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1,2,3-Triazoles Fused to Aromatic Rings

Belén Abarca and Rafael Ballesteros-Garrido

Abstract The structure, synthesis, reactivity and applications of 1,2,3-triazoles fused to aromatic rings are described. These compounds have been classified in two groups by a structural approach: (a) fused 1,2,3-triazoles without a bridgehead nitrogen atom and (b) fused 1,2,3-triazoles with a bridgehead nitrogen atom. Although both systems present a similar structure, the synthetic procedures and their reactivity are different.

Keywords 1,2,3-Triazoles · Benzotriazoles · Triazolopyridines · Triazolopyrimidines

Contents

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Abbreviations

2-PyCHO	2-Pyridylcarboxyaldehyde
AIBN	Azobisisobutyronitrile
ArNs	Aromatic nucleophilic substitution
Boc	Tertbutoxycarbonyl
Bt	1*H*-1,2,3-Benzotriazol
BuLi	Butyllithium
Cod	Cyclooctadiene
DMAD	Dimethyl acetylenedicarboxylate
DMF	Dimethylformamide
El	Electrophile
Et	Ethyl
FVT	Flash vacuum thermolysis
LDA	Lithium diisopropylamide
LiTMP	Lithium tetramethylpiperidine
NBS	*N*-Bromosuccinimide
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
NOS	Nitric oxide synthase
Nu	Nucleophile
OAc	Acetoxy
Ph	Phenyl
THF	Tetrahydrofuran
TMSCN	Trimethylsilyl cyanide
$TMSN_3$	Trimethylsilyl azide
Tp	[1,2,3]triazolo[1,5-*a*]pyridine
TPT	Triazolopyridine-pyridine-triazolopyridine
TsN_3	Tosyl azide

1 Introduction

Fused 1,2,3-triazoles represent a large family of compounds that are applied in different scientific fields, covering from organic synthesis until copper conservation or highly energetic materials. The scope of the fused triazoles treated in this chapter involves systems with two aromatic rings of which one is a 1,2,3-triazole ring and the other is a six-membered aromatic ring. Such compounds have extensively been reviewed in the Comprehensive Heterocyclic Chemistry collection [1, 2]. In order to classify these compounds a structural approach has been reported: (a) Compounds without any bridged nitrogen atom, and the simplest structure is benzotriazole (**Bt**, **1**) reported by Chattaway and Orton in 1901 [3] (Fig. 1). This compound was initially named as azimido benzene. (b) Compounds with one of the three nitrogen acting as a bridge atom, with [1,2,3]triazolo[1,5-*a*]pyridine (**Tp**, **2**) as

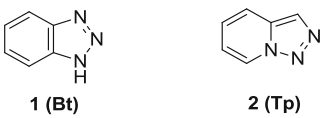


Fig. 1 1,2,3-Triazoles fused to aromatic rings

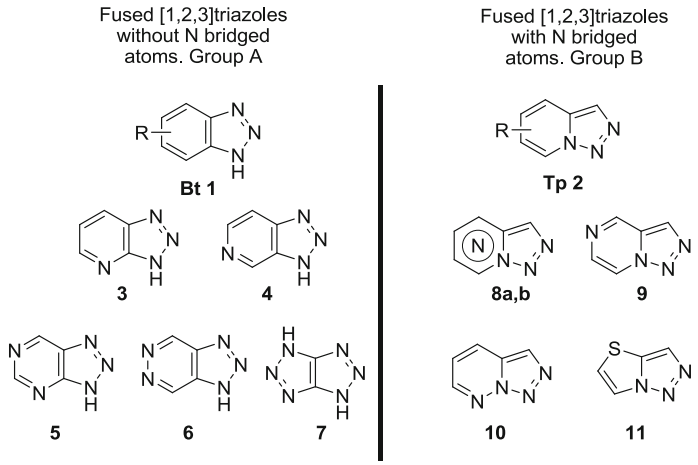


Fig. 2 Fused 1,2,3-triazoles classification

the simplest compound of the group. The first report concerning this structure was the corresponding protonated compound reported in 1953 by Kuhn and Munzing [4]. Although both systems present a similar structure, the synthetic approaches towards them and their reactivity show themselves to be completely different.

2 1,2,3-Triazoles Fused to Aromatic Rings, Structure and Classification

Fused 1,2,3-triazoles having no nitrogen bridge atoms are a large family of compound with benzotriazole **1** as the most studied. The fusion of 5- and 6-membered aromatic rings, with the former 1,2,3-triazole, allows the possibility of another heterocyclic ring (i.e. pyridine) replacing benzene. [1,2,3]Triazolo[4,5-*b*] pyridine (**3**) or [1,2,3]triazolo[4,5-*c*]pyridine (**4**) are the closest systems to **1** reported in the literature (Fig. 2). [1,2,3]Triazolo[4,5-*d*]pyrimidine (**5**) and [1,2,3]-triazolo[4,5-*d*] pyridazine (**6**) systems are also included in this group (Fig. 2). Although these compounds represent the majority of the reported structures, some examples of fused 5+5 aromatic ring 7 can also be found in the literature; however, they are rare structures not deeply investigated compared to the 5+6 family.

The second family of fused 1,2,3-triazoles involves the sharing of one of the 1,2,3-triazole nitrogen atoms by both aromatic rings (either 6+5 or 5+5). As

mentioned before, the simplest compound of this group is [1,2,3]triazolo[1,5-*a*] pyridine (**2**, **Tp**). In this family, pyrimidine [1,5-*a*] (**8a**) and [1,5-*c*] (**8b**), pyrazine (**9**) and pyridazine (**10**) derivatives have also been reported and even some examples of 5+5 systems **11**. This family has been significantly less applied in comparison to the benzotriazole analogues, although they have interesting properties due to the presence of the nitrogen atom in both aromatic rings.

3 Group A: Fused 1,2,3-Triazoles Without a Bridgehead Nitrogen Atom

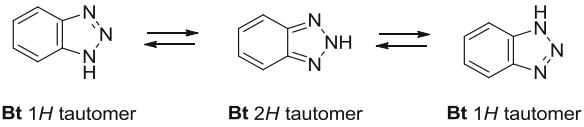
3.1 Structure: Tautomerism and Ring-Chain Isomerization

The particular arrangement of the three nitrogen atoms of benzotriazole gives rise to a special feature for these compounds. Firstly, benzotriazole shows proton tautomerism (Scheme 1). 1*H* and 2*H* **Bt** structures are in equilibrium. Wofford et al. reported in 1982 that in solution the 1H tautomer is the major compound [5]. However, several studies indicate that the 2H tautomer is observed in the gas phase at 0°K, with tautomer 1H increases its population at higher temperature. In terms of lone pair repulsion, it is clear that the 2H tautomer is more stable; however, theoretical calculations indicate that the more stable is the 1H tautomer [6].

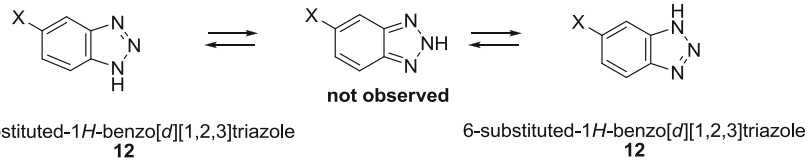
This particular characteristic has consequences for the benzotriazole nomenclature, and as long as two 1*H* structures are possible (Scheme 2), the mixture of them must be specified, for example, 5(6)-substituted-1*H*-benzotriazole (**12**).

This kind of phenomena is also present in *N*-alkylated benzotriazoles (Scheme 3). Known as cationtropic tautomerism and initially reported by Katritzky, this peculiarity allows the equilibrium between 1N and 2N alkylated **Bt**. *N*-Dialkylmethyl-aminobenzotriazole **13** exists as the N1 isomer in the solid state; however, in solution (in nonpolar solvents) or the gas phase, both isomers are present in a 2:1 ratio [7]. Analogues with oxygen **14a** [8] or sulphur **14b** have also the same feature [9]; however, with these heteroatoms, the interconversion is less fast and both 1N and 2N systems can be isolated.

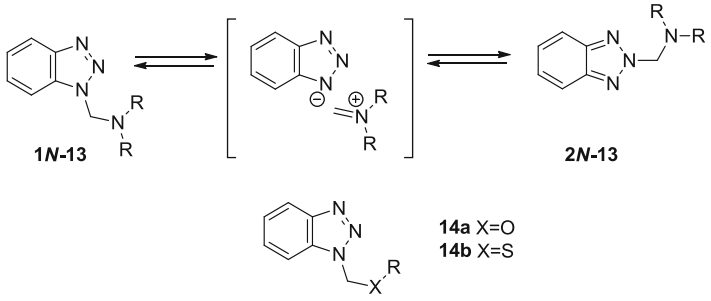
Benzotriazoles also present a particular property in their structures that has been less studied. Indeed they present an opened form in equilibrium with a closed form. Normally this equilibrium is completely on the closed form because of its larger stability. The open form may correspond to a molecule with resonance structures like an ortho-quinoid diazoimine and a benzene ring with a diazonium and an amide as substituents (Scheme 4). Although the detection of the opened forms remains difficult, Katritzky has reported one example with a compound that requires this form as the intermediate to explain the observed equilibrium between the two structures. The only possibility to go from structure **15A** to structure **15B** is through such opened form [10]. This isomerization, being anecdotic in the benzotriazole family, is very common in triazolopyridines (Scheme 4).



Scheme 1 Benzotriazole tautomerism



Scheme 2 Substituted benzotriazole tautomerism



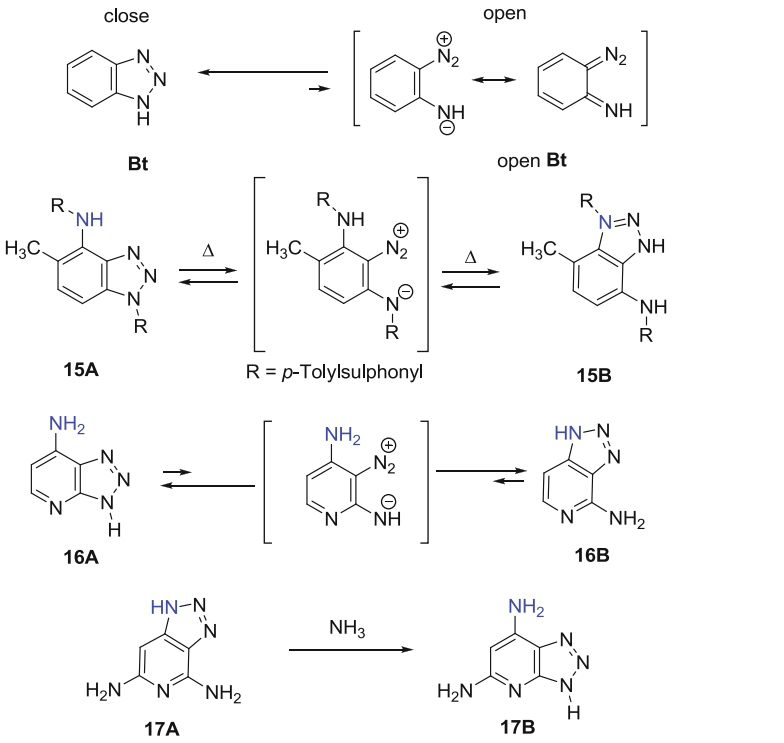
Scheme 3 Cationtropic tautomerism

For example, compound **16** is in equilibrium between **A** and **B** forms; hence it must be necessary to go through the open form [11]. Compound **17A** is also a good example of this ring-chain isomerization. In the presence of ammonia at 150°C, it converts into **17B** by means of an opened diazo system [12, 13].

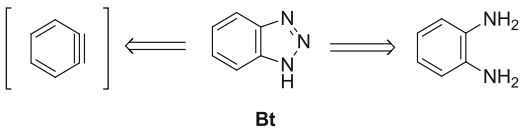
3.2 Synthesis of Benzotriazoles and Triazolopyridines

The preparation of benzotriazole can be realized by different strategies, either by [2+4] cycloaddition from an aryne or by the azotation of ortho-disubstituted diaminobenzene (Scheme 5). Interestingly, the most employed methodology relies on the use of ortho-diaminobenzenes as building blocks. Peterson reported in 1940 the protocol that has been employed for the preparation of benzotriazole and substituted benzotriazoles [14].

Some examples report the use of ortho-nitro anilines that are in situ reduced to obtain the diamine. Oxygenated derivative **18** was obtained during the formation of the triazole ring with hydrazine from 2-chloronitrobenzene [15].



Scheme 4 Ring-chain isomerization

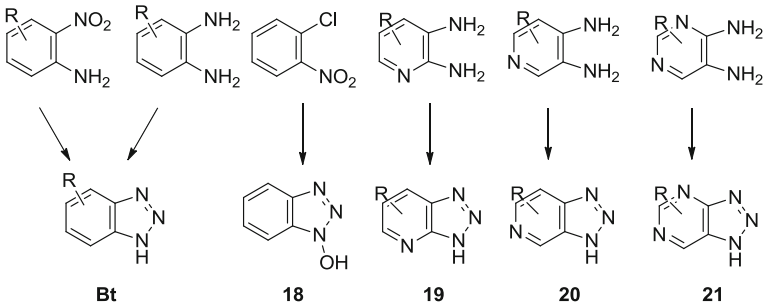


Scheme 5 Retrosynthetic approach

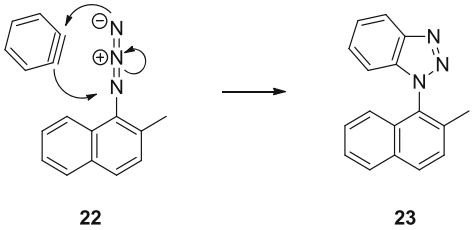
Applying a similar approach with the corresponding diamino derivatives, pyridine (**19**, **20**) and pyrimidine (**21**) derivatives were also obtained [16–19] (Scheme 6). This strategy can be applied to a large family of compounds and has allowed the preparation of more complex molecules derived from diamino pyridines [19, 20].

In the literature there are a few examples involving the aryne approach; however, they remain less employed. This 2+4 cycloaddition to obtain benzotriazoles was first reported by Kulagowski [21] (Scheme 7). Azide derivative **22** reacts with the corresponding aryne to form benzotriazole **23**.

