A Facile approach to dibenzo [*b,f*] [1,6] naphthyridines using Vilsmeier Conditions

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Abstract

A series of 1,6-naphthyridines have been synthesized. When 4-chloro 2-methyl quinoline 1a on reaction with aniline yielded 4-quinolinamine 2a which upon cyclisation afforded the titled compounds 3a using Vilsmeier conditions.

Introduction

Among heterocyclic compounds, 1,6-naphthyridines have received much interest and attention especially due to their pharmacological activities.[1-5] Some recent investigation indicated that 1,6-naphthyridines posses human cytogalovirus inhibitors.[6-7] As number of heterocycles have been synthesized using Vilsmeier reagent,[8-12] we have adapted for same approach to prepare 6-methyl dibenzo[*b,f*] [1,6] naphthyridines. The reaction route is shown in **Scheme I.**

Experimental

General information

Thin layer chromatography was used to access the reactions and purity of products. Mps. were determined on a Boetius Microheating Table and Mettler-FP5 melting apparatus and are uncorrected. IR spectra were obtained on Shimadzu–8201FT IR instrument as KBr pellets and only noteworthy absorption levels (cm^{-1}) are listed. ^{1}H-NMR spectra were recorded on Varian AMX-400 MHz spectrometer in $CDCl_3$ solution; chemical shifts are expressed in ppm (δ) relative TMS, coupling constants (J) in Hz and signal multiplicities are represented by s (singlet), bs (broadsinglet) and m (multiplet). Mass spectra were determined on a Jeol SX- 102 mass spectrometer. CHN analyses were carried out on Carlo Erba 106 and Perkin-Elmer Model 240 analysers.

Typical Procedure

Synthesis of quinolinoamines: 4-hydroxy-2-methyl quinoline was prepared by earlier reported procedure,[13] which on treatment with $POCl_3$ gave 4-chloro 2-methyl quinolines 1a as starting substrates.

Respective 4-chloro-2-methyl quinolines (1a-f, 0.002 mole), distilled aniline (0.002 mole) in anhydrous ethanol (20 ml), were refluxed for about 6 hrs. After the completion of

reaction, inferred through TLC, the reaction mixture was reduced to about half of its volume and allowed to cool. The solid separated was collected and recrystallized from $CHCl_3$- MeOH(1:1)2a-f.

Synthesis of respective 1,6-naphthyridines: To an ice-cooled, magnetically stirred solution of quinolinamines (2a-f, 0.001 mole) in DMF (0.003 mole), $POCl_3$ (0.007 mole) was added drop wise. The reaction mixture was heated on a water bath for 16 hours. Then it was poured into crushed ice (200gm) and neutralized with sodium hydroxide solution. The solid obtained was filtered off and purified by column chromatography over silica gel using petroleum ether-ethyl acetate (80:20) as an eluant to give 3a-f.

Results and Discussion

The reaction between 4-chloro-2-methyl quinolines (1a, 0.002 mole) and distilled aniline (0.002 mole) in anhydrous ethanol (20 ml) when refluxed for about 6 hours, afforded the product 2a; (Yield 92%, M.P. 214 °C). It's IR spectrum showed strong absorption bands at 3413 cm^{-1} due to NH group. The ^{1}H-NMR spectrum revealed a single proton broad singlet at δ 10.9, accountable for –NH proton and a singlet at δ 6.7 was accountable for C_3 proton in quinoline ring. The protons of methyl group were observed at δ 2.4 as a singlet. A multiplet in the region δ 7.4-7.9 (9H) accounted for the absorption of aromatic protons. The mass spectrum and elemental analysis further supported the existing compound 2a.

When quinolinamine (2a, 0.001 mole) was treated with phosphoryl chloride (0.007 mole) and dimethyl formamide (0.003 mole) gave the desired product 3a; (Yield 81%, M.P. 154 °C). The ^{1}H NMR spectrum revealed the disappearance of singlet at δ 6.7 thereby the loss of C_3 proton due to the cyclisation and sharp singlet at δ 2.4 due to methyl protons. All the other nine aromatic proton resonance's exhibited their absorptions between δ 6.8 – 7.4 as an unresolved multiplet. The mass spectrum showed the molecular ion peak at m/z 244. The elemental analysis further corroborated with the molecular formula $C_{17}H_{12}N_2$. All the above spectral and analytical data supported the structure of 3a as 6-methyl dibenzo [*b,f*] [1,6] naphthyridines.This reaction sequence leading to 3b-f was confirmed by their spectral data.(**Table II**)

