Fluorinated Pyrido[2,3-*c*]pyridazines. I. Reductive Cyclization of Ethyl 2-Diazo-2-(5-fluoro-2-halonicotinoyl)acetate with Trialkylphosphine[1)]

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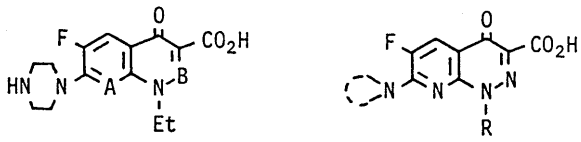
A new and convenient synthesis of 6-fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylate derivatives was achieved. One-pot reactions of ethyl 2-diazo-2-(6-chloro- and 6-tolylthio-5-fluoro-2-halonicotinoyl)acetates (9a and 9b, c) with tri-*n*-butylphosphine or tricyclohexylphosphine gave ethyl 7-chloro- and 7-tolylthio-6-fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylates (12a and 12b), respectively. The reaction of 9a—c with triphenylphosphine gave {[1-ethoxycarbonyl-1-(6-chloro- and 6-tolylthio-5-fluoro-2-halonicotinoyl)methylene]hydrazono}triphenylphosphoranes (10a—c, R = Ph), which were hydrolyzed to the corresponding hydrazones 11a—c. Intramolecular cyclization of the hydrazones 11b and 11c furnished an alternative and efficient synthesis of 12b. Possible mechanisms for the reaction of 9 leading to 12 are discussed.

Keywords reductive cyclization; 2-diazo-2-(2-halonicotinoyl)acetate; trialkylphosphine; triphenylphosphine; phosphazine; ring construction; pyrido[2,3-*c*]pyridazine

The pyridonecarboxylic acid antibacterials such as norfloxacin (**1**)[2)] and enoxacin (**2**)[3)] are now widely used in clinical practice. Their chemical structures have in common a 4(1*H*)-oxopyridine-3-carboxylic acid moiety, which has been accepted as an indispensable functional group for the antibacterial activity. In the previous paper,[4b)] we reported the synthesis and antibacterial activity of the 6-fluoro- and 6,8-difluoro-4(1*H*)-oxocinnoline-3-carboxylic acid derivatives including "aza-norfloxacin" (**3**). As part of our research program on chemical modifications of the common moiety, we have prepared "aza-enoxacin" and some related 7-substituted 1-alkyl-6-fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylic acids (**4**).

Several methods for the construction of a 4(1*H*)-oxopyrido[2,3-*c*]pyridazine ring have been reported thus far,[5)] but they are not available for the synthesis of a key intermediate, 7-halo- or 7-arylthio-6-fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylate (**12a** or **12b**), which is convertible to the desired compounds **4**. We had previously reported a new method for fused pyridazine ring construction leading to 4(1*H*)-oxopyrimido[4,5-*c*]pyridazine- and 4(1*H*)-oxocinnoline-3-carboxylates by the reductive cyclization of 2-diazo-3-(4-chloropyrimidin-5-yl)-3-oxopropionates and 2-diazo-2-(2-fluorobenzoyl)acetates, respectively, with trialkylphosphine.[4a,6)] As an extension of that work, we applied the method to the synthesis of 6-fluoropyrido[2,3-*c*]pyridazine **12** by using ethyl 2-diazo-2-(5-fluoro-2-halonicotinoyl)acetates (**9a—c**) as key intermediates; this is the primary subject of the present paper.[1)]

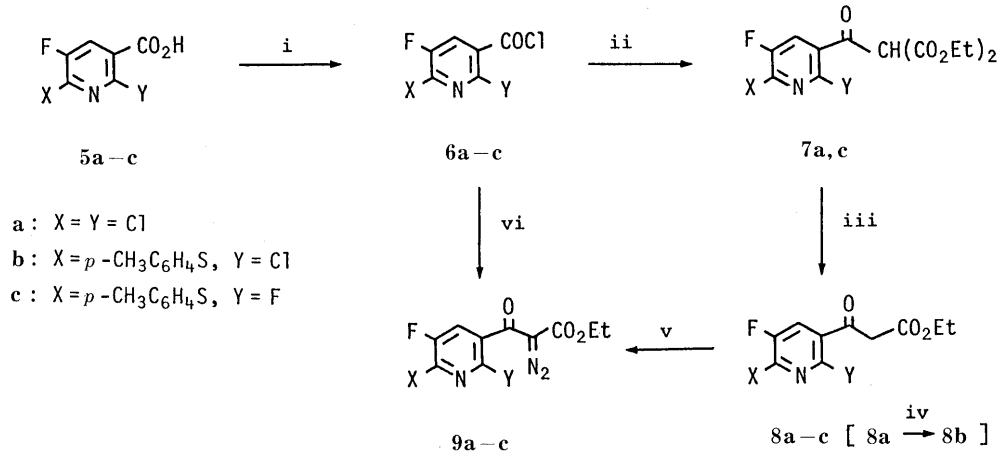
The α-diazo-β-ketoesters **9a—c** were prepared by two



1 : A = B = CH
2 : A = N, B = CH
3 : A = CH, B = N

4 : R = alkyl

Chart 1



5a—c
a : X = Y = Cl
b : X = *p*-$CH_3C_6H_4S$, Y = Cl
c : X = *p*-$CH_3C_6H_4S$, Y = F

6a—c
7a, c
9a—c
8a—c [8a → 8b]

reagents : i $SOCl_2$; ii $EtOMgCH(CO_2Et)_2$; iii H_3O^+; iv *p*-$CH_3C_6H_4SK$ in EtOH; v *p*-$CH_3C_6H_4SO_2N_3/Et_3N$; vi N_2CHCO_2Et at 50–55°C

Chart 2

TABLE I. Reaction of the Diazoesters **9** with Trialkylphosphines; Reaction Conditions and Yields of the Products

Compd.	R_3P	Reaction conditions			Yields (%) of products		
	R	Solvent	Tempt.	Time (h)	**10a—c**	**11a—c**	**12a, b**
9a	Ph	iso-Pr_2O	rt	26	[a]	**11a** (93)	[b]
	c-Hex	iso-Pr_2O	rt	18	**10a** (80)	**11a** (11)	[b]
	n-Bu	iso-Pr_2O	rt	18	[a]	**11a** (35)	**12a** (21)
			refl	2[c]	[a]	[a]	**12a** (16)
9b	Ph	iso-Pr_2O	rt	20	**10b** (83)	[a]	[b]
	n-Bu	iso-Pr_2O	rt	20	[a]	**11b** (66)	**12b** (29)
			refl	5[c]	[a]	**11b** (46)	**12b** (46)
		Diglyme	125—130°C	3[c]	[a]	**11b** (19)	**12b** (56)
9c	Ph	iso-Pr_2O	rt	23	**10c** (80)	[a]	[b]
			refl	3[c]	**10c** (88)	**11c** (6)	**12b** (5)
	c-Hex	iso-Pr_2O	rt	11	[a]	**11c** (15)	**12b** (66)
	n-Bu	iso-Pr_2O	rt	3	[a]	[a]	**12b** (61)
			rt	18	[a]	[a]	**12b** (71)
			rt	64	[a]	**11c** (5)	**12b** (85)
			refl	0.5[c]	[a]	[a]	**12b** (80)
			refl	2[c]	[a]	[a]	**12b** (74)
			refl	3[c]	[a]	[a]	**12b** (35)

c-Hex = cyclohexyl; rt = room temperature; refl = reflux. *a*) Not isolated. *b*) Not detectable. *c*) The reaction mixture was stirred at room temperature for 30 min and then heated to reflux.

methods (Chart 2). The first was the condensation of the acid chlorides **6b** and **6c** with ethyl diazoacetate and the second was the diazotization of the β-ketoesters **8a—c** with tosyl azide. The β-ketoesters **8a** and **8c**, in turn, were obtained by condensation of **6a** and **6c** with diethyl ethoxymagnesiummalonate and subsequent acidic hydrolysis of the intermediary nicotinoyl malonates **7a** and **7c**, respectively. Compound **8b** was prepared by a regiospecific displacement reaction of **8a** with potassium *p*-thiocresol in ethanol.

