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Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Four Extra Heteroatoms 2:2

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Comprehensive Heterocyclic Chemistry IV

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Four Extra Heteroatoms 2:2

Author Contact Information

Aurélie Claraz

Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Sud, Université Paris-Saclay, 1, av. de la Terrasse, Gif-sur-Yvette 91198 Cedex, France.

aurelie.claraz@cnrs.fr

+33 1 69 82 30 84

Abstract

Bicyclic 5-6 systems with one ring junction nitrogen atom and two extra heteroatoms (nitrogen, sulfur and oxygen) in both cycles are reviewed in this chapter. Literature data from 2007 to 2019 are considered. Among all the possible ring systems, 18 different structural backbones have been found in this period covering various triazolothiadiazines, oxadiazolotriazines, thiadiazolotriazines, and triazolotriazines derivatives. Fully as long as partially unsaturated regioisomers are examined. Most references deal with [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines. Theoretical methods, structural determinations and thermodynamic properties of the aforementioned ring systems are briefly discussed while their reactivity and syntheses are detailed. Notable applications of important compounds are also listed.

Keywords

triazolothiadiazine; oxadiazolotriazine; thiadiazolotriazine; triazolotriazine; cyclization; cyclocondensation; Dimroth rearrangement.

Nomenclature

Ac	Acetyl group
Ac ₂ O	Acetic anhydride
AcOH	Acetic acid
AcONa	Sodium acetate
Alk	Alkyl group
Ar	Aryl group
Bn	Benzyl group
Bu	Butyl group
BSA	<i>N,O</i> -bis-(trimethylsilyl)acetamide
Boc	<i>tert</i> -butyloxycarbonyl
CHEC	Comprehensive heterocyclic chemistry
Cy	Cyclohexyl group
D	Debye
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DFT	Density functional theory
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DTG	Differential Thermogravimetric
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	Electrospray ionization
Et	Ethyl group
Et ₃ N	Triethylamine
EtOH	Ethanol
eV	Electron Volt
HMDSO	Hexamethyldisiloxane
HOMO	Highest Occupied Molecular Orbital
<i>i</i> -Pr	<i>Iso</i> -Propyl group
LUMO	Lowest Unoccupied Molecular Orbital
Me	Methyl group
MeOH	Methanol
MS	Mass spectra
MW	Microwave
NBS	<i>N</i> -Bromosuccinimide
NMR	Nuclear Magnetic Resonance
Ph	Phenyl group
PIDA	Phenyliodine(III) diacetate
PivOH	Pivalic acid
PPA	Polyphosphoric acid
Pr	Propyl group
PTSA	<i>para</i> -Toluenesulfonic acid
Py	Pyridine
QSAR	Quantitative Structural Activity Relationship
S _N Ar	Aromatic nucleophilic substitution
STAT	Signal Transducer and Activator of Transcription
<i>t</i> -Bu	<i>tert</i> -Butyl group
TBAB	Tetrabutyl ammonium bromide
TD-DFT	Time dependent density functional theory
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
UDP	Uridine diphosphate

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11.19.1 Introduction

This chapter focuses on the bicyclic 5-6 systems with one ring junction nitrogen atom and four extra heteroatoms in a 2:2 distribution over both rings. These systems have been previously reviewed in CHEC-II(1996) and CHEC-III(2008).¹⁻² Herein, literature between 2007-2019 is covered. Among all the possible ring systems, 18 different structural backbones have been reported during this period. They correspond to various triazolothiadiazines **1-4**, oxadiazolotriazines **5**, thiadiazolotriazines **6-7**, and triazolotriazines **8-18**. Consequently, the additional heteroatoms are nitrogen, sulfur and oxygen (Figure 1). <Figure 1 near here>

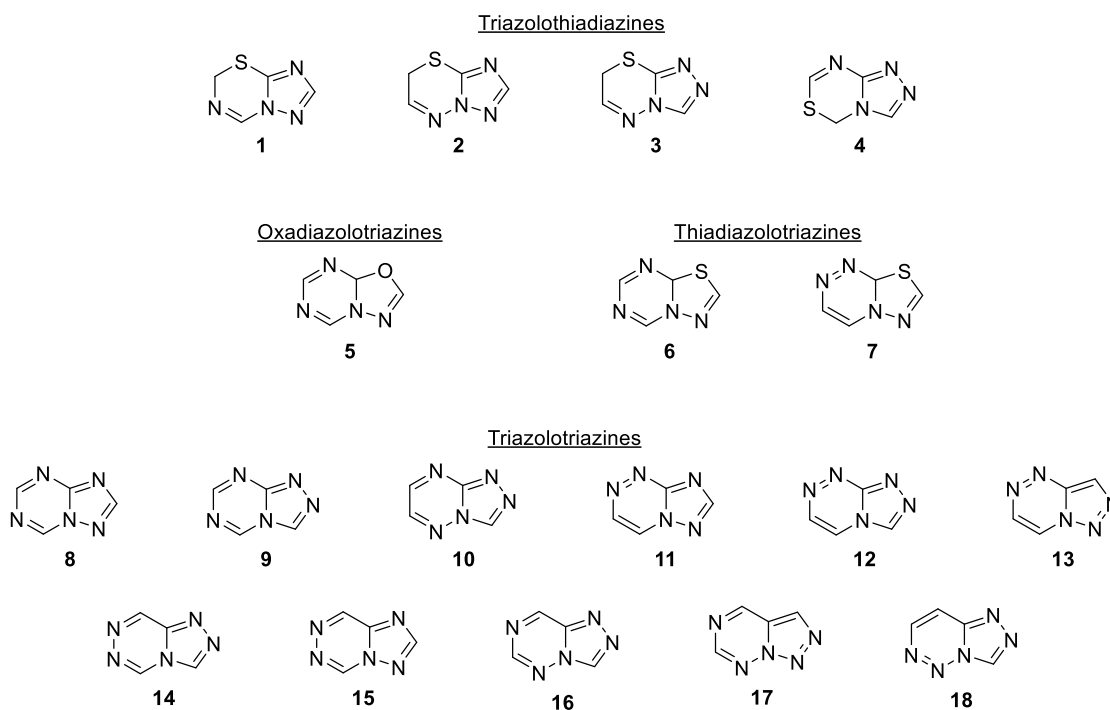


Figure 1

Fully as long as partially unsaturated systems are examined. Most references are devoted to [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **3**. Other important compounds are [1,2,4]triazolo[1,5-*a*][1,3,5]triazines **8**, [1,2,4]triazolo[4,3-*b*][1,2,4]triazines **10** and [1,2,4]triazolo[5,1-*c*][1,2,4]triazines **11**. Other structures were discussed in CHEC-III(2008) but no new related references have appeared since then. Conversely, structural backbones **2**, **4** and **13** are new and are disclosed.

11.19.2 Theoretical Methods

In the course of the synthesis of [1,2,4]triazolo[1,2,4]triazines, the formation of [1,2,4]triazolo[1,5-*d*][1,2,4]triazine **19** instead of expected [1,2,4]triazolo[4,3-*d*][1,2,4]triazine **20** (see section 11.19.6.5.4) was rationalized by DFT calculations using Gaussian 09 suit of programs (6-311+G(2d,p) 41WB97XD and 6-311+G(2d,p) WB97XD basis). The data confirmed that product **19** (arising from a Dimroth rearrangement) was thermodynamically more stable than **20** (Figure 2).³ <Figure 2 near here>.

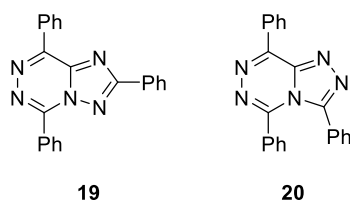
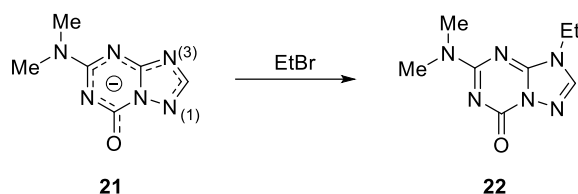


Figure 2

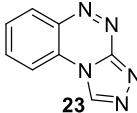
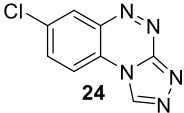
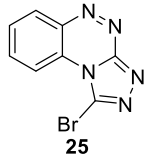
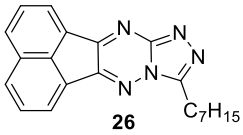
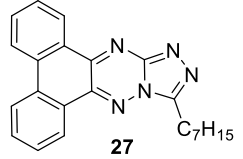
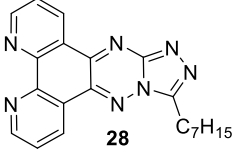
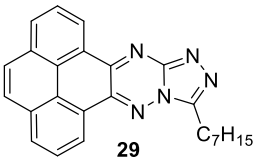
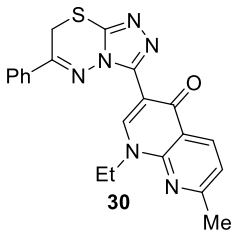
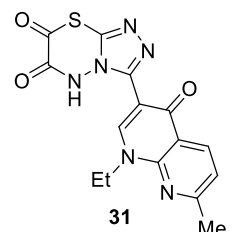
The anion **21** of 5-amino-substituted [1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7(3*H*)-one possesses five resonance structures allowing the alkylation with ethyl bromide to potentially take place at five reactive sites. The activation energy values for the ethylation of the less hindered positions (*i.e.* N3, N1 and O atoms) were calculated using the B3LYP/6-311++G(d,p) method. The lowest activation energy was found at the N3 atom but the difference with the *O*-alkylation was very small (only 1.1 kJ.mol⁻¹). From a thermodynamic point of view, the energy of the N3-ethyl product was by far the lowest. The experimental result confirmed this computational study and only 3-ethyl-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7(3*H*)-one **22** was isolated (see section 11.19.5.1.1) (Scheme 1).⁴ <Scheme 1 near here>



Scheme 1

Theoretical log P, dipole moments and energies of the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) of various benzo[*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazines **23-25** were determined by quantum chemical calculations (Table 1, entries 1-3).⁵ Dipole moments and orbital energies have been also calculated for fused heterocyclic compounds **26-29**. Experimental values of the LUMOs energies were determined after measurement of the redox potentials and were slightly higher than the calculated ones. In **28**, the two nitrogen atoms lowered the LUMO energy by 0.24 eV compared to **27** and **29**. These results suggested that the presence of heteroatoms affected more the LUMOs energies than the extension of the conjugation. Such low LUMO value augured a potential use of **28** as a n-type active molecules for organic transistors and organic photovoltaics (Table 1, entries 4-7).⁶ With the aim to establish quantitative structure activity relationship (QSAR) for antifungal activities of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **30-31**, log P and polarizabilities were calculated (Table 1, entries 8-9).⁷ <Table 1 near here>

Table 1: Calculated log P, dipole moments, polarizabilities and HOMO/LUMO energies for various heterocycles

Entry	Compound	Log P	μ (D)	Pol. ^a (Å ³)	HOMO (eV)	LUMO ^b (eV)	Ref.
1	 23	1.34	7.517	-	-7.511	4.018	5
2	 24	1.11	5.784	-	-7.793	3.666	5
3	 25	2.91	7.19	-	-7.169	3.919	5
4	 26	-	11.2	-	-6.32	-3.12 (-3.59)	6
5	 27	-	10.1	-	-6.10	-3.38 (-3.71)	6
6	 28	-	5.8	-	-	-3.56 (-3.95)	6
7	 29	-	10.2	-	-6.05	-3.38 (-3.77)	6
8	 30	2.64	-	42.56	-	-	7
9	 31	0.96	-	33.68	-	-	7

^a Polarizability. ^b Experimental values (based on measured redox potentials) are reported between brackets.

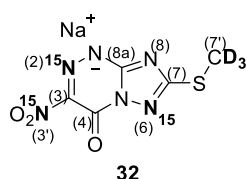
Time-dependent density functional theory (TD-DFT) has been used to examine the relationship between molecular structure and the one- and two photon absorption properties of conjugated energetic molecules 4-amino-3,7-dinitro-[1,2,4]triazolo[5,1-c][1,2,4]triazine derivatives. Such study dealt with physical chemistry and will not be detailed in this chapter.⁸⁻⁹

11.19.3 Experimental Structural Methods

11.19.3.1 NMR results

¹H and ¹³C NMR data for new compounds have been routinely reported. ¹³C and ¹⁵N NMR spectra of isotopes [¹⁵N,²H]-containing bicycle **32** have been thoroughly analyzed (Table 2).¹⁰ <Table 2 near here>

Table 2: ¹³C and ¹⁵N NMR data of compound **32** in DMSO-*d*₆



Atom	δ (ppm)	J (Hz)
C(7')	13.4	$^1J_{C,D} = 21$
C(7)	166.3	$^2J_{C,N(5)} = 5.1$; $^3J_{C,D} = 0.7$
C(8a)	160.7	$^2J_{C,N(2)} = 2.1$; $^2J_{C,N(5)} = 0.4$
C(3)	145.15	$^1J_{C,N(2)} = 1.8$; $^1J_{C,N(3')} = 23.4$; $^1J_{C,N(3')} = 23.4$; $^3J_{C,N(1)} = 1.4$
C(4)	143.4	$^2J_{C,N(2)} = 1.3$; $^2J_{C,N(3')} = 5.3$; $^2J_{C,N(5)} = 3.3$
N(6)	259.9	-
N(2)	397.2	$^2J_{N(2),N(3')} = 6.3$
N(3')	368.4	$^2J_{N(2),N(3')} = 6.3$

The ¹⁹F NMR data of newly synthesized 3-fluoro[1,2,4]triazolo[5,1-c][1,2,4]triazin-4(1*H*)-one derivatives **33** have been reported. A significant downfield shift has been noticed for **33** (from -114 to -115 ppm) compared to triazolopyrimidinones **34** (from -169 to -171 ppm) which has been rationalized by the electron-withdrawing effect of the triazine nitrogen atom N2 (Figure 3).¹¹ <Figure 3 near here>

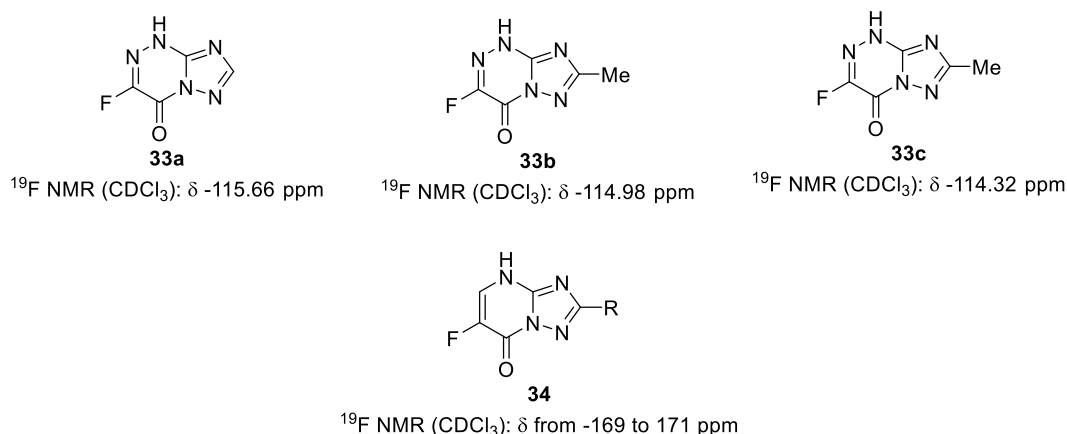
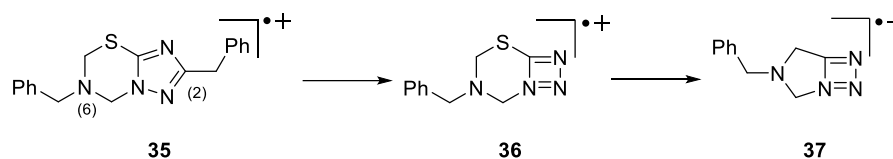


Figure 3

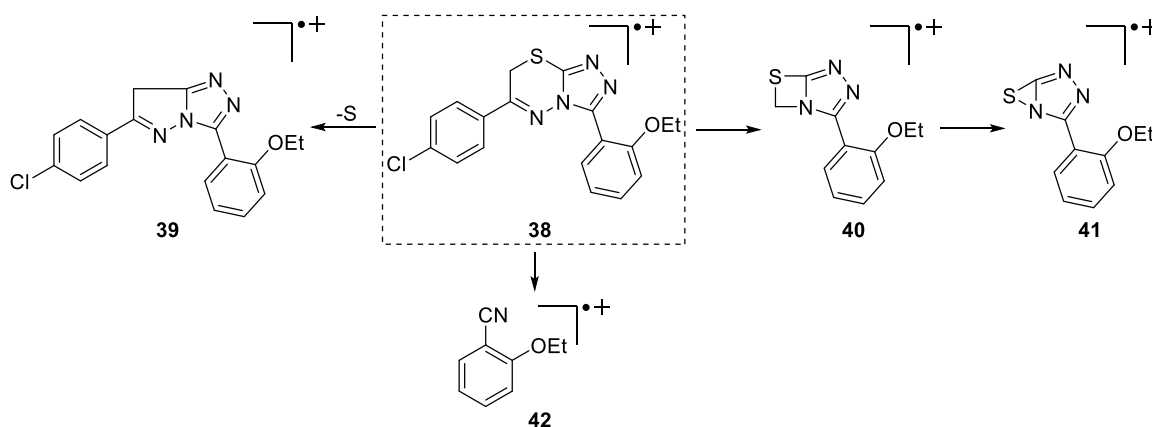
11.19.3.2 Mass spectrometry

Mass spectrometry has been routinely used for the characterization of new compounds through measurement of molecular ions. In some cases, more detailed fragmentations patterns have been analyzed. In a study on 2,6-disubstituted-6,7-dihydro-5*H*-1,2,4-triazolo[3,2-*b*]-1,3,5-thiadiazines (cf. Section 11.19.6.3.1), the analyses of the ESI-MS spectra have revealed a common fragmentation pattern. A representative example is depicted in scheme 2 for ion **35**. The loss of the substituent at the C2 position led to triazacyclobutadiene **36** which undergo elimination of sulfur to produce bicyclic 5-4 fragment **37**. The cleavage of the C-N bond at N6 position could be also clearly identified.¹² <Scheme 2 near here>.



Scheme 2

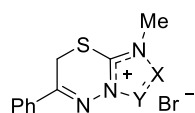
Elimination of sulphur from the thiadiazine ring has been also observed for 7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivative **38** leading to fragment **39**. Fragmentation of the thiadiazine ring from molecular ion **38** gave also rise to thiazetine **40** and thiaziridine **41**. The loss of benzonitrile **42** was characteristic of the 3-aryl-1,2,4-triazole moiety (Scheme 3).¹³ <Scheme 3 near here>



Scheme 3

11.19.3.2 X-Ray investigations

The crystal structures of two [1,3,4]triazolo[*b*][1,3,4]-thiadiazinium bromide salts **43** and **44** (cf. Section 11.19.6.3.4) were determined by Laus *et al.* (Figure 4). In the case of **43**, the data were solved and refined in the monoclinic space group $P2_1/n$. Numerous C–H...Br contacts have been detected forming a three-dimensional network. For compound **44**, the data were solved and refined in the monoclinic space group $P2_1/c$. Three CH...Br interactions allowed the bromide anions to link the cations into cyclic dimers.¹⁴ <Figure 4 near here>



43: X = N, Y = CH .1/2 EtOH

44: X = CH, Y = N

Figure 4

For biological applications, many derivatives of bicyclic systems of this chapter have been designed and the structures of the newly synthesized compounds were confirmed by single crystal X-ray crystallography. Some examples are depicted in figure 5.^{15–16} Such analyses were very useful to establish the conformation of the molecules in the solid states. For triazolothiadiazine **47** the six-membered thiadiazine ring is distorted from planarity and the two phenyl substituents are located nearly perpendicular to each other.¹⁷ The distortion of the thiadiazine ring has been also observed for compound **48** and **49**. For the latter, the dihedral angle between the bicyclic system and the 2,4-dichlorophenyl substituent is 50.74°.^{18–19} <Figure 5 near here>

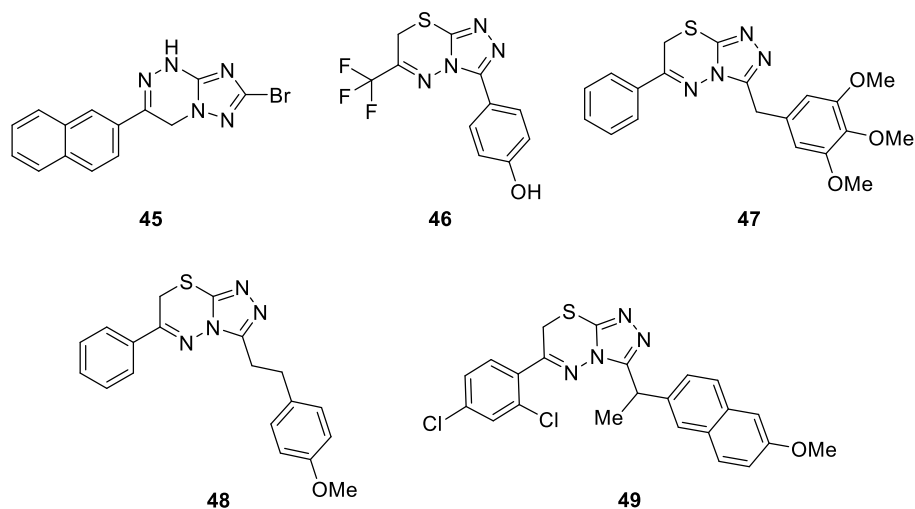


Figure 5

The distinction between regioisomer of heterocyclic compounds could not always be performed via NMR methods even with conventional ^1H - ^1H and ^1H - ^{13}C NMR correlation experiments or nuclear Overhauser effect (NOE) spectroscopy. As such, X-Ray analyses have been often used to ascertain the structure of products from reactions with multiple possible reaction sites or involving putative rearrangements. For instance, the structure of [1,2,4]triazolo[1,5-*d*][1,2,4]triazine **50** was determined by X-Ray analysis. It was crucial to reveal that the product was not the [1,2,4]triazolo[4,3-*d*][1,2,4]triazine derivative and that the reaction probably involved a Dimroth

rearrangement (cf. Section 11.19.6.5.4) (Figure 6).³ In the following sections (11.19.5; 11.19.6; 11.19.7), a precision will be added when the structure of the products has been certified by X-Ray analyses. <Figure 6 near here>

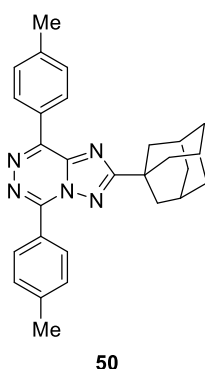
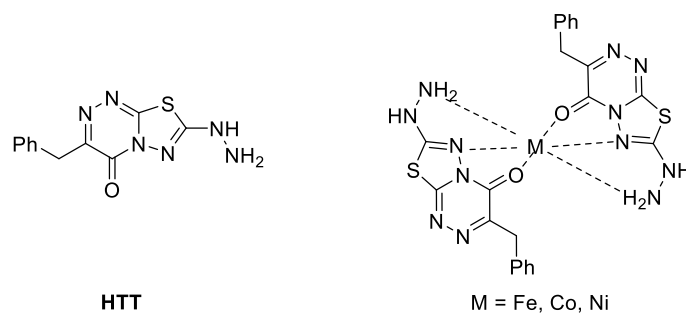


Figure 6

11.19.4 Thermodynamic aspects

The coordination of bicyclic fused ring system 3-benzyl-7-hydrazinyl-4*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-one (ligand **HTT**) to some metal ions have been studied. More particularly, **HTT** and three complexes have been subjected to thermal decomposition. The thermodynamic activation parameters of decomposition processes (*i.e.* activation energy E^* , enthalpy ΔH^* , entropy ΔS^* and Gibbs free energy change ΔG^*) have been evaluated from the differential thermogravimetric (DTG) curves by the Coats–Redfern method. Some data are outlined in table 3.²⁰ <Table 3 near here>

Table 3: Thermodynamic data of the thermal decomposition of metal complexes of **HTT**.



