A New Dimerization Reaction Producing 2-Amino-9-oxopyrrolo-[2,1-*b*]quinazoline-1-carbonitriles and Analogous Pyrrolo-[1,2-*a*]thieno[3,2-*d*]pyrimidinecarbonitriles

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A series of 2-alkylthio-4-oxo-3-quinazolineacetonitriles **4** and 2-alkylthio-4-oxothieno[3,2-*d*]pyrimidine-3-acetonitriles **8** was prepared. Upon treatment with sodium hydride, compounds **4** and **8** react to give 2-amino-4,9-dihydro-9-oxopyrrolo[2,1-*b*]quinazoline-1-carbonitriles **9** and 6-amino-4,9-dihydro-9-oxopyrrolo[1,2-*a*]thieno[3,2-*d*]pyrimidine-7-carbonitriles **10**, respectively. The transformation of compounds **4** and **8** to the tricyclic aminonitriles **9** and **10** involves a dimerization step followed by a pyrrole cyclization. The *tert*-butyl ester derivatives **4d** and **8d** upon treatment with sodium hydride underwent a Thorpe-Ziegler cyclization to provide enaminoesters of fused 1,3-thiazines (**16** and **17**, respectively) as major products.

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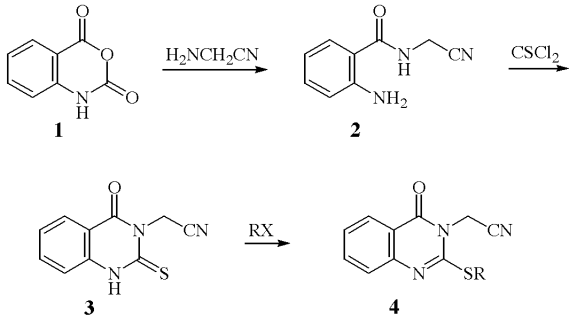
Cysteine proteases, a group of proteolytic enzymes, are important targets for the design of enzyme inhibitors, because of their role in important biological processes and their pathophysiological significance in several disease states. Amino acid and dipeptide derived nitriles are reported to inhibit several cysteine proteases [1]. We have prepared a series of 2-alkylthio-4-oxo-3-quinazolineacetonitriles and isosteric thieno[3,2-*d*]pyrimidine-3-acetonitriles. The reaction of these heterocyclic acetonitriles with thiols under basic conditions was investigated as a model reaction for the interaction of these compounds with cysteine proteases [2]. In the course of this mechanistic study [3], a dimerization reaction of the fused 2-alkylthiopyrimidin-3-acetonitriles was observed. In this paper, we wish to report the synthesis of 2-alkylthio-4-oxo-3(4*H*)-quinazolineacetonitriles **4a-d** and 2-alkylthio-4-oxothieno[3,2-*d*]-pyrimidine-3(4*H*)-acetonitriles **8a-d** and their dimerization to fused pyrrolopyrimidines upon treatment with sodium hydride.

A three-step synthesis, starting from isatoic anhydride **1** was utilized for the preparation of the 2-alkylthio-3-quinazolineacetonitriles **4** (Scheme 1). The 2-Amino-*N*-(cyanomethyl)benzamide **2** obtained by the reaction of **1** with aminoacetonitrile was reacted with thiophosgene to form the 4-oxo-2-thioxo-3-quinazolineacetonitrile **3**. Compounds **4a-d** were prepared in high yields by base catalyzed treatment of **3** with the appropriate alkyl halide in aqueous acetone at room temperature. The thienopyrimidineacetonitriles **8** were synthesized from the isothiocyanate **6** *via* the thioureidothiophene **7** (Scheme 2). A one-pot reaction with the appropriate alkyl halide, involving *S*-alkylation and cyclocondensation [4] afforded the 2-alkylthio thienopyrimidineacetonitriles **8a-d**.

