NUCLEOPHILIC SUBSTITUTION of 2,4-DICHLORO-QUINOLINE-3-CARBONITILE WITH DIFFERENT NUCLEOPHILES. SYNTHESIS of SEVERAL NEW QUINOLINE-3-CARBONITRILE DERIVATIVES

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Abstract: 2,4-Dichloroquinoline-3-carbonitrile (**1**) reacted with several nucleophiles produced a novel substituted quinolines. Nucleophilic substitution of **1** with thiolate anions leads to the thio ethers **2a-c**. Acid hydrolysis of **2a** afforded the corresponding 4-quinolinones **3**. The amino-quinoline **5a,b; 7a,b** and pyrazoloquinoline **9** are prepared by nucleophilic substitution of **1** with amines and N_2H_4, respectively. Nucleophilic substitution of **1** with azide anion yielded the azidoquinoline **10**, which reacted with H_2/Pd and PPh_3 to give the quinoline derivatives **13a-c**.

Introduction

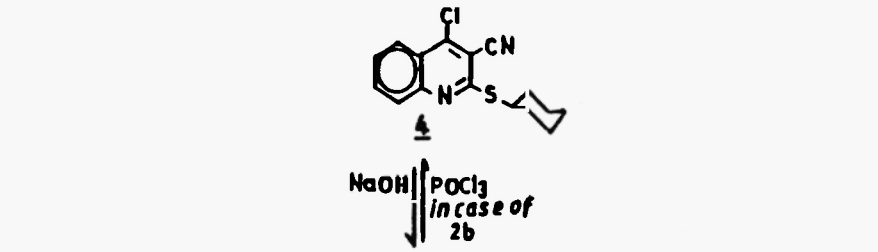
The interesting biological and medicinal activities (1-4) of quinoline derivatives prompted us to exert a great effort to synthesize several quinolines. As a continuation of our work on the synthesis of a variety of quinolines and condensed quinolines (5), the present investigation describes the synthesis of novel substituted quinolines via the action of a variety of nucleophiles on 2,4-dichloroquinoline-3-carbonitrile (**1**)(6, 7).

The t-butylthiolate anion has been used to introduce a mercapto moiety into various heterocyclic systems (8-10), since it has been shown that the t-butyl group can be eliminated by miniral acids (10-11). This reaction has been used in the present investigation as a rout for the synthesis of 3-cyano-2-mercapto-4(1H)-quinolone (**3**).

Results and Discussion

The nucleophilic substitution reactions of **1** with thiolate anions were performed in 2-propanol, as solvent, at reflux temperature. The reaction of **1** with t-butylthiolate anion yielded the product **2a,** where the nucleophilic substitution first take place at position 2. Structure of this compound

was readily established based on the IR spectrum, Which revealed significantly an carbonyl function at 1570 cm^{-1}, characteristic for 4-quinolinones (12), whereas 2-quinolinones are known to have carbonyl absorption at 1650-1670 cm^{-1} (12,13). Consequently, the structure of isomeric 2-quinolinone for compound **2a** could be excluded. Acid hydrolysis of **2a** with a mixture of concentrated hydrochloric acid and 1-propanol, resulted in the formation of the corresponding 2-mercaptoquinolones **3**. Not surprisingly, the t-butyl group in **2a** was cleaved under these reaction conditions too, leading to **3**. Similarly, reaction of **1** with cyclohexyl- and benzyl- thiolate anions yielded the corresponding quinoline derivatives **2b** and **2c**, respectively. Treatment of **2b** with phosphoryl chloride yielded 4-chloro-2-cyclohexylthio-quinoline-3-carbonitrile (**4**). As expected, reacting compound **4** with NaOH at reflux temperature, affords 4-quinolones **2b**.

