TRANSFORMATION OF 2,4,6-TRIARYLVERDAZYLS INTO 1,2,4-TRIAZOLE DERIVATIVES BY THE ACTION OF BROMOCYANOMETHANES

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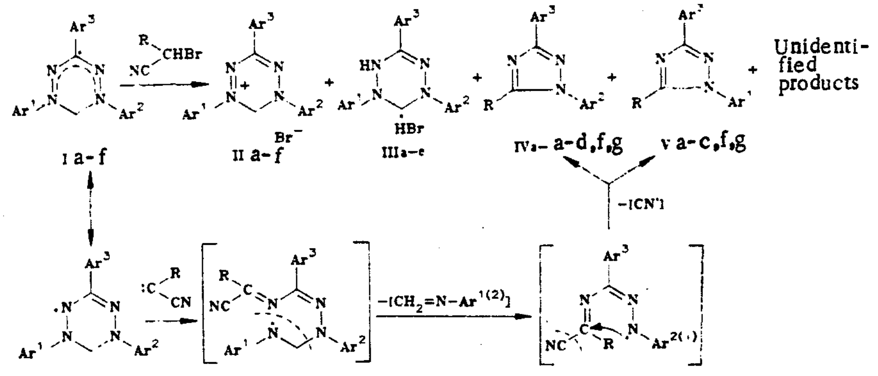
The reaction between 2,4,6-triarylverdazyls and bromocyanomethanes was studied from the preparative and kinetic aspects. A possible reaction mechanism is discussed. New 1,3,5-triarylsubstituted 1,2,4-triazoles were obtained.

Transformations of stable verdazyl radicals into derivatives of 1,2,4-triazole are known [1]. It was shown in [2] that the fragmentation of 1,2,4-triazoles in the mass spectrometer proceeds through the stage of formation of the diaziridine cation-radical. Therefore, we have previously [3, 4] assumed that in the reaction of 2,4,6-triphenylverdazyl with dicyano- and cyanoethoxycarbonylbromomethanes, the corresponding diaziridines are formed. The main support for this supposition was the presence in the mass spectrometer of molecular ions and the characteristic fragment with m/z 194. However, the alkaline and hydrochloric acid hydrolysis of the compounds obtained led to the known 1,3-diphenyl-1,2,4-triazole. Hence, it can be concluded that cyanomethanes with geminal hydrogen atoms and bromine cause the fragmentation of 2,4,6-triphenylverdazyl to 5-substituted derivatives of 1,3-diphenyl-1,2,4-triazoles and not to diaziridines.

To clarify the characteristic patterns of fragmentation of verdazyls, we studied systems in which the reagents and substrates contain various substituents. In the present article, we obtained the products of the reaction of dicyano- and cyanoethoxycarbonylbromomethanes with 2,4,6-triarylverdazyl radicals Ia-f. We found that in the reaction, 1,3,5- trisubtituted 1,2,4-triazoles IV, V are formed (see scheme, Tables 1 and 2) and also the known 2,4,6-triarylverdazylium bromides II and the hydrobromide salts of 2,4,6-triarylleucoverdazyl III.



I—III a $Ar^1=Ar^2=C_6H_5$, $Ar^3=C_6H_4OCH_3$-*p*; b $Ar^1=Ar^2=C_6H_4OCH_3$-*p*, $Ar^3=C_6H_5$; c $Ar^1=Ar^2=Ar^3=C_6H_4OCH_3$-*p*; d $Ar^1=C_6H_4OCH_3$-*p*, $Ar^2=Ar^3=C_6H_5$; e $Ar^1=Ar^3=C_6H_4OCH_3$-*p*, $Ar^2=C_6H_5$; f $Ar^1=Ar^2=C_6H_5$, $Ar^3=C_6H_4NO_2$-*p*; IV*, V a $Ar^1=Ar^2=C_6H_5$, $Ar^3=C_6H_4OCH_3$-*p*; b $Ar^1=Ar^2=C_6H_4OCH_3$-*p*, $Ar^3=C_6H_5$; c $Ar^1=Ar^2=Ar^3=C_6H_4OCH_3$-*p*; d $Ar^2=Ar^3=C_6H_5$; f,g $Ar^1=Ar^2=C_6H_5$, $Ar^3=C_6H_4NO_2$-*p*; a-d,f e R=CN, g $R=CO_2C_2H_5$. Yield : II a-d — 50%, II f — 28%, III a-e — 20%, III f — 22%

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*Compound IVd was obtained in [3] and was studied previously in [6].

