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Bakers' yeast catalyzed synthesis of benzothiazoles in an organic medium

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ABSTRACT

The cyclocondensation of 2-aminothiophenol and aldehydes has been carried out in dichloromethane using bakers' yeast as a catalyst for obtaining 2-aryl/heteryl benzothiazoles in good yields.

1. Introduction

Benzothiazoles bearing substituents at C_2 position are of great interest as these structural frameworks have proved to be an important class of privileged bicyclic substructures owing to their potent utility as imaging agents for β-amyloid, antituberculotic, chemiluminescent agents, calcium channel antagonists, antitumour, antiparasitics and photosensitizers.[1–6]

Numerous methods have been reported for the synthesis of benzothiazoles. The most commonly used method involves the condensation of 2-aminothiophenol with substituted nitriles, carboxylic acids, aldehydes, acyl chlorides or esters.[7] A number of catalysts, namely, (pmIm)Br,[8] I_2,[9] $ZrOCl_2{\cdot}8H_2O$,[10] TMSCl,[11] H_2O,[12] PCC[13] and CAN[14] have been used in the cyclocondensation of 2-aminothiophenol and aldehydes. The other route is based on Jacobson's cyclization of thiobenzanilides.[15] But this route requires a multistep reaction sequence. Many of these methods have disadvantages such as drastic reaction conditions, tedious work-up, possibility of side reactions and generation of acidic/metallic wastes. Therefore, it was felt that there is an urgent need to overcome the above limitations by developing an efficient and convenient methodology for the synthesis of benzothiazoles.

Biocatalysis represents an effective and preferable alternative to the standard synthesis of fine chemicals and optically active compounds. Biocatalysts are excellent catalysts as they can perform regio- and stereo-specific reactions under mild conditions and can accept non-natural compounds as substrates. Biocatalyzed conversions with living cells (whole-cell) with the ability to regenerate their own respective cofactors are frequently more advantageous.[16]

The use of bakers' yeast (whole-cell biocatalyst) to perform functional group transformations of compounds has become a well established and valuable methodology in organic syntheses.[17] Bakers' yeast (*Saccharomyces cerevisiae*) is a very effective biocatalyst for the reduction of ketones to optically active alcohols,[18] reduction of the C–C double bond,[19] regioselective reduction of nitro compounds,[20] reduction of β-ketoester to β-hydroxy esters,[21] oxidation of sulfide to sulfoxide,[22] acyloin condensation reaction, etc.[23]

Bakers' yeast has been extensively used to carry out various organic transformations and can be used in the synthesis of heterocyclic compounds such as isoxazolines,[24] 1,4-dihydropyridines,[25] 3,4-dihydro-pyrimidine-2-(1*H*)-ones[26] and polyhydroquinolines.[27] Csaba and co-workers reported the formation of 2-furylbenzothiazoles from furylthioanilides by employing bakers' yeast.[28]

The majority of bakers' yeast-mediated organic reactions have been conducted in an aqueous medium to retain its activity. An aqueous medium is not applicable for dehydration reactions and therefore the use of enzymes in organic solvents is gaining much importance.[29] Biocatalysis in organic solvents have numerous advantages such as (i) high solubility of most organic compounds in organic solvents, (ii) ability to carry out reactions which are impossible in water, (iii) relative ease of product recovery from organic solvents and (iv) insolubility of enzymes in organic solvents which permits their easy recovery and reuse, thus eliminating the need for immobilization.

Considering all the above facts, we turned our attention to developing an efficient methodology for the cyclocondensation of 2-aminothiophenol with aldehydes in non-aqueous media (organic

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solvents) under relatively mild reaction conditions by using an easily available, cheaper biocatalyst, that is, bakers' yeast. To the best of our knowledge, the synthesis of benzothiazoles by the cyclocondensation of 2-aminothiophenol and aldehydes mediated by bakers' yeast has not been previously reported.

