through one-pot three component Mannich reaction using BY as biocatalyst but could not be able to get the desired product, where as we got the imines of aldehydes as major products [Scheme 1] and the desired product is formed in minor or traces amount. Furthermore, no acetophenone imine formation was observed. This result gives us rethink to get the desired products of β-aminoketones by using BY. We decided to check the reaction of imines with acetophenones through the nucleophilic addition of acetophenones to imines pathway and to our encouragement, we got the product in good yields. Thus, herewith we wish to report the result of our studies for the formation of β-aminoketones through the nucleophilic addition of acetophenones to imines [Scheme 1].

2. EXPERIMENTAL

All the solvents were distilled and dried before use. The chemicals were purchased from commercial vendors and were used without any further purification. The reactions were monitored using TLC on silica gel 60 plates, with a typical ratio of petroleum ether ethyl acetate (8:2) as mobile phase. The ^{1}H-NMR spectra were recorded on a Varian-400MR spectrometer at 400MHz using $CDCl_3$ and TMS as solvent and internal standard, respectively. DIP Mass Spectrum was recorded on an Agilent - G6160 A infinity lab LC/MSD/IQ mass spectrometer.

2.1. General procedure for the Synthesis of β-amino carbonyl compounds (Mannich Bases) (3a-k) through the nucleophilic addition of acetophenones to imines catalyzed by BY: Representative example of 3-(4-hydroxyphenyl)-3-((4-nitrophenyl)amino)-1-phenylpropan-1-one (3a)

Schiff base obtained from 4-Nitroaniline and 4-Hydroxybenzaldehyde (1a) (1 mmol), acetophenone (2a) (1 mmol) is taken in 10 mL of Ethanol. To this 500 mg BY were added. The reaction mixtures were kept stirring on an orbital shaker for 3 days. After the completion of the reaction as indicated by TLC (ethyl acetate: hexane 20% as eluent), the reaction mixtures were filtered through Celite to remove the BY. The residue was washed with ethanol and filtered. To the obtained filtrate water (20 mL) was added and it is extracted with ethyl acetate (2 × 30 mL). The combined organic layers were collected and sodium sulfate is added to remove the moisture. The organic layers were evaporated to get the pure crude product. The obtained product was recrystallized with ethanol to get the pure β-amino carbonyl compounds **(3a)** in good to 90% yield. All the other compounds are known and synthesized by following the above general procedure and are characterized by their melting point, mass, and 1H-NMR spectral analysis.



Scheme 1: Mannich reaction catalyzed by Baker's yeast.

2.2. Spectral data for the synthesized compounds

2.2.1. 1.3-(4-hydroxyphenyl)-3-((4-nitrophenyl)amino)-1-phenylpropan-1-one (3a)

Yield % 90: m. p.: 121–123°C: ^{1}HNMR: (400 MHz,) δ 9.87 (s, 1H), 8.19–8.15 (m, 2H), 7.83–7.79 (m, 2H), 7.26 (s, 6H), 6.96–6.89 (m, 4H), 2.37 (s, 1H), 1.25 (s, 2H). Mass: 362.3.

2.2.2. 2.1,5-dimethyl-4-((3-oxo-3-phenyl-1-(3,4,5-trimethylphenyl)propyl)amino)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (3b)

Yield % 93: m. p.: 154–156°C: ^{1}HNMR: (400 MHz) δ 9.69 (s, 1H), 7.45 (dt, J = 8.6, 7.7 Hz, 5H), 7.26 (s, 4H), 7.12 (s, 2H), 3.92 (s, 6H), 3.89 (s, 3H), 3.16 (s, 2H), 2.50 (s, 2H), 1.57 (s, 6H). Mass: 454.3.

2.2.3. 3.3-(2,4-dichlorophenyl)-3-((4-nitrophenyl)amino)-1-phenylpropan-1-one (3c)

Yield % 88: m. p.: 150–152°C: ^{1}HNMR (400 MHz) δ 8.11–8.13 (d, 2H), 7.34–7.38 (t, 2H), 6.80–6.82 (d, 2H), 6.69–6.73 (t, 2H), 6.08 (m, 4H), 3.66 (d, 1H), 3.31 (d, 2H), 2.01 (s, 1H), Mass: 415.1.

