Chemistry of Heterocyclic Compounds, Vol. 42, No. 5, 2006

NOVEL SYNTHESIS OF 2-AMINO-3-HETARYL-4(5H)-OXOTHIOPHENES

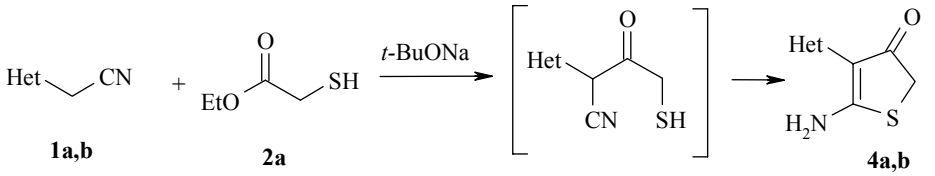
Yu. M. Volovenko, T. A. Volovnenko, and A. V. Dobrydnev

3-Cyano-3-hetaryl-2-oxopropyl thioacetates were obtained by the acylation of hetarylacetonitriles with acetylmercaptoacetyl chloride. Their reaction with amines led to the formation of 2-amino-3-hetaryl-4(H)-oxothiophenes.

Keywords: acetylmercaptoacetyl chloride, 2-amino-3-hetaryl-4(5H)-oxothiophenes, 3-cyano-3-hetaryl-2-oxopropylethanethioates, hetarylacetonitriles.

The acylation of aryl- and hetarylacetonitriles with various acylating agents (the anhydrides, halides, and esters of amino-substituted [1-3], mercapto-substituted [4-6], hydroxy-substituted [7, 8], and chloro-substituted [9-12] carboxylic acids of the aliphatic, aromatic, and heterocyclic series), leading to the formation of pyridine [2, 3], pyrrole [2, 10, 11], thiophene [4, 6], quinoline [9], and benzopyran [7, 8] derivatives, was studied earlier. The presence of functional groups in the molecules of these compounds makes it possible to modify them for the production of substances with valuable characteristics and, in particular, biologically active products.

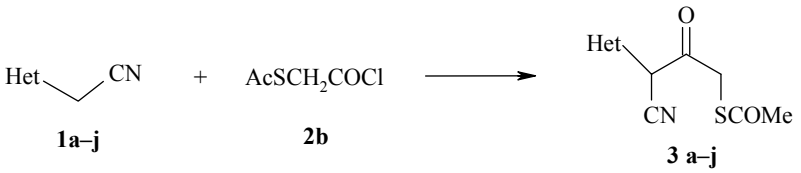
The acylation of hetarylacetonitriles **1a**,**b** with ethyl mercaptoacetate **2a** in the presence of sodium *tert*-butoxide, which clearly takes place through a C-acylation stage, was described earlier [6]. However, it is not possible to isolate the 3-cyano-3-hetaryl-2-oxopropanethiols that form since they undergo cyclization under the reaction conditions with the formation of 2-amino-3-hetaryl-4(5H)-oxothiophenes.



1a,b **2a** **4a,b**

In the present work we attempted to confirm the proposed reaction scheme. With the use of a more active acylating agent (the acid chloride **2b**) it was possible to conduct the acylation under milder conditions (in DMF at room temperature). The products, which were isolated in the individual form and with good yields, were the S-acyl derivatives **3a-j**.

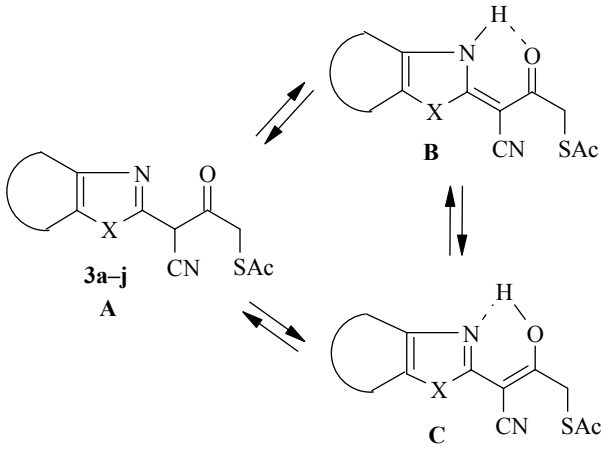
Taras Shevchenko Kiev National University, Kiev, Ukraine; e-mail: tavolov@mail.univ.kiev.ua.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 680-685, May, 2006. Original article submitted March 11, 2003.



