SYNTHESIS OF 6-CHLORO-7-PHENYLDIBENZO[b,h][1,6]NAPHTHYRIDINES

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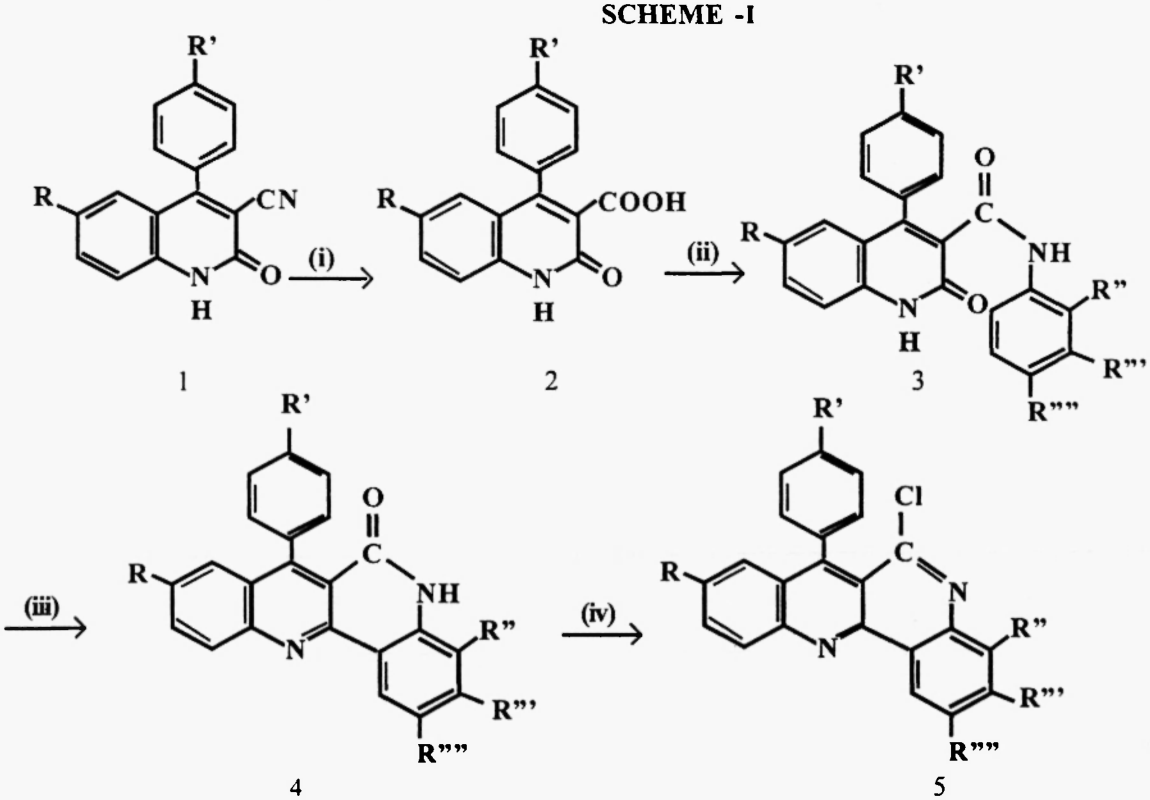
Abstract : Synthesis of title compounds and derivatives is reported by the cyclisation of 4-phenyl-3-carboxanilidoquinoline-2(1H)ones 3 with PPA obtained from their corresponding acids 2. 2-oxo-4-phenylquinolin-3-carboxylic acid 2 which inturn were prepared from 3-cyano-4-phenyquinolin-2(1H)ones by acid hydrolysis.

Introduction: Many of the benzo and dibenzonaphthyridines display bactericidal, fungicidal, and chemotherapeutic activity[1]. Very few reports have so far appeared on the synthesis of dibenzo[b,h][1,6]naphthyridines and their pharmacological activities[1-10]. Recently, we reported the synthesis of 7-unsubstituted derivatives of dibenzo[b,h][1,6]naphthyridin-6(5H)-ones by cyclization of 4-H derivatives of 2-oxoquinolin-3-carboxanilides with PPA[11]. Herein, we report a new approach to the synthesis of 7-aryl substituted dibenzo[b,h][1,6]naphthyridines starting from 2-oxo-3-cyano-4-phenylquinolines1. (Scheme I).

