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ORIGINAL RESEARCH ARTICLE

Synthesis of some 1, 8- Naphthyridine Derivatives with Comparative Studies of Cyclization in Two Different Acids

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ABSTRACT

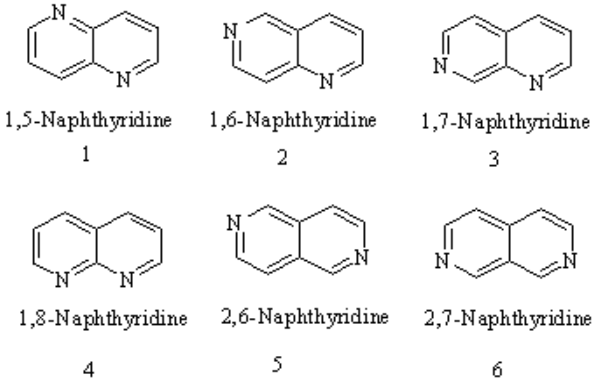
Synthesis of some new 1,8-naphthyridines (out of which four are new) derivatives were described. The synthesized compounds were prepared by the condensation of 2,6-diaminopyridine and 1,3-dicarbonyl compounds with various chemical reagents. However, there are significant effects on yields and isomer ratios depending on the use of perchloric or phosphoric acids in the condensation reaction. Based on the isomer ratios, some probable reaction mechanisms are proposed. The purity of the new synthesized compounds were checked by performing TLC using appropriate solvent and the spots were visualized in the UV light. The chemical structure of the compounds were confirmed by FT-IR, ^{1}H, ^{13}C- NMR spectroscopy.

Key words: 1-8 naphthyridine, 2,6-diaminopyridine, 1,3-dicarbonyl, Orthophosphoric acid 85%, perchloric acid 60%, pentanedione, butanedione, benzoylacetone , dibenzoylmethane.

INTRODUCTION

The first naphthyridine derivatives were 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 [2] (**Fig 1**).

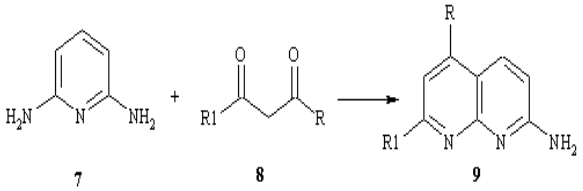
Fig 1: Naphthyridines isomers



Recently, there are numerous studies including this present work, have reported the preparation of 1, 8-naphthyridines via a variety of pathways [3-7].

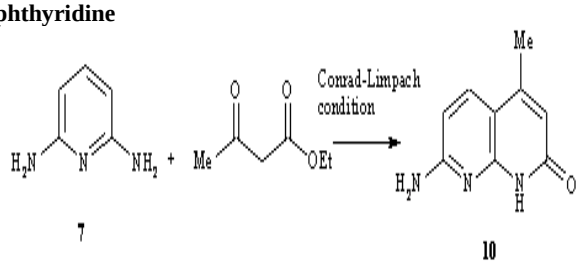
The reactions between 2,6-diaminopyridine **7** and 1,3-dicarbonyl compound **8** gave compound **9** [8].

Scheme 1: Synthesis of substituted 1-8 naphthyridine



On the other hand, the condensation reaction of 2,6-diaminopyridine **7** with ethylacetoacetate under Conrad-Limpach conditions yield 2-oxo compound **10** [9].

Scheme 2: Synthesis of 2-Oxo-(4-methyl-7-amino)1-8-naphthyridine



Substituted 1,8-naphthyridine was obtained via the skraup reaction in good yield, the condensation reaction of 2-aminopyridine substituted in the 6-position with an electron-

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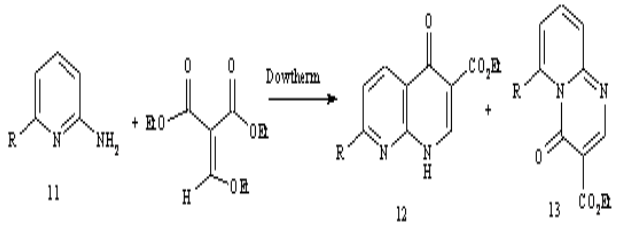
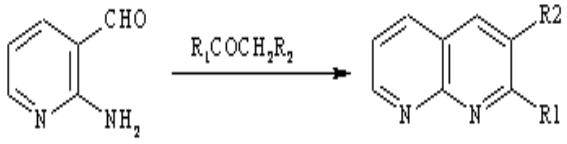
releasing group [R= Me, OEt, NHR] **11** with diethyl ethoxymethylenemalonate (EMME) followed by cyclization in Dowtherm afforded 1,8-naphthyridin-4-one **12** and isomeric pyridopyrimidinone **13** [10].

