Efficient and Eco-friendly Synthesis of 1,7-Naphthyridines

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Abstract

A microwave-promoted new easy, efficient, clean and environmentally benign method for the synthesis of 1,7- naphthyridineand its derivatives from 2-cyano-3-pyridylacetonitrile has been developed. The desired products were isolated in excellent yields and high purity under eco-friendly conditions. The synthesized compounds were characterized by the IR, UV-Visible and ^{1}H NMR spectral analyses along with elemental analysis.

Keywords: Microwave, eco-friendly, pyridylacetonitrile, naphthyridines

Introduction

Among the nitrogenous heterocycles, naphthyridines and their derivatives represent an important class of organic molecules that attract the interest of both synthetic and medicinal chemists due to their exceptionally broad spectrum of biological activities as well as their use as important binding units in the molecular design of synthetic receptors [1].

Naphthyridine derivatives attract interest because of their broad spectrum of biological activities and practical importance. Their synthesis, properties, reactivity and biological activity have been covered in several reviews by Litvinov [2-5]. These compounds are used in diagnostics and treatment of different bacterial and viral (HIV) infections and are synthesized as potential anti-malarials and anticancer agents. They are also used in agriculture for parasite control as preservatives and components of lubricating coolants in industry for metal processing and in analytical chemistry asligands. The biological activities of 1,8-naphthyridine derivatives have received mostattention [5].However,1,7-naphthyridines have recently attracted interest as selective Tumor Progression Loci-2 (Tpl2) kinase inhibitors as the kinase is an attractive targetfor the treatment of rheumatoid arthritis [6-7]. In addition, 1,7-naphthyridines have shown antiparasitic activities [8] and potential as new therapeutic antitumor agents [9].

Naphthyridines are generally synthesized using quinolone as well as pyridineas backbones and several common synthetic routes have been extensively explored and reported [10-11]. In the recent past, reports on microwave technology for the synthesis of heterocycles and macromolecules have been well documented in the literature [12-13]. The main benefits of performing reactions under microwave

conditions are the significant enhancement of reaction rates, higher product yields as well as conforming to global demands on utilizing green technology [14].Thus, microwave induced organic synthesis becomes a part of green chemistry. Now-a-days it is also termed as e-chemistry because it is easy, economic, effective and eco-friendly.The cyclization of o-cyanobenzylcyanides to isoquinolines and naphthyridines is well reviewed [15]. However, no publications are available for the eco-friendly synthesis of 1,7-naphthyridines from cyclization of 2-cyano-3-pyridylacetonitrile.The present study reports a microwave assisted synthesis of 1,7-naphthyridines from easily available and cheap chemical namely ethyl-2-cyano-3-pyridylacetate.

Experimental

Instruments and Technique

All the chemicals were purchased from Merck. The microwave irradiations were performed using a commercial / kitchen microwave oven model BMO: 700T (BPL- make). The melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 521 grating spectrophotometer. Solid compounds were sampled as KBr unless otherwise indicated, and liquid compounds as a film supported between sodium chloride plates. The ultraviolet spectra were obtained on a Perkin-Elmer Model 350 spectrophotometer using absolute methanol as solvent. Nuclear magnetic resonance spectra were determined on a Varian High Resolution Nuclear Magnetic Resonance Model A-60 spectrometer. Solvents used were deuteriochloroform ($CDCl_3$) and dimethyl-tetramethylsilane was used as sulfoxide-d_6 (DMSO-d_6) an internal reference (TMS = 0 p.p.m.). The chemical shifts are expressed in δ-scale downfield from TMS and proton signals are indicated as *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet. The TLC was run on silica gel plates using acetone-benzene (1:3) as the irrigant. All compounds were analysed satisfactorily for C, H and N using Carl-Ebra 1106 elemental analyser in micro analytical laboratory.

Experimental Methods

(a) Preparation of 6-Amino-8-bromo-1,7-naphthyridine(V)

2-Cyano-3-pyridylacetonitrile (IV) (1.1 g) was dissolved in 75 ml of dry ether and cooled to -5^{0}C to 0^{0}C. Anhydrous hydrogen bromide was bubbled through the solution for 2 hours and the resulting mixture was poured immediately into a solution containing excess sodium bicarbonate. The yellow precipitate was filtered off, washed with several small portions of water and dried, yielding 1.25 g of 6-amino-8- bromo-1,7-naphthyridine (V) (72.7%). Recrystallization from chloroform-benzene gave yellow prisms, m.p. 181^{0}C (with dec.).