Complexes	T (°C)	Rate (s ⁻¹)	Thermodynamic data (kJ.mol ⁻¹)			
			E*	ΔS*	ΔH*	ΔG*
HTT	25-430	3.3 x 10 ⁷	92.92	-100.0	90.68	117.7
[Fe(HTT) ₂]Cl ₃	26-150	4.0 x 10 ¹¹	80.23	-53.00	79.92	101.1
[Co(HTT) ₂]Cl ₂	25-100	1.6 x 10 ¹³	98.15	-41.3	97.69	195.4
[Ni(HTT) ₂]Cl ₂	28-141	3.4 x 10 ⁵	46.23	-125.9	157.1	253.5

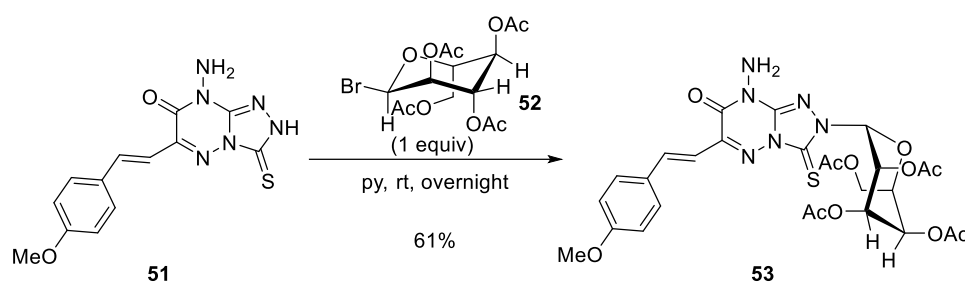
11.19.5 Reactivity

11.19.5.1 Reaction at ring nitrogen atoms

11.19.5.1.1 *N*-alkylation/acylation

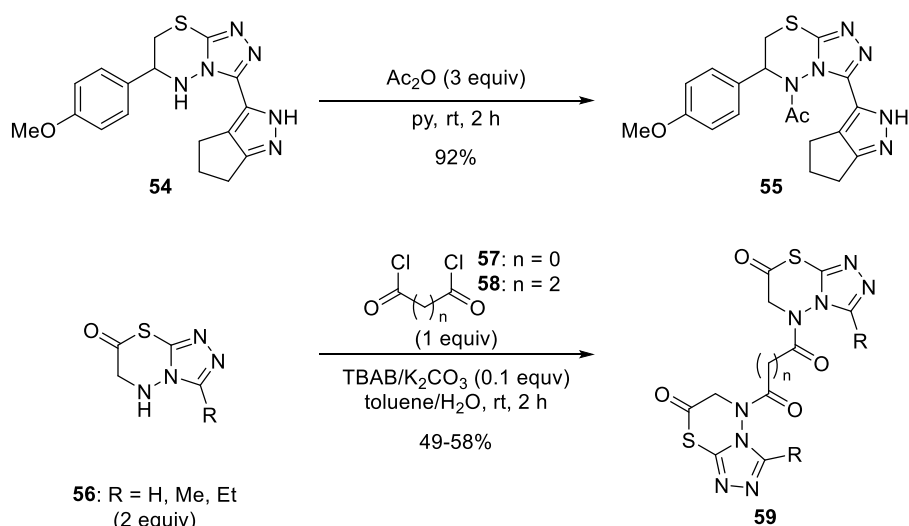
11.19.5.1.1(i) [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines

Direct glycosylation of compound **51** with glucopyranosyl bromide **52** in pyridine at room temperature offered a convenient selective synthesis of 2-glycosyl derivative **53** (Scheme 4).²¹ <Scheme 4 near here>



Scheme 4

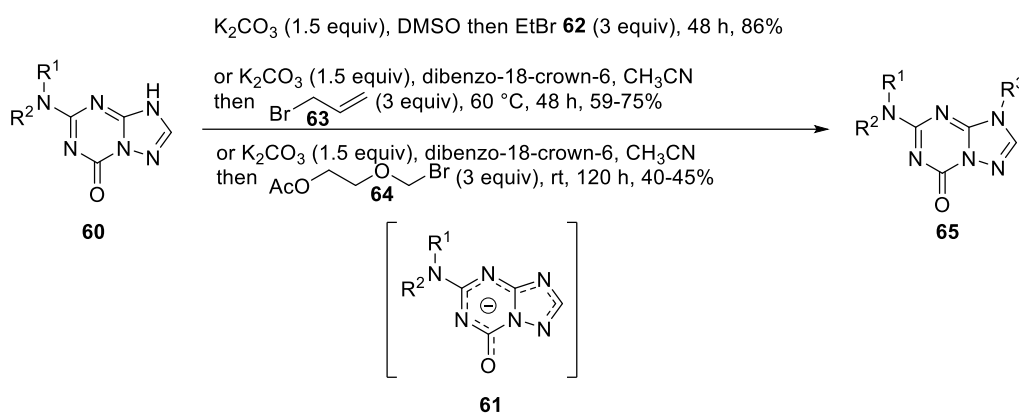
Two examples of acylation of ring nitrogen atom of the aforementioned ring system are depicted in scheme 5. *N*-acylation of dihydrotriazolothiadiazine **54** bearing a fused cyclopentyl-pyrazole substituent with acetic anhydride occurred selectively on the thiadiazine ring.²² *N*-acylation of triazolothiadiazinone **56** with oxalyl chloride **57** or succinyl chloride **58** under phase-transfer catalysis produced dimers **59** (Scheme 5).²³ <Scheme 5 near here>



Scheme 5

11.19.5.1.1(ii) [1,2,4]triazolo[1,5-*a*][1,3,5]triazines

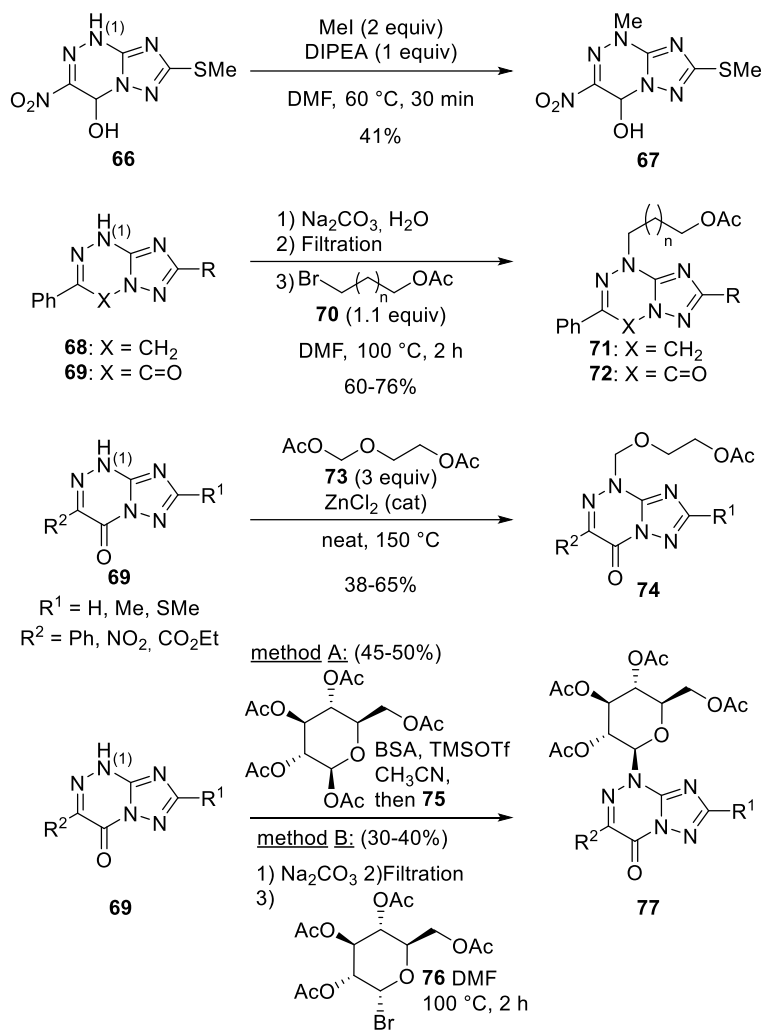
Despite five resonance structures of the anion **61**, the *N*-alkylation of [1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7(3*H*)-one **60** with bromoethane **62**, allyl bromide **63** or (2-acetoxyethoxy)methyl bromide **64** occurred selectively at the N3 position. DFT calculations related to the ethylation reaction confirmed the experimental results (Scheme 6).⁴ <Scheme 6 near here>



Scheme 6

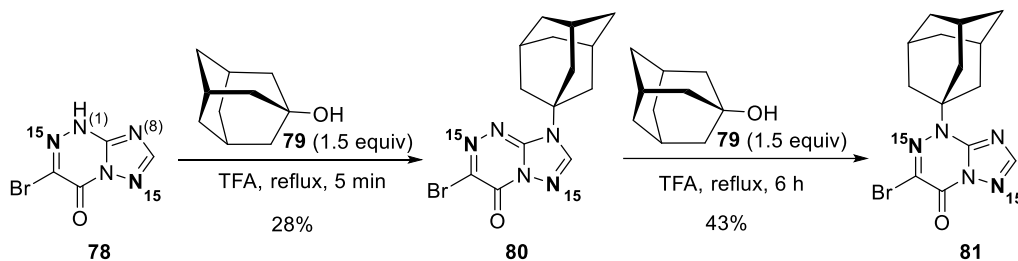
11.19.5.1.1(iii) [1,2,4]triazolo[5,1-c][1,2,4]triazines

As depicted in scheme 7, *N*-alkylations and *N*-glycosylations of 1,4-dihydro-[1,2,4]triazolo[5,1-c][1,2,4]triazine derivatives **66** and **68** and [1,2,4]triazolo[5,1-c][1,2,4]triazin-4(1*H*)-one derivatives **69** took place at the N1 position. *N*-methylation of dihydro-triazolotriazinol **66** was performed with diisopropylethylamine and iodomethane.²⁴ *N*-alkylations of dihydro-triazolotriazines **68** and triazolotriazinones **69** were carried out by treatment of the corresponding sodium salts with bromoalkyle **70**.²⁵⁻²⁶ The fusion of **69** with an excess of (2-acetoxyethoxy)methyl acetate **73** at 150 °C in the presence of ZnCl_2 afforded regioselectively the corresponding 1-(2-acetoxyethoxy)methyl derivatives **74**.²⁷⁻²⁸ Two methods were developed for the *N*-glycosylation of **69**: treatment of **69** with *N,O*-bis(trimethylsilyl)acetamide and trimethylsilyl triflate followed by addition of β -D-glucose pentaacetate **75** (method A) or reaction of the sodium salts of **69** with tetra-acetyl- α -D-bromoglucose **76** in DMF under heating (method B). In both cases, the *N*-glycosylations took place at the N1 position affording nucleosides **77** with β -configurations. The method A, which gave slightly better yields, was also applied to the incorporation of a tri-*O*-acetyl- β -D-ribofuranosyl group (Scheme 7).²⁹ <Scheme 7 near here>



Scheme 7

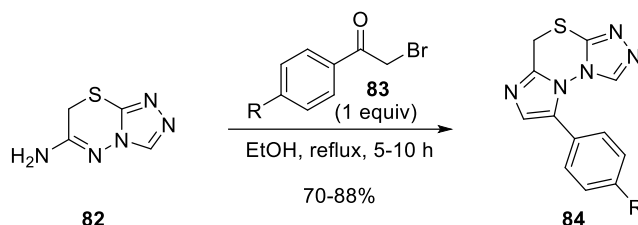
Interestingly, it has been found that the adamantylation of [¹⁵N₂]-[1,2,4]triazolo[5,1-c][1,2,4]triazin-4(1H)-one **78** with adamantanol **79** in trifluoroacetic acid first occurred at the N8 position of the bicyclic system. Indeed, after five minutes under reflux, compound **80** was isolated. However, prolonged reflux with excess of 1-adamantanol **79** led to complete isomerization with attachment of the adamantyl group at the N1 position (compound **81**). The structures of regioisomers **80** and **81** were determined by NMR spectroscopy with analysis of the ¹H-¹⁵N (*J*_{HN}) and ¹³C-¹⁵N (*J*_{CN}) coupling constants (Scheme 8).³⁰ <Scheme 8 near here>



Scheme 8

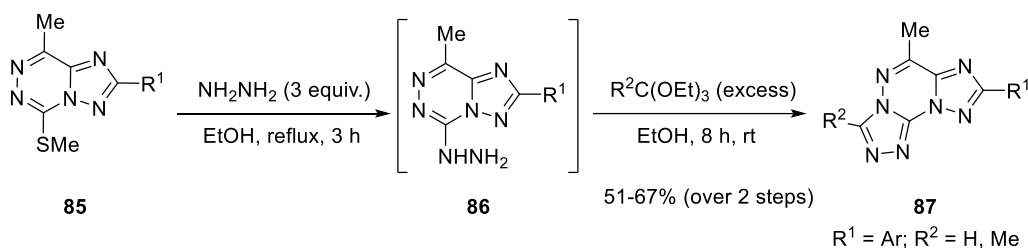
11.19.5.1.2 Construction of a new fused-ring with one bridgehead nitrogen atom

Amino-triazolothiadiazine **82** was treated with phenacyl bromide **83** in ethanol allowed the building of a fused imidazole ring to afford tricyclic compound **84** in good yield (Scheme 9).³¹ <Scheme 9 near here>



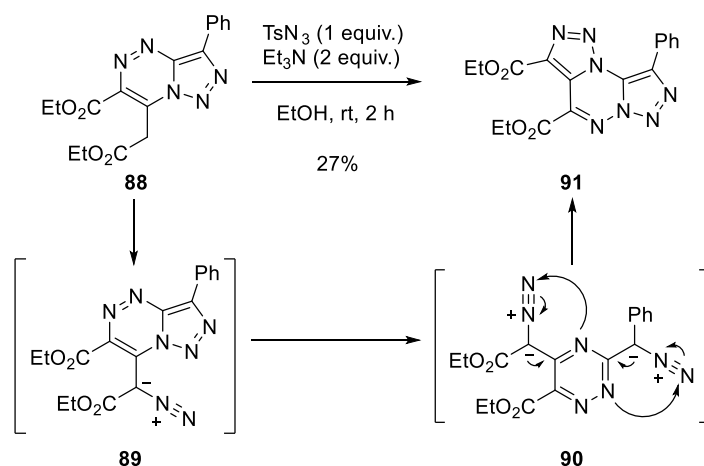
Scheme 9

Nucleophilic displacement of the thiomethyl group of triazolotriazine derivative **85** by hydrazine hydrate furnished the corresponding hydrazino derivative **86**. The latter was not isolated and was directly engaged in a cyclocondensation with triethylorthoesters under heating in ethanol to afford bis-triazolotriazine derivatives **87** (Scheme 10).³² <Scheme 10 near here>



Scheme 10

Treatment of triazolotriazine **88** bearing a methylene group with *p*-toluenesulfonyl azide as diazo-transfer reagent afforded tricyclic compound **91** in low yield. From a mechanistic point of view, the authors proposed that this interesting transformation would proceed through a diazo-transfer reaction to produce diazo **89**. A subsequent ring opening of the (1,2,3)-triazole would furnish bis-diazo intermediate **90** which would undergo two new cyclizations to build the novel-fused triheterocyclic product **91** (Dimroth rearrangement).³³ (Scheme 11) <Scheme 11 near here>

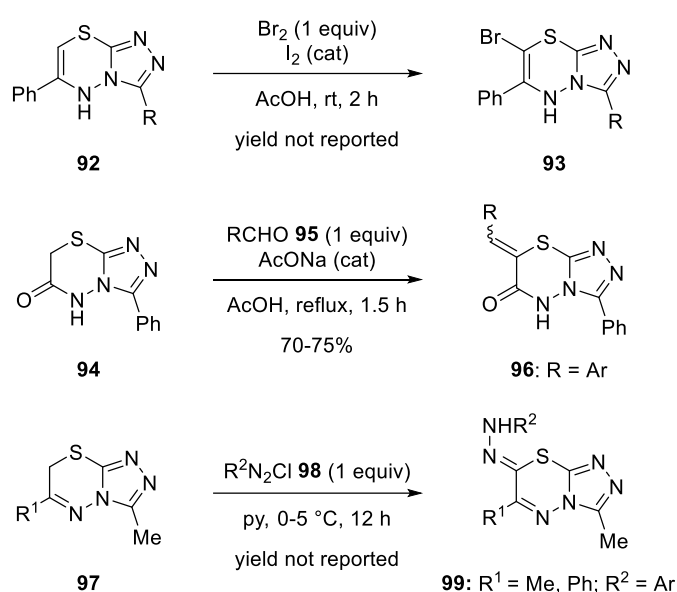


Scheme 11

11.19.5.2 Reaction at ring carbon atoms

11.19.5.2.1 Functionalization of C-H bonds

As displayed in scheme 12, various functionalizations of the C7 atom of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives have been reported. Bromination of **92** has been carried out with bromine and iodine as a catalyst in acetic acid to yield the corresponding 7-bromo derivatives **93**. These compounds were prepared for further amination through nucleophilic substitution (see section 11.19.5.2.2).³⁴ A Knoevenagel reaction between triazolothiadiazinone **94** and aromatic aldehydes **95** in the presence of a catalytic amount of sodium acetate in acetic acid furnished arylidenes **96**.³⁵ Treatment of 7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives **97** with aryldiazonium salts **98** in pyridine delivered phenylhydrazone derivatives **99**.³⁶ <Scheme 12 near here>

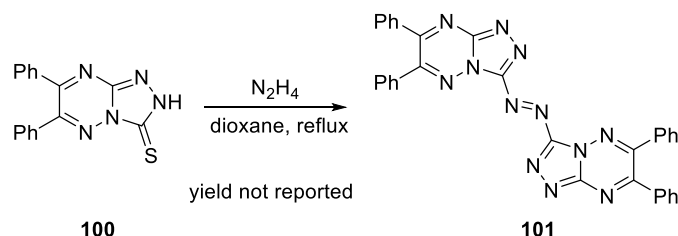


Scheme 12

11.19.5.2.2 Nucleophilic substitution

11.19.5.2.2(i) [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines

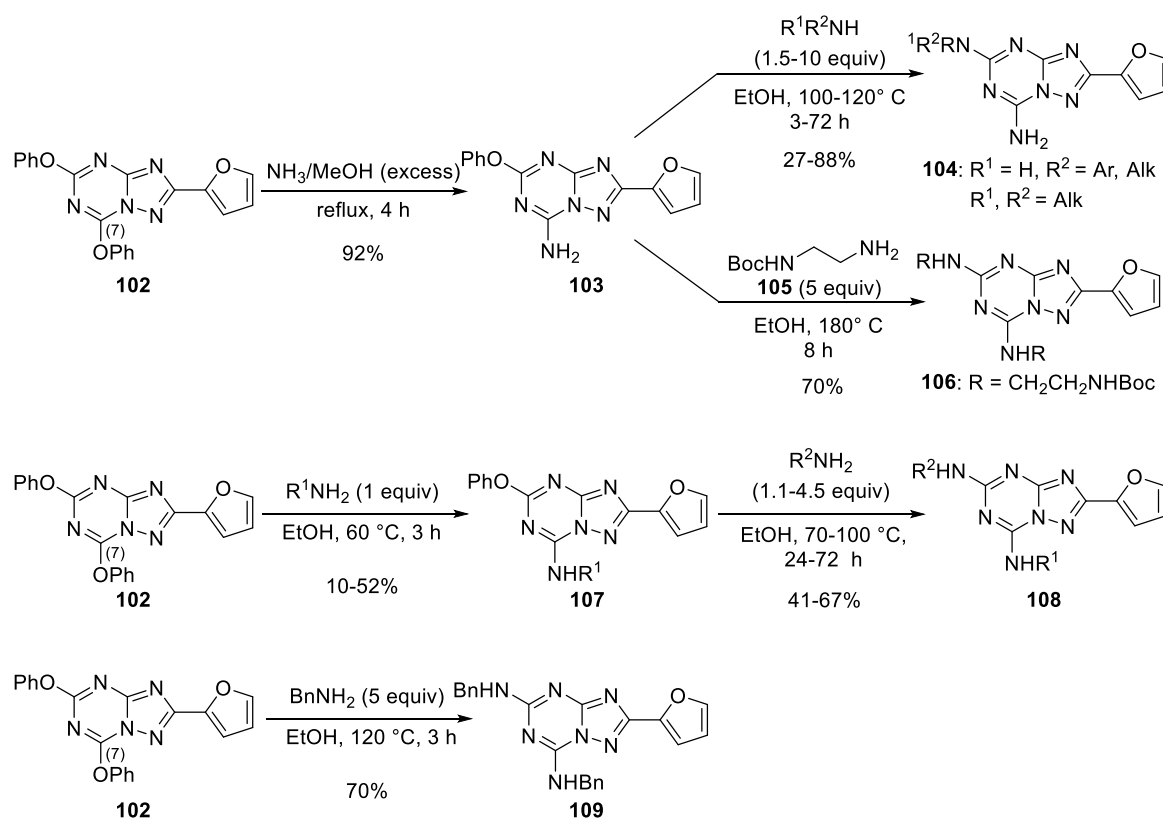
Treatment of thione derivative **100** with hydrazine hydrate in dioxane under reflux furnished diazene **101** with the removal of hydrogen sulfide gas (Scheme 13).³⁷ <Scheme 13 near here>



Scheme 13

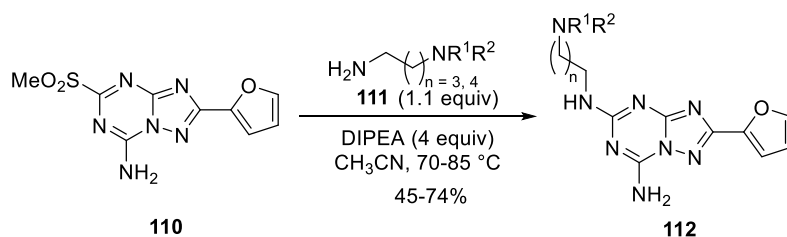
11.19.5.5.5(ii) [1,2,4]triazolo[1,5-*a*][1,3,5]triazines

As shown in scheme 14, the substitution of 5,7-diphenoxy-[1,2,4]triazolo[1,5-*a*][1,3,5]triazine derivative **102** by an amine occurred first at the C7 position. For instance, treatment of **102** with an excess of ammonia in methanol produced 5-phenoxy-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-amine **103**. The latter has been then engaged in a second nucleophilic substitution with various primary or secondary amines in ethanol at 120 °C to form *N*^{5,7}-alkyl-[1,2,4]triazolo[1,5-*a*][1,3,5]triazine-5,7-diamines **104**. Also of note, a disubstitution occurred when compound **103** reacted with an excess of mono Boc ethylenediamine **105** at 180 °C furnishing *N*^{5,7}-dialkyl-[1,2,4]triazolo[1,5-*a*][1,3,5]triazine-5,7-diamines **106**. The synthesis of [1,2,4]triazolo[1,5-*a*][1,3,5]triazine-5,7-diamines **108** bearing two different alkylamino groups at C5 and C7 was performed by a first reaction between **102** and one equivalent of an alkylamine at 60 °C producing *N*-alkyl-[1,2,4]triazolo[1,5-*a*][1,3,5]triazine-7-amines **107** in low to moderate yields. The second substitution could be performed in harsher reaction conditions affording **108** in moderate to good yields. Finally, *N*^{5,7}-dibenzyl-[1,2,4]triazolo[1,5-*a*][1,3,5]triazine-5,7-diamines **109** was easily prepared from diphenoxy derivative **102** and an excess of dibenzyl amine (Scheme 14).³⁸⁻⁴⁰ <Scheme 14 near here>



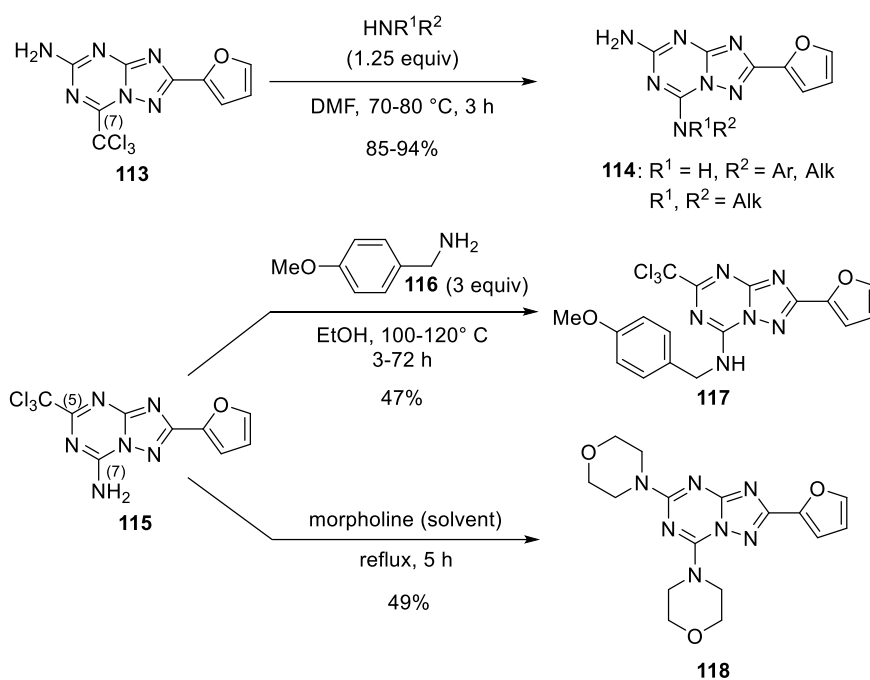
Scheme 14

5-(Methylsulfonyl)-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-amine **110** has also been used for the introduction of alkyl amines **111** at C5. As shown in scheme 15, with diisopropyl amine in acetonitrile under heating, *N*⁵-alkyl-[1,2,4]triazolo[1,5-*a*][1,3,5]triazine-5,7-diamines **112** was obtained in good yields.⁴¹⁻⁴² Other procedures were also developed for the introduction of different alkylamines or alcohol at C5 from **110** but the yields were much lower (8-33%).⁴³⁻⁴⁵ <Scheme 15 near here>



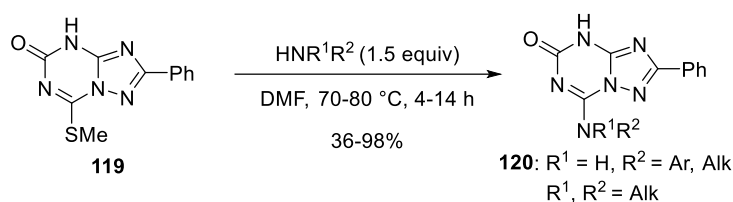
Scheme 15

As outlined in scheme 16, the synthesis of 1,2,4-triazolo[1,5-*a*][1,3,5]triazin-amines has been also performed by exploring the reactivity of highly electrophilic trichloromethyl-containing 1,3,5-triazine ring. The trichloromethyl substituent at C7 on compound **113** readily underwent nucleophilic substitution with primary alkyl or aromatic amines as long as secondary amines affording *N*⁷-substituted-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5,7-diamines **114** in excellent yields. Interestingly, the substitution of trichloromethyl group at C5 of **115** was more problematic.⁴⁶⁻⁴⁷ Indeed, with an excess of benzylamine **116**, the trichloromethyl substituent at C5 was untouched and only transamination at C7 was observed giving rise to compound **117** in moderate yield. With morpholine as a solvent, the substitution took place at both positions leading to dimorpholine-containing triazolotriazine **118** (Scheme 16).⁴⁸ <Scheme 16 near here>



Scheme 16

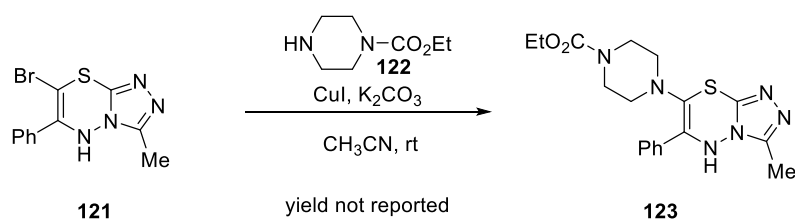
Finally, the nucleophilic replacement of the methylthio group of triazolotriazinone **119** proceeded smoothly with a variety of amines affording amino-substituted heterocycles **120** in moderate to excellent yields (Scheme 17).⁴⁸ <Scheme 17 near here>



Scheme 17

11.19.5.2.2(iii) [1,2,4]triazolo[4,3-*b*][1,2,4]triazine

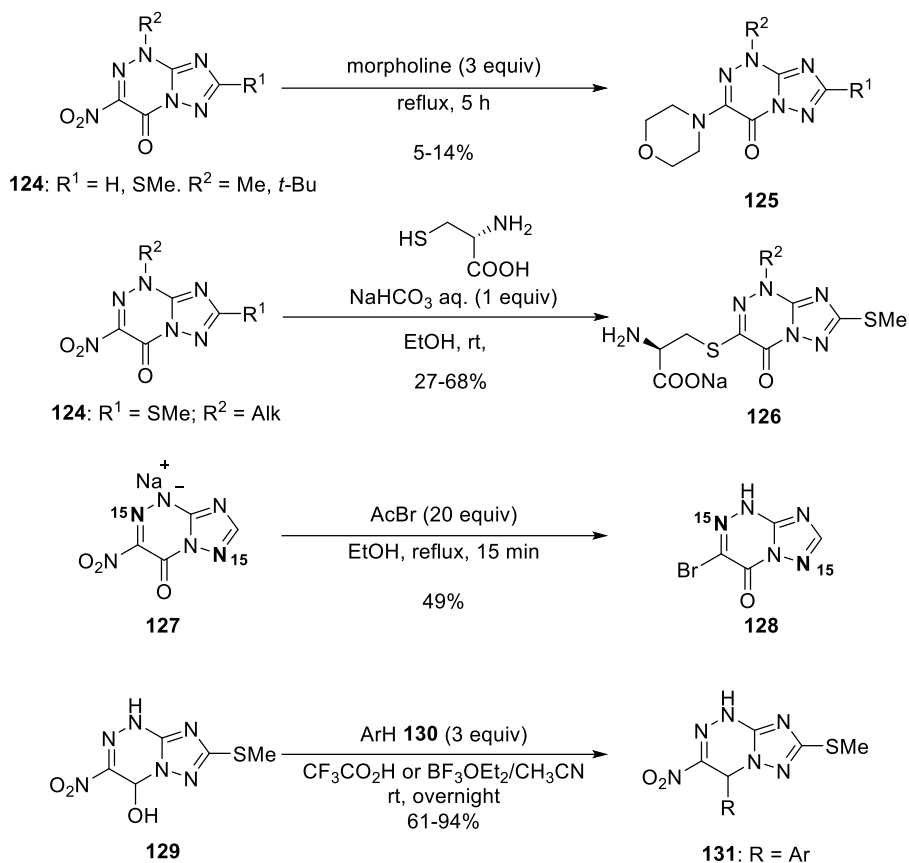
Coupling reaction between bromotriazolotriazine **121** and piperazine ester **122** with copper yielded amino derivative **123** (Scheme 18).³⁴ <Scheme 18 near here>



