Iranian Journal of Catalysis 7(4), 2017, 337-340

IRANIAN JOURNAL OF CATALYSIS

# Baker's yeast catalyzed Henry reaction: Biocatalytic C-C bond formation

**Prabhakar Shrivas, Nitesh Punyapreddiwar, Atul Wankhade, Sangesh Zodape, Umesh Pratap***

*Department of Chemistry, Visvesvaraya National Institute of Technology, Nagpur, 440 010, India.*

Received 19 May 2017; received in revised form 16 August 2017; accepted 25 August 2017

ABSTRACT

The C-C bond formation is an important reaction in organic synthesis to obtain value-added intermediates. Therefore, in this paper an attempt has been made to accelerate the Henry reaction (C-C bond formation) between aryl aldehydes and nitromethane using less expensive whole cell biocatalyst, baker's yeast (BY). The scope of the methodology was also tested for the heteryl aldehyde i.e. 2-chloro-3-formyl quinoline to obtain the corresponding quinoline containing nitroalcohol. The developed protocol is highly efficient and completely environmentally friendly. The work addressed the issue of non-aqueous biocatalysis, since Henry reaction catalysed by baker's yeast has been carried out in ethanol.

***Keywords***: *Baker's yeast, Biocatalysis, Henry reaction, β-Nitroalcohol.*

## 1. Introduction

Formation of C-C bond is an essence of organic synthesis [1]. Henry reaction is one of the widely used reactions of immense importance for the formation of C-C bond and synthesizing β-nitroalcohols [2,3]. This reaction is gaining much importance due to wide utility of β-nitroalcohols in organic synthesis. This is a valuable synthon for the preparation of useful intermediates to obtain 2-nitroketones, nitroalkenes, β-aminoalcohols, required to synthesize some natural products and antibiotics [4]. Moreover, the nitro group opens the way for further modifications by reduction, Nef reaction and displacement by the carbon, sulfur and azide nucleophile [5]. β-Hydroxy nitroalkanes are invaluable precursors for synthetic targets including (R)- denopamine and (R)- arbutamine [6].

In view of useful applications of Henry reaction, several methods have been developed to access β-nitroalcohols, including use of various metallic catalysts [7], ionic bases [8], heterogeneous solid acids [9], surfactants [10], phosphines [11], guanidine [12], $SmI_2$ [13], ionic liquid [14], cyclane [15], organic base [16], phosphonium salt [17], dendrimer and cyclodextrine [18,19].

[*]Corresponding author email: umeshpratap2014@gmail.com
Tel.: +91 71 2280 1773

There are a few reports on the use of enzymes such as hydroxynitrile lyase derived from Hevea brazilensis [20], transglutaminase [21] and diaminoacylase [22] for accelerating Henry reaction.

Baker's yeast is readily available and inexpensive and its use does not require any special training in microbiology [23]. Consequently, baker's yeast is very popular among organic chemists [24]. The synthesis of alcohols by the reduction of a variety of ketones using whole cells of baker's yeast is a well-established technology in organic synthesis. Besides redox reactions, baker's yeast can catalyze cyclocondensation leading to value added heterocycle [25].

The use of biocatalyst in organic media is a subject of considerable interest because many of the organic substrates are insoluble in aqueous medium, which is often used for enzymatic reactions [26]. However, when enzymes are placed in an organic solvent, their activity was markedly reduced. Therefore, the solvent engineering in biocatalysis is necessary to overcome this limitation. The use of baker's yeast as a catalyst for Henry reaction has not yet been explored.

In continuation of our earlier efforts [27], to explore the hidden potential of baker's yeast in organic synthesis, a green protocol has been developed for synthesis of β-nitro alcohols using baker's yeast in organic solvent, ethanol.

