Baker's yeast: An efficient, green and reusable biocatalyst for the one-pot synthesis of biologically important *N*-substituted decahydroacridine-1,8-dione derivatives

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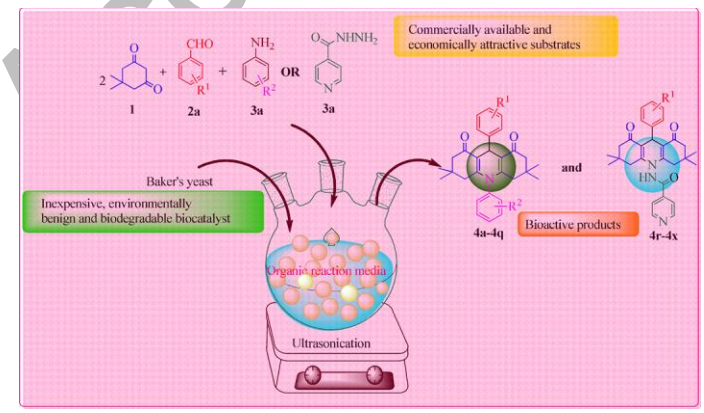
Abstract

A green approach for one-pot three-component synthesis of *N*-substituted decahydroacridine-1,8-diones is offered for the first time using baker's yeast (*Saccharomyces cerevisiae*) as a biocatalyst under ultrasonication. Due to growing safety and environmental concerns, enzymatic methods were constantly investigated as an attractive alternative to toxic and non-specific chemical approaches. This method is relatively simple, efficient, inexpensive, and environment-friendly. The catalyst was recovered and reused and also the recyclability of baker's yeast resulted in excellent yields of products without loss of any catalytic activity.

GRAPHICAL ABSTRACT



KEYWORDS: Baker's yeast, Acridine-1,8-diones, Tandem reaction, Biocatalyst, Ultrasonication.

INTRODUCTION

Modern industries necessarily need to exploit renewable resources in a sustainable manner, promoting bio-based environmentally friendly or beneficial technologies in order to keep competitive market positions[1] and create high-performing materials for a range of application.[2,3] Now a day's steps are being taken, mainly due to increasing economic, social, legal, and environmental pressures, to avoid further degradation of ecological balance. Therefore, the so-called Green Chemical Processes where the "best available technology" not entailing excessive cost and aspiring to "performance without pollution" can be used in industrial processes.[4-6]

In the last decade, biocatalysis has been integrated into mainstream organic synthesis,[7, 8] particularly in the pharmaceutical industry.[9] This can be largely attributed to its numerous environmental and economic benefits. The catalyst (an enzyme) is derived from renewable resources and is biocompatible, biodegradable, and essentially nonhazardous and nontoxic. Biocatalysis avoids the use of scarce precious metals and the associated, often prohibitive, costs of removing traces of noble metal catalysts from the end product.

Also the impression that biocatalytic based processes are per se more ecological or sustainable than their chemical alternatives. Nevertheless, the environmental

friendliness and the economic feasibility of the whole process must be clarified and evaluated for every single procedure.[10] Baker's yeast (*Saccharomyces cerevisiae*) is the first and most popular whole cell biocatalyst, economical and neither toxic nor pathogenic, which has been used for different organic transformations. Here the focus lies on reaction types that are of high interest for the industry.

Many biologically important molecular scaffolds can easily be synthesized from readily available starting materials with the help of multi-component reactions (MCRs).[11-14] Multicomponent reactions (MCRs) allow for rapid synthesis of drug-like compound libraries by combining three or more reagents into a single product in one step.[14c]

The acridine and acridine-1,8-dione derivative are an important class of nitrogen heterocycles that can be converted into biologically important compounds exhibiting favorable biological and pharmaceutical properties, such as anti-malaria,[15] anti-tumor,[16] anti-cancer,[17] fungicidal,[18] cytotoxic,[19] anti-multidrug-resistant,[20] antimicrobial,[21] and are widely prescribed as calcium β-blockers.[22,23] Additionally, 1,8-dioxo-decahydroacridines were created to act as laser dyes,[24,25] and used as photo initiators.[26]

