REACTION OF 2-AMINO-5-R-PHENYL-1,3,4-THIADIAZOLES WITH UNSATURATED ACIDS AND ACID CHLORIDES

I. V. Zubets, S. N. Vergizov,
I. V. Viktorovskii, and K. A. V'yunov

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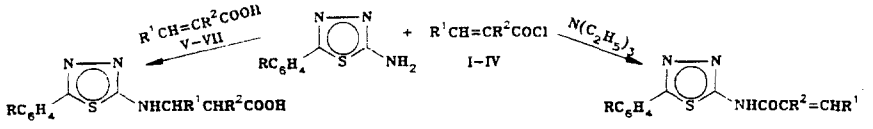
Reaction of 2-amino-5-R-phenyl-1,3,4-thiadizoles with unsaturated acids and acid chlorides in the presence of trimethylamine takes place exclusively at the amino group to form the 2-carboxyalkyl- and 2-acylamino- derivatives, respectively.

2-Amino-1,3,4-thiadiazoles, including their acyl derivatives, are substances showing biological activity and finding use in medicine and agriculture [1]. The aim of this work is to study the reaction of 2-amino-5-R-phenyl-1,3,4-thiadiazoles with the α,β-unsaturated acid chlorides I-IV and with the acids themselves V-VIII.

Acylation of aminothiadiazoles by the acid chlorides I-IV using triethylamine in tetrahydrofuran occurs (on heating) exclusively at the amino group to form the 2-acylamino-5-R-phenyl-1,3,4-thiadiazoles VIII-XXV (Table 1).



XXVI-XXXI

VIII R=3-NO_2, R^1=R^2=H; IX R=4-NO_2, R^1=R^2=H; X R=4-Br, R^1=R^2=H; XI R=2-F, R^1=R^2=H; XII R=4-F, R^1=R^2=H; XIII R=4-Cl, R^1=R^2=H; XIV R=R^1=R^2=H; XV R=3-NO_2, R^1=H, R^2=CH_3; XVI R=4-NO_2, R^1=H, R^2=CH_3; XVII R=4-Br, R^1=H, R^2=CH_3; XVIII R=2-F, R^1=H, R^2=CH_3; XIX R=4-F, R^1=H, R^2=CH_3; XX R=3-NO_2, R^1=C_6H_5, R^2=H; XXI R=4-Br, R^1=C_6H_5, R^2=H; XXII R=F, R^1=C_6H_5, R^2=H; XXIII R=4-F, R^1=C_6H_5, R^2=H, XXIV R=4-Cl, R^1=C_6H_5, R^2=H; XXV R=R^2=H, R^1=C_6H_5; XXVI R=3-NO_2, R^1=R^2=H; XXVII R=4-Br, R^1=R^2=H; XXVIII R=4-Br, R^1=H, R^2=CH_3; XXIX R=4-F, R^1=H, R^2=CH_3; XXX R=R^1=R^2=H, XXXI R=4-Br, R^1=CH_3, R^2=H

The IR spectra of the thiadiazoles VIII-XXV show characteristic thiazole ring absorptions (1430-1485 and 1620-1635 cm^{-1}) [2] together with three new bands. Two bands in the regions 1665-1690 and 1515-1560 cm^{-1} were assigned to carbonyl group absorption (amide I) and to δ_{NH} amd ν_{C-H} (amide II) absorptions. The third at 1610-1590 cm^{-1} was assigned to a

