



Ammonium chloride; as a mild and efficient catalyst for the synthesis of some 2-arylbenzothiazoles and bisbenzothiazole derivatives

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ABSTRACT

An efficient protocol has been developed for the preparation of a series of 2-arylbenzothiazoles derivatives from condensation of 2-aminothiophenol with aromatic aldehydes using ammonium chloride, which is a very inexpensive, metal-free and readily available reagent. The target compounds were obtained in good to excellent yields (58-92%) under fairly mild reaction conditions at room temperature.

1. Introduction

The 2-substituted benzothiazoles moiety is very interesting in the area of medicinal and biological chemistry. The benzothiazolyl system possesses highly selective and potent antitumor activity. Also, the 2-(4-dimethylamino phenyl)-benzothiazole is an integral component used for the treatment of Alzheimer disease. The presence of the benzo thiazole nucleus is essential in the thermally stable rigid-rod polymers with high tensile strength and modulus. They have also found applications in industry as antioxidants, antifungal-vulcanization accelerators, and as a dopant in a light-emitting organic electroluminescent device [1-3]. Thus, the synthesis of this benzothiazole moiety is always a great challenge.

In general, benzothiazoles are synthesized by condensation of 2-aminothiophenol with carboxylic acid derivatives [4], one-pot reaction of 2-aminothiophenol with β -chlorocinam aldehydes using *p*-TsOH [5], condensation of 2-aminothiophenol with acid chlorides [6], esters [7], arylation of benzothiazoles with aryl bromides at 150 °C in a sealed tube catalyzed by Pd(OAc)₂, Cs₂CO₃, and CuBr with P(*t*-Bu)₃ as ligand [8], multistep synthetic approaches of 2-arylbenzothiazoles [9] or Suzuki biaryl coupling of 2-arylbenzothiazoles with aryl boronic acid [10].

On the other hand, the most general synthetic approach for synthesis of 2-arylbenzothiazoles involves condensation of 2-aminothiophenols with aldehydes using various oxidants such as MnO₂/SiO₂ [11], *p*-TsOH or graphite on the surface of solid mineral supports under microwave irradiation [12], I₂/DMF [13], 1-phenyl-3-methylimidazolium bromide [PmIm]Br under microwave irradiation [14], activated carbon (Shirasagi KL or Darco® KB) under oxygen atmosphere [15], O₂ or H₂O₂ in the presence of Sc(OTf)₃ [16], CAN [17], electro oxidation [18], direct condensation of 2-aminothiophenol with aromatic

aldehydes under microwave irradiation [19], Dowex 50W [20], H₂O₂/Fe(NO₃)₃ [21], solid heteropoly acid supported on silica gel (Cu_{3/2}PMO₁₂O₄₀/SiO₂) [22], alum (KAl(SO₄)₂·12H₂O) [23], Bakers yeast [24], trichloroisocyanuric acid [25], perchloric acid-doped polyaniline [26] and tungstophosphoric acid impregnated zirconium phosphate [27].

However, many of these procedures are associated with one or more disadvantages such as the use of toxic, expensive catalyst, hazardous and carcinogenic solvents, e.g., nitro benzene and dioxane, multistep processes, and loss of the catalyst. Therefore, it was felt that there is an urgent need to overcome the above limitations by developing an efficient, simple and green methodology for the synthesis of benzo thiazoles.

2. Experimental

2.1. General procedures and instrumentation

Chemicals were obtained from Merck and Fluka. IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr). ¹³C and ¹H-NMR spectra were obtained using Jeol FT NMR 90 MHz spectrometer in CDCl₃ using TMS as an internal reference. Melting points were determined in open capillary tubes in a Stuart BI Branstead Electrothermal Cat No: IA9200 apparatus and uncorrected.

2.2. General procedure for the preparation of 2-arylbenzothiazoles

To a stirred solution of aldehydes (1 mmol) in 5 mL methanol/water (15:1, v:v), 2-aminothiophenol (1.2 mmol) and ammonium chloride (70 mol %) were added. The mixture was

Table 1. NH₄Cl-Catalyzed synthesis of 2-arylbenzothiazoles 2a-1.

