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Dedicated to the memory of Professor, Doctor of Chemical Sciences P. N. Gaponik

Synthesis of tetrazole and its derivatives by heterocyclization reaction involving primary amines, orthoesters, and azides

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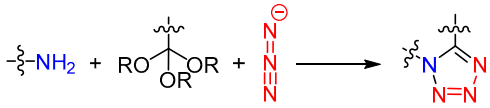


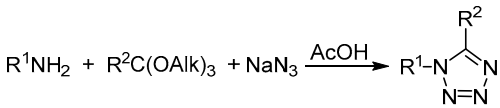
This review provides comprehensive analysis of literature data on the heterocyclization reaction of primary amines, orthoesters, and azides, which can be used for the preparation of tetrazole, its 1-mono- and 1,5-disubstituted derivatives.

Keywords: orthoesters, primary amines, tetrazole, heterocyclization, multicomponent reaction.

The current progress in the design of new energetic materials is largely associated with synthetic studies of tetrazole and its derivatives.[1] Tetrazoles possess a unique combination of properties – significant thermal stability along with high positive values of the enthalpy of formation and the highest nitrogen content among organic compounds (80% for tetrazole itself).[2] Due to these properties, tetrazoles are considered as components of highly effective propellants, explosives, pyrotechnics, as well as gas generating compositions.[1] The main product of their thermal decomposition is nitrogen, and this fact motivates the interest toward tetrazoles as "green" energetic materials. Besides that, the nature of tetrazole ring provides possibilities for its existence not only in the form of neutral molecule, but as anionic and cationic derivatives[3] – tetrazolates[4] and tetrazolium salts,[5] opening pathways for rational design of polyfunctional materials on the basis of tetrazoles, including energetic materials that exist as ionic liquids.[6] For these reasons, it is important to develop new synthetic methods and to improve the classical procedures for the preparation of tetrazole derivatives.

A relatively simple method was proposed in the early 1970s that enabled the synthesis of tetrazole, its 1-mono- and 1,5-disubstituted derivatives by a three-component heterocyclization reaction of primary amines or their salts with orthoesters and sodium azide in acetic acid medium (Scheme 1).[7]

Scheme 1



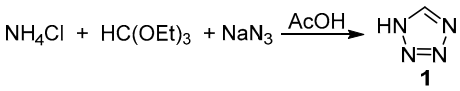
This method was patented first in Japan,[7] and then by the same authors also in the USA, West Germany, and France.[8] The concise examples described in the patents were insufficient for evaluating the preparative potential and safety of the reaction, since the authors merely claimed the possibility of obtaining a few tetrazole derivatives by this method. Several subsequent patents were devoted to the application of this method for the synthesis of tetrazol-1-ylacetic acid, which was further used for obtaining antibiotics of cephalosporin series.[9] The first systematic study of the heterocyclization reaction involving primary amines, orthoesters, and azides was performed at the Belarusian State University by the group of Prof. P. N. Gaponik in the 1980s and 1990s. It was shown that this reaction has a general character and can be used for the preparation of a wide range of 1-monosubstituted tetrazoles.[10] This approach was recognized as one of the most convenient

both for the synthesis of the simplest tetrazoles and for the introduction of tetrazol-1-yl group into various polyfunctional substrates.[11] A series of studies was performed over the last decade in order to improve this synthesis of 1-substituted tetrazoles by using various catalysts and optimizing the process conditions. The goal of this review is to provide generalization and detailed analysis of literature data regarding the use of heterocyclization reaction between primary amines, orthoesters, and azides for the preparation of 1-substituted tetrazoles.

Synthesis of tetrazole

The simplest 1*H*-tetrazole (**1**) can be formed by heating ammonium chloride, triethyl orthoformate (TEOF), and sodium azide in glacial acetic acid medium (Scheme 2). Several variations on the basis of this reaction have been published, which propose different reactant ratios and reaction conditions. The data given in Table 1 show that high yields of tetrazole can be reached by using an excess of TEOF. The optimal reaction conditions include maintaining for 2–3 h at a temperature above 70°C. Heating for a longer time did not result in higher yields of tetrazole. It should be also noted that the approximately 90% yields of 1*H*-tetrazole (**1**) were reported for crude product that had not been purified by recrystallization.

Scheme 2



1

Table 1. The conditions for synthesis and yields of 1*H*-tetrazole (**1**)

Reagent ratio NH_4Cl : NaN_3 : TEOF, mol	T, °C	Time, h	Yield, %
1 : 1.1 : 1.8	70	3	89[8a]
1 : 1.1 : 1.8	100	2	94[12]
1 : 1 : 3	80	16	51[13]
3 : 1 : 3	90	10	92[14]
1 : 1 : 3	80	10	60[15]
1 : 1.3 : 1.8	Δ	24	70[16]
1 :1.2* : 3	60–65	6	90[17]

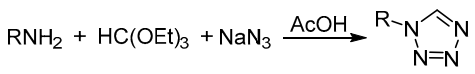
* Azidotrimethylsilane was used.

This approach has been often used by researchers for obtaining 1*H*-tetrazole (**1**), since it is a valuable precursor for the synthesis of various derivatives, including energetic tetrazolates.[1,2]

Synthesis of 1-monosubstituted tetrazoles

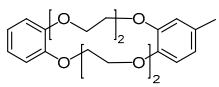
The use of primary amines or their salts in the heterocyclization process allows to obtain 1-monosubstituted tetrazoles **2** (Scheme 3, Table 2). Amines of various nature can be used in the reaction: alkyl-, aryl-, and hetarylamines.

