An efficient synthesis of phenyl-substituted dibenzonaphthyridines

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A one-pot synthesis of 9-chloro-6-methyl-7-phenyldibenzo[*b,h*][1,6]naphthyridines from 4-chloro-2-methylquinolines is reported. Since the yield of the dibenzonaphthyridine was low, in an alternative method the title compounds were prepared from the 4-chloro-2-methylquinolines *via* 2-methyl-4-[(4-chlorophenyl)amino]quinolines as intermediates, which provided improved yields.

Keywords: quinolines, fused 1,6-naphthyridines

Quinoline alkaloids in general and phenylaminoquinolines in particular have attracted considerable attention because of their powerful antimalarial property.[1] Since the discovery of the cinchona alkaloids as antimalarial agents the quinoline (π-electron deficient heterocycle) core has become a "privileged structure" for the design and development of new drugs.

Interest in naphthyridine derivatives arises from their exceptionally broad spectrum of biological activities. They are used in the therapy of human disease including AIDS[2,3] and cancer.[4] In particular, some dibenzonaphthyridines, *viz.* quinoline dimers, act as potent and selective 3-phosphoinositide-dependent kinase-I inhibitors.[5]

A literature survey revealed that the reactions of chloroquinolines have been studied extensively, the objective being to obtain substitution products possessing biological activity.[6,7]

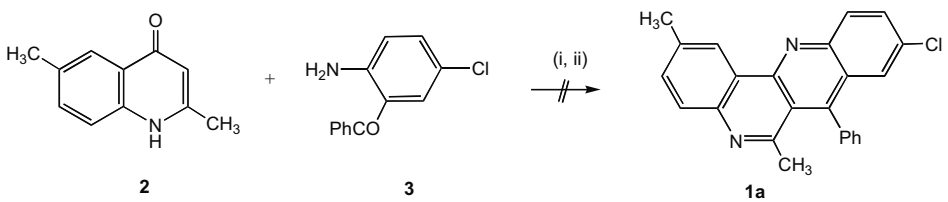
There are several references to the synthesis of simple dibenzonaphthridines,[8-11] but only very few accomplish their construction through anilinoquinolines [(*N*-phenylamino) quinolines].[12,13] Here we report the synthesis of phenyl substituted dibenzo[*b,h*][1,6]naphthyridines utilising 4-chloro-2-methylquinolines in two different ways, one of the methods involving (*N*-phenylamino)quinolines as intermediates.

Results and discussion

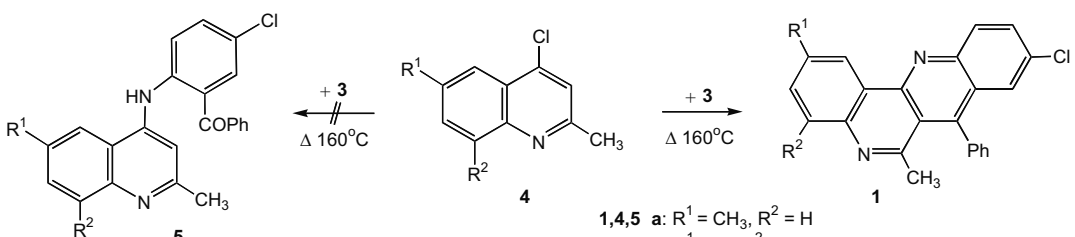
Since the approach to the preparation of the 9-chloro-2,6-dimethyl-7-phenyldibenzo[*b,h*][1,6]naphthyridine (**1a**) from the reaction of 2,6-dimethylquinolin-4(1*H*)-one (**2**) and 2-amino-5-chlorobenzophenone (**3**) under acidic condition, similar to our earlier report,[14] was not successful (Scheme 1), we considered an alternative approach in which 4-chloro-2,6-dimethylquinoline (**4a**) was treated with the amino-benzophenone (**3**) under neat conditions at 160 °C for half an hour in the hope of obtaining the ketone **5a** which may be a suitable intermediate to the target molecule **1a** (Scheme 2).

The structure of the product was established by spectral means. The absence of a C=O group in the IR and ^{13}C NMR spectra revealed that the expected uncyclised compound **5a** was not formed. The absence of C_3-H of a quinoline moiety in its ^1H NMR spectrum confirmed this view. Its mass spectrum showed the molecular ion peak at *m/z* 368 (M^+) as the base peak and the isotopomeric satellite peak at *m/z* 370. All the spectral and analytical data were in agreement with the cyclised structure, namely 9-chloro-2,6-dimethyl-7-phenyldibenzo[*b,h*][1,6]naphthyridine (**1a**). The preparations were generalised with other substituted chloroquinolines (**4b–d**) to afford the respective dibenzonaphthyridines (**1b–d**).

