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MECHANOCHEMICAL SYNTHESIS OF 2-ARYLBENZOTHIAZOLE USING CELLULOSE SULFURIC ACID AS A BIODEGRADABLE AND REUSABLE CATALYST

Kirti S. Niralwad

Department of Chemistry, NutanMahavidyalaya, Selu, Dist-Parbhani.
Corresponding Author-email :ghorade.ishwar@gmail.com

Abstract:-The condensation of several aromatic/heteroaromatic aldehydes with 2-aminothiophenol catalyzed by cellulose sulfuric acid in the solid-state by grinding method under solvent-free conditionafforded 2-arylbenzothiazoles. This method provides several advantages including environmental friendliness, short reaction times, high yields and a simple work-up procedure. Moreover, the catalyst was successfully reused without significant loss of activity.

Key words: 2-Arylbenzothiazoles, Aldehydes, 2-Aminothiophenol, Cellulose Sulfuric acid, Grinding.

Introduction:

Benzothiazole and their derivatives are very important groups of heterocyclic compounds,[1] and are well known for their biological and pharmaceutical activities, such as antimicrobial,[2]antiglutamate/antiparkinsonism agents[3] and antitumour,[4] which exhibit nanomolar inhibitory activity against a range of human breast, ovarian, colon and renal cell lines *in vitro*. In addition, they represent one of the most promising antiamyloid therapies for treatment of a number of a heterogeneous family of diseases referred to generically as amyloidosis, including Alzheimer's disease (AD), type II diabetes, variant Creutzfeldt-Jakob disease, painful joints associated with long term hemodialysis and rare cases of hereditary insomnia.[5,6]

In general, benzothiazoles are synthesized by condensation of 2-aminothiophenol with carboxylic acid derivatives,[7] the base induced cyclization of the corresponding 2 haloanilides,[8] or the radical cyclization of thioacylbenzanilides.[9] On the other hand, the most general synthetic approaches for 2-aryl benzothiazoles involves: (i)arylation of benzothiazole with aryl bromides at 150°C in a sealed tube catalyzed by $Pd(OAc)_2$, Cs_2CO_3 and CuBr with t-Bu_3P as ligand,[10] or Suzuki biaryl-coupling of 2-bromobenzothiazole with aryl boronic acids,[11](ii) oxidative cyclisation of phenolic Schiff's bases derived from the condensation of 2-aminothiophenols and aldehydes using various oxidants such as $Sc(OTf)_3$ using molecular oxygen,[12]pyridinium chlorochromate[13] and very recently *via* electrooxidation,[14] a modification of such strategy that involves flash vacuum pyrolysis and photolysis of 2-methylthio-*N* (arenylidene)anilines has been reported,[15](iii) condensation of 2-aminothiophenols with carboxylic acids under microwave irradiation[16] or with polymer-bound esters in the presence of a Lewis acid,[17](iv) direct condensation of 2-aminothiophenol with aromatic aldehydes[18,19] However, most of these synthetic approaches suffer from drawbacks such as harsh reaction conditions, lengthy procedures, expensive catalysts which may be harmful to the environment. As a consequence, the introductions of new methods to overcome the limitations are still an important challenge.

Mechanochemistry is characterized by the application of mechanical energy (e.g. by compression, shear, or friction) to achieve chemical transformations. It has a variety of applications in areas as diverse as nanoscience or engineering of minerals, but these aspects will not be treated here. Furthermore, it allows performing chemical reactions, serving as a complement to traditional strategies based on thermal or irradiative activation[21]. Historically, the first mechanochemical reactions were achieved by grinding reactants together with a mortar and pestle, an approach that is sometimes referred to as "grindstone chemistry". While this technique does not require specialized equipment and is therefore easy to perform in any laboratory, it has the limitations of not being practical unless reaction times are short and not being always easy to reproduce, as it is dependant on the physical strength of the operator[22].

Recently, it is shown that the use of solid acidic catalysts has gained importance in organic synthesis due to several advantages such as, operational simplicity, no toxicity, reusability, and ease of isolation after completion of the reaction. Biopolymers, especially 'cellulose' and its derivatives[23] have some unique properties, which make them attractive alternatives for conventional organic or inorganic supports for catalytic applications. Among others, they are extremely inert, inexpensive, biodegradable and environmentally benign which allows various reaction conditions to be employed. Cellulose is the most

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abundant renewable natural material in the world. It has been widely studied during the past decades because it is both biodegradable and a renewable resource.

