A Convenient Selective *N*-Alkylation of 4-Oxo-1,4-dihydro-2-quinoline Carboxylic Acid

Dolorès Edmont, Jacques Chenault*

Institut de Chimie Organique et Analytique, Université d'Orléans, B.P. 6759, 45067 Orléans Cedex 2, France
Fax +33 2 3841-7281; E-mail: jacques.chenault@univ-orleans.fr
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Abstract: The selective *N*-alkylation of 4-oxo-1,4-dihydro-2-quinoline carboxylic acid has been achieved from 1,2-dihydro[1,4]oxazino[4,3-a]quinoline-4,6-dione by the 2-morpholinone ring opening. In the same time, we have developed a new methodology to obtain the 1,2-dihydro[1,4]oxazino[4,3-a]quinoline-4,6-dione that involves an intramolecular cyclization of the 2-chloroethyl 6-fluoro-4-oxo-1,4-dihydro-2-quinoline carboxylate.

Key words: *N*-alkylation, heterocycles, quinolines, ring-opening, intramolecular cyclization

Quinolones, more known for their antibacterial activity, sometimes display hypoglycaemic activity. Indeed, according to Baker and Bramhall[1] in 1972, these molecules act on the glucose metabolic pathway.

Recent work[2] has clearly shown the efficacy of some quinolones for inhibiting the activity of the ATP-K^+ channel of the β cell pancreatic membrane, thereby inducing the production of insulin. These quinolones act according to a mechanism similar to that found with sulfonylureas.

Recently, we reported the in vivo activities of some quinolinoylguanidines,[3] and encouraged by these promising results, we therefore decided to investigate the structure / activity relationships of the *N*-[(2-quinolin)carbonyl]guanidines. We were interested in the selective introduction of a functional group at the nitrogen atom of 4-oxo-1,4-dihydro-2-quinoline carboxylic acid.

Historically *N*-alkyl quinoline-2-carboxylic acids have been obtained from *N*-alkyl anilines, using the method of Conrad and Limpach,[4] or from 2-amino acetophenones and derivatives, by condensation with diethyl oxalate using ethoxide as the base.[5] Nevertheless, these two methods only provide routes to derivatives with alkyl substituents such as isoamyl, propyl or ethyl because of the chemistry involved in the synthesis of the quinolinic skeleton and moderate yields are often obtained.

Previously, by using standard alkylation methodology of the quinoline ring using sodium hydride and iodomethane, Jaen et al.[6] obtained a mixture of *N*-alkylated and *O*-alkylated products in 22% and 78% yield, respectively. This reaction revealed that a competitive alkylation takes place due to the prototropic equilibrium shown in Scheme 1.

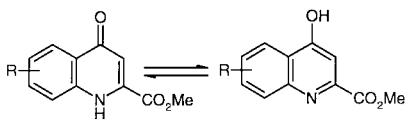
The key to the successful synthesis of these new *N*-alkylated quinolines lies in the preparation of the 8-fluoro-1,2-dihydro[1,4]oxazinoquinoline-1,4-dione **3** (Scheme 2).

The starting synthon **1** was obtained by condensation of dimethyl acetylene dicarboxylate with 4-fluoroaniline, followed by a cyclization in diphenylether at reflux, as described in a previous paper.[3] The intermediate[7] 2-chloroethyl 6-fluoro-4-oxo-1,4-dihydro-2-quinoline carboxylate **2**, was obtained by a simple transesterification with chloroethanol and a catalytic amount of sulfuric acid (Scheme 2). The intramolecular cyclization[8] of **2** was achieved in good yield using potassium carbonate in DMF at 100 °C. The structure of the tricyclic compound **3** has been confirmed by ^{1}H and ^{13}C NMR data of an identical structure 7,8,9,10-tetrafluoro-1,2-dihydro[1,4] oxazino[4,3-a]quinoline-4,6-dione obtained by Saloutin et al.[9] from ethyl pentafluorobenzoyl pyruvate (3 steps with an overall yield of 14%).

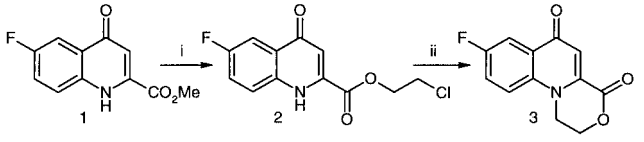
Using this method, we have optimized a new synthesis for 1,2-dihydro[1,4]oxazino[4,3-a] quinoline-4,6-dione; the route requires 4 steps from commercially available arylamines and the desired product is obtained with a yield three times that of existing methods (46%).

