A New General Synthesis of 2-Methylbenzothiazoles

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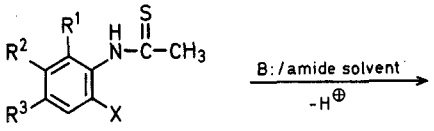
2-Methylbenzothiazoles are most commonly prepared by one of two well known methods[1]. The first of these, of which there are numerous variations, requires prior synthesis of an *o*-aminobenzenethiol or a derivative thereof. The second method involves oxidative intramolecular cyclization of a thioacetanilide.

Reported here is an equally convenient general synthesis of 2-methylbenzothiazoles (**2**) brought about by intramolecular nucleophilic displacement of aryl halide by anionic sulfur of 2′-halothioacetanilides (**1**) in amide solvents. The thioacetanilides are prepared by the reaction of the corresponding acetanilides with phosphorus pentasulfide in refluxing benzene.



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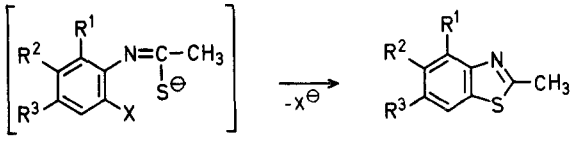

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1, 2	R^1	R^2	R^3	X
a	H	H	H	Cl
b	H	Cl	H	Cl
c	H	H	Cl	Cl
d	Cl	H	Cl	Cl
e	H	NO_2	H	Cl
f	H	H	NO_2	Cl
g	H	H	CH_3	Br

As can be seen (Table 2), activation by a strong electron-withdrawing group *para* to the leaving halide is not necessary to effect the reaction in good yield. Most likely, the powerful nucleophilicity of anionic sulfur, particularly in amide solvents[2], coupled with irreversibility and correct geometry for ring closure provide sufficient driving force. A similar reactivity was noted in the synthesis of aryl thioethers by the reaction of an aryl halide and a thiolate ion in amide solvents[3]. Although conversion of **1** to **2** is generally carried out with excess base, the preparation of **2c** in 69% yield with one mol equivalent of sodium methoxide rules out aryne intermediacy (i.e. dehydrohalogenation of the benzene ring followed by nucleophilic attack of anionic sulfur and protonation by solvent). It is noteworthy that 2-phenylbenzothiazole has been prepared from 2-chlorothiobenzanilide and potassium amide in liquid ammonia via an aryne mechanism[4].

While the current study is limited to the preparation of 2-methylbenzothiazoles, it should be recognized that the method is potentially applicable to many 2-substituted benzothiazoles.

Table 1. 2′-Halothioacetanilides (**1**) from 2′-Haloacetanilides and Phosphorus Pentasulfide

Product	Yield (%)	m.p.	Molecular formula[a]
1a	52	62–64°	C_8H_8ClNS (185.7)
1b	66	121–123°	$C_8H_7Cl_2NS$ (220.1)
1c	74	97.5–99.5°	$C_8H_7Cl_2NS$ (220.1)
1d	71	114–116°	$C_8H_6Cl_3NS$ (254.6)
1e	71	119–121°	$C_8H_7ClN_2O_2S$ (230.7)
1f	51	80.5–82°	$C_8H_7ClN_2O_2S$ (230.7)
1g	56	85.5–87.5°	$C_9H_{10}BrNS$ (245.0)

[a] All compounds gave satisfactory elemental analyses (C ±0.5%, H ±0.3%, N ±0.2%).

