A Facile Synthesis of 3-Substituted 2-Cyanoquinazolin-4(3*H*)-ones and 3-Alkyl-2-cyanothieno[3,2-*d*]pyrimidin-4(3*H*)-ones *via* 1,2,3-Dithiazoles

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The reaction of methyl anthranilate with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) in the presence of pyridine (2 equivalents) in dichloromethane at room temperature gave methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilate (**3a**) (50% yield), which reacted with sterically less hindered primary alkylamines to give directly 3-alkyl-2-cyanoquinazolin-4(3*H*)-ones **5** in moderate to good yields. With *tert*-butylamine, *N*-(2-methoxycarbonylphenyl)iminocyanomethyl *N*-(*tert*-butyl) disulfide **7** and methyl 2-(*N*-cyanothioformamido)anthranilate (**8**) were isolated in 33% and 59% yields, respectively. The cyano group of quinazoline **5a** (R = CH_3) is readily displaced by various nucleophiles to give 2-substituted quinazolinones **11-19**, which indicates that compounds **5** can be utilized as starting materials for the synthesis of new 2-substituted quinazolines. Similarly 3-alkyl-2-cyanothieno[3,2,-*d*]pyrimidin-4(3*H*)-ones **22** were prepared from methyl 3-[*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)]-2-thiophencarboxylate (**21**) in moderate to good yields.

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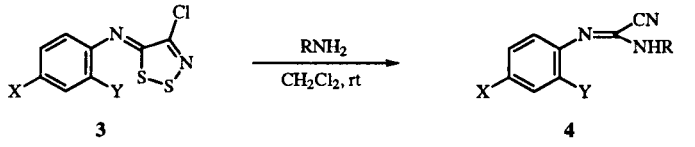
2,3-Disubstituted quinazolin-4(3*H*)-ones have attracted much attention for the last four decades owing to their potential biological activities [1]. Their synthetic methods have been extensively studied [2]. Surprisingly 2-cyanoquinazolin-4(3*H*)-ones have been seldom reported. There appear to be only two compounds, *i.e.*, 3-amino-2-cyanoquinazolin-4(3*H*)-one (**1**) [3] and 2-cyano-1-methylquinazolin-4(1*H*)-one (**2a**) [4] in the literature. The former was prepared in three steps in 42% yield starting from 2-hydroxypyrazolo[5,1-*b*]quinazolin-9-one and the latter by treatment of 2-carbamoyl-1-methylquinazolin-4(1*H*)-one (**2b**) with pyrophosphoryl chloride at 0°, followed by stirring at 40° in 51% yield. Since a cyano group is a good leaving group, 2-cyanoquinazolin-4(3*H*)-ones would be promising starting materials for a facile synthesis of various 2-substituted quinazolin-4(3*H*)-ones. We envisaged that methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilate (**3a**) would be a good precursor for the synthesis of 2-cyanoquinazolin-4(3*H*)-ones, since **3a** would be expected to give formamidine **4a** by treatment with primary alkylamines in view of the formation of **4b-c** as a minor product from the reaction of 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles **3b-c** with ethylamine in dichloromethane at room temperature [5] (Scheme 1). The intramolecular cyclization by a nucleophilic attack of the amino group to the ester carbonyl carbon would give 3-alkyl-2-cyanoquinazolin-4(3*H*)-ones **5**. We prepared **3a** from 3,4-dichloro-1,2,3-dithiazolium chloride (Appel's salt) (**6**) [6] and anthranilate and then compounds **3a** were subjected to the reactions with various primary alkylamines (Scheme 2). The results are described herein.

Scheme 1

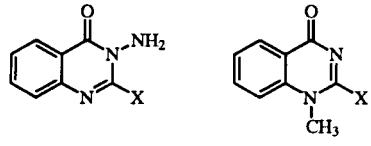


3

a, X = H, Y = CO_2CH_3
b, X = NO_2, Y = H
c, X = CH_3O, Y = H

4

a, X = H, Y = CO_2CH_3
b, X = NO_2, Y = H, R = CH_2CH_3
c, X = CH_3O, Y = H, R = CH_2CH_3



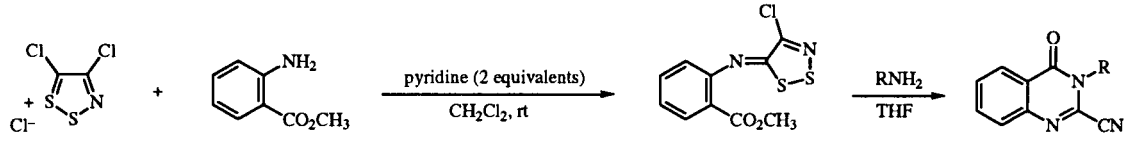
1
X = CN

2
a, X = CN
b, X = $CONH_2$

Results and Discussion.

Treatment of **3a** with less bulky primary alkylamines in tetrahydrofuran at room temperature did not give cyanoformamidines, analogous to **4a-c** as isolable prod-

Scheme 2



6 **3a** **5**

ucts. Instead, the desired compounds **5** were obtained in moderate to good yields. The reaction conditions and yields and melting points of **5** are summarized in Table 1

Table 1

Reaction Conditions, and Yields of Compounds **5**

Compound **3a** mmoles	Amine	mmoles	Time hours	Compound	Yield [c] %	Mp (°C)
3.50	R = CH_3 [a]	10.62	1	**5a**	73	164-165 [d]
0.73	R = CH_3CH_2 [b]	3.65	1	**5b**	81	142-144 [e]
1.84	R = $(CH_3)_2CH$	2.60	4	**5c**	74	85-86 [e]
1.24	R = *n*-$CH_3(CH_3)_3CH_2$	4.96	1	**5d**	67	liquid
1.18	R = $C_6H_5CH_2$	3.54	24	**5e**	63	129 [d]
1.86	R = NH_2	7.47	2	**1**	60	206-207 [d]

[a] 40% Aqueous solution. [b] 70% Aqueous solution. [c] Isolated yields. [d] From a mixture of dichloromethane and *n*-hexane. [e] From *n*-hexane.