The reactions of the α-diazo-β-ketoester **9** with triphenyl-, tricyclohexyl- and tri-*n*-butylphosphines were examined (Chart 3) and the results are summarized in Table I, which includes the reaction conditions and the yields of the products. The reaction of **9a** with triphenylphosphine in diisopropyl ether at room temperature failed to give directly the expected ethyl 7-chloro-6-fluoro-4(1*H*)-oxopydido[2,3-*c*]pyridazine-3-carboxylate (**12a**), but yielded exclusively the intermediary triphenylphosphazine **10a** (R = Ph). However, this compound **10a** was so labile to moisture that the hydrazone **11a** was isolated in 93% yield with concomitant elimination of triphenylphosphine oxide during the work-up procedure. A similar treatment of **9a** with tricyclohexylphosphine gave the tricyclohexylphosphazine **10a** (R = cyclohexyl), which was isolated as an unstable solid in 80% yield along with an 11% yield of **11a**; even when the reaction temperature was elevated, no cyclized product **12a** was isolated. On treatment of **9a** with tri-*n*-butylphosphine at room temperature, the reductive cyclization occurred to give the desired product **12a** though in a poor (*ca.* 21%) yield, together with the hydrazone **11a** as a major product. Elevation of the reaction temperature did not increase the yield of **12a**, but led to the formation of unidentified products which probably arose from the reaction at the C-6 position in the pyridine ring. Therefore, the C-6 chloro atom of **9a** was replaced by a less reactive *p*-tolylthio group (giving **9b**), which could be substituted with a variety of amines at a later step.

The reaction of **9b** with tri-*n*-butylphosphine at room temperature gave **12b** in 29% yield. Elevation of the reaction temperature enhanced the yield to 46—56%. The unsatisfactory yield appeared to be due to the lower reactivity of the C-2 chloro atom. Hence, after the C-2 chlorine atom of **9b** was replaced by a more reactive fluorine atom, the reactivity of the resulting **9c** was examined.

On treatment of **9c** with tri-*n*-butylphosphine at room temperature, the reductive cyclization proceeded successfully to give **12b** in a yield of 61—85% depending on the reaction time (from 3 to 64 h), as shown in Table I. A shorter refluxing time (0.5—2 h) at the elevated temperature enhanced the yield of **12b**, whereas a longer reaction period caused a decrease in yield along with the formation of a complex mixture of unidentified products. Treatment of **9c** with tricyclohexylphosphine also caused smooth cyclization to give **12b** in a good yield. On the contrary, the treatment of **9c** with triphenylphosphine at room temperature gave preferentially the triphenylphosphazine **10c** (R = Ph). However, when the reaction was carried out in refluxing diisopropyl ether for 3 h, compound **12b** was obtained in only 5% yield, the main product being **10c** (R = Ph) in 88% yield. The reaction of the α-diazo-β-ketoester **9c** with tri-*n*-butylphosphine most efficiently produced the cyclized compounds **12**, particularly **12b** in a one-pot process.

The phosphazines **10a—c** were, on the whole, too unstable to be purified and gradually decomposed when allowed to stand under ambient conditions. The triphenylphosphazine **10c** (R = Ph), for example, changed gradually in a chloroform or dioxane solution, even at room temperature, into **9c** and triphenylphosphine oxide; when heated in dry dioxane at 65—70 °C for 1.5 h, **10c** (R = Ph) reverted to **9c** and triphenylphosphine oxide in 96 and 82% yields, respectively. Moreover, the triphenylphosphazine **10c** (R = Ph) was converted, in the presence of moisture, into the hydrazone **11c** and triphenylphosphine oxide; even passage through the silica gel column completely transformed **10c** (R = Ph) into **11c**. In general, the conversion of

the phosphazine **10a—c** to the hydrazone **11a—c** proceeded efficiently on refluxing merely in a mixture of methanol and water.

Intramolecular cyclization of the hydrazones **11** to the pyrido[2,3-*c*]pyridazines **12** was then examined (Chart 3); the results are given in Table II, which includes the reaction conditions and the yields of the products. On reflux of the hydrazones **11a—c** in diisopropyl ether or dioxane, cyclization failed to occur. However, when heated at 125—130 °C in diglyme, the hydrazones **11b** and **11c** underwent cyclization to give **12b** in 11 and 65% yields, respectively. The use of a base accelerated the cyclization. Thus, reflux of **11c** for 8 h in dioxane in the presence of sodium bicarbonate gave **12b** in 98% yield. With potassium *tert*-butoxide as a base, the cyclization of **11c** proceeded smoothly even at room temperature in a shorter time.

TABLE II. Cyclization of the Hydrazones **11** to the Pyrido[2,3-*c*]pyridazines **12**; Reaction Conditions and Yields of the Products

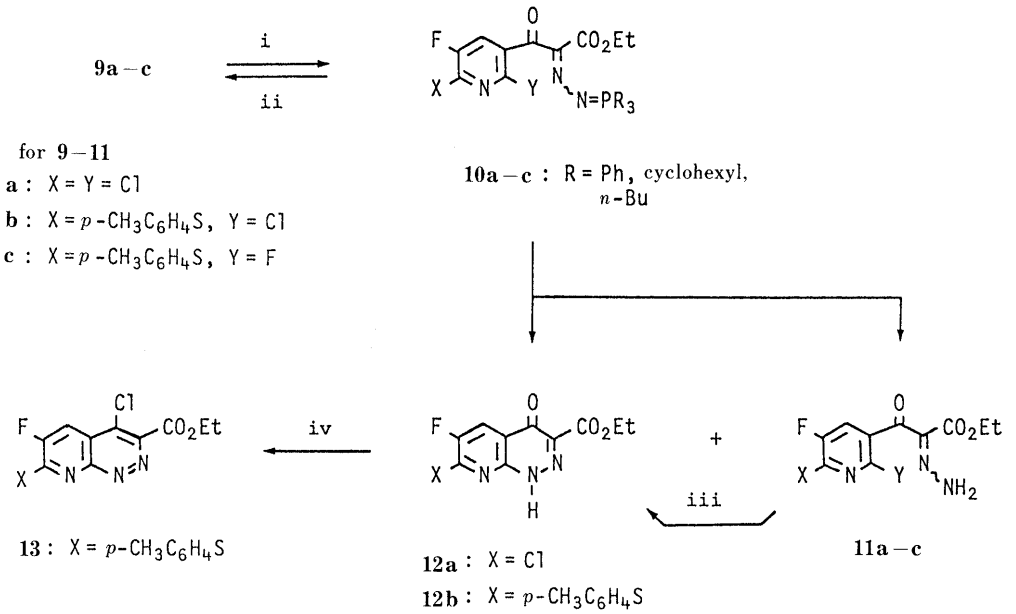
Compd.	Reaction conditions[a]			Yields (%) of products	
	Solvent	Base	Time (h)	**12**	Others
11a	iso-Pr_2O	[b]	7	[c]	rc
	Dioxane	K_2CO_3	3.5	[d]	**9a** (63)
	Dioxane	*tert*-BuOK	rt, 2	[c]	**8a** (37)
11b	iso-Pr_2O	[b]	7	[c]	rc
	Diglyme	[b]	7	**12b** (11)	**9b** (15), rc
	Dioxane	*tert*-BuOK	rt, 0.5	[c]	**8b** (39)
11c	iso-Pr_2O	[b]	7	[c]	rc
	Dioxane	[b]	7	**12b**[d]	rc
	Diglyme	[b]	1.5	**12b** (65)	[e]
	Dioxane	$NaHCO_3$	8	**12b** (98)	[e]
	Dioxane	*tert*-BuOK	rt, 1	**12b** (89)	[e]