***Analytical Data*:**

Calculated for $C_8H_6N_2Br$: C, 42.88; H, 2.68; N, 18.76; Br, 35.67

Found: C, 42.80; H, 2.71; N, 18.64; Br, 35.85

(b)Preparation of 6-Amino-1,7-naphthyridine (VI)

6-Amino-8-bromo-1,7-naphthyridine (V) (0.67 g; 3.0 mmoles) was dissolved in 150 ml of absolute ethanol. An alcoholic solution of potassium hydroxide (0.45 g in 10 ml ethanol) and 10%palladium on charcoal (0.075 g) were added and the mixture was hydrogenated for 45 min. at room temperature and 30 p.s.i. The catalyst was filtered off and the filtrate was diluted with 500 ml of water. The solution was extracted with three 200 ml portions of methylene chloride and the combined extract was dried over anhydrous sodium sulfate. The solvent was evaporated leaving 0.35 g of 6-amino-1,7-naphthyridine (VI) (77.8% yield). Recrystallization from methylene chloride-benzene gave yellow prisms, m.p. 174^{0}C.

***Analytical Data*:**

Calculated for $C_8H_7N_3$: C, 66.21; H, 4.83; N, 28.96

Found: C, 66.12; H, 4.94; N, 28.90

(c)Preparation of 6,8-Dihydrazino-l,7-naphthyridine (VII)

6-Amino-8-bromo-l,7-naphthyridine (V) (1.5 g; 6.7 mmoles) was dissolved in 20 ml of dioxane and 10 ml. of 85% hydrazine hydrate was added drop wise. The mixture was refluxed at 110^{0}C for 8 minutes in the microwave oven and cooled to room temperature. The yellow precipitate was filtered off and washed with small amounts of water to give 0.80 g of 6,8-dihydrazino-2,6-naphthyridine (VII) (64.5% yield), m.p. 149^{0}C. A small sample was sent for elemental analysis without further purification.

***Analytical Data*:**

Calculated for $C_8H_{10}N_6$: C, 50.51: H, 5.30: N, 44.19

Found: C, 50.75; H, 5.50; N, 44.04

(d)Preparation of 1,7-Naphthyridine (I)

6,8-Dihydrazino-l,7-naphthyridine (VII) (0.8 g: 4.2 mmoles) was dissolved in 8 ml of acetic acid and 16 ml of water. This was poured slowly into 80 ml of 10% hot copper sulfate solution and the mixture was boiled for 3 minutes in the microwave oven. It was made strongly alkaline with 20% sodium hydroxide solution and extracted continuously with ether for 2 days. The ethereal solution was dried over anhydrous sodium sulfate and the solvent was evaporated leaving 0.2 g of tan oil. Purification by chromatography and recrystallization from dry petroleum ether gave 0.10 g of 1,7-naphthyridine as white crystals (67.2% yield), m.p. 60^{0}C : lit[16]: 57-60^{0}C.

***Analytical Data*:**

Calculated for $C_8H_6N_2$: C, 73.85; H, 3.75; N, 21.54

Found: C, 73.97; H, 3.92: N, 21.85

Results and Discussion

The synthesis of 1,7-naphthyridine (I) from ethyl-2-cyano-3-pyridylacetate (II) is outlined in *Chart-1*. Treatment of II, a by-product in the cyanation of ethyl 3-pyridylacetate in the process of the preparation of 4-cyano-3-pyridylacetonitrile, with 28 percent ammonium hydroxide solution gave 76.4 percent yield of 2-cyano-3-pyridylacetamide (III). Dehydration of III with phosphorus oxychloride in pyridine produced 2-cyano-3-pyridylacetonitrile (IV) in 88.2 percent yield. Cyclization of IV with anhydrous hydrogen bromide gave 72.7 percent of 6-amino-8-bromo-l,7-naphthyridine (V). Reaction of V with 85 percent hydrazine hydrate afforded 64.5 percent yield of 6,8-dihydrazino-l,7-naphthyridine (VI) and the oxidation of VI with 10 percent copper sulfate solution gave 67.2 percent yield of 1,7-naphthyridine (I).This compound was so soluble in aqueous solution that it was isolated only after the basic solution was continuously extracted with ether for two days. This afforded a new route for the synthesis of 1,7-naphthyridine.

