A CONVENIENT SYNTHESIS OF 8,9,10,11-TETRAHYDRODIBENZO[b,h[[1,6]NAPHTHYRIDIN-6(5H)ONES

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Abstract : Substituted 8,9,10,11-tetrahydrodibenzo[b,h][1,6]naphthyridin-6(5H)ones (5) have been synthesized by the condensation of 4-amino-3-formylquinolin-2(1H)ones (4) with cyclohexanone in presence of acetic acid and sulphuric acid. The precusors have been obtained by the amination of 4-chloro-3-formylquinolin-2(1H)ones (3).

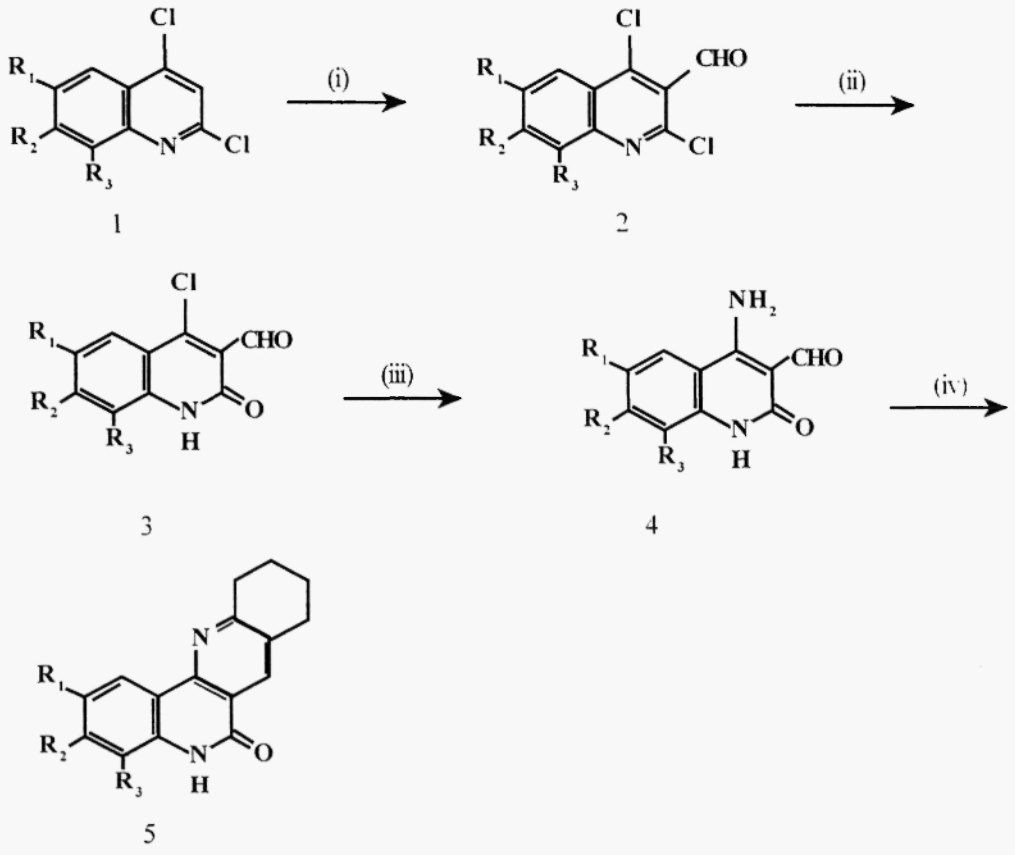
Introduction: Many of the naphthyridines have shown bactericidal and fungicidal activities[1]. Very few reports have so far appeared in the literature on the synthesis of dibenzo[b,h][1,6]naphthyridines and their pharmacological activities[1-11] Here-in, we report a convenient method to synthesise 8,9,10,11-tetrahydrodibenzo[b,h][1,6]naphthyridin-6(5H)ones starting from 4-chloro-3-formylquinolin-2(1H)ones (3) which inturn were prepared by the hydrolysis of 2,4-dichloro-3-formylquinolines (2). The compounds 2 were prepared by the formylation of 2,4-dichloroquinolines (1). (Scheme-I).

