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New Method for Thioamide Synthesis from 1,3-Dithietane-2,4-diylidene-bis(benzoyl- or 2-furoyl-acetonitrile)

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Dedicated to Prof. Dr. Rolf Borsdorf on the Occasion of his 65th Birthday

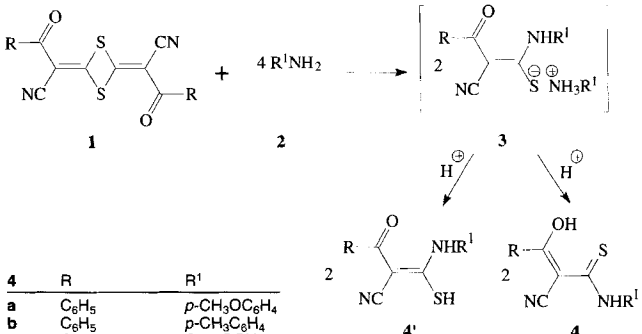
It is known that alkyl 1,3-dithietane-2,4-diylidene-bis(cyanoacetate) easily undergoes nucleophilic substitution reactions with amines [1, 2] on positions 2 and 4 of the heterocyclic ring with ring opening and subsequent formation of dinucleophiles of the type of 3-amino-2-cyano-3-mercaptoacrylates. Starting from these materials, a great number of compounds both acyclic and heterocyclic can be obtained in just one step, which are of great interest not only from synthetic but also from biological point of view, such as diazepines [3, 4], oxazepines [5, 6], substituted 1,3,4-oxadiazoles [7, 8] as well as other heterocyclic compounds [9, 10, 11, 12].

Recently, the dithietanes **1** derived from furoyl and benzoylacetonitrile were prepared. This fact enables the preparation of new acyclic and heterocyclic compounds with potential biological activity [13].

For that reason, we investigated the reactions of the dithietanes **1** with amines **2**, the results of which are presented here.

The use of an ethanol–chloroform mixture (1:1) as a solvent in reactions of this type is recommended in the literature [1, 2, 3, 4]. Under these conditions, we did not obtain good results. Therefore, dimethylformamide–chloroform was used, in which the reactions proceed easily with good yields. By adding hydrochloric acid to the reaction mixture the thioamides **4** precipitated.

The 2-cyano-3-hydroxy-thioacrylamide structure of compounds **4** was confirmed by NMR and IR spectra. A singlet between 16 and 17 ppm corresponds to a signal, which is characteristic of enolic protons in intramolecular hydrogen bonds [14, 15]. In the ^{13}C-NMR of **4c** a signal at δ = 186.1 ppm was found, which can be assigned to the C=S group [16]. Furthermore, the IR absorptions between 1230 and 1290 cm^{-1} are consistent with thiocarbonyl groups [14] and the



4	R	R¹
a	C_6H_5	p-$CH_3OC_6H_4$
b	C_6H_5	p-$CH_3C_6H_4$
c	C_6H_5	$C_4H_3OCH_2$
d	C_4H_3O	p-$CH_3OC_6H_4$
e	C_4H_3O	p-$CH_3C_6H_4$
f	C_4H_3O	$C_4H_3OCH_2$

Scheme 1

lack of signals belonging to carbonyl and thiol groups allows the exclusion of the alternative tautomeric structure **4'**.

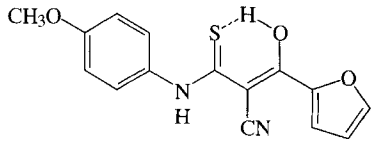
The IR spectrum of **4c** in carbon tetrachloride shows two absorptions, one at 3370 cm^{-1}, which can be assigned to a hydroxyl group intramolecularly bounded by hydrogen bridge, and the other one at 3305 cm^{-1} belonging to the amino group.

In order to gain some insight about the stereochemistry of the thioamides **4**, we carried out semiempirical calculations (PM3) of full geometry optimization for compound **4d**. As start geometries those of the *Z-s-cis*, *Z-s-trans*, *E-s-cis* and *E-s-trans* were used obtained by means of molecular mechanics using the program PC-MODEL. The results are shown in Table 1.

Table 1 Energy values calculated for compound **4d**

Starting Geometry	E_T (eV)	ΔE (kJ/mole)
Z-s-cis	-3349.62	0.00
Z-s-trans	-3349.62	0.31
E-s-cis	-3349.34	27.46
E-s-trans	-3349.41	20.75

As can be seen from the data given in Table 1, in case of the Z-configuration the same result was obtained (the *s-cis* form) starting from both *s-cis* and *s-trans*. It seems that an energetic barrier for the transformation of *Z-s-trans* into *Z-s-cis* does not exist or it is extremely low. In the *Z-s-cis* conformation the hydrogen bond, suggested by NMR, can be formed making this geometrical form to be the most stable one. The calculated bond order for this hydrogen bond is 0.144 and the calculated distance between these two atoms is 1.835 Å, which is in the range of this class of bonds. The energy values of the *E*-configuration are higher than those obtained for Z, as can be expected. Considering a Maxwell–Boltzman distribution, it is calculated that 100% of the *Z-s-cis* form exist at 25 °C. The results described here are in good agreement with experimental data. The most probable structure for **4d** is shown in Scheme 2.



