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

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A new and convenient synthesis of 6-fluoro-4(1H)-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(1H)-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, which were cyclized to 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) and enoxacin (2) are now widely used in clinical practice. Their chemical structures have a common a 4(1H)-oxopyridine-3-carboxylic acid moiety, which has been accepted as an indispensable functional group for the antibacterial activity. In the previous paper, we reported the synthesis and antibacterial activity of the 6-fluoro- and 6,8-difluoro-4(1H)-oxocinnolone-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(1H)-oxopyrido[2,3-c]pyridazine-3-carboxylic acids (4).

Several methods for the construction of a 4(1H)-oxopyridino[2,3-c]pyridazine ring have been reported thus far, but they are not available for the synthesis of a key intermediate, 7-halo- or 7-arylthio-6-fluoro-4(1H)-oxopyridino[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(1H)-oxopyrimido[4,5-c]pyridazine- and 4(1H)-oxocinnolone-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. 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.

The 2-diazo-β-ketoesters 9a-c were prepared by two

![Diagram](chart1.png)

Reagents: i SOCl₂; ii EtO₂CH(CO₂Et)₂; iii H₂O⁺; iv p-CH₃C₆H₄SO₂Na; v p-CH₃C₆H₄SO₂Na; vi N₂CHCO₂Et at 50-55°C

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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 \( \beta \)-ketoesters 8a-c with tosyl azide. The \( \beta \)-ketoesters 8a and 8c, in turn, were obtained by condensation of 6a and 6c with diethyl ethoxymagnesiummalonate and subsequent acidic hydrolysis of the intermediary nicotinyl 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 \( \alpha \)-diazo-\( \beta \)-ketoester 9 with triphenyl-, tricyclohexyl- and \( \alpha \)-\( \alpha \)-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(1H)-oxopyridido[2,3-c]pyridazine-3-carboxylate (12a), but yielded exclusively the intermediary triphenylphosphazene 10a (R = Ph). However, this compound 10a was so labile to moisture that the hydrazine 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 tricyclohexylphosphazene 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 \( \alpha \)-\( \alpha \)-butylphosphine at room temperature, the reductive cyclization occurred to give the desired product 12a though in a poor (ca. 21%) yield, together with the hydrazine 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-\( \alpha \)-\( \alpha \)-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-\( \alpha \)-\( \alpha \)-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 triphenylphosphazene 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 \( \alpha \)-\( \alpha \)-\( \alpha \)-diazo-\( \beta \)-ketoester 9c with tri-\( \alpha \)-\( \alpha \)-butylphosphine most efficiently produced the cyclized compounds 12, particularly 12b in a one-pot process.

The phosphazenes 10a-c were, on the whole, too unstable to be purified and gradually decomposed when allowed to stand under ambient conditions. The triphenylphosphazene 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 triphenylphosphazene 10c (R = Ph) was converted, in the presence of moisture, into the hydrazine 11c and triphenylphosphine oxide; even passage through the silica gel column completely transformed 10c (R = Ph) into 11c. In general, the conversion of
the phosphazene 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. Use of the 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

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Solvent</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yields (%) of products</th>
<th>Other(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td>iso-Pr₂O</td>
<td>11a</td>
<td>7</td>
<td>9a (63)</td>
<td>8a (37)</td>
</tr>
<tr>
<td></td>
<td>Dioxane</td>
<td>11b</td>
<td>11b</td>
<td>9b (15), re</td>
<td></td>
</tr>
<tr>
<td>11b</td>
<td>iso-Pr₂O</td>
<td>11b</td>
<td>7</td>
<td>8b (39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diglyme</td>
<td>11b</td>
<td>0.5</td>
<td>8b (98)</td>
<td></td>
</tr>
<tr>
<td>11c</td>
<td>iso-Pr₂O</td>
<td>11c</td>
<td>7</td>
<td>12a (11)</td>
<td>12b (65)</td>
</tr>
<tr>
<td></td>
<td>Dioxane</td>
<td>11c</td>
<td>7</td>
<td>12b (89)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NaHCO₃</td>
<td>12b</td>
<td>12b</td>
<td>12b (89)</td>
<td></td>
</tr>
</tbody>
</table>

* a) The hydrazones 11 were heated to reflux in iso-Pr₂O or dioxane and at 125—130°C in diglyme. b) Without a base. c) Not detectable. d) A trace amount. e) Not isolated. rc=recycling 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 (νNH) and 3150 (νOH) cm⁻¹ and three strong bands (νCO) at 1735, 1690 and 1645 cm⁻¹, whereas in a chloroform solution, it shows two absorption bands at 3375 (νNH) and 3200 (νOH) 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 trialkylyphosphine leading to the pyrido[2,3-c]pyridazine 12b are given in Chart 4. Compound 9c reacts with trialkylyphosphine to form initially the trialkylphosphazene 10c, which then would undergo hydration to 14 (path a), followed competitively, or either...
by elimination of trialkyphosphine oxide to give the hydrazone 11c or by cyclization with loss of trialkyphosphine 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 hydrazones 11a or the triphenylphosphazenes 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-butylphosphazene 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(1H)-oxopyridine[2,3-c]pyrazidine-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(1H)-oxopyridine[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 (1H-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 Na2SO4.