Entry	Aldehyde (1a-1)	2-Arylbenzothiazole ^a (2a-1)	Time (Min)	Yield (%) ^b	Observed M.p. (°C)	Reference M.p. (°C)
1			30	84 (80,70) ^c	113-114	112-114
2			40	80	103-105	101-103
3			30	82	120-122	120-121
4			60	74	127-128	127-128
5			40	70	84-86	85
6			50	64	52-54	53-54
7			30	86	129-131	132
8			30	84	82-83	83-84
9			40	86	159-161	160-161
10			30	80	116-118	115-117
11			20	84	163-164	162-164
12			20	92	182-183	181-182

^a All the isolated products were characterized by their physical properties, by (¹H and ¹³C NMR and IR spectra, and by direct comparison with literature data.

^b Isolated yields.

^c The same catalyst was used for each of the three runs.

stirred at room temperature for an appropriate time (Table 1). The progress was monitored by TLC (Ethyl acetate:hexane, 8:2). After the complete conversion of the substrate, H₂O (3 mL) was added to the reaction mixture, and was allowed to stand at room temperature for 10 min. During this time, the pure products formed which were collected by filtration. Then, the residue was recrystallized from EtOH (5 mL) to afford the pure products.

2.3. Recycling of the catalyst

At the end of the reaction, the catalyst was filtered, washed with diethyl ether, dried at 100 °C for 1 h, and reused in another reaction. The recycled catalyst was used for two reactions without observation of appreciable lost in its catalytic activities (Entry 1, Table 1).

2.4. Selected physical and spectral data of the 2-aryl benzothiazoles

2.4.1. 2-Phenylbenzothiazole (2a) [19]

Yield: 84%. M.p.: 113-114 °C. IR (KBr, ν, cm⁻¹): 3064, 1588, 1555, 1509, 1478, 1433, 1244, 962, 766. ¹H NMR (90 MHz, CDCl₃, δ, ppm): 7.41-8.08 (m, ArH). ¹³C NMR (22.5 MHz, CDCl₃, δ, ppm): 77.10 (CDCl₃), 121.53, 123.23, 125.09, 126.22, 127.52, 128.91, 130.83, 133.64, 135.08, 154.19, 167.93.

2.4.2. 2-(4-Methoxyphenyl)benzothiazole (2c) [19]

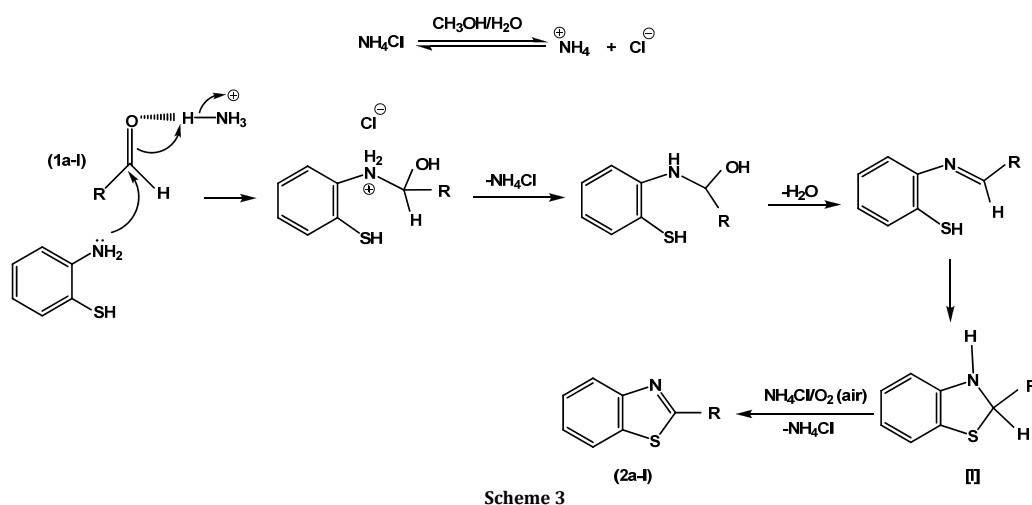
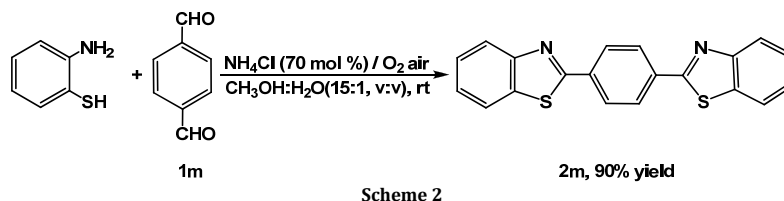
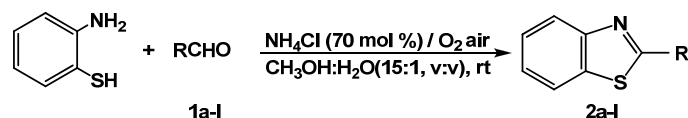
Yield: 82%. M.p.: 120-122 °C. IR (KBr, ν, cm⁻¹): 3023, 2996, 2900, 2836, 1605, 1521, 1485, 1260, 832. ¹H NMR (90 MHz, CDCl₃, δ, ppm): 3.82 (s, 3H, OMe), 7.00-7.95 (m, 8H, ArH). ¹³C NMR (22.5 MHz, CDCl₃, δ, ppm): 77.10 (CDCl₃), 55.45 (OCH₃), 114.43, 121.53, 122.90, 124.81, 126.21, 129.16, 134.91, 154.38, 162.02, 167.85.

