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ALKYLATION AND RELATED ELECTROPHILIC REACTIONS AT ENDOCYCLIC NITROGEN ATOMS IN THE CHEMISTRY OF TETRAZOLES

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Abstract – This review summarizes the results of studies of reactions between tetrazoles and various electrophilic agents, published over the past twenty years. Where possible, mechanisms of the reactions are discussed in detail and consideration is given to how the rate and selectivity of processes are influenced by the nature of reactants, parameters of reaction medium, and by other factors.

Dedicated to Prof. J. Elguero on the occasion of his 65th anniversary

1. INTRODUCTION

Tetrazoles are five-membered unsaturated heterocycles with four nitrogen atoms in the ring. Peculiarities of the π-electron system of the tetrazole ring and availability of lone electron pairs of the endocyclic nitrogens allow these heteroatoms to be attacked by various electrophilic reagents. Reactions of this type can be subdivided into three groups, namely, protonation, introduction of substituents, and formation of complexes.

Protonation of tetrazoles has been covered comprehensively in specialized reviews,[1-3] whereas the results of studies on electrophilic reactions of the other two groups are as yet little systematized.[4-6] The authors of the present review tried to close one of these gaps and in doing so to acquaint the international scientific community with the most interesting works of their colleagues from the former Soviet Union.

At the present time, introduction of an appropriate *N*-substituent into an already existing tetrazole cycle is the most common and facile synthetic pathway to *N*-substituted tetrazoles and 1,3- and 1,4-substituted tetrazolium salts. Moreover, some compounds, such as 2-alkyltetrazoles, still can be synthesized in practice by this means only. Aside from an enormous variety of alkyl substituents, many other groups can be introduced by electrophilic reactions at nitrogen atoms of the tetrazole ring, including acyl,[7,8] imidoyl,[9] silyl,[10] phosphoryl,[11] sulfonyl,[12] aryl,[13] vinyl,[14] and amino[15] functions. Scheme 1 represents, in a generalized form, virtually all known to date routes of the introduction of *N*-substituents into the tetrazole cycle.

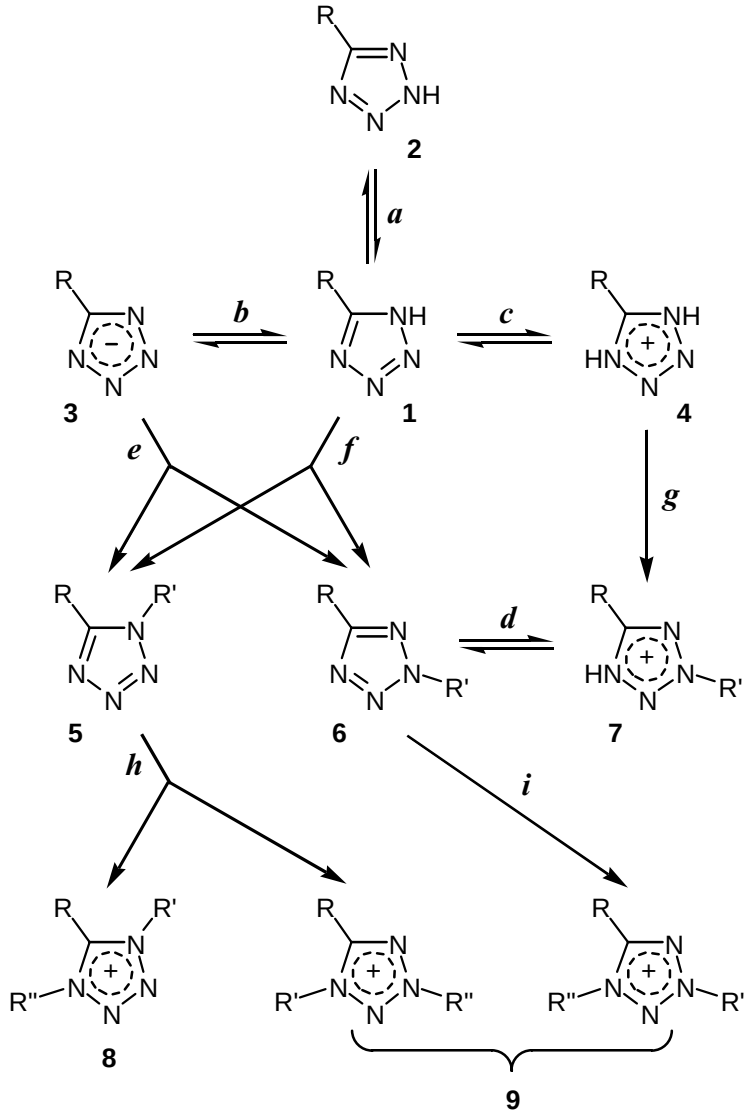
The present review summarizes results of studies on *N*-alkylation, addition onto multiple bonds, and some other electrophilic reactions, which are widely used in syntheses of *N*-substituted tetrazoles. Where possible, primary attention is given to the mechanisms of reactions involving particular tetrazole species as substrates. Recent years have seen considerable progress in understanding these matters, which, however, were not addressed in the latest general reviews devoted to the chemistry of tetrazoles.[5,6]

2. TETRAZOLES AS SUBSTRATES OF ELECTROPHILIC REACTIONS

As shown in Scheme 1, all possible forms of existence of *N*-unsubstituted tetrazoles (**1**–**4**), as well as *N*-substituted tetrazoles (**5**) and (**6**), are capable of reacting with electrophiles. Obviously, the efficient use of these reactions for the synthesis of target compounds can be attained only through understanding regularities, which govern reactivities of both tetrazole substrates and electrophilic reagents, and regioselectivity of processes.

2.1. *N*-UNSUBSTITUTED TETRAZOLES

Thermodynamic and kinetic parameters of reactions between a particular electrophile and tetrazole species (**1**–**4**) would obviously differ. To identify the form(s) that a *N*-unsubstituted tetrazole actually enters into a reaction, quantitative data on equilibria (***a***–***c***) and other relevant dissociative equilibria under the particular reaction conditions are essential.



Scheme 1

Molecules of *N*-unsubstituted tetrazoles can exist as both 1*H*- and 2*H*-tautomers (**1** and **2**, respectively), and these two forms exist in equilibrium in solutions. At the present time, systematic quantitative data on equilibrium (***a***) in solutions are not available. Nonetheless, it has been shown by different techniques that the ratio of **1** to **2** depends on both polarity of solvent and nature of the substituent at position 5 of the tetrazole ring.[1,4,16] In general terms, solvents of high polarity and electron-donating substituents tend to increase the fraction of **1**. ^{15}N NMR spectroscopy has been used to advantage in experimental studies of prototropic equilibrium (***a***). Thus, for solutions of tetrazole in DMSO, the equilibrium mixture was shown to contain 90 to 99% of the 1*H*-form,[17,18] whereas solutions of 5-cyano- and 5-trifluoromethyltetrazole were found to contain substantial amounts of the 2*H*-tautomers.[19]

N-Unsubstituted tetrazoles are moderately strong NH-acids, which form stable tetrazolate anions (**3**) upon deprotonation (equilibrium (***b***)). Acidity of tetrazoles was studied mostly for their aqueous solutions where pK_a values lie in the range of –0.8 (5-nitrotetrazole) to about 6 (5-aminotetrazoles), depending on electronic properties of the substituent at position 5 of the tetrazole ring.[20]

N-Unsubstituted tetrazoles also act as weak organic bases. Their protonation (equilibrium (***c***)) was studied for solutions in aqueous sulfuric acid and some other acids.[1-3] Tetrazoles were found to behave as Hammett bases with pK_{BH^+} values ranging from –1.8 (5-methyltetrazole) to –9.3 (5-nitrotetrazole)[20] to –10.9 (monoprotonated 5,5'-ditetrazole)[21] in aqueous sulfuric acid solutions. It has been shown by different methods that nitrogen atom in position 4 of the ring is the protonation site in both *N*-unsubstituted and *N*-substituted tetrazoles.[3,5]

To date, dissociative equilibria of salts of tetrazoles have been the subject of few studies. According to electrical conductivity measurements, sodium, potassium, and cesium 5-phenyltetrazolates are practically completely dissociated at concentrations of up to 10^{-3} *M* in such organic solvents as acetonitrile, nitromethane, and DMSO.[22,23] At higher concentrations, the equilibrium is shifted to the formation of ion pairs and more complex structures. In the same solvents, however, ammonium 5-phenyltetrazolate exists in the associated form only[22] due to the formation of a hydrogen bond involving nitrogen atom in position 1 of the tetrazole cycle (*cf.* Section 4.1.1.3). Such an association is likely to take place in the case of mono-, di-, and trialkylammonium tetrazolates as well, whereas for solutions of tetraalkylammonium tetrazolates in dipolar aprotic solvents, the equilibrium appears to be shifted toward free ions.[23] Data on behavior of 1*H*,4*H*-tetrazolium salts in organic solvents seem to be lacking. One may suggest that these salts, much like trisubstituted tetrazolium salts,[24] are associated in solvents with low dielectric constant.

