THE REACTION OF N-R-2-CYANOTHIOACETAMIDES WITH ETHYL[(ARYL)HYDRAZONO]CHLOROACETATES

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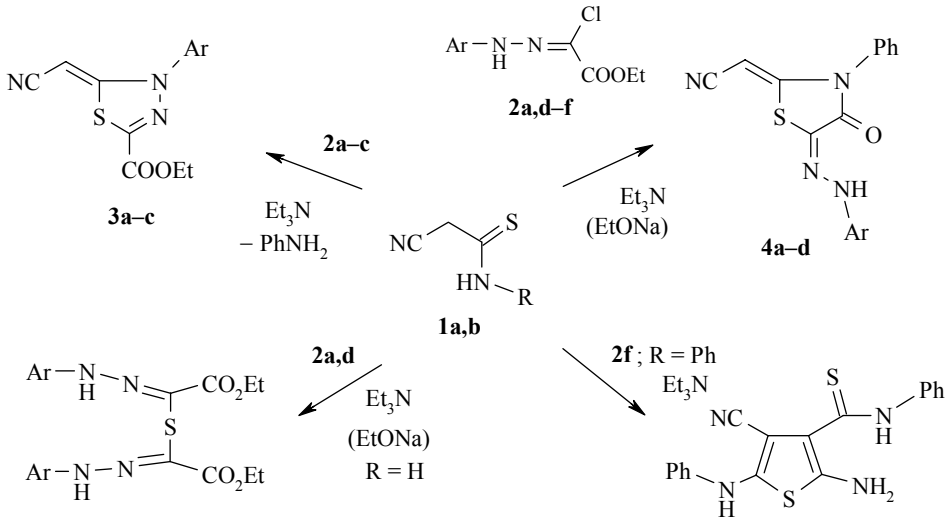
Depending on the nature of the substituents in the starting reagents and the basicity of the medium the cyclization of N-R-2-cyanothioacetamides with ethyl [(aryl)hydrazono]chloroacetates gives 3-aryl-2-cyanomethylidene-5-ethoxycarbonyl-1,3,4-thiadiazoles, 5-arylhydrazono-2-cyanomethylidene-3-phenyl-thiazolidin-4-ones, di[(aryl)hydrazono](ethoxycarbonylmethyl) sulfides, and 5-amino-3-cyano-2-phenyl-amino-4-(N-phenylaminothiocarbonyl)thiophene.

Keywords: N-R-2-cyanothioacetamide, ethyl [(aryl)hydrazono]chloroacetate, 1,3,4-thiadiazole, thiazolidin-4-one, thiophene, cyclization.

The chemistry of thioamides containing an active methylene group has been extensively developed over the last 5 years [1-4]. These thioamides have four reactive centers and are ambident substrates which makes them promising starting materials for the synthesis of the different five and six- membered heterocycles thiopyran-4-ones [2, 3], piperidine-2-thiones [3, 4], pyrroles [5], 1,2,3-thiadiazoles [6], and thiazolines [7].

It is known that [(aryl)hydrazono]chloroacetate esters also show a dual reactivity and can react both with dinucleophiles [8, 9] and with dipolarophiles [8, 10, 11].



1 a R = Ph; **b** R = H; **2a**, **3a**, **4c**, **5a** Ar = Ph; **2b**, **3b** Ar = 3-MeC_6H_4; **2c**, **3c** Ar = 4-FC_6H_4; **2d**, **4a**, **5b** Ar = 3-$CF_3C_6H_4$; **2e**, **4b** Ar = 4-$CHF_2SO_2C_6H_4$; **2f**, **4d** Ar = 4-$MeOC_6H_4$

