

# Advances in the chemistry of 1,2,3,4-tetrazines

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The experimental and theoretical chemistry of 1,2,3,4-tetrazines have been actively studied in the last 20 years. The increasing interest in this class of compounds is due to the fact that the 1,2,3,4-tetrazine ring is a promising building block for the development of energetic and physiologically active compounds. The review considers various types of 1,2,3,4-tetrazines including completely unsaturated non-annulated tetrazines and their *N*-oxides; nitrogen-substituted tetrazines; annulated tetrazines with a nitrogen atom common to two heterocycles; 1,2,3,4-tetrazine 1,3-dioxides fused to benzene, pyridine, 1,2,3-triazole or 1,2,5-oxadiazole ring; and also 1,2,3,4-tetrazine 1,3-dioxide fused to one more 1,2,3,4-tetrazine 1,3-dioxide ring. Methods of synthesis and reactivity of these compounds, their crystallographic features, spectral characteristics and thermal stability are described. The results of quantum chemical studies for 1,2,3,4-tetrazine derivatives are presented. The prospects of using 1,2,3,4-tetrazines as energetic compounds are discussed.

The bibliography includes 189 references.

**Keywords:** 1,2,3,4-tetrazines, *N*-oxides, heterocyclic compounds, energetic compounds, cyclization, annulation, thermal stability, quantum chemical calculations.



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## 1. Introduction

The chemistry of 1,2,3,4-tetrazines is a relatively new area of the heterocyclic chemistry, which has been successfully developing in recent decades. Biologically active representatives, in particular, a new class of nitric oxide (NO) donors, have been found among these compounds. However,

the primary feature responsible for high interest in these derivatives is that the four nitrogen atoms linked to one another account for the high energy content of molecules, which is important for the development of explosives and components of solid composite propellants. The 1,2,3,4-tetrazine skeleton serves as an attractive base for the design of these molecules. In

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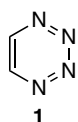
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*Current research interests:* chemistry of energetic compounds, chemistry of nitro compounds.

Translation: Z.P.Svitanko.

addition, 1,2,3,4-tetrazines are of considerable interest for theoretical chemistry in relation to the issue of heterocycle aromaticity.

The review considers derivatives of non-annulated 1,2,3,4-tetrazine (**1**)<sup>†</sup> and its annulated analogues, including completely unsaturated and partly reduced compounds. 1,2,3,4-Tetrazine *N*-oxides are also considered. This publication continues the previous review<sup>1</sup> covering the period of 1994–2003 and includes publications up to the beginning of 2023. New methods of synthesis, reactivity, and physicochemical characteristics of 1,2,3,4-tetrazines are discussed.



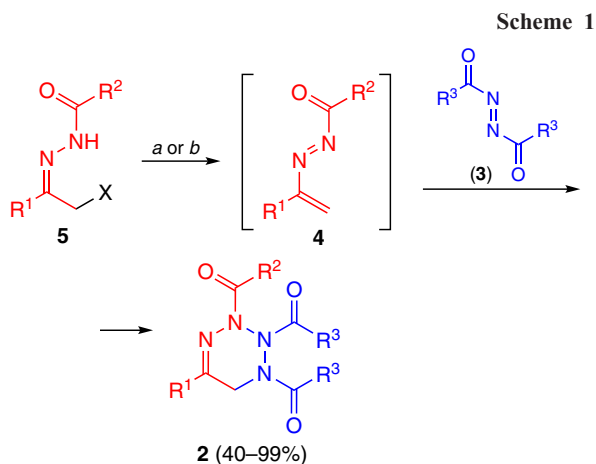
Structure 1

1,2,3,4-Tetrazines are the subjects of some chapters in the periodic edition *Comprehensive Heterocyclic Chemistry III* (2008) and *Comprehensive Heterocyclic Chemistry IV* (2021).<sup>2,3</sup> Energetic 1,2,3,4-tetrazines are considered in a special part of a monograph.<sup>4</sup> The synthesis of 1,2,3,4-tetrazine *N*-oxides is discussed in reviews,<sup>5–8</sup> in a survey paper<sup>9</sup> devoted to fused heterocyclic energetic compounds and covering publications of 2012–2019, and in a review.<sup>10</sup>

## 2. Synthesis and reactivity

### 2.1. *N*-Substituted 1,2,3,4-tetrazines

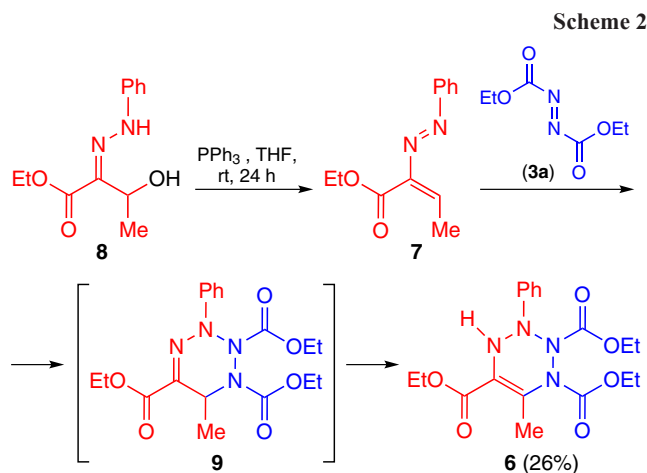
The synthesis of 1,2,3,6-tetrahydro-1,2,3,4-tetrazines **2** includes the [4+2]-cycloaddition reaction of azodicarboxylic acid derivatives (**3**) with 1,2-diazabuta-1,3-dienes **4**, which are generated *in situ* from  $\alpha$ -halohydrazone **5** under the action of bases (Scheme 1).<sup>11,12</sup> The reaction gives products in good yields (40–99%), it is easily scalable and makes it possible to vary substituents in the target tetrazines over wide limits.



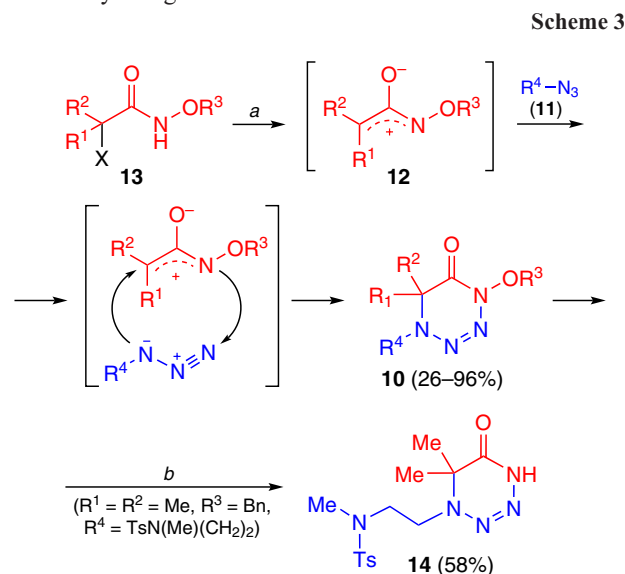
- (a)  $K_2CO_3$  (1.2 equiv.), THF, rt, 18–30 h (yield of **2**: 50–99%);  
 (b)  $Na_2CO_3$  (2 equiv.),  $CH_2Cl_2$ , 30 °C, 12 h (yield of **2**: 40–89%);  
 $R^1 = Ph, 4-MeOC_6H_4, 4-MeC_6H_4, 4-Bu^tC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-O_2NC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 2,4-Cl_2C_6H_3, 2,5-F_2C_6H_3, Bu^t$ ;  
 $R^2 = Me, Ph, OMe, OBu^t, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeOC_6H_4, Bu^t$ ;  
 $R^3 = OEt, OPr^t, OBu^t, OBn, N$ -piperidinyl;  
 $X = Cl, Br$

<sup>†</sup> Completely unsaturated non-annulated 1,2,3,4-tetrazine **1** has not been synthesized to date.

The method of synthesis of 1,2,3,4-tetrahydro-1,2,3,4-tetrazine **6** differs by the fact that 1,2-diazabuta-1,3-diene **7** is generated from hydrazone **8** on treatment with triphenylphosphine at room temperature (rt) (Scheme 2).<sup>13</sup> The intermediate tetrazine **9** isomerizes during the reaction to give product **6**.

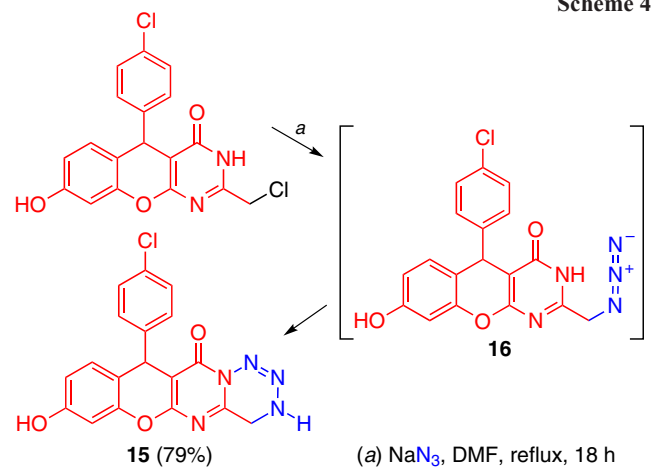


A new synthetic route to 1,2,3,4-tetrazines **10** is based on the [3+3]-cycloaddition of azides **11** to azaoxyallylic intermediates **12**, which are generated *in situ* from the corresponding  $\alpha$ -halohydroxamides **13** under the action of potassium carbonate in hexafluoroisopropyl alcohol (Scheme 3).<sup>14</sup> Compounds **10** represent a new type of 1,2,3,4-tetrazines with an alkoxy substituent at the tetrazine nitrogen atom. The reaction proceeds under mild conditions and gives products containing pharmacophore groups and fragments of natural compounds such as vitamin E, cholesterol, lithocholic acid, celecoxib and zidovudine (AZT). The catalytic hydrogenation of tetrazine **10a** [ $R^1 = R^2 = Me, R^3 = Bn, R^4 = (CH_2)_2N(Me)Ts$ , where Ts is *p*-toluenesulfonyl (tosyl)] is accompanied by cleavage of the N–O bond yielding tetrazine **14**.

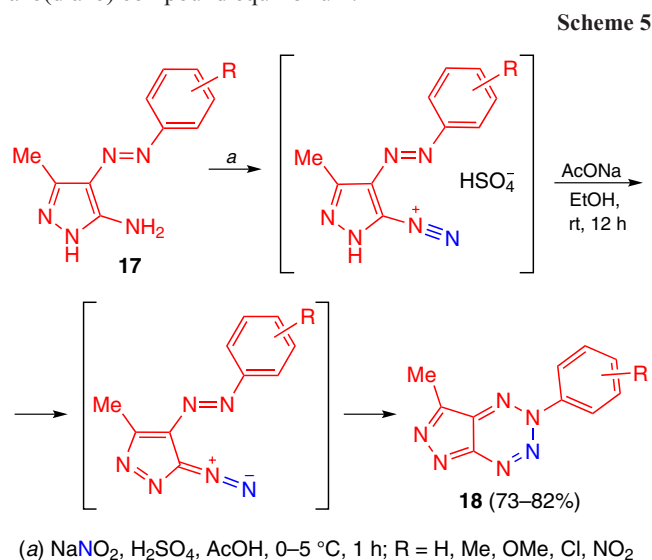


- (a)  $Na_2CO_3$  (2 equiv.),  $(F_3C)_2CHOH$ , rt, 2 h;  
 (b)  $H_2$ , Pd/C, MeOH, rt;  
 $R^1 = H, Me; R^2 = Me, Ph; R^1-R^2 = (CH_2)_5$ ;  
 $R^3 = Me, Et, Bu^t, Bn, etc.$ ;  
 $R^4 = Bn, 4-MeC_6H_4CH_2, 4-ClC_6H_4CH_2, 4-BrC_6H_4CH_2, 3-BrC_6H_4CH_2, 2-MeC_6H_4CH_2, TsN(Me)(CH_2)_2, EtO_2CCH_2, MeO_2C(CH_2)_4, cyclo-C_6H_{11}, etc.$ ;  
 $X = Br, Cl$

One more approach to the formation of a tetrazine ring was demonstrated in relation to the synthesis of tetrazine **15**. The synthesis is based on the intramolecular reaction of the azide group with the pyrimidinone nitrogen atom in azide derivative **16**. Compound **16** is prepared by the reaction of the corresponding chloro derivative with  $\text{NaN}_3$  (Scheme 4).<sup>15</sup>

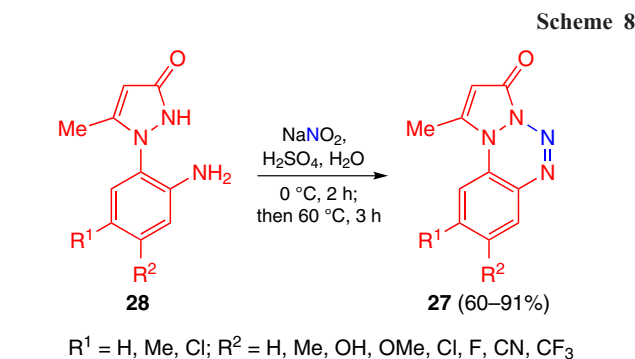
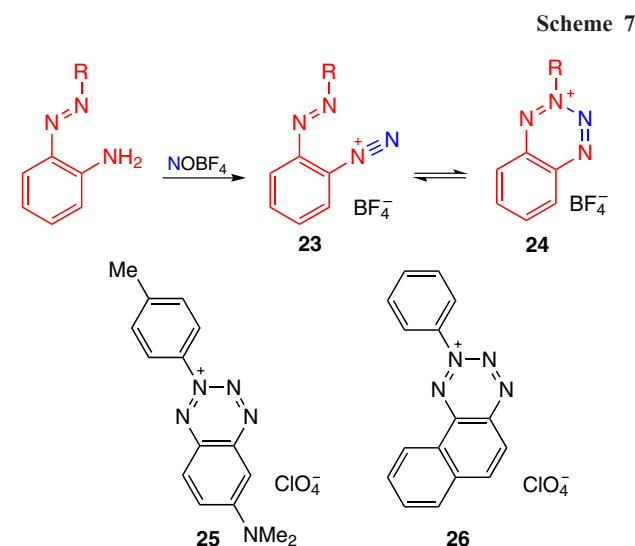
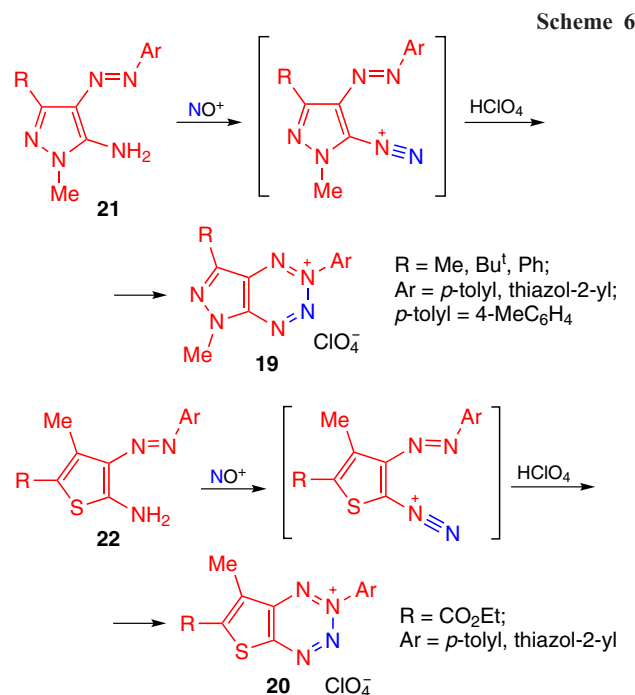


A series of substituted 5-aryl-3-methylpyrazolotetrazines **18** were synthesized by cyclization of diazo compounds obtained by diazotization of arylazopyrazoles **17** with sodium nitrite in a mixture of sulfuric and acetic acids followed by treatment of the intermediate diazonium salts with sodium acetate (Scheme 5).<sup>16</sup> Compounds **18** are fairly stable: their melting points ( $T_m$ ) vary from 145 to 228 °C, depending on the nature of substituents in the benzene ring. Note that tetrazines of this type do not always exist in the cyclic form, some of them occur in the tetrazine  $\rightleftharpoons$  azo(diazo) compound equilibrium.<sup>1</sup>



Heteroannulated tetrazine perchlorates **19** and **20** were obtained by diazotization of aminopyrazole **21** and aminothiophene **22** (Scheme 6). The cyclic structure of the tetrazinium salt **19** was confirmed by X-ray diffraction analysis.<sup>17</sup>

Diazonium salts **23** prepared by diazotization of the corresponding amines may exist in equilibrium with the closed-ring tetrazinium form **24** (Scheme 7). The position of equilibrium depends on the nature of the substituent R. In the case where R = Ph, the compound exists in the open form, while in the presence of electron-donating alkyl substituents, there is

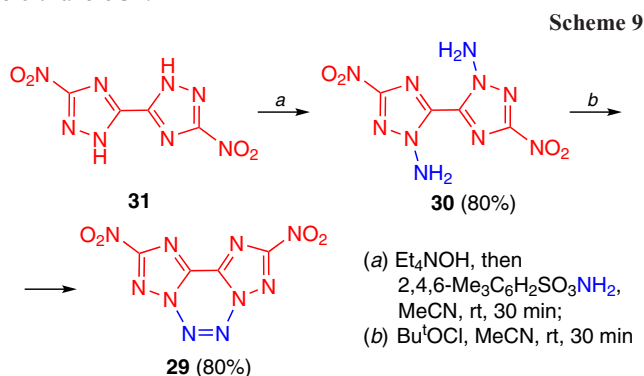


equilibrium in which the closed-ring form prevails (for example, for R = Me the tautomer ratio **23**:**24** is 3:7 according to NMR spectroscopy data).<sup>1</sup> In 2018, it was shown that the electron-donating substituents in the benzene ring (such as a dimethylamino group) completely shift the equilibrium towards closed-ring isomer **25**. Compound **26** also exists as the cyclic form.<sup>18</sup>

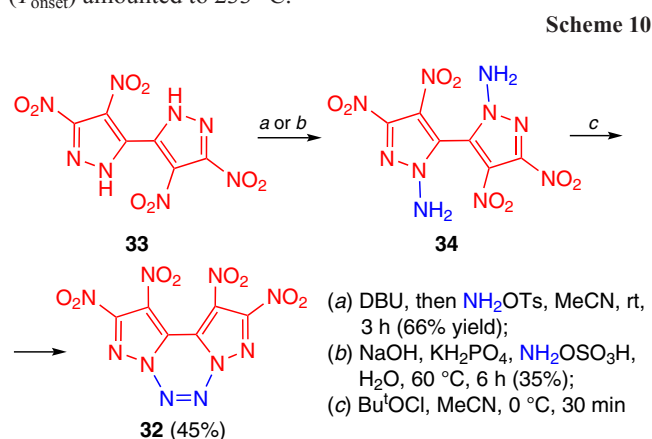
New substituted pyrazolobenzotetrazin-3-ones **27** were synthesized in good yields<sup>19–21</sup> using a previously developed procedure,<sup>22</sup> based on the diazotization of 1-(2-aminophenyl)-pyrazol-3-ones **28** (Scheme 8). Tetrazines **27** are also fairly stable ( $T_m = 143–238$  °C, depending on the substituents in the benzene ring).

## 2.2. Annulated 1,2,3,4-tetrazines with a nitrogen atom common to two heterocycles

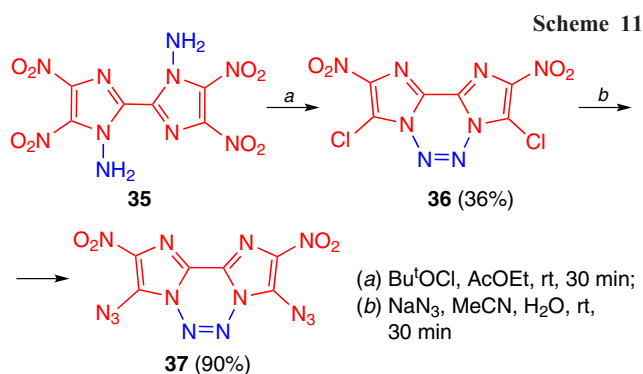
Tetrazine **29** with  $T_m = 138$  °C (dec.) with fused to two nitrotriazole rings was formed in a high yield when diamine **30** was allowed to react with *tert*-butyl hypochlorite (Scheme 9).<sup>23</sup> *O*-Mesitylenesulfonylhydroxylamine was used for amination of bis-triazole **31**.



