PHASE-TRANSFER CATALYZED ALKYLATION OF PYRAZOLES AND 1,2,4-TRIAZOLE WITH cis- AND trans-1,4-DICHLORO-2-BUTENES

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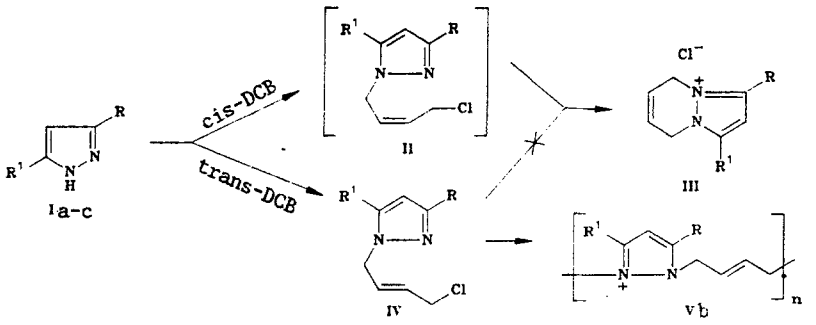
634:542.971.3:543.422

The phase-transfer catalyzed (PTC) alkylation of pyrazoles and 1,2,4-triazole with cis- and trans-1,4-dichloro-2-butenes (DCB) has been examined. The monoalkylation products of pyrazoles with cis-DCB are bicyclic salts formed by intramolecular cyclization of the intermediate cis-1-(4-chloro-2-butenyl)pyrazoles. The corresponding trans-compounds are incapable of cyclization, but on prolonged standing they undergo intermolecular polyquaternization. Both cis- and trans-DCB undergo phase-transfer catalyzed reaction with 1,2,4-triazole to give polymeric quaternary salts. Conditions have been worked out for the dehydrochlorination of 1-(4-chloro-2-butenyl)azoles to 1-(butadien-2-yl)azoles.

We have previously described a method for the alkylation of azoles with functionally-substituted alkyl halides [1]. We have now examined the phase-transfer catalyzed reactions of pyrazoles (Ia-c) and 1,2,4-triazole (VIII) with cis- and trans-DCB in order to obtain the novel 1-(buta-1,3-dienyl)azole monomers.

It has been found that in a catalytic two-phase liquid–liquid system, reaction of pyrazoles with cis- and trans-DCB in the presence of triethylbenzylammonium chloride (TEBAC) in the absence of a solvent gives, depending on the reactant ratios, either mono- or bis-alkylation products. For instance, under monoalkylation conditions (a fourfold molar amount of DCB), the products of the reaction of pyrazoles (Ia-c) with cis-DCB are the 5,8-dihydropyrazolo[1,2-a]-9-pyridazinium salts (IIIa-c), formed by intramolecular cyclization of the intermediate 1-cis-pyrazoles (II) at $N_{(2)}$. Alkylation with trans-CDB, however, gives the 1-trans-pyrazoles (IV), which are incapable of intramolecular cyclization. On prolonged storage (20-30 days), these gradually undergo intermolecular quaternization to give poly-salts, shown below for (Vb).



I a R=R¹=H; b R=CH₃, R¹=H and R=H, R¹=CH₃; c R=R¹=CH₃

The optimum reactant ratio (I):DCB:NaOH giving the highest yields of monoalkylation products (56-72%) is 1:4:2. Under these conditions, in addition to (III) and (IV), low yields (11-30%) of 1,4-bis(pyrazol-1-yl)-2-butenes with the cis- (VI) and trans- (VII) configurations are obtained, which become the main reaction products (~80%) when the (I):DCB ratio is 2:1. (Formula, next page, under Fig. 1.)

