A Facile Synthesis of 3-Amino-5-substitutedaminoisothiazole-4-carboxylic Acid Derivatives

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A facile, general and one-pot method for the preparation of 3-amino-5-substituted-aminoisothiazole-4-carboxylic acid derivatives, in high yields, by the aminative cyclization of 3-amino-3-mercaptoacrylonitriles is described.

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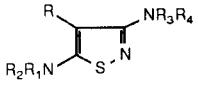
Amine derivatives of the isothiazole ring system are of interest as novel bioactive agents. A broad spectrum of biological activities has been reported for derivatives of 3- and 5-aminoisothiazoles [2-7]. Although cyclization and other metathetical methods have been developed for the synthesis of 3- and 5-isothiazolamines, the chemistry of isothiazole-3,5-diamines has received only limited attention [8,9]. A few 3,5-diamines, **1** described in the literature have been prepared through the oxidative cyclization of relatively inaccessible thiocarbamoylacetamidines, **2** [10,11].



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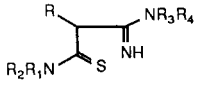

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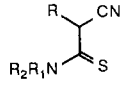

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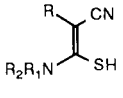

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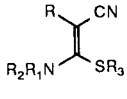

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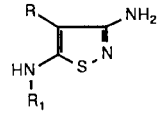
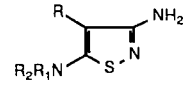
Functionalized nitriles such as thiocarbamoylacetonitriles, **3**, 3-amino-3-mercaptoacrylonitriles, **4**, and cyanoketene *S,N*-acetals, **5**, have, in recent years, been explored as readily accessible precursors for 4,6-diaminopyrimidines [12], 3,5-diaminopyrazoles [13-17] and 2,4-diaminothiophenes [18-22]. Analogous to the alkylative cyclization of 3-amino-3-mercaptoacrylonitrile intermediates, **4**, to diaminothiophenes, we found that the aminative cyclization of 3-amino-3-mercaptoacrylonitriles with aqueous chloramine yields isothiazole-3,5-diamines. Earlier, such an aminative cyclization method has been employed by Hartke and coworkers for the synthesis of a few 3-aminoisothiazoles [23]. Herein, we describe the preparation of 3,5-diaminoisothiazole-4-carboxylic acid derivatives **6a-z** and **7a-d**. These are of interest as substrates for pyrimidine annelation reactions [24] and as precursors for isothiazole analogues of antiinflammatory *N*-arylanthranilic acids [25].



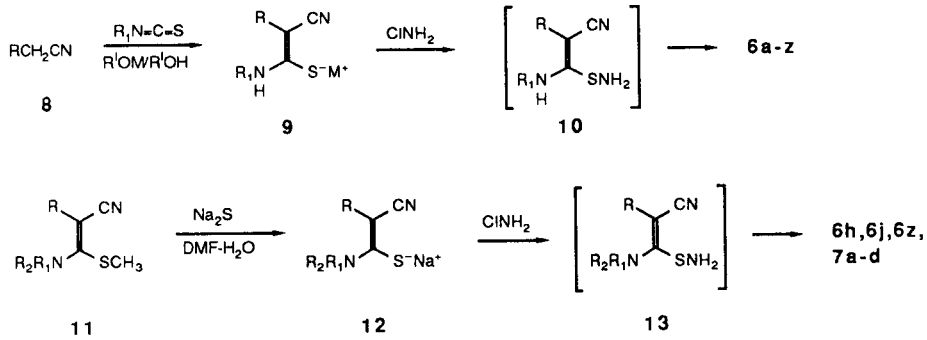


6a, R = CN, R_1 = CH_3
6b, R = $CO_2C_2H_5$, R_1 = CH_3
6c, R = CN, R_1 = C_2H_5
6d, R = $CO_2C_2H_5$, R_1 = C_2H_5
6e, R = CN, R_1 = CH_2=CH–CH_2
6f, R = CN, R_1 = *n*-C_4H_9
6g, R = CN, R_1 = $C_6H_5CH_2$
6h, R = CN, R_1 = C_6H_5
6i, R = CO_2CH_3, R_1 = C_6H_5
6j, R = $CO_2C_2H_5$, R_1 = C_6H_5
6k, R = $CO_2C(CH_3)_3$, R_1 = C_6H_5
6l, R = CN, R_1 = 2-$CH_3C_6H_4$
6m, R = $CO_2C_2H_5$, R_1 = 2-$CH_3C_6H_4$
6n, R = CN, R_1 = 4-$CH_3C_6H_4$
6o, R = $CO_2C_2H_5$, R_1 = 4-$CH_3C_6H_4$
6p, R = CN, R_1 = 4-$CH_3OC_6H_4$
6q, R = $CO_2C_2H_5$, R_1 = 4-$CH_3OC_6H_4$
6r, R = CN, R_1 = 3-$CF_3C_6H_4$
6s, R = $CO_2C_2H_5$, R_1 = 3-$CF_3C_6H_4$
6t, R = CN, R_1 = 2-ClC_6H_4
6u, R = $CO_2C_2H_5$, R_1 = 2-ClC_6H_4
6v, R = CN, R_1 = 3-ClC_6H_4
6w, R = $CO_2C_2H_5$, R_1 = 3-ClC_6H_4
6x, R = CN, R_1 = 4-ClC_6H_4
6y, R = $CO_2C_2H_5$, R_1 = 4-ClC_6H_4
6z, R = CN, R_1 = 4-$CH_3C_6H_4SO_2$

7a, R = CN, R_2R_1N = morpholino
7b, R = CN, R_2R_1N = 4-methylpiperazino
7c, R = CN, R_2R_1N = piperidino
7d, R = CN, R_2R_1N = pyrrolidino