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: 2,4-Dichloroquinolines (1a-e).- A mixture of aniline (6.8 g, 0.05 mole), malonic acid (5.2 g, 0.05 mole) and phosphorous oxychloride (50 mL) was refluxed under dry conditions for 15hrs, cooled to room temperature, poured over crushed ice carefully and allowed to stand overnight. The solid settled was filtered to dryness and extracted with petroleum ether, purified over a column of silica gel (60-120 mesh: 50 g) eluting with pet.ether-benzene (4:1) to give 1a. The product was recrystallised from pet.ether-benzene mixture (50:50v/v). (Table 1)

Typical Procedure: 2,4-Dichloro-3-formylquinolines (2a-e).- Phosphorous oxychloride (108 mL, 1.18 mole) was cooled in an ice-water bath. Dry dimethylformamide (35 mL) was added to it slowly with stirring over 15 minutes. A white precipitate formed during the addition. The reaction mixture was warmed gently to dissolve the precipitate

SCHEME -I



(i). $DMF/POCl_3$ (ii). 6N HCl (iii). dry NH_3 gas, Ethanol (iv). Cyclohexanone, CH_3COOH / H_2SO_4

a. $R_1=R_2=R_3=H$
b. $R_1=CH_3$; $R_2=R_3=H$
c. $R_1=R_3=H$; $R_2=CH_3$
d. $R_1=OCH_3$; $R_2=R_3=H$
e. $R_1=R_3=H$; $R_2=OCH_3$

and produce a clear solution to which was added 2,4-dichloroquinoline (80 g, 0.22 mole) in small portions with stirring over a period of 30-40 minutes. Heating the mixture on a steam bath for 5 hrs gave a dark red-brown solution. Excess phosphorous oxychloride was removed and the mixture was poured into crushed ice and allowed to stand at room temperature overnight. The solid was collected by filtration. The filtrate was treated with concentrated ammonium hydroxide in portions to pH-7. The yellow-brown precipitate which formed was collected. The combined precipitates were vacuum dried and then extracted with hot ethyl acetate (6 x 200 mL) leaving a brown insoluble residue which was discarded. Upon cooling, a yellow precipitate formed in the combined ethyl acetate extracts and filtration gave the 2,4,-dichloro-3-formylquinoline, purified over a column of silica gel (60-120 mesh:50g) using pet.ether-ethyl acetate (50:50v/v). The product was recrystallized from ethyl acetate. (Table 2).

Typical procedure. 4-Chloro-3-formylquinoline-2(1H)ones (3a-e).- A mixture of 2,4-dichloro-3-formylquinoline (0.005 mole) was added 35 mL of aqueous hydrochloric acid and refluxed for 1 hr and then allowed to cool to room temperature. The reaction mixture was poured on to crushed ice, when 4-chloro-3-formylquinolin-2(1H)one separated as yellow solid. It was filtered washed with water, dried and recrystallized from aqueous acetic acid. (Table 3).

Typical procedure. 4-Amino-3-formylquinoline-2(1H)ones (4a-e).- To a stirred solution of 3 (0.01mole) in 40 mL of ethanol was passed dry ammonia gas for 8 hours at 0-20°C. It was left aside for a day. The product separated was filtered, purified using column chromatography over silicagel (60-120 mesh:50g) using pet.ether-ethyl acetate mixture (50:50v/v) as eluant. The product was recrystallized from pet.ether-ethyl acetate (95:5v/v). (Table 4).

Typical procedure. 8,9,10,11-Tetrahydrodibenzo[b,h][1,6]naphthyridin-6(5H)ones (5a-e).- Compound 4 (0.01 mole) was dissolved in a mixture of cyclohexanone (0.02 mole) and acetic acid, sulphuric acid (0.1 mole) was added and refluxed for 10 hrs. The cold solution was poured on to a mixture of conc-aqueous ammonia (40 mL) in (20 g) of ice, which gave a brown tarry product. After extraction with chloroform, drying, evaporation and addition of diethylether, the brown solid obtained was purified by chromatrography over silica gel (60-120 mesh:50g) using pet.ether-ethyl acetate (95:5v/v) as eluant. The product was recrystallized from ethyl acetate. (Table 5).

