SYNTHESIS OF 4- AND 7-QUINOLINESULFONAMIDES FROM 4,7-DICHLOROQUINOLINE

Krzysztof Marciniec and Andrzej Maślankiewicz*

Department of Organic Chemistry, The Medical University of Silesia,
Jagiellońska 4, 41-200 Sosnowiec, Poland
E-mail: maslankiewicz@sum.edu.pl

Abstract – Action of sodium methanethiolate (in boiling DMF) towards 4,7-dichloroquinoline (1) or 7-chloro-1-methyl-4(1H)-quinolinone (11) occurred via chlorine ipso-substitution followed by methanethiolato-S-demethylation to yield dithiolate 1A or thiolate 18A, which were: i) subjected to S-methylation, ii) oxidatively chlorinated to quinolinesulfonyl chlorides (5 or 14 and 15). Oxidative chlorination of 4,4'-bis (7-chloroquinolinyl) disulfide (7) led to 7-chloro-4-quinolinesulfonyl chloride (8). All quinolinesulfonyl chlorides 5, 8, 14 and 15 were effectively converted to corresponding azinesulfonamides 6, 9, 16 and 17.

INTRODUCTION

Compounds containing both 4- and 7-quinolinesulfamoyl moieties are potential candidates for drugs since they exhibited potent antivirus,1,2 anticoagulant,3 anticancer,4,5 antidepressive,6 and antibacterial activity.7 7-Quinolinesulfonyl chlorides and fluorides used for the formation of 7-quinolinesulfonyl unit incorporated in the above mentioned compounds was generated as follows: i) from haloquinolines via 7-quinoline-metaloorganic derivatives which were then subjected to reaction with sulfur dioxide and the resulting 7-quinolinesulfinic acid derivatives were chlorinated to the respective 7-quinolinesulfonyl chlorides,1,1 ii) by chloro- or fluorosulfonation of 8-hydroxyquinoline derivatives,1 iii) by oxidative chlorination of the respective 7-benzylthioquinolines.4 Due to instability of 4-quinolinesulfonyl chlorides7 syntheses of the respective sulfonamides were rarely reported.

To extend previous study on transformation of haloquinolines via quinolinethiols to quinolinesulfonyl chlorides,8 we turned our attention to 4,7-dichloroquinoline (1), easy available industrial product, as a source of the title 4- and 7-quinolinesulfonyl chlorides and sulfonamides.
RESULTS AND DISCUSSION
Testaferri, Tiecco, Tingoli et al.9 demonstrated that the action of sodium alkanethiolate towards haloarenes and some haloazines induced halogen ipso-substitution leading to the respective alkylthio derivatives, which were then S-dealkylated to the respective arene- or azinethiolates in a one-pot process performed with an excess of sodium methane- or ethanethiolate.

The same methodology was recently applied by us to the transformation of haloquinolines to quinolinethiolates.8 They could be trapped similarly as reported by Testaferri, Tiecco, Tingoli9 by methylation to methylthioquinoline and additionally8 by oxidation to disulfides or by oxidative chlorination to quinolinesulfonyl chlorides.

Thus, the first step in our approach to the title 4- and 7-quinolinesulfonic acid derivatives was the reaction of 4,7-dichloroquinoline (1) with an excess of sodium methanethiolate (in boiling DMF). To confirm the structure of the expected 4,7-quinolinedithiolate (2A), crude thiolate fraction was methylated to 4,7-dimethylthioquinoline (2). Dithiolate 2A was acidified to non-isolated dithiol 2T, which was then oxidatively chlorinated with sodium hypochlorite in conc. hydrochloric acid or with gaseous chlorine in 80 % acetic acid. This should led to 4,7-dichlorosulfonylquinoline (4) but as 4-chlorosulfonylquinoline undergoes decomposition even at 0 °C to 4-chloroquinoline and sulfur dioxide,7,8 oxidative chlorination of 2T resulted directly in 4-chloro-7-chlorosulfonylquinoline (5).

