Chemistry of Heterocyclic Compounds, Vol. 49, No. 3, June, 2013 (Russian Original Vol. 49, No. 3, March, 2013)

DIRECTION OF 3-BROMOTHIOPHENE ACYLATION WITH SUCCINYL CHLORIDE

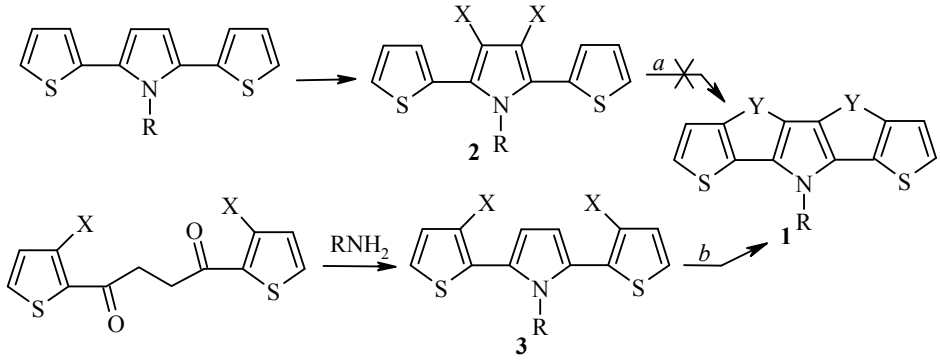
V. I. Smirnov[1], A. V. Afanas'ev[1], I. S. Prostakishin[1], and L. I. Belen'kii[2]*

In the reaction of 3-bromothiophene with succinyl chloride in the presence of $AlCl_3$, a mixture of three isomeric dibromo-substituted 1,4-di(2-thienyl)butane-1,4-diones was formed. The main component was the unsymmetrical 1-(3-bromo-2-thienyl)-4-(4-bromo-2-thienyl)butane-1,4-dione rather than 1,4-di-(3-bromo-2-thienyl)butane-1,4-dione expected according to the orientation rules.

Keywords: 3-bromothiophene, dibromo-1,4-di(2-thienyl)butane-1,4-diones, succinyl chloride, thiophene, acylation.

In recent years, 2,5-di(2-thienyl)pyrroles have been used more frequently for the preparation of organic polymers and semiconductors [1, 2]. It is also known that such compounds are capable of exhibiting photochromic properties [3, 4].

In addition, coplanar polycyclic conjugated systems **1**, alternative paths for the synthesis of which are presented in the scheme below, can be obtained on the basis of dithienylpyrroles. It is clear that the dithienylpyrrole precursor in both cases during cyclization must adopt the thermodynamically unfavorable, nearly coplanar conformation with strong steric interactions between the substituents in the heterocycles.



*To whom correspondence should be addressed, e-mail: libel@ioc.ac.ru.

[1]M. V. Lomonosov Moscow Academy of Fine Chemical Technology, 86 Vernadskogo Ave., Moscow 119571, Russia; e-mail: mitht406@mail.ru.
[2]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Ave., Moscow 119991, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 416-422, March, 2013. Original article submitted August 8, 2012; revision submitted January 25, 2013.

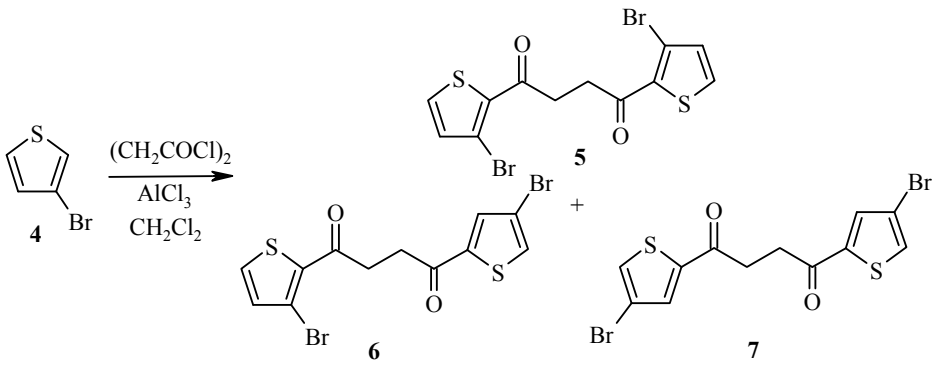
Our previous attempt to obtain compounds **1** by the cyclization of dithienylpyrroles **2**, disubstituted at the β-positions of pyrrole ring (R = Me, *p*-C_8H_{17}, X = CH_2OH) (path *a*), was unsuccessful due to competing intermolecular processes [5]. At the same time, we hoped that the use of precursors **3** with substituents at positions 3 and 3' of the thiophene rings would make it possible to synthesize the targeted polycyclic compounds **1** (path *b*).