1a–j **2b** **3 a–j**

1, **3a** Het = benzimidazol-2-yl, **b** Het = 1-methylbenzimidazol-2-yl, **c** Het = 5,6-dimethylbenzimidazol-2-yl, **d** Het = 1-ethylbenzimidazol-2-yl, **e** Het = benzothiazol-2-yl, **f** Het = 4-(*p*-tolyl)thiazol-2-yl, **g** Het = 4-(4-chlorophenyl)thiazol-2-yl, **h** Het = 4-(4-bromophenyl)thiazol-2-yl, **i** Het = 1-benzylbenzimidazol-2-yl, **j** Het = 5-trifluoromethylbenzothiazol-2-yl

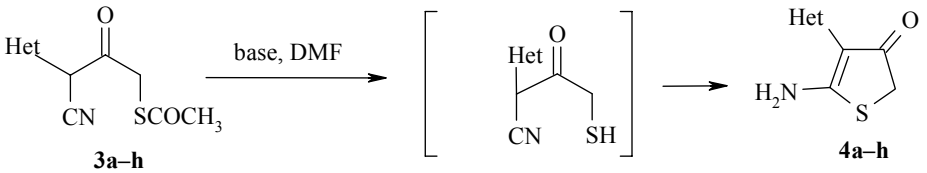
For compounds **3a-j** it is possible to assume that theoretically three tautomeric forms **A**, **B**, and **C** can exist.



X = NH, NMe, NEt, NCH_2Ph, S

The choice in favor of one of the possible tautomeric forms can be made on the basis of the IR and ^1H NMR spectra. Thus, the IR spectra contain a strong band for the stretching vibrations of the conjugated nitrile group in the region of 2200-2180 and a band in the region of 3180-3150 cm^{-1}, which we assigned to the stretching vibrations of the NH bond in the heterocycle. In the ^1H NMR spectra in the region of 2.37-2.39 ppm there is a singlet for the protons of the S-acetyl group and a two-proton singlet for the methylene group in the region of 4.02-4,14 ppm. Since the chelated proton at the nitrogen atom is subject to the descreening effect of the carbonyl group and the heterocyclic ring, its signal is observed downfield at 12.74-13.67 ppm in the form of a one-proton singlet that disappears with the addition of D_2O. On the basis of the foregoing we consider that compounds **3a-j** (Tables 1 and 2) exist in the NH tautomeric form **B** with an intramolecular hydrogen bond.

The S-acetyl derivatives **3a-h** are readily deacetylated by the action of ammonia, diethylamine, or piperidine with the formation of reactive γ-mercaptonitriles. Their cyclization leads to the 2-amino-3-hetaryl-4(5H)-oxothiophenes **4a-h** (Table 3).



3a–h **4a–h**

TABLE 1. The Characteristics of 3-Cyano-3-(2-hetaryl)-2-oxopropyl Ethanethioates **3a-j**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C*	Yield, %
		N	S		
3a	$C_{13}H_{11}N_3O_2S$	15.41 / 15.37	11.83 / 11.79	>300	78
3b	$C_{14}H_{13}N_3O_2S$	14.69 / 14.62	11.20 / 11.16	262	85
3c	$C_{15}H_{15}N_3O_2S$	14.01 / 13.94	10.68 / 10.64	>300	65
3d	$C_{15}H_{15}N_3O_2S$	14.04 / 13.94	10.70 / 10.64	193	80
3e	$C_{13}H_{10}N_2O_2S_2$	9.70 / 9.65	22.19 / 22.08	253	82
3f	$C_{16}H_{14}N_2O_2S_2$	8.53 / 8.48	19.54 / 19.41	205	68
3g	$C_{15}H_{11}ClN_2O_2S_2$	8.02 / 7.98	18.33 / 18.28	245	68
3h	$C_{15}H_{11}BrN_2O_2S_2$	7.16 / 7.09	16.26 / 16.22	247	65
3i	$C_{20}H_{17}N_3O_2S$	11.61 / 11.56	8.90 / 8.82	159	75
3j	$C_{14}H_9F_3N_2O_2S_2$	7.95 / 7.82	17.94 / 17.89	303-304	69

* Compounds **3a**,**c**,**f-j** were recrystallized from DMF, **3b** from toluene, **3d**,**e** from *n*-BuOH.