Electronic structure of species (**1**–**4**) was studied using various semiempiric and *ab initio* quantum chemical methods, prototropic tautomerism (***a***) of the tetrazole cycle being in the focus of attention, though.[25-29] Tetrazolate anion (**3**, R = H) was shown to possess a quasi-aromatic structure with aromaticity indices comparable to those of benzene[30,31] whereas non-ionized species (**1**) and (**2**) displayed considerably lower aromaticity. Calculations identified 1*H*,4*H*-tetrazolium cation (**4**, R = H) as the most stable form of protonated tetrazole[27,32,33] in full agreement with the experimentally determined protonation site. In contrast to the highly aromatic tetrazolate anion, 1*H*,4*H*-tetrazolium cation featured second to the lowest aromaticity among all protonated azoles.[31] Structures of lithium and ammonium tetrazolates were studied using early semiempiric methods CNDO and CNDO/2.[34,35] It is notable that MNDO-calculated gas-phase proton affinities of tetrazolates and neutral *N*-unsubstituted tetrazoles correlate with the experimentally measured acidity and basicity constants, respectively.[32,33]

2.2. *N*-SUBSTITUTED TETRAZOLES

As shown in Scheme 1, 1- and 2-substituted tetrazoles (**5**) and (**6**) interact with electrophilic reagents to form tetrazolium salts (**8**) and (**9**). Physical and chemical properties of isomeric *N*-substituted tetrazoles differ markedly. Thus, compared with 2-isomers, 1-substituted tetrazoles manifest higher dipole moments,[36] stronger base properties,[37] and greater ability to form complexes with salts of transition metals.[38,39] Acting as weak organic bases, both 1- and 2-substituted tetrazoles get protonated at nitrogen atom in position 4 of the cycle (*cf.* equilibrium (***d***), Scheme 1), as clearly demonstrated by a ^{15}N NMR study.[40]

Electronic structure of *N*-substituted tetrazoles was studied using several semiempiric quantum chemical methods.[33,41] The calculations showed that among three “pyridine-like” nitrogen atoms of the heteroring, that in position 4 was characterized by the highest electron density in both 1- and 2-substituted tetrazoles.

Furthermore, this atom was shown to possess the highest proton affinity as well.[33] These findings imply that nitrogen atom in position 4 of the cycle of both species (**5**) and (**6**) should be the primary target for electrophilic attack. It was also found that, unlike 2-substituted tetrazoles, 1-isomers were characterized by a relatively small difference between proton affinities of the adjacent atoms N4 and N3.[33] This feature is consistent with experimentally observed formation of a single type of product in exhaustive alkylation of 2-substituted tetrazoles as opposed to the bifurcation of the process in the case of 1-substituted tetrazoles (routes (***i***) and (***h***) in Scheme 1, respectively).

3. ELECTROPHILIC REAGENTS

As of now, a broad spectrum of reagents has been used for introducing substituents onto nitrogen atoms of the tetrazole ring through electrophilic reactions. These reagents include esters of sulfuric, arylsulfonic, nitric, and acetic acids; alkyl, aryl, and acyl halogenides; compounds containing double bonds; Mannich bases; diazo compounds; epoxides; alcohols; anhydrides of carboxylic acids, *etc*. When considering reaction mechanisms, it is well to bear in mind that under conditions of a particular reaction, electrophilic reagents themselves may undergo transformations prior to the immediate interaction with the reaction substrates.

At the present time, a more or less general picture of relative reactivities of various electrophiles toward tetrazole substrates can hardly be figured despite the abundance of preparative experiments. Such a situation is caused by the lack of systematic quantitative studies. In this regard, a paper[10] published in 1990 is noteworthy. The authors of that work developed empirical additive "reaction potentials" for several alkylating agents and reaction solvents. Practical applicability of these potentials, expressed in pK_a units, as well as their physical meaning, is as yet unclear. Nevertheless, this innovative work unambiguously demonstrated that the reactivities of different alkylating agents could be compared only with consideration for the nature of both alkylation substrates and reaction solvent.

4. MECHANISMS OF ELECTROPHILIC REACTIONS AT RING NITROGENS

4.1. *N*-UNSUBSTITUTED TETRAZOLES

Reactions of *N*-unsubstituted tetrazoles with electrophilic reagents have been the subject of a large number of works. Among them, publications dealing with mechanisms of alkylation of *N*-unsubstituted tetrazoles have been appearing since the late 1970s. Below, available data on the mechanisms for different tetrazole substrates are summarized and discussed.

4.1.1. TETRAZOLATES

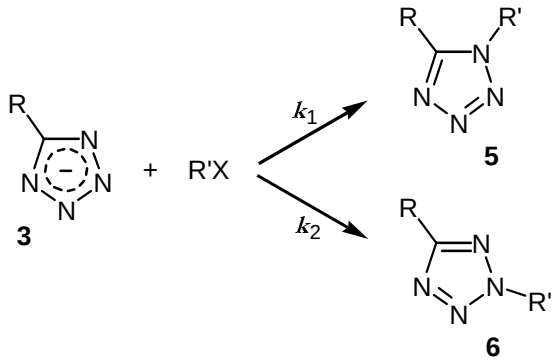
Reactions of *N*-unsubstituted tetrazoles with electrophilic reagents are usually carried out in aqueous or aqueous alcoholic solutions of alkalies, in aprotic organic solvents in the presence of basic agents (carbonates, amines, hydrides), or under phase-transfer catalysis. Under these conditions, reaction substrates

can be represented by free tetrazolate anions, ion pairs, hydrogen-bonded species, and more complex agglomerates. Among these species, alkylation of tetrazolate anions has received the most extensive study.

4.1.1.1. FREE TETRAZOLATE ANIONS

When considering mechanisms of interaction of tetrazolate anions with electrophilic agents (route (***e***) in Scheme 1), regioselectivity of the process is the central issue. Now, it has become a matter of common knowledge that monoalkylation of a tetrazolate anion generally leads to the formation of two isomeric *N*-alkyltetrazoles (**5** and **6**, R' = Alk), and that their ratio depends on reaction temperature and on electronic and spatial properties of the substituent at position 5 of the tetrazole ring. In general terms, increasing the reaction temperature decreases the fraction of **6**, whereas strengthening of electron-withdrawing properties and/or buildup of effective volume of the substituent tend to increase it.

Interpretation of the phenomenon of concurrent formation of **5** and **6** has long been the subject of discussions. Thus, on the basis of preparative experiments, authors of early publications believed, that isomers (**5**) and (**6**) were formed through the substitution of hydrogen atoms in tautomers (**1**) and (**2**), respectively.[1] This explanation evidently collapsed since it was recognized that both tautomers dissociated in the presence of basic agents to form tetrazolate anion (**3**), which acts as the unique substrate of alkylation. It was therefore suggested[16] that formation of isomers (**5**) and (**6**) resulted from electrophilic attacks at two distinct reaction centers of the ambident tetrazolate anion (**3**), namely, at atoms N1(N4) and N2(N3). In this case, regioselectivity of the process should be governed by the relationship between rate constants[42] k_1 and k_2 (Scheme 2).



