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SYNTHESIS OF 2-AMINO-4-ARYL-3-CYANO-5-HYDROXYIMINO-4,5-DIHYDROTHIOPHENES

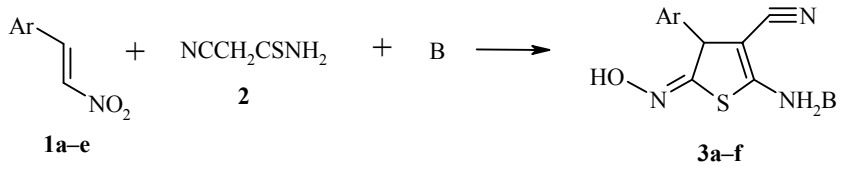
K. S. Chunikhin, L. A. Rodinovskaya, and A. M. Shestopalov

The Michael addition of cyanothioacetamide to nitrostyrenes was investigated. Previously unknown 2-amino-4-aryl-3-cyano-5-hydroxyimino-4,5-dihydrothiophenes were obtained.

Keywords: Nitrostyrenes, cyanothioacetamide, Michael addition.

Aliphatic nitro compounds are of interest as reactive starting materials in the synthesis of heterocycles both with and without a nitro group [1]. We made a systematic study of the reactions of α-carbonyl and α,β-unsaturated nitro compounds with various CH-nucleophiles and determined their regioselectivity, which depends on the structure of the initial compounds and the reaction conditions. It has been shown that the products from the reactions of the nitro compounds with the CH-nucleophiles can be both acyclic compounds and heterocycles of the indolizine, thiophene, and pyridine series [2-5].

We established that the reaction between the nitrostyrenes **1a-e**, cyanothioacetamide **2**, and an equivalent of tetramethylethylenediamine (TMEDA) or morpholine takes place in ethanol at room temperature with the formation of compounds **3a-f** with yields of 30-60%.



1a–e **2** **3a–f**

1a, **3a**,**f** Ar = Ph; **1**, **3 b** Ar = 4-ClC_6H_4, **c** Ar = 2-C_4H_3S, **d** Ar = 4-FC_6H_4, **e** Ar = 4-$MeOC_6H_4$;

3 a–e B = 0.5($Me_2NCH_2CH_2NMe_2$), **f** B = 

Compounds **3a-f** are complexes of 2-amino-4-aryl-3-cyano-5-hydroxyimino-4,5-dihydrothiophenes with the bases in ratios of 2:1 in the case of TMEDA **3a-e** and 1:1 in the case of morpholine **3f**. By conducting the reaction in the presence of ethyl ether it is possible to obtain compounds **3a-f** with yields of 50-80% [6].

Further study of the reaction showed that compounds not containing the base combined into a complex can be isolated. Thus, 2-amino-4-aryl-3-cyano-5-hydroxyimino-4,5-dihydrothiophene **4a** is formed with an almost quantitative yield when the nitrostyrene **1a** is briefly boiled with cyanothioacetamide **2** in the presence of

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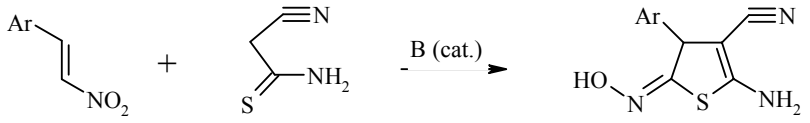
N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913; e-mail: chunihin@yandex.ru, e-mail: amsh@zelinsky.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1472-1477, October, 2007. Original article submitted July 18, 2003. Revision submitted June 14, 2007.

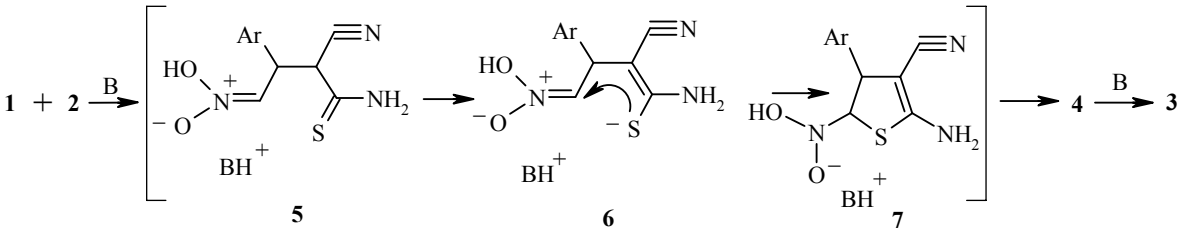
catalytic amounts of morpholine. We were also able to obtain compounds **4b-e** with high yields by stirring the corresponding nitrostyrenes **1a-d**,**f** with cyanothioacetamide **2** in ethanol at room temperature with the addition of catalytic amounts of morpholine.



