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1,2,4-Triazine *N*-oxides and their annelated derivatives

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Abstract. This review deals with the synthesis and properties of 1,2,4-triazine *N*-oxides and their annelated derivatives. Methods for the incorporation of the *N*-oxide group in the 1,2,4-triazine ring by direct oxidation and cyclisation involving nitro, nitroso, and isonitroso groups are discussed. Reactions of 1,2,4-triazine *N*-oxides with electrophiles, nucleophiles, and dienophiles are considered. The effect of the *N*-oxide group on the chemical shifts in the ^{1}H, ^{13}C, and ^{14}N NMR spectra and the specific features of decomposition of 1,2,4-triazine *N*-oxides under electron impact are analysed. The bibliography includes 107 references.

I. Introduction

The present review discusses methods for the synthesis of 1,2,4-triazine *N*-oxides and reactions of these compounds. 1,2,4-Triazine is a heterocycle incorporated in many natural and synthetic compounds that possess biological activity and many practically useful properties.

The presence of the *N*-oxide group in the azine ring makes it sensitive both to nucleophilic and electrophilic attack and expands substantially the synthetic prospects for modifying nitrogen-containing heterocycles.[1] This is the reason for the ever increasing interest of investigators in heterocyclic *N*-oxides. A series of reviews on the chemistry of pyridine *N*-oxides,[2] pyrimidine *N*-oxides,[3] and quinoxaline *N*-oxides[4] have been published in the 90s. A monograph[5] and several reviews[6–9] on 1,2,4-triazines include special chapters on the chemistry of triazine *N*-oxides. However, data on the methods for the synthesis, reactivity, and properties of these compounds have not been systematised to date. The goal of this review is to bridge this gap.

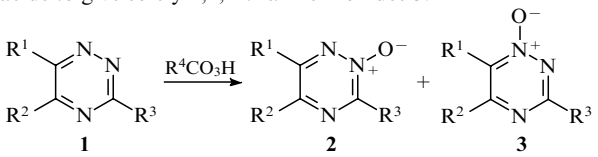
II. Methods for the synthesis of 1,2,4-triazine *N*-oxides

Two main approaches are used to synthesise azines containing the *N*-oxide fragment. First, oxidation of nitrogen atoms of the ring with organic peracids or hydrogen peroxide in acidic media and, second, closing the azine ring with the participation of nitro, nitroso, or isonitroso groups to give an *N*-oxide group.[1] Both of these methods are used for the synthesis of 1,2,4-triazine *N*-oxides.

1. Synthesis of 1,2,4-triazine 1- and 2-oxides by oxidation of 1,2,4-triazines

N-Oxides are formed rather readily in reactions of 1,2,4-triazines with organic peracids or hydrogen peroxide in the presence of carboxylic acids. In this case, only two of the three possible isomers are formed, namely, 1- and 2-oxides. The ratio of these isomers depends on the type of substituents in the starting 1,2,4-triazine.

For example, oxidation of 3-amino-1,2,4-triazines **1** gives mainly 2-oxides **2**. 3-Alkoxy-1,2,4-triazines **1** react with organic peracids to give solely 1,2,4-triazine 1-oxides **3**.[11–14]



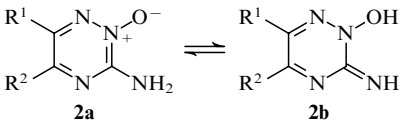
1 **2** **3**

R^1	R^2	R^3	Oxidising agent	Yield (%)		Ref.
				2	**3**	
H	H	NH_2	*m*-$ClC_6H_4CO_3H$	80	0	10
H	Me	NH_2	*m*-$ClC_6H_4CO_3H$	80	0	10
H	H	$NH(CH_2)_2Cl$	*m*-$ClC_6H_4CO_3H$	51	0	10
H	Me	$NH(CH_2)_2Cl$	*m*-$ClC_6H_4CO_3H$	77	0	10
H	Ph	$NH(CH_2)_2Cl$	*m*-$ClC_6H_4CO_3H$	35	0	10
H	H	OMe	*m*-$ClC_6H_4CO_3H$	0	30	11
Me	Me	NH_2	H_2O_2/AcOH	30	0	12
H	Ph	NH_2	H_2O_2/AcOH	37	0	13
H	Ph	NHCOMe	H_2O_2/AcOH	45	0	13
H	Ph	NHCOEt	H_2O_2/AcOH	41	0	13
Me	Me	H	$PhCO_3H$	0	30	14
Ph	Ph	H	$PhCO_3H$	0	17	14
H	Ph	H	$PhCO_3H$	0	26	14
H	H	OMe	$PhCO_3H$	0	15	14
Ph	Ph	OMe	$PhCO_3H$	0	23	14
H	Me	OMe	$PhCO_3H$	0	26	14
H	Ph	OMe	$PhCO_3H$	0	39	14

Obviously, the possibility of amino – imino tautomerism **2a** ⇄ **2b** in 3-amino-1,2,4-triazine *N*-oxides stabilises the products of oxidation at position 2 of the triazine system.[10]

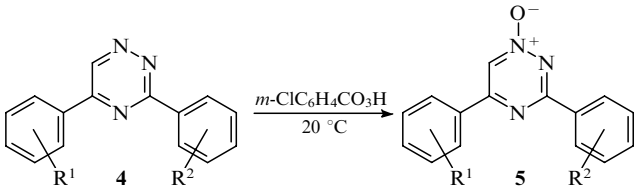
D N Kozhevnikov, V L Rusinov, O N Chupakhin Ural State Technical University, ul. Mira 19, 620002 Ekaterinburg, Russian Federation. Fax (7-343) 274 04 58. Tel. (7-343) 274 04 58 (D N Kozhevnikov), (7-343) 274 44 26. E-mail: azine@htf.rcupi.e-burg.su (O N Chupakhin)

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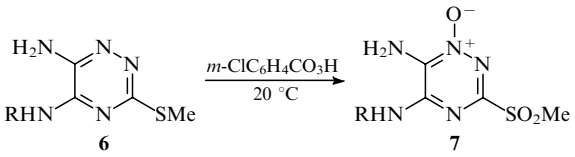
2a **2b**

Oxidation of 3,5-diaryl-1,2,4-triazines **4** with *m*-chloroperbenzoic acid gives 1,2,4-triazine 1-oxides **5** in 75% – 98% yields.[15]



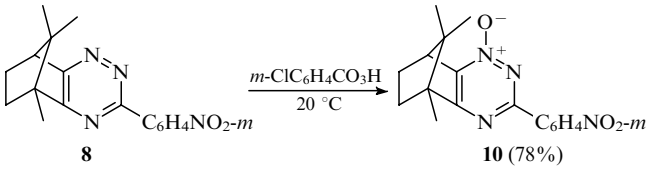
R^1 = H, 2-Me, 3-Me, 4-Me, 2-Cl, 3-Cl, 4-Cl, 3-CF_3;
R^2 = H, 4-Br, 2-F, 3-F, 4-F, 4-Cl, 4-CF_3.

5,6-Diamino-3-methylsulfonyl-1,2,4-triazine 1-oxides **7** were prepared under the same conditions from 5,6-diamino-3-methylthio-1,2,4-triazines **6** in 60% – 80% yields.[16]

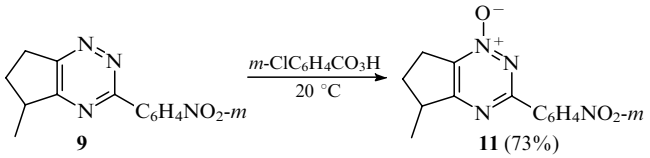


R = H, CH_2Ph.

Oxidation of 1,2,4-triazines containing the camphor (compound **8**) or methylcyclopentane fragments (compound **9**)[17] with *m*-chloroperbenzoic acid affords solely triazine 1-oxides **10** and **11**.

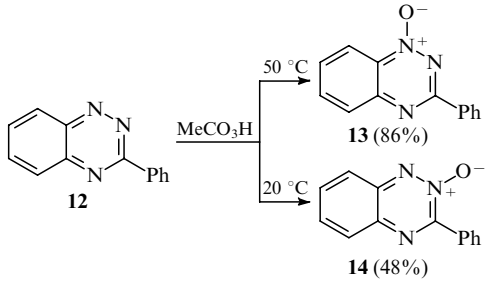


8 **10** (78%)

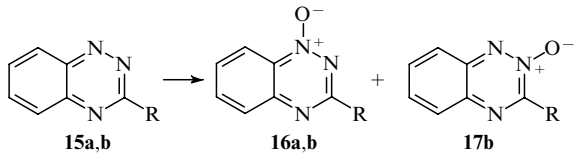


9 **11** (73%)

The reaction pathway also depends on the temperature. The reaction of 3-phenyl-1,2,4-benzotriazine **12** with peracetic acid affords 3-phenyl-1,2,4-benzotriazine 1-oxide **13** at 50 °C and 2-oxide **14** at 20 °C.[18] Only the 1-oxide **16a** was obtained in 28% yield in the oxidation of 3-unsubstituted 1,2,4-benzotriazine **15a**. Oxidation of 3-methyl-1,2,4-benzotriazine **15b** under the same conditions gives a mixture of 3-methyl-1,2,4-benzotriazine 1-oxide **16b** and 2-oxide **17b** in 25% and 10% yields, respectively.



12 **13** (86%) **14** (48%)

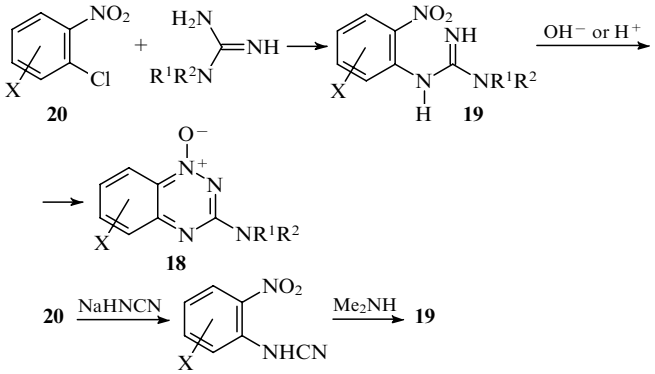


15a,**b** **16a**,**b** **17b**

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

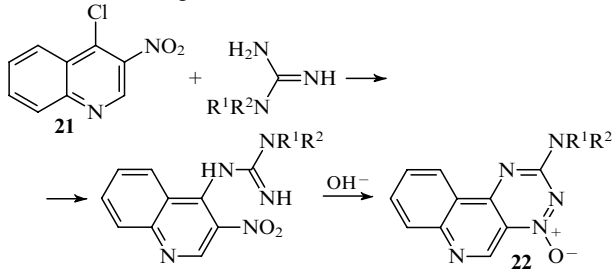
2. Synthesis of 1,2,4-triazine 1-oxides by cyclisation involving a nitro group

Aromatic and heteroaromatic nitro-compounds containing a guanidine fragment at the *ortho*-position relative to the nitro group readily undergo cyclisation in alkaline or acidic media to give benzo- or hetero-annelated 1,2,4-triazine 1-oxides. For example, 3-amino-1,2,4-benzotriazine 1-oxide **18** was obtained in 1913 by treatment of 2-nitrophenylguanidine **19** with an alkali.[19] Subsequently, this approach was used to synthesise a number of 3-amino-1,2,4-benzotriazine 1-oxides of the type **18**.[20–27] It is noteworthy that compound **19** can be obtained either by the reaction of guanidine with 2-nitrochlorobenzene **20** or by treatment of compound **20** with sodium cyanamide and dimethylamine (in the latter case, compounds **19** and **20** with $R^1 = R^2$ = Me are formed).



