9.13 Other Tetrazines and Pentazines

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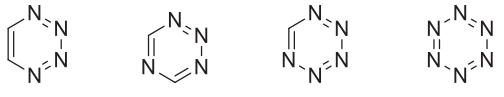
9.13.1 Introduction

This article discusses 1,2,3,4-tetrazines (**a**), 1,2,3,5-tetrazines (**b**), pentazines (**c**) and hexazine (**d**).

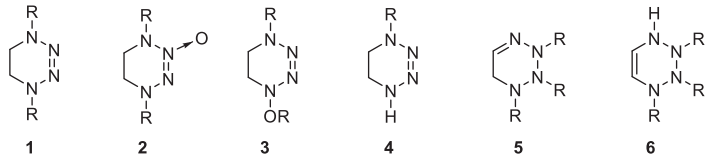


a **b** **c** **d**

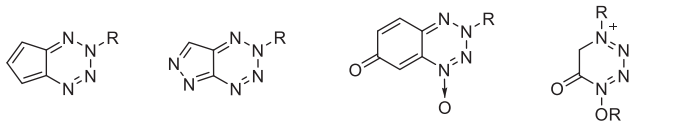
Below are listed all the currently known ring systems (**1**–**43**) with confirmed structures bearing the above rings, as well as their *N*-oxides, with the exception of systems with ring-junction nitrogen atoms. The R groups at the N atoms are carbon substituents (R = Alk, Ar, CO_2Alk, COAr etc.) (R≠H); the substituents at the carbon atoms of the rings are not shown.

The list contains partially unsaturated forms of 1,2,3,4-tetrazines with one double bond (**1**–**6**), fused and non-fused tetrazines with two double bonds (**7**–**10**, **40**, **41**), non-fused fully unsaturated tetrazines (**11**, **12**, **42**), partially and fully unsaturated carbocyclic derivatives of tetrazines (**7**, **9**, **13**–**15**), partially and fully unsaturated tetrazines annulated with heterocycles (**8**, **25**–**38**) including [1,2,3,4]tetrazino[5,6-*e*][1,2,3,4]tetrazine 1,3,6,8-tetraoxide (TTTO) **39**, fully unsaturated tricyclic ring systems (**16**, **17**, **23**, **24**) and four-ring systems (**18**–**22**, **37**, **38**).

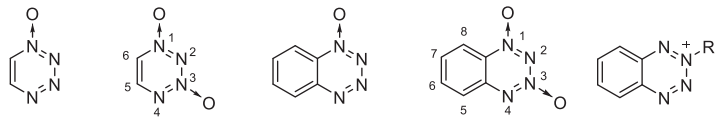
 https://doi.org/10.1016/B978-0-12-818655-8.00064-0



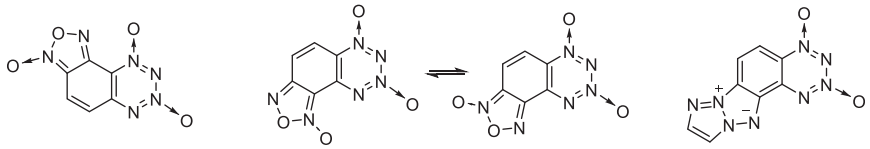
1 **2** **3** **4** **5** **6**



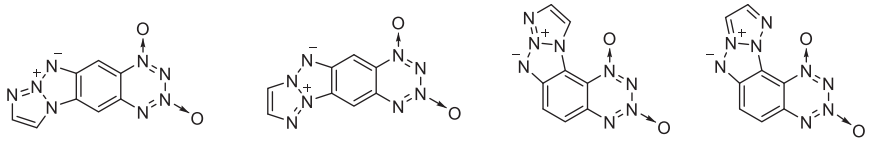
7 **8** **9** **10**



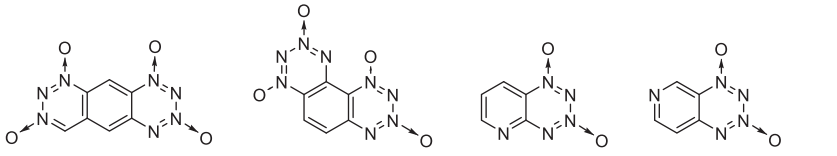
11 **12** **13** **14** **15**



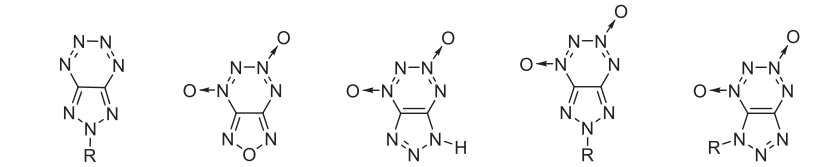
16 **17** **18**



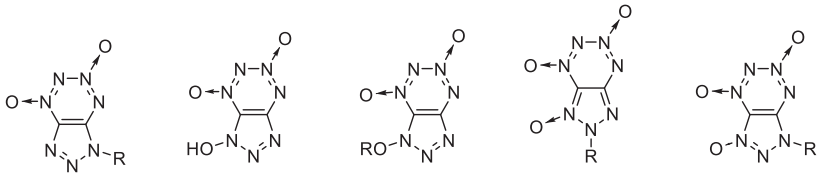
19 **20** **21** **22**



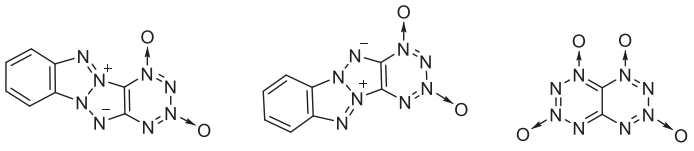
23 **24** **25** **26**



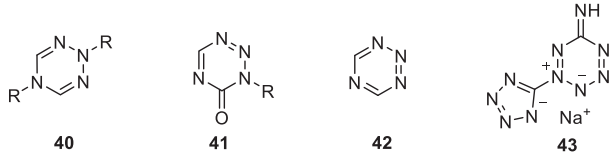
27 **28** **29** **30** **31**



32 **33** **34** **35** **36**



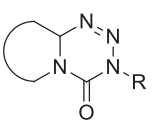
37 **38** **39**



40 **41** **42** **43**

The subjects of this article are non-heteroannulated compounds and their carbocyclic derivatives. A comprehensive description of 1,2,3,4-tetrazines fused with heterocycles, as well as tri- and four-cyclic ring systems containing tetrazine moieties, is presented in

other Chapters. However, some information about these compounds, mostly concerning structural features of these compounds compared to other 1,2,3,4-tetrazines, is given in this article. Fused systems with ring-junction nitrogen atoms (**44–46**) are not discussed in this article.



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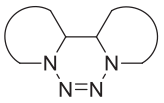

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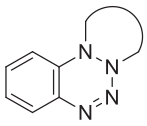

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1,2,3,4-Tetrazines, 1,2,3,5-tetrazines, pentazines and hexazine were previously reviewed in CHEC-I(1984), CHEC-II(1996) and CHEC-III(2008)[1–3] and in review.[4] The present article updates prior works and reviews the literature since 2008, with a focus on the most significant advances in reactivity, synthesis and application. During this period, a number of new structural types of tetrazines have been described, including non-annulated systems **3**, **4**, **11**, **12**, bicyclic 6-5 systems **29–36**, bicyclic 6-6 system **39**, tricyclic systems **16** and **17**, and tetracyclic ring systems **18–22**, **37** and **38**.

9.13.2 Theoretical methods

9.13.2.1 Aromaticity and structure

Aromaticity is among the most useful and popular terms in organic chemistry and related fields,[5] but it is also one of the most controversial and debated issues in theoretical and computational chemistry.[6] The definition of aromaticity is enumerative in nature, i.e., it is described by a collection of physicochemical properties determining specific features of a cyclic or polycyclic π-electron molecule. The criteria of aromaticity are based on energy (increased stability), molecular geometry (very low alternation of bond lengths), magnetism (induction of diatropic ring current by external magnetic field) and reactivity (tendency to preserve the π-electron structure in chemical reactions). These criteria, that can be represented as numbers are termed "aromaticity indices."

There are a number of papers dealing with the question: to what degree are various indices of aromaticity or other molecular characteristics interrelated? The conclusion of those papers is that aromaticity is a multidimensional phenomenon. Aromaticity indices do not necessarily refer to the same aspects of aromaticity, in other words, aromaticity indices do not always "speak in the same voice."

Qualitatively, heterocycles with six-membered rings were considered as modified benzenes where a CH moiety is replaced by a heteroatom. And one of the most exciting issues in this case is: does the aromaticity of benzene change as N atoms replace the CH groups sequentially?

Matito et al.[6] introduced a series of 15 aromaticity tests that can be used to analyze the advantages and drawbacks of a group of aromaticity descriptors (PDI, $FLU^{½}$, MCI, I_{NB}, I_{ring}, I_{NG}, HOMA, NICS(0), NICS(1), $NICS(1)_{zz}$). It was shown for benzene, pyridine, diazines, and triazine that these indices showed dissimilar orders of aromaticity. Furthermore, none of these indices followed the aromaticity order found by calculation of REs: benzene > pyridine > pyridazine > pyrimidine > pyrazine > s-triazine.[6,7] Hexazine (N_6) was used as a "laboratory rat" to analyze the ability of a given index to account for the change in the size of the atoms forming the aromatic ring. The authors relying on Sakai's work[8] expected a reduction in aromaticity for the chair-like nonplanar optimized N_6 structure compared to benzene. In general, most indices indicate a slight loss of aromaticity on passage from benzene to fully optimized N_6 species. Only the PDI, NICS(1), and NICS(1)zz indices fail to account for this aromaticity order. The NICS errors were not clearly explained. As to the PDI, its error was attributed to both the chair-like structure of N_6 and the atom size dependence of this index.

Li et al.[9] presented "refined evidence" based on magnetic ($NICS(0)\pi zz$) and energetic criteria (extra cyclic resonance energy (ECRE) based on the block localized wave function) to document the essential invariance of aromaticity along the entire azine series (pyridine, diazines, triazines, tetrazines, pentazine and hexazine). The $NICS(0)\pi zz$ index showed almost no change in aromaticity from benzene (−36.1 ppm) through all the azines (−35.6 ± 1.8 ppm). The ECRE azine data (30 ± 2.8 kcal mol^{-1}) remained close for the entire set from benzene to hexazine and confirmed the general $NICS(0)\pi zz$ conclusions.

Raczyńska[10] noticed that the results reported in the literature not always confirm the strong aromatic character of N_6. The author assumed the discrepancies of the literature data to be a consequence of different geometries of N_6 and different criteria of aromaticity employed in quantum-chemical calculations. To avoid discrepancies in geometrical parameters of N_6, its structure was re-examined using various quantum-chemical methods (HF, MP2, DFT) and various basis sets [6-31G(d), 6-31+G(d), and 6-311+G(d,p)]. All possible conformations were considered to find the minima for the cyclic N_6 structure. The aromaticity of cyclic N_6 was measured using the harmonic oscillator model of electron delocalization (HOMED) index and compared to that of benzene. Also, the effect of monoprotonation on π-electron delocalization was studied at the same levels of theory and compared to that of benzene. The HOMED indices for N_6 and N_6H^+ are close to unity, therefore the aromaticity of hexazine N_6 is similar to that of benzene. Quantum-chemical calculations showed that protonation of N_6 does not change π-electron delocalization in the ring because π-electrons of the ring are not involved in the formation of the NH bond. The proton affinity of N_6 seems to be considerably lower than that of benzene.

Medeleanu et al.[11] as well as Sánchez-Sanz[12] theoretically studied at the B3LYP/6-311+G(d,p) level of theory the structural and aromatic properties of benzene and naphthalene derivatives where one or more –CH = groups is replaced with a nitrogen, phosphorous or arsenic atom. Păuşescu et al. investigated the aromaticity by means of geometric (Bird (I_6), HOMA indices), energetic (aromatic stabilization energy [ASE]) and magnetic criteria (NICS index). Based on these criteria, it was concluded that all hetero-benzenes exhibit an aromatic character, which generally decreases from N- to As-containing compounds and from one to six substituted CH groups. According to I_6, aromaticity increases in the series: 1,2,3,4-tetrazine (86) < 1,2,4,5-tetrazine (87) < pentazine (90) < 1,-2,3,5-tetrazine (91) < hexazine (100). In the case of HOMA, the order is different: 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). According to the calculated ASE values, 1,2,3,4-tetrazine, pentazine, and hexazine are antiaromatic compounds (ASE is strongly negative), 1,2,4,5-tetrazine is a nonaromatic compound (ASE has a small positive value close to zero), and 1,2,3,5-tetrazine is an aromatic compound (ASE is strongly positive). The para delocalization index (PDI) and multicenter delocalization index (MCI) were also employed to estimate the aromatic character of the test compounds. According to the calculated values of PDI and MCI the tetrazines, pentazine and hexazine are more aromatic compounds than benzene. This conclusion contradicts the results of previous studies.

