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Novel Synthesis and Reactions of 5,7-Dialkyl-4,6-dioxo-4,5,6,7-tetrahydro-isothiazolo[3,4,-*d*]pyrimidine-3-carbonitriles and 6-Methyl-4-oxo-4*H*-1-aza-5-oxa-2-thiaindene-3-carbonitrile

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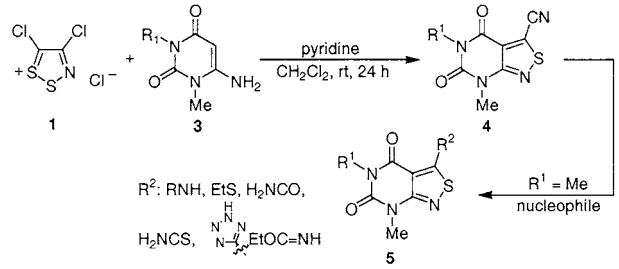
ABSTRACT



5,7-Dialkyl-4,6-dioxo-4,5,6,7-tetrahydroisothiazolo[3,4-*d*]pyrimidine-3-carbonitriles 4, prepared from 6-amino-1,3-dialkyluracils 3 and 4,5-dichloro-5*H*-1,2,3-dithiazolium chloride (Appel's salt) 1, are utilized for the preparation of new derivatives of 4 bearing amino, alkylthio, amido, thioamido, tetrazolyl, and carboximidic acid ethyl ester groups at position 3. Similarly, the reactions of 6-methyl-4-oxo-4*H*-1-aza-5-oxa-2-thiaindene-3-carbonitrile 8, prepared from 4-amino-6-methyl-2-pyrone 6 and 1, with alkyl- and arylamines in DMF at 50 °C and reflux afforded different isothiazole derivatives 11 and 17, respectively. On the other hand, treatment of 8 with 1,3-diaminopropane in THF at room temperature, followed by chromatography on silica gel, gave 3-(2-oxopropyl)-6,7,8-trihydro-4*H*-1-thia-2,5,9-triazacyclopentacyclononene-4,10-dione 12 in 59% yield.

3-Aminoisothiazolo[3,4-*d*]pyrimidine-4,6-diones are an interesting class of compounds since some of them have been reported to be useful as sedatives[1] and inflammation[1] and adenosine 3′,5′-cyclophosphate phosphodiesterase inhibitors.[1,2] They were synthesized in 11−59% yields by treating 6-amino-1,3-dialkyluracil with DMF−thionyl chloride in $CHCl_3$ at reflux.[2] A short time afterward, 5,7-dimethyl-3-glycosylaminoisothiazolo[3,4-*d*]pyrimidine-4,6-diones were reported to be prepared in 92−96% yields by the reactions of 6-amino-1,3-dimethyluracil with glycosyl isothiocyanates.[3] On the other hand, treatment of 6-amino-1,3-dialkyluracil with CS_2 and dimethyl sulfate gave 6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbodithioic acid methyl ester, which were subsequently reacted with I_2 in DMSO to give 3-methylthioisothiazolo[3,4-*d*]pyrimidine-4,6-diones.[4,5]

These compounds were reacted with amines, amides, and active methylene compounds to give isothiazolo[3,4-*d*]-pyrimidine-4,6-diones bearing a corresponding substituent

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[†] Seoul National University.
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(1) Furukawa, Y.; Miyashita, O. *Ger. Offen.* 2,453,212, **1975**.
(2) Furukawa, Y.; Miyashita, O.; Shima, S. *Chem. Pharm. Bull.* **1976**, *24*, 970−978.
(3) Takahashi, H.; Nimura, M.; Ogura, H. *Chem. Pharm. Bull.* **1979**, *27*, 1147−1152.

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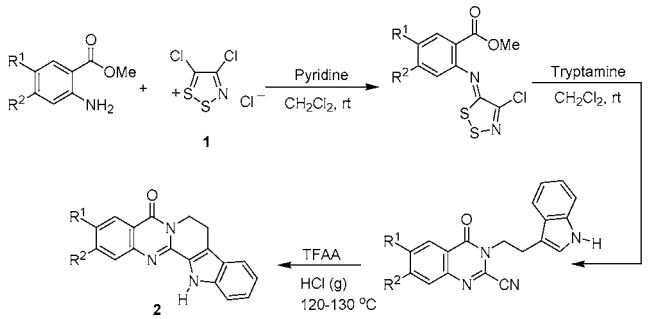
at the C-3 position.[4] No other isothiazolo[3,4-*d*]pyrimidine-4,6-diones have been hitherto reported.