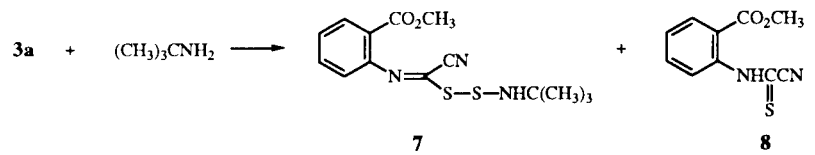
Table 2

^1H NMR, IR, and Mass Spectral and Analytical Data of **1** and **5a-e**

Compound	^1H nmr ($CDCl_3$) δ (ppm)	ir (KBr) (cm^{-1})	ms m/z	Molecular Formula	Analysis % Calcd./Found C	H	N
5a	3.79 (*s*, 3H, Me), 7.92-7.59 (m, 3H, ArH), 8.34 (d, 1H, J = 8.0 Hz, ArH)	1689, 1574	185 (M^+, 100%), 157 (22), 145 (79)	$C_{10}H_7N_3O$	64.86 64.75	3.81 3.79	22.70 22.59
5b	1.46 (t, 3H, J = 8.0 Hz, CH_3), 4.34 (q, 2H, J = 8.0 Hz, CH_2), 7.07-7.88 (m, 3H, ArH), 8.24 (d, 1H, J = 8.0 Hz, ArH)	2224, 1670, 1578, 1456	199 (M^+, 82%), 171 (100), 154 (21), 146 (63), 143 (30)	$C_{11}H_9N_3O$	66.32 66.27	4.55 4.47	21.09 21.04
5c	1.70 (d, 6H, J = 7.0 Hz, $2CH_3$), 5.18 (hept, 1H, J = 7.0 Hz, $CHCH_3$), 7.51-7.81 (m, 3H, ArH), 8.24 (d, 1H, J = 8.0 Hz, ArH)	2224, 1693, 1574, 1453	213 (M^+, 44%), 171 (100), 143 (27)	$C_{12}H_{11}N_3O$	67.59 67.49	5.20 5.15	19.71 19.62
5d	0.65 (t, 3H, J = 8.0 Hz, CH_3), 1.16-1.57 (m, 4H, $2CH_2$), 1.67-2.01 (m, 2H, CH_2), 4.23 (t, 2H, J = 8.0 Hz, CH_2N), 7.54-7.86 (m, 3H, ArH), 8.26 (d, 1H, J = 8.0 Hz, ArH)	2240, 1683, 1576, 1456	241 (M^+, 30%), 226 (22), 213 (59), 199 (34), 185 (37), 172 (100)	$C_{14}H_{15}N_3O$	69.69 69.63	6.27 6.29	17.41 17.54
5e	5.47 (*s*, 2H, CH_2), 7.24-7.89 (m, 8H, ArH), 8.34 (d, 1H, J = 8.0 Hz, ArH)	2232, 1685, 1571, 1456	261 (M^+, 96%), 244 (17), 91 (100)	$C_{16}H_{11}N_3O$	73.55 73.49	4.24 4.28	16.08 16.11
1	5.91 (*s*, 2H, NH_2), 7.89 (m, 3H, ArH), 8.22 (d, 1H, J = 8.0 Hz, ArH)	2240, 1683, 1606, 1459	186 (M+, 70%), 157 (100)	$C_9H_6N_4O$	58.06 58.11	3.25 3.22	30.09 30.05

and analytical and ^1H nmr, ir, and mass spectroscopic data in Table 2. With *tert*-butylamine, the corresponding quinazolinone **5** was not formed. Instead, disulfide **7** and cyanothioformamide **8** were isolated in 33% and 59% yields, respectively (Scheme 3). Compound **7** was completely transformed to **8** by repeated column chromatography.

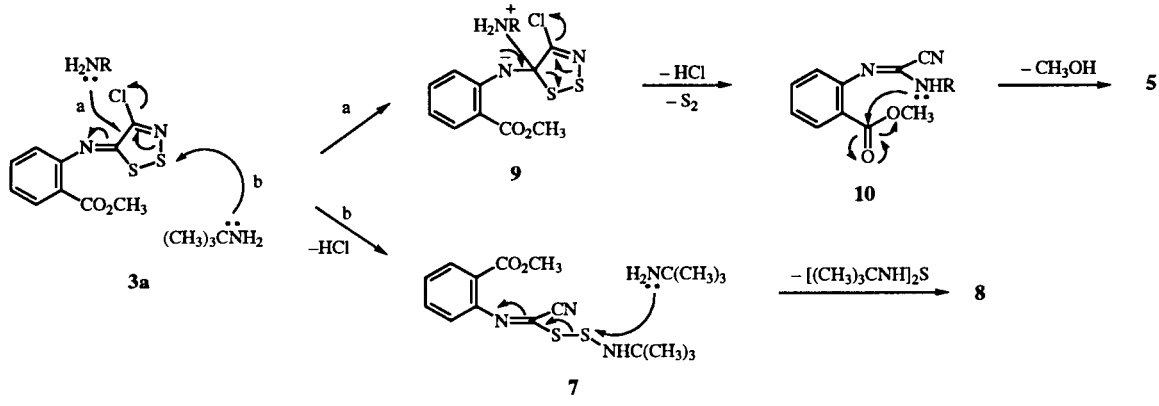
Scheme 3



7 **8**

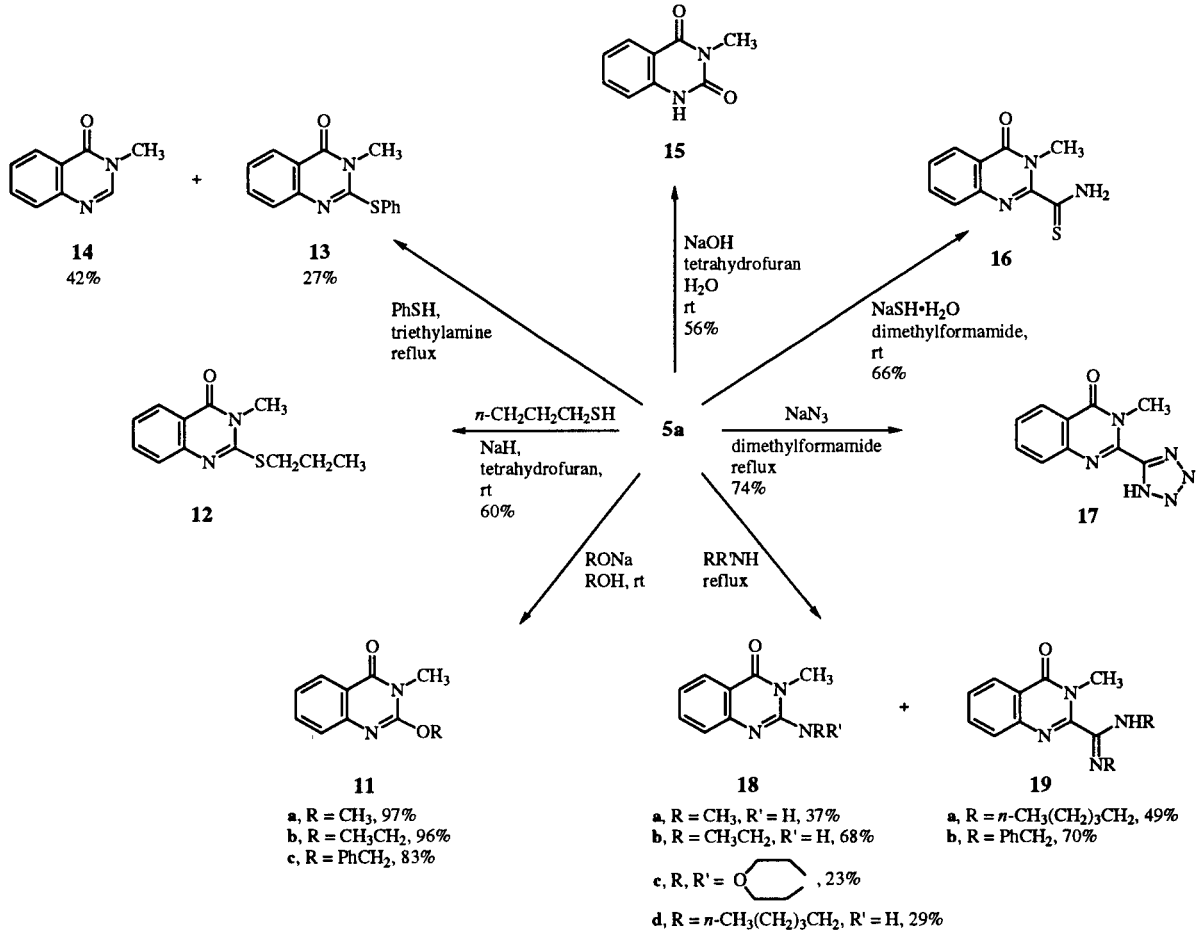
The mechanism for the formation of **5** may be rationalized by nucleophilic attack of primary alkylamine to C-5 of compound **3a** to give an intermediate **9** (path a), which extrudes hydrogen chloride and disulfur to give cyanoamidine **10** (Scheme 4). Intramolecular nucleophilic attack of the amino group to the ester carbonyl carbon takes place rapidly to yield quinazolinones **5**. However, when a bulky *tert*-butylamine is used, it attacks S-2 of **3a**, rather than C-5 to give unstable disulfide **7** (path b). Nucleophilic attack of a second molecule of *tert*-butylamine or other nucleophilic species to sulfur next to the nitrogen atom of disulfide **7** would give cyanothioformamide **8**.

