A Convenient Synthesis of 2,3-Disubstituted Benzo[*b*][1,8]naphthyridines; A Novel Annelation Reaction of 2,3-Disubstituted Quinolines

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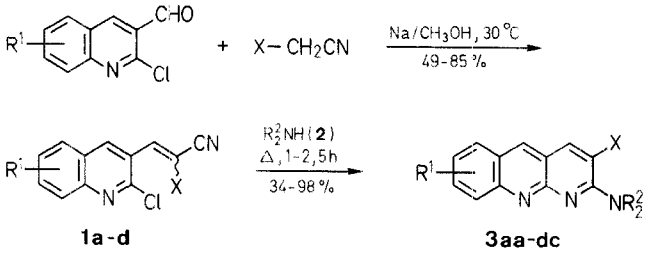
2-Chloro-3-(2-substituted 2-cyanovinyl)quinolines undergo cyclization on reaction with an excess of a secondary amine to give 3-substituted 2-aminobenzo[*b*][1,8]naphthyridines in moderate to high yields.

A method for the synthesis of 3-substituted 2-aminobenzo[*b*][1,8]naphthyridines (pyrido[2,3-*b*]quinolines) has hitherto not been described. Earlier work in the field led either to 2- or 5-oxo derivatives of the partially saturated ring system[2-9] or to 2,4-diaminobenzo[*b*][1,8]naphthyridines.[10] We now report a convenient synthesis of the title compounds by reaction of 2-chloro-3-formylquinolines with appropriately substituted acetonitriles in methanol in the presence of sodium methoxide to give 2-chloro-3-(2-substituted 2-cyanovinyl) quinolines **1** in 49–85% yield and cyclization of these compounds **1** by reaction with an excess of a secondary amine **(2)**. The desired 3-substituted 2-aminobenzo[*b*][1,8]naphthyridines **3** are thus obtained in 34–98% yields (based on **1**).

Table. Compounds **1** and **2** Prepared

Product	Yield (%)	m.p. (°C)	Molecular Formula[a]	MS *m/e* (M^+)	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (ppm)
1a	80	178	$C_{18}H_{10}Cl_2N_2$ (325.1)	324	2250 (C≡N)	6.70–7.95 (m, =CH, 8 H_{arom}); 8.55 (s, 4-H)
1b	85	118	$C_{18}H_{10}Cl_2N_2S$ (357.1)	356	2250 (C≡N)	7.20–8.0 (m, =CH, 8 H_{arom}); 8.65 (s, 4-H)
1c	66	225–227	$C_{20}H_{14}Cl_2N_2O_2$ (385.1)	384	2250 (C≡N)	3.95 (s, 6H, 2 OCH_3); 7.00–7.80 (m, =CH, 6 H_{arom}); 8.65 (s, 4-H)
1d	49	206	$C_{20}H_{14}Cl_2N_2O_2S$ (417.1)	416	2250 (C≡N)	4.05 (s, 6H, 2 OCH_3); 7.30–8.10 (m, =CH, 6 H_{arom}); 8.50 (s, 4-H)[b]
3aa	54	138	$C_{23}H_{20}ClN_3$ (373.7)	373	1605 (C=N)	1.65 (br s, 6H, 3 CH_2); 3.25 (br s, 4H, 2N $-CH_2$); 7.10–7.80 (m, 9 H_{arom}); 8.55 (s, 5-H)
3ab	46	148–150	$C_{22}H_{18}ClN_3O$ (375.6)	375	1605 (C=N)	3.32 (br s, 4H, 2N $-CH_2$); 3.74 (br s, 4H, 2O $-CH_2$); 7.10–7.80 (m, 9 H_{arom}); 8.55 (s, 5-H)
3ac	50	120–122	$C_{23}H_{21}ClN_4$ (388.6)	388	1605 (C=N)	2.35 (s, 3H, CH_3); 2.60, 3.40 (2 br s, 4H each, 2 CH_2–CH_2); 7.10–7.85 (m, 9 H_{arom}); 8.55 (s, 5-H)
3ba	89	106	$C_{23}H_{20}ClN_3S$ (405.7)	405	1610, 1605 (C=N)	1.70 (br s, 6H, 3 CH_2); 3.25 (br s, 4H, 2N $-CH_2$); 7.10–7.90 (m, 9 H_{arom}); 8.45 (s, 5-H)
3bb	86	126	$C_{22}H_{18}ClN_3OS$ (407.7)	407	1615, 1605 (C=N)	3.27 (br s, 4H, 2N $-CH_2$); 3.80 (br s, 4H, 2O $-CH_2$); 7.20–7.80 (m, 9 H_{arom}); 8.45 (s, 5-H)
3bc	40	148	$C_{23}H_{21}ClN_4S$ (420.7)	420	1610, 1605 (C=N)	2.30 (s, 3H, CH_3); 2.52, 3.25 (2 br s, 4H each, 2 CH_2–CH_2); 7.20–8.00 (m, 9 H_{arom}); 8.50 (s, 5-H)
3ca	98	180	$C_{24}H_{24}ClN_3O_2$ (433.7)	433	1620, 1610 (C=N)	1.62 (br s, 6H, 3 CH_2); 3.15 (br s, 4H, 2N $-CH_2$); 3.85, 3.95 (2s, 3H each, 2 OCH_3); 6.80–7.80 (m, 7 H_{arom}); 8.50 (s, 5-H)[c]
3cb	67	172–174	$C_{24}H_{22}ClN_3O_3$ (435.7)	435	1615, 1605 (C=N)	3.25 (br s, 4H, 2N $-CH_2$); 3.78 (br s, 4H, 2O $-CH_2$); 3.95 (s, 6H, 2 OCH_3); 6.90–7.90 (m, 7 H_{arom}); 8.65 (s, 5-H)
3cc	62	140	$C_{25}H_{25}ClN_4O_2$ (448.7)	448	1615, 1605 (C=N)	2.30 (s, 3H, CH_3); 2.50, 3.22 (2 br s, 4H each, 2 CH_2–CH_2); 3.85, 3.95 (2s, 3H each, 2 OCH_3); 7.15–7.90 (m, 7 H_{arom}); 8.60 (s, 5-H)
3da	50	oil	$C_{25}H_{24}ClN_3O_2S$ (465.7)	465	1615, 1605 (C=N)[d]	1.65 (br s, 6H, 3 CH_2); 3.12 (br s, 4H, 2N $-CH_2$); 3.85, 3.90 (2s, 3H each, 2 OCH_3); 6.80–7.70 (m, 7 H_{arom}); 8.35 (s, 5-H)
3db	42	186	$C_{24}H_{22}ClN_3O_3S$ (467.7)	467	1610 (C=N)	3.25 (br s, 4H, 2N $-CH_2$); 3.77 (br s, 4H, 2O $-CH_2$); 3.92, 3.95 (2s, 3H each, 2 OCH_3); 6.80–7.75 (m, 7 H_{arom}); 8.55 (s, 5-H)
3dc	34	140–142	$C_{25}H_{25}ClN_4O_2S$ (480.7)	480	1615, 1610 (C=N)	2.35 (s, 3H, CH_3); 2.58, 3.25 (2 br s, 4H each, 2 CH_2–CH_2); 3.95 (s, 6H, 2 OCH_3); 6.80–8.00 (m, 7 H_{arom}); 8.55 (s, 5-H)