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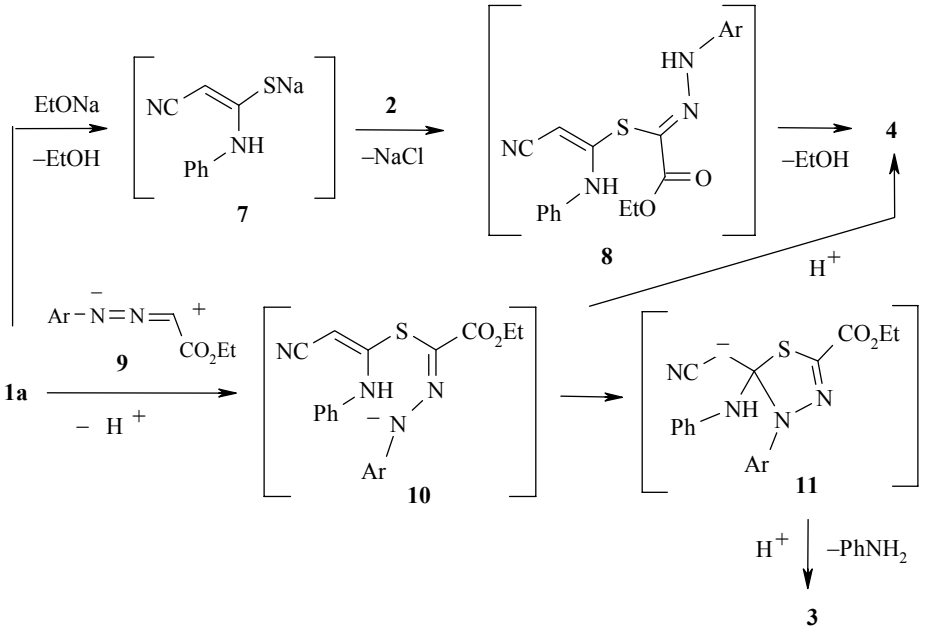
The aim of our work was to study the cyclocondensation of N-R-2-cyanothioacetamides **1a,b** with the ethyl [(aryl)hydrazono]chloroacetate **2a-f** in the presence of base.

It was found that the course of this reaction depends both on the nature of the substituents found on the N atom of the thioamides **1a,b** and in the phenyl ring of the hydrazones **2a-f** and on the strength of the base. The reaction gives rise to 3-aryl-2-cyanomethylidene-5-ethoxycarbonyl-1,3,4-thiadiazoles **3a-c**, 5-arylhydrazono-2-cyanomethylidene-3-phenylthiazolidin-4-ones **4a-d**, di[(aryl)hydrazono](ethoxycarbonylmethyl) sulfides **5a,b**, and 5-amino-3-cyano-2-phenylamino-4-(N-phenylaminothiocarbonyl)thiophene **6** (Tables 1 and 2).



The ^{1}H NMR spectra of compounds **3a-c** and **4a-d** (Table 3) show characteristic methylidene and aromatic proton signals at 4.57-4.84 and 7.16-7.56 ppm respectively. The ^{1}H NMR spectra of the 1,3,4-thiadiazoles **3a-c** and the sulfides **5a,b** also show signals for ethoxy group protons (as triplets and quartets at 1.20-1.32 and 4.19-4.37 ppm respectively) and the spectra of the thiazolidin-4-ones **4a-d**, sulfides **5a,b**, and thiophene **6** show signals for the NH group protons at 10.47-11.32 ppm. The IR spectra of compounds **3a-c**, **4a-d**, and **6** shown absorption bands for Ar, C≡N, and C=C at 3100-3000, 2220-2200, and 1610-1570 cm^{-1} respectively. The IR spectra of products **3a-c**, **4a-d**, and **5a,b** show the presence of C=O group stretching at 1720-1680 cm^{-1} and of **4a-d** and **5** an NH group at 3400-3200 cm^{-1}.

