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# A New Cinnoline Ring Construction by the Reaction of 2-Diazo-3-(2-fluorophenyl)-3-oxopropionates with Tri-*n*-butylphosphine

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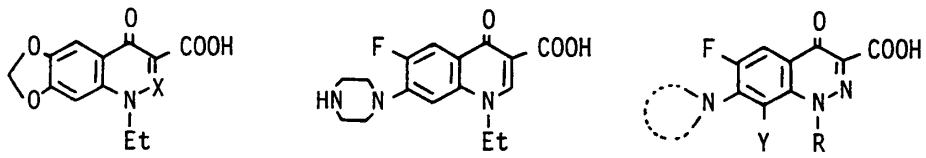
A new and convenient synthesis of 4-hydroxycinnoline-3-carboxylate derivatives was developed. Reactions of ethyl 2-diazo-3-(2,4,5-triflurophenyl- and 2,3,4,5-tetrafluorophenyl)-3-oxopropionates (**2a** and **2c**) with tri-*n*-butylphosphine afforded ethyl 6,7-difluoro- and 6,7,8-trifluoro-4-hydroxycinnoline-3-carboxylates (**5a** and **5c**) and ethyl 2-hydrazono-3-(2,4,5-trifluorophenyl- and 2,3,4,5-tetrafluorophenyl)-3-oxopropionates (**6a** and **6c**), respectively. When triphenylphosphine was used, the reaction of **2a**—**c** afforded [[1-ethoxycarbonyl-2-oxo-2-(halogenated phenyl)ethylidene]hydrazono]triphenylphosphoranes (**3a**—**c**), which were hydrolyzed to give the corresponding hydrazones **6a**—**c**. An alternate and efficient synthesis of **5a** and **5c** was accomplished by an intramolecular cyclization of **6a** and **6c**, respectively. A base-catalyzed cyclization of the methylhydrazone **7** gave ethyl 7-chloro-6-fluoro-1-methyl-1,4-dihydro-4-oxocinnoline-3-carboxylate (**8**). Possible mechanisms for the reaction of **2** leading to **5** are discussed.

**Keywords**——reductive cyclization; 2-diazo-3-oxopropionate; tri-*n*-butylphosphine; triphenylphosphine; phosphazine; ring construction; cinnoline

Oxolinic acid (Ia)[1] and norfloxacin (II),[2] which both contain a 4-oxoquinoline-3-carboxylic acid skeleton, are pyridonecarboxylic acid antibacterials with potent activity. On the other hand, cinoxacin (Ib),[3] the chemical structure of which is characterized by a 4-oxocinnoline-3-carboxylic acid moiety, also shows good antibacterial activity mainly against gram-negative bacteria. The activity and antibacterial spectrum of cinoxacin, however, are weaker and narrower than those of oxolinic acid and norfloxacin. We have been interested in the chemical modification of cinoxacin, in the hope of developing new antibacterial agents with improved activity.

The present study was undertaken to develop a new synthetic method for a cinnoline ring which could be converted to 7-substituted 1-alkyl-6-fluoro- and 6,8-difluoro-1,4,-dihydro-4-oxocinnoline-3-carboxylic acids (III).

With respect to direct synthesis of 4-hydroxycinnoline-3-carboxylic acid derivatives, three methods have been reported thus far: (i) the Richter synthesis[4] based on the



Ia: X = CH
Ib: X = N

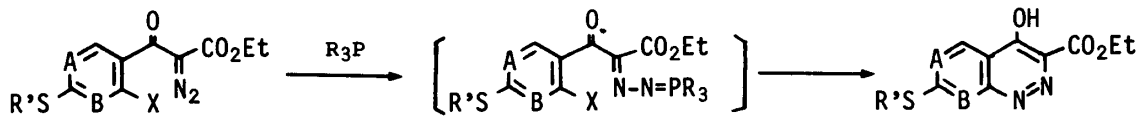
II

III: R = H, alkyl
Y = H, F

Chart 1

diazotization of *o*-aminophenylpropiolic acids, followed by cyclization, (ii) the Barber synthesis[5] based on the Friedel-Crafts cyclization of mesoxalyl chloride phenylhydrazone or α-carbethoxyglyoxylyl chloride *N*-substituted phenylhydrazone, and (iii) the synthesis by condensation of diethyl mesoxalate with α-alkyl substituted phenylhydrazone in the presence of polyphosphoric ester.[6] These methods have found only limited application. The usefulness of the Richter synthesis, for example, depends on the availability of the starting materials, *o*-aminophenylpropiolic acids, few of which are readily accessible. In the Barber synthesis, Shoup and Castle[7] demonstrated that two isomeric products, 5- and 7-substituted 4-hydroxycinnolines, were obtained from the cylization when a substituent was located at position 3 of the phenyl ring.

