Microwave-Assisted "Green" Synthesis of 2-Alkyl/ ArylBenzothiazoles in One Pot: A Facile Approach to Anti-tumor Drugs

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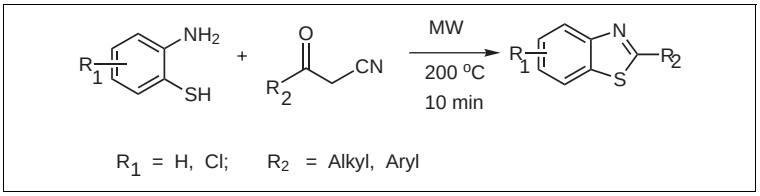

A series of new 2-alkyl/arylbenzothiazoles has been synthesized on the basis of the potent and selective *in vitro* anti-tumor properties of 2-(3,4-diethoxyphenyl)-5-fluorobenzothiazole. The synthesis of benzothiazole analogs was achieved *via* microwave irradiation of a 1:1 mixture of *o*-aminothiophenol and alkyl/aryl acylacetonitriles at temperature of 200 °C for 10 min. The yields are very good to excellent. All the products were characterized by ^{1}H nmr, ^{13}C nmr and elemental analysis.

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Introduction.

An important task for synthetic scientists in recent years has been fulfilling the increasing medical need for the potent and selective *in-vitro* antitumor drugs. Several structurally related benzothiazoles were found to be a major class of potent ligands for the aryl hydrocarbon receptor (AHR), which translocates with the drug to cell nuclei [1]. As shown in Figure 1, some best-known examples of this class are the arylamines 2-(4-amino-3-methylphenyl)-benzothiazole (**1**) and the 5-fluoro analogue (**2**). A further class of anti-tumour benzothiazoles, obtained originally from the oxidation of 2-(4-hydroxyphenyl)benzothiazole with hypervalent iodine oxidant [2], is the 4-hydroxycyclohexadienone substituted benzothiazole (**3**). This derivative proved to be the prototype of a new series of "quinols" with potent antitumor activity against renal and colon cancer cell lines that affects cell-signalling events downstream of the redox regulatory protein thioredoxin [3]. The investigational prodrug Phortress (**4**) [4], which has potent activity against human mammary tumor xenografts [5] is currently in phase 1 clinical trial in the UK. There are several methods [6-8] to synthesize arylbenzothiazoles. Most of them involve longer routes or use of expensive chemicals or in some cases [9] use of solid (silica gel) support. In our previous study [10] we reported a simple and convenient way of preparing a variety of substituted benzothiazoles under microwave irradiation from commercially available β-keto esters. Herein we report an improved method for the preparation of benzothiazoles from readily available starting materials.

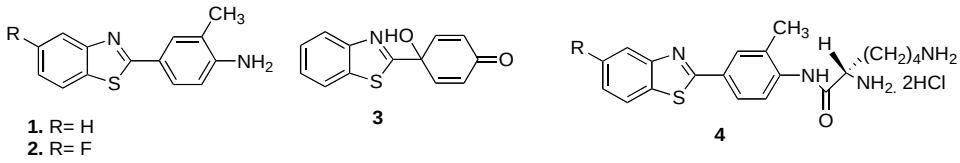
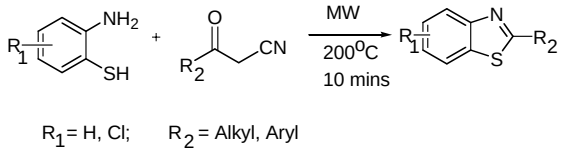


Figure 1

Results and Discussion.

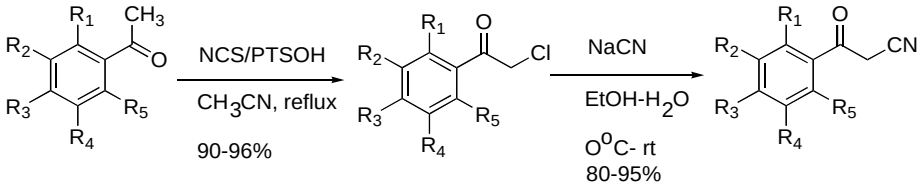
The utility of microwave reaction in organic synthesis is well documented [11]. 2-Alkyl/2-aryl benzothiazoles were obtained by microwave irradiation of 1:1 mixture of 2-aminothiophenol and alkyl/aryl acylacetonitriles under solvent-free conditions (see Scheme 1).

