The Synthesis of Some 4*H*-Pyrimido[2,1-*b*]benzothiazol-4-ones

Robert J. Alaimo

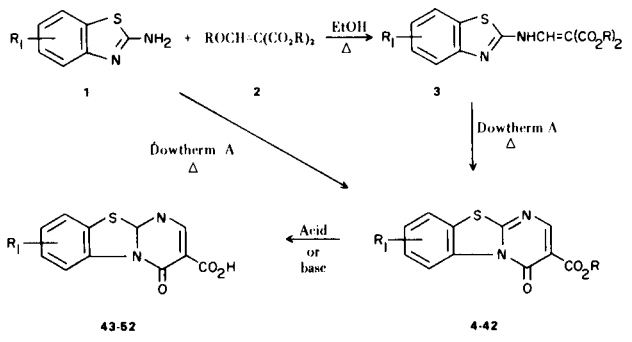
Chemistry Division, Norwich Pharmacal Company,
Division of Morton-Norwich Products, Inc., Norwich, New York 13815

Received April 7, 1973

A series of 8-substituted and 7,8-disubstituted-4-oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)-carboxylic acids and esters including a 9-aza analog were synthesized from substituted 2-amino-benzothiazoles and diethyl ethoxymethylenemalonate. The 9-aza analog, ethyl 8-methoxy-4-oxo-3-(4*H*-pyrido[3′,2′:4,5]thiazolo[3,2-*a*]pyrimidine)carboxylate (**56**), represents the first preparation of this new heterocyclic ring. These compounds were examined for antiparasitic activity, however, no significant activity was detected.

The reported biologic activity of a significant number of compounds containing condensed pyrimidine ring systems (1) and the antiparasitic activity shown by many benzothiazole compounds (2) prompted an investigation of the 4*H*-pyrimido[2,1-*b*]benzothiazole ring system to examine its antiparasitic properties. The first examples of this ring system were described in 1951 (3), with two more examples reported in 1962 (4). More recent reports have increased the number of these compounds in the literature (5), (6), (7).

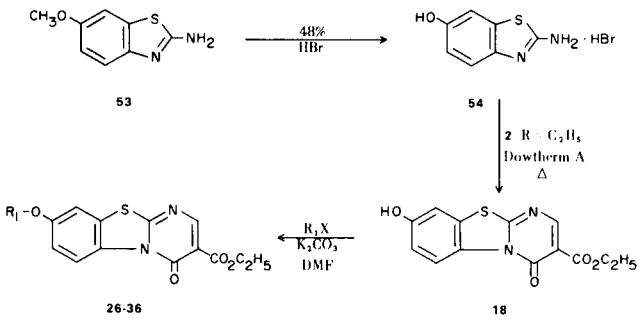
The general method for the synthesis of the 4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones reported herein involves the reaction of suitably substituted 2-aminobenzothiazoles (**1**) with alkoxymethylenemalonate esters (**2**). When the initial condensation was carried out in alcohol as previously reported, the product was the corresponding 2-(benzothiazolyl)aminomethylenemalonate (**3**), (5). These intermediates were readily cyclized to the corresponding pyrimido[2,1-*b*]benzothiazoles in hot Dowtherm A. However, since the complete reaction could be accomplished more conveniently in one step by heating a mixture of **1** and **2** in Dowtherm A until the theoretical amount of alcohol had been collected, the compounds **4-42** were prepared by this method. Acid or base hydrolysis of selected esters provided the corresponding acids (**43-52**).



1 2 3 43-52 4-42

The general method used for the preparation of 2-aminobenzothiazoles involves the reaction of a suitably substituted aniline with thiocyanogen [$(SCN)_2$] and the subsequent cyclization of the intermediate by heat or acid. The thiocyanogen is normally generated *in situ* by the action of bromine on an inorganic thiocyanate in a nonaqueous solvent (8), (9).

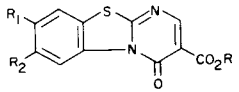
The ethyl 8-alkoxy-4-oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)carboxylates (**26-36**) were prepared from 2-amino-6-methoxybenzothiazole (**53**). Treatment of **53** with 48% hydrobromic acid provided the corresponding 6-hydroxy analog **54**. Condensation and cyclization of **54** with **2** gave the pyrimido[2,1-*b*]benzothiazole **18** in high yield. Compound **18** was used as an intermediate in the preparation of other 8-alkoxy substituted pyrimido-[2,1-*b*]benzothiazoles **26-36** by alkylation with alkyl halides in DMF solution.