We had previously reported the fused pyridazine ring construction leading to pyrimido[4,5-*c*]pyridazines[8] and fluorinated pyrido[2,3-*c*]pyridazines[9] by using the reductive cyclization reaction of 2-diazo-3-(4-chloropyrimidin-5-yl)- and 3-(2,5-difluoropyridin-3-yl)-3-oxopropionates (IV) with triphenyl- and trialkylphosphines, respectively (Chart 2).




IV V VI

A = N, CF X = Cl, F
B = N R = Ph, *n*-Bu
R' = $CH_3$, *p*-$CH_3C_6H_4$

Chart 2

As an extension of our work, the previous methods[8,9] were applied to the reaction of ethyl 2-diazo-3-(2-fluorophenyl)-3-oxopropionates (**2**) with triphenyl- or trialkylphosphine, which would afford 4-hydroxycinnoline-3-carboxylates (**5**) required for the preparation of III. The requisite 2-diazo-3-oxopropionates **2a**—**c** were prepared from ethyl 3-(2,4,5-trihalophenyl- and 2,3,4,5-tetrafluorophenyl)-3-oxopropionates (**1a**—**c**) with tosyl azide. The reaction of **2** was examined with triphenylphosphine at first. When **2a** was allowed to react with triphenylphosphine in diisopropyl ether at room temperature, pale yellow precipitates gradually appeared during the course of the reaction. The precipitate was revealed to be the triphenylphosphazine **3a** from its infrared (IR) spectrum, which lacked the N≡N absorption band at 2150 $cm^{-1}$ observed in the spectrum of the diazo compound **2a**. The phosphazine **3a** was so labile in a solvent that it was converted into the hydrazone **6a** and triphenylphosphine oxide, partially through the recrystallization process and completely through silica gel column chromatography with chloroform. The same treatment of **2b** and **2c** with triphenylphosphine, followed by column chromatography of the intermediates **3b** and **3c** gave the hydrazones **6b** and **6c**, respectively. Alternatively, the conversion of **3a**—**c** to **6a**—**c** proceeded efficiently when **3a**—**c** were treated with a refluxing mixture of methanol and water. An attempted cyclization of **3a**—**c** into **5a**—**c** on refluxing with a solvent such as diisopropyl ether and dioxane was unsuccessful. This finding suggests that the triphenylphosphazine **3** would be less reactive.

On the other hand, tri-*n*-butylphosphine is stronger in both basicity and nucleophilicity than triphenylphosphine. It is expected, therefore, that the tributylphosphazine **4** which might be derived from **2** would be more reactive than the triphenylphosphazine **3** mentioned above, so that direct cyclization to the cinnoline derivative **5** might occur under mild conditions.