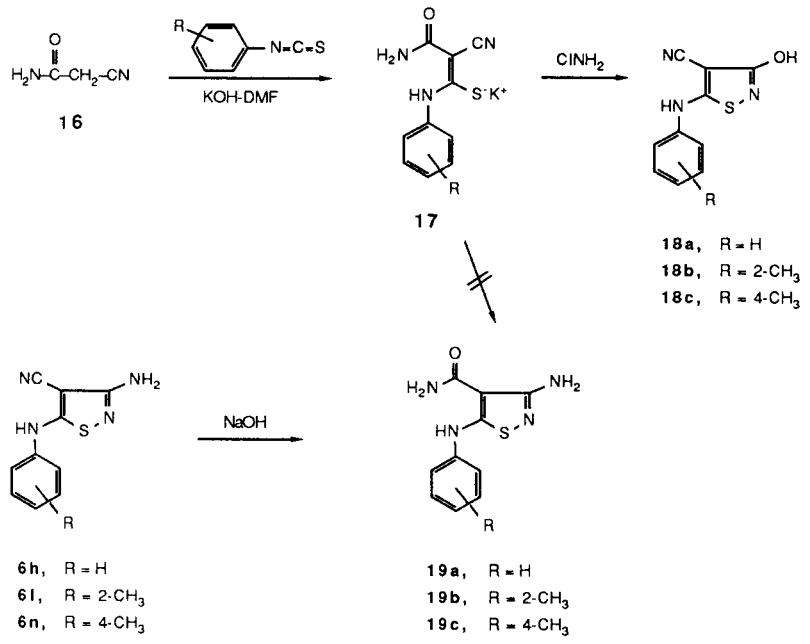
Two facile methods employed for the preparation of salts of 3-amino-3-mercaptoacrylonitriles, **9** and **12**, were: (i) base-promoted condensation of isothiocyanates with active methylene nitriles and (ii) reaction of *S*-methylcyanoketene-*S,N*-acetals, **11**, with sodium sulfide in aqueous dimethylformamide. The intermediates, **9** and **12**, thus generated were reacted *in situ* with aqueous chloramine at 0° to yield the 3-amino-5-substituted aminoisothiazole-4-carboxylic acid derivatives, **6a-z** and **7a-d**, in an essentially one-pot procedure. These isothiazole cyclizations probably proceed *via* the nonisolable sulfenamide intermediates, **10** and **13** (Scheme I).

Scheme I



11a, R = CN, R_2R_1N = C_6H_5NH
11b, R = $CO_2C_2H_5$, R_2R_1N = C_6H_5NH
11c, R = CN, R_2R_1N = 4-$CH_3C_6H_4SO_2NH$
11d, R = CN, R_2R_1N = morpholino
11e, R = CN, R_2R_1N = 4-methylpiperazino
11f, R = CN, R_2R_1N = piperidino
11g, R = CN, R_2R_1N = pyrrolidino

Scheme II



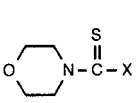
18a, R = H
18b, R = 2-CH_3
18c, R = 4-CH_3

6h, R = H
6l, R = 2-CH_3
6n, R = 4-CH_3

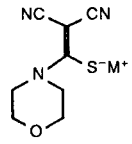
19a, R = H
19b, R = 2-CH_3
19c, R = 4-CH_3

The two methods utilized for the generation of mercaptoacrylonitrile intermediates are complementary to each other in that the 3-*N,N*-disubstituted intermediates, **12**, inaccessible by method (i) could be readily obtained by method (ii). By employing malononitrile or cyanoacetic acid esters and the appropriate isothiocyanate as the starting materials in method (i), or by the use of 2-cyano- or 2-carboalkoxycyanoketene-*S,N*-acetal in method (ii), a variety of 3-amino-5-alkylamino-, dialkylamino-, arylamino- and tosylaminoisothiazole-4-carbonitriles and carboxylic acid esters were synthesized in moderate to good yields.

The intermediates for the cyclization to 5-dialkylaminoisothiazoles could also be generated directly from the active methylene nitriles by the use of an appropriate thiocarbamoylating agent in place of an isothiocyanate. In one example studied, it was found that malononitrile could be thiocarbamoylated with a thiocarbamoyl chloride, **14a**, a thionourethane, **14b**, or a dithiocarbamate, **14c**, and the intermediate, **15**, cyclized *in situ* with chloramine to yield 3-amino-5-morpholinoisothiazole-4-carbonitrile, **7a**, in 38, 25 and 19% yields, respectively.



14a, X = Cl
14b, X = OC_2H_5
14c X = SCH_3



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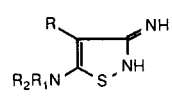
Cyclization of cyanoacetamide derived intermediates, **17**, with chloramine yielded only the 3-hydroxyisothiazole-4-carbonitriles, **18a-c**, instead of the anticipated aminocarboxamides, **19a-c**. The hydroxyisothiazoles, **18a-c**, were also isolated as minor byproducts in the cyclization of ethyl cyanoacetate - aryl isothiocyanate adducts to the aminoesters, **6j**, **6m**, and **6o**. The desired aminoamides, **19a-c**, could, however, be prepared by the hydrolysis of the corresponding aminonitriles, **6h**, **6l** and **6n**, respectively (Scheme II).

All the isothiazole-3,5-diamines are colorless crystalline solids, except for the 5-arylamino-4-cyanoisothiazoles which are pale brown to buff colored crystals. While most of the 3-amino-4-ethoxycarbonylisothiazoles are moderately soluble in ethanol, the corresponding 4-cyanoisothiazoles are sparingly soluble. In general, the melting points of the 4-cyanoisothiazoles are much higher than those of the corresponding esters. While the 5-alkylamino- and 5-dialkylamino-3-aminoisothiazoles are soluble in dilute hydrochloric acid, the 5-arylamino analogs are nearly insoluble.