a) The hydrazones **11** were heated to reflux in iso-Pr_2O or dioxane and at 125—130 °C in diglyme. *b*) Without a base. *c*) Not detectable. *d*) A trace amount. *e*) Not isolated. rc = recovery of the starting compound **11**; rt = room temperature.

However, a similar treatment of the hydrazones **11a** and **11b** with potassium *tert*-butoxide resulted exclusively in a Wolff-Kishner type reduction to give the β-ketoesters **8a** and **8b**, respectively. No reaction conditions resulting in the transformation of **11a** to **12a** were found. In this particular case, therefore, only the hydrazone **11c** afforded the cyclized compound **12b**, in an excellent yield.

Keto-enol tautomerization of the cyclized compounds **12** is formally possible and hence their infrared (IR) and ultraviolet (UV) spectra were examined. In the solid state, compound **12b**, for example, shows two absorption bands at 3200 (ν NH) and 3150 (ν OH) cm^{-1} and three strong bands (ν CO) at 1735, 1690 and 1645 cm^{-1}, whereas in a chloroform solution, it shows two absorption bands at 3375 (ν NH) and 3200 (ν OH) cm^{-1} along with two strong carbonyl absorption bands at 1730 and 1630 cm^{-1}. For comparison, the 4-chloro analogue **13** with an enol-type ring system was derived from 12b with phosphorus oxychloride. The IR spectrum (in KBr disk) of **13** shows a carbonyl absorption band at 1725 cm^{-1}. These data suggest that **12b** exists as a mixture of the keto and enol tautomers in the solid state, but predominantly (not exclusively) as the keto-form in the chloroform solution. This was supported by a comparison between the UV spectra (in ethanol) of **12b** and **13**. Thus, compound **12b** shows four absorption maxima at 202, 248, 355 and 371 nm, whereas **13** shows three absorption maxima at 216, 268 and 360 nm; the spectrum of **12b** is clearly different from that of **13**, indicating that **12b** exists as the keto-form in the ethanol solution. The tautomerism of **12a** was essentially the same as that of **12b**.

Probable mechanisms for the reaction of the α-diazo-β-ketoester **9c** with trialkylphosphine leading to the pyrido[2,3-*c*]pyridazine **12b** are given in Chart 4. Compound **9c** reacts with trialkylphosphine to form initially the trialkylphosphazine **10c**, which then would undergo hydration to **14** (path a), followed competitively, or either



reagents : i R_3P in iso-Pr_2O; ii heat in dry dioxane; iii heat or *tert*-BuOK in dry dioxane; iv $POCl_3$

Chart 3

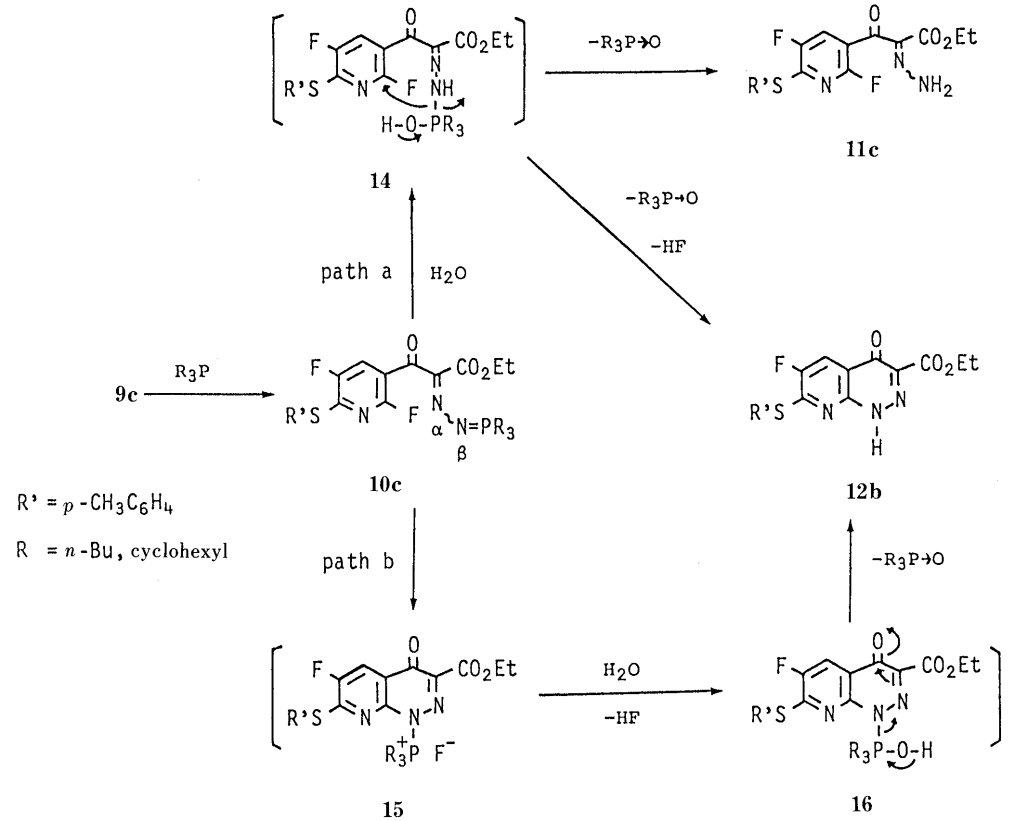


Chart 4

by elimination of trialkylphosphine oxide to give the hydrazone **11c** or by cyclization with loss of trialkylphosphine oxide and hydrogen fluoride to give the pyrido[2,3-*c*]pyridazine **12b**. Preference for either reaction course, **10c**→**14**→**11c** or **10c**→**14**→**12b**, may depend on the nucleophilicity of the *β*-nitrogen in **14** and the reactivity of the C-2 position in the pyridine ring. In fact, the reaction of **9a**—**c** with triphenylphosphine gave no cyclized product **12**, but provided the hydrazone **11a** or the triphenylphosphazines **10b** and **10c**. The reactions of **9a** and **9b** (Y=Cl) with the more active tri-*n*-butylphosphine took both reaction courses to produce **11a**/**12a** and **11b**/**12b**, respectively. On a similar treatment of **9c** (Y=F) with tri-*n*-butylphosphine, the ring closure proceeded preferentially to give **12b**. Thus, the combination of the tri-*n*-butyl group and the C-2 fluorine atom of the phosphazine **10c** favors the ring closure. Another possible pathway is shown by the reaction sequence **10c**→**15**→**16**→**12b** (path b); thus, the highly reactive tri-*n*-butylphosphazine **10c** would undergo intramolecular cyclization into the phosphonium salt **15**, which would be hydrolyzed *via* **16** to give **12b**. Due to the electron-donating effect, the *n*-butyl and cyclohexyl groups in **10c** favor the ring closure *via* path b more than does the phenyl group.

