JOC Article

Substituted 2-Methylene-1,3-oxazolidines, -1,3-thiazolidines, -1,3-benzothiazines, -1,3-oxazines, and Substituted Imidazopyrimidinediones from $Cl(CH_2)_nNCO$ and $Cl(CH_2)_nNCS$ and Active Methylene Compounds

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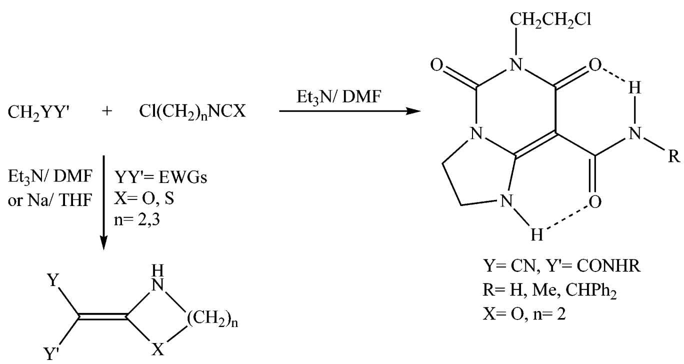

The reaction of ω-chloroalkyl isocyanates $Cl(CH_2)_nNCO$ ($n = 2$ (**2**), 3 (**4**)) and isothiocyanate $Cl(CH_2)_2$-NCS (**3**) with active methylene compounds CH_2YY' **1** in the presence of Et_3N or Na give 2-YY′-methylene-1,3-oxazolidines, (*E*,*Z*)-1,3-thiazolidines, and 1,3-oxazines from **2**, **3**, and **4**, respectively. 2-(Chloromethyl)-phenyl isocyanate **8** gives with **1** the corresponding benzo-oxazines. Ethyl 2-isothiocyanatobenzoate **10** gives the corresponding benzothiazolinone, whereas the analogous isocyanate **12** gives noncyclic enols. Ethoxycarbonyl isothiocyanate **14** gives an open-chain thioenol or an enol-thioamide. The cyanoamides $CH_2(CN)CONHR$, R = H, Me, $CHPh_2$, give with Et_3N and **2** the bicyclic imidazopyrimidinediones **16**, derived from two molecules of **2**, but with their preformed Na salt they give the 1,3-oxazolidines. Reaction of cyanoacetamide with **3** in the presence of Na gave a tricyclic triaza(thia)indacene, derived from two molecules of **3**. A reaction mechanism involving an initial attack of the anion $\mathbf{1}^-$ on the N=C=X (X = O, S) moiety gives an anion **18**, which cyclizes intramolecularly and after tautomerization gives the mono-ring heterocycle. With the cyanoamides, the N^- site of the ambident ion **18** attacks another molecule of **2** giving the anion **20**, which by intramolecular attack on the CN, followed by expulsion of the Cl^- gives the bicyclic **16** after tautomerization.

Introduction

Reaction of active methylene compounds carrying two strongly electron-withdrawing groups Y, Y′ with organic isocyanates[1] and isothiocyanates[2] under basic conditions frequently form the corresponding amides (thioamides) or their enols (thioenols) either as mixtures or as one of the pure species, depending on Y and Y′. The reaction (eq 1) was extensively investigated by us.[3] The enols or thioenols are polyfunctional dipolar species with vicinal NHR and OH or SH groups on an electrophilic vinylic carbon. We reasoned that if the alkyl group R of the RNCO or RNCS will carry a terminal leaving group

(1) Mukhopadhyaya, J. K.; Sklenak, S.; Rappoport, Z. *J. Am. Chem. Soc.* **2000**, *122*, 1325.

(2) Basheer, A.; Rappoport, Z. Kyushu International Conference on Physical Organic Chemistry (KISPOC 11), Sep 12−15, 2005, Abstract book, pp 1−2.

(3) (a) Mukhopadhyaya, J. K.; Sklenak, S.; Rappoport, Z. *J. Org. Chem.* **2000**, *65*, 6856. (b) Lei, Y. X.; Cerioni, G.; Rappoport, Z. *J. Org. Chem.* **2001**, *66*, 8379. (c) Lei, Y. X.; Casarini, D.; Cerioni, G.; Rappoport, Z. *J. Org. Chem.* **2003**, *68*, 947. (d) Lei, Y. X.; Casarini, D.; Cerioni, G.; Rappoport, Z. *J. Phys. Org. Chem.* **2003**, *16*, 525. (e) Basheer, A.; Rappoport, Z. *J. Org. Chem.* **2004,** 69, 1151.

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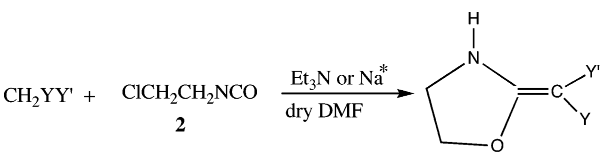
$$CH_2YY' + RNCX \xrightarrow[\text{dry DMF}]{Et_3N} Y'YCHCXNHR/Y'YC{=}C(XH)NHR \quad (1)$$

1 **2:** X = O; **3:** X = S

such as chlorine, reaction of the CH_2YY' with the isocyanate or isothiocyanate, e.g., $Cl(CH_2)_nNCX$, $n = 2, 3$, X = O, S, will be followed or be coupled with Cl^- expulsion by the X (or XH) functionality to give heterocyclic systems. We therefore reacted several active methylene compounds (**1**) with β-chloroethyl isocyanate (**2**), with β-chloroethyl isothiocyanate (**3**), and with γ-chloropropyl isocyanate (**4**) and related derivatives and obtained the corresponding 2-YY′-substituted methylene 1,3-N,O- and N,S-heterocyclic systems. Some other products were also formed.

Results

Reaction and Structure Assignment of the Monocyclic Hetereocycles. Reaction of 15 active methylene compounds **1a**−**o**, where Y,Y′ are various combinations of ester, cyano, carbonyl, amido, and sulfonyl groups with **2** in the presence of Et_3N or sometimes with a Na metal, resulted in a rapid formation of Et_3NHCl or NaCl with the more acidic **1** and a slower formation with the less acidic **1**. On addition of water the corresponding 2-substituted methylene-1,3-oxazolidines (**5a**−**o**) precipitated in high yields (eq 2). When Y and/or Y′ are



(2)

1a: Y = CN, Y' = CO_2Me
1b: Y = Y' = $CO_2CH_2CF_3$
1c: YY' = Barbituric acid moiety
1d: YY' = Meldrum's acid moiety
1e: Y = Y' = CN
1f: Y = CO_2Et, Y' = COMe
1g: Y = CONHPh, Y' = COMe
1h: Y = $SO_2C_4F_9$, Y' = COMe
1i: Y = Y' = COMe
1j: YY' = Dimedone moiety
1k: Y = CN, Y' = $CONMe_2$
1l: Y = CN, Y' = CONHMe
1m: Y = CN, Y' = $CONH_2$
1n: Y = $CO_2CH_2CF_3$, Y' = CO_2Me
1o: Y = Y' = CO_2Me
* With **1k**-**1m**

