Reaction of Metallo *S*-Alkyl *N*-Cyanodithioiminocarbonates and Alkyl *N*-Cyanocarbamates with Hydrazine. A Novel Preparation of 5-Amino-3-mercapto-1,2,4-triazole

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Metal salts of *S*-alkyl-*N*-cyanodithioiminocarbonates **7** react as *electrophiles* with hydrazine hydrate to form 5-amino-3-mercapto-1*H*-1,2,4-triazole **1**. The novel 4-cyanothiosemicarbazide **9** is proposed as the intermediate which cyclizes to the aromatic triazole. The rate determining step is addition of hydrazine to the iminocarbonate and is second order. Other nucleophiles such as substituted hydrazines and amines failed to react. Exchange of either or both sulfurs with oxygen leads to decomposition or mixtures of products.

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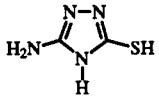
Introduction.



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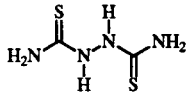
Because of its importance as a synthetic intermediate or formulation additive [1-7], 5-amino-3-mercapto-1*H*-1,2,4-triazole **1** has been prepared in several ways, most of which fall into one of three categories based on the heterocyclic precursor: 2,5-dithiobiurea (**2**) [8], aminoguanidine (**3**) [9], or thiosemicarbazide (**4**) [4,10]. Each of these precursors is a substituted hydrazine which can be modified for preparation of **1**. An alternate route is the combination of *unsubstituted* hydrazine (as the hydrate) and a compliment containing two non-equivalent electrophilic sites.



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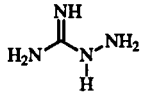

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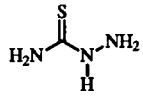

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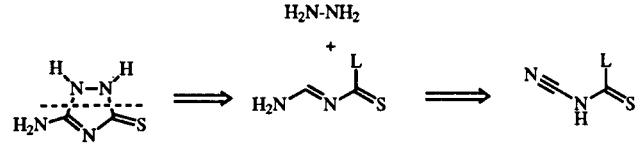
Retrosynthetic Analysis.

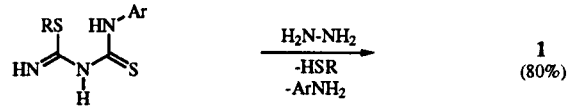
Scission of the 2,3- and 1,5-bonds of **1** produces hydrazine and intermediate **5**, which could be derived from substituted cyanamide **6** containing the leaving group L (Scheme 1). Clarkson and Landquist [10a] have demonstrated the validity of this retrosynthesis by reacting hydrazine and ((arylamino)thioxomethyl)carbamimidothioic esters (Scheme 2), but a simpler version of their approach was envisioned.

Scheme 1



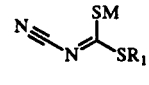
1 **5** **6**

Scheme 2



1 (80%)

The *N*-cyanodithioiminocarbonate esters **7** and **8** (M = metal) contain the necessary components of **6** (L = R_1S). The *S*,*S*-diesters **8** have been reacted with hydrazines [11] to produce several types of heterocycles but the monoesters **7** have only been used as *nucleophiles* with one exception: ammonia addition to **7a** (R_1 = CH_3) in ethanol in a sealed vessel [12].



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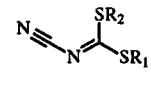


8

A critical question was the role of substitution at sulfur: was it necessary for both sulfurs to be substituted such that the iminocarbonate would function as an electrophile? Since the target compound was the 2-mercapto-

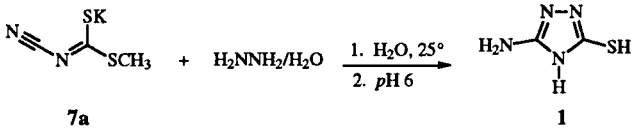
heterocycle, use of **8** would have afforded the *S*-substituted heterocycle [11e] and subsequent dealkylation [13] would have been required to prepare **1**. However, use of **7** would lead directly to **1** (loss of R_1SH). This report describes *unknown* reactions of **7** as *electrophiles* in the addition of hydrazine and briefly discusses the same chemistry of *N*-cyanocarbamates.

Results and Discussion.

Preparation of **1**.