Sánchez-Sanz[12] investigated the aromaticity by means of magnetic criteria. However, the author computed not merely NICS (0), (1), (2) values but also profiles and isosurfaces. In general, NICS(1) and (2) values are close to those of benzene showing the aromatic behavior of the studied compounds. It was found that initial NICS values highly depend on the number of N substitutions. Furthermore, the author showed the effect of the proximity of nuclei on NICS values and proved the statement that NICS(0) values do not provide reliable measures of aromaticity. 3D NICS isosurfaces provided a 3D spatial view of the aromaticity of the compounds studied, confirming the results on NICS values and profiles and being particularly useful in the cases of twisted structures.

Elguero et al.[13] theoretically studied, at the B3LYP/6-311++G(d,p) level, 92 derivatives of benzene where CH groups were replaced with N and P atoms (all the combinations). Analysis of the different isomers leads to the conclusions that the N-N interaction destabilizes the molecules by about 100 kJ mol^{-1}, which is explained by the repulsion of electron pairs of the neighboring nitrogen atoms. RCP(H) indices (in a.u.) – the total energy density at the ring critical point – were employed to estimate the aromatic character of the test compounds. According to RCP(H), aromaticity increases in the series: 1,2,4,5-tetrazine (0.0094) < 1,2,3,5-tetrazine (0.0103) < 1,2,3,4-tetrazine (0.0106) < pentazine (0.0115). The authors noticed that magnetic and energetic aromaticity criteria were almost orthogonal while NICS(1) and RCP(H) were not congruent.

Pakiari and Bagheri[14] introduced a new electric field gradient(EFG) method which was employed to study the aromaticity of 89 cyclic compounds such as substituted benzenes, heterocyclic and polycyclic compounds. The EFG procedure for aromaticity evaluation is as follows (for benzene as an example):

$$\triangle EFG^{(0.5)} = 6 \times EFG^{(0.5)}_{benzene} - 6 \times EFG^{(0.5)}_{ethane} - 3 \times \left(EFG^{(0.5)}_{ethylene} - EFG^{(0.5)}_{ethane}\right)$$

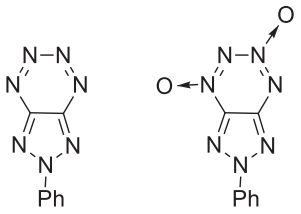
$EFG^{(0.5)}$ is the EFG value measured at 0.5 Å above the bond. By analogy, the authors calculated $\triangle EFG^{(0)}$. To evaluate the aromaticity of heterocyclic compounds, the $EFG^{(0.5)}$ or $EFG^{(0)}$ of $H_2N—NH_2$, HN═NH, $H_2N—CH_3$ and HN═CH_2 should be used. The ΔEFG(0.5) value is negative for antiaromatic compounds and positive for aromatic ones. The authors assert the flexibility and simplicity of EFG to make this method rather an easy procedure for aromaticity assessment. It was used to assess the aromaticity of the tetrazines, pentazine and hexazine. The general trend for *N*-substituted benzenes is: the aromaticity decreases as the number of N atoms increases. The results were compared to those of NICS(0) and NICS(1) and rather a good agreement was shown.

A group of scientists suggested[15] an aromaticity index based on interaction coordinates corrected (AIBICC). AIBICC is a modified version of aromaticity index based on interaction coordinates (AIBIC) introduced[16] by the same authors earlier. AIBIC worked well for aromatic hydrocarbons, but in the case of heterocyclic systems it overestimated the aromaticity indicating many of them to be more aromatic than benzene. The authors explained this as follows: "The electron density of a heterocyclic aromatic fragment is partially localized near the more electronegative atom(s) of the ring. This reduces the delocalization, and hence the heterocylic systems are expected to be less aromatic than the analogous carbocyclic systems. This reduction in the delocalized electron density is not included in AIBIC. Therefore, a correction based on Pauling's electronegativity equation has been introduced to the AIBIC methodology." Interaction coordinates (ICs) are defined as $IC = (i)_k = C_{ik}/C_{kk}$ where i and k are the internal coordinates and the compliance constants. The IC is a measure of how the coordinate i (bond or angle) responds (length and angle changes) for constrained optimization when the coordinate k (bond or angle) is stretched by one unit. This also measures the electron density associated with the coordinate k. The sum of the ICs is a measure of the delocalized electron density associated with the aromatic ring of the fictitious aromatic fragment. The AIBICC values have been computed for azabenzenes including tetrazines and pentazine. AIBICC predicts the contiguous nitrogen containing azines to be more aromatic than the corresponding non-contiguous nitrogen containing ones, i.e., for the tetrazines aromaticity decrease in the series: 1,2,3,4-tetrazine >1,2,3,5-tetrazine >1,2,4,5-tetrazine. Pentazine has a value closer to pyridine because the symmetry is similar (one atom in the ring is different). The authors assume the aromaticity trends to be generally in line with the expectations based on chemical intuition.

9.13.2.2 Stability

Aromaticity does not guarantee the stability of a molecule. The experimental difference in the thermal stabilities of tetrazine **47** and tetrazine dioxide **48** is an illustrative example of this phenomenon. Despite the fact that the aromaticity of the tetrazine ring is

significantly higher than that of the tetrazine 1,3-dioxide ring (according to geometric and magnetic criteria), the thermal stability of compound **48** (decomposes at temperatures above 200 °C) is much higher than that of compound **47** (slowly decomposes at room temperatures).[17]



47 **48**

Haas et al.[18] studied the factors affecting the stability of N_x compounds and their oxygen derivatives by considering their electronic structure. In contrast to $(CH)_x$ compounds, the major role is played by the antibonding orbitals formed by the σ orbitals of the nitrogen atoms analogous to the nonbonding MO of ammonia. These "nonbonding" MOs are high-lying and can interact with π MOs of similar energy. The interaction induced by out-of-plane vibrations can lead to non-planar molecules with reduced stability. Calculations indicate that in neutral cyclo-N_6, the HOMO is a σ orbital and the LUMO is a π^* orbital; strong interaction between the two leads to weak bonding and easily breakable bonds. The neutral cyclo-N_6 is a second-order Jahn-Teller system that is spontaneously distorted to a nonplanar structure, making it highly reactive, for instance, by having a small barrier to dissociation. It is suggested that to achieve stability, N_x systems should be constructed so as to minimize the mixing between π and σ electrons, which is only possible if the system is planar. One of the ways of inducing σ-π separation is to localize the "nonbonding" σ electrons by attaching oxygen atoms or other electron-attracting agents to them. It reduces electrostatic repulsion and results in the separation of the σ and π systems. The authors also made a bond order analysis which showed the N—N bonds in cyclo-N_6O_3 to be single and the π-electron contribution to their bonding to be minimal. In contrast, the N—O bond in these molecules is essentially a double bond. It is concluded that N_6O_3 is neither aromatic nor antiaromatic; it does not possess a conjugate π system. Also bond lengths are not a useful measure of the nature of bonding in these N_xO_y molecules and other means of characterizing the bonding stability are required.

Politzer and Murray[19] discussed nitrogen catenation involving at least three linked nitrogen atoms specifically in five- and six-membered heterocyclic rings. The authors also considered the relationship between nitrogen content and stability. It was shown that replacing CH units by nitrogen atoms in the molecular frameworks of polyazoles and polyazines has a destabilizing effect. Several reasons have been suggested to help explain why nitrogen catenation reduces molecular stability:

1. N—N bond energies (single, double, or intermediate) are usually weaker than those of the corresponding C—N. Their formation increases the positive contribution to $\triangle H_f$ and the energy content of the molecule and thus destabilizes it.
2. The presence of two linked doubly coordinated nitrogens may facilitate decomposition through the formation of the very stable N_2 molecule.
3. Repulsion between the lone pairs of adjacent doubly coordinated nitrogens.
4. Interactions between certain molecular orbitals that make destabilizing contributions.

The authors offered a useful tool, the electrostatic potential, which sheds light on the relative stabilities of polyazoles and polyazines. The electrostatic potential is a real physical property of any system of nuclei and electrons, which directly reflects the distribution of the positive and negative charges (protons and electrons) within the system. It can be determined experimentally by diffraction techniques as well as computationally. It was shown that there are strongly negative electrostatic potentials in the lone pair regions of the doubly coordinated nitrogens which reflect the dominance of electronic charge in these regions. The authors assume a repulsive (destabilizing) effect where such nitrogens are adjacent to each other and there is a strong overlap between the negative regions. It is consistent with lone pair repulsion, being related to the reduced stability resulting from nitrogen catenation in both polyazoles and polyazines. The introduction of appropriately positioned *N*-oxide linkages is one way to overcome the reduction in stability caused by nitrogen catenation.

This concept was discussed in other works[20–22] of these authors focusing on two computed properties, the molecular electrostatic potential and the local ionization energy. They suggested that the effect of *N*-oxide formation is to "dilute" the negative potentials associated with catenated doubly-coordinated nitrogens, spreading them over larger areas and lessening the internal repulsion. This is at least partially responsible for the stabilization of catenated polyazines. However, the possibility of stabilization depends on the number of *N*-oxides introduced into the molecule as well as their positions relative to each other. For instance, if oxygens are on adjacent nitrogens, the N(O)—N(O) bond is weakened. It was found that in nearly every case of NN(O)—N(O) or NN(O)—N(O)N combinations, the six-membered ring opened during the optimization process with breakage of the N(O)—N(O) bond. 1,2,3,4-Tetrazine 1,2,3-trioxide was the only molecule of this type in which the ring stayed intact. In 1,2,3,4-tetrazine 1,2,3,4-tetraoxide, all three N(O)—N(O) bonds were broken to release two NO molecules.

Bartošková and Friedl[23] found that electrostatic potential describes very precisely the structures of high-nitrogen *N*-heteroaromatics and their thermodynamic properties. The author assumed it may be used for the study of high-nitrogen energetic materials composed of azine and azole units.

Zhang et al.[24] theoretically studied the influence of *N*-oxide introduction on the stability of various N-rich heteroaromatics including tetrazines, pentazines and hexazine, based on the analysis of chemical bonds, frontier orbitals, aromaticity and charge distributions in these compounds. These scientists believe that the introduction of an *N*-oxide fragment mainly causes a decrease in molecular stability. The presence of this fragment induces the elongation of bonds adjacent to the N—O bond, i.e., the N—O bond enhancement or shortening is accomplished at the expense of elongation or weakening of the neighboring bonds. According to molecular orbital analysis the addition of an *N*-oxide also narrows the HOMO-LUMO gap and potentially increases the photochemical reactivity. The introduction of O-atom may result in ring-chain isomerization for N-rich systems, such as 1,2,3,4-tetrazine 1-oxide. They found that the *N*-oxide introduction reduces aromaticity as the NICS(1)zz becomes less negative. At the same time, the authors noticed that the introduction of O-atoms can occasionally enhance molecular stability, such as in 1,2,3,4-tetrazine 1,3-dioxide, by promoting σ-π separation and relieving the lone-pair repulsion among the neighboring N-atoms. As can be seen, they just agree with the conclusions of Haas et al.[18] Another reason for stabilization of 1,2,3,4-tetrazine 1,3-dioxide is the positive–negative alternating arrangement of charges which strengthens the ring and protects the structure from ring-chain isomerization.

Tan et al.[25] used cage (or ring) strain energy, suggested earlier by the same research group as a quantitative method to estimate the stability of cage-like molecules and N—N average bond energy, to estimate the stability of polynitrogen molecules such as hexazine, naphthalene-like N_{10} and their polyoxygen derivatives. It was shown that in contrast with benzene, N_6 as well as N_{10} are strained molecules. The introduction of O-atoms reduces the strain significantly for N_6 and moderately for N_{10}.

Goddard et al.[26] reported DFT molecular dynamics simulations which provided a detailed, molecular-level description of the initial decompositions and reactions of TTTO **39** in condensed phase under various conditions. The authors focused on thermal decomposition of two most stable predicted TTTO crystals, c1-$P2_12_12_1$ and *c2-Pbca*. It was shown that the initial reaction of c1-$P2_12_12_1$TTTO at lower pressure is unimolecular decomposition leading to the formation of two N_2O molecules with a barrier of 45.9 kcal mol^{-1}, while at higher pressure it is intermolecular oxygen transfer with a barrier of 40.1 kcal mol^{-1}. The decomposition reaction mechanism of *c2-Pbca*TTTO involves first combining two TTTO molecules and then releasing an N_2 molecule (barrier 48.1 kcal mol^{-1}). The authors noted that the reaction barriers found for TTTO are higher than the NO_2 dissociation barrier for RDX (39.0 kcal mol^{-1}) or HMX (39.8 kcal mol^{-1}) and the N–NO_2 homolysis reaction barrier (37.6 kcal mol^{-1}) of CL-20. Therefore, they suggested that TTTO may be a high performance explosive with higher thermal stability.

