Reactions of N-Hydroxysuccinimide Esters of Anthranilic Acids with Anions of β-Keto Esters. A New Route to 4-Oxo-3-quinolinecarboxylic Acid Derivatives

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A new approach for the synthesis of 4-oxo-3-quinolinecarboxylic acid derivatives is described. This methodology involves the C-acylation of the anions of appropriate β-keto esters with novel N-hydroxysuccinimide esters of anthranilic acids. The intermediate C-acylation products 3 are spontaneously cyclized to afford 3-ethoxycarbonyl-4-oxoquinoline derivatives 4. The introduction of a variety of substituents at positions 1 and 2 of the quinoline ring is feasible with the selection of suitable anthranilic acids and β-keto esters. The structure of the obtained 2-substituted 3-ethoxycarbonyl-4-oxoquinolines was confirmed by IR and NMR spectral data.

Key words quinolones; N-hydroxysuccinimide esters; C-acylation reaction

4-Oxo-3-quinolinecarboxylic acid derivatives constitute a class of heterocyclic compounds of great importance in pharmaceutical science. The group of antibacterial agents collectively known as ‘quinolones,’ comprises quinoline and 1,8-naphthyridine derivatives containing the 4-oxo-3-carboxylic acid moiety. The synthesis and evaluation of antibacterial activity of related compounds is a field of continuing research in medicinal chemistry. Apart from their antimicrobial activity, 4-oxo-3-quinolinecarboxylic acid derivatives have shown anticoagulant and antitumor activity. The inhibition of calpain I by quinolinecarboxamides has been reported. The inhibition of human erythrocyte calpain I by quinolinecarboxamides has been reported. The antibacterial activity of related carboxamides, with or without a substituent at position 2, has also been examined. The antibacterial activity of tricyclic derivatives containing an N-1 to C-2 bridge has been studied in the past few years. 2-Substituted 4-hydroxy-3-quinolinecarboxamides have shown antiarthritic and analgesic activities and it was stated that the nature of the substituent at position 2 specifies the actual activity of these derivatives. A series of 3-quinolinecarboxamides has been designed as serotonin 5-HT₃ receptors antagonists.

Recently, we have established a convenient methodology for the construction of quinoline-2,4-dione derivatives, which involves the C-acylation of active methylene compounds with 3,1-benzoxazin-4-ones. A variety of 3-substituted 4-hydroxyquinolin-2-one derivatives, which have found attention lately as N-methyl-D-aspartate (NMDA) receptors antagonists, can be prepared according to this method. However, this approach is limited to N-unsubstituted analogues and we have failed to extend its applicability to the synthesis of 2-substituted 3-quinolinecarboxylic acid derivatives. In the literature, there have been relatively few investigations concerning the preparation of 2-substituted 3-quinolinecarboxylic acid derivatives. The most widely used method involves the reaction of isatoic anhydrides with β-keto esters and the cyclization of the intermediate C-acylation compounds. Although, this approach appears to be general, the use of polar solvents with high boiling points and elevated reaction temperatures are required. Nevertheless, the yields reported are low in many cases. Alternative active derivatives of anthranilic acids, capable of reacting with nucleophiles under mild conditions, would be very useful for the preparation of various heterocyclic compounds possessing interesting biological properties.

Results and Discussion

In the course of our studies concerning the synthesis of quinoline derivatives, we elected to prepare the N-hydroxysuccinimide (HOSu) esters of anthranilic acids 1a—c as starting materials in reactions with anions of β-keto esters to produce the 2-substituted 3-ethoxycarbonylquinolin-4-ones 4a—i, as outlined in Chart 1.

The HOSu esters of many N-protected α-amino acids have been prepared and found wide application in peptide synthesis. Especially, the HOSu ester of anthranilic acid (2a) has been found to be an efficient agent for 2-aminobenzoylation of amines. According to the literature preparation, condensation of anthranilic acid with HOSu in the presence of N,N’-dicyclohexylcarbodiimide (DCC) and a catalytic quantity of 4-dimethylaminopyridine resulted the HOSu ester 2a in 52% yield. Recrystallization from propanol-1 was necessary to obtain the product in acceptable purity. Several attempts made to optimise this procedure gave no satisfactory results. The low yield may be attributed to the formation of

\[
\text{HO}-\text{NHR}_1 + \text{RCO}_2\text{H} \rightarrow \text{RCO}_2\text{NHR}_1
\]

\[
\begin{array}{c}
\text{HO}-\text{NHR}_1 + \text{H} \rightarrow \text{HOSu ester of anthranilic acid (2a)}
\\
\text{HO}-\text{NHR}_1 + \text{Me} \rightarrow \text{Me ester of anthranilic acid (2b)}
\\
\text{HO}-\text{NHR}_1 + \text{Ph} \rightarrow \text{Ph ester of anthranilic acid (2c)}
\end{array}
\]

