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Mohammad AsifGlocal School of Pharmacy,
Glocal University, Mirzapur
Pole, Saharanpur, Uttar
Pradesh, India**Abdul Hafeez**Glocal School of Pharmacy,
Glocal University, Mirzapur
Pole, Saharanpur, Uttar
Pradesh, India

A brief study of synthetic, chemical and pharmacological activities of naphthyridine derivatives: A mini review

Mohammad Asif and Abdul HafeezDOI: <https://doi.org/10.33545/26646765.2022.v4.i1a.46>

Abstract

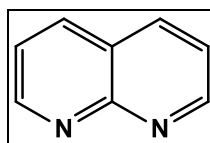
Heterocyclic compounds are of fundamental importance to biological process and are wide spread of natural products. Heterocyclic compounds are finding an increasing use as intermediates in organic synthesis. Heterocyclic compounds are organic compounds that contain a ring structure containing atom in addition to carbon, as part of the ring. Many of the heterocyclic ring systems are of fundamental importance to living systems. Naphthyridine is the name commonly given to the fused-ring system resulting from the fusion of two pyridine rings through two adjacent carbon atoms, each ring thus containing only one nitrogen atom. Many heterocyclic have important pharmaceutical properties and have a wide range of applications: they are predominant among the types of compounds used as pharmaceuticals, as agro chemicals and as veterinary products. The 1, 8-Naphthyridine derivatives are reported to possess a wide spectrum of biological activities such as antibacterial, antimalarial, anti-inflammatory, antitumor, antiviral, and other useful biological and chemical applications.

Keywords: Heterocyclic compounds, Naphthyridine, biological activities

Introduction

In recent years, Naphthyridine with fused rings like benzo, benzopyrido, diazanaphtho and benzoquino-lino have been widely reported. These naphthyridines display characteristic properties in multifarious pharmacological and chemotherapeutic activities. The 3-formylquinolin-2(1H) ones are the unique starting precursors for further [b] and [c] annelation for various ring systems and for many functional group interconversions. Many derivatives of naphthyridines and quinolines could be prepared out of them and several of them possess diverse biological properties [1, 5]. It is also known that when one biologically active compound is fused with another ring system, there will be enhanced biological activity. Recently there has been increased interest in the synthesis of Naphthyridine derivatives and their application in medicinal chemistry as quinoline bioisosteres. 1, 8-Naphthyridine and there. Derivatives represent one of the most active classes of compound possessing a wide spectrum of biological activities [6, 7]. 1, 8-Naphthyridine derivatives acquired a special place in the heterocyclic field because of their diversified activities such as antimicrobial [8-12], antiviral, anti-HIV [13, 15], anticancer, cytotoxic [16, 18], antiinflammatory [19], antimalarial [20, 21], antithrombotic [22] and anticipated biological activities [23, 30].

The first representative of the series, since 1, 8-naphthyridine was considered to be the naphthalene analogue of pyridine. Six possible naphthyridines are

