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Cyanamides in the Synthesis of 1,3-Thiazole and 1,3-Thiazine Derivatives

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Abstract—Hetaryl, aroyl, and aryl cyanamides react with 2-sulfanylbenzoic acid, 2-aminobenzenethiol, and 2-aminoethanethiol to give derivatives of 2-amino-4*H*-1,3-benzothiazin-4-one, 1,3-benzothiazol-2-amine, and 4,5-dihydro-1,3-thiazol-2-amine.

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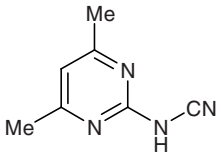
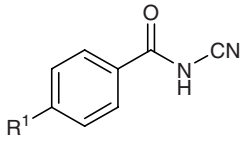
Cyanamides are convenient building blocks in the synthesis of various aliphatic, aromatic, and heterocyclic compounds [1]. Conjugation between lone electron pair on the amino nitrogen atom and the triple C≡N bond increases the electron density on the cyano nitrogen atom. Just enhanced nucleophilicity of the latter in combination with fairly high electrophilicity of the triple-bonded carbon atom is responsible for the high reactivity of cyanamides in various heterocyclizations. Advances in the preparative chemistry of cyanamides and accessibility of such sulfur-containing compounds as 2-sulfanylbenzoic acid (**I**), 2-aminobenzenethiol (**II**), and 2-aminoethanethiol (**III**; it is also known as radioprotective agent Mercamine) make it possible to widely use these compounds in the synthesis of S,N-containing heterocycles.

2-Amino-4*H*-1,3-benzothiazin-4-one derivatives (**IV**) can be obtained from acid **I** via reactions with compounds having a cyano group, e.g., phenylcarbamoyl cyanide [2], cyanamide H_2NCN, cyanoguanidine, and cyanourea [3, 4]. We used as cyano components cyanamides **V**–**XI**. Methods of preparation of these compounds were reviewed in [5].

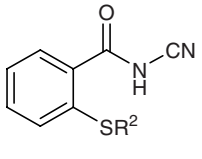
The reaction of acid **I** with cyanamides may involve initial nucleophilic attack by the cyano nitrogen atom on the electrophilic carbonyl carbon atom. However, it seems more likely that the reaction begins with addition of soft nucleophilic SH group at the triple-bonded carbon atom with formation of intermediate thiourea derivative **A**. The subsequent intramolecular cyclization yields benzothiazinones **IV** as shown in Scheme 1. This reaction sequence is supported by the following. First, heterocyclic analog of 2-sulfanylbenzoic acid (**I**), 2-sulfanylpyridine-3-carboxylic acid, in which the nucleophilicity of the SH group is reduced, reacted only with compound **VIa** containing a fairly electrophilic carbon atom in the cyanamide moiety; as a result, the corresponding 2-amino-4*H*-pyrido[3,2-*e*]-



