THE SERENDIPITOUS FORMATION OF AN UNUSUAL METHYL *N'*-CYANO-*N*-[5-METHYLTHIO-1,2,4-TRIAZOL-3-YLIDENE]CARBA MIMIDOTHIOATE AND SUBSEQUENT REACTIONS

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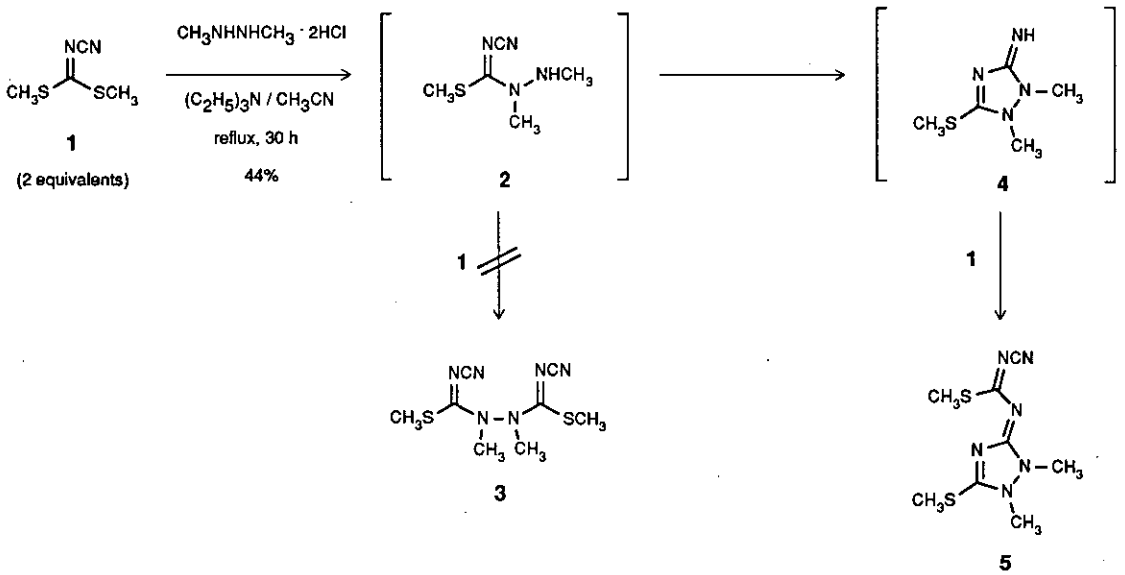
Abstract - Dimethyl cyanocarbamimidodithioate (**1**) (2 equivalents) reacts with 1,2-dimethylhydrazine to afford the cyclic derivative, methyl *N'*-cyano-*N*-(5-methylthio-1,2,4-triazol-3-ylidene)carbamimidothioate (**5**), instead of an expected acyclic derivative. The triazole (**5**) undergoes di-addition-elimination reactions with primary aliphatic amines to afford *N''*-cyano-*N*-(5-amino-1,2,4-triazol-3-ylidene)guanidines (**6**).

We desired to prepare the acyclic **3** as an intermediate in the preparation of *N',N'''*-dicyano-1,2-hydrazinedicarboximidamides for biological testing. The reaction of 1,2-dimethylhydrazine with dimethyl cyanocarbamimidodithioate (**1**) should afford intermediate (**2**), which we believed would reversibly form the non-aromatic triazole (**4**). Further reaction of **2** with a second equivalent of **1** would afford the desired intermediate (**3**). The reaction pathway took another course. Dimethyl cyanocarbamimidodithioate (**1**) is known to undergo a cyclization reaction with hydrazine and methylhydrazine to afford aromatic 3-amino-5-methylthio-1,2,4-triazoles.[1] The reaction of two equivalents of the dimethylthio carbamate (**1**) with the free base of 1,2-dimethylhydrazine in refluxing acetonitrile also gave a cyclization product, the triazole (**5**). Not only does intermediate (**2**) cyclize to give intermediate (**4**), but the imino function of **4** must display more powerful nucleophilic properties than the hydrazine function of intermediate (**2**) to react with **1**, and form the unusual triazole (**5**). The imino function of **4** is part of an

imbedded guanidine function, the nucleophilicity of which may be increased by the pseudourea functionality. Guanidine is known to possess very high base strength (pKa = 13.65) and nucleophilicity.[2] In contrast to the reactivity displayed by the proposed intermediate (**4**), the reaction of hydrazine hydrate with two equivalents of **1** in acetonitrile at reflux for four days gave only the mono-addition cyclization product, 3-amino-5-methylthio-1,2,4-triazole (70%).[1]

