Russian Journal of General Chemistry, Vol. 74, No. 9, 2004, pp. 1418–1422. Translated from Zhurnal Obshchei Khimii, Vol. 74, No. 9, 2004, pp. 1529–1533.

Phosphorus Pentasulfide and Lawesson Reagent in Synthesis of 1,3-Thiazole-4-thiol Derivatives

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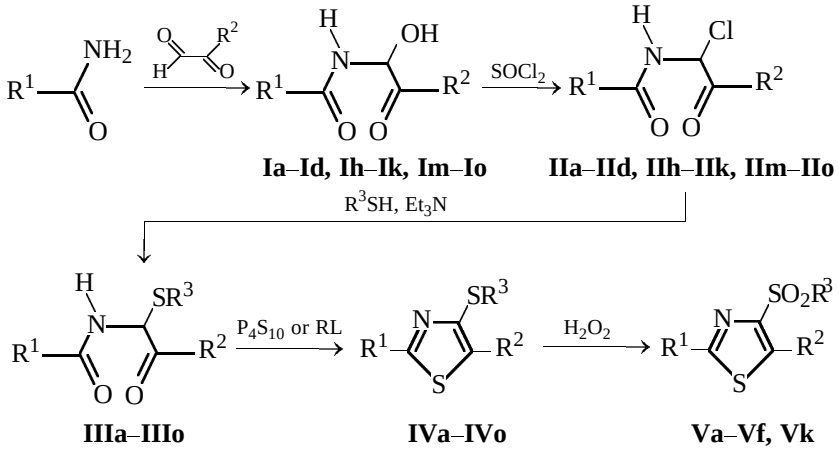
Received October 28, 2002

Abstract — Available S-amidophenacylation products of thiols and sulfanylphenols on treatment with phosphorus pentasulfide or, which is better, Lawesson reagent convert into the corresponding 1,3-thiazole-4-thiol derivatives that are easily oxidized with hydrogen peroxide. The latter reaction was used to introduce a series of alkyl- or arylsulfonyl groups in the 4 position of the thiazole ring. This general approach significantly extends the limited range of synthetic procedures for 1,3-thiazole-4-thiol derivatives.

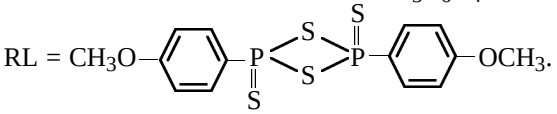
We have already used adducts of carboxamides and phenylgyoxal and its analogs **I** to prepare a series of functional derivatives of azoles and azines [1–3]. In the present work we showed that available reagents **I** by means of a simple sequence **I** → **II** → **III** → **IV** presented in Scheme 1 can be converted into novel derivatives of 1,3-thiazole-4-thiol. The key stage of the process is the reaction of S-amidophenacylation products and similar compounds with phosphorus pentasulfide or Lawesson reagent, whose application field has been considered in detail in the reviews [4, 5]. The **III** → **IV** transition involves not only sulfurization of the S-amidophenacylation products, but also their cyclization. Evidence for this conclusion comes from the disappearance from the IR spectra of two strong bands at 1620–1660 and 1660–1700 cm^{-1}, belonging to stretching vibrations of different carbonyl groups in compounds **III**. The formation of the

Scheme 1.



Ia–Id, Ih–Ik, Im–Io **IIa–IId, IIh–IIk, IIm–IIo** **IIIa–IIIo** **IVa–IVo** **Va–Vf, Vk**

R^1 = H, R^2 = 4-$CH_3C_6H_4$ (**a**); R^1 = CH_3, R^2 = C_6H_5 (**b**); R^1 = CH_3, R^2 = 4-$CH_3C_6H_4$ (**c**); R^1 = R^2 = C_6H_5 (**d–g**); R^1 = C_6H_5; R^2 = 4-$CH_3C_6H_4$ (**h**); R^1 = C_6H_5, R^2 = 2-thienyl (**i**); R^1 = 4-ClC_6H_4, R^2 = 4-FC_6H_4 (**j**); R^1 = 4-$CH_3OC_6H_4$, R^2 = C_6H_5 (**k, l**); R^1 = 2-furyl, R^2 = C_6H_5 (**m**); R^1 = 2-furyl, R^2 = 2-thienyl (**n**); R^1 = 2-thienyl, R^2 = C_6H_5 (**o**); R^3 = C_2H_5 (**IIId–Vd**), $C_6H_5CH_2$ (**IIIm, IIIo, IVm, IVo**), C_6H_5 (**IIIe, IIIk–Ve, Vk**), 4-ClC_6H_4 (**IIIa, IIIb, IIIf, IIIh–IIIj, IIIl, IIIo, IVa, IVa, IVf, IVh–IVj, IVl, IVn, Va, Va, Vf**), 4-$CH_3C_6H_4$ (**IIIc, IIIg, IVc, IVg, Vc**);