A similar synthetic route was utilized to prepare tetrazine **32** with two dinitropyrazole rings fused to the tetrazine ring (Scheme 10).<sup>24</sup> The amination of bis-pyrazole **33** with *O*-tosylhydroxylamine (in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene, DBU) or with hydroxylamine-*O*-sulfonic acid resulted in the formation of diamine **34**, which was then oxidized into tetrazine **32** by the reaction with *tert*-butyl hypochlorite in MeCN. This tetrazine proved to be thermally stable:  $T_m = 205$  °C, the onset decomposition temperature ( $T_{\text{onset}}$ ) amounted to 233 °C.



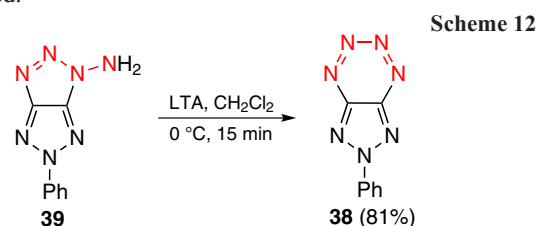
The oxidation of aminated bis-imidazole **35** with *tert*-butyl hypochlorite involved not only N=N bond formation, but was also accompanied by nucleophilic substitution of the nitro group in position 5 substituted with the chloride ion. This gave thermally stable dichloro derivative **36** ( $T_m = 215$  °C) (Scheme 11).<sup>25</sup> When this compound reacted with  $\text{NaN}_3$  in a mixture of MeCN and  $\text{H}_2\text{O}$ , the chlorine atoms were easily replaced with azido groups, thus yielding tetrazine **37**, which started to decompose at temperatures above  $>111$  °C.



## 2.3. Completely unsaturated 1,2,3,4-tetrazines

### 2.3.1. Annulated 1,2,3,4-tetrazines

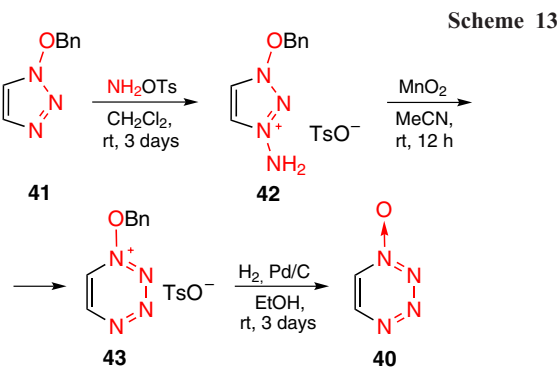
The first completely unsaturated annulated tetrazine **38** was synthesized for the first time by Ohsawa and co-workers<sup>‡</sup> in 1988. The key step of the synthesis was expansion of the 1,2,3-triazole ring in compound **39** via the oxidation with lead tetraacetate (LTA) (Scheme 12).<sup>1</sup> Tetrazine **38** proved to have low thermal stability and slowly decomposed at room temperature. Subsequently this class of compounds was not investigated.



### 2.3.2. Non-annulated 1,2,3,4-tetrazine 1-oxides

Benzoannulated tetrazine 1-oxides were considered in our previous review,<sup>1</sup> and no studies devoted to compounds of this class have appeared since 2004.

The first non-annulated 1,2,3,4-tetrazine 1-oxide **40** was obtained from 1-(benzyloxy)-1,2,3-triazole **41** (Scheme 13) in three steps.<sup>26</sup> Initially, this triazole was aminated with *O*-tosyl hydroxylamine, then the resulting tosylate **42** was oxidized with  $\text{MnO}_2$  to give salt **43**. The reaction mechanism is apparently similar to the mechanism of formation of tetrazine **38** (see Scheme 12) and includes a ring expansion step. The Pd/C-catalyzed reduction of salt **43** with hydrogen furnished tetrazine 1-oxide **40**, which was characterized by electron impact

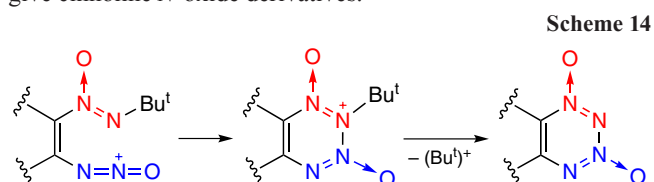


<sup>‡</sup> T.Kaihoh, T.Itoh, K.Yamaguchi, A.Ohsawa. *J. Chem. Soc., Chem. Commun.*, 1608 (1988); <https://doi.org/10.1039/C39880001608>

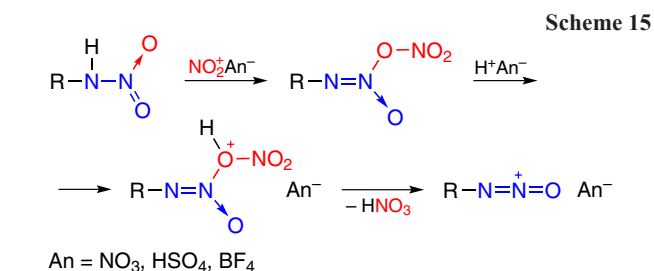
mass spectrum and by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. The thermal stability of this tetrazine was not studied.

### 2.3.3. 1,2,3,4-Tetrazine 1,3-dioxides

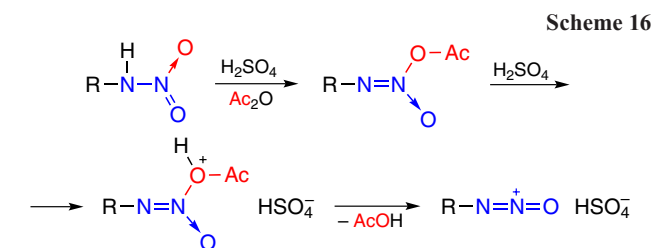
The general approach to the formation of 1,2,3,4-tetrazine 1,3-dioxide (TDO) ring is based on the intramolecular reaction of the *tert*-butyl-*NNO*-azoxy group with oxodiazonium ion  $[\text{R}-\text{N}=\text{N}=\text{O}]^+$  followed by elimination of the *tert*-butyl cation (Scheme 14). The existence of the oxodiazonium ion as an intermediate species was confirmed by experiments in which this species was intramolecularly trapped by the benzene ring to give cinnoline *N*-oxide derivatives.<sup>27</sup>



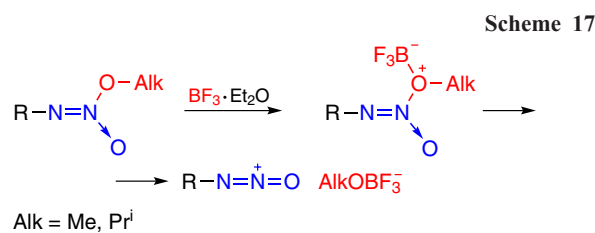
Methods for TDO synthesis differ from one another by the way of generation of oxodiazonium ions. The first tetrazine 1,3-dioxides were prepared by the nitration method (Scheme 15), which consists in the reaction of primary nitramines, usually generated *in situ*, with nitrating agents ( $\text{NO}_2\text{BF}_4$ ,  $\text{N}_2\text{O}_5$ ).<sup>1</sup> Recently, nitronium sulfates were used as nitrating agents.<sup>28</sup>



In recent years, new methods for the generation of oxodiazonium ion have been developed. The acetylation method includes the intermediate formation of *O*-acetylated nitramines, which dissociate in acid media, giving rise to the  $[\text{R}-\text{N}=\text{N}=\text{O}]^+$  ion (Scheme 16).<sup>29,30</sup> Nitramine is usually formed *in situ*. This method is suitable for the preparation of annulated 1,2,3,4-tetrazine 1,3-dioxides. The starting compounds used in these reactions are aromatic and heteroaromatic compounds (benzenes, 1,2,5-oxadiazoles, 1,2,3-triazoles, 1,2,3,4-tetrazine 1,3-dioxide) containing amino- and *tert*-butyl-*NNO*-azoxy groups in neighbouring positions (see Sections 2.3.3.2, 2.3.3.3).



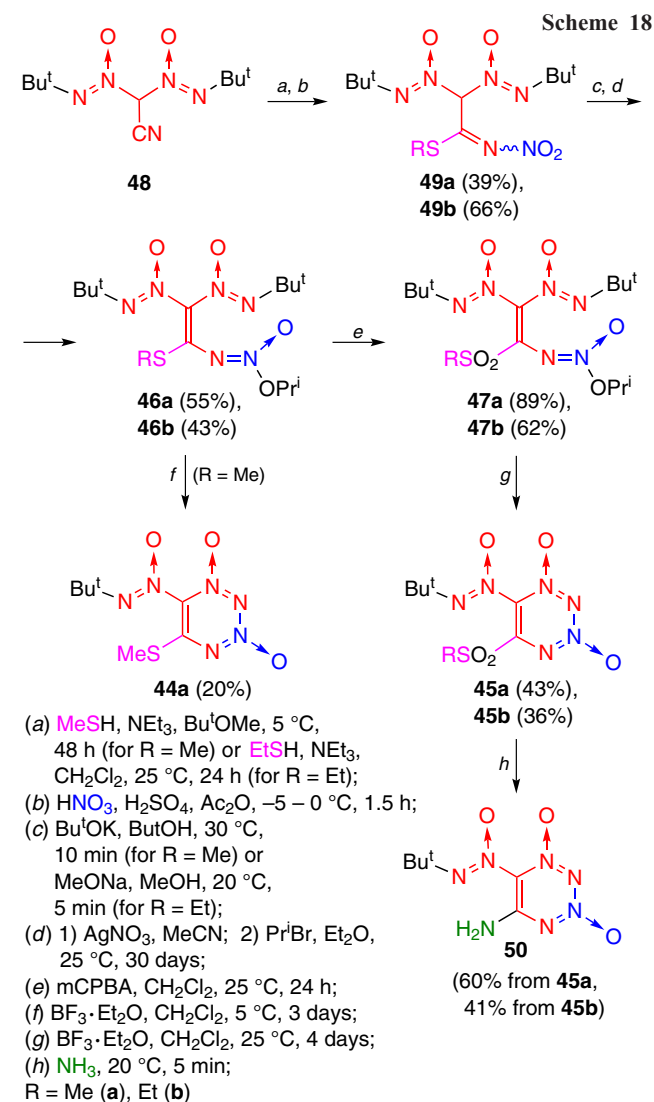
One more method for the generation of the oxodiazonium ion, *O*-alkylation method, includes the reaction of *O*-alkylated nitramines with boron trifluoride etherate or with acids (Scheme 17). This method is suitable for the synthesis of both annulated<sup>31</sup> and non-annulated tetrazine 1,3-dioxides (see Section 2.3.3.1.1).



#### 2.3.3.1. Non-annulated 1,2,3,4-tetrazine 1,3-dioxides

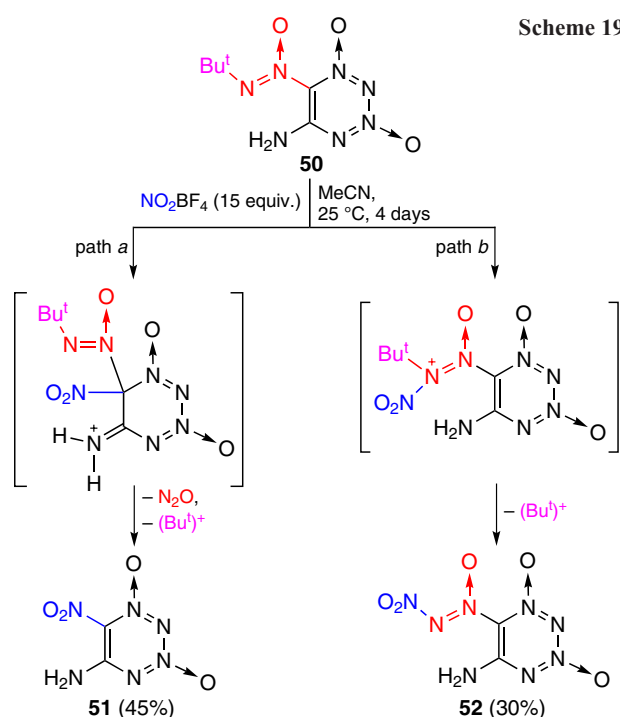
##### 2.3.3.1.1. Synthesis from aliphatic precursors

The approach to the synthesis of non-annulated TDOs from aliphatic precursors is based on the intramolecular reaction of alkenes containing a *tert*-butyl-*NNO*-azoxy group and an *O*-alkylated *N*-(nitro)amino group in neighbouring positions (Scheme 18). The cyclization is induced by boron trifluoride etherate. The plausible reaction mechanism is shown above in Scheme 17. Non-annulated TDOs **44a** and **45a,b** were obtained from azoxyalkenes **46a** and **47a,b**, respectively.<sup>32,33</sup> The azoxyalkenes, in turn, were prepared by reacting bis(*tert*-butyl-*NNO*-azoxy)acetonitrile (**48**) with alkanethiols and subsequent nitration and *O*-alkylation of the intermediate *N*-nitroimines **49a,b**. The oxidation of compounds **46a,b** afforded sulfones **47a,b**. The best yields of TDOs were attained when sulfones **47a,b**. The best yields of TDOs were attained when sulfones



with electron-withdrawing alkylsulfonyl substituents were used. The relatively low yield of product **44a** (20%) can be attributed to the fact that in this case, the intermediate oxidiazonium cation is fairly unstable and easily eliminates  $N_2O$  to give a vinyl cation stabilized by a methanethiol group. The alkylsulfonyl groups at the C(5) atom in TDOs **45a,b** are readily substituted with ammonia to give product **50**. The replacement of the methanethiol group by ammonia in compound **44a** also affords TDO **50**, but in a lower yield (18–20%).

The reaction of 5-amino-6-(*tert*-butyl-*NNO*-azoxy)tetrazine 1,3-dioxide **50** with an excess of  $NO_2BF_4$  in MeCN gives rise to 5-amino-6-nitro derivative **51** in 45% yield [ $T_m = 195–200$  °C (dec.)]<sup>34</sup> and TDO **52** in 30% yield [ $T_m = 110–112$  °C (dec.)] (Scheme 19).<sup>35</sup> Apparently, product **51** is formed by the electrophilic substitution mechanism of the *tert*-butyl-*NNO*-azoxy group by the nitro group (path *a*), while compound **52** is produced by the electrophilic substitutive *N*-nitration (path *b*).

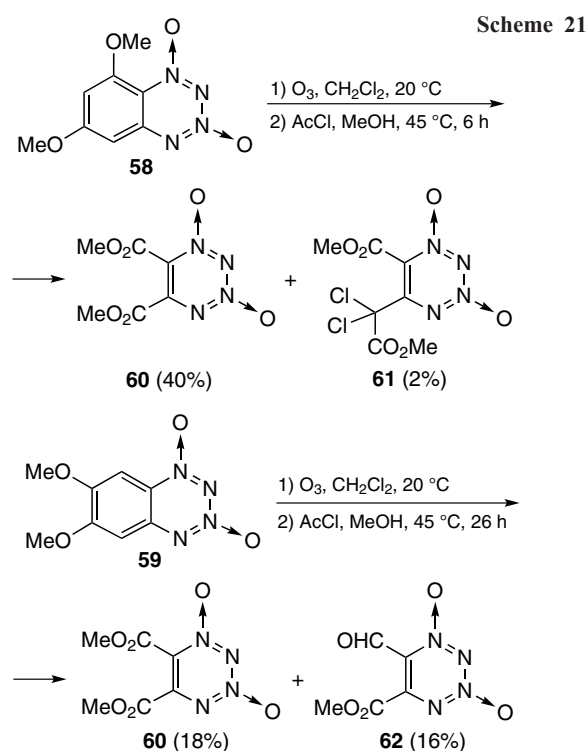
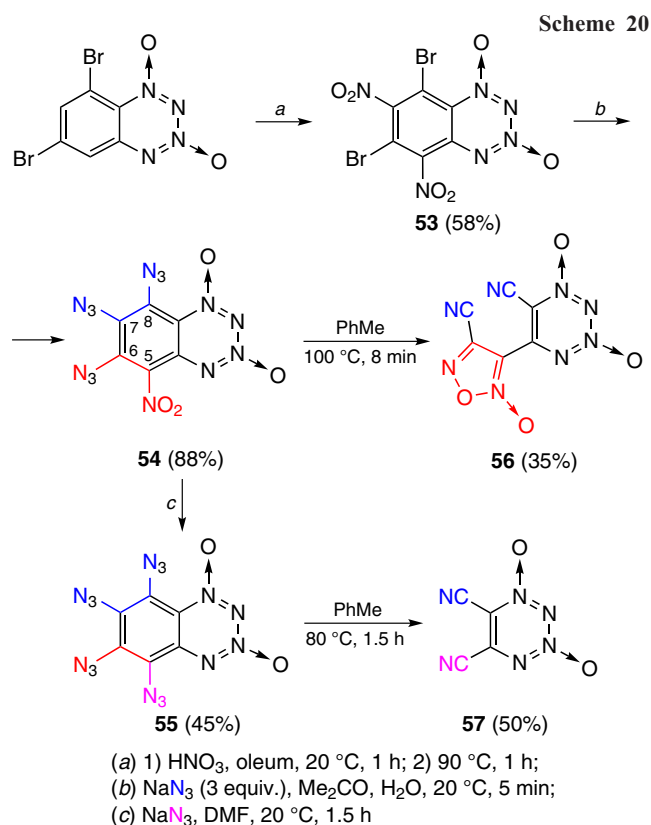


### 2.3.3.1.2. Synthesis from benzotetrazine 1,3-dioxides

An alternative approach to the synthesis of non-annulated TDOs is benzene ring opening in benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs), which can be accomplished in two ways.

The first one is thermolysis of polyazido-substituted BTDOs. The latter were synthesized from 6,8-dibromo-5,7-dinitro-BTDO **53**, which was obtained by nitration of 6,8-dibromo-BTDO (Scheme 20). The reaction of compound **53** with  $NaN_3$  led to tri- and tetra-azido-BTDOs (**54** and **55**) depending on the reaction conditions.<sup>36</sup> Heating of a toluene solution of triazidonitro-BTDO **54** at 100 °C for a few minutes resulted in benzene ring opening to give non-annulated TDO **56** [ $T_m = 165–167$  °C (dec.)]. 5,6-Dicyanotetrazine dioxide **57** [ $T_m = 110–130$  °C (dec.)] was obtained by heating tetraazido-BTDO **55** in toluene at 80 °C for 1.5 h.

The second way for benzene ring opening is ozonolysis of BTDOs containing electron-donating substituents.<sup>37</sup> Ozonolysis of dimethoxy derivatives **58** and **59** in  $CH_2Cl_2$  with subsequent treatment of the primary ozonides with AcCl in MeOH resulted in 5,6-di(methoxycarbonyl)tetrazine dioxide **60** ( $T_m = 93–96$  °C, decomposition temperature ( $T_{dec}$ ) > 190 °C) as the major product



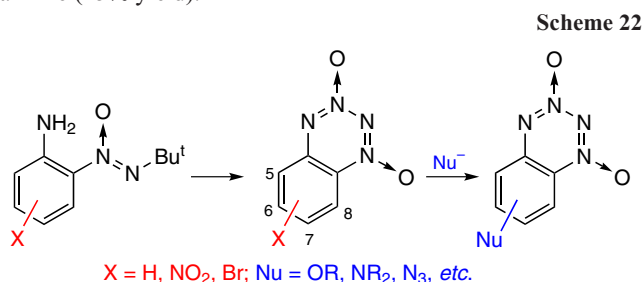
(Scheme 21). Compounds **61** [ $T_m = 156–158$  °C (dec.)] and **62** were formed in these reactions in lower amounts.

