Preparation and Reactivity of 3-Amino-2,4-dichloroquinoline

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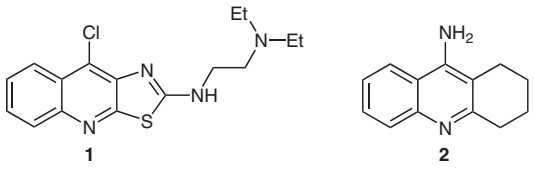
Received: 23.03.2012; Accepted after revision: 01.07.2012

Abstract: A simple and efficient synthesis of 2-substituted 3-amino-4-chloroquinolines and 2,4-disubstituted 3-aminoquinolines was carried out by reacting 3-amino-2,4-dichloroquinoline with various oxygen-, sulfur- and nitrogen-containing nucleophiles.

Key words: heterocycles, quinolones, dichloroquinoline, aminoquinoline, substitution

Quinoline derivatives are a class of heterocyclic compounds that have importance in organic chemistry and pharmaceutical chemistry; these compounds are also precursors for many biologically active compounds.[1,2] The best-known quinoline alkaloid is quinine, which has been widely used to treat malaria.[3] Some new thiazolo[5,4-*b*]quinolines have recently been considered as potential anticancer drugs (**1**).[4,5] The structurally related tacrine (**2**) received notable importance for the development of drugs against Alzheimer's disease (Figure 1).[6]



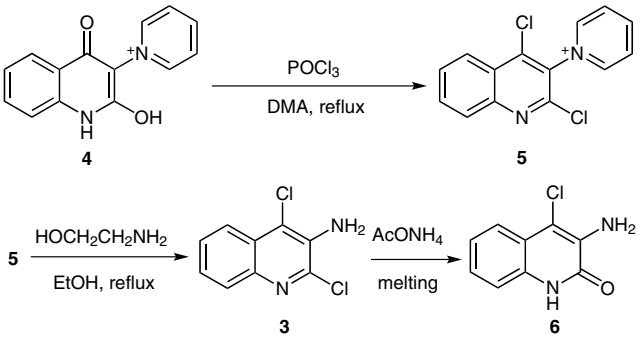
1 2

Figure 1 Structure of thiazolo[5,4-*b*]quinoline with anticancer activity **1** and parasympathomimetic tacrine (**2**)

Our interest was in the synthesis of 3-amino-2,4-dichloroquinoline (**3**) from compound **4**, which was chosen as a simple and versatile starting material (Scheme 1).[7] The reaction of compound **4** with an excess of phosphorus oxychloride and a catalytic amount of *N*,*N*-dimethylaniline (DMA) gave compound **5** in good yield. The chlorination of **4** using thionyl chloride or phosphorus oxychloride, in the absence of a catalyst, was not successful.

Although compound **5** is considered to be a pyridinium salt, it was not isolated in crystalline form, and it was used in the crude form in the subsequent reaction steps. The transformation of compound **5** into **3** was performed using an amine base in an ethanolic solution. Many aliphatic amines were tested in this reaction, and 2-aminoethanol was favored because of its higher boiling point. This ring-opening reaction of the pyridinium salts is referred to as Zincke cleavage and has been described earlier.[7,8]

After the recrystallization from methanol, compound **3**, in the form of a white powder, can be used for other reactions.



Scheme 1 Synthesis of compound **3**

Melted ammonium acetate was reacted with compound **3**, and product **6** was isolated as the main product.

Based on this reaction scheme, a series of 2-substituted 3-amino-4-chloroquinolines was prepared by reacting compound **3** with various oxygen-, sulfur- and nitrogen-containing nucleophiles. Several 2,4-disubstituted 3-aminoquinolines were isolated when some thiophenols were used (Scheme 2).

Compounds **8**–**13** were prepared by reacting compound **3** with sodium alcoholate in the corresponding alcohol. Crude products in the forms of white powders were obtained after the addition of cold water to the reaction mixture. The reactions of the phenols and thiols (or thiophenols) were carried out in DMF solution containing a two-molar excess of the corresponding nucleophile and a four-molar excess of potassium carbonate as a base. Under these conditions, crude products were isolated after the evaporation of the DMF under reduced pressure and extraction with ethyl acetate or diethyl ether from the reaction mixture diluted with water. Both of the thiophenol derivatives were separated using column chromatography.