SCHEME -I



(i) dil. H_2SO_4,CH_3COOH (ii) $SOCl_2$, $ArNH_2$,Pyridine (iii) PPA (iv) $POCl_3$,Me_2NH

a.	R=R'=R"=R'''-R''''=H	b.	R=Cl;R'=R"=R'''=R''''=H
c.	R=R"=Cl;R'=R'''=R''''=H	d.	R=Cl;R'=R'''=R''''=H;R"=CH_3
e.	R=Cl=R'=R'''=R''''=H;R"=OCH_3	f.	R=Cl;R'=R"=R''''=H;R'''=CH_3
g.	R=Cl;R'=R"=R'''=H;R''''=CH_3	h.	R=Cl;R'=R"=R'''=H;R''''=OCH_3
i.	R=CH_3;R'=R"=R'''=H	j.	R=R"=R'''=R''''=H;R'=CH_3

Experiemental : Melting points were determined on a Boetius Microheating table and are uncorrected. IR Spectra were recorded on a Perkin-Elmer-597 Infrared Spectrophotometer as KBr pellets. ^{1}H NMR spectra were recorded on a Bruker WH-270(270 MHz) NMR spectrometer or on an EM-390 (90MHz) NMR spectrometer in $CDCl_3$ unless otherwise specified. Mass spectra were recorded on a a Jeol-D300 mass spectrometer or on Finnigan MAT 8230 GC/mass spectrometer. Elemental analyses were performed by Cario-Elmer 1106 and Perkin-Elmer model 1240 CHN analyser. For all compounds satisfactory microanalyses were obtained (C, H, N $\pm$0.4%)

Typical Procedure. 4-Phenyl-3-carboxanilidoquinoline-2(1H)ones (3a-j).- A solution of 2 (0.01 mole) and thionyl chloride (0.02mole) was refluxed on a water-bath for 3 hrs. Excess thionyl chloride was removed by co-distillation with dry benzene and the resultant acid chloride was taken in dry benzene. This soultion was then added dropwise to a cooled and stirred solution of aniline(0.01 mole) and pyridine (0.02mole) in dry benzene. After 1 hr, the reaction mixture was poured over crushed ice. The solid which separated was collected, dried and chromatographed over silica get (60-12 mesh:50g) using pet.ether-ethyl acetate (40:80v/v). The product was recrystallized from ethyl acetate (Table1).

Typical Procedure. 7-Phenyldibenzo[b,h][1,6]naphthyridin-6(5H)ones (4a-j).- A mixture of a 3 (0.003mole) and poly-phosphoric acid (6g) (prepared by mixing 1.8 parts by weight of P_2O_5 and 1 part by weight of H_3PO_4) was collected, washed with water and sodium bicarbonate (10%), dried and chromatographed over silica get (60-120mesh:50g) using benzene-ethyl acetate (60:40v/v) as eluent. The product was recrystallized from ethyl acetate (Table 2).

Typical Procedure. 9-Chloro-7-penyldibeno[b,h][1,6]naphthyridines (5a-j).- Compound 4 (0.002mole) in phosphorus oxychloride (10 mL) and N,N dimethylaniline (3-4drops) was refluxed for 4 hrs, cooled and poured onto crushed ice. The solid separted was collected, dried and chromatographed over silica get (60-120mesh:50g) using pet.ether-ethyl acetate (95:5v/v). The product was recrystallized from ethyl acetate (Table 3)

Results and discussion.- 2-aminobenzopehane was reacted with ethyl cyanoacetate at 180°C for 6 hours to get 3-cyano-4-phenylquionlin-2(1H)one 1a. Hydrolysis of 1a with 4N H_2SO_4 and acetic acid gave the acid 2a which decomposed at 302°C in 75% yield. Its IR spectrum showed peak at 3100cm^{-1} (COOH). The acid chloride obtained from 2a on treatment with thionyl chloride, was then reacted to a mixture of aniline and pyridine in dry benzene to furnish 3a which melted at 124°C. Its IR spectrum showed peak at 1640cm^{-1} (NHC=O). The anilide so obtained was then heated with PPA for 5 hours to get the cyclised compound 4a in 50% yields, which decomposed at 310°C. Its IR spectrum showed peaks at 1680cm^{-1} (NHC=O) & 3200cm^{-1}(NH). The cyclised compound namely 7-phenyldibenzo[b,h][1,6]naphthyridin[5H]one was then converted to chloro compound by refluxing with $POCl_3$ and N,Ndimethyl aniline for 4 hours, followed by usual work up gave a product in 50% yield with mp 168°(d). Its ^{1}H-NMR spectrum showed signals at 7.0-7.3 (m,5H,C_2-H,C_3-H,C_4-H,C_5-H,C_6-H); 7.35-7.45 (m,6H,C_1-H,C_4-H,C_8-H,C_9-H,C_{10}-H&C_{11}-H); 7.47-7.51 (t,2H, C_1-H,C_2-H). The mass spectrum gave molecular ion at peak at m/e and M+2 peak at m/e 342. The compound was identified as 9-chloro-7 phenyldibenzo [b,h][1,6]naphthyridine 5a.

