Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 3 [7] June 2014: 108-115

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.533
Universal Impact Factor 0.9804

REVIEW ARTICLE

Review of Studies Focused on Heterocyclic Compounds Containing a Heteroatom and Aromaticity Evaluation Methods

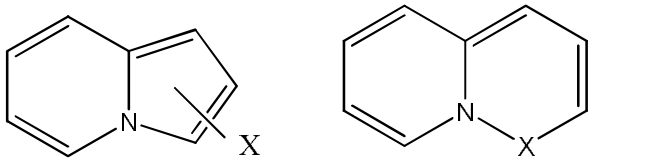
Mojdeh Yousefian Langroudi
Department of Chemistry, Organic Branch, Islamic Azad University of Rasht, Rasht, Iran
Email: mozhdeh.yousefian14@gmail.com

ABSTRACT
Aromaticity is one of the most important concepts in chemistry and is of particular interest in understanding the structure and properties of heterocyclic compounds. There is still much debate on the subject that which of the reactivity, energy, magnetic and geometric patterns can better assess this feature. On other hand, heterocyclic compounds play an important role in biological processes. Hence, the scientists are trying to understand the chemistry of heterocyclic in order to improve the quality of human life. Structural study of many of these compounds due to limited synthetic methods is difficult; however, using chemical calculations, assessments of sustainability and magnetic properties of many known or unknown heterocyclic compounds would be possible. This study reviews the various criteria of Aromaticity evaluation of heterocyclic compounds containing a common heteroatom at two rings junction to achieve a comprehensive view of these methods.
Keywords: *Aromaticity, NICS, $(HOMO-LUMO)_{gap}$, Susceptibility exaltations*

Received 09.03.2014 **Revised 12.04.2014** **Accepted 04.06.2014**

INTRODUCTION

Heterocyclic compounds play an important role in biological processes; hence, the scientists are trying to understand the chemistry of heterocyclic compounds in order to improve the quality of human life [1]. Structural study of many of these compounds due to limited synthetic methods is difficult; however, using chemical calculations, assessments of sustainability and magnetic properties of many known or unknown heterocyclic compounds would be possible. Aromaticity is of particular importance in understanding the structure and properties of heterocyclic compounds. In recent years, the quantitative assessment of Aromaticity has become possible using which the aromatic properties of heterocyclic compounds and their polycyclic fused derivatives can be determined [2]. This study reviews the various criteria of Aromaticity evaluation of heterocyclic compounds containing a common heteroatom at two rings junction to achieve a comprehensive view of these methods.



1-a) X= N, O **2-a)** X=CH^+, O , S , NH

Figure 1: Two groups of heterocyclic compounds containing a heteroatom at the junction of two rings

The (a-1) group is structurally a neutral compound similar to in dole, while in the conjugate structure of (a-2), if (x = CH^+), the positive charge on the nitrogen is placed at the junction of the two rings (Figure 1).

- **Definition of Indolizines and Phosphaindolizines**

In addition to purines and most of fused heterocyclic compounds with benzene such as indole, which are biologically important, a number of other aromatic cyclic and polycyclic fused heterocyclic compounds

has been identified that the most important of them contain one nitrogen or phosphorus at the junction of rings. The nitrogen-or phosphorus-containing heterocyclic compounds at the junction of the two rings are referred respectively as Indolizines (3-a) and Phosphaindolizines (4-a) (Figure 2). Although these compounds are not found in nature, but according to studies, they have unique structural and magnetic properties.

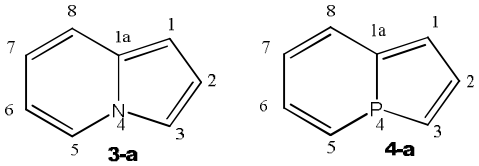


Figure 2: Indolizines and Phosphaindolizines

- **Aromaticity in indolizines**

These systems and their derivatives with naphthalene, indole and a group of heterocyclic compounds considered structurally as purinesderivatives are isoelectronic. Thus, indolizines can be considered as a 10- π electron system, containing high and low electron rings [3]. Four pairs of electrons from 4 double bonds and an electron pair of nitrogen can participate in the system Aromaticity.