In connection with exploring the synthetic utility of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) (**1**),[6] much attention has recently focused toward the reactions of 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles with nucleophiles. For example, the reactions of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazole-5-ylidene)anthranilates with tryptamine produced 2-cyano-3-[2-(indol-3-yl)ethyl]-4(3*H*)quinazolinones, which underwent cyclization on heating with TFAA/HCl (g) to afford quinazolinocarboline alkaloids **2** (Scheme 1).[7]

Scheme 1



We have found that the reaction of **1** (2.0 equiv) with 6-amino-1,3-dimethyluracil (R^1 = Me) (**3a**) in the presence of pyridine (4.5 equiv) in CH_2Cl_2 (25 mL) at room temperature gave 5,7-dimethyl-4,6-dioxo-4,5,6,7-tetrahydroisothiazolo[3,4-*d*]pyrimidine-3-carbonitrile (R^1 = Me) (**4a**) in 80% yield (Scheme 2). Under the same conditions, analogous compounds **4** having a different alkyl substituent at the C-5 position were prepared from **1** and various 3-alkyl-6-amino-1-methyluracils **3**, themselves prepared according to the reported procedures.[8] Yields of **4** are summarized in Table 1.[9]

Table 1. Yields of **4a**−**i**

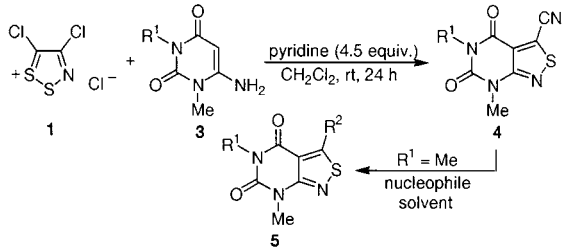
compd	R^1	yield[a] (%)	compd	R^1	yield[a] (%)
4a	Me	80	**4f**	3-butenyl	47
4b	Et	74	**4g**	4-pentenyl	35
4c	*i*-Pr	81	**4h**	4-pentynyl	14
4d	*n*-Bu	57	**4i**	Bn	78
4e	allyl	47			

[a] Isolated yields.

The lower yields of **4e**−**h** compared with those of **4a**−**d**,**i** may be due to the reactions of a double or triple bond on R^1 of **3** with **1** in view of the complex mixtures obtained from **1** (2 equiv) and ethyl vinyl ether in the presence of pyridine (3 equiv) under the same foregoing conditions.

The cyano group of **4a** was readily displaced or transformed by reactions with various nucleophiles from which new isothiazolo[3,4-*d*]pyrimidine-4,6-dione derivatives **5** were prepared (Scheme 2). For example, treatment of **4a** with

Scheme 2



n-$PrNH_2$ (2.0 equiv) in DMF (5 mL) for 1 h at reflux gave 5,7-dimethyl-3-(*n*-propylamino)-7*H*-isothiazolo[3,4-*d*]pyrimidine-4,6-dione (**5a**). Similar reaction with allylamine (2.5 equiv, 1 h) and tryptamine (1.6 equiv, 5 h) under the same conditions afforded analogous compounds **5b** and **5c**, respectively. Ethylthio derivative **5d** was prepared by stirring a mixture of **4a**, EtSH (3.2 equiv) and NaH (3.0 equiv) in THF (10 mL) for 3 h. An amide **5e** was obtained by treating **4a** with NaOH (2.9 equiv) in a mixed solvent (THF/H_2O = 10 mL/2 mL, rt, 1 h). Thioamide **5f** was obtained from **4a** (109 mg, 0.49 mmol) and $NaSH{\cdot}xH_2O$ (126 mg) in DMF (5 mL, rt, 1 h). Tetrazole derivative **5g** was obtained from **4a** and NaN_3 (2.7 equiv) in DMF (5 mL, reflux, 1 h). Carboximidic acid ethyl ester **5h** was obtained by treating **4a** with Na (2.2 equiv) in EtOH (10 mL, rt, 1 h). However, the reduction of the cyano group by $LiAlH_4$ (2.5 molar equiv) in THF at either rt or reflux temperature did not occur, with **4a** being recovered in 80% yield. Reaction conditions and yields of **5a**−**h** are summarized in Table 2.

