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A Rich Array of Reactions of Cyanomonothiocarbonylmalonamides RNHCSCH(CN)CONHR′ and Their Thioenols RNHC(SH)═C(CN)CONHR′[1]

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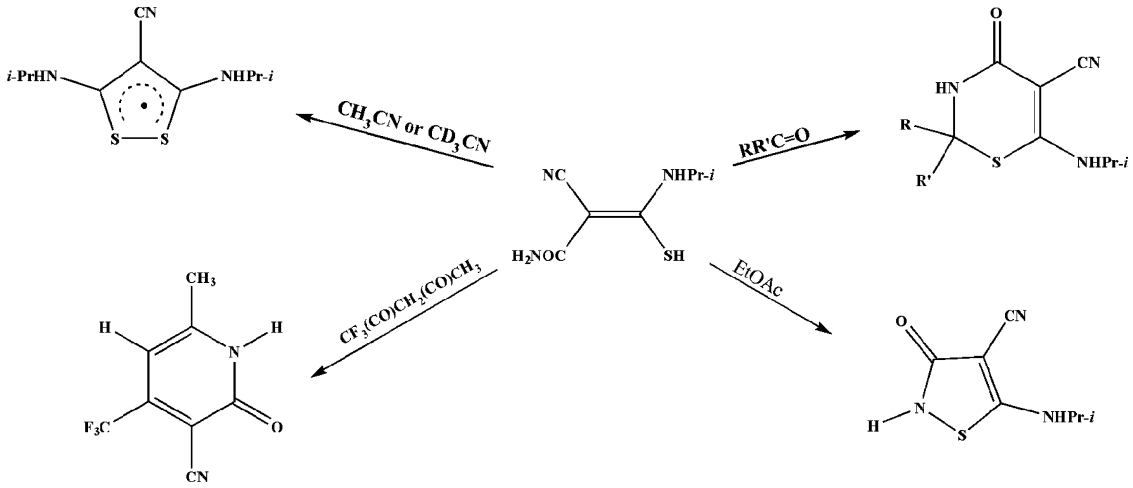

The thioenols derived from cyanomonothiocarbonylmalonamides and a cyanodithiocarbonylmalonamide were found to be very reactive species. They react under a variety of conditions such as crystallization, reaction with several carbonyl compounds, and reactions with another thioenol molecule to give a variety of products, mostly heterocycles, including substituted 2,3-dihydroisothiazole-3-ones and 3-thione, 2-substituted methylenethiazoles, 3,4-dihydro-1,3-thiazine-4-ones and 4-thiones, divinyl sulfides, a 1,2-dithiolane radical, and a 3,7-diaza[3.3.0]bicyclooctane derivative. Mechanisms suggested for these reactions include radical mechanisms, nucleophilic substitutions, and condensations.

Introduction

In recent years, we prepared many enols of carboxylic acid amides Y′YC═C(OH)NRR′ (Y, Y′ = electron-withdrawing groups, EWGs) **1** and/or their tautomeric amides Y′YCH-CONRR′ **2** and studied their properties, including the equilibrium constants K_{Enol} between the two tautomers.[1,2] Initial studies on their functionalization included reactions with diazomethane,[3] an intramolecular cyclization of derivatives prepared analogously to the formation of **1** and **2**,[4] and their oxa-ene reactions with 4-phenyl-1,2,4-triazoline-3,5-dione.[5] Fewer thio analogues of these species are known,[6,7] and an extensive series of "formal"[8] cyanomonothiocarbonylmalonamides **4** were isolated.[7] X-ray

(1) Preliminary report: Basheer, A.; Rappoport, Z. Kyushu International Symposium on Physical Organic Chemistry (KISPOC XI), Fukuoka September 12−15, 2005, Abstract O01.

(2) (a) Mukhopadhyaya, J. K.; Sklenak, S.; Rappoport, Z. *J. Am. Chem. Soc.* **2000**, *122*, 1325. (b) Mukhopadhyaya, J. K.; Sklenak, S.; Rappoport, Z. *J. Org. Chem.* **2000**, *65*, 6856. (c) Lei, Y. X.; Cerioni, G.; Rappoport, Z. *J. Org. Chem.* **2000**, *65*, 4028. (d) Lei, Y. X.; Cerioni, G.; Rappoport, Z. *J. Org. Chem.* **2001**, *66*, 8379. (e) Lei, Y. X.; Casarini, D.; Cerioni, G.; Rappoport, Z. *J. Phys. Org. Chem.* **2003**, *16*, 525. (f) Lei, Y. X.; Casarini, D.; Cerioni, G.; Rappoport, Z. *J. Org. Chem.* **2003**, *68*, 947. (g) Basheer, A.; Rappoport, Z. *J. Org. Chem.* **2004**, *69*, 1151. (h) Basheer, A.; Yamataka, H.; Ammal, S. C.; Rappoport, Z. *J. Org. Chem.* **2007**, *72*, 5297. (i) Song, J.; Yamataka, H.; Rappoport, Z. *J. Org. Chem.* **2007**, *72*, 7605.

(3) Lei, Y. X.; Rappoport, Z. *J. Org. Chem.* **2002**, *67*, 6971.

(4) Basheer, A.; Rappoport, Z. *J. Org. Chem.* **2006**, *71*, 9743.

(5) Basheer, A.; Rappoport, Z. *J. Org. Chem.* **2008**, *73*, 184.

(6) For examples of thioenols which were observed or investigated in solution, see: Sklenak, S.; Apeloig, Y.; Rappoport, Z. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2269, and ref 7.

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CHART 1

$$R^3NHCSC(CN)=C(OH)NR^1R^2 \underset{}{\overset{K_{Enol}}{\rightleftharpoons}} R^3NHCSCH(CN)CONR^1R^2 \overset{K_{Thioenol}}{\rightleftharpoons} R^3NHC(SH)=C(CN)CONR^1R^2 \quad (1)$$

Enol **3** Amide **4** Thioenol **5**

a: $R^1 = R^2 = Me$, $R^3 = Me$
b: $R^1 = R^2 = Me$, $R^3 = i$-Pr
c: $R^1 = H$, $R^2 = Me$, $R^3 = Ph$
d: $R^1 = H$, $R^2 = Me$, $R^3 = p$-An
e: $R^1 = H$, $R^2 = Me$, $R^3 = 1$-Np
f: $R^1 = H$, $R^2 = Me$, $R^3 = Me$
g: $R^1 = R^2 = H$, $R^3 = Ph$
h: $R^1 = R^2 = H$, $R^3 = p$-An
i: $R^1 = R^2 = H$, $R^3 = 1$-Np
j: $R^1 = R^2 = H$, $R^3 = i$-Pr
k: $R^1 = R^2 = H$, $R^3 = t$-Bu
l: $R^1 = H$, $R^2 = CH_2Ph$, $R^3 = i$-Pr
m: $R^1 = H$, $R^2 = Ph$, $R^3 = t$-Bu
n: $R^1 = H$, $R^2 = Ph$, $R^3 = Ph$
o: $R^1 = H$, $R^2 = Ph$, $R^3 = i$-Pr
p: $R^1 = H$, $R^2 = Ph$, $R^3 = Et$

$$PhNHCSC(CN)=C(SH)NH_2 \underset{}{\overset{K_{Thioenol}}{\rightleftharpoons}} PhNHCSCH(CN)CSNH_2 \overset{K_{Thioenol}}{\rightleftharpoons} PhNHC(SH)=C(CN)CSNH_2 \quad (2)$$

6 **7** **8**

structures of some of them in the solid state were determined, and their simultaneous equilibria (K_{Enol} and $K_{Thioenol}$) with the tautomeric enols **3** or the thioenols **5** were determined in solution.[7]

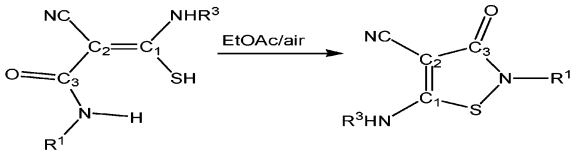
Species **3**/**4**/**5** carry several functional groups such as the nucleophilic NHR, OH, or SH groups, the electrophilic C═C bond, and Y/Y′, all of which are capable of undergoing a variety of reactions. Coupled with the easy oxidation of the SH group, they can potentially participate in a wide array of reactions, making these species useful synthones.

In the present work, we investigated several reactions of the **3**/**4**/**5** systems, mostly reactions leading to heterocyclic systems.[9] We found that a small structural variation can change the nature of the products. Several reactions of the dithio analogues were also studied.

Results and Discussion

Sixteen formal systems **3a-p**/**4a-p**/**5a-p** whose equilibrium constants in solution (Chart 1, eq 1) were determined earlier[7] were investigated, and the structures of the various types of products were determined. These are given below, and a representative X-ray structure for each type of product is given either in the text or in the Supporting Information. Few reaction mechanisms are suggested. The reactions are divided into those involving one or two molecules of **3**/**4**/**5**. When available, reactions of the formal cyanodithiocarbonylmalonamide analogues **6**/**7**/**8** (Chart 1, eq 2) are given together with the analogous reactions of **3**/**4**/**5**.

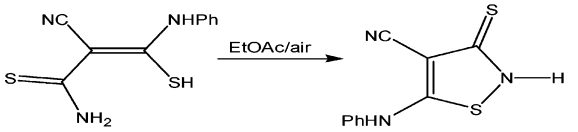
a. Reactions Involving One Molecule of 3/4/5. 1. Formation of 2,3-Dihydroisothiazole-3-one and 2,3-Dihydroisothiazole-3-thione Derivatives. When formal compounds **4a**−**d**,**f**,**l** where $R^2 = Me$, were crystallized from EtOAc at rt, only one of the corresponding precursors **3**/**4**/**5** was isolated.[7] However, when their analogues **5e** ($R^1 = Me$, $R^3 = 1$-Np) and **5g**−**k** ($R^1 = H$, $R^3 = Ph$, *p*-An, 1-Np, *i*-Pr, *t*-Bu) were crystallized from EtOAc in air, the five-membered substituted 4-cyano-2,3-dihydroisothiazole-3-ones **9a**−**f** were formed (eq 3). These are formal cyclic oxidation products, where a dihydrogen was lost between the *cis*-SH and NHR groups of the thioenols **5**. The apparent oxidant is air oxygen since, when **3e**/**4e**/**5e** was crystallized from EtOAc under nitrogen, the open-chain enol **3f** ($R^1 = Me$, $R^2 = H$, $R^3 = 1$-Np), whose X-ray structure and NMR data are known,[7] was isolated. When formal **4j** was kept for more than 40 h in AcOEt, only signals for the **3j**/**4j**/**5j** mixture were observed, and reaction of formal **4i** under nitrogen showed signals of **3i**/**4i**, whereas the cyclic **9c**, **9d**, and **9f** were obtained under air. A similar reaction of the formal cyanodithiocarbonylmalonamide **6** under air gave the analogous 5-anilido-4-cyano-2,3-dihydroisothiazole-3-thione **10** (eq 4).



