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The Production of Benzothiazoles in an Organic Solvent DMF Catalyzed by Baker's Yeast

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Abstract: ***Benzothiazoles are an important class of privileged organic compounds of medicinal significance due to their recognized biological and therapeutic activities. As such, these heterocycles constitute key structural motifs that exhibit a wide range of biological properties. Benzothiazoles are bicyclic ring systems. In the 1950s, a number of benzothiazoles were intensively studied as central muscle relaxants. Since then medicinal chemists have not taken active interest in this chemical family. Biologist's attention was drawn to this series when the pharmacological profile of Riluzole was discovered. Riluzole is a drug used to treat amyotrophic lateral sclerosis. After that, benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activities.1 A large number of therapeutic agents are synthesized with the help of benzothiazole nucleus. During recent years there have been some interesting developments in the biological activities of benzothiazole derivatives. These compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities.2 The 2 - Substitued benzothiazole has emerged in its usage as a core structure in the diversified therapeutic applications. The studies of structure–activity relationship interestingly reveal that change of the structure of substituent group at C - 2 position commonly results the change in its bioactivity. It shows different properties like Anti - cancer[3 - 4], Anti - bacterial[5, 6, 7], Anti - tuberculosis[8], Anti - diabetic, Anti - inflammatory[9 - 12], Anti - viral, Anti - oxidant[13 - 15]. In the present work an efficient and cost effective synthetic protocol have been developed for 2 - arylbenzothiazoles using milder reaction conditions, carrying the condensation of 2 - aminothiophenols and aryl aldehydes in organic solvent medium like DMF inpresence of active dry baker's yeast.***

Keywords: Benzothiazole, Anti - inflammatory, Anti - bacterial, Baker's yeast, DMF etc

1. Introduction

Benzothiazole is a fascinating organic compound belonging to the family of bicyclic heterocycles. Its core structure consists of a benzene ring fused to a five - membered thiazole ring, containing both nitrogen and sulfur atoms. This unique arrangement gives benzothiazole a diverse range of properties and applications. It is found naturally in some foods and even in certain marine organisms. It's used as a food additive due to its distinctive sulfurous odor and meaty flavor. Benzothiazole derivatives play a crucial role in the rubber industry as vulcanization accelerators, improving the properties of rubber products. They are also employed as antioxidants to prevent oxidative degradation. Some benzothiazole derivatives act as plant growth regulators, influencing plant development. Benzothiazole and its derivatives exhibit a wide spectrum of biological activities, making them valuable in medicinal chemistry. Some benzothiazole compounds show promising anti - cancer properties, targeting various cancer cell lines. They possess antibacterial activity, inhibiting the growth of bacteria. Certain benzothiazole derivatives are effective against Mycobacterium tuberculosis, the bacteria responsible for tuberculosis. These compounds have shown potential in managing diabetes by regulating blood sugar levels. Benzothiazole derivatives can reduce inflammation, making them useful in treating inflammatory diseases. Some derivatives exhibit antiviral activity, inhibiting the replication of viruses. They possess antioxidant properties, protecting cells from oxidative damage.

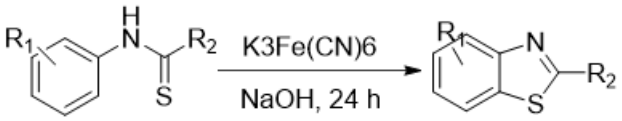
These structural frameworks have potent utility as imaging agents for β - amyloids, antituberculotics, chemiluminescents, calcium channel antagonists, antiparasitics and photosensitizers.1[6] The benzothiazole moiety with some substitution shows promising antitumor activity. Aminomethylphenyl, carbonitrile and bis amidino substituted 2 - styryl benzothiazoles show selective growth inhibitory properties against human cancer cell lines[17] proliferation of cells[18] and cytostatisis[19] respectively. Several chlorinated and fluorinated derivatives of this moiety exhibit excellent *in vitro* as well as *in vivo* antitumor activity.

2. Literature Review

These wide biological and synthetic applications have prompted organic chemists to develop convenient synthetic methodologies for obtaining variety of the benzothiazoles. There are numerous methods reported to construct this value added heterocyclic system. Following is a brief review on the methods, practiced for obtaining 2 - aryl benzothiazoles.