Thus, the synthesis of 1,8-dioxo-decahydroacridine derivatives is currently of great importance. Some new methods have been developed to improve the reaction efficiency in the synthesis of 1,8-dioxo-decahydroacridine using catalysts such as urea,[27] hydroxylamine,[28] ammonium acetate on basic alumina,[29] ammonium bicarbonate,[30]

ammonium hydroxide and various appropriate amines or ammonium acetate.[31] Additional methods have included conventional heating of organic solvents in the presence of Amberlyst-15,[32] benzyl triethyl ammonium chloride (TEBAC),[33] the use of microwave irradiation,[34,35] and using ionic liquids.[36,37] Furthermore, 9,10-diarylacridine-1,8-diones have also been prepared using *p*-dodecylbenzenesulfonic acid (DBSA),[38] $Zn(OAc)_2.2H_2O$, ammonium chloride or *L*-proline/proline [39], CAN [40] and the sulfonated organic heteropoly acid salts, $[MIMPS]_3PW_{12}O_{40}$ and $[TEAPS]_3PW_{12}O_{40}$.[41] However, these methodologies suffer from one or more shortcomings, such as low yield, prolonged reaction time, use of toxic organic solvents and employ costly and hazardous catalysts as well as cumbersome work-up procedures. Therefore, introducing clean processes and utilizing eco-friendly catalysts, which can be easily recycled at the end of the reaction, have received increasing attention.

Conversely, in comparison with conventional thermal heating, Ultrasound irradiation is a powerful technique, which is being used frequently to accelerate organic transformations.[42-45] It is one of the most widely used laboratory methods for the disruption of cells of baker's yeast for the fast release of enzymes.[46] The ability of ultrasonic irradiation methods to accelerate and, occasionally, to increase the chemical reactions yield have attracted the scientific community for its use over the last decades. Despite the widespread use of ultrasonic energy in various research disciplines, only recently the synergetic use of ultrasonication and enzymes to enhance reactions has been described. [47-50]

The demand for an environmentally benign procedure utilizing a heterogeneous and reusable catalyst led our investigations to develop a safe alternative method for the synthesis of acridine-1,8-dione derivatives. Bearing the above points in mind, we believe this to be the first ever report on a sonically enhanced one-pot multicomponent reaction in organic media using the environmentally benign baker's yeast (*Saccharomyces cerevisiae*) as a whole cell biocatalyst.

RESULT AND DISCUSSION

In this study, we describe for the first time, a sustainable one-pot synthesis of *N*-substituted 1,8-dioxo-decahydroacridines **4a–4t** (Scheme 1) under ultrasonication at room temperature in organic media using baker's yeast (*Saccharomyces cerevisiae*) as a whole cell biocatalyst.

There is scanty information on the use of enzymes for the acceleration of tandem condensation. Isolated lipases have been found to catalyze this type of condensation.[51,52] The use of isolated pure enzymes to accelerate organic transformations has several drawbacks such as high cost, narrow substrate specificities and in some cases low performance under nonnatural conditions.

Here, we have attempted the tandem condensation using a cheaper whole cell biocatalyst, baker's yeast (*Saccharomyces cerevisiae*). The cell of baker's yeast acts as a mini reactor and produces a variety of enzymes and is known to provide specific enzyme for specific reaction. Baker's yeast has the ability to catalyze various organic

transformations.[53] It is also used in the formation of CQC double bonds *via* acyloin condensation,[54,55] and Michael addition reaction.[56] Due to this important aspect, baker's yeast is gaining much importance in organic synthesis.[57]

Initially, our investigations started with an optimization study of model reaction by allowing cyclocondensation of dimedone **(1)**, benzaldehyde **(2a)** and aniline **(3a)** in presence of baker's yeast (*Saccharomyces cerevisiae*) (Scheme 1). To see the effect of reaction medium on the rate and yield of the reaction we carried model reaction in various solvents under stirring at room temperature.