9.13.2.3 Reactivity and complexation properties

Alkorta et al.[27] carried out ab initio MP2/aug′-cc-pVTZ calculations to investigate tetrel-bonded complexes formed between CO_2 and aromatic bases: pyridine, diazines, triazines, tetrazines and pentazine. Tetrazines, as well as pentazine form either planar CO_2 complexes in which a single nitrogen atom is an electron-pair donor to the carbon of the CO_2 molecule or perpendicular complexes in which two adjacent nitrogen atoms donate electrons to CO_2, with bond formation occurring along an N—N bond. The binding energies of these complexes vary from 12.7 to 15.9 kJ mol^{-1}. As a rule, planar structures have larger binding energies than perpendicular ones. The binding energies of planar complexes also tend to increase as the distance across the tetrel bond decreases. In planar complexes, charge transfer occurs from an N lone pair to the remote in-plane π^*C–O orbital. In perpendicular complexes, charge transfer occurs from an N—N bond to the adjacent π^*O–C–O orbital of CO_2. The decrease in the bending frequency of the CO_2 molecule and in the ^{13}C chemical shielding of the C atom in CO_2 upon complex formation are larger in planar structures compared to perpendicular ones. EOM-CCSD spin-spin coupling constants ^{1t}J(N-C) for complexes with planar structures are very small but still correlate with the N-C distance across the tetrel bond.

Houk et al.[28] used density functional theory (M06-2X) to study the cycloadditions of benzene and 10 different azabenzenes, including 1,2,3,4- and 1,2,3,5-tetrazine, with ethylene dienophile. These reactions were analyzed with the distortion/interaction model. One of the aims of the study was to identify the origins of different reactivities of benzene and azabenzenes. It was shown that replacement of CH with N increases Diels-Alder reactivity of azadienes not only due to the more favorable orbital interaction but also to the smaller distortion energy. The out-of-plane bending dihedral angle distortions of these aromatic dienes make a major contribution to the distortion energy of the Diels-Alder transition states. This was attributed to the σ-aromaticity of dienes, i.e., nitrogen substitution causes electron localization and reduces σ-aromaticity.

Sastry et al.[29] employed high level ab initio and hybrid DFT methods to investigate the interaction of metal ions (Li^+ and Mg^{2+}) with N and P substituted six membered heteroaromatics including tetrazines and pentazine. The authors concluded that the N-substituted heteroaromatics show a strong preference for cation-σ binding over cation-π binding with metal ions. The metal ion interaction with N-substituted heteroaromatics leads to a decrease of their aromatic character.

Leszczynski et al.[30] developed computational protocols for the prediction of standard reduction potentials of N-heterocyclic compounds, including 1,2,3,5-tetrazine, in dimethyl formamide and their standard oxidation potentials in acetonitrile.

Scott et al.[31] investigated the adsorption of azines on selected adsorption sites of carbonaceous materials from the gas phase by quantum chemical methods at the density functional level, applying both periodic and cluster approaches with M06-2X and BLYP functionals including dispersion forces (BLYP-2D).

9.13.2.4 NMR spectroscopy

Del Bene et al. published a series of works in which ab initio EOM-CCSD calculations were performed to evaluate one-bond ^{1}J(C—C), ^{1}J(N—C), and ^{1}J(N—N) spin-spin coupling constants,[32] one-bond C—F coupling constants ^{1}J(C—F) and three-, four-, and five-bond F—F coupling constants ^{n}J(F—F),[33] and 2-, 3- and 4-bond ^{15}N—^{19}F coupling constants in azines and flouroazines.[34] Krivdin et al.[35] performed a systematic study of the accuracy factors for the computation of ^{15}N NMR chemical shifts in comparison with available experimental data in the series of 72 various substituted azines (substituents: CH_3, F, Cl, Br, NH_2, OCH_3, SCH_3, $COCH_3$, $CONH_2$, COOH, CN). It was found that the best computational scheme for azines at the DFT level is KT3/pcS-3//pc-2 (IEF-PCM). Using this protocol, ^{15}N NMR chemical shifts for substituted azines, including pentazine, were calculated.

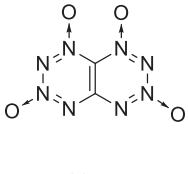
9.13.2.5 Enthalpy of formation and energetic properties

The heterocycles under consideration are nitrogen-rich scaffolds based on which modern high-energy density compounds can be constructed by chemical manipulations. Quantum-chemical calculations allow one to estimate the performance properties of compounds and select the most promising objects for their synthesis. The enthalpy of formation is required for assessing the potential performance of an energetic compound.[36] At present, the standard approach includes the calculation of the enthalpies of formation in the gas phase by various quantum chemical composite (for instance, Gaussian-n or Complete Basis Set) and DFT methods using the standard atomization reaction procedure and the isodesmic reaction method. The condensed-phase enthalpies of formation needed to investigate the thermodynamic stability and performance of energetic compounds can be determined using the gas-phase enthalpy of formation and enthalpy of phase transition (either sublimation or vaporization). Various methods exist for estimating the enthalpies of sublimation or vaporization, one of which was suggested by Suntsova and Dorofeeva.[37] They suggested the improved electrostatic potential model for estimating enthalpies of sublimation of nitrogen-rich energetic compounds, including tetrazines. The results were compared with the experimental enthalpies of sublimation for 185 compounds and the accuracy of predicted values was shown to be within $\pm$20 kJ mol^{-1}. Detonation parameters are usually calculated using special computer programs, for instance EXPLO6 computer code. Promising high-energy compounds based on the 1,2,3,4-tetrazine 1,3-dioxide and 1,2,3,5-tetrazine scaffolds have been studied intensively in the last decade. Some of these works are discussed below.

Zhu et al.[38] studied a series of non-annulated 1,2,3,4-tetrazine 1,3-dioxide derivatives with different substituents and bridging groups (–NO_2, –NF_2, –ONO_2, –$C(NO_2)_3$, –NH–, –N=N–). The calculated detonation velocities and pressures indicate that the –NO_2, –NF_2, –ONO_2, –$C(NO_2)_3$, or –NH– groups are effective structural units for enhancing the detonation performance of the derivatives. Some derivatives possess quite a good set of properties (detonation performance, thermal stability, oxygen balance, and other desirable properties) and may be considered as target compounds for the synthesis.

Among 1,2,3,4-tetrazine 1,3-dioxides annulated with five-membered cycles, furoxan-annulated compounds are of special interest. Calculations of some characteristics of isomers were performed by Xia et al.[39] It was shown that these compounds have high solid phase enthalpy of formation (~700 kJ mol^{-1}) and possess impressive explosive performance at relatively low density (1.84 g cm^{-3}): detonation velocity ~9.5 km s^{-1}, heat of detonation ~2050 cal g^{-1}, detonation pressure ~41 GPa.

According to Tan,[40] tetraazapentalene **49** is an interesting compound and a real synthetic challenge for chemists. It has not only high density (2.047 g cm^{-3}) and superior explosive performance (solid phase enthalpy of formation 1479.9 kJ mol^{-1}, detonation velocity 10.387 km s^{-1}, detonation pressure 57.42 GPa) but also low sensitivity combined with high heat stability. Besides that, Tan et al. examined structure **50** where benzene is annulated with three TDO cycles. They showed that the explosive characteristics of this compound lie between CL-20 and HMX, therefore it may be of considerable interest as a HEDM.



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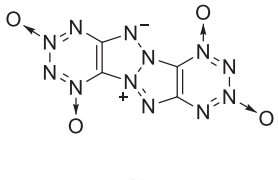

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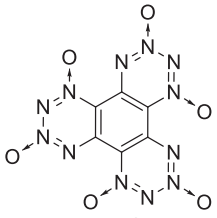

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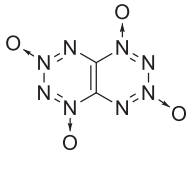

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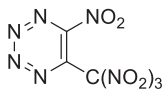

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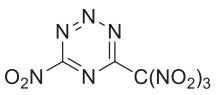


53

For a long time, TTTO **39** and iso-TTTO **51** had been the protagonists of calculations. Several groups of scientists[40–43] predicted superior explosive performance: solid phase enthalpy of formation ~850–990 kJ mol^{-1}, detonation velocity ~9.7–10.9 km s^{-1}, heat of detonation ~2000 cal g^{-1}, detonation pressure ~43–60 GPa. A wide range of energy density-dependent characteristics is a result of the fact that researchers used various methods to estimate the density of TTTO **39** and iso-TTTO **51**. Density values in

different works vary in the range from 1.9 to 2.3 g cm^{-3}. Politzer et al.[43] used the modified equation proposed by Rice et al.,[44] wherein intermolecular interactions within the crystal were taken into account via the electrostatic potentials on the molecular surfaces. Christe et al.[45] as well as Wang et al.[42] used the empirical atom/functional group volume additivity method developed by Ammon.[46]

Zhu et al.[47] used a density functional theory method to study the enthalpies of formation, electronic structures, energetic properties, and pyrolysis mechanisms of a series of trinitromethyl-substituted heterocycles, including 1,2,3,4-tetrazine and 1,2,3,5-tetrazine derivatives **52** and **53**. The calculated enthalpies of formation of these compounds are 541.87 and 448.65 kJ mol^{-1} respectively. The detonation properties of **52** are close to the properties of HMX, and those of **53** are close to RDX. Analysis of the bond dissociation energies for several relatively weak bonds suggests that the ring–NO_2 and $(NO_2)_2C—NO_2$ bond cleavage is likely to occur in the thermal decomposition of these compounds. Considering the detonation performance and thermal stability, compound **53** was regarded by the authors as a potential candidate for HEDMs.

9.13.3 Experimental structural methods

9.13.3.1 X-ray analysis

In addition to several structures of 1,2,3,4-tetrazine derivatives reviewed in previous CHEC editions,[1–3] single crystal X-ray and X-ray powder diffraction structural analyzes have become available for the following compounds:

Non-annulated 1,2,3,4-tetrazine 1,3-dioxides:

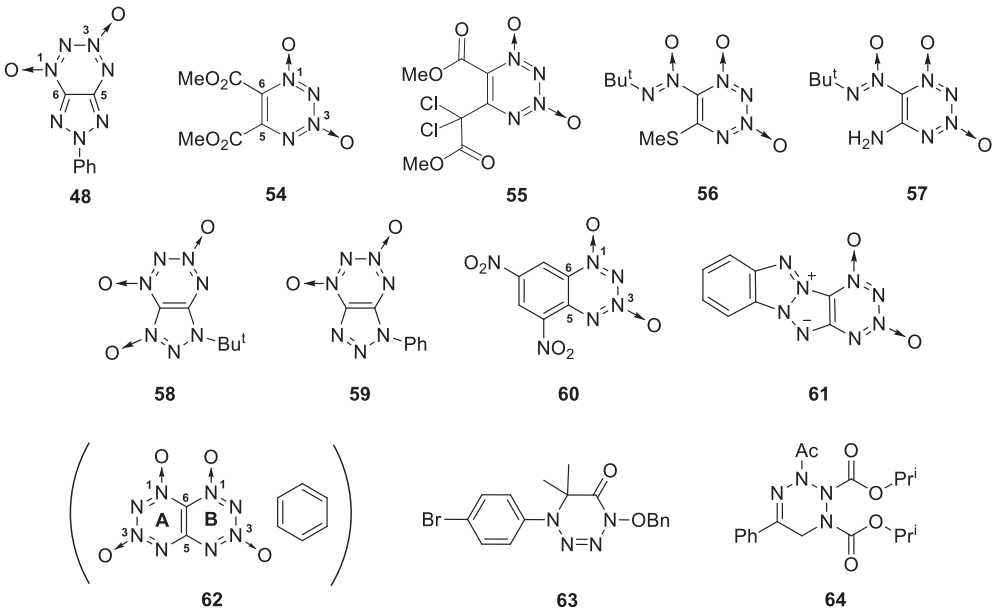
- Dimethyl 1,2,3,4-tetrazine-5,6-dicarboxylate 1,3-dioxide **54** exists as two structurally similar molecules in the independent part of the unit cell. The 1,2,3,4-tetrazine 1,3-dioxide rings are nearly planar and the N—N bonds are similar in length, indicating an effective cyclic conjugation.[48]
- Methyl 5-(1,1-dichloro-2-ethoxy-2-oxoethyl)-1,2,3,4-tetrazine-6-carboxylate 1,3-dioxide **55**. The 1,2,3,4-tetrazine 1,3-dioxide ring has a boat conformation with N(3) and C(6) atoms deviating from the ring's mean-square plane by 0.064(1) and 0.052 (1) Å. The deviation from planarity is probably a result of steric repulsion of the two bulky substituents at the C(1) and C(6) positions causing a violation of cyclic conjugation.[48]
- 6-(*tert*-Butyl-*NNO*-azoxy)-5-methylthio-1,2,3,4-tetrazine 1,3-dioxide **56** forms four polymorphs as colorless crystals.[49]
- 5-Amino-6-(*tert*-butyl-*NNO*-azoxy)-1,2,3,4-tetrazine 1,3-dioxide **57** forms two polymorphs as colorless crystals.[50]