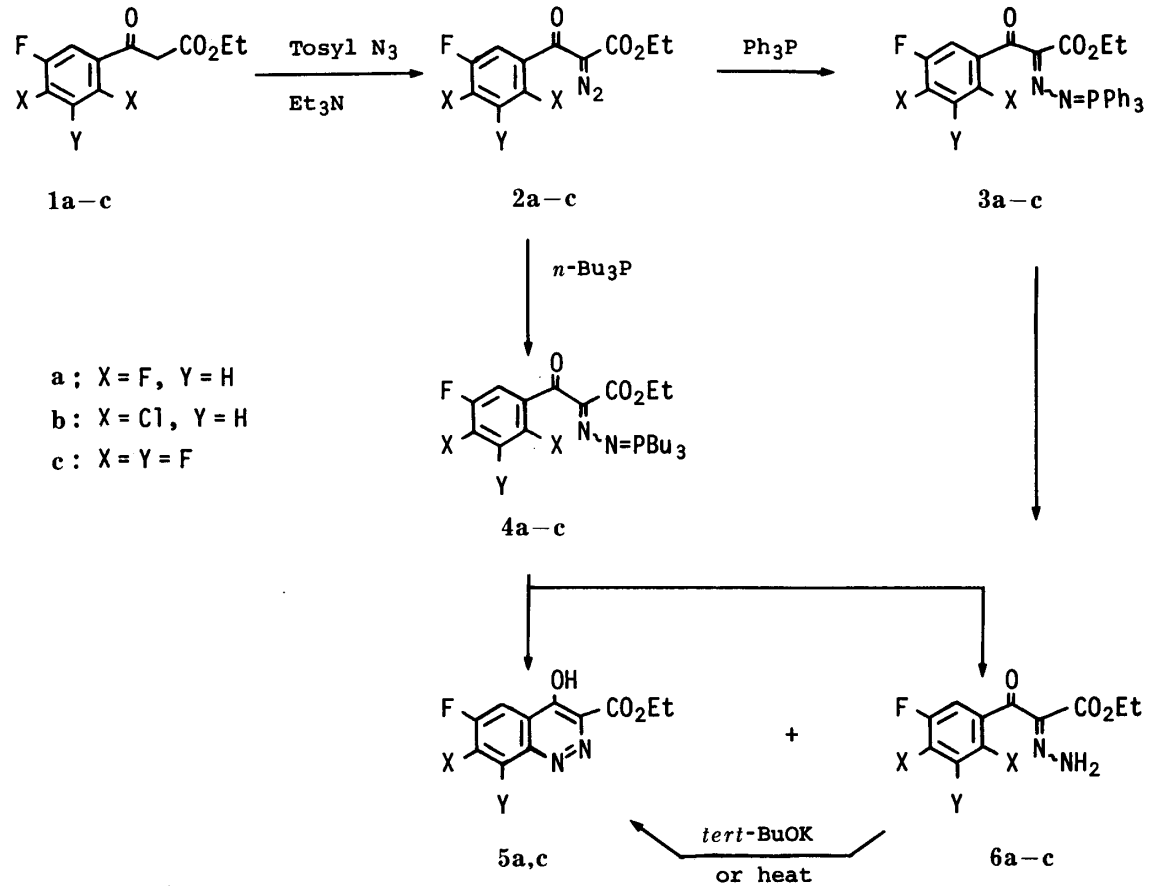



Chart 3

Treatment of **2a** with tributylphosphine in diisopropyl ether at room temperature, however, failed to give directly the expected **5a**, but yielded the intermediate tributylphosphazine **4a**, a yellow oil unstable to moisture. The phosphazine **4a** was converted smoothly into the hydrazone **6a** on silica gel chromatography. However, direct cyclization of **2a** into **5a** was effected by heating with tributylphosphine in diisopropyl ether for 7 h to give **5a** in 22% yield, together with **6a** in 51% yield and tributylphosphine oxide. The use of dioxane as a solvent in this reaction caused smooth cyclization in a shorter period (1.5 h) to give **5a** in 60% yield. Extension of the reaction time led to unfavorable results. The reaction of **2c** under almost the same conditions gave a 54% yeild of **5c**. In the case of **2b**, an attempted cyclization was unsuccessful, merely giving **6b**, probably owing to the lower reactivity of the C-2 position in the phenyl ring. The results of the reactions of **2a**—**c** with tributylphosphine, are summarized in Table I, which includes the reaction conditions and yields of the products. The assigned structures for **5a**, **c** and **6a**—**c** were confirmed by elemental analysis and spectroscopic evidence.

When the hydrazones **6a** and **6c** were heated in either dioxane or diglyme, an intramolecular cyclization occurred smoothly to give the cinnoline derivatives **5a** and **5c**, respectively. Thus, **6a** and **6c** (X = F), for example, were smoothly cyclized into **5a** and **5c** in 70 and 87% yields on refluxing in dioxane for 12 h and in diglyme for 3.5 h, respectively. Either extension of the reaction time or elevation of the reaction temperature led to an increase in yield. Regarding the reaction of **6b** (X = Cl), no reaction conditions leading to **5b** were found. The results are summarized in Table II showing the reaction conditions and yields of the products.

Alternatively, treatment of the hydrazone **6c** (X = F) with potassium *tert*-butoxide in

TABLE I. Reaction Conditions and Yields of Products in the Reaction of **2** with Tri-*n*-butylphosphine

| Starting compd. | Reaction conditions[a] | | Yields of products (%) | |
|---|---|---|---|---|
| | Solvent | Time (h) | **5a—c** | **6a—c** |
| **2a** | iso-$Pr_2O$ | 7 | 22.2 | 51.1 |
| **2a** | Dioxane | 1.5 | 60.2 | —[b] |
| **2b** | Dioxane | 2 | <1 | 87.2 |
| **2c** | iso-$Pr_2O$ | 10 | 44.1 | 18.3 |
| **2c** | Dioxane | 2 | 54.1 | —[b] |

*a*) The reaction mixture was stirred initially at room temperature for 30 min and then heated to reflux. *b*) A negligible yield.

TABLE II. Reaction Conditions and Yields of the Cinnolines **5** in Cyclization of the Hydrazones **6**

| Starting compd. | Reaction conditions[a] | | Yields of **5a—c** (%) |
|---|---|---|---|
| | Solvent | Time (h) | |
| **6a** | iso-$Pr_2O$ | 7 | 1.3 |
| **6a** | Dioxane | 5 | 29.4 |
| **6a** | Dioxane | 12 | 70.4 |
| **6a** | Diglyme | 4 | 64.2 |
| **6b** | Dioxane | 5 | —[b] |
| **6b** | Diglyme | 2 | —[b] |
| **6c** | iso-$Pr_2O$ | 8 | —[b] |
| **6c** | Dioxane | 6 | 18.8 |
| **6c** | Diglyme | 3.5 | 87.2 |

*a*) Compound **6** was heated to reflux in the solvent, except for diglyme, in which it was heated at 130—135 °C. *b*) A negligible yield.