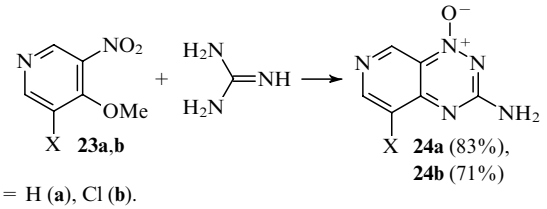
X = H, Me, Cl, Br, NO_2, OMe, CN.

In a similar way, 3-amino-1,2,4-triazino[6,5-*c*]quinoline 4-oxides **22** were synthesised in 62% – 95% yields by the reaction of 4-chloro-3-nitroquinoline **21** with guanidine followed by cyclisation of substituted guanidines formed in an alkaline medium.[28]



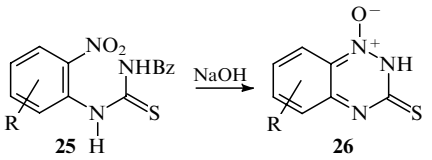
R^1 = H, Me; R^2 = H, Me, Et, Bu^n, n-$C_{10}H_{21}$, Bn, $(CH_2)_2NEt_2$.

The reaction of 4-methoxy-3-nitropyridines **23a**,**b** with guanidine under similar conditions affords 3-aminopyrido[3,4-*e*]-1,2,4-triazine 1-oxides **24a**,**b**.[29]



X = H (**a**), Cl (**b**).

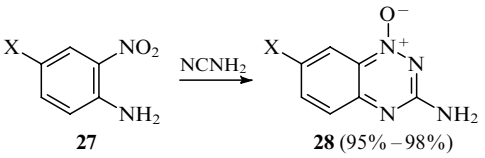
Cyclisation of *N*-(2-nitrophenyl)-*N′*-benzoylthiourea and its derivatives (compounds **25**) in an alkaline medium affords the corresponding 1,2,4-benzotriazine-3(2*H*)-thione 1-oxides **26**.[30]



25 **26**

R = H (77%), 5-Cl (72%), 7-Cl (80%), 6-SH (40%), 7-Me (72%), 7-OMe (75%).

The reaction of *o*-nitroaniline and its 4-substituted derivatives (compounds **27**) with cyanamide gives 3-amino-1,2,4-benzotriazine 1-oxides **28**.[22]

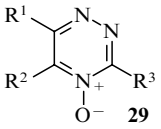


27 **28** (95%–98%)

X = H, Me, OMe, Br, Cl, OPh, CN, NO_2.

3. Preparation of 1,2,4-triazine 4-oxides by cyclisation involving a nitroso or isonitroso group

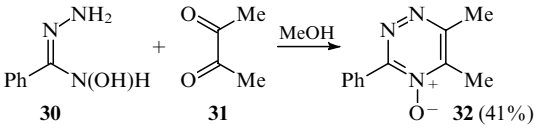
Unlike 1- and 2-oxides, 1,2,4-triazine 4-oxides **29** are not formed upon direct oxidation of the corresponding 1,2,4-triazines.



29

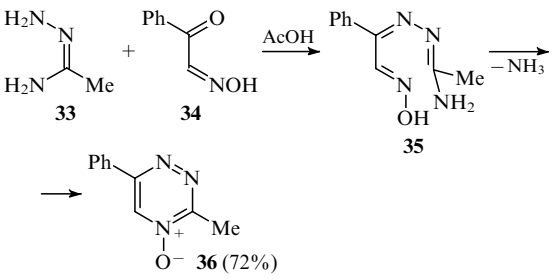
Therefore, the only possibility to prepare 1,2,4-triazines with the *N*-oxide group at position 4 is to synthesise the triazine cycle from compounds with nitroso or isonitroso groups. The synthesis can be carried out in several ways.

The reaction of hydroxyamidrazone **30** with dimethylglyoxal **31** in methanol affords 5,6-dimethyl-3-phenyl-1,2,4-triazine 4-oxide **32**.[31]



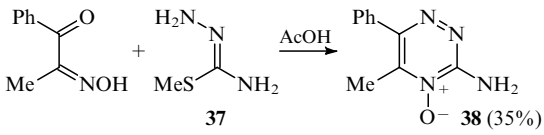
30 **31** **32** (41%)

The condensation of amidrazone **33** with phenylglyoxal monooxime **34** occurs through the formation of hydrazone **35**. The elimination of an ammonia molecule from compound **35** gives 3-methyl-6-phenyl-1,2,4-triazine 4-oxide **36** in a good yield.[31]



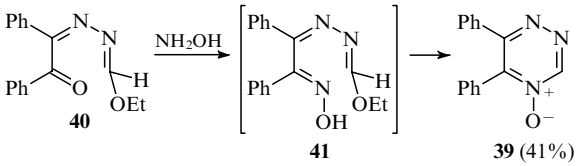
33 **34** **35** **36** (72%)

If aminoguanidine or *S*-methylisothiosemicarbazide **37** are used instead of amidrazone, 3-amino-1,2,4-triazine 4-oxides are formed. 3-Amino-5-methyl-6-phenyl-1,2,4-triazine 4-oxide **38** was synthesised in this way.[32,33]



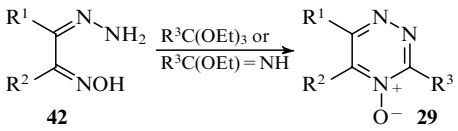
37 **38** (35%)

5,6-Diphenyl-1,2,4-triazine 4-oxide **39** was obtained by the reaction of diphenylglyoxal mono-2-ethoxymethylenehydrazone **40** with hydroxylamine.[31] Obviously, formation of the intermediate **41** followed by its cyclisation to 1,2,4-triazine 4-oxide **39** occurs in this case.



40 **41** **39** (41%)

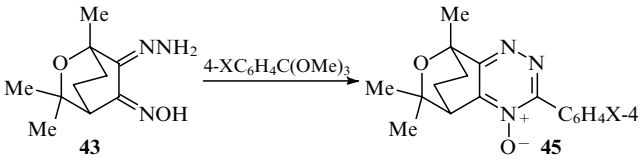
A more promising method for the synthesis of 1,2,4-triazine 4-oxides is the cyclisation of α-hydrazonooximes **42** with orthocarboxylates or iminoesters. Rather a wide range of 1,2,4-triazine 4-oxides **29** was synthesized using this method.[31,34–38]

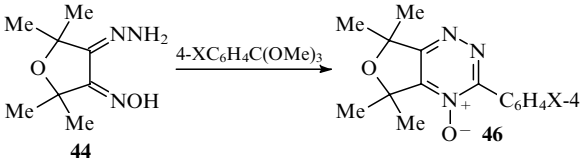


42 **29**

R^1	R^2	R^3	Yield of **29** (%)	Ref.
Reagent $R^3C(OEt)_3$				
Me	H	Me	40	34
Me	Me	Me	80	34
Ph	Ph	Me	70	34
Me	H	Ph	53	34
Ph	Me	Me	70	34
Ph	Me	Et	60	34
Ph	Me	Ph	70	34
2-$NO_2C_6H_4$	H	H	89	36
4-$NO_2C_6H_4$	H	H	84	34
4-$NO_2C_6H_4$	H	H	89	36
4-$MeOC_6H_4$	H	H	80	34
Ph	H	H	86	31
Ph	H	Ph	57	31
Ph	Me	H	27	31
Me	Me	H	51	31
Me	H	H	23	31
Bu^t	H	H	59	38
Bu^t	H	Me	65	38
Bu^t	H	Ph	43	38
Reagent $R^3C(OEt)=NH$				
4-$MeOC_6H_4$	H	4-$NO_2C_6H_4$	16	34
Ph	Me	4-$NO_2C_6H_4$	25	34
4-$NO_2C_6H_4$	H	4-$MeOC_6H_4$	16	34
Ph	H	4-$MeOC_6H_4$	45	34
Ph	H	4-$NO_2C_6H_4$	54	34
Ph	H	Me	51	31

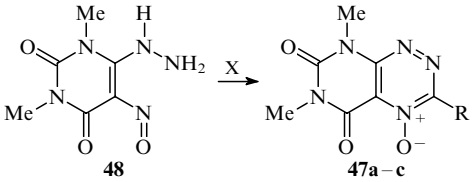
Similarly, reactions of 5-isonitroso-1,3,3-trimethyl-2-oxabicyclo[2.3.3]octan-6-one hydrazone **43** and 4-isonitroso-2,2,5,5-tetramethyltetrahydrofuran-3-one **44** with the corresponding orthobenzoates afford 3-aryl-5,8-dihydro-6,6,8-trimethyl-5,8-ethanopyrano[4,3-*e*]-1,2,4-triazine 4-oxides **45** and 3-aryl-5,7-dihydro-5,5,7,7-tetramethylfurano[3,4-*e*]-1,2,4-triazine 4-oxides **46**.[39]





X = Me, OMe, NO_2, CF_3, Cl, Br, F.

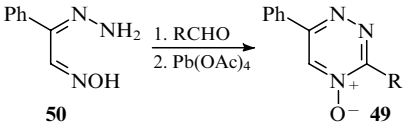
Annelated 1,2,4-triazine 4-oxides, *viz.*, 3-R-fervenulin 4-oxides **47**, were synthesised from 6-hydrazino-1,3-dimethyl-5-nitrosouracil **48**.[40–42] Orthoesters, formic acid, or DMF in the presence of $POCl_3$ or dimethyl sulfate can be used as cyclisation agents.



X is cyclisation agent; R = H (**a**), Me (**b**), Et (**c**).

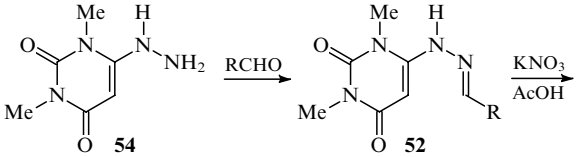
Compound	Cyclisation agent (X)	Yield of **47** (%)	Ref.
47a	$HC(OEt)_3$	71	40–42
47b	$MeC(OEt)_3$	76	40–42
47c	$EtC(OEt)_3$	85	40
47a	HCOOH	54	40
47a	$DMF–POCl_3$	72	40
47a	$DMF–Me_2SO_4$	43	40

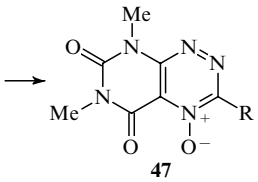
A new, rather simple method for the synthesis of 1,2,4-triazine 4-oxides **49** was suggested recently. It involves the condensation of isonitrosoacetophenone hydrazone **50** with aldehydes followed by oxidation of the condensation product with lead tetraacetate. This is a simple way to obtain 1,2,4-triazine 4-oxides with almost any aliphatic, aromatic, and heteroaromatic substituents at position 3 of the triazine cycle.[43]



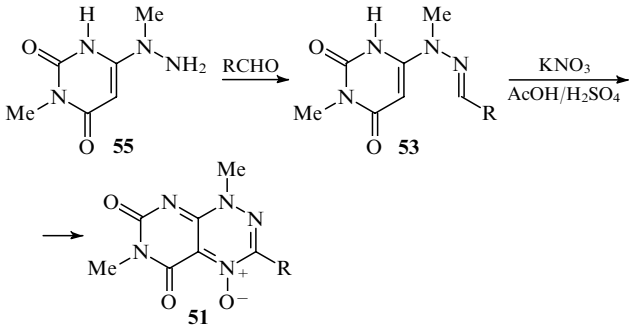
R = Me, Et, Pr^i, C_7H_{15}, Ph, 4-$NO_2C_6H_4$, 4-BrC_6H_4, .

To prepare fervenulin 4-oxides **47** or toxoflavine 4-oxides **51**, it is convenient to use the reaction of 1,3-dimethyl-2,4-dioxopyrimidin-6-yl hydrazone **52** or *N*-(3-methyl-2,4-dioxopyrimidin-6-yl) *N*-methylhydrazone **53** with potassium nitrate in acetic acid.[44–48] Sometimes, diethylazo diformate is used instead of potassium nitrate.[49] In this case, cyclisation occurs simultaneously with the formation of the NO group. Compounds **52** and **53** were synthesised from the corresponding hydrazines **54** and **55** and aldehydes.



