Journal of Molecular Catalysis B: Enzymatic 68 (2011) 94–97

Contents lists available at ScienceDirect

Journal of Molecular Catalysis B: Enzymatic

journal homepage: www.elsevier.com/locate/molcatb

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

Umesh R. Pratap, Dhanaji V. Jawale, Balaji S. Londhe, Ramrao A. Mane*

Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431 004, MS, India

ARTICLE INFO

Article history:
Received 16 May 2010
Received in revised form
23 September 2010
Accepted 29 September 2010
Available online 7 October 2010

Keywords:
Baker's yeast, 1,4-Benzothiazine
Ultrasonication
Cyclocondensation
2-Aminothiophenol

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.

* Corresponding author. Tel.: +91 240 240311; fax: +91 240 2400291.
E-mail address: manera@indiatimes.com (R.A. Mane).

1381-1177/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcatb.2010.09.018

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**)

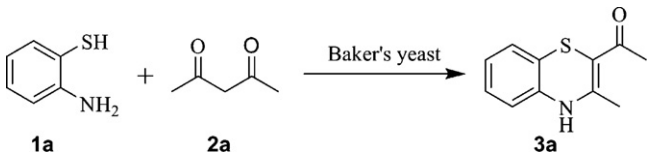
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, 3H), 2.08 (s, 3H), 2.38 (s, 3H), 4.13 (q, 3H), 6.15 (S, 1H, NH), 7.15 (d, J = 8.0 Hz, 1H), 7.24 (t, 1H, J = 4.0 and 8.0 Hz, 1H), 7.63 (d, J = 4.0 Hz, 1H).

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].