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Reaction of Phenylmalonyl Dichloride with 3-Phenylpropynamide and Transformations of the Product by the Action of Some Nucleophiles

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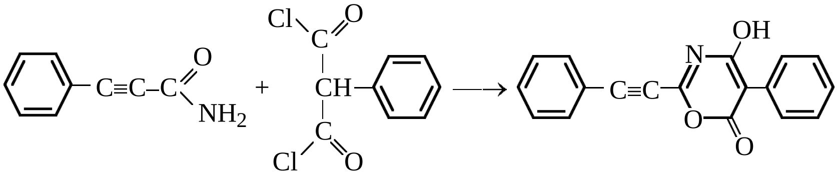
Abstract—Phenylmalonyl dichloride reacted with 3-phenylpropynamide to give 4-hydroxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one. Treatment of the latter with hydrazine afforded 3,5-disubstituted 1,2,4-triazole. Reactions of 4-hydroxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one with methanol and ethanol led to formation of the corresponding malonamic acid esters. The structure of the products was proved by the ^{1}H and ^{13}C NMR and IR spectra, quantum-chemical calculations (PM3, MNDO, MINDO3), and some chemical transformations.

Monosubstituted malonyl dichlorides are known to react with aromatic amides to give 5-substituted 2-aryl-4-hydroxy-6*H*-1,3-oxazin-6-ones in good yield [1–4]. We thought it reasonable to examine reactions of monosubstituted malonyl dichlorides with unsaturated carboxamides with a view to elucidate their direction and scope. Here we report on the reaction of phenyl malonyl dichloride with 3-phenylpropynamide (Scheme 1) and transformations of the product in reactions with some nucleophiles (Schemes 2, 3).

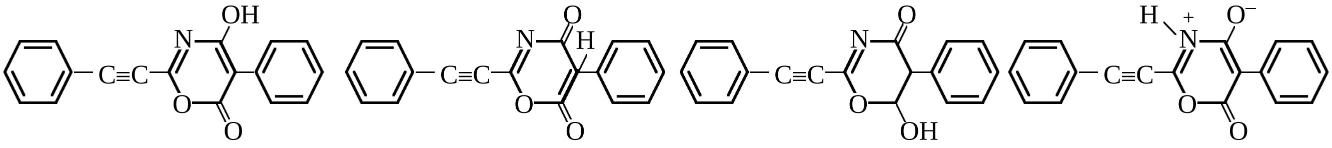
3-Phenylpropynamide (**I**) reacted with phenylmalonyl dichloride (**II**) in refluxing dichloroethane (reaction time 1 h) to afford 4-hydroxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one (**III**) in 73% yield (Scheme 1, Table 1).

Scheme 1.



I **II** **III**

Compound **III** can exist as four tautomers **A**–**D**. Semiempirical quantum-chemical calculations (PM3, MNDO, MINDO3; HyperChem 3.0 for Windows) of the electronic structure of possible tautomeric forms showed that the most energetically favorable tautomer of oxazine **III** is structure **A**. Below are given the energies of formation (kcal mol^{-1}) of tautomers **A**–**D**, calculated by the PM3, MNDO, and MINDO3 methods.



A **B** **C** **D**

Table 1. Yields, melting points, R_f values, and elemental analyses of compounds **III–VII**

Comp. no.	Yield, %	mp, °C	R_f^a	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
III	73	222–224	0.15	74.8	3.7	4.9	$C_{18}H_{11}NO_3$	74.8	3.8	4.8
IV	92	154–156	0.43	78.8	4.9	16.3	$C_{17}H_{13}N_3$	78.8	5.0	16.2
V	84	168–170	0.72	71.1	4.7	4.3	$C_{19}H_{15}NO_4$	71.0	4.7	4.4
VI	88	162–164	0.72	71.7	5.2	4.3	$C_{20}H_{17}NO_4$	71.7	5.1	4.2
VII	81	148–150	0.73	75.2	4.3	4.7	$C_{19}H_{13}NO_3$	75.3	4.3	4.6

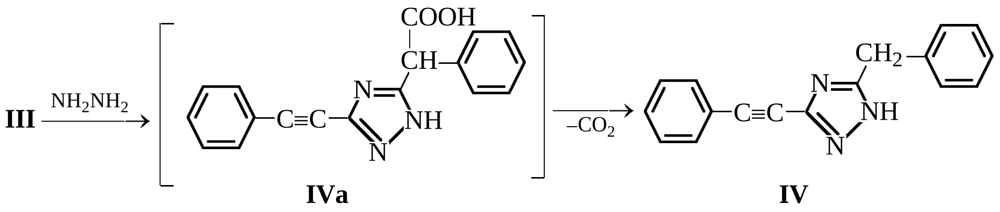
[a] Eluent ethyl acetate.