2.2.4. 4.3-(4-chlorophenyl)-3-((4-nitrophenyl)amino)-1-phenylpropan-1-one (3d)

Yield % 90: m. p.: 113–115°C: ^{1}HNMR: (400 MHz) δ 8.12 (dd, J = 8.6, 1.4 Hz, 2H), 7.39–7.31 (m, 2H), 6.81 (dd, J = 8.4, 1.1 Hz, 2H), 6.71 (ddd, J = 8.4, 7.0, 1.2 Hz, 2H), 6.05 (s, 6H), 3.67 (s, 1H), 1.25 (s, 2H). Mass: 380.2.

2.2.5. 5.3-(4-methoxyphenyl)-3-((4-nitrophenyl)amino)-1-phenylpropan-1-one (3e)

Yield % 90: m. p.:121–123°C: 1HNMR: (400 MHz,) δ 8.11 (d, J = 8.2 Hz, 20H), 7.01 (d, J = 8.8 Hz, 12H), 6.87 (d, J = 8.9 Hz, 35H), 6.16 (s, 5H), 3.92 (s, 5H), 3.80 (s, 16H), 3.75 (s, 5H), 3.51 (s, 5H). Mass: 376.8.

2.2.6. 6.3-(4-(dimethylamino)phenyl)-1-phenyl-3-(phenylamino)propan-1-one (3f)

Yield % 93: m. p.: 202–204°C: ^{1}HNMR: (400 MHz) δ 7.77–7.73 (m, 2H), 7.43–7.36 (m, 4H), 6.72 (dd, J = 12.7, 9.0 Hz, 4H), 6.18 (d, J = 7.6 Hz, 1H), 3.31 (s, 1H), 3.05 (d, J = 8.5 Hz, 6H), 2.85 (s, 2H). Mass: 344.3.

2.2.7. 7.4-((1-(4-(diphenylamino)phenyl)-3-oxo-3-phenylpropyl)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (3g)

Yield % 90: m. p.: 167–169°C: ^{1}HNMR: (400 MHz) δ 9.67 (s, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.43 (ddd, J = 8.7, 5.6, 2.3 Hz, 6H), 7.26 (s, 13H), 7.13 (d, J = 7.5 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 3.16–3.09 (m, 3H), 2.85 (s, 3H), 2.46 (s,1H), 2.15 (s, 2H). Mass: 578.5.

2.2.8. 8.3-(4-hydroxy-3-methoxyphenyl)-3-((4-methoxyphenyl) amino)-1-phenylpropan-1-one (3h)

Yield % 92: m. p.: 135–137°C: ^{1}H NMR (400 MHz) δ 8.36 (s, 2H), 7.61 (d, J = 1.7 Hz, 2H), 7.26 (s, 1H), 7.24 (d, J = 1.8 Hz, 1H), 7.22 (d, J = 1.7 Hz, 1H), 7.21 (s, 1H), 7.19 (s, 1H), 6.97 (d, J = 8.1 Hz, 2H), 6.93 (s, 1H), 6.92–6.90 (m, 2H), 3.98 (s, 4H), 3.83 (s, 5H). Mass: 377.2.

2.2.9. 9.3-(4-hydroxyphenyl)-3-((2-nitrophenyl)amino)-1-phenylpropan-1-one (3i)

Yield % 88: m. p.: 283–285°C: ^{1}HNMR: (400 MHz) δ 9.87 (s, 1H), 8.12 (dd, J = 8.6, 1.4 Hz, 1H), 7.82–7.80 (m, 3H), 7.36 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.26 (s, 4H), 6.97–6.93 (m, 4H), 6.81 (dd, J = 8.4, 1.1 Hz, 1H), 6.71 (ddd, J = 8.4, 7.0, 1.2 Hz, 1H), 5.89 (s, 1H), 3.50 (s, 2H). Mass: 363.3.