Reactions of compound **3** with excess amounts of amines were carried out without solvent, and the crude products were isolated after the evaporation of the amine and/or extraction with diethyl ether. Compound **7** was prepared by the reaction of **3** with sodium azide in DMF and isolated

SYNLETT 2012, 23, 2205–2208
Advanced online publication: 31.08.2012
DOI: 10.1055/s-0032-1316733; Art ID: ST-2012-D0272-L
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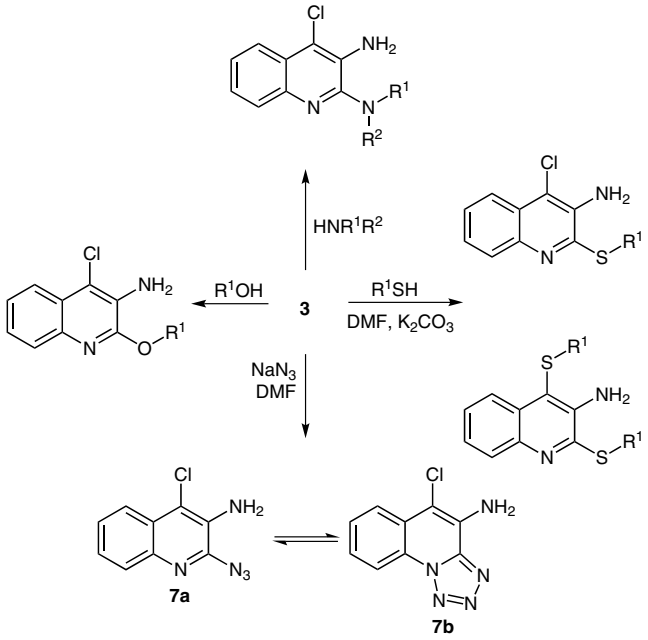


Scheme 2 Reaction of compound **3** with various nucleophiles

after addition of water (extraction to ethyl acetate is possible).

All prepared compounds are listed in Table 1.

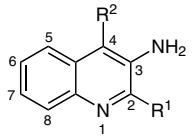
We concluded that position 2 on the quinoline ring is much more reactive in nucleophilic replacement reactions than position 4. Only very strong nucleophiles (e.g. thiophenolate ions) attack both positions and yield two products. The higher reactivity of the C-2 position was concluded from 2D NMR of molecules **8** and **32**. Their structure was proved by the HMBC experiment. The interaction between hydrogens of the methyl group in compound **8** with carbon C-2 (δ = 153 ppm) is seen as the cross-peak. This carbon has no cross-peak interaction with any aromatic hydrogen. This cross-peak interaction from hydrogen (δ = 7.78 ppm) on C-5 must be present if C-4 is substituted by methoxy group. The same situation is valid for hydrogen of NH group and hydrogen on C-11 of compound **32**. The reactivity of positions 2 and 4 are the opposite of the reactivity of these positions in 2,4-dichloro-3-substituted quinolines when the substituent in position 3 is an electron-withdrawing group such as a cyano group.[9]

The chemical structure and regioselectivity were confirmed with mass spectrometry (CIMS) and NMR[10–17] (one- and two-dimensional NMR spectra are available as Supporting Information). The numbering of carbons for NMR purposes is shown on the structure in Table 1.

Acknowledgment

This project was supported in part by the Ministry of Education, Youth and Sport of the Czech Republic (grants IGA 453103071/31).