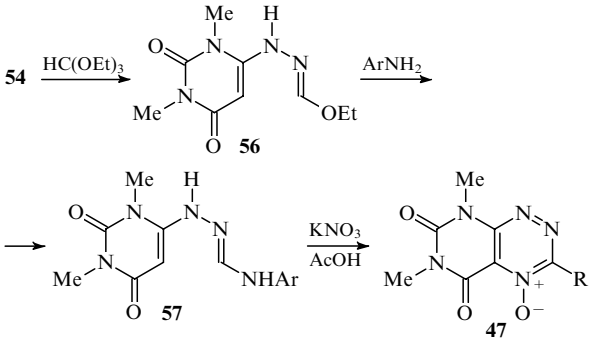


R	Yield of **47** (%)	Ref.
Ph	68	44
	54	49
4-ClC_6H_4	50	44
	43	49
3,4-$Cl_2C_6H_3$	65	44
	61	49
4-$MeOC_6H_4$	63	49
4-$Me_2NC_6H_4$	58	49
4-$NO_2C_6H_4$	45	44



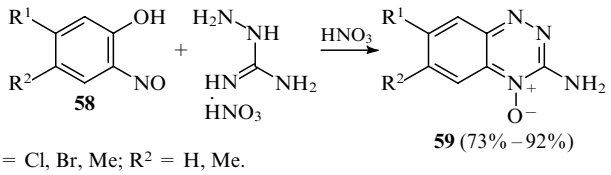
R	Yield of **51** (%)	Ref.
H	56	48
Me	63	49
Ph	51	48
4-ClC_6H_4	46	48
3,4-$Cl_2C_6H_3$	67	48
4-MeC_6H_4	54	48
4-$Me_2NC_6H_4$	50	49
PhCH=CH	46	48
	61	48

3-Anilinofervenulin 4-oxides **47** (R = ArNH) were obtained by the reaction of 6-hydrazino-1,3-dimethyluracil **54** with triethyl orthoformate followed by substitution of the ethoxy group in the resulting hydrazide **56** with an aniline residue and further cyclisation of compound **57** under nitrosation conditions.[46]



R = ArNH = PhNH (51%), 4-ClC_6H_4NH (63%), 4-BrC_6H_4NH (49%), 4-$MeOC_6H_4NH$ (47%), 4-MeC_6H_4NH (56%).

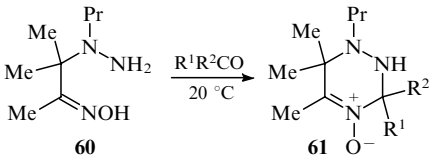
2-Nitrosophenols **58** react with aminoguanidine nitrate in the presence of nitric acid. This method gave 3-amino-1,2,4-benzotriazine 4-oxides **59**.[50]



58 **59** (73%–92%)

R^1 = Cl, Br, Me; R^2 = H, Me.

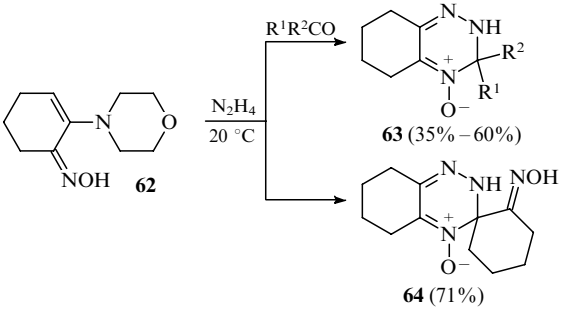
Reaction of 3-hydrazino-3-methylbutan-2-one oxime **60** with aldehydes and ketones affords 3-R^1-3-R^2-1,3,4,6-tetrahydro-5,6,6-trimethyl-1,2,4-triazine 4-oxides **61**.[51]



60 **61**

R^1 = H, Me; R^2 = H, Me, Pr^i.

Condensation of 1-morpholino-6-oximinocyclohexene **62** with hydrazine hydrate and ketones gives 2,3,5,6,7,8-hexahydro-1,2,4-benzotriazine 4-oxides **63**. In the absence of a carbonyl compound, this reaction leads to spiro compound **64**.[52]

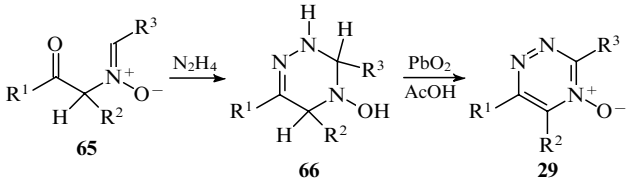


62 **63** (35%–60%) **64** (71%)

R^1, R^2 = Me, CH_2Ph; R^1-R^2 = $(CH_2)_5$, $(CH_2)_6$.

4. Other methods for the synthesis of 1,2,4-triazine 4-oxides

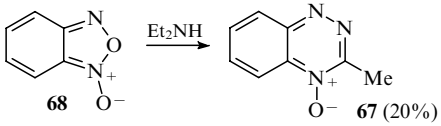
There is a method for the synthesis of 1,2,4-triazine 4-oxides that is fundamentally different from those discussed above.[53] The reaction of nitrones **65** with an excess of hydrazine afforded 4-hydroxy-2,3,4,5-tetrahydro-1,2,4-triazines **66**. Subsequent oxidation with Pb(IV) oxide resulted in the corresponding triazine 4-oxides **29**.



65 **66** **29**

R^1	R^2	R^3	Yield of **29** (%)
Ph	Me	Et	57
Ph	Me	Ph	70
Me	Me	Ph	52
Ph	H	Ph	51

3-Methyl-1,2,4-benzotriazine 4-oxide **67** was obtained by the reaction of benzofurazan oxide **68** with diethylamine.[54, 55]



68 **67** (20%)

III. Physicochemical characteristics of 1,2,4-triazine *N*-oxides

The incorporation of an *N*-oxide fragment in the 1,2,4-triazine molecule changes substantially the ^1H, ^{13}C, and ^{15}N NMR spectra.

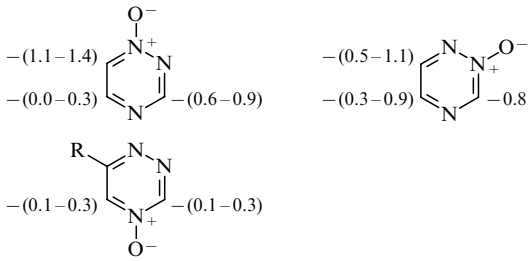
In ^1H NMR spectra of 1,2,4-triazine 1-oxides, the signals of the protons at positions 3 and 6 are observed at 9.00 and 8.04 ppm, *i.e.*, they are shifted upfield by 0.6–0.7 and 1.1–1.2 ppm, respectively, in comparison with those in the 1,2,4-triazines, but the signal of the H(5) proton (8.57 ppm) remains almost unchanged.[10, 14, 56]

A comparison of the ^1H NMR spectra of 1,2,4-triazine 4-oxides with those of the corresponding 1,2,4-triazines shows that the signals of the H(3) and H(6) protons have an almost similar upfield shift ($\Delta\delta$ = −0.8 ppm), and their chemical shifts are 8.82 and 8.42 ppm, respectively. The signal of the H(5) proton is also shifted upfield by 0.3 ppm (δ = 8.00 ppm) (Table 1).[10]

Table 1 Chemical shifts of cyclic protons in the ^1H NMR spectra of 1,2,4-triazines and their *N*-oxides in $CDCl_3$.

Compound	δ/ ppm			$\Delta\delta$/ ppm			Ref.
	H(3)	H(5)	H(6)	H(3)	H(5)	H(6)	
1,2,4-Triazine	9.63	8.53	9.24				10
1,2,4-Triazine 1-oxide	9.00	8.57	8.04	−0.63	0.04	−1.20	10, 14
1,2,4-Triazine 2-oxide	8.82	8.00	8.42	−0.81	−0.53	−0.82	10
3-Methoxy-1,2,4-triazine		8.56	9.16				56
3-Methoxy-1,2,4-triazine 1-oxide		8.37	7.83		−0.19	−1.33	14
3-Methoxy-1,2,4-triazine 2-oxide		7.70	8.12		−0.86	−1.04	10
3-Amino-1,2,4-triazine [a]		8.53	8.88				10
3-Amino-1,2,4-triazine 2-oxide [a]		8.19	8.23		−0.34	−0.65	10
3-(*N*,*N*-Dimethylamino)-1,2,4-triazine		8.14	8.15				10
3-(*N*,*N*-Dimethylamino)-1,2,4-triazine 1-oxide		7.76	7.86		−0.38	−0.65	10
3-Morpholino-1,2,4-triazine		8.14	8.54				57
3-Morpholino-1,2,4-triazine 2-oxide		7.81	8.54		−0.33	−0.52	10
6-Methyl-1,2,4-triazine	9.55	8.55					31
6-Methyl-1,2,4-triazine 4-oxide	9.28	8.22		−0.27	−0.33		31
6-Phenyl-1,2,4-triazine	9.52	8.91					31
6-Phenyl-1,2,4-triazine 4-oxide	9.31	8.60		−0.21	−0.31		31

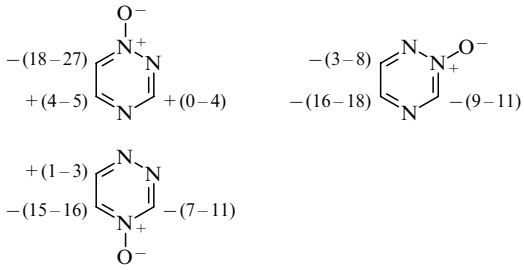
[a] In [$^2H_6$]DMSO.



The incorporation of an *N*-oxide group at position 4 of the triazine system shifts the signals of the H(3) and H(5) protons upfield by 0.1–0.3 ppm (the 9.28–9.47 and 8.55–8.90 ppm regions). It should be noted that, unlike the case of 1,2,4-triazines, these signals in 1,2,4-triazine 4-oxides appear as doublets (J = 1.8 Hz) (see Table 1).[31]

The ^{13}C NMR spectra are also changed upon the introduction of the *N*-oxide fragment. In 1,2,4-triazine 4-oxides, the signals of the carbon atoms in the *ortho*- and *para*-positions with respect to the N−O fragment are shifted upfield by 18–20 ppm for 1-oxides, 9–18 ppm for 2-oxides, and 10–15 ppm for 4-oxides in comparison with those of the corresponding 1,2,4-triazines,[39,58–62] but the signal of the carbon atom in the *meta*-position is almost not shifted (Table 2).[10,39]

Thus, comparison of the ^{13}C NMR spectra of 1,2,4-triazines and their oxides allows one to determine easily the position of the *N*-oxide group.



^{15}N NMR spectroscopic data also allow the determination of the position of the *N*-oxide group. On going from 1,2,4-triazines to their 1-oxides, the maximum upfield shift is observed for the nitrogen atom in position 1 [$\Delta\delta$ = −(83–87) ppm]. The signals of the N(2) and N(4) atoms are shifted upfield to a much smaller extent [$\Delta\delta$ = −(39–46) ppm and $\Delta\delta$ = −(22–24) ppm, respectively]. For 1,2,4-triazine 2-oxides, the situation is somewhat different. The signals of the N(1) and N(2) atoms are shifted upfield by almost the same value [$\Delta\delta$ = −(70–75) ppm], but the signal of the nitrogen atom in position 4 is almost not shifted [$\Delta\delta$ = −(13–23) ppm] (Table 3).[63–65]

The IR spectra of 1,2,4-triazine *N*-oxides,[53] as well as those of *N*-oxides of other azines,[1] contain a characteristic band of stretching vibration of the N−O group in the region near 1250 cm^{-1}.