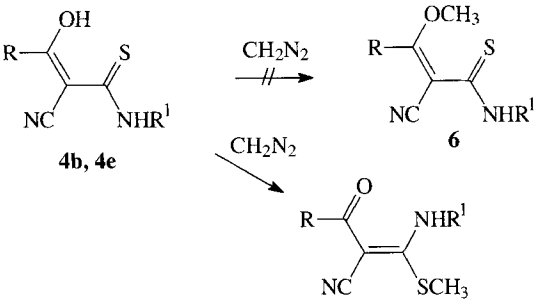
4d

Scheme 2

The existence of a hydrogen bonding between enolic protons and sulphur atoms has also been reported before by Larsson, Lawesson [15] and Rudorf [17].

The synthesis of thioamides starting from dithietanes **1** by reaction with amines is characterized by its simplicity and versatility and permits the preparation of a great number of different thioamides. Other methods described elsewhere have the handicap of being too specific [18] or too exigent in the reaction conditions [19].

The methylation of the thioamides **4b** and **4e** with diazomethane [20] was performed to obtain, possibly, a new type of push–pull systems **6**.



5	R	R^1
a	C_6H_5	p-$CH_3C_6H_4$
b	C_4H_3O	p-$CH_3C_6H_4$

Scheme 3

However, the NMR and IR spectra of the reaction products proved that compounds **5** were formed instead of **6**. In the ^1H NMR spectra of **5a** and **5b** the CH_3S signal was found at δ/ppm = 2.32 and 2.29, respectively. This fact, joined with the absence of signals in the typical region of methoxy protons, proves that an *S*-alkylation had taken place. These results are in good agreement with those reported by Larsson and Lawesson for thioesters of β-hydroxydithiocinnamic acids [15].

Also the ^{13}C NMR spectra are in good accordance with the proposed structures. The ^{13}C signals at δ/ppm = 191.8 and 175.5, respectively, can be assigned to the carbonyl group.

In the IR spectra of ketene-*N,S* acetals **5** the absorptions from carbonyl groups appear approximately at 1590 cm^{-1}. This abnormally low position can be explained on the basis of hydrogen bonds between these groups and the amino group of these molecules, which produces a decrease of the force constant of the carbonoxygen double bond. Similar results have been obtained by other authors [21, 22].

The methylation with dimethyl sulfate as reported by Tominaga *et al.* [23] gave the same results as before, but the yields were raised.

Finally, the identity of the compounds obtained by this method were compared with those obtained by the reactions of ketene-*S,S* acetals derived from furoyl and benzoylacetonitriles with amines [13]. It was found that the reaction products obtained for both ways are identical.

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Experimental

Melting points were determined on a BÜCHI hot stage microscope and are uncorrected. The recording of NMR spectra was performed on spectrometers BRUKER ACF 250 and JEOL FX90Q. The IR spectra were obtained on an FTIR Philips PU9600 spectrophotometer and mass spectra were obtained on an LKB 9000 spectrometer.

Elemental analysis was performed on an EAGER 200-

SUMMARY.

The calculations were performed on an IBM PC 80486DX/33MHz by means of the program MOPAC ver. 6.0 using PM3 Hamiltonian.

Synthesis of 2-cyano-3-hydroxy-thioacrylamides (4) General procedure

0.01 mole dithietane **1** and 0.02 mole amine **2** in 20 mL of a mixture of dimethylformamide/chloroform (1:1) were refluxed for two hours. The mixture was left until it reached room temperature, then 10 mL ethanol were added, and it was acidified with hydrochloric acid. The formed solids were filtered and recrystallized from ethanol.

2-Cyano-3-hydroxy-3-phenyl-N-(p-methoxyphenyl)-thioacrylamide (**4a**)

Yellow needles; yield 1.92 g (61.5%), *m.p.* 172–173 °C. – ^{1}H NMR($CDCl_3$): δ/ppm = 16.56 (1H, s, OH); 9.04 (1H, s, NH); 7.85 (2H, m, *o*-C_6H_5); 7.55 (3H, m, *m*-C_6H_5, *p*-C_6H_5); 7.31(2H, m, *o*-C_6H_4); 6.98 (2H, m, *m*-C_6H_4); 3.83 (3H, s, O–CH_3). – IR(KBr): ν_{max}/cm^{-1} = 3269 OH, 3216 NH, 2208 CN, 1253 C=S.