4-Amino-6-methyl-2-pyrone (**6**) and 4-aminocoumarin (**7**), which are types of enamino ketones, underwent analogous reactions with **1** to give 6-methyl-4-oxo-4*H*-1-aza-5-oxa-2-thiaindene-3-carbontirile (**8**) and 4-oxo-4*H*-chromeno[4,3-

(4) Okuda, H.; Tominaga, Y.; Matsuda, Y.; Kogayashi, G. *Heterocycles* **1979**, *12*, 485−488.

(5) Okuda, H.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1979**, *99*, 989−992; *Chem. Abstr.* **1980**, *92*, 128845w.

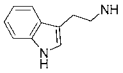
(6) (a) Appel, R.; Janssen, H.; Siray, M.; Knoch, F. *Chem. Ber.* **1985**, *118*, 1632−1643. (b) Kim, K. *Sulfur Rep.* **1998**, *21*, 147−210. (c) Rakitin, O. A.; Rees, C. W.; Vlasova, O. G. *J. Chem. Soc., Chem. Commun.* **1996**, 1273−1274.

(7) Mohanta, P. K.; Kim, K. *Tetrahedron Lett.* **2002**, *43*, 3993−3996.

(8) Priego, E.-M.; Camarasa, M.-J.; Pérez-Dérez, M.-J. *Synthesis* **2001**, 478.

(9) **Typical Procedure:** To a suspension of 4-chloro-5*H*-1,2,3-dithiazolium chloride **1** (454 mg, 2.18 mmol) in CH_2Cl_2 (20 mL) was added 6-amino-1,3-dimethyluracil (168 mg, 1.08 mmol), followed by dropwise of addition pyridine (391 mg, 4.94 mmol). The mixture was stirred for 24 h at room temperature. Water (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (25 mL × 3). The combined extracts were dried over $MgSO_4$. Evaporation of the solvent, followed by chromatography of the residue on a silica gel (70−230 mesh, 2 × 10 cm) with *n*-hexane as an eluant, gave sulfur. Subsequent elution with a 5:1 mixture of *n*-hexane and EtOAc gave 4-chloro-5*H*-1,2,3-dithiazole-5-thione (52 mg, 14%). Continuous elution with the same solvent mixture (3:1) gave 5,7-dimethyl-4,6-dioxo-4,5,6,7-tetrahydroisothiazolo[3,4-*d*]pyrimidine-3-carbonitrile (**4a**) (192 mg, 80%): mp 208−210 °C (CH_2Cl_2−*n*-hexane): IR (KBr) 2208, 1706, 1661, 1568, 1501, 1408, 1354, 1277, 1235, 1178, 1078, 979, 950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 3H, CH_3), 3.69 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 30.9, 108.5, 119.7, 138.1, 150.5, 154.9, 157.0. Anal. Calcd for $C_8H_6N_4O_2S$: C, 43.24; H, 2.72; N, 25.21; S, 14.43. Found: C, 43.33; H, 2.74; N, 25.14; S, 14.27.

Table 2. Solvents, Reaction Times, Temperature, and Yields of **5a**−**h**

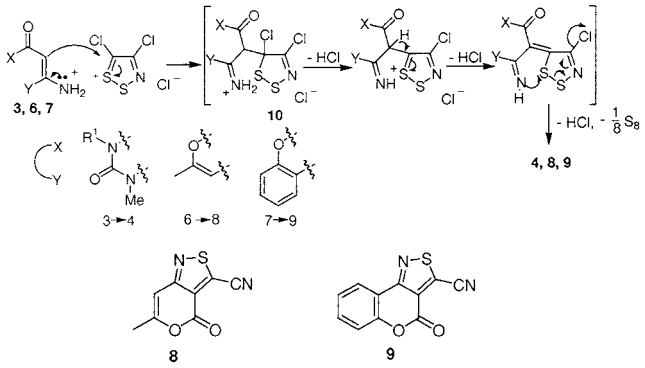
entry	solvent	time h	temp °C	compd	R^2	yield[a] %
1	DMF	1	reflux	**5a**	*n*-PrNH	97
2	DMF	1	reflux	**5b**		94
3	DMF	5	reflux	**5c**		74
4	THF	3	rt	**5d**	EtS[b]	92
5	THF/H_2O	1	rt	**5e**	H_2NCO[c]	53
6	DMF	1	rt	**5f**	H_2NCS[d]	33
7	DMF	1	reflux	**5g**		81
8	EtOH	1	rt	**5h**	EtOC=NH[f]	80

[a] Isolated yields. [b] EtS^- was prepared from EtSH and NaH in THF at room temperature. [c] NaOH was used as a nucleophile. [d] $NaSH{\cdot}xH_2O$ in DMF was used. [e] NaN_3 in DMF was used. [f] EtO^- was generated from Na and absolute EtOH.

c]isothiazole-3-carbonitrile (**9**) in 50 and 66% yields, respectively.