2,6-Dichloro-5-fluoronicotinic Acid (5a) (a) A stirred mixture of 2,6-dichloro-5-fluoropyridine-3-carboxylic acid (31) (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 (H2O-EtOH) (lit.89 mp 153–154°C). IR cm⁻¹: 1700, 1647, 1610 (υC=O, υCH2, υCH3), 3440, 2930 (υOH, υNH, υCH2, υCH3, υCH), 1650 (υC=O), 1450 (υCH2, υCH3), 1380 (υCH2, υCH3, υCH), 1180 (υC=O), 820, 750 (υC=O, υC=C).

(b) A stirred mixture of 2,6-dichloro-5-fluoronicotinonitrile (31) (30 g, 157 mmol) and concentrated H2SO4 (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 mixture of ethyl 2,5-difluoro-6-(p-tolylthio)nicotinate (31) (30 g, 97 mmol), tert-ButOH (240 ml), H2O (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–H2O).
Anal. Caled for C_{6}H_{12}F_{10}N_{2}O_{3}: C, 55.51; H, 3.23; F, 13.15; 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⁺). H-NMR (60 MHz, CDCl₃-DMSO-d₆): 2.41 (3H, s, CH₃), 7.26 (2H, d, J=8 Hz, phenyl H), 7.49 (2H, d, J=8 Hz, phenyl H), 7.70 (1H, d, J=7.5 Hz, C₆H₅), ca. 8.0 (1H, br s, COOH, exchanged with D₂O).

In a similar manner, ethyl 2-chloro-5-fluoro-6-(p-tolylthio)nicotinoylacetate (8a) was subjected to hydrolysis to give 9a, an olefinic acid, mp 155–156°C (EIMS). Anal. Caled for C_{14}H_{18}ClO_{3}N: C, 62.80; H, 5.48; N, 7.70. Found: C, 62.82; H, 5.49; N, 7.59. IR cm⁻¹: 3400 (OH), 1730 (C=O). 

2-Chloro-5-fluoro-6-(p-tolylthio)nicotinoylacetate (8a) A solution of p-toluenesulfonic acid (3.0 g, 20 mmol) in EtOH (70 ml) was added to a stirred solution of p-tetrafluorobenzene (3.7 g, 20 mmol) in EtOH (70 ml) at room temperature. The reaction mixture was then diluted with EtOAc. The residue was washed with water, and dried. The filtrate was neutralized with NaOH and then concentrated in vacuo. The residue was recrystallized from CHCl₃-CH₂Cl₂, and then dried, and the final product was characterized by IR, NMR, and elemental analysis. 

1-Chloro-2-nitrobenzene (9) A solution of p-toluenesulfonyl chloride (10.0 g, 51 mmol) in CH₂Cl₂ (20 ml) was added under cooling to a stirred solution of the β-ketoester 8a (14.0 g, 50 mmol) and NaI (N, 71 ml) in CH₂Cl₂ (100 ml). The solution was stirred for an additional 15 min, and then extracted with ether. The residue was then recrystallized from CHCl₃-CH₂Cl₂, and then dried, and the final product was characterized by IR, NMR, and elemental analysis. 

Diethyl 2-Chloro-5-fluoro-6-(p-tolylthio)nicotinoylacetate (9a) A mixture of magnesium (2.9 g, 18 mmol) and absolute EtOH (1.7 ml) and CCl₄ (0.3 ml) was heated. When the evaporation of hydrogen gas began, a solution of diethyl malonate (19.8 g, 124 mmol) in absolute EtOH (17 ml) and dry Et₂O (100 ml) was added portionwise to the initial mixture with stirring. After the evaporation 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 Et₂O (50 ml) was added portionwise over 10 min to the above mixture. The solution was stirred for an additional 10 min, and then dried with 2 N HCl (80 ml) under cooling. The organic layer was separated and dried. Evaporation of the solvent left 4.5 g of an oil. EIMS m/z: 216 (M⁺ - Cl), 176 (M⁺ - CH₃), 174, 131, 120, 95, 82, 79, 78, 77, 60, 43, 31, 29, 28, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3. 

