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

Aurélie Claraz

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

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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, thidiazolotriazines, 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; thidiazolotriazine; triazolotriazine; cyclization; cyclocondensation; Dimroth rearrangement.

Nomenclature
Ac Acetyl group
Ac₂O Acetic anhydride
AcOH Acetic acid
AcONa Sodium acetate
Alk Alkyl group
Ar Aryl group
Bn Benzyl group
Bu Butyl group
BSA N,O-bis-(trimethylsilyl)acetamide
Boc tert-butyloxy carbonyl
CHEC Comprehensive heterocyclic chemistry
Cy Cyclohexyl group
D Debye
DABCO 1,4-diazabicyclo[2.2.2]octane
DCC N,N'-Dicyclohexylcarbodiimide
DCE 1,2-Dichloroethane
DCM Dichloromethane
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFT</td>
<td>Density functional theory</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>DTG</td>
<td>Differential Thermogravimetric</td>
</tr>
<tr>
<td>EDCI</td>
<td>1-Ethyl-3-(3-dimethylaninopropyl)carbodiimide</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl group</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>eV</td>
<td>Electron Volt</td>
</tr>
<tr>
<td>HMDSO</td>
<td>Hexamethyldisiloxane</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
</tr>
<tr>
<td>i-Pr</td>
<td>Iso-Propyl group</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl group</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectra</td>
</tr>
<tr>
<td>MW</td>
<td>Microwave</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl group</td>
</tr>
<tr>
<td>PIDA</td>
<td>Phenyliodine(III) diacetate</td>
</tr>
<tr>
<td>PiVOH</td>
<td>Pivalic acid</td>
</tr>
<tr>
<td>PPA</td>
<td>Polyphosphoric acid</td>
</tr>
<tr>
<td>Pr</td>
<td>Propyl group</td>
</tr>
<tr>
<td>PTSA</td>
<td>para-Toluenedisulfonic acid</td>
</tr>
<tr>
<td>Py</td>
<td>Pyridine</td>
</tr>
<tr>
<td>QSAR</td>
<td>Quantitative Structural Activity Relationship</td>
</tr>
<tr>
<td>S$_p$Ar</td>
<td>Aromatic nucleophilic substitution</td>
</tr>
<tr>
<td>STAT</td>
<td>Signal Transducer and Activator of Transcription</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-Butyl group</td>
</tr>
<tr>
<td>TBAB</td>
<td>Tetrabutyl ammonium bromide</td>
</tr>
<tr>
<td>TD-DFT</td>
<td>Time dependent density functional theory</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMSOTf</td>
<td>Trimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>UDP</td>
<td>Uridine diphosphate</td>
</tr>
</tbody>
</table>
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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).<sup>1,2</sup> 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, thiadizolotriazines 6-7, and triazolotriazines 8-18. Consequently, the additional heteroatoms are nitrogen, sulfur and oxygen (Figure 1).<sup>3</sup> <Figure 1 near here>

![Figure 1](image)

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) W897XD basis). The data confirmed that product 19 (arising from a Dimroth rearrangement) was thermodynamically more stable than 20 (Figure 2).<sup>3</sup> <Figure 2 near here>
The anion 21 of 5-amino-substituted [1,2,4]triazolo[1,5-α][1,3,5]triazin-7(3H)-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-α][1,3,5]triazin-7(3H)-one 22 was isolated (see section 11.19.5.1.1) (Scheme 1).

![Scheme 1](image)

Theoretical log P, dipole moments and energies of the highest occupied and lowest unoccupied molecular orbitales (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). 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 LUMO 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). 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).
Table 1: Calculated log P, dipole moments, polarizabilities and HOMO/LUMO energies for various heterocycles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Log P</th>
<th>$\mu$ (D)</th>
<th>Pol. $^a$(Å³)</th>
<th>HOMO (eV)</th>
<th>LUMO $^b$ (eV)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1.34</td>
<td>7.517</td>
<td>-</td>
<td>-7.511</td>
<td>4.018</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1.11</td>
<td>5.784</td>
<td>-</td>
<td>-7.793</td>
<td>3.666</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2.91</td>
<td>7.19</td>
<td>-</td>
<td>-7.169</td>
<td>3.919</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>-</td>
<td>11.2</td>
<td>-</td>
<td>-6.32</td>
<td>-3.12</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>-</td>
<td>10.1</td>
<td>-</td>
<td>-6.10</td>
<td>-3.38</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>-</td>
<td>5.8</td>
<td>-</td>
<td>-3.56</td>
<td>-3.95</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>-</td>
<td>10.2</td>
<td>-</td>
<td>-6.05</td>
<td>-3.38</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>2.64</td>
<td>-</td>
<td>42.56</td>
<td>-</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>0.96</td>
<td>-</td>
<td>33.68</td>
<td>-</td>
<td>-</td>
<td>7</td>
</tr>
</tbody>
</table>