Scheme 3:



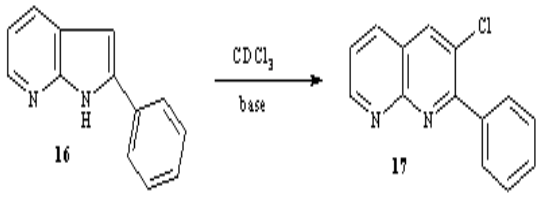
The Friedlander condensation of 2-aminonicotinaldehyde **14** with ketones and other active methylene compound gave compound **15** [11].

Scheme 4:



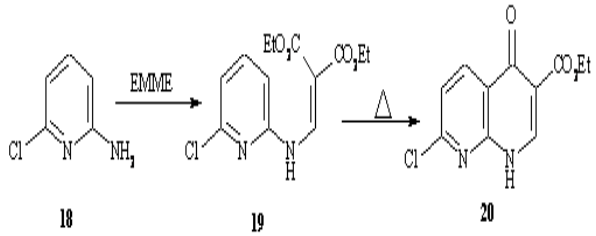
Treatment of 2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine **16** with chloroform and alkali caused ring-expansion to a 1,8-naphthyridine **17** [12].

Scheme 5



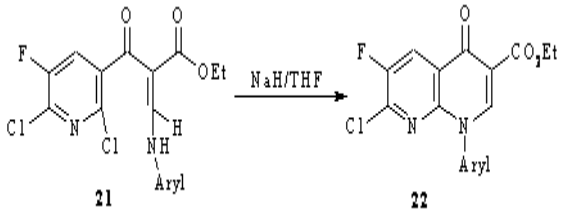
Recently, in the synthesis of 1,8-naphthyridines have led to the reexamination of ring closures with the appropriate functional groups. By using well-known reaction of 2-amino-6-chloropyridine **18** with diethylethoxymethylenemalonate (EMME) gave aminomethylenemalonate **19**, upon the thermal cyclization of compound **19** (Gould-Jacobs reaction) yield 1,8-naphthyridin-4-one derivative **20** [13].

Scheme 6



On the other hand the reaction of 1-aryl substituted compound **21** via the cyclization of ethylacrylates Yielded 1,8-naphthyridin-4-one derivative **22** [14].

Scheme 7



EXPERIMENTAL:

Chemistry:

Melting points were determined with a Gallenkamp (London, U.K.) melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian 200 BB (200 MHz) with TMS as an internal standard in $CDCl_3$ and $DMSOd_6$ for all compounds. MS spectra were acquired using mass spectrometer type AMD 604 with direct inlet, AMD Intectra, Germany (ionization energy 70 eV). The purity of the products was confirmed by TLC on Merck plates (Kieselgel60 F254) with the use of appropriate solvent, and the spots were visualized in the UV light. Elemental analyses were determined using Automatic Elemental Analyzer CHN Model 2400 Perkin Elmer (USA). All the results of elemental analyses (C, H, N.) were within ± 0.4 % of the theoretical values.

General procedure for the synthesis of 1,8-naphthyridines:

1,8-naphthyridine derivatives were prepared by reaction of equimolar (1.09g, 10mmol) of 2,6-diaminopyridine and 1,3-dicarbonyl compound, the mixture was suspended in 60% perchloric acid (10-15ml) and stirred at stated temperature and stated time. The mixture was cooled, then the mixture was poured into water (150ml) and kept in the refrigerator for 2 h. From here onwards, the work-up varies with the specific naphthyridine.

2-Amino-5,7-dimethyl-1,8-naphthyridine 23.

Reaction of 2,6-diaminopyridine (1.09g, 10mmol) with 2,4-pentanedione (1.00 g, 10 mml) at 60° for 6 hr. The obtained product was filtered off and basified with 20% NaOH solution. The resultant precipitate was filtered and recrystallized from $MeOH/H_2O$.

Yield % : 75 % , M.p: 217 ^{0}C.