Reduction of compound V with 10 percent palladium on charcoal in alcoholic potassium hydroxide solution gave 6-amino-l,7-naphthyridine (VII) in 81.2 percent yield. The results are compared to the conventional methods (Table-1).

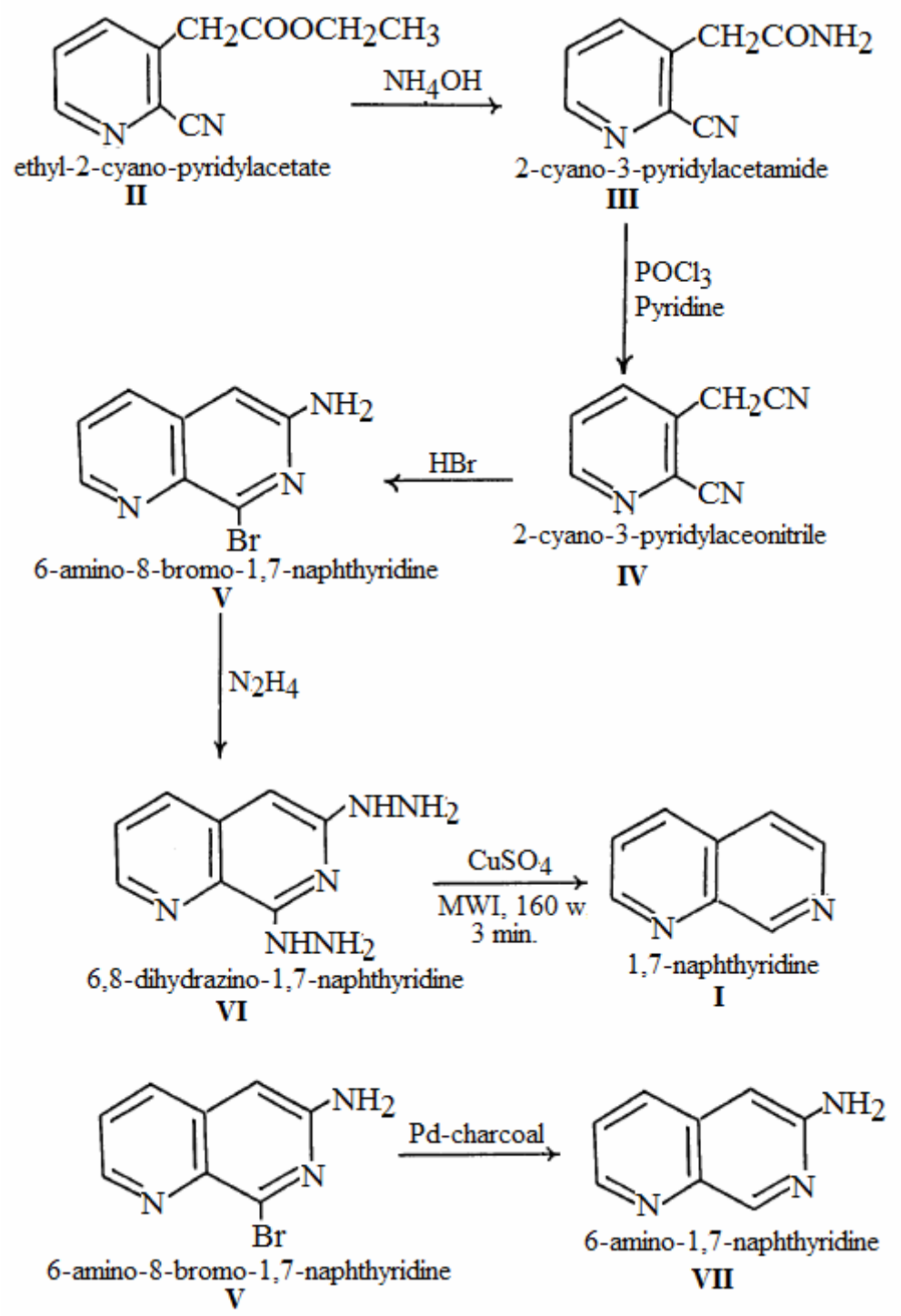
Table-1: Comparison of % yield of synthesized compounds