The reaction sequence leading to 5a was then extended to synthesis 5b-5j.

Table-I Physical and spectroscopic Data of 1a-j[a].

compd	mp°C (Yield %)	IR cm^{-1}	^{1}H NMR[b] (δ)ppm	MS m/z (m+)
3a	124 (60)	1640 1660 3220	6.9-7.3(m,5H,C_2''-H,C_3''-H,C_4''-H,C_5''-H,C_6''-H);7.4-7.58 (m,7H,C_6-H,C_7-H,C_2'-H,C_3'-H,C_4'-H,C_5'-H,C_6'-H); 7.6(m,2H,C_5-H & C_8-H)12.3(s,1H,NH);10.3(s,1H,N'-H)	340
3b	192-194	1640 1600 3400	7.2-7.8(m,9H,C_3'-H,C_4'-H,C_5'-H,C_7'-H,C_2''-H,C_3''-H,C_4''-H, C_5''-H,& C_6''-H);7.9(d,2H,C_2'-H&C_6'-H,J=8.135Hz);8.0(s,1H, C_5-H);8.1(d,1H,C_8-H,J=8.225Hz)12.1(s,1H,N H)12.1(s,1H,NH)	376
3c	180-182 (60)	1640 1660 3440	6.4-6.5(m,5H,C_2''-H,C_3''-H,C_4''-H,C_5''-H&C_6''-H);7.3-7.7(m,3H, C_4'-H,C_5'-H&C_6'-H);7.8-8.0(m,4H,C_3'-H,C_5'-H,C_7-H&C_8-H); 10.7(s,1H,N'H)12.1(s,1H,NH)	409
3d	195-197 (66)	1640 1650 3150	6.9-7.3(m,9H,C_3'-H,C_4'-H,C_5'-H,C_6'-H,C_2''-H,C_3''-H,C_4''-H, C_5''-H& C_6''-H);7.35(s,1H,C_5-H);7.42(m,2H,C_7-H,C_8-H); 10.95(s,1H,N'H);12.01(s,1H,NH);2.3(s,3H,C_2'-CH_3)	388 390
3e	188-190 (62)	1640 1660	3.9(s,3H,C_2'-OCH_3);6.9-7.1(m,5H,C_2''-H,C_3''-H,C_4''-H,C_5''-H &C_6''-H);7.5-7.6(m,3H,C_4'-H,C_5'-H,C_7-H);7.6 7.7 (d,3H,C_5-H, C_8-H&C_6-H);7.8(d,1H,C'$_3$-H,J=.7.9Hz,1.12Hz);10.4 (s,1H,N'-H);12.8(s,1H,NH)	404 406
3f	213-214 (60)	1640 1660 3220	2.3(s,3H,C_3'-CH_3);6.75-7.0(m,5H,C_2''-H,C_3''-H,C_4''-H,C_5''-H &C_6''-H);7.4-7.5(m,4H,C_2'-H,C_4'-H,C_5'-H&C_6'-H);7.55-7.7 (m,C_5-H,C_7-H&C_8-H);10.7(s,1H,N'H);11.9(s,1H,NH)	388 390
3g	215-216 (62)	1640 1660 3220	2.3(s,3H,C_4'-CH_3);7.0-7.15(m,5H,C_2''-H,C_3''-H,C_4''-H,C_5''-H &C_6''-H);7.4(m,3H,C_3'-H,C_5'-H,C_7'-H);7.4-7.6(m,4H,C_2'-H, C_6'-H,C_5-H&C_8-H);10.2(s,1H,N'H);11.9(s,1H,NH)	388 390
3h	193-195 (62)	1640 1660 3220	3.82(s,3H,C_4'-OCH_3);7.2-7.32(m,5H,C_2''-H,C_3''-H,C_4''-H,C_5''-H& C_6''-H);11.45(m,3H,C_5-H,C_6-H,C_7-H,C_8-H);7.5-7.59(m,4H,C_2'-H C_3'-H,C_5'-H&C_6'-H);10.3(s,1H,N'-H);12.0(s,1H,NH)	404 406
3i	225-227 (60)	1640 1660 3220	-----	354
3j	174-175	1640 1660 3400	2.35(s,3H,C_6-CH_3);6.9-7.3(m,5H,C_2''-H,C_3''-H,C_4''-H,C_5''-H &C_6''-H);7.34-7.5,(m,5H,C_2'-H,C_3'-H,C_4'-H,C_5'-H,C_6'-H); 7.55-7.68(m,3H,C_5-H,C_7-H&C_8-H);9.91(s,1H,N'H);11.92(s,1H,NH)	354

