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Heterylation of 3-R^1-5-R^2-1,2,4-Triazoles with Derivatives of 3,5-Dinitro-1,2,4-Triazole

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Abstract—Heterylation of 3-R^1-5-R^2-1,2,4-triazoles (pK_a 3–12) with *N*-alkyl-, *N*-alkenyl-, *N*-alkoxycarbonyl-, *N*-oxoalkyl-, *N*-nitroxyalkyl, and *N*-nitroaminoalkyl-3,5-dinitro-1,2,4-triazoles results in substitution of a nitro group in 5 position of the dinitro compound yielding 1-R-methyl-3-nitro-5-(3-R^1-5-R^2-1,2,4-triazolyl)-1,2,4-triazoles. The side processes: Hydroxide-ion attack on C^5 and (or) N^1 of the ring both in the substrate and in the target compound afford 1-R-methyl3-nitro-1,2,4-triazol-5-ones, 3,5-dinitro-1,2,4-triazole and NH-acids of N–C-bitriazole series. Optimal reaction media are aprotic dipolar substances, and for compounds prone to heterolysis ethyl acetate–water systems. The azole pK_a is the decisive factor controlling the composition and the ratio of reaction products. The process is promising for azoles with pK_a > 5, and the optimal range of pK_a is 8–10.

In the 1,2,4-triazole series numerous modifications of structure and syntheses of new derivatives of the series were carried out starting from N-substituted 3,5-dinitro-1,2,4-triazoles. The most common are reactions of nucleophilic substitution of the nitro group in 5 position with various agents [1–6]. In some of these studies as nucleophilic reagents were used azoles, mostly 1,2,4-triazoles [2–5]. The NH-acids of the 1,2,4-triazole series were subjected mainly to N-arylation, publications on N-heterylation besides those mentioned above are few in number. Therewith reactions were frequently carried out with haloderivatives where the group to be replaced was activated by an acceptor located either out of the ring or in the ring of the aromatic [6–10] or heteroaromatic system [11–14] respectively. For instance, the N-arylation of 1,2,4-triazole with highly reactive 2,4-dinitro-1-fluorobenzene readily proceeds even without bases (DMSO, 20°C) [8]. Besides 1,2,4-triazole [7, 8, 10, 13] in reaction with halobenzenes were used also its alkyl- [12], amino- [7, 11], and even nitro derivatives [6, 9], in particular, 3,5-dinitro-1,2,4-triazole [6]. But whereas the target N-arylation of the 3-nitro-1,2,4-triazole (DMSO, 20°C, yield 38% [9]) was fairly successful, the attempt to picrylate the low-basic 3,5-dinitro-1,2,4-triazole (acetonitrile, 20°C [6]) did not afford the expected 1-picryl derivative. The isolated products of the reaction originated from substitution in 5 position of the triazole ring (3-nitro-1-picryl-5-chloro-1,2,4-triazole and 3-nitro-1-picryl-1,2,4-triazol-5-one). It was suggested that these products arose due to transformations of the target product, 3,5-dinitro-1-picryl-1,2,4-triazole which formed but was instable under the reaction conditions. If it were true and substitution of nitro group in position 5 was preceded by N-arylation then in [6] was achieved arylation of the least basic among all 1,2,3-triazolides (pK_a of the conjugate NH-acid was –0.66 [15]). If the C^5-substitution occurred in the reagent before the N-arylation then arylation proceeded also with anions of relatively strong NH-acids: 3-nitro-5-chloro-1,2,4-triazole and 3-nitro-1,2,4-triazol-5-one, pK_a 3–4 [15].

The arylation or heterylation of triazoles is carried out without solvent [11] or in polar aprotic media, predominantly in DMF [8, 13], DMSO [7–9], or acetonitrile [6, 8] both in the presence of acids [6, 8, 9, 11, 12, 14] or in their absence [7, 8, 11], at heating [8, 12] and in the cold [6–9]. In [10] arylation was performed by Ulmann procedure (pyridine, CuO). In the media of low polarity (benzene) the substitution does not occur at all [8], and proton-donor solvents are of low efficiency, especially with triazolides of elevated basicity [8, 11].

The N-substitution in the triazole ring was non-selective only at arylation of the neutral molecule of 1,2,4-triazole proper or its C-alkylated analogs (fusion of reagents, boiling thereof in ethanol [12]), and among the arising N^4- and N^1-isomers the latter prevailed (80–95%). In arylation (heterylation) of 5-amino-1,2,4-triazole the reaction first occurred at the amino group [7, 11], and only on adding a base the substitution was successfully performed at the

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heteroatom in the ring [7]. The identification of products was commonly done on the evidence of ^{1}H NMR spectra, but in most cases, also in [11], the structure of products was not rigorously proved.

The most complete discussion on heterylation of 3-R^1-5-R^2-1,2,4-triazoles was done in publications concerning replacement of a nitro group or a halogen atom in the derivatives of 3,5-dinitro-1,2,4-triazole [2–5] and in methylated 3- or 5-halo-1,2,4-triazoles [12].

Among substrates brought to the fore are compounds with the functional groups in the N-alkyl fragment. This leads to complications during heterylation process but affords new reactive compounds. And in this respect the interest arises not only from N–C-bitriazoles proper but also due to the opportunity to estimate the effect of a substituent in the substrate on the direction and selectivity of the process. These data provide a possibility to reveal the general rules of the reaction, the limits of its application, and to forecast the results of a synthesis depending on the structural characteristics of both participants.

In the present study we used in heterylation mono- (**I**–**VI**) and disubstituted at the carbon atoms 1,2,4-triazoles (**VII**–**XIII**) with C-substituents of various types. The compounds under study were characterized by a wide range of pK_a (6–11 and 3–12 respectively [5, 15], As heterylating agents were applied *N*-alkyl-, *N*-alkenyl-, *N*-alkoxycarbonyl-, *N*-oxoalkyl-, *N*-nitroxyalkyl, and *N*-nitroaminoalkylderivatives of 3,5-dinitro-1,2,4-triazole (**XIV**–**XXVII**) [4, 16].