Compound	m.p.(in K)	% Yield	
		Conventional method	Green method
I	333	18.2%	67.2%
V	454	36.3%	72.7%
VI	447	39.6%	77.8%
VII	422	27.8%	64.5%

In the infrared spectrum of III, the presence of the primary amide group was shown by bands at 3390, 3195, 1662 and 1614 cm^{-1}.The NMR spectrum of III showed three well-defined quartets at 8.53, 7.87 and 7.55 ppm, which were assigned to the alpha (H_6), para (H_4) and meta (H_5) protons, respectively ($J_{4,5}$= 8.0 cps, $J_{4,6}$ = 1.6 cps, $J_{5,6}$ = 4.5 cps). The amino group protons gave rise to the broad bands at 7.02 and 7.SS ppm. The latter band was overlapped by the H_5 quartet. Themethylene protons were assigned to the singlet at 3.62 ppm.

The dehydration product of III was determined to be 2-cyano-3-pyradylacetonitrile (IV).Evidence for this structure was the presence in the IR spectrum as a doublet at 2262 and 2234 cm^{-1} (C≡N stretch), a strong band at 1431 cm^{-1} (CH_2 deformation for CH_2 group lying between an ethylenic and a cyano group) [15], and bands at 811 and 766 cm^{-1} (2,3- disubstituted pyridine ring) [16]. The NMR spectrum exhibited three

well-defined quartets at 8.70, 8.04 and 7.63 ppm which were assigned to the alpha (H_6), para (H_4)and meta (H_5) protons, respectively ($J_{4,5}$ = 1.0 cps, $J_{4,6}$ = 8.0 cps, $J_{5,6}$ = 4.9 cps). The singlet at 4.03 ppm was due to the methylene protons.



Scheme-1: Microwave assisted synthesis of 1,7-naphthyridines

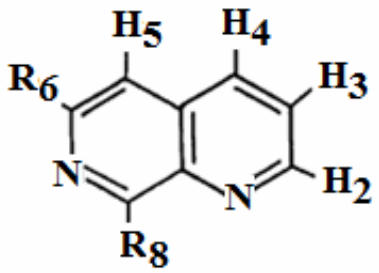
The cyc1ization product of compound IV was determined to be 6-amino-8-bromo-1,7 naphthyridine from its infrared and NMR spectra. The infrared spectrum exhibited bands at 3374, 3316 and 3199 cm^{-1}(NH_2 asym. and sym. stretch) and 1639 cm^{-1}(NH_2 deformation). A strong band at 833 cm^{-1} indicated the presence of a 2,3-disubstitutted pyridine ring [17]. The NMR spectrum of V showed three well-defined quartets centered at 8.47, 7.98 and 7.33 ppm, which were assigned to H_2, H_4 and H_3, respectively ($J_{2,3}$= 4.0 cps, $J_{2,4}$= 1.6 cps, $J_{3,4}$= 8.6 cps). The singlet at 6.50 ppm was due to the isolated proton, H_5. The up-field displacement of the chemical shift of H_5 from that of the other *meta* proton, H_3, indicated the shielding effect of the *ortho* amino group [18]. The remaining broad band at 6.25 ppm was assigned to the primary amino group protons.

The NMR spectrum of compound VII exhibited three well-defined quartets at 8.39,7.80 and 7.22 ppm which were assigned to H_2, H_4 and H_3, respectively ($J_{2,4}$= 1.5 cps, $J_{3,4}$= 8.4 cps, $J_{2,3}$= 4.0 cps), a singlet at 6.49 ppm for H_5 and another singlet at low field (8.77 ppm) for H_8.

a) 1H NMR spectroscopic study of l,7-naphthyridine:

The NMR spectrum of l,7-naphthyridine (Figugre-1) shows an AMX pattern due to H_4, H_3 and H_2, and an AX pattern due to H_5 and H_6, while H_8 appears as an isolated proton singlet. In the spectrum of 1,7-naphthyridine, the singlet at 9.66 p.p.m. is assigned to the most deshielded proton, H_8. The assignment of the low field peaks for the remaining alpha protons, H_2 and H_6, is made by noting that H_2 is part of an AMX system and H_6 is part of an AX system. Thus, the quartet at 9.14 p.p.m. is due to H_2 ($J_{2,3}$= 4.2 c.p.s., $J_{2,4}$ = 1.6 c.p.s.) and the doublet at 8.73 p.p.m. is attributed to H_6 ($J_{5,6}$ = 5. 7 c. p. s.). The A part of the H_6 AX system corresponds to the doublet centered at 7.72 p.p.m. and is consequently H_5. The nature of the splitting pattern clearly shows that the "broad doublet" centered at 8.26 p.p.m. is due to H_4 ($J_{3,4}$ = 8.4 c.p.s.), and the remaining quartet centered at 7.67 p.p.m. is due to H_3 ($J_{4,2}$ = 4.2 c.p.s., $J_{3,4}$ = 8.4 c.p.s.). An expanded scale spectrum of the H_4 portion shows that each band of this doublet is further split into a quartet, which arises from the metacoupling of H_4 with H_2 ($J_{2,4}$ = 1.6 c.p.s.) and the long range coupling of H_4 with H_8 ($J_{4,8}$ = 0.8 c.p.s.).

The chemical shifts and the spin-spin coupling constants of 1,7-naphthyridine and some of its derivatives are shown in Table-2 and the respective NMR spectra in figure-1,2 &3.



b) IR spectroscopic study of l,7-naphthyridines:

As in the case of benzenoid hydrocarbons, heterocyclic compounds show the C-H stretching vibrations in the region 3100 - 3000 cm^{-1} as a series of multiple absorptions [19].1,7-Naphthyridine and its derivatives display two bandsappear both above and below 3000 cm^{-1}. The unsubstituted 1,7-naphthyridine has peaks at 3090, 3055, 3045, 2965, 2930 and 2855 cm^{-1} (Figure-4).

Table-2: NMR spectra of 1,7-naphthyridine & its derivatives

Compound	R_6	R_8	Chemical shifts δ (in ppm)						
			H_2	H_3	H_4	H_5	H_6	H_8	Other
I (in $CDCl_3$ soln.)	H	H	9.14	7.67	8.24	7.72	8.73	9.66	
V(in DMSO-d_6 soln.)	NH_2	Br	8.47	7.33	7.98	6.50			6.25(NH_2)
VII (in DMSO-d_6 soln.)	NH_2	H	8.39	7.22	7.80	6.49		8.77	5.98(NH_2)
			Spin-spin coupling constants J (in cps)						
			$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,8}$	$J_{5,6}$	$J_{5,8}$	
I (in $CDCl_3$ soln.)	H	H	4.2	1.6	8.4	0.8	5.5	1.0	
V(in DMSO-d_6 soln.)	NH_2	Br	4.0	1.6	8.6				
VII (in DMSO-d_6 soln.)	NH_2	H	4.0	1.5	8.4	0.8			

The l,7-Naphthyridine and its derivatives also show five bands in the 1600 - 1350 cm^{-1} region which are assigned to the ring skeletal vibrations. These bands occur in the range 1600±10, 1585±5, 1470±10, 1430±10 and 1372±8 cm^{-1}. The intensity of the band near 1430 cm^{-1} is relatively weak compared to that of the other four bands.

The 1,7-Naphthyridine and its derivatives show two or three bands in 900-700 cm^{-1} region. The unsubstituted 1,7-naphthyridine displays three bands at 853, 819 and 783 cm^{-1} which are due to the isolated hydrogen at C-8, to the two adjacent hydrogens at C-5 and C-6, and to the three adjacent hydrogens at C-2, C-3 and C-4, respectively. The 6-substituted 1,7 naphthyridines show a strong band near 770 cm^{-1} which is attributed to the C-H out-of-plane deformation vibration of three adjacent hydrogens at C-2, C-3 and C-4 and another band in the region 823 – 833 cm^{-1} due to an isolated hydrogen at C-5 or C-8.

c) UV-Visible spectroscopic study of l,7-naphthyridines:

The ultraviolet spectra of 1,7-naphthyridines and their derivatives (Table-3) all show three main types of absorption bands. Mason, in his review of the literature [20], found that these three types of

bands, classified as α-, ρ-and β-bands, applied to all hetero-aromatic molecules. These bands arise from π-π*electron transitions.

The intensities of these bands vary in the order,

$$\beta > \rho > \alpha$$

and the wavelengths in the order,

$$\alpha > \rho > \beta$$

so that the bands in the spectrum of the present compounds are easily assigned (Figure-5).

