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O.N. Chupakhin on his 70th Anniversary

Oxidative Cyclization of 2-Arylhydrazonothioacetamides

M. L. Vasil'eva[1], M. V. Mukhacheva[1], N. P. Bel'skaya[1], V. A. Bakulev[1], R. J. Anderson[2], and P. V. Groundwater[2]

[1] *Ural State Technical University, ul. Mira 19, Yekaterinburg, 620002 Russia*
e-mail: belska@htf.ustu.ru

[2] *University of Sunderland, Warncliffe Street, Sunderland SR1 3SD, UK*
e-mail: roz.Anderson@sunderland.ac.uk

Abstract—Intramolecular oxidative cyclization of 2-arylhydrazonothioacetamides was studied, and applicability limits of this reaction for the synthesis of 2-aryl-1,2,3-thiadiazol-5(2*H*)-imines were determined.

Thioamides are known to readily undergo oxidation. Depending on the substrate structure, oxidant nature, and reaction conditions, the products may be both linear compounds [1] and complex heterocyclic systems [1–30]. For example, primary thioamides are converted into nitriles by the action of mild oxidants [1, 3–5], or they undergo cyclization to 1,2,4-thiadiazoles through intermediate formation of dimers [1–9]. Oxidation of thiobenzamides provides a convenient synthetic route to benzothiazoles [10–11]. Functionalization of thioamides via introduction of additional oxidation-sensitive groups gives rise to monocyclic and fused heterocyclic compounds [12–29]. Oxidative intramolecular cyclization of propanedithioamides leads to formation of 3,4-diamino-1,2-dithiolium salts [12–16]. When a thioamide molecule contains a carbamoyl or amino group, various isothiazoles can be obtained [17–21]. Oxidation of thiocarbamoyl enamine derivatives could give benzothiazoles, isothiazoles, and pyrroles [22–25], while secondary thioamides derived from γ,δ-alkenes are oxidized with iodine to afford γ-butyrothiolactones with high stereoselectivity [27]. According to the data of [28–30], oxidative cyclization of arylhydrazonothioacetamides yields 5-amino-2-phenyl-1,2,3-thiadiazolium salts.

Taking into account that some 1,2,3-thiadiazole derivatives were recently shown to exhibit high biological activity [31–34], we planned to further develop the procedure for dehydrocyclization of 2-arylhydrazonothioacetamides (which was proved on a few examples) and determine its applicability limits for the synthesis of a large series of 1,2,3-thiadiazole derivatives. For this purpose, we examined intramolecular dehydrogenation of arylhydrazonothioacetamides having various substituents in the aromatic ring (both electron-donor and electron-acceptor) and R' groups (Scheme 1).

In all cases, the oxidation of arylhydrazonothioacetamides **I** with bromine in acetic acid afforded 2-aryl-5-imino-2,5-dihydro-1,2,3-thiadiazole hydrobromides **II** as the major products (yield 14–99%; Table 1). Their structure was confirmed by the spectral data (Tables 2–4) and elemental analyses (Table 1). The ^{1}H NMR spectra of compounds **II** (Table 2) contained signals from protons in the aromatic ring and substituent in position *4* of the thiadiazole ring; also, two broadened one-proton singlets and one two-proton singlet were present in the region of δ 10 ppm, which correspond to protonated imino group. 1,2,3-Thiadiazoles **II** showed in the mass spectra (Table 4) the molecular ion peak with a relative intensity of 1.2 to 91% and peaks of fragment ions arising from elimination of the side-chain substituents. Characteristically, the electron impact mass spectra contained peaks from stable fragment ions formed by decomposition of the thiadiazole ring. For example, cleavage of the N–S bond in the molecular ion, followed by extrusion of sulfur, gives ion F_6, and simultaneous cleavage of the N–S and N–C^2 bonds gives rise to the

Scheme 1.

a: Br$_2$, AcOH
b: I$_2$, AcOH
c: NCS, AcOEt
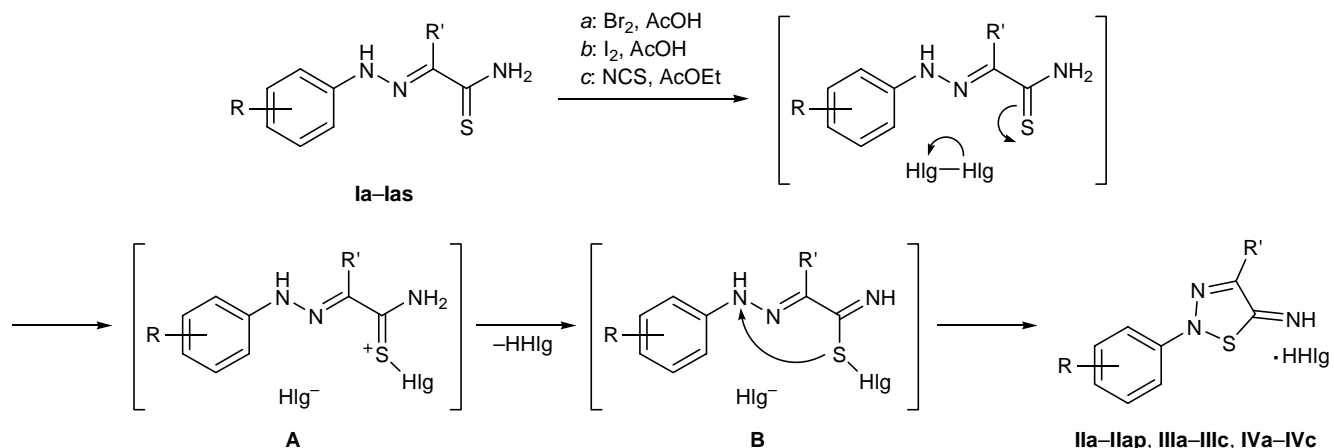
I, R = 4-OMe, R' = CONH$_2$ (**a**), CONHMe (**b**), CONHCH$_2$CH$_2$OMe (**c**), CONHC$_6$H$_{11}$ (**d**), CONHC$_6$H$_4$OMe-4 (**e**), CONHPh (**f**), CONHC$_6$H$_4$Cl-4 (**g**), COOEt (**h**), CON(CH$_2$CH$_2$)$_2$NMe (**i**); R = H, R' = CONH$_2$ (**j**), COOEt (**k**); R = 4-F, R' = CONH$_2$ (**l**), CONHMe (**m**), CONHC$_6$H$_{11}$ (**n**), CONHCH$_2$Ph (**o**), CONHC$_6$H$_4$OMe-4 (**p**), CONHPh (**q**), CONHC$_6$H$_4$Cl-4 (**r**), CN (**s**); R = 4-Cl, R' = CONH$_2$ (**t**), CONHMe (**u**), CONHC$_6$H$_{11}$ (**v**), CONHCH$_2$Ph (**w**), CONHC$_6$H$_4$OMe-4 (**x**), CONHPh (**y**), CONHC$_6$H$_4$Cl-4 (**z**), COOEt (**aa**), CN (**ab**), CON(CH$_2$CH$_2$)$_2$NMe (**ac**), CON(CH$_2$CH$_2$)$_2$ (**ad**); R = 4-CONH$_2$, R' = CONH$_2$ (**ae**), CONHMe (**af**), CONHC$_6$H$_{11}$ (**ag**), CONHCH$_2$Ph (**ah**), CONHPh (**ai**), CONHC$_6$H$_4$Cl-4 (**aj**), CON(CH$_2$CH$_2$)$_2$ (**ak**); R = 4-COOEt, R' = CONH$_2$ (**al**); R = 4-NO$_2$, R' = CONH$_2$ (**am**); R = 3-CF$_3$, R' = CON(CH$_2$CH$_2$)$_2$ (**an**); R = 2-OMe, R' = CONHMe (**ao**); R = 2-Cl, R' = CONH$_2$ (**ap**), CONHMe (**aq**); R = 2,6-Cl$_2$, R' = CON(CH$_2$CH$_2$)$_2$NMe (**ar**), CONH(CH$_2$CH$_2$)O (**as**); **II**, Hlg = Br; R = 4-OMe, R' = CONH$_2$ (**a**), CONHMe (**b**), CONHCH$_2$CH$_2$OMe (**c**), CONHC$_6$H$_{11}$ (**d**), CONHC$_6$H$_3$Br-3-OMe-4 (**e**), CONHPh (**f**), CONHC$_6$H$_4$Cl-4 (**g**), CON(CH$_2$CH$_2$)$_2$NMe (**h**), COOEt (**i**); R = H, R' = CONH$_2$ (**j**), COOEt (**k**); R = 4-F, R' = CONH$_2$ (**l**), CONHMe (**m**), CONHC$_6$H$_{11}$ (**n**), CONHCH$_2$Ph (**o**), CONHPh (**p**), CONHC$_6$H$_4$Cl-4 (**q**), CN (**r**); R = 4-Cl, R' = CONH$_2$ (**s**), CONHMe (**t**), CONHC$_6$H$_{11}$ (**u**), CONHCH-$_2$Ph (**v**), CONHPh (**w**), CONHC$_6$H$_4$Cl-4 (**x**), COOEt (**y**), CN (**z**), CON(CH$_2$CH$_2$)$_2$NMe (**aa**), CON(CH$_2$CH$_2$)$_2$ (**ab**); R = 4-CONH$_2$, R' = CONH$_2$ (**ac**), CONHMe (**ad**), CONHC$_6$H$_{11}$ (**ae**), CONHCH$_2$Ph (**af**), CONHPh (**ag**), CONHC$_6$H$_4$Cl-4 (**ah**), CON(CH$_2$CH$_2$)$_2$ (**ai**); R = 4-COOEt, R' = CONH$_2$ (**aj**); R = 4-NO$_2$, R' = CONH$_2$ (**ak**); R = 2-OMe, R' = CONHMe (**al**); R = 2-Cl, R' = CONH$_2$ (**am**), CONHMe (**an**); R = 2,6-Cl$_2$, R' = CON(CH$_2$CH$_2$)$_2$NMe (**ao**), CON(CH$_2$CH$_2$)O (**ap**); **III**, Hlg = I; R = 4-OMe, R' = CONHC$_6$H$_4$OMe-4 (**a**); R = 4-F, R' = CONHC$_6$H$_4$OMe-4 (**b**); R = 4-Cl, R' = CONHC$_6$H$_4$OMe-4 (**c**); **IV**, Hlg = Cl; R = OMe, R' = CONH$_2$ (**a**); R = C$_6$H$_4$CF$_3$-3, R' = CON(CH$_2$CH$_2$)$_2$ (**b**); R = 4-COOEt, R' = CONH$_2$ (**c**).