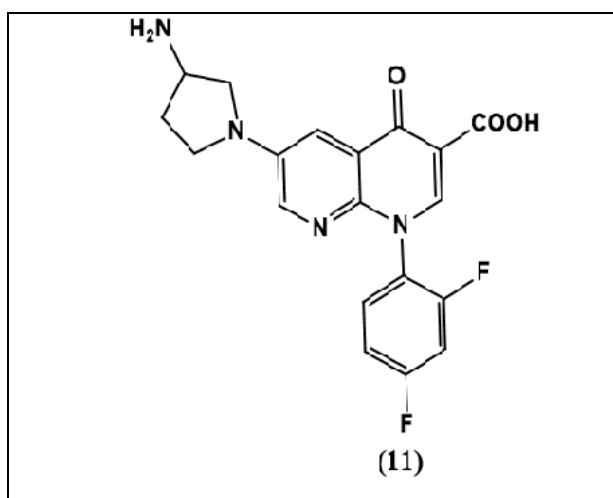
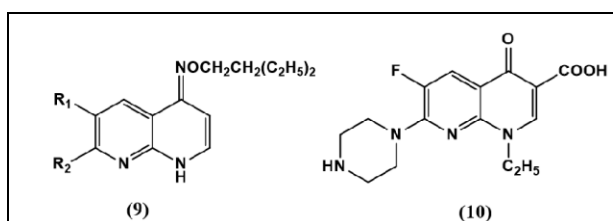
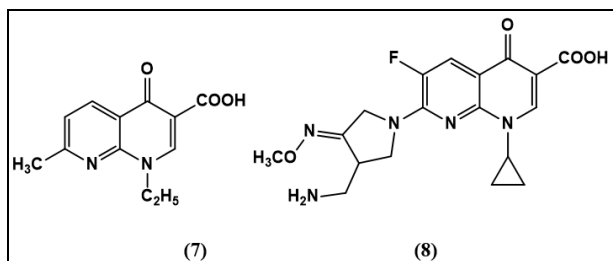
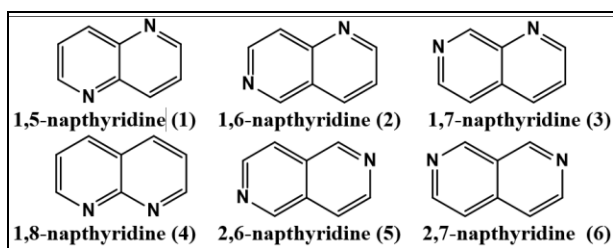


1.8: naphthyridine (1)

1, 8-Naphthyridine derivatives are reported to possess a wide spectrum of biological activities such as diuretic, antimalarial, anti-inflammatory, antitumor, antihypertensive and antibacterial activities.

Corresponding Author:**Mohammad Asif**Glocal School of Pharmacy,
Glocal University, Mirzapur
Pole, Saharanpur, Uttar
Pradesh, India

1, 8-Naphthyridine derivatives have attracted considerable attention because the 1, 8-naphthyridine skeleton is present in many compounds that have been isolated from natural substances, with various biological activities. Nalidixic acid (7), for example, possesses strong antibacterial activity and used mainly for the treatment of urinary tract infections with gram negative pathogens. In addition, Catifloxacin (8) is antimicrobial and antibacterial. It is known that (*E*)- and (*Z*)-*O*-(diethyl amino)ethyl oximes of 1,8-naphthyridine series (9) are potential drugs for local anaesthesia⁸, and 1-(2-fluorobenzyl)-3-(2-tolyl)-1,8-naphthyridin-2(*1H*)-one (10) is used for the treatment of memory disorders, in particular, Alzheimer's disease. 2-Amino-*N*-hydroxy-1, 8-naphthyridine-3-carboxamide (11) possesses herbicidal properties and used for the selective control of weeds in barley, wheat, maize, sorghum and rice crops.



Halogeno-1,8-naphthyridine have proved to be valuable intermediates, halogeno-1,8-naphthyridine shows different antimicrobial activities. Examples are Enoxacin, Tosufloxacin, Trovafloxacin etc. 1,8-Naphthyridine derivatives also react with adenosine receptors of subtypes A1

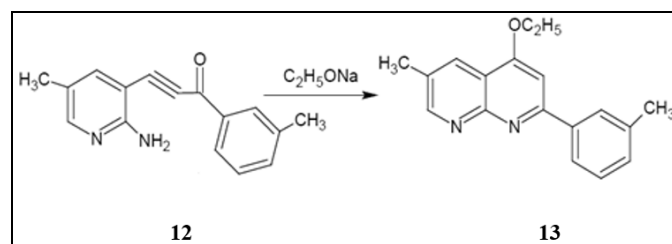
and A2. The important biological properties just described stimulated studies on the synthesis of various functionalized (particularly, at positions 2, 4 and 7) 1, 8-naphthyridines, with the goal of designing new drugs for oral administration. Some 3-phenyl-1,8-naphthyridines which carry piperidyl, piperazinyl or morpholinyl groups or an *N*-diethanolamine side-chain in the 2- or 7- and 2,7- positions have been reported to show significant activity as inhibitors of human platelets aggregation induced by arachidonate and collagen. In addition, 4-(*N*-methylenecycloalkylamino)-1, 8-naphthyridine derivatives substituted in positions 2 and 7 are effective as anti-hypertensive agents. The 7-Amino-2-(4-carboxypiperazin-1-yl)-4-phenyl-1,8-naphthyridine has been synthesized and reported to have marked activity against *Mycobacterium tuberculosis*.