Annulated 1,2,3,4-tetrazine 1,3-dioxides:

- 1-*tert*-Butyl-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,3,4]tetrazine 3,4,6-trioxide **58**.[51]
- 1-Phenyl-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,3,4]tetrazine 4,6-dioxide **59**.[17]
- 2-Phenyl-2*H*-[1,2,3]triazolo[4,5-*e*][1,2,3,4]tetrazine 4,6-dioxide **48**. Heterocyclic fragments in the crystals of compounds **59** and **48** are virtually planar with the r.m.s. deviation from least-squares equal to 0.023 Å in **59** and 0.012 Å in **48** Exocyclic oxygen atoms are also co-planar with the rings with a maximal deviation of 0.074 Å for O(2) in **48**. The presence of two oxygen atoms in tetrazine **48** induced slightly more pronounced bond length alternation as compared to tetrazine **47**.[52]
- 5,7-Dinitrobenzo-1,2,3,4-tetrazine 1,3-dioxide **60** forms two polymorphs and has wave-like packing.[53]
- 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 **61** (the structure was confirmed by powder X-ray diffraction). The refinement of the tetraazapentalene **61** structure against powder diffraction data implied restraints of molecular geometry, so only general peculiarities of crystal packing can be considered. In a crystal of **61**, the molecules are involved in various non-specific interactions such as C–H⋯O. Despite the planarity of the molecule, no π⋯π stacking interaction is observed in the crystal.[54]
- Tetrazino-tetrazine 1,3,6,8-tetraoxide (complex with benzene) **62**. Attempts to grow single crystals of TTTO **39** were unsuccessful and even indexing of this compound from powder was not feasible due to possible full-molecule disorder, common for such symmetric structures. However, the benzene complex **62** obtained by crystallization from benzene is ordered. The molecules of TTTO and benzene are packed into stacks with average distances between the planes of molecular rings equal to 3.242(3) and 3.244(2) Å from two sides of TTTO molecule. Such short distances imply relatively strong donor–acceptor interactions and charge transfer between the molecules. The alternation of N—N bond lengths in TTTO molecule is similar to that in benzotetrazine 1,3-dioxides unlike non-annulated tetrazine **54** where all N—N bonds are almost of the same length.[50]

Non-annulated dihydro- and trihydro-1,2,3,4-tetrazines:

- 4-(benzyloxy)-1-(4-bromobenzyl)-6,6-dimethyl-1,6-dihydro-1,2,3,4-tetrazin-5(4H)-one **63** (only crystal data given).[55]
- Diisopropyl 3-acetyl-5-phenyl-1,2,3,4-tetrazine-1,2(3H,6H)-dicarboxylate **64** (only crystal data given).[56]



48 **54** **55** **56** **57**

58 **59** **60** **61**

62 **63** **64**

9.13.3.2 NMR, IR, UV spectroscopy and mass spectrometry

A detailed analysis of the vibrational spectra of benzotetrazine 1,3-dioxide **65** and its substituted derivatives as well as furazano-annulated tetrazine 1,3-dioxide **28** was reviewed previously (Table 1).[3,4]

In addition to previous studies,[3,4] ultraviolet (UV) spectra for tetracyclic compounds of structural types **18–22**,[57–59] tetracyclic compounds of types **37**,**38**,[54] and heteroannulated non-aromatic 1,2,3,4-tetrazines of type **8** were studied.[60]

In a large majority of the reviewed studies, electron impact (EI) ionization at 70 eV and/or high-resolution mass spectrometry were used for routine characterization of the prepared compounds. Basic fragmentation patterns and routine results have been published previously.[1–3] A detailed information about the fragmentation of 1,2,3,4-tetrazine 1,3-dioxides can be found in review.[4]

^{1}H, ^{13}C, ^{14}N NMR spectroscopic methods have been used extensively for the structural confirmation of the reviewed compounds. A number of techniques were employed for assignment of signals, including ^{1}H-^{1}H, ^{1}H-^{15}N, ^{1}H-^{13}C HSQC and HMBC experiments.

A distinctive feature of the ^{13}C NMR spectra of 1,2,3,4-tetrazine 1,3-dioxide derivatives is a significant broadening of the signal from the C atom directly bonded to the *N*-oxide fragment of the 1,2,3,4-tetrazine 1,3-dioxide ring which is a result of the spin-spin coupling of the ^{13}C and ^{14}N nuclei in particular. This feature should be taken into account in the assignment of signals in the ^{13}C NMR spectra.

In the case of 1,2,3,4-tetrazine 1-oxide **140**, due to the difficulty in purification and reaction scaling, ^{1}H, ^{13}C NMR along with mass spectrometry were the only methods used to establish the structure.[61]

Table 1 Bond lengths (Å) in 1,2,3,4-tetrazine 1,3-dioxide rings for compounds **48**, **54–60, 62**.

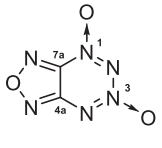
Compound	*Molecule*	*C(5)–C(6)*	*C(6)–N(1)*	*C(5)–N(4)*	*N(1)–N(2)*	*N(2)–N(3)*	*N(3)–N(4)*	*N(1)–O(1)*	*N(3)–O(3)*
48	–	1.388(3)	1.374(3)	1.363(3)	1.333(3)	1.405(3)	1.310(3)	1.244(3)	1.237(3)
54	**A**	1.3717(16)	1.3721(15)	1.3397(15)	1.3445(14)	1.3558(14)	1.3363(14)	1.2468(12)	1.2430(13)
	B	1.1972(14)	1.3691(15)	1.3401(15)	1.3461(14)	1.3507(14)	1.3391(14)	1.2412(12)	1.2442(13)
55	–	1.3911(4)	1.3688(3)	1.3252(3)	1.3542(4)	1.3452(4)	1.3457(4)	1.2367(4)	1.2260(3)
56	**A**	1.354(11)	1.351(10)	1.372(10)	1.381(9)	1.326(10)	1.354(9)	1.238(9)	1.254(9)
	B	1.394(11)	1.332(10)	1.348(10)	1.372(8)	1.346(8)	1.318(9)	1.249(8)	1.244(8)
	C	1.449(10)	1.331(9)	1.343(10)	1.366(9)	1.330(9)	1.338(8)	1.250(8)	1.244(8)
	D	1.386(11)	1.319(10)	1.334(10)	1.373(9)	1.345(9)	1.340(8)	1.262(8)	1.256(8)
57	**A**	1.3988(18)	1.3426(16)	1.3448(17)	1.3671(15)	1.3303(15)	1.3263(15)	1.2447(14)	1.2490(14)
	B	1.4089(17)	1.3399(16)	1.3461(17)	1.3658(15)	1.3380(15)	1.3256(15)	1.2529(14)	1.2416(14)
58	–	1.3779(17)	1.3561(18)	1.3478(17)	1.3463(17)	1.3905(16)	1.3243(16)	1.2404(15)	1.2339(15)
59	–	1.380(3)	1.363(3)	1.340(3)	1.343(3)	1.385(2)	1.329(2)	1.241(2)	1.242(2)
60	**A**	1.41567	1.40279	1.34707	1.31171	1.39686	1.32591	1.23920	1.22843
	B	1.42311	1.40712	1.34480	1.30637	1.39092	1.31419	1.23911	1.21706
62	Ring **A**	1.375(3)	1.388(3)	1.350(3)	1.348(2)	1.390(2)	1.328(3)	1.231(2)	1.229(2)
	Ring **B**	1.375(3)	1.389(3)	1.356(3)	1.344(3)	1.387(3)	1.325(3)	1.224(2)	1.230(2)

Table 2 Selected ^{13}C and ^{14}N NMR data of 1,2,3,4-tetrazine 1,3-dioxides **28, 39, 54, 56, 57**, **65** and **66**.

Compound (solvent)	*^{13}C NMR* δ_C, *ppm*	*^{14}N NMR* δ_N ($\Delta\nu_{1/2}$, *Hz*), *ppm*	*References*
28 (acetone-d_6)	144.4 (br., C-7a) 156.6 (C-4a)	–44 (N-3, 60) –53 (N–1,10) –106 (N-4, 300)	4
39(Ac_2O/CD_2Cl_2)	128.6 (br., C-8a), 158.6 (C-4a)	–39 (N-3 and N-6, 32) –54 (N-1 and N-8, 13) –91 (N-4 and N-5, 480)	50
54 ($CDCl_3$)	124.5 (br. C-6) 150.0 (C-5)	–39 (N-1, 50) –43 (N-3, 70)	48
56 ($CDCl_3$)	133.3 (br., C-6) 163.6 (C-5)	–42 (N-1, 40) –62 (N-3, 80)	49
57 (acetone-d_6)	127.4 (br., C-6) 154.5 (C-5)	–39 (N-1, 25) –59 (N-3, 60)	50
65 (acetone-d_6)	129.0 (br, C-8a) 144.7 (C-4a)	–22 (N-2, 400) –40 (N-1,20) –48 (N-3,30) –85 (N-4, 400)	4
66 (acetone-d_6)	137.1 (br., C-7a) 154.4 (C-4a)	–42 (N-3, 50) –50 (N-1, 20)	62

^{14}N NMR spectroscopy is especially useful for identifying positively charged nitrogen atoms in *N*-oxide fragments of tetrazine rings. Earlier, all nitrogen signals of the 1,2,3,4-tetrazine 1,3-dioxide ring in benzo- and furazano-annulated tetrazine 1,3-dioxides **65** and **28** were unambiguously assigned using various NMR techniques. Benzotetrazine 1,3-dioxide **65** shows two narrow signals in the ^{14}N NMR spectrum, where the N-1 signal ($\delta = -40$ ppm, $\Delta\nu_{1/2} = 20$ Hz) is narrower than the N-3 signal ($\delta = -48$ ppm, $\Delta\nu_{1/2} = 30$ Hz). In the case of furazano-annulated 1,3-dioxide **28**, the N-3 signal ($\delta = -44$ ppm, $\Delta\nu_{1/2} = 60$ Hz) is observed in nearly the same region, whereas the N-1 signal ($\delta = -52.7$ ppm, $\Delta\nu_{1/2} = 10$ Hz) was shifted upfield. These facts were used in the signal assignment of new non-annulated tetrazine 1,3-dioxides and compounds annulated with five and six membered heterocycles.

As one can see from Table 2, the ^{14}N spectrum of 1,2,3,4-tetrazine 1,3-dioxides in inviscid solutions (acetone-d_6 or $CDCl_3$) show rather narrow signals of N-1 and N-3 atoms, and the N-1 signal is narrower than the N-3 one. The signals of other N-atoms in the ring are broad. For example, in the case of benzotetrazine 1,3-dioxide **65**, the half width of N-2 and N-4 signals is 400 Hz.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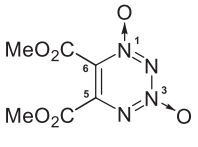
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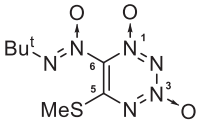
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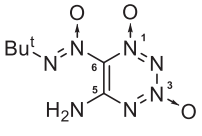
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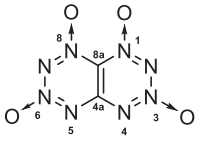
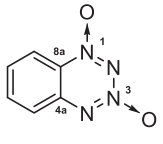

39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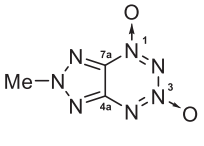

66

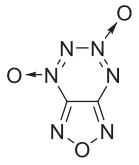
9.13.4 Thermal stability

The thermal stability of fully unsaturated 1,2,3,4-tetrazines is an important feature of this class of heterocycles. The tetrazine ring without substituents at nitrogen atoms is rather thermally unstable. For example, triazolo-annulated tetrazine **47** slowly decomposes at room temperature with release of N_2 molecules.[52] The stability of benzotetrazine 1-oxides depends on the substituents in the benzene ring. However, even the most stable ones also decompose at room temperature.[63] The first step in their decomposition involves ring opening to afford 1-azido-2-nitrosobenzenes. 1,2,3,4-Tetrazine 1,3-dioxides, both annulated and non-annulated, have enhanced thermal stability that also depends on the substituents. As a rule, benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs) of structural type **14** melt with decomposition in the range of 170–250 °C. Of the known BTDOs, the BTDO bearing two 2*H*-1,2,3-triazol-2-yl substituents at the 6- and 7-positions is most stable (mp 296 °C).[58]

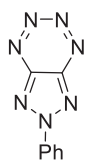
However, some BTDOs are not so thermally stable. While furoxano-annulated BTDO **67** is quite stable (mp 204 °C),[64] isomeric BTDO **68** decomposes already at 90 °C, possibly due to an intramolecular reaction of furoxan and tetrazine 1,3-dioxide rings.[65]

While furazano-1,2,3,4-tetrazine 1,3-dioxide **28** melts with decomposition at 110–112 °C,[66] demonstrating that electron withdrawing substituents reduce the stability of tetrazine 1,3-dioxide ring, the 1,2,3-triazolo-annulated compound **48** similar in structure is quite stable.[17]

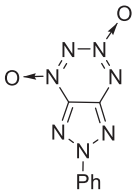
Non-annulated tetrazine 1,3-dioxide **69** with electron-withdrawing nitrile substituents decomposes at 110–130 °C.[67] Compound **54** with methoxycarbonyl substituents is more stable and decomposes at 190 °C.[48] Tetrazine 1,3-dioxide **70** with one electron-withdrawing nitro group and one electron-donating amino group is also rather stable (it decomposes at 195–200 °C).[68]



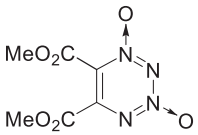
28
mp 112 °C decomp.



