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Conjugate addition of malononitrile on chalcone: Biocatalytic C—C bond formation

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ABSTRACT

An efficient, cost effective and environmentally friendly protocol has been developed for the Michael addition of malononitrile on 1,3-diaryl-2-propen-1-ones (Chalcones) using very cheaper, easily available natural catalyst, baker's yeast. The whole cells of yeast excellently worked in nonaqueous medium, ethanol without decrease in catalytic activity.

1. Introduction

The Michael addition of nucleophile to α, β-unsaturated carbonyl compounds represents one of the most important carbon–carbon forming reactions in organic synthesis.This reaction is an excellent way to make variety of synthetic and natural bioactive molecules [1].

The Michael addition on chalcones i.e. 1,3-diaryl-2-propen-1-ones is largely studied becuase of their utility in making of polysubstituted benzenes and some other heterocyclic molecules [2]. The chalcones are the natural compounds belong to flavoid family, they are having diverse biological activities,such as antimalarial, anticancer, antiprotozoal, antiulcer, antiinflamatory *etc* [3]. The Michael addition on chalcone with malononitrile produces highly useful intermediate for the synthesis of biological active heterocyclic ring due to presence of nitrile group [4].

The Michael additions are generaly conducted using strong base at elevated temperature. Due to the presence of strong base, with side reactions occur such as multiple condensations, polymeriations and rearrangements [5].

The conjugate addition of malononitrile on chalcone is relatively less explored. The malononitrile is an equivalent of 1,3-dicarbonyl compound and it has strong electron withdrawing property due to the presence of nitrile group. It is a versatile functional group for further transformations [6]. Therefore, the development of efficient Michael addition involved malononitrile is still highly desirable.

A few methods were reported for the Michael addition of malononitrile on chalcones using different catalysts, which are suffering with one or otherkinds of disadvantages. Wang et al., have used squaramide as organocatalyst in which catalyst preparations is necessary that reqiures more time [7]. Guandium lactate ionic liquiud catalysed protocol is also reported which involve the making of catalyst and reaction need lowering of tempreture i.e 0 °C [8]. Russo et al., reported cinchona alkoloids catalyst which is much more costlier [9]. The readily available TBAB as a catalyst has also been utilized but reaction require elevated tempreture i.e reflux for the completion of reaction [10]. Li et al., have developed a method using ruthenium complex *i.e.* $RuCl_2[(R, R)\text{-DPEN}](PPh_3)_2$ [11]. The use of ruthenium copmplexes is a costly affair due to the high price of ruthenium salts. Shi et al., reported quinine catalysed reaction but required more time (80 h) [12]. When chemical catalysts are used for this reaction, the process always suffer with lower yields of the products, tedious work-up procedures, possibility of side reactions *etc.* [13–16] Therefore there is need to over come these drawbaks for Michael addition of malononitrile on chalcone.

Biocatalysts are the key elements in the toolbox of organic chemist becuase of their pathbreaking applications in non natural reactions like aldol reaction [17], Henry reaction [18], Knovenagel condensation, [19] Michael addition [20,22] *etc*. Among the known biocatalysts to date baker's yeast is a versatile, cheaper whole cell biocatalyst having applications in oxidations, reductions, cyclocondensations and Michael addition reactions [23]. It was found that

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Table 1
Effect of solvent on Michael addition on chalcone catalysed by baker's yeast.[a]

Entry	Solvent	Time (h)	Yield[b] (%)
1	H_2O	25	–
2	MeOH	18	71
3	EtOH	18	83
4	DCM	25	30
5	DMF	25	45
6	ACN	25	51
7	DMSO	25	61
8	THF	25	50
9	EtOH	25	–

[a] Reaction condition: Chalcone (5 mmol), malononitrile (5 mmol), 2 g baker's yeast and 20 mL solvent at room temp.
[b] Isolated yield.

the baker's yeast is not much explored as a catalyst for Michael addition for C—C bond formation.

Naturaly biocatalysts work efficiently in aqueous environment but it is not much useful for most of the organic reactions because substrates are not soluble in aqueous medium and also there is possibility of side reactions, therefore the use of biocatalyst in organic solvent is gaining much importance.The advantages of biocatalyst in organic solvent such as (1) high solubility of organic substrates (2) easy recovery of the product (3) insolubility of biocatalysts in organic solvents permit their easy recovery and reuse [21–24].

Considering the above facts, we have developed an efficient methodology for the Michael addition of malononitrile on chalcone in organic solvent under relatively mild reaction conditions using baker's yeast as catalyst, which is easily available and cheaper than other chemical catalyst used for catalysing this reaction.

2. Results and discussion

In order to obtain best experimental conditions, we have considered reaction of chalcone (**1a**) with malononitrile in presence of baker's yeast as standard model reaction to get product **3a**.

