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RAPID AND CONVENIENT THERMAL OR MICROWAVE-ASSISTED SYNTHESIS OF SUBSTITUTED 2-PHENYLBENZOTHIAZOLES

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A simple one-step method for the synthesis of biologically relevant 2-phenylbenzothiazoles has been developed, using sodium metabisulfite as an oxidant following condensation between 2-aminothiophenol and substituted benzaldehydes. Attractive features of this new method include excellent yields under both microwave-assisted or thermal conditions (it is tolerant of a variety of substituents on the phenyl ring) and simple product isolation without the need for chromatographic purification.

Keywords: Antitumor agents; bicyclic compounds; heterocycles; microwave synthesis; 2-phenylbenzothiazoles

INTRODUCTION

Structurally simple 2-phenyl-1,3-benzothiazole derivatives have been shown to possess remarkable biological properties, particularly in the area of cancer drug discovery.[1,2] For example, 2-(4-amino-3-methylphenyl)benzothiazole (DF 203) was found to possess potent and selective antitumor activity against panels of human cancer cell lines, and a fluorinated DF 203 prodrug (Phortress) has now entered clinical trials for cancer.[3–5] The structurally related 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610) has also shown potent and selective in vitro antitumor properties[6] reminiscent of the (aminophenyl)benzothiazole series. In addition, (aminophenyl)benzothiazole derivatives have attracted considerable interest in potential diagnosis of Alzheimer's disease using positron emission tomography,[7,8] progressing to clinical evaluation in the case of Pittsburgh compound B. The structures of these biologically relevant 2-phenylbenzothiazole derivatives are presented in Fig. 1.

The synthesis of 2-phenylbenzothiazoles is most commonly accomplished by the thermal or microwave-promoted condensation of 2-aminothiophenol with either

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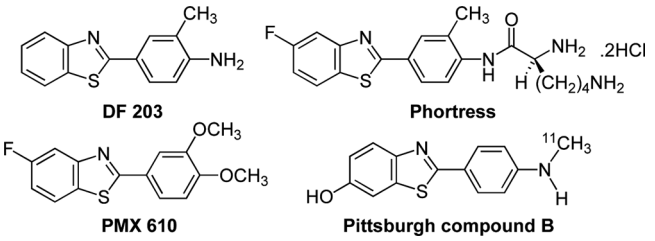


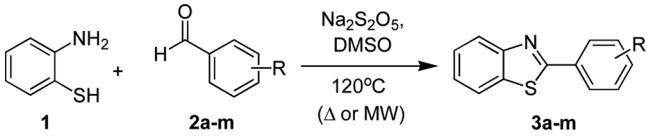
Figure 1. Biologically relevant 2-phenylbenzothiazoles.

a substituted benzoic acid derivative (usually in a high-boiling solvent such as polyphosphoric acid) or a benzaldehyde. Synthetic methods and biological activity for selected 2-phenylbenzothiazoles have recently been reviewed.[9] A wide range of substituted benzaldehydes is commercially available; nevertheless in the case of benzaldehydes, the initial product is a 2,3-dihydrobenzothiazole that must be further oxidized to the fully aromatic benzothiazole. An example of where further oxidation is required is the microwave-promoted synthesis[10] of 2-substituted benzothiazoles from benzaldehydes, where oxidation was achieved in the presence of cocatalysts/oxidants such as iodine,[11,12] silica gel,[13] or zirconium(IV) oxide chloride/copper(II) sulfate.[14] However, because these procedures required chromatographic purification following microwave irradiation, there is still a need for the development of straightforward synthetic routes to 2-phenylbenzothiazoles characterized by simple product isolation and (nonchromatographic) purification. Sodium metabisulfite ($Na_2S_2O_5$), an inexpensive and nontoxic inorganic oxidant, has previously been used in the microwave-promoted synthesis of 2-arylbenzimidazoles from benzaldehydes and *o*-phenylenediamine.[15]

In this work, we developed a simple method for rapid access to a range of substituted 2-phenylbenzothiazoles that could be applied to a parallel (library) synthesis format, requiring no chromatographic purification. To meet our criteria of a rapid one-pot method with simple workup and purification, we were particularly attracted to the microwave method[10] using substituted benzaldehydes and 2-aminothiophenol as condensation partners. We now report a simple and high-yielding synthesis of substituted 2-phenylbenzothiazoles under microwave-promoted or thermal conditions from various benzaldehydes and 2-aminothiophenol in the presence of sodium metabisulfite. The related oxidant, silica-supported sodium hydrogen sulfate, has previously been reported as a heterogenous catalyst for the synthesis of 2-arylbenzothiazoles in excellent yield.[16] Our new sodium metabisulfite–promoted method features short reaction times with simple product isolation without the need for column chromatography and is ideally suited for parallel (library) synthesis applications.

