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Synthesis of 4-Quinolone Derivatives

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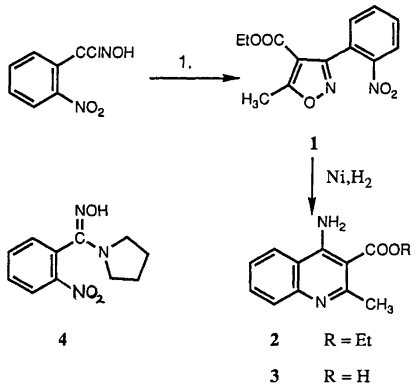
Routes to 4-amino-2-alkyl substituted quinoline-3-carboxylic acids and 3-acyl-2-phenyl and 3-acyl-2-alkyl substituted 4-quinolones have been devised by application of isoxazole chemistry and Heck–Stille couplings.

In continuation of our studies on the use of isoxazoles as intermediates in synthesis[1–3] we have studied alternative routes to 4-quinolone derivatives. These compounds are of interest as broad-spectrum antimicrobials.[4] Characteristic of these compounds is the presence of a carboxylic group at C-3 and these structural features have guided the present synthetic work. Furthermore we wished to find a route to the corresponding 4-imino derivatives, i.e., 4-aminoquinoline-3-carboxylates. In our first synthesis we used arylacetylenes as one of the starting materials. This choice limited the generality of the method because of limited stability and accessibility of the arylacetylenes. Therefore we now apply the Heck–Stille couplings with stannyl compounds as a key step.[5,6]



Scheme 1. Ethyl 3-pyrrolidinocrotonate, Et_3N.

Results and discussion

Scheme 1 shows the route to 4-aminoquinoline-3-carboxylic acid. Ethyl 3-oxobutanoate was reacted with pyrrolidine to give the enamine, which underwent cycloaddition to 2-nitrobenzonitrile oxide, generated from the corresponding hydroxamoyl chloride, to give the isoxazole **1**. The chlorination of 2-nitrobenzaldehyde oxime was performed with *tert*-butyl hypochlorite at 0–5 °C, which gave better results than *N*-chlorosuccinimide. Catalytic reduction of **1** over Raney-Ni in one step reduced the nitro group and cleaved the isoxazole ring. The product cyclized spontaneously to the quinoline derivative **2**. Basic hydrolysis of the ester gave the desired amino acid **3**. Occasionally the pyrrolidide oxime **4** was isolated as a by-product.

The synthesis of 3-acylated 4-quinolones is shown in Scheme 2. The stannyl compound **5** was prepared and coupled with iodobenzenes according to known procedures[2,5] to give **6** and subsequent catalytic reduction gave the enamine **7**. By using anilides an alternative mode of cyclization was made possible between the activated methylene and the anilide carbonyl to give **9**. When **7a** was heated in refluxing acetic acid in the presence of NaOAc for 7 h a mixture of **9a**, 63%, and **10a**, 27%, was obtained. Traces of **8a** were observed. When the same conditions were applied to **7b** the reaction stopped at the dione stage **8b**, 94%. Thermolysis of **8b** at 140 °C for 3 h gave **9b**, 43%. 2-Phenyl-4-quinolone **10b** was the principal product when **7b** was heated in acidic water–ethanol solution.

Starting from the 3-alkoxy substituted stannyl compound **5**, R = OCH_3, the 3-amino-3-methoxy substituted compound **7c** was prepared. However, we were not successful in cyclizing **7c** by various methods to the desired carboxylated 4-quinolone. 2-Acetamidoacetophenone, **11**, was obtained by heating **7c** in refluxing acetic acid containing sodium acetate.