(3)

5e: $R^1 = Me$, $R^3 = 1$-Np
5g: $R^1 = H$, $R^3 = Ph$
5h: $R^1 = H$, $R^3 = p$-An
5i: $R^1 = H$, $R^3 = 1$-Np
5j: $R^1 = H$, $R^3 = i$-Pr
5k: $R^1 = H$, $R^3 = t$-Bu

9a: $R^1 = H$, $R^3 = Ph$
9b: $R^1 = H$, $R^3 = p$-An
9c: $R^1 = H$, $R^3 = 1$-Np
9d: $R^1 = H$, $R^3 = i$-Pr
9e: $R^1 = H$, $R^3 = t$-Bu
9f: $R^1 = Me$, $R^3 = 1$-Np



(4)

8 **10**

The structures of the two solid derivatives **9d** and **9f** were determined by X-ray crystallography. Both ORTEP drawings together with the full crystallographic data are given in the Supporting Information. The C(1)−C(2), C(2)−C(3), C(3)−O, and C(1)−S bond lengths of **9d** are 1.384(2), 1.437(3), 1.233(3), and 1.7356(18) Å and of **9f** are 1.386(3), 1.450(3), 1.237(2), and 1.7315(18) Å, respectively. The C(1)−C(2) bond lengths are typical for those in push−pull ethylenes, as found in Y,Y′-activated enols [2a,b,d−i] and thioenols.[7] In **9d**, where $R^1 = H$, each molecule is intermolecularly hydrogen bonded by N−H···O and N−H···N moieties to two other molecules, where the N···O and the N···N nonbonding distances are 2.722(2) and 3.014(2) Å, respectively. In **9f**, only two molecules are hydrogen bonded by an N−H···O moiety where the N···O nonbonding distance is 2.913(2) Å.

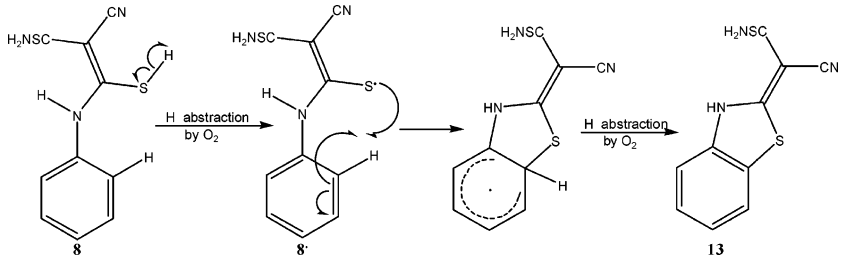
The compositions and structures of the six compounds were consistent with the elemental analysis (Table S3 in the Supporting Information) and with the NMR spectra in solution

(7) Basheer, A.; Rappoport, Z. Submitted for publication.

(8) "Formal" is used since in solution the three species **3**, **4**, and **5** are simultaneously present for most systems and the solid-state structure is not necessarily that in solution. When it seems reasonable that one of the species participates in a reaction, its structure is given.

(9) Formation of a plethora of products, mostly heterocycles, from thioamides including cyanothioacetamides was reviewed (Jagodzinski, T. S. *Chem. Rev.* **2003**, *103*, 197; Litvinov, V. P. *Russ. Chem. Rev.* **1999**, *68*, 737). None of the precursors is written as the thioenol, and only 2-*N*-substituted thioamido-1,3-indanedione may have the thioenol structure.

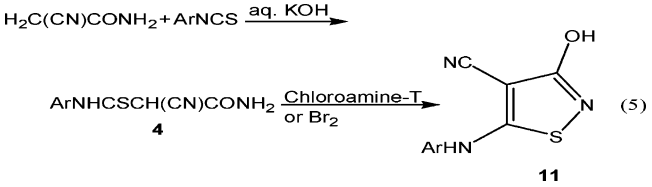
SCHEME 1. Suggested Mechanism for the Formation of 13



(Tables S1 and S2 in the Supporting Information). The ^{1}H NMR spectra show two NH signals for **9a**−**e** (e.g., δ(NH) = 7.95 and δ(NHR^3) = 10.19 for **9a**) and **10** (two overlapping signals at 9.83 ppm). Only one NH signal was observed for **9f**, and the Me signal appears as a singlet compared with the NHMe doublet in the precursor **5e**.[7] The ^{13}C NMR spectra show two low field signals at 164.88−165.18 and 165.53−167.74 ppm ascribed to C$_\alpha$ (=C(NHR^3)S) and the C=O groups.

We suggest that the thioenols **5**, which are present in the **3**/**4**/**5** equilibria in solution,[7] are oxidized by air to give **9** and water. Although **9** can tautomerize to the heterocyclic isothiazole-3-ol, this is not supported by our data.

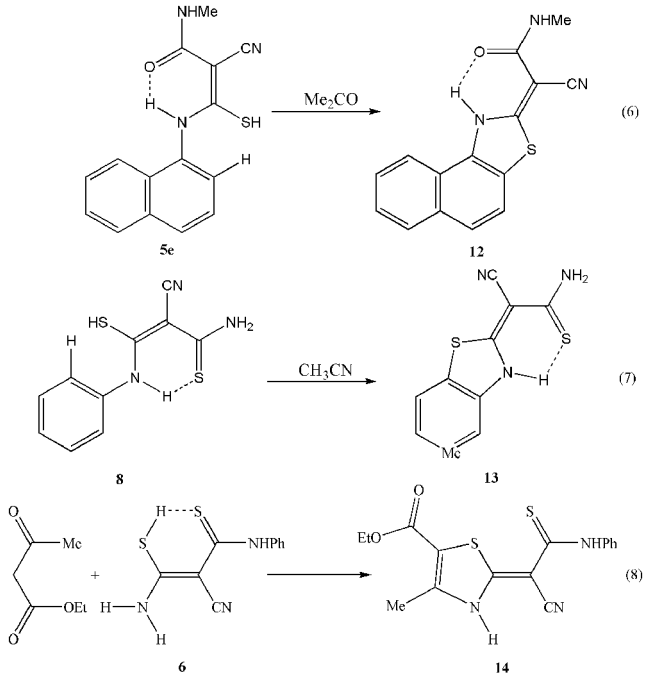
Similar 2,3-dihydroisothiazole-3-ones, including **9a**−**d**, were recently reported, and their biological activity was investigated.[10] However, although their synthesis formally resembles eq 3, it differs from it in important details.[10a] Its first step is the reaction of cyanoacetamide with ArNCS in the presence of aqueous KOH to give the amide **4**, R^1 = H, which cyclizes in the presence of an added oxidant such as chloramine-T or Br$_2$ to a product written as the tautomer of **9**-the substituted isothiazole-3-ol **11** (eq 5). No supporting X-ray data for structure **11** are given.



The 2,3-dihydroisothiazole-3-thione **10** displays in the ^{1}H NMR spectrum Ph−H signals and two additional 1H singlets at 8.57 (br) and 12.9 ppm in DMSO-d_6 ascribed to the two NH hydrogens. In the ^{13}C NMR spectrum, each of the 10 carbons appears separately. The highest field carbon is at 76.10 ppm and the lowest field at 169.5 and 188.6 ppm, ascribed to C$_\alpha$ (=C(NHR^3)S) and the C=S groups.

2. Formation of 2-Substituted Methylene Thiazoles. Crystallization of **5e** from acetone in air and of the dithio derivative **6**/**7**/**8** from acetonitrile yields the 2-substituted methylenenaphtho-2,3-dihydrothiazole and benzo-2,3-dihydrothiazole **12** and **13**, respectively (eqs 6 and 7). When **5e** was crystallized from EtOAc under nitrogen, evaporation of the solvent after >30 h gave no **12**, and only the signals of the starting material were observed. Crystallization of **7** from ethyl acetoacetate gave the aliphatic 2,3-dihydrothiazole **14** (eq 8).

The solid-state structures of **12**, **13**, and **14** were determined by X-ray diffraction. The ORTEP drawing and the complete data are given in the Supporting Information. On the basis of the solid-state structures, especially the double bond lengths of 1.381(3) Å for **12**, 1.402(2) Å for **13**, and 1.414(7) Å for **14**, it seems that all derivatives had retained the push−pull moieties of their precursors. Each derivative is intermolecularly hydrogen bonded to a second molecule by an N−H···O hydrogen bond for **12** and an N−H···N bond for **13** and **14**.

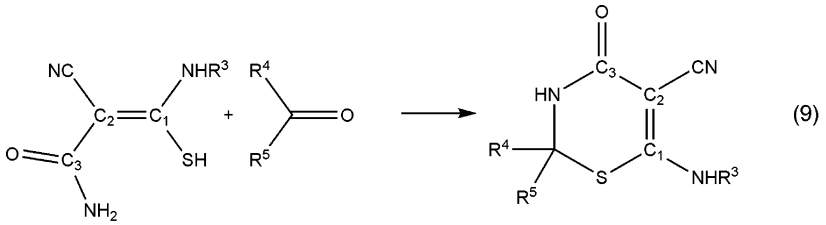


The ^{1}H NMR spectra of **12** display two NH signals at 13.92 and 5.80 ppm in CDCl$_3$ (12.87 and 7.32 ppm in DMSO-d_6), ascribed to the hydrogen-bonded N−H···O moiety and the non-hydrogen-bonded NHMe, respectively. Three NH signals were observed for **13**. The lowest field one at 12.97 ppm was ascribed to the intramolecular hydrogen-bonded N−H···S moiety, and the other signals at 7.90 and 8.57 ppm belong to the NH$_2$ group. In **14**, which has an *E*-configuration, an intramolecular hydrogen bond is absent according to the solid-state structure. The ^{13}C spectrum of **12** displays two low field signals at 166.03 and 166.78 ppm which are ascribed to the C$_\alpha$ and C=O groups. For **13**, the low field signals appear at 169.05 and 188.66 ppm and are ascribed, as in **10**, to the C$_\alpha$ and C=S groups, respectively. These signals of **12** and **13** resemble those of the precursors **5e** and **8**.