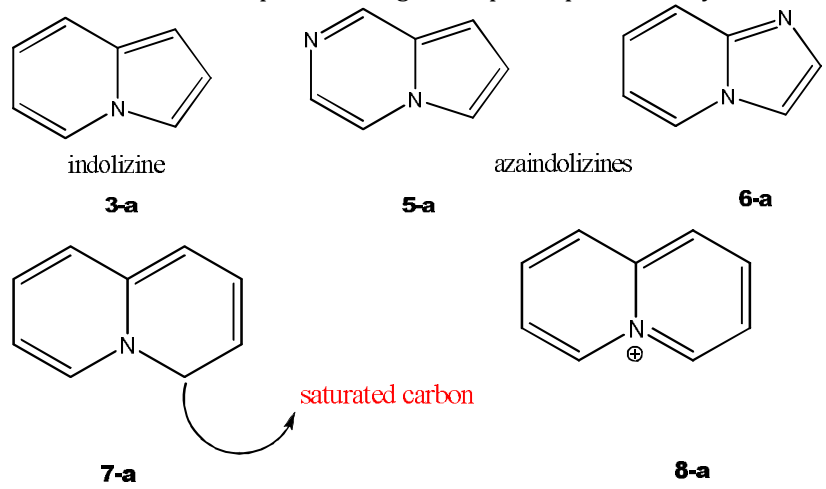


Figure 3: Some two-loop system with a 10- π electron

From apparent structure view, *4H-Quinolizine*(a-7) is not aromatic due to presence of saturated atom, since the pairing is lost. But, quinoliziniumcation (a-8), formed formally by loss of hydride from *quinolizine*, is an aromatic 10 π electron, which is isoelectronic with naphthalene.

Chemical - quantum ***computations*** of indolizines and their derivatives show that resonance stability of these compounds is mainly due to the presence of the pyrrole rings, while phospha indolizines are less stable [4]. Although nitrogen or sulfur counterparts are used in practice, but organic phosphorous compounds have certain properties.

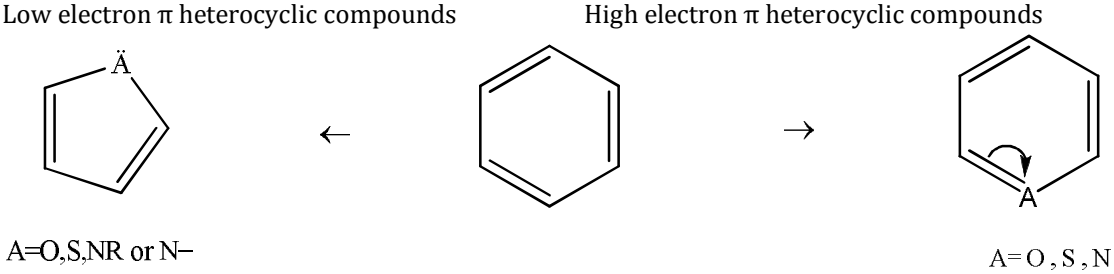


Figure 4: Modified hetero aromatic compounds of benzene [5, 6]

- **Bond length in indolizine**

The ring geometrical form has been suggested as a measure to describe aromaticity [7]. Today, using the X-ray, the bond length inside and outside the ring can be determined. Accordingly, the Harmonic Oscillator Modeling Aromaticity (HOMA) model has been used as an index to describe the aromatic feature in many of π-electron systems [8]. Generally, the length of the ring bonds is the average of simple

and double bonds. All bonds are the same in benzene (1.395Å), but the bonds length is variable in a non-cyclic conjugated poly-N.