### 2.3.3.2. Benzoannulated 1,2,3,4-tetrazine 1,3-dioxides

#### 2.3.3.2.1. Benzo-1,2,3,4-tetrazine 1,3-dioxides with functional groups. 'Billiard' reaction

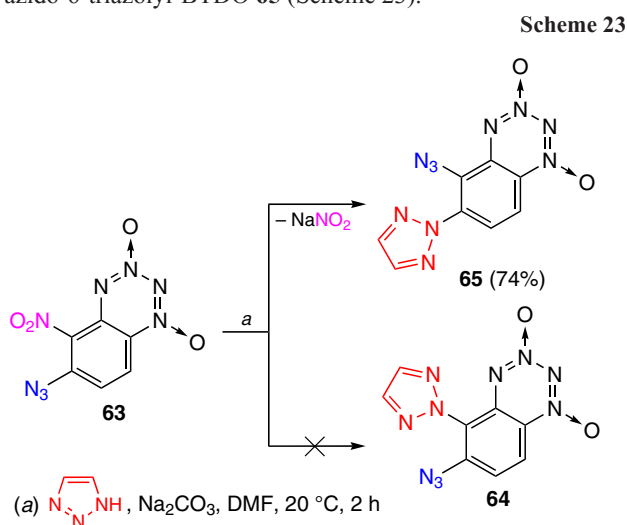
Unsubstituted benzo-1,2,3,4-tetrazine 1,3-dioxide and some nitro- and bromo-substituted BTDOs are prepared by closure of a TDO

ring in benzenes containing amino- and *tert*-butyl-*NNO*-azoxy groups in neighbouring positions (Scheme 22). The cyclization is accomplished *via* the nitration or acetylation method (most often, the intermediate nitramines are not isolated) (see Schemes 15 and 16) or by the *O*-alkylation method (see Scheme 17). The benzo derivatives thus formed can be introduced into electrophilic substitution reactions. In relation to nitration and bromination, it was shown<sup>38</sup> that in terms of the ease of these reactions, the positions in the benzene ring vary as follows: 5~7>8>6. The successive use of cyclization and nitration reactions made it possible to develop a one-pot method for the synthesis of 5,7-dinitro-BTDO from 2-(*tert*-butyl-*NNO*-azoxy) aniline (45% yield).<sup>39</sup>

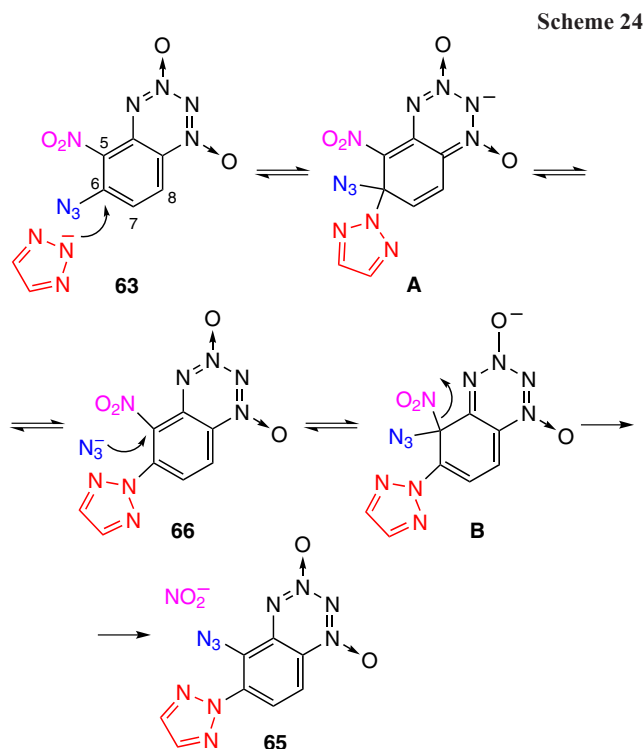


The brominated and nitro-substituted BTDOs easily undergo nucleophilic substitution reactions, in which the tetrazine ring remains intact (see Scheme 22). In relation to the reactions of mono- and di-bromo-substituted BTDOs with the methoxide anion, it was shown<sup>40</sup> that in terms of the ease of nucleophilic substitution, positions in the benzene ring are arranged as 6>8>7>5.

The unusual nucleophilic substitution with 1,2,3-triazole resulted in the discovery of a ‘billiard’ reaction for this series of compounds. In order to prepare BTDOs annulated with tetraazapentalene systems, an attempt was made to synthesize a derivative containing triazole moiety in position 5. However, the reaction of compound **63** with sodium azide did not give the expected 6-azido-5-triazolyl derivative **64**, but instead furnished an isomer with the inverted positions of substituents, namely, 5-azido-6-triazolyl-BTDO **65** (Scheme 23).<sup>41</sup>



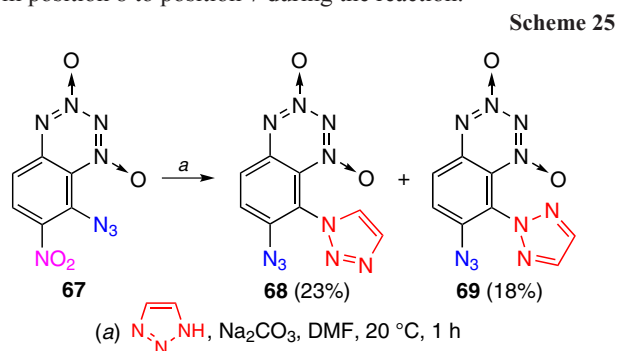
The formation of product **65** can be explained in the following way (Scheme 24). In the first step, the triazole anion attacks BTDO **63** at position 6 to give the anionic  $\sigma$ -complex **A**. This is followed by elimination of azide anion to give intermediate **66**. However, the reaction does not stop at this stage: now the azide ion itself acts as a nucleophile and attacks position 5 of



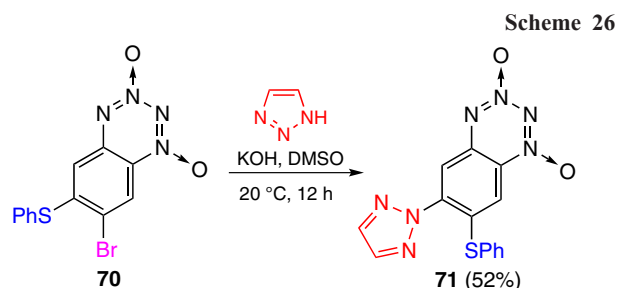
intermediate **66** to form anionic  $\sigma$ -complex **B**, and the subsequent elimination of the nitrite anion leads to BTDO **65**.

This unusual cascade of nucleophilic substitution reactions in which a nucleofuge turns into a nucleophile can be called a ‘billiard’ reaction. To our knowledge, such cascades of reactions have not been observed earlier among benzene derivatives.

A similar ‘billiard’ process occurs when BTDO **67** reacts with 1,2,3-triazole in the presence of a base; this gives a mixture of isomers **68** and **69** (Scheme 25).<sup>41</sup> The azido group migrates from position 8 to position 7 during the reaction.



One more example of the ‘billiard’ process is the conversion of BTDO **70** to compound **71** *via* the reaction with 1,2,3-triazole in the presence of a base (Scheme 26).<sup>41</sup> In this case, the benzenethiol group migrates from position 6 to position 7.



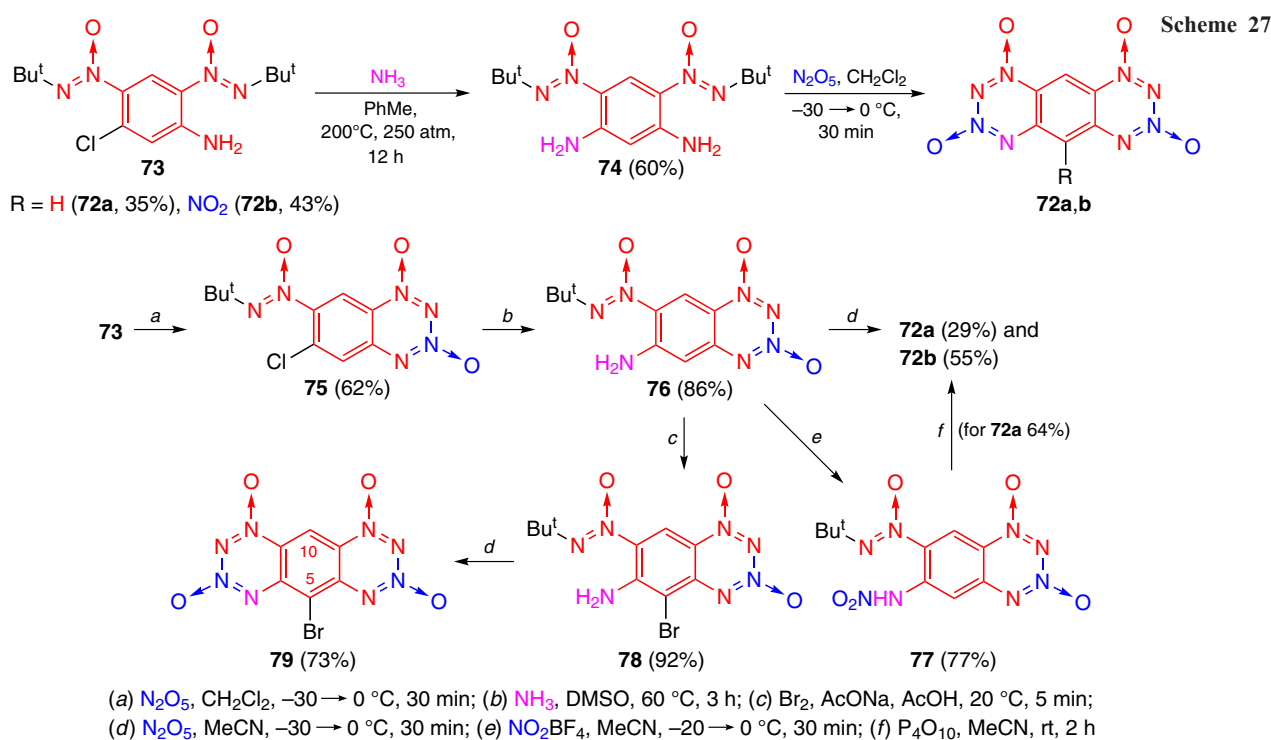
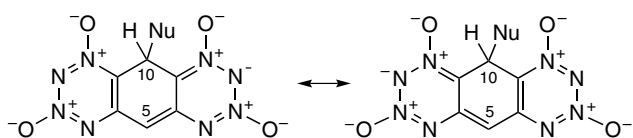
Similarly to the azido group in the above examples, the benzenethiol group acts as a nucleofuge in the first step and as a nucleophile in the second step.

### 2.3.3.2.2. Annulation with a second tetrazine 1,3-dioxide ring

Tetrazinobenzotetrazine 1,3,7,9-tetraoxides (TBTTOs) **72a,b** were synthesized by simultaneous or successive closure of two TDO rings (Scheme 27).<sup>42</sup> In the former case, chloroaniline **73** was converted to phenylenediamine **74** by treatment with  $\text{NH}_3$  at 250 atm. Cyclization of **74** by the nitration method under the action of  $\text{N}_2\text{O}_5$  in  $\text{CH}_2\text{Cl}_2$  resulted in the closure of both tetrazine rings and formation of TBTTOs **72a** and **72b** in a nearly 1:1 ratio. In the latter case, chloroaniline **73** was first cyclized on treatment with  $\text{N}_2\text{O}_5$  to give BTDO **75**, and then the chlorine atom was substituted with an amino group *via* the reaction with ammonia. Tetrazine ring closure in amino derivative **76** induced by the reaction with  $\text{N}_2\text{O}_5$  in  $\text{CH}_2\text{Cl}_2$  gave TBTTOs **72a** and **72b** in a ratio close to 1:2. The nitration of compound **76** with one equivalent of  $\text{NO}_2\text{BF}_4$  afforded nitramine **77**, which was cyclized by the phosphorylation method by treatment with  $\text{P}_4\text{O}_{10}$  in MeCN to give unsubstituted TBTTO **72a** without an impurity of nitro derivative **72b**. The bromination of compound **76** yielded benzotetrazine dioxide **78**, which was converted to TBTTO **79** by treatment with an excess of  $\text{N}_2\text{O}_5$  in MeCN.

TBTTOs start to decompose without melting at 140–160 °C. It was found that these compounds, including the unsubstituted compound **72a**, were highly sensitive to hydrolysis. This is, most likely, due to the ease of formation of the thermodynamically stable anionic  $\sigma$ -complex, in which the negative charge is distributed over both TDO rings, *via* an attack by a nucleophile on position 10.

#### Structure of anionic $\sigma$ -complexes



An attempt to replace the bromine atom in 5-bromo derivative **79** with nucleophiles was unsuccessful, probably due to the fact that nucleophiles attack position 10 much more easily than position 5.

### 2.3.3.2.3. Annulation with tetraazapentalenes

The initial compounds used for the preparation of benzotetrazine dioxides annulated with tetraazapentalenes (T-BTDOs) represent BTDOs that contain azide and 1,2,3-triazole groups in neighbouring positions.

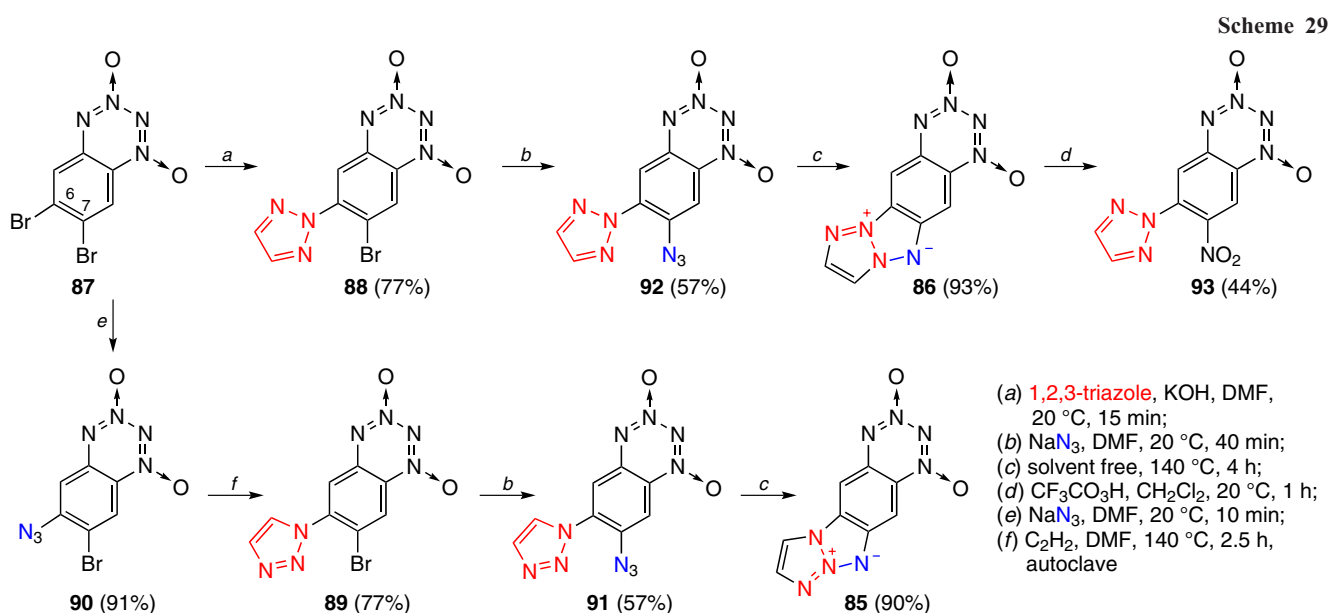
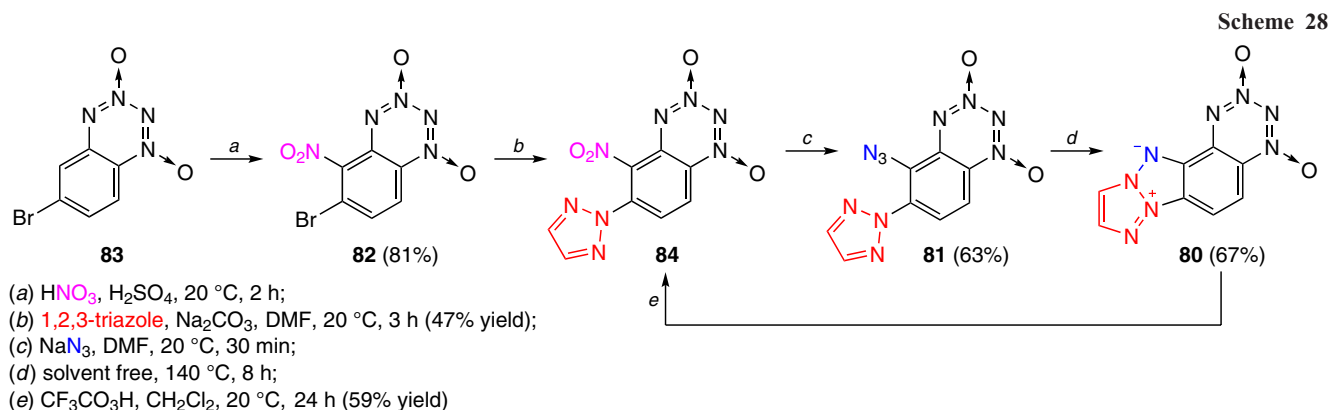
T-BTDO **80** with a tetraazapentalene system fused at the C(5)–C(6) bond was prepared from 5-azido-6-(1,2,3-triazol-2-yl)benzotetrazine dioxide **81** (Scheme 28).<sup>43</sup> This precursor was obtained using two successive nucleophilic aromatic substitution reactions. First, 6-bromo-5-nitro-BTDO **82**, obtained by nitration of 6-bromo-BTDO **83**, was treated with 1,2,3-triazole in DMF in the presence of  $\text{Na}_2\text{CO}_3$  to replace the bromine atom in position 6 with a 1,2,3-triazole moiety. Then the nitro group in position 5 was replaced with an azido group *via* the reaction of BTDO **84** with sodium azide in DMF.

Heating of benzotetrazine dioxide **81** without a solvent at 140 °C for 8 h resulted in the formation of T-BTDO **80** in 67% yield.<sup>43</sup> The structure of this product was confirmed by its oxidation with trifluoroperoxyacetic acid ( $\text{CF}_3\text{CO}_3\text{H}$ ) giving 5-nitro-6-(triazol-2-yl)-BTDO **84**.

According to differential thermal analysis (DTA) at a heating rate of 10 °C  $\text{min}^{-1}$ , T-BTDO **80** decomposes without melting: the decomposition starts at 245 °C, while the onset of intense decomposition is observed at 280 °C.