The mechanism for the formation of this product can be interpreted as *via* the formation of the intermediate **6** by the elimination of HCl, which further catalyses the cyclisation by the protonation of the 2'-carbonyl group to form the oxonium ion intermediate **6**. Its reaction at the quinoline C_3-position by intramolecular electrophilic cyclisation gives the intermediate **7** which on aromatisation to **8** and subsequent loss of a water molecule under the influence of acid yields the final product **1** (Scheme 3).



Scheme 1 *Reagents:* (i) H_2SO_4/AcOH, (ii) HCl/EtOH



Scheme 2

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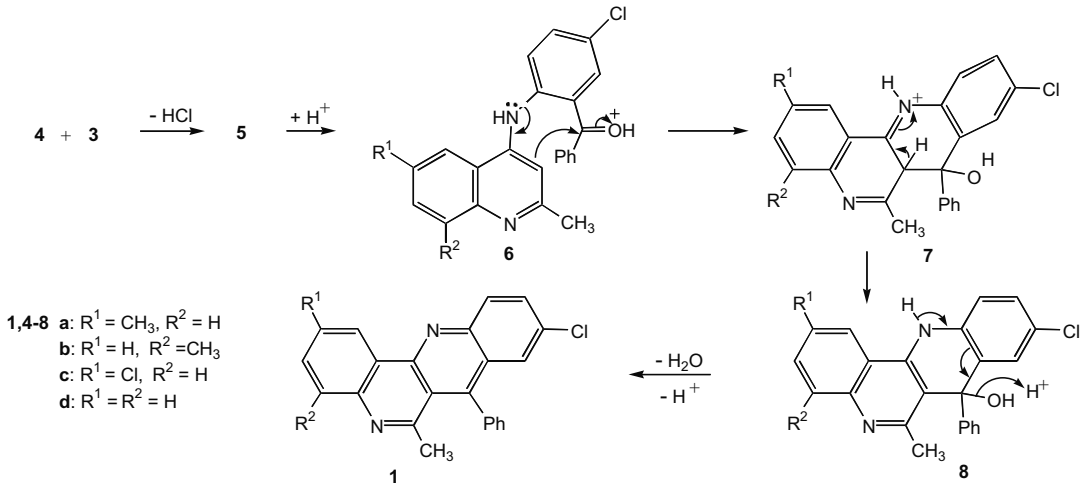


Scheme 3

The yields of the one pot synthesis of the dibenzonaphthyridine (**1a–d**) as outlined in Scheme 2 were only moderate (*ca* 24%), so we devised an alternative route in which 4-chloro-2-methylquinoline (**4a**) was heated with *p*-chloroaniline (**9**) under neat conditions at 160 °C for half an hour (Scheme 4). The product obtained was assigned as 4'-chloro-2,6-dimethyl-4-(*N*-phenylamino)quinoline (**10a**) which was found to be in tautomeric equilibrium with its imino form (**11a**) on the basis of two broad NH signals in its ^{1}H NMR spectrum. The reaction was extended to other chloroquinolines (**4b–d**) to obtain the respective anilinoquinolines (**10b–d**).

