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Synthesis and Antibacterial Activity of 8-Methyl Benzo[b]Naphtho[f][1,6]-Naphthyridines

T. SURESH, R. NANDHA KUMAR and P.S. MOHAN*
Department of Chemistry, Bharathiar University, Coimbatore-641 046, India
E-mail: ps_mohan_in@yahoo.com

The treatment of 4-chloro-2-methylquinoline with aniline yielded 4-quinolinamine, which upon cyclization afforded the titled compounds using Vilsmeier conditions. All the synthesized compounds have been screened for their antibacterial activities against *Salmonella typhii* and *Aeromonas hydrophila*.

Key Words: 4-Chloro-2-methylquinoline, α-Naphthylamine, 4-Quinolinamine, 1,6-Naphthyridines, Vilsmeier reagent.

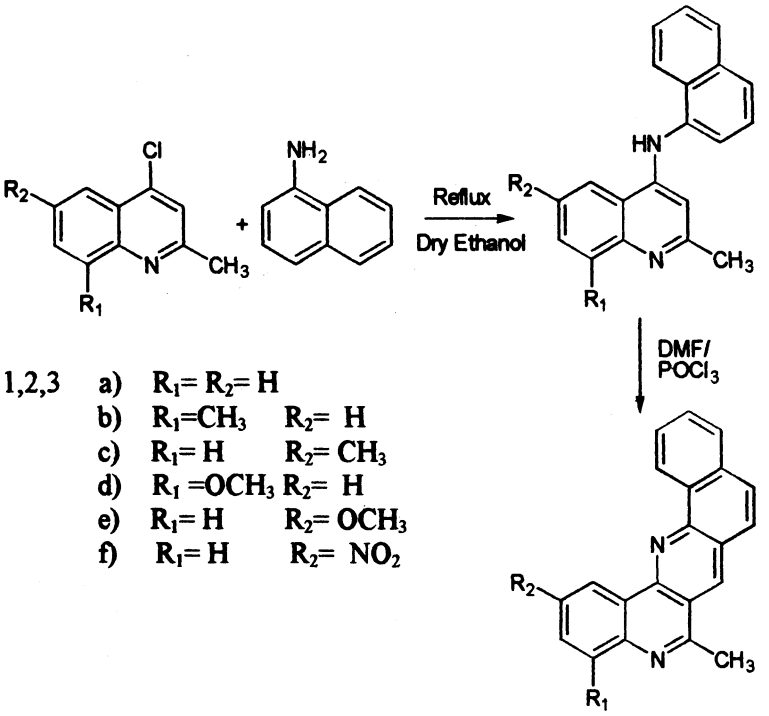
INTRODUCTION

Among heterocyclic compounds, 1,6-naphthyridines have received much interest and attention, especially due to their pharmacological activities[1–5]. Recent investigation indicated that 1,6-naphthyridines possess human cytogalovirus inhibitors.[6] As a number of heterocycles have been synthesized using Vilsmeier reagent[7–11] and due to our continued interest in the chemistry of 1,6-naphthyridines, we undertook the synthesis and antibacterial activity studies on new naphthyridine moiety. The reaction sequence leading to the formation of title compound is outlined in **Scheme-1**.

EXPERIMENTAL

General information

Thin layer chromatography was used to access the reactions and purity of products. M.p.s 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 (broad singlet) 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 240 analysers.



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) $R_1 = H$ $R_2 = NO_2$

Typical Procedure

Synthesis of quinolinoamines: 4-Hydroxy-2-methyl quinoline was prepared by earlier reported procedure,[12] 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), α-naphthylamine (0.002 mole) in anhydrous ethanol (20 mL) were refluxed for about 6.5 h. 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 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 dropwise. The reaction mixture was heated on a water bath for 16 h. Then it was poured into crushed ice (200 g) 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 (75 : 25) as an eluant to give **3a–f**.

RESULTS AND DISCUSSION

The reaction between 4-chloro-2-methyl quinolines (**1a**, 0.002 mole) and α-naphthylamine (0.002 mole) in anhydrous ethanol (20 mL) when refluxed for about 6.5 h, afforded the product **2a** (yield 85%, m.p. 235°C). Its IR spectrum showed strong absorption bands at 3525 cm^{-1} due to NH group. The ^{1}H-NMR

spectrum revealed a single proton broad singlet at δ 4.1, accountable for —NH proton and a singlet at δ 6.5 was accountable for C_3 proton in quinoline ring. The protons of methyl group were observed at δ 2.2 as a singlet. A multiplet in the region δ 7.2–8.4 (11H) accounted for the absorption of aromatic protons. The mass spectrum and elemental analysis further supported the existing compound **2a** (Table-1).