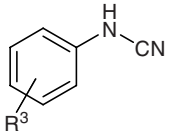
V



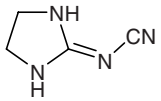
VIa, **VIb**



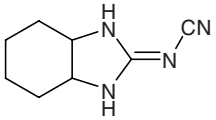
VIIa, **VIIb**



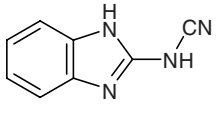
VIIIa, **VIIIb**



IX



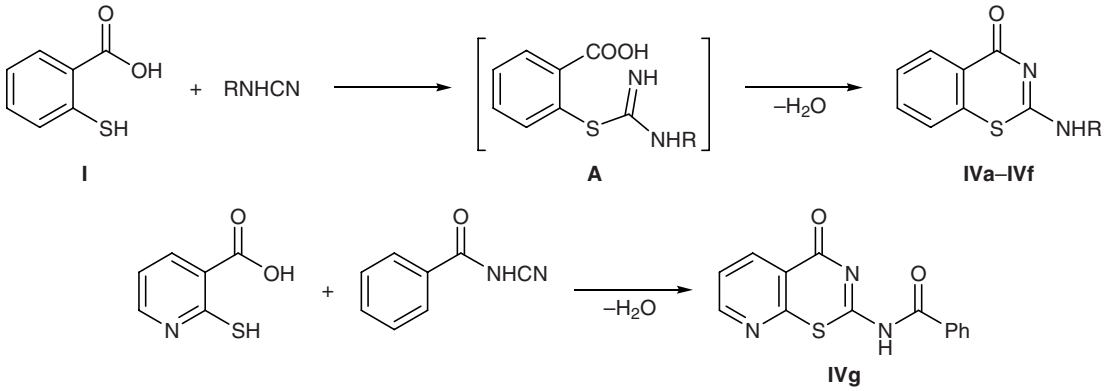
X



XI

R^1 = H (**a**), 4-Cl (**b**); R^2 = Me (**a**), Et (**b**); R^3 = 2-MeO (**a**), 4-MeO (**b**).

Scheme 1.



IV, R = 4,6-dimethylpyrimidin-2-yl (**a**), 2-$MeOC_6H_4$ (**b**), 4-ClC_6H_4CO (**c**), 2-$MeSC_6H_4CO$ (**d**), 2-$EtSC_6H_4CO$ (**e**), 4,5-dihydro-1*H*-imidazol-2-yl (**f**).

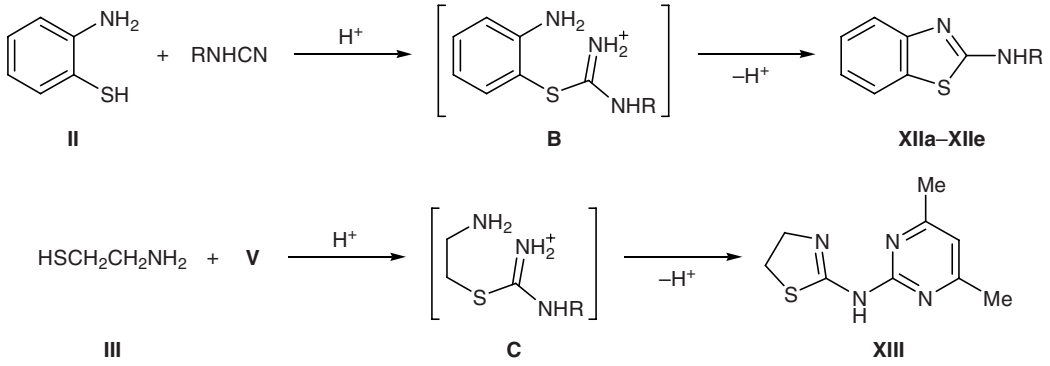
[1,3]thiazin-4-one derivative **IVg** was obtained. 2-Sulfanylpyridine-3-carboxylic acid failed to react with cyanamides **V** and **VIII**–**XI**, and the initial compounds were recovered from the reaction mixtures. Second, no reaction occurred between cyanamides and salicylic acid [3] which is an oxygen-containing analog of **I**. Finally, in keeping with published data [6], heterocyclizations of 2-sulfanylbenzoic acid (**I**) with dielectrophiles most frequently involve intermediate sulfides.

The thiazole ring can also be built up on the basis of the N–C–C–S dinucleophilic system [7] in compounds **II** and **III**. Ring closures with such 2-aminothiols require an electrophilic one-carbon fragment. Benzothiazole derivatives may be obtained from 2-aminobenzenethiol (**II**) and carboxylic acids [8] or their derivatives [9, 10], including nitriles [11, 12]. Reactions with some hetaryl-substituted cyanamides were also reported [13]. However, when such compounds were heated with thiol **II** in boiling ethanol over a period of 5 h, only the corresponding disulfide was formed as a result of oxidation. We found that the use of hydrochloric acid as general acid catalyst ensures shorter reaction time and prevents formation of by-products (Scheme 2).