As a result of the present work, a new and efficient one-pot synthesis of ethyl 6-fluoro-7-(*p*-tolylthio)-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylate (**12b**) was accomplished by treatment of the *α*-diazo-*β*-ketoester **9c** with tri-*n*-butylphosphine. Another method for the preparation of **12b** was the intramolecular cyclization of the hydrazone **11c** derived in a stepwise manner from **9c** *via* **10c**. Of the two methods, the latter is more practical than the former.

The synthesis, starting from **12b**, and the antibacterial activity of 7-substituted 1-alkyl-6-fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylic acids (**4**) will be reported in the following 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 for KBr tablets, unless otherwise noted. Abbreviations are as follows: s=strong, m=medium, w=weak, sh=shoulder. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60, 80, and 100 MHz with Varian EM-360, FT-80A, and HA-100 spectrometers, respectively. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Electron impact mass spectra (EIMS) were recorded on a Hitachi RMU-6 or JEOL JMSD-300 spectrometer. UV spectra in EtOH were recorded on a Shimadzu UV-260 UV-visible recording spectrophotometer. The extract was dried over anhydrous Na_2SO_4.

2,6-Dichloro-5-fluoronicotinic Acid (5a) (a) A stirred mixture of 2,6-dichloro-5-fluoropyridine-3-carboxamide[7] (32 g, 153 mmol) and 35% HCl (200 ml) was heated at 135—140 °C for 3 h, and then diluted with water (200 ml). The resulting crystals were collected by filtration and washed with water to give 26.1 g (81%) of **5a** as colorless crystals, mp 155—156 °C (H_2O–EtOH) (lit.[8b] mp 153—154 °C). IR cm^{-1}: 1700. ^{1}H-NMR (60 MHz, DMSO-d_6): 8.43 (1H, d, $J_{H,F}$=8 Hz, C_4-H), *ca.* 14.0 (1H, br s, COOH, exchangeable with D_2O).

(b) A stirred mixture of 2,6-dichloro-5-fluoronicotinonitrile[7] (30 g, 157 mmol) and concentrated H_2SO_4 (60 ml) was heated at 65—75 °C for 1 h, and then water (60 ml) was added dropwise to the mixture under ice-cooling over 30 min, during which period the internal temperature was kept below 100 °C. The mixture was again heated at 100—110 °C for 1.5 h, and then diluted with water (60 ml). The resulting crystals were collected by filtration and washed with water to give 29.9 g (91%) of **5a**.

2-Chloro-5-fluoro-(5b) and 2,5-Difluoro-6-(*p*-tolylthio)nicotinic Acids (5c) A stirred mixture of ethyl 2,5-difluoro-6-(*p*-tolylthio)nicotinate[7] (30 g, 97 mmol), *tert*-BuOH (240 ml), H_2O (120 ml) and 1 N NaOH (112 ml) was heated at 65—70 °C for 30 min. The solution was treated with charcoal, and then adjusted to pH 2 with 1 N HCl (130 ml) under ice-cooling. The resulting crystals were collected by filtration and washed with water to give 25.4 g (93%) of **5c** as colorless needles, mp 172—174 °C (MeOH–H_2O).

Anal. Calcd for $C_{13}H_9F_2NO_2S$: C, 55.51; H, 3.23; F, 13.51; N, 4.98; S, 11.40. Found: C, 55.59; H, 3.50; F, 13.51; N, 4.93; S, 11.65. IR cm^{-1}: 1680. EIMS *m/z*: 281 (M^+). ^{1}H-NMR (60 MHz, $CDCl_3$/DMSO-d_6): 2.41 (3H, s, CH_3), 7.26 (2H, d, J=8 Hz, phenyl H), 7.49 (2H, d, J=8 Hz, phenyl H), 7.97 (1H, dd, $J_{H,F}$=8, 7 Hz, C_4-H), *ca.* 8.0 (1H, br s, COOH, exchangeable with D_2O).

In a similar manner, ethyl 2-chloro-5-fluoro-6-(*p*-tolylthio)nicotinate[7] was subjected to hydrolysis to give a 95% yield of **5b** as colorless needles, mp 185—186 °C (AcOEt–*n*-hexane). *Anal.* Calcd for $C_{13}H_9ClFNO_2S$: C, 52.44; H, 3.05; Cl, 11.91; F, 6.38; N, 4.70; S, 10.77. Found: C, 52.20; H, 3.07; Cl, 11.62; F, 6.52; N, 4.57; S, 11.03. IR cm^{-1}: 1690, 1610. EIMS *m/z*: 297 (M^+). ^{1}H-NMR (60 MHz, $CDCl_3$/DMSO-d_6): 2.37 (3H, s, CH_3), 7.23 (2H, d, J=8 Hz, phenyl H), 7.47 (2H, d, J=8 Hz, phenyl H), 7.87 (1H, d, $J_{H,F}$=8 Hz, C_4-H), *ca.* 10.0 (1H, br s, COOH, exchangeable with D_2O).

2,6-Dichloro-5-fluoronicotinoyl Chloride (6a), 2-Chloro-5-fluoro- (6b) and 2,5-Difluoro-6-(*p*-tolylthio)nicotinoyl Chlorides (6c) A stirred suspension of **5a** (28.5 g, 136 mmol) and $SOCl_2$ (113 ml) was heated to reflux for 1 h. The solution was concentrated to dryness under reduced pressure, and the residue was distilled *in vacuo* to give **6a** (25.1 g, 81%) as a colorless oil, bp 108—110 °C (4 mmHg). IR (neat) cm^{-1}: 1775. ^{1}H-NMR (60 MHz, $CDCl_3$): 8.23 (1H, d, $J_{H,F}$=8 Hz, C_4-H). Compound **6a** was used in the next step without further purification.

The carboxylic acids **5b** and **5c** were treated in a similar manner, giving the acid chlorides **6b** and **6c** in 84 and 71% yields, respectively. Compound **6b**, colorless crystals, was used in the next reaction step without further purification. Compound **6c**: mp 73—74 °C, colorless crystals. *Anal.*Calcd for $C_{13}H_8ClF_2NOS$: C, 52.10; H, 2.69; Cl, 11.83; F, 12.68; N, 4.67; S, 10.70. Found: C, 52.38; H, 2.68; Cl, 11.84; F, 12.77; N, 4.46; S, 10.84. IR cm^{-1}: 1770. ^{1}H-NMR (60 MHz, $CDCl_3$): 2.40 (3H, s, CH_3), 7.27 (2H, d, J=8 Hz, phenyl H), 7.47 (2H, d, J=8 Hz, phenyl H), 8.06 (1H, dd, $J_{H,F}$=8, 7 Hz, C_4-H).