Scheme 18

11.19.5.2.2(iv) [1,2,4]triazolo[5,1-*c*][1,2,4]triazine

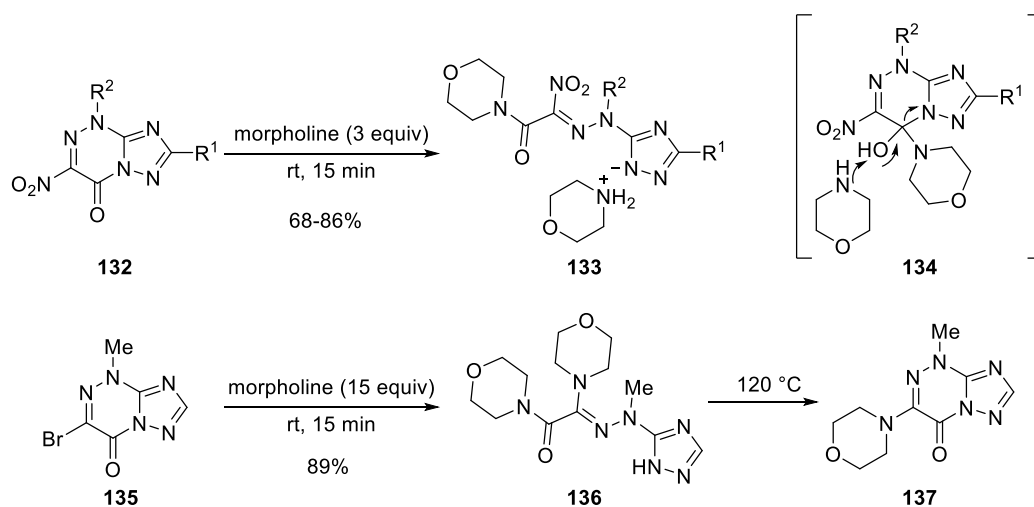
As shown in scheme 19, replacement of the nitro group at C3 of various [1,2,4]triazolo[5,1-*c*][1,2,4]triazine derivatives has been reported with different nucleophiles. Introduction of a morpholinyl substituent on **124** proceeded sluggishly with an excess of morpholine under reflux (see also section 11.19.5.2.3).⁴⁹ Substitution with cysteine as *S*-nucleophile was easier producing cysteine-containing fused system **126**. Similar transformation was also demonstrated with glutathione as *S*-nucleophile.⁵⁰ The substitution of the nitro group of salt **127** by bromide was performed with acetyl bromide to furnish bromo derivative **128** in moderate yield.²⁶ Nucleophilic addition of electron rich aromatic (hetero)cycles **130** on 3-nitro-1,4-dihydro-[1,2,4]triazolo[5,1-*c*][1,2,4]triazin-4-ol **129** under acidic reaction conditions led to 3-nitro-4-aryl-1,4-dihydro-[1,2,4]triazolo[5,1-*c*][1,2,4]triazine **131** (Scheme 19).²⁴ <Scheme 19 near here>



Scheme 19

11.19.5.2.3 Ring-opening

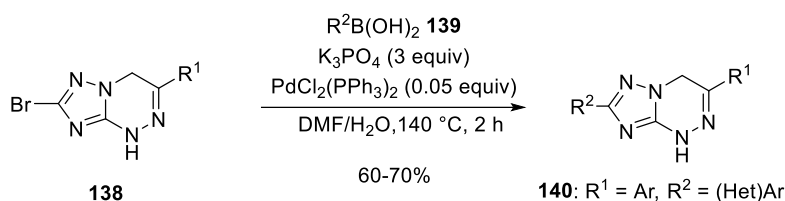
Treatment of nitrotriazolotriazinones **132** with three equivalents of morpholine at room temperature resulted in the formation of morpholinium **133** via nucleophilic addition of the amine function to the carbonyl group (intermediate **134**) and the ring opening of the triazine ring. Morpholine-containing hydrazone **136** was obtained from bromotriazolotriazinones **135** with a large excess of morpholine. Cyclization of **136** occurred upon heating at 120 °C to form nitrotriazolotriazinone **137** (Scheme 20).¹¹ <Scheme 20 near here>



Scheme 20

11.19.5.2.4 Cross-coupling

Suzuki cross-couplings between 7-bromo-1,4-dihydro-[1,2,4]triazolo[5,1-c][1,2,4]triazine derivatives **138** and various boronic acids **139** furnished 7-aryl substituted derivatives **140** in good yields (Scheme 21).²⁵ <Scheme 21 near here>

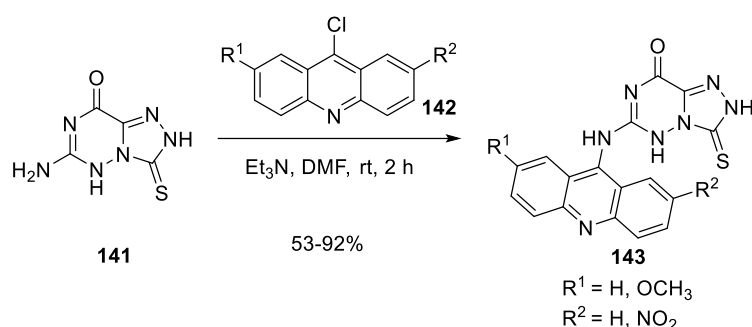


Scheme 21

11.19.5.3 Transformation of substituents

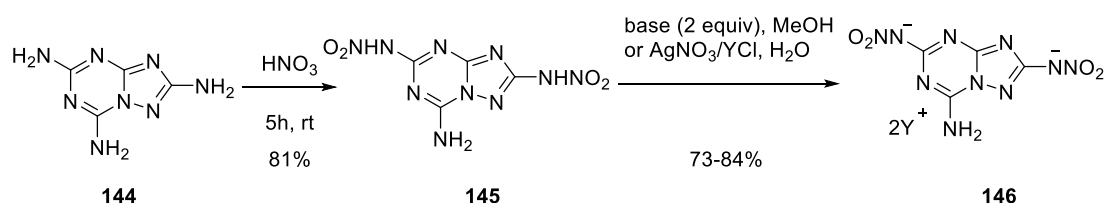
11.19.5.3.1 N-arylation and N-nitration

Arylation of the amino substituent of triazolotriazinone **141** has been reported through nucleophilic aromatic substitution with 9-chloro acridines **142** in DMF in the presence of triethylamine (Scheme 22).⁵¹⁻⁵² <Scheme 22 near here>.



Scheme 22

Nitration of [1,2,4]triazolo[1,5-*a*][1,3,5]triazine-2,5,7-triamine **144** with nitric acid occurred only on the amino substituents at position 2 and 5 providing 2,5-dinitramide-7-amino derivative **145**. The corresponding salts **146** having various counter-cations were obtained by direct treatment with a base or through the intermediate formation of the silver salts (Scheme 23).⁵³ <Scheme 23 near here>

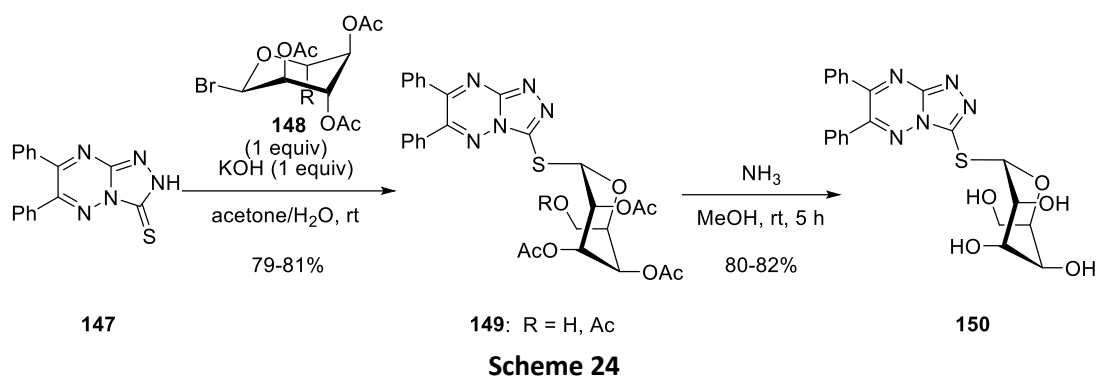


Scheme 23

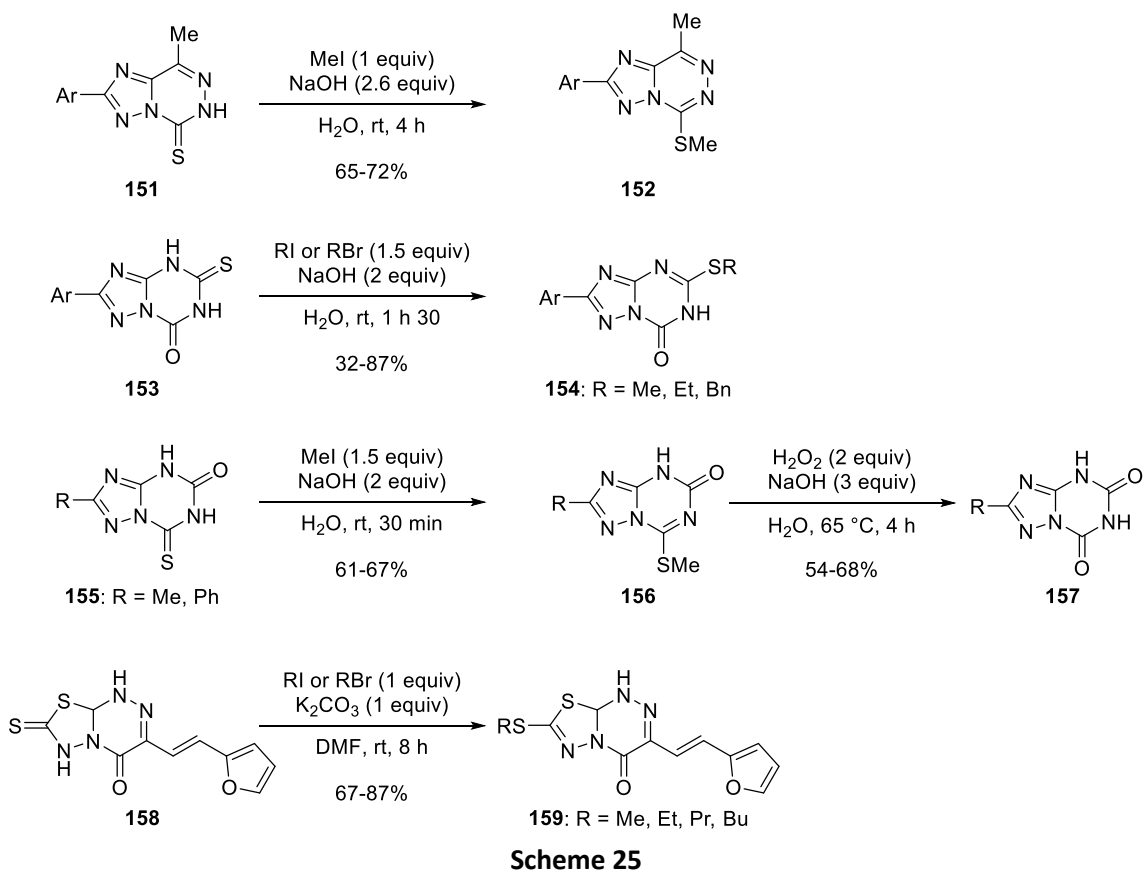
11.19.5.3.2 S-alkylation

Reaction between thiols **147** and D-gluco-pyranosyl bromide **148** in the presence of potassium hydroxide gave the corresponding acetylated thioglycoside derivatives **149** in good yields. After that,

the deacetylation proceeded efficiently by treatment with methanolic ammonia at 0 °C to furnish deacetylated glycoside **150** (Scheme 24).⁵⁴ <Scheme 24 near here>

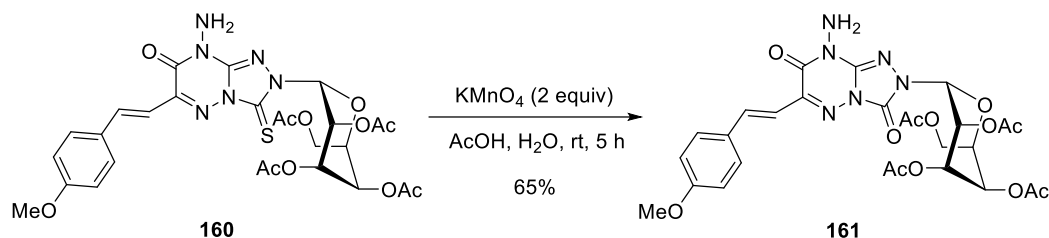


As outlined in scheme 25, *S*-alkylation of thioxo-heterocycles has been reported on various fused systems. Triazolotriazine-thiones **151** could be efficiently treated with methyl iodide in an aqueous solution of sodium hydroxide at room temperature to produce the corresponding (methylthio)triazolotriazine **152**. Such product was prepared for further *ipso*-substitution of the thiomethyl group (cf. Section 11.19.5.1.2).³² Under similar reaction conditions, *S*-alkylation of thioxo-triazolotriazinone **153** and **155** furnished alkylthio-triazolotriazinones **154** and **156**. Methylthio-derivative **156** has been treated with hydrogen peroxide in aqueous alkaline solution to form the corresponding triazolotriazine-dione **157**.⁵⁵⁻⁵⁶ Finally, *S*-alkylation of the thiocarbonyl group of thiadiazole-thione **158** has been performed in DMF with potassium hydroxide to produce various thioalkyl derivatives **159** (Scheme 25).⁵⁷ <Scheme 25 near here>



11.19.5.3.3 Thiocarbonyl to carbonyl group transformation

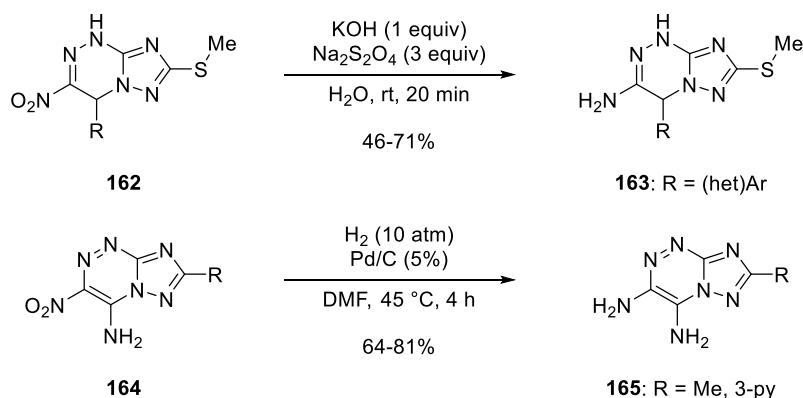
Conversion of the thiocarbonyl group of thioxotriazolotriazinone **160** into the corresponding carbonyl group has been described by El-Barbary *et al.* with potassium permanganate at room temperature furnishing **161** in good yield (Scheme 26).²¹ <Scheme 26 near here>



Scheme 26

11.19.5.3.4 Reduction

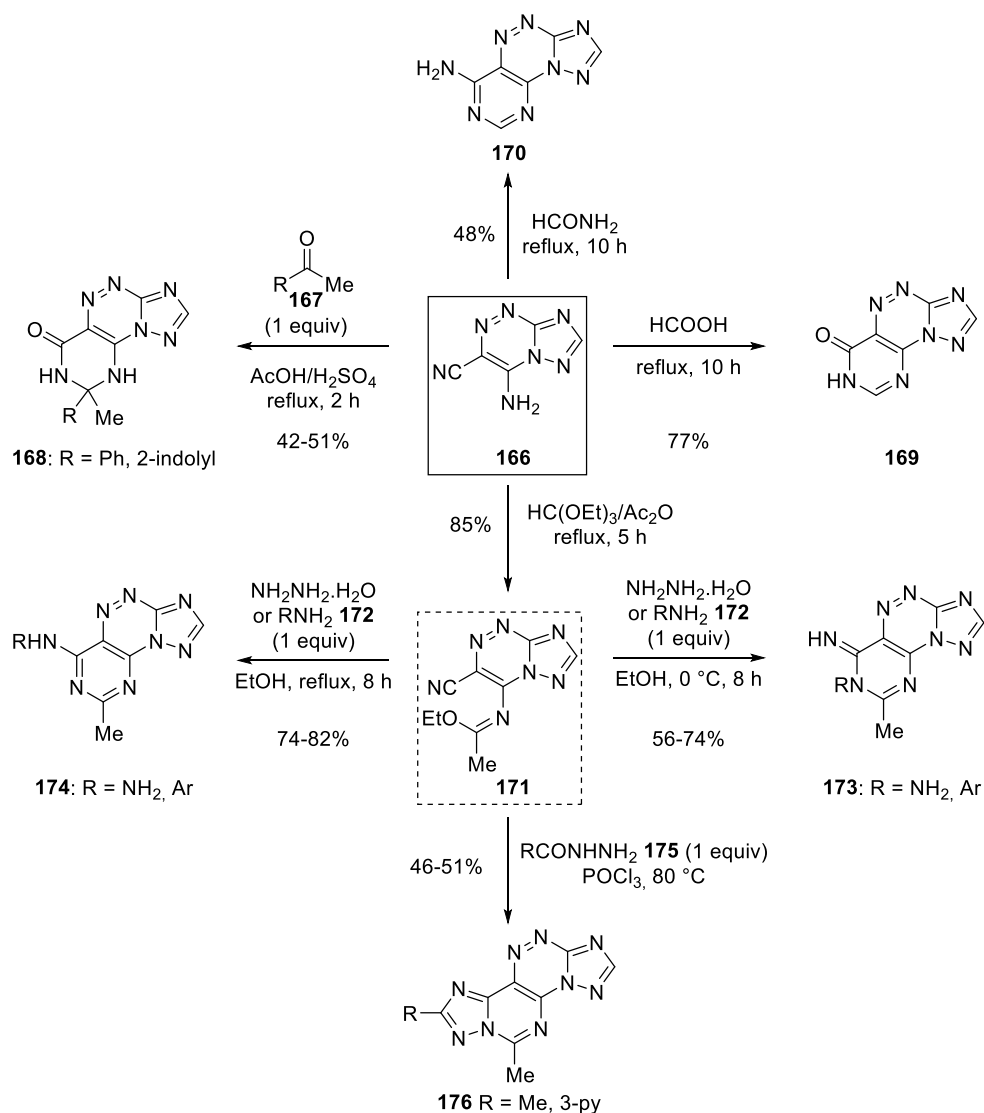
Sodium dithionite in an aqueous alkaline solution was used for selective reductions of the nitro group of dihydrotriazolotriazine **162**. Partial hydrogenolysis of the methylsulfanyl substituent was observed with catalytic hydrogenation.²⁴ In contrast, reduction of 3-nitro[1,2,4]triazolo[5,1-c][1,2,4]triazin-4-amines **164** was carried out *via* catalytic hydrogenation over Pd/C under high pressure to produce the corresponding 3,4-diamine derivatives **165**. In this case, sodium dithionite was not suitable (Scheme 27).⁵⁸ <Scheme 27 near here>



Scheme 27

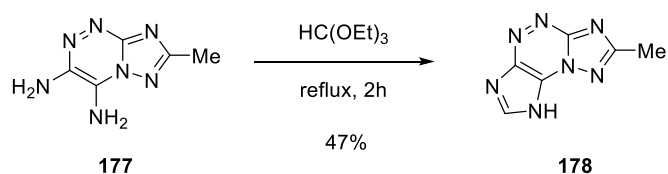
11.19.5.3.4 Construction of a fused ring

By taking advantage of the cyano and amino substituents of triazolotriazine **166**, various fused tricyclic compounds have been built: refluxing in formic acid or in a solution of aromatic ketones **167** in acetic acid afforded pyrimidones **168** and **169**; treatment with formamide allowed the construction of amino-pyrimidine **170**. Alternatively, condensation with triethylorthoformate yielded ethyl acetamidate **171**, which has been used in turn for the formation of polyheterocyclic fused systems. As such, treatment of **171** with hydrazine hydrate or aniline **172** in ethanol at low temperature furnished pyrimidine imine **173**. Conducting the latter transformation under reflux led to arylamino- or hydrazinyl- pyrimidines **174**. Finally, reaction between acetamidate **171** and hydrazide **175** in refluxing phosphorus oxychloride gave rise to tetracyclic compound **176** (Scheme 28).⁵⁹ <Scheme 28 near here>



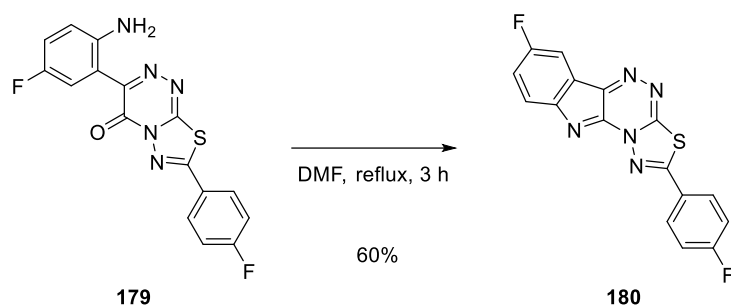
Scheme 28

Condensation of [1,2,4]triazolo[5,1-c][1,2,4]triazine-3,4-diamines **177** with triethylorthoformate under reflux allowed the building of tricyclic system **178** with a fused-imidazole (Scheme 29).⁵⁸ <Scheme 29 near here>



Scheme 29

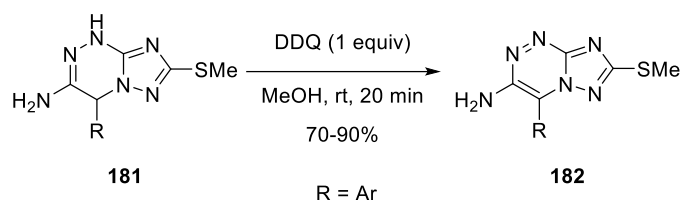
Intramolecular condensation of the aminophenyl substituent with the carbonyl group of thiadiazolotriazinone derivative **179** occurred in DMF under reflux furnishing indole-fused thiadiazolotriazine **180** (Scheme 30).⁶⁰ <Scheme 30 near here>



Scheme 30

11.19.5.4 Oxidation of the ring

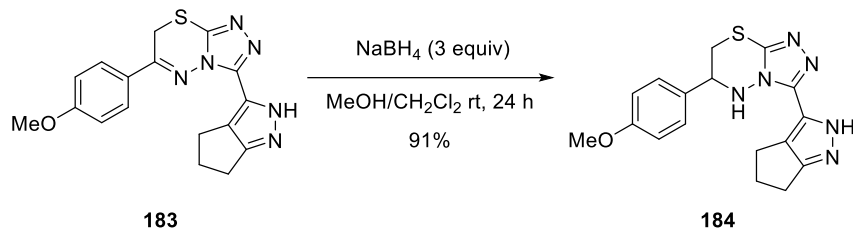
Aromatization of 1,4-dihydro-[1,2,4]triazolo[5,1-c][1,2,4]triazines **181** by oxidative dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol resulted in the formation of the corresponding 6-aminoazolo[5,1-c]triazine derivatives **182** in good yields. Other oxidizing agents such as potassium permanganate, hydrogen peroxide, potassium hexacyanoferrate(III), ammonium persulfate and phenyliodine diacetate were not suitable for this transformation (Scheme 31).²⁴ <Scheme 31 near here>



Scheme 31

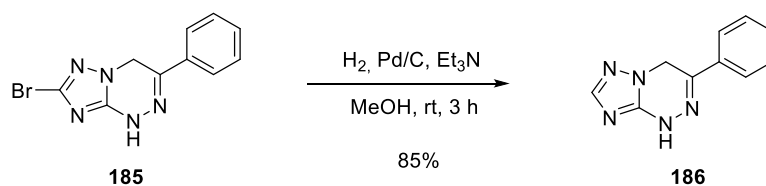
11.19.5.5 Reduction of the ring

Treatment of triazolothiadiazine **183** with sodium borohydride yielded the corresponding dihydrothiadiazine **184** (Scheme 32).²² <Scheme 32 near here>



Scheme 32

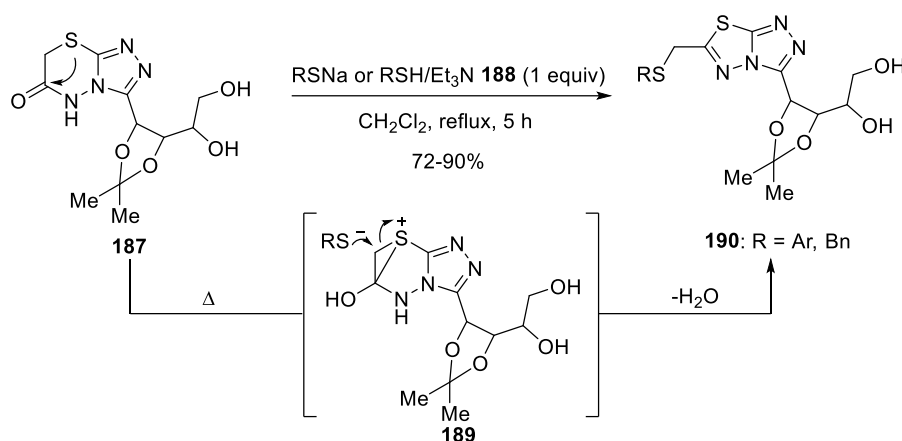
Removal of the bromo substituent of 7-bromo-1,4-dihydro-[1,2,4]triazolo[5,1-c][1,2,4]triazines **185** has been carried out through catalytic hydrogenation over Pd/C (Scheme 33).²⁵ <Scheme 33 near here>



Scheme 33

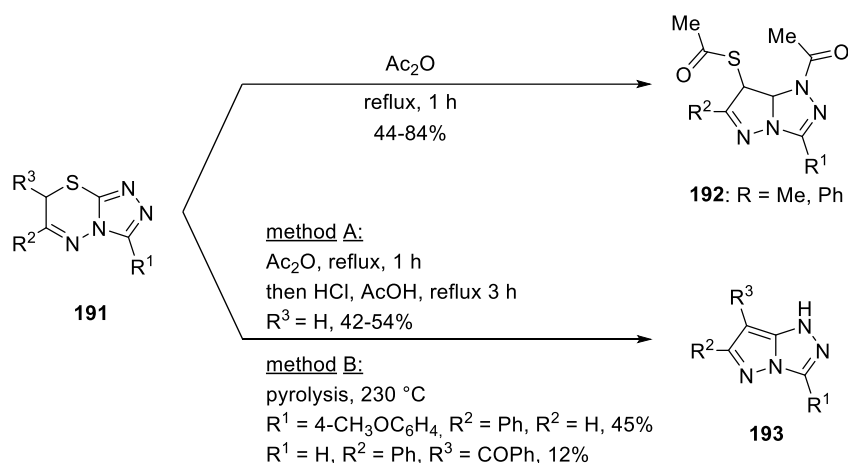
11.19.5.6 Ring contraction

This section concerns only triazolothiadiazines of type **3** in which contraction of the six-membered ring has been observed under some reaction conditions. Contraction of the thiadiazinone ring occurred when 5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6(7*H*)-one derivative **187** was treated with thiolates **188** in dichloromethane under reflux affording [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **190**. This transformation would involve the formation of episulphonium **189**, which would undergo ring opening by thiolates **188** (Scheme 34).⁶¹ <Scheme 34 near here>



Scheme 34

Heating 7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives **191** in acetic anhydride readily resulted in a ring-contraction of the fused six-membered thiadiazine leading to 1-acetyl-7-acetylsulfanyl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazoles **192**. A one-pot conversion to pyrazolo[5,1-*c*][1,2,4]triazole **193** was performed by subsequent treatment with hydrogen chloride through deacetylation/desulfurization. Alternatively, fused heterocycles **193** was also obtained by pyrolysis of **191** (Scheme 35).⁶²⁻⁶⁴ <Scheme 35 near here>



Scheme 35

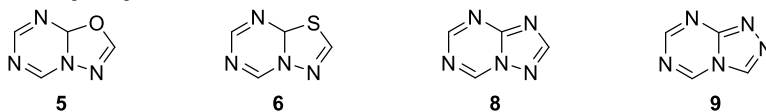
11.19.6 Ring Synthesis through cyclization or cyclocondensation of a monocyclic system

The synthesis of the bicyclic 5-6 systems mainly involved the construction of the second heterocycle by cyclization or cyclocondensation of the first cycle. In some cases, the two cycles have been built in tandem or one-pot sequential two-step processes from acyclic compounds or from another ring. Because of the quite large number of possible ring systems belonging to this chapter, this section is divided according to the structure of the six-membered ring. As depicted in figure 7, the synthesis of fused-thiadiazines with [1,3,5]- and [1,3,4]-heteroaromatic arrangements will be discussed first. Then, the preparation of fused triazines with [1,3,5]-, [1,2,4]- and [1,2,3]- arrangements will be reviewed sequentially. For fused [1,2,4]triazines, the site of the fusion (*i.e.*, *b*-, *c*-, *d*-, and *f*-fusion) will be distinguished due to the abundance of data. Also of note, in each section, processes involving the closure of the five- or the six-membered rings have been differentiated when appropriate. Such organization was also used in CHEC-III(2008). It has the advantage to highlight the use of versatile common starting materials for the construction of various fused systems (Figure 7). <Figure 7 near here>

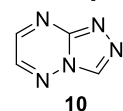
Triazolothiadiazines



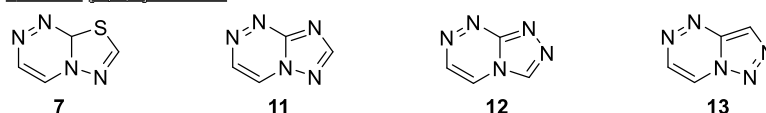
Fused [1,3,5]triazines



b-Fused [1,2,4]triazines



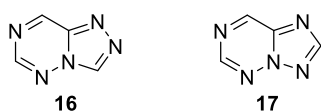
c-Fused [1,2,4]triazines



d-Fused [1,2,4]triazines



f-Fused [1,2,4]triazines



Fused [1,2,3]triazines

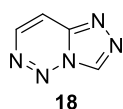
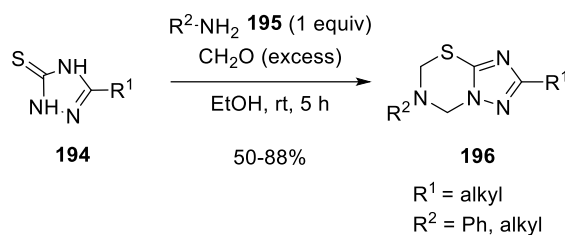


Figure 7

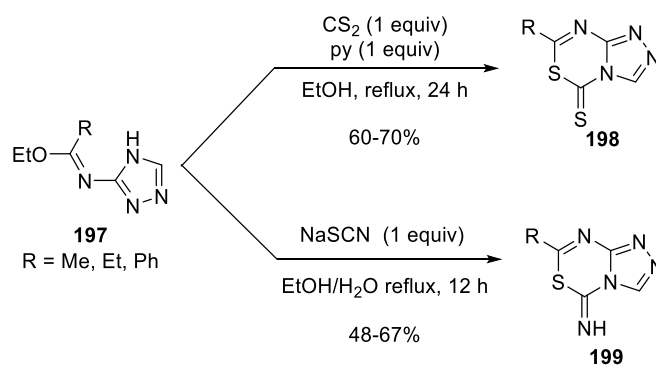
11.19.6.3 Synthesis of Fused Thiadiazines

11.19.6.3.1 Thiadiazines with 1,3,5-heteroatomic arrangement

The preparation of 2,6-disubstituted-6,7-dihydro-5*H*-1,2,4-triazolo[3,2-*b*]-1,3,5-thiadiazines has been reported by Tozkoparan *et al.* (Scheme 36). In their study, a bis-three-component Mannich type reaction between various 1,2,4-triazole-5-thiones **194**, primary alkyl amines and formaldehyde furnished the corresponding fused heterocyclic derivatives **196** in moderate to high yields (up to 88%).¹² <Scheme 36 near here>



Hajri *et al.* have reported that treatment of *N*-(4*H*-1,2,4-triazol-3-yl) carboximidates **197** with carbon disulfide in the presence of pyridine would afford [1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazine-5-thiones **198** in good yields. The authors assumed that the reaction would proceed through the regioselective nucleophilic addition of N4 nitrogen atom of **198**. Alternatively, the reaction of **197** with an equimolar of sodium thiocyanate would allow the construction of [1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazin-5-imines in moderate yields. The structures of obtained regioisomers were not ascertained by X-Ray analyses (Scheme 37).⁶⁵ <Scheme 37 near here>

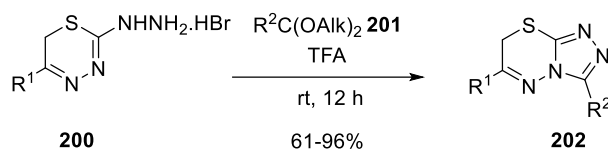


11.19.6.3.3 [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazines

As already mentioned above, among all the possible ring systems of this chapter, the most extended literature concerns derivatives of this ring system (type **3**). Indeed, this skeleton represents an important class of heterocyclic compounds possessing a wide range of biological activities and many derivatives have been synthesized during the last period. Full description of all particular compounds cannot be covered in this chapter. Extensive literature data can be found in CHEC-II(1996) and CHEC-III(2008). Herein, only transformations involving new type of reactive partners will be summarized.

