A New Facile Synthesis of 4-Oxo-1,4-dihydrocinnolines

Clara Baldoli, Emanuela Licandro,* Stefano Mairoana, Ernesto Menta,1 Antonio Papagni*

Dipartimento di Chimica Organica e Industriale dell'Università. Via Goli 19, I-20133 Milano, Italy

2-(2-Aminoaryl)-2-oxo-triphenylphosphoniumyldienes 2a–d, readily available by standard procedures, are converted into 4-oxo-1,4-dihydrocinnolines 7a–d by treatment with nitrous acid and subsequent basic hydrolysis of the intermediate phosphoranes 6a–d.

Several methods for the synthesis of 4-oxo-1,4-dihydrocinnolines derivatives are reported in the literature. Those involving intramolecular cyclization of ortho-acyl and ortho-alkynyl substituted aryl diazonium ions are the usual preparative methods for these classes of compounds.2 However the above syntheses depend on the availability of such starting materials as o-aminophenylpropionic acids or o-aminocacetophenones, few of which are readily available.

We became engaged in the synthesis of 4-oxo-1,4-dihydrocinnolines due to the pharmacological importance of some of them3 and thus we needed a method to synthesize the 4-oxo-1,4-dihydrocinnoline ring system starting from easily available raw materials. In connection with our studies on arylazomethylene-triphenylphosphoranes we were aware that the coupling of diazonium ions with stabilized phosphoranes leads to the formation of a carbon-nitrogen bond and results in compounds A.4

\[
\text{ArN}_3^+ + \text{R} \rightarrow \underset{\text{Ar}}{\text{N}} - \underset{\text{P(C6H5)_3}}{\text{N}} \rightarrow \text{A}
\]

We report here that such a reaction, when applied intramolecularly to arenediazonium ions arising from appropriately built amines 2a–d, conveniently affords the intermediates 6a–d; which on hydrolysis give 4-oxo-1,4-dihydrocinnolines derivatives 7a–d (Scheme C). Compounds 2a–d were prepared in good yield by two different routes (Schemes A and B).

\[
1a-c \\
1-2 \quad R^1 \quad R^2 \quad R^3 \\
a \quad H \quad H \quad H \\
b \quad H \quad -\text{OCH}_3 \quad - \\
c \quad \text{CH}_3 \quad H \quad H \\
\]

Scheme A

As outlined in Scheme A, 2-amino-benzoic acid methyl esters 1a–c were reacted with the “in situ” generated methylenetriphenylphosphorane to give 2a–c (Table 1). The acylation of methylenetriphenylphosphorane using acylchlorides is a well known procedure5 while the reaction using esters seems to be less common.6 Such a method, which appears to have synthetic potential, is particularly useful when amino groups are present, as described here. Alternatively (Scheme B) the reaction of o-nitroaroyl chloride 3a, c, d with i-butoxycarbonylmethylenetriphenylphosphorane afforded compounds 4a, c, d (Table 2); acidic hydrolysis and decarboxylation of the i-butoxycarbonyl group gave compounds 5a, c, d (Table 2). Reduction of the nitro
Table 1. 2-(Aminoaryl)-2-oxo-triphenylphosphonium methyldides 2a-d Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Method</th>
<th>Yield (%)</th>
<th>m.p. (°C) (solvent)</th>
<th>Molecular Formula</th>
<th>1H-NMR (CDCl3/TMS) δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>A</td>
<td>70</td>
<td>161-162 (C2H2OH)</td>
<td>C20H22N2OP</td>
<td>4.15 (d, 1H, H-2); J2.3 = 24 Hz; 5.6 (br, s, 2H, H-3, H-5); 6.8-7.1 (m, 2H, H-4); 7.2-7.8 (m, 15H) + H-6</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>A</td>
<td>60</td>
<td>143-145 (C2H2OH)</td>
<td>C20H22N2OP</td>
<td>4.1 (br d, 1H, H-2); J2.3 = 24 Hz; 5.7 (br s, 2H, H-3, H-5); 6.1 (s, 1H, H-4); 7.1-7.8 (m, 15H) + H-6</td>
</tr>
<tr>
<td>2c</td>
<td>A</td>
<td>165</td>
<td>182-183 (C2H2OH)</td>
<td>C20H22N2OP</td>
<td>2.1 (s, 3H, CH3); 4.3 (br d, 1H, H-2); J2.3 = 24 Hz; 5.8 (br s, 2H, H-3, H-5); 6.5 (d, 1H, H-5); 7.05 (dd, 1H, H-4, J2.3 = 8 Hz, J6.7 = 1 Hz); 7.3-8.0 (m, 15H) + H-6</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>B</td>
<td>67</td>
<td>134-135 (t-C2H2OH)</td>
<td>C20H22N2OP</td>
<td>4.2 (br d, 1H, H-2); J2.3 = 24 Hz; 5.6 (br s, 2H, H-3, H-5); 6.45 (d, 1H, H-3, J2.3 = 9 Hz); 7.0 (dd, 1H, H-4, J2.3 = 8 Hz, J6.7 = 2.5 Hz); 7.3-8.0 (m, 15H) + H-6</td>
</tr>
</tbody>
</table>

