Photochromic dihetarylethenes

13.* Optimization of conditions for the acylation of 2,5-dimethylthiophene with squaric acid dichloride

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The conditions for acylation of 2,5-dimethylthiophene with squaric acid dichloride were optimized, and 3,4-bis(2,5-dimethylthiophen-3-yl)cyclobut-3-ene-1,2-dione was obtained in good yield. X-ray diffraction analysis demonstrated that the by-product has the structure of 1a,1b-dichloro-5-(2,5-dimethylthiophen-3-yl)-3-hydroxy-4,5a-dimethyl-1b,4a,5,5a-tetrahydro-1a*H*-1-thiacyclopropa[*a*]pentalen-2-one.

Key words: 2,5-dimethylthiophene, squaric acid dichloride, acylation, protonation, oligomerization.

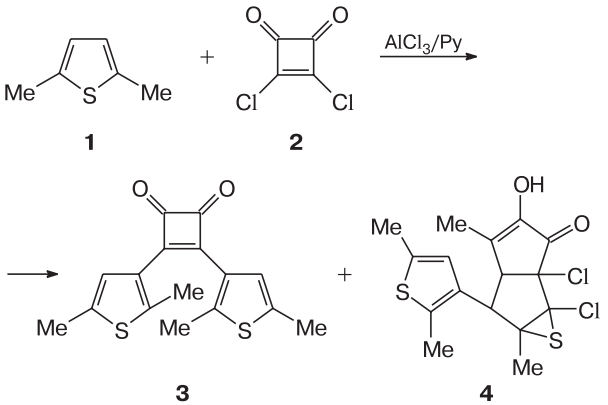
Previously,[2,3] we have developed a new approach to the synthesis of photochromic derivatives of maleic anhydride. Its first step involved the reaction of 2,5-dimethylthiophene (**1**) with squaric acid dichloride (**2**) in the presence of $AlCl_3$ and Py. This reaction afforded 3,4-bis(2,5-dimethylthiophen-3-yl)cyclobut-3-ene-1,2-dione (**3**) as the major product and a noticeable amount of compound **4**. We faced problems in the elucidation of the structure of this compound.

The aim of the present study was to optimize the conditions of the synthesis of the target cyclobutenedione **3**, establish the structure of compound **4**, minimize side processes, and examine the influence of the temperature, the amount of the catalyst, and the nature of the solvent.

We found that the reaction in dichloroethane in the presence of $AlCl_3$ and Py at temperatures varying from −20 to 0 °C afforded compounds **3** and **4** in yields of 30—60 and 18—40%, respectively, the yields being dependent on the temperature, reaction time, and reagent ratio. Acylation of 2,5-dimethylthiophene (**1**) with squaric acid dichloride (**2**) in the absence of Py as well as a decrease in the amount of the catalysts led to a sharp decrease in the yield of product **3** and an increase in the recovery of the starting 2,5-dimethylthiophene. Lowering of the temperature (below −30 °C) did not prevent the formation of by-product **4**, whereas higher temperature (>0 °C) favored to an increase in the amount of resinification products.

The structure of the target product **3** was confirmed by the data from ^{1}H NMR spectroscopy, mass spectrometry, elemental analysis,[2,3] and X-ray diffraction study.[3] In the present study, the ^{13}C NMR spectrum of dione **3** was also recorded (the assignment of the signals was made with the use of the data for 3,4-diphenylbutene-1,2-dione[4]) and the assignment of the maximum peak in the mass spectrum of **3** was corrected. We failed to establish the structure of compound **4** by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. It was X-ray diffraction analysis that allowed us

