1,2,3-Thiadiazolo[5,4-*b*]pyrimidin-4(5*H*)ones

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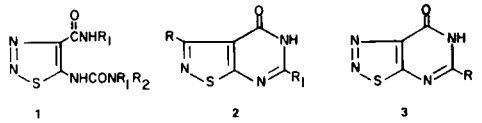
Received June 22, 1976

The synthesis of 1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4(5*H*)ones substituted in the 6-position with hydrogen, all possible isomers of alkyl methyl through butyl, and 2,2-dimethylpropyl is described.

J. Heterocyclic Chem., 13, 1141 (1976).

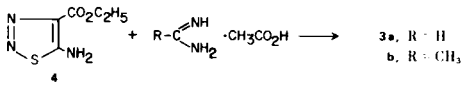
Based on the known herbicidal activity of 4-carboxamido-5-ureido-1,2,3-thiadiazoles (**1**) (1) and of isothiazolopyrimidinones (**2**) (2), the preparation of what can be viewed as a chemical juxtaposition of these two families of compounds, the 1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-ones (**3**), was undertaken.



1 2 3

R,R$_1$,R$_2$ = H, straight or branched chain lower alkyl

The simplest route to these compounds involves the reaction of 5-amino-4-carboethoxy-1,2,3-thiadiazole (**4**) with the appropriate amidine acetate (3). This approach was successfully employed to prepare **3** where the substituent at position 6 was hydrogen or methyl (4). It

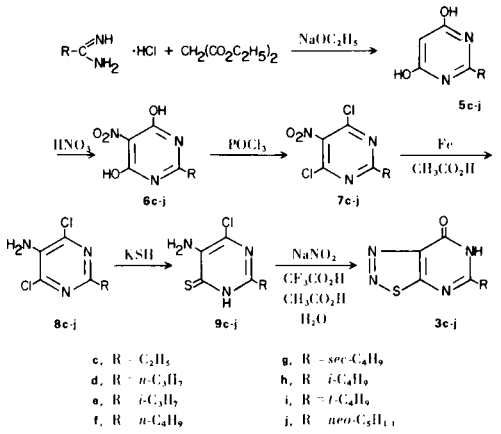


4

was necessary to use the acetate salt of the amidine instead of the more common hydrochloride salt (5). The most convenient synthesis of amidine acetates is reaction of the corresponding ortho ester with ammonia and acetic acid (6).

In the higher alkyl cases, especially branched chain, formation of the required ortho esters by alcoholysis of the corresponding imidates is severely limited by steric hindrance. For this reason, the above route could not be used to prepare higher homologs of **3**. An alternate route outlined in Scheme 1, afforded a general synthesis of the desired compounds (7).

Scheme I



5c-j

6c-j 7c-j

8c-j 9c-j 3c-j

c, R = C_2H_5 g, R = *sec*-C_4H_9
d, R = *n*-C_3H_7 h, R = *i*-C_4H_9
e, R = *i*-C_3H_7 i, R = *t*-C_4H_9
f, R = *n*-C_4H_9 j, R = *neo*-C_5H_{11}

EXPERIMENTAL

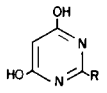
Melting points and boiling points are uncorrected. Elemental analyses were performed at FMC Corporation, Princeton, New Jersey. The ir and nmr spectra of all compounds were consistent with the assigned structures. Representative examples of procedures for different types of compounds are given below. Where not specifically described, the procedures for preparing related compounds are essentially identical.

6-Methyl-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4(5*H*)one (**3b**).

A solution of ethyl 5-amino-1,2,3-thiadiazole-4-carboxylate (0.85 g., 0.005 mole) and acetamidine acetate (1.0 g., excess) in 10 ml. of 2-ethoxyethanol was refluxed for 3.5 hours. Concentration to dryness at reduced pressure gave a brown oil which was chromatographed on silica gel. Elution with 5% methanol in chloroform gave after evaporation 0.28 g. (33%) grey solid. Purification was by sublimation (205°/0.01 torr). Analytical data appear in Table VI.