3. Results and discussion

The development of cost-effective and environmentally benign catalytic systems is one of the main themes of modern organic synthesis. Ammonium chloride (NH₄Cl) is a very inexpensive, eco-friendly and easily available catalyst; it has been reported as catalyst for synthesis of various organic compounds. It has effectively promoted Claisen rearrangement [28], Biginelli synthesis of 3,4-dihydropyrimidinones [29], the thia-michael addition reaction [30], the one-pot synthesis of diindolymethanes [31], and the synthesis of Quinoxalines [32].

In continuation of our research on synthesis 2-arylbenzothiazoles [33-35], here, we report a very simple synthesis of 2-arylbenzothiazoles by the condensation of 2-aminothiophenol with aromatic aldehydes under mild condition at room temperature (Scheme 1).

The aim of this study is to utilize an eco-friendly NH₄Cl-CH₃OH system for the synthesis of 2-arylbenzothiazoles at ambient temperature using ammonium chloride as catalyst and methanol as the benign reaction medium in medicinal chemistry [32]. In order to investigate the optimal conditions



for these reactions, we start by examining the influence of the reaction time and the solvent effect at room temperature. Methanol/ water (15:1, v:v) was the best solvent among those tested (EtOH, H₂O, CH₃CN, CH₂Cl₂, CHCl₃).

Finally, we have developed this synthetic method for the preparation of additional extended bisbenzothiazole derivatives in a 2:1:0.7 molar ratio of 2-aminothiophenol to 1,4-benzenedicarbaldehyde to NH₄Cl (70 mol%) in MeOH/H₂O (15:1, 10 ml) (Scheme 2). The reaction proceeded smoothly for 25 min at room temperature using the present protocol and the desired product **2m** was obtained in 90% isolated yield. The isolated product was characterized by their physical properties, by ¹H and ¹³C NMR and IR spectra, and by direct comparison with literature data [25].

Scheme 3 briefly shows the catalytic behavior of ammonium chloride throughout predicted mechanistic pathway for the synthesis of 2-arylbenzothiazoles. Ammonium chloride may activate the carbonyl compounds by hydrogen bonding to promote the reaction via the nucleophilic attack of amines [11-35].

It is important to mention that, when the same reaction with ammonium chloride was carried out under nitrogen atmosphere (in absence of oxygen), the reactions stopped at the benzothiazoline [I] stage, which never proceeded to benzothiazoles **2a-I**. This surely proves that aerial oxygen is absolutely essential for the oxidation step leading to the formation of benzothiazoles.

In conclusion, we have developed an economically, and environmentally friendly catalyzed process for simple and efficient synthesis of 2-arylbenzothiazoles and bisbenzothiazole. The present methodology offers very attractive features such as reduced reaction times, high yields, recycling of the catalyst, mild reaction conditions, acid-free, metal-free,

readily available system, if compared with other catalysts. This will have wide scope in organic synthesis.

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