Diethyl 2-Chloro-5-fluoro-6-(p-tolylthio)nicotinoylacetate (9a) A solution of p-toluenesulfonyl chloride (10.0 g, 51 mmol) in CH₂Cl₂ (20 ml) was added under cooling to a stirred solution of the β-ketoester 8a (4.3 g, 12 mmol) and NaI (N, 30 ml) in CH₂Cl₂ (50 ml). The solution was stirred for an additional 15 min, and then cooled to room temperature for 30 min, and concentrated in vacuo below 50°C. After addition of 2 N NaOH solution (100 ml) and ice-water (100 ml), the mixture was then extracted with EtOAc. The extract was dried and the solvent was then evaporated off in vacuo below 50°C. The residue was then recrystallized from EtOH-n-hexane to give 4.2 g (89% of 9a) as colorless needles, mp 99–100°C. 

Anal. Caled for C_{14}H_{18}ClO_{3}N: C, 58.85; H, 5.33; Cl, 9.00; F, 4.82; N, 10.65. Found: C, 58.85; H, 5.33; Cl, 9.00; F, 4.82; N, 10.65. IR cm⁻¹: 1730 (C=O), 1660 (CH=O), 1490 (N=O). 

By the procedure (a) for 9a, the diethyl diazoacetate (9a) was treated with the nicotinoyl chloride 6b to give 9b in 82% yield. 

Diethyl 2-Chloro-5-fluoro-6-(p-tolylthio)nicotinoylacetate (9a) (a) Ethyl diazoacetate (16.6 g, 146 mmol) was added portionwise to a suspension of the nicotinoyl chloride 6c (16.0 g, 53.4 mmol) in CHCl₃ (6 ml) under cooling. The mixture was then 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. Caled for C_{14}H_{15}F_{2}N_{2}O_{3}S: C, 54.11; H, 3.47; F, 10.07; N, 11.14; S, 8.50. Found: C, 54.07; H, 3.33; F, 10.03; N, 10.62; S, 7.61. IR cm⁻¹: 1840 (N=O), 1620 (C=O). 

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\[ J = 7 F, \text{CH}_2 \text{CH}_2 J \], 2.42 (3H, s, CH\(_3\)), 4.26 (2H, q, J = 7Hz, CH\(_2\)CH\(_3\)), 7.30 (2H, d, J = 8Hz, phenyl H), 7.53 (2H, d, J = 8Hz, phenyl H), 7.55 (1H, dd, J\(_{12}\) = 8, 7 Hz, CH\(_2\) C).  

(b) In a similar manner to that described for \( \text{9a} \), the \( \beta \)-ketoester \( \text{8c} \) was treated with \\( \text{OsO}_4 \), giving \( \text{9c} \) in 88% yield.  

A suspension of triphenylphosphine 10c (R = Ph) (639 mg, 1 mmol) in dry dioctane (12 ml) was heated at 65—70°C for 1.5 h. The solution was concentrated to dryness in vacuo to leave an oil residue, which was chromatographed on silica gel with CH\(_2\)Cl\(_2\) as an eluent to give \( \text{9c} \) (360 mg, 96%) and triphenylphosphine oxide (22%) as the major isomer, 1.38 (3H, t, J = 7Hz, CH\(_2\)CH\(_3\)), 4.26 (2H, q, J = 7Hz, CH\(_2\)CH\(_3\)), 7.50 (1H, d, J\(_{12}\) = 8Hz, C\(_6\)H\(_5\)), 8.5—10.5 (2H, brs, NH\(_2\), exchangeable with D\(_2\)O). The minor isomer, 1.28 (3H, t, J = 7Hz, CH\(_2\)CH\(_3\)), 4.25 (q, J = 7Hz, CH\(_2\)CH\(_3\)).  

(ii) 1-[Ethoxycarbonyl-1-(2,5-difluoro-6-p-tolyphenoxy)]methyl[ethylene]hydroxytriphosphonophene (10b, R = Ph) was added at room temperature to a stirred suspension of \( \text{9a} \) (800 mg, 2.03 mmol) in isopropyl alcohol (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 2 h. The resulting crystals were collected by filtration and recrystallized from EthOH-isopropyl alcohol to give \( 1.83 \) (83% of \( 10 \) = R = Ph) as pale yellow prisms, mp 121—122°C (isopropyl alcohol). Anal. Calcd. for \( C_{25}H_{22}F_2N_2O_5PS; \) C, 65.67; H, 4.41; F, 5.94; N, 6.57; P, 5.87; S, 6.81. Found: C, 65.67; H, 4.41; F, 5.94; N, 6.57; P, 5.87. IR cm\(^{-1}\): 1725, 1655, 1585.  