[a] Satisfactory microanalyses obtained: C ±0.40, H ±0.37, N ±0.25.
[b] Measured in trifluoroacetic acid solution.
[c] ^{13}C-NMR ($CDCl_3$/TMS): δ = 24.59, 26.37, 52.44, 56.07, 135.16, 139.85, 145.22, 148.95, 154.15, 159.92 ppm.
[d] Neat.



1a-d **3aa-dc**

1	R^1	X	2	R^2_2N
a	H	4-ClC_6H_4	**a**	piperidino
b	H	4-ClC_6H_4S	**b**	morpholino
c	6,7-$(OCH_3)_2$	4-ClC_6H_4	**c**	4-methylpiperazinyl
d	6,7-$(OCH_3)_2$	4-ClC_6H_4S		

The reaction time of the second step largely depends on the excess of amine used. A 10–50 fold excess of amine **2** shortens the required reaction time to 1–2.5 hours. The reaction does not proceed when less then 2 molecular equivalents of amine are used.

2-Chloro-3-[2-(4-chlorophenyl or 4-chlorophenylthio)-2-cyanovinyl] quinolines (1a–d); General Procedure:

Sodium (1.4 g, 0.06 g-atom) is dissolved in dry methanol (100 ml). To this solution are added 4-chlorophenylacetonitrile (6.064 g, 0.04 mol) or 4-chlorophenylthioacetonitrile (7.344 g, 0.04 mol) and the 2-chloro-3-formylquinoline (0.04 mol); the mixture is stirred at room temperature (30 °C) for 5 min, then diluted with water (125 ml). The precipitated solid product **1** is isolated by suction, washed thoroughly with water, and recrystallized from chloroform/hexane.

3-Substituted 2-Aminobenzo[*b*][1,8]naphthyridines (3); General Procedure:

A solution of a quinoline derivative **1** (0.004 mol) and an appropriate secondary amine **2** (0.12 mol) is refluxed with stirring for 1–2.5 h, then allowed to cool to room temperature (30 °C). Ice-cold water (75 ml) is added, the solution is extracted with chloroform (2 × 50 ml), and the organic layer is concentrated to a volume of ~4 ml. This liquid is filtered through a 22 cm layer of basic alumina using chloroform as eluent. Removal of the solvent followed by crystallization of the residue from chloroform/petroleum ether/benzene furnishes the product **3**.

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