1a-d,f **2** **4a-e**

1, 4 a Ar = Ph, **b** Ar = 4-ClC_6H_4, **c** Ar = 2-C_4H_3S, **d** Ar = 4-FC_6H_4; **1f, 4e** Ar = 4-BrC_6H_4

The reaction mechanism probably includes initial addition of the cyanothioacetamide **2** to the nitrostyrenes **1** by a Michael reaction with the formation of the adduct **5** and subsequent intramolecular cyclization with participation of the aci form of the nitro compound **6**. If a sufficient quantity of the base is present the thiophenes **4** are converted into the complexes **3**.



It is known that nitrostyrenes are capable of adding various nucleophiles, such as CH acids, by a Michael reaction [7]. At the same time it is known that cyanothioacetamide on account of its CH acidity has been used in the synthesis of sulfur-containing heterocycles [8].

TABLE 1. The Characteristics of Compounds **3a-f** and **4a-e**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, % (method)
		C	H	N	S		
3a	$C_{28}H_{34}N_8O_2S_2$	57.94 / 58.11	5.67 / 5.92	19.21 / 19.36	10.87 / 11.08	127128	59 (A), 70 (B)
3b	$C_{28}H_{32}Cl_2N_8O_2S_2$	51.79 / 51.93	4.78 / 4.98	17.17 / 17.30	9.78 / 9.90	114-115	23 (A), 80 (B)
3c	$C_{24}H_{30}N_8O_2S_4$	48.59 / 48.79	4.97 / 5.12	19.21 / 18.97	21.87 / 21.71	127-128	56 (A), 65 (B)
3d	$C_{28}H_{32}F_2N_8O_2S_2$	54.59 / 54.71	5.07 / 5.25	18.31 / 18.23	10.27 / 10.43	124-125	25 (A)
3e	$C_{30}H_{38}N_8O_4S_2$	56.29 / 56.41	6.07 / 6.00	17.37 / 17.54	9.87 / 10.04	138-139	53 (A), 65 (B)
3f	$C_{15}H_{18}N_4O_2S$	56.49 / 56.58	5.77 / 5.70	17.71 / 17.60	9.88 / 10.07	135-136	56 (A)
4a	$C_{11}H_9N_3OS$	57.19 / 57.13	3.97 / 3.92	18.01 / 18.17	13.67 / 13.86	154-155	98 (A), 75 (B)
4b	$C_{11}H_8ClN_3OS$	50.01 / 49.72	3.18 / 3.03	15.97 / 15.81	12.16 / 12.07	144-145	80 (B)
4c	$C_9H_7N_3OS_2$	45.59 / 45.55	2.92 / 2.97	17.41 / 17.71	27.17 / 27.02	147-148	78 (B)
4d	$C_{11}H_8FN_3OS$	53.09 / 53.00	3.07 / 3.23	16.51 / 16.86	12.77 / 12.86	153-154	75 (B)
4e	$C_{11}H_8BrN_3OS$	42.39 / 42.60	2.27 / 2.60	13.71 / 13.55	10.57 / 10.34	155-156	78 (B)

TABLE 2. ^{1}H IR and NMR Spectra of the Synthesized Compounds

Com-pound	IR spectrum, ν, cm^{-1}				^{1}H NMR spectrum, δ, ppm (^3J, Hz)				
	CN	NH_2,	C=NOH	OH	NH_2, (2H, s)	OH, (1H, s)	Ar, Alk	H-4, (1H, s)	Base
3a	2200	1632	1592		7.45	11.53	7.21-7.39 (5H, m)	5.09	2.14 (6H, s); 2.30 (2H, s)
3b	2192	1640	1590		7.49	11.58	7.25 (2H, m); 7.41 (2H, s)	5.14	2.12 (6H, s); 2.31 (2H, s)
3c	2192	1632	1584		7.52	11.54	7.00 (2H, m); 7.35 (1H, m)	5.39	2.12 (6H, s); 2.31 (2H, s)
3d	2192	1636	1592		7.39	11.42	7.10 (2H, m); 7.29 (21H, m)	5.13	2.12 (6H, s); 2.31 (2H, s)
3e	2190	1638	1580		7.44	11.51	3.80 (3H, s, CH_3); 6.91 (2H, d, J = 7.8, Ar); 7.08 (2H, d, J = 7.8, Ar)	5.01	2.12 (6H, s); 2.31 (2H, s)
3f*	2200	1632	1592		7.45	11.53	7.21-7.39 (5H, m)	5.09	2.65 (4H, m); 3.48 (4H, m)
4a	2200	1632	1592	3432	7.45	11.53	7.21-7.39 (5H, m)	5.09	
4b	2188	1628	1584	3620	7.49	11.58	7.25 (2H, d, J = 7.7, Ar); 7.41 (2H, d, J = 7.7, Ar)	5.12	
4c	2196	1628	1584	3428	7.45	11.54	7.00 (2H, m); 7.45 (1H, m)	5.39	
4d	2196	1628	1584	3628	7.52	11.62	7.10-7.30 (4H, m)	5.13	
4e	2188	1632	1580	3612	7.41	11.53	7.21 (2H, d, J = 7.8, Ar); 7.59 (2H, d, J = 7.8, Ar)	5.09	

* ^{13}C NMR spectrum, δ, ppm: 45.74 and 67.00 ($C_{morpholine}$); 53.40 (C-3); 69.49 (C-4); 117.51 (C≡N); 127.50; 128.76; 141.10 (C_6H_5); 153.85 (CNH_2); 158.56 (C=NOH).