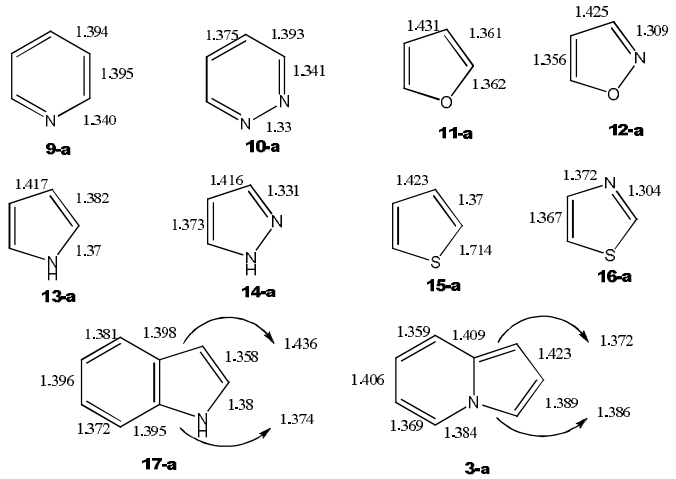


Figure 5: Bond length of some hetero aromatic compounds

The bond length of six-membered compounds (a-9 and a-10) is the average of simple and double bonds values. The carbon - carbon bond length indicates little change in the 6-memberedsingle-ring rings close to benzene levels. Accordingly, it can be concluded that there is a significant cyclicnon-localization in π electrons of these compounds.

On the other hand, the sevalues for five-membered heterocyclic compounds represent considerable changes, which correspond with localized structures. Due to the involvement of different hetero atoms, direct comparison of bonds length is not possible; however, the oxygen-containing heterocyclic compounds typically show the highest bond establishment.

In any case, even in oxygen-containing heterocyclic compounds, the length of bonds differs from simple or double bonds length. All of these five-membered cyclic systems show evidence suggesting non-localized cyclic structures, but its value is less than six-membered heterocyclic compounds. Bothdi cyclic five-memberedindole and indolizine systems (a-17 and a-3) have the highest bond establishment in five-member rings compared to pyrrole, and in general, this feature is true for other heterocyclic merged compounds in comparison with similar single-ring compounds.

- **Aromaticity in phospha indolizines and other phosphorus-containing heterocyclic compounds**

Nyulaszi successfully synthesized phospholes with flat tri coordinated phosphorus [9]. Replacement of CH groups with P, due to changes in bond lengths and planar structure, has a great impact on cyclic aromaticity [10]. Replacement of bulky groups in the phosphorus atom, due to reinforcing effect, turns the pyramidal structure of phosphorus to a flat form. According to reduced pyramid-shaped of tri coordinated phosphorus in phospholes, the aromatic properties will increase.

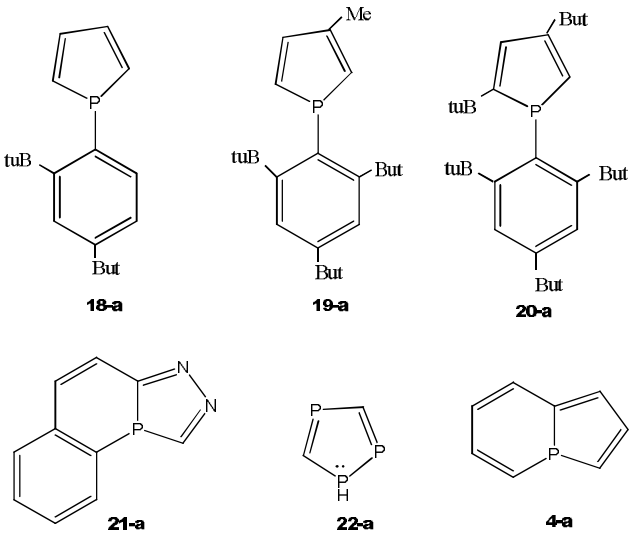


Figure 6: Phosphaindolizines and other phosphorus-containing heterocyclic compounds

