Synthesis of 8-Hydroxyquinolines with Amino and Thioalkyl Functionalities at Position 4

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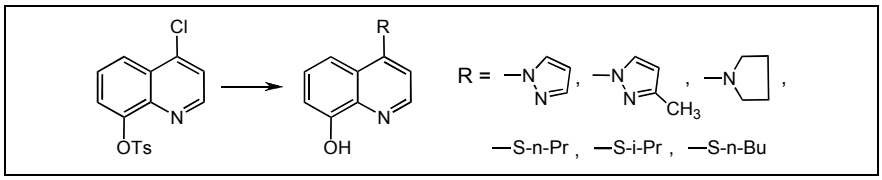

Six 8-hydroxyquinolines with amino and thioalkyl functionalities at position 4 have been prepared. The synthesis starts with chlorination of the readily available 4-hydroxy-8-tosyloxyquinoline to give 4-chloro-8-tosyloxyquinoline in 94% yield. Treatment of the 4-chloro-8-tosyloxyquinoline with sulphur and nitrogen nucleophiles produces the target 4-amino and 4-thioalkyl-8-hydroxyquinolines in more than 70% yield. In case of sulphur nucleophiles and pyrrolidine, the removal of the protecting tosyl group at position 8 occurs simultaneously with the substitution of chlorine at position 4.

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INTRODUCTION

Quinoline derivatives are widely used in many applications, in medicine they are used in the treatment of inflammatory diseases [1] and also are very well known as antimalarial drugs [2-5].

8-Hydroxyquinolines are also involved in the structures of some electrically important materials, such as Alq_3, which is commonly used as an emitter in OLED's due to its excellent electronic properties [6-10].

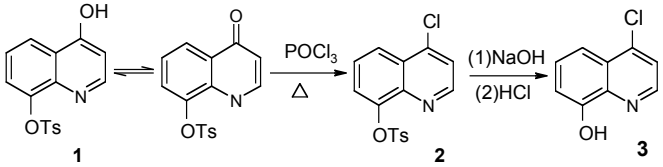
In our previous work [11], we succeeded to produce 4-alkoxy-8-hydroxyquinolines from 4,8-dihydroxyquinoline by protecting the hydroxyl group at position 8 and carrying out the desired alkylation reactions on position 4 to give 4-alkoxy-8-tosyloxyquinoline.

In our present work we have chlorinated 4-hydroxy-8-tosyloxyquinoline and reacted the chlorinated product with various nitrogen and sulphur nucleophiles to produce rare 8-hydroxyquinolines with amino or thioalkyl groups at position 4.

RESULTS AND DISCUSSION

4-hydroxy-8-tosyloxyquinoline **1** was chlorinated with phosphorus oxychloride to give 4-chloro-8-tosyloxyquinoline **2** in an excellent yield (94%), the chlorination could easily be performed in a large scale (10 g). 4-Chloro-8-tosyloxyquinoline could be hydrolyzed to give 4-chloro-8-hydroxyquinoline **3** in a 79% yield (Scheme 1) [12].

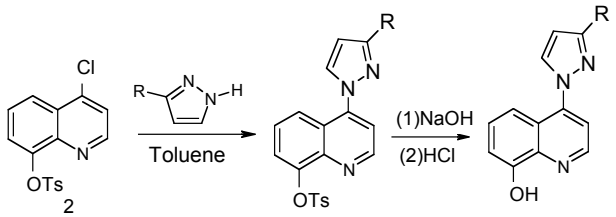
Scheme 1. Synthesis and hydrolysis of **2**.



After chlorination of **1** [11], 4-chloro-8-tosyloxyquinoline **2** was allowed to react with different nitrogen and sulphur nucleophiles.

The reaction between **2** and pyrazole or 3-methylpyrazole in toluene produced 4-pyrazolyl-8-tosyloxyquinoline **4** in 83% yield and 4-(3-methylpyrazolyl)-8-tosyloxyquinoline **5** in 81% yield respectively (Scheme 2).

Scheme 2. General route for the synthesis of 4-pyrazolyl -8-hydroxyquinolines.