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TABLE 1. Fragmentation Products of 2,4,6-Triarylverdazyls Ia-f by the Action of Cyanocarbenes

Experiment	Compound	1,2,4-Triazole	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
				C	H	N		C	H	N	
1	Ia	IV a	132	69,6	4,4	20,3	$C_{16}H_{12}N_4O$	69,5	4,4	20,3	29
2	Ib	IV b	109	69.8	4,5	20,3	$C_{16}H_{12}N_4O$	69,5	4,4	20,3	33
3	Ic	IV c	158	66,8	4,6	18,2	$C_{17}H_{14}N_4O$	66,7	4,6	18,3	34
4	Id	IV d	100								23
		V b	109								7
5	Ie	IVc	158								6
		Va	132								24
6	If	IVf	181	61,2	3,1	24,0	$C_{15}H_9N_5O_2$	61,3	3,1	24,0	50
7	If	IV g	162	60,3	4,2	16,6	$C_{17}H_{14}N_4O_4$	59,5	4,2	16,6	50

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*In percent of the amount of 2,4,6-triarylverdazyl used in the reaction.

TABLE 2. Spectral Characteristics of 1,3-Diaryl-5R-1,2,4-triazoles IV

Compound	IR spectrum, cm^{-1} (KBr)	UV spectrum*, λ_{max}, nm (log ε)	PMR spectrum (acetone-D_4), ppm (HMDS)	Mass spectrum**, m/z (%)
IV a	760, 840, 1470, 1480, 1500, 1620, 1050—1260 (C—O—C), 2250 (C≡N), 2840 (CH, OCH_3)	262 (4,55), 303 sh	3,82 (3H, s, OCH_3); 7,02 (2H, d, J=8,8*** Hz, 3-Ar); 7,63 (3H, m, 1-Ar); 7,86 (2H, m, 1-Ar); 8,03 (2H, d, J=8,8 Hz., 3-Ar)	276 (100), 261 (10,5), 121 (8), 105 (26,3), 91 (52,6), 77 (26,3), 64 (15,8)
IV b	730, 830, 1450, 1520, 1610, 1030—1260 (C—O—C), 2250 (C≡N), 2850 (CH, OCH_3)	250 (4,35), 296 sh	3,86 (3H, s, OCH_3); 7,22 (2H, d, J=8,8 Hz, 1-Ar); 7,46 (3H, m, 3-Ar); 7,83 (2H, d, J=8,8 Hz., 1-Ar); 8,14 (2H, m, 3-Ar)	276 (100), 261 (1,5), 121 (77), 91 (7,7)
IV c	760, 830, 1460, 1480, 1520, 1610, 1040—1260 (C—O—C), 2250 (C≡N), 2840 (CH, OCH_3)	266 (4,49), 306 sh	3,89 (3H, s, OCH_3); 3,94 (3H, s, OCH_3); 7,02 (2H, d J=8,8 Hz, 3-Ar); 7,23 (2H, d, J=8,8 Hz, 1-Ar); 8,08 (2H, d, J=8,8 Hz., 3-Ar)	306 (100), 291, 275, 263, 239, 167, 149, 127, 121****
IV d	730, 760, 1120, 1170, 1440, 1480, 1500, 1590, 2255 (C≡N)	248 (4,29), 293 sh	7,50 (3H, m, 3-Ar); 7,68 (3H, m, 1-Ar); 7,88 (2H, m, 1-Ar); 8,10 (2H, m, 3-Ar)	246 (67), 194 (18), 91 (100)
IV f	730, 860, 1110, 1610, 1350—1530, (NO_2), 2250 (C≡N)	294 (4,39)	7,65 (3H, m, 1-Ar); 7,88 (2H, m, 1-Ar); 8,32 (4H, s, 3-Ar)	291 (40), 245 (10), 181 (18), 167 (30), 149 (100), 91 (80), 77 (62), 64 (33)
IV g	730, 1150, 1240, 1500, 1600, 1350—1530 (NO_2), 1730 (C=O)	299 (4,33)	1,18 (3H, t, J=7,5 Hz, CH_3); 4,26 (2H, q, J=7,5 Hz, CH_2); 7,56 (5H, m, 1-Ar); 8,32 (4H, s, 1-Ar)	338 (100), 309 (10), 293 (13), 239 (13), 180 (8), 132 (18), 118 (64), 91 (59)

*The UV spectra of compounds IVa, b, g were obtained in acetonitrile; IVc, f — in ethanol; and IVd — in n-hexane.