Tautomer	PM3	MNDO	MINDO3
A	13.1	–7.2	–54.6
B	13.6	–3.9	–54.1
C	20.7	2.1	–50.0
D	23.1	15.0	–48.4

The results of quantum-chemical calculations are confirmed by the spectral data. The ^{13}C NMR spectrum of 4-hydroxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one (**III**) in DMSO-d_6 contains signals corresponding to sp^2-hybridized carbon atoms in the benzene (δ_C 118.1–132.7 ppm) and oxazine rings (δ_C 97.2, 147.8, 160.0, 164.7 ppm) and *sp*-hybridized carbon atoms at the triple bond (δ_C 80.8 and 91.7 ppm). In the ^{1}H NMR spectrum we observed signals from aromatic protons (δ 7.36–7.73 ppm) and proton of the hydroxy group on C^4 (δ 13.40 ppm). Crystalline oxazine **III** displayed in the IR spectrum absorption bands at 1750 [ν(C=O)], 1600 [ν(C=C)], 1540 [ν(C=N)], and 2210 cm^{-1} [ν(C≡C)].

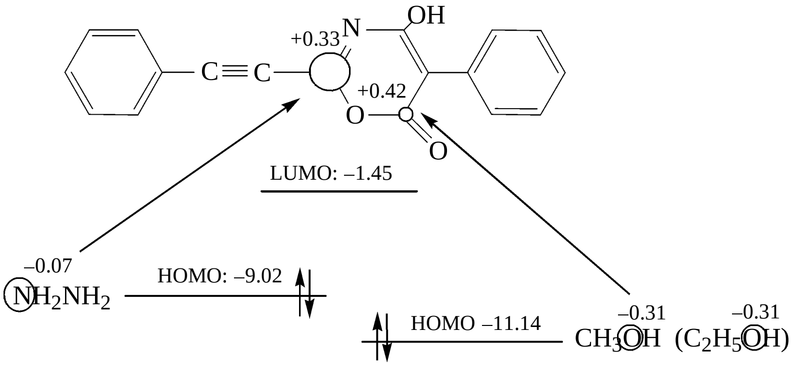
The reaction of oxazine **III** with hydrazine in methanol at 20–22°C (24 h) gave 92% of 5-benzyl-3-phenylethynyl-1,2,4-triazole (**IV**) (Scheme 2, Table 1) as a result of cleavage of the C^2–O bond in the initial oxazine. Presumably, unstable intermediate triazole **IVa** undergoes decarboxylation to final product **IV**. The structure of triazole **IV** was confirmed by ^{1}H NMR and IR spectroscopy.

Scheme 2.



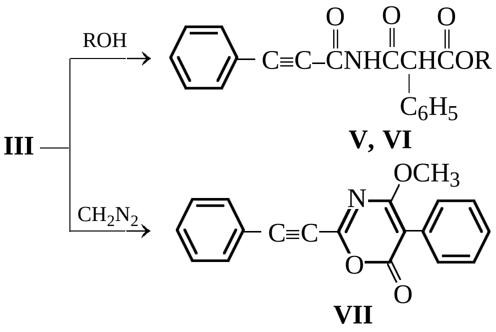
The ^{1}H NMR spectrum of **IV** in DMSO-d_6 contained signals from protons in the benzene rings (δ 7.30–7.49 ppm) and methylene protons (δ 3.80 ppm). In the IR spectrum of crystalline triazole **IV** absorption bands at 1570–1645 [ν(C=C)], 1600 [ν(C=N)], 3310 [ν(NH)], and 2220 cm^{-1} [ν(C≡C)] were present.

