CONDENSATION OF 5-AMINOISOTHIAZOLES WITH *N*-METHYL-IMIDOYL CHLORIDE. RING-TRANSFORMATION WITH PARTICIPATION OF 10-S-3 TYPE SULFURANE

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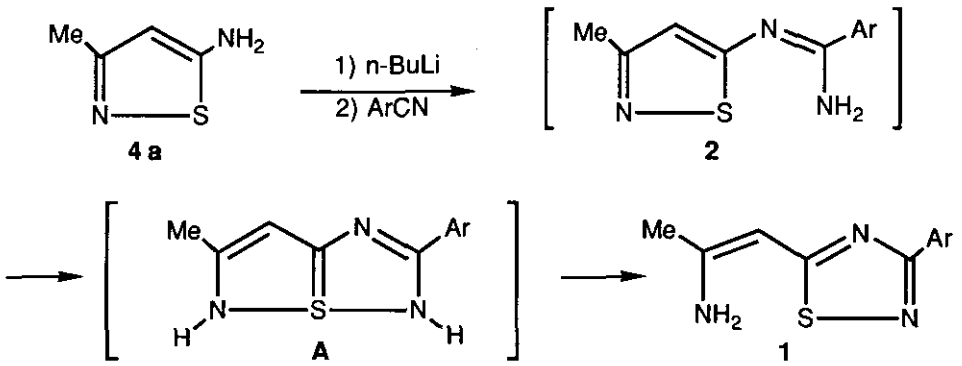
Abstract- In the presence of 1,4-diazabicyclo[2.2.2]octane, 5-amino-3-methylisothiazole (**4a**) in acetonitrile condensed with *N*-methyl-*p*-chlorobenzimidoyl chloride (**5a**) to afford two kinds of compounds along with several minor products. One of the two was 1 : 1 condensed product (**6a**) and the other was 2 : 1 condensed product (**7a**). The latter compound was obtained in higher yield when an excess **4a** was treated with **5a**. On the other hand, in the absence of the additional base, 2 : 3 condensed compound (**8a**) was isolated as a major product besides **6a** and **7a**. **8a** was obtained by treatment of **7a** with 2 equiv. of imidoyl chloride in 21% yield. Reaction of 5-amino-3-phenylisothiazole (**4b**) with imidoyl chloride (**5a,b**) furnished the analogous products. On the other hand, condensation of 5-amino-3-phenylisoxazole (**4c**) with **5a** furnished the oxygen analogue (**6d**) corresponding to **6b** as a sole isolated product. The formation of **7** is explained by ring-transformation from isothiazole into thiadiazole *via* hypervalent 10-S-3 type sulfurane (**B**).

According to a variety of investigations of heterocycles containing sulfur atom, it has been suggested that 10-S-3 type sulfurane is an important intermediate in several reactions.[1,2] In a previous paper, we reported that a ring transformed thiadiazole derivative (**1**) instead of the expected isothiazole derivative (**2**) was isolated as a sole product in the reaction of 5-amino-3-methylisothiazole with arylnitrile.[3a] The fact was explained by invoking 10-S-3 sulfurane (**A**) as a intermediate. In connection with this finding, we describe in this paper results of the reaction of 5-aminoisoazole derivatives (**4a-c**) with imidoyl chloride (**5a,b**) under several conditions.



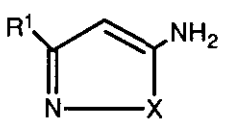
Scheme 1

RESULTS AND DISCUSSION

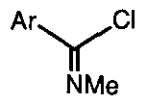
Condensation of 5-aminoisothiazole (**4a,b**) with each imidoyl chloride (**5a,b**) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) or triethylamine (Et_3N) in acetonitrile gave two kinds of products respectively; a more polar compound (**6a-c**) and a less polar one (**7a-c**). In the absence of the base, the reaction afforded a polar yellow substance (**8a-c**) besides **6a-c** and **7a-c**. The results and spectral data are summarized in Tables 1, 2, and 3. Judging from the mass spectra and/or the elemental analyses, it was concluded that **6** is a 1 : 1 condensed product with elimination of HCl, **7** is a 2 : 1 condenced product with elimination of methylamine

hydrochloride, and **8** is a 2 : 3 condenced product with elimination of methylamine and 3 x HCl.

