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Dedicated to the memory of the teacher,
Professor Boris S. Drach

Reaction of 2-Acylamino-3,3-dichloroacrylonitriles with 2-Aminothiophenol

O. V. Shablykin, S. A. Chumachenko, and V. S. Brovarets

Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine,
ul. Murmanskaya 1, Kiev-94, 02660, Ukraine
e-mail: brovarets@bpci.kiev.ua

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Abstract—Reactions of 2-acylamino-3,3-dichloroacrylonitriles with 2-aminothiophenol in the presence of triethylamine was shown to lead to 2-aryl-3,3-bis(2-aminophenylsulfanyl)acrylonitrile, which suffered a transformation into 5-amino-4-(benzothiazol-2-yl)oxazole derivatives at heating without solvent. The formation of the same compounds from these reagents proceeded in one step in the presence of *N*,*N*-dimethylaniline. The presence of primary amino groups in the derivatives of 5-aminooxazole was confirmed by acylation and further transformation, which was used also for indroduction of various biophoric sites in 5 position of the oxazole ring.

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Substitution of chlorine atoms in 2-acylamino-3,3-dichloroacrylonitriles (**I**) by nitrogen- and sulfur-containing nucleophiles is of stable interest, because such reactions can be used for producing a variety of functionalized heterocycles [1–5].

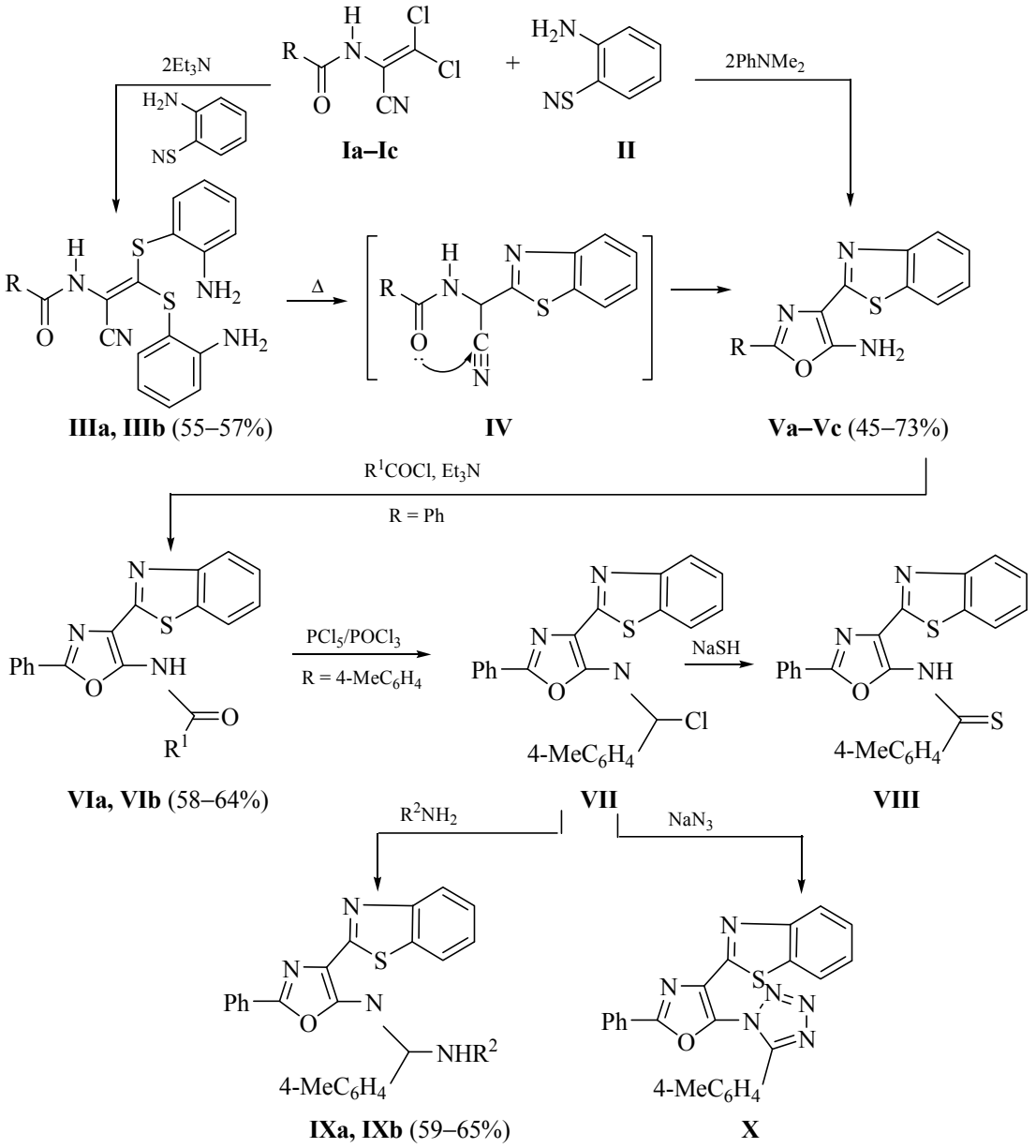
We have investigated the reaction of 2-acylamino-3,3-dichloroacrylonitriles **I** with 2-aminothiophenol (**II**) (Scheme 1). It should be noted that depending on the used base the difference exists in the nature of interaction of reagents. Thus, in the case of triethylamine, the reaction proceeds rapidly and leads to acyclic products **III** formed by the replacement of two labile chlorine atoms in the reagents **I** with two 2-aminothiophenol residues. But under the influence of a weak base, *N*,*N*-dimethylaniline, the condensation is slow and leads to substituted oxazoles **V**.