Table 1. Yields, melting points, and elemental analyses of 1,2,3-thiadiazoles **IIa–IIap**, **IIIa–IIIc**, and **IVa–IVc** and 1,2,4-thiadiazoles **Va–Vc**

Comp. no.	Method[a]	Yield, %	mp, °C	Found, %		Formula	Calculated, %	
				N	S		N	S
IIa	a	51	266	19.63	10.05	C$_{10}$H$_{11}$BrN$_4$O$_2$S	19.58	9.67
IIb	a	99	250	16.57	9.52	C$_{11}$H$_{13}$BrN$_4$O$_2$S	16.23	9.28
IIc	a	90	195	16.02	9.22	C$_{13}$H$_{17}$BrN$_4$O$_3$S	15.69	8.96
IId	a	99	241	13.42	7.73	C$_{16}$H$_{21}$BrN$_4$O$_2$S	13.56	7.45
IIe	a	86	223	10.56	6.43	C$_{17}$H$_{17}$Br$_2$N$_4$O$_3$S	10.83	6.18
IIf	a	72	215	11.46	8.56	C$_{12}$H$_{14}$BrN$_3$O$_3$S	11.67	8.89
IIg	a	99	238	13.50	7.48	C$_{16}$H$_{14}$BrClN$_4$O$_2$S	13.18	7.26
IIh	a	65	226	17.25	8.02	C$_{14}$H$_{20}$BrN$_5$O$_2$S	16.91	7.73
IIi	a	83	242	11.79	9.04	C$_{12}$H$_{14}$BrN$_3$O$_3$S	11.67	8.89
IIj	a	51	225	18.38	10.73	C$_9$H$_9$BrN$_4$OS	18.60	10.63
IIk	a	60	205	12.90	10.00	C$_{11}$H$_{12}$BrN$_3$O$_2$S	12.73	9.71
IIl	a	81	221	17.34	10.61	C$_9$H$_{10}$BrFN$_4$OS	17.55	10.00
IIm	a	97	250	16.08	9.46	C$_{10}$H$_{10}$BrFN$_4$OS	16.82	9.61

Table 1. Contd.