On the other hand, condensation of 3 equiv. of 5-amino-3-phenylisoxazole (**4c**) with imidoyl chloride (**5a**) furnished the corresponding oxygen analogue (**6d**) as a sole isolable product in 63% yield.

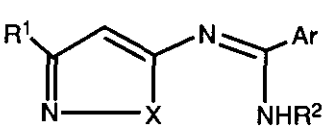


	R^1	X
4a	Me	S
4b	C_6H_5	S
4c	C_6H_5	O

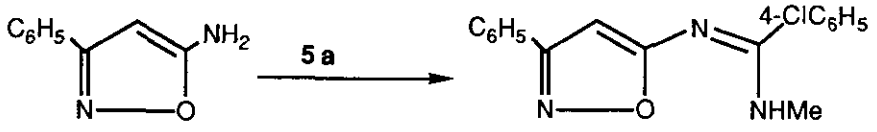


5a : Ar=4-ClC_6H_4

5b : Ar=C_6H_5



	R^1	Ar	R^2	X
6a	Me	4-ClC_6H_4	Me	S
6b	C_6H_5	C_6H_5	Me	S
6c	C_6H_5	4-ClC_6H_4	Me	S
6d	C_6H_5	4-ClC_6H_4	Me	O
6e	Me	4-ClC_6H_4	t-$BuMe_2Si$	S



4c **6d**

Scheme 2

Table 1. Reaction Conditions and Product Distribution in Condensation of 5-Aminoisoazoles (**4a-c**) with Imidoyl Chloride (**5a,b**) in Acetonitrile

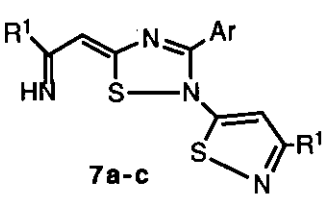
starting materials		[4]/[5]	base	products (yield)			recovered
							4a (%)
4	**5**			**6** (%)	**7** (%)	**8** (%)	
4a	**5a**	1.0/1.1	DABCO[a]	**6a** 11	**7a** 29	-	29
4a	**5a**	1.0/1.1	Et_3N	5	15	-	19
4a	**5a**	1.0/1.1	-	-	3	**8a** 49	40
4a	**5a**	3.0/1.0	-	-	63[b]	-	-
4b	**5b**	1.0/1.1	-	**6b** 34	**7b** 31	**8b** 7	-
4b	**5b**	1.0/1.1	Et_3N	66	13	-	-
4b	**5a**	1.0/1.1	-	**6c** 30	**7c** 27	**8c** 14	-
4c	**5a**	3.0/1.0	-	**6d** 63[b]	-	-	-

[a], 1,4-diazabicyclo[2.2.2]octane. [b], yield based on imidoyl chloride (**5a**).

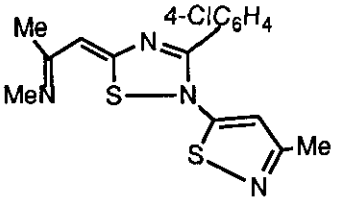
Structural Assignment of 6. In ^1H nmr spectrum of **6a**, there are observed the following characteristic signals, i.e., δ 3.03 (d, J = 4 Hz, 3H) for *N*-Me, δ 5.38-5.95 (bs, 1H) for NH, δ 6.20 (s, 1H) for the isothiazole ring proton together with signals for the isothiazole methyl, δ 2.40 (s, 3H), and aromatic protons. The spectrum was very similar to that of *N*-silylated derivative (**6e**) except for signals resulted from *tert*-butyldimethylsilyl group.[3b] The doublet signal for *N*-methyl protons indicates that the ring-transformation did not occur under the reaction conditions. Thus, the structure of **6a** was assigned as a normal 1 : 1 condensation product. By the similar reasoning, structure of **6b,c** was assigned to the analogous derivatives (Tables 2 and 3).