2. Results and discussion

Herein, we report an efficient and economic synthesis of 2-arylbenzothiazoles under relatively milder reaction conditions by employing yeast. It was interesting to observe that benzothiazoles were synthesized in good yields catalyzed by dry bakers' yeast in dichloromethane. In order to get the best experimental condition, we have considered the reaction of *p*-anisaldehyde and 2-aminothiophenol in the presence of bakers' yeast as a standard model reaction.

To evaluate the effect of the solvent, we carried out the model reaction in different solvents namely water (H_2O), ethanol/water, ethanol (EtOH), methanol (MeOH), 1,4-dioxane, acetonitrile (ACN), N,N-dimethylformamide (DMF) and dichloromethane (DCM). The use of water or water/ethanol as solvent gave poor yields. (Table 1, entries 1 and 2). Solvents like ethanol, methanol, 1,4-dioxane, acetonitrile, DMF gave moderate yields (Table 1, entries 3–7). When the reaction was run in dichloromethane, the yield of benzothiazole was found relatively better (Table 1, entry 8). Therefore, dichloromethane was selected as a solvent for this reaction.

To examine the catalytic efficiency of bakers' yeast, the model reaction was run in the absence of yeast in dichloromethane. There was no conversion even after 40 h.

To generalize our methodology with respect to aldehydes, we have synthesized several 2-arylbenzothiazoles by the reactions of various aldehydes and 2-aminothiophenol using bakers' yeast in dichloromethane, Scheme 1 (Table 2).

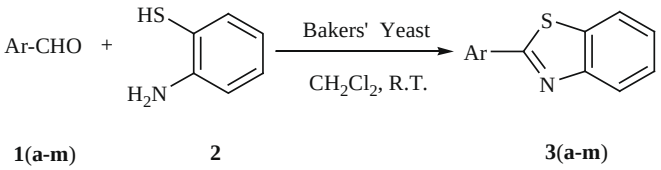
A variety of aldehydes containing electron-donating and electron-withdrawing groups were successfully employed to prepare corresponding benzothiazoles. No significant substituent effect was observed on the yields of the products. It can be seen further that 2-arylbenzothiazole bearing nitro functionality on the aryl ring was obtained in good yields (Table 2, entries 10 and 11). Under the reaction conditions, no expected reduction of nitro functionality was observed. Encouraged by these results, we have also carried out the cyclocondensation of some heterocyclic aldehydes, that is, pyridine-2-carboxaldehyde and furfuraldehyde with 2-aminothiophenol to obtain the respective benzothiazoles (Table 2, entries 12 and 13) in moderate yields.

Bakers' yeast is a known source of extracellular enzymes. These enzymes might be accelerating the cyclocondensation of 2-aminothiophenol and aldehydes by forming either an initial enzyme–2-aminothiophenol non-covalent complex or an enzyme–aldehyde complex, resulting in intermediate benzothiazolines **4**. The coenzymes, nicotinamide adenosine dinucleotide /flavin adenosine dinucleotide-dependent oxidoreductase available in bakers' yeast,[28] may be catalyzing the aromatization of **4** by dehydrogenation involving hydride ion transfer and the subsequent abstraction of a proton (Scheme 2). The second step could be a rate determining step. The intermediate **4** may have better solubility in DCM compared to other solvents, thus permitting better interaction with the cofactors resulting in high yields of the benzothiazoles.

Table 1
Effect of solvent on the synthesis of 2-(4-methoxy phenyl)-benzothiazole catalyzed by bakers' yeast

Entry	Solvent	Yield[a] (%)
1	H_2O	22
2	EtOH:H_2O	30
3	EtOH	57
4	MeOH	59
5	1,4-Dioxane	55
6	ACN	62
7	DMF	71
8	DCM	80

[a] Isolated yields.



1(a-m) **2** **3(a-m)**

Scheme 1.