53 54 26-36 18

Condensation and cyclization of 2-amino-6-methoxy-pyrido[2,3-*d*]thiazole (**55**) (10) with diethyl ethoxy-methylenemalonate (**2**, R = C_2H_5) led to the preparation of ethyl 8-methoxy-4-oxo-3-(4*H*-pyrido[3′,2′:4,5]thiazolo-[3,2-*a*]pyrimidin)carboxylate (**56**), a previously unreported ring system.

TABLE I

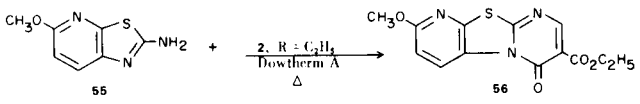


Compound (a)	R	R_1	R_2	Yield %	M.p. °C	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4	C_2H_5	H	H	81	136-138	$C_{13}H_{10}N_2O_3S$	56.92	3.68	10.22	56.71	3.71	10.22
5	C_2H_5	CH_3O	H	85	187-189	$C_{14}H_{12}N_2O_4S$	55.25	3.98	9.21	55.16	3.94	9.19
6	C_2H_5	Br	H	67	166-168	$C_{13}H_9BrN_2O_3S$	44.20	2.57	7.93	43.92	2.54	7.92
7	CH_3	H	H	70	185-186	$C_{12}H_8N_2O_3S$	55.38	3.10	10.76	54.97	3.14	10.67
8	C_2H_5	CH_3	H	55	171-172	$C_{14}H_{13}N_2O_3S$	58.12	4.53	9.68	58.06	4.30	9.59
9	C_2H_5	CH_3S	H	77	184-185	$C_{14}H_{12}N_2O_3S_2$	52.48	3.78	8.75	52.36	3.78	8.74
10	C_2H_5	CH_3CONH	H	63	275-277	$C_{15}H_{13}N_3O_4S$	54.37	3.95	12.68	54.01	3.94	12.61
11	C_2H_5	C_2H_5O	H	100	173-176	$C_{15}H_{14}N_2O_4S$	56.59	4.43	8.80	56.54	4.40	8.92
12	C_2H_5	C_2H_5OCO	H	63	163-164	$C_{16}H_{14}N_2O_5S$	55.48	4.07	8.09	55.33	3.95	7.97
13	C_2H_5	CH_3O	CH_3O	61	216-218	$C_{15}H_{14}N_2O_5S$	53.88	4.22	8.38	53.38	4.24	8.45
14	C_2H_5	NO_2	H	60	241-243	$C_{13}H_9N_3O_5S$	48.90	2.84	13.16	48.84	2.82	13.07
15	C_2H_5	O-CH_2-O		62	212-214	$C_{14}H_{10}N_2O_5S$	52.82	3.17	8.80	52.68	3.15	8.54
16	C_2H_5	NH_2SO_2	H	30	285-287	$C_{13}H_{11}N_3O_5S_2$	44.18	3.14	11.89	43.90	3.12	12.02
17	C_2H_5	C_2H_5O	C_2H_5O	60	169-171	$C_{17}H_{18}N_2O_5S$	56.33	5.07	7.73	56.03	4.98	7.97
18	C_2H_5	HO	H	85	269-271	$C_{13}H_{10}N_2O_4S$	53.78	3.47	9.65	53.55	3.50	9.76
19	C_2H_5	HO	HO	77	273-275	$C_{13}H_{10}N_2O_5S$	50.97	3.29	9.15	50.53	3.27	9.08
20 (b)	C_2H_5	NH_2	H	55	195-199	$C_{13}H_{11}N_3O_3S$	53.97	3.83	14.52	53.80	3.75	14.51
21	C_2H_5	F	H	85	153-155	$C_{13}H_9FN_2O_3S$	53.42	3.10	9.59	53.41	3.17	9.51
22	C_2H_5	$(CH_3)_2CHO$	$(CH_3)_2CHO$	52	150-153	$C_{19}H_{22}N_2O_5S$	58.44	5.68	7.18	58.44	5.51	7.33
23	CH_3	C_2H_5O	H	72	205-207	$C_{14}H_{12}N_2O_4S$	55.25	3.97	9.21	54.97	4.17	9.24
24	C_2H_5	CH_3	Cl	44	196-199	$C_{14}H_{11}ClN_2O_3S$	52.09	3.43	8.68	52.23	3.50	8.78
25	C_2H_5	Cl	H	62	169-172	$C_{13}H_9ClN_2O_3S$	50.57	2.94	9.07	50.46	3.08	9.33
26	C_2H_5	$CH_3CH_2CH_2O$	H	85	146-148	$C_{16}H_{16}N_2O_4S$	57.81	4.95	8.43	58.01	4.86	8.51
27	C_2H_5	CH_2=CH-O-CH_2CH_2O	H	55	179-180	$C_{17}H_{16}N_2O_5S$	56.66	4.48	7.77	56.73	4.72	7.86
28	C_2H_5		H	50	120-122	$C_{18}H_{18}N_2O_4S$	60.31	5.06	7.82	60.23	5.21	7.82
29	C_2H_5	$C_6H_5CH_2O$	H	100	182-184	$C_{20}H_{16}N_2O_4S$	63.14	4.24	7.36	62.92	4.18	7.48
30	C_2H_5	$(CH_3)_2CHO$	H	40	109-112	$C_{16}H_{16}N_2O_4S$	57.81	4.85	8.43	57.53	4.97	8.35