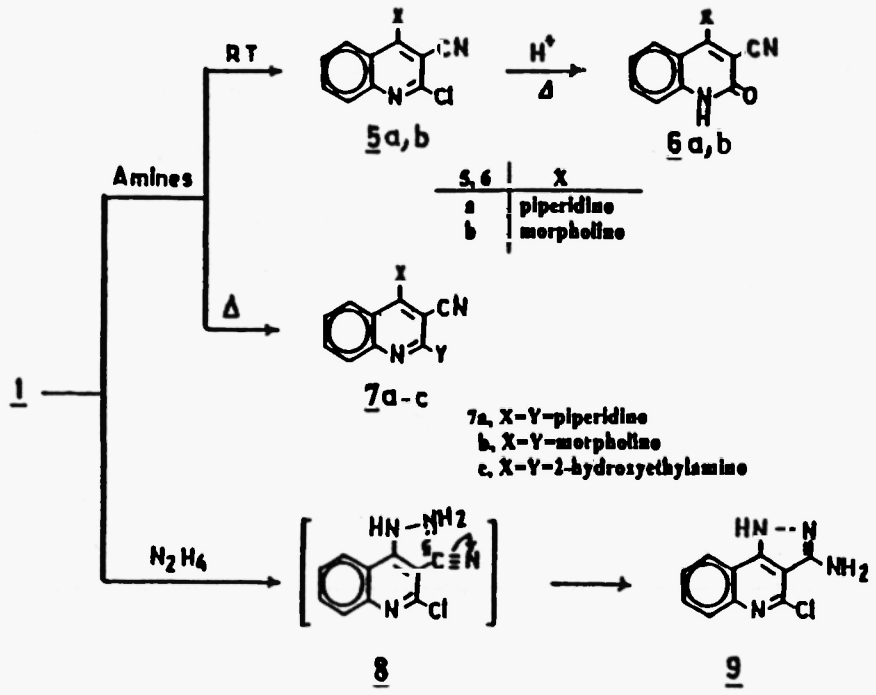


2a, R= t-butyl, X= OH
b, R= Cyclohexyl, X= OH
c, R= Benzyl, X= Cl

Scheme 1

Compoud **1** was allowed to react with various amines, caused a fast attack of the amino group at position 4 followed by displacement of chlorine. When **1** was treated with piperidine and morpholine in DMF at room temperature, rapid substitution of the halogen atom occured to yield 2-chloro-4-(1-piperidino- or 4-morpholino)-quinoline-3-carbonitrile **5a,b**. Beside the analytical and spectroscopic proof of the structure of **5a,b** (see Experimental), it was also proven chemically by acid hydrolysis with a mixture of acetic acid /water (5:1), which resulted in the formation of the corresponding 2-quinolinones **6a,b**. The structure of isomeric 4-quinolinones for compound **6a,b** was readily excluded based on the IR spectrum, which revealed an amide carbonyl function at