The absoption maximum in the UV spectrum of 3,4-diphenyl-1,2,4-triazine 4-oxide is around 286 nm ($\log\varepsilon$ = 4.57).[53]

Table 3 Signals of cyclic nitrogen atoms in the ^{15}N NMR spectra of 1,2,4-triazines and their *N*-oxides[63] in [^{2}H$_6$]DMSO relative to MeNO$_2$.

Compound	δ / ppm			$\Delta\delta$/ ppm		
	N(1)	N(2)	N(4)	N(1)	N(2)	N(4)
1,2,4-Triazine	40.0	2.0	−62.0			
1,2,4-Triazine 1-oxide	−43.0	–	–	−83	–	–
3-Methoxy-1,2,4-triazine	36.0	−58.0	−124.4			
3-Methoxy-1,2,4-triazine 1-oxide	−50.0	−97.1	−148.0	−86.0	−38.9	−23.6
3-Amino-1,2,4-triazine	35.7	−61.0	−130.0			
3-Amino-1,2,4-triazine 1-oxide	−51.1	−107.0	−152.0	−86.8	−46.0	−22.0
3-Amino-1,2,4-triazine 2-oxide	−39.0	−137.0	−153.0	−74.7	−76.0	−23.0

Table 2 Chemical shifts of carbon atoms in the ^{13}C NMR spectra of 1,2,4-triazine *N*-oxides in [^{2}H$_6$]DMSO.

Compound	δ/ ppm			$\Delta\delta$/ ppm			Ref.
	C(3)	C(5)	C(6)	C(3)	C(5)	C(6)	
1,2,4-Triazine 1-oxide[a]	158.5	152.7	129.7	−0.4	3.1	−21.1	60
1,2,4-Triazine 2-oxide[a]	143.5	132.5	146.0	−14.6	−17.1	−4.8	60
3-Methoxy-1,2,4-triazine 1-oxide[a]	166.5	154.0	124.5	2.5	4.0	−18.5	10
3-Methoxy-1,2,4-triazine 2-oxide[a]	152.5	130.0	135.5	−11.5	−20.0	−7.5	10
3-Amino-1,2,4-triazine 1-oxide	165.0	155.9	120.7	1.7	6.1	−19.9	60
3-Amino-1,2,4-triazine 2-oxide	151.6	132.4	134.9	−11.7	−17.4	−5.7	60
3-(*N*,*N*-Dimethylamino)-1,2,4-triazine 1-oxide[a]	161.0	152.0	120.0	1.0	4.0	−18.0	10
3-(*N*,*N*-Dimethylamino)-1,2,4-triazine 2-oxide[a]	151.0	132.0	133.0	−9.0	−16.0	−5.0	10
3-Amino-5,6-dimethyl-1,2,4-triazine 1-oxide	166.0	164.3	119.4	3.9	5.4	−27.7	60
3-Amino-5,6-dimethyl-1,2,4-triazine 2-oxide	148.9	140.2	144.2	−13.2	−18.7	−2.9	60
3-Amino-5,6-dimethyl-1,2,4-triazine 4-oxide	154.4	143.0	148.7	−7.7	−15.9	1.6	60
5-Methyl-1,2,4-triazine 1-oxide[a]	158.7	166.1	129.1	1.7	5.6	−21.8	60
6-Phenyl-1,2,4-triazine 1-oxide	149.9	132.0	157.5	–	–	–	60
3-Methyl-6-phenyl-1,2,4-triazine 4-oxide	159.4	131.4	156.4	–	–	–	60
3,6-Diphenyl-1,2,4-triazine 4-oxide	156.2	132.8	155.6	–	–	–	60
3-Ethyl-6-phenyl-1,2,4-triazine 4-oxide	161.9	131.4	156.3	–	–	–	60
5-Ethyl-5-(indol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	161.0	135.5	156.7	–	–	–	62
5-(1-Methylindol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	149.0	139.4	157.3	–	–	–	62
3-Ethyl-5-(1-methylindol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	160.8	136.0	135.8	–	–	–	62
5-(1-Methylindol-3-yl)-3,6-diphenyl-1,2,4-triazine 4-oxide	156.1	136.1	156.0	–	–	–	62
5-(2-Methylindol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	149.9	142.8	160.9	–	–	–	62
3-Methyl-5-(2-methylindol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	157.9	140.2	158.9	–	–	–	62

[a] In $CDCl_3$.

A molecular ion peak (often with the maximum intensity) and intense $[M-16]^+$ and $[M-17]^+$ peaks typical of this class of compounds are observed in the mass spectra of 1,2,4-triazine 1- and 2-oxides. The fragmentation of 1,2,4-triazine 1- and 2-oxides is similar, which prevents an unambiguous determination of the position of the *N*-oxide group.[62,66,67] However, a somewhat different picture is observed in the case of 1,2,4-triazine 4-oxides. The characteristic feature of their mass spectra is the existence of an intense molecular ion peak and a very weak $[M-16]^+$ peak.[31]

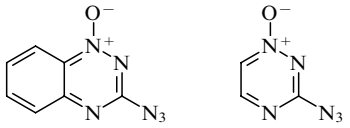
The X-ray diffraction data for 3,6-diphenyl-5-(indol-3-yl)-1,2,4-triazine 4-oxide[62] showed that the 1,2,4-triazine 4-oxide fragment and the substituents are non-coplanar, the slopes of the corresponding planes being within 30–50°.

IV. Chemical properties of 1,2,4-triazine-*N*-oxides

1. Tautomerism

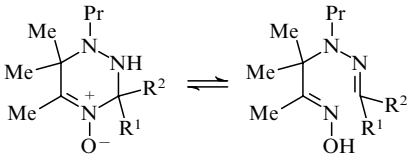
The amino–imino tautomerism is typical of 3-amino-1,2,4-triazine 4-oxides **2a**. This is the reason for the formation of 2-oxides in the oxidation of 3-amino-1,2,4-triazines **1**.[10]

3-Azido-1,2,4-benzotriazine 1-oxides **69** exist only in the form of azides, both in the crystal state and in solution. This is also true for 3-azido-1,2,4-triazine 1-oxides **70**, which have not been found in the tetrazole form in any aggregation state.[68–70]



69 **70**

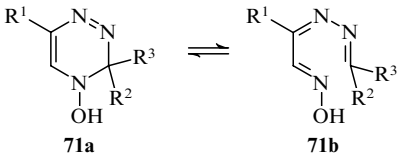
Ring–chain tautomerism is observed for the series of 1,2,3,6-tetrahydro-1,2,4-triazine 4-oxides **61**.[51] These compounds exist solely as hydrazones **61b** both in solution and in the crystal form. In aprotic non-polar solvents (*e.g.*, CCl_4), the fraction of the cyclic form **61a** is as high as 45%, depending on the nature of the substituents R^1 and R^2.



61a **61b**

R^1	R^2	Proportion of the forms in CCl_4 (%)	
		61a	**61b**
Me	Me	25	75
H	H	45	55
Me	H	40	60
Pr^i	H	10	90
p-ClC_6H_4	H	0	100

Ring–chain transformations are also observed for 3,4-dihydro-4-hydroxy-1,2,4-triazines **71**. For example, compounds **71** in DMSO-d_6 exist both in a cyclic form **71a** and in an open form **71b**. It was found that aliphatic substituents at position 3 of 3,4-dihydro-1,2,4-triazine **71** shift the equilibrium towards the cyclic form **71a**, while aromatic and heteroaromatic substituents, towards the open form **71b** (Table 4). An increase in temperature increases the fraction of hydrazone **71b**. Analysis of high-resolution mass spectra of these compounds made it possible to find out that the cyclic form **71a** prevails (70%–90%) in the gas phase.[71]

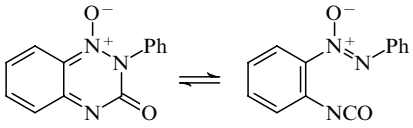


71a **71b**

Table 4. Ratio of the cyclic (**71a**) to the open (**71b**) forms of 3,4-dihydro-4-hydroxy-6-phenyl-1,2,4-triazine **71** in [$^2H_6$]DMSO and in gas phase.[71]

R^1	R^2	R^3	Isomer ratio (%)			
			solution		gas phase	
			71a	**71b**	**71a**	**71b**
Ph	H	Me	100	0	72	22
Ph	H	Et	100	0		
Ph	H	Pr^i	100	0	90	10
Ph	H	C_7H_{15}	90	10	80	20
Ph	H	Ph	23	77	82	18
Ph	H	2-$NO_2C_6H_4$	5	95		
Ph	H	4-$NO_2C_6H_4$	8	92		
Ph	H	4-HOC_6H_4	7	93	75	25
Ph	H	3,4-$(HO)_2C_6H_3$	35	65	85	15
Ph	H	4-BrC_6H_4	15	85	11	89
Ph	H	4-$NMe_2C_6H_4$	0	100		
Ph	H	CO_2H	100	0		
Ph	H		7	93		
Ph	Me	Me	90	10		
Ph	Me	Ph	50	50		
Ph	Me	CH_2CO_2Et	0	100		
Ph	$-(CH_2)_4-$		96	4		
Ph	$-(CH_2)_5-$		82	18		
Me	H	4-$NO_2C_6H_4$	0	100		
Me	H	4-HOC_6H_4	0	100		
Me	H	4-$NMe_2C_6H_4$	0	100		

2-Phenyl-1,2,4-benzotriazin-3(2*H*)-one 1-oxide **72**, which exists in the cyclic form **72a** when in the crystal, undergoes ring opening in solution to give 2-isocyanatoazoxybenzene **72b**.[72]

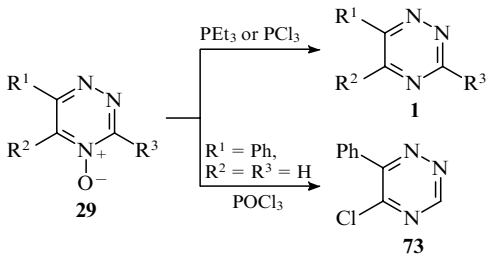


72a **72b**

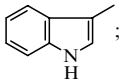
2. Deoxygenation

Elimination of oxygen (deoxygenation) occurs in 1,2,4-triazine *N*-oxides, as well as in other azine *N*-oxides, upon treatment with reducing agents.

The reaction of 1,2,4-triazine *N*-oxides **29** with triethylphosphine or PCl_3 resulted in the corresponding 1,2,4-triazines **1** (in 65%–95% yield), which were impossible to synthesise by other methods.[31,35] If $POCl_3$ is used in this reaction, deoxygenation is accompanied by chlorination of 1,2,4-triazine. For example, 5-chloro-6-phenyl-1,2,4-triazine **73** was obtained in 37% yield from 6-phenyl-1,2,4-triazine 4-oxide.[73]

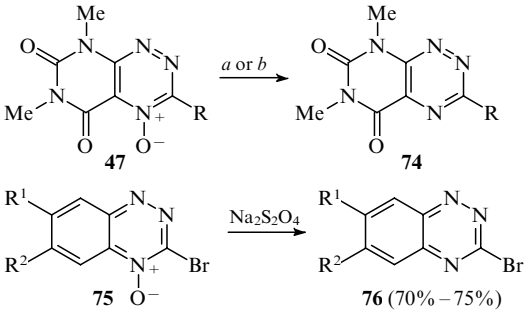


29 **1** **73**

R^1 = H, Me, Ph, 4-$MeOC_6H_4$; R^2 = H, Me, Ph, ;

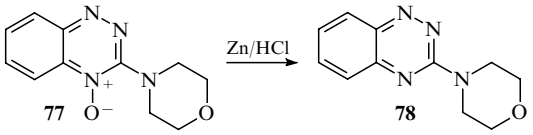
R^3 = H, Me, Ph.