5a: Y = CN, Y' = CO_2Me
5b: Y = Y' = $CO_2CH_2CF_3$
5c: YY' = Barbituric acid moiety
5d: YY' = Meldrum's acid moiety
5e: Y = Y' = CN
5f: Y = CO_2Et, Y' = COMe
5g: Y = CONHPh, Y' = COMe
5h: Y = $SO_2C_4F_9$, Y' = COMe
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5k: Y = CN, Y' = $CONMe_2$
5l: Y = CN, Y' = CONHMe
5m: Y = CN, Y' = $CONH_2$
5n: Y = $CO_2CH_2CF_3$, Y' = CO_2Me
5o: Y = Y' = CO_2Me

potential enolization sites, such as COMe or a barbituric acid residue (i.e., **1c**,**f**−**j**), the cyclization via reaction of the Y or Y′ could give an alternative 1,4-O,N-heterocyclic 7-membered ring, but this was not found. Table S1 (Supporting Information) indicates that apparently only one isomer, judged by the observed single NH ring signal, is formed. This can be due either to formation of only the most stable isomer or to a rapid interconversion of *E* and *Z* isomers, as found for highly dipolar push−pull systems resembling our compounds.[4] Since *E* and *Z* isomers of enols formed according to eq 1, which are structurally related to compounds **5**, are frequently observed, solutions of several compounds **5** where Y ≠ Y′ were cooled. When a solution of **5f** in $CDCl_3$ which shows at rt one signal at δ 11.14 ppm was cooled to 220 K, the ^{1}H NMR spectrum displayed two isomers (δ (NH) signals at 9.56 ppm for the *E* isomer and 11.15 for the *Z* isomer) in a *Z*/*E* ratio of 98:2. The assignment is based on the expected stronger H-bond for the *Z* isomer.

TABLE 1. *E*/*Z* Ratio and δ(NH) Values (ppm) for Compounds 5 and 6 at Several Temperatures

Y	Y′	solvent	X	*T* (K)	*E* or *Z*	% yield	δ(NH)
COMe	CO_2Et	$CDCl_3$	O	298	*a*	100	11.14
				220	*Z*	98	11.15
					E	2	9.56
			S	298	*Z*	70	12.06
					E	30	10.14
CN	CO_2Me		O	298	*a*	100	8.56
			S	298	*E*	94	9.15
					Z	6	6.37
COMe	CONHPh		O	298	*a*	100	11.28
				240	*Z*	99	11.23
					E	1	9.63
		DMSO-d_6	S	298	*a*	100	10.25[b]
		DMF-d_7		220	*Z*	79	11.17
					E	21	10.31
CO_2Me	$CO_2CH_2CF_3$	$CDCl_3$	O	298	*a*	100	9.24[b]
				240	*Z*	73	9.53
					E	27	9.11

[a] Rapid *E*/*Z* interconversion takes place. [b] Broad signal.

Likewise, the two rt ^{1}H NMR δ(NH) signals at 11.28 and 12.46 ppm of **5g** appear at 240 K at 11.23 and 12.60 ppm with 99% intensity together with 1% of two new signals at 9.63 and 10.68 ppm. The major isomer was assigned as *Z* on the basis of its favorable NH···O=CCH_3 hydrogen bond. Cooling of **5n**, which shows at rt only one broad δ(NH) signal at 9.25 ppm, to 240 K gave a 73:27 *Z*/*E* isomer ratio, with δ(NH) at 9.11 (*E*) and 9.53 (*Z*) ppm. The data are summarized in Table 1.

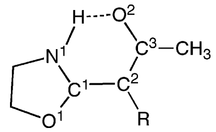
The structures were consistent with the elemental analysis (Table S8, Supporting Information), with the ^{1}H , ^{13}C NMR and 2D NMR spectra, and with the known structures of compounds **5a**,[5] **5d**,[6−8a] **5e**,[7,8c] and **5i**.[5] X-ray diffraction of compounds **5f** and **5h** corroborated the structures and the configuration assignments. In both cases, the NH is cis and hydrogen bonded (cf. the N···O nonbonded distances in Table 2) to the C=O of the acetyl group, which is the stronger hydrogen bond acceptor among the pairs of Y and Y′ groups.[9] The main bond lengths and angles are given in Table 2, and the full crystallographic data are given in the Supporting Information.

The ^{1}H NMR δ(NH) (Table S1, Supporting Information) indicates the importance of intramolecular hydrogen bonding in compounds **5**. In $CDCl_3$, it appears at 7.75−11.29 ppm with the lowest value of 7.75 ppm for **5e** having two CN groups that are incapable of forming an intramolecular hydrogen bond. The next low value is 8.56 ppm for **5a**, with one cyano and one ester group. The three higher values at 11.14−11.29 ppm are for **5f**−**i**, where Y′ = COMe, the strongest hydrogen bond acceptor among our Y and Y′.[9] The δ(NH) of **5e** in DMSO-d_6 is at 2.38 ppm lower field than in $CDCl_3$, presumably indicating a stronger intermolecular hydrogen bonding with the DMSO-d_6.

(4) (a) Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: Weinheim, 1985. (b) Sandström, J. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; Wiley: Chichester, 1994; Chapter 6, p 405.

(5) Huang, Z-T.; Zhang, P.-C. *Chem. Ber.* **1989**, *122*, 2011.
(6) Jeon, M. K.; Kim, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3107.
(7) Huché, M.; Lhommet, G. *J. Heterocycl. Chem.* **1986**, *23*, 701.
(8) (a) Huang, Z-T.; Shi, X. *Synth. Commun.* **1990**, *20*, 1321. (b) Huang, Z.-T.; Shi, X. *Synthesis* **1990**, 162. (c) Ishida, T.; Osaka, H.; Nogami, T.; Yamazaki, R.; Yasui, M.; Iwasaki, F.; Mizoguchi, A.; Kuhata, M.; Uemiya, T.; Nishimura, A. *Synth. Met.* **1993**, 2013. (d) Gompper, R.; Töpfl, W. *Chem. Ber.* **1962**, *95*, 182.
(9) Laurent, C.; Berthelot, M.; Graton, J. In *The Chemistry of Phenols*; Rapoport, Z., Ed.; Wiley: Chichester, 2003; Chapter 8, p 529.

TABLE 2. Selected Crystallographic Data for 5f and 5h



	bond length (Å)	
	5f (R = C^7O_2Et)	**5h** (R = $SO_2C_4F_9$)
C(1)−C(2)	1.393(9)	1.423(5)
C(2)−C(3)	1.429(10)	1.467(5)
C(2)−C(7)	1.481(9)	
C(2)−S(1)		1.708(4)
C(1)−N (1)	1.326(8)	1.294(5)
C(1)−O(1)	1.323(8)	1.330(4)
C(3)−O(2)	1.236(8)	1.229(6)
N(1)−H	0.96(7), 0.96(7)	0.81(4), 0.81(4)[a]
O(2)···H	1.99(6), 2.11(7)[a]	2.03(4), 2.30(4)[a]
N(1)···O(2)	2.560(8), 2.889(8)[a]	2.584(4), 2.909(5)[a]

	angle (deg)	
	5f (R = C^7O_2Et)	**5h** (R = $SO_2C_4F_9$)
O(1)−C(1)−N(1)	110.4(6)	111.5(3)
C(3)−C(2)−C(7)	119.9(6)	
C(3)−C(2)−S(1)		122.9(3)

[a] Symmetry transformations used to generate equivalents atom: $-x + 1, -y + 1, -z + 1$.