Comp. no.	Method[a]	Yield, %	mp, °C	Found, %		Formula	Calculated, %	
				N	S		N	S
IIn	*a*	81	263	13.33	8.25	$C_{15}H_{18}BrFN_4OS$	13.97	7.98
IIo	*a*	52	260	13.18	7.51	$C_{15}H_{16}BrFN_4OS$	13.69	7.82
IIp	*a*	95	266	11.53	6.48	$C_{15}H_{12}BrFN_4OS$	11.79	6.74
IIq	*a*	98	286	13.28	7.82	$C_{15}H_{11}BrClFN_4OS$	13.05	7.46
IIr	*a*	69	>300	14.87	10.89	$C_9H_6BrFN_4S$	14.66	10.63
IIs	*a*	84	253	16.89	9.17	$C_9H_8BrClN_4OS$	16.71	9.55
IIt	*a*	90	>300	16.45	9.35	$C_{10}H_{10}BrClN_4OS$	16.06	9.17
IIu	*a*	52	>300	13.70	7.85	$C_{15}H_{18}BrClN_4OS$	13.43	7.67
IIv	*a*	86	263	13.38	7.74	$C_{16}H_{14}BrClN_4OS$	13.18	7.53
IIw	*a*	87	267	13.78	7.95	$C_{15}H_{12}BrClN_4OS$	13.63	7.79
IIx	*a*	96	275	12.98	7.25	$C_{15}H_{11}BrCl_2N_4OS$	12.58	7.19
IIy	*a*	23	193	11.79	8.13	$C_{11}H_{11}BrClN_3O_2S$	11.52	7.89
IIz	*a*	55	>300	14.40	10.15	$C_9H_6BrClN_4S$	14.10	10.06
IIaa	*a*	94	>300	16.91	7.83	$C_{13}H_{17}BrClN_5OS$	16.75	7.66
IIab	*a*	99	270	14.92	8.48	$C_{13}H_{14}BrClN_4OS$	14.39	8.23
IIac	*a*	99	>300	20.20	9.50	$C_{10}H_{10}BrN_5O_2S$	20.35	9.30
IIad	*a*	76	305	19.76	9.15	$C_{11}H_{12}BrN_5O_2S$	19.55	8.94
IIae	*a*	81	246	16.80	7.69	$C_{16}H_{19}BrN_5O_2S$	16.43	7.51
IIaf	*a*	97	>300	16.16	7.52	$C_{17}H_{22}BrN_5O_2S$	16.20	7.37
IIag	*a*	78	251	16.84	7.81	$C_{16}H_{14}BrN_5O_2S$	16.67	7.62
IIah	*a*	92	288	15.32	7.22	$C_{16}H_{13}BrN_5O_2S$	15.42	7.05
IIai	*a*	56	>300	14.15	8.35	$C_{14}H_{16}BrN_5O_2S$	14.61	8.04
IIaj	*a*	39	>300	15.44	8.43	$C_{12}H_{13}BrN_4O_3S$	15.01	8.58
IIak	*a*	13	300	20.49	9.32	$C_9H_8BrN_5O_3S$	20.23	9.25
IIal	*a*	69	247	16.60	8.98	$C_{10}H_{11}BrN_4O_2S$	16.23	9.29
IIam	*a*	81	228	16.81	7.72	$C_9H_8BrClN_4OS$	16.72	8.01
IIan	*a*	79	225	16.19	9.17	$C_{10}H_{10}BrClN_4OS$	16.05	9.23
IIao	*a*	83	249	15.63	7.32	$C_{14}H_{16}BrCl_2N_5OS$	15.49	7.08
IIap	*a*	52	135	12.63	7.42	$C_{13}H_{13}BrCl_2N_4O_2S$	12.73	7.29
IIIa	*b*	65	165	11.21	6.73	$C_{17}H_{17}IN_4O_3S$	11.55	6.59
IIIb	*b*	67	218	12.01	6.98	$C_{16}H_{14}FIN_4O_2S$	11.84	6.77
IIIc	*b*	33	126	11.10	6.79	$C_{16}H_{14}ClIN_4O_2S$	11.49	6.54
IVa	*c*	69	270	19.63	11.32	$C_{10}H_{11}ClN_4O_2S$	19.58	11.19
IVb	*c*	55	220	14.52	8.58	$C_{14}H_{14}ClF_3N_4OS$	14.81	8.45
IVc	*c*	78	300	15.65	9.03	$C_{12}H_{13}ClN_4O_3S$	15.38	8.79
Va	*a*[b]	99	249	22.43	6.48	$C_{20}H_{18}Cl_2N_8O_2S$	22.22	6.35
Vb	*a*[b]	95	250	13.50	5.18	$C_{30}H_{32}Cl_2N_8O_2S$	13.43	5.00
Vc	*a*[b]	25	300	28.25	6.52	$C_{18}H_{14}N_{10}O_6S$	28.11	6.43

[a] Method *a*: oxidation with bromine in acetic acid at room temperature; method *b*: oxidation with iodine in acetic acid at room temperature; method *c*: oxidation with *N*-chlorosuccinimide in ethyl acetate at room temperature.

[b] Reflux, 10 min.

Table 2. IR and ^{1}H NMR spectra of 1,2,3-thiadiazoles **IIa–IIap**, **IIIa–IIIc**, and **IVa–IVc** and 1,2,4-thiadiazoles **Va–Vc**

Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum (DMSO-d_6), δ, ppm
IIa	1680 (C=O); 3220, 3360, 3450 (NH)	3.85 s (3H, OCH$_3$), 7.12 d and 7.81 d (4H, H$_{arom}$, J = 9.1 Hz), 7.98 s (1H, CONH), 8.35 s (1H, CONH), 9.75 s (2H, NH$_2^+$)
IIb	1660 (C=O); 2280, 3340, 3420 (NH)	2.88 d (3H, CH$_3$, J = 4.9 Hz), 3.86 s (3H, OCH$_3$), 7.13 d and 7.79 d (4H, H$_{arom}$, J = 9.2 Hz), 8.85 q (1H, CONH, J = 4.9 Hz), 9.66 s (1H, NH$_2^+$), 9.74 s (1H, NH$_2^+$)
IIc	1660 (C=O); 2820, 2920 (CH); 3100, 3240 (NH)	3.28 s (3H, OCH$_3$), 3.47–3.52 m (4H, CH$_2$CH$_2$), 3.85 s (3H, OCH$_3$), 7.18 d and 7.84 d (4H, H$_{arom}$, J = 9.1 Hz), 9.05 t (1H, CONH, J = 5.0 Hz), 9.64 s (1H, NH$_2^+$), 9.73 s (1H, NH$_2^+$)
IId	1660 (C=O); 2850, 2930 (CH); 3310, 3400 (NH)	1.30–1.89 m (10H, C$_6$H$_{11}$), 3.85 s (3H, OCH$_3$), 4.68–4.84 m (1H, CH), 7.13 d and 7.85 d (4H, H$_{arom}$, J = 9.1 Hz), 8.63 d (1H, CONH, J = 8.4 Hz), 9.56 s (1H, NH$_2^+$), 9.68 s (1H, NH$_2^+$)
IIe	1660 (C=O); 3250, 3320, 3360 (NH)	3.86 s (6H, OCH$_3$), 7.07 d (1H, H$_{arom}$, J = 9.2 Hz), 7.69 d.d (1H, H$_{arom}$, J = 2.4, 6.4 Hz), 7.14 d and 7.91 d (4H, H$_{arom}$, J = 9.2 Hz), 8.04 d (1H, H$_{arom}$, J = 2.4 Hz), 9.72 s (1H, NH$_2^+$), 9.77 s (1H, NH$_2^+$), 10.52 s (1H, CONH)
IIf	1660 (C=O); 3100, 3180, 3310, 3450 (NH)	3.87 s (3H, OCH$_3$), 7.11–7.18 m (2H, H$_{arom}$), 7.37 t (2H, H$_{arom}$, J = 8.2 Hz), 7.52 d (1H, H$_{arom}$, J = 8.8 Hz), 7.75 d and 7.89 d (4H, H$_{arom}$, J = 8.8 Hz), 9.85 s (1H, NH$_2^+$), 9.92 s (1H, NH$_2^+$), 10.48 s (1H, CONH)
IIg	1660 (C=O); 3200, 3310, 3450 (NH)	3.88 s (3H, OCH$_3$), 7.14 d and 7.79 d (4H, H$_{arom}$, J = 8.8 Hz), 7.36 d and 7.89 d (4H, H$_{arom}$, J = 8.8 Hz), 9.76 s (2H, NH$_2^+$), 10.62 s (1H, CONH)
IIh	1620 (C=O); 2920, 2980, 3060 (CH); 3340, 3420 (NH)	2.83 s (3H, CH$_3$), 3.33 s (3H, CH$_2$), 3.86 s (3H, OCH$_3$), 4.25 br.s (5H, CH$_2$), 7.09 d and 7.67 d (4H, H$_{arom}$, J = 9.1 Hz), 11.70 s (2H, NH$_2^+$)
IIi	1680 (C=O); 2840, 2940, 3000 (CH); 3310, 3450 (NH)	1.39 t (3H, CH$_3$, J = 7.3 Hz), 3.85 s (3H, OCH$_3$), 4.47 q (2H, CH$_2$, J = 7.3 Hz), 7.21 d and 7.75 d (4H, H$_{arom}$, J = 9.2 Hz), 9.75 s (2H, NH$_2^+$)
IIj	1660 (C=O); 3040, 3050 (CH); 3100, 3150, 3300 (NH)	7.49–7.54 m (1H, H$_{arom}$), 7.59–7.65 m (2H, H$_{arom}$), 7.88–7.92 m (2H, H$_{arom}$), 8.06 s (1H, CONH), 8.46 s (1H, CONH), 9.88 s (2H, NH$_2^+$)
IIk	1680 (C=O); 3010 (CH); 3100, 3160, 3300 (NH)	1.38 t (3H, CH$_3$, J = 6.9 Hz), 4.48 q (2H, CH$_2$, J = 6.9 Hz), 7.54–7.78 m (3H, H$_{arom}$), 7.79–7.80 m (2H, H$_{arom}$), 9.90 s (2H, NH$_2^+$)
IIl	1680 (C=O); 3180, 3280, 3400, 3480 (NH)	7.37 t (2H, H$_{arom}$, J = 8.2 Hz), 7.92–7.98 m (3H, H$_{arom}$, CONH), 8.30 s (1H, CONH), 10.00 s (2H, NH$_2^+$)
IIm	1660(C=O); 3060 (CH); 3140, 3160, 3200, 3300, 3450 (NH)	2.89 d (3H, CH$_3$, J = 4.9 Hz), 7.36–7.43 m (2H, H$_{arom}$), 7.89–7.97 m (2H, H$_{arom}$), 8.88 q (1H, CONH, J = 4.9 Hz), 9.77 s (1H, NH$_2^+$), 9.87 s (1H, NH$_2^+$)
IIn	1660 (C=O); 2850, 2920 (CH); 3200, 3240, 3340, 3360 (NH)	1.22–1.89 m (10H, C$_6$H$_{11}$), 3.78–3.89 m (1H, CH), 7.33–7.43 m (2H, H$_{arom}$), 7.94–8.01 m (2H, H$_{arom}$), 8.57 d (1H, CONH, J = 8.2 Hz), 9.76 s (1H, NH$_2^+$), 9.86 s (1H, NH$_2^+$)
IIo	1650 (C=O); 2920, 3060 (CH); 3280, 3450 (NH)	4.54 d (2H, CH$_2$, J = 6.4 Hz), 7.19–7.44 m (7H, H$_{arom}$), 7.90–7.97 m (2H, H$_{arom}$), 9.46 t (1H, CONH, J = 6.1 Hz), 10.01 s (2H, NH$_2^+$)
IIp	1680 (C=O); 2930, 3050 (CH); 3140, 3200, 3300, 3450 (NH)	7.62–7.76 m (4H, H$_{arom}$), 8.04–8.08 m (5H, H$_{arom}$), 9.85 s (1H, NH$_2^+$), 9.92 s (1H, NH$_2^+$), 10.81 s (1H, CONH)
IIq	1680 (C=O); 3250, 3350, 3450 (NH)	7.36–7.47 m (2H, H$_{arom}$), 7.37 d and 7.79 d (4H, H$_{arom}$, J = 8.8 Hz), 8.00–8.07 m (2H, H$_{arom}$), 9.93 br.s (2H, NH$_2^+$), 10.64 s (1H, CONH)
IIr	1600 (C=O); 2250 (CH); 3060, 3200, 3250 (NH)	7.42–7.49 m (2H, H$_{arom}$), 7.90–7.96 m (2H, H$_{arom}$), 9.89 s (2H, NH$_2^+$)