In some cases were introduced variations in the reaction temperature, reagents concentration, their ratio, and in the base type. As a rule the synthesis was carried out at heating in an aprotic polar solvent, most often in acetone with addition of 10% of water to increase the solubility (Tables 1–3). The reagents were used in equimolar amounts that had been established before to be feasible [5]. The reaction rate, completeness of substrate conversion, the composition and ratio of the reaction products were monitored by TLC and ^{1}H NMR spectroscopy. The products obtained as a rule were identical to those prepared and described before [2–5, 17]; the structure of substances obtained for the first time was confirmed by analytical data and spectral characteristics that are given in Experimental.

It should be specially noted that non-uniqueness of the reaction direction originated both from its conditions and the structure of the substrates under consideration. The heterylation was carried out with the salts of sufficiently weak NH-acids, i.e., virtually all reactions occurred in the media at pH over 7. Under alkaline conditions the derivatives of 3,5-dinitro-1,2,4-triazoles can react with the hydroxide anion giving rise to the corresponding triazolones due to the substitution of a nitro group. This reaction was observed formerly as a side process with the majority of the substrates of this group in their reactions with any nucleophilic reagents [1–5], in particular, with 3-R^1-5-R^2-1,2,4-triazolides [2–5]. Besides both the original and target compounds in the alkaline medium sometimes suffer heterolysis at the bond connecting the triazole ring with the functionalized N-alkyl substituent [2–5], and in a number of compounds the reactions at the functional groups also cannot be excluded. All these processes significantly affect the synthetic results; moreover, in some cases one or another side process can dominate or be the only direction of the reaction.

We established that under the conditions used in this study (90% aqueous acetone, 60°C) the reaction with the majority of the objects proceeded in the target direction: Triazole heterylation occurred with nitro group replacement in the position 5 of the substrate, but the formation of the target bitriazoles **XXIII**–**XLIII** was accompanied with side processes (the yield of N–C-bitriazole at the total conversion of substrate was always below 80%) (Tables 1–3). The side reactions were due to the attack of hydroxide anion on positions C^5 and N^1 in the ring. The first reaction resulted in triazolones **L**–**LVII** and was observed practically always. A rare exception present the cases where occurs only heterolysis by the type of reverse Michael reaction: interaction of 3,5-dinitro-1-(3-oxobutyl)-1,2,4-triazole (**XV**) with 5-amino-1,2,4-triazole (**I**) (Table 2), or of 3,5-dinitro-1-(2-nitroethyl)-1,2,4-triazole (**XXII**) and nitroamine **XIX** with 3-nitro-1,2,4-triazole (**VI**) in acetone (Table 3).

The best suitable for investigation of structure (basicity) effect on the ratio of the main and side reactions occurring at position C^5 in the series of NH-acids under consideration is 1-methyl-3,5-dinitro-1,2,4-triazole (**XIV**) (set **I**, Table 1). The reactions of the same reagents with a substrate that certainly suffers N^1–C-heterolysis, 3,5-dinitro-1-(2-oxobutyl)-1,2,4-triazole (**XV**), are collected in set **II** (Table 2).

The comparison of results permits evaluation of the effect of azole pK_a on the second side reaction, N^1-devinylation. Finally, the contribution of the proper structure of the substrate into the overall

Table 1. Process conditions and products yield in reaction of 1-methyl-3,5-dinitro-1.2.4-triazole (**XIV**) with triazoles **I**–**IV, VI**–**XIII** [(**XIV**)/(triazole–reagent)/NaOH = 1 : 1 : 1, 90% aqueous acetone]

Reagent			Temperature, °C	Time, h	Products of C^5-substitution			
Compd. no.	pK_a	c, mol l^{-1}			Compd. no.	Bitriazole yield, %	Triazolone **L** yield, %	Overall yield, %
I	11.08	0.23	60	0.5	**XXIII**	0	0	Tarring
		0.60	20	24		70	28	98
II	10.08	0.23	60	0.5	**XXIV**	53	11	64[a]
		0.60	20	24		83	17	100
III	8.64	0.23	60	1	**XXV**	79	19	98
IV	8.11	0.23	60	0.5	**XXVI**	75	22	97
		0.60	20	24		36	10	46
VI	6.05	0.23	60	7	**XXVII**	60	30	90
		0.44	60	4		62	30	92
		0.60	20	144		60	30	90
VII	12.12	0.23	60	0.5	**XXVIII**	0	0	Tarring
		0.60	20	3		55	35	90
		0.60	20	24		65	35	90
VIII	9.60	0.23	60	1	**XXIX**	82	10	92
		0.60	20	24		54	8	62
IX	9.11	0.23	60	1	**XXX**	85	11	96
		0.60	20	24		40	7	47
X	7.05	0.23	60	3	**XXXI**	50	45	95
		0.60	20	24		23	32	55
		0.60	20	72		46	40	86
		0.23	75[b]	8		47	46	93
XI	6.75	0.23	60	3	**XXXII**	42	52	94
XII	5.22	0.23	60	24	**XXXIII**	18	66	84
XIII	3.05	0.23	60	24	–	0	60	60

All solvents contained 10 vol% of water. [a] Tarring. [b] Solvent EtOAc.