The uv spectrum of **5** provided evidence for the structural assignment. Two π-π^* transitions, characteristic of a highly conjugated π system, were seen in the uv spectrum at 249 nm and 300 nm with large molar absorptivities, 15,900 and 23,600, respectively. Additionally, the ^{13}C-nmr spectrum displayed four widely distributed quaternary carbon signals. An electron deficient guanidino carbon at 175 ppm and one nitrile carbon at 117 ppm were observed. Based on this data, the structure of **5** was assigned as shown in Scheme 1.

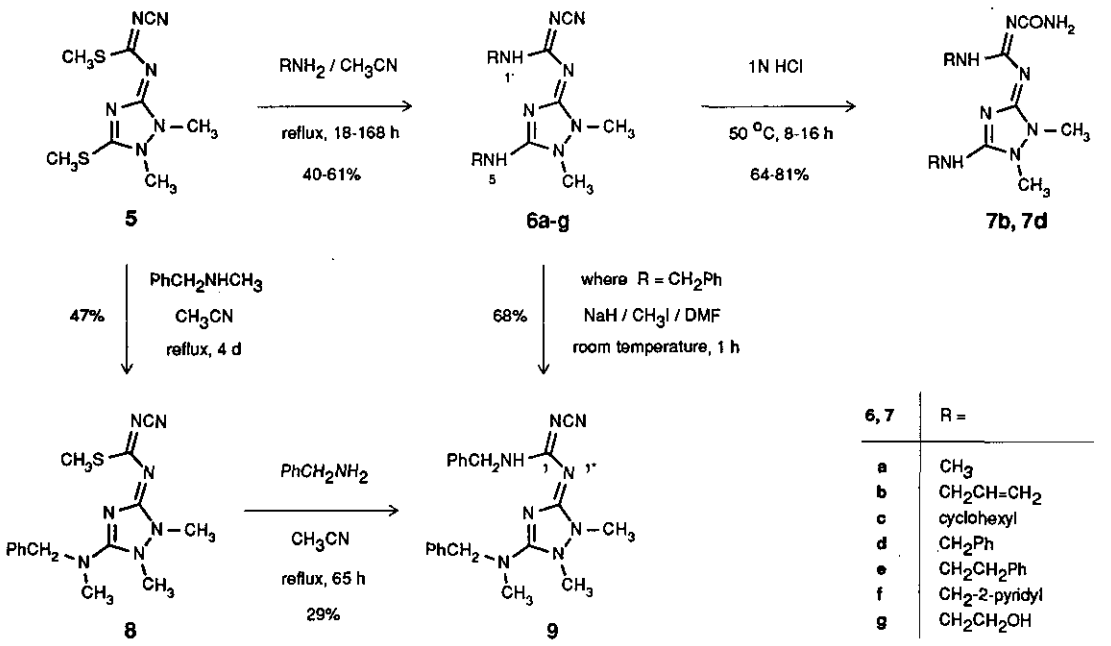
Scheme 1



In exploring the chemistry of this novel triazole (**5**),[3] we have found that reaction with excess primary aliphatic amines affords the di-addition products (**6a-6g**). Treatment of **6b** and **6d** with dilute acid at 50 °C for 8-16 h gave the *N*-carbamates (**7b**) and (**7d**), respectively. The anion of **6d** readily formed with sodium hydride in DMF and reacted with iodomethane to give a monomethyl derivative (**9**). The methyl derivative (**9**) was also prepared via the intermediate **8**, which was obtained by the prolonged reaction of **5** with excess

N-methylbenzylamine. Treatment of **8** with benzylamine gave the derivative (**9**) which was compared to the material prepared by methylation of **6d**. The ^{1}H-nmr spectra of both materials were identical and their mixture melting point was undepressed. The EI and CI mass spectra of **9** both gave fragments (M^+-157 and MH^+-157, respectively) which result from scission of the N1*-C1 bond, suggesting that the structure shown was correct. Digestion of **9** in refluxing concentrated hydrochloric acid gave both benzylamine and *N*-methylbenzylamine by GC analysis.

