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Addition of 4-Ethoxyimidazoles to Dimethyl Acetylenedicarboxylate and Transformation of the Adducts to Pyrimidin-5-yl Acetates[1)]

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Four new 4-ethoxy-2-substituted imidazoles (**1**) were synthesized and high reactivity toward electrophiles was observed at the 5-position rather than the N atoms. For example, **1** reacted with dimethyl acetylenedicarboxylate to afford dimethyl (4-ethoxyimidazol-5-yl)fumarates (**6**) and -maleates (**5**). When **6** was treated with acid, a novel ring transformation occurred to give methyl (6-ethoxycarbonyl-3,4-dihydro-4-oxopyrimidin-5-yl)acetates (**12**).

Keywords——4-ethoxyimidazole; pyrimidin-5-yl acetate; ring transformation; synthesis; benzylation; addition; dimethyl acetylenedicarboxylate

Imidazole derivatives are well known as useful chemical compounds that show many biological activities and can be used therapeutically.[2)] Recently new imidazole acetic acid derivatives having diuretic and antihypertensive activities have been found.[3)]

In the course of studying *N*-unsubstituted 4-ethoxyimidazoles we found that the 5-position rather than the N atoms exhibits high reactivity toward electrophiles. Thus, the reaction between 4-ethoxy-2-phenylimidazole (**1a**) and benzyl chloride did not give the *N*-benzyl derivative (**2a**) but the 5-benzyl (**3a**) and the 5,5-dibenzyl (**4a**) derivatives as shown in Chart 1.

Taking advantage of the reactivity of C-5 position, we studied the C–C bond formation of 4-ethoxy-2-substituted imidazoles and synthesized new imidazole derivatives.

Synthesis and Reactivity of 4-Ethoxy-2-substituted Imidazoles (1)

To date, there has been only one article[4)] reporting the synthesis of *N*-unsubstituted 4-ethoxyimidazoles in yields of 10—35% from acylglycinamides. We modified the reaction conditions used by Kato *et al.*[4)] to get **1a** in 80% yield. Under similar conditions, four new 4-ethoxy-2-substituted imidazoles (**1b—e**) were synthesized. The Vilsmeier reaction of **1a** gave the 5-formyl derivative (**11a**) in 86% yield. The reaction of **1a** with dimethyl acetylenedicarboxylate (DMAD) gave dimethyl (4-ethoxy-2-phenylimidazol-5-yl)fumarate (**6a**) and -maleate (**5a**). The structural determinations of **5a** and **6a** were carried out by means of elemental analyses, proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectroscopy, and chemical reactions. As these two compounds gave the same imidazole succinate (**9a**) on catalytic hydrogenation, **5a** and **6a** are geometrical isomers. Compound **5a** was identified as the (*Z*)-isomer, as it reacted with benzylamine in the presence of trimethyl aluminum[5)] to afford the maleimide derivative (**10a**) (Chart 2).

The structures of **5b—e** and **6b—e**, which were obtained by the reaction between **1b—e** and DMAD, were determined by comparison of the NMR spectra with those of **5a** and **6a**. Namely, the vinyl protons of **6a—e** appeared at lower fields by about 50 Hz than those of **5a—e** (Table I). This value was consistent with that calculated from the chemical shifts for olefinic