TABLE-1
PHYSICAL AND SPECTRAL DATA OF COMPOUNDS **2a–f**

Compd.	m.p. (°C)	Yield (%)	IR (KBr) (cm^{-1})	Anal. (%) Calcd. (Found) C	H	N	m.f.	^{1}H NMR ($CDCl_3$) δ/ppm
2a	235	85	3525	83.88 (82.67)	6.34 (6.76)	9.78 (10.53)	$C_{20}H_{18}N_2$	2.2 (s, 3H, CH_3) 4.1 (bs, 1H, —NH) 6.5 (s, 1H, =CH) 7.2–8.4 (m, 11H, Ar—H)
2b	207	79	3432	83.96 (82.38)	6.71 (6.34)	9.33 (8.67)	$C_{21}H_{20}N_2$	2.7 (s, 6H, 2 × CH_3) 5.9 (bs, 1H, —NH) 6.8 (s, 1H, =CH) 7.2–8.1 (m, 10H, Ar—H)
2c	168	60	3128	83.96 (81.33)	6.71 (6.98)	9.33 (8.98)	$C_{21}H_{20}N_2$	2.9 (s, 6H, 2 × CH_3) 6.1 (bs, 1H, —NH) 6.3 (s, 1H, =CH) 7.2–8.2 (m, 10H, Ar—H)
2d	210	62	3024	79.72 (78.54)	6.37 (6.78)	8.85 (9.33)	$C_{21}H_{20}N_2O$	2.5 (s, 3H, CH_3) 3.9 (s, 3H, —OCH_3) 6.2 (s, 1H, =CH) 6.5 (bs, 1H, —NH) 7.2–7.6 (m, 10H, Ar—H)
2e	210	55	3300	79.72 (79.14)	6.37 (6.94)	8.85 (8.98)	$C_{21}H_{20}N_2O$	2.2 (s, 3H, CH_3) 3.5 (s, 3H, —OCH_3) 6.7 (s, 1H, =CH) 7.6–8.1 (m, 10H, Ar—H) 11.1 (bs, 1H, —NH)
2f	163	45	3153	72.49 (73.43)	5.17 (5.33)	12.68 (13.28)	$C_{20}H_{17}N_3O_2$	2.3 (s, 3H, CH_3) 5.9 (s, 1H, =CH) 6.8–7.5 (m, 10H, Ar—H) 9.2 (bs, 1H, —NH

When quinolinamine (**2a**, 0.001 mole) was treated with phosphoryl chloride (0.007 mole) and dimethyl formamide (0.003 mole) it gave the desired product **3a**; (yield 72%, m.p. 130°C). The ^{1}H NMR spectrum revealed the disappearance of singlet at δ 6.5, thereby the loss of C_3 proton due to the cyclisation and sharp singlet at δ 2.1 due to methyl protons. All the other eleven aromatic proton resonances exhibited their absorptions between δ 7.2–7.7 as an unresolved multiplet. The mass spectrum showed the molecular ion peak at m/z 294. The

elemental analysis further corroborated the m.f. $C_{21}H_{14}N_2$. All the above spectral and analytical data supported the structure of **3a** as 8-methyl benzo[b]naphtho[f][1,6]naphthyridines This reaction sequence leading to **3b–f** was confirmed by their spectral data. (Table-2).

TABLE-2
PHYSICAL AND SPECTRAL DATA OF COMPOUNDS **3a–f**

Cmpd.	m.p. (°C)	Yield (%)	Anal. (%) Calcd. (Found)			m.f.	^{1}H NMR ($CDCl_3$) δ/ppm
			C	H	N		
3a	130	72	85.69 (84.44)	4.79 (4.98)	9.52 (10.43)	$C_{21}H_{14}N_2$	2.1 (s, 3H, CH_3) 7.0–7.7 (m, 11H, Ar—H)
3b	185	60	85.69 (84.72)	5.23 (5.48)	9.08 (9.88)	$C_{22}H_{16}N_2$	2.4 (s, 6H, 2 × CH_3) 6.5–7.5 (m, 10H, Ar—H)
3c	176	62	85.69 (83.88)	5.23 (5.44)	9.08 (8.76)	$C_{22}H_{16}N_2$	2.2 (s, 6H, 2 × CH_3) 7.2–8.1 (m, 10H, Ar—H)
3d	212 d	55	81.46 (80.79)	4.97 (5.18)	8.84 (9.27)	$C_{22}H_{16}N_2O$	1.8 (s, 3H, CH_3) 3.7 (s, 3H, —OCH_3) 7.2–7.7 (m, 10H, Ar—H)
3e	230	52	81.46 (82.49)	3.86 (3.79)	8.64 (8.77)	$C_{22}H_{16}N_2O$	2.4 (s, 3H, CH_3) 3.9 (s, 3H, —OCH_3) 6.8–7.3 (m, 10H, Ar—H)
3f	152	45	74.33 (73.54)	5.17 (5.33)	12.38 (12.57)	$C_{22}H_{13}N_2O_2$	2.6 (s, 3H, CH_3) 7.0–7.6 (m, 10H, Ar—H)

All the synthesized compounds were screened for their antibacterial activities against *Salmonella typhi* and *Aeromonas hydrophilla* and were done for the compounds by using the disc diffusion method.[13, 14] Bacteria were cultured in nutrient agar medium and used as inoculum for study. Bacterial cells were swabbed on to nutrient agar medium [prepared from NaCl (5.0 g), peptone (5.0 g), beef extract powder (3.0 g), yeast extract powder (3.0 g), agar (20.0 g) in 100 mL distilled water; pH = 7.5 ± 0.2] in petri plates. The compounds to be tested were dissolved in chloroform to final concentrations of 0.5, 1 and 2% and soaked in filter paper discs of 5 mm diameter and 1 mm thickness. These discs were placed on the already seeded plates and incubated at 35 ± 2°C for 24 h. The diameter (mm) of the inhibition zone around each disc was measured after 24 h. According to the observation, the toxicity increases with the increase in concentration of the test solution containing new compounds.

The antibacterial activity revealed that the compounds **(3a–f)** were highly active against *Salmonella typhi* and *Aeromonas hydrophilla* obviously due to 1,6-naphthyridine ring systems. The compounds **(2a–f)** were also moderately active against both the bacteria.

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