Synthetic Studies Using α,β-Unsaturated Nitriles: A Convenient Preparation of 1,3-Benzothiazole Derivatives

Koji SAITO, Satoshi KAMBE*, Yukihiro NAKANO

Oyama National College of Technology, Oyama-shi, Tochigi, 323, Japan

Akio SAKURAI

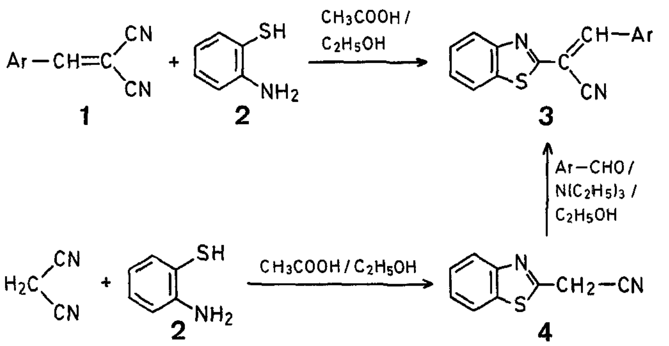
The Institute of Physical and Chemical Research, Wako-shi, Saitama, 351, Japan

Hiroshi MIDORIKAWA

Department of Domestic Science, Showa Women's University, Tokyo, 154, Japan

In one of our previous studies[1-6] on the synthesis of pesticidal heterocyclic compounds from α,β-unsaturated nitriles as starting materials, we reported that the reaction of 2-aminobenzenethiol (**2**) with benzylidenemalononitriles **1** resulted in the formation of 2-amino-6-(2-aminophenylthio)-4-aryl-3,5-dicyanopyridines[7]. Although a number of papers[8-14] have been published concerning the synthesis of 1,3-benzothiazole derivatives from **2**, 2-benzylidenecyanomethyl-1,3-benzothiazoles **3** have not previously been prepared from **1** and **2**. We report here that **3** can be prepared from **1** and **2** in ethanol containing acetic acid (Method A). The reaction of **2** with malononitrile formed 2-cyanomethyl-1,3-benzothiazole (**4**) in a good yield. Product **4** was easily condensed with aromatic aldehydes to give **3** in high yields (Method B).

In addition, we describe the simple synthesis of 3*H*-pyrido[2,1-*b*][1,3]-benzothiazole derivatives from **3** and malononitrile or cyanomethyl-1,3-benzothiazole (**4**).



Compound **4** and aromatic aldehydes in tetrahydrofuran containing triethylamine react at reflux temperature in a 2 : 1 molar ratio to give 1-amino-2-(1,3-benzothiazol-2-yl)-4-cyano-3-aryl-3*H*-pyrido[2,1-*b*][1,3]benzothiazole (**5**) through Michael addition (Method A). When a mixture of **3** and **4** in tetrahydrofuran containing triethylamine was refluxed, the same product **5** was obtained in a good yield (Method B). When malononitrile was used instead of **4**, the reaction led to the formation of 1-amino-2,4-dicyano-3-aryl-3*H*-pyrido[2,1-*b*][1,3]benzothiazole **6** (Method A). Product **6** may also be obtained by condensation of **4** with **1** in tetrahydrofuran containing triethylamine under reflux (Method B).

In these reactions, the nature of the substituent present in the benzene ring has little effect on the reaction. Further work is in progress to explore the potential utility of α,β-unsaturated nitriles for the synthesis of other heterocyclic systems.