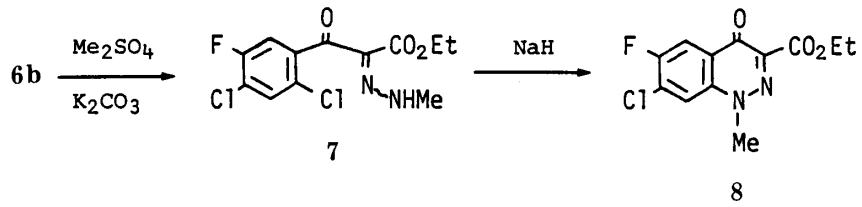



Chart 4

dioxane below 10 °C led to the cyclization, giving a 31% yield of the cinnoline **5c**, along with the ketoester **1c** and the diazo compound **2c**. The reaction of **6b** (X = Cl) with potassium *tert*-butoxide occurred exclusively through the Wolff–Kishner type process to give **1b** in 79% yield. On the other hand, when the methylhydrazone **7**, derived from the methylation of **6b** with dimethyl sulfate, was treated with sodium hydride in dioxane, ethyl 7-chloro-6-fluoro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylate (**8**) was obtained in 93% yield.

Possible mechanisms for the reaction of **2** (X = F) with tri-*n*-butylphosphine leading to **5** (X = F) are depicted in Chart 5. The diazo compound **2** reacts with tributylphosphine to form initially the tributylphosphazine **4**. The phosphazine **4** would be subjected to hydration to **9**, followed by elimination of tributylphosphine oxide to give the hydrazone **6**, which would finally undergo the ring closure to form **5**. Practically, the conversion of the isolated hydrazone **6** into **5** hardly proceeded on heating in boiling diisopropyl ether, whereas the reaction of **2** with tributylphosphine took place more easily, resulting in a 20—45% yield of **5**. These facts suggest that the route involving the hydrazone **6** may not be the principal one, but, probably, the intermediate **9** may concertedly undergo intramolecular cyclization, accompanied with elimination of phosphine oxide and hydrogen fluoride, to give **5** (path a). Another possible pathway might be the reaction sequence **4**→**10**→**11**→**5** (path b). Thus, the highly reactive phosphazine **4** would undergo cyclization into the phosphonium salt **10**, which would be hydrolyzed *via* **11** to give **5**.

As a result of the present work, a new and convenient synthesis of 4-hydroxycinnoline-3-carboxylates **5** was developed. Thus, the one-pot reaction of the diazo compound **2a** or **2c** (X = F) was effected by treatment with tributylphosphine to give **5a** or **5c**, respectively. An alternative preparation of **5a** and **5c** was accomplished by the intramolecular cy-

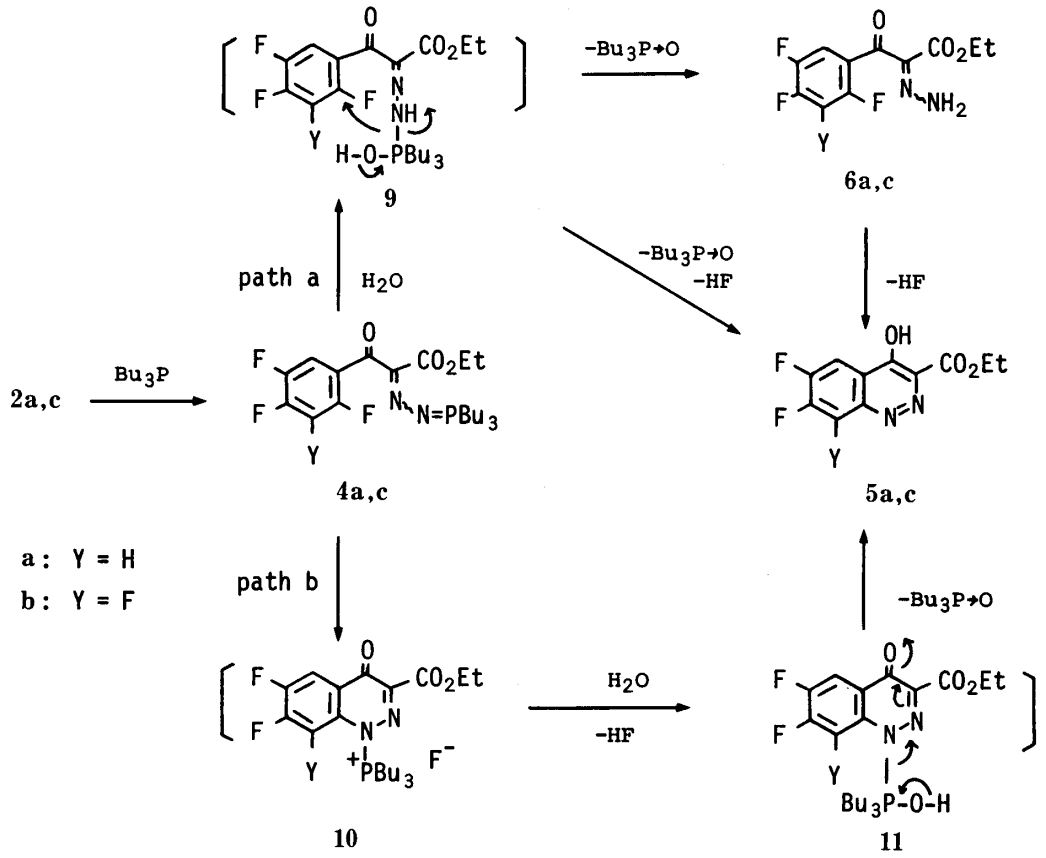



Chart 5

clization of the hydrazones **6a** and **6c**, respectively, derived stepwise from **2** *via* either **3** or **4**.