Scheme 4



Compound **5a** was treated with various nucleophiles to give 2-substituted quinazolinones. The results are summarized in Scheme 5. Treatment of **5a** with sodium hydroxide in alcohol solvents at room temperature gave 2-alkoxyquinazolinones **11a-c** in good to excellent yields. Compounds **11a-b** were synthesized by methylation of 2-methoxy- and 2-ethoxyquinazolin-4(3*H*)-ones, which were produced by treatment of the corresponding 2,4-dialkoxyquinazolines with sodium in ethanol [7]. The reaction with *n*-propanethiol in the presence of sodium hydride in tetrahydrofuran at room temperature gave 2-(*n*-propylthio)qinazolinone **12** in 60% yield. Compound **12** was known and prepared in 60% yield by treatment of 3-methyl-2-mercaptoquinazolin-4(3*H*)-one with *n*-propyl

Scheme 5



bromide in the presence of ethanolic sodium hydroxide [8]. The starting mercapto compound was prepared by the reaction of anthranilic acid with methyl isothiocyanate [8]. Similar treatment with thiophenol under the same conditions as for *n*-propanethiol did not give 2-phenylthio derivative **13**. Only **5a** was quantitatively recovered. However, heating of a mixture of **5a** and thiophenol in the presence of triethylamine without a solvent at reflux gave **13** and 3-methylquinazolin-4(3*H*)-one (**14**) in 27% and 42% yields, respectively. Treatment of **5a** with sodium hydroxide in a mixture of tetrahydrofuran and water (25:1, v/v) at room temperature gave 3-methylquinazolin-2,4-dione (**15**) in 56% yield. Compound **15** was reported to be synthesized by hydrolysis of **11b** with aqueous hydrochloric acid [7]. The reaction of **5a** with sodium hydrosulfide monohydrate in *N,N*-dimethylformamide at room temperature gave 2-thioamidoquinazolin-4(3*H*)-one **16** in 66% yield. Interestingly, the cyano group of **5a** was not displaced by an azide ion in *N,N*-dimethylformamide at reflux. Instead, a tetrazole **17**, a [2 + 3] cycloadduct, was isolated in 74% yield. On the other hand, compound **5a** was quantitatively recovered from the reactions of **5a** with either alkyl- or arylamines at reflux (*p*-anisylamine in *p*-xylene, morpholine in *p*-xylene, methylamine (40% aqueous solution in tetrahydrofuran). However, 2-alkylaminoquinazolinones **18a-c** were obtained by heating a mixture of **5a** and the corresponding alkylamines, *i.e.*, methyl- and ethylamines, morpholine, respectively without a solvent at reflux. In addition, compound **15** was isolated in 21% yield when 40% aqueous methylamine was used. The reaction with *n*-pentylamine under the same conditions gave an analogous product **18d** and an amidine **19a** in 29% and 49% yields, respectively. Similar treatment with benzylamine gave only amidine **19b** in 70% yield. Literature survey shows that compound **18a** was prepared in 75% yield by heating of 4-dicyanomethyliden-2,3-dimethylquinazolin in the presence of acid [9], and 2-arylamino-3-methylquinzaolinones were prepared in three steps starting from *o*-azidoacetanilide in 97% yield [10].

The methodology involving Appel's salt and 2-aminoaryl carboxylate for the preparation of pyrimidinone derivatives was applied to methyl 3-amino-2-thiophenecarboxylate **20** in order to synthesize 3-alkyl-2-cyanothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **22**. Since much attention has been focused on the discovery and development of new types of 2,3-disubstituted thieno[3,2-*d*]-pyrimidin-4(3*H*)-ones owing to their diverse and potential biological activities, such as antiulcer [11], antihypertensive [12], antiinflammatory [13], antirheumatic [14], and angiotension II antagonist activities [15].

The reaction of **20** with Appel's salt **6** under the same conditions as for compound **3a** gave dithiazole **21** (67%), which reacted with primary alkylamines to afford 3-alkyl-2-cyanothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **22** and/or cyanoformamidines **23** as major products, depending on the bulkiness of the amines (Scheme 6). The reaction conditions and yields, and melting points of compounds **22** and **23** are summarized in Table 3 and their analytical and ^{1}H nmr and ir spectroscopic data in Table 4.

The reaction of **21** with simple alkylamines, *i.e.*, methyl- and ethylamines, proceeded smoothly at room temperature

Scheme 6

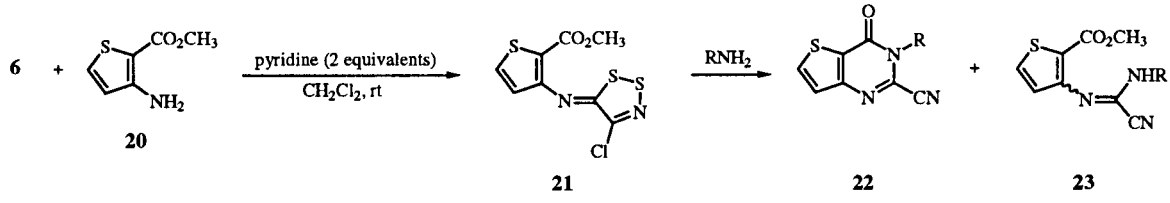


Table 3

Reaction Conditions and Yields and Melting Points of Compounds **22** and **23**

Compound **21** mmoles	Amines mmoles		Solvent	Temp. (°C)	Time hours	Compound	Yield [a] %	Mp (°C)	Compound	Yield [a] %	Mp (°C)
2.44	R = CH_3	15.10	tetrahydrofuran	rt	2	**22a**	80	141-142 [b]			
1.82	R = CH_3CH_2	12.36	tetrahydrofuran	rt	4	**22b**	84	109-111 [b]			
1.74	R = $(CH_3)_2CH$	3.89	CH_2Cl_2	rt	18				**23a**	67	62-64 [d]
1.74	R = $(CH_3)_2CH$	9.14	tetrahydrofuran	reflux	26	**22c**	52	92-94 [b]	**23a**	3	
0.871	R = $(CH_3)_3C$	3.42	CH_2Cl_2	rt	15				**23b**	59	liquid
1.57	R = *n*-$CH_3(CH_2)_3CH_2$	4.61	tetrahydrofuran	reflux	1.5	**22d**	83	50-51 [b]			
1.37	R = $PhCH_2$	3.45	tetahydrofuran	reflux	30	**22e**	64	128-129 [c]			
1.80	R = piperonyl	3.93	tetrahydrofuran	reflux	24	**22f**	71	171-173 [c]			

[a] Isolated yields. [b] From a mixture of chloroform and *n*-hexane. [c] From ethyl acetate. [d] From a mixture of *n*-hexane and dichloromethane.

