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

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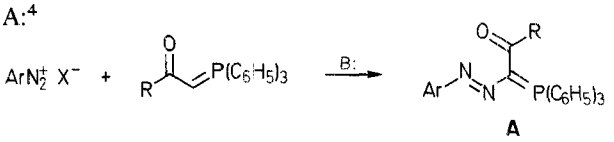
2-(2-Aminoaryl)-2-oxo-triphenylphosphoniumethylides **2a–d**, readily available by standard procedures, are converted into 4-oxo-1,4-dihydrocinnolines **7a–d** by treatment with nitrous acid and subsequent basic hydrolysis of the intermediate phosphoranes **6a–d.**

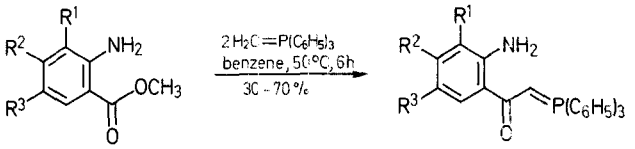
Several methods for the synthesis of 4-oxo-1,4-dihydrocinnolines derivatives are reported in the literature. Those involving intramolecular cyclization of *ortho*-acyl and *ortho*-alkynyl substituted aryl diazonium ions are the usual preparative methods for these classes of compounds.[2] However the above syntheses depend on the availability of such starting materials as *o*-aminophenylpropiolic acids or *o*-aminoacetophenones, 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 them[3] 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 arylazomethylenetriphenylphosphoranes 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]



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**).

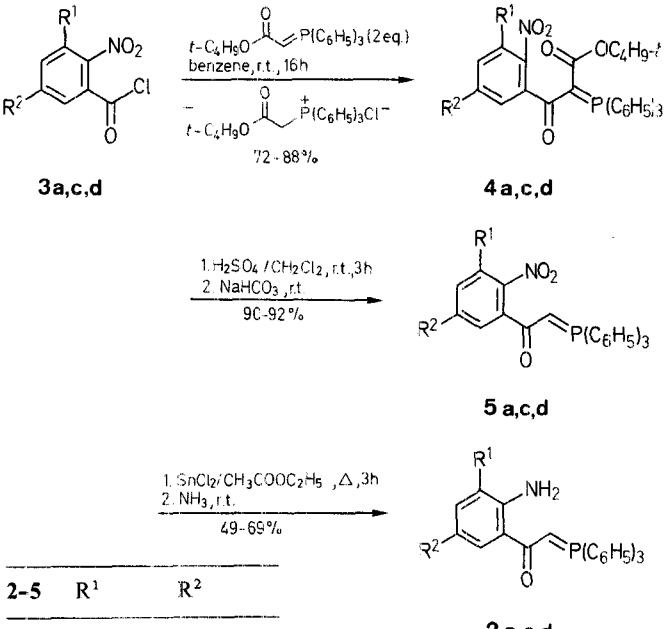


1a–c **2a–c**

1-2	R^1	R^2	R^3
a	H	H	H
b	H	$-OCH_2O-$	
c	CH_3	H	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 procedure[5] 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*-nitroaryloyl chlorides **3a, c, d** with *t*-butoxycarbonylmethylenetriphenylphosphorane afforded compounds **4a, c, d** (Table 2); acidic hydrolysis and decarboxylation of the t-butoxycarbonyl group gave compounds **5a, c, d** (Table 2). Reduction of the nitro



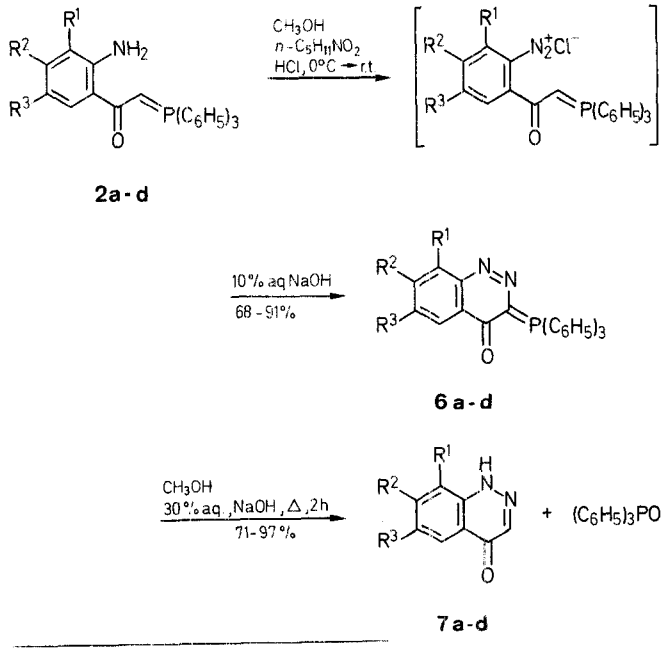
3a,c,d **4a,c,d** **5a,c,d** **2a,c,d**

2-5	R^1	R^2
a	H	H
c	CH_3	H
d	H	Cl

Scheme **B**

substituent with $SnCl_2$ led to compounds **2a, c, d** (Table 1). Overall yields of reactions reported in Schemes A and B are comparable, however *t*-butoxycarbonylmethylenetriphenylphosphorane is easier to handle and store than methylenetriphenylphosphorane.

