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Stéphanie Norsikian. Bicyclic 5-5 Systems With One Bridgehead (Ring Junction) Nitrogen Atom: Four Extra 1-Heteroatoms 3:1 (2007–2018). Reference Module in Chemistry, Molecular Sciences and Chemical Engineering, Elsevier, 2020, 10.1016/B978-0-12-818655-8.00031-7 . hal-03038263

HAL Id: hal-03038263

<https://hal.science/hal-03038263>

Submitted on 3 Dec 2020

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Bicyclic 5-5 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Four Extra 1-Heteroatoms 3:1 (2007-2018).

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Introduction	1
I. Theoretical methods	2
1. Imidazole, benzimidazoles, pyrazole and indazole series	2
2. Azidothiazole system	2
3. Oxazole compounds	3
II. Synthesis, reactivity and applications of 5-5 bicyclic Ring systems	4
References	9

Abstract

The main results concerning the studies of bicyclic 5-5 systems with one bridgehead (ring junction) nitrogen atom: four extra 1-heteroatoms 3:1 published in the period 2007 to 2018 are discussed in this review.

Keywords

Bicyclic 5-5 systems, Heterocycles, Azido/tetrazole equilibrium, Theoretical studies, Azidation, Cycloaddition, Applications, Synthesis, Tautomerism, Reactivity.

Introduction

This review summarizes the main developments concerning fused bicyclic 5-5 ring systems with one bridgehead nitrogen atom and four additional heteroatoms as depicted in Figure 1. During these last twelve years, a lot of theoretical studies were carried out to better understand azido-tetrazole isomerism and to predict the cyclic or azid form of these compounds. Progress has also been made in their preparation and these products can generally find applications in the medical or industrial field.

Figure 1. Overview of bicyclic 5-5 systems depicted in this review

I. Theoretical methods

1. Imidazole, benzimidazoles, pyrazole and indazole series

In 2010, Alkorta *et al* studied the azido-tetrazole tautomerism in imidazole, benzimidazoles, pyrazole and indazole series for neutral molecules and the corresponding azolates. (1) The energies associated with these molecules were calculated as well as transitions states using two different levels (B3LYP/6-31G(d) and G3B3). Determination of NICS(1) values and AIM analysis were also carried out.

For the *E/Z* isomerism of azole, it was found that conformation **LP1** is preferred to **NH1** by 19.8 kJ mol⁻¹ and **LP2** is preferred to **CH1** by 8.7 kJ mol⁻¹ (**Scheme 1**). A small effect (1.1 kJ mol⁻¹) was observed for the case of indazole and for the azolate, the difference is reduced to 3.1 kJ mol⁻¹ in average for all the cases. These conformational preferences can be explained by the attractive LP/H interactions in **LP1** and **LP2** and by the LP/LP repulsions (in red) in **NH1** and **CH1**. The activation energy for the azido/tetrazole process was not determined because these compounds exist as azides. However, deprotonation has a large effect on the equilibrium and corresponds to the stabilization of the tetrazole adducts (73 kJ mol⁻¹ in average).

Scheme 1

For 2-azido-1*H*-imidazole, the effect of CuCl on the azido/tetrazole isomerism was carried out using DFT calculations (B3LYP/6-31G(d), B3LYP/6-311++G(d,p), and CBS-QB3). (2) The results showed that the presence of a Cu-catalyst allows tetrazoles to react like azide.

2. Azidothiazole system

In 2009, Abu-Eittah and coll. explored the electronic structure of azidothiazole that favors the exclusive formation of the tetrazolo-derivative using B3LYP/6-311G** level of theory. (3)

The factors which lead preferentially to ring closure of azidothiazole to thiazolo-tetrazole start with the electronic structure of the thiazole ring. The valence atomic orbitals of S-atom in the thiazole ring are not hybridized, i.e the S-atom is bonded in the thiazole ring while the atom is in its ground state. This leads to a bond angle C2-S1-C5 of 87.88 that push-up of the azide group. Moreover, a low rotational barrier of the azido group in the *trans-cis* isomerization was found (6.16 kcal mol⁻¹) as well as a significant increase of the dipole moment of the tetrazole isomer. The low values of the energies of the transition states favor cyclization (**Scheme 2**).