Scheme 3



2

Table 2. Yields of tetrazoles **2**

R	Yield, %	R	Yield, %
Me, Et, Bu	82–86[18]	2-(3-Nitro-1,2,4-triazol-1-yl)ethyl	20[38]
Me, Et, Pr, Bu	30–40[19]	Ph	85[18]
i-Pr	35[20]	4-MeC_6H_4	80[39]
c-Pr	74[21], 29[22]	2-, 3-, 4-$O_2NC_6H_4$	90[40]
t-Bu	80[23]	4-$(PhCH_2)_2NC_6H_4$	68[41]
i-Bu	14[20]	4-$MeCONHC_6H_4$	79[42]
Cyclopentyl	28[24]	4-$MeCOC_6H_4$	92[43]
Cyclohexyl	36[24]	4-$(PhOC(=O)NH)C_6H_4$	84[44]
$PhCH_2$	67[25], 83[26]	4-F-3-ClC_6H_3	89[21]
$CyCH_2$	55[27]	4-I-2-MeC_6H_3	73[21]
4-$MeOC_6H_4CH_2$	66[25]	2-I-4-ClC_6H_3	90[45]
2-HO-3-I-5-*t*-$BuC_6H_2CH_2$	56[28]	3-I-4-$MeOC_6H_3$	60[46]
$PhCH_2CH_2$	71[21]	4-$(4\text{-}O_2NC_6H_4)C_6H_4$	91[21]
$HOCH_2CH_2$	79[29]	3,4,5-$(MeO)_3C_6H_2$	95[47]
$MeOCH_2CH_2$	90[30]	1-Naphthyl	73[21]
$Me_2NCH_2CH_2$	78[18]	2-Naphthyl	10[48]
$N_3CH_2CH_2$	77[18]	3-(HOOCCH=CH)C_6H_4	86[17]
$C(CH_2Cl)_3$	75[18]	4-$HO_2CC_6H_4$	91[21]
$C(CH_2OH)_3$	58[18]	2-$HO_2CC_6H_4$	69[49]
$HO_2CCH_2CH_2$	80[18]	5-Cl-2-$HO_2CC_6H_3$	88[50]
$HO_2CCH_2CHPhCH_2$	79[31]	2-HOC_6H_4	12[49]
$ClCH_2CH_2$	70[32]	2-HO-4-$O_2NC_6H_3$	90[49]
XCH_2CH_2 (X = Br, F)	20[33]	2-HO-5-$O_2NC_6H_3$	80[49]
$BrCH_2CH_2CH_2$	29[34]	2-HO-4,6-$(O_2N)_2C_6H_2$	80[17]
$H_2C{=}CHCH_2$	84[18]	3-F-4-(*t*-BuOOC)C_6H_3	94[51]
$HC{\equiv}CCH_2$	44[35]	Ferrocenyl	56[52]
1-Ad	84[21,36]	4-Ferrocenylphenyl	68[52]
1-Ad(Me)CH	85[21]		73[53]
2-Furylmethyl	93[37]		

The reaction begins already at room temperature, but the optimal conditions are at 80–100°C temperature with the molar ratio of RNH_2 : TEOF : NaN_3 : AcOH = 1:3:1.1:8.[17,18] The reaction under these conditions, as a rule, was complete in 2–3 h and provided the target tetrazoles in yields above 70%. In the case of arylamines, the amount of TEOF could be reduced to 2 equiv without noticeable decrease in the yield of the final 1-aryltetrazole. Despite the fact that the optimal conditions and the ratio of reagents for performing this heterocyclization reaction have been known for a relatively long time, even today some researchers often use insufficient amounts of the orthoester and acetic acid, resulting in low yields of the target tetrazoles. Only in the case of arylamines the amount of acid can be decreased to 4–6 equiv without significantly impacting the yield.

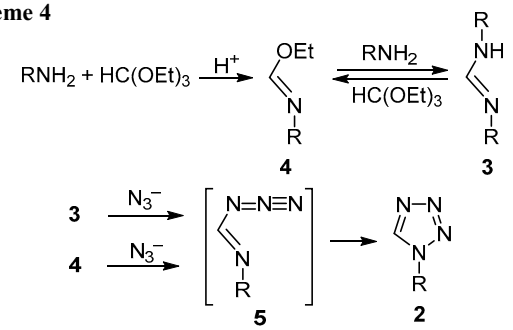
The reaction path and the yield of the final product are significantly affected by the order of reagent addition. The best procedure involves addition of acetic acid to a suspension of amine and azide in TEOF, which prevents the loss of azidating agent *via* evolution of hydrazoic acid. The evolution of hydrazoic acid was minimized by portionwise addition of acetic acid to the reaction mixture. The gas phase concentration of HN_3 above the reaction mixture was 1–1.5 vol % at the beginning and 0.5–0.7 vol % at the end of the reaction.[17]

The most convenient approach according to the availability of starting materials and taking into account the procedures for the isolation of final products was the use of free amines or their hydrochlorides, but the reaction was quite successful also with other salts: nitrates, sulfates, and oxalates.[18]

The mechanism of heterocyclization reaction was studied in detail in the case of aniline and monoethanolamine.[18] It was found that in both cases the first stage of the reaction involved the formation of the respective disubstituted amidines **3** as intermediates (Scheme 4), which were isolated from the reaction mixture as acetates. These intermediates precipitated at the moment when acetic acid was added to the mixture of TEOF, sodium azide, and amine. The precipitation of intermediates was accompanied by characteristic thickening of the reaction mixture. The reaction, as a rule, proceeded analogously during the synthesis of other tetrazoles.

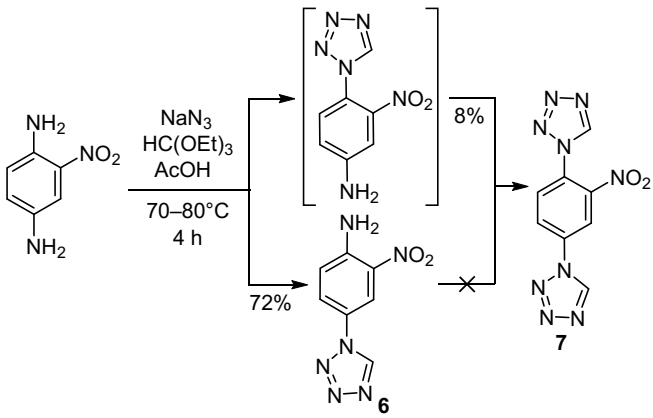
It is known that the reaction of aliphatic orthoesters with amines leads to the formation of both amidines **3** and iminoesters **4** (Scheme 4). As it was demonstrated[54] for the example of aniline and TEOF, the main reaction product was iminoester **4**, but it quickly reacted with the excess amine, forming the respective amidine **3** (R = Ph). The reaction was reversible under the conditions of acidic catalysis. The equilibrium can be shifted toward one or the other side depending on the reaction conditions, the ratio of reagents, and the structure of the starting amines. On the basis of the aforementioned considerations, as well as the results obtained by studying the reactivity of various amidines in the reaction with TEOF and sodium azide,[55] two probable mechanisms of the heterocyclization reaction were proposed, one of which may dominate depending on the nature of the starting amine. In the case of R = Ar, the azide ion apparently reacts both with amidine **3** and iminoester **4**, while in the case of R = Alk the reaction proceeds only with the respective iminoester **4**.