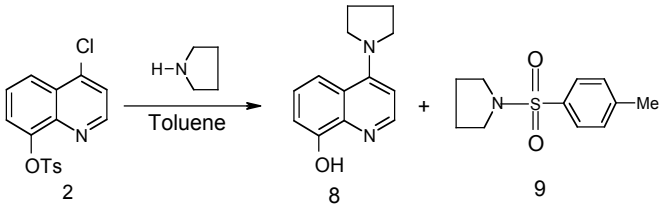
4, R = H
5, R = Me

6, R = H
7, R = Me

4-Pyrazolyl-8-hydroxyquinoline **6** and 4-(3-methylpyrazol)yl-8-hydroxyquinoline **7** were produced from **4** and **5** by hydrolysis using sodium hydroxide in aqueous ethanol followed by acidification of the alkaline reaction mixture with hydrochloric acid (Scheme 2). The products were formed in 79 and 77% yields respectively.

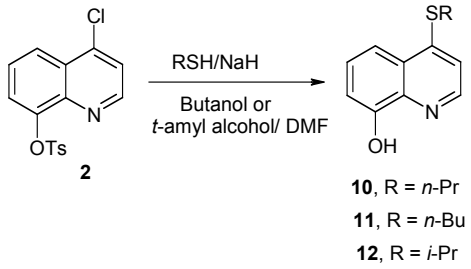
The reaction between 4-chloro-8-tosyloxyquinoline **2** and pyrrolidine in toluene produced 4-pyrrolidinyl-8-hydroxyquinoline **8** together with *N*-tosyl-pyrrolidine **9** (Scheme 3) [13]. Compound **8** could be separated from **9** by addition of hot ethyl acetate to the mixture. Compound **9** was separated by filtration, and after cooling to room temperature **8** appeared from the filtrate as bright yellow crystals in 62%.

Scheme 3. Synthesis of **8**.



The substitution reactions involving the sulphur nucleophiles needed a strong base [14]. NaH was used to deprotonate the thiols. The resulting sodium thiolates from *n*-butanethiol and *n*-propanethiol were refluxed with 4-chloro-8-tosyloxyquinoline **2** in butanol to produce *n*-propylthio-8-hydroxyquinoline **10** and 4-*n*-butylthio-8-hydroxyquinoline **11** in good yields (70 and 71% yield respectively) (Scheme 4). Similarly to the reaction between pyrrolidine and **2**, the reaction between sodium thiolates and **2** produced the deprotected 8-hydroxyquinolines **10** and **11** directly by a simultaneous removal of the protecting tosyl group. The reaction between **2** and isopropanethiol was performed in *t*-amyl alcohol in the presence of DMF to afford 4-isopropylthio-8-hydroxyquinoline **12** in a good yield (77%) (Scheme 4).

Scheme 4. General route for the synthesis of 4-thioalkyl-8-hydroxyquinolines



EXPERIMENTAL

Synthesis of 4-chloro-8-tosyloxyquinoline (2). 4-Hydroxy-8-tosyloxyquinoline **1** [11], (3.15 g, 10 mmol) and phosphorus oxychloride (25 mL) was refluxed for 1 hour. After cooling to room temperature, the reaction mixture was poured into an ice-NH_4OH mixture with stirring. The precipitate formed was collected by filtration and washed with water to give the title compound (3.13 g, 94%). Recrystalization from toluene gave yellowish white crystals of Mp 141-142 °C; ir (KBr): ν 3052, 2362, 1585, 1493, 2461, 1372, 1174 cm^{-1}; ^{1}H nmr (200 MHz, DMSO-d_6): δ 2.34 (3H, s), 7.35 (2H, d, J = 8.2 Hz), 7.61 (1H, dd, J = 7.6Hz), 7.68-7.80 (4H, m), 8.08 (1H, dd, J = 8.4 Hz), 8.74 (1H, d, J = 4.7 Hz); ^{13}C nmr (50 MHz, DMSO-d_6): δ 21.9, 123.4, 123.9, 124.1, 127.8, 128.7, 129.2 (2C), 130.7 (2C), 132.9, 142.1, 142.6, 145.8, 146.5, 151.7; hrms: calcd for $C_{16}H_{12}NO_3NaSCl$ ([M+Na]$^+$) 356.0124, found 356.0133.

General procedure for the synthesis of 4-amino-8-tosyloxyquinolines. 4-chloro-8-tosyloxyquinoline **2** (1 equivalent) was refluxed with the amine derivative (5 equivalents) in toluene for 5 hours, the reaction mixture was then concentrated and allowed to cool to room temperature. The crystals formed were collected by filtration and recrystalized from the proper solvent.