Table 2. Contd.

| Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum (DMSO-d_6), δ, ppm
IIs	1680 (C=O); 3080 (CH); 3180, 3250, 3380, 3480 (NH)	7.59 d and 7.96 d (4H, H$_{arom}$, J = 9 Hz), 8.02 s (1H, CONH), 8.41 s (1H, CONH), 10.04 s (2H, NH$_2^+$)
IIt	1670 (C=O); 2930, 3050 (CH); 3240, 3310 (NH)	2.88 d (3H, CH$_3$, J = 4.9 Hz), 7.59 d and 7.96 d (4H, H$_{arom}$, J = 9 Hz), 8.85 q (1H, CONH, J = 4.9 Hz), 10.01 s (2H, NH$_2^+$)
IIu	–	1.21–1.91 m (10H, C$_6$H$_{11}$), 3.85 m (1H, CH), 7.59 d and 7.95 d (4H, H$_{arom}$, J = 8.9 Hz), 8.59 d (1H, CONH, J = 7.9 Hz), 10.07 s (2H, NH$_2^+$)
IIv	1650 (C=O); 2910, 3050 (CH); 3150, 3260 (NH)	4.54 d (2H, CH$_2$, J = 6 Hz), 7.22–7.39 m (5H, H$_{arom}$), 7.58 d and 7.91 d (4H, H$_{arom}$, J = 9 Hz), 9.50 t (1H, CONH, J = 6 Hz), 10.07 s (2H, NH$_2^+$)
IIw	1660 (C=O); 3090 (CH); 3280, 3350 (NH)	7.16 t (1H, H$_{arom}$, J = 7.4 Hz), 7.38 t (2H, H$_{arom}$, J = 8.0 Hz), 7.75 d (2H, H$_{arom}$, J = 7.3 Hz), 7.63 d and 8.02 d (4H, H$_{arom}$, J = 9.2 Hz), 10.12 br.s (2H, NH$_2^+$), 10.55 s (1H, CONH)
IIx	1670 (C=O); 3040, 3090 (CH); 3210, 3340, 3420 (NH)	7.49 d and 7.80 d (4H, H$_{arom}$, J = 8.8 Hz), 7.75 d and 8.04 d (4H, H$_{arom}$, J = 9.0 Hz), 9.88 s (1H, NH$_2^+$), 9.96 s (1H, NH$_2^+$), 10.84 s (1H, CONH)
IIy	1750 (C=O); 2980, 3010 (CH); 3120, 3270, 3450 (NH)	1.43 t (3H, CH$_3$, J = 7.0 Hz), 4.49 q (2H, CH$_2$, J = 7.0 Hz), 7.61 d and 7.82 d (4H, H$_{arom}$, J = 8.9 Hz), 9.99 s (2H, NH$_2^+$)
IIz	–	7.65 d and 7.90 d (4H, H$_{arom}$, J = 8.9 Hz), 10.01 s (2H, NH$_2^+$)
IIaa	1600 (C=O); 2905, 2970, 3040 (CH); 3150, 3280, 3430 (NH)	2.87 s (3H, CH$_3$), 3.17–3.39 m (6H, CH$_2$), 4.58 br.s (2H, CH$_2$), 7.69 d and 7.79 d (4H, H$_{arom}$, J = 9.0 Hz), 10.04 s (2H, NH$_2^+$)
IIab	1600 (C=O); 2870, 2980, 3080 (CH); 3230, 3450 (NH)	1.87–2.07 m (4H, CH$_2$), 3.62 t (2H, CH$_2$, J = 6.5 Hz), 3.93 t (2H, CH$_2$, J = 6.5 Hz), 7.59 d and 7.76 d (4H, H$_{arom}$, J = 8.9 Hz), 10.14 s (1H, NH$_2^+$), 10.19 s (1H, NH$_2^+$)
IIac	1680 (C=O); 3160, 3220, 3260, 3370 (NH)	8.04 s (1H, CONH), 7.97 d and 8.09 d (4H, H$_{arom}$, J = 8.5 Hz), 8.48 s (1H, CONH), 9.88 s (2H, CONH$_2$), 10.08 s (1H, NH$_2^+$), 10.13 s (1H, NH$_2^+$)
IIad	1660 (C=O); 3110, 3180, 3240, 3340, 3405 (NH)	2.88 d (3H, CH$_3$, J = 4,6 Hz), 7.39 s (1H, CONH), 7.98–8.08 m (5H, H$_{arom}$, CONH), 8.97 t (1H, CONH, J = 4.6 Hz), 10.05 s (2H, NH$_2^+$)
IIae	1680 (C=O); 2850, 2915, 3060 (CH); 3250, 3300, 3400 (NH)	1.20–1.90 m (10H, C$_6$H$_{11}$), 3.84 m (1H, CH), 7.38 s (1H, CONH), 7.98–8.09 m (5H, H$_{arom}$, CONH), 8.67 d (1H, CONH, J = 7.0 Hz), 10.09 s (2H, NH$_2^+$)
IIaf	1670 (C=O); 3050 (CH); 3210, 3400 (NH)	4.55 d (2H, CH$_2$, J = 6.0 Hz), 7.21–7.39 m (6H, H$_{arom}$, CONH), 7.97–8.09 m (5H, H$_{arom}$, CONH), 9.56 t (1H, CONH, J = 6.0 Hz), 10.09 s (2H, NH$_2^+$)
IIag	1650 (C=O); 3050, 3090 (CH); 3180, 3210, 3400 (NH)	7.16 t (1H, H$_{arom}$, J = 7.3 Hz), 7.38 m (3H, H$_{arom}$, CONH), 7.79 d (2H, H$_{arom}$, J = 7.3 Hz), 8.13 m (5H, H$_{arom}$, CONH$_2$), 10.13 s (1H, NH$_2^+$), 10.22 s (1H, NH$_2^+$), 10.57 s (1H, CONH)
IIah	–	7.29–8.25 m (10H, H$_{arom}$, CONH$_2$), 10.13 s (1H, NH$_2^+$), 10.25 s (1H, NH$_2^+$), 10.73 s (1H, CONH)
IIai	–	1.86–2.03 m (4H, CH$_2$), 3.65 t (2H, CH$_2$, J = 6.8 Hz), 3.92 t (2H, CH$_2$, J = 6.5 Hz), 7.43 s (1H, CONH), 7.8 d and 8.01 d (4H, H$_{arom}$, J = 8.8 Hz), 8.01 s (1H, CONH), 10.24 s (2H, NH$_2^+$)
IIaj	1700 (C=O); 2980, 3030 (CH); 3160, 3260, 3400 (NH)	1.35 t (3H, CH$_3$, J = 7.1 Hz), 4.35 q (2H, CH$_2$, J = 7.1 Hz), 8.04 d and 8.13 d (5H, H$_{arom}$, CONH, J = 8.9 Hz), 8.56 s (1H, CONH), 10.07 s (1H, NH$_2^+$), 10.47 s (1H, NH$_2^+$)

