SYNTHESIS OF 3-THIENYL-SUBSTITUTED ISOTHIAZOLINES-2 AND 1,2,4-THIADIAZOLES BASED ON NITRILE SULFIDES OF THE THIOPHENE SERIES

M. M. Krayushkin, M. A. Kalik, and A. Ya. Kudryavtseva

UDC 547.732

The reaction of substituted α- and β-thienylcarboxamides with chlorocarbonylsulfenyl chloride gave 5-thienyl-substituted 1,3,4-oxathiazol-2-ones. Decarboxylation of the latter by heating in o-dichlorobenzene generated in situ α- and β-thienylnitrile sulfides, which in the presence of dipolarophiles [dimethyl fumarate, N-phenylmaleinimide, chloro(trichloro)acetonitrile] give the corresponding 3-thienyl-substituted Δ^2-isothiazolines and 5-chloromethyl(trichloromethyl)-1,2,4-thiadiazoles.

Keywords: *thienylcarboxamides, chlorocarbonylsulfenyl chloride, 5-thienyl-substituted 1,3,4-oxathiazol-2-ones, nitrile sulfides, 3-thienyl-substituted Δ^2-isothiazolines and 5-chloromethyl(trichloromethyl)-1,2,4-thiadiazoles.*

In earlier work we obtained 2-methylthio(methylsulfonyl)-3-thiophenecarbonitrile oxides; it was shown that they enter readily into 1,3-dipolar ring addition reactions with the formation of 3-thienyl-substituted five-membered heterocycles of type A [1, 2].

The present article describes the synthesis of sulfur analogs of similar compounds (Δ^2-isothiazolines and 1,2,4-thiadiazoles), containing the endocyclic fragment C=N−S and which are of interest from the standpoint of biological activity [3]. The possibility has been shown of using α- and β-thienylnitrile sulfides, generated *in situ* from the corresponding 1,3,4-oxathiazolones-2.

The oxathiazolones (**1a-c**) were obtained with high yields by the reaction of α- and β-thienylcarboxamines (**2a-c**) with chlorocarbonylsulfenyl chloride [4]. The IR spectra contain a doublet band of the carbonyl group in the region 1740-1770 cm^{-1}; this is noticed for some unsaturated compounds, in particular Δ^2-oxazolinones-5, and can be the result of an interaction of the vibrations of the C=O group with adjacent bonds or Fermi resonance [5].

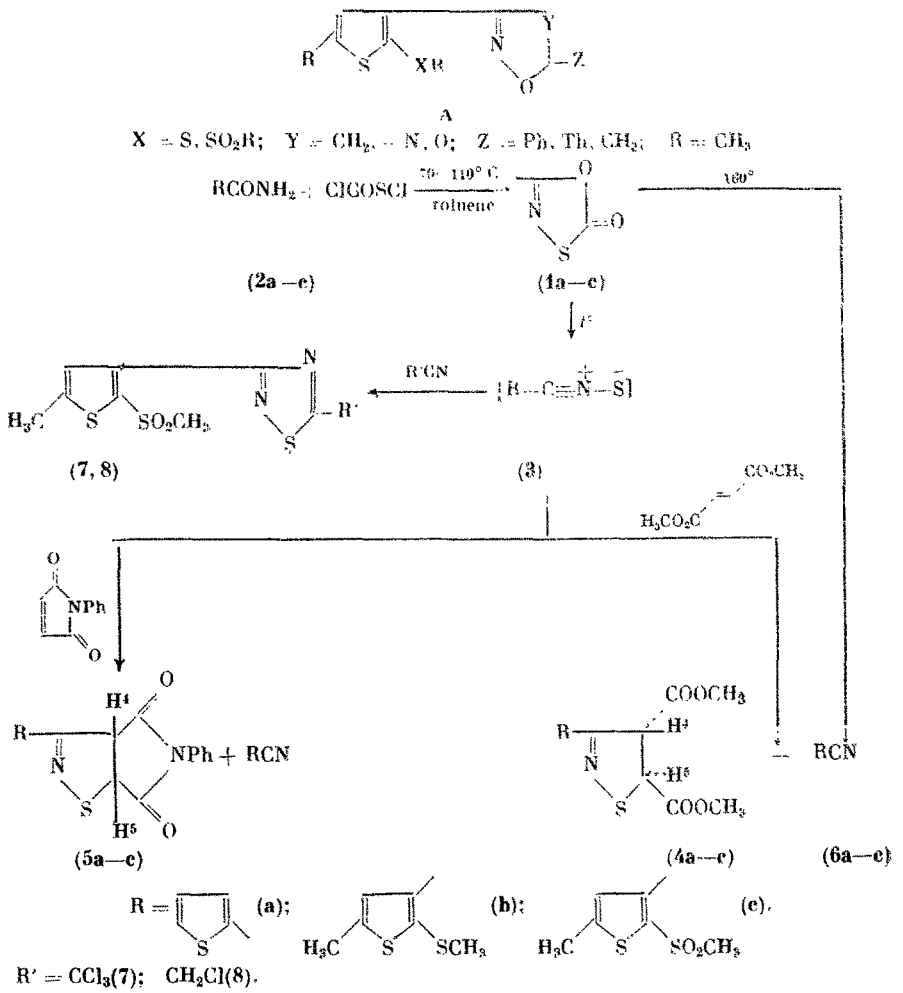
The unstable thienylnitrile sulfides (**3**) were generated by the thermal decarboxylation of the oxathiazolones **1a-c** [6]. Performance of the reaction in the presence of an excess of activated dipolarophiles (dimethyl fumarate and N-phenylmaleinimide [7]) leads to 3-thienyl-substituted *trans*-Δ^2-isothiazoline-4,5-dicarboxylates (**4a-c**) and *cis*-N-phenyl-Δ^2-isothiazoline-4,5-dicarboxylates (**5a-c**), respectively, the spatial structure of which was confirmed by PMR spectra (see scheme below). Besides the adducts, the mixture contains the corresponding nitriles (**6a-c**) (13-18%), which were isolated by column chromatography. The compound **6b** has also been synthesized independently by the dehydration of 2-methylthio-5-methyl-3-thiophene aldoxime [1]. The nitriles formed are probably the products of the thermal desulfuration of the nitrile sulfides **3**, running in parallel. In fact, in the absence of dipolarophiles heating of **1c** gave only 2-methylsulfonyl-5-methyl-3-thiophenecarbonitrile **6c** (80-90%) and sulfur.