When the progress of the reaction was followed by GC, it was found that cis-DCB is 2.6 times more reactive than trans-DCB. The kinetic plots (Fig. 1) for the extent of reaction

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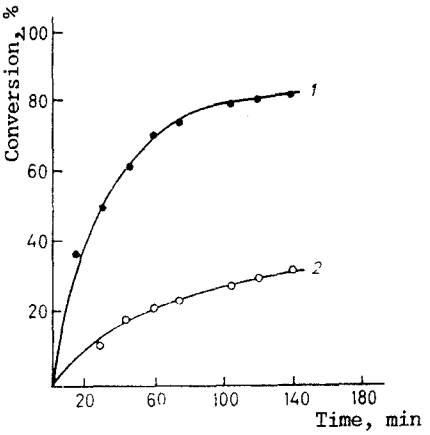
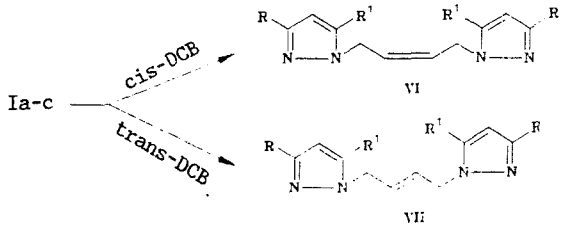


Fig. 1. Kinetic plots for conversion versus reaction time for the alkylation of (Ib) with cis-DCB (1) and trans-DCB (2).



against reaction times show a clear difference in the reactivities of the geometric isomers. For example, while the extent of reaction of cis-DCB after 2 h is 80%, only 30% of trans-DCB has reacted after this time. Such behavior of the isomers is in accordance with literature reports of the higher reactivity in nucleophilic substitution of allyl chlorides bearing a cis-γ-substituent to the CH_2Cl group [2].

Alkylation of 3(5)-methylpyrazole with DCB affords a mixture of isomers, with the methyl group in the 3- and 5-positions in the ring. The composition and structures of (III-VII) were confirmed by their elemental analyses and IR and PMR spectroscopy. For example, according to the PMR spectra, the isomer ratio in (IVb) is 72:28 ($3\text{-}CH_3$:$5\text{-}CH_3$). Assignment of the isomers was made from the chemical shifts of the methyl protons, obtained in CCl_4 and benzene. In benzene [3], the methyl group in the 5-position of the heterocycle undergoes a high-field shift. According to PMR, (VIIb) consists of the three possible isomers with the methyl groups in positions 3,3', 5,5', and 3,5' of the hetero-ring, and the PMR spectrum of (VIb) consists of two sets of signals, assigned to the isomers with the methyl groups in the 3,3'- and 3,5'-positions (Tables 1 and 2). Compounds (IVa-c) and (VIIa-c) show stretching vibrations of the pyrazole rings at 1530-1560 cm^{-1}, and out-of-plane vibrations of the trans-N=CH bond at 970-980 cm^{-1}. In the spectra of the salts (IIIa-c), the absorption of the pyrazole rings is shifted by 10 cm^{-1} to lower frequencies (1520-1550 cm^{-1}).

In contrast to the pyrazoles, alkylation of 1,2,4-triazole requires somewhat different conditions, namely an anhydrous medium, and a solid–liquid phase system (dioxane–KOH–TEBAC), since it is known that no reaction occurs in aqueous solution [1]. Attempts to isolate (IX) resulted, instead of the usual intramolecular cyclization to give (X), in spontaneous polyquaternization at $N_{(4)}$ to give the poly-salt (XI).

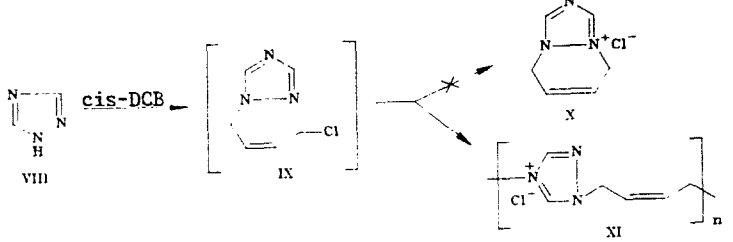


TABLE 1. PMR Spectra of Pyrazoles (IVb), (VIb), and (VIIb)