Vmax (KBr) 3195m, 306m, 1647s, 1619s, 1588s, 1558m, 1519s, 1416s, 1374s, 1335s, 1190w, 804m cm^{-1}. **^{1}H-NMR**. δ (ppm) (200MHz, $CDCl_3$) 2.48,s,3H,5-Me; 2.56,s,3H,7-Me; 4.88,br,2H,2-NH_2; 6.63,d,j 9Hz, 1H,H3; 6.84,s,1H,H6; 7.94,d,j 9Hz, 1H,H4. **^{13}C-NMR**. δ(50MHz, $DMSOd_6$) 17.51.5-Me; 24.23, 7-Me; 111.96, C3; 114.07, C4a; 118.84, C6; 134.33,C4; 145.69,C5; 155.18, C8a; 159.47,C7; 160.24,C2. **M.S** m/z: 174 (M+1,

12%), 173(M,100), 172(16), 146(19), 141(2), 131(5), 104(4), 87(3), 77(5), 51(2).

2-Amino-5,7-di (trifluromethyl)-1,8-naphthyridine 24.

Reaction of 2,6-diaminopyridine (1.09 g, 10 mmol) with 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (2.08 g, 10 mmol) at 50 °C for 3 days. The precipitate was filtered off and basified with 20 % sodium hydroxide solution. The resultant precipitate was filtered and recrystallized from EtOH / H_2O.

Yield: 70 %, M.p: 210-211°C, Vmax(KBr) 3337m, 3210m, 1647m, 1523m, 1474m,1433m, 1388 m, 1282 s, 1215 m, 1134s, 876 m, 806 m, 665 m cm^{-1}. **^{1}H-NMR**. δ(ppm) (200 MHz, $CDCl_3$) 5.93, br,2H,2-NH_2; 7.02, d,j 9Hz,1H,3H; 7.75, s,1H,6H; 8.20,dq, j 9Hz,j 1.8Hz,1H,H4. **^{13}C - NMR**. δ(50MHz, $DMSOd_6$) 109.02,C6; 113.79,C4a; 120.96,q,j 275Hz;5-CF_3 and 7-CF_3; 118, C3; 133.55, C4; 135.34,q,j 32Hz,147.80, q, j 35Hz,C5 and C7; 156.98 , C8a ;161.79,C2. **M.S** m/z 282 (M+1, 12%), 281(M,100), 262(10) , 254(35), 234(25) , 185(5), 158(2), 75(2), 69(8), 63(3).

2-Amino-5-methyl-7-trifluoromethyl-1,8-naphthyridine 25a.

2-amino-5-trifluoromethyl-7-methyl-1,8-naphthyridine 25b.

Reaction of 2,6-diaminopyridine (1.09 g, 10 mmol) with 1,1,1-trifluoro-2,4-pentanedione (1.54 g, 10 mml) at 60° for 24 hours. The precipitate was filtered off and basified with 20 % sodium hydroxide solution. The resultant precipitate was filtered and recrystallized from EtOH/H_2O

Yield: 90 %, M.p: 254 °C dec.

Vmax (KBr) 3495m, 3315s,3195m,1632s,1570m, 1517m,1471m,1498s, 1258s, 1146s, 912m, 858m,804m,783wcm^{-1}. **^{1}H-NMR**.δ(ppm) (200MHz, $CDCl_3$) 2.69, s,3H,s, 5-Me; 5.27,br ,2H,2-NH2; 6.89,d,j 9Hz,1H,H3; 7.37,s ,1H,H6; 8.12, d, j 9Hz,1H,H4. **^{13}C-NMR**. δ (50MHz, $DMSOd_6$) 17.75,5-Me; 113.55, C3;115.13, C6;117.90,C4a; 127.17,q, j 275Hz,7-CF3; 134.00,C4; 147.25 , q, j 33Hz, C7; 148.23, C5; 155.93, C8a; 161.39,C2. **M.S** m/z 282 (M+1, 12 %), 227 (M,100), 226(19), 208(7), 206(16), 200(41), 199(7), 181(12), 180(24), 179 (4),158(6) , 143(3) ,131 (13), 114(8), 104(11), 77(8), 69(7), 63(6), 51(4).

However, at concentration 85% H_3PO_4, the other isomer **25b** could be isolated. The resultant precipitate was filtered off and the filtrate was adjusted to pH 7 with 20% NaOH, the final precipitation was filtered and recrystallization from 95 % EtOH afforded beige needles. Treatment of the beige needles with 20% NaOH solution yielded a solid product, which was recrystallized from H_2O/EtOH.

