REACTION OF 2-AMINO-5-ARYL-1,3,4-OXADIAZOLES WITH COMPOUNDS WITH ACTIVATED DOUBLE BONDS

V. Ya. Alekseeva, I. V. Viktorovskii, S. I. Yakovlev, and K. A. V'yunov

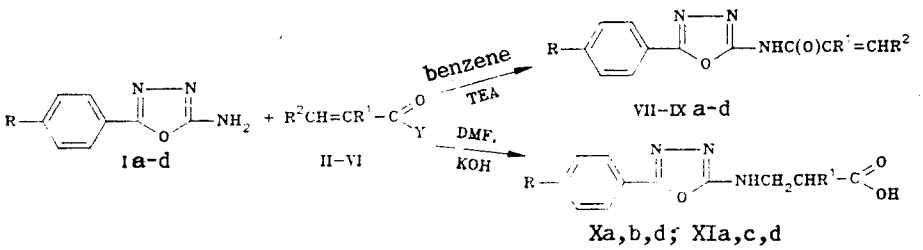
UDC 547.793.4'391.04:543.51

The reaction of 2-amino-5-aryl-1,3,4-oxadiazoles with unsaturated acids and their chlorides was studied. It was shown by IR spectroscopy and mass spectrometry that acylation with acrylic, methacrylic, and cinnamic acid chlorides takes place at the nitrogen atom of the exocyclic amino group. Depending on the solvent, two reaction pathways are realized with unsaturated acids: acylation of the starting 2-amino-5-aryl-1,3,4-oxadiazole occurs in bromobenzene, while nucleophilic addition to the unsaturated acid molecule is realized in DMF in the presence of potassium hydroxide.

2-Amino-5-aryl-1,3,4-oxadiazoles may display dual reactivity in acylation and alkylation reactions [1]. The alkylation of 2-amino-1,3,4-oxadiazoles takes place at the endocyclic $N_{(3)}$ atom, while acylation takes place at the nitrogen atom of the exocyclic amino group [1, 2].

The reaction of 2-amino-1,3,4-oxadiazoles with α, β-unsaturated carbonyl compounds has not been described. It is known that 2-aminobenzoxazoles react with unsaturated acids at the allyl fragment to form addition products [3].

The aim of the present research was to investigate the reaction of 2-amino-5-aryl-1,3,4-oxadiazoles I with unsaturated acids and their chlorides.



I a R=H, b R=F, c R=Br, d R=CH_3O; II, IV, V R^1=H, III, VI R^1=CH_3; II, III, V, VI R^2=H, IV R^2=C_6H_5, II—IV Y=Cl, V, VI Y=OH; VII, IX, X R^1=H, VIII, XI R^1=CH_3, VII, VIII, X, XI R^2=H, IX R^2=C_6H_5

The acylation of oxadiazoles I with the unsaturated acid chlorides II-IV in the presence of an equimolar amount of triethylamine in benzene at 70-80°C proceeds selectively at the exocyclic nitrogen atom to give 2-acylamino-5-aryl-1,3,4-oxadiazoles VII-IX (Table 1). The structures of the substances obtained are confirmed by the IR spectra. In addition to absorption bands that are characteristic for the oxadiazole ring at 1030 and 970 cm^{-1} ($\nu_{C\text{-}O\text{-}C}$, $\delta_{C\text{-}O\text{-}C}$) and 1605 cm^{-1} ($\nu_{C=N}$), bands corresponding to stretching vibrations of the C=O bond at 1670-1700 cm^{-1} (amide I), as well as an amide II band at 1540-1590 cm^{-1} [4], appear in the spectra. An analysis of the mass spectra of VII-IX shows that they are not stable with respect to electron impact and have a low-intensity molecular-ion peak (M^+); the M^+ peaks in the spectra of IX are the least intense, since the presence of a phenyl group in the side chain facilitates the formation of F_2 and F_4 fragments and substantially increases their contribution to the total ion current (Table 2). The most characteristic fragmentation pathway is cleavage of the exocyclic amide bond [5]; $CHR^2{=}CR^1{-}C{\equiv}O^+$ ions, the intensities of the peaks of which amount to 20-100% of the maximum peak, are formed. A confirmation of the addition of the acyl residue to the exocyclic amino group is the McLafferty rearrangement, as a result of which a proton of the allyl fragment migrates to the nitrogen atom of the heteroring in the 3 position, and an imino derivative of starting I is formed.