Synthesis of 1,8-naphthyridine

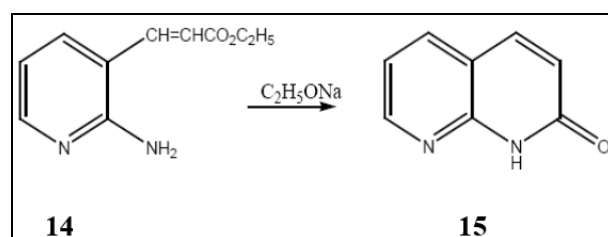
Primary synthesis of 1,8-naphthyridines may be done by cyclization of appropriate aliphatic substrates, with or without auxiliary synthons, by cyclization of appropriate substituted pyridines with or without synthons or from other heterocyclic substrates by several process [31-35].

From a single pyridine substrate

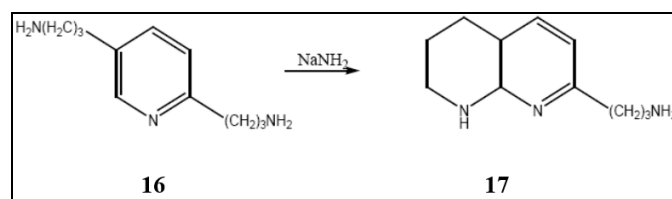
5-Methyl-3-(*m*-tolylethynyl)-2-pyridinamine (12) on treatment with sodium ethoxide in the presence of ethanol on cyclisation produced 4-ethoxy-6-methyl-2-*m*-tolyl-1, 8-naphthyridine (13).



The 3-(2-Ethoxycarbonylvinyl)-2-pyridinamine (14) on treatment with sodium ethoxide underwent cyclisation to form 1, 8-naphthyridin-2(*1H*)-one (15) in ethanol

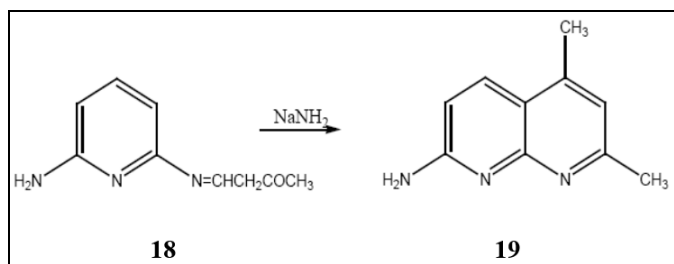


The 2,5-Bis (3-aminopropyl)pyridine (16) on treatment with NaNH₂ in toluene after cyclisation gave 2-(3-aminopropyl)-1,2,3,4-tetrahydro-1,8-naphthyridine(17).



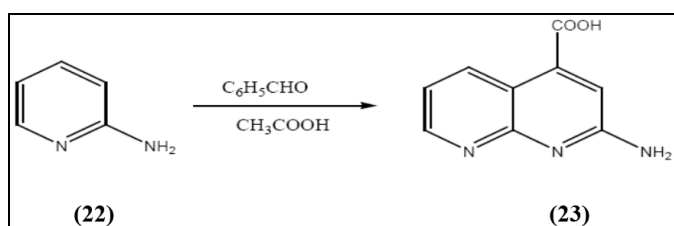
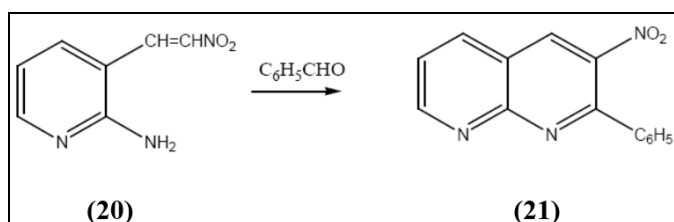
The 6-(2-acetyl-1-methylethylidene) amino-2-pyridinamine (18) gives 5, 7-dimethyl-1,8-naphthyridin-2-amine (19) after cyclisation on treatment with NaNH₂ in presence of

phosphoric acid at 100 °C.