The question arose about the influence of the base on the mechanism of interaction of the reagents **I** and **II**. At first glance it seems that at the early stages of the process different intermediates, **A** and **B**, can be generated leading to different final compounds, **III** and **V**, respectively (Scheme 2).

However, it is unlikely that the *hard* N-nucleophile interacts with the *soft* center, the dichlorovinyl group, faster than the *soft* S-nucleophile, even in the presence of a weak base. It is logical to assume that the first stage of the process leads to the same adduct **B** regardless of the nature of base. The intermediate **B** is then transformed differently then the used base is weak or strong (Scheme 3).

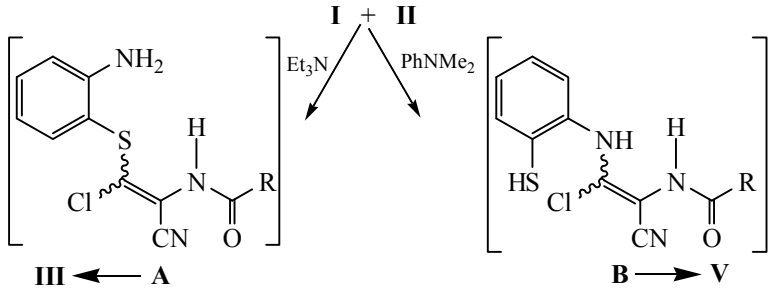
There is no doubts in the high lability of the chlorine atoms in the structure **B:** firstly, the α-effect operates, as in many other α-halosulfides, and secondly, the chlorine atoms are additionally activated by the acceptor nitrile group. Therefore, in the presence of a weak base obviously an intramolecular cyclization occurs with further elimination of hydrogen chloride, which is advantageous because it facilitates the formation of aromatic thiazole ring: **B** → **D**. On the other hand, at the action on **B** of a strong base a rapid splitting a hydrogen chloride may proceed even in the early stages of the process. This results in an inert enamide structure **D** with the hardly labile chlorine atom that has been proved experimentally for many types of the enamidonitriles ArSCCl=C(CN)NHCOR, which do not interact even with highly basic amines. Although it seems that all these facts confirm the possible mechanism of formation of the final products in the complex process **I** + **II** → **V**, yet it must be

Scheme 1.