$^a$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

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

**Table 2: \(^13\)C and \(^15\)N NMR data of compound 32 in DMSO-d\(_6\)**

<table>
<thead>
<tr>
<th>Atom</th>
<th>(\delta) (ppm)</th>
<th>(J) (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(7')</td>
<td>13.4</td>
<td>(^1)J_C,D = 21</td>
</tr>
<tr>
<td>C(7)</td>
<td>166.3</td>
<td>(^2)J_C,N(5) = 5.1; (^3)J_C,D = 0.7</td>
</tr>
<tr>
<td>C(8a)</td>
<td>160.7</td>
<td>(^2)J_C,N(2) = 2.1; (^2)J_C,N(5) = 0.4</td>
</tr>
<tr>
<td>C(3)</td>
<td>145.15</td>
<td>(^1)J_C,N(3') = 1.8; (^1)J_C,N(3) = 23.4; (^1)J_C,N(3) = 23.4; (^3)J_C,N(1) = 1.4</td>
</tr>
<tr>
<td>C(4)</td>
<td>143.4</td>
<td>(^2)J_C,N(2) = 1.3; (^2)J_C,N(3') = 5.3; (^2)J_C,N(5) = 3.3</td>
</tr>
<tr>
<td>N(6)</td>
<td>259.9</td>
<td>-</td>
</tr>
<tr>
<td>N(2)</td>
<td>397.2</td>
<td>(^2)J_N(2),N(3') = 6.3</td>
</tr>
<tr>
<td>N(3')</td>
<td>368.4</td>
<td>(^2)J_N(2),N(3') = 6.3</td>
</tr>
</tbody>
</table>

The \(^19\)F NMR data of newly synthesized 3-fluoro[1,2,4]triazolo[5,1-c][1,2,4]triazin-4(1H)-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>
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-5H-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>.

Elimination of sulphur from the thiadiazine ring has been also observed for 7H-[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>
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 P2₁/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 P2₁/c. Three CH...Br interactions allowed the bromide anions to link the cations into cyclic dimers.¹⁴

![Figure 4](image)

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](image)

The distinction between regioisomer of heterocyclic compounds could not always be performed via NMR methods even with conventional ¹H-¹H and ¹H-¹³C 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](image1)

11.19.4 Thermodynamic aspects

The coordination of bicyclic fused ring system 3-benzyl-7-hydrazinyl-4H-[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 \(\Delta H^*\), entropy \(\Delta S^*\) and Gibbs free energy change \(\Delta G^*\)) 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.

<table>
<thead>
<tr>
<th>Complexes</th>
<th>(T) (°C)</th>
<th>Rate (s(^{-1}))</th>
<th>Thermodynamic data (kJ.mol(^{-1}))</th>
</tr>
</thead>
</table>
| HTT       | 25-430     | 3.3 x 10\(^7\)   | \(\begin{array}{cccc}
E^* & \Delta S^* & \Delta H^* & \Delta G^* \\
92.92 & -100.0 & 90.68 & 117.7 \\
80.23 & -53.00 & 79.92 & 101.1 \\
98.15 & -41.3 & 97.69 & 195.4 \\
46.23 & -125.9 & 157.1 & 253.5 \\
\end{array}\) |
| \([\text{Fe(HTT)}_2\text{Cl}_3]\) | 26-150     | 4.0 x 10\(^{11}\) | \(\begin{array}{cccc}
E^* & \Delta S^* & \Delta H^* & \Delta G^* \\
80.23 & -53.00 & 79.92 & 101.1 \\
98.15 & -41.3 & 97.69 & 195.4 \\
46.23 & -125.9 & 157.1 & 253.5 \\
\end{array}\) |
| \([\text{Co(HTT)}_2\text{Cl}_2]\) | 25-100     | 1.6 x 10\(^{13}\) | \(\begin{array}{cccc}
E^* & \Delta S^* & \Delta H^* & \Delta G^* \\
80.23 & -53.00 & 79.92 & 101.1 \\
98.15 & -41.3 & 97.69 & 195.4 \\
46.23 & -125.9 & 157.1 & 253.5 \\
\end{array}\) |
| \([\text{Ni(HTT)}_2\text{Cl}_2]\) | 28-141     | 3.4 x 10\(^5\)   | \(\begin{array}{cccc}
E^* & \Delta S^* & \Delta H^* & \Delta G^* \\
80.23 & -53.00 & 79.92 & 101.1 \\
98.15 & -41.3 & 97.69 & 195.4 \\
46.23 & -125.9 & 157.1 & 253.5 \\
\end{array}\) |
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]