## 2. **Experimental**

### *2.1. General*

All solvents and reagents used were obtained from commercial suppliers (Sigma and s.d. fine chemicals). $^{1}H$ and $^{13}C$ NMR spectra were recorded on Bruker Avance-II FT at 300 and 75 MHz respectively using TMS as internal standard and DMSO-$d_6$ as a medium. Mass spectral data were determined by the JEOL AccuTOF DART mass spectrometer. The dry baker's yeast was purchased from AB Maurya, India Pvt. Ltd.

### *2.2. Procedure for the Henry reaction*

A mixture of aldehyde (9 mmol), nitromethane (9 mmol), and baker's yeast (2 g) was stirred at room temperature for 30 h in ethanol (15 mL). The progress of the reaction was monitored by thin layer chromatography using petroleum ether: ethyl acetate (3:1). After 30 h, the reaction mixture was filtered using a silica bed to remove the catalyst and was washed with ethanol (50 mL). Water (50 mL) was added to the filtrate and the product was extracted using ethyl acetate (2x40 mL). Organic layer was dried over sodium sulphate and solvent was distilled under reduced pressure. The crude product obtained was purified by column chromatography using petroleum ether and ethyl acetate.

*Spectal data of 1-(2-chloro-6-methylquinolin-3-yl)-2-nitroethanol (**5a**):*

m.p.= 154-156 ºC. $^{1}H$ NMR: δ = (300 MHz, DMSO-$d_6$): δ= 2.55 (s, 3H), 3.44 (s, 1H, OH), 4.46 (dd, 1H, $J_1$ = 12.4 Hz, $J_2$ = 12.4 Hz), 4.84 (dd, 1H, $J_1$ = 2.4Hz, $J_2$= 2.4 Hz), 5.89 (d, 1H, $J$ = 12.0 Hz), 7.26 (s, 1H), 7.59 (d, 1H, $J$ = 13.2 Hz), 7.90 (d, 1H, $J$ = 11.2 Hz.), 8.40 (s, 1H) ppm. $^{13}C$ NMR (75 MHz, DMSO- $d_6$): δ = 21.3, 67.7, 80.0, 126.4, 127.0, 127.4, 131.2, 132.8, 136.5, 137.3, 145.5 ppm. DART-MS (ESI$^{+}$ mode): m/z= 267 (M$^{+}$).

## 3. Results and Discussion

This work reports an efficient and economic synthesis of β-nitroalcohols under mild conditions using baker's yeast in ethanol. The reported β-nitroalcohols were synthesized in good yield catalyzed by dry baker's yeast in ethanol.

In order to get best experimental conditions, the reaction of benzaldehyde with nitromethane in presence of baker's yeast was considered as a standard model reaction at room temperature to obtain products **3a**.

The model reaction was carried out using different solvents. The screening of the solvent was started with natural solvent i.e. water but the desired product (**3a**) was obtained in very low yield, even after 30 h (Table 1, entry 1). It would happen due to insolubility of benzaldehyde in water. Therefore, we turned our attention towards the use of organic solvents. The first choice was ethanol as it is a green solvent which can dissolve both the reactants. Surprisingly successful formation of the desired products (**3a**) was achieved after 30 h with 86% yield (Table 1, entry 2).

After successful formation of the product in ethanol, other solvents like methanol, acetonitrile, DMF, THF and dichloromethane were screened for the model reaction.

The yield of products **(3a)** in other solvents was found to be inferior compared to that in ethanol (Table 1, entry 3-7). Considering the above result, we chose ethanol as a suitable solvent for baker's yeast catalyzed Henry reaction.

In order to check the catalytic role of baker's yeast in Henry reaction, we carried out a model reaction in different solvents without adding baker's yeast. It became clear that there was no appreciable formation of the desired product **3a** (Table 1, entry 8-14). According to this result, it was concluded that baker's yeast is essential to carry out the Henry reaction.