Table 1 Chemical Structures of the Prepared Compounds



Compound	R^1	R^2	Yield (%)	Mp (°C)	Compound	R^1	R^2	Yield (%)	Mp (°C)
8	MeO	Cl	90	89– 92	**22**	4-FC_6H_4S	Cl	43	122–124
9	EtO	Cl	80	89– 90	**23**	4-ClC_6H_4S	Cl	33	147–150
10	$MeOCH_2CH_2O$	Cl	78	74– 75	**24**	4-BrC_6H_4S	Cl	45	156–158
11	$EtOCH_2CH_2O$	Cl	75	70– 72	**25**	4-$MeOC_6H_4S$	Cl	44	86– 89
12	$HOCH_2CH_2O$	Cl	79	129–132	**26**	PhS	PhS	40	120–122
13	$(Me)_2NCH_2CH_2O$	Cl	70	76– 79	**27**	4-FC_6H_4S	4-FC_6H_4S	40	99–102
14	PhO	Cl	50	111–114	**28**	4-ClC_6H_4S	4-ClC_6H_4S	25	120–123
15	2-MeC_6H_4O	Cl	43	123–125	**29**	4-BrC_6H_4S	4-BrC_6H_4S	40	148–150
16	4-MeC_6H_4O	Cl	25	104–107	**30**	4-$MeOC_6H_4S$	4-$MeOC_6H_4S$	40	128–130
17	4-ClC_6H_4O	Cl	50	131–133	**31**	EtNH	Cl	68	140–143
18	4-BrC_6H_4O	Cl	55	143–145	**32**	*n*-BuNH	Cl	85	59– 62
19	4-IC_6H_4O	Cl	50	150–152	**33**	Et_2N	Cl	49	gel form
20	$MeO(O)CCH_2S$	Cl	77	83– 86	**34**	BnNH	Cl	35	149–152
21	PhS	Cl	45	94– 97	**35**	PhNH	Cl	25	169–171