Table 2. 2-Methylbenzothiazoles (**2**) from the Anion of 2′-Halothioacetanilides (**1**) in Amide Solvent

Product	Yield (%)	m.p. (Lit. m.p.)	Molecular formula
2a	61[a]	153–155°[a] (153.3°)[a,5]	C_8H_7NS (149.2)
2b	59	67–69° (69.5–71°)[6]	C_8H_6ClNS (183.7)
2c	69	84–86° (85–86.5°)[7]	C_8H_6ClNS (183.7)
2d	88	105–107°	$C_8H_5Cl_2NS$[b] (218.1)
2e	85	134–136° (137°)[8]	$C_8H_6N_2O_2S$ (194.2)
2f	44	167–169° (167°)[9]	$C_8H_6N_2O_2S$ (194.2)
2g	50[a]	184–185°[a] (173°)[a,10]	C_9H_9NS[c] (163.2)

[a] Value for product isolated as picrate salt.

[b] calc. C 44.1 H 2.3 N 6.4
found 44.5 2.6 6.1
Mass spectrum: $m/e = 216.95$ ($M^{\oplus}$).
^{1}H-N.M.R. (DMSO-d_6): $\delta = 2.82$ (s, 3H, CH_3), 7.50 (d, 1 H_{arom}), 7.95 ppm (d, 1 H_{arom}).

[c] Elemental analysis for picrate salt:
$C_{15}H_{12}N_4O_7S$ (392.4) calc. C 45.9 H 3.1 N 14.3
found 45.8 3.2 14.1
^{1}H-N.M.R. (100 MHz, $CH_3OD/CDCl_3$): $\delta = 2.46$ (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 7.28–7.81 (m, 3 H_{arom}), 8.96 ppm (s, 2 H_{arom}).

Preparation of 2′-Halothioacetanilides (1); General Procedure:
Equimolar amounts of 2′-haloacetanilides and phosphorus pentasulfide are stirred for 4 h in 10 parts of refluxing benzene [except **f**, which is reacted for 20 h]. The reaction mixture is cooled to 25° and filtered. After extracting the residue with a small volume of ether, the combined solution is extracted 2 times with an equal volume of 10% aqueous sodium hydroxide. The combined aqueous extract is acidified at 10° with hydrochloric acid. The precipitated 2′-halothioacetanilides are collected and recrystallized from hexane/ether (see Table 1).

Preparation of 2-Methylbenzothiazoles (2); General Procedure:
With the exception of **2e** and **2f**, 2-methylbenzothiazoles are prepared by heating **1** (0.01–0.02 mol) with a 20% excess of sodium hydride at 150° for 2 h in 5 parts of *N*-methyl-2-pyrrolidinone. [Sodium hydride is used to insure a hydroxide free media. When sodium hydroxide is used as the base, the products are sometimes contaminated with 2′-chloroacetanilides.] After cooling to room temperature, the reacted mixture is poured into 10–15 volumes of water. (No flaming or dangerous exotherm was observed). Compound **2c** is also prepared in identical yield (69%) from **1c** (4.4 g, 0.02 mol) and sodium methoxide (1.08 g, 0.02 mol) in *N*-methyl-2-pyrrolidinone (22 ml) as above. The formed methanol is allowed to boil off. With the exception of **2a** and **2g**, the precipitated product is collected by filtration and recrystallized from hexane. In the case of **2a** and **2g**, the diluted reaction mixture is twice extracted with 50 ml of ether. The combined ether extract is washed with cold water, dried, decolorized with carbon, and mixed with an ether solution of picric acid. The precipitated picrate requires no further purification.

2-Methyl-5-nitrobenzothiazole (2e):
Compound **1e** is reacted with a 100% excess of 1,1,3,3-tetramethylguanidine in 5 parts of dimethylformamide. The reaction is allowed to proceed exothermically and is then held at 60° for thirty minutes. After quenching with water, the precipitated product is collected and recrystallized from benzene/hexane.

2-Methyl-6-nitrobenzothiazole (2f):
Compound **1f** (4.6 g, 0.02 mol) is reacted with sodium methoxide (1.5 g, 0.03 mol) in *N*-methyl-2-pyrrolidinone (23 ml) at 110° for 45 minutes. The reaction mixture is poured into water (250 ml) and the precipitate is collected and recrystallized from 2-butanone to give **2f**; yield: 1.7 g.

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