Recently, several synthetically useful organic transformations using bio-supported, biodegradable and recyclable cellulose sulphuric acid (CSA) as a catalyst have been reported in the literature[24-26].Owing to the numerous advantages associated with this cheap and non hazardous catalyst, we have considered cellulose sulfuric acid to be an ideal heterogeneous acid catalyst for the synthesis of 2-arylbenzothiazole. Herein, we would like to report the facile and ecofriendly methodology for the synthesis of 2-arylbenzothiazole.

Experimental Section:

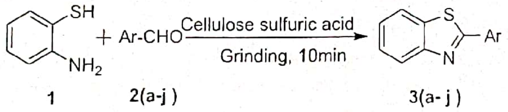
^{1}H NMR spectra were recorded on Mercury plus Varian at 400 MHz in $CDCl_3$ as a solvent and TMS as an internal standard. IR spectra were recorded on a Perkin Elmer FTIR using KBr discs. Mass spectra were recorded on Micromass Quattro II using electrospray Ionization technique. The preparation of cellulose sulphuric acid by the dropwise addition of chlorosulfonic acid to DEAE cellulose (Merck) suspended in hexane has been carried out as previously described[27]

Typical experimental procedure

A mixture of 2 aminothiophenol (1 mmol), aldehyde (1 mmol) and cellulose sulfuric acid (0.5 g) were ground at room temperature with a mortar and pestle. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 7:3). After completion of the reaction, the reaction mixture was cooled and dichloromethane (25 mL) was added. The catalyst was filtered from the reaction mixture, it was then washed with water (10 cm^3) and dried over Na2SO4. The filtrate was concentrated under vacuum to obtain the product **3(a-j)**. All the products were characterized from their spectral data.

Results and Discussion:

In continuation of our research work on the development of eco-friendly reactions[28] using novel synthetic methodologies[29], herein, we have developed methodology for the synthesis of 2-arylbenzothiazole using cellulosesulphuric acid which makes use of mild catalyst under solvent-free condition over the reported procedure as depicted in (**Scheme 1**).



Scheme 1:-Synthetic route for the synthesis of benzothiazoles

Here we have carried out the reaction of 2-aminothiophenol (**1**) and 4-methoxy benzaldehyde (**2a**) catalyzed by cellulose sulfuric acid by grinding method, has been considered as a standard model reaction.

We have screened a number of different catalysts on model reaction, herein, the result revealed that, when the reaction was carried out in the presence of NH_4VO_3, KH_2PO_4, acidic alumina, Amberlite-IR 120, sulphamic acid, it gave lower yield of product. While at the same time, when the reactions was conducted using cellulose sulfuric acid as a catalyst it gave excellent yields of product in short reaction time. (**Table 1**, entry 6).

After optimizing the screening of different catalyst, we have studied the concentration of catalyst on model reactions, with catalyst concentration 0.1, 0.2, 0.3, 0.4g the reaction was proceed with very lower yield of product, but at concentration 0.5 and 0.6 g the yield of product is excellent(**Table 2**, entry 5&6).

The generality of this method was examined by the reaction of 2-aminothiophenol and several substituted aryl/heteroaryl aldehydes withcellulose sulfuric acid as a catalyst using mortal & pistol, the results are shown in **Table 3**. Here, we have found that both aldehydes bearing electron-donating substituents (**Table 3**, entries 1, 5) and electron-withdrawing (**Table 3**, entries 3, 4) substituents gave desired benzothiazoles in excellent yields. With both electron withdrawing and electron donating groups the reaction proceeds smoothly, with a slight increase in the yield when the aryl substituents was an electron withdrawing group. It can be seen further that 2-arylbenzothiazole bearing nitro functionality on the aryl ring was obtained in good yields (**Table 3**, entries 3, 4). This method is also applicable for the reaction of heteroaromatic aldehyde with 2-aminothiophenol affording the corresponding 2-heteroaryl benzothiazoles in better yields (**Table 3**, entries 9, 10). The synthesized compounds were compared (MS, NMR, and IR) with compounds that were prepared by using the literature method.[30]This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds. The developed methodology is simple with good to excellent yields.

Our attention was then directed towards the possibility of reusability of catalyst is highly preferable for greener process. The reusability of the catalyst in the model reaction was checked as shown

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in (**Table 4**). The separated catalyst can be reused after washing with $CHCl_3$ and dried over anhydrous Na_2SO_4. The catalyst was removed in excellent yields and was used in mentioned reaction for five times, the observation revealed that as the number of the recycle of catalyst increases the activity decreases.