11.19.6.3.3(i) closure of the five-membered ring

Cyclocondensation of 2-hydrazinyl-6*H*-1,3,4-thiadiazines **200** with orthoesters **201** in the presence of trifluoroacetic acid furnished triazolothiadiazines **202** in good to excellent yields (Scheme 38).⁶⁶ <Scheme 38 near here>

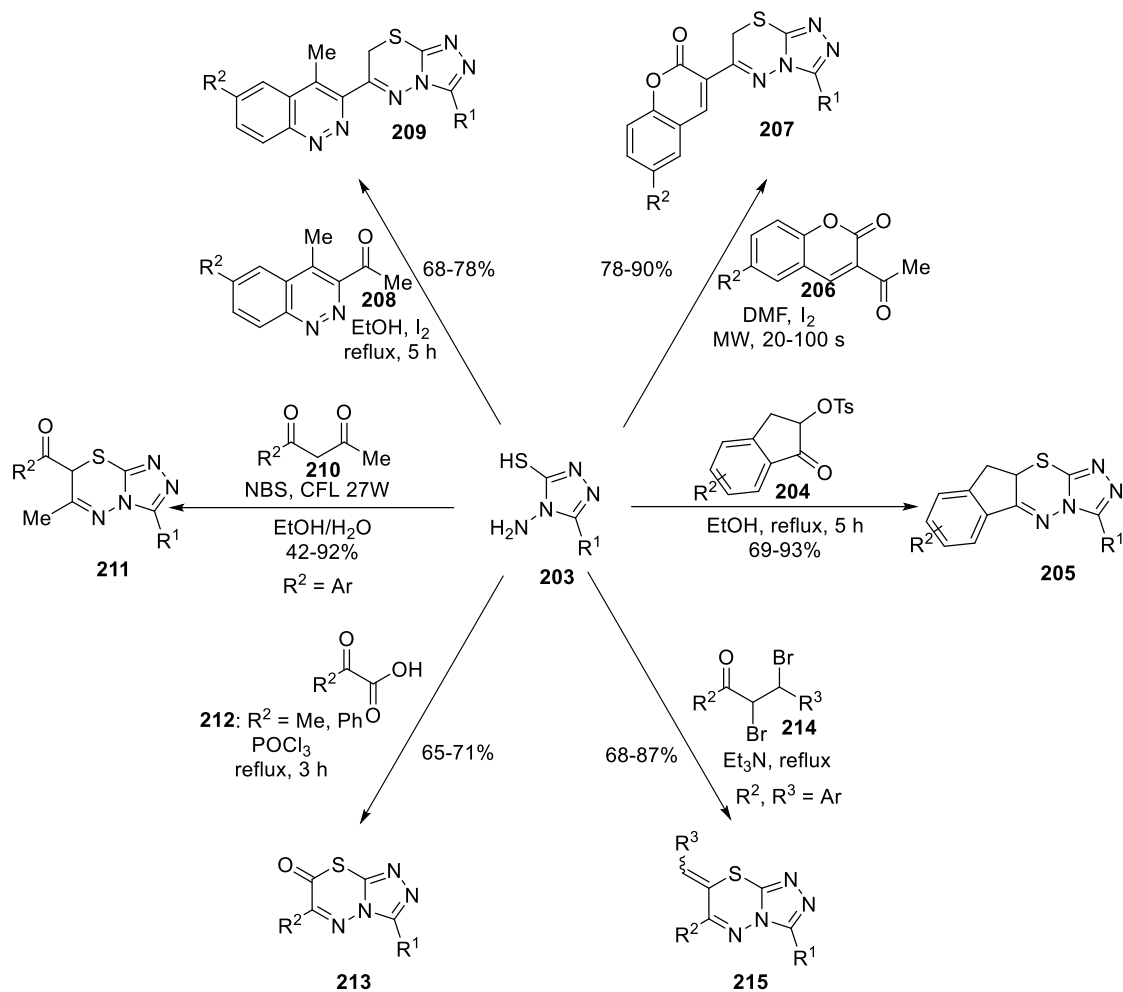


Scheme 38

11.19.6.3.3(ii) closure of the six-membered ring

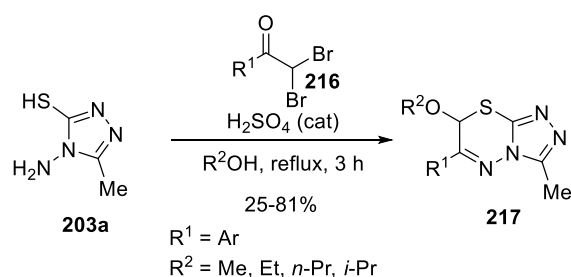
11.19.6.3.3(ii)(a) synthesis from 4-amino-4*H*-1,2,4-triazole-3-thiol derivatives

As displayed in Scheme 39, condensation of 4-amino-4*H*-1,2,4-triazole-3-thiols **203** with various ketones bearing a leaving group at the α -position of the carbonyl function represents one of the most efficient ways for the construction of this ring system (see also CHEC-III(2008) and CHEC-II(1996)). Dihydroindeno derivatives **205** have been obtained in good yields from 2-tosyloxy-1-indanones **204**.⁶⁷ Iodine-mediated *in-situ* generation of α -iodo-ketones from 3-acetyl-coumarines **206** under microwave irradiation allowed the construction of coumarinyl-triazolothiadiazines **207**.⁶⁸ Similar strategy has been used for the synthesis of cinnoline derivatives **209**.⁶⁹ Visible-light mediated bromination of β -diketones **210** with *N*-bromo succinimide (NBS) furnished regioselectively 6-methyl 2-aryl substituted triazolothiadiazines **211** in excellent yields. A solvent free protocol was also established with a catalytic amount of *p*-toluene sulfonic acid with slightly lower yields.⁷⁰ Reactions with acetyl or benzoyl formic acids **212** in phosphorus oxychloride under reflux yielded 7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-ones **213**.⁷¹ Condensation with α,β -dibromoketones **214** gave rise to arylidene derivatives **215**.⁷²⁻⁷⁴ <Scheme 39 near here>



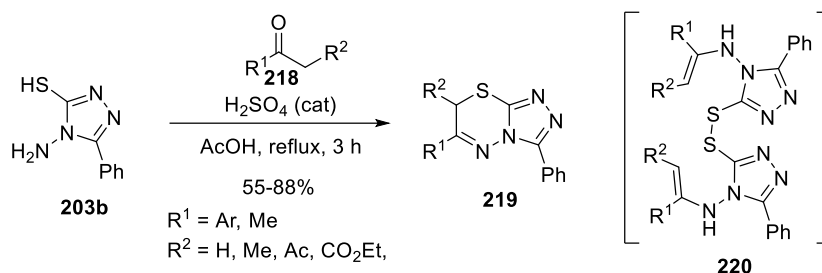
Scheme 39

7-alkoxy-6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives **217** were synthesized upon treatment of **203a** with α,α -dibromoacetophenones **216** in different alcohols under reflux (Scheme 40).⁷⁵ <Scheme 40>



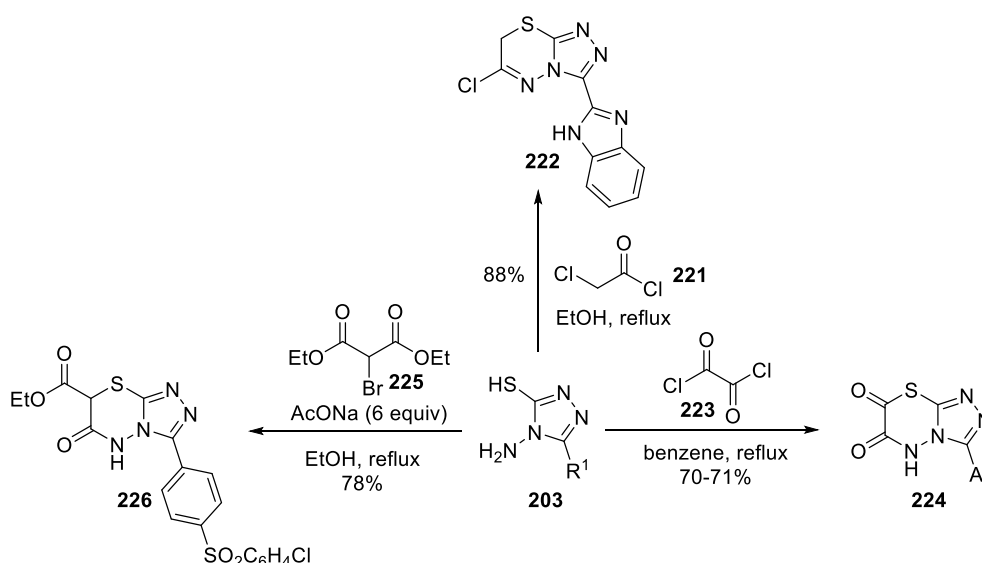
Scheme 40

Reactions of 4-amino-4H-1,2,4-triazole-3-thiols **203b** with ketones **218** in boiling acetic acid in the presence of a catalytic amount of sulfuric acid afforded triazolothiadiazine **219** in moderate to good yields. According to the authors, the transformation might proceed through the formation of disulphide **220**, which would undergo intramolecular nucleophilic substitutions with the enamine functions (Scheme 41).⁷⁶ <Scheme 41 near here>



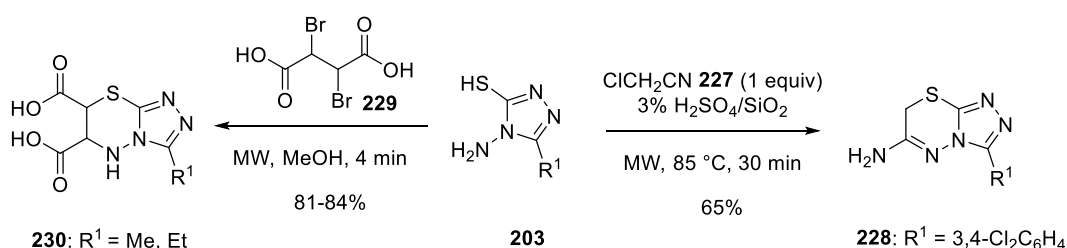
Scheme 41

Esters and acyl chlorides have also been employed as electrophiles. Chloroacetyl chloride **221** furnished 6-chloro-triazolothiadiazine **222**;⁷⁷ oxalyl chloride **223** and bromomalonate **225** led to triazolothiadiazin-6-ones **224** and triazolothiadiazin-6,7-diones **226** respectively (Scheme 42).^{7,78}



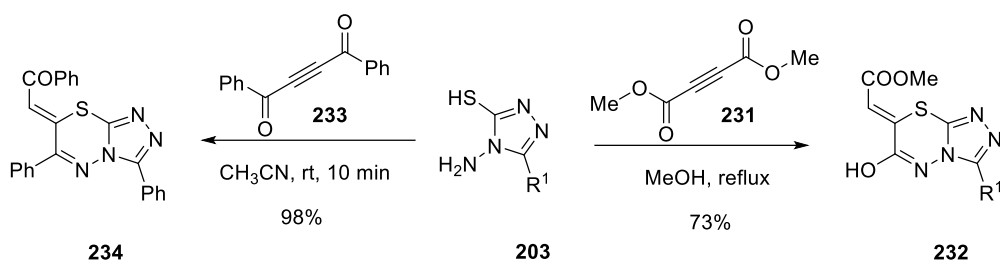
Scheme 42

Treatment of **203** with 2-chloroacetonitrile **227** in the presence of sulphuric acid immobilized on silica gel under microwave irradiation afforded triazolothiadiazin-6-amine **228** (Scheme 43).⁷⁹ Also under microwave irradiation, cyclocondensation with 2,3-dibromosuccinic acid **229** furnished diacid derivatives **230** in high yields.⁸⁰



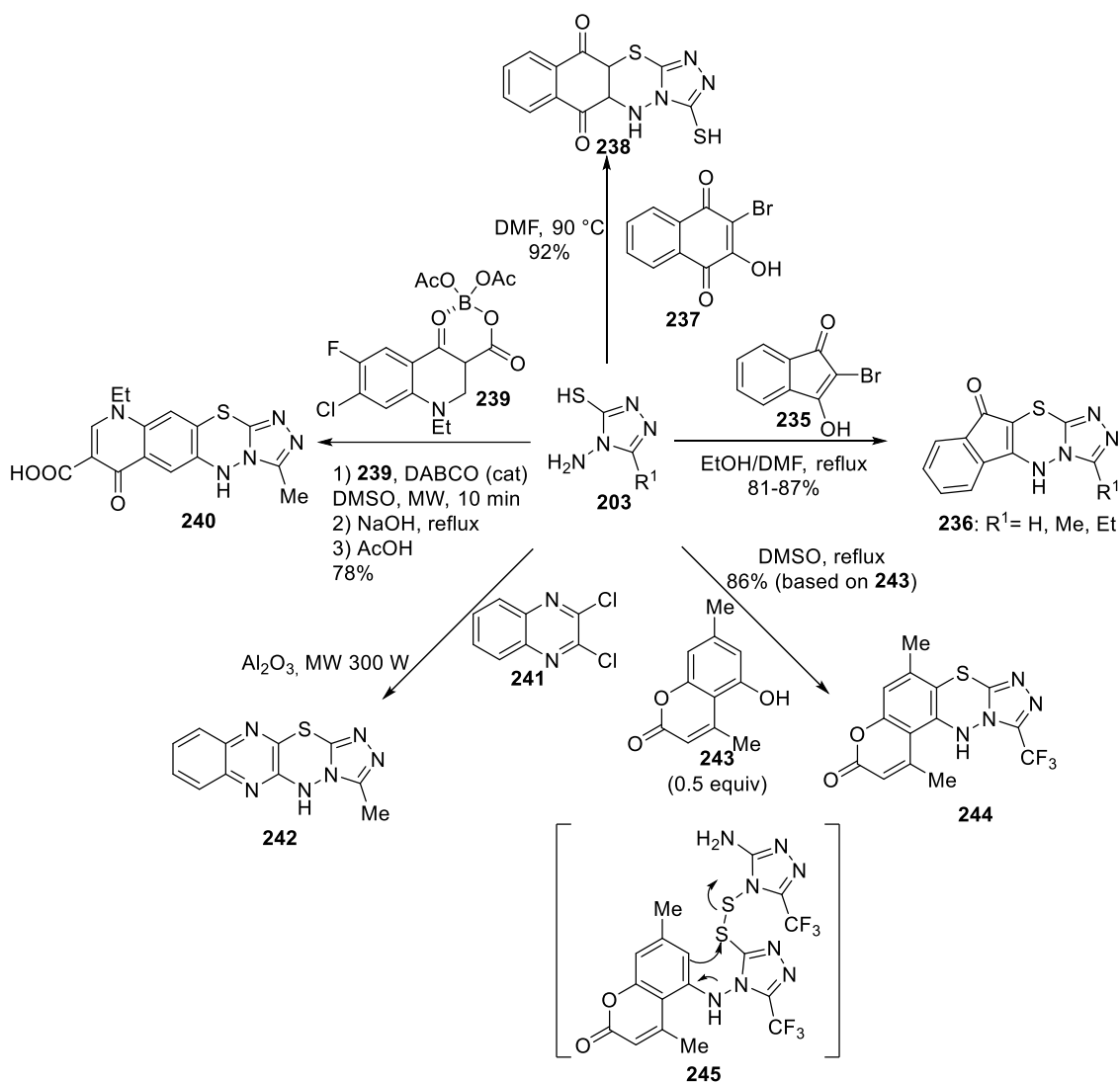
Scheme 43

Triazoles **203** reacted also with alkynes; namely dimethylacetylene dicarboxylate **231** and dibenzoylacetylene **233**. The corresponding highly functionalized triazolothiadiazines **232** and **234** were obtained in good to excellent yields (Scheme 44).⁸¹⁻⁸²



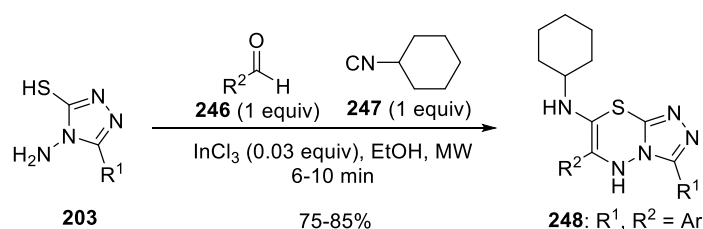
Scheme 44

As shown in scheme 45, various polycyclic derivatives have also been obtained from **203**. 2-bromo-indandione **235** and 2-bromo-3-hydroxynaphtalene-1,4-dione **237** produced regioselectively tetracyclic linear derivative **236** and fused indanones **238** in excellent yields.⁸³⁻⁸⁴ Similar transformation was performed under microwave irradiation in the presence of piperidine as a base.⁸⁵ Borate complex **239** of 7-chloro-6-fluoro-quinolinone carboxylic acid underwent regioselectively bisnucleophilic aromatic substitution under microwave irradiation in the presence of a catalytic amount of DABCO to form quinoline derivative **240** in high yields.⁸⁶ Compound **203** was adsorbed on alumina and treated with 2,3-dichloroquinoxaline **241** under microwave irradiation to furnish fused systems **242**.⁸⁷ Treatment of 5-hydroxycoumarin derivative **243** with two equivalents of triazole **203** gave rise to coumarino-triazolothiadiazine **244**. It has been assumed that this reaction proceeded through the cyclization of disulphide intermediate **245**.⁸⁸ <Scheme 45 near here>



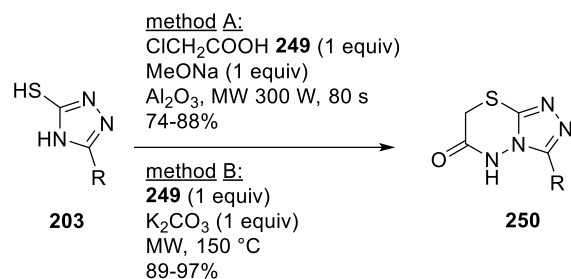
Scheme 45

A three-component reaction between triazoles **203**, aromatic aldehydes **246** and cyclohexyl isocyanide **247** has been developed. The reaction was performed under microwave irradiation with a catalytic amount of indium trichloride furnishing triazolothiadiazines **248** in high yields in very short reaction times (Scheme 46).⁸⁹ <Scheme 46 near here>



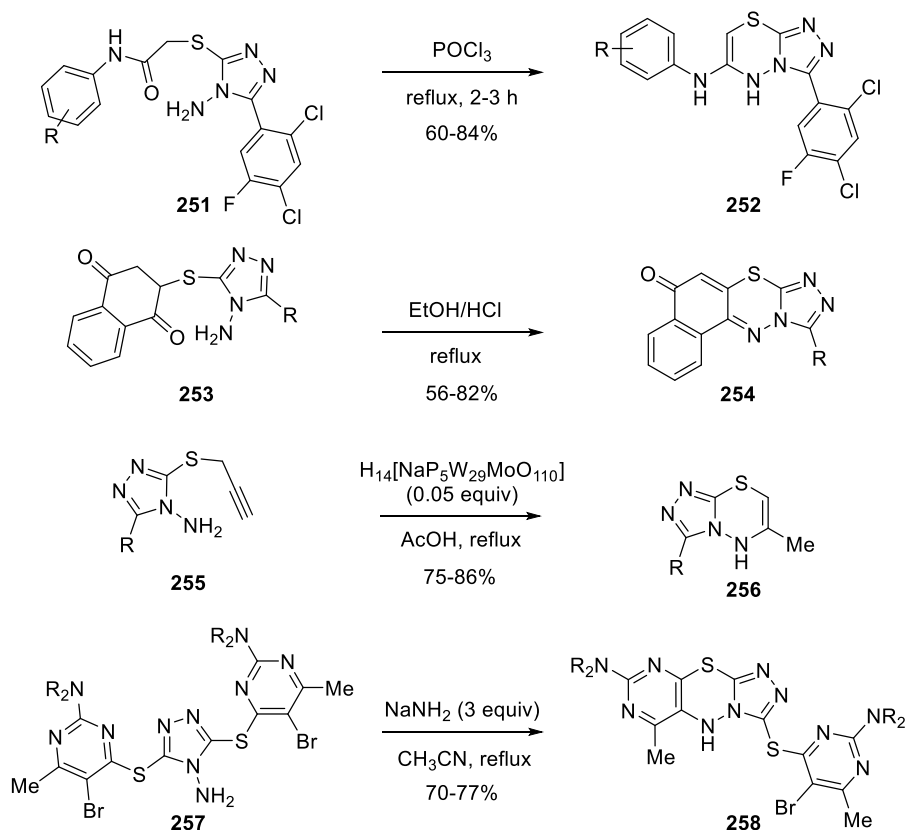
Scheme 46

Absorption of **203**, chloroacetic acid **249** and sodium methoxide over alumina followed by microwave irradiation produce [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6(7*H*)-one **250**.⁹⁰ Alternatively, simple solvent-free reaction of **203** with **249** and potassium carbonate under microwave irradiation was also possible.⁹¹ (Scheme 47) <Scheme 47 near here>



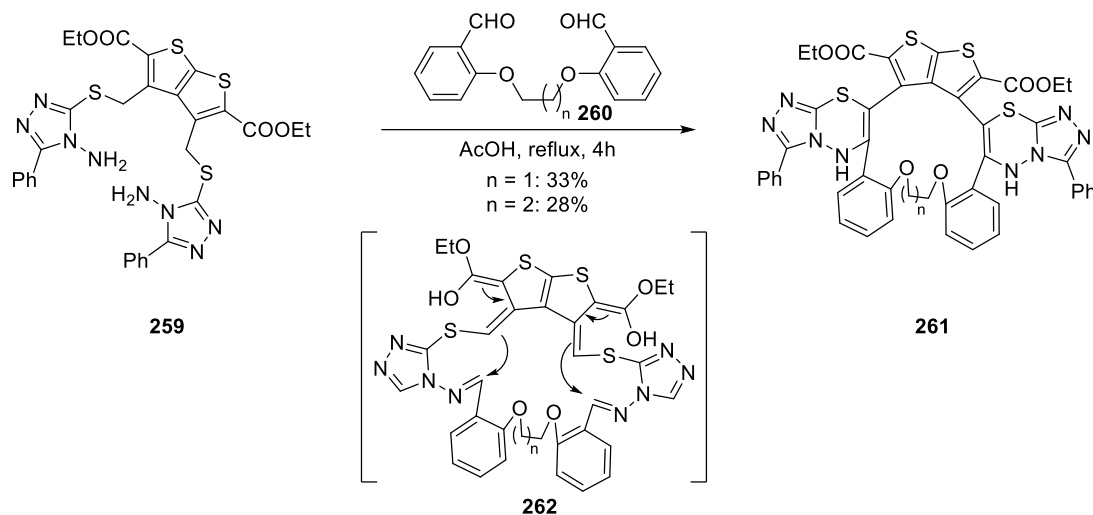
Scheme 47

As depicted in scheme 48, various 3-thioether-4*H*-1,2,4-triazol-4-amine derivatives have been employed in intramolecular processes. Intramolecular cyclocondensation of the amino group with the carbonyl function of amide **251** allowed the construction of fused thiadiazines rings **252**. Similarly, condensation with the carbonyl group of mercapto-naphthalene-1,4-dione substituent of **253** furnished fused system **254**.⁹²⁻⁹³ The alkyne functional group of propargyl thioether **255** underwent intramolecular hydroamination in the presence of a catalytic amount of heteropolyacids to build 6-methyl-triazolothiadiazine **256**.⁹⁴ Intramolecular aromatic nucleophilic substitution ($\text{S}_{\text{N}}\text{Ar}$) of heteroaryl thioether **257** furnished pyrimido[5,4-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **258** in good yields.⁹⁵ Other series of pyrimidotriazolothiadiazines have been also reported via similar direct $\text{S}_{\text{N}}\text{Ar}$ of bomopyrimidine thioethers⁹⁶⁻⁹⁷ or with a preceding S-N type Smiles rearrangement.⁹⁸ These works, dealing with the construction of polyheterocyclic compounds, go little beyond the scope of this chapter and will not be described in any further details. <Scheme 48 near here>

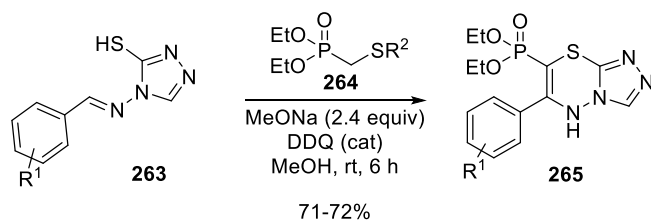


Scheme 48

Cyclocondensation of bis(3-thioether-4*H*-1,2,4-triazol-4-amine) derivative **259** with bis(aldehydes) **260** in refluxing acetic acid afforded macrocycles **261** in decent yields. The reaction might have proceeded *via* initial formations of macrocyclic diimines **262**. The latter would undergo intramolecular Mannich-type reactions with *in-situ* generated vinylogous ketene acetals to form the two triazolothiadiazines rings (Scheme 49).⁹⁹ <Scheme 49 near here>