Scheme 2



The structure of **9** was confirmed by single crystal X-ray diffraction (Figure 1). One striking feature of the crystal structure was the planarity of all the nitrogen atoms in this structure (see Figure 2). The mean deviation from the plane was only 0.16 Å. The high degree of electron conjugation was also noted in the uv spectrum. Similar to **5**, the spectrum of **9** displayed two π-π^* transitions at 243 nm and 283 nm with large molar absorptivities. Another structural feature of **9** included an intramolecular H-bond interaction between the N1' proton and the N-4 nitrogen of 2.0 Å. The N1' and N5 nitrogens are both sp^2 hybridized which was noted on examination of the bond angles. The bond angles for C7'-N1'-C1 and C7#-N5-C5 were 125° and 120°, respectively. The dihedral angles for C7'-N1'-C1-N1" and C7#-N5-C5-N4 were 3° and 14°, respectively. Therefore, the lone pair of electrons on N1' is aligned with the extended π-system, while the

lone pair of electrons on N5 is rotated slightly out of the π-system plane possibly due to the non-bonded interaction of the C51 and C11 methyl groups (Figure 2).

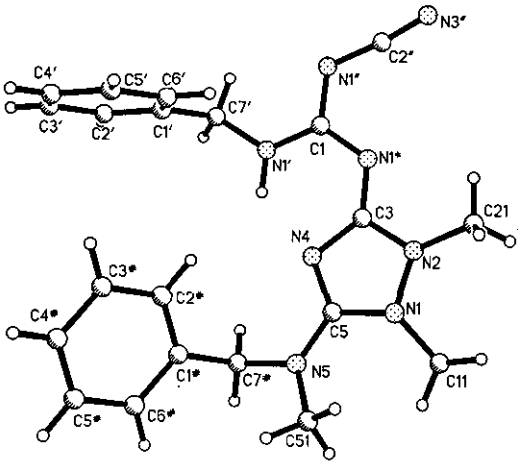


Figure 1. X-Ray crystallographic structure of 9.

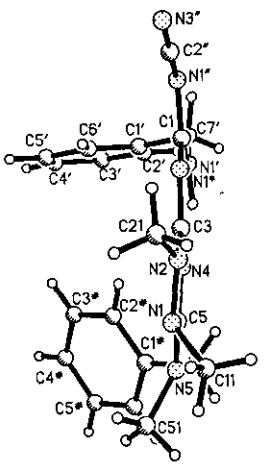


Figure 2. 90° View of 9 along the xy plane of figure 1.

Based on the structural features described above, the rationale for obtaining the observed regiochemistry in the formation of **8** and **9** is described below. Since **6d** contains a highly conjugated π-system, the N-5 proton of **6d** is more acidic than the N-1' proton. The resulting anion can be delocalized over the π-system of nine atoms. Additionally, methylation at the nitrogen atoms other than at N-5 would interrupt this stabilized conjugated π-system. The rationale for the regiochemistry of the *N*-methylbenzylamine addition to **5** afford **8** follows similar reasoning. Addition to the 5-position of the triazole affords an intermediate with significant charge delocalization thereby giving an intermediate of lower energy than one arising from addition to the guanidino carbon.

The triazoles (**6**) and (**7**) described in this paper are novel heterocyclic derivatives bearing an unusual embedded conjugated imine chromophore.[3] These derivatives are obtained in moderate yields from commercially available materials in two to three reaction steps.

Table 1. Methylthio Displacement Reactions of Carbamimidothioates (**5**) and (**8**) by Amines.