Table 1:-Screening of catalyst[a]

Entry	Catalyst	Time(min)	Yield[b](%)
1	NH_4VO_3	10	40
2	KH_2PO_4	10	46
3	Acidic Al_2O_3	10	55
4	Amberlite-IR 120	10	57
5	Sulphamic acid	10	60
6	Cellulose sulfuric acid	10	92

[a]Reaction conditions:- **1** (1 mmol), **2a**(1 mmol), Catalyst (0.5 g), [b]Isolated yield

Table 2:-Screening of catalystconcentration[a]

Entry	Catalyst(g)	Time(min)	Yield[b](%)
1	0.1	10	75
2	0.2	10	78
3	0.3	10	80
4	0.4	10	85
5	0.5	10	92
6	0.6	10	92

[a]Reaction conditions:- **1** (1 mmol), **2a**(1 mmol), [b]Isolated yield

Table 3:-Synthesis of 2-arylbenzothiazole[a]

Entry	Product	Ar	Time (min)	Yield (%)[b]	M.P(°C)[18]
1	**3a**	4-OCH_3-C_6H_4	9	91	121-122
2	**3b**	C_6H_5	12	90	114-115
3	**3c**	3-NO_2-C_6H_4	8	92	181-183
4	**3d**	4-NO_2-C_6H_4	7	94	226-227
5	**3e**	2-OCH_3-C_6H_4	12	89	104-105
6	**3f**	2-Cl-C_6H_4	9	87	73-75
7	**3g**	4-Br-C_6H_4	8	91	134-135
8	**3h**	4-Cl-C_6H_4	10	90	117-118
9	**3i**	2-Thienyl	9	91	101-102
10	**3j**	2-Pyridyl	10	92	135-137

[a]Reaction conditions:- **1** (1 mmol), **2 (a-j)**(1 mmol), catalyst (0.5 g), [b]Isolated yield.

All the compounds characterised by their spectroscopy method ^{1}HNMR, Mass, IR and melting point and compare to their authentic sample[30]

Table 4: Synthesis of 2-arylbenzothiazoles **3a** with recovery of catalyst.

Cycle	Fresh	First	Second	Third	Fourth
Yield (%)[a]	91	88	87	86	86

[a]Isolated yield.

Conclusions:

In conclusion, cellulose sulfuric acid was found to be an efficient catalyst for the reaction of 2-aminothiophenol and several substituted aryl/heteroaryl aldehydes to afford the corresponding 2-arylbenzothiazole in good to excellent yields. The main advantages of the present synthetic protocol are mild, solvent-free conditions, ecofriendly catalyst and easy reaction work-up procedure. It is expected that the present methodology will find application in organic synthesis

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30.**Spectral Data of Principal Compounds.** (3a) 2-(4-Methoxyphenyl)-1,3-benzothiazole : IR (ν_{max}, KBr, cm^{-1}): 3104, 3062, 1605, 1585; ^{1}H-NMR: δ 8.11 (d, *J* = 7.6 Hz, 1H, Ar-H); 8.03-8.10 (m, 3H, Ar-H), 7.55 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.44 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.10 (d, *J* = 7.8 Hz, 2H, Ar-H), 3.85 (s, 3H, OCH$_3$), MS m/z 241 (M+1). (3b): 2-Phenyl-1,3-benzothiazole: IR (ν_{max}, KBr, cm^{-1}): 3070, 3015, 1610, 1585; ^{1}H-NMR: δ 8.15 (d, *J* = 7.8 Hz, 1H, Ar-H); 8.10-8.12 (m, 3H, Ar-H), 7.55-7.60 (m, 4H, Ar-H), 7.50 (t, *J* = 7.8 Hz, 1H, Ar-H), MS m/z 211 (M+1). **(3d):** 2-(4-Nitrophenyl)-1,3-

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benzothiazole: IR (ν_{max}, KBr, cm^{-1}): 3088, 3032, 1620, 1581; ^{1}H-NMR: δ 8.8 (d, J = 8.0 Hz, 2H, Ar-H); 8.30 (d, J = 8.0 Hz, 2H, Ar- H); 8.25 (d, J = 8.0 Hz, 1H, Ar-H); 8.06 (d, J = 8.0 Hz, 1H, Ar-H); 7.44-7.49 (m, 2H, Ar-H); MS m/z 256.(M+1). (3i): 2-Thienyl-1,3-benzothiazole: IR (ν_{max}, KBr, cm^{-1}): 3082, 3043, 1623; ^{1}H-NMR: δ 8.22 (d, J = 8.0 Hz, 1H, Ar-H); 8.15 (d, J = 8.0 Hz, 1H, Ar-H); 7.75 (d, J= 4.0 Hz, 1H, thiophene CH); 7.70 (d, J = 4.0 Hz, 1H, thiophene CH); 7.60-7.63 (m, 2H, Ar-H); 7.35 (t, J = 4.0 Hz, 1H, thiophene CH): MS m/z 217.0 (M+1).