Table 2. Contd.

Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum (DMSO-d_6), δ, ppm
IIak	1680 (C=O); 3000, 3050 (CH); 3100, 3160 3280, 3340, 3450 (NH)	8.09 s (1H, CONH), 8.21 d and 8.39 d (4H, H$_{arom}$, J = 9.1 Hz), 8.54 s (1H, CONH), 10.27 s (1H, NH$_2^+$), 10.32 s (1H, NH$_2^+$)
IIal	–	2.89 d (3H, CH$_3$, J = 4.6 Hz), 4.08 s (3H, OCH$_3$), 7.15 t (1H, H$_{arom}$, J = 7.3 Hz), 7.44 d (1H, H$_{arom}$, J = 7.3 Hz), 7.47 t (1H, H$_{arom}$, J = 7.3 Hz), 8.00 d (1H, H$_{arom}$, J = 7.3 Hz), 8.86 q (1H, CONH, J = 4.6 Hz), 9.77 s (1H, NH$_2^+$), 9.87 s (1H, NH$_2^+$)
IIam	–	7.54–7.73 m (2H, H$_{arom}$), 7.84–7.88 m (2H, H$_{arom}$), 7.98 s (1H, CONH), 8.13 s (1H, CONH), 10.00 s (1H, NH$_2^+$), 10.06 s (1H, NH$_2^+$)
IIan	–	2.86 d (3H, CH$_3$, J = 4.8 Hz), 7.55–7.77 m (3H, H$_{arom}$), 7.85 m (1H, H$_{arom}$), 8.76 q (1H, CONH, J = 4.8 Hz), 10.04 s (1H, NH$_2^+$), 10.08 s (1H, NH$_2^+$)
IIao	–	1.85–1.99 m (4H, CH$_2$), 2.57 s (3H, CH$_3$), 3.43–3.78 m (4H, CH$_2$), 7.59–7.74 m (3H, H$_{arom}$), 10.27 s (1H, NH$_2^+$), 10.49 s (1H, NH$_2^+$)
IIap	–	3.72 m (8H, CH$_2$), 7.79 s (3H, H$_{arom}$), 10.19 s (2H, NH$_2^+$)
IIIa	–	3.75 s (6H, OCH$_3$), 6.89 d and 6.94 d (4H, H$_{arom}$, J = 9.0 Hz), 7.52 d and 7.54 d (4H, H$_{arom}$, J = 9.0 Hz), 9.19 s (1H, CONH), 9.45 s (2H, NH$_2^+$)
IIIb	–	3.77 s (3H, OCH$_3$), 7.54–7.58 m (2H, H$_{arom}$), 7.01 d and 7.66 d (4H, H$_{arom}$, J = 9.1 Hz), 8.07–8.11 m (2H, H$_{arom}$), 9.69 br.s (2H, NH$_2^+$), 10.68 s (1H, CONH)
IIIc	1660 (C=O); 2910, 3080 (CH); 3260, 3440 (NH)	3.78 s (3H, OCH$_3$), 7.00 d and 7.65 d (4H, H$_{arom}$, J = 4.8 Hz), 7.75 d and 8.07 d (4H, H$_{arom}$, J = 4.8 Hz), 9.79 br.s (2H, NH$_2^+$), 10.69 s (1H, CONH)
IVa	–	4.09 s (3H, OCH$_3$), 7.13–7.52 m (2H, H$_{arom}$), 8.00–8.09 m (3H, H$_{arom}$, CONH), 8.38 s (1H, CONH), 9.54 s (1H, NH$_2^+$), 9.62 s (1H, NH$_2^+$)
IVb	–	2.51 m (4H, CH$_2$), 3.64 t (2H, CH$_2$, J = 6.7 Hz), 3.95 t (2H, CH$_2$, J = 6.7 Hz), 7.76–7.84 m (2H, H$_{arom}$), 7.95–8.05 m (2H, H$_{arom}$), 10.3 s (1H, NH$_2^+$), 10.66 s (1H, NH$_2^+$)
IVc	1700 (C=O); 2900 2980, 3050 (CH); 3160, 3210 3350 (NH)	1.35 t (3H, CH$_3$, J = 7.1 Hz), 4.36 q (2H, CH$_2$, J = 7.1 Hz), 8.03 d (2H, H$_{arom}$, J = 8.9 Hz), 8.11–8.15 m (3H, H$_{arom}$, CONH), 8.56 s (1H, CONH), 10.07 s (1H, NH$_2^+$), 10.47 s (1H, NH$_2^+$)
Va	1660 (C=O); 2930 3040, 3080 (CH); 3140, 3180 3300, 3380, 3420 (NH)	2.99 d (6H, 2CH$_3$, J = 4.6 Hz), 7.62 d and 7.91 d (8H, H$_{arom}$, J = 8.9 Hz), 8.91 q (2H, 2CONH, J = 4.6 Hz), 9.82 s (1H, NH), 9.93 s (1H, NH)
Vb	1660 (C=O); 2920, 3020, 3080 (CH); 3120, 3260, 3340, 3440 (NH)	1.16–1.89 m (20H, 2C$_6$H$_{11}$), 3.82–3.85 m (2H, 2CH), 7.63 d and 7.96 d (8H, H$_{arom}$, J = 9.2 Hz), 8.63 d (2H, 2CONH, J = 8.2 Hz), 9.85 s (1H, NH), 9.93 s (1H, NH)
Vc	1680 (C=O); 2860, 2890, 2920, 3020 (CH); 3120, 3220, 3270, 3360, 3420 (NH)	8.19–8.27 m (2H, CONH), 8.15 d and 8.42 d (8H, H$_{arom}$, J = 9.1 Hz), 8.59 s (2H, CONH), 10.20 s (1H, NH), 10.59 s (1H, NH)