Scheme 2

Quantitative relationships between the nature of substituents in 5-(substituted phenyl)tetrazolates and regioselectivity of alkylation were studied independently in several laboratories. These studies revealed the existence of linear correlations between the regioselectivity factor log$F$ (where F = [**6**]/[**5**] = k_2/k_1) and σ-constants of substituents in the phenyl moiety. Such dependences were observed for alkylation of 5-(substituted phenyl)tetrazolate anions with dimethyl sulfate in aqueous buffer solutions[43] and in acetonitrile;[44] with methyl iodide in aqueous ethanol[16,42] and in the water–dichloromethane system in the presence of a phase-transfer catalyst;[34] and with ethyl bromoacetate in acetonitrile.[45] The dependences found were described by equations of the type:

$\log F = \Delta\rho \cdot \sigma + \text{const}$

where $\Delta\rho = \rho_2 - \rho_1$, and ρ_1, ρ_2 are Hammett constants from the expressions $\log k_1 = \rho_1 \cdot \sigma + \text{const}$ and $\log k_2 = \rho_2 \cdot \sigma + \text{const}$. Furthermore, the $\Delta\rho$ values were found to decrease regularly with increase in reaction temperature[44,45] to reflect the observed rise in partial yield of N2-alkylated tetrazoles (**6**). Extrapolation of the plot of $\Delta\rho$ *vs*. $1/T$, where T is thermodynamic temperature, to $\Delta\rho = 0$ gave isoselective temperature β_F, which equaled to 345 K for alkylation of 5-(substituted phenyl)tetrazolate anions with dimethyl sulfate[44] and to 340 K for the alkylation with ethyl bromoacetate.[45] Since $\Delta\rho$ values are positive at temperatures below β_F, increase in electron-withdrawing properties of the substituent at position 5 of the tetrazole ring favours increased formation of 2-substituted tetrazoles (**6**) rather than that of 1-isomers (**5**). However, at temperatures above β_F, the inverse effect is possible, while this interesting conclusion has yet to be confirmed experimentally.

The regioselectivity factor $\log F$ was also found to correlate linearly with $1/T$.[44,45] The slope of this dependence was shown to be equal to $\Delta E = E_1 - E_2$, where E_1 and E_2 are activation energies of formation of isomers (**5**) and (**6**), respectively. These findings provided explanation for the experimentally observed effect of reaction temperature on regioselectivity of alkylation: the fact that increase in reaction temperature results in a growth of the fraction of 1-isomer (**5**) is the direct consequence of E_1 being higher than E_2.

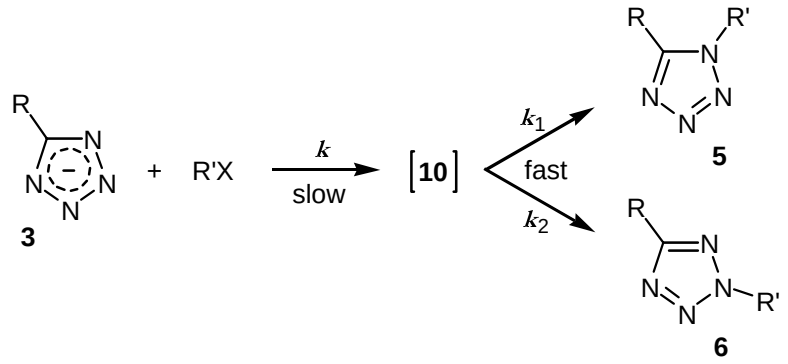
An adequate analysis of the effect of a broader range of substituents at position 5 of the tetrazole cycle on regioselectivity of alkylation of tetrazolate anions has yet to be carried out, while some attempts have been already undertaken.[46] However, there are strong grounds to believe that the above-discussed regularities, revealed for 5-(substituted phenyl)tetrazolates, are general ones and can be extended, with necessary adjustments, to tetrazolates with any substituents.

Kinetic studies undertaken along with the investigation of regioselectivity[44,45] led to a radically new concept of mechanism of the reaction under consideration. It was shown that the overall rate of alkylation of 5-(substituted phenyl)tetrazolate anions with dimethyl sulfate[44] and with ethyl bromoacetate[45] depended on electronic nature of substituents in the phenyl moiety. Specifically, electron-donating substituents speeded up the reaction, while electron-withdrawing ones tended to slow it down. Linear correlation between logarithm of the reaction rate constant k and σ-constants of phenyl substituents of the type:

$\log k = \rho \cdot \sigma + \text{const}$

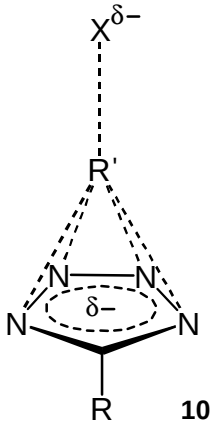
was clearly observed in a broad temperature range. In this case, however, the slope of the dependence (*i.e.*, Hammett constant ρ) appeared to be virtually temperature-independent, which implies that isokinetic temperature β_k is infinite. These findings led to the conclusion that interaction between tetrazolate anion and electrophile and formation of reaction products (**5**) and (**6**) take place at different stages of a more complex process than that described by Scheme 2. Activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$, calculated from the temperature dependence of rate constants, indicated that the rate-limiting stage of reaction was a bimolecular process. This conclusion was further corroborated by the results of comparative experiments on alkylation of 5-phenyltetrazolate anion with dimethyl sulfate and with its deutero-analogue.[47] These data, combined with the magnitude and sign of Hammett constant ρ, suggested[44,45] that the interaction between tetrazolate anion and electrophile constituted the slower reaction stage. This bimolecular process conceiv-

ably results in the formation of a labile intermediate (**10**), which irreversibly transforms into isomeric tetrazoles (**5**) and (**6**) at the next, kinetically uncontrolled, stage (Scheme 3).



Scheme 3

It should be particularly emphasized that the distinctive feature of this two-stage mechanism is that the rate and regioselectivity of the overall reaction are determined by two separate, kinetically independent, processes. According to Scheme 3, reaction rate is governed by the properties of the substituent R in tetrazolate anion (**3**), by the reactivity of electrophile R'X, and by the parameters of reaction medium. Formation of reaction products, on the other hand, is controlled solely by the nature of intermediate (**10**). The latter converts into isomeric *N*-substituted tetrazoles (**5**) and (**6**) by two parallel monomolecular processes, and the ratio of the products formed follows the above-discussed regularities. Structure of intermediate (**10**) was not elaborated in the publications cited, and Scheme 4 depicts a hypothetical structure proposed by the authors of this review.



Scheme 4

The effect of parameters of reaction medium on the rate and regioselectivity can be illustrated by the following example. It was shown that, when going from anhydrous to a water-containing acetonitrile featuring nearly identical dielectric constant, the rate of alkylation of 5-phenyltetrazolate anion with dimethyl sulfate decreased substantially due to the specific solvation of the substrate with water molecules.[48] The ratio of two reaction products changed as well thus reflecting inevitable solvation-related changes in the

structure of intermediate (**10**).

In closing this section, it should be noted that there are grounds to believe that the outlined concept of mechanism could be ultimately expanded to some related reactions of tetrazolate anions, such as acylation,[7,10] silylation,[10] interaction with α-epoxides,[49] *etc*. This suggestion, however, should be confirmed (or disproved) by further studies.

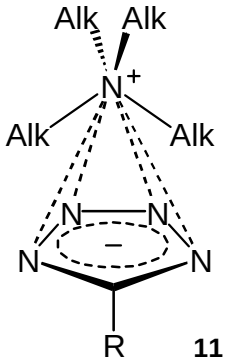
4.1.1.2. ION PAIRS

Free tetrazolate anions (**3**) emerge from complete dissociation of salts of *N*-unsubstituted tetrazoles. However, for conditions of actual preparative experiments, account must be taken of processes of ionic association as they could result in changing both nature of tetrazole substrates and mechanism of reactions. The association of ions in ion pairs, as well as specific solvation of tetrazolates, noticeably affects the rate and/or regioselectivity of the reactions under consideration. Yet, these phenomena have not been the subjects of systematic studies.

An early attempt to relate ionic association in alkali metal salts of 5-phenyltetrazole to the rate and regioselectivity of their alkylation with dimethyl sulfate,[23] undertaken by one of the authors of the present review, now does not appear to be quite adequate. Indeed, in that work, it was recognized that sodium, potassium, and cesium salts of 5-phenyltetrazole were completely dissociated under the conditions used. Therefore, in all cases studied, alkylation substrates were free 5-phenyltetrazolate anions rather than ion pairs. The observed minor variations in the alkylation rate constant upon going from one cation to another seem to lie within the range of instrumental error.