Sodium dithionite can be used for the reduction of 1,2,4-triazine 4-oxides. This method has been used in the synthesis of fervenulins **74** from fervenulin 4-oxides **47**[41] and 3-bromo-1,2,4-benzotriazines **76** from 3-bromo-1,2,4-benzotriazine 4-oxides **75**.[69] Boiling of fervenulin 4-oxide **47** in DMF results in its thermal deoxygenation to form fervenulin **74**.[40]

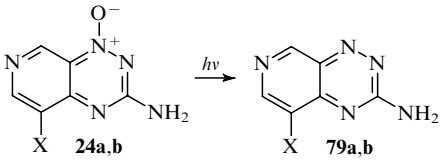


(*a*): $Na_2S_2O_4$ (55% – 90%); (*b*): DMF, 150 °C (60%).

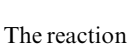
The reaction of 3-morpholino-1,2,4-benzotriazine 4-oxide **77** with zinc in hydrochloric acid afforded 3-morpholino-1,2,4-benzotriazine **78**.[74]



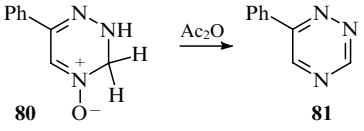
UV irradiation of 3-aminopyrido[4,3-*e*]-1.2.4-triazine 1-oxides **24a**,**b** or 1,2,4-triazine 4-oxides **29** is also accompanied by the loss of the *N*-oxide group [75, 76] and gives the corresponding 3-aminopyrido[4,3-*e*]-1,2,4-triazines **79a**,**b** or 1,2,4-triazines **1**.



X = H (**a**), Cl (**b**).



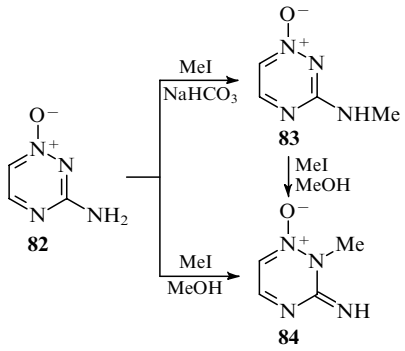
The reaction of 2,3-dihydro-6-phenyl-1,2,4-triazine 4-oxide **80** with acetic anhydride leads to deoxygenation and aromatisation of the former to give 6-phenyl-1,2,4-triazine **81**.[77]



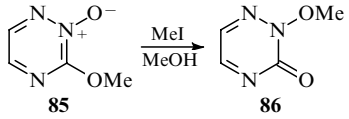
3. Reaction with electrophilic agents

a. Alkylation

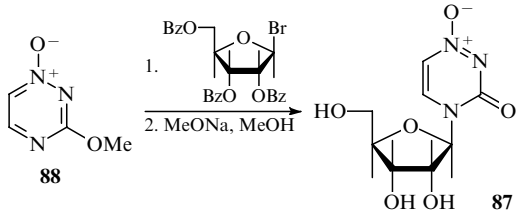
The reaction of 3-amino-1,2,4-triazine 1-oxide **82** with methyl iodide in the presence of sodium bicarbonate results in methylation of the amino group to give 3-methylamino-1,2,4-triazine 1-oxide **83**. In neutral media, the N(3) atom of the cycle in 1,2,4-triazine 1-oxide **82** undergoes methylation resulting in 3-imino-2-methyl-1,2,4-triazine 1-oxide **84**. It is interesting that 1-oxide **83** undergoes rearrangement to 1-oxide **84** in methanol in the presence of methyl iodide.



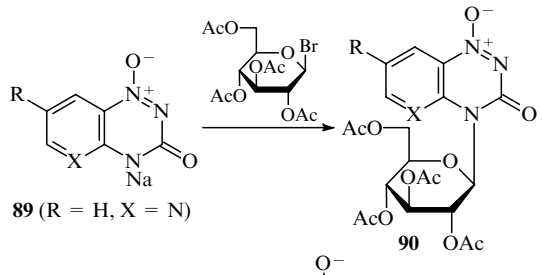
3-Methoxy-1,2,4-triazine 1-oxide **85** undergoes the same rearrangement under the same conditions and transforms into 2-methoxy-1,2,4-triazin-3-one **86**.[78]

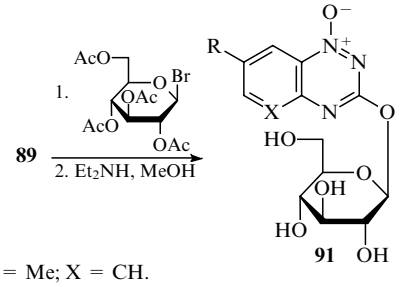


An abnormal nucleoside, 4-(β-D-ribofuranosyl)-1,2,4-triazin-3(4*H*)-one 1-oxide **87**, was obtained in 38% yield by the reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide with 3-methoxy-1,2,4-triazine 1-oxide **88** followed by the removal of the benzoyl protective groups with sodium methoxide.[11]



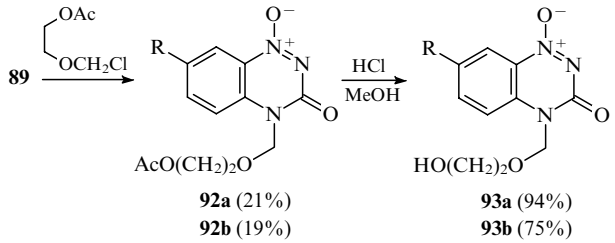
The reaction of the sodium salt of pyrido[2,3-*e*]-1.2.4-triazine-3(4*H*)-one 1-oxide **89** (X = N) or 1,2,4-benzotriazine-3(4*H*)-one 1-oxides **89** (X = CH) with acetobromoglucose allows one to obtain the tetraacetyl derivatives of β-D-glucopyranosides **90**, the deacetylation of which affords nucleosides **91**.[79]





R = Me; X = CH.

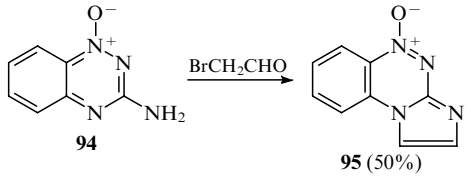
The reaction of compounds **89** (X = CH; R = H, Me) with 2-chloromethoxyethyl acetate results in *N*-alkylation products **92a**,**b**. Their subsequent hydrolysis affords 4-(2-hydroxyethoxymethyl)-1,2,4-benzotriazin-3(4*H*)-one 1-oxides **93a**,**b**.[79]



92a (21%) **93a** (94%)
92b (19%) **93b** (75%)

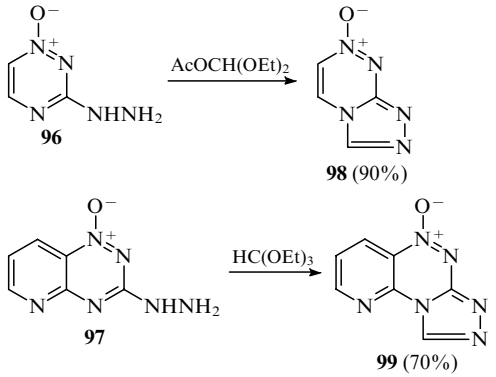
R = H (**a**), Me (**b**).

3-Amino-1,2,4-benzotriazine 1-oxide **94** undergoes the Chichibabin reaction with bromoacetaldehyde to give imidazo[2,1-*c*]-1.2.4-benzotriazine 1-oxide **95**.[80]



94 **95** (50%)

Reactions of 3-hydrazino-1,2,4-triazine 1-oxide **96** or 3-hydrazinopyrido[2,3-*c*]-1.2.4-triazine 1-oxide **97** with diethoxymethyl acetate or triethyl orthoformate followed by cyclisation afford the corresponding pyrazolo[3,4-*c*]-1.2.4-triazine 6-oxides **98** and **99**.[81–83]

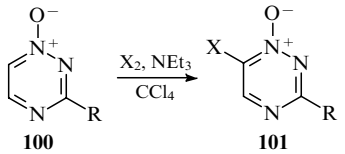


96 **98** (90%)

97 **99** (70%)

b. Electrophilic substitution of hydrogen

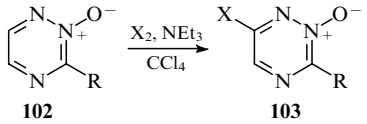
Halogenation of 3-R-1,2,4-triazine 1- and 2-oxides has been described.[67,84] The reaction of 3-methoxy and 3-amino(alkylamino)-1,2,4-triazine 1-oxides **100** with chlorine or bromine in CCl_4 in the presence of triethylamine results in the corresponding 6-chloro- or 6-bromo-1,2,4-triazine 1-oxides **101**.



100 **101**

X = Cl, Br; R = OMe, NH_2, NHMe, NMe_2.

Halogenation of 3-methoxy- and 3-methyl(dimethyl)amino-1,2,4-triazine 2-oxides **102** occurs in a similar way to give 6-halo-derivatives **103**.

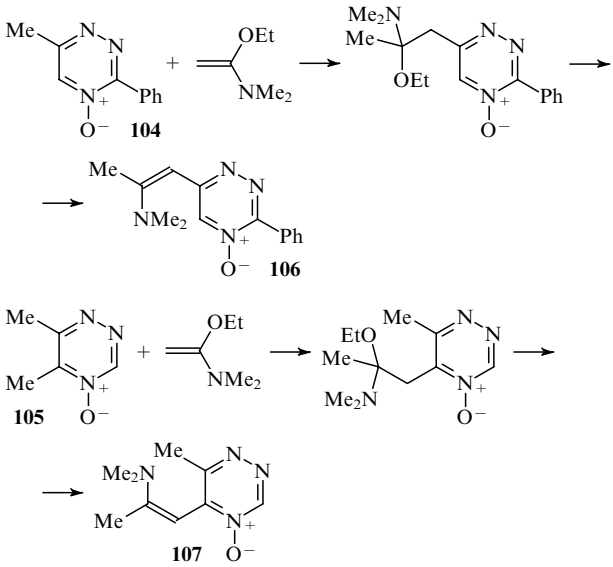


102 **103**

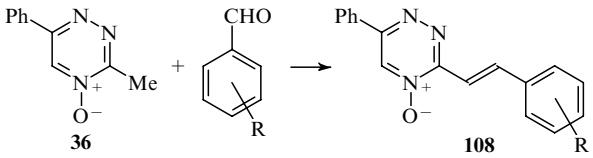
X = Cl, Br; R = OMe, NHMe, NMe_2.

c. Other reactions

1-(Dimethylamino)-1-ethoxyethylene acts as an electrophilic agent in the reactions with 1,2,4-triazine 4-oxides **104** and **105** containing a methyl group at position 5 and/or 6. The addition of an olefin to the methyl group followed by elimination of ethanol results in the corresponding (2-dimethylamino)-1-propenyl-1,2,4-triazine 4-oxides **106** and **107**.[85]



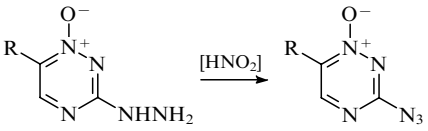
The reactivity of the hydrogen atoms of the methyl group in 1,2,4-triazine 4-oxide **36** allows one to make this compound react with nitrobenzaldehydes. This reaction gave 3-[2-(R-nitrophenyl)-vinyl]-6-phenyl-1,2,4-triazine 4-oxides **108**.[76]



36 **108**

R = 2-NO_2 (27%), 3-NO_2 (47%), 4-NO_2 (48%).

The reaction of 3-hydrazino-1,2,4-triazine 1-oxides **109** with nitrous acid affords 3-azido-1,2,4-triazine 1-oxides **110**.[68,84]



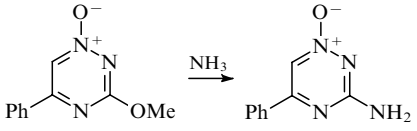
109 **110**

R = H (80%), Me(82%), Ph (85%).