Product	Reaction Time (h)	Yield (%)	mp (°C) (Solvent)	Ir (KBr) ν (cm^{-1})	^{1}H-Nmr (TMS)[a] δ, J (Hz)	Ms (70 eV) m/z
6a	168	59	271-273[b] (CH_3OH)	2165, 1668	3.22 (s, 3H), 3.52 (s, 3H), 3.84 (s, 3H), 4.03 (s, 3H), 12.00 (s, 2H)	222 (M^+), 207
6b	29	58	198-201[b] (CH_3CN)	3230, 2170, 1660	3.40, 3.44 (2s, 6H), 3.92 (m, 4H), 5.0-5.4 (cm, 4H), 5.7-6.1 (cm, 2H), 8.12 (bt, 1H)	274 (M^+), 259
6c	56	61	270[b] ($(C_2H_5)_2O$)	2255, 1650	1.0-2.2 (bm, 22H), 3.30 (s, 3H), 3.35 (s, 3H)	358 (M^+)
6d[c]	20	58	236-238 (*CH_3OH*)	2270, 1665	3.40, 3.44 (2s, 6H), 4.45 (m, 4H), 7.22, 7.25 (*2s, 10H*), 8.40 (*bt, 1H*)	374(M^+), 360
6e	18	40	176-178 (CH_3CN)	2150, 1645	2.85 (bt, J = 5, 4H), 3.2-3.8 (m, 10H), 7.2 (bs, 10H), 8.05 (bt, 2H)	402 (M^+)
6f	56	61	185-186 ($(C_2H_5)_2O$)	2160, 1655	3.44 (s, 3H), 3.52 (s, 3H), 4.55 (d, J = 5, 2H), 4.78 (s, 2H), 7.1-7.8 (m, 6H), 8.40 (cm, 2H), 9.00 (bt, 1H)	376 (M^+)
6g	24	58	193-195 (CH_3CN)	2140	3.0-3.8 (bm, 14H), 5.2 (bm, 2H), 8.0-8.55 (bm, 2H)	282 (M^+)
8	96	47	110-112 (CH_3CN/ $(C_2H_5)_2O$)	2162, 1645	2.38 (s, 3H), 3.06 (s, 3H), 3.40, 3.43 (2s, 6H), 4.67 (s, 2H), 7.33 (s, 5H)	329 (M^+), 314, 282
9	65	29	155-157 (CH_3CN/ $(C_2H_5)_2O$)	d	3.00 (s, 3H), 3.35, 3.40, (2s, 6H), 4.41 (d, J = 5, 2H), 4.52 (s, 2H), 7.0-7.4 (cm, 10H), 8.15 (bs, 1H)	388 (M^+), 373, 231

[a]Spectra were recorded with DMSO-d_6 as solvent for **6a-g** and with $CDCl_3$ for **8** and **9**. [b]Decomposition point. [c]Uv(EtOH) λ_{max}(nm) (ε) = 218 (12,800), 244 (23,200), 281 (25,500). [d]See experiment section.

Table 2. Microanalytical Data for New Compounds.

Product	Molecular Formula	Calcd			Found		
		C	H	N	C	H	N
6a	$C_8H_{14}N_8$	43.23	6.35	50.42	43.05	6.33	50.18
6b	$C_{12}H_{18}N_8$	52.54	6.61	40.85	52.65	6.48	40.90
6c	$C_{18}H_{30}N_8$	60.31	8.43	31.26	59.97	8.41	31.38
6d	$C_{20}H_{22}N_8$	64.15	5.92	29.92	64.05	5.83	29.98
6e	$C_{22}H_{26}N_8$	65.65	6.51	27.84	65.25	6.53	27.73
6f	$C_{18}H_{20}N_{10}\cdot¼H_2O$[a]	56.71	5.38	36.57	56.83	5.38	36.76
6g	$C_{10}H_{18}N_8O_2$	42.55	6.43	39.69	42.26	6.65	39.24
8	$C_{15}H_{19}N_7S$	54.69	5.81	29.76	54.64	5.73	29.45
9	$C_{21}H_{24}N_8$	64.93	6.23	28.84	65.00	6.28	28.78

[a] Karl Fischer analysis: Calcd. H_2O 1.18, Found H_2O 0.91.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 467 spectrophotometer or on a Nicolet 20SX FTIR. Uv spectra were obtained using a Cary 15. ^{1}H-Nmr spectra were determined in the indicated solvent on a Perkin-Elmer R24B, a Varian HA-100, or a JEOL-FX270. ^{13}C-Nmr spectra were determined on a JEOL FX60 and partial off-resonance decoupling was performed to aid in the signal assignments. Mass spectra were recorded on a JEOLCO JMS-1-OCS for electron impact (EI) or on a NERMAG R 10-1C for chemical ionization (CI). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN and carbon, hydrogen, and nitrogen analyses were within $\pm$0.4% of the theoretical values.