Diethyl 2,6-Dichloro-5-fluoro- (7a) and 2,5-Difluoro-6-(*p*-tolylthio)nicotinoylmalonates (7c) A mixture of magnesium (2.9 g, 118.4 mmol), absolute EtOH (1.7 ml) and CCl_4 (0.3 ml) was heated. When the evolution of hydrogen gas began, a solution of diethyl malonate (19.8 g, 124 mmol) in absolute EtOH (17 ml) and dry Et_2O (100 ml) was added portionwise to the initial mixture with stirring. After the evolution of hydrogen gas had ceased, the reaction mixture was refluxed for 30 min and then cooled. A solution of the acid chloride **6a** (24.7 g, 108 mmol) in dry Et_2O (50 ml) was added portionwise over 10 min to the above stirred mixture. The solution was stirred for an additional 10 min, and then acidified with 2 N HCl (80 ml) under ice-cooling. The organic layer was separated and dried. Evaporation of the solvent left 40.5 g of **7a** as an oil. EIMS *m/z*: 316 (M^+ −Cl). IR (neat) cm^{-1}: 1760 (sh), 1730, 1650, 1620. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.27 (6H, t, J=7 Hz, 2 × $CH_2C\underline{H}_3$), 2.40 (3H, s, CH_3), 3.9—4.6 (1H, m, CH), 4.08 and 4.42 (each 2H, q, J=7 Hz, each $C\underline{H}_2CH_3$), 7.55 (1H, d, $J_{H,F}$=7 Hz, C_4-H). Compound **7a** was used in the next reaction step without further purification.

The acid chloride **6c** (4.2 g, 14 mmol) was treated in a similar manner, giving **7c** (6.0 g) as an oil. EIMS *m/z*: 423 (M^+). IR (neat) cm^{-1}: 1755, 1735, 1690, 1610. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.27 (6H, t, J=7 Hz, 2 × $CH_2C\underline{H}_3$), 2.40 (3H, s, CH_3), 4.27 (4H, q, J=7 Hz, 2 × $C\underline{H}_2CH_3$), 5.05 (1H, d, J=3 Hz, CH), 7.27 (2H, d, J=8 Hz, phenyl H), 7.47 (2H, d, J=8 Hz, phenyl H), 7.97 (1H, dd, $J_{H,F}$=8, 7 Hz, C_4-H).

Ethyl 2,6-Dichloro-5-fluoro- (8a) and 2,5-Difluoro-6-(*p*-tolylthio)nicotinoylacetates (8c) A stirred mixture of the crude nicotinoylmalonate **7a** (40.5 g), *p*-toluenesulfonic acid (20 mg) and water (100 ml) was heated to reflux for 2 h and then cooled. The solution was extracted with iso-Pr_2O. The extract was dried and the solvent was evaporated off. The residue was triturated with *n*-hexane and the resulting crystals were collected by filtration to give 22.2 g (74% in two steps from **6a**) of **8a** as colorless needles, mp 69—70 °C (Et_2O–*n*-hexane) (lit.[8b] mp 64—65 °C). IR cm^{-1}: 3100, 1630. ^{1}H-NMR (60 MHz, $CDCl_3$): the enol form, 1.37 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.31 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.83 (1H, s, olefinic H), 7.87 (1H, d, $J_{H,F}$=8 Hz, C_4-H), 12.66 (1H, s, enolic OH, exchangeable with D_2O); the keto form, 1.27 (t, J=7 Hz, $CH_2C\underline{H}_3$), 4.31 (q, J=7 Hz, $C\underline{H}_2CH_3$), 4.10 (s, CH_2), 7.87 (d, $J_{H,F}$=8 Hz, C_4-H). The ratio of the enol/keto tautomers was determined to be approximately 2/1 on the basis of the signal intensities of the methyl protons of the ethoxycarbonyl groups.

The nicotinoylmalonate **7c** was treated in a similar manner, giving **8c** in 58% yield (in two steps from **6c**). Compound **8c**: mp 94—95 °C (Et_2O–*n*-hexane), colorless needles. *Anal.* Calcd for $C_{17}H_{15}F_2NO_3S$: C, 58.11; H, 4.30; F, 10.81; N, 3.99; S, 9.13. Found: C, 57.94; H, 4.45; F, 10.64; N, 3.86; S, 9.30. IR cm^{-1}: 3100 (w, OH), 1640 (sh), 1615. ^{1}H-NMR (60 MHz, $CDCl_3$): the enol form (*ca.* 100%); 1.33 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.42 (3H, s, CH_3), 4.28 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.87 (1H, s, olefinic H), 7.27 (2H, d, J=8 Hz, phenyl H), 7.50 (2H, d, J=8 Hz, phenyl H), 7.95 (1H, dd, $J_{H,F}$=9, 8 Hz, C_4-H), 12.83 (1H, s, enolic OH, exchangeable with D_2O).

Ethyl 2-Chloro-5-fluoro-6-(*p*-tolylthio)nicotinoylacetate (8b) A solution of potassium hydroxide (3.50 g, 6.25 mmol) in EtOH (70 ml) was added to a stirred solution of *p*-thiocresol (7.5 g, 6.0 mmol) in EtOH (130 ml). The β-ketoester **8a** (14.0 g, 5.0 mmol) was added to the resulting solution under ice-cooling. After an additional 1 h of stirring at room temperature, the resulting crystals were collected by filtration, washed with water, and dried. The filtrate was neutralized with AcOH and then concentrated to dryness *in vacuo*. The residual crystals were washed with water, dried, and combined with the initial crystals. A solution of the combined crystals in hexane was chromatographed on silica gel with $CHCl_3$–*n*-hexane (1:4) and subsequently with $CHCl_3$ as an eluent to give **8b** (15.6 g, 85%) as colorless needles, mp 55—56 °C (EtOH). *Anal.* Calcd for $C_{17}H_{15}ClFNO_3S$: C, 55.51; H, 4.11; Cl, 9.64; F, 5.16; N, 3.81; S, 8.72. Found: C, 55.47; H, 4.19; Cl, 9.38; F, 5.04; N, 3.81; S, 9.01. IR cm^{-1}: 3100 (vw) 1750 (w), 1650 (sh), 1620 (s). EIMS *m/z*: 367 (M^+), 332, 321, 280. ^{1}H-NMR (80 MHz, $CDCl_3$): the enol form (*ca.* 66%), 1.32 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.40 (3H, s, CH_3), 4.26 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.78 (1H, s, olefinic H), 7.20 (2H, d, J=8 Hz, phenyl H), 7.45 (2H, d, J=8 Hz, phenyl H), 7.60 (1H, d, $J_{H,F}$=9 Hz, C_4-H), 12.53 (1H, s, enolic OH, exchangeable with D_2O); the keto form (*ca.* 34%); 1.25 (t, J=7 Hz, $CH_2C\underline{H}_3$), 4.04 (s, CH_2), 4.26 (q, J=7 Hz, $C\underline{H}_2CH_3$), 7.22 (d, J=8 Hz, phenyl H), 7.60 (d, J=8 Hz, phenyl H), 7.65 (d, $J_{H,F}$=9 Hz, C_4-H).