Scheme 4



The heterocyclization process clearly involves a sequence of nucleophilic substitution reactions, therefore its rate must significantly depend on the basicity of the amine used in the reaction. Indeed, the results of kinetic studies with respect to the heterocyclization of substituted anilines, obtained by using ^{1}H NMR spectroscopy, showed that the less basic amines at otherwise equal conditions showed weaker reactivity under the process conditions.[17,18] In this case, the yield of the target product can be improved by extending the reaction duration to 5–6 h and increasing the reaction temperature to 110°C. However, after reaching certain pK_{BH^+} value, even the use of most forcing reaction conditions failed to yield the respective tetrazoles. Thus, for example, 2,4-dinitroaniline (pK_{BH^+} ~ –4.5) did not participate in the heterocyclization reaction, which can be explained specifically by the weak basicity of this compound.[17] Tetrazoles also could not be obtained from 4-fluoro-3-nitroaniline and 2,6-dibromo-4-nitroaniline, which, according to the authors, was also associated with the weak basicity of these compounds.[21] The low basicity of 2-nitro-4-(tetrazol-1-yl)aniline (**6**) allowed to explain its formation as the major product during the heterocyclization reaction of 2-nitro-1,4-phenylenediamine (Scheme 5). Bis-(tetrazole) **7** at the same time was obtained in a low yield.[56]

Scheme 5



The use of large amounts of acetic acid in the synthesis of 1-substituted tetrazoles by heterocyclization method is justified by the nucleophilicity of the amines. On one hand, it is a weak acid that probably cannot completely protonate the starting amines, which are still capable of nucleophilic attack on TEOF at the first stage of the process. On the other hand, acetic acid facilitates the cleavage of ethoxy group from the orthoester or iminoester and binds the eliminated ethanol in the form of ethyl acetate.[10b] Besides that, the action of acetic acid on sodium azide liberates hydrazoic acid, which then serves as a source of active nucleophile (azide ion) at the stage where azidoazomethine **5** is formed (Scheme 4). Quantum-chemical calculations for the reaction between *N*-methyl-*O*-ethylformiminoester **4** (R = Me) and hydrazoic acid also point to the important role of acetic acid in this process. Thus, in the absence of acid catalysis, the approach of starting reagents is

accompanied by a very substantial rise of system energy, which reaches the maximum (100.06 kJ) when the length of the newly formed C–N bond is 1.9 Å. At the same time, the introduction of two or three acetic acid molecules lowers the activation barriers of the process to 45.69 and 36.49 kJ, respectively.[10a]

Ethylenediamine and a series of aryldiamines participate in the heterocyclization reaction at both amino groups, regardless of the reagent ratio used, forming bis(tetrazoles) **8** (Scheme 6, Table 3).[17,18,35,40,48,56–66] Such a course of this reaction is apparently linked either to the formation of a cyclic amidine at the initial stage in the case of ethylenediamine or to the activation of second amino group through remote electronic effects transferred *via* the aromatic ring in the case of aryldiamines.

Scheme 6

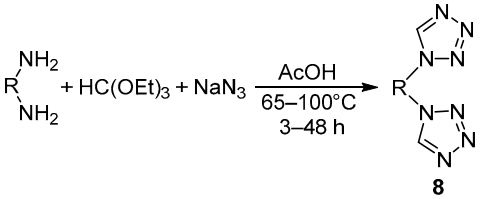
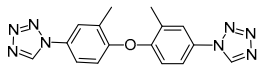
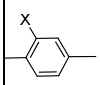


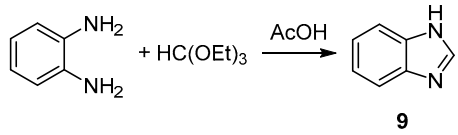
Table 3. Yields of tetrazoles **8**, obtained according to Scheme 6

R	Yield, %	R	Yield, %
CH_2CH_2	60[18], 80[57]	$CH_2(m\text{-}C_6H_4)CH_2$	64[63]
CMe_2CH_2	65[58]	$(p\text{-}C_6H_4)O(p\text{-}C_6H_4)$	89[17]
(1*R*,2*R*)-CHPhCHPh	10[59]		81[64]
$CH_2CH(OH)CH_2$	10[60]	$CH_2(p\text{-}C_6H_4)CH_2$	68[65]
$(CH_2)_4$	48[61]	 X = Cl	38[56]
$(CH_2)_n$ (n = 5, 7, 9)	6–22[62]	X = Me	82[56]
$(CH_2)_n$ (n = 6, 8, 10, 12)	25–40[48]	X = MeO	63[56]
$p\text{-}C_6H_4$	94[40]	 X = OCH_2CH_2O	99[66]
$m\text{-}C_6H_4$	91[40]	X = $(OCH_2CH_2)_2O$	99[66]
$(p\text{-}C_6H_4)(p\text{-}C_6H_4)$	80[35]	 X = $(OCH_2CH_2)_3O$	97[66]
Fluorene-2,7-diyl	75[35]	X = $O(CH_2)_2NPh(CH_2)_2O$	91[66]
$(p\text{-}C_6H_4)CH_2(p\text{-}C_6H_4)$	85[35]	X = $S(CH_2)_2O(CH_2)_2S$	65[66]
Cyclohex-1,2-diyl	35[35]	X = $S(CH_2)_2NPh(CH_2)_2S$	45[66]

It should be noted that *o*-phenylenediamine under analogous conditions formed benzimidazole **9** (Scheme 7), once again confirming the formation of amidines during the reaction of orthoesters with amines. There was no further transformation of compound **9**, representing a cyclic amidine, into the respective tetrazole, apparently due to the stabilization of the molecule by formation of a conjugated aromatic system.[40]

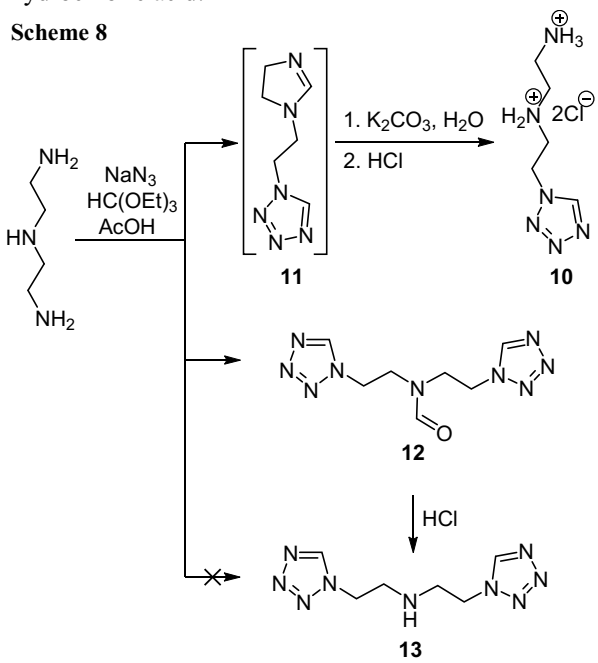
As a result of the reaction between diethylenetriamine with TEOF and sodium azide (molar ratio 1:6:2.2) in acetic acid, 1-(5-amino-3-azapentyl)tetrazole dihydrochloride (**10**) was isolated as the main product in 91% yield