TABLE I
(Continued)

Compound (a)	R	R_1	R_2	Yield %	M.p. °C	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
31	C_2H_5	$HC{\equiv}CCH_2O$	H	100	194-196	$C_{16}H_{12}N_2O_4S$	58.52	3.68	8.53	58.49	3.68	8.62
32	C_2H_5	$CH_3(CH_2)_3O$	H	53	138-139	$C_{17}H_{18}N_2O_4S$	58.94	5.24	8.09	58.86	5.36	8.05
33	C_2H_5	$CH_3(CH_2)_4O$	H	100	115-118	$C_{18}H_{20}N_2O_4S$	59.97	5.59	7.77	59.90	5.59	7.77
34	C_2H_5	$(CH_3)_2CHCH_2O$	H	100	131-133	$C_{17}H_{18}N_2O_4S$	58.94	5.24	8.09	58.82	5.25	8.12
35	C_2H_5	$(CH_3)_2CHCH_2CH_2O$	H	100	123-126	$C_{18}H_{20}N_2O_4S$	59.97	5.59	7.77	60.05	5.65	7.85
36	C_2H_5	$CH_3CH_2(CH_3)CHO$	H	82	89-92	$C_{17}H_{18}N_2O_4S$	58.94	5.24	8.09	58.86	5.19	8.08
37	C_2H_5	$CH_3C(=O)$	H	76	237-239	$C_{15}H_{12}N_2O_4S$	56.95	3.82	8.86	56.62	4.00	9.05
38	C_2H_5	$CH_3C(=NOH)$	H	84	264-266	$C_{15}H_{13}N_3O_4S$	54.37	3.95	12.68	54.32	3.78	12.82
39	C_2H_5	HO_2C	H	77	260-262	$C_{14}H_{10}N_2O_5S$	52.82	3.17	8.80	53.07	3.36	8.78
40	C_2H_5	Cl	Cl	83	201-202	$C_{13}H_8Cl_2N_2O_3S$	45.50	2.35	8.16	45.46	2.41	8.27
41	C_2H_5	Cl	(9-Cl)	72	206-208	$C_{13}H_8Cl_2N_2O_3S$	45.50	2.35	8.16	45.34	2.33	8.16
42	C_2H_5	C_2H_5	H	51	137-138	$C_{15}H_{14}N_2O_3S$	59.58	4.67	9.27	59.51	4.75	9.22
43 (c)	H	H	H	86	221-222	$C_{11}H_6N_2O_3S$	53.65	2.46	11.38	53.59	2.47	11.35
44	H	CH_3O	H	100	247-249	$C_{12}H_8N_2O_4S{\cdot}H_2O$	48.98	3.43	9.52	49.22	3.54	9.72
45	H	Br	H	100	266-267	$C_{11}H_5BrN_2O_3S$	40.62	1.55	8.62	40.55	1.56	8.54
46	H	C_2H_5O	H	70	204-206	$C_{13}H_{10}N_2O_4S$	53.78	3.47	9.65	53.50	3.57	9.70
47	H	CH_3O	CH_3O	100	263-266	$C_{13}H_{10}N_2O_5S$	50.97	3.29	9.15	50.85	3.42	9.43
48	H	CH_3S	H	100	244-245	$C_{12}H_8N_2O_3S$	49.30	2.76	9.58	49.20	2.67	9.45
49	H	NO_2	H	76	254-258	$C_{11}H_5N_3O_5S$	45.36	1.73	14.43	45.26	1.85	14.40
50	H	$O\text{-}CH_2\text{-}O$		95	303-306	$C_{12}H_6N_2O_5S$	49.65	2.08	9.65	49.52	2.23	9.60
51	H	Cl	H	89	255-256	$C_{11}H_5ClN_2O_3S$	47.06	1.79	9.98	47.35	1.91	10.07
52	H	HO	H	100	312-314	$C_{11}H_6N_2O_4S$	50.38	2.31	10.68	50.39	2.57	10.97
56	C_2H_5	CH_3O	H	73	187-189	$C_{13}H_{11}N_3O_4S$	51.14	3.63	13.76	50.99	3.58	13.98