Structural Assignment of 7. In ^1H nmr spectrum of **7a**, two singlets for two kinds of methyl groups are seen at δ 2.35 (imino-C-methyl) and 2.53 (isothiazole methyl) along with two singlets at δ 6.20 (isothiazole H) and 6.48 (vinyl H). The

distinct difference of chemical shift at δ 7.45 and 8.67 between ortho and meta protons of the aromatric ring clearly suggests that the ring is directly conjugated with an electron-withdrawing heterocycle, i. e., thiadiazole in this case.[3a,4] The 2 : 1 condensation product (**7a**) was obtained as a sole product (63%) by reaction in the presence of 3 equiv. of 5-amino-3-methylisothiazole (**4a**). However, the oxygen analogue (**6d**) did not condense with the second **4c** even in the presence of excess **4c**. Methylation of **7a** occurred readily with dimethylsulfonium methylide in tetrahydrofuran to give imino-*N*-methyl derivative (**9**) in good yield. The ^{1}H nmr spectrum of **7a** in CF_3CO_2H solution did not show magnetic equivalence of the two vinylic protons nor the two methyl protons,[3c] thereby demonstrating that the compound should not possess time-averaged C_{2v} symmetry even under the acidic conditions. On the basis of the above spectral data, ring-transformed structure such as **7a** is preferred over that represented by **7a'**. It is noteworthy that the compound was stable under dilute acidic conditions where any ordinary imino function is easily hydrolyzed into the corresponding carbonyl compound. ^{1}H nmr data and chemical behaviors of the other derivatives (**7b,c**) are consistent with those of **7a** as shown in Table 2.

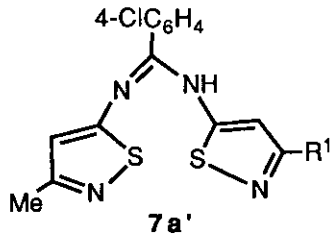


7a-c

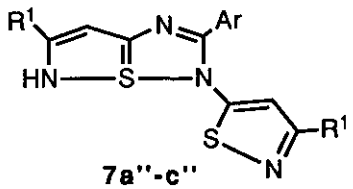


9

	R^1	Ar
7a	Me	4-ClC_6H_4
7b	C_6H_5	C_6H_5
7c	C_6H_5	4-ClC_6H_4



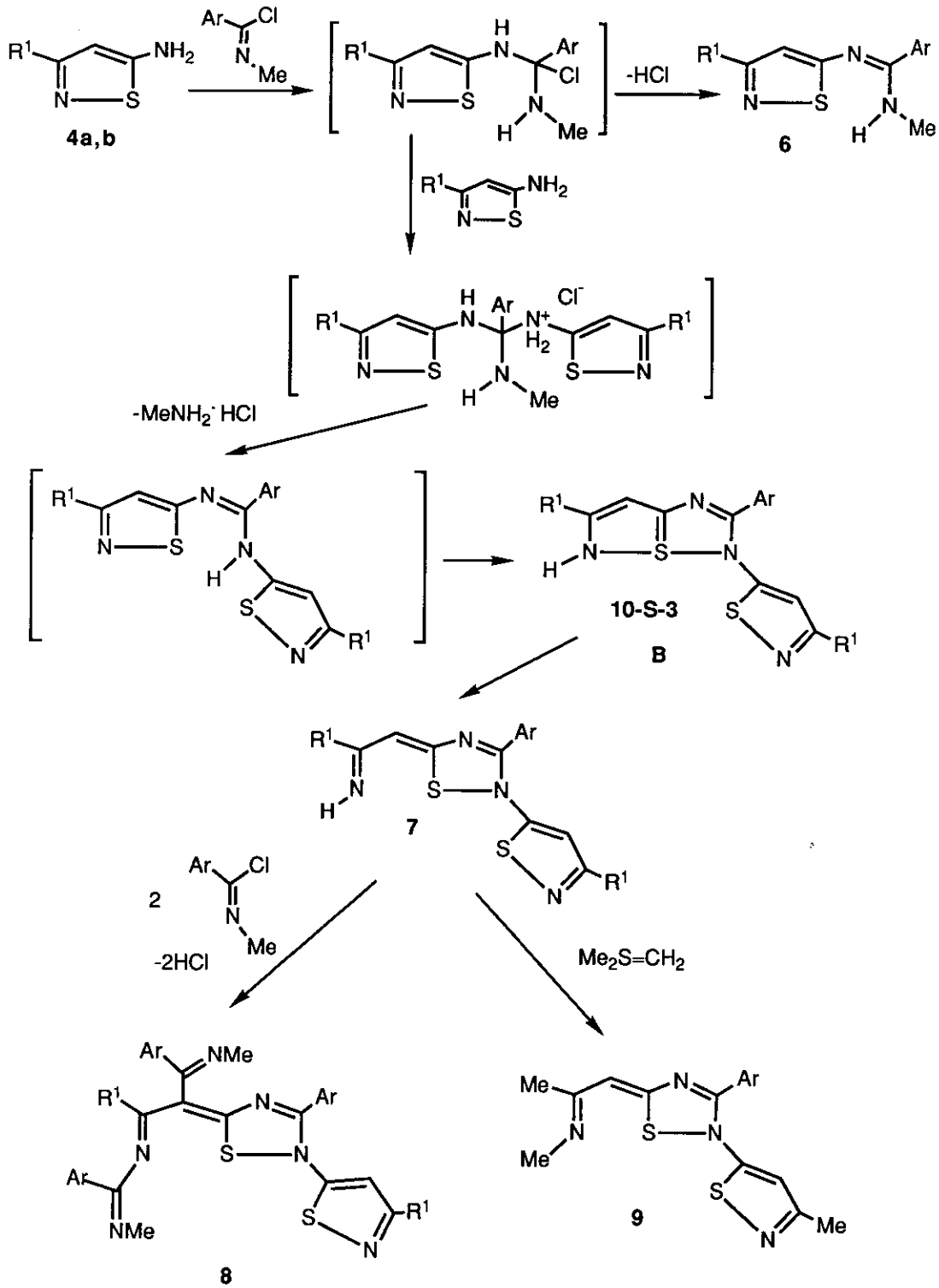
7a'