TABLE 1. Reaction Products of N-R-2-Cyanothioacetamides 1**a**,**b** with Ethyl [(aryl)hydrazono]chloroacetates **2a-f** in the Presence of Base

Thioa-mide	Base	Hydra-zone	Product	Yield, %	Thio-amide	Base	Hydra-zone	Product	Yield, %
1a	Et_3N	**2a**	**3a**	53	**1b**	Et_3N	**2d**	**5b**	52
1a	Et_3N	**2b**	**3b**	57	**1a**	Et_3N	**2f**	**6**	51
1a	Et_3N	**2c**	**3c**	62	**1a**	EtONa	**2a**	**4c**	68
1a	Et_3N	**2d**	**4a**	65	**1a**	EtONa	**2e**	**4b**	70
1a	Et_3N	**2e**	**4b**	63	**1a**	EtONa	**2f**	**4d**	32
1b	Et_3N	**2a**	**5a**	60	**1b**	EtONa	**2a**	**5a**	47

The formation of different products for the reaction of the thioacetamides **1a,b** with the [(aryl)hydrazono]-chloroacetates **2a-f** is explained by the fact that the interaction is evidently brought about by a different mechanism.

TABLE 2. Parameters for the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C
		C	H	N	
3a	$C_{13}H_{11}N_3O_2S$	56.92 / 57.13	3.81 / 4.06	15.20 / 15.37	127-128
3b	$C_{14}H_{13}N_3O_2S$	58.80 / 58.52	4.87 / 4.56	14.35 / 14.62	122-124
3c	$C_{13}H_{10}FN_3O_2S$	53.81 / 53.60	3.27 / 3.46	14.22 / 14.43	148-150
4a	$C_{18}H_{11}F_3N_4OS$	55.90 / 55.67	3.04 / 2.85	14.65 / 14.43	295-296
4b	$C_{18}H_{12}F_2N_4O_3S_2$	49.95 / 49.77	3.05 / 2.78	13.02 / 12.90	278-280
4c	$C_{17}H_{12}N_4OS$	63.49 / 63.74	3.54 / 3.78	17.72 / 17.49	265-267
4d	$C_{18}H_{14}N_4O_2S$	61.82 / 61.70	4.22 / 4.03	16.19 / 15.99	238-240
5a	$C_{20}H_{22}N_4O_4S$	58.24 / 57.96	5.12 / 5.35	13.77 / 13.52	135-137
5b	$C_{22}H_{20}F_6N_4O_4S$	47.88 / 48.00	3.42 / 3.66	9.91 / 10.18	108-110
6	$C_{18}H_{14}N_4S_2$	61.90 / 61.69	3.84 / 4.03	16.24 / 15.99	255-258*