It must be pointed out that, in distinction from the analogous nitrile oxides, a change in the nature of the substituent in the thiophene ring has no noticeable effect on the yield of the product of ring addition and the duration of the reaction; on the contrary, the nature of the dipolarophile acquires the decisive role. Thus, the reaction with styrene, which proceeds with a high yield with the nitrile oxides of the thiophene series, did not lead to the corresponding adduct in the instance of the nitrile sulfide **3c**: only the nitrile **6c** was formed with a yield of ~70%. The influence of the nature of the substituent in the dipolarophile shows clearly in the reaction of the nitrile sulfide **3c** with substituted acetonitriles. Thus, with trichloroacetonitrile the yield of 5-trichloromethyl-1,2,4-thiadiazole (**7**), the structure of which has been confirmed by the ^{13}C NMR spectrum,

N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow. Translated from Izvestiya Akademii Nauk, Seriya Khimicheskaya, No. 8, pp. 1892-1897, August, 1992. Original article submitted August 9, 1991.

1063-5211/92/4108-1477$12.50

reaches 50-60%, while with monochloroacetonitrile only 14-30% of the 5-chloromethyl-substituted thiadiazole (**8**) is formed (depending on the excess of the dipolarophile); the reaction does not take place with unsubstituted acetonitrile nor with cyanacetamide: only desulfuration of the nitrile sulfide **3c** occurs. A similar activating effect of electron-acceptor substituents has been noticed in [8] for aromatic nitriles.



The authors are grateful to I. P. Yakovlev for evaluation of the IR spectra.

EXPERIMENTAL

The IR spectra were taken on a Specord IR-275 spectrometer; the ^1H NMR spectra were obtained on Bruker WM-250 (250 MHz) and Jeol FX-90Q (90 MHz) spectrometer, and the ^{13}C NMR spectrum on a Bruker AM-300 instrument. The molecular masses were determined on Varian MAT CH-6 and Varian MAT 311A spectrometers at an ionizing potential of 70 eV, with direct introduction of the substance into the ion source. TLC was carried out on Silufol UV-254 sheets (eluent ethyl acetate:hexane) and column chromatography on silica gel L (100-160 mesh). Elemental analysis data, constants, yields, and spectral characteristics of the synthesized compounds are presented in Table 1.

Amide of 2-Methylthio-5-methyl-3-thiophenecarboxylic Acid (2b). A sample of 5 g (3 mmoles) of 2-methylthio-3-thiophenecarboxylic acid [9] and 8.4 ml (12 mmoles) of $SOCl_2$ was refluxed for 30 min; the excess of $SOCl_2$ was stripped off, the residue dissolved in benzene and purged for 1 h with a stream of dry NH_3. The precipitate was filtered off, washed with cold water, and recrystallized.

