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1,3- and 1,4-Substituted tetrazolium salts

S V Voitekhovich, P N Gaponik, O A Ivashkevich

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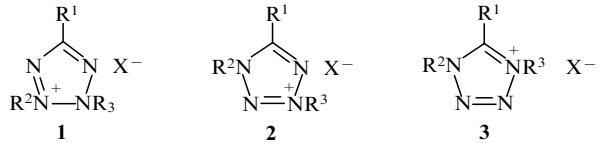
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Abstract. The published data on the synthesis, physicochemical properties, structures and reactions of 1,3-(1,3,5)- and 1,4-(1,4,5)-substituted tetrazolium salts are systematised and generalised. Their applications as starting compounds in the preparative chemistry of heterocyclic derivatives and some other branches of science and technology are reviewed. The bibliography includes 122 references.

I. Introduction

Compounds containing positively charged tetrazole rings have been known since the end of the 19th century, since the first description of 2,3-substituted tetrazolium salts **1**. Later, these compounds were given considerable attention in connection with their reduction into brightly coloured formazane under the action of various reagents. At present, practical applications of 2,3-substituted tetrazolium salts are based on chemical, biochemical, electrochemical and radiochemical reduction. These compounds proved to be especially useful in biochemical, microbiological, histochemical and cytochemical studies, analytical chemistry and clinical analysis as well as components of ionising radiation monitors and photosensitive materials, germination indicators of grain crops and phase-transfer catalysts.[1–5] Other types of tetrazolium salts which differ in the positions of substituents at the nitrogen atoms have not received much attention until recently.

The situation has changed in the past decade owing to the appearance of a great number of publications devoted to 1,3- (**2**) and 1,4-substituted (**3**) tetrazolium salts.



1 **2** **3**

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In many respects, this is due to the development of synthetic methods including selective procedures, which make possible direct synthesis of tetrazolium salts **2** and **3** with predetermined compositions and structures which can be use in organic chemistry and some other branches of science and technology. However, systematised data on the synthesis, properties and applications of these compounds are still absent in the literature. Previously published reviews[1–5] deal with the description of mostly 2,3-substituted tetrazolium salts. The reviews devoted to the chemistry of tetrazoles[6–8] and some of its particular aspects[9–11] published in the past decade provide separate and, sometimes,[8,10,11] very scarce data on 1,3- and 1,4-substituted tetrazolium salts.

The aim of the present review is to generalise the information on 1,3- and 1,4-substituted tetrazolium salts over the past 10 – 15 years in order to highlight current trends in their synthesis with special emphasis on the availability of tetrazolium salts and their efficacy in organic synthesis. Earlier publications that have not been cited in other reviews and monographs are also surveyed.

Depending on the nature of the substituent at C(5), tetrazolium salts **2** and **3** can be divided into two groups, *viz*., 1,3- and 1,4-disubstituted tetrazolium salts containing a labile hydrogen atom at the carbon atom of the heterocycle and 1,3,5- and 1,4,5-trisubstituted tetrazolium salts where $R^1 \neq H$. Yet another class of 1,3,5-trisubstituted tetrazolium salts, *viz.*, compound **2** with the substituent R^1 represented by an anionic group [O^-, NH^-, $^-C(CN)_2$, *etc*.], are referred to as mesoionic tetrazoles.[12] As the behaviour of these internal salts differs drastically from that of ordinary tetrazolium salts, they are not considered in the present review.

II. Methods for the synthesis of tetrazolium salts

All currently known approaches to the synthesis of 1,3- and 1,4-substituted tetrazolium salts can be classified into two main groups: (1) transformations of tetrazoles and (2) heterocyclisation of polynitrogenous linear structures.

The first group includes a broad range of processes, in the first place, direct exhaustive alkylation of tetrazoles at the endocyclic nitrogen atoms, *i.e*., quaternisation. Reactions involving exocyclic atoms of mesoionic tetrazoles and 1,4-dihydrotetrazoles and reactions affecting both endo- and exocyclic atoms of functionalised tetrazoles leading to the formation of annelated tetrazolium salts are also related to this group. Conversions of some tetrazolium salts into other ones do not have as a rule any preparative

significance and are considered in the section devoted to the chemical properties of tetrazolium salts.

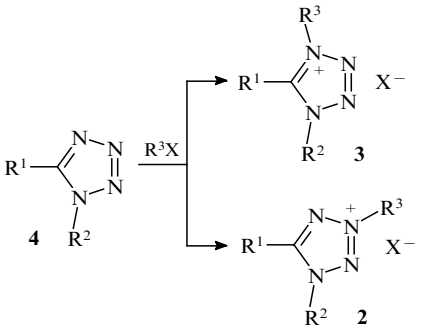
The second group includes few heterocyclisation reactions the main advantage of which is that they exclude the use of tetrazoles in the synthesis of tetrazolium salts.

Quaternisation of tetrazoles is the most popular and simple procedure for the synthesis of 1,3- and 1,4-substituted tetrazolium salts. This method is based on two approaches which differ in the nature of the alkylating reagents and the reaction media. The practical significance of quaternisation reactions has increased considerably in the past decade owing to the ready availavility of diverse tetrazole derivatives.[6–10]

1. Quaternisation of tetrazoles in organic media

In the early 1950's, it was shown for the first time that *N*-substituted tetrazoles, particularly 1-aryl-5-methyltetrazoles, react with methyl iodide to yield quaternary salts.[1] Later, it was established that quaternisation is largely a general process which involves all isomeric *N*-substituted tetrazoles [13–37] including fused ones;[16, 20, 24, 34] the role of alkylating reagents is played by alkyl halides, alkyl sulfates, oxonium salts and related compounds of which methylating and ethylating reagents [13–37] as well as α-halogeno carbonyl compounds (bromoacetone [18, 35, 37] and phenacyl bromides [21, 27, 35, 37]) are studied most extensively. The mechanisms of quaternisation of *N*-substituted tetrazoles still remain obscure. It can be assumed, however, that similar to other azoles, quaternisation of tetrazoles occurs by an S_N2 mechanism. The azole molecule, which plays the role of a nucleophilic reagent with respect to alkyl halide, passes into a quaternised form. This reaction is accompanied by the Walden inversion.[38, 39]

Quaternisation of tetrazoles for the synthesis of tetrazolium salts poses certain problems. In the first place, this is due to the non-selectivity of this reaction due to the ambident character of the tetrazolium ring [3, 6, 7] and the necessity to separate the mixtures of isomeric tetrazolium salts formed. Thus quaternization of 1-mono- and 1,5-disubstituted tetrazoles **4** yields a mixture of isomeric tetrazolium salts **2** and **3**.[13, 15–25, 27, 28, 31, 32–37]



In the case of 1-monosubstituted tetrazoles **4** (R^1 = H), the predominant reaction is the attack at the N(4) atom [13, 15, 18, 21, 28, 33] manifesting the highest basicity (proton affinity) irrespective of the nature of the R^2 substituent.[6, 8, 40] The presence of a substitutent at C(5) increases the content of the 1,3-substituted tetrazolium salt **2** which becomes predominant in the presence of bulky substituents R^1. Individual salts can be isolated from the mixtures owing to differences in the solubilities of the isomers. In most cases, 1,4,5-isomers are soluble in water and lower alcohols less readily than 1,3,5-isomers. Sometimes, individual salts **3** precipitate immediately.[14, 22, 25, 32] This approach is largely used in the synthesis of 1,4-substituted tetrazolium salts (Table 1).

The use of 2-mono- and 2,5-disubstituted tetrazoles for the synthesis of 1,3-substituted tetrazolium salts seems to be more appropriate, since the quaternisation of the latter proceeds selectively at the N(4) atom (Table 2). However, by reason of the lower basicity of this type of tetrazole,[41] their quaternisation requires more drastic conditions (elevated temperatures and sometimes high pressure) than that for tetrazoles **4**.[3, 17, 18, 21, 23, 27–29, 35–37]

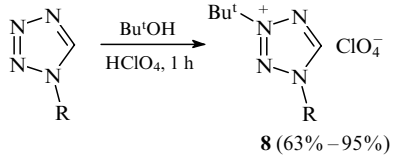
The use of tetrazole and its 5-monosubstituted derivatives **5** as starting compounds in the synthesis of tetrazolium salts is rather attractive, since the methods for the preparation of compounds **5** have been well developed.[42] Nevertheless, exhaustive alkylation of this type of tetrazole has been studied for a limited number of compounds only. Thus the methylation of 5-methyltetrazole with an excess of methyl iodide (40 °C, 10 days) yields a mixture of 1,4,5- and 1,3,5-trimethyltetrazolium iodides in a 68 : 32 ratio.[14] Later, it was found that tetrazoles with substituents in position 5 react with an excess of dimethyl sulfate upon heating to give 1,3-(**6**, X = $MeSO_4^-$) and 1,4-dimethyl-5-R-tetrazolium methyl sulfates (**7**, X = $MeSO_4^-$) (Table 3).[32, 33] The ratio of the isomers formed depends on the nature of the substituent at the C(5) atom; owing to steric factors, the proportion of the 1,3,5-isomer **6** increases in the following order: R = Me, Et, Ph, Bu^t (19%, 31%, 55% and 91%, respectively).[32] The isolation of the main isomer is achieved by precipitation of the corresponding perchlorates [32] and picrates [33] (see Table 3).

To conclude, special mention should be made of a study [26] which represents an approach to the mathematical estimation of the feasibility of quaternisation and alkylation of some azoles including tetrazoles. The authors attempted to correlate the sum of normalised potentials with pK_a values of azoles and demonstrated the applicability of these principles in several reactions.

2. Quaternisation of tetrazoles in acidic media

The methods for the synthesis of tetrazolium salts based on quaternisation of tetrazoles with alcohols in acidic media were proposed in the past decade [22, 30, 33, 36, 43–49] and are being intensively developed at present. The studies into the alkylation of 5-R-tetrazoles in strong acids which, contrary to the reactions occurring in neutral media, proceed selectively at the N(2) atom, formed the basis for these methods.[50–52] Kinetic studies and an analysis of reaction mechanisms revealed that the selectivity is due to blocking of the most nucleophilic N(4) atom because of its protonation.[53, 54] Later, it was found that the regioselectivity of the tetrazole alkylation in acidic media remains in the quaternisation. This allowed development of efficient procedures for the synthesis of tetrazolium salts and enlargement of their range by virtue of quaternising reagents that made it possible to introduce branched substituents onto the 'pyridine' nitrogen atom. It is now established that quaternisation of tetrazoles can be effected by alcohols that generate stable carbocations (*e.g.*, *tert*-butyl [17, 22, 33, 36, 45–49] and diacetone alcohols,[46, 47] 2,5-dimethylhexane-2,5-diol,[36] isopropyl alcohol,[49] 1-phenylethanol,[49] adamantan-1-ol [43] and α-ferrocenyl-substituted alcohols) in acidic media.[44] These reactions are usually carried out in strong mineral acids (*e.g.*, perchloric, sulfuric, tetrafluoroboric) [33, 36, 45–49] or biphasic systems consisting of an organic solvent (ether, dichloromethane) and an acid.[17, 22, 44] The direction of quaternisation cannot always be predicted unequivocally, since it depends on many factors, such as the nature of the substrate and the alkylating reagent, medium acidity and reaction time.

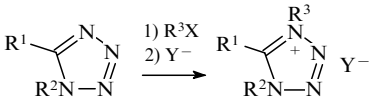
1,3-Disubstituted tetrazolium salts **8** and **9** were obtained in high yields by quaternisation of 1-monosubstituted tetrazoles with *tert*-butyl [36, 45, 47] and isopropyl [49] alcohols in 72% perchloric acid at 20 °C and contained no admixtures of the corresponding 1,4-isomers.

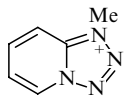
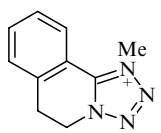
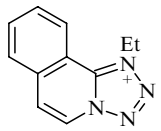


8 (63%–95%)

R = Me, Et, Bu^t, Bn, cyclo-C_6H_{11}.

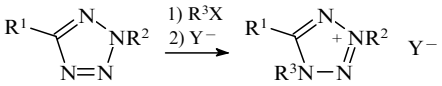
Table 1. The synthesis of 1,4-substituted tetrazolium salts by quaternisation of 1-mono- and 1,5-disubstituted tetrazoles.



R^1	R^2	R^3X	Quaternisation conditions		Y	Yield (%)	M.p. /°C	Ref.
			T /°C	t /h				
Me	Me	Me_2SO_4	20–25	216	I	50	266	18
Me	Me	Me_2SO_4	120	1	ClO_4	59	205–206	22
Et	Me	Me_2SO_4	120	1	ClO_4	51	146–147	22
Pr^i	Me	Me_2SO_4	120	1	ClO_4	41	155–157	22
Pr^i	Me	Me_2SO_4	120	1	PF_6	28	177–178	22
Me	Bu^t	Me_2SO_4	120	1	BF_4	21	112–114	22
CH_2Bu^t	Me	Me_2SO_4	120	1	ClO_4	41	185–186	22
CH_2Bu^t	Me	Me_2SO_4	120	1	BF_4	22	166–168	22
Bn	Me	Me_2SO_4	120	1	BPh_4	44	207–210 [a]	22
Pr^i	Ph	Me_2SO_4	120	1	PF_6	30	144–145	22
CH_2Bu^t	Ph	Me_2SO_4	120	1	PF_6	44	237 [a]	22
$Me_2NCH=CH$	Ph	Me_2SO_4	80	4	ClO_4	58	160–161	25
$Me_2NCH=CH$	Ph	MeI	100	24	ClO_4	60	160–161	25
$Me_2NCH=CH$	4-MeC_6H_4	Me_2SO_4	80	4	ClO_4	69	154–155	25
$Me_2NCH=CH$	4-PhC_6H_4	Me_2SO_4	80	4	ClO_4	85	166–167	25
$Me_2NCH=CH$	4-$MeOC_6H_4$	Me_2SO_4	80	4	ClO_4	55	153–154	25
$Me_2NCH=CH$	4-FC_6H_4	Me_2SO_4	80	4	ClO_4	61	168–169	25
$Me_2NCH=CH$	4-FC_6H_4	Et_2SO_4	90	8	ClO_4	22	116–117	25
$Me_2NCH=CH$	4-ClC_6H_4	Me_2SO_4	80	4	ClO_4	65	193–194	25
$Me_2NCH=CH$	4-ClC_6H_4	Et_2SO_4	90	8	ClO_4	28	126–127	25
$Me_2NCH=CH$	4-BrC_6H_4	Me_2SO_4	80	4	ClO_4	70	208–209	25
$Me_2NCH=CH$	4-BrC_6H_4	Et_2SO_4	90	8	ClO_4	32	146–147	25
$Me_2NCH=CH$	4-IC_6H_4	Me_2SO_4	80	4	ClO_4	84	209–210	25
$Me_2NCH=CH$	4-IC_6H_4	Et_2SO_4	90	8	ClO_4	43	157–158	25
MeS	Me	Me_2SO_4	70–80	0.5	BF_4	69	141–143	17
MeS	Bu^t	Me_3OBF_4	40	12	BF_4	95	121–123	17
H	Me	$BrCH_2COPh$	80	96	Br	90	145–148	21
Me	Me	$BrCH_2COC_6H_4Br$-4	70–75	96	Br	70	170–171	27
Me	Me	$BrCH_2COC_6H_4NO_2$-4	70–75	120	Br	35	130–135	27
Me	Pr^n	$BrCH_2COPh$	70–75	72	Br	79	156–157	27
Me	Pr^i	$BrCH_2COPh$	70–75	48	Br	84	157–158	27
Me	Bu^i	$BrCH_2COPh$	70–75	24	Br	79	155	27
Me	cyclo-C_6H_{11}	$BrCH_2COPh$	70–75	5	Br	75	182–184	27
NH_2	CH_2COMe	Me_2SO_4	20–25	48	Br	14	240 [a]	35
NH_2	Me	$BrCH_2COPh$	90	8	Br	88	220 [a, b]	35
CH_2COMe	Me	$BrCH_2COMe$	50–55	288 [c]	BF_4	33	124–127	37
H	CH_2COMe	MeI	50	5.5 [d]	I	35	130	18
Me	CH_2COMe	MeI	50	5.5 [d]	I	43	162–163	18
Me	Me	$BrCH_2COMe$	50	6 [d]	Br	65	157–158	18
Ph	Me	Me_2SO_4	35	15	ClO_4	78	159–160	23
$C_6H_4NO_2$-3	Me	Me_2SO_4	35	15	ClO_4	83	135–137	23
		Me_2SO_4	82	1	BF_4	75	131–135	24
		Me_2SO_4	82	1	BF_4	80	267–269	24
		Et_3OBF_4	20	20	BF_4	65	185–187	24

[a] With decomposition; [b] M.p. of the corresponding semihydrate; [c] the reaction was carried out in the presence of $AgBF_4$; [d] the reaction was carried out under high pressure.

