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Synthesis of 4-Alkoxy-8-hydroxyquinolines†

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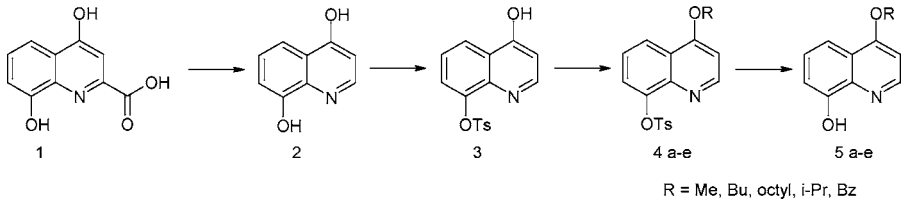

Quinolines with a hydroxyl group at the 8-position and an alkoxy group at the 4-position are rare compounds. In this paper the synthesis of five 4-alkoxy-8-hydroxyquinolines is reported. The key reaction in the synthetic route is a selective protection of the hydroxyl group at C-atom 8 in 4,8-dihydroxyquinoline with a tosyl group and the hydrolytic removal of the protective group after the alkylation. The tosyl group is stable during the alkylations with various alkylating agents in the presence of sodium hydride.

Introduction

Substituted quinoline compounds can be found in many applications. In medicine they have attracted interest as antimalarial drugs[1] and therapeutic drugs for inflammatory diseases.[2] Quinolobactin, a naturally occurring quinoline, has been identified as a siderophore that pseudomonas produce to complex iron.[3]

Other important applications of 8-hydroxyquinolines derivatives such as tris(8-hydroxyquinoline) aluminum (Alq_3) exploit their unique electronic characteristics, and considerable attention has recently been focused on their potential utility as electron transporter and light-emitting layer in organic light-emitting devices (OLEDs).[4] A computer simulations for Alq_3 has predicted that its optical properties can be modified by changing the substitution pattern of 8-hydroxyquinoline. Particularly, an electron-donor group at C-atom 4 of 8-hydroxyquinoline increases the intrinsic luminescence yield.[5]

Protection of the functional group is required frequently when a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound. Previously[6] it has been shown that the 8-hydroxyl group of 4,8-dihydroxylquinoline can be alkylated prior to the alkylation of the hydroxyl group at the 4-position. The yield of the alkylated compound was low, and moreover it was not proven that the alkyl group at 8-position can be removed without a simultaneous removal of the alkyl group at 4-position. In this paper, we describe a selective protection of the 8-hydroxyl group in 4,8-dihydroxyquinoline with an easily removable tosyl group. The protected compound can be synthesized in an almost quantitative yield and was found to be stable enough in the consequent alkylation step. The stability of the tosyl group in 4-hydroxy-8-tosyloxyquinoline can be utilized to produce 4-alkoxy-8-tosyloxyquinolines that undergo hydrolysis in an alkaline environment readily to afford 4-alkoxy-8-hydroxyquinolines. Potentially, 4-hydroxy-8-tosyloxyquinoline can also serve as a starting material in the synthesis of other 4-position heteroatom functionalized 8-tosyloxyquinolines and their derivatives.[7]

Results and Discussion

The commercially available xanthurenic acid **1** was decarboxylated to give 4,8-dihydroxyquinoline **2** in a excellent (96%) yield[8] (Scheme 1).

The hydroxyl group at the 8-position was easily deprotonated by using a 1:1 molar ratio of NaOH to the diol **2**. The tosyl

† Contribution from the Empart group of Infotech Oulu.

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(7) Synthetic procedure to produce other 4-position-substituted 8-tosyloxyquinoline, and its derivatives will be published during our future work.

