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N-Hydroxymethylation of 3-Aryl-2-cyanoprop-2-enethioamides

V. V. Dotsenko[a,b,*], E. A. Chigorina[c,d], and S. G. Krivokolysko[a]

[a] *Kuban State University, Krasnodar, 350040 Russia*
[b] *North Caucasus Federal University, Stavropol, 355009 Russia*
[c] *National Research Center "Kurchatov Institute"–IREA, Moscow, 107076 Russia*
[d] *National Research Center "Kurchatov Institute," Moscow, 123182 Russia*
**e-mail: victor_dotsenko_@mail.ru*

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Abstract—Hydroxymethylation of (*E*)-3-aryl-2-cyanoprop-2-enethioamides with an aqueous alcoholic solution of formaldehyde has afforded (*E*)-3-aryl-*N*-(hydroxymethyl)-2-cyanoprop-2-enethioamides. The predictive analysis of the biological activity of the obtained compounds *in silico* has been carried out.

Keywords: 2-cyanoethanethioamide, (*E*)-3-aryl-2-cyanoprop-2-enethioamides, *N*-hydroxymethylation, *N*-(hydroxymethyl)thioamides, Mannich reaction

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The products of 2-cyanoethanethioamide **1** condensation with aldehydes—(*E*)-3-aryl-2-cyanoacrylthioamides **2** (3-aryl-2-cyanoprop-2-enerhioamides)—have been recognized as readily available and multipurpose precursors in the chemistry of S,N-compounds [1–3], primarily of the heterocyclic series: derivatives of thiophene, thienoazines, 1,3,5-thiadiazine, etc. [4–11].

Unsaturated thioamides **2** readily form the derivatives of hexahydropyrimido[4,3-*b*][1,3,5]thiadiazine **3** [12–15] or decahydropyrimido[4′,5′:4,5]pyrimido[2,1-*b*][1,3,5]-thiadiazine **4** [16] as a result of cascade transformations under the Mannich reaction conditions (Scheme 1). The derivatives of 1,3,5-thiadiazine exhibit broad range of biological activity and utilitarian properties [10, 11, 17–19], therefore, the development of facile methods of synthesis of fused 1,3,5-thiadiazine is a topical issue.