Reaction of **7a** ($R_1 = CH_3$) with hydrazine hydrate at *ambient temperature* provided **1** in about 75% yield (Scheme 3) after acidification of the reaction mixture to *p*H 6 [14]. Not only is this a new reaction [15] in which an monoester **7** serves as an *electrophile* but an economically viable route to an important agrochemical intermediate.

Scheme 3



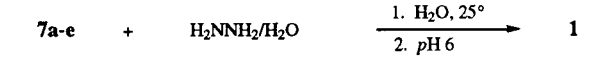
7a **1**

The reaction proceeds slowly at room temperature so typical preparation temperatures are between 45° and 60° (higher temperatures result in noticeable decomposition of **7a**). The reaction can be done at concentrations up to 40 wt % of **7a** and in organic, aqueous or mixed solvent systems. Typical yields range from 65 to 80% with purities (hplc) above 96%. Reaction times are between 1 and 4 hours at elevated temperatures, with longer times providing only a few percent more product. Up to two equivalents of hydrazine have been used but more than one and a quarter equivalents are unnecessary (impure product isolated, no yield improvement).

The salts **7** can be kept in solution after formation [15] and reacted directly with hydrazine hydrate or can be isolated prior to cyclization; yields and purities are not significantly affected. However, if crude **7** is suspended in an organic wash solvent for a short time (to remove trace quantities of **8**, see Experimental) [16], isolated and dried before reaction with hydrazine hydrate, then **1** is obtained in 75% yield with greater than 98% purity.

Four other monoesters **7b-e** were prepared according to Wittenbrook [16] and were reacted with hydrazine hydrate to test reaction generality (Table); each provided reasonable yields of **1**.

Table



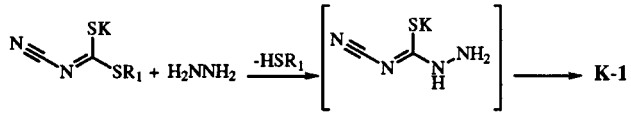
7	R_1	Reaction Time (hours)	Yield of **1** (%)
a	CH_3	2 [a]	81
b	C_2H_5	18	80
c	n-C_4H_9	18	77
d	$C_6H_5CH_2$	18	80
e	H_2NCOCH_2	18	58

[a] Reaction temperature = 60°.

Mechanism.

Initial hydrazine attack at the imino carbon is probably followed by expulsion of alkylthiol to form the intermediate 4-cyanothiosemicarbazide **9** (Scheme 4). Ring closure to **1** is so rapid that **9** could not be detected in the reaction medium by ^{13}C nmr.

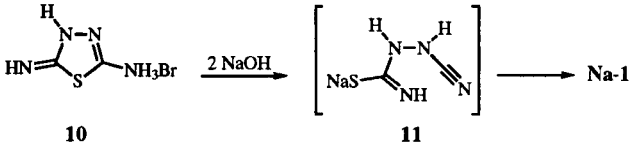
Scheme 4



7 **9**

This is in accord with the proposed mechanism [17] for reaction of thiadiazole **10** with base which proceeds through the regioisomeric 1-cyanothiosemicarbazide **11** (Scheme 5). If **9** and **11** are drawn in their carbodiimide resonance forms, the reactivity of these intermediates is even more clearly seen [18].

Scheme 5



10 **11**

Reiter has proposed a similar pathway for the reaction of diesters **8** with hydrazines [11d]. Since intermediates have not been observed nor isolated for these reactions, the best evidence for this site-specific addition is found in the reactions of **8** with amines in which the isoureas have been isolated [19]. Extrapolation of this reactivity to that of **8** with hydrazines seems reasonable, and extension to the monoesters **7** follows [20].

Kinetics.

The reaction rates of iminocarbonates **7a** and **7e** with hydrazine hydrate were determined at 42° and 40°, respectively, in 40 wt % aqueous solutions. The disappearance of **7a** or **7e** was monitored by uv at 295 nm. Two runs at different concentrations were done for both **7a** and **7e** with measurements taken only during the first 8 hours (about five half-lives). The t = ∞ value (20 hours) for **7** was not used because the absorbance at 295 nm was primarily due to metallo-**1** after about 8 hours.

expected to be similar to those of **7a**, and **7d** was not used due to interfering absorbances in the uv. Attempts to obtain a pseudo-first order rate constant with excess hydrazine hydrate led to product decomposition.