Scheme 1



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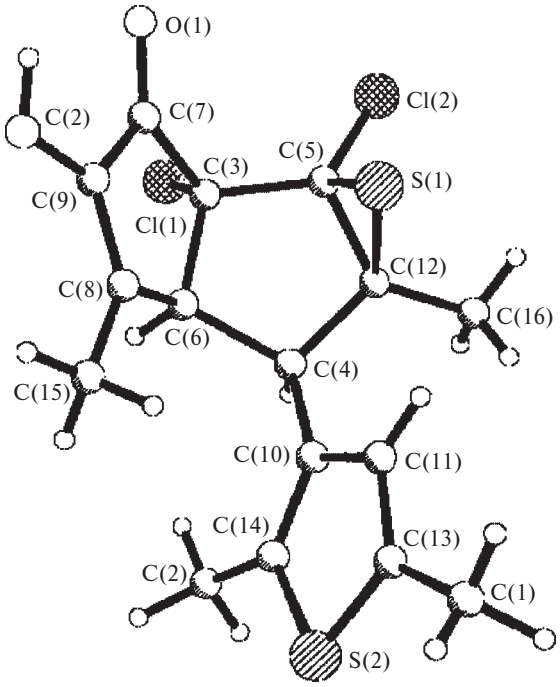


Fig. 1. Molecular structure of compound **4**.

to unambiguously identify compound **4** as 1a,1b-dichloro-5-(2,5-dimethylthiophen-3-yl)-3-hydroxy-4,5a-dimethyl-1b,4a,5,5a-tetrahydro-1a*H*-1-thiacyclopropa[*a*]pentalen-2-one (Scheme 1).

The molecular structure of compound **4** is shown in Fig. 1. The core of the molecule consists of three fused rings, *viz.*, the cyclopentane ring (**A**), the cyclopentene ring (**B**), and the three-membered sulfur-containing heterocycle (**C**). The cyclopentane fragment adopts an envelope conformation with the C(6) atom deviating from the plane (planar to within 0.005 Å) through the remaining four atoms of the ring by 0.326 Å. The ring **B** adopts a flattened envelope conformation with the C(6) atom deviating from the plane through the remaining four atoms by 0.170 Å. The C(8)—C(9) bond length (1.341 Å) corresponds to that of the double sp^2—sp^2 bond. The dihedral angles between the planar fragments of the rings **A** and **B** and of the rings **A** and **C** are 119.10° and 108.30°, respectively. The rings **B** and **C** are bent from the ring **A** in the same direction along the C(3)—C(6) and C(5)—C(12) bonds, respectively, thus imparting a buckled shape to the fused tricyclic fragment of the molecule. The chlorine atoms occupy *exo* positions with respect to the core of the molecule. The pseudoequatorial thiophene ring at C(4) is rotated relative to the planar fragment of the ring **A** by 52.40° and it is in the *endo* orientation with respect to the core of the molecule. The principal geometric parameters of compound **4** are given in Tables 1 and 2. All bond lengths and bond angles have standard values.

Table 1. Principal bond lengths (*d*) in molecule **4**

Bond	*d*/Å	Bond	*d*/Å
C(3)—C(7)	1.521(3)	C(8)—C(9)	1.341(3)
C(3)—C(5)	1.531(3)	C(8)—C(15)	1.489(3)
C(3)—C(6)	1.549(3)	C(10)—C(14)	1.362(3)
C(4)—C(12)	1.511(3)	C(10)—C(11)	1.425(3)
C(4)—C(10)	1.511(3)	C(11)—C(13)	1.362(3)
C(4)—C(6)	1.565(2)	C(12)—C(16)	1.498(3)
C(5)—C(12)	1.481(3)	C(13)—C(1)	1.494(4)
C(6)—C(8)	1.514(3)	C(14)—C(2)	1.495(4)
C(7)—C(9)	1.448(3)		