The optimization study was started by screening of various solvents for model reaction.The screening of the solvent was initiated from natural solvent i.e water (H_2O), the malononitrile (5 mmol) and chalcone (5 mmol) in water (20 mL) was stirred for 25 h but there was no formtion of desired product observed (Table 1**, entry 1**). It may be due to the in solubility of chalcone in water.

To overcome this problem we turned our attention towards the use of various organic solvents *e.g.* protic, aprotic, polarand nonpolar solvents.

Then the model reaction was run in methanol (MeOH). Interestingly within 18 h of the reaction 71% yield of desired product was isolated (Table 1**, entry 2**). Inspired by this result model recation was carried out in ethanol (EtOH), surprisingly 83% yield of desired product was obtained in 18 h of reaction time (Table 1**, entry 3**).

Then other solvents like dichloromethane (DCM), dimethylformamide (DMF), acetonitrile (ACN), dimethylsulphoxide (DMSO), tetrahydrofuran (THF) were screened for model reaction, even after 25 h less yield of product **3a** was obtained as compared to yield obtained in ethanol (Table 1, **Entry 4–8**).

The model reaction proceeds in all organic solvents but it was interesting to observe that the yield of product **3a** obatined was highest in ethanol within 18 h of stirring (Table 1**, entry 2**). Therefore ethanol was selected as a solvent for the Michael addition of malononitrile on different chalcones.

To find out optimum amount of baker's yeast needed for the reaction, various amounts of yeast were studied. Initailly reaction was done using 0.5 g of yeast which doesn't gave desired product even after 25 h of stirring. Therefore amount was increased to 1 g, then the reaction was incomplete in 25 h giving 35% yield of the **3a**. Then we again increased amount of yeast to 2, 3 and 4 g to run model reaction. When 3 and 4 g of catalyst were used, there was no proper stirring to reaction mixture takes place beacuse of increase in mass, hence the reactants not mixed properly, results in a unreacted chalcone isolation. Based on above result we have concluded that the 2 g of yeast for model reaction is optimum.

Table 2
Michael addition on chalcone with malononitrile catalysed by baker's yeast.[a]

Entry	R_1	R_2	Product[c]	Yield[b](%)
1	H	H	3a	83
2	H	4-NO_2	3b	76
3	H	4-Cl	3c	85
4	H	2-Cl	3d	74
5	H	4-$N(CH_3)_2$	3e	67
6	H	4-OCH_3	3f	78
7	H	2-Furyl	3g	65
8	H	4-F	3h	70
9	H	4-CH_3	3i	65
10	4-OH	H	3j	52
11	4- OCH_3	H	3k	66
12	4 –OCH_3	4-Cl	3l	60
13	4-OH	4-Cl	3m	68
14	2-OH	H	3n	66
15	2-OH	4-Cl	3o	72

[a] Reaction condition: Chalcone (5 mmol), malononitrile (5 mmol), 2 g baker's yeast and 20 mL ethanol at room temp).
[b] Isolated yield.
[c] Product were confirmed by physical constant, ^{1}H NMR and ^{13}C NMR analysis [8,9,11,12].

To generalise this methodology the variety of chalcones were reacted with malononitrile (Scheme 1**)** using baker's yeast in ethanol to obtain desired products in good to moderate yields (Table 2**, entry 1–15**). The required chalcones were prepared by using substituted acetophenones and benzaldehydes in presence of sodium hydroxide in aqueous ethanol.

When the malononitrile was added on chalcone of unsubstituted acetophenone and aldehyde with electron withdrawing substituent resulted in higher yields of the products (Table 2**, entry 2–9)** and when it is added on chalcone where both the aryl ring are substituted then the yields of the products are decreased (Table 2**, entry 10–15).**

To examine the need of baker's yeast to catalyse C—C bond formation, the model reaction was run in absence of baker's yeast in ethanol. It was found that there was no conversion even after 25 h (Table 1 **entry 9**). From this result it is cleared that baker's yeast is essential to carry out the C—C bond formation between chalcone and malononitrile.

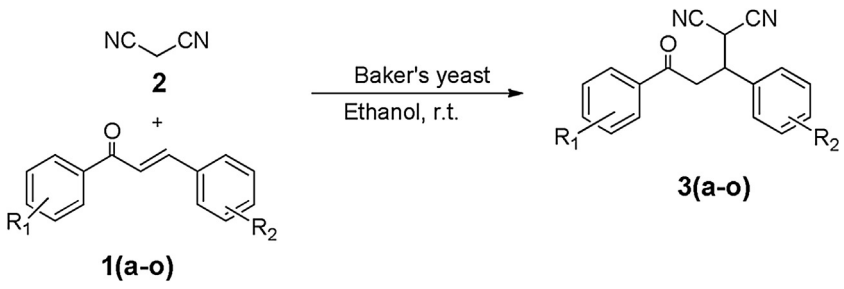
3. Experimental Section

3.1. General

The active dry baker's yeast is procured from AB Mauri India Pvt. Ltd. All chemicals were purchased from commercial suppliers and used without further purifications. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer at ambient temperatures in $CDCl_3$ as solvent, Thin Layer chromatography was carried out using aluminium backed plates precoated with silica gel 60 were visualized by quenching of UV fluorescence.

