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REVIEW ARTICLE

Studies of Physicochemical Properties and Reactivity of Naphthyridine Derivatives: An Overview

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ABSTRACT

Aliterature review studies of physicochemical properties and reactivity of naphthyridine derivatives due to their broad spectrum activity. The research work still looking for the promising compound of these derivatives and also the aim of our studies to activate this area of research and propose these derivatives as a target compounds that could be oriented as pharmaceutical compounds in medicine.

INTRODUCTION:

The first naphthyridine derivatives was prepared in 1893 by Reissert who suggested the name naphthyridine.[1] generally, naphthyridines are compounds having two pyridine rings without any nitrogen atom occupying bridgehead positions. Other different names are used for naphthyridine such as diazanaphthalenes or pyridopyridines but naphthyridine is the most popularly used name. There are six possible isomeric compounds (figure 1).

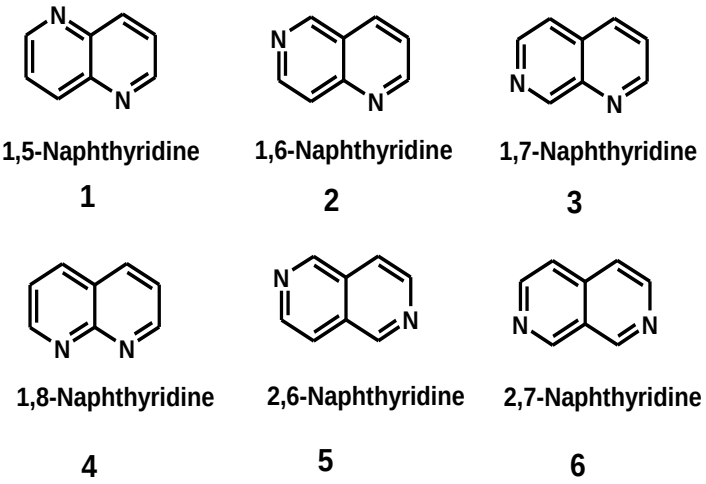

Figure 1: naphthyridines isomers

1. PHYSICOCHEMICAL PROPERTIES:

The Physical Properties and X-ray crystallographic analysis recorded that all naphthyridines are planar with the exception of 1,8-naphthyridine is non-planar due to repulsion of the nitrogen lone pairs of electrons, but becomes planar when chelation with metal atom. [3] The weaker bases of parent naphthyridines than quinoline (pka 4.94) and isoquinoline (pka 5.40) are attributed to the electron-withdrawing inductive effect of one doubly bonded nitrogen atom to the other. [4] In the fact that 1,6-naphthyridine (pka 3.78) and1,7-naphthyridine (pka 3.63) are stronger bases as compared to the 1,5-naphthyridine (pka 2.91) and 1,8-naphthyridine (pka 3.39) ,and also both of the new derivatives are stronger bases as compared with the the pka value of quinoline and isoquinoline which they are consistent protonation occurring on N-6 and N-7 of the 1,6- and 1,7- isomer respectively. [5] A new series of fluorophore derivatives from 1,8-naphthyridine were developed and shown the first naphthyridine PET sensor that can signal Cd selectively with fluorescent enhancement and red-shift. Other 1,8–naphthyridines were found to be fluorescent in solution and they were studied in the presence of Cu+ and Cu2+ ions and it was verified that the metal causes the quenching of their fluorescence emission, due to the formation of complexes between the naphthyridine and the metal.[6,7]

Many 1,8-naphthyridine derivatives were characterized by single crystal X-ray diffraction analysis, and a comprehensive study of their spectroscopic properties involving experimental and theoretical studies. They found an intramolecular 1,3-hydrogen transfer and photoinduced isomerization for some derivatives while flexible structures was observed under 365 nm light irradiation. Quantum chemical calculations revealed that the dinuclear complexes with structural asymmetry exhibit different metal-to-ligand charge-transfer transitions.[8]

2. REACTIVITY:

The naphthyridines possess ten delocalized π–electrons which are located in five molecular orbitals and they are distorted by the presence of the nitrogen atoms that causing an electron drift in that direction. This perturbation causes the position ortho and para to the nitrogen atoms to have π–electron densities than the meta positions and this led to electrophilies react preferentially at a position meta to a ring nitrogen and nucleophiles at ortho and para positions. However, because naphthyridines are π–electrons deficient, they are highly

