Chemistry of Heterocyclic Compounds, Vol. 41, No. 2, 2005

NEW METHOD OF SYNTHESIS OF 2-AMINO-4(5H)-OXOTHIOPHENES

Yu. M. Volovenko and T. A. Volovnenko

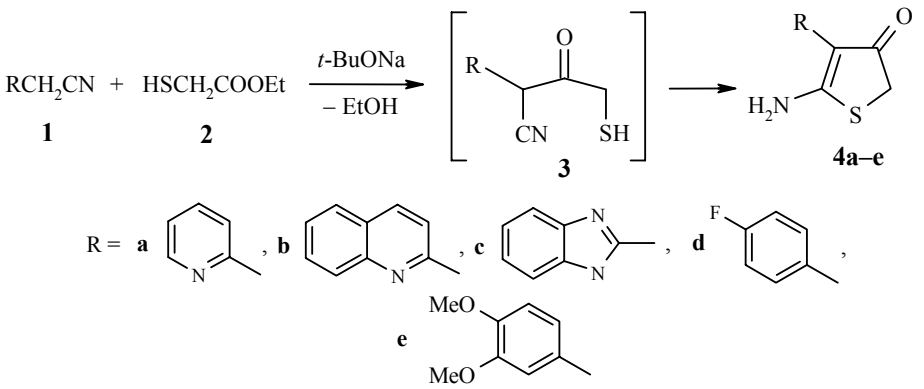
A new method is proposed for the synthesis of 2-amino-4(5H)-oxothiophenes with aryl and hetaryl substituents in position 3 of the molecule by the acylation of aryl- and 2-azahetarylacetonitriles with mercaptoacetic acid ethyl ester.

Keywords: aryl- and 2-azahetarylacetonitriles, mercaptoacetic ester, 2-amino-3-aryl-4(5H)-oxothiophenes, 2-amino-3-hetaryl-4(5H)-oxothiophenes.

Interest in the chemistry of 2-aminothiophenes is caused by the wide spectrum of their useful properties. Medicinal preparations [1-4], agents for plant protection [5-7], and intermediates for the synthesis of dyes [8-10] have been made from them. At present the main methods of obtaining substituted 2-aminothiophenes are the cyclization of γ-mercaptonitriles [11, 12] and syntheses from α-mercaptocarbonyl compounds (Gewald reaction) [13-15]. The synthesis of 2-amino-4(5H)-oxothiophenes with aryl and hetaryl substituents in position 3 of the molecule has not been developed in practice. Work of Japanese scientists is known [16], which describes 2-amino-(5H)-thiophen-4-ones with phenyl and 4-chlorophenyl substituents in position 3 of the molecule, displaying spasmolytic properties.

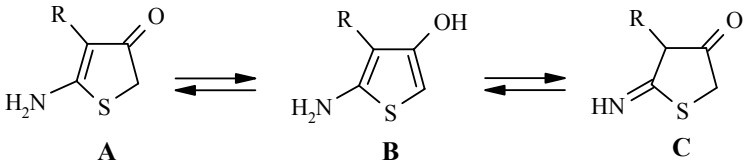
Previously we synthesized 2-amino-4(5H)-oxothiophenes by the reaction of 4-chloro-2-hetaryl-3-oxobutyronitriles with sodium hydrosulfide [17]. The reaction proceeds through a stage of exchanging the chlorine atom for a sulfhydryl group with subsequent addition of this group to the triple bond of the nitrile group.

In the present work a new method is proposed for the synthesis of 2-amino-3-aryl- and 3-hetaryl-4(5H)-oxothiophenes based on the acylation of aryl- and azahetarylacetonitriles with mercaptoacetic ester. The reaction proceeds in *tert*-butyl alcohol in the presence of sodium *tert*-butylate.



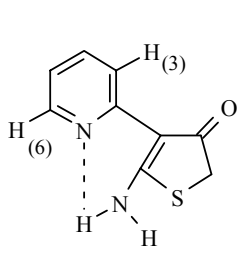
Kiev Taras Shevchenko National University, Kiev 01033, Ukraine; e-mail: olgakh@mail.univ.kiev.ua.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 202-205, February, 2005. Original article submitted September 12, 2002.

By the action of base on the substituted acetonitrile **1** a carbanion is generated which attacks the carbon atom of the ester group of mercaptoacetic ester **2** and the C-acyl derivative **3** is formed. The presence in the molecule of two reactive centers (the nucleophilic mercapto group and the electrophilic nitrile group) leads to intramolecular cyclization with the formation of 2-amino-4(5H)-oxothiophenes **4a-e**. The obtained compounds may exist in three tautomeric forms **A**, **B**, and **C**.