a Melting points are uncorrected.
b Satisfactory microanalyses obtained: C ± 0.4, H ± 0.2, N ± 0.3.
c Recorded on a Varian EM 390 spectrometer.

Table 2. 2-(Nitroaryl)-2-oxo-triphenylphosphoniumalkylides 4a, c, d and 5a, c, d Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>m.p. (°C) (solvent)</th>
<th>Molecular Formula</th>
<th>1H-NMR (CDCl3/TMS) δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>88</td>
<td>195-196 (CH2OH)</td>
<td>C20H22N2O6P</td>
<td>0.9 [s, 8H, C(CH2)2]; 7.1-8.1 (m, 19H) + H-6</td>
</tr>
<tr>
<td>4c</td>
<td>72</td>
<td>179-190 (CH2OH)</td>
<td>C20H22N2O4P</td>
<td>0.9 [s, 8H, C(CH2)2]; 2.35 (s, 3H, CH3); 7.0-7.9 (m, 18H)</td>
</tr>
<tr>
<td>4d</td>
<td>82</td>
<td>213-214 (CH2OH)</td>
<td>C20H22N2O5P</td>
<td>0.9 [s, 9H, C(CH2)3]; 7.1-8.0 (m, 18H)</td>
</tr>
<tr>
<td>5a</td>
<td>92</td>
<td>161-162 (benzene)</td>
<td>C20H22N2O4P</td>
<td>7.1-7.8 (m, 19H) + H-6; 1H, CH=p</td>
</tr>
<tr>
<td>5c</td>
<td>91.5</td>
<td>178-180 (benzene)</td>
<td>C20H22N2O4P</td>
<td>2.4 (s, 3H, CH3); 7.0-7.8 (m, 18H) + H-6</td>
</tr>
<tr>
<td>5d</td>
<td>90</td>
<td>201-202 (CH2OH)</td>
<td>C20H22N2O4P</td>
<td>7.1-7.8 (m, 18H) + 1H, CH=p</td>
</tr>
</tbody>
</table>

a Melting points are uncorrected.
b Satisfactory microanalyses obtained: C ± 0.5, H ± 0.1, N ± 0.2.
c Recorded on a Varian EM 390 spectrometer.

Table 3. 4-Oxo-3-triphenylphosphoranylidene-3,4-dihydrocinnolines 6a-d Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>m.p. (°C) (solvent)</th>
<th>Molecular Formula</th>
<th>1H-NMR (CDCl3/TMS) δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>91</td>
<td>172-173 (CH2CN)</td>
<td>C20H22N2O5P</td>
<td>7.2-8.2 (m, 19H) + H-6</td>
</tr>
<tr>
<td>6b</td>
<td>78</td>
<td>240-241 (t-C2H2OH)</td>
<td>C20H22N2O5P</td>
<td>7.2-7.7 (m, 19H) + H-6</td>
</tr>
<tr>
<td>6c</td>
<td>68</td>
<td>213-214 (CH2CN)</td>
<td>C20H22N2O5P</td>
<td>2.9 (s, 3H, CH3); 7.2-8.1 (m, 18H)</td>
</tr>
<tr>
<td>6d</td>
<td>80</td>
<td>209-210 (dioxane)</td>
<td>C20H22N2O5P</td>
<td>7.2-8.3 (m, 18H)</td>
</tr>
</tbody>
</table>

a Melting points are uncorrected.
b Satisfactory microanalyses obtained: C ± 0.35, H ± 0.2, N ± 0.3.
c Recorded on a Varian EM 390 spectrometer.

d Basic hydrolysis of phosphoranes 6a-d gave the 4-oxo-1,4-dihydrocinnolines derivatives 7a-d and triphenylphosphine oxide (Table 4).