A reasonable suggested mechanism for formation of **12** and **13** involves an intramolecular aromatic radical substitution. The

(10) (a) Zhang, W.; Ricketts, W.; An, H.; Hong, Z. U.S. Patent 2004/0039037, February 26, 2004. (b) Varaprasad, C. V. N. S.; Barawkar, D.; El Abdellaoui, H.; Chakravarty, S.; Allan, M.; Chen, H.; Zhang, W.; Wu, J. Z.; Tam, R.; Hamatake, R.; Lang, S.; Hong, Z. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3975.

CHART 2

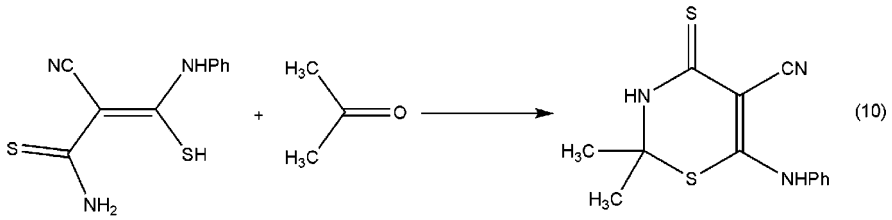


(9)

5g: R^1= R^2= H, R^3= Ph
5h: R^1= R^2= H, R^3= *p*-An
5i: R^1= R^2= H, R^3= 1-Np
5j: R^1= R^2= H, R^3= *i*-Pr
5k: R^1= R^2= H, R^3= *t*-Bu

15a: R^4= R^5= Me
15b: R^4= R^5= CD_3
15c: R^4R^5= -$(CH_2)_5$-
15d: R^4= Me, R^5= Et
15e: R^4= Me, R^5= CH_2Ph
15f: R^4= Me, R^5= CH_2CO_2Et
15g: R^4= Me, R^5= CH_2COMe
15h: R^4= H, R^5= *p*-An

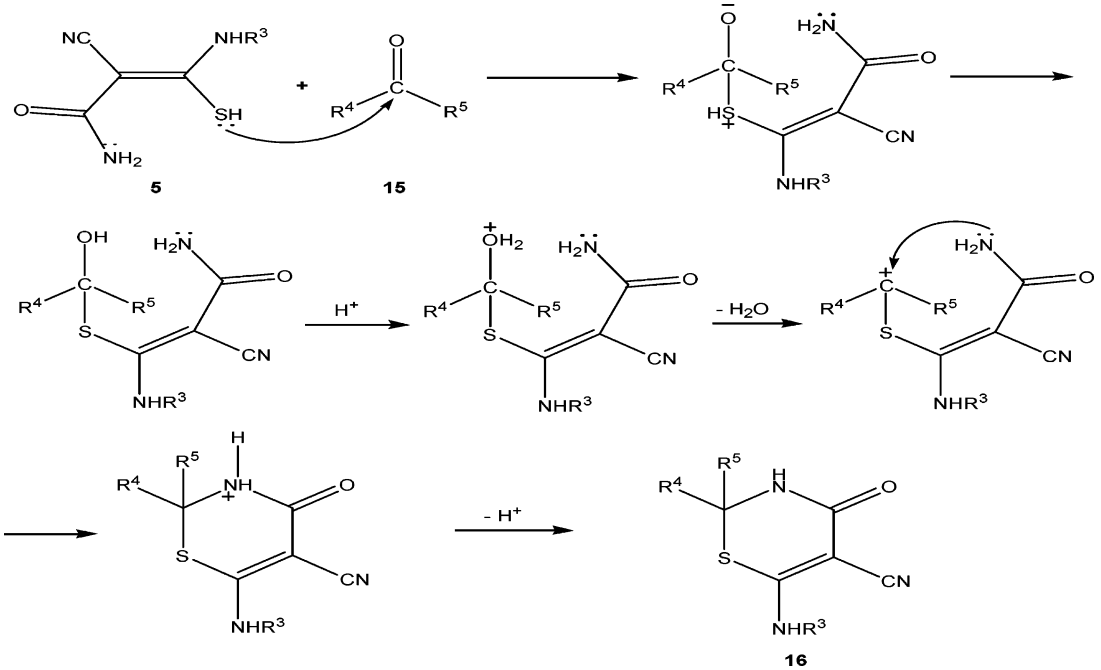
16a: R^4= R^5= Me, R^3= Ph
16b: R^4= R^5= Me, R^3= *p*-An
16c: R^4= R^5= Me, R^3= 1-Np
16d: R^4= R^5= Me, R^3= *i*-Pr
16e: R^4= R^5= Me, R^3= *t*-Bu
16f: R^4= R^5= CD_3, R^3= Ph
16g: R^4= R^5= CD_3, R^3= *p*-An
16h: R^4= R^5= CD_3, R^3= *i*-Pr
16i: R^4R^5= -$(CH_2)_5$-, R^3= Ph
16j: R^4R^5= -$(CH_2)_5$-, R^3= *i*-Pr
16k: R^4= Me, R^5= Et, R^3= *i*-Pr
16l: R^4= Me, R^5= Et, R^3= *p*-An
16m: R^4= Me, R^5= CH_2Ph, R^3= *i*-Pr
16n: R^4= Me, R^5= CH_2CO_2Et, R^3= *i*-Pr
16o: R^4= Me, R^5= CH_2COMe, R^3= *i*-Pr
16p: R^4= H, R^5= *p*-An, R^3= *i*-Pr



(10)

8 **15a** **17**

SCHEME 2. Suggested Mechanism for a Formation of 20



5 **15** **16**

sulfur-centered thiyl radicals (**5e**• and **8**•), formed by hydrogen abstraction by air oxygen from **5e** and **8**, respectively, attack an adjacent aromatic carbon to form the thiazoles after abstraction of hydrogen radical by oxygen from the intermediate radical (Scheme 1).

It is suggested that the formation of **14** also begins by abstraction of the S−H hydrogen of **6** by oxygen, followed by attack of the thiyl radical on the vinylic C_β of the enol tautomer of ethyl acetoacetate **15** to form a C−S bond. This is followed by abstraction of the OH hydrogen by oxygen. An intramo-

lecular nucleophilic attack of the NH_2 on the adjacent formed carbonyl, followed by intramolecular proton transfer and elimination of water gives **14**.

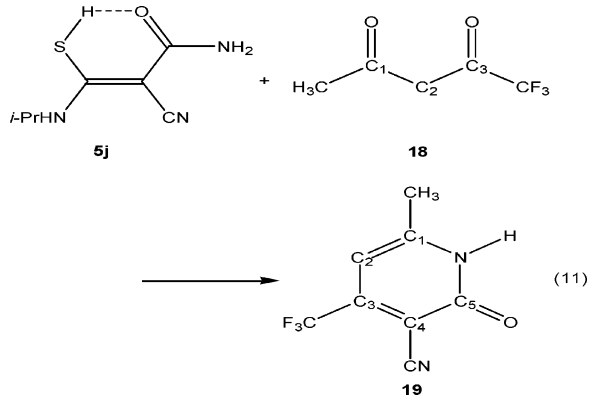
3. Formation of 3,4-Dihydro-1,3-thiazine-4-one and 3,4-Dihydro-1,3-thiazine-4-thione. When thioenols **5g**−**k**, having an unsubstituted amido nitrogen and monosubstituted thioamido nitrogen (R^3 = Ph, *p*-An, 1-Np, *i*-Pr, *t*-Bu), were crystallized from a ketonic solvent **15a**−**g** (e.g., acetone, methyl ethyl ketone) or from anisaldehyde **15h**, the six-membered 2,2-dialkyl-6-alkylamino- (or arylamino)-5-cyano-3,4-dihydro-1,3-thiazine-4(1*H*)-one **16a**−**o** or the 2-anisyl derivative **16p** were obtained in high yields by a condensation reaction with a loss of water (Chart 2, eq 9). The structures of three products **16d**, **16k**, and **16p**, derived from acetone, ethyl methyl ketone, and anisaldehyde, respectively, were determined by X-ray crystallography. The ORTEPs and the full crystallographic data for the three compounds are given in the Supporting Information. A similar reaction, giving products **16** with different R^3−R^5 substituents in the presence of a catalytic amount of *p*-toluenesulfonic acid, was reported by Vovk and co-workers[11] at about the same time of our preliminary report.[1] None of the products **16b**−**p** are identical with those reported by Vovk. An analogous reaction took place with the dithio precursor analogue **8** to give the unknown substituted 3,4-dihydrothiazine-4-thione **17** (Chart 2, eq 10).

The X-ray diffraction data of **16d**, **16k**, and **16p** show the dihydrothiazine-4-one structure. The ORTEP and the crystallographic data are given in the Supporting Information. The C(1)−C(2), C(2)−C(3), C(3)−O, and C(1)−S bond lengths are 1.3940(19), 1.4554(18), 1.2395(17), and 1.7452(14) Å for **16d**, 1.388(4), 1.453(4), 1.234(4), and 1.743(3) Å for **16k**, and 1.394(6), 1.459(6), 1.229(5), and 1.723(6) Å [1.758(4) Å] for **16p**, respectively. The C(1)−C(2) bond lengths are typical for push−pull enol systems activated by EWGs,[2a,b,d−i,7] similar to the enol/thioenol systems. Each molecule in the three structures is intermolecularly hydrogen bonded to two other molecules: to the first molecule by an N−H···O moiety where the N−H bond length is 0.78(5)−1.02(6) Å, and the O···H and the N···O nonbonding distances are 1.84(6)−2.08(5) and 2.828(6)−2.8995(16) Å. The second molecule is hydrogen bonded by an N−H···N moiety where the N−H bond length is 0.65(5)−1.03(4) Å, and the N···H and N···O nonbonding distances are 2.03(6)−2.50(6) and 2.858(5)−3.091(7) Å.