Yield: 25% , M.p: 197-199 °C.

Vmax(KBr) 3424m,1670s,1597s,1525m, 1380s, 1264s ,1209 m , 1127s,894m, 803m cm^{-1}. ^{1}H - NMR. δ(ppm) (200MHz, $CDCl_3$) 2.74,s, 3H,7-Me; 5.49,br,2H,2-NH_2 ; 6.84,d,j 9Hz,1H,H3; 7.33,s,1H,H6; 8.12,dq,j 9Hz, j 1Hz,1H,H4. ^{13}C-NMR. δ(50MHz, $DMSOd_6$) 25.53,7-Me; 110.48,C4a; 112.94,C3;115.35,q,j 5Hz,C6; 123.25,q,j 275Hz,5-CF3;134.22,d,j 2Hz,C4; 134.92, q,j 32Hz,C5; 156.98, C8a; 159.75,C7; 161.90,C2. M.S m/z 228 (M+1, 12 %), 227(M,100), 200(48), 172(3), 152(5), 131(20), 113(5), 90(10) , 69(10), 63(22), 51 (9).

2-Amino-5-trifluoromethyl-7-(2-thienyl)-1,8-naphthyridine 26a.

2-amino-5--(2- thienyl)—7-trifluoromethyl-1,8-naphthyridine 26b.

The reaction of 2,6-diaminopyridine (1.09g, 10mmol) with 4,4,4-trifluoro-1-(2-thienyl)-1,3-butanedione (2.22g,10mmol) at 50 °C for 5 days in 85 % H_3PO_4. The precipitate was filtered off and basified with 20 % NaOH. The resultant precipitate was filtered and recrystallized from ethanol. Yield: 50 %, M.p: 263-264 °C dec.

Vmax (KBr) 3478m, 3270br, 3150br, 1638s, 1586s, 1539m, 1514m, 1437m, 1412m, 1389s, 1266s,

1142s,1118s,965m,869m,832m,800m,717m cm^{-1}.

^{1}H-NMR. δ(ppm) (200MHz, $CDCl_3$) 5.40, br, 2H,2-NH_2; 6.82,d, j 9Hz,1H, H3; 7.16, dd,j 5Hz,j 3.7Hz,1H,H4;7.52,dd,j 5Hz,j1.0Hz,1H,H3; 7.81,dd,j 3.8Hz,j1.0Hz, 1H,H2; 7.83,s, 1H,H6;8. 13,dq,j 9Hz, 1H, H4. **^{13}C-NMR**. δ(50MHz, $DMSOd_6$) 109.48,q ,j 5.0Hz, C6; 109.97,C4a; 114.47, C3;123.31, q, j 275 Hz, 5-CF_3; 127.99 and 128.70,C3´ and C5´; 130.54,C4';132.60,C4, 134.06, q, j 31Hz, C5; 144.13,C2';153.34, C8a; 157.18,C7; 161.26, C2. M.S, m/z 297 (M+2,4%), 296(M+1,11), 295 (M,100), 276(4), 269(9), 268(41), 262(4), 251(3), 223(4), (3), 172(4), 149(9), 126(5), 108(4), 90(3), 75(3), 69(7), 63(7), 58(3).

On the other hand, when the reaction was performed with 2,6-diaminopyridine (10.9 g, 0.1 mol) and 4,4,4-trifluoro-1-(2'-thienyl)-1,3-butanedione (22.2g,0.1mol) in 60 % $HClO_4$ (100 ml) at 50 °C for 5 days, the other isomer **26b** could be isolated. The filtered solid was

recrystallized from ethanol to obtain four successive crops of crystals, the third crop, after basification was identified via HPLC to contain predominantly isomer **26b**. The third crop was forced out of the ethanol solution by water and recrystallized from ethanol to give yellow needles (m.p.276-277 °C), which on basification gave a solid product, filtered of, and recrystallized from EtOH.

Yield: 20 %, M.p: .219-221°C.