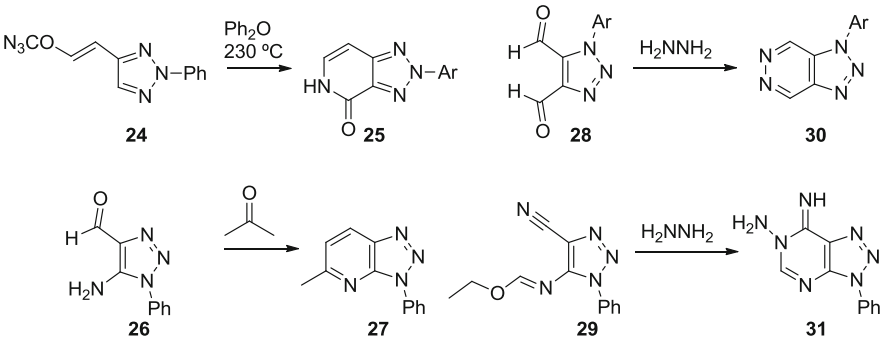
Despite these two strategies being the most common, some alternatives are possible with more complex heterocyclic compounds, based on the initial presence of the triazole ring in the reagent (Scheme 8). For example, triazole **24** undergoes cyclization to form compound **25** [22]. Treatment in acetone of compound **26** allows the formation of triazolopyridine **27** [23]. When 2 heteroatoms are present on the



Scheme 6 Synthons for benzotriazoles and triazolopyridines



Scheme 7 Benzotriazole synthesis through arynes

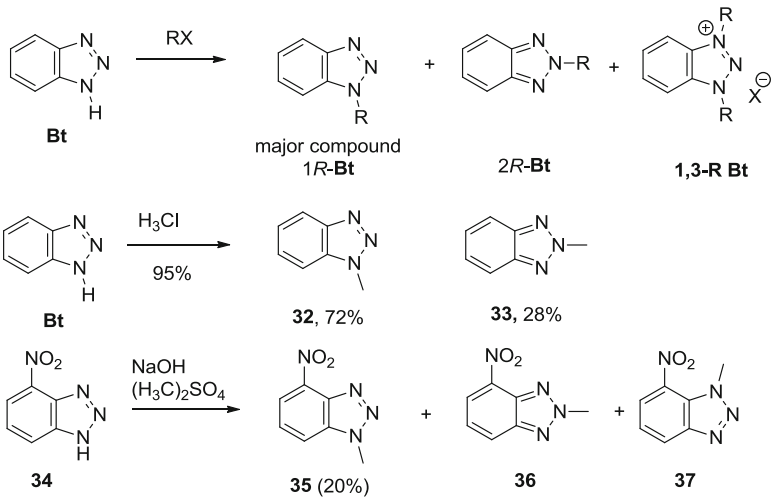


Scheme 8 Alternative approach

6-membered ring, other strategies can be employed. In Scheme 8 we show that 1,2,3-triazoles **28** and **29** react with hydrazine to afford compounds **30** [24] and **31** [25].

3.3 Reactivity of Benzotriazoles and Triazolopyridines

The chemical reactivity of benzotriazoles and triazolopyridines can be presented in two parts: (1) functionalization of the triazole ring and the (2) functionalization of the benzene or heterocyclic (commonly pyridine) ring.



Scheme 9 Alkylation of benzotriazoles

3.3.1 Functionalization of the Triazole Ring

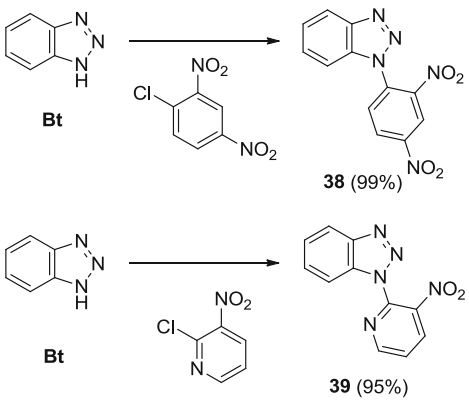
Alkylation

When **Bt** is reacted with alkyl halides, up to three compounds can be observed (Scheme 9): compounds derived from monosubstitution at position 1/3N (major) or 2N and, in some cases, 1,3-disubstituted compounds. Direct methylation of **Bt** affords with high yield (95%), a mixture between 1N-**32** and 2N-**33** methylated compounds in a 72/28 ratio [26]. However, the complexity of these reactions increases when benzotriazole has different substituents on the benzene ring (i.e. nitro substituent, compound **34**) (Scheme 9). In this compound N1 and N3 are no longer the same and the simplest reaction (i.e. methylation) affords at least 3 different compounds **35**, **36** and **37** [27].

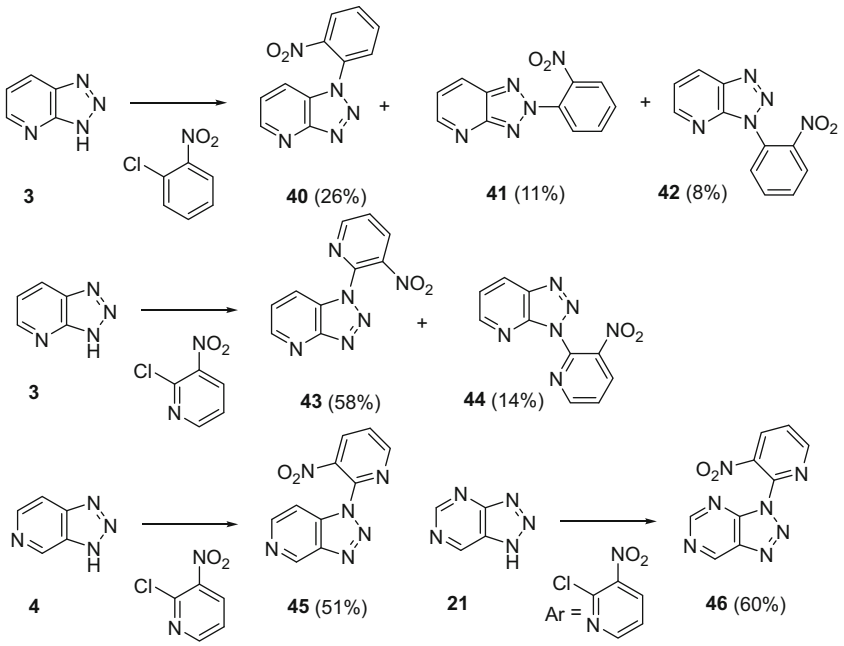
Arylation

Bt acts as a nucleophile in aromatic nucleophilic substitution; exclusive substitution at 1N is observed. Reactions with chloronitrobenzenes are described, affording compounds **38** and **39** in high yields (Scheme 10) [28, 29].

With triazolopyridine derivatives, this behaviour has also been observed. Although no direct reaction with methylene iodide has been reported, reactions with chloronitrobenzene or chloronitropyridine are present in the literature (Scheme 11). Triazolopyridine **3** reacts with either chloronitrobenzene or chloronitropyridine to form compounds **40**, **41** and **42** or **43** and **44** [30, 31]. In both cases the nitrogen atom from the triazole ring is more reactive than the one on the pyridine nitrogen. Triazolopyridine **4** reacts under similar conditions affording



Scheme 10 Benzotriazole as nucleophile in ArNs

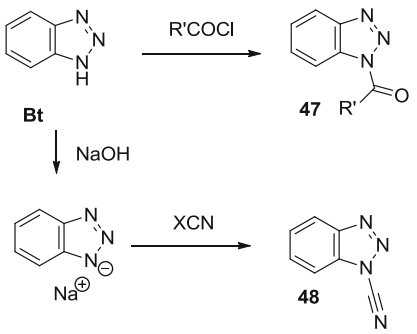


Scheme 11 Triazolopyridines and triazolopyrimidines as nucleophiles in ArNs

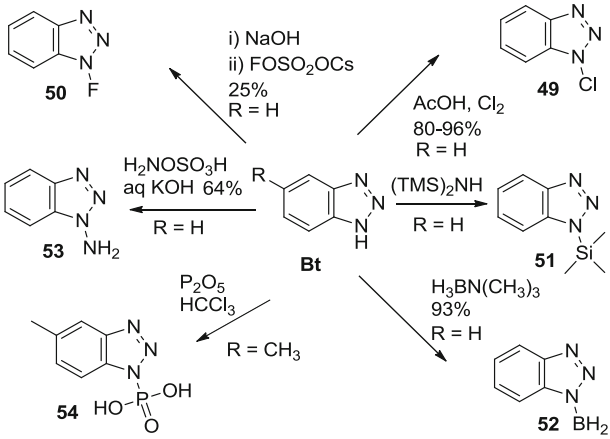
exclusively compound **45**. Triazolopyrimidine **21** affords **46** as a single compound in 60% [24].

N1 Functionalization by Different Substituents

Reaction of **Bt** with acyl chlorides allows the preparation of ketones/amides **47** [32]. Even the introduction of a cyano substituent has been achieved. When the



Scheme 12 N1 functionalization



Scheme 13 N1 functionalization of **Bt** and methyl derivative

corresponding sodium salt of **Bt** is treated with ClCN [33] or BrCN [34], compound **48** is obtained (65 and 90%) (Scheme 12).

The introduction of other atoms has also been reported at position 1 (Scheme 13). Chlorination affords compound **49** in good yield [35]; fluorination [36] takes place with moderate yields affording **50** in 25%. Silylation and borylation have also been reported in the literature to form compounds **51** and **52** with moderate to good yields [37]. Amino and phosphorus derivatives **53** and **54** have also been reported in moderate to good yield [38, 39].

Some of these types of reactions have also been reported with triazolopyridines; shown in Fig. 3 are some of these less common compounds [38–42]. Compounds **55**–**57** are in agreement with the regioselectivity indicated before (Scheme 10).

At this point of the chapter, it is important to remark that almost all applications of **Bt** in organic synthesis deal with *N*-substituted **Bt**. Katritzky has reported many of these original contributions (more than 700) and has written several reviews covering the preparation and application of these compounds [32].

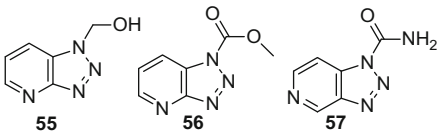
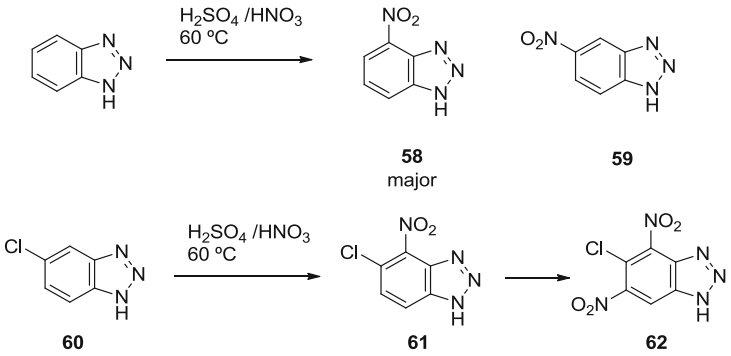


Fig. 3 Triazolopyridine derivatives



Scheme 14 Nitration of **Bt**

3.3.2 Functionalization of the Benzene or Pyridine Ring

The introduction of functional groups on the benzotriazole trends to be performed on the benzene ring prior to the formation of the triazole ring. Nevertheless there are some reactions that are carried out on the benzotriazole ring that allow the functionalization of the benzene ring.

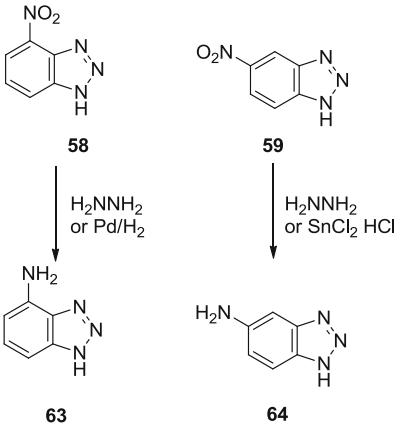
Nitration

Direct nitration of benzotriazole does indeed proceed at positions 4 and 5 with preference at the 4th position [10, 43]; thus compound **58** is the major isomer compared to **59** (Scheme 14). With chlorine-substituted systems **60**, mononitration [44] and dinitration [45] can be realized by increasing the temperature from 60 to 120°C, leading to compounds **61** and **62**. None of these reactions have been reported in the literature for triazolopyridines.

Amination

It remains essential to remark that no direct amination has been reported with benzotriazole. The reduction of nitro groups is the most employed strategy towards the synthesis of amino benzotriazoles (Scheme 15). Hydrazine or Pd/H_2 reductions are the most common methodologies to prepare 4-aminobenzotriazole **63** [10]. The

Scheme 15 **Bt** amino derivatives



derivative at position 5 compound **64** is less common and has been reported by reduction either with hydrazine or with $SnCl_2$ under acid medium [44, 46]. Those reduction conditions did not affect the benzene ring.

Halogenation

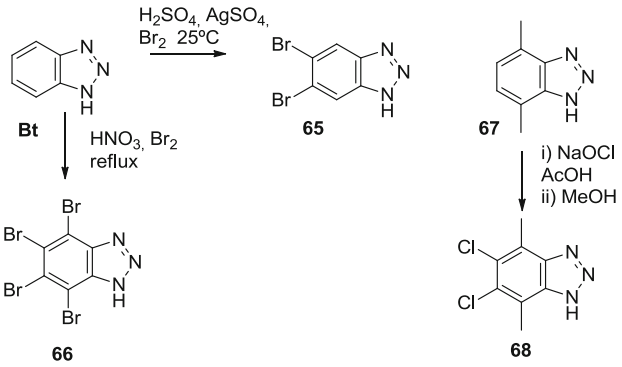
Direct halogenation has been mainly achieved with bromine leading either to dibromation at positions 5 and 6 (Scheme 16, compound **65**) or tetrabromation (compound **66**) with the harshest conditions [47]. The only example reported of chlorination is the reaction of 4,7-dimethyl benzotriazole **67** with NaOCl in acid medium [48]. Compound **68** is obtained under these conditions. No direct fluorination or iodination is reported.

An alternative approach towards the preparation of iodo derivatives relies on diazonium salts. Treatment of **64** with $NaNO_2$ affords the corresponding diazonium salt **69** that undergoes reaction with potassium iodide yielding the monoiodine derivative **70** in low yield (32%) (Scheme 17) [49].

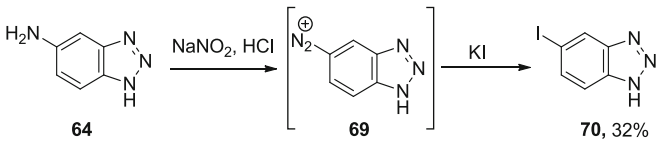
Oxidation and Reduction

Oxidation and reduction are performed on the substituents attached to the benzotriazole ring. It has been reported that strong oxidation of 5-methyl benzotriazole **71** leads to the corresponding acid **72** in good yield (Scheme 18) [50]; however, extreme oxidant conditions can result in the complete destruction of the benzene ring as it will be shown later.