The introduction of the carbonylguanidine moiety was also envisaged based on ring opening of **3** with guanidine. However, even after refluxing for 72 hours, the nucleophilic substitution did not take place, with the starting material **3** being recovered unchanged (Scheme 3).

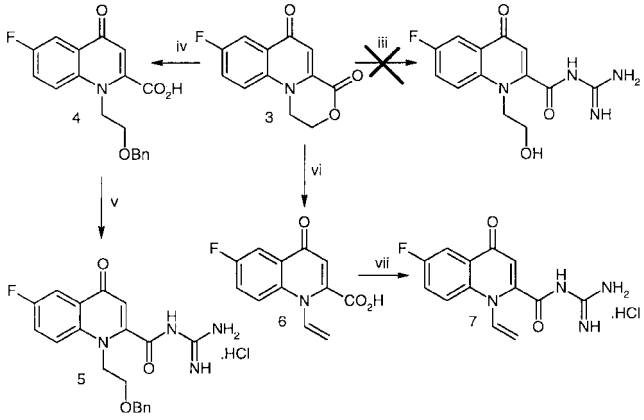
Since the 2-morpholinone ring of **3** was opened during saponification and recyclized under acidic conditions, it was possible to isolate the ring-opened form by addition of an excess of benzylbromide to the reaction mixture, followed by acidification with aqueous hydrochloric acid 3 N. This led to the selective introduction of an *N*-[2-(benzyloxy)] ethyl group[10] onto the quinoline nitrogen atom. An esterification[11] using iodoethane and potassium carbonate in DMF, followed by reaction with guanidine,[12] gave the desired *N*-[(2-quinolin)carbonyl]guanidine[13] compound **5**, isolated as its hydrochloride salt.



Scheme 1



Scheme 2 i) chloroethanol, sulfuric acid (cat), 77%; ii) K_2CO_3, DMF, 100 °C, 72%.



Scheme 3 iii) DMF, guanidine; iv) [a] NaOH 6 N, benzyl bromide, reflux; [b] HCl 3 N, 50%; v) [a] DMF, K_2CO_3, EtI, 50 °C, 89%; [b] DMF, guanidine, 24 h; [c] HCl 3 N, 62%; vi) [a] DMF, MeONa, 50 °C; [b] HCl 3 N, 79%; vii) [a] DMF, K_2CO_3, EtI, 50 °C, 76%; [b] DMF, guanidine, 24 h; [c] HCl 3 N, 72%.

We also introduced an *N*-vinylic group onto the quinoline nitrogen atom. The synthesis of **6** was developed based on ring opening of **3** with sodium methoxide.[14] The formation of this new compound **6** may be explained by a deprotonation at the alpha position to the nitrogen atom. As for compound **4**, an esterification[11] of **6**, followed by reaction with guanidine,[12] gave compound **7**.[13]

In summary, we have selectively alkylated the nitrogen atom of a 2-quinoline carboxylic acid via the ring opening of the 8-fluoro-1,2-dihydro [1,4]oxazino[4,3-a]quinoline-4,6-dione. The introduction of these two new functional groups, *N*-[2-(benzyloxy)]ethyl and *N*-vinyl, offer routes to a wide variety of further analogues in order to perform some structural modifications within the framework of our SAR studies. In addition, we have developed a new route to 1,2-dihydro [1,4]oxazino[4,3-a]quinoline-4,6-dione in 4 steps from commercially available arylamines with an overall yield of 46%. We are currently studying the 2-morpholinone-ring opening reaction using nucleophilic, electrophilic or reducing agents.