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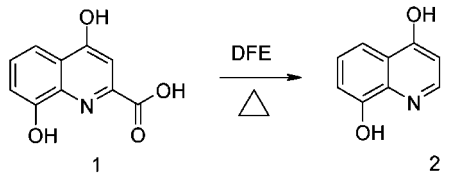
SCHEME 1



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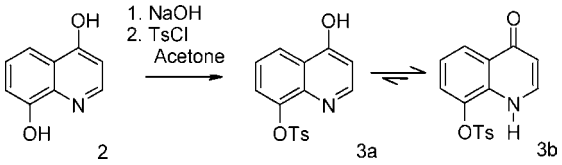
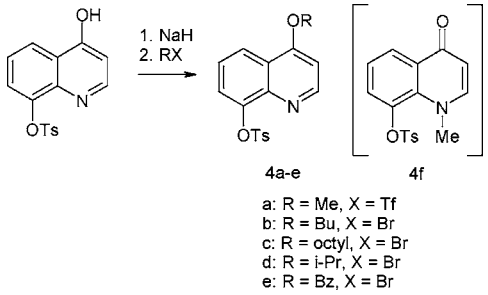


SCHEME 3

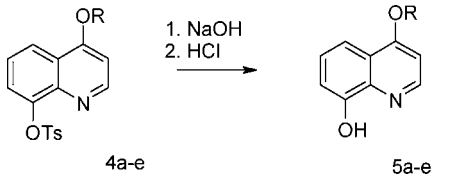


group was then attached to the monosodium salt of the diol **2** in 95% yield by using *p*-toluenesulfonyl chloride in a water/acetone solution[9] (Scheme 2). The protection reaction was found to be easily scaled up. The structure of the protected compound 4-hydroxy-8-tosyloxyquinoline **3** was actually found to be **3b** instead of **3a**. The ^{1}H NMR spectrum of **3** showed clearly a coupling between the N-H proton and the proton at C-2.

The next step in our synthetic scheme was the alkylation of the compound **3** with various alkylating agents. NaH was used as a base to deprotonate the 4-hydroxyl group of the quinoline (Scheme 3).[10]

To produce **4a**, tosylated quinoline **3** was reacted with NaH to afford the corresponding sodium salt of **3**. Methyl trifluoromethanesulfonate was then added to the salt to give the O-methylated quinoline **4a** in a moderate 47% yield. Also the N-methylated quinoline **4f** was formed during the treatment of the sodium salt with methyl trifluoromethanesulfonate. Attempts to increase the amount of O-alkylated product **4a** by changing the solvent from DMF to the nonpolar cyclohexane gave rise to the formation of the N-methylated quinoline exclusively.[11] In DMF the ratio between the N-methylated quinoline **4f** and the O-methylated quinoline **4a** was 1:10, varying slightly when the amount of alkylating reagent or solvent was changed. Both alkylated products could be separated by flash chromatography.

SCHEME 4



The other alkoxylated tosyloxyquinolines **4b**−**e** were also prepared by using the NaH deprotonation of the tosylated quinolinol **3** followed by subsequent treatment of the sodium salt with alkyl halides in DMF (Scheme 3) to afford the products **4b**−**d** in good yields (74−78%) and **4e** in a moderate 56% yield. The formation of any N-alkylated products could not be detected in the reactions between the bulky alkyl halides and the sodium salt of **3**. An excess of alkyl halide was found to be necessary in order to obtain a time efficient alkylation.

Treatment of 4-alkoxy-8-tosyloxyquinolines **4a**−**e** with sodium hydroxide in a water/alcohol mixture followed by neutralization with hydrochloric acid gave the final 4-alkoxy-8-hydroxyquinolines **5a**−**e** (Scheme 4) in good yields (72−79%).

Conclusions

Commercially available xanthurenic acid can be effectively decarboxylated to give 4,8-dihydroxyquinoline. Selective protection of the 8-hydroxyl group with *p*-toluenesulfonyl chloride gives 4-hydroxy-8-tosyloxyquinoline in a high yield, and the compound can be used as a starting material to produce 4-alkoxy-8-tosyloxyquinolines. The protective tosyl group can easily be removed by hydrolysis to afford 4-alkoxy-8-hydroxyquinolines in good yields.