Vmax(KBr) 350.1m, 3296w, 3248w, 3113m,1614s, 1567m,1422s, 1380s,1341s, 1266s, 1142s, 804m, 719m cm^{-1}. **^{1}H-NMR**. δ(ppm) (200MHz, $CDCl_3$) 7.07, d,j 9.2Hz, 1H,H3;7.35, dd,j 3.6Hz,j5. Hz,1H, H4; 7.36,br,2H,2-NH_2; 7.53,s,1H,H6; 7.60, dd,j1.2Hz, j3.6Hz, 1H,H3; 7.93, dd,j, 1.2Hz,j 5. 1Hz, 1H,H5; 8.33, d,j9.2Hz, 1H,H4. **^{13}C-NMR**. δ(50MHz, $DMSOd_6$) 112.39, C6; 115.84, C4a , 116.34,C3; 121.4a, q,j275Hz, 7-CF_3; 128.48, C3';129.36, C5';130.04, C4';134.69,C4;136.81, C2'; 142.86,C5;147.38,q,j33. 6Hz,C7; 156.92,C8a; 161.50,C2.

M.S, m/z 297 (M+2, 6%), 296(M+1, 16), 295(M,100) , 294(13) ,276(6), 274(16) , 268(48), 248(11), 232(4), 209(4), 197(5), 183(4), 172(10), 165(4), 148(11), 138(6), 133(4). 114(4), 99(5), 86(6), 75(5), 69(10), 63(8), 58(4).

2-Amino-5-phenyl-7-trifluoromethyl-7-1,8-naphthyridine 27a.

2-amino-5-trifluoromethyl-7-phenyl-1,8-naphthyridine 27b.

The mixture of 2-aminopyridine compound with 4,4,4-trifluoromethyl-1-phenyl-1,3-butanedione (1.08 g, 10 mmol) over 28°C for 45 days. The solid product was filtered of and recrystallized from ethanol gave yellow prisms (M.p. 274-275 °C), treatment of product with 20 % NaOH. The obtained product was filtered off, and then recrystallized from EtOH as white needles. Yield: 60 %, M.p. 209 °C

Vmax (KBr) 3465s,3292w, 3255w, 3075br, 1641s, 1564m, 1518m, 1466m, 1444m,1415s, 1385m, 1277m, 1258m, 1194m, 1172s, 1124s,981m, 858m, 834m, 807m, 769m, 705m, 769m, 622m, 603m, 509m, 453m,437 mcm^{-1}.

^{1}H-NMR. δ(ppm) (200MHz, $CDCl_3$) 5.76,br ,2H,2-NH_2; 6.85,d,j 9Hz,1H,H3;7.50m, 6H,ArH and H6m8.00, d, j9Hz, 1H,H4. ^{13}C-NMR. δ(200MHz, $DMSOd_6$) 112.61, C6, 116.09, C3;116.32, C4a;121.60, q, j 275Hz,7-CF_3; 128.82,129.00, and 129.43, C2', C3',C4',C5' and C6'; 134.89, C4; 136.34, C1' ; 147.25, q,j 33Hz,C7; 150.66,C5; 156,64, C8a; 161.43,C2.

M.S m/z 290 (M+1, 14%),289 (M,100),268(18),262(27), 242(6), 226(6), 192(7) ,164(7), 110(4), 96(5), 84(5),77(5), 69(9), 51(7).

However, when the reaction was carried out in 85 % H_3PO_4 over 28 °C for 45 days, it was possible to isolate the other isomer **27b**. The cooled diluted reaction mixture afforded very little precipitate; the filtrate when adjusted to pH5, gave a precipitate which was filtered of and recrystallized from ethanol to give yellow needles. Basification of the mixture afforded a solid which was recrystallized from ethanol yielded 27b**.** Yield: 13 %, M.p. 253-254 °C.

Vmax(KBr) 3472m, 3285w, 3255w, 3105m, 1641s, 1591s, 1520m, 1495m, 1463m, 1445m, 1412m, 1369s, 1291m, 1265s, 1211m, 1146s,1118s, 980m, 869m, 830m, 802m,775m, 684s, 651m, 419m. ^{1}H-NMR. δ(ppm) (200MHz, $CDCl_3$) 7.04, d,j9.2Hz, 1H,H3; 7.3 , br, 2H,2-NH_2 ; 7.55, m, 3H,H3',H4' and H5';8.05,s, 1H,H6; 8.09, dq,j9.2Hz,j 1.8Hz,1H, H4; 8.30, m, 2H, H2' and H6'. ^{13}C-NMR δ(50MHz, $DMSOd_6$) 110.18,C4a; 110.42,q,j 5.0Hz, C6; 115.07, C3;125.89, q,j275Hz, 5-CF_3; 127.21,C2' and C6'; 128.83,C4';130.09, C3' and C5'; C4; 134.12, q,j 30.7Hz, C5;137.77, C1'; 157.39,C8a; 157.58,C7; 161.23, C2, 132.52. M.S, m/z 290 (M+1, 18%), 289 (M,100), 288(21), 270(5), 263(8), 262(30), 261(8), 251(3),241(2), 221(6), 220(33), 203(3), 192(7), 177(2), 166(4), 77(10), 63(8), 51(7).