Ethyl 2-Diazo-2-(2,6-dichloro-5-fluoronicotinoyl)acetate (9a) A solution of *p*-toluenesulfonyl azide (10.0 g, 51 mmol) in CH_3CN (20 ml) was added under ice-cooling to a stirred solution of the β-ketoester **8a** (14.0 g, 50 mmol) and Et_3N (7 ml, 51 mmol) in CH_3CN (100 ml). The stirred solution was allowed to stand under ice-cooling for an additional 15 min, and then at room temperature for 1 h. The solution was concentrated to dryness *in vacuo* below 50 °C, and then 2 N NaOH (30 ml) was added to the residue under ice-cooling. The mixture was extracted with AcOEt. The extract was dried and the solvent was evaporated off *in vacuo* below 50 °C. The oily residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give **9a** (14.6 g, 88%) as a golden yellow oil, which was crystallized from iso-Pr_2O–*n*-hexane to give colorless needles, mp 89—90 °C. *Anal.* Calcd for $C_{10}H_6Cl_2FN_3O_3$: C, 39.24; H, 1.94; Cl, 23.12; F, 6.21; N, 13.73. Found: C, 39.14; H, 2.07; Cl, 23.32; F, 5.98; N, 13.77. EIMS *m/z*: 270 (M^+ −Cl), 242, 192. IR cm^{-1}: 2150 (N≡N), 1720, 1630. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.25 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.45 (1H, d, $J_{H,F}$=7 Hz, C_4-H).

Ethyl 2-Diazo-2-[2-chloro-5-fluoro-6-(*p*-tolylthio)nicotinoyl)acetate (9b) (a) A solution of *p*-toluenesulfonyl azide (2.6 g, 13.2 mmol) in CH_3CN (3 ml) was added under ice-cooling to a stirred solution of the β-ketoester **8b** (4.43 g, 12.1 mmol) and Et_3N (2 ml) in CH_3CN (50 ml). The solution was stirred under ice-cooling for an additional 15 min and then at room temperature for 30 min, and concentrated to dryness *in vacuo* below 50 °C. After addition of 2 N NaOH (10 ml) and ice-water (100 ml), the mixture was extracted with Et_2O. The extract was dried and the solvent was evaporated off *in vacuo* below 50 °C. The resulting crystals were recrystallized from EtOH–*n*-hexane to give 4.23 g (89%) of **9b** as colorless needles, mp 99—100 °C. *Anal.* Calcd for $C_{17}H_{13}ClFN_3O_3S$: C, 51.85; H, 3.33; Cl, 9.00; F, 4.82; N, 10.67; S, 8.14. Found: C, 52.03; H, 3.44; Cl, 9.03; F, 4.86; N, 10.65; S, 8.21. IR cm^{-1}: 2150 (N≡N), 1720, 1625. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.19 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.40 (3H, s, CH_3), 4.20 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.20 (1H, d, $J_{H,F}$=7.5 Hz, C_4-H), 7.21 (2H, d, J=8 Hz, phenyl H), 7.45 (2H, d, J=8 Hz, phenyl H).

(b) According to the procedure (a) for **9c**, ethyl diazoacetate was treated with the nicotinoyl chloride **6b** to give **9b** in 82% yield.

Ethyl 2-Diazo-2-[2,5-difluoro-6-(*p*-tolylthio)nicotinoyl]acetate (9c) (a) Ethyl diazoacetate (16.6 g. 146 mmol) was added portionwise to a stirred suspension of the nicotinoyl chloride **6c** (16.0 g, 53.4 mmol) in $CHCl_3$ (6 ml) under ice-cooling. The mixture was stirred for 15 min, allowed to stand at room temperature for 1 h, and then heated at 50—55 °C for 18 h; during the reaction course the mixture gradually formed a clear yellow solution with evolution of nitrogen gas. The solution was concentrated to dryness *in vacuo* below 60 °C to leave an oily residue, which was chromatographed on neutral alumina with AcOEt as an eluent, followed by crystallization from *n*-hexane to give **9c** (15.8 g, 79%) as colorless needles, mp 88—89 °C. *Anal.* Calcd for $C_{17}H_{13}F_2N_3O_3S$: C, 54.11; H, 3.47; F, 10.07; N, 11.14; S, 8.50. Found: C, 54.30; H, 3.33; F, 10.16; N, 11.02; S, 8.73. IR cm^{-1}: 2140 (N≡N), 1710, 1630, 1610. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.23 (3H, t,

$J=7$ Hz, $CH_2C\underline{H}_3$), 2.42 (3H, s, CH_3), 4.26 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.30 (2H, d, $J=8$ Hz, phenyl H), 7.53 (2H, d, $J=8$ Hz, phenyl H), 7.55 (1H, dd, $J_{H,F}=8$, 7 Hz, C_4-H).

(b) In a similar manner to that described for **9a**, the β-ketoester **8c** was treated with tosyl azide, giving **9c** in 88% yield.

(c) A suspension of triphenylphosphazine **10c** (R = Ph) (639 mg, 1 mmol) in dry dioxane (12 ml) was heated at 65—70 °C for 1.5 h. The solution was concentrated to dryness *in vacuo* to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$ as an eluent to give **9c** (360 mg, 96%) and triphenylphosphine oxide (227 mg, 82%).

Reactions of 9a—c with triphenylphosphine (Table I); (i) Ethyl 2-Hydrazono-2-(2,6-dichloro-5-fluoronicotinoyl)acetate (11a) Triphenylphosphine (1.32 g, 5.04 mmol) was added at room temperature to a stirred suspension of **9a** (1.53 g, 5 mmol) in iso-Pr_2O (40 ml). After being stirred for an additional 26 h, the solution was concentrated to dryness *in vacuo*. The oily residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give **11a** (1.43 g, 93%) and triphenylphosphine oxide (1.25 g, 95%). Compound **11a**: mp 145 °C (iso-Pr_2O–*n*-hexane), colorless crystals. *Anal.* Calcd for $C_{10}H_8Cl_2FN_3O_3$: C, 38.98; H, 2.62; Cl, 23.01; F, 6.17; N, 13.64. Found: C, 38.92; H, 2.56; Cl, 23.31; F, 6.04; N, 13.61. IR cm^{-1}: 3370, 3200, 1675. 1665, 1570. EIMS *m/z*: 307 (M^+). ^{1}H-NMR (80 MHz, $CDCl_3$) (a mixture of two geometrical isomers): the major isomer, 1.38 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.36 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.50 (1H, d, $J_{H,F}=8$ Hz, C_4-H), 8.5—10.5 (2H, br s, NH_2, exchangeable with D_2O); the minor isomer, 1.28 (t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.25 (q, $J=7$ Hz, CH_2CH_3).