The aminoisothiazoles synthesized were characterized by elemental, uv, ir, ^{1}H nmr, and mass spectral analysis. Both 3-amino-5-alkylamino- and 3-amino-5-dialkylaminoisothiazoles exhibit two characteristic uv absorptions around 215 and 260 nm, while their 5-arylamino analogs show three absorptions around 220, 285 and 315 nm. The ir spectra of the aminoisothiazoles exhibit the N-H stretching absorptions in the region 3500-3180 cm^{-1}. The isothiazole-4-carbonitriles show a strong conjugated C≡N stretching absorption at 2220-2200 cm^{-1}. The conjugated C=O absorption of the 3,5-diaminoisothiazole-4-carboxylic acid esters was found at 1680-1660 cm^{-1}. The EI mass spectra of all the aminoisothiazoles exhibit intense molecular ion peaks which are often the base peaks.

The diaminoisothiazoles, **6a-z** and **7a-d**, may, in principle, exist in different tautomeric forms arising from the amine-imine tautomerism. In all cases studied, the ^{1}H nmr spectra of the isothiazoles in deuteriochloroform or dimethylsulfoxide-d_6 reveal the presence of a two proton singlet at 5.0 to 6.0 ppm, corresponding to the NH_2 group at C-3, thus excluding 3-imino tautomeric forms such as **20**.

For compounds **6a-z**, structures **21** and **22** represent the two possible 5-imino tautomeric forms with a primary amine function at C-3. The uv absorption pattern of 5-alkylaminoisothiazoles, **6a-g**, closely resembles that of **7a** and **7d**, which are incapable of existing in 5-imino forms. Furthermore, the coupling of the secondary NH protons with the adjacent protons of the alkyl group, as observed in the spectra of **6b** (doublet for methyl group protons) and **6d** (quintet for the methylene protons of the ethyl group), supports the 5-amino tautomeric structure. In the case of those derivatives where an aryl group is attached to the 5-N, the observed chemical shift of 9.2 to 10.0 ppm for the secondary NH in the spectra of **6h**, **6j**, **6m**, **6n**, and **6o** is indicative of the residence of the proton on the nitrogen bearing the aryl group. Thus, the available evidences indicate that the 3,5-diaminoisothiazoles studied exist preferentially in the diamine form, **6**.



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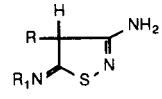

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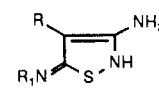

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EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The uv absorption spectra were determined using a Beckman model 24 spectrometer. The ir spectra were recorded on a Perkin-Elmer 337 Grating Spectrophotometer. The ^{1}H nmr spectra were taken on a Varian A-60 spectrometer using tetramethylsilane as the internal standard. EI mass spectra were obtained on a Varian Atlas CH-7 Spectrometer at 70ev ionizing beam, using direct insertion probe.

The starting materials **11a** [26], **11c**, [27], **11d**, **11f** and **11g** [28] were prepared by literature methods. The compounds **11b** [17], and **11e** [29], mp 116-118° (benzene-hexane), were prepared essentially according to the procedure described for **11a**.

Preparation of Aqueous Chloramine [23].

Chlorine gas (3.67 g, 0.052 mole) was absorbed in a mixture of ice (40 g) and 25% aqueous sodium hydroxide solution (25 ml) maintained at 0° by external cooling. The mixture was cooled in an ice bath, stirred and treated with an excess of an ice-cold 10% aqueous ammonium hydroxide solution (25 ml). After the exothermic reaction is complete, the volume of the mixture was made up to 125 ml with ice water.

3-Amino-5-(methylamino)isothiazole-4-carbonitrile (**6a**).

The following experiment is typical of the procedure employed for the synthesis of 3,5-diaminoisothiazoles from active methylene nitriles.

To an ice-cold solution of sodium ethoxide (0.025 mole), prepared by dissolving sodium (0.6 g, 0.025 g-atom) in absolute ethanol (25 ml) was added malononitrile (1.65 g, 0.025 mole), followed by methyl isothiocyanate (1.85 g, 0.025 mole). The mixture was stirred at room temperature for 12 hours, cooled and then treated with freshly prepared aqueous chloramine solution (125 ml). After allowing the reaction mixture to stir at room temperature for 24 hours, the product was collected by filtration and dried in air. Crystallization from dimethylformamide-ethanol yielded 2.5 g (65%) of **6a** as colorless crystals, mp 257-259°; ir (Nujol): 3450, 3350 and 3220 (NH), 2200 (CN), 1615 cm^{-1}; uv (95% ethanol): λ max nm (log ε) 218 (4.30), 260 (4.11); ^{1}H nmr (trifluoroacetic acid): δ 3.2 (s, 3H, CH_3), 7.8 (broad s, 1H, NH); ms: m/e 154 (M^+).

Anal. Calcd. for $C_5H_6N_4S$: C, 38.96; H, 3.90. Found: C, 39.05; H, 4.14.

3-Amino-5-(methylamino)isothiazole-4-carboxylic Acid Ethyl Ester (**6b**).

The experimental procedure described for the preparation of **6a** was

employed, except that the mixture of sodium ethoxide, ethyl cyanoacetate and methyl isothiocyanate was refluxed for 10 minutes, allowed to cool and stirred at room temperature for 12 hours before being reacted with chloramine. Recrystallization of the crude product from ethanol afforded 3.0 g (60%) of **6b** as colorless crystals, mp 145-147°; ir (Nujol): 3500, 3360, 3300, 3180 (NH), 1680, 1590 cm^{-1}; uv (95% ethanol): λ max nm (log ε) 225 (4.42), 262 (4.25); ^1H nmr (dimethylsulfoxide-d_6): δ 1.28 (t, J = 7.1 Hz, 3H, ethyl CH_3), 2.85 (d, J = 4.9 Hz, 3H, CH_3N, collapses to a singlet on deuterium oxide exchange), 4.26 (q, J = 7.1 Hz, 2H, CH_2), 6.22 (broad s, 2H, NH_2, deuterium oxide exchangeable), 7.70 (q, J = 4.8 Hz, 1H, NH, deuterium oxide exchangeable); ms: m/e 201 (M^+).