Most often used for the preparation of 2,5-di(2-thienyl)pyrroles is the Paal–Knorr reaction, as a result of which 1,4-bis(2-thienyl)butane-1,4-diones undergo cyclization upon the action of primary amines in an acidic medium and form the targeted compounds in high yields. From the same diketones in a similar way, it is possible to obtain structures containing a thiophene or furan ring in place of the pyrrole ring. 1,4-Dithienylbutane-1,4-diones are therefore suitable starting compounds for the synthesis of a whole series of systems like terthienyl.

A number of syntheses of these diketones have been described in the literature. Notable among them is the Michael–Stetter condensation, which involves the addition of aldehydes at the activated double bond of enones in the presence of a cyanide or thiazolium salt [6, 7]. We note also the method proposed by Kulinkovich and co-workers, which is based on the condensation of acetylthiophenes with bromoacetylthiophenes by the action of various bases [8]. A disadvantage of these and many other methods is that they are multistage processes (if we start from the corresponding thiophenes).

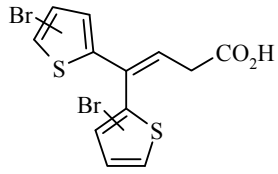
The most promising version of the synthesis of symmetrical 1,4-dithienylbutane-1,4-diones is the single-stage acylation of the correspoding thiophenes with succinyl chloride. However, under the standard conditions for thiophene acylation with $SnCl_4$ as catalyst, only the monoacylation product 4-oxo-4-(2-thienyl)-butyric acid was formed [9]. It was possible to obtain 1,4-di(2-thienyl)butane-1,4-dione [10] and its analogs by this method in the presence of aluminum chloride. However, the yields of the targeted diketones mostly did not exceed 50% [10-12], and only in the case of 2-bromothiophene did the yield amount to 61% [13]. The reasons for this were discussed in the work [12].

It should be noted that nearly all the papers on the acylation of thiophenes with succinyl chloride only concern the first member of the series and its 2-substituted derivatives. The only exception is 3-methylthiophene, the acylation of which was examined briefly in the work [11]. It therefore seemed of interest to investigate the acylation of 3-bromothiophene (**4**) with succinyl dichloride under Friedel–Crafts conditions as a possible direct method for the synthesis of 1,4-bis(3-bromothiophen-2-yl)butane-1,4-dione (**5**). It must be emphasized that subsequent substitution of the bromine atoms in thiophene rings opens up wide possibilities for the modification of compound **5**. Moreover, the highest yield of the corresponding 1,4-diketone was obtained in the reaction of succinyl chloride with 2-bromothiophene [13].



However, the 3-bromothiophene (**4**) gave a multicomponent mixture upon acylation, the ^{1}H NMR spectrum of which indicated that besides the targeted diketone **5** it also contained two of its isomers **6** and **7**. The total yield of compounds **5-7** amounted to ~42%.

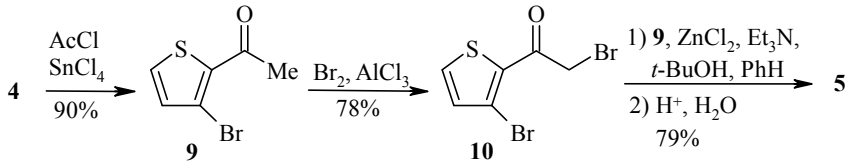
The spectrum of the reaction mixture also contained signals belonging, in our opinion, to the unsaturated acids **8**. In particular, the chemical shifts of the triplet at 6.16 ppm (1H, J = 7.4 Hz) and its associated doublet at 3.33 ppm (2H, J = 7.4 Hz) practically coincided with the values for the vinyl proton and the CH_2 group of analogous compounds that we obtained earlier by the action of succinyl chloride on thiophene, 2-bromothiophene and 2-methylthiophene [12].



