A new synthetic route to aminothiazolinones

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Novel 2-(5-R-1,3,4-thiadiazol-2-yl)aminothiazolin-4-ones **6a—h** and 2-imino-3-(5-R-1,3,4-thiadiazol-2-yl)thiazolidin-4-ones **7a—h** were prepared by treating *N*-(5-R-1,3,4-thiadiazol-2-yl)thioureas **4a—h** with chloroacetic acid on various solid supports under microwave irradiation. Tautomeric mixtures of compounds **6a—h** and **7a—h** were obtained in all cases. In alkaline and neutral media, compounds **6a—h** were the major products, while in acid media, **7a—h** were the major products

Key words: aminothiazolinones, iminothiazolidinones, thiadiazoles, thioureas, tautomers, solid supports.

1,3,4-Thiadiazole derivatives are known for their antibacterial, antifungal, and antiviral activities,[1—3] and thiazol-4-ones are useful structural components used in medicinal chemistry for designing drugs.[4—7] Moreover, thiazol-4-ones have been reported as central nervous system and cardiovascular system stimulants.[8,9] Keeping in view the diverse biological activities of the parent heterocyclic systems, it was thought worthwhile to synthesize (Scheme 1) some novel aminothiazolinones **6a—h** and iminothiazolidinones **7a—h** by condensation of thioureas **4a—h** with chloroacetic acid in alkaline, acidic, and neutral media.

The synthesis was carried out on inorganic solid supports using microwave irradiation.[10] For comparison, some reactions were conducted by the conventional heating method.

Results and Discussion

Thiadiazolylthioureas **4a—h** were condensed with equimolar amounts of chloroacetic acid in alkaline, acidic, and neutral media to obtain oxothiazolinylaminothiadiazoles **6a—h** and iminooxothiazolidinylthiadiazoles **7a—h**. In each case, both isomers were formed, but in basic and neutral media, compounds **6a—h** were obtained as major products, while in acidic media, **7a—h** predominated. The predominance of either **6a—h** or **7a—h** in the reaction mixture is dictated by their stabilities in the reaction medium used.[11,12] Indeed, the imino isomers **7a—h** are less stable in alkaline and neutral media and more stable in acidic media, while the amino isomers **6a—h** are less stable in acidic media and more stable in alkaline and neutral media.

The reactions were carried out both with microwave and conventional heating for a comparative study of the reaction methodologies. Microwave reactions took 3.3—5.1 min for completion leading to the formation of **6a—h** and **7a—h**, whereas in conventional reactions, this required 1.0—1.5 h. The yields of compounds **6a—h** and **7a—h** in microwave reactions were 70—85 and 65—80%, respectively, whereas in the conventional reactions, the yields were 55—67 and 46—62%, respectively. The amounts of trace products ranged from 1.5 to 3.5% in different media (Table 1).

The chemical transformations led to ring closure reactions probably *via* the intermediates **5a—h**. The formation of compounds **6a—h** and **7a—h** was confirmed by the appearance of an IR band at 1725—1735 cm^{-1}, which is due to the C=O group in the ring. The IR band at 3247—3257 cm^{-1} confirms the presence of a secondary amino group —NH— in compounds **6a—h**, while the band at 1685—1705 cm^{-1} is indicative of the presence of the imino group =NH in compounds **7a—h**. In the ^1H NMR spectrum, the signal with δ 2.1—2.5 corresponds to the CH_2 group, while that with δ 3.2—3.7 is due to the NH group. The signal with δ 9.5—10.5 attests to the presence of the imino group proton (=NH) in compounds **7a—h**. All the data of the IR and NMR spectra are identical for isomers **6a—h** and **7a—h**, except for the data for the —NH— and =NH groups, respectively (Table 2). The elemental analysis data (C, H, and N) are also the same for both isomers with a variation ±0.4% from the calculated values (see Table 2). Close melting points of respective isomeric **6** and **7** are caused apparently by their mutual transformations on melting.