Treatment of 4-hydroxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one (**III**) with boiling methanol or ethanol in 0.5–1.0 h resulted in cleavage of the C^6–O bond in the oxazine ring with formation of the corresponding esters **V** and **VI** (yield 84 and 88%, respectively; Scheme 3, Table 1). The ^{13}C NMR spectra of compounds **V** and **VI** in DMSO-d_6 contained signals from sp^3-hybridized carbon atoms in the alkyl groups and PhCH group (δ_C 13.8–61.2 ppm), aromatic carbon atoms (δ_C 118.8–132.9 ppm), carbonyl carbon atoms (δ_C 151.6–168.5 ppm), and *sp*-hybridized carbon atoms at the triple bond (δ_C 82.8–89.3 ppm). In the ^{1}H NMR spectra of **V** and **VI**, aromatic proton signals appeared at δ 7.35–7.65 ppm, signal from the PhCH proton was located at δ 5.20–5.21 ppm, alkyl proton signals were present at δ 1.16–4.13 ppm, and the amide proton signal was observed at δ 11.86–11.89 ppm.



Scheme of interaction between 4-hydroxy-5-phenyl-2-phenylethynyl-6H-1,3-oxazin-6-one (**III**) with nucleophiles. Shaded circles denote contributions of the corresponding AOs to the LUMO of oxazine **III** and HOMO of hydrazine, methanol, and ethanol; and the numbers above the circles denote the charges of the corresponding atoms.

Scheme 3.



R = CH_3, C_2H_5.

By reaction of oxazine **III** with excess diazomethane in diethyl ether at 20–22°C (1 h) we obtained 4-methoxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one (**VII**) in 81% yield (Scheme 3, Table 1). Compound **VII** can be regarded as a model of tautomer **A**. The ^1H and ^{13}C NMR and IR spectra of **VII** were fully consistent with the corresponding data for initial oxazine **III**, except for signals belonging to the 4-methoxy group (δ 3.94 ppm, δ_C 55.8 ppm).

The direction of the reactions of oxazine **III** with hydrazine and alcohols conforms to the results of calculations of the electronic structure of the reagents, according to which the reaction of oxazine **III** with hydrazine is orbital-controlled while the reaction with methanol or ethanol is charge-controlled (see figure, Table 2). Scheme 4 illustrates the mechanisms of reactions of oxazine **III** with nucleophiles.

EXPERIMENTAL

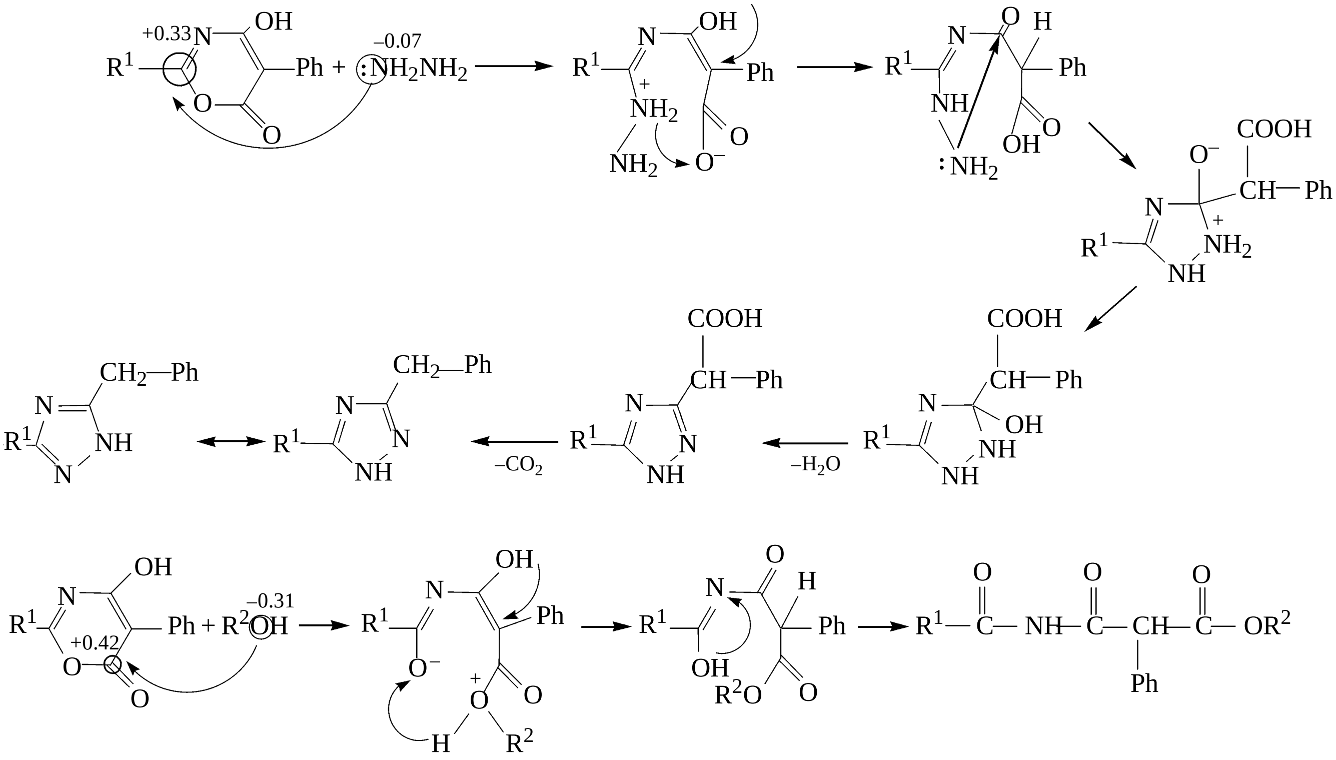
The IR spectra were recorded on a Specord IR-75 spectrometer from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-500 instrument from solutions in DMSO-d_6. The progress of reactions was monitored by thin-layer chromatography on Sorbfil plates using ethyl acetate as eluent.