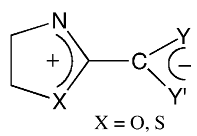


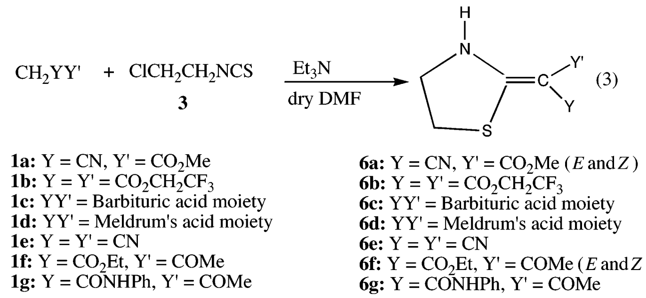
FIGURE 1. Dipolar contribution to the hybrid **5** or **6**.

The ^{13}C NMR spectra (Table S2, Supporting Information) of compounds **5** (and of **6**, **7**, **9**, **11**, **13**, and **15**) indicate their high dipolar structures. As shown in Figure 1, C_α (carrying X = O, S and N) is highly positive while C_β (carrying YY′) is highly negative. For compounds **5**, C_α appears at 170.11−173.96 ppm, an extremely low field for a vinylic carbon, with low structure sensitivity. C_β appears at 34.79−99.46 ppm, a high field for a vinylic carbon, with higher sensitivity to the nature of Y and Y′. The higher field is for Y′Y = $(CN)_2$, at 34.79 ppm for **5e**, followed by ca. 56 ppm for the cyano ester and cyano amide derivatives. Higher values at ca. 89−90 ppm are for **5f**−**h**, where Y′ = COMe. For **5i** and **5j**, the values are 99.46 (103.4)[5] and 96.45 ppm, respectively. Consequently, the difference in $\Delta C_{\alpha\beta}$ is mainly due to differences in δC_β. The extremes in $\Delta C_{\alpha\beta}$ of ca. 139 ppm for **5e**, and 81.3 for **5h**, reflect contributions from both the dipolar structure and the hydrogen bonding.[10] Large differences were observed earlier for enols.[1−3]

The partial single bond character of the formal C1−C2 double bond is shown by the bond lengths of 1.393 and 1.423 Å (Table 2) which are longer than a normal C═C bond.

Compounds **5k**−**m** were prepared from the sodium salt of **1k**−**m** in THF. The reaction with Et_3N gave different products (for details see below).

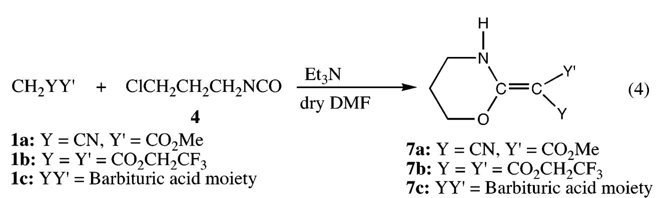
Reaction of seven compounds **1** with the isothiocyanate **3** under similar conditions gave the corresponding 2-substituted methylene-1,3-thiazolidines (**6a**−**g**) (eq 3). For the three unsymmetrical products when Y ≠ Y′, the ^{1}H NMR spectra showed that **6a** and **6f** are formed as a mixture of *E* and *Z* isomers, whereas **6g** apparently appeared only as a single isomer at rt (see below).



The Y and Y′ signals in the two isomers differed by <0.03 ppm, whereas the NH signals differed appreciably: by ca. 2.8 and 1.9 ppm for **6a** and **6f**, respectively. The isomer with the lower field NH group was formed in both cases in excess, the *E*/*Z* ratios being 94:6 for **6a** and 30:70 for **6f**. The structure was deduced as having a stronger intramolecular hydrogen bond with the EWG cis to the NH, which is CO_2Me (over CN, the *E* isomer) for **6a** and COMe (over CO_2Et, the *Z* isomer) for **6f**. The ratios are integration averages of various signals. System **6g** displays broad δ(NH) in DMSO-d_6, suggesting a rapid *E*/*Z* interconversion on the NMR time scale. In DMF-d_7 at 220 K, two isomers were observed in a *Z*/*E* ratio of 79:21. The data for compounds **5** and **6** are compared in Table 1.

Comparison of the δ(NH) for **5a**−**g** and **6a**−**g** (Table S1, Supporting Information) indicates a higher field signal for the O- than for the S-derivative, except when Y′Y = $(CN)_2$ (Table S1). This could be due to the electronegativity difference of O and S. The solvent effect on δ(NH) is appreciable. For **5e**, it is at 3.26 ppm lower field in DMSO-d_6 than in $CDCl_3$.

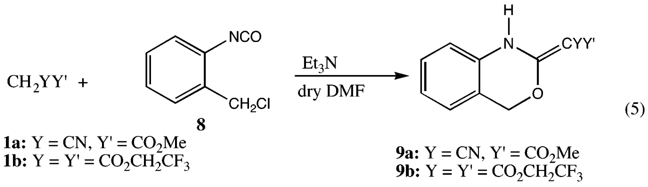
^{13}C NMR spectra of compounds **6** (Table S2, Supporting Information) differ from those of compounds **5** in that C_α is at 171.10−177.85 ppm and C_β is at 42.4−104.20, with the maximum $\Delta C_{\alpha\beta}$ of 135 ppm for **6e**. **6a**,[8b] **6e**,[8b,c] and **6f**[8b] were previously prepared by a different method from **1a**, **1c**, and **1f**, but only one isomer of **6a** or **6f** was observed by NMR. The configuration assignment was based on the same H-bond reasoning. **6d** was prepared similarly.[8a] **6a** was also prepared by cyclization of $MeO_2CC(CN)$═$C(SMe)NH_2$.[8d] The one isomer reported was presented in the *Z* configuration.



Under the same conditions, reaction of **1a**−**c** with γ-chloropropyl isocyanate (**4**) gave the 2-substituted methylene-1,3-oxazines **7a**−**c** (eq 4). The analogous 2-(chloromethyl)phenyl isocyanate (**8**) reacted with **1a** and **1b** to give the corresponding benzoxazines **9a** and **9b** (eq 5).

The structural assignments of **6**, **7**, and **9** are based on the elemental analysis and the similarity of the ^{1}H NMR (δ = 9.60−11.52 ppm for the NH group, Table S1) to those of compounds **5** (Table S1, Supporting Information).

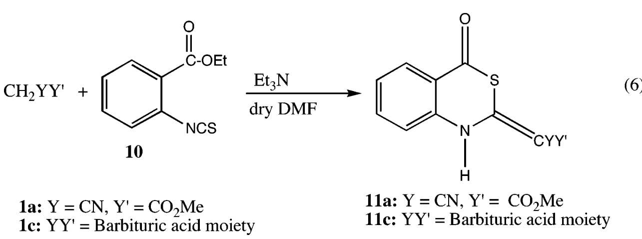
(10) (a) Fischer, G.; Rudorf, W.-D.; Kleinpeter, E. *Magn. Reson. Chem.* **1991**, *29*, 212. Fischer, G.; Kleinpeter E. *Magn. Reson. Chem.* **1991**, *29*, 204. Klinepeter, E.; Schulenberg, A. *Tetrahedron. Lett*. **2005**, *46*, 5997. (b) Kleinpeter, E.; Klod, S.; Rudorf, W.-D. *J. Org. Chem.* **2004**, *69*, 4317.



