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Baker's yeast catalyzed synthesis of 1,4-benzothiazines, performed under ultrasonication

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ABSTRACT

An efficient and simple one pot method has been developed for the synthesis of 1,4-benzothiazines by allowing the condensation of 2-aminobenzenethiols and 1,3-dicarbonyls using cheaper biocatalyst, baker's yeast. The role of ultrasonication in the rate expediting of the condensation has been discussed.

1. Introduction

1,4-Benzothiazines have attracted great deal of interest as a synthetic target because of their broad spectrum of biological activities [1]. 1,4-Benzothiazines have been reported to exhibit wide pharmacological activities such as antagonists [2], anticancer [3], vasorelaxant [4], antidiabetic [5], antihypertensive [6] and antimicrobial [7]. 1,4-Benzothiazines have also been used as dyestuff in industry [8].

Because of their diverse biological significance synthetic chemists have developed numerous routes for the syntheses of 1,4-benzothiazine derivatives. One of the most widely employed methods for the preparation of 1,4-benzothiazines is the oxidative cyclocondensation of 2-aminobenzenethiols with 1,3-dicarbonyl compounds using DMSO/microwave irradiation/H_2O_2–NaOH [9]. This route has two steps; (i) step first includes the oxidation of 2-aminobenzenethiols to respective disulfides and (ii) the cyclocondensation of the disulfides with 1,3-dicarbonyls to the corresponding 1,4-benzothiazines. Another method includes the separate condensations of 2-aminobenzenethiols with alkynes [10] and α-haloketones or α-haloesters [11].

These methods require the use of toxic organic solvents, organic/inorganic bases and explosive/corrosive oxidants. Therefore, the design of new, concise and efficient synthetic route for this important class of compounds using easily accessible reagents and catalysts is highly desired.

The use of biocatalysts in organic synthesis is very promising. Biocatalysts show remarkable chemo, regio and stereoselectivities. In most of the transformations carried using biocatalysts, no side reaction products are generated. Therefore, critical processes are found to become simple [12]. Among the various possible biocatalysts baker's yeast (*Saccharomyces cerevisiae*) has emerged as a one of the frequently employed microorganisms in whole cell form due to its high bioavailability and easy handling. It is found to display its catalytical behavior even at mild conditions in aqueous as well as in organic media.

Baker's yeast is having ability to catalyze different types of organic transformations [13,14]. Literature survey reveals that there are some reports on the baker's yeast catalyzed cyclocondensations leading to 2-furyl benzothiazoles [15], isoxazolines [16], polyhydroquinolines [17], benzotraizole oxides [18], 1,4-dihydropyridines [19], and 3,4-dihydropyrimidine-2-(1H)-ones [20].

Considering the demerits of the classical synthesis of 1,4-benzothiazines and to explore the use of biocatalysts in the cyclocondensations, here we thought to develop an efficient biocatalytical route for the cyclocondensation. As a part of our ongoing research program on biocatalysis [21] and the synthesis of 1,4-benzothiazine [22], here we have explored the use of baker's yeast as a biocatalyst for the synthesis of 1,4-benzothiazines.

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2. Experimental

2.1. General

Melting points were determined by open capillary method and are uncorrected. Progress of the reaction was monitored by thin layer chromatography on MERKs silica plates. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-300 (300 MHz FT NMR) using TMS as internal standard. Mass spectral data were determined by JEOL AccuTOF DART mass spectrometer. Baker's yeast was obtained from local market. All chemicals used were reagent grade and used without further purification.

2.2. General experimental procedure

To the stirred solution of 2-aminobenzenethiol (10 mmol) in methanol (25 mL), active dry baker's yeast (2 g) and β-dicarbonyl (10 mmol) were added. Then the reaction mixture was sonicated at 20 kHz for 3 h at 25–30 °C. The progress of the reaction was monitored by thin layer chromatography by using ethyl acetate: pet ether (2:8) as eluent. After completion of the reaction the reaction mass was filtered through the bed of celite (1 g). From the filtrate, the solvent methanol was removed under reduced pressure and the crude products isolated were crystallized from hot ethanol (Table 2, entries 1–10).