The structures are consistent with the elemental analysis, the ^1H and ^{13}C spectra in solution, and the known structure of compound **16a**. Two NH signals were observed for all derivatives **16a**−**p** and **17**, one for the cyclic NH at higher field and another at a lower field for the NHR^3 group when R^3 = Ar in DMSO-d_6 (e.g., δ = 8.11 and 10.34 for **16c**) and very close shifts when R^3 = *i*-Pr (e.g., δ = 7.94 and 7.97 for **16d**). Additional data are given in Table S1 in the Supporting Information. The spectra of **16** and **17** also display the signals for R^4 and R^5 derived from the carbonyl compound **15**. A new signal observed in the spectra (also in **17**) at ca. 62 ppm is ascribed to the sp^3 carbon α to the sulfur. The amido carbonyl of **5**, the thioamido carbonyl of **8**, and their C_α signals were retained in **16** and **17** and appear at 164.55−165.19 and 165.53−168.65 ppm for **16a**−**p** and at 186.95 and 161.80 ppm for **17**.

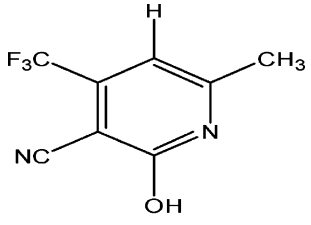
The suggested mechanism (Scheme 2) involves a nucleophilic attack of the thioenol SH group or of its conjugate base on the carbonyl group of the ketone or aldehyde. Proton transfer to the alkoxide moiety is followed by protonation and water loss and then by cyclization of the NH_2 on the positive center. A related route starting with NH_2 attack on the carbonyl is also possible. The formation of **17** takes place analogously. The possibility that the reaction of **8** gives a dithioketal isomer of **17** is excluded by the observed ^{13}C NMR C=S signal of **17** at a low field.

4. Formation of 3-Cyano-6-methyl-4-trifluoromethyl-2-pyridone (19). The reaction of **5j** with trifluoroacetylacetone **18** yields the 2-pyridone derivative **19** (eq 11).



This is the only product in this work that does not contain sulfur. The structure of solid **19** was determined by X-ray crystallography. The ORTEP (see numbering of atoms in **19**) and the crystallographic data are given in the Supporting Information, and the structure is supported by the C1−C2, C2−C3, C3−C4, C4−C5, C1−N, C5−N, and C5−O bond lengths of 1.366(3), 1.394(3), 1.382(3), 1.443(3), 1.351(3), 1.375(2) and 1.235(2) Å, respectively.

2-Pyridone is the favorable tautomer in the solid[12a] and mostly in solution.[12b,13] However, preference of 2-hydroxypyridine derivatives *in solution* is also known.[13] The low field signal at 13.36 ppm in DMSO-d_6 can be ascribed to either the NH of **19** or to the OH of the hydroxypyridine **20**, whereas the signal at 6.65 ppm was ascribed to the vinylic hydrogen present in both **19** and **20**.



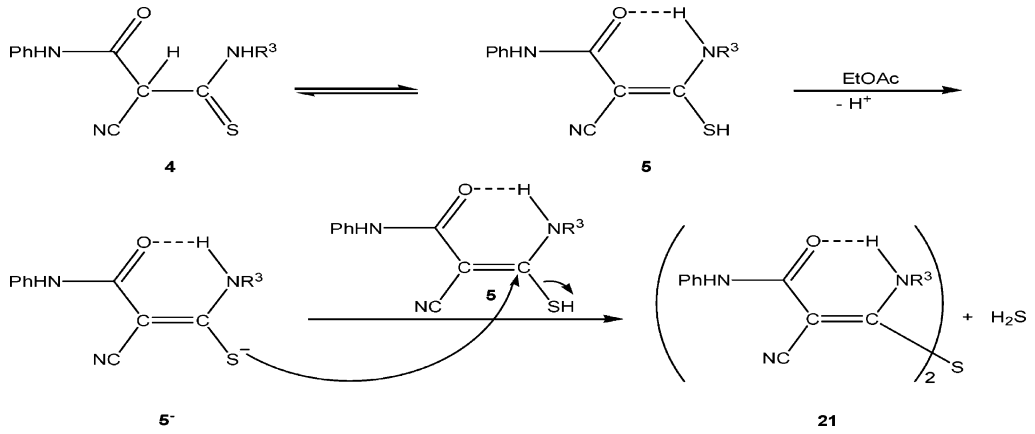
20

(11) (a) Vovk, M.; Sukach, V. A.; Chernega, A. N.; Pyrozhenko, V. V.; Bol'but, A. V.; Pinchuk, A. M. *Heteroat. Chem.* **2005**, *16*, 426. (b) For an earlier work, see: Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1610.

(12) (a) Almof, J.; Kvick, A.; Olovsson, I. *Acta Crystallogr.* **1971**, *B27*,-1201. (b) Wheeler, G. L.; Ammon, H. L. *Acta Crystallogr.* **1974**, *B30*, 680. (c) Beak, P.; Fry, F. S., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 1700.

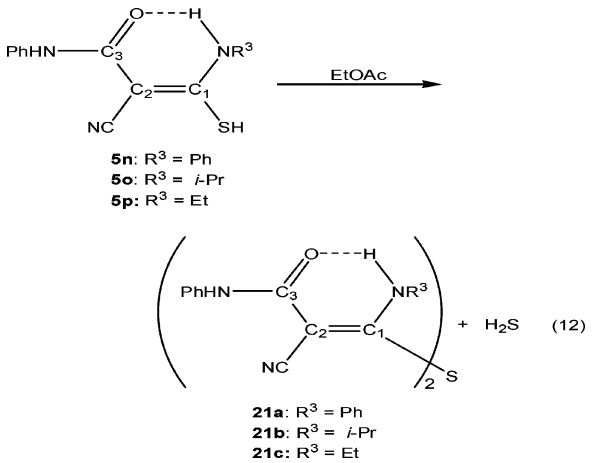
(13) For discussion on the pyridine-2-one/2-hydroxypyridine tautomerism in solution and the gas phase, see: (a) Beak, P. *Acc. Chem. Res.* **1977**, *10*, 186. (b) Katritzky, A. R.; Karelson, M.; Malhorta, N. *Heterocycles* **1991**, *32*, 127. (c) Katritzky, A. R.; Karelson, M.; Harris, P. A. *Heterocycles* **1991**, *32*, 329. (d) *March's Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, 6th ed.; Smith, M. B., March, J., Eds. Wiley: Hoboken, NJ, 2007; p 103. (e) Forlani, L.; Cristoni, G.; Boga, C.; Todesco, P. E.; Del Vecchio, E.; Selva, S.; Monari, M. *ARKIVOC* **2002**, *XI*, 198.

SCHEME 3. Suggested Mechanism for a Formation of 21



We suggest that the 2-pyridone is formed from the reaction of trifluoroacetylacetone with the anion of 2-cyanoacetamide which was obtained in turn from decomposition of the thioenol **5j**. Loss of an EWG from methane substituted by three EWGs is known. For example, a $CO_2CH_2CF_3$ group is lost on heating $PhNHC(OH)=C(CO_2CH_2CF_3)_2$[2d] or on attempted crystallization at −20 °C of $(MeO)_2P(=O)CH(CO_2CH_2CF_3)CONHAn$-*p*,[2i] and a $CO_2CH(CF_3)_2$ group is lost on attempted crystallization at −20 °C of $(MeO)_2P(=O)CH(CO_2CH(CF_3)_2)-CONHC_6F_5$.[2i] We do not know the mechanism of this process, although attack of a weak base (e.g., **19**) on the *i*-PrNHC=S group can displace the anion of cyanoacetamide. Indeed, condensation of **18** with cyanoacetamide in the presence of NaOEt[14a] or piperidine[14b] gave **19**. The same synthesis, with the product written as **20**, was reported earlier.[14c] Condensation of **18** with malononitrile also gave **19**.[14d]

b. Reactions Involving Two Molecules of 3/4/5. 1. Formation of Divinyl Sulfide Derivatives. When the *N*-phenyl-*N*′-substituted cyanomonothiocarbonylmalonamides **5n**−**p** were crystallized from EtOAc, the corresponding symmetrical sulfides **21a**−**c**, formed by a loss of H_2S between the thioenol groups of two molecules, were isolated (eq 12).



5n: R^3 = Ph
5o: R^3 = *i*-Pr
5p: R^3 = Et

21a: R^3 = Ph
21b: R^3 = *i*-Pr
21c: R^3 = Et

The structure of the sulfide **21b** (R = *i*-Pr) was determined by X-ray diffraction. The ORTEP (see numbering in **21**) and the full crystallographic data are given in the Supporting Information. The solid state **21b** is symmetrical with *E*,*E*-configuration, that is, with *cis*-CN and S moieties. The *cis*-PhNHCO and *i*-PrNH groups are hydrogen bonded to one another as shown in eq 12. The X-ray unit cell contains two independent molecules with C(1)−C(2), C(2)−C(3), and C(3)−O bond lengths of 1.403(3) (1.394(3)), 1.461(4) (1.463(3)), and 1.253(3) Å (1.228(3) Å), respectively. The N···O nonbonding distances are 2.597(3) and 2.606(3) Å.

Attempted crystallization of the *t*-Bu derivative **4m**, which displays the amide **4m** (20%), the enol **3m** (32%), and the thioenol **5m** (48%) in $CDCl_3$ solution,[7] from EtOAc yielded elementary sulfur S_8, indicating the high reactivity and instability of the species.

The two NH signals of **21a**−**c** in the ^{1}H NMR spectra appear at 7.56−8.18 ppm for the CONHPh group and at 10.73−12.07 ppm for the intramolecularly N−H···O hydrogen-bonded CONHR^3 group. The ^{13}C NMR spectra showed the C_α [(NR^3)CS] and C=O signals at 160.2 and 165.27 ppm. The ^{1}H and ^{13}C NMR spectra of **21a**−**c** resemble those of their precursors **5n**−**p**,[7] except for the absence of the SH signal.