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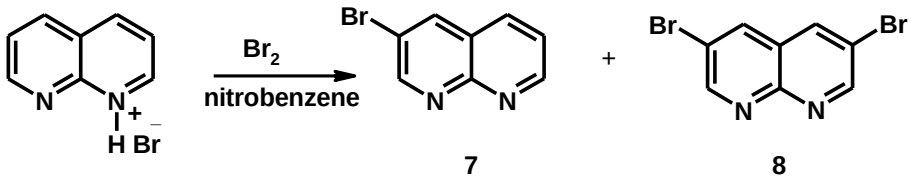
susceptible to nucleophilic attack and strongly deactivated for electrophilic attack. [9]

2.1. ELECTRO PHILIC SUBSTITUTION:

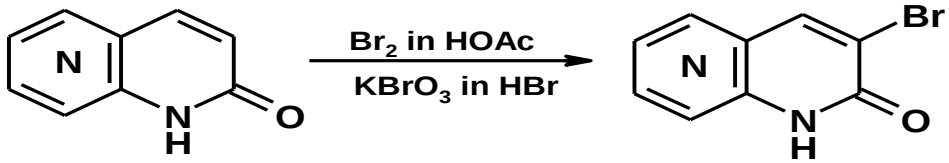
In the bromination of 1,8-naphthyridine hydrobromide with 1:1 equivalent ratio of bromine in nitrobenzene, the 3-bromo-1,8-naphthyridine **(7)** and 3,6-dibromo-1,8-naphthyridine **(8)** were obtained in equivalent ratio (1:1), but compound **(8**) is obtained in 73% yield when equivalent ratio of bromine is (2:5) (Scheme 1). [10]



7 8

Scheme1

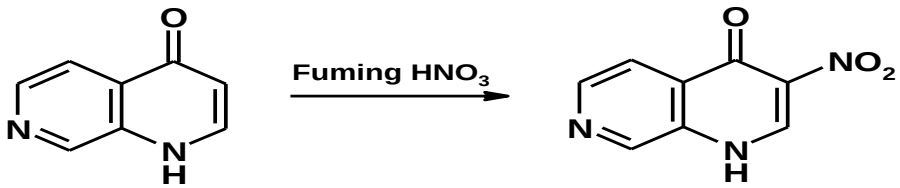
However, presence of electron-donating substituents facilitates electrophilic substitution and hence bromination was proceed under much milder conditions as shown in conversion of naphthyridone derivatives **(9)** into 3-bromo-naphthyridone derivatives **(10)** Scheme 2.[11]



9 10

Scheme 2

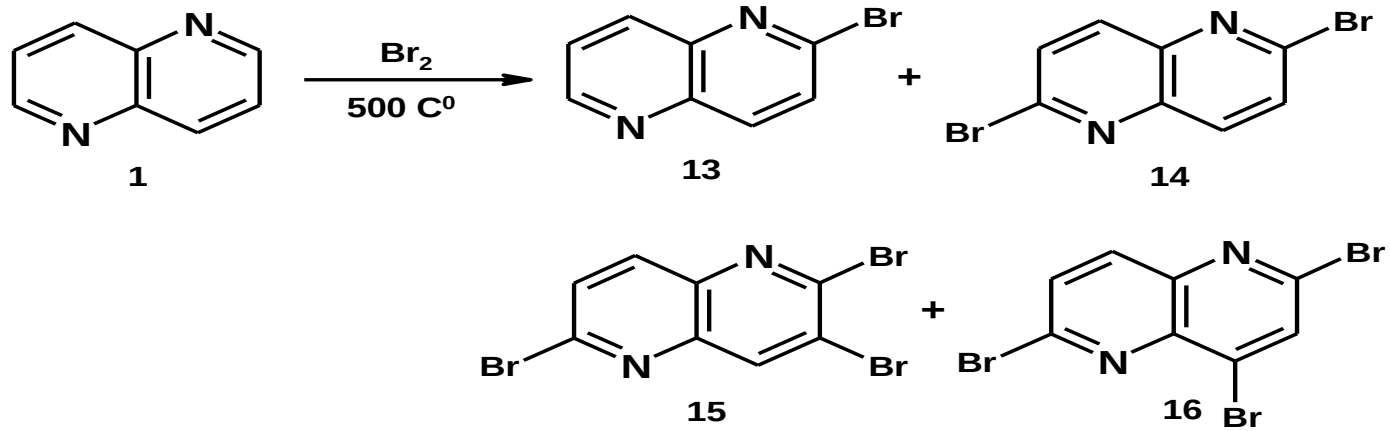
Oxidation reaction with $KClO_3$ in HCl [12] and the nitration occurs only when electron-donating groups are present in the 2-or 4-position.Thus, 1,7-naphthyridone **(11)** can be mononitrated to 3-nitro-1,7-naphthyridone **(12)** Scheme 3. [13]



