Synthesis of 1-Aryl-4-oxo-1*H*,4*H*-cinnoline-3-carboxylic Acid Esters

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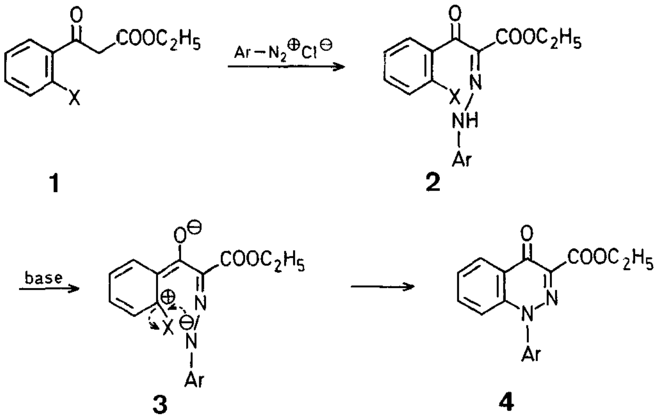
A useful synthesis of 1-aryl-4-oxo-1*H*,4*H*-cinnolines having a 3-acyl, 3-carboxylate, or similar 3-substituent has been described[1]. The β-keto ester (**1**; $X = NO_2$) was converted into phenylhydrazone (**2**; $X = NO_2$) by coupling with an arenediazonium salt. Treatment with aqueous ethanolic sodium carbonate solution gave the zwitterion (**3**; $X = NO_2$) and intramolecular nucleophilic attack led to displacement of nitrite ion and formation of cinnolone-ester **(4)**. We obtained more satisfactory results using anhydrous potassium carbonate in butan-2-one in the ester synthesis as aqueous conditions caused partial hydrolysis giving ester **(4a)** and some of the corresponding acid. Attempts to apply this procedure to 2,4-dichlorobenzenediazonium chloride were unsuccessful. The hydrazone **(2b)** could not be cyclised even under strongly basic conditions (e.g. with sodium hydride in *N*,*N*-dimethylacetamide) probably owing to steric factors and to deactivation of the intermediate ion by electron-withdrawing groups.

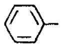
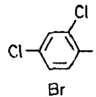
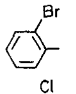
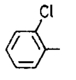
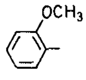
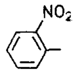
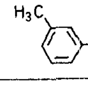
We have found that ethyl 2-fluorobenzoylacetate (**1**; X = F) is an excellent starting material as it can be prepared from commercially available 2-fluorobenzoyl chloride and diethyl ethoxymagnesiomalonate by Bowman's method[2] and it can safely be distilled without decomposition. Reaction with diazonium salts forms the corresponding arylhydrazones (**2**; X = F). Cyclisation of the zwitterions (**3**; X = F) occurs readily with potassium carbonate in refluxing butan-2-one to give products **(4)**. The strongly electron-attracting fluoride is a very good leaving group and steric hindrance to reaction is minimised. This procedure has given good yields of cinnolone-esters **(4a-g)** without isolation of the intermediate hydrazones (Table).



Ethyl 2-Fluorobenzoylacetate (1; X = F):
2-Fluorobenzoyl chloride (50 g) is condensed with diethyl ethoxymagnesiomalonate (from magnesium, 0.32 mol) in benzene as described by Bowman[2]. The isolated acylmalonate in acetic acid (200 ml) containing concentrated sulphuric acid (1.0 ml) is boiled gently for 80 min, cooled, and poured into ice/water (800 ml). Isolation with 1:1 benzene/petroleum ether (b.p. 40-60 °C) (3 x 200 ml) and fractional distillation gives ethyl 2-fluorobenzoylacetate; yield: 38.7 g (58%), b.p. 104-108 °C/3 torr (Lit.[3], b.p. 125 °C/1.5 torr).

Ethyl 1-(2,4-Dichlorophenyl)-4-oxo-1*H*,4*H*-cinnoline-3-carboxylate (4b); Typical Procedure:
2,4-Dichloroaniline (steam-distilled, dried, and finely powdered; 4.86 g, 0.03 mol) is dissolved in acetic acid (18 ml), water (9 ml), and concentrated hydrochloric acid (9 ml) by heating. The solution is cooled below 5 °C (hydrochloride precipitates) and diazotised by gradual addition of sodium nitrite solution (2.5 g) in water (10 ml). The diazonium salt solution is added over 15 min to an ice-cooled solution of sodium acetate (20 g, anhydrous) and the 2-fluoro-ester **1** (6.3 g, 0.03 mol) in ethanol (100 ml) and 1 molar sodium carbonate solution (200 ml). After the mixture has been stirred at about 0 °C for 2 h, it is diluted with water (500 ml) and rapidly extracted with ethyl acetate (3 x 150 ml). The combined extracts are washed with water (100 ml), dried with sodium sulphate, and evaporated in vacuo. Butan-2-one (100 ml) and potassium carbonate (anhydrous, 12 g) are added to the residue and the mixture is boiled under reflux for 6 h (bath 110 °C).

Table. Compounds **4a-g** prepared

Product No.	Ar	Yield[a] [%]	m.p. [°C][b]	Molecular formula[c] or Lit. m.p. [°C]	
a		76	154-156°	152°[1]	
b		64	127-129°	$C_{17}H_{12}N_2Cl_2O_3$	(363.2)
c		88	166-168°	$C_{17}H_{13}BrN_2O_3$	(373.2)
d		57	154-156°	$C_{17}H_{13}ClN_2O_3$	(328.7)
e		72	133-135°	$C_{18}H_{16}N_2O_4$	(324.3)
f		71	178-180°	$C_{17}H_{13}N_3O_5$	(339.3)
g		65	165-167°	$C_{18}H_{16}N_2O_3$	(308.3)

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[a] Yield of pure, isolated product, recrystallised from ethyl acetate.
[b] Not corrected.
[c] Satisfactory microanalyses obtained: C ±0.17, H ±0.10, N ±0.24.

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The mixture is filtered hot and the solid is washed with hot ethyl acetate (3 × 50 ml). Evaporation of the combined filtrates in vacuo, followed by addition of water (100 ml), filtration, and crystallisation from ethyl acetate, gives *ethyl 1-(2,4-dichlorophenyl)-4-oxo-1*H,*4*H*-cinnoline-3-carboxylate* **(4b)**; yield: 7.02 g (65%); m.p. 127–129 °C.

In one experiment, the solution after diazo-coupling is filtered and the crude hydrazone is washed with water. Recrystallisation from ethyl acetate gives *ethyl 3-(2-fluorophenyl)-2,3-dioxopropanoate 2-(2,4-dichlorophenylhydrazone)* **(2b)**; yield: 7.54 g (66%); yellow crystals; m.p. 121–123 °C.

$C_{17}H_{13}Cl_2FN_2O_3$	calc.	C 53.28	H 3.42	N 7.31
(383.2)	found	53.48	3.51	7.31

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[1] A. A. Sandison, G. Tennant, *J. Chem. Soc. Chem. Commun.* **1974**, 752.

[2] R. E. Bowman, *J. Chem. Soc.* **1950**, 322.

[3] W. F. Hoffstadt, *U. S. Patent* 3056675 (1962); *C. A.* **58**, 14172 (1963).

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