The aromaticity of 1 - (2, 4-di-tert- butylphenyl) phosphole (a-18), which is determined with MNDO molecular calculations at HF/6-31G* and B3LYP/6-31G* levels, is similar to aromaticity of furan [11].
The gradual flattening of the tri coordinated phosphorus in phosphole occurring due to the increased spatial volume of interchangeable group occurs has been demonstrated by geometrical optimizing of alkyl aryl phospholes at HF/6-31G * level. Aromaticity indices increase by reducing pyramidal form of the structure, which occurs due to the increased conjugation of the structure. In photoelectron spectrum, increased aromaticity represents the reduction of ionization energy of the electron pair of phosphorus. In fact, *1-(2', 4', 6'-tri-tert-butylphenyl)-3-methyl-phosphole* (a-19) is the first phosphole doing electrophilic substitution [12].
1-(2',4',6'-tri-tert-butylphenyl)-3-methyl-phosphole (a-19), with the lowest ionization energy reported for phosphole, represents aromaticity increase based on various indicators which are consistent with experimental data [10].
Molecular calculations at B3LYP/6-311+G** level for diphospholes, tri phospholes (a-22) and phosphaindolizines (a-4 and a-21) refer to their aromatic structure. The π –aromatic system switch flat tri coordinated phosphorus are the largest aromatic systems among the nitrogen-containing rings or Chalcogen hetero atoms (A6 group elements in the periodic table). 1 - (2, 4-tri-tert- butylphenyl) - 5, 3di-tert- butyl- 1,2,4 - tri phosphole (a-20) has been assessed with several criteria and resulted data show that it is highly very aromatic and planar [11].

- **Impact of molecular environment on the heterocyclic compounds Aromaticity**

Aromaticity changes in different environments. The effect of molecular environment on interactions determines the Aromaticity of asymmetrical heterocyclic compounds. The comparative calculations of Aromaticity indicators of molecules in the gas phase and in the condensed mediators with a dielectric constant greater than 1, with or without hydrogen bonds, show consistent results for a set of nitrogen-containing heterocyclic compounds, including imidazole, pyrrole, Pyrazole, H1-1, 2,4 - triazole and Benzimidazole.
Aromaticity indices increase based on abinitio calculations from gas phase to the condensed phases (dioxane, aqueous solutions or solid phase) [13, 14]. For the hetero cyclic compounds with high hydrogen-bonding, such as imidazole in the solid phase, aromaticity increase is not be significant that can be due to the increased1&2 bond length, which is caused by formation of hydrogen bonds between H (1) and N (1) (2).

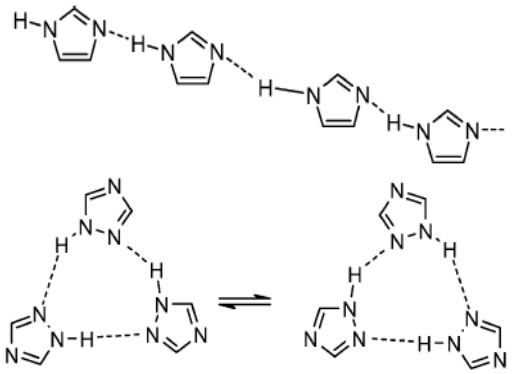
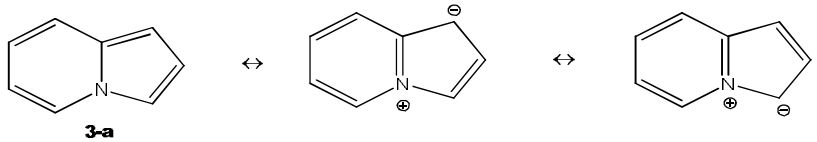


Figure 7: Hydrogen bond in imidazole and tri-azole

Therefore, aromaticity comparison of heterocyclic compounds should be performed by data collected in similar molecular environment. Solid-state proton transfer in tri-azole derivatives has been recently demonstrated by NMR. NMR shows that the type of density in solid phase depends on substitution in tri-azoles ring. Tri-azolescan form two cyclic A and B trimmers at solid state with transferring three protons (Figure 7).
Chemical reactivity of indolizines
Indolizine is an electron-rich system, which is similar to indole regarding reactivity but with higher basic properties (-3.5).