TABLE 2. The Spectral Characteristics of Compounds **3a-j**

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm (*J*, Hz)
	C=O ($SCOCH_3$)	CN	
3a	1693	2180	2.38 (3H, s); 4.04 (2H, s); 7.25 (1H, t, *J* = 3.2); 7.27 (1H, t, *J* = 2.8); 7.49 (1H, d, *J* = 2.8); 7.51 (1H, d, *J* = 3.2); 12.92 (2H, s)
3b	1690	2180	2.37 (3H, s); 3.95 (3H, s); 4.10 (2H, s); 7.32 (2H, t, *J* = 6.8); 7.61 (1H, d, *J* = 8); 7.65 (1H, d, *J* = 7.6); 13.26 (1H, s)
3c	1695	2180	2.28 (6H, s); 2.38 (3H, s); 4.02 (2H, s); 7.27 (2H, s); 12.74 (2H, s)
3d	1690	2200	1.4 (3H, m); 2.38 (3H, s); 4.13 (2H, s); 4.54 (2H, m); 7.34 (2H, t, *J* = 6.8); 7.68 (2H, d, *J* = 7.6)
3e	1700	2180	2.39 (3H, s); 4.13 (2H, s); 7.36 (1H, t, *J* = 7.6); 7.52 (1H, t, *J* = 7.6); 7.68 (1H, d, *J* = 8); 7.97 (1H, d, *J* = 8); 13.67 (1H, s)
3f	1690	2180	2.30 (3H, s); 2.38 (3H, s); 4.09 (2H, s); 7.32 (2H, d, *J* = 8.4); 7.43 (1H, s); 7.65 (2H, d, *J* = 7.6);] NH – exchange with water
3g	1690	2180	2.38 (3H, s); 4.09 (2H, s); 7.55 (1H, s); 7.57 (2H, d, *J* = 9.2); 7.80 (2H, d, *J* = 8); NH – exchange with water
3h	1695	2180	2.37 (3H, s); 4.09 (2H, s); 7.55 (1H, s); 7.69 (2H, d, *J* = 8.4); 7.73 (2H, d, *J* = 8); NH – exchange with water
3i	1690	2200	2.38 (3H, s); 4.11 (2H, s); 5.83 (2H, s); 7.20-7.72 (9H, m); 13.48 (1H, s)
3j	1690	2180	2.38 (3H, s); 4.14 (2H, s); 7.69 (1H, d, *J* = 8.8); 7.90 (1H, s); 8.2 (1H, d, *J* = 7.2); 13.61 (1H, s)

TABLE 3. The Characteristics of 2-Amino-3-hetaryl-4(5H)-oxothiophenes **4c-h**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C*	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	Yield, %
		N	S			
4c	$C_{13}H_{13}N_3OS$	16.34 / 16.20	12.51 / 12.36	>300	2.28 (6H, s); 3.89 (2H, s); 7.30 (1H, s); 7.35 (1H, s); 9.48 (1H, s); 10.07 (1H, s); 11.78 (1H, s)	71
4d	$C_{13}H_{13}N_3OS$	16.21 / 16.20	12.42 / 12.36	228	1.26 (3H, m); 3.83 (2H, s); 4.26 (2H, m); 7.20 (2H, t, *J* = 7.2); 7.56 (1H, d, *J* = 7.2); 7.59 (1H, d, *J* = 6.8); 8.66 (1H, s); 8.97 (1H, s)	80
4e	$C_{11}H_8N_2OS_2$	11.32 / 11.28	26.00 / 25.82	>300	3.83 (2H, s); 7.29 (1H, t, *J* = 8); 7.39 (1H, t, *J* = 6.8); 7.83 (1H, d, *J* = 7.2); 7.92 (1H, d, *J* = 7.2); 9.75 (1H, s); 10.09 (1H, s)	69
4f	$C_{14}H_{12}N_2OS_2$	9.83 / 9.71	22.27 / 22.23	>300	2.34 (3H, s); 3.89 (2H, s); 7.25 (2H, d, *J* = 8); 7.75 (1H, s); 7.90 (2H, d, *J* = 8); 9.56 (1H, s); 9.73 (1H, s)	65
4g	$C_{13}H_9ClN_2OS_2$	9.13 / 9.07	20.73 / 20.72	>300	3.90 (2H, s); 7.49 (2H, d, *J* = 8.4); 7.90 (1H, s); 8.08 (2H, d, *J* = 8.4); 9.62 (2H, s)	65
4h	$C_{13}H_9BrN_2OS_2$	8.00 / 7.93	18.17 / 18.15	>300	3.90 (2H, s); 7.62 (2H, d, *J* = 8); 7.91 (1H, s); 8.00 (2H, d, *J* = 8.4); 9.61 (2H, s)	68

* Compound **4s** was recrystallized from DMF, **4d-h** from *n*-BuOH.