Results and discussions

The starting compound 2,4-dichloroquinoline 1a was prepared by the condensation of aniline and malonic acid with $POCl_3$ which melted at 95°C in 70% yield (Lit mp 68°C)[12]. The compound 1a on treatment with $POCl_3$/DMF gave a product with m.p. 119°C in 60% yield (Lit m.p. 119°C)[13]. The IR spectrum of this compound showed peaks at 2950 cm^{-1} (CH), 1680 cm^{-1} (CHO) and 1600 cm^{-1} (C=N). The ^1H NMR spectrum of this compound showed signals at δ 7.50-8.00(m,3H,C_5-H,C_6-H&C_7-H);8.40(d,1H,C_8-H);10.50(s,1H,CHO). The mass spectrum gave molecular ion peak m/z 225. The compound was identified as 2,4-dichloro-3-formylquinoline 2a. Hydrolysis of 2,4-dichloro-3-formylquinoline with 6N HCl gave a product with m.p. 144°C in 60% yield. The IR spectrum of the compound showed absorptions at 1680 cm^{-1} (CHO) and 1630 cm^{-1} (-NH-CO-) . The mass spectrum gave molecular ion peak at m/z 207. The compound was identified as 4-chloro-3-formylquinoline-2(1H)one 3a. Amination of 4-chloro-3-formylquinoline-2(1H)one (3a) by passing dry ammonia gas in ethanol at ice cold condition gave a product with m.p. 171°C in 80% yield. The IR spectrum of the compound showed peaks at 1680 cm^{-1} (CHO), 1640 cm^{-1} (-NH-CO-) and 3200 cm^{-1} (br) NH_2. The ^1H NMR showed signals at δ 7.45-8.00(m,4H,C_5-H,C_6-H,C_7-H& C_8-H);8.83(s,2H,NH_2);9.2(s,1H,NH);10.55(s,1H,CHO). The mass spectrum gave molecular in peak at m/z 188. It was identified as 4-amino-3-formylquinoline-2(1H)one 4a.

The compound 4a on condensation with cyclohexanone with acetic acid and sulphuric acid at 120°C for 10 hrs gave a product which on purification furnished a brown compound (m.p.>280°C) in 70% yield. Its IR spectrum showed disappearance of peak at 1680 cm^{-1}. The compound showed negative tests for aldeyde and aminogroup. The ^1H NMR spectrum of the compound showed signals at δ 1.59-1.94(m,4H,C_8-2H&C_{11}-H); 1.26-1.42(m,4H,C_9-2H&C_{10}-2H);7.8(m,2H,C_2-H,C_3-H);8.6(m,1H,C_1-H);8.01(m,1H,C_4-H);7.97(s,1H,C_7-H);12.1(s,1H,NH). The

mass spectrum gave molecular ion peak at m/z 250. The compound was identified as 8,9,10,11-tetrahydrodibenzo [b,h][1,6]naphthyridin-6(5H)one 5a. The reactions sequence leading to 1a was then extended to synthesise 1b-1e.

Table 1 Physical and Spectroscopic data of 1a-e

Compd	m.p.°C (Yield %)	IR (ν)cm^{-1}	^{1}H NMR (δ)ppm	MS m z (M+)
1a	68[12] (70)	1605	7.40-8.10(m,aromatic)	198, 200,202
1b	95 (72)	1605	2.5(s,3H,C_6-CH$_3$);7.64-7.98(m,2H,C_7-H& C_8-H);8.3(s,1H,C_5-H);8.9(s,1H,C_1-H)	212 214,216
1c	102 (72)	1605	2.6(s,3H,C_7-CH$_3$);7.7(m,2H,C_5-H&C_6-H); 8.5(s,1H,C_8-H);8.71((s,1H,C_1-H)	212 214,216
1d	130 (72)	1605	3.97(s,3H,C_6-OCH$_3$);7.33-7.52(m,3H, C_7-H,C_5-H,C_7-H);7.95(d,1H,C_8-H)	228 230,232
1e	156 (70)	1605	-----	228 230,232