Unfortunately, reliable quantitative data on the rate and regioselectivity of reactions of ion pairs formed by tetrazolate anions and alkali metal cations are not available at the present time, and drawing generalizations from the results of numerous preparative experiments could lead to misconception. This is especially true in regard to the evaluation of regioselectivity since the amounts and ratio of two isomeric reaction products (**5**) and (**6**) isolated using distillation, fractional crystallization, or flash chromatography may not reflect actual picture. Nonetheless, several series of uniform experiments unambiguously demonstrated that regioselectivity of reactions of ion pairs of tetrazolates was governed by the same factors as discussed in Section 4.1.1.1. Here, studies on regioselectivity of alkylation of sodium tetrazolates with chloromethyl derivatives of ferrocene[50] and with methyl iodide[46] can be cited as examples.

Unlike the case of mono-, di-, and trialkylammonium salts (*cf*. Section 4.1.1.3), reactions of tetraalkylammonium tetrazolates yield isomeric products (**5**) and (**6**) in ratios analogous to those observed for the reactions of the same tetrazolates in the form of free anions.[47] This is a good indirect evidence for the similarity or, possibly, identity of mechanisms. Indeed, tetraalkylammonium tetrazolates are known to dissociate completely in organic solvents under certain conditions.[23] Alternatively, in the ion pair formed by a tetraalkylammonium cation and a tetrazolate anion, the cation is sited, by hypothesis,[34] over the plane of the ring (Scheme 5). As a result, the heterocycle in species (**11**) is not hindered for the electrophilic attack from the opposite direction and the reaction mechanism will essentially match Scheme 3.



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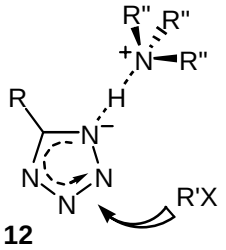
Scheme 5

4.1.1.3. HYDROGEN-BONDED SPECIES

Mechanism of electrophilic reactions involving ammonium or mono/di/trialkylammonium salts of *N*-unsubstituted tetrazoles seems to differ from that discussed above. In aprotic solvents, these salts exist as hydrogen-bonded complexes[51] of the type shown in Scheme 6. Electronic structure of species (**12**) differs essentially from that of tetrazolates (**3**) either as free anions or in ion pairs in that the aromaticity of the heterocycle is considerably disrupted due to the involvement of nitrogen atom N1 in the hydrogen bond. It is quite possible that electrophilic attack at such substrates would be directed frontally toward the bond N2—N3 (Scheme 6) rather than normally to the plane of the heterocycle as it occurs in the case of highly aromatic tetrazolate anions.



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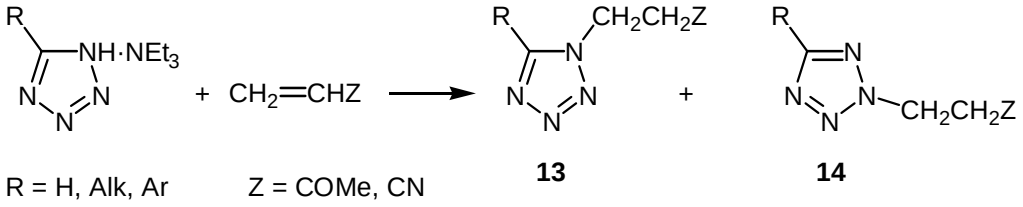
Scheme 6

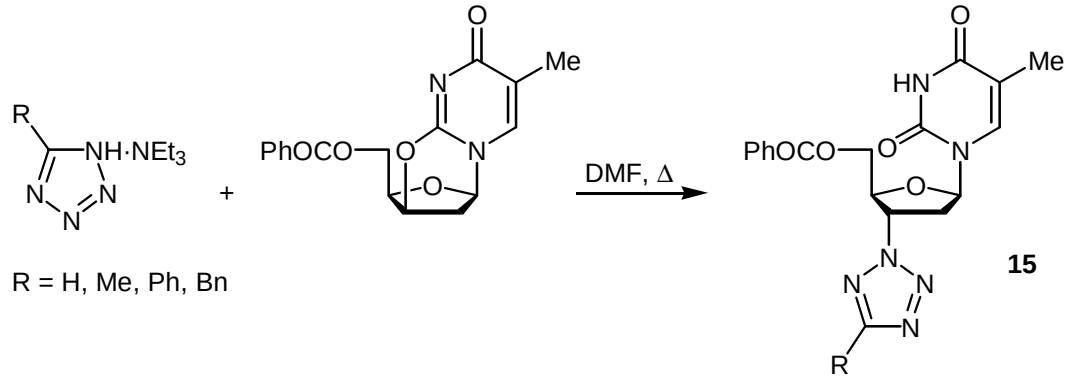
This assumption, together with the obviously increased steric hindrance to the formation of 1-substituted tetrazoles, helps explain experimental findings. Thus, it was shown that the reaction of triethylammonium salts of 5-aryltetrazoles with methyl vinyl ketone yielded 2-substituted derivatives (**14**, Z = COMe) as the only or vastly predominant reaction products.[35,51] Yet, more compact substituents at position 5 of the heterocycle afforded formation of both 1- and 2-substituted tetrazoles (**13**) and (**14**) in comparable amounts[38] (Scheme 7).

Unusually high regioselectivity was also observed for the reaction of triethylammonium salts of tetrazole and 5-monosubstituted tetrazoles with 5'-*O*-benzoyl-2,3'-anhydrothymidine.[52-54] Here, only 2-substituted tetrazoles (**15**) were found to form independently of the nature of the substituent at position 5 of the tetrazole ring (Scheme 8). It seems plausible that the exclusive formation of 2-isomers in this case is dictated by steric factors, since the electrophile, 5'-*O*-benzoyl-2,3'-anhydrothymidine, features a bulky

three-dimensional structure. This assumption is corroborated by the fact that the same regioselectivity was detected when using sodium hydride instead of triethylamine.[55] On the other hand, the pattern observed could be due to a radical change in the reaction mechanism.

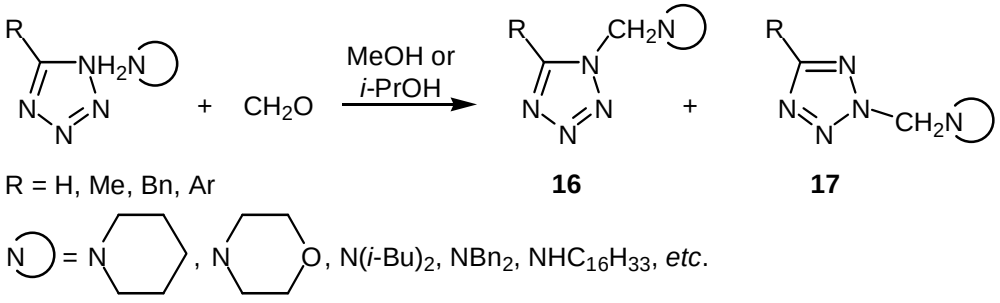


Scheme 7



Scheme 8

Reaction specific to mono- and dialkylammonium salts of *N*-unsubstituted tetrazoles is their interaction with formaldehyde. This reaction occurs under mild conditions[56-58] and leads to the formation of *N*-aminomethyltetrazoles (Scheme 9).



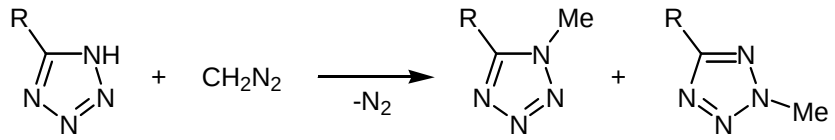
Scheme 9

Mechanism of this process was not studied, however, it is reasonable to assume that it proceeds through the initial formation of *N*-hydroxymethyltetrazoles by analogy with Scheme 7. The hydroxy compounds subsequently react with the released amine to give final products (**16**) and (**17**). The true regioselectivity of the formation of 1- and 2-substituted derivatives in this reaction could not be evaluated due to the readily occurring isomerization of both *N*-hydroxymethyl- and *N*-aminomethyltetrazoles (*cf.* Section 4.2).

4.1.2. NEUTRAL TETRAZOLES

Reactions discussed below are represented in a generalized form by route (***f***) in Scheme 1. The exact nature of tetrazole substrates undergoing electrophilic attack in these processes is as yet unknown. These reactions were grouped into this section based on the fact that under the conditions employed, *N*-unsubstituted tetrazoles would exist predominantly as non-ionized species.