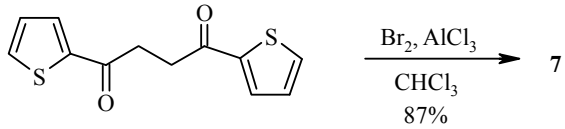
8

After treatment with a solution of $NaHCO_3$, the obtained mixture was separated into ketone and acid fractions (~45 and ~35% yields, respectively). Unfortunately we were unable to isolate the individual ketones and acids. Authentic samples were therefore prepared in order to establish the ratios of compounds **5-7** in the ketone fraction.

The previously unknown diketones **5** and **6** were synthesized by the Kulinkovich method [8] from 3-bromothiophene (**4**) and 2-acetylthiophene (**11**).



The previously described diketone **7** [14, 15] was obtained in 87% yield (mp 134-136°C) through bromination of 1,4-di(2-thienyl)butane-1,4-dione in the presence of an excess of aluminum chloride by analogy to the preparation of 2-acetyl-4-bromothiophene (**12**) [16].



We note that the procedure presented in the paper [14] has only slight differences from ours, and the ^{1}H NMR spectrum of the compound that we obtained matches that described in the paper [14], but a melting point of 172°C was reported there for the product **7**. At the same time, a melting point of 142-143°C [15], close to our value, was given for the diketone **7** obtained by the Stetter method and purified by silica gel chromatography. It can therefore be assumed that the melting point of the diketone **7** given in the paper [14] is a misprint.

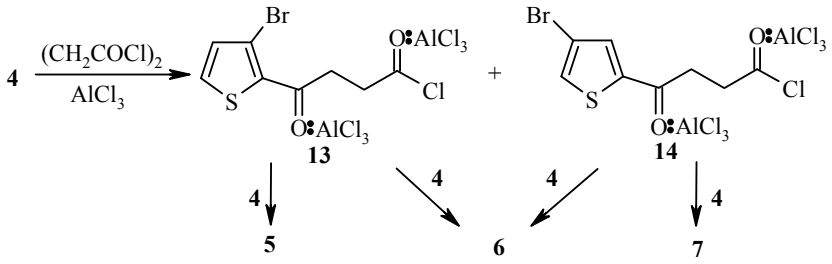
The structure of the diketones **5** and **6** was confirmed by the ^{1}H and ^{13}C NMR spectra, and by elemental analysis, and the previously obtained diketone **7** was also characterized by ^{1}H NMR spectroscopy (Table 1).

Unfortunately, the signals of the diketone **6** in the ^{1}H NMR spectra, recorded in $CDCl_3$, overlapped with the signals of the other two isomers. However, in deuterobenzene these three diketones gave some separate signals, and this enabled determination of their ratio in the reaction mixture.

TABLE 1. ^{1}H NMR Spectra of 1,4-Bis(bromo-2-thienyl)butane-1,4-diones $R^1C_4H_2SCOCH_2CH_2COC_4H_2SR^2$ **5–7**

Diketones			Chemical shifts, δ, ppm (*J*, Hz)					
			$H_{aliph.}$		$H_{arom.}(R^1C_4H_2S)$		$H_{arom.}(R^2C_4H_2S)$	
	R^1	R^2	$R^1C_4H_2SCOCH_2$	$CH_2COC_4H_2SR^2$	β-H (d)	α-H (d)	β-H (d)	α-H (d)
Solvent $CDCl_3$								
5	3-Br	3-Br	3.50 (s)	3.50 (s)	7.12 (*J* = 5.2)	7.53 (*J* = 5.2)	7.12 (*J* = 5.2)	7.53 (*J* = 5.2)
6	3-Br	4-Br	3.53 (t, *J* = 6.3)	3.34 (t, *J* = 6.3)	7.12 (*J* = 5.2)	7.53-7.55 (m)	7.53-7.55 (m)	7.71 (*J* = 1.4)
7	4-Br	4-Br	3.36 (s)	3.36 (s)	7.55 (*J* = 1.3)	7.72 (*J* = 1.3)	7.55 (*J* = 1.3)	7.72 (*J* = 1.3)
Solvent C_6D_6								
5	3-Br	3-Br	3.16 (s)	3.16	6.52 (*J* = ~5)	7.10 (*J* = ~5)	6.52 (*J* = ~5)	7.13 (*J* = ~5)
6	3-Br	4-Br	3.13 (t, *J* = 6.3)	2.70 (t, *J* = 6.3)	6.52 (*J* = ~5)	7.12 (*J* = ~5)	6.67 (*J* = 1.4)	7.13 (*J* = 1.4)
7	4-Br	4-Br	2.66 (s)	2.66 (s)	6.67 (*J* = 1.5)	7.10 (*J* = 1.4)	6.67 (*J* = ~1.5)	7.10 (*J* = 1.4)