Scheme 1



Scheme 2

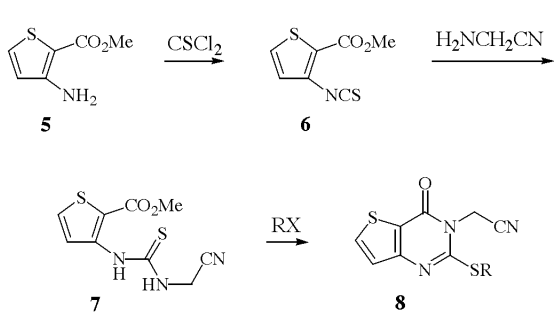


Table 1

2-(Alkylthio)-4-oxo-3(4*H*)-quinazolineacetonitriles **4** and 2-(Alkylthio)-4-oxothieno[3,2-*d*]pyrimidine-3(4*H*)-acetonitriles **8**

Compound	Yield (%)	mp (°C) (solvent)	Molecular Formula	Analysis Calcd./Found C	H	N	^{1}H NMR [a] δ (deuteriochloroform)	EI-MS (70 eV) m/z (%)
4a	92	180-180.5 (EtOH)	$C_{11}H_9N_3OS$	57.13 56.92	3.92 3.83	18.17 18.03	2.75 (s, 3H, CH_3), 5.10 (s, 2H, CH_2), 7.42-7.47 (m, 1H), 7.59-7.63 (m, 1H), 7.73-7.77 (m, 1H), 8.22-8.25 (m, 1H)	231 (M^+, 100)
4b	88	97-97.5 (cyclohexane)	$C_{13}H_{13}N_3OS$	60.21 60.37	5.05 5.10	16.20 16.13	1.11 (t, 3H, CH_3), 1.86 (sextet, 2H, CH_3CH_2), 3.36 (t, 2H, SCH_2), 5.09 (s, 2H, CH_2), 7.27-7.46 (m, 1H), 7.57-7.60 (m, 1H), 7.72-7.78 (m, 1H), 8.21-8.24 (m, 1H)	259 (M^+, 22), 217 ($M^+ - C_3H_6$, 100)
4c	92	129-130 (EtOH)	$C_{17}H_{13}N_3OS$	66.43 66.39	4.26 4.26	13.67 13.64	4.62 (s, 2H, SCH_2), 5.05 (s, 2H, CH_2), 7.30-7.36 (m, 3H), 7.43-7.50 (m, 3H), 7.64-7.67 (m, 1H), 7.75-7.79 (m, 1H), 8.22-8.26 (m, 1H)	307 (M^+, 78), 91 ($C_7H_7^+$, 100)
4d	79	140-141 (ethyl acetate/ cyclohexane)	$C_{16}H_{17}N_3O_3S$	57.99 57.97	5.17 5.17	12.68 12.65	1.49 (s, 9H, CH_3), 4.03 (s, 2H, SCH_2), 5.11 (s, 2H, CH_2), 7.42-7.48 (m, 1H), 7.53-7.56 (m, 1H), 7.72-7.76 (m, 1H), 8.21-8.25 (m, 1H)	331 (M^+, 21), 275 ($M^+ - C_4H_8$, 44), 258 ($M^+ - C_4H_9O$, 43), 57 ($C_4H_9^+$, 100)
8a	89	189-190 (EtOH)	$C_9H_7N_3OS_2$	45.56 45.41	2.97 2.96	17.71 17.63	2.73 (s, 3H, CH_3), 5.12 (s, 2H, CH_2), 7.26 (d, J = 5.3 Hz, 1H), 7.82 (d, J = 5.3 Hz, 1H)	237 (M^+, 100)
8b	91	103-104 (acetone/ water)	$C_{11}H_{11}N_3OS_2$	49.79 49.74	4.18 4.15	15.84 15.80	1.10 (t, 3H, CH_3), 1.84 (sextet, 2H, CH_3CH_2), 3.33 (t, 2H, SCH_2), 5.12 (s, 2H, CH_2), 7.23 (d, J = 5.2 Hz, 1H), 7.81 (d, J = 5.3 Hz, 1H)	265 (M^+, 25), 223 ($M^+ - C_3H_6$, 100)
8c	71	135-137 (acetone/ water)	$C_{15}H_{11}N_3OS_2$	57.49 57.34	3.54 3.63	13.41 13.33	4.59 (s, 2H, SCH_2), 5.05 (s, 2H, CH_2), 7.27-7.49 (m, 6H), 7.83 (d, J = 5.3 Hz, 1H)	313 (M^+, 99), 91 ($C_7H_7^+$, 100)
8d	62	150-151 (ethyl acetate/ diethyl ether)	$C_{14}H_{15}N_3O_3S_2$	49.84 49.63	4.48 4.48	12.45 12.45	1.49 (s, 9H, CH_3), 4.01 (s, 2H, SCH_2), 5.13 (s, 2H, CH_2), 7.23 (d, J = 5.3 Hz, 1H), 7.81 (d, J = 5.3 Hz, 1H)	337 (M^+, 16), 281 ($M^+ - C_4H_8$, 39), 264 ($M^+ - C_4H_9O$, 34), 57 ($C_4H_9^+$, 100)