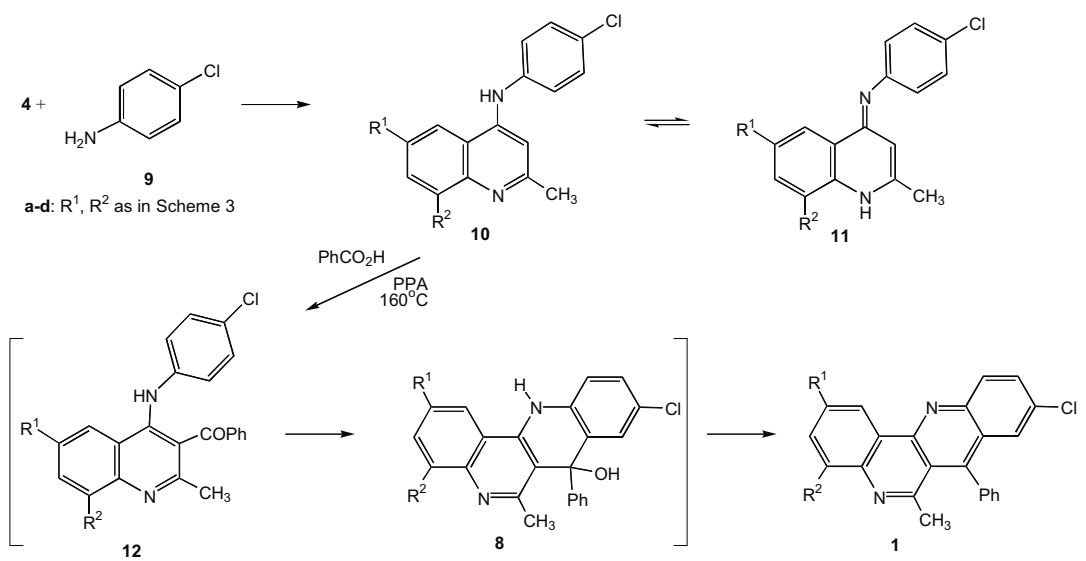
The anilinoquinoline **10a** was heated with benzoic acid in the presence of polyphosphoric acid to 160 °C for five hours to give the product. From the TLC, mixed melting point and superimposable IR spectra, the compound was identified as the same (**1a**) as that obtained earlier from 4-chloro-2-methylquinoline (**1**) and 2-amino-5-chlorobenzophenone in the one pot synthesis under neat conditions. A plausible route to the product, through the intermediate **12** *via* benzoylation of **10** at the quinoline 3-position, and acid-catalysed cyclisation to the aniline ring through the intermediate **8** as proposed above, is shown in Scheme 4.

Even though the synthesis involves two steps to the product, the overall yield was somewhat better (*ca* 31%) than the one pot synthesis. The yields of the products obtained from the above two methods are compared in Table 1.

In conclusion: alternative routes are described for the preparation of four substituted dibenzo[*b,h*][1,6]naphthyridines.

Table 1 Comparison of yields: Method 1 (Scheme 2) and Method 2 (Scheme 4)

			Yields/%			
			Method 1		Method 2	
Products	R^1	R^2	One-pot **4** → **1**	**4** → **10**	**10** → **1**	overall
1a	CH_3	H	23	70	43	30
1b	H	CH_3	25	75	45	34
1c	Cl	H	22	65	40	26
1d	H	H	25	72	45	33



Scheme 4

The compounds synthesised were tested for antimicrobial activity against the species *Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumoniae and Vibrio cholerae.*

Experimental

Melting points were determined on a Mettler FP 51apparatus (Mettler Instruments, Switzerland). IR spectra were recorded on a Shimadzu FTIR-8201PC spectrophotometer (Shimadzu, Japan) using KBr discs. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX 400 spectrometer; the chemical shifts are expressed in parts per million (ppm) from tetramethylsilane (TMS) as internal reference. Mass spectra (MS) were recorded on AutoSpec EI + Shimadzu QP 2010 PLUS GC-MS mass spectrometer. Microanalyses were performed on a Vario EL III model CHNS analyser (Vario, Germany) at the Department of Chemistry, Bharathiar University. The purity of the products was tested by TLC with plates coated with silica gel-G with petroleum ether, ethyl acetate and methanol as developing solvents.

Preparation of 9-chloro-6-methyl-7-phenyldibenzo[b,h][1,6]naphthyridines (1) from 4-chloro-2-methylquinolines (4), general procedure

The appropriate 4-chloro-2-methylquinoline (**4**, 1 mmol) was heated with 2-amino-5-chlorobenzophenone (**3**, 0.23 g, 1 mmol) under neat conditions at 160 °C for half an hour. The product was washed with water, adsorbed and purified by chromatography on silica gel, eluting with petroleum ether : ethyl acetate (98:2) to get **1** which was then recrystallised from methanol.