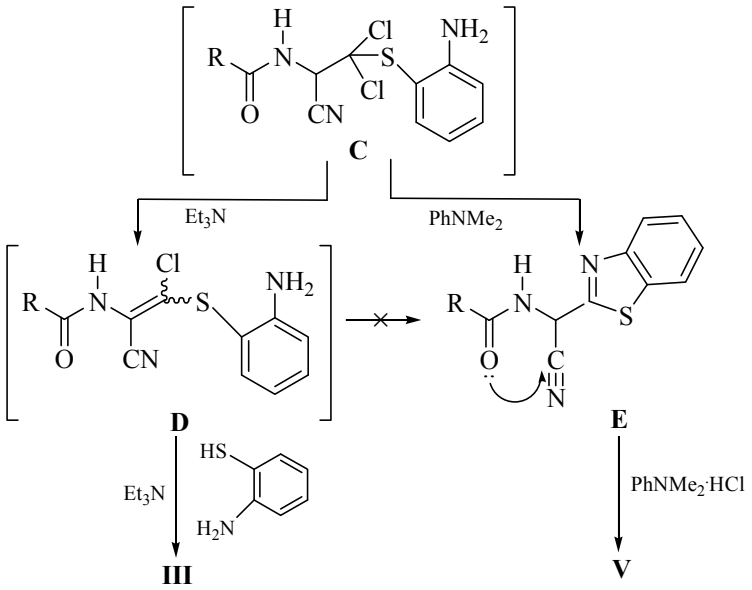


I, V: R = Me (**a**), Ph (**b**), 4-MeC_6H_4 (**c**); **III**: R = Ph (**a**), 4-MeC_6H_4 (**b**); **IV**: R^1 = Me (**a**), 4-MeC_6H_4 (**b**); **IX**: R^2 = H (**a**), Me (**b**).

Scheme 2.



Scheme 3.



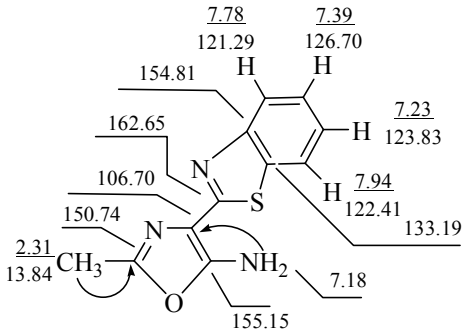
recognized that for the unequivocal evidence further special studies are needed. Nevertheless, the structure of new 5-amino-1,3-oxazole derivatives **V** was reliably proven using a complex of spectral and chemical studies. For example, it was found using infrared spectra that in this cyclocondensation nitrile and acylamine residues participated (Table 2). A complex study by the methods of the ^{1}H and ^{13}C NMR correlation spectroscopy (COSY, NOESY, HMQC and HMBC) was carried out with one of these compounds (**Va**), and characteristic signals in the ^{13}C NMR spectra and the main correlations confirming the proposed structure were found (see the figure).

Products **Vb** and **Vc** were synthesized also by authentic procedure, at heating the compounds **IIIa** and **IIIb**, respectively, at 150°C in a vacuum (20 mm Hg). In this case, in the first stage the cyclization is likely to occur to the substituted benzothiazole **IV** with liberation of the 2-aminothiophenol molecule, by analogy with the published data [6]. Then proceeds a known intramolecular cyclization [7–9] involing the amide fragment and the nitrile group which leads to the 5-aminooxazole derivatives **V**.

The presence of primary amino groups in compounds **V** was evidenced not only by the ^{1}H NMR spectra, but also by acylation and further reaction of compound **VIb** with phosphorus pentachloride, which led to the expected imidoyl chloride **VII**. Based on the last reaction we succeeded to carry out condensations with sodium hydrogen sulfide, ammonia, methylamine, and sodium azide. These reactions are important not only to prove the structure of the key compounds **V**, but are also of considerable preparative interest for the introduction of various biophoric sites to the 5 position of the oxazole ring (compounds **VIII–X**, Scheme 1).

EXPERIMENTAL

IR spectra of the compounds were recorded on a Vertex 70 spectrometer from the tablets with KBr. The ^{1}H NMR spectra were recorded on a Varian-300 instrument (300 MHz), the NMR spectra of heteronuclear ^{1}H–^{13}C correlation were obtained on a Mercury-400 spectrometer (400 and 100 MHz respectively) from solutions in DMSO-d_6 with TMS as an internal reference. The melting points were measured on a Fisher–Johns unit.



