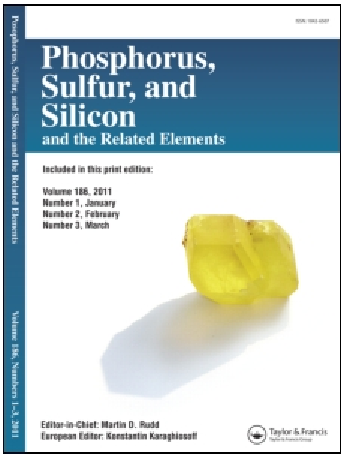

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Microwave-Assisted Preparation of 2-Substituted Benzothiazoles

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*2-Substituted benzothiazoles (**3a–h**) were prepared from the condensation reaction of 2-aminothiophenol **1** with aldehydes **2** in the presence of P-Ts-OH and graphite on the surface of solid mineral supports without using any oxidizing agent under microwave irradiation.*

Keywords 2-Aminothiophenol; aldehyde; benzothiazole; microwave irradiation; solid support

INTRODUCTION

The application of microwave energy in organic synthesis has attracted a substantial amount of attention in the past few years.[1,2] The main benefits of performing reactions under microwave irradiation are the significant rate enhancements and the higher product yields. Also, apart from traditional solution phase chemistry, the use of solid supports such as clays, zeolites, silica gel, and alumina has gained increased attention in organic synthesis.[3] Furthermore, the most important advantages of these reagents are the simplification of reaction work-up and product isolation.

Benzothiazoles have been found to exhibit a wide spectrum of biological activities. They have shown antitumor,[4–6] antimalarial,[7] and fungicide activity.[8] They are also an important class of industrial chemicals. Many kinds of 2-substituted benzothiazoles are utilized as vulcanization accelators in the manufacture of rubber,[9] as fluorescent brightening agents in textile dyeing,[10] and in the leather industry.[11]

These compounds have been prepared from the condensation reaction of carboxylic acid, ester, amide, or nitrile with 2-aminothiophenol

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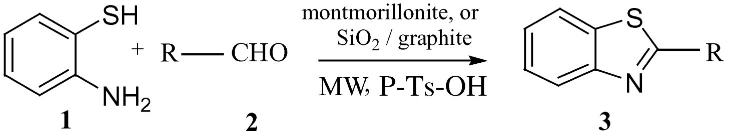
in the presence of polyphosphoric acid.[12] They have also been prepared from cyclization of thiobenzanilide by potassium ferricyanide (Jacobson's method)[13] and other reagents.[14] Tabakovic and Hoffman prepared them from benzanalide.[15] Formation of 2-aryl benzothiazoles from the reaction of 2-aminothiophenol with carboxylic acids, aldehydes in the presence of an oxidant[16,17] and orthoesters[18] were also reported in the literature. Recently they have been prepared from oxidative coupling between thiophenols and aromatic nitriles.[19]

RESULTS AND DISCUSSION

Previously we have reported formation of 2-substituted benzothiazoles from the reaction of 2-aminothiophenols and *S*-methylisothioamide hydroiodides.[20] Under similar conditions, the reaction of 2-aminothiophenol with aldehydes did not give any result. Inspired by recent work on the Pechman reaction on graphite/montmorillonite K-10 and pyrolysis of urea supported on graphite, in which the strong thermal effect of graphite was reported in the literature,[21] the mixture of silica gel and graphite was used as solid support. Formation of these compounds from aldehydes in the presence of an oxidant such as nitrobenzene and MnO_2 have been reported in the literature.[17]

In this research, we have prepared 2-substituted benzothiazoles **3a–h** from the reaction of 2-aminothiophenol **1** and aldehydes **2** in the presence of P-Ts-OH in two different methods without using any oxidant (Scheme 1, Table I).



SCHEME 1

Method A: The reaction was carried out either on the surface of a mixture of silica gel and graphite as well as montmorillonite K-10 and graphite as solid support (Table I).

Method B: The reaction was performed on the surface of silica gel without mixing it with graphite. To get the thermal effect of graphite, the whole beaker and the reaction mixture was placed in a Teflon® vessel filled with graphite (Table II).