2-Amino-5-methyl-7-phenyl-11,8-naphthyridine (28)

The reaction of 2-aminopyridine compound with benzoylacetone in equimolar (1.62g,10mmol) at 60° for 6 hr. The mixture was cooled, and then the precipitate was filtered off and basified with 20%NaOH solution. The resultant precipitate was filtered of and recrystallized from EtOH.

Yield: 90 %, M.p: 250 °C dec.,

Vmax (KBr) 3367w, 3330m, 3202m, 1655s, 1612s,1577s, 1514s,1495m,1408s ,1375m, 1344s, 858m, 805m, 768s,688s,572m,477m cm^{-1}. ^{1}H-NMR. δ(ppm) (200MHz, $CDCl_3$) 2.66,s, 3H,5-Me;5.02,br,2H,2-NH2;6.75,d, j 9Hz,1H,H3; 7.50, m, 3H, and 8.30,m.2H, ArH, 7.56 ,s ,1H ,H6 ;8.07,d ,j9Hz, 1H,H4.^{13}C-NMR δ(50MHz, $DMSOd_6$) 17.85,5-Me;112.46,C3; 115.20, C6;115.34, C4a;126.95, C2' and C6'; 128.64,C4', 129.23,C3' and C5'; 133.85, C4; 139.12, C1' ;145.72, C5;156.64, C8a; 156.95,C7 ;160.78,C2. M.S, m/z 236 (M+1,16 %), 235 (M,100), 234(43),

220(30), 208(21), 207(11), 190(7), 178(4), 165(5), 152(3), 139(3), 127(3), 117(3) (13) ,103(12), 90(5), 77(13), 63(9), 51(9).

2-Amino-5,7-diphenyl-1,8-naphthyridine 29.

Compound **29** was obtained in analogical manner as for compounds **24-28**, dibenzoylmethane (2.24 g, 10 mmol) was added and the reaction was continued as before.

Yield: 31%, M.p: 264 °C.

Vmax(KBr) 3330m,3195m, 1765s, 1640m, 1660m, 1563s, 1515m, 1487m, 1463m, 1408m, 1356s, 1125m, 1027m, 807m, 696s, 603m, 511m cm^{-1}. ^{1}H-NMR δ(ppm) (200MHz, $CDCl_3$) 5.09, br, 2H,2-NH_2; 6.70,d,J9Hz,1H,H3;7.50,m,8H and 8.50,m,2H,ArH;7.67,s,1H,H6;7.96,d,J 9Hz,1H,H4. ^{13}C-NMR. δ(50MHz, $DMSOd_6$) 113.30, C3;113.57, C4a;114.42, C6; 127.16, 128.48, 128.69 and 129.45, ArCH; 134.75, C4; 137.54 and 138.99, ArC;149.13,C5;157.00 and 157.18,C7 and C8a;160.84,C2. M.S, m/z 298 (M+1, 9%), 297 (M,55), 296(100), 279(8), 254(5), 220(4), 191(3), 166(4), 148(7), 139(6), 126(4), 113(4), 77(9), 63(4), 51(7).

RESULTS AND DISCUSSION

The synthesized compounds **23-29** were performed by the reaction of 2,6-diaminopyridine **7** with 1,3-dicarbonyl compounds **8** in the presence of 60 % perchloric acid or 85 % *o*-phosphoric acid. Survey in the literature review reveals, there is a very little work has been carried out for synthesized naphthyridine derivatives with perchloric acid and our comparative studies with the two acids are tabulated in (**Table 1)**.

Based on the data was described in the **Table 1**. It may be conclude that the significant differences between two acids as cyclizing agents and the reactions are facile with reasonable yields. In general, perchloric acid affords better yields than phosphoric acid, but the two acids produce very different isomer ratios. However, perchloric acid affords better yields of compound **27** and **29** than phosphoric acid. both possible isomers are formed in compounds **25**-**27** in differing ratios depending on the cyclizing acid used.