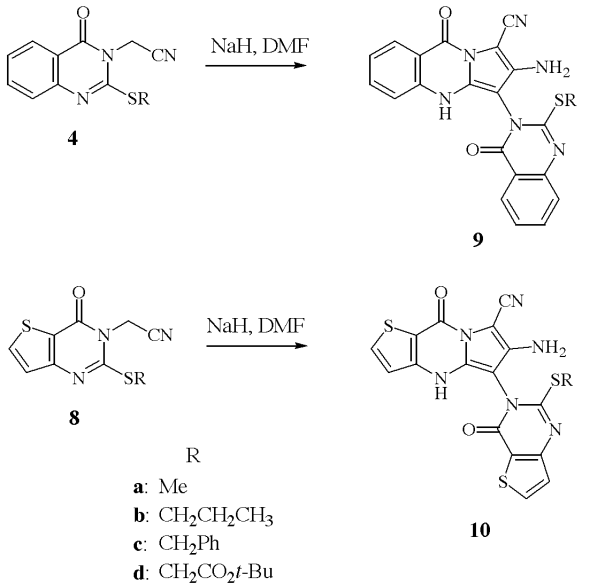
[a] Aromatic protons, unless otherwise assigned.

The structures of **4a-d** and **8a-d** were confirmed based on elemental analyses, mass spectra, and ^{1}H nmr data (Table 1). Compounds **4** and **8** are the first examples of bicyclic 4(3*H*)-pyrimidinones fused at C-5 and C-6, which have a cyanomethyl and an alkylthio moiety at positions 3 and 2.

Compounds **4** and **8** are heterocyclic substituted acetonitriles containing an activated methylene group, which should be deprotonated under strong basic conditions. The acidity of this methylene group is supported by the downfield shifted methylene signals of **4a-d** and **8a-d** which appear in the range of 5.05-5.13 ppm (Table 1). However, the resulting carbanion is not situated at a favorable distance from any electrophilic site in the molecule. Therefore, under basic conditions an intermolecular reaction might be expected. When **4a-c** and **8a-c** were treated with sodium hydride in dimethylformamide at 0° for one hour the products **9a-c** and **10a-c** (Scheme 3) were conveniently obtained in good yields (Table 2). Treatment of the *tert*-butyl ester derivatives **4d** and **8d** with sodium hydride provided **9d** and **10d** only as by-products; the reaction course of **4d** and **8d** is discussed below. The structures of **9a-d** and **10a-d** were confirmed based on elemental analyses, mass spectra, ir spectra, and ^{1}H nmr values (Table 2). The analytical and spectroscopic data indicated that the reaction products are dimers of the starting heterocycles and that one alkylthio group is lost. The ^{1}H nmr spectra of **9a-d** and **10a-d** showed two signals exchangeable with deuterium oxide: a singlet arising from one proton at 12.17-12.92 ppm, and a singlet integrating for two protons in the range of 6.43-6.46 ppm (for **9a-d**) or 6.26-6.30 ppm (for **10a-d**). The latter signal clearly indicated the presence of a NH_2 moiety in the reaction products. From these data, the pyrroloquinazoline and pyrrolothienopyrimidine structures **9** and **10** could be unambiguously deduced.

