Direct Monobromination of Substituted 4-Oxoquinoline-3-carboxylic Acid Derivatives

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N-Bromosaccharin in the presence of pyridinium poly(hydrogen fluoride) can be used for monobromination of ethyl esters of 6- and 7-substituted-4-oxo-1,4-dihydroquinoline-3-carboxylic acids. The reactions take place at the C_6 or C_8 positions, depending on the types and positions of the substituents.

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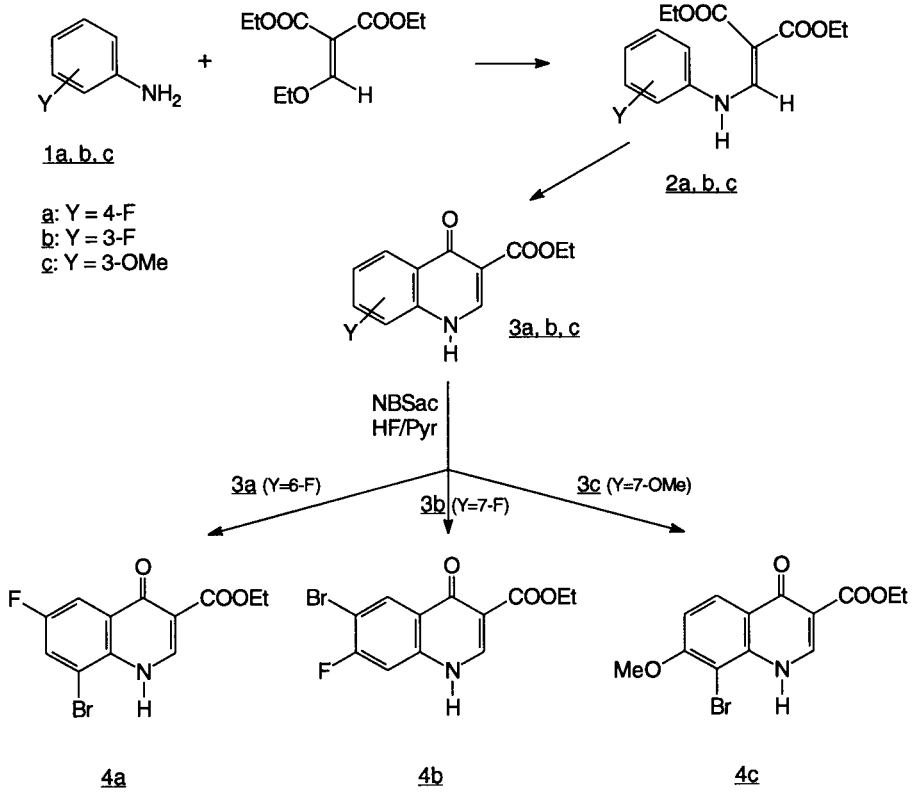
Quinolines react with halogens and interhalogens to form a whole series of halogen and interhalogen complexes of varying thermal stability [1]. On the other hand, much less is known about the halogenation of 4-oxoquinolines [2] at the present time with the most important derivatives showing very good antibacterial activity on Gram-negative and Gram-positive bacteria. It has been shown that C_6 and C_7 substituents have a major influence on the antibacterial activity spectrum, and a fluorine atom at position 6 is the most common substituent.

Direct monobromination of the benzene ring in 4-oxoquinoline-3-carboxylic acid is unknown. We would like to determine the possibility of introducing a bromine atom into positions 5, 6, 7 or 8 of the ethyl esters of 6- and 7-fluoro- and 7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid which were synthesized as illustrated in Scheme 1.

Bromination of **3a, 3b** or **3c** was carried out using bromine or bromine in the presence of aluminum bromide or ferric bromide. The colour of bromine disappeared, but in the ^1H nmr spectra, signals corresponding to hydrogen atoms at the positions 2, 5, 6 or 7 and 8 remained, so we concluded that substitution on the benzene ring of the 4-quinolone did not take place; only molecular complexes with bromine were formed.

Previously, we have established that *N*-bromosaccharin (NBSac) in the presence of pyridinium poly(hydrogen fluoride) can serve as a source of BrF species which then serves as a reagent for the electrophilic aromatic bromination of activated and deactivated benzene derivatives [3].