Presumably, the heterocyclization involves intermediate formation of thioureas **B** and **C**. A similar intermediate was presumed in the reactions of 2-aminobenzenethiol (**II**) with *N*,*N*′-diarylcarbodiimides [14] (which may be regarded as structural analogs of cyanamides) and aromatic nitriles [11]. Protonation of the imino nitrogen atom in intermediate thiourea **B** facilitates subsequent elimination of that nitrogen atom. An analogous mechanism with participation of type **C** intermediate was proposed previously for the formation of 2-aminodihydrothiazole from *S*-aminoethylisothiuronium bromide on heating [15]. In the reaction with cyanamide **X** incorporating a basic guanidine fragment, 2 equiv of HCl was necessary.

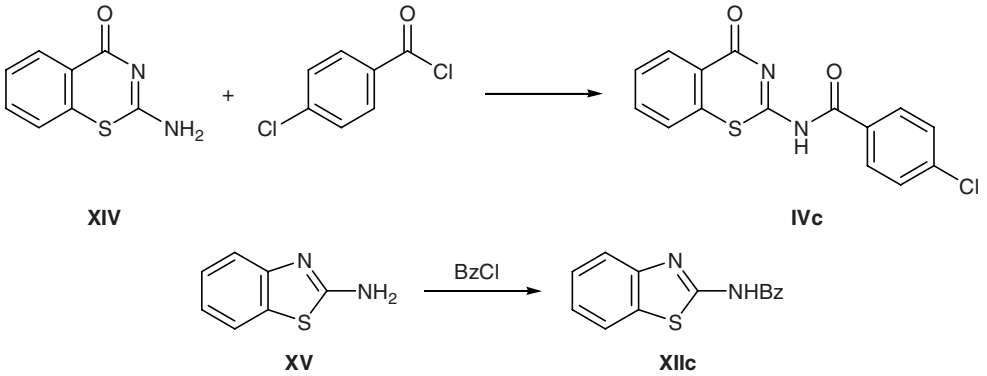
The structure of benzothiazinone **IVc** and benzothiazole **XIIc** was confirmed by independent syn-

Scheme 2.



XII, R = 4,6-dimethylpyrimidin-2-yl (**a**), 4-$MeOC_6H_4$ (**b**), PhCO (**c**), 2-$EtSC_6H_4CO$ (**d**), 3a,4,5,6,7,7a-hexahydro-1*H*-benzimidazol-2-yl (**e**).

Scheme 3.



theses, acylation of 2-amino-4*H*-1,3-benzothiazin-4-one (**XIV**) and 1,3-benzothiazol-2-amine (**XV**) with 4-chlorobenzoyl chloride and benzoyl chloride, respectively (Scheme 3).

EXPERIMENTAL

The progress of reactions and the purity of products were monitored by TLC using Merck UV-254 plates; eluent chloroform–methanol (20:1). The ^{1}H NMR spectra were measured on a Bruker AC-300 spectrometer (300 MHz) relative to TMS as internal reference.

2-(4,6-Dimethylpyrimidin-2-ylamino)-4*H*-1,3-benzothiazin-4-one (IVa). *a*. A mixture of 1.54 g (10 mmol) of acid **I** and 1.48 g (10 mmol) of cyanamide **V** in dioxane was heated for 5 h under reflux. It was then evaporated on a rotary evaporator, and the residue was recrystallized from dioxane–DMF (1:1). Yield 1.00 g (35%), mp 240–241°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 2.48 s (6H, CH_3), 6.90 s (1H, 5′-H), 7.42–7.53 m (2H, H_{arom}), 7.63 t (1H, H_{arom}, J = 7 Hz), 8.22 d (1H, H_{arom}, J = 8 Hz), 11.85 br.s (1H, NH). Found, %: C 59.36; H 4.17; N 19.86. $C_{14}H_{12}N_4OS$. Calculated, %: C 59.14; H 4.25; N 19.70.