2.2.10. 10.1-phenyl-3-(phenylamino)-3-(3,4,5-trimethoxyphenyl)propan-1-one (3j)

Yield % 92: m. p.: 148–150°C: ^{1}HNMR: (400 MHz) δ 8.36 (s, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.32–6.97 (m, 8H), 6.85 (s, 1H), 3.95 (d, J = 2.6 Hz, 6H), 3.94 (s, 2H), 3.91 (d, J = 6.4 Hz, 4H), 3.49 (s, 1H). Mass: 392.5.

2.2.11. 11.3-(4-chlorophenyl)-1-phenyl-3-(phenylamino) propan-1-one (3k)

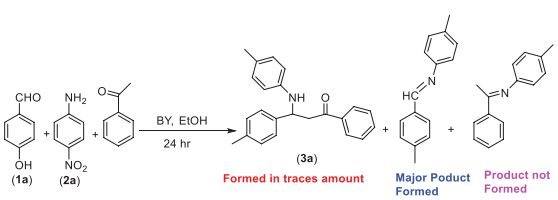
Yield % 90: m. p.: 113–115°C: ^{1}HNMR (400 MHz,) δ 7.74 (d, J = 8.8 Hz, 3H), 7.48–7.40 (m, 4H), 7.32 (dd, J = 5.0, 3.6 Hz, 1H), 6.71 (dd, J = 8.9, 3.9 Hz, 3H), 3.10 (d, J = 3.3 Hz, 4H), 3.02 (s, 1H), 2.46 (s, 2H). Mass: 335.2.

3. RESULTS AND DISCUSSION

In continuation of our ongoing work for the synthesis of Mannich bases, i.e., β-aminocarbonyl compounds. We started our experiments with the reactions of 4-Hydroxybenzaldehyde **(1a)**, 4-Nitroaniline **(2a)**, and acetophenone, in the presence of BY in ethanol in one pot. We got the desired product of Mannich base **(3a)** in trace amounts which is in agreement with our earlier report, where we confirmed that the Schiff bases of the aldehydes are the major product [Scheme 2].

To optimize the reaction conditions, the reaction of 4-Hydroxybenzaldehyde **(1a)**, 4-Nitroaniline **(2a)**, and acetophenone was performed using different solvents at different time of intervals by employing BY as biocatalyst at room temperature. The results are summarized in Table 1. While screening the effect of solvents, it has been observed that THF, DCM, Benzene, toluene, and ethyl acetate did dot result any product as the reaction did not proceed in these solvents using BY/RT/12 h [Entries 1-5 of Table 1]. When the ethanol is used as a solvent in BY/RT/12 h only Schiff base is formed [Entry 6 of Table 1]. Even when the reaction is carried out in ethanol using BY at room temperature for 24 h, only the Schiff base is formed [Entry 7 of Table 1]. Interestingly, when this reaction is continued for further 12 h, i.e., totally for 36 h the traces amount of the desired product is formed [Entry 8 of Table 1]. Then, we decided to carry out the reaction by making the Schiff base first and then the addition of acetophenone to get the desired products. To our surprises and as per our expectation, the reactions worked and at BY/RT/12 h, we observed, the 35% yield [Entry 9 of Table 1] and for BY/RT/24 h 60% yield [Entry 10 of Table 1]. Finally, we got the 90% yield, when we carried out the reaction using BY at RT for 36 h [Entry 11 of Table 1].

Thus, with the optimized condition in our hand, we started to synthesize the desired Mannich bases **(3a-k)** to check the effect of the substituent [Scheme 3]. The synthesized compounds by this method are characterized by their physical data and by ^{1}H-NMR and mass spectral analysis, which are given in the experimental section. The synthesized compounds are known compounds and the results are in the agreement with the reported methods.

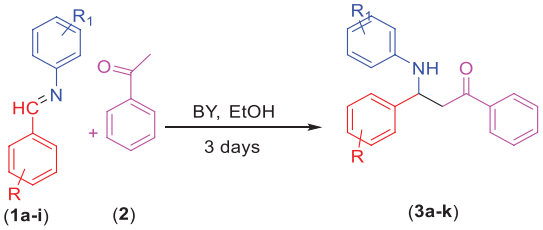


Scheme 2: Mannich reaction catalyzed by Baker's yeast.