Scheme 2

The effect of the type and position of substituents in the thiazole ring on the azido-tetrazole equilibrium was also theoretically investigated (B3LYP/6-311G**) (**Scheme 3**). With electron-donating substituents (R and $R' = \text{NH}_2, \text{OH}$), the equilibrium is shifted to the tetrazole isomer and in some cases, the azide cannot be isolated. In the contrary, with electron withdrawing substituent (R and $R' = \text{NO}_2, \text{CN}$), the equilibrium is shifted to the azide side and the tetrazole isomer is not isolated in some cases. Moreover, the effect of the substituent is more important at the C5 position (near to the S atom) than to the C4 (near to the N atom). (4)

Scheme 3

DFT studies (B3LYP/6-311+G(d,p)) were also performed in the case of azidobenzothiazole derivatives (**Scheme 4**). (5) For 2-azidobenzothiazole, at room temperature, in the gas-phase there is a small difference of $3.09 \text{ kcal mol}^{-1}$ between the *trans* and *cis* isomer, the *cis* being the more stable. The azide-tetrazole isomerism was found to be initiated by a π -atomic orbital overlap process rather than by electrostatic attraction process. The activation energy for the transformation reaction of azidobenzothiazole to tetrazole was found to be $23.32 \text{ kcal mol}^{-1}$ for 2-azidobenzothiazole. The presence of different substituents in different positions of the six membered ring proved to have a weak effect on the values of this activation energy.

Scheme 4

3. Oxazole compounds

A comparative study using DFT calculations at B3LYP/6-311+G(d,p) in gas phase and solution phase was later carried out to investigate the azido-tetrazole ring chain isomerism equilibrium as a function of the nature of X (NH, O, S) in the azole system (**Scheme 5**). (6)

By increasing the electronegativity of X atom in the 1,3-azole ring, the relative energies are increased and the azido isomers are more stabilized. The relative stability of the tetrazole isomers can be maximized to a great extent by increasing the polarity of solvent, which can be explained by the larger dipole moment of the tetrazole adduct. In 2-azido-1,3-oxazole ($X=\text{O}$) and 2-azido-1,3-imidazole ($X=\text{NH}$), the azido-tetrazole isomer equilibrium is shifted to azido isomers side and the equilibrium is shifted to the tetrazole isomer when $X=\text{S}$.

Scheme 5

II. Synthesis, reactivity and applications of 5-5 bicyclic Ring systems

In the last review, various synthetic approaches for the elaboration of 5-5 bicyclic ring systems were described. (7) For examples, these derivatives were previously prepared using photochemical reactions, nucleophilic aromatic substitution or cycloaddition of azides with heteroatom-bonded nitriles.

In the period 2007-2018, the most frequently used method for their preparation involves cyclization process after the incorporation of an azide function.

This latter can be introduced by classical nucleophilic substitution reaction with system bearing halides groups (I (8) or Cl (9)). As example, 1-(4-cyanophenyl)-8-methyl-tetrazolo [4,5':2,3]pyrazolo[4,3c]piridazine **2** was obtained in 71% yield after refluxing chloride **1** with sodium azide in acetic acid for 4 h (**Scheme 6**). (10) In the same manner, starting with the chloropyrazole compound **3**, its reaction with NaN_3 in refluxing butanol affords the tetrazolo derivative **4** in 83% yield (**Scheme 6**). (11)

Scheme 6

2-Benzimidazole **6** was also prepared in 60% yield according to this procedure and this compound was found to have activity against the colon carcinoma cell (HCT) with the IC_{50} of 18.1 $\mu\text{g/mL}$ (**Scheme 7**). (12)

Scheme 7

Another way for introducing the azide group is the reaction of tosyl azide with organometallic reagent such as in the **Scheme 8**. In this case, treatment of **7** with an excess of $n\text{-BuLi}$ and

reaction of the corresponding organolithiated intermediated with TsN_3 allows the production of the monoazide **8** in 38% yield. (13) DMDO's oxidation of the latter results in a single spiroimidazole that undergoes valence tautomerism to the corresponding tetrazole **9**.