Benzothiazinones **IVb**–**IVf** were synthesized in a similar way.

2-(2-Methoxyphenylamino)-4*H*-1,3-benzothiazin-4-one (IVb). After evaporation of the reaction mixture, the residue was recrystallized from propan-2-ol. Yield 0.80 g (28%), mp 131–132°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.78 s (3H, OCH_3), 6.93–7.25 m (4H, H_{arom}), 7.44 t (2H, H_{arom}, J = 9 Hz), 7.51 t (1H, H_{arom}, J = 8 Hz), 8.19 d (1H, H_{arom}, J = 9 Hz), 11.79 br.s (1H, NH). Found, %: C 63.34; H 4.16; N 9.74. $C_{15}H_{12}N_2O_2S$. Calculated, %: C 63.36; H 4.25; N 9.85.

4-Chloro-*N*-(4-oxo-4*H*-1,3-benzothiazin-2-yl)-benzamide (IVc). Yield 1.05 g (33%), mp 238–240°C (*a*).

b. 4-Chlorobenzoyl chloride, 1.87 g (10.5 mmol), was added to a solution of 1.78 g (10 mmol) of thiazinone **XVI** in 10 ml of anhydrous pyridine, and the mixture was stirred for 2 h and diluted with cold water. The precipitate was filtered off and recrystallized from DMF. Yield 1.39 g (44%), mp 237–239°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 7.22 t (1H, H_{arom}, J = 7 Hz), 7.35 d (1H, H_{arom}, J = 9 Hz), 7.55 d (2H, H_{arom}, J = 8 Hz), 7.65 d (1H, H_{arom}, J = 8 Hz), 7.76 t (1H, H_{arom}, J = 8 Hz), 7.93 d (2H, H_{arom}, J = 9 Hz), 12.52 s (1H, NH). Found, %: C 56.60; H 2.84; N 8.96. $C_{15}H_9ClN_2O_2S$. Calculated, %: C 56.88; H 2.86; N 8.84.

2-Methylsulfanyl-*N*-(4-oxo-4*H*-1,3-benzothiazin-2-yl)benzamide (IVd). Yield 1.87 g (57%), mp 194–195°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 2.42 s (3H, SCH_3), 7.20 t (1H, H_{arom}, J = 8 Hz), 7.33 d (1H, H_{arom}, J = 9 Hz), 7.45–7.56 m (2H, H_{arom}), 7.61–7.75 m (2H, H_{arom}), 8.21 br.s (1H, H_{arom}), 8.29 d (1H, H_{arom}, J = 8 Hz), 12.41 s (1H, NH). Found, %: C 58.50; H 3.74; N 8.64. $C_{16}H_{12}N_2O_2S_2$. Calculated, %: C 58.52; H 3.68; N 8.53.

2-Ethylsulfanyl)-*N*-(4-oxo-4*H*-1,3-benzothiazin-2-yl)benzamide (IVe). Yield 1.57 g (46%), mp 185–187°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 1.47 t (3H, $CH_2C\mathbf{H}_3$, J = 7 Hz), 2.92 q (2H, $C\mathbf{H}_2CH_3$, J = 8 Hz), 7.21 t (1H, H_{arom}, J = 7 Hz), 7.33–7.76 m (5H, H_{arom}), 8.32 br.s (1H, H_{arom}), 8.28 d (1H, H_{arom}, J = 8 Hz), 12.60 s (1H, NH). Found, %: C 59.82; H 4.28; N 8.22. $C_{17}H_{14}N_2O_2S_2$. Calculated, %: C 59.63; H 4.12; N 8.18.

2-(Imidazolidin-2-ylideneamino)-4*H*-1,3-benzothiazin-4-one (IVf). Yield 1.60 g (65%), mp 278–280°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.62 s (4H, CH_2), 7.39–7.50 m (2H, H_{arom}), 7.60 t (1H, H_{arom},

J = 10 Hz), 8.21 d (1H, H_{arom}, J = 14 Hz), 8.48 s (2H, NH). Found, %: C 53.46; H 4.01; N 22.72. $C_{11}H_{10}N_4OS$. Calculated, %: C 53.65; H 4.09; N 22.75.