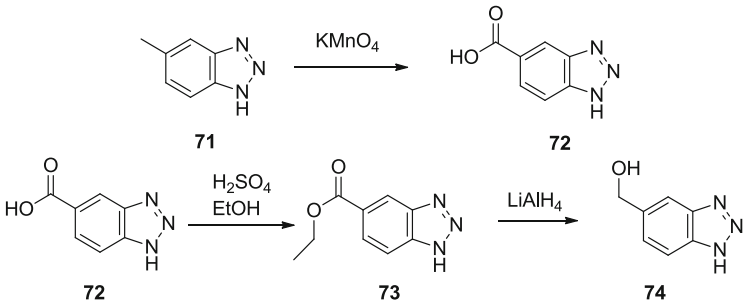
The structure of benzotriazole resists classical Fischer esterification conditions (H_2SO_4). Thus ester **73** has been reported [51]. Furthermore typical reduction reagents like $LiAlH_4$ allow reduction of functional groups without modification of the aromatic core, affording compound **74** [51] (Scheme 18).



Scheme 16 Halogenation of **Bt**



Scheme 17 Iodation of aminobenzotriazole



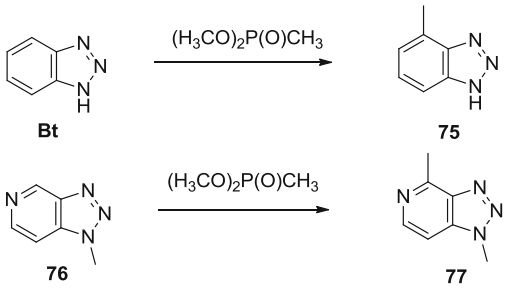
Scheme 18 Oxidation and reduction of benzotriazoles

Methylation

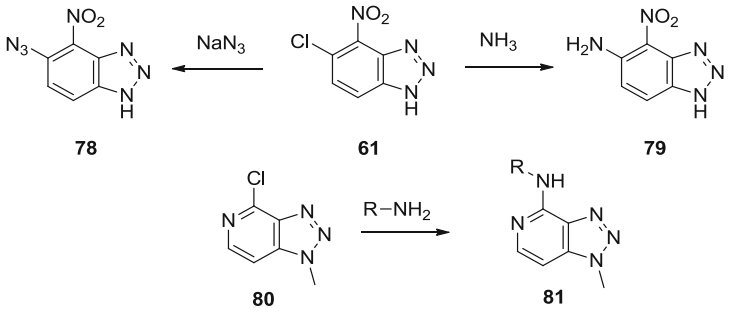
Methylation of benzotriazole has also been achieved in 80% yield by reaction with $(H_3CO)_2P(O)CH_3$ yielding to compound **75** (Scheme 19) [52]. These kinds of reactions are rarely reported in the literature with triazolopyridines; however, the regioselective methylation of compound **76** towards **77** [53, 54] has been described.

Aromatic Nucleophilic Substitution

Aromatic nucleophilic substitution has also been achieved with benzotriazoles but almost all examples required nitro groups to activate the system [45]. Compounds



Scheme 19 Methylations of **Bt** and methyl triazolopyridine **76**



Scheme 20 Aromatic Nucleophilic Substitution

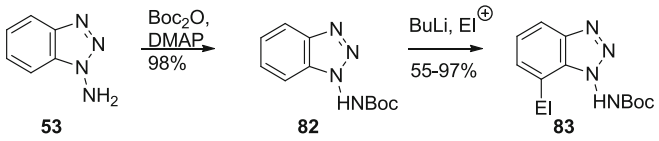
78 and **79** are obtained by means of this reaction (Scheme 20). Some examples are also reported with chlorinated triazolopyridines. Compound **80** undergoes aromatic nucleophilic substitution with primary amines leading to **81** [54].

Lithiation

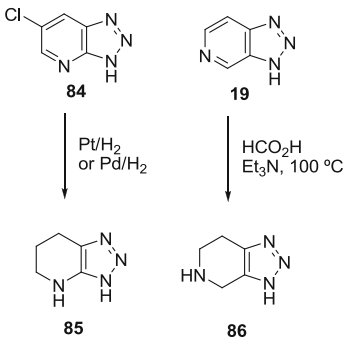
Benzotriazole can also be functionalized by reaction with BuLi; however, it requires Boc protection of 1N (Scheme 21). The only reported example is from compound **53**. After Boc protection (compound **82**), regioselective lithiation and subsequent trapping have been performed, affording compound **83** [38].

Hydrogenation

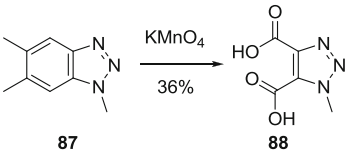
As apparent from the examples above, the benzene ring from **Bt** resists many different conditions. No references concerning the hydrogenation of this compound or derivatives have been reported. However, triazolopyridine derivatives undergo hydrogenation under particular conditions (Scheme 22). Compounds **84** and **19** under reducing conditions result in triazolopiperidines **85** and **86** [16, 56].



Scheme 21 Lithiation of compound **53**



Scheme 22 Hydrogenation of triazolopyridines



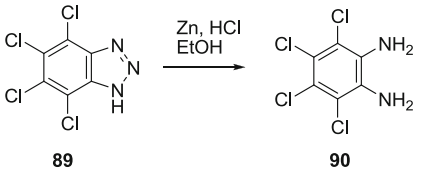
Scheme 23 Oxidation of benzene ring

3.3.3 Triazole Ring-Opening Reaction

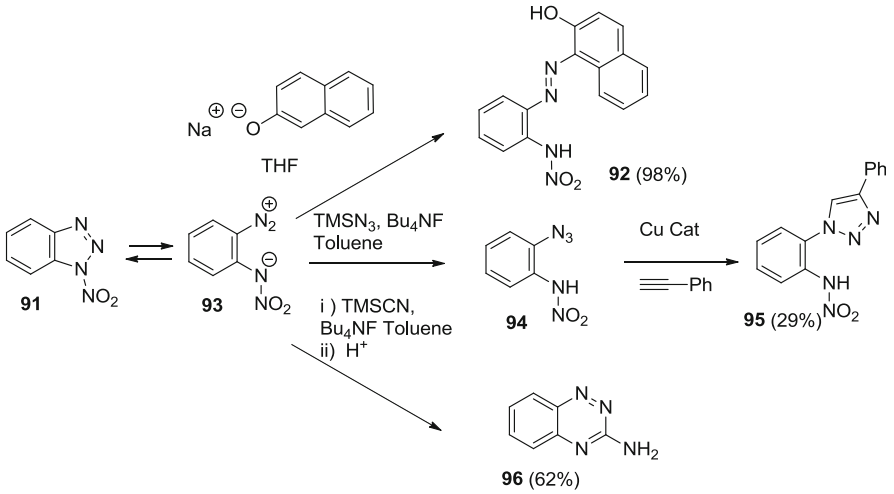
The triazole ring in **Bt** is very stable as it can be seen by means of the reaction conditions reported in the previous examples. As an example, it is interesting to show that extreme oxidative conditions lead to the destruction of the benzene ring instead of the triazole one. Compound **87** affords triazole **88** under strongly oxidative conditions (Scheme 23) [57].

However, some reactions are reported that involve the destruction of the triazole ring leading to a benzene system. For example, tetrachlorobenzotriazole **89** reacts under strongly reducing conditions, affording the corresponding diamine **90** [58] (Scheme 24).

A second example of a ring-opening reaction starts from nitro compound **91** [59]. The presence of the nitro substituent destabilizes the triazole ring, and some ring-opening reactions have been reported [60]. Adduct **92** can be obtained in excellent yield via azo coupling reaction of intermediate diazonium salt **93** with the basic form of napht-2-ol. The formation of this compound can be explained



Scheme 24 Opening of the triazole ring in **89**



Scheme 25 Opening of the triazole ring in **91**

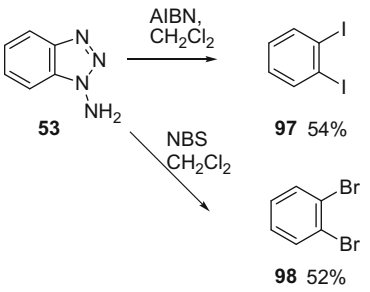
through an open form of **91** with the structure **93**. This ionic form can undergo direct ArNs, leading to compound **94** that was subsequently transformed into a triazole by means of click chemistry (compound **95**). Finally, compound **91** has also been reported as a precursor of exotic heterocyclic compounds like **96** (Scheme 25).

1-Aminobenzotriazole **53** has a particular and interesting behaviour [61, 62] (Scheme 26) giving diiodobenzene **97** and dibromobenzene **98** in moderate yields by radical reactions.

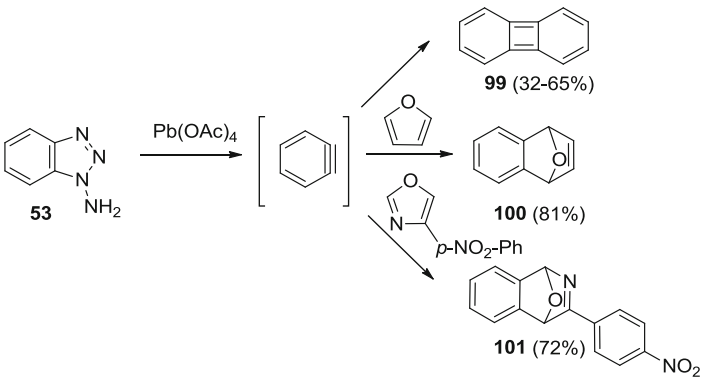
This amino derivative allows the generation of an aryne as the intermediate in the presence of lead acetate (Scheme 27). Despite not being the most employed aryne source, some examples have been reported [63–65]. Adduct **99** that combines two arynes can be obtained in moderate yield. In a similar way, reaction with furan or oxazole leads to the corresponding cycloaddition adducts **100** and **101** in good yields.

Even more surprisingly, diaminobistriazole **102** also shows this behaviour [66] (Scheme 28). This compound performs double-aryne generation, affording more complex structures in moderate to good yields. Adducts **103** and **104** are obtained with good yields.

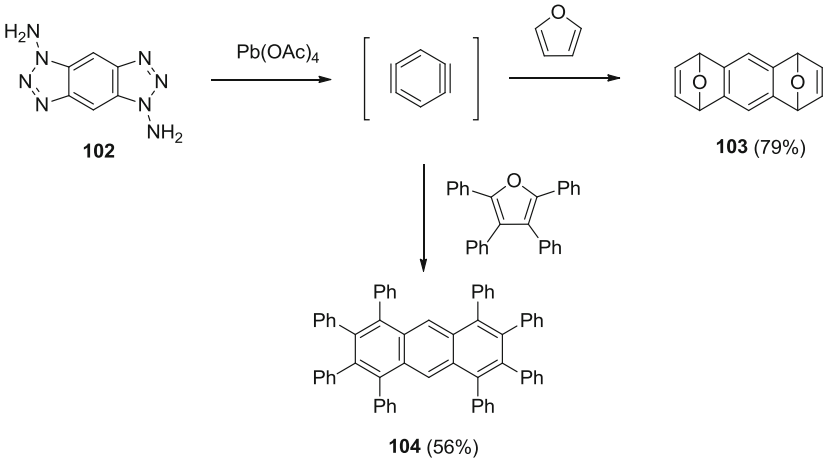
Another approach towards the cleavage of the triazole ring relies on the preparation of salts. Grignard addition to compound **105** generates intermediate **106** that



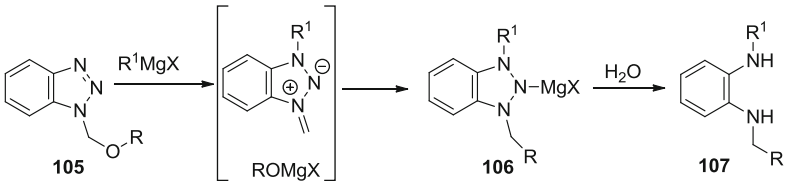
Scheme 26 Triazole ring opening in 1-aminobenzotriazole **53**



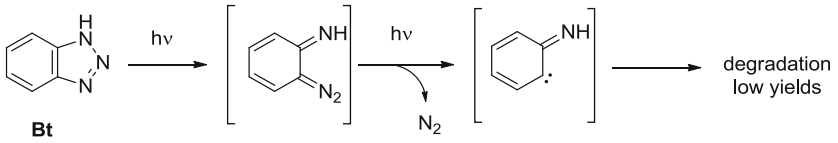
Scheme 27 Aminobenzotriazole **53** as aryne source



Scheme 28 Diaminobistriazol **102** as double-aryne source



Scheme 29 Benzodiamine **107** preparation from benzotriazole **105**



Scheme 30 Photochemical decomposition of **Bt**

in the presence of water decomposes towards the diamine derivative **107** (Scheme 29) [67]. However, the presence of the ether moiety is required for this reactivity.

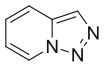
An alternative towards the activation of the triazole ring is the photochemical approach; nevertheless, benzotriazole shows itself to be extremely stable, and low yields are obtained of the corresponding photodegradation products from nitrogen elimination [68] (Scheme 30).

4 Group B: Fused 1,2,3-Triazoles with a Bridgehead Nitrogen Atom

Fused 1,2,3-triazoles with a bridgehead nitrogen atom are those systems when one of the three nitrogen atoms from the triazole ring belongs also to the second aromatic ring. As it has been outlined before, these compounds are represented by the parent [1,2,3]triazolo[1,5-*a*]pyridine (Fig. 4). This compound **Tp** is the simplest member of this family, and although having similar features like benzotriazole, it has also particular characteristics that are not present in the **Bt** family.