5-Thienyl-Substituted 1,3,4-Oxythiazol-2-ones (1a-c). A solution of 10 mmoles of amide **2a-c** in 20 ml toluene was treated with 15 mmoles ClCOSCl, kept for 2 h at 70-80°C, and then for 6 h at 90-100°C; the solvent was stripped off and the residue recrystallized.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Yield, %	Mp, °C[a]	IR spectrum ($CHCl_3$, ν, cm^{-1})	PMR spectrum ($CDCl_3$, δ, ppm, J, Hz)	Mass spectrum, m/z (I, %)	Empirical formula	Found/calculated, % C	H	S	N
1a[b]	67	81–83	1750–1770 (C=O)	7.15 t (1H, 4-H, $J_{4,5}$ = 5.25, $J_{4,3}$ = 4.0); 7.62 d (1H, 5-H, $J_{5,4}$ = 5.25); 7.72 d (1H, 3-H, $J_{3,4}$ = 4.0)	185(20), 111(100), 109(8)	$C_6H_3NO_2S_2$ (185.2)				
1b	71	120–122	1755–1770 (C=O)	2.35 d (3H, CH_3); 2.52 s (3H, SCH_3); 6.95 d, 1H, 4-H)	245(67), 171(100), 154(17)	$C_8H_7NO_2S_3$ (245.3)	39.28 / 39.16	2.79 / 2.88	39.25 / 39.21	5.64 / 5.70
1c	80	141–143	1150 (SO₂), 1330 (SO₂), 1740–1780 (C=O)	2.59 d (3H, CH_3); 3.49 s (3H, SO_2CH_3); 7.29 d (1H, 4-H)	277(28), 203(100)	$C_8H_7NO_4S_3$ (277.3)	34.82 / 34.64	2.42 / 2.54	34.39 / 34.69	4.80 / 5.05
2b	90	139–142	1655 (C=O), 3050, 3150 (NH_2)	[c] 2.32 d (3H, CH_3); 2.50 s (3H, SCH_3); 7.12 d (1H, 4-H)	187(100), 170(13), 154(60)	$C_7H_9NOS_2$ (187.3)	44.99 / 44.89	4.96 / 4.84	34.22 / 34.24	7.47 / 7.48
4a	45	44–46	1725 (C=O)	3.78 s (3H, 4-OCH_3); 3.8 s (3H, 5-OCH_3); 4.82 d, 5.08 d (2H, 4-H, 5-H, $J_{4,5}$ = 4); 7.06 t (1H, 4′-H, $J_{4,5}$ = 5.5, $J_{4,3}$ = 4.0); 7.37–7.43 m (2H, 3′-H, 5′-H)	285(70), 254(56), 226(55), 194(100)	$C_{11}H_{11}NO_4S_2$ (285.4)	46.59 / 46.30	3.95 / 3.89	22.36 / 22.48	5.34 / 4.91
4b	50	99.5–102	1735 (C=O)	2.44 d (3H, CH_3); 2.55 s (3H, SCH_3); 4.25 s (3H, 4-OCH_3); 4.3 s (3H, 5-OCH_3); 4.75 d, 5.45 d (2H, 4-H, 5-H, $J_{4,5}$ = 3.8); 7.00 d (1H, 4′-H)	345(100), 287(64), 254(88), 239(36)	$C_{13}H_{15}NO_4S_3$ (345.5)	45.52 / 45.20	4.55 / 4.38	27.64 / 27.85	4.32 / 4.06
4c	63	107–109	1145 (SO₂), 1330 (SO₂), 1735 (C=O)	2.50 d (3H, CH_3); 3.33 s (3H, SO_2CH_3); 3.65 s (3H, 4-OCH_3); 3.8 s (3H, 5-OCH_3); 4.9 d, 5.15 d (2H, 4-H, 5-H, $J_{4,5}$ = 4.5); 6.98 d (1H, 4′-H)	377(9), 318(37), 287(39), 207(24), 201(100)	$C_{13}H_{15}NO_6S_3$ (377.5)	41.25 / 41.36	4.05 / 4.01	25.61 / 25.49	3.80 / 3.71

TABLE 1 (continued)