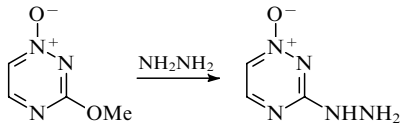
4. Reactions with nucleophilic agents

a. Nucleophilic substitution of readily leaving groups

Substitution of nucleofugal groups is a widespread method for the modification of 1,2,4-triazine *N*-oxides. The reaction of 3-methoxy-5-phenyl-1,2,4-triazine 1-oxide **111** with ammonia afforded 3-amino-5-phenyl-1,2,4-triazine 1-oxide **112**. The reaction of 3-methoxy-1,2,4-triazine 1-oxide **87** with hydrazine results in 3-hydrazino-1,2,4-triazine 1-oxide **113**.[14]

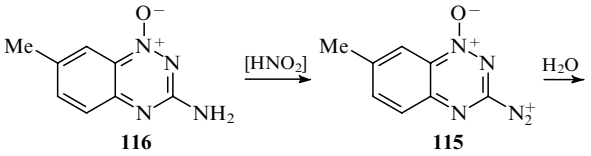


111 **112** (51%)

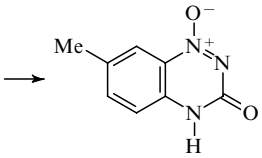


87 **113** (94%)

7-Methyl-1,2,4-benzotriazin-3(4*H*)-one 1-oxide **114** can be obtained in a good yield by replacement of the diazo group by OH in 3-diazo-7-methyl-1,2,4-benzotriazine 1-oxide **115**, which is formed upon the reaction of the corresponding amino derivative **116** with nitrous acid.[79]

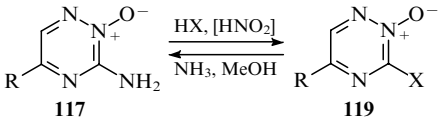


116 **115**



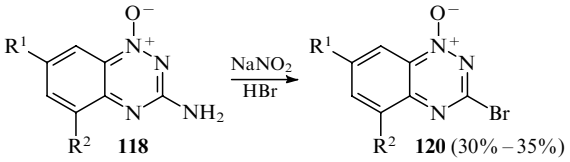
114 (88%)

Similarly, diazotisation of 3-amino-1,2,4-triazine 2-oxides **117** or 1-oxides **118** results in the replacement of the diazo group by a halogen on treatment with hydrochloric or hydrobromic acids and affords the corresponding 2-oxides **119** [10] or 1-oxides **120**.[69]



117 **119**

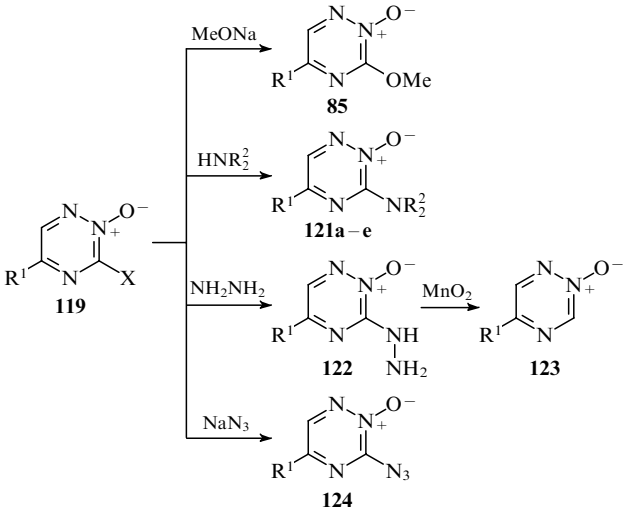
X = Cl: R = H (34%), Me (32%), Ph (26%); X = Br, R = H (47%).



118 **120** (30%–35%)

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

In turn, the halogen atom can be replaced by a different functional group. 3-Methoxy-1,2,4-triazine 2-oxide **85** (R = H) was obtained by the reaction of 3-bromo-1,2,4-triazine 2-oxide **119** with sodium methoxide. When secondary amines are used as nucleophiles, 3-amino-derivatives of 1,2,4-triazine 2-oxides **121a**–**e** are formed. 3-Hydrazino-1,2,4-triazine 2-oxide



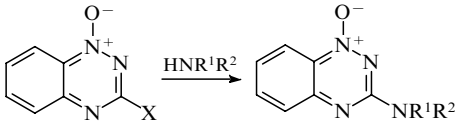
119 **85** **121a–e** **122** **123** **124**

R^1 = H, Me; X = Br.

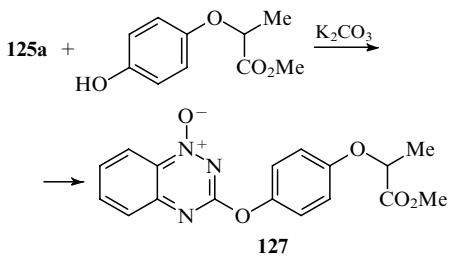
Compound	R^1	NR^2_2	Yield (%)	Ref.
85	H		10	10
121a	H		95	10
121b	Me		90	10
121c	H		93	10
121d	H		95	10
121e	H	NMe_2	93	10
122	H		69	10
123	H		27	10
124	H		86	68

122 was synthesised by the replacement of bromine in 2-oxide **119** by hydrazine. The subsequent oxidation of compound **122** with Mn(IV) oxide afforded 1,2,4-triazine 2-oxide **123**,[10] but the reaction of compound **119** with sodium azide gave 3-azido-1,2,4-triazine 2-oxide **124**.[68]

Reactions of 3-chloro- or 3-methylthio-1,2,4-benzotriazine 1-oxides **125a**,**b** with amines result in 3-amino-derivatives of 1,2,4-benzotriazine 1-oxides **126**.[24, 74, 86, 87] Replacement of the halogen in 3-chloro-1,2,4-benzotriazine 1-oxide **125a** upon the reaction with methyl 2-(4-hydroxyphenoxy)propionate proceeds in a similar way. For example, compound **127** was synthesised by this method.[88, 89]



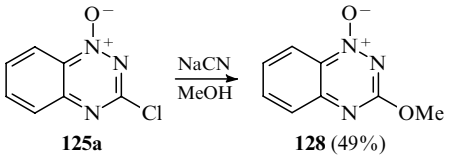
125a,**b** **126**



127

X = Cl (**a**), SMe (**b**).

Replacement of chlorine in the 3-chloro-derivative **125a** on treatment with sodium cyanide in methanol affords 3-methoxy-1,2,4-benzotriazine 1-oxide **128**.[90]



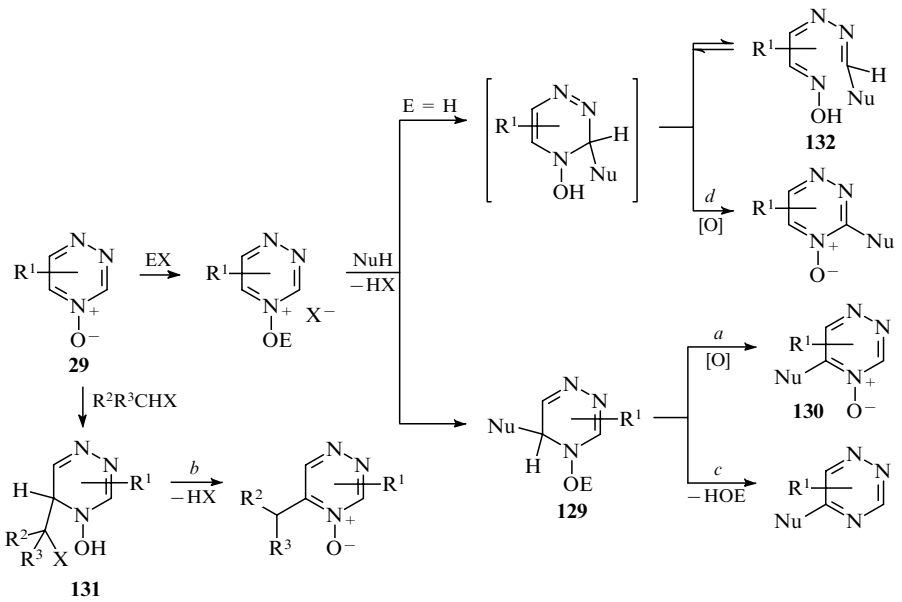
125a **128** (49%)

b. Nucleophilic substitution of hydrogen

The mechanism of the nucleophilic substitution of hydrogen (S_NH) in 1,2,4-triazine *N*-oxides has been studied in most detail using 1,2,4-triazine 4-oxides **29** as an example. This mechanism is common to all 1,2,4-triazine 4-oxides. The reactions of nucleophilic substitution of hydrogen in 4-oxides **29** occur according to the 'addition–elimination' scheme; the process can stop at the step of addition to form adducts **129**. Due to the low probability of the elimination of such a particle as a hydride ion,[91] aromatisation of these adducts can follow several paths.

Oxidative aromatisation leads to products of the S_NH-reaction of the type **130** [Scheme 1, pathway (*a*)]. Auto-aromatisation of the σ^H-adducts in two directions is also possible. For example,

Scheme 1

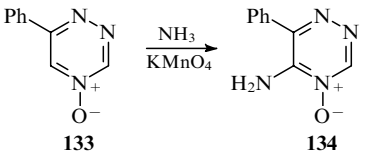


E = H, COR^4.

1,2-elimination of HX is possible in nucleophiles carrying a vicarious nucleofugal group X. In this case, a hydrogen atom is eliminated from the substrate and the X group is eliminated from the reactive fragment of the σ^H-adduct **131** [Scheme 1, pathway (*b*)]. Makosza [92] named such reactions vicarious nucleophilic substitution.

Another variant of auto-aromatisation is the elimination of the HOE molecule from the σ^H-adduct **129** which is formed from the cationic derivatives of 1,2,4-triazine *N*-oxides [Scheme 1, pathway (*c*)]. In this case, S_NH-substitution is accompanied by the loss of an oxygen atom. It should be noted that both the hydrogen atom and the vicarious OE group are eliminated from the substrate fragment of the intermediate. Conceptually, mediated (vicarious) nucleophilic substitution of hydrogen atom is observed in this case. Sometimes, the σ^H-adducts exist in a non-cyclic form. The ring opens readily after the addition of a nucleophile to the 1,2,4-triazine 4-oxide. This process is reversible and the equilibrium is shifted towards the open form **132** [Scheme 1, pathway (*d*)]. In this way, the σ^H-adduct is eliminated from the reaction; however, it exists in quasi-steady-state concentrations and can be easy oxidised to the corresponding 1,2,4-triazine 4-oxide.