Alkylation with diazomethane. *N*-Unsubstituted tetrazoles were long believed to react with diazomethane to yield the corresponding N2-methylated derivatives (**19**) as major products[46] (Scheme 10).

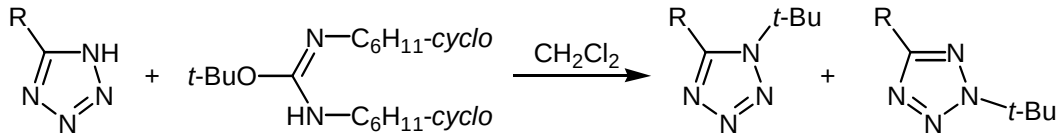


18 **19**

Scheme 10

However, by the data of the authors of the present review, alkylation with diazomethane provides isomeric 1- and 2-methyltetrazoles (**18**) and (**19**) in the ratio close to that observed for alkylation of the respective tetrazolates with dimethyl sulfate or methyl iodide. A plausible explanation for such a similarity is that the first stage of the process is a (fast) proton transfer from the NH-acidic (*cf*. Section 2.1) heterocycle to a diazomethane molecule. Then, at the rate-limiting stage, the resultant tetrazolate anion and protonated diazomethane are likely to form an intimate ion pair with the structure analogous to that of (**10**). In this case, reaction proceeds essentially by the mechanism described by Scheme 3 thus obeying known regularities. Unfortunately, a detailed study of this reaction presents experimental difficulties since the determination of concentration of diazomethane in solutions has always been troublesome. It should be noted also that alkylation of tetrazoles with diazomethane is currently rarely used because of its highly toxic and explosive nature.

Alkylation with O-tert-butyl-N,N'-dicyclohexylisourea provides mixtures of isomeric 1- and 2-*tert*-butyltetrazoles[59] (**20**) and (**21**) (Scheme 11) and seems to be the only common practical method for the synthesis of 1-*tert*-butyltetrazoles. The isourea results from a preliminary reaction of *tert*-butyl alcohol with *N*,*N*'-dicyclohexylcarbodiimide in the presence of catalytic amounts of copper(I) chloride.

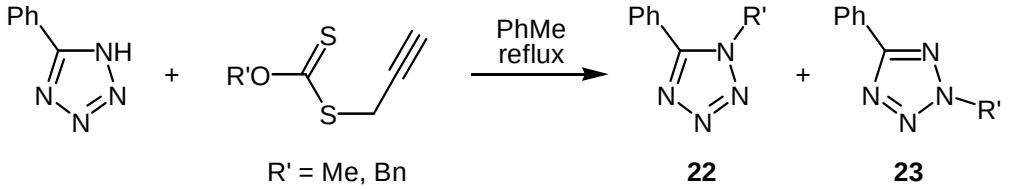


R = NH_2, Ph, SMe, Cl

20 **21**

Scheme 11

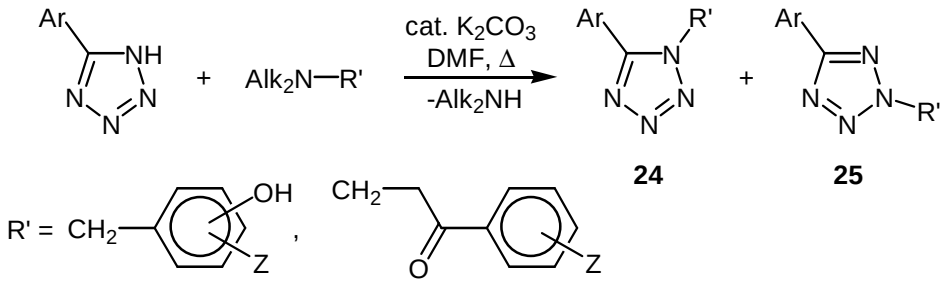
O-Alkyl-S-propargyl xanthates (dithiocarbonates) were reported recently as useful esterification reagents capable of reacting with NH-acids as well.[60,61] The latter was demonstrated by the methylation[60] and benzylation[61] of 5-phenyltetrazole (Scheme 12). The methylation gave a 1:7 mixture of 1- and 2-substituted 5-phenyltetrazoles (**22**) and (**23**), whereas the only reaction product detected in the benzylation was the corresponding 2-alkyl derivative (**23**). The true species interacting with substrates in this reaction are thought to be betaines, which result from a sigmatropic rearrangement of *S*-propargyl xanthates.



Scheme 12

It should be noted that, much like the alkylation with diazomethane, the two reactions discussed above apparently involve a proton transfer from the tetrazole cycle to the molecule of alkylating agent followed by the formation of an intimate ion pair of the structure somewhat similar to **10**. Hence, one can suggest that in these cases as well the ratio of N1- and N2-alkylation products is governed the known factors.

Alkylation with Mannich bases derived from substituted phenols[62] and from acetophenones[63] was examined in a series of 5-aryltetrazoles. The reaction was carried out in the presence of catalytic amounts of potassium carbonate and proceeded efficiently at temperatures *ca*. 150 °C to give mixtures of isomeric products (**24**) and (**25**) (Scheme 13). As in the cases discussed previously, the ratio of **24** to **25** was found to depend both on electronic properties of the aryl substituent in the tetrazole cycle and on spatial factors.

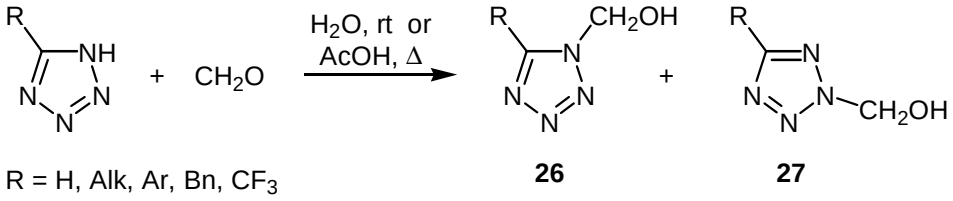


Scheme 13

It was supposed that the immediate alkylating agents in this process were the corresponding vinylidene[64]/vinyl[63] compounds formed upon deamination of the starting Mannich bases under the reaction conditions. Furthermore, it is reasonable to assume that the emerging secondary amine would react with *N*-unsubstituted tetrazole to give a substrate of the type (**12**). The process of alkylation in this case is described essentially by Scheme 7 (Section 4.1.1.3) and the ratio of isomeric products is dictated by the appropriate regularities. Interestingly enough, the regioselectivity of the alkylation of 5-aryltetrazoles with Mannich

bases could be influenced by the action of ultrasound.[64] This particular phenomenon, as well as the reaction mechanism in general, remains to be studied.

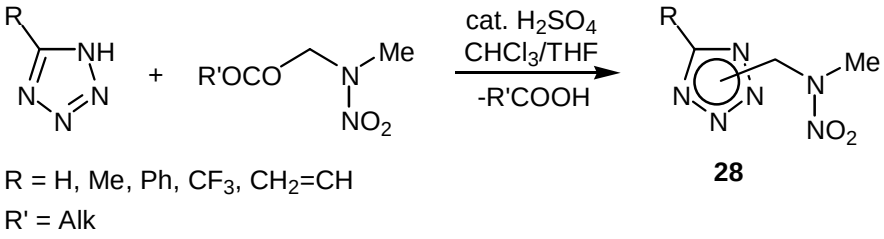
Hydroxymethylation. *N*-Unsubstituted tetrazoles were found to react slowly with formaldehyde in aqueous solution at pH = 5 to produce mixtures of 1- and 2-hydroxymethyl derivatives[65] (**26**) and (**27**) (Scheme 14). In the case of poor solubility of starting tetrazoles, sodium tetrazolates could be brought into the reaction. More recently, it was shown that the use of acetic acid as the reaction medium drastically shortened reaction time and alleviated problems with solubility.[58]



Scheme 14

The true regioselectivity of the process could not be evaluated since individual isomers (**26**) and (**27**) are capable of interconversion (*cf*. Section 4.2) and they exist in a dynamic equilibrium in solutions.[58]

Alkylation with esters of 2-nitro-2-azapropanol. This reaction proceeds in neutral organic solvents in the presence of catalytic amounts of sulfuric acid[66] (Scheme 15). The regioselectivity of the process has not been assessed.