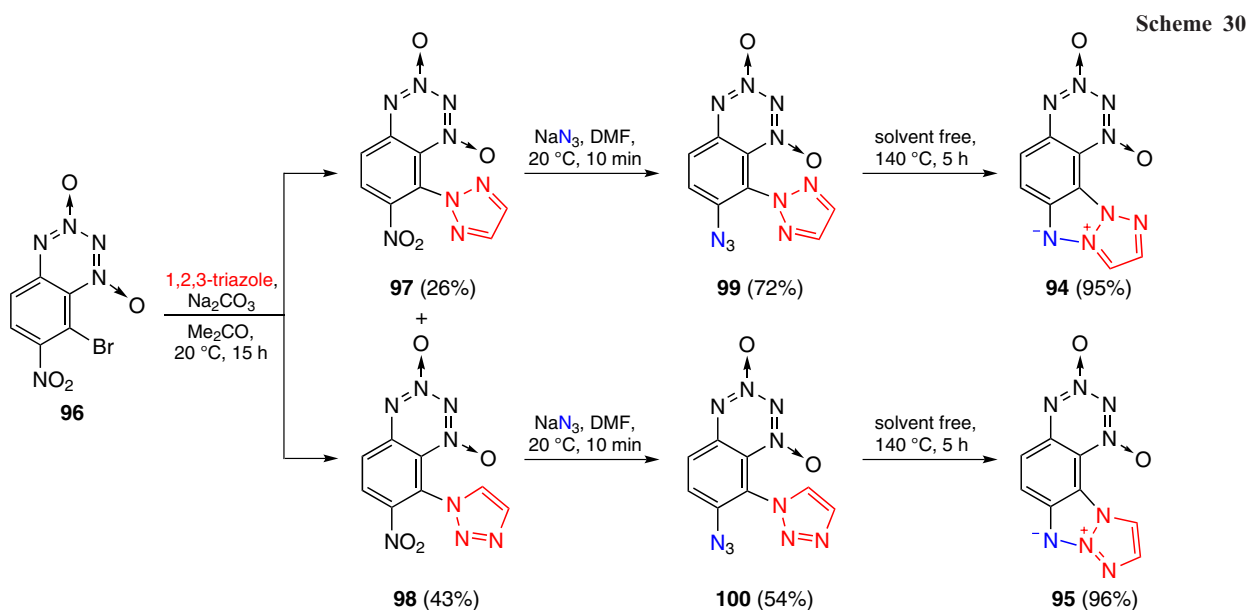
A similar synthetic approach was used to obtain T-BTDOs **85** and **86** with a tetraazapentalene system fused at the C(6)–C(7) bond.<sup>44</sup> The reaction of 6,7-dibromo-BTDO **87** with 1,2,3-triazole in the presence of a base resulted in the replacement of a bromine atom in position 6 giving rise to (triazol-2-yl)-BTDO **88** in 77% yield (Scheme 29). Triazol-1-yl-substituted isomer **89** was isolated upon this reaction in only 5% yield. Meanwhile, a good yield of this isomer was attained upon the cycloaddition of acetylene to the azido group in BTDO **90**, which was obtained





by reaction of compound **87** with  $\text{NaN}_3$ . The bromine atom in position 7 of the triazole-substituted BTDOs **89** and **88** is readily replaced with the azido group when these compounds are allowed to react with  $\text{NaN}_3$ ; the reactions afford products **91** and **92**, respectively. Heating of these BTDOs without a solvent at

140 °C furnishes compounds **85** and **86**, respectively. The structure of T-BTDO **86** was confirmed by its oxidation to afford 7-nitro-(6-triazol-2-yl)benzotetrazine dioxide **93** (see Scheme 29).



The results of DTA (heating rate of 10 °C min<sup>-1</sup>) demonstrated that T-BTDOs **85** and **86** start to decompose without melting. For compound **85**, the decomposition starts at 210 °C, while the onset of intense decomposition is observed at 250 °C; for isomer **86**, these values are 215 and 235 °C, respectively. These compounds are somewhat less stable than T-BTDO **80**, in which annulation occurs at the C(5)–C(6) bond.

Benzotetrazine dioxides **94** and **95** with a tetraazapentalene system attached at the C(7)–C(8) bond were synthesized as described in Scheme 30.<sup>45</sup> In the reaction of 8-bromo-7-nitro-BTDO **96** with 1,2,3-triazole in the presence of Na<sub>2</sub>CO<sub>3</sub>, bromine atom was rapidly displaced to give isomers **97** and **98** in 3:5 ratio. The mixture was easily separated by extraction with benzene in which the major isomer **98** is virtually insoluble. Despite the fact that position 8 in benzo-1,2,3,4-tetrazine 1,3-dioxides is activated towards nucleophilic substitution reactions to a higher extent than position 7, the triazole ring is not a good leaving group, and, hence, the nitro group at position 7 is substituted when BTDOs **97** and **98** react with NaN<sub>3</sub>; this results in the formation of products **99** and **100**, respectively. Heating of these compounds without a solvent at 140 °C affords T-BTDOs **94** (95% yield) and **95** (96% yield).

The results of DTA (heating rate of 10 °C min<sup>-1</sup>) showed that compounds **94** and **95** decompose without melting. For T-BTDO **94**, the temperatures of the onset of decomposition and the onset of the intense decomposition are 220 and 245 °C, respectively. For compound **95**, these values are 220 and 235 °C, respectively. In terms of stability, these derivatives resemble compounds **85** and **86** and are somewhat inferior to T-BTDO **80**.

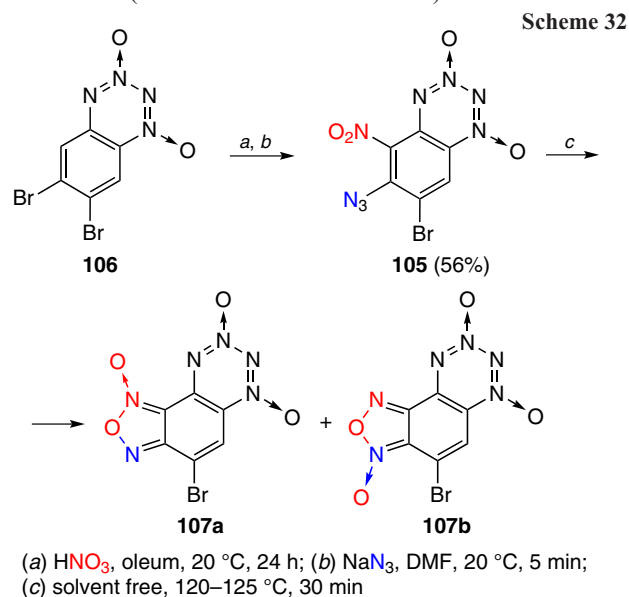
#### 2.3.3.2.4 Annulation with a furoxan ring

The starting compounds used to prepare benzo-1,2,3,4-tetrazine 1,3-dioxides annulated with a furoxan ring (F-BTDO) are BTDOs in which the azido and nitro groups are located in the neighbouring positions. These precursors were synthesized from appropriate BTDOs *via* electrophilic and/or nucleophilic substitution reactions.

6-Azido-5-nitro-BTDO **101** was obtained in 82% yield by nitration of 6-azido derivative **102** with one equivalent of HNO<sub>3</sub> in H<sub>2</sub>SO<sub>4</sub> (Scheme 31). The nitration occurs almost exclusively at position 5. Compound **101** was also prepared by substitution of bromine in 6-bromo-5-nitro-BTDO **103** with an azide group on treatment with sodium azide (85% yield). The formation of the furoxan ring took place when BTDO **101** was heated without a solvent at 100 °C or in AcOH at 90 °C. The <sup>1</sup>H and <sup>13</sup>C NMR spectra recorded at 297 K demonstrated that F-BTDO **104** exists

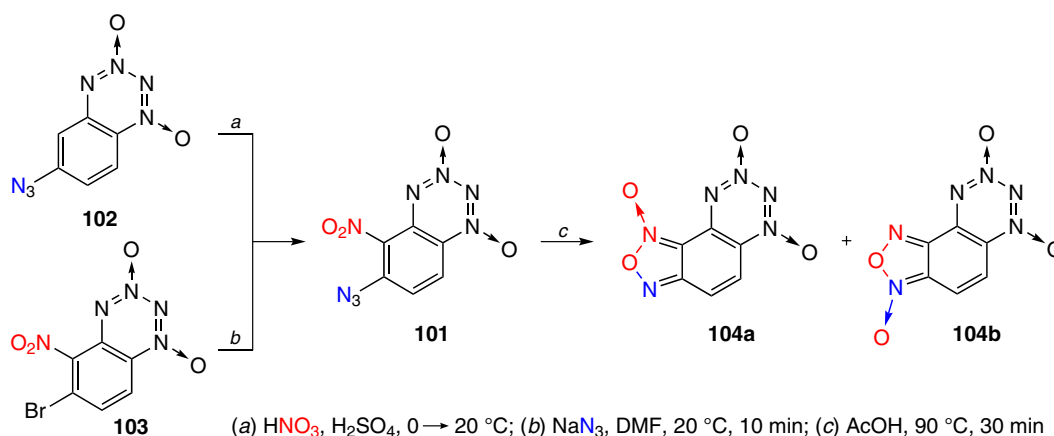
as a 1:1 equilibrium mixture of isomers **104a** and **104b** (*T*<sub>m</sub> = 204 °C) (83% total yield).<sup>46</sup>

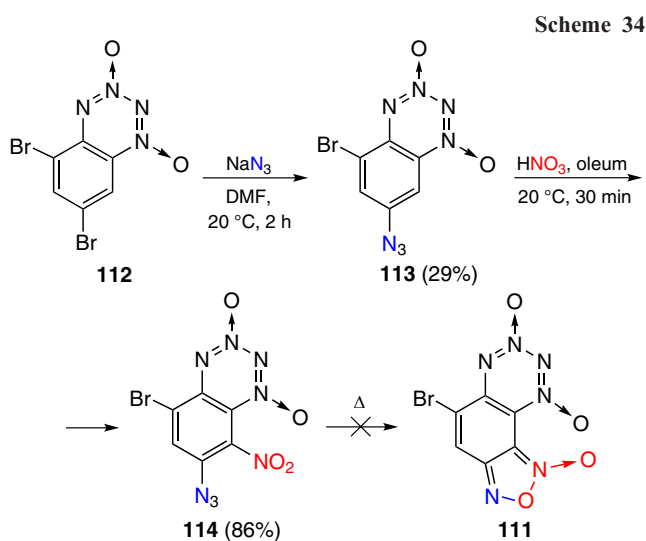
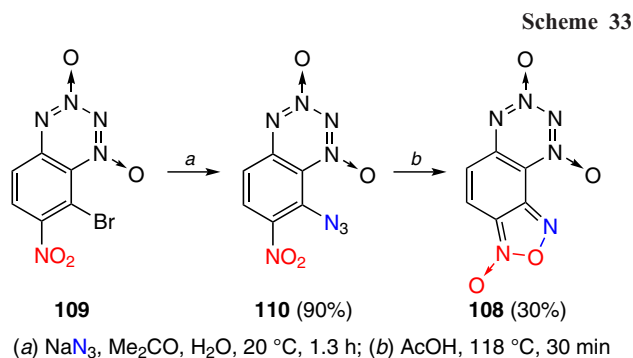
Benzotetrazine dioxide **105** was synthesized by nitration of 6,7-dibromo derivative **106** at position 5 followed by treatment with sodium azide (Scheme 32). The azido group replaced only the bromine atom at position 6. The cyclization of BTDO **105** proceeded under somewhat more rigorous conditions than in the previous case, namely, on heating without a solvent at 120–125 °C. The resulting bromo-substituted F-BTDO **107** (*T*<sub>m</sub> = 95–105 °C) was also an equilibrium mixture of two isomers (66% total yield), but in this case, isomer **107a** predominated (the **107a**:**107b** ratio was 9:1).



For the synthesis of F-BTDO **108** with a furoxan ring fused at the C(7)–C(8) bond, the bromine atom in 8-bromo-7-nitro-BTDO **109** was substituted with an azido group, and then 8-azido-7-nitro-BTDO **110** was kept in AcOH at 118 °C (Scheme 33). These conditions are somewhat more rigorous than those required to obtain F-BTDO **104** with fusion at the C(5)–C(6) bond. Product **108** proved to be less thermally stable than F-BTDO **104**: it melted without decomposition at 74–76 °C and started to decompose at temperatures above 90 °C. The low thermal stability is likely to be responsible for the low yield (30%).<sup>47</sup> The cause for the low stability of this compound is apparently in the easy interaction of the furoxan ring with the *N*-oxide oxygen atom of the tetrazine ring.

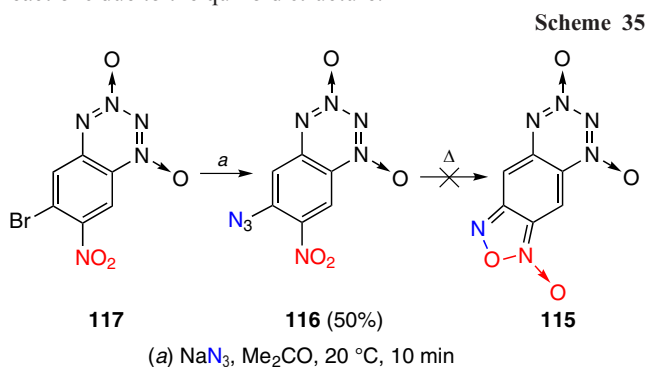
An attempt to obtain F-BTDO **111** according to Scheme 34 did not meet with success. The reaction of 5,7-dibromo



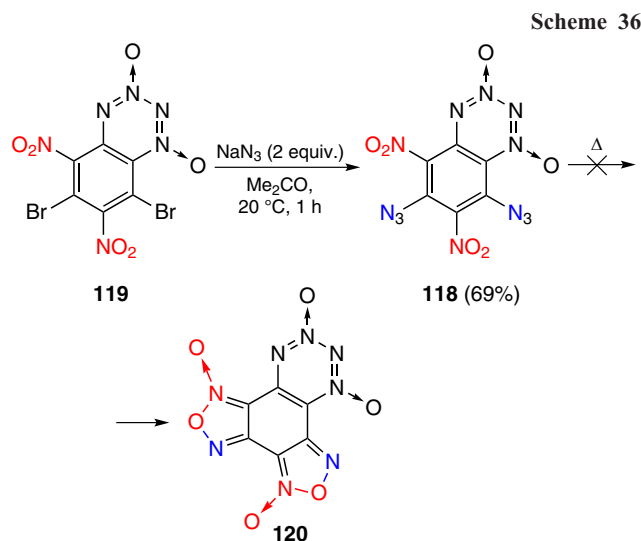


derivative **112** with  $\text{NaN}_3$  gave 7-azido-5-bromo-BTDO **113** as the major product. The minor isomer, 5-azido-7-bromo-BTDO, was formed in a yield of only 12%. The nitration of compound **113** involved position 8 and gave benzotetrazine dioxide **114**; heating of this product under various conditions yielded only resinification products. The cyclization is probably hampered by the steric strain in the cyclic transition state and also by low thermal stability of F-BTDOs of this type.

The attempted preparation of F-BTDO **115** by Scheme 35 also failed. 6-Azido-7-nitro-BTDO **116** is easily formed when the bromine atom in compound **117** is replaced with an azido group. However, heating of BTDO **116** under various conditions gave only resinification products. Probably, this is due to high reactivity of F-BTDO **115**, which is susceptible to intermolecular reactions due to the quinoid structure.



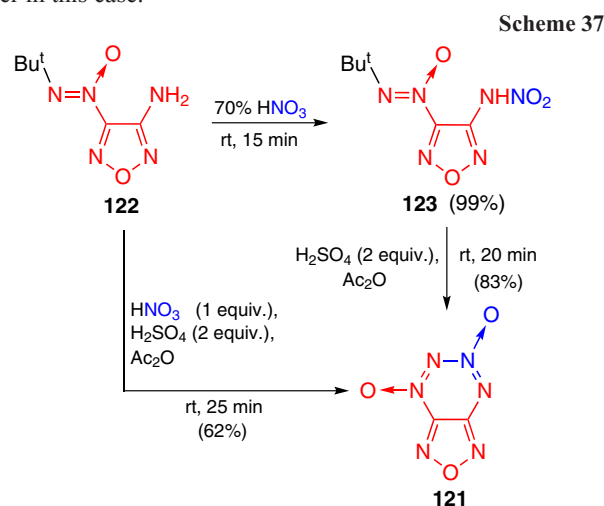
Heating of 6,8-diazo-5,7-dinitro-BTDO **118**, obtained by the reaction of compound **119** with sodium azide, gave only products of resinification (Scheme 36). The target F-BTDO **120** with two furoxan rings was not formed under these conditions.



### 2.3.3.3. Heteroannulated 1,2,3,4-tetrazine 1,3-dioxides

#### 2.3.3.3.1. Annulation with a furazan ring

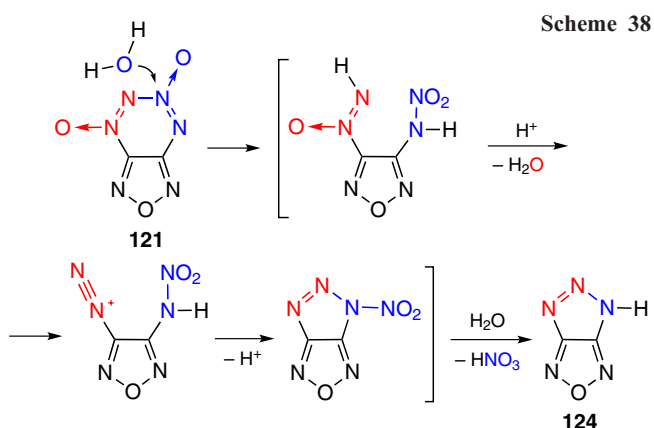
Furazanotetrazine 4,6-dioxide (FTDO) **121** was synthesized for the first time by the nitration method from aminofurazan **122** without isolation of intermediate nitramine **123**.<sup>48</sup> Later, an improved two-step method was developed; the method included the preparation of nitramine **123** by the nitration of aminofurazan **122** with 70%  $\text{HNO}_3$  and the subsequent cyclization by the acetylation method (Scheme 37).<sup>29,30</sup> This approach can also be used to prepare FTDO in one step, but the yield of the product is lower in this case.



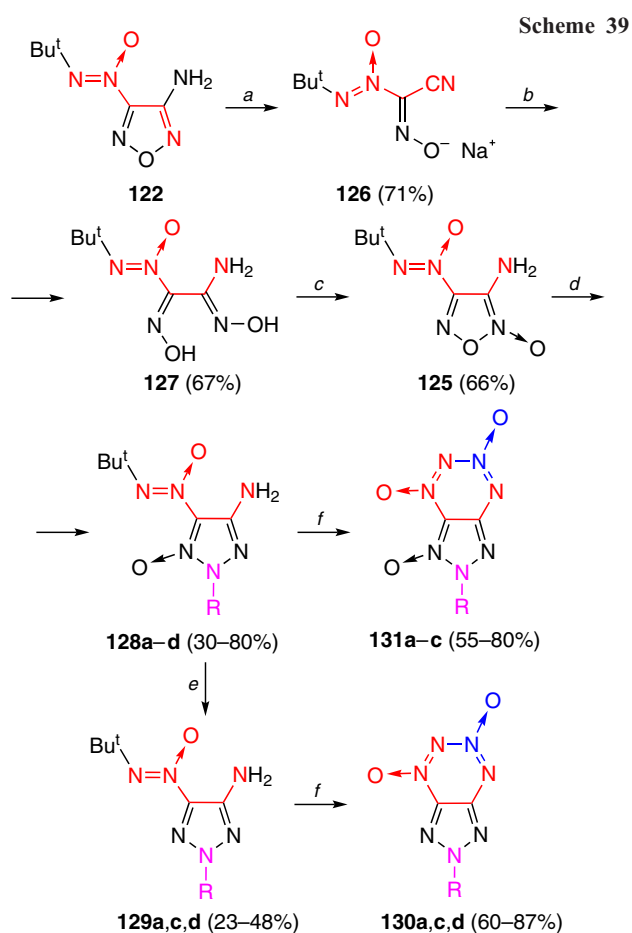
At room temperature, FTDO **121** is stable to the action of water, but at 80 °C, it is completely hydrolyzed within 2 h to yield triazolofurazan **124** (Scheme 38).<sup>49</sup> A probable mechanism of hydrolysis starts with the attack by water on the N(3) atom of the tetrazine ring.

#### 2.3.3.3.2. Annulation with a 1,2,3-triazole ring

Aminofuroxan **125** served as the starting compound for the synthesis of a number of tetrazine dioxides annulated with 1,2,3-triazole and 1,2,3-triazole 1-oxide rings. Compound **125** was synthesized from furazan **122** in three step, which included furazan ring opening to give the sodium salt of cyanoxime **126**, which was then converted to amidoxime **127**, and the subsequent

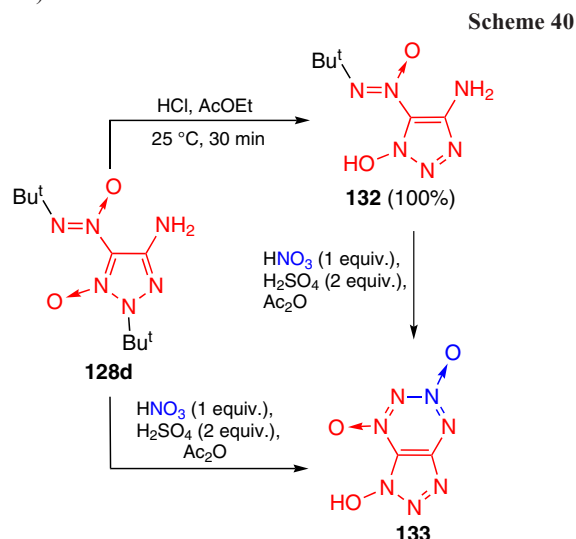


cyclization gave furoxan **125** (Scheme 39).<sup>50</sup> 1,2,3-Triazole 1-oxides **128a–d** were obtained by reacting this furoxan with aliphatic amines.<sup>51</sup> The reduction of compounds **128a,c,d** to 1,2,3-triazoles **129a,c,d** followed by the reaction with the  $\text{HNO}_3\text{--H}_2\text{SO}_4\text{--Ac}_2\text{O}$  system afforded triazolotetrazine dioxides **130a,c,d**.<sup>52</sup> The cyclization of 1,2,3-triazole 1-oxides **128a–c** induced by the same system of reagents afforded TDO **131a–c** fused with triazole 1-oxides.