Thus, some novel oxothiazolylaminothiadiazoles **6a—h** and iminooxothiazolidinylthiadiazoles **7a—h** were synthesized using either microwave irradiation or conventional heating by the reaction of thiadiazolylthioureas **4a—h** and chloroacetic acid in alkaline, acid, and neutral

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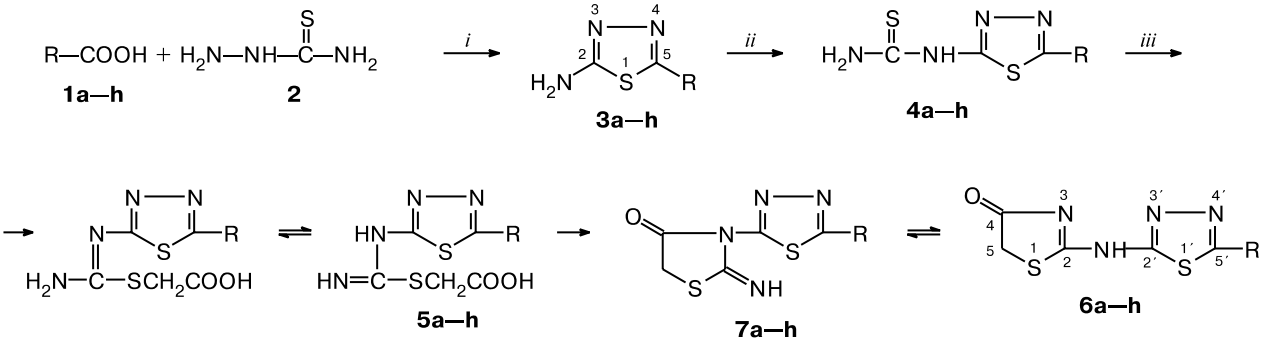
Scheme 1



R = Me (**a**), Ph (**b**), 3-pyridyl (**c**), 4-pyridyl (**d**), 2-furyl (**e**), 2-thienyl (**f**), $Me(CH_2)_6$ (**g**), $Me(CH_2)_8$ (**h**)

Reagents and conditions: *i*. Al_2O_3 (acidic), μv; *ii*. Al_2O_3 (acidic), μv, NH_4CNS; *iii*. $ClCH_2COOH$, μv.

media. Compounds **6a—h** were obtained in alkaline and neutral media, whereas **7a—h** were obtained in acidic media, together with trace amounts of the other isomer.

Experimental

Microwave irradiation was carried out in a Kenstar Microwave Oven, Model No. OM9925E (2450 MHz, 800 W). IR spectra were recorded on a Perkin—Elmer FTIR-1710 spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Hitachi R-600 (60 MHz) instrument. Elemental analysis was performed using a Heraeus CHN-Rapid Analyzer. The temperatures of the reaction mixtures were measured using an AZ, Mini Gun Type noncontact thermometer, Model 8868. Melting points were determined on a Thomas Hoover Melting Point Apparatus and were not corrected. The chemical shifts δ in the ^{1}H NMR spectra were referred to internal tetramethylsilane. The purity of compounds was checked by TLC on aluminum plates coated with silica gel (Merck).

Column chromatography was carried out using activated alumina (Brockmann activity I, ~150 mesh, specific surface area 155 $m^2\ g^{-1}$; the pH of the aqueous suspension was 4±0.5, 7.0±0.5, and 9±0.5 for acidic, neutral, and alkaline media, respectively).