Scheme 7



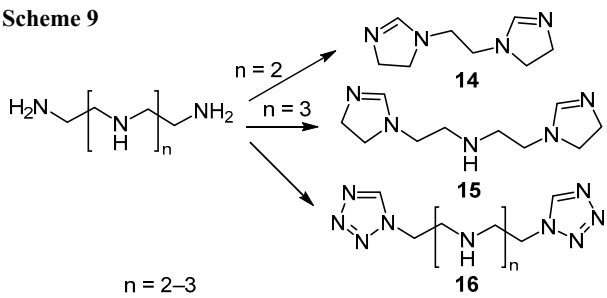
(Scheme 8).[67] The process involves the formation of 1-[2-(4,5-dihydro-1*H*-imidazol-1-yl)ethyl]-1*H*-tetrazole (**11**) as intermediate, which undergoes cleavage of dihydroimidazole ring upon treatment of reaction mixture with potassium carbonate. Apparently, the dihydroimidazole ring was stable in the presence of TEOF and azide ion. The intermediate tetrazole **11** was isolated as the respective hydrochloride in 87% yield by treatment of the reaction mixture with hydrochloric acid. When the amount of TEOF was decreased to 3.6 equiv, compound **11** was obtained in 27% yield.[68] The formyl derivative **12** was obtained at the same time as a by-product in 5% yield and was quantitatively converted to tetrazole **13** in the presence of hydrochloric acid.

Scheme 8



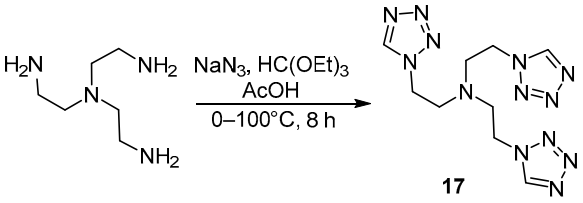
Triethylenetetramine and tetraethylenepentamine participated in the heterocyclization reaction analogously, leading to the formation of mainly 1,2-bis(4,5-dihydroimidazol-1-yl)ethane (**14**) and bis[2-(4,5-dihydroimidazol-1-yl)ethyl]-amine **15**, respectively. Bis(tetrazolylamines) **16** were formed in these processes as minor products in 5–8% yields (Scheme 9).[68]

Scheme 9



Heterocyclization of tris(2-aminoethyl)amine occurred at all three primary amino groups. However, the yield of tris[2-(1*H*-tetrazol-1-yl)ethyl]amine **17** was only 10% (Scheme 10) .[69]

Scheme 10



The presence of a carboxyl or hydroxy group at the *ortho* position relative to the amino group did not prevent the tetrazolation of anthranilic acid[49] and its derivatives,[50] as well as *o*-aminophenols[17,49] (Table 2). Tetrazolation was easily performed with 3-aminobenzopyranoids,[70] 4-aminobenzenesulfonamide and its *N*-substituted derivatives,[21] 3-aminoquinolin-4(1*H*)-ones,[71] as well as with 1-[3-(2-aminoethyl)-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide,[72] forming the respective tetrazole derivatives **18**–**22** in 54–98% yields (Fig. 1).

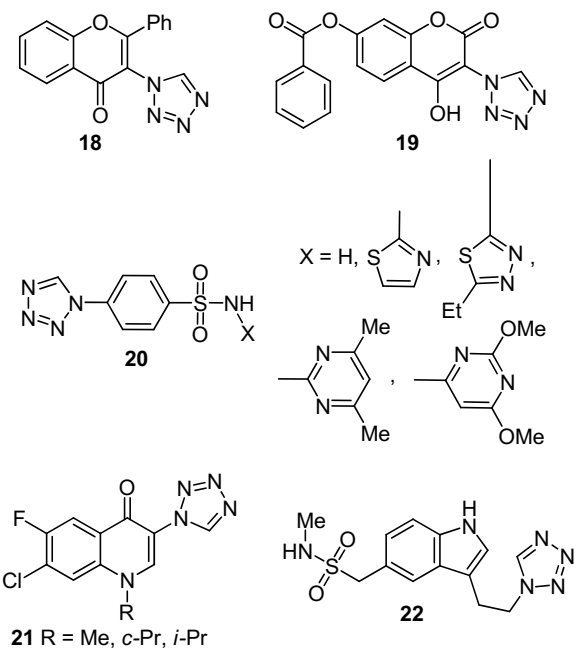
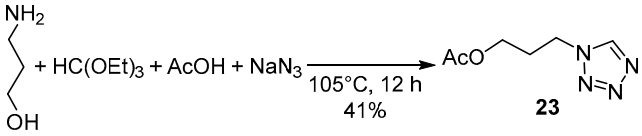


Figure 1. The structures of compounds **18**–**22**, obtained by heterocyclization of functionally substituted arylamines.

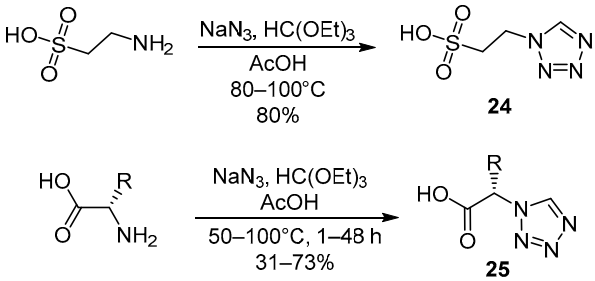
The hydroxy group also was not involved in the case when monoethanolamine was used in this reaction. At the same time, the tetrazolation of 3-aminopropan-1-ol gave derivative **23** (Scheme 11). Apparently, the heterocyclization in the latter case was accompanied by esterification.[73]

Scheme 11



The amino groups of taurine and some α-amino acids were transformed quite smoothly to 1-tetrazolyl group, resulting in 31–80% yields of tetrazoles **24**[74] and **25**,[17,75,76] respectively (Scheme 12). It has been noted[76] that tetrazolation of cystine and cysteic acid failed due to their low solubility in the reaction medium.