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]

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

Despite five resonance structures of the anion 61, the N-alkylation of [1,2,4]triazolo[1,5-a][1,3,5]triazin-7(3H)-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]
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 ZnCl₂ 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 trflate 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). 25 <Scheme 7 near here>
Interestingly, it has been found that the adamantylation of $[^{15}\text{N}_2]-[1,2,4]\text{triazolo}[5,1-c][1,2,4]\text{triazin}-4(1H)-\text{one}$ $78$ 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 $^{1}H-^{15}\text{N}$ ($J_{HN}$) and $^{13}\text{C}-^{15}\text{N}$ ($J_{CN}$) coupling constants (Scheme 8).

```
Scheme 7

Scheme 8

Scheme 8 near here>
```
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).<ref>Scheme 9 near here></ref>

\[
\begin{align*}
\text{82} & \xrightarrow{\text{EtOH, reflux, 5-10 h}} \text{84} \\
\text{N} & \text{N} & \text{N} & \text{N} & \text{N} & \text{N} & \text{N} & \text{SMe} & \text{R} & \text{Ph}
\end{align*}
\]

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).<ref>Scheme 10 near here></ref>

\[
\begin{align*}
\text{85} & \xrightarrow{\text{EtOH, reflux, 3 h}} \text{86} & \xrightarrow{\text{R^2C(OEt)_3 (excess)}} \text{87} \\
\text{N} & \text{N} & \text{N} & \text{N} & \text{R}^1 & \text{SMe} & \text{Me} & \text{NH}_2 & \text{Me} & \text{R}^2
\end{align*}
\]

Scheme 10

Treatment of triazolotriazine 88 bearing a methylene group with p-toluenesulfonfyl 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).<ref>Scheme 11 near here></ref>
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 7H-[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>

\[
\text{Scheme 12}
\]

11.19.5.2.2 Nucleophilic substitution

11.19.5.2.2(i) [1,2,4]triazolo[3,4-\(b\)][1,3,4]thiadazines

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>

\[
\text{Scheme 13}
\]
As shown in scheme 14, the substitution of 5,7-diphenoxy-[1,2,4]triazolo[1,5-α][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-α][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^6-alkyl-[1,2,4]triazolo[1,5-α][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^6,7-dialkyl-[1,2,4]triazolo[1,5-α][1,3,5]triazine-5,7-diamines 106. The synthesis of [1,2,4]triazolo[1,5-α][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-α][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-α][1,3,5]triazine-5,7-diamines 109 was easily prepared from diphenoxy derivative 102 and an excess of dibenzyl amine (Scheme 14).

5-(Methylsulfonyl)-[1,2,4]triazolo[1,5-α][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^6-alkyl-[1,2,4]triazolo[1,5-α][1,3,5]triazine-5,7-diamines 112 was obtained in good yields. 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%).
As outlined in scheme 16, the synthesis of 1,2,4-triazolo[1,5-\(\alpha\)][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-\(\alpha\)][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).\(^{48}\)

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).\(^{49}\)
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).