The synthesis and antibacterial activity of 7-substituted 1-alkyl-6-fluoro- and -6,8-difluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic acids (III, R = alkyl) obtained from **5a** and **5c** will be reported in a separate paper.

## Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Jasco A-102 spectrometer. Proton nuclear magnetic resonance ($^1$H-NMR) spectra were taken at 80 MHz with a Varian FT-80A spectrometer. Chemical shifts are expressed in $\delta$ (ppm) values with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi RMU-6 or JEOL JMSD-300 spectrometer. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-visible recording spectrophotometer UV-260 in EtOH.

**Ethyl 2-Diazo-3-(2,4,5-trifluorophenyl)-3-oxopropionate (2a)**——A solution of *p*-toluenesulfonyl azide (5.4 g, 27.4 mmol) in $CH_3CN$ (5 ml) was added at below 10 °C to a stirred solution of ethyl 2,4,5-trifluorobenzoylacetate[10] (**1a**) (6.15 g, 25 mmol) and triethylamine (4 ml, 28.9 mmol) in $CH_3CN$ (70 ml). The solution was stirred at below 10 °C for an additional 15 min and then at room temperature for 2 h. The mixture was concentrated to dryness *in vacuo* below 50 °C, then 2 N sodium hydroxide (25 ml) was added to the residue under ice-cooling. The mixture was extracted with $CHCl_3$. The extract was washed with water and dried over $Na_2SO_4$, and the $CHCl_3$ was evaporated off *in vacuo* below 50 °C. The oily residue was chromatographed on silica gel with hexane–$CHCl_3$ (10 : 1) as an eluent to give **2a** (6.15 g, 90.4%) as a colorless oil. *Anal.* Calcd for $C_{11}H_7F_3N_2O_3$: C, 48.54; H, 2.59; F, 20.94; N, 10.29. Found: C, 48.27; H, 2.57; F, 20.94; N, 10.27. IR (neat) $cm^{-1}$: 2150 (N≡N), 1720, 1630 (C=O). $^1$H-NMR ($CDCl_3$): 1.27 (3H, t, $J$ = 7.5 Hz, $CH_2C\underline{H}_3$), 4.25 (2H, q, $J$ = 7.5 Hz, $C\underline{H}_2CH_3$), 6.95 (1H, m, $J_{H,F}$ = 10, 10, 6 Hz, aromatic H), 7.30 (1H, m, $J_{H,F}$ = 10, 9, 6 Hz, aromatic H).

**Ethyl 2-Diazo-3-(2,4-dichloro-5-flurophenyl)-3-oxopropionate (2b)**——By a similar procedure to that used for **2a**, ethyl 2,4-dichloro-5-fluorobenzoylacetate (**1b**)[10] (5.58 g, 20 mmol) was converted to **2b** (5.67 g, 93%) as colorless prisms, mp 47—48 °C (hexane). *Anal.* Calcd for $C_{11}H_7Cl_2FN_2O_3$: C, 43.31; H, 2.31; Cl, 23.24; F, 6.23; N, 9.18. Found: c, 43.21; H, 2.13; Cl, 23.21; F, 6.43; N, 9.35. IR (KBr) $cm^{-1}$: 2125 (N≡N), 1710, 1630 (C=O). $^1$H-NMR

($CDCl_3$): 1.20 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 4.20 (2H, q, $J$=7.5 Hz, $C\underline{H}_2CH_3$), 7.08 (1H, d, $J$=8 Hz, aromatic H), 7.44 (1H, d, $J$=6 Hz, aromatic H).

**Ethyl 2-Diazo-3-(2,3,4,5-tetrafluorophenyl)-3-oxopropionate (2c)**——By a similar procedure to that used for **2a**, ethyl 2,3,4,5-tetrafluorobenzoylacetate (**1c**)[11] (10.0 g, 37.9 mmol) was converted to **2c** (9.72 g, 88.4%) as colorless prisms, mp 40.5 °C (hexane). *Anal.* Calcd for $C_{11}H_6F_4N_2O_3$: C, 45.53; H, 2.08; F, 26.19; N, 9.65. Found: C, 45.60; H, 2.13; F, 26.33; N, 9.69. IR (KBr) $cm^{-1}$: 2150 (N≡N), 1720, 1635 (C=O).