Scheme 1



The results are shown in Table 1. The solid products were crystallized from ethyl acetate-hexane mixtures where the

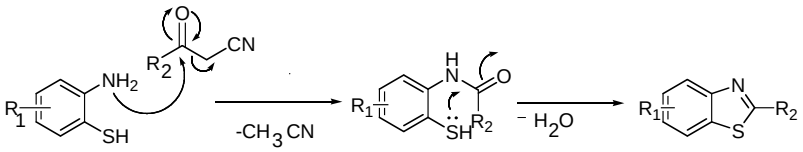
Scheme 2



liquid products were purified by column choromatography. The yields range from good to excellent. Most of the starting alkyl/aryl acylacetonitriles are commercially available or can be easily prepared from bromo or chloro precursors by a literature procedure [12] (Scheme 2).

Thus a variety of alkyl/aryl acylacetonitrile can be prepared in a much more convenient manner than the previously reported procedure [10]. The most plausible mechanistic pathway (Scheme 3) involves nucleophilic attack of the $-NH_2$ group of 2-aminothiophenol to the carbonyl carbon of the nitrile compound. The elimination of acetonitrile was confirmed by GC/MS and nmr analysis of the reaction mixtures. In the second step, intramolecular nucleophilic attack by the $-S^{\theta}$ anion gives an

Scheme 3



adduct from which water is eliminated to give the titled compounds. The experimental setup is simple. One simply mixes the 2-aminothiophenol and alkyl/aryl acylacetonitrile in a test tube. Then the mixture is irradiated without any solvent or solid support with microwaves (150 W output) at 200 °C for 10 min. The crude reaction mixture is either crystallized (for solid products) or chromatographed on silica gel. The reaction can be scaled up to multi gram quantities without diminution of yield. For example, a three-gram sample of compound **7c** was obtained in 98% yield from 2-aminothiophenol and 3-oxo-3-*p*-tolylpropionitrile in a one batch reaction.

EXPERIMENTAL

Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. ^1H and ^{13}C nmr spectra were recorded on a 400 MHz multi-nuclear nmr spectrometer. Chemical shifts are reported in reference to TMS as internal standard. Elemental analyses were obtained from Southern Methodist University Analytical Service Laboratories. All chemicals were purchased from commercial sources. The microwave experiments were done on a microwave (POB 200) instrument at 150 W output power.

2-Phenylbenzo[*d*]thiazole (**7a**).

This compound was obtained as a white crystalline solid, mp 111-113 °C (Lit. [10], mp 112-114 °C.)

2-(4-Fluorophenyl)benzo[*d*]thiazole (**7b**).

This compound was obtained as a colorless white solid, mp 97-99 °C. ^1H nmr (deuteriochloroform): 7.20-7.21 (m, 3H, aromatic), 7.42-7.51 (m, 2H, aromatic), 7.92-8.10 (m, 3H, aromatic). ^{13}C nmr (deuteriochloroform): 116.4, 116.6, 122.0, 123.6, 125.6, 126.8, 129.8, 129.9, 130.3, 135.4, 154.5, 163.6, 166.1.

Anal. Cald. for $C_{13}H_8FNS$: C, 68.10; H, 3.52; N, 6.11. Found C, 68.11; H, 3.52; N, 6.12.

2-*p*-Tolylbenzo[*d*]thiazole (**7c**).

This compound was obtained as a yellowish solid, mp 81-83 °C. ^1H nmr (deuteriochloroform): 2.44 (s, 3H, CH_3), 7.31 (d, *J*=7.1 Hz, 2H, aromatic), 7.39 (dd, *J* =7.5 Hz, 7.8 Hz, 1H, aromatic), 7.50 (dd, *J* =7.5 Hz, 7.8 Hz, 1H, aromatic), 7.90 (d, *J* =7.5 Hz, 1H, aromatic), 8.01 (d, *J* =7.1 Hz, 2H, aromatic), 8.09 (d, *J* =7.5 Hz, 1H, aromatic). ^{13}C nmr (deuteriochloroform): 21.9, 121.9, 123.5, 125.4, 126.6, 127.8, 130.1, 131.3, 135.3, 141.8, 154.5, 168.6.

Anal. Cald.for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22. Found C, 74.62; H, 4.93; N, 6.23.