To our surprise, we found that the ratio of the diketones **5**:**6**:**7** was 1.0:1.6:0.5. At the same time, in the model reaction of 3-bromothiophene (**4**) with acetyl chloride in the presence of $AlCl_3$, the isomeric ketone ratio amounted to ~10:1 in favor of the expected 2-acetyl-3-bromothiophene (**9**). If succinyl chloride and the intermediate acyl chloride complexes **13** and **14** exhibited the same regioselectivity towards 3-bromothiophene (**4**) as acetyl chloride, then the complexes **13** and **14** would be formed at the first acylation stage in the same ~10:1 ratio, which would lead to ~81:18:1 mixture of the diketones **5**, **6**, and **7** at the second stage of the reaction.



Such a deviation can be explained by the steric hindrance due to the bromine atom, which hinders an attack towards position 2 by the bulky $AlCl_3$ complexes of succinyl chloride or by the acyl chloride complexes **13** and **14**. During the formation of diketone **4**, the steric hindrance should appear at both acylation stages, whereas for the diketone **5** it should appear at one of the stages only.

Thus, the acylation of 3-bromothiophene with succinyl chloride is not a feasible method for the synthesis of 1,4-bis(3-bromo-2-thienyl)butane-1,4-dione due to the formation of at least three isomeric diketones. At the same time, the preferential formation of the unsymmetrical diketone in this reaction may be of some interest, although the possibility of its isolation requires further investigation.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer (300 and 75 MHz, respectively) with the residual proton signals of chloroform (7.27 ppm) or benzene (7.16 ppm) as standard for ^{1}H nuclei, and chloroform (77.0 ppm) for ^{13}C nuclei. The reaction progress and the product purity were

monitored by TLC on Silufol UV-254 plates with 1:4 ethyl acetate–hexane, 1:2 methylene chloride–petroleum ether (40-60°C), and other mobile phases, with visualization in iodine vapor or in UV light. The melting points were determined on a Boetius microscope hot stage apparatus.

2-Acetyl-3-bromothiophene (**9**) [17], 3-bromo-2-(bromoacetyl)thiophene (**10**) [18], and 2-acetyl-4-bromothiophene (**12**) [16], as well as succinyl chloride [19] were obtained by known methods. 2-Acetylthiophene (**11**) and 3-bromothiophene (**4**) were purchased from Sigma-Aldrich.

Reaction of 3-Bromothiophene with Succinyl Chloride (General Method). A solution of succinyl chloride (0.50 ml, 4.5 mmol) and 3-bromothiophene (**4**) (0.95 ml, 10.0 mmol) in dry CH_2Cl_2 (3 ml) was added dropwise with cooling and stirring to a suspension of $AlCl_3$ (4.10 g, 30.7 mmol) in dry CH_2Cl_2 (7 ml). The mixture was then refluxed with stirring for 6 h and poured onto ice (60-70 g), conc. HCl (1 ml) was added, and the mixture was stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×30 ml). The combined organic extracts were washed with 2 N HCl solution and twice with water, dried over Na_2SO_4, filtered, and evaporated on a rotary evaporator to give the product as an oil (1.85 g) (a mixture of the diketones **5-7** and the acids **8**).

The mixture was dissolved in CH_2Cl_2 and washed three times with a saturated solution of sodium bicarbonate. The organic phase was separated, dried over Na_2SO_4, and evaporated on a rotary evaporator. The product was obtained as oil (0.77 g, 42% yield, a mixture of diketones **5-7**). According to the ^{1}H NMR spectrum, the ratio of **5** : **6** : **7** was equal to 1.0:1.6:0.5.