Scheme 1. Reagents and conditions: (a) MeSNa (excess), DMF, reflux, 4h. (b) rt, HCl. aq. (c) Cl2, 17 °C, 30 min. (d) thiourea, rt, then H2O, OH-, then H+. (e) aq. K3Fe(CN)6. (f) NaOCl. aq., conc. HCl. aq. (g) NH3 aq., rt.
Synthesis of 7-chloro-4-chlorosulfonylquinoline (8) from 4,7-dichloroquinoline (1) was performed as outlined in Scheme 1. The key-step was the chlorination of 4,4'-bis (7-chloroquinolinyl) disulfide (7) in hydrochloric acid at -8 °C. Despite the instability of sulfonyl chloride 8, compound 8 could be extracted with cold (-5 °C) deuterochloroform immediately after the synthesis and fully characterized (at 0 °C, up to 1 h) with $^1$H and $^{13}$C NMR spectra. Moreover, both NMR spectra showed that content of compound 8 in CDCl$_3$ solution reached 99 % and that 8 is practically free from 4,7-dichloroquinoline (1). Due to the instability of the sulfonyl chloride 8, it should be immediately consumed e.g. by amination to the respective sulfonamide 9.

4,7-Dichloroquinoline (1) could be easy transformed to 7-chloro-1-methyl-4(1H)-quinolinone (11) via 1-methylquinolinium methylsulfate (10a)$^{10}$ (Scheme 2). It encouraged us to extend the methodology presented in Scheme 1 for derivatives of 4-quinolinone, such as 11. The reaction of the 7-chloro-4-quinolinone derivative 11 with an excess of sodium methanethiolate gave the expected thiolate 18A,

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\begin{align*}
\text{Y} & = \text{Cl}, \ Y = \text{SO}_2\text{NH}_2 \\
1, \ Y = \text{Cl} & \quad 6, \ Y = \text{SO}_2\text{NH}_2 \\
\text{Cl} & \quad (\text{MeO})_2\text{SO} \\
1, \ Y = \text{Cl} & \quad 6, \ Y = \text{SO}_2\text{NH}_2 \\
\text{Me} & \quad \text{MeOSO}_3^{-} \\
10a, \ Y = \text{Cl} & \quad 10b, \ Y = \text{SO}_2\text{NH}_2 \\
11, \ Y = \text{Cl} & \quad 12, \ Y = \text{SO}_2\text{NH}_2 \\
\end{align*}
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Scheme 2. Reagents and conditions: (a) MeSNa (excess), MeDMF, reflux, 4h. (b) HCl, aq, rt. (c) aq. K$_3$Fe(CN)$_6$. (d) rt, OH$. (e) gaseous Cl$_2$, or NaOCl, aq., -8 °C. (f) NH$_3$ aq., rt.
trapped by methylation to methylthio derivative 12 or by oxidation to disulfide 13. Oxidative chlorination of 13 (in conc. hydrochloric acid with gaseous chlorine or sodium hypochlorite, 0 °C) led to a multicomponent mixture of unstable products. Assuming that it contained the sulfonylchloride derivative 14, this mixture was subjected to amination. Sulfonamide fraction was isolated in a typical manner and was separated by recrystallization from DMF to sulfonamides 16 (7.3 %) and 17 (41 %). It indicates that sulfonyl chlorides 14 and 15 were components of mixture obtained by oxidative chlorination of 13 and that action of chlorination agents towards 13 induced both oxidative chlorination of disulfide moiety and chlorination of pyridinone ring of 13. These results are close to the Wright and Hallstrom’s observation concerning the oxidative chlorination of 6-phenyl-4-hydroxy-2-mercaptopyrimidine leading to a multicomponent mixture of unstable products, trapped as sulfonamides by reaction with benzylamine with yield ca. 22 %. 7-Sulfamoyl-1-methyl-4-quinolinone 12 could be also prepared from 4-chloro-7-sulfamoylquinoline 6 via 1-methylquinolinium methylsulfate (10b). (Scheme 2)

CONCLUSION
Previously elaborated methodology based on formation of quinolinethiolate function from chloroquinolines and an excess of sodium methanethiolate followed by oxidative chlorination of quinolinethiolate or diquinolinyl disulfide to quinolinesulfonyl chlorides could be successfully applied for the preparation of quinolinesulfonyl chlorides 5 and 8, and quinolinesulfonamides 16 and 17 starting from 4,7-dichloroquinoline (1).