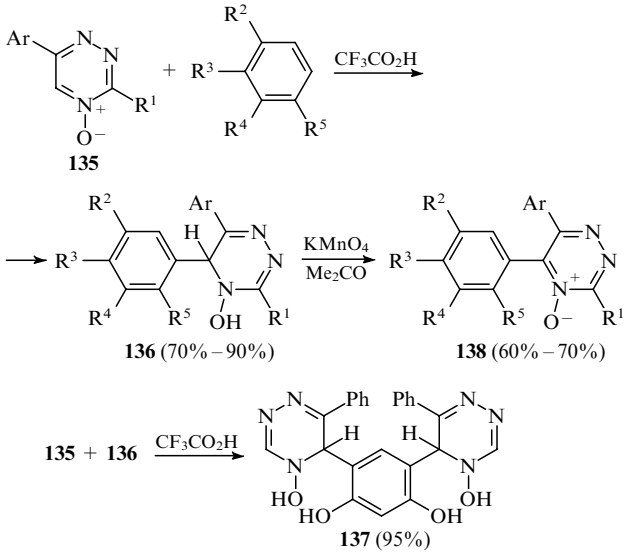
Oxidative aromatisation [see Scheme 1, path (*a*)] is achieved by the amination of 6-phenyl-1,2,4-triazine 4-oxide **133** with liquid ammonia in the presence of potassium permanganate as the oxidising agent. The reaction affords 5-amino-6-phenyl-1,2,4-triazine 4-oxide **134**.[93]



The reaction of 6-aryl-1,2,4-triazine 4-oxides **135** with phenol, 2,6-dimethylphenol, resorcinol and phenetol in the presence of trifluoroacetic acid results in stable σ^H-adducts, 6-aryl-2,4-dihydro-4-hydroxy-5-Nu-1,2,4-triazines **136** (Nu = 2-hydroxy-, 2-ethoxy-, 4-ethoxy- or 2,4-dihydroxyphenyl). The reaction of resorcinol ($R^2 = R^4 = OH$, $R^3 = R^5 = H$) with a twofold excess of triazine *N*-oxide **135** ($R^1 = H$, Ar = Ph) affords 4,6-bis(4-hydroxy-6-phenyl-1,2,4-triazin-5-yl)resorcinol **137**.[94]

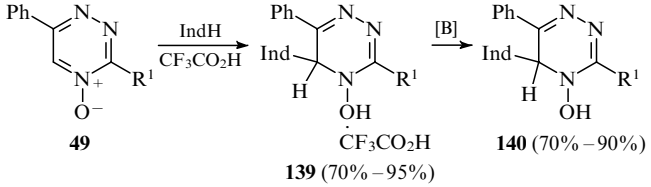
The formation of σ^H-adducts in S_NH-reactions of azine *N*-oxides was confirmed directly for the first time by the isolation and identification of compounds **136**. Before that, it was only postulated in the discussions of the mechanism of such reactions.

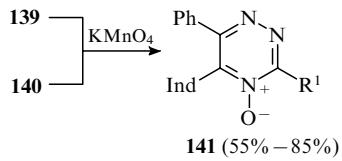
Dihydro-1,2,4-triazines **136** are rather stable compounds. Boiling in butanol, DMF, or trifluoroacetic acid does not result in their thermal dehydration [see Scheme 1, pathway (*c*)]. At the same time, their oxidative aromatisation [pathway (*b*)] occurs readily and in high yields. For example, compounds **136** react with potassium permanganate in acetone to form 6-aryl-5-(4-hydroxyphenyl)-1,2,4-triazine 4-oxides **138**.[94]



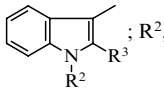
Ar = Ph, *p*-ClC_6H_4; R^1 = H, Me; R^2, R^3, R^4, R^5 = H, OH, OEt.

3-R^1-6-phenyl-1,2,4-triazine 4-oxides **49** react with indole or its 1- or 2-methyl derivatives in a similar way. When the reaction is carried out in the presence of trifluoroacetic acid, stable 4-hydroxy-5-(indol-3-yl)-6-phenyl-4,5-dihydro-1,2,4-triazines are formed.[62] They were isolated both as trifluoroacetates **139** and as free bases **140**. Oxidative aromatisation of the σ^H-adducts obtained with potassium permanganate in acetone affords 3-R^1-5-(indol-3-yl)-6-phenyl-1,2,4-triazine 4-oxides **141**.[62]

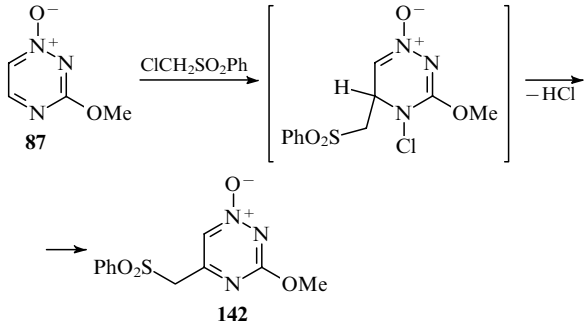




141 (55% – 85%)

R^1 = H, Me, Et, Ph; Ind = ; R^2, R^3 = H, Me.

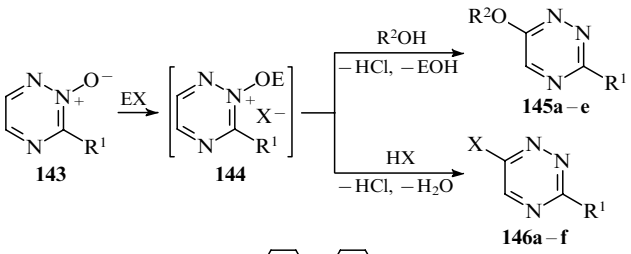
The reaction of 3-methoxy-1,2,4-triazine 1-oxide **87** with chloromethyl phenyl sulfone gives an intermediate adduct, whose further aromatisation [see Scheme 1, path (*b*)] leads to 3-methoxy-5-(phenylsulfonyl)-1,2,4-triazine 1-oxide **142** in 70% yield.[95]



Another variant of auto-aromatisation occurs in the reaction of 3-amino-1,2,4-triazine 2-oxides **143** with alcohols in the presence of HCl or acetyl chloride. Elimination of water or acetic acid from the adduct **144** results in 3-amino-6-alkoxy-1,2,4-triazines **145a – e.**[84]

It should be noted that 1,2,4-triazine 1-oxides do not react with alcohols under these conditions.[84]

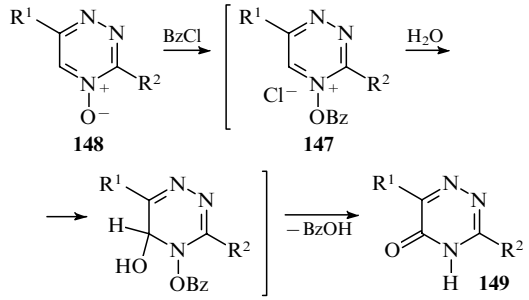
6-Chloro(bromo)-3-amino-1,2,4-triazines **146a – f** were obtained on passing gaseous hydrogen chloride or hydrogen bromide through a solution of 3-amino-1,2,4-triazine 2-oxide **143**.[67]



R^1 = NH_2, NHMe, NMe_2, , ; E = H, Ac; X = Cl, Br; R^2 = Me, Et, Pr^i.

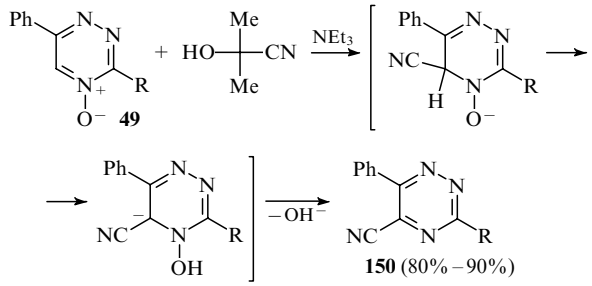
Compound	R^1	R^2O	X	Yield (%)	Ref.
145a	NH_2	OMe		71	84
145b	NH_2	OEt		64	84
145c	NHMe	OMe		50	84
145d	NMe_2	OMe		51	84
145e	NH_2	OPr^i		65	84
146a	NHMe		Cl	85	68
146b	NMe_2		Cl	64	67
146c			Cl	80	67
146d			Cl	50	67
146e	NHMe		Br	25	67
146f	NMe_2		Br	41	67

Acyl salts of 1,2,4-triazine 4-oxides **147** synthesised by the reaction of benzoyl chloride with the corresponding 1,2,4-triazine 4-oxides **148** react with water according to pathway (*c*) (Scheme 1). It is evident that after addition of the nucleophile at position 5 of the triazine ring, auto-aromatisation of the adduct occurs with elimination of benzoic acid and formation of 1,2,4-triazin-5-ones **149**.[76]



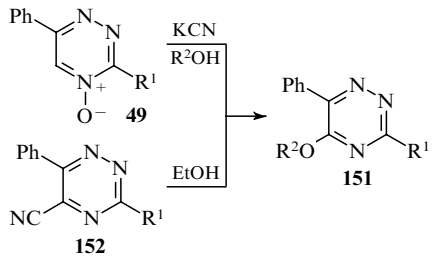
R^1, R^2 = H, Me, Et.

The reaction of 1,2,4-triazine 4-oxides **49** with acetone cyanohydrin in the presence of triethylamine affords 5-cyano-1,2,4-triazines **150**.[96]



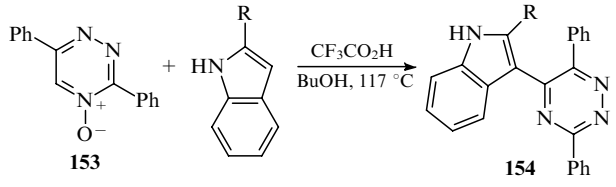
R = H, Me, Ph.

If potassium cyanide in alcohols (ethanol, propanol, isopropanol) is used as a cyanating agent, 5-alkoxy-1,2,4-triazines **151** are formed in 80% – 90% yields. Their formation can be explained by replacement of the cyano group by an alkoxide. In fact, 5-cyano-1,2,4-triazines **152** slowly react with ethanol at room temperature to give 3-R^1-6-phenyl-5-ethoxy-1,2,4-triazines **151**.[96]



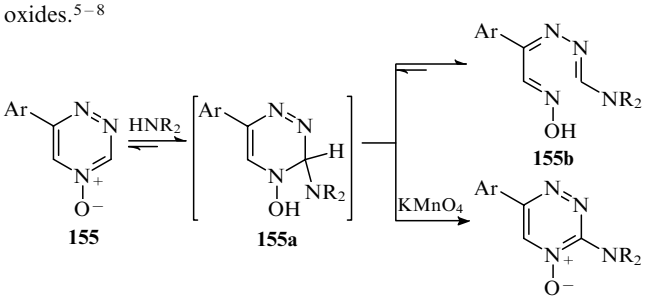
R^1 = H, Me, Ph; R^2 = Et, Pr^i.

The reaction of 1,2,4-triazine 4-oxide **153** with indole or 2-methylindole in boiling butanol in the presence of trifluoroacetic acid is accompanied by auto-aromatisation of the products of addition of the nucleophile to the 1,2,4-triazine 4- oxide and results in 5-(indol-3-yl)- and 5-(2-methylindol-3-yl)-3,6-diphenyl-1,2,4-triazines **154**.[97]



R = H (30%), R = Me (55%).