Principal correlations (shown by arrows) and assignment of signals (ppm) in the ^{1}H and ^{13}C NMR spectra of compound **Va.**

Table 1. Spectral data of synthesized compounds

Comp. no.	IR spectrum (KBr), ν, cm^{-1}	^{1}HNMR spectrum (DMSO-d_6), δ, ppm
IIIa	2210 (C≡N), 3100–3600 (NH as.)	4.89 s (2H, NH_2), 5.39 s (2H, NH_2), 6.32–7.89 m (13H, C_6H_5, 2 C_6H_4), 10.18 s (1H, NH)
IIIb	2210 (C≡N), 3100–3600 (NH as.)	2.38 s (3H, CH_3), 5.00 s (2H, NH_2), 5.44 s (2H, NH_2), 6.42–7.80 m (12H, $3C_6H_4$), 10.14 s (1H, NH)
Va	1645 [δ(NH_2)], 2100–2300 (no bands), 3150, 3240 (NH_2)	2.35 s (3H, CH_3), 7.06 br.s (2H, NH_2), 7.19–7.90 m (4H, C_6H_4)
Vb	1650 [δ(NH_2)], 2100–2300 (no bands), 3160, 3250 (NH_2)	7.31–8.02 m (9H, C_6H_5, C_6H_4), 7.64 br.s (2H, NH_2)
Vc	1650 [δ(NH_2)], 2100–2300 (no bands), 3170, 3255 (NH_2)	2.37 s (3H, CH_3), 7.27–7.77 m (8H, $2C_6H_4$), 7.59 br.s (2H, NH_2)
VIa	3100–3600 (NH as.)	2.43 s (3H, CH_3), 7.42–8.20 m (9H, C_6H_5, C_6H_4), 11.82 s (1H, NH)
VIb	3180–3550 (NH as.)	2.45 s (3H, CH_3), 7.39–8.10 m (13H, C_6H_5, $2C_6H_4$), 11.06 s (1H, NH)
VIII	3200–3500 (NH as.)	2.41 s (3H, CH_3), 7.39–8.20 m (13H, C_6H_5, $2C_6H_4$), 12.36 s (1H, NH)
IXa	3100–3500 (NH as.)	2.42 s (3H, CH_3), 7.39–8.42 m (13H, C_6H_5, $2C_6H_4$), 7.82 br.s (1H, NH), 8.45 br.s (1H, NH)
IXb	3200–3400 (NH as.)	2.30 s (3H, CH_3), 3.56 s (3H, CH_3), 7.08–8.11 m (13H, C_6H_5, $2C_6H_4$), 7.82 br.s (1H, NH), 8.83 br.s (1H, NH)
X	2100–2300, 3000–3500 (no bands)	2.42 s (3H, CH_3), 7.18–8.33 m (13H, C_6H_5, $2C_6H_4$)

Table 2. Yields, melting points, and data of elemental analysis of compounds **III, V–X**

Comp. no.	Yield, %	mp, °C	Found, %		Formula	Calculated, %	
			N	S		N	S
IIIa	57	167–168	13.12	15.05	$C_{22}H_{18}N_4OS_2$	13.39	15.32
IIIb	55	111–112	12.81	14.59	$C_{23}H_{20}N_4OS_2$	12.95	14.82
Va	45	173–174	18.03	13.71	$C_{11}H_9N_3OS$	18.17	13.86
Vb	68[a]	243–244	14.09	10.57	$C_{16}H_{11}N_3OS$	14.32	10.93
Vc	73[a]	251–252	13.65	10.25	$C_{17}H_{13}N_3OS$	13.67	10.43
VIa	58	175–177	12.39	9.63	$C_{18}H_{13}N_3O_2S$	12.53	9.56
VIb	64	237–238	10.09	7.62	$C_{24}H_{17}N_3O_2S$	10.21	7.79
VII	95	227–228	9.61	7.13	$C_{24}H_{16}ClN_3OS$[b]	9.77	7.46
VIII	45	215 (decomp.)	9.75	14.92	$C_{24}H_{17}N_3OS_2$	9.83	15.00
IXa	65	144–145	13.44	7.61	$C_{24}H_{18}N_4OS$	13.65	7.81
IXb	59	230–231	13.03	7.58	$C_{25}H_{20}N_4OS$	13.20	7.55
X	86	170 (decomp.)	18.99	7.07	$C_{24}H_{16}N_6OS$	19.25	7.35

[a] By method *a*. [b] Found,%: Cl 8.39. Calculated,%: Cl 8.25.

