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Note

A convenient synthesis of 2-chlorobenzo[*b*][1,8] naphthyridines

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2-Chlorobenzo[*b*][1,8]naphthyridines **4a-f** are synthesised in good yields utilizing 3-(2-chloro-3-quinolyl)acrylic acids **2a-f** as the starting compounds.

Keywords: Naphthyridines, acrylic acid

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Several [1,8]naphthyridines and their derivatives are well documented for their pharmacological properties exhibiting anti-bacterial, anti-fungal[1], anti-malarial, anti-hypertensive[2], antimycobacterial[3]and anti-thrombic[4] activities.

Earlier workers from our laboratory have reported the synthesis of 1,2,3,4-tetrahydrodibenzo[*b,g*][1,8] naphthyridines[5] from 2-chloro-3-formylquinolines and 6-phenyl-1,2,3,4-tetrahydrodibenzo[*b,g*][1,8]naphthyridines[6] from 2-chloro-3-formyl-4-phenylquinolines in good yields. Herein, we report a convenient method for the synthesis of 2-chlorobenzo[*b*][1,8]naphthyridines **4a-f** in good yields from 3-(2-chloro-3-quinolyl)-acrylic acids **2a-f**.

Results and Discussion

A convenient preparation for the benzo fused [1,8]-naphthyridines was achieved by utilizing 2-chloro-3-formylquinolines as the starting compounds, which in turn were prepared by following Meth-Cohn *et al.*[7] procedure. They were converted to the oxo compounds by refluxing with 4*M* HCl. Subsequently, were condensed with malonic acid under the conditions of Knoevenagel reaction to furnish 3-(2-oxo-1,2-dihydro-3-quinolyl)acrylic acids[8] **1a-f**.

The compound **1a** upon dehydroxychlorination with freshly distilled phosphorus oxychloride resulted in a creamy white compound. This was followed by recrystallisation from pet. ether- ethyl acetate (10:1, v/v) giving rise to colourless crystals, m.p. 188-89°C, yield 72%.

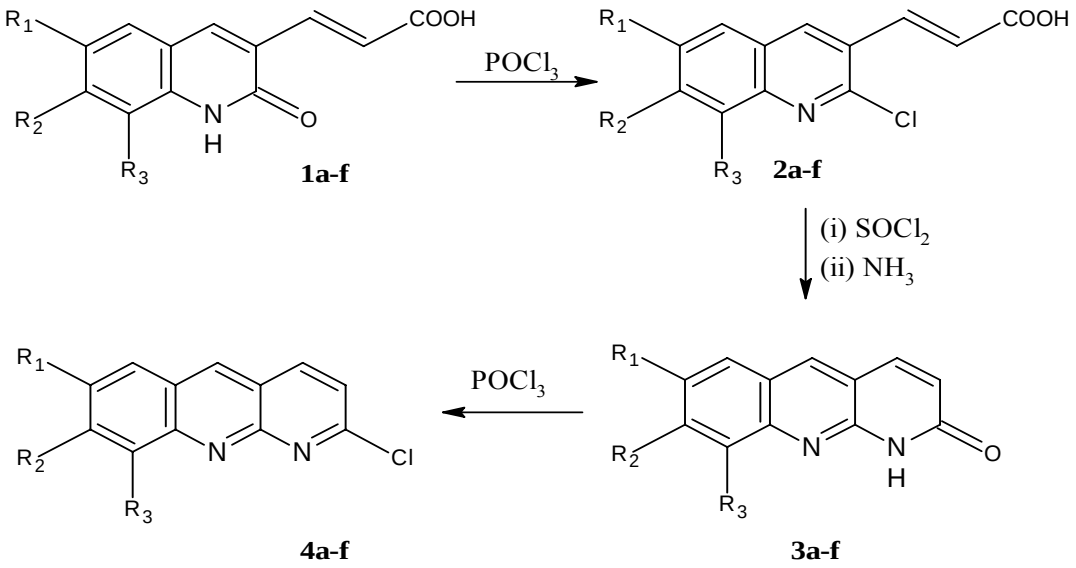
The IR spectra displayed bands at 1690 (–C=O), 1030 (–C–Cl), and 3400 cm^{-1} (-OH). Its ^{1}H NMR spectra showed singlet at δ 8.45 for C_4-H, –COOH peak at 12.5, doublets for vinyl protons at 6.54, 8.01 with J = 16 Hz, typical of *trans* configuration, multiplet for C_5, C_6, C_7, C_8-H at δ 7.63 - 7.84. Its mass spectra with the m/z value at 233(M^+) and 235(M+2) (one third the intensity of the parent peak) confirmed the structure of the compound as 3-(2-chloro-3-quinolyl)acrylic acid **2a** (**Scheme I)**.

