A NEW APPROACH TO THE SYNTHESIS OF BENZO[b][1,8]NAPHTHYRIDIN-4(1H)ONES.

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Abstract : Condensation of 3-acetyl-4-phenylquinoline-2(1H)ones 1 with benzaldehydes give 4-phenyl-3-cinnamoylquinolin-2(1H)ones 2 which inturn were converted to 2-chloro-3-cinnamoyl-4-phenylquinolines. 3. Compounds 3 were then aminated with p-aminobenzensulfonamide and then subjected to bromination-dehydrobromination step to yield 2,5-diphenylbenzo[b][1,8]naphthyridin-4(1H)ones 5.

Introduction : Interesting pharmacological properties have been associated with [1,8]naphthyridine and its derivatives[1-4]. Some [1,8]naphthyridin-2(1H)one derivatives have been reported to possess anti-allergic, anti-inflammatroy properties[2,3] and some with leukotrine formation inhibiting properties[4]. Earlier benzo fused [1,8]naphthyridines were constructed by several methods[5-12]. The first benzo[b][1,8]naphthyridine derivative was obtained by reaction of ethyl-2-aminoquinoline-3-carboxylate with diethyl malonate[7]. Subsequently 2-amino-and 5-amino- derivatives were reportedly obtained from 2,6-diaminopyridine[8] and 3-cyanopyridine[10] respectively. 2,3-disubstituted derivatives and 6,7,8,9-tetrahydro derivaties of benzo[b][1,8]naphthyridine were preparedby applying Friedlander synthesis with 2-aminoquinoline-3-carbaldehydes[11a] and 2-aminonicotinaldehyde[11b] respectively. We herewith report a method to synthesise hitherro unknown 2,5-diphenyl benzo[b][1,8]naphthyridin-4(1H)one 5a-h and its derivatives starting from 3-acetyl-4-phenyl quinolin-2(1H)ones 1a-d via the intermediates 3-cinnamoyl-4-phenylquinolin-2(1H)ones 2a-h.

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 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[13]. 3-Acetyl-4-phenylquinolin-2(1H)ones (1a).- A mixture of 2-aminobenzophenone 19.7g (0.1mol) and freshly distilled ethyl acetoacetate 12.7mL (0.1mol) was heated in an oil bath at 160°C for 6 hrs. The solid separated was collected and washed with ethyl acetate and recrystallised from methanol. (Table 1).

Typical Procedure. 4-Phenyl-3-cinnamoylquinolin-2(1H)ones (2a).- A solution of 2.18g (0.055 mole) of NaOH in water (20mL) and 95% ethanol (12.25 mL) were introduced into a ice-cooled bottle. Into the alkaline solution, pure compound 1a 11.32 g (0.043 mole) was added. After 20 minutes, benzaldehyde 4.06mL (0.04 mole) was added at

once, and the temperature was maintained between 15-30°C. After 2-3 hours, the mixture became so thick that stirring was no longer effective. The stirrer was removed and the mixture was left in a ice-bath for 10 hours. The solid was then collected, washed with water, 15% ethanol, dried and chromatographed over silica-gel (60-120 mesh:50g) using pet. ether-ethyl acetate (70:30v/v). The compound was recrystallised from ethyl acetate(Table II).

Typical Procedure. 2-Chloro-3-cinnamoyl-4-phenylquinolines (3a).- Compound 2a 3.15g (0.01 mole) in $POCl_3$ (10 mL) was refluxed for 3 hrs cooled and poured into crushed ice. The separated solid was collected, dried and chromatographed over silica gel (60-120 mesh:50g) using pet. ether-ethyl acetate(95:5v/v). The product was recrystallised from pet. ether-ethyl acetate (50:50v/v) mixture (Table III).

Typical Procedure. 2,5-Diphenylbenzo[b][1,8]naphthyridin-4(1H)ones (5a).- A mixture of compound 3a 3.69g (0.01mole) and p-aminobenzenesulfonamide 1.72g (0.01 mole) was fused at 180°c for 4 hrs[14]. The black solidified mass isolated was cooled and digested with hot ethanol (50 mL) and poured into 10% aqueous sodium carbonate solution and heated on a water bath for 2hrs, cooled and extracted with chloroform. The chloroform extract was washed with water (3 x 50mL) dried and evaporated. The compound obtained as a pasty mass was used without purification for the next step.