9-Chloro-2,6-dimethyl-7-phenyldibenzo[b,h][1,6]naphthyridine (**1a**): Colourless prisms (0.083 g, 23%), m.p. 250–252 °C. IR: ν_{max} 1625 and 1609 cm^{-1} (C=N). NMR: δ_H 2.27 (s, 3H, C6-CH_3), 2.67 (s, 3H, C2-CH_3), 7.39–7.64 (m, 7H, C8, C3, C2'-6'H), 7.77 (dd, 1H, C10-H, J_m = 2.28, J_o = 9.08 Hz), 7.90 (d, 1H, C4-H, J = 8.16 Hz), 8.31(d, 1H, C11-H, J = 9.08 Hz), 9.10 (s, 1H, C1-H); δ_C 19.7 (C6-CH_3), 20.9 (C2-CH_3), 118.0 (C8), 122.8 (C9), 125.1 (C1), 126.3 (C2', C6'), 127.9 (C3'-5'), 128.1 (C1'), 129.5 (C7), 129.8 (C7a), 131.9 (C10), 132.2 (C11), 132.9 (C4), 135.8 (C3), 137.9 (C2), 144.2 (C12b), 146.8 (C6a), 147.2 (C11a), 148.5 (C12a), 149.9 (C4a), 159.1 (C6). MS: *m/z* (%) 370–368 (M$^+$, 35/100), 367 (25), 353 (12), 333 (15), 332 (8), 166 (15), 77 (32), 41 (35). Anal. Calcd for $C_{24}H_{17}ClN_2$: C, 78.26; H, 4.62; N, 7.61. Found: C, 77.95; H, 4.34; N, 7.38%.

9-Chloro-4,6-dimethyl-7-phenyldibenzo[b,h][1,6]naphthyridine (**1b**): Colourless needles (0.092 g, 25%), m.p. 245–247 °C. IR ν_{max}: 1630 and 1608 cm^{-1} (C=N). NMR: δ_H 2.29 (s, 3H, C6-CH_3) 2.82 (s, 3H, C4-CH_3), 7.38–7.67 (8H, m, C2-H, C3-H, C8-H, C2'-6'-H), 7.77 (dd, 1H, C10-H, J_m = 2.24, J_o = 9.08 Hz), 8.30 (d, 1H, C11-H, J = 9.08 Hz), 9.17 (d, 1H, C1-H, J = 7.92 Hz); δ_C 17.7 (C6-CH_3), 29.6 (C4-CH_3), 117.8 (C8), 122.4 (C9), 124.4 (C1), 125.9 (C2', C6'), 126.5 (C3'-C5'), 127.5 (C1'), 128.5 (C7), 128.9 (C7a), 129.8 (C10), 131.2 (C11), 131.7 (C4), 132.0 (C3), 136.2 (C2), 138.3 (C12b), 143.1 (C6a), 146.9 (C11a), 147.7 (C12a), 149.1 (C4a), 158.0 (C6). MS: *m/z* (%) 370/368 (M$^+$, 33/100), 367 (12), 353 (5), 333 (8), 332 (20), 317 (5), 166 (10), 51 (20). Anal. Calcd for $C_{24}H_{17}ClN_2$: C, 78.26; H, 4.62; N, 7.61. Found: C, 78.10; H, 4.52; N, 7.49%.

2,9-Dichloro-6-methyl-7-phenyldibenzo[b,h][1,6]naphthyridine (**1c**): White solid (0.081 g, 22%), m.p. 255–257 °C. IR: ν_{max} 1635 and 1617 cm^{-1} (C=N). NMR: δ_H 2.28 (s, 3H, C6-CH_3), 7.38–7.74 (m, 7H, C8-H, C3-H, C2'-6'-H), 7.80 (dd, 1H, C10-H, J_m = 2.32, J_o = 9.08 Hz), 7.93 (d, 1H, C4-H, J = 8.60 Hz), 8.30 (d, 1H, C11-H, J = 9.08 Hz), 9.28 (d, 1H, C1-H, J = 2.32 Hz); δ_C 18.1 (C6-CH_3), 117.9 (C8), 121.8 (C9), 126.0 (C1), 127.0 (C2', C6'), 128.1 (C3'-C5'), 128.5 (C_1'), 128.9 (C7), 129.7 (C7a), 132.5 (C10), 132.8 (C11), 133.2 (C4), 136.1 (C3), 138.0 (C2), 144.0 (C12b), 147.1 (C6a), 147.2 (C11a), 149.4 (C12a), 150.1 (C4a), 160.0 (C6). MS: *m/z* (%) 392–390/388 (M$^+$, 11/64/100), 387 (70), 373 (20), 353 (30), 318 (10), 165 (15), 77 (8), 51 (12). Anal. Calcd for $C_{23}H_{14}Cl_2N_2$: C, 71.19; H, 3.61; N, 7.21. Found: C, 70.93; H, 3.48; N, 7.11%.