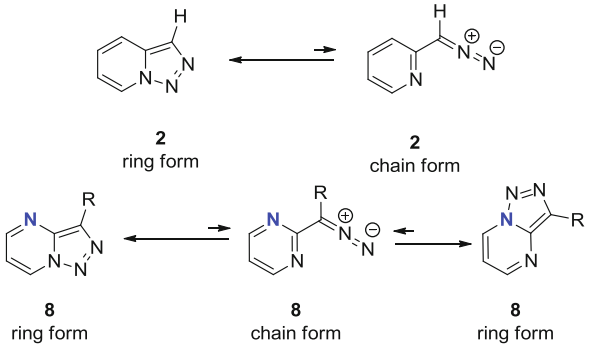
4.1 Structure: Tautomerism and Ring-Chain Isomerization

Compared to the benzotriazole family, these compounds do not present H-tautomerism. However, they indeed show also a ring-chain isomerization. This phenomenon is even more common than in the **Bt** family (Scheme 31) [69]. The

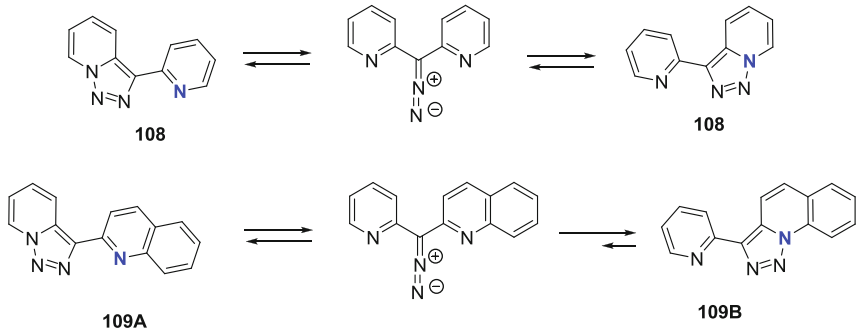


2

Fig. 4 Parent compound of the [1,2,3]triazolo[1,5-*a*]pyridine family



Scheme 31 Ring-chain isomerization in triazolopyridine **2** and triazolopyrimidine **8**

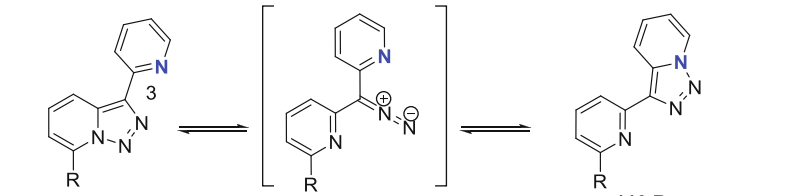


Scheme 32 Ring-chain isomerization in triazolopyridines **108** and **109**

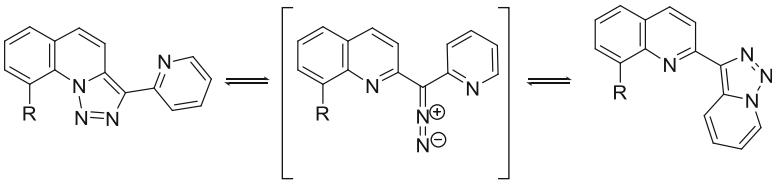
open chain form of these systems is a classic diazo compound. Triazolopyrimidine **8** also presents this equilibrium [70]. As it will be described later, these compounds can react like a diazo compound.

This phenomenon became even more interesting when the substituent R is a 2-pyridyl [71] **108** or 2-quinolyl [72] **109**, because then there are 2 structures in equilibrium. Through an open intermediate with a diazo structure, the cyclization can take place, involving one of the two different nitrogen atoms. Similarly to what has been reported with **Bt**, the most electron-rich nitrogen (or the less hindered) is preferred for the triazole ring formation (Scheme 32).

For 3-(2-pyridyl)-triazolopyridine **108**, both structures are exactly the same; however, in the case of potential equilibrium **109A** and **109B**, there is an interesting difference in the structure of both isomers. There are some studies about the



Scheme 33 Ring-chain isomerization in 7-substituted -3-(2′-pyridil)-triaolopiridines **110**

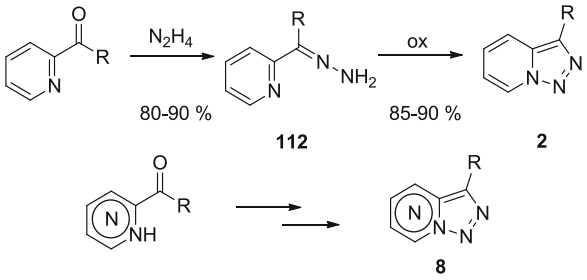


Scheme 34 Ring-chain isomerization in 9-substituted -3-(2′-pyridil)-triazoloquinolines **111**

ring-chain isomerism of 7-substituted-3-(2-pyridyl)-triazolopyridines **110** and 9-substituted-3-(2-pyridyl)-triazoloquinolines **111** [71, 72].

Traditionally these structures had been noted as **A** compounds for those bearing the substitution on the triazolopyridine (or triazoloquinoline) ring and **B** for those obtained after the isomerization. In compound **110** with a methyl group as substituent, a mixture of **A/B** products is observed, and although they can easily be identified by NMR (Scheme 33), these systems cannot be separated because they isomerize at room temperature. Theoretical calculations support these findings. Electronic properties of the substituent were found determinant. Electron-withdrawing substituents favour a **B** structure. Electron donors tend to result in the **A** structure.

Triazoloquinolinepyridines **111** behave similarly. However, initially both **A** and **B** structures are nonequivalent and only **A** is observed (Scheme 34). The introduction of a substituent modifies the **A/B** ratio. Also in this case, electron-withdrawing and bulky substituents afford the **B** structure, and small and donor substituents afford the **A** structure.



Scheme 35 General approach towards the synthesis of **2** and **8**

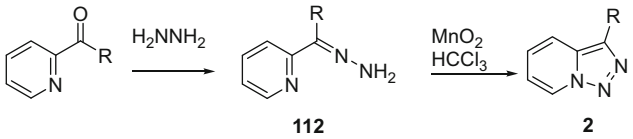
4.2 Synthesis

All examples concerning the synthesis of these compounds involve the preparation of alpha-substituted pyridines. Indeed pyridines are the major starting reagents for the preparation of **Tp**. There are several methodologies reported. The most common approach involves 2-pyridyl aldehydes or ketones that react with hydrazine leading to hydrazone **112** that then is submitted to oxidation (analogous to the Staudinger approach to diazo compounds) affording the desired compounds **Tp 2** (Scheme 35). This strategy is also employed for the other members of the families like triazolo[1,5-*a*] or [1,5-*c*]pyrimidines **8** [70, 73].

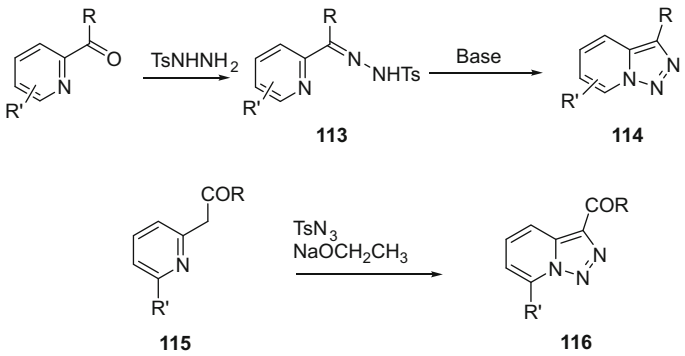
Boyer et al. [74] published the first synthesis of [1,2,3]triazolo[1,5-*a*]pyridines of type **2**. Hydrazones **112** were oxidized using Ag_2O to give the diazo intermediates which undergo an intramolecular cyclization, affording [1,2,3]triazolo[1,5-*a*] pyridines **2**. Although Ag_2O provided triazolopyridines in good yields, Boyer and Ramage [75] replaced it by potassium ferrocyanide. However, along with **Tp** several side reaction products were obtained. Many other oxidants, like nickel peroxide, lead tetraacetate and copper (I) salts, have been tested [76, 77]. Comparing all published synthetic ways to obtain [1,2,3]triazolo[1,5-*a*]pyridines using this methodology, the oxidation with manganese (IV) oxide (MnO_2) due to its low cost and the good and reproducible yields made it the reagent of choice. Manganese oxide was successfully employed by Abarca [78] to prepare triazolopyridines on gram scale (Scheme 36).

In order to avoid the oxidation step that can show incompatibilities with other functional groups, Boyer and Goebel [79] developed another variant of Bamford-Stevens approach to obtain triazolopyridines. They were synthesized after condensation of tosylhydrazine with the corresponding 2-pyridyl aldehydes or ketones. This reaction led to tosylhydrazones **113**. Following a basic treatment with NaOH or KOH, derivatives **114** were obtained. In this way, they succeeded in the synthesis of 3-phenyl, 3-picolinoyl and [1,2,3]triazolo[1,5-*a*]pyridines in high yields without use of oxidizing agent (Scheme 37). Other bases like morpholine were also employed to prepare, for example, 7-methyltriazolopyridine [80], 5-methoxytriazolopyridine [81] or their bromine analogues [82].

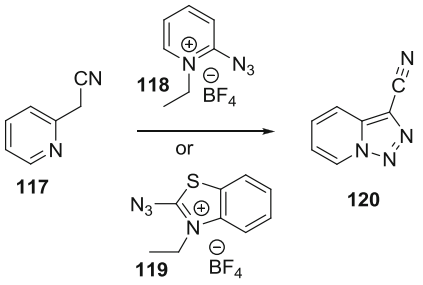
A third original approach relies on the reaction with azides. From 2-acylmethylpyridines **115** with tosylazide (TsN_3) in the presence of sodium



Scheme 36 Abarca approach to **Tp**



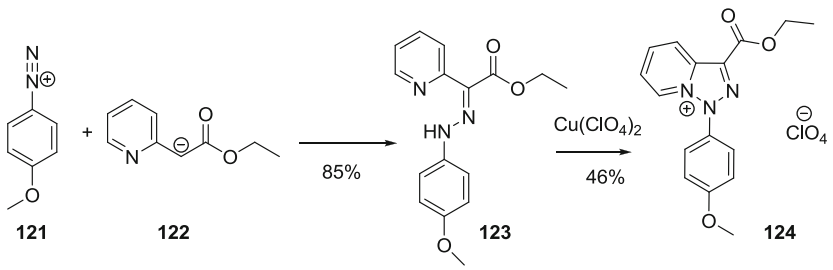
Scheme 37 Tosylhydrazine and Tosylazide approaches



Scheme 38 Preparation of **120**

ethoxide, Regitz obtained triazolopyridine derivatives with moderate to high yields (50–80%) [83, 84], compounds **116** were obtained by this procedure. From compound **117** and other different azides, like 2-azido-1-ethylpyridinium tetrafluoroborate **118** [85] or 2-azido-3-ethylbenzothiazolium tetrafluoroborate **119**, the cyano derivative **120** was obtained (Scheme 38) [86].

The previous strategies are the most commonly employed; however, some alternatives have also appeared that allow the formation of the 1,2,3-triazole ring with substitution at N1 [87]. This approach employs a diazo compound **121** that reacts with the anion **122** leading to a substituted hydrazine **123**. Oxidation with copper (II) perchlorate leads to the 1-subtituted triazolopyridinium perchlorate salt **124** in moderate yield (Scheme 39).



Scheme 39 Preparation of 1-subtituted triazolopyridinium **124**

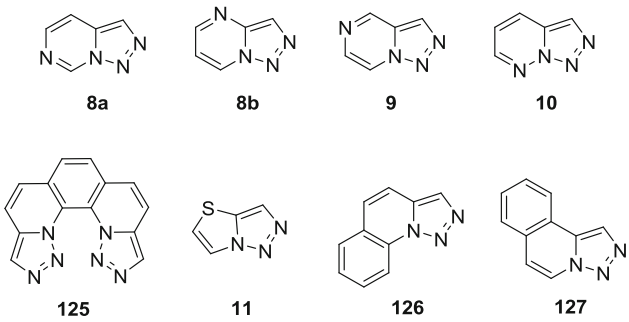


Fig. 5 Different structures of **B** family

These strategies have been applied with different starting reagents. Although the number of examples synthesized is significantly smaller that in **Bt** family, some interesting structures **8–11** and **125 –127** have been reported [70, 73, 74, 88–90] (Fig. 5).

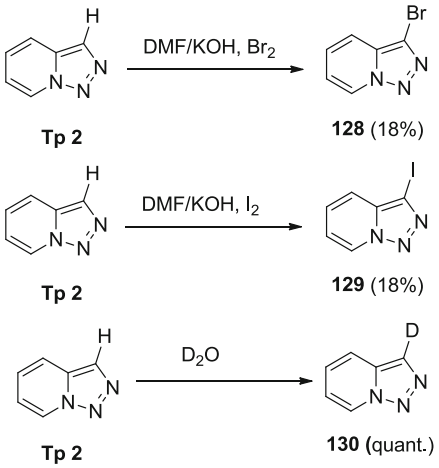
4.3 Reactivity of the Triazolopyridines Family

4.3.1 Functionalization of the Triazole Ring

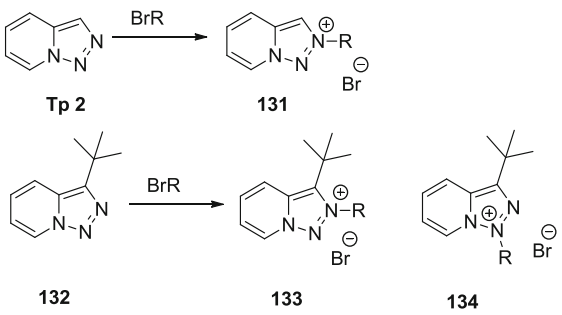
Halogenation

This family has significant differences in terms of reactivity regarding **Bt**. Triazolopyridine with no substituent at position 3 can be bromated or iodinated in basic medium, giving compounds **128** and **129** with moderate yields [91, 92]. It is also important to remark that the proton in position 3 is acidic and exchanges with deuterium just by heating in D_2O, leading to compound **130** (Scheme 40).

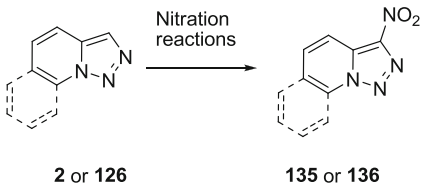
Scheme 40 Substitution at position **3** of parent compound **2**



Scheme 41 Alkylation of **Tp**



Scheme 42 Nitration of **2** and **126**



Alkylation

Alkylation to give triazolopyridinium salts has also been reported on these systems. Normally they are alkylated at nitrogen 2, obtaining structures like compound **131**. However, with large substituents at position 3 [93, 94], like tert-butyl derivative **132**, mixtures of **133** (N2) and **134** (N1) alkylated products are observed (Scheme 41).

Nitration

Nitration of these systems with no substitution at position 3 can also be performed, affording nitrotriazolopyridines **135** [95] and nitrotriazoloquinolines **136**

[96]. However, these reactions gave low yields and side products derived from the opening of the triazole ring (Scheme 42) (see 4.3.3).