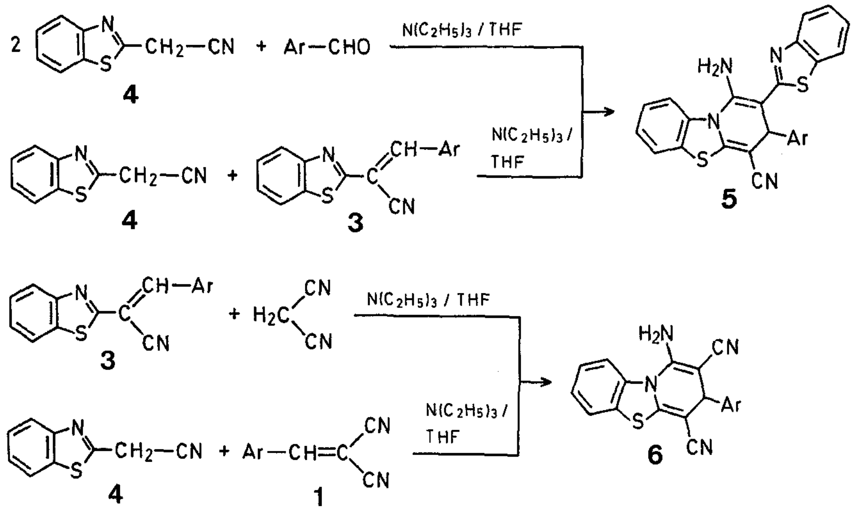


Table. Compounds **3**, **5**, and **6** prepared

Compound No.	Ar	Yield [%]		m.p. [°C]	Molecular formula[a]	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
		A	B				
3a	C_6H_5	46	80	121-123°	$C_{16}H_{10}N_2S$ (262.3)	2230	7.5-7.7 (m, 5 H_{arom}); 7.9-8.2 (m, 4 H_{arom}); 8.48 (s, 1 H, =CH—)
3b	4-H_3C—C_6H_4	54	72	147-148°	$C_{17}H_{12}N_2S$ (276.2)	2230	2.38 (s, 3 H, CH_3); 7.1-7.7 (m, 4 H_{arom}); 7.8-8.2 (m, 4 H_{arom}); 8.38 (s, 1 H, =CH—)
3c	4-H_3CO—C_6H_4	62	68	143-144°	$C_{17}H_{12}N_2OS$ (292.2)	2225	3.90 (s, 3 H, CH_3); 7.0-7.7 (m, 4 H_{arom}); 7.9-8.3 (m, 4 H_{arom}); 8.30 (s, 1 H, =CH—)
3d	4-Cl—C_6H_4	51	67	148-150°	$C_{16}H_9ClN_2S$ (296.8)	2230	7.3-7.8 (m, 4 H_{arom}); 7.9-8.3 (m, 4 H_{arom}); 8.40 (s, 1 H, =CH—)
5a	C_6H_5	36	61	220-221°	$C_{25}H_{16}N_4S_2$ (436.4)	3360, 2190	4.82 (s, 1 H, =CH—); 7.2-8.1 (m, 9 H_{arom}); 8.40 (s, 1 H, NH_2)
5b	4-H_3C—C_6H_4	53	60	245-246°	$C_{26}H_{18}N_4S_2$ (450.4)	3360, 2200	2.20 (s, 3 H, CH_3); 4.75 (s, 1 H, CH); 7.0-8.1 (m, 12 H_{arom}); 8.40 (s, 2 H, NH_2)
5c	4-H_3CO—C_6H_4	20	40	231-232°	$C_{26}H_{18}N_4OS_2$ (466.4)	3350, 2200	3.70 (s, 3 H, CH_3); 4.80 (s, 1 H, CH); 7.0-8.3 (m, 12 H_{arom}); 8.55 (s, 2 H, NH_2)
5d	4-Cl—C_6H_4	37	64	254-256°	$C_{25}H_{15}ClN_4S_2$ (470.9)	3400, 2200	4.95 (s, 1 H, CH); 7.5-8.5 (m, 12 H_{arom}); 8.60 (s, 2 H, NH_2)
6a	C_6H_5	67	64	190-191°	$C_{19}H_{12}N_4S$ (328.3)	3420, 3320, 2190	4.57 (s, 1 H, CH); 6.52 (s, 2 H, NH_2); 7.0-7.9 (m, 9 H_{arom})
6b	4-H_3C—C_6H_4	73	64	195-196°	$C_{20}H_{14}N_4S$ (342.3)	3440, 3330, 2210	2.35 (s, 3 H, CH_3); 4.60 (s, 1 H, CH); 6.65 (s, 2 H, NH_2); 7.1-8.1 (m, 8 H_{arom})
6c	4-H_3CO—C_6H_4	65	58	193-194°	$C_{20}H_{14}N_4OS$ (358.3)	3430, 3320, 2195	3.70 (s, 3 H, CH_3); 4.50 (s, 1 H, CH); 6.50 (s, 2 H, NH_2); 7.0-7.9 (m, 8 H_{arom})
6d	4-Cl—C_6H_4	67	50	210-211°	$C_{19}H_{11}ClN_4S$ (362.8)	3430, 3340, 2210	4.70 (s, 1 H, CH); 6.70 (s, 2 H, NH_2); 7.4-8.1 (m, 8 H_{arom})

[a] All products gave satisfactory microanalyses (C ±0.27%, H ±0.27%, N ±0.24%, S ±0.34%).