Anal. Calcd. for $C_7H_{11}N_3O_2S$: C, 41.77; H, 5.51. Found: C, 41.93; H, 5.81.

3-Amino-5-(ethylamino)isothiazole-4-carbonitrile (**6c**).

This compound was prepared by the same procedure employed for the preparation of **6a**. From malononitrile (1.65 g, 0.025 mole) and ethyl isothiocyanate (2.18 g, 0.025 mole) there was obtained, after crystallization from dimethylformamide-ethanol, 2.5 g (60%) of **6c** as colorless crystals, mp 203-205°; ir (Nujol): 3470, 3380, 3260 (NH), 2200 (CN), 1640 cm^{-1}; uv (95% ethanol): λ max nm (log ε) 218 (4.27), 262 (4.07): ^1H nmr (trifluoroacetic acid): δ 1.5 (t, 3H, CH_3), 3.4 (m, 2H, CH_2), 7.7 (broad m, NH); ms: m/e 168 (M^+).

Anal. Calcd. for $C_6H_8N_4S$: C, 42.83; H, 4.79. Found: C, 43.01; H, 5.03.

3-Amino-5-(ethylamino)isothiazole-4-carboxylic Acid Ethyl Ester (**6d**).

The same procedure as used in the synthesis of **6b** was employed. Crystallization of the crude product obtained from the reaction of ethyl cyanoacetate (2.83 g, 0.025 mole) and ethyl isothiocyanate (2.18 g, 0.025 mole), from ethanol afforded 2.7 g (50%) of **6d** as colorless crystals, mp 103-105°; ir (Nujol): 3440, 3410, 3300, 3180 (NH), 1675 cm^{-1}; uv (95% ethanol): λ max nm (log ε) 218 (4.29), 266 (4.08); ^1H nmr (deuteriochloroform): δ 1.32 (t, 3H, ethylamino CH_3), 1.34 (t, 3H, ester CH_3), 3.2 (quintet, 2H, CH_2N), 4.4 (q, 2H, CH_2O), 5.7 (broad s, 2H, NH_2), 7.45 (m, 1H, NH); ms: m/e 215 (M^+).

Anal. Calcd. for $C_8H_{13}N_3O_2S$: C, 44.63; H, 6.09. Found: C, 44.86; H, 6.39.

5-(Allylamino)-3-aminoisothiazole-4-carbonitrile (**6e**).

This compound was prepared by the same procedure employed for the preparation of **6a**. Crystallization of the crude product from ethanol afforded 2.5 g (56%) of **6e** as colorless crystals, mp 153-155°; ir (Nujol): 3440, 3350, 3220 (NH), 2210 (CN), 1620 cm^{-1}; uv (95% ethanol): λ max nm (log ε) 217 (4.28), 262 (4.10); ^1H nmr (trifluoroacetic acid): δ 4.1 (broad m, 2H, CH_2N), 5.7 (m, 3H vinylic H), 7.9 (broad m, NH); ms: m/e 180 (M^+).

Anal. Calcd. for $C_7H_8N_4S$: C, 46.65; H, 4.47. Found: C, 46.96; H, 4.84.

3-Amino-5-(*n*-butylamino)isothiazole-4-carbonitrile (**6f**).

The same procedure as used in the synthesis of **6a** was employed. The crude product was crystallized from ethanol to yield 2.0 g (41%) of **6f** as colorless crystals, mp 165-167°; ir (Nujol): 3470, 3380, 3260 (NH), 2220 (CN), 1640 cm^{-1}; uv (95% ethanol): λ max nm (log ε) 217 (4.26), 262 (4.09); ms: m/e 196 (M^+).

Anal. Calcd. for $C_8H_{12}N_4S$: C, 48.95; H, 6.16. Found: C, 49.10; H, 6.17.

3-Amino-5-[(phenylmethyl)amino]isothiazole-4-carbonitrile (**6g**).

This compound was prepared by the same procedure employed for the synthesis of **6a**. Recrystallization of the crude product from dimethylformamide-ethanol yielded 3.0 g (52%) of **6g** as colorless crystals, mp 192-194°; ir (Nujol): 3480, 3400, 3260 (NH), 2240 (CN), 1650 cm^{-1}; uv (95% ethanol): λ max nm (log ε) 212 (4.35), 262 (4.14); ^1H nmr (deuteriochloroform + trifluoroacetic acid): δ 4.6 (broad s, 2H, CH_2N), 7.45 (s, 5H, aryl-H), 8.2 (broad m, NH); ms: m/e 230 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38. Found: C, 57.20; H, 4.60.

3-Amino-5-(phenylamino)isothiazole-4-carbonitrile (**6h**).

Method A.

The same procedure as used in the preparation of **6a** was employed. Following the reaction with chloramine solution, the *p*H of the reaction mixture was adjusted to 7-8 with dilute aqueous hydrochloric acid before isolation of the product by filtration. Recrystallization of the crude product from dimethylformamide-ethanol yielded 3.8 g (65%) of **6h**, mp 230-232°; ir (potassium bromide): 3460, 3360, 3240 (NH), 2210 (CN), 1630 cm^{-1}; uv (95% ethanol): λ max nm (log ε) 212 (4.33), 282 (4.19), 310 (4.03); ^1H nmr (trifluoroacetic acid): δ 7.52 (s, 5H, aryl-H), 9.45 (broad s, NH); ms: m/e 216 (M^+).