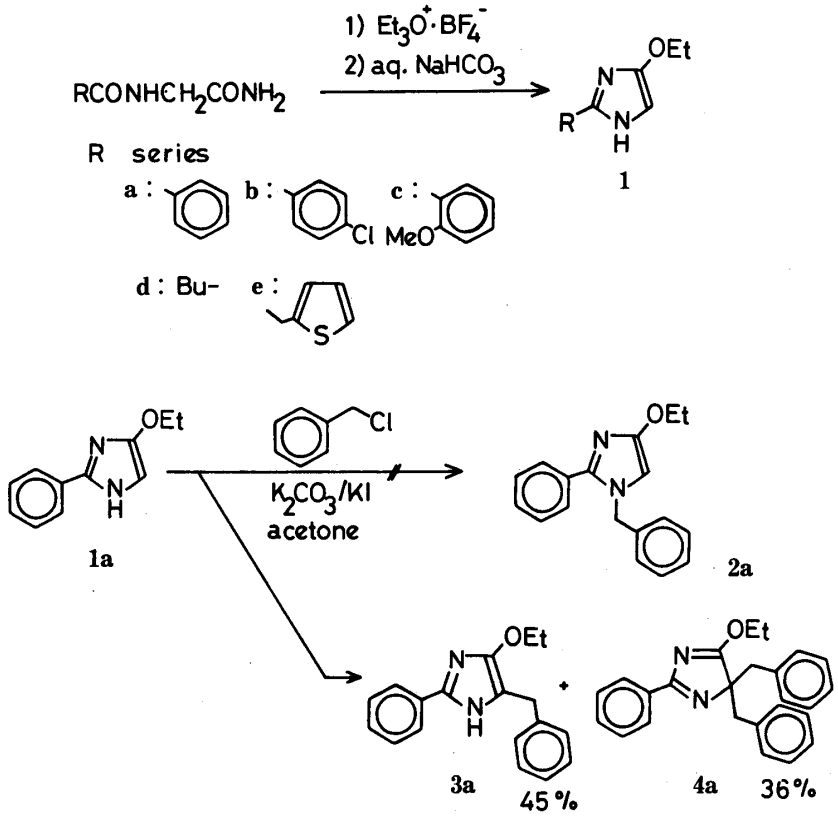

Chart 1

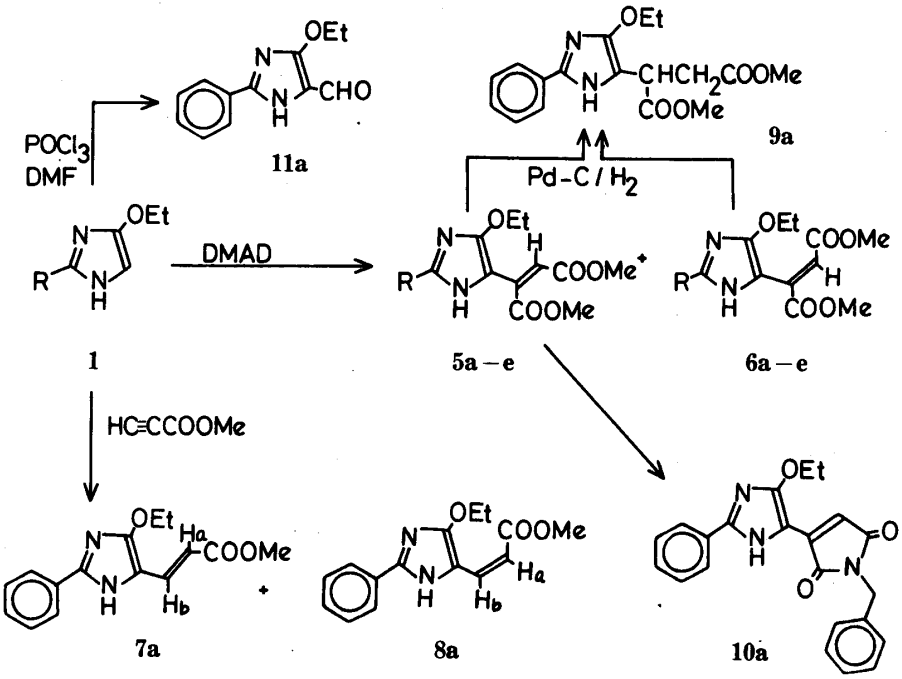

Chart 2

protons.[6] The reaction of **1a** with methyl propiolate gave (*E*)- and (*Z*)-methyl 3-(4-ethoxy-2-phenylimidazol-5-yl)acrylates (**7a** and **8a**). In the NMR spectra of **7a** and **8a**, the coupling constants between H_a and H_b were 16 and 12 Hz, respectively, so that the former was the (*E*)-isomer and the latter was the (*Z*)-isomer.

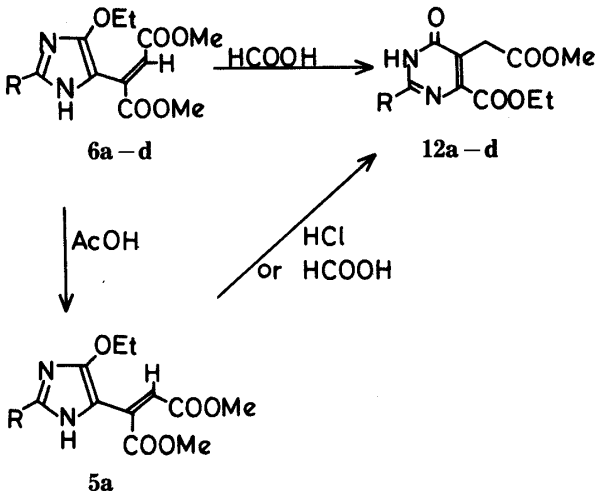

Chart 3

TABLE I. Chemical Shifts (δ) of Vinyl Protons of **5a**—**e** and **6a**—**e**

Series	5	6
a	5.85[a]	6.30[a]
b	5.47[a]	6.20[a]
c	5.35[b]	6.03[b]
d	5.35[b]	5.97[b]
e	5.35[b]	5.95[b]

a) DMSO-d_6. *b*) $CDCl_3$.