Experimental Section

4,8-Dihydroxyquinoline (2). Xanthurenic acid **1** (15.0 g, 73.1 mmol) was added to diphenylether (150 mL) at 235 °C. The mixture was stirred at 240−250 °C under N_2 for 2.5 h. The mixture was cooled and diluted with high-boiling petroleum ether (180 mL). The precipitate was filtered and washed with petroleum ether to provide **2** (11.3 g, 96%) as a crude product, which was used in the next step without further purification. For analysis a small amount of the crude product was recrystallized from ethanol. Mp: 321 °C[12]. IR (KBr): ν 3400, 3345, 3043, 2957, 2461 (br), 1788, 1623 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.06 (1H, d, J = 7.3 Hz), 7.07−7.15 (2H, m), 7.56 (1H, dd, J = 7.9 Hz), 7.78 (1H, d, J = 7.0 Hz), 10.88 (1H, br s), 11.39 (1H, br s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.1, 114.7, 115.2, 123.5, 127.4, 131.0, 139.3, 147.2, 177.4. HRMS: calcd for $C_9H_8NO_2$ ([M + H]$^+$) 162.0555, found 162.0567.

4-Hydroxy-8-tosyloxyquinoline (3). 4,8-Dihydroxyquinoline **2** (7.00 g, 43.4 mmol) was dissolved in sodium hydroxide solution (1 M, 45.9 mL, 45.9 mmol). The clear solution was cooled to room temperature, and *p*-toluenesulfonyl chloride (8.28 g, 43.4mmol) in

(8) Our initial route to prepare **2** involved the use of the Gould−Jacobs reaction of substituted anilines with diethyl ethoxymethylenemalonate. Unfortunately, cyclization led to less than 30% yield, and all attempts to improve the yield were unsuccesful. For a review of Gould−Jacobs reaction, see: Gould, R. G.; Jacobs, W. A. J. *Am. Chem. Soc.* **1939**, *61*, 2890.

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(10) Our initial effort to alkylate tosylated quinoline **3** involved the use of potassium carbonate, potassium iodide, and alkyl halide according to the general method of the Claisen O-alkylation. With that method, alkylation products **4b,d** were obtained in moderate yields.

(11) An opposite effect of solvents is seen in alkylation of 2-pyridone: Hopkins, G. C.; Jonak, J. P.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 4040.

(12) Grandjean, D.; Dhimane, H.; Pommelet, J.-C.; Chuche, J. *Bull. Soc. Chim. Fr.* **1989**, *5*, 657 reports a melting point of 197 °C; however, the melting point differs strongly from our melting point, 320 °C, which is much closer to the melting point of 2,4-dihydroxyquinoline, 355 °C: *CRC Handbook of Chemistry and Physics*, 62nd ed.; Weast, R. C., Ed.; CRC Press Inc.: Boca Raton, FL, 1982.

acetone (15 mL) was slowly added to the solution. The mixture was stirred for 3 h. Water (50 mL) was added, and the precipitate was filtered off and washed with water (80 mL) and acetone (80 mL). The title compound **3** (13.0 g, 95%) was obtained as a powder. The crude product was used directly in the next step without further purification. For analysis a small amount was recrystallized from ethanol as white crystals. Mp: 237 °C. IR (KBr): ν 3052, 2941, 2883, 1644 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.38 (3H, s), 6.05 (1H, d, J = 7.5 Hz), 7.28 (1H, t, J = 7.9 Hz), 7.39−7.45 (3H, m), 7.73 (1H, t, J = 6.6 Hz), 7.81 (2H, d, J = 8.3 Hz), 8.00 (1H, dd, J = 7.9 Hz), 11.50 (1H, d, J = 4.9 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.6, 109.8, 123.0, 124.3, 124.4, 127.7, 129.2 (2C), 130.5 (2C), 131.0, 133.6, 138.5, 140.4, 146.8, 177 (carbonyl C-atom signal in the ^{13}C NMR spectrum is visible in its 2D HMBC spectrum). HRMS: calcd for $C_{16}H_{14}NO_4S$ ([M + H]$^+$) 316.0644, found 316.0648.