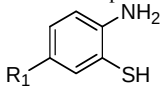
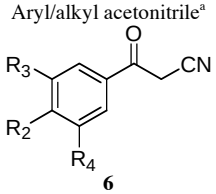
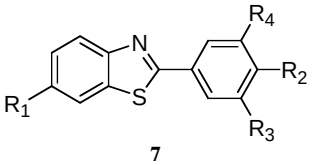
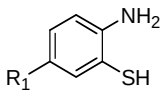
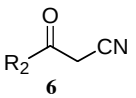
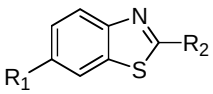
4-(Benzo[*d*]thiazol-2-yl)benzonitrile (**7d**).

This compound was obtained as a brownish solid, mp 101-102 °C. ^1H nmr (deuteriochloroform): 7.55 (dd, *J* =7.5 Hz, 7.8 Hz, 2H, aromatic), 7.85 (d, *J* =8.2 Hz, 2H, aromatic), 8.01 (dd, *J* =2.5 Hz, 7.5 Hz, 2H, aromatic), 8.06 (d, *J* =8.2 Hz, 2H, aromatic). ^{13}C nmr (deuteriochloroform): 112.5, 117.1, 122.1, 125.1, 127.3, 127.8, 132.5, 132.6, 133.8, 140.1, 169.5.

Anal. Cald.for $C_{14}H_8N_2S$: C, 71.16; H, 3.41; N, 11.86. Found C, 71.17; H, 3.44; N, 11.86

Table 1

Yields of Titled Compounds **7**

Entry	2-Aminothiophenol	Aryl/alkyl acetonitrile[a]	Benzothiazoles	Yield[b] (%)
	 **5**	 **6**	 **7**	
1a	R_1 = H	R_2, R_3, R_4 = H	R_1, R_2, R_3, R_4 = H	98
1b	R_1 = H	R_2 = F, R_3, R_4 = H	R_1, R_3, R_4 = H, R_2 = F	95
1c	R_1 = H	R_2 = CH_3, R_3, R_4 = H	R_1, R_3, R_4 = H, R_2 = CH_3	98
1d	R_1 = H	R_2 = CN, R_3, R_4 = H	R_1, R_3, R_4 = H, R_2 = CN	77
1e	R_1 = H	R_2,+R_3, = $(CH=CH)_2$, R_4 = H	R_1, R_4 = H, R+R_3 = $(CH=CH)_2$	94
1f	R_1 = H	R_2, R_3, R_4 = OCH_3	R_1, = H, R_2, R_3, R_4 = OCH_3	93
1g	R_1 = H	R_2 = OCH_3, R_3, R_4 = H	R_1, R_3, R_4 = H, R_2 = OCH_3	95
1h	R_1 = Cl	R_2, R_3, R_4 = H	R_1 = Cl, R_2, R_3, R_4 = H	91
1i	R_1 = Cl	R_2+R_3, = $(CH=CH)_2$ R_4 = H	R_1 = Cl, R_4 = H, R_2+R_3 = $(CH=CH)_2$	93
1j	R_1 = Cl	R_2 = OCH_3, R_3, R_4 = H	R_1 = Cl, R_3, R_4 = H, R_2 = OCH_3	91
1k	R_1 = Cl	R_2,R_3 = H, R_4 = OCH_3	R_1 = Cl, R_2, R_3 = H, R_4 = OCH_3	86
1l	R_1 = Cl	R_2 = F, R_3, R_4 = H	R_1 = Cl, R_3, R_4 = H, R_2 = F	94
	 **5**	 **6**	 **7**	
1m	R_1 = H	R_2 = $CH(CH_3)_2$	R_1 = H, R_2 = $CH(CH_3)_2$	89
1n	R_1 = H	R_2 = $C(CH_3)_3$	R_1 = H, R_2 = $C(CH_3)_3$	86
1o	R_1 = H	R_2 = Furan	R_1 = H, R_2 = Furan	95
1p	R_1 = Cl	R_2 = $C(CH_3)_3$	R_1 = Cl, R_2 = $C(CH_3)_3$	88

[a]See reference 12 for detailed procedure; [b]Isolated pure yield.

2-(Naphthalen-2-yl)benzo[*d*]thiazole (**7e**).