4.3.2 Functionalization of the Pyridine Ring

Lithiation

This family of compounds presents a general reactivity that is completely different from benzotriazoles. Indeed all triazolopyridines undergo regioselective metallation at position 7 with butyllithium [80]. Trapping with electrophiles allows the preparation of 7-substituted derivatives **137**. This regioselectivity can be explained by the directed effect by N1 towards peri-metallation (Scheme 43).

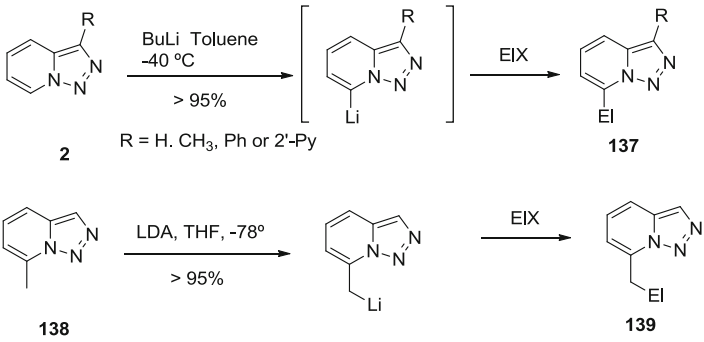
The regioselective metallation at position 7 has been employed for the preparation of a large variety of compounds. This includes also all compounds that were studied in the ring-chain isomerization (see Sect. 4.1 Schemes 33 and 34). This position is extremely activated, undergoing lithiation even when a methyl group is at this place, for example, in compound **138** leading to **139** [80, 97]. This result indicates how different can be the reactivity of **Bt** and **Tp** families. Some studies have been performed [81] by introducing *ortho*-directing groups to metallation on the triazolopyridine ring, like compound **140**, trying to get lithiation in different positions. Nevertheless the metallation with LDA provided exclusively 7-substitued triazolopyridines **141** (Scheme 44).

So far, only few examples of metallation at other positions were described in the literature. Nevertheless, in 1995, Jones reported the reaction of 3-cyano-[1,2,3]triazolo[1,5-*a*]pyridine **120** with LDA [98]. Although this reaction provides a complex mixture of products after trapping with trimethylsilyl chloride, 4-substituted triazolopyridine **142** was identified. However, the low yield remained an important drawback from a synthetic point of view (compound from dimetallation **143** was also isolated and some other side products like **144** and **145**) (Scheme 45).

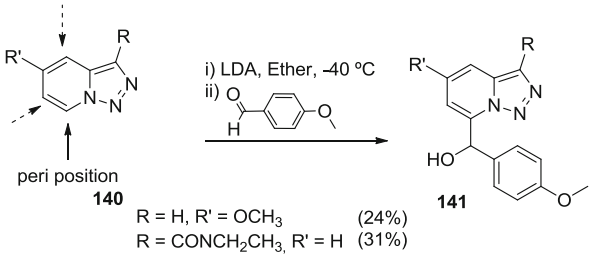
As reported also by Jones, 4-substitution could be achieved with 7-trimethylsilyl-3-carboxamide-[1,2,3]triazolo[1,5-*a*]pyridine (**146**) but lead to compound **147** in very low yield (5%) [98] (Scheme 46).

One important reaction reported with lithium derivatives is the dimerization. Under specific conditions, heterocyclic π-deficient compounds can undergo dimerization. This kind of aryl–aryl coupling is known, but it was not intensively investigated. The reaction of dimerization of [1,2,3]triazolo[1,5-*a*]pyridines was observed by Abarca and Ballesteros for the first time in 1997 (Scheme 47). When 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine (**148**) was treated with LDA at −40°C in THF followed by trapping with 2-pyridylcarboxaldehyde, expected compound **149** was obtained. However, the corresponding dimer **150** was also obtained as a side product [99].

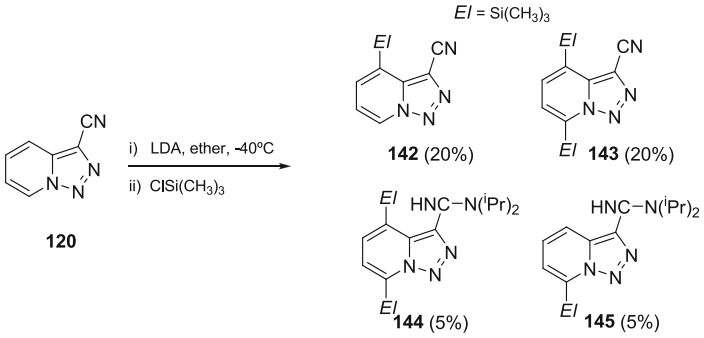
Due to the interesting structure of this dimer, the authors modified the reaction conditions in order to favour dimerization [82]. They found out that the optimal



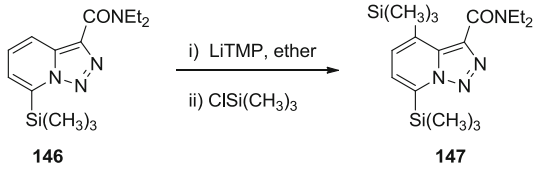
Scheme 43 Regioselective metallation of **Tp**



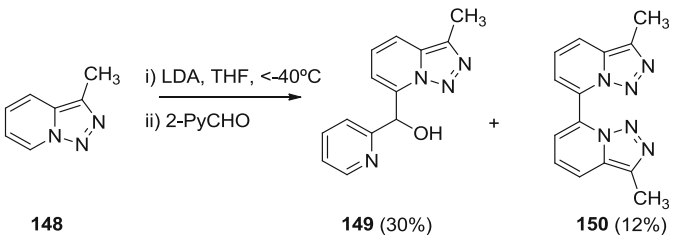
Scheme 44 Regioselective metallation of substituted **Tp**



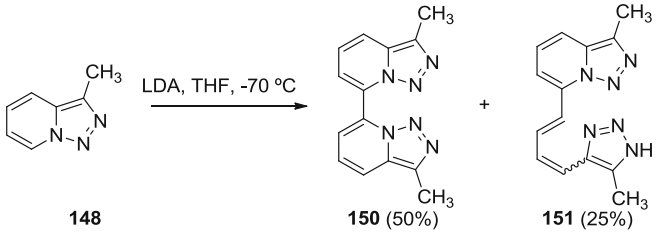
Scheme 45 Metallation of **120**



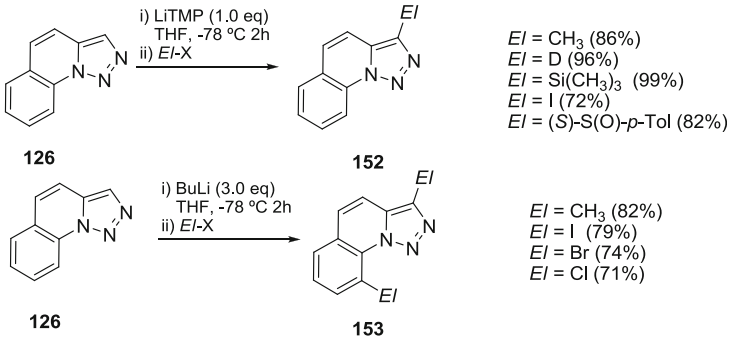
Scheme 46 Metallation of **146**



Scheme 47 First synthesis of **150**



Scheme 48 Optimized synthesis of **150**

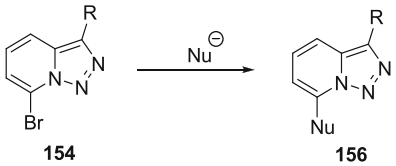


Scheme 49 Mono- and dimetallation of **126**

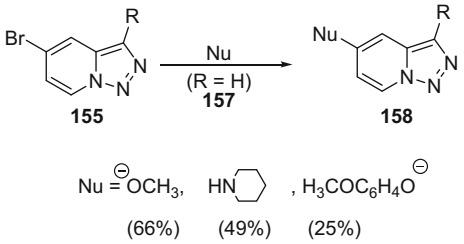
conditions were LDA (1 eq)/THF/−70°C. After 9 h, the dimer **150** was obtained in a 50% yield, but surprisingly, another side product (1-(3-methyl-[1,2,3]triazolo [1,5-*a*]pyridin-7-yl)-4-(5-methyl-1*H*-1,2,3-triazol-4-yl)-1,3-buta-dienyl) (**151**) was formed in a non-negligible amount (25%) (Scheme 48).

Other compounds of this group of fused 1,2,3-triazoles with a N-bridgehead tend to have particular reactivity. Indeed triazoloquinolines **126** can be metallated at position 3 with LiTMP giving compounds **152**, after trapping with electrophiles, in good yield. However, when 3 equiv. of BuLi are employed, double lithiation can be achieved, affording, after trapping, 3,9-disubstituted triazoloquinolines **153** [100] (Scheme 49).

Scheme 50 Aromatic nucleophilic substitution in C7



Scheme 51 Aromatic nucleophilic substitution in C5



Reactions with Nucleophiles

The [1,2,3]triazolo[1,5-*a*]pyridines do not react directly with nucleophiles. However, some ArNs reactions with the halogenated derivatives 7-bromo-3-substituted-[1,2,3]triazolo[1,5-*a*]pyridines (**154**) and 5-bromo-3-substituted-[1,2,3]triazolo[1,5-*a*]pyridines (**155**) are described [82, 101]. Compounds **154** react with nucleophiles like sodium methoxide, sodium 4-methoxyphenolate or sodium benzenethiolate in DMF at 90°C to give substituted compounds **156** in high yields. Also, in ethanol at 80°C, sodium hydrazine and sodium piperidine afforded substitution products **156** in respectively 60 and 65% yield. No reaction occurs with sodium azide and potassium cyanate [101] (Scheme 50).

5-Bromotriazolopyridine **157** reacts with nucleophiles allowing the functionalization at the C5 position leading to compounds like **158** [82] (Scheme 51). No reaction occurs when the reaction is carried out with the chlorinated derivative or with 6-bromo-[1,2,3]triazolo[1,5-*a*]pyridine.

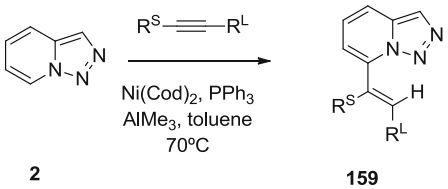
Position 7 of **Tp 2** has also been reported as suitable for direct CH activation in the presence of $Ni(COD)_2$ and disubstituted alkynes leading to compounds **159** in good yields (85–90%) [102] (Scheme 52).

Hydrogenation Reactions of Triazolopyridines

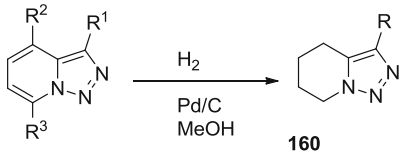
In 1999, Abarca et al. published a study on the hydrogenation of several triazolopyridines **2** by means of heterogeneous catalysis under mild conditions (Pd/C, methanol, 25°C, atmospheric pressure) and obtained 4,5,6,7-tetrahydrotriazolopyridines **160** as indicated in Scheme 53 [103]. This particular feature is completely different from benzotriazoles where the hydrogenation remains difficult and only was reported with some pyridine derivatives.

When the triazolopyridine is substituted by a methyl group in position 3, the reactions lead to the formation of the tetrahydro derivative in good yield. However,

Scheme 52 Direct 7-CH activation (R^S small substituent, R^L large substituent)

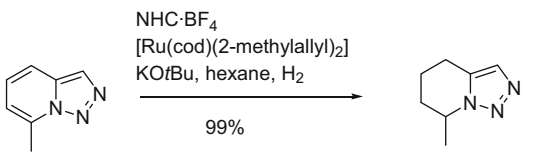


Scheme 53 Heterogeneous hydrogenation



$R^1 = R^2 = R^3 = H$	R = H (90%)
$R^1 = CH_3$, $R^2 = R^3 = H$	R = CH_3 (100%)
R^1 = 2-Py, $R^2 = R^3 = H$	R = 2-Py (46%)
R^1 = 2-Th, $R^2 = R^3 = H$	R = 2-Th (32%)
$R^1 = H$, $R^2 = CH_3$, $R^3 = H$	No reaction
$R^1 = R^2 = H$, $R^3 = CH_3$	No reaction
$R^1 = COOC_2H_5$, $R^2 = R^3 = H$	R = $COOC_2H_5$ (50%)
$R^1 = CN$, $R^2 = R^3 = H$	R = CH_2NH_2 (30%)

Scheme 54 Homogeneous hydrogenation

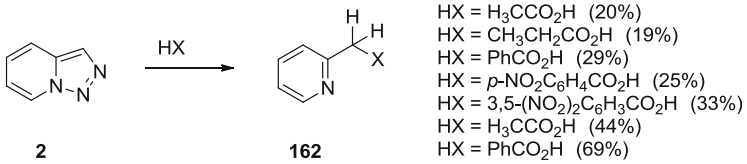


if the methyl group is on the pyridine ring, no hydrogenation product was observed and the starting material was recovered. When the pyridine is substituted with a thiophene at position 3, the 4,5,6,7-hydrogenated product was obtained in low yield (32%) even with increased catalyst charge. This can be explained by the poisoning effect of sulphur towards palladium. On the other hand, the authors highlighted that the presence of electron-withdrawing substituents at the C3 position decreases the reactivity towards hydrogenation.

Recently Glorius has reported a homogeneous hydrogenation of substituted triazolopyridines **138** in excellent yields and high enantiomeric ratio (*e.r*) by means of Ru NHC complexes to obtain triazolopiperidines **161** (Scheme 54) [97].

4.3.3 Opening Reactions of the Triazole Ring in Triazolopyridines

Triazolopyridine **2** and its derivatives undergo triazole ring-opening reaction with loss of dinitrogen in many different conditions. These compounds tend to afford pyridines in the presence of acids. The first paper about this was published by Boyer



Scheme 55 Triazole ring-opening reaction with organic acids

and Wolford in 1958. In their study [104], with carboxylic acids at high temperature, the triazole ring degrades with loss of dinitrogen to provide pyridine esters **162** in moderate yields (Scheme 55).

Jones performed an exhaustive and methodological study [105] about the ring-opening reaction with loss of nitrogen molecule with electrophiles like sulphuric acid, acetic acid, halogens (Cl_2 and Br_2) and selenium dioxide (Table 1).

Reaction with bromine and iodine has also described with compound **163**, giving the formation of the corresponding derivatives **164** and **165** [106] (Scheme 56).