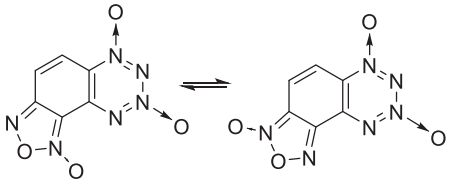
47
mp 76-77 °C decomp.



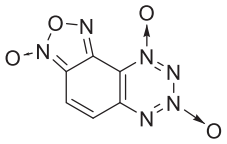
48
decomp. >200 °C



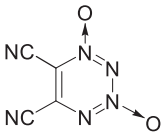
54
mp 93-96 °C, decomp. >190 °C



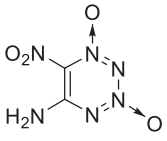
67
mp 204 °C decomp.



68
mp 72-74 °C, decomp. >90 °C



69
mp 110-130 °C decomp.

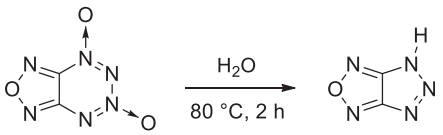


70
decomp. 195-200 °C

9.13.5 Reactivity of fully conjugated rings

9.13.5.1 Nucleophilic attack at nitrogen

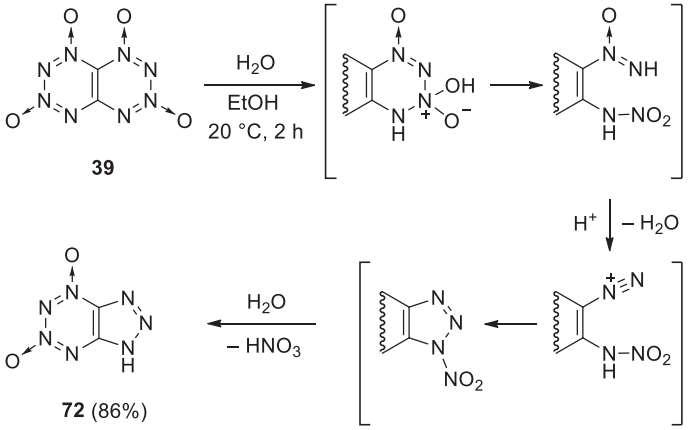
The 1,2,3,4-tetrazine 1,3-dioxide (TDO) ring annulated with a benzene ring is rather resistant to water, acids and bases. However, the situation changes if the TDO ring is annulated with strong electron withdrawing heterocycles. At room temperature, furazano-annulated TDO **28** is not hydrolyzed, but at 80 °C hydrolysis is completed in 2 h to give furazanotriazole **71** (Scheme 1).[69]



28 **71** (42%)

Scheme 1

The hydrolysis of TTTO **39** in 50% aqueous EtOH at 20 °C is completed within 2 h to give triazolo-TDO **72** (Scheme 2).[50] The plausible mechanism of hydrolysis involves an H_2O attack at the N-3 atom followed by TDO ring opening, protonation of the azoxy group and elimination of an H_2O molecule to afford a diazonium cation, which undergoes cyclization with the neighboring nitramine group to yield an *N*-nitrotriazole. Further hydrolysis of the latter gives triazolo-TDO **72**.

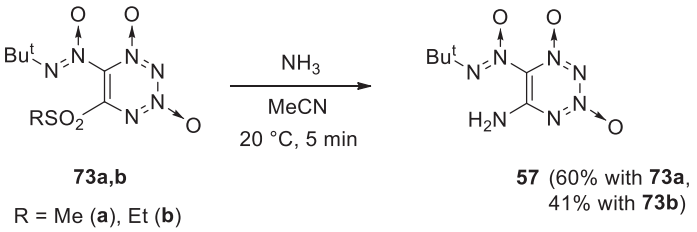


39 **72** (86%)

Scheme 2

9.13.5.2 Nucleophilic attack at carbon

Alkylsulfonyl groups at the C-5 atom of TDOs **73a,b** can be readily substituted with ammonia to give amino-substituted TDO **57** in good yields (Scheme 3).[50]



73a,b

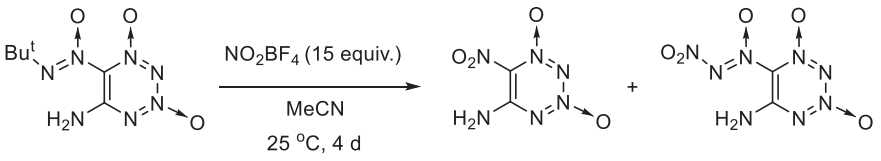
R = Me (**a**), Et (**b**)

57 (60% with **73a**, 41% with **73b**)

Scheme 3

9.13.5.3 Electrophilic attack at carbon

The reaction of amino-substituted TDO **57** with excess nitronium tetrafluoroborate afforded 5-amino-6-nitro-TDO **70** and 5-amino-6-(nitro-*NNO*-azoxy)-1,2,3,4-tetrazine 1,3-dioxide **74** (Scheme 4).[68,70] A plausible mechanism for the formation of TDO **70** involves electrophilic substitution of the (*tert*-butyl-*NNO*-azoxy) group with a nitro group. Substitutive nitration of the *tert*-butyl group in TDO **57** affords TDO **74**.



57

70 (45%)

74 (30%)

Scheme 4

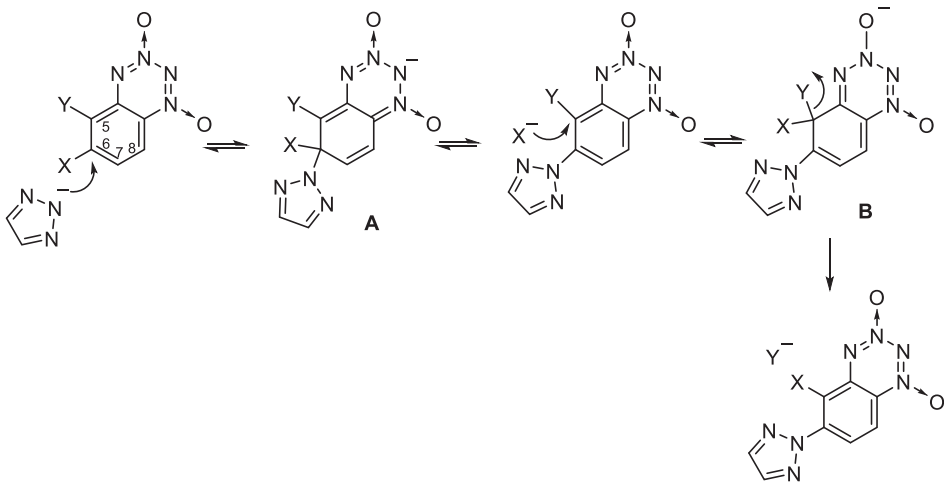
9.13.6 Reactivity of substituents attached to ring carbon atoms

9.13.6.1 Benzo-1,2,3,4-tetrazine 1,3-dioxides

Previously, it was reported that benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs) underwent electrophilic and nucleophilic aromatic substitution reactions in all positions of the benzene ring.[3,4] When BTDOs were nitrated or brominated, the reactivity of positions changed in the order $5 \approx 7 > > 8 > 6$. When bromo or nitro groups in BTDOs were replaced by nucleophiles ($MeNH_2$, NaN_3, MeOK), the opposite order of position reactivity was observed, $6 > 8 > 7 > 5$. Over the past decade, new examples of such reactions were reported and a number of new BTDOs bearing functional groups were synthesized. These substances served as starting materials for the synthesis of BTDOs annulated with tetraazapentalene and furoxan rings.

9.13.6.1.1 Unusual nucleophilic displacement with 1,2,3-triazole

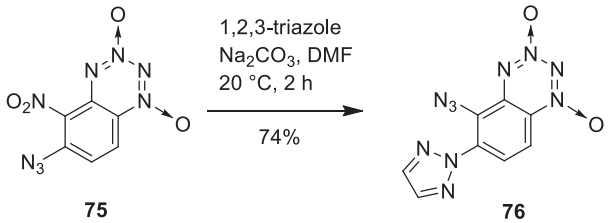
1,2,3-Triazole reacts with BTDOs bearing two adjacent nucleofuges X and Y in an unusual manner. The plausible mechanism of this reaction is shown in Scheme 5. First, the 1,2,3-triazole anion displaces the anion X^- from the more reactive position 6. Then this



Scheme 5

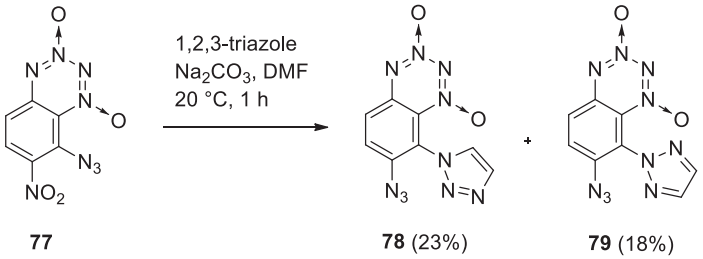
anion X^- displaces the adjacent group Y. This cascade of S_NAr reactions in which nucleofuge X turns into nucleophile X in the course of the reaction can be called a "billiard" process. It becomes possible due to the fact that the 1,2,3,4-tetrazine 1,3-dioxide ring stabilizes both Meisenheimer type anions A and B.[71] Scheme 5 shows the case where groups X and Y are in positions 5 and 6. However, these two groups can occupy positions **6** and **7** as well as **7** and **8**.

The example of the "billiard" reaction is shown in Scheme 6. 1,2,3-Triazole reacts with 6-azido-5-nitro-BTDO **75** in the presence of Na_2CO_3 to give 5-azido-6-(1,2,3-triazol-1-yl)-BTDO **76**.



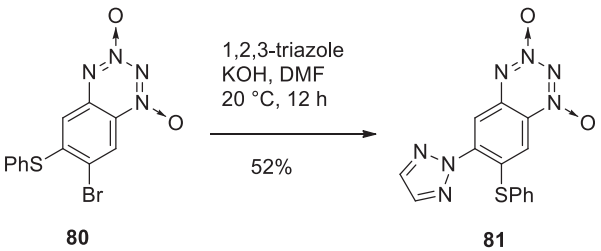
Scheme 6

A similar "billiard" process occurs in the reaction of BTDO **77** with 1,2,3-triazole in the presence of a base. The azido group moves from position 8 to position 7 during the reaction (Scheme 7). The ratio of triazol-1-yland triazol-2-yl BTDOs **78** and **79** is 1.3:1.