**The differences between the mass spectra of compounds IVa-c, f, g and the data in [2] are probably due to the initial splitting of groups in the aryl substituents.

***The signals of the ortho- and meta-protons in the paramethoxy-substituted rings (the AA'BB' spin system) can be considered as doublets, if the low-intensity components are neglected.

****The peak intensity of all ions is less than 5% of maximal.

We believe that the fragmentation process of 2,4,6-triarylverdazyl I to triazoles IV, V involves the reaction of the initial radical with the electrophilic carbene, which is possibly formed as an intermediate particle under the influence of the second molecule of verdazyl [4]. The ability of dicyanobromomethane to give carbene in the presence of bases has been described in [5]. Verdazyls are fairly strong bases in reactions with acids [1], and therefore salts II and III can be regarded as disproportionation products of the radicals by the action of hydrogen bromide. The unequal yield of these salts is due to the nature of the substituent in triarylverdazyl and is explained by a secondary reaction of the electrophilic carbene formed with salt III. For salt II, a known electrophile [1], this reaction is not very probable. In this case, when the salt is kinetically destabilized by electron-acceptor substituents, the ratio of products II and III approaches unity. Thus, in experiments 6 and 7 (Table 1), 28% of II and 22% of III were isolated. The presence of fragment R-$C_{(5)}$ in the heterocyclic ring of triazoles IV, V, also confirms indirectly the formation of an intermediate carbene in the reaction studied.

It is known [1] that verdazyls are fairly strong electron donors, and in the reactions with electrophiles, the most probable reaction centers are the $N_{(1)}$ or $N_{(5)}$ atoms, carrying the highest negative charge and the largest fraction of the unpaired electrons. A similar reaction mechanism is possibly also realized in the reaction of 2,4,6-triarylverdazyl radical with the electrophilic carbene at the $N_{(1)}$ or $N_{(5)}$ atoms of the tetrazine ring, which further leads to splitting of the $N_{(1)}$—$N_{(2)}$ bond, followed by intramolecular cyclization and elimination. This scheme is confirmed by the fact that in the case of radicals Id and Ie, in which $Ar^1 \neq Ar^2$, the formation of a mixture of two triazoles IV and V with different substituents at the $C_{(3)}$ and $N_{(1)}$ atoms of the heterocyclic ring is observed in all cases (see experiments 4, 5, Table 1). The ratio of the yields of the fragmentation products in experiments 4 and 5 also agrees with the proposed scheme. In fact, the fragment with the para-methoxy-substituted phenyl is eliminated most easily, and in the reaction with verdazyl Ie mostly Va is formed, while in the case of verdazyl Id, it is triazole IVd. It is probable that the $N_{(1)}$—$N_{(2)}$ bond in 2,4,6-triarylverdazyl radicals with donor substituents at the para-position of the phenyl at $N_{(2)}$ is weaker compared with the unsubstituted aryl.

According to the data of the quantum chemical investigation of the influence of the nature of the substituents on the physicochemical properties of 1,2,3,4-tetrahydro-sym-tetrazines, a decrease of 1 eV in the electronegativity of the substituent at the $N_{(2)}$ atom (corresponding to the introduction of a donor substituent, see [7]) leads to decrease in the strength of the $N_{(1)}$—$N_{(2)}$ bond in verdazyl by 11.37 kJ/mole. For the $N_{(4)}$—$N_{(5)}$ bond this value is not more than 0.86 kJ/mole. The acceptor substituents have an opposite effect, but to a somewhat higher degree (12.22 and 0.88 kJ/mole, respectively).*