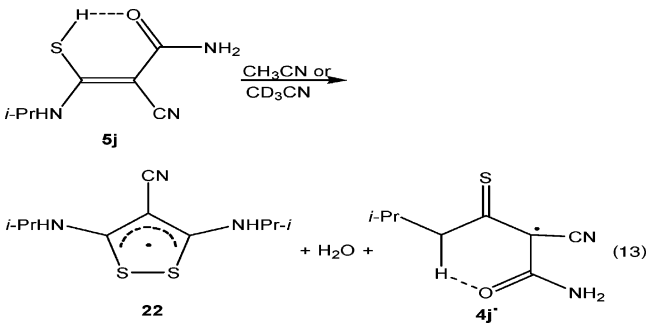
The suggested mechanism for formation of **21** is given in Scheme 3. The CN and CONHPh groups increase the acidity of the SH, and its ionization gives the thiolate anion **5**$^-$. Although **5**$^-$ is less nucleophilic than a simple RS$^-$ due to the EWGs, it is still sufficiently nucleophilic to attack the positive C_α of another molecule of **5** with displacement of an HS$^-$ nucleofuge to give the divinyl sulfide. Such an S_NV replacement of a RS$^-$ nucleofuge by an R′S$^-$ nucleophile in a β-EWG system was investigated kinetically by Bernasconi and co-workers.[15]

2. Formation of a 1,2-Dithiolane Heterocycle. On attempted crystallization of **3j/4j/5j** from acetonitrile or acetonitrile-d_3, an unusual product composed of three molecules is obtained. One is a symmetrical five-membered 3,5-bis(isopropylamino)-[1,2]-dithiolane-4-carbonitrile moiety **22**, the second (**4j**•) is derived from the amide **4j** by loss of hydrogen, and both are hydrogen bonded by a water molecule (Figure 1) whose one hydrogen is hydrogen bonded to the oxygen of the latter and the oxygen is

(14) (a) Portnoy, S. *J. Org. Chem.* **1965**, *30*, 3377. (b) Narsaiah, B.; Sivaprasad, A.; Venkatarnam, R. V. *Org. Prep. Proced. Int.* **1993**, *25*, 116. (c) Greene, J. L.; Montgomery, J. A. *J. Med. Chem.* **1963**, *6*, 294. (d) Maitraie, D. V.; Venkat Reddy, G.; Rama Rao, V. V. V. N. S.; Ravi Kanth, S.; Shanthan Rao, P.; Narsaiah, B. *J. Fluorine Chem.* **2002**, *118*, 73.

(15) (a) Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z. *Can. J. Chem.* **1999**, *77*, 584; *ARKIVOC* **2000**, 161. (b) Bernasconi, C. F.; Ketner, R. J.; Ragains, M. C.; Chen, X. Rappoport, Z. *J. Am. Chem. Soc.* **2001**, *123*, 2155.

hydrogen bonded to one of the NH groups of **22** (eq 13). The X-ray data are of high quality and reliable: all the hydrogens were located and the *R* factor is 0.03.



Compound **22** is completely symmetric: the C(11)−C(12) and C(12)−C(13) bonds have bond lengths of 1.403(2) Å, the C(11)−S(2) and C(13)−S(3) bond lengths are 1.7467(17) and 1.7438(16) Å, respectively, and the C(11)−N(5) and C(13)−N(6) bond lengths are 1.309(2) and1.310(2) Å, respectively. The ring is completely planar. The full crystallographic data are given in the Supporting Information of ref 7. The absence of hydrogens on the ring carbons of **22** and on the C−CN carbon of **4j**• indicates a valence deficiency in both moieties. Tentative structures are therefore "long-lived intermediates": a delocalized allylic cation, anion, or radical for **22**, and a complementary delocalized anion, cation, or radical, respectively, for **4j**•. Comparison with X-ray data of structurally related neutral amides[7] shows that the C−S and C−C bonds are longer than those in the amides. The two 4-cyano-1,2-dithiolane crystal structures in the literature[16a,b] are not helpful in solving the structural problems, as is the NMR spectrum in solution, which does not have to be the same as that in the solid. In $CDCl_3$, the **3j**/**4j**/**5j** composition is 61/24/10,[7] and several signals are broad and overlap other signals.

There are arguments for and against each type of long-lived intermediates, based on the stability of the systems and the substituent effect. We believe that the most likely intermediates are two radicals. This is based on the observed X-ray structures of several 4-EWG-1,2-dithia-3,5-diazolyl radicals. These systems are the analogues of **22**, where two nitrogens replace the two carbons, and an EWG (e.g., Cl or fluoro-substituted phenyl groups) replaces the cyano.[17] There are few systems where the 5-nitrogen is replaced by a carbon.[18] Moreover, even a radical pair was observed by X-ray crystallography.[19]

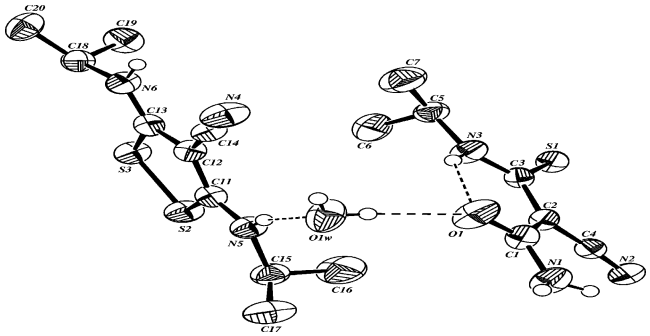
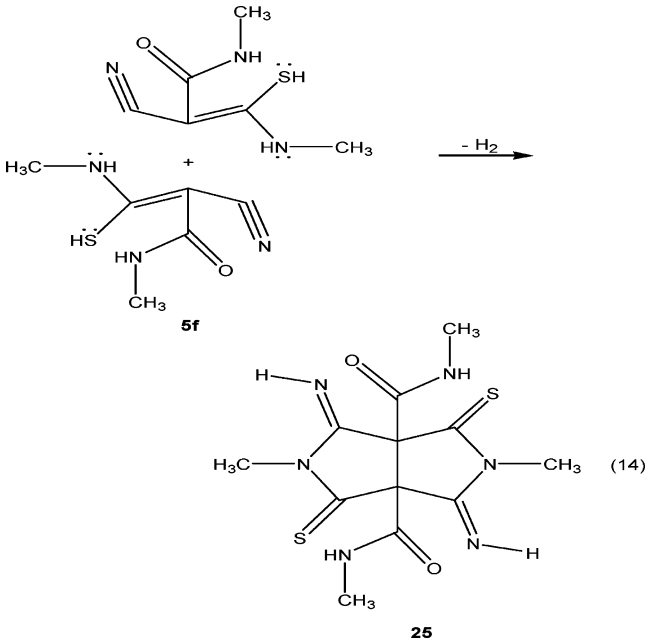


FIGURE 1. The ORTEP drawing of the **22**-H_2O-**4j**• adduct.

A tentative mechanism of formation of radical **22** is given in Scheme 4. As in the formation of **19**, the $CONH_2$ can be initially lost, although the details are unclear, and the anion **23** formed then attacks a molecule of **4j** to form the cyanodithiocarbonylmalonamide **24** by expulsion of the cyanoacetamide anion. The latter undergoes thioenolization, followed by loss of the SH hydrogen by air oxidation, and attack of the thiyl radical on the C═S bond will lead to the radical **22**. Other variants for the S−S bond formation via the well-known[20] oxidative sulfhydryl−disulfide reaction can also be suggested. Thioenolization and hydrogen abstraction by air oxygen can also lead to the radical **4j**•.

Formation of a 3,7-Diaza[3.3.0]bicyclooctane-4,8-dithione Derivative (25). Crystallization of **3f**/**4f**/**5f** from $CDCl_3$ at rt under air yielded mainly the enol **3f**[7,21] and few crystals of the 1,5-bis(methylcarbamoyl)-3,7-dimethyl-2,6-diimino-3,7-diaza-[3.3.0]bicyclooctane-4,8-dithione **25** (eq 14). When the crystallization was conducted under nitrogen, only a mixture of **3f**/**4f**/**5f** was recovered.



The solid-state structure of **25** is given in Figure 2, and the full crystallographic data are given in the Supporting Information. It shows that **25** is intramolecularly hydro-

(16) (a) Yokoyama, M.; Shiraishi, T.; Hatanaka, H.; Ogata, K. *Chem. Commun.* **1985**, 1704. (b) Cmelik, R.; Marek, J.; Pazdera, P. *Heterocycl. Commun.* **2002**, *8*, 55.

(17) (a) Antorrrena, G.; Dabies, J. E.; Hartley, M.; Palacio, F.; Rawson, J. M.; Smith, J. N. B.; Steiner, A. *Chem. Commun*. **1999**, 1393. (b) Bond, A. D.; Haynes, D. A.; Pask, C. M.; Rawson, J. M. *J. Chem. Soc., Dalton Trans*. **2002**, 2522. (c) Clarke, C. S.; Pascu, S. I.; Rawson, J. M. *CrystEngComm* **2004**, *6*, 79. (d) Alberola, A.; Less, R. J.; Pask, C. M.; Rawson, J. M.; Palacio, F.; Oliete, P.; Paulsen, C.; Yamaguchi, A.; Farley, R. D.; Murphy, D. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4782. (e) Heams, N. G. R.; Preuss, K. E.; Richardson, J. F.; Bin-Salamon, S. *J. Am. Chem. Soc.* **2004**, *126*, 9942.

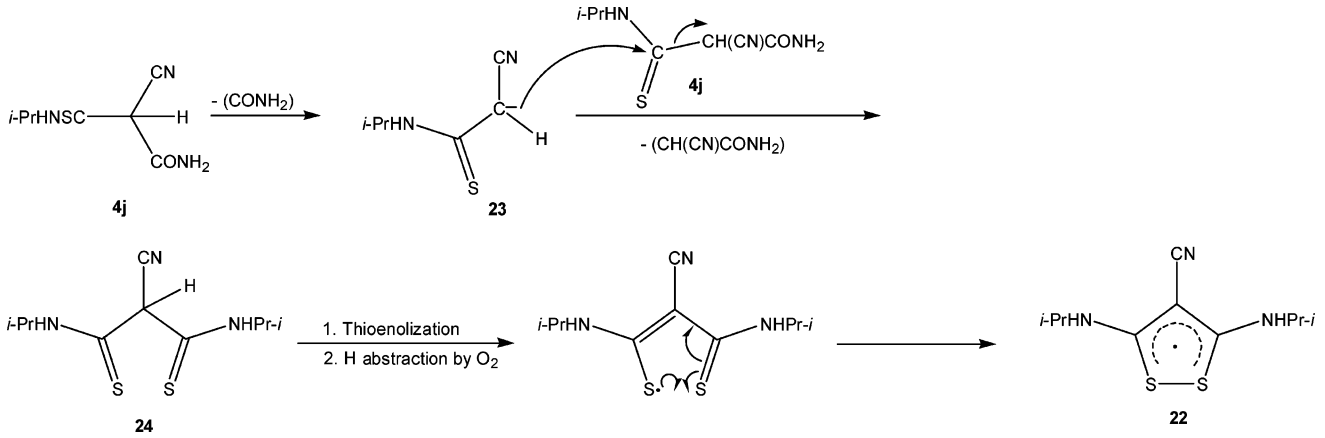
(18) (a) Beer, L.; Britten, J. F.; Clements, O. P.; Haddon, R. C.; Itkis, M. E.; Maikovich, K. M.; Oakley, R. T.; Reed, R. W. *Chem. Mater*. **2004**, *16*, 1564. (b) Oakley, R. T.; Reed, R. W.; Robertson, C. M.; Richardson, J. F. *Inorg. Chem.* **2005**, *44*, 1837. (c) Barclay, T. M.; Beer, L.; Cordes, A. W.; Oakley, R. T.; Preuss, K. E.; Taylor, N. J.; Reed, R. W. *Chem. Commun.* **1999**, 531.