Scheme 7

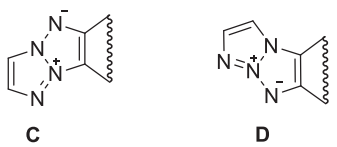
The conversion of BTDO **80** into BTDO **81** in the reaction with 1,2,3-triazole in the presence of a base (Scheme 8) is yet another example of a "billiard" process. In this case, the thiophenyl group moves from position 6 to position 7. Like the azido group in the previous examples, the thiophenyl group acts as a nucleofuge in the first stage and as a nucleophile in the second stage of the reaction.[71]



Scheme 8

9.13.6.1.2 Nucleophilic displacement as a synthetic route to benzotetrazine1,3-dioxides annulated with tetraazapentalene fragments

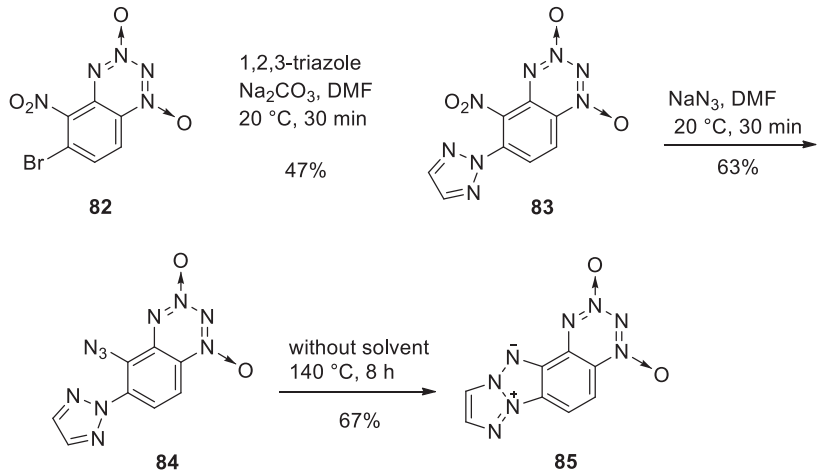
Compounds containing tetraazapentalene systems **C** (*Z*-system) or **D** (Y-system) and the 1,2,3,4-tetrazine 1,3-dioxide scaffold in a molecule might have been of interest as materials with a high heat of formation. The precursors of these compounds are BTDOs bearing an adjacent azido group and a 1,2,3-triazole ring.



BTDO **85** annulated with the *Z*-tetraazapentalene system at the C(5)–C(6) bond was prepared by the synthetic sequence outlined in Scheme 9. To obtain 5-azido-6-(triazol-2-yl)-BTDO **84**, two successive nucleophilic substitution reactions were used. First, the bromine

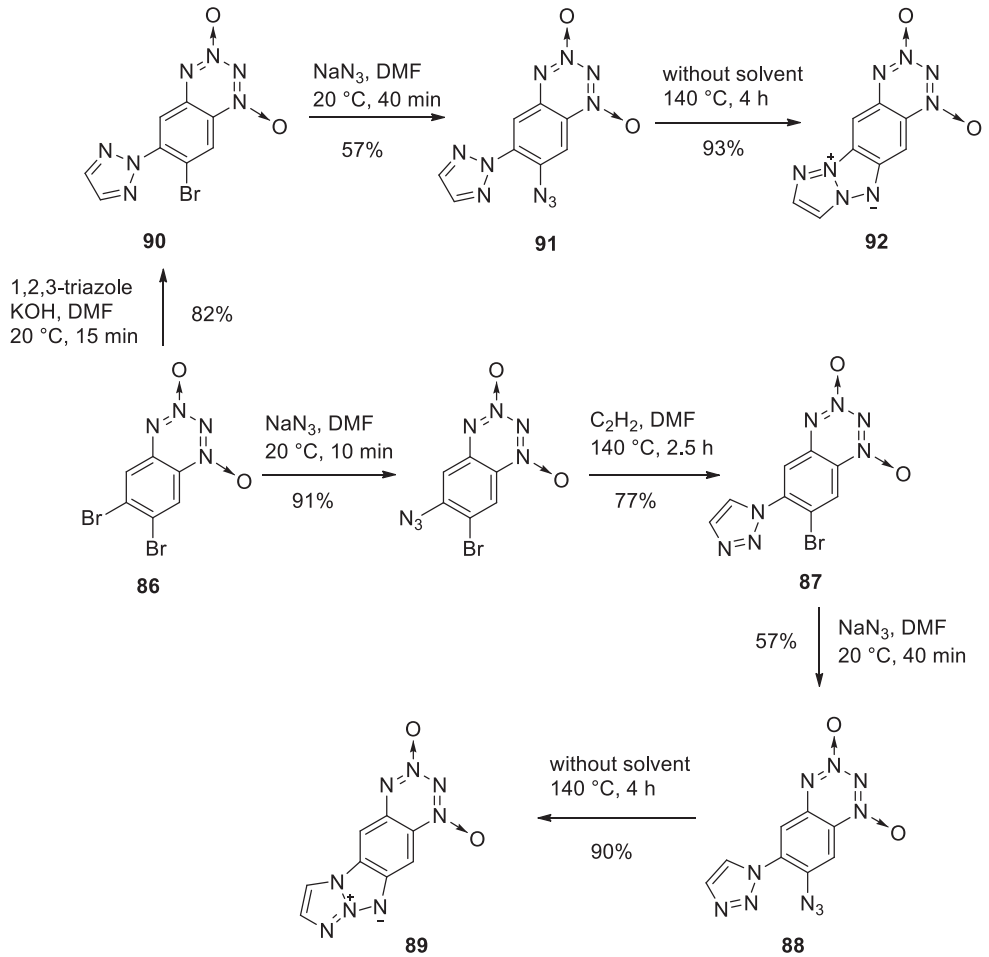
atom in BTDO **82** was replaced with 1,2,3-triazole. The reaction occurred in the presence of a base, to give only one triazol-2-yl isomer. Next, the nitro group in BTDO **83** was replaced by an azido group. Heating BTDO **84** at 140 °C for 8 h without a solvent afforded BTDO **85** in 67% yield.[57]

A synthetic route to BTDOs **89** and **92** annulated with Y- and Z-tetraazapentalene systems at the C(6)–C(7) bond is shown in Scheme 10. Replacement of bromine in position 6 of BTDO **86** by an azido group, subsequent cycloaddition of acetylene and further



Scheme 9

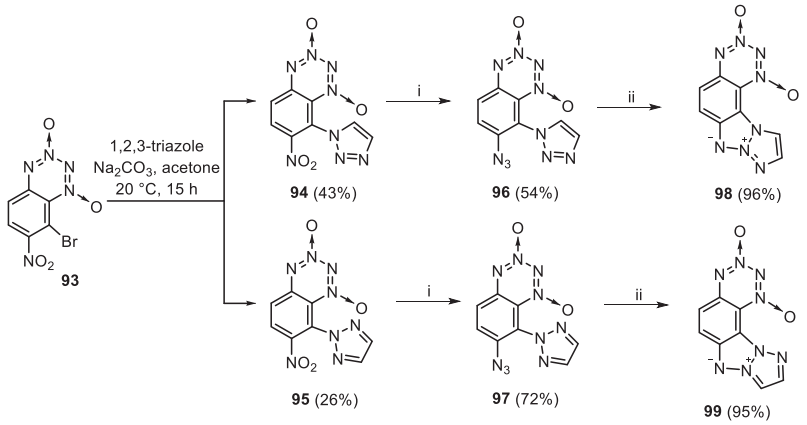
substitution of bromine in position 7 of BTDO **87** by an azido group afforded 7-azido-6-(triazol-1-yl)-BTDO **88**. To obtain isomeric 7-azido-6-(triazol-2-yl)-BTDO **91**, another synthetic sequence was used. The reaction of BTDO **86** with 1,2,3-triazole in the presence of a base led almost exclusively to one triazol-2-yl substituted isomer **90** in 82% yield. The following replacement of bromine by the azido group led to BTDO **91**. The heating of BTDOs **88** and **91** without solvent at 140 °C for 8 h afforded annulated BTDO **89** (90%) and **92** (93% yield), respectively.[58]



Scheme 10

In the reaction of BTDO **93** with 1,2,3-triazole in the presence of a base, both triazol-1-yl and triazol-2-yl isomer **94** and **95** were formed in a ratio of 5:3 (Scheme 11). The subsequent reaction of these isomers with sodium azide afforded the corresponding isomers **96** and **97**. Their heating at 140 °C afforded BTDOs **98** annulated at the C(6)–C(7) bond with Y- and *Z*-tetraazapentalenes, respectively.[59]

The structure of BTDOs annulated with tetraazapentalene systems was confirmed by spectral investigations (NMR, UV) and chemical reactions, including the oxidation of tetraazapentalene moieties to give *ortho*-nitro-1,2,3-triazolylTDOs.



Reagents and conditions: i) NaN_3, DMF, 20 °C, 10 min; ii) heating without solvent, 140 °C, 5 h

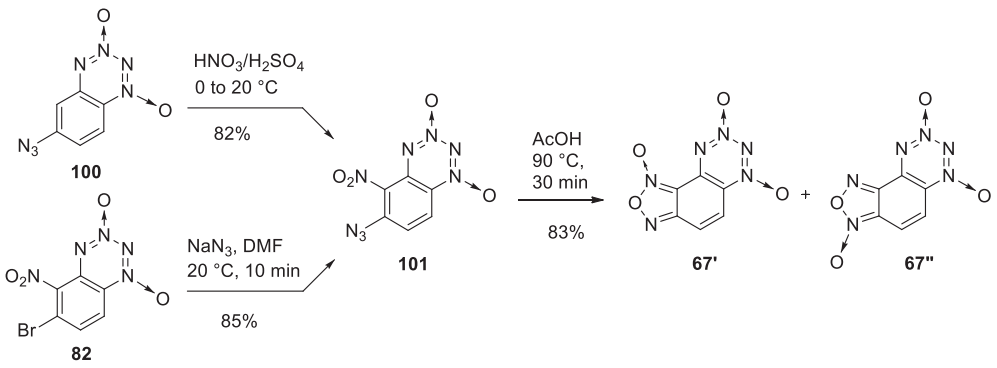
Scheme 11

9.13.6.1.3 Nucleophilic and electrophilic displacements as a synthetic route to benzotetrazine 1,3-dioxides annulated with a furoxan ring

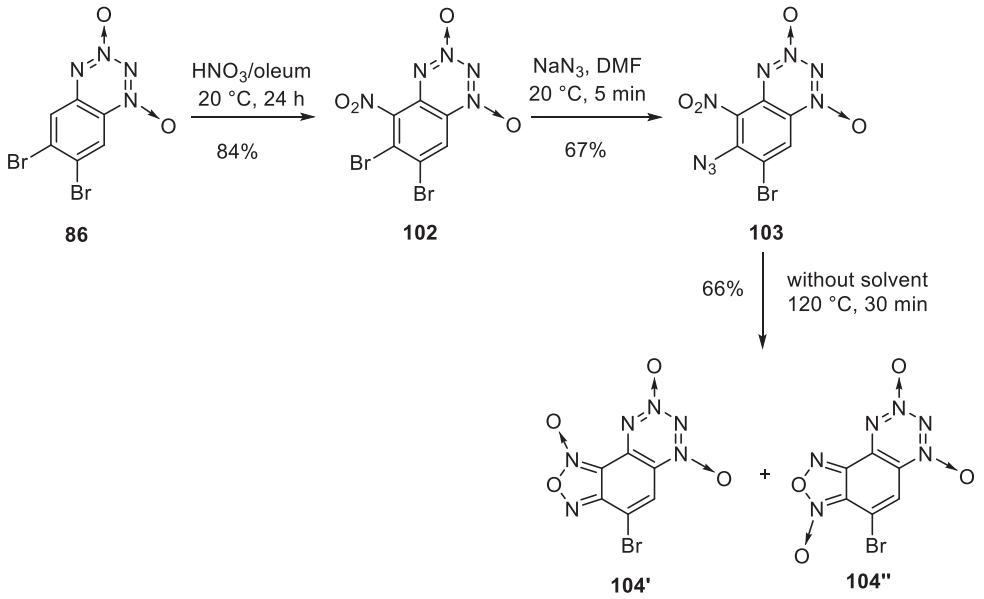
A traditional approach, i.e., an intramolecular reaction of neighboring azido and nitro groups, was used for the annulation of BTDOs with a furoxan ring. The starting compounds were obtained using nucleophilic and electrophilic aromatic substitution reactions.

6-Azido-5-nitro-BTDO **101** was obtained by nitration of 6-azido-BTDO **100** (Scheme 12). As expected, nitration occurred almost exclusively in the 5-th position. BTDO **101** was also synthesized from BTDO **82** by replacing bromine with an azido group.[64] BTDO **103** was synthesized by nitration of dibromo-BTDO **86** followed by replacement of bromine in position 6 of BTDO **102** with an azido group (Scheme 13). BTDOs annulated with furoxan ring at the C(5)–C(6) bond were obtained by heating BTDOs **101** (Scheme 12) and **103** (Scheme 13). Cyclization of the former takes place on heating at 90 °C in AcOH. The latter underwent cyclization under slightly more drastic conditions (heating without a solvent at 120–125 °C).