Anal. Calcd. for $C_{10}H_8N_4S$: C, 55.54; H, 3.73. Found: C, 55.87; H, 3.94.

Method B.

An ice-cold solution of **11a** (4.3 g, 0.02 mole) in dimethylformamide (20 ml) was treated with a solution of fused sodium sulfide (70%, 2.23 g, 0.02 mole) in water (10 ml). After allowing to stir at room temperature for 24 hours, the mixture was cooled and treated with freshly prepared aqueous chloramine solution (100 ml). Isolation of the product as described under method A afforded 3.0 g (69%) of **6h**, identical in all respects with the product obtained by method A.

3-Amino-5-(phenylamino)isothiazole-4-carboxylic Acid Methyl Ester (**6i**).

The experimental procedure described for the preparation of **6a** was employed, except that a solution of sodium methoxide in methanol was used as the base. From methyl cyanoacetate and phenyl isothiocyanate there was obtained after recrystallization from methanol 1.5 g (24%) of **6i** as colorless crystals, mp 166-168°; ir (Nujol): 3500, 3270, 3180 (NH), 1650 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45. Found: C, 53.01; H, 4.66.

3-Amino-5-(phenylamino)isothiazole-4-carboxylic Acid Ethyl Ester (**6j**).

Method A.

The procedure described for the preparation of **6a** was employed. Following the reaction with aqueous chloramine, the solid material was collected by filtration and the alkaline filtrate was saved for the isolation of the byproduct **18a**. Recrystallization of the crude product from ethanol afforded 3.0 g (46%) of **6j** as colorless crystals, mp 148-150°; ir (Nujol): 3490, 3290, 3180 (NH), 1650 cm^{-1}; uv (95% ethanol): λ max nm (log ε) 222 (4.32), 286 (4.18), 316 (4.02); ^1H nmr (deuteriochloroform): δ 1.4 (t, 3H, CH_3), 4.4 (q, 2H, CH_2), 5.5 (broad s, 2H, NH_2), 7.2 (m, 5H, aryl-H), 9.96 (broad s, 1H, NH); ms: m/e 263 (M^+).

Anal. Calcd. for $C_{12}H_{13}N_3O_2S$: C, 54.73; H, 4.98; N, 15.96. Found: C, 54.38; H, 5.14; N, 16.11.

Method B.

A solution of fused sodium sulfide (70%, 3.34 g, 0.03 mole) in water (10 ml) was added to a cooled solution of **11b** (7.86 g, 0.03 mole) in dimethylformamide (30 ml). The mixture was heated on a steam bath for 8 hours, cooled and treated with freshly prepared aqueous chloramine solution (150 ml). After allowing the mixture to stir at room temperature for 24 hours, the product was collected by filtration and crystallized from ethanol to obtain 3.0 g (38%) of **6j**, identical in all respects with the product obtained by Method A.

3-Amino-5-(phenylamino)isothiazole-4-carboxylic Acid *t*-Butyl Ester (**6k**).

The procedure described for the preparation of **6a** was employed, except that a solution of potassium *t*-butoxide in *t*-butyl alcohol was used as the base. From *t*-butyl cyanoacetate and phenyl isothiocyanate there was obtained after recrystallization from *t*-butyl alcohol 3.7 g (51%) of **6k** as colorless crystals, mp 145-147°; ir (Nujol): 3500, 3280, 3180 (NH), 1670 cm^{-1}; ms: m/e 291 (M^+).

Anal. Calcd. for $C_{14}H_{17}N_3O_2S$: C, 57.71; H, 5.88. Found: C, 57.96; H, 6.06.

3-Amino-5-[(2-methylphenyl)amino]isothiazole-4-carbonitrile (**6l**).

The same procedure as used for the preparation of **6a** was employed. Prior to the isolation of the product, the *p*H of the reaction mixture was

adjusted to 7-8 with dilute hydrochloric acid. Recrystallization of the crude product from ethanol yielded 3.5 g (61%) of **6l**, mp 176-178°; ir (Nujol): 3470, 3370 (NH), 2220 (CN), 1610 cm^{-1}; ms: m/e 230 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38. Found: C, 57.04; H, 4.54.

3-Amino-5-[(2-methylphenyl)amino]isothiazole-4-carboxylic Acid Ethyl Ester (**6m**).

The procedure described for the preparation of **6a** was employed. Following the reaction with chloramine, the solid material was collected by filtration and the filtrate was saved for isolation of the byproduct **18b**. Recrystallization of the crude product from ethanol afforded 4.3 g (62%) of **6m** as colorless crystals, mp 138-140°; ir (Nujol): 3500, 3290, 3180 (NH), 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.40 (t, 3H, ester CH_3), 2.36 (s, 3H, aryl-CH_3), 4.42 (q, 2H, CH_2), 5.70 (broad s, 2H, NH_2, deuterium oxide exchangeable), 7.20 (m, 4H, aryl-H), 9.87 (broad s, 1H, NH); ms: m/e 277 (M^+).

Anal. Calcd. for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45. Found: C, 56.50; H, 5.79.

3-Amino-5-[(4-methylphenyl)amino]isothiazole-4-carbonitrile (**6n**).

This compound was prepared by the same procedure as employed for the preparation of **6a** except that the product was isolated by filtration after adjusting the *p*H of the reaction mixture to 7-8 by the addition of dilute hydrochloric acid. Crystallization of the crude product from dimethylformamide-ethanol afforded 2.5 g (44%) of **6n**, mp 233-235°; ir (Nujol): 3460, 3280, 3170 (NH), 2220 (CN), 1630 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 2.43 (s, 3H, CH_3), 7.33 (s, 4H, aryl-H), 9.25 (broad s, NH); ms: m/e 230 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38. Found: C, 57.45; H, 4.44.