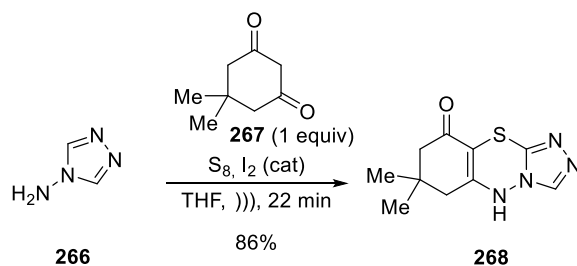


Addition of thioalkyl-containing phosphonates **264** to 4-(benzylideneamino)-4*H*-1,2,4-triazole-3-thiol derivatives **263** in the presence of a catalytic amount of DDQ led to 7-phosphonate substituted triazolothiadiazines **265**. Under these oxidative reaction conditions, the cyclization occurred *via* elimination of the thioalkyl group (Scheme 50).¹⁰⁰ <Scheme 50 near here>



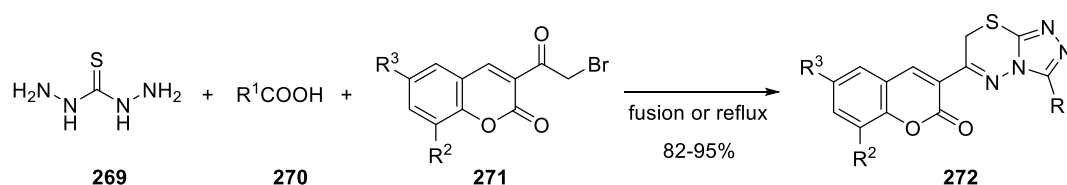
11.19.6.3.3(ii)(b) other route

Treatment of amino-triazole **266** with dimedone **267**, sulphur powder and iodine as a catalyst under sonication produced fused system **268** in high yield (Scheme 51).¹⁰¹ <Scheme 51 near here>

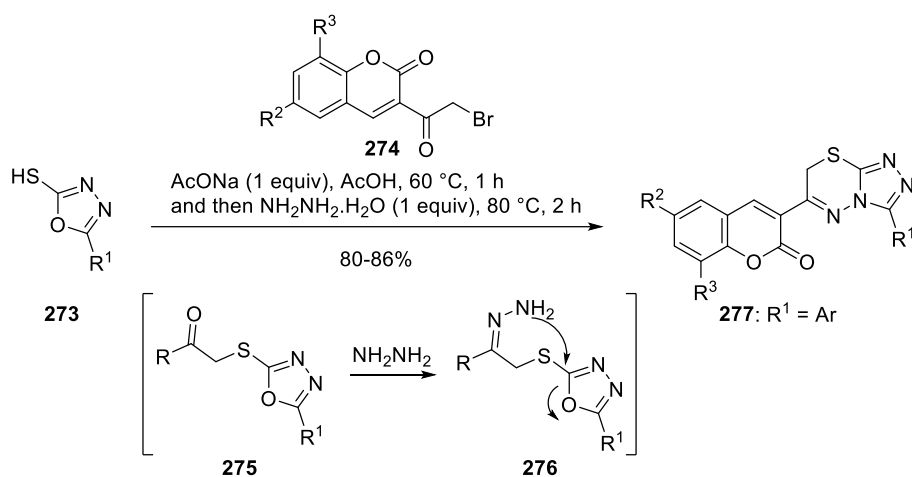


11.19.6.3.3(iii) construction of both rings (closure of the six-membered ring at the last step)

A one-pot sequential multi-components reaction between thiosemicarbazides **269**, carboxylic acids **270** and substituted 3-(2-bromoacetyl)coumarins **271** has been developed. This convenient procedure was performed under solvent-free conditions delivering the bicyclic systems **272** in high yields (Scheme 52).¹⁰² <Scheme 52 near here>

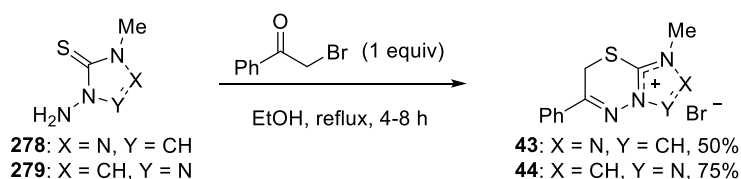


Reaction of 5-aryl-1,3,4-oxadiazole-2-thiol **273** with (bromoacetyl)coumarin **274** in the presence of sodium acetate in boiling acetic acid followed by the addition of hydrazine hydrate afforded triazolothiadiazine **277**.¹⁰³ The transformation would have proceeded through the *in-situ* generation of thioether **275** followed by ring opening of the oxazole moiety via hydrazone **276**. Similar deconstruction of oxadiazole rings in acetic acid with hydrazine have also been reported from isolated thioether derivatives of type **275**.¹⁰⁴⁻¹⁰⁸ Such transformations delivered usually the corresponding triazolothiadiazines in high yields (Scheme 53). <Scheme 53 near here>



11.19.6.3.4 [1,2,4]Triazolo[*b*][1,3,4]thiadiaziniums

With the aim to determine their crystal structures (cf. Section 11.19.3.2), [1,2,4]triazolo[*b*][1,3,4]thiadiazinium bromide salts **43** and **44** were prepared by reacting the corresponding *N*-amino-*N'*-methyl-1,2,4-triazolo-5-thiones **278** and **279** with phenacyl bromide in ethanol (Scheme 54).¹⁴ <Scheme 54 near here>



Scheme 54

11.19.6.5 Synthesis of Fused Triazines

11.19.6.5.1 Synthesis of fused [1,3,5]-triazines

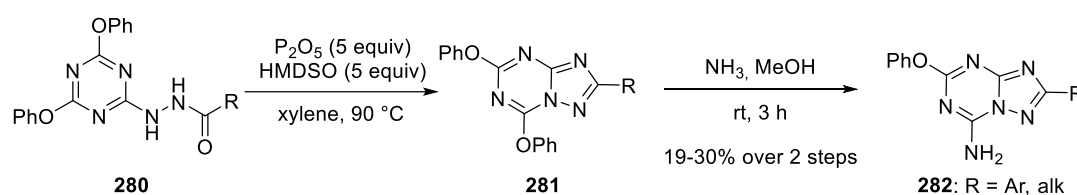
Since 2007, the preparation of four bicyclic skeletons with fused 1,3,5-triazines has been reported: [1,3,4]oxadiazolo[3,2-*a*][1,3,5]triazines **5**, [1,3,4]thiadiazolo[3,2-*a*][1,3,5]triazines **6**, [1,2,4]triazolo[1,5-*a*][1,3,5]triazines **8** and [1,2,4]triazolo[4,3-*a*][1,3,5]triazines **9** (see Figure 7). While triazolotriazines **8-9** have been synthesized through either the ring closure of the 5- or the 6-membered rings, oxadiazolo- and thiadiazolo-triazines **5-6** have been prepared only *via* the late construction of the 6-membered ring.

11.19.6.5.1(i) closure of the five-membered ring

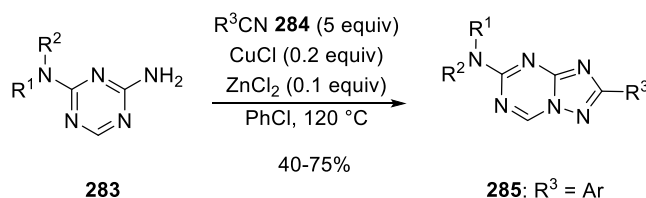
11.19.6.5.1(i)(a) [1,2,4]triazolo[1,5-*a*][1,3,5]triazines

Important transformations for the construction of this fused system through the ring closure of the 5-membered ring have already been reviewed in CHEC-II(1996) and CHEC-III(2008). Herein are described some complementary approaches.

Cyclodehydration of hydrazides **280** in anhydrous xylene with an excess of phosphorus pentoxide and hexamethyldisiloxane (HMDSO) led to the formation of triazolotriazine **281** *via in-situ* Dimroth type rearrangement. Due to stability problems, **281** was transformed directly to the corresponding amino-derivatives **282** by treating with methanolic ammonia (Scheme 55).^{40,109} <Scheme 55 near here>

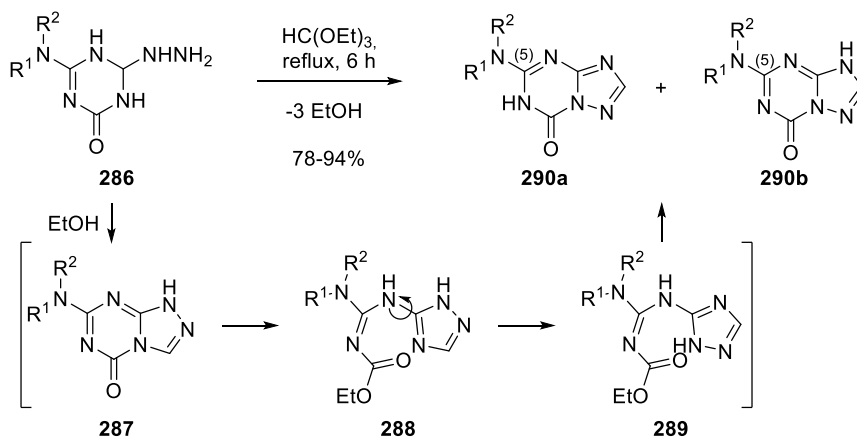


Copper-catalyzed oxidative (3+2)-cycloadditions between 1,3,5-triazin-2-amines **283** and aryl nitriles **284** furnished fused systems **285** in moderate to good yields. The structure of the products was confirmed by single crystal X-ray structure analysis (Scheme 56).¹¹⁰ <Scheme 56 near here>

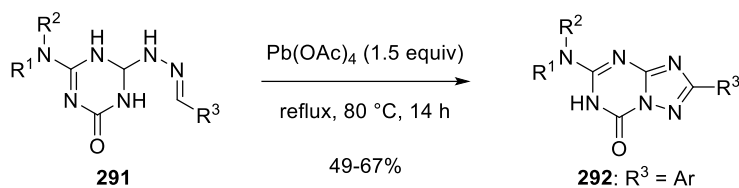


Condensation of 6-hydrazinyl-1,3,5-triazin-2-one derivatives **286** with triethyl orthoformate proceeded *via* a Dimroth-type rearrangement to afford triazolotriazinones **290**. Indeed, nucleophilic addition of *in-situ* generated ethanol to the carbonyl group of fused intermediate **287** would open the triazine ring and generate **288**. A rotation of 1,2,4-triazole ring around the C-N sigma bond would allow the ring closure of 1,2,4-triazine to take place on intermediate **289** giving rise to thermodynamically more stable bicyclic compounds **290**. The position of the proton on these

products depends on the substituents of the *exo*-amino group at C5. The structures of the products have been unambiguously proven by X-Ray analyses (Scheme 57).¹¹¹ Similar transformations have also been reported in formic acid instead of triethyl orthoformate with slightly lower yields.¹¹² <Scheme 57 near here>

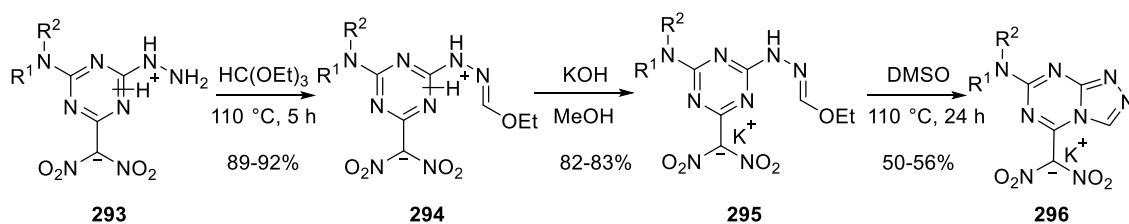


Oxidative cyclization of hydrazones **291** with lead(IV) tetraacetate in acetic acid proceeded also *via* a Dimroth-type rearrangement to produce 2-aryl-substituted triazolotriazinones **292**. The structure was also confirmed by X-ray crystal structure analysis (Scheme 58).¹¹³ <Scheme 58 near here>



11.19.6.5.1(i)(b) [1,2,4]triazolo[3,4-*a*][1,3,5]triazines

Only one example of preparation of [1,2,4]triazolo[3,4-*a*][1,3,5]triazines through the ring closure of the five-membered ring has been reported during the last decade. It concerns the potassium salts **296** of 5-dinitromethyltriazolotriazine derivatives, which have been synthesized in three steps from zwitterionic hydrazino compounds **293**: formation of ethoxymethylidenehydrazino derivatives **294** by heating in triethylorthoformate, treatment with potassium hydroxide in methanol to afford potassium salt **295** followed by construction of the five-membered ring by heating in dimethylsulfoxide. X-ray crystal structure analyses have proven the structure of the products (Scheme 59).¹¹⁴ <Scheme 59 near here>

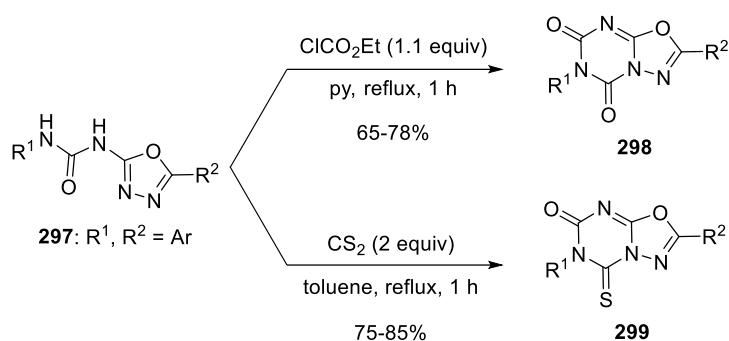


11.19.6.5.1(ii) closure of the six-membered ring

11.6.5.1(ii)(a) [1,3,4]oxadiazolo- and thiadiazolo-[3,2-*a*][1,3,5]triazines

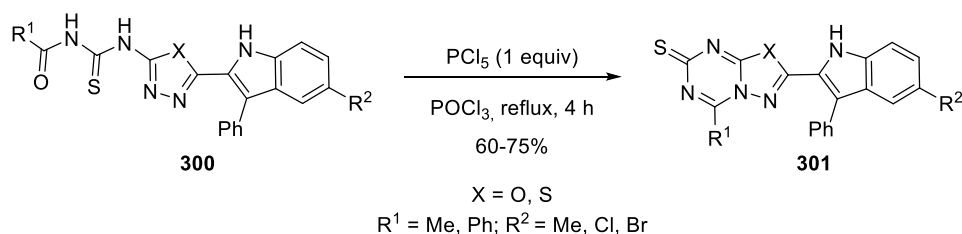
All the reported procedures for the access to this fused ring systems rely on the use of 2-amino-1,3,4-oxa- or thia-diazole derivatives which undergo a cyclocondensation or an intramolecular cyclization to build the triazine ring.

Cyclization of ureas **297** with ethyl chloroformate yielded [1,3,4]oxadiazolo[3,2-*a*][1,3,5]triazine-5,7-diones **298**. Alternatively, treatment with carbon disulfide furnished 5-thioxo derivatives **299** (Scheme 60). Good yields were obtained with both procedures (Scheme 60).¹¹⁵ <Scheme 60 near here>



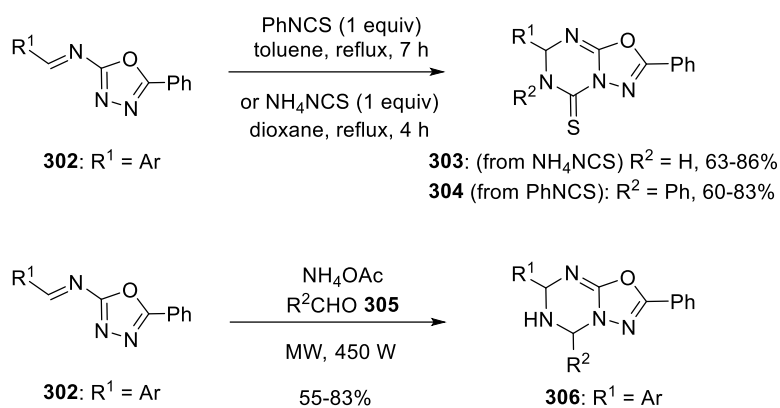
Scheme 60

Cyclodehydration of *N*-(carbamothioyl)acetamides **300** with phosphorus pentachloride in refluxing phosphorus oxychloride furnished [1,3,4]thia- and oxadiazolo[3,2-*a*][1,3,5]triazine-7-thiones **301** (Scheme 61).¹¹⁶ <Scheme 61 near here>



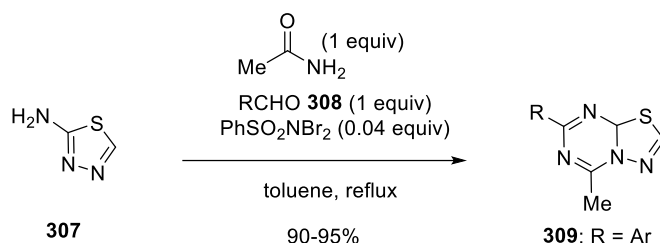
Scheme 61

As depicted in scheme 62, oxadiazolo[3,2-*a*][1,3,5]triazine-5-thione derivatives have been synthesized from imines **302**. Treatment with ammonium thiocyanate in dioxane under reflux afforded various 7-aryl-substituted fused systems **303** while the use of phenyl isocyanate in refluxing toluene gave rise to 6-phenyl-7-aryl-disubstituted derivatives **304**. In both cases, moderate to good yields were obtained.¹¹⁷ A multicomponent reaction between imines **302**, aromatic aldehydes **305** and ammonium thiocyanate under microwave irradiation produced dihydro-oxadiazolotriazines **306** in good yields (the diastereoselectivities were not reported).¹¹⁸ (Scheme 62) <Scheme 62 near here>



Scheme 62

2-Amino-1,3,4-thiadiazole **307** has been directly engaged in a multicomponent reaction with aromatic aldehydes **308** and acetamide produced thiadiazolotriazines **309** in excellent yields. The reactions were carried out in toluene under reflux in the presence of a catalytic amount of benzene sulphonamide dibromide. (Scheme 63)¹¹⁹ <Scheme 63 near here>

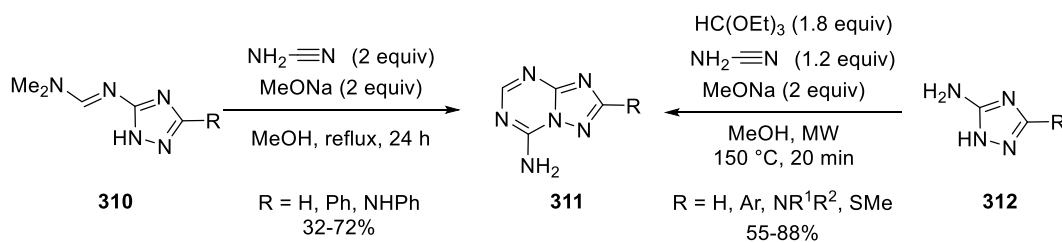


Scheme 63

11.19.6.5.1(ii)(b) [1,2,4]triazolo[1,5-*a*][1,3,5]triazines

The access to [1,2,4]triazolo[1,5-*a*][1,3,5]triazines through the construction of the 6-membered ring was achieved from 3-amino-1,2,4-triazole derivatives.

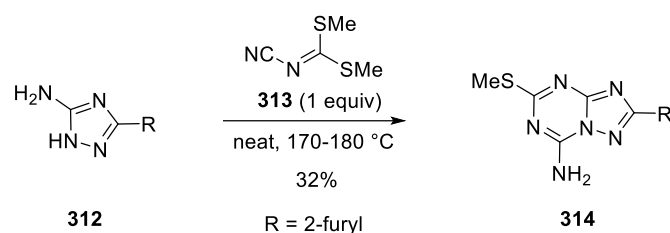
Dimethylformimidamides **310** reacted smoothly with cyanamide in the presence of sodium methoxide under heating to afford 7-amino-triazolotriazine **311**. A modest yield of 32% was obtained from unsubstituted **310** while a substantial improvement was observed with a phenyl or 2-aminophenyl substituent.¹²⁰ A more convenient procedure was thereafter reported by directly engaging 3-amino-1,2,4-triazoles **312** in a three-component reaction with triethyl orthoformate and cyanamide under microwave irradiation. In this case, higher yields were obtained with very short reaction times (Scheme 64).¹²¹⁻¹²² <Scheme 64 near here>



Scheme 64

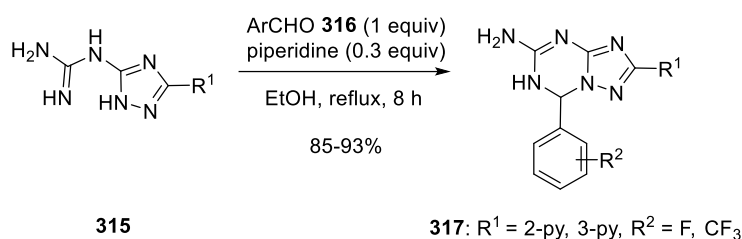
It has been demonstrated that *N*-cyanodithioiminocarbonate **313** can react with 3-amino-1,2,4-triazole **312** providing an access to 5-(methylthio)-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-amine **314**, a

synthetic intermediate of high interest. The reaction was carried out under neat at high temperature (Scheme 65).^{43-44,123} <Scheme 65 near here>



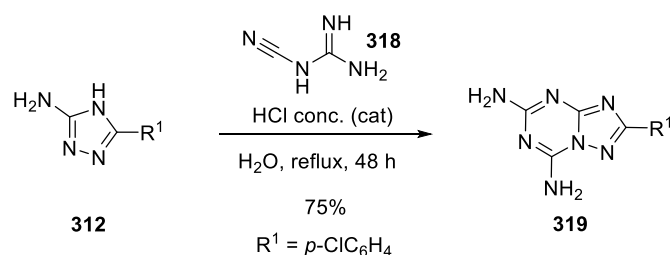
Scheme 65

Condensation of guanidine **315** with aromatic aldehydes **316** in the presence of a catalytic amount of piperidine in refluxing ethanol allowed the isolation of 6,7-dihydro-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-5-amine **317** in very good yields (Scheme 66).¹²⁴ <Scheme 66 near here>



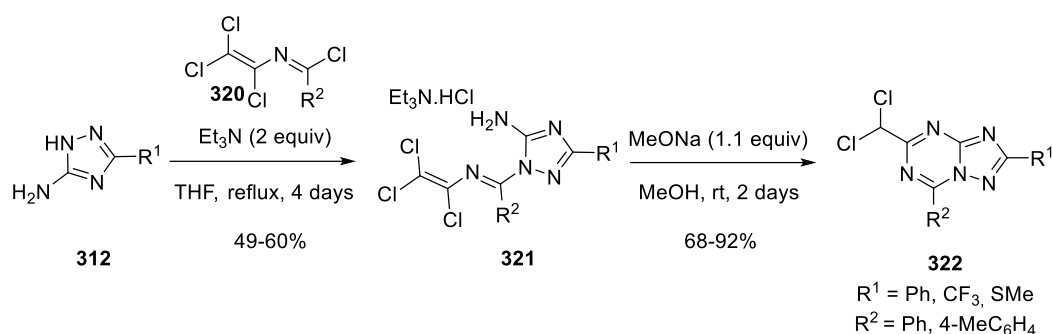
Scheme 66

The synthesis of 5,7-diaminotriazolotriazine **319** was achieved *via* the reaction of 3-amino-1,2,4-triazole **312** with cyanoguanidine **318** in water containing a catalytic amount of concentrated hydrochloric acid. The reaction mechanism is assumed to proceed through the nucleophilic addition of the triazole exocyclic amino function on the cyano group of cyanoguanidine followed by subsequent cyclization through elimination of one molecule of ammonia (Scheme 67).¹²⁵⁻¹²⁶ <Scheme 67 near here>

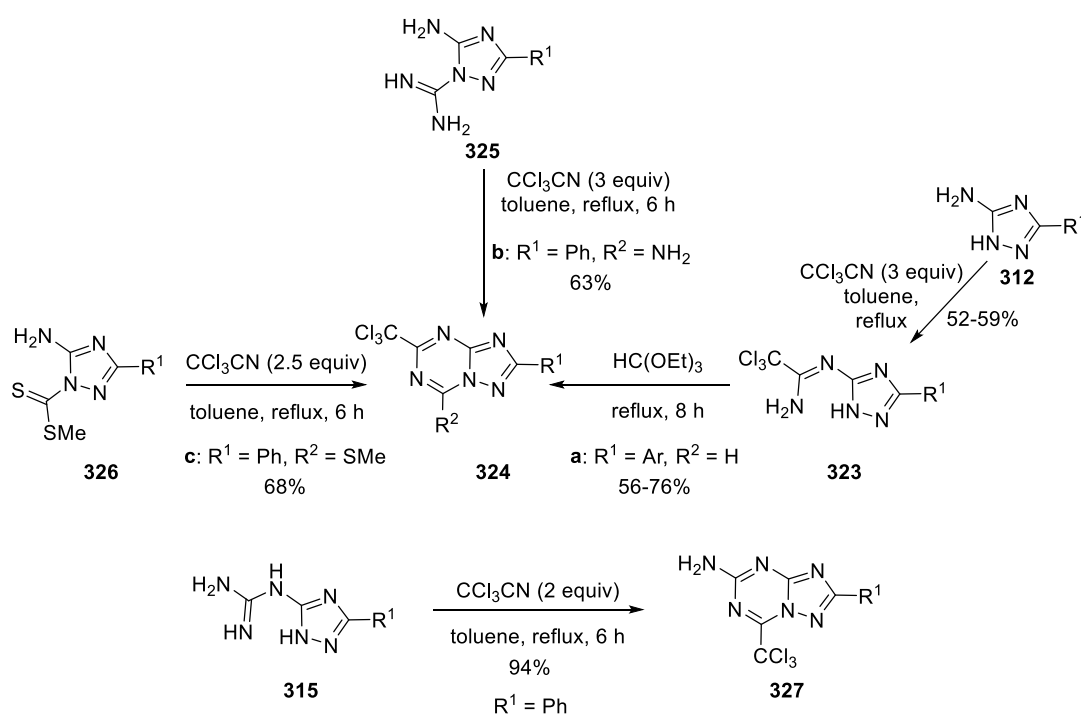


Scheme 67

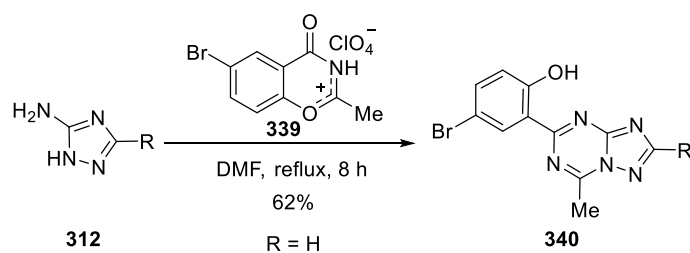
Reaction of polychloro 2-azabutadiene **320** with 3-amino-1,2,4-triazoles **312** in the presence of triethylamine produced N1-imino triazole **321** which cyclized to dichloromethyl-containing triazolotriazine **322** upon treatment with sodium methoxide (Scheme 68).¹²⁷ The structures were confirmed by X-Ray analysis. <Scheme 68 near here>



As shown in scheme 69, various trichloromethyl-containing triazolotriazines have been synthesized by using trichloroacetonitriles as reactive partners. 3-amino-1,2,4-triazoles **312** reacted with trichloroacetamide to afford trichloroacetamides **323**. The latter was subsequently cyclocondensed with triethyl orthoformate under reflux to form 5-trichloromethyl triazolotriazines **324a**.¹²⁸ Treatment of guanidine **325** with trichloroacetonitrile in toluene under reflux afforded 7-amino derivative **324b** through the elimination of ammonia. Alternatively, 7-thiomethyl derivative **324c** was obtained from methyl carbamodithioate **326** through the elimination of hydrogen sulfide.⁴⁸ Finally, the use of guanidine **315** furnished 5-amino-7-trichloromethyl triazolotriazines **327** in excellent yield (Scheme 69).⁴⁶⁻⁴⁷ <Scheme 69 near here>