(iii) 1-[Ethoxycarbonyl-1-(2,5-difluoro-6-p-tolyphenoxy)]methyl[ethylene]hydroxytriphosphonophene (10c, R = Ph) was a solution of triphenylphosphate (550 mg, 2.02 mmol) in \\( \text{CH}_2\text{Cl}_2\) at room temperature to a stirred solution of \( \text{9a} \) (700 mg, 1.86 mmol) in isopropyl alcohol (10 ml). The reaction mixture was allowed to stand for an additional 2.3 h. The resulting crystals were collected by filtration and recrystallized from EthOH-isopropyl alcohol to give \( 1.83 \) (80% of \( 10 \) = R = Ph) as pale yellow prisms, mp 121—122°C (isopropyl alcohol). Anal. Calcd. for \( C_{26}H_{24}F_2N_2O_5PS; \) C, 65.72; H, 4.41; F, 5.94; N, 6.57; P, 5.87; S, 6.81. Found: C, 65.72; H, 4.41; F, 5.94; N, 6.57; P, 5.87. IR cm\(^{-1}\): 1725, 1650, 1600. EIMS m/z: 377 (M\(^+\)), 375 (M\(^+\)-2). The residue was triturated with hexane and the crystals were collected by filtration and recrystallized from EthOH-isopropyl alcohol to give \( 1.83 \) (80% of \( 10 \) = R = Ph) as pale yellow prisms, mp 121—122°C (isopropyl alcohol). Anal. Calcd. for \( C_{26}H_{24}F_2N_2O_5PS; \) C, 65.72; H, 4.41; F, 5.94; N, 6.57; P, 5.87. Found: C, 65.72; H, 4.41; F, 5.94; N, 6.57. IR cm\(^{-1}\): 1715, 1620, 1580. The filtrate was concentrated to dryness in vacuo, and the residue was crystallized from EthOH-n-hexane to give the hydrate \( 11a \) (169 mg, 11%).  

Conversion of 10b, c to 11b, c (Table 1); (ii) Ethyl 2-Hydroxy-2-[2,5-chloro-fluo-5-p-tolyloxy]acetate (11b) A Typical Procedure: A solution of 10b (R = Ph) (950 mg, 1.45 mmol) in MeOH (16 ml) and H\(_2\)O (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 the solution was added slowly to a soft yellow precipitate, water-dried, and evaporated. The yellow residue was chromatographed on silica gel with CHCl\(_3\) as an eluent to give \( 11b \) (63% mg, 11%) as colorless needles, triphenylphosphine oxide (365 mg, 96%), and \( 11b \) (507 mg, 88%). Compound 11b mp 132°C (EtOH), colorless prisms. Anal. Calcd. for \( C_{26}H_{24}F_2N_2O_5PS; \) 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, 8.93; F, 4.92; N, 10.61; S, 8.19. IR cm\(^{-1}\): 3400, 3200, 1680, 1640, 1585. EIMS m/z: 395 (M\(^+\)). The residue was triturated with hexane and the crystals were collected by filtration and recrystallized from EthOH-n-hexane to give the hydrate \( 11a \) (169 mg, 11%).  

Approximate Cyiation of the Hydrate \( 11a \) (Table 1) Typical Procedure: A stirred mixture of \( 11a \) (200 mg), anhydrous K\(_2\)CO\(_3\) (140 mg) and diocon (20 ml) was heated to reflux for 3.5 h, and then concentrated to dryness in vacuo. The residue was dissolved in CHCl\(_3\), and the solution was washed with water, dried, and evaporated. The residue was triturated with hexane and the crystals were collected by filtration and recrystallized from EthOH-n-hexane to give the hydrate \( 11a \) (169 mg, 11%).
was crystallized from iso-Pr₂O- 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 CHCl₃ and the extract was dried. The solvent was evaporated off, and the residue was chromatographed on silica gel with CHCl₃ 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 1)

Typical Procedures: (a) A mixture of 11e (1.05 g, 2.77 mmol), NaHCO₃ (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 11e (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 CHCl₃, and this solution was washed with water, dried and evaporated. The residue was triturated with iso-Pr₂O, 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 11e (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-tolythio)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 CHCl₃ and ice-water, the mixture was neutralized with 2 N Na₂CO₃ and then extracted with CHCl₃. The extract was dried and concentrated to dryness in vacuo. The residue was chromatographed on silica gel with CHCl₃, as an eluent to give 13 (1.23 g, 89%) as pale yellow needles, mp 142—143 °C. Anal. Calcd for C₁₇H₁₄ClF₄N₂O₃S: 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. ¹H-NMR (80 MHz, CDCl₃): 1.47 (3H, t, J=7 Hz, CH₂CH₂CH₃), 2.44 (3H, s, CH₃), 4.55 (2H, d, J=7 Hz, CH₂CH₂CH₃), 7.30 (2H, d, J=8 Hz, phenyl H), 7.55 (2H, d, J=8 Hz, phenyl H), 8.00 (1H, d, J=8 Hz, C₅-H). UV λmax (log ε nm): 216 (4.42), 268 (4.39), 360 (4.04).

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References and Notes

1) This work was disclosed in part in Japan. Patent Kokai 60-185781 (1985) [Chem. Abstr., 104, 207292k (1986)].