**Table 1**. Effect of solvent on the synthesis of β-nitroalcohol **3a** (1-phenyl-2-nitroethanol) catalyzed by baker's yeast.[a]

| Entry | Solvent | Time (h) | Yield (%)[b] |
|---|---|---|---|
| 1 | $H_2O$ | 30 | 10 |
| 2 | EtOH | 30 | 86 |
| 3 | MeOH | 30 | 70 |
| 4 | DMF | 30 | 51 |
| 5 | DCM | 30 | 48 |
| 6 | THF | 30 | 49 |
| 7 | ACN | 30 | 65 |
| 8 | EtOH | 30 | 05[c] |
| 9 | MeOH | 40 | N.R.[c] |
| 10 | DMF | 40 | N.R.[c] |
| 11 | DCM | 40 | N.R.[c] |
| 12 | THF | 40 | N.R.[c] |
| 13 | ACN | 40 | N.R.[c] |

[a]Reaction condition: Benzaldehyde ( 9 mmol), nitromethane (9 mmol) and baker's yeast (2 g) in different solvent at room temperature under stirring.
[b]Isolated yield.
[c]Reaction in absence of beaker's yeast.

**Table 2.** Effect of amount of baker's yeast on the synthesis of β-nitroalcohol **3b** (2-nitro-1-(4-nitrophenyl) ethanol)

| Entry | Amount (g) | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | 0.5 | 30 | 23 |
| 2 | 1.0 | 30 | 42 |
| 3 | 1.5 | 30 | 68 |
| 4 | 2.0 | 30 | 90 |
| 5 | 2.5 | 30 | 90 |

The catalyst amount was increased from 0.5 g to 2.5 g for the product **(3b)** (Table 2, entry 1-5**),** which was a yellow solid. It was found that the maximum yield of the product **(3b)** was obtained when 2 g of the catalyst (baker's yeast) was used (Table 2, entry 4). Further increments of amount of catalyst gave same yield of product **(3b)** Therefore, 2 g of catalyst (baker's yeast) was used for all the reactions (Table 2, entry 5). Since after the reaction, yeast cells got ruptured, therefore, reusability of catalysts was not possible.

To apply this methodology to aldehyde, several β-nitroalcohols were synthesized by the reaction of diversely substituted aryl aldehydes with nitromethane using baker's yeast as a catalyst in ethanol (Scheme 1).

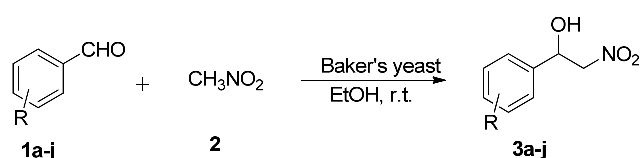
A variety of aldehydes containing electron donating and withdrawing groups were successfully employed to prepare corresponding β-nitroalcohols (Table 3, entry 1-10). The result showed that aldehydes bearing nitro groups on the aryl ring gave a good yield of the product (Table 3, entry 2).

Considering these positive results, another nitroalkane i.e. nitroethane was used to synthesise corresponding nitroalcohols, but it was found that addition of one carbon to nitrolkane did not form any desired products even after 30 h. It might be due to reduced reactivity of the nitroethane compared to nitromethane.

Inspired by these results, the above methodology was employed for a heterocyclic aldehyde i.e. 2-chloro-quinoline-3-carbaldehyde (Scheme 2) and from Table 3, entry 11, it is apparent that this aldehyde smoothly underwent a reaction in non-aqueous solvent, ethanol, giving moderate yield of the Henry product.

In comparison with earlier methods, our methodology is more advantageous because most of the catalyst like PTC derived from chinchona alkaloid, nonporous catalyst, aminofunctionalized MCM-41, Cu(I) Complex, chloroaluminate ionic liquid, dendronized piperidine were not readily available; they need to be prepared in a time consuming and costly process before catalysis.