Table 4

Analytical, ^1H NMR and IR Spectroscopic Data of Compounds **22** and **23**

Compound	^1H NMR δ (ppm)	IR (cm^{-1})	Molecular Formula	Analysis % Calcd./Found C	H	N	S
22a	3.82 (s, 3H, CH_3),7.36 (d, 1H, J = 5.3 Hz, =CH), 7.88 (d, 1H, J = 5.3 Hz, =CH)	1681, 1549, 1482, 1443	$C_8H_5N_3OS$	50.25 50.45	2.64 2.78	21.98 21.69	16.77 16.75
22b	1.50 (t, 3H, J = 7.2 Hz, CH_3), 4.42 (q, 2H, J = 7.2 Hz, CH_2), 7.41 (d, 1H, J = 5.2 Hz, =CH), 7.90 (d, 1H, J = 5.2 Hz, =CH)	1674, 1545, 1482, 1448	$C_9H_7N_3OS$	52.67 52.57	3.44 3.42	20.47 20.57	15.62 15.76
23a	1.23 (d, 6H, J = 7.2 Hz, $2CH_3$), 3.84 (s, 3H, OCH_3), 3.90 (s, br, 1H, CH), 5.37 (s, br, 1H, NH), 7.37 (d, 1H, J = 5.5 Hz, =CH), 7.82 (s, br, 1H, =CH) [a]	2224, 1689, 1634, 1571, 1570, 1435	$C_{11}H_{13}N_3O_2S$	52.57 52.42	5.21 5.18	16.72 16.80	12.76 12.88
22c	1.52 (d, 6H, J =7.2 Hz, $2CH_3$), 5.53 (s, br, 1H, CH), 7.42 (d, 1H, J = 5.2 Hz, =CH), 7.90 (d, 1H, J = 5.2 Hz, =CH)	1665, 1558, 1517, 1444	$C_{10}H_9N_3OS$	54.78 54.92	4.14 4.08	19.16 19.18	14.62 14.52
22d	0.93 (t, 3H, J = 7.1 Hz, CH_3), 1.37-1.46 (m, 4H, CH_2CH_2), 1.81-1.89 (m, 2H, CH_2), 4.32 (t, 2H, J = 8.3 Hz), 7.40 (d, 1H, J = 5.3 Hz, =CH), 7.89 (d, 1H, J = 5.3 Hz, =CH)	2224, 1670, 1550, 1486, 1450	$C_{12}H_{13}N_3OS$	58.28 58.33	5.30 5.42	16.99 17.06	12.96 13.05
22e	5.51 (s, 2H, CH_2), 7.23-7.66 (m, 5H, ArH), 7.41 (d, 1H, J = 5.5 Hz, =CH), 7.88 (d, 1H, J = 5.5 Hz, =CH) [a]	2232, 1681, 1542, 1483 1443	$C_{14}H_9N_3OS$	62.91 62.98	3.39 3.43	15.72 15.63	12.00 12.18
22f	5.44 (s, 2H, CH_2), 5.97 (s, 2H, CH_2), 6.80 (d, 1H, J = 8.4 Hz, ArH), 7.03-7.06 (m, 2H, ArH), 7.41 (d, 1H, J = 5.3 Hz, CH), 7.91 (d, 1H, J = 5.3 Hz, CH)	2224, 1686, 1542, 1493, 1442	$C_{15}H_9N_3O_3S$	57.87 57.78	2.91 2.86	13.50 13.41	10.30 10.51
23b	1.22 (s, 9H, $C(CH_3)_3$), 3.82 (s, 3H, OCH_3), 4.82 (s, br, 1H, NH), 6.78 (br, 1H, =CH), 7.49 (d, 1H, J = 5.5 Hz, =CH) [a]	1698, 1584, 1510, 1430, 1405	$C_{12}H_{15}N_3O_2S$	54.32 54.38	5.70 5.65	15.84 15.77	12.09 12.20

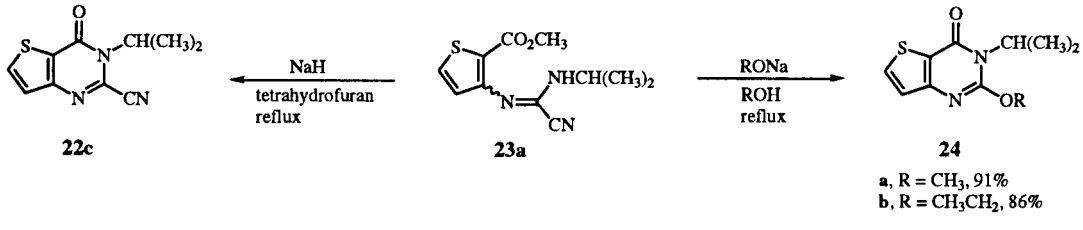
[a] Taken from 80 MHz nmr spectrophotometer, otherwise from 300 MHz nmr spectrophotometer.

to give pyrimidinones **22a** and **22b**, respectively. However, with a little bulkier isopropylamine in dichloromethane at room temperature, only cyanoamidine **23a** was obtained. By heating at reflux in tetrahydrofuran for a prolonged reaction time (26 hours) was obtained **22c** (52%) together with **23a** (3%). Similarly, the reaction with *tert*-butylamine in dichloromethane at room temperature gave cyanoformamidine **23b** (59%). The results indicate that pyrimidinones **22** are formed *via* the formation of cyanoformamidines **23** and that a cyanoformamidine possesing a bulky group on the amino nitrogen atom does not undergo cyclization reaction to give pyrimidinones **22**.

Apart from the reaction with *n*-pentylamine, the reactions with both of benzyl- and piperonylamines under the same reaction conditions proceeded slowly to give the corresponding pyrimidinones **22e-f**. Presumably a steric hindrance arising from the phenyl group may be responsible for the long reaction times. To the best of our knowledge, no pyrimidinones having a cyano group at C-2 have been reported, although the synthesis of thieno[3,2-*d*]-pyrimidin-4(3*H*)-one backbone structures has been achieved by a method involving **20** and different types of condensing agents as starting materials [16]. Compound **23a** reacted with sodium alkoxide in methanol or ethanol at reflux to give 2-methoxy- **24a** (91%) and 2-ethoxypyrimidones **24b** (86%), respectively, whereas **22c** (79%) was obtained by treatment with sodium hydride at reflux (Scheme 7).