9-Chloro-6-methyl-7-phenyldibenzo[b,h][1,6]naphthyridine (**1d**): Colourless prisms (0.088 g 25%), m.p. 242–244 °C. IR: ν_{max} 1627 and 1611 cm^{-1} (C=N). NMR: δ_H 2.26 (s, 3H, C6-CH_3), 7.39–7.70 (m, 8H, C2-H, C3-H, C8-H, C2'-6'-H), 7.75 (dd, 1H, C10-H, J_m = 2.26, J_o = 9.08 Hz), 7.91 (d, 1H, C4-H, J = 8.49 Hz), 8.29 (d, 1H, C11-H, J = 9.08 Hz), 9.18 (d, 1H, C1-H, J = 8.01 Hz); δ_C 17.9 (C6-CH_3), 118.1 (C8), 121.1 (C9), 125.8 (C1), 127.3 (C2', C6'), 128.8 (C3'-C5'), 129.0 (C1'), 129.2 (C7), 130.1 (C7a), 132.3 (C10), 132.9 (C11), 134.1 (C4), 136.6 (C3), 138.3 (C2), 143.8 (C12b), 147.3 (C6a), 147.6 (C11a), 149.9 (C12a), 150.2 (C4a), 158.9 (C6). MS: *m/z* (%) 356–354 (M$^+$, 28/90), 353 (100), 339 (15), 319 (25), 304 (35), 77 (20), 65 (12), 51 (10). Anal. Calcd for $C_{23}H_{15}ClN_2$: C, 77.97; H, 4.24; N, 7.91. Found: C, 77.88; H, 4.30; N, 7.82%.

Preparation of 4'-chloro-2-methyl-4-(N-phenylamino)quinolines (**10**) *from 4-chloro-2-methyl quinolines* (**4**)*, general procedure*

The 4-chloro-2-methylquinoline (**1**, 2 mmol) was heated with *p*-chloroaniline (0.255 g. 2 mmol) under neat conditions at 160 °C for half an hour. The product was washed with water, adsorbed and purified by chromatography on silica gel, eluting with ethyl acetate: methanol (95: 5) mixture to get the anilinoquinoline **3** which was then recrystallised from methanol.

4'-Chloro-2,6-dimethyl-4-(N-phenylamino)quinoline (**10a**): Colourless needles (0.399 g, 70%), m.p. >300 °C. IR: ν_{max} 3467 cm^{-1} (NH). NMR: δ_H 2.54 (s, 3H, C2-CH_3), 2.59 (s, 3H, C6-CH_3), 6.75 (s, 1H, C3-H), 7.48–7.94 (m, 6H, C7-, C8-, C2'-, C3'-, C5', C6'-H), 8.51 (s, 1H, C5-H), 10.58 (b s, 1H, C4-NH amino form), 14.31 (b s, 1H, N1-H imino form. The ratio of amino form: imino form 1: 1); δ_C 19.7 (C2-CH_3), 21.1 (C6-CH_3), 100.1 (C3), 116.3 (C4a), 119.5 (C2', C6'), 122.5 (C3', C5'), 127.0 (C5), 129.8 (C4'), 131.0 (C8), 135.1 (C7), 136.4 (C6), 136.5 (C1'), 136.8 (C8a), 153.4 (C4), 154.0 (C2). MS: *m/z* (%) 284–282 (M$^+$, 32/100), 267 (40), 266 (20), 252 (15), 247 (10), 130 (18), 123 (25), 77 (12). Anal. Calcd for. $C_{17}H_{15}ClN_2$: C, 72.34; H, 5.32; N, 9.93. Found: C, 71.72; H, 5.11; N, 9.41%.

4'-Chloro-2,8-dimethyl-4-(N-phenylamino)quinoline (**10b**): White solid (0.423 g, 75%), m.p. >300 °C. IR: ν_{max} 3378 cm^{-1} (NH). NMR: δ_H 2.84 (s, 3H, C2-CH_3), 2.91(s, 3H, C8-CH_3), 6.51 (s, 1H, C3-H), 7.35-7.60 (m, 6H, C6-, C7-, C2'-, C3'-, C5'-, C6'-H), 8.71 (d, 1H, C5-H, J = 7.12 Hz), 10.64 (b s, 1H, C4-NH amino form), 12.94 (b s, 1H, N1-H imino form. The ratio of amino form: imino form 1: 1); δ_C 18.3 (C2-CH_3), 24.8 (C8-CH_3), 100.3 (C3), 117.4 (C4a), 118.8 (C2', C6'), 123.5 (C3', C5'), 127.2 (C5), 130.0 (C4'), 131.5 (C6), 135.9 (C7), 137.2 (C8), 137.3 (C1'), 137.9 (C8a), 151.4 (C4), 152.6 (C2). MS: *m/z* (%) 284–282 (M$^+$, 37/100), 267 (10), 266 (5), 251 (10), 247 (28), 123 (35), 89 (15), 51 (10). Anal. Calcd for $C_{17}H_{15}ClN_2$: C, 72.34; H, 5.32; N, 9.93. Found: C, 72.05; H, 5.20; N, 9.22%.