Table 2. Process conditions and products yield in reaction of 1-(3-oxobutyl)-3,5-dinitro-1,2,4-triazole (**XV**) with triazoles **I**–**XII** [(**XV**)/(triazole–reagent)/NaOH = 1 : 1 : 1, c 0.44 mol l^{-1}, conversion of substrate **XV** 100%]

Reagent no.	Solvent	Temperature, °C	Products of C^5-substitution				Share of heterolysis, %
			bitriazole no.	yield of bitriazole, %	yield **LI**, %	overall yield, %	
I	Acetone	20	–	0	Traces	–	Tarring
II	Acetone	60	**XXXIV**	21	45	69	34
	EtOAc	80		69	28	97	3
III	Acetone	60	**XXXV**	65	30	95	5
	EtOAc	80		68	31	99	1
IV	Acetone	60	**XXXVI**	79	22	92	8
	EtOAc	80		63	35	98	2
V[a]	Acetone	60	**XXXVII**	68	28	96	4
VI	Acetone	60	**XXXVIII**	39	20	59	41[b]
	Acetone	20		40	20	60	40[c]
	Acetone	60		35	20	55	45[d]
	CH_3CN	80		57	20	77	23
	EtOAc	80		67	31	98	2
	Ethanol	80		25	70	95	5

Table 2. (Contd.)

Reagent no.	Solvent	Temperature, °C	Products of C^5-substitution				Share of heterolysis, %
			bitriazole no.	yield of bitriazole, %	yield **LI**, %	overall yield, %	
VII	Acetone	20	**XXXIX**	25	3	28	62[e]
	Acetone	60		0	0	0	Tarring
VIII	Acetone	60	**XL**	40	35	75	25
	CH_3CN	80		50	30	80	20
IX	Acetone	60	**XLI**	58	37	95	5
	CH_3CN	80		77	20	97	3
Œ	Acetone	60	**XLII**	35	30	65	35
	CH_3CN	80		52	28	80	20[e]
XI	Acetone	60	**XLIII**	34	30	64	35
XII	Acetone	60	–	0	20	20	80

All solvents contained 10 vol% of water.

[a] pK_a 8.11.

[b] Time 6 h.

[c] Time 120 h, c 0.7 mol l^{-1}.

[d] Triethylamine base.

[e] Conversion 90%, 24 h.

[f] c 0.5 mol l^{-1}.

Table 3. Process conditions and products yield in reaction of 3-nitro-1,2,4-triazole (**VI**) with derivatives of 3,5-dinitro-1,2,4-triazole **XIV**–**XXII** [(**XIV**–**XXII**)/(**VI**)/NaOH = 1 : 1 : 1, 60°C, c 0.23 mol l^{-1}]

Substrate		Products of C^5-substitution							Conversion, %	Time of reaction, h
		N–C-Bitriazole			Triazolone			Overall yield, %		
Compd. no.	R_f	Compd. no.	R_f	Yield, %	Compd. no.	R_f	Yield, %			
XIV	0.58	**XXVII**	0.48	60[a]	**L**	0.28	30	90	95	7
XV	0.56	**XXXVIII**	0.46	42[a]	**LI**	0.20	20	62	100[c]	6
				69[b]			30	99	100[c]	12
XVI[d]	0.62	**XLIV**	0.51	14[a]	**LII**	0.32	54	66	93	3
				30[b]			15	45	90	6
XVII	0.65	**XLV**	0.40	47[a]	**LIII**	0.25	34	81	100[c]	8
				55[b]			41	96	100	12
XVIII	0.67	**XLVI**	0.43	40[a]	**LIV**	0.28	40	80	90	8
XIX	0.51	**XLVII**	0.39	0[a]	**LV**	0.25	50	50	100[c]	2
				70[b]			28	98	100[c]	4
XX	0.51	**XLVIII**	0.41	60[a]	**LVI**	0.25	30	90	95	7
XXI	0.60	**XLIX**	0.36	50[a]	**LVII**	0.15	30	80	90	6
XXII	0.28	–	–	0[a]	–	–	0	0	100[e]	0.5

[a] 90% aqueous acetone.

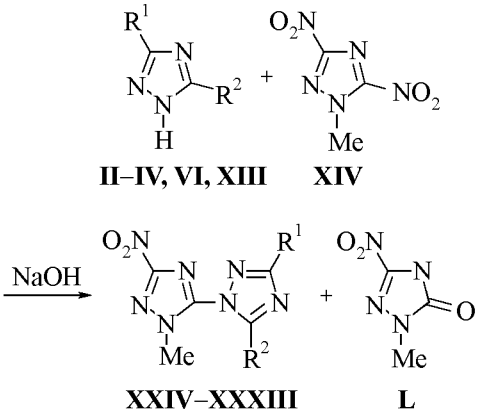
[b] EtOAc: 80°C for compounds **XV**–**XVII**, 20°C for compound **XIX**.

[c] Partial heterolysis.

[d] Yield of product **LIX** 27 and 45% in acetone and EtOAc respectively.

[e] Yield of 1-(2-nitroethyl)-3-nitro-1,2,4-triazole (**LVIII**) 95%.

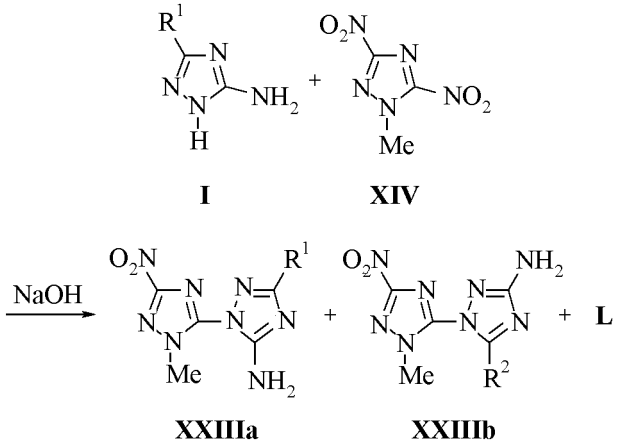
Scheme 1.



II–IV, VI, XIII **XIV** **XXIV–XXXIII** **L**

R^2 = H: R^1 = H (**II, XXIV**), N_3 (**III, XXV**), Cl (**IV, XXVI**), NO_2 (V, XXVII); R^2 = NH_2: R^1 = NH_2 (VII, XXXII), N_3 (**VIII, XXIX**), Cl (**IX, XXX**), NO_2 (**X, XXXI**); R^1 = NO_2, R^2 = Me (**XI, XXXII**), R^1 = R^2 = Cl (**XII, XXXIII**), R^2 = Br (**XIII**).