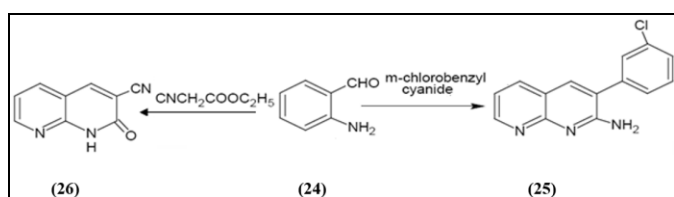


From pyridine substrate and synthon(S)

The 3-(2-Nitrovinyl)-2-pyridinamine (20) underwent condensation with benzaldehyde (Ph CHO) in xylene and gave 3-nitro-2-phenyl-1,8-naphthyridine (21). The 2-Pyridinamine (22) on treatment with benzaldehyde and subsequently with acetic acid produced 2-phenyl-1,8-naphthyridine-4-carboxylic acid (23) in ethanol.



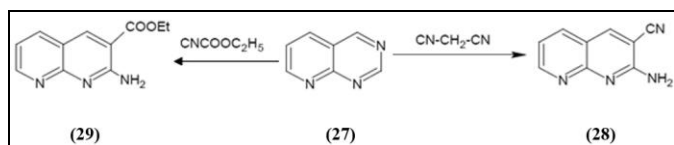
The 2-Amino-3-pyridinecarbonitrile (24) on treatment with m-chlorobenzyl cyanide, KOH/H₂O on microwave irradiation produced 3-m-chlorophenyl-1,8 naphthyridin-2-amine (25). The same substrate (24) with ethyl cyano acetate in ethanol and trace amounts of piperidine gave 2-oxo-1, 2-dihydro-1,8-naphthyridine-3-carbonitrile (26).



From other heterocyclic substrates

Pyrido [2, 3-d] pyrimidine's as substrates

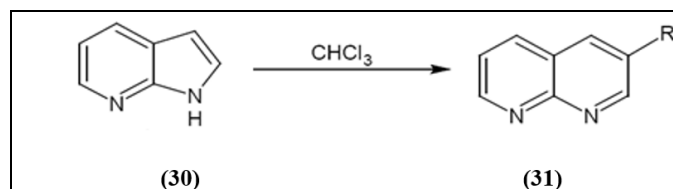
Pyrido [2, 3-d] pyrimidine (27) with malononitrile in methanol, gave 2-amino-1, 8-naphthyridine-3-carbonitrile (28) and with ethyl cyano acetate gave ethyl 2-amino-1, 8-naphthyridine-3-carboxylate.



Pyrrolo [2, 3-b] pyridines as substrates

Prolog [2, 3-b] pyridines (30) underwent pyrolysis in chloroform to give a separable mixture of 1, 8-naphthyridine

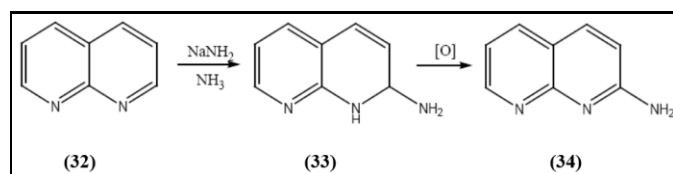
(R=H) and 3-chloro-1, 8-naphthyridine (31) (R= Cl)



Reactions of 1,8-naphthyridines

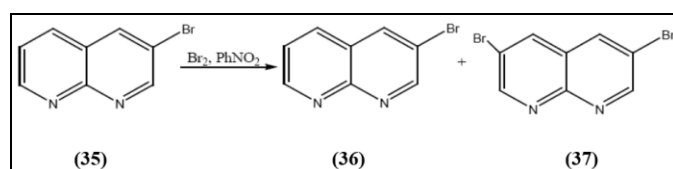
C-Amination

The 1,8-Naphthyridine (32) on treatment with NaNH_2 in NH_3 and then KMnO_4 gave 1,8-naphthyridin-2-amine (34) the intermediate dihydro adduct (33) was clearly involved