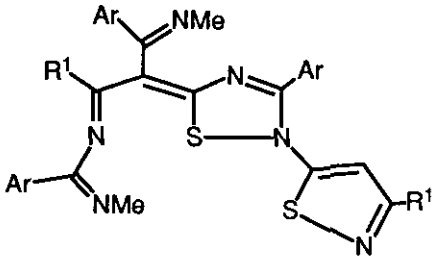
7a''-c''

The results show that the formation of **7** involves that the cleavage of an N-S bond in the isothiazole ring and the formation of another N-S bond in the thiadiazole ring. It is realized that **7a-c** are formed *via* 10-S-3 intermediate (**B**) by a loss of methyl amine hydrochloride followed by ring-transformation (Scheme 3). Thus, 1,3,6-triazo-6a-thiapentalen (**B**) is not isolable but may be a higher energy intermediate or a transition state on the way to the products. Nevertheless, 10-S-3 sulfurane (**7a''-c''**) contribution to **7a-c** could not completly be excluded in view of the chemical behavior (the imino moiety was considerably stable under the hydrolysis conditions).

Structural Assignment of 8. The third condensation product (**8a**) was recrystallized from hexane-dichloromethane to give yellow crystals, mp 202.5-204 °C. The elemental analysis of **8a** gave a satisfactory result for $C_{31}H_{25}N_6Cl_3S_2$ which indicates [2 x **1a** + 3 x **5b**] - [3 x HCl + $MeNH_2$] but the parent peak was not found in the EI mass spectrum. In the ^1H nmr spectrum, there were observed the following characteristic signals, δ 2.18 (s, 3H, imino-C-methyl), 2.43 (s, 3H, isothiazole methyl) and δ 3.23 (s, 3H), 3.52 (s, 3H) for two imino-*N*-methyl groups, and δ 8.24 (d, J = 10 Hz, 2H) for ortho protons of the aromatic ring attached to the thiadiazole ring together with the other aromatic signals. It is deduced from the ^1H nmr spectrum that one isothiazole ring is transformed into the thiadiazole ring on which the Ar group is attached. This is supported by the down-field shift of the ortho protons in the Ar group.[4] According to the above considerations, the structure of **8a** is assigned as the pictured formulus. Treatment of **7a** with two equiv. of imidoyl chloride (**5a**) gave a yellow crystalline product (**8a**) in 21% yield along with the recovered **7a** in 78% yield. The structure of **8b,c** was assigned on the basis of the same reasoning as that for **8a**.



