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Synthesis and Properties of New N-(Hydroxyalkyl) thioacrylamides †

Arina A. Reshetnikova [1], Arina G. Levchenko [1] and Victor Dotsenko [1,2]

[1] Department of Organic Chemistry and Technologies, Kuban State University, 149 Stavropolskaya Str., 350040 Krasnodar, Russia; email1@email.com (A.A.R.); email2@email.com (A.G.L.); email3@email.com (V.D.)
[2] Department of Organic Chemistry, North-Caucasus Federal University, 1 Pushkina Str., 355017 Stavropol, Russia
* Correspondence:
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Abstract

Cyanothioacetamide readily reacts with aromatic aldehydes in an aqueous-alcoholic medium in the presence of triethylamine as a catalyst, resulting in arylmethylene cyanothioacetamides (3-aryl-2-cyanothioacrylamides). The latter react with formaldehyde (HCHO), yielding N-(hydroxymethyl) derivatives. This work proposes a method for preparation of new derivatives of N-(hydroxyalkyl)thioacrylamides. The details of the synthesis and spectral data are discussed. Biological effects are also considered as 2,4-D herbicide antidotes (safeners).

Keywords: thioamides; thioacrylamides; cyanothioacetamide; hydroxymethylation

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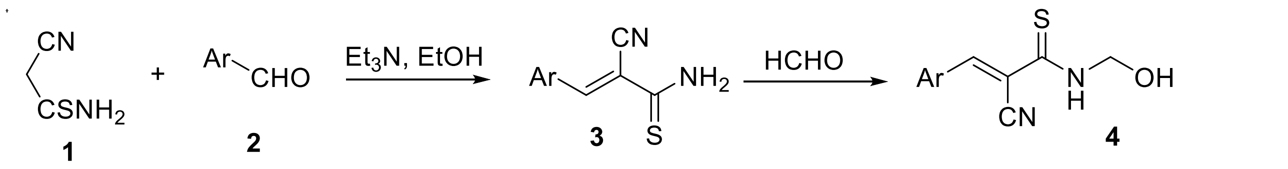
1. Introduction

N-(Hydroxymethyl)thioamides are readily available compounds that are widely used in the synthesis of nitrogen- and sulfur-containing heterocycles, such as 1,3-thiazines, 1,2,4-dithiiazoles, 1,3,5-oxathiazines, 1,3,5-thiadiazines, thiazolidines, and others. In addition to their application in fine organic synthesis, N-(hydroxymethyl)thioamides are also used for other purposes. For example, some representatives of this series act as bidentate ligands for creating selective sorbents for heavy metal ions such as Cu(II), Cd(II), and Hg(II) [1,2]. These compounds are intermediates in the synthesis of a number of biologically active substances [3,4]. At the same time, the literature presents a limited number of methods for obtaining such compounds, and the variability of structures is not sufficiently high. Thus, N-(hydroxyalkyl)thioamides belong to a promising group of compounds, and the development of methods for their synthesis can be considered an important problem.

2. Results and Discussion

The starting compound **3** was obtained from cyanothioacetamide **1** and aromatic aldehydes **2** in an aqueous-alcoholic medium using a basic catalyst (Scheme 1) [5]. The compound **3** was then reacted with HCHO at 60 °C (Scheme 1) [5]. To confirm the structure of compounds **3** and **4**, spectral methods (IR, ^{1}H and ^{13}C NMR spectroscopy) were used (Scheme 1, Figure 1).



Scheme 1. Ar = 4-ClC_6H_4 (**4a**), 4-BrC_6H_4 (**4b**), 3,4-(MeO)$_2C_6H_3$ (**4c**), 4-HO-3-MeO-5-$NO_2C_6H_2$ (**4d**), 2-$NO_2C_6H_4$ (**4e**).