RESULTS AND DISCUSSION

We report herein a simple, one-pot method for the synthesis of biologically relevant 2-phenylbenzothiazoles (**3a–m**) from 2-aminothiophenol (**1**) and substituted benzaldehydes (**2a–m**) using sodium metabisulfite as a mild oxidant in dimethylsulfoxide (DMSO) at 120 °C under both thermal and microwave conditions (Scheme 1).



Scheme 1. Reaction conditions for the synthesis of substituted 2-phenylbenzothiazoles.

Our investigations of solvent effects found that the most efficient conditions for formation of benzothiazole product under thermal or microwave conditions were obtained when DMSO was used as solvent. The efficiency of DMSO in promoting reaction is likely a result of its optimal reagent dissolution and oxidizing agent properties, and efficient dissolution is a particularly important consideration for microwave-promoted reactions. Formation of benzothiazole products in excellent yield could also be achieved using dimethylformamide (DMF) at 90 °C as solvent, although in these cases reaction times were longer (>2 h), in part because of the lower solubility of reaction components in DMF. Although the use of sodium metabisulfite or DMSO alone led to product formation, use of these reagents in combination led to a significant reduction in reaction time (to 25–120 min). Heating at greater temperatures in the microwave led to shorter reaction times; however, the formation of by-products necessitated chromatographic purification of product, leading to more lengthy and complex purification procedures. In a typical optimized procedure, 2-aminothiophenol (3.13 mmol) and benzaldehyde (3.16 mmol) in the presence of sodium metabisulfite (3.16 mmol) and DMSO (2 mL) were heated under thermal or microwave conditions at 120 °C for the specified time (Table 1). On addition of water, the corresponding substituted 2-phenylbenzothiazoles were

Table 1. Isolated product yields for the thermal and microwave-promoted synthesis of 2-arylbenzothiazoles[a]

		Time (min)		Yield (%)[a]				
Entry	Benzaldehyde	Δ	MW	Δ	MW	Mp (°C)	Lit. mp (°C)	Ref.
a	4-OH	30	60	83	80	228–230	227	13
b	3-OH	30	30	85	84	159–160	161–163	17
c	4-OMe	35	30	83	76	122–124	123–125	18
d	3-OMe	25	30	80	70	80–81	81–82	19
e	3,4-OMe	30	30	88	75	129–131	132–133	12
f	3,4,5-OMe	35	45	81	76	142–145	141–144	20
g	4-Br	30	25	80	82	127–129	132	11
h	4-NO_2	120	90	97	85	230–232	228–230	18
i	3-NO_2	120	90	75	80	186–188	183–185	12
j	4-CF_3	120	60	91	90	156–159	161–162	21
k	4-CN	120	60	95	98	169–172	169–170	21
l	3-Cl	120	60	95	90	97–99	96.5	22
m	3-F	120	60	90	88	71–73	—[b]	23

[a]All yields refer to isolated products that were characterized by mp, ^{1}H NMR, ^{13}C NMR, mass spectrometry, and microanalysis (% C, H, N).

[b]Compound identity established by comparison of ^{1}H NMR data.

obtained in good to excellent yields in high purity. All products were fully characterized (mp, ^{1}H and ^{13}C NMR, mass spectrometry and % C, H, N microanalysis) and compared to previous literature values (Table 1).

To investigate the scope of the reaction, both electron-withdrawing and electron-donating groups on the benzaldehyde were studied. Products containing both electron-donating groups (e.g., OMe, **3c–d**) or electron-withdrawing groups (e.g., NO_2, **3h–i**) were efficiently transformed to the corresponding 2-phenylbenzothiazole products in excellent yield following simple product workup and isolation. Notably phenolic benzaldehydes (**3a, b**; R = 4-OH or 3-OH) gave good yields of product without the need for either protection of the phenolic group or further purification. Alternatively, heating the reaction components in DMF at 90 °C gave rise to products (**3a–m**) in >75% yield following the same simple workup procedure, although with longer reaction times (4–10 h).