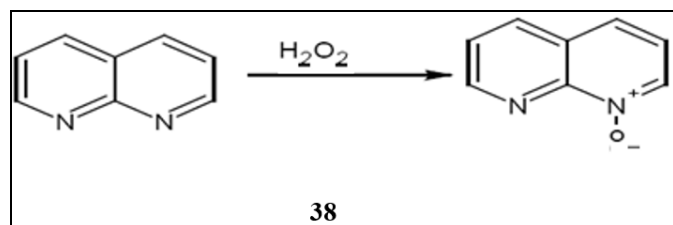
Halogenation

The 1, 8-Naphthyridine hydro bromide (35) gave a separable mixture of 3-bromo-1, 8-naphthyridine (36) and 3, 6-dibromo-1, 8-naphthyridine (37) on treatment with Br_2 in PhNO_2 at 175°C yield was 30% each

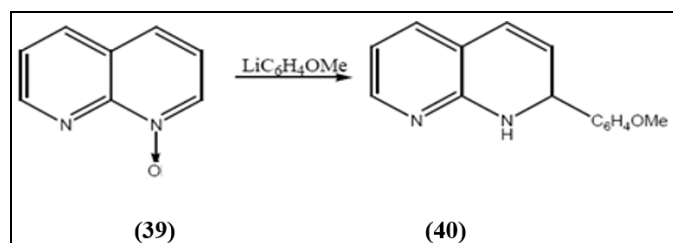


N-oxidation

The 1, 8-naphthyridine undergo oxidation in the presence of H_2O_2 and benzoic acid to form its 1-oxide derivative (38)



The 1, 8-Naphthyridine-1-oxide (39) with o-methoxyphenyllithium gave 2-o-methoxyphenyl-1,8-naphthyridine (40) in diethylether30.



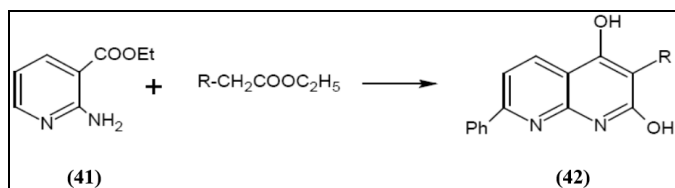
Synthetic routes of 1,4-naphthyridine nucleus

Four routes involved in synthesis of 1, 8-naphthyridine ring a) Niementowski synthesis b) Friedlander synthesis c) Reductive cyclization d) Intramolecular nucleophilic cyclization

Niementowski synthesis

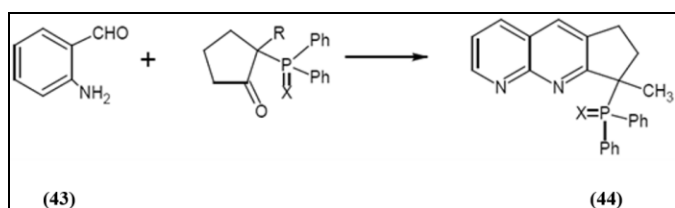
In the first route Hitherto31 described was an extension of the

Niementowski synthesis to the preparation of 1, 8-naphthyridine-2, 4-diols. 7-phenyl-1, 8-naphthyridine-2, 4-diols (42) by the condensation of ethyl-2-amino-6-phenyl nicotianae (41) with simple esters in the presence of sodium.

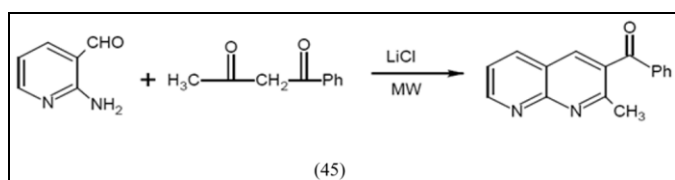


Friedlander synthesis

In the second route Friedlander was described. For the synthesis of [1, 8] naphthyridine derivatives containing phosphorus. The first 2, 3 alkene substituted [1, 8] naphthyridine (44) bearing a phosphorus moiety have been synthesized by the Friedlander annulations of 2-aminonicotinaldehyde (43) with diphenyl phosphoryl cyclopentanones.