The kinetic data are consistent with a rate-limiting, second order step of hydrazine addition to the iminocarbon (*vide supra*). Whether intramolecular nitrogen addition to the cyano group of tetrahedral intermediate **12** leading to **13** is faster than alkylthiol expulsion leading to **9** cannot be determined from these data but both are certainly much

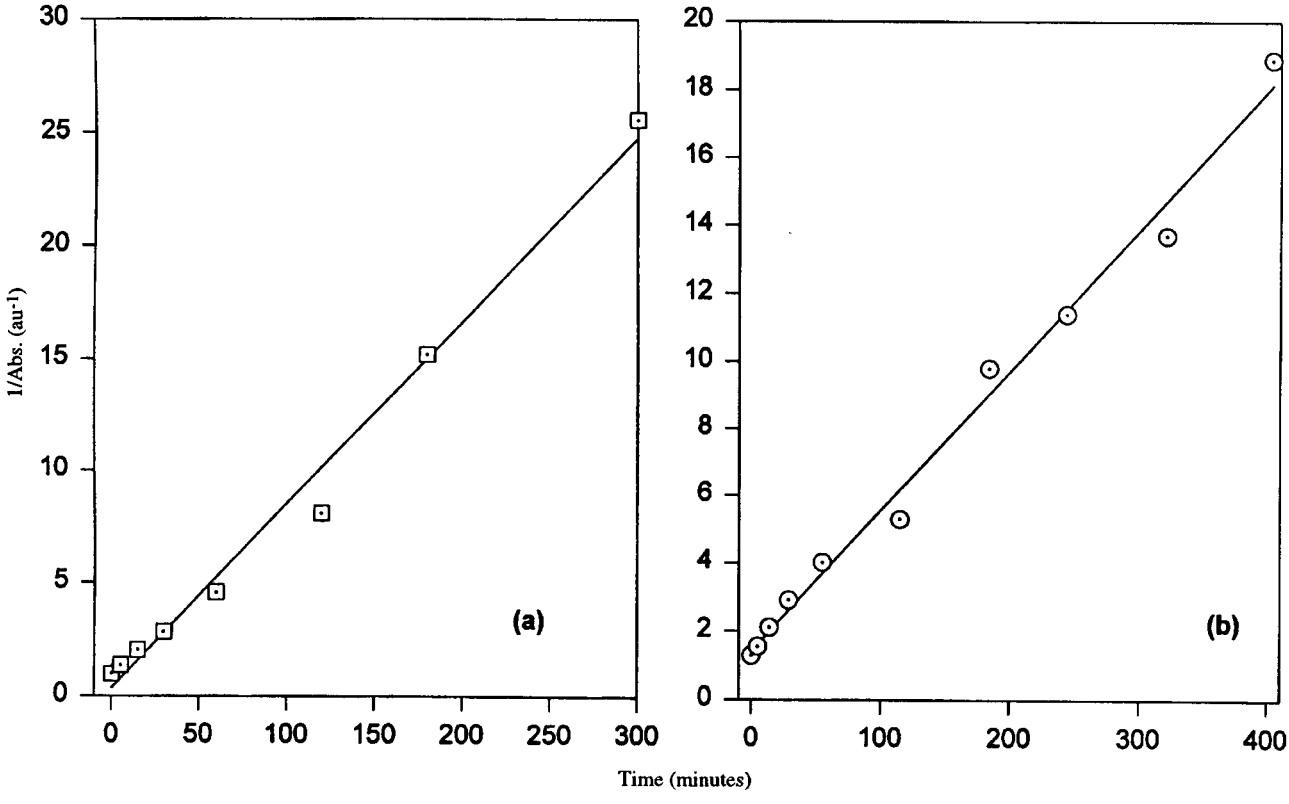


Figure. Plot of 1/Abs *vs.* time for reaction of hydrazine hydrate with (a) **7a** at 1.0 *M* and 42° and (b) **7e** at 0.98 *M* and 40°.