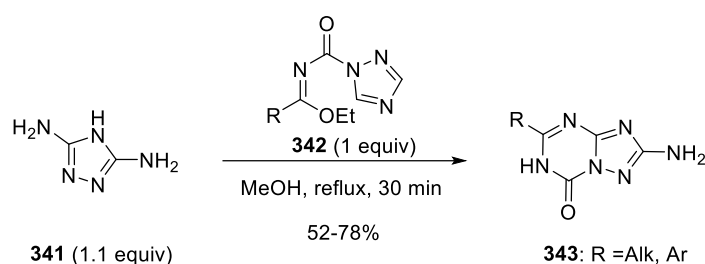


It is worth mentioning that analogous reactions from guanidines **315** or **325** in ethanol instead of toluene proceeded through elimination of chloroform and resulted in the formation of 5,7-diaminotriazolotriazines **319**. The role of ethanol in this reaction was tentatively explained by initial formation of imidate **328** which would react with the guanidine group to produce adduct **329**. Subsequent elimination of chloroform would afford intermediate **330**, which would undergo intramolecular cyclocondensation giving rise to **319** (Scheme 70).⁴⁶⁻⁴⁸ <Scheme 70 near here>



Scheme 73

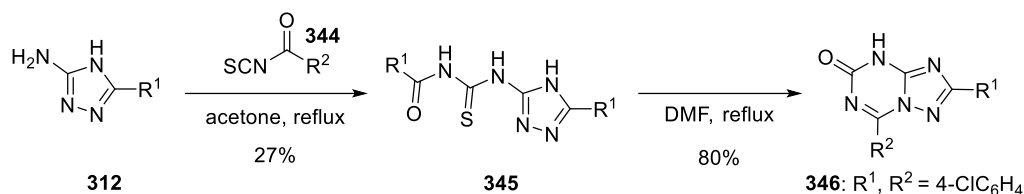
[1,2,4]Triazolo[1,5-*a*][1,3,5]triazin-7-one derivatives **343** have been accessed through the reaction between 1,2,4-triazole-3,5-diamine **341** and *N*-triazolide imidates **342** in good yields. The structure of the reported bicyclic compounds has been unambiguously proven by X-ray crystallography (Scheme 74).¹³² <Scheme 74 near here>



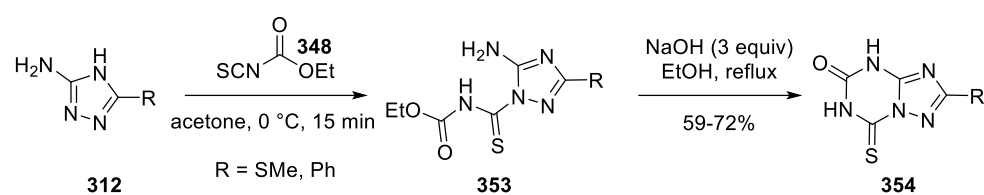
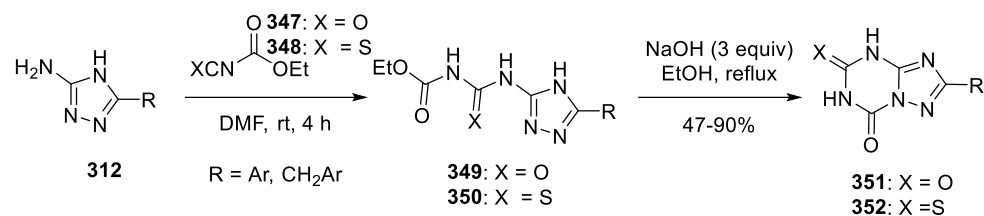
Scheme 74

As summarized in scheme 75, reactions between 3-amino-1,2,4-triazoles **312** and iso(thio)cyanate derivatives provide efficient ways for the construction of various [1,2,4]triazolo[1,5-*a*][1,3,5]triazin-(thi)ones or triazin-diones over two steps. The use of benzoylthiocyanate **344** yielded the corresponding open chain thiourea analogue **345** which cyclized to the triazolotriazine-5-thione derivative **346** upon heating under reflux in DMF.⁸⁸ The use of ethoxycarbonyliso(thio)cyanates **347** and **348** in DMF gave the (thio)ureas **349** and **350** derivatives which upon heterocyclization in alkaline medium led to triazolotriazine-5,7-diones **351** and 5-thioxotriazolotriazine-7-ones **352** respectively.^{55-56,133-134} Interestingly, when the reaction between **312** and **348** was carried out under kinetic control in acetone, it was possible to isolate the thiourea **353** arising from the *N*-alkylation of the triazole ring. As such, cyclization in ethanolic sodium hydroxide under reflux yielded 7-thioxotriazolotriazine-5-ones **354**.⁵⁶ (Scheme 75) <Scheme 75 near here>

reaction with benzoyl isothiocyanates



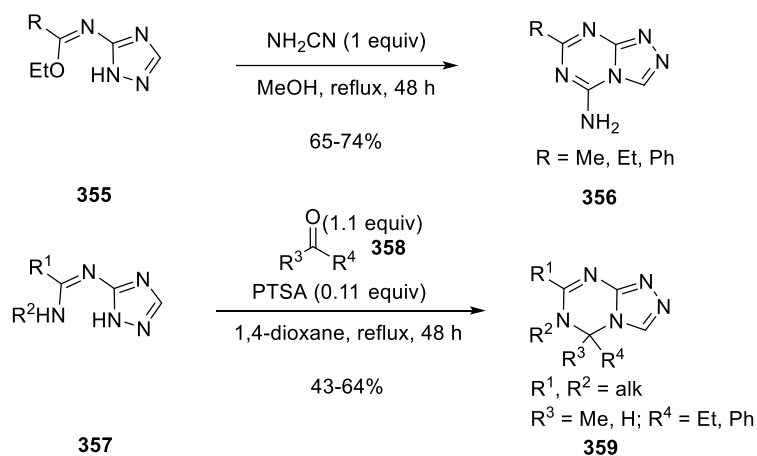
reactions with ethoxycarbonyl iso(thio)cyanates



Scheme 75

11.6.5.1(ii)(c) [1,2,4]triazolo[3,4-*a*][1,3,5]triazines

Recently, Hajri *et al.* have reported the synthesis of triazolotriazin-amines **356** through the reaction between carboximidates **355** and cyanamide in methanol under reflux (Scheme 76).⁶⁵ The same authors prepared dihydrotriazolotriazines **359** by cyclocondensation of amidines **357** with carbonyl compounds **358** in the presence of a catalytic amount of *p*-toluenesulfonic acid in 1,4-dioxane under reflux.¹³⁵ Unfortunately, there was no X-ray crystallography analyses to ascertain the structure of the obtained regioisomers of type [1,2,4]triazolo[3,4-*a*][1,3,5]triazines rather than [1,2,4]triazolo[1,5-*a*][1,3,5]triazine. <Scheme 76 near here>



Scheme 76

11.19.6.5.2 Synthesis of *b*-fused [1,2,4]-triazines

During the last period, [1,2,4]triazolo[4,3-*b*][1,2,4]triazines (structures **10**) are the only type of [1,2,4] triazines which have been described with *b*-fusion. The construction of these fused bicyclic systems could proceed either through the ring closure of the five-membered ring or the six-membered ring.

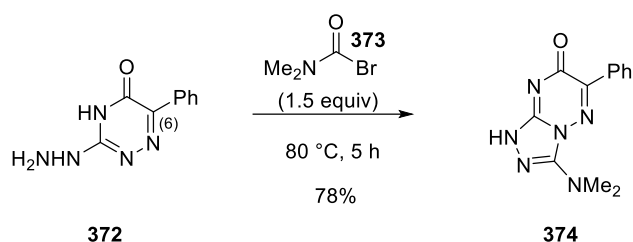
11.6.5.2(i) closure of the five-membered ring

3-Hydrazino-1,2,4-triazine and their derivatives were suitable starting materials for the cyclization of 1,2,4-triazole rings with *b*-fusion (Table 4). In these cases, the heterocyclization of such compounds proceeded regioselectively at the N2 atom of the triazine ring providing the [1,2,4]triazolo[4,3-*b*][1,2,4]-triazine derivatives and not [1,2,4]triazines with *c*-fusions (see section 11.6.5.3(i)). For instance, reaction of **360** with carbon disulfide in refluxing ethanol in the presence of potassium hydroxide allowed the construction of fused 1,2,4-triazole-3-thione **361** in good yield (entry 1).^{37,54} Treatment of **360** with benzoyl cyanide furnished fused system **362** through elimination of hydrogen cyanide and water (entry 2). Interestingly, diimino derivative **363** was obtained upon condensation with two equivalents of cyanoacetic acid (entry 3).¹³⁶ Thermal cyclocondensation of hydrazine **360** with triethyl orthoformate afforded triazolotriazine **365** (entry 4).¹³⁷ Hydrazides **366** (easily prepared via EDCI-mediated coupling of hydrazine **360** with 2-arylacetic acids) could cyclize to triazolotriazines **367** under heating in acetic acid in moderate to excellent yields (entry 5).¹³⁸⁻¹³⁹ Of note, such an approach has been applied to the synthesis of CF_2 -containing compounds. Treatment of hydrazone **368** with bromine in acetic acid under heating resulted in the formation of dihydro-triazolotriazine **369** (entry 6).¹⁴⁰ Such a cyclization has been also carried out from hydrazone **370** in refluxing anhydride acetic allowing the construction of *N*-acetyl triazoles **371** in good yields (entry 7).⁵⁴ <Table 4 near here>

Table 4: Preparation of [1,2,4]triazolo[4,3-*b*]triazines from 3-hydrazino-1,2,4-triazine and their derivatives.

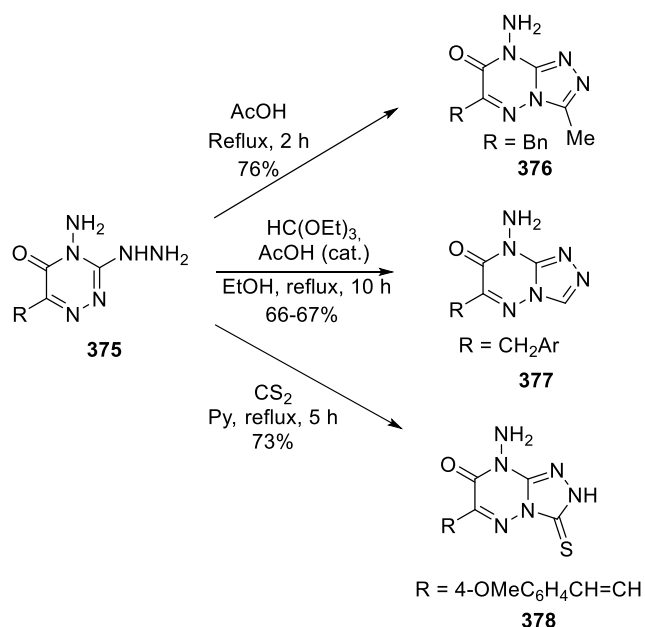
Entry	Starting material	Reaction conditions	Product	Yield	Ref.
1	 360	CS ₂ , KOH, EtOH, reflux, 15 h	 361	78%	37,54
2	 360	PhCOCN (2 equiv), DMF, reflux, 2 h	 362	57%	136
3	 360	CNCH ₂ COOH (2 equiv), DMF, reflux, 2 h	 363	69%	136
4	 364	HC(OEt) ₃ , reflux, 2 h	 365	63%	137
5	 366 X = H, F R = Ar, OAr	AcOH, 100 °C, 2 h	 367	63-88%	138-139
6	 368 X = Cl, Br	Br ₂ , AcOH, rt, 2 h	 369	61-76%	140
7	 370 n = 3, 4	Ac ₂ O, reflux, 1 h	 371	75-78%	54

In a similar fashion, 3-hydrazino-1,2,4-triazin-5-ones have been employed to access triazolotriazinone derivatives. For example, acylation of **372** with *N,N*-dimethylcarbamoyl bromide **373** led to the formation of bicyclic compound **374** in 78% yield. It is worth mentioning that this cyclization did not occur when the phenyl group was replaced by a *tert*-butyl substituent at C6 (Scheme 77).¹⁴¹ <Scheme 77 near here>



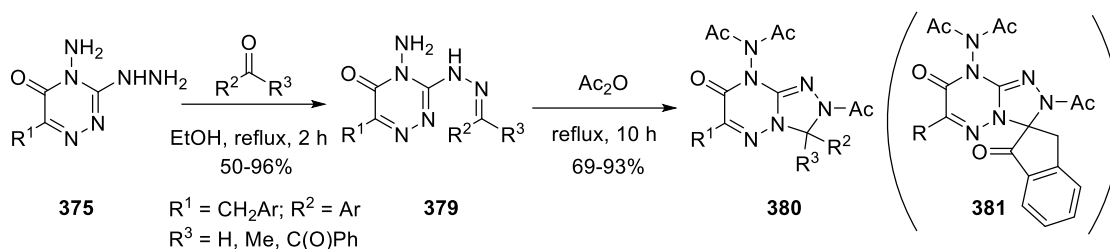
Scheme 77

As depicted in scheme 78, the multi nucleophilic centered 4-amino-hydrazinotriazinones **375** have been also demonstrated as versatile building blocks for the construction of various heterocyclic derivatives bearing the 1,2,4-triazine moiety. More specifically, the construction of triazolotriazines has been performed in acetic acid under reflux to produce the 6-methyl derivative **376** in good yield.¹⁴² Condensation of **375** with triethyl orthoformate in refluxing ethanol in the presence of a catalytic amount of acetic acid furnished triazolotriazine **377**.¹⁴³ Alternatively, thioxotriazolotriazinone **378** could be obtained by treatment of **375** with carbon disulfide in pyridine under reflux.²¹ <Scheme 78 near here>



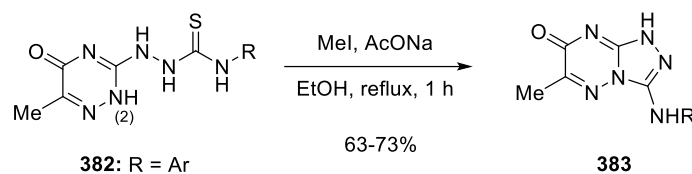
Scheme 78

Finally, reaction of **375** with various carbonyl compounds allowed the regioselective formation of the corresponding hydrazones **379**. The latter could be treated with acetic anhydride to access triacetylated heterobicyclic derivatives **380**.¹⁴² Noteworthy, such an approach has been employed for the construction of spirocyclic compounds **381** by using isatin as carbonyl derivative (Scheme 79).¹⁴³ <Scheme 79 near here>



Scheme 79

Treatment of thiosemicarbazide **382** with methyl iodide and sodium acetate in boiling ethanol afforded the triazolotriazine **383**. From a mechanistic point of view, methylation of the thione sulfur would furnish the corresponding thioether which would undergo intramolecular cyclization at N2 of the 1,2,4-triazin-5(2H)-one **383** to build the triazole ring after elimination of methylmercaptan (Scheme 80).¹⁴⁴ In contrast, using dicyclohexylcarbodiimide as alkylating agent led to the *c*-fused 1,2,4-triazine through cyclization at N4 (see section 11.6.5.3(i)). <Scheme 80 near here>



Scheme 80

11.6.5.2(ii) closure of the six-membered ring

As previously mentioned in CHEC-III(2008), all procedures for the synthesis of [1,2,4]triazolo[4,3-*b*][1,2,4]triazine derivatives (structures **10**) by cyclization of the six-membered ring exploit the reactivity of 3,4-diamino[1,2,4]triazoles **384**. These bis-nucleophiles can easily react with various reagents bearing two electrophilic sites in vicinal positions (Table 5). For instance, Fusco *et al.* have reported the condensation of such diamines with various cyclic 1,2-aromatic diketones **385** to furnish the corresponding multicyclic ring systems **386** (entry 1).⁶ The reaction was carried out in acetic acid under reflux overnight. Symmetric compound **388** has been obtained by using tetraketone **387** (entry 2). The same kind of transformation has been described by Nami *et al.* with isatin **389** in methanol under reflux producing tricyclic compound **390** in good yield (entry 3).¹⁴⁵ 3-(α -tosyloxyacetyl)coumarins **391** (easily prepared from 3-acetylcoumarins and Köser reagent) has been also used as efficient reaction partners to access various coumarinyl-containing triazolotriazines **392** in high yield. The reaction proceeded successfully in ethanol under reflux in the presence of a catalytic amount of potassium carbonate (entry 4).¹⁴⁶ <Table 5 near here>

Table 5: Construction of [1,2,4]triazolo[4,3-*b*][1,2,4]triazines by condensation of diamines **25** with bis-electrophilic reagents

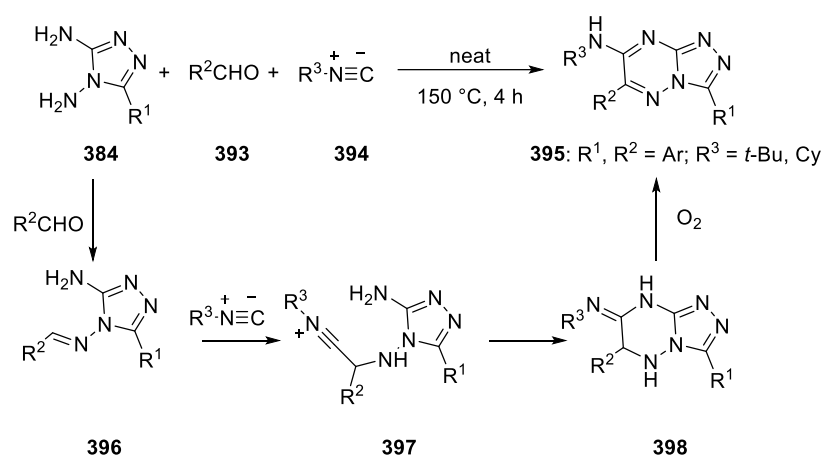
$\text{H}_2\text{N}-\text{N}(\text{R})-\text{N}(\text{H}_2)-\text{N}(\text{R})-\text{N}(\text{H}_2)-\text{N}(\text{R})-\text{N}(\text{H}_2)$
 $\xrightarrow{\text{reagent}}$

384

Entry	Reagent	Reaction conditions	Product	Yield	Ref.
1	 385^a	AcOH, reflux, overnight	 386: R = C ₇ H ₁₅	not reported	6
2	 387	AcOH, reflux, overnight	 388: R = C ₇ H ₁₅	not reported	6
3	 389	MeOH, reflux	 390: R = Me	68%	145
4	 391	K ₂ CO ₃ , reflux, 4-5 h	 392: R = Ar; X = H, Cl, Br	79-85%	146

a

A simple, efficient and environmentally friendly approach has been reported by Zonouzi and Mahdavi *et al.* via a three-component reaction of diamines **384**, aldehyde **393** and isocyanide **394** under solvent-free condition at 150 °C. The reactions went to completion within 4 hours furnishing the corresponding products **395** in high yields. From a mechanistic point of view, regioselective condensation of aldehyde **393** with the 4-amino substituent of **384** would form imine **396** which would undergo nucleophilic addition of isocyanide **394** to produce intermediate **397**. Building of the six-membered ring by intramolecular addition of the 3-amino substituent on the nitrilium followed by subsequent tautomerization and aerobic oxidation of **398** would yield triazolotriazines **395** (Scheme 81).¹⁴⁷<Scheme 81 near here>

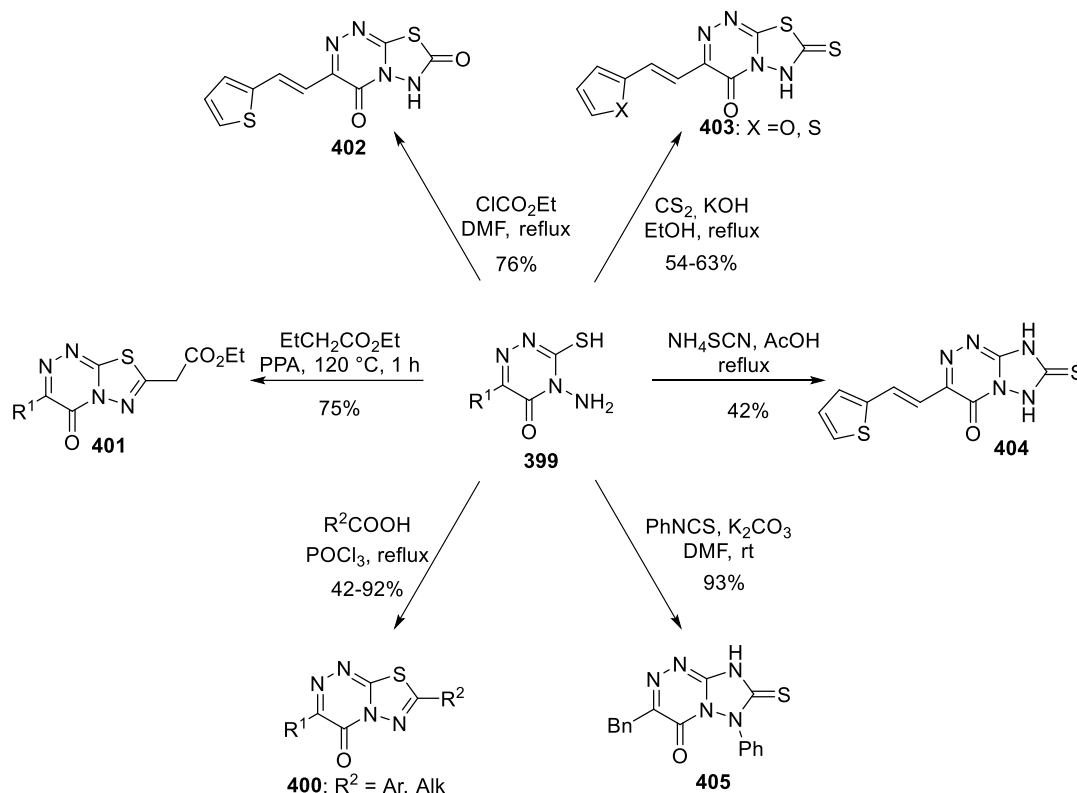


Scheme 81

11.19.6.5.3 Synthesis of *c*-fused [1,2,4]-triazines

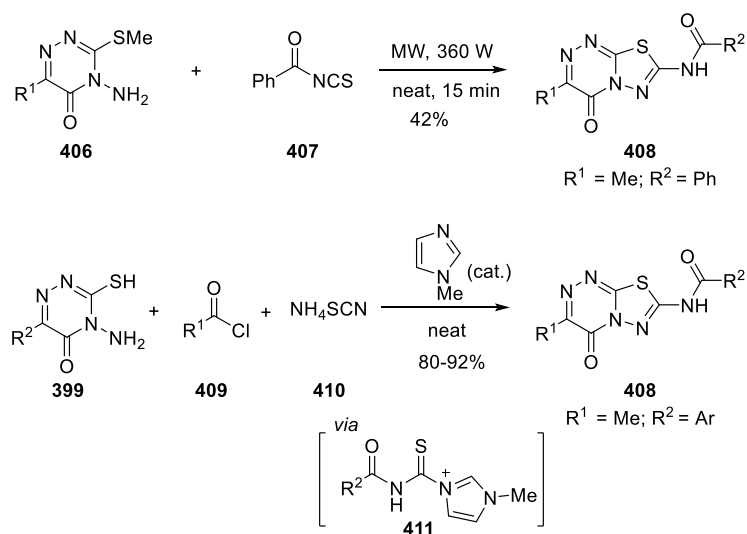
11.6.5.3(i) closure of the five-membered ring

As depicted in scheme 82, 4-amino-3-mercapto[1,2,4]triazine-5(4*H*)ones **399** are versatile starting reagents for the construction of various *c*-fused 1,2,4-triazin-4-ones. Condensation with an equimolar amount of carboxylic acid in refluxing phosphorus oxychloride offered a rapid access to 4*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-ones **400**. Aromatic as long as aliphatic carboxylic acids could be efficiently used and high yields were generally obtained.^{148–155} Treatment with ethylcyanoacetate in polyphosphoric acid under heating produced acetate derivative **401** in good yield through elimination of ammonia.¹⁵⁶ Reaction with ethyl chloroformate delivered fused 1,3,4-thiadiazolidin-2-one **402** while thione derivatives **403** were obtained by treatment with carbon disulfide in an ethanolic solution of potassium hydroxide.^{57,157} Addition of ammonium thiocyanate to compound **399** in glacial acetic acid yielded fused 1,2,4-triazolidine-3-thione **404**¹⁵⁷ while *N*-phenyl substituted derivative **405** has been produced in excellent yield by treatment with phenyl isothiocyanate in the presence of potassium carbonate.¹⁴⁸ (Scheme 82) <Scheme 82 near here>



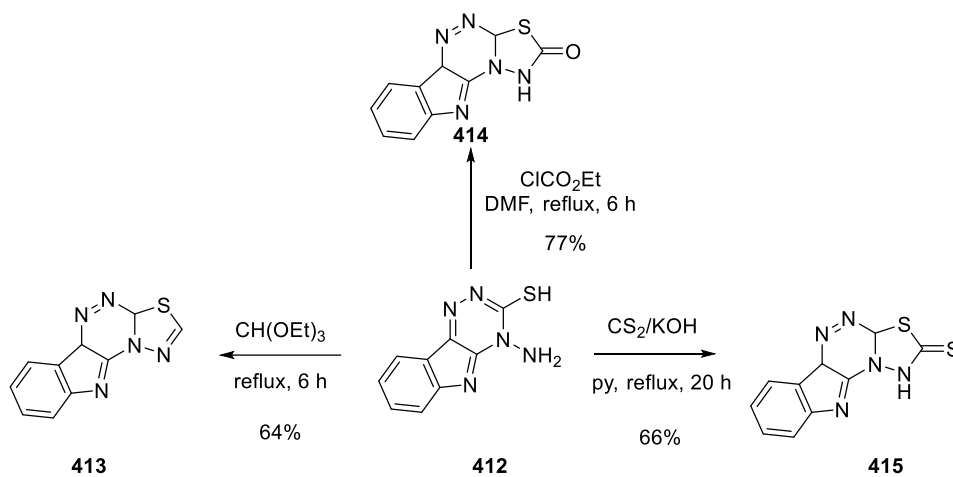
Scheme 82

Reaction between methylthio derivative **406** and benzoyl isothiocyanate **407** enabled the construction of fused thiadiazole **408** in moderate yield.¹⁵⁸ This transformation has been also reported *via* a three-component reaction between triazinone **399**, aroyl chlorides **409** and ammonium thiocyanate **410** in the presence of a catalytic amount of *N*-methylimidazole under solvent-free conditions to afford fused thiadiazole derivatives **408** in excellent yields. In this case, the aroyl isothiocyanate was *in situ* generated by reaction between aroyl chloride **409** and ammonium thiocyanate **410** and would be activated by *N*-methylimidazole through intermediate **411** (Scheme 83).¹⁵⁹ <Scheme 83 near here>



Scheme 83

In a similar fashion, various [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazines **413-415** containing an indole moiety have been synthesized by cyclocondensation reaction of 4-amino-4*H*-[1,2,4]triazino[5,6-*b*]indole-3-thiol **412** with triethyl orthoformate, ethyl chloroformate or carbone disulfide respectively (Scheme 84).¹⁶⁰ <Scheme 84 near here>



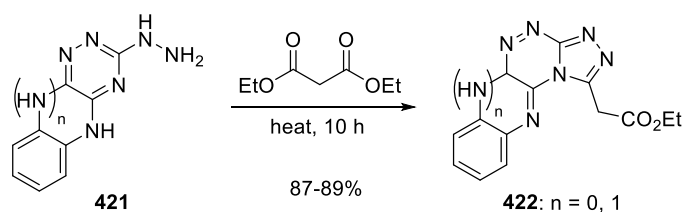
Scheme 84

The oxidative cyclization of triazinylhydrazone derivatives has been used to access [1,2,4]triazolo[3,4-*c*][1,2,4]triazines. As discussed above (see section 11.6.5.2(i)), such starting reagents have been also applied to the construction of 1,2,4-triazines with *b* fusion. The comparative nucleophilicities of N2 or N4 in the 1,2,4-triazine ring might govern the course of orientation of the reaction and the substituents on the 1,2,4-triazine ring might play an important role. As shown in table 6, phenyliodine(III) diacetate,¹⁶¹ thionyl chloride^{140,162} and acetic anhydride¹⁶³ have been employed to perform this oxidative transformation. It is worth pointing out that the cyclization of **368** with thionyl chloride gave rise to [1,2,4]triazolo[3,4-*c*]triazines **418** while *b*-fused 1,2,4-triazines were obtained when bromine in acetic acid was used as an oxidant highlighting the crucial role of the reaction conditions on the regioselectivity (Table 6, entry 2 vs Table 4, entry 6). <Table 6 near here>

Table 6: Preparation of [1,2,4]triazolo[3,4-c]triazines through oxidative cyclization of triazinyldiazone derivatives.