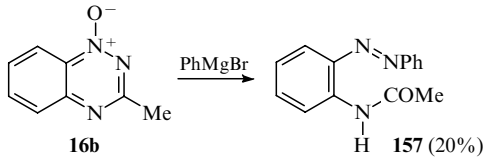
The reaction of 6-aryl-1,2,4-triazine 4-oxides **155** with dialkylamines or cycloalkylamines occurs by pathway (*d*) (Scheme 1).[98] The adducts **155a**, which are in equilibrium with the open-chain form, *N*,*N*-disubstituted 3-aryl-1,4,5-triaza-1,3,5-hexatrien-1-ols **155b**, are formed in the first step. In this case, the equilibrium is shifted towards the compounds **155b**. In spite of the low concentration of the form **155a**, oxidation of the compounds **155** with potassium permanganate in solution affords 3-amino-6-aryl-1,2,4-triazine 4-oxides **156**. It is noteworthy that it is possible to withdraw the cyclic tautomer from the reaction zone, which allows one to obtain the products of hydrogen substitution at position 3 of the triazine system when the position 5 is free. Such a substitution has been carried out for the first time. Note that all the experimental data obtained until now have indicated that position 5 is the most reactive in 1,2,4-triazines and their oxides.[5–8]



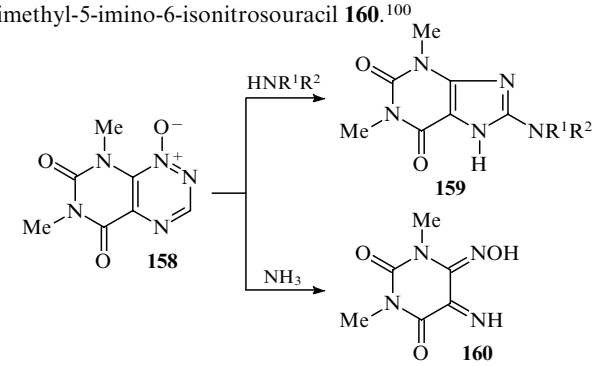
NR_2 = NMe_2, NEt_2, N, N, N, NH, N, O; Ar = Ph, *p*-ClC_6H_4.

c. Reaction of 1,2,4-triazine *N*-oxides with nucleophiles accompanied by destruction of the ring

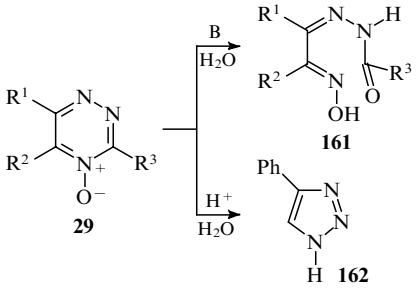
In addition to the formation of nucleophilic substitution products, the reaction of 1,2,4-triazine *N*-oxides with nucleophiles results in the opening, narrowing, or fragmentation of the 1,2,4-triazine ring. For example, the reaction of 3-methyl-1,2,4-benzotriazine 1-oxide **16b** with phenylmagnesium bromide affords 2-phenylazoacetanilide **157**.[99]



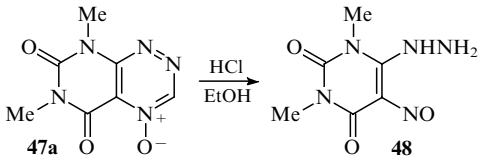
The reaction of fervenulin 1-oxides **158** with secondary amines results in narrowing of the triazine ring and formation of 2-amino-5,7-dimethylimidazo[4,5-*e*]pyrimidine-4,6(5*H*,7*H*)-diones **159**. The reaction of the same *N*-oxide with ammonia affords 1,3-dimethyl-5-imino-6-isonitrosouracil **160**.[100]



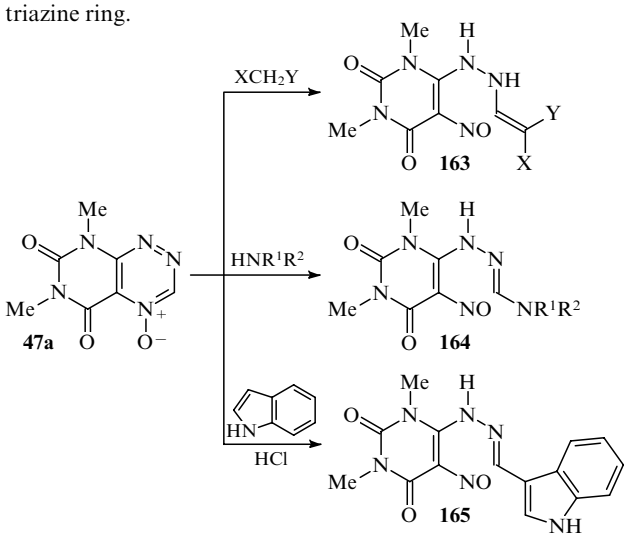
1,2,4-Triazine 4-oxides undergo hydrolysis both in acidic and basic media. For example, in the presence of 2 M KOH, opening of the triazine ring in 1,2,4-triazine 4-oxides **29** occurs with the formation of *N*′-(2-hydroxyiminoethylidene)hydrazides of carboxylic acids **161**. Hydrolysis of the 4-oxides **29** in acid media results in narrowing of the 1,2,4-triazine ring to 1,2,3-triazole, in particular, in the formation of the compound **162**.[76]



The reaction of fervenulin 4-oxide **47a** with hydrogen chloride in ethanolic solution leads to the opening of the triazine ring and the formation of 1,3-dimethyl-5-nitroso-6-hydrazouracil **48**. In fact, this reaction is reverse to that for the synthesis of the fervenulin 4-oxide.[40, 101]



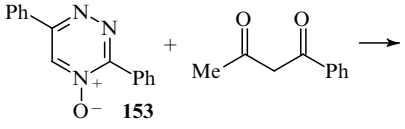
Reactions of the fervenulin 4-oxide **47a** with CH-active compounds are also accompanied by the destruction of the triazine ring.

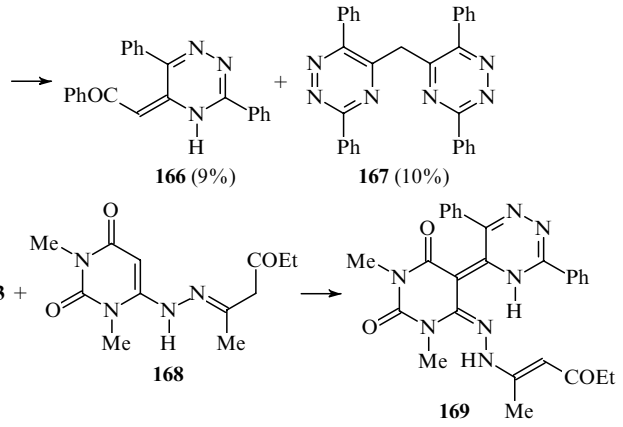


X, Y = CO_2Et, COMe; X = NO_2, Y = CO_2Et.

In this case, 1,3-dimethyl-5-nitroso-6-(*N*′-ethen-1-ylhydrazino)uracils **163** are formed.[102] Fervenulin 4-oxide **47a** reacts with amines or indoles in a similar way. The nucleophilic attack is accompanied by opening of the 1,2,4-triazine ring and formation of 6-aminomethylenehydrazino-1,3-dimethyl-5-nitrosouracil **164**[103] or 1,3-dimethyl-5-nitroso-6-[*N*′-(indol-3-yl)methylidenehydrazino]uracil **165**.[104, 105]

The reaction of 3,6-diphenyl-1,2,4-triazine 4-oxide **153** with benzoylacetone under basic catalysis conditions (DMSO, NEt_3) affords 1,2,4-triazine **166** in 9% yield and bis(1,2,4-triazin-5-ylmethane) **167**.[97] According to literature data,[97] the 1,3-dimethyluracil derivative **168** with two reactive centres reacts with the *N*-oxide **153** at the uracil fragment only to form compound **169**.



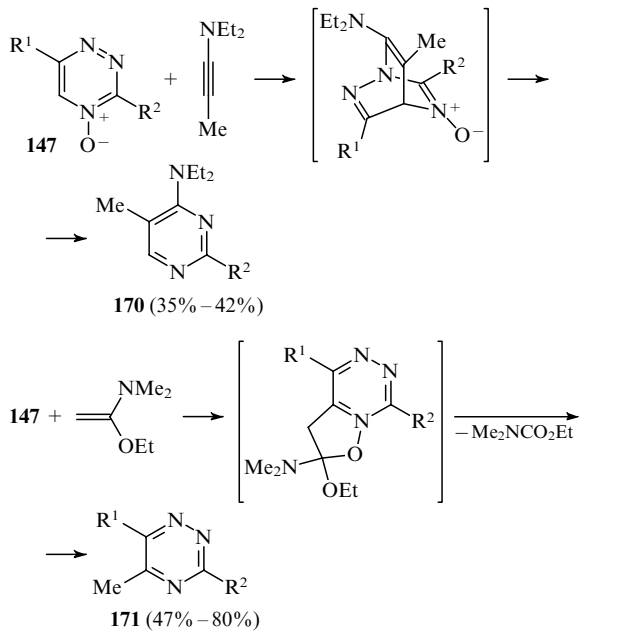


166 (9%) **167** (10%)

168 **169**

5. Reactions with dienophiles

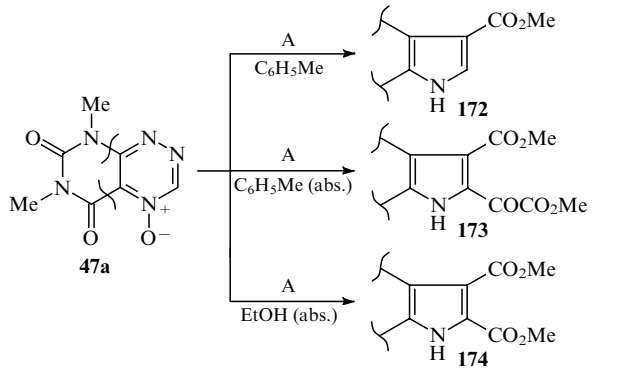
The direction of the reaction of 1,2,4-triazine *N*-oxides with dienophiles differs substantially from that for 1,2,4-triazines. 1,2,4-Triazine 4-oxides **147** act as 1,3-dienes only in the reaction with *N*,*N*-diethyl-*N*-(1-propynyl)amine giving 2-R^2-5-methyl-4-(dimethylamino)pyrimidines **170**. The reaction of these 1,2,4-triazine 4-oxides with 1-(dimethylamino)-1-ethoxyethylene occurs as 1,3-dipolar cycloaddition to produce the corresponding 5-methyl-1,2,4-triazines **171**.[85]



147 **170** (35%–42%)

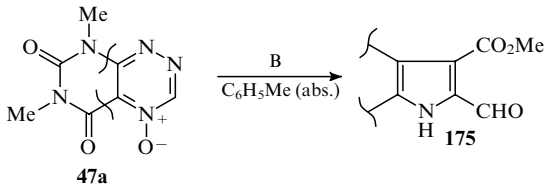
171 (47%–80%)

The reaction of the fervenulin 4-oxide **47a**, which is not substituted at position 3, with dimethyl acetylenedicarboxylate in various solvents affords compounds **172**–**174**.



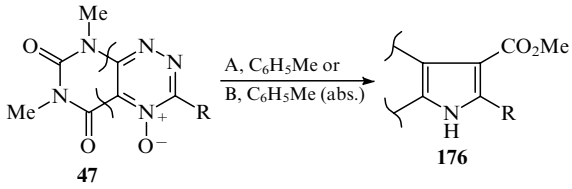
47a **172** **173** **174**

If methyl propionate is used as the reagent, 6-formyl-7-(methoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **175** is formed.



47a **175**

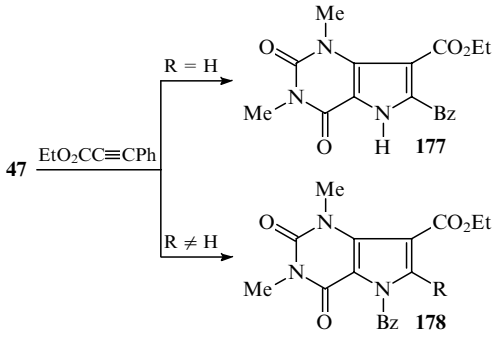
A similar reaction of 3-substituted fervenulin 4-oxides **47** (R = Me, Et, Ph) with alkyl acetylenecarboxylates gives compounds **176**.



47 **176**

A — $MeO_2CC{\equiv}CCO_2Me$; B — $MeO_2CC{\equiv}CH$.

The reaction of fervenulin 4-oxides **47** with ethyl phenylpropionate also follows the pathway described above to give, depending on the presence of a substituent at position 3, 6-benzoyl- or 6-R-5-benzoyl-7-(ethoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **177** and **178**, respectively.[106, 107]



177 **178**

V. Conclusion

A variety of methods for the synthesis and subsequent transformations of 1,2,4-triazine *N*-oxides makes these compounds very promising for the preparation of new 1,2,4-triazines with or without the *N*-oxide group. Methods of direct functionalisation of unsubstituted triazines (S_NH-processes) and their transformations under the action of nucleophilic agents and dienophiles resulting in azapyrines are of undisputable interest for the synthesis of new biologically active compounds.

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