Leningrad Technological Institute, Leningrad 198013. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 825-829, June, 1990. Original article submitted June 7, 1988; revision submitted June 6, 1989.

0009-3122/90/2606-0689$12.50

TABLE 1. Characteristics of VII-XI*

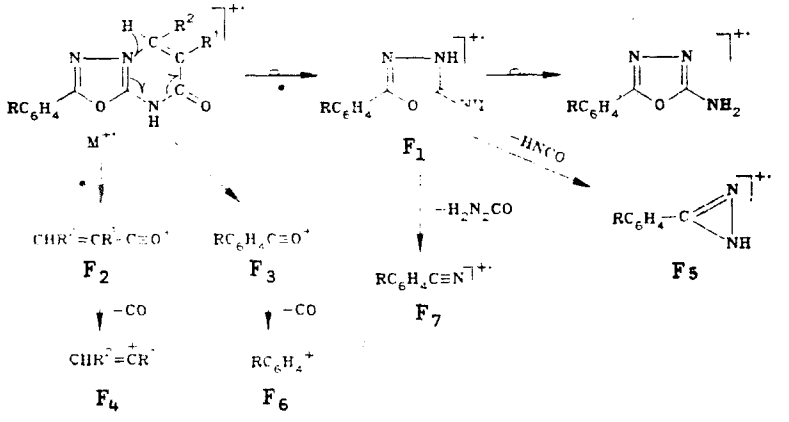
Compound	Empirical formula	mp, °C	Yield, %	Compound	Empirical formula	mp, °C	Yield, %
VIIa	$C_{11}H_9N_3O_2$	182	80	IXb	$C_{17}H_{12}FN_3O_2$	215	71
VIIb	$C_{11}H_8FN_3O_2$	259	75	IXc	$C_{17}H_{12}BrN_3O_2$	193...195	79
VIIc	$C_{11}H_8BrN_3O_2$	225...227	63	IXd	$C_{18}H_{14}N_3O_3$	135...136	63
VIId	$C_{12}H_{10}N_3O_3$	175	59	Xa	$C_{11}H_{11}N_3O_3$	131	65
VIIIa	$C_{12}H_{11}N_3O_2$	203...204	67	Xb	$C_{11}H_{10}FN_3O_3$	135...136	53
VIIIb	$C_{12}H_{10}FN_3O_2$	159...160	73	Xd	$C_{12}H_{13}N_3O_4$	143	60
VIIIc	$C_{12}H_{10}BrN_3O_2$	192...193	84	XIa	$C_{11}H_{13}N_3O_3$	236...237	71
VIIId	$C_{13}H_{13}N_3O_3$	187	57	XIc	$C_{11}H_{12}BrN_3O_3$	192...193	83
IXa	$C_{17}H_{13}N_3O_2$	204	83	XId	$C_{13}H_{16}N_3O_4$	210	65

*Compounds VIIa-d and VIIIa-d were synthesized by methods A and B, while IXa-d were synthesized by method A.