2-(2-Aminoaryl)-2-oxo-triphenylphosphoniumethylides **2a–d** thus prepared were very easily transformed into compounds **6a–d** (Table 3) by a spontaneous intramolecular coupling of the corresponding intermediates, the diazonium ions (Scheme **C**).



2a-d **6a-d** **7a-d**

6-7	R^1	R^2	R^3
a	H	H	H
b	H	$-OCH_2O-$	
c	CH_3	H	H
d	H	H	Cl

Scheme **C**

Table 1. 2-(2-Aminoaryl)-2-oxo-triphenylphosphoniumethylides **2a–d** Prepared

Product	Method	Yield (%)	m.p. (°C)[a] (solvent)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ (ppm)
2a	A	70	161–162 (C_2H_5OH)	$C_{26}H_{22}NOP$ (395.4)	4.15 (d, 1H, –CH=P, J_{HP} = 24 Hz); 5.6 (br s, 2H, $-NH_2$); 6.3–6.6 (m, 2H, H-3, H-5); 6.8–7.1 (m, 1H, H-4); 7.2–7.8 (m, 15H_{arom} + H-6)
	B	69			
2b	A	60	143–145 (C_2H_5OH)	$C_{27}H_{22}NO_3P$ (437.4)	4.1 (br d, 1H, –CH=P, J_{HP} = 24 Hz); 5.7 (br s, 2H, $-NH_2$); 5.8 (s, 2H, $-O-CH_2-O-$); 6.1 (s, 1H, H-3); 7.1–7.8 (m, 15H_{arom} + H-6)
2c	A	165	182–183 (C_2H_5OH)	$C_{27}H_{24}NOP$ (407.4)	2.1 (s, 3H, CH_3-3); 4.3 (br d, 1H, –CH=P, J_{HP} 24 Hz); 5.8 (br s, 2H, $-NH_2$); 6.5 (dd, 1H, H-5, $J_{5,6}$ = 9 Hz, $J_{5,4}$ = 8 Hz); 7.05 (dd, 1H, H-4, $J_{4,5}$ = 8 Hz, $J_{4,6}$ = 1 Hz); 7.3–8.0 (m, 15H_{arom} + H-6)
	B	49			
2d	B	67	134–135 (i-C_3H_7OH)	$C_{26}H_{21}ClNOP$ (427.8)	4.2 (br d, 1H, –CH=P, J_{HP} 24 Hz); 5.6 (br s, 2H, $-NH_2$); 6.45 (d, 1H, H-3, $J_{3,4}$ = 9 Hz); 7.0 (dd, 1H, H-4, $J_{4,3}$ = 9 Hz, $J_{4,6}$ = 2.5 Hz); 7.1–8.0 (m, 15H_{arom} + H-6)

[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-(2-Nitroaryl)-2-oxo-triphenylphosphoniumalkylides **4a, c, d** and **5a, c, d** Prepared

Product	Yield (%)	m.p. (°C)[a] (solvent)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ (ppm)
4a	88	195–196 (CH_3OH)	$C_{31}H_{28}NO_5P$ (525.5)	0.9 [s, 9H, $C(CH_3)_3$]; 7.1–8.1 (m, 19H_{arom})
4c	72	179–180 (CH_3OH)	$C_{32}H_{30}NO_5P$ (539.5)	0.9 [s, 9H, $C(CH_3)_3$]; 2.35 (s, 3H, CH_3); 7.0–7.9 (m, 18H_{arom})
4d	82	213–214 (CH_3OH)	$C_{31}H_{27}ClNO_5P$ (559.9)	0.9 [s, 9H, $C(CH_3)_3$]; 7.1–8.0 (m, 18H_{arom})
5a	92	161–162 (benzene)	$C_{26}H_{20}NO_3P$ (425.4)	7.1–7.8 (m, 19H_{arom}, 1H, CH=P)
5c	91.5	178–180 (benzene)	$C_{27}H_{22}NO_3P$ (439.4)	2.4 (s, 3H, CH_3); 7.0–7.8 (m, 18H_{arom}, 1H, CH=P)
5d	90	201–202 (CH_3OH)	$C_{26}H_{19}ClNO_3P$ (459.8)	7.1–7.8 (m, 18H_{arom} + 1H, CH=P)