It is noteworthy that the cyano group of cyanoformamidine **23b** was converted to a formyl group by treatment

Scheme 7

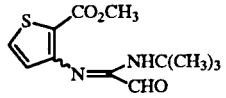


22c **23a** **24**

a, R = CH_3, 91%
b, R = CH_3CH_2, 86%

with sodium hydride in tetrahydrofuran at reflux, yielding compound **25** (37%). Again, the bulkiness of the *tert*-butyl group prevents the compound **22b** from cyclizing to give a pyrimidinone derivative.

In addition, treatment of **21** with ethanolamine (2 equivalents) for 3 days in tetrahydrofuran at room temperature gave pyrimidinones **26** and **27** in 9% and 63% yields, respectively (Scheme 8). Compound **26** was converted to compound **27** (74%) in tetrahydrofuran at reflux.



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Scheme 8

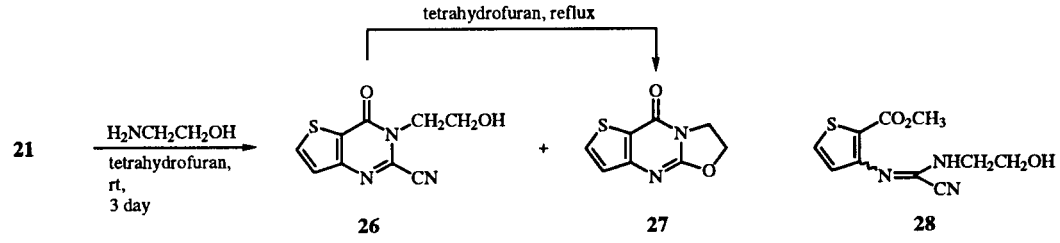

Table 5

^{1}H NMR, IR, and Mass Spectral Data of Compounds **18** and **19**

Compound	R	R'	^{1}H NMR ($CDCl_3$) δ (ppm)	IR (cm^{-1})	MS m/z	Molecular Formula	Analysis % Calcd./Found C	H	N
18a	CH_3	H	3.12 (d, 3H, J = 5 Hz, CH_3), 3.52 (s, 3H, CH_3), 4.73 (s, 1H, NH), 7.16-7.21 (m, 1H, ArH), 7.42 (d, 1H, J = 8 Hz, ArH), 7.57-7.63 (m, 1H, ArH), 8.11-8.14 (m, 1H, ArH)	3376, 1648, 1574, 1525	189 (M^+, 100%), 160 (67), 131 (22), 119 (43)	$C_{10}H_{11}N_3O$	63.48 63.62	5.86 5.83	22.21 22.09
18b	CH_3CH_2	H	1.26 (t, 3H, J = 7 Hz, CH_3), 3.39-3.73 (m, 2H, CH_2), 3.47 (s, 3H, CH_3), 4.62 (s, br, 1H, NH), 7.01-7.65 (m, 3H, ArH), 8.03-8.13 (m, 1H, ArH) [a]	3336, 1656, 1597	203 (M^+, 100%), 188 (12), 175 (64)	$C_{11}H_{13}N_3O$	65.01 65.16	6.45 6.38	20.67 20.81
18c	morpholine	H	3.24 (t, 4H, J = 6 Hz, $2CH_2$), 3.59 (s, 3H, CH_3), 3.86 (t, 4H, J = 6 Hz, $2CH_2$), 7.13-7.71 (m, 3 H, ArH), 8.19 (d, 1H, J = 8 Hz, ArH) [a]	1666, 1577, 1470	245 (M^+, 16%), 217 (12), 200 (14), 188 (100)	$C_{13}H_{15}N_3O$	63.66 63.54	6.16 6.23	17.13 16.98
18d	[b]	H	0.90 (t, 3H, J = 6 Hz, CH_3), 1.25-1.75 (m, 6H, $3CH_2$), 3.51 (m, 2H, NCH_2), 3.48 (s, 3H, CH_3), 4.49 (s, 1H, NH), 7.01-7.68 (m, 3H, ArH), 8.06-8.15 (m, 1H, ArH) [a]	3368, 1648, 1576, 1555 1525	245 (M^+, 24%), 202 (22), 189 (27), 175 (100)	$C_{14}H_{19}N_3O_2$	68.54 68.38	7.81 7.75	17.13 17.33
19a	[b]		0.88 (t, 6H, J = 6 Hz, $2CH_3$), 1.31 (s, br, 8H, $4CH_2$), 1.62 (s, br, 4H, $2CH_2$), 3.16 (s, br, 4H, $2CH_2$), 3.55 (s, 3H, NCH_3), 7.50-7.55 (m, 1H, ArH), 7.68-7.80 (m, 2H, ArH), 8.27 (d, 1H, J = 8 Hz, ArH) [a]	3352, 1675, 1640, 1589, 1523	342 (M^+, 36%) 285 (43), 271 (33), 201 (30), 186 (100)	$C_{20}H_{30}N_4O$	70.14 70.31	8.83 8.89	16.36 16.29
19b	$PhCH_2$		3.37 (s, 3H, CH_3), 4.44 (s, 4H, $2CH_2$), 7.25-7.74 (m, 13H, ArH), 7.34 (s, 1H, NH), 8.16 (d, 1H, J = 8 Hz, ArH)	3216, 1667, 1635, 1590, 1504		$C_{24}H_{22}N_4O$	75.37 75.48	5.80 5.72	14.65 14.69

[a] Taken from 80 MHz nmr spectrophotometer, otherwise 300 MHz nmr spectrophotometer. [b] $CH_3(CH_2)_3CH_2$.

The formation of cyanoformamidine **28**, which is believed to be the precursor of **26**, was confirmed by the gc-ms analysis of the reaction mixture which was obtained by quenching the reaction mixture in 15 hours.

Compound **27**, reported to possess a significant antigastric secretion activity [17], was prepared through either four steps or two steps including 2-chloroethyl isocyanate, which is rather expensive.

In summary, *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilate prepared from methyl anthranilate and Appel's salt is an excellent starting material for the synthesis of 2-cyanoquinazolinones which reacted with various nucleophiles to give 2-substituted quinazolinones. Similar reactions of methyl 3-[*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)]-2-thiophenecarboxylate with various alkylamines gave 3-alkyl-2-cyanothieno[3,2-*d*]pyrimidon-4(3*H*)-ones in moderate to good yields.

EXPERIMENTAL

Methyl *N*-4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilate (**3a**) was prepared according to the literature procedure [18].

General Procedure for the Preparation of 3-Alkyl-2-cyanoquinazolin-4(3*H*)-ones **5**.

To a solution of **3a** (0.73-3.50 mmoles) in tetrahydrofuran (40 ml) was added alkylamines (2.60-10.62 mmoles). The mixture was stirred for an appropriate time at room temperature. After removal of the solvent *in vacuo*, the residue was extracted with dichloromethane (2 x 30 ml). The extracts were dried over anhydrous magnesium sulfate. Removal of the solvent gave a residue which was chromatographed on a silica gel (1.5 x 7 cm). Elution with *n*-hexane gave sulfur. Elution next with a mixture of *n*-hexane and ethyl acetate (10:1) gave **5**. Consult Table 1 for reaction conditions of each reaction and yields of compounds **5**, and Table 2 for analytical and spectroscopic data of compounds **5**.