Abarca and Ballesteros also studied the ring-opening reaction of triazolopyridine dienic derivatives **166** and **167** in sulphuric acid, acetic acid and selenium (IV) oxide [99] (Scheme 57). These reactions afford the corresponding alcohols **168** and **169** with sulphuric acid; esters **170** and **171** were obtained with acetic acid. With selenium oxide, however, compound **166** does not react, but **167** gives the corresponding ketone **172**.

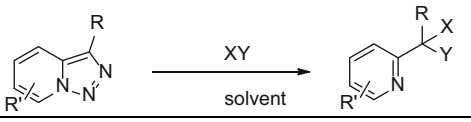
As it has been noted before, the triazolopyridines can be in equilibrium with an opened form. This form is a diazo compound; thus reactivity similar to diazo compounds should be observed. This behaviour was initially reported by Wentrup in the 1960s–1970s [91]. Flash vacuum thermolysis of compound **173** affords complex compound **174** that is explained by means of the chemistry of diazo form **175** (Wolff rearrangement) [107] (Scheme 58).

Other reaction reported in the literature by Wentrup is the thermal treatment of **2** in presence of fumaronitrile, leading to cyclopropane **176**. This result can be explained by the formation of a carbene intermediate from the diazo derivative [108], (Scheme 59).

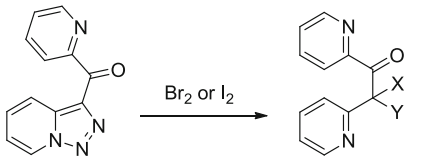
Abarca and Ballesteros also reported of the generation of carbenes in the course of their study on the thermal decomposition of 7-bromotriazolopyridine **177** [109]. The carbene intermediate can be generated by loss of dinitrogen in the corresponding diazo compound before electrophile attack, as indicated in Scheme 59. In this work traces of compound **178** were isolated, and cyclopropanes **179** and **180** were also formed probably by "cyclopropanation" between the carbene and **178** (Scheme 60).

More recently Gevorgyan reported the reaction of 7-chlorotriazolopyridine **181** with rhodium acetate and alkynes or nitriles to afford indolizines **182** and imidazopyridines **183**. Its formation is explained through a diazo intermediate [110] (Scheme 61).

Table 1 Systematic study of the ring-opening reaction in different conditions



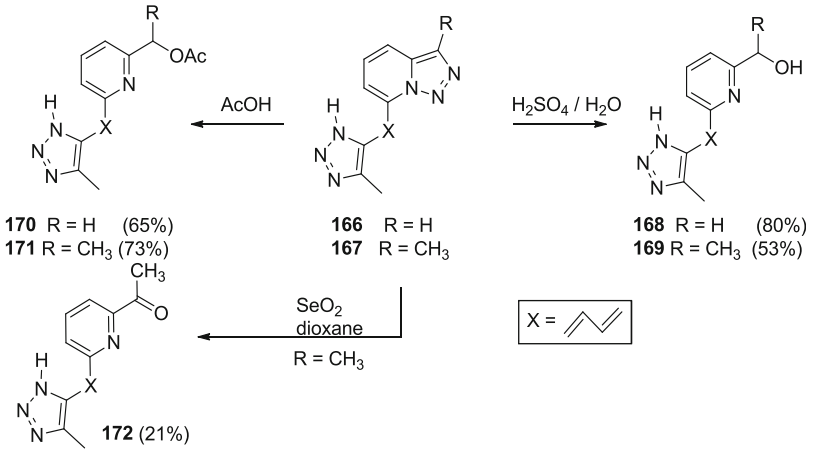
Entry	R	R′	XY	Solvent	X	Y	Yield (%)
1	H	H	Cl_2	CCl_4	Cl	Cl	67
2	H	H	Br_2	CCl_4	Br	Br	75
3	H	H	NBS	CCl_4	Br	Br	79
4	H	H	Hg(OAc)	AcOH	HgOAc	OAc	60
5	H	5–OCH_3	Br_2	CH_2Cl_2	Br	Br	30
6	H	5-OCH_3	H_2SO_4	H_2O	H	OH	78
7	H	7-(*p*-$MeOC_6H_4CHOH$)	Br_2	CH_2Cl_2	Br	Br	98
8	H	7-$(C_6H_5)_2CHOH$	Br_2	CH_2Cl_2	Br	Br	76
9	H	H	H_2SO_4	H_2O	H	OH	78
10	H	H	AcOH	AcOH	H	OAc	70
11	H	H	SeO_2	Dioxane	=O Ketone		89
12	CH_3	H	H_2SO_4	H_2O	H	OH	69
13	CH_3	H	AcOH	AcOH	H	OAc	98
14	CH_3	H	SeO_2	Chlorobenzene	=O Ketone		84
15	H	4-CH_3	Br_2	CCl_4	Br	Br	58
16	H	5-CH_3	Br_2	CH_2Cl_2	Br	Br	30
17	H	5-CH_3	H_2SO_4	H_2O	H	OH	80
18	H	6-CH_3	AcOH	AcOH	H	OAc	98
19	H	7-CH_3	SeO_2	Dioxane	=O Ketone		<10
20	H	7-CH_3	SeO_2	Xylene	=O Ketone		100
21	$CONEt_2$	H	H_2SO_4	H_2O	H	OH	70
22	$CONEt_2$	H	AcOH	AcOH	H	OAc	73
23	$CONEt_2$	H	SeO_2	Xylene	=O Ketone		80
24	H	7-CH_2OH	SeO_2	Xylene	=O Ketone		50
25	H	7-O CH_3	H_2SO_4	H_2O	H	OH	80
26	H	7-O CH_3	SeO_2	Chlorobenzene	=O Ketone		60
27	CH_3	7-(*p*-anysol)	SeO_2	Chlorobenzene	=O Ketone		70
28	CH_3	7-piperidinyl	AcOH	AcOH	H	OAc	75



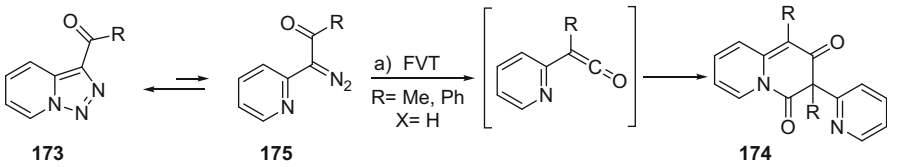
163

164 X = Y = Br
165 X = Y = I

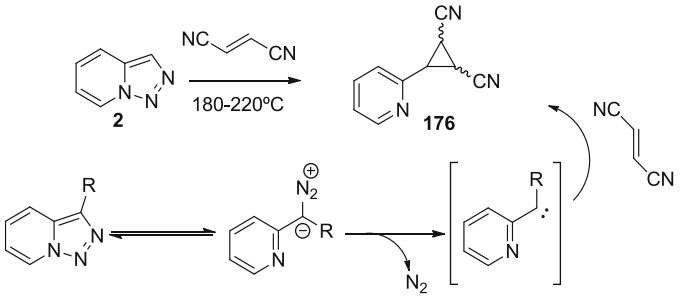
Scheme 56 Triazole ring-opening reaction with bromine or iodine



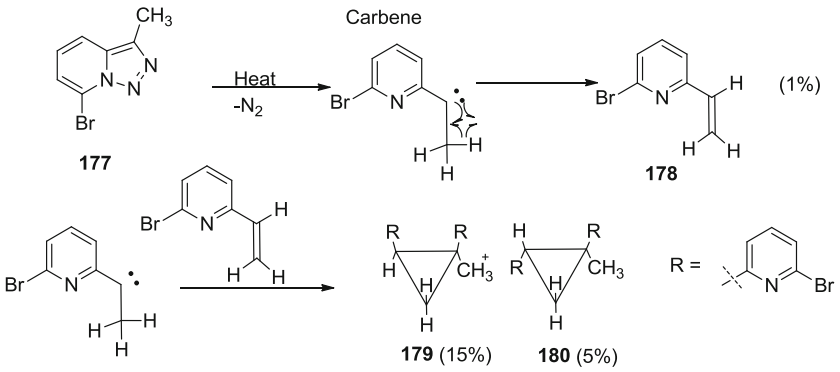
Scheme 57 Triazole ring-opening reactions of **166** and **167**



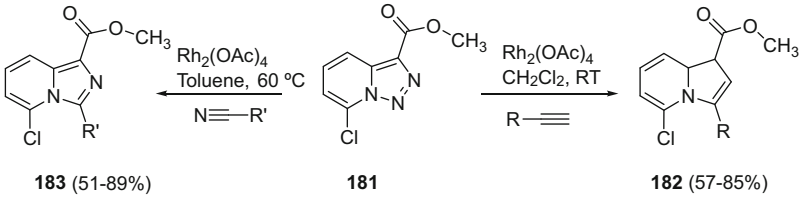
Scheme 58 Diazo compound behaviour of **173**



Scheme 59 Cyclopropane formation from **2**



Scheme 60 Cyclopropane formation from **177**

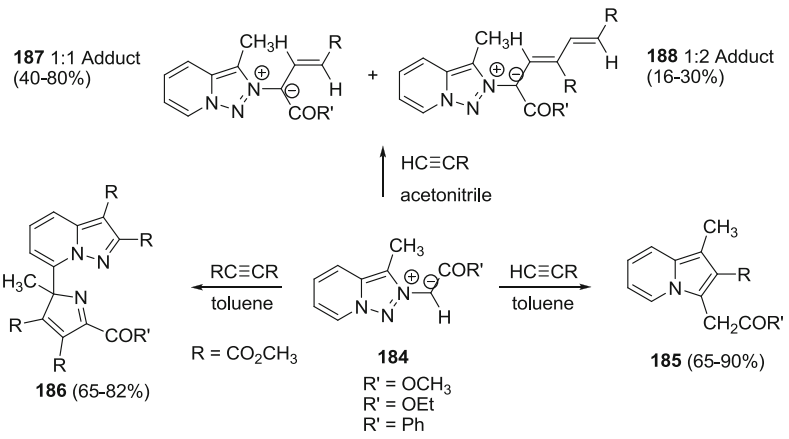


Scheme 61 Rhodium mediated **181** decomposition through a diazo intermediate

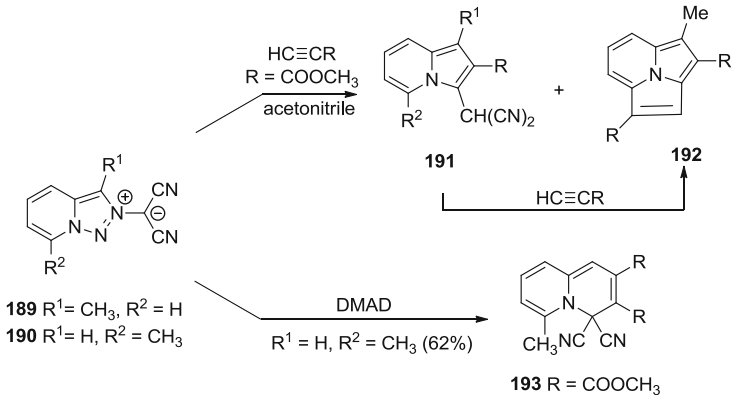
There are also some examples of triazole opening reaction with triazolopyridinium ylides. Initially, these experiments were performed with [1,2,3]triazolo[1,5-*a*]pyridinium ylide **184** and acetylenic esters [111–114]. The authors found out that these reactions were extremely solvent polarity dependent and the results could vary according to the acetylenic ester (Scheme 62).

When the synthesis was performed in toluene with methyl propiolate, indolizines **185** were obtained, providing a new way to synthesize this heterocycle [113]. When dimethyl acetylenedicarboxylate (DMAD) was used as dipolarophile in toluene, pyrazolo[1,5-*a*]pyridines **186** were obtained after the addition of two molecules of DMAD. In both cases cleavage of the N^2–N^3 bond occurred, leading to the triazole ring opening, and a 1,3-dipolar cycloaddition was observed. The structure of these compounds was confirmed by single X-ray [112]. However, when acetonitrile was used as solvent, the reaction of the ylides **184** with methyl propiolate gives in each case two products characterized as 1:1 **187** and 1:2 **188** adducts, with ylide structure and without triazole ring opening.

2-Dicyanomethyl-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridinium ylide **189** and 2-dicyanomethyl-7-methyl-[1,2,3]triazolo[1,5-*a*]pyridinium ylide **190** were also studied. The reactivity of these compounds towards acetylenic esters is different depending on the dipolarophile [115], but always produces the triazole ring-opening reaction with loss of nitrogen. 3-Methylated (R^1=CH_3, R^2=H) ylide **189** reacts with methyl propiolate in acetonitrile as solvent to provide indolizine



Scheme 62 Triazole ring-opening reaction of ylide **184**



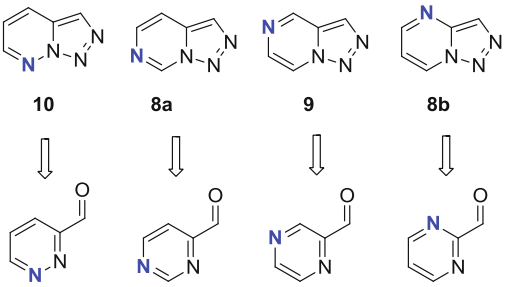
Scheme 63 Ring-opening reactions of **189** and **190**

191 and cyclizine **192**. The reaction performed with the 7-methylated (R^1=H, R^2=CH_3) ylide **190** provided exclusively the indolizine. 7-Methylated ylide reacted with DMAD to afford 4*H*-4,4-dicyan-2,3-dimethoxycarbonyl-6-methylquinolizine **193** (Scheme 63).

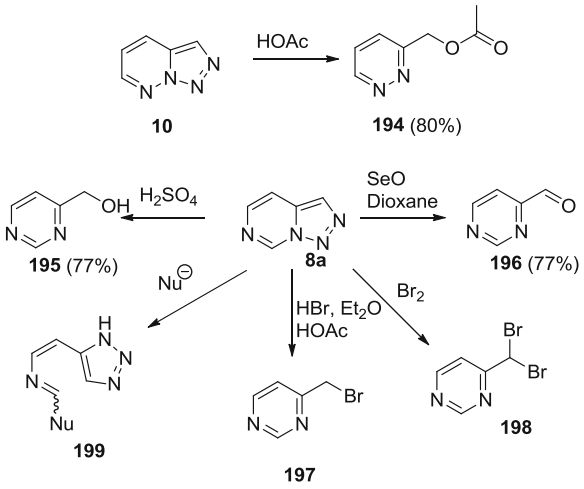
4.4 Reactivity of Triazolodiazines

Triazolodiazines represent a less explored family. These compounds are depicted in Scheme 64. In all cases those compounds are obtained by hydrazine/oxidation methodology of the corresponding aldehyde [70, 73]. Despite of not being

Scheme 64 Four nitrogen atom-containing molecules



Scheme 65 Ring-opening reactions on **10** and **8a**

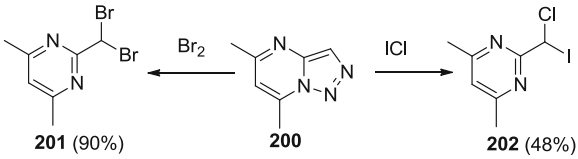


extensively studied from a chemical point of view, many of these structures are evaluated in pharmacological studies.