ion [R^{1}C$_6$H$_4$N$_2$]$^+$. The peak of fragment ion F$_5$ is especially strong, and this ion is often the most abundant (Scheme 2). In keeping with the data in Table 4, introduction of electron-acceptor substituents into the aromatic ring of 2-aryl-5-imino-2,5-dihydro-1,2,3-thiadiazoles **II** leads to reduction in the relative intensity of the molecular ion peak, indicating that its stability decreases.

The oxidation of arylhydrazonothioacetamides **Iu** and **Iv** in boiling acetic acid (118°C) gave 1,2,4-thiadiazoles **Va** and **Vb** in 95 and 99% yield, respectively. An analogous transformation was observed previously [28, 29] when 2-phenyl-1,2,3-thiadiazol-5(2H)-imines were heated in boiling pyridine over a period of 30–40 min. Scheme 3 illustrates a probable mechanism of the above transformation, which includes formation of

Scheme 2.
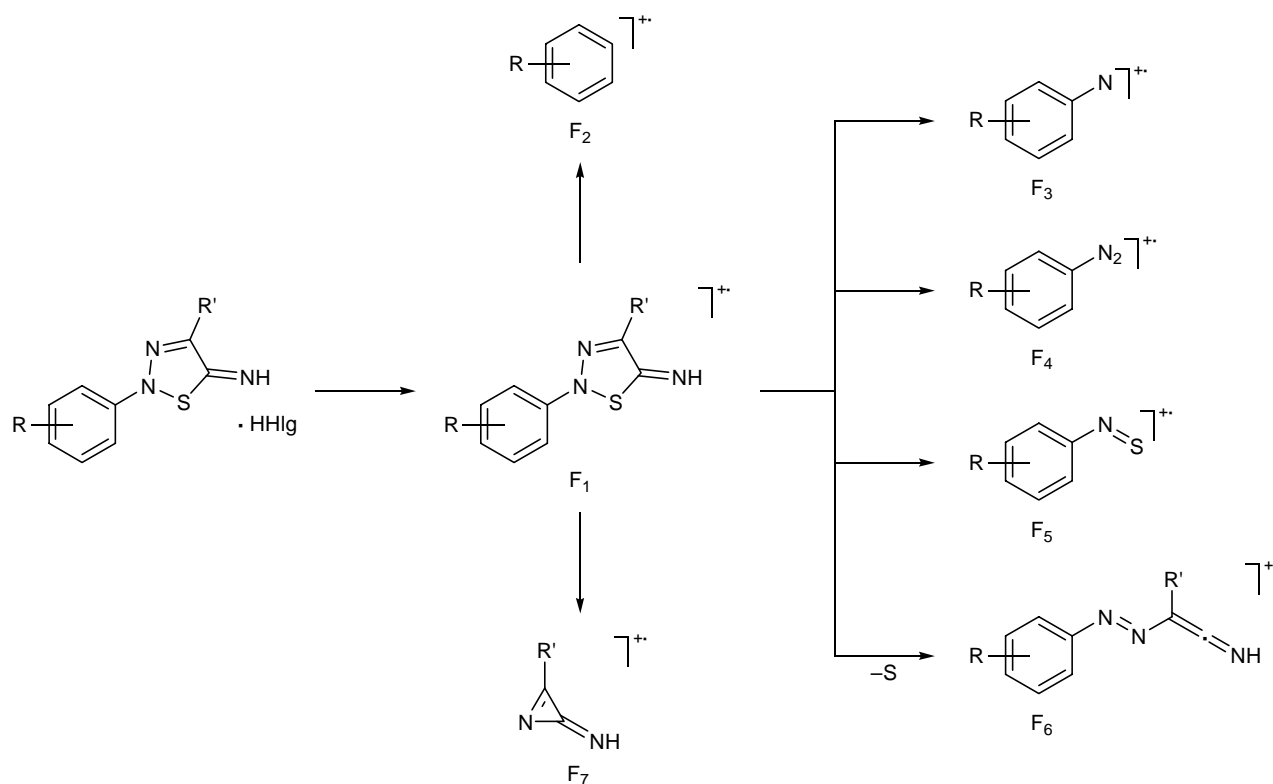
intermediate **C** via elimination of sulfur from compound **II**. 1,5-H shift in **C** yields (arylhydrazono)acetonitrile **D** which then reacts with the second molecule of initial thiadiazole as a latent 1,3-dipole, leading to final 1,2,4-thiadiazole **V**. This scheme seems to be feasible taking into account the mass spectra of 1,2,3-thiadi-azoles **II** (Table 4): the formation of fairly abundant fragment ion F_6, whose molecular weight coincides with that of azoketene imine **C**, was observed for all the compounds **II** prepared. On the other hand, 1,2,4-thiadiazole system could also be formed via oxidative condensation according to the mechanism

Scheme 3.
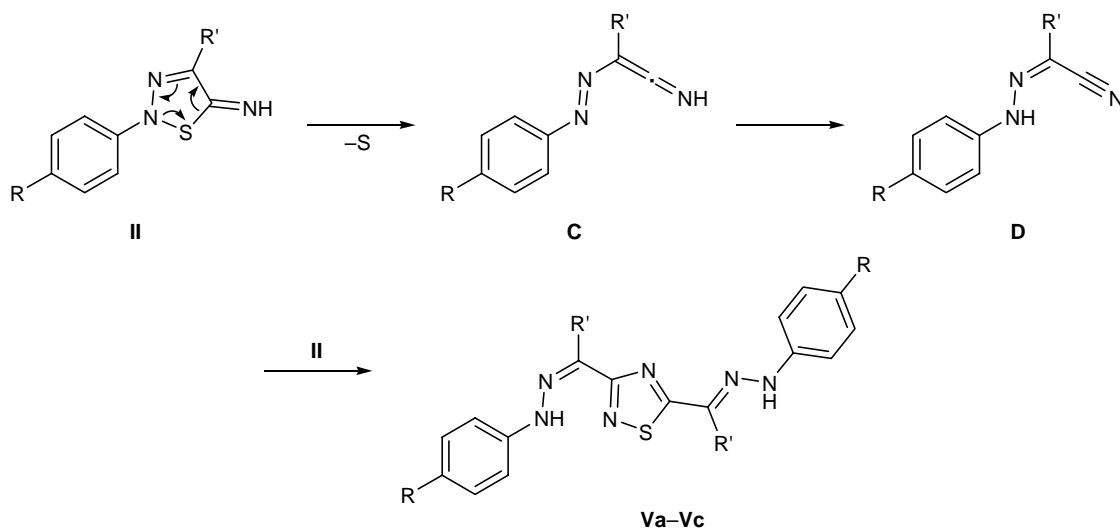
V, R = Cl, R' = CONHMe (**a**); CONHC$_6$H$_{11}$ (**b**); R = NO$_2$, R' = CONH$_2$ (**c**).