TABLE 2. Intensities of the Peaks of the Characteristic Ions (Σ, %, 40) of VII-IX at an Ionization Energy of 70 eV

Compound	Σ, %							
	M^+	F_1	F_2	F_3	F_4	F_5	F_6	F_7
VIIa	4,9	1,2	22,7	19,1	—	2,0	5,3	2,9
VIIb	4,1	0,7	23,1	17,2	—	2,9	7,7	4,3
VIIc	2,4	7,9	20,1	11,1	—	1,0	1,7	0,9
VIId	2,9	2,7	18,8	11,8	—	1,8	4,3	10,1
VIIIa	4,3	9,2	11,2	9,9	12,3	8,6	16,2	8,6
VIIIb	3,7	1,5	7,3	8,3	17,2	2,2	5,0	0,9
VIIIc	1,5	1,0	9,5	13,3	13,3	2,0	8,3	4,5
VIIId	2,3	0,9	7,3	15,3	17,4	5,7	7,2	3,0
IXa	0,5	1,0	7,9	2,1	15,2	3,5	1,5	—
IXb	0,5	1,1	44,4	4,4	12,5	2,8	4,2	1,6
IXc	0,7	1,0	30,7	5,0	14,0	3,0	4,0	2,3
IXd	1,0	0,6	27,7	3,8	15,2	2,5	2,5	3,5

The fragmentation of acyl derivatives VII-IX can be represented by the scheme



The data obtained constitute evidence that products of acylation at the exocyclic nitrogen atom are formed in the reaction of oxadiazoles I with unsaturated acid chlorides II-IV. Products of acylation at the amino group were isolated when the reaction of I with acrylic acid (V) and methacrylic acid (VI) was carried out in refluxing bromobenzene. The structures of the products isolated from the reaction with the unsaturated acids and their identification with respect to the reaction products obtained in the reaction of oxadiazoles I with the chlorides of the corresponding acids follow from the absence of melting-point depressions and were proved by IR spectroscopic and mass-spectrometric data.

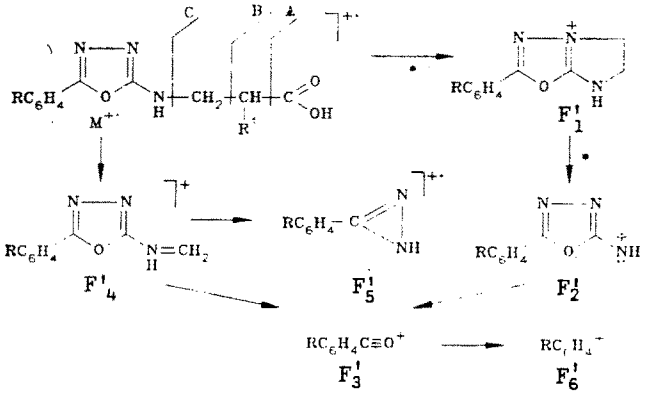
TABLE 3. Intensities of the Peaks of the Characteristic Ions (Σ, %, 40) of X and XI at an Ionization Energy of 70 eV

Compound*	Σ, %					
	F'_1	F'_2	F'_3	F'_4	F'_5	F'_6
Xa	2,0	0,5	11,1	1,0	2,9	3,3
Xb	9,1	3,3	2,4	7,1	1,5	3,3
Xd	10,3	2,7	3,7	3,5	4,3	2,7
XIa	20,4	7,2	1,1	15,6	3,2	4,8
XIc	16,5	5,0	6,8	3,2	1,0	2,5
XId	25,4	7,9	1,7	16,9	1,7	2,0

*For all of the compounds, the value for M^+ was 0.1.

Products of addition to the carbon–carbon multiple bond were obtained when the reaction was carried out in DMF in the presence of potassium hydroxide. The structures of these products (X, XI) were proved by the IR spectra and were confirmed by the mass spectra (Table 3). The IR spectra of X and XI contain intense bands corresponding to stretching vibrations of a carbonyl group at 1630-1700 cm^{-1}, as well as absorption bands that were assigned to deformation vibrations of a C=O bond and deformation vibrations of a hydroxy group attached to a carbonyl group at 1220-1250 cm^{-1} and 1400-1444 cm^{-1}, respectively. In addition, a characteristic band that arises as a result of out-of-plane deformation vibrations of a hydroxy group appears at 930-940 cm^{-1}.