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). Substitution with cysteine as S-nucleophile was easier producing cysteine-containing fused system 126. Similar transformation was also demonstrated with glutathione as S-nucleophile. The substitution of the nitro group of salt 127 by bromide was performed with acetyl bromide to furnish bromo derivative 128 in moderate yield. 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).
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).
11.19.5.2.4 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).

\[
\begin{align*}
\text{Br} &\xrightarrow{\text{K}_3\text{PO}_4 (3 \text{ equiv})} \text{PdCl}_2(\text{PPPh}_3)_2 (0.05 \text{ equiv})} \\
&\xrightarrow{\text{DMF/H}_2\text{O, 140 °C, 2 h}} \text{R}_2\text{B(OH)}_2 \\
\end{align*}
\]

\[138 \rightarrow 140: R^1 = \text{Ar}, R^2 = (\text{Het})\text{Ar}\]

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).

\[
\begin{align*}
\text{H}_2\text{N} &\xrightarrow{\text{Et}_3\text{N, DMF, rt, 2 h}} \text{Cl} \\
&\xrightarrow{\text{R}^1, \text{R}^2} \text{O} \\
\end{align*}
\]

\[141 \rightarrow 143: R^1 = \text{H, OCH}_3 \\
R^2 = \text{H, NO}_2\]

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).

\[
\begin{align*}
\text{H}_2\text{N} &\xrightarrow{\text{HNO}_3} \text{O}_2\text{NNH}_2 \xrightarrow{\text{base (2 equiv), MeOH or AgNO}_3/YCl, H}_2\text{O} \\
&\xrightarrow{\text{2Y}^-} \text{NH}_2 \\
\end{align*}
\]

\[144 \rightarrow 146: 73-84\%\]

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).  

As outlined in scheme 25, S-alkylation of thiooxo-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). Under similar reaction conditions, S-alkylation of thioxotriazolotriazinone 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. 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).
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).<Scheme 26 near here>

![Scheme 26](image)

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. 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).<Scheme 27 near here>

![Scheme 27](image)

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).<Scheme 28 near here>
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).<ref>Scheme 29 near here</ref>

Intramolecular condensation of the aminophenyl substituent with the carbonyl group of thiaiazolotriazinone derivative 179 occurred in DMF under reflux furnishing indole-fused thiaiazolotriazine 180 (Scheme 30).<ref>Scheme 30 near here</ref>
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 phenylidonium diacetate were not suitable for this transformation (Scheme 31).24

11.19.5.5 Reduction of the ring

Treatment of triazolothiadiazine 183 with sodium borohydride yielded the corresponding dihydrothiadiazine 184 (Scheme 32).22

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
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 5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6(7H)-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]

Heating 7H-[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-1H-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]
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
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-5H-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%).

\[
\text{R}^2\text{NH}_2 195 \text{ (1 equiv)} \rightarrow \text{CH}_2\text{O (excess)} \rightarrow \text{EtOH, rt, 5 h} \rightarrow 196
\]

Scheme 36

Hajri et al. have reported that treatment of N-(4H-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).

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-6H-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

\[ R^1 \quad \text{N} \quad \text{N} \quad \text{HBr} \quad R^2 \quad \text{N} \quad \text{N} \quad \text{C} \quad \text{N} \quad \text{C} \quad \text{O} \quad \text{OA} \quad \text{TFA} \quad \text{rt. 12 h} \quad \text{yield: 61-96\%} \]

\[ 200 \quad \text{201} \quad \text{202} \]

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-4H-1,2,4-triazole-3-thiol derivatives

As displayed in Scheme 39, condensation of 4-amino-4H-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 way 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 7H-[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

\[ \text{Scheme 39 near here} \]
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).

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).
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).78

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

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
As shown in scheme 45, various polycyclic derivatives have also been obtained from 203. 2-bromoindandione 235 and 2-bromo-3-hydroxynaphtalene-1,4-dione 237 produced regioselectively tetracyclic linear derivative 236 and fused indanones 238 in excellent yields. Similar transformation was performed under microwave irradiation in the presence of piperidine as a base. 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. Compound 203 was adsorbed on alumina and treated with 2,3-dichloroquinoxaline 241 under microwave irradiation to furnish fused systems 242. 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.
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).

Adsorption 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(7H)-one 250. Alternatively, simple solvent-free reaction of 203 with 249 and potassium carbonate under microwave irradiation was also possible.
As depicted in scheme 48, various 3-thioether-4H-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-napthalene-1,4-dione substituent of 253 furnished fused system 254. 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. Intramolecular aromatic nucleophilic substitution (SNAr) of heteroaryl thioether 257 furnished pyrimido[5,4-e][1,2,4]triazolo[3,4-b][1,3,4]thiadiazines 258 in good yields. Other series of pyrimidotriazolothiadiazines have been also reported via similar direct SNAr of bomopyrimidine thiothers or with a preceding S-N type Smiles rearrangement. 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 detail. <Scheme 48 near here>
Cyclocondensation of bis(3-thioether-4H-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). Addition of thioalkyl-containing phosphonates 264 to 4-(benzylideneamino)-4H-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).