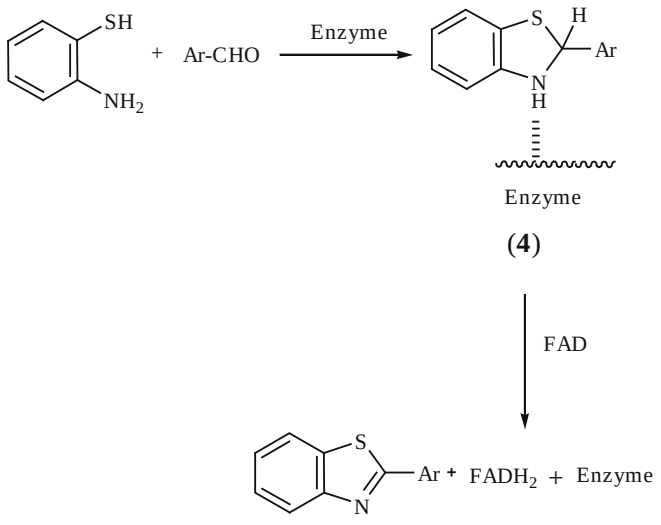
Table 2
Synthesis of 2-arylbenzothiazole derivatives catalyzed by bakers' yeast

Entry	Ar	Product[b]	Yields[a] (%)	Ref.
1	4-$OCH_3C_6H_4$	3a	80	11
2	$-C_6H_5$	3b	75	11
3	4-$N(CH_3)_2$ C_6H_4	3c	79	11
4	4-$CH_3C_6H_4$	3d	67	30c
5	2-OH C_6H_4	3e	69	30d
6	2-ClC_6H_4	3f	72	30a
7	4-ClC_6H_4	3g	84	30b
8	4-BrC_6H_4	3h	82	30b
9	4-FC_6H_4	3i	74	30b
10	3-$NO_2C_6H_4$	3j	71	30a
11	4-$NO_2C_6H_4$	3k	77	30a
12	2-pyridyl	3l	51	11
13	2-furyl	3m	57	28

[a] Isolated yields.
[b] Products were characterized by comparison of their ^{1}H NMR, MS[31] and melting points with those reported in the literature.

3. Conclusion

In summary, here we can claim that for the first time bakers' yeast has been successfully employed to catalyze the condensation of 2-aminothiophenol and aldehydes in DCM to yield 2-substituted benzothiazoles in moderate to good yields under mild reaction condition. This protocol is user-friendly and could be an attractive



Scheme 2.

tool for the synthesis of highly functionalized bioactive benzothiazoles.

4. General experimental procedure for 2-substituted benzothiazoles

A mixture of an aldehyde (8 mmol), 2-aminothiophenol (8 mmol), bakers' yeast (2 g), was stirred at room temperature for 24 h in DCM. The progress of the reaction was monitored by thin layer chromatography, using petroleum ether/ethyl acetate (7:3) as a solvent system. After completion of the reaction, bakers' yeast was filtered through a bed of Celite, and the filtrate was concentrated under reduced pressure. On cooling, the solid product obtained was separated and crystallized from ethanol to afford the pure benzothiazole.

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31. Spectral data for selected compounds: Compound **3a**: 1H NMR (DMSO-d_6, 400 MHz) δ: 3.85 (s, 3H), 7.1 (d, J = 8.8 Hz, 2H), 7.4 (t, J = 7.6 Hz, 1H), 7.5 (t, J = 8 Hz, 1H), 8.0 (d, 1H), 8.05 (d, J = 8.2, 2H), 8.1 (d, J = 7.6 Hz, 1H). MS (ESI): m/z = 242.1 (M+H). Compound **3e**: 1H NMR (DMSO-d_6, 400 MHz) δ: 7.0 (t, J = 7.6 Hz, 1H), 7.1(d, J = 8 Hz, 1H), 7.4 (m, 2H), 7.5 (t, J = 7.1, 1H), 8.05 (d, 1H), 8.1 (m, 2H), 11.1 (s, 1H). MS (ESI): m/z = 228.1 (M+H).