The behavior of X and XI under electron impact is determined by the presence of a carboxy group, which decreases their volatilities and thermal stabilities [5]. A very low-intensity M^+ peak is characteristic for the mass spectra of these compounds, and fragmentation proceeds with parallel cleavage of the bonds in the exocyclic fragment (pathways A, B, and C). The fragmentation of X and XI can be represented by the scheme



Intense peaks of F_1' fragment ions are observed in the mass spectra of X and XI. The formation of the F_2' ion from the F_1' ion and the F_3' ion from the M^+ ion was confirmed by metastable transitions. Thus the indicated cleavages of the bonds in the exocyclic fragment of the molecule provide evidence that the reaction of I with unsaturated acids is realized at the exocyclic amino group. In addition, the small (0.1-1.5) values of the ratios of the intensities of the ion peaks $I[M - CH_2–CH(R^1)COOH]^+/I[M - CH(R^1)COO]^+$ also provide evidence that the nitrogen atom of the exocyclic amino group participates in the reaction [6].

Thus, in benzene in the presence of triethylamine and in bromobenzene unsaturated acids and their chlorides react in the same way with oxadiazoles I. From the point of view of the concept of hard and soft acids and bases the nitrogen atom of the exocyclic amino group, on which the most negative charge is concentrated, is acylated [7]. In the case of the reaction with the unsaturated acids in DMF in the presence of potassium hydroxide activation of the amino group occurs, and it is capable of undergoing nucleophilic addition with the allyl fragment of the unsaturated acid.

EXPERIMENTAL

The mass spectra were recorded with an LKB-2091 spectrometer using a system for direct introduction of the samples; the ionizing-electron energy was 70 eV, and the recording of the spectra was accomplished by means of a light-ray oscillograph. The IR spectra of KBr pellets of the compounds were recorded with an IKS-29 spectrometer. The starting 2-amino-5-aryl-1,3,4-oxadiazoles Ia-d were obtained by the method in [8].

The characteristics of the synthesized compounds are presented in Tables 1-3. The results of elementary analysis were in agreement with the calculated values.

N-(5-Phenyl-1,3,4-oxadiazol-2-yl)acrylamide (VIIa). A. A 0.51-g (5 mmoles) sample of triethylamine and a solution of 0.45 g (5 mmoles) of acrylyl chloride in 5 ml of benzene were added in the course of 10 min with stirring to a suspension of 0.81 g (5 mmoles) of 2-amino-5-phenyl-1,3,4-oxadiazole (Ia) in 30 ml of benzene, after which the mixture was stirred and refluxed for 2 h. The solution was then cooled, and the precipitated triethylamine hydrochloride was removed by filtration. The benzene was removed by distillation, and the residue was recrystallized from acetonitrile to give 0.86 g (80%) of acrylamide VIIa with mp 182°C. IR spectrum: 1485 ($\nu_{C=C}$), 1606 ($\nu_{C=N}$), 3350 cm^{-1} (NH). Mass spectrum, m/z (%): 215 (M^+, 20), 187 (15), 161 (9), 118 (15), 117 (10), 105 (89), 91 (80), 77 (20), 56 (30), 55 (100).

Compounds VIIb-d were similarly obtained.

B. A 0.18-g sample of acrylic acid (V) was added with stirring to 0.81 g (5 mmoles) of Ia in 30 ml of bromobenzene, and the mixture was refluxed for 5 h. It was then cooled and treated with petroleum ether, and the resulting precipitate was removed by filtration to give 0.51 g (47%) of a product with mp 182-183°C.

Compound VIIb was similarly obtained.