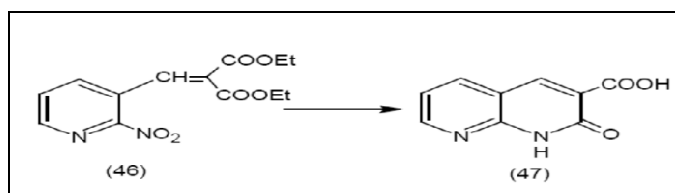


The Friedlander condensation of 2-amino nicotinaldehyde with active methylene compounds in the presence of catalyst Lithium chloride under the two non-conventional methods like microwave Irradiation and by grinding in a mortar afforded the corresponding 1,8-Naphthyridines (45). Both these methodologies are attractive as they are relatively nontoxic, economical and highly effective. The results shows that microwave procedure as slightly superior to the solid-state methods in terms of reduced time period and better yields.



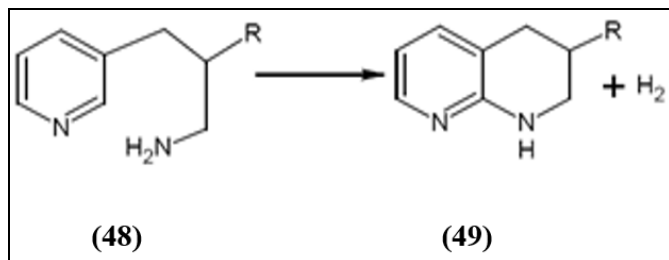
Reductive cyclization

The third route was investigated for synthesis of 1,2-dihydro-1-hydroxy 2-oxo-1,8-naphthyridine-3-carboxylate (47) by reductive cyclization of B-(3-nitro-4-pyridyl) acrylic acid (46).



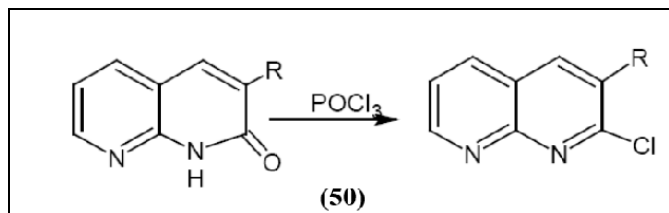
Intramolecular nucleophilic cyclization

The fourth route was investigated for synthesis of 1, 2,3, 4-Tetrahydro-3-phenyl-1, 8- naphthyridine (49) by intramolecular nucleophilic cyclization of a 3-(3-pyridyl)-propylamine (48) in the presence of sodium.



Preparation of halogeno-1, 8-naphthyridine Halogenolysis of 1, 8-naphthyridinones

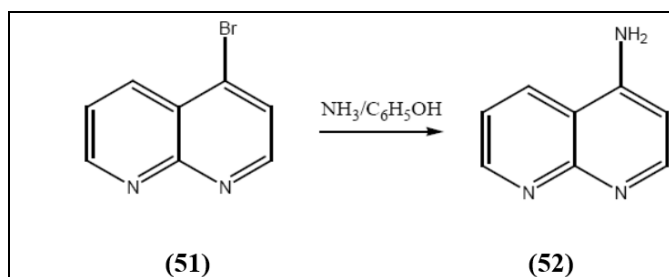
The 1, 8-naphthyridine-2-one reacts with phosphoryl chloride in microwave Irradiation forms 2-chloro-3-substituted-1,8-naphthyridine(50).³⁵



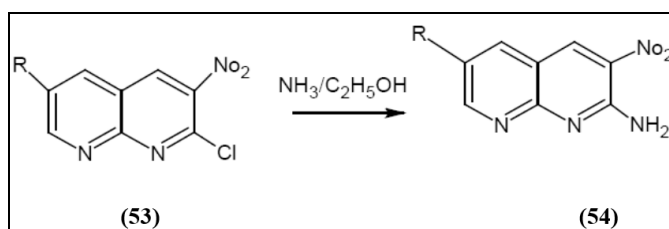
Reactions of halogeno-1, 8-naphthyridine

Aminolysis

The 4-Bromo-1, 8-naphthyridine (51) gave 1, 8-naphthyridin-4-amine (52) on treatment with NH₃ in phenol at 170 °C.