Reactions between **1a**, Et_3N, and PhNCO in 1,2-dichloroethylene at reflux or of [PhNHCOC(CN)CO_2CH_3]Et_3NH and $ClCH_2CH_2Cl$ in DMF at 100 °C were conducted, but no intermolecular cyclization was observed. After acidification of the reaction mixture, the corresponding known enol[3a] (*Z*)-PhNHC(OH)=C(CN)CO_2Me was obtained.

The reaction of the singly activated CH_3NO_2, CH_3CN, and CH_3COCH_3 with **2** under the normal reaction conditions gave no heterocycle but only the urea derivative [Cl$(CH_2)_2$NH]$_2$CO.

Replacement of an Ethoxy Group. On replacing the CH_2-Cl group of **8** by CO_2Et, ethoxy group expulsion giving a C=O-substituted heterocycle was successful only with ethyl *o*-isothiocyanatobenzoate (**10**), which gave with **1a** 47% of methyl cyano(1,4-dihydro-2-oxo-1*H*-3,1-benzothiazin-2-ylidene)acetate (**11a**) (eq 6). It shows signals for two isomers in a



78:22 *E*/*Z* ratio in $CDCl_3$. The assignment is based on our experience that the *E* isomer with a N−H···O=C hydrogen bond displays a lower field δ(NH) at 12.85 ppm compared with 12.13 ppm for the *Z* isomer. Compound **11a** was previously prepared by the reaction of 2,4-bis(methoxycarbonyl)-1,3-dithietane with methyl anthranilate, but only the *E* isomer was observed.[11] In DMSO-d_6, only one NH signal was observed at 11.50 ppm. This is likely due to a rapid interconversion of the two isomers, giving an average NH signal, since a higher rotational barrier was calculated in CD_2Cl_2 than in DMF for analogues of compounds **5**.[10b] However, in THF-d_8 only one NH signal was observed at δ 12.77, 12.78, 12.76, and 12.75 ppm at rt, 260, 200, and 180 K, respectively. An intermediate with an SH IR band, presented as the thioenol analogue of compound **13a** (see below) which then cyclizes to **11a**, was reported for this reaction.[11] With barbituric acid, **10** gave the analogue **11c** (eq 6).

Formation of the Open-Chain Enol or Thioenol. The reactions of the oxygen analogue of **10** and ethyl *o*-isocyanatobenzoate (**12**) with methyl cyanoacetate **1a** and with barbituric acid **1c** gave exclusively the noncyclized enol of amide **13a** and the enol on the barbituric acid moiety **13c**, respectively (eq 7). The OH and NH signals of **13a** are at 15.87 and 11.83 ppm, respectively, values typical for enols of amides with two EWGs groups on C_β. In DMSO-d_6, only signals at 11.44 and 5.99 ppm, ascribed to the NH and CH of the isomeric amide **13a′**, were observed. In CD_3CN, a 48:52 **13a′**/**13a** ratio was observed. Such an amide/enol equilibrium favors the enol in $CDCl_3$ and the

(11) Peske, K. *Synthesis* **1976**, 386.

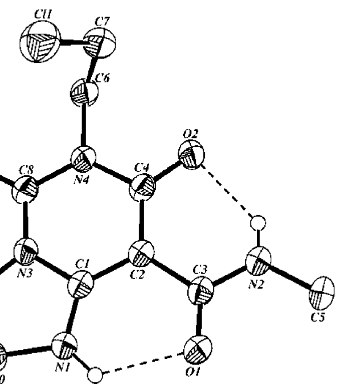
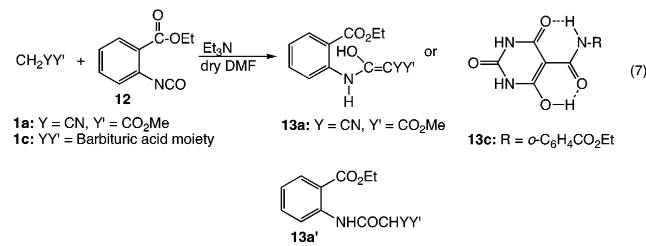
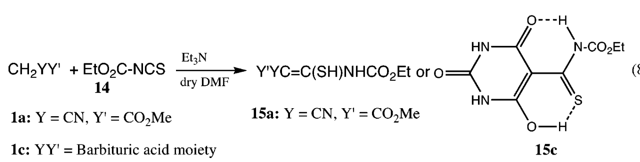


FIGURE 2. ORTEP drawing of **16a**.

amide in DMSO-d_6.[1−3] NMR data are in Tables S3 and S4 (Supporting Information).

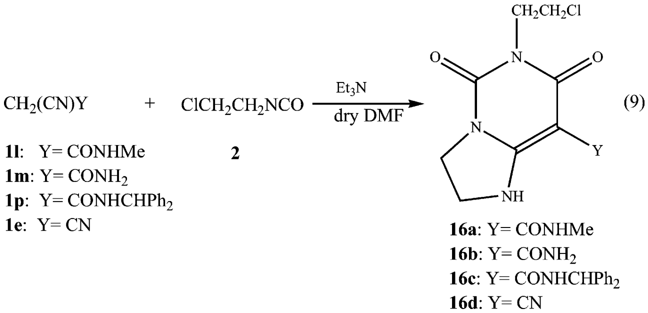
In contrast with the aromatic isothiocyanate which give heterocycles **11**, the aliphatic α-ethoxycarbonyl isothiocyanate (**14**) gaves with **1a** and **1c** the noncyclic thioenol **15a** and the enol on the barbituric acid moiety of the thioamide **15c** (eq 8). NMR data are in Tables S3 and S4 (Supporting Information).



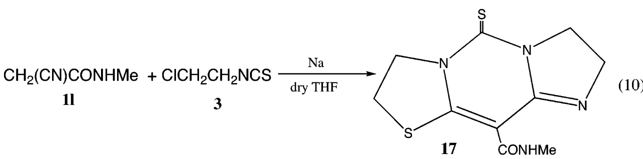


Formation of Polycyclic Products. In contrast with other compounds **1** (eq 2), the reactions of excess β-chloroethyl isocyanate **2** with substituted cyanoacetamides **1l**,**m**,**p** and malononitrile **1e** in the presence of Et_3N gave products which are apparently derived from one cyanoamide molecule and two molecules of **2**. One Cl was lost, while the chloroethyl group of the other was retained in the pyrimidinedione [6-(2-chloroethyl)-5,7-dioxo-1,2,3,5,6,7-hexahydroimidazo[1,2-*c*]pyrimidine-8-carboxamides] (or 8-nitrile) products **16** (eq 9). The data are in Tables S5 and S6. When using a 1:2:1 ratio of **1l**, Et_3N and **2**, both the cyclic **5l** and the bicyclic **16a** were formed in a 1:2 ratio, whereas at 1:2:2 or 1:1:3 ratio, only **16a** was formed. As expected, the yield of isolated **16** was much higher (86%) in the latter, compared with the former case (29%). With **1e** only **5e** was formed with a 1:1:1 ratio, but only **16d** with a 1:1:2 ratio. The structure of **16a** was determined by X-ray crystallography (Figure 2). Few bond lengths and angles are in Table S7. The full crystallographic data are given in the Supporting Information.