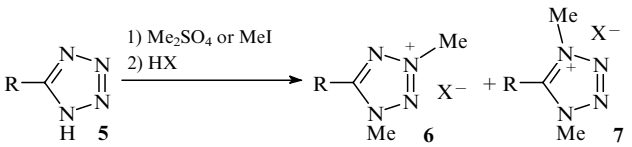
Table 2. The synthesis of 1,3-substituted tetrazolium salts by quaternisation of 2-mono- and 2,5-disubstituted tetrazoles.



R^1	R^2	R^3X	Quaternisation conditions		Y	Yield (%)	M.p. /°C	Ref.
			T /°C	t /h				
CH_2COMe	Me	$BrCH_2COPh$	60	14 [a]	BF_4	57	159–161	37
CH_2CO_2Me	Me	$BrCH_2COPh$	60	10 [a]	BF_4	81	123–124	37
CH_2CO_2Me	Me	$BrCH_2COC_6H_4Br$-4	60	10 [a]	BF_4	82	107–109	37
CH_2COMe	Me	$BrCH_2COMe$	60	10 [a]	BF_4	57	oil	37
CH_2CO_2Me	Me	$BrCH_2COMe$	60	7 [a]	BF_4	60	145	37
CH_2COMe	Ph	$BrCH_2COPh$	60	14 [a]	BF_4	80	210–211	37
CH_2COMe	Ph	$BrCH_2COMe$	60	14 [a]	BF_4	60	145	37
NH_2	Me	$BrCH_2COMe$	60	5	Br	45	140–170	35
NH_2	Me	$BrCH_2COPh$	90	2.9	Br	60	230	35
H	Me	$BrCH_2COPh$	60	2 [a]	Br	69	138–140	21
H	Me	$BrCH_2COC_6H_4Br$-4	60	2 [a]	Br	55	171–172	21
H	Me	$BrCH_2COC_6H_4NO_2$-4	60	2 [a]	Br	62	153–154	21
Me	Me	$BrCH_2COPh$	60	2	Br	57	142–146	21
H	CH_2COPh	Me_2SO_4	20	2	Br	91	121–122	21
H	$CH_2COC_6H_4Br$-4	Me_2SO_4	20	2	Br	78	135–137	21
H	$CH_2COC_6H_4NO_2$-4	Me_2SO_4	20	2	Br	82	132–134	21
Me	CH_2COPh	Me_2SO_4	20	2	Br	96	115–117	21
Ph	Ph	Me_2SO_4	80	8	ClO_4	85	209–210	29
C_6H_4Me-4	Ph	Me_2SO_4	80	8	ClO_4	86	224–226	29
C_6H_4OMe-4	Ph	Me_2SO_4	80	8	ClO_4	87	228–230	29
C_6H_4Cl-4	Ph	Me_2SO_4	80	8	ClO_4	90	255–257	29
Ph	$C_6H_4NO_2$-4	Me_2SO_4	80	8	ClO_4	87	272–273	29
Ph	C_6H_4Me-4	Me_2SO_4	80	8	ClO_4	82	243–245	29
Ph	C_6H_4OMe-4	Me_2SO_4	80	8	ClO_4	88	230–232	29
Ph	C_6H_4Cl-4	Me_2SO_4	80	8	ClO_4	91	265–267	29
H	CH_2COMe	$MeSO_3F$	20	0.17	FSO_3	92	84–86	18
Me	CH_2COMe	MeI	50	0.23 [b]	I	46	144	18
C_6H_4OMe-4	Me	Me_2SO_4	60	1.25	ClO_4	68	144–145	23
C_6H_4Me-4	Me	Me_2SO_4	60	1.25	ClO_4	73	142–144	23
C_6H_4Me-3	Me	Me_2SO_4	60	1.25	ClO_4	62	103–104	23
Ph	Me	Me_2SO_4	60	1.25	ClO_4	78	129–131	23
C_6H_4I-4	Me	Me_2SO_4	60	1.25	ClO_4	77	140–142	23
C_6H_4Br-3	Me	Me_2SO_4	60	1.25	ClO_4	69	165	23
$C_6H_4NO_2$-3	Me	Me_2SO_4	60	1.25	ClO_4	87	138–139	23
$C_6H_4NO_2$-4	Me	Me_2SO_4	60	1.25	ClO_4	87	204	23

[a] The reaction was carried out in the presence of $AgBF_4$; [b] the reaction was carried out under high pressure.

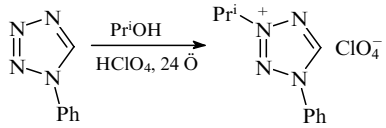
Table 3. The synthesis of 1,3- and 1,4-dimethyl-5-R-tetrazolium salts **6** and **7** by quaternisation of 5-R-tetrazoles **4**.



5 **6** **7**

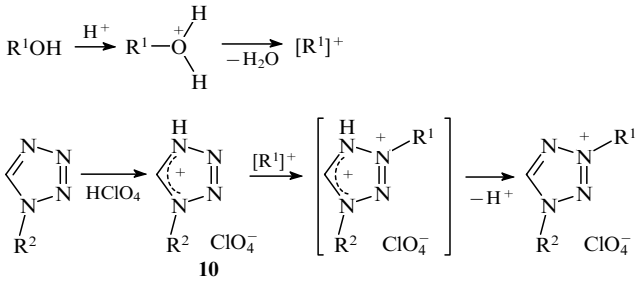
Salt	R	Alkylating reagent	X	Quaternisation conditions		Yield (%)	M.p. /°C	Ref.
				T /°C	t /h			
6	Me	MeI	I	40	240	26	266 [a]	14
6	Bu^t	Me_2SO_4	ClO_4	90	1	72	149–150	32
7	Me	MeI	I	40	240	51	130 [a]	14
7	Me	Me_2SO_4	ClO_4	90	1	69	204–205	32
7	Me	Me_2SO_4	$2,4,6\text{-}(NO_2)_3C_6H_2O$	90	2	35	164–166	33
7	Et	Me_2SO_4	ClO_4	90	1	60	144–146	32

[a] With decomposition.



9 (37%)

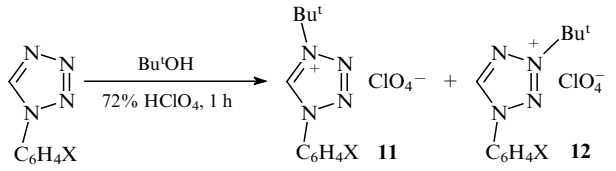
The regioselectivity of quaternisation is achieved by virtue of complete protonation of 1-R-tetrazole at the most nucleophilic nitrogen atom N(4) with the formation of the 1-R-4*H*-tetrazolium cation **10** in which the N(2) and N(3) atoms are susceptible to electrophilic attack. The attack at the N(2) atom is sterically hindered due to the presence of a substituent at the N(1) atom. Therefore, the carbocation generated from the alcohol, attacks the tetrazolium cation at the N(3) atom.[45]

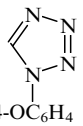


10

The assumption of a reaction of the azolium cation with the carbocation is unusual at first glance; however, the results of quantum-chemical calculations [45, 53] suggest that such a reaction is possible, since the N(2) and N(3) atoms of the 1-R-4*H*-tetrazolium cation **10** retain sufficiently high π-electron density.

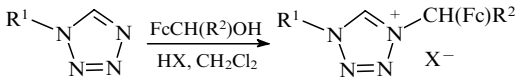
Selective preparation of 1,3-disubstituted tetrazolium salts demands special conditions to be met, which ensure complete protonation of the starting tetrazoles [45] and exclude the possibility of isomerisation of 1,3-substituted tetrazolium salts into the corresponding 1,4-isomers in the course of the reaction.[45, 55] Moreover, quaternisation occurs smoothly only in the case of 1-alkyltetrazoles.[45] 1,4-Disubstituted tetrazolium salts **11** are formed as reaction products in the quaternisation of some 1-aryltetrazoles with *tert*-butyl alcohol. Their proportion increases in the presence of electron-withdrawing groups in the aryl substituent,[36, 45, 47, 49] which is explained [49] by lower basicity of 1-aryltetrazoles in comparison with their alkyl analogues.[41]



X	Ratio of isomers **12** : **11**	X	Ratio of isomers **12** : **11**
2-CO_2H	100 : 0	3-Me	90 : 10
4-OMe	100 : 0	3-OMe	87 : 13
		H	86 : 14
		3-Br	82 : 18
		4-COMe	60 : 40
		3-NO_2	50 : 50

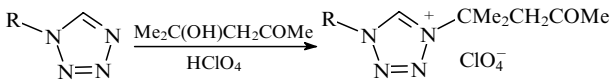
4-OC$_6$H$_4$

Under certain conditions, individual 1,4-disubstituted tetrazolium salts **13** and **14** can also be prepared by quaternisation of 1-R-tetrazoles with α-ferrocenyl-substituted [44] or diacetone alcohols.[46, 47]



13 (48% – 94%)

R^1 = Bn, Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$; R^2 = H, Me, Ph; Fc = C$_5$H$_4$FeC$_5$H$_5$; X = ClO$_4$, BF$_4$.



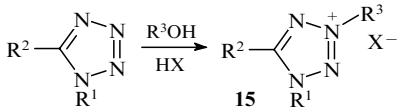
14 (63% – 94%)

R = Me, Bn, cyclo-C$_6$H$_{11}$, Ph, 4-MeOC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 2-HO$_2$CC$_6$H$_4$, 2-HO-4(5)-NO$_2$C$_6$H$_3$.

Because of steric hindrances, the aforementioned isomerisation of tetrazolium salts is not realised in the quaternisation of 1,5-disubstituted tetrazoles, which allows selective preparation of 1,3,5-trisubstituted tetrazolium salts **15** (Table 4).

1,3-Disubstituted tetrazolium salts **16** (R^2 = H) are formed in high yields upon quaternisation of 2-monosubstituted tetrazoles with alcohols in the presence of acids (Table 5). The yields of 1,3,5-trisubstituted derivatives in the reaction of 2,5-disubstituted

Table 4. The synthesis of 1,3,5-trisubstituted tetrazolium salts **15** by quaternisation of 1,5-disubstituted tetrazoles with alcohols in acidic media.

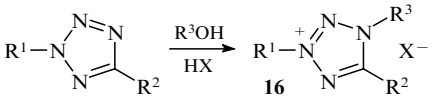


15

R^1	R^2	R^3	Quaternisation conditions		Yield (%)	M.p. /°C	Ref.
			HX	*t* /h			
Me	MeS	Bu^t	54% HBF_4 [a]	15	67	131 – 133	17
Bu^t	MeS	Bu^t	54% HBF_4 [a]	15	64	154 – 155	17
Me	Pr^i	Bu^t	54% HBF_4 [a]	15	48	129 – 131	22
Me	Me	Bu^t	54% HBF_4 [a]	15	52	149 – 150 [b]	22
Me	Me	Bu^t	48% HBF_4	48	40	151 – 152	30
Me	Me	Bu^t	40% $HClO_4$	48	46	140 – 141	30
CH_2 = CH	Me	Bu^t	48% HBF_4	48	40	50 [b]	30
Me	Me	$CMe_2CH_2C(O)Me$	72% $HClO_4$	12	75	115 – 117	46

[a] Solution in diethyl ether; [b] with decomposition.

Table 5. The synthesis of 1,3- and 1,3,5-substituted tetrazolium salts **16** by quaternisation of 2-mono- and 2,5-disubstituted tetrazoles with alcohols in acidic media.



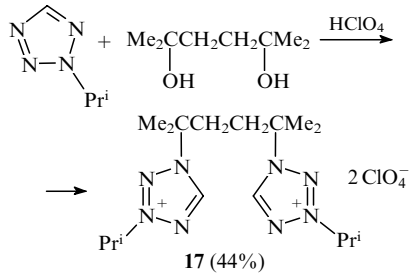
16

R^1	R^2	R^3	Quaternisation conditions		Yield (%)	M.p. /°C	Ref.
			HX	*t* /days			
Me	H	Bu^t	72% $HClO_4$	2	95	150 [a]	48
Me	H	Bu^t	48% HBF_4	3	56	155–156	30
Et	H	Bu^t	72% $HClO_4$	2	80	133–135	48
Et	H	Bu^t	48% HBF_4	3	72	136–137	30
Pr^i	H	Bu^t	72% $HClO_4$	2	96	130–131	48
Bu^t	H	Bu^t	72% $HClO_4$	3	74	120–122	48
$CH_2=CHCH_2$	H	Bu^t	72% $HClO_4$	2	89	143–145	48
$CH_2=CHCH_2$	H	Bu^t	48% HBF_4	3	62	105–107	30
$CH_2=CMe$	H	Bu^t	72% $HClO_4$	2	88	145 [a]	48
$CH_2BrCHMe$	H	Bu^t	72% $HClO_4$	2	75	78–80	48
$MeC(O)CH_2CH_2$	H	Bu^t	72% $HClO_4$	2	70	97–99	48
Me	H	$CMe_2CH_2C(O)Me$	72% $HClO_4$	2	94	133–135	46
Et	H	$CMe_2CH_2C(O)Me$	72% $HClO_4$	2	63	79–81	46
Pr^i	H	$CMe_2CH_2C(O)Me$	72% $HClO_4$	2	70	69–71	46
Ad	H	Ad [b]	74% H_2SO_4	9	21 [c]	240–241	43
Me	$CH_2=CH$	Bu^t	48% HBF_4	3	45	50 [a]	30
Bu^t	$CH_2=CH$	Bu^t	48% HBF_4	3	50	138–140 [a]	30
Et	Me	Bu^t	48% HBF_4	3	33	130–132	30

[a] With decomposition; [b] Ad is 1-adamantyl; [c] isolated as pechlorate.

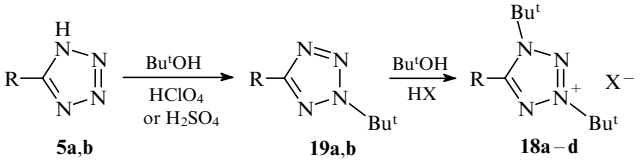
tetrazoles with *tert*-butyl alcohol in the presence of HBF_4 (see Ref. 30) do not exceed 50% (see Table 5), apparently due to steric hindrances preventing the introduction of the substituent into position N(4).

The synthesis of the salt **17** shows that quaternisation can successfully involve diols, which opens up new opportunities for the selective synthesis of binuclear tetrazolium salts.[36]



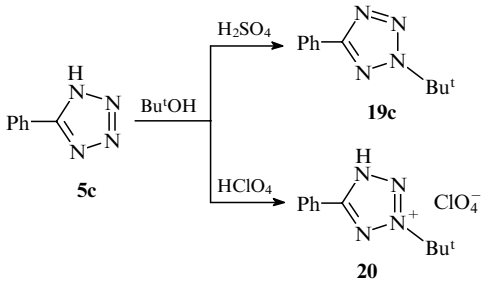
17 (44%)

1,3-Di-*tert*-butyl-5-R-tetrazolium salts **18a**–**d** were prepared by exhaustive alkylation of tetrazole (**5a**) and 5-methyltetrazole (**5b**) with *tert*-butyl alcohol in the presence of strong acids.[33,45] The selectivity of alkylation is explained by the intermediate formation of 2-*tert*-butyl-5-R-tetrazoles **19a**,**b** in which only the



5a,**b** **19a**,**b** **18a**–**d**

Compound **18**	R	X	Yield (%)	Ref.
a	H	ClO_4	80	45
b	Me	ClO_4	59	45
c	H	$2,4,6\text{-}(NO_2)_3C_6H_2$	62	33
d	Me	$2,4,6\text{-}(NO_2)_3C_6H_2$	10	33



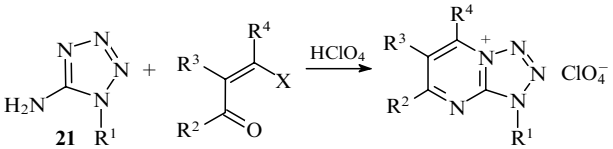
5c **19c** **20**

N(4) atom is accessible for quaternisation. In the case of 5-phenyltetrazole (**5c**), the expected tetrazolium salts are not formed, presumably due to steric hindrances. In this case, 2-*tert*-butyl-5-phenyltetrazole (**19c**) [33] or its protonated form, *viz*., 3-*tert*-butyl-5-phenyl-1*H*-tetrazolium perchlorate (**20**), was isolated as the alkylation product.[45]

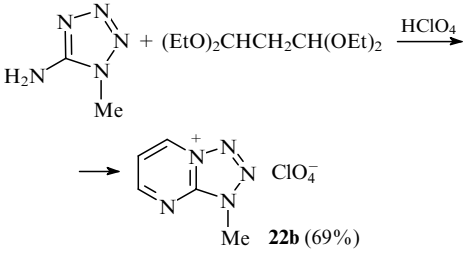
It may be expected that the methods for the synthesis of tetrazolium salts based on quaternisation of tetrazoles in the presence of strong acids will be developed further. Their attractiveness is due both to the availability of the starting compounds and the selectivity and simplicity of the reactions. The use of novel functionalised reagents in the quaternisation reaction will enable one to extend the range of available tetrazolium salts.