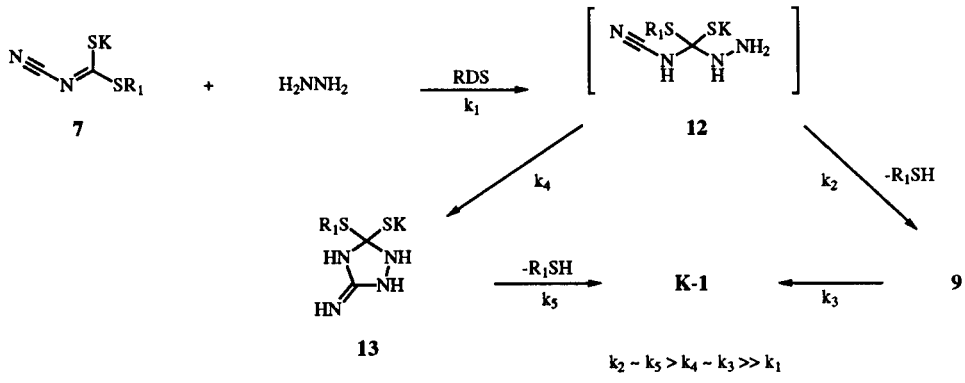
Representative plots are shown in the Figure for reactions of **7a** and **7e** with hydrazine hydrate. Plots of 1/Abs *vs.* time yielded straight lines with correlation coefficients better than 0.980. As the initial concentration of **7** was increased close to one molar, the initial reaction rates increased so rapidly that without careful temperature control, the plot of 1/Abs *vs.* time became decidedly curved. A kinetic test with 0.106 *M* **7a** at 40° had no significant exotherm and gave a plot of 1/Abs *vs.* time as a straight line (corr. coeff. = 0.999).

It was suspected that the expulsion of methanethiol from the reaction mixture may have had an effect on the observed rate so **7e** was prepared in order to determine if leaving group choice were important; the data indicated no such bias. Results from reactions of **7b** or **7c** were faster than the initial hydrazine addition (Scheme 6). From the chemistry of **8** with amines [19], the expulsion of R_1SH would seem to occur prior to ring closure.

Reactions of **7** with other Nucleophiles.

Reactions of **7a** with substituted hydrazines, amines or alkoxides gave only decomposition, a direct contrast to reactions of **8** [21]. Even more surprising was the failure of **7a** to react with hydroxylamine [22]. It is suspected that the aromaticity of **1** drives the reaction with hydrazine hydrate whereas the products from addition of other nucleophiles do not have aromatic stability. The exceptional nucleophilicity of hydrazine may also have an effect.

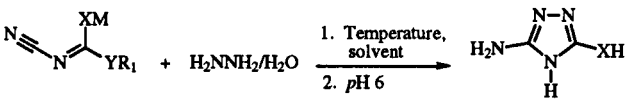
Scheme 6



Reactions of Monothio- and Dioxo-**7** with Hydrazine Hydrate.

The monothio analogs of **7**, potassium *O*-ethyl *N*-cyanothionoiminocarbonate (**14**) and potassium *S*-methyl *N*-cyanothiolcarbamate (**15**) and the dioxo analog potassium *O*-ethyl *N*-cyanocarbamate (**16**) [21d,23] were reacted with hydrazine hydrate in various solvents. The product from **14** would have been **1** with expulsion of R_1OH, and from **15** or **16** the product would have been 5-amino-3-hydroxy-1,2,4-triazole **17** (Scheme 7). Ester **14** was heated with hydrazine hydrate in water or 2-propanol at about 45° but only decomposition was seen. Ester **15** was heated with hydrazine hydrate in water, 2-propanol or 1-butanol at reflux for 2 to 4 hours without reaction [24]. Carbamate **16a** ($R_1 = CH_3$) was heated with hydrazine hydrate in 2-propanol for 2 hours at reflux without reaction (92% recovery of **16a**). These results suggest that two sulfurs are necessary on the iminocarbon for reaction to occur with hydrazine when the iminocarbonates are in the *salt* forms.

Scheme 7



X = S, Y = O, **14**
X = O, Y = S, **15**
X, Y = O, **16**
M = K, H

X = S, **1**
X = O, **17**

Reactions of *N*-Cyanocarbamates with Hydrazine Hydrate.