Reaction of cyanoacetamide **1l** with **3** in the presence of Na gave a product which arose from reaction of **1l** with two molecules of **3** (eq 10). It is not an analogue of **16a**, since microanalysis shows the absence of chlorine. Its analysis and ^{1}H NMR spectrum fit a tricyclic structure, which was tentatively assigned to 4-thioxo-2,3,5,6-tetrahydro-1-thia-3a,4a,7-triaza-5-



indacene-8-*N*-methylcarboxamide (**17**). Attempts to obtain crystals for X-ray crystallography have failed so far.



Discussion

Mechanism of Product Formation. **(a) Formation of the Monocycle and Bicycle Products.** A mechanism for formation of the monocyclic products **5** and the bicyclic product **16** is suggested in Scheme 1. In the initial step, the active methylene compound **1** reacts with the base to form the ambident anion $\mathbf{1}^-$, demonstrated for N-substituted cyanoacetamide. The *carbon* center of $\mathbf{1}^-$ attacks the carbon of the O=C=N moiety of **2** giving the ambident ion **18**. The negative *oxygen* site of the latter is in a favorable conformation to intramolecularly displace a Cl^- from the C−Cl bond, giving the unsaturated oxazoline **19**. A N=C−CH → HNC=C tautomerization, whose driving force is the formation of the stabilizing C=C/YY′ conjugation in **19**, gives the observed product **5**. Compounds **6**, **7**, **9**, and **11** are formed analogously. Formation of these 5- and 6-membered rings is favored over alternative cyclizations forming (i) an aziridine ring by Cl displacemet from the C−Cl bond by the *nitrogen* center, (ii) a 4-membered ring by attack of either the *nitrogen* or the *oxygen* centers of ion **18** on the CN group, or (iii) a 5-membered ring formed by *carbon* (C^-) attack on the C−Cl bond. For cyanoacetamides **1m**,**l**,**p**, **5** is formed from their preformed Na salts in THF. Whereas the non-CN compounds shown in eqs 2−4 give **5**, **6** or **7**, when the reaction of the three cyanoamides was conducted in the presence of excess Et_3N it gave the bicyclic products **16a**−**c**.

Formation of compounds **16** is ascribed to a series of consecutive reactions starting with **18** and another molecule of **2**. Their structural assignment is based on microanalysis and NMR data. An X-ray diffraction of **16a** (Figure 2) shows a CH_2CH_2Cl moiety and O(2)···H(2N) and O(1)···H(1N) hydrogen bonds lengths of 2.02(3) and 2.13(3) Å. The N(2)···O(2) and N(1)···O(1) nonbonding distances are 2.688(3) and 2.717(2) Å, and the C(1)−C(2) double bond length is 1.396(3) Å. The ^1H NMR δ(N−H) are at δ 8.91−9.85 (Table S5, Supporting Information), and in the ^{13}C NMR $\delta C_\alpha = 165.6-167.8$, δC_β ca. 81, and $\Delta C_{\alpha\beta} = 84.6-87$ ppm (Table S6, Supporting Information). A long-range $^1H-^{13}C$ correlation (HMBC) allows detection of 2- and 3-bond correlations which provide a full ^{13}C assignment, in line with the X-ray structure.

Formation of **16** starts with attack of the N^- center of **18** on the carbon of the N=C=O moiety of **2** giving the ambident ion **20**, presumably resembling the beginning of the nucleophilic polymerization of organic isocyanates.[12] The nitrogen site of **20** attacks the adjacent cyano group, forming an $=N^-$ substituted pyrimidinedione moiety. Such cyclizations on cyano groups are well-known.[13] A Cl^- displacement by the O^- site of **20** from the C−Cl bond which should give oxazoline **23** or its tautomeric oxazolidine was not observed, despite its resemblance to the **18** → **19** → **5** reaction. Apparently, the attack of the N-site of **20** on the CN group is faster.

Reactions of either the nitrogen or oxygen sites of **20** on the other CH_2CH_2Cl group should give alternative stable 5-membered oxazolidine or pyrazoline rings, which were not observed.

Attack of the new nitrogen anion on the adjacent C−Cl bond of **21** forms an imidazoline ring fused to the pyrimidine ring in product **22**. Tautomerization of the unconjugated N=C−CH moiety in the 5-membered ring shifts the double bond to the 6-membered ring and forms **16**, which is stabilized by $C=C(CO)_2$ conjugation. An internal rotation in **20** followed by attack of the O^- on the adjacent CN and cyclization and tautomerization to give the strained product **24** with fused 6- and 7-membered rings was not observed.

In the cyanomalonamide anion **18**, a proton transfer from the CONHR group to the N of the $CON^-CH_2CH_2Cl$ will give an isomer of ambident ion **18**. Analogous processes to those in Scheme 1 will give isomers of **16** and **24** where the R and the CH_2CH_2Cl groups were exchanged, but none of these or other products had been observed.

There are still insufficient data derived from Scheme 1 for broad generalizations since a small variation in structure, base, or concentration can lead to unexpected products. Nevertheless, in the formation of **16** a competition between nucleophilic attacks on a C−Cl bond and on an adjacent CN by either an O^- or an N^- center of an ambident ion occurs; the latter route is preferred when the ring formed is a 5- or 6-membered ring.