The mechanism for the formation of compounds **4**, **8**, and **9** may be explained by a nucleophilic attack of an enamino carbon of **3**, **6**, and **7** to C-5 of **1**, yielding an intermediate **10**, which loses successively three molecules of HCl and a sulfur to give compounds **4**, **8**, and **9** (Scheme 3).

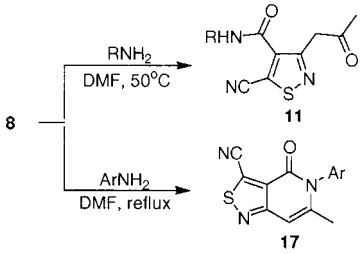
Scheme 3



Treatment of **8** with primary alkylamines in DMF at 50 °C gave 5-cyano-3-(2-oxopropyl)isothiazole-4-carboxylic acid alkylamide **11** (Scheme 4), which may be biologically important.[10]

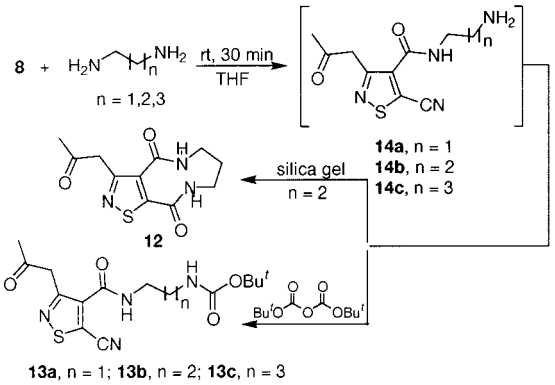
On the other hand, the reaction of **8** with secondary alkylamine or primary arylamine for 24 h did not occur even at 100 °C. The reaction of **8** with 1,3-diaminopropane (1.0 equiv) in THF for 0.5 h at room temperature, followed by removal of the solvent, gave **14b** as a yellow sticky material. However, attempts to purify this material by column chromatography (silica gel, 70−230 mesh) gave 3-(2-oxopropyl)-

Scheme 4



6,7,8-trihydro-4*H*-1-thia-2,5,9-triazacyclopentacyclononene-4,10-dione (**12**) (R_f = 0.6, EtOAc) in 59% yield (Scheme 5). The structure of **12** was determined on the basis of the

Scheme 5



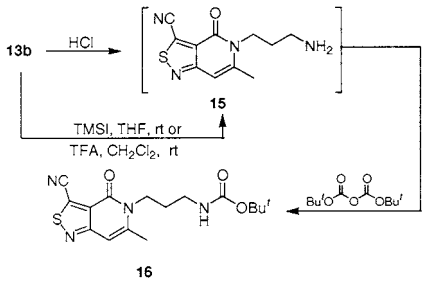
spectroscopic (^1H and ^{13}C NMR, HRMS) data. The addition of $(BOC)_2O$ (2.9 equiv) to **14b** for 30 min gave BOC-protected amino compound **13b** in 69% yield.

On the other hand, the same reactions with ethylenediamine and 1,4-diaminobutane under the same conditions gave yellow sticky materials **14a** and **14c**, which did not convert to the corresponding cyclization products analogous to **12**. However, as for **13b**, compounds **13a** and **13c** were obtained by treating **14a** and **14c** with $(BOC)_2O$ in 68 and 61% yields, respectively. Also, hydrolysis of **13b** with concentrated HCl did not give back **14b** but gave a new compound **15** (Scheme 6). Treatment with either TMSI (1.2 equiv) in THF or TFA in CH_2Cl_2 gave conceivably the same results. Upon addition of $(BOC)_2O$, [3-(3-cyano-6-methyl-4-oxo-4*H*-isothiazolo[4,3-*c*]pyridin-5-yl)propyl]carbamic acid *tert*-butyl ester (**16**) was formed.