- (a)  $\text{NaNO}_2$ ,  $\text{AcOH}$ ,  $\text{Et}_2\text{O}$ ,  $15^\circ\text{C}$ , 1.5 h;  
 (b)  $\text{NH}_2\text{OH}\cdot\text{HCl}$ ,  $\text{NaHCO}_3$ ,  $\text{MeOH}$ ,  $65^\circ\text{C}$ , 1.5 h;  
 (c)  $\text{Br}_2$ ,  $\text{HCl}$ ,  $\text{H}_2\text{O}$ ,  $1\text{--}4^\circ\text{C}$ , 10 min;  
 (d)  $\text{RNH}_2$ ,  $\text{MeOH}$ ;  
 (e)  $\text{Zn}$ ,  $\text{AcOH}$ ,  $\text{EtOH}$ ,  $25^\circ\text{C}$ , 2 h;  
 (f)  $\text{HNO}_3$  (1 equiv.),  $\text{H}_2\text{SO}_4$  (2 equiv.),  $\text{Ac}_2\text{O}$ ;  
 R = Me (a), Et (b), Pr<sup>i</sup> (c), Bu<sup>t</sup> (d)

The *tert*-butyl group is readily removed from the nitrogen atom of triazole **128d** in an acid medium to give hydroxytriazole **132** (Scheme 40).<sup>52</sup> The treatment of this product with the  $\text{HNO}_3\text{--H}_2\text{SO}_4\text{--Ac}_2\text{O}$  system resulted in the formation of 1-hydroxytriazolo-TDO **133** in 62% yield. Compound **133** was also prepared in one step without isolation of intermediate triazole **132**, but the product yield was somewhat lower in this case (45%).

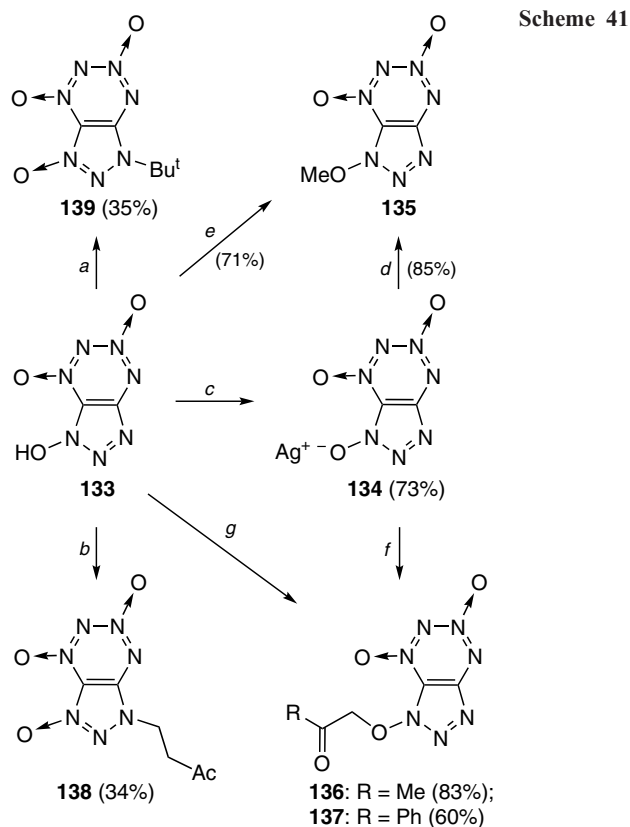


The alkylation of TDO **133** and its Ag salt **134** with various reagents (diazomethane, diazoacetone, bromoacetone,  $\alpha$ -bromoacetophenone, methyl iodide, methyl vinyl ketone or *tert*-butyl alcohol in acid medium) resulted in the synthesis of a number of new triazolo-1,2,3,4-tetrazine 1,3-dioxide derivatives (Scheme 41). The reaction of TDO **133** with diazo compounds and the reactions of salt **134** with halo derivatives afford, most often, *O*-alkylated compounds **135–137**.<sup>53</sup> The reaction of TDO **133** with methyl vinyl ketone and with *tert*-butyl alcohol in acid medium is directed towards the nitrogen atom of the triazole ring and gives *N*(3′)-substituted products **138** and **139**, respectively.<sup>52,53</sup>

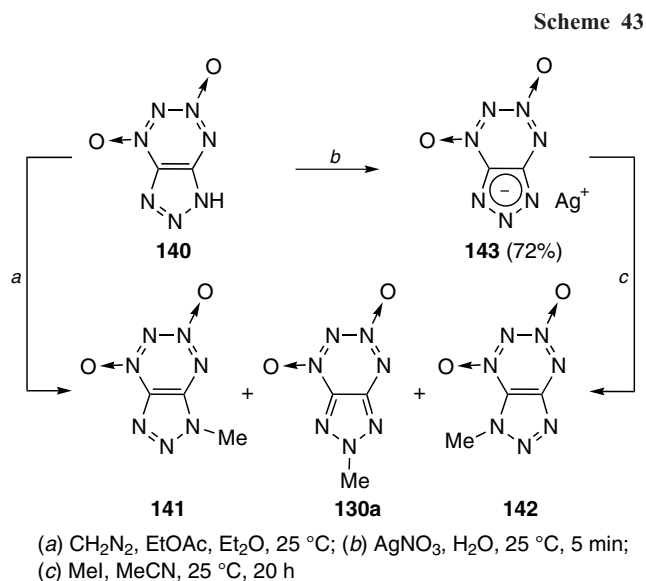
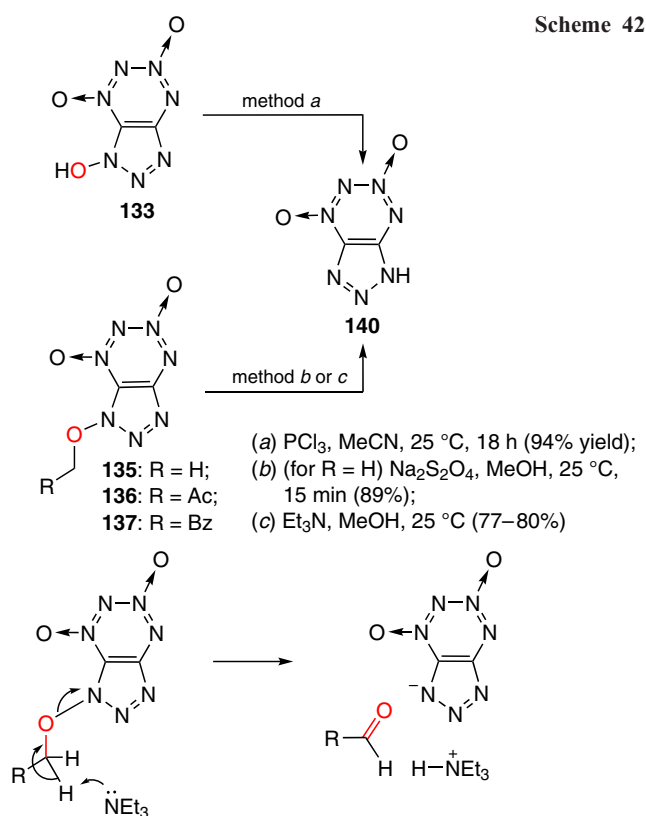
Three methods have been developed to remove the hydroxyl group from hydroxytriazolo-TDO **133** and prepare triazole derivative **140** in high yields (77–94%): (a) reduction of 1-hydroxytriazolo-TDO **133** by treatment with  $\text{PCl}_3$  in acetonitrile; (b) reduction of 1-methoxytriazolo-TDO **135** with  $\text{Na}_2\text{S}_2\text{O}_4$ ; and (c) reaction of 1-alkoxytriazolo-TDOs **135–137** with  $\text{Et}_3\text{N}$  in methanol (Scheme 42). The mechanism of the latter non-classical reduction includes, most likely, elimination of the active proton to give the corresponding aldehyde, which was isolated in one case. The tetrazine ring remains intact in these reactions.<sup>54</sup>

Methylation of triazolo-TDO **140** with diazomethane afforded isomers **141**, **130a**, and **142** in 41 : 33 : 26 ratio in a total yield of 34% (Scheme 43). Isomer **141** was formed as the major methylation product. In the case where Ag salt **143** was methylated with methyl iodide in acetonitrile, three isomers were also formed (83% total yield), but **130a** was the major product (the **141**, **130a** and **142** isomer ratio was 30 : 56 : 14). In both reactions, the thermodynamically less stable isomer **142** was formed in the lowest amount.

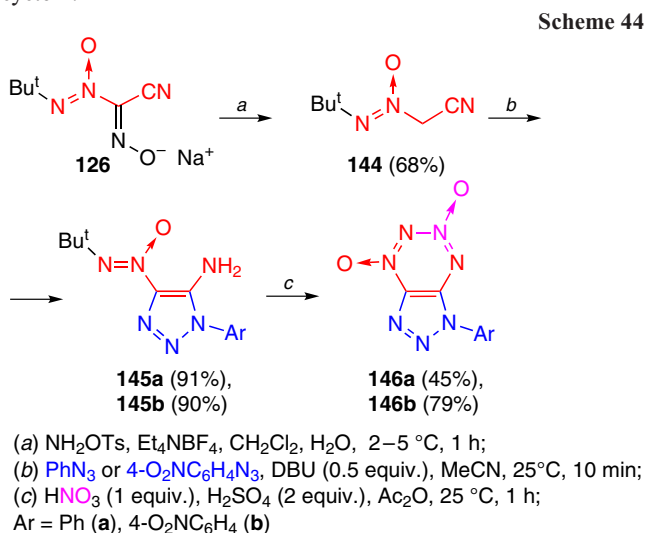
The above-described approach is unsuitable for the synthesis of aryl-substituted triazolo-TDOs. For the synthesis of these compounds, an alternative route was developed, in which (*tert*-butyl-*N*(*N*-azoxy)acetonitrile (**144**) containing an active methylene unit served as the key compound (Scheme 44). This



- (a)  $\text{Bu}^t\text{OH}$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{CF}_3\text{CO}_2\text{H}$ , rt, 5 min;  
 (b)  $\text{AcCH}=\text{CH}_2$ ,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , MeCN, 25 °C, 1 h;  
 (c)  $(\text{NH}_4)_2\text{CO}_3$ ,  $\text{AgNO}_3$ ,  $\text{H}_2\text{O}$ , 25 °C, 10 min;  
 (d) MeI, MeCN, 25 °C, 1.5 h;  
 (e)  $\text{CH}_2\text{N}_2$ , EtOAc,  $\text{Et}_2\text{O}$ , 25 °C;  
 (f)  $\text{AcCH}_2\text{Br}$  or  $\text{BzCH}_2\text{Br}$ , MeCN, 25 °C, 5 h;  
 (g)  $\text{AcCHN}_2$ ,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , MeCN, 25 °C, 10 min (yield of **136**: 75%)

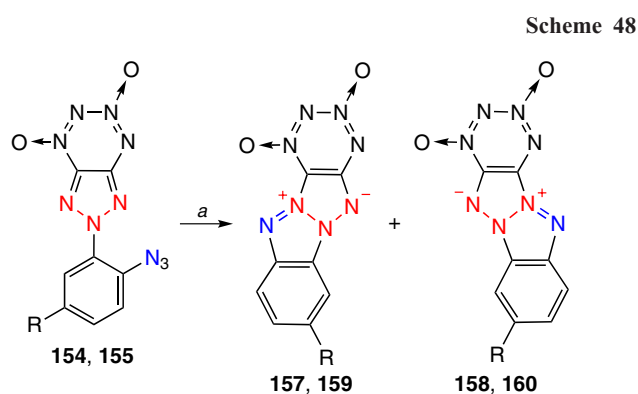
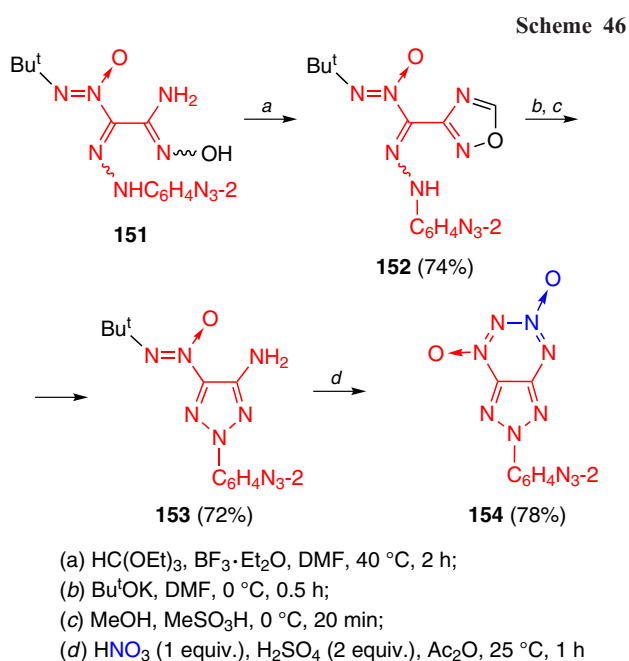
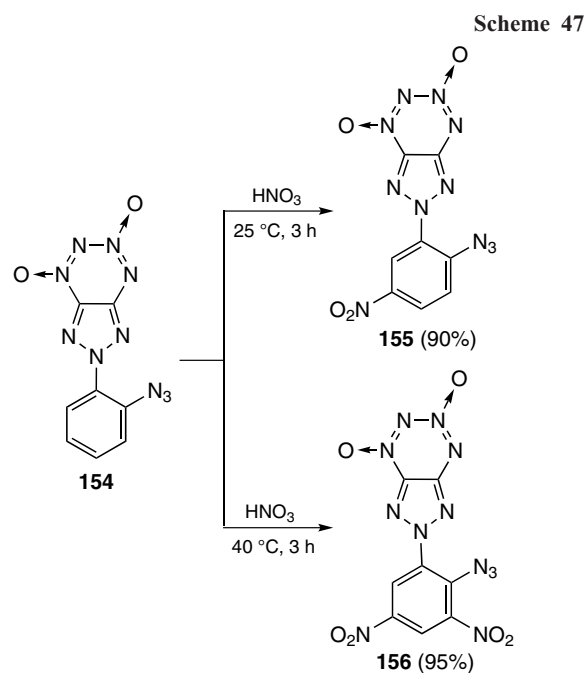
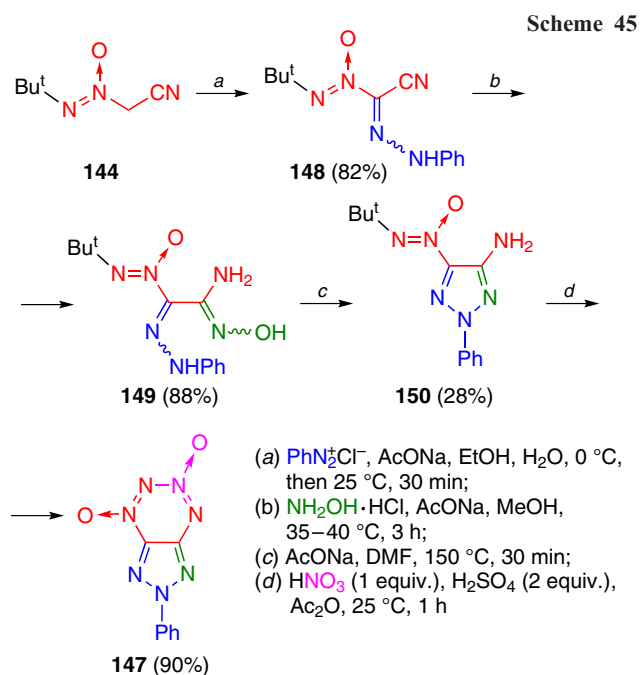


nitrile was prepared by reductive amination of cyanoxime sodium salt **126**.<sup>55</sup> 1-Aryltriazoles **145a,b** were obtained by the reaction of nitrile **144** with aryl azides in the presence of a base. The cyclization of these triazoles to aryl-substituted triazolo-TDO **146a,b** was induced by the  $\text{HNO}_3$ – $\text{H}_2\text{SO}_4$ – $\text{Ac}_2\text{O}$  system.<sup>56</sup>



For the synthesis of 2-phenyltriazolo-TDO **147**, nitrile **144** was reacted with phenyldiazonium chloride; this gave hydrazone **148**, which was converted to amidoxime **149** upon the reaction with hydroxylamine (Scheme 45). On heating at 150 °C in dimethylformamide in the presence of sodium acetate, amidoxime **149** cyclized to triazole **150**, which was then treated with the  $\text{HNO}_3$ – $\text{H}_2\text{SO}_4$ – $\text{Ac}_2\text{O}$  system to give 2-phenyltriazolo-TDO **147**.<sup>56</sup>

Amidoxime **151**, containing a 2-azidophenyl group, was produced similarly to amidoxime **149** (see Scheme 45); however, ring closure to give 1,2,3-triazole by the heating in dimethylformamide failed. Therefore, this amidoxime was converted to oxadiazole **152** and further to triazole **153** by the reaction with a base (Boulton–Katritzky rearrangement). This was followed by elimination of the formyl group in methanol in the presence of methanesulfonic acid (Scheme 46). 2-Azido-phenyltriazolo-TDO **154** was synthesized by the reaction of triazole **153** with the  $\text{HNO}_3$ – $\text{H}_2\text{SO}_4$ – $\text{Ac}_2\text{O}$  system.<sup>57</sup>



(a) 1,2- $\text{Cl}_2\text{C}_6\text{H}_4$ , 170 °C; R = H (154, 157, 158),  $\text{NO}_2$  (155, 159, 160)

The nitration of triazolo-TDO **154** with concentrated  $\text{HNO}_3$  at room temperature furnished mononitrated product **155**,<sup>57</sup> while the reaction at 40 °C led to doubly nitrated derivative **156** (Scheme 47).<sup>58</sup>

When triazolo-TDO **154** was heated in 1,2-dichlorobenzene at 170 °C for 2.5 h, ring closure took place to give isomeric tetraazapentalenes **157** ( $T_{\text{dec}} > 183$  °C) and **158** in 5.3:1 ratio in a total yield of 75% (Scheme 48).<sup>57</sup> The cyclization of nitro derivative **155** under the same conditions proceeded in 30 min and afforded isomers **159** ( $T_{\text{dec}} > 191$  °C) and **160** in 1.1:1 ratio (91% total yield).

Dinitro derivative **156** cyclized on heating in toluene at 110 °C (Scheme 49).<sup>58</sup> The azido group mainly reacted with the neighbouring nitro group, thus giving furoxan **161** ( $T_{\text{dec}} > 190$  °C) in 68% yield. The isomeric tetraazapentalenes **162** and **163** were produced in 5% yield each. Markedly higher yields of tetraazapentalene **162** were attained when tetraazapentalenes

**157** or **159** were nitrated with a mixture of nitric and sulfuric acids: 63 and 54%, respectively.<sup>57</sup>

According to differential scanning calorimetry (DSC) data (10 °C  $\text{min}^{-1}$  heating rate), the onset decomposition temperature of tetraazapentalene **162** is 234 °C; this is much higher than that of isomer **163**, which starts to decompose at 158 °C.