N-(5-Phenyl-1,3,4-oxadiazol-2-yl)methacrylamide (VIIIa). A. A 0.51-g (5 mmole) sample of triethylamine and a solution of 0.53 g (5 mmoles) of methacrylyl chloride in 5 ml of benzene were added with stirring in the course of 10 min to 0.81 g (5 mmoles) of Ia in 30 ml of benzene, after which the mixture was refluxed with stirring for 2 h. It was then cooled and poured into cold water, and the precipitated VIIIa was removed by filtration to give 0.78 g (67%) of a product with mp 203-204°C (from ethanol). IR spectrum: 1506 ($\nu_{C=C}$), 1711 ($\nu_{C=O}$), 1606 ($\nu_{C=N}$), 3295 cm^{-1} (NH). Mass spectrum, m/z (%): 229 (M^+, 27), 161 (57), 145 (21), 118 (53), 105 (61), 103 (52), 91 (30), 89 (21), 86 (20), 77 (100), 69 (69).

Compounds VIIIb-d were similarly obtained.

B. A 0.21-g (5 mmoles) sample of methacrylic acid (VI) was added with stirring to 0.81 g (5 mmoles) of Ia in 30 ml of bromobenzene, and the mixture was refluxed for 5-6 h. It was then cooled and treated with ether, and the resulting precipitate was removed by filtration to give 0.57 g (50%) of a product with mp 203-204°C.

Compounds VIIIb, c were similarly obtained.

N-(5-Phenyl-1,3,4-oxadiazol-2-yl)cinnamide (IXa). A solution of 0.83 g (5 mmoles) of cinnamyl chloride in 5 ml of benzene was added with stirring to 0.81 g (5 mmoles) of Ia and 0.51 g (5 mmoles) of triethylamine in 20 ml of benzene, and the resulting reaction mixture was heated for 3 h at 70°C. It was then cooled and treated with 100 ml of water, and the precipitated IXa was removed by filtratoin to give 1.21 g (83%) of a product with mp 204°C (from ethanol). IR spectrum: 1493 ($\nu_{C=C}$), 1693 ($\nu_{C=O}$), 1598 ($\nu_{C=N}$), 3230 cm^{-1} (N–H). Mass spectrum: m/z (%): 291 (M^+, 1), 214 (15), 161 (5), 147 (70), 131 (60), 118 (19), 117 (70), 103 (100), 101 (60), 77 (11), 51 (70).

Compounds XIb-d were similarly obtained.

2-[N-(2-Carboxyethyl)amino]-5-phenyl-1,3,4-oxadiazole (Xa). A 0.25-g sample of KOH and 0.36 g (10 mmoles) of acid V were added with stirring to 0.81 g (5 mmoles) of Ia in 10 ml of DMF, after which the mixture was stirred for 5-6 h at 100°C. It was then cooled and treated with 5% HCl, and the precipitated Xa was removed by filtration to give 0.75 g (65%) of a product with mp 131°C (from benzene). IR spectrum: 1219 ($\delta_{C=O}$), 1410 (δ_{OH}), 1600 ($\nu_{C=N}$), 1693 cm^{-1} ($\nu_{C=O}$). Mass spectrum, m/z (%): 233 (M^+, 1), 188 (18), 117 (27), 105 (100), 77 (30), 73 (80), 72 (80), 59 (13), 55 (77), 45 (27), 44 (67).

Compounds Xb, d were similarly obtained.

2-[N-(2-Carboxyproplyamino]-5-phenyl-1,3,4-oxadiazole (XIa). A 0.25-g sample of KOH and 0.42 g (10 mmoles) of acid VI were added with stirring to 0.81 g (5 mmoles) of Ia in 10 ml of DMF, after which the mixture was stirred for 7 h at 120-130°C. It was then cooled and treated with 5% HCl, and the resulting precipitate (XIa) was removed by filtration to give 0.88 g (71%) of a product with mp 236-237°C (from benzene). IR spectrum: 1233 ($\delta_{C=O}$), 1443 (δ_{OH}), 1595 ($\nu_{C=N}$), 1690 cm^{-1} ($\nu_{C=O}$). Mass spectrum, m/z (%): 247 (M^+, 0.2), 188 (100), 174 (70), 161 (9), 159 (35), 118 (16), 103 (16), 77 (24), 76 (10), 56 (20), 44 (20).