Table 3. ^{13}C NMR spectra of 1,2,3-thiadiazoles **IIa** and **IIy** in DMSO-d_6[a]
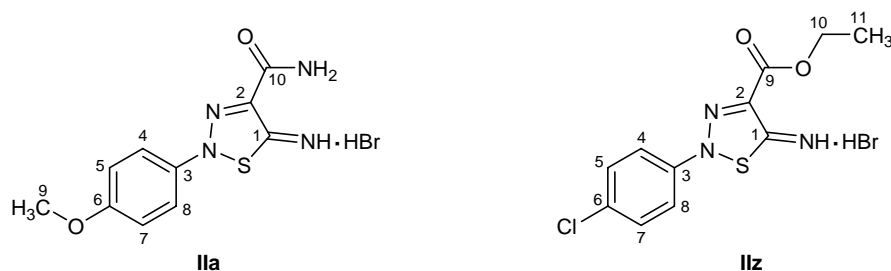
| Compound no.	Chemical shifts δ_C, ppm
IIa	55.8 q (C^9, ^1J = 144.3 Hz), 115.2 d.d (C^5, C^7, ^1J = 163.3, ^2J = 4.8 Hz,), 121.9 d.d (C^4, C^8, ^1J = 164.1, ^2J = 5.4 Hz), 131.6 d (C^2, ^2J = 7.8 Hz), 132.6 t.t (C^3, ^2J = 9.5, ^3J = 2.8 Hz), 159.9 m (C^6), 162.2 s (C^{10}), 169.3 s (C^1)
IIy	14.1 s (C^{11}, ^1J = 126.5, ^2J = 2.7 Hz), 62.2 t.q (C^{10}, ^1J = 148.7, ^2J = 4.4 Hz), 122.2 d.d (C^5, C^7, ^1J = 172.7, ^2J = 5.8 Hz), 130.3 d.d.d (C^4, C^8, ^1J = 170.1, ^2J = 5.5, ^3J = 0.8 Hz), 131.3 s (C^2), 134.1 t.t (C^3, ^2J = 10.4, ^3J = 3.2 Hz), 138.0 t.t (C^6, ^2J = 9.5, ^3J = 2.3 Hz), 160.2 t (C^9, ^2J = 3.6 Hz), 170.3 s (C^1)

[a] The signals were assigned, and the coupling constants were determined, using the Gate and BB techniques.

proposed in [2, 6] for alkylthioamides, i.e., by reaction of adduct **B** (Scheme 1) with the second molecule of initial arylhydrazonothioacetamide **I**, which is accompanied by elimination of hydrogen sulfide (Scheme 4). Each of the above mechanisms may be operative under the given conditions, and their probability is determined by the stability of 1,2,3-thiadiazole **II** (Scheme 3) and relative reactivities of the hydrazone and thioamide nitrogen atoms in initial compound **I** (Scheme 4). As a result, either intramolecular cyclization or intermolecular reaction occurs. An essential difference between these mechanisms is elimination of either sulfur (Scheme 3) or hydrogen sulfide (Scheme 4). It should be noted that the oxidation products were often contaminated with sulfur to greater or lesser extent. However, in no cases evolution of hydrogen sulfide was observed. This fact may be regarded as an indirect evidence for the greater

probability for formation of 1,2,4-thiadiazoles via initial intramolecular cyclization of thioacetamides **I** into 1,2,3-thiadiazoles **II** according to Scheme 1.

The oxidative condensation of hydrazones **Ia–Iak** by the action of bromine in acetic acid is characterized by good yields. The yield of the final product tends to decrease with rise in the electron-acceptor power of the substituent in the aromatic ring. In the oxidation of arylhydrazonothioacetamides **Ial** and **Iam**, the yields were 39 and 13%, respectively, and a large amount of the initial hydazone was present in the reaction mixture. Presumably, electron-acceptor substituent in the aromatic ring, despite its remoteness from the reaction center, strongly reduces the nucleophilicity of the sulfur atom, thus hampering formation of adduct **B** (Scheme 1). The use of a harder reagent, *N*-chlorosuccinimide (NCS) allowed us to raise the yields of the oxidation products from compounds **Ial** and **Ian**.

Scheme 4.

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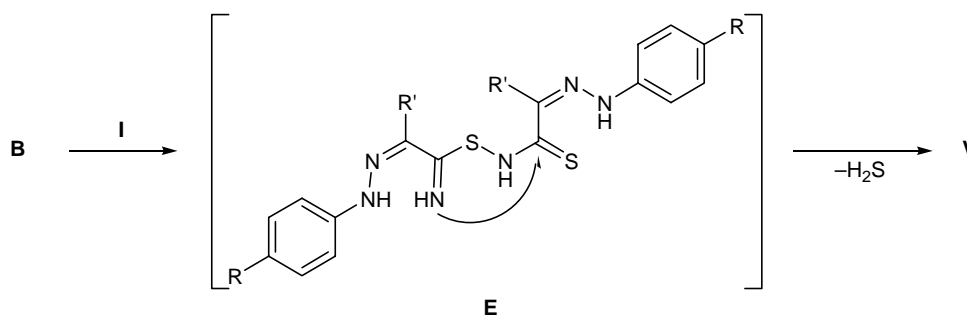
Table 4. Mass spectra of 1,2,3-thiadiazole derivatives **IIa–IIj**, **Ill–IIak** and **IIIa–IIIc**, *m/z* (I_{rel}, %)