Chart 1

\[
\begin{array}{c}
\text{HO}_2\text{C} + \text{HC} = \text{C} (\text{HO}) \rightarrow \text{HOSu ester of anthranilic acid (2a)}
\\
\text{HO}_2\text{C} + \text{Me} \rightarrow \text{Me ester of anthranilic acid (2b)}
\\
\text{HO}_2\text{C} + \text{Ph} \rightarrow \text{Ph ester of anthranilic acid (2c)}
\end{array}
\]

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polyamide products due to partial intermolecular condensation of the active amino ester. In the case of the N-substituted anthranilic acids we expected that the secondary amino group would display low nucleophilicity and further protection prior the active ester formation would be unnecessary. Actually, application of a standard protocol involving the condensation of equimolar amounts of 1b (or 1c) and HOSu in the presence of 1 eq of DCC afforded the active ester 2b (or 2c) in high yield (88 and 76% for 2b and 2c respectively). The HOSu esters 2b and 2c produced with this procedure were pure solids and could be used without further purification. These products proved to be stable for a long period, even under storage at room temperature.

The reactions of active esters 2a—c with anions of β-keto esters were performed using a three-fold excess of the β-keto ester and sodium hydride (method A). At least one eq excess of the anion is required to react with the highly acidic methine proton of the tricarbonyl compounds 3. Under these conditions the C-acylation products 3 undergo spontaneous cyclization to the desired quinolones 4. This cyclization clearly involves attack of the amine nucleophile to the ketonic group of the intermediate 3 and subsequent dehydration produces 3-ethoxycarbonyl-4-oxoquinolines 4. The alternative reaction path involving attack at the ester carbonyl of the intermediate 3 would afford 3-acyl-4-hydroxyquinolin-2-ones. However, formation of quinolin-2-ones was not observed. The N-substituted 4-oxoquinolines 4d—i were isolated by evaporation of the solvent in vacuo after washing the reaction mixture with water to remove the water-soluble byproduct HOSu and the excess of the β-keto ester. Quinolones 4a—c possessing an acidic proton were extracted in water and precipitated after acidification of the aqueous extract. Attempts to isolate intermediates 3 were unsuccessful. These compounds may be water-soluble or unstable to the work-up procedure.

Under the conditions mentioned above, reasonable yields of quinolin-4-ones 4 were obtained only after prolonged reaction times. Modification of the reaction conditions in the case of the N-phenyl active ester 2c resulted in the formation of quinolones 4g—i in shorter reaction times (method B). Thus, ester 2c was stirred with 2.2 eq of the anion of ethyl acetooacetate at room temperature for 2 h, then the temperature was raised slowly to 80 °C and the mixture refluxed for 1 h. Work-up afforded compound 4g in good yield. The obtained yields are summarized in Table 1.

Although compounds 4d—i, bearing a substituent on N-1, clearly possess a 4-oxoquinoline structure, compounds 4a—c may also adopt the tautomeric 4-hydroxyquinoline structure as shown in Fig. 1.

The structure of compounds 4a—i was established based on IR and NMR spectral data. The IR spectra of compounds 4d—i in Nujol show absorptions at 1710—1730 cm⁻¹ for the ester carbonyl and 1620 cm⁻¹ for the ring carbonyl, as expected for their 3-ethoxycarbonyl-4-oxoquinoline structure. The presence of similar absorptions at 1710—1720 cm⁻¹ and 1630—1640 cm⁻¹ for compounds 4a—c, indicates a 4-quinoline structure for these derivatives, as well. This assignment is in agreement with previously published structural studies of related N-unsubstituted derivatives.

The structure of quinolones 4a—i in solution was studied by 1H- and 13C-NMR spectroscopy. The proton NMR spectra of compounds 4a—c exhibit a broad signal approximately at 12 ppm which can be assigned either as a OH or an enolic OH proton of the 4-oxo- or 4-hydroxyquinoline form, respectively. Although, proton NMR spectral data do not serve to discriminate the two possible tautomeric forms, 13C-NMR data (see Table 2) indicate the existence of compounds 4a—c in the 4-oxoquinoline form in solution. The 13C chemical shifts of 4a—c have no significant difference from the corresponding N-substituted compounds indicating a similar structure for all these compounds. Furthermore, the C-4a signals of compounds 4a—c appear approximately at 125 ppm, a value representative of 4-oxoquinoline derivatives.