There are few biocatalysts known for Henry reaction including hydroxynirile lyase from *H. barasilensis* and acylase enzymes. These enzymes require more time to complete the reaction (48 h giving 73% and 22-90% yield of the product), while yields are less than those of present methods (Table 4). The baker's yeast, which is much cheaper in comparison to other catalysts, is readily available.

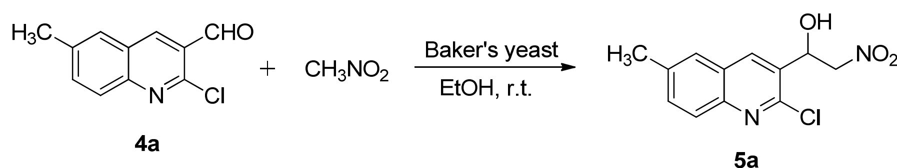



**Scheme 1**. Baker's yeast catalyzed Henry reaction of aryl aldehydes and nitromethane.

**Table 3.** Baker's yeast catalyzed Henry reaction of aromatic aldehydes with nitromethane.[a]

| Entry | R | Product | Yield (%)[b] |
|---|---|---|---|
| 1 | H | 3a | 86 |
| 2 | 4-$NO_2$ | 3b | 90 |
| 3 | 4-OH | 3c | 76 |
| 4 | 4-Cl | 3d | 82 |
| 5 | 4-$N(CH_3)_2$ | 3e | 66 |
| 6 | 2-Cl | 3f | 68 |
| 7 | 2-OH | 3g | 56 |
| 8 | 4-OMe | 3h | 58 |
| 9 | 3- $NO_2$ | 3i | 65 |
| 10 | 3-$NO_2$ | 3j | 55 |
| 11 | 6-$CH_3$ | 5a | 55 |

[a]Reaction conditions: Aromatic aldehyde (9 mmol), nitromethane (9 mmol) and baker's yeast (2 g) in ethanol (20 mL) at room temperature for 30 h.
[b]Isolated yield.




**Scheme 2.** Baker's yeast catalyzed Henry reaction of quinolinyl aldehydes and nitromethane.

**Table 4.** Comparison of the present methodology with other reported methods.

| Entry | Catalyst | Time | Yield (%) | Ref. |
|---|---|---|---|---|
| 1 | N,N′-Dioxide/Cu(I) Complex | 72 h | 35-99 | [30] |
| 2 | Chiral phase transfer catalyst derived from cinchona alkaloids | 1 h | 89-99 | [29] |
| 3 | Aminofunctionalized MCM-41 | 15 min. to 6 h | Mixtrue of products | [9] |
| 4 | Chloroaluminate ionic liquid | 16 h | 2-77 | [14] |
| 5 | Dendronized piperidine | 36 h | 8-95 | [31] |
| 6 | Hydroxynitrile Lyase from H. brasiliensis | 48 h | 73 | [20] |
| 7 | Acylase | 48 h | 22-90 | [28] |
| 8 | Baker’s yeast | 30 h | 55-90 | This work |

## 4. Conclusions

In summary, in this study baker’s yeast is successfully employed to catalyze Henry reaction to synthesis of β- nitroalcohols. It is green and an excellent example of non-aqueous biocatalysis. The products obtained were good enough to moderate yields under mild conditions. This work is completely eco-friendly**.**


## Acknowledgements

Authors are thankful to Science and Engineering Research Board, New Delhi for providing financial support (SB/EMEQ-279/2013). Authors are grateful to SAIF, Chandigarh University and SAIF, CDRI for providing spectral characterizations.


## References


[1] C.J. Li, Chem. Rev. 105 (2005) 3095-3166.

[2] S.S. Ganesan, A. Ganesan, J. Kothandapani, Synlett 25 (2014) 1847-1850.

[3] J.D. White, S. Shaw, Org. Lett. 14 (2012) 6270-6273.

[4] J. Boruwaa, N. Gogoia, P.P. Saikiaa, N.C. Barua, Tetrahedron Asymm. 17 (2006) 3315-3326.