The chloro acid was then reacted with thionyl chloride followed by cyclisation with ammonia. The resulting solid **3a** was then recrystallised from dry methanol. This was further treated with phosphorus oxychloride to get **4a**. The reaction sequence was then extended to synthesise **4b-f**. The structures of **3a-f** and **4a-f** were unambiguously deduced from IR, ^{1}H NMR, mass spectra and elemental analysis.

Experimental Section

Melting points were determined using Raaga melting point apparatus and are uncorrected. The IR spectra were recorded on an FTIR 8201(PC)S spectrometer as KBr pellets and the absorption frequencies are expressed in cm^{-1}; ^{1}H NMR spectra in $CDCl_3$ on a Gemini-200MHz or on a Varian AMX 400 spectrometer (chemical shifts in δ, ppm) using TMS as an internal standard. Elemental analysis was performed by Elemental Analyser Vario EL III and the values are within the permissible limits (+0.4%). The mass spectra were recorded by EIMS technique on an Autospec mass spectrometer. The crude products were checked with TLC and purified by column chromatography using silica gel (60-120 mesh).

Preparation of 3-(2-chloro-3-quinolyl)acrylic acids 2a-f. 3-(2-Oxo-1, 2-dihydro-3-quinolyl)acrylic acid **1** (1.56 g, 0.008 *M*) was refluxed with 8 mL phosphoryl chloride (excess) in an oil-bath for 3 hr. The mixture was then cooled and poured into crushed ice. The separated solid was filtered, washed with



(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= R_2=H, R_3= CH_3
(e). R_1= OCH_3, R_2= R_3=H
(f). R_1=H, R_2= R_3= -CH=CH-CH=CH-

Scheme I

Table I — Physical and spectral data of **2a-f, 3a-f** and **4a-f**

Compd	m.p (˚C)	Calcd (Found) % C	H	N	Yield (%)	MS m/z	^{1}H NMR ($CDCl_3$-δ, ppm)
2a	188-89	61.69 61.71	3.45 3.11	5.99 5.67	72	233, 235	-
2b	192-93	63.04 62.99	4.07 3.92	5.66 5.67	68	247, 249	-
2c	108-09	63.04 62.89	4.07 3.82	5.66 5.50	68	247, 249	-
2d	207-08	63.04 62.71	4.07 4.01	5.66 5.43	79	247, 249	-
2e	222-23	59.22 59.18	3.82 3.79	5.31 5.28	62	263, 265	-
2f	260-61	67.74 67.76	3.55 3.27	4.94 4.59	64	283, 285	-
3a	221-22	73.46 73.15	4.11 4.06	14.28 14.21	51	196	8.75(s, 1H, NH), 8.14(s, 1H, C_5-H), 7.10-8.11(m, 7H, C_3, C_4, C_5, C_6,C_7, C_8, C_9-H)
3b	164-65	74.27 74.21	4.79 4.72	13.33 13.30	69	210	8.65(s, 1H, NH), 2.63(s, 3H, -CH_3), 7.43-8.21(m, 6H, C_3, C_4, C_5, C_6, C_8, C_9-H)
3c	198-99	74.27 74.11	4.79 4.67	13.33 13.01	70	210	8.60(s, 1H, NH), 2.61(s, 3H, -CH_3), 7.41-8.17(m, 6H, C_3, C_4, C_5, C_6, C_7, C_9-H)
3d	183-84	74.27 74.20	4.79 4.63	13.33 13.23	69	210	8.59(s, 1H, NH), 2.59(s, 3H, -CH_3), 7.39-8.14(m, 6H, C_3, C_4, C_5, C_6, C_7, C_8-H)