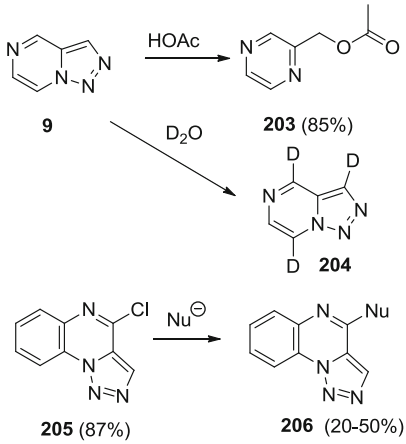
The presence of the two nitrogen atoms in the six-membered ring induces instability of these systems which are, contrary to almost all of the previous examples, water sensitive. For compound **10** only ring-opening reaction with acetic acid has been reported yielding to acetate **194** [73]. Triazolo[1,5-*c*]pyrimidine **8a** has been extensively studied by Abarca and Jones and behaves similar to triazolopyridine **2** [116]. The compound **8a** of acid leads to a ring-opening reaction affording alcohol **195** with H_2SO_4 and ketone **196** with selenium dioxide. Monohalogenation can be achieved with HBr, leading to compound **197**. Jones reported also on the dehalogenation of this molecule with molecular bromine, affording compound **198** [80]. However, in these reactions the presence of a large amount of side products is reported. This has been associated to the instability of these compounds. Indeed, the presence of nucleophiles induces the ring opening of the pyrimidine moiety, leading to triazoles **199** [116] (Scheme 65).

The reactivity of compound **8b** has not been studied; it is only known that dimethyl derivative **200** undergoes ring-opening reaction with bromine, leading

Scheme 66 Reactivity of **200**



Scheme 67 Reactivity of **9** and **205**



to compound **201**. In a similar way, when **200** is treated with ICl, halogenated compound **202** is obtained in moderate yield [117] (Scheme 66).

The reaction of pyrazine **9** with acetic acid has also been reported yielding compound **203** in good yield [73]. Despite not being deeply studied, Wentrup reported on the deuteration of this compound with D_2O [91], being able to introduce 3 deuterium atoms (**204**). Of this particular structure, more conjugated analogues, like compound **205**, have been reported [118]. Compound **205** reacts with nucleophiles in moderate yields affording **206** [119] (Scheme 67).

5 Applications of Fused 1,2,3-Triazoles

5.1 Benzotriazole Applications

Benzotriazoles resist hot sulphuric acid or melted KOH treatment; even strong oxidants or reductants ($KMnO_4$, $LiAlH_4$) do not affect this system. Taking into consideration that benzotriazole is relatively cheap and stable up to 400°C, several applications have been reported in different fields.

5.1.1 Organic Synthesis

Katritzky is the main researcher on the application of these compounds in organic synthesis [32]. Several reviews, patents and research articles are reported in the literature just concerning its application in organic synthesis [120–122]. The key point of benzotriazole is that it can be easily introduced into different molecules by means of different reactions. Substitution [32], addition or even three-component reactions had been reported for this purpose. Once **Bt** is attached to a molecule, it can be used under different approaches: as leaving group [123, 124], *ortho*-directing group [125], as cation stabilizer [67], radical precursor [126], etc. Today more than 1,000 publications employ benzotriazoles as a synthetic tool. Schematic examples about the use of **Bt** in organic synthesis are shown in Fig. 6.

In this field it is important to stress the utility of some benzotriazoles in peptide synthesis [127] (Fig. 7). The compounds used in this synthesis are derivatives of hydroxy triazoles **18** [15, 128]. Compounds **207**, **208** and **209** are commercially available and largely employed for amide bond formation with a high degree of racemization suppression [129–131].

5.1.2 Medicinal Applications

The benzotriazole structure (5+6 aromatic rings) displays similarities with the natural bases adenine and guanine (Fig. 8). For this reason it is not surprising that it is considered as a preferential scaffold in pharmaceutical chemistry as long as it allows subsequent derivatization. In particular pyrimidine derivatives tend to be employed [132–134].

5.1.3 Coordination Chemistry and Metal Organic Frameworks

Benzotriazole and its derivatives had also been applied in coordination chemistry and metal organic frameworks [135–138], in particular, carboxylic derivatives **73** [139] or even more complex molecules **214** [137] (Fig. 9). The particular arrangement of the nitrogen atoms allows coordination with different angles; thus coordination polymers and metal organic frameworks have been obtained. Although this is not the most common nitrogenated ligand employed, its reports reveal particular features that are difficult to obtain with other compounds. Furthermore, these structures are stable.

5.1.4 Photostabilizers, Photographic Application and Sensors

Hydroxyphenylbenzotriazole **215** [140, 141] has been used as photostabilizer of polymers. With the addition of this compound, their stability towards light

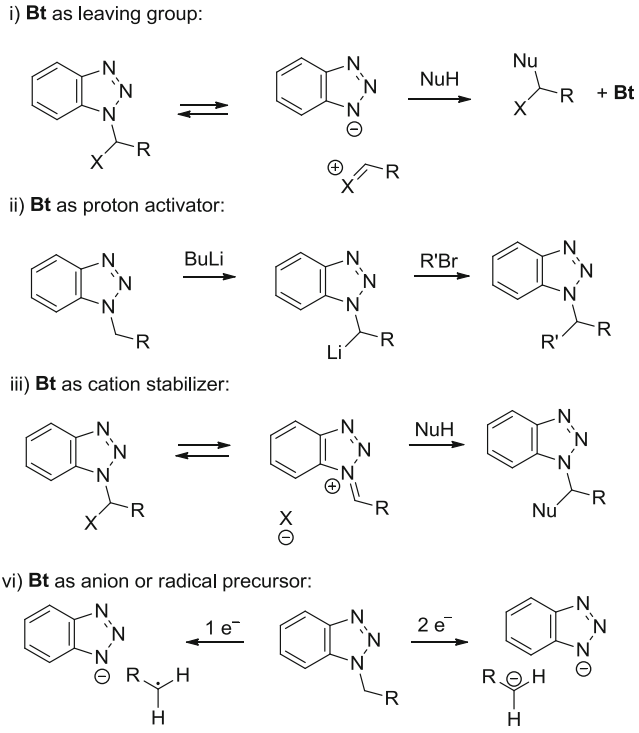


Fig. 6 Benzotriazole in organic synthesis

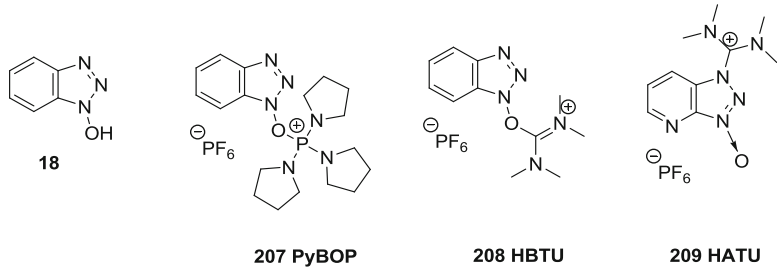


Fig. 7 Benzotriazole-based peptide coupling reagents

increases. In a similar way, compound **216** is employed as a fog inhibitor in the processing of silver photographic material [142] (Fig. 10). The particular facility towards the formation of benzotriazole **218** from the ortho-diamine **217** has been employed as a switch on sensor for NO. The initial molecule presents almost zero emission, but when NO is in the atmosphere, the formation of the benzotriazole ring in **218** leads to a strong emission [143].

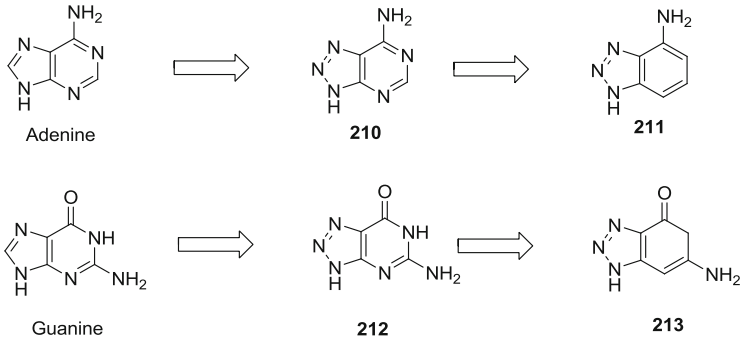


Fig. 8 Analogy between benzotriazole **Bt** and pyrimidinic bases

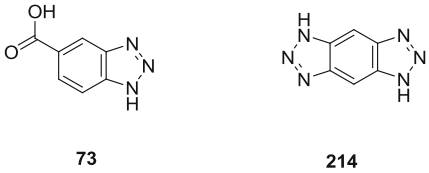


Fig. 9 Benzotriazole-based ligands employed for the preparation of metal organic frameworks

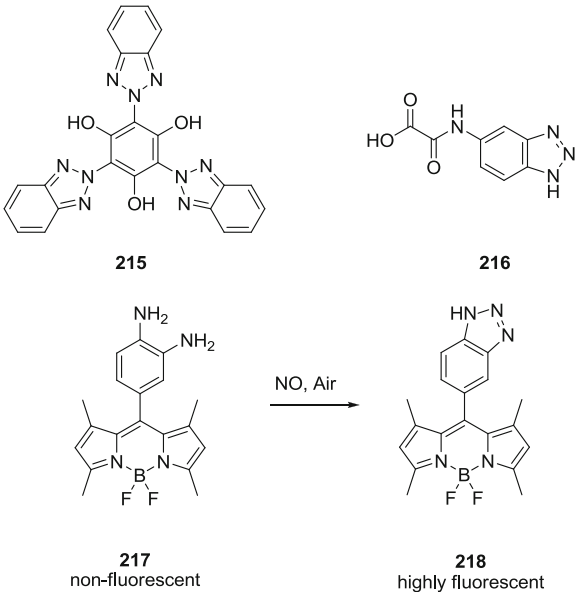


Fig. 10 Benzotriazole-based compounds as photostabilizers and sensors

5.1.5 Copper Conservation

Benzotriazole has been reported as a copper corrosion inhibitor. Indeed copper and copper alloys are treated with a benzotriazole solution [144, 145]. This method has also been applied for brass, steel, cast iron or aluminium to prevent corrosion [146].

5.2 Applications of Triazolopyridines with Nitrogen as Bridgehead Atom

Their reactivity has been shown to be a powerful tool to get access to extremely important compounds in many different yields.

5.2.1 Organic Synthesis

Synthesis of 2,6-Asymmetrically Disubstituted Pyridines and Quinolines

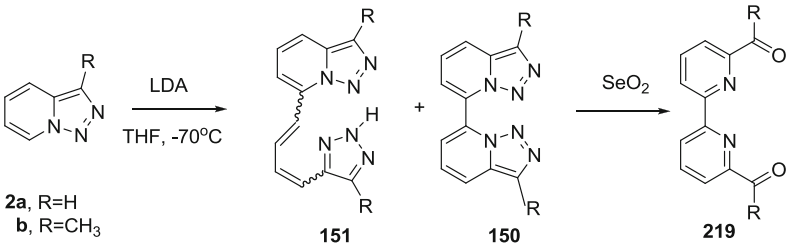
The triazole ring has been employed as an activating and protecting group of 2 aldehyde/ketone pyridines or quinolone. The combination of the triazole ring formation, lithiation, trapping with electrophiles and ring-opening reactions is a powerful strategy to prepare 2,6-asymmetrically disubstituted pyridines or 2,8-asymmetrically disubstituted quinolines. These kinds of molecules are difficult to obtain by other procedures. However, by means of the triazolopyridine chemistry, several compounds have been obtained [80, 82, 100, 147].

A New Route to 2,2′-Bipyridines

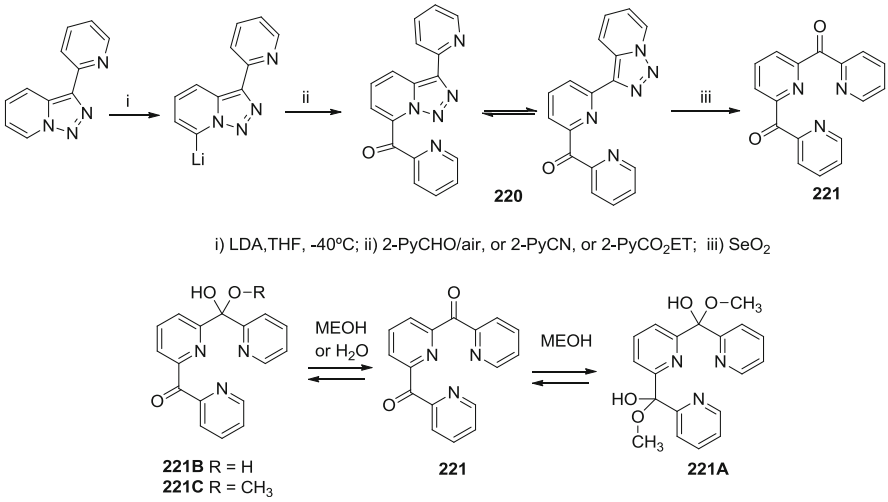
As has been described, the usual reaction between triazolopyridines and lithium reagents at −40°C gives a 7-lithio derivative that can be trapped by electrophiles [80, 147]. This reaction is temperature dependent, and at −70°C in THF as solvent, a new reaction occurs, giving two products, the 7,7′-bitriazolopyridine **150** and the butadiene **151** [82] (see Scheme 48). Like all simple triazolopyridines, bitriazolo-pyridines **150** react with electrophiles to produce 2,2′-bipyridines **219** (Scheme 68). With these reactions, a general route to 2,2′-bipyridines has been discovered with a variety of substituents in the 6 and 6′ positions [82]. These compounds have use in supramolecular chemistry because of their great complexing power for metal ions, and, in particular, 2,2′-disubstituted-6,6′-bipyridines are useful building blocks for oligo-bipyridines, which spontaneously form helical metal complexes [148].