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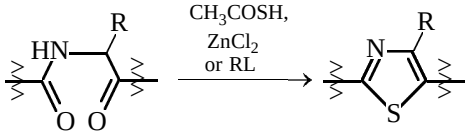
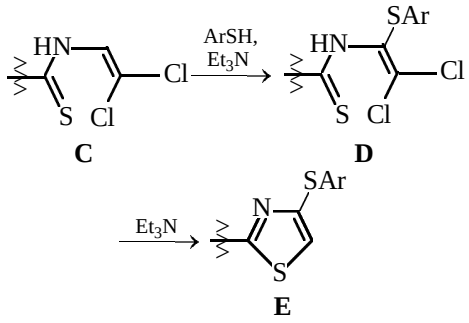
thiazole ring was also confirmed by the disappearance of the broad band of stretching vibrations of associated N–H bond at 3240–3415 cm^{-1}. Comparison of the ^1H NMR spectra of a series of related pairs of compounds **III** and **IV** reveals disappearance of the >CH–NH– group as a result of intramolecular cyclocondensation that proceeds more directionally when Lawesson reagent is used instead of phosphorus pentasulfide. Finally, note that a heterocyclization like **A** → **B** has already been observed with analogs of compounds **III** bearing no functional substituents α to the amide residue [6, 7].



A **B**

R = H, Alk, Ar, Ht.

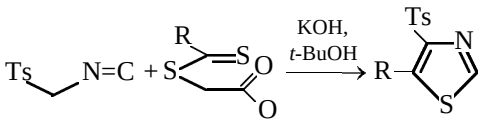
Thus, the fact that the reactions of compound **III** with phosphorus pentasulfide and Lawesson reagent provide 1,3-thiazole derivatives casts no doubts. The scope of application of the cyclization **III**→**IV** proved to be rather wide, as seen from the structures of the starting S-amidophenacylation products and their analogs (Table 1), as well as of the corresponding 1,3-thiazole derivatives containing various alkylsulfanyl and arylsulfanyl groups in the 4 position of the ring (Table 2). Previously 4-arylsulfanyl substitution of the thiazole fragment was effected via the sequence **C** → **D** → **E** [8].



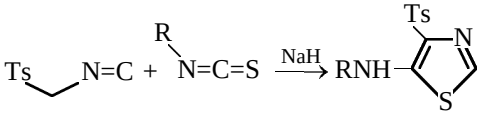
C **D** **E**

It is quite evident that this approach has a much narrower application field compared to the cyclization **III**→**IV**, since only a few *N*-(2,2-dichloroethenyl)-amides of aromatic thiocarboxylic acids are available; moreover, these compounds can only be used for preparing substituted 2-aryl-1,3-thiazole-4-thiols. At the same time, the transformation **III** → **IV** makes possible synthesis of 1,3-thiazole-4-thiol derivatives bearing the hydrogen in the 2 position, as well as various alkyl, aryl, and heteryl substituents.

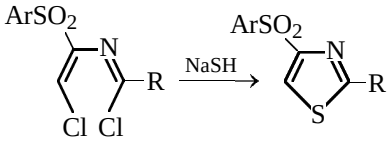
Scheme 2.



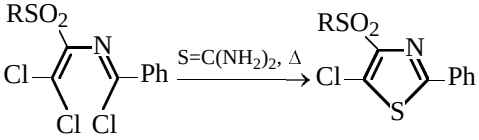
R = Ar, 2-furyl [9].



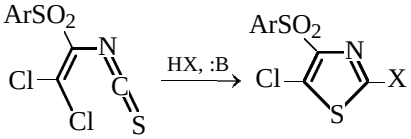
R = Alk, Ar [10].



R = C_6H_5, $(CH_3)C$ [11].



R = Alk, Ar [12].



X = AlkO, AlkS, ArS, AlkNH, Alk_2N, ArNH, HtNH, etc. [13].

X = AlkO, AlkS, ArS, AlkNH, Alk_2N, ArNH, HtNH, etc [13].