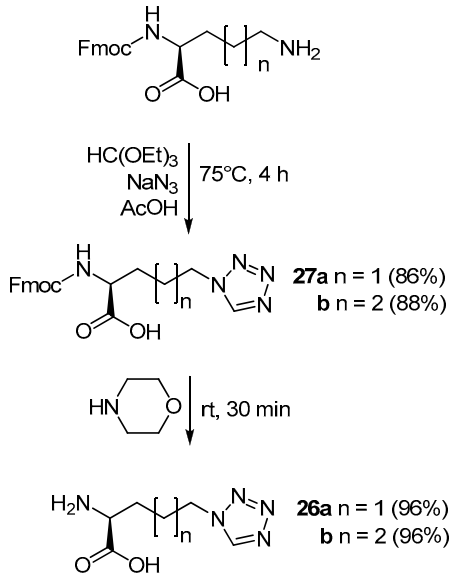
Scheme 12



R = *i*-Pr, $PhCH_2$, *i*-$PrCH_2$, Ph, 4-$HOC_6H_4CH_2$, (4-imidazolyl)CH_2, (3-indolyl)CH_2, $MeS(CH_2)_2$, $HO_2C(CH_2)_2$, $H_2NC(=NH)NH(CH_2)_3$

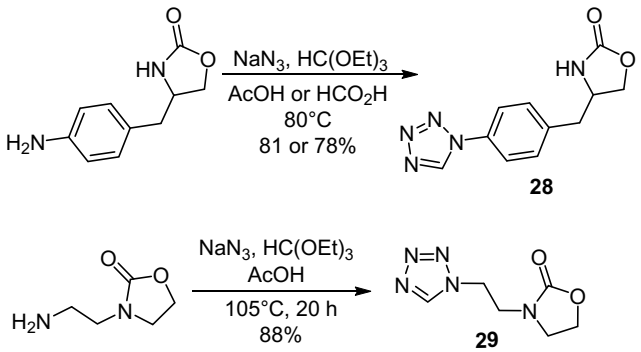
For the purpose to obtain tetrazole derivatives of L-ornithine **26a** and L-lysine **26b**, the reaction was performed with these amino acids bearing protecting groups at the α-amino functionality. The fluorenylmethyloxycarbonyl (Fmoc) protecting group was found to be effective under the heterocyclization reaction conditions and intermediates **27** were isolated in high yields (Scheme 13).[77]

Scheme 13



As demonstrated in the case of synthesis of compounds **28**[72] and **29**[68] from the respective amines (Scheme 14), the oxazolidin-2-one moiety did not undergo any changes under the heterocyclization reaction conditions.

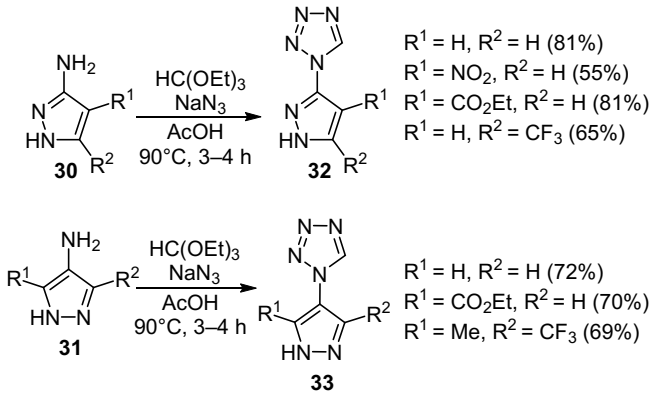
Scheme 14



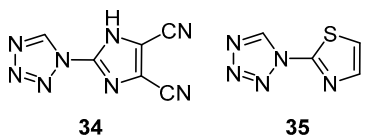
There is a significant scientific and practical interest in tetrazolation of heterocyclic amines, such as aminoazoles. This interest is mostly motivated by design of energetic compounds for specific applications,[78–81] ligands containing multiple nitrogen atoms for coordination chemistry,[78,81] as well as biologically active compounds.[82–86]

Reactions of 3- and 4-aminopyrazoles, as well as their *C*-derivatives **30** and **31**, TEOF, and sodium azide have been shown to provide high yields of the respective 1-(pyrazol-3-yl)- and 1-(pyrazol-4-yl)tetrazoles **32** and **33** (Scheme 15).[82]

Scheme 15



1-Monosubstituted tetrazoles **34** and **35** of imidazole[79] and thiazole[17] series were also obtained by a similar procedure in 65 and 47% yields, respectively (Fig. 2).

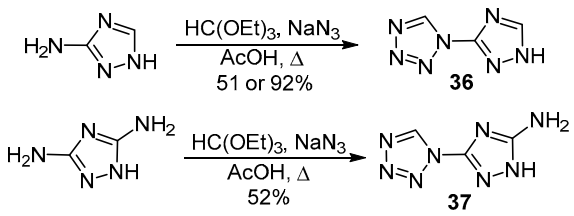


34 **35**

Figure 2. The structures of compounds **34** and **35**, obtained by heterocyclization of 2-amino-4,5-dicyanoimidazole and 2-amino-thiazole.

Heterocyclization of 3-amino-1,2,4-triazole was used to synthesize 1-(1,2,4-triazol-3-yl)tetrazole (**36**) in 92[79] and 51%[80] yields. Tetrazolation of 3,5-diamino-1,2,4-triazole, despite the excess of TEOF and sodium azide, produced only the monotetrazolation product **37** (Scheme 16).[79]

Scheme 16



It has been shown that the reaction of 5-aminotetrazole, TEOF, and sodium azide resulted in the formation of 5-(tetrazol-1-yl)tetrazole (**38**) (Scheme 17).[78] 2-Methyl-5-(tetrazol-1-yl)tetrazole **39** was similarly obtained from 5-amino-2-methyltetrazole. At the same time, 5-amino-1-methyltetrazole did not participate in heterocyclization reaction under the indicated conditions, which was explained by the effects of steric hindrance. It should be noted that compound **38** has high sensitivity to impact and friction. In general, tetrazol-1-ylazoles **36**–**39** have shown promising energetic characteristics (Table 4) and are of interest as components of explosive and gas generating compositions.

Scheme 17

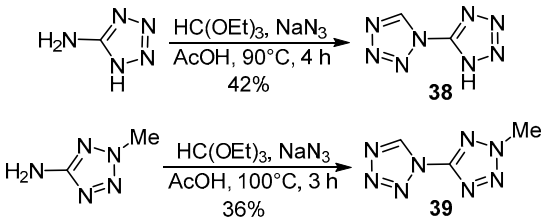


Table 4. Energetic characteristics of tetrazol-1-ylazoles **36**–**39**

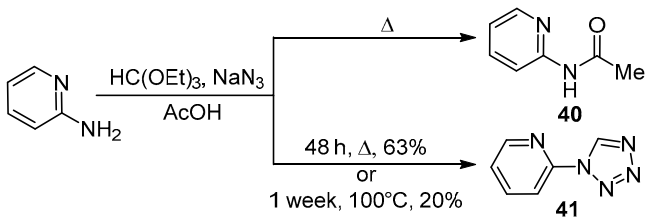
Characteristics*	**36**[79]	**37**[79]	**38**[78]	**39**[78]
N, %	71.5	73.7	81.1	73.7
O, %	–87.6	–84.2	–57.9	–84.1
D, km·s^{-1}	6.68	6.61	8.36	7.59
Q, kJ·kg^{-1}	3807	3485	4769	4301
ΔH_f, kJ·mol^{-1}	454	439	622	592
P, GPa	28.2	21.3	18.92	18.37
Decomp. temp., °C	243	238	145	135

* N – nitrogen content, O – oxygen balance, D – velocity of detonation, Q – heat of explosion, ΔH_f – enthalpy of formation in solid state, P – detonation pressure, decomp. temp. – temperature of decomposition.