11 12

Scheme 3

However, when 1,5-naphthyridine (**1)** undergoes gas-phase bromination a mixture of 6-bromo-1,5-naphthyridine **(13)**, 2,6-dibromo-1,5-naphthyridine **(14)**, 2,6,7-tribromo-1,5-naphthyridine **(15)** and 2,6,8-tribromo-1,5-naphthyridine **(16)** were obtained Scheme.4. [14]



1 13 14 15 16

Scheme 4

2.2: NUCLEOPHILIC SUBSTITUTION

Naphthyridines are a very useful and efficient method to synthesize substituted naphthyridines because of their easly nucleophilic attack. There are numerous investigations using nitrogen nucleophilies. [15,16] The replacement of halogen by an amino group provides potential application in synthetic chemistry and is therefore a topic of great interest. It is apparent that nucleophilic substitution can proceed in three pathways namely, ipso, cine and tele substitutions figure 2.[17]

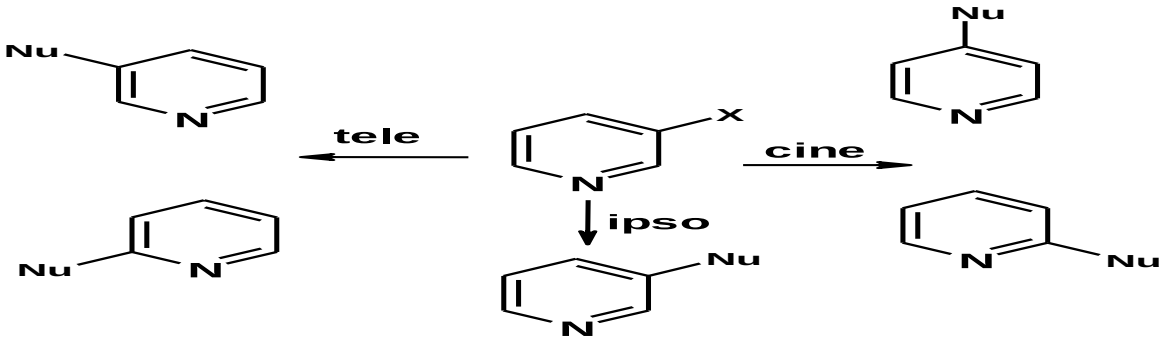


Figure 2: ipso, cine and tele nucleophilic substitution of naphthyridines

The mechanism for the formation of both cine and ipso products can be explained via a didehydronaphthyridine intermediate **(19)**, so, the reactions of 4-bromonaphthyridine **(20)** and 3-bromonaphthyridine **(21)** with potassium amide in liquid ammonia afford 4-aminonaphthyridine **(22)** and 3-aminonaphthyridine (**23)** figure 3**.** [18]

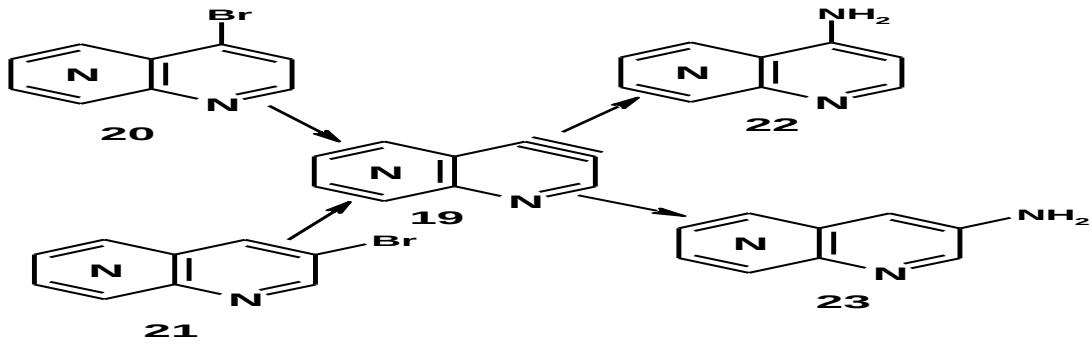
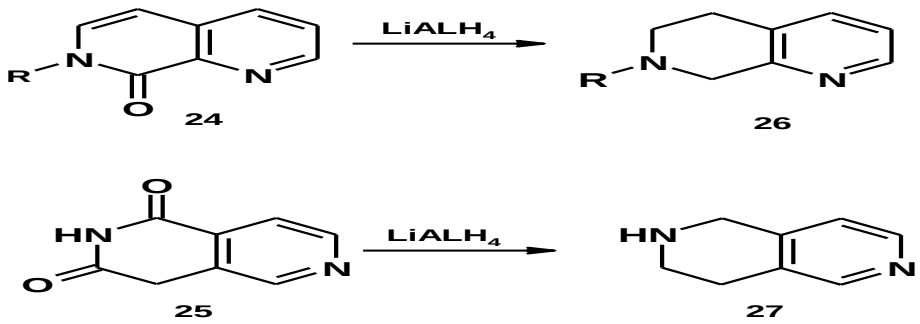