Synthesis of 4-pyrazolyl-8-tosyloxyquinoline (4). The title compound was prepared by the previous procedure by reacting **2** (3.3 g, 10 mmol) and pyrazole (3.36 g, 49 mmol) in toluene (25 mL), the white crystals formed (3 g, 83%) were recrystalized from ethanol, mp 146 °C; ir (KBr): 3275, 3105, 3055, 2959, 1594, 1506, 1437, 1371 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$): δ 2.36 (3H, s), 6.55 (1H, t, J = 2.6 Hz), 7.20 (2H, d, J = 8.5 Hz), 7.40 (1H, d, J = 4.8 Hz), 7.49-7.62 (2H, m), 7.80-7.89 (4H, m), 8.22 (1H, dd, J = 8.5 Hz), 8.80 (1H, d, J = 4.8 Hz); ^{13}C nmr (50 MHz, $CDCl_3$): δ 22.0, 108.7, 116.3, 123.3, 123.8, 124.3, 127.2, 129.1 (2C), 129.9 (2C), 131.7, 133.2, 142.9, 143.6, 144.3, 145.7, 145.9, 151.1; hrms calcd for $C_{19}H_{16}N_3O_3S$ ([M+H]$^+$) 366.0912, found 366.0919.

Synthesis of 4-(3-methylpyrazole)yl-8-tosyloxyquinoline (5). The title compound was prepared by the previous procedure by reacting **2** (3.3 g, 10 mmol) and 3-methylpyrazole (4 mL, 49 mmol) for 5 hours. The yellowish white crystals formed (3 g, 81%) were collected by filtration and recrystalized from ethanol; mp 145 °C; ir (KBr): 3110, 3056, 2928, 1741, 1594, 1506, 1431, 1372, 1171 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$): δ 2.34 (3H, s), 2.38 (3H, s), 6.32 (1H, d, J = 2.6 Hz), 7.22 (2H, d, J = 8.4 Hz), 7.33 (1H, d, J = 4.7 Hz), 7.52-7.61 (2H, m), 7.76-7.82 (3H, m), 8.23-8.28 (1H, dd, J = 8.6 Hz), 8.75 (1H, d, J = 4.8 Hz); ^{13}C nmr (50 MHz, $CDCl_3$): δ 14.1, 22.0, 108.9, 115.9, 123.3, 123.9, 124.2, 127.0, 129.1 (2C), 129.9 (2C), 132.4, 133.2, 143.7, 144.4, 145.6, 146, 151.0, 152.6; hrms calcd for $C_{20}H_{17}N_3O_3NaS$ ([M+Na]$^+$) 402.0888, found 402.0871.

General procedure for the cleavage of the tosyl group. The 4-amino-8-tosyloxyquinoline derivative (1 equivalent) was refluxed with NaOH (5 equivalents) in aqueous ethanol for 1 hour, diluted with water and neutralized with HCl to pH 7. The powder formed was collected by filtration and recrystalized from the proper solvent.

Synthesis of 4-chloro-8-hydroxyquinoline (3). The previous procedure was followed by reacting (1 g, 3.0 mmol) of **2** and (2 *M*, 7.5 mL, 15 mmol) NaOH in ethanol (10 mL), after neutralization the powder formed was recrystalized from ethanol to give light yellow needles (0.85 g, 79%) [15], mp 145-146 °C , mp (lit. [12] 145-146°C); ir (KBr): 3186 (br), 1625, 1571, 1502, 1400, 1263 cm^{-1}; ^{1}H nmr (200 MHz, DMSO-d_6): δ 7.15 (1H, t, J = 4.5 Hz), 7.55 (2H, d, J = 4.7 Hz), 7.73 (1H, d , J = 4.7 Hz), 8. 74 (1H, d, J = 4.7 Hz), 10.15 (1H, br s); ^{13}C nmr (50 MHz, DMSO-d_6): δ 113.5, 114.1, 122.8, 127.3, 129.9, 140.2, 142.1, 148.6, 154.7; hrms calcd for C_9H_7NOCl ([M+H]$^+$) 180.0216, found 180.0206.