Scheme 2.



I **XIV** **XXIIIa** **XXIIIb**

process may be evaluated for example on the reaction of 3-nitro-1,2,4-triazole (**VI**) with triazoles functionally-substituted in the *N*-alkyl fragment **XIV–XXII** (set **III**, Table 3).

It was shown that in heterylation 3,5-1-methyl-1,2,4-triazole (**XIV**) is transformed according to the target direction when reacting with the most of triazoles **I–XII** under study, and only with relatively strong NH-acids (pK_a 3 and less), e.g., with 5-bromo-3-nitro-1,2,4-triazole (**XIII**), the only reaction product is 5-bromo-1-methyl-3-nitro-1,2,4-triazol-5-one (**L**). With reagents of pK_a > 5 the triazolones were obtained alongside the corresponding N–C-bitriazoles **XXIII–XXXIII** (Scheme 1).

The heterylation occurred virtually selective at the azole heteroatom N^1, and only with 5-amino-1,2,4-triazole (**I**) was definitely observed nonselective heterylation, and the N^1- and N^2-isomers **XXXIIIa, b** [5] were isolated and identified (Scheme 2).

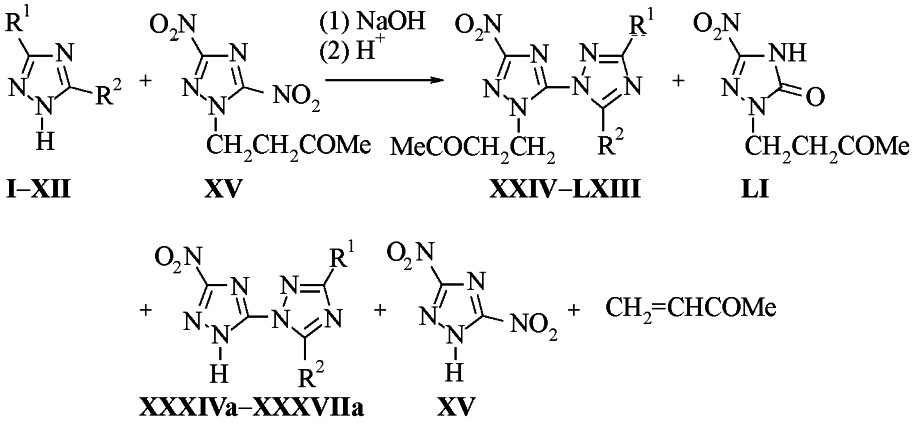
Neither aminoazole I nor any other 3-R-5-amino-1,2,4-triazole underwent heterylation at the amino group: The structure of the heterylation products was proved not only by spectral data but also by oxidation of the N–C bitriazole amino compounds into the corresponding azo derivatives [5]). The side product of heterylation triazolone L originates exclusively from the substrate. The target products, the corresponding N–C-bitriazoles, are not converted into triazolone **L** under the synthesis conditions: Bitriazole **XXVII** after heating for 6 h in 0.1 N water–acetone solution of NaOH was recovered quantitatively.

Thus in the process under study occur two independent reactions: the C^5 position of the substrate is attacked by azolide and hydroxide anions. Consequently the yields of the main and side products should depend on the reactivity of these nucleophilic agents and on their concentration. Since the concentration of the hydroxide ion under conditions of the actual synthesis is controlled by the pK_a of the azole, i.e., pH of the medium changes with replacement of a reagent, it is presumable that the final result depends just on the acid-base characteristics of the triazole.

The rate of C^5-substitution of the nitro group in substrate **XIV**, runs set **I**, and the ratio of the main and side products vary in a fairly wide range and actually depend on the pK_a of the reagent (Table 1). The relationships are similar both for mono- (**I–VI**) and disubstituted (**VII–XII**) triazoles, i.e., the steric factors do not significantly affect either the selectivity of heterylation or the ratio of the main and side product.

The rate of substrate conversion in general grows with increasing basicity of triazolide. This can be controlled by changing temperature and reagents concentration. Therewith the temperature factor is more important than the concentration one, and with reagents of various basicity it is recommended to use these parameters in different combinations depending on pK_a of the azole. Thus with triazoles with pK_a larger than 10 the heating of reagents in acetone provides tarring, and to obtain the desired products the synthesis temperature should be reduced to 18–20°C; to intensify the process with this group objects a higher concentration of reagents (within reasonable limits) is required, and the completeness of conversion is achieved at longer reaction time. With the reagents of pK_a in the range 9 → 5 both the tempera-

Scheme 3.



R^2 = H: R^1 = H (**II, XXXIV**), N_3 (**III, XXXV**), Cl (**IV, XXXVI**), Br (**V, XXXVII**), NO_2 (**VI, XXXVIII**); R^2 = NH_2: R^1 = NH_2 (**VII, XXXIX**), N_3 (**VIII, XL**), Cl (**IX, XLI**), NO_2 (**X, XLII**); R^1 = NO_2, R^2 = Me (**XI, XLIII**).

ture and concentration should be increased; therewith for the azoles of low basicity (pK_a below 6) the high conversion is attained only at a long reaction time.

Note that at the corresponding choice of reaction conditions the substrate conversion is fairly high, and with reagents of pK_a > 6 it is close to quantitative (overall yield of C^5-substitution products is over 95%). However the ratio of the target bitriazole and the side product, triazolone, is considerably different for reagents of unlike basicity. At the same time for a given triazole the ratio of products of C^5-substitution remains virtually unchanged at varying reagents concentration, temperature, or replacing solvent: ethyl acetate instead of acetone. In the latter case the reaction occurs at the phase boundary, and with a considerably lower rate.