It is noteworthy that the 1-(2-aminophenyl)-1,3-dioxo-2-alkylidenetriphenylphosphoranes 8, obtained by reduction of the corresponding nitrile compound, was not stable and cyclized spontaneously to give the 2,4-dioxo-1,2,3,4-tetrahydro-3-(triphenylphosphoranylidene)-quinoline 9.

![Image of chemical structure]

Anthrancic acid methyl ester 1a is commercially available. Compounds 1b, c were prepared as previously described.8,9
1-\textit{r}-Butoxy carbonyl-2-(2-nitroaryl)-2-oxo-triphenylphosphonium methylides 4a, c, d; General Procedure:

A solution of the appropriate \textit{o}-nitrorylchloride (3 (10 mmol) in dry benzene (10 ml) is slowly added to a solution of 1-butoxy carbonylmethyltriphenylphosphorane (7.3 g, 20 mmol) in dry benzene (30 ml). The resulting solution is kept at room temperature overnight. The precipitated 1-butoxy carbonylmethyltriphenylphosphorane hydrochloride is collected by filtration and the organic layer is washed with 5% sodium hydrogen carbonate solution (2×10 ml), dried with sodium sulfate and evaporated. The products are then purified by crystallization (Table 2).

Hydrolysis and Decarboxylation of 4a, c, d: 2-(2-Nitroaryl)-2-oxo-triphenylphosphonium methylides 5a, c, d; General Procedure:

To a solution of phosphonates 4a, c, d (5 mmol) in dichloromethane (10 ml), 85% sulfuric acid (2 ml) is added. After stirring for 3 h at room temperature, the solution is washed with 5% sodium hydrogen carbonate solution (2×75 ml), dried with sodium sulfate, and evaporated. From the residue, the phosphonates 5a, c, d are recovered by crystallization (Table 2).

2-(2-Aminoaryl)-2-oxo-triphenylphosphononethiates 2a–c; General Procedure:

Method A: To a stirred slurry of methyltriphenylphosphonium chloride (1.2 g, 10 mmol) and sodium amide (1.57 g, 40 mmol) in anhydrous benzene (120 ml) under nitrogen with stirring at room temperature overnight, a solution of antrilinic acid methyl esters (15 mmol) in anhydrous benzene (20 ml) is added. The resulting mixture is kept at 50°C for 6 h. Sodium iodide is then filtered off at room temperature and the solvent evaporated. From the crude residue the compounds 2a–c are recovered as solid compounds by treatments with a little benzene at room temperature and purified by crystallization (Table 1).

Method B: Tin(II) chloride dihydrate (5.64 g, 25 mmol) is added to a solution of \textit{o}-nitroaryl)methyltriphenylphosphoranes 5a, c, d (5 mmol) in ethyl acetate (40 ml). After refluxing for 3 h, the mixture is allowed to cool to room temperature, made alkaline with concentrated ammonia and extracted with benzene (2×50 ml). The organic layer is then dried with sodium sulfate and evaporated. From the crude residue the phosphonates 2a, c, d are recovered by crystallization (Table 1).

4-Oxo-3-triphenylphosphorylidenes-3,4-dihydroquinolines 6a–d; General Procedure:

To a solution of phosphonates 2a–d (5 mmol) in methanol (10 ml) and 36% hydrochloric acid (0.3 ml), 4-methylimidazole (1.12 g, 9.5 mmol) is added in 10 min at 0°C. After 15 min the solution is allowed to warm to room temperature, made alkaline (pH = 8–9) with 10% aqueous sodium hydroxide, diluted with water (40 ml) and extracted with chloroform (2×30 ml). The organic layer is dried with sodium sulfate and evaporated. The products are collected by filtration after treatment of the crude residue with ether and purified by crystallization (Table 3).

4-Oxo-1,4-dihydroquinolines 7a–d; General Procedure:

A solution of 3-triphenylphosphoranylidene-4\(1\)H-dioxoquinolines 6a–d (1 mmol) in methanol (10 ml) and 30% sodium hydroxide (1 ml) is refluxed for 2 h. Methanol is evaporated, the residue treated with water and the tripodheyphosphate oxide is extracted with dichloromethane (2×20 ml). The aqueous layer is then treated with 10% hydrochloric acid (3.5 ml) and the \(4(1)\)H-dioxo-quinolines 7a–d collected by filtration. The products are then purified by crystallization (Table 4).

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(1) Present affiliation, Boehringer Biochimia Robin S.p.A., Via Uguzzoni 5, I-20126 Milano, Italy.
(3) See for example C. A. 1970, 73, 77269.