Experimental

^1H and ^{13}C NMR spectra were recorded with tetramethylsilane (TMS) as an internal standard at 200 and 50 MHz, respectively. Preparative TLC was performed on silica gel (60, $PF_{254+366}$, Merck) glass plates,

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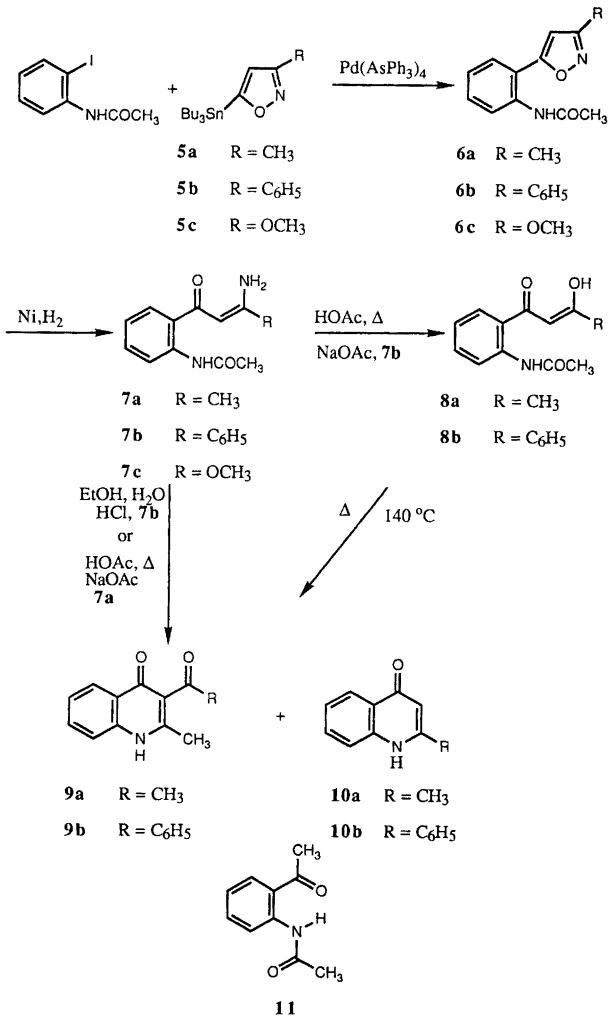

Scheme 2.

20 × 20 × 0.18 cm, and column chromatography (CC) on silica gel (70–230 mesh, Merck). Tributylstannylacetylene,[7] ethyl 3-pyrrolidinocrotonate,[8] *t*-butyl hypochlorite,[9] 3-methoxy-, 3-methyl- and 3-phenyl-5-(tributylstannyl)-isoxazole[2,5] and tris(dibenzylideneacetone)dipalladium (Pd_2dba_3)[10] were prepared according to published procedures.

Ethyl 3-(2-nitrophenyl)-5-methylisoxazole-4-carboxylate, **1**. 2-Nitrobenzaldehyde oxime (110 mg) was chlorinated with *tert*-butyl hypochlorite (100 mg) at ca. 5 °C in ethyl acetate (1.6 ml). When the green colour changed to yellow ethyl 3-pyrrolidinocrotonate (260 mg) in ethyl acetate (1 ml) was added after which triethylamine was added dropwise (200 mg). The solution was stirred for 16 h, washed with dilute hydrochloric acid and water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by prep. TLC (SiO_2, CH_2Cl_2–EtOAc, 95:5) to give **1** (120 mg, 66%) as a yellow oil which slowly crystallized, m.p. 72–74 °C from aqueous ethanol. ^1H NMR ($CDCl_3$): δ 1.07 (3 H, t, $J = 7$ Hz), 2.73 (3 H, s), 4.07 (2 H, q, $J = 7$ Hz), 7.51 (1 H, dd, $J = 7.6$ and 2 Hz), 7.6–7.75 (2 H, m), 8.22 (1 H, dd, $J = 7.6$ and 2 Hz). UV (EtOH): λ_{max} 258 nm, IR (film): 1720 (s), 1600 (s), 1520 (s) cm^{-1}. Minute amounts of **4** were occasionally isolated from the TLC plate. ^1H NMR ($CDCl_3$): δ 1.85 (4 H, m), 3.15 (4 H, m), 7.42 (1 H, dd, $J = 8$ and 1 Hz), 7.55 (1 H, td, $J = 8$ and 1 Hz), 7.7 (1 H, t, $J = 8$ Hz), 8.1 (1 H, d, $J = 8$ Hz).