Table I

2-Alkyl-4,6-dihydroxypyrimidines

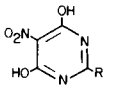


Compound	R	M.p. °C	% Yield	Formula	Analysis Calcd. C	H	N	Found C	H	N
5c	CH_3CH_2-	>280 (a)	64	$C_6H_8N_2O_2$	51.42	5.75	19.99	51.14	6.04	19.74
5d	$CH_3CH_2CH_2$-	>300 (b)	87	$C_7H_{10}N_2O_2$	54.53	6.54	18.17	54.54	6.63	17.89
5e	$(CH_3)_2CH$-	>275 (c)	47	$C_7H_{10}N_2O_2$	54.53	6.54	18.17	54.48	6.46	17.96
5f	$CH_3(CH_2)_3$-	>300 (d)	54	$C_8H_{12}N_2O_2$	57.14	7.14	16.66	57.59	7.35	16.67
5g	$CH_3CH_2CH(CH_3)$-	265-270	68	$C_8H_{12}N_2O_2$	57.14	7.14	16.66	56.99	7.15	16.37
5h	$(CH_3)_2CHCH_2$-	>275	78	$C_8H_{12}N_2O_2$	57.14	7.14	16.66	56.87	7.20	16.44
5i	$(CH_3)_3C$-	242-245 (e)	46	$C_8H_{12}N_2O_2$	57.14	7.14	16.66	57.11	7.30	16.47
5j	$(CH_3)_3CCH_2$-	>300	65	$C_9H_{14}N_2O_2 \cdot H_2O$	53.98	8.06	13.99	54.09	7.70	13.88

(a) Lit. m.p. 299° dec. (8). (b) Lit. m.p. 300° dec. (9). (c) Lit. m.p. 296° dec. (10). (d) Lit. m.p. 300° dec. (11). (e) Lit. m.p. 242-246° (12).

Table II

2-Alkyl-4,6-dihydroxy-5-nitropyrimidines



Compound	R	M.p. °C	% Yield	Formula	Analysis Calcd. C	H	N	Found C	H	N
6c	CH_3CH_2-	275 d (a)	87	$C_6H_7N_3O_4 \cdot H_2O$	35.47	4.47	20.69	35.26	4.72	20.16
6d	$CH_3CH_2CH_2$-	290 d	32	$C_7H_9N_3O_4$	42.21	4.55	21.10	40.95	4.45	20.85
6e	$(CH_3)_2CH$-	280 d	82	$C_7H_9N_3O_4 \cdot H_2O$	38.71	5.11	19.35	39.06	5.32	19.30
6f	$CH_3(CH_2)_3$-	279 d (b)	47	$C_8H_{11}N_3O_4$	45.07	5.20	19.71	45.55	5.24	19.48
6g	$CH_3CH_2CH(CH_3)$-	265-270 d	67	$C_8H_{11}N_3O_4 \cdot H_2O$	41.67	5.67	18.18	42.04	5.85	18.35
6h	$(CH_3)_2CHCH_2$-	>250	62	$C_8H_{11}N_3O_4$	45.07	5.20	19.71	44.92	5.19	19.52
6i	$(CH_3)_3C$-	>250 (c)	75	$C_8H_{11}N_3O_4$	45.07	5.20	19.71	45.13	4.95	19.91
6j	$(CH_3)_3CCH_2$-	290 d	65	$C_9H_{13}N_3O_4$	47.57	5.72	18.50	47.80	6.00	18.67

(a) Lit. m.p. >260° dec. (13). (b) Lit. m.p. 265° dec. (11). (c) Lit. m.p. >300° (12).

4,6-Dihydroxy-2-(2-methylprop-1-yl)pyrimidine (**5h**).

The procedure used by Henze and McPherson (8) to prepare **5c** was applied to the preparation of **5h** on a one mole scale. The crude product (131 g., 78%) was recrystallized from 45% aqueous ethanol. Analytical data appear in Table I.

4,6-Dihydroxy-2-isopropyl-5-nitropyrimidine (**6e**).

Compound **5e** (123 g., 0.8 mole) was nitrated by the method of Boon, Ramage and Jones (14). Strict temperature control is required. If cooled below 25° little reaction occurs, and if heated above 40°, the reaction proceeds too vigorously resulting in very poor yields, yield, 163 g. (82%). Recrystallization was effected from aqueous ethanol. Analytical data appear in Table II.

4,6-Dichloro-2-(2,2-dimethylpropyl)-5-nitropyrimidine (**7j**).

Compound **6j** was chlorinated according to the procedure described by Boon, Ramage and Jones (14). The solid product was purified by sublimation (48°/0.03 torr), yield, 41.3 g. (93%). Analytical data appear in Table III.

5-Amino-2-*n*-butyl-4,6-dichloropyrimidine (**8f**).

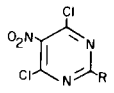
Compound **7f** (198 g., 0.8 mole) was reduced according to the procedure of Inoue, Saggiomo and Nodiff (7a). Distilled yield, 152.1 g., (87%). Analytical data appear in Table IV.

5-Amino-6-chloro-2-isopropylpyrimidin-4(3*H*)thione (**9e**).