### 2.3.3.3.3. Annulation with a pyridine ring

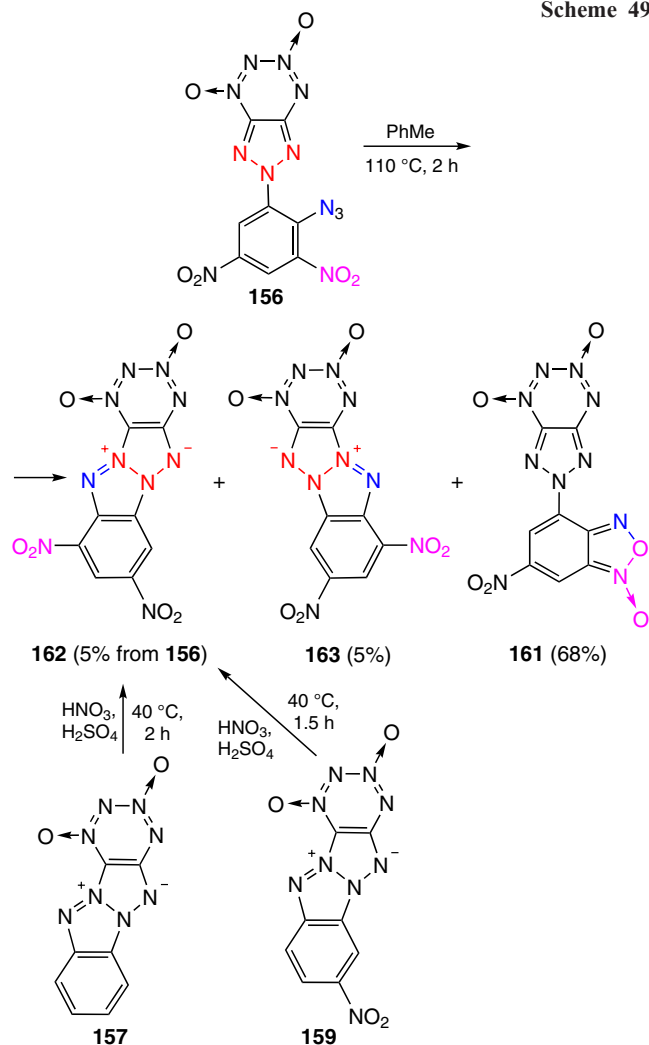
The reaction of 2-amino-3-(*tert*-butyl-*NNO*-azoxy)pyridine (**164**) with an excess of  $\text{N}_2\text{O}_5$  in dichloromethane resulted in the formation of pyrido-TDO **165** and its nitro derivative **166** in 1:2 ratio (Scheme 50).<sup>59</sup>

The isomeric pyrido-TDO **167** was synthesized from pyridine **168** using nitronium tetrafluoroborate as a tetrazine ring closure reagent (Scheme 51). The use of  $\text{N}_2\text{O}_5$  proved inefficient in this case.

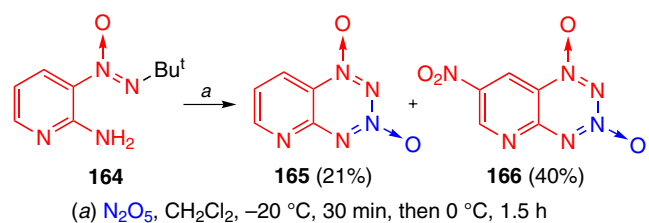
### 2.3.3.3.4. Annulation with a tetrazine 1,3-dioxide ring

Tetrazinotetrazine 1,3,6,8-tetraoxide (TTTO) **169** was synthesized in 22% yield from TDO **50** using the  $\text{HNO}_3\text{--H}_2\text{SO}_4\text{--Ac}_2\text{O}$  system of reagents (Scheme 52).<sup>33</sup> This compound was fairly thermally stable, but it was completely

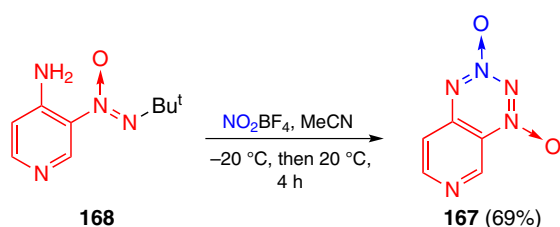
Scheme 49



Scheme 50

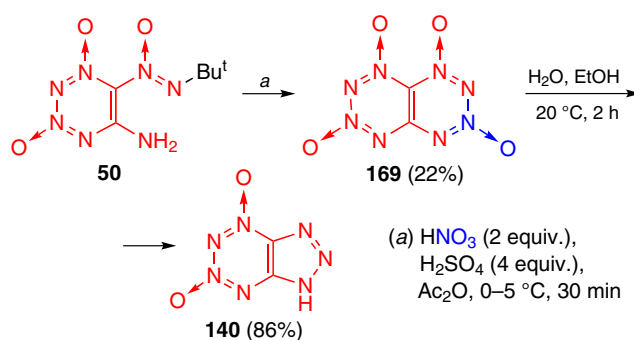


Scheme 51



Scheme 52

hydrolyzed in 50% aqueous EtOH at 20 °C in 2 h to be converted to triazolo-TDO **140**. The mechanism of hydrolysis appears to be the same as for FTDO **121** (see Scheme 38), starting with the attack by a water molecule on the N(3) atom of the tetrazine ring.



According to DSC data, for compound **169**, the decomposition onset temperature amounts to 158 °C at a heating rate of 5 °C min<sup>-1</sup> and to 165 °C at a heating rate of 10 °C min<sup>-1</sup>. The peak of the decomposition temperature is 183 °C at a heating rate of 10 °C min<sup>-1</sup>.

### 3. Theoretical methods for the study of 1,2,3,4-tetrazines

#### 3.1. Aromaticity

This chapter addresses the aromaticity of 1,2,3,4-tetrazines in comparison with the aromaticity of other six-membered rings.

The concept of aromaticity is widely used in organic chemistry.<sup>60,61</sup> By aromaticity is meant a complex multilateral phenomenon described by means of numerical ‘aromatic indices’ (related to energy, geometry, magnetic behaviour and reactivity), which determine the specific properties of a cyclic or polycyclic  $\pi$ -electronic system (see, for example, Ref. 62). Considerable attention is paid to the changes in aromaticity that take place when a CH group in an aromatic hydrocarbon is replaced by a heteroatom. For example, using magnetic [nucleus-independent chemical shifts, NICS(0) $\pi_{zz}$ ] and energetic (extra cyclic resonance energy, ECRE) criteria, it was shown<sup>63</sup> that the aromaticity of azines (pyridines, diazines, triazines, tetrazines, pentazine and hexazine) remains virtually invariable. Similar conclusions were drawn by Sánchez-Sanz,<sup>64</sup> who found that the NICS(1) and NICS(2) values for azines are close to these values for benzene. Meanwhile, the author demonstrated that NICS(0) cannot serve as a good criterion of aromaticity since at a zero distance, NICS(0) strongly depends on the number of nitrogen atoms, which is not the case for NICS(1) or NICS(2). The necessity of careful use of various types of NICS for evaluation of the azine aromaticity was also noted by Serbian scientists.<sup>65</sup> An international research team<sup>66</sup> proposed an original method for evaluation of aromaticity based on a comparison of the <sup>1</sup>H NMR chemical shifts of the methyl protons in 15,16-dimethyldihydropyrene ( $\delta = -4.25$  ppm) and its fused derivatives. The authors proceeded from the assumption that the greater the aromaticity in the fused ring, the greater the decrease in the ring currents in dihydropyrene and, consequently, the greater the downfield shifts of methyl proton signals. The researchers stated that the aromaticity of azines can be estimated at 95–100% of the benzene aromaticity.

Results of a different type were obtained by Păușescu *et al.*<sup>67</sup> Relying on energetic (aromatic stabilization energy, ASE), geometric [Bird’s index ( $I_6$ ), harmonic oscillator model of aromaticity, HOMA] and magnetic (NICS) criteria, this research group demonstrated that all N-, P- and As-substituted benzenes are aromatic, but the aromaticity decreases in the series from

N- to As-substituted compounds and with increasing number of heteroatoms in the system from one to six. It is noteworthy that the application of different criteria results in different series of aromaticity of azines. For example, according to the  $I_6$  index, the aromaticity increases in the order: 1,2,3,4-tetrazine (86) < 1,2,4,5-tetrazine (87) < pentazine (90) < 1,2,3,5-tetrazine (91) < hexazine (100). Meanwhile, HOMA predicts a different sequence: 1,2,4,5-tetrazine (0.823) < 1,2,3,5-tetrazine (0.978) < pentazine (0.993) < 1,2,3,4-tetrazine (0.995) < hexazine (0.999). It is also notable that, according to the ASE criterion, 1,2,3,4-tetrazine, pentazine and hexazine are even antiaromatic systems. Similar results were obtained by Spanish scientists,<sup>68</sup> who used, in addition to NICS(1), the total energy density at the ring critical point [RCP(H)]. According to this criterion, aromaticity increases in the order: 1,2,4,5-tetrazine (0.0094) < 1,2,3,5-tetrazine (0.0103) < 1,2,3,4-tetrazine (0.0106) < pentazine (0.0115), which does not differ much from the HOMA series. The trend towards decreasing aromaticity in azobenzenes was noted by Pakiari and Bagheri,<sup>69</sup> who proposed a new electric field gradient (EFG) method to estimate the aromaticity, and by Dey and co-workers,<sup>70,71</sup> who used the aromaticity index based on interaction coordinates (AIBIC) they developed. A decrease in the aromaticity of azabenzenes was noted by Báez-Grez *et al.*<sup>72</sup> The authors emphasized that this decrease is insignificant, and a considerable degree of aromaticity is still retained for azabenzenes.

A separate task is to elucidate the relationship between the molecular aromaticity and stability, since the presence of aromaticity does not ensure by itself a high stability of the structure, which is critical, for example, for energetic materials.<sup>73</sup> This relationship was studied in detail by Fabian and Lewars.<sup>74</sup> One goal of the authors was 'to locate the point or region between highly stable molecules like benzene and pyridine and the unstable hexaazabenzene'. For this purpose, they performed quantum chemical calculations of the thermodynamic and kinetic stability parameters and homodesmotic ring-opening energies of azabenzenes and estimated the aromaticity based on the geometric (Bird's index) and magnetic (NICS) criteria. The authors stated that, although azabenzenes are aromatic, the successive replacement of the CH groups with N atoms still results in a steady decrease in the stability, which is attributable to the electrostatic repulsion of the lone pair electrons of nitrogen and/or weakening of the C–N and N–N bonds caused by n-electron donation to the antibonding  $\sigma^*$  orbital.

Using delocalization index, Mandado *et al.*<sup>75</sup> concluded that the aromaticity of tetrazines tends to increase with increasing number of N–N bonds. However, the authors also noted that the stability seems to be determined not so much by aromaticity as by other structural factors, including intramolecular electrostatic repulsion. The idea of decreasing stability as a result of electrostatic repulsion of the lone pairs of electrons was supported by Elguero *et al.*,<sup>68</sup> who estimated system destabilization to be  $\sim 100$  kJ mol<sup>-1</sup> after the appearance of an N–N bond in the molecule. Two factors affecting the relative stability of tetrazines, namely, steric repulsion and hyperconjugation, were also considered. According to Liang *et al.*,<sup>76</sup> the latter plays a crucial role.

The effect of introduction of the N→O group on the aromaticity of azines and other *N*-heterocycles was studied in detail by Yuan *et al.*<sup>77</sup> The authors note that the appearance of the *N*-oxide group leads, most often, to a decrease in the aromaticity compared to the non-oxidized analogue. Similar results were obtained in a comparison of the properties of tetrazine **38** (see Scheme 12) and tetrazine dioxide **147** (see

Scheme 45): aromaticity was much higher for the tetrazine ring than for the tetrazine 1,3-dioxide one (in terms of the geometric and magnetic criteria).<sup>56</sup>

### 3.2. Thermal stability

Politzer and Murray<sup>78</sup> put forward several explanations for the fact why catenation<sup>§</sup> of nitrogen atoms leads to destabilization of the molecule.

1. The energy of the N–N bond is usually lower than the C–N bond energy; the formation of the N–N bond makes a positive contribution to the enthalpy of formation and increases the energy content of the molecule, which results in molecule destabilization.

2. The presence of two linked nitrogen atoms can facilitate the degradation of the compound because of the potential possibility of the release of a stable N<sub>2</sub> molecule.

3. Destabilizing interaction of the molecular orbitals (the lack of stability of higher azabenzenes and the stabilizing effect of the N→O group from the standpoint of the molecular orbital theory were considered in detail by Haas and co-workers<sup>79</sup>).

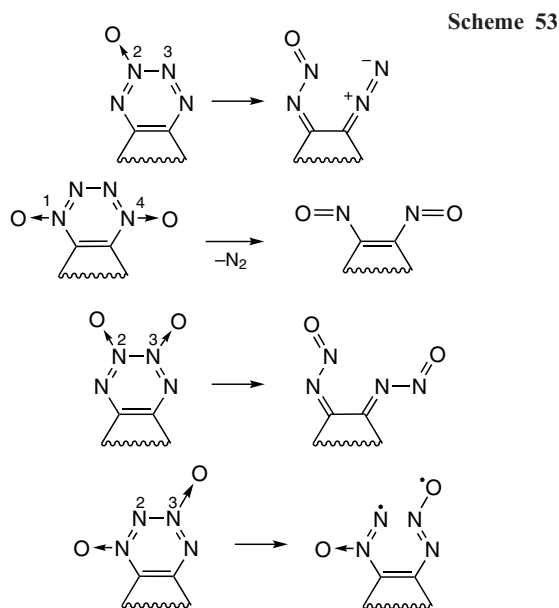
4. Repulsion between the lone pairs of electrons of the linked nitrogen atoms. In the authors' opinion, this effect is confirmed by the highly negative electrostatic potential of azines in the region of the lone pairs of double-bonded nitrogen atoms, which is indicated by the presence of a negative charge in this space. Correspondingly, a destabilizing effect appears when these negatively charged regions overlap. One of the solutions to this problem proposed by the authors is to introduce an N→O group into the molecule.<sup>80–82</sup> They assumed that this group dilutes the negative potential by spreading it over a larger area, which reduces the internal repulsion. However, note that stabilization is achieved only at a definite arrangement of N→O groups relative to each other.

The effect of the N→O group on the stability of azines and other *N*-heterocycles was discussed on the basis of analysis of chemical bonds, frontier orbitals and charge distribution.<sup>77,83</sup> The authors state that, as a rule, the introduction of this group leads to destabilization of the system, as: (i) this induces elongation and, hence, weakening of the bonds adjoining the N→O bond (this effect was also noted in another study<sup>84</sup>); (ii) the gap between the frontier orbitals decreases, which can potentially increase the photochemical activity of the molecule; (iii) ring–chain isomerization can be facilitated, as in the case of 1,2,3,4-tetrazine 1-oxides. Presumably, the hypothetical structures depicted in Scheme 53 would also be unstable.<sup>85</sup> For example, tetrazine 2-oxide would be unstable because it is subject to the ring–chain tautomerism to give diazonitrosoimine. Tetrazine 2,3-dioxide can readily undergo ring opening to give dinitrosoimine, while tetrazine 1,4-dioxide tends to eliminate an N<sub>2</sub> molecule to give thermodynamically stable dinitroso compound. Nevertheless, the authors agree with the statement that the introduction of an N→O group may stabilize the molecule under certain circumstances, *e.g.*, in 1,2,3,4-tetrazine 1,3-dioxides, in which the weakest N(2)–N(3) bond is broken with difficulty because of the formation of the energetically unfavourable azoxy radical.

The use of molecular dynamics made it possible to describe in detail the initial stage of decomposition mechanism for TTTO **169** and also reactions occurring in the condensed phase during the decomposition of this compound (see Scheme 52) under various conditions.<sup>86</sup> According to the calculations, the

<sup>§</sup> Catenation is bonding of atoms of the same element into chains.

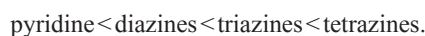




activation barrier for TTTO decomposition is higher than that for the homolytic cleavage of the N–NO<sub>2</sub> bond in RDX, HMX and hexanitrohexaazaisowurtzitane (CL-20), which suggests a high thermal stability of this compound. Degradation pathways were also discussed for superhalogens built from annulated 1,2,3,4-tetrazines.<sup>87</sup> Pyrolysis of PTDO was studied using molecular dynamics.<sup>88</sup> In the case of 1,2,3,4-tetranitro-1,2,3,4-tetrazinane and other cyclic polynitramines, the mechanism of pyrolysis was studied by calculation and analysis of bond dissociation energies (C–C, C–N and N–N bonds in the ring and the N–NO<sub>2</sub> bond).<sup>89</sup> Note that the dissociation energy of the weakest bond is often used to evaluate the thermal stability of energetic compounds.<sup>90–96</sup>

### 3.3. Reactivity

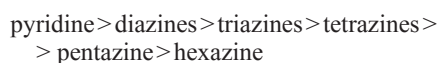
The cycloaddition reactions of ethylene to various azines, including 1,2,3,4-tetrazines, was addressed by several research groups.<sup>97,98</sup> It was noted that the reactivity of azadienes increases in the following series:



The cycloaddition was shown to be regioselective, in particular, the formation of a new C–C bond is more preferable than the formation of a C–N bond.

Alkorta and Elguero<sup>99</sup> investigated the annular tautomerism of various indazoles, including the 4,5,6,7-tetraaza derivative. As expected, the 1*H*-tautomer, *i.e.*, indazole in which a benzene-like aromatic structure was retained in the six-membered ring, proved to be most stable in most cases.

Several studies are devoted to the complexes of azines with other molecules (H<sub>2</sub>O, CO<sub>2</sub>),<sup>100,101</sup> metal ions (Li<sup>+</sup> and Mg<sup>2+</sup>)<sup>102</sup> and supramolecules (cyclophane ExBox<sup>4+</sup>).<sup>103</sup> It was shown that the strength of hydrogen bonds between azines and water decreases in the series



due to the fact that the ability of the nitrogen atom to act as a hydrogen bond acceptor decreases. 1,2,3,4-Tetrazines can form both planar (more preferable) and perpendicular complexes with CO<sub>2</sub> with a binding energy of 12.7–15.9 kJ mol<sup>-1</sup>. In the case of

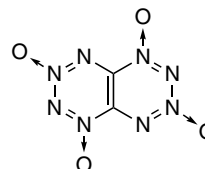
metal ions, cation–σ binding is more favourable than cation–π binding. In addition, the authors emphasize that the formation of these complexes decreases the aromaticity of the 1,2,3,4-tetrazine ring. A new approach (induced-polarization energy map) was developed for prediction of the geometry of ionic π-complexes. The potential of the method was demonstrated in relation to the complex formation of BF<sub>4</sub><sup>-</sup> with 5,6-difluoro-1,2,3,4-tetrazine and other fluorinated azines.<sup>104</sup> Host–guest type complexes containing 1,2,3,4-tetrazine as a component were studied<sup>105</sup> using an approach based on upgraded AMOEBA force field.

1,2,3,4-Tetrazines were proposed as building blocks for the construction of new systems: aromatic superhalogens.<sup>87</sup> Leszczynski and co-workers<sup>106</sup> developed a method for estimating the electron affinities and the standard reduction potentials in DMF for various *N*-heterocycles, including 1,4-dimethyl-1,4,5,6-tetrahydro-1,2,3,4-tetrazine, and the standard oxidation potentials in MeCN. Scott *et al.*<sup>107</sup> studied the adsorption of azines on carbon materials using quantum chemical methods.