Addition of thioalkyl-containing phosphonates 264 to 4-(benzylideneamino)-4H-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).

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).
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).<ref>Scheme 52 near here></ref>

![Scheme 52](image)

Reaction of 5-aryl-1,3,4-oxadiazole-2-thiol 273 with (bromoacetyl)coumarine 274 in the presence of sodium acetate in boiling acetic acid followed by the addition of hydrazine hydrate afforded triazolothiadiazine 277. 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. Such transformations delivered usually the corresponding triazolothiadiazines in high yields (Scheme 53).<ref>Scheme 53 near here></ref>

![Scheme 53](image)

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).<ref>Scheme 54 near here></ref>

![Scheme 54](image)
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-α][1,3,5]triazines 5, [1,3,4]thiadiazolo[3,2-α][1,3,5]triazines 6, [1,2,4]triazolo[1,5-α][1,3,5]triazines 8 and [1,2,4]triazolo[4,3-α][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-α][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).

\[ \text{Scheme 55} \]

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).

\[ \text{Scheme 56} \]

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).\textsuperscript{111} Similar transformations have also been reported in formic acid instead of triethyl orthoformate with slightly lower yields.\textsuperscript{112}

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).\textsuperscript{113}

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).\textsuperscript{114}
11.6.5.1(ii) closure of the six-membered ring

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-thiox derivatives 299 (Scheme 60). Good yields were obtained with both procedures (Scheme 60).<Scheme 60 near here>

\[
\text{Scheme 60}
\]

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).<Scheme 61 near here>

\[
\text{Scheme 61}
\]

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. 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).<Scheme 62 near here>
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)

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. 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).

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).

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).

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).

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). The structures were confirmed by X-Ray analysis.
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 trichloroacetimidines 323. The latter was subsequently cyclocondensed with triethyl orthoformate under reflux to form 5-trichloromethyl triazolotriazines 324.\(^\text{128}\) 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.\(^\text{48}\) Finally, the use of guanidine 315 furnished 5-amino-7-trichloromethyl triazolotriazines 327 in excellent yield (Scheme 69).\(^\text{46-47}\) <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).\(^\text{46-48}\) <Scheme 70 near here>
Oxidative annulation reaction of amidines 331 with benzaldehyde produced 5,7-diphenyltriazolotriazine 335. In this transformation, condensation of 331 with benzaldehyde would form intermediate 332. The latter would cyclize in the presence of a catalytic amount of copper (I) and iodine through complex 333 to build dihydrotiazine 334 followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 71). <Scheme 71 near here>
[1,2,4]Triazolo[1,5-α][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).  

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-α][1,3,5]triazin-(thi)ones or triazin-diones over two steps. The use of benzoylisothiocyanate 344 yielded the corresponding open chain thiourea analogue 345 which cyclized to the triazolotriazine-5-thione derivative 346 upon heating under reflux in DMF. The use of ethoxycarbonylisothiocyanates 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. 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. (Scheme 75)
Recently, Hajri et al. have reported the synthesis of triazolotriazin-azines 356 through the reaction between carboximidates 355 and cyanamide in methanol under reflux (Scheme 76). 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. Unfortunately, there was no X-ray crystallography analyses to ascertain the structure of the obtained regioisomers of type [1,2,4]triazololo[3,4-a][1,3,5]triazines rather than [1,2,4]triazololo[1,5-a][1,3,5]triazine. <Scheme 76 near here>
11.6.5.2 Synthesis of \(b\)-fused [1,2,4]-triazines