Table 2. Principal bond angles (ω) in molecule **4**

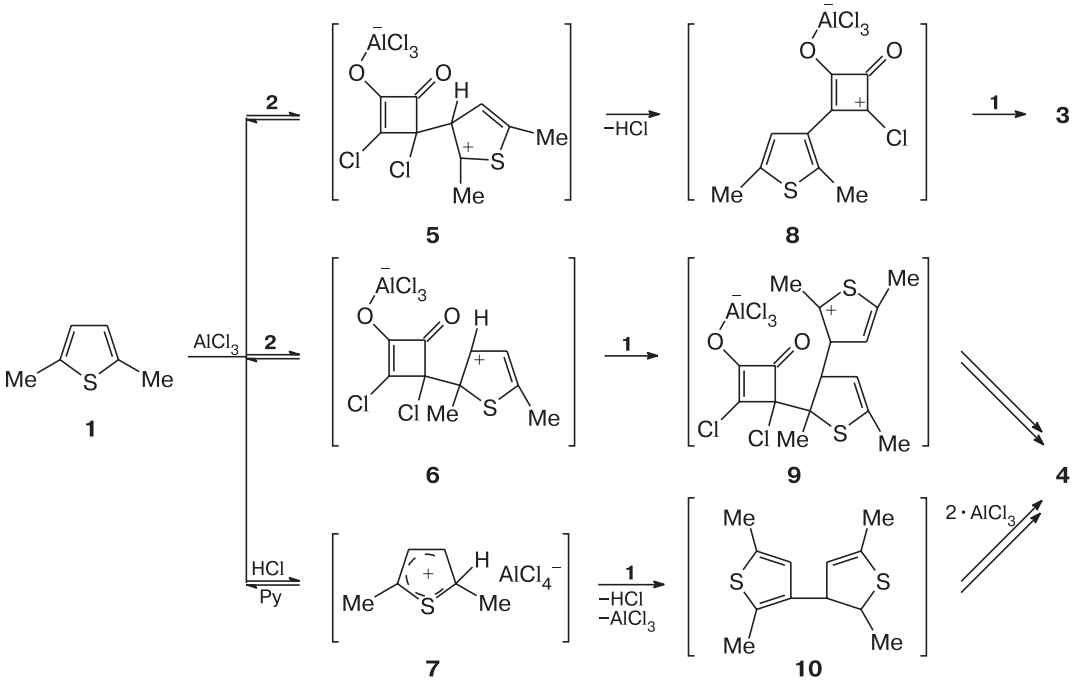
Angle	ω/deg	Angle	ω/deg
C(5)—S(1)—(12)	47.84(8)	C(9)—C(8)—C(15)	124.7(2)
C(13)—S(2)—C(14)	93.06(11)	C(9)—C(8)—C(6)	111.2(2)
C(7)—C(3)—C(5)	112.7(2)	C(15)—C(8)—C(6)	123.9(2)
C(7)—C(3)—C(6)	105.26(15)	C(8)—C(9)—O(2)	125.5(2)
C(5)—C(3)—C(6)	105.10(14)	C(8)—C(9)—C(7)	112.0(2)
C(7)—C(3)—C(11)	109.56(12)	O(2)—C(9)—C(7)	122.5(2)
C(5)—C(3)—C(11)	111.67(13)	C(14)—C(10)—C(11)	112.2(2)
C(6)—C(3)—C(11)	112.38(13)	C(14)—C(10)—C(4)	122.1(2)
C(12)—C(4)—C(10)	115.3(2)	C(11)—C(10)—C(4)	125.7(2)
C(12)—C(4)—C(6)	106.57(14)	C(13)—C(11)—C(10)	114.2(2)
C(10)—C(4)—C(6)	117.9(2)	C(5)—C(12)—C(16)	123.3(2)
C(12)—C(5)—C(3)	110.1(2)	C(5)—C(12)—C(4)	108.2(2)
C(12)—C(5)—C(12)	121.49(15)	C(16)—C(12)—C(4)	117.7(2)
C(3)—C(5)—C(12)	117.55(14)	C(5)—C(12)—S(1)	64.6(11)
C(12)—C(5)—S(1)	67.57(11)	C(16)—C(12)—S(1)	117.9(2)
C(3)—C(5)—S(1)	113.41(13)	C(4)—C(12)—S(1)	114.2(4)
C(l2)—C(5)—S(1)	116.96(11)	C(11)—C(13)—C(1)	128.3(3)
C(8)—C(6)—C(3)	103.41(14)	C(11)—C(13)—S(2)	109.8(2)
C(8)—C(6)—C(4)	122.4(2)	C(1)—C(13)—S(2)	121.8(2)
C(3)—C(6)—C(4)	105.6(15)	C(10)—C(14)—C(2)	128.3(2)
O(1)—C(7)—C(9)	127.4(2)	C(10)—C(14)—S(2)	110.7(2)
O(1)—C(7)—C(3)	125.5(2)	C(2)—C(14)—S(2)	121.1(2)
C(9)—C(7)—C(3)	107.0(2)		