a. Recrystallised from pet.ether-ethyl acetate (40:60v/v) b) in $CDCl_3$+DMSO-d_6

Table -II Physical and spectroscopic Data of 4a-j[a]

compd	mp°C (Yield %)	IR cm^{-1}	^{1}H NMR[b] (δ)ppm	MS m/z (m+)
4a	310(d) (50)	1680 3200	7.3-7.5(m,5H,C_2'-H,C_3'-H,C_4'-H,C_5'-H,&C_6'-H);7.5-7.7(m, 4H,C_2-H,C_3-H,C_9-H&C_{10}-H);7.96(d,1H,C_4-H,J=8.521Hz);12.5 (s,1H,NH)	322 294 279
4b	300(d) (49)	1680 3200	7.3-7.5(m,7H,C_2-H,C_3-H,C_2'-H,C_3'-H,C_4'-HC_5'-H&C_6'-H); 7.5-7.76(m,5H,C_1-H,C_4-H&C_{11}-H);12.1(s,1H,NH)	356 358,360
4c	278-280 390(50)	1690 3300	7.3-7.7(m,7H,C_2'-H,C_3'-H,C_4'-H,C_5'-H,C_6'-H,C_2-H&C_{10}-H);7.8 (d,1H,C_1-H,J-9.25Hz);8.4(d,1H, C_3-H J=9.2Hz);8.5 (s,1H,C_8-H);12.3(s,1H,NH)	392 394
4d*	281-283 (55)	1680 3400	------	370 372
4e	298-299 (50)	1690 3400	3.5(s,3H,C_4-OCH_3);7.27.55(m,5H,C_2'-H,C_3'-H,C_4'-H,C_5'-H& C_6'-H);7.6-7.7(m,3H,C_2-H,C_{10}-H&C_{11}-H);7.82(d,1H,C_1-H,) J=8.4Hz);8.4(d,1H,C_3-H),8.5(s,1H,C_8-H);12.3(s,1H,NH)	386 388
4f	295 (54)	1685 3300	2.23(s,SH,C_3-CH_3);6.8-7.1(m,8H,C_2-H,C_4-H,C_{10}-H,C_2'-H,C_3'-H, C_4'-H,C_5'-H & C_6'-H);7.3(s,1H,C_1-H);7.55(d,1H,C_{11}-H); 7.7(s,1H, C_8-H);11.7(s,1H,NH)	370 372
4g	279-281 (50)	1685 3300	2.32(s,3H,C_2-CH_3);7.0-7.2(m,5H,C_2'-H,C_3'-H,C_4'-H,C_5'-H& C_6'-H);7.25-7.4(m,3H,C_3-H,C_8-H&C_{10}-H);7.45-7.52(m,3H, C_1-H,C_4-H,&C_{11}-H);11.2(s,1H,NH)	370 372
4h*	294-295 (49)	1680 3200	-------	386
4i	255(d) (48)	1670 3250	2.32(s,3H,C_9-CH_3);7,2-7.5(m,5H,C_2'-H,C_3'-H,C_4'-H,C_5'-H& C_6'-H);7.55-7.62(m,4H,C_2'-H,C_3'-H,C_8-H&C_9-H);7.65(m,3H, C_1-H,C_4-H,C_{11}-H);11.52(s,1N,NH)	336
4j	269-270 (50)	1680 3250	2.2(s,3H,C_4'-CH_3);6.9-7.0(m,4H,C_2'-H,C_3'-H,C_5'-H&C_6'-H); 7.0-7.1(m,4H,C_2-H,C_3-H,C_8-H,C_9-H&C_{10}-H); 7.15-7.3(m,4H, C_1-H,C_4-H,C_8-H&C_{11}-H);12.7(s,1H,NH)	336

a). Recrystallied from Benzene-ethyl acetate(60:40v/v) b) in $CDCl_3$+DMSO-d_6
d). decomposed * insoluble in $CDCl_3$+DMSO-d_6