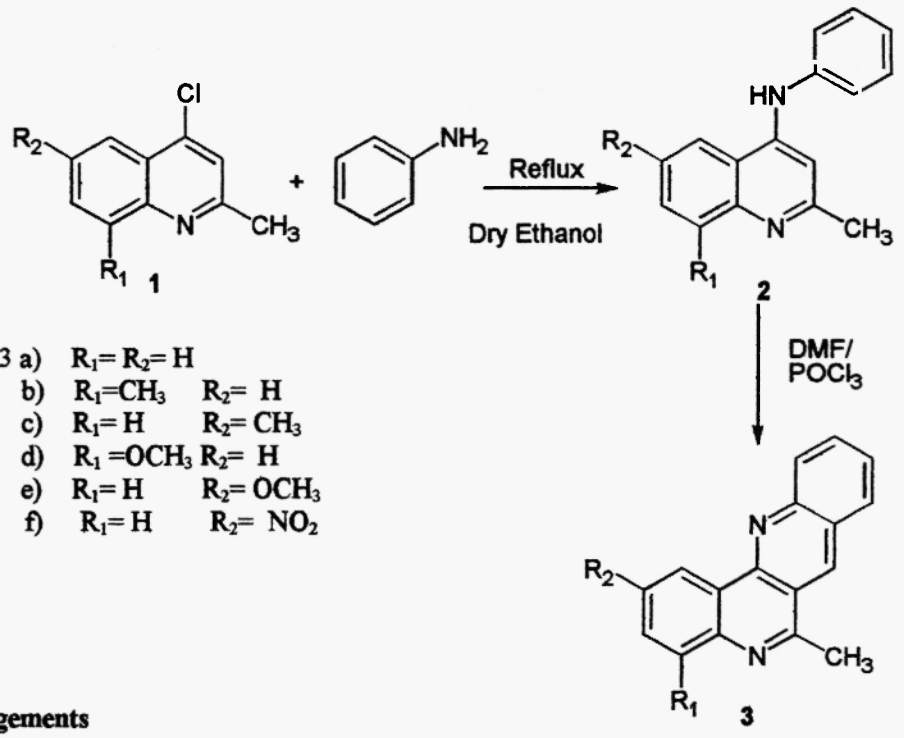
Table I - Physical and spectral data of compounds 2a-f

Compd	M. P (°C)	Yield (%)	IR cm^{-1} (KBr)	Elemental Analysis Calcl. (Found) C	H	N	Molecular Formula	^1H NMR ($CDCl_3$) δ/ppm
2a	214	92	3413	81.32 (81.25)	6.82 (6.73)	11..85 (11.83)	$C_{16}H_{16}N_2$	2.4 (s, 3H, CH_3) 6.7 (s, 1H, =CH) 7.4- 7.9 (m, 9H, Ar-H) 10.9 (bs, 1H, -NH)
2b	247	86	3320	81.56 (81.32)	7.25 (7.34)	11.19 (11.07)	$C_{17}H_{18}N_2$	2.4 (s, 6H, 2 xCH_3) 6.5 (s, 1H, =CH) 7.4-7.9 (m, 8H,Ar-H) 10.7 (bs, 1H, -NH)
2c	142	82	3125	81.56 (81.44)	7.25 (7.12)	11.19 (11.17)	$C_{17}H_{18}N_2$	2.8 (s, 6H, 2xCH_3) 6.8 (s, 1H, =CH) 7.2-7.7 (m, 8H,Ar-H) 11.0 (bs, 1H, -NH)
2d	187	73	3220	76.66 (76.52)	6.81 (6.72)	10.52 (10.33)	$C_{17}H_{18}N_2O$	2.5 (s, 3H, CH_3) 3.9 (s, 3H, -OCH_3) 6.2 (s, 1H, =CH) 7.2-7.6 (m, 8H,Ar-H) 10.5 (bs, 1H, -NH)
2e	210	65	3300	76.66 (76.64)	6.81 (6.63)	10.52 (10.42)	$C_{17}H_{18}N_2O$	2.2 (s, 3H, CH_3) 3.5 (s, 3H, -OCH_3)) 6.7 (s, 1H, =CH) 7.6-8.1 (m, 8H,Ar-H) 11.1 (bs, 1H, -NH)
2f	133	55	3130	68.31 (68.43)	5.37 (5.33)	14.94 (14.88)	$C_{16}H_{15}N_3O_2$	2.3 (s, 3H, CH_3) 5.9 (s, 1H, =CH) 6.8-7.5 (m, 8H,Ar-H) 9.2 (bs, 1H, -NH)

Table II - Physical and spectral data of compounds 3a-f

Compd	M P (°C)	Yield (%)	Elementalanalysis Calcl. (found) C	H	N	Molecular Formula	^{1}H-NMR ($CDCl_3$) δ/ppm
3a	154	81	83.58 (83.44)	4.95 (4.98)	11.47 (11.54)	$C_{17}H_{12}N_2$	2.4 (s, 3H, CH_3) 6.8-7.4 (m, 9H, Ar-H)
3b	174	73	83.69 (83.72)	5.46 (5.48)	10.84 (10.88)	$C_{18}H_{14}N_2$	2.3 (s, 6H, 2 x CH_3) 6.5-7.5 (m, 8H, Ar-H)
3c	167	65	83.69 (83.66)	5.46 (5.53)	10.84 (10.91)	$C_{18}H_{14}N_2$	2.1 (s, 6H, 2 x CH_3) 7.2-8.1 (m, 8H, Ar-H)
3d	212	67	78.81 (78.79)	5.14 (5.18)	10.21 (10.27)	$C_{18}H_{14}N_2O$	2.4 (s, 3H, CH_3) 3.7 (s, 3H, -OCH_3) 7.2-7.7 (m, 8H, Ar-H)
3e	187	62	78.81 (78.87)	5.14 (5.10)	10.21 (10.26)	$C_{18}H_{14}N_2O$	2.4 (s, 3H, CH_3) 3.9 (s, 3H, -OCH_3) 6.8-7.3 (m, 8H, Ar-H)
3f	158	58	70.58 (70.54)	3.83 (3.79)	14.53 (14.57)	$C_{17}H_{11}N_3O_2$	2.2 (s, 3H, CH_3) 7.0-7.6 (m, 8H, Ar-H)

Scheme I



1,2,3 a) $R_1 = R_2 = H$
b) $R_1 = CH_3$ $R_2 = H$
c) $R_1 = H$ $R_2 = CH_3$
d) $R_1 = OCH_3$ $R_2 = H$
e) $R_1 = H$ $R_2 = OCH_3$
f) $R_1 = H$ $R_2 = NO_2$

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