Scheme 1



As it is known that the group, bonded at the N_1 position of the quinolone, has an influence on the reactivity of the benzene ring [2], we used *N*-unsubstituted compounds. In a typical experiment, 2.4 mmoles of NBSac was suspended in pyridinium poly(hydrogen fluoride) and stirred for half an hour at 0°, 2 mmoles of substrate was then added and the reaction mixture was stirred at room temperature for four hours. After isolation, the product obtained from the reaction of the ethyl ester of 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, revealed in its nmr spectrum two doublet of doublet signals at δ = 8.26 ppm with coupling constants of 7.8 and 2.4 Hz and at δ = 8.2 ppm with J = 8.4 and 2.4 Hz and a doublet of doublet in the ^{19}F nmr spectrum. On the basis of ^1H and ^{19}F nmr spectra together with the mass spectrum with m/z: 315 ($M^+ + 2$) and 313 (M^+), we determined that substitution took place at the C_8 position with formation of the ethyl ester of 8-bromo-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4a**, Scheme 1). The reaction with the 7-fluoro derivative under the same reaction conditions resulted in a product which revealed a ^1H nmr doublet signal at δ = 8.85 ppm with a coupling constant of 7.6 Hz, corresponding to H_5 and a doublet at 8.06 ppm with a coupling constant of 9.3 Hz, corresponding to H_8. The mass spectrum showed that monobromination ran our with the formation of the 6-bromo-7-fluoro derivative **4b**. Monobromination took place also in the case of the 7-methoxy derivative; 8-bromo-7-methoxy substituted product **4c** was obtained. The ^1H nmr spectrum showed two doublets at δ = 7.27 and 8.18 ppm, with a coupling constant of 9 Hz. The disappearance of the coupling between H_6 and H_8 (J = 2.4 Hz) in the ^1H nmr spectrum indicated that bromination occurred at C_8 in the 4-quinolone molecule.

We also prepared ethyl esters of 1-ethyl-6- and 7-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 1-ethyl-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and we found that bromination of these compounds under the same reaction conditions as in previous cases did not take place, or that the conversion was too low to enable us to isolate pure products.

From the results obtained, we can conclude that *N*-bromosaccharin in the presence of pyridinium poly(hydrogen fluoride) can serve as a reagent for monobromination of ethyl esters of 6- and 7-substituted-4-oxo-1,4-dihydroquinoline-3-carboxylic acid derivatives.

EXPERIMENTAL

The ^1H nmr spectra were recorded on Varian VXR-300 spectrometer in trifluoroacetic acid, using TMS as the internal reference. The ^{19}F nmr spectra were recorded on Varian EM 360 L spectrometer at 56.4 MHz also in trifluoroacetic acid with fluorotrichloromethane as the internal standard. Mass spectra and high resolution mass measurements were taken on an Autospec QVG Analytical spectrometer. Melting points are uncorrected. Pyridinium poly(hydrogen fluoride) was prepared according to Olah's procedure [4]. NBSas was prepared by the method of Sanchez and Fumarola [5].

General Procedure for the Preparation of Ethyl Esters of 6- and 7-Substituted-4-oxo-1,4-dihydroquinoline-3-carboxylic Acids **3a,b,c**.

A substituted aniline **1a,b,c** (0.15 mole) and diethyl ethoxymethylenemalonate (28.8 g, 0.15 mole) were stirred for one hour at 110-120° and the ethanol produced was distilled off. The crude acrylates **2a,b,c** were poured into a hot high boiling ether such as diphenyl ether, through which a rapid stream of argon was passed. The temperature was rapidly increased to 240-250° and the reaction mixture was stirred at that temperature for 30 minutes. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered, washed with tetrachloromethane and dried. The solid was recrystallized from a mixture of DMF and acetone to give 26.1 g (74%) of **3a**, mp 276-278° (lit [6] 288-289°) and 21.85 g (62%) of **3b**, mp 308-311° (lit [7] 308-309°). The ethyl ester of 7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was prepared according to the procedure, described in ref [8] to give 23.71 g (64%) of **3c**, mp 271-273 (lit [8] 275°).

Ethyl Ester of 6-Fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**3a**).

This compound had ^1H nmr: δ/ppm 1.42 (t, J = 7 Hz, 3H), 4.50 (q, J = 7 Hz, 2H), 7.63 (ddd, J = 10.5, 9, 3.3 Hz, 1H, H_7), 7.9 (dd, J = 10.5, 4.7 Hz, 1H, H_8), 8.01 (dd, J = 10.3, 3.3 Hz, 1H, H_5), 8.81 (s, 1H, H_2); ^{19}F nmr: −105.9 (m, 1F).

Anal. Calcd. for $C_{12}H_{10}FNO_3$: C, 61.28; H, 4.29; N, 5.96. Found: C, 61.67; H, 4.03; N, 6.05.

Ethyl Ester of 7-Fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**3b**).