During the last period, [1,2,4]triazolo[4,3-\textit{b}][1,2,4]triazine (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-\textit{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). 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 cycanoacetic acid (entry 3). Thermal cyclocondensation of hydrazine 360 with triethyl orthoformate afforded triazolotriazine 365 (entry 4). 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). 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). 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).
Table 4: Preparation of [1,2,4]triazolo[4,3-b]triazines from 3-hydrazino-1,2,4-triazine and their derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Reaction conditions</th>
<th>Product</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhNHNH2</td>
<td>CS2, KOH, EtOH, reflux, 15 h</td>
<td>PhNHNH2</td>
<td>78%</td>
<td>37,54</td>
</tr>
<tr>
<td>2</td>
<td>PhCOCN (2 equiv), DMF, reflux, 2 h</td>
<td>PhCOCN</td>
<td>57%</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CNCH2COOH (2 equiv), DMF, reflux, 2 h</td>
<td>CNCH2COOH</td>
<td>69%</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>MeNCOO</td>
<td>HC(OEt)3, reflux, 2 h</td>
<td>MeNCOO</td>
<td>63%</td>
<td>137</td>
</tr>
<tr>
<td>5</td>
<td>ArNHNH2</td>
<td>AcOH, 100 °C, 2 h</td>
<td>ArNHNH2</td>
<td>63-88%</td>
<td>138-139</td>
</tr>
<tr>
<td>6</td>
<td>Br2, AcOH, rt, 2 h</td>
<td>Br2, AcOH</td>
<td>61-76%</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>PhNHNH2</td>
<td>Ac2O, reflux, 1 h</td>
<td>PhNHNH2</td>
<td>75-78%</td>
<td>54</td>
</tr>
</tbody>
</table>

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>
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. Condensation of 375 with triethyl orthoformate in refluxing ethanol in the presence of a catalytic amount of acetic acid furnished triazolotriazine 377. Alternatively, thioxotriazolotriazinone 378 could be obtained by treatment of 375 with carbon disulfide in pyridine under reflux.

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. Noteworthy, such an approach has been employed for the construction of spirocyclic compounds 381 by using isatin as carbonyl derivative (Scheme 79). <Scheme 78 near here>
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). 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>

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). 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). 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).<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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Reaction conditions</th>
<th>Product</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcO\textsubscript{H}, reflux, overnight</td>
<td>[386](R = C\textsubscript{6}H\textsubscript{15})</td>
<td>not reported</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>AcOH, reflux, overnight</td>
<td>[388](R = C\textsubscript{6}H\textsubscript{15})</td>
<td>not reported</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MeOH, reflux</td>
<td>[390](R = Me)</td>
<td>68%</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>K\textsubscript{2}CO\textsubscript{3}, reflux, 4-5 h</td>
<td>[392](R = Ar; X = H, Cl, Br)</td>
<td>79-85%</td>
<td>146</td>
<td></td>
</tr>
</tbody>
</table>

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).\textsuperscript{147} <Scheme 81 near here>
11.6.5.3 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(4H)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 4H-[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.\textsuperscript{148-155} Treatment with ethylcyanoacetate in polyphosphoric acid under heating produced acetate derivative 401 in good yield through elimination of ammonia.\textsuperscript{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.\textsuperscript{57,157} Addition of ammonium thiocyanate to compound 399 in glacial acetic acid yielded fused 1,2,4-triazolidine-3-thione 404\textsuperscript{157} while N-phenyl substituted derivative 405 has been produced in excellent yield by treatment with phenyl isothiocyanate in the presence of potassium carbonate.\textsuperscript{148} (Scheme 82) \textsuperscript{<Scheme 82 near here>
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 \textit{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).\(^{159}\)
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-4H-[1,2,4]triazino[5,6-b]indole-3-thiol 412 with triethyl orthoformate, ethyl chloroformate or carbone disulfide respectively (Scheme 84).<Scheme 84 near here>

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, thionyl chloride and acetic anhydride 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 triazinylhydrazone derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="416.png" alt="Image" /></td>
<td>PIDA, DCM, rt, 1 h</td>
<td><img src="417.png" alt="Image" /></td>
<td>82-91%</td>
<td>161</td>
</tr>
<tr>
<td>2</td>
<td><img src="368.png" alt="Image" /></td>
<td>SOCl(_2), 75 °C, 4 h</td>
<td><img src="418.png" alt="Image" /></td>
<td>50-77%</td>
<td>140, 162</td>
</tr>
<tr>
<td>3</td>
<td><img src="419.png" alt="Image" /></td>
<td>Ac(_2)O, 100 °C, 10 h</td>
<td><img src="420.png" alt="Image" /></td>
<td>74%</td>
<td>163</td>
</tr>
</tbody>
</table>

Heating hydrazines 421 in diethyl malonate afforded triazolotriazines 422 bearing an ester functional group (Scheme 85).