Cyclization products **IV** are easily oxidized by hydrogen peroxide, which was used to prepare a series of 4-alkyl(aryl)sulfonyl-substituted thiazoles **V**. Inspite of the fact that five approaches for introducing alkyl- or arylsulfonyl groups in the 4 position of the thiazole ring have been developed, they all, as seen from Scheme 2, are not universal and fail to provide most of substituted thiazoles **V** presented in Table 3. Consequently, the whole sequence **I** → **II** → **III** → **IV** → **V** studied in this work contributes significantly into the range of approaches to introducing sulfur-containing groups in the 4 position of the thiazole ring.

EXPERIMENTAL

The IR spectra were measured on a Specord M-80 spectrometer in KBr pellets. The ^1H NMR spectra were measured on a Varian VXR-300 spectrometer in DMSO-d_6 against internal TMS. The yields, constants, and elemental analyses are listed in Tables 1–3, and

Table 1. Constants, yields, and elemental analyses of S-amidophenacylation products and their analogs **III**

Comp. no.	Yield, %	mp, °C[a]	Found, %			Formula	Calculated, %		
			Cl	N	S		Cl	N	S
IIIa	72	90–92	10.06	4.25	9.28	$C_{16}H_{14}ClNO_2S$	11.09	4.38	10.03
IIIb	86	113–114	11.03	4.34	10.30	$C_{16}H_{11}ClNO_2S$	11.19	4.42	10.12
IIIc	84	136–138	–	4.15	10.68	$C_{17}H_{17}NO_2S$	–	4.68	10.71
IIId	74	107–109	–	4.43	10.48	$C_{17}H_{17}NO_2S$	–	4.68	10.71
IIIe	78	116–118	–	3.78	10.02	$C_{21}H_{17}NO_2S$	–	4.03	9.23
IIIf	80	114–116	8.14	–	9.72	$C_{21}H_{16}ClNO_2S$	9.28	–	9.75
IIIg	83	128–130	–	3.17	9.21	$C_{22}H_{19}NO_2S$	–	3.88	8.87
IIIh	88	106–108	8.29	–	8.22	$C_{22}H_{18}ClNO_2S$	8.95	–	8.01
IIIi	82	110–112	8.92	–	16.78	$C_{19}H_{14}ClNO_2S$	9.14	–	16.53
IIIj	88	149–151	16.13	–	7.32	$C_{21}H_{14}Cl_2FNO_2S$	16.33	–	7.38
IIIk	72	112–113	–	3.56	8.28	$C_{22}H_{19}NO_3S$	–	3.71	8.49
IIIl	85	115–117	8.52	–	7.86	$C_{22}H_{18}ClNO_3S$	8.61	–	7.78
IIIm	78	110–112	–	3.87	8.87	$C_{20}H_{17}NO_3S$	–	3.99	9.12
IIIn	72	140–142	9.24	–	17.15	$C_{17}H_{12}ClNO_3S_2$	9.38	–	16.97
IIIo	80	146–148	–	3.79	17.31	$C_{20}H_{17}NO_2S_2$	–	3.81	17.45

[a] After crystallization from ethanol.

Table 2. Constants, yields, and elemental analyses of substituted 1,3-thiazole-4-thiols **IV**

Comp. no.	Yield, %	mp, °C[a]	Found, %			Formula	Calculated, %		
			Cl	N	S		Cl	N	S
IVa	61	–[b]	9.55	–	17.95	$C_{16}H_{12}ClNS_2$	11.15	–	20.17
IVb	54 (82)[c]	46–48	10.86	4.28	20.12	$C_{16}H_{12}ClNS_2$	11.15	4.41	20.17
IVc	59	–[b]	–	–	18.09	$C_{18}H_{17}NS_2$	–	–	20.59
IVd	58	54–56	–	4.37	21.13	$C_{17}H_{15}NS_2$	–	4.71	21.56
IVe	50 (76)	116–118	–	3.89	18.34	$C_{21}H_{15}NS_2$	–	4.05	18.56
IVf	51	98–100	9.12	3.43	17.18	$C_{21}H_{14}ClNS_2$	9.33	3.69	16.89
IVg	56 (87)	85–87	–	3.86	17.93	$C_{22}H_{17}NS_2$	–	3.90	17.84
IVh	69	111–113	8.64	3.37	15.84	$C_{22}H_{16}ClNS_2$	9.00	3.56	16.28
IVi	55	125–127	9.02	3.58	24.93	$C_{19}H_{12}ClNS_2$	9.19	3.63	24.92
IVj	62 (90)	146–147	15.98	3.01	14.87	$C_{21}H_{12}Cl_2FNS_2$	16.40	3.24	14.83
IVk	58	94–96	–	3.42	17.60	$C_{22}H_{17}NOS_2$	–	3.75	17.07
IVl	57 (84)	130–132	3.07	8.31	15.74	$C_{22}H_{16}ClNOS_2$	8.65	3.42	15.64
IVm	52	56–58	–	3.92	19.23	$C_{20}H_{15}NOS_2$	–	4.01	18.35
IVn	54	104–106	9.34	3.26	24.92	$C_{17}H_{10}ClNOS_3$	9.43	3.73	25.59
IVo	57	79–81	–	3.71	26.41	$C_{20}H_{15}NS_3$	–	3.83	26.32

[a] From ethanol. [b] The compound was isolated as an oil and used in further transformations without additional purification. [c] Here and hereinafter, parenthesized are the yields of the reactions with Lawesson reagent.

the ^{1}H NMR spectra are presented in Table 4.