Table 1: Optimization of synthesis of β-aminocarbonyl compounds (Mannich Bases) through the nucleophilic addition of acetophenones to imines catalyzed by baker's yeast (BY).

S. No.	Reactants	Solvent	Reaction condition	Yield % of 3a
1	4-Hydorxybenzaldehyde (**1a**), 4-Nitroaniline (**2a**) and acetophenone	THF	BY/RT/12 hr	NR
2	4-Hydorxybenzaldehyde (**1a**), 4-Nitroaniline (**2a**) and acetophenone	DCM	BY/RT/12 hr	NR
3	4-Hydorxybenzaldehyde (**1a**), 4-Nitroaniline (**2a**) and acetophenone	Benzene	BY/RT/12 hr	NR
4	4-Hydorxybenzaldehyde (**1a**), 4-Nitroaniline (**2a**) and acetophenone	Toluene	BY/RT/12 hr	NR
5	4-Hydorxybenzaldehyde (**1a**), 4-Nitroaniline (**2a**) and acetophenone	EtOAc	BY/RT/12 hr	NR
6	4-Hydorxybenzaldehyde (**1a**), 4-Nitroaniline (**2a**) and acetophenone	Ethanol	BY/RT/12 hr	Only Schiff base formation is observed
7	4-Hydorxybenzaldehyde (**1a**), 4-Nitroaniline (**2a**) and acetophenone	Ethanol	BY/RT/24 hr	Schiff base formed
8	4-Hydorxybenzaldehyde (**1a**), 4-Nitroaniline (**2a**) and acetophenone	Ethanol	BY/RT/36 hr	Schiff base formed majorly and trace amount of Mannich base is observed
9	Schiff base and acetophenone*	Ethanol	BY/RT/12 hr	35% of Mannich base is formed
10	Schiff base and acetophenone*	Ethanol	BY/RT/24 hr	60% of Mannich base is formed
11	Schiff base and acetophenone*	Ethanol	BY/RT/36 hr	90% of Mannich base is formed

Note: *NR=No reaction, *The reaction is done by reacting 4-Hydroxybenzaldehyde (1a), 4-Nitroaniline (2a) for 12 h to first form the Schiff bases, then acetophenone is added to get the desired Mannich base (**3a**)



Scheme 3: Synthesis of β-aminocarbonyl compounds (Mannich Bases) (3a-k) through the nucleophilic addition of acetophenones to imines catalyzed by Baker's yeast.

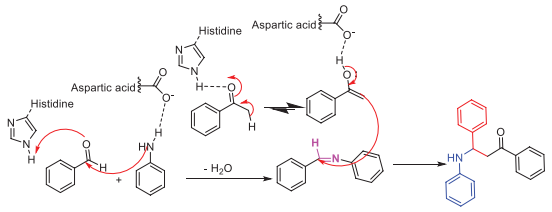


Figure 4: Tentative mechanism of β-aminocarbonyl compounds (Mannich Bases) (3a-k) through the nucleophilic addition of acetophenones to imines catalyzed by Baker's yeast.

