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SYNTHESIS OF 6-METHYLBENZO-[*b*]PYRIDO[3,2-*f*][1,6]NAPHTHYRIDINES FROM 4-CHLORO-2-METHYLQUINOLINE

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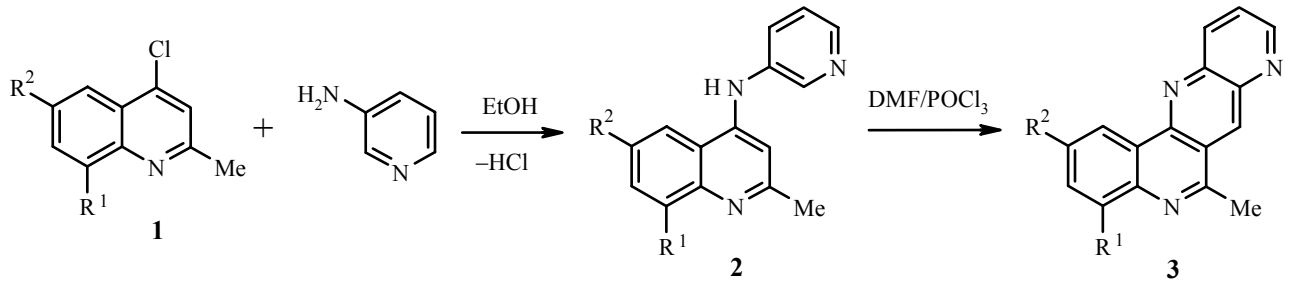
4-Chloro-2-methylquinolines in reaction with 3-aminopyridine yielded 4-quinolinamines, which upon cyclisation under Vilsmeier–Haak conditions afforded the title compounds.

Keywords: 3-aminopyridine, 4-chloro-2-methylquinoline, 1,6-naphthyridine, 4-quinolinamine, Vilsmeier–Haak conditions.

Among heterocyclic compounds 1,6-naphthyridines have received much interest and attention especially due to their pharmacological activities [1-4]. A recent investigation indicated that 1,6-naphthyridines possess properties of human cytomegalovirus inhibitors [5]. A number of heterocyclic compounds has been synthesized using Vilsmeier reagent for cyclization purposes [6-12].

In present work the coupling of 4-haloquinolines with 3-aminopyridine by nucleophilic subsitution resulted in quinolinamines. The latter were further cyclized by Vilsmeier–Haak reagent.



1-3 a $R^1 = R^2 = H$; **b** $R^1 = Me$, $R^2 = H$; **c** $R^1 = H$, $R^2 = Me$; **d** $R^1 = OMe$, $R^2 = H$; **e** $R^1 = H$, $R^2 = OMe$; **f** $R^1 = H$, $R^2 = NO_2$

The reaction between equimolar amount of 4-chloro-2-methylquinoline and 3-aminopyridine in anhydrous ethanol for 6.5 h afforded the product **2a** (Table 1). Its IR spectrum showed strong absorption bands at 3413 cm^{-1} due to NH group.The ^1H 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 H(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**. The series of the sequence was also carried out (Table 2).

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TABLE 1. Characteristics of the Synthesized Compounds **2a-f** and **3a-f**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{15}H_{15}N_3$	73.50 / 75.92	6.43 / 6.37	17.81 / 17.71	197	92
2b	$C_{16}H_{17}N_3$	77.12 / 76.46	6.93 / 6.82	16.84 / 16.72	>300	86
2c	$C_{16}H_{17}N_3$	77.23 / 76.46	6.99 / 6.82	16.56 / 16.72	163	82
2d	$C_{16}H_{17}N_3O$	71.65 / 71.89	6.45 / 6.41	15.33 / 15.72	188	73
2e	$C_{16}H_{17}N_3O$	71.44 / 71.89	5.76 / 6.41	16.33 / 15.72	218	65
2f	$C_{15}H_{14}N_4O_2$	62.77 / 63.82	5.65 / 5.00	19.76 / 19.85	120	55
3a	$C_{16}H_{11}N_3$	78.67 / 78.35	5.17 / 4.52.	17.76 / 17.13	185	81
3b	$C_{17}H_{13}N_3$	78.34 / 78.74	5.33 / 4.52	16.64 / 16.20	210	73
3c	$C_{17}H_{13}N_3$	79.33 / 78.74	4.97 / 4.52	16.93 / 16.20	193	65
3d	$C_{17}H_{13}N_3O$	75.31 / 74.14	5.33 / 4.76	16.27 / 15.26	160	67
3e	$C_{17}H_{13}N_3O$	74.56 / 74.14	6.13 / 4.76	15.87 / 15.26	197	62
3f	$C_{16}H_{10}N_4O_2$	65.72 / 66.20	3.98 / 3.47	18.76 / 19.30	183	58