The three-component heterocyclization reaction described above has been used for the synthesis of several tetrazoles from 6-amino-2-benzofuran-1(3*H*)-one,[83] as well as from 2-aminothiophene derivatives[84–87] and 3-amino-benzofuran derivatives.[86]

The reaction of 2-aminopyridine with equimolar amounts of TEOF and sodium azide in refluxing acetic acid gave *N*-(2-pyridyl)acetamide (**40**) as the main product (Scheme 18). The target compound 1-(2-pyridyl)tetrazole (**41**) was obtained in 63% yield by using a large excess of TEOF (17 equiv) refluxing the reaction mixture for 48 h.[88] Another research group was able to obtain tetrazole **41** in 20% yield by using 1 equiv of TEOF and heating at 100°C for 1 week.[48]

Scheme 18



At the same time, 3-aminopyridine was transformed into the respective 1-substituted tetrazole **42** in 52% yield by using trimethyl orthoformate (1.6 equiv relative to the amine) and sodium azide (1.5 equiv) upon refluxing the reaction mixture for 6 h.[89] 3,6-Diaminoacridine under heterocyclization reaction conditions in the presence of 3 equiv of TEOF was tetrazolated at both amino groups, forming tetrazole **43** in 77% yield (Fig. 3).[35]

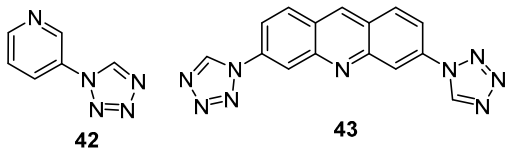
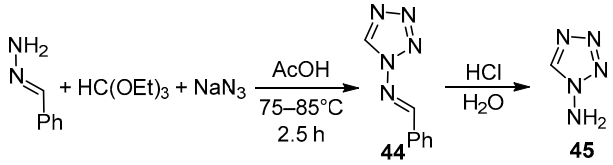


Figure 3. The structures of heterocyclization reaction products obtained from 3-aminopyridine and 3,6-diaminoacridine.

The attempts to perform heterocyclization reactions with hydroxylamine, melamine, phenylhydrazine, and hydrazine did not produce unequivocal results and failed to yield individual compounds,[17,18] even though the derivative of the latter with benzaldehyde was easily transformed into 1-benzylideneaminotetrazole **44** (Scheme 19). The treatment of tetrazole **44** with hydrochloric acid allowed to obtain 1-aminotetrazole (**45**) in 62% overall yield. It was noted that tetrazole **45** exploded when initiated by hard impact or friction.[90]

Scheme 19

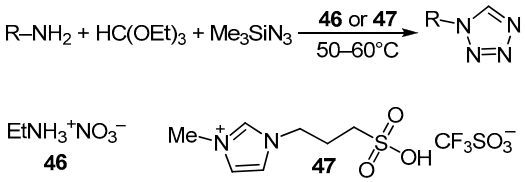


One of the drawbacks of the considered heterocyclization reaction is the formation of some amount of hydrazoic acid during this procedure. As was noted above,[17] the evolution of HN_3 in gas phase was insignificant during the reaction itself, but the presence of even small amounts of hydrazoic acid in the solution during evaporation of the reaction mixture at reduced pressure can be potentially dangerous when the process is scaled up from laboratory to industrial scale. In order to mitigate this problem, it was shown[17] that the excess of sodium azide and the dissolved hydrazoic acid at the end of the reaction can be destroyed by adding sodium or potassium nitrite to the reaction mixture, which did not complicate the procedure for isolation of final products. According to chromatographic analysis, the liquid part of waste products from the reaction, which was obtained when the solvents were removed from the reaction mixture by distillation, was a mixture of water, ethanol, ethyl acetate, ethyl formate, and acetic acid. This liquid waste was easily separated into two fractions by distillation (the first fraction at 65–100°C consisted of water (up to 10%), ethanol (up to 10%), ethyl acetate, and ethyl formate (>80%); the second fraction >100°C consisted of aqueous acetic acid solution). The obtained solvent fractions may be reused for various technological purposes.

Azidotrimethylsilane (TMSA) is a reagent that in recent years has been employed more frequently in the chemistry of heterocyclic compounds. The use of TMSA instead of inorganic azides is often more convenient, enables many reactions under milder conditions and, as a rule, improves process safety. As shown in the literature,[17] the replacement of sodium azide with azidotrimethylsilane in heterocyclization reaction did not noticeably affect the purity and yields of the obtained tetrazoles. Besides that, the studies performed by us using aniline, *tert*-butylamine, and monoethanolamine showed that selecting TMSA as reagent allowed to reduce the amount of acetic acid by one half, compared to the reaction with sodium azide, and the product yields did not decrease. The heterocyclization process proceeded even with a minimal (1–2 equiv) amount of acid, but the yields of the respective tetrazoles in that case were lower by 15–20%. Furthermore, salts of primary amines reacted with TEOF and TMSA even in the absence of acetic acid. The yields of tetrazoles in those cases were much lower, compared to the reactions performed in acetic acid medium. Apparently, when TMSA was used in heterocyclization reactions, the acid was needed only for the interaction of primary amine with TEOF, and was not consumed for the generation of active nucleophile, as in the case when sodium azide was used as the azidating agent.

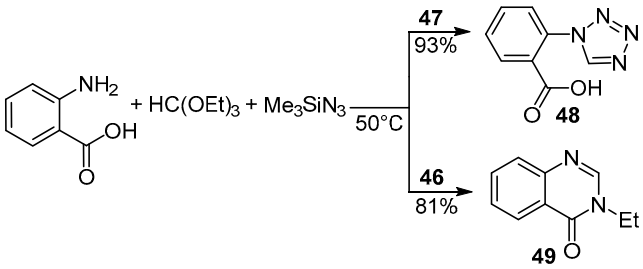
High yields (85–95%) of substituted 1-aryltetrazoles, as well as 1-(2-pyridyl)tetrazole (89%), 1-benzyltetrazole (78%), and 1-furfuryltetrazole (77%) were obtained by using TMSA in heterocyclization reaction of the respective primary amines in ionic liquid media instead of acetic acid: in ethylammonium nitrate (**46**) or 3-methyl-1-(3-sulfopropyl)imidazol-3-ium trifluoromethanesulfonate (**47**) (Scheme 20).[91] When the reaction was performed in ionic liquid **46**, the yields of the obtained 1-monosubstituted tetrazoles, as a rule, were somewhat lower than when the reaction was performed in the more acidic ionic liquid **47**.