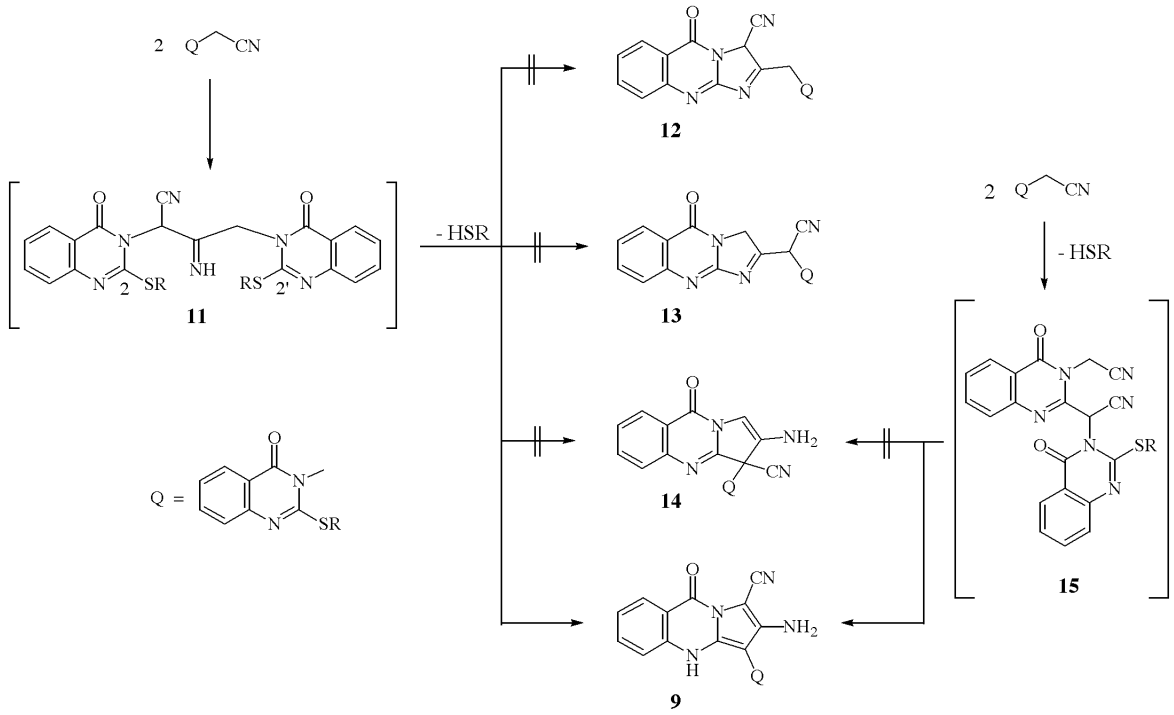
The reaction of the heterocyclic substituted acetonitriles **4** and **8** can be envisioned to occur by the mechanism shown for the quinazoline series in Scheme 4. The initial step might be a Thorpe reaction involving an intermolecular attack of the carbanion adjacent to the cyano group at the cyano group of another molecule.

Scheme 3



at the adjacent electrophilic C(2) or C(2') carbon of intermediate **11** would lead to the formation of the fused imidazoles **12** or **13**, respectively. However, neither structure **12** or **13**, nor tautomers that might be formed from **12** or **13**, are in agreement with the ^{1}H nmr data for the reaction products that we obtained. The same is the case for another isomeric structure, the pyrroloquinazoline **14**, that might be formed by the attack of the (deprotonated) methine moiety at the C(2') carbon of **11**. An attack of the activated methylene group at the C(2) carbon of **11**, followed by displacement of the alkylthio group and subsequent tautomeric rearrangement would form the final products **9**. The structures of the 2-aminopyrrolo[2,1-*b*]quinazoline-1-carbonitriles **9** (and the analogous pyrrolothienopyrimidines **10**) are completely in agreement with the spectral data for the reaction products that we obtained. The reaction products **9** could also be formed by an intermolecular attack of the activated methylene group initially at the C(2) carbon to form the dinitrile **15** [5]. The ^{1}H nmr data of the reaction products are not consistent with **15**, an isomer of **9**. However, a subsequent Thorpe-Ziegler cyclization [6] of the intermediate **15** and a tautomeric rearrangement could easily provide **9**. Thus, the

Scheme 4



The initially formed dimer **11** could subsequently react to displace one alkylthio group. Four different cyclizations leading to a fused five-membered ring are conceivable. Nucleophilic attack of the imino nitrogen

transformation of **4** and **8** to the heteroaromatic aminonitriles **9** and **10** occurs *via* a dimerization step followed by a pyrrole cyclization. However, we can not distinguish between the two possible mechanisms.

Table 2

9-Oxopyrrolo[2,1-*b*]quinazoline-1-carbonitriles **9** and 9-Oxopyrrolo[1,2-*a*]thieno[3,2-*d*]pyrimidine-7-carbonitriles **10**