The reactions which are likely to occur in the acylation of 2,5-dimethylthiophene (**1**) with 3,4-dichlorobutene-1,2-dione (**2**) in the presence of $AlCl_3$ and Py are shown in Scheme 2.

Presumably, three main competitive reactions occur in the acylation of 2,5-dimethylthiophene (**1**) with squaric acid dichloride (**2**). The initial electrophilic attack of a chloride **2**—$AlCl_3$ complex can be directed on both the β position (intermediate **5**) and the α position (intermediate **6**) of the 2,5-dimethylthiophene ring. Apparently, protonation of thiophene **1** giving rise to σ-complex **7** also contributes to the process.

The attack on the β position affords intermediate **5** whose dehydrochlorination produces zwitterion **8**. The

Scheme 2



latter attacks dimethylthiophene **1** also at the β position thus giving rise to the target product **3**.

Apparently, hypothetical intermediate **6** results from the attack of the complex of $AlCl_3$ with squaric acid dichloride (**2**) on the α position of 2,5-dimethylthiophene (**1**). The reaction of intermediate **6** with another molecule of dimethylthiophene **1** produces bipolar ion **9** with a bond between two β-carbon atoms of the thiophene rings. Its further transformation affords compound **4**. However, the details of this process call for special investigation.

Yet another possible direction of this process involves the binding of free 2,5-dimethylthiophene (**1**) with HCl resulting from the electrophilic substitution and $AlCl_3$ to form a rather stable σ-complex **7**, which has been observed by us previously.[2,3] This process can lead to both the recovery of the starting compound and oligomerization induced by the reaction of σ-complex **7** with the second molecule of 2,5-dimethylthiophene (**1**) giving rise to dimer **10**. Examples of condensation of thiophene and its homologs in the presence of protic and aprotic acids were documented.[5—7] In our opinion, the reaction of intermediate **10** with chloride **2** in the presence of $AlCl_3$ can also afford anomalous product **4**.

We expected that the yield of the target diketone **3** would be increased and the formation of compound **4** would be suppressed by preventing the formation of σ-complex **7**, which could be achieved by either adding a base or decreasing the polarity of the medium. Actually, the use of Py for the purpose of decomposing of σ-complex **7** led to an increase in the yield of the target product **3** (Table 3, *cf.* entries *1* and *2—5*). This effect can be explained by both the regeneration of dimethylthiophene **1** and the fact that the transformation of intermediates **5** ⟶ **8** proceeds more readily. However, the use of Py did not prevent the formation of product **4**.

Better results were obtained in media of lower polarity. Thus side processes were suppressed and compound **3** was obtained in substantially higher yield when the reaction was carried out in a dichloroethane—heptane mixture (see Table 3, entries *6—8*). A decrease in the medium polarity necessarily leads to a lowering of the solvation energy and, consequently, to an increase in the activation barriers of the reactions under consideration. It is believed that a decrease in polarity hinders predominantly the formation of product **4** in the course of which rearomatization of intermediate **6** cannot take place. At the same time, a lowering of the solvent polarity leads to a decrease in stability of σ-complex **7** and facilitates the transformation of intermediates **5** ⟶ **8**.