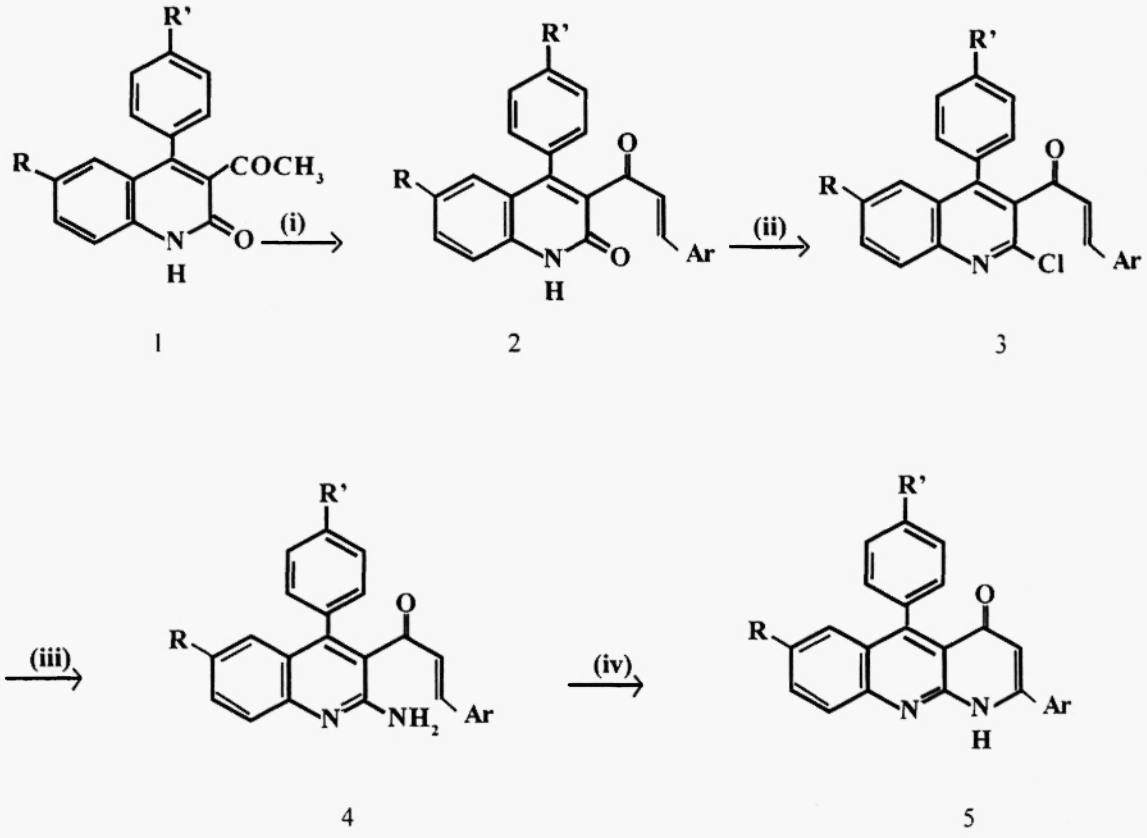
The pasty mass in dry chloroform was stirred well and bromine (0.02 mole) in dry $CHCl_3$ (20 mL) was added dropwise under cooling 0-5°C. After 5-6 hrs, the bromo compound precipitated as an yellow solid. Excess chloroform was removed by distillation and purification was performed by column chromatography over silica gel (60-120 mesh:50g) using pet.ether-ethyl acetate (20:80v/v). The product obtained was used immediately for the cyclization step, otherwise it become pasty after sometime.

To an alcoholic solution of KOH (15% 30 mL), compound obtained above was added and the mixture refluxed on a water bath for 2-3 hrs. Distilled triethyl amine (5 mL) was then added into the boiling mixture and reflux was continued for one additional hour. Excess ethanol was removed under reduced pressure, the cooled residue was poured into ice-cold water. The separated solid was collected, washed with dil HCl in order to remove excess triethyl amine and again with water. The pure product was obtained by column chromatography over silica gel (60-120 mesh:50g) using benzene-ethyl acetate (50:50v/v). The product was recrystallized from ethanol (Table IV).