Synthesis of 4-pyrazolyl-8-hydroxyquinoline (6). The tosyl group in **4** was cleaved by reacting (1 g, 2.7 mmol) of **4** and NaOH (2 *M*, 6.75 mL, 13.5 mmol) The precipitate formed was collected and recrystalized from methanol to give the title compound as yellowish white crystals (1.37 g, 79%). mp 105 °C; ir (KBr): 3312, 3049, 1942, 1746, 1590, 1515, 1407 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$): δ 6.56 (1H, t, J = 2.4 Hz), 7.20-7.24 (1H, dd, J = 7.6 Hz), 7.43-7.51 (2H, m), 7.74-7.86 (1H, dd, J = 8.6 Hz), 7.87 (1H, d, J = 1.5 Hz),7.93 (1H, D, J = 2.4 Hz), 8.68 (1H, br s), 8.77 (1H, d, J = 8.7 Hz); ^{13}C nmr (50 MHz, $CDCl_3$): δ

108.5, 111.2, 114.4, 116.4, 122.9, 129.1, 131.6, 140.4, 142.7, 144.8, 148.2, 152.9; hrms calcd for $C_{12}H_{10}N_3O$ ([M+H]$^+$) 212.0824, found 212.0827.

Synthesis of 4-(3-methylpyrazol)yl-8-hydroxyquinoline (7). The title compound was prepared by refluxing (1 g, 2.6 mmol) and NaOH (2 *M*, 6.5 mL, 13 mmol) in ethanol.

After acidification the powder formed (0.45 g, 79%) was recrystalized from methanol to give **7** as light yellow crystals of mp 99-100 °C; ir (KBr): 3335, 3114, 2929, 1921, 1587, 1519, 1418 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$): δ 2.44 (3H, s), 6.38 (1H, d, *J* = 2.4 Hz), 7.21-7.25 (1H, dd, *J* = 7.6 Hz), 7.46-7.54 (2H, m), 7.76-7.81 (1H, dd, *J* = 8.6 Hz), 8.87 (1H, d, *J* = 2.4 Hz), 8.44 (1H, br s), 8.81 (1H, d, *J* = 4.7 Hz); ^{13}C nmr (50 MHz, $CDCl_3$): δ 14.2, 108.7, 110.8, 114.5, 116.0, 122.7, 128.9, 132.3, 140.5, 144.8, 148.2, 152.4, 152.8; hrms calcd for $C_{13}H_{12}N_3O$ ([M+H]+) 226.0980, found 226.0961.

Synthesis of 4-pyrrolidinyl-8-hydroxyquinoline (8). The title compound was prepared by refluxing **2** (3.3 g, 10 mmol) and pyrrolidine (4 mL, 49 mmol) in toluene for 9 hours. After cooling the resulting mixture of products was boiled in ethyl acetate and filtered. The precipitate was found to be *N*-tosyl-pyrrolidine **9**. Cooling the filtrate to room temperature produced bright yellow crystals of the titled compound (1.3 g, 62%). mp 141-142 °C; ir (KBr): 3277, 2967, 2852, 1520, 1417, 1347 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$): δ 2 (4H, quintet), 3.71 (4H, t, *J* = 6.2 Hz), 6.43 (1H, d, *J* = 5.3 Hz), 6.65 (1H, s), 7.09 (1H, d, *J* = 7.5 Hz), 7.18-7.26 (1H, t, *J* = 8.6 Hz), 7.73 (1H, dd, *J* = 8.7 Hz), 8.36 (1H, d, *J* = 5.5 Hz); ^{13}C nmr (50 MHz, DMSO-d_6): δ 26.3 (2C), 52.6 (2C), 104.0, 110.1, 116.0, 121.5, 124.3, 140.9, 148.2, 152.8, 153.4; hrms calcd for $C_{13}H_{15}N_2O$ ([M+H]$^+$) 215.1184, found 215.1172.

***N*-tosyl-pyrrolidine (9).** Mp 123 °C, mp (lit. [13] 122-123 °C); ^{1}H nmr (200 MHz, $CDCl_3$): δ 1.73 (4H, quintet, *J* = 3.3 Hz), 3.21 (4H, t, *J* = 6.6 Hz), 7.32 (2H, d, *J* = 7.6 Hz), 7.72 (2H, d, *J* = 8.2 Hz); hrms calcd. for $C_{13}H_{15}NO_2NaS$ ([M+Na]$^+$) 248.0721, found 248.0718.

General procedure for the preparation of 4-thioalkyl-8-hydroxyquinolines. NaH in 60% oil dispersion in paraffin oil (6 equivalent) washed with *n*-hexane (5 mL), and the thiol derivative (5 equivalent) were stirred vigorously and 4-chloro-8-tosyloxyquinoline **2** (1 equivalent) dissolved in 1-butanol or *tert*-amyl alcohol (10 mL) was added. The reaction mixture was refluxed under N_2 atmosphere for 28 h. The solvent was removed by evaporation and water (15 mL) was added. The pH was adjusted with hydrochloric acid (1 *M*) to 7.1-7.2. The residue was kept in an ice bath for 10 minutes, filtered and washed with water (50 mL) and recrystalized from the proper solvent.