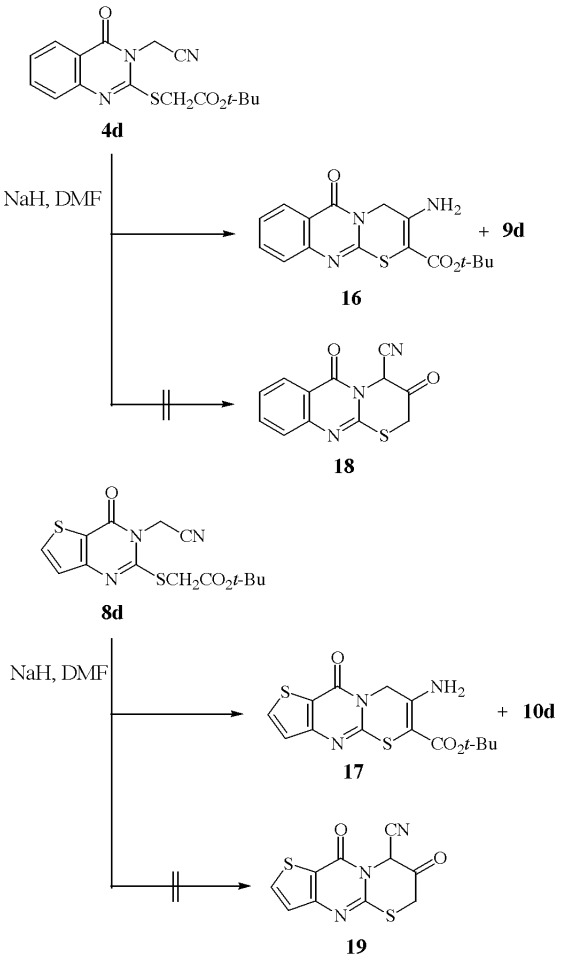
Compound	Yield (%)	mp (°C)	Molecular Formula	Analysis Calcd./Found C	H	N	IR [a] (cm^{-1})	^{1}H NMR (dimethyl-d_6 sulfoxide) [b] δ	FAB-MS MH^+
9a	79	>320 (dec.) [c]	$C_{21}H_{14}N_6O_2S$	60.86 60.54	3.40 3.49	20.28 19.99	2190 (CN), 1696, 1644 (C=O)	2.46 (s, 3H, CH_3), 6.46 (s, 2H [f], NH_2), 7.22-7.32 (m, 2H), 7.43-7.50 (m, 1H), 7.61-7.65 (m, 1H), 7.68-7.75 (m, 1H), 7.80-7.86 (m, 1H), 8.08-8.12 (m, 2H), 12.18 (s, 1H [f], NH)	415
9b	73	>310 (dec.) [c]	$C_{23}H_{18}N_6O_2S$	62.43 62.11	4.10 4.15	18.99 18.75	2188 (CN), 1696, 1640 (C=O)	0.95 (t, 3H, CH_3), 1.67 (sextet, 2H, CH_3CH_2), 3.00-3.15 (m, 2H, SCH_2), 6.43 (s, 2H, [f], NH_2), 7.21-7.31 (m, 2H), 7.43-7.49 (m, 1H), 7.59-7.63 (m, 1H), 7.68-7.74 (m, 1H), 7.79-7.86 (m, 1H), 8.06-8.13 (m, 2H), 12.17 (s, 1H [f], NH)	443
9c	66	318- 320 [c]	$C_{27}H_{18}N_6O_2S$	66.11 65.82	3.70 3.71	17.13 17.14	2190 (CN), 1696, 1644 (C=O)	4.36 (d, J = 13.5 Hz, 1H, CH_2), 4.41 (d, J = 13.5 Hz, 1H, CH_2), 6.43 (s, 2H [f], NH_2), 7.20-7.31 (m, 5H), 7.42-7.52 (m, 3H), 7.66-7.74 (m, 2H), 7.81-7.88 (m, 1H), 8.06-8.12 (m, 2H), 12.19 (s, 1H [f], NH)	491
9d	10	>250 (dec.) [e]	$C_{26}H_{22}N_6O_4S•H_2O$	58.64 58.37	4.54 4.57	15.78 15.68	2190 (CN), 1696, 1644 (C=O)	1.40 (s, 9H, CH_3), 3.83 (s, 2H, CH_2), 6.45 (s, 2H [f], NH_2), 7.23-7.33 (m, 2H), 7.44-7.55 (m, 2H), 7.69-7.76 (m, 1H), 7.80-7.87 (m, 1H), 8.07-8.13 (m, 2H), 12.23 (s, 1H [f], NH)	515
10a	58	>330 (dec.) [d]	$C_{17}H_{10}N_6O_2S_3•H_2O$	45.94 46.39	2.72 2.92	18.91 18.89	2190 (CN), 1684, 1630 (C=O)	2.42 (s, 3H, CH_3), 6.27 (s, 2H [f], NH_2), 7.03 (d, 1H), 7.41 (d, 1H), 8.16 (d, 1H), 8.21 (d, 1H), 12.88 (s, 1H [f], NH)	427
10b	51	312-314 [c]	$C_{19}H_{14}N_6O_2S_3$	50.21 49.83	3.10 3.44	18.49 18.01	2192 (CN), 1684, 1630 (C=O)	0.93 (t, 3H, CH_3), 1.65 (sextet, 2H, CH_3CH_2), 2.95-3.09 (m, 2H, SCH_2), 6.26 (s, 2H [f], NH_2), 7.03 (d, 1H), 7.39 (d, 1H), 8.15 (d, 1H), 8.20 (d, 1H), 12.85 (s, 1H [f], NH)	455
10c	76	300-302 [d]	$C_{23}H_{14}N_6O_2S_3•H_2O$	53.06 53.42	3.10 3.01	16.14 16.11	2192 (CN), 1686, 1632 (C=O)	4.31 (d, J = 13.5 Hz, 1H, CH_2), 4.37 (d, J = 13.5 Hz, 1H, CH_2), 6.28 (s, 2H [f], NH_2), 7.03 (d, 1H), 7.21-7.30 (m, 3H), 7.40-7.46 (m, 3H), 8.15 (d, 1H), 8.22 (d, 1H), 12.88 (s, 1H [f], NH)	503
10d	5	>325 (dec.) [e]	$C_{22}H_{18}N_6O_4S_3•H_2O$	48.52 48.51	3.70 3.64	15.43 15.20	2192 (CN), 1686, 1632 (C=O)	1.41 (s, 9H, CH_3), 3.80 (s, 2H, CH_2), 6.30 (s, 2H [f], NH_2), 7.05 (d, 1H), 7.30 (d, 1H), 8.17 (d, 1H), 8.20 (d, 1H), 12.92 (s, 1H [f], NH)	527