The fraction of the N–C-bitriazoles in the reaction products is over 65–70% only for the reagents with pK_a > 8. With decreasing pK_a the yield of the target product is reduced and accordingly grows the amount of triazolone **L**. The latter is prevailing in heterylation of azoles of low basicity (pK_a around 5), moreover, it has been already mentioned that in the case of 5-bromo-3-nitro-1,2-4-triazole triazolone L is the only product of the substrate conversion. Unexpectedly with compounds of pK_a over 10 the fraction of triazolone **L** in the reaction products was greater than with the reagents of pK_a 8–10. This fact is apparently due to the high alkalinity of the medium. Therefore it should be avoided by heterylation with no base but under more rigid conditions.

In a more complicated case, at heterylation of the same triazole series **I–XII** with butanone **XV** (runs set **II**, Table 2) the general trends observed with triazole **XIV** are conserved but appear some specific features of the process. Alongside the formation of bitriazoles **XXXIV–XLIII** and the attendant triazolone **LI** the second type of side process is evident: attack of hydroxide ion on the N^1 position and heterolysis at the bond ring–N-substituent both in the substrate and the target product (a version of reverse Michael reaction). As a result arise the salts of the corresponding NH-acids **XVa, XXXIVa–XXXVIIa** (Scheme 3).

We reported elsewhere [3] on the synthetic opportunities provided by the reaction of butanone **XV** with azoles, primarily the development of preparation method for NH-acids of N–C-biazole series of **XXXIVa–XXXVIIa** type based on heterylation–dealkylation. The substances obtained in this series were described in [3, 5].

It should be noted that in general the synthesis of the N–C-bitriazole is successful only when dealkylation of the substrate and especially of the reaction product is minimal.

Note that in all runs disregarding the synthesis conditions and the reagent characteristics in the reaction products were detected compounds originating from decomposition of the substrate, butanone **XV** (in the reaction mixture were present a sodium salt of 3,5-dinitro-1,2,4-triazole and methyl vinyl ketone, and the yield of C^5-substitution products was considerably less than quantitative). The heterolysis of the target N–C-bitriazoles to the corresponding NH-acids in its turn became detectable only with the reagents of high basicity (at pK_a of the conjugate NH-acid 9 and more), and only at prolonged reaction time. This fact is a practical confirmation of the

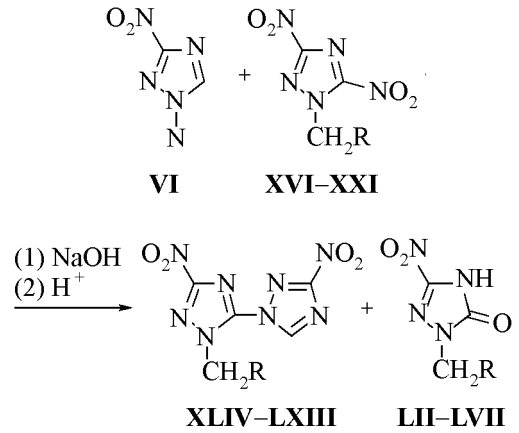
higher thermodynamic stability of the target products as compared to the original compounds, and it is reasonable if the pK_a of the NH-acids in N–C-bitriazole series (1–2 [3]) and that of 3,5-dinitro-1,2,4-triazole (–0.66 [15]) are considered.

To prevent the heterolysis of the reaction product is especially important when it contains an amino group (compounds **XXXI**–**XLI**) since the eliminated methyl vinyl ketone would attack the amino group providing addition products (data of ^{1}H NMR spectroscopy). The separation of the latter products is not easy. But at careful monitoring of the substrate consumption (TLC) and at timely workup of the reaction mixture the bicyclic NH-acids form in the mentioned reactions only in trace amounts.

To avoid the heterolysis it is sometimes feasible to carry out the synthesis not in acetone solution but in a two-phase system (ethyl acetate–water). However this procedure may be recommended, firstly, with the highly reactive reagents (pK_a > 8) for the reaction rate at the phase boundary is notably slower, and, secondly, the reaction products must be soluble in ethyl acetate (this is not the case with amino compounds).

Although in the set **II** for butanone **XV** the overall yield of C^5-substitution products is notably lower in acetone than in the set **I** with analogous reagents, the ratio of the corresponding N–C-bitriazole and triazolone remains practically at the same level (Tables 1, 2). The lower yield in the set **II** is due to the N^1-heterolysis. However the above data show that the type of N^1-substituent in these substrates virtually does not affect the ratio of C^5-substitution products. Yet the range of application of butanone **XV** to heterylation is considerably limited with respect to the reagent structure (pK_a). For instance, with a group of highly basic azoles **I, II, VII**, pK_a > 10, under standard conditions prevailed the decomposition of the substrate, and the yield of bitriazoles **XXIV, XXXIX** did not exceed 25%. The heterylation product of 4-amino-1,2,4-triazole (**I**) was not obtained at all due to virtually quantitative heterolysis of the original butanone and to tarring from polymerization of the arising methyl vinyl ketone. In its turn ketone **XXXIX** was successfully isolated apparently because of its low solubility: It separated into heterophase. On the other hand, among the reagents of low basicity (pK_a < 6) we failed to obtain the product of heterylation with butanone **XV** of triazole **XII**, pK_a 5.22. Yet with substrate **XIV** triazole **XII** afforded the corresponding bitriazole **XXXVIII**, although in a low yield.

Scheme 4.



VI **XVI–XXI** **XLIV–LXIII** **LII–LVII**

R = Ac (**XVI, XLIV, LII**), CH_2COOMe (**XVII, XLV, LIII**), COOMe (**XVIII, XLVI, LIV**), $N(NO_2)Me$ (**XIX, XLVII, LV**), $CH(ONO_2)Me$ (**XX, XLVIII, LVI**), Vin (**XXI, XLIX, LVII**).