Scheme 3

EXPERIMENTAL
Melting points were taken in open capillary tubes and are uncorrected. All NMR spectra were recorded on a Bruker AVANS 400 spectrometer operating at 400.22 MHz and 100.64 MHz for 1H and 13C nuclei, respectively, in deuteriochloroform (CDCl3) or in hexadecuterodimethyl sulfoxide (DMSO-d6) solutions with tetramethylsilane (δ 0.0 ppm) as internal standard. TLC analyses were performed employing Merck’s silicagel 60 F254 plates and a solution of chloroform-ethanol (19 : 1, v/v) as an eluent (system I) or a mixture of CH2Cl2/ethanol, (19 : 1, v/v) (system II) and Merck’s aluminium oxide 60 F254 neutral (type E) plates using mixture of chloroform – ethanol (19 : 1, or 10 : 1, v/v) as an eluent (system III). Sodium methanethiolate
was prepared from methanethiol and sodium methoxide (1 mol. eqv.) in methanol solution as reported previously.8

Reaction of chloroquinoline (1) or (11) with sodium methanethiolate leading to quinoline-4,7-dithiolate (2A) or 1-methyl-1,4-dihydro-4-oxoquinoline-7-thiolate (18A) (Procedure A)

A mixture of chloroquinoline (1) or (11) (4 mmol), sodium methanethiolate (5 molar eqvs. for each chlorine substituent) and dry DMF (24 mL) was boiled with stirring under argon atmosphere for 4 h. (The reaction must be carried out in hood as it proceeds with strong evolution of dimethyl sulfide). This mixture was assigned as solution A for the reaction with 1 or as solution B for the reaction with quinolinone 11. It was then cooled to 70 °C and the volatile components were evaporated under vacuum from water bath. The residue was cooled down in an ice-water bath, (under argon atmosphere) carefully acidified with 20 % hydrochloric acid (8 mL) and then kept at vacuum to remove methanethiol. This residue contains crude (non-isolated) 4,7-dimercaptoquinoline (2T) or 1-methyl-1,4-dihydro-4-oxoquinoline-7-thiol (18T) and could be used for the preparation of sulfonyl chloride 5 or sulfonamides 16 and 17.

Methylation of quinoline-4,7-dithiolate (2A) or 1-methyl-1,4-dihydro-4-oxoquinoline-7-thiolate (18A) (Procedure B)

Methyl iodide (0.37 mL, 5.9 mmol for the reaction with 2A or 0.18 mL, ca. 2.9 mmol for reaction with 18A) was added dropwise on stirring to a solution composed of 8 % aqueous sodium hydroxide (15 mL) and solution A or solution B (3mL, containing ca. 0.5 mmol of thiolate 2A or thiolate 18A - prepared as described above in procedure A). The stirring was continued at rt for 1 h. The solid was filtered off, washed with water and dried on air. It was recrystallized from aqueous EtOH or from DMF to give 4,7-dimethylthioquinoline (2) (0.1 g (91 %) or 1-methyl-7-methylthio-1,4-dihydro-4-oxoquinoline (18) (0.09 g, (90 %).

4,7-Dimethylthioquinoline (2)

mp 103-104 °C (ethanol-water). ¹H NMR (CDCl₃), δ: 2.60 (s, 3H, SCH₃), 2.65 (s, 3H, SCH₃), 7.03 (d, 1H, J=4.8 Hz, H3), 7.39 (dd, 1H, J=8.8 Hz, J=1.9 Hz, H6), 7.75 (d, 1H, J=1.9 Hz, H8), 7.95 (d, 1H, J=8.8 Hz, H5), 8.66 (d, 1H, J=4.8 Hz, H2). Anal. Calcd for C₁₁H₁₁NS₂ (221.33): C 59.69, H 5.01, N 6.33. Found: C 59.52, H 5.00, N 6.50.