$C_{17}H_{14}N_2O_2S$	Calcd.	C 65.80	H 4.51	N 4.03	S 10.32
(310.4)	Found	C 65.95	H 4.64	N 4.19	S 9.72

2-Cyano-3-hydroxy-3-phenyl-N-(p-methylphenyl)-thioacrylamide (**4b**)

Yellow needles; yield 1.64 g (55.5%), *m.p.* 171–172 °C. – ^{1}H-NMR($CDCl_3$): δ/ppm) =16.56 (1H, s, OH); 9.04 (1H, s, NH); 7.89 (2H, m, *o*-C_6H_5); 7.55 (3H, m, *m*-C_6H_5, *p*-C_6H_5); 7.32(4H, m, C_6H_4); 2.39 (3H, s, CH_3). – IR(KBr): ν_{max}/cm^{-1} = 3284 OH/NH, 2208 CN, 1298 C=S.

$C_{17}H_{14}N_2OS$	Calcd.	C 69.38	H 4.76	N 9.52	S 10.88
(294.4)	Found	C 68.92	H 4.73	N 9.35	S 11.30

2-Cyano-3-hydroxy-3-phenyl-N-(2-furyl-methyl)-thioacrylamide (**4c**)

White needles; yield 1.31 g (46.0%); *m.p.* 132–133 °C. – ^{1}H NMR($CDCl_3$): δ/ppm = 16.26 (1H, s, OH); 7.93 (1H, s, NH); 7.85 (2H, m, *o*-C_6H_5); 7.54 (3H, m, *m*-C_6H_5, *p*-C_6H_5); 7.41 (1H, q, 5-C_4H_3O); 6.37 (2H, m, 3,4-C_4H_3O); 4.87 (2H, s, CH_2). – ^{13}C-NMR($CDCl_3$): δ/ppm = 186.1 (C=S); 181.8 (HO–C=); 148.0 (2-C_4H_3O), 143.1 (5-C_4H_3O); 133.8 (*i*-C_6H_5); 132.6 (*p*-C_6H_5); 128.7 (*o*-C_6H_5); 128.7 (*m*-C_6H_5); 117.5 (CN); 110.7 (3-C_4H_3O); 109.6 (4-C_4H_3O); 86.2 (NC–C=), 41.8 (CH_2). – IR(KBr): ν_{max}/cm^{-1} = 3305 OH/NH, 2201 CN, 1282 C=S.

$C_{15}H_{12}N_2O_2S$	Calcd.	C 63.38	H 4.22	N 9.85	S 11.25
(284.3)	Found	C 63.09	H 4.33	N 9.78	S 11.08

2-Cyano-3-(2-furyl)-3-hydroxy-N-(p-methoxyphenyl)-thioacrylamide (**4d**)

Yellow needles; yield 2.02 g (67.0%); *m.p.* 186 °C. – ^{1}H NMR($CDCl_3$): δ/ppm = 16.43 (1H, s, OH); 8.99 (1H, s, NH); 7.74 (1H, q, 5-C_4H_3O); 7.56 (1H, q, 3-C_4H_3O); 7.36 (2H, d, *o*-C_6H_4); 7.01 (2H, d, *m*-C_6H_4); 6.68 (1H, q, 4-C_4H_3O); 3.84 (3H, s, OCH_3). – IR(KBr): ν_{max}/cm^{-1} = 3253 OH/NH, 2212 CN, 1252 C=S.

$C_{15}H_{12}N_2O_3S$	Calcd.	C 60.00	H 4.00	N 9.33	S 10.66
(300.3)	Found	C 59.98	H 4.08	N 9.31	S 10.25

2-Cyano-3-(2-furyl)-3-hydroxy-N-(p-methylphenyl)-thioacrylamide (**4e**)

Greenish-yellow needles; yield 2.23 g (77.9%), *m.p.* 180–181 °C. – ^{1}H NMR($CDCl_3$): δ/ppm = 16.43 (1H, s, OH); 9.01 (1H, s, NH); 7.74 (1H, q, 5-C_4H_3O); 7.59 (1H, q, 3-C_4H_3O), 7.26 (4H, m, C_6H_4); 6.64 (1H, q, 4-C_4H_3O); 2.39 (3H, s, CH_3). – IR(KBr): ν_{max}/cm^{-1} = 3250 OH/NH, 2212 CN, 1236 C=S. – MS: *m/e* (%): 300 (78), 283 (4), 267 (16), 95 (99), 77 (8), 27 (100).