TABLE 2. IR and ^{1}H NMR spectra of the compounds **2a-f** and **3a-f**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm
2a	3413 (NH), 1699 (C=N)	2.4 (3H, s, CH_3); 6.7 (1H, s, C_3H); 7.4-7.9 (8H, m, Ar–H); 10.9 (1H, br. s, H)
2b	3320 (NH), 1637 (C=N)	2.4 (6H, s, $2CH_3$); 6.5 (1H, s, C_3H); 7.4-7.9 (8H, m, Ar–H); 10.7 (1H, br. s, NH)
2c	3125 (NH), 1620 (C=N)	2.8 (6H, s, $2CH_3$); 6.8 (1H, s, C_3H); 7.2-7.7 (7H, m, Ar–H); 11.0 (1H, br. s, NH)
2d	3220 (NH), 1690 (C=N)	2.5 (3H, s, CH_3); 3.9 (3H, s, OCH_3); 6.2 (1H, s, C_3H); 7.2-7.6 (7H, m, Ar–H); 10.5 (1H, br. s, NH)
2e	3300 (NH), 1619 (C=N)	2.2 (3H, s, CH_3); 3.5 (3H, s, OCH_3); 6.7 (1H, s, C_3H); 7.6-8.1 (7H, m, Ar–H); 11.1 (1H, br. s, NH)
2f	3130 (NH), 1576 (C=N)	2.3 (3H, s, CH_3); 5.9 (1H, s, C_3H); 6.8-7.5 (7H, m, Ar–H); 9.2 (1H, br. s, NH)
3a	1680 (C=N), 1620 (C=N)	2.4 (3H, s, CH_3); 6.8-7.4 (8H, m, Ar–H)
3b	1613 (C=N), 1588 (C=N)	2.3 (6H, s, $2CH_3$); 6.5-7.5 (7H, m, Ar–H)
3c	1690 (C=N), 1637 (C=N)	2.1 (6H, s, $2CH_3$); 7.2-8.1 (7H, m, Ar–H)
3d	1620 (C=N), 1590 (C=N)	2.4 (3H, s, CH_3); 3.7 (3H, s, OCH_3); 7.2-7.7 (7H, m, Ar–H)
3e	1630 (C=N), 1648 (C=N)	2.4 (3H, s, CH_3); 3.9 (3H, s, OCH_3); 6.8-7.3 (7H, m, Ar–H)
3f	1678 (C=N), 1565 (C=N)	2.2 (3H, s, CH_3); 7.0-7.6 (7H, m, Ar–H)

When quinolinamine **2a** was treated with Vilsmeier–Haak reagent (phosphoryl chloride and dimethylformamide) the desired product **3a** was obtained. The ^{1}H NMR spectrum indicated the disappearance of singlet at δ 6.7, thereby proving the loss of H(3) proton due to cyclization. A sharp singlet at δ 2.4 is due to methyl protons. All the other nine aromatic proton resonances exhibited their absorptions between δ 6.8 and 7.4 as an unresolved multiplet. The mass spectrum showed the molecular ion peak at *m/z* 245. The spectral and analytical data supported the structure of **3a** as 6-methylbenzo[*b*]pyrido[3,2-*f*][1,6]-naphthyridines.This reaction sequence leading to **3b-f** was confirmed by their spectral and analytical data (Table 1, 2).

EXPERIMENTAL

Thin layer chromatography was used to assess the reactions and the purity of products. Melting points were determined on a Boetius Microheating Table and Mettler-FP5 Melting apparatus and are uncorrected. IR spectra were recorded in Shimadzu-820IFT instrument in KBr disc and only noteworthy absorption levels (reciprocal centimeter) are listed. ^{1}H NMR spectra were recorded in an AMX-400 (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), and m (multiplet). Mass spectra were recorded on a Jeol-D-300 mass spectrometer. CHN analyses were carried out on a Carlo Erba 106 and Perkin–Elmer 240 analysers.

4-Chloro-2-methylquinolines 1 were prepared by treatment of respective 4-hydroxy-2-methylquinolines with $POCl_3$ (for the synthesis of 4-hydroxy-2-methylquinolines see [14]).

Synthesis of 4-Quinolinamines. Respective 4-chloro-2-methylquinolines **1a-f** (0.002 mol) and 3-aminopyridine (0.002 mol) in anhydrous ethanol (20 ml) were refluxed for about a 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 mol) in DMF (0.003 mol), $POCl_3$ (0.007 mol) was added dropwise. The reaction mixture was heated on a water bath for 16 h. Then it was poured into crushed ice (200 gm) 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 eluent to give **3a-f.**

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