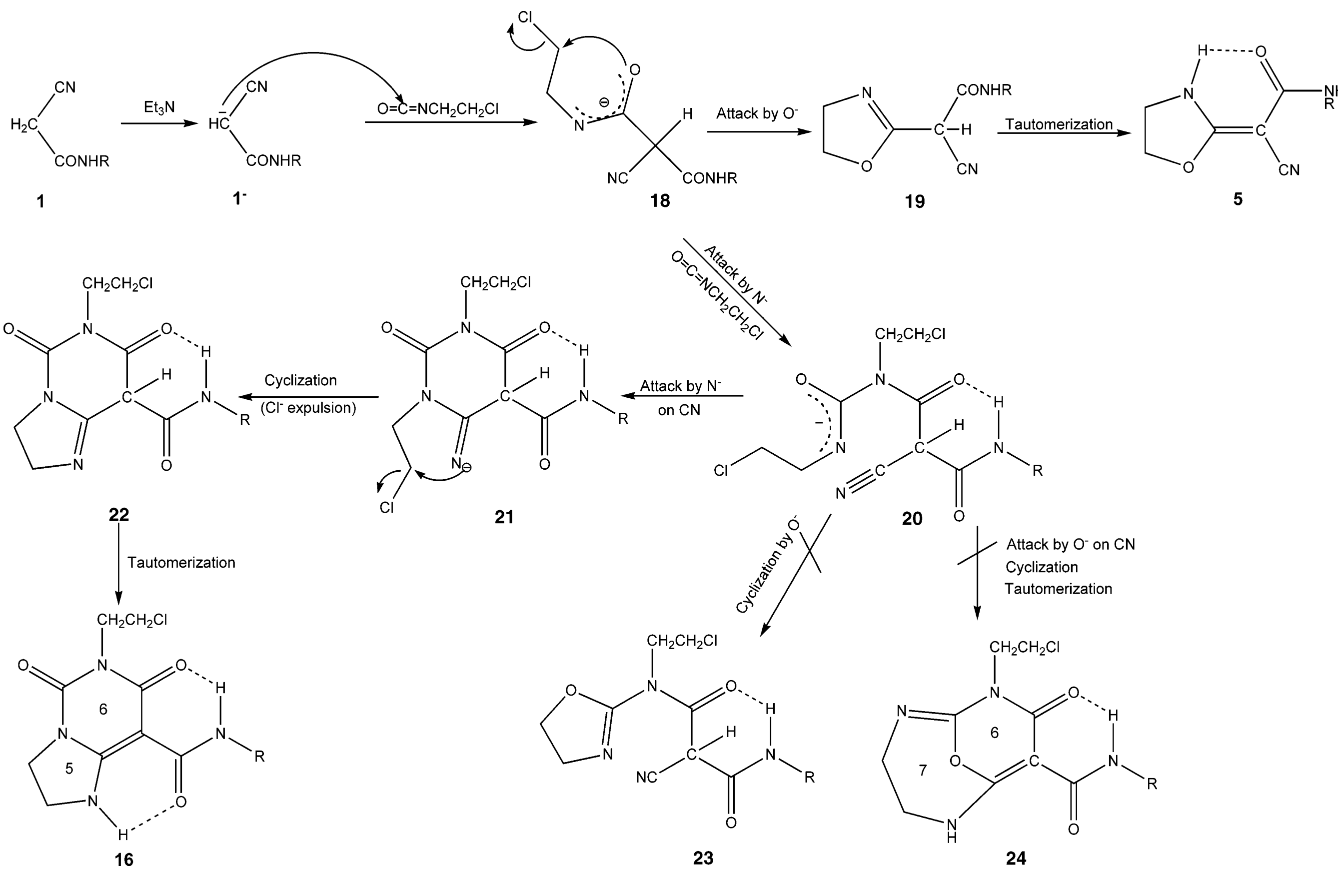
Why are products **5** are formed from the sodium salt of the cyanoacetamides, but **16** is formed in the presence of Et_3N, whereas **5** is formed from other precursors **1**? Formation of the bicyclic **16** requires precursors containing cyano groups. Second, although different ion pairing with Na^+ vs Et_3N^+ should affect the N^- vs O^- selectivity of the reactions leading to **5** and **16**, in the highly dissociating DMF solvent, ion pairing should be insignificant. Third, the bimolecular reaction leading to **16** should be faster with a higher concentration of **2**, as is indeed observed. Both this rate and that for formation of **5** should increase with the sodium salt which generates more of the reacting anion $\mathbf{1}^-$, so that the product distribution should not change. However, the fact that the **5**/**16** ratio changes also with the Et_3N concentration suggests that both reactions compete, but with higher concentration of $\mathbf{1}^-$ the bimolecular reaction with **2** becomes dominant. At present it seems that a much more comprehensive study is required to understand this behavior.

Addition of $\mathbf{1}^-$ to simple isocyanates forms **25**, the analogue of **18** lacking a nucleofuge on R. Protonation of **25** on nitrogen forms amide **26**, and on oxygen it gives the hydroxyimine **27** which can be rearranged to enol **28**. Compounds **26**−**28** can also interconvert by an ionization−protonation route (eq 11). However, anion **18** gives no observable enol, although its

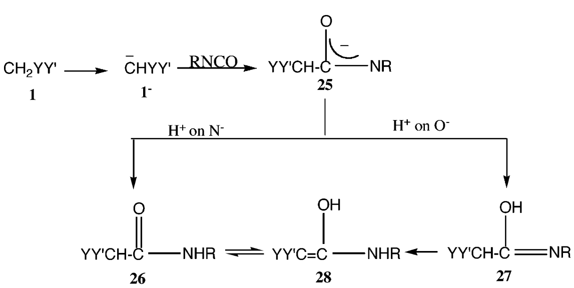
(12) Ulrich, H. *Chemistry and Technology of Isocyanates*; Wiley: New York, 1996; pp 51−52.

(13) E.g., (a) Meyers, A.; Sircar, J. C. In *The Chemistry of the Cyano Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1970; Chapter 8, p 341. (b) Fatiadi, A. J. In *The Chemistry of Functional Groups. Supplement C. The Chemistry of Triple-bonded Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; Chapter 26, pp 1243−1250.

SCHEME 1. Mechanism for Formation of 5 and 16



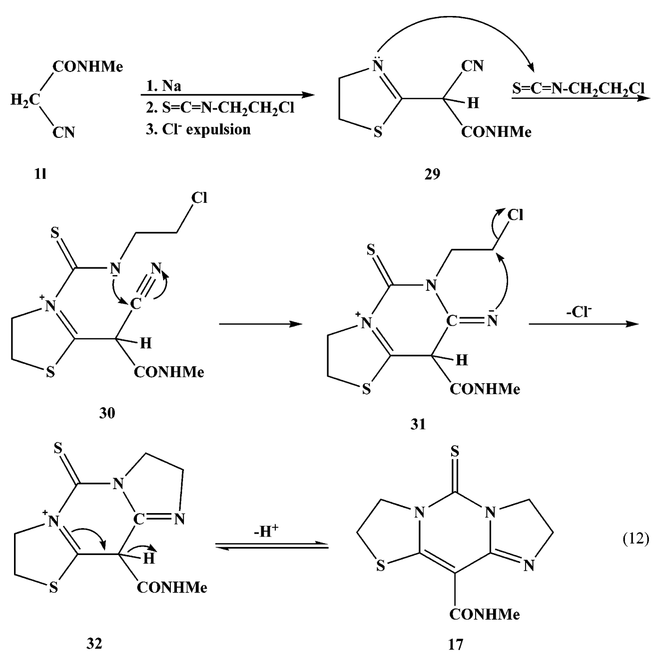
protonation should be fast. If **18** and its enol are present in an equilibrium, they will disappear by irreversible cyclization to **19**. The more nucleophilic enolate should be the active nucleophile. Since **18** is sufficiently long-lived to participate in the reaction forming **16**, the Cl^- expulsion is not concerted with formation of **18**.



(11)

(b) Formation of the Tricyclic Product. A tentative mechanism for the formation of the tricyclic **17** is shown in eq 12. The initial nucleophilic attack of the anion of **1l** on **3** followed by Cl^- expulsion gives the thiazoline **29** (cf. formation of **19** in Scheme 1). The N site of **29** attacks the ═C═ of another molecule of **3**, forming the ambident ion **30**, whose N^- site attacks a CN, forming the imine ion **31**, which displaces Cl^- to give **32**. A proton loss results in formation of **17**.

(**c) Competition of Various Routes when EtO^- Is a Potential Leaving Group.** A delicate balance between protonation and nucleofuge expulsion occurs in the reactions of **10** and **12** where the potential EtO^- nucleofuge is relatively poor compared with Cl. Apparently, protonation is faster than C═O addition in the anion derived from **12**, so that enol **13** is formed.



