

Solid-Phase Synthesis of 2-Arylbenzothiazole Using Silica Sulfuric Acid under Microwave Irradiation

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The condensation of several aromatic/heteroaromatic aldehydes with 2-aminothiophenol catalyzed by silica sulfuric acid under microwave irradiation afforded 2-arylbenzothiazoles in high yields and short reaction times under solvent-free conditions. The major advantages of the present method are good yields, ecofriendly, reusable catalyst, mild and solvent-free reaction conditions.

Key Words: 2-Arylbenzothiazoles, Aldehydes, 2-Aminothiophenol, Silica sulfuric acid, Microwave-irradiation

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 agents³ 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 anti-amyloid 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 thioacylbenzylidene.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, Cs₂CO₃ and CuBr with *t*-Bu₃P 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 chlorochromate¹³ 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 irradiation¹⁶ or with polymer-bound esters in the presence of a Lewis acid,¹⁷ (iv) direct condensation of 2-aminothiophenol with aromatic aldehydes,^{18,19} under microwave-irradiation.²⁰⁻²² 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.

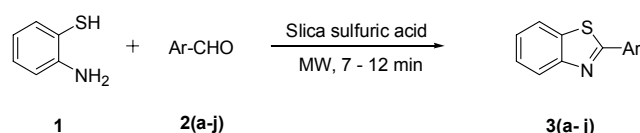
The science of green chemistry is developed to meet the increasing demand of environmentally benign chemical processes. The application of microwaves (MWs), as an efficient heating source for organic reactions and it has been reported in the literature.²³ The main advantages of MW irradiation usage were: very short reaction time and the solvent less procedures which are eco-friendly.^{24,25} To the best of our knowledge MW irradiation has been mostly reported as a heating technique particularly for low molecular weight compound chemical modifications.

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. Silica sulfuric acid has emerged as an efficient heterogeneous catalyst in which sulfuric acid is immobilized on the surface of silica gel *via* covalent bond has the prospect to be used as a substitute for sulfuric acid. The use of silica sulfuric acid as a catalyst that meets the demand for various chemical transformations such as synthesis of thionitrites,²⁶ synthesis of Beckmann rearrangement,²⁷ deprotection of acetals,²⁸ and sulfonation of aromatic rings.²⁹ Owing to the numerous advantages associated with this cheap and non hazardous catalyst, we have considered silica 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

Microwave oven (LG Smart Chef MS-255R operating at 2450 MHz having maximum out put power of 960 W) was used for microwave irradiation. ¹H NMR spectra were recorded on Mercury plus Varian at 400 MHz in CDCl₃ 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.

Typical experimental procedure. A mixture of 2-aminothio-

**Scheme 1.** Synthetic route for the synthesis of benzothiazoles

phenol (1 mmol), aldehyde (1 mmol) and silica sulfuric acid (100 mg) were taken in a beaker (50 mL). The reaction mixture was mixed properly with the help of glass rod and irradiated in a microwave oven at 45W, for the time indicated in Table 2. 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 cm³) and dried over anhydrous CaCl₂. The filtrate was concentrated under vacuum to obtain the product **3(a-j)**. All the products were characterized from their spectral data.^{32p}

Results and Discussion

In continuation of our research work on the development of novel synthetic methodologies, using solid acid catalyst³⁰ and microwave irradiation techniques,³¹ herein, we have developed methodology for the synthesis of 2-arylbenzothiazole using silica sulphuric acid which makes use of mild catalyst under solvent-free condition over the reported procedure as depicted in (Scheme 1).

Here we have carried out the reaction of 2-aminothiophenol (**1**) and 4-methoxy benzaldehyde (**2a**) catalyzed by silica sulfuric acid under microwave irradiation, it 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 KH₂PO₄, NH₄VO₃, acidic alumina, Amberlite-IR 120, sulphamic acid under microwave-irradiation it gave lower yield of product even after prolonged reaction time. While at the same time, when the model reaction was carried out under reflux condition it gave comparatively low yields of products. However when the same reactions was conducted under microwave irradiation using silica sulfuric acid as a catalyst it gave excellent yields of product in short reaction time. (Table 1, entry 6).

After optimizing the catalyst, the generality of this method was examined by the reaction of 2-aminothiophenol and several substituted aryl/heteroaryl aldehydes using silica sulfuric acid as a catalyst under microwave-irradiation, the results are shown in Table 2. Here, we have found that both aldehydes bearing electron-donating substituents (Table 2, entries 1, 5) and electron-withdrawing (Table 2, 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 2, entries 3, 4). This method is also applicable for the reaction of heteroaroma-

Table 1. Screening of catalyst^a

| entry | catalyst | Under MW | | Under reflux | |
|-------|---------------------------------------|------------|------------------------|--------------|------------------------|
| | | time (min) | yield (%) ^b | time (h) | yield (%) ^b |
| 1 | KH ₂ PO ₄ | 10 | 32 | 5 | 26 |
| 2 | NH ₄ VO ₃ | 10 | 53 | 5 | 46 |
| 3 | Acidic Al ₂ O ₃ | 10 | 57 | 5 | 45 |
| 4 | Amberlite-IR 120 | 10 | 64 | 5 | 51 |
| 5 | Sulphamic acid | 10 | 70 | 5 | 58 |
| 6 | Silica sulfuric acid | 10 | 91 | 5 | 76 |

^aReaction conditions: **1** (1 mmol), **2a** (1 mmol), Catalyst (100 mg), ^bIsolated yield.