TABLE 1. Properties of the Synthesized Compounds

Compound	Empirical formula	mp, °C	Yield, %	Compound	Empirical formula	mp, °C	Yield, %
VIII	$C_{11}H_8N_4O_3$	201...203	83	XX	$C_{17}H_{12}N_4O_3$	350	86
IX	$C_{11}H_8N_4O_3$	199...201	92	XXI	$C_{17}H_{12}BrN_3O$	338...339	83
X	$C_{11}H_8BrN_3O$	187...189	97	XXII	$C_{17}H_{12}FN_3O$	311...312	87
XI	$C_{11}H_8FN_3O$	158...160	84	XXIII	$C_{17}H_{12}FN_3O$	347...348	85
XII	$C_{11}H_8FN_3O$	150...152	87	XXIV	$C_{17}H_{12}ClN_3O$	345	81
XIII	$C_{11}H_8ClN_3O$	189...191	90	XXV	$C_{17}H_{13}N_3O$	298...300	80
XIV	$C_{11}H_9N_3O$	197...199	81	XXVI	$C_{11}H_{10}N_4O_4$	204...206	92
XV	$C_{12}H_{10}N_4O_3$	240...241	91	XXVII	$C_{11}H_{10}BrN_3O_2$	184...186	97
XVI	$C_{12}H_{10}N_4O_3$	211...213	89	XXVIII	$C_{12}H_{12}BrN_3O_2$	185...187	82
XVII	$C_{12}H_{10}BrN_3O$	230...232	82	XXIX	$C_{12}H_{12}FN_3O_2$	166...168	89
XVIII	$C_{12}H_{10}FN_3O$	214...216	99	XXX	$C_{12}H_{13}N_3O_2$	108...110	80
XIX	$C_{12}H_{10}FN_3O$	208...210	97	XXXI	$C_{12}H_{12}BrN_3O_2$	155...157	85

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TABLE 2. Mass Spectra* of 2-Acylamino-5-R-phenyl-1,3,4-thiadiazoles VIII-XXV

Compound	m/z (% relative intensity to peak maximum)
VIII	276 (11), 248 (15), 247 (6), 222 (5), 120 (12), 100 (10), 86 (11), 74 (7), 69 (6), 57 (7), 55 (100)
IX	276 (10), 249 (15), 222 (75), 120 (18), 100 (12), 86 (75), 74 (85), 71 (70), 61 (30), 57 (65), 55 (100)
X	^{a}309 (21), ^{a}281 (36), ^{a}255 (25), ^{a}199 (11), ^{a}182 (9), ^{a}181 (21), 120 (25), 103 (25), 100 (54), 74 (61), 55 (100)
XI	249 (19), 221 (16), 195 (14), 139 (19), 120 (15), 100 (16), 95 (12), 75 (9), 74 (15), 73 (69), 55 (100)
XII	249 (12), 221 (15), 139 (14), 120 (11), 100 (14), 95 (12), 74 (14), 73 (11), 69 (15), 56 (42), 55 (100)
XIII	^{b}265 (20), ^{b}237 (18), ^{b}211 (23), ^{b}155 (15), ^{b}138 (8), ^{b}137 (16), 100 (21), 75 (14), 74 (29), 73 (100), 55 (81)
XIV	231 (23), 203 (17), 202 (11), 177 (16), 121 (18), 104 (11), 100 (18), 77 (22), 74 (17), 73 (60), 55 (100)
XV	290 (21), 222 (21), 142 (11), 120 (60), 114 (11), 76 (8), 74 (28), 70 (6), 69 (96), 60(6), 41 (100)
XVI	290 (7), 222 (92), 134 (13), 120 (22), 76 (13), 75 (12), 74 (100), 69 (33), 63 (11), 60 (19), 41 (33)
XVII	^{a}323 (17), ^{a}255 (17), ^{a}199 (11), ^{a}182 (6), 142 (17), 120 (29), 114 (24), 102 (13), 74 (52), 69 (54), 41 (100)
XVIII	263 (32), 195 (13), 142 (15), 139 (28), 120 (8), 114 (18), 95 (15), 75 (9), 74 (15), 69 (82), 41 (100)
XIX	263 (38), 195 (11), 142 (15), 139 (27), 120 (10), 114 (17), 95 (17), 75 (9), 74 (11), 69 (83), 41 (100)
XX	352 (33), 324 (5), 306 (17), 222 (95), 195 (38), 131 (100), 120 (17), 104 (85), 103 (90), 102 (28), 74 (61)
XXI	^{a}385 (5), ^{a}199 (3), 132 (10), 131 (100), 120 (7), 103 (37), 102 (6), 77 (19), 71 (5), 57 (8), 51 (6).
XXII	325 (18), 297 (3), 149 (5), 139 (7), 132 (6), 131 (100), 120 (5), 104 (5), 103 (47), 77 (10), 55 (5)
XXIII	325 (31), 222 (6), 195 (22), 139 (7), 131 (100), 122 (4), 120 (6), 104 (4), 103 (37), 77 (10), 55 (45)
XXIV	^{b}341 (74), ^{b}211 (98), ^{b}155 (98), 137 (55), 131 (100), 120 (47), 111 (61), 103 (100), 77 (55), 75 (74), 74 (98)
XXV	307 (75), 279 (10), 177 (6), 132 (11), 131 (100), 121 (12), 103 (100), 102 (7), 77 (67), 55 (5)