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(10) **Preparation of 1-(2,4-Dichloroquinolin-3-yl)pyridinium Salt (5)**:
Compound **4** (20 g, 83.6 mmol) and *N*,*N*-dimethylaniline (1.26 g, 10.4 mmol) were mixed and phosphorus oxychloride (200 mL, 2.14 mol) was added all at once. The reaction mixture was stirred vigorously and heated. Compound **4** gradually dissolved yielding a yellow solution that was heated to boiling for 3 h. The end of the reaction was determined using TLC. After the reaction was complete, the phosphorus oxychloride was removed by distillation under reduced pressure, and the crude product was mixed with toluene (2 × 40 mL). Toluene was properly removed by distillation under reduced pressure. Compound **5** was isolated in the form of a brown gel, which immediately solidified to form a brown resin.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.53 (dd, 2 H, *J* = 6.7, 1.3 Hz, py), 9.10 (tt, 1 H, *J* = 7.9, 1.4 Hz, py), 8.63 (dd, 2 H, *J* = 7.9, 6.8 Hz, py), 8.40 (ddd, 1 H, *J* = 8.4, 1.3, 0.6 Hz, H-5), 8.28 (ddd, 1 H, *J* = 8.5, 1.2, 0.6 Hz, H-8), 8.19 (ddd, 1 H, *J* = 8.4, 7.0, 1.4 Hz, H-7), 8.03 (ddd, 1 H, *J* = 8.3, 7.0, 1.3 Hz, H-6). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 150.6, 147.4, 147.3, 144.5, 141.7, 134.9, 131.8, 130.9, 125.8, 124.9, 130.1, 129.3.
(11) **Procedure for the Preparation of 3-Amino-2,4-dichloroquinoline (3)**: Crude product **5** isolated in the previous reaction step was dissolved in EtOH (600 mL). The solution was heated to boiling, and ethanolamine (40 g, 0.65 mol) was added over a period of 20 min. The reaction mixture changed color from yellow to purple. The reaction mixture was heated to boiling for 16 h with vigorous stirring. During this time, another portion of ethanolamine (40 g, 0.65 mol) was added in small parts to the reaction mixture to bring the pH of the solution into the alkaline range (the fumes evolving from the reaction mixture must give a blue color on moistened pH paper). It is necessary to note that the amount of ethanolamine used for this reaction step and the reaction time depends on the quality of the phosphorus oxychloride removal in the previous step. The end of the reaction was determined using TLC and HPLC. EtOH was removed by distillation under reduced pressure. To a sufficiently concentrated reaction mixture (170 g), H_2O was added, and compound **3** solidified in the form of a white solid. The product was washed with H_2O and dried (8.4 g; 47% yield calculated on compound **4**).
Note: Ethylamine and aq methylamine were both successfully used for this reaction instead of ethanolamine. When using these compounds, the reactions were carried out in pressure tubes; $C_9H_6Cl_2N_2$ (211.99); mp 115–119 °C. MS: *m*/*z* (%) = 213.2 (100) [M(^{35}Cl) + H]$^+$, 215.2 (60), 217.1 (10).
^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.90 (ddd, 1 H, *J* = 8.4, 1.4, 0.6 Hz, H-5), 7.82 (ddd, 1 H, *J* = 8.3, 1.2, 0.6 Hz, H-8), 7.62 (ddd, 1 H, *J* = 8.4, 6.9, 1.3 Hz, H-6), 7.52 (ddd, 1 H, *J* = 8.3, 6.9, 1.4 Hz, H-7), 6.13 (s, 2 H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 140.4, 139.6, 136.4, 128.8, 128.6, 126.7, 126.6, 122.1, 118.0.
(12) **Procedure for the Preparation of 3-Amino-4-chloroquinolin-2(1*H*)-one (6)**: Compound **3** (0.4 g, 1.87 mmol) and ammonium acetate (3.45 g, 44.75 mmol) were mixed and the reaction mixture was stirred in an oil bath in the melted state (160 °C) for 6 h. The end of the reaction was determined using TLC. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layer was dried and concentrated. A white crystalline powder was obtained with a yield of 0.1 g (yield: 28%); $C_9H_7ClN_2O$ (194.02); mp 227–233 °C. MS: *m*/*z* (%) = 195.1 (100) [M(^{35}Cl) + H]$^+$, 197.1 (35).
^{1}H NMR (400 MHz, DMSO-d_6): d = 12.1 (bs, 1 H, NH), 7.59 (dd, 1 H, *J* = 7.6, 1.0 Hz, H-5), 7.29-7.27 (m, 2 H, H-7, H-8), 7.22 (t, 1 H, *J* = 7.8 Hz, H-6), 5.76 (s, 2 H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): d = 157.0, 135.4, 131.3, 125.9, 123.1, 121.6, 119.8, 115.5, 111.1.
(13) **Procedure for the Preparation of 5-Chlorotetrazolo[1,5-*a*]quinolin-4-amine (7)**: Compound **3** (1 g, 4.7 mmol) was dissolved in DMF (4.6 g). To this solution was added a suspension of sodium azide (0.5 g, 7.7 mmol) in DMF (15.8 g). The reaction mixture was stirred vigorously and heated to 100 °C for 5.5 h. During this time, another portion of DMF (10.5 g) was added. The end of the reaction was determined using TLC. DMF was removed by distillation under reduced pressure, and the reaction mixture was extracted with EtOAc. The organic layer was dried and concentrated. The product was obtained in the form of almost white powder (0.75 g, 73%); $C_9H_6ClN_5$ (219.03); mp 243–244 °C. MS: *m*/*z* (%) = 220.1 (100) [M(^{35}Cl) + H]$^+$, 222.1 (30).
^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.39 (dd, 1 H, *J* = 8.2, 1.0 Hz, H-8), 7.92 (dd, 1 H, *J* = 8.3, 1.0 Hz, H-5), 7.66 (ddd, 1 H, *J* = 8.4, 7.3, 1.3 Hz, H-6), 7.57 (ddd, 1 H, *J* = 8.4, 7.3, 1.3 Hz, H-7), 6.84 (s, 2 H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.6, 130.5, 129.1, 126.5, 124.6, 123.9, 123.3, 116.6, 106.4.
(14) **Representative Procedure for the Preparation of 3-Amino-4-chloro-2-methoxyquinoline (8)**: Compound **3** (0.13 g, 0.61 mmol) was dissolved in hot MeOH (2 mL). Into this solution a solution of sodium methoxide (0.2 g, 3.7 mmol) in MeOH (4 mL) was added, and the reaction mixture was heated to boiling for 2 h. The end of the reaction was determined using TLC. The addition of H_2O to the reaction mixture led to the solidification of the product in the form of a white solid (yield: 0.11 g, 90%); $C_{10}H_9ClN_2O$ (208.04); mp 89–92 °C. MS: *m*/*z* (%) = 208.9 (100) [M(^{35}Cl) + H]$^+$, 210.9 (33).
^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.78 (dd, 1 H, *J* = 7.6, 1.9 Hz, H-5), 7.68 (dd, 1 H, *J* = 7.5, 1.8 Hz, H-8), 7.43- 7.36