The optimization study was started by screening of various solvents for model reaction. The releative activity of the baker's yeast (*Saccharomyces cerevisiaes*) immobilized was higher than the free baker's yeast (*Saccharomyces cerevisiaes*). Immobilized cells were more resistant to organic solvents than free cells. Therefore, during the whole-cell biocatalyzing process in organic media the immobilization of microorganisms not only has the advantage of easy separation but also can enhance the tolerance of cells. Despite the ideal environmental profile of water, its use in organic reactions is limited due to the low dissolving ability of most organic substrates, a characteristic that reduces the reaction rate. Moreover, as the enantioselectivity in water could be reduced by the side effects of the different enzymes in the yeast cell, organic solvents can alter the enantioselectivity to an even greater degree when compared to the corresponding transformations in water.[58] Therefore, the quest for a solvent with a minimal impact on the environment, e.g., a green solvent, is of the utmost importance.

Their greenness is attributed mainly to their unique physical properties, such as low volatility and high stability, and to their recyclability and reusability. However, the advantages of better substrate solubility or improved enzyme stability should be balanced against the price of solvent and additional efforts for downstream processing. Inspired by this, The screening of the solvent was initiated from natural solvent i.e water (H_2O), dimedone **(1)**, benzaldehyde **(2a)** and aniline **(3a)** in water was stirred for 28 h but there was formation of desired product observed in trace amount (Table 1, entry 1). It might be due to sparingly solubility of substrates in aqueous medium. To overcome this problem we turned our attention towards the use of various organic solvents. Although there were earlier reports of the use of enzymes in organic media,[59] it was the seminal paper by Zaks and Klibanov in 1984,[60] describing enzymatic catalysis at 100 ˚C in organic media, that heralded the era of "nonaqueous enzymology".[61] They observed that many enzymes were actually more thermally stable in organic solvents, than in water, leading to the realization that biocatalysis had a much broader scope than was previously thought possible. Additional benefits of biocatalysis in nonaqueous media include easier product recovery from low-boiling organic solvents and elimination of microbial contamination.[62] so we turned our attention towards the use of various organic solvents e.g. protic, aprotic, polar and nonpolar solvents. Then the model reaction was run in water-ethanol (H_2O-EtOH). Interestingly within 22 h of the reaction 30 % yield of desired product was isolated (Table 1, entry 2). Inspired by this result model recation was carried out in ethanol (EtOH), surprisingly 47% yield of desired product was obtained in 20 hr of reaction time (Table 1, entry 3). Then other solvents like methanol (CH_3OH), 1,4-dioxane, dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane

(DCM) and acetonitrile (ACN), were screened for model reaction, even after 25 h less yield of product **4a** was obtained as compared to yield obtained in acetonitrile (Table 1, entry 4–8). It varied from 47% to 60% in different solvents. The model reaction proceeds in all organic solvents but it was interesting to observe that the yield of product **4a** obtained was highest in acetonitrile within 22 h of stirring (Table 1, entry 9). Therefore acetonitrile was selected as a solvent for such reaction.

It is clear from (Table 1) that the reaction performed without ultrasound afforded comparatively lower yields even after longer reaction time under ambient condition. In order to verify the effect of ultrasound, we performed the same transformations under ultrasonication, were this transformation successfully carried out under ultrasound irradiation at room temperature in comparatively short duration (3–5 h) with moderate to good yield (65–84%) (Table 1). It is apparent that the ultrasound can accelerate the reaction significantly. After having these results we decided to carry all reaction by using ultrasonic irradiation, compare to the other cell disruption method, the release of product by ultrasound has certain selectivity, which makes ultrasound more attractive in organic synthesis, Therefore, in the present system; ultrasound was found to have beneficial effect on the synthesis of title compounds.