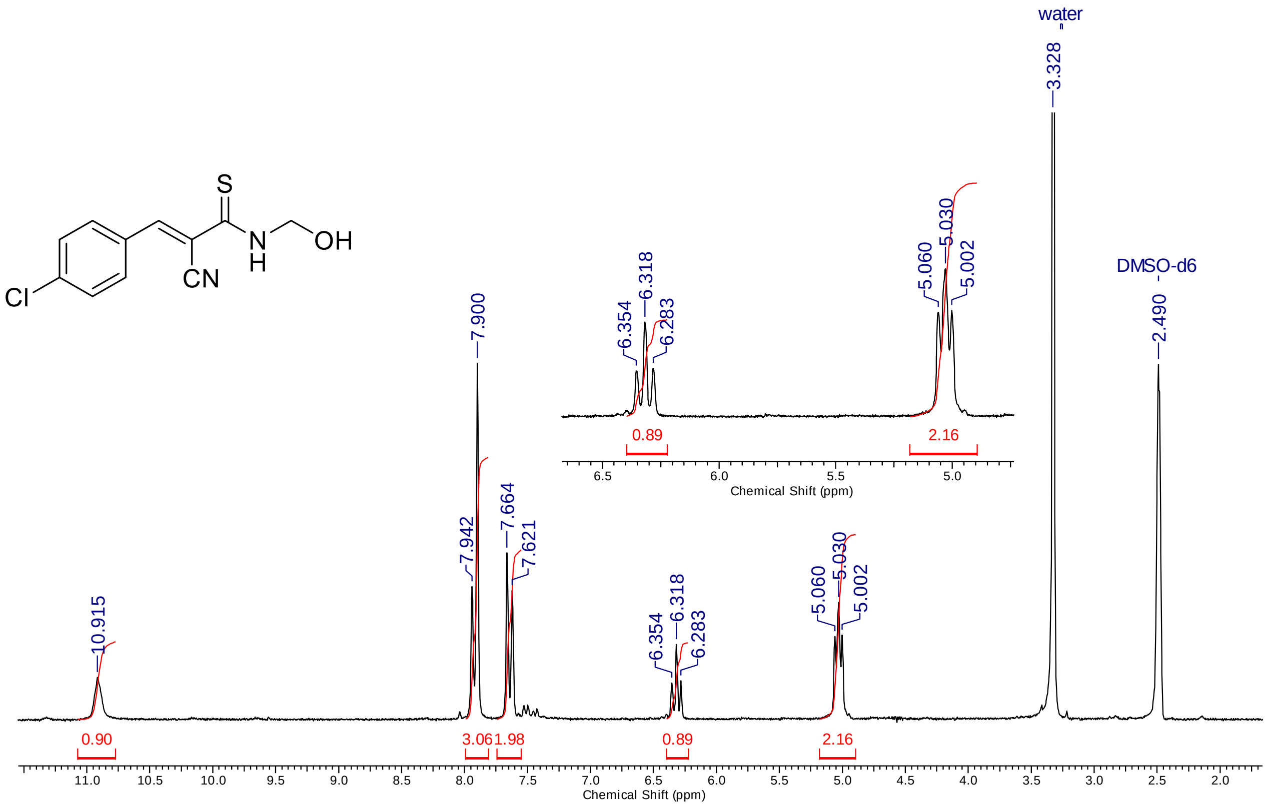
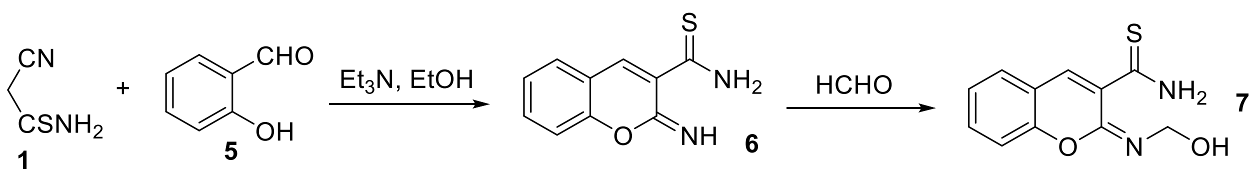


Figure 1. ^{1}H NMR spectrum (DMSO-d_6) of (*E*)-N-(Hydroxymethyl)-3-(4-chlorophenyl)-2-cyanoprop-2-enthioamide **4a**.

It is known that salicylaldehyde **5**, when reacting with cyanothioacetamide **1**, undergoes intramolecular cyclization, forming product **6**. The resulting substance interacts with HCHO to form compound **7** (Scheme 2).



Scheme 2.

To determine the biological activity of compounds **4** and **7**, the Pass Online service was used. Compounds **4** are more likely to exhibit properties as inhibitors of tyrosine kinases (87.4%) and S-methyltransferase of homocysteine (78.2%); they may also exhibit antitumor properties (78.8%) and, to a lesser extent, anti-psoriatic properties (57.3%). The predicted undesirable effects include adrenal cortex hypoplasia (67.9%) and anemia (53.8%). Compound **7** is more likely to exhibit properties as a spasmolytic, diuretic (62.6%), membrane integrity agonist (53.9%), and antifungal agent (44.5%); it is also a potential anti-tuberculosis agent (42.8%). Negative effects may include causing acne (73.2%), various allergic reactions (55.7%), and carcinogenicity (for mice—63.8%).

Compounds **4a** and **4c** were tested for herbicide safening activity (for reviews see [6,7]) against the herbicide 2,4-D on sunflower seedlings of the Master variety. The results showed that both compounds have significant activity: for compound **4a**, antidote effect was 66%, and for **4c**, it was 30%. The obtained data are promising for further research.

3. Experimental

Synthesis of starting compounds 3a–e and 6. In a 50 mL beaker, 0.01 mol of the starting aldehyde and 0.01 mol of cyanothioacetamide **1** [8] in 15 mL of ethanol was placed. Catalytic amounts of Et_3N (2 drops) were added. A yellow or orange precipitate formed within a few minutes, the solid was filtered off and washed with alcohol. The compounds were further reacted without additional purification.