TABLE 3. IR and ^{1}H NMR Spectra of the Compounds Synthesized

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (SSCC, *J*,Hz)
3a	3080, 2210, 1700, 1580, 1530, 1500, 1450, 1410, 1395, 1360	1.32 (3H, t, *J* = 6.9, C<u>H</u>$_3$CH$_2$); 4.37 (2H, q, *J* = 6.9, CH$_3$C<u>H</u>$_2$); 4.62 (1H, s, NC–CH=); 7.56 (5H, m, C_6H_5)
3b	3050, 3000, 2200, 1710, 1610, 1565, 1490, 1450, 1400, 1380	1.33 (3H, t, *J* = 6.6, C<u>H</u>$_3$CH$_2$); 2.50 (3H, s, CH$_3$); 4.39 (2H, q, *J* = 6.6, CH$_3$C<u>H</u>$_2$); 4.62 (1H, s, NC–CH=); 7.35 (3H, m, H_{Ar}); 7.46 (1H, m, H_{Ar})
3c	3100, 3000, 2210, 1710, 1570, 1510, 1490, 1405, 1380, 1320	1.33 (3H, t, *J* = 6.9, C<u>H</u>$_3$CH$_2$); 4.38 (2H, q, *J* = 6.9, CH$_3$C<u>H</u>$_2$); 4.57 (1H, s, NC–CH=); 7.41 (2H, m, 4-FC_6H_4); 7.61 (2H, m, 4-FC_6H_4)
4a	3230, 3100, 2220, 1720, 1590, 1500, 1430, 1405, 1380, 1340	4.79 (1H, s, NC–CH=); 7.27-7.72 (9H, m, H_{Ar}); 10.97 (1H, s, NH)
4b	3230, 3190, 3100, 2220, 1720, 1590, 1490, 1420, 1380, 1350	4.84 (1H, s, NC–CH=); 7.14 (1H, t, *J* = 52.5, CHF_2); 7.45-7.61 (7H, m, H_{Ar}); 7.85 (2H, d, *J* = 8.7, 4-C_6H_4); 11.32 (1H, s, NH)
4c	3250, 3100, 2200, 1720, 1580, 1500, 1450, 1380, 1320, 1280	4.73 (1H, s, NC–CH=); 6.99 (1H, m, H_{Ar}); 7.29 (4H, m, H_{Ar}); 7.41 (2H, m, H_{Ar}); 7.58 (3H, m, H_{Ar}); 10.74 (1H, s, NH)
4d	3240, 3000, 2200, 1720, 1580, 1560, 1500, 1375, 1280, 1250	3.73 (3H, s, CH_3O); 4.70 (1H, s, NC–CH=); 6.91 (2H, d, *J* = 8.5, 4-C_6H_4); 7.22 (2H, d, *J* = 8.5, 4-C_6H_4); 7.40 (2H, m, H_{Ar}); 7.59 (3H, m, H_{Ar}); 10.65 (1H, s, NH)
5a	3200, 3050, 3000, 1680, 1600, 1540, 1480, 1450, 1370, 1320	1.23 (3H, t, *J* = 6.9, C<u>H</u>$_3$CH$_2$); 4.21 (2H, q, *J* = 6.9, CH$_3$C<u>H</u>$_2$); 7.04 (1H, m, C_6H_5); 7.36 (4H, m, C_6H_5); 10.86 (1H, s, NH)
5b	3200, 3150, 3000, 1680, 1620, 1600, 1550, 1500, 1420, 1340	1.20 (3H, t, *J* = 6.6, C<u>H</u>$_3$CH$_2$); 4.19 (2H, q, *J* = 6.6, CH$_3$C<u>H</u>$_2$); 7.29 (1H, d, *J* = 7.2, H_{Ar}); 7.55 (1H, m, H_{Ar}); 7.65 (1H, d, *J* = 8.7, H_{Ar}); 7.70 (1H, s, H_{Ar}); 11.00 (1H, s, NH)
6	3400, 3050, 2220, 1600, 1500, 1480, 1380, 1330, 1280	7.16-7.37 (7H, m, H_{Ar} + NH_2); 7.57-7.72 (6H, m, H_{Ar}); 10.47 (1H, s, NH)

Treatment of the thioacetamide **1a** with sodium acetate gives the thiolate **7** which reacts with the chloroacetates **2a,e,f** as with 1,2-dielectrophiles by a [3+2] type cyclocondensation. It is likely that the intermediates in this reaction are the sulfides **8** which eliminate ethanol to give the thiazolidin-4-ones **4b-d**. It should be noted that, in this case, the substituent in the phenyl rings of the [(aryl)hydrazono]chloroacetates **2a,e,f** starting materials do not affect the course of the cyclocondensation.

As is known [8, 10, 12], the reaction of excess triethylamine with the [(aryl)hydrazono]chloroacetates **2** is a method for preparing nitrilimine **9** *in situ* which probably electrophilically attacks thioamide **1a** to give the intermediate product **10**. The direction of the cyclization of sulfides **10** depends on the nature of the substituents in the phenyl rings of the starting chloroacetates **2a-e**. The presence of electron acceptor substituents lowers the electron density on the negatively charged N atom of compound **10**, deactivating it and leading to the formation of the thiazolidin-4-ones **4a,b**.