Compound	Position of the CH_3 group in the ring	δ, ppm (J, Hz)						
		CH_3, s	NCH_2, m	CH_2Cl	—CH=CH—	ring protons		
						3-H	4-H	5-H
IV-trans*	3	2,26	4,02	4,66 m	5,72 d,t.t, H_A; 5,93 d,t.t, H_B; (15,2)	—	6,03 d (2,2)	7,27 d (2,1)
IV-trans*	5	2,24	4,00	4,68 m	5,52 d,t.t, H_A; 5,90 d,t.t, H_B; (16,8)	7,38 m	6,03 d	—
VI-cis	3,3′	2,26	4,73 ... 4,77	—	5,65 ... 5,86 m	—	6,03 br	7,30 d (2,2)
VI-cis	3,5′	2,26	4,73 ... 4,77	—	5,65 ... 5,86 m	7,37 br	6,02 br	—
VII-trans	3,3′	2,27	4,62 ... 4,69	—	5,77 m	—	6,01 br	7,25 d
VII-trans	3,5′	2,23	4,62 ... 4,69	—	5,62 ... 5,71 m	7,38 br	6,01 br	7,23 d
VII-trans	3,5′	2,22	4,62 ... 4,69	—	5,54 m	7,38 br	6,01 br	—

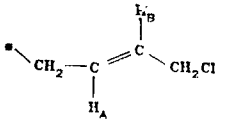


TABLE 2. PMR Spectra of Pyrazoles (XVb) and (XVc)

Compound	Position of CH_3 in ring	δ, ppm; J, Hz							
		CH_3, s	3-H	4-H	5-H	H_A, H_B*	H_C*	H_D*	H_E*
XV-trans	3	2,29	—	6,04 d	7,36 m	5,03 ... 5,35m	7,52 m; J_{BC}=17,5; J_{AC}=10,2; J_{EC}=1,1	5,64 d.d; J_{DE}=9,4; J_{DC}=11,1	6,48 d.d
XV-cis	5	2,23	7,36 m	6,05 d	—	5,03 ... 5,53m	7,52 m	5,77 d.d; J_{DE}=9,3; J_{DC}=11,1	6,41 d.d
XV-trans	3	2,24	—	5,99 m	7,46	5,03 ... 5,53m	6,31 m; J_{BC}=16,9; J_{AC}=10,3; J_{EC}=0,9	6,60 d.d; J_{DE}=13,8 J_{DC}=10,3	6,86 d.d
XV-trans	5	2,26	—	—	—	—	—	—	—
XV cis	3,5	2,15and 2,21	—	5,81 s	—	5,00 ... 5,40 m	7,80 d.d; J_{BC}=17,3 J_{AC}=10,5	5,63 m	6,37 d J_{ED}= =9,6

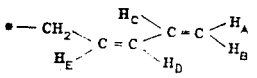


TABLE 3. Dehydrochlorination of a Mixture of Isomeric 1-(4-Chloro-2-butenyl)-3-methyl- and 1-(4-Chloro-2-butenyl)-5-methyl-pyrazoles (IVb) (isomer ratio 72:28)*

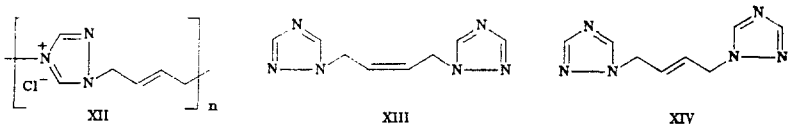
R^2	Compound (XVIb)				
	empirical formula	bp, °C (mm)	n_D^{20}	d_4^{20}	yield, % (yield of diene (XVb), %
CH_3	$C_9H_{14}N_2O$	85 (1)	1,4930	1,0060	75,0 (13,3)
C_2H_5	$C_{10}H_{16}N_2O$	90 (1)	1,4900	0,9831	71,0 (26,8)
C_4H_9	$C_{12}H_{20}N_2O$	120 (1)	1,4885	0,9617	25,0 (45,0)
i-C_3H_7	$C_{11}H_{18}N_2O$	108 (1)	1,4900	0,9615	11,0 (82,0)
t-C_4H_9	—	—	—	—	— (91,0)

TABLE 4. Properties of (IIIa-c), (IVa-c) (VIIa-c), (XIII), (XIV), (XVa-c), and (XVII)

