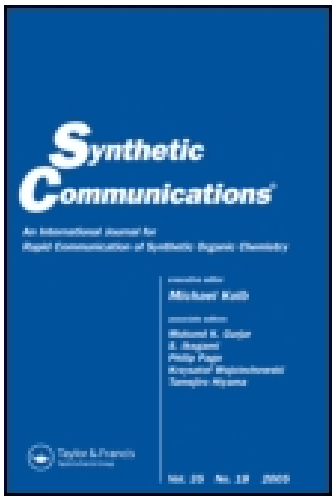

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MICROWAVE-INDUCED SOLVENT-FREE SYNTHESIS OF 2-ARYLBENZOTHIAZOLES USING p-TsOH

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MICROWAVE-INDUCED SOLVENT-FREE SYNTHESIS OF 2-ARYLBENZOTHIAZOLES USING *p*-TsOH

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ABSTRACT

A simple and efficient procedure has been developed for the synthesis of 2-arylbenzothiazoles by a one-pot reaction of *o*-aminothiophenol with β-chlorocinnamaldehydes using *p*-TsOH under microwave irradiation.

Key Words: 2-Arylbenzothiazoles; *p*-TsOH; Microwave-activation; Solvent-free conditions

The synthesis of benzothiazoles and their derivatives has been of considerable interest to organic and medicinal chemists for many years as large number of drugs[1–5] contain this heterocyclic nucleus. These have been used as optical brightners and dyes.[6,7] Poly (*p*-phenylene benzobisthiazole) (PBT) is rigid rod polymer with excellent thermal and oxidative stability and good hydrolytic and chemical resistance.

Numerous methods are available for the synthesis of 2-arylbenzothiazoles. The important ones include: the reaction of *o*-aminothiophenols

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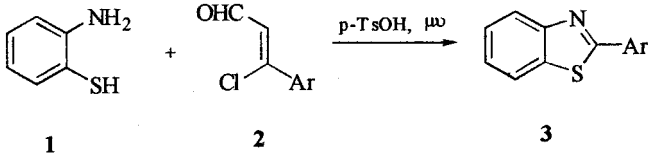
with benzoic acid or its derivative in polyphosphoric acid (PPA),[8] polyphosphate ester[9] or a mixture of methanesulfonic acid and phosphorus pentoxide;[10] the action of selenoamides on *o*-aminothiophenol;[11] reaction of copper(I)thiobenzoate and 2-iodoanilines;[12] by palladium catalyzed condensation of arylaldehydes with *o*-aminothiophenol followed by dehydrative cyclization.[13,14] Most of these protocols, however, suffer from drawbacks, namely longer reaction periods and the use of corrosive acids, toxic metallic compounds that result in generation of waste streams.

In the wake of health and economic awareness, it is desirable to device a safe and metal free method with minimum disposable waste.[15] Microwave-assisted reactions in solvent-free conditions have gained popularity because of rapid reaction rates, cleaner reaction, and ease of manipulation.[16] The need of clean synthesis,[15,17] and our involvement in the area of solvent-free microwave-assisted reactions,[18] prompted us to search for an efficient and eco-friendly protocol for the synthesis of 2-arylbenzothiazoles.

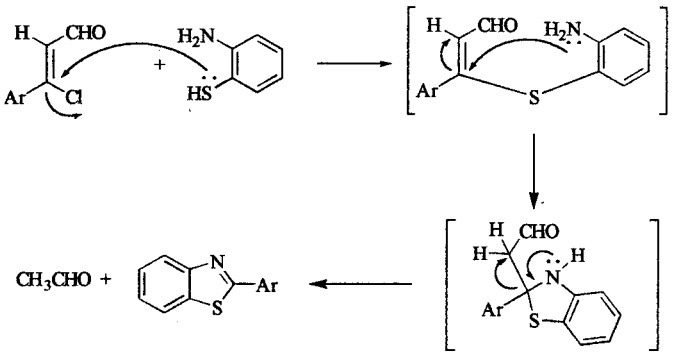
In 1991, it has been reported[19] that when *o*-aminothiophenol is treated with 2-chloro-1-formyl-2-trifluoromethyl-1-phenylethene, it leads to the formation of 2-trifluoromethylbenzothiazole along with benzothiazepine, which loses sulphur at room temperature to give quinoline. However, if trifluoromethyl group is replaced with methyl group, then exclusively benzothiazepine is formed. Based on this strategy, we have carried out the reaction of *o*-aminothiophenol with β-chlorocinnamaldehydes without having electron-withdrawing group like trifluoromethyl group in the presence of *p*-TsOH under microwave irradiation. It has been found that 2-arylbenzothiazoles were obtained in moderate to good yield (Sch. 1).