4',6-Dichloro-2-methyl-4-(N-phenylamino)quinoline (**10c**): White solid (0.416 g, 65%), m.p. >300 °C. IR: ν_{max} 3468 cm^{-1} (NH). NMR: δ_H 2.61 (s, 3H, C2-CH_3), 6.81 (s, 1H, C3-H), 7.48–8.13 (m, 6H, C7-, C8-, C2'-, C3'-, C5'- and C6'-H), 8.89 (s, 1H, C5-H) 10.74 (br s, 1H, C4-NH amino form), 14.71 (br s 1H, N1-H imino form. The ratio of amino form: imino form 1: 1); δ_C 20.1 (C2-CH_3), 99.8 (C3), 115.2 (C4a), 117.9 (C2', C6'), 124.0 (C3', C5'), 128.5 (C5), 131.0 (C4'), 132.1 (C6), 136.1 (C8), 138.1 (C7), 138.8 (C1'), 139.1 (C8a), 152.9 (C4), 154.3 (C2). MS: *m/z* (%) 306–304/302 (M$^+$, 39/66/100), 301 (95), 287 (50), 286 (10), 267 (35), 232 (12), 122 (28), 52 (8). Anal. Calcd for $C_{16}H_{12}Cl_2N_2$: C, 63.58; H, 3.99; N, 9.27. Found: C, 63.35; H, 3.88; N, 8.99%.

4'-Chloro-2-methyl-4-(N-phenylamino)quinoline (**10d**): White solid (0.386 g, 72%), m.p. >300 °C. IR: ν_{max} 3475 cm^{-1} (NH). NMR: δ_H 2.60 (3H, s, C2-CH_3), 6.69 (s, 1H, C3-H), 7.46–8.08 (m, 7H, C6-, C7-, C8-, C2'-, C3'-, C5'-, C6'-H), 8.51 (d, 1H, C5-H, J = 7.20 Hz), 10.61 (b s, 1H, C4-NH amino form), 13.91 (b s, 1H, N1-H imino form. The ratio of amino form: imino form 1: 1); δ_C 19.5 (C2-CH_3), 100.6 (C3), 117.0, (C4a), 118.1 (C2', C6'), 124.0 (C3', C5'), 127.1 (C5), 130.7 (C4'), 131.9 (C6), 137.0 (C8), 137.5 (C7), 138.2 (C1'), 138.4 (C8a), 152.4 (C4), 153.0 (C2). MS: *m/z* (%) 270–268 (M$^+$, 34/100), 267 (85), 253 (55), 233 (25), 232 (18), 124 (10), 90 (8), 76 (10). Anal. Calcd for. $C_{16}H_{13}ClN_2$: C, 71.64; H, 4.85; N, 10.45. Found: C, 71.52; H, 5.05; N, 10.38%.

Preparation of 9-chloro-6-methyl-7-phenyldibenzo[b,h][1,6]naphthyridine (**1**) *from 4'-chloro-2-methyl-4-(N-phenylamino)quinoline* (**10**)*, general procedure*

A mixture of 4'-chloro-2-methyl-4-(N-phenylamino)quinoline (**10**, 1 mmol) and benzoic acid (0.122 mg, 1.1 mol) was added to polyphosphoric acid (P_2O_5, 1 g and H_3PO_4, 0.5 mL) and heated at 160 °C for five hours. The reaction mixture was poured into ice water and neutralised with saturated sodium bicarbonate solution to remove the excess of benzoic acid. The crude product obtained was purified by column chromatography over silica gel using petroleum ether : ethyl acetate mixture (98 : 2) to get a pale yellow solid. The product was recrystallised using methanol as prisms. From the TLC and superimposable IR spectra, the compound was identified as the same one obtained from the earlier one-pot synthesis of 4-chloro-2-methylquinoline (**4**) with 2-amino-5-chlorobenzophenone under neat conditions. Further, the mixed melting point of this compound and the compound obtained earlier from the one-pot synthesis was undepressed. The yields of the products obtained by the two methods are compared in Table 1.

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