Result and Discussion : Compound 1a, prepared by reacting 2-aminobenzophenone with ethyl acetoacetate, was then condensed with benzaldehyde (NaOH/H_2O/ethanol) to afford 2a (75% yield, IR peaks at 1720, 1640cm^{-1}, mass peak at m/z 351). Upon refluxing with $POCl_3$ followed by workup, compound 2a gave the 2-chloro derivative 3a (95% yield, IR showed absence of peaks at 3200, and 1640cm^{-1}, presence of peak at 1700cm^{-1}, mass peaks at m/z 369, 371). Equimolar mixture of 3a and p-aminobenzenesulfonamide was fused at 180°c for 4 hours, digested in hot ethanol and then poured into aq. Na_2CO_3. This was followed by heating in water-bath for 2 hours and extraction with $CHCl_3$. The pasty mass of aminated product 4a so obtained was then brominated ($Br_2/CHCl_3$). The product was then refluxed with alcoholic solution of KOH for 3 hour, followed by addition of triethylamine and refluxing for 1 additional hour. The resulting product upon work-up was identified as 5a (42% yield, IR peaks at 3400 (NH) and 1680 (C=O) cm-1, mass peak at m/z 348).

The reaction sequence leading to 5a was then extended to synthesise 5b-5h (Scheme-1). Since this sequence utilizes simple o-aminobenzophenones and benzaldehydes which are available in varieties,it make a more general approach to synthesise the titled compounds.

SCHEME -I



1 2 3

4 5

(i) ArCHO, NaOH (ii) $POCl_3$ (iii) p-aminobezenesulfonamide (iv) Br_2 (v) Et_3N, Alc.KOH

a.	R = R' = H; Ar = C_6H_5	b.	R = R' = H; Ar = 4-ClC_6H_4
c.	R = H ;R' = Cl; Ar = C_6H_5	d.	R = H ;R' = Cl; Ar = 4-ClC_6H_4
e.	R = H ;R' = CH_3 ;Ar = C_6H_5	f.	R = H ;R' = CH_3; Ar = 4-ClC_6H_4
g.	R = CH_3 ;R' = H; Ar = C_6H_5	h.	R = CH3 ;R' =H; Ar = 4-ClC_6H_4

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REFERENCES

1. P.A. Lowe,in "Comprehensive Heterocyclic chemistry" Vol II (Ed. By A.R. Katritzky and C.W.Rees) p.p. 581-627 Pergamon press Ltd. Oxford, New york (1984).
2. N.P. Buu-Hoi, P.Jacquignon, D.C. Thang, T. Bartnik, J.Chem. Soc., Perkin Trans-I 263 (1972).
3. K.G.Gupta, S.V.Kessar and B.Singh, Appl. Microbiol., 19, 1017 (1970).
4. P.L. Nyce, D. Gala, M.Steinman, Synthesis., 571 (1991).
5. W. Marchwald and H. Dettmar Ber., 35, 296 (1902).
6. I. Ninomiya, T. Kiguchi, S.Yamauchi and T.Naito J.Chem. Soc., Perkin Trans-I 1861 (1976).
7. G. Koller and E. Strang, Monatsh. Chem., 50, 144 (1928).
8. M.J. Kabachnik, J.Gen. Chem.,USSR (Engl. Transl). 9, 1734 (1939); Chem. Abstr., 34, 3748 (1940).
9. A.I. Mikhalev and M.E. Konshin, Kim. Geterotsikl. Soedin., 1241 (1977).
10. N.I.Shramm and M.E. Konshin, ibid., 674 (1982); Chem. Abstr., 99, 92173n (1982).
11. a) A.Godard and G.Queguiner, J.Heterocyclic Chem., 19, 1289 (1982); b)R.P.Thummel and D.K. Kohli, J.Heterocyclic Chem., 14, 685 (1977).
12. O.Meth-Cohn and B.Tarnowski, Tetrahedron Lett., 21, 3721(1980).
13. R.Camps, Arch. Pharm., 240 135(1902).
14. M.Murugesan, K.Ramasamy and P.Shanmugam, Z. Naturforsch., 35B, 746 (1980).

Table - I. Physical and Spectroscopic Date of 1a-d[a].