In order to be able to carry out synthesis of 2-arybenzothiazoles in a faster and more efficient way, eliminating the use of solvent and reflux conditions, we investigated the influence of microwave irradiation on a neat mixture of *o*-aminothiophenol **1** and β-chlorocinnamaldehyde[20] **2** and *p*-TsOH. After some experimentation with respect to molar ratios of reagents, and the irradiation time and power level of microwave set-up, we have found a set of conditions that generally provides 2-arylbenzothiazoles **3** in moderate to good yields. These conditions employed a 1.25 : 1 ratio



1 **2** **3**

Scheme 1.



Scheme 2.

of *o*-aminothiophenol **1** and β-chlorocinnamaldehyde **2**, using 100 mg of *p*-TsOH. 2-Arylbenzothiazoles were purified by passing through column of silica gel. The minor products may also be formed (TLC, cannot be isolated), and we have reported only the major product i.e. 2-arylbenzothiazoles.

The proposed mechanism involves initial nucleophilic displacement of chlorine by sulphur followed by nucleophilic addition of nitrogen to conjugated C=C leading to ring closure as shown in Sch. 2.

In order to see whether these conditions work under non-microwave experiment, reactions under the similar conditions of time and temperature as in microwave experiment, were carried out in a pre-heated oil-bath. It has been found that though the reaction did takes place, but the yield was quite low (Table 1). Further, if the reaction is continued for longer time period, products obtained are still in lower yields (Table 1), which indicate that effect of microwave irradiation is not purely thermal and a specific microwave effect may be involved.

Microwaves interact with polar states and it has been suggested that microwave effect may be higher in cases where transition state is more polar than ground state. In the proposed mechanism, the transition state is more polar and maximum rate enhancement has been observed in case of 2-(4-nitrophenyl) benzothiazole, where transition state (Sch. 3) is expected to be most polar of all the cases studied (3 g, Δ 1.5 min, 38%, 75 min, 68%; MW 1.5 min, 85%).

In conclusion, the present procedure using *p*-TsOH provides an efficient one-pot synthesis of 2-arylbenzothiazoles from *o*-aminothiophenol and β-chlorocinnamaldehydes. The notable advantages of this procedure are: (a) operational simplicity; (b) fast reaction; (c) environment friendly; (d) general applicability accommodating a variety of substitution patterns.

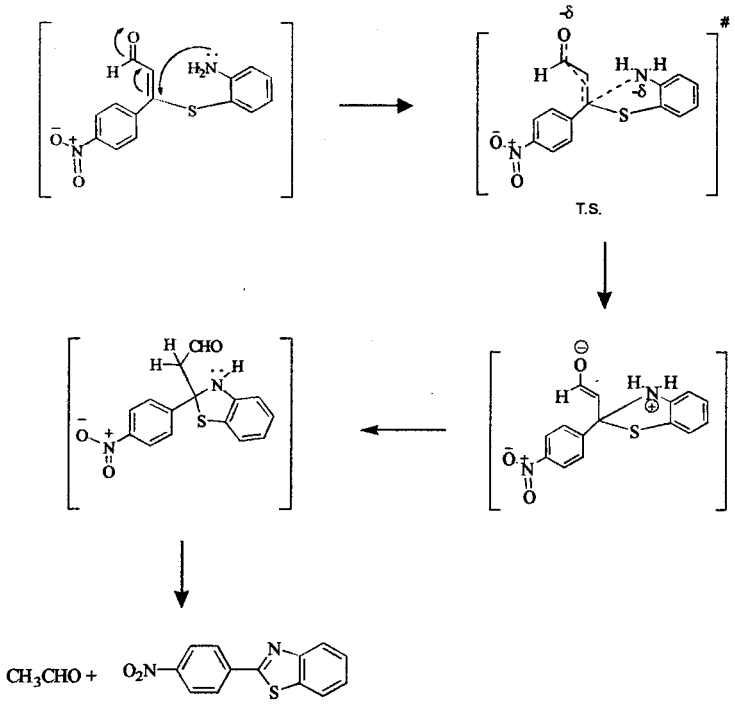
Table 1. Synthesis of 2-Arylbenzothiazoles (**3a–i**) (2 mmol) Under Microwave Irradiation and Pre-heated Oil-Bath Using *p*-TsOH (100 mg) (Power = 300 W)