*M^+ and the ten most intense mass spectral peaks are given; for chloro and bromo compounds the ions containing the ^{79}Br(a) and ^{35}Cl(b) isotopes are quoted.

TABLE 3. Mass Spectra* of 2-Carboxyalkylamino-5-R-phenyl-1,3,4-thiadiazoles

Compound	m/z (% relative intensity to peak maximum)					
	M^+	fragmentation type				other fragments
		A	B	C	D	
XXVI	294 (5)	45 (9)	59 (100)	73 (9)	88 (20)	222 (9), 120 (6), 102 (10), 61 (13), 60 (13), 56 (12)
XXVII	327 (55)	45 (60)	59 (22)	73 (11)	88 (22)	^{a}256 (74), ^{a}199 (55), ^{a}182 (91), ^{a}181 (34), 120 (100), 60 (81)
XXVIII	^{a}341 (10)	45 (4)	73 (100)	87 (2)	102 (13)	^{a}296 (8), ^{a}199 (11), ^{a}182 (16), 120 (26), 100 (22), 76 (13)
XXIX	281 (21)	45 (10)	73 (19)	87 (2)	102 (12)	236 (16), 208 (18), 180 (31), 139 (27), 121 (100), 86 (19)
XXX	263 (73)	45 (5)	73 (50)	—	—	218 (25), 177 (100), 158 (12), 131 (25), 121 (43), 104 (64), 103 (16), 74 (32)
XXXI	^{a}341 (22)	45 (35)	59 (35)	87 (19)	102 (30)	281 (47), ^{a}255 (27), ^{a}199 (27), ^{a}182 (41), 120 (28), 86 (100)

*M^+ and the ten most abundant mass spectral peaks are given, for bromo compounds the ions containing the ^{79}Br isotope (a) are given.

$\nu_{C=C}$ absorption of the conjugated C=C–C=O system. The position of all of the thiadiazole bands agree well with literature data [3, 4]. Compounds VIII-XXV show a single band in the region 3405-3420 cm^{-1} for the amide group [5].

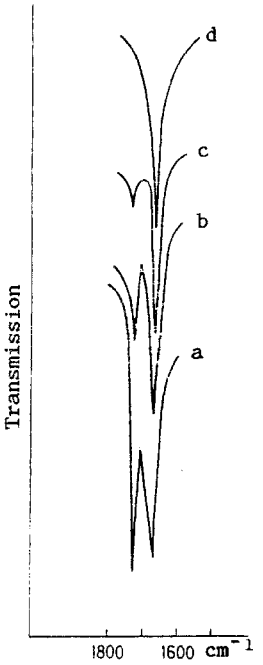


Fig. 1. IR spectra of the acylation products of 2-amino-5-(4-fluorophenyl)-1,3,4-thiadiazole with benzoyl chloride at 20°C: a) 30 min after reaction completion; b) after 10 h; c) after 15 h; d) after 24 h.

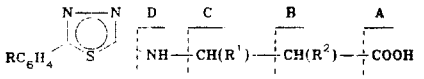
Analysis of the mass spectra of VIII-XXV (Table 2) shows that the thiadiazole ring is stable to electron impact. The most characteristic course of fragmentation is the fission of the CO—N and CO—C single bonds in the exocyclic function, typical for amides [6].

Dissociative ionization of VIII-XXV includes both the simple N—CO fission and a migration of one of the vinyl group protons to the exocyclic nitrogen atom. This is a distinctive feature of compounds acylated at the amino group [7]. Elimination of the exocyclic moiety leads to fragment ions, further fission of which is similar to the fragmentation of the starting 2-amino-5-R-phenyl-1,3,4-thiadiazoles [8].