Cmpd	Yield (%)	m.p. (°C)	IR λ(cm^{-1})	MS m z (M−)
1a	80	240-242	3100,2900,1640	263
1c	82	257-259	3100,2900,1640	298,300
1e	82	262-264	3200,2900,1650	277
1g	82	265-266	3100,2900,1650	277

a) Recrystallized from methanol

Table - II. Physical and spectroscopic Data of 2a-h[a]

Cmpd	Yield (%)	m.p. (°C)	IR (cm-1)	1HNMR (δ)ppm	MS m/z (M−)
2a	65	164	1670-1640 3300	4.9(dd,2H,-CH=CH, J=9.1Hz,2.0&2.13,Hz);7.15-7.9(m,3H,C_6-H C_7-H&C_8-H);7.3-7.4(m,10H,C_2'-H,C_3'-H,C_4'-H,C_5'-H,C_6'-H,	351

				C_2"-H,C_3"-H,C_4"-H,C_5"-H&C_6"-H) 9.1(s,1H,NH)	
2b	56	151-152	1680,3300	5.1(dd,2H-CH=CH, J=6.7, Hz, 1.35,1.36 Hz);7.2-7.45(m,9H,	385
				C_2"-H,C_3"-H,C_4"-H,C_5"-H,C_6"-H,C_2'-H,C_3'-H,C_4'-H &C_5'-H);	387
				7.7-7.8 (m,3H,C_5-H,C_7-H&C_8-H),9.15 (s,1H,NH)	
2c	66	115-116	1680,3300	4.8(dd,2H,-CH=CH-J=6.92 Hz 1.985 Hz),7.0-7.3(m,10H,C_2'-H,	385
				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),	387
				7.6-7.8(d,3H,C_5-H,C_7-H,&C_8-H),8.95(s,1H,NH)	
2d	60	139(d)	1670,3200	5.0(dd,2H-CH=CH-J=8.0HZ,1.38HZ),7.5-7.7(m,9H,C_2'-H,	419
				C_3'-H,C_5'-H,C_6'-H,C_2"-H,C_3"-H,C_5"-H&C_6"-H,C_3"-H,C_5'-H&	421
				C_6"-H);7.9-8.0 (m,2H,C_7-H,C_8-H);8.09(s,1H,C_5-H);	
				9.22(s,1H,NH)	
2e.	48	148-150	1680,3300	2.55(s,3H,C_6CH_3);4.78-4.81(dd,2H,-CH=CH)J=3.831Hz,	
				2.53,2.55Hz);7.26-7.35(m,10H,C_2'-H,C_3'-H,C_4'-H,C_5'-H,	365
				C_6'-H,C_2"-H,C_3"-H,C_4"-H,C_5"-H,C_6"-H);7.8(d,2H,	
				C_7-H,C_8-H,J=8.012Hz);7.8(s,1H,C_5-H);8.91(s,1H,NH)	
2f	48	152-153	1680,3300	5.1(dd,2H,-CH=CH,J=6.23,Hz,2.12Hz)2.3(s,3H,C_6-CH_3)	399
				7.2-7.4(m,9H,C_2'-H,C_3'-H,C_5'-H,C_6'-H,C_2"-H,C_3"-H,C_4"-H,	401
				C_5"-H,&C_6"-H);7.62(s,1H,C_5-H);7.75(d,2H,C_7-H&C_8-H,	
				J=8.152HZ)9.0(s,1H,NH)	
2g	50	161-162	1670,3300	2.32(s,3H,C_4"-CH_3)4.95(dd,2H,-CH=CH)-J=7.10,2Hz,	365
				1.35,38Hz);6.6-6.95(m,4H,C_2"-H,C_3"-H,C_5"-H&C_6"-H);	
				7.25-7.5(m,5H,C_2'-H,C_3'-H,C_4'-H,C_5'-H,C_6'-H, &C_6'-H);7.65	
				(d,2H,C_6-H&C_7'-Hj=8.132 Hz);7.72(m,2H,C_5-H&C_8-H);	
				9.1(s,1H,NH)	
2hb	48	155-156	1680,3300	2.31(s,3H,C_4"-CH_3);5.0(m,2H-CH=CH-)7.0-7.4(m,8H	399
				,C_2'-H,C_3'-H,C_5'-H,C_6'-H,C_2"-H,C_3"-H,C_4"-H,C_6"-H);	401
				7.6-7.8(m,4H,C_5-H,C_6-H,C_7-H&C_8-H)9.12(s,1H,NH)	

a. Recrystallized from ethyl acetate. b) NMR in $CDCl_3$+DMSO-d_6 d) decomposed.

