SYNTHESIS OF CYANOAMINOTHIOPHENES WITH ACTIVE FUCTIONAL GROUPS

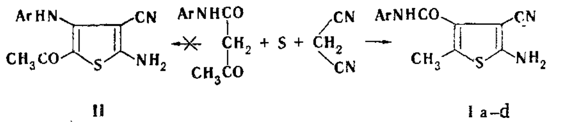
L. G. Sharanina and S. N. Baranov

UDC 547.733'853.7.07

2-Amino-3-cyano-4-N-arylcarbamoyl-5-methylthiophenes were obtained by condensation of arylamides of acetoacetic acid with sulfur and malononitrile in absolute alcohol. 4-Amino-6-N-arylcarbamoyl-5-methylthieno[2,3-d]pyrimidines are formed by reaction of the condensation products with formamide.

2-Aminothiophenes containing alkyl or aryl groups in the 3,4 positions were obtained by Knoevenagel condensation of carbonyl compounds with sulfur and nitriles containing an active methylene group [1, 2].

We have carried out a condensation of the Knoevenagel type using anilides of acetoacetic acid, malononitrile, and sulfur in ethanol. One might have expected the formation of 2-amino-3-cyanothiophenes of the I or II type:

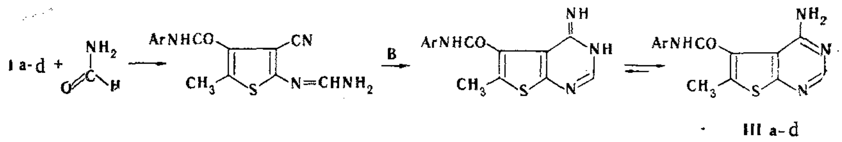


a Ar = C_6H_5; b Ar = 4-$CH_3C_6H_4$; c Ar = 4-ClC_6H_4; d Ar = 2,5-$Cl_2C_6H_3$

We have shown that the reaction leads primarily to derivatives of the I type (Table 1). A small amount of 3-cyano-4-methyl-5-anilino-2-pyridone was isolated as a side product; the structure of the side product was confirmed by alternative synthesis by a known method for the preparation of pyridone [3] from acetoacetic acid anilide and malononitrile in dimethylformamide in the presence of an organic base.

The IR spectra of 2-amino-3-cyanothiophenes I, contain four absorption bands of free and bonded amino groups at 3200-3500 cm^{-1} [4, 5]. The absorption band at 2220 cm^{-1} is affiliated with the stretching vibrations of a nitrile group bonded to an aromatic heterocycle [4, 5]. The intense broad absorption band with two maxima at 1610 and 1645 and a shoulder at 1660 cm^{-1} apparently corresponds to the deformation vibrations of the aromatic rings, the stretching vibrations of the oxo group, and the deformation vibrations of the amino group [4, 5].

The presence of vicinal functional amino and nitrile groups made it possible to carry out the reaction of substituted thiophene with formamide. 4-Aminothieno[2,3-d]pyrimidines III (Table 2) were isolated in quantitative yields. On the basis of the available data [2, 6, 7], the following scheme can be assumed for the reaction:



To choose between structures of the I or II types, we carried out the hydrolysis of both the 2-aminothiophene derivatives and the 4-aminothieno[2,3-d]pyrimidines. The hydrolysis of compounds of the I type by refluxing in alcoholic alkali apparently proceeds with cleavage of the thiophene ring, and the reaction

---

Donetsk State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 196-198, February, 1974. Original article submitted October 2, 1972.

TABLE 1. 2-Amino-3-cyano-4-N-arylcarbamoyl-5-methylthiophenes (Ia-d)

Compound	Ar	Mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	N	S	C	H	N	S	
Ia	C_6H_5	199	$C_{13}H_{11}N_3OS$	60,4 60,6	4,4 4,2	16,2 16,5	12,4 12,3	60,7	4,3	16,3	12,5	70
Ib	4-$CH_3C_6H_4$	232	$C_{14}H_{13}N_3OS$	62,0 61,8	4,8 4,9	15,3 15,6	11,9 11,7	62,0	4,8	15,5	11,8	63
Ic	4-ClC_6H_4	226	$C_{13}H_{10}ClN_3OS$[a]	53,5 53,4	3,6 3,6	14,0 14,3	11,0 10,8	53,5	3,5	14,4	11,0	60
Id	2,5-$Cl_2C_6H_3$	312	$C_{13}H_9Cl_2N_3OS$[b]	47,5 47,6	2,8 2,6	12,6 12,7	9,7 9,8	47,9	2,8	12,9	9,8	68

---

[a] Found, %: Cl 12.3, 12.1. Calculated, %: Cl 12.2.

[b] Found, %: Cl 21.7, 21.5. Calculated, %: Cl 21.4.

TABLE 2. 4-Amino-5-N-arylcarbamoyl-6-methylthieno[2,3-d]-pyrimidines (IIIa-d)

Compound	Ar	Mp, °C	Empirical formula	Found, %				Calc., %			
				C	H	N	S	C	H	N	S
IIIa	C_6H_5	314	$C_{14}H_{12}N_4OS$	59,3 59,1	4,5 4,5	19,9 20,0	10,9 11,1	59,1	4,3	19,7	11,3
IIIb	4-$CH_3C_6H_4$	315	$C_{15}H_{14}N_4OS$	60,7 60,2	5,1 4,9	18,5 18,5	10,4 10,6	60,4	4,7	18,8	10,7
IIIc	4-ClC_6H_4	316	$C_{14}H_{11}ClN_4OS$[a]	52,9 52,3	3,3 3,4	17,4 17,7	9,9 9,8	52,7	3,5	17,6	10,0
IIId	2,5-$Cl_2C_6H_3$	345	$C_{14}H_{10}Cl_2N_4OS$[b]	47,5 47,3	3,0 2,7	15,4 15,7	8,9 8,8	47,6	2,9	15,9	9,1

---

[a] Found, %: Cl 11.0, 11.0. Calculated, %: Cl 11.1.