3-a

Figure 8: Preferred resonant forms inpyrrole or *pyridinium*rings

In indolizines, proton replacement is done at carbon 3instead of nitrogen (Fig. 2), since otherwise the π system aromaticity is disrupted. The 6-membered ring of indolizines is not very similar to pyridine, since it does not act like imine and rarely does *nucleophilic* addition. *Electrophilic* substitution reaction occurs at carbon-3 in indolizines; but in the presence of a strong acid, the reaction takes place at carbon 1 (Figure 9).

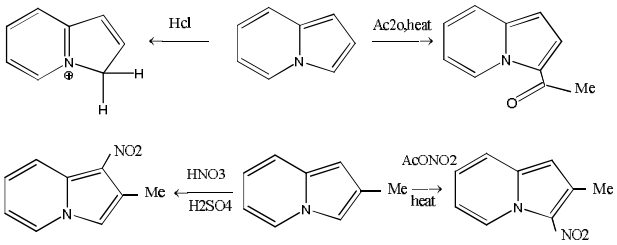


Figure 9: Electrophilic attack in indolizines

- **Reaction with lithium and organic lithium-containing compounds**

Other reactions in which indolizines participate include reaction with lithium and organic lithium-containing compounds (Figure 10). The reaction occurs in the pyridine ring at the site of carbon5 (Figure 2).

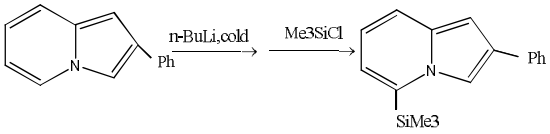


Figure 10: Adding lithium to indolizines

Reduction reaction in acidic solution can fully saturate the dihydro derivatives, which depends on the type of catalyst (Figure 11).

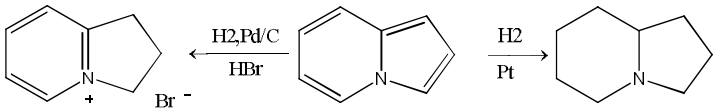


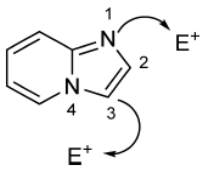
Figure 11: Reduction reaction in indolizines (partial or complete reduction of indolizines depends on the type of catalyst)

- **Azaindolizines**

Azaindolizines are nitrogen- containingindolizines or other heteroatoms substituted with carbon. If nitrogen atoms are placed in the 6-membered ring, they form imine system; thus, they will be more vulnerable to the attackof *nucleophilic* compounds. If nitrogen atoms are placed in the 5-membered ring, they will act similar to azoles such as imidazole, pyrazole, triazole and tetrazole.

- *Imidazo*[*1*,*2*-a] *pyridine*

Imidazo [*1*, *2*-a] *pyridines* are aromatic systems in which the nitrogen attached to the (4-N) bridge shares its electron pairs in the aromaticity. Thus, the nitrogen atom is not *nucleophilic, and the nucleophilic* attack on the nitrogen occurs at N-1.



Electrophilic substitution occurs at carbon 3 in mild condition; but in case of filled position, the substitutions can be made at carbon 5.

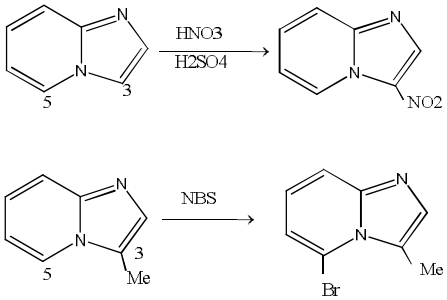
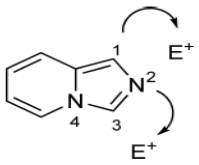


Figure 12: Electrophilic substitution in *Imidazo* [*1*, *2*-a] *pyridines*

- *Imidazo* [*1*,*5*-a] *pyridine*

Imidazo [*1*, *5*-a] *pyridines* are aromatic systems in which the (N-4) *bridged nitrogen* shares its electron pairsin the aromaticity. Thus, this nitrogen atom is not *nucleophilic, and the nucleophilic* attack on the nitrogen occurs at N-2.