**[[1-Ethoxycarbonyl-2-(2,4,5-trifluorophenyl)-2-oxoethylidene]hydrazono]triphenylphosphorane (3a)**——Triphenylphosphine (2.80 g, 10.7 mmol) was added at room temperature to a stirred solution of **2a** (2.72 g, 10 mmol) in iso-$Pr_2O$ (50 ml). The mixture became a pale yellow solution. The solution was stirred for an additional 3 h, during which period yellow precipitates gradually appeared. The precipitates were collected by filtration to give **3a** (4.75 g, 89%) as yellow prisms, mp 100—100.5 °C. IR (KBr) $cm^{-1}$: 1715, 1635. Since further purification of **3a** was practically impossible owing to partial decomposition, the product **3a** was used in the next step without further purification.

**[[1-Ethoxycarbonyl-2-(2,4-dichloro-5-fluorophenyl)-2-oxoethylidene]hydrazono]triphenylphosphorane (3b)**——In a similar manner to that described for **3a**, **2b** (1.52 g, 5 mmol) was converted to **3b** (4.93 g, 87%) as pale yellow prisms, mp 80—81 °C. IR (KBr) $cm^{-1}$: 1725, 1640. Compound **3b** was used in the next reaction step without further purification.

**[[1-Ethoxycarbonyl-2-(2,3,4,5-tetrafluorophenyl)-2-oxoethylidene]hydrazono]triphenylphosphorane (3c)**——In a similar manner to that described for **3a**, compound **2c** (580 mg, 2 mmol) was converted to **3c** (1.0 g) as a viscous yellow oil. IR (KBr) $cm^{-1}$: 1715, 1640. Compound **3c** was used in the next reaction step without further purification.

**Ethyl 6,7-Difluoro-4-hydroxycinnoline-3-carboxylate (5a)**——Method A: A solution of tri-*n*-butylphosphine (680 mg, 3.37 mmol) in iso-$Pr_2O$ (5 ml) was added to a stirred solution of **2a** (816 mg, 3 mmol) in iso-$Pr_2O$ (12 ml) at room temperature. The mixture was stirred for 30 min, and refluxed for 7 h. The resulting precipitates were collected by filtration and recrystallized from MeOH–$CHCl_3$ to give **5a** (169 mg, 22.2%) as colorless prisms, mp 270—272.5 °C (dec.). *Anal.* Calcd for $C_{11}H_8F_2N_2O_3$: C, 51.98; H, 3.17; F, 14.95; N, 11.02. Found: C, 52.28; H, 3.35; F, 15.12; N, 10.72. IR (KBr) $cm^{-1}$: 3150, 1710, 1570. $^1$H-NMR (DMSO-$d_6$): 1.30 (3H, t, $J$=7 Hz, $CH_2C\underline{H}_3$), 4.30 (2H, q, $J$=7 Hz, $C\underline{H}_2CH_3$), 7.67 (1H, dd, $J_{H,F}$=7, 11 Hz, $C_5$-H), 8.00 (1H, dd, $J_{H,F}$=10, 8 Hz, $C_8$-H), 13.9 (1H, br s, 4-OH, exchangeable with $D_2O$). UV $\lambda_{max}$ nm (log ε): 208 (4.39), 251 (3.94), 334 (4.10), 347 (4.04).

The mother liquor of the recrystallization was concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (50:1) to give **6a** (420 mg, 51.1%), as colorless prisms, and tributylphosphine oxide, which was identified by comparison with an authentic specimen. The physical data for **6a** are given later.

Method B: A solution of *n*-$Bu_3P$ (680 mg, 3.37 mmol) in dry dioxane (4 ml) was added to a stirred solution of **2a** (816 mg, 3 mmol) in dry dioxane (12 ml) at room temperature. The mixture was stirred for 30 min, gently refluxed for 5 h and concentrated to dryness *in vacuo*. iso-$Pr_2O$ was added to the oily residue and the resulting solid was filtered off, giving 459 mg (60.2%) of **5a**.

Method C: A solution of **6a** (2.74 g, 10 mmol) in dioxane (140 ml) was refluxed for 16 h with stirring. The solution was concentrated to dryness *in vacuo*. iso-$Pr_2O$ was added to the residue. The resulting solid was collected by filtration, washed with water and dried, giving 1.79 g (70.4%) of **5a**.

**Ethyl 6,7,8-Trifluoro-4-hydroxycinnoline-3-carboxylate (5c)**——Method A: In a similar manner to method A for **5a**, treatment of **2c** (870 mg, 3 mmol) with *n*-$Bu_3P$ (670 mg, 3.3 mmol) gave **5c** (360 mg, 44.1%), as pale yellow needles, and **6c** (160 mg, 18.3%). **5c**: mp 228—229 °C (EtOH–hexane). *Anal.* Calcd for $C_{11}H_7F_3N_2O_3$: C, 48.54; H, 2.59; F, 20.94; N, 10.29. Found: C, 48.74; H, 2.51; F, 21.05; N, 10.22. MS *m/z*: 272 ($M^+$). IR (KBr) $cm^{-1}$: 3200, 1710, 1580. $^1$H-NMR ($CDCl_3$): 1.45 (3H, t, $J$=7 Hz, $CH_2C\underline{H}_3$), 4.50 (2H, q, $J$=7 Hz, $C\underline{H}_2CH_3$), 7.88 (1H, m, $J_{H,F}$=10, 8, 2 Hz, $C_5$-H), *ca.* 12.0 (1H, br s, 4-OH, exchangeable with $D_2O$). UV $\lambda_{max}$ nm (log ε): 208 (4.35), 253 (3.87), 333 (4.09), 345 (4.03). The physical data of **6c** are given later.