To examine the catalytical efficiency of baker's yeast (*Saccharomyces cerevisiaes*), reaction of dimedone **(1)**, benzaldehyde **(2a)** and aniline **(3a)** in acetonitrile was performed in the absences of yeast as the control experiment where we found that

there was no formation of the product. The result indicates that the baker's yeast (*Saccharomyces cerevisiaes*) is necessary to catalyze the reaction.

After obtaining the optimized reaction conditions, thereafter the investigation studied the reaction between a series of aromatic aldehydes and aromatic amines or isoniazide with 1,3-cyclohexanediones. To assess the general applicability of this method under the given optimized reaction conditions, a wide range of divergent aldehydes and anilines possessing varying substituent's, in the presence of two equivalents of 1,3-cyclohexanediones, were allowed to undergo this three-component condensation. The nature of the functional group on the aldehyde/aniline aromatic rings exerted a slight influence on the reaction time. -Cl, -F, -Me, -OMe and -NO_2 were found to be compatible under the optimized reaction conditions. Heteroaromatic aldehydes, such as 2-Furan-2-carbaldehyde and 2-thiophene-2-carbaldehyde was equally amenable to these conditions (Table 2, entry 15,16**)**. An attempt was made to synthesize 1,8-dioxo-decahydroacridine by reacting the aliphatic aldehyde, instead of arylaldehyde, aliphatic aldehyde was less reactive than arylaldehyde, no product was obtained when aliphatic aldehyde was used, It seems that this protocol has its limitations. Also, both hydrazine hydrate and phenyl hydrazine similarly underwent well to the conversion (Table 2, entry 25). The active site of baker's yeast (*Saccharomyces cerevisiae*) forms an enzyme substrate complex with the aldehyde and dimedone more effectively and enhances the rate of reaction resulting in an increase in the product yield and a decrease in reaction time. The ultrasound irradiation technique was also established to be compatible with all listed substrates (Table 2).

Representative results are summarized in (Table 2). Product formation was confirmed by ^{1}H NMR, ^{13}C NMR, elemental analysis and melting point data.

Catalyst Recycles

Reusability is one attractive advantage of biocatalyst, which could decrease the cost of enzyme in practical application. The reusability of the baker's yeast was also evaluated. The reusability were studied by three cycles including the use of fresh catalyst for the synthesis of 1,8-dioxo-decahydroacridines. In every cycle, the catalyst was almost quantitatively recovered and after second and third use of catalyst decreasing yield is not much more significant as shown in **Figure 1**.

Reaction Mechanism

Baker's yeast is a known source of oxidoreductase and lipases.[63] Among these enzymes oxidoreductases have been found to be utilized in organic synthesis. However, the use of lipases produced by baker's yeast has not been explored to undergo knovengel condensation or similar type of condensation. In this route the lipase, produced by baker's yeast might be for enhancing electrophilic character of aldehydic carbon forming hydrogen bonding with carbonyl oxygen, thereby accelerating the rate of addition of aldehyde to dimedone to generate intermediate, This probably expedites the Michael addition of second dimedone on the first intermediate and then cyclocondensation with aniline leading to the desired *N*-substituted decanhydroacridine-1,8-diones.

EXPERIMENTAL

General Information

All chemicals were purchased and used by further purification. Melting points were determined on a open capillary tube and are uncorrected. Progress of the reaction was monitored by thin layer chromatography on Merck's silica plates. ^{1}H NMR spectra were recorded on Bruker Avance 300 MHz instruments using TMS as internal standard, ^{13}C NMR spectra were recorded on Bruker AvII- 400 MHz instruments, and elemental analysis recorded on elemental analyzers Euro-E 3000.

Ultrasound Instrumentation

All the reactions were carried out in Bandelin Sonorex (with a frequency of 35 kHz and a nominal power 200 W) ultrasonic bath was used for ultrasonic irradiation. Built-in heating, 30–80 ˚C there-mostatically adjustable. The reaction vessel placed inside the ultrasonic bath containing water.