Table 2. Physical and Spectroscopic data of 2a-e

Compd	mp °C (Yield %)	IR (ν)cm^{-1}	^{1}H NMR (δ)ppm	MS m z (M+)
2a	119[13] (60)	2950 1680 1600	7.50-8.00(m,3H,C_5-H,C_6-H&C_7-H); 8.40(d,1H,C_8-H);10.50(s,1H,CHO)	225 227,229
2b	121 (60)	2960 1680 1600	2.40(s,3H,C_7-CH$_3$);7.50-7.90(m,2H,C_5-H& C_7-H);8.00(d,1H,C_8-H);10.49(s,1H,CHO)	239 241,243
2c	150 (58)	2965 1680 1600	2.52(s,3H,C_7-CH$_3$);7.7-7.91(m,2H, C_5-H&C_6-H);8.43(m,1H,C_8-H); 10.55(s,1H,CHO)	239 241,243
2d	152 (58)	2950 1676 1590	4.00(s,3H,C_6-OCH$_3$);7.50-7.70(m,2H, C_5-H,C_7-H);7.98(d,1H,C_8-H); 10.50(s,1H,CHO)	255 257,259
2e	181 (60	2960 1680 1600	3.49(s,3H,C_7-OCH$_3$);7.1-7.8(m,3H,C_5-H, C_6-H&C_8-H);10.40(s,1H,CHO)	255 257,259

Table 3. Physical and Spectroscopic data of 3a-e

Compd	mp °C (Yield %)	Elemental Analysis (Found)			IR (ν)cm^{-1}	MS m/z
		C	H	N		(M+)
3a	144 (60)	57.97 (57.96)	2.89 (2.88)	6.76 (6.75)	1680 1630.	207 209
3b*	164 (60)	59.72 (59.71)	3.62 (3.60)	6.33 (6.33)	1680 1620.	221 223
3c	210 (62)	59.72 (59.70)	3.62 (3.61)	6.33 (6.34)	1670 1630	221 223
3d	199 (60)	55.69 (55.67)	3.37 (3.36)	5.90 (5.91)	1690 1660	237 239
3e	202 (60)	55.69 (55.68)	3.37 (3.35)	5.90 (5.910	1680 1650	237 239

* 2.5(s,3H,C_6-CH_3);7.51-7.91(m,2H,C_6-H,C_7-H);8.41(d,1H,C_8-H);8.68(m,1H,NH);10.55(s,1H,CHO)

Table 4. Physical and Spectoscopic data (4a-e)

Compd	mp.°C (Yield %)	IR (ν)cm^{-1}	^{1}H NMR (δ)ppm	MS m z (M+)
4a	171 (80)	1680,1640 3200	7.45-8.00(m,4H,C_5-H,C_6-H,C_7-H&C_8-H); 8.83(s,2H,NH_2);9.2(s,1H,NH);10.55(s,1H,CHO)	188
4b	144 (82)	1690,1640 3220	2.5(s,3H,C_6-CH_3);7.51-7.86(m,2H,C_5-H,C_7-H); 8.01(d,1H,C_8-H);6.48(s,2H,NH_2);9.2(s,1H,NH); 9.94(s,1H,CHO)	202
4c	231 (72)	1680,1640 3220	———	202
4d	221 (72)	1680,1635 3300	3.95(s,3H,C_6-OCH_3);7.66-7.91(m,2H,C_5-H& C_7-H);8.40(d,1H,C_8-H);7.67(s,2H,NH_2); 8.75(s,1H,NH_2);10.11(s,1H,CHO)	218
4e	241 (75)	1680,1640 3200	4.07(s,3H,C_7-OCH_3);7.5-7.7(m,2H,C_5-H&C_6-H) 8.96(s,1H,C_8-H);8.83(s,2H,NH_2);9.1(s,1H,NH); 10.12(s,1H,CHO)	218

Table 5. Physical and Spectroscopic data of (5a-e).