Replacement of bromine with an azido group in BTDO **93** afforded 8-azido-7-nitro-BTDO **105** (Scheme 14). Its cyclization at 118 °C in AcOH gave BTDO **68** annulated with a furoxane ring at the C(7)–C(8) bond in 30% yield. The relatively low yield was due to the rather low thermal stability of this BTDO.[65]



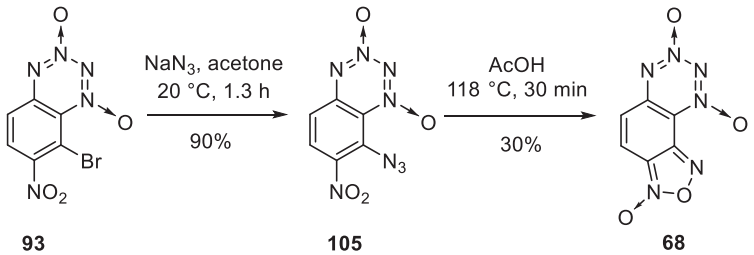
Scheme 12



Scheme 13

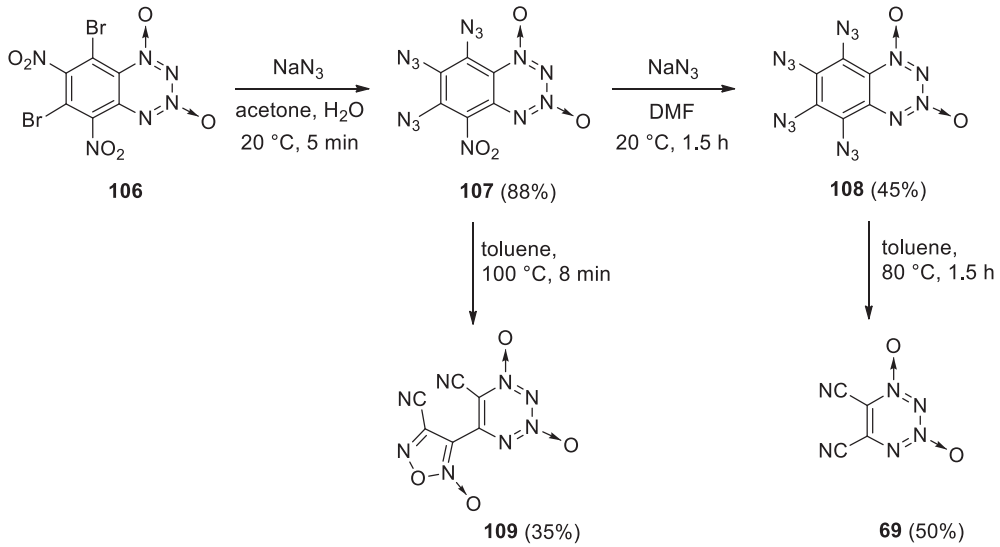
9.13.6.1.4 Benzene ring opening

BTDOs **107** and **108** served as the starting materials in thermal benzene ring-opening reactions to give the first non-annulated 1,2,3,4-tetrazine 1,3-dioxides **109** and **69** (Scheme 15).[72] The reaction of 6,8-dibromo-5,7-dinitro-BTDO **106** with sodium azide



Scheme 14

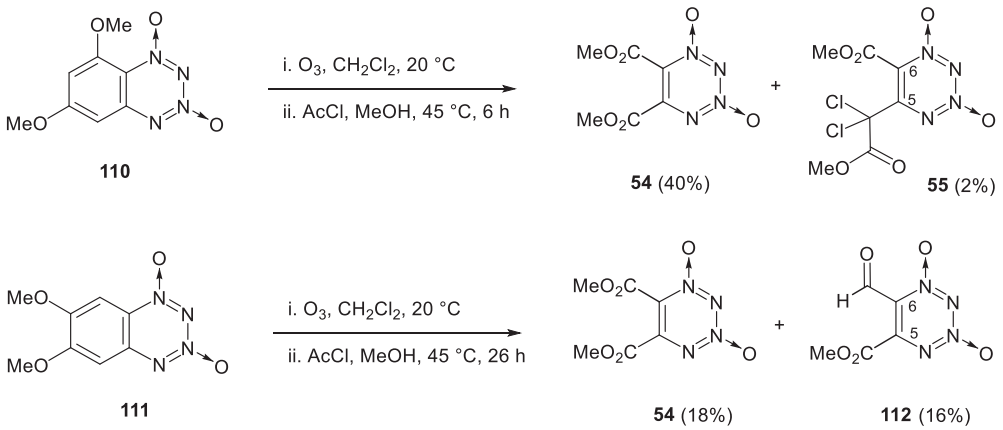
(3 equiv.) in acetone-water solution gave 6,7,8-triazido-5-nitro-BTDO **107** (Scheme 15). Substitution of the nitro group in BTDO **107** with sodium azide afforded 5,6,7,8-tetraazido-BTDO **108**. Heating a toluene solution of BTDO **107** at 100 °C for 8 min afforded non-annulated TDO **109** in 35% yield. 5,6-Dicyano-TDO **69** was obtained in 50% yield by heating BTDO **108** in toluene at 80 °C for 1.5 h.



Scheme 15

Ozonolysis is an alternative method for the synthesis of non-annulated 1,2,3,4-tetrazine 1,3-dioxides. The ozonolysis of dimethoxy-BTDOs **110** and **111** (Scheme 16) in CH_2Cl_2 followed by treatment of the primary ozonides with HCl in MeOH furnished 5,6-di(methoxycarbonyl)-1,2,3,4-tetrazine 1,3-dioxide **54** as the main product. Tetrazine 1,3-dioxides **55** and **112** were formed as minor products of these reactions.[48]

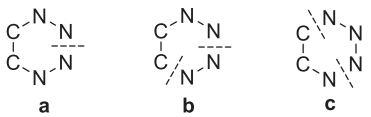
9.13.7 Ring synthesis



Scheme 16

9.13.7.1 1,2,3,4-Tetrazines ring synthesis

The 1,2,3,4-tetrazine ring system was built from the following types of precursors or precursor combinations:



(*a*)-Mode. This widely used mode involves the formation of one bond between two N atoms. It was treated in previous editions of CHEC[1–3] and comprises:

1. oxidation of N-NH_2 groups,
2. coupling of azo and diazo groups,
3. coupling of azo and diazonium groups,
4. coupling of azoxy and diazonium groups,
5. coupling of azoxy and oxodiazonium groups.

(*b*)-Mode. [4 + 2] Cycloaddition reactions. In CHEC-II and CHEC-III[2,3] cycloaddition reactions of 1,2-diaza-1,3-dienes with azodicarboxylates giving 1,2,3,6-tetrahydro-1,2,3,4-tetrazines were discussed.

(*c*)-Mode. [3 + 3] Cycloaddition reactions. This is a new mode which was not used previously.

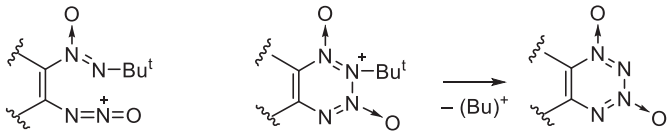
Besides that, 1,2,3,4-tetrazine ring synthesis was carried out by transformations of other heterocyclic rings. For example, the first fully conjugated 1,2,3,4-tetrazine **47** was synthesized by 1-amino-1,2,3-triazole ring expansion.[2] A new method for the synthesis of nonannulated tetrazine 1,3-dioxides involves the benzene ring opening in benzoannulated tetrazine 1,3-dioxides.

Recent syntheses published since 2008 or not reviewed previously are reviewed below.

9.13.7.1.1 Formation of one bond between two N atoms (Mode A). Coupling of azoxy and oxodiazonium groups

The only known synthetic route to the 1,2,3,4-tetrazine 1,3-dioxide ring involves the intramolecular reaction of *tert*-butyl-*NNO*-azoxy group with an oxodiazonium ion (Scheme 17) followed by elimination of a *tert*-butyl cation.

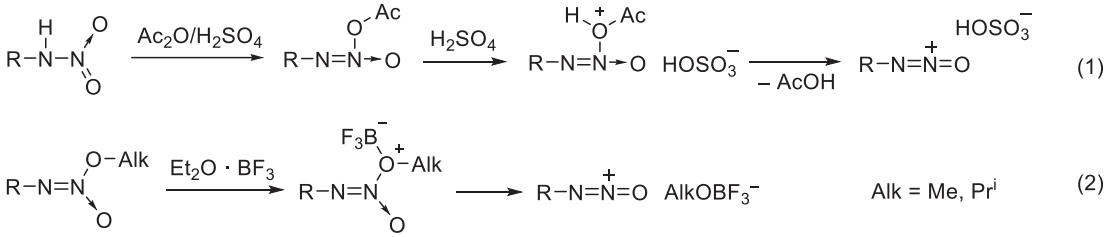
The oxodiazonium ion is a hypothetical moiety but its existence was supported by its intramolecular capturing by the benzene ring.[73,74] In addition to the previously known methods of generation of this ion ("nitrating method" involving the reaction of



Scheme 17

nitramines with nitrating reagents),[4] two new methods were reported. The "acetylating method" involves the synthesis of *O*-acetylated nitramines which dissociate in acidic media affording the $(—N{=}N{=}O)^+$ ion (Scheme 18, Eq. 1). The nitramine was usually generated in situ by the reaction of the appropriate amine with HNO_3. This method is suitable for synthesizing annulated 1,2,3,4-tetrazine 1,3-dioxides. Aromatic compounds (benzenes, 1,2,5-oxadiazole, 1,2,3-triazoles) with neighboring amino and *tert*-butyl-*NNO*-azoxy groups were used as the starting materials.[74,75]

Another method for generating the oxodiazonium ion involved the treatment of *O*-alkylated nitramines with boron trifluoride-etherate (Scheme 18, Eq. 2). This method is suitable for the synthesis of both annulated[67] and non-annulated



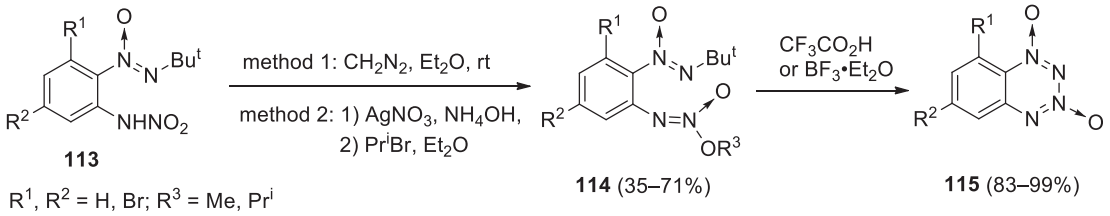
Scheme 18

1,2,3,4-tetrazine 1,3-dioxides.[49] Specific examples of using these methods are shown below.

9.13.7.1.1.1 Oxodiazonium ion from *O*-alkylnitramines

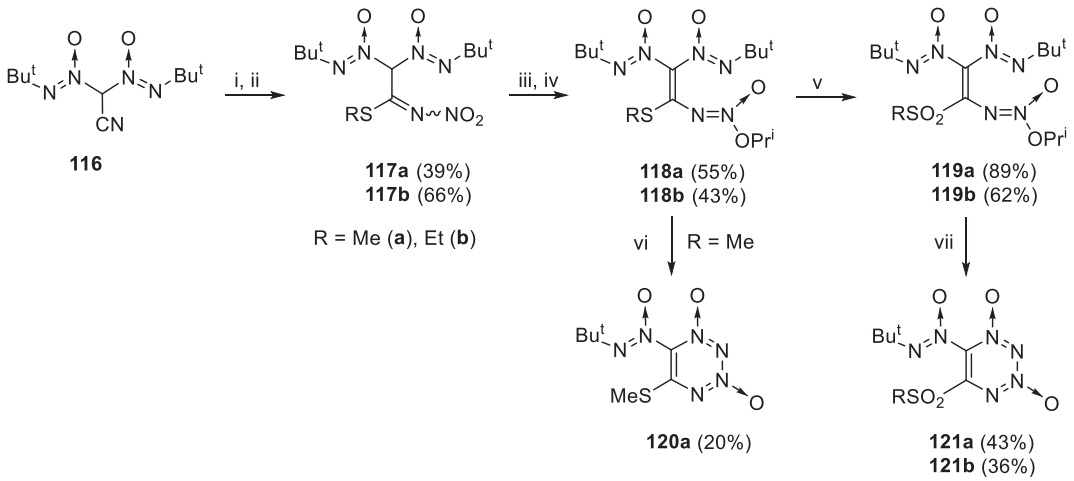
A new method for the synthesis of benzotetrazine 1,3-dioxides (BTDOs) **115** involved the treatment of *O*-alkyl derivatives of 2-(*tert*-butyl-*NNO*-azoxy)-*N*-nitroanilines **114** with trifluoroacetic acid or excess $BF_3{\cdot}Et_2O$ (Scheme 19).[67] *O*-Alkyl derivatives were obtained from nitramines **113** by alkylation.