The approach proposed in the present study is most efficient when different solvent ratios are used in two steps of acylation (see Scheme 2) at the β position of 2,5-dimethylthiophene (**1**). In the first step where more reactive squaric acid dichloride (**2**) acts as the acylating agent, heptane and dichloroethane are taken in a ratio of 2 : 1. In the second step involving less reactive monoacylation product **8** as the acylating agent, the same solvents are taken in a reverse ratio (1 : 2).

Table 3. Influence of the reaction conditions on the yield of 1,2-bis(2,5-dimethylthiophen-3-yl)ethanedione (**3**) (*Y*) from 2,5-dimethylthiophene (**1**) and squaric acid dichloride (**2**)

Entry	Reagent ratio (**1** : **2** : $AlCl_3$: Py)[a]	T_1[b] °C	T_2[c] °C	Solvent ratio[d]	t[e]/h at T_1 (T_2)	Y (%)
1	1 : 0.6 : 1.05 : 0	−30	20	1 : 0	2 (3)	9
2	1 : 0.6 : 1.1 : 0.8	−20	5	1 : 0	3 (4)	48
3	1 : 0.6 : 1.1 : 0.45[f]	−25	20	1 : 0	1.5 (2)	63
4	1 : 0.6 : 2.1 : 0.45[f]	−32	20	1 : 0	4 (6)	38
5[g]	1 : 0.6 : 1.1 : 0.6[f]	−20	20	1 : 0	5 (6)	42
6	1 : 0.5 : 1 : 0	−20	5	1 : 1	3 (28)	52
7[g]	1 : 0.5 : 2 : 0[f]	−20	10	2 : 1	3 (32)	75
8	1 : 0.5 : 2 : 0[f]	−20	10	3 : 1	3 (20)	69

[a] Molar ratio.
[b] The lowest reaction temperature.
[c] The highest reaction temperature.
[d] Dichloroethane : heptane.
[e] Reaction time.
[f] The reaction was carried out in an atmosphere of argon.
[g] The experiment is given in detail in the Experimental section.

The use of a mixture of the solvents not only allowed us to prevent the formation of complex **7** and by-product **4** but also made it possible to substantially slow down electrophilic oligomerization (resinification), which is virtually inevitable upon acylation of compounds of the thiophene series in the presence of $AlCl_3$. However, this solvent ratio is not regarded as constant and can be changed depending on the activity and solubility of the substrate and on the temperature. The reaction may be started in pure heptane with the gradual addition of dichloroethane.

To summarize, we optimized the conditions for the acylation of 2,5-dimethylthiophene (**1**) with squaric acid dichloride (**2**) and established the structure of the resulting unusual by-product. Variations in the temperature and the solvent ratio in the reaction mixture in different steps of the process enabled us to control the rate of acylation and perform this reaction under mild conditions. The proposed procedure can be used not only for acylation of compounds of the thiophene series with squaric acid dichloride but also for acylation of other aromatic systems with different agents if one faces problems associated with electrophilic oligomerization (resinification) or the formation of stable σ-complexes of type **7**.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$. The mass spectra (EI) were measured on a Kratos instrument (70 eV) with direct inlet of the sample into the ion source. The melting points were determined on a Boetius stage and were not corrected. The completion of the reactions was judged from the TLC data on Silufol UV-254 plates (light petroleum—AcOEt, 6 : 1, as the solvent system). Column chromatography was carried on Al_2O_3 (Brockmann activity II, neutral) and silica gel Acros (0.060—0.200 mm).

Dichloroethane was dried by refluxing over P_2O_5 for 3 h followed by distillation. Heptane was used without purification. Squaric acid dichloride was prepared according to a modified procedure[8] (DMF and a catalytic amount of a NaCl—KCl mixture were used as the catalysts; dichloroethane was used as the solvent instead of benzene) and recrystallized from heptane.