Compound	mp.°C (yield)	IR (ν)cm^{-1}	^{1}H NMR (δ)ppm	MS m/z M+
5a	>280 (70)	1640 1446 3100	1.59-1.94(m,4H,C_8-2H&C_{11}-2H)1.26-1.42 (m,4H,C_9-2H&C_{10}-2H);7.8(m,2H,C_2-H, C_1-H);8.6(m,1H,C_1-H);8.01(m,1H,C_4-H); 7.97(s,1H,C_7-H);12.1(s,1H,NH)	250
5b	>280 (75)	1640 1446 3100	1.89-2.15(m,4H,C_8-2H&C_{11}-2H);1.06-1.75 (m,4H,C_9-2H&C_{10}-2H);7.9(s,1H,C_7-H); 7.21-7.60(m,3H,C_1-H,C_3-H&C_4-H);2.51(s,3H, C_2-CH_3);12.10(br.s,1H,NH)	264
5c	>280 (76)	1645 1440 3030	2.7(s,3H,C_3-CH_3);2.09-2.50(m,4H,C_8-2H& C_{11}-2H);1.25-1.62(m,4H,C_9-2H&C_{10}-2H); 7.7-7.90(m,2H,C_1-H&C_2-H);8.1(s,1H,C_4-H) 8.6(s,1H,C_7-H);12.13(br.s,1H,NH)	264
5d	>280 (76)	1645 1420,3100	—	264
5e	>280 (75)	1640 1446,3100	3.9(s,3H,-C_4-OCH_3);2.17-2.44(m,4H,C_8-2H &C_{11}-2H);1.25-1.59(m,4H,C_9-2H&C_{10}-2H); 7.19-7.89(m,3H,C_1-H,C_2-H&C_3-H);8.0(s,1H, C_7-H)12.2(s,1H,NH)	280

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References:

1. P.A. Lowe University of Salford, "Comprehensive Heterocyclic Chemistry", **Vol II** (Pergmon press Ltd., Oxford., New York) pp 581 - 627 (1984)
2. W. W. Paulder and T.J.Kress, *Adv. Heterocyclic Chem., Vol II.* (Academic Press, New York and London) 123 (1970)
3. A. Godard and G.J. Quequinor, *J. Heterocyclic Chem.*, **19(b),** 1289 (1982); *Chem.Abstr.* **99.** 22344m (1983).
4. N.M. Fathy, A.S. Aly. F. Abd-El-Mohi and F.M.E.Abdel-Megeid, *Egypt. J.Chem.*, **29(5),** 609 (1987); *Chem., Abstr,* **110,** 231409w (1989).
5. W.Stadlbauer, *Monatsh Chem.*, **118(11),** 1297 (1987); *Chem. Abstr.*, **108,** 204525h (1988).
6. G.R. Clemo and W.H. Perkin, *J. Chem. Soc.*, 1608 (1924).
7. O. Roussel, N.P. Buu Hoi and P. Jacquignon, *J.Chem. Soc.*, 5459 (1965).
8. R. Oels, R. Storer and D. W. Young *J. Chem. Soc.*, **Perkin. Trans I,** 2546 (1977).
9. J.L. Asherson and D.W. Young, *ibid,* 512 (1980).
10. P. Roschger and W . Stadlbauer, *Ann.*, **3**, 401 (1991).
11. S.P. Rajendran and S. Vijayalakshmi, *Indian. J. Chem.*, **33B,** 159 (1994).
12. Buchmann, F.J. Hamilton, C.S. *J.Am. Chem. Soc.*, **64,** 1358 (1942)
13. K. Ashok, G. Sridevi and Y. Umadevi, *Synthesis.*, **6**, 623 (1993)

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