Synthesis of Pyridylcarbonylpyridines

Pyridyl carbonyl pyridyl triazolopyridine **220** is obtained from 3-(2-pyridyl)-triazolopyridine by the typical reaction of lithiation and trapping the lithio



Scheme 68 New synthesis of bipyridines



Scheme 69 Synthesis of bis-(pyridylcarbonyl)pyridine

derivative by 2-PyCHO/air or 2-$PyCO_2Et$ or 2-PyCN. Its triazole ring-opening reaction with SeO_2 formed a bis-pyridylcarbonyl-pyridine **221** [149] (Scheme 69). This compound undergoes hydration or reaction with methanol, leading to compounds **221A**, **221B** and **221C**.

The discovery of this synthesis of compound **221**, using triazolopyridines as building blocks, has been the beginning of a new study looking for new polynitrogenated potential helicating ligands or coordination supramolecular compounds from triazolopyridines with potential magnetic or photochemical properties [150]. The aim of this study was the synthesis of oligopyridylcarbonylpyridines **222** and related compounds. In Fig. 11 there are some examples of the synthesized compounds with this methodology in different conditions [149–152].

Pyridylcarbonylpyridine (PyCOPyCOPy) **221** is a ligand very often used in coordination chemistry to form clusters or helicates with different structures and very interesting magnetic properties. Figure 12 shows the molecular formula of some examples synthesized from **221** and with application in these fields.

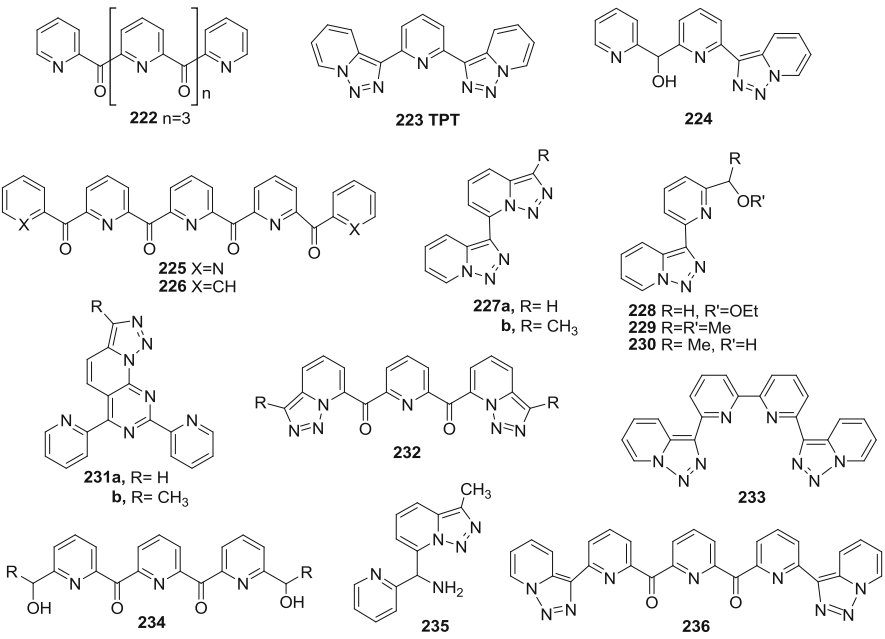


Fig. 11 Oligopyridylcarbonylpyridines and related compounds

Complexes with silver **237** and **238** and copper **239** and **240** [153] and with iron **241**–**244** [154], the first icosanuclear Co cluster exhibiting superparamagnetic relaxation **245** [155], an *S*-shaped pentanuclear Cu^{II} cluster **246** [156], clusters of Cu^{II}_4 **247** and Co^{II}_4 **248** with ferromagnetic interactions [157], a Ni^{II}_5 cluster **249** with a $S = 5$ ground state exhibiting slow magnetic relaxation and a high spin-reversal barrier have been described [158]; complexes **250**–**252** (Cu^{II}_4, Co^{II}_4 and Ni^{II}_6) are also synthesized in the presence of sodium azide with very interesting ferromagnetic intramolecular interactions [159]. Structural, magnetic and spectroscopic studies have been done with **253** (Fe^{III}) [160]. Isomorphous replacement of M^{II} ions in M^{II}-Gd^{II} dimers **254** (M^{II}=Cu^{II} (**a**), Mn^{II} (**b**), Ni^{II} (**c**), Co^{II} (**d**), Zn^{II} (**e**) [161], Fe^{II} (**f**) [162]) has been studied; magnetic susceptibility measures indicate a ferromagnetic interaction for (**a**), antiferromagnetic for (**b**–**e**) and weakly ferromagnetic for (**f**).

There is a second-generation family of ligands derived from metal ion-assisted reactivity of di-2,6-(2-pyridylcarbonyl)pyridine **221**. A $Mn^{II/III}_4$ rhombus was synthesized by nucleophilic attack of the carbanion $^{-}CH_2COCH_3$ at the carbonyl carbon atoms of (py)CO(py)CO(py), in the presence of Mn^{n+} ions under basic conditions; the cationic cluster $[Mn_4(OH)_2(L)_2(H_2O)_2](ClO_4)_4$ **255**, where L^{2-} is the (py)C(CH_2COCH_3)(O^{-})(py)C(CH_2COCH_3)(O^{-})(py) dianion, was synthesized and characterized [163]. Complex **255** is antiferromagnetically coupled with an unusual $S = 2$ ground state resulting from spin frustration effects within the triangular Mn_3 subunits of the cluster.

237 $[\{Ag(\mathbf{121})\}(ClO_4)]_\infty$
238 $[\{Ag(\mathbf{121})(NO_3)\}\cdot CH_3CN]_\infty$
239 $[Cu(\mathbf{121B})]_2(BF_4)_2\cdot 2H_2O$
240 $[Cu(\mathbf{121C})]_2(CLO_4)_2\cdot 2H_2O$
241 $[Fe_3(\mathbf{121A})_2(\mu\text{-}OCH_3)_2Cl_2]\ (FeCl_4)\cdot H_2O$
242 $Fe(\mathbf{121B})Cl_2\cdot H_2O$
243 $Fe(\mathbf{121B})Cl_2\cdot THF$
244 $Fe(\mathbf{121C})Cl_2\cdot THF$
245 $[Co_{20}\ (\mu_3\text{-}OH)_6(O_2CMe)_4(\mu_2\text{-}O_2CMe)_{12}(\mu_3\text{-}O_2CMe)_6(HL)_4(DMF)_2]\cdot 2H_2O\cdot 1.6DMF$, where HL^{3-} = pyC(O)(OH)pyCO$_2$py^{3-}.
246 $[Cu_5(O_2CMe)_6\{pyC(O)(OH)\ pyC(O)(OH)py\}_2]$
247 $[Cu_4\{py(C(O)_2pyC(O)(OEt)py\}(O_2CMe)_5\,(EtOH)_2]$
248 $[Co_4\ \{py(C(O)(OMe)pyC(O)(OMe)py\}_2(O_2CMe)_2(N_3)_2]$
249 $[Ni_5\{pyCOpyC(O)(OMe)py\}_2(O_2CMe)_4(N_3)_4(MeOH)_2]\cdot 2.6MeOH\cdot 2.6H_2O$
250 $[Cu_4(N_3)_2\{pyC(OMe)(O)pyC(OMe)(O)py\}_2(MeOH)_2]\ (ClO_4)\cdot 2MeOH$
251 $[Co_4(N_3)_2(NO_3)\ \{pyC(OMe)(O)pyC(OMe)\ (O)py\}_2]\cdot 0.5MeOH$
252 $[Ni_6(CO_3)(N_3)_6\{pyCOpyC(O)(OMe)py\}_3(MeOH)_2(H_2O)]$-$[Ni_6(CO_3)(N_3)_6\{pyCOpyC(O)(OMe)py\}_3(MeOH)_3](ClO_4)_2\cdot 1.8MeOH$
253 $[Fe2\{pyCO(OMe)pyCO(OMe)py\}_2(MeO)_2](ClO_4)_2.MeOH$
254 $[M^{II}Gd^{II}\{pyCO(OEt)pyC(OH)(OEt)py\}_3(ClO_4)_2.EtOH$ [M^{II} = Cu^{II} (**a**), Mn^{II} (**b**), Ni^{II} (**c**), Co^{II} (**d**), Zn^{II} (**e**), Fe^{II} (**f**).
255 $[Mn_4(OH)_2(L)_2(H_2O)_2](ClO_4)_4$, where L^{2-} is the pyC(CH_2COCH_3)(O^-) pyC(CH_2COCH_3)(O^-)py dianion,

Fig. 12 Molecular formulas of complexes **237–255**

5.2.2 Triazolopyridines as Building Blocks in Supramolecular Chemistry

All triazolopyridines have interesting ligand properties to form polynuclear complexes with different metal ions. These molecules may also have the ability to complex other cationic, neutral or anionic species of biomedical or environmental relevance to form supramolecular compounds, which may have interesting magnetic or fluorescent properties, and could act as luminescent molecular chemosensors.

The following are the preliminary experiments accomplished in supramolecular chemistry, with some of the compounds described in this chapter.

X-ray single-crystal studies and magnetic, photomagnetic and colorimetric measurements of a series of iron(II)-3-(2-pyridyl)-triazolopyridine (**TP**) complexes $[Fe(\mathbf{TP})_3](BF_4)_2$ **256**, $[Fe(\mathbf{TP})_2](NCS)_2\cdot 2CHCl_3$ **257**, $[Fe(\mathbf{TP})_2](NCS)_2\cdot H_2O$ **258** and $[Fe(\mathbf{TP})_2](NCSe)_2$ **259** have been studied and have been characterized as new mononuclear spin crossover compounds [164].

A molecular chemosensor for metal ions, anions and amino acids has been described, the Zn(II) complex of compound **231b** [165]. This system permits the

direct detection of anions without using competitive reactions or dyes. One of the most interesting aspects is the discrimination between nitrite and nitrate anions. The ability of the Zn(II) complex to interact and quantify amino acids has been explored for L-glutamate and L-aspartate.

Triazolopyridine **223** (**TPT**) (Fig. 11) possessing fluorescent properties has been studied as molecular chemosensor for Zn(II), nitrite and cyanide anions. The fluorescence behaviour of **TPT** was checked in the presence of the divalent transition metal ions Co^{2+}, Ni^{2+} and Cu^{2+} and of the post-transition metal ions Zn^{2+}, Cd^{2+} and Pb^{2+}. Zn(**TPT**)$^{2+}$ 1:1 complex in solution was checked with different monovalent anions (F^-, Cl^-, Br^-, I^-, CN^-, SCN^-, NO_2^-, NO_3^-). In all cases, quenching of the emission was produced. Complex Zn(**TPT**)$^{2+}$ is a sensor for anions specially cyanide and nitrite [166].

A tetranuclear complex of Cu(II) with compound **110B** (R = 2-PyCO-) with magnetic properties has been described; the structure shows a cubane tetrameric complex of copper(II) with the hemiacetalate of the 2-pyridyl-[1,2,3]triazolo[1,5-*a*] pyrid-7-ylmethanone and a S_4 symmetry. The Cu_4O_4 core corresponds to a distorted cubane [167]. The magnetic behaviour of the complex is typical for compounds displaying significant intramolecular antiferromagnetic coupling.

5.2.3 Pharmacological Studies

There are no [1,2,3]triazolo[1,5-*a*]pyridines used as pharmaceutical compounds. This section reports preliminary studies of the pharmacological interest of some triazolopyridines.

Synthesis and Evaluation of 7-Arylhydroxymethyltriazolopyridines as Potential Cardiovascular Agents

7-Arylhydroxymethyltriazolopyridines might be considered as structural analogues of benzyltetrahydroisoquinoline and bisbenzyltetrahydroisoquinoline alkaloids that have the ability to block calcium channels and/or antagonize α_1-adrenoreceptors, and may have applications in the treatment of cardiovascular disorders. A series of these triazolopyridine derivatives **260** have been synthesized (Fig. 13), and the activity as relaxants of vascular smooth muscle has been tested in isolated aortic rings precontracted by noradrenaline looking for activity as antagonists of the α_1-adrenoreceptors present in this tissue and stimulated by noradrenaline. The lack of a relaxant action excludes the possibility that these compounds act as α_1-adrenoreceptors antagonists.

Addition of depolarizing solution to the aortic ring induces a sustained contractile response in the absence of endothelium. In these conditions, opening of voltage-sensitive calcium channels and calcium entry promotes this contractile response. Subsequent addition of these compounds in cumulative concentrations, once the contractile plateau induce by depolarizing solution had been reached, did

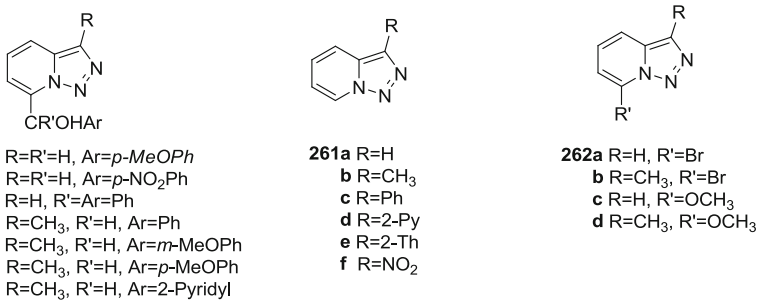


Fig. 13 Triazolopyridines with potential pharmacological activity tested

not modify the tone, thus suggesting that none of the compounds tested can block calcium entry through voltage-dependent calcium channels [168].

Biological Evaluation of [1,2,3]Triazolo[1,5-*a*]pyridines as New Neural Nitric Oxide Synthase Inhibitors

The importance of nitric oxide (NO) as a biological messenger in numerous physiological processes has been demonstrated to a growing extent over the last decades. This molecule is indeed involved in various fundamental functions such as neurotransmission [169], blood pressure and blood flow regulation [170] and platelet aggregation and inflammation [171]. Overproduction of nitric oxide plays a role in a variety of disorders. Nitric oxide is synthesized in several cell types from L-arginine by different isoforms of nitric oxide synthase (NOS).

A series of inhibitors of this enzyme is constituted by heterocycles such as substituted indazoles or imidazoles. The 3- or 7-substituted indazoles are potent nNOS inhibitors [172, 173]. [1,2,3]Triazolo[1,5-*a*] pyridines can be considered as aza-analogues of indazoles, and some studies have been done to test the possibility that the triazolopyridines can be (NO) synthase inhibitors. A number of 3- and 7-substituted triazolopyridines **261** and **262** (Fig. 13) have been synthesized and have been tested [174]. The triazolopyridines evaluated have small activity, and the results indicate that a NH group is necessary for the interaction with the NOS.

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