Gentle heating of the aminothiadiazoles with the unsaturated acids V-VII does not cause any reaction but fusion (160°C) leads to addition of the amino group to the multiple bond to form the 2-carboxyalkylamino-5-R-phenyl-1,3,4-thiadiazoles XXVI-XXXI.

The IR spectra of XXVI-XXXI show intense carbonyl stretching absorptions at 1660-1675 cm^{-1}, out of plane deformation vibrations for the hydroxyl group at 950 cm^{-1}, and a complex, intense band for the stretching vibration of the OH group [7] at 3300-2500 cm^{-1}.

A sequential dissociation in the exocyclic molecular fragment of the type A, B, C, or D occurs in the mass spectra of XXVI-XXXI (Table 3). Dissociation α to the heterocycle (Type D) to form fragment ions comprises up to 30% of the maximum spectral peak and is a certain indication that addition of acids I-IV occurs selectively at the amino group:



Acylation of the amino group in the reaction with unsaturated acid chlorides I-IV is observed only in the case of cinnamic acid III with formation of compound XXI also being obtained using cinnamoyl chloride.

EXPERIMENTAL

IR Spectra were recorded on an IRS-29 instrument in the region 3500-4000 cm^{-1} for KBr tablets (Fig. 1). Mass spectra for VIII-XXXI were taken on an LKB-2091 using direct introduction of the sample and an ionization energy of 70 and 20 eV. Purity of the materials was

monitored by TLC on Silufol-254 plates with UV detection and using chloroform–isopropanol (7:1) as eluent.

Elemental analytical data for C, H, N, and S agreed with that calculated.

The acid chlorides V-VII were obtained by methods [9, 10].

N-(5-Phenyl-1,3,4-thiadiazol-2-yl)acrylamide (XIV). A solution of acryloylchloride (0.45 g, 5 mmole) in tetrahydrofuran (5 ml) was added over 45 min to 2-amino-5-phenyl-1,3,4-thiadiazole (0.89 g, 5 mmole) and triethylamine (0.51 g, 5 mmole). The mixture was heated to 66°C and held at this temperature for 1 h, cooled to room temperature, and filtered to remove the precipitate of triethylamine hydrochloride. The filtrate was poured into iced water and the crystalline precipitate dried and recrystallized from isopropanol. Yield 0.72 g (81%) with mp 197-199°C.

Compounds VIII-XIII, XV-XX, XXII-XXV were prepared similarly.

2-[N-(2-Carboxyethyl)amino]-5-(4-bromophenyl)-1,3,4-thiadiazole (XXVII). A mixture of 2-amino-5-(4-bromophenyl)-1,3,4-thiadiazole (0.65 g, 2.5 mmole) and acrylic acid (0.18 g, 2.5 mmole) was heated at 165°C for 1 h, cooled to room temperature and aqueous ammonia (10%, 70 ml) was added. The precipitated solid was filtered off and recrystallized from DMF to give 0.63 g (97%) with mp 184-186°C.

Compounds XXVI, XXVIII-XXXI were prepared similarly.

N-[5-(4-Bromophenyl-1,3,4-thiadiazol-2-yl)]-3-phenylprop-2-en-1-one (XXI). A solution of cinnamoyl chloride (0.83 g, 5 mmole) was added to a solution of 2-amino-5-(4-bromophenyl)-1,3,4-thiadiazole (1.28 g, 5 mmole) and triethylamine (0.51 g, 5 mmole) in anhydrous THF (25 ml). The reaction mixture was heated at 66°C for 1 h, cooled to room temperature and the triethylamine hydrochloride filtered off. The filtrate was stirred for 30 min with NaOH (2%, 40 ml) and the crystalline precipitate filtered off, dried and crystallized from ethanol. Yield 1.59 g (83%) with mp 338-339°C.

2-[N-(2-Carboxyethyl)amino]-5-(4-bromophenyl)-1,3,4-thiadiazole. The filtrate was separated after removal of compound XXI. The aqueous layer was acidified to pH 2.0 and the precipitated solid filtered off, washed with aqueous ammonia (10%), and water, dried and crystallized from DMF. Yield 0.12 g (7%) with mp 183-185°C.

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