2.2.1. 1-(3-Methyl-4H-benzo[b][1,4]thiazine-2-yl)ethanone (**3a**)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H), 2.42 (3H, s, CH_3), 5.91 (s, 1H, NH), 6.98–8.21 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.68, 153.41, 139.36, 127.44, 126.36, 124.99, 120.49, 115.43, 98.15, 30.24, 21.41.

ESI DARTMS: calculated for $C_{11}H_{11}NOS + 1$: 206.0561; found: 206 0611.

2.2.2. 1-(3,7-Dimethyl-4H-benzo[b][1,4]thiazin-2-yl)ethanone (**3d**)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (s, 3H), 2.20 (s, 3H), 2.45 (s, 3H), 5.91 (s, 1H, NH), 7.01 (t, 1H, J = 4.0 and 8.0 Hz, 1H), 6.37 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 4.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.49, 28.96, 29.92, 110.12, 114.61, 127.33, 129.37, 133.49, 135.13, 136.17, 153.54 and 194.13.

ESI DARTMS: calculated for $C_{12}H_{13}NOS + 1$: 220.0717; found: 220.1154.

2.2.3. Ethyl 3,7-dimethyl-4H-benzo[b][1,4]thiazine-2-carboxylate (**3e**)

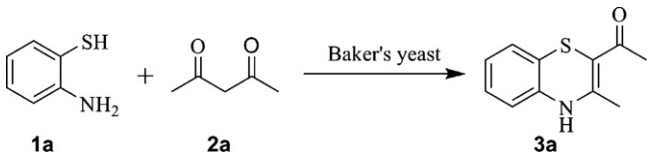
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, 3H), 2.08 (s, 3H), 2.38 (s, 3H), 4.13 (q, 3H), 6.15 (S, 1H, NH), 7.15 (d, J = 8.0 Hz, 1H), 7.24 (t, 1H, J = 4.0 and 8.0 Hz, 1H), 7.63 (d, J = 4.0 Hz, 1H).

ESI DARTMS: calculated for $C_{13}H_{15}NO_2S + 1$: 250.0823; found: 250.0796.

3. Results and discussion

Here, we describe very simple and one pot protocol for the synthesis of 1,4-benzothiazines. This involves the oxidative cyclocondensation with 2-aminobenzenethiols with 1,3-dicarbonyl compounds, expedited by baker's yeast as a whole cell biocatalyst at ambient temperature.

Our investigations started with an optimization study of model reaction by allowing cyclocondensation of 2-aminobenzenethiol (**1a**) and acetyl acetone (**2a**) in presence of baker's yeast (Scheme 1). To see the effect of reaction medium on the rate and yield of the reaction we carried model reaction in various solvents like water, dichloromethane, ethanol and methanol under stirring at room temperature (rt).



1a 2a 3a

Scheme 1.

Initially when the reaction was run in water at room temperature (rt) it was found that the cyclocondensation did not occurred and the intermediate disulfide (**4**) (Table 1, entry 1) was formed even after prolonged stirring (40 h). When the model reaction was performed in the solvent like dichloromethane, the starting materials were recovered (Table 1, entry 2). When the cyclocondensation was carried in ethanol, the noticeable yield of 1,4-benzothiazine was observed after 20 h of stirring (Table 1, entry 3). Inspired by this, we next investigated the effect of methanol on the yield and time of the reaction. Here reaction time was found to be decreased to 10 h and the yield was increased to 78% (Table 1, entry 4). After having these results we decided to carry the model reaction by using ultrasonic irradiation, as ultrasonication is one of the most widely used laboratory methods for the disruption of cells of baker's yeast for the fast release of enzymes [23].

Ultrasound assisted (US) reaction of 2-aminobenzenethiol and acetyl acetone in ethanol, carried at room temperature gave 68% yield of the product within 6 h (Table 1, entry 5). Same reaction when carried in methanol the reaction time has been decreased by 3 h and the yield was found to be increased to 82% (Table 1, entry 6). In view of these observations we have selected methanol as the reaction medium for baker's yeast catalyzed synthesis of 1,4-benzothiazines.