Table -III Physical and spectroscopic Data of 5a-j[a]

compd	mp°C (Yield %)	IR cm^{-1}	^1H NMR[b] (δ)ppm	MS m/z (m+)
5a	168(d) (50)	1160 1590	7.0-7.3(m,5H,C_2'-H,C_3'-H,C_4'-H,C_5'-H,C_6'-H);7.35-7.45(M,6H, C_3-H,C_4-H,C_8-H,C_9-H,C_{10}-H&C_{11}-H);7.47-7.51(T,2H,C_1-H& C_2-H)	340 342
5b	201 (79)	1180 1600	7.5-8.0(m,8H,C_2-H,C_3-H,C_4-H,C_2'-H,C_3'-H,C_4'-H,C_5'-H& C_6'-H;8.1-8.2(m,2H,C_9-H&C_{11}-H);8.3-8.5(m,2H,C_1-H,C_8-H)	374 376
5c	197-198 (75)	1160 1605	7.5-7.6(m,5H,C_2'-H,C_3'-H,C_4'-H,C_5'-H,&C_6'-H);7.6-7.9(m,2H, C_2-H,C_{10}-H);8.0-8.2(m,2H,C_1-H&C_{12}-H);8.3-8.4(m,1H,C_3-H); 8.5(s,1H,C_8-H)	409 411 413,415
5d	209 (80)	1140 1605	2.3(s,3H,C_4-CH_3);7.2-7.42(m,5H,C_2'-H,C_2'-H,C_4'-H,C_5'-H& C_6'-H);7.45-7.5(2H,C_2-H&C_3-H);7,52-7.65(m,4H,C_1-H,C_8-H, C_{10}-H&C_{11}-H)	389 391
5e	188 (80)	1140 1605	3.92(s,3H,C_4-OCH_3);7.3-7.9(m,5H,C_2;-H,C_3'-H,C_4'-H,C_5'-H,& C_6'-H);8.0-8.2(m,2H,C_8-H&C_{10}-H);8.3(d,1H,C_{11}-H,J=9.0HZ); 8.78-8.85(d,1H,C_3-H;J=13.2Hz)	405 407
5f	210 (80)	1560 1600	2.47(s,3H,C_3-H,CH_3);6.8-7.0(m,2H,C_2-H&C_4-H);7.2-7.5(m,5H, C_2'-H,C_3'-H,C_4'-H,C_5'-H&C_6'-H);8.2(d,2H,C_1-H&C_{11}-H) j=10.213Hz);8.55(s,1H,C_8-H)	389 391
5g	188 (80)	1590 1600	2.6(s,3H,C_2-CH_3);7.0-7.3(m,5H,C_2'-H,C_3'-H,C_4'-H,C_5'-H&C_6'-H); 7.3-7.39(m,3H,C_1-H,C_3-H&C_4-H)7.5-7.66(m,2H,C_{10}-H&C_{11}-H); (s,1H,C8-H)	389 391
5h	213(d) (80)	1540 1600	3.85(s,3H,C_2-OCH_3);7.5-7.7(d,5H,C_2'-H,C_3'-H,C_4'-H,C_5'-H& C_6'-H);7.78(d,2H,C_3-H&C_4-H,J=12.64Hz);8.4-8.5(m,2H,C_8 &C_{11}-H); 8.85(s,1H,C_1-H)	405 407 409
5i	184-185 (80)	1590 1600	2.42(s,3H,C_9-CH_3);7.0-7.5(m,8H,C_2-H,C_3-H,C_2'-H,C_3'-H,C_4'-H C_5'-H,C_6'-H&C_{10}-H);7.52-7.6(m,3H,C_4-H,C_8-H&C_{11}-H);7.96 (m,1H,C_1-H)	354 356
5j	189-190 (80)	1580 1600	2.45(s,3H,C_4'-CH_3);7.1-7.4(m,9H,C_2-H,C_3-H,C_8-H,C_9-H,C_{10}-H, C_2'-H,C_3'-H,C_4'-H,C_5'-H&C_6'-H)7.4-7.6(m,3H,C_1-H,C_4-H&C_{12}-H)	354 356

a. Recrystallised from Pet.ether-ethyl acetate(95:5v/v) b) in $CDCl_3$ d) decomposed.

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