3. Miscellaneous methods based on the transformations of tetrazole derivatives

Disubstituted tetrazoles containing reactive groups at the C(5) atom react with bifunctional reagents to give annelated tetrazolium salts. It was shown, in particular,[56] that the condensation of 1-substituted 5-aminotetrazoles **21** with β-diketones, β-chlorovinyl ketones and aldehydes as well as with malonaldehyde acetals yields 1-substituted tetrazolo[1,5-*a*]pyrimidinium salts **22a**,**b**. This reaction proceeds at 20 °C or upon short-term heating of solutions of the reactants in acids (*e.g*., acetic, trifluoroacetic, perchloric) or in ethanol in the presence of perchloric acid.



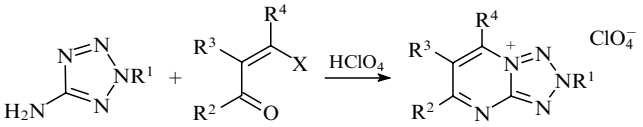
21 **22a** (26%–91%)



22b (69%)

R^1 = Me, CH=CH$_2$, CH$_2$CH=CH$_2$, Bn, Ph, HO$_2$CCH$_2$; R^2 = H, Me, Ph; R^3 = H, Me; R^4 = H, Me, Ph; R^3–R^4 = (CH$_2$)$_4$; X = Cl, OH.

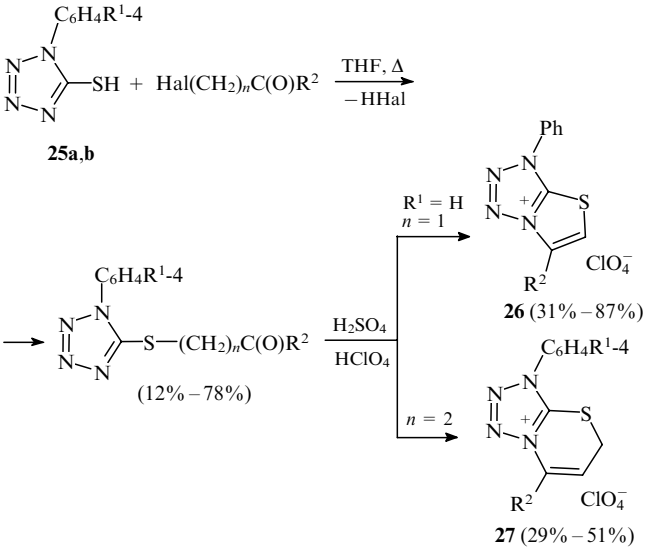
2-Substituted 5-aminotetrazoles **23** generate 2-substituted tetrazolo[1,5-*a*]pyrimidinium salts **24** under analogous conditions.[56]



23 **24** (22%–98%)

R^1 = Me, CH$_2$CH=CH$_2$, Bn; R^2 = H, Me, Ph, CO$_2$H; R^3 = H, Me; R^4 = H, Me, Ph; R^3–R^4 = (CH$_2$)$_4$; X = Cl, OH.

1-Aryl-5-mercaptotetrazoles **25a**,**b** react with α- and β-halogeno ketones with heating to give tetrazolylthioalkyl ketones which undergo cyclisation under the action of sulfuric acid in the presence of $HClO_4$ to give thiazolo[3,2-*d*]tetrazolium (**26**) and tetrazolo[5,4-*b*][1,3]thiazinium perchlorates **27**, respectively.[7, 57]



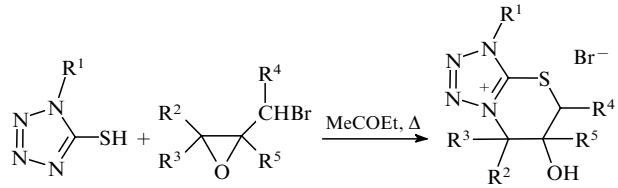
25a,**b** (12%–78%) **26** (31%–87%) **27** (29%–51%)

R^1 = H (**25a**), Cl (**25b**);

26: R^1 = H: R^2 = Bu^t, Et, Ad, Ph, 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-C$_6$H$_5$C$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$;

27: R^1 = H, Cl: R^2 = Ph, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$.

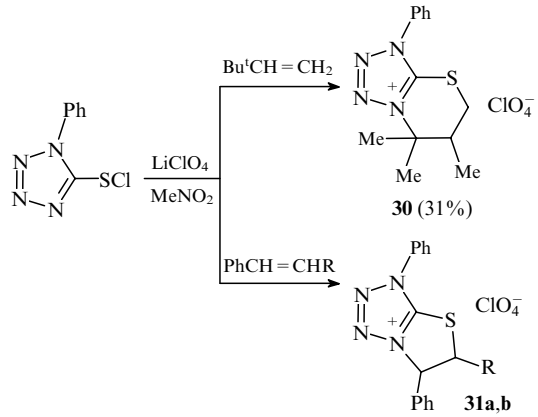
Treatment of 5-mercaptotetrazoles **25a** and **28** substituted by epoxy bromides in position N(1) with heating affords 6-hydroxy-1-R-6,7-dihydro-5*H*-tetrazolo[5,4-*b*][1,3]thiazinium bromides **29** in relatively low yields.[57]



25a, **28** **29** (8%–46%)

R^1 = Ph, cyclo-C$_6$H$_{11}$; R^2, R^3, R^4, R^5 = H, Me.

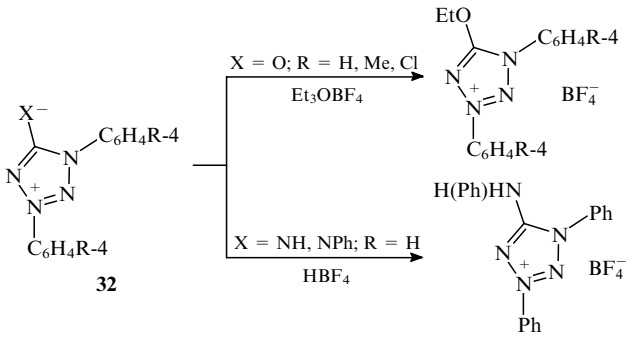
The reaction of 1-phenyltetrazol-5-ylsulfenyl chloride with 3,3-dimethylbut-1-ene in nitromethane in the presence of lithium perchlorate yields 7,8-dihydro-6,6,7-trimethyl-2-phenyl-6*H*-tetrazolo[4,5-*b*][1,3]thiazinium perchlorate (**30**). It has been shown that the heterocyclic compound **30** is formed in the Ad_E reaction of an alkene with sulfenyl chloride due to the tandem rearrangement–cyclisation occurring by a π-route.[58] The reaction of this sulfenyl chloride with styrene or 1-phenylpropene yields 2,3-dihydrothiazolo[3,2-*d*]tetrazolium salts **31a**,**b**.[59]



30 (31%)

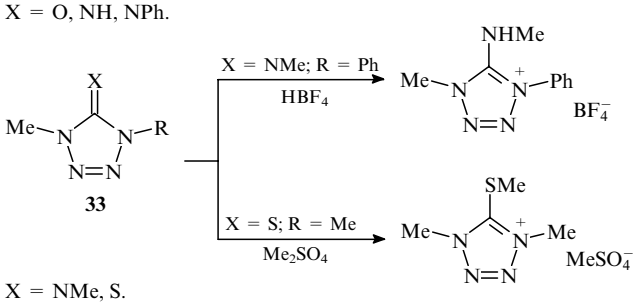
R = H (**a**, 47%), Me (**b**, 52%).

1,3,5- and 1,4,5-Trisubstituted tetrazolium salts can be prepared in more than 70% yields from mesoionic tetrazoles **32** [12, 60, 61] and 1,4-dihydrotetrazoles **33**,[17, 62] in which the exocyclic atoms are readily involved in alkylation and protonation.



32

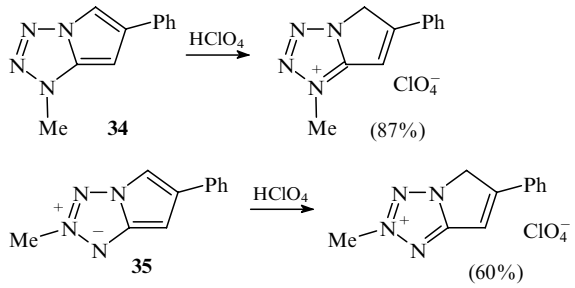
X = O, NH, NPh.



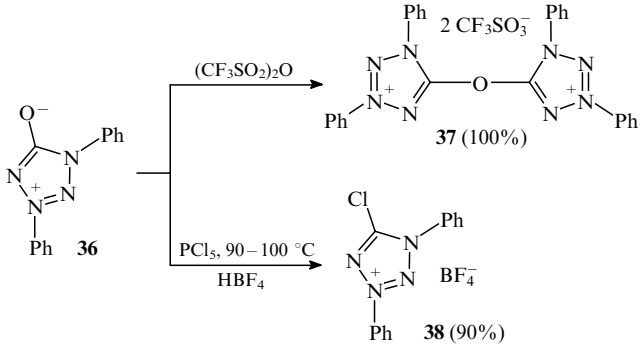
33

X = NMe, S.

Analogous reactions with fused tetrazole derivatives, with pyrrolotetrazoles **34** and **35** in particular, also proceed smoothly.[63]

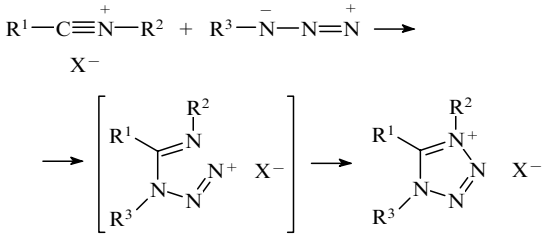


Special mention should be made of the reaction of readily available 1,3-diphenyltetrazolium-5-olate [12] (**36**) with phosphorus pentachloride [61] and trifluoromethanesulfonic anhydride [64] which yields functionalised tetrazolium salts **37** and **38**.

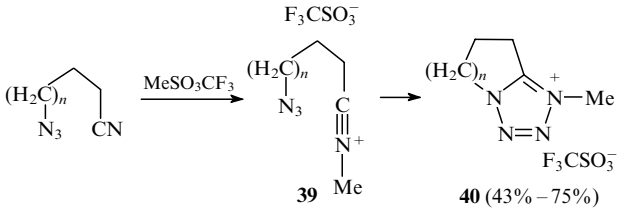


4. Heterocyclisation reactions

The main advantage of the synthesis of tetrazolium salts by heterocyclisation is that this excludes preliminary synthesis of tetrazole derivatives. Reactions of alkyl and aryl azides with nitrilium salts which proceed as [3 + 2]-cycloaddition and result in 1,4,5-trisubstituted tetrazolium salts in good yields have the greatest preparative significance (Table 6).[22, 65, 66]

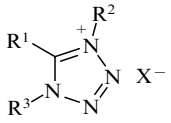


An intramolecular version of this reaction is also known. It was shown[31] that cyclisation of the *in situ* generated *N*-methyl-ω-azidonitrilium triflates **39** is a rather convenient and efficient procedure for the synthesis of annelated 1,4,5-trisubstituted tetrazolium salts **40**.



n = 1–3.

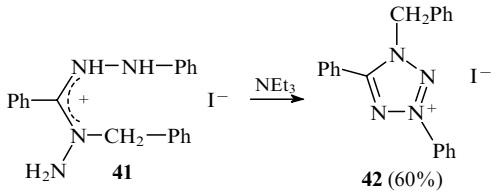
Table 6. The synthesis of 1,4,5-trisubstituted tetrazolium salts by the reaction of azides with nitrilium salts.



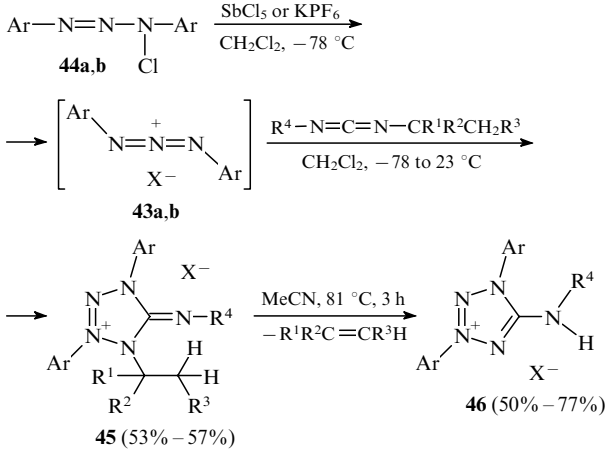
R^1	R^2	R^3	X	Yield (%)	M.p. /°C	Ref.
Pr^i	Me	Me	BF_4	71	100–101	22
Bu^tCH_2	Pr^i	Me	BF_4	52	166–168	22
Me	Me	Me	FSO_3	41	205–206	22
Me	Me	Me	FSO_3	80	155–158	65
Me	Me	Ph	F_3SO_3	87	210–211 [a]	22
Pr^i	Me	Bu^tCH_2	BF_4	77	144	22
Pr^i	Me	Ad	FSO_3	32	129–130	22
Me	Me	Bn	FSO_3	71	oil	65
Me	Et	Et	FSO_3	58	118–119	65
cyclo-C_6H_{11}	Me	Bn	FSO_3	60	128–129	65
Bu^t	Me	Bn	FSO_3	60	oil	65
Ph	Me	Me	FSO_3	75	145–148	65
Ph	Me	Bn	FSO_3	70	135	65
Ph	Et	Et	FSO_3	55	165–167	65
Ph	Et	Et	$SbCl_6$	55	204	65
Ph	Et	Et	BF_4	53	130	65
Ph	Ph	Me	$SbCl_6$	78	176	65
Ph	Ph	Bn	$SbCl_6$	65	156	65
Ph	Ph	Ph	$SbCl_6$	52	172	65
cyclo-C_3H_5	Me	Me	PF_6	97	219	66
All	Me	Me	PF_6	51	100–101	66
(*E*)-MeCH=$CHCH_2$	Me	Me	PF_6	48	93	66
(*E*)-Bu^tCH=$CHCH_2$	Me	Me	PF_6	57	133–134	66
(*E*)-PhCH=$CHCH_2$	Me	Me	PF_6	11	165–170	66
(*E*)-MeCH=CH	Me	Me	PF_6	48	190–192	66
(*Z*)-EtCH=CH	Me	Me	PF_6	60	77–79	66

[a] With decomposition.

Heterocyclisation reactions can also be employed for the synthesis of 1,3,5-trisubstituted tetrazolium salts. The use of these reactions is limited due to the low availability of the starting reagents; it has been reported, however,[7] that the hydrazinium salt **41** is converted into 1-benzyl-3,5-diphenyltetrazolium iodide (**42**) under the action of a base.