N-[2-aryl(heteryl)-1-hydroxy-2-oxoethyl]carboxamides **Ia**–**Id, Ih**–**Ik, Im**–**Io** and *N*-[2-aryl(heteryl)-1-chloro--2-oxoethyl]carboxamides **IIa**–**d, IIh**–**IIk, IIn**–**IIp** were prepared by published procedures [1].

***N*-[2-Aryl(heteryl)-1-alkylsulfanyl(arylsulfanyl)-2-oxoethyl]carboxamides IIIa–IIIo**. To a solution of 0.006 mol of compounds **IIa**–**IId, IIh**–**IIk, IIm**–**IIp** in 100 ml of anhydrous acetonitrile, 0.066 mol of triethylamine and 0.066 mol of the corresponding thiol were added in succession. The resulting mixture

Table 3. Constants, yields and elemental analyses of 4-alkyl(aryl)sulfonyl-substituted 1,3-thiazoles **V**

Comp. no.	Yield, %	mp, °C[a]	Found, %		Formula	Calculated, %	
			N	S		N	S
Va	78	157–159	3.90	18.10	$C_{16}H_{12}ClNO_2S_2$	4.00	18.33
Vb	82	120–122	3.86	18.62	$C_{16}H_{12}ClNO_2S_2$	4.00	18.33
Vc	92	134–136	4.02	18.32	$C_{18}H_{17}NO_2S_2$	4.08	18.67
Vd	86	104–106	4.14	19.42	$C_{17}H_{15}NO_2S_2$	4.25	19.47
Ve	89	102–104	3.62	16.65	$C_{21}H_{15}NO_2S_2$	3.71	16.99
Vf	90	118–120	3.34	15.42	$C_{21}H_{14}ClNO_2S_2$	3.40	15.57
Vk	82	142–144	3.42	15.74	$C_{22}H_{17}NO_2S_2$	3.44	15.74

[a] From DMF–water, 10 : 1.

Table 4. ^{1}H NMR spectra of compounds **III**–**V**

Comp. no.	δ, ppm ($CDCl_3$)
IIIb	2.1 s (3H, CH_3), 6.60 d (1H, CH, $^3J_{HH}$ 13.9 Hz), 6.78 d (1H, NH, $^3J_{HH}$ 13.9 Hz), 7.18–7.93 m (9H, C_6H_4, C_6H_5)
IIIf	6.80 d (1H, CH, $^3J_{HH}$ 10.8 Hz), 7.20–8.00 m (15H, C_6H_4, $2C_6H_5$, NH)
IIIg	2.35 s (3H, CH_3), 6.78 d (1H, CH, $^3J_{HH}$ 10.7 Hz), 7.08–8.03 m (15H, C_6H_4, $2C_6H_5$, NH)
IIIl	3.80 s (3H, CH_3O), 7.00 d (1H, CH, $^3J_{HH}$ 11.3 Hz), 7.03–8.03 m (13H, $2C_6H_4$, C_6H_5), 9.20 d (1H, NH, $^3J_{HH}$ 11.3 Hz)
IVa	2.39 s (3H, CH_3), 7.19–7.48 m (8H, $2C_6H_4$), 8.77 s (1H, C^2H, thiazole fragment)
IVb	2.71 s (3H, CH_3), 7.11–7.64 m (9H, C_6H_5, C_6H_4)
IVc	2.27 s (3H, CH_3), 2.36 s (3H, CH_3), 2.68 s (3H, CH_3), 7.02–7.48 m (8H, $2C_6H_4$)
IVd	1.33 s (3H, CH_3), 3.24 s (2H, CH_3), 7.36–7.95 m (10H, $2C_6H_5$)
IVe	3.82 s (3H, OCH_3), 7.00–7.92 m (14H, $2C_6H_5$, C_6H_4)
IVi	7.13–7.90 m (12H, C_6H_4, C_6H_5, 2-thienyl)
IVl	3.85 s (3H, OCH_3), 6.90–7.85 m (13H, 2 C_6H_4, C_6H_5)
IVm	4.45 s (2H, CH_2), 7.25–7.97 m (13H, $2C_6H_5$, 2-furyl)
Vd	1.26 s (3H, CH_3), 3.48 q (2H, CH_2), 7.45–7.98 m (10H, $2C_6H_5$)
Vk	3.83 s (3H, OCH_3), 7.08–7.95 m (14H, $2C_6H_5$, C_6H_4)

was left to stand for 12 h at 20–25°C, 50 ml of water was added, the precipitate that formed was filtered off, dried, and purified by crystallization.