**Table 1. 3-Ethoxycarbonyl-4-oxoquinolines Obtained with the New Methodology**

<table>
<thead>
<tr>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>Method</th>
<th>Yield (%)</th>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>Method</th>
<th>Yield (%)</th>
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<tr>
<td>4a</td>
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<td>A</td>
<td>34</td>
<td>4g</td>
<td>Ph</td>
<td>Me</td>
<td>A</td>
<td>65</td>
</tr>
<tr>
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<td>H</td>
<td>Pr⁵</td>
<td>A</td>
<td>28</td>
<td>4g</td>
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<td>B</td>
<td>72</td>
</tr>
<tr>
<td>4c</td>
<td>H</td>
<td>Ph</td>
<td>A</td>
<td>13</td>
<td>4h</td>
<td>Ph</td>
<td>Pr⁵</td>
<td>A</td>
<td>55</td>
</tr>
<tr>
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<td>M</td>
<td>Me</td>
<td>A</td>
<td>26</td>
<td>4h</td>
<td>Ph</td>
<td>Pr⁵</td>
<td>B</td>
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</tr>
<tr>
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<td>Me</td>
<td>Ph</td>
<td>A</td>
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<td>4i</td>
<td>Ph</td>
<td>Ph</td>
<td>B</td>
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</tr>
</tbody>
</table>

**Fig. 1**

4-Oxoquinoline 4-Hydroxyquinoline

In summary, the synthetically and biologically interesting title compounds can be prepared in one step under mild conditions and in good yields. The proposed methodology provides useful intermediates for the synthesis of more complex substrates in the "quinolone" series.

**Experimental**

Melting points were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 267 spectrometer. The NMR spectra were recorded on a Gemini-2000 300 MHz spectrometer. Chemical shifts are quoted in ppm (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, m=multiplet).

**2-Aminobenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester 2a** Following the literature procedure the title compound was obtained in 42% yield as a yellow solid, mp 158—162 °C (from 1-propanol) (lit. mp 161.5—163 °C). IR (Nujol) cm⁻¹: 3480 (νO, ester and imide), 1730 (C=O). NMR (CDCl₃): δ: 2.89 [4H, s, (CH₂)₂], 3.65 (2H, s, NH₂), 6.64—6.70 (2H, m, 5-H, 3-H), 7.35 (1H, pseudotriplet, 4-H), 7.97 (1H, dd, J₁,₂=8.8 Hz, J₂,₃=1.5 Hz, 6-H). 13C-NMR (CDCl₃): δ: 25.5 (CH₂), 105.1 (C-1), 116.7, 116.8 (C-3, C-5), 131.2 (C-4), 136.3 (C-6), 151.9 (C-2), 162.8 (ArCO), 169.8 (CON).
2-Methylaminobenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester 2b A solution of DCC (2.5 mmol, 5.16 g) in 1,2-dimethoxyethane (DME) (15 ml) was added dropwise over a period of 20 min to a solution of N-methylanthranilic acid (2.5 mmol, 3.78 g) and HOSu (2.5 mmol, 2.88 g) in DME (50 ml) under cooling in an ice-water bath. The mixture was stirred at room temperature for 48 h and the precipitated solid was filtered off and washed with DME. The filtrate was evaporated in vacuo and the solid residue treated with diethyl ether, filtered off and washed with diethyl ether to afford compound 2b as a yellow solid (5.46 g, 88%), mp 142—146 °C.

**Method B:** The reaction mixture [compound 2a (0.94 g, 4.0 mmol), ethyl benzoylacetate (2.3 g, 15 mmol) and sodium hydride (55—60% sodium hydride in oil; 0.44 g, 10 mmol) in anhydrous benzene (40 ml)] was stirred for 3 d and worked-up according to procedure (a) to afford an oily residue which crystallized after standing at room temperature for 2—3 d.

**1.4-Dihydro-2-methyl-4-oxoquinoline-3-carboxylic Acid Ethyl Ester 4a** The reaction mixture [compound 2a (0.78 g, 3.3 mmol), ethyl acetacete (1.3 g, 10 mmol) and sodium hydride (55—60% sodium hydride in oil; 0.20 g, 5.0 mmol) in anhydrous benzene (30 ml)] was added dropwise over a period of 20 min to a solution of N-phenylanthranilic acid (2.5 mmol, 3.78 g) and HOSu (2.5 mmol, 2.88 g) in DME (80 ml) under cooling in an ice-water bath. The mixture was stirred at room temperature for 24 h and the precipitated solid was filtered off and washed with DME. The filtrate was evaporated in vacuo and the oily residue was treated with diethyl ether and the formed solid was filtered off and washed with diethyl ether to afford compound 2c as a green solid (5.92 g, 76%), mp 126—128 °C (from 2-propanol).