This compound was obtained as a white solid, mp 125-127 ºC. ^{1}H nmr (deuteriochloroform): 7.42 (d, *J* =7.7 Hz, 1H, Hz, 1H, aromatic), 8.50 (s, 1H, aromatic). ^{13}C nmr (deuteriochloroform): 122.0, 123.6, 124.8, 125.6, 126.8, aromatic), 7.44-7.57 (m, 3H, aromatic), 7.89-7.97 (m, 4H, aromatic), 8.14 (d, *J* =7.3 Hz, 1H, aromatic), 8.22 (d, *J* =7.3 aromatic), 7.44-7.57 (m, 3H, aromatic), 7.89-7.97 (m, 4H, aromatic), 8.14 (d, *J* =7.3 Hz, 1H, aromatic), 8.22 (d, *J* =7.3 Hz, 1H, aromatic), 8.50 (s, 1H, aromatic). ^{13}C nmr (deuteriochloroform): 122.0, 123.6, 124.8, 125.6, 126.8, 127.3, 127.8, 127.9, 128.2, 129.2, 131.4, 133.5, 135.0, 135.5, 154.6, 168.5.

Anal. Calcd. for $C_{17}H_{11}NS$: C, 78.13; H, 4.24; N, 5.36. Found C, 78.15; H, 4.25; N, 5.37.

2-(3,4,5-Trimethoxyphenyl)benzo[*d*]thiazole (**7f**).

This compound was isolated as a viscous oil. The ^{1}H nmr and ^{13}C nmr was identical to that obtained in previous study [10].

2-(4-Methoxyphenyl)benzo[*d*]thiazole (**7g**).

This compound was obtained as a yellowish white solid. Mp 78-79°C. . ^{1}H nmr (deuteriochloroform): 3.98 (s, 3H, -OMe), 6.99 (d, *J*= 7.8 Hz, 2H, aromatic), 7.06-7.37 (m, 4H, aromatic), 7.91 (d, *J*= 8.1 Hz, 1H, aromatic), 8.12 (d, *J*=8.1 Hz, 1H, aromatic). ^{13}C nmr (deuteriochloroform): 55.6, 112.3, 117.8, 120.6, 122.1, 123.7, 125.3, 126.8, 130.3, 135.3, 136.1, 154.8, 160.1, 168.3.

Anal. Calcd.for $C_{14}H_{10}ClNOS$: C, 69.68; H, 4.59; N, 5.80. Found C, 69.71; H, 4.59; N, 5.82.

6-Chloro-2-phenylbenzo[*d*]thiazole (**7h**).

This compound was isolated as a yellow solid, mp 102-106 °C. (Lit. [10] 102-105 °C.

6-Chloro-2-(naphthalen-2-yl)benzo[*d*]thiazole (**7i**).

This compound was obtained as a yellowish solid. Mp 111-113 °C. ^{1}H nmr (deuteriochloroform): 7.39 (d, *J*= 7.8 Hz, 1H, aromatic), 7.57-7.59 (m, 2H, aromatic), 7.89 (dd, *J* =7.5 Hz, 7.8 Hz, 1H, aromatic), 7.95-7.99 (m, 3H, aromatic), 8.10 (s, 1H, aromatic), 8.19 (d, *J* = 7.8 Hz, 1H, aromatic), 8.56 (s, 1H, aromatic). ^{13}C nmr (deuteriochloroform): 122.7, 123.4, 124.7, 125.9, 126.0, 127.3, 128.1, 128.3, 129.3, 131.1, 133.6, 133.9, 134.1, 135.3, 151.6, 169.1.

Anal. Calcd. for $C_{17}H_{10}ClNS$: C, 69.03; H, 3.41; N, 4.74. Found C, 69.09; H, 3.5; N, 4.75.

6-Chloro-2-(4-methoxyphenyl)benzo[*d*]thiazole (**7j**).

This compound was obtained as a yellowish solid. mp 135-137°C. ^{1}H nmr (deuteriochloroform): 3.90 (s, 3H, -OMe), 7.01 (d, *J* = 8.7 Hz, 2H, aromatic), 7.32 (s, 1H, aromatic), 7.34 (d, *J* = 7.8 Hz, 1H, aromatic), 7.78 (d, *J* =7.8 Hz, 1H, aromatic), 8.03 (d, *J*=8.7 Hz, 2H, aromatic). ^{13}C nmr (deuteriochloroform): 55.8,

114.8, 122.5, 123.0, 125.5, 126.4, 129.6, 132.5, 133.5, 155.5, 162.6.