2-Amino-3-hetaryl-4(5H)-oxothiophenes **4a-h** are high-melting crystalline compounds. The oxothiophenes **4a**,**b** were identical in their physicochemical characteristics with the previously obtained compounds [4, 6]. The structure of compounds **4a-h** is confirmed by the IR and ^{1}H NMR spectra and also by elemental analysis. Thus, in the ^{1}H NMR spectra the signals for the protons of the amino group are observed either in the form of two one-proton singlets in the region of 8.66-9.75 and 8.97-10.09 ppm, which appear as a result of the nonequivalence of the protons of the amino group due to the presence of the intramolecular hydrogen bond, or in the form of a broad two-proton signal. These signals disappear with the addition of D_2O. The two-proton singlet in the region of 3.83-3.92 ppm belongs to the protons of the methylene group of the thiophene ring. In the IR spectra of compounds **4a-h** the absorption of the nitrile group in the region of 2200-2180 cm^{-1}, characteristic of the initial compounds **3a-h**, is absent, and two absorption bands due to the stretching vibrations of the primary amino group are observed in the regions of 3340-3330 (the asymmetric vibrations) and 3200-3259 cm^{-1} (the symmetric vibrations). The absorption of the carbonyl group is not observed in the IR spectra of the compounds, and this agrees with data for compounds containing a β-enaminoketone fragment [10]. Thus, according to the spectral data, compounds **4a-h** exist in the form of amino ketones and not in the alternative tautomeric forms (enol or hydroxyimine).

EXPERIMENTAL

The reactions and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in the 9:1 chloroform–methanol system. The ^{1}H NMR spectra were obtained on a Varian Mercury-400 spectrometer (400 MHz) in DMSO-d_6 with TMS as internal standard. The IR spectra were recorded on a Pye-Unicam SP 3-300 instrument. The melting points were measured on a small-scale heater instrument of the Boetius type with an Analytik VEB RNMK 05 observation device.

3-Cyano-3-hetaryl-2-oxopropyl Thioacetates 3a-j (General Procedure). To a solution of the hetarylacetonitrile **1a-j** (5 mmol) in DMF (5 ml) at room temperature (25°C) we added acetylmercaptoacetyl chloride **2b** (5.5 mmol). The reaction mixture was left for 12 h, and the precipitate was filtered off, washed with water, dried, and recrystallized.

2-Amino-3-hetaryl-4(5H)-oxothiophenes 4a-h (General Procedure). To a solution of the respective compound **3a-j** (5 mmol) in DMF (5 ml) we added the base (ammonia, diethylamine, piperidine) (10 mmol). The mixture was left at 30-40°C for 24 h. The precipitate was filtered off, washed with water, dried, and recrystallized from the appropriate solvent.

REFERENCES

1. F. S. Babichev, Yu. M. Volovenko, and V. S. Talanov, *Dokl. Akad. Nauk Ukr.SSR, Ser. B,* 508 (1977).
2. Yu. M. Volovenko, L. V. Gofman, and F. S. Babichev, *Ukr. Khim. Zh.*, **45**, 857 (1979).
3. F. S. Babichev and Yu. M. Volovenko, *Khim. Geterotsikl. Soedin.*, 557 (1977).
4. Yu. M. Volovenko and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, 1425 (1977).
5. Yu. M. Volovenko, V. A. Litenko, E. V. Dashkovskaya, and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, 1047 (1982).
6. Yu. M. Volovenko and T. A. Volovnenko, *Khim. Geterotsikl. Soedin.*, 202 (2005).
7. Yu. M. Volovenko, V. A. Litenko, A. D. Kapustyan, and F. S. Babichev, *Dokl. Akad. Nauk Ukr. SSR, Ser. B*, 40 (1981).
8. Yu. M. Volovenko, V. A. Litenko, T. V. Khrapak, and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, 1476 (1983).

9. Yu. M. Volovenko, Yu. M. Pustovit, and F. S. Babichev, *Dokl. Akad. Nauk Ukr. SSR, Ser. B*, 44 (1981).
10. Yu. M. Volovenko, T. A. Volovnenko, A. V. Tverdokhlebov, and I. G. Ryabokon', *Zh. Org. Khim.*, **37**, 1389 (2001).
11. Yu. M. Volovenko, T. A. Volovnenko, and A. V. Tverdokhlebov, *Khim. Geterotsikl. Soedin.*, 1102 (2001).
12. Yu. M. Volovenko, O. V. Khilya, T. A. Volovnenko, and A. V. Turov, *Dopovidi NAN Ukraini*, 128 (2003).