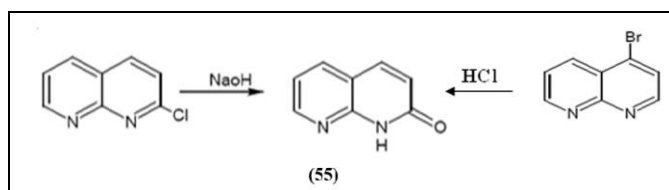


The 2-chloro-3-nitro-1,8-naphthyridine (53) gave 3-nitro-1,8-naphthyridin-2-amine (54) on treatment with NH₃ in ethanol at 110 °C.



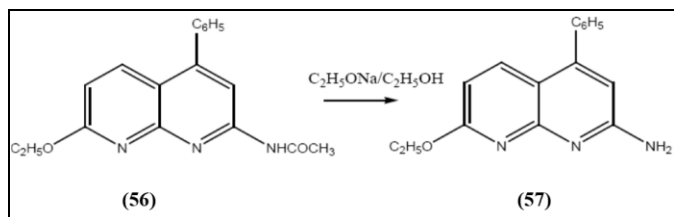
Hydrolysis

In alkaline hydrolysis 2-chloro-1,8-naphthyridine reacts with NaOH to form 1,8-naphthyridine-2(1H)-one (55). In acidic condition 4-bromo-1, 8-naphthyridine with HCl to form 1,8-naphthyridine-2(1H)-one.



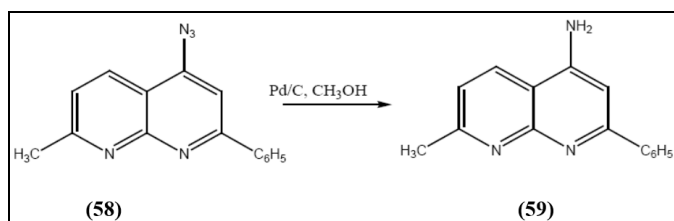
1.4 Preparation of amino-1,8-naphthyridine From Acylamino-1,8-naphthyridine

The 2-Acetamido-7-ethoxy-4-phenyl-1,8-naphthyridine (56) reflux with sodium ethoxide in ethanol gave 7-ethoxy-4-phenyl-1,8-naphthyridin-2-amine (57).



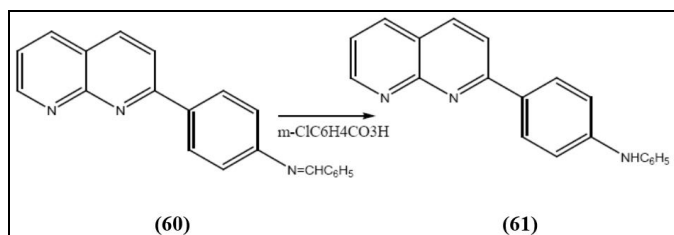
Conversion of a azido to amino naphthyridine

The 4-Azido-7-methyl-2-phenyl-1, 8-naphthyridine (58) gave 7-methyl-2-phenyl-1,8-naphthyridin-4-amine (59) with Pd/C in methanol, H₂O at 20°C.

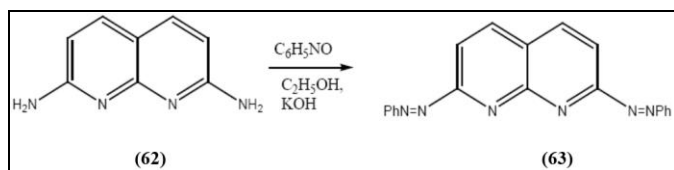


Reactions of amino-1,8-naphthyridine

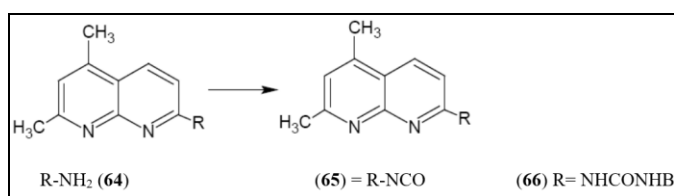
The 2-p-(Benzylideneamino) phenyl-1,8-naphthyridine (60) underwent oxidation to give 2-p-benzamidophenyl-1,8-naphthyridine (61) on treatment with m-ClC₆H₄CO₃H.