1-Methyl-7-methylthio-1,4-dihydro-4-oxoquinoline (18)

mp 165-166 °C (DMF). ¹H NMR (CDCl₃), δ: 2.58 (s, 3H, SCH₃), 3.76 (s, 3H, NCH₃), 6.23 (d, 1H, J=7.8 Hz, H3), 7.13 (d, 1H, J=1.6 Hz, H8), 7.25 (dd, 1H, J=8.2 Hz, J=1.6 Hz, H6), 7.44 (d, 1H, J=7.8 Hz, H2), 8.33 (d, 1H, J=8.2 Hz, H5). Anal. Calcd for C₁₁H₁₁NOS (205.27): C 64.36, H 5.40, N 6.82. Found: C 64.21, H 5.26, N 6.64.
Preparation of diquinolinyl disulfide (13)

A solution of crude 1-methyl-1,4-dihydro-4-oxoquinoline-7-thiol (18T) (prepared as presented in procedure A) was dissolved in 8.5 % aqueous sodium hydroxide (52 mL) and oxidized to disulfide 13 with 8 % aqueous potassium ferricyanide as reported previously for 4,4’-bis(7-chloroquinolinyl disulfide) (7).12

7,7’-Bis(1-methyl-1,4-dihydro-4-oxoquinolinyl) disulfide (13)

mp 296-297 ºC (DMF). 1H NMR (DMSO-\textit{d}_6), \( \delta \): 3.76 (s, 6H, 2 x CH\textsubscript{3}), 6.02 (d, 2H, \( J \)=7.7 Hz, 2 x H\textsubscript{3}), 7.57 (dd, 2H, \( J \)=8.5 Hz, \( J \)=1.5 Hz, 2 x H\textsubscript{6}), 7.82 (d, 2H, \( J \)=1.5 Hz, 2 x H\textsubscript{8}), 7.94 (d, 2H, \( J \)=7.7 Hz, 2 x H\textsubscript{2}), 8.16 (d, 2H, \( J \)=8.5 Hz, 2 x H\textsubscript{5}). \textit{Anal.} Calcd for C\textsubscript{20}H\textsubscript{16}N\textsubscript{2}O\textsubscript{2}S\textsubscript{2} (380.47): C 63.16, H 4.24, N 7.36. Found: C 63.35, H 4.42, N 7.11.

Preparation of 4-chloro-7-quinolinesulfonyl chloride (5)

6 % Aqueous solution of sodium hypochlorite (39.5 g, 38 mL, 26.6 mmol) was cooled down to 5 ºC and then dropped within 30 min to a cold well-stirred mixture of hydrochloric acid solution of 4,7-dimercaptouquinoline (2T) (ca. 4 mmol) (prepared from 4,7-dichloroquinoline according to procedure A), conc. hydrochloric acid (12 mL) and CHCl\textsubscript{3} (12 mL) at such a rate that temperature was maintained below 10 ºC. The mixture was poured into 60 g of ice. The chloroform layer was separated, and aqueous layer was extracted with CHCl\textsubscript{3} (3 x 10 mL). The chloroform extracts were combined, washed with water and dried over anhydrous sodium sulfate. CHCl\textsubscript{3} was evaporated to leave solid residue. The residue was recrystallized from benzene to give 4-chloro-7-quinolinesulfonyl chloride (5) (0.83 g, 79 %).

The same results were obtained by chlorination of hydrochloric acid solution of 4,7-dimercaptouquinoline (2T) in the presence of 30 mL of glacial acetic acid (15-17 ºC) with the use of gaseous chlorine as reported previously for chlorination of thioquinolines.8

4-Chloro-7-quinolinesulfonyl chloride (5) was aminated to 4-chloro-7-quinolinesulfonamide (6) (0.62 g, 82 %) with aqueous ammonia as described previously for pyridine- and quinolinesulfonyl chlorides.8

4-Chloro-7-quinolinesulfochloride (5)

mp 165-166 ºC (benzene). 1H NMR (CDCl\textsubscript{3}), \( \delta \): 7.68 (d, 1H, \( J \)=4.7 Hz, H\textsubscript{3}), 8.12 (dd, 1H, \( J \)=8.8 Hz, \( J \)=1.7 Hz, H\textsubscript{6}), 8.46 (d, 1H, \( J \)=8.8 Hz, H\textsubscript{5}), 8.78 (d, 1H, \( J \)=1.6 Hz, H\textsubscript{8}), 8.95 (d, 1H, \( J \)=4.7 Hz, H\textsubscript{2}). \textit{Anal.} Calcd for C\textsubscript{9}H\textsubscript{5}Cl\textsubscript{2}NO\textsubscript{2}S (262.11): C 41.24; H 1.92; N 5.34; S 12.23. Found: C 41.48; H 2.19; N 5.31; S 12.02.