[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

Product	Yield (%)	m.p. (°C)[a] (solvent)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ (ppm)
6a	91	172–173 (CH_3CN)	$C_{26}H_{19}N_2OP$ (405.8)	7.2–8.2 (m, 19H_{arom})
6b	78	240–241 (i-C_3H_7OH)	$C_{27}H_{19}N_2O_3P$ (450.4)	6.0 (s, 2H, $-OCH_2O-$); 7.2–7.7 (m, 17H_{arom})
6c	68	213–214 (CH_3CN)	$C_{27}H_{21}N_2OP$ (420.4)	2.9 (s, 3H, CH_3); 7.2–8.1 (m, 18H_{arom})
6d	80	209–210 (dioxane)	$C_{26}H_{18}ClN_2OP$ (440.9)	7.2–8.3 (m, 18H_{arom})

[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.

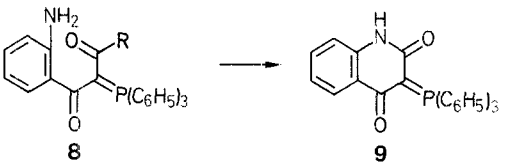
Table 4. 4-Oxo-1,4-dihydrocinnolines **7a–d** Prepared

Product	Yield (%)	m.p. (°C)[a] (solvent)	Molecular Formula or Lit. m.p. (°C)	^{1}H-NMR (Solvent/TMS)[b] δ (ppm)
7a	97	225–227 (CH_3OH)	225[4] 233.5–234[4]	(DMSO-d_6): 7.35–8.15 (m, 5H_{arom}); 13.5 (br s, 1H, OH)
7b	93	327–328 (dec) (AcOH)	316–318[4]	(DMSO-d_6): 6.3 (s, 2H, $-O-CH_2-O-$); 7.4 (s, 1H, H-8); 7.6 (s, 1H, H-5); 8.8 (s, 1H, H-3)
7c	78	219–221 (CH_3OH)	$C_9H_8N_2O$[c] (160.2)	(CF_3COOH): 3.0 (s, 3H, CH_3); 7.9–8.6 (m, 3H_{arom}); 9.15 (s, 1H, H-3)
7d	71	296–297 (CH_3OH)	294–295[4]	(DMSO-d_6): 3.2 (br s, 1H, OH); 7.3–7.9 (m, 4H_{arom})

[a] Melting points are uncorrected.
[b] Recorded on a Varian EM 390 spectrometer.
[c] calc. C 67.81 H 5.06 N 17.53
found 67.47 5.07 17.48

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-aminoaryl)-1,3-dioxo-2-alkylidenetriphenylphosphoranes **8**, obtained by reduction of the corresponding nitro compound, was not stable and cyclized spontaneously to give the 2,4-dioxo-1,2,3,4-tetrahydro-3-(triphenylphosphoranylidene)-quinoline **9**.[7]



8 **9**

Anthranilic acid methyl ester **1a** is commercially available. Compounds **1b, c** were prepared as previously described.[8,9]

1-*t*-Butoxycarbonyl-2-(2-nitroaryl)-2-oxo-triphenylphosphoniumethylides 4a, c, d; General Procedure:

A solution of the appropriate *o*-nitro-aryloylchloride **3** (10 mmol) in dry benzene (10 ml) is slowly added to a solution of *t*-butoxycarbonylmethylenetriphenylphosphorane (7.5 g, 20 mmol) in dry benzene (30 ml). The resulting solution is kept at room temperature overnight. The precipitated *t*-butoxycarbonylmethylenetriphenylphosphorane 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-triphenylphosphoniumethylides 5a, c, d; General Procedure:

To a solution of phosphoranes **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 hydrogencarbonate solution (2 × 75 ml), dried with sodium sulfate, and evaporated. From the residue, the phosphoranes **5a, c, d** are recovered by crystallization (Table 2).

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

Method A: To a stirred slurry of methylenetriphenylphosphoranes [prepared from methyl triphenylphosphonium iodide (12.2 g, 30 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 anthranilic 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 treatment 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 *o*-nitroaryloylmethylenephosphoranes **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 phosphoranes **2a, c, d** are recovered by crystallization (Table 1).

4-Oxo-3-triphenylphosphoranyliden-3,4-dihydrocinnolines 6a–d; General Procedure:

To a solution of phosphoranes **2a–d** (5 mmol) in methanol (10 ml) and 36% hydrochloric acid (0.5 ml), *n*-pentylnitrite (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-dihydrocinnolines 7a–d; General Procedure:

A solution of 3-triphenylphosphoranyliden-4(1 *H*)oxo-cinnolines **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 triphenylphosphine 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*)oxo-cinnolines **7a–d** collected by filtration. The products are then purified by crystallization (Table 4).

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