### 3.4. Physicochemical properties

Del Bene *et al.*<sup>108–110</sup> published a series of studies in which they found spin–spin coupling constants through one and several bonds [ $J(\text{C}-\text{C})$ ,  $J(\text{C}-\text{N})$ ,  $J(\text{N}-\text{N})$  and  $J(\text{N}-\text{F})$ ] for various azines and fluorinated azines using quantum chemical calculations. Bagheri *et al.*<sup>111</sup> reported the results of calculations of <sup>1</sup>H NMR chemical shifts and spin–spin coupling constants [ $J(\text{N}-\text{H})$ ,  $J(\text{N}-\text{F})$ ,  $J(\text{H}-\text{F})$ ] for azine–HF complexes, where azine is pyridine, pyridazine, 1,2,3-triazine, 1,2,3,4-tetrazine, pentazine or hexazine. For iso-TTTO **170**, the <sup>13</sup>C NMR spectrum was calculated. The presence of only one signal in the spectrum was attributed to the C<sub>2h</sub> symmetry of the molecule.<sup>112</sup>

**Structure 170**



The vibrational spectra (IR, Raman) were calculated for some annulated TDOs by semiempirical and *ab initio* methods.<sup>112–115</sup> In the case of 1,2,3,4-tetranitro-1,2,3,4-tetrazinane, theoretical IR spectra were used to predict thermodynamic properties: standard molar heat capacity, entropy and enthalpy.<sup>116</sup> The rotation potential and the nonlinear optical properties of phenyl-substituted diazines and tetrazines were investigated by Alyar *et al.*<sup>117</sup> The calculations of the photoelectron spectra and vertical ionization energies for 12 azabenzenes were also reported.<sup>118</sup>

### 3.5. Energetic properties

The procedure of estimation of energetic properties of a compound usually includes several stages using quantum chemical calculations.

First, the standard enthalpy of formation of a molecule in the gas phase is calculated using various empirical, semiempirical and *ab initio* methods.<sup>119,120</sup> The methods used most often include composite methods such as Gaussian-n (Gn) and complete basis set (CBS) models or density functional theory (DFT) methods using atomization and/or isodesmic reactions (see, for example, Refs 121 and 122).

The next stage is to calculate the standard enthalpy of formation of a molecule in the condensed phase; for this purpose, it is necessary to know the enthalpy of phase transition (sublimation or evaporation). It is noteworthy that, despite the availability of a variety of approximate methods (for details, see, e.g., Ref. 119), the exact calculation of phase transition enthalpies is still a challenging task. An interesting solution providing an accuracy of  $\pm 20 \text{ kJ mol}^{-1}$  based on the electrostatic potential method (Politzer scheme<sup>123</sup>) was reported by Dorofeeva and Suntsova.<sup>124</sup> One more approach is to use a combined method proposed by Muravyev *et al.*,<sup>125</sup> which implies a high-level calculation (W2-F12 and/or W1-F12) of the enthalpy of formation of a molecule in the gas phase in combination with thermogravimetric measurement of the enthalpy of sublimation at a low external pressure (up to 0.2 Pa). Both approaches have been applied to various classes of organic compounds, including 1,2,3,4-tetrazine 1,3-dioxides.

The third stage implies the calculation of the compound density, which is performed using two main approaches: method of molecular volumes<sup>126</sup> and the method proposed by Ammon.<sup>127</sup>

The final stage is to predict the energetic properties, particularly, to calculate the detonation parameters using dedicated software programs, for example, BKW,<sup>128</sup> EXPLO5 (Ref. 129), CHEETAH<sup>130</sup> and their later versions. Note that the validity and correctness of the data obtained with these programs is a debated issue.<sup>131</sup> Other important characteristics of energetic materials are thermal stability (see above) and impact sensitivity. For estimation of the latter, a method has been developed under the assumption that the impact sensitivity is correlated with the free space in the crystal lattice of the compound.<sup>132–134</sup>

A number of energetic compounds based on annulated 1,2,3,4-tetrazine and 1,2,3,4-tetrazine 1,3-dioxide have been proposed,<sup>90,91,135–137</sup> and the enthalpy of formation, density and detonation characteristics have been calculated for them. As substituents, the authors used commonly known explosives groups such as  $\text{NO}_2$ ,  $\text{NF}_2$ ,  $\text{ONO}_2$ ,  $\text{C}(\text{NO}_2)_3$  and polynitrogen heterocycles.

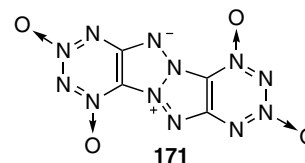
Among polycyclic systems, primary attention was paid to 1,2,3,4-tetrazines and 1,2,3,4-tetrazine 1,3-dioxides fused to five-membered rings, including furazan,<sup>138–141</sup> furoxan,<sup>140,142,143</sup> pyrazole,<sup>144,145</sup> imidazole,<sup>146</sup> oxazole,<sup>146</sup> 1,2,3- and 1,2,4-triazole,<sup>145,147,148</sup> and their *N*-oxides. Among tetrazines fused to six-membered rings, fused dinitrobenzene,<sup>39</sup> pyridine,<sup>149</sup> pyrazine<sup>93,113,150,151</sup> and piperazine<sup>92,93</sup> derivatives have been studied. Benzenes fused to two<sup>152</sup> or three tetrazine 1,3-dioxide rings<sup>153</sup> have been addressed. As a rule, the calculated energetic characteristics of 1,2,3,4-tetrazines and 1,2,3,4-tetrazine 1,3-dioxides fused to five- and six-membered heterocycles are similar to or exceed those of conventional energetic compounds, which allows experts to consider such derivatives to be a promising class of explosives. In most cases, these compounds have high density ( $d \geq 1.8 \text{ g cm}^{-3}$ ), a good oxygen balance, high positive enthalpy of formation ( $\Delta H_f \geq 500 \text{ kJ mol}^{-1}$ ), detonation velocity  $D$  of  $\geq 9 \text{ km s}^{-1}$  and acceptable impact sensitivity and thermal stability. Some representatives of this class are unique compounds, e.g., isomers of a bicyclic system containing two 1,2,3,4-tetrazine 1,3-dioxide rings, TTTO **169** (see Scheme 52) and iso-TTTO **170** (see above), which were proposed for the first time in 1999 by Churakov and co-workers.<sup>154</sup>

Later, characteristics of compounds **169** and **170** were calculated by a few research groups, who predicted excellent energetic properties ( $\Delta H_f = 850\text{--}990 \text{ kJ mol}^{-1}$ ,  $D \approx 9.7\text{--}10.9 \text{ km s}^{-1}$ , heat of explosion of  $\sim 2000 \text{ cal g}^{-1}$  and the detonation pressure of  $\sim 43\text{--}60 \text{ GPa}$ ) and impact sensitivity

comparable with that of 1,3,5,7-tetranitro-1,3,5,7-tetraazacyclooctane (HMX).<sup>86,112,140,149,153,155–161</sup> The wide scatter of the results is also due to the difficulty of calculating the crystal lattice and density for these compounds, which ranged from 1.9 to  $2.45 \text{ g cm}^{-3}$  depending on the basic method used.<sup>126,127</sup>

One more outstanding compound is TDO **171**, which represents a 1,3a,4,6a-tetraazapentalene system fused to two 1,2,3,4-tetrazine 1,3-dioxide rings. According to calculations, this compound has record-high density and detonation parameters ( $d = 2.047 \text{ g cm}^{-3}$ ,  $\Delta H_f = 1479.9 \text{ kJ mol}^{-1}$ ,  $D = 10.387 \text{ km s}^{-1}$ , and detonation pressure of 57.42 GPa) and low impact sensitivity together with high thermal stability.<sup>150,153</sup>

Structure 171



## 4. Experimental methods for the study of 1,2,3,4-tetrazines

### 4.1. X-ray diffraction studies

Over the last 15 years, X-ray diffraction data were reported for the following structural types of 1,2,3,4-tetrazines.<sup>4</sup>

**Non-annulated 1,2,3,4-tetrazine 1,3-dioxides.** Dimethyl-1,2,3,4-tetrazine-5,6-dicarboxylate 1,3-dioxide (**60**) has two crystallographically independent molecules in a unit cell. The tetrazine 1,3-dioxide ring is virtually planar and the N–N bond lengths are nearly equal, which attests to effective conjugation.<sup>37</sup>

Unlike TDO **60**, methyl 5-(1,1-dichloro-2-methoxy-2-oxoethyl)-1,2,3,4-tetrazine-6-dicarboxylate 1,3-dioxide (**61**) contains a 1,2,3,4-tetrazine 1,3-dioxide ring in the boat conformation in which the N(3) and C(6) atoms are outside the plane of the ring, which is apparently due to the steric repulsion of bulky substituents in C(5) and C(6) positions.

6-(*tert*-Butyl-*NNO*-azoxy)-5-methylthio-1,2,3,4-tetrazine 1,3-dioxide (**44a**) exists as four crystallographically independent molecules in a unit cell.<sup>32</sup>

5-Amino-6-(*tert*-butyl-*NNO*-azoxy)-1,2,3,4-tetrazine 1,3-dioxide (**50**) has two crystallographically independent molecules in a unit cell.<sup>33</sup>

**Annulated 1,2,3,4-tetrazine 1,3-dioxides.** Among compounds of this structural type, the following were studied by X-ray diffraction: 2-methyl-2*H*-[1,2,3]triazolo[4,5-*e*][1,2,3,4]-tetrazine 4,6-dioxide (**130a**),<sup>164</sup> 1-*tert*-butyl-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,3,4]tetrazine 3,4,6-trioxide (**139**),<sup>52</sup> 2-methyl-2*H*-[1,2,3]triazolo[4,5-*e*][1,2,3,4]tetrazine 1,5,7-trioxide (**131a**),<sup>28</sup> 1-phenyl-1*H*-[1,2,3]triazolo[4,5-*e*]-[1,2,3,4]tetrazine 4,6-dioxide (**146a**)<sup>56</sup> and 2-phenyl-2*H*-[1,2,3]-triazolo[4,5-*e*]-[1,2,3,4]tetrazine 4,6-dioxide (**147**).<sup>56</sup>

1,2,3,4-Tetrazine 1,3-dioxides **130a**, **139**, **146a** and **147** with a fused 1,2,3-triazole ring are nearly planar structures characterized by minor deviation of atoms from the mean plane. The oxygen atoms are also located in the plane of the heterocyclic system. The presence of two oxygen atoms in the TDO ring makes a weighty contribution to the bond length alternation, which can be seen when comparing the parameters of TDO **147** and tetrazine **38** containing no *N*-oxide oxygen atoms. In the

<sup>4</sup> Earlier X-ray diffraction data for tetrazine derivatives can be found in the literature.<sup>1,2,162,263</sup>

crystal packing of compounds **130a** and **139**, apart from relatively weak and apparently non-directional O...O, C-H...O and C...N contacts, there are also rather strong O... $\pi$ (N) contacts (with distances of 2.235 Å in TDO **130a** and 2.884 Å in TDO **139**) between the lone pair of electrons of oxygen and the  $\pi$ -systems of the heterocycle nitrogen atoms.

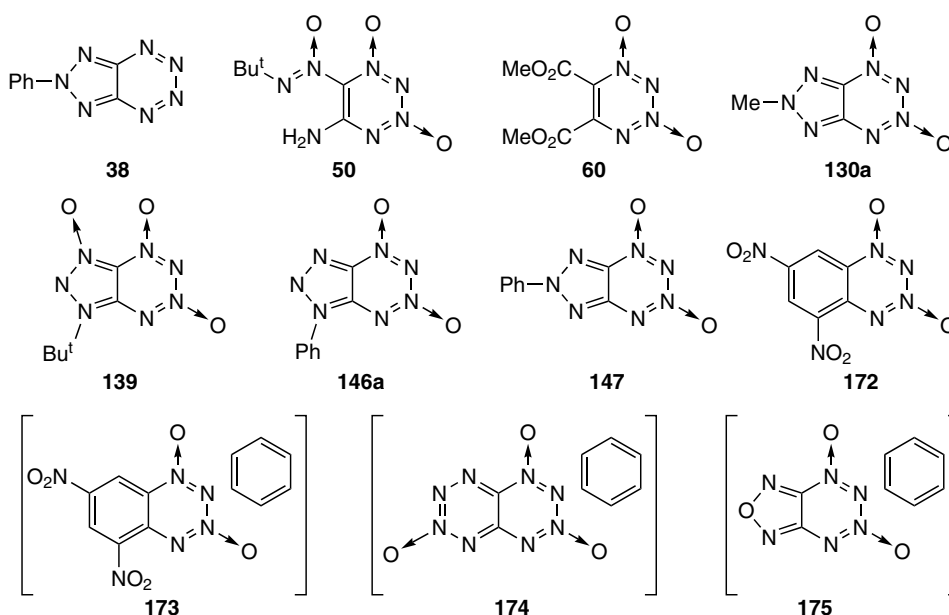
On the basis of furazanotetrazine 4,6-dioxide (**121**), a 1 : 1 solvate complex with benzene and a co-crystal with benzotrifuroxan (3 : 1) were obtained.<sup>165,166</sup>

The benzo-tetrazine system in 5,7-dibromobenzo- (**112**)<sup>83,167</sup> and 5,7-dinitrobenzo-1,2,3,4-tetrazine 1,3-dioxides (**172**) is virtually planar. Compound **172** has two crystallographically independent molecules in a unit cell, which have wave-like packing.<sup>39</sup> In the case of compound **112**, the dihedral angle between the benzene and tetrazine rings is 2°. The exocyclic oxygen and bromine atoms are located virtually in the same plane as the corresponding rings. A different situation is characteristic of dinitro-BTDO **172**, particularly the nitro group located in position 5 is actually coplanar to the bicyclic system. Meanwhile, the nitro group in position 7 is considerably rotated

(~25°) relative to the plane of the fused rings due to the steric repulsion between the nitro group oxygen atoms and the tetrazine N(1) atom. A noticeable N–N bond length alternation is observed in the tetrazine ring of compounds **112** and **172**.

Crystallization of 7-nitropyridino[2,3-*e*][1,2,3,4]tetrazine 1,3-dioxide (**166**) from benzene affords 1 : 1 solvate formed as a charge transfer complex, which splits off benzene in vacuum or on heating above 50 °C. The TDO **166** and benzene molecules in the crystal are parallel to one another, with the benzene ring being projected onto the pyridine ring. The molecule of **166** is almost planar; the bond lengths in the tetrazine ring differ only slightly from the corresponding bond lengths in benzo-tetrazine 1,3-dioxides.<sup>59</sup>

Tetrazinotetrazine 1,3,6,8-tetraoxide (**169**) crystallizes from benzene to give 1 : 1 solvate complex, which has a stack packing in the crystal. As in the case of compound **166**, solvate of TTTO **169** and benzene is a charge transfer complex, characterized by rather strong donor–acceptor interactions. The N–N bond alternation in TTTO **169** is similar to that for benzo-TDO derivatives.<sup>33</sup>



**Figure 1.** 1,2,3,4-Tetrazine derivatives studied by X-ray diffraction.

**Table 1.** Some bond lengths (Å) for 1,2,3,4-tetrazine derivatives according to X-ray diffraction data.

Compound	Bond								Ref.
	C(5)–C(6)	C(6)–N(1)	C(5)–N(4)	N(1)–N(2)	N(2)–N(3)	N(3)–N(4)	N(1)–O(1)	N(3)–O(3)	
<b>38</b>	1.383(9)	1.332(7)	1.354(8)	1.323(8)	1.388(8)	1.328(7)	–	–	168–170
<b>50</b>	1.3988(18)	1.3426(16)	1.3448(17)	1.3671(15)	1.3303(15)	1.3263(15)	1.2447(14)	1.2490(14)	33
<b>60</b>	1.3717(16)	1.3721(15)	1.3397(15)	1.3445(14)	1.3558(14)	1.3363(14)	1.2468(12)	1.2430(13)	37
<b>130a</b>	1.381(2)	1.375(2)	1.356(2)	1.3383(19)	1.4028(19)	1.315(2)	1.2404(18)	1.2414(18)	164
<b>139</b>	1.3779(17)	1.3561(18)	1.3478(17)	1.3463(17)	1.3905(16)	1.3243(16)	1.2404(15)	1.2339(15)	52
<b>146a</b>	1.380(3)	1.363(3)	1.340(3)	1.343(3)	1.385(2)	1.329(2)	1.241(2)	1.242(2)	56
<b>147</b>	1.388(3)	1.374(3)	1.363(3)	1.333(3)	1.405(3)	1.310(3)	1.244(3)	1.237(3)	56
<b>157</b>	1.383(4)	1.391(4)	1.357(3)	1.321(3)	1.382(3)	1.308(3)	1.233(3)	1.2347(3)	57
<b>172</b>	1.41567	1.40279	1.34707	1.31171	1.39686	1.32591	1.23920	1.22843	39
<b>173</b>	1.375(3)	1.388(3)	1.348(2)	1.390(2)	1.328(3)	1.350(3)	1.231(2)	1.229(2)	59
	1.375(3)	1.389(3)	1.344(3)	1.387(3)	1.325(3)	1.356(3)	1.224(2)	1.230(2)	
<b>174</b>	1.375(3)	1.388(3)	1.348(2)	1.390(2)	1.328(3)	1.350(3)	1.231(2)	1.229(2)	33
	1.375(3)	1.389(3)	1.344(3)	1.387(3)	1.325(3)	1.356(3)	1.224(2)	1.230(2)	
<b>175</b>	1.375	1.394	1.363	1.356	1.410	1.354	1.222	1.219	165

The structure of 5,11-dehydro-5*H*,11*H*-[1,2,3,4]tetrazino[5',6':4,5][1,2,3]triazolo[2,1-*a*][1,2,3]benzotriazole 1,3-dioxide (**157**) was confirmed by powder X-ray diffraction. In the crystal, these molecules are involved in various non-specific interactions such as C–H···O contacts. Although the molecule is planar, no  $\pi\cdots\pi$  stacking is present in the crystal.<sup>57</sup>

**Non-annulated dihydro- and trihydro-1,2,3,4-tetrazines.** The X-ray diffraction data for 4-(benzoyloxy)-1-(4-bromobenzyl)-6,6-dimethyl-1,6-dihydro-1,2,3,4-tetrazin-5(4*H*)-one (**10**) were reported by Xu *et al.*,<sup>14</sup> and those for diisopropyl 3-acetyl-5-phenyl-1,2,3,4-tetrazine-1,2(3*H*,6*H*)-dicarboxylate (**2**) were described by Zhao *et al.*<sup>11</sup>

**Annulated 1,2,3,4-tetrazines.** The structure of 2-phenyl-2*H*-[1,2,3]triazolo[4,5-*e*][1,2,3,4]tetrazine (**38**)<sup>168–170</sup> was discussed above.

1,2,9,10-Tetranitrodipyrzolo[1,5-*d*:5',1'-*f*][1,2,3,4]tetrazine (**32**) has four crystallographically independent molecules in a unit cell. The heterocyclic system is planar, and the nitro groups are rotated relative to the core because of the steric interactions with each other.<sup>24</sup>

The structure of 3,8-dichloro-2,9-dinitroimidazo[1,2-*d*:2',1'-*f*][1,2,3,4]tetrazine (**36**) was determined for its complex with *N,N*,4-trimethylbenzenesulfamide.<sup>25</sup>

3,8-Diazido-2,9-dinitroimidazo[1,2-*d*:2',1'-*f*][1,2,3,4]tetrazine (**37**) has four crystallographically independent molecules in a unit cell. The heterocyclic system is planar, the nitro groups are coplanar, while the azido groups are somewhat rotated relative to the plane (by  $\sim 5$  and  $7^\circ$ ).<sup>25</sup>

2,9-Dinitrobis([1,2,4]triazolo[1,5-*d*:5',1'-*f*][1,2,3,4]tetrazine (**29**) crystallizes as two polymorphs:  $\alpha$  (from toluene) and  $\beta$  (from acetone). The heterocyclic system is planar, and the nitro groups are coplanar.<sup>23</sup>

The above data can be summarized by stating that the TDO ring is planar or virtually planar in both annulated and non-annulated compounds, with moderate alternation of the endocyclic bond lengths, which attests to efficient  $\pi$ -electron delocalization. Table 1 summarizes the X-ray diffraction data for the most characteristic representatives of this class (Fig. 1).

## 4.2. NMR, IR and UV spectroscopy and mass spectrometry

The vibrational spectra of benzotetrazine 1,3-dioxides and FTDO **121** were analyzed in detail in a previous review.<sup>1</sup> In the period considered there, IR spectroscopy was mainly used to confirm the structures of new compounds.

Apart from the data reported previously,<sup>1,162</sup> UV spectra were recorded for dinitrobenzo- (Ref. 39) and tetraazapentalene-fused<sup>59</sup> TDOs, tricyclic compounds<sup>43–45</sup> and tetrazines **18**.<sup>16</sup>

Mass spectrometry was used to characterize new compounds. The fragmentation of some tetrazine 1,3-dioxide derivatives is described in detail in the previous review.<sup>1</sup>

<sup>1</sup>H, <sup>13</sup>C, <sup>14</sup>N and <sup>15</sup>N NMR spectroscopy is a routine method for determination and validation of the structures of various substituted 1,2,3,4-tetrazines. Complete signal assignment is often performed using special techniques (<sup>1</sup>H–<sup>15</sup>N, <sup>1</sup>H–<sup>13</sup>C HMBG and HSQC, INEPT).