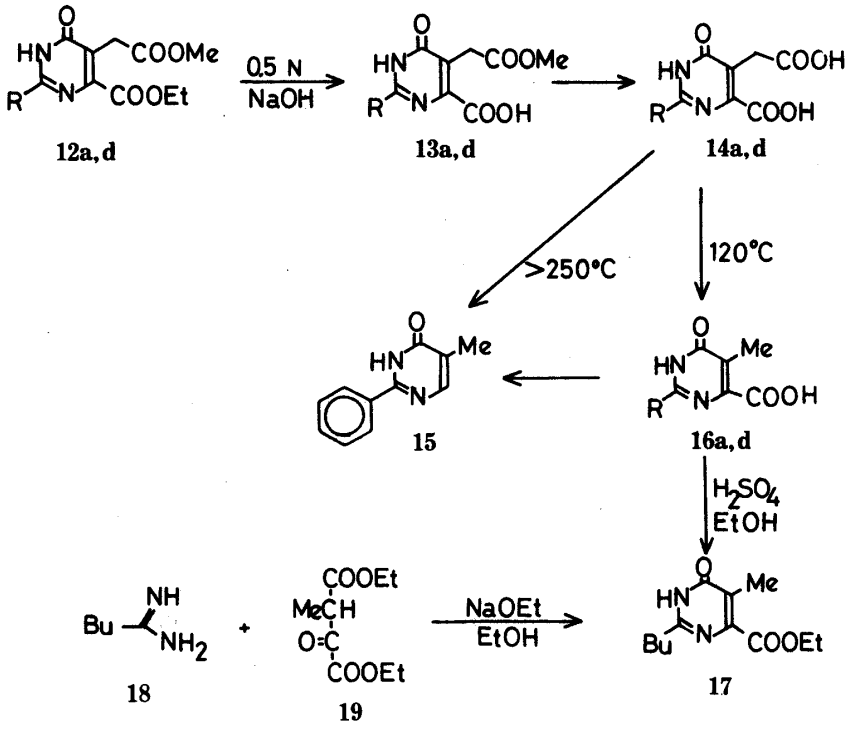

Chart 4

Transformation of 5 to Pyrimidin-5-yl Acetates (12)

A mixture of **6a**, acetic acid and 1,2-dichloroethane was refluxed to afford **5a** in 78% yield. Treatment of **5a** in a mixture of 1 N HCl and dioxane at 60—65 °C gave methyl (6-ethoxycarbonyl-3,4-dihydro-4-oxo-2-phenylpyrimidin-5-yl)acetate (**12a**) in 46% yield; **6a** was also converted to the same compound (**12a**) by heating in formic acid. This result might be explained by the isomerization of **6a** to **5a** followed by the transformation of **5a** to **12a**. Compound **12a** was also obtained in 75% overall yield from **1a** when the reaction was carried out without isolation of **5a** and **6a**. Similarly, **12b**—**d** were prepared from **5b**—**d** and **6b**—**d** (Chart 3).

The structures of the products **12** were determined on the basis of elemental analyses, NMR and mass spectra and a sequence of degradative reactions as shown in Chart 4.

Hydrolysis of **12a** with 1.6 eq of sodium hydroxide in aqueous methanol gave the