[a] In potassium bromide pellets. [b] Aromatic protons, unless otherwise assigned. [c] Recrystallization from ethyl acetate/cyclohexane. [d] Recrystallization from 2-methoxyethanol/water. [e] See Experimental. [f] Exchangeable with deuterium oxide.

Reaction of the *tert*-butyl ester derivatives **4d** and **8d** with sodium hydride provided the tricyclic enamino-esters **16** and **17** as the major products (Scheme 5). The reaction involves an intramolecular nucleophilic attack of the deprotonated thiomethylene moiety at the nitrile group followed by the tautomeric rearrangement of the imine to the more stable enamine [7,8]. Similar Thorpe-Ziegler cyclizations have found broad application for the synthesis of five-membered heterocycles [6,8]; the examples presented here involve the less common formation of fused thiazines. Additionally, the dimerization reaction occurred to form **9d** and **10d**, respectively, which could be separated from the major products (**16** and **17**) by fractional crystallization. The Dieckmann condensation products **18** and **19** were not formed in this reaction probably due to the lower reactivity of the *tert*-butyl ester carbonyl.

In conclusion, we discovered a convenient preparation of heteroaromatic aminonitriles of the pyrrolo[2,1-*b*]-quinazoline ring system and of the isosteric pyrrolo[1,2-*a*]-thieno[3,2-*d*]pyrimidine ring system by a new dimerization reaction. Despite several reports dealing with the chemistry and biological activity of pyrrolo[2,1-*b*]-quinazolines [9], 2-aminosubstituted pyrrolo[2,1-*b*]quinazolin-9-ones are still unknown. Only one pyrrolo[2,1-*b*]-quinazolin-9-one containing an aromatic pyrrole ring (2-phenylpyrrolo[2,1-*b*]quinazolin-9(4*H*)-one) has been described in the literature so far [10].

Scheme 5



EXPERIMENTAL

Thin-layer chromatography was performed using aluminum sheets coated with 0.2 mm silica gel 60 F_{254} (Merck). Melting points were obtained on a Büchi capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 16PC FTIR. ^{1}H nmr spectra were determined on a Varian Gemini 300 instrument. Mass spectra were recorded on a Varian MAT 1125 spectrometer. Elemental analyses were performed by Atlanta Microlab Inc., Norcross, GA. Isatoic anhydride (**1**), methyl 3-amino-2-thiophenecarboxylate (**5**), aminoacetonitrile bisulfate, thiophosgene, and the alkyl halides were purchased from Aldrich Co., Milwaukee, WI. Methyl 3-isothiocyanatothiophene-2-carboxylate (**6**) was prepared from **5** and thiophosgene according to a reported procedure [11], mp 56-58°, ref [12] 54-56°.