Subsequently the other substituted 2-aminobenzenethiols and 1,3-dicarbonyl compounds were subjected under the optimized reaction conditions to obtain the respective 1,4-benzothiazines. The results are recorded in Table 2 (Scheme 2). From these results it seems that the baker's yeast accepts broad array of substrate combinations. One of the substrates 1,3-diphenyl 1,3-propanedione failed to react with 2-aminobenzenethiol. This indicates that baker's yeast does not accept the substrate 1,3-diphenyl 1,3-propanedione (Table 2, entry 10). The chemical reactivity of 1,3-diphenyl 1,3-dicarbonyls has been well explored in presence of other catalysts and obtained respective 1,4-benzothiazines. However, under the optimized reaction conditions 1,3-diphenyl 1,3-dicarbonyl did not undergo cyclocondensation.

To investigate the role of baker's yeast in cyclocondensation the model reaction was run in absence of baker's yeast, no formation

Table 1
Effect of solvent on the reaction of 2-aminobenzenethiol and acetyl acetone.[a]

Entry	Solvent	Reaction conditions	Time (h)	Yield (%)[b]
1	Water	rt	<40	90[c]
2	Dichloromethane	rt	<40	–
3	Ethanol	rt	20	61
4	Methanol	rt	10	78
5	Ethanol	US	6	68
6	Methanol	US	3	82
7	Methanol	US	4 days	n.d.
8	Methanol	US	10	n.d.

n.d. = not detected.

[a] Reaction conditions: 2-aminobenzenethiol (8 mmol), acetyl acetone (8 mmol), baker's yeast (2 g) in 25 mL solvent.

[b] Isolated yields.

[c] Formation of disulfide (**4**). Formation of disulfide was confirmed by the comparison of the M.P. and spectral studies with disulfide prepared by earlier method [27].

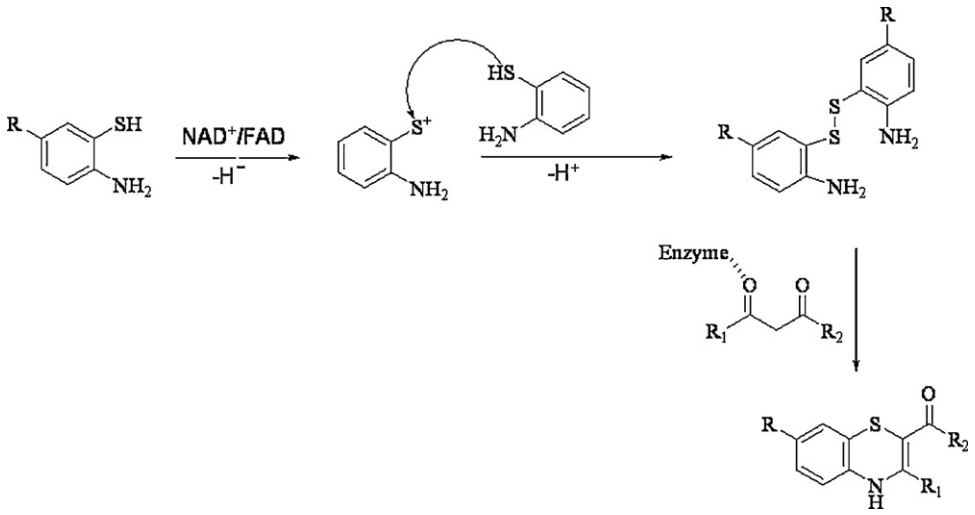
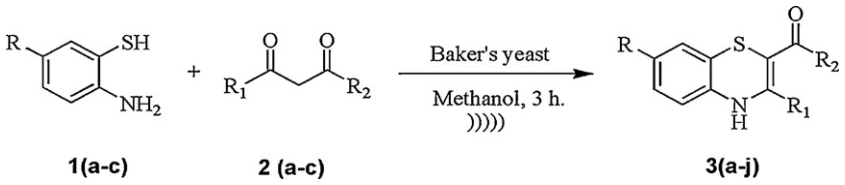


Fig. 1. Plausible mechanism for the formation of 1,4-benzothiazines.