3-Amino-5-[(4-methylphenyl)amino]isothiazole-4-carboxylic Acid Ethyl Ester (**6o**).

The same procedure as used for the preparation of **6a** was employed. Following the reaction with chloramine, the solid was collected by filtration and the filtrate was saved for isolation of the byproduct **18c**. Recrystallization of the crude product from ethanol yielded 3.6 g (52%) of **6o** as colorless crystals, mp 138-140°; ir (Nujol): 3490, 3270 (NH), 1660 cm^{-1}; uv (95% ethanol): λ max nm (log ε) 222 (4.34), 285 (4.18), 320 (4.06); ^1H nmr (deuteriochloroform): δ 1.40 (t, 3H, ester CH_3), 2.30 (s, 3H, aryl-CH_3), 4.40 (q, 2H, CH_2), 5.50 (broad s, 2H, NH_2), 7.13 (m, 4H, aryl-H), 9.83 (broad s, 1H, NH).

Anal. Calcd. for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45. Found: C, 56.42; H, 5.80.

3-Amino-5-[(4-methoxyphenyl)amino]isothiazole-4-carbonitrile (**6p**).

This compound was prepared by the same procedure as described for the synthesis of **6a** except that the product was isolated by filtration after adjusting the *p*H of the reaction mixture to 7-8 by addition of dilute hydrochloric acid. Recrystallization from ethanol yielded 5.4 g (44%) of **6p**, mp 213-215°; ir (Nujol): 3440, 3340, 3220 (NH), 2210 (CN), 1620 cm^{-1}; ms: m/e 246 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_4OS$: C, 53.64; H, 4.09. Found: C, 53.86; H, 4.48.

3-Amino-5-[(4-methoxyphenyl)amino]isothiazole-4-carboxylic Acid Ethyl Ester (**6q**).

The same procedure as employed for the preparation of **6a** was used. Recrystallization of the crude product from ethanol yielded 3.5 g (48%) of **6q**, mp 114-116°; ir (Nujol): 3480, 3300, 3180 (NH), 1670 cm^{-1}; ms: m/e 293 (M^+).

Anal. Calcd. for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15. Found: C, 53.34; H, 5.35.

3-Amino-5-[[3-(trifluoromethyl)phenyl]amino]isothiazole-4-carbonitrile (**6r**).

This compound was prepared by the same procedure as described for the preparation of **6a** except that the product was isolated by filtration after adjusting the *p*H of the reaction mixture to 7-8 by the addition of dilute hydrochloric acid. Recrystallization from ethanol yielded 4.0 g (56%) of **6r**, mp 204-206°; ir (Nujol): 3460, 3350, 3280, 3240 (NH), 2210 (CN), 1610 cm^{-1}; ms: m/e 284 (M^+).

Anal. Calcd. for $C_{11}H_7F_3N_4S$: C, 46.47; H, 2.48. Found: C, 46.57; H, 2.72.

3-Amino-5-[[3-(trifluoromethyl)phenyl]amino]isothiazole-4-carboxylic Acid Ethyl Ester (**6s**).

The same procedure as used for the preparation of **6a** was employed. Recrystallization of the crude product from ethanol afforded 3.5 g (42%) of **6s**, as colorless crystals, mp 112-114°; ir (Nujol): 3460, 3360, 3180 (NH), 1650 cm^{-1}; ms: m/e 331 (M^+).

Anal. Calcd. for $C_{13}H_{12}F_3N_3O_2S$: C, 47.12; H, 3.65. Found: C, 47.08; H, 3.94.

3-Amino-5-[(2-chlorophenyl)amino]isothiazole-4-carbonitrile (**6t**).

This compound was prepared by the same procedure as described for the preparation of **6a** except that the product was isolated by filtration after adjusting the *p*H of the reaction mixture to 7-8 by the addition of dilute hydrochloric acid. Recrystallization of the crude product from ethanol yielded 3.0 g (48%) of **6t**, mp 158-160°; ir (Nujol): 3450, 3350, 3220 (NH), 2220 (CN), 1630 cm^{-1}.

Anal. Calcd. for $C_{10}H_7ClN_4S$: C, 47.90; H, 2.81. Found: C, 47.79; H, 3.04.

3-Amino-5-[(2-chlorophenyl)amino]isothiazole-4-carboxylic Acid Ethyl Ester (**6u**).

The same procedure as used for the preparation of **6a** was employed. Recrystallization from ethanol afforded 3.0 g (40%) of **6u** as colorless crystals, mp 147-149°; ir (Nujol): 3480, 3280, 3180 (NH), 1660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.48 (t, 3H, CH_3), 4.50 (q, 2H, CH_2), 5.62 (broad s, 2H, NH_2), 7.4 (m, 4H, aryl-H).

Anal. Calcd. for $C_{12}H_{12}ClN_3O_2S$: C, 48.40; H, 4.06. Found: C, 48.33; H, 4.24.

3-Amino-5-[(3-chlorophenyl)amino]isothiazole-4-carbonitrile (**6v**).

This compound was prepared by the same procedure as described for the synthesis of **6a** except that the product was isolated by filtration after adjusting the *p*H of the reaction mixture to 7-8 by the addition of dilute hydrochloric acid. Recrystallization of the crude product from dimethylformamide-ethanol yielded 2.5 g (40%) of **6v**, mp 236-238°; ir (Nujol): 3470, 3320, 3180 (NH), 2220 (CN), 1640 cm^{-1}.

Anal. Calcd. for $C_{10}H_7ClN_4S$: C, 47.90; H, 2.81. Found: C, 47.82; H, 2.82.

3-Amino-5-[(3-chlorophenyl)amino]isothiazole-4-carboxylic Acid Ethyl Ester (**6w**).