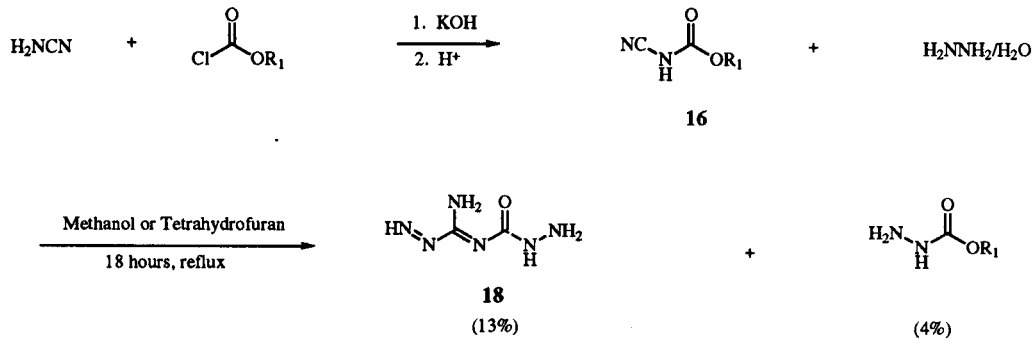
The protonated forms of **7** and **14** (M = H) were not prepared due to their expected instability [25]; all attempts to prepare protonated **15** led to decomposition. It was possible, however, to prepare alkyl *N*-cyanocarbamates **16** (M = H) by reaction of cyanamide with chloroformates (Scheme 8). These carbamates were more stable than the monothio analogs but still had sufficient reactivity to require their immediate use [26].

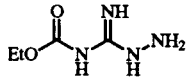
Reaction of **16b** ($R_1 = C_2H_5$) or **16c** ($R_1 = n\text{-}C_4H_9$) with hydrazine hydrate in methanol or tetrahydrofuran at 65° for 18 hours afforded **18** as an insoluble white solid in about 13% yield. The filtrates contained predominantly the carbazates as the second major components (4% yield). That cyanamide was displaced at the carbonyl carbon was surprising but not without precedent [19c]. The hydrazide **18** was formed by addition of two equivalents of hydrazine to **16** followed by loss of hydrogen; the fate of the hydrogen is unknown. Reaction of **16b** in water or in tetrahydrofuran with 5 equivalents of hydrazine hydrate gave ethyl carbazate (yield not determined) with only a trace of **18** detected; reactions in 1-butanol, benzene, or ethoxyethanol or in tetrahydrofuran with 2 equivalents of hydrazine hydrate gave many products, one of which was ethyl (amino(hydrazino)methylene)carbamate **19** (identified by gc-ms). None of the desired hydroxy triazole **17** was detected in any reactions with **16** so work with the cyanocarbamates was abandoned.

Conclusions.

A novel reaction of ester salts **7** with hydrazine hydrate has been explored in which **7** function as *electrophiles* to produce 5-amino-3-mercapto-1,2,4-triazole **1**. The reaction proceeds under a wide range of conditions and pro-

Scheme 8





19

vides **1** in good to excellent yield. Product of high quality can be obtained if **7** is washed with an organic solvent prior to addition of hydrazine hydrate. The reaction is second order with substitution at the iminocarbon preceding ring closure. Replacing one sulfur of **7** with oxygen either causes decomposition of **7** or renders the resultant *N*-cyanoiminocarbonates unreactive. Replacement of both sulfurs with oxygen leads to many products in the reactions with hydrazine hydrate.

EXPERIMENTAL

Melting points (mp) were obtained on a Fisher Johns Hot Plate melting point apparatus and are uncorrected. Solvents were used as obtained from the supplier as either reagent or hplc grade. The ^1H and ^{13}C nmr spectra were recorded on a Bruker AC-250 spectrometer in deuteriochloroform, deuterium oxide, dimethyl sulfoxide-d_6 or methanol-d_4 with the solvent as reference. Chemical shifts are reported in ppm (δ); multiplicities are given as s (singlet), d (doublet), t (triplet), q (quadruplet), or m (multiplet). Mass spectra were obtained on a Finnegan MAT ITS 40 Magnum ion trap gc/mass spectrometer or were provided by Oneida Research Services of Whitesboro, NY; Oneida also performed the elemental analyses.

Potassium Methyl *N*-Cyanodithioiminocarbonate (**7a**).

Water (1.58 liters), acetone (1.45 liters), and dipotassium *N*-cyanodithioiminocarbonate **7f** (M = R_1 = K; 348.2 g, 1.8 moles) [28] were mixed, the solution was cooled to 3° and methyl chloride (102.8 g, 2.04 moles) was added over 70 minutes at or below 7°. The mixture was stirred and allowed to warm overnight. It was concentrated to give a wet yellow-white paste which was suspended in acetone (1.25 liter; 4 ml/(g product theoretical)) and stirred for 5 minutes. The mixture was filtered to yield white potassium chloride (124 g, 93%). A sample of this solid was dissolved in water to give a clear, colorless solution indicating that **7f** (insoluble in acetone, yellow in water) had been consumed. The filtrate was concentrated at 50° to a yellow-white solid which was suspended in dichloromethane (900 ml; 3 ml/(g of product); to remove **8a**) and stirred for 30 minutes. The solid was collected by filtration, washed with dichloromethane (100 ml) and dried to yield 235 g (77%) of **7a** as a white, crystalline solid, mp 212-217° (lit mp [16a] 214-216°); ^1H nmr (deuterium oxide): δ 2.40 (s, 3H); ^{13}C nmr (deuterium oxide): δ 212.9, 119.8, 18.7; uv (water): λ max 270.3 nm (ε 12,600).