1) Jacobson cyclization

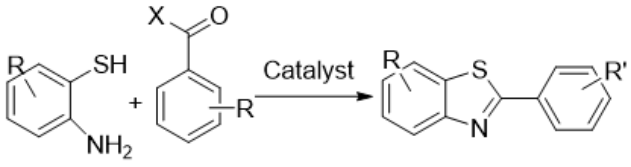
Simple and effective method to synthesize benzothiazole derivatives includes thecyclization (Jacobson cyclization, **Scheme 1**) of substituted thiobenzanilidine (in the presence of aqueous sodium hydroxide and potassium ferricyanide). But this route requires a multistep reaction sequence.2[0]



Scheme 1

2) Condensation of 2 - aminothiophenols

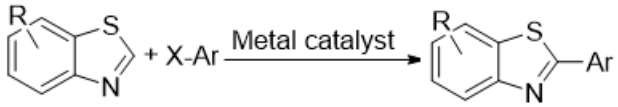
The most widely used method involves the condensation of 2 - aminothiophenol with substituted nitriles, carboxylic acids, aldehydes, acyl chlorides or esters (**Scheme2).** A number of catalysts, namely, (pmIm) Br, I_2, $ZrOCl_2$: $8H_2O$, TMSCl, H_2O, PCC, CAN, PTSA, SDS, cyclodextrin, CTAB, P_2O_5/MW, H_2O_2/HCl, phosphoric acid,, have been used in the cyclo condensation of 2 - aminothiophenol and aldehydes.[2] [1 - 26]



X = H, Cl, OH, OEt

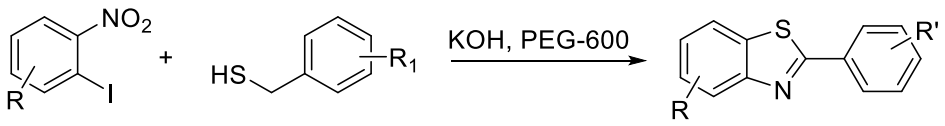
Scheme 2

3) **Direct arylation at 2 - position of benzothiazoles (Scheme 3)** by employing various metal catalyst viz. Pd (OAc) 2, NiBr2, PXPd/Cu (Xantphos) I (dichlorobis (chloro - di - tert - butylphosphine) palladium CuI /PPh3 and copper oxide has also been reported.[27 - 29]



Scheme 3

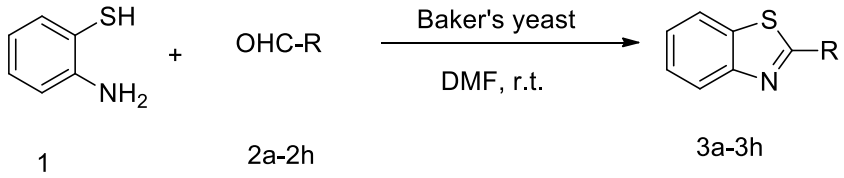
Recently the cross - coupling condensation of nitro - substituted aryl halides with benzylthiols using KOH and polyethylene glycol has been demonstrated to afford benzothiazole derivatives via a novel synthetic pathway. This condensation has been found to be completed within 2 h at room temperature.[30] (Scheme 4)



Scheme 4

3. Methodology

In the present work an efficient and cost effective synthetic protocol have been developed for 2 - arylbenzothiazoles using milder reaction conditions, carrying the condensation of 2 - aminothiophenols and aryl aldehydes in organic medium in presence of active dry baker's yeast. It was observed that the yields of benzothiazoles were found to be better.



1 2a-2h 3a-3h

Scheme: I

Experimental Section:

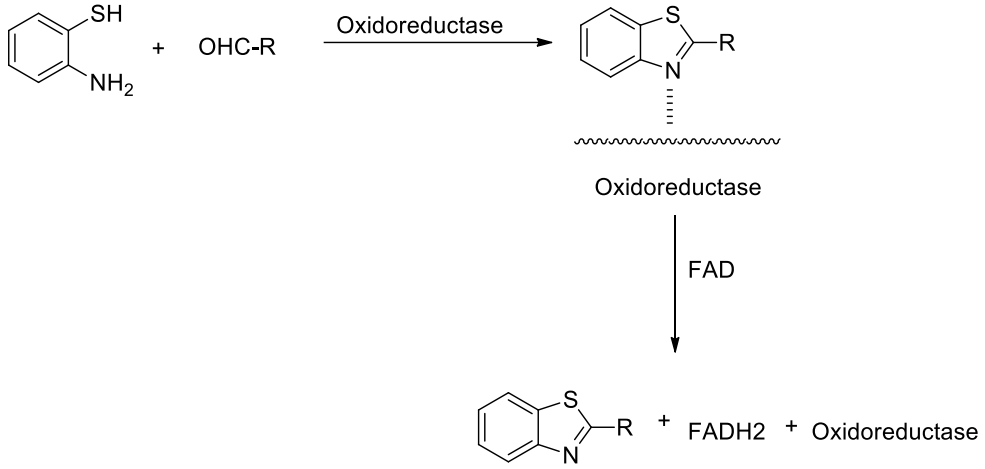
General procedure for the synthesis 2 - substituted benzothiazoles (3a - 3h):