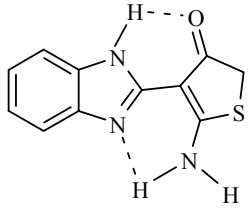


Analysis of spectral data showed that products **4a-e** exist in the keto form **A** and not in the tautomeric enol form **B**. This is indicated by the presence of a two-proton singlet for the methylene group of the thiophene ring at 3.69-3.92 ppm, and by an absorption band for a conjugated keto group in the IR spectra at 1620-1630 cm^{-1}. At the same time the presence of two absorption bands for the amino group at 3150-3400 cm^{-1} excludes the imine form **C**.

There are several special features in the ^1H NMR spectra of compounds **4a-e** recorded in DMSO-d_6 in the region of aromatic proton absorption. For 2-amino-3-(2-pyridinyl)-4(5H)-oxothiophene **4a** there are two doublets at low field at 8.46 ppm (1H, J = 5.5 Hz) and 8.60 ppm (1H, J = 8.0 Hz) belonging to protons of the pyridine nucleus. The sizes of the coupling constants enable assignment of the doublet at 8.46 ppm to the H(6) proton and at 8.60 ppm to H(3). However it is well known [18] that the α-protons of pyridine resonate at the lowest field. Such an unusual paramagnetic shift for a proton in position 3 of a pyridine nucleus is explained by its proximity to the oxygen atom in the β-position of the thiophene ring. To achieve a similar interaction the molecule must be planar, which may be brought about only as a result of the presence of an intramolecular hydrogen bond between the protons of the amino group and the nitrogen atom of the pyridine ring. In reality the protons of the amino group give two signals in the ^1H NMR spectrum, a singlet at 10.73 ppm (chelated proton) and a singlet at 9.22 ppm. In the case of 2-amino-3-(2-quinolinyl)-4(5H)-oxothiophene **4b** the protons of the amino group resonate at 11.34 ppm (chelated proton) and at 9.49 ppm.



4a



4c

The ^1H NMR spectrum of 2-amino-3-(2-benzimidazolyl)-4(5H)-oxothiophene **4c** is of particular interest. Three signals of exchanging protons were observed in it at 9.55, 10.07, and 12.01 ppm. The first two singlets belong to amino group protons and the last at lowest field corresponds to the N–H proton of the benzimidazole nucleus. Its significant paramagnetic shift is caused by the formation of an intramolecular hydrogen bond with the oxygen atom of the keto group in the thiophene nucleus. The structures of the synthesized 2-amino-3-aryl-4(5H)-oxothiophenes **4d,e** are confirmed completely by the spectral data. In the ^1H NMR spectra a two-proton singlet is observed for the methylene group of thiophene at 3.7 ppm and the protons of the amino group, in the absence of a chelating center, give a broadened singlet at 7.86 (compound **4d**) and 7.81 ppm (compound **4e**).

EXPERIMENTAL

A check on the progress of reactions and the purity of the synthesized compounds was carried out by TLC on Silufol UV 254 plates in the system chloroform—methanol, 9 : 1. The ^{1}H NMR spectra were measured on a Varian Mercury 400 (400 MHz) spectrometer in DMSO-D_6, internal standard was TMS. The IR spectra were recorded on a Pye Unicam SP 3-300 instrument. Melting points were measured on a Boetius type miniature hot stage with a VEB Analytik PNMK 05 eyepice.

2-Amino-4(5H)-oxothiophenes 4a-e (General Procedure). Sodium *tert*-butylate (0.005 mol) and ethyl mercaptoacetate (**2**) (0.0055 mol) were added to a solution of the appropriate acetonitrile **1** in *tert*-butyl alcohol (30 ml). The reaction mixture was boiled for 2-4 h, checking the completeness of conversion chromatographically. The reaction mixture was evaporated in vacuum, water (20 ml) was added, the solution was acidified to pH 7 with acetic acid, the solid was filtered off, and recrystallized from a suitable solvent.

2-Amino-3-(2-pyridyl)-4(5H)-oxothiophene (4a). Yield 75%; mp 182-183°C (toluene). IR spectrum (KBr), ν, cm^{-1}: 3400 (NH), 1620 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.75 (2H, s, H-5); pyridine protons; 7.11 (1H, t, *J* = 6.0, H-5); 7.75 (1H, t, *J* = 7.8, H-4); 8.46 (1H, d, *J* = 5.5, H-6); 8.60 (1H, d, *J* = 8.0, H-3); 9.22 (1H, s, N–H); 10.73 (1H, s, N–H). Found, %: N 14.31, S 16.73. $C_9H_8N_2OS$. Calculated, %: N 14.57; S 16.68.