Comparison of the spectra of 1,7-naphthyridines with the spectrum of pyridine (α-band, 251 mμ, log ε = 3.30; ρ-band, 192 mμ, log ε= 3.80; β-band, 175 mμ, log ε= 4.90) shows a strong bathochromic displacement of all the bands in the naphthyridines relative to the corresponding bands in pyridine.

Table-3: Ultraviolet Absorption Maxima and Their Corresponding Log E Values of 1,7-Naphthyridine and its Derivatives in Methanol

Compound	α-band		ρ-band		β-band	
	mμ	log ε	mμ	log ε	mμ	log ε
1,7-Naphthyridine (I)	312 301	3.21 3.26	261	3.50	219	4.37
6-Amino-8-bromo-1,7-Naphthyridine (V)	385	3.47	290	3.71	241	4.55
6,8-Dihydroazino-1,7-Naphthyridine (VI)	387	3.54	314	3.89	245	4.36
6-Amino-1,7-Naphthyridine (VII)	376	3.41	286	3.76	238	4.64

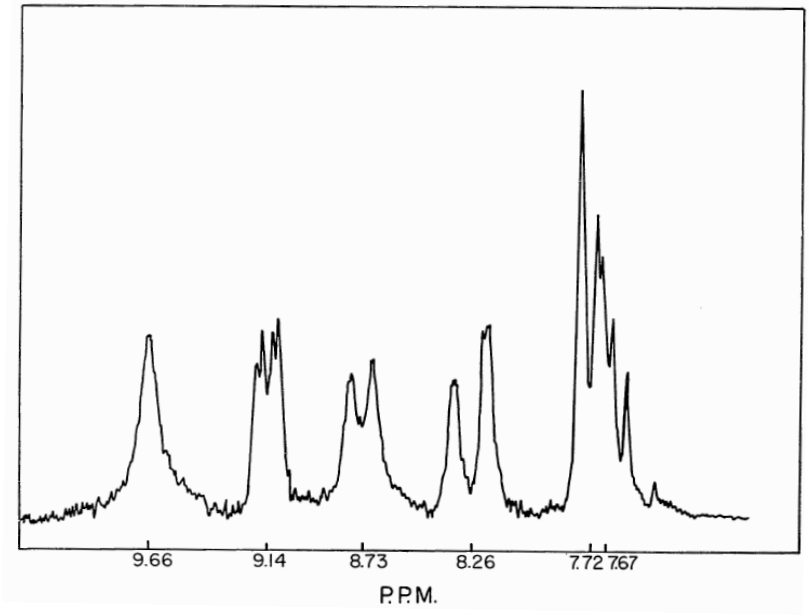


Figure-1:NMR Spectrum of 1,7-Naphthyridine (I) in $CDCl_3$

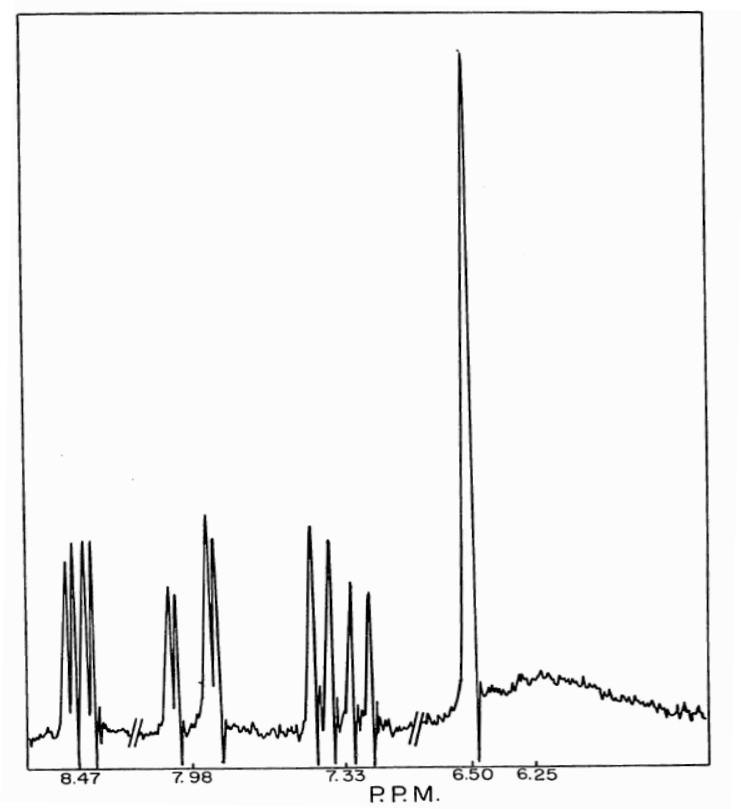


Figure-2: NMR Spectrum of 6-Amino-8-bromo-1,7-naphthyridine (VI) in DMSO-d_6

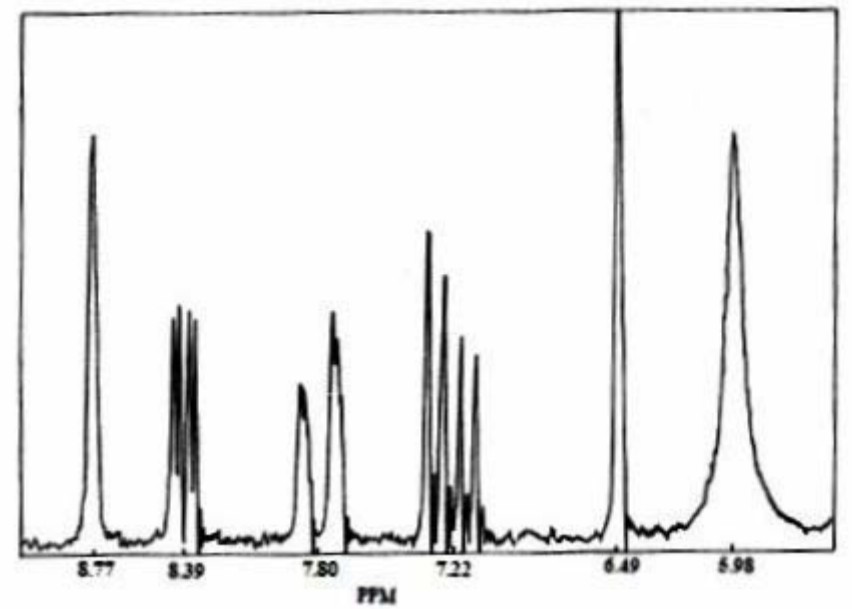


Figure-3: NMR Spectrum of 6-Amino-1,7-naphthyridine (VII) in DMSO-d_6

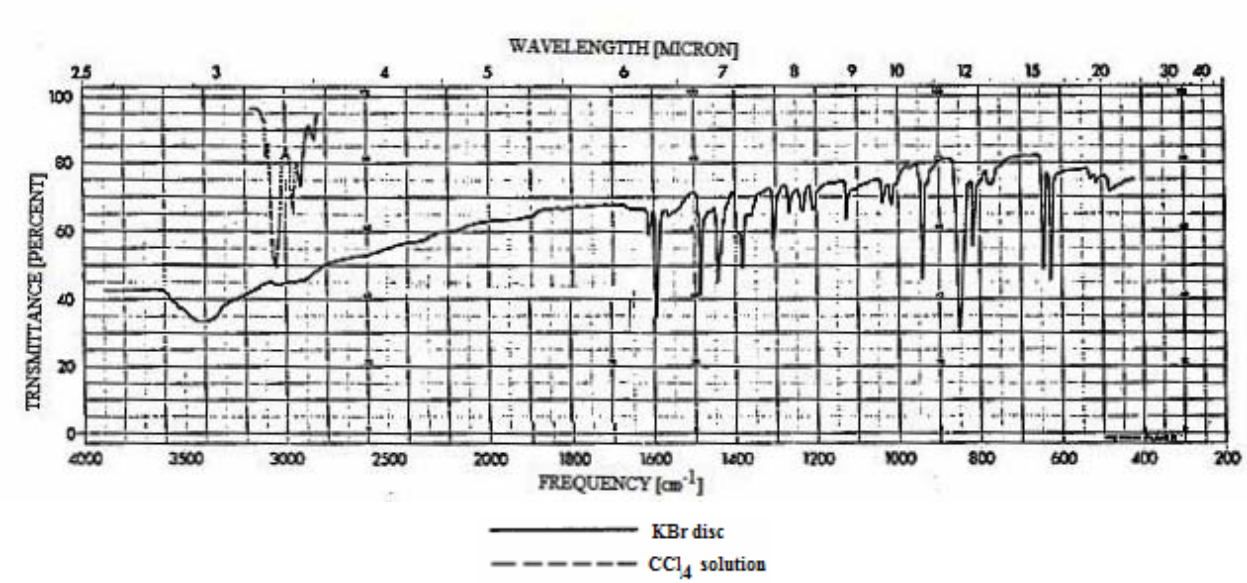


Figure-4: Infrared Spectrum of 1,7-naphthyridine (I)