A mixture of aldehydes (8 mmol), 2 - aminothiophenol (8 mmol), baker's yeast (2 g), was stirred at room temperature in DMF (25 mL). The progress of the reaction was monitored by thin layer chromatography, using petroleum ether/ethyl acetate (7: 3) as a solvent system. After 24 h of stirring reaction mass was filtered through a bed of celite to remove the baker's yeast as a residue and the filtrate was concentrated under reduced pressure. On cooling, the solid product obtained was separated and crystallized from ethanol to afford the pure benzothiazoles (**Table 2**).

4. Result and Discussion

In order to find the best experimental conditions, the cyclocondensation of *p*anisaldehyde and 2 - aminothiophenol, carried in the presence of baker's yeast was considered as standard model reaction. To evaluate the effect of the solvents, the model reaction was run in different solvents namely water (H2O), ethanol/water, ethanol (EtOH), methanol (MeOH), 1, 4 - dioxane, acetonitrile (ACN) and N, Ndimethylformamide (DMF). The use of water orwater/ethanol as solvent gave poor yields. Solvents like ethanol, methanol, 1, 4 - dioxane, acetonitrile gave moderate yields. When the reaction was run in N, Ndimethylformamide (DMF), the yield of benzothiazole was found relatively better. Therefore, N, Ndimethylformamide (DMF) was selected as a solvent for this reaction. To examine the catalytic efficiency of baker's yeast, the model reaction was then run in the

absence of yeast in dichloromethane. There was no conversion even after 40h. To generalize our methodology with respect to aldehydes, we have synthesized several 2 - arylbenzothiazoles by the reactions of various aldehydes and 2 - aminothiophenol using baker's yeast in N, Ndimethylformamide (DMF). A variety of aldehydes containing electron donating and electron withdrawing groups were successfully employed to prepare corresponding benzothiazoles. Here for the first time bakers' yeast has been successfully employed to catalyze the condensation of 2 - aminothiophenol and aldehydes in N, Ndimethylformamide (DMF) to yield 2 - substituted benzothiazoles in moderate to good yields under mild reaction condition. This protocol is user - friendly and could be an attractive tool for the synthesis of highly functionalized bioactive benzothiazoles.



Mechanism for the formation of benzothiazole.

Table 1: Effect of solvents on the synthesis of 2 - (4 - methoxy phenyl) - benzothiazole, catalyzed by baker's yeast.

Entry	Solvent	Percentage yield (%)
1	H_2O	20
2	EtOH: H_2O	28
3	EtOH	59
4	MeOH	60
5	1, 4 - dioxane	58
6	ACN	64
7	DMF	75

Spectral data of representative compound of the series, 2 - (4 - methoxyphenyl) benzothiazole (3a):
1H NMR (DMSO - *d6*, 400 MHz): δ= 3.85 (s, 3H, OCH3), 7.09 (d, *J* = 8.8 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 8 Hz, 1H), 8.03 (d, 1H), 8.07 (d, *J* = 8.2, 2H) and 8.09 (d, *J* = 7.6 Hz, 1H).
13C NMR (75 MHz, CDCl3): δ= 55.6, 114.5, 121.7, 122.9, 124.9, 126.4, 126.5, 129.3, 135.0, 159.3, 162.09 and 168.0.
MS (ESI+ mode): m/z = 242.1 (M+).

Table 2: Synthesis of 2 - aryl benzothiazole derivatives catalyzed by baker's yeast (**Scheme I**).

Entry	R	Products	Percentage Yield (%)	M. P (°C)
1	4 - $OCH_3C_6H_4$	3a	85	120 - 122
2	C_6H_5	3b	78	112 - 115
3	4 - N $(CH_3)_2$ C_6H_4	3c	80	175 - 178
4	4 - $CH_3C_6H_4$	3d	70	87 - 89
5	2 - OH C_6H_4	3e	72	130 - 133
6	2 - ClC_6H_4	3f	74	72 - 75
7	4 - ClC_6H_4	3g	86	114 - 117
8	4 - BrC_6H_4	3h	84	130 - 135

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