2-Amino-3-(2-quinolyl)-4(5H)-oxothiophene (4b). Yield 62%; mp 278°C (DMF). IR spectrum (KBr), ν, cm^{-1}: 3300 (NH), 1620 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.80 (2H, s, H-5); quinoline protons; 7.48 (1H, t, *J* = 7.6, H-7); 7.69 (1H, t, *J* = 7.6, H-6); 7.87 (1H, d, *J* = 8.4, H-5); 8.06 (1H, d, *J* = 8.4, H-8); 8.28 (1H, d, *J* = 8.4, H-4); 8.81 (1H, d, *J* = 9.2, H-3); 9.49 (1H, s, N–H); 11.34 (1H, s, N–H). Found, %: N 11.70; S 13.34. $C_{13}H_{10}N_2OS$. Calculated, %: N 11.56; S 13.23.

2-Amino-3-(2-benzimidazolyl)-4(5H)-oxothiophene (4c). Yield 65%; mp 273°C (*n*-butanol). IR spectrum (KBr), ν, cm^{-1}: 3350 (NH), 1630 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.92 (2H, s, H-5); benzimidazole protons; 7.12 (2H, t, *J* = 3.4, H-5, H-6); 7.52 (1H, d, *J* = 5.21, H-4); 7.61 (1H, d, *J* = 4.0, H-7); 9.55 (1H, s, N–H); 10.07 (1H, s, N–H); 12.01 (1H, s, N-H). Found, %: N 18.12; S 13.90. $C_{11}H_9N_3OS$. Calculated, %: N 18.17; S 13.86.

2-Amino-3-(4-fluorophenyl)-4(5H)-oxothiophene (4d). Yield 70%; mp 198°C (*o*-xylene). IR spectrum (KBr), ν, cm^{-1}: 3200 (NH), 1630 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.70 (2H, s, H-5); aromatic protons; 7.18 (2H, d, *J* = 8.4, H-3, H-6); 7.30 (2H, d, *J* = 5.6, H-2, H-5); 7.86 (2H, br. s, N–H). Found, %: N 6.70; S 15.50. $C_{10}H_8FNOS$. Calculated, %: N 6.69; S 15.32.

2-Amino-3-(3,4-dimethoxyphenyl)-4(5H)-oxothiophene (4e). Yield 65%; mp 192°C (ethyl acetate). IR spectrum (KBr), ν, cm^{-1}: 3300 (NH), 1630 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.69 (2H, s, H-5); 3.72 (3H, s, OCH_3); 3.75 (3H, s, OCH_3); aromatic protons; 6.79 (1H, d, *J* = 8.4, H-5); 6.82 (1H, s, H-2); 6.95 (1H, d, *J* = 8.4, H-6); 7.81 (2H, br. s, NH). Found, %: N 5.62; S 12.80. $C_{12}H_{13}NO_3S$. Calculated, %: N 5.5; S 12.76.

REFERENCES

1. M. Nakanishi, T. Tahara, and K. Araki, *J. Med. Chem.*, **16**, 214 (1973).
2. C. Horig and H. Koch, *Pharmazie*, **28**, 553 (1973).
3. J. D. Ramanathan, D. G. Namboothiri, and G. F. Shah, *J. Indian Chem. Soc.*, **55**, 822 (1978).
4. D. Binder, O. Hromatka, and C. R. Noe, *Arch. Pharm. (Weinheim Ger.)*, **313**, 587 (1980).
5. J. V. Karabinos and L. G. Nickell, US Patent 4013681; *Ref. Zh. Khim.*, 220321P (1977).
6. K. Dickore and K. Lurssen, Ger. Patent 2817449; *Ref. Zh. Khim.*, 6O388P (1980).
7. Yu. A. Sharanin and V. K. Promonenkov, *Synthesis of Aminothiophenes* (*Review information NIITEKhIM, Ser Khim. Agents for Plant Protection*), Moscow (1981).

8. R. D. McClelland, D. B. Baird, J. S. Campbell, and B. R. Fishwick, Brit. Patent 1546574; *Ref. Zh. Khim.*, 3N216P (1980).
9. S. Tada, Jpn. Patent 56100780; *Ref. Zh. Khim.*, 11N177P (1983).
10. P. Gordon and P. Gregory in G. N. Vorozhtsova (editor), *Organic Chemistry of Dyes* [Russian translation], Mir, Moscow (1987), 344 pp.
11. E. Benary, *Chem. Ber.*, **43**, 1943 (1910).
12. J. L. Isidor and R. L. McKee, *J. Org. Chem.*, **38**, 3615 (1973).
13. K. Gewald, *Chem. Ber.*, **98**, 3571 (1965).
14. H. Schafer and K. Gewald, *J. Prakt. Chem.*, **316**, 684 (1974).
15. K. Gewald, *Khim. Geterotsikl. Soedin.*, 1299 (1976).
16. U. Suminori, K. Kazuo, and T. Kunihiko, Jpn. Patent 19090; *Chem. Abstr.*, **69**, 10352 (1968).
17. Yu. M. Volovenko and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, 1425 (1977).
18. V. A. Mironov and S. A. Yankovskii, *Spectroscopy in Organic Chemistry* [in Russian], Khimiya, Moscow (1985).