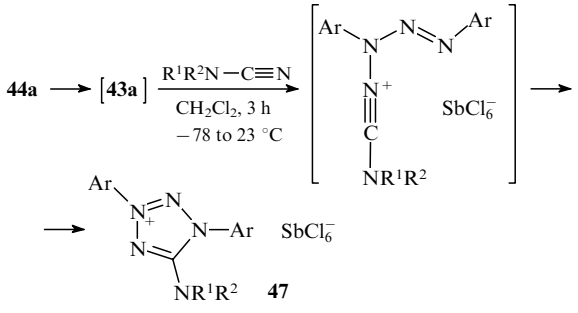


1,3-Diaza-2-azoniaallene salts **43a**,**b** [Ar = 2,4,6-$Cl_3C_6H_2$ (**a**), 4-ClC_6H_4 (**b**)] generated *in situ* from *N*-chlorotriazenes **44a**,**b** react with carbodiimides to give dihydrotetrazolium derivatives **45** which are converted into 5-alkylamino-1,3-diaryltetrazolium salts **46** upon heating.[67,68]



Ar	R^1	R^2		R^3	R^4	X
2,4,6-$Cl_3C_6H_2$	H	Me		H	Pr^i	$SbCl_6$
2,4,6-$Cl_3C_6H_2$	H		$(CH_2)_4$		cyclo-C_6H_{11}	$SbCl_6$
2,4,6-$Cl_3C_6H_2$	Me	Me		H	Bu^t	$SbCl_6$
4-ClC_6H_4	H	Me		H	Pr^i	PF_6
4-ClC_6H_4	H		$(CH_2)_4$		cyclo-C_6H_{11}	PF_6

The use of cyanamides in this reaction leads to 5-dialkylamino-1,3-diaryltetrazolium salts **47**.[67,68]



R^1	R^2	Yield (%)
Bu^t	H	34
Me	Me	61
Me	Pr^i	65
Pr^i	Pr^i	71

III. Physicochemical properties and structures of tetrazolium salts

In the individual state and under normal conditions, tetrazolium salts are stable crystalline compounds (except for the salts containing the $MeSO_4^-$ anion) frequently isolated as viscous fluids (see, *e.g.*, Refs 23, 28, 32). 1,4-Dialkyltetrazolium perchlorates manifest higher melting temperatures than the 1,3-isomers.[45] Certain 1,3-dialkyltetrazolium perchlorates possess rather low (for ionic compounds) melting temperatures (~70–80 °C, see, *e.g.*, Refs 45, 46, 48). This allows the preparation of ionic fluids possessing unique properties presently established for other azolium salts.[69,70]

1. NMR spectra

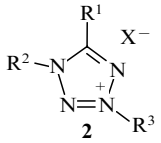
NMR spectroscopy is one of the main techniques for the identification of tetrazolium salts. The chemical shift (CS) of the endocyclic carbon atom in the ^{13}C NMR spectra strongly depends on the isomer type. The signals for carbon C(5) in 1,3-substituted tetrazolium salts **2** are downfield shifted by 7–16 ppm in comparison with the corresponding signals for 1,4-isomers[71,72] (Table 7). It is noteworthy that the nature of the substituents at the nitrogen atoms of the ring has little effect on the CS, being equal to ~147–151 ppm for 1,3-disubstituted, and ~138–142 ppm for 1,4-disubstituted tetrazolium salts. In the case of trisubstituted derivatives, the magnitude of the CS depends critically on the nature of the substituent at C(5). The signal of the C(5) atom characteristic of all ^{13}C NMR spectra is shifted upfield in the following series of substituents: Pr^i > Me > NH_2 > Cl > Br > I.[15,18,21,22,28,61,71–75] A comparative study[71,72] of the NMR spectra of tetrazolium salts and related tetrazoles revealed that the quaternisation at the α-nitrogen atom of *N*-substituted tetrazoles little affects the magnitude of the CS of the C(5) atom (~1–4 ppm), while the quaternisation of the β-atom significantly changes it as can be evidenced from the downfield shift of 7–10 ppm. The slight change in the CS observed upon quaternisation of the N(4) atom is due to the oppositely directed effect of two factors, *viz.*, the electronegative group $\overset{+}{N}=$ (the downfield shift) and the decrease in the order of the N–C bond in the cation formed as a result of polarisation (the upfield shift).

The ^1H NMR spectra of tetrazolium salts non-substituted in position 5 are characterised by a downfield shift of the signal for the proton at the endocyclic carbon atom and a significant (by ~20 Hz) increase in the spin–spin coupling constant (SSC) $^1J(^{13}C-^1H)$ in comparison with the starting compounds.[23,30,44,71,72] The CS value of the proton at C(5) strongly depends on the structure of the salt and the type of solvent. Chemical shifts of isomeric 1,3- and 1,4-disubstituted tetrazolium salts differ by ~0.5–1 ppm and even more.[30,43–49] Thus the CS of 1,4-dialkyltetrazolium perchlorates and tetrafluoroborates are 11.1–11.9 ppm, whereas those of 1,3-isomers are 10.2–10.9 ppm [in $(CD_3)_2SO$]. On going from DMSO to MeCN, the signal for the proton in the ^1H NMR spectrum is shifted upfield (10.6–10.9 ppm for 1,4-substituted and 9.6–10.1 ppm for 1,3-substituted derivatives).[30,43–49]

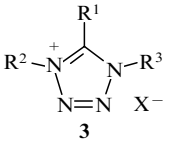
Identification of tetrazolium salts on the basis of ^1H NMR spectra often makes use of characteristic CS of the protons of the substituent owing to magnetic equivalence (or non-equivalence) of the groups. Thus the CS of the protons in the alkyl groups (Me, Et, Bu^t) in positions N(1) and N(4) differ considerably from those of the analogous substituents at the atoms C(5) and N(3).[3,14,17,18,21,35,36,49,71]

NMR spectroscopy allows both identification of tetrazolium salts and an analysis of the conjugation of the tetrazole fragment with the substituent. Thus the change in the CS of the carbon atoms of the vinyl group in the ^{13}C NMR spectra upon quaternisation of vinyltetrazoles allows one to conclude that there is a decrease in the *p*,π-conjugation in *N*-vinyltetrazolium salts and an increase in the *p*,π-conjugation in *C*-vinyltetrazolium salts as compared to the starting tetrazoles.[28] These data are consistent with the results of quantum-chemical calculations of geometric

Table 7. The chemical shift values of the signals of C(5) atoms of 1,3- (**2**) and 1,4-substituted tetrazolium (**3**) salts determined from ^{13}C NMRspectra (δ).



2



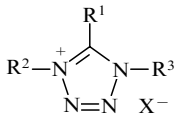
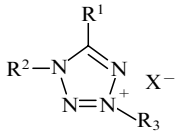
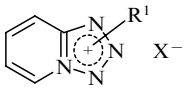
3

R^1	R^2	R^3	X	Solvent	Compound		Ref.
					2	**3**	
H	H	Ph	HSO_4	H_2SO_4	147.3	138.2	15
H	Et	Ph	BF_4	$(CD_3)_2CO$	148.3	140.3	15
NH_2	Me	Me	Cl	$(CD_3)_2SO$	158.1	148.5	73
NH_2	CH_2COPh	Me	Br	$(CD_3)_2SO$	158.7	148.9	35
$CH_2=CH$	Me	Me	$MeSO_4$	CD_3OD	162.7	149.4	28
Me	Me	CH_2COMe	I	D_2O	161.7	154.7	18
H	Ph	Ph	BF_4	$(CD_3)_2SO$	147.5	–	60
NH_2	Ph	Ph	BF_4	$(CD_3)_2SO$	157.7	–	61
N_3	Ph	Ph	BF_4	$(CD_3)_2SO$	155.9	–	61
Cl	Ph	Ph	BF_4	$(CD_3)_2SO$	153.9	–	60
Br	Ph	Ph	BF_4	$(CD_3)_2SO$	143.2	–	60
I	Ph	Ph	BF_4	$(CD_3)_2SO$	117.3	–	60
Hg	Ph	Ph	BF_4	$(CD_3)_2SO$	183.3	–	60
EtO	Ph	Ph	BF_4	$(CD_3)_2SO$	160.6	–	74
EtS	Ph	Ph	BF_4	$(CD_3)_2SO$	162.7	–	74
MeS	Me	Me	Cl	$(CD_3)_2SO$	162.4	–	73
Me	Me	Me	ClO_4	$(CD_3)_2SO$	–	152.7	22
Et	Me	Me	ClO_4	$(CD_3)_2SO$	–	154.9	22
H	Me	$CH_2=CH$	$MeSO_4$	CD_3OD	–	142.1	28

and electronic structures of these compounds. Also, correlations were found between the difference in CS of the carbon atoms of the vinyl group and the difference in the calculated effective charges on these atoms. [28]

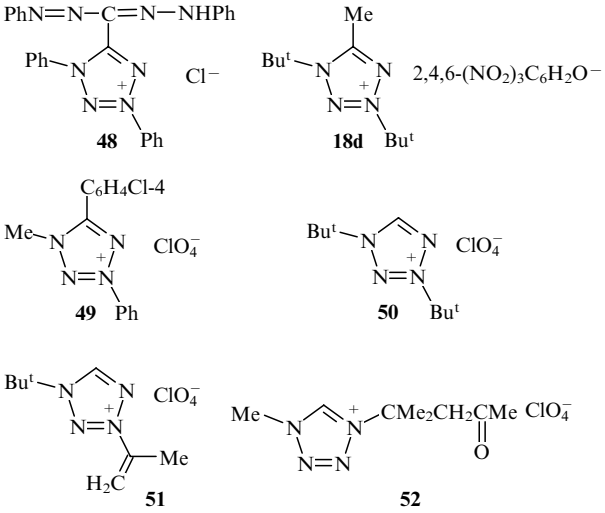
In recent years, ^{15}N and ^{14}N NMR spectroscopies (see Refs 28, 71 – 79) have become a popular approach to the solution of various structural problems related to tetrazolium salts. Thus this method allowed reliable determination of the direction of quaternisation [28, 34] and protonation [78, 79] of *N*-substituted tetrazoles. The most significant shift in the NMR spectrum (up to 115 ppm) upon transition from tetrazoles to tetrazolium salts is observed for the signal of the nitrogen atom directly involved in quaternisation. The CS values of endocyclic nitrogen atoms depend substantially on the type of the salt and the nature of the substituents (Table 8). An analysis of ^{15}N and ^{14}N NMR spectra of some 1,3,5-trisubstituted tetrazolium salts prompted the conclusion that the positive charge of the cation is predominantly localised on the N(3) atom,[28, 74 – 77] which is consistent with the X-ray diffraction data.[33, 48]

Table 8. The chemical shift values of the signals of endocyclic nitrogen atoms of tetrazolium salts determined from ^{15}N NMR spectra (δ).

Compound	R^1	R^2	R^3	X	N(1)	N(2)	N(3)	N(4)	Solvent	Ref.
	$CH_2=CH$	Me	Me	$MeSO_4$	−148.1	−17.5	−17.5	−148.1	CD_3OD	28
	H	$CH_2=CH$	Me	$MeSO_4$	−127.5	−22.2	−14.4	−142.5	CD_3OD	28
	NH_2	Me	Me	Cl	−182.0	−27.7	−27.7	−182.0	$(CD_3)_2SO$	73
	H	Bu	H	HSO_4	−130.5	−11.5	−17.0	−147.5	H_2SO_4	40
	$CH_2=CH$	Me	Me	$MeSO_4$	−148.1	−17.9	−101.2	−76.1	CD_3OD	28
	MeS	Me	Me	Cl	−148.6	−16.5	−100.9	−71.1	$(CD_3)_2SO$	73
	NH_2	Me	Me	Cl	−179.1	−30.6	−109.0	−107.4	$(CD_3)_2SO$	73
	H	Ph	Ph	BF_4	−129.8	−33.5	−92.4	−73.3	CD_3CN	76
	Cl	Ph	Ph	BF_4	−132.7	−22.4	−90.7	−73.3	$(CD_3)_2SO$	76
	N_3	Ph	Ph	BF_4	−153.1	−31.8	−97.5	−97.6	$(CD_3)_2SO$	76
	Hg	Ph	Ph	BF_4	−118.4	−26.9	−87.2	−59.7	$(CD_3)_2SO$	76
	EtO	Ph	Ph	BF_4	−158.4	−36.8	−103.4	−112.7	$(CD_3)_2SO$	74
	EtS	Ph	Ph	BF_4	−139.8	−26.8	−93.2	−83.8	$(CD_3)_2SO$	74
	H	H	Me	HSO_4	−144.6	−20.3	−96.8	−65.8	CD_3CN	40
	3-Me	–	–	BF_4	−132.2	−42.4	−95.3	−78.4	$(CD_3)_2SO$	34
	4-Me	–	–	BF_4	−129.0	−39.7	−12.8	−165.8	$(CD_3)_2SO$	34
	3-Et	–	–	BF_4	−132.6	−43.6	−84.7	−81.0	$(CD_3)_2SO$	34
	4-Et	–	–	BF_4	−128.6	−39.1	−14.8	−154.6	$(CD_3)_2SO$	34

2. X-Ray diffraction analysis

By now, crystal structures of eight tetrazolium salts, *viz*., 5-(1,5-diphenyl-3-formazanyl)-1,3-diphenyltetrazolium chloride (**48**),[3] 1,3-di-*tert*-butyl-5-methyltetrazolium picrate (**18d**),[33] 5-(4-chlorophenyl)-1-methyl-3-phenyl- (**49**),[29] 1,3-di-*tert*-butyl- (**50**),[48] 1-*tert*-butyl-3-isopropenyl- (**51**),[48] 1-(2,2-dimethyl-4-oxopentyl)-4-methyltetrazolium perchlorates (**52**),[46] tetrazolo[4,5-*b*][1,3]thiazinium- (**30**)[58] and thiazolo[3,2-*d*]tetrazolium perchlorates **31b,** have been established.[59]



The tetrazole rings in tetrazolium salts and other tetrazole derivatives are planar. The parameters of the tetrazole ring depend critically on the type of the salt. Thus the C(5)–N(1) [1.317(4) Å] and C(5)–N(4) [1.315(4) Å] bond lengths in the cation **52** are practically identical and intermediate between the double and ordinary bond lengths, N(2)–N(3) [1.276(4) Å] being the shortest bond and close to a double bond. The values of the bond angles at the N(2) and N(3) atoms practically coincide with that in a regular pentagon, while those at the N(1) and N(4) atoms approximate it. These data suggest that the structure of the 1,4-disubstituted tetrazole ring is close to that of a symmetrical ring with delocalisation of the excess positive charge over the N(4)–C(5)–N(1) fragment.[46] A similar structure is characteristic of the tetrazole ring of fused 1,4,5-trisubstituted tetrazolium salts **30** (see Ref. 58) and **31b** (see Ref . 59).

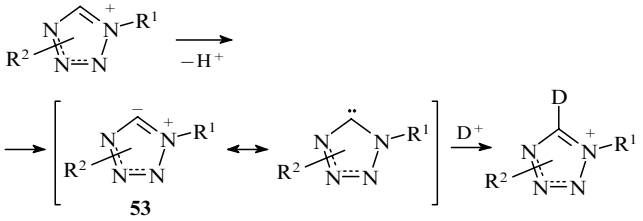
The heterocycles of 1,3-substituted tetrazolium salts are nonsymmetrical. The N(2)–N(3) [1.287(3)–1.299(3) Å] bond in the cations **18d**, **48**–**51** is the shortest bond; the N(4)–C(5) [1.300(4)–1.314(3) Å] bond length differs from it only insignificantly. This suggests that the positive charge of 1,3-substituted tetrazolium salts is predominantly localised on the N(3) atom rather than on the N(1) atom which represents the quaternisation site.[48] The non-coincidence of the quaternisation site and the site of localisation of the positive charge in the case of some tetrazolium salts was established experimentally: the quaternisation of *N*-substituted tetrazoles differing in the positions of substituents gave identical compounds.[30,48] The exocyclic N–C bonds in the cations under study lie in the plane of the ring. Their lengths are rather similar and differ only insignificantly from the length of the corresponding ordinary bond N–C with the exception of the N(3)–C(Me) bond in the cation **51**. Its length [1.440 Å] is somewhat smaller than that of an ordinary bond, while its torsion angles deviate by no more than 10.6° from 0° or 180°, which is suggestive of the conjugation of the π-systems of the tetrazole ring with the C=C bond.[48]

IV. Reactions of tetrazolium salts

Systematic studies of the chemical properties of 1,3- and 1,4-substituted tetrazolium salts were not carried out until recently. This section is devoted to the consideration of the most important electrophilic and nucleophilic substitution reactions of tetrazolium salts at the carbon atom of the heterocycle and other transformations under the action of various reagents.