Product	Ar	Reaction Temp.[a] (°C)	MW Time (min)	MW Yield (%)	Δ (Oil-Bath) Time (min)	Δ (Oil-Bath) Yield (%)	M.P. (°C) Found/Reported
3a	4-OMeC_6H_4[b]	112–114	2.5	52	2.5	22	119–21/121.5–22[21]
					60[e]	45	
3b	4-OEtC_6H_4[b]	110–112	2.5	58	2.5	27	97–98[d]
					70[e]	45	
3c	C_6H_5[b]	110–112	2.0	65	2.0	33	113/113–114[23]
					65[e]	53	
3d	4-BrC_6H_4[c]	112–114	2.0	75	2.0	35	130–31/132–33[21]
					65[e]	58	
3e	4-ClC_6H_4[c]	118–120	2.0	74	2.0	30	119–21/120–21[21]
					65[e]	55	
3f	4-FC_6H_4[c]	118–120	1.5	78	1.5	27	98–99/102.5–103.5[21]
					65[e]	60	
3g	4-$NO_2C_6H_4$[c]	122–124	1.5	85	1.5	38	229–30/229–31[22]
					75[e]	68	
3h	2,4-$(Cl)_2C_6H_3$[b]	120–122	1.5	77	1.5	20	146–47/148–49[23]
					70[e]	55	
3i	3,4-$(Cl)_2C_6H_3$[c]	119–121	1.5	82	1.5	28	117–18/118–20[23]
					75[e]	67	

[a]Final temperature is measured at the end of exposure during microwave experiment by immersing glass thermometer in the reaction mixture (approximate temperature range).
[b]Purified by column of silica gel using pet. ether: EtOAc (9.5 : 0.5) as eluant.
[c]Purified by column of silica gel using pet. ether: EtOAc (9.8 : 0.2) as eluant.
[d]IR (KBr): 2957, 1577, 1462, 1365, 1262, 1042 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.37–1.48 (t, 3H, $-OCH_2CH_3$), 4.06–4.13 (q, 2H, $-OCH_2CH_3$), 6.90–7.10 (m, 2H, C_3'-H and C_5'-H), 7.27–7.55 (m, 2H, C_5-H and C_6-H), 7.75–7.90 (d, C_2'-H and C_6'-H), 8.0–8.21 (d, 2H, C_4-H and C_7-H). *m/z* (%): 255 (97.01%). Elemental analysis: Found C, 70.52; H, 5.04; N, 5.56. $C_{15}H_{13}NOS$ requires C, 70.58; H, 5.09; N,5.49.
[e]Time which gives maximum yield in an oil-bath, after which no further increase in yield has been observed, rather decomposition of products takes place.

EXPERIMENTAL

Melting points (uncorrected) were determined by Toshniwal melting point apparatus. IR spectra (ν_{max} in cm^{-1}) were recorded on Shimadzu-435 spectrophotometer using KBr disc and ^1H NMR spectra in $CDCl_3$ (chemical shifts in δ, ppm) on Varian EM-390 (90 MHz) or Bruker AM-250 (250 MHz)



Scheme 3.

using TMS as an internal standard. The mass spectra were performed on Delsi/NERMAG spectral 30 spectrometer. Microwave irradiation was carried out using a BPL BMO 800T domestic oven having maximum power output of 800 W.

General Procedure for the Synthesis of 2-Arylbenzothiazoles 3

To a mixture of *o*-aminothiophenol (2.5 mmol) and β-chlorocinnamaldehyde (2 mmol) in a borosil beaker (50 mL), *p*-TsOH (100 mg) was added and the reaction mixture was mixed properly with the help of a glass rod. The paste thus obtained was irradiated in a microwave oven at 300 W for the appropriate time (Table 1). The reaction was monitored by TLC after every 30 s of irradiation. On cooling, the reaction mixture was extracted with dichloromethane (3×15 mL) and washed with 5% aq. NaOH and finally with water (2×20 mL). The extract was dried over anhydrous sodium

sulfate and on removal of the solvent under gentle vacuum, the residue was purified by passing through column of silica gel to give **3a–g** in 52–85%.

The structure of the products were confirmed by IR, ^{1}H NMR, mass spectral data, elemental analysis and comparison with authentic samples prepared according to literature methods.

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