Ethyl 4-amino-2-methylquinoline-3-carboxylate, **2**. Isoxazole **1** (300 mg) was catalytically reduced over Raney-Ni in ethanol. The reduction was stopped when **4** equivalents of H_2 had been absorbed. The mixture was filtered through a thin layer of Celite and washed with aqueous ethanol. The filtrate was evaporated *in vacuo*, and the residue dissolved in chloroform, washed with water, dried over $MgSO_4$ and evaporated to give practically pure **2** (88%). It was crystallized from CCl_4–CH_2Cl_2, 9:1, white crystals, m.p. 135–137 °C. ^1H NMR ($CDCl_3$): δ 1.42 (3 H, t, $J = 7$ Hz), 2.80 (3 H, s), 4.41 (2 H, q, $J = 7$ Hz), 7.00 (2 H, br s), 7.39 (1 H, t, $J = 7.5$), 7.64 (1 H, t, $J = 7.5$), 7.74 (1 H, d, $J = 7.5$), 7.86 (1 H, d, $J = 7.5$). IR (KBr): 1670, 1620, 1550 cm^{-1}. MS: *m/z* 230 (M^+). The hydrochloride **2** precipitated as white needles, m.p. 226–228 °C from dilute aqueous hydrochloric acid.

4-Amino-2-methylquinoline-3-carboxylic acid, **3**. Compound **2** (40 mg) was hydrolysed with NaOH (2 equivs.) in aqueous ethanol at 80 °C for 3 h. The solution was neutralized with hydrochloric acid, evaporated *in vacuo* and methanol added. The sodium chloride was filtered off and the methanol evaporated off to give the amino acid **3**, 20 mg, 57%. Recrystallization in water gave crystals, m.p. 231–234 °C. ^1H NMR ($CDCl_3$–CD_3OD, 7:1): δ 2.76 (3 H, s), 7.44 (1 H, td, $J = 7.5$ and 1 Hz), 7.55 (1 H, dd, $J = 7.5$ and 1 Hz), 7.66 (1 H, td, $J = 7.5$ and 1 Hz), 8.05 (1 H, dd, $J = 7.5$ and 1 Hz). MS: *m/z* 202 (M^+, 78%), 184 (100%).

5-(2-Acetamidophenyl)-3-methylisoxazole, **6a** was prepared according to the procedure described for **6b** from 2-iodoacetanilide and 3-methyl-5-tributylstannylisoxazole, m.p. 97–98 °C from ethanol: water, 1:1, yield 92%. The reaction time was 22 h and the temperature was kept at 48 °C. ^1H NMR ($CDCl_3$): δ 2.12 (3 H, s), 2.30 (3 H, s), 6.28 (1 H, s), 7.1 (1 H, t, $J = 7.5$ Hz), 7.34 (1 H, t, $J = 7.5$ Hz), 7.5 (1 H, d, $J = 7.5$ Hz), 8.13 (1 H, d, $J = 7.5$ Hz), 8.65 (1 H, br s). MS: *m/z* 216 (M^+, 68%), 174 (100%), 145 (61%), 133 (68%), 120 (58%), 104 (73%).

5-(2-Acetamidophenyl)-3-phenylisoxazole, **6b**. 2-Iodoacetanilide (2.0 g, 7.7 mmol), $Pd_2(dba)_3$ (0.17 g, 0.19 mmol) and $AsPh_3$ (0.47 g, 1.54 mmol) were stirred in dioxane (12 ml) under N_2 for 15 min. 3-Phenyl-5-tributylstannylisoxazole (4.0 g, 9.2 mmol) was added and the mixture was reacted for 1–2 days at 50 °C with stirring. The reaction was followed by TLC (SiO_2, Et_2O–petroleum, 3:1). The mixture was filtered through Celite, evaporated

in vacuo and chromatographed (SiO_2, Et_2O–petroleum, 3:1) to give **6b**, 2.1 g, ca. 100%, practically pure. It was recrystallized from benzene–cyclohexane, light brown crystals, m.p. 148–50°C. ^1H NMR ($CDCl_3$): δ 2.25 (3 H, s), 6.81 (1 H, s), 7.22 (1 H, t, J = 8 Hz), 7.4–7.6 (4 H, m), 7.63 (1 H, d, J = 7.5 Hz), 7.85 (2 H, dd, J = 7 and 2.5 Hz), 8.35 (1 H, d, J = 8 Hz), 8.58 (1 H, br s).