Scheme 20



Remarkably, in the case of anthranilic acid the reaction with TMSA and TEOF in the aforementioned ionic liquids proceeded in different ways. While the expected tetrazole **48** was formed in ionic liquid **47**, the formation of 3-ethylquinazolin-4(3*H*)-one **49** was observed in ionic liquid **46** (Scheme 21).[91]

Scheme 21



Methylated polyvinylpyridinium azide crosslinked with divinylbenzene can serve as an alternative source of azide ion, replacing sodium azide in heterocyclization reactions of a wide range of substituted anilines. The reaction was performed in acetic acid at 100°C for 10–25 min, by using a 2.5-fold excess of TEOF. The yields of the target 1-aryltetrazoles under these conditions reached 90–98%. The authors noted the safety and stability of the aforementioned polymeric azide upon prolonged storage. Besides that, the methylated polivinylpyridinium azide was transformed during the heterocyclization process into the respective acetate, which was easily isolated from the reaction mixture by filtration. The subsequent treatment of acetate with sodium azide allowed to regenerate the polymeric azide and to reuse it in the synthesis.[92]

A series of publications have appeared in recent years that examine the possibilities for updating the "classical" process for heterocyclization of primary amines by replacing acetic acid with other reagents and solvents. For example, it has been shown[93] that the use of ionic liquids, *N*-butylimidazolium salts **50** (Fig. 4), instead of acetic acid allowed to obtain 1-aryltetrazoles in higher than 80% yields. The reaction was performed at 100°C for 15–35 min with 1:1:1.2:3 ratio of amine – sodium azide – TEOF – ionic liquid **50**. The authors emphasized that the reaction did not proceed at temperatures below 60°C, as well as when using 1,3-dibutylimidazolium salts **51** (Fig. 4). At the same time, other authors[94] reported that the transformation of the same arylamines to the respective 1-aryltetrazoles could be achieved in 85–90% yields by using a 10:1 mixture of DMSO and ionic liquid **51** (X = Br)

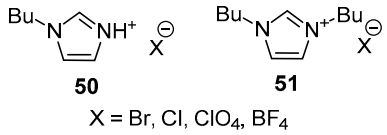
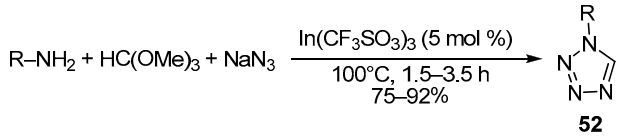


Figure 4. The structures of ionic liquids studied as substitutes for acetic acid in the heterocyclization of anilines.

as solvent in the heterocyclization reaction at room temperature and keeping the same reagent ratio.

It was established that indium(III) triflate was an effective catalyst for the synthesis of 1-monosubstituted tetrazoles **52** by heterocyclization of primary amines with trimethyl orthoformate and sodium azide (Scheme 22).[95] The reaction was performed at 1:1:1.2 ratio of amine – sodium azide – orthoester for 1.5–3.5 h in the absence of solvent and allowed to obtain a wide range of 1-aryltetrazoles in 80–92% yields. The use of solvents (acetonitrile, 1,2-dichloroethane, and 2-methoxyethanol) resulted in slightly decreased yields of the final tetrazoles. It was shown in the case of *n*-butyl-, *tert*-butyl-, and cyclohexylamines that alkylamines were also converted under these conditions to the respective tetrazoles in 75, 70, and 80% yields, respectively. Suitable catalysts, as shown in the case of aniline, also include indium chloride, zinc triflate, magnesium perchlorate, and zinc perchlorate, but the yields of 1-phenyltetrazole obtained with these catalysts were lower by 20–30%. High yields (70–90%) of 1-aryltetrazoles, as well as 1-benzyl-, 1-furfuryl-, and 1-ethyl-2-phenyltetrazoles were also obtained by using ytterbium triflate as catalyst.[96,97] The process was performed in 2-methoxyethanol at 100°C for 6–9 h at 1:1:1.2 ratio of amine – sodium azide – TEOF. It was noted that the reaction did not proceed in the absence of catalyst.

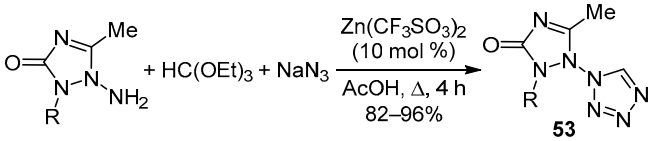
Scheme 22



R = Bu, *t*-Bu, $PhCH_2$, Ph, 4-MeC_6H_4, 2,3-$Me_2C_6H_4$, 2-$MeOC_6H_4$, 2-ClC_6H_4, 4-FC_6H_4, 2-Cl-3-FC_6H_3, 4-$EtO_2CC_6H_4$, 3-$O_2NC_6H_4$, (*S*)-CH(Ph)Me, Cy

Zinc triflate showed high catalytic activity in tetrazolation reactions of 4-amino-5-methyl-2-phenyl-2*H*-1,2,4-triazol-3(4*H*)-ones (Scheme 23).[98] It was noted that tetrazoles **53** did not form under analogous conditions in the absence of zinc salts. Similar catalytic activity in this process was observed also with ytterbium triflate.

Scheme 23



R = 4-XC_6H_4, 3-XC_6H_4; X = H, Me, Cl, Br, NO_2, MeO

The effectiveness of a range of "exotic" catalysts that could be employed instead of acetic acid has been reported in a series of relatively recent publications. Examples of such catalysts include magnetite nanoparticles coated with silica impregnated with chlorosulfonic acid,[99] zeolite $Na_2[Al_2Si_3O_{10}]\cdot 2H_2O$,[100] a magnetic ionic liquid on the basis of chitosan,[101] Fe_3O_4–SiO_2 particles carrying Cu(II) complexes with salicylic aldehyde,[102] isatin,[103] and 1,4-dihydroxyanthraquinone,[104] γ-Al_2O_3–$AlCl_3$,[105] $FeCl_3$–SiO_2,[106] $FeCl_3$,[107] P_2O_5–SiO_2,[108] trifluoromethanesulfonimide,[109] methylsulfonic acid,[110] SiO_2–H_3BO_3,[111] SiO_2–OSO_3H,[112] carbon nanotubes carrying Cu(II) complex with 4'-phenyl-2,2':6',2"-terpyridine,[113] ZnS nanoparticles,[114] Co_2FeO_4,[115] and copper nanoparticles immobilized on bentonite.[116] Practically all of the publications mentioned above claimed 80–95% yields of the respective 1-substituted tetrazoles obtained from approximately similar series of substituted anilines, as well as benzylamine, *n*-butylamine, and cyclohexylamine, while using the catalysts listed above. The reactions were usually performed by heating in the absence of solvent, using amine, sodium azide, and orthoester in 1:1:1.2 ratio.