Scheme 8

The diazotation reaction is also a conventional method for the incorporation of the azide group.(8) This technique can be carried out on heterocyclic amine followed by subsequent treatment with sodium azide as illustrated in **Scheme 9**. Using 85% phosphoric acid, nitric acid and aqueous sodium nitrite followed by addition of aqueous sodium azide, various benzothiazoles could be synthesized. (9) These compounds, as mixture of tetrazole/azide **11/12**, were further employed in CuAAC chemistry leading efficiently to triazolobenzothiazole derivatives **13**. With 6-nitrobenzothiazolotetrazole that exists exclusively as the tetrazole tautomer, the corresponding triazolobenzothiazole could be obtained in 50% yield. (2)

Scheme 9

The diazotation reaction can be carried out directly from 2-hydrazino heterocyclic derivatives. For example, the hydrazine moiety of **14** was effectively used for the construction of tetrazolo fused systems **15** ($\text{R} = \text{H}, \text{Br}$) after reaction with nitrous acid at room temperature (**Scheme 10**). The obtained compounds were tested for their *in vitro* antibacterial activity and showed good activity against Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*). (14)

Scheme 10

The synthesis of the imidazo[1,2-e]tetrazolone derivative **19** was also performed by nitrosation of 2-hydrazinyl-1H-imidazol-5-one derivative **18** with sodium nitrite and hydrochloric acid at 50 °C (**Scheme 12**). The *in vitro* activity of the obtained compound was screened against various bacteria (*Ershia*, *Staphylococcus*, *Proteus*, *Escherichia coli*, *Salmonella*) and the results showed mild antibacterial activities for this compound. (16) Tetrazol-5-one compounds **21** were prepared in the same way (**Scheme 12**). (17) **21a** (Ar = thienyl) showed antifungal activity (*Aspergillus niger* and *candida albicans*) as well as anti Gram-negative strains (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Salmonella typhimurium*) activities, while **21b** (Ar = 4-Cl-C₆H₄) showed only antifungal activity.

For their use as components in propellants and explosives, the synthesis of *N*-nitroso- **25** and *N*-nitraminotetrazole **26** was investigated (**Scheme 13**). (18) Their preparation starts from the *S*-methyl-isothiuronium hydriodides **22** that reacts with hydrazine to furnish the guanidinium derivative **23**. Treatment with nitrous acid furnished 5-aminotetrazole **24**, which was converted to nitraminotetrazole **26** with acetic acid/nitric acid system or by dehydration of the corresponding nitrate **27** with concentrated sulfuric acid. Nitraminotetrazole **26** can also be obtained in 80% yield from nitrosoamine **25** after treatment with peroxytrifluoroacetic acid.

Scheme 13

The *N*-nitroso- and *N*-nitraminotetrazoles **25** and **26** were fully characterized (IR, Raman, NMR spectroscopies, X-ray diffraction...) and theoretical calculations (B3LYP/6-31G(d,p), NBO analysis) were carried out. For the nitrotetrazole **25**, the NBO analysis showed two significant interactions of the nitrogen lone pair (p-LP(N5)) with the two unoccupied, localized antibonding $\pi^*(\text{C1-N4})$ and $\pi^*(\text{O1-N6})$ orbitals. For *N*-nitrosoamine **25**, N,N rotational barriers with respect to the N-N bonds were calculated and the results showed that the *s-cis* conformation (sp) was favored over the *s-trans* (ap). The rotation barriers were found to be 18 kcal mol⁻¹ for **25** and 9.4 kcal mol⁻¹ for **26**. For *N*-nitraminotetrazoles **26**, the heat of formation, determined experimentally using bomb calorimetry, resulted in positive values (+ 85.2 kcal mol⁻¹) and the calculated detonation velocity (7181 m s⁻¹) was found to reach values of TNT and nitroglycerine.