***N*-(4-Oxo-4*H*-pyrido[3,2-*e*][1,3]thiazin-2-yl)-benzamide (IVg).** A solution of 2.33 g (15 mmol) of 2-sulfanylpyridine-3-carboxylic acid and 2.19 g (15 mmol) of cyanamide **VIa** in 20 ml of *N*,*N*-dimethylacetamide was heated for 5 h at 100°C. The mixture was cooled and poured into 150 ml of cold water, and the precipitate was filtered off and recrystallized from propan-2-ol–dioxane (1:2). Yield 0.46 g (10%), mp 232°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 7.50 m (2H, H_{arom}), 7.59 m (2H, H_{arom}), 8.19 m (2H, H_{arom}), 8.54 m (1H, H_{arom}), 8.81 s (1H, H_{arom}), 12.77 br.s (1H, NH). Found, %: C 59.46; H 3.09; N 14.93. $C_{14}H_9N_3O_2S$. Calculated, %: C 59.30; H 3.18; N 14.82.

***N*-(4,6-Dimethylpyrimidin-2-yl)-1,3-benzothiazol-2-amine (XIIa).** *a*. Concentrated hydrochloric acid, 1.8 ml (20 mmol), was slowly added dropwise under stirring to a mixture of 2.50 g (20 mmol) of 2-aminobenzenethiol (**II**) and 2.96 g (20 mmol) of cyanamide **V** in 20 ml of isopropyl alcohol, and the mixture was carefully heated to the boiling point and maintained boiling over a period of 1 h. It was then cooled and poured into 150 ml of cold water, a solution of 0.8 g (20 mmol) of sodium hydroxide in 50 ml of water was added, and the precipitate was filtered off and recrystallized from dioxane. Yield 4.56 g (89%), mp 245–246°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.42 s (6H, CH_3), 6.87 s (1H, 5′-H), 7.22 t (1H, H_{arom}, J = 7 Hz), 7.39 t (1H, H_{arom}, J = 8 Hz), 7.68 d (1H, H_{arom}, J = 9 Hz), 7.92 d (1H_{arom}, J = 9 Hz), 11.62 br.s (1H, NH). Found, %: C 60.86; H 4.67; N 21.96. $C_{13}H_{12}N_4S$. Calculated, %: C 60.92; H 4.72; N 21.86.

1,3-Benzothiazoles **XIIb**–**XIId** were synthesized in a similar way.

***N*-(4-Methoxyphenyl)-1,3-benzothiazol-2-amine (XIIb).** The product was recrystallized from toluene–petroleum ether (2:1). Yield 1.79 g (35%), mp 154–155°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 3.77 s (3H, OCH_3), 7.12 d (2H, H_{arom}, J = 9 Hz), 7.53–7.68 m (4H, H_{arom}), 8.10 d (1H, H_{arom}, J = 9 Hz), 8.25 d (1H, H_{arom}, J = 9 Hz), 10.36 s (1H, NH). Found, %: C 65.76; H 4.56; N 11.02. $C_{14}H_{12}N_2OS$. Calculated, %: C 65.60; H 4.72; N 10.93.