Electrophilic substitution occurs at carbon 1(Figure 13); however, compared with its isomers, changing the position occurs in the 5-membered ring. Hence, the changes lead to placement of formed ylide at carbon 3.

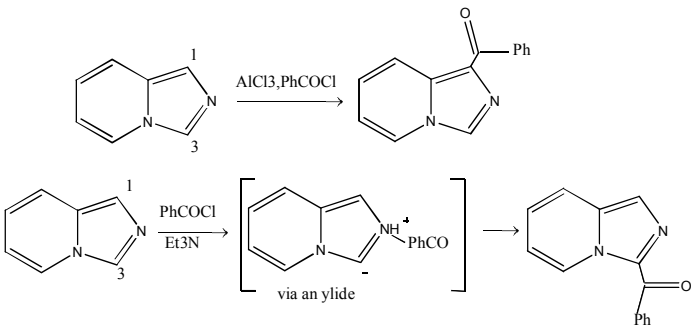


Figure 13: Electrophilic substitution in *Imidazo* [*1*, *5*-a] *pyridines*

Lithium addition reaction occurs at position 3 for both *imidazo* pyridines. However, depending on the substituent type at position 3, the substitution can occur at carbons 5 or 8 (Figure 14).

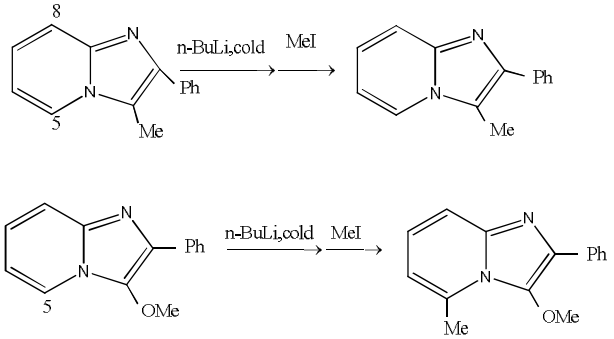


Figure 14: Lithium addition in *Imidazo* [*1*, *5*-a] *pyridines*

- **Other azaindolizines**

The [1, 2, 3] triazolo [1, 5-a] pyridine and Tetrazolo [1, 5-a] pyridine can be both ring in equilibrium with open- ring forms. The closed-ring form is often predominant. Tetrazolo pyridines can mainly be present in both forms, depending on the type of substituent in the rings. Tetrazolo pyridine is found in closed form, but its 5 - chloro derivative can be found in the open form (Figure 15).

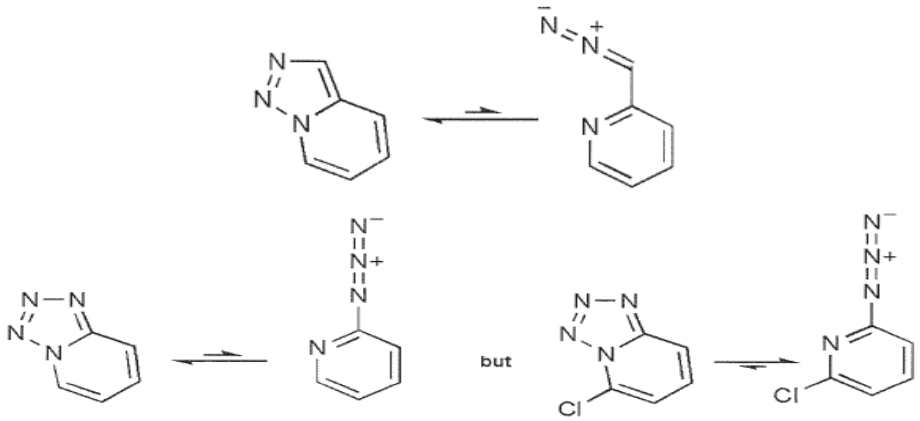


Fig 15: The preferred forms of open and closed loopsin [1, 2, 3] triazolo [1, 5-a] pyridine and Tetrazolo [1, 5-a] pyridine

Systems with more nitrogen count show different reactivity in the six-membered ring, but their common feature is easy placement of the 6-membered ring under *nucleophilic* addition reaction. In fact, some of them are very reactive and become hydrated even exposed to moist air (Figure 16).