4-Chloro-7-quinolinesulfonamide (6)

mp 223-224 ºC (ethanol-water). 1H NMR (DMSO-\textit{d}_6), \( \delta \): 7.68 (s, 2H, NH\textsubscript{2}), 7.92 (d, 1H, \( J \)=4.7 Hz, H\textsubscript{3}), 8.11 (dd, 1H, \( J \)=8.8 Hz, \( J \)=1.6 Hz, H\textsubscript{6}), 8.41 (d, 1H, \( J \)=8.8 Hz, H\textsubscript{5}), 8.48 (d, 1H, \( J \)=1.6 Hz, H\textsubscript{8}), 8.97 (d, 1H, \( J \)=4.7 Hz, H\textsubscript{2}). \textit{Anal.} Calcd for C\textsubscript{9}H\textsubscript{7}ClN\textsubscript{2}O\textsubscript{2}S (242.67): C 44.54; H 2.91; N 11.54; Found: C 44.72; H 3.07; N 11.42.
Synthesis of 7-chloro-4-quinolinesulfochloride (8)

Solution of 4,4'-bis(7-chloroquinolinyl disulfide (7) (0.39g, 1 mmol) in conc. hydrochloric acid (10 mL) was cooled in an ice-salt bath down to -10 °C. Then, cold 6 % aqueous solution of sodium hypochlorite (8.2 g, 7.8 mL, 5.5 mmol) was added dropwise within 15 min to the above well-stirred mixture at such a rate that temperature was maintained between -8 to -10 °C. The mixture was poured into 60 g of ice and, due to instability of 7-chloro-4-quinolinesulfonfonyl chloride (8), the solution was aminated with cold ammonia as described previously for pyridine- and quinolinesulfonfonyl chlorides with chlorosulfonyl substituent in the aza-activated position. Aqueous ammonia insoluble solid was filtered off and air-dried to give 4,7-dichloroquinoline (1) (0.12 g, 31 %). Further work-up of the filtrate resulted in 7-chloro-4-quinolinesulfonamide (9) (0.27 g, 56 %).

For purpose of 1H and 13C NMR analysis of 8, chlorination of disulfide 7 was performed in the presence of deuterochloroform (5 mL). Organic layer was separated, washed with ice-cold water and dried over anhydrous sodium sulfate. Both types of NMR spectra showed that the content of compound 8 in CDCl3 solution reached 99 % and that 8 is practically free from 4,7-dichloroquinoline (1). Amination of chloroform extract of 8 performed as above led to 4,7-dichloroquinoline (1) (0.20 g, 52 %) and 7-chloro-4-quinolinesulfonamide (9) (0.18 g, 38 %).

7-Chloro-4-quinolinesulfonyl chloride (8)

1H NMR (CDCl3), δ: 7.92 (dd, 1H, J=9.0 Hz, J=1.5 Hz, H6), 8.05 (d, 1H, J=5.4 Hz, H3), 8.41 (d, 1H, J=9.0 Hz, H5), 8.89 (d, 1H, J=1.5 Hz, H8), 9.18 (d, 1H, J=5.2 Hz, H2). 13C NMR (CDCl3), δ: 121.7, 122.3, 125.9, 126.7, 132.8, 139.1, 143.1, 144.0, 153.5.

7-Chloro-4-quinolinesulfonamide (9)

mp 190-191 °C (EtOH-water). 1H NMR (DMSO-d6), δ: 7.86 (dd, 1H, J=8.2 Hz, J=2.0 Hz, H6), 7.98 (d, 1H, J=4.4 Hz, H3), 8.08 (s, 2H, NH2), 8.26 (d, 1H, J=2.0 Hz, H8), 8.64 (d, 1H, J=8.2 Hz, H5), 9.15 (d, 1H, J=4.4 Hz, H2). Anal. Calcd for C9H7ClN2O2S (242.67): C 44.54; H 2.91; N 11.54. Found: C 44.31, H 3.01, N 11.62.