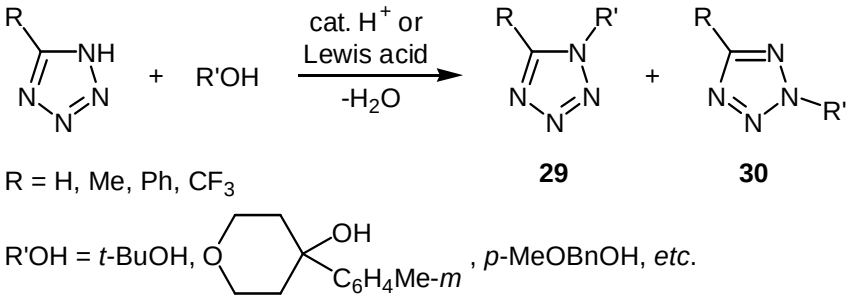


Scheme 15

It is assumed that the reaction occurs through the initial formation of a relatively stable 2-nitro-2-azapropyl carbenium cation, which then interacts with the heterocycle.[66] This credible speculation, however, still needs to be confirmed experimentally.

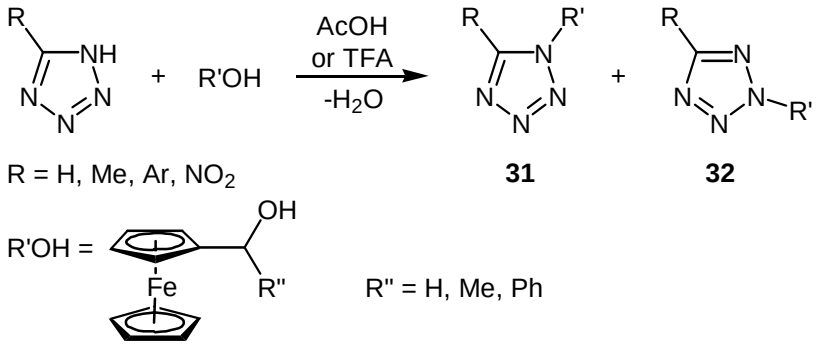
Alkylation with alcohols can be performed under a variety of conditions (Schemes 16–18). Alcohols, readily generating carbenium cations in the presence of acidic catalysts, were found to react with *N*-unsubstituted tetrazoles yielding mixtures of N1- and N2-alkylated products. The reaction can be carried out in neutral organic solvents (chloroform,[67] dichloromethane, acetonitrile, nitromethane[68]) in the presence of catalytic amounts of sulfuric[67] or *p*-toluenesulfonic[68] or a Lewis acid,[68] such as boron trifluoride ethe-

rate, zinc triflate, *etc* (Scheme 16). As one might expect, both electron-withdrawing and voluminous substituents at position 5 of the tetrazole cycle disfavour the formation of 1-substituted tetrazoles (**29**).



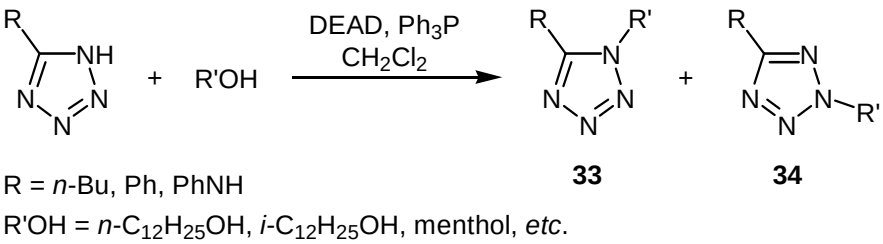
Scheme 16

Another choice of reaction conditions can be exemplified by the alkylation of *N*-unsubstituted tetrazoles with α-ferrocenyl alcohols in glacial acetic[69,70] and trifluoroacetic acid[71] medium (Scheme 17). Here, too, the fraction of N2-alkylated products (**32**) was observed to increase with strengthening electron-withdrawing properties of the substituent at position 5 of the tetrazole cycle.[69] On the ground that such a feature is peculiar to alkylation of tetrazolates, it was suggested[70,71] that α-ferrocenyl carbenium cations formed interacted with tetrazolate anions. However, considering moderate acidity of tetrazoles, formation of tetrazolate anions seems unlikely under the conditions used.



Scheme 17

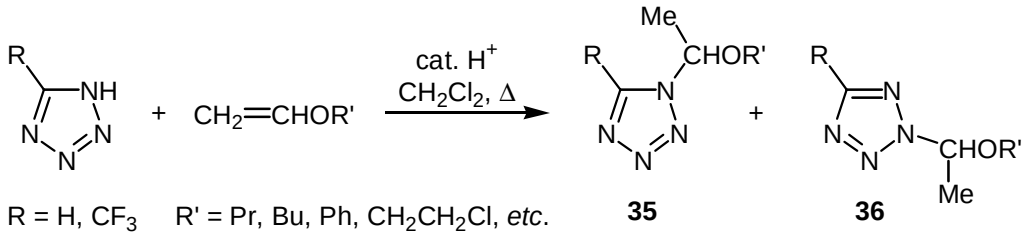
More recently, it was shown that *N*-unsubstituted tetrazoles could be alkylated with primary and secondary aliphatic alcohols using Mitsunobu protocol[72] (Scheme 18).



Scheme 18

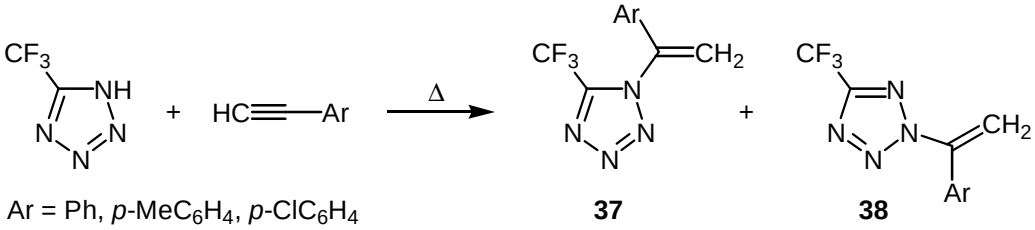
Direct comparison of isolated yields of **33** and **34** from the Mitsunobu alkylation and from the reaction of triethylammonium salts of the same tetrazoles with the respective alkyl bromides showed that both processes gave the two isomeric products in similar ratios.[72] In the case of secondary alkyl groups, the alkylation with alcohols provided notably higher overall yields.

Addition onto carbon-carbon multiple bonds. *N*-Unsubstituted tetrazoles are capable of formal addition onto the double bonds in vinyl ethers.[73,74] The reaction is acid-catalyzed and the heterocycle forms a bond with the α-carbon atom of the vinyl moiety (Scheme 19). 2-Substituted tetrazoles (**36**) were detected as the predominantly formed products.[73,74]



Scheme 19

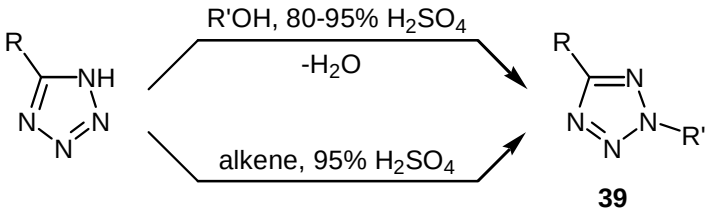
It will be recalled that in the case when trialkylammonium salts of tetrazoles were brought into a similar reaction (*cf*. Scheme 7), the addition site was the β-carbon of vinyl group. At the present time, it is unclear whether such dissimilarity is due to the different nature of the tetrazole substrates or it is caused by other factors. A plausible explanation is that vinyl ethers undergo protonation under reaction conditions to from carbenium cations, which then act as immediate alkylating species. As the formation of a secondary carbenium cation is preferable, the protonation occurs at the terminal carbon atom of the vinyl group. Subsequent interaction of such cation with the tetrazole cycle leads the observed α-addition products.
Addition onto the triple bonds in arylacetylenes occurs in a similar fashion[74] to yield α-substituted *N*-vinyltetrazoles (**37**) and (**38**) (Scheme 20). So far, 5-trifluoromethyltetrazole has been the only reported tetrazole to be brought into this reaction. It is notable that in this case interaction proceeded in the absence of a foreign catalyst due to the enhanced acidity of the substrate.[74]



Scheme 20

4.1.3. PROTONATED TETRAZOLES (TETRAZOLIUM CATIONS)

Recently, formation of 2-alkyl derivatives as the sole products of the reaction of *N*-unsubstituted tetrazoles with secondary and tertiary aliphatic alcohols[75] or corresponding alkenes[76] in sulfuric acid media (Scheme 21) has been reported.