Methyl *N'*-Cyano-*N*-[1,2-dihydro-1,2-dimethyl-5-methylthio-3*H*-1,2,4-triazol-3-ylidene]carbamimidothioate (5). To a suspension of 1,2 dimethylhydrazine dihydrochloride (27.3 g, 0.2 mol) in acetonitrile (200 ml) at 0°C is added dropwise a solution of triethylamine (61 ml, 0.44 mol) in acetonitrile (150 ml). A solution of dimethyl cyanocarbamimidodithioate (1) (60 g, 0.41 mol) in acetonitrile (150 ml) is then added dropwise. The reaction mixture is refluxed for 30 h. Upon cooling and concentration under vacuum a solid is obtained. The residue is recrystallized twice from methanol/acetonitrile (1:1) (500 ml) to give **5** as light yellow crystals; yield: 22.4 g (44%); mp 213-216°C. Ms (EI) m/z 256 (M^+), 209; ir (KBr) v 2160, 1560 cm^{-1}; uv (EtOH) λmax (nm) (ϵ) 249 (15,900), 300 (23,600); ^{1}H-nmr (DMSOd_6/TMS) δ 2.40 (s, 3H), 2.76 (s, 3H), 3.72 (s, 3H), 3.77 (s, 3H); ^{13}C-nmr (DMSO-d_6/TMS) δ 13.97 (q), 14.88 (q), 30.67 (q), 32.68 (q), 116.63 (s), 155.94 (s), 157.30 (s), 174.65 (s). Anal. Calcd for $C_8H_{12}N_6S_2$: C, 37.48; H, 4.72; N, 32.78. Found: C, 37.86; H, 4.74; N 33.06.

***N''*-Cyano-*N'*-cyclohexyl-*N*-[5-cyclohexylamino-1,2-dihydro-1, 2-dimethyl-3*H*-1,2,4-triazol-3-ylidene] guanidine (6c); Typical Procedure.** To a 500 ml round bottom flask, equipped with a reflux condenser, stirrer, and drying tube are added **5** (10.0 g, 39.1 mmol), cyclohexylamine (30.94 g, 312 mmol), and acetonitrile (150 ml). The reaction mixture is refluxed for 56 h and, upon cooling, crystallization occurs and the product is collected. Recrystallization from ether (200 ml) affords **6c** as a white powder; yield: 8.6 g (61%) (Table 1 and 2).

[[1,2-Dihydro-1,2-dimethyl-5-(2-propenylamino)-3*H*-1,2,4-triazol-3-ylidene] amino] (2-propenylamino)-methyleneurea (7b). **6b** (23 g, 84 mmol) and 1 N HCl (250 ml, 250 mmol) are combined and heated at 50°C for 16 h. Upon cooling and concentration to dryness, a colorless glass is obtained. Water (500 ml) is added and the mixture is extracted with three (300 ml) portions of CH_2Cl_2. The organic extracts are combined, dried over $MgSO_4$, and concentrated to dryness yielding 23 g of crude product as a light yellow foam. Recrystallization from ethyl acetate/hexanes (1:1) (1 l) gives **7b** as a white powder; yield: 20.0 g (81%); mp 126-128°C. Ms (EI) m/z 292 (M^+); ^{1}H-nmr ($CDCl_3$/TMS) δ 3.06 (s, 3H), 3.24 (s, 3H), 3.85 (bt, J = 6 Hz, 2H) 4.03 (bt, J = 6 Hz, 2H), 5.0-5.3 (m, 4H), 5.5-6.2 (m, 6H); ^{13}C-nmr ($CDCl_3$/TMS) δ 30.73 (q), 34.31 (q), 42.49 (t), 42.82 (t), 114.8 (t), 115.5 (t), 134.8 (d), 135.3 (d), 157.5 (s), 166.3 (s), 167.0 (s), 167.4 (s). Anal. Calcd for $C_{12}H_{20}N_8O$: C, 49.30; H, 6.70; N, 38.33. Found: C, 49.31; H, 7.05; N, 38.28.