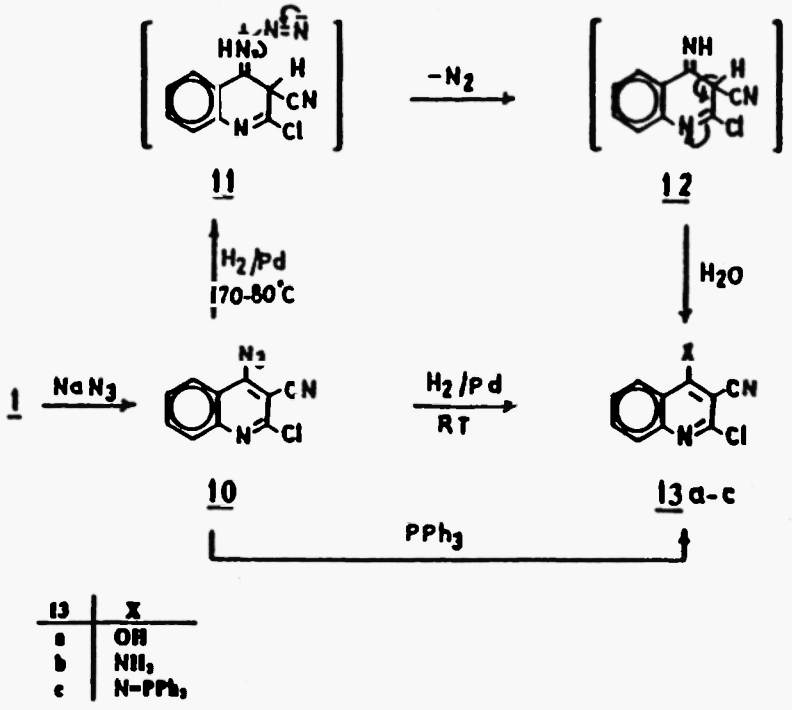
1650-1670 cm^{-1}. The exchange of both halogen atoms in **1**, by piperidino, morpholino and 2-hydroxyethylamino, leading, in excellent yields, to compounds **7a-c**, requires an excess of the amines and a higher reaction temperature (boiling DMF), since the introduction of the first amino group diminishes the reactivity of the remaining chloro atom cosiderably (14). Reaction of **1** with hydrazine hydrate, at room temperature, yielded a new heterocyclic compound **9**. The formation of **9** is assumed to proceed via the nucleophilic attack of one molecule of hydazine at position 4 in compound **1** to give the intermediate **8**, which then undergoes intramolecular cyclization giving the pyrazolo[4,3-c]quinoline derivative **9** (see Scheme 2). Structure **9** was assigned to this product on the basis of analytical and spectral data. Thus, IR spectra showed the absence of cyano band; ^{1}H-NMR spectrum showed, a singlet at δ = 5.68 and 13.18 ppm assigned to NH_2 and pyrazole NH, respectively, in addition to signals due to aromatic protons and ^{13}C-NMR spectrum revealed signals at δ = 142.5 ppm characteristic for C-4 in compound **9** (see Experimental)(15).



Scheme 2

In conjunction with this work, compound **1** was reacted with azide, proceeded with substitution of chlorine in position 4 to give 4-azido-2-chloro-quinoline-3-carbonitrile (**10**). The presence of azido group at position 4 for compound **10** was emphasized chemically by

hydrogenation of this azide **10**, with using palladium as catalyst, at different temperature. At room temperature, catalytic hydrogenation of **10** in DMF gave 4-aminoquinolines **(13b)**. While, catalytic hydrogenation of **10** at 70-80°C afforded 2-chloro-4-oxo-4(1H)quinoline-3-carbonitrile **(13a)**, through the interme-diates **11** and **12** (see Scheme 3). The azido group in **10** was further investigated through the reaction with triphenylphosphine in dry toluene at reflux temperature to give **(13c)**, in high yield.



Scheme 3

The above mentioned experimental observations indicate that, 2,4-dichloroquinoline-3-carbonitrile **1** is excellent starting material for the synthesis of many substituted quinolines, which are not otherwise readily accessible, in high yield, and under mild reaction conditions.

Experimental

M.P.'s were measured on a GallenKamp melting apparatus, Mod. MFB-595 and are uncorrected. -IR spectra were recorded on a Perkin Elimer 298 spectrophtometer (KBr pellets). -^{1}H NMR spectra were recorded on a varian XL-200 (90 MHz) spectrometer with DMSO as solvent and TMS as internal standard. Chemical shifts are expressed in δ values (ppm). ^{13}C NMR spectrum was measured on a varian XL-200 (90 MHz) spectrometer. Microanalyses were performed on a C, H, N-Automat Carlo Erba 1106 in the Institute of Organic Chemistry. Karl-Franzens University, Graz, Austria.

Synthesis of 2-alkylthio-4-substituted-quinoline-3-carbonitriles (2a-c): General Procedure: Sodium (50 mmol) was added to 2-propanol (30 ml). The reaction was dissolved by heating under reflux, whereupon the appropriate mercaptan (50 mmol) was slowly added. After cooling to room temperature, the solution became semisolid. Compound **1** (10 mmol) was added and the reaction mixture was refluxed for 20 hours. It was then poured into ice/water and acidified with cold dilute HCl to pH = 3. The resulting solid product was collected by filtration, washed well with water and dried. Compound **2b** can also be prepared by refluxing compound **4** with NaOH (6N) for 8 hrs.