The above stated shows that in the case in question it is just the heterolysis that requires especially careful adjustment of reaction conditions for azoles heterylation. Therefore just in the runs of this set we tried besides the variation of reaction temperature and reagents concentration to introduce changes into the reagents ratio, type of base, and solvent. Apart acetone we applied acetonitrile, ethyl acetate, and ethanol (the derivatives of 3,5-dinitro-1,2,4-triazole are unstable in DMF and DMSO). The workup of the reaction mixtures was performed either at complete conversion of the substrate (TLC monitoring) or after keeping for 24 h (with reagents of low activity). At the use of a small excess of triazole salt (10%) even with the reagent with the optimal pK_a value (triazole **IX**, pK_a 9.11) we observed only intensified side reactions, in particular, triazolone **LI** formation, and therewith very sharply changed the ratio of the C^5-substitution products (**XLI**/**LI**) 3.85 : 1 and 1.6 : 1 respectively]. This fact obviously is due to increased pH of the reaction medium. Similar results were obtained also at excess substrate: 10% excess substrate naturally increased only the triazolone fraction. Neither the use of organic base instead of alkali changed the situation, although here we were able to apply anhydrous solvents.

The problem was treated more efficiently by choosing solvent [in this respect in Table 2 are presented mainly the results obtained with 3-nitro-1,2,4-triazole (**VI**) characterized by low activity, pK_a 6.05]. We achieved its heterylation by going over from acetone to ethyl acetate and acetonitrile. In the

latter grew both the fraction of C^5-substitution products and bitriazole yield, but the substrate decomposition still exceeded 20%. The heterolysis was virtually fully suppressed in ethyl acetate and ethanol but if in the former considerably enhanced the bitriazole fraction (**XXXVIII**/**LI** 2.16 : 1 and 2 : 1 for ethyl acetate and acetone respectively) then in the latter grew the triazolone fraction (**XXXVIII/LI** 1 : 3). It is presumable that in ethyl acetate the decomposition of substrate is prevented by its presence in the organic phase during the reaction on the phase boundary (ethyl acetate/aqueous alkali). This mode of performing the process is feasible, especially with the compounds from azole series having pK_a over 10 and less than 8, although it requires longer time.

The relations disclosed in the study of sets **I** and **II** were further used in heterylation of 3-nitro-1,2,4-triazole (**VI**) with various substrates **XVI–XXII**, set **III** (Scheme 4).

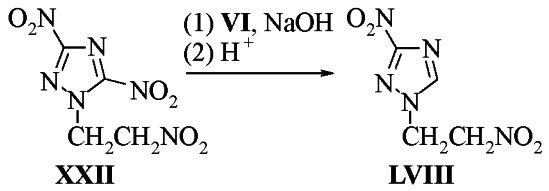
Compounds **XVIII, XIX–XXI** react analogously to methyl derivative **XIV**, with similar rates and, save ester **XVIII**, give nearly two times more bitriazoles than triazolones (in the case of compound **XVIII** the substitution products arise in equivalent amounts, Table 3). The triazolones were mostly identified by comparison with compounds described in [2, 18]; compound **LV** was prepared for the first time by procedure [18].

With ester **XVII**, an analog of butanone **XV**, the results were predictable and similar to those observed with compound **XV**, the same side reactions: The attack of hydroxide anion on positions 1 and 5 of the substrate leading to *N*-heterolysis and to nitro group replacement with triazolone formation. However in acetone ester **XVII** decomposed twice slower than ketone **XV**.

At the same time 3,5-dinitro-1-(2-nitroethyl)-1,2,4-triazole (XXII) as already mentioned under similar conditions (acetone) underwent only heterolysis: at the complete conversion of the original compound that occurred very fast the products of C^5-substitution were not even detected, and the eliminated highly reactive nitroethylene *in situ* effected nitroethylation of the reagent to 3-nitro-1-(2-nitroethyl)-1,2,4-triazole (**LVIII**) [2] in virtually quantitative yield (Scheme 5).

Thus the thermodynamic stability of substrates, the products of 3,5-dinitro-1,2,4-triazole addition to compounds with the activated double bond, under heterylation conditions decreased in the series **XVII, XV, XXII.**

Scheme 5.



XXII **LVIII**

The main drawback of this group of compounds, their tendency to heterolysis, significantly affects the yield of heterylation products. At the same time just this property, the possibility of further cleavage of a labile group at nitrogen atom after substituting a nitro group in such derivatives of 3,5-dinitro-1,2,4-triazole, opens a way to new NH-acids of triazole series, in particular, to N–C-bitriazoles. This opportunity was utilized in [3, 4]. To this end can be applied both butanones and propionates, but two points should be taken into consideration, the conservation of the substrate and the product under the preparation conditions, and the ratio between the target C^5-substitution product and the attendant triazolone. The data of Table 3 evidence that although the esters of **XVII** type are more thermodynamically stable, the use of ketone is more favorable: heteryl-substitution in ester **XVII** is the prevailing direction but the fraction of triazolone **LIII** in its substitution products is 1.5 times greater. And since the application of ethyl acetate practically suppresses the heterolysis for both substrates, the problem is solved by the use of two-phase system (ethyl acetate–aqueous alkali).