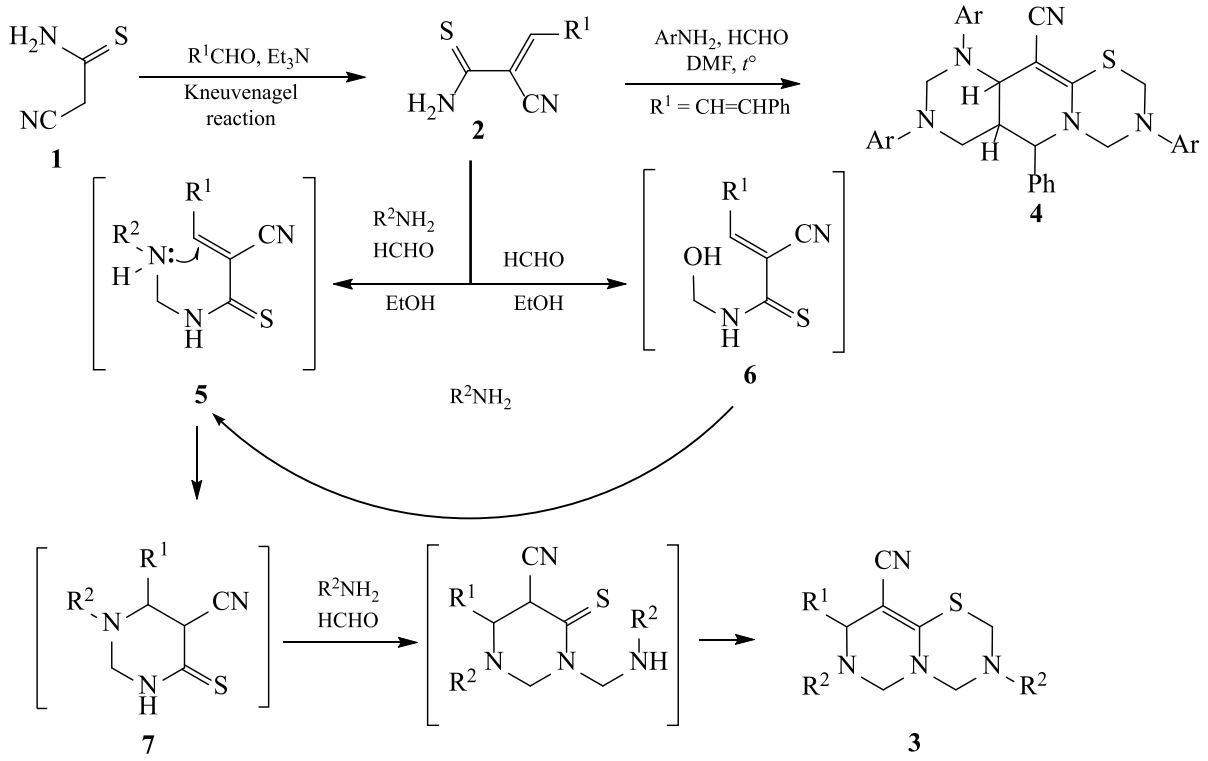
The first stage likely consists in N-aminomethylation of thioamides **2**, followed by cyclization of *N*-(aminomethyl)thioamides **5** into perhydropyrimidines **7** and then closing of 1,3,5-thiadiazine cycle. However, N-hydroxymethylation affording *N*-(hydrohymethyl)-thioamides **6** at the first stage cannot be ruled out. None of the intermediates **5**–**7** has been isolated.

Herein we investigated the interaction of formaldehyde with 3-aryl-2-cyanoacrylthioamides **2** as a possible route to *N*-(hydroxymethyl)thioamides **6**, promising thioamidoalkylating agents and possible intermediates in the synthesis of 1,3,5-thiadiazine heterocycles.

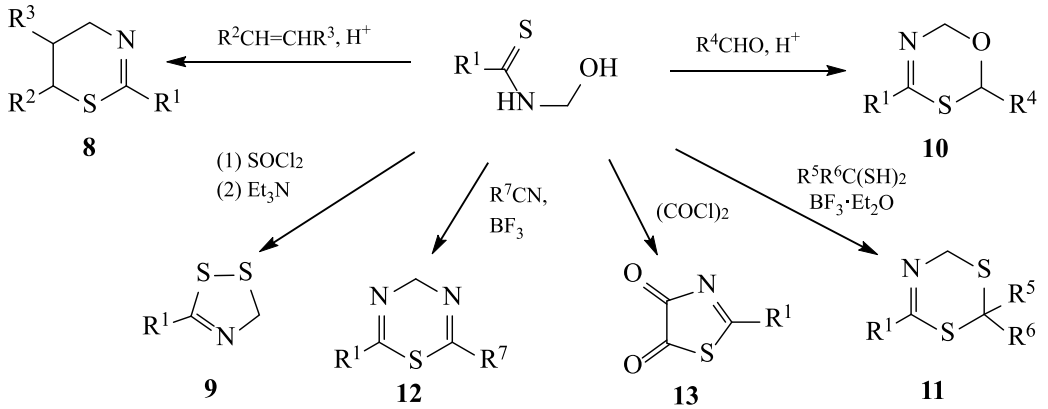
N-(Hydroxymethyl)thioamides are relatively readily formed from formaldehyde and thioamides containing primary or secondary amino groups, often in the presence of base [20–28]. These compounds exhibit enhanced hydrophilicity (in comparison with thioamides) and can be used as bidentate ligands for the creation of sorbents selective with respect to heavy metals ions [29–31], thioamidoalkylating agents [20, 24–25, 32–34], and as the reagents in the synthesis of derivatives of 1,3-thiazine **8** [26, 35, 36], 1,2,4-dithiazoles **9** (with pronounced fungicide action) [37–39], 6*H*-1,3,5-oxathiazine **10** [27, 40], 4*H*-1,3,5-dithiazine **11** [41, 42], 4*H*-1,3,5-thiadiazine **12** [43], or thiazolidine **13** [44] (Scheme 2). Moreover, *N*-(hydroxymethyl)thioamides have exhibited antibacterial [22, 45, 46] and antileprous [47] properties and are key intermediates in the synthesis of the series of biologically active compounds [23, 48–50].