(a) Recrystallization of **4-42** was accomplished by use of ethanol, nitromethane or combinations thereof. (b) Prepared by catalytic hydrogenation of **14** using 5% Pd/C catalyst in ethanol. (c) Recrystallization of **43-52** was accomplished by use of DMF, nitromethane or combinations thereof.



The compounds **4-42** were assigned the 4-one structure rather than the 2-one structure as a result of several observations. Primarily, analogous synthetic reports give the 4-one assignment (5), (6), (7). In addition, the nmr spectra of the compounds **4-42** all show the characteristic downfield shift of H_6 from the main aromatic signal. This proton (H_6) shift has been explained on the basis that the 4-one function is held in a rigid form, coplanar with the aromatic ring, thus exerting a deshielding effect (11). The H_6 proton of **4-42** signal is in the region of δ 8.7-9.2, whereas the other aromatic protons are in the region of δ 6.7-8.0.

The nmr of the 9-aza derivative **56** also shows the consistent downfield shift for H_6. The nmr spectrum of **56** shows a triplet at δ 1.38 and a quartet at δ 4.39 assigned to the ethyl ester function; a 3 proton singlet at 3.98 for the 8-methoxy group; a 1 proton singlet at δ 8.71 assigned to H_2; H_6 and H_7 each appear as 1 proton doublets centered at δ 9.15 and δ 6.87, respectively. The ultraviolet spectrum of **56** is remarkably similar to the uv spectra of the other 4-one compounds **4-42** with a uv maximum at 358 nm. The ir spectrum of **56** shows carbonyl bands at 5.85 and 5.95 microns of nearly equal intensities. All these data are consistent with the 4-one structure assignement for **56**.

The 4*H*-pyrimido[2,1-*b*]benzothiazoles **4-56** reported herein were tested in a number of antiparasitic screening programs against various helminths and coccidia, but no significant activity was observed.

EXPERIMENTAL (12)

The 2-aminobenzothiazoles **1** were prepared according to the literature procedures outlined (8), (9) and were not purified, but used crude in subsequent reactions.

General Procedure (A) for the Preparation of Alkyl 4-Oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)carboxylates **4-42**. Example: Ethyl 8-Methoxy-4-oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)carboxylate (**5**).

A mixture of 2-amino-6-methoxybenzothiazole (**53**) (90 g., 0.5 mole) and diethyl ethoxymethylenemalonate (**2**, R = C_2H_5) (110 g., 0.5 mole) in Dowtherm A (750 ml.) was heated at 220° with stirring until 54 ml. of condensate had been collected (theory 57 ml.). The reaction mixture was then cooled and filtered and the product washed with hexane. The crude product weighed 127 g. (85%) and was recrystallized from ethanol.

General Procedure (B) for the Preparation of 4-Oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)carboxylic Acids (**43-52**). Example: 8-Bromo-4-oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)carboxylic Acid (**45**).