The same procedure as used for the preparation of **6a** was employed. Recrystallization of the crude product from ethanol afforded 2.5 g (34%) of **6w**, as colorless crystals, mp 120-122°; ir (Nujol); 3490, 3270, 3160 (NH), 1660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.48 (t, 3H, CH_3), 4.50 (q, 2H, CH_2), 5.60 (broad s, 2H, NH_2), 7.48 (m, 4H, aryl-H).

Anal. Calcd. for $C_{12}H_{12}ClN_3O_2S$: C, 48.40; H, 4.06. Found: C, 48.64; H, 4.36.

3-Amino-5-[(4-chlorophenyl)amino]isothiazole-4-carbonitrile (**6x**).

This compound was prepared by the same procedure as described for the synthesis of **6a** except that the product was isolated by filtration after adjusting the *p*H of the reaction mixture to 7-8 by the addition of dilute hydrochloric acid. Recrystallization of the crude product from dimethylformamide-ethanol yielded 3.0 g (48%) of **6x**, mp 236-238°; ir (Nujol): 3460, 3300, 3180 (NH), 2220 (CN), 1630 cm^{-1}.

Anal. Calcd. for $C_{10}H_7ClN_4S$: C, 47.90; H, 2.81. Found: C, 48.16; H, 2.98.

3-Amino-5-[(4-chlorophenyl)amino]isothiazole-4-carboxylic Acid Ethyl Ester (**6y**).

The same procedure as used for the preparation of **6a** was employed. Recrystallization of the crude product from ethanol yielded 3.0 g (40%) of **6y**, as colorless crystals, mp 144-146°; ir (Nujol): 3500, 3320, 3180 (NH), 1670 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}ClN_3O_2S$: C, 48.40; H, 4.06. Found: C, 48.50; H, 4.35.

3-Amino-5-[[(4-methylphenyl)sulfonyl]amino]isothiazole-4-carbonitrile (**6z**).

Method A.

The same procedure as described for the preparation of **6a** was employed. Following the reaction with aqueous chloramine, the mixture was filtered, the filtrate was cooled and acidified with diluted hydrochloric acid. The product was collected by filtration. Crystallization from dimethylformamide-ethanol yielded 2.0 g (27%) of **6z**, as colorless crystals, mp 287-289°; ir (potassium bromide): 3440, 3340, 3220 (NH), 2230 (CN), 1660 cm^{-1}; ms: m/e 294 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_4O_2S_2$: C, 44.88; H, 3.42. Found: C, 45.14; H, 3.72.

Method B.

To a solution of **11c** (2.0 g, 6.83 mmole) in dimethylformamide (15 ml) was added a solution of fused sodium sulfide (70%, 0.76 g, 6.83 mmoles) in water (5 ml). The mixture was heated on a steam bath for 24 hours, cooled and treated with freshly prepared aqueous chloramine solution (50 ml). After allowing the mixture to stir at room temperature for 24 hours, the reaction mixture was cooled, acidified with dilute hydrochloric acid and the solid obtained was collected by filtration. Recrystallization of the crude product from dimethylformamide-ethanol yielded 1.1 g (54%) of **6z**, identical in all respects with the product obtained by Method A.

3-Amino-5(4-morpholinyl)isothiazole-4-carbonitrile (**7a**).

This compound was prepared from **11d** by employing Method B as described for the preparation of **6j** from **11b**. Recrystallization of the crude product from dimethylformamide-ethanol yielded 4.5 g (71%) of **7a**, as colorless crystals, mp 194-196°; ir (Nujol): 3390, 3300, 3180 (NH), 2210 (CN), 1640 cm^{-1}; uv (methanol): λ max nm (log ε) 214 (4.12), 267 (4.06): ms: m/e 210 (M^+).

Anal. Calcd. for $C_8H_{10}N_4OS$: C, 45.70; H, 4.79. Found: C, 45.39; H, 4.97.

Alternative Methods of Preparation of **7a**.

(i) Sodium hydride (50% dispersion in mineral oil, 2.4 g, 0.05 mole) was washed free of mineral oil with anhydrous benzene and suspended in anhydrous dimethylformamide (15 ml). The suspension was cooled in an ice bath and treated with a solution of malononitrile (1.65 g, 0.025 mole) in dimethylformamide (10 ml). The mixture was stirred at room temperature for 3 hours, cooled to 0° and treated dropwise with a solution of **14a** (4.14 g, 0.025 mole) in dimethylformamide (10 ml). After allowing the mixture to stir at room temperature for 12 hours, it was cooled and treated with aqueous chloramine solution (125 ml). Workup of the reaction mixture afforded 2.0 g (38%) of **7a**.

(ii) The isothiazole, **7a**, was also obtained in 25% yield by the above procedure by employing **14b** as the thiocarbamoylating agent, in the presence of an equivalent of sodium ethoxide in ethanol as the base.

(iii) The isothiazole, **7a**, was obtained in 19% yield by the above procedure by employing **14c** as the thiocarbamoylating agent in the presence of an equivalent of potassium hydroxide in dimethylformamide.

3-Amino-5(4-methyl-1-piperazinyl)isothiazole-4-carbonitrile (**7b**).

This compound was prepared from **11e** by employing Method B as described for the preparation of **6j**. Recrystallization of the crude product from methanol yielded 3.48 (51%) of **7b**, as colorless crystals, mp 158-160°; ir (Nujol): 3420, 3310, 3190 (NH), 2210 (CN), 1650 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.36 (s, 3H, CH_3), 2.56 (t, 4H, CH_2), 3.60 (t, 4H, CH_2), 4.90 (broad s, 2H, NH_2); ms: m/e 223 (M^+).

Anal. Calcd. for $C_9H_{13}N_5S$: C, 48.41; H, 5.87. Found: C, 48.67; H, 5.99.

3-Amino-5-(1-piperidinyl)isothiazole-4-carbonitrile (**7c**).