Scheme 2.

of product was observed even after 4 days of stirring in methanol and even 10 h under ultrasonication (Table 1, entries 7 and 8).

Baker's yeast was inactivated by heating at 100 °C in water for 1 h and dead cells thus obtained after centrifugation were used in place of active baker's yeast for the model reaction. It was found that neither the disulfide nor the cyclcondensed product was formed. We also carried the two step synthesis of 1,4-benzothiazine to know the reaction sequence. 2-Aminothiophenol and activated baker's yeast were irradiated under ultrasound in methanol for 30 min. The reaction mass was filtered and filtrate was found to be a solution of disulfide (**4**). In successive step to this disulfide solution acetyl acetone and active baker's yeast were added and the reaction mass was further sonicated for 2.5 h. Then the filtrate on evaporation gave crude 1,4-benzothiazine (**3a**).

To see the role of baker's yeast in the oxidative cyclocondensation model reaction was carried under nitrogen atmosphere. This reaction gave good yield of 1,4-benzothiazine (**3a**). From this result it was confirmed that the role baker's yeast is crucial for catalyzing the cyclocondensation and yeast catalyzed reaction does not require air for the oxidation.

Table 2
Baker's yeast catalyzed synthesis of 1,4-benzothiazines (**3a–j**) under ultrasonic irradiation.[a]

Entry	R	R_1	R_2	Product[c]	Yield (%)[b]
1	H	CH_3	CH_3	**3a**	82
2	H	CH_3	OC_2H_5	**3b**	71
3	H	CH_3	Ph	**3c**	55
4	CH_3	CH_3	CH_3	**3d**	80
5	CH_3	CH_3	OC_2H_5	**3e**	68
6	CH_3	CH_3	Ph	**3f**	47
7	Cl	CH_3	CH_3	**3g**	66
8	Cl	CH_3	OC_2H_5	**3h**	53
9	Cl	CH_3	Ph	**3i**	51
10	H	Ph	Ph	**3j**	n.d.

n.d. = not detected.

[a] Reaction conditions: 2-aminobenzenethiols (8 mmol), 1,3-dicarbonyls (8 mmol), baker's yeast (2 g) in MeOH (25 mL) at 25–30 °C for 3 h.

[b] Yield refers to isolated products.

[c] Physical constants and spectral data of all compounds are in accordance with earlier observations [26].

The mechanism of the cyclocondensation of 2-aminothiophenols and 1,3-dicarbonyls, carried in the presence of oxidants leading to 1,4-benzothiazines has been already established [24] and it is confirmed that the oxidants initially oxidize 2-aminothiophenols to respective disulfides which subsequently undergo the cyclocondensations with the 1,3-dicarbonyls to give the desired 1,4-benzothiazines.

Baker's yeast has variety of enzymes [14,25]. Amongst them NAD^+/FAD dependant oxidoreductases are widely employed in organic synthesis. The conversion of 2-aminobenzenethiols into corresponding disulfides would have taken place because of oxidative co-enzymes, NAD^+/FAD, produced by baker's yeast. The oxidants might be abstracting hydride ion from one of the thiol molecules and then the mercapto group of other molecules would be nucleophilicaly attack on the electron deficient sulfur to form intermediates, disulfides (**4**). The yeast enzyme(s) has site of polyactivations. Probably these sites might be helping for the activation of 1,3-dicarbonyls by forming 1,3-dicarbonyl: enzyme noncovalent complexes. This might be helping to enhance localized concentration of the 1,3-dicarbonyls. In view of this, the rate of the condensation of the disulfides and 1,3-dicarbonyls would have been increased, resulting into 1,4-benzothiazines (**3a–j**). A proposed mechanistic path is presented in Fig. 1.

4. Conclusions

First time we have demonstrated the use of baker's yeast as whole cell biocatalyst to accelerate the oxidative cyclization of 2-aminibenzenethiols and 1,3-dicarbonyl compounds in an organic medium, carried for obtaining 1,4-benzothiazines. The role of ultrasonication in expedition of the biocatalyzed cyclocondensation has

also been mentioned. The principle of this strategy could be useful for another type of reactions. Further such types of investigations are underway in our laboratory and will be reported in due course.

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