(19) Kaawano, M.; Sano, T.; Abe, J.; Ohashi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 8106.

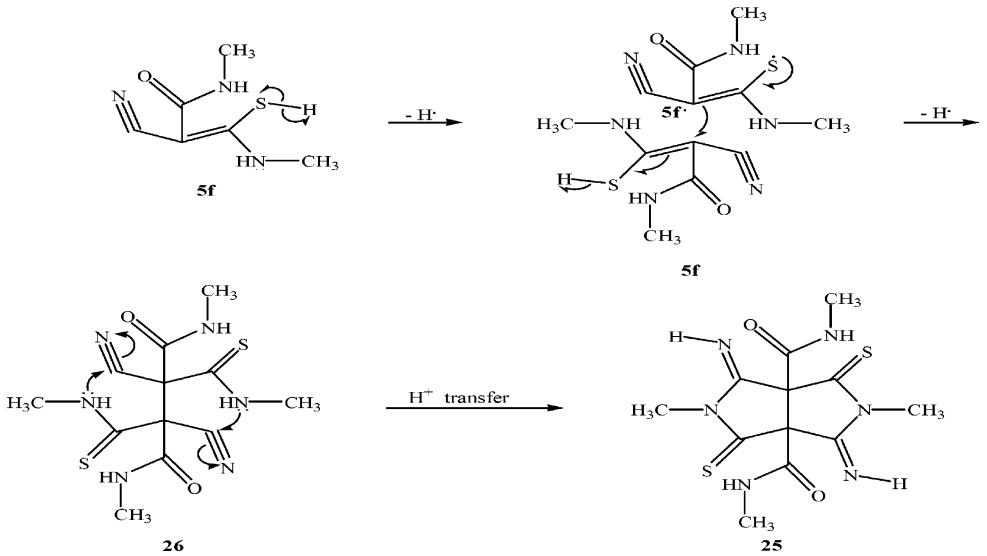
(20) Capozzi, G.; Modena, G. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; Wiley: Chichester, UK, 1974; Chapter 17, p 785.

(21) Basheer, A.; Rappoport, Z. *Org. Lett.* **2006**, *8*, 5931.

SCHEME 4. Suggested Mechanism for Formation of 22



SCHEME 5. Suggested Mechanism for a Formation of 25



gen bonded by an N(1)−H···N(2) moiety and intermolecularly hydrogen bonded to two other molecules by an N(2)−H···O(2′) moiety (Figure 2). The N(1)−H and N(2)−H bond lengths are 0.82(2)−0.83(3) and 0.84(3)−0.89(3) Å, respectively, and the N(2)···H and N(1)···N(2) nonbonding distances are 2.12(3)−2.16(3) and 2.815(3)−2.820(3) Å, respectively. The O(1′)···H and N(2)···O(1′) nonbonding distances are 2.21(3)−2.24(3) and 3.055(3)−3.069(2) Å, respectively. The C(1)−C(2), C(2)−C(3), C(2)−C(2′), C(1′)−C(2′), and C(2′)−C(3′) bond lengths are 1.535(3)−1.543(3) Å, typical lengths for a C−C single bond.[22] The C(1)−O(1) and C(1)−O(1′) bond lengths are 1.230(2) and 1.231(2) Å, respectively, values close to that of a C═O double bond.[22] Finally, the C(3)−S(1) and C(3′)−S(1′) bond lengths are 1.626(2) and 1.623(2) Å, respectively, slightly shorter than a C═S double bond length.[22] The amount of **25** was too small for obtaining NMR spectra.

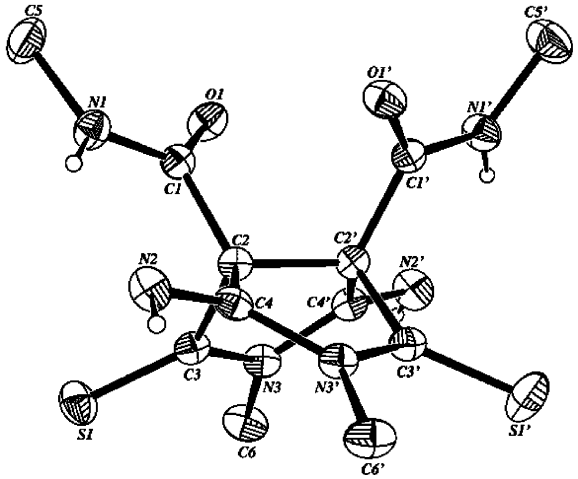


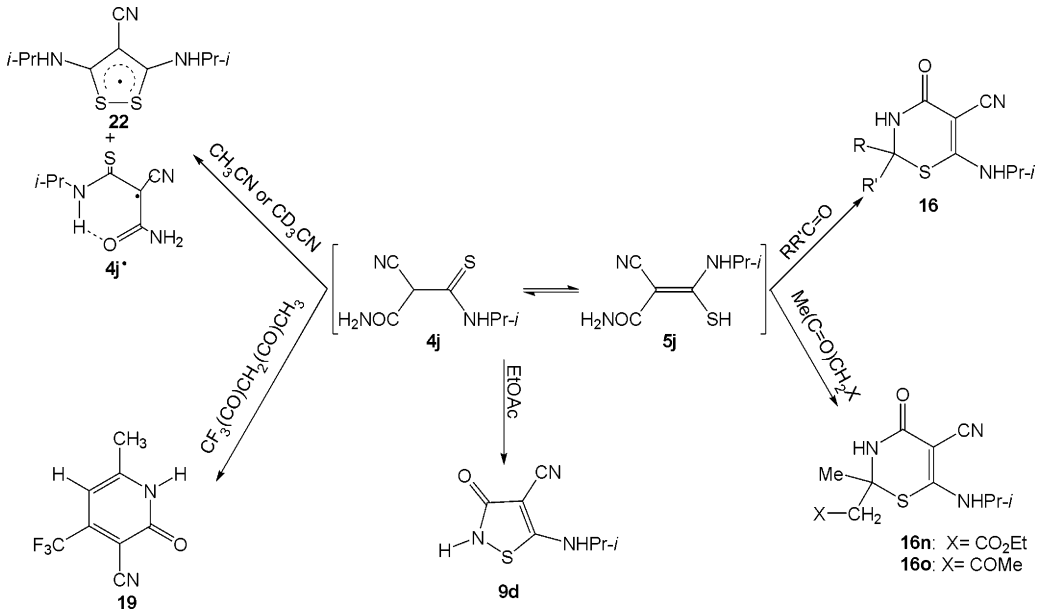
FIGURE 2. The ORTEP drawing of **25**.

Attempts to obtain other compounds with a similar skeleton from the structurally related **3a**/**4a**/**5a**, EtNHCSCH(CN)CONHMe, or *i*-PrNHCSCH(CN)CONHPr-*i* failed, and only amide, enol, and/or thioenol mixtures were obtained in solution, and the amide structure was obtained for the first system in the solid state.[7]

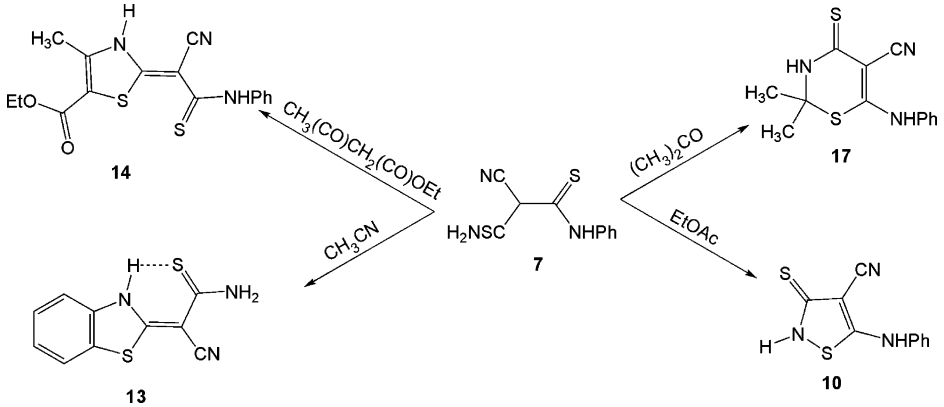
From its structure, **25** is the condensation product of two identical molecules of **3f**, **4f**, or **5f** with a loss of a H_2 molecule. The most likely precursor is the thioenol **5f**, which exists as 7% in the isomer mixture in $CDCl_3$.[7,21] The first step in the suggested mechanism is hydrogen abstrac-

(22) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1.

SCHEME 6. The Various Products Formed from 4j/5j



SCHEME 7. Various Products Formed from the Dithio 7/8 System



tion by the air oxygen from the S−H bond of **5f** to form the thiyl radical **5f**• whose electron is partially delocalized on C$_\beta$ of its double bond. Attack by this C$_\beta$ radical on C$_\beta$ of a second molecule of **5f** concerted with or followed by expulsion of H• from the SH bond generates **26** containing the future central bond of **25**. Separate attacks of the NH nitrogens on the adjacent carbons of the cyano groups (written together in Scheme 5), followed by proton transfers, complete the formation of the two five-membered rings to give **25** (Scheme 5).