This compound was prepared from **11f** by employing Method B as described for the preparation of **6j**. Recrystallization from methanol afforded 3.5 g (56%) of colorless crystals, mp 186-188°; ir (Nujol): 3440, 3280, 3180 (NH), 2200 (CN), 1620 cm^{-1}.

Anal. Calcd. for $C_9H_{12}N_4S$: C, 51.90; H, 5.81. Found: C, 52.14; H, 6.00.

3-Amino-5-(1-pyrrolidinyl)isothiazole-4-carbonitrile (**7d**).

This compound was prepared from **11g** by employing Method B as described for the preparation of **6j**. Recrystallization from methanol yielded 3.1 g (53%) of **7d** as colorless crystals, mp 212-214°; ir (Nujol): 3420, 3320, 3220 (NH), 2220 (CN), 1650 cm^{-1}; uv (methanol): λ max nm (log ε) 220 (4.29), 267 (4.66).

Anal. Calcd. for $C_8H_{10}N_4S$: C, 49.46; H, 5.19. Found: C, 49.27; H, 5.29.

5-(Phenylamino)-3-hydroxyisothiazole-4-carbonitrile (**18a**).

To a cooled suspension of finely divided potassium hydroxide (85%, 1.65 g, 0.025 mole) in dimethylformamide (30 ml) was added cyanoacetamide (2.1 g, 0.025 mole), followed by phenyl isothiocyanate (3.38 g, 0.025 mole). After allowing the reaction mixture to stir at room temperature for 24 hours, it was cooled again and treated with aqueous chloramine solution (125 ml). The mixture was stirred at room temperature for 12 hours, filtered and the filtrate was cooled and acidified with dilute hydrochloric acid. The product obtained was removed by filtration and purified by dissolution in dilute alkali followed by precipitation with dilute hydrochloric acid. Crystallization from dimethylformamide-ethanol yielded 1.5 g (28%) of **18a**, mp 224-226° dec; ir (potassium bromide): 3260, 2220 (C≡N), 1645 cm^{-1}; uv (95% ethanol): λ max nm (log ε) 206 (4.36), 285 (4.14); uv (0.1*N* sodium hydroxide): λ max nm (log ε) 224 (4.27), 280 (3.99), 328 (4.05); ms: m/e 217 (M^+).

Anal. Calcd. for $C_{10}H_7N_3OS$: C, 55.28; H, 3.25. Found: C, 55.06; H, 3.53.

The compound **18a** could also be isolated in 9% yield by acidification and workup of the alkaline aqueous mother liquor obtained in the preparation of **6j** by Method A.

5-[(2-Methylphenyl)amino]-3-hydroxyisothiazole-4-carbonitrile (**18b**).

This compound was prepared by the same procedure as described for the preparation of **18a**. Crystallization from methanol yielded 1.5 g (26%) of **18b**, mp 199-201° dec; ir (Nujol): 3240, 2220 (CN), 1650 cm^{-1}; ms: m/e 231 (M^+).

Anal. Calcd. for $C_{11}H_9N_3OS$: C, 57.12; H, 3.92. Found: C, 56.85; H, 4.20.

Compound **18b** was also isolated in 10% yield by acidification and workup of the alkaline filtrate obtained in the preparation of **6m**.

5-[(4-Methylphenyl)amino]-3-hydroxyisothiazole-4-carbonitrile (**18c**).

This compound was prepared by the same procedure as described for the preparation of **18a**. Crystallization from methanol yielded 1.7 g (29%) of **18c**, mp 222-224° dec; ir (Nujol): 3240, 2220 (C≡N), 1620 cm^{-1}; ms: m/e 231 (M^+).

Anal. Calcd. for $C_{11}H_9N_3OS$: C, 57.12; H, 3.92. Found: C, 57.14; H, 4.17.

Compound **18c** was also isolated in 7% yield by acidification and workup of the alkaline filtrate obtained in the preparation of **6o**.

3-Amino-5-(phenylamino)isothiazole-4-carboxamide (**19a**).

A suspension of **6h** (2.16 g, 0.01 mole) in 10% sodium hydroxide solution (60 ml) was refluxed for 8 hours. The reaction mixture was cooled, filtered and the filtrate was neutralized with 10% aqueous hydrochloric acid. The solid obtained was filtered off, washed and dried in air. Crystallization from dimethylformamide-ethanol yielded 1.8 g (77%) of **19a**, mp 232-234°; ir (Nujol): 3400, 3350, 3200, 3180 (NH), 1650 cm^{-1}; uv (95%

ethanol): λ max nm (log ε) 205 (4.26), 223 (4.17), 310 (4.18); ms: m/e 234 (M^+).

Anal. Calcd. for $C_{10}H_{10}N_4OS$: C, 51.26; H, 4.30. Found: C, 51.40; H, 4.47.

3-Amino-5-[(2-methylphenyl)amino]isothiazole-4-carboxamide (**19b**).

This compound was prepared by the same procedure as described for the preparation of **19a**. Crystallization from dimethylformamide-ethanol afforded 1.4 g (56%) of **19b**, mp 208-210°; ir (Nujol): 3400, 3300 (NH), 1630 cm^{-1}; ms: m/e 248 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_4OS$: C, 53.21; H, 4.87. Found: C, 53.35; H, 5.09.

3-Amino-5-[(4-methylphenyl)amino]isothiazole-4-carboxamide (**19c**).

This compound was prepared by the same procedure as described for the preparation of **19a**. Crystallization from dimethylformamide-ethanol yielded 1.8 g (73%) of **19c**, mp 220-224°; ir (Nujol); 3400, 3300, 3180 (NH), 1660 cm^{-1}; ms: m/e 248 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_4OS$: C, 53.21; H, 4.87. Found: C, 53.22; H, 4.97.

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