Acylation of 2,5-dimethylthiophene (1) with squaric acid dichloride (2) in the presence of Py. A solution of squaric acid dichloride (**2**) (1.51 g, 0.01 mol) in dichloroethane (15 mL) and a solution of 2,5-dimethylthiophene (**1**) (2.24 g, 0.02 mol) in dichloroethane (15 mL) were added dropwise with stirring to a suspension of $AlCl_3$ (5.34 g, 0.04 mol) in dichloroethane (15 mL) at −20 °C in an atmosphere of argon. The reaction mixture was stirred at this temperature for 3 h. Then the temperature was raised to 0 °C, the reaction mixture was kept for 1 h, Py (0.79 g, 0.01 mol) was added, the temperature was raised to ~20 °C, and the reaction mixture was stirred at this temperature until the starting 2,5-dimethylthiophene (**1**) was completely consumed (TLC data). Then the reaction mixture was poured onto ice and the aqueous phase was extracted with $CHCl_3$. The extracts and the organic layer were combined, washed with a 3% $NaHCO_3$ solution and water until the washing water became neutral, and dried with $MgSO_4$. The solvent was distilled off and the residue was chromatographed (silica gel—Al_2O_3, light petroleum (60—80 °C)—AcOEt mixture, 6 : 1) to isolate compounds **3** and **4**.

3,4-Bis(2,5-dimethylthiophen-3-yl)cyclobut-3-ene-1,2-dione (3). The yield was 1.26 g (42%), m.p. 131—132 °C (heptane—benzene). ^1H NMR, δ: 6.88 (s, 1 H, H arom.); 2.51 (s, 3 H, Me); 2.41 (s, 3 H, Me). The characteristics of dione **3** are identical with those reported previously.[2,3] ^{13}C NMR, δ: 195.75 (CO); 183.45 (C=C); 145.20 (C(2)); 138.29 (C(5)); 126.83 (C(3)); 124.74 (C(4)); 15.83 (C(2)Me); 15.11 (C(5)Me). MS, m/z (I_{rel} (%)): 302 $[M]^+$ (60); 246 $[M - 2\,CO]^+$ (100).

1a,1b-Dichloro-5-(2,5-dimethylthiophen-3-yl)-3-hydroxy-4,5a-dimethyl-1b,4a,5,5a-tetrahydro-1a*H*-1-thiacyclopropa[*a*]pentalen-2-one (4). The yield was 1.42 g (38%), m.p. 203—204 °C (EtOH). ^1H NMR, δ: 1.32 (s, 3 H, C(5a)Me); 1.75 (s, 3 H, C(4)Me); 2.40 (s, 6 H, C(2′)Me, C(5′)Me); 3.52—3.58 (m, 1 H, H(5)); 4.06 (d, 1 H, C(4a)H, $J \approx 10$ Hz); 5.11 (br.s, 1 H, OH); 6.73 (s, 1 H, C(4′)H). ^{13}C NMR, δ: 146.77, 145.83, 136.69, 124.06, 66.91, 58.21, 43.55, 21.66, 15.30, 13.15, 12.63. MS (for ^{35}Cl), m/z (I_{rel} (%)): 374 $[M]^+$ (36); 339 $[M - Cl]^+$ (85).

Acylation of 2,5-dimethylthiophene (1) with squaric acid dichloride (2) in a dichloroethane—heptane mixture. A solution of 2,5-dimethylthiophene (**1**) (2.24 g, 0.02 mol) in heptane (15 mL) and a solution of squaric acid dichloride (**2**) (1.51 g, 0.01 mol) in dichloroethane (15 mL) were added dropwise with stirring to a suspension of $AlCl_3$ (5.34 g, 0.04 mol) in heptane (15 mL) at the temperature from −15 to −20 °C in an atmosphere of argon. After 3 h, dichloroethane (45 mL) was added, the temperature was increased to 7—10 °C, and the reaction mixture was stirred at this temperature for 23—25 h. Then the reaction mixture was poured onto ice and the aqueous phase

was extracted with $CHCl_3$. The extracts and the organic layer were combined, washed with a 3% $NaHCO_3$ solution and water until the washing water became neutral, and dried with $MgSO_4$. The solvent was distilled off and the residue was chromatographed on Al_2O_3 (light petroleum (60—80 °C)—AcOEt mixture, 6 : 1). Yellow crystalline compound **3**, which was identical with the above-described sample, was isolated in a yield of 2.26 g (75%).