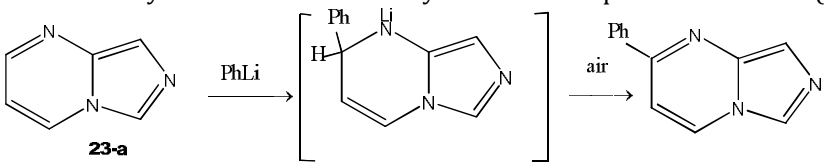


Figure 16: *Nucleophilic* addition as the dominant reaction in azaindolizines

- **Synthesis of indolizines and azaindolizines**

Synthesis of imidazo pyridines and some of triazolo pyridines are mainly done via two methods: Dipolar cyclo-addition or cyclo-condensation (Figs. 17 & 18). Most of synthesis paths begin from pyridines or azines.

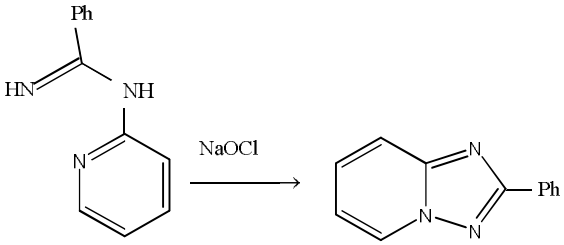


Figure 17: An example of cyclo-addition reaction in [1, 2, 3] triazolo [1, 5-a] pyridine

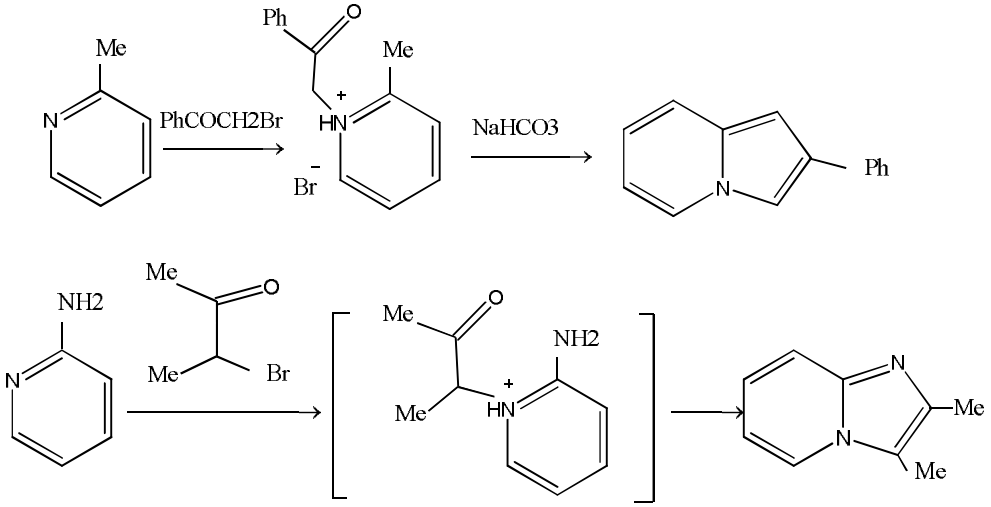


Figure 18: An example of the synthesis of indolizine and imidazo [1, 2 -a] pyridine through cyclo-condensation

The [1, 2, 3] triazolo [1, 5-a] pyridines and Tetrazolo pyridines are typically synthesized through open - ring form (Figure 19). The TsN3 (Tosylazide) is the used reagent, but because of its explosive capability, the ArN3 is used.