Potassium Ethyl *N*-Cyanodithioiminocarbonate (**7b**).

Water (30 ml), methanol (30 ml), and **7f** (25.1 g, 129 mmoles) were mixed under nitrogen and to the solution was added ethyl iodide (20.1 g, 129 mmoles) over 55 minutes at 20°. The mixture was stirred 5 hours and concentrated to give a wet yellow-white paste to which was added ethanol (3 x 100 ml, to remove water) and the mixture was concentrated. The slurry was suspended in ethyl acetate, filtered (removed potassium iodide and unreacted **7**), concentrated and suspended in dichloromethane (125 ml) for 30 minutes. The solid was collected by filtration and dried to yield 19.3 g (81%) of **7b** as a white powder, mp 156-157° (lit mp [29] 149-152°); ^1H nmr (methanol-d_4): δ 1.23 (t, 3H, J = 7.3 Hz), 2.95 (q, 2H, J = 7.3 Hz); ^{13}C nmr (methanol-d_4): δ 211.9, 120.6, 30.5, 14.5.

Potassium *n*-Butyl *N*-Cyanodithioiminocarbonate (**7c**).

Water (30 ml), methanol (30 ml), and **7f** (25.1 g, 129 mmoles) were mixed under nitrogen and to the solution was added *n*-butyl iodide (23.8 g, 130 mmoles) over 1 hour and 40 minutes at 25°. The mixture was stirred overnight and concentrated to give a wet yellow-white paste to which was added ethanol (2 x 150 ml) and the mixture was concentrated. The slurry was suspended in acetone (100 ml), filtered and concentrated. The residue was suspended ethyl acetate (200 ml) for 30 minutes, filtered, concentrated and suspended in dichloromethane (150 ml) for 30 minutes. The solid was collected by filtration and dried to yield 20.5 g (74%) of **7c** as a white powder, mp 194-196° (lit mp [29]

157-167°); ^{1}H nmr (methanol-d_4): δ 0.91 (t, 3H, J = 7.3 Hz), 1.39 (sextuplet, 2H, J = 7.4 Hz), 1.59 (quint., 2H, J = 7.3 Hz), 2.98 (q, 2H, J = 7.3 Hz); ^{13}C nmr (methanol-d_4): δ 212.1, 120.6, 36.2, 32.4, 23.0, 14.0.

Potassium Benzyl *N*-Cyanodithioiminocarbonate (**7d**).

Water (30 ml), methanol (30 ml), and **7f** (25.6 g, 132 mmoles) were mixed under nitrogen and to the solution was added benzyl chloride (16.7 g, 132 mmoles) over 40 minutes at 25°. The mixture was stirred overnight and concentrated to give a wet yellow-white paste which was suspended in acetone (200 ml), filtered and concentrated. The residue was suspended ethyl acetate (75 ml), dried (sodium sulfate), filtered, diluted with ethyl acetate (75 ml) and the product was precipitated by the careful addition of diethyl ether (300 ml). The solid was collected by filtration and dried to yield 20 g (62%) of **7d** as a white powder, mp 213-214° (lit mp [29] 206-212°); ^{1}H nmr (methanol-d_4): δ 4.26 (s, 2H), 7.25 (m, 5H); ^{13}C nmr (methanol-d_4): δ 210.9, 139.1, 129.9, 129.3, 127.8, 120.4, 41.1.

Potassium Amidomethyl *N*-Cyanodithioiminocarbonate (**7e**).