When the reaction is carried out in phosphoric acid, the two isomers **25a** and **25b** in the ratio 1.5:1 respectively was obtained, which was not at variance with the finding of Williams, et al.[15] However, when the reaction is done in perchloric acid, isomer **25a** is predominantly formed. The two isomers **26a** and **26b** was obtained in both acids with the former isomer being overwhelmingly the main product in phosphoric acid. Williams and Rooney[16] mention only one isomer **26b** with a melting point, 256-258 °C. In our hands, isomer **26a** has a m.p.263-265° C and isomer **26b** has a m.p. 219-221 °C. It appears that Williams and Rooney have wrongly assigned the structure of their isomer which should be **26a**. The two isomers **27a** and **27b** are also obtained in both acids with the former being the main product in perchloric acid. It is apparent that the overall pattern of the isomer ratio is consistent with the following observations:

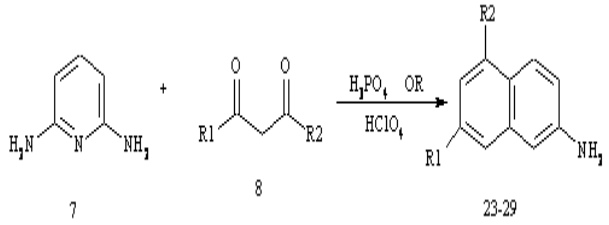
1- The initial nucleophilic attack is on the carbonyl carbon attached to the more electron-withdrawing substituent.
2- The nucleophilic attack in 1. is more enhanced in examples **25** and **27** when the reaction is carried out in perchloric acid than in phosphoric acid.
3- The nucleophilic attack in 1. is more enhanced in compound **26** when the reaction is done in phosphoric acid than in perchloric acid.
4- The nucleophilic attack in 1. Produces exclusively only one isomer **28** in both acids.
5- The initial nucleophilic attack appears to involve directly the nitrogen atom for compound **25**, **27** and **28** as shown in scheme 9; however in example **26**, the pyridinyl ring carbon atom probably promotes the initial nucleophilic attack as shown in scheme 10.

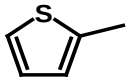
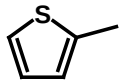
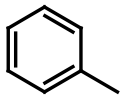
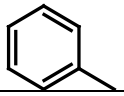
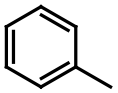
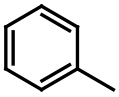
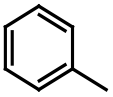
The ratios of the isomer mixtures were determined by HPLC. Indeed, the HPLC retention times of the isomers as shown in (**Table 2**) are not at variance with the fact that invariably the isomers bearing the CF_3 substituent at the 5-positionof the naphthyridine nucleus are more lipid soluble (longer retention times) than the 7-CF_3 isomers.

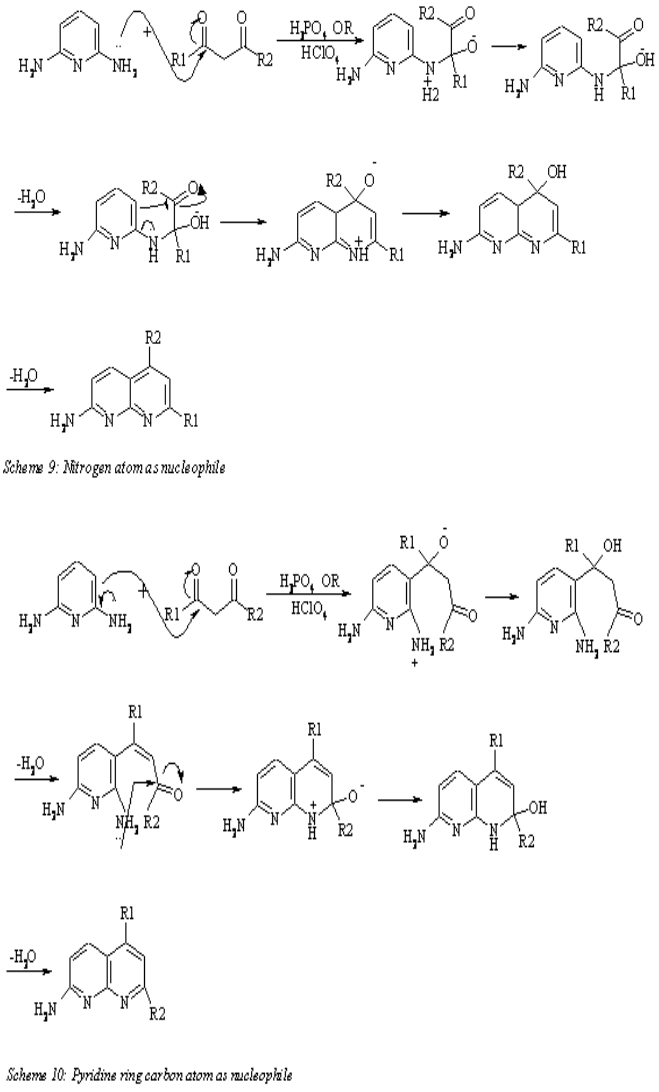
It is also interesting to observe if the isomers formed do undergo equilibration. From (**Table 3)**, it can be deduced that no equilibration is occurring because the isomer ratios obtained are essentially unchanged within experimental variations. The decreasing weights, however, reflect a percentage recovery of about 86 % in both acids. Incidentally, the isomers are easily differentiated on the basis or their ^{1}H-NMR sperctra; the proton in the 4-position of the naphthyridine nucleus shows a long range