We found that unsaturated thioamides **2a**–**2e** readily reacted with excess of 37% aqueous solution of formaldehyde at heating in EtOH in the absence of any catalyst, to form earlier unknown N-hydroxymethylation products **6a**–**6e** (Scheme 3). *N*-(Hydroxymethyl)-thioamides **6** were somewhat less colored in comparison with the starting compounds **2**. Moderate yield (46–60%) could be explained by noticeably higher solubility of the compounds in aqueous-alcoholic media (in comparison with thioamides **2**) as well as occurrence of side solvolysis reaction (retro-Knoevenagel) of the starting

Scheme 1.



Scheme 2.



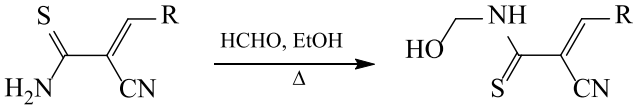
acrylthioamides **2**. The addition of basic (K_2CO_3) as well as acidic (aq. HCl) catalysts led to tarring of the reaction mixture.

Structure of the obtained compounds was confirmed by the data of NMR and IR spectroscopy as well as HPLC–MS. The ^{1}H NMR spectra of compounds **6** contained the following characteristic signals: Ar–C<u>H</u>= singlet at 7.90–8.09 ppm, broadened NH singlet at 10.22–10.99 ppm, CH_2 multiplet (5.00–5.07 ppm), and OH triplet (5.87–6.33 ppm). The IR spectra contained the absorption bands assigned to stretching of N–H, O–H, and conjugated C≡N bonds.

The preparation of *N*-(1*H*-benzotriazol-1-ylmethyl)-thioamides and their use as efficient thioamidoalkylating agents has been described in [51–55]. The attempt to prepare *N*-(1*H*-benzotriazol-1-ylmethyl)-3-(2-chlorophenyl)prop-2-enethioamide **14** via short-term refluxing of 1*H*-benzotriazole, thioamide **2a**, and HCHO in EtOH led to a product which was identified (HPLC–MS and NMR) as hardly separable mixture of the starting compound **2a**, *N*-(hydroxymethyl)thioamide **6a**, thioamide **14**, and 1*H*-benzotriazol-1-ylmethanol **15** (Scheme 4) [56].

Preliminary screening of the promises of practical application of compounds **6a**–**6e** was performed via

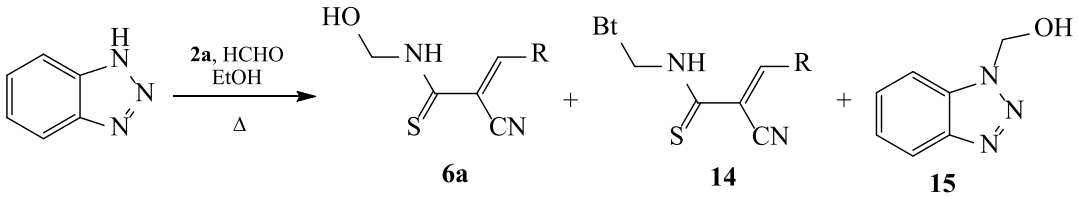
Scheme 3.