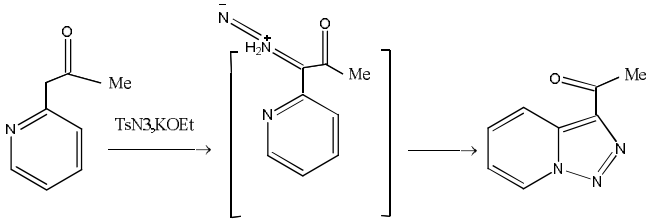


Figure 19: Synthesis of [1, 2, 3] triazolo [1, 5-a] pyridine

Compounds with several nitrogen atoms in the 6-membered ring produce azines containing more nitrogen atoms through condensation or cyclo-addition (Fig. 20) (azines are mostly pyridine derivatives, but sometimes have 5-membered rings).

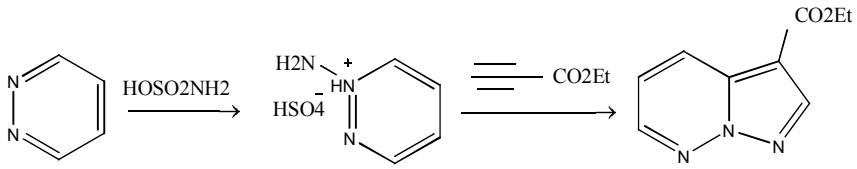


Figure 20: An example of the synthesis of pirazolo [1, 5-b] pyridazine with dipolar cyclo-addition

CONCLUSIONS

Although many experimental and theoretical studied have been conducted on the chemistry of heterocyclic compounds, the current information about the heterocyclic compounds containing one atom at the infusion site of the rings is insignificant. In this study, the methods and definitions related to indolizines and phosphaindolizines, aromaticity in indolizines, bond length in indolizines, aromaticity in phosphaindolizines and phosphor-containing heterocyclic compounds, the influence of the molecular environment on the heterocyclic compounds, reactivity with lithium and organic lithium-containing compounds, azaindolizines, the synthesis of indolizines and azaindolizines were reviewed and a full understanding of all these methods was provided.

REFERENCES

1. A. F. Pozharskii, A. T. Soldatenkov, A. R. Katritzky, (1997). Heterocycles in Life and Society, 1st. ed. Wiley: New York, 301.
2. K. Jug, D. C. Oniciu, A. R. Katritzky,(2001). *Chem. Rev, 101*, 1421.
3. M.Tišler, (1980). *Pure AppI.chem*,52, 1611.
4. A. Albert,(1993). *Heterocyclic Chemistry,* 2nd ed. Oxford University Press: New York, 547 (1968). [5] M. Cohen, S. W. Benson, *Chem. Rev*, 93, 2419.
5. A. A. Deniz, K. S. Peters, G. J. Snyder,(1999). *Science*, 286, 1119.
6. A. R. Katritzky,(1985). *Handbook of Heterocyclic Chemistry*, Pergamon Press: Oxford, 571.
7. T. Eicher, S. Hauptmann,(1995). *The Chemistry of Heterocycles. Structure, Reactions, Syntheses, and Applications*, Georg Thieme Verlag: Stuttgart, 504.
8. A. R. Katritzky, A. F. Pozharskii,(2000). *Handbook of Heterocyclic Chemistry*, 2nd ed Pergamon Press: Oxford.
9. L. Nyulaszi, L. Soos, G. Keglevich, (1999). *J. Organomet. Chem*, 566, 29
10. L. Nyulaszi, (2000).*Tetrahedron*, 56, 79
11. L. Nyulaszi, J. F. Nixon, *J.* (1999). *Organomet. Chem*, 588, 28 174.
12. G. Keglevich, Z. Bo¨cskei, , M. Keseru¨, K. UÄ jsza´ szy, L. D. Quin (1997) *J. Am. Chem. Soc*, 119, 5095.
13. A. R. Katritzky, M. Karelson, A. P. Wells, (1996) *J. Org. Chem*, 61, 1619 (1996).
14. H. Fallah-Bagher-Shaidaei, R. Farkhonde, L. Ghalandari-Navideh(2011). *Computational and Theoretical Chemistry*, 963, 525..

Citation of This Article

Mojdeh Y L. Review of Studies Focused on Heterocyclic Compounds Containing a Heteroatom and Aromaticity Evaluation Methods. Bull. Env. Pharmacol. Life Sci., Vol 3 [7] June 2014: 108-115