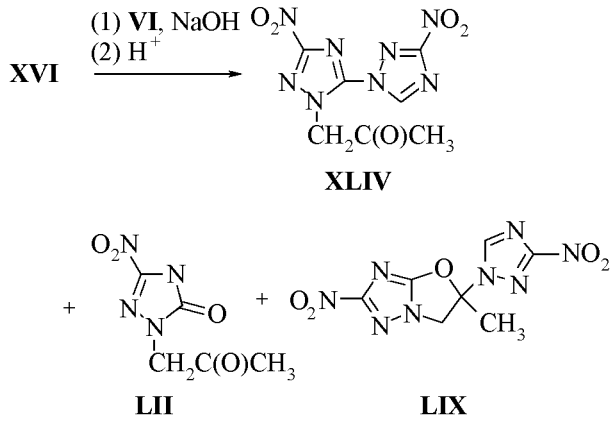
It turned out that heterolysis is characteristic not only for the products of 3,5-dinitro-1,2,4-triazole condensation with activated olefins **XV, XVII, XXII**, but also for nitroamine **XIX** (Table 3). Compound **XIX** alongside the main reaction underwent both side processes. Therewith at more stringent conditions in the substrate prevails heterolysis at the bond ring–N-substituent, and under the conditions acceptable for the majority of the other substrates (acetone, 60°C) this compound totally decomposes to afford sodium salt of 3,5-dinitro-1,2,4-triazole and triazolone **LV**. Still we succeeded in performing heterylation under very mild conditions (ethyl acetate–water, 20°C). The heterolysis of the substrate was practically suppressed, and the triazolone yield notably decreased. It seems that nitroamine **XIX** is characterized by abnormally high reactivity since it rapidly reacts with 3-nitro-1,2,4-triazole at the phase boundary at room temperature.

Thus a fragment $-CH_2NNO_2-$ introduces into position 1 of the triazole ring sharply increases the lability of the nitro group in 5 position. This fact may be understood considering the specific structure of nitroaminomethyl group that firstly can act as acceptor with respect to the ring, and secondly can be conjugated with the N^2-aza group of the ring (along the chain $:N-CH_2-N^1-N^2=$). The latter interaction should change the general conjugation in the ring and thus weaken the bond of C^5 with the heteroatom of the leaving group. It is appropriate also to mention here another uncommon fact that evidences the specific effect of the nitroaminomethyl group as a substituent in the N-alkyl chain of triazole on the activity of the C^5-substituent. It turned out that similarly and also readily occurred the substitution by 3-nitro-1,2,4-triazole of a halogen atom in the analog of nitroamine **XIX**, 5-bromo-3-nitro-1-(2-nitro-2-azapropyl)-1,2,4-triazole, whereas failed all the other attempts to use in this reaction alternative 1-R-5-bromo-3-nitro-1,2,4-triazoles (120–180 h, 60°C, acetone, trace amounts of N–C bitriazoles **XXVII, XLVI, XLVIII**).

It is generally known that halogen atom in 1,2,4-triazoles is of low lability: Its abnormally low reactivity toward nucleophilic substitution in the series of derivatives of 5-bromo-3-nitro-1,2,4-triazole is proved by kinetic studies [19]. To N-methylated 3(5)-halo-1,2,4-triazoles in reaction with triazolides were applied drastically rigid conditions (DMF, 150–220°C, up to 48 h) [13]. This inertness of the substrates may be due to the specificity of the halogen conjugation with the ring, and the most probable reason of this anomaly is the already observed in the series of nitrogen-containing heteroaromatic compounds deactivation of the halogen atom by its direct polar conjugation with the aza group in the appropriate position in the ring [20] (in the 1,2,4-triazole it is the aza group in 2 position: conjugation along the chain $C^5-N^4-C^3-N^2$). Till recently there were no exceptions from this rule in the 1,2,4-triazole series. The first abnormally active halogen atom was found in the 5-bromo-1-vinyl-3-nitro-1,2,4-triazole [21], and now in 5-bromo-3-nitro-1-(2-nitro-2-azapropyl)-1,2,4-triazole. In both compounds in the N^1-substituent is present a group with +R-donor properties. Thus the nitroamino group activates the position 5 in triazole both for 5-nitro and 5-halo derivatives by virtue of participation of the lone electron pair of the nitroamine nitrogen in the general conjugation.

In reaction of 3-nitro-1,2,4-triazole with propanone **XVI** occurs quite unusual side process: Alongside N–C-bitriazole **XLIV** and triazolone **LII** forms a product isomeric to the target ketone **XLIV**, 5-methyl-5-(3-nitro-1,2,4-triazol-1-yl)-5,6-dihyrooxazolo[3,2-*b*]-1,2,4-triazole (**LIX**) (Scheme 6).

Scheme 6.



Under standard conditions in this case formation of side products dominated (**LII**/**XLIV**/**LIX** = 3 : 1 : 2). The use of ethyl acetate instead of acetone sharply reduced the triazolone amount and increased the yield of azolyl derivatives, but the ratio of the latter changed insignificantly (**LII**/**XLIV**/**LIX** = 0.5 : 1 : 1.5]. Oxazolotriazole **LIX** arose apparently by the parallel attack of triazolate anion on the carbon atom of the carbonyl group in the side chain of the substrate followed by its joining to the ring through elimination of a nitro group in the intermediate. The contribution of this reaction is greater than that of the *N*-heterylation of 3-nitro-1,2,4-triazole. Note that a similar transformation was observed once again only with 5-methyl-3-nitro-1,2,4-triazole (**XI**) [17].

Alkoxycarbonyl and nitroxy groups in esters **XVII, XVIII, XX**, and also the double bond in allyl derivative XXI do not suffer transformations in the course of heterylation, and the only side process with these substrates is triazolone formation (Table 3).

Regretfully, the number of samples in the set **III** is not sufficient for final conclusions on the influence produced by substituent in substrate on the heterylation process, but in general when the N^1-substituent is insensitive to the bases its type insignificantly affects the products composition: the reaction affords only C^5-substitution products with prevalence as a rule of the N-substituted N–C-bitriazole. A trend is observed to acceleration of the reaction rate and increase in the triazolone fraction with growing acceptor character of the N-alkyl substituent in the substrate, and nitroamine **XIX** holds a special posi-

tion. Summing up all the above stated we can assume that heterylation of azoles and 1,2,4-triazoles in particular is the easiest and sufficiently general synthetic method for N–C-biazoles, also those with a functional group in a side chain.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometer Perkin-Elmer R-12 (60 MHz) in DMSO-d_6, internal reference HMDS. IR spectra were recorded on Specord 75IR instrument from films. Molecular weights were determined by the reversed ebullioscopy in acetone. TLC was performed on Silufol UV-254 plates, solvents system hexane–acetone–ethyl acetate, 5 : 2 : 1; R_f 0.58 (**XIV**), 0.56 (**XV**).