5-(2-Acetamidophenyl)-3-methoxyisoxazole, **6c** was prepared according to the procedure for **6b** from 2-iodoacetanilide and 3-methoxy-5-tributylstannylisoxazole. The chromatographic eluent was methanol–chloroform, 1:9. M.p. 145–148°C from ethanol–dichloromethane, yield 88%. ^1H NMR ($CDCl_3$): δ 2.17 (3 H, s), 3.98 (3 H, s), 6.09 (1 H, s), 7.13 (1 H, t, J = 8 Hz), 7.39 (1 H, t, J = 8 Hz), 7.48 (1 H, d, J = 8 Hz), 8.21 (1 H, d, J = 8 Hz), 8.5 (1 H, br s). ^{13}C NMR ($CDCl_3$): δ 173.1, 170.4, 169.2, 135.9, 131.8, 129.0, 125.0, 123.8, 118.2, 94.0, 57.6, 25.3. MS: m/z 232 (M^+, 23%), 190 (100%).

Reduction of **6a** was carried out in methanol as described for **6b**. Compound **7a** was obtained as yellow crystals, m.p. 106–109°C, 76%. ^1H NMR ($CDCl_3$): δ 2.05 (3 H, s), 2.22 (3 H, s), 5.5 (1 H, br s), 5.68 (1 H, s), 7.03 (1 H, td, J = 8 and 1 Hz), 7.39 (1 H, td, J = 8 and 1 Hz), 7.67 (1 H, dd, J = 8 and 1 Hz), 8.57 (1 H, d, J = 8 Hz), 10.1 (1 H, br s), 11.7 (1 H, br s). MS: m/z 218 (M^+, 42%). Compound **7a** was unchanged after being heated at 130°C for 3 h.

Reduction of **6b** was carried out in dioxane over Raney-Ni in the presence of boric acid.[2] The reduction mixture was filtered through a thin layer of Celite, washed with methanol and the filtrate evaporated *in vacuo*. The residue was dissolved in chloroform–water and the organic phase was dried over $MgSO_4$ and evaporated to give **7b**, 89% as light yellow needles, m.p. 116–118°C from methanol. ^1H NMR ($CDCl_3$): δ 2.23 (3 H, s), 5.6–5.8 (1 H, br s), 6.1 (1 H, s), 7.06 (1 H, t, J = 8 Hz), 7.4–7.6 (4 H, m), 7.63 (2 H, dd, J = 8 and 1 Hz), 7.78 (1 H, dd, J = 8 and 1 Hz), 8.6 (1 H, d, J = 8.5 Hz), 10.25 (1 H, br s), 11.65 (1 H, br s). ^{13}C NMR ($CDCl_3$): δ 193.2, 169.5, 164.6, 139.9, 137.7, 132.6, 131.5, 129.6, 129.2, 126.9, 126.6, 122.9, 121.4, 94.1, 26.0.

Reduction of **6c** was carried out in a methanol–dioxane mixture as described for **6b**. Compound **7c** was obtained as a golden-brownish oil in 94% yield. ^1H NMR ($CDCl_3$): δ 2.17 (3 H, s), 3.83 (3 H, s), 5.34 (1 H, s), 5.6 (1 H, br s), 7.03 (1 H, t, J = 8 Hz), 7.38 (1 H, t, J = 8 Hz), 7.63 (1 H, d, J = 8 Hz), 8.52 (1 H, d, J = 8 Hz), 9.9 (1 H, br s), 11.6 (1 H, br s). ^{13}C NMR ($CDCl_3$): δ 191.3, 171.1, 169.5, 139.3, 132.0, 128.5, 127.3, 123.0, 121.4, 77.1, 56.0, 25.9. MS: m/z 234 (M^+, 45%).

1-(2-Acetamidophenyl)-3-phenylpropane-1,3-dione, **8b** was obtained by heating **7b** in acetic acid saturated with sodium acetate at 110°C for 20 h. The solvent was evaporated off, the residue was partitioned between chloroform and water and the organic phase evaporated to give crude **8b**. It was purified by TLC (SiO_2, CH_2Cl_2, 5% EtOAc), 94%, semisolid redbrown material, which could not be crystallized. ^1H NMR ($CDCl_3$): δ 2.25 (3 H, s), 6.80 (1 H, s), 7.13 (1 H, t, J = 7 Hz), 7.4–7.6 (4 H, m), 7.82 (1 H, d, J = 7 Hz), 7.95 (2 H, d, J = 7 Hz), 8.63 (1 H, d, J = 7 Hz), 11.1 (1 H, br s). MS: m/z 281.4 (M^+), 222.4, 162.3, 120.2.