The 1, 8-Naphthyridine-2,7-diamine (62) with nitrobenzene gave 2,7-bis phenyl azo-1,8-naphthyridine (63) on treatment with alcoholic KOH in H₂O.

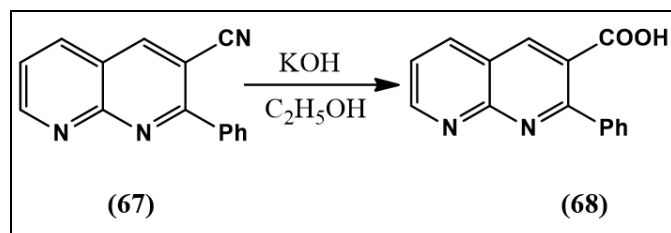


The 5,7-Dimethyl-1,8-naphthyridin-2-amine (64, R=NH₂) gave 2-isocyanato-5,7-dimethyl-1,8-naphthyridine (65, R=NCO) as a minor product (7%) via an imidazole[1,2-a][1,8]naphthyridine intermediate. The same substrate (64, R=NH₂) with butyl isocyanate afforded 2-N-butylureido-5,7-dimethyl-1,8-naphthyridine (66, R=NHCONHBu) on reflux with toluene.



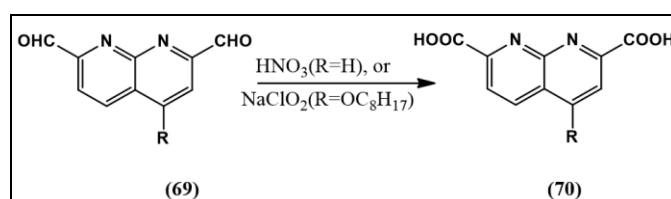
Preparation of 1, 8-naphthyridine carboxylic acid By hydrolysis of 1, 8-naphthyridinecarbonitriles

The 2-Phenyl-1,8-naphthyridine-3-carbonitrile (67, R=CN) gave the corresponding 3-carboxylic acid (68, R=CO₂H) on reflux with alcoholic KOH in water for 14 h at 70 °C, the yield was found to be 76%.



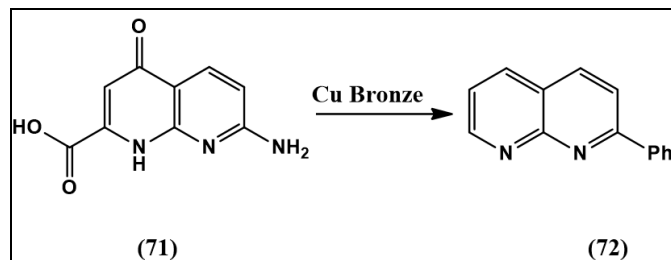
By oxidation of 1,8-naphthyridinecarbaldehydes

The 1,8-Naphthyridine-2,7-dicarbaldehyde (69, R=H) gave 1,8-naphthyridine-2,7-dicarboxylic acid (70, R=H) on refluxing with 80% HNO₃.



Reaction of 1, 8-naphthyridine carboxylic acid Decarboxylation

The 7-Amino-4-oxo-1, 4-dihydro-1,8-naphthyridine-2-carboxylic acid (71) gave 2-phenyl-1,8-naphthyridine (72) on treating with Cu bronze at 260 °C.



Conclusion

Drug discovery research is a highly creative and stimulating work environment where people are driven to succeed by personal and scientific objectives. Many heterocycles have important pharmaceutical properties and biological applications like used as pharmaceuticals, agro chemicals and veterinary products. They are also used as optical brightening agents, as antioxidants, as copolymers, solvents, photographic sensitizers, corrosion inhibitors and additives with a variety of other functions [36-40]. Many dye stuffs and pigments have heterocyclic structures.

Conflict of Interest

Not available

Financial Support

Not available

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