X-ray diffraction study of compound 4. Transparent pale-yellow prismatic crystals of compound **4** ($C_{16}H_{16}Cl_2O_2S_2$) were grown from a benzene—heptane solution. The crystals are monoclinic, at 20 °C: a = 9.261(3) Å, b = 12.221(4) Å, c = 15.526(4) Å, β = 102.39(2)°, V = 1716.3(8) Å^3, d_{calc} = 1.452 g cm^{-3}, space group $P2_1/n$, Z = 4. The unit cell parameters and the intensities of 4157 independent reflections were measured on an automated four-circle Siemens P3/PC diffractometer (Mo-Kα radiation, graphite monochromator, $\theta/2\theta$ scanning technique in the range $2.14 \le \theta \le 28.06°$). The structure was solved by direct methods, which revealed all nonhydrogen atoms, and refined by the full-matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms. The positions of the H atoms were located from difference electron density syntheses and refined isotropically by the least-squares method. The final reliability factors were as follows: R = 0.043 (based on 3312 observed reflections with $I > 2\sigma(I)$); Rw = 0.104 (based on all independent reflections). All calculations were carried out with the use of the SHELXTL PLUS program package (Version 5.03+). The atomic coordinates and thermal parameters were deposited with the Cambridge Structural Database. The molecular structure of compound **4** is shown in Fig. 1. Data for the structures of analogous compounds were lacking in the Cambridge Structural Database (as of October 2001). The principal geometric parameters of molecule **4** are given in Table 1.

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References

1. M. M. Krayushkin, F. M. Stoyanovich, O. Yu. Zolotarskaya, E. I. Chernoburova, N. N. Makhova, V. N. Yarovenko, I. V. Zavarzin, A. Yu. Martynkin, and B. M. Uzhinov, *Khim. Geterotsikl. Soedin.*, 2002, 185 [*Chem. Heterocycl. Compd.,* 2002, **38** (Engl. Transl.)].
2. V. Z. Shirinian, N. V. Kosterina, A. V. Kolotaev, L. I. Belen´kii, and M. M. Krayushkin, *Khim. Geterotsikl. Soedin.*, 2000, 261 [*Chem. Heterocycl. Compd.,* 2000, **36** (Engl. Transl.)].
3. V. Z. Shirinian, M. M. Krayushkin, L. I. Belen´kii, L. G. Vorontsova, Z. A. Starikova, A. Yu. Martynkin, V. L. Ivanov, and B. M. Uzhinov, *Khim. Geterotsikl. Soedin.*, 2001, 81 [*Chem. Heterocycl. Compd.,* 2001, **37** (Engl. Transl.)].
4. A. Perjessy, K. Bowden, W. M. F. Fabian, O. Hritzova, N. Pronayova, Z. Šustekova, and A. Al-Najjar, *Monatsh. Chem.*, 1999, **130**, 515.
5. L. I. Belen´kii, *Khim. Geterotsikl. Soedin.*, 1992, 733 [*Chem. Heterocycl. Compd.,* 1992, **28** (Engl. Transl.)].
6. T. Sone, M. Kuto, and T. Kanno, *Chem. Lett.*, 1982, 1195.
7. P. D. Clark, K. Clarke, D. F. Ewing, and R. M. Scrowston, *J. Chem. Soc., Perkin Trans. 1*, 1980, 677.
8. M. Ohno, Y. Yamamoto, Y. Shirasaki, and S. Eguchi, *J. Chem. Soc., Perkin Trans. 1*, 1993, 263.

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