Compound	Yield, %	T. mp, °C[a]	IR spectrum ($CHCl_3$, ν, cm^{-1})	PMR spectrum ($CDCl_3$, δ, ppm, J, Hz)	Mass spectrum m/z (I, %)	Empirical formula	Found/Calculated, % C	H	S	N
5a	60	195–197	1710[d] (C=O)	[b] 4.86 d, 4.98 d (2H, 4-H, 5-H, J = 10.5); 6.85 t (1H, 4′-H, $J_{4,5}$ = 5, $J_{4,3}$ = 3); 7.05–7.3 m (6H, Ph, 5′-H); 7.60 d (1H, 3′-H, $J_{3,4}$ = 3)	314(98), 201(8), 166(100)	$C_{15}H_{10}N_2O_2S_2$ (314.4)	57.30 / 57.30	3.24 / 3.21	19.70 / 20.39	8.89 / 8.91
5b	65	130–132	1725[d] (C=O)	[e] 2.45 d (3H, CH_3); 2.55 s (3H, SCH_3); 5.2 d, 5.5 d (2H, 4-H, 5-H, $J_{4,5}$ = 11.04); 7.2–7.6 m (6H, Ph, 4′-H);	374(27), 328(6), 202(13), 173(100)	$C_{17}H_{14}N_2O_2S_3$ (374.5)	54.66 / 54.52	4.13 / 3.77	25.82 / 25.69	7.78 / 7.48
5c	61	173–175	1145 1320 (SO_2) 1720 (C=O)	2.55 d (3H, CH_3); 3.35 s (3H, SO_2CH_3); 5.15 d, 5.25 d (2H, 4-H, 5-H, $J_{4,5}$ = = 10); 7.15 d (1H, 4′-H); 7.3–7.5 m (5H, Ph)	406(20), 326(33), 299(100)	$C_{17}H_{14}N_2O_4S_3$ (406.5)	50.52 / 50.22	3.68 / 3.47	23.65 / 23.67	6.32 / 6.89
6b	83	26–28	2238 (C≡N)	2.45 d (3H, CH_3); 2.6 s (3H, SCH_3); 6.8 d (1H, 4-H)	169(100), 154(83), 136(25), 122(16), 110(33)	$C_7H_7NS_2$ (169.8)	49.82 / 49.67	4.13 / 4.17	37.53 / 37.89	8.29 / 8.28
6c	80	130–132	1155 1340 (SO_2) 2220 (C≡N)	2.58 d (3H, CH_3); 3.3 s (3H, SCH_3); 7.10 d (1H, 4-H)	201(32), 186(19), 148(10), 146(18), 138(100)	$C_7H_7NO_2S_2$ (201.3)	41.75 / 41.77	3.46 / 3.51	31.44 / 31.86	6.59 / 6.96
7	52[f] (59)	144–146	1150 1320 (SO_2)	2.50 d (3H, CH_3); 3.58 s (3H, SO_2CH_3); 7.41 d (1H, 4-H)	377(100), 362(39), 340(24), 314(71), 172(22)	[g] $C_9H_7Cl_3N_2O_2S_3$ (377.7)	28.68 / 28.62	2.19 / 1.87	25.20 / 25.47	7.44 / 7.41
8	37[f] (14)	130–132	1145 1320 (SO_2)	2.50 d (3H, CH_3); 3.67 s (3H, SO_2CH_3); 5.0 s (2H, CH_2Cl); 7.49 d (1H, 4-H)	308(100), 295(20), 245(23), 172(18)	[g] $C_9H_9ClN_2O_2S_3$ (308.8)	35.49 / 34.99	2.92 / 2.94	30.66 / 31.15	8.85 / 9.07

Notes. a) Eluent hexane:ethyl acetate 2:1 (**4a, 5b, c, 7, 8**), 1:1 (**4c**), 5:1 (**4b**); solvent for recrystallization EtOH (**1a-c, 4c, 5a, c, 7, 8**), hexane (**4a, b, 5b, 6b**), hexane and EtOH (**6c**), H_2O (**2b**). b) Obtained earlier by method [10] with a yield of 44%. c) PMR spectrum in CD_3CN. d) IR spectrum: as KBr tablets. e) PMR spectrum in CD_3CN:C_6D_6 1:1. f) Tenfold excess of dipolarophile. g) Found/Calculated Cl, %: **7**) 27.87/28.16; **8**) 11.29/11.48.

Nitrile of 2-Methylsulfonyl-5-methyl-3-thiophenecarboxylic Acid (6). A solution of 0.3 g (1.1 mmoles) of the oxathiazolone **1c** in 5 ml o-$C_6H_4Cl_2$ was kept in a stream of argon for 40 min at 160°C; the solvent was removed in vacuum and the solid residue recrystallized.