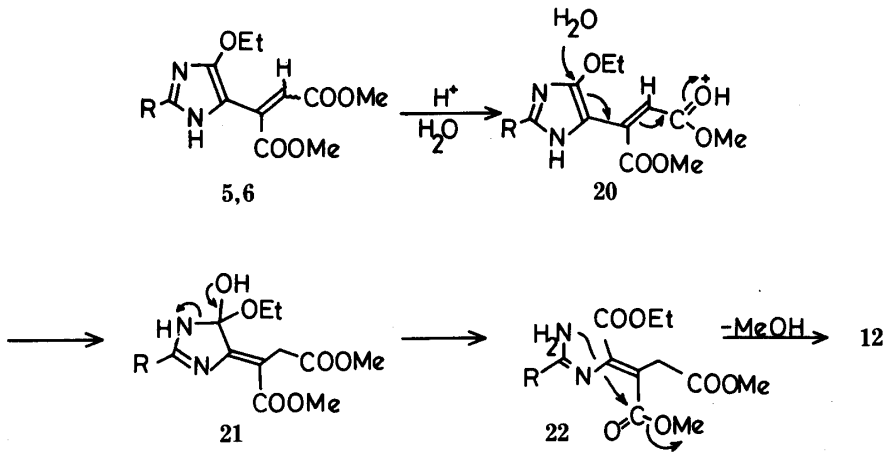

Chart 5

monocarboxylic acid (**13a**) and further alkali treatment gave the dicarboxylic acid (**14a**). Decarboxylation of **14a** by heating gave the 5-methyl derivative[7] (**15** or **16a**) depending upon the reaction temperature. Similarly, hydrolysis of **12d** with a large excess of sodium hydroxide followed by heating at 120 °C afforded **16d**. Esterification of **16d** gave the ethyl ester (**17**), whose melting point and NMR spectral data were identical with those of the sample synthesized by coupling diethyl 2-oxo-3-methylsuccinate (**19**) with pentanamidine (**18**).[8] The mechanism of the reaction which produced **12** from **5** or **6** is speculated to be as shown in Chart 5. Protonation of **5** and **6** makes the 4-position susceptible to attack by water to give **21**. This unstable intermediate appears to undergo rupture of the imidazole ring to give **22**, which is recyclized to a stable pyrimidine (**12**).

There have been few reports concerning C–C bond formation reactions of imidazoles except for hydroxymethylation[9] and Mannich reactions.[10] Moreover, there have been no reports to date concerning the reactivity of *N*-unsubstituted 4-alkoxyimidazoles.[11] We have found high reactivity at the 5-position of 4-ethoxy-2-substituted imidazoles (**1**), an addition reaction of **1** to an active triple bond, and a novel transformation reaction of the adducts (**5** and **6**) to the pyrimidine derivatives (**12**). These pyrimidines cannot be produced by the ordinary well-known methods.[12] Since compounds **12** have two carboxyesters, they might be good precursors for the synthesis of compounds with more complicated heterocyclic systems, such as pyrido[3,4-*d*]pyrimidine.[13]

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were obtained on a Varian EM-360 NMR spectrometer, a Varian T-60 NMR spectrometer, and a Varian XL-100 A NMR spectrometer. For flash column chromatography Silica gel 60 (Merck 0.040—0.063 mm, Art 9385) was used. Infrared (IR) and ultraviolet (UV) spectra were recorded on a Hitachi 215 spectrophotometer and a Hitachi EPS-3T spectrometer, respectively. Mass spectra (MS) were determined on a JEOL JMS01SC-2 spectrometer.

4-Ethoxy-2-substituted Imidazole (1)——A mixture of Meerwein reagent[14] (140 g), which was prepared from $BF_3 \cdot OEt_2$ (375 ml), epichlorohydrin (140 g) in ethyl ether (1 l), and hippuric amide (120 g) in CH_2Cl_2 (1 l) was stirred for 7 d at room temperature. The reaction mixture was poured into an aqueous saturated $NaHCO_3$ solution (5 l) to separate **1a** (103 g) as colorless needles (82% yield), mp 176—177 °C (lit.[4] 169—171 °C). Compounds **1b—e** were synthesized similarly. **1b**: Colorless needles (61% yield), mp 209—210 °C (dec.) (from EtOH). *Anal.* Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; Cl, 15.92; N, 12.58. Found: C, 59.45; H, 5.07; Cl, 16.21; N, 12.06. **1d**: Pale yellow powder (52% yield), mp 65—66 °C (from $CHCl_3$). *Anal.* Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 63.92; H, 9.63; N, 16.32. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7 Hz), 2.63 (2H, t like, J=8 Hz), 3.98 (2H, q, J=7 Hz), 6.13 (1H, s). **1c**: Pink plates (88% yield), mp 101—102 °C (from isopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t,

$J=7$ Hz), 3.92 (3H, s), 4.07 (2H, q, $J=7$ Hz), 6.27 (1H, s), 6.7—7.3 (3H, m), 8.1—8.3 (1H, m). **1e**: Gray prisms (35% yield), mp 124—125 °C (from ethyl acetate–isopropyl ether). *Anal.* Calcd for $C_{10}H_{12}N_2OS$: C, 57.66; H, 5.81; N, 13.45. Found: C, 57.63; H, 5.76; N, 13.22. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (3H, t, $J=7$ Hz), 3.88 (2H, q, $J=7$ Hz), 4.01 (2H, s), 6.15 (1H, s), 6.7—7.0 (2H, m), 7.1—7.4 (1H, m).