Method B: A stirred solution of **6c** (9.2 g, 31.5 mmol) in dry diglyme (176 ml) was heated at 130—135 °C for 3.5 h. The solution was concentrated to dryness *in vacuo*. The residual solid was washed with water and dried to give **5c** (7.5 g, 87.2%).

Method C: Potassium *tert*-butoxide (174 mg, 1.55 mmol) was added at below 10 °C to a stirred solution of **6c** (376 mg, 1.29 mmol) in dry dioxane (7 ml). After an additional 1.5 h of stirring, the mixture was concentrated to dryness *in vacuo*. The residue was washed with diluted AcOH and extracted with $CHCl_3$. The extract was dried over $Na_2SO_4$ and the $CHCl_3$ was evaporated off. The resulting solid was recrystallized from EtOH–iso-$Pr_2O$ to give **5c** (109 mg, 31.1%).

**Ethyl 2-Hydrazono-3-(2,4,5-trifluorophenyl)-3-oxopropionate (6a)**——A suspension of **3a** (2.67 g, 5 mmol) in an MeOH (8 ml)–$H_2O$ (12 ml) mixture was gently refluxed for 3 h with stirring. The mixture gradually formed a solution. The solution was concentrated to dryness *in vacuo* and the residue was dissolved in $CHCl_3$. This solution was washed with water and dried over $Na_2SO_4$, and the $CHCl_3$ was evaporated off. The residue was chromatographed on silica gel with $CHCl_3$–EtOH (20:1) as an eluent to give **6a** (1.34 g, 98%) as colorless prisms, mp 110—111 °C (iso-$Pr_2O$), and triphenylphosphine oxide (1.32 g, 95%). *Anal.* Calcd for $C_{11}H_9F_3N_2O_3$: C, 48.18; H, 3.31; F, 20.79; N, 10.22. Found: C, 48.27; H, 3.18; F, 20.83; N, 10.11. IR (KBr) $cm^{-1}$: 3375, 3200, 1680, 1650, 1620. MS *m/z*: 274 ($M^+$). $^1$H-

NMR ($CDCl_3$): 1.32 (3H, t, $J$=7 Hz, $CH_2C\underline{H}_3$), 4.32 (2H, q, $J$=7 Hz, $C\underline{H}_2CH_3$), 6.92 (1H, m, $J_{H,F}$=10, 10, 6 Hz, aromatic H), 7.43 (1H, m, $J_{H,F}$=10, 9, 6 Hz, aromatic H), 9.25 (2H, br s, $NH_2$, exchangeable with $D_2O$).

**Ethyl 2-Hydrazono-3-(2,4-dichloro-5-fluorophenyl)-3-oxopropionate (6b)**——In a similar manner to that described for **6a**, compound **3b** (1.10 g, 1.94 mmol) was transformed to **6b** (578 mg, 97%) as colorless prisms, mp 139—140 °C (EtOH). *Anal.* Calcd for $C_{11}H_9Cl_2FN_2O_3$: C, 43.02; H, 2.95; Cl, 23.09; F, 6.19; N, 9.12. Found: C, 42.84; H, 2.70; Cl, 23.26; F, 6.17; N, 9.21. MS *m/z*: 306 ($M^+$). IR (KBr) $cm^{-1}$: 3325, 3150, 1670, 1650. $^1$H-NMR ($CDCl_3$): 1.35 (3H, t, $J$=7 Hz, $CH_2C\underline{H}_3$), 4.34 (2H, q, $J$=7 Hz, $C\underline{H}_2CH_3$), 7.10 (1H, d, $J_{H,F}$=9 Hz, aromatic H), 7.35 (1H, d, $J_{H,F}$=6 Hz, aromatic H), 9.30 (2H, br s, $NH_2$, exchangeable with $D_2O$).