2-t-Butylthio-4-oxo-1(4H)quinoline-3-carbonitrile (2a): Yield 70%; m.p. 239-240°C. from DMF, $\nu_{max/cm-1}$ (KBr) 3200-2800 (NH), 2220 (CN), 1570 (CO). δ_H (DMSO) 1.45 (9H, s), 7.42-8.16 (4H, m). (Found: C, 65.11; H, 5.64; N,10.79; S, 12.13. $C_{14}H_{14}N_2OS$ requires C, 65.09; H, 5.46; N, 10.84; S, 12.41 %).

2-Cyclohexylthio-4-oxo-1(4H)quinoline-3-carbonitrile (2b): Yield 85%; m.p. 268-271°C from DMF; $\nu_{max/cm-1}$ (KBr) 3420 (NH), 2220 (CN), 1570 (CO). δ_H (DMSO) 1.15-2.10 (11H, br), 7.76 (3H, m,), 8.10 (1H, d). (Found: C, 67.67; H, 5.54; N,10.03; S, 11.01. $C_{16}H_{16}N_2OS$ requires C, 67.57; H, 5.67; N, 9.85; S, 11.28 %).

2-Benzylthio-4-chloroquinoline-3-carbonitrile (2c): Yield 84%; m.p. 185-186°C from DMF/EtOH, $\nu_{max/cm-1}$ (KBr) 2220 (CN), 1610 (C=N) cm^{-1}. δ_H (DMSO) 4.67 (2H, s), 7.40 (6H, m), 7.88 (2H, m), 8.60 (1H, d). (Found: C, 65.88; H, 3.86; N, 9.02. $C_{17}H_{11}ClN_2S$ requires C, 65.68; H, 3.57; N, 9.01%).

3-Cyano-2-mercapto-4(1H)-quinolone (3): To a suspension of **2a** (1.9 mmol) in 2-propanol (10 ml), conc. HCl (10 ml) was added. The reaction mixture was refluxed for 6 hours. After concentration and cooling at room temperature, the resulting solid product was collected by filtration, washed well with water and dried. Yield 82%; m.p. 269-270 °C from acetic acid, $\nu_{max/cm-1}$ (KBr) 3200-2700 (NH), 2240 (CN), 1565 (CO).(Found: C, 59.40; H, 3.09; N, 13.68; S, 15.65. $C_{10}H_6N_2OS$ requires C, 59.39; H, 2.99; N, 13.85; S, 15.86%).

4-Chloro-2-cyclohexylthio-quinoline-3-carbonitrile (4): Compound **2b** (1.1 mmol) in $POCl_3$ (5 ml) was refluxed for 30 minutes. The excess $POCl_3$ was evaporated under reduced pressure. The resulting solid product was neutralized with a cold dilute KOH and collected by filtration, washed with water and dried. Yield 94%; m.p.115-116°C from 1,2-dichloroethane, $\nu_{max/cm-1}$ (KBr) 2240 (CN), 1620 (C=N). (Found: C, 63.61; H, 5.09; Cl, 11.83; N, 9.20; S, 10.30. $C_{16}H_{15}ClN_2S$ requires C, 63.45; H, 4.99; Cl, 11.72; N, 9.25; S, 10.59%).

Synthesis of 4-(1-piperidino- or 4-morpholino)-2-substituted-quinoline-3-carbonitriles 5a,b; 7a,b: General Procedure: To a solution of **1** (2.2 mmol) in DMF (10 ml), piperidine, or morpholine (4.4 mmol) was added. The reaction mixture was stirred at room temperature for 15 minutes, then poured into cold water. The resulting solid product was collected by filtration and dried to give **5a,b**. Compounds **7a,b** were prepared following the same procedure at reflux temperature.

2-Chloro-4-(1-piperidino)-quinoline-3-carbonitrile (5a): Yield 97%; m.p. 159-160°C from DMF/MeOH, $\nu_{max/cm-1}$ (KBr) 2220 (CN), 1620 (C=N), δ_H (CF_3CO_2H): 1.72 (6H, s), 3.86 (4H, s), 7.30-7.96 (4H, m). (Found: C, 66.27; H, 5.04; Cl, 12.81; N, 15.44. $C_{15}H_{14}ClN_3$ requires C, 66.28; H, 5.19; Cl, 13.06; N, 15.46%).