5-Substituted 2-amino-1,3,4-thiadiazoles **3a—h** and 5-substituted 2-thioureido-1,3,4-thiadiazoles **4a—h** were prepared by well-established published procedures.[13,14]

2-(4-Oxo-2-thiazolin-2-ylamino)-1,3,4-thiadiazoles 6a—h and 2-(2-imino-4-oxothiazolidin-3-yl)-1,3,4-thiadiazoles 7a—h (general procedure). *A.* Equimolar amounts (each 0.1 mol) of thioureas **4a—h** and chloroacetic acid were dissolved in EtOH

Table 1. Reaction times, yields, and melting points of compounds **6a—h** and **7a—h** prepared under microwave radiation and under conventional conditions in alkaline (I), neutral (II), and acidic (III) media

Compound	M.p. /°C	Microwave radiation						Conventional conditions					
		t/min			Yield (%)			*t*/h			Yield (%)		
		I	II	III	I	II	III	I	II	III	I	II	III
6a	187	4.0	4.1	3.3	70	68	2.0	1.1	1.1	1.0	55	51	1.5
6b	195	4.2	4.1	4.0	73	70	2.5	1.4	1.3	1.3	58	55	2.0
6c	221	5.0	4.8	4.4	77	74	2.5	1.5	1.4	1.2	60	56	2.0
6d	145	4.5	4.3	4.2	85	82	3.0	1.4	1.3	1.1	62	60	2.5
6e	198	4.3	4.2	4.0	82	79	2.0	1.3	1.2	1.1	65	61	2.5
6f	110	5.0	4.9	4.3	78	75	2.5	1.4	1.3	1.3	67	63	3.0
6g	217	4.4	4.2	4.2	72	68	2.0	1.5	1.4	1.2	60	56	2.5
6h	227	5.1	4.8	4.5	85	81	3.0	1.3	1.1	1.0	63	60	3.0
7a	182	4.0	4.1	3.3	3.0	2.0	65	1.1	1.1	1.0	2.5	2.0	46
7b	190	4.2	4.1	4.0	3.0	2.5	71	1.4	1.3	1.3	3.0	2.5	52
7c	215	5.0	4.8	4.4	3.5	2.0	72	1.5	1.4	1.2	3.0	2.0	57
7d	132	4.5	4.3	4.2	2.0	1.5	78	1.4	1.3	1.1	3.5	2.0	60
7e	185	4.3	4.2	4.0	3.0	1.5	80	1.3	1.2	1.1	3.0	2.5	59
7f	103	5.0	4.9	4.3	2.5	2.0	73	1.4	1.3	1.3	2.5	2.0	62
7g	207	4.4	4.2	4.2	3.0	2.5	71	1.5	1.4	1.2	3.0	2.0	58
7h	219	5.1	4.8	4.5	3.5	2.5	79	1.3	1.1	1.0	2.5	2.5	61

Table 2. Elemental analysis data and spectral characteristics of compounds **6a—h** and **7a—h**