A similar synthetic approach was also applied to prepare non-annulated tetrazine 1,3-dioxides **120a** and **121a,b** (Scheme 20)[49,50] from azoxyalkenes **118a** and **119a,b**. The best yields of TDOs were achieved in the case of azoxyalkenes **119a,b**



Scheme 19

bearing electron-withdrawing alkylsulfonyl groups. Azoxyalkenes **118a** and **119a,b** were prepared from bis(*tert*-butyl-*NNO*-azoxy) acetonitrile **116** by reactions with alkylthiols followed by nitration and *O*-alkylation of the intermediate *N*-nitroimines **117a,b**. Oxidation of compounds **118a,b** led to sulfones **119a,b**.

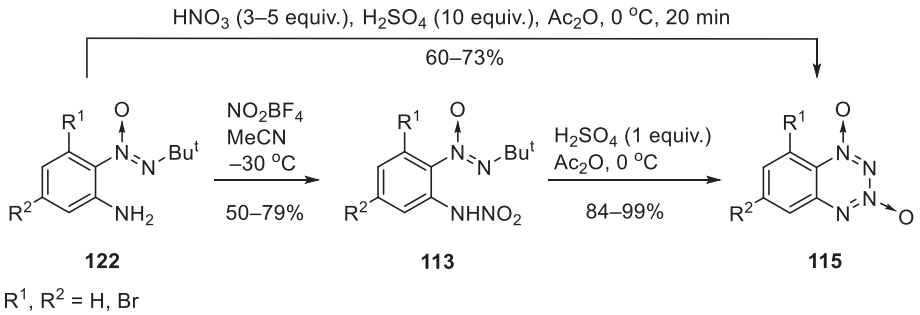


Reagents and conditions: i) for R = Me: MeSH, NEt_3, Bu^tOMe, 5 °C, 48 h; for R = Et: EtSH, NEt_3, CH_2Cl_2, 25 °C, 24 h; ii) HNO_3, H_2SO_4, Ac_2O, –5 – 0 °C, 1.5 h; iii) for R = Me: Bu^tOK, Bu^tOH, 30 °C, 10 min; for R = Et: MeONa, MeOH, 20 °C, 5 min; iv) 1) $AgNO_3$, MeCN, 2) Pr^iBr, Et_2O, 25 °C, 30 d; v) mCPBA, CH_2Cl_2, 25 °C, 24 h; vi) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 5 °C, 3 d; vii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 25 °C, 4 d.

Scheme 20

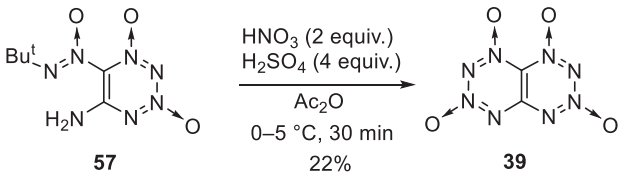
9.13.7.1.1.2 Oxodiazonium ion from nitramines

BTDOs **115** (Scheme 21) were obtained by the "acetylating method". In the first stage, anilines **122** were nitrated with nitronium tetrafluroborate to give nitramines **113**. Then the latter were treated with sulfuric acid in acetic anhydride solution to afford BTDOs **115** in good yields.[74] A one-step procedure involving treatment of amines **122** with the $HNO_3/H_2SO_4/Ac_2O$ system of reagents was also effective.



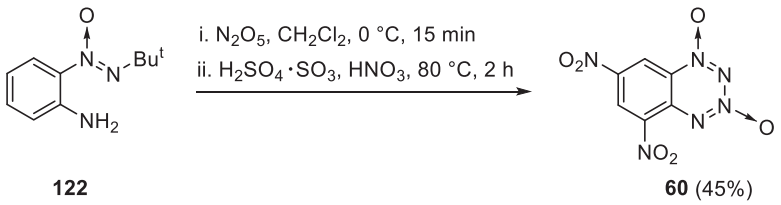
Scheme 21

The "acetylating method" was widely used to obtain tetrazine 1,3-dioxides annulated with heterocycles such as furazane and 1,2,3-triazoles (see the appropriate Chapters of this edition). The formation of the TDO ring using the $HNO_3/H_2SO_4/Ac_2O$ system of reagents was successfully implemented in the synthesis of TTTO **39** from TDO **57** (Scheme 22).[50]



Scheme 22

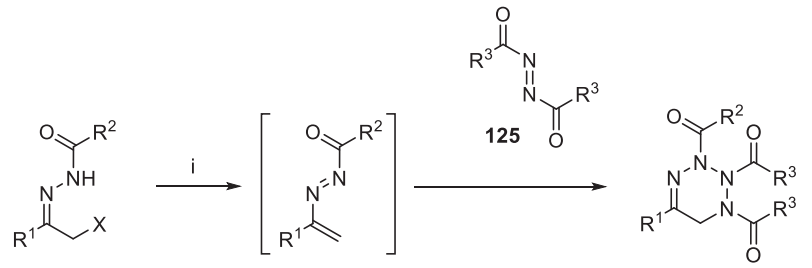
The improved one-pot synthesis of 5,7-dinitro-BTDO **60** by the "nitrating method" was reported (Scheme 23).[53] BTDO **122** was treated with N_2O_5 in CH_2Cl_2 solution followed by the reaction with HNO_3 and 20% oleum.



Scheme 23

9.13.7.1.2 [4 + 2] Cycloaddition reactions (Mode B*)*

A modified method for the synthesis of 1,2,3,6-tetrahydro-1,2,3,4-tetrazines **126** included the [4 + 2]-cycloaddition reaction of azodicarboxylic acid derivatives **125** with 1,2-diaza-1,3-butadienes **124** which were generated in situ from α-halohydrazones **123** on treatment with a base (Scheme 24).[56,76] The reaction occurred in good yields (40–99%), was well scalable and allowed one to vary substituents in the target tetrazines in a wide range.

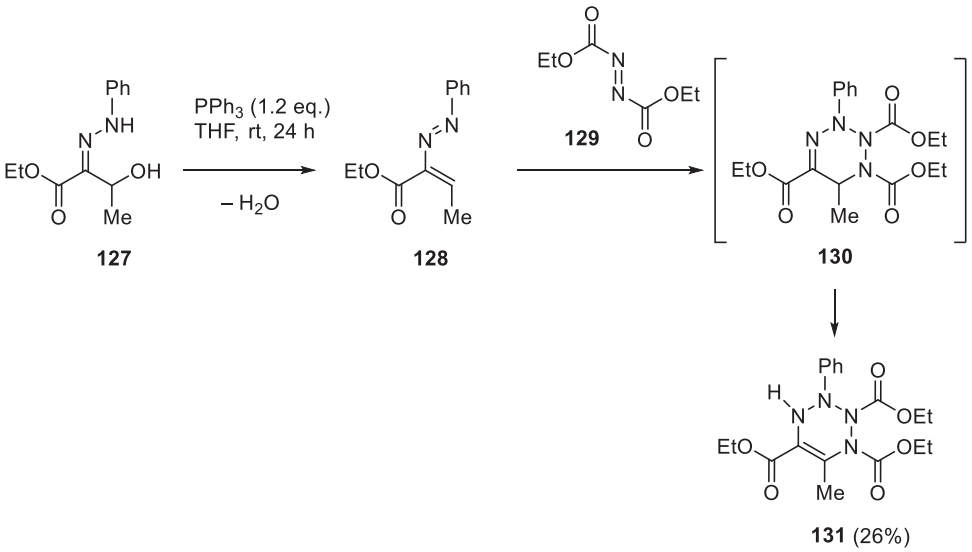


R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$Bu^tC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4,4-$NO_2C_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,5-$F_2C_6H_3$, Bu^t; R^2 = Me, Ph, OMe, OBu^t, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, Bu^t; R^3 = OEt, OPr^i, OBu^t, OBn, *N*-piperidinyl; X = Cl, Br.

Reagents and conditions: i) K_2CO_3 (1.2 eq.), THF, rt, 18–30 h (**12**: 50–99%) or Na_2CO_3 (2 equiv.), CH_2Cl_2, 30 °C, 12 h (**12:** 40–89%).

Scheme 24

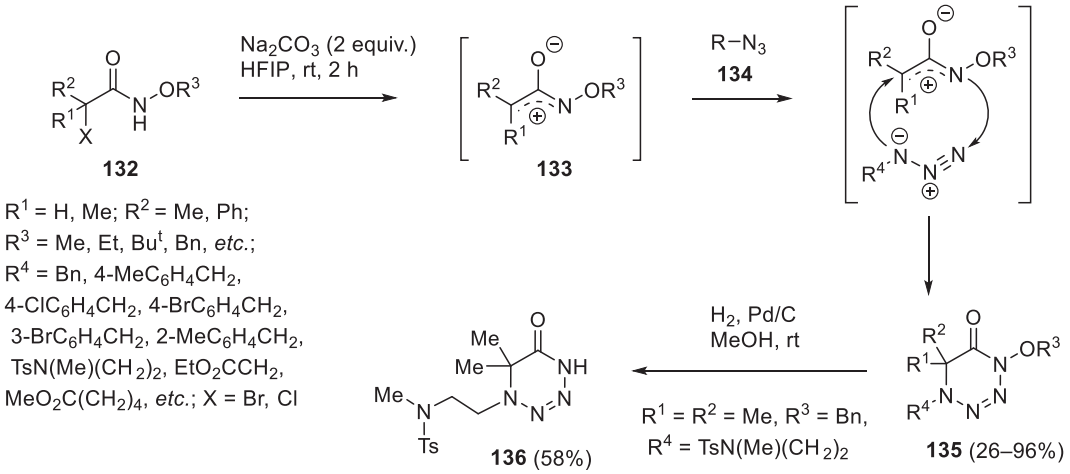
The synthesis of 1,2,3,6-tetrahydro-1,2,3,4-tetrazine **131** differs in that the generation of diazadiene **128** from hydrazone **127** occurred under the action of triphenylphosphine (Scheme 25). Intermediate tetrazine **130** underwent isomerization in the course of the reaction to give tautomeric tetrazine **131**.[77]



Scheme 25

9.13.7.1.3 [3 + 3] Cycloaddition (Mode C)

A formal [3 + 3] cycloaddition reaction between azides **134** and azaoxyallyl cations **133** formed in situ was implemented, which provided an efficient pathway to synthesize 1,2,3,4-tetrazines **135** in good yields under mild conditions. Azides **134** contained moieties of natural and medicinal substances, such as celecoxib, vitamin E, cholesterol, lithocholic acid and zidovudine (AZT). α-Bromohydroxamates **132**, in which the R^3 group was a moiety of vitamin E, was also used in this reaction.[55] Catalytic hydrogenation of tetrazine **135** resulted in the cleavage of the N—O bond and formation of tetrazine **136** in 58% yield (Scheme 26).



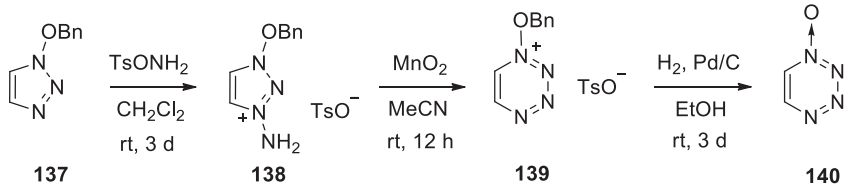
Scheme 26

9.13.7.1.4 Benzene ring cleavage

Non-annulated 1,2,3,4-tetrazine 1,3-dioxides (BTDOs) **69** and **109** were synthesized by thermolysis of azido substituted benzo-1,2,3,4-tetrazine 1,3-dioxides.[72] Non-annulated BTDOs **54**, **55** and **112** were obtained by ozonolysis of methoxy substituted BTDOs[48] (for details see Section 9.13.6.1.4).

9.13.7.1.5 Ring synthesis by transformations of other heterocyclic rings

The first non-annulated 1,2,3,4-tetrazine 1-oxide **140** was synthesized by ring expansion of the 1,2,3-triazole ring (Scheme 27). The synthesis was accomplished in three stages from 1-(benzyloxy)-1,2,3-triazole **137** which was aminated with tosylhydroxylamine to produce 1-amino-3-(benzyloxy)-1,2,3-triazolium tosylate **138**. The latter was oxidized with MnO_2 to give presumably nitrene that undergoes ring expansion to give salt **139**. Subsequent reduction of this salt with hydrogen (Pd/C catalyst) afforded tetrazine 1-oxide **140** which was characterized by MS (DEI+), ^{1}H and ^{13}C NMR.[61]



Scheme 27

9.13.8 Important compounds and application

It was reported previously that benzotetrazine 1,3-dioxides were found to be thiol-dependent NO-donors and exhibit diverse kinds of biological activity.[3,4] However, no new studies in this area were reported over the past decade. In the most recent studies, the 1,2,3,4-tetrazine 1,3-dioxide ring was considered to be a promising scaffold for synthesizing new high energy density compounds, such as TTTO **39**,[50] FTDO **28**,[66] 5-amino-6-nitro-TDO **70**[68] and 5,7-dinitro-BTDO **60**.[53]

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