A solution of potassium hydroxide (35.4 g., 0.63 mole) in 600 ml. of methanol was saturated with hydrogen sulfide, then cooled in ice during the addition of **8e** (64.7 g., 0.31 mole). The reaction was refluxed for 3 hours, then concentrated to dryness. The residue was dissolved in water, and the solution brought to *p*H 6 by addition of acetic acid. The precipitated product was collected by filtration and recrystallized from aqueous ethanol, yield, 49.3 g. (77%). Analytical data appear in Table V.

Table III

2-Alkyl-4,6-dichloro-5-nitropyrimidines

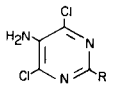


Compound	R	M.p. °C or B.p. °C torr	% Yield	Formula	Analysis Calcd. C	H	N	Found C	H	N
7c	CH_3CH_2-	78-80/.28 (a)	70	$C_6H_5Cl_2N_3O_2$	32.43	2.25	18.91	32.03	2.44	18.29
7d	$CH_2CH_2CH_3$	40-42	80	$C_7H_7Cl_2N_3O_2$	35.59	2.96	17.79	35.29	2.97	18.02
7e	$CH(CH_3)_2$	33-34 76-79/.35	73	$C_7H_7Cl_2N_3O_2$	35.59	2.96	17.79	35.69	2.89	18.11
7f	$(CH_2)_3CH_3$	119/.7 (b)	62	$C_8H_9Cl_2N_3O_2$	38.42	3.62	16.80	38.57	3.92	16.91
7g	$CH(CH_3)CH_2CH_3$	38-40	98	$C_8H_9Cl_2N_3O_2$	38.42	3.62	16.80	38.48	3.72	16.44
7h	$CH_2CH(CH_3)_2$	34-37	96	$C_8H_9Cl_2N_3O_2$	38.42	3.62	16.80	38.19	3.58	17.07
7i	$C(CH_3)_3$	79-81.5 (c)	89	$C_8H_9Cl_2N_3O_2$	38.42	3.62	16.80	38.57	3.92	16.91
7j	$CH_2C(CH_3)_3$	50-54	93	$C_9H_{11}Cl_2N_3O_2$	40.93	4.20	15.91	41.11	4.47	15.79

(a) Lit. b.p. 78°/0.2 (13). (b) Lit. b.p. 142-143°/17 (11). (c) Lit. m.p. 83-84° (12).

Table IV

2-Alkyl-5-amino-4,6-dichloropyrimidines

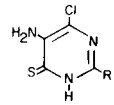


Compound	R	M.p. °C or B.p. °C torr	% Yield	Formula	Analysis Calcd. C	H	N	Found C	H	N
8c	CH_2CH_3	97/.75 (a)	50	$C_6H_7Cl_2N_3$	37.56	3.64	21.85	37.27	3.82	21.96
8d	$CH_2CH_2CH_3$	107-109/.6	70	$C_7H_9Cl_2N_3$	40.80	4.40	20.39	40.69	4.37	20.21
8e	$CH(CH_3)_2$	51-53	58	$C_7H_9Cl_2N_3$	40.80	4.40	20.39	40.54	4.46	20.68
8f	$(CH_2)_3CH_3$	100/.25	87	$C_8H_{11}Cl_2N_3$	43.66	5.04	19.09	43.86	5.27	18.91
8g	$CH_2(CH_3)CH_2CH_3$	63-65	19	$C_8H_{11}Cl_2N_3$	43.66	5.04	19.09	43.80	5.04	19.35
8h	$CH_2CH(CH_3)_2$	85-89/.07	87	$C_8H_{11}Cl_2N_3$	43.66	5.04	19.09	43.96	5.00	19.31
8i	$C(CH_3)_3$	92-94	94	$C_8H_{11}Cl_2N_3$	43.66	5.04	19.09	43.78	5.31	19.30
8j	$CH_2C(CH_3)_3$	81-82	93	$C_9H_{13}Cl_2N_3$	46.17	5.60	17.95	46.02	5.77	18.25

(a) Lit. b.p. 86°/0.3 (13).