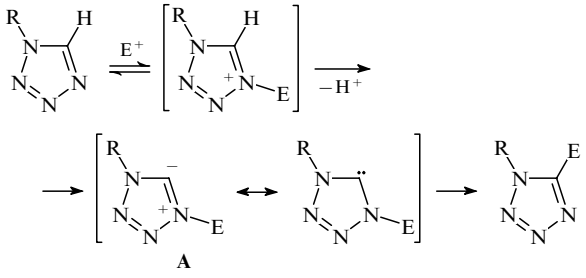
1. Substitution reactions at the carbon atom of the heterocycle

Only very few cases of substitution of the hydrogen atom in position C(5) of 1-monosubstituted tetrazoles were described before the 1980's. These include deuterium–hydrogen exchange, lithiation, mercuration and bromination.[72,80,81] It was believed that the problems encountered in the electrophilic substitution of hydrogen were caused by the deactivation of position 5 by annular nitrogen atoms.[82] With regard to disubstituted tetrazolium salts, the only known case was the isotope exchange in alkaline and acid media.



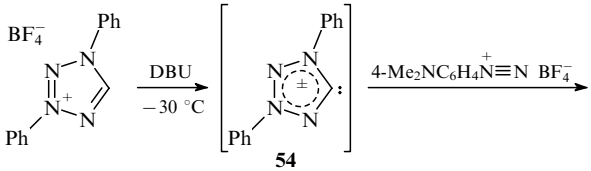
It is assumed that this exchange proceeds through the intermediate formation of ylide **53** or its isoelectronic analogue, carbene. It was shown that the kinetic CH-acidity changes in the following order: 2-R-tetrazoles < 1-R-tetrazoles < 1,3-disubstituted tetrazolium salts < 1,4-disubstituted tetrazolium salts.[80,81,83–85]

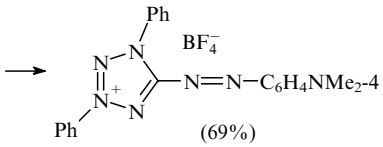
The first successful attempts at aminomethylation[86,87] and iodination of 1-R-tetrazoles were reported in the late 1980's–early 1990's.[88,89] The experimental data suggest that these reactions proceed through the intermediate formation of an ylide, which accounts for the introduction of a substituent into position 5. This reaction begins with an attack of an electrophilic reagent at the most nucleophilic N(4) atom and the formation of a tetrazolium cation, which is further deprotonated into the intermediate ylide (carbene) **A** stabilised by intramolecular rearrangement.



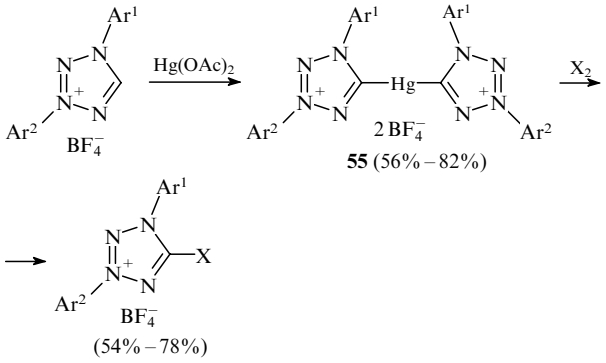
E = I, CH_2NAlk_2; R = Ar, Alk, H.

Simultaneously electrophilic substitution at the C(5) atom of tetrazolium salts was reported. It was shown, in particular, that the substitution of lithium for hydrogen in 2,3-diaryltetrazolium salts occurs under the action of *tert*-butyllithium or lithium bis(trimethylsilyl)amide.[90,91] The condensation of 1,3-diphenyltetrazolium tetrafluoroborate with a diazonium salt in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which favours the formation of a mesoionic carbene, *viz*., 1,3-diphenyltetrazolylene (**54**), has been described.[60]



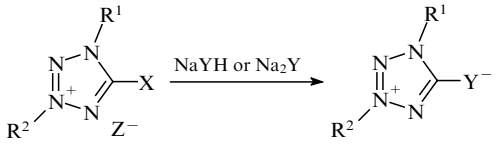


It was found that 1,3-diaryltetrazolium salts undergo mercuration upon heating with mercury(II) acetate in dimethyl sulfoxide to yield bis(tetrazolio)mercury(II) salts **55** the mercury atom in which is easily replaced by a halogen.[60]



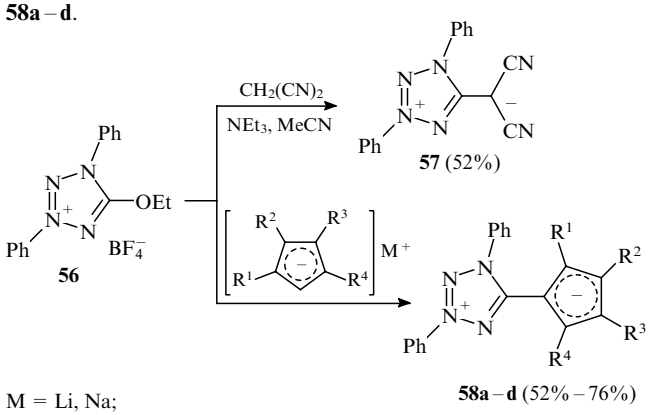
Ar^1 = Ph, 4-MeC_6H_4; Ar^2 = Ph, 4-$MeOC_6H_4$; X = Cl, Br, I.

Nucleophilic substitution at the C(5) atom of tetrazolium salts has been studied in more detail and is often employed in the synthesis of mesoionic tetrazoles. Thus it was shown that the ethoxy [92] and the methylthio groups [73] and the chlorine atom [60] of 1,3,5-trisubstituted tetrazolium salts can be replaced by sulfide, hydroxide and selenide ions.



R^1, R^2 = Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4; X = Cl, OEt, SMe; Y = O, S, Se; Z = BF_4, $MeSO_4$.

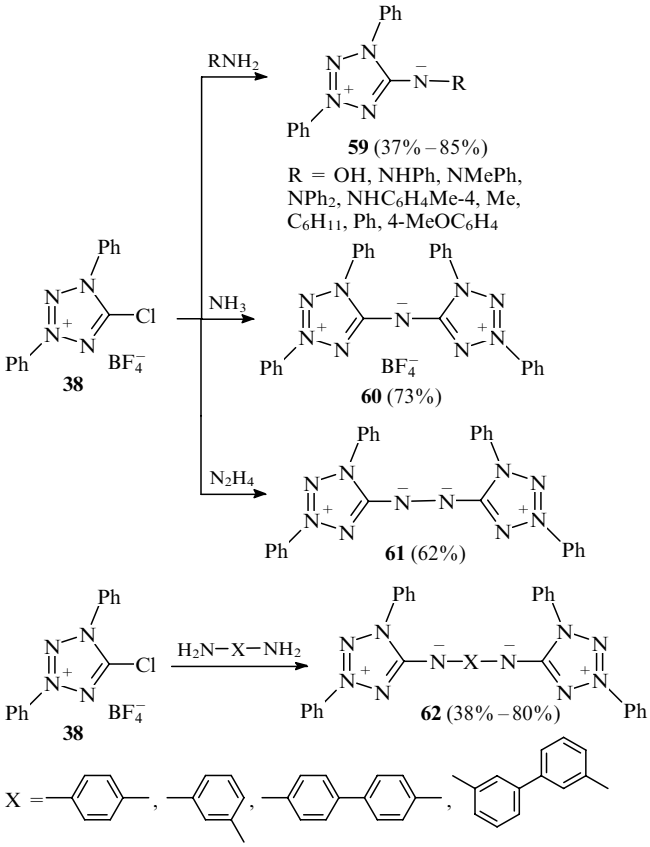
5-Ethoxy-1,3-diphenyltetrazolium tetrafluoroborate (**56**) reacts with C-nucleophiles, *e.g.*, malonic dinitrile,[93] lithium and sodium cyclopentanedienide,[94,95] indenide, fluorenide and cyclopenta[*def*]phenanthrenide [95] to give mesoionic tetrazoles **57** and **58a – d**.



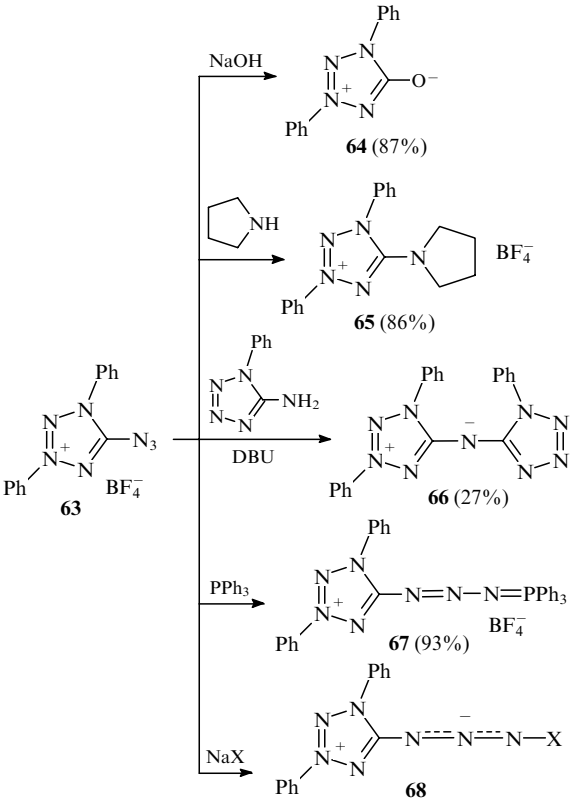
M = Li, Na;
$R^1 = R^2 = R^3 = R^4$ = H (**a**);
$R^1 = R^2$ = H, $R^3 – R^4$ = CH=CHCH=CH (**b**);
$R^1 – R^2$ = CH=CHCH=CH, $R^3 – R^4$ = CH=CHCH=CH (**c**);
$R^1 – R^4$ = =CH–CH=C(Ph)–CH=CH–C(Ph)=CH–CH=CH–CH= (**d**).

Mesoionic tetrazolium amides **59** were prepared by the reaction of 5-chloro-1,3-diphenyltetrazolium tetrafluoroborate **38** with N-nucleophiles, such as aliphatic amines,[96] aniline, hydroxylamine, *N*-mono- and *N*,*N*-disubstituted hydrazines.[60]

The reaction of the salt **38** with ammonia yielded bistetrazolioamide **60** as the main product;[60] the reaction with hydrazine and arylenediamines [97] gave tetrapolar mesoionic bistetrazoles **61**, **62**.



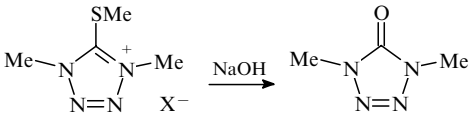
5-Azido-1,3-diphenyltetrazolium tetrafluoroborate (**63**) prepared by the reaction of sodium azide with the salt **38** has rich synthetic potential. The attack of strong nucleophiles, *e.g.*,



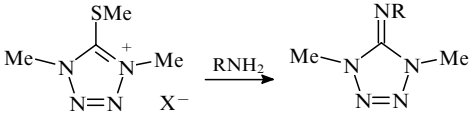
X = CN (93%), $SO_2C_6H_4$Me-4 (46%).

sodium hydroxide or amines at the endocyclic carbon atom, yields substitution products. Weaker nucleophiles, such as the cyanide ion, *p*-toluenesulfonate anion, triphenylphosphine, *etc*., attack the terminal nitrogen atom to give the addition products **67** and **68**.[61]

The nucleophilic substitution at the C(5) atom in 1,4,5-trisubstituted tetrazolium salts has been described exclusively for 1,4-dimethyl-5-(methylthio)tetrazolium salts. It was shown that they react with bases to give 1,4-dihydro-1,4-dimethyltetrazoles **69** and **70** (yields 27% – 40%).[7,17,62]



69

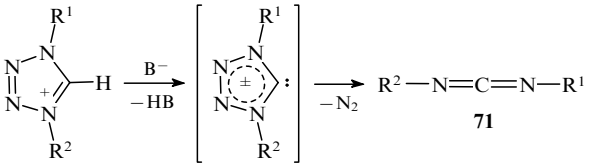


70

X = BF_4, $MeSO_4$; R = Me, PhNH.

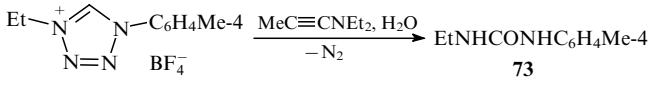
2. The action of bases

The majority of currently known tetrazolium salts are sensitive to bases. A base attacks predominantly the two carbon atoms with the lowest electron density, *viz*., the C(5) atom and the carbon atoms in the α-position relative to the nitrogen atoms of the heterocycle, which leads to the opening of the tetrazole ring, dealkylation or self-condensation. The salts devoid of substituents at the C(5) atom are the most susceptible to bases. The abstraction of the hydrogen atom under the action of bases is accompanied by the formation of heteroaromatic carbenes, *viz*., tetrazolidenes. The latter, in turn, undergo fragmentation the direction of which depends on the type of the salt used. It was shown[13,98] that 1,4-disubstituted tetrazolium salts are split into molecular nitrogen and carbodiimides **71** under the action of tertiary amines at 20 °C. Along with other reactions, this reaction is used in the synthesis of carbodiimides (see Ref. 99) and is the sole procedure in the synthesis of, *e.g*., vinylcarbodiimides.[13]



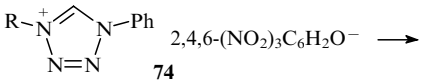
71

The carbodiimides formed, being highly reactive compounds,[99] react with an excess of the base or the solvent, or undergo intramolecular cyclisation. Thus the reaction of 1-ethyl-4-(*p*-tolyl)tetrazolium tetrafluoroborate (**72**) with diethylpropynylamine in the presence of water gives *N*-ethyl-*N′*-(*p*-tolyl)-urea (**73**).[98]

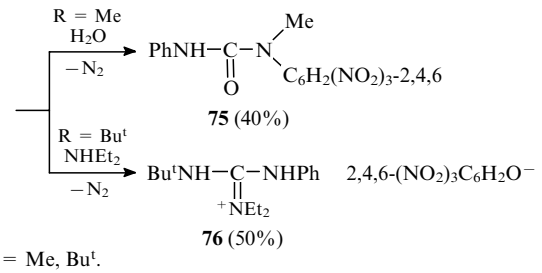


72

4-Alkyl-1-phenyltetrazolium picrates **74** are decomposed slowly in the presence of water to yield trisubstituted urea **75**; after treatment with diethylamine, they are converted into guanidinium picrate **76**.[33]



74

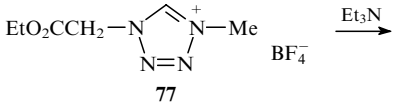


75 (40%)

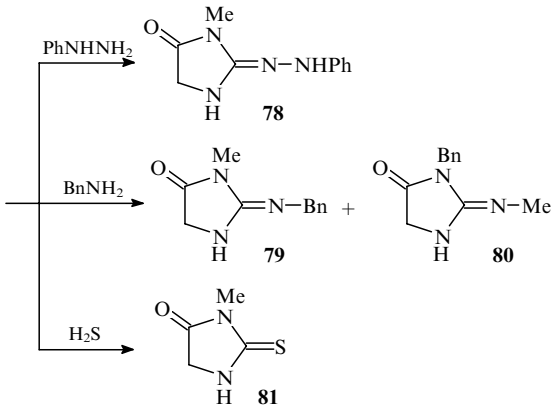
76 (50%)

R = Me, Bu^t.