2-Chloro-4-(4-morpholino)-quinoline-3-carbonitrile (5b): Yield 98%; m.p. 180-182°C from DMF/MeOH, $\nu_{max/cm-1}$ (KBr) 2220 (CN), 1620 (C=N). δ_H (DMSO) 3.55-3.93 (8H, m), 7.50-8.18 (4H, m). (Found: C, 61.31; H, 4.44; Cl, 12.68; N, 15.36. $C_{14}H_{12}ClN_3O$ requires C, 61.42; H, 4.42; Cl, 12.97; N, 15.35%).

2,4-Di-(1-piperidino)-quinoline-3-carbonitrile (7a): Yield 97%; m.p. 158-160°C from DMF, $\nu_{max/cm-1}$ (KBr) 2210 (CN), 1610 (C=N). (Found: C, 75.07; H, 7.32; N, 17.15. $C_{20}H_{24}N_4$ requires C, 74.97; H, 7.55; N, 17.48%).

2,4-Di-(4-morpholino)-quinoline-3-carbonitrile (7b): Yield 96%; m.p. 153-154°C from DMF, $\nu_{max/cm-1}$ (KBr) 2220 (CN), 1610 (C=N). δ_H (DMSO) 3.33-3.93 (16H, m), 7.59-8.04 (4H, m). (Found: C, 67.15; H, 6.35; N, 16.94. $C_{18}H_{20}N_4O_2$ requires C, 66.65; H, 6.21; N, 17.27%).

Synthesis of 4-(1-piperidino- or 4-morpholino)-2-oxo-1(2H)-quinoline-3-carbonitriles (6a,b); General Procedure: A solution of **5a,b** (4 mmol) in a mixture of acetic acid (10 ml) and H_2O (2 ml) was refluxed for 3 hours. The solvent was then removed under reduced pressure and the resulting solid product was collected by filtration and dried.

4-(1-Piperidino)-2-oxo-1(2H)quinoline-3-carbonitrile (6a): Yield 97%; m.p. 270-273°C from DMF, $\nu_{max/cm-1}$ (KBr) 3120 (NH), 2220 (CN), 1650 (CO). δ_H (DMSO) 1.44-1.82 (6H, m), 3.32-3.57 (4H, m), 7.00-7.70 (4H, m), 11.60 (1H, s). (Found: C, 70.94; H, 6.24; N, 16.81. $C_{15}H_{15}N_3O$ requires C, 71.12; H, 5.97; N, 16.59%).

4-(4-Morpholino)-2-oxo-1(2H)quinoline-3-carbonitrile (6b): Yield 84%; m.p. 287-289°C from DMF, $\nu_{max/cm-1}$ (KBr) 3300, 3210 (NH), 2200 (CN), 1655 (CO). δ_H (DMSO) 3.40-3.88 (8H, m), 7.05-7.80 (4H, m), 11.64 (1H, s). (Found: C, 66.02; H, 5.01; N, 16.21. $C_{14}H_{13}N_3O_2$ requires C, 65.87; H, 5.13; N, 16.46%).

Synthesis of 2,4-Di-(2-hydroxyethylamino)-quinoline-3-carbonitrile (7c): Compound **1** (4.5 mmol) was refluxed with ethanolamine (15 ml) for 30 minutes and then poured into cold H_2O. The precipitated solid product was filtered off and dried. Yield 96%; m.p. 163-164°C from DMF/MeOH; $\nu_{max/cm-1}$ (KBr) 3340, 3260, 3140 (NH), 2220 (CN), 1620 (C=N). δ_H (DMSO) 3.40-3.63 (4H, m,), 3.70-3.82 (4H, m), 4.80-5.0 (2H, m), 6.15 (1H, s), 7.02-7.54 (4H, m), 8.08 (1H, d). (Found: C, 62.08; H, 5.75; N, 20.34. $C_{14}H_{16}N_4O_2$ requires C, 61.75; H, 5.92; N, 20.57%).