1-R-Methyl-3-nitro-5-(3-R^1-5-R^2-1,2,4-triazol-1-yl)-1,2,4-triazoles XXIII–XLIX. To a solution of 0.02–0.03 mol of 3-R^1-5-R^2-1,2,4-triazole **I–XIII** in 5 ml of water containing 0.02–0.93 mol of sodium hydroxide (triethylamine) at 18–20°C while stirring was poured a solution of 0.025 mol of N-substituted 3,5-dinitro-1,2,4-triazole **XIV–XXII** [2, 4, 15] in 45 ml of acetone (acetonitrile, ethyl acetate, ethanol). The reaction mixture was kept at 20°C or in the boiling solvent till 90–100% conversion of the substrate (TLC monitoring). The solvent was evaporated, the residue was weighed and analyzed by TLC and ^{1}H NMR spectroscopy. Then 20 ml of water was added to the residue, the mixture was stirred for 20 min, the insoluble residue (bitriazole) was filtered off, washed with water on filter (2 × 10 ml), dried at 50°C, weighed, and analyzed (TLC, ^{1}H NMR spectroscopy; the target compound may contain the initial substrate as impurity). N–C-bitriazoles **XXIII–XLIX** was purified by recrystallization.

The combined filtrate and washings were acidified by 10% sulfuric acid till pH 1, extracted with ethyl acetate (3 × 25 ml), the extract was washed with water and dried with calcined magnesium sulfate, the solvent was removed in a vacuum of a water-jet pump, the residue was weighed and analyzed (TLC and ^{1}H NMR spectroscopy). In reaction products were present predominantly the corresponding triazolones **L–LVIII** and sometimes the original azole and impurity of a heterolysis product from the target compound, NH-acids of N–C bitriazole series **XXXIVa–XXXVIIa**. When in the crude product prevailed triazolones the latter (**L–LVIII**) were isolated by crystallization. The mother liquor after crystallization was evaporated, the residue was put into water, treated with sodium carbonate till pH was 2 units lower than pK_a of the original azole, the azole was extracted into ethyl acetate, the organic layer was separated, and the water layer was evaporated till dryness. The residue was treated with 2% sulfuric acid, the reaction product was extracted into ethyl acetate. On evaporating the solvent the residue was recrystallized. All the compounds isolated were identical to those described in the literature: N–C-bitriazoles **XXIII–XLVI, XLIX** [2–5], 1-R-methyl-3-nitro-1,2,4-triazole-5-ones **L–LIV, LVI, LVII** [2, 18], 3-nitro-1- (2-nitroethyl)-1,2,4-triazole LVIII [3], 5-methyl5-(3-nitro-1,2,4-triazol-1-yl)-5,6-dihydro-oxazolo[3,2-*b*]-1,2,4-triazole **LIX** [17].

3-Nitro-1-(2-nitro-2-azapropyl)-5-(3-nitro-1,2,4-triazol-1-yl)-1,2,4-triazole (XLVII). mp 197–198°C (ethanol). IR spectrum (ν, cm^{-1}): 840 s, 850 w, 865 w, 990 s, 1020 w, 1050 w, 1080 w, 1180 m, 1220 w, 1280 s, 1305 s, 1340 v.s, 1380 w, 1430 s, 1450 m, 1500 m, 1525 m, 1560–1580 v.s. ^{1}H NMR spectrum (δ, ppm): 9.90 s (1H, C^{5}H), 6.65 s (2H, CH_2), 3.69 s (3H, CH_3). Found, %: C 23.3; H 2.1; N 44. *M* 320. $C_6H_6N_{10}O_6$. Calculated, %: C 22.94; H 1.93; N 44.58. *M* 314.17.

3-Nitro-1-(2-nitroxypropyl)-5-(3-nitro-1,2,4-triazol-1-yl)-1,2,4-triazole (XLVIII). mp 124–125°C (chloroform). IR spectrum (ν, cm^{-1}): 840 v.s, 890 m, 940 w, 1000 m, 1060 w, 1140 w, 1180 w, 1250 w, 1280 s, 1315 s, 1350 w, 1390 w, 1440 s, 1460 w, 1515 s, 1570 v.s, 1585 s, 1650 v.s. ^{1}H NMR spectrum (δ, ppm): 9.50 s (1H, C^{5}H), 5.80 d (2H, CH_2), 5.05 m (1H, CH), 1.55 s (3H, CH_3). Found, %: C 25.8; H 2.1; N 38.5. *M* 323. $C_7H_7N_9O_7$. Calculated, %: C 25.5; H 2.1; N 38.3. *M* 329.18.

3-Nitro-1-(2-nitro-2-azapropyl)-1,2,4-triazole-5-one (LV). mp 181–182°C (ethanol). IR spectrum (ν, cm^{-1}): 805 m, 870 s, 940 s, 1020 s, 1070 m, 1100 m, 1140 m, 1240 w, 1260 m, 1280 s, 1340 m, 1360 m, 1380 m, 1420 w, 1470 m, 1550 s, 1750 v.s. ^{1}H NMR spectrum (δ, ppm): 6.00 s (2H, CH_2), 3.56 s (3H, CH_3). Found, %: C 21.9; H 2.9; N 38.1. *M* 210. $C_4H_6N_6O_5$. Calculated, %: C 22.0; H 2.8; N 38.5. *M* 218.12. The compound was also prepared by an independent synthesis by treating 1-(2-nitro-2-azapropyl)-3,5-dinitro-1,2,4-triazole (**XIX**) with a base by procedure [18].

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