Another method for the incorporation of the azide group into aromatic ring was also described via copper catalyzed C-H azidation of aniline directed by amino group (**Scheme 14**). (19) The reaction was carried out with aniline **28** in the presence of azidotrimethylsilane and TBHP using a catalytic amount of CuBr in CH₃CN at 30 °C to give a mixture of 1.7/1 of the mono and diazidated derivative in 73% yield. The mono-azidated compound **29** was then further functionalized to access tetrazole **30** by reaction with BrCN as described by Sharpless and Demko in 2001. (20)

Scheme 14

5-5 Bicyclic ring systems can also be constructed from 1,5-disubstituted tetrazoles. 1-Substituted 5-sulfonyltetrazoles were regiospecifically prepared through the intermolecular cycloaddition of organic azide with *p*-toluenesulfonyl cyanide. (21) This strategy was used to synthesize **31**, which was treated in the presence of sodium bicarbonate in dioxane/H₂O at 80 °C (**Scheme 15**). (22) This allowed the formation of the bicyclic system **32** by intramolecular displacement of the *p*-toluenesulfonyl group.

Scheme 15

From mercaptotetrazole **33**, 5,6-dihydrothiazolo[3,2-d]tetrazole **34** was produced in 32% yield using Mitsunobu reaction (**Scheme 16**). (23)

The same strategy was used for the preparation of **40**, which was evaluated as potent anti-inflammatory, analgesic and anti-ulcer agent. (25)

$$\begin{array}{c}
 \text{RO}-\text{P}(=\text{O})(\text{OR})-\text{C}\equiv\text{Cl} \quad \mathbf{41} \\
 + \quad \text{S}=\text{N}(\text{R}^1)-\text{N}=\text{N}-\text{N}(\text{R}^1) \quad \mathbf{42} \\
 \xrightarrow{\text{AcCN, } 20^\circ\text{C}} \\
 \text{through} \quad \left[\text{RO}-\text{P}(=\text{O})(\text{OR})-\text{C}\equiv\text{S}^+=\text{N}(\text{R}^1)-\text{N}=\text{N}-\text{N}(\text{R}^1) \right] \text{Cl}^- \quad \mathbf{43} \\
 \rightarrow \text{RO}-\text{P}(=\text{O})(\text{OR})-\text{C}_4\text{H}_2\text{S}_2\text{N}_4(\text{R}^1)_2 \text{Cl}^- \quad \mathbf{44} \\
 \xrightarrow{-\text{MeCl}} \text{MeO}-\text{P}(=\text{O})(\text{OR})-\text{C}_4\text{H}_2\text{S}_2\text{N}_4(\text{R}^1)_2 \quad \mathbf{45}
 \end{array}$$

R = Me, Et, *i*Pr
 R¹ = Me, Ph, NH₂

Scheme 18

Concerning industrial applications, 5-5 bicyclic ring systems were previously described for imaging materials, photographic, solar cell and inkjet applications. (7) They are also used for dye compounds and more recently, these products could find application in the field of agriculture as herbicides (such as product **46**) (28) and fungicides (such as products **47-50**) (Figure 2). (29)

Figure 2. Patented 5-5 bicyclic ring systems for agricultural applications

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Biographical Sketch

Stéphanie Norsikian studied chemistry at the University of Paris VI, where she obtained her Ph.D. degree in 1999, under the supervision of Professors J.-F. Normant and I. Marek. After post-doctoral trainings in the groups of Professor D. M. Hodgson (Oxford, U.K), Professor G. Guillaumet (Orléans, France) and Professor H. Kagan (Orsay, France), she was appointed by the CNRS as Chargée de Recherche in 2002 in the group of Professor A. Lubineau (Orsay). In January 2007, she joined Professor J.-M. Beau's group at the Institut de Chimie des Substances Naturelles (CNRS-Gif sur Yvette). Since January 2015, she is working in the team "Probes and Modulators for Biological Targets" (Chemical-Biology Department-ICSN). Her research interests are in the field of glycochemistry, organometallic chemistry, multicomponent reactions, total synthesis of biomolecules and flow chemistry.