The synthesis of 2-amino-3-cyano-4,5-dihydrothiophenes has previously been represented by a few examples [9-12], and the formation of compounds **3** and **4** was quite unexpected. The expected products were 2,5-diamino-4-aryl-3-cyanothiophenes [13]. Earlier we obtained 2N-acylated derivatives of 2,5-diamino-4-aryl-3-cyanothiophenes [4] on the basis of Michael addition of α-nitro ketones to arylmethylene-cyano-thioacetamides. Compounds of the 2-amino-3-cyanothiophene series are of interest as biologically active compounds [14] and as starting compounds in the synthesis of annulated heterocycles [15]. The reaction of thioamides with nitrostyrenes has hardly been studied at all. Two examples of the reaction of β-nitrostyrenes with N-aryl-substituted thioamides of 3-oxopropionic acids leading to the formation of 3-aroyl-4-aryl-2-arylamino-5-hydroxyimino-4,5-dihydrothiophenes are known [16, 17].

The structure of compounds **3a-f** and **4a-e** was established by IR and ^{1}H NMR spectroscopy. Apart from the signals of the aryl protons the ^{1}H NMR spectra contain signals of the amino group in the region of 7.39-7.52 ppm, close to the data obtained for 2-amino-3-cyano-4,5-dihydrothiophenes (7.12-7.30 ppm) [11]. Compounds **3a-f** and **4a-e** are characterized by signals for the H-4 protons in the region of 5.01-5.39 ppm, observed in 3-aroyl-4-aryl-2-arylamino-5-hydroxyimino-4,5-dihydrothiophenes [16, 17]. The spectra also contain broad singlets for the OH groups in the range of 11.42-11.58 ppm. The IR spectra contain strong absorption bands for the conjugated nitrile group in the region of 2188-2200 and for the amino group in the region of 1628-1640 cm^{-1}, characteristic of 2-amino-3-cyano-4,5-dihydrothiophenes [11]. The hydroxy group of compounds **4a-e** appears in the region of 3432-3620 and the C=NOH double bond in the region of 1580-1592 cm^{-1}, and this agrees with published data [18].

EXPERIMENTAL

The melting points of the compounds were determined on a Kofler bench. The IR spectra were recorded in tablets with potassium bromide on a Perkin-Elmer 577 instrument. The ^{1}H NMR spectra were obtained in DMSO-d_6 on a Bruker WM-250 spectrometer (250 MHz) with TMS as standard. Elemental analysis was performed on a Perkin-Elmer CHN analyzer.

Complexes of 2-Amino-4-aryl-3-cyano-5-hydroxyimino-4,5-dihydrothiophenes with Amines 3a-f (Tables 1 and 2). A. A suspension of cyanothioacetamide **2** (0.1 g, 1 mmol) and respective *trans*-2-nitrostyrene **1a-e** (1 mmol) in ethanol (1.5 ml) was heated until homogeneous. The solution was then cooled to 25-30°C, a solution of TMEDA (0.06 g, 0.52 mmol) or morpholine (0.1 ml, 1.1 mmol) in ethanol (0.5 ml) was added, and the mixture became hot. When crystallization centers were created colorless crystals of compounds **3a-f** separated.

B. To a suspension of the cyanothioacetamide **2** (0.1 g, 1 mmol) and the respective nitrostyrene **1a-e** (1 mmol) in ethyl ether (2 ml) TMEDA (0.06 ml, 0.52 mmol) in ether (0.5 ml) was added. The mixture was stirred at room temperature, and crystals separated when hexane (0.5 ml) was added. The precipitate was filtered off and washed with ether and hexane.

2-Amino-3-cyano-4-aryl-5-hydroxyimino-4,5-dihydrothiophenes 4a-e (Tables 1 and 2). A. To a solution of cyanothioacetamide **2** (0.2 g, 2 mmol) and nitrostyrene **1a** (0.3 g, 2 mmol) in acetonitrile (5 ml) morpholine (0.2 ml) was added. The reaction mixture was boiled for 3 min and cooled to room temperature, then distilled water (1 ml) was added, and the mixture was stirred for 10 min. Yield 0.45 g (98%); mp 154-155°C. The precipitate was filtered off and washed with water and hexane

B. To a solution of cyanothioacetamide **2** (0.5 g, 5 mmol) and the respective nitrostyrene **1a-d**,**f** (5 mmol) at room temperature dropwise with vigorous stirring a solution of morpholine (0.02 ml) in ethanol (1 ml) was added. The mixture was stirred, and colorless crystals of compounds **4a-e** appeared. To the solution with stirring water (3 ml) was added. The precipitate was filtered off and washed with a 1:1 mixture of water and ethanol, with water, and with hexane.

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