2-Amino-*N*-(cyanomethyl)benzamide (**2**).

Aminoacetonitrile bisulfate (38.5 g, 250 mmoles) and isatoic anhydride **1** (19.6 g, 120 mmoles) were added to a mixture of sodium hydroxide (9.6 g, 240 mmoles) and water (250 ml). The mixture was stirred on a boiling water-bath for 45 minutes and a portion of the product was collected by filtration and recrystallized from water to obtain 8.0 g of compound **2**. An additional portion of the product (6.1 g) was isolated after cooling the filtrate overnight. Colorless crystals; yield 64%; mp 94-95°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 4.22 (d, 2H, CH_2), 6.49-6.55 (m, 3H), 6.70-6.73 (m, 1H), 7.15-7.20 (m, 1H), 7.45-7.48 (m, 1H), 8.85 (t, broad, 1H, NH); ms (70 eV): m/z 175 (M^+, 53%), 119 (100%).

Anal. Calcd. for $C_9H_9N_3O$•0.5 H_2O: C, 58.69; H, 5.47; N, 22.81. Found: C, 58.97; H, 5.25; N, 22.71.

1,4-Dihydro-4-oxo-2-thioxo-3(2*H*)-quinazolineacetonitrile (**3**).

A solution of **2** (3.68 g, 20 mmoles) in dichloromethane (350 ml) was added over a period of 5 minutes to a mixture of thiophosgene (2.75 g, 24 mmoles), dichloromethane (100 ml), ice-water (160 ml), and potassium carbonate (5.5 g, 40 mmoles). The mixture was stirred for 2 hours at 0° and the precipitate that formed was removed by filtration and washed with water to give 3.6 g (83%) of **3** as a slightly yellow solid; mp 264-266° (ethyl acetate/cyclohexane); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 5.28 (s, 2H, CH_2), 7.36-7.43 (m, 2H, aromatic), 7.77-7.83 (m, 1H, aromatic), 7.99-8.02 (m, 1H, aromatic); ms (70 eV): m/z 217 (M^+, 100%).

Anal. Calcd. for $C_{10}H_7N_3OS$: C, 55.29; H, 3.25; N, 19.34. Found: C, 55.42; H, 3.56; N, 19.00.

2-(Alkylthio)-4-oxo-3(4*H*)-quinazolineacetonitriles **4a-d**.

General Procedure.

A solution of sodium hydroxide in water (1 *M*, 4.4 ml) was added to a mixture of **3** (870 mg, 4 mmoles), the appropriate alkyl halide (iodomethane, 1-bromopropane, benzyl chloride, *tert*-butyl chloroacetate, respectively, each 5 mmoles), and acetone (10 ml). The resulting mixture was stirred at room temperature for 24 hours, diluted with water and cooled. The precipitate was collected by filtration, dried, and recrystallized as indicated (Table 1).

Methyl 3-[3-(Cyanomethyl)thioureido]thiophene-2-carboxylate (**7**).

Compound **6** (2.99 g, 15 mmoles) was added to a stirred mixture of aminoacetonitrile bisulfate (2.77 g, 18 mmoles) and triethylamine (1.82 g, 18 mmoles) in dimethylformamide (75 ml). After stirring at room temperature for 2 hours, the reaction mixture was cooled at -10° for 1 hour, diluted with water, and cooled at 0° for 2 hours to produce 3.2 g (84%) of **7** as light brown crystals; mp 142-143°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.82 (s, 3H, CH_3), 4.56 (d, 2H, CH_2), 7.85 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 5.5 Hz, 1H), 9.47 (t, 1H, NH), 10.23 (s, 1H, NH); ms (70 ev): m/z 255 (M^+, 94%), 223 (M^+ - CH_3OH, 100%).

Anal. Calcd. for $C_9H_9N_3O_2S_2$: C, 42.34; H, 3.55; N, 16.46. Found: C, 42.15; H, 3.56; N, 16.33.

2-(Alkylthio)-4-oxothieno[3,2-*d*]pyrimidine-3(4*H*)-acetonitriles **8a-d**.

General Procedure.

Following the general procedure to prepare **4a-d** the appropriate alkyl halide was reacted with compound **7** (1.05 g, 4 mmoles). The crude products were recrystallized as indicated (Table 1).