Ultrasound Promoted General Synthesis Of N-Substituted 1,8-Dioxo-Decahydroacridines (4a-Q)

A mixture of 5,5-dimethylcyclohexane-1,3-dione **1a** (1.31 gm, 2 mmole), benzaldehyde **2a** (500 mg, 1 mmole) and aniline **3a** (650 mg,1 mmole) was dissolve in acetonitrile (20 mL). To this stirred solution active dry baker's yeast (1 gm) was added. The resulting reaction mass was further irradiated at room under ultrasonication for stipulated time mentioned in (Table 2) at room temerature. The progress of the reaction was monitored by thin layer chromatography (TLC) by using pet ether: ethyl acetate (18:2) as the eluent. After 3 h, the reaction mass was filtered through the bed of Celite. The filtrate was

concerted under reduced pressure to get the solid product and crystallized from hot ethanol to get pure product. The compound was characterized by melting point, ^{1}H NMR, and Mass spectrum, and the results obtained are summarized in (Table 2).

Ultrasound Promoted General Synthesis Of N-Substituted 1,8-Dioxo-Decahydroacridines (4r-Y)

The mixture of 5,5-dimethylcyclohexane-1,3-dione **1a** (1.31 gm, 2 mmol), aldehyde **2a** (500 mg, 1 mmol) and isoniazid **3a** (640 mg, 1 mmol) was dissolve in acetonitrile (20 mL). To this stirred solution active dry baker's yeast (1 gm) was added. The resulting reaction mass was further irradiated at room under ultrasonication for stipulated time mentioned in (Table 2) at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC) by using pet ether: ethyl acetate (18:2) as the eluent. After 3 h, the reaction mass was filtered through the bed of Celite. The filtrate was concerted under reduced pressure to get the solid product and crystallized from hot ethanol to get pure product. The recovered baker's yeast was reused for 3-4 consecutive runs in this reaction without any significant loss in yield and activity. The product was confirmed by melting point, ^{1}H NMR, ^{13}C NMR, elemental analysis and the results obtained are summarized in (Table 2).

CONCLUSION

In conclusion, non-aqueous solvent with one-pot three component condensation of pharmaceutically important precursor *N*-substituted decanhydroacridine-1,8-dione was demonstrated to be a suitable support for baker's yeast. The baker's yeast played key

roles in achieving high stability and reusability without significant lose in enzyme activity and enantioselectivity. The developed protocol might be useful for the synthesis of *N*-substituted 1,8-dioxo-decahydroacridines derivatives. Exploring the use of baker's yeast within the sustainable chemistry concept, this protocol covers waste minimization; the use of alternative solvents and energies; the use of renewable resources and biocatalysts recycling. It is valuable resource for researchers and industrialists working in green chemistry and sustainability.

ACKNOWLEDGEMENTS

This work was supported by Special Assistance Programme (SAP), University Grants Commission, New Delhi, India, intended to encourage the pursuit of excellence and teamwork in advanced teaching and research to accelerate the realization of international standards in specific fields, and also Sophisticated Analytical Instrumentation Facility, Chandigarh, for providing characterization facility for this work.

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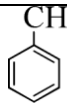
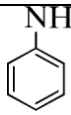
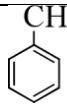
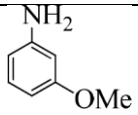
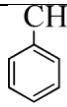
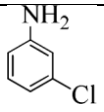
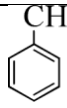
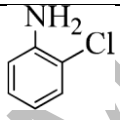
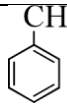
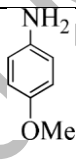
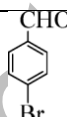
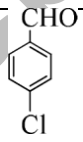
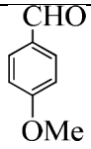
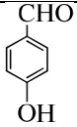
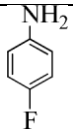
Table 1. Screening of solvent on the synthesis of **4a**.[a]