4-Alkylsulfanyl(arylsulfanyl)-2-R^1-5-R^2-1,3-thiazoles IVa–IVo. *a*. A mixture of 0.003 mol of compound **IIIa–IIIo**, 0.67 g of phosphorus pentasulfide, and 30 ml of chlorobenzene was stirred for 2 h at 100°C. The solvent was removed in a vacuum, after which 15 ml of 10% aqueous sodium hydroxide and 40 ml of chloroform were added in succession. The organic layer was separated, dried with anhydrous magnesium sulfate, the solvent was removed in a vacuum, and the residue was purified by crystallization.

b. A mixture of compound **IIIb, IIIe, IIIg, IIIj, or IIIl**, 0.005 mol of Lawesson reagent [5], and 50 ml of anhydrous toluene was heated at 110°C with stirring for 3 h, and then left to stand for 12 h at 20–25°C. The solvent was removed in a vacuum, and the residue was treated with 15 ml of 10% aqueous sodium hydroxide, filtered off, and purified by crystallization from ethanol. Mixed sample of the products obtained by procedures *a* and *b* showed no melting point depression, and their IR spectra were also identical.

4-Alkylsulfonyl(arylsulfonyl)-2-R^1-5-R^2-1,3-thiazoles Va–Vf and Vk. To a solution of 0.001 mol of compound **IVa–IVf, or Vk** in 10 ml of glacial acetic acid heated to 100°C, 10 ml of 30% hydrogen peroxide was added in 2-ml portions over the course of 20–30 min. The resulting mixture was left to stand for 1 h at 20–25°C. The precipitate that formed was

filtered off, washed with water, and purified by crystallization.

REFERENCES

1. Drach, B.S., Dolgushina, I.Yu., and Kirsanov, A.V., *Zh. Org. Khim.,* 1973, vol. 9,. no 2, p. 414.
2. Drach, B.S., Dolgushina, I.Yu., and Sinitsa, A.D., *Khim. Geterotsikl. Soedin.,* 1974, no. 7, p. 928.
3. Drach, B.S., Dolgushina, I.Yu., and Sinitsa, A.D., *Zh. Obshch. Khim.,* 1975, vol. 45, no. 6, p. 1251.
4. Cherkasov, R.A., Kutyrev, G.A., and Pudovik, A.N., *Tetrahedron,* 1985, vol. 41, no. 13, p. 2567.
5. Cava, M.P. and Levinson, M.I., *Tetrahedron,* 1985, vol. 41, no. 22, p. 5061.
6. Zav'yalov, S.I., Budkova, T.K., and Larionova, M.N., *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1976, no. 6, p. 1411.
7. Nishio, T. and Ori, M., *Helv. Chim. Acta,* 2001, vol. 84, no. 8, p. 2347.
8. Vinogradova, T.K., Turov, V.V., and Drach, B.S., *Zh. Org. Khim.,* 1990, vol. 26, no. 6, p. 1302.
9. Oldenziel, O.H. and Van Leusen, A.M., *Tetrahedron Lett.,* 1972, no. 27, p. 2777.
10. Van Nispen, S.P.J.M., Bregman, J.H., Van Engen, D.G., and Van Leunsen, A.M., *Recl. Trav. Chim. Pays-Bas,* 1982, vol. 101, no. 1, p. 28.
11. Rudenko, E.A., Seferov, S.O., Chervonyi, V.A., Kharchenko, A.V., and Drach, B.S., *Ukr. Khim. Zh.,* 1991, vol. 57, no. 5, p. 530.
12. Kharchenko, A.V., Seferov, S.O., Zyabrev, V.S., Chervonyi, V.A., Vdovenko, S.I., and Drach, B.S., *Ukr. Khim. Zh.,* 1993, vol. 59, no. 6, p. 637.
13. Babiy, C.B., Zyabrev, V.S., and Drach, B.S., *Zh. Obshch. Khim.,* 2002, vol. 72, no. 11, p. 1834.