General Procedure for Synthesis of 4-Alkoxylated 8-Tosylloxyquinoline with NaH as Base. Synthesis of 4-Methoxy-8-tosyloxyquinoline (4a). NaH (176 mg, 7.33 mmol) in 60% oil dispersion was washed with cyclohexane or *n*-pentane (5 mL), and 4-hydroxy-8-tosyloxyquinoline **3** (1.50 g, 4.76 mmol) in dimethylformamide (30 mL) was added. The mixture was stirred at room temperature until H_2 evolution was completed, and methyl trifluoromethanesulfonate (0.78 mL, 7.11 mmol) was slowly added under N_2. After 2 h the reaction mixture was poured into water (200 mL) and allowed to stand at room temperature overnight. The precipitate was collected by filtration and washed with water. The final purification by flash chromatography[13] (10 mL methanol/1.5 L 1:1 acetone/*n*-hexane) afforded the title compound (738 mg, 47%) as off-white crystals. Mp: 127 °C. IR (KBr): ν 3029, 2954, 2849 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (3H, s), 4.02 (3H, s), 7.05 (1H, d, J = 5.5 Hz), 7.40 (2H, d, J = 8.4 Hz), 7.47−7.55 (2H, m), 7.82 (2H, d, J = 8.4 Hz), 8.06 (1H, dd, J = 8.4 Hz), 8.66 (1H, d, J = 5.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.6, 56.8, 102.4, 121.3, 122.7, 122.8, 125.7, 128.8 (2C), 130.3 (2C), 132.9, 142.3, 145.2, 145.8, 152.6, 161.8. HRMS: calcd for $C_{17}H_{16}NO_4S$ ([M + H]$^+$) 330.0800, found 330.0799.

***N*-Methyl-8-tosyloxyquinolin-4-one (4f).** In the described reaction above the title compound formed in the ratio 1:10 to O-alkylated product. For analysis a small amount was purified with flash chromatography (10 mL methanol/1.5 L 1:1 acetone/*n*-hexane). Mp: 156 °C. IR (KBr): ν 3068, 2965, 1627 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (3H, s), 3.91 (3H, s), 6.06 (1H, d, J = 7.8 Hz), 7.20 (1H, dd, J = 7.8 Hz), 7.30 (1H, t, J = 7.9 Hz), 7.48 (2H, d, J = 8.4 Hz), 7.75 (2H, d, J = 8.3 Hz), 7.82 (1H, d, J = 7.8 Hz), 8.14 (1H, dd, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.7, 45.3, 109.7, 123.6, 125.7, 127.1, 128.9 (2C), 129.7, 130.9 (2C), 131.3, 135.3, 138.3, 147.1, 148.3, 175.5. HRMS: calcd for $C_{17}H_{15}NO_4NaS$ ([M + Na]$^+$) 352.0619, found 352.0652.

General Procedure for Synthesis of 4-Alkoxylated 8-Hydroxyquinoline. Preparation of 4-Methoxy-8-hydroxyquinoline (5a). 4-Methoxy-8-tosyloxyquinoline **4a** (819 mg, 2.49 mmol), sodium hydroxide (1 M, 7.50 mL, 7.50 mmol), and methanol (15 mL) were refluxed for 4 h.[14] The solution was cooled to room tempetature, and the pH was adjusted with hydrochloric acid (1 M) to 7.2. The mixture was concentrated in vacuo, and water (20 mL) was added. The precipitate was filtered and washed with water. Recrystallization from ethanol gave the product **5a** (325 mg, 75%) as off-white crystals. Mp: 118 °C. IR (KBr): ν 3262 (br), 3023, 2938, 2841 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 4.00 (3H, s), 6.99−7.09 (2H, m), 7.36 (1H, t, J = 8.0 Hz), 7.52 (1H, dd, J = 8.2 Hz), 8.66 (1H, d, J = 5.2 Hz), 9.62 (1H, br s). ^{13}C NMR (50 MHz, DMSO-d_6): δ 56.9, 102.2, 112.0, 112.4, 122.3, 127.4, 140.1, 150.0, 154.0, 162.6. HRMS: calcd for $C_{10}H_{10}NO_2$ ([M + H]$^+$) 176.0712, found 176.0690.

Acknowledgment. The authors thank Mrs. Päivi Joensuu for high-resolution mass spectrometric data.

Supporting Information Available: Experimental procedures and spectroscopic data of compounds **4b**−**e** and **5b**−**e** and IR, ^{1}H NMR, ^{13}C NMR, and high resolution mass spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Silica gel with 0.040−0.063 mm particle size was used as a support in every flash chromatography purification procedures.

(14) In other hydrolysis reactions ethanol was used instead of methanol to help dissolution.