Benzylation of 4-Ethoxy-2-phenylimidazole (1a)——A mixture of **1a** (1.8 g, 10 mmol), benzyl chloride (1.3 g), K_2CO_3 (1.3 g) and KI (1.3 g) in acetone (50 ml) was refluxed for 18 h. The mixture was concentrated to dryness under reduced pressure to give the residue, which was extracted with ethyl acetate to afford a crude sample. The crude sample was purified by column chromatography on silica gel (120 g) using ethyl acetate–hexane (1 : 10) as an eluent to give **3a** (1.2 g, 45% yield) and **4a** (1.3 g, 36% yield). **3a**: Colorless needles, mp 180—181 °C (from petroleum ether). *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.63; H, 6.43; N, 10.29. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 1.35 (3H, t), 3.92 (2H, s), 4.22 (2H, q), 7.0—7.9 (10H, m).

4a: Colorless needles, mp 97—98 °C (from petroleum ether). *Anal.* Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.56; N, 7.60. Found: C, 81.47; H, 6.52; N, 7.80. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t), 3.23 (4H, q), 4.25 (2H, q), 6.9—7.9 (15H, m).

4-Ethoxy-5-formyl-2-phenylimidazole (11a)——$POCl_3$ (1.9 ml) was added dropwise to dimethylformamide (DMF) (6.5 ml) under ice-cooling. After the addition was complete, **1a** (3.0 g, 16 mmol) was added to the mixture and the whole was stirred for 20 min at room temperature. The mixture was treated with ethyl ether to yield a precipitate, which was dissolved in 1 N HCl (50 ml) and heated at 60—70 °C for 5 min to precipitate pink needles (2.97 g, 86% yield), mp 179—180 °C (from EtOH). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60; N, 12.95. Found: C, 66.63; H, 5.47; N, 12.72. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (3H, t), 4.61 (2H, q), 7.2—8.4 (5H, m), 9.62 (1H, s).