Scheme 3



Possible Structure of **8a-c**

	R^1	Ar
8a	Me	4-ClC_6H_4
8b	C_6H_5	C_6H_5
8c	C_6H_5	4-ClC_6H_4

Finally, the results in the reaction of **4a,b** with **5a,b** are summarized in Scheme 3. The ring-transformation is understandable by invoking the intermediacy of 10-S-3 sulfurane (**B**) in which a hypervalent sulfur atom should take part in stabilizing the system.

EXPERIMENTAL

All the melting points are uncorrected. The ir spectra were obtained with a Hitachi 215 grating ir spectrophotometer. The ^1H nmr measurements were carried out on a Varian T-60 instrument, using tetramethylsilane as the internal reference. The physical properties of each compound are summarized in Table 2.

5-Amino-3-methylisothiazole (4a) and 5-Amino-3-phenylisothiazole (4b). The isothiazole derivatives (**4a,b**) were prepared by a previously reported method.[5,6] Each imidoyl chloride (**5a,b**) was obtained by treatment of the corresponding acid amide with thionyl chloride. **5a**; bp 81 °C/0.6 mmHg (112 °C/30 mmHg)[7]. **5b**; bp 69 °C/2.0 mmHg.

Reaction of Isothiazole Derivatives (4a,b) with Imidoyl Chloride (5a,b). General Method. To a solution of **4a** (490 mg, 4.3 mmol) and 1,4-diazabicyclo[2.2.2]octane (580 mg, 5.2 mmol) in 20 ml of acetonitrile was added *N*-methyl-*p*-chlorobenzimidoyl chloride (890 mg, 4.7 mmol) in 5 ml of the same solvent at 0 °C and the mixture was stirred for 39 h at room temperature. After the

mixture was filtered, the solvent was removed and the residue was separated by preparative tlc on silica gel to afford each product; 5-[*p*-chlorophenyl-(*N*-methylamino)methyleneamino]-3-methylisothiazole (**6a**, 11%), 2,5-dihydro-5-(2-iminopropylidene)-2-[5-(3-methylisothiazolyl)]-1,2,4-thiadiazole (**7a**, 29%), and the starting material (**4a**, 29%).

The results under the different conditions are summarized in Table 1. In the absence of additional base, separation by preparative tlc was carried out after neutralization of the reaction mixture.

Methylation of 7a. 2,5-Dihydro-5-[2-(*N*-methylimino)propylidene]-2-[5-(3-methylisothiazolyl)]-1,2,4-thiadiazole (9). To a solution of trimethylsulfonium iodide (280 mg, 1.0 mmol) in 10 ml of tetrahydrofuran was added dropwise butyllithium (0.42 ml of 1.6 M hexane solution) at 0 °C. After 1 h of stirring, a solution of **7a** (150 mg, 0.42 mmol) in 12 ml of the same solvent was added. Stirring was maintained at gentle reflux for 1 h before the mixture was poured onto ice and extracted with dichloromethane. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to yield a solid (90 mg, 60%). Recrystallization from ether-hexane afforded a pure sample of **9** as colorless crystals (see Table 2).

Reaction of 7a with 5a. To a solution of **7a** (188 mg, 0.54 mmol) in 20 ml of acetonitrile was added **5a** (210 mg, 1.1 mmol) in 5 ml of the same solvent. The reaction mixture was stirred at room temperature for 2 days. The mixture was poured into aqueous sodium bicarbonate solution and the product was extracted into dichloromethane. The organic layers were combined and washed with water, dried over $MgSO_4$, and concentrated to furnish yellow solid. Thin layer chromatographic separation gave 74 mg (21%) of **8a** and 147 mg (78%) of **7a**.

Reaction of 5-Amino-3-phenylisoxazole (4c)[8] with 5a. 5-[*p*-Chlorophenyl-(*N*-methylamino)methyleneamino]-3-phenylisoxazole (6d). By a method similar to that used in the condensation of **4a** with **5a**, 1 : 1