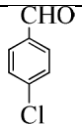
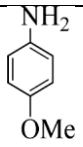
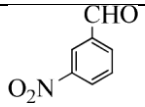
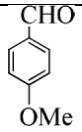
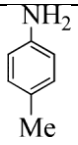
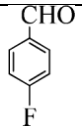
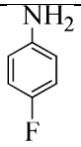
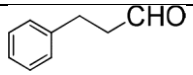
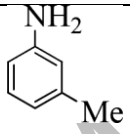
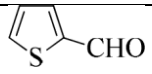
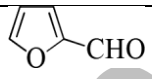
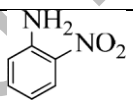
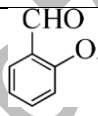
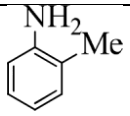
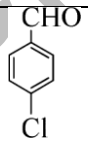
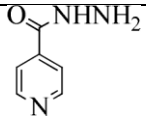
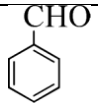
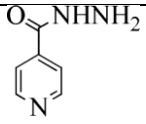
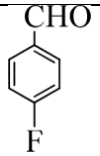
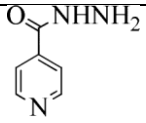
Sr. No	Solvent	Time (h)		Yield (%)[b]	
		With US	Without US	With US	Without US
1.	Water	7	28	44	22
2.	Water/Ethanol	5	22	48	30
3.	Ethanol	5	20	58	47
4.	Methanol	5	27	60	49
5.	1,4-dioxane	4	21	62	55
6.	DMF	3	26	63	52
7.	THF	5	24	71	60
8.	DCM	7	23	56	50
9.	CH_3CN	3	22	88	65

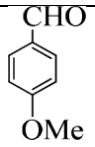
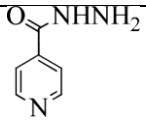
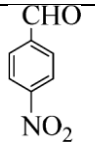
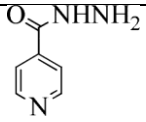
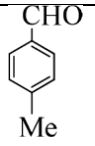
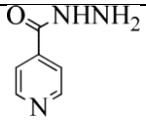
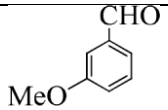
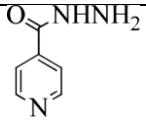
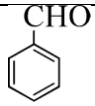
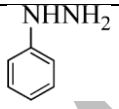
[a]Reaction conditions: dimedone (2 mmole), benzaldehyde (1 mmole), and aniline (1 mmole), baker's yeast (1gm) and solvent (10 mL) at rt,

[b]Isolated yield

Table 2. Baker's yeast catalyzed synthesis of *N*-substituted decanhydroacridine-1,8-diones **4 (a-y)** under ultrasonic irradiation.[a]

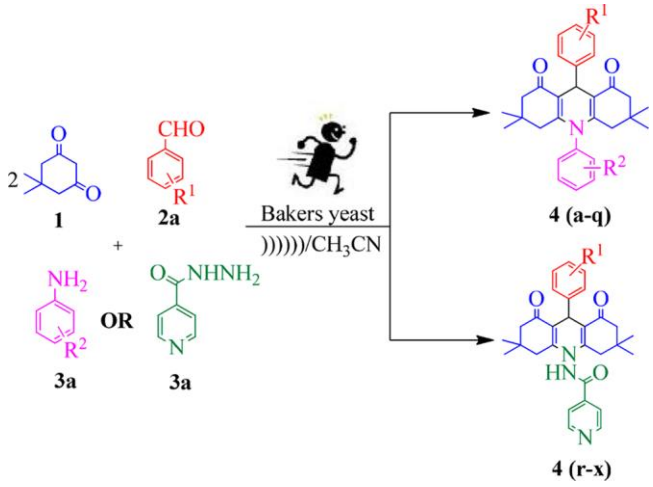
Sr. No.	Product	Aldehyde	Aniline/INH	Time (h:min)	M.P. (°C) [29,64]	Yield (%)[b]
1.	**4a**			04:10	270-273	83
2.	**4b**			03:35	184-187	80
3.	**4c**			03:50	177-180	76
4.	**4d**			04:00	188-190	73
5.	**4e**			03:50	175-178	84
6.	**4f**			03:40	>300	74
7.	**4g**			03:35	242-244	78
8.	**4h**			02:55	219-223	76
9.	**4i**			04:20	263-267	72