Concentrated hydrochloric acid was added to the aqueous layer to pH 2, and the product was extracted with CH_2Cl_2 (3×25 ml). The organic layer was washed with hydrochloric acid solution (1:10) and with water, dried over Na_2SO_4, and evaporated. The product was obtained as an oil (0.66 g, 36%), which presumably represented a mixture of the acids **8**. The losses of 0.42 g were due to the difficulty of separating the stable emulsions, as the acids **8** acted as surfactants. The ^{1}H NMR spectrum in $CDCl_3$ contained coupled triplet at 6.16 ppm (1H) and doublet at 3.33 ppm (2H), J = 7.4 Hz, characteristic of such acids, where the chemical shifts matched the previously obtained analogs [12]. There were also poorly resolved partially overlapping proton signals from the isomeric bromine-substituted thienyl groups.

1,4-Bis(3-bromothiophen-2-yl)butane-1,4-dione (5). $ZnCl_2$ (2.65 g, 19.4 mmol) was calcined under vacuum for 15 min at ~300°C. The flask was then cooled, and a solution of *tert*-butyl alcohol (1.4 ml, 15.0 mmol) and triethylamine (2.1 ml, 15.0 mmol) in dry benzene (10 ml) was added to it. The mixture was stirred for 2 h until the zinc chloride had completely dissolved, after which 2-acetyl-3-bromothiophene (**9**) (3.00 g, 14.6 mmol) and 3-bromo-2-(bromoacetyl)thiophene (**10**) (2.77 g, 9.7 mmol) were added. The reaction mixture was stirred for seven days, after which 5% H_2SO_4 was added. The precipitate was filtered off and washed with benzene. The filtrate was washed with a 5% solution of NaCl, dried over $MgSO_4$, filtered, and evaporated to dryness on a rotary evaporator. The residue was washed on the filter with cold methanol and recrystallized from benzene to give the diketone **5**. Yield 3.14 g (79%); mp 136-138°C. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 36.2 ($\underline{C}H_2CO$); 115.1; 132.9; 134.3; 138.7; 191.2 (CO). Found, %: C 35.37; H 1.90. $C_{12}H_8Br_2O_2S_2$. Calculated, %: C 35.31; H 1.98.

1-(3-Bromothiophen-2-yl)-4-(4-bromothiophen-2-yl)butane-1,4-dione (6). This product was obtained by a similar procedure from ketone **10** (1.48 g, 5.2 mmol) and 2-acetyl-4-bromothiophene (**12**) (1.60 g, 7.8 mmol), *t*-BuOH (0.75 ml, 7.8 mmol), triethylamine (1.10 ml, 7.8 mmol) in dry benzene (5 ml), and zinc chloride (1.42 g, 10.4 mmol). The mixture was stirred for 14 days. The obtained product **5** was recrystallized from ethanol. Yield 0.88 g (42%); mp 133-137°C. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 32.5 ($\underline{C}H_2CO$); 35.4 ($\underline{C}H_2CO$); 110.6; 114.3; 130.7; 132.3; 133.5; 133.9; 137.8; 143.8; 190.1 (CO); 190.3 (CO). Found, %: C 35.45; H 1.81. $C_{12}H_8Br_2O_2S_2$. Calculated, %: C 35.31; H 1.98.

1,4-Bis(4-bromothiophen-2-yl)butane-1,4-dione (7). 1,4-Di(2-thienyl)butane-1,4-dione (0.200 g, 0.8 mmol) was added to a suspension of aluminum chloride (0.375 g, 2.3 mmol) in dry chloroform (10 ml), after which a solution of bromine (0.12 ml, 2.4 mmol) in dry chloroform (3 ml) was added dropwise with cooling. The reaction mixture was stirred for ~16 h and poured into a 2 N HCl solution, and the mixture was stirred for

20-30 min. The organic layer was separated and extracted with chloroform (3×10 ml). The combined extract was washed with a dilute solution of sodium carbonate and with water, dried over $MgSO_4$, evaporated, and the residue was triturated in a small amount of cold ethanol. The precipitate was filtered off and dried. Yield 0.28 g (87%); mp 134-136°C ($CHCl_3$). The ^1H NMR spectrum agreed fully with the spectrum given in the work [14].