2,4,6-Triarylverdazyls Ia–e react with the substrates used practically instantaneously, and therefore the slower reaction with verdazyl If was studied kinetically. The rate of the reaction was monitored from the change in the optical density of radical If [$(20\text{-}50 \cdot 10^{-2}$ mmole/liter] at λ_{max} 740 nm (ε 3270) in a 1:1 benzene–nitrobenzene mixture at 20°C. The reaction is described by a kinetic equation of the second order. The rate constants k_2 of the reaction with dicyanobromomethane [$(26\text{-}69) \cdot 10^{-2}$ mmole/liter] and cyanoethoxycarbonylbromomethane [$(10\text{-}35) \cdot 10^{-1}$ mmole/liter] are (1.97 ± 0.02) and $(1.87 \pm 0.06) \cdot 10^{-2}$ liter/mole·sec, respectively. The lack of correlation of the order of the reaction with the molecularity indicates a multistage and complex process. It is probable that at the first stage radical I reacts with the substrate, forming an adduct, which decomposes by the action of a second molecule of the radical at the second stage. While decomposing, it forms a mixture of hydrobromide salt of base III with the quaternary triarylverdazlium salt II. The thus generated carbene, as the result of its reaction with the tetrazine ring of the radical, leads to the formation of 1,3,5-substituted 1,2,4-triazoles. This reaction may perhaps be suggested as a method for synthesis under mild conditions of the above triazoles with cyano and ethoxycarbonyl groups at the 5-position, for which there are at present no fairly convenient methods of synthesis.

EXPERIMENTAL

The UV spectra were run on a Specord UV-VIS spectrophotometer, the IR spectra on a UR-20 spectrophotometer, the PMR spectra on a WP-200 (Bruker) spectrometer, and the mass spectrum on a MS-1302 mass spectrometer.

The products were purified by crystallization, and the purity was controlled by TLC. The solvents (acetone, acetonitrile, benzene, nitrobenzene, hexane, ethanol) were purified before use by known methods [10]).

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*The changes in the values of charges on the $N_{(1)}$ and $N_{(5)}$ atoms of the verdazyl radical in the presence of substitutents are inappreciable, while the influence of the corresponding spin characteristics corresponds qualitatively to the effects caused by differences in the strength of the N–N bonds.

The preparative experiments were carried out by the method described below. A 1-mmole portion of 2,4,6-triarylverdazyl [1] and 1 mmole of dicyanobromomethane [8] or cyanoethoxycarbonylbromomethane are mixed together in 25 ml of benzene. On the following day the precipitated mixture of salts is filtered, dried, and analyzed for the content of salt II (λ_{max}, ε [1]), and also for the total bromide ion content. From this, the amount of the hydrobromide salt of III is found. The filtrate is evaporated to a minimal volume and the mixture of compounds (see Table 1, experiments 4, 5) is separated in a thin layer of Silpearl brand silica gel, with elution by benzene (development in UV light). The reaction product is washed with acetonitrile. After the evaporation of solvent, the residue is crystallized from ethanol.

In experiments 1, 2, 3, 6, and 7 (Table 1), the filtrate is evaporated to dryness in an aspirator, and the fragmentation product is extracted from the residue by multiple extraction by a 3:1 hexane—benzene mixture.

Since verdazyl If is slightly soluble in benzene, the preparative experiments were carried out in its mixture with acetonitrile (1:2).

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SYNTHESIS OF SUBSTITUTED 5-DIETHOXYMETHYL-5-ETHYLOXAZOLIDINES

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Mixtures of stereoisomeric 2-diethoxymethyl-5-ethyloxazolidines with one of the stereoisomeric forms predominating were obtained by the reaction of 2-ethyl-2-formyloxirane diethyl acetal with alkyl-substituted Schiff bases in ethanol solution.

Oxazolidines can be obtained in a low yield by the reaction of Schiff bases with alkyl-substituted oxiranes in the presence of Lewis acids [1]. It was of interest to study the reaction of Schiff bases with 2-ethyl-2-formyloxirane acetal [2], to try to carry out by this path the synthesis of oxazolidines containing an acetal grouping, and also to study the regiodirectivity and stereoselectivity of the course of these reactions.

It was found that the reaction of 2-ethyl-2-formyloxirane diethyl acetal (I) on heating with alkyl-substituted Schiff bases IIa-h in ethanol solution in all cases proceeds regioselectively and leads to the formation of oxazolidines IIIa-h (Table 1). The ratio of the stereoisomeric forms thus varies according to the data of the PMR spectra within 4:1-5:1.

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