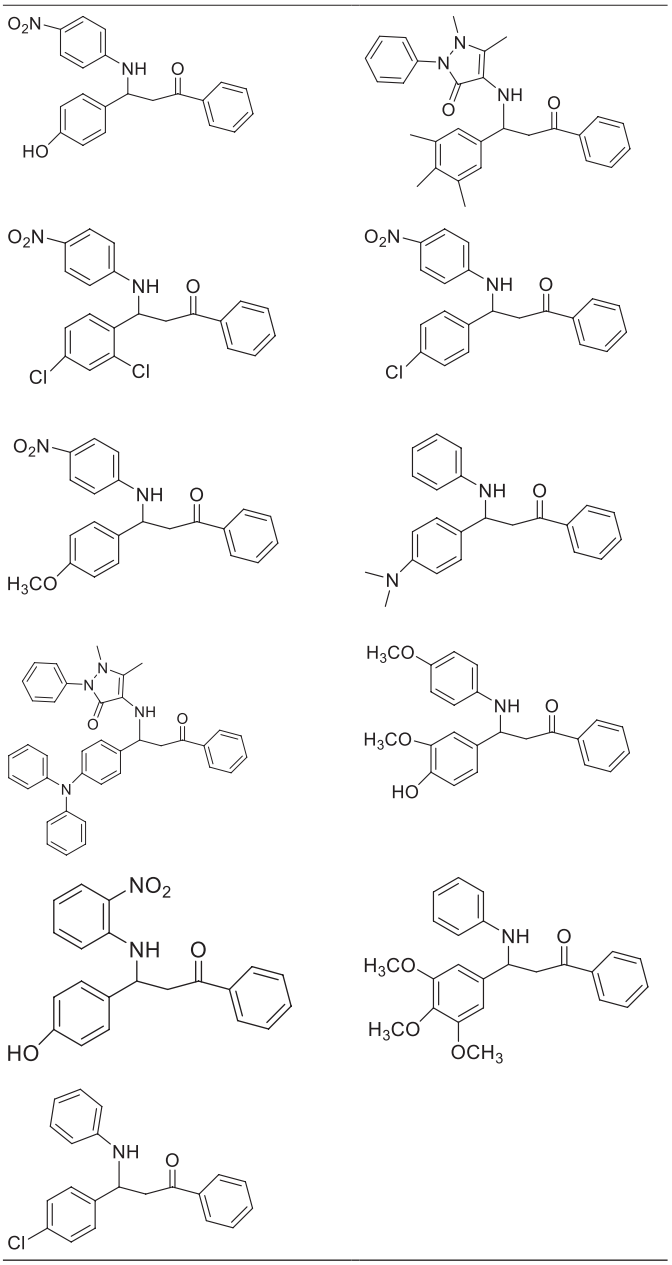
The signals observed in the ^{1}H-NMR spectra of the Mannich bases are given in experimental section. In the ^{1}H-NMR spectra of all the Mannich bases synthesized, prominent signals which are originating from C2 methylene group is appearing in the 3–4 ppm region as a doublet of doublet or multipletes were detected. Proton bonded for C3 carbon atom appears in the range of 4–5ppm as triplet or multipletes. Proton bonded for C3 carbon atom appears in the range of 4–5 ppm as triplet or multiplets. The aromatic protons attached to the aromatic carbons from rings A, B, and C appear as multiplets and doublets in the range of 6–9 ppm of the aromatic region. All the masses are confirmed.

To put insight into the reaction mechanism of the present method, it is anticipated that the amino acid residues such as histidine, serine, and aspartate anion present with the enzymes of BY responsible to activate the reactants, resulting into acceleration of the rates of present reaction. The plausible mechanism of the Mannich base formation is depicted in Figure 4. BY first binds with the histidine proton and makes the chelation with the oxygen atom of the carbonyl group and polarizing the carbonyl bond to facilitate the nucleophilic aniline which binds with the aspartic anion to increase its nucleophilicity to attack on the carbonyl group and later on upon dehydration gives the corresponding Schiff base. After the formation of the Schiff base, the acetophenone again binds with the histidine proton and making the chelation with the oxygen atom of the acetophenone carbonyl group and converting it into its enol form. Then, this enol form binds with the carboxylate ion of aspartic acid to convert acetophenone into a nucleophilic enol which then attacks on the imine bond through nucleophilic attack and forming the new C-C bond and then finally by potation of nitrogen produce the final Mannich base. The proposed mechanism is in agreement with the reported mechanism the nucleophilic addition of acetophenones to imines [73].

4. CONCLUSION

Thus, we can conclude that the developed method is an efficient and facile method for the synthesis of β-aminoketones (3a-k) through the nucleophilic addition of acetophenones to imine bases using BY as bio-catalyst. The reactions were very facile and work under a mild and eco-friendly environment using ethyl alcohol (C_2H_5OH) as green solvent and BY as a bio-catalyst. Furthermore, the present method is very efficient as simple workup gives the products in good to excellent yields. Thus, it is anticipated that the present newly developed method will open a new route for the chemist to prepare the β-aminoketones

Table 2: Structures of the synthesized compounds (**3a-k**).



through the nucleophilic addition of acetophenones to imine bases in a facile and eco-friendly environment.

5. ACKNOWLEDGMENTS

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