Reaction of 3-Bromothiophene (4) with Acetyl Chloride. A solution of 3-bromothiophene (**4**) (0.64 ml, 6.8 mmol) and acetyl chloride (0.50 ml, 7.0 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise over 20 min with stirring and cooling to a suspension of aluminum chloride (1.6 g, 12.0 mmol) in CH_2Cl_2 (10 ml). At the end of the addition, the mixture was heated with stirring for 6 h to 40°C, poured onto ice (100 g), conc. HCl (1 ml) was added, and the mixture was stirred for a further 1 h. The organic phase was separated, and the aqueous layer was extracted with methylene chloride (3×25 ml). The combined extract was washed with hydrochloric acid solution and with water, dried over Na_2SO_4 ,filtered and evaporated, after which 1.27 g (91%) of a mixture of isomeric 2-acetyl-3-bromothiophene (**9**) and 2-acetyl-4-bromothiophene (**12**) was obtained in a ratio of 10:1 (according to the ^1H NMR spectrum).

REFERENCES

1. G. G. Abashev, A. Yu. Bushueva, and E. V. Shklyaeva, *Khim. Geterotsikl. Soedin.*, 167 (2011). [*Chem. Heterocycl. Compd*., **47**, 130 (2011).]
2. K. Ogura, R. Zhao, H. Yanai, K. Maeda, R. Tozawa. Sh. Matsumoto, and M. Akazome, *Bull. Chem. Soc. Jpn*., **75**, 2359 (2002).
3. S. Varis, M. Ak, C. Tanyeli, I. M. Akhmedov, and L. Toppare, *Eur. Polymer J*., **42**, 2352 (2006).
4. J. P. Zonde, M. R. J. Elsegood, and K. S. Ryder, *Acta Cryst*., **C60**, 0166 (2004).
5. L. I. Belen'kii, G. P. Gromova, and V. I. Smirnov, *Khim. Geterotsikl. Soedin.*, 1356 (2008). [*Chem. Heterocycl. Compd*., **44**, 1092 (2008)].
6. H. Stetter and M. Schreckenberg, *Tetrahedron Lett*., **14**, 1461 (1973).
7. H. Stetter and B. Rajh, *Chem. Ber*., **109**, 534 (1976).
8. N. M. Nevar, A. V Kel'in, and O. G. Kulinkovich, *Synthesis*, 1259 (2000).
9. W. Horton, *J. Org. Chem*., **14**, 761 (1949).
10. A. Merz and F. Ellinger, *Synthesis*, 462 (1991).
11. P. E. Just, K. I. Chahe-Ching, and P. C. Lacaze, *Tetrahedron,* **58**, 3467 (2002).
12. V. I. Smirnov, A. V. Afanas'ev, L. I. Belen'kii, *Khim. Geterotsikl. Soedin.*, 1485 (2010). [*Chem. Heterocycl. Compd*., **46**, 1199 (2010)].
13. S. E. Ellinger, *Neue Synthesestrategie zu α- und α,ω-substituierten Oligo- und Polythiophenen und deren Selbstorganisation,* Diss., Ulm (2006).
14. V. Duchenet, C. G. Andrieu, J.-M. Catel, and G. Le Costumer, *Phosphorus*, *Sulfur Silicon Relat. Elem*., **118**, 117 (1996).
15. P. Bilik, F. Tanious, A. Kumar, W. D. Wilson, D. W. Boykin, P. Colson, C. Houssier, M. Facompré, Ch. Tardy, and Ch. Bailly, *ChemBioChem*, **2**, 559 (2001).
16. Ya. L. Goldfarb, G. P. Gromova, and L. I. Belen'kii, *Izv. Akad. Nauk SSR*, *Ser. Khim.*, 1228 (1971).
17. V. A. Smirnov, A. V. Zimichev, G. A. Lyzhova, and A. E. Lipkin, *Khim. Geterotsikl. Soedin.*, 35 (1982). [*Chem. Heterocycl. Compd.*, **18**, 28 (1982)].
18. V. A. Smirnov and A. E. Lipkin, USSR Pat. 341800; *Byul. Izobret.*, No. 19, 101 (1972).
19. Weygand-Hilgetag, *Experimental Methods in Organic Chemistry* [Russian translation], Khimiya, Moscow (1968), p. 234.