Reaction of **3a** with *tert*-Butylamine.

Compound **3a** (498 mg, 1.81 mmoles) was treated with *tert*-butylamine (397 mg, 5.43 mmoles) in tetrahydrofuran (30 ml) for 24 hours at room temperature. The mixture was worked up as described for the preparation of **5** and chromatographed on a silica gel (1.5 x 10 cm). Elution with *n*-hexane gave sulfur (75 mg, 0.292 mmole). Elution with a mixture of *n*-hexane and ethyl acetate (10:1) gave *N*-(*tert*-butyl) *N'*-(2-methoxycarbonylphenylimino)cyanomethyl disulfide (**7**) (193 mg, 33%), liquid; ir (neat): 3304, 2952, 2208, 1717, 1594, 1472 cm^{-1}; ^1H nmr (deuteriochloroform, 80 MHz): δ 1.23 (s, 9H, $C(CH_3)_3$), 3.81 (s, 3H, CH_3), 6.69-6.87 (m, 1H, ArH), 7.17-7.64 (m, 2H, ArH), 8.02 (d, 1H, J = 8 Hz, ArH).

Anal. Calcd. for $C_{14}H_{17}N_3O_2S_2$: C, 51.99; H, 5.30; N, 12.99; S, 19.83. Found: C, 51.82; H, 5.28; N, 13.08; S, 19.99.

Elution with the same solvent mixture gave methyl *N*-(cyanothioformamido)anthranilate (**8**) (234 mg, 59%), which was recrystallized from a mixture of dichloromethane and *n*-hexane, mp 124-125°; ir (potassium bromide): 2944, 1674, 1584, 1523 cm^{-1}; ^1H nmr (deuteriochloroform, 80 MHz): δ 3.91 (s, 3H, CH_3), 7.21-7.76 (m, 2H, ArH), 8.15 (d, 1H, J = 8 Hz, ArH), 9.19 (d, 1H, J = 8 Hz, ArH).

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.53; H, 3.66; N, 12.72; S, 14.56. Found: C, 54.60; H, 3.59; N, 12.85; S, 14.76.

General Procedure for the Preparation of 2-Alkoxy-3-methylquinazolin-4(3*H*)-ones **11a-c**.

For **11a** (R = CH_3), 3,4-dihydro-3-methyl-4-oxoquinazolinecarbonitrile (0.38 mmole) was added to a solution of sodium hydroxide (30 mg, 0.76 mmole) in methanol (30 ml). For **11b** (R = CH_2CH_3) and **11c** (R = $C_6H_5CH_2$), **3a** (0.36-0.49 mmole), sodium (1.74-2.22 mmoles) and ethanol (30 ml) and benzyl alcohol (30 ml) were used respectively. The mixture was stirred for 1 hour for **11a-b** and 16 hours for **1c** and then neutralized with hydrochloric acid. The solvent was removed *in vacuo* and the residue was extracted with dichloromethane (2 x 25 ml). The extracts were dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was recrystallized from *n*-hexane.

2-Methoxy-3-methylquinazolin-4(3*H*)-one (**11a**).

This compound had mp 90-91° (lit 93° [7]); ir (potassium bromide): 1674, 1603, 1470 cm^{-1}; ^1H nmr (deuteriochloroform, 80 MHz): δ 3.47 (s, 1H, NCH_3), 4.07 (s, 1H, OCH_3). 7.13-7.68 (m, 3H, ArH), 8.16 (d, 1H, J = 8 Hz, ArH).

2-Ethoxy-3-methylquinazolin-4(3*H*)-one (**11b**).

This compound had 96% yield, mp 75-76° (lit 75-76° [7]); ir (potassium bromide): 1670, 1602, 1557, 1470 cm^{-1}; ^1H nmr (deuteriochloroform, 80 MHz): δ 1.43 (t, 3H, J = 7 Hz, CH_3), 3.49 (s, 1H, NCH_3), 4.53 (q, 2H, J = 8 Hz, CH_2), 7.15-7.68 (m, 3H, ArH), 8.10 (d, 1H, J = 8 Hz, ArH).

2-Benzyloxy-3-methylquinazolin-4(3*H*)-one (**11c**).

This compound was obtained in 83% yield, liquid; ir (neat): 3024, 1675, 1600, 1560, 1470 cm^{-1}; ^1H nmr (deuteriochloroform, 80 MHz): δ 3.51 (s, 3H, CH_3), 5.52 (s, 2H, CH_2), 7.11-7.74 (m, 8H, ArH), 8.20 (d, 1H, J = 8 Hz, ArH); ms: m/z 266 (M^+, 53%), 180 (2), 160 (6), 146 (5), 119 (4), 91 (100).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.31; H, 5.37; N, 10.38.

Preparation of 3-Methyl-2-(*n*-propylthio)quinazolin-4(3*H*)-ones **12**.

Compound **3a** (78 mg, 0.42 mmole) was added to the solution of sodium hydride (78 mg, 3.25 mmoles) in tetrahydrofuran (25 ml). The mixture was stirred for 24 hours at room temperature, followed by quenching with water (10 ml). The solvent was evaporated *in vacuo* and the aqueous solution was extracted with dichloromethane (2 x 25 ml). The extracts were worked up as usual. Elution with a mixture of dichloromethane and *n*-hexane (1:1) gave an unknown mixture. Subsequent elution with the same solvent mixture (3:1) gave 3-methyl-2-(*n*-propylthio)quinazolin-4(3*H*)-one (**12**) (57 mg, 60%), which was recrystallized from methanol; mp 55-56° (lit 84° [8]); ir (neat): 1669, 1600, 1539, 1458 cm^{-1}; ^1H nmr (deuteriochloroform, 80 MHz): δ 1.03 (t, 3H, J = 7 Hz, CH_3), 1.79 (m, 2H, CH_2), 3.27 (t, 2H, J = 7 Hz, CH_2), 3.59 (s, 3H, CH_3), 7.20-7.72 (m, 3H, ArH), 8.21 (d, 1H, J = 8 Hz, ArH); ms: m/z 234 (M^+, 13%), 219 (10), 201 (23), 192 (100), 159 (20).

Anal. Calcd. for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96; S, 13.68. Found: C, 61.63; H, 6.09; N, 11.90; S, 13.54.

Preparation of 3-Methyl-2-phenylthioquinazolin-4(3*H*)-one (**13**).

A mixture of **3a** (115 mg, 0.62 mmole) and thiophenol (1.073 g, 9.74 mmoles) was heated in the presence of triethylamine (363 mg, 3.59 mmoles) for 24 hours at reflux. After removal of thiophenol *in vacuo*, the residue was chromatographed on a silica gel (1.5 x 15 cm). Elution with a mixture of ethyl acetate and *n*-hexane (1:5) gave **13** (38 mg, 27%), which was recrystallized from a mixture of dichloromethane and *n*-hexane, mp 136-139°; ir (potassium bromide): 1667, 1539, 1459 cm^{-1}; ^1H nmr (deuteriochloroform, 80 MHz): δ 3.69 (s, 3H, CH_3), 7.13-7.69 (m, 8H, ArH), 8.13-8.22 (m, 1H, ArH).