(ii) {[1-Ethoxycarbonyl-1-(2-chloro-5-fluoro-6-(*p*-tolylthio)nicotinoyl)-methylene]hydrazono}triphenylphosphorane (10b, R = Ph) Triphenylphosphine (560 mg, 2.14 mmol) was added at room temperature to a stirred suspension of **9b** (800 mg, 2.03 mmol) in iso-Pr_2O (15 ml); the mixture did not form a solution. After 15-min stirring, new pale yellow crystals appeared. The mixture was allowed to stand for an additional 20 h. The resulting crystals were collected by filtration to give 1.1 g (83%) of **10b** (R = Ph) as pale yellow prisms, mp 121—122 °C (iso-Pr_2O). *Anal.* Calcd for $C_{35}H_{28}ClFN_3O_3PS$: C, 64.07; H, 4.30; Cl, 5.40; F, 2. 90; N, 6.40; P, 4.72; S, 4.89. Found: C, 64.30; H, 4. 42; Cl, 5.41; F, 2.96; N, 6.44; P, 4.95; S, 5.08. IR cm^{-1}: 1725, 1635, 1585.

(iii) {[1-Ethoxycarbonyl-1-(2,5-difluoro-6-(*p*-tolylthio)nicotinoyl)methylene]hydrazono}triphenylphosphorane (10c, R = Ph) A solution of triphenylphosphine (530 mg, 2.02 mmol) in iso-Pr_2O (5 ml) was added at room temperature to a stirred solution of **9c** (700 mg, 1.86 mmol) in iso-Pr_2O (10 ml). The reaction mixture was allowed to stand for an additional 23 h. The resulting crystals were collected by filtration to give 950 mg (80%) of **10c** (R = Ph) as yellow crystals, mp 133—134 °C. *Anal.* Calcd for $C_{35}H_{28}F_2N_3O_3PS$: C, 65.72; H, 4.41; F, 5.94; N, 6.57; P, 4.84; S, 5.01. Found: C, 65.74; H, 4.53; F, 5.70; N, 6.34; P, 4.94; S, 5.20. IR cm^{-1}: 1725, 1630, 1600. EIMS *m/z*: 377 ($M^+ - 262$). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.38 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.37 (3H, s, CH_3), 4.43 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.2—7.8 (20H, m, aromatic H).

Reaction of 9a with Tricyclohexylphosphine (Table I); {[1-Ethoxycarbonyl-1-(2,6-dichloro-5-fluoronicotinoyl)methylene]hydrazono}tricyclohexylphosphorane (10a, R = Cyclohexyl) Tricyclohexylphosphine (1.44 g, 5.14 mmol) was added at room temperature to a stirred solution of **9a** (1.53 g, 5 mmol) in iso-Pr_2O (25 ml). The mixture formed a wine-colored solution and then gradually turned pale yellow. The solution was kept at room temperature for an additional 15 h with stirring. The resulting crystals were collected by filtration to give 2.33 (80%) of **10a** (R = cyclohexyl) as yellow prisms, mp 117—118 °C (iso-Pr_2O). *Anal.* Calcd for $C_{28}H_{39}Cl_2FN_3O_3P$: C, 57.34; H, 6.70; Cl, 12.09; F, 3.24; N, 7.16; P, 5.28. Found: C, 57.60; H, 7.00; Cl, 12.11;F, 3.01; N, 7.06; P, 5.49. IR cm^{-1}: 1715, 1620, 1580. The filtrate was concentrated to dryness *in vacuo*, and the residue was crystallized from EtOH–*n*-hexane to give the hydrazone **11a** (169 mg, 11%).

Conversion of 10b, c to 11b, c (Table II); (i) Ethyl 2-Hydrazono-2-[2-chloro-5-fluoro-6-(*p*-tolylthio)nicotinoyl]acetate (11b) A Typical Procedure: A suspension of **10b** (R = Ph) (950 mg, 1.45 mmol) in MeOH (16 ml) and H_2O (4 ml) was gently refluxed for 4.5 h with stirring. The solution was concentrated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$, and this solution was washed with water, dried and evaporated. The oily residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give **9b** (63 mg, 11%) as colorless needles, triphenylphosphine oxide (365 mg, 96%), and **11b** (507 mg, 88%). Compound **11b**: mp 122 °C (EtOH), colorless prisms. *Anal.* Calcd for $C_{17}H_{15}ClFN_3O_3S$: C, 51.58; H, 3.82; Cl, 8.96; F, 4.80; N, 10.62; S, 8.10. Found: C, 51.79; H, 4.02; Cl, 9.13; F, 4.92; N, 10.61; S, 8.19. IR cm^{-1}: 3400, 3200, 1680, 1640, 1585. EIMS *m/z*: 395 (M^+). ^{1}H-NMR (80 MHz, DMSO-d_6) (a mixture of two geometrical isomers): the major isomer, 1.26 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.35 (3H, s, CH_3), 4.25 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.28 (2H, d, $J=8$ Hz, phenyl H), 7.48 (2H, d, $J=8$ Hz, phenyl H), 7.89 (1H, d, $J_{H,F}=9$ Hz, C_4-H), 10.65 (2H, br s, NH_2, exchangeable with D_2O); the minor isomer, 1.05 (t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.00 (q, $J=7$ Hz, $C\underline{H}_2CH_3$), 11.75 (br s, NH_2, exchangeable with D_2O).

(ii) Ethyl 2-Hydrazono-2-[2,5-difluoro-6-(*p*-tolylthio)nicotinoyl)]acetate (11c) A Typical Procedure: A stirred suspension of **10c** (R = Ph) (2.25 g, 3.52 mmol) in MeOH (16 ml) and H_2O (4 ml) was gently refluxed for 2 h, during which period the mixture formed a solution and then gave precipitates. The precipitates were collected by filtration and recrystallized from MeOH–H_2O to give 1.30 g (98%) of **11c** as colorless crystals, mp 140 °C. *Anal.* Calcd for $C_{17}H_{15}F_2N_3O_3S$: C, 53.82; H, 3.99; F, 10.02; N, 11.08; S, 8.45. Found: C, 53.78; H, 4.13; F, 10.12; N, 10.95; S, 8.69. IR cm^{-1}: 3400, 3200, 1675. 1635, 1610. EIMS *m/z*: 379 (M^+), 359, 305, 287, 277, 164. ^{1}H-NMR (100 MHz, DMSO-d_6) (a mixture of two geometrical isomers): the major isomer, 1.22 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.36 (3H, s, CH_3), 4.24 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.30 (2H, d, $J=8$ Hz, phenyl H), 7.46 (2H, d, $J=8$ Hz, phenyl H), 7.98 (1H, dd, $J_{H,F}=9$, 7 Hz, C_4-H), *ca.* 10.55 (2H, br s, NH_2, exchangeable with D_2O); the minor isomer, 1.08 (t, $J=7$ Hz, $C\underline{H}_2C\underline{H}_3$), 4.04 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 8.01 (1H, dd, $J_{H,F}=9$, 7 Hz, C_4-H), *ca.* 11.4 (br s, NH_2, exchangeable with D_2O).