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(m, 2 H, H-6, H-7), 5.72 (s, 2 H, NH_2), 4.04 (s, 3 H, Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.3, 138.2, 130.4, 127.1, 125.6, 125.6, 124.7, 121.4, 114.8, 54.3.

(15) **Representative Procedure for the Preparation of 3-Amino-4-chloro-2-(4-methylphenoxy)quinoline** (**16**): K_2CO_3 (1.29 g, 9.33 mmol) and 4-methylphenol (0.5 g, 4.62 mmol) were mixed with DMF (6 mL). Into this suspension a solution of compound **3** (0.5 g, 2.35 mmol) dissolved in DMF (5 mL) was added. The reaction mixture was heated to 120 °C for 4.5 h. The end of the reaction was determined using TLC. After the reaction was complete, the K_2CO_3 was filtered off, and the solution was concentrated under reduced pressure. The crude product was mixed with an aqueous solution of K_2CO_3 (10%) and extracted with Et_2O. The organic layers were separated and dried. The evaporation of Et_2O under reduced pressure and the addition of MeOH led to the solidification of the product in the form of a white powder (yield: 0.17 g, 25%); $C_{16}H_{13}ClN_2O$ (284.07); mp 104–107 °C. MS: *m*/*z* (%) = 285.2 (100) $[M(^{35}Cl) + H]^+$, 287.1 (32).
^1H NMR (400 MHz, DMSO-d_6): d = 7.82 (ddd, 1 H, *J* = 8.2, 1.4, 0.5 Hz, H-5), 7.47 (ddd, 1 H, *J* = 8.2, 1.3, 0.5 Hz, H-8), 7.45-7.30 (m, 2 H, H-6, H-7), 7.26 (dd, 2 H, *J* = 8.7, 0.6 Hz, ArH), 7.17 (d, 2 H, *J* = 8.5 Hz, ArH), 6.01 (s, 2 H, NH_2), 2.35 (s, 3 H, Me). ^{13}C NMR (100 MHz, DMSO-d_6): d = 152.7, 151.3, 137.7, 134.5, 130.7, 130.3, 127.4, 126.2, 125.7, 125.2, 122.1, 121.4, 116.0, 20.9.