In conclusion, we have developed a simple one-step procedure for the synthesis of biologically relevant 2-phenylbenzothiazoles under either thermal or microwave-promoted conditions. Careful control over reaction conditions allowed the efficient synthesis of a range of benzothiazoles in excellent yield with simple product isolation and purification. Work is under way to extend this simple protocol to 2-arylbenzothiazoles substituted on the benzothiazole ring and to investigate their biological properties.

EXPERIMENTAL

Instruments and Reagents

The microwave-assisted reactions were performed using a CEM Discover single-mode microwave synthesizer by moderating the initial power (100 W). NMR spectra were recorded on a Bruker Avance 500-MHz instrument. All starting materials and reagents were purchased (Sigma-Aldrich, UK) and used without further purification. For illustrative purposes, the preparative method and spectroscopic data for 4-benzothiazol-2-yl-phenol (**3a**, thermal conditions) and 4-bromophenylbenzothiazole (**3g**, microwave conditions) are presented.

Typical Synthesis for 4-Benzothiazol-2-yl-phenol (3a) (Thermal Conditions)

A mixture of 2-aminothiophenol (0.33 mL, 3.13 mmol), 4-hydroxybenzaldehyde (0.39 g, 3.16 mmol), and sodium metabisulfite (0.60 g, 3.16 mmol) in DMSO (2 mL) was heated at 120 °C for 30 min. The reaction mixture was allowed to cool to room temperature, excess water was added, and the solid precipitate was collected by filtration. The precipitate was washed with excess water and dried to give 4-benzothiazol-2-yl-phenol (**3a**) in 83% yield. Mp 228–230 °C (lit.[13] 227 °C). ^{1}H NMR (500 MHz; DMSO-d_6) 10.30 (1H, s, OH), 8.07 (1H, d, J 7.0 Hz, H-4), 7.98 (1H, d, J 8.0 Hz, H-7), 7.93 (2H, d, J 8.5 Hz, H-2′, H-6′), 7.50 (1H, t, J 7.5 Hz, H-5), 7.4 (1H, t, J 7.5 Hz, H-6), 6.94 (2H, d, J 8.5 Hz, H-3′, H-5′). ^{13}C NMR (125 MHz, DMSO-d_6) 167.43, 160.49, 153.7, 134.08, 129.01, 126.38, 124.86,

124.03, 122.26, 122.06, 116.06. Anal. calculated for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.43; H, 4.05; N, 6.25.

Typical Synthesis of 4-Bromophenylbenzothiazole (3g) (Microwave Conditions)

A homogenous mixture of 2-aminothiophenol (0.33 mL, 3.13 mmol), 4-bromobenzaldehyde (0.58 g, 3.16 mmol), and sodium metabisulfite (0.60 g, 3.16 mmol) in DMSO (2 mL) was irradiated in a sealed tube at 120 °C for 25 min by moderating the initial power (100 W). The reaction mixture was allowed to cool to room temperature, excess water was added, and the solid precipitate was collected by filtration. The precipitate was washed with excess water and dried to give 4-bromobenzothiazole (**3g**) in 82% yield. Mp 127–129 °C (lit.[11] 132 °C). ^{1}H NMR (500 MHz; $CDCl_3$) 8.10 (1H, d, *J* 8.0 Hz, H-4), 7.99 (2H, d, *J* 7.5 Hz, H-3′, H-5′), 7.93 (1H, d, *J* 8.0 Hz, H-7), 7.65 (2H, d, *J* 7.5 Hz, H-2′, H-6′), 7.53 (1H, t, *J* 8.0 Hz, H-6), 7.43 (1H, t, *J* 8.0 Hz, H-5). ^{13}C NMR (125 MHz, $CDCl_3$) 166.69, 154.11, 135.07, 132.59, 132.25, 128.92, 126.51, 125.46, 125.42, 123.35, 121.67. Anal. calcd. for $C_{13}H_8BrNS$: C, 53.81; H, 2.78; N, 4.82. Found: C, 53.91; H, 2.78; N, 4.70.

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