10.	**4j**			03:15	252-254	75
11.	**4k**			03:40	278-281	70
12.	**4l**			03:45	280-285	75
13.	**4m**			04:00	110-113	76
14.	**4n**			03:30	261-263	73
15.	**4o**			05:10	278-280	71
16.	**4p**			03:00	242-244	75
17.	**4q**			04:10	281-283	78
18.	**4r**			03:45	160-163	75
19.	**4s**			03:40	240-243	71
20.	**4t**			04:20	217-221	79

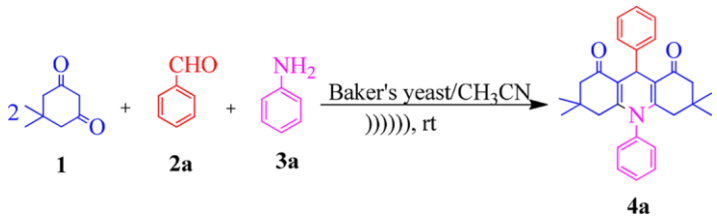
21.	**4u**			03:50	217-220	77
22.	**4v**			03:35	92-94	72
23.	**4w**			04:15	85-87	73
24.	**4x**			03:45	153-155	71
25.	**4y**			04.15	167-169	72

[a]Reaction conditions: dimedone (2 mmole), benzaldehyde (1 mmole), and aniline (1 mmole), baker's yeast (1gm) and solvent (20 mL) at rt, [b]Isolated yield

Scheme 1. General scheme for the synthesis of *N*-substituted 1,8-dioxo-decahydroacridines.



Scheme 2. Standard model reaction



Scheme 3. Plausible mechanism for the synthesis of *N*-substituted-1,8-dioxo-decahydroacridines.

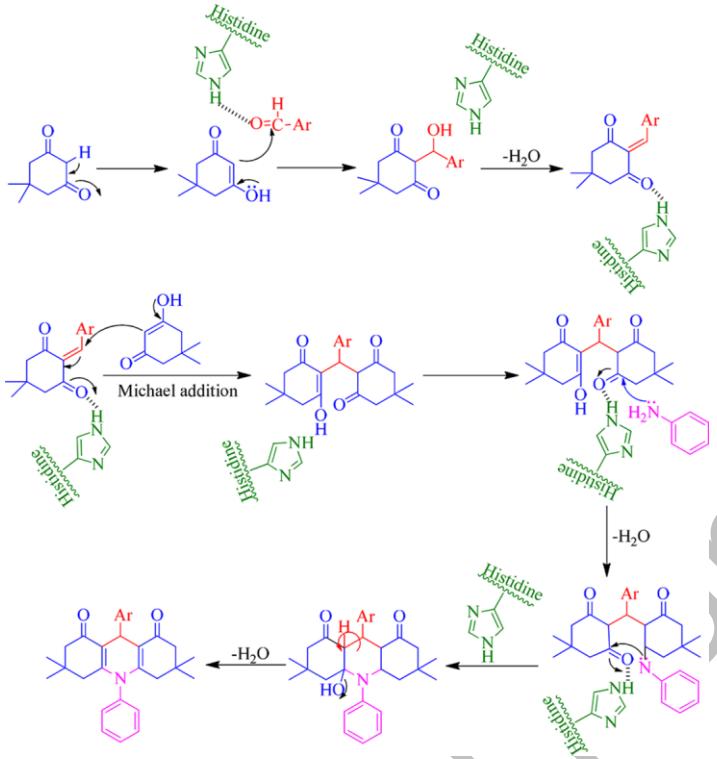


Figure 1. Reuse and recovery of baker's yeast and its effect on yield.