[[1,2-Dihydro-1,2-dimethyl-5-[phenylmethylamino]-3*H*-1,2,4- triazol-3-ylidene]amino] [(phenylmethyl)-amino]methylene]urea (7d). Hydrolysis of **6d** (25 g, 67 mmol) in 1N HCl (200 ml) as described above for **7b** gives **7d** as a white solid; yield: 16.7 g (64%); mp 67-69°C. ^{1}H-Nmr ($CDCl_3$/TMS) δ 2.98 (s, 3H), 3.11 (s, 3H), 4.38 (m, 4H), 5.4-5.9 (bm, 4H), 7.18 (s, 10H); ^{13}C-nmr ($CDCl_3$/TMS) δ 30.86 (q), 34.44 (q), 44.05 (t), 44.38 (t), 126.8 (d), 127.0 (d), 127.2 (d), 128.3 (d), 138.9 (s), 139.4 (s), 157.8 (s), 166.4 (s), 167.0 (s), 167.4 (s). Anal. Calcd for $C_{20}H_{24}N_8O$: C, 61.21; H, 6.16; N, 28.55. Found: C, 60.82; H, 6.26; N, 28.37.

***N*''-Cyano-*N*-[1,2-dihydro-1,2-dimethyl-5-[(methyl)(phenylmethyl)amino]-3*H*-1,2,4-triazol-3-ylidene]-*N*'-phenylmethylguanidine (9).** A sodium hydride dispersion (50%) (280 mg, 5.9 mmol) is prewashed under N_2 with pentane and then is suspended in DMF (2 ml). The triazole **6d** (2.0 g, 5.3 mmol) in DMF (20 ml) is added dropwise at room temperature and the mixture is stirred for 30 min. Iodomethane (0.37 ml, 5.9 mmol) in DMF (5 ml) is added and the reaction is stirred for 1 h at room temperature. Ethyl acetate (250 ml) is added and the mixture is washed with four (200 ml) portions of saturated brine solution. The resulting organic portion is dried over $MgSO_4$, filtered, and concentrated to give a solid. Recrystallization from $CH_3CN/(C_2H_5)_2O$ (1:1) (100 ml) affords **9** as white crystals; yield: 1.4 g (68%); mp 157-160°C. The mixture melting point of this material and the material prepared according to Table 1 is undepressed (mp 157-159°C). Ms (EI) m/z 388 (M^+), 231 (M^+ - 157); ms (CI) mz 389 (MH^+), 232 (MH^+-157); ir (KBr) v 3310, 2160, 1638 cm^{-1}; uv (EtOH) λmax (nm) (ε) 243 (29,900), 283 (28,400); ^{1}H-nmr ($CDCl_3$/TMS) δ 3.00 (s, 3H), 3.35, 3.40 (2s, 6H), 4.41 (d, J = 5 Hz, 2H), 4.53 (s, 2H), 7.0-7.4 (m, 10H), 8.18 (bt, J = 5 Hz, 1H).

X-Ray Crystal Structure Analysis of 9. Suitable crystals were obtained by crystallization from acetonitrile-ether. $C_{21}H_{24}N_8$, mol. wt. = 388.47, D_{cal} = 1.256 g/cm^3, space group P1bar (#2), Z = 2, a = 9.470(2) Å, b = 10.521(2) Å, c = 11.367(1) Å: α = 81.16(1)°, β = 66.88(1)°, γ = 89.85(1)°, Vol. = 1027.2(3) Å, μ(Mo) = 0.75 cm^{-1}, no absorption correction applied. A total of 4507 reflections were collected, of which 3151 were observed [$I > 3\sigma$ (I)], in an ω-scan mode on a Nicolet R3m diffractometer using graphite monochromated Mo-K_α (0.71069 Å) radiation. The structure was solved by direct phase determination methods and refined by 'cascading blocked diagonal least square' algorithm [SHELXTL (5.1) by G.M. Sheldrick] to a final R = 4.70%.

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