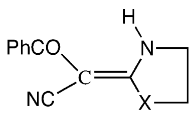
(12)

However, the analogue anions formed from the isothiocyanato derivative **10** have a much more nucleophilic S^- center, so that an efficient nucleofuge expulsion giving **11a** and **11c** is preferred to a thioenol formation by protonation. The thioenol analogue of **11a** was tentatively written as an intermediate which cyclizes to **11a** under neutral conditions,[11] so that we may have missed such an intermediate under our basic conditions. A thiolate reaction center is insufficient to give cyclization to a high energy strained 4-membered ring. This happens in the reaction of **14** for which protonation of the intermediate anion to the open-chain thioenol **15a** or the enol-thioamide **15c** is preferred over cyclization.

Internal Rotation in Compounds 5 and 6. The unsymmetrical compounds **5** display signals for an apparent single isomer at rt, whereas the unsymmetrical compounds **6** show two isomers at rt. By lowering the temperature of solutions of several compounds **5**, the rate of internal rotation around the C(1)−C(2) formal double bond is reduced and two isomers are observed. Consequently, the rotational barrier around the C(1)−C(2) bond is lower for **5** than for **6**.

Precedents for lower barriers in O- vs S-derivatives are known for push−pull alkenes, $Me_2NCH{=}CH(C{=}X)R$,[14] for amides vs thioamides,[15] and for substituted oxa- vs thiadiazoles.[16] The *N*-methylthiazolidine analogue of **5o** displays a low barrier of <9.4 kcal/mol in toluene.[17]

The closer compounds to ours are **5p** and **6h**. The oxygen derivative **5p** showed only signals for one isomer, and the rotational barrier could not be measured, whereas **6h** displayed two isomers with $\Delta G^{\ddagger}$ (kJ/mol) of 67.2 (T_c 330 K) in DMF, 68.2 (T_c 335 K) in DMSO, and ≥76.9 (T_c > 380 K) in CD_2Cl_2. The HF/6-311G** calculated barriers for **5p** and **6h** are 85.2 and 112.7, respectively.



5p X = O
6h X = S

Consequently, $\Delta G^{\ddagger}$(**6h**) ≫ $\Delta G^{\ddagger}$(**5p**) and two isomers of **6h** were observed. It was concluded that the length of the central double bond is the parameter to quantify the push−pull effect and that the difference between the high occupation of the π and the low occupation of the π^* orbital of the O and S derivatives accounts for the difference in the barriers of the N,S- and N,O-heterocycles.[10b]

Experimental Section

Materials. Compounds **1** were either commercial or prepared by standard procedures. Compounds **2**−**4**, **8**, **10**, **12**, and **14** were purchased from a commercial supplier.

NMR and Analytical Data. The NMR data for compounds **5**−**7**, **9**, **10**, and **11c** are given in Tables S1 and S2, for **14** and **15c** in Tables S3 and S4 and for **16a**−**d** in Tables S5 and S6. Analytical data, mp's, and yields for all compounds are given in Table S8 (Supporting Information).

Reaction of β-Chloroethyl Isocyanate 2 with 1a,b, 1d−j, and 1n,o. The procedure used with minor modifications in the reaction rates, the solvent, and the yields is demonstrated for bis(2,2,2-trifluoroethyl) malonate **1b**: A solution of **1b** (1.35 g, 5 mmol) in dry DMF (10 mL) under nitrogen turned warm when dry Et_3N (1.5 mL,10 mmol) was added. After being stirred for 10 min, **2** (0.43 mL, 5 mmol) was added, the solution became warm, and Et_3NHCl was formed immediately. After being stirred overnight at rt, the solution was filtered, the filtrate was added dropwise to a cold 2 N HCl solution (50 mL), and the white precipitate formed was filtered, washed with cold water (100 mL), and dried at rt, giving 1.46 g (4.3 mmol, 87%) of pure **5b**, mp 118 °C. Crystals for X-ray diffraction of **5f** and **5h** were obtained from chloroform. The acetylacetone derivative **5i**, mp 134 °C, was crystallized in 79% yield during filtration of the Et_3NHCl from the DMF solution.

The dimedone derivative **5j** was prepared similarly except that the precipitate obtained after the addition of **2** contained both **5j** and Et_3NHCl. Shaking with cold water (50 mL) gave pure **5j**, mp 206−7 °C, in 82% yield after filtration and drying.

Reaction of β-Chloroethyl Isocyanate 2 with *N,N*-Dimethylcyanoacetamide 1k, *N*-Methylcyanoacetamide 1l, and Cyanoacetamide 1m. On addition of **1k** (0.56 g, 5 mmol) to a suspension of Na (0.12 g, 5.2 mmol) in dry THF (20 mL) under nitrogen hydrogen was evolved. After the mixture was stirred overnight at rt, a white precipitate was formed. A solution of **2** (0.43 mL, 5 mmol) in dry THF (10 mL) was added dropwise to the solution during 30 min, and the precipitate was dissolved. The reaction mixture was refluxed for 4 h, and the formed NaCl was filtered. The solvent was evaporated, giving crude **5k**. Crystallization from EtOAc−petroleum ether (40−60 °C) followed by cooling for 48 h gave 0.67 g (3.70 mmol, 74%) of **5k**, mp 160 °C.

Reaction of β-Chloroethyl Isothiocyanate 3 with 1a,b and 1d−g. The reactions of **1a**,**b** and **1d**−**g** with **3** were conducted as described for the reaction with **2**. Only with **1g** (1.77 g, 10 mmol) was the precipitate obtained immediately after addition of **3** (0.96 mL, 10 mmol) a mixture of **6g** and Et_3NHCl. Cold water (50 mL) was added with stirring for 20 min. The insoluble solid was filtered, washed with cold water (100 mL), and dried at 60 °C, giving 2.39 g (9.1 mmol, 91%) of pure **6g**, mp 204 °C dec. In the preparation of **6f**, after the Et_3NHCl was filtered and the solution was poured into a 2 N HCl solution, no precipitate was obtained. The mixture was extracted (3 × 50 mL EtOAc), washed with water (2 × 100 mL), and dried, most of the solvent was evaporated, and the remainder gave after standing overnight 88% yield of yellow crystals of **6f**, mp 80−2 °C.

Reaction of γ-Chloropropyl Isocyanate 4 and *o*-2-Chloromethyl Phenyl Isocyanate 8 with Compounds 1a−c and 1a,b, Respectively. The procedure is identical with that described for the reaction with **2**, except for a slower reaction when Et_3NHCl started to precipitate only 2 h after the addition of the isocyanates **4** and **8**.

Reaction of Barbituric Acid 1c with β-Chloroethyl Isocyanate 2 and Isothiocyanate 3, γ-Chloropropyl Isocyanate 4, and Ethyl *o*-Isothiocyanatobenzoate 10. A similar procedure used with all of these compounds is demonstrated for the reaction with **2**: To a $CaCl_2$-protected solution of barbituric acid (1.28 g, 10 mmol) in dry DMF (10 mL) was added dry Et_3N (6 mL, 20 mmol). The solution became warm, and a precipitate was formed. After being stirred for 15 min at rt, **2** (0.85 mL, 10 mmol) was added, and the mixture was stirred overnight at rt. After 4 h reflux the yellow color turned brown. The precipitate is a mixture of Et_3NHCl and **5c**. After being shaken with cold water (100 mL), the remaining solid was filtered, washed with cold water (200 mL) and then with acetone (100 mL), and dried at rt, giving 1.88 g (95%) of pure **5c**, mp 217 °C dec.