Compound	Found / Calculated (%)			Molecular formula	IR (KBr), ν/cm^{-1}	^{1}H NMR ($CDCl_3$ + DMSO-d_6), δ
	C	H	N			
6a, **7a**	33.8 33.6	2.8 2.8	26.3 26.1	$C_6H_6N_4OS_2$	1730 (C=O) 3250 (N—H) 1690 (=N—H)	2.4 (s, 2 H, CH_2) 3.5 (s, 1 H, NH) 10.5 (s, 1 H, =NH) 1.2 (s, 3 H, CH_3)
6b, **7b**	47.9 47.8	2.9 2.9	20.3 20.3	$C_{11}H_8N_4OS_2$	1728 (C=O) 3247 (N—H) 1687 (=N—H)	2.2 (s, 2 H, CH_2) 3.3 (s, 1 H, NH) 10.0 (s, 1 H, =NH) 7.2—7.6 (m, 5 H, Ar—H)
6c, **7c**	43.5 43.3	2.7 2.5	25.4 25.2	$C_{10}H_7N_5OS_2$	1732 (C=O) 3252 (N—H) 1695 (=N—H)	2.3 (s, 2 H, CH_2) 3.4 (s, 1 H, NH) 10.3 (s, 1 H, =NH) 7.3—8.1 (m, 4 H, Ar—H)
6d, **7d**	43.5 43.3	2.7 2.5	25.4 25.2	$C_{10}H_7N_5OS_2$	1731 (C=O) 3252 (N—H) 1695 (=N—H)	2.3 (s, 2 H, CH_2) 3.4 (s, 1 H, NH) 10.3 (s, 1 H, =NH) 7—8 (m, 4 H, Ar—H)
6e, **7e**	40.7 40.6	2.3 2.3	21.1 21.0	$C_9H_6N_4O_2S_2$	1725 (C=O) 3251 (N—H) 1685 (=N—H)	2.1 (s, 2 H, CH_2) 3.2 (s, 1 H, NH) 9.5 (s, 1 H, =NH) 6.1—6.3 (m, 3 H, furyl)
6f, **7f**	38.6 38.3	2.2 2.1	19.9 19.8	$C_9H_6N_4OS_3$	1727 (C=O) 3253 (N—H) 1688 (=N—H)	2.2 (s, 2 H, CH_2) 3.3 (s, 1 H, NH) 10.0 (s, 1 H, =NH) 7.1—7.2 (m, 3 H, thienyl)
6g, **7g**	48.5 48.3	6.2 6.1	18.9 18.7	$C_{12}H_{18}N_4OS_2$	1732 (C=O) 3255 (N—H) 1697 (=N—H)	2.4 (s, 2 H, CH_2) 3.5 (s, 1 H, NH) 10.5 (s, 1 H, =NH) 1.0 (t, 3 H, CH_3) 1.5 (m, 10 H, CH_2) 2.2 (t, 2 H, CH_2)
6h, 7h	51.6 51.5	6.8 6.8	17.2 17.2	$C_{14}H_{22}N_4OS_2$	1735 (C=O) 3257 (N—H) 1705 (=N—H)	2.5 (s, 2 H, CH_2) 3.7 (s, 1 H, NH) 10.5 (s, 1 H, =NH) 1.0 (t, 3 H, CH_3) 1.5 (m, 14 H, CH_2) 2.2 (t, 2 H, CH_2)

and the solution was adsorbed on basic Al_2O_3 (20 g) at pH 9.5. The mixture was dried in air and subjected to microwave radiation at 120 °C (the irradiation times are given in Table 1). On completion of the reaction (TLC monitoring), product **6a—h** together with trace amounts of **7a—h** was eluted by EtOH (4×20 mL). The solvent was recovered through distillation under reduced pressure.

The same reactions were carried out using acidic (pH 4.5) and neutral (pH 7.0) Al_2O_3. In the acidic medium, compound **7a—h** is the major product ($R_f \approx 0.5$) and compound **6a—h** ($R_f \approx 0.7$) was the minor product; in the neutral medium, **6a—h** is the major product and **7a—h** is the minor product. The workup procedure was done as in the case of alkaline Al_2O_3.

B. A mixture of compound **4a—h** (0.1 mol), chloroacetic acid (0.1 mol), and NaOAc (0.2 mol) was dissolved in water (alkaline medium). The resulting solution was refluxed (see Table 1). Product **6a—h** was isolated on cooling the reaction mixture after completion of the reaction (TLC monitoring, benzene—ethyl acetate, 70 : 30). The product was recrystallized from water.

For the reaction in an acidic medium, 10 mL of a dilute solution of HCl in EtOH (10 mL of 1 *N* HCl in 100 mL of EtOH) was added to an aqueous solution containing thiourea **4a—h** (0.1 mol) and chloroacetic acid (0.1 mol) and the resulting solution was refluxed until the reaction was completed. The workup procedure was done as described above for the alkaline medium to give products **7a—h**.

In neutral media, an aqueous solution of thioureas **4a—h** and chloroacetic acid was heated at reflux to afford compounds **6a—h**.

Trace amounts of products **7a—h** were formed in alkaline and neutral media, and traces of **6a—h** were formed in acidic media. Isomers **6a—h** and **7a—h** were separated by column chromatography.

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