A distinctive feature of the <sup>13</sup>C NMR spectra of 1,2,3,4-tetrazine 1,3-dioxides and 1,2,3,4-tetrazine 1-oxides is signal broadening for the carbon atom bound to the *N*-oxide group of the ring, caused, in particular, by the <sup>13</sup>C and <sup>14</sup>N spin–spin coupling. The signal of this carbon atom is observed, most often, at  $\delta = 120$ – $140$  ppm. The signal of the second carbon atom of the ring appears at  $145$ – $165$  ppm.<sup>26</sup>

The <sup>14</sup>N NMR spectra of the indicated compounds usually exhibit two relatively narrow signals for the nitrogen atoms of the TDO *N*-oxide groups, which formally bear a positive charge. Previously, complete signal assignment for the nitrogen atoms of the TDO ring was performed for benzo- and furazan-fused derivatives. It was found that in the spectra of BTDO, the signal of the N(1) atom ( $\delta = -40$  ppm,  $\Delta\nu_{1/2} = 20$  Hz) is more narrow and is located at a lower field than the signal of N(3) ( $\delta = -48$  ppm,  $\Delta\nu_{1/2} = 30$  Hz). In the case of FTDO, the signal of N(3) ( $\delta = -44$  ppm,  $\Delta\nu_{1/2} = 60$  Hz) is located in the same region as that for BTDO, whereas the narrow N(1) signal ( $\delta = -53$  ppm,  $\Delta\nu_{1/2} = 10$  Hz) is shifted upfield. The spectra of TDO fused to a pyridine ring<sup>59</sup> and non-annulated compounds are also similar to the spectrum of BTDO: the narrow signal of N(1) is located in a lower field ( $\delta \sim -40$  ppm), while the signals of N(3) are shifted upfield to  $\delta \sim -60$  ppm in the case of TDO **44a** and **52**. In the spectrum of compound **60** with two identical substituents, the signal of N(3) ( $\delta = -43$  ppm,  $\Delta\nu_{1/2} = 70$  Hz) is shifted downfield and almost coincides with the N(1) signal ( $\delta = -39$  ppm,  $\Delta\nu_{1/2} = 50$  Hz).<sup>32,33,37</sup> The spectra of triazolo- (Refs 52, 54, 56) and tetraazapentalene-fused<sup>57</sup> TDOs are similar to the spectrum of FTDO. In the spectra of these compounds, the signal of N(1) occurs at  $-50$  to  $-70$  ppm, while the signal of N(3) is located at  $\delta = -37$  to  $-43$  ppm, with the latter signal ( $\Delta\nu_{1/2} = 45$ – $120$  Hz) being usually twice as wide than the former one ( $\Delta\nu_{1/2} = 10$ – $50$  Hz). It is of interest that the spectrum of TTTO **169** ( $\delta = -39$  [N(3,6)] ppm with  $\Delta\nu_{1/2} = 32$  Hz and  $-54$  [N(1,8)] ppm with  $\Delta\nu_{1/2} = 13$  Hz) also resembles more closely the spectrum of FTDO than the spectrum of BTDO.<sup>33</sup>

The structure of tetrazines **18** containing no *N*-oxide groups was also confirmed by <sup>15</sup>N NMR spectroscopy. The signals of the N(1) atom for structures of this type are manifested at  $-140$  to  $-150$  ppm, while the signals of N(2) occur at  $-20$  to  $-30$  ppm.<sup>24,25</sup>

## 4.3. Thermal stability

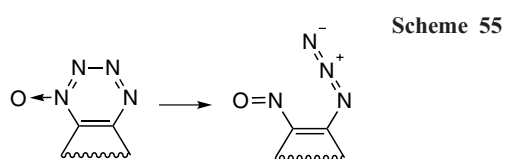
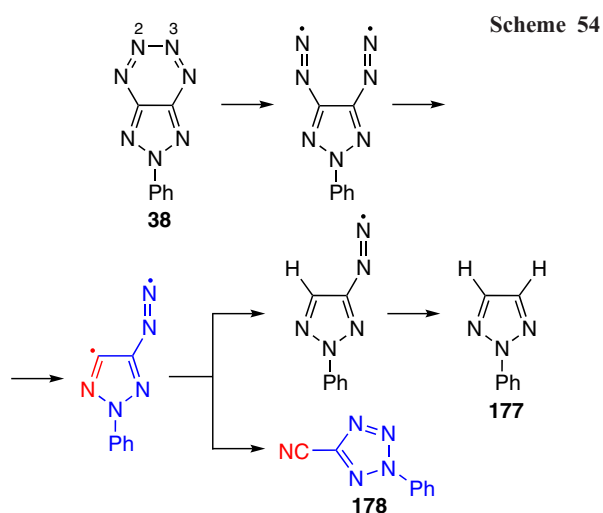
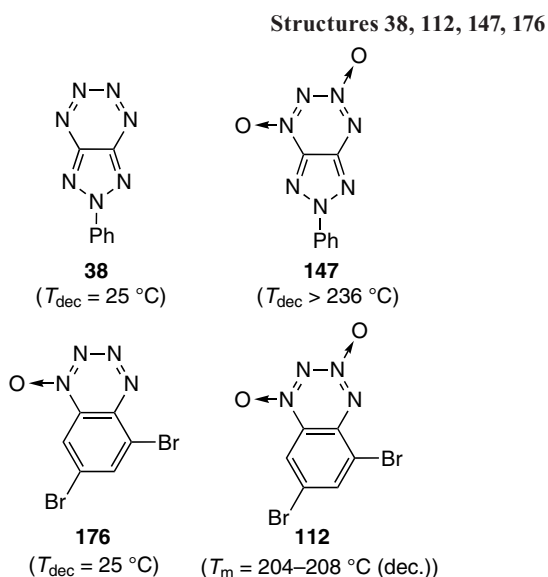
Thermal stability is a key characteristic of energetic materials determining the possibility of their practical use. Compounds with a decomposition temperature of not lower than  $130$  °C are considered to be potentially acceptable for this purpose. The structural and electronic factors that influence the thermal stability of 1,2,3,4-tetrazines and their *N*-oxides in comparison with other azabenzenes are discussed above from the theoretical standpoint (see Section 3.1). Below we consider the experimental data for the most prominent representatives of this class.

A comparison of the stability of pairs of compounds **38** and **147** or **112** and **176** clearly demonstrates the stabilizing effect of two *N*-oxide groups located in positions 1 and 3 of the tetrazine ring. Indeed, tetrazine **38** (Ref. 168) or benzotetrazine 1-oxide **176** (Ref. 1) decompose already at room temperature, unlike analogous dioxides **112** and **147**.

Presumably, decomposition of tetrazine **38** starts with the cleavage of the weakest N(2)–N(3) bond, which is followed by elimination of N<sub>2</sub> to give biradical intermediate, which can either detach hydrogen atoms from the solvent and thus afford triazole **177** or rearrange to cyanotetrazole **178** (Scheme 54).

The instability of tetrazine 1-oxide **176** is associated with easy irreversible opening of the tetrazine ring, which results in the formation of *o*-azido nitroso compounds (Scheme 55).

Non-annulated TDOs with electron-withdrawing and/or electron-donating substituents are stable compounds with decomposition temperature above  $160$  °C (see Section 2.3.3.1,



Schemes 18 and 19). Exceptions are dicyano derivative **57**, which melts with decomposition at 110–130 °C<sup>36</sup> and 5-amino-6-(nitro-*NNO*-azoxy)-TDO **52** [ $T_{\text{m}} = 110\text{--}112\text{ }^{\circ}\text{C}$  (dec.)].<sup>35</sup> In the latter case, low thermal stability may be associated with degradation of nitro-*NNO*-azoxy group rather than the proper tetrazine ring at this temperature.

Benzotetrazine dioxides **80**, **85**, **94** and **95** with a fused tetraazapentalene system (see Section 2.3.3.2.3, Schemes 28–30)<sup>43–45</sup> and F-BTDO **104** possess a high thermal stability with the decomposition temperature above 200 °C (see Section 2.3.3.2.4, Schemes 31–33).<sup>46</sup> However, F-BTDO **108** ( $T_{\text{m}} = 74\text{--}76\text{ }^{\circ}\text{C}$ ,  $T_{\text{dec}} = 90\text{ }^{\circ}\text{C}$ ) is thermally less stable than compound **104**. This is probably caused by the interaction of the furoxan ring with the *N*-oxide oxygen atom of tetrazine.<sup>47</sup> The thermal stability of anthracene type TBTTO **72a,b** and **79** is at a reasonable level: these compounds decompose without melting at 140–160 °C (see Section 2.3.3.2.2, Scheme 27).<sup>42</sup>

1,2,3-Triazolo- (**140**) and 1-hydroxy-1,2,3-triazolo-TDO (**133**) start to decompose at 150 and 182 °C, respectively.<sup>52,54</sup> The thermal stability of these *H*-forms is comparable with the thermal stability of their silver salts: Ag salt **134** starts to decompose at 197 °C, the onset of decomposition of Ag salt **143** is 182 °C.<sup>53,54</sup> Apparently, the temperature of ~150–200 °C characterizes the stability of the anions of these heterocyclic systems (Table 2).

Alkyl- and aryl-substituted triazolo-TDO **130a,c,d**, **142**, **146a,b** and **147** are ~50 °C more stable than the corresponding *H*-form **140** (Refs 52–54, 56) (see Table. 2). A similar situation is observed for derivatives **131a–c**. In the case of *O*-alkylated TDOs **135–137** and 3-substituted compounds **138**, **139**, the thermal stability is somewhat lower than that of *H*-form **133**.<sup>53</sup>

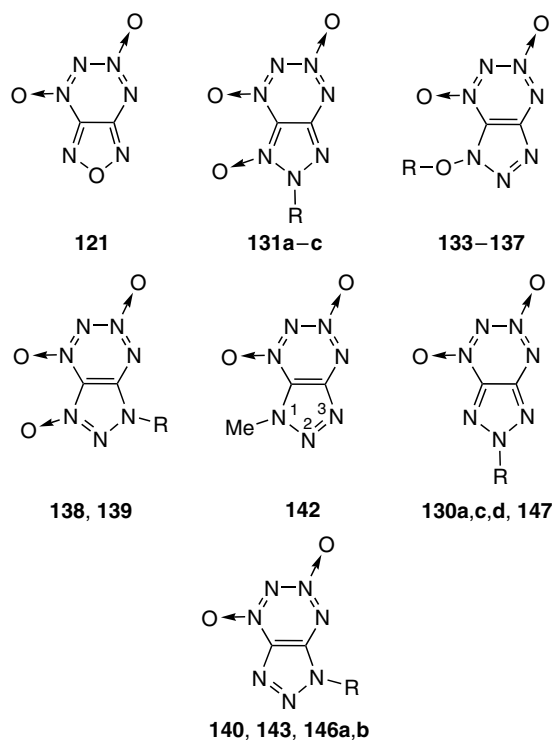
Furazanotetrazine dioxide **121** is isoelectronic to triazolo-TDO **130a–c**, **147**; however, it is much less thermally stable [ $T_{\text{m}} = 113\text{ }^{\circ}\text{C}$  (dec.)].<sup>48</sup> Nevertheless, compound **121** is considered to be a promising component of energetic materials and rocket propellants; therefore, its thermal decomposition was studied in the solid state, in a melt and in a solution in dinonyl phthalate.<sup>171,172</sup> The authors obtained a stoichiometric equation for the thermal decomposition of FTDO **121** and found kinetic and thermodynamic parameters of the process. It was noted that decomposition of this compound includes two macroscopic stages, with the second stage proceeding with self-acceleration. In the initial stage, decomposition obeys the first-order kinetics.

Tetrazine dioxides **157–160**, **162**, **163** fused to a tetraazapentalene system are similar in stability to the triazole analogues and decompose without melting (see Section 2.3.3.3.2, Schemes 48 and 49).<sup>57</sup> Dinitrobenzene derivative **162** is the most thermally stable according to DSC data (heating rate of 10 °C min<sup>-1</sup>). The temperature of the onset of decomposition of this tetraazapentalene is 234 °C. Meanwhile, its isomer **163** proved to be much less stable and started to decompose at 158 °C, which is presumably due to a change in the decomposition mechanism.

**Table 2.** Melting points and decomposition temperatures of some tetrazine dioxides (Fig. 2).

Compound	R	$T_{\text{m}}$ , °C	Ref.
<b>121</b>	–	112–113 (dec.)	48
<b>133</b>	H	180–185 (dec.)	54
<b>134</b>	Ag	>197 (see <sup>a</sup> )	53
<b>135</b>	Me	155–159 (dec.)	53
<b>136</b>	CH <sub>2</sub> Ac	136–138 (dec.)	53
<b>137</b>	CH <sub>2</sub> Bz	133–139 (dec.)	53
<b>131a</b>	Me	220–222 (dec.)	52
<b>131b</b>	Et	208–209 (dec.)	52
<b>131c</b>	Pr <sup>i</sup>	231–232 (dec.)	52
<b>138</b>	(CH <sub>2</sub> ) <sub>2</sub> Ac	158–164 (dec.)	53
<b>139</b>	Bu <sup>t</sup>	176–177 (dec.)	53
<b>142</b>	–	200–201 (dec.)	54
<b>130a</b>	Me	198–199 (dec.)	52
<b>130c</b>	Pr <sup>i</sup>	173–175, >177 (dec.)	52
<b>130d</b>	Bu <sup>t</sup>	151–152, >154 (dec.)	52
<b>147</b>	Ph	>236 (see <sup>a</sup> )	56
<b>140</b>	H	163–173 (dec.)	52
<b>143</b>	Ag	>192 see <sup>a</sup> )	54
<b>146a</b>	Ph	233–236 (dec.)	56
<b>146b</b>	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	207–208 (dec.)	56

<sup>a</sup> Temperature of the onset of decomposition without melting.



**Figure 2.** Structures of energetic 1,2,3,4-tetrazine 1,3-dioxides.

Pyrido-TDOs **165–167** are fairly stable and melt without decomposition in the 179–228 °C range (see Section 2.3.3.3.3, Schemes 50 and 51).<sup>59</sup> Compound **169** is also thermally stable, despite the hydrolytic sensitivity (see Section 2.3.3.3.4, Scheme 52).<sup>33</sup>

Among tricyclic compounds **29, 32, 36, 37**, the lowest stability was found for tetrazine **29** with two fused nitrotriazole rings [ $T_m = 138$  °C (dec.)] (see Section 2.2, Schemes 9–11).<sup>23,173</sup> Dinitropyrazole analogue **32** has a much higher stability ( $T_m = 205$  °C,  $T_{onset} > 233$  °C), which is attributable to conjugation of the system and the nature of the pyrazole ring.<sup>24</sup> Chloronitroimidazole derivative **36** is also stable ( $T_m = 215$  °C), but the replacement of the chlorine atom by an azido group induces a sharp decrease in the thermal stability of tetrazine **37**, which starts to decompose even at 111 °C.<sup>25</sup>

## 5. Applications of 1,2,3,4-tetrazine derivatives

As indicated above, in recent years, 1,2,3,4-tetrazines have been mainly proposed as promising building blocks for the design of new energetic compounds with energy characteristics surpassing characteristics of the known compounds. Primary attention was paid to the molecules in which the 1,2,3,4-tetrazine 1,3-dioxide core was modified with various explosophoric groups or heterocycles. In most cases, these studies are theoretical; their main goal is to select the most interesting compounds out of the whole array (see Section 3.1).

Among 1,2,3,4-tetrazine 1,3-dioxides for which methods of synthesis have been developed, the greatest number of studies are devoted to FTDO **121**, as this compound has been considered as a promising component of energetic materials and rocket propellants. The standard enthalpy of formation in the solid phase<sup>174</sup> and the enthalpy of sublimation<sup>114</sup> were measured for this compound. The trends of variation of the density of FTDO on long-term storage were determined by the pycnometer

method, powder X-ray diffraction and IR spectroscopy.<sup>175</sup> It was shown that the sensitivity of compound **121** to mechanical impact<sup>176,177</sup> and electric pulses<sup>178</sup> are at the level of these characteristics for initiating explosives; this restricts the practical applicability of this compound in a pure state. Meanwhile, it was found that the co-crystal of FTDO and benzotrifuroxan (1:3) has a lower mechanical sensitivity.<sup>166</sup> A number of formulations based on these compounds have been studied in detail,<sup>172,179–181</sup> with most attention being attracted by the **121–2,4-dinitro-2,4-diazapentane** system.<sup>182–187</sup> The interaction of FTDO with some organic solvents was studied.<sup>188</sup>

5,7-Dinitro-BTDO **172** was evaluated as a possible substitute for some of regularly used explosives.<sup>39</sup> The standard enthalpy of formation of this compound in the solid phase was determined experimentally. The mechanical and electrical spark of this compound proved to be at the level of those for hexogen. Specialists placed high hopes on TTTO **169**, as indicated by a large number of theoretical studies devoted to this derivative (see Section 3.1).<sup>86,189</sup> However, the applicability of this compound is restricted by its moderate hydrolytic stability.

Among the synthesized molecules with high nitrogen contents, compounds **29, 32** and **37** (see Schemes 9–11) with a fused tricyclic system incorporating a 1,2,3,4-tetrazine ring were considered as promising initiating and brisant explosives, combining high density, good thermal stability and calculated detonation characteristics comparable with those for CL-20.<sup>23</sup>

Previously, it was reported that benzotetrazine 1,3-dioxides are thiol-dependent NO donors exhibiting biological activity.<sup>1,2</sup> No recent studies on this subject are available.

## 6. Conclusion

Analysis of the literature devoted to 1,2,3,4-tetrazines shows that the interest in this class of compounds has persisted over the last 20 years. First of all, this is due to the fact that the 1,2,3,4-tetrazine core characterized by high energy content is a good base for the design of energetic compounds. In quite a few theoretical papers published recently, numerous energetic compounds based on this core have been proposed and their physicochemical and performance characteristics have been estimated. A large body of synthetic studies have been carried out and original approaches to the synthesis of new representatives of 1,2,3,4-tetrazines have been proposed. It has been shown that some of them can be considered as promising components of energetic materials and rocket propellants.

1,2,3,4-Tetrazines are also attractive objects for theoretical studies that discuss fundamental aspects of chemistry such as aromaticity of heterocycles and stability of long chains consisting of nitrogen atoms. Study of 1,2,3,4-tetrazines would make it possible to predict methods for increasing the stability of polynitrogen systems.

This review demonstrates that the chemistry of 1,2,3,4-tetrazines has a great potential for further research and is intended to stimulate the development of methods for the synthesis of hypothetical energetic compounds of this class, numerous representatives of which are described in theoretical studies.

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## 7. List of abbreviations and symbols

The following abbreviations and symbols are used in the review:

BTDO — benzo-1,2,3,4-tetrazine 1,3-dioxide(s),

*D* — detonation velocity,  
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,  
DSC — differential scanning calorimetry,  
DTA — differential thermal analysis,  
F-BTDO — 1,2,3,4-benzotetrazine 1,3-dioxide(s) fused with a furazan ring,  
FTDO — furazanotetrazine 4,6-dioxide,  
 $\Delta H_f$  — enthalpy of formation,  
LTA — lead tetraacetate,  
Nu — nucleophile,  
rt — room temperature,  
 $T_{dec}$  — decomposition onset temperature,  
 $T_m$  — melting point,  
 $T_{onset}$  — temperature of intense decomposition onset,  
TBTTO — tetrazinobenzotetrazine 1,3,7,9-tetraoxide(s),  
T-BTDO — 1,2,3,4-benzotetrazine 1,3-dioxide(s) fused with tetraazapentalenes,  
TDO — 1,2,3,4-tetrazine 1,3-dioxide(s),  
Ts — *p*-toluenesulfonyl (tosyl),  
TTTO — tetrazinotetrazine 1,3,6,8-tetraoxide.

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