It has been reported[13] that consecutive treatment of 1-(ethoxycarbonylmethyl)-4-methyltetrazolium tetrafluoroborate (**77**) with triethylamine and then with benzylamine, phenylhydrazine or hydrogen sulfide yields hydantoins **78**–**81**. Unfortunately, neither the methodology of these reactions, nor the yields of the target products have been reported.[13]



77

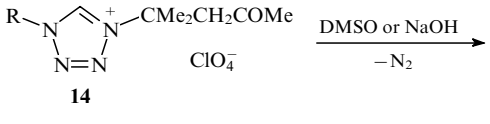


78

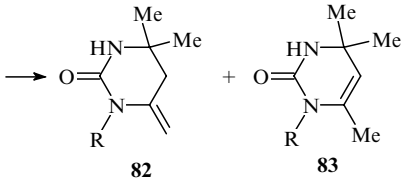
79 **80**

81

1-R-4-(2-Methyl-4-oxopentan-2-yl)tetrazolium perchlorates **14** evolve nitrogen in the presence of bases to be transformed into 4,4-dimethyl-1-R-6-methylidene-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ones **82** and 4,4,6-trimethyl-1-R-3,4-dihydropyrimidin-2(1*H*)-ones **83,** the latter being predominant.[47]



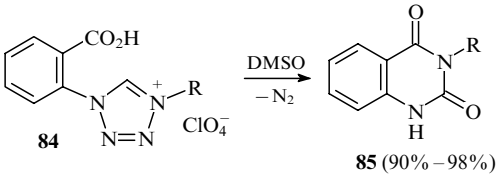
14



82 **83**

R = Ph, Bn.

3-Monosubstituted quinazoline-2,4(1*H*,3*H*)-diones **85** are formed in high yields on dissolution of 4-alkyl-1-(2-carboxyphenyl)tetrazolium perchlorates **84** in dimethyl sulfoxide.[47]

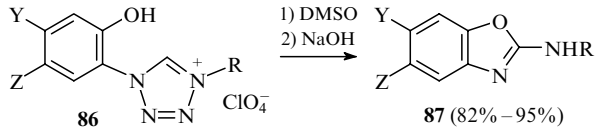


84

85 (90% – 98%)

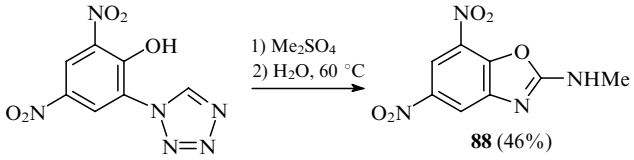
R = Bu^t, CMe_2CH_2COMe.

4-Alkyl-1-(2-hydroxyaryl)tetrazolium perchlorates **86** undergo recyclisation into 2-alkylaminobenzooxazoles **87** under the action of bases.[47]

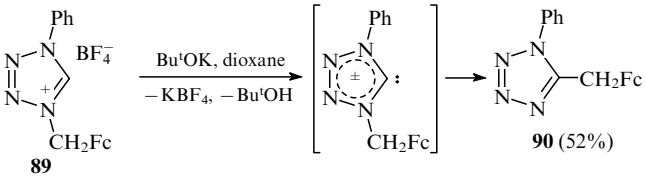


R = Bu^t, CMe_2CH_2COMe; Y = H, NO_2; Z = H, NO_2.

Preparation of 2-methylamino-5,7-dinitrobenzooxazole (**88**) is an example of a successful conversion of readily available 1-monosubstituted tetrazoles into benzooxazoles without the intermediate isolation of the tetrazolium salt.[100]

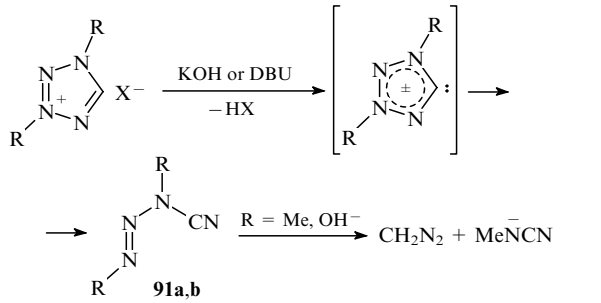


1-Aryl-4-ferrocenylalkyltetrazolium salts undergo dealkylation by aqueous ammonia or sodium carbonate at 20 °C to yield 1-aryltetrazoles and ferrocenylalkyl alcohols. 1-Ferrocenylmethyl-4-phenyltetrazolium tetrafluoroborate (**89**) undergoes the Stevens rearrangement in the presence of potassium *tert*-butoxide in dioxane to give 1,5-disubstituted tetrazole **90**.[44]



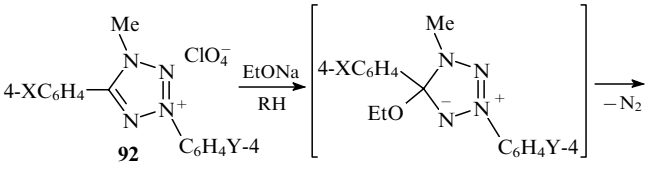
Fc = $C_5H_4FeC_5H_5$.

1,3-Disubstituted tetrazolium salts react with strong bases to give 1,3-disubstituted 3-cyanotriazenes **91a**,**b**.[60, 82] Compound **91a** is decomposed under the action of the hydroxide ion resulting in diazomethane and methylcyanamide anion.



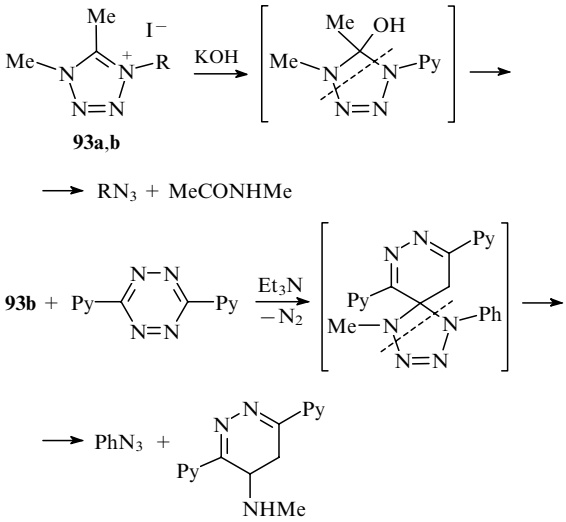
R = Me (**a**), Ph (**b**); X = Cl, BF_4.

3,5-Diaryl-1-methyltetrazolium salts **92** are resistant to the action of Et_3N in toluene at 20 °C, but react vigorously with sodium ethoxide in benzene or toluene to yield a complex mixture of reaction products among which biaryls are predominant.[29]



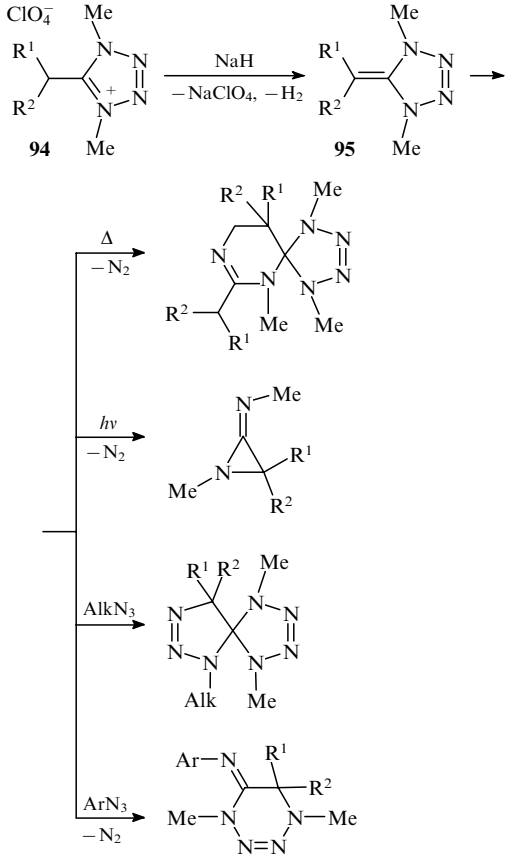
Y = H: X = H, Me, MeO, Cl; X = H: Y = H, NO_2, Me, MeO, Cl;
R = Ph, C_6H_4Me-4.

1,4,5-Trisubstituted tetrazolium salts **93a**,**b** undergo N-dealkylation[98] or fragmentation in the presence of bases,[25, 101] and ring-opening products always contain alkyl or aryl azide.



R = Me (**a**), Ph (**b**).

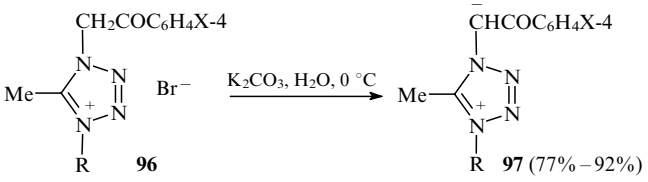
1,4,5-Trialkyltetrazolium salts **94** undergo deprotonation under the action of sodium hydride in tetrahydrofuran. This reaction has been studied in sufficiently great detail, since it allows one to prepare 1,4-dihydro-5-alkylidenetetrazoles **95**, the starting compounds in the synthesis of iminoaziridines, tetrazines, and other nitrogen-containing heterocyclic systems.[66, 102]



R^1, R^2 = H, Alk.

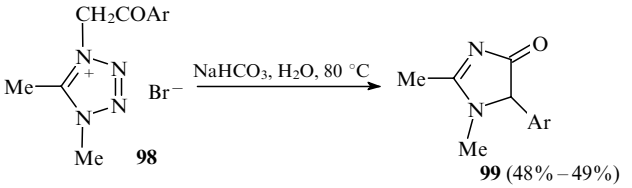
Some interesting conversions of *N*-acyl- and *N*-phenacyltetrazolium salts under the action of bases have been described.[21, 27, 35, 103, 104] It was shown that tetrazolium salts can be converted into ylides, fused tetrazoles, and other heterocyclic molecules. The direction of these reactions depends on the nature

of the reagent and the substituents in the substrate. Thus 1-alkyl-5-methyl-4-phenacyltetrazolium bromides **96** are converted into ylides **97** under the action of aqueous solutions of potassium carbonate.[27]

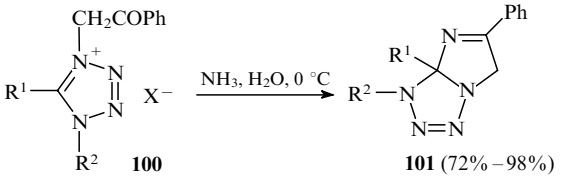


R = Me, Pr^n, Pr^i, Bu^i, CH_2Bu^t, cyclo-C_6H_{11}; X = H, Br, NO_2.

Similar conversions were observed in the case of 1,3-di- and 1,3,5-trisubstituted tetrazolium salts containing a phenacyl group at N(1) or N(3) atoms.[21] 1,5-Dimethyl-4-phenacyltetrazolium salts **98** undergo recyclisation into 1,2,5-trisubstituted imidazol-4-ones **99** upon heating with aqueous sodium hydrogencarbonate.[103] Analogous salts **100** yield 3*a*,6-dihydro-3*H*-imidazo-[1,2-*d*]tetrazoles **101** in a reaction with aqueous ammonia.[104]

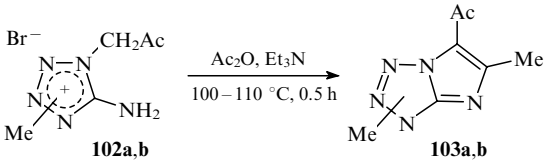


Ar = Ph, C_6H_4Br-4.



R^1 = Me, Et, Pr, Pr^i, cyclo-C_6H_{11}, Ph, Bn, $CH_2C_6H_4NO_2$-4;
R^2 = Me, Et, Bn; X = Br, I, ClO_4, $SbCl_6$, PF_6.

1-Acetylmethyl-5-amino-3- (**102a**) and -4-methyltetrazolium bromides (**102b**) undergo cyclisation into 6-acetyl-2,5-dimethyl-2*H*- (**103a**) and 6-acetyl-3,5-dimethyl-3*H*-imidazo[1,2-*d*]tetrazoles (**103b**) under the action of acetic anhydride and triethylamine.[35]

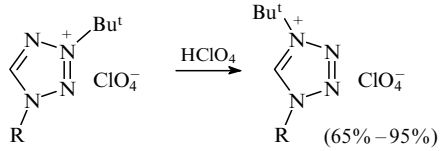


103a: 3-Me (86%); **103b**: 4-Me (51%).

3. The action of acids

The heterocycle in tetrazolium salts is usually resistant to acids. In reactions with acids, the modification affects only the substituents and is usually followed by their elimination and migration into another position of the ring.

It was found that 1-R-3-*tert*-butyltetrazolium perchlorates are slowly converted into 1-R-4-*tert*-butyltetrazolium perchlorates on storage in perchloric acid.[45, 47, 55]



R = Me, Et,Bu^t, cyclo-C_6H_{11}, Ph, 2-$HO_2CC_6H_4$, 2-HO-5-$NO_2C_6H_3$, 2-HO-4-$NO_2C_6H_3$.

Higher thermodynamic stability of 1,4-disubstituted tetrazolium salts in comparison with their 1,3-isomers is the driving force of this process as can be evidenced from the results of quantum-chemical calculations of the heats of formation and total energies of isomeric tetrazolium cations carried out with the use of semi-empirical[28, 45] and *ab initio* methods (Table 9) with full optimisation of the cation geometry.

1-*tert*-Butyl-3-R-tetrazolium salts do not undergo isomerisation in perchloric acid, but partly lose their *tert*-butyl groups.[45] The conversion of 1-R-3-*tert*-butyltetrazolium salts into the corresponding 1,4-isomers is accompanied by a partial loss of the *tert*-butyl group.[45, 55] Nothwithstanding, storage of 1-R-3-*tert*-butyltetrazolium salts with perchloric acid has been employed for the synthesis of 1-R-4-*tert*-butyltetrazolium salts.[45, 47]

In contrast to 1,3-disubstituted tetrazolium salts, 1,3,5-trisubstituted derivatives do not undergo isomerisation under similar conditions but are subject to dealkylation.[45] This property of 1,3,5-trisubstituted tetrazolium salts was used in the synthesis of mono- and binuclear 1,5-disubstituted tetrazoles where alkyl substituents are introduced into position N(1) of the tetrazole ring of 2,5-disubstituted tetrazoles with subsequent elimination of the *tert*-butyl substituent (the yields of the target products are 78% – 94%).[36, 106]

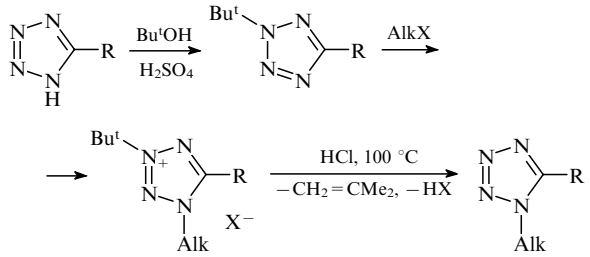
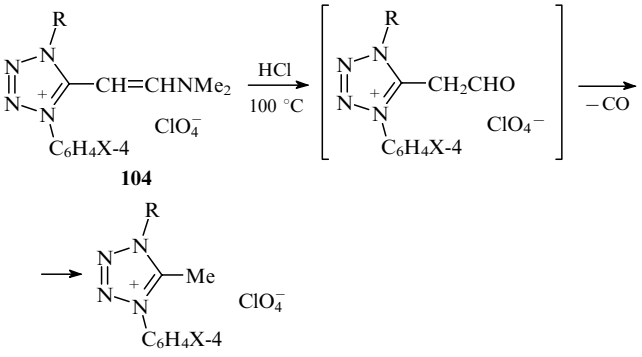


Table 9. The relative stability of tetrazolium cations (data from *ab initio* quantum-chemical calculations).

Compound	Method	Total energy of 1,4,5-isomer /kJ mol^{-1}	Total energy of 1,3,5-isomer /kJ mol^{-1}	ΔE /kJ mol^{-1}	Ref.
Protonated 1*H*,5*H*-tetrazole	STO-3G	−560438.6	−560416.0	22.6	105
	3-21G	−564290.9	−564267.5	23.4	105
	6-31G	−567204.6	−567189.5	15.1	105
	6-31G*//6-31G	−567545.4	−567537.7	7.7	105
	6-31G**	−567573.5	−567566.1	7.4	see [a]
	MP2/6-31G**	−567554.4	−567543.8	10.6	see [a]
Protonated 1-methyl-5*H*-tetrazole	6-31G	−653363.5	−653350.6	12.9	78
N(1)-Methyltetrazolo[1,5-*a*]pyridine	GIAO-CHF	−1180387.0	–	76.7	34
N(3)-Methyltetrazolo[1,5-*a*]pyridine	GIAO-CHF	–	−1180310.3	76.7	34

[a] Original author's data.