2a–2e **6a–6e**

R = 2-ClC_6H_4 (**2a**, **6a**, **14**), 4-ClC_6H_4 (**2b**, **6b**), furan-2-yl (**2c**, **6c**), 4-$(Me_2N)C_6H_4$ (**2d**, **6d**), 4-HO-3-$MeOC_6H_3$ (**2e**, **6e**); Bt—1*H*-benzotriazole-1-yl.

Scheme 4.



6a **14** **15**

R = 2-ClC_6H_4.

in silico analysis of the similarity to known drugs (drug-likeness). The ADMET parameters (Absorption, Distribution, Metabolism, Excretion, Toxicity) as well as biological activity were predicted using the following software: OSIRIS Property Explorer [57], SwissADME [58], admetSAR [59], Molinspiration Property Calculation Service [60], AntiBac-Pred [61], and PASS Online [62, 63]. The OSIRIS Property Explorer was used for the estimation of *c*Log*P* (lipophilicity), log*S* (solubitity), TPSA (Topological Polar Surface Area), risks of the side effects (including mutagenicity, carcinogenicity, irritant action, and effects on reproductive performance), drug-likeness parameter, and overall assessment of the pharmacological potential (drug score) of the compounds [57]. The structures were screened for the correspondence to the Lipinski's "rule of five" (*c*Log*P* ≤ 5.0, molecular mass *M* ≤ 500, TPSA ≤ 140, number of hydrogen bond acceptors ≤ 10, and number of hydrogen bond donors ≤ 5) [64–66]. The data calculated using OSIRIS Property Explorer service are collected in Table 1.

The obtained results showed that compounds **6a–6d** conformed to the "rule of five" with respect to solubility, lipophilicity, TPSA, and molecular mass. However, low estimates of the pharmacological potential (drug score) and similarity to the known drugs (drug-likeness) were obtained; moreover, high toxicity risks were predicted. The calculated ADMET parameters [58, 59] predicted good gastro-intestinal absorption of the compounds and the possibility of penetration through hematoencephalic barrier (except for compound **6e**, Table 2). The calculation using admetSAR [59] showed that the compounds corresponded to the group III (US EPA) with respect to acute peroral toxicity (500 mg/kg < LD_{50} < 5000 mg/kg). The calculations also revealed low probability of mutagenicity/ carcinogenicity in the Ames test (except for

Table 1. Toxicity risks and physico-chemical parameters of compounds **6a–e** as calculated using OSIRIS Property Explorer service

Comp. no.	Toxicity risk[a]				Physico-chemical parameters					
	A	B	C	D	*c*Log*P*	Log*S*	*M*	TPSA[b]	drug likeness[c]	drug Score[d]
6a	±	+	+	+	1.86	–4.26	252	88.14	–3.25	0.071
6b	±	+	+	+	1.86	–4.26	252	88.14	–3.03	0.072
6c	+	+	+	+	0.44	–3.2	208	101.2	–4.32	0.059
6d	+	+	+	+	1.15	–3.56	261	91.38	–8.22	0.056
6e	±	+	+	+	0.84	–3.24	264	117.6	–3.26	0.08

[a] "±" sign marks predicted moderately high toxicity, "+" denotes high toxicity risk. A—Mutagenicity, B—carcinogenicity, C—irritant action, D—effects on reproductive performance.
[b] Topological Polar Surface Area.
[c] Similarity to drugs.
[d] Pharmacological potential of the compound.