Compound	Empirical formula	bp, °C (1 mm)	mp, °C	n_D^{20}	d_4^{20}	Yield, %
IIIa	$C_7H_9ClN_2$	—	175	—	—	54
IIIb	$C_8H_{11}ClN_2$	—	185	—	—	60
IIIc	$C_9H_{13}ClN_2$	—	280	—	—	65
IVa	$C_7H_9ClN_2$	81	—	1,5200	1,1900	72
IVb	$C_8H_{11}ClN_2$	84	—	1,5200	1,1289	71
IVc	$C_9H_{13}ClN_2$	97	—	1,5210	1,1144	60
VIa	$C_{10}H_{12}N_4$	130	45 ... 46	—	—	83
VIb*	$C_{12}H_{16}N_4$	140	—	1,5340	1,0711	85
VIc	$C_{14}H_{20}N_4$	150	—	1,5260	1,0463	82
VIIa	$C_{10}H_{12}N_4$	133	59 ... 60	—	—	74
VIIb†	$C_{12}H_{16}N_4$	145	—	1,5330	1,0700	85
VIIc	$C_{14}H_{20}N_4$	—	88 ... 89	—	—	78
XIII	$C_8H_{10}N_6$	200	—	1,5420	—	60
XIV	$C_8H_{10}N_6$	205	104 ... 105	—	—	54
XVa	$C_7H_8N_2$	46	—	1,5780	0,9984	84
XVb	$C_8H_{10}N_2$	54	—	1,5700	0,9963	87
XVc	$C_9H_{12}N_2$	73	—	1,5700	0,9741	85
XVII	$C_6H_7N_3$	72	—	1,5600	1,0925	45

*Picrate, mp 124-125°C.
†Picrate, mp 182-183°C.

The product of the reaction of (VIII) with trans-DCB under monoalkylation conditions is the poly-salt (XII) with the trans-configuration. Under bisalkylation conditions, however, the cis- (XIII) and trans- (XIV) 1,4-bis-(1,2,4-triazol-1-yl)-2-butenes were obtained.

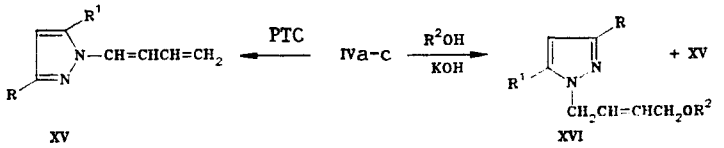


XII XIII XIV

In the IR spectra of (XI-XIV), absorption is seen for the triazole ring (1510 cm^{-1}) and the double bonds (1640 cm^{-1}). In addition, the spectra of (XI) and (XIII) show absorption at 730 cm^{-1} characteristic of the cis-N=CH bond, and those of (XII) and (XIV) absorption at 970 cm^{-1}, characteristic of the trans-N=CH bond.

It has thus been established that the formation of a given monoalkylation product is largely determined by the type of azole. The fact that on passing from pyrazole to 1,2,4-triazole quaternization occurs readily with the involvement of the second sp^2-hybridized nitrogen $N_{(4)}$, to give the polymeric salts (XI), rather than intramolecular quaternization at $N_{(2)}$ in the intermediate monoalkylation products, provides further confirmation of the high nucleophilicity of the 4-position in 1-substituted 1,2,4-triazoles [4].

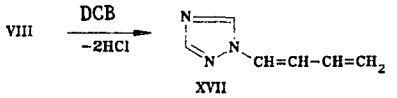
Compounds (IV) were converted into 1-(1,3-butadienyl)pyrazoles (XV) by dehydrohalogenation with alcoholic and aqueous alkali (phase-transfer catalyzed). It was found that, in the first case, in addition to elimination, nucleophilic replacement of the allyl chlorine atom by the alcohol residue occurred.



XV XVI

The effect of the type of alcohol on the course of the dehydrochlorination of (IVb) was examined (Table 3). It will be seen that as the length and branching of the hydrocarbon radical in the alcohol is increased, the yield of the substitution product (XVI) decreases. Dehydrochlorination of the pyrazoles (IVa-c) in aqueous alkali in the two-phase system benzene–water enabled difficulties to be avoided and high yields of the dienepyrazoles to be obtained.

In view of the impossibility of isolating non-quaternized monoalkylation products of 1,2,4-triazole, 1-(1,3-butadienyl)-1,2,4-triazole was obtained in a somewhat different way. In this instance, it was found possible to carry out alkylation and dehydrochlorination in a single step, in a solid–liquid phase system (dioxane–KOH–TEBAC).