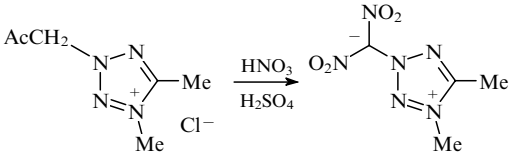
Boiling of 1-alkyl-4-aryl-5-(2-dimethylaminovinyl)tetrazolium perchlorates **104** in hydrochloric acid leads to the modification of the substituent at the C(5) atom.[25]



104

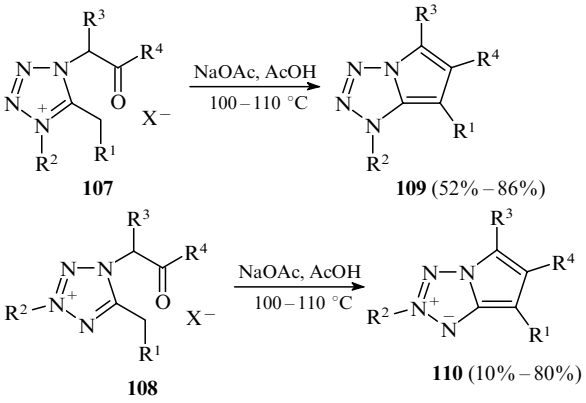
R = Me, Et; X = H, Me, F, Cl, Br, I.

Treatment of 3-acetylmethyl-1,5-dimethyltetrazolium chloride (**105**) with a nitrating mixture results in mesoionic tetrazole **106**.[107]



105 **106** (35%)

1,4,5- (**107**) and 1,3,5-trisubstituted tetrazolium salts (**108**) undergo cyclisation into 1*H*- and 2*H*-pyrrolotetrazoles **109** and **110** upon heating in acetic acid in the presence of sodium acetate.[37]



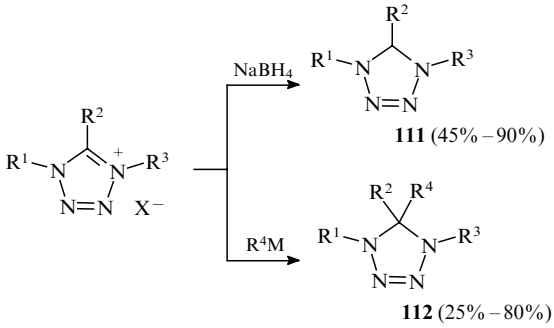
107 **109** (52% – 86%)

108 **110** (10% – 80%)

R^1 = MeCO, CO_2Me; R^2 = Me, Ph; R^3 = H, Me;
R^4 = Me, Ph, 4-BrC_6H_4; X = BF_4, $MeSO_4$.

4. The action of reducing and oxidising reagents

Tetrazolium salts are highly resistant to oxidising and reducing reagents; their heterocycles are not opened when treated with these reagents. Thus the oxidation of 1,3-diaryl-5-mercaptotetrazolium salts with concentrated nitric acid leads merely to the elimination of the substituent from position C(5) and the formation of 1,3-diaryltetrazolium salts,[60] while treatment of 5-azido-1,3-diphenyltetrazolium tetrafluoroborate (**63**) with hydroiodic acid or sodium sulfite results in the reduction of the azido group to the amino group.[61] At the same time, 1,4,5-trialkyl(aryl)tetrazolium salts are reduced to trisubstituted dihydrotetrazoles **111** with sodium borohydride in ethanol. These salts undergo alkylation in reactions with organolithium compounds and vinylmagnesium bromide to give tetrasubstituted dihydrotetrazoles **112**.[65]



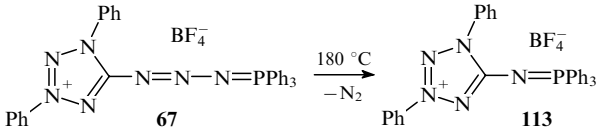
111 (45% – 90%)

112 (25% – 80%)

R^1 = Me, Et, Oh; R^2 = Ph, Me, cyclo-C_6H_{11}, Bu^t; R^3 = Me, Et, Bn, Ph;
R^4 = Me, Ph, PhC≡C, CH_2=CH; M = Li, MgBr.

5. Thermolysis

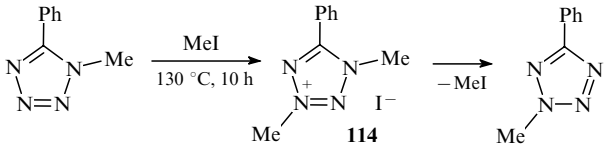
The published data on the thermal stability of tetrazolium salts are rather scarce. It was shown [6, 14] that of 1,3- and 1,4-dimethyl-5-R-tetrazolium iodides, the 1,4,5-isomers are more stable. Their decomposition begins at temperatures above 265 °C (R = Me) and 130 °C (R = Ph), whereas that of 1,3,5-isomers occurs even at 130 and 70 °C, respectively. *N*-Demethylation is the main process of thermolysis leading to the formation of disubstituted tetrazoles.[6, 14] Thermolysis of 1,3,5-trisubstituted derivative **67** is accompanied by the evolution of nitrogen and the formation of the salt **113** in 94% yield.[61]



67 **113**

Recently, the thermal stabilities of 1-methyl-4-phenyl-, 1,4,5-trimethyl-, 1,3-di-*tert*-butyl-5-methyl- and 1,3-di-*tert*-butyltetrazolium picrates have been studied using differential scanning calorimetry and complex thermal analysis (heating rate 5 °C per min in a nitrogen atmosphere).[33] Among those, 1,4,5-trimethyltetrazolium picrate [initial temperature of intense decomposition (T_d) 215 °C] manifested the highest stability. 1-Methyl-4-phenyltetrazolium picrate (T_d = 100 °C) appeared to be the least stable, which may be attributed to the easy abstraction of proton from the carbon atom of the heterocycle. Special mention should be made of the enhanced thermal resistance of poly-*N*,*N*′-dimethyl-5-vinyltetrazolium perchlorate in comparison with poly-*N*-methyl-5-vinyltetrazole. According to complex thermal analysis data, the decomposition of polymeric tetrazolium perchlorate is observed at temperatures above 275 °C, whereas the non-quaternised polymer is decomposed at 230 °C.[108]

2-Methyl-5-phenyltetrazole is the main reaction product in the attempted synthesis of tetrazolium salts by quaternisation of 1-methyl-5-phenyltetrazole with methyl iodide at 130 °C.[6] The resulting isomerisation is due to the specificity of thermolysis of the initially formed tetrazolium salt **114**; its decomposition yields predominantly 2,5-disubstituted tetrazole.[6]



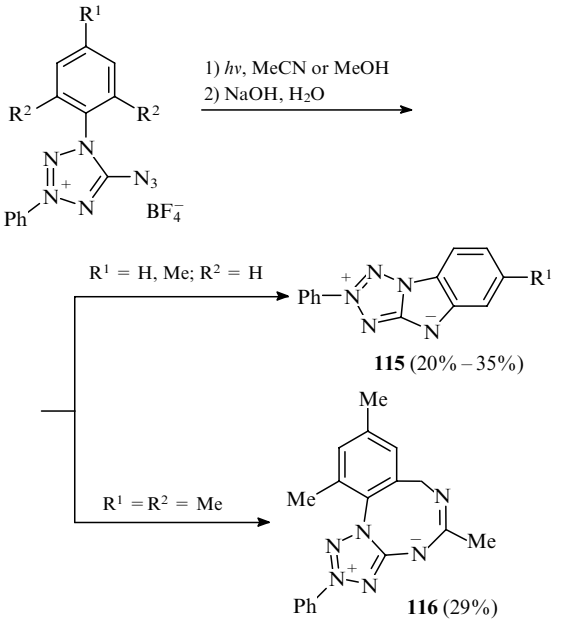
114

The formation of tetrazolium complexes is usually the key step in the isomerisation of *N*-substituted tetrazoles, which occurs under the action of alkylating reagents [6, 109] or acids.[43, 55, 110, 111]

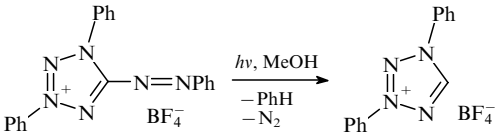
6. Photolysis

The photochemical conversions of some azido-, azo- and triazo-1,3-diaryltetrazolium derivatives have been studied recently.[112–114] It was found [112, 113] that the tetrazole rings of the

compounds under study are resistant to UV irradiation. Among other conversions, only the reactions of 5-azido-1,3-diaryltetrazolium salts, which yield hardly accessible tricyclic mesoionic compounds **115** and **116**, deserve special mention.

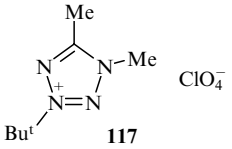


UV Irradiation of 1,3-diphenyl-5-phenyltetrazolium tetrafluoroborate is accompanied by the evolution of nitrogen and the formation of 1,3-diphenyltetrazolium tetrafluoroborate and benzene.[114]



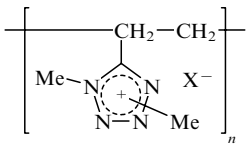
V. Applications of tetrazolium salts

Until recently, 1,3- and 1,4-substituted tetrazolium salts have not been sufficiently investigated due to their unavailability and data concerning their applications are virtually absent from the literature. However, the development of procedures for their synthesis have given strong impetus to their investigations, particularly in those areas where 2,3-substituted tetrazolium salts (*e.g.*, phase-transfer catalysts, reagents for the separation of metals, *etc.*) were conventionally used before. There is evidence of successful applications of 3-*tert*-butyl-1,5-dimethyltetrazolium perchlorate (**117**) as a phase-transfer catalyst in oxidation reactions catalysed by the permanganate ion.[115]



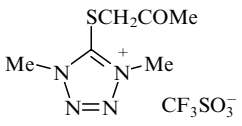
117

It is of note that 1,3-substituted tetrazolium salts have a number of advantages over 2,3-derivatives in such reactions.[116] First, these methods allow one to obtain 1,3,5-trisubstituted tetrazolium salts with various types of substituents at the carbon and nitrogen atoms of the tetrazole ring and thus to vary their physicochemical properties (*e.g.*, thermal stability, solubility, *etc.*). The methods for the synthesis of 2,3-disubstituted tetrazolium salts exclude the introduction of alkyl substituents to the nitrogen atoms of the tetrazole ring, which limits the array of available derivatives.[1–3] Of no less importance is the relative stability of 1,3-substituted tetrazolium salts in reductive media; therefore, they can be used in phase-transfer reduction reactions, whereas 2,3-substituted derivatives are converted into formazanes even under the action of weak reducing agents.[1–3] Recently, a series of poly-5-vinyltetrazolium salts **118** prepared by exhaustive methylation of poly-5-vinyltetrazole have been examined as sorbents for the extraction of palladium ions from various solutions in the form of $PdCl_4^{2-}$. These include an efficient adsorbent for the selective extraction of palladium ions from spent palladation electrolytes.[108] It was found that 1,4-dimethyl-5-[(2-oxopropyl)thio]tetrazolium triflate (**119**) inhibits transglutaminase,[117] and 5-(2-anilinovinyl)-1-(4-chlorophenyl)-4-ethyltetrazolium iodide (**120**) manifests antiarrhythmic activity.[118]

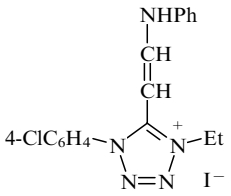


118

X = BF_4^-, ClO_4^-, $MeSO_4^-$

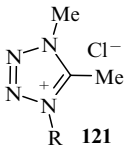


119



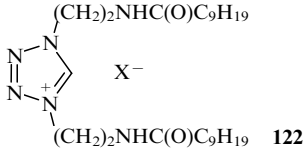
120

The addition of 1-aryl- and 1-cyclohexyl-4,5-dimethyltetrazolium chlorides **121** to photographic dyes decreases the light sensitivity of photomaterials and enhances image sharpness.[119] 1,4-Bis(2-decanoylaminoethyl)tetrazolium methylsulfate and perchlorate **122** have been patented as corrosion inhibitors and disinfectants.[120] Tetrazolo[1,5-*a*]pyridinium salts **123**, **124** have found application as sensitisers in the recording layers of electrophotographic materials.[56, 121]



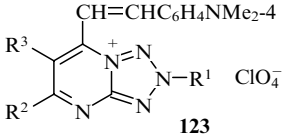
121

R = cyclo-C_6H_{11}, 2-ClC_6H_4, 3,4-$Me_2C_6H_3$



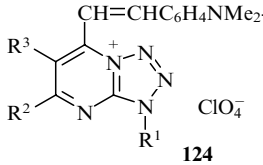
122

X = ClO_4, $MeSO_4$



123

R^1 = Me, Bn; R^2 = H, Me, Ph, CH=$CHC_6H_4NMe_2$-4; R^3 = H, Me



124

R^1 = Me, $CH_2CH=CH_2$, Ph; R^2 = H, Me, Ph, CH=$CHC_6H_4NMe_2$-4; R^3 = H, Me

However, 1,3- and 1,4-substituted tetrazolium salts present the greatest interest as starting materials in the synthesis of various (including hardly accessible) heterocyclic systems. Condensation reactions of these salts are employed in the synthesis of annelated heterocycles. These reactions are specific and often the only way to the synthesis of imidazo-[35, 103] and pyrrolotetrazoles.[37] It was shown that recyclisation of 1,4-substituted tetrazolium salts is a convenient procedure for the synthesis of three-, five- and six-membered nitrogenous heterocycles, such as iminoaziridines and tetrazines,[66, 102] imidazolones,[103] benzooxazoles and quinazolinediones.[47, 100] The conversions of substituents at the carbon atom of the heterocycles of 1,3,5- and 1,4,5-trisubstituted tetrazolium

salts can be used in the high-yield synthesis of mesoionic tetrazoles.[21, 27, 60, 94, 95, 112–114] The use of tetrazolium salts for the generation of N-heteroaromatic carbenes,[44, 59, 122] which occupy a special place in the chemistry of carbenes by virtue of their peculiar structures and reactivities, especially holds great promise.[83, 122]

VI. Conclusion

Significant progress has been achieved in the synthesis and investigation of physicochemical properties of 1,3-(1,3,5)- and 1,4-(1,4,5)-substituted tetrazolium salts in the past 10–15 years. The interest in these studies is largely due to the development of methods for selective functionalisation of the tetrazole ring, which permits direct introduction of substituents on the carbon and nitrogen atoms of the heterocycle, and the recently discovered isomerisation of 1,3-disubstituted tetrazolium salts into the corresponding 1,4-disubstituted derivatives. In turn, the availability of tetrazolium salts has stimulated the search for novel areas of their applications, particularly for synthetic purposes. Recyclisation and condensation reactions of tetrazolium salts and transformations of substituents at the carbon atom of the heterocycle proved to be useful tools in the synthesis of various organic compounds. Elucidation of the synthetic potentials of tetrazolium salts presents considerable interest for further progress in preparative chemistry of nitrogen-containing heterocyclic systems and organic chemistry on the whole. In-depth studies into the properties of novel 1,3-(1,3,5)- and 1,4-(1,4,5)-substituted tetrazolium salts will make it possible to extend the range of their practical applications, *e.g.*, the design of polynitrogenous ionogenic polymers and ionic fluids resembling those of other azolium salts and possessing unique properties. Of no less importance are further studies into tetrazole quaternisation and possible involvement of functionalised C- and N-tetrazole derivatives and various alkylating reagents in this reaction. The knowledge of regularities underlying the formation of tetrazolium cations will enhance the potentialities of quaternisation and protonation reactions for the activation of the tetrazole ring in the substitution reactions occurring at the endocyclic carbon atom.