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; S, 11.95. Found: C, 67.08; H, 4.52; N, 10.58; S, 11.79.

Subsequent elution with ethyl acetate gave 3-methylquinazolin-4(3*H*)-one (**14**) (34 mg, 42%), which was recrystallized from a mixture of dichloromethane and *n*-hexane, mp 104-107° (lit 104-108° [19]).

Preparation of 3-Methyl-2-oxoquinazolin-4(3*H*)-one (**15**).

To a solution of **3a** (100 mg, 0.54 mmole) in tetrahydrofuran (25 ml) was added 5% aqueous sodium hydroxide (1 ml). The mixture was stirred for 4 hours at room temperature and then neutralized with hydrochloric acid. The mixture was worked up as described for compounds **5**. Elution with a mixture of *n*-hexane and ethyl acetate (2:1) gave unknown mixtures (26 mg). Subsequent elution with the same solvent mixture (1:1) gave **15** (52 mg, 56%), which was recrystallized from a mixture of dichloromethane and *n*-hexane, mp 241-244° (lit 242° [7]).

Preparation of 2-Thioamidoquinazolin-4(3*H*)-one (**16**).

To a solution of **3a** (60 mg, 0.32 mmole) in *N,N*-dimethylformamide (5 ml) was added sodium hydrosulfide hydrate (125 mg, 2.23 mmoles). The mixture was stirred for 2 hours at room temperature. After removal of the solvent, water (90 ml) was added to the residue, which was extracted with dichloromethane (3 x 30 ml). The extracts were dried over anhydrous magnesium sulfate and worked up as usual. Chromatography (1.5 x 7 cm) of the mixture using a mixture of *n*-hexane and ethyl acetate (1:1) as an eluent gave **16** (45 mg, 66%), which was recrystallized from a mixture of dichloromethane and *n*-hexane, mp 210-213°; ir (potassium bromide): 3320, 3248, 1685, 1614, 1576, 1461 cm^{-1}; ^1H nmr (deuteriochloroform + dimethyl-d_6 sulfoxide, 80 MHz): δ 3.64 (s, 3H, CH_3), 7.34-7.84 (m, 3H, ArH), 8.20 (d, 1H, J = 8 Hz, ArH), 10.06 (d, br, 2H, NH_2); ms: m/z 219 (M^+, 56%), 185 (100), 157 (17), 145 (69).

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16; S, 14.62. Found: C, 54.59; H, 4.16; N, 19.22; S, 14.77.

Preparation of 3-Methyl-5-tetrazolylquinazolin-4(3*H*)-one (**17**).

To a solution of **3a** (92 mg, 0.50 mmole) in *N,N*-dimethylformamide (25 ml) was added sodium azide (163 mg, 2.5 mmoles). The mixture was refluxed for one hour and then the solvent was removed *in vacuo*. The residue was treated with 30% aqueous hydrochloric acid to give solids **17** (85 mg, 74%), which was recrystallized from ethanol, mp 210° dec; ir (potassium bromide): 3016, 1640, 1584, 1534, 1467 cm^{-1}; ^1H nmr (deuteriochloroform + dimethyl-d_6 sulfoxide, 300 MHz): δ 3.85 (s, 3H, CH_3), 7.53 (t, 1H, J = 8 Hz, ArH), 7.69-7.79 (m, 2H, ArH), 8.20 (d, 1H, J = 8 Hz, ArH), 10.19 (s, br, 1H, NH); ms: m/z 200 (M^+-28, 84%), 171 (82), 157 (6), 144 (18), 131 (13), 116 (12), 103 (100).

Anal. Calcd. for $C_{10}H_8N_6O$: C, 52.63; H, 3.54; N, 36.82. Found: C, 52.49; H, 3.65; N, 36.85.

General Procedure for the Preparation of 2-Alkylamino-3-methylquinazolin-4(3*H*)-ones (**18**).

A mixture of **3a** (0.57-0.59 mmole) and alkylamines (43.1-123.6 mmoles) was heated for an appropriate time at reflux until no spot corresponding to **3a** had observed on a thin layer chromatogram. After removal of the amine used *in vacuo*, water (25 ml) was added to the residue, which was extracted with dichloromethane (3 x 25 ml). The extracts were dried (magnesium sulfate) and the mixture was worked up as usual. Chromatography (1.5 x 10 cm) of the reaction mixture obtained from only methylamine reaction using a mixture of *n*-hexane and ethyl acetate (1:1) as an eluent gave **15** (21%). Elution with the same solvent mixture (1:4) gave 3-methyl-2-(methylamino)quinazolin-4(3*H*)-one (**18a**) (37%), which was recrystallized from a mixture of dichloromethane and *n*-hexane, mp 195° (lit 197° [9]). Subsequent elution with acetone gave an unknown (34 mg). When ethylamine was employed, chromatography of the reaction mixture using a mixture of *n*-hexane and ethyl acetate (1:1) as an eluent gave 2-ethylamino-3-methylquinazolin-4(3*H*)-one (**18b**) (68%), which was recrystallized form a mixture of dichloromethane and *n*-hexane, mp 135-136°. Elution with acetone gave an unknown (15 mg). When morpholine was used 3-methyl-2-(4-morpholino)quinazolin-4(3*H*)-one (**18c**) was isolated (23%) by the same treatment as described for **18b**; mp of **18c**, 94-95° (from dichloromethane and *n*-hexane). When *n*-pentylamine was used 3-methyl-2-(*n*-pentyl)quinazolin-4(3*H*)-one (**18d**) was isolated (29%), mp of **18d**, 120-121° (from a mixture of dichloromethane and *n*-hexane). Elution with the same solvent mixture (1:1) gave 2-[*N*-(*n*-pentyl)-*N'*-(*n*-pentyl)]amidinyl-3-methylquinazolin-4(3*H*)-one (**19a**) (49%). In the case of the reaction with benzylamine, chromatography of the reaction mixture using the same solvent mixture (1:1) as that for **19a** gave 2-(*N*-benzyl-*N'*-benzyl)amidinyl-3-methylquinazolin-4(3*H*)-one (**19b**) (70%) which is a liquid. Consult Table 5 for analytical and ^1H nmr, ir, and mass spectroscopic data of **18** and **19**.

Preparation of Methyl 3-[*N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)]-2-thiophenecarboxylate (**21**).

To a mixture of methyl 3-amino-2-thiophenylcarboxylate (633 mg, 4.03 mmoles) and 4,5-dichloro-1,2,3- dithiazolium chloride (888 mg, 4.26 mmoles) in dichloromethane (100 ml) was added pyridine (702 mg, 8.87 mmoles) in dichloromethane (10 ml) for 20 minutes. The mixture was stirred for two hours at room temperature, and worked up as described in the literature [5]. Elution with a mixture of *n*-hexane and ethyl acetate (3:1) gave **21** (788 mg, 67%), which was recrystallized from a mixture of dichloromethane and *n*-hexane, yellowish needle type crystals, mp 126-127°; ^1H nmr (deuteriochloroform, 80 MHz): δ 3.81 (s, 3H, CH_3), 6.87 (d, 1H, J = 5.5 Hz, =CH), 7.57 (d, 1H, J = 5.5 Hz, =CH); ir (potassium bromide): 1698, 1594, 1507, 1430 cm^{-1}.