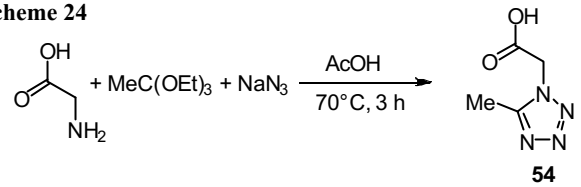
Unfortunately, the analysis of results reported in these publications casts serious doubts on their reliability. For example, ^{1}H NMR spectra of the obtained 1-aryltetrazoles (in $CDCl_3$ or DMSO-d_6 solutions), as reported by the authors, usually contained the characteristic signal of proton bonded to tetrazole ring carbon atom in the range of 7.8–8.3 ppm, while this signal should be expected at 9.0 ppm in spectra acquired in $CDCl_3$ and around 10.0 ppm in spectra acquired in DMSO-d_6.[117] We also question the transformation of *o*-phenylenediamine claimed by many authors, reported as giving high yields of the respective bis-(tetrazole), since it is known that the main product from reactions of *o*-phenylenediamine with TEOF is benzimidazole (Scheme 7).

The physicochemical characteristics of the products claimed in these reports are also in doubt: 1-(*n*-butyl)-tetrazole with mp 141–143°C,[99–102,106] 1-benzyltetrazole with mp 130–122°C,[99–102] and 1-cyclohexyltetrazole with mp 168–170°C.[99,102] In fact, 1-(*n*-butyl)tetrazole is a liquid with bp 112–114°C (0.5 mmHg),[18] 143–145°C (2 mmHg),[118] while 1-benzyltetrazole has mp of 58–60°C[88,91,119] and 1-cyclohexyltetrazole melts at 48–49°C.[120]

Synthesis of 1,5-disubstituted tetrazoles

Already the first patents regarding the studied heterocyclization reaction showed the possibility of using it for the synthesis of 1,5-disubstituted tetrazoles. In order to achieve this, the process was performed with orthoacetate, allowing to synthesize 5-methyltetrazol-1-ylacetic acid (**54**) from glycine (Scheme 24).[7,8]

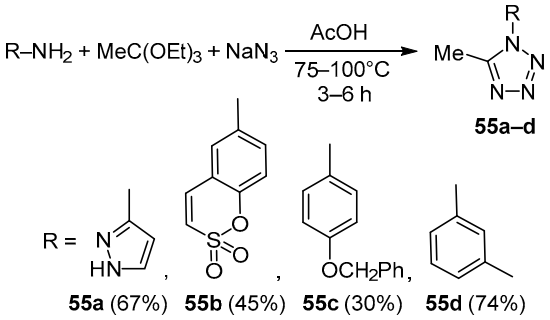
Scheme 24



54

This approach was subsequently rarely used for the synthesis of 1,5-disubstituted tetrazoles, primarily due to the insufficient availability of substituted orthoesters. Several examples were published for the preparation of 1-substituted 5-methyltetrazoles **55a**,[82] **55b**,[121] **55c**,[122] **55d**[123] (Scheme 25) from primary amines and triethyl orthoacetate.

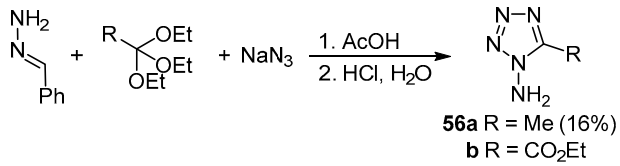
Scheme 25



55a (67%) **55b** (45%) **55c** (30%) **55d** (74%)

There are reports about the synthesis of 1-amino-5-methyltetrazole **56a**[124] and ethyl 1-aminotetrazol-5-yl-acetate **56b**[125] by heterocyclization of benzylidene-hydrazine with triethyl orthoacetate and ethyl 2,2,2-triethoxyacetate, respectively (Scheme 26).

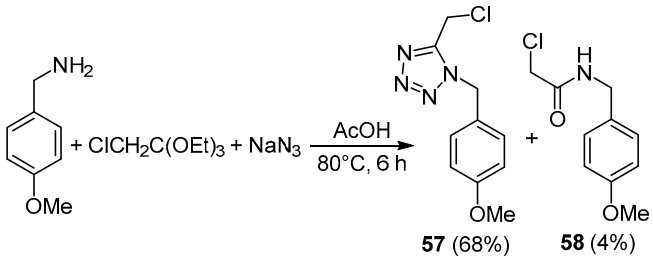
Scheme 26



56a R = Me (16%)
b R = CO_2Et

The reaction of *p*-methoxybenzylamine, 2-chloro-1,1,1-triethoxyethane, and sodium azide led to 1-substituted 5-chloromethyltetrazole **57**.[126] Amide **58** was identified as a by-product of this reaction (Scheme 27).

Scheme 27



57 (68%) **58** (4%)

Thus, in the years since its discovery, the method for synthesis of tetrazole and its 1-substituted derivatives by heterocyclization of primary amines with triethyl orthoformate and sodium azide in acetic acid was actively used in laboratory practice, becoming the most effective

approach for the preparation of a wide range of 1-alkyl-, aryl-, and hetaryltetrazoles. The limited use of this method for the preparation of 1,5-disubstituted tetrazoles was associated with the difficult access to substituted orthoesters. As a rule, the maximum yields of the target 1-substituted tetrazoles were achieved when performing the reaction in the temperature range of 80–100°C and 1:3:1.1:8 molar ratio of amine : orthoester : NaN_3 : AcOH. In the case of arylamines, the excess of orthoester can be decreased to 1.5–2 equiv without a noticeable reduction in the yields of the final 1-aryltetrazoles. Despite the fact that several research groups have demonstrated the possibility of replacing sodium azide in the heterocyclization reaction with organic azides, while acetic acid can be replaced with ionic liquids and various catalysts, including nano-structured systems, so far there is no clear need for widespread use of such approaches for the preparation of 1-substituted tetrazoles. Taking into account that tetrazole and its derivatives have good stability in combination with significant energetic potential and high nitrogen content, the studied heterocyclization reaction is of significant scientific and practical interest for targeted synthesis of promising energetic compounds that can be used in composite solid rocket propellants, pyrotechnic, explosive, and gas generating mixtures.

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