XVII

According to PMR and GC, the dieneazoles (XVa-c) obtained by phase-transfer catalyzed dehydrochlorination of (IVa-c) have differing stereoisomeric compositions. For instance, (XVc) is the pure cis-isomer, while (XVa) and (XVb) are mixtures of the cis- and trans-isomers in ratios of 50:50 and 70:30 respectively. In addition to the two stereoisomers, (XVb) contained the two structural isomers with a cis-(3-CH_3): cis-(5-CH_3):trans-(3-CH_3):trans-(5-CH_3) ratio of 40:30:25:5. PMR spectral data are given in Tables 1 and 2, and the physicochemical properties of the products in Table 4.

EXPERIMENTAL

IR spectra were obtained on a UR-20 in thin films and KBr disks, and PMR spectra on Perkin-Elmer R-12B and Bruker WP-200 instruments in $CDCl_3$, CCl_4, or benzene, internal standard TMS. Kinetic measurements of the actual concentrations of the isomeric DCB in the samples were obtained using the method described in [5] by GC on an LKhM-8MD instrument, column 1.5 m × 3 mm, packed with Inertone AW-HMDS (0.20-0.25 mm) soaked in 10% Carbowax 20 M. The carrier gase (helium) flow rate was 50 ml/min.

The geometric isomers of DCB were separated by fractionating a 40/60 mixture of the cis- and trans-isomers through a fractionating column of length 30 cm, diameter 4 cm, with a metallic packing, still temperature 95°C, pressure 62 mm, R = 7. cis-DCB, bp 47°C (10 mm); n_D^{20} = 1.4800; d_4^{20} = 1.1364 (99.4% pure by GC). trans-DCB: bp 53°C (10 mm); n_D^{20} = 1.4870; d_4^{20} = 1.1873 (99.5% pure by GC) [6]. The elemental analyses for C, H, and N were in agreement with the calculated values.

General Method for the Monoalkylation of Pyrazoles and 1,2,4-Triazole with cis- and trans-DCB.

1) A mixture of 0.1 mole of (Ia-c), 0.2 mole of sodium hydroxide, 1.2 g of TEBAC, 20 ml of water, and 0.4 mole of cis- or trans-DCB was stirred at 40°C for 2 h. The organic layer was extracted with ether, washed with water, and dried over Na_2SO_4. After removal of the ether and excess DCB at 60-80°C (5 mm), the residue was worked up as follows.

A. In the case of cis-DCB the product was kept for 2 h at 80°C, and the resulting solid treated with acetone. The solid 1,3-disubstituted 5,8-dihydropyrazolo[1,2-a]pyridazinium salt (IIIa-c) was filtered off, washed with acetone, and dried in air to constant weight.

B. In the case of trans-DCB, the product was fractionated to give (IVa-c). The physicochemical constants and yields of the compounds are given in Table 4.

2) A mixture of 0.1 mole of 1,2,4-triazole, 0.1 mole of potassium hydroxide, 1.2 g of TEBAC, and 50 ml of dioxane was kept for 30 min at 70°C, cooled to 20°C, 0.3 mole of cis- or trans-DCB added, and the mixture stirred for 5 h at 40°C. The mixture was filtered, and the solvent and excess DCB removed. On attempted distillation, the residue solidified. The solid was dissolved in 20 ml of water, precipitated with acetone (100 ml), filtered, and dried to constant weight to give 10.2 g (65%) of the polymer (XII), mp 180-200°C, $[\eta]$ = 0.03, and 11 g (70%) of polymer (XI), mp 140-160°C, $[\eta]$ = 0.025.

General Method for the Bisalkylation of Pyrazoles and 1,2,4-Triazole with cis- and trans-DCB.

1) To a mixture of 0.1 mole of (Ia-c), 0.25 mole of sodium hydroxide, 1.2 g of TEBAC, and 20 ml of water was added over 30 min at 60°C 0.05 mole of cis- or trans-DCB. The mixture was heated at this temperature for 1.5 h. The organic layer was extracted with ether, and dried over Na_2SO_4. After removal of the ether, the residue (VIa-c and VIIa-c) was fractionated in vacuo (Table 4).

2. A mixture of 0.1 mole of 1,2,4-triazole, 0.1 mole of potassium hydroxide, and 1.2 g of TEBAC in 30 ml of 1,4-dioxane was stirred for 30 min at 70°C, 0.05 mole of cis- or trans-DCB added over 30 min, and stirring continued at this temperature for 5 h. The mixture was filtered, the solvent removed, and the residue (XIII or XIV) fractionated in vacuo (Table 4).