Table 2. Synthesis of 2-arylbenzothiazole^a

| entry | product | Ar | time (min) | yield (%) ^b | mp (°C) ¹⁸ |
|-------|-----------|---------------------------------------------------|------------|------------------------|-----------------------|
| 1 | 3a | 4-OCH ₃ -C ₆ H ₄ | 9 | 91 | 120 - 122 |
| 2 | 3b | C ₆ H ₅ | 12 | 90 | 113 - 114 |
| 3 | 3c | 3-NO ₂ -C ₆ H ₄ | 8 | 92 | 181 - 182 |
| 4 | 3d | 4-NO ₂ -C ₆ H ₄ | 7 | 94 | 226 - 228 |
| 5 | 3e | 2-OCH ₃ -C ₆ H ₄ | 12 | 89 | 103 - 105 |
| 6 | 3f | 2-Cl-C ₆ H ₄ | 9 | 87 | 72 - 74 |
| 7 | 3g | 4-Br-C ₆ H ₄ | 8 | 91 | 133 - 134 |
| 8 | 3h | 4-Cl-C ₆ H ₄ | 10 | 90 | 116 - 118 |
| 9 | 3i | 2-Thienyl | 9 | 91 | 100 - 102 |
| 10 | 3j | 2-Pyridyl | 10 | 92 | 135 - 136 |

^aReaction conditions: **1** (1 mmol), **2(a-j)** (1 mmol), catalyst (100 mg).

^bIsolated yield. All the compounds characterised by their spectroscopy method ¹HNMR, Mass, IR and melting point and compare to their authentic sample¹⁸

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

| cycle | fresh | first | second | third | fourth |
|------------------------|-------|-------|--------|-------|--------|
| Yield (%) ^a | 91 | 88 | 85 | 79 | 76 |

^aIsolated yield.

tic aldehyde with 2-aminothiophenol affording the corresponding 2-heteroaryl benzothiazoles in better yields (Table 2, entries 9, 10). The synthesized compounds were compared (MS, NMR, and IR) with compounds that were prepared by using the literature method.¹⁸ 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 in (Table 3). The separated catalyst can be reused after washing with CHCl₃ and dried over anhydrous CaCl₂. 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.

Conclusions

In conclusion, silica 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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- Spectral Data of Principal Compounds (**3a**): 2-(4-Methoxyphenyl)-1,3-benzothiazole: IR (ν_{\max} , KBr, cm^{-1}) 3105, 3060, 1604, 1585; $^1\text{H-NMR}$ δ 8.11 (d, $J = 7.6$ Hz, 1H, Ar-H); 8.01-8.10 (m, 3H, Ar-H), 7.53 (t, $J = 8.0$ Hz, 1H, Ar-H), 7.43 (s, $J = 7.8$ Hz, 1H, Ar-H), 7.12 (d, $J = 7.8$ Hz, 2H, Ar-H), 3.87 (s, 3H, OCH_3), MS m/z 241 (M+1). (**3b**): 2-Phenyl-1,3-benzothiazole: IR (ν_{\max} , KBr, cm^{-1}) 3068, 3015, 1609, 1588; $^1\text{H-NMR}$ δ 8.16 (d, $J = 7.8$ Hz, 1H, Ar-H); 8.07-8.12 (m, 3H, Ar-H), 7.54-7.60 (m, 4H, Ar-H), 7.48 (t, $J = 7.8$ Hz, 1H, Ar-H), MS m/z 211 (M+1). (**3d**): 2-(4-Nitrophenyl)-1,3-benzothiazole: IR (ν_{\max} , KBr, cm^{-1}) 3088, 3032, 1618, 1582; $^1\text{H-NMR}$ δ 8.9 (d, $J = 8.0$ Hz, 2H, Ar-H); 8.32 (d, $J = 8.0$ Hz, 2H, Ar-H); 8.23 (d, $J = 8.0$ Hz, 1H, Ar-H); 8.02 (d, $J = 8.0$ Hz, 1H, Ar-H); 7.44-7.53 (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; $^1\text{H-NMR}$ δ 8.22 (d, $J = 8.0$ Hz, 1H, Ar-H); 8.13 (d, $J = 8.0$ Hz, 1H, Ar-H); 7.74 (d, $J = 4.0$ Hz, 1H, thiophene CH); 7.69 (d, $J = 4.0$ Hz, 1H, thiophene CH); 7.54-7.63 (m, 2H, Ar-H); 7.33 (t, $J = 4.0$ Hz, 1H, thiophene CH); MS m/z 217.0 (M+1).