Reactions of 9a—c with Tri-*n*-butylphosphine (Table I); (i) Ethyl 7-Chloro-6-fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylate (12a) A Typical Procedure: A solution of tri-*n*-butylphosphine (1.20 g, 6.0 mmol) in iso-Pr_2O (25 ml) was added to a stirred solution of **9a** (1.53 g, 5.0 mmol) in iso-Pr_2O (25 ml) under ice-cooling. Stirring was continued for 15 min, then the solution was allowed to stand at room temperature for an additional 18 h and concentrated to dryness *in vacuo*. The residue was triturated with *n*-hexane. The resulting crystals were collected by filtration and recrystallized from EtOH–iso-Pr_2O to give 280 mg (21%) of **12a** as colorless needles, mp 226—227 °C. *Anal.* Calcd for $C_{10}H_7ClFN_3O_3$: C, 44.22; H, 2.60; Cl, 13.05; F, 6.99; N, 15.47. Found: C, 44.32; H, 2.58; Cl, 12.81; F, 6.77; N, 15.39. IR cm^{-1}: 3150 (m), 1720 (m), 1690 (s), 1635 (vs), 1600 (ms); IR ($CHCl_3$, 1 mm) cm^{-1}: 3375 (m), 3200 (w), 1730 (vs), 1640 (vs), 1610 (s). EIMS *m/z*: 271 (M^+), 226, 199, 198, 172, 171. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.40 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.45 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 8.29 (1H, d, $J_{H,F}=6.5$ Hz, C_5-H), *ca.* 13 (1H, br, NH, exchangeable with D_2O). UV λ_{max} (log ε) nm: 204 (4.29), 213 (sh, 4.25), 251 (4.11), 295 (3.53), 348 (sh, 4.11), 363 (4.14). The filtrate was concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$ as an eluent, followed by crystallization from EtOH–*n*-hexane, to give the hydrazone **11a** (540 mg, 35%).

(ii) Ethyl 6-Fluoro-7-(*p*-tolylthio)-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylate (12b) (Table I) Typical Procedures: (a) Tri-*n*-butylphosphine (870 mg, 4.31 mmol) was added to a stirred suspension of **9b** (1.47 g, 3.74 mmol) in dry diglyme (60 ml) at room temperature. The solution was stirred for 30 min, then heated at 125—130 °C for 3 h, and concentrated to dryness *in vacuo*. The residue was triturated with EtOH–*n*-hexane, and the resulting crystals were collected by filtration to give 560 mg (42%) of **12b** as colorless prisms. The filtrate was concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$, and subsequently with $CHCl_3$–AcOEt (50 : 1) as an eluent to give **11b** (280 mg, 19%) and **12b** (190 mg, 14%). Compound **12b**: mp 225—226 °C (EtOH–iso-Pr_2O), colorless prisms. *Anal.* Calcd for $C_{17}H_{14}FN_3O_3S$: C, 56.82; H, 3.93; F, 5.29; N, 11.69; S, 8.92. Found: C, 56.86; H, 3.95; F, 5.08; N, 11.53; S, 8.74. IR cm^{-1}: 3200 (mw), 3150 (w), 1735 (s), 1690 (ms), 1645 (ms), 1610 (vs); IR ($CHCl_3$, 1 mm) cm^{-1}: 3375 (m) (NH), 3200 (w), 1730 (s), 1630 (vs), 1610 (s). EIMS *m/z*: 359 (M^+), 314, 287. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.38 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.42 (3H, s, CH_3), 4.40 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.25 (2H, d, $J=8$ Hz, phenyl H), 7.45 (2H, d, $J=8$ Hz, phenyl H), 8.00 (1H, d, $J_{H,F}=8$ Hz, C_5-H), 9.5—10.5 (1H, br, NH, exchangeable with D_2O). UV λ_{max} (log ε) nm: 202 (4.33), 215 (sh, 4.24), 248 (4.33), 355 (4.30), 371 (4.34).

(b) Tri-*n*-butylphosphine (808 mg, 4 mmol) was added to a stirred suspension of **9c** (1.51 g, 4 mmol) in iso-Pr_2O (20 ml) at room temperature. During the reaction course, the mixture formed a yellow solution, and then gave a soft yellow solid which gradually formed colorless crystals. Stirring was continued for 3 h, then the resulting crystals were collected by filtration to give 880 mg (61%) of **12b**.

Attempted Cyclization of the Hydrazone 11a (Table II) Typical Procedures: (a) A stirred mixture of **11a** (200 mg), anhydrous K_2CO_3 (140 mg) and dioxane (6 ml) was heated to reflux for 3.5 h, and then concentrated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$, and this solution was washed with water, dried and evaporated. The residue

was crystallized from iso-Pr_2O–*n*-hexane to give **9a** (125 mg, 63%). A trace amount of **12a** was obtained from the filtrate.

(b) Potassium *tert*-butoxide (1.07 g, 8.77 mmol) was added to a stirred solution of **11a** (1.35 g, 4.38 mmol) in dry dioxane (20 ml) under ice-cooling. The mixture was stirred for 2 h at room temperature. The solution was concentrated to dryness *in vacuo*. After addition of dilute AcOH, the mixture was extracted with $CHCl_3$ and the extract was dried. The solvent was evaporated off, and the residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give the *β*-ketoester **8a** (456 mg, 37%). Compound **12a** was not obtained.

Intramolecular Cyclization of the Hydrazones 11b and 11c to 12b (Table II) Typical Procedures: (a) A mixture of **11c** (1.05 g, 2.77 mmol), $NaHCO_3$ (350 mg, 4.17 mmol) and dioxane (15 ml) was heated to reflux for 8 h. The resulting crystals were collected by filtration and washed with water to give 974 mg (98%) of **12b**.

(b) A mixture of **11c** (700 mg, 1.85 mmol) and dry diglyme (7 ml) was heated at 125—130 °C for 1.5 h and then concentrated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$, and this solution was washed with water, dried and evaporated. The residue was triturated with iso-Pr_2O, and the resulting crystals were collected by filtration to give 430 mg (65%) of **12b**. In a similar manner, **11b** gave **12b** in 11% yield.

(c) Potassium *tert*-butoxide (450 mg, 4.02 mmol) was added portionwise to a stirred solution of **11c** (760 mg, 2.01 mmol) in dry dioxane (15 ml) at room temperature. Stirring was continued for 1 h, then the solution was neutralized with dilute AcOH, and concentrated to dryness *in vacuo* to leave a crystalline residue. After addition of water, the crystals were collected by filtration and dried to give 640 mg (89%) of **12b**.

Ethyl 4-Chloro-6-fluoro-7-(*p*-tolylthio)pyrido[2,3-*c*]pyridazine-3-carboxylate (13) A stirred mixture of **12b** (1.31 g, 3.65 mmol) and phosphorus oxychloride (7 ml) was heated at 100 °C for 2 h. The solution was concentrated to dryness *in vacuo*. After addition of $CHCl_3$ and ice-water, the mixture was neutralized with 2 N Na_2CO_3 and then extracted with $CHCl_3$. The extract was dried and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give **13** (1.23 g, 89%) as pale yellow needles, mp 142—143 °C. *Anal.* Calcd for $C_{17}H_{13}ClFN_3O_2S$: C, 54.04; H, 3.47; Cl, 9.38; F, 5.03; N, 11.12; S, 8.49. Found: C, 54.22; H, 3.27; Cl, 9.51; F, 4.89; N, 11.06; S, 8.55. IR cm^{-1}: 1725, 1610. EIMS *m/z*: 377 (M^+), 376, 362, 332, 305, 304. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.47 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.44 (3H, s, CH_3), 4.55 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.30 (2H, d, J=8 Hz, phenyl H), 7.55 (2H, d, J=8 Hz, phenyl H), 8.00 (1H, d, $J_{H,F}$=8.5, C_5-H). UV λ_{max} (log ε) nm: 216 (4.42), 268 (4.39), 360 (4.04).

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References and Notes

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