Synthesis of N-(hydroxymethyl)thioacrylamides 4 (a–e) and 2-iminocoumarine 7. In a 25 mL beaker, 0.0021 mol of the starting compound (**3a–e**, **6**) was placed. Then 3 mL (excess) of 37% aq. HCHO was added, and the temperature in the system was maintained at 50–55 °C, stirring for 40 min, during which the solution acquires a more intense orange color. Upon cooling, a precipitate formed, which was filtered off and washed with cold distilled water.

(*E*)-N-(Hydroxymethyl)-3-(4-chlorophenyl)-2-cyanoprop-2-ene thioamide (4a). Yellow powder, 0.34 g (64%). R_f = 0.43 (ethyl acetate). IR spectrum, ν, cm^{-1}: 3444 br, 3322 br (O-H, N-H), 2204 br (C≡N). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 5.06 m (2H, CH_2), 6.33 t (1H, OH), 7.65 d (2H, H Ar), 7.91 s (1H, CH=), 7.93 d (2H, H Ar), 10.93 br.s (1H, NH). ^{13}C NMR spectrum (101 MHz, DMSO-d_6) δ, ppm: 70.0 (-CH_2OH). 113.91 (=C(CN)-), 116.70 (C≡N), 129.93 (C Ar), 132.18 (C Ar), 132.20 (C Ar), 137.14 (C^1 Ar), 145.38 (CH=), 189.60 (C=S),

(*E*)-N-(Hydroxymethyl)-3-(4-bromophenyl)-2-cyanoprop-2-ene thioamide (4b). Yellow powder weighing 0.34 g (68%). IR spectrum, ν, cm^{-1}: 3415 br, 3317 br (O-H, N-H), 2204 br (C≡N). ^{13}C NMR spectrum (101 MHz, DMSO-d_6) δ, ppm: 70.0 (-CH_2OH), 113.85 (=C(CN)-), 116.62 (C≡N), 132.81 (C Ar), 132.21 (C Ar), 131.65 (C, Ar), 132.37 (C Ar), 145.39 (CH=), 189.49 (C=S).

(*E*)-N-(Hydroxymethyl)-3-(3,4-dimethoxyphenyl)-2-cyanoprop-2-ene thioamide (4c). Light orange powder weighing 0.34 g (62%). R_f = 0.473 (ethyl acetate). IR spectrum, ν, cm^{-1}: 3415 br, 3241 br (O-H, N-H), 2221 br (C≡N). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 7.16 d (1H, H Ar), 6.34 t (1H, OH), 5.06 d (2H, CH_2), 7.57 d (1H, H Ar), 7.68 c (1H, CH=), 8.07 s (1H, H Ar), 9.99 br.s (1H, NH), 3.86 s (3H, CH_3), 3.82 s (3H, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6) δ, ppm: 149.25 (C Ar), 148.12 (C Ar), 126.21 (C Ar), 124.80 (C Ar), 117.59 (C Ar), 117.53 (C Ar), 153.10 (CH=), 109.53 (=C(CN)-), 112.79 (C≡N), 193.12 (C=S), 109.51 (CH_2OH), 56.36 (OCH_3), 56.00 (OCH_3).

(*E*)-N-(Hydroxymethyl)-3-(4-hydroxy-3-methoxy-5-nitrophenyl)-2-cyanoprop-2-ene thioamide (4d). Ochre powder weighing 0.32 g (64%). IR spectrum, ν, cm^{-1}: 3415 br, 3317 br (O-H, N-H), 2204 br (C≡N). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 3.93 s (3H, CH_2O), 3.97 s (2H, CH_3), 7.64 c (1H, H Ar), 7.96 br.d (1H, H Ar), 8.11 s (1H, CH=), 9.88 br.t (1H, OH). ^{13}C NMR spectrum (101 MHz, DMSO-d_6) δ, ppm: 192.56 (C=S), 193.93 (2C, Ar), 150.51 (CH=), 150.14 (C Ar), 148.25 (C Ar), 146.45 (C Ar), 145.86 (C Ar), 137.64 (C Ar), 122.30 (=C(CN)-), 127.24 (C≡N), 57.28 (CH_2OH), 57.16 (CH_3).

2-(Hydroxymethylamino)-2H-chromen-3-carbothioamide (7). Ochre powder weighing 0.35 g (51%). R_f = 0.451 (ethyl acetate). IR spectrum, ν, cm^{-1}: 3400 br (O-H), 3317 br, 3203 br (NH). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 5.740 t (1H, OH), 8.85 s (1H, H Ar), 7.79 d (1H, H Ar), 7.57 t (1H, H Ar), 7.24 d (1H, H Ar), 7.27 d (1H, H Ar), 5.01 d (2H, CH_2), 10.04 br.s (2H, NH_2). ^{13}C NMR spectrum (101 MHz, DMSO-d_6) δ, ppm: 192.75

(C=S), 153.50 (C=N), 146.74 (C, Ar), 144.16 (C, Ar), 133.72 (C, Ar), 130.80 (C, Ar), 124.96 (C, Ar), 123.22 (C, Ar), 118.73 (C, Ar), 115.54 (C, Ar), 71.52 (CH_2OH).

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