coupling with the fluorine atoms of the 5-trifluoromethyl substituent [15].

Scheme 8: Synthesis of 1,8-Naphthyridines 23-29



Compound No.	R^1	R^2
23	Me	Me
24	CF_3	CF_3
25a	CF_3	Me
25b	Me	CF_3
26a		CF_3
26b	CF_3	
27a	CF_3	
27b	CF_3	
28		Me
29		



Scheme 9: Nitrogen atom as nucleophile

Scheme 10: Pyridine ring carbon atom as nucleophile

Table 1: Comparison of the effects of acid media on the formation of 1,8-naphthyridines(23-29)

60 % $HClO_4$	85 % H_3PO_4	Literature
75 % yield of compound (**23**) 60 °C / 6 hours	95 % yield of compound (**23)** 60 °C / 6 hours	85% yield [2] , 100 ° C / 1hour in H_3PO_4
70 % yield of compound **(24**) 50 °C / 3 days	70 % yield of compound (**24**) 50 °C / 3day	67 % yield [38] 90 °C / 6 hrs in H_3PO_4
95% yield of 19(cpd.**25a**):1(cpd.**25b**) 60°/24 hours	80 % yield of 1.5 (cpd.**25a**): 1(cpd.**25b**) 60 °C / 24 hours	86 % yield [38] 2.2 (cpd.**25a**):1(cpd.**25b**) 90 °C / 6 hrs in H_3PO_4
56 % yield of 1.8(cpd.**26a**): 1(cpd.**26b**) 50 °C / 5 days	51 % yield of 11.7 (cpd.**26a**): 1(cpd.**26b**)	15.3 % yield [44] 90 °C / 6 hrs in H_3PO_4
70 % yield of 8 (cpd **27a**):1(cpd.**27b**) 28 °C / 45 days	37 % yield of 1.8(cpd **27a**): 1(cpd.27b) 28 °C / 45 days	Not reported
90 % yield of compound (**28**) 60 °C / 24 hrs	84 % yield of compound (**28**) 60°/ 24 hrs	80 % yield [22] 140 °C / 2 hrs in H_3PO_4
31 % yield of compound (**29**) 70 °C / 3 days	3 % yield of compound (**29**) 70 °C / 3 days	Not reported

Table 2: HPLC Retention Times (min)

(**25a**)	(**25b**)	(**26a**)	(**26b**)	(**27a**)	(**27b**)	(**28**)
4.7	5.7	12.5	11.5	11.8	15.8	5.9

Table 3: Attempted Equlibration Studies On compounds (25a) and (25b)

Initial isomer ratio	13(**25a**):1(**25b**) Wt = 1000 mg	2(**25a**):1(**25b**) Wt = 1500 mg
Acid medium	60 % $HClO_4$	85 % H_3PO_4
Isomer ratio after first equilibration attempt at 60 °C / 24 hrs	30(**25a**):1(**25b**) Wt = 860 mg	4.8(**25a**):1(**25b**) Wt = 1335 mg
Isomer ratio after second equilibration attempt at 60°/24 hrs	99(**25a**):1(**25b**) Wt = 757 mg	1(**25a**):1.2(**25b**) Wt = 1148 mg
Isomer ratio after third equilibration attempt at 60 °C / 24 hrs	111(**25a**):1(**25b**) Wt = 711 mg	1.8(**25a**):1(**25b**) Wt = 953 mg

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