$C_{15}H_{12}N_2O_2S$	Calcd.	C 63.38	H 4.22	N 9.85	S 11.26
(284.3)	Found	C 63.03	H 4.23	N 9.78	S 11.08

2-Cyano-3-(2-furyl)-3-hydroxy-N-(2-furyl-methyl)-thioacrylamide (**4f**)

Brown needles; yield 1.60 g (58.0%), *m.p.* 147–148 °C. – ^{1}H NMR($CDCl_3$): δ/ppm = 16.10 (1H, s, OH); 7.90 (1H, s, NH); 7.69 (2H, 2q, 3-C_4H_3O, 5-C_4H_3O); 7.49 (1H, q, 5-$C_4H_3OCH_2$); 7.36 (1H, q, 4-C_4H_3O); 6.37 (2H, q, 3-$C_4H_3OCH_2$, 4-$C_4H_3OCH_2$); 4.87 (2H, d, CH_2). – IR(KBr): ν_{max}/cm^{-1} = 3303 OH/NH, 2208 CN, 1234 C=S.

$C_{13}H_{10}N_2O_3S$	Calcd.	C 56.93	H 3.64	N 10.21	S 11.67
(274.3)	Found	C 57.03	H 3.83	N 10.19	S 11.60

Methylation of thioamides

Method A: 0.01 mole thioamide **4** is dissolved in 50 mL of an ether-methanol mixture (1:1) in a 100 mL flask, 0.5g tosylnitrosamine, 6 mL ethanol and 5 mL ether are placed in a 50 mL flask. The two flasks are connected by means of a glass tube inserted in the solution and 2 mL KOH (60%) are added. A rapid bubbling is observed. At the end of reaction the solution of the methylated thioamide is stored at low temperature for precipitating the product, which is filtered off and recrystallized from ethanol.

Method B: 0.01 mole thioamide and 0.01 mole dimethyl sulfate in 10 mL dimethylformamide are refluxed for one hour. After reaching room temperature the mixture is acidified with hydrochloric acid forming an oil. The aqueous phase is removed and the oil is poured into water for few hours. The solid formed is filtered off and recrystallized from ethanol.

2-Benzoyl-3-methylthio-3-(p-toluidino)acrylonitrile (**5a**)

Yellow crystals; yield 0.81 g (26.0%, method A), 1.49 g (48.0 %, method B); *m.p.* 153–155 °C. – ^{1}H NMR($CDCl_3$): δ/ppm = 13.89 (1H, s, NH,); 7.85 (2H, m, *o*-C_6H_5); 7.46 (3H, m, *m*-C_6H_5, *p*-C_6H_5); 7.24 (4H, m, C_6H_4); 2.37 (3H, s, CH_3), 2.32 (3H, s, SCH_3). – ^{13}C NMR($CDCl_3$): δ/ppm = 191.8 (C=O), 173.0 (H_3CS–C=); 138.4 (*i*-C_6H_5); 137.9, 134.8 (*p*-C_6H_4, *i*-C_6H_4); 131.8 (*p*-C_6H_5); 130.1 (*m*-C_6H_4); 128.4 (*m*-C_6H_5); 128.1 (*o*-C_6H_4); 124.8 (*o*-C_6H_5); 120.3 (CN), 76.6 (-C=CN); 21.1 (CH_3), 17.6 (SCH_3). – IR(KBr): ν_{max}/cm^{-1} = 2201 CN, 1595 C=O.

$C_{18}H_{16}N_2OS$	Calcd.	C 70.12	H 5.19	N 9.09	S 10.38
(318.4)	Found	C 69.68	H 5.54	N 9.46	S 10.07

2-(2-Furoyl)-3-methylthio-3-(p-toluidino)acrylonitrile (**5b**)

Shining yellow crystals; yield 0.82 g (27.5%, method A) 1.23 g (41.0%, method B); *m.p.* 145–146 °C. – ^{1}H NMR($CDCl_3$): δ/ppm = 13.15 (1H, s, NH); 7.96 (1H, q, 5-C_4H_3O); 7.48 (1H, q, 3-C_4H_3O); 7.27 (4H, m, C_6H_4); 6.71 (1H, q, 4-

C_4H_3O); 2.31 (3H, s, CH_3); 2.29 (3H, s, SCH_3). – ^{13}C NMR: δ/ppm = 175.5 (C=O); 172.7 $H_3CS-\underline{C}=$); 150.3 (2-C_4H_3O); 147.2 (5-C_4H_3O); 137.0, 135.2 (*p*-C_6H_4, *i*-C_6H_4); 130.0 (*m*-C_6H_4); 124.6 (*o*-C_6H_4); 119.5 (CN); 118.3 (3-C_4H_3O); 112.5 (4-C_4H_3O); 82.6 (NC–$\underline{C}=$); 20.7 (CH_3), 17.1 (SCH_3). – IR(KBr): ν_{max}/cm^{-1} = 2200 CN, 1589 C=O.

$C_{16}H_{14}N_2O_2S$	Calcd.	C 64.46	H 4.69	N 9.39	S 10.76
(298.4)	Found	C 63.98	H 4.59	N 9.70	S 10.62

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