R = H, Alk, Ph, CF_3

R' = *i*-Pr, *t*-Bu, *cyclo*-C_6H_{11}

alkene = CH_2=CHMe, CH_2=CMe_2, *cyclo*-C_6H_{10}

Scheme 21

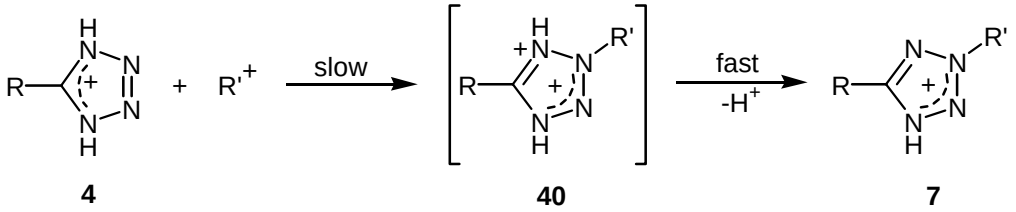
The reaction proceeded at room temperature to give 2-substituted tetrazoles (**39**) in high to nearly quantitative yield in a short time (≤ 1 h). No formation of N1-alkylated products was detected regardless of electronic and spatial properties of the substituent at position 5 of the tetrazole ring. Such reaction course could not be interpreted within the framework of the developed concepts of reactivity of *N*-unsubstituted tetrazoles. Hence, considering acidity of the reaction medium and basicity of tetrazoles, it was suggested that in this case they underwent alkylation while being protonated and that the exceptional regioselectivity arose from the protonated tetrazole cycle being the substrate of alkylation.[75]

Conclusive evidence on the nature of N2-regioselective alkylation of tetrazoles was provided by subsequent kinetic studies[77,78] that dealt with the alkylation of 5-phenyltetrazoles with isopropyl alcohol in sulfuric acid media. In the first of these works, effect of medium acidity (84–99% H_2SO_4) on the reaction rate was studied and obtained data were used for elucidating mechanism of the reaction. When considering possible mechanisms, it was taken into account that under the reaction conditions both *N*-unsubstituted tetrazoles and alcohols are subject to protolytic equilibria according to the following equations:

$$TH + H^+ \overset{K_{BH^+}(tetr.)}{\rightleftharpoons} TH_2^+$$

$$R'OH + H^+ \overset{K_{BH^+}(alc.)}{\rightleftharpoons} R'OH_2^+ \overset{K_{R^+}}{\rightleftharpoons} R'^+ + H_2O$$

where TH is a non-ionized tetrazole (**1**); TH_2^+ is a protonated tetrazole (**4**); R'OH is an alcohol capable of forming carbenium cation R'^+; K_{BH^+}(tetr.) and K_{BH^+}(alc.) are the basicity constants for TH and R'OH, respectively; and is K_{R^+} the equilibrium constant of formation of the carbenium cation from protonated alcohol $R'OH_2^+$. Since the reaction under consideration was found to be of the second order overall and of the first order with regard to either of TH and R'OH,[77] the following hypotheses on the interaction at the rate-limiting stage were tested: {TH + R'OH}, {TH + $R'OH_2^+$}, {TH + R'^+}, {TH_2^+ + R'OH}, {TH_2^+ + $R'OH_2^+$}, and {TH_2^+ + R'^+}. Further analysis showed that the only hypothesis to fit in the experimental kinetic data was {TH_2^+ + R'^+}. It was, therefore, concluded that the two species interacting at the rate-limiting stage were protonated tetrazole and carbenium cation. Protonation of an *N*-unsubstituted tetrazole (**1**) is known to occur at position 4 of the heterocycle (*cf.* Section 2.1) to give a symmetrical 1*H*,4*H*-tetrazolium cation (**4**). In the latter, only atoms N2 and N3 are accessible for electrophilic attack whereas both N1 and N4 are blocked by the attached protons. With atoms N2 and N3 being, in fact, identical, this distinctive feature explains the exceptional regioselectivity of the reaction (Scheme 22).



4 **40** **7**

Scheme 22

Interaction of two positively charged entities seems rather unusual at first sight, however, MNDO quantum chemical calculations for a series of 5-substituted 1*H*,4*H*-tetrazolium cations revealed that these structures were characterized by a substantial electron density localized on atoms N2, N3.[78] Hence, it seems plausible that one of these atoms could be attacked by the carbenium cation which, apparently, is an extremely potent electrophile. This attack results in the formation of an unstable intermediate (**40**). As it follows from the analysis of kinetic isotope effect observed in experiments employing $D_2SO_4 – D_2O$ system,[77] the process ends up in a fast splitting off of a proton from the intermediate to give protonated 2-substituted tetrazole (**7**). Properties of *N*-substituted tetrazoles as weak bases were discussed previously (Section 2.2).

Effect of electronic nature of the substituent at position 5 of the tetrazole ring on the rate of N2-regioselective alkylation was studied in a series of 5-(substituted phenyl)tetrazoles.[78] As one might expect, electron-withdrawing substituents tended to slow down the reaction, whereas electron-donating ones – to accelerate it. It was found that logarithm of the true rate constant k correlated with σ° constants of phenyl substituents as $\log k = \rho \cdot \sigma° + \text{const}$. The sign and magnitude of Hammett constant ρ in this dependence were consistent with the proposed reaction mechanism. It is noteworthy that logarithm of the true rate constant was also found to correlate with the MNDO-calculated net effective charges on atoms N2, N3 of 1*H*,4*H*-5-(substituted phenyl)tetrazolium cations.[78]

According to the suggested mechanism, exclusive formation of 2-substituted derivatives upon alkylation with carbenium cations results from 1*H*,4*H*-tetrazolium cations (**4**) being the sole reaction substrates. In terms of protolytic equilibrium (***c***) (Scheme 1), this means that *N*-unsubstituted tetrazoles, entering the reaction, are completely protonated. Practically, this condition is achieved in media of a sufficiently high acidity, such as concentrated sulfuric or perchloric[79] acids, where ionization ratio $I = [\mathbf{4}]/[\mathbf{1}]$ is of the order of 10^3 or higher. On the other hand, the same mechanism implies that should medium acidity fail to provide the complete protonation of the tetrazole cycle, while still being sufficient for the generation of a carbenium cation, the reaction would occur at both N1- and N2-positions (*cf.* Section 4.1.2). This inference was substantiated experimentally by the results of alkylation of tetrazole with *tert*-butyl alcohol in phosphoric acid media where formation of both 1- and 2-*tert*-butyltetrazoles was detected.[76] Moreover, it was shown that, in full agreement with the proposed mechanism, fraction of the 1-isomer steadily grew with decreasing concentration of phosphoric acid, *i.e.* with decreasing extent of the tetrazole cycle protonation.

More recently, spectrum of alcohols and alkenes used for the N2-regioselective alkylation of tetrazoles in sulfuric acid media has been extended to include 1-adamantanol,[80-82] 1-halo-2-propanols,[83] and 3-bromopropene.[83] Reaction with the latter halogenated compounds was found to be rather slow[83] presumably due

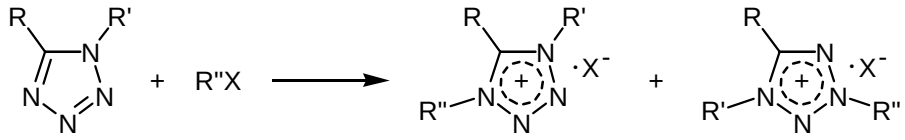
to a more difficult formation of the respective carbenium cations. Mention may be made also of alkylation of 5-phenyltetrazole with cyclohexene and several other alkenes in the presence of *p*-toluenesulfonic acid performed under drastic conditions with limited success.[84]

In closing this section, it should be remarked that the regioselective introduction of *N*-substituents by the reaction of protonated azole heterocycle with carbenium cation, an approach initially developed[75,76] and investigated[77,78] by the authors of the present review in the tetrazole series, has been subsequently extended to other heterocyclic compounds, such as 1,2,4-triazoles,[85,86] and imidazoles.[87] Interestingly enough, failure of attempts to alkylate 4-phenyl-1,2,3-triazole in a concentrated sulfuric acid medium, also undertaken by the authors of the present review, prompted a detailed study of basicity of this compound to reveal an unusual pattern of its protonation.[88,89]

4.2. *N*-SUBSTITUTED TETRAZOLES

Alkylation of *N*-substituted tetrazoles leads to the formation of tetrazolium salts (routes (***h***) and (***i***) in Scheme 1) and hence is referred to as exhaustive alkylation. At the present time, notion of mechanism(s) of this process is far from complete, however one can find some parallels between regularities of exhaustive alkylation and protonation of *N*-substituted tetrazoles.