This compound had ^1H nmr: δ/ppm 1.50 (t, J = 7 Hz, 3H), 4.63 (q, J = 7 Hz, 2H), 7.72 (td, J = 10, 1.7 Hz, 1H, H_6), 7.94 (dd, J = 9.3, 1.7 Hz, 1H, H_8), 8.66 (dd, J = 10, 6 Hz, 1H, H_5), 9.36 (s, 1H, H_2); ^{19}F nmr: 90.44 (ddd, J = 10, 9.3, 6 Hz, 1F); ms: m/z (%) 236 ($M^+ + 1$, 8), 235 (M^+, 61), 190 (26), 189 (100), 188 (19), 162 (13), 144 (16), 107 (15).

Anal. Calcd. for $C_{12}H_{10}FNO_3$: C, 61.28; H, 4.29; N, 5.96. Found: C, 61.52; H, 4.31; N, 6.05.

Ethyl Ester of 7-Methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**3c**).

This compound had ^1H nmr: δ/ppm 1.42 (t, J = 7 Hz, 3H), 4.01 (s, 3H), 4.47 (q, J = 7 Hz, 2H), 7.38 (dd, J = 9, 2.4 Hz, 1H, H_6), 7.45 (d, J = 2.4 Hz, 1H, H_8), 8.36 (d, J = 9 Hz, 1H, H_5), 9.1 (s, 1H, H_2).

General Bromination Procedure for Ethyl Esters of 6- and 7-Substituted-4-oxo-1,4-dihydroquinoline-3-carboxylic Acids **3a, 3b, 3c**.

NBSac (0.628 g, 2.4 mmoles) was suspended in pyridinium poly(hydrogen fluoride) (4 ml) and stirred at 0° for half an hour, when 2 mmoles of substrate was added. The reaction mixture was stirred at room temperature and after four hours poured into an ice-cold water (15 ml), the precipitate was filtered off, washed with water, aqueous sodium bicarbonate with water again, then suspended in dichloromethane, filtered and dried. The crude

product was recrystallized several times from the mixture of DMF and acetone, to give **4a** (0.40 g, 64%) mp 280-283°, **4b** (0.426 g, 68%) mp 297-300° and **4c** (0.430 g, 66%) mp 231-235°.

Ethyl Ester of 8-Bromo-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**4a**).

This compound had ^{1}H nmr: δ/ppm 1.49 (t, J = 6.9 Hz, 3H), 4.63 (q, J = 6.9 Hz, 2H), 8.2 (dd, J = 8.4, 2.4 Hz, 1H, H_7), 8.26 (dd, J = 7.8, 2.4 Hz, 1H, H_5), 9.31 (s, 1H, H_2); ^{19}F nmr: −104.8 (dd, J = 8.4, 7.8 Hz, 1F); ms: m/z (%) 315 (M^++2, 7), 313 (M^+, 7), 269 (19), 267 (20), 235 (32), 189 (100), 133 (22).

Anal. Calcd. for $C_{12}H_9BrFNO_3$: C, 45.88; H, 2.88; N, 4.46. Found: C, 45.75; H, 3.07; N, 4.45.

Ethyl Ester of 6-Bromo-7-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**4b**).

This compound had ^{1}H nmr: δ/ppm 1.6 (t, J = 7 Hz, 3H), 4.8 (q, J = 7 Hz, 2H), 8.06 (d, J = 9.3 Hz, 1H, H_8), 8.85 (d, J = 7.6 Hz, 1H, H_5), 9.4 (s, 1H, H_2); ^{19}F nmr: −87.8 (dd, J = 9.3, 7.6 Hz, 1F); ms: m/z (%) 315 (M^++2, 18), 313 (M^+, 18), 269 (44), 267 (42), 236 (20), 235 (77), 190 (47), 189 (100), 188 (45), 162 (35), 161 (19), 133 (37), 101 (31), 81 (10).

Anal. Calcd. for $C_{12}H_9BrFNO_3$: C, 45.88; H, 2.88; N, 4.46. Found: C, 46.16; H, 2.92; N, 4.82.

Ethyl Ester of 8-Bromo-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**4c**).

This compound had ^{1}H nmr: δ/ppm 1.28 (t, J = 7 Hz, 3H), 4.0 (s, 3H), 4.25 (q, J = 7 Hz, 2H), 7.27 (d, J = 9 Hz, 1H, H_6), 8.18 (d, J = 9 Hz, 1H, H_5), 8.42 (s, 1H, H_2); ms: m/z (%) 327 (M^++2, 48), 325 (M^+, 48), 281 (100), 279 (86), 200 (31), 53 (27).

Anal. Calcd. for $C_{13}H_{12}BrNO_4$(**4c**): C, 47.86; H, 3.71; N, 4.29. Found: C, 47.47; H, 3.41, N, 4.39.

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