**Ethyl 2-Hydrazono-3-(2,3,4,5-tetrafluorophenyl)-3-oxopropionate (6c)**——Triphenylphosphine (4.13 g, 15.1 mmol) was added to a stirred solution of **2c** (4.35 g, 15 mmol) in iso-$Pr_2O$ (90 ml) at room temperature. After an additional 3 h of stirring, the solution was allowed to stand overnight. The resulting yellow solution was concentrated to dryness *in vacuo*. The viscous residue was chromatographed on silica gel with $CHCl_3$ to give **6c** (3.38 g, 88.6%) as colorless prisms, mp 135—136 °C (AcOEt–hexane), and triphenylphosphine oxide. *Anal.* Calcd for $C_{11}H_8F_4N_2O_3$: C, 45.22; H, 2.76; F, 26.01; N, 9.59. Found: C, 45.33; H, 2.88; F, 26.21; N, 9.72. MS *m/z*: 292 ($M^+$). IR (KBr) $cm^{-1}$: 3340, 3160, 1670, 1650, 1620, 1585. $^1$H-NMR ($CDCl_3$): 1.35 (3H, t, $J$=7 Hz, $CH_2C\underline{H}_3$), 4.35 (2H, q, $J$=7 Hz, $C\underline{H}_2CH_3$), 7.0—7.4 (1H, m, aromatic H), *ca.* 9.35 (2H, br s, $NH_2$, exchangeable with $D_2O$).

**Ethyl 3-(2,4-Dichloro-5-fluorophenyl)-3-oxo-2-(2-methylhydrazono)propionate (7)**——Dimethyl sulfate (300 mg, 2.38 mmol) was added to a stirred mixture of **6b** (650 mg, 2.12 mmol), anhydrous $K_2CO_3$ (400 mg, 2.9 mmol) and $CH_3CN$ (10 ml) at room temperature. After an additional 18 h of stirring, the mixture was concentrated to dryness *in vacuo*. The residue was taken up in $CHCl_3$, and the solution was washed with water, and then dried over $Na_2SO_4$. The $CHCl_3$ was evaporated off. The residue was chromatographed on silica gel with hexane–$CHCl_3$ (2 : 1 to 1 : 1) as an eluent to give **7** (210 mg, 30.8%), as colorless plates, mp 99—100 °C (iso-$Pr_2O$–hexane). *Anal.* Calcd for $C_{12}H_{11}Cl_2FN_2O_3$: C, 44.88; H, 3.45; Cl, 22.08; F, 5.92; N, 8.72. Found: C, 44.86; H, 3.53; Cl, 21.84; F, 5.85; N, 8.72. IR (KBr) $cm^{-1}$: 3150, 1720, 1660, 1590. MS *m/z*: 320 ($M^+$). $^1$H-NMR ($CDCl_3$): major geometrical isomer: 1.35 (3H, t, $J$=7 Hz, $CH_2C\underline{H}_3$), 3.30 (3H, d, $J$=4 Hz, $NHC\underline{H}_3$), 4.30 (2H, q, $J$=7 Hz, $C\underline{H}_2CH_3$), 7.10 (1H, d, $J_{H,F}$=8 Hz, aromatic H), 7.37 (1H, d, $J_{H,F}$=6 Hz, aromatic H), *ca.* 11.6 (1H, br s, $N\underline{H}CH_3$, exchangeable with $D_2O$); minor geometrical isomer: 1.15 (t, $J$=7 Hz, $CH_2C\underline{H}_3$), 3.55 (d, $J$=4 Hz, $NHC\underline{H}_3$), 4.13 (q, $J$=7 Hz, $C\underline{H}_2CH_3$), 7.05 (d, $J$=8 Hz, aromatic H), 7.37 (d, $J$=6 Hz, aromatic H), *ca.* 13.4 (br s, $N\underline{H}CH_3$).

**Ethyl 7-Chloro-6-fluoro-1-methyl-1,4-dihydro-4-oxocinnoline-3-carboxylate (8)**——Sodium hydride (60% suspension in mineral oil, 76 mg, 1.9 mmol) was added at below 10 °C to a stirred solution of **7** (510 mg, 1.59 mmol) in dry dioxane (25 ml). After an additional 10 min of stirring, the mixture was heated at 90—95 °C for 15 min and concentrated to dryness *in vacuo*. The residual solid was washed with water and dried, followed by recrystallization from EtOH–iso-$Pr_2O$ to give **8** (423 mg, 93.4%) as colorless prisms, mp 178—179 °C. *Anal.* Calcd for $C_{12}H_{10}ClFN_2O_3$: C, 50.63; H, 3.54; Cl, 12.45; F, 6.67; N, 9.84. Found: C, 50.54; H, 3.53; Cl, 12.42; F, 6.52; N, 9.62. MS *m/z*: 284 ($M^+$), 239, 212, 185. IR (KBr) $cm^{-1}$: 1720, 1620, 1600. $^1$H-NMR ($CDCl_3$): 1.45 (3H, t, $J$=7 Hz, $CH_2C\underline{H}_3$), 4.15 (1H, s, $N_1$-$C\underline{H}_3$), 4.45 (2H, q, $J$=7 Hz, $C\underline{H}_2CH_3$), 7.58 (1H, d, $J_{H,F}$=6 Hz, $C_8$-H), 8.10 (1H, d, $J_{H,F}$=9 Hz, $C_5$-H). UV $\lambda_{max}$ nm (log $\varepsilon$): 220 (4.36), 261 (4.09), 348 (4.13), 358 (4.11).

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