Figure 3: mechanism formation of cine and ipso products

Aminodehalogenations involving tele and ipso substitution have been reviewed. The replacement of a halogen by a hydrogen atom is conveniently achieved by initial reaction with hydrazine followed by oxidation with copper (II) sulphate. [19]

2.3. REDUCTION:

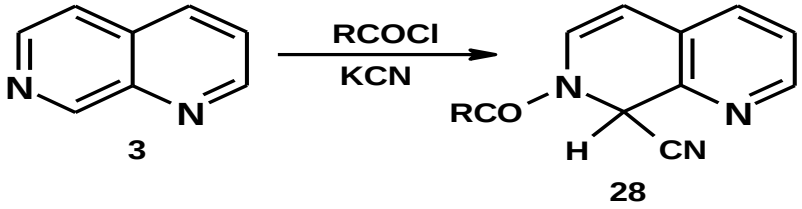
The hydrogenation over PtO_2 or Pd gives preferentially tetrahydro products.[20] But sodium and alcohol afford the fully reduced trans isomers only. However, both cis and trans isomers were obtained when reduction is done over PtO_2 in acetic acid. The hydrogenation of naphthyridine has been reviewed. [21] Lithium aluminum hydride changes the 8-oxo-1,7-naphthyridine **(24)** and the 4,6-dioxo-1,5- naphthyridine **(25)** into tetrahydro-1,7-naphthyridine **(26)** and tetrahydro-1,5- naphthyridine **(27)** respectively Scheme 5. [22.23]



Scheme 5

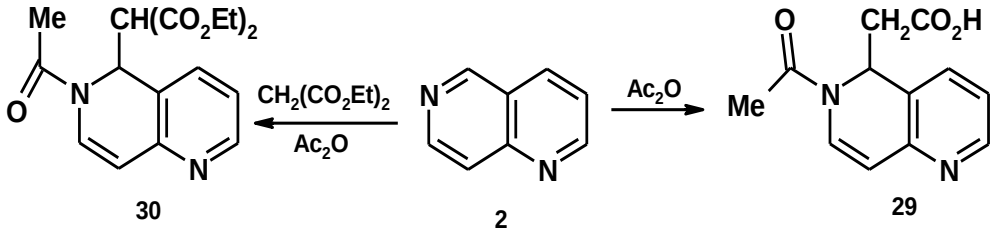
2.4. ADDITION REACTION:

The Reissert reaction of naphthyridine with acyl halides and potassium cyanide has been studied including conversion of 1,7-naphthyridine (**3**) into 7-acyl-8-cyano-1,7-naphthyridine (**28**) Scheme 6. [24]



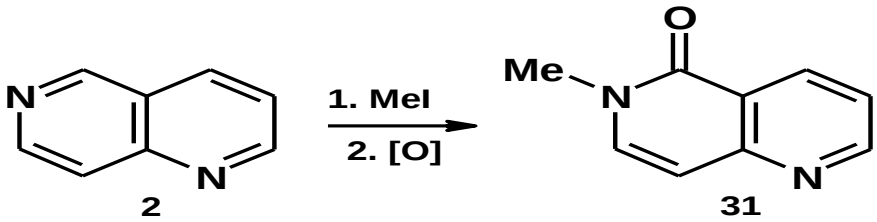
Scheme 6

In the addition reaction of 1,6-naphthyridine **(2)** with acetic anhydride, 6-acetyl-1,6-naphthyridine-5-acetic acid **(29)** was obtained, while the reaction of 1,6-naphthyridine **(2)** with diethyl malonate and acetic anhydride gave 6-acetyl-5- diethyl malonate-1,6-naphthyridine **(30)** Scheme 7. [25,26]



Scheme 7

N-alkylation preferentially takes place on the isoquinoline nitrogen as shown in the reaction of 1, 6-naphthyridine **(2)** to give 6-methyl-1, 6-naphthyridone **(31)** Scheme 8. [27]



Scheme 8

ACKNOWLEDGEMENTS:

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