A similar procedure, using barbituric acid (0.128 g, 1 mmol) and **10** (0.173 g, 1 mmol) gave the product **11c** (89%), mp 385 °C dec. EtOH was also identified.

Reactions of Barbituric Acid 1c with Ethyl *o*-Isocyanatobenzoate 12 and Ethoxycarbonyl Isothiocyanate 14. The procedure for barbituric acid (0.15 g, 1.2 mmol) with **12** (0.23 mL, 1.2 mmol) resembles that for the reaction with **10**, except that after the addition of **12** and stirring for 30 min, the precipitate had dissolved, and after additional stirring overnight and acidification with cold 2 N HCl solution (20 mL), 0.32 g (1 mmol, 84%) of the enol **13c**, mp 220 °C, was obtained.

(14) Dabrowski, J; Kozerski, L. *Org. Magn. Reson.* **1972**, *4*, 137. Dabrowski, J.; Kamienska-Trela, K. *Org. Magn. Reson.*, **1972**, *4*, 421. Filleux-Blanchard, M. L.; Mabon, F.; Martin, G. J. *Tetrahedron. Lett* **1974**, 3907. Filleux-Blanchard, M. L.; Clesse, F.; Bignebat, J.; Martin, G. J. *Tetrahedron Lett.* **1969**, 981.

(15) Piccinni-Leopardi, C.; Fabre, O.; Zimmerman, D.; Reisse, J.; Cornea, F.; Fulea, C. *Can. J. Chem.* **1977**, *55*, 2649.

(16) Liljefors, T. *Org. Magn. Reson.* **1974**, *6*, 144.

(17) Shvo, Y.; Belsky, I. *Tetrahedron* **1969**, *25*, 4649.

In a similar procedure for the reaction of barbituric acid (1.28 g, 10 mmol) with **14** (1.31 g, 10 mmol), the precipitate was dissolved immediately and the warmed mixture turned orange. When the solution was dropped into cold 2 N HCl (20 mL), the enol **15c** (2.43 g, 8.97 mmol), mp 365 °C dec, was obtained in 90% yield.

Reaction of Methyl Cyanoacetate 1a with Ethyl *o*-Isocyanatobenzoate 12, Ethyl *o*-Isothiocyanatobenzoate 10, and Ethoxycarbonyl Isothiocyanate 14. The procedure is demonstrated in the reaction with **12**. To a mixture of **1a** (0.1 g, 1 mmol) and dry Et_3N (0.3 mL, 2 mmol) in dry DMF (2 mL) in a $CaCl_2$-protected flask was added **12** (0.17 mL, 1 mmol), and the solution became warmer. After being overnight at rt, the yellow solution turned brown. It was added dropwise into a cold 2 N HCl solution (10 mL), and the yellow precipitate formed was filtered, washed with cold water (20 mL), and dried at rt, giving 0.27 g (0.93 mmol, 93%) of the crude enol **13a**. Recrystallization from EtOAc−petroleum ether (40−60 °C) gave the pure enol, mp 124 °C.

In contrast, the reaction of **1a** (100 mg, 1 mmol) with **10** (0.17 mL, 1 mmol) gave 122 mg (4.69 mmol, 47%) of **11a**, mp 207−8 °C, and ethanol.

The reaction between **1a** (1 g, 10 mmol) and **14** (1.31 g, 10 mmol) gave 2.02 g (8.78 mmol, 88%) of the thioenol **15a**, mp 151−2 °C.

Reaction of β-Chloroethyl Isocyanate with Cyanoacetamide 1m, *N*-Methylcyanoacetamide 1l, and *N*-Benzhydrylcyanoacetamide 1p in the Presence of Et_3N. The reaction is demonstrated for the reaction forming **16a** from **1l**. Products **16b** and **16c** were obtained similarly: To a solution containing **1l** (0.98 g, 10 mmol) and dry Et_3N (3 mL, 20 mmol) was added **2** (0.85 mL, 10 mmol). After the mixture was stirred overnight at rt, the Et_3NHCl was filtered. The filtrate was added dropwise to a cold solution of 2 N HCl, and a precipitate was formed only after the solution was kept overnight in the refrigerator. It was filtered and dried at rt, giving 0.78 g (2.86 mmol, 57% based on **2**, 29% based on **1l**) of cotton-like crystals, mp 260−1 °C. The solid was dissolved in $CHCl_3$, and the solvent was evaporated slowly, giving **16a** as needles suitable for X-ray diffraction (Figure 2). When the initial ratio of **2** to **1l** was 3:1, the initial precipitate contained both Et_3NHCl and **16a**. The Et_3NHCl was then dissolved in 2 N HCl solution, and the remaining **16a** was obtained in 86% (based on **1l**) after crystallization. When the **1l**/Et_3N/**2** molar ratio was 1:1:1, both **5** and **16** were formed in a 1:2 ratio. Anal. Calcd for **16a** $C_{10}H_{13}ClN_4O_3$: C, 44.04; H, 4.77; N, 20.55; Cl, 13.03. Found: C, 44.21; H, 4.77; N, 20.59; Cl, 12.80.

Reaction of β-Chloroethyl Isothiocyanate 3 and *N*-Methylcyanoacetamide 1l in the Presence of Na. To a solution of **1l** (0.98 g, 10 mmol) in dry THF (30 mL) under nitrogen was added Na (0.23 g, 10 mmol), and hydrogen gas evolved. A solution of **3** (0.96 mL, 10 mmol) in dry THF (20 mL) was added dropwise during 20 min. The mixture was refluxed for 6 h, and NaCl was precipitated. The residue was added dropwise into a cold solution of 2 N HCl, and the yellow precipitate formed was filtered and dried, giving 0.68 g (2.54 mmol, 51%) of **17**, mp 282−4 °C. Anal. Calcd for $C_{10}H_{12}N_4OS_2$: C, 44.78; H, 4.48; N, 20.89. Found: C, 44.75; H, 4.54; N, 20.50; Cl, 0. ^1H NMR ($CDCl_3$, rt) δ: 2.90 (3H, d, J = 4.8 Hz, Me), 3.19 (2H, t, J = 7.7 Hz, SCH_2), 3.95−4.14 (4H, m, NCH_2CH_2N), 4.57 (2H, t, J = 7.7 Hz, NCH_2). ^{13}C NMR ($CDCl_3$, rt) δ: 25.93 (q, J = 138.2 Hz, Me), 27.22 (t, J = 145.4 Hz, SCH_2), 49.90 (t, J = 148.1 Hz, NCH_2), 52.41 (t, J = 144.4 Hz, NCH_2), 54.20 (t, J = 148.4 Hz), 97.44 (s, C_β); 150.58 (s, C═N), 158.96 (s, C═O), 163.93 (s, C═S), 169.12 (s, C_α).

Acknowledgment. We are indebted to Dr. Shmuel Cohen for the X-ray structure determination and to the Israel Science Foundation for support.

Supporting Information Available: The ORTEPs of **5f** and **5h**, the cif's of **5f, 5h** and **16a**, and Tables S1−S8 of NMR, crystallographic and analytical data. This material is available free of charge via the Internet at http://pubc.acs.org.

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