2-Amino-4,9-dihydro-9-oxopyrrolo[2,1-*b*]quinazoline-1-carbonitriles **9a-c** and 6-Amino-4,9-dihydro-9-oxopyrrolo-[1,2-*a*]thieno[3,2-*d*]pyrimidine-7-carbonitriles **10a-c**.

General Procedure.

Compound **4** or **8** (each 2 mmoles) was added at 0° to a mixture of sodium hydride (48 mg, 2 mmoles) and dimethylformamide (7.5 ml). The reaction mixture was stirred at 0° for 1 hour, diluted with brine (300 ml) and extracted with ethyl acetate (3 × 120 ml). The combined organic layers were washed with water (300 ml) and dried (sodium sulfate). The solution was evaporated under reduced pressure and the residue was washed with a small amount of cold methanol. The products are shown in Table 2.

Treatment of *tert*-Butyl [[3-(Cyanomethyl)-3,4-dihydro-4-oxo-2-quinazolinyl]thio]acetate (**4d**) with Sodium Hydride.

Compound **4d** (662 mg, 2 mmoles) was treated with sodium hydride according to the procedure described above. The crude product was recrystallized from ethanol to obtain 245 mg (37%) of *tert*-butyl 3-amino-4,6-dihydro-6-oxo[1,3]thiazino-[2,3-*b*]quinazoline-2-carboxylate **16**, mp 225-226°; ir (potassium bromide): ν 1670 cm^{-1} (C=O); ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.46 (s, 9H, CH_3), 4.91 (s, 2H, CH_2), 7.43-7.56 (m, 2H, aromatic), 7.77-7.83 (m, 1H, aromatic), 7.84-7.94 (s, broad, 1H, NH, exchangeable with deuterium oxide), 8.07-8.13 (m, 1H, aromatic), 8.12-8.22 (s, broad, 1H, NH, exchangeable with deuterium oxide); ms (70 eV) m/z 331 (M^+, 27%), 275 ($M^+ - C_4H_8$, 97%), 231 ($M^+ - C_4H_8 - CO_2$, 100).

Anal. Calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68. Found: C, 58.19; H, 5.24; N, 12.81.

The ethanol filtrate was concentrated to a small volume, the resulting solid was collected and recrystallized from acetone/*n*-hexane to afford 55 mg (10%) of compound **9d** (Table 2).

Treatment of *tert*-Butyl [[3-(Cyanomethyl)-3,4-dihydro-4-oxothieno[3,2-*d*]pyrimidin-2-yl]thio]acetate (**8d**) with Sodium Hydride.

Compound **8d** (674 mg, 2 mmoles) was treated with sodium hydride according to the procedure described above. The crude product was washed with methanol (15 ml) to obtain 280 mg (42%) of *tert*-butyl 7-amino-8,10-dihydro-10-oxothieno-[3',2':4,5]pyrimido[2,1-*b*][1,3]thiazine-6-carboxylate **17**. An analytical sample was obtained by recrystallization from ethanol, mp 217-218°; ir (potassium bromide): ν 1670 cm^{-1} (C=O); ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.45 (s, 9H, CH_3), 4.91 (s, 2H, CH_2), 7.29 (d, 1H), 7.80-7.92 (s, broad, 1H, NH, exchangeable with deuterium oxide), 8.20 (d, 1H), 8.12-8.28 (s, broad, 1H, NH, exchangeable with deuterium oxide); ms (70 eV): m/z 337 (M^+, 19%), 281 ($M^+ - C_4H_8$, 100%), 237 ($M^+ - C_4H_8 - CO_2$, 74%).

Anal. Calcd. for $C_{14}H_{15}N_3O_3S_2$: C, 49.84; H, 4.48; N, 12.45. Found: C, 49.81; H, 4.59; N, 12.54.

The methanol filtrate was evaporated, the resulting solid was recrystallized first from acetone/*n*-hexane and afterwards from methanol/water with silica gel to obtain 25 mg (5%) of compound **10d** (Table 2).

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REFERENCES AND NOTES

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[2] Compounds **4** and **8** react with thiols under basic conditions *via* thioimidates generated by the attack of the thiolate at the nitrile function. The subsequent ring closure provides alkylthio derivatives of imidazo[2,1-*b*]quinazolinones and imidazo[1,2-*a*]thieno[3,2-*d*]pyrimidinones, respectively. This "trapped thioimidate" cyclization might be useful for the design of new types of cysteine protease inhibitors [3].

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