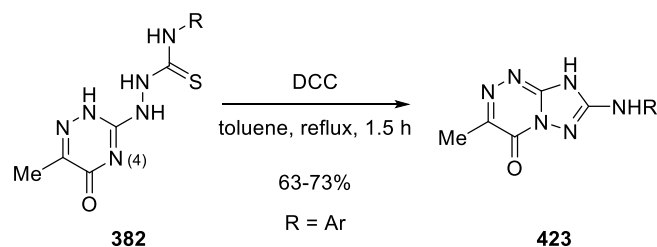
Entry	Starting material	Conditions	Product	Yield	Ref.
1	 416: R = Ar	PIDA, DCM, rt, 1 h	 417	82-91%	161
2	 368: R = Ar; X = H, Cl, Br	SOCl ₂ , 75 °C, 4 h	 418	50-77%	140,162
3	 419	Ac ₂ O, 100 °C, 10 h	 420	74%	163

Heating hydrazines **421** in diethyl malonate afforded triazolotriazines **422** bearing an ester functional group (Scheme 85).¹⁶³ <Scheme 85 near here>



Scheme 85

S-Alkylation of thiosemicarbazide **382** with dicyclohexylcarbodiimide in toluene under reflux afforded the triazolotriazine **423** via cyclization at the N4 position of the triazinone (Scheme 86).¹⁴⁴ In contrast, as previously discussed (see section 11.6.5.2(i)), the use of methyl iodide as alkylating agent led to the *b*-fused 1,2,4-triazine. <Scheme 86 near here>

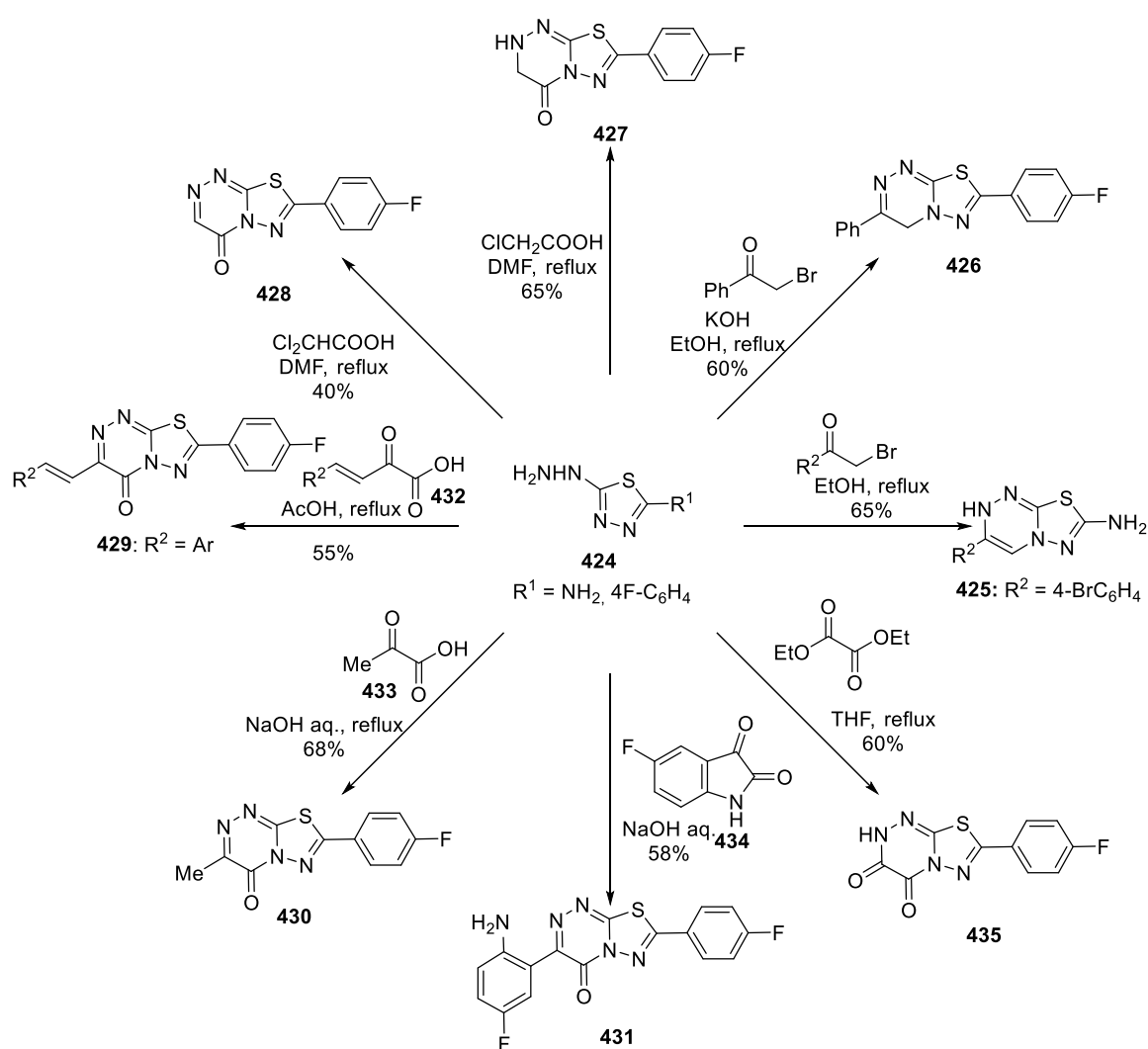


Scheme 86

11.6.5.3(ii) closure of the six-membered ring

11.6.5.3(ii)(a) [1,3,4]thiadiazolo[2,3-c][1,2,4]triazines

Two publications are related to the preparation of [1,3,4]thiadiazolo[2,3-c][1,2,4]triazine derivatives through the ring closure of the six-membered ring. In both cases 5-hydrazino-1,3,4-thiadiazole derivatives **424** were used as starting reagents. Treatment with phenacyl bromides in refluxing ethanol furnished 4-aryl-2*H*-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazine derivative **425** and 3-aryl-4*H*-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazine **426** when the reaction was performed in the presence of potassium hydroxide. Different [1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-4-one derivatives **427-431** have been obtained by using monochloroacetic acid, dichloroacetic acid, α -ketoacids **432-433** or diketone **434**. Finally, condensation with diethyl oxalate in THF afforded [1,3,4]thiadiazolo[2,3-c][1,2,4]triazine-3,4-dione **435** (Scheme 87).¹⁶⁴⁻¹⁶⁵ <Scheme 87 near here>



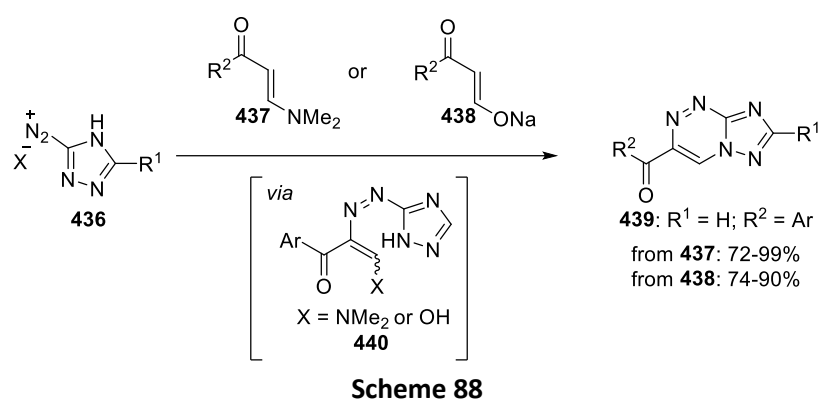
Scheme 87

11.6.5.3(ii)(b) [1,2,4]triazolo[5,1-d][1,2,4]triazines and [1,2,3]triazolo[5,1-d][1,2,4]triazines

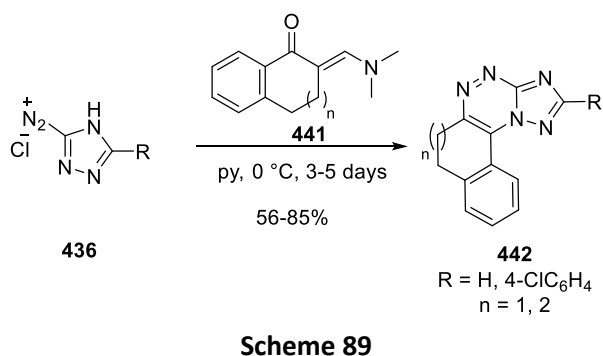
➤ From diazonium salts

As already mentioned in CHEC-III(2008), transformation of [1,2,4]triazole-3-diazonium salts **436**, easily available by diazotation of aminotriazoles, is a very appealing approach for the synthesis of

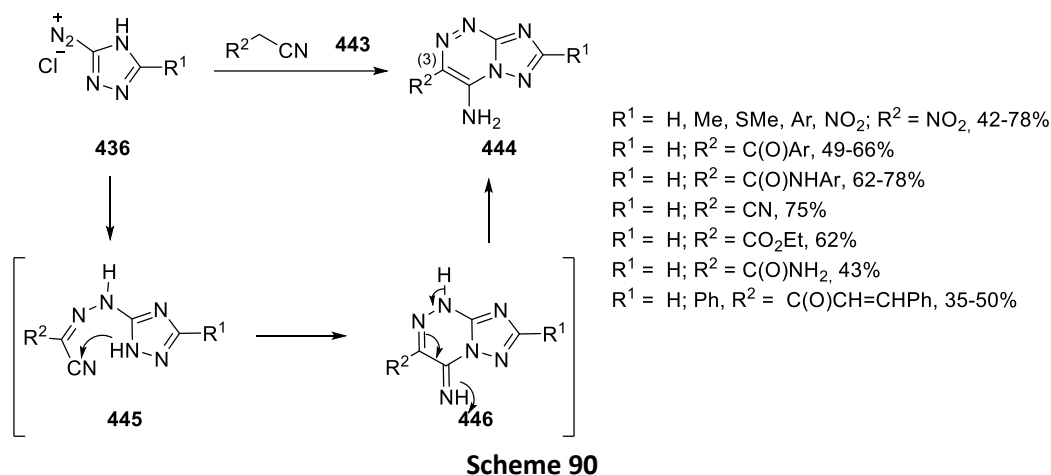
[1,2,4]triazolo[5,1-c][1,2,4]triazine derivatives (type **11**). These starting materials already contain the five nitrogen atoms in the correct sequence and, thus, their reaction with proper reagents can give rise to the cyclized products in one single step. In the last period, it has been by far the most employed synthetic route. Reactions with enaminone derivatives **437** gave access to 3-benzoyl [1,2,4]triazolo[3,2-c][1,2,4]triazine derivatives **439** after elimination of dimethylamine.^{166–178} Such transformations usually occurred in ethanol at low temperature in the presence of a base (pyridine or sodium acetate). Similar transformations have been also reported by using sodium salts **438** of 3-oxopropenolate derivatives yielding the corresponding acylated fused rings **439** after dehydration.^{179–183} Very high yields were obtained in both procedures with diazenes **440** being the key intermediates (Scheme 88). <Scheme 88 near here>



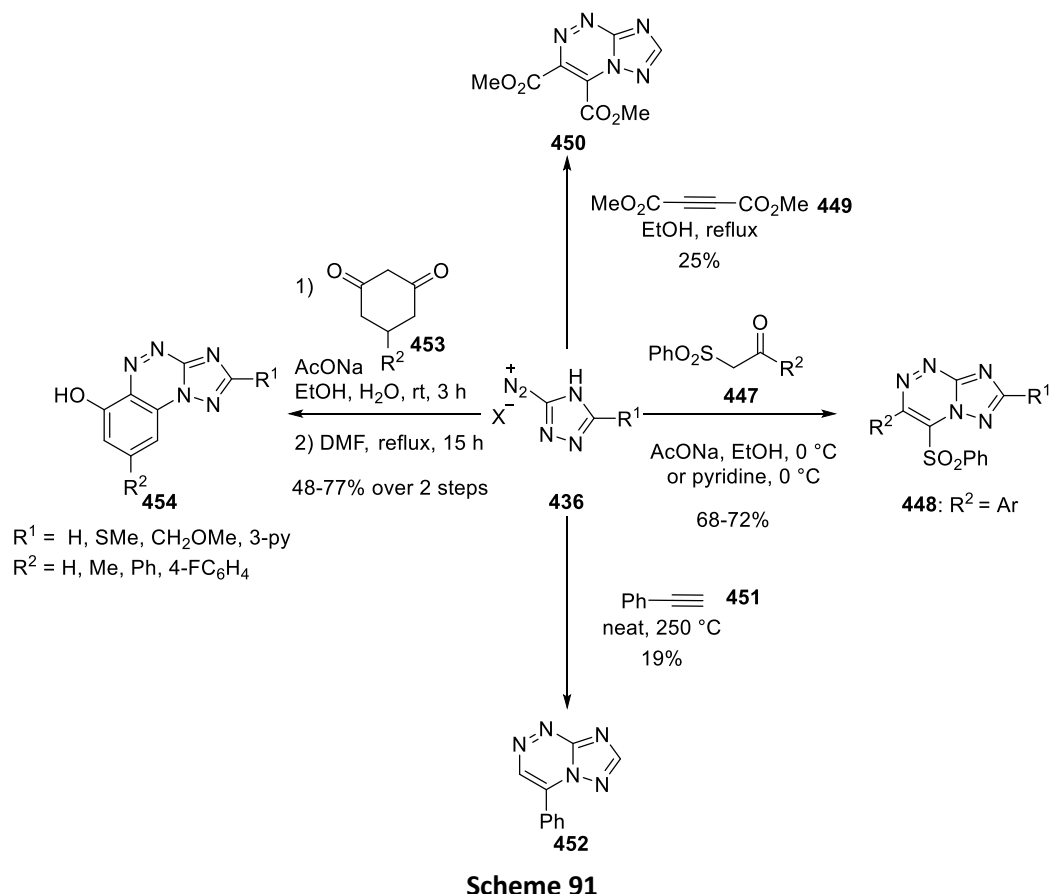
Reaction of diazonium salts **436** with exocyclic enaminones **441** in pyridine at 0 °C furnished tetracyclic compound **442** in moderate to good yields (Scheme 89).^{125,184} <Scheme 89 near here>



Cyano compounds **443** bearing an α -electron withdrawing group have been also widely used as reaction partners in the coupling reactions with diazonium salt **436** allowing the construction of [1,2,4]triazolo[5,1-c][1,2,4]triazin-4-amine derivatives **444** with various substituents at C3 (*i.e.* nitro,^{185–186,58} aryls,^{187–190} carbamoyls,^{191–194} cinnamoyl,¹⁹⁵ and cyano or ethyl carboxylate¹⁹⁶). From a mechanistic point of view, reaction between **436** and **443** afforded hydrazones **445** which would undergo cyclization to generate fused systems **446**. A subsequent tautomerization would form the desired triazolotriazolines **444**. In some cases, the hydrazones **445** have been isolated. Usually, the reactions started at low temperature in ethanol in the presence of sodium acetate or in pyridine to get hydrazones **445** while the cyclization step might need to be performed under reflux (Scheme 90). <Scheme 90 near here>

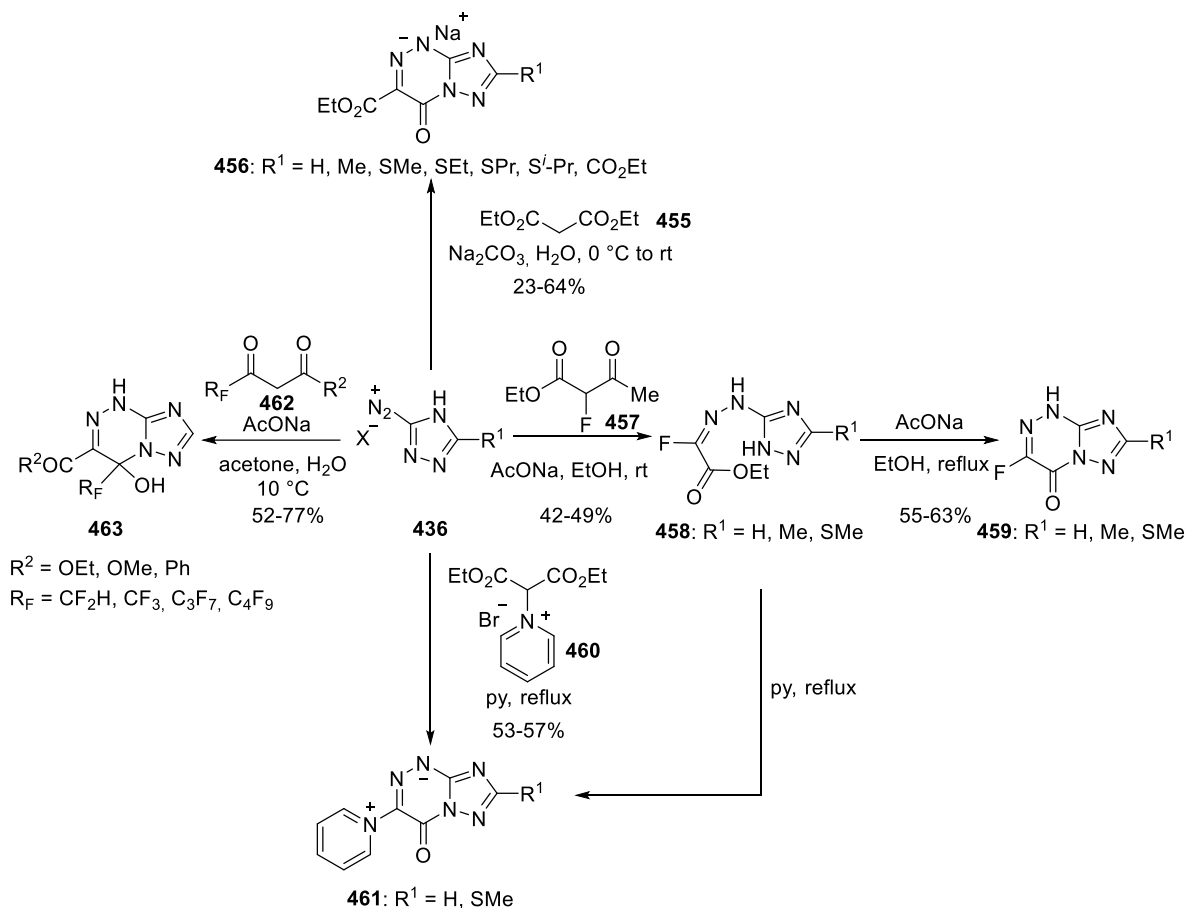


The access to 4-(phenylsulfonyl)-[1,2,4]triazolo[5,1-c][1,2,4]triazines **448** has been accomplished by treatment of diazos **436** with β -ketosulfones **447** in good yields.¹⁹⁷⁻¹⁹⁸ Reactions with dimethylacetylene dicarboxylate **449** or phenylacetylene **451** gave rise to the corresponding 3-phenyl and 3,4-dimethyl dicarboxylate derivatives **450** and **452** respectively.¹²⁵ Coupling with 1,3-cyclohexadienones **453** furnished [1,2,4]triazolo[5,1-c][1,2,4]benzotriazin-6-ols **454** (Scheme 91).¹⁹⁹ <Scheme 91 near here>



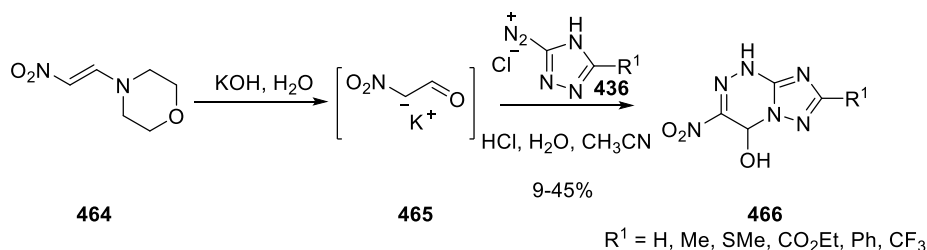
Diazonium salts **436** have also been used for the synthesis of partially saturated fused systems by coupling with various β -ketoester or malonate derivatives. As shown in scheme 92, reaction with diethyl malonate **455** in the presence of sodium carbonate afforded triazolotriazinones **456** bearing

an ethylcarboxylate substituent at C3.²⁰⁰ These compounds were isolated in the form of sodium salts to increase the water solubility and the bioavailability at the expense of the yields which were quite low. Treatment with ethyl 2-fluoroacetoacetate **457** in the presence of sodium acetate formed hydrazones **458** which were converted to fluorinated triazolotriazinones **459** upon heating in a solution of sodium acetate in ethanol. Interestingly, heating hydrazones **458** in pyridine furnished pyridinium **461**. The latter could be also directly obtained by treating diazonium salts **436** with diethyl α -pyridinium malonate **460** in pyridine under reflux.¹¹ Polyfluoroalkyl-containing 1,3-dicarbonyl reagents **462** have been used to access various 7-hydroxy-7-polyfluoroalkyl dihydrotriazolotriazines **463** in moderate to good yields (Scheme 92).²⁰¹⁻²⁰³ <Scheme 92 near here>



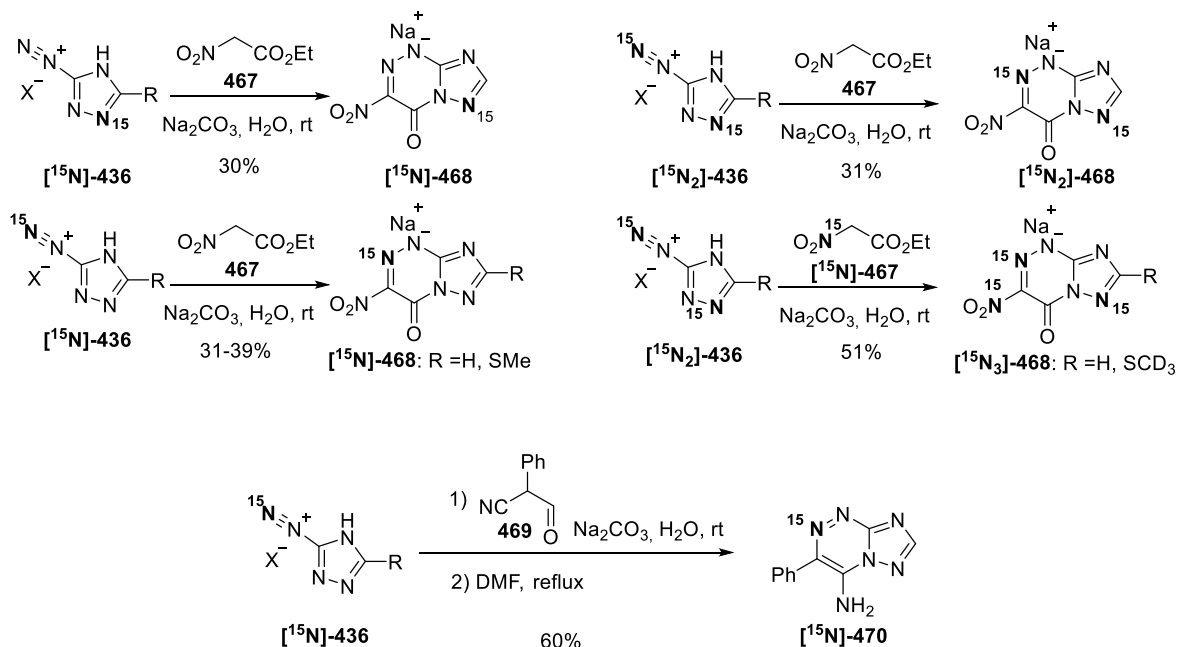
Scheme 92

A convenient procedure for the *in-situ* generation of nitroacetaldehyde potassium salt **465** from 1-morpholino-2-nitroethene **464** has allowed the preparation of 3-nitro-4-hydroxy-1,4-dihydroazolo[5,1-c][1,2,4]triazines **466** in modest yields (Scheme 93).²⁰⁴ <Scheme 93 near here>



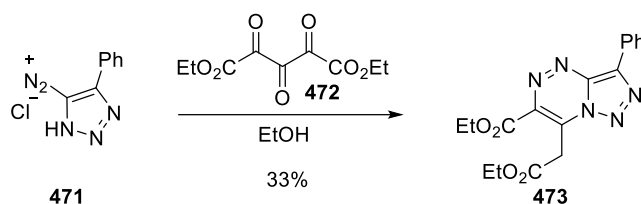
Scheme 93

Labelled diazonium salts **436** have been used for the synthesis of [¹⁵N] and [²H,¹⁵N]-labelled 3-nitrotriazolotriazinones **468** with ¹⁵N isotope in the triazole and/or triazine rings by treatment with (labelled) ethylnitroacetate **467**. Similarly, [¹⁵N]-labelled triazolotriazin-4-amine **470** has been obtained from α-phenyl-α-formylacetonitrile **469** (Scheme 94).^{10,30,205} <Scheme 94 near here>



Scheme 94

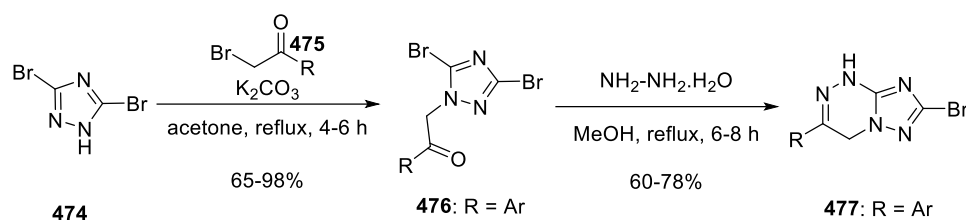
By exploiting similar strategy, the use of [1,2,3]triazole-5-diazonium salts can give rise to [1,2,3]triazolo[5,1-c][1,2,4]triazines (structures **13**). As such, coupling of diazo compound **471** with diethyl-2-oxopropane-1,3-dicarboxylate **472** delivered fused heterocycle **473** in modest yield (Scheme 95).³³ <Scheme 95 near here>



Scheme 95

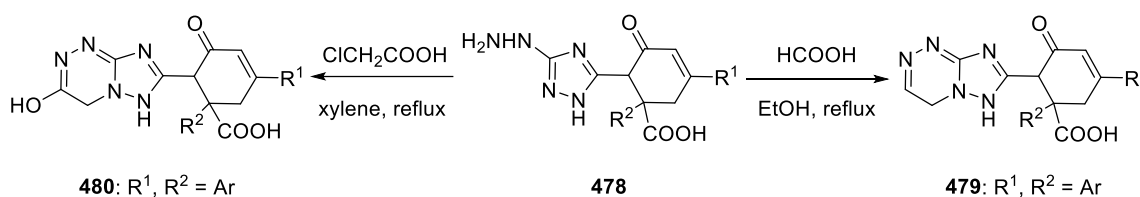
➤ Other routes

A two steps procedure from 3,5-dibromo-1*H*-1,2,4-triazole **474** (easily prepared by bromination of 1,2,4-triazole) has been also published for the synthesis of [1,2,4]triazolo[3,2-*c*][1,2,4]triazines. Nucleophilic substitution with bromomethyl aryl ketone **475** occurred at N1 delivering the corresponding N-alkylated triazole **476** which was treated with hydrazine in methanol under reflux to build the fused triazine ring **477** (Scheme 96).^{15,25} <Scheme 96 near here>



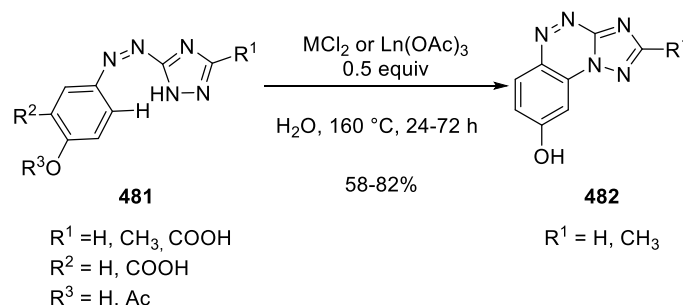
Scheme 96

Hydrazinotriazoles **478** have been treated with formic acid or chloroacetic acid under reflux to furnish the corresponding dihydrotriazolotriazines **479** and dihydrotriazolotriazinols **480** respectively (Scheme 97).²⁰⁶ <Scheme 97 near here>