The data in Table II correspond to Method A in which the reaction took place on the surface of both silica gel and montmorillonite together with graphite. In this method we had difficulty extracting the product from the fine powder of graphite. To bring about the thermal effect of

TABLE I Condensation of 2-Aminothiophenol 1 with Aldehydes 2

Aldehyde	R	Product
2a	C_6H_5	**3a**
2b	$4\text{-}NO_2\text{-}C_6H_4$	**3b**
2c	$3\text{-}NO_2\text{-}C_6H_4$	**3c**
2d	$4\text{-Cl-}C_6H_4$	**3d**
2e	$3\text{-Cl-}C_6H_4$	**3e**
2f	$MeOOC\text{-}C_6H_4$	**3f**
2g	$4\text{-CN-}C_6H_4$	**3g**
2h	$4\text{-OH-}C_6H_4$	**3h**

graphite, we used another technique in which the reaction mixture and silica gel were mixed in a beaker, which was then placed in a Teflon, vessel filled with graphite (Method B). It seems that the increase in reaction rate, higher yield, and lower power are all because of the higher temperatures caused by the use of graphite. The cleaner work-up in this method also has a role in its higher yields. The results are summarized in Table III.

High yield, short reaction time, and pure products are advantages of both procedures in comparison to other methods. Easy work-up in Method B makes the reaction even simpler in respect to Method A. The data for the synthesis of benzothiazoles under different conditions are shown in Table II and Table III.

EXPERIMENTAL

All products are known compounds and were characterized by comparing their spectral and physical data with those of known samples.

TABLE II Physical Characterization and Conditions for Preparation of 2-Substituted Benzothiazoles (Method A)

	Time (min)		Yield (%)					
Products	K-10	SiO_2	K-10	SiO_2	Power (watt)	M.p (°C)	Lit. M.p (°C)	Ref.
3a	10	12	96	91	150	113.2	111–114	12
3b	6	10	90	86	500	229.2	227–231	22
3c	4	4	75	69	300	182.5	185	24
3d	12	16	82	78	150	113	112–116	23
3e	12	14	97	82	300	96.5	97–99	25
3f	10	10	98	98	150	164	166	23
3g	6	6	84	78	150	162	167	23
3h	6	8	84	64	300	221	226	24

TABLE III Physical Characterization and Conditions for Preparation of 2-Substituted Benzothiazoles (Method B)

Products	Yield (%)	Time (min)	Power (watt)	M.p (°C)
3a	97	6	150	113.2
3b	96	6	150	229.2
3c	93	4	150	182.5
3d	94.5	8	150	113
3e	98	8	150	96.5
3f	98	6	150	164
3g	96	6	150	162
3h	92	6	150	221

Melting points were taken on an Electrothermal 9100 melting point apparatus. IR spectra were recorded with a Shimadzu IR-408 spectrometer (KBr). The ^{1}H NMR spectra were determined in chloroform-d and DMSO-d$_6$ solution on a Bruker DRX-500 Avance (500 MHz). Microwave irradiation was carried out using a commercial microwave oven, Moulinex AET 5. Merck silica gel 60GF254 was used for analytical and preparative TLC.

General Procedure for the Synthesis of 2-Substituted Benzothiazoles (Method A)

p-Toluen sulphonic acid (5 mmol) was added to the mixture of either silica gel or montmorillonite (3gr), graphite (1gr), 2-aminothiophenol (2 mmol), and aldehyde (2 mmol), and was well ground in a mortar. The mixture was then subjected to microwave irradiation in an open Pyrex beaker at appropriate power and time (Table II). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with either ethyl acetate, and in some cases dichloromethane, or methanol, (150 ml) by using Soxhilet apparatus. The extracts were then combined and evaporated under *vacuo*. The resulting oil or solid was washed with ether and crystallized from ethanol to give the corresponding 2-substituted benzothiazoles.

General Procedure for the Synthesis of 2-Substituted Benzothiazoles (Method B)

p-Toluen sulphonic acid (5 mmol) was added to the mixture of silica gel (3gr), 2-aminothiophenol (2 mmol), and aldehyde (2 mmol), and was well ground in a mortar. The mixture was poured in a Teflon vessel, placed in a beaker filled with graphite, and then subjected to microwave irradiation at appropriate power and time (Table III). 2-Substituted benzothiazoles were obtained in the same way as mentioned in Method A.

In conclusion the synthesis of a series of 2-substituted benzothiazoles could be achieved from the reaction of 2-aminothiophenol and aldehydes on the surface of either silica gel or montmorillonite by using graphite to provide heat, without using any oxidant. These findings offer further evidence that the coupling of microwave energy together with the mixture of solid mineral support and graphite will bring a thermal effect and therefore make the reaction easier.

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