Table-III Physical spectroscopic Data of 3a-h[a]

Cmpd	yield (%)	m.p. (°C)	IR ν(cm-1)	^{1}HNMR (δ)ppm	MS m/z (M−)
3a.	95	94-95	3300,1660	5.1(m,2H,-CH-CH),6.6-6.95(m,5H,C_2'-H,C_3'-H,C_4'-H,C_5'-H	369
				&C_6'-H);7.3-7.47(m,7H,C_2"-H,C_3"-H,C_4"-H,C_5"-H,C_6"-H,C_6-H	371
				C_7-H);7.53(s,1H,C_5'-H);7.62(d,1H,C_8-H)	
3b	94	92-94	3300,1660	5.1-5.15(m,2H,-CH=CH-)7.7-8.0(m,9H,C_2'-H,C_3'-H,C_4'-H,C_5'-H,	403
				C_6'-H,C_2"-H,C_3"-H,C_5"-H&C_6"-H);8.25(s,1H,C_5-H;	405
				8.0-8.15(m,2H,C_7-H,&C_8-H)	407
3c	92	89-90	3200,1670	—	403,405
					407

3d	90	115-116	3200,1670	---	437,439 441,443
3e	95	102-104	3200,1660	2.1(s,3H,C_6-CH_3)5.0-5.05(dd,2H-CH=CH-J=6.52 Hz,2.01,2.02 Hz)7.5-7.75(m,10H,C_2'-H,C_3'-H,C_4'-H,C_5'-HC,'-H,C_2''-H,C_3''-H,C_4''-H,C_5''-H&C_6''-H):7.8(s,1H,C_5-H):7.92(d,2H,C_5-H&C_8-HJ=8.125 Hz)	383 385
3f.	92	119-120	3100,1660	---	417 419,421
3g.	89	87-88	3200,1660	2.31(s,3H,C_4''-CH_3)5.12(m,2H,-CH=CH-):7.1-7.9(m,9H,C_2''-H C_3''-H,C_5''-H&C_6''-H,C_2'-H,C_3'-H,C_5'-H&C_8'-H):7.95(m,3H,C_6-H,C_8-H&C_9-H)	383 385
3h.	90	86-88	3200,1680	---	417,419 421

a) Recrystallised from pet.ether-ethyl acetate (50:50v/v)

Table - IV. Physical and Spectroscopic Data of compound 5(a-h)[a]

Cmpd	yield (%)	m.p. (°C)	IR ν(cm^{-1})	^{1}HNMR (δ) ppm	MS m z (M−)
5a	42	310-312	3400,1680	7.1-7.5(m,12H,C_2'-H,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,C_7-H&C_8-H);7.65(d,1H,C_9-H,J=851Hz);7.8(s,1H,C_6-H);7.95(s,1H,C_2-H);9.9 (s,1H,NH)	348
5b	40	280(d)	3400,1680	7.2-7.55(m,5H,C_2''-H,C_3''-H,C_4''-H,C_5''-H&C_6''-H);7.6-7.8 (m,7H,C_2'-H,C_3'-H,C_4'-H,C_5'-H&C_6'-H,C_7'-H&C_8'-H): 8.0(s,1H,C_3-H);8.0(d,1H,C_9-H,J=8.23Hz)'9.7(s,1H,NH)	382 384
5c	40	298-299	3400,1680	6.6-7.0(m,10H,C_2'-H,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)7.6(2H,C_6-H&C_8-H);8.2(d,1H,C_9-H,J=9.0 Hz);8.4(s,1H,C_3-H);10.2(s,1H,NH)	382 384
5d.	38	298(d)	3300,1670	7.1-7.3(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_4'-H,C_5'-H&C_6'-H);8.0(s,1H,C_6-H): 8.2(m,2H,C_8-H&C_9-H);8.9(s,1H,NH)	416 418,420
5e.	35	300(d)	3300,1670	insoluble in DMSO-d_6 and $CDCl_3$	362
5f.	38	300(d)	3250,1680	2.5(s,3H,C_7-CH_3);7.45-7.7(m,10H,C_2-ph&C_5-ph);7.71-7.9 (m,2h,C_6-H, C_8-H);8.15(d,1H,C_9-H);8.56(s,1H,C_3-H): 9.92(s,1H,NH)	396 398
5g.	36	300(d)	3300,1680	2.5(s,3H,CH_3)'7.1-7.55(m,9H,C_2'-H,C_3'-H,C_4'-H,C_5'-H,C_6'-H,C_2''-HC,''-H,C_5''-H&C_6''-H)'7.6-7.7(m,2H,C_7-H,C_8-H);7.7-7.9 (m,2H,C_6-H&C_9-H);8.15(s,1HC,-H);10.0 (s1H,NH)	362
5h.	32	296(d)	3200,1670	----	396,398

a) Recrystallized from ethanol. b) NMR in $CDCl_3$+DMSO-d_6 d) decomposed.

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