We did not find other 3,7-diaza[3.3.0]bicyclooctane systems in the literature. However, an isomeric skeleton to **25** in which the four double bonds are within the bicyclic systems (e.g., 1,4-disubstituted amino-3,6-dithiomethyl-2,5-diazapentalenes) is known.[23]

Conclusions

A main feature of the present work is the variety of products formed from thioenol/amide systems. No product formed from the enol **3** was observed, and thioenols display high reactivity. Since both **4** and **5** are present in a rapid equilibrium in solution, we suggested in each case the most probable precursor which fit a suggested reasonable mechanism. Several products are formed from the same precursor under a variety or even similar conditions, suggesting similar barriers to their formation. In Scheme 6, the five- and six-membered ring systems formed from **4j/5j** are summarized; in Scheme 7, the four types of products formed from the dithio system **7**/**8** are shown, and in Scheme 8, the three products formed from **4e**/**5e** are given. Due to this variety, it is difficult to predict what will be the products of yet unstudied substituted precursors **3**/**4**/**5** under certain conditions.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded as described previously.[24]

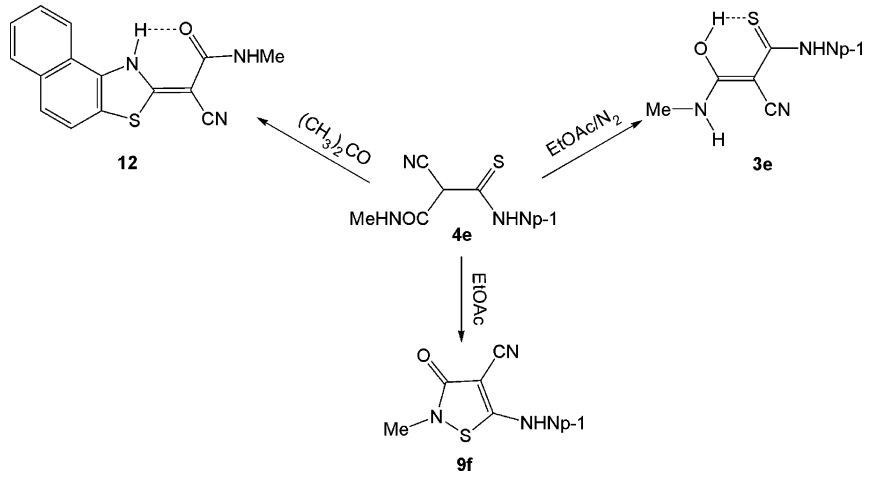
Solvents and Materials. The **3a**−**p**/**4a**−**p**/**5a**−**p** and **6**/**7**/**8** systems were available from our previous work.[7] The other precursors and the deuteriated solvents were purchased from a commercial supplier and used without further purification.

Isothiazole-3-ones 9a−**f from Air Oxygen Oxidation of Thioenols 5e and 5g**−**k.** The procedure is demonstrated for the reaction of the 1-naphthyl derivative **9f**. Compound **5e** (141 mg,

(23) Closs, F.; Breimaier, W.; Frank, W.; Gompper, R.; Hohenester, A. *Synth. Met.* **1989**, *29*, E537.

(24) Frey, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1996**, *118*, 5169.

SCHEME 8. The Various Products Formed from Formal 4e



0.5 mmol) was dissolved in ethyl acetate (2 mL) with stirring for 5 min and then kept for 3 days at room temperature. The colorless crystals that precipitated were dried at room temperature to give 75 mg (0.267 mmol, 53%) of the pure 2-methyl-5-(naphthalen-1-ylamino)-3-oxo-2,3-dihydroisothiazole-4-carbonitrile **9f**, mp 237−238 °C. Anal. Calcd for $C_{15}H_{11}N_3OS$: C, 64.06; H, 3.91; N, 14.95. Found: C, 63.84; H, 3.95; N, 14.94. ^{1}H NMR (DMSO-d_6, 298 K, 400 MHz) δ: 3.01 (3H, s), 7.58 (1H, t, J = 7.6 Hz), 7.32 (3H, m), 7.99−8.06 (3H, m), 11.12 (1H, s). ^{13}C NMR (DMSO-d_6, 298 K, 100.62 MHz) δ: 30.3, 72.6, 114.6, 122.6, 124.6, 126.2, 127.6, 127.8, 128.9, 129.2, 129.5, 134.3, 134.6, 166.7, 169.7.

The spectral and analytical data for derivatives **9a**−**f**, which were obtained similarly, are given in Tables S1−S3 in the Supporting Information.

5-Phenylamino-3-thioxo-2,3-dihydroisothiazole-4-carbonitrile 10, mp 208−209 °C (89 mg, 0.39 mmol), was obtained from the formal cyanodithiocarbonylmalonamide **7** (118 mg, 0.5 mmol) in 76% yield by a procedure similar to that described for formation of **9b**. Anal. Calcd for $C_{10}H_7N_3S_2$: C, 51.50; H, 3.00; N, 18.02. Found: C, 51.77; H, 2.86; N, 17.58. ^{1}H NMR (DMSO-d_6, 298 K, 400 MHz) δ: 7.25−7.49 (3H, m), 7.86−8.03 (2H, m), 9.83 (2H, s). ^{13}C NMR (DMSO-d_6, 298 K, 100.62 MHz) δ: 88.9 (s), 116.4 (s), 125.7 (d, J = 162 Hz), 128.3 (d, J = 163 Hz), 130.0 (d, J = 163 Hz), 139.2 (t, J = 9.3 Hz), 162.3 (s), 187.4 (s).

2-Cyano-*N*-methyl-2-(1*H*-naphtho[1,2-*d*]thiazol-2-ylidene)acetamide 12. When a formal thioenol **5e** (141 mg, 1 mmol) was dissolved in ethyl acetate under air, it gave colorless crystals which were filtered and dried in air at rt to give the pure 2-cyano-*N*-methyl-2-(1*H*-naphtho[1,2-*d*]thiazol-2-ylidene)acetamide **12** (97 mg, 0.35 mmol, 70%), mp 258−260 °C. Anal. Calcd for $C_{15}H_{11}N_3OS$: C, 64.06; H, 3.91; N, 14.95. Found: C, 63.92; H, 4.00; N, 14.67. ^{1}H NMR ($CDCl_3$, 298 K, 400 MHz) δ: 2.98 (3H, d, J = 4.8 Hz), 5.80 (1H, q, J = 3.1 Hz), 7.12 (1H, d, J = 8.7 Hz), 7.57−7.67 (3H, m), 7.95 (1H, d, J = 8.0 Hz), 8.02 (1H, d, J = 8.2 Hz), 13.92 (1H, s). ^{1}H NMR (DMSO-d_6) δ: 2.72 (3H, s), 7.32 (1H, br s), 7.53−7.67 (2H, m), 7.78 (1H, d, J = 8.3 Hz), 7.89 (1H, d, J = 8.3 Hz), 8.02 (1H, d, J = 8.0 Hz), 8.77 (1H, d, J = 7.8 Hz), 12.87 (1H, s). ^{13}C NMR (DMSO-d_6, 298 K, 100.62 Hz) δ: 26.9, 67.1, 118.5, 119. 9, 121.0, 123.1, 123.9, 124.1, 126.6, 127.0, 128.9, 132.4, 134.7, 166.0, 166.8.

2-(3*H*-Benzothiazol-2-ylidene)-2-cyanothioacetamide 13. A reaction similar to the formation of **12** took place when the formal cyanodithiocarbonylmalonamide **7** (118 mg, 0.5 mmol) was dissolved in acetonitrile, and 2-(3*H*-benzothiazol-2-ylidene)-2-cyanothioacetamide **13**, mp 221−222 °C, was obtained in 68% yield (79 mg, 0.34 mmol). Anal. Calcd for $C_{10}H_7N_3S_2$: C, 51.50; H, 3.00; N, 18.03. Found: C, 51.59; H, 2.99; N, 17.82. ^{1}H NMR (DMSO-d_6, 298 K, 400 MHz) δ: 7.28 (1H, t, J = 7.9 Hz), 7.43 (1H, t, J = 7.2 Hz), 7.62 (1H, d, J = 6.8 Hz), 7.86 (1H, d, J = 7.8 Hz), 7.90 (1H, br s), 8.57 (1H, br s), 12.97 (1H, s). ^{13}C NMR (DMSO-d_6, 298 K, 100.62 MHz) δ: 76.1 (s), 113.9 (d, J = 167 Hz), 117.7 (s), 122.6 (d, J = 162 Hz), 124.2 (d, J = 164 Hz), 127.1 (s), 127.6 (d, J = 164 Hz), 138.8 (s), 169.1 (s), 188.7 (s).

5-[Cyano(phenylthiocarbamoyl)methylene]-3-methyl-2,3-dihydrothiazole-2-carboxylic Acid Ethyl Ester 14. When the formal cyanodithiocarbonylmalonamide **7** (118 mg, 0.5 mmol) was dissolved in ethyl acetoacetate (2 mL) at rt and the solution stood for 1 week, 5-[cyano(phenylthiocarbamoyl)methylene]-3-methyl-2,3-dihydrothiazole-2-carboxylic acid ethyl ester **14** (74 mg, 0.32 mmol, 64%), mp 183−184 °C, was formed. Anal. Calcd for $C_{16}H_{15}N_3O_2S_2$: C, 55.65; H, 4.35; N, 12.17. Found: C, 55.28; H, 4.60; N, 11.33. ^{1}H NMR (DMSO-d_6, 298 K, 400 MHz) δ: 1.28 (3H, t, J = 7.1 Hz), 2.58 (3H, s), 4.27 (2H, q, J = 7.0 Hz), 7.17 (1H, t, J = 7.4 Hz), 7.34 (2H, t, J = 7.9 Hz), 7.45 (2H, d, J = 7.1 Hz), 10.07 (IH, s), 13.08 (1H, br s). ^{13}C NMR (DMSO-d_6, 298 K, 100.62 MHz) δ: 14.7, 30.5, 61.4, 78.8, 110.0, 117.4, 125.7, 128.7, 140.6, 147.5, 161.8, 167.2, 186.5.