Water (80 ml), acetone (70 ml) and **7f** (16.48 g, 84.9 mmoles) were mixed and 2-bromoacetamide (11.1 g, 80.5 mmoles) in acetone (80 ml) was added dropwise below 20° over 30 minutes. The mixture was stirred overnight and concentrated at 50° *in vacuo*. Ethanol (100 ml) was added to remove the residual water several times. The residue was diluted with acetone (200 ml), filtered, and the filter cake washed with acetone. The acetone layer was concentrated and the residue was washed with ethyl acetate (200 ml). The layers were separated and the aqueous layer was concentrated; ethanol (5 x 100 ml) was used to remove the residual water. The liquid residue was diluted with acetone (200 ml) and dried (sodium sulfate), filtered and concentrated. The residual solid was suspended in ethyl acetate (200 ml) for 15 minutes, decanted, suspended again in ethyl acetate (200 ml) for 15 minutes, collected by suction and dried (suction, 2 minutes; vacuum pump, 1 hour). The ethyl acetate layers contained multiple products and were discarded. The yield of **7e** as a yellow powder was 14.75 g (86%), mp 167-169°; ir (nujol): 3375, 3288, 3234 and 3178 (NH), 2169 (CN), 1671 (CO), 1603, 1402, 1359 (CH_2), 1242, 1171, 1127, 1079, 1061 cm^{-1}; ^{1}H nmr (methanol-d_4): δ 4.78 (NH_2), 3.71 (CH_2); ^{13}C nmr (methanol-d_4): 209.5, 174.6, 119.9, 39.8; uv (water): λ max 279.4 (ε = 10450).

Anal. Calcd. for $C_4H_4KN_3OS_2$: C, 22.52; H, 1.89; N, 19.70, S, 30.06. Found: C, 22.68; H, 2.01; N, 19.74; S, 28.70.

5-Amino-3-mercapto-1*H*-1,2,4-triazole (**1**). Representative Example.

Water (15 ml) and **7a** (10.0 g, 58.7 mmoles) were mixed and hydrazine hydrate (54.4% hydrazine, 3.5 ml, 59.4 mmoles) was added at 30° and the solution was stirred for 1 hour. The solution was heated to 55° for 1 hour, cooled overnight, and acidified to *p*H 5.6 with concentrated hydrochloric acid. The solid was collected by suction, washed with water, acetone and dried to yield **1**, 5.3 g (77%) as white powder, mp >300° (lit mp [10] >300°); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 163.0, 152.7; uv (water): λ max sodium salt 193.2 nm (ε 10290); 247 nm (ε 8470).

Representative Kinetic Run. Reaction of **7a** with Hydrazine Hydrate.

A solution of **7a** (18.95 g, 111.3 mmoles) in water (110 ml) was placed in a constant temperature bath which had equilibrated to 42.2° over 18 hours. When the solution reached 42°, hydrazine hydrate (6.58 g, 111.4 mmoles) was added rapidly. Methanethiol generation began after about 5 minutes, increased to a rapid pace after about 15 minutes and gradually slowed over the remainder of the reaction. Measurement of **7a** concentration was accomplished as follows: one milliliter aliquots were removed by Eppendorf pipette and diluted to 100 ml. A one milliliter aliquot of the first dilution was diluted to 100 ml and the uv absorbance was measured at 295 nm. Aliquots were taken only during the first 8 hours and the mixture was stirred overnight. The mixture was filtered, cooled to ambient and acidified to *p*H 6 to yield **1** as a white powder (10.51 g, 81%).

Reaction of Ethyl *N*-Cyanocarbamate **16b** with Hydrazine Hydrate.

Ethyl *N*-cyanocarbamate **16b** (4.5 g, 40 mmoles) in methanol (40 ml) was stirred under nitrogen and hydrazine hydrate (2.37 g, 40 mmoles) was added at once. After an exotherm to 35° the solution was heated to reflux for 19 hours, cooled and filtered. The filter cake was dried by suction to yield **18** (0.44 g, 13%) as a white powder: mp 250° dec; ir (potassium bromide): 3300, 3288, 3217 and 3181 (NH), 1722 (CO), 1639, 1603, 1547, 983 cm^{-1}; ^{13}C nmr (dimethyl sulfoxide-d_6): 154.1, 151.2; ms: methane CI m/z 131 (M+1,100), 130 (27), 114 (37), 84 (16).

Anal. Calcd. for $C_2H_6N_6O$: C, 18.46; H, 4.65; N, 64.60. Found: C, 18.57; H, 4.70; N, 63.90.

The filtrate was concentrated and the residue taken up in dichloromethane, filtered to remove residual **18**, and examined by tlc, ^{13}C nmr and gc-ms. The major component was ethyl carbazate as determined by comparison with an authentic sample.

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