In the case of electron donor substituents (Ar = Ph, 3-MeC_6H_4) the intermediate **10** undergoes an intramolecular nucleophilic attack at the activated double bond and is converted to the intermediate product **11**. Intermediate **11** adds a proton and eliminates arylamine to form the 1,3,4-thiadiazoles **3a-c**.

The products of the reaction of thioamide **1b** with the chloroacetates **2a,d** in the presence of both triethylamine and also of sodium ethylate are the sulfides **5a,b**. This fact occurs because thioamide **1b** in basic medium can decompose to malonodinitrile and hydrogen sulfide [13]. Alkylation of the latter by the hydrazones **2a,b** also leads to preparation of the sulfides **5a,b**.

Formation of thiophene **6** is explained by the low reactivity of ethyl [(4-methoxyphenyl)hydrazono]-chloroacetate **2f**. Hence thioamide **1a** is dimerized via a Gewald reaction [14] in triethylamine as was shown by us earlier [15]. It should be noted that the chloroacetate **2f** does not react with other dinucleophiles as has been reported in [9].

Hence by variation of the substituent in the starting [(aryl)hydrazono]chloroacetates and the medium basicity it is possible to target in preparative yields (51-70%) the synthesis of the heterocycles 3-aryl-2-cyanomethylidene-5-ethoxycarbonyl-1,3,4-thiadiazoles and 5-arylhydrazono-2-cyanomethylidene-3-phenyl-thiazolin-4-ones. The reaction of [(aryl)hydrazono]chloroacetates with 2-cyanothioacetamide is a method of synthesizing di(carbethoxy[(aryl)hydrazono]methyl)sulfides in 52-60% yield.

EXPERIMENTAL

^{1}H NMR Spectra were recorded on a Varian-300 (300 MHz) spectrometer using DMSO-d_6 and with TMS as internal standard. IR Spectra were taken on a UR-20 instrument for KBr tablets.

Reaction of N-R-2-cyanothioacetamides 1a,b with ethyl [(aryl)hydrazono]chloroacetates 2a-f in the presence of triethylamine. A solution of the chloroacetate **2a-f** (2 mmol) in ethanol (30 ml) was added dropwise with stirring to a solution of the thioamide **1a,b** (0.352 g, 2 mmol) and triethylamine (0.404 g, 4 mmol) in ethanol (30 ml) at 0°C. The reaction product was stirred for 5-6 h at 0°C and 5-6 h at 20°C. Ethanol was evaporated on a rotary evaporator and the crystalline residue was washed with water (5 x 40 ml), dried, and recrystallized from ethanol.

Reaction of N-R-2-cyanothioacetamides 1a,b with ethyl [(aryl)hydrazono]chloroacetates 2a,e,f in the presence of sodium ethylate. A solution of the chloroacetate **2a,e,f** (2 mmol) in anhydrous ethanol (30 ml) was added with stirring to a solution of the thioamide **1a,b** (0.352 g, 2 mmol) and sodium ethylate (0.136 g, 2 mmol) in anhydrous ethanol (30 ml) at 0°C. The reaction product was stirred for 3-4 h at 20°C until the crystallization had finished and the precipitated thiazolidin-4-one **4b-d** (sulfide **5a**) was filtered off, washed with water (2×30 ml), dried, and recrystallized from ethanol.

Synthesis of 5-amino-3-cyano-2-phenylamino-4-(N-phenylaminothiocarbonyl)thiophene (6). A solution of the chloroacetate **2f** (0.513 g, 2 mmol) in ethanol (30 ml) was added with stirring to a solution of the thioamide **1a** (0.352 g, 2 mmol) and triethylamine (0.404 g, 4 mole) in ethanol (30 ml) at 0°C. The reaction product was stirred for 5-6 h at 0°C and for 5-6 h at 20°C. The precipitate was washed with ether (2x5 ml), dried, and recrystallized from ethanol.

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