Table 2. Calculated ADMET parameters (Absorption, Distribution, Metabolism, Excretion, Toxicity) for compounds **6a**–**6e**

Comp. no.	Gastro-intestinal absorption[a]	Permeation through hematoencephalic barrier[a]	Inhibition of cytochromes P450 (CYPs)[a]					Ames test[a]	Acute toxicity (rats) LD_{50}, log [1/(mol/kg)]
			CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4		
6a	+ 0.8544	+ 0.8122	+	+	+	–	–	+ 0.5363	2.4684
6b	+ 0.8624	+ 0.8406	+	+	+	–	+	+ 0.5128	2.5466
6c	+ 0.8999	+ 0.8577	+	–	–	–	–	– 0.5790	2.6156
6d	+ 0.7173	+ 0.6971	+	–	–	–	–	+ 0.5214	2.5859
6e	+ 0.8789	– 0.7855	+	–	–	–	–	– 0.5061	2.5286

[a] "+" and "–" signs mark the presence and the absence of the effect, respectively, the number gives the probability of the effect.

compounds **6c**, **6e**). The calculations using Molinspiration Property Calculation Service pointed at the highest probability of kinases inhibition activity for compounds **6d**, **6e** (Molinspiration bioactivity score –0.24).

The prediction of antibacterial activity using AntiBac-Pred service [61] evidenced possible activity of compound **6g** towards pathogenic Gram-positive bacteria *Nocardia transvalensis* [confidence (*C*) 0.34, calculated as the excess of the activity probability over that of inactivity, $P_A > P_I$]. The data obtained using PASS Online service [62, 63], compounds **6a**, **6b**, **6d**, **6e** should exhibit antitumor activity (tyrosine kinases inhibition with probability 0.77–0.87).

In summary, (*E*)-3-aryl-2-cyanoprop-2-enethioamides readily reacted with formaldehyde to form (*E*)-3-aryl-*N*-(hydroxymethyl)-2-cycnoprop-2-enethioamides. Prediction of biological activity of the compounds revealed poor prospects of their bioscreening. Reactions of thioamidoalkylation involving the obtained compounds and the prospects of their application in agricultural chemistry are currently under investigation.

EXPERIMENTAL

^{1}H NMR spectra were recorded using Bruker DPX-400 (400.40 MHz) and Bruker WP200 (199.97 MHz) spectrometers in DMSO-d_6 or $CDCl_3$ with TMS or residual solvent protons as internal reference. IR spectra were recorded using IKS-29 spectrometer (Vaseline oil). HPLC–MS analysis was performed using a Shimadzu LC-10AD liquid chromatograph equipped with Shimadzu SP D-10A UV–Vis (254 nm) and Sedex 75 ELSD detectors and paired with PE SCIEX API 150EX mass spectrometer (ES-API ionization). Elemental analysis was performed using a Carlo Erba 1106 C,H,N analyzer. Purity of the products was monitored by TLC on Silufol UV254 plates (eluent: acetone–hexane 1 : 1, visualization of spots with iodine vapor, UV detection).

Starting (*E*)-3-aryl-2-cyanoprop-2-enethioamides **2** were obtained via the interaction of 2-cyanoethanethioamide **1** [67] with aromatic aldehydes in the presence of Et_3N as catalyst [68].

Preparation of (*E*)-3-aryl-*N*-(hydroxymethyl)-2-cyanoprop-2-enethioamides 6a–e (*general procedure*). Equal volume of 37% aqueous solution of HCHO was added to a suspension of 0.5 g of the unsaturated thioamide **2a**–**2e** in 3–4 mL of EtOH, and the mixture was refluxed during 3–5 min. The product which was crystallized from the formed light red solution was filtered off, washed with cold EtOH, and dried. Analytical-pure compounds **6a**–**6e** were obtained.