2-Acylamino-3,3-bis(2-aminophenylsulfanyl)acrylonitrile (IIIa, IIIb). To a mixture of 0.02 mol of 2-aminothiophenol and 0.025 mol of *N*,*N*-dimethylaniline in 20 ml of dimethylformamide was added at 0–10°C a solution of 0.01 mol of compound **Ib** or **Ic** in 20 ml of tetrahydrofuran. The mixture was stirred for 12 h at 20–30°C, the solvent was removed in a vacuum, the residue was treated with 10 ml of aqueous ethanol (1:1), the precipitate was filtered off, washed with water, and compounds **IIIa, IIIb** were purified by crystallization from ethanol.

2-Alkyl(aryl)-5-amino-4-(benzothiazol-2-yl)-1,3-oxazole (Va–Vc). *a*. To a solution of 0.01 mol of a compound **Ia–Ic** in 20 ml of ethanol was added 0.02 mol of 2-aminothiophenol and 0.025 mol of *N*,*N*-dimethylaniline, the mixture was stirred for 2 weeks at 20–30°C, the precipitate was filtered off, washed with water and cold ethanol, and then compound **Va–Vc** formed was purified by crystallization from acetonitrile.

b. 0.01 mol of compound **IIIa** or **IIIb** was heated in a vacuum (20 mm Hg) at 150°C till the evolution of 2-aminothiophenol ceased. Then the melt was cooled, ground in ethanol, and filtered. Compounds **Vb, Vc** were purified by crystallization from acetonitrile, yield 46–55%. The mixed samples of compounds **Vb** or **Vc** obtained by different methods did not give depression of the melting point; IR and ^{1}H NMR spectra of the respective samples were identical.

5-Acylamino-4-(benzothiazol-2-yl)-2-phenyl-1,3-oxazole (VIa, VIb). To a suspension of 0.01 mol of compound **Vb** in 10 ml of pyridine was added 0.011 mol of acetyl or 4-toluyl chloride, the reaction mixture was refluxed for 4 h, cooled, and 20 ml of water was added to it. The precipitate formed was filtered off, washed with 5 ml of diethyl ether, and compound **VIa** or **VIb** obtained was purified by crystallization from ethanol.

***N*-[4-(Benzothiazol-2-yl)-2-phenyloxazol-5-yl]-4-methylbenzimidoyl chloride (VII)**. To a solution of 0.01 mol of phosphorus pentachloride in 10 ml of phosphorus oxychloride was added 0.01 mol of amide **VIb**, the mixture was refluxed for 4 h, cooled to 20°C, 0.1 ml of acetone was added, and the mixture was stirred at 20°C for 1h. Then the solvent was removed in a vacuum, to the residue was added diethyl ether, and the precipitate formed was filtered off, dried in a vacuum (1 mm Hg) at 70°C, and compound **VII** obtained was used for further syntheses without additional purification.

***N*-[4-(Benzothiazol-2-yl)-2-phenyloxazol-5-yl]-4-methylthiobenzamide (VIII)**. To a suspension of 0.01 mol of compound **VII** in 20 ml of acetonitrile was added 0.025 mol of sodium hydrogen sulfide, the mixture was stirred for 3 h, then 20 ml of water was added, and the precipitate formed was filtered off. Compound **VIII** obtained was purified by crystallization from ethanol.

***N*-[4-(Benzothiazol-2-yl)-2-phenyloxazol-5-yl]-4-methylbenzamidine (IXa, IXb)**. Through a suspension of 0.01 mol of compound **VII** in 20 ml of anhydrous ethanol at 20–25°C ammonia or methylamine was passed for 30 min. The solvent was then removed in a vacuum, the residue was treated with water, the precipitate formed was filtered off, and compound **IXa** or **IXb** was purified by crystallization from aqueous ethanol (1:1).

4-(Benzothiazol-2-yl)-5-[5-(4-methylphenyl)tetrazol-1-yl]-2-phenyl-1,3-oxazole (X). To a suspension of 0.01 mole of compound **VII** in 20 ml of acetonitrile was added 0.03 mol of sodium azide, the mixture was stirred at 20–25°C for 48 h, the precipitate formed was filtered off and washed with water. Compound **X** was purified by crystallization from ethanol.

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