Nitrile of 2-Methylthio-5-methyl-3-thiophenecarboxylic Acid (6b).* A sample of 2 g (11 mmoles) of 2-methylthio-5-methyl-3-thiophenealdoxime [1] and 0.88 g fused AcONa was refluxed for 3 h in 20 ml Ac_2O, poured into water with ice, and $NaHCO_3$ added. The oil separated was extracted with ether; the extract was washed with water, dried with $MgSO_4$, the ether was stripped off, and the residue recrystallized.

3-(2-Thienyl)-, (2-Methylthio-5-methyl-3-thienyl)-, and (2-Methylsulfonyl-5-methyl-3-thienyl)-N-phenyl-2-isothiazoline-4,5-dicarboximides (5a-c). A weight (0.75 mmole) of thienyloxathiazolone **1a-c** was added gradually to a solution of 3 mmoles N-phenylmaleinimide in 3-4 ml o-$Cl_2C_6H_4$, heated to 150°C (for **1b** to 115-120°C), kept at this temperature until the complete disappearance of the oxathiazolone (checked by TLC), and cooled to 20°C. The precipitate of dicarboximide **5a** formed was filtered off and recrystallized; solutions of **5b** and **c** were chromatographed on a column and the products recrystallized. Separated 13-18% of nitriles **6b, c**, N-phenylmaleinimide, and dicarboximides **5b** and **c**.

Dimethyl Esters of 3-(2-Thienyl)-, 3-(2-Methylthio-5-methyl-3-thienyl)-, and 3-(2-Methylsulfonyl-5-methyl-3-thienyl)-2-isothiazoline-4,5-dicarboxylic Acids (4a-c). A weight (3 mmoles) of oxathiazolone **1a-c** was added gradually to a solution of 12 mmoles dimethyl fumarate in 15-20 ml o-$Cl_2C_6H_4$ at 140°C (for **1b** at 110°C) and kept at this temperature in a stream of argon for 14 h (for **1e** for 10.5 h). The solution was cooled and chromatographed on a column; mixtures of adducts with dimethyl fumarate or nitrile were obtained, from which the pure esters **4a-c** were isolated by recrystallization.

3-(2-Methylsulfonyl-5-methyl-3-thienyl)-5-chloromethyl- and 3-(2-Methylsulfonyl-5-methyl-3-thienyl)-5-trichloromethyl-1,2,4-thiadiazoles (8, 7). Prepared as described above from 3 mmoles oxathiazole **1c** and a fourfold excess of $ClCH_2CN$ and CCl_3CN, respectively, in o-$Cl_2C_6H_4$ at 140°C for 10 h (for 8 and 5 h for **7**). ^{13}C NMR spectrum of **7** [$CDCl_3$, δ, ppm ($J_{^{13}C-^1H}$, Hz)], 15.44 q (Me, J = 129.5); 44.94 q (SO_2Me, J = 136.7); 167.29 s (C^3); 190.64 s (C^5); 87.81 s (CCl_3); **thienyl:** 130.09 d (C^4, J = 170.9); 134.94 s (C^3); 139.6 s (C^2); 146.75 d (C^5, J = 7.3).

REFERENCES

1. M. M. Krayushkin, M. A. Kalik, V. K. Zav'yalova, and V. S. Bogdanov, *Khim. Geterotsikl. Soedin.*, No. 3, 403 (1988).
2. M. M. Krayushkin, M. A. Kalik, V. K. Zav'yalova, and E. Yu. Zvezdina, in: Abstracts of 14th Internat. Conf. on the Chemistry of Organosulfur Compounds, Lodz' (1990), p. 25.
3. F. Kurzer in: *Advances in Heterocyclic Chemistry,* Vol. 32, A. R. Katritzky (ed.), Academic Press, New York–London (1982), p. 285.
4. E. Müllbauer and W. Weiss, British Patent No. 1,079,348 (1967); *Chem. Abstr.*, **68**, 69000 (1968).
5. E. S. Levitina, I. P. Yakovlev, E. D. Lubuzh, L. F. Godunova, E. I. Karpeiskaya, and E. I. Klabunovskii, *Khim. Geterotsikl. Soedin.*, No. 8, 1133 (1989).
6. R. M. Paton, *Chem. Soc. Rev.*, **18**, No. 1, 35 (1989).
7. R. K. Howe and J. E. Franz, *J. Org. Chem.*, **43**, No. 19, 3742 (1978).
8. R. K. Howe and J. E. Franz, *J. Org. Chem.*, **39**, No. 1, 962 (1974).
9. Ya. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, *Zh. Obshch. Khim.*, **29**, No. 11, 3631 (1959).
10. A. Senning and J. Sch. Rasmussen, *Acta Chem. Scand.*, **27**, No. 6, 2161 (1973).

*Obtained for the first time by V. K. Zav'yalova in our laboratory.