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). 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.
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-2H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazine derivative 425 and 3-aryl-4H-[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](image)

11.6.5.3(ii)(b) [1,2,4]triazolo[5,1-c][1,2,4]triazines and [1,2,3]triazolo[5,1-c][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 aryloyls,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).
The access to 4-(phenylsulfonyl)-[1,2,4]triazolo[5,1-c][1,2,4]triazines 448 has been accomplished by treatment of diazo 436 with β-ketosulfones 447 in good yields. 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. Coupling with 1,3-cyclohexadienones 453 furnished [1,2,4]triazolo[5,1-c][1,2,4]benzotriazin-6-ols 454 (Scheme 91).

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.\textsuperscript{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 \textsuperscript{457} in the presence of sodium acetate formed hydrazones \textsuperscript{458} which were converted to fluorinated triazolotriazinones \textsuperscript{459} upon heating in a solution of sodium acetate in ethanol. Interestingly, heating hydrazones \textsuperscript{458} in pyridine furnished pyridinium \textsuperscript{461}. The latter could be also directly obtained by treating diazonium salts \textsuperscript{436} with diethyl α-pyridinium malonate \textsuperscript{460} in pyridine under reflux.\textsuperscript{1} Polyfluoroalkyl-containing 1,3-dicarbonyl reagents \textsuperscript{462} have been used to access various 7-hydroxy-7-polyfluoroalkyl dihydrotriazolotriazines \textsuperscript{463} in moderate to good yields (Scheme 92).\textsuperscript{201‒203} <Scheme 92 near here>

\begin{center}
\includegraphics[width=\textwidth]{Scheme_92}
\end{center}

Scheme 92

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

\begin{center}
\includegraphics[width=\textwidth]{Scheme_93}
\end{center}

Scheme 93
Labelled diazonium salts 436 have been used for the synthesis of $^{15}$N and $^{2}$H,$^{15}$N-labelled 3-nitrotiazolotriazinones 468 with $^{15}$N isotope in the triazole and/or triazine rings by treatment with (labelled) ethylnitroacetate 467. Similarly, $^{15}$N-labelled triazolotriazin-4-amine 470 has been obtained from α-phenyl-α-formylacetonitrile 469 (Scheme 94).<ref>Scheme 94 near here</ref>

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)<ref>Scheme 95 near here</ref>

A two steps procedure from 3,5-dibromo-1H-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)<ref>Scheme 96 near here</ref>

➤ Other routes
Hydrazinotriazoles 478 have been treated with formic acid or chloroacetic acid under reflux to furnish the corresponding dihydrotiazolotriazines 479 and dihydrotiazolotriazinols 480 respectively (Scheme 97).<Scheme 97 near here>

Dong et al. have reported the building of the 1,2,4-triazine ring by transition or lanthanide metal-promoted intramolecular C-Hamination of (aryldiaz enyl)triazoles 481 in water at 160 °C in an autoclave. When a transition metal was used as a promoter, the complex [M(482)(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).<Scheme 98 near here>

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. Treatment of 3-(triazolyldihydrinylidene)furan-2(3H)-ones 486 in ethanol under heating in the presence of triethylamine produced triazolotriazin-5-one derivatives 487 in high yields. 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. 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](image)

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).<Scheme 100 near here>
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
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. 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(2H)-thiones 514 respectively. (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

11.6.5.6 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).<Scheme 104 near here>

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).<Scheme 105 near here>

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]thiadazines
522 and 523 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. 525 is able to selectively inhibit STAT3 in the presence of STAT1. 526 and 527 are inhibitors of phosphodiesterase 4 and UDP-galactopyranose mutase respectively (Figure 8).<Figure 8 near here>
The synthesis of heterobivalent ligand 528 was based on the chemical structure of the dopamine receptor D_{2}R 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. 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).

Figure 8

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

530 and 531 are inhibitors of kinases such as c-Met. Triazolotriazinone 532 is a potent herbicide (Figure 10).

![Figure 10](near here)

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. L-argininium salt 533 exhibits increased antiviral activity with better oral bioavailability compared to the sodium salt Triazavirine. Cysteine-containing Triazavirine 534 displays numerous antiviral activities against for example Influenza A (H3N2) and B, West Nile virus, coronaviruses, yellow fever virus...

![Figure 11](near here)

11.19.8.2 Other applications

Triazolotriazines 535-537 are promising candidates as high-energy and insensitive explosives (Figure 12).

![Figure 12](near here)

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).
Acknowledgement

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References


**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.