**Phenylaminoquinolone 2,5-Dioxopyrrolidin-1-yl Ester 2c** A solution of DCC (2.5 mmol, 5.16 g) in DME (15 ml) was added dropwise over a period of 20 min to a solution of N-phenylanthranilic acid (2.5 mmol, 3.54 g) and HOSu (2.5 mmol, 2.88 g) in DME (80 ml) under cooling in an ice-water bath. The mixture was stirred at room temperature for 24 h and the precipitated solid was filtered off and washed with DME. The filtrate was evaporated in vacuo, the oily residue treated with diethyl ether and the formed solid was filtered off and washed with diethyl ether to afford compound 2c as a green solid (5.46 g, 88%), mp 142—146 °C. Anal. Calcd for C_{18}H_{15}NO_{3}: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.68; H, 5.12; N, 4.80. IR (Nujol) cm⁻¹: 1720 (C=O, ester), 7.34 (1H, s, NH), 7.0 Hz, CH₂CH₂CH₃), 2.37 (3H, s, CH₃), 4.21 (2H, q, J = 7.0 Hz, OCH₂CH₃), 7.32 (1H, pseudotriplet, 6-H), 7.51 (1H, d, J₆₇ = 8.2 Hz, 8-H), 7.65 (1H, pseudotriplet, 7-H), 8.04 (1H, dd, J₇₈ = 7.9 Hz, J₆₇ = 1.3 Hz, 5-H), 11.85 (1H, s, NH). **1.4-Dihydro-4-oxo-2-propylquinolinone-3-carboxylic Acid Ethyl Ester 4b** The reaction mixture [compound 2a (1.18 g, 5.0 mmol), ethyl butyralacetate (2.83 g, 15 mmol) and sodium hydride (55—60% sodium hydride in oil; 0.65 g, 15 mmol) in anhydrous benzene (45 ml)] was stirred for 2 d and worked-up according to procedure (a) to afford compound 4b as a white solid (0.36 g, 28%), mp 215—216 °C (from dichloromethane-light petroleum). Anal. Calcd for C_{19}H_{17}NO₂: C, 74.58; H, 6.61; N, 5.40. Found: C, 74.48; H, 6.61; N, 5.38. IR (Nujol) cm⁻¹: 1720 (C=O, ester), 1630 (C=O, ketone), 1610 (C=O, ketone). **1H-NMR (CDCl₃) δ: 0.88 (3H, t, J = 7.9 Hz, CH₂CH₂CH₃), 3.72 (1H, pseudotriplet, 6-H), 7.51 (1H, d, J₆₇ = 8.2 Hz, 8-H), 7.65 (1H, pseudotriplet, 7-H), 8.04 (1H, dd, J₇₈ = 7.9 Hz, J₆₇ = 1.3 Hz, 5-H), 11.85 (1H, s, NH).**
1,4-Dihydro-1-methyl-4-oxo-2-propylquinoline-3-carboxylic Acid

Ester 4e The reaction mixture [compound 2b (0.62 g, 2.5 mmol), ethyl butyrylacetate (1.20 g, 7.6 mmol) and sodium hydride (55—60% sodium hydride in oil; 0.33 g, 7.6 mmol) in anhydrous benzene (30 ml)] was stirred for 3 d and worked-up according to procedure (b) to afford the title compound as a beige solid (0.56 g, 60%).

1,4-Dihydro-1-methyl-4-oxo-2-phenylquinoline-3-carboxylic Acid Ethyl Ester 4f The reaction mixture [compound 2b (0.62 g, 2.5 mmol), ethyl benzoylacetate (0.43 g, 2.2 mmol) and sodium hydride (50—60% sodium hydride in oil; 0.33 g, 6.6 mmol) in anhydrous benzene (30 ml)] was stirred at room temperature for 2 h and under reflux for 1 h. Work-up according to procedure (b) afforded the title compound as a white solid (0.78 g, 2.5 mmol), mp 222—223°C (from diethyl ether). Anal. Calc. For C20H17NO3: C, 78.16; H, 5.19; N, 3.91. IR (Nujol) cm⁻¹: 3410 (OH), 1720 (C=O, ester), 1620 (C=O, ketone), 1600 (C=C). 1H-NMR (CDCl₃) δ: 7.28—7.51 (6H, m, 6-H, 7-H, 2-Ph, NPh), 7.72—7.85 (1H, m, 7-H, NPh), 8.45 (1H, dd, J=7.8 Hz, J=5.5 Hz, 5-H).

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References