4-Hydroxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one (III). A mixture of 2.90 g of 3-phenylpropynamide (**I**) and 4.77 g of phenylmalonyl dichloride (**II**) in 30 ml of dry 1,2-dichloroethane was heated for 1 h under reflux. The precipitate was fil-

Table 2. HOMO and LUMO energies, total charges (*q*) on the carbon atoms in the heteroring, and their orbital coefficients (*w*) in the LUMO of oxazine **III** and HOMO and LUMO energies, total charges of atoms (*q*), and their orbital coefficients (*w*) in the HOMO of nucleophiles, calculated by the PM3 method

Compound	*E*, eV		*q*				*w*			
	HOMO	LUMO	C^2	C^4	C^6	Nu	C^2	C^4	C^6	Nu
Oxazine **III**	–8.77	–1.45	0.33	0.20	0.42	–	–0.49	0.32	–0.05	–
Hydrazine	–9.02	2.76	–	–	–	–0.07	–	–	–	–0.26
Methanol	–11.14	3.51	–	–	–	–0.31	–	–	–	–0.19
Ethanol	–11.13	3.36	–	–	–	–0.31	–	–	–	–0.10

Scheme 4.



tered off, washed with dichloroethane, and dried. Yield 4.22 g.

5-Benzyl-3-phenylethynyl-1,2,4-triazole (IV). A mixture of 0.29 g of 4-hydroxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one (**III**) and 0.03 g of hydrazine in 20 ml of methanol was stirred for 24 h at room temperature using a magnetic stirrer. The precipitate was filtered off, washed with methanol, and dried. Yield 0.24 g.

Methyl 3-oxo-2-phenyl-3-(phenylpropynoylamino)propionate (V). A mixture of 0.29 g of 4-hydroxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one (**III**) in 20 ml of methanol was heated for 0.5 h under reflux. The precipitate was filtered off, washed with methanol, and dried. Yield 0.27 g.

Ethyl 3-oxo-2-phenyl-3-(phenylpropynoylamino)propionate (VI). A mixture of 0.29 g of 4-hydroxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one (**III**) in 20 ml of anhydrous ethanol was heated for 1 h under reflux. The precipitate was filtered off, washed with methanol, and dried. Yield 0.29 g.

4-Methoxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one (VII). A mixture of 0.29 g of 4-hydroxy-5-phenyl-2-phenylethynyl-6*H*-1,3-oxazin-6-one (**III**) and excess diazomethane in 20 ml of diethyl ether was stirred for 1 h at room temperature using a magnetic stirrer. The precipitate was filtered off, washed with methanol, and dried. Yield 0.25 g.

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