References

1. A W Nineham *Chem. Rev.* **55** 355 (1955)
2. W D Hooper *Rev. Pure Appl. Chem.* **19** 221 (1969)
3. A B Zhivich, G I Koldobskii, V A Ostrovskii *Khim. Geterotsikl. Soedin.* 1587 (1990) [a]
4. A K Pikaev, Z K Kriminskaya *Usp. Khim.* **67** 745 (1998) [*Russ. Chem. Rev.* **67** 671 (1998)]
5. D S Daniel *Chem. Appl. Leuco Dyes* 207 (1997); *Chem. Abstr.* **127** 163 093 (1997)
6. R N Butler, in *Comprehensive Heterocyclic Chemistry II* Vol. 4 (Eds A R Katritzky, C W Rees, E F V Scriven) (Oxford; New York: Pergamon Press, 1996) p. 621
7. H R Meier, H Heimgartner, in *Methoden der Organischen Chemie (Houben-Weyl)* Bd. E8d (Stuttgart: Georg Thieme, 1994) p. 664
8. G I Koldobskii, V A Ostrovskii *Usp. Khim.* **63** 847 (1994) [*Russ. Chem. Rev.* **63** 797 (1994)]
9. D Moderhack *J. Prakt. Chem.-Chem. Ztg.* **340** 687 (1998)
10. P N Gaponik, in *Khimicheskie Problemy Sozdaniya Novykh Materialov i Tekhnologii* (Chemical Problems of Creation of New Materials and Technologies) (Ed. V V Sviridov) (Minsk: Belorussian University, 1998) p. 185
11. V A Ostrovskii, A O Koren *Heterocycles* **53** 1421 (2000)
12. C G Newton, C A Ramsden *Tetrahedron* **38** 2965 (1982)
13. O M Zimmerman, R A Olofson *Tetrahedron Lett.* 3453 (1970)
14. T Isida, S Kozima, S-i Fujimori, K Sisido *Bull. Chem. Soc. Jpn.* **45** 1471 (1972)
15. A Könnecke, E Lippmann, E Kleinpeter *Tetrahedron* **33** 1399 (1977)
16. R Faure, J P Galy, E J Vincent, J Elguero *Magn. Res. Chem.* **11** 507 (1978)
17. H Quast, L Bieber *Chem. Ber.* **114** 3253 (1981)
18. V V Semenov, V S Bogdanov, B S El'yanov, L G Mel'nikova, S A Shevelev, V M Zhulin, A A Fainzil'berg *Khim. Geterotsikl. Soedin.* 1118 (1982) [a]
19. H Quast, U Nahr *Chem. Ber.* **116** 3427 (1983)
20. A Messmer, G Hajos, J Fleischer, M Czugler *Monatsch. Chem.* **116** 1227 (1985)
21. D Moderhack, A Lembcke *J. Chem. Soc., Perkin Trans. 1* 1157 (1986)
22. H Quast, L Bieber, G Meichner *Liebigs Ann. Chem.* 469 (1987)
23. I Yu Shirobokov, M V Chekushina, V A Ostrovskii, G I Koldobskii, G B Erusalimskii *Khim. Geterotsikl. Soedin.* 502 (1988) [a]
24. A Messmer, G Hajos, Z Juhasz-Riedl, P Sohar *J. Org. Chem.* **53** 973 (1988)
25. G W Fischer *J. Prakt. Chem.* **331** 885 (1989)
26. M Begtrup, P Larsen *Acta Chem. Scand., Ser. B* **44** 1050 (1990)
27. D Moderhack, D-O Bode *J. Chem. Soc., Perkin Trans. 1* 1483 (1992)
28. P N Gaponik, O A Ivashkevich, V N Naumenko, T B Kovalyova, T N Andreeva *Spectrochim. Acta, Part A* **49** 135 (1993)
29. R N Butler, J P Duffy, E P Nibhradaigh, P McArdile, D Cunningham *J. Chem. Res.* (*S*) 216 (1994)
30. P N Gaponik, Yu V Grigor'ev, T N Andreeva, I I Maruda *Khim. Geterotsikl. Soedin.* 915 (1995) [a]
31. H Quast, J Balthasar, A Fuss, U Nahr, W Nudling *Liebigs Ann. Chem.* 671 (1997)
32. P N Gaponik, V P Karavai, Yu V Grigor'ev *Dokl. Akad. Nauk Bel.* **41** (5) 66 (1997)
33. P N Gaponik, S V Voitekhovich, O A Ivashkevich, A S Lyakhov, A A Govorova *Khim. Geterotsikl. Soedin.* 657 (1998) [a]
34. P Cmoch, J W Wiench, L Stefaniak, J Sitkowski *J. Mol. Struct.* **477** 119 (1999)
35. D Moderhack, B Holtmann *J. Prakt. Chem.-Chem. Ztg.* **342** 591 (2000)
36. P N Gaponik, S V Voitekhovich, A S Lyakhov *Khim. Geterotsikl. Soedin.* 387 (2000) [a]
37. D Moderhack, D Decker, B Holtmann *J. Chem. Soc., Perkin Trans 1* 720 (2001)
38. A F Pozharskii *Teoreticheskie Osnovy Khimii Geterotsiklov* (Theoretical Foundations of Heterocyclic Chemistry) (Moscow: Khimiya, 1985)
39. I P Gol'dshtein, L D Khamaganova, A N Fedotov, E S Domnina *Zh. Fiz. Khim.* **65** 959 (1991) [b]
40. V N Naumenko, A O Koren, P N Gaponik *Magn. Res. Chem.* **30** 558 (1992)
41. V N Naumenko, P N Gaponik, A O Koren', M M Degtyarik *Izv. Akad. Nauk Bel., Ser. Khim. Nauk* (1) 64 (1993)
42. V Yu Zubarev, V A Ostrovskii *Khim. Geterotsikl. Soedin.* 867 (2000) [a]
43. V V Saraev, E L Golod *Zh. Org. Khim.* **33** 629 (1997) [c]
44. V I Boev, E M Krasnikova, A I Moskalenko, E I Pil'ko, L V Snegur, V N Babin, Yu S Nekrasov *Zh. Obshch. Khim.* **67** 1386 (1997) [d]
45. P N Gaponik, S V Voitekhovich, I I Maruda, A A Kulak, O A Ivashkevich *Pol. J. Chem.* **72** 2247 (1998)
46. P N Gaponik, S V Voitekhovich, A S Lyakhov, I I Maruda *Khim. Geterotsikl. Soedin.* 1222 (1999) [a]
47. S V Voitekhovich, P N Gaponik, A S Lyakhov, O A Ivashkevich *Pol. J. Chem.* **75** 253 (2001)
48. S V Voitekhovich, P N Gaponik, A S Lyakhov, O A Ivashkevich *Khim. Geterotsikl. Soedin.* 1035 (2001) [a]
49. S V Voitekhovich, P N Gaponik, O A Ivashkevich *Izv. Nat. Akad. Nauk Bel., Ser. Khim. Nauk* (1) 62 (2002)
50. USSR P. 1 544 772; *Byull. Izobret.* (17) 3 (1990)
51. A O Koren', P N Gaponik *Khim. Geterotsikl. Soedin.* 1280 (1991) [a]
52. S V Voitekhovich, P N Gaponik, A O Koren *Mendeleev Commun.* 41 (1997)
53. A O Koren, P N Gaponik, V A Ostrovskii *Int. J. Chem. Kinet.* **25** 1043 (1993)
54. A O Koren, P N Gaponik, V A Ostrovskii *Int. J. Chem. Kinet.* **27** 919 (1995)
55. P N Gaponik, S V Voitekhovich *Zh. Org. Khim.* **34** 788 (1998) [c]
56. I P Bachkovskii, V A Chuiguk *Ukr. Khim. Zh.* **53** 319 (1987)
57. H Alper, R W Stout *J. Heterocycl. Chem.* **10** 569 (1973)
58. G N Borisova, A V Borisov, I V Bodrikov, V K Bel'skii, A I Lutsenko, V A Smit, G A Kutyrev *Zh. Org. Khim.* **30** 760 (1994) [c]

59. A V Borisov, V K Bel'skii, G N Borisova, V K Osmanov, Zh V Matsulevich, T V Goncharova *Khim. Geterotsikl. Soedin*. 763 (2001) [a]
60. S Araki, Y Wanibe, F Uno, A Morikawa, K Yamamoto, K Chiba, Y Butsugan *Chem. Ber*. **126** 1149 (1993)
61. S Araki, K Yamamoto, M Yagi, T Inoe, H Fukagawa, H Hattori, H Yamamura, M Kawai, Y Butsugan *Eur. J. Org. Chem*. 121 (1998)
62. H Quast, A Fuss, U Nahr *Chem. Ber*. **118** 2164 (1985)
63. D Moderhack, D Decker, B Holtmann *J. Chem. Soc., Perkin Trans. 1* 729 (2001)
64. S Araki, J Mizuya, Y Butsugan *J. Chem. Soc., Perkin Trans. 1* 2439 (1985)
65. B Carbony, R Carrie *Tetrahedron* **40** 4115 (1984)
66. H Quast, T Hergenrother *Liebigs Ann. Chem*. 581 (1992)
67. W Wirschun, M Winkler, K Lutz, J C Jochims *J. Chem. Soc., Perkin Trans. 1* 1755 (1998)
68. W Wirschun *J. Prakt. Chem.-Chem. Ztg*. **340** 300 (1998)
69. K R Seddon *Kinet. Katal*. **37** 743 (1996) [e]
70. P Wasserscheid, W Keim *Angew. Chem*. **112** 3926 (2000)
71. P N Gaponik, O A Ivashkevich *Izbrannye Nauchnye Trudy BGU, Khimiya* (Selected Proceedings of Belorussian State University) Vol. 5 (Minsk: Belorussian State University, 2001) p. 353
72. P N Gaponik, Doctoral Thesis in Chemical Sciences, Research Institute for Physical Chemical Problems of Belorussian State University, Minsk, 2000
73. W Bocian, J Jazwinski, W Kozminski, L Stefaniak, G A Webb *J. Chem. Soc., Perkin Trans. 2* 1327 (1994)
74. W Bocian, J Jazwinski, W Kozminski, L Stefaniak, G A Webb *Magn. Res. Chem*. **32** 284 (1994)
75. J Jazwinski, W Kozminski, L Stefaniak, G A Webb *Magn. Res. Chem*. **32** 746 (1994)
76. J Jazwinski, O Staszewska, L Stefaniak, S Araki, G A Webb *J. Mol. Struct*. **523** 103 (2000)
77. J Jazwinski *Bull. Pol. Acad. Sci., Chem*. **48** 35 (2000)
78. R M Claramunt, D Sanz, G Boyer, J Catalan, J L G de Paz, J Elguero *Magn. Res. Chem*. **31** 791 (1993)
79. R M Claramunt, D Sanz, C Lopez, J A Jimenez, M L Jimeno, J Elguero, A Fruchier *Magn. Res. Chem*. **35** 35 (1997)
80. G I Koldobskii, V A Ostrovskii, V S Poplavskii *Khim. Geterotsikl. Soedin*. 1299 (1981) [a]
81. R N Butler, in *Comprehensive Heterocyclic Chemistry* Vol. 5 (Eds A R Katritzky, C W Rees) (Oxford; New York: Pergamon Press, 1984) p. 791
82. M R Grimmett, in *Comprehensive Organic Chemistry* Vol. 4 (Eds D Barton, W D Ollis) (Oxford: Pergamon Press, 1979)
83. O P Shvaika, N I Korotkikh, A F Aslanov *Khim. Geterotsikl. Soedin*. 1155 (1992) [a]
84. P N Gaponik, V N Naumenko, Yu V Grigor'ev, T A Madzievskaya *Vest. Belorus. Univ., Ser. 2* (1) 9 (1995)
85. L I Belen'kii, L D Chuvylkin *Khim. Geterotsikl. Soedin*. 1535 (1996) [a]
86. V P Karavai, P N Gaponik *Khim. Geterotsikl. Soedin*. 564 (1985) [a]
87. V P Karavai, P N Gaponik *Khim. Geterotsikl. Soedin*. 66 (1991) [a]
88. P N Gaponik, Yu V Grigor'ev, A O Koren' *Khim. Geterotsikl. Soedin*. 1699 (1988) [a]
89. Yu V Grigor'ev, P N Gaponik *Izv. Akad. Nauk. Bel., Ser. Khim. Nauk* (1) 73 (1992)
90. R H Lowack, R Weiss *J. Am. Chem. Soc*. **112** 333 (1990)
91. R Weiss, R H Lowack *Angew. Chem*. **103** 1183 (1991)
92. R N Hanley, W D Ollis, Ch A Ramsden *J. Chem. Soc., Perkin Trans. 1* 741 (1979)
93. R N Hanley, W D Ollis, Ch A Ramsden, I S Smith *J. Chem. Soc., Perkin Trans. 1* 744 (1979)
94. S Araki, Y Butsugan *J. Chem. Soc., Chem. Commun*. 789 (1983)
95. S Araki, Y Butsugan *J. Chem. Soc., Perkin Trans. 1* 2545 (1984)
96. J Jazwinski *Pol. J. Chem*. **73** 1719 (1999)
97. S Araki, K Yamamoto, T Inoe, K Fujimoto, H Yamamura, M Kawai, Y Butsugan, J-K Zhou, E Eichhorn, A Rieker, M Huber *J. Chem. Soc., Perkin Trans. 2* 985 (1999)
98. G Scherowsky, I Pickardt *Chem. Ber*. **116** 186 (1983)
99. M Mikolajczyk, P Kielbasinski *Tetrahedron* **37** 233 (1981)
100. S V Voitekhovich, P N Gaponik *Khim. Geterotsikl. Soedin*. 1141 (1997) [a]
101. E G Kovalev, V A Anufriev, G L Rusinov *Khim. Geterotsikl. Soedin*. 1691 (1990) [a]
102. H Quast, A Fuss, W Nudling *Eur. J. Org. Chem*. 317 (1998)
103. D Moderhack, A Lembcke *Chem.-Zeit*. **109** 432 (1985)
104. D Moderhack, D-O Bode, D Shomburg *Chem. Ber*. **126** 129 (1993)
105. O My, J L G de Paz, M Yanez *J. Phys. Chem*. **90** 5597 (1986)
106. A O Koren, P N Gaponik, O A Ivashkevich, T B Kovalyova *Mendeleev Commun*. 10 (1995)
107. V V Semenov, S A Shevelev, L G Mel'nikova *Mendeleev Commun*. 58 (1993)
108. S V Voitekhovich, P N Gaponik, O A Ivashkevich, in *Vtoroi Vserossiiskii Karginskii Simpozium 'Khimiya i Fizika Polimerov v Nachale XXI Veka' (Tez. Dokl.), Chernogolovka, 2000* [The Second Kargin All-Russian Symposium 'Chemistry and Physics of Polymers in the Beginning of the XXIth Century' (Abstracts of Reports), Chernogolovka, 2000] Vol. 1, p. 1
109. A I Podgurskii, S G Zlotin, M M Krayushkin, O A Luk'yanov *Izv. Akad. Nauk SSSR, Ser. Khim*. 236 (1985) [f]
110. A V Sachivko, V P Tverdokhlebov, I V Tselinskii *Zh. Org. Khim*. **22** 1112 (1986) [c]
111. S V Voitekhovich, P N Gaponik *Izv. Akad. Nauk. Bel., Ser. Khim. Nauk* **68** (2) (2000)
112. S Araki, H Hattori, N Shimizi, K Ogawa, H Yamamura, M Kawai *J. Heterocycl. Chem*. **36** 863 (1999)
113. S Araki, H Hattori, H Yamamura, M Kawai *J. Heterocycl. Chem*. **37** 1129 (2000)
114. S Araki, H Hattori, K Ogawa, M Kuzuya, T Inoe, H Yamamura, M Kawai *J. Chem. Soc., Perkin Trans. 1* 2476 (2001)
115. Yu V Grigor'ev, Author's Abstracts of Candidate Thesis in Chemical Sciences, St Petersburg State Technical Institute (Technical University), St-Petersburg, 1998
116. G I Koldobskii, A B Zhivich, V A Ostrovskii *Zh. Obshch. Khim*. **62** 3 (1992) [d]
117. Eur. P. 411 894; *Chem. Abstr*. **115** 29 338 (1991)
118. US P. 5 183 813; *Chem. Abstr*. **119** 108 996 (1993)
119. Jpn. P. 05 27 368; *Chem. Abstr*. **119** 59 638 (1993)
120. BRD P. 4 218 585; *Chem. Abstr*. **120** 107 029 (1994)
121. USSR P. 934 443; *Byull. Izobret*. (21) 220 (1982)
122. W A Herrmann, C Köcher *Angew. Chem., Int. Ed. Engl*. **36** 2162 (1997)

[a] — *Chem. Heterocycl. Compd. (Engl. Transl.)*
[b] — *Russ. J. Phys. Chem. (Engl. Transl.)*
[c] — *Russ. J. Org. Chem. (Engl. Transl.)*
[d] — *Russ. J. Gen. Chem. (Engl. Transl.)*
[e] — *Kinet. Catal. (Engl. Transl.)*
[f] — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*