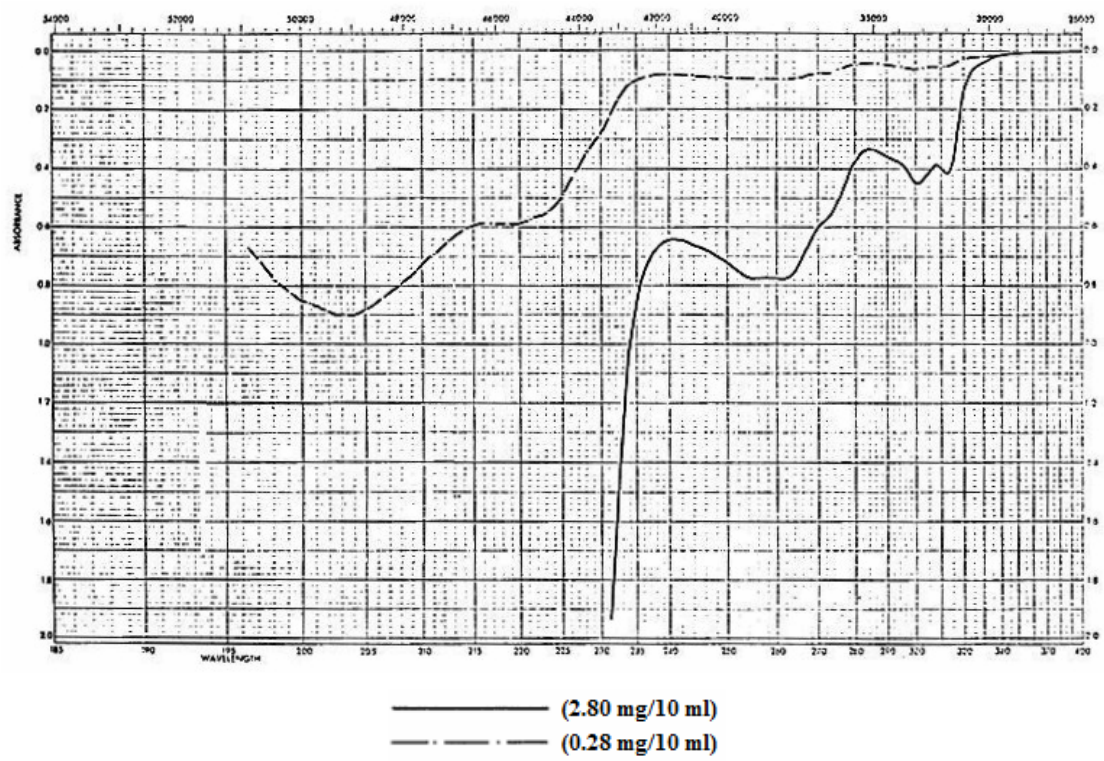


Figure-5: Ultraviolet Spectra of 1,7-naphthyridine (I) in Methanol

Conclusion

A new method for the synthesis of 1,7-naphthyridine from 2-cyano-3-pyridylacetonitrile was developed. It involved the cyclization of 2-cyano-3-pyridylacetonitrile to 6-amino-8-bromo-l,7-naphthyridine by the action of hydrogen bromide, conversion of the cyclization product to 6,8-dihydrazino-l,7-naphthyridine by reaction with hydrazine hydrate and oxidation of the latter compound

with copper sulfate to unsubstituted 1,7-naphthyridineunder microwave irradiation which is simple, mild, efficient and ecofriendly from green chemistry point of view.

In conclusion, we observed better yields in a shorter period compared to the conventional methodsin the present protocol. We describe here an efficient and environmentally benign synthesis of 1,7-naphthyridine and its derivatives.

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