(*E*)-*N*-(Hydroxymethyl)-3-(2-chlorophenyl)-2-cyanoprop-2-enethioamide (6a). Yield 49%, orange crystals. IR spectrum, ν, cm^{-1}: 3415, 3300–3210 (O–H, N–H), 2222 (C≡N). ^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm: 5.02–5.07 m (2H, CH_2), 6.33 t (1H, OH, ^3J = 7.0 Hz), 7.49–7.67 m (3H, H_{Ar}), 7.96–7.99 m (1H, H_{Ar}), 8.09 s (1H, CH=), 10.98–10.99 m (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 235.1 $[M - H_2O + H]^+$, 331.1 $[M + DMSO + H]^+$, 487.3 $[2M - H_2O + H]^+$, 522.5 $[2M + NH_4]^+$, 741.5 $[3M - H_2O + H]^+$. Found, %: C 52.17; H 3.71; N 11.16. $C_{11}H_9ClN_2OS$. Calculated, %: C 52.28; H 3.59; N 11.08. M_{calc} 252.72.

(*E*)-*N*-(Hydroxymethyl)-3-(4-chlorophenyl)-2-cyanoprop-2-enethioamide (6b). Yield 46%, orange

powder. IR spectrum, ν, cm^{-1}: 3390, 3325 (O–H, N–H), 2222 (C≡N). ^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm: 5.00–5.06 m (2H, CH_2), 6.32 t (1H, OH, ^3J = 7.1 Hz), 7.64 d (2H, $H^{3,5}_{Ar}$, ^3J = 8.6 Hz), 7.90 s (1H, CH=), 7.92 d (2H, $H^{2,6}_{Ar}$, ^3J = 8.6 Hz), 10.90–10.92 m (1H, NH). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 4.29 t (1H, OH, ^3J = 8.4 Hz), 5.22–5.26 m (2H, CH_2), 7.49 d (2H, $H^{3,5}_{Ar}$, ^3J = 8.6 Hz), 7.93 d (2H, $H^{2,6}_{Ar}$, ^3J = 8.6 Hz), 8.59–8.62 m (1H, NH), 8.72 s (1H, CH=). Mass spectrum, *m*/*z* (I_{rel}, %): 235.3 [$M - H_2O + H]^+$, 253.1 [$M + H]^+$, 331.1 [M + DMSO + $H]^+$, 487.3 [$2M - H_2O + H]^+$, 522.3 [$2M + NH_4]^+$. Found, %: C 52.26; H 3.63; N 11.05. $C_{11}H_9ClN_2OS$. Calculated, %: C 52.28; H 3.59; N 11.08. M_{calc} 252.72.

(*E*)-*N*-(Hydroxymethyl)-3-(furan-2-yl)-2-cyanoprop-2-enethioamide (6c). Yield 54%, orange-brown powder. IR spectrum, ν, cm^{-1}: 3420, 3210 (O–H, N–H), 2215 (C≡N). ^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm: 5.00–5.04 m (2H, CH_2), 6.20 t (1H, OH, ^3J = 7.2 Hz), 6.83–6.84 m (1H, H^4_{furyl}), 7.41 d (1H, H^3_{furyl}, ^3J = 3.7 Hz), 7.90 s (1H, CH=), 8.13–8.14 m (1H, H^5_{furyl}), 10.63–10.64 m (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 209.1 [$M + H]^+$, 269.3 [$M - H_2O$ + DMSO + $H]^+$, 287.1 [M + DMSO + $H]^+$, 399.1 [$2M - H_2O + H]^+$, 434.4 [$2M + NH_4]^+$, 607.5 [$3M - H_2O + H]^+$. Found, %: C 51.87; H 3.93; N 13.46. $C_9H_8N_2O_2S$. Calculated, %: C 51.91; H 3.87; N 13.45. M_{calc} 208.24.

(*E*)-*N*-(Hydroxymethyl)-3-[(4-dimethylamino)-phenyl]-2-cyanoprop-2-enethioamide (6d). Yield 60%, red crystals. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 5.02–5.05 m (2H, CH_2), 6.07 t (1H, OH, ^3J = 7.1 Hz), 6.82 d (2H, $H^{3,5}_{Ar}$, ^3J = 8.8 Hz), 7.87 d (2H, $H^{2,6}_{Ar}$, ^3J = 8.8 Hz), 7.96 s (1H, CH=), 10.31–10.32 m (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 262.3 [$M + H]^+$, 379.5 [M + DMSO + $K]^+$, 397.3 [$M + H_2O$ + DMSO + $K]^+$, 523.3 [$2M + H]^+$. Found, %: C 59.70; H 5.83; N 16.11. $C_{13}H_{15}N_3OS$. Calculated, %: C 59.74; H 5.79; N 16.08. M_{calc} 261.34.