***N*-(1,3-Benzothiazol-2-yl)benzamide (XIIc).** Yield 3.05 g (60%), mp 178–180°C (*a*).

b. Benzoyl chloride, 2.95 g (21 mmol), was added dropwise to a solution of 3.00 g (20 mmol) of 1,3-benzothiazol-2-amine (**XV**) in 10 ml of anhydrous pyridine. The mixture was stirred for 0.5 h at room temperature and diluted with cold water, and the precipitate was filtered off and recrystallized from dioxane. Yield 3.15 g (62%), mp 177–179°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 7.33 d (1H, H_{arom}, J = 8 Hz), 7.45 t (1H, H_{arom}, J = 7 Hz), 7.55 m (2H, H_{arom}), 7.63 t (1H, H_{arom}, J = 7 Hz), 7.79 d (1H, H_{arom}, J = 8 Hz), 8.03 d (1H, H_{arom}, J = 8 Hz), 8.17 d (2H, H_{arom}, J = 8 Hz), 12.88 s (1H, NH). Found, %: C 66.15; H 3.98; N 11.04. $C_{14}H_{10}N_2OS$. Calculated, %: C 66.12; H 3.96; N 11.02.

2-Ethylsulfanyl-*N*-(1,3-benzothiazol-2-yl)benzamide (XIId). Yield 2.01 g (32%), mp 118–120°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 1.33 t (3H, $CH_2C\mathbf{H}_3$, J = 7 Hz), 2.98 q (2H, $C\mathbf{H}_2CH_3$, J = 7 Hz), 7.38–7.56 m (5H, H_{arom}), 7.65 d (1H, H_{arom}, J = 8 Hz), 7.76 d (1H, H_{arom}, J = 8 Hz), 12.78 s (1H, NH). Found, %: C 61.04; H 4.57; N 8.94. $C_{16}H_{14}N_2OS_2$. Calculated, %: C 61.12; H 4.49; N 8.91.

***N*-(3a,4,5,6,7,7a-Hexahydro-1*H*-benzimidazol-2-yl)-1,3-benzothiazol-2-amine (XIIe).** Concentrated hydrochloric acid, 1.8 ml (20 mmol), was added dropwise under stirring to a mixture of 1.68 g (10 mmol) of 2-aminobenzenethiol (**II**) and 1.25 g (10 mmol) of cyanamide **X** in 20 ml of isopropyl alcohol, and the mixture was heated for 1 h at the boiling point. It was then cooled and poured into 150 ml of cold water, a solution of 0.8 g (20 mmol) of sodium hydroxide in 50 ml of water was added, and the precipitate was filtered off and recrystallized from dioxane. Yield 0.76 g (28%), mp 260–262°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 1.3–1.5 m (4H, CH_2), 1.75 d (2H, CH_2, J = 6 Hz), 2.1 d (2H, CH_2, J = 12 Hz), 3.1 d (2H, CH, J = 5 Hz), 7.1 t (1H, H_{arom}, J = 7 Hz), 7.25 t (1H, H_{arom}, J = 8 Hz), 7.51 d (1H, H_{arom}, J = 8 Hz), 7.7 d (1H, H_{arom}, J = 8 Hz), 8.1 s (1H, NH). Found, %: C 61.76; H 5.96; N 20.54. $C_{14}H_{16}N_4S$. Calculated, %: C 61.74; H 5.92; N 20.57.

***N*-(4,6-Dimethylpyrimidin-2-yl)-4,5-dihydrothiazol-2-amine hydrochloride (XIII).** A mixture of 2.27 g (20 mmol) of 2-aminoethanethiol hydrochloride and 2.96 g (20 mmol) of cyanamide **V** in 15 ml of dioxane was heated while adding distilled water until complete decoloration of the mixture. The mixture was then heated for 2 h under reflux and filtered, the filtrate was evaporated on a rotary evaporator, and the residue was recrystallized from propan-2-ol–water (2:1). Yield

2.01 g (41%), mp 168°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 2.34 s (6H, CH_3), 3.12 d.t (2H, SCH_2, $J_{4,5}$ = 7, $J_{5,5}$ = 21 Hz), 3.75–3.88 m (2H, CH_2), 7.58 s (1H, 5′-H), 6.92 s (1H, NH), 10.09 br.s (HCl). Found, %: C 44.33; H 4.95; N 22.78. $C_9H_{12}N_4S\cdot$HCl. Calculated, %: C 44.15; H 4.81; N 22.89.

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