3-Acetyl-2-methyl-4-quinolone, **9a** *and 2-methyl-4-quinolone,* **10a**. Compound **7a** (50 mg) was heated in acetic acid (0.5 ml) in the presence of sodium acetate (0.3 g) at 110°C for 7 h. The acetic acid was removed *in vacuo* and the residue was washed with diethyl ether and ethyl acetate and filtered. Evaporation of the filtrate and purification of the residue by TLC (SiO_2, Et_2O, 2% MeOH and Et_2O, 6% MeOH) gave **9a**, 29 mg, 63% yellow crystals, m.p. 256–260°C from methanol, and **10a**, 10 mg, 27%. ^1H NMR ($CDCl_3$): **9a**, δ 2.59 (3 H, s), 2.70 (3 H, s), 7.34 (1 H, d, J = 7.5 Hz), 7.37 (1 H, td, J = 7.5 and 1 Hz), 7.61 (1 H, td, J = 7.5 and 1 Hz), 8.35 (1 H, dd, J = 7.5 and 1 Hz). ^{13}C NMR (CD_3OD, $CDCl_3$, 1:3): **9a**, δ 205.3, 179.0, 154.4, 140.6, 134.3, 127.4, 127.2, 126.3, 122.2, 119.3, 33.7, 21.0. MS: m/z 201 (M^+), 186, 159, 158, 130. The spectral data of **10a** agree with the lit.[11] data. A third band contained ca. 10% of impure **8a**. ^1H NMR ($CDCl_3$): δ 2.23 (6 H, s), 6.18 (1 H, s), 7.1 (1 H, t, J = 8 Hz), 7.50 (1 H, t, J = 8 Hz), 7.69 (1 H, d, J = 8 Hz), 8.62 (1 H, d, J = 8 Hz), 11.8 (1 H, br s). MS: m/z 219 (M^+), 191, 162, 120, 106 (100%).

3-Benzoyl-2-methyl-4-quinolone, **9b**. The dione **8b** (25 mg) was heated at 140°C for 3 h and the product purified by TLC (SiO_2, Et_2O, 3% MeOH) to give **9b**, 10 mg, 43%, as yellow crystals, decomp. ca. 270°C from methanol. The compound darkens at ca. 250°C. ^1H NMR ($CDCl_3$): δ 2.30 (3 H, s), 7.28–7.40 (4 H, m), 7.42–7.60 (2 H, m), 7.86 (2 H, d, J = 7.5 Hz), 8.3 (1 H, d, J = 7.5 Hz). MS: m/z 263 (M^+).

2-Phenyl-4-quinolone, **10b**. Compound **7b** (98 mg) was heated at 90°C in acidic ethanol–water solution (1:2, 12 ml, 1 M HCl) for 4 h. The hydrochloride of **10b** (50 mg, 65%) precipitated on cooling, m.p. 195–200°C. The free base **10b** was formed by addition of triethylamine. MS: m/z 221.084 (M^+); calc. $C_{15}H_{11}NO$, 221.258. ^1H NMR (CD_3OD): δ 6.58 (1 H, s), 7.4–7.9 (8 H, m), 8.27 (1 H, d, J = 8 Hz). Small amounts of **9b** were detected in the filtrate.

2-Acetamidoacetophenone, **11**. was obtained by heating **7c** in refluxing acetic acid saturated with sodium acetate for 36 h. The solvent was evaporated off, the residue partitioned between CH_2Cl_2–Et_2O and water and the organic phase was separated, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in chloroform, filtered and evaporated to give **11**, 10 mg, 66%, as a dark golden

semisolid. ^{1}H NMR ($CDCl_3$): δ 2.24 (3 H, s), 2.67 (3 H, s), 7.12 (1 H, t, J = 8 Hz), 7.56 (1 H, t, J = 8 Hz), 7.90 (1 H, d, J = 8 Hz), 8.74 (1 H, d, J = 8 Hz), 11.7 (1 H, br s). MS: m/z 177 (M^+, 19%), 135 (46%), 120 (100%). The spectrum was identical with that of an authentic specimen.

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