Comp. no.	F_1	F_2	F_3	F_4	F_5	F_6	F_7
IIa	250 (79.1)	107 (13.9)	121 (31.5)	135 (2.7)	153 (100)	218 (14.3)	97 (0)
IIb	264 (49.6)	107 (16.3)	121 (39.5)	135 (3.5)	153 (100)	232 (30.8)	111 (0)
IIc	308 (14.9)	107 (44.0)	121 (61.7)	135 (14.7)	153 (49.3)	276 (78.4)	155 (9.1)
IId	332 (36.4)	107 (19.3)	121 (37.1)	135 (4.3)	153 (13.5)	401 (12.4)	267 (0)
IIe	435 (8.2)	107 (24.6)	121 (57.1)	135 (5.3)	153 (45.8)	294 (42.0)	173 (6.7)
IIf	326 (45.8)	107 (24.6)	121 (57.1)	135 (5.3)	153 (45.8)	294 (42.0)	173 (6.7)
IIg	360 (20.5)	107 (25.2)	121 (54.9)	135 (6.2)	153 (31.8)	328 (33.4)	207.5 (0)
IIh	333 (3.6)	107 (17.5)	121 (7.2)	135 (6.4)	153 (4.8)	301 (21.1)	155 (9.1)
IIi	279 (93.7)	107 (19.5)	121 (49.6)	135 (4.2)	153 (100)	247 (15.8)	126 (2.1)
IIj	220 (41.7)	77 (77.6)	91 (24.0)	105 (8.5)	123 (100)	188 (36.8)	97 (2.6)
Ill	252 (27.6)	95 (31.5)	109 (32.8)	123 (3.5)	141 (100)	206 (14.6)	97 (1.2)
IIm	238 (39.9)	95 (24.5)	109 (30.8)	123 (4.3)	141 (100)	220 (9.3)	111 (0)
IIn	320 (37.6)	95 (32.7)	109 (38.2)	123 (14.0)	141 (100)	288 (25.9)	179 (8.8)
IIo	328 (10.6)	95 (15.7)	109 (18.1)	123 (4.4)	141 (39.2)	296 (8.3)	187 (1.2)
IIp	314 (28.8)	95 (74.1)	109 (100)	123 (15.2)	141 (83.0)	282 (10.2)	173 (70.7)
IIq	348 (51.6)	95 (49.5)	109 (66.7)	123 (9.5)	141 (53.2)	316 (34.7)	207.5 (0)
IIr	220 (9.8)	95 (30.1)	109 (11.5)	123 (3.4)	141 (3.4)	188 (6.1)	79 (0)
IIs	254.5 (40.7)	111.5 (31.2)	125.5 (29.7)	139.5 (3.2)	157.5 (100)	222.5 (21.1)	97 (0)
IIt	268.5 (27.8)	111.5 (26.1)	125.5 (27.1)	139.5 (5.8)	157.5 (100)	236.5 (18.8)	111 (0)
IIu	336.5 (7.6)	111.5 (35.0)	125.5 (28.8)	139.5 (12.4)	157.5 (100)	304.5 (46.1)	179 (18.5)
IIv	344.5 (4.2)	111.5 (8.7)	125.5 (7.0)	139.5 (1.6)	157.5 (14.9)	312.5 (9.8)	187 (1.2)
IIw	330.5 (20.4)	111.5 (21.1)	125.5 (16.9)	139.5 (3.6)	157.5 (19.7)	298.5 (27.4)	173 (1.5)
IIx	364.5 (35.2)	111.5 (36.5)	125.5 (38.9)	139.5 (5.4)	157.5 (33.1)	332.5 (23.0)	207.5 (2.8)
IIy	283.5 (52.7)	111.5 (29.7)	125.5 (41.0)	139.5 (4.9)	157.5 (100)	251.5 (14.1)	126 (1.8)
IIz	236.5 (9.5)	111.5 (48.7)	125.5 (5.7)	139.5 (2.4)	157.5 (2.3)	204.5 (1.0)	79 (8.6)
IIaa	337.5 (20.4)	111.5 (17.7)	125.5 (4.3)	139.5 (6.4)	157.5 (2.5)	305.5 (28.0)	178 (2.5)
IIab	308.5 (2.3)	111.5 (15.9)	125.5 (6.5)	139.5 (4.7)	157.5 (16.9)	276.5 (8.2)	151 (2.7)
IIac	263 (3.7)	120 (25.5)	134 (18.7)	148 (3.0)	166 (2.2)	231 (81.8)	97 (0)
IIad	277 (13.8)	120 (19.0)	134 (8.7)	148 (2.2)	166 (51.2)	245 (30.6)	111 (0)
IIae	345 (5.3)	120 (29.3)	134 (13.3)	148 (5.1)	166 (20.0)	313 (52.4)	179 (2.8)
IIaf	353 (1.7)	120 (8.8)	134 (2.5)	148 (0)	166 (5.7)	321 (81.8)	97 (0)
IIag	339 (4.1)	120 (19.8)	134 (5.1)	148 (1.6)	166 (7.7)	307 (21.9)	173 (0)
IIah	373 (2.1)	120 (15.5)	134 (2.6)	148 (0)	166 (3.7)	341 (7.4)	173 (0)
IIai	317 (0)	120 (21.9)	134 (2.8)	148 (2.0)	166 (6.4)	285 (13.0)	151 (2.4)
IIaj	292 (48.8)	149 (39.8)	163 (35.6)	177 (2.4)	195 (85.9)	260 (100.0)	143 (0)
IIak	265 (10.4)	122 (22.1)	136 (10.0)	150 (5.6)	168 (18.5)	233 (48.5)	221 (0)
IIIa	342 (41.7)	107 (24.3)	121 (44.5)	135 (5.3)	153 (4.8)	301 (21.1)	180 (0)
IIIb	346 (23.9)	95 (22.1)	109 (7.5)	123 (100)	141 (8.6)	314 (2.6)	203 (0)
IIIc	362.5 (1.2)	111.5 (18.8)	125.5 (3.9)	139.5 (3.0)	157.5 (100)	328 (19.9)	203 (0)

However, the oxidation of 4-nitrophenylhydrazono-thioacetamide **Iam** with NCS afforded 1,2,4-thiadi-azole **Vc** as the only cyclic product.

As follows from the results of oxidation of aryl-hydrazonothioacetamides **Iao**–**Ias** having one or two substituents in the *ortho* positions, steric factor does not affect the intramolecular cyclization to an appreciable extent. The oxidative cyclization of hydrazones containing a 4-methoxyphenylcarbamoyl group by the action of bromine was accompanied by bromination of the aromatic ring. In order to avoid this side process, we performed oxidation of hydrazones **Ie**, **Ip**, and **Iy** with iodine under analogous conditions. In this case, no halogenation of the aromatic ring occurred, and the corresponding 2-aryl-5-imino-*N*-(4-methoxyphenyl)-2,5-dihydro-1,2,3-thiadiazole-4-carboxamides **IIIa**–**IIIc** were isolated in high yields.

Thus the results of the present study allowed us to determine the applicability limits for the synthesis of 1,2,3-thiadiazoles by oxidation of arylhydrazonothio-acetamides and showed that electron-acceptor substituents in the aromatic ring destabilize the thiadiazole ring, favoring transformation into 1,2,4-thiadiazole derivatives.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrometer (400 and 100.00 MHz, respectively) using DMSO-d_6 as solvent and TMS as internal reference. The mass spectra were obtained on a Varian MATT-311A instrument; accelerating voltage 3 kV; energy of ionizing electrons 70 eV. The melting points were not corrected. The progress of reactions and the purity of products were monitored by TLC on Sorbfil UV-254 plates (ethanol–chloroform, 1:2).

Oxidation of arylhydrazones I with bromine (*general procedure, method a*)**.** A solution of 8 mmol of bromine in 5 ml of acetic acid was added with stirring to a solution of 2 mmol of 2-phenylhydrazono-thioacetamide **I** in 100 ml of acetic acid, heated to 40°C. The mixture was stirred for 5 h at room temperature, and the precipitate was filtered off and recrystallized from ethanol.

Oxidation of arylhydrazones I with iodine (*general procedure, method b*)**.** The procedure was the same as in *a*, but a solution of 8 mmol of iodine in 5 ml of acetic acid was added.

Oxidation of arylhydrazones I with *N*-chloro-succinimide (*general procedure, method c*)**.** *N*-Chloro-succinimide, 6 mmol, was added under stirring to a solution of 2 mmol of 2-phenylhydrazonothioacet-amide **I** in 100 ml of ethyl acetate. The mixture was stirred for 5 h at room temperature, and the precipitate was filtered off and recrystallized from ethanol.

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