Compounds XIc, d were similarly obtained.

LITERATURE CITED

1. G. Werber, F. Buccheri, and F. Maggio, *J. Heterocycl. Chem.*9, 107 (1972).
2. A. Katritizky (ed.), *Comprehensive Heterocyclic Chemistry*, Vol. 5, Pergamon Press (1984), p. 134.
3. V. B. Kalcheva, L. S. Peshakova, and D. A. Simov, *Khim. Geterotsikl. Soedin.*, No. 11, 1497 (1984).
4. L. Bellamy, *Infrared Spectra of Complex Molecules*, Methuen, London (1958).
5. N. S. Vul'fson, V. G. Zaikin, and A. I. Mikaya, *Mass Spectrometry of Organic Compounds* [in Russian], Khimiya, Moscow (1986), p. 312.
6. V. G. Saprykina, R. F. Ambartsumova, and I. I. Rozhkova, *Khim. Geterotsikl. Soedin.*, No. 7, 986 (1986).
7. H. G. Bartel, M. Nofz, C. Scholz, and M. Budel, *Z. Chem.* **22**, 414 (1982).
8. R. K. Bansal and G. Bhagchandani, *J. Indian Chem. Soc.* **59**, 277 (1982).

SYNTHESIS OF 4-CHLORO-7-DIALKYLAMINOCOUMARINS

M. A. Kirpichenok, S. K. Gorozhankin, and I. I. Grandberg

UDC 547.587.51.07'564.4'476.1.04: 543.422

A series of 4-chloro-7-dialkylaminocoumarins has been synthesized by heating m-diethylaminophenol, m-N-piperidinophenol, m-N-morpholinophenol, and 8-hydroxyjulolidine, respectively, with malonic acids in the presence of excess phosphorus oxychloride. The feasibility of preparing other 4-substituted 7-aminocoumarins from these 4-chloro derivatives has been demonstrated using as an example the reactions of 4-chloro-7-diethylaminocoumarins with sodium ethoxide, hydrazine, and dibutylamine. The spectral and luminescence characteristics of these newly synthesized compounds have been investigated.

Traditional methods for the synthesis of 4-substituted 7-aminocoumarins are generally based on the classical Pechman condensation of m-aminophenols with β-ketoacetic acid esters, or on modifications of this reaction [1]. The synthesis of each individual new 7-aminocoumarin derivative depends, therefore, on the availability of the corresponding carbonyl compound and on the selection of optimal reaction conditions.

An approach which seems to us to be just as promising would involve the use of reactive compounds already incorporating the aminocoumarin fragment. As part of our goal of searching for possible synthons in this regard, we have developed a method for the synthesis of 4-chloro-7-dialkylaminocoumarins.

4-Chloro-7-dialkylaminocoumarins I-VII were prepared by heating equivalent amounts of m-dialkylaminophenols with malonic acid or an appropriate alkylmalonic acid in the presence of excess phosphorus oxychloride (see scheme below).

The intermediates in this reaction are 4-hydroxy-7-dialkylaminocoumarins, which react with excess $POCl_3$ to give the final 4-chloro derivatives I-VII. This fact was confirmed by the reaction of m-diethylaminophenol with malonic acid; 4-hydroxy-7-diethylaminocoumarin [2] was isolated and identified from the reaction mixture, and upon further treatment with $POCl_3$ gave coumarin I.

The yields of compounds I-VII were in the 15-40% range (Table 1). In the case of the synthesis of coumarins I, V, and VII side products in the form of compounds VIII-X were also isolated from the reaction mixtures; these were formed in 10-15% yield as a result of condensation of the intermediate 4-hydroxycoumarins with a second molecule of malonic acid.

K. A. Timiryazev Moscow Agricultural Academy, Moscow.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 830-835, June, 1990. Original article submitted May 18, 1988.