Anal. Calcd. for $C_8H_5ClN_2O_2S_3$: C, 32.82; H, 1.72; N, 9.57; S, 32.85. Found: C, 32.78; H, 1.74; N, 9.48; S, 32.69.

General Procedure for the Preparation of 2-Cyano-3-alkylthieno[3,2-*d*]pyrimidin-4-ones **22**.

To a solution of **21** (0.87-2.44 mmoles) in tetrahydrofuran or dichloromethane (100 ml) was added an alkylamine (2-3 molar equivalents). The mixture was stirred for an appropriate time at room or reflux temperature. After removal of the solvent *in*

vacuo, the residue was chromatographed on a silica gel (2 x 10 cm). Elution with *n*-hexane gave a small amount of sulfur and unknown mixtures. Subsequent elution with ethyl acetate gave compounds **22**. In the case of the reaction with isopropylamine, *N*-(2-methoxycarbonylthienyl)-*N'*-(isopropyl)cyanoformamidine (**23a**), followed by 2-cyano-3-(isopropyl)thieno[3,2-*d*]pyrimidin-4-one (**22c**) was eluted by using ethyl acetate.

Consult Table 3 for reaction conditions and yields, and melting points of compounds **22** and **23**, and Table 4 for analytical and ^{1}H nmr, and ir spectroscopic data.

General Procedure for the Preparation of 2-Alkoxy-3-isopropylthieno[3,2-*d*]pyrimidin-4-ones **24**.

A mixture of **23a** (0.8-0.9 mmole) and sodium hydroxide in alcohol was heated for two hours at reflux and then the solvent was evaporated off under reduced pressure. The mixture was worked up as for compounds **11**. Chromatography using a mixture of *n*-hexane and ethyl acetate (1:1) gave compounds **24**, recrystallized from a mixture of *n*-hexane and chloroform.

2-Methoxy-3-(isoproproylyl)thieno[3,2-*d*]pyrimidin-4-one (**24a**).

This compound was obtained in 91% yield, mp 100-102°; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 1.48 (d, 6H, J = 7.0 Hz, $C(CH_3)_2$), 4.07 (s, 3H, OCH_3), 5.50 (s, br, 1H, CH), 7.12 (d, 1H, J = 5.2 Hz, =CH), 7.68 (d, 1H, J = 5.2 Hz, =CH); ir (potassium bromide): 1667, 1570, 1472 cm^{-1}; ms: m/z 224 (M^+, 100%), 182 (86.1), 152 (75.6), 125 (32.2).

Anal. Calcd. for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49; S, 14.30. Found: C, 53.67; H, 5.45; N, 12.32; S, 14.51.

3-Ethoxy-3-(isopropyl)thieno[3,2-*d*]pyrimidin-4-one (**24b**).

This compound was obtained in 86% yield, mp 49-51°; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 1.48 (t, 3H, J = 7.0 Hz, CH_3), 1.51 (d, 6H, J = 7.4 Hz, $C(CH_3)_2$), 4.51 (q, 2H, J = 7.0 Hz, CH_2), 5.53 (s, br, 1H, CH), 7.10 (d, 1H, J = 5.3 Hz, =CH), 7.67 (d, 1H, J = 5.3 Hz, =CH); ir (potassium bromide): 1667, 1563, 1472 cm^{-1}.

Anal. Calcd. for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.76; S, 13.45. Found: C, 55.53; H, 5.97; N, 11.64; S, 13.59.

2-Cyano-3-(isopropyl)thieno[3,2-*d*]pyrimidin-4-one (**22c**).

A mixture of **23a** (177 mg, 0.704 mmole) and sodium hydride (20 mg, 0.83 mmole) in dried tetrahydrofuran (30 ml) was heated for fifteen hours at reflux and then the solvent was evaporated under reduced pressure. The reaction mixture was worked up as described for the compounds **24**. Elution with ethyl acetate gave **22c** (122 mg, 79%).

2-(*tert*-Butyamino)-2-(2-methoxycarbonylthiophen-3-ylimino)ethanal (**25**).

Treatment of **23b** (74 mg, 0.279 mmole) with sodium hydroxide under the same conditions as for **23a** gave **25** (28 mg, 37%), liquid; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 1.41 (s, 9H, $(CH_3)_3$), 3.88 (s, 3H, OCH_3), 4.66 (s, br, 1H, NH), 7.43 (d, 1H, J = 5.5 Hz, =CH), 8.00 (d, 1H, J = 5.5 Hz, =CH), 9.30 (s, br, 1H, CHO); ir (potassium bromide): 3320, 2952, 1666 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44; S, 11.95. Found: C, 53.85; H, 5.93; N, 10.38; S, 11.89.

Reaction of **21** with Ethanolamine.

(A) To a solution of **21** (947 mg, 3.23 mmoles) in tetrahydrofuran (30 ml) was added ethanolamine (486 mg, 7.86 mmoles), which was stirred at room temperature for three days and worked up as usual. Chromatography of the residue on a silica gel column (1.5 x 15 cm, 230-400 mesh) using a mixture of *n*-hexane and dichloromethane (4:1) as eluent gave a small amount of sulfur and unknown mixtures. Subsequent elution with a mixture of *n*-hexane and ethyl acetate (1:1) gave 2-cyano-3-(2-hydroxyethyl)thieno[3,2-*d*]pyrimidin-4-one (**26**) (62 mg, 9%); recrystallized from a mixture of methanol and chloroform, mp 170-172°; ^{1}H nmr (deuteriochloroform + dimethyl-d_6 sulfoxide, 300 MHz): δ 3.89 (q, 2H, J = 7.2 Hz, OCH_2), 4.44 (t, 2H, J = 7.2 Hz, NCH_2), 4.99 (t, 1H, J = 7.2 Hz, OH), 7.42 (d, 1H, J = 5.2 Hz, =CH), 7.99 (d, 1H, J = 5.2 Hz, =CH); ir (potassium bromide): 3504, 2232, 1646, 1541, 1483 cm^{-1}.

Anal. Calcd. for $C_9H_7N_3O_2S$: C, 48.86; H, 3.19; N, 18.99; S, 14.49. Found: C, 48.69; H, 3.14; N, 19.05; S, 14.62.

Elution with ethyl acetate gave oxazolo[3,2-*a*]thieno-[3,2-*d*]pyrimidin-5-one (**27**) (396 mg, 63%), recrystallized from chloroform: mp 187-188° (lit 183-185° [17]).

(B) The same reaction described in (A) was carried out for fifteen hours, and then the reaction mixture was subjected to gc-ms. One peak corresponding to *N*-(2-hydroxyethyl)-*N'*-(2-methoxycarbonylthiophen-3-ylimino)cyanoformamidine (**28**) showed mass numbers as follows; ms: m/z 256 (M^+, 80.9%), 221 (29.2), 192 (33.5), 160 (54.5), 128 (59.4), 96 (32.0), 64 (100).

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