[b] Found, %: Cl 19.8, 20.1. Calculated, %: Cl 20.1.

products could not be identified. Hydrolysis in acetic acid leads to 2-acetamido-3-cyano-4-carboxy-5-methylthiophene (IV); the nitrile group is not involved in this reaction, in accordance with the data in [8].

4-Aminothieno[2,3-d]pyrimidine IIIa is hydrolyzed to 4-amino-5-carboxy-6-methylthieno[2,3-d]-pyrimidine (V) in an alcohol solution of potassium hydroxide.

Thus the presence of an N-arylcarbamoyl grouping in the products of condensation of acetoacetic acid anilides with malononitrile and sulfur is confirmed; this is evidence in favor of structures of the I and III type for the products.

EXPERIMENTAL

The individualities of all of the synthesized compounds were confirmed by thin-layer chromatography (TLC) on a fixed layer of silica gel–gypsum in chloroform–acetone–carbon tetrachloride (3 : 3 : 5). The IR spectra of KBr pellets of the compounds were recorded.

2-Amino-3-cyano-4-N-phenylcarbamoyl-5-methylthiophene (Ia, Table 1). A 3.6 g (0.02 mole) sample of acetoacetic acid anilide and 0.8 g (0.025 g-atom) of sulfur were dissolved in 10 ml of anhydrous ethanol while heating on a water bath, after which the solution was cooled to room temperature, and 1.32 g (0.02 mole) of malononitrile and 2 ml of morpholine were added. The reaction mixture began to darken and warmed up to 60-65°; it was heated at 60° for 30 min. It was then cooled to room temperature, during which a brick-red precipitate formed; the alcohol solution was diluted with a twofold to threefold amount of water for complete precipitation. The precipitate was removed by filtration and washed with ethanol. Crystallization from ethanol (chloroform) gave a small amount (0.1-0.2 g) of insoluble 3-cyano-4-methyl-6-phenylamino-2-pyridone with mp 266°. Dilution of the alcohol solution with water gave 3.6 (70%) of Ia.

Thiophene derivatives Ib-d (Table 1) were similarly obtained.

4-Amino-5-N-phenylcarbamoyl-6-methylthieno[2,3-d]pyrimidine (IIIa, Table 2). A mixture of 0.73 g (0.28 mole) of Ia and 5 ml of formamide was heated at 190° on an oil bath for 15 min. It was then cooled, and IIIa was crystallized to give 0.8 g (about 100%) of shiny colorless plates with mp 314° (from dioxane). IR spectrum: ν_{NH_2} 3512, 3406; δ_{NH_2} 1625; $\nu_{C=O}$ 1680 cm^{-1}.

4-Aminothieno[2,3-d]pyrimidine derivatives IIIb-d (Table 2) were similarly obtained.

2-Acetamido-2-cyano-3-carboxy-5-methylthiophene (IV). A 0.52 g (0.002 mole) sample of Ia was refluxed in a mixture of 5 ml of concentrated hydrochloric acid and 5 ml of glacial acetic acid for 4 h. The mixture was then cooled to room temperature and worked up to give 0.24 g (50%) of a white precipitate of IV with mp 324° (from dioxane). IR spectrum: 2220 ($C\equiv N$), 1720 cm^{-1} (COOH). Found, %: C 48.1, 48.0; H 3.7, 3.5; N 12.3, 12.5; S 14.0, 14.1. $C_9H_8N_2O_3S$. Calculated, %: C 48.2; H 3.6; N 12.5; S 14.3.

4-Amino-5-carboxy-6-methylthieno[2,3-d]pyrimidine (V). A 0.4 g (0.014 mole) sample of IIIa was refluxed in alcoholic potassium hydroxide solution for 4 h. The reaction mixture was treated with hydrochloric acid until it was weakly acidic, and the mixture was filtered to give 0.075 g (26%) of V with mp 333° (from dioxane). Found, %: C 46.2, 45.9; H 3.2, 3.1; N 20.0, 19.7; S 15.3, 15.4. $C_8H_7N_3O_2S$. Calculated, %: C 46.0; H 3.4; N 20.2; S 15.4. IR spectrum: a number of absorption bands at 3200-3500 cm^{-1}; δ_{NH_2} 1630 cm^{-1}; ν_{COOH} 1720 cm^{-1}.

LITERATURE CITED

1. K. Gewald, E. Schinke, and H. Bötteher, Ber., 99, 94 (1966).
2. E. C. Taylor and I. E. Berger, Angew. Chem., 78, 144 (1966).
3. U. Basu, J. Indian Chem. Soc., 7, 815 (1930).
4. A. R. Katritzky and A. P. Ambler, in: Physical Methods in Heterocyclic Chemistry, Chap. 10, Academic (1963).
5. K. Nakanishi, Infrared Spectra and Structure of Organic Compounds [Russian translation], Mir, Moscow (1965).
6. E. C. Taylor and A. Abul-Husn, J. Org. Chem., 31, 342 (1966).
7. E. C. Taylor, A. McKillop, and R. V. Pavindrathan, Angew. Chem., 78, 332 (1966).
8. Yu. A. Sharanin, Dissertation [in Russian], Leningrad (1967).