Dehydrochlorination of (IVb) with Alcoholic Potassium Hydroxide. A mixture of 0.1 mole of (IVb), 0.15 mole of potassium hydroxide, and 50 ml of the appropriate alcohol (Table 3) was heated for 8 h at 80°C, filtered, the alcohol removed, and the residue fractionated in vacuo. The composition of the reaction products and the physicochemical properies of the 1-(4-alkoxy-2-butenyl)-3(5)-methylpyrazoles are given in Table 3.

Phase-Transfer Catalyzed Dehydrochlorination of (IVa-c). A mixture of 0.1 mole of (IVa-c), 0.3 mole of potassium hydroxide, 1.2 g of TEBAC, 10 ml of water, and 50 ml of benzene was stirred for 5-6 h. The organic layer was separated, washed with water, and dried over $MgSO_4$. The solvent was removed, and the residue vacuum distilled (Table 3).

1-(1,3-Butadienyl)-1,2,4-triazole (XVII). A mixture of 0.1 mole of 1,2,4-triazole, 0.1 mole of potassium hydroxide, 1.2 g of TEBAC, and 50 ml of 1,4-dioxane was kept for 30 min at 75°C. After cooling, the mixture was treated with 0.5 mole of a mixture of cis- and trans-DCB (40/60), and stirred for 5 h at 40°C. A further 0.2 mole of potassium hydroxide was then added, and the mixture heated to 70°C with stirring for 3 h. It was then filtered, the solvent removed, and the residue distilled in vacuo to give (XVII) (Table 4).

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CALCULATION OF THE CYCLIZATION OF 2-DIAZOETHANIMINE TO 1H-1,2,3-TRIAZOLE BY THE MINDO/3 METHOD

V. A. Bakulev and I. P. Gloriozov

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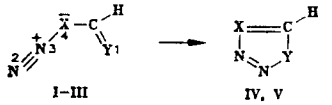
It is shown that the MINDO/3 approximation can be used for the calculation of the cyclization of 2-diazoethanimine and its 2-aza analog. It was found that, as in the case of the azidoimine, the formation of the new bond during cyclization results from reaction of the unshared electron pair at the nitrogen atom of the imino group with the terminal nitrogen atom of the diazo group.

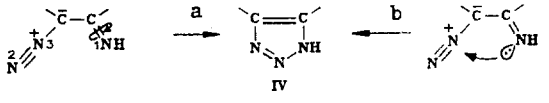
The nitrogen analogs of α-diazocarbonyl compounds, i.e., α-diazoimines, are highly reactive substances which undergo cyclization to isomeric 1H-1,2,3-triazoles even under the conditions of production. They are intermediate compounds in the generation of iminoketenes and iminocarbenes and also in the synthesis of imidazoles and triazoles [1-3]. Study of the relationships governing the cyclization of α-diazoimines therefore opens up prospects for a greater understanding of the rearrangements of five-membered heterocycles and the directed synthesis of various derivatives of 1,2,3-triazole, including those possessing strong biological activity [4].



I-III IV, V

I, IV X=CH, Y=NH; II, V X=N, Y=NH; III X=CH, Y=CH_2

At the same time there are a series of unresolved questions in the chemistry of these compounds. For example, it is not clear why the α-diazoimines (I) undergo cyclization more quickly than the azidoimines (II) while they, in turn, undergo cyclization much more quickly than the derivatives of vinydiazomethane (III) [1, 5-7]. It is also unclear as to how the cyclization of the diazoimines takes place, i.e., by an electrocyclic mechanism (a) or, like the azidoimine (II), without rotation about the C=N bond (b) [8].



IV

In order to answer these questions we undertook a calculation for the cyclization of 2-diazoethanimine (I) to 1H-1,2,3-triazole (IV) by the MINDO/3 method using the VIKING programs [9]. However, it is well known that the methods of the CNDO family, which satisfactorily describe the characteristics of azapentalene aromatic compounds, have proved inadequate for the study of azido–tetrazole isomerization [8]. This is why the cyclization of azidoazomethine (II), which is the aza analog of the diazoimine (I), was studied by the ab initio method in the STO-3G basis set [8]. In this connection in order to determine the suitability of the adopted method for solution of the problem we first undertook a calculation for the cyclization

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