Synthesis of 4-*n*-propylthio-8-hydroxyquinoline (10). The titled compound was prepared by the previous procedure by reacting NaH (216 mg, 9.00 mmol) and 1-propanethiol (0.69 mL, 7.53 mmol). 4-Chloro-8-tosyloxyquinoline **2** (500 mg, 1.50 mmol) dissolved in 1-butanol (10 mL) was added. The product formed was recrystalized from aqueous ethanol to give light brown crystals. mp 101°C; ir (KBr): 3280 (br), 2960, 2924, 2868, 1619 (m), 1558 (s) cm^{-1}; ^{1}H nmr (200 MHz, DMSO-d_6): δ 1.05 (3H, t, *J* = 7.3 Hz), 1.74 (2H, sextet, *J* = 7.3 Hz), 3.16 (2H, t, *J* = 7.2 Hz), 7.03-7.12 (1H, m), 7.40-7.45 (3H, m), 8.64 (1H, d, *J* = 4.7 Hz), 9.80 (1H, br s); ^{13}C nmr (50 MHz, DMSO-d_6): δ 13.5, 21.5, 32.0, 111.8, 113.1, 116.6, 126.6, 127.7, 137.7, 147.2, 147.2, 154.0; hrms calcd for $C_{12}H_{14}NOS$ ([M+H] +) 220.0796, found 220.0791.

Synthesis of 4-*n*-butylthio-8-hydroxyquinoline (11). The title compound was prepared by using the previous procedure from NaH (218 mg, 9.08 mmol), 1-butanethiol (0.83 ml, 7.50 mmol) and 4-chloro-8-tosyloxyquinoline **2** (500 mg, 1.50 mmol). Recrystallization from aqueous ethanol afforded **11** (249 mg, 71%) as light brown crystals. mp 121°C; ir (KBr): 3275 (br), 2955, 2922, 2862, 1622 (m), 1559 cm^{-1}; ^{1}H nmr (200 MHz, DMSO-d_6): δ 0.91 (3H, t, *J* = 7.2 Hz), 1.45 (2H, sextet, *J* = 7.2 Hz), 1.69 (2H, quintet, *J* = 7.2 Hz), 3.16 (2H, t, *J* = 7.2 Hz), 7.04-7.13 (1H, m), 7.39-7.45 (3H, m), 8.64 (1H, d, *J* = 4.8 Hz), 9.80 (1H, br s); ^{13}C nmr (50 MHz, DMSO-d_6): δ 13.7, 21.8, 29.9, 30.0, 111.8, 113.1, 116.6, 126.6, 127.7, 137.7, 147.2, 147.3, 154.0; hrms: calcd for $C_{13}H_{16}NOS$ ([M+H] +) 234.0953, found 234.0967.

Synthesis of 4-*iso*propylthio-8-hydroxyquinoline (12). NaH (216 mg, 9.00 mmol), 2-methyl-2-butanol (10 mL) and 2-propanethiol (0.72 mL, 7.48 mmol) were stirred together. After 1 ½ h. 4-chloro-8-tosyloxyquinoline 2 (500 mg, 1.50 mmol) and DMF (5 ml) were added. The reaction mixture was refluxed for 24 h. The product was recrystalized from aqueous ethanol to give 12 (253 mg, 77%) as light brown crystals. mp 125°C; ir (KBr): ν 3319 (br), 2969 (m), 2923 (m), 2866 (w), 1621 (m), 1556 (s) cm-1; 1H nmr (200 MHz, DMSO-d6): δ 1.39 (6H, d, J = 6.5 Hz), 3.85 (1H, septet, J = 6.4 Hz), 7.07-7.11 (1H, m), 7.39-7.48 (3H, m), 9.81 (1H, br s); ^{13}C nmr (50 MHz, DMSO-d6): δ 23.3, 35.6, 112.5, 113.9, 118.6, 127.5, 128.3, 138.6, 147.1, 147.8, 154.6; hrms calcd for $C_{12}H_{14}NOS$ ([M+H]+) 220.0796, found 220.0828.

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[15] This compound is prepared in a better yield using the tosyl protecting group during the synthetic route, see reference 12.