[5] R. Kowalczyk, L. Sidorowicz, J. Skarzewski, Tetrahedron Assymm. 18 (2007) 2581-2586.

[6] H. Li, B. Wang, L. Deng, J. Am. Chem. Soc. 128 (2006) 732-733.

[7] C. Palomo, M. Oiarbid, A. Laso, Angew Chem. Int. Ed. 44 (2005) 3881-3884.

[8] M.A. Poupart, G. Fazal, S. Goulet, L. T. Mar, J. Org. Chem. 64 (1999) 1356-1361.

[9] A. Anan, R. Vathyam, K.K. Sharma, T. Asefa, Catal. Lett. 126 (2008) 142-148.

[10] R. Ballini, G. Bosica, J. Org. Chem. 62 (1997) 425-427.

[11] J.A. Weeden, J.D. Chisholm, Teterahedron Lett. 47 (2006) 9313-9316.

[12] J. Han, Y. Xu, Y. Su, X. She, X. Pan, Catal. Commun. 9 (2008) 2077-2079.

[13] J.M. Concellón, H.R. Solla, C. Concellón, J. Org. Chem. 71 (2006) 7919-7922.

[14] A. Kumar, S.S. Pawar, J. Mol. Catal. A: Chem. 235 (2005) 244-248.

[15] C.V. Bray, X.F. Wu, J.B. Sortais, C. Darcel, Teterahedron Lett. 51 (2010) 4555-4557.

[16] A. Shi, S. Kadam, S.S. Kim, Bull. Korean Chem. Soc. 30 (2009) 1767-1770.

[17] D. Uraguchi, S. Sakaki, T. Ooi, J. Am. Chem. Soc. 129 (2007) 12392-12393.

[18] I. Morao, F.P. Cossio, Teterahedron Lett. 38 (1997) 6461-6464.

[19] K. Kanagaran, P. Suresh, K. Pitchumani, Org. Lett. 12 (2010) 4070-4073.

[20] R. Yuryev, S. Briechle, M.G. Khadjawi, H. Griengl, A. Liese, ChemCatChem 2 (2010) 981-986.

[21] R.C. Tang, Z. Guan, Y.H. He, W. Zhu, J. Mol. Catal. B: Enzym. 63 (2010) 62-67.

[22] J.L. Wang, X. Li, H.Y. Xie, B.K. Liu, X.F. Lin, J. Biotechnol. 145 (2010) 240-243.

[23] J. Stewart, K. Reed, C. Martinez, J. Zhu, G. Margaret, M. Kayser, J. Am. Chem. Soc. 120 (1998) 3541-3548.

[24] R. Csuk. B.I. Glaenzer, Chem. Rev. 91 (1991) 49-97.

[25] Q.M. Wu, J.L. XuXia, J.L. Wang, X.F. Lin, Adv. Synth. Catal. 351 (2009) 1833-1841.

[26] R. Leon, P. Fernandes, H.M. Pinheiro, J.M.S. Cabral, Enzym. Microb. Technol. 23 (1998) 483-500.

[27] N.D. Punyapreddiwar, S.P. Zodape, A.V. Wankhade, U.R. Pratap, J. Mol. Catal. B: Enzym. 133 (2016) 124-126.

[28] W.J. Xia, Z.B. Xie, G.F. Jiang, Z.G. Le, Molecules 18 (2013) 13910-13919.

[29] P.K. Vijaya, S. Murugesan, A. Siva, Org. Biomol. Chem. 14 (2016) 10101-10109.

[30] H. Mei, X. Xiao, X. Zhao, B. Fang, X. Liu, L. Lina, X. Fenga, J. Org. Chem. 80 (2015) 2272-2280.

[31] B. Yi, Y. Yin, Z. Yi, W. Zhou, H. Liu, N. Tan, H. Yang, Tetrahedron Lett. 57 (2016) 2320-2323.