(16) **Representative Procedure for the Preparation of 3-Amino-4-chloro-2-(4-chlorophenylthio)quinoline (23) and 3-Amino-2,4-bis(4-chlorophenylthio)quinoline (28)**: K_2CO_3 (1.29 g, 9.33 mmol) and 4-chlorothiophenol (0.67 g, 4.63 mmol) were mixed with DMF (6 mL). Into this suspension a solution of compound **3** (0.5 g, 2.35 mmol) dissolved in DMF (5 mL) was added. The reaction mixture was heated to 120 °C for 30 min. The end of the reaction was determined using TLC. After the reaction was complete, the K_2CO_3 was filtered off, and the solution was concentrated under reduced pressure. The crude product was mixed with H_2O and extracted with Et_2O. The organic layers were separated and dried. The Et_2O was removed by distillation under reduced pressure and the crude product was dissolved in toluene. Both of 4-chlorothiophenol derivatives (**23**, **28**) (and the corresponding disulfide that was observed as a by-product) were separated using liquid column chromatography (stationary phase: silica gel; mobile phase: toluene). Compound **23**: yield: 0.25 g, 33%; compound **28**: yield: 0.25 g, 25%. Compound **23**: $C_{15}H_{10}Cl_2N_2S$ (319.99); mp 147–150 °C. MS: *m*/*z* (%) = 320.9 (100) $[M(^{35}Cl) + H]^+$, 322.8 (65), 324.8 (15). ^1H NMR (400 MHz, DMSO-d_6): δ = 7.88 (dd, 1 H, *J* = 8.2, 1.3 Hz, H-5), 7.56 (d, 2 H, *J* = 8,6 Hz, ArH), 7.56–7.54 (m, 1 H, H- 8), 7.52 (d, 2 H, *J* = 8,6 Hz, ArH), 7.52–7.50 (m, 1 H, H- 6), 7.41 (dt, 1 H, *J* = 7.6, 1.2 Hz, H-7), 5.86 (s, 2 H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.0, 141.1, 136.8, 135.8, 134.0, 129.7, 129.4, 128.6, 127.9, 126.1, 125.9, 122.0, 117.2. Compound **28**: $C_{21}H_{14}Cl_2N_2S_2$ (427.99); mp 120–123 °C. MS: *m*/*z* (%) = 428.9 (100) $[M(^{35}Cl) + H]^+$, 430.8 (70), 431.8 (25)^1H NMR (400 MHz, DMSO-d_6): d = 7.95 (dd, 1 H, *J* = 8.3, 0.8 Hz, H-5), 7.57 (d, 2 H, *J* = 8.8 Hz, ArH), 7.56– 7.53 (m, 1 H, H-8), 7.53 (d, 2 H, *J* = 8.7 Hz, ArH), 7.42 (dt, 1 H, *J* = 7.6, 1.2 Hz, H-6), 7.34 (dt, 1 H, *J* = 7.5, 1.3 Hz, H-7), 7.29 (d, 2 H, *J* = 8.6 Hz, ArH), 7.04 (d, 2 H, *J* = 8.6 Hz, ArH), 6.03 (s, 2 H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): d = 148.4, 143.0, 141.4, 135.9, 134.2, 134.0, 131.0, 129.7, 129.4, 129.4, 129.3, 128.9, 128.7, 128.0, 125.6, 123.7, 110.8.

(17) **Representative Procedure for the Preparation of N^2-Butyl-4-chloroquinoline-2,3-diamine (32)**: Compound **3** (0.5 g, 2.35 mmol) was dissolved in *n*-butylamine (6.8 g, 93 mmol). The reaction mixture was stirred and heated to boiling for 13 h. Then, the excess of *n*-butylamine was removed by distillation under reduced pressure. The addition of MeOH–H_2O (1:1) yielded the product in the form of a white solid (yield 0.5 g, 85%); $C_{13}H_{16}ClN_3$ (249.10); mp 59–62 °C. MS: *m*/*z* (%) = 250.1 (75) $[M(^{35}Cl) + H]^+$, 252.1 (24) ^1H NMR (400 MHz, DMSO-d_6): δ = 8.46 (dd, 1 H, *J* = 8.2, 0.9 Hz, H-8), 7.64 (dd, 1 H, *J* = 8.1, 1.2 Hz, H-5), 7.26 (ddd, 1 H, *J* = 8.3, 7.0, 1.5 Hz, H-7), 7.18 (ddd, 1 H, *J* = 8.2, 7.0, 1.3 Hz, H-6), 6.60 (t, 1 H, *J* = 4.9 Hz, NH), 5.63 (s, 2 H, NH_2), 3.49 (dt, 2 H, *J* = 7.0, 5.1 Hz, CH_2), 1.63 (tt, 2 H, *J* = 11.1, 7.5 Hz, CH_2), 1.41 (qt, 2 H, *J* = 14.4, 7.3 Hz, CH_2), 0.94 (t, 3 H, *J* = 7.4 Hz, Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.6, 141.1, 128.8, 125.8, 125.2, 122.5, 122.3, 121.2, 114.2, 41.3, 31.3, 20.3, 14.3.

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