Scheme 97

Dong *et al.* have reported the building of the 1,2,4-triazine ring by transition or lanthanide metal-promoted intramolecular C-H amination of (aryldiazenyl)triazoles **481** in water at 160 °C in an autoclave. When a transition metal was used as a promoter, the complex [M(**482**)₂(H₂O)₄].2H₂O was obtained. With lanthanide metals instead, the uncomplexed heterocycles **482** were directly isolated in good yields. In both cases, decarboxylation and deacetylation of the substituents on the phenyl rings occurred (Scheme 98).²⁰⁷ <Scheme 98 near here>

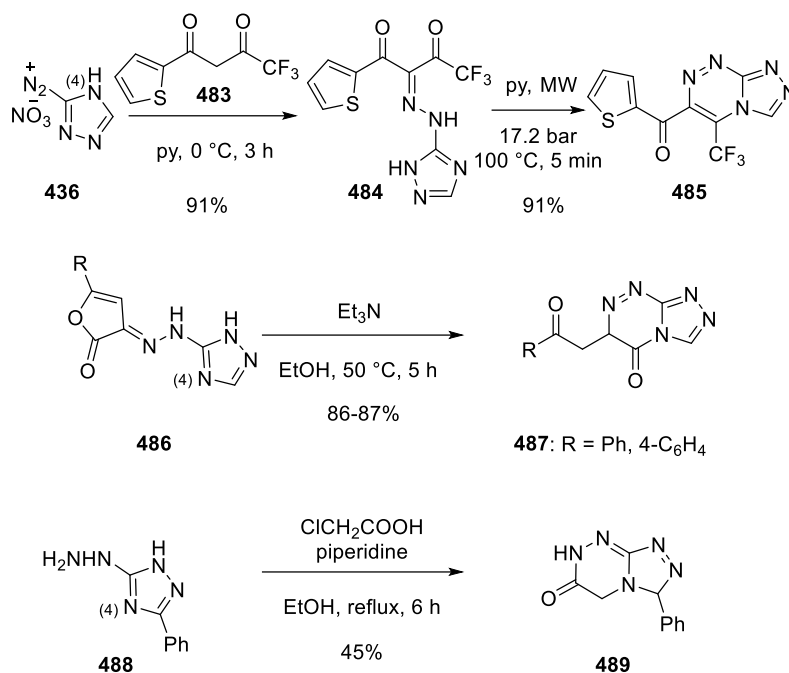


Scheme 98

11.6.5.3(ii)(c)[1,2,4]triazolo[3,4-c][1,2,4]triazines

Three different approaches have been published for the synthesis of [1,2,4]triazolo[3,4-c][1,2,4]triazines (structures **12**) since 2007 (Scheme 99). Shaaban has reported that trifluoromethylated diketone **483** reacted with diazonium salt **436** at low temperature to form hydrazone **484** which could cyclized under pressurized microwave irradiation to produce CF₃-containing triazolotriazine **485**.²⁰⁸ Treatment of 3-(triazolylylhydrazinylidene)furan-2(3H)-ones **486** in ethanol under heating in the presence of triethylamine produced triazolotriazin-5-one derivatives **487** in high yields.²⁰⁹ The formation of triazolotriazin-6-one derivatives **489** has been described through the reaction between 5-hydrazinyl-3-phenyl-3H-[1,2,4]triazole **488** and chloroacetyl chloride in refluxing ethanol in the presence of piperidine.²¹⁰ In these three procedures, it is the N4 atom of the triazole rings which would react. These results contrast with the examples reviewed in the

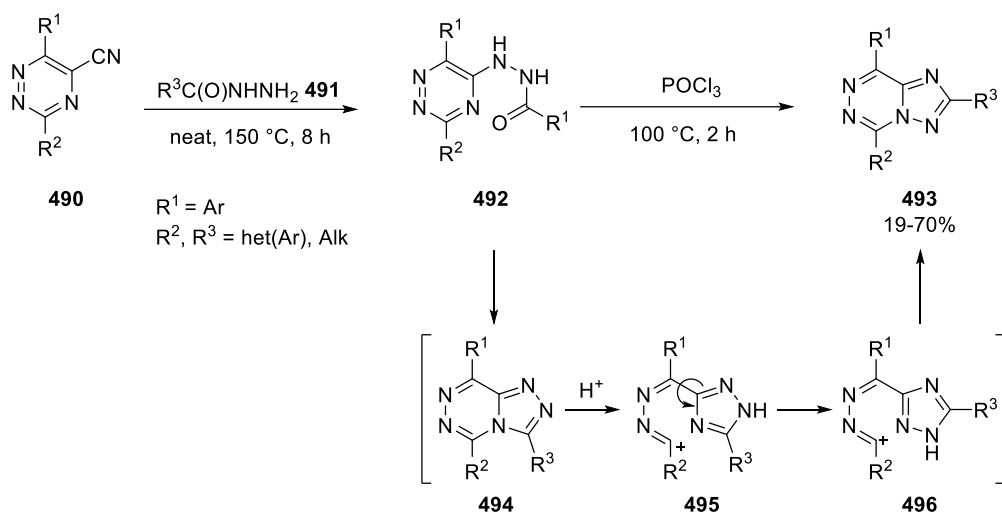
previous section (11.6.5.3(II)(b), reactions at N1). Unfortunately, there was no X-Ray analysis to ascertain the reported structures. <Schema 99 near here>



Schema 99

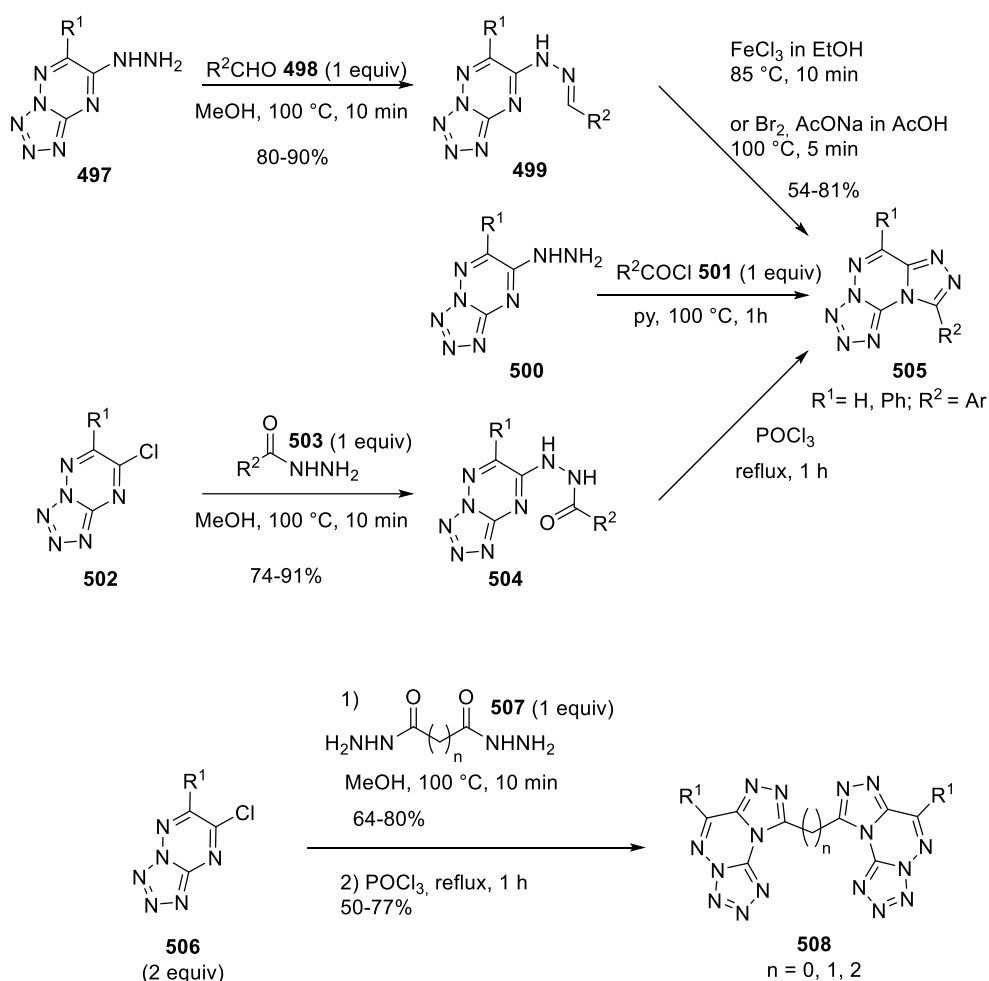
11.19.6.5.4 Synthesis of *d*-fused [1,2,4]-triazines

Starting from 5-cyano-1,2,4-triazines **490**, two successive solvent-free reactions (*i.e.* ipso-substitution of the cyano group by hydrazides **491** followed by dehydrative cyclization of **492** in phosphorus oxychloride) allowed the construction of [1,2,4]triazolo[1,5-*d*][1,2,4]triazine derivatives **493**. It is worth mentioning that this sequence could be carried out in one-pot without isolation of **492** with slightly higher yields. From a mechanistic point of view, it was assumed that **493** was obtained *via* a Dimroth-type rearrangement of *in-situ* generated [1,2,4]triazolo[4,3-*d*][1,2,4]triazine **494**. Indeed, ring opening of the triazine ring would lead to intermediate **495** under acid conditions. A rotation of 1,2,4-triazole ring around the C-C sigma bond would allow the ring closure of 1,2,4-triazine to take place on intermediate **496** affording thermodynamically more stable product **493** (Scheme 100).³ <Scheme 100 near here>



Scheme 100

Three synthetic routes have been described by El-Badry *et al.* for the construction of tetrazolo-fused [1,2,4]triazolo[4,3-*d*][1,2,4]triazine derivatives **505** (Scheme 101). Condensation of hydrazines **497** with equimolar amount of aromatic aldehydes **498** afforded the corresponding hydrazones **499** which was subjected to a dehydrogenative cyclization with bromine in acetic acid in the presence of sodium acetate or with an ethanolic iron(III) chloride solution. One pot cyclization of hydrazines **500** with aromatic acid chlorides **501** was also possible. Finally, an alternative route was proposed by reacting chloro derivative **502** with equimolar amount of aromatic hydrazides **503** followed by dehydrative cyclization in phosphorus oxychloride. Interestingly, by following the latter route, bistetrazolotriazolotriazine derivatives **508** could be obtained from two equivalents of **506** and one equivalent of oxalic, malonic, or succinic dihydrazide **507** (Scheme 101).²¹¹ <Scheme 101 near here>

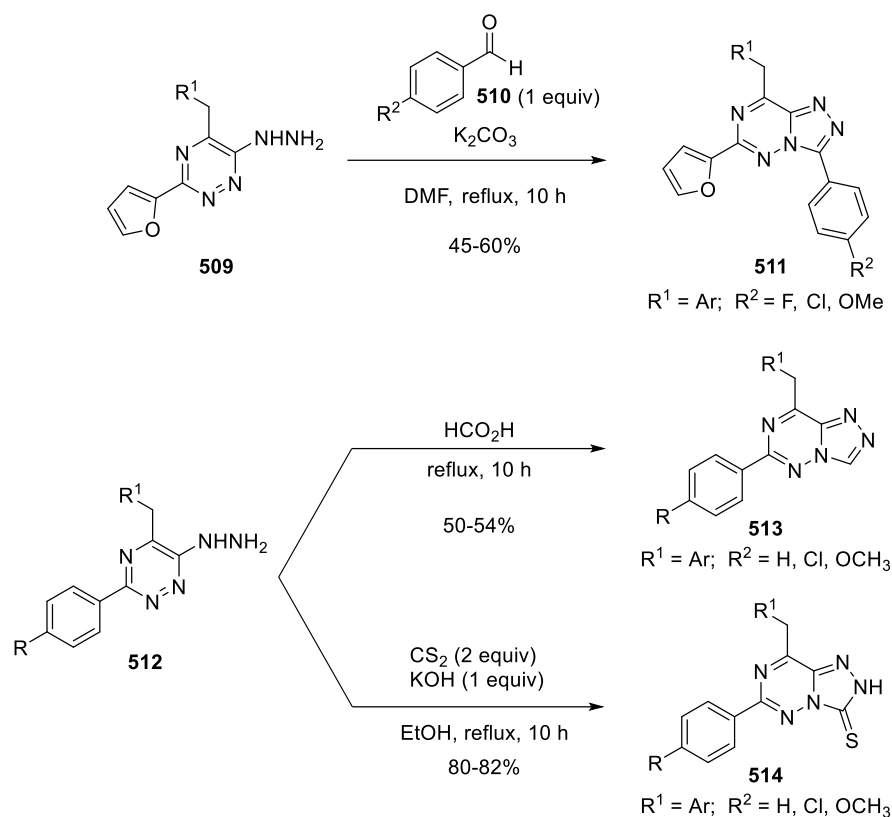


Scheme 101

11.19.6.5.5 Synthesis of *f*-fused [1,2,4]-triazines

11.6.5.5(i) closure of the five-membered ring

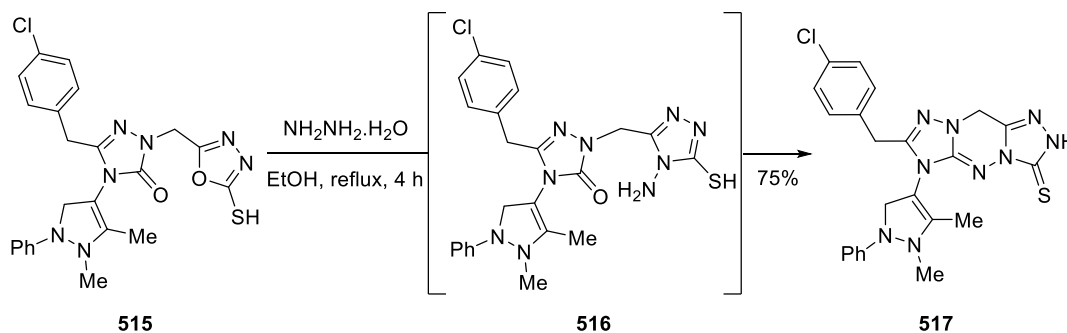
Only two publications relate to the synthesis of [1,2,4]triazolo[3,4-*f*][1,2,4]triazine ring systems *via* cyclization of the five-membered ring. Treatment of hydrazinotriazine **509** with aromatic aldehydes **510** in the presence of potassium carbonate in dimethylformamide afforded bicyclic systems **511** in moderate yields.²¹² In a similar way, condensation of hydrazine derivatives **512** with formic acid or carbon disulfide gave rise to [1,2,4]triazolo[3,4-*f*][1,2,4]triazines **513** and [1,2,4]triazolo[3,4-*f*][1,2,4]triazine-3(2*H*)-thiones **514** respectively.²¹³ (Scheme 102) <Scheme 102 near here>



Scheme 102

11.6.5.5(ii) construction of both rings (closure of the six-membered ring at the last step)

The construction of [1,2,4]triazolo[3,4-f][1,2,4]triazines by the ring closure of the triazine ring has been reviewed in CHEC-II(1996) and CHEC-III(2008). In 2010, Demirbas *et al.* have reported an original synthesis of this fused ring system by a cascade reaction involving construction of the [1,2,4]triazole from oxadiazole **515** followed by ring closure of the triazine. As shown in Scheme 103, treatment of **515** with hydrazine hydrate led to 4-amino-1,2,4-triazine **516** which was not isolated and was directly converted to triazolotriazine **517** in good yield by intramolecular condensation with the closed carbonyl functional group.²¹⁴ <Scheme 103 near here>

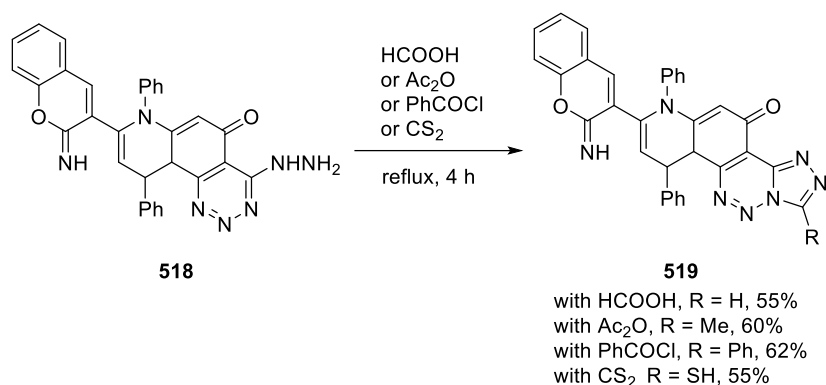


Scheme 103

11.19.6.5.6 Synthesis of Fused [1,2,3]-triazines

With the aim to synthesize variously substituted chromene systems, hydrazine derivative **518** has been engaged in different cyclizations with formic acid, acetic anhydride, benzoyl chloride and

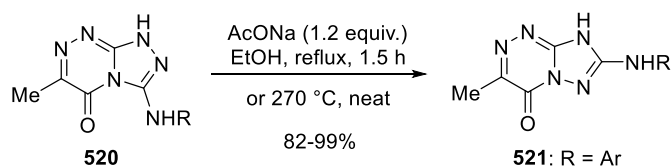
carbon disulfide affording the corresponding [1,2,4]triazolo[4,3-c][1,2,3]triazine derivatives **519** in moderate yields (Scheme 104).²¹⁵ <Scheme 104 near here>



Scheme 104

11.19.7 Ring Synthesis by Transformations of Another Bicyclic system

Staninets et al. have found that [1,2,4]triazolo[3,4-c][1,2,4]triazine **520** could isomerize to [1,2,4]triazolo[1,5-c][1,2,4]triazine **521** upon heating in refluxing ethanol in the presence of sodium acetate in very good yield (Dimroth rearrangement). Also of note, the same transformation could be carried out quantitatively by simply heating **520** at 270 °C in a sand bath under neat conditions (Scheme 105).¹⁴⁴ <Scheme 105 near here>



Scheme 105

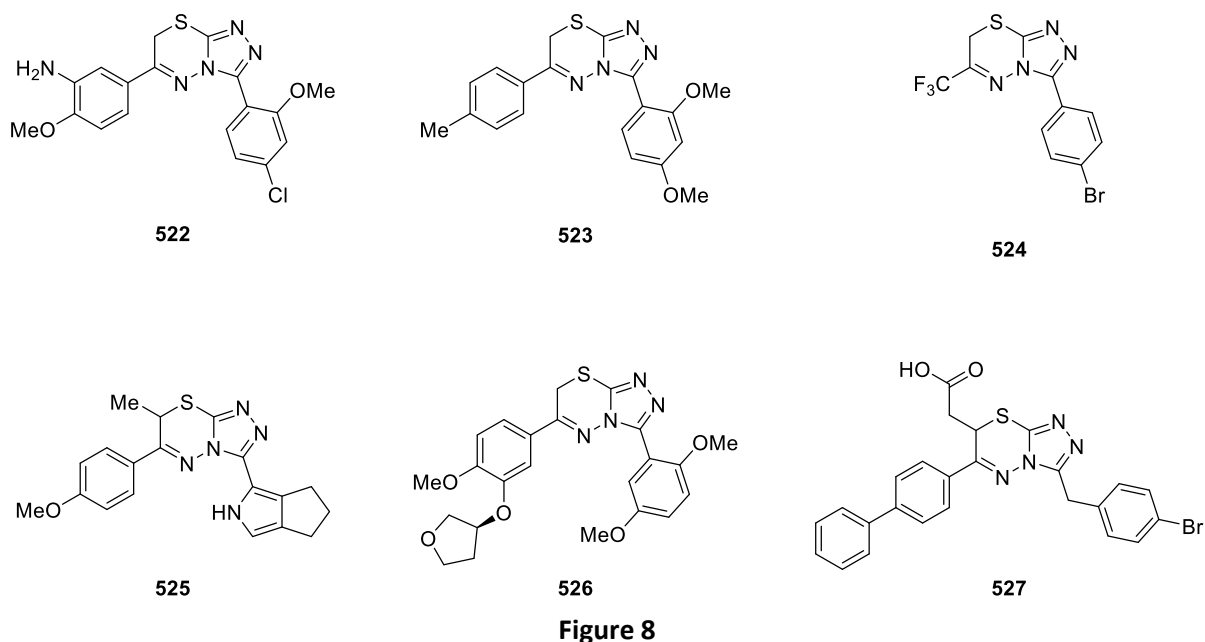
11.19.8 Important Compounds and Applications

11.19.8.1. Biological and agrochemical applications

The main purpose of designing new derivatives of the ring systems belonging to this chapter was to evaluate their biological properties. Some of them have shown valuable biological activities and have been patented.

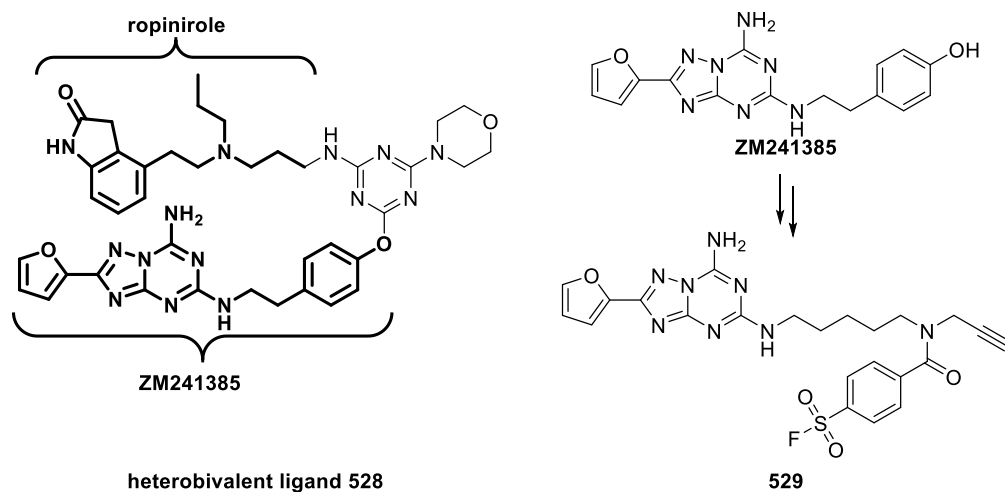
11.19.8.1(i) [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines

522²¹⁶ and **523**²¹⁷ are activators of caspases and inducers of apoptosis. **523** is also an antineoplastic compound with activity against MES-SA and P388 and their multi-drug resistant cells. **524** exhibits anti-tuberculosis activity.²¹⁸ **525** is able to selectively inhibit STAT3 in the presence of STAT1.²¹⁹ **526**²²⁰ and **527**²²¹ are inhibitors of phosphodiesterase 4 and UDP-galactopyranose mutase respectively (Figure 8). <Figure 8 near here>



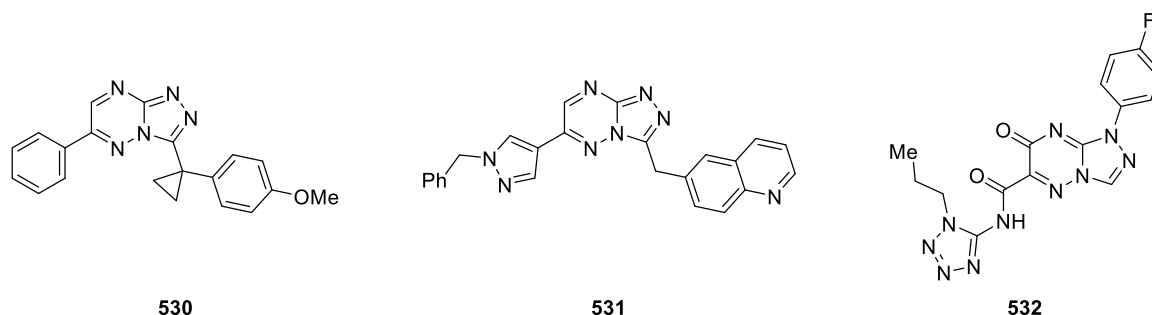
11.19.8.1(ii) [1,2,4]triazolo[1,5-*a*][1,3,5]triazines

The synthesis of heterobivalent ligand **528** was based on the chemical structure of the dopamine receptor D₂R agonist ropinirole and the adenosine receptor (A_{2A}R) antagonist ZM 241385. This ligand maintained the potency of the original pharmacophores and could therefore be tested as a potential treatment of Parkinson disease.⁴⁴ The antagonist ZM241385 has been also used as a starting point to design irreversibly binding human A_{2A}R ligand **529**. The latter features an electrophilic fluorosulfonyl moiety to covalently bind to the receptor and a terminal alkyne as a probe. Click ligation with a sulfonated cyanine-3 fluorophore allows visualization of the receptor on SDS-PAGE (Figure 9).⁴¹



11.19.8.1(iii) [1,2,4]triazolo[4,3-*b*][1,2,4]triazines

530²²² and **531**²²³ are inhibitors of kinases such as c-Met. Triazolotriazinone **532** is a potent herbicide (Figure 10).²²⁴ <Figure 10 near here>



530

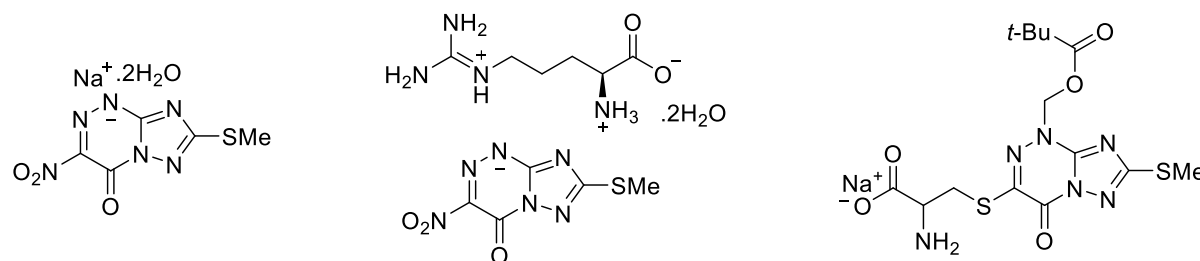
531

532

Figure 10

11.19.8.1(iv) [1,2,4]triazolo[5,1-*c*][1,2,4]triazines

Triazavirine[®] is an inhibitor of Influenza A and B virus replication.²²⁵ L-argininium salt **533** exhibits increased antiviral activity with better oral bioavailability compared to the sodium salt Triazavirine[®].²²⁶ Cysteine-containing Triazavirine[®] **534** displays numerous antiviral activities against for example Influenza A (H_xN_y) and B, West Nile virus, coronaviruses, yellow fever virus...²²⁷ (Figure 11). <Figure 11 near here>



Triazavirine[®]

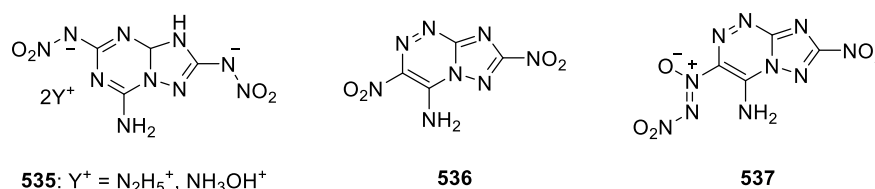
533

534

Figure 11

11.19.8.2 Other applications

Triazolotriazines **535-537** are promising candidates as high-energy and insensitive explosives (Figure 12).^{53,185,228} <figure 12 near here>



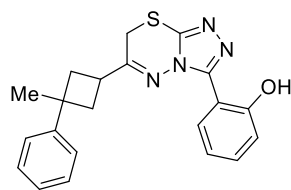
535: Y⁺ = N₂H₅⁺, NH₃OH⁺

536

537

Figure 12

A fluorescent triazolothiadiazine sensor **538** immobilized on polyvinyl chloride membrane has been developed for sensitive detection of Pb(II) ions. In addition to high reproducibility and reversibility of the fluorescence signal, the sensor also exhibits good selectivity over common metal ions (Figure 13).²²⁹ <figure 13 near here>



538

Figure 13

Acknowledgement

The author thanks CNRS for financial support.

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Change History

June 2020. A. Claraz updated the abstract, Figure 1, the entire text of this chapter, the references section and added Figures 2-13, Schemes 1-105 and Tables 1-6.