—Contd

Table I — Physical and spectral data of **2a-f, 3a-f** and **4a-f** —*Contd*

Compd	m.p (°C)	Calcd (Found) % C	H	N	Yield (%)	MS m/z	^{1}H NMR ($CDCl_3$-δ, ppm)
3e	195-96	69.02 68.99	4.46 4.39	12.38 12.30	60	226	8.90(s, 1H, NH), 3.41 (s, 3H, OCH_3), 7.49-8.22(m, 6H, C_3, C_4, C_5, C_6, C_8, C_9-H)
3f	210-11	78.03 77.96	4.06 3.81	11.38 11.07	65	246	9.01(s, 1H, -NH), 7.72-9.16 (m, 9H, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}-H),
4a	157-58	67.15 67.10	3.29 3.19	13.05 12.95	70	214, 216	7.25-8.31(m, 7H, C_3, C_4, C_5, C_6,C_7, C_8, C_9-H)
4b	139-40	68.28 68.20	3.97 3.89	12.25 12.18	81	228, 230	2.68(s, 3H, -CH_3), 7.31-8.42(m, 6H, C_3, C_4, C_5, C_6, C_8, C_9-H)
4c	146-47	68.28 68.19	3.97 3.92	12.25 12.20	74	228, 230	2.61(s, 3H, -CH_3), 7.30-8.39(m, 6H, C_3, C_4, C_5, C_6,C_7, C_9-H)
4d	141-42	68.28 68.15	3.97 3.90	12.25 12.17	87	228, 230	2.59(s, 3H, -CH_3), 7.28-8.35(m, 6H, C_3, C_4, C_5, C_6,C_7, C_8-H)
4e	161-62	63.81 63.75	3.71 3.72	11.45 11.40	73	244, 246	3.45 (s, 3H, OCH_3) 7.42-8.54(m, 6H, C_3, C_4, C_5, C_6, C_8, C_9-H)
4f	185-86	72.60 72.46	3.43 3.07	10.58 10.37	73	264, 266	7.82-9.21 (m, 9H, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}-H),

water and purified by column chromatography over silica gel using pet. ether-ethyl acetate (10:1) as eluent **(Table I)**.

Preparation of benzo[b][1,8]naphthyridin-2(1*H*)ones 3a-f. Compound **2** (2.3 g, 0.01 *M*) was refluxed with thionyl chloride (10 mL) for 45 min. Excess thionyl chloride was removed by co-distillation with benzene and the resulting acid chloride was dissolved in dry chloroform. The chloroform solution was dropped slowly into 100 mL of the ammonia solution with stirring and cooling the flask in an ice-bath. Ammonia gas was also passed during the addition. After the addition was over, stirring was continued for 4-5 hr and then refluxed on a water-bath for 3 hr. The solid that separated was filtered, washed with water, dried and recrystallised from methanol.

Preparation of 2-chloro benzo[b][1,8]naphthyridines 4a–f. Compound **3** (1.96 g, 0.01 *M*) was refluxed with excess phosphoryl chloride (8 mL) for 3 hr in a steam-bath. The reaction mixture was then poured into crushed ice after the completion of the reaction. The crude solid was then chromatographed using pet. ether- ethyl acetate (10:1) as the eluent. The compound was again recrystallised from pet. ether-ethyl acetate (10:1) to afford colourless crystals.

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