Table 2. ^{1}H Nmr and Ir Spectral Data of New Compounds

compd	mp, °C (from solvent)	^{1}H nmr (δ, $CDCl_3$)	ir (KBr), cm^{-1}
6a	oil	2.40 (s, 3H), 3.03 (d, *J*=4 Hz, 3H), 6.20 (s, 1H), 5.38-5.95 (bs, 1H), and 7.22, 7.40 (ABq, *J*=8 Hz, 4H)	-
6b	157.5-158.5 (ether-CH_2Cl_2)	3.13 (d, *J*=4 Hz, 3H), 6.90 (s, 1H), 4.90-5.50 (br s, 1H), 7.28-7.65 (m, 8H), and 7.65-8.05 (m, 2H)	3350 and 1590
6c	142.0-144.0 (ether-hexane)	2.95 (br s, 3H), 6.78 (s, 1H), 5.80-6.28 (br s, 1H), 7.13-7.42 (m, 7H), and 7.59-7.81 (m, 2H)	3400 and 1590
6d	142.5-144.0 (ether-hexane)	3.05 (d, *J*=5 Hz), 5.19 (s, 1H), 5.87-6.42 (br s, 1H), and 7.17-7.75 (m, 9H)	3300 and 1460
7a	169.0-170.0 ($CHCl_3$)	2.35 (s, 3H), 2.53 (s, 3H), 6.20 (s, 1H), 6.48 (s, 1H), 7.62 (s, 1H), and 7.45, 8.67 (ABq, *J*=9 Hz, 4H)	-
7b	viscous oil	5.21 (s, 1H), 7.12 (s, 1H), 7.19-7.59 (m, 10H), 7.63-7.85 (m, 2H), 7.90-8.12 (m, 2H), and 8.40-8.65 (m, 2H)	-
7c	155.5-157.0 (ether-hexane)	5.10-5.80 (br s, 1H), 7.08 (s, 1H), 7.15-7.53 (m, 9H), 7.60-7.80 (m, 2H), 7.81-8.18 (m, 2H), and 8.36 (d, *J*=8 Hz, 2H)	3150 and 1550
8a	202.5-204.0 (CH_2Cl_2-hexane)	2.18 (s, 3H), 2.43 (s, 3H), 3.23 (s, 3H), 3.52 (s, 3H), 7.18-7.82 (m, 11H), and 8.24 (d, *J*=10 Hz, 2H)	1340
8b	viscous oil	3.38 (s, 3H), 3.57 (s, 3H), 6.67-7.93 (m, 22H), 7.93-8.21 (m, 2H), and 8.28-8.61 (m, 2H)	-
8c	172.0-173.5 (CH_3CN)	3.33 (s, 3H), 3.63 (s, 3H), 7.03-8.77 (m, 19H), 8.00-8.22 (m, 2H), and 8.43 (d, *J*=10 Hz, 2H)	1338
9	120.5-122.0 (ether-hexane)	2.33 (s, 3H), 2.52 (s, 3H), 3.53 (s, 3H), 6.24 (s, 1H), 6.80 (s, 1H), and 7.36, 8.29 (ABq, *J*=9 Hz, 4H)	1530

condensation product (**6d**, 84 mg, 63%) was obtained from **4c** (200 mg, 1.3 mmol) and **5a** (80 mg, 0.43 mmol).

Table 3. Elemental Analyses and/or Mass Spectra of New Compounds

compd	fomula	Anal. Found/(Calcd)			Mass, m/z
		C,	H,	N,	
6 a	$C_{12}H_{12}N_3ClS$				265, 267
6 b	$C_{17}H_{15}N_3S$	69.80	5.20	14.43	293
		(69.59	5.15	14.32)	
6 c	$C_{17}H_{14}N_3ClS$	62.32	4.20	12.94	367, 369
		(62.28	4.30	12.82)	
6 d	$C_{17}H_{14}N_3OCl$	65.47	4.42	13.73	311, 313
		(65.49	4.53	13.48)	
7a	$C_{15}H_{13}N_4ClS_2$	51.73	3.80	16.06	348, 350
		(51.64	3.76	16.06)	
7b	$C_{25}H_{18}N_4S_2$				438
7c	$C_{25}H_{17}N_4ClS_2$	63.35	3.52	11.82	472, 474
		(63.48	3.62	11.85)	
8a	$C_{31}H_{25}N_6Cl_3S_2$	57.19	3.89	12.86	
		(57.10	3.86	12.89)	
8c	$C_{41}H_{29}N_6Cl_3S_2$	63.13	3.78	10.82	
		(63.44	3.77	10.83)	
9	$C_{10}H_{15}N_4ClS_2$	52.86	4.09	15.47	362, 364
		(52.95	4.17	15.44)	

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