Preparation of 1-methyl-1,4-dihydro-4-oxo-7-quinolinesulfonamide (16) and
3-chloro-1-methyl-1,4-dihydro-4-oxo-7-quinolinesulfonamide (17) from chlorination products of

7,7'-bis(1-methyl-1,4-dihydro-4-oxoquinolinyl) disulfide (13)

Mixture of disulfide (13) (0.38g, 1 mmol) and conc. hydrochloric acid (10 mL) was cooled down in an ice-salt bath to -10 °C and then chlorinated with cold 6 % aqueous solution of sodium hypochlorite (8.2 g, 7.8 mL, 5.5 mmol) as described above for disulfide 7. The mixture was poured into 60 g of ice and then treated at 10 °C with conc. ammonia (12 mL) and stirred at 45 °C for 30 min. The solid was filtered off. The filtrate was concentrated to dryness at vacuum. The residue was triturated with cold water (10 mL)
and the solid was filtered off and dried on air to give the product (0.29 g) with mp 291-295 °C. The crude product (0.58 g, from two runs) was recrystallized from DMF (6 mL) to give 0.44 g (41 %) of TLC homogeneous 3-chloro-1-methyl-1,4-dihydro-4-oxo-7-quinolinesulfonamide (17) with mp 316-318 °C. The filtrate was concentrated to 1/3 volume and left in refrigerator for the night. The precipitate was filtered off to give 0.08 g of solid with mp 265-268 °C. It was recrystallized from DMF to afford 0.06 g (7.3 %) of 1-methyl-1,4-dihydro-4-oxo-7-quinolinesulfonamide (16) with mp 277-278 °C.

1-Methyl-1,4-dihydro-4-oxo-7-quinolinesulfonamide (16) mp 277-278 °C (DMF). $^1$H NMR (DMSO-$d_6$), δ: 3.83 (s, 3H, CH$_3$), 6.20 (d, 1H, $J$=7.6 Hz, H3), 7.61 (s, 2H, NH$_2$), 7.71 (dd, 1H, $J$=8.4 Hz, $J$=1.6 Hz, H6), 8.00-8.03 (m, 2H, H2 and H8), 8.25 (d, 1H, $J$=8.4 Hz, H5). Anal. Calcd for C$_{10}$H$_{10}$N$_2$O$_3$S (238.26): C 50.41, H 4.23, N 11.76. Found: C 50.11, H 4.36, N 11.93.

3-Chloro-1-methyl-1,4-dihydro-4-oxo-7-quinolinesulfonamide (17) mp 316-318 °C (DMF). $^1$H NMR (DMSO-$d_6$), δ: 3.88 (s, 3H, CH$_3$), 7.65 (s, 2H, NH$_2$), 7.83 (dd, 1H, $J$=8.3 Hz, $J$=1.3 Hz, H6), 8.07 (d, 1H, $J$=1.3 Hz, H8), 8.37 (d, 1H, $J$=8.3 Hz, H5), 8.57 (s, 1H, H2). Anal. Calcd for C$_{10}$H$_9$ClN$_2$O$_3$S (272.70): C 44.04, H 3.33, N 13.00. Found: C 44.25, H 3.51, N 13.22.

Preparation of 1-methyl-1,4-dihydro-4-oxo-7-quinolinesulfonamide (16) from 4-chloro-7-quinolinesulfonamide (6) 4-Chloro-7-quinolinesulfonamide (6) (0.24 g, ca.1 mmol) and dimethyl sulfate (0.57 mL, 6 mmol) was stirred at 80 °C within 2 h. It was then cooled to rt and triturated with ether (5 mL) up to full solidifying. The solid was filtered off and dried under vacuum to give 0.36 g of 1-methyl-7-sulfoamoylquinolinium methylsulfate (10b). Crude 10b was dissolved in water (7 mL), then sodium bicarbonate (0.34 g, 4 mmol) was added and the mixture was gently boiled for 2 h. Solid was filtered off, dried on air and finally recrystallized from DMF to give quinolinone 16 (0.19 g, 80 %) with mp and Rf value identical to the sample prepared from chlorination of disulfide 13.

**REFERENCES (AND NOTES)**