Synthesis of 3-amino-4-chloro-1H-pyrazolo[4,3-c]quinoline (9): To a solution of **1** (2.2 mmol) in DMF (10 ml), hydrazine hydrate (4.4 mmol) was added. The reaction mixture was stirred at room temperature for 15 minutes, then poured into cold water. The precipitated product was collected by filtration and dried. Yield 88%, m.p. >360°C from DMF; $\nu_{max/cm-1}$ (KBr) 3440, 3330, 3130 (NH, NH_2); 1620 (C=N). δ_H (DMSO) 5.68 (2H, s), 7.54-7.92 (3H, m), 8.19-8.40 (1H, m), 13.18 (1H, s). ^{13}C-NMR (DMSO) δ 101.7 (C-3a); 115.0 (C-9a); 120.8, 125.6, 127.2, 128.4 (Ar-C); 141.5 (C-9b); 142.5 (C-4); 143.1 (C-5a); 148.0 (C-3). (Found: C, 54.76; H, 3.61; Cl, 15.91; N, 25.45. $C_{10}H_7ClN_4$ requires C, 54.92; H, 3.23; Cl, 16.23; N, 25.62%).

4-Azido-2-chloroquinoline-3-carbonitrile (10): To a solution of **1** (2.2 mmol) in DMF (30 ml), sodium azide (2.2 mmol) was added. After stirring for 17 hours at room temperature, water was added and the resulting solid product was collected by filtration and dried. Yield 94%, m.p. 136-138 °C from MeOH. $\nu_{max/cm-1}$ (KBr) 2220 (CN), 2120 (N_3), 1610 (C=N). (Found: C, 52.30; H, 1.81; Cl, 15.40; N, 30.70. $C_{10}H_4ClN_5$ requires C, 52.29; H, 1.75; Cl, 15.46; N, 30.49%).

Synthesis of 2-chloro-4-substituted-quinoline-3-carbonitriles (13a,b); General procedure: To a solution of **10** (8.7 mmol) in DMF (80 ml), 5% Pd/C (200 mg) and CH_3COONa (17.5 mmol) were added. H_2 was then bubbled through and the reaction mixture was heated at 70-80°C, until no starting materials were detected by TLC (8 hours). The mixture was filtred and the filtrate was evaporated to dryness in vacuo. The residue was triturated with water and the resulting solid product was collected by filtration, washed with water and dried. In the case of **13b**, the reaction mixture was stirred for 8 hours at room temperature. Then, it was worked up as described for **13a**.

2-Chloro-4-oxo-4(1H)-quinoline-3-carbonitrile (13a): Yield 73%, m.p. 309-310°C from DMF/H_2O; $\nu_{max/cm-1}$ (KBr) 3180, 3120 (NH); 2230 (CN); 1585 (CO). (Found: C, 58.96; H, 2.57; Cl, 17.47; N, 13.68. $C_{10}H_5ClN_2O$ requires C, 58.68; H, 2.46; Cl, 17.35; N, 13.69%).

4-Amino-2-chloroquinoline-3-carbonitrile (13b): Yield 88%; m.p. 303-305°C from DMF, $\nu_{max/cm-1}$ (KBr) 3380, 3350, 3210 (NH); 2220 (CN); 1620 (C=N). (Found: C, 59.02; H, 3.08; Cl, 17.61; N, 20.91. $C_{10}H_6ClN_3$ requires C, 58.97; H, 2.97; Cl, 17.43; N, 20.63%).

2-Chloro-4-(triphenylphosphinylideneamino)-quinoline-3-carbonitrile(13c):

A solution of **10** (34.9 mmol) and Ph_3P (34.9 mmol) in toluene (80 ml) was refluxed for 20 minutes. The solvent was removed in vacuo and the resulting solid product was collected by filtration and dried. Yield 96%, m.p. 223-224°C from toluene; $\nu_{max/cm-1}$ (KBr) 2220 (CN), 1610 (C=N). (Found: C, 72.70; H, 4.10; N, 8.92. $C_{28}H_{19}ClN_3P$ requires C, 72.48; H, 4.13; N, 9.06%).

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