Anal. Calcd.for $C_{14}H_{10}ClNOS$: C, 60.98; H, 3.66; N, 5.08. Found C, 61.00; H, 3.67; N, 5.08.

6-Chloro-2-(3-methoxyphenyl)benzo[*d*]thiazole (**7k**).

This compound was obtained as a yellowish white solid. mp 75-78°C. ^{1}H nmr (deuteriochloroform): 3.93 (s, 3H, -OMe), 7.07 (dd, *J* =2.5 Hz, 7.8 Hz, 1H, aromatic), 7.36-7.43 (m, 2H, aromatic), 7.62-7.66 (m, 2H, aromatic), 7.81(d, *J* =7.8Hz, 1H, aromatic), 8.06 (d, *J* =2.5Hz, 1H, aromatic). ^{13}C nmr (deuteriochloroform): 112.5, 118.0, 120.6, 122.6, 123.4, 126.0, 130.5, 132.7, 133.7, 134.9, 155.3, 160.4.

Anal. Calcd. for $C_{14}H_{10}ClNOS$: C, 60.98; H, 3.66; N, 5.08. Found C, 60.99; H, 3.68; N, 5.09.

6-Chloro-2-(4-fluorophenyl)benzo[*d*]thiazole **(7l)**.

This compound was obtained as a light yellow solid, mp 151-153°C. ^{1}H NMR (deuteriochloroform): 7.18-7.27 (m, 2H, aromatic), 7.37 (dd, *J* = 2.3Hz, 7.8 Hz, 1H, aromatic), 7.81 (d, *J* =7.8 Hz, 1H, aromatic), 8.04-8.09 (m, 3H, aromatic). ^{13}C NMR (deuteriochloroform): 116.5, 116.7, 122.6, 123.4, 126.1, 129.9, 130.0, 132.8, 133.6, 155.3, 168.3.

Anal. Calcd. for $C_{13}H_7ClFNS$: C, 59.21; H, 2.68; N, 5.31. Found C, 59.23; H, 2.67; N, 5.39.

2-Isopropylbenzo[*d*]thiazole (**7m**).

This compound was isolated as a colorless oil. Its ^{1}H nmr and ^{13}C nmr spectra were identical to those previously reported [10].

2-*tert*-Butylbenzo[*d*]thiazole (**7n**).

This compound was isolated as a yellow solid, mp 65-67 °C (Lit. [10] mp 65-68 °C).

2-(Furan-2-yl)benzo[*d*]thiazole (**7o**).

This compound was obtained as a yellowish solid, mp 108-109 °C. ^{1}H nmr (deuteriochloroform): 6.99 (s, 1H, aromatic), 7.38 (dd, *J* =7.5 Hz, 7.8 Hz, 1H, aromatic), 7.49 (dd, *J*= 7.5 Hz, 7.8 Hz, 1H, aromatic), 7.55 (s, 1H, aromatic), 7.88 (d, *J* =7.8 Hz, 1H, aromatic), 8.04 (d, *J* = 7.8 Hz, 1H, aromatic), 8.13 (s, 1H, aromatic). ^{13}C nmr (deuteriochloroform): 109.6, 121.9, 122.2, 123.2, 125.4, 126.7, 134.7, 143.0, 144.6, 154.1, 160.5.

Anal. Calcd.for $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96. Found C, 65.69; H, 3.56; N, 6.98.

2-*tert*-Butyl-6-chlorobenzo[*d*]thiazole (**7p**).

This compound was obtained as a colorless oil. ^{1}H nmr (deuteriochloroform): 1.51 (s, 9H,-C(CH_3)$_3$), 7.31 (d, *J* = 7.8 Hz, 1 H, aromatic), 7.74 (d, *J* = 7.8 Hz, 1H, aromatic), 7.98 (s, 1H, aromatic). ^{13}C nmr (deuteriochloroform): 31.0, 38.8, 122.5, 123.0, 125.3, 132.1, 133.6, 154.5, 184.3.

Anal. Calcd.for $C_{11}H_{12}ClNS$: C, 58.53; H, 5.36; N, 5.36. Found C, 58.56; H, 5.41; N, 6.21.

Conclusions.

In conclusion, we have developed an efficient solvent free method for the facile synthesis of biologically important benzothiazoles. This provides a good example of the successful use of microwave irradiation for eco-friendly direct solvent-free synthesis in organic reactions.

Acknowledgements

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