2-Cyanomethyl-1,3-benzothiazole (4):

A equimolar mixture of 2-aminobenzenethiol (**2**; 1.25 g, 10 mmol), malononitrile (0.66 g, 10 mmol), and acetic acid (10 mmol) in ethanol (10 ml) is magnetically stirred at room temperature until no further precipitate is produced, and then allowed to stand overnight. The resultant pale yellow precipitate is isolated by suction, and recrystallized from ethanol; yield 1.4 g (80%); m.p. 101–102 °C.

$C_9H_6N_2S$	calc.	C 62.07	H 3.47	N 16.09	S 18.37
(174.1)	found	62.19	3.47	16.09	18.40

I.R. (Nujol): $\nu = 2250\ \text{cm}^{-1}$.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 4.72$ (s, 2H, —CH$_2$—); 7.00–7.80 (m, 2H$_{\text{arom}}$); 7.80–8.27 ppm (m, 2H$_{\text{arom}}$).

2-Benzylidenecyanomethyl-1,3-benzothiazoles (3); General Procedure:

Method A: To a mixture of benzylidenemalononitrile **1** (10 mmol) and 2-aminobenzenethiol (**2**; 1.25 g, 10 mmol) in ethanol (10 ml), acetic acid (10 mmol) is added. The mixture is heated under reflux for 3 h, and then allowed to stand overnight. The resultant yellow precipitate is isolated by suction and recrystallized.

Method B: To a mixture of 2-cyanomethyl-1,3-benzothiazole (**4**; 1.74 g, 10 mmol) and the aromatic aldehyde (10 mmol) in ethanol (10 ml), triethylamine (a few drops) is added, and the mixture is magnetically stirred at room temperature for 4 h, and then allowed to stand overnight. Work-up is as described under Method A. Recrystallization solvent: **3a**, ethanol; **3b**–**3d**, tetrahydrofuran/ethanol (1 : 1).

1-Amino-2-(1,3-benzothiazol-2-yl)-4-cyano-3-aryl-3*H*-pyrido[2,1-*b*][1,3]benzothiazoles (5); General Procedure:

Method A: To a mixture of 2-cyanomethyl-1,3-benzothiazole (**4**; 1.74 g, 10 mmol) and an aromatic aldehyde (5 mmol) in tetrahydrofuran (5 ml), triethylamine (a few drops) is added. The mixture is heated under reflux for 8 h. A crystalline matter precipitates during the reaction. After cooling, the resultant precipitate is isolated by suction, washed with ethanol (5 ml), and then recrystallized from tetrahydrofuran/ethanol (1 : 1).

Method B: To a mixture of 2-cyanomethyl-1,3-benzothiazole (**4**; 1.74 g, 10 mmol) and the benzylidenecyanomethyl-1,3-benzothiazole **3** (10 mmol) in tetrahydrofuran (5 ml), triethylamine (a few drops) is added, and the mixture is heated under reflux for 6 h. Work-up is as described under Method A.

1-Amino-2,4-dicyano-3-aryl-3*H*-pyrido[2,1-*b*][1,3]benzothiazoles (6); General Procedure:

Method A: To a mixture of benzylidenecyanomethyl-1,3-benzothiazole **3** (10 mmol) and malononitrile (10 mmol) in tetrahydrofuran (5 ml), triethylamine (a few drops) is added, and the mixture is heated under reflux for 5 h. The reaction mixture is allowed to stand overnight and the resultant precipitate is isolated by suction. Recrystallization from tetrahydrofuran/ethanol (1 : 1) gives **6**.

Method B: To a mixture of 2-cyanomethyl-1,3-benzothiazole (**4**; 1.74 g, 10 mmol) and the benzylidenemalononitrile (10 mmol) in tetrahydrofuran (5 ml), triethylamine (a few drops) is added, and the mixture is heated under reflux for 5 h. Work-up is as described under Method A.

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