3.2. Typical procedure for the synthesis of *3a*

A mixture of 1,3-phenyl-2-propen-1-one, **1a** (5 mmol), and malononitrile, **2** (5 mmol) was stirred at room temperature in ethanol (20 mL), after homogeneous solution is formed, baker's yeast (2 gm) was added to reaction mixture.Then the reaction was continuously stirred at room temperature at 500 rpm on magnetc



Scheme 1. Baker's yeast catalysed Michael addition of malononitrile on chalcones.

stirrer.The progress of the reaction mixture was monitored by thin layer chromatography, after 18 h reaction mixture was filtered to remove the catalyst and washed with excess of ethanol.There action mixture was concentrated under vacuum followed by addition of ethylacetate.Thus obtained organic layer was separated, dried over anhydrous Na_2SO_4. The organic layer was evaporated under vacum to obtain crude product, **3a**. The crude product obtained was purified by column chromatography using silica as adsorbent and mixture of ethyl acetate and *n*-haxane (1:3) as a mobile pahse.

All other products (**3b-o**) are synthesized following above procedure. The structures of the products are confirmed by NMR spectroscopy.

3.3. Spectral data of the compounds

2-[1(4-chlorophenyl)(3-Oxo1,3-diphenylpropyl)malononitrile] (3b):^{1}HNMR-(400 MHz, $CDCl_3$) δ(ppm) 3.69 (2H,dd, *J = 5.6 Hz, J = 8.6* Hz), 3.95(1H,m), 4.62 (1H,d, *J = 5.4 Hz*), 7.25-7.96 (9H, m).^{13}**CNMR-(**100 MHz, $CDCl_3$) δ (ppm) 28.72, 39.98, 40.69, 111.52, 111.72, 129.0, 129.4, 129.59, 134.33, 134.96, 135.27, 135.66, 196. 34.

2-[1(-2-chlorophenyl)(3-Oxo-1,3-diphenylpropyl)]malononitrile (3d): ^{1}HNMR-(400 MHz, $CDCl_3$) δ (ppm) 3.51(2H, dd, *J = 5.2 Hz, J =* 8.8 *Hz*), 4.56(1H, d, *J = 5.2 Hz),*7.20-7.89(9H,m).^{13}**C NMR-**(100 MHz, $CDCl_3$) δ (ppm) 33.9, 42.94,127.0, 127.76, 128.14, 128.30, 130.0,133.14, 133.67,140.8,198.36.

2-[1-(4-*N*,*N*-Dimethyl)(3-Oxo-1, 3-diphenylpropyl)malononitrile (3e):

^{1}**H NMR**- (400 MHz, $CDCl_3$) δ (ppm) 2.95 (s, 6H), 3.62 (2H, dd, *J = 5.6 Hz, J = 8.4 Hz*), 4.56(1H,m),4.57 (1H, d, *J = 5.4 Hz*), 6.7-7.30 (9H, m).^{13}**CNMR**(100 MHz,$CDCl_3$)δ(ppm)29.28, 40.3, 40.62, 112.02, 112.57, 123.58, 128.10, 128.72, 128.87, 133.9, 135.89, 156.7, 197.2.

2-[3-(4-hydroxy phenyl)(3-Oxo-phenyl)]malononitrile (3j):

^{1}**HNMR**- (400 MHz,$CDCl_3$) δ (ppm) 3.69 (2H, dd, *J = 5.2 Hz, J = 8.4 Hz*), 3.96 (1H, dt), 4.55 (1H, d, *J = 5.4 Hz*), 6.9-7.76 (9H,m), 11.75 (s,1H).^{13}**CNMR-**(100 MHz, $CDCl_3$) δ (ppm) 29.03, 39.6, 40.94, 111.59, 111.7, 118.9, 119.46, 127.9, 129.41, 129.53, 136.1, 137.45, 162.55, 201.88.

4. Conclusion

In summary, here an efficient Michael addition of malononitrile on chalcone in ethanol catalysed by baker's yeast is developed. The protocol is green, simple and high yielding. The work stengthen the idea of whole cell biocatalysis in organic solvent i.e. nonaqoues enzymology.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcatb.2016.08.004.

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