Interestingly, compounds **17**, whose structures are analogous to **15**, were obtained when **8** was treated with arylamines in DMF at reflux (Scheme 4). An analogous reaction involving benzimidazole derivatives and 4-hydroxy-6-methyl-2-pyrone was reported.[11] However, heating **11a** and

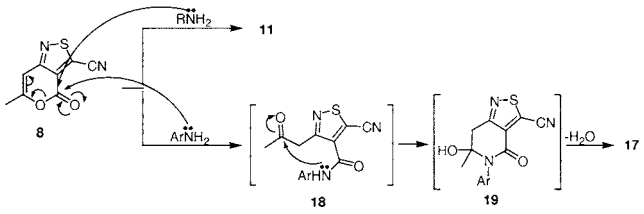
(10) (a) Gutri, C. C. C.; Garozzo, A.; Siracusa, M. A.; Sarva, M. C.; Castro, A.; Geremia, E.; Pinizzotto, M. R.; Guerrera, F. *Bioorg. Med. Chem.* **1999**, *7*, 225−230. (b) Volpp, G. P. U.S. Patent 3,375,161, 1968. (c) Hatehard, W. R. U.S. Patent 3,155,678, 1964.

Scheme 6



11b in DMF at reflux did not give a cyclization product analogous to **17**. The formation of **11** and **17** may be rationalized by a nucleophilic attack of primary alkyl- and arylamines to the carbonyl carbon, followed by a cleavage of an acyl−oxygen bond to give **11** and **18**, respectively (Scheme 7). However, when arylamines were employed, an

Scheme 7



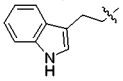
intermediate **18** analogous to **11** was conceived to undergo rapid cyclization to yield **19**. Dehydration of **19** would give **17**. It is uncertain why compound **11** did not give a cyclization product analogous to **17**. Presumably, the basicity of the medium may be critical to the success of the cyclization.

In the meantime, treatment of compound **9** with *n*-$PrNH_2$ (3 equiv) for 1 h under the same conditions as for the reactions of **8** showed many spots on TLC (1:2 EtOAc/*n*-hexane). Separation of the reaction mixture by chromatography failed. Reaction times and yields of **17** are summarized in Table 3.

The fact that only **14b** was converted to **12** in the presence of silica gel suggests that enthalpy as well as entropy effects are involved in this cyclization. Molecular mechanics calculations (Hyper Chem 5.0) show that the energy of **12** is 30.36 kcal/mol, whereas those of 8- and 10-membered cyclic compounds analogous to **12** are calculated to be 44.88

(11) Kihel, A. E.; Benchidmi, M.; Essassi, E. M.; Bauchat, P.; Danion-Bougot, R. *Synth. Commun.* **1999**, *29*, 2435−2445.

Table 3. Reaction Times and Yields of **11** and **17**

compd	R	time, h	yield,[a] %
11a	*n*-Pr	1	70
11b	*i*-Pr	0.5	70
11c	Bn	0.5	53
11d	Ally	1.5	70
11e	*t*-Bu	2	64
11f	*n*-Pentyl	0.5	73
11g	*n*-Hexyl	0.5	67
11h		1	66
17a	4-$MeOC_6H_4$	14	46
17b	4-ClC_6H_4	24	28
17c	4-MeC_6H_4	24	48
17d	3,5-$(MeO)_2C_6H_3$	48	41
17e	2,5-$(MeO)_2C_6H_3$	48	18

[a] Isolated yields.

and 29.74 kcal/mol, respectively. In view of the formation of 9-membered cyclic compound **12**, whose energy is 0.62 kcal/mol higher than that of 10-membered cyclic compound, the entropy factor leading to a 9-membered ring may be more favorable than the formation of a 10-membered cyclic compound. It is uncertain how silica gel promotes the cyclization of **14b** to give **12**.

In summary, various new 3-substituted isothiazolo[3,4-*d*]-pyrimidine-4,6-diones **5** were prepared by the reactions of 6-amino-1,3-dialkyluracils with Appel's salt, followed by transformation of the cyano groups with various nucleophiles. Similarly, 6-methyl-4-oxo-4*H*-1-aza-5-oxo-2-thiaindene-3-carbonitriles were prepared from 4-amino-6-methyl-2-pyrone and Appel's salt. The reactions of carbonitriles with alkyl- and arylamines gave 5-cyano-3-(2-oxopropyl)isothiazole-4-carboxylic acid alkylamides **11** and 5-aryl-6-methyl-4-oxo-4,5-dihydroisothiazolo[4,3,-*c*]pyridine-3-carbonitriles **17**, respectively, whereas the reaction with 1,3-diaminopropane gave **14b**, which was converted to nine-membered cyclic compound **12** on a silica gel and BOC-protected amino compound **13b** by treatment with $(BOC)_2O$.

Acknowledgment. Financial support from the BK21 program is highly acknowledged.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra IR and elemental analyses of **4b**−**i**, **5a**−**h**, **8**, **9**, **11a**−**h**, **12**, **13a**−**c**, **16**, **17a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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