(*E*)-3-(4-Hydroxymethyl-3-methoxyphenyl)-*N*-(hydroxymethyl)-2-cyanoprop-2-enethioamide (6e). Yield 51%, yellow powder. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 5.06–5.07 m (2H, CH_2), 5.87 t (1H, OH, ^3J = 7.0 Hz), 6.89 d (1H, H^5_{Ar}, ^3J = 8.4 Hz), 7.40 d (1H, H^6_{Ar}, ^3J = 8.4 Hz), 7.71 s (1H, H^3_{Ar}), 8.03 s (1H, CH=), 10.02 br. s (1H, ArO<u>H</u>), 10.22–10.23 m (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 265.3 [$M + H]^+$, 382.3 [$M + NH_4]^+$, 546.3 [$2M + NH_4]^+$. Found, %: C 54.61; H 4.55; N 10.66. $C_{12}H_{12}N_2O_3S$. Calculated, %: C 54.53; H 4.58; N 10.60. M_{calc} 264.30.

Interaction of 3-(2-chlorophenyl)-2-cycnoprop-2-enethioamide 2a with formaldehyde and 1*H*-benzotriazole. Excess (1.0 mL) of 37% aqueous solution of formaldehyde was added at stirring to a suspension of 500 mg (2.25 mmol) of compound **2a** and 270 mg (2.27 mmol) of 1*H*-benzotriazole in 5 mL of 96% ethanol. The mixture was refluxed during 5 min. Upon ~ 15 min cooling, the precipitate was formed from the light red solution; it was filtered off, washed with ethanol, and dried. 379 mg of orange powder was obtained, which was identified (^{1}H NMR data) as a mixture of *N*-(hydroxymethyl)thioamide **6a** (~37 mol %), 1*H*-benzotriazol-1-ylmethanol **15** (~40 mol %), starting thioamide **2a** (~14 mol %), and the product of aminomethylation **14** (~9 mol %). The following signals of the components were identified in the ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: compound **2a**, 8.27 s (1H, CH=), 9.73 br. s ($CSNH_2$), 10.25 br. s ($CSNH_2$); compound **6a**, 5.03–5.07 m (2H, CH_2), 6.32 m (1H, OH), 8.10 s (1H,CH=), 10.98–10.99 m (1H, NH); 1*H*-benzotriazol-1-ylmethanol **15**, 6.02 d (2H, C<u>H</u>$_2$OH, ^3J = 7.0 Hz), 7.19 t (1H, OH, ^3J = 7.0 Hz), 8.06 d (1H, H^4_{Ar}, ^3J = 8.6 Hz); compound **14**, 6.60 d (2H, C<u>H</u>$_2$NH, ^3J = 5.1 Hz), 8.17 s (1H, CH=), 11.66 (1H, CH_2N<u>H</u>, ^3J = 5.1 Hz). Mass spectrum, *m*/*z*: 120.4 [*M* (BtH) + $H]^+$, 150.1 [*M* (**15**) + $H]^+$, 223.3 [*M* (**2a**) + $H]^+$, 331.1 [*M* (**6a**) + DMSO + $H]^+$, 354.1 [*M* (**14**) + $H]^+$, 487.0 [$2M$ (**6a**) – H_2O + $H]^+$, 522.2 [$2M$ (**6a**) + $NH_4]^+$, 709.2 [$2M$ (**14**) + $H]^+$, 1062.2 [$3M$ (**14**) + $H]^+$.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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