6-Substituted Amino-2,2-dialkyl-4-oxo-3,4-dihydro-2*H*-[1,3]-thiazine-5-carbonitriles 16a−o. The procedure is demonstrated for the reaction of **5j** with acetone. When the thioenol **5j** (185 mg, 1 mmol) was dissolved in acetone (2 mL) and the mixture was stirred for 5 min and kept at room temperature overnight, colorless crystals were precipitated. The crystals were filtered, washed with ether, and dried at room temperature to give 211 mg (0.94 mmol, 94%) of the pure 6-isopropylamino-2,2-dimethyl-4-oxo-3,4-dihydro-2*H*-[1,3]thiazine-5-carbonitrile **16d**, mp 203−204 °C. Anal. Calcd for **16d**: C, 53.33; H, 6.67; N, 18.67. Found: C, 53.37; H, 6.74; N, 18.56. ^{1}H NMR ($CDCl_3$, 298 K, 400 MHz) δ: 1.30 (6H, d, J = 6.6 Hz), 1.76 (6H, s), 3.86 (1H, oct, J = 6.5 Hz), 5.90 (1H, d, J = 8.3 Hz), 7.00 (1H, s). ^{1}H NMR (DMSO-d_6, 298 K, 400 MHz) δ: 1.20 (6H, d, J = 6.5 Hz), 1.62 (6H, s), 3.86 (1H, oct, J = 4.7 Hz), 7.94 (1H, s), 7.97 (1H, d, J = 8.6 Hz). ^{13}C NMR (DMSO-d_6, 298 K, 100.62 MHz) δ: 22.8 (q, J = 127 Hz), 29.9 (q, J = 129 Hz), 48.2 (d, J = 138 Hz), 61.4 (s), 72.5 (s), 117.7 (s), 165.2 (s), 165.5 (s).

The analogous 2-anisyl derivative **16p** was prepared similarly from **5j** and anisaldehyde.

The spectral and analytical data for **16a**−**p** are given in Tables S1−S3 in the Supporting Information.

6-Phenylamino-2,2-dimethyl-4-thioxo-3,4-dihydro-2*H*-[1,3]-thiazine-5-carbonitrile 17. Reaction of formal cyanodithiocarbonylmalonamide **7** (59 mg, 0.25 mmol) in acetone (1 mL) under the condition used for preparation **16a**−**p** yielded the 6-phenylamino-2,2-dimethyl-4-thioxo-3,4-dihydro-2*H*-[1,3]thiazine-5-carbonitrile **17**, mp 232−233 °C, in 87% yield (51 mg, 0.218 mmol). Anal. Calcd for **17**: C, 56.73; H, 4.73; N, 15.27; S, 22.27. Found: C, 56.76; H, 4.89; N, 15.14; S, 22.83. ^{1}H NMR (DMSO-d_6, 298 K, 400 MHz) δ: 1.61 (6H, s), 7.27 (2H, d, J = 7.3 Hz), 7.33 (1H, t,

J = 7.4 Hz), 7.42 (2H, t, J = 7.8 Hz), 9.82 (1H, s), 10.30 (1H, s). ^{13}C NMR (DMSO-d_6, 298 K, 100.62 MHz) δ: 28.6 (q, J = 130 Hz), 62.6 (s), 86.6 (s), 117.1 (s), 126.7 (d, J = 163 Hz), 127.9 (d, J = 163 Hz), 129.5 (d, J = 163 Hz), 138.0 (t, J = 9.3 Hz), 161.8 (s), 187.0 (s).

3-Cyano-6-methyl-4-trifluoromethyl-2(1*H*)-pyridone, 19. Colorless crystals of **19** (65 mg, 0.32 mmol, 64%), mp 232−233 °C (lit.[14a,25] mp 232−234 °C, lit.[14b,d] mp 234 °C), were obtained after dissolving **5j** (93 mg, 0.5 mmol) in trifluoroacetylacetone **18** (2 mL) and keeping the mixture under air for 48 h at rt. Anal. Calcd for $C_8H_5F_3N_2O$: C, 47.52; H, 2.48; N, 13.86. Found: C, 47.25; H, 2.48; N, 13.88. ^{1}H NMR (DMSO-d_6, 298 K, 400 MHz) δ: 2.38 (3H, s), 6.65 (1H, s), 13.36 (1H, s). ^{13}C NMR (DMSO-d_6, 298 K, 100.62 MHz) δ: 20.0, 96.6, 102.1, 114.0, 121.7 (q, J = 276 Hz), 146.4 (q, J = 32 Hz), 157.4, 161.0.

Divinyl Sulfides 21a−c from Thioenols 5n−p. The disulfides **21a−c** were prepared similarly under the same condition as demonstrated for formation of **21b**. The thioenol **5o** (261 mg, 1 mmol) was dissolved in ethyl acetate (2 mL), and the mixture was kept at rt for 48 h. The orange crystals obtained were filtered and dried in air at rt to give the pure bis[(2-cyano-2-phenylcarbamoyl-1-isopropylamino)vinyl] sulfide **21b**, mp 218−220 °C, in 79% yield (192 mg, 0.39 mmol). Anal. Calcd for $C_{26}H_{28}N_6O_2S$: C, 63.93; H, 5.74; N, 17.21. Found: C, 64.15; H, 5.91; N, 17.33. ^{1}H NMR ($CDCl_3$, 298 K, 400 MHz) δ: 1.37 (12H, d, J = 6.5 Hz), 4.30 (2H, oct, J = 6.5 Hz), 7.12 (2H, t, J = 7.4 Hz), 7.33 (4H, t, J = 8.2 Hz), 7.47 (4H, d, J = 7.7 Hz), 7.56 (2H, s), 11.22 (2H, q, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 298 K, 100.62 MHz) δ: 23.6 (q, J = 128 Hz), 49.7 (d, J = 140 Hz), 76.1 (d, J = 3.6 Hz), 118.4 (s), 120.6 (d, J = 163 Hz), 124.7 (d, J = 162 Hz), 129.0 (d, J = 162 Hz), 137.0 (t, J = 7.9 Hz), 160.0 (d, J = 4.1 Hz), 165.3(d, J = 3.0 Hz).

Bis[(2-cyano-2-phenylcarbamoyl-1-anilido)vinyl] Sulfide 21a. Mp 236−7 °C. Anal. Calcd for $C_{32}H_{24}N_6O_2S$: C, 69.05; H, 4.35; N, 15.10. Found: C, 69.29; H, 4.12; N, 15.20. ^{1}H NMR ($CDCl_3$, 298 K, 400 MHz) δ: 7.17−7.24 (6H, m), 7.29 (2H, d, J = 7.8 Hz), 7.36−7.46 (12H, m), 7.75 (2H, s), 12.04 (2H, s). ^{13}C NMR ($CDCl_3$, 298 K, 100.62 MHz) δ: 62.6, 72.1, 118.0, 124.5, 125.1, 125.8, 127.3, 129.07, 129.4, 136.0, 136.4, 160.5, 163.4.

Bis[(2-cyano-2-phenylcarbamoyl-1-ethylamino)vinyl] Sulfide 21c. Mp 220−221 °C. Anal. Calcd for $C_{24}H_{24}N_6O_2S$: C, 62.59; H, 5.25; N, 18.25. Found: C, 62.41; H, 5.18; N, 17.95. ^{1}H NMR ($CDCl_3$, 298 K, 400 MHz) δ: 1.36 (6H, t, J = 7.2 Hz), 3.74 (4H, pent, J = 7.1 Hz), 7.12 (2H, t, J = 7.3 Hz), 7.32 (4H, t, J = 8.0 Hz), 7.45 (4H, d, J = 7.9 Hz), 7.63 (2H, s), 10.73 (2H, s).

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Formation of 3,5-Bis(isopropylamino)-[1,2]-dithiolane-4-carbonitrile/4j•/H_2O 22. Crystallization of **4j** (185 mg, 1 mmol) from acetonitrile or from acetonitrile-d_3 (4 mL) at rt gives a three-molecule associate: the radical **4j•** which is intermolecularly hydrogen bonded by one water molecule to the 3,5-bis(isopropylamino)-[1,2]-dithiolane-4-carbonitrile radical **22**. Anal. Calcd for $C_{17}H_{28}N_6O_2S_3$: C, 45.94; H, 6.38; N, 21.60. Found: C, 44.62; H, 6.07; N, 17.90. ^{1}H NMR (DMSO-d_6, 298 K, 400 MHz) δ: 1.09 (6H, br), 1.25 (12H, J = 6.6 Hz), 3.35 (2.5H, br s), 3.69 (2.5H, s), 4.43 (1H, s), 5.02 (0.3H, s), 5.81 (1H, br s), 7.55 (0.5H, d, J = 6.5 Hz), 9.96 (0.5H, s) 10.21 (1.6H, br s).

1,5-Bis(methylcarbamoyl)-3,7-dimethyl-2,6-diimino-3,7-diaza-[3.3.0]bicyclooctane-4,8-dithione (25). When the formal cyanomonothiomalonamide **4f** (86 mg, 0.05 mmol) was dissolved in chloroform (5 mL) and the solution was kept overnight, colorless crystals of the enol **3f** accompanied by few yellow crystals of **25**, mp 287−288 °C, were formed. The crystals of **25** were sufficient only for X-ray diffraction but not for the NMR spectral measurements.

Reactions under Nitrogen. (a) Formal compound **4j** was dissolved in AcOEt under nitrogen, and the mixture was stirred for 5 min and then kept for more than 40 h at rt. The solvent was evaporated, and the remainder was dissolved in $CDCl_3$ and its ^{1}H NMR spectrum shows signals for the **3j**/**4j**/**5j** mixture. In a similar reaction of **4i** under nitrogen, the spectrum in THF-d_8 showed only signals for the enol **3i**. (b) Compound **4e** was dissolved in acetone, and the solution stood under nitrogen at rt for more than 30 h. After evaporation of the solvent, the solid obtained showed in the ^{1}H NMR spectrum signals for the enol **3e** and the thioenol **5e**. From crystallization of **4e** in EtOAc under nitrogen, crystals of **3e** were isolated. (c) Dissolution of **4f** in $CDCl_3$ under nitrogen for 24 h showed only signals for the **3f**/**4f**/**5f** mixture.

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Supporting Information Available: CIFs of compounds **9d**, **9f**, **12**, **13**, **14**, **16d**, **16k**, **16p**, **19**, **21b**, and **25**, Tables S1 and S2 of ^{1}H and ^{13}C NMR of **9a−f** and **16a−p** and Table S3 of analytical data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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