Ethyl 8-bromo-4-oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)-carboxylate (**6**) (25 g., 0.07 mole) was boiled under reflux with stirring in 48% hydrobromic acid (300 ml.) for 3 hours. The cooled mixture was filtered and the product washed with aqueous alcohol. The crude product weighed 22 g. (100%). Recrystallization from nitromethane provided analytically pure material.

Ethyl 8-Methoxy-4-oxo-3-(4*H*-pyrimido[3′,2′:4,5]thiazolo[3,2-*a*]-pyrimidine)carboxylate (**56**).

Condensation and cyclization of 2-amino-6-methoxypyrido-[2,3-*d*]thiazole (**55**) (10) with diethyl ethoxymethylenemalonate (**2**, R = C_2H_5) according to the general procedure (A) resulted in formation of **56** in 73% yield.

2-Amino-6-hydroxybenzothiazole Hydrobromide (**54**).

A solution of 2-amino-6-methoxybenzothiazole (100 g., 0.55 mole) in 48% hydrobromic acid (1000 ml.) was heated under reflux with stirring for 4.5 hours. The hot solution was treated with charcoal and filtered. Crystallization took place on cooling and the product was removed by filtration. The crude product (100 g., 74%) was recrystallized from methanol/ether to provide analytical material which melted at 248-252°.

Anal. Calcd. for $C_7H_6N_2OS$·HBr: C, 34.02; H, 2.86; N, 11.34. Found: C, 33.88; H, 2.92; N, 11.29.

General Procedure (C) for the Preparation of Alkyl 8-Alkoxy-4-oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)carboxylates (**26-36**). Example: Ethyl 8-*n*-Butoxy-4-oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)carboxylate (**32**).

To a warm (60°) solution of **18** (8.0 g., 0.028 mole) and anhydrous potassium carbonate (7.0 g., 0.05 mole) in DMF (100 ml.) was added *n*-butyl iodide (8.0 g., 0.04 mole). The reaction mixture was then stirred and heated at 70° for 4 hours, then poured onto ice and allowed to crystallize. The crude product (5.0 g., 53%) was recrystallized from ethanol to provide analytical material.

Acknowledgment.

The author wishes to acknowledge the technical assistance of Miss Yvonne M. Miller and Mr. James B. Sheffer in the preparation of compounds included in this publication. Microanalyses were performed by Mr. Marvin Tefft and Mr. Grant Gustin.

REFERENCES

(1) "Medicinal Chemistry," 3rd Edition, A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970, pages 72, 544 and 719.

(2) "May's Chemistry of Synthetic Drugs," 5th Edition, G. M. Dyson, Ed., Longmans, London, England, 1959, p. 557.

(3) H. Antaki and V. Petrow, *J. Chem. Soc.*, 551 (1951).

(4) R. Gompper and W. Topfl, *Chem. Ber.*, **95**, 2871 (1962).

(5) S. African Patent 6707053; *Chem. Abstr.*, 70, 47489b (1969).

(6) G. T. F. Galasko and S. S. Israelstam, *J. S. Afr. Chem. Inst.*, 22, 121 (1969); *Chem. Abstr.*, 71, 70532q (1969).

(7) D. W. Dunwell and D. Evans, *J. Chem. Soc. (C)*, 2094, 1971.

(8) J. L. Wood in "Organic Reactions," Vol. III, Roger Adams, Ed., John Wiley and Sons, New York, N.Y., 1947, p. 240.

(9) R. J. Alaimo, *J. Heterocyclic Chem.*, **8**, 309 (1971).

(10) C. O. Okafor, *J. Med. Chem.*, 10, 126 (1967).

(11) A. W. Chow, D. R. Jakas, B. P. Trotter, N. M. Hall and J. R. E. Hoover, *J. Heterocyclic Chem.*, 10, 71 (1973).

(12) Melting points were taken in open capillaries using a Mel-Temp melting point apparatus and are uncorrected. Ir spectra were determined in Nujol mull with a Perkin-Elmer Infracord. Uv spectra were obtained in ethanol on a Perkin-Elmer model 350. Nmr spectra were obtained on a Varian A-60A spectrophotometer in deuteriochloroform.