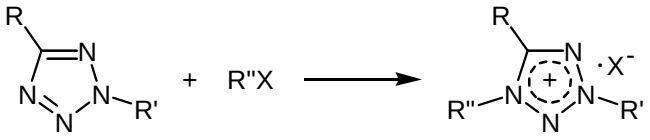
Exhaustive alkylation of 1-substituted tetrazoles (**5**) generally produces mixtures of isomeric 1,4-substituted (**8**) and 1,3-substituted (**9**) tetrazolium salts (Scheme 23).



5 **8** **9**

Scheme 23

Unlike 1-isomers, 2-substituted tetrazoles (**6**) can be alkylated only at position 4 of the cycle to give 1,3-substituted tetrazolium salts (**9**) (Scheme 24).



6 **9**

Scheme 24

As one might expect, interaction of *N*-substituted tetrazoles with dialkyl sulfates, haloalkanes and analogous alkylating agents is substantially slower than that of tetrazolates. For this reason, exhaustive alkylation with these agents is often carried out without solvent. It was reported that the process could also be notably intensified under high pressure (≥ 5000 atm).[90] This effect was attributed to the known

trend of acceleration of quaternization of nitrogen bases with increasing pressure. 1-Methyl-5-aryltetrazoles were shown to possess greater reactivity in exhaustive alkylation with dimethyl sulfate as compared with the respective 2-isomers,[91] what is consistent with their relative basicities (*cf.* Section 2.2). Systematic studies of factors, influencing ratio between products (**8**) and (**9**) formed upon exhaustive alkylation of 1-substituted tetrazoles with dialkyl sulfates, haloalkanes, *etc*., seem to be lacking. Yet, in most cases, formation of 1,4-isomers (**8**) was reported as predominant in the absence of spatial hindrances.

Uncompromising regioselectivity of exhaustive alkylation of 2-substituted tetrazoles was exploited in a recently developed elegant procedure[92] for synthesis of 1-alkyltetrazoles starting from *N*-unsubstituted ones (Scheme 25). This three-step reaction sequence, utilizing an N2-regioselective *tert*-butylation in the first step, was reported to provide isomerically pure products (**41**) in high to nearly quantitative yield.

R = H, Me, Ph, CH_2=CH, CF_3 Alk = Me, Et, *n*-Bu

X = OSO_2OMe, OSO_2Ph, TsO, $OEt_2 \cdot BF_4$

41

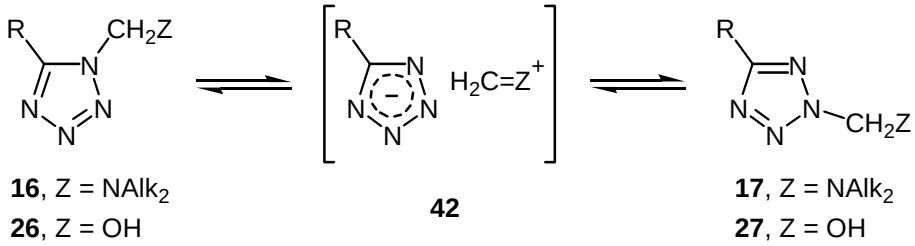
Scheme 25

Recent works on alkylation of *N*-unsubstituted tetrazoles with carbenium cations generated from alcohols under action of acids (*cf.* Sections 4.1.2 and 4.1.3) have prompted the use of the same approach for the exhaustive alkylation as well. It was shown that reactions of these highly reactive electrophiles with *N*-substituted tetrazoles followed the general pattern represented by Schemes 23 and 24.[93] Comparative analysis of accounts[93-95] dealing with the acid-promoted exhaustive alkylation of 1-substituted tetrazoles suggests that the ratio between isomeric tetrazolium salts (**8**) and (**9**) formed is apparently influenced by the acidity of reaction medium. An emerging trend is that in the media of minimal acidity, nitrogen atom in position 4 of the 1-substituted tetrazole cycle is the primary alkylation site[94] in the absence of steric hindrances, much like the case of neutral alkylating agents. However, the alkylation at N4 is progressively suppressed with increasing medium acidity,[93,95] thus giving way to the alternative alkylation at N3. This is presumably due to the protonation of the tetrazole cycle that results in the formation of the 1-substituted 4*H*-tetrazolium cation (*cf.* Section 2.2). In the latter, atoms N2 and N3 would be still accessible for electrophilic attack by a carbenium cation (*cf.* mechanism discussed in Section 4.1.3), with atom N3 being less sterically hindered. These factors combined could ultimately account for 1,3-isomers (**9**) being the only reaction products formed in the media of high acidity.[95]

It is pertinent to note that when evaluating regioselectivity of alkylation of *N*-substituted tetrazoles, one should also take into account possible isomerization of **8** into **9** and *vice versa*. So far, there have been few reports dealing with such transformations,[91,95] and further studies in this field are warranted.

Interconversions of isomeric *N*-substituted tetrazoles are as yet little studied and their possible mechanisms remain subjects for discussion. Individual *N*-aminomethyltetrazoles (**16**), (**17**) and *N*-hydroxymethyltetrazoles (**26**), (**27**) were found to form equilibrium mixtures containing both isomers upon dis-

solution in neutral organic solvents, such as nitromethane, toluene, and chloroform.[57,58] This process was suggested to occur by a dissociation–recombination mechanism[57] involving formation of ion pairs of tetrazolates (**42**) as shown in Scheme 26.



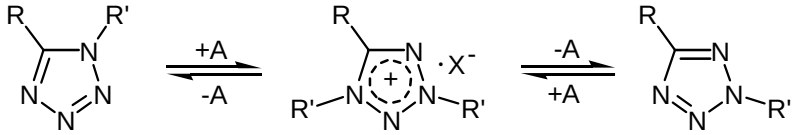
16, Z = $NAlk_2$
26, Z = OH

42

17, Z = $NAlk_2$
27, Z = OH

Scheme 26

However, in other cases reported,[71,79,81,82,96] interconversions of isomeric *N*-substituted tetrazoles are likely to proceed through the intermediate formation of tetrazolium structures (**43**) (Scheme 27). Isomerization of this type either requires the presence of an appropriate alkylating agent[96] or takes place in acidic media where the *N*-substituent could be split out to form a carbenium cation. [71,79,81,82]



5 **43** **6**

A = R'X or R'^{+}, X^{-}

Scheme 27

As a final point of this section, it might be well to remark that with due regard for all accomplishments made, there is still ample room for systematic experimental and theoretical studies of electrophilic reactions at nitrogen atoms of *N*-substituted tetrazoles.

5. CONCLUSION

In the past twenty years, considerable advances have been made in understanding intricate processes of interaction of various tetrazole substrates with electrophilic agents. Among others, the efforts devoted to the fundamental issues of the chemistry of tetrazoles have contributed significantly to this understanding, thus proving once again that “nothing is more practical than a good theory”. For the first time, an adequate level of knowledge has been reached to enable one to interpret and to predict results of reactions of different tetrazole substrates with various electrophiles. On the basis of theoretical notions of reaction mechanisms, novel procedures for regioselective, high-yield syntheses of previously unavailable *N*-substituted tetrazoles have been developed. A tendency to extend theoretical and experimental approaches, developed primarily for the chemistry of tetrazoles, to other members of the family of azoles becomes more and

more pronounced. This steady trend provides a new impulse for further development of theoretical and experimental chemistry of polynitrogenous heterocycles.

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