Table V

2-Alkyl-5-amino-6-chloropyrimidin-4(3*H*)thiones

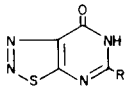


Compound	R	M.p. °C	% Yield	Formula	Analysis Calcd. C	H	N	Found C	H	N
9c	CH_2CH_3	>250 (a)	83	$C_6H_8ClN_3S$	38.00	4.25	22.15	36.68	4.51	21.21
9d	$CH_2CH_2CH_3$	>250	55	$C_7H_{10}ClN_3S$	41.27	4.95	20.63	41.08	4.95	21.31
9e	$CH(CH_3)_2$	>250	77	$C_7H_{10}ClN_3S$	41.27	4.95	20.63	41.24	4.90	20.95
9f	$(CH_2)_3CH_3$	130-150 (a)	52	$C_8H_{12}ClN_3S$	44.13	5.56	19.30	43.62	5.57	17.92
9g	$CH(CH_3)CH_2CH_3$	133-135	44	$C_8H_{12}ClN_3S$	44.13	5.56	19.30	43.87	5.80	19.27
9h	$CH_2CH(CH_3)_2$	>260 (a)	78	$C_8H_{12}ClN_3S$	44.13	5.56	19.30	43.40	5.70	18.25
9i	$C(CH_3)_3$	162-164	50	$C_8H_{12}ClN_3S$	44.13	5.56	19.30	44.39	5.95	18.71
9j	$CH_2C(CH_3)_3$	176-178	89	$C_9H_{14}ClN_3S$	46.64	6.09	18.13	47.23	6.25	17.57

(a) Not purified, used crude in the next step.

Table VI

2-Alkyl-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4(5*H*)ones



Compound	R	M.p. °C	% Yield	Formula	Analysis Calcd. C	H	N	Found C	H	N
3a	H	230-231 (a)	66	$C_4H_2N_4OS$	31.16	1.31	36.35	31.40	1.46	36.60
3b	CH_3-	239-242	33	$C_5H_4N_4OS$	35.72	2.40	33.33	36.31	2.76	33.17
3c	CH_2CH_3	213-216	36	$C_6H_6N_4OS$	39.56	3.29	30.76	39.42	3.63	30.48
3d	$CH_2CH_2CH_3$	145-149 d	68	$C_7H_8N_4OS$	42.85	4.08	28.57	42.26	4.22	27.92
3e	$CH(CH_3)_2$	210-213	59	$C_7H_8N_4OS$	42.85	4.08	28.57	42.87	4.19	28.28
3f	$(CH_2)_3CH_3$	163-165	68	$C_8H_{10}N_4OS$	45.71	4.80	26.66	45.53	4.75	26.80
3g	$CH(CH_3)CH_2CH_3$	149-152	49	$C_8H_{10}N_4OS \cdot \frac{1}{4}C_6H_6$ (b)	49.66	5.04	24.38	49.65	5.12	24.64
3h	$CH_2CH(CH_3)_2$	138-141	56	$C_8H_{10}N_4OS$	45.71	4.80	26.66	45.20	4.89	26.03
3i	$C(CH_3)_3$	226-229 d	60	$C_8H_{10}N_4OS$	45.71	4.80	26.66	45.61	4.75	26.41
3j	$CH_2C(CH_3)_3$	188-191	56	$C_9H_{12}N_4OS$	48.21	5.39	24.98	48.33	5.50	24.85

(a) Lit. m.p. 230-231° (3). (b) This amount of benzene was confirmed by pmr spectroscopy.

6-(2,2-Dimethylpropyl)-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4(5*H*)-one (**3j**).

A solution of **9j** (24.5 g., 0.12 mole) in 725 ml. of trifluoroacetic acid was added dropwise to a chilled solution of sodium nitrite (19.5 g., 0.25 mole) in 925 ml. of acetic acid and 580 ml. of water. The reaction mixture was stirred 2 hours at 0-5°, then allowed to warm to room temperature overnight. The reaction mixture was concentrated to approximately 100 ml. Dilution with water and extraction with chloroform gave the product as a yellow solid that was recrystallized from benzene, yield, 14.5 g. (56%). Analytical data appear in Table VI.

Acknowledgment.

The author wishes to acknowledge the skillful technical assistance of Richard Angel in the preparation of the compounds described herein.

REFERENCES AND NOTES

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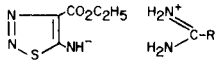
(3) E. C. Taylor and E. E. Garcia, *J. Org. Chem.*, **29**, 2121 (1964).

(4) These are the cases where the amidine acetates are commercially available.

(5) The necessity of using the acetate is explained by the unexpected acidity of **4** whose pK_a must lie between that of



acetic acid and hydrochloric acid. Consequently, when the acetate is used, **4** must displace acetate to form a salt, **i**, as a necessary first step in the reaction.

(6) E. C. Taylor and W. A. Ehrhart, *J. Am. Chem. Soc.*, 82, 3188 (1960).

(7a) S. Inoue, A. J. Saggiomo and E. A. Nodiff, *J. Org. Chem.*, 26, 4504 (1961); (b) Details of the final step courtesy of J. A. Montgomery and Y. F. Shealy, Southern Research Institute.

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