References and Notes

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(7) Typical experimental procedure for the transesterification: 3 g (13.57 mmol) of **1** in 50 mL of chloroethanol and 2 mL of sulfuric acid were stirred under reflux overnight. After evaporation of the solvent under vacuum, the residue was washed with water, filtered and dried under vacuum. ^{1}H NMR (250 MHz, DMSO-d_6) 12.24 (s, 1H, NH), 7.99 (dd, 1H, J = 5.0, 9.0 Hz, H-8), 7.69 (dd, 1H, J = 9.0, 3.0 Hz, H-5), 7.62 (ddd, 1H, J = 9.0, 10.0, 3.0 Hz, H-7), 6.70 (s, 1H, H-3), 4.60 (t, 2H, J = 5.0 Hz, OCH_2), 3.96 (t, 2H, J = 5.0 Hz, CH_2Cl). ^{13}C NMR (62.89 MHz, DMSO-d_6) 44.94, 68.83, 111.07, 111.46, 124.47, 129.12, 140.21, 141.14, 161.67, 164.68, 166.03, 178.01. Mass spectrum m/z (ionspray®): 270 (M^+, 100%), 272 (M^++2, 30%).
(8) Typical experimental procedure for the intramolecular cyclization: To a solution of 5.8 g of **2** in 174 mL of DMF, was added 3.4 g of potassium carbonate and the reaction mixture was stirred at 100 °C during 4 hours. After evaporation of the solvent, the residue was acidified with HCl 3 N and concentrated. The residue was dissolved in DMF, inorganic salts filtered and the DMF evaporated. Compound **3** was then filtered and washed with acetonitrile. ^{1}H NMR (250 MHz, DMSO-d_6) 7.95 (dd, 1H, J = 5.0, 9.0 Hz, H-8), 7.74-7.83 (m, 2H, H-5 and H-7), 6.74 (s, 1H, H-3), 4.76 (t, 2H, J = 5.0 Hz, OCH_2), 4.48 (t, 2H, J = 5.0 Hz, NCH_2). ^{13}C NMR (62.89 MHz, DMSO-d_6) 42.32, 64.95, 109.40, 110.87, 120.15, 121.91, 127.93, 136.35, 137.31, 158.95, 159.85, 175.33. Mass spectrum m/z (ionspray®): 234 (MH^+, 100%).
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(10) Procedure for **4**: 1.5 g of **3** in 13 mL of NaOH 6 N and 2.3 mL of benzyl bromide were stirred under reflux overnight. The reaction mixture was then acidified at 0 °C, and filtered. The precipitate was washed with water and diethyl ether. ^{1}H NMR (250 MHz, DMSO-d_6) 7.98 (dd, 1H, J = 4.0, 9.0 Hz, H-8), 7.78 (dd, 1H, J = 9.0, 3.0 Hz, H-5), 7.62 (ddd, 1H, J = 9.0, 9.5, 3.0 Hz, H-7), 7.07-7.18 (m, 5H, H_{arom}), 6.35 (s, 1H, H-3), 4.71 (t, 2H, J = 5.0 Hz, OCH_2), 4.35 (s, 2H, OCH_2Ar), 3.64 (t, 2H, J = 5.0 Hz, NCH_2). ^{13}C NMR (62.89 MHz, DMSO-d_6) 48.51, 68.09, 72.77, 110.33, 110.43, 122.00, 122.07, 127.87, 128.01, 128.92, 129.10, 138.17, 138.70, 147.64, 159.48, 165.87, 176.35. Mass spectrum m/z (ionspray®): 342 (MH^+, 100%).
(11) Typical procedure for the esterification: To a solution of 1 equiv of the acid in 2 mL of DMF, was added 3 equiv of potassium carbonate and the reaction mixture was stirred at room temperature during 1 hour. Then 0.2 mL of iodoethane was added and the reaction mixture was heated at 50 °C during 4 hours. After evaporation of the solvent, the crude product was extracted into CH_2Cl_2, which was washed with water, dried ($MgSO_4$) and evaporated. Purification was done by column chromatography (CH_2Cl_2).
(12) Typical procedure for the guanylation: To a solution of 1 equiv of the ester in 2.5 mL of DMF, was added 5 equiv of guanidine. After 24 hours at room temperature, the reaction mixture was added to 100 mL of cold water. The precipitate was then filtered, washed with water and dried under vacuum.

(13) The both new *N*-[(2-quinolin)carbonyl]guanidine **5** and **7** have been fully characterized by mp, IR, MS or ^{1}H and ^{13}C NMR spectra. The purities were found to be satisfactory for the pharmacological tests.

(14) Procedure for **6**: To a solution of 1 g of **3** in 9 mL of DMF, was added 400 mg of MeONa and the reaction mixture was then stirred for 3 hours at room temperature. The solvent was removed under vacuum and the residue was acidified with HCl 3 N. The precipitate was filtered, washed with water and dried under vacuum. ^{1}H NMR (250 MHz, DMSO-d_6) 7.77 (dd, 1H, J = 9.1, 3.14 Hz, H-5), 7.71 (dd, 1H, J = 4.71, 9.42 Hz, H-8), 7.58 (ddd, 1H, J = 9.42, 3.14, 9.16 Hz, H-7), 7.24 (dd, 1H, J = 15.07, 7.54 Hz, CH), 6.32 (s, 1H, H-3), 5.63 (dd, 1H, J = 7.54, 1.0 Hz, CH_2), 5.47 (dd, 1H, J = 15.07, 1.0 Hz, CH_2). ^{13}C NMR (62.89 MHz, DMSO-d_6) 108.57, 109.41, 118.60, 120.89, 121.35, 126.78, 134.43, 136.96, 145.55, 158.78, 164.04, 175.71. Mass spectrum m/z (ionspray®): 234 (M^+, 100%).

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