Dimethyl (4-Ethoxy-2-phenyl-, 2-*p*-Chlorophenyl- and 2-*o*-Methoxyphenylimidazol-5-yl)fumarate (6a, b, c) and -maleate (5a, b, c)——DMAD (4.0 g, 1 eq) was added to a stirred suspension of **1a** (4.0 g, 21.3 mmol) in toluene (25 ml) at room temperature. The mixture was warmed at 50—60 °C for 1 h. After cooling, **6a** precipitated as a yellow powder (2.1 g, 29% yield). The mother liquor was concentrated *in vacuo* to give the residue, which was purified by column chromatography on silica gel (250 g) using ethyl acetate–hexane (1 : 1) as an eluent to afford **5a** as orange plates (3.1 g, 44% yield). **6a**: mp 185—186 °C (from toluene). *Anal.* Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 62.15; H, 5.23; N, 8.15. ^{1}H-NMR (DMSO-d_6) δ: 1.29 (3H, t, $J=7$ Hz), 3.69 (3H, s), 3.80 (3H, s), 4.33 (2H, q, $J=7$ Hz), 6.30 (1H, s), 7.4—8.2 (5H, m). ^{13}C-NMR (DMSO-d_6) δ: 166.2 (s), 165.6 (s), 157.4 (s), 145.0 (s), 137.4 (s), 129.2 (s), 129.0 (d), 128.3 (d), 125.8 (d), 107.3 (s), 105.0 (d), 64.8 (t), 51.9 (q), 51.0 (q), 14.7 (q). UV λ_{max}^{EtOH} nm: 248, 295 (s), 372; $A_{372}/A_{248}=2.76$. **5a**: mp 107—109 °C (from petroleum ether). *Anal.* Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.88; H, 5.50; N, 8.36. ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, t, $J=7$ Hz), 3.72 (3H, s), 3.79 (3H, s), 4.30 (2H, q, $J=7$ Hz), 5.85 (1H, s), 7.0—7.9 (5H, m). ^{13}C-NMR (DMSO-d_6) δ: 169.4 (s), 167.8 (s), 159.1 (s), 144.0 (s), 137.0 (s), 129.3 (s), 129.1 (s), 128.7 (d), 125.3 (d), 107.4 (s), 104.2 (d), 65.2 (t), 52.5 (q), 52.0 (q), 14.8 (q). UV λ_{max}^{EtOH} nm: 252, 296, 388; $A_{372}/A_{248}=1.39$. Compounds **5b**, **6b** and **5c**, **6c** were similarly synthesized from **1b** and **1c**, respectively. **5b**: Yellow needles (35% yield), mp 114—115 °C (from $CHCl_3$). *Anal.* Calcd for $C_{17}H_{17}ClN_2O_5$: C, 55.97; H, 4.70; Cl, 9.72; N, 7.68. Found: C, 55.97; H, 4.77; Cl, 9.88; N, 7.61. ^{1}H-NMR (DMSO-d_6) δ: 1.32 (3H, t, $J=7$ Hz), 3.72 (3H, s), 3.78 (3H, s), 4.28 (2H, q, $J=7$ Hz), 5.47 (1H, s), 7.20 (2H, AB type, $J=9$ Hz), 7.68 (2H, AB type, $J=9$ Hz). **6b**: Yellow flakes (34% yield), mp 198—199 °C (from $CHCl_3$). *Anal.* Calcd for $C_{17}H_{17}ClN_2O_5$: C, 55.97; H, 4.70; N, 7.68. Found: C, 55.62; H, 4.52; N, 7.90. ^{1}H-NMR (DMSO-d_6) δ: 1.34 (3H, t, $J=7$ Hz), 3.73 (3H, s), 3.78 (3H, s), 4.29 (2H, q, $J=7$ Hz), 6.20 (1H, s), 7.20 (2H, AB type, $J=9$ Hz), 7.85 (2H, AB type, $J=9$ Hz). **5c**: Yellow prisms (28% yield), mp 126—127 °C (from hexane). *Anal.* Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.86; H, 5.42; N, 7.56. ^{1}H-NMR ($CDCl_3$) δ: 5.35 (1H, s). **6c**: Yellow prisms (13% yield), mp 131—132 °C (from acetone–hexane–isopropyl ether). *Anal.* Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.23; H, 5.48; N, 7.71. ^{1}H-NMR ($CDCl_3$) δ: 6.03 (1H, s).

Dimethyl (2-Butyl- and 2-Thenyl-4-ethoxyimidazol-5-yl)fumarate (6d, e) and -maleate (5d, e)——A mixture of **1d** (4.28 g, 25 mmol) and DMAD (4.0 g, 1 eq) in $CHCl_3$ (100 ml) was refluxed for 20 min. The mixture was evaporated *in vacuo* to give the residue, which was purified by column chromatography on silica gel (100 g) using $CHCl_3$–MeOH (1%) as an eluent to furnish **5d** (1.27 g), **6d** (1.93 g) and a mixture of **5d** and **6d** (4.59 g, in a molar ratio of 8 : 5). Both **5d** and **6d** were obtained as syrups. Treatment of **5d** with HCl gave the HCl salt as colorless prisms but the HCl salt of **6d** was unstable. **5d**: Syrup. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t like), 1.30—2.00 (4H, m), 1.37 (3H, t, $J=6$ Hz), 2.73 (2H, t like, $J=8$ Hz), 3.78 (3H, s), 3.88 (3H, s), 4.33 (2H, q, $J=6$ Hz), 5.35 (1H, s). **5d** HCl salt: Colorless prisms, mp 145—147 °C (dec.). *Anal.* Calcd for $C_{15}H_{23}ClN_2O_5$: C, 51.95; H, 6.68; N, 8.08. Found: C, 51.94; H, 6.68; N, 8.08. **6d**: Syrup. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t like), 1.20—1.90 (4H, m), 1.34 (3H, t, $J=6$ Hz), 2.59 (2H, t like, $J=8$ Hz), 3.69 (3H, s), 3.90 (3H, s), 4.31 (2H, q, $J=6$ Hz), 5.97 (1H, s). Compounds **5e** and **6e** were similarly synthesized from **1e**, each as a red syrup (46% and 54% yields, respectively). **5e** gave its oxalate as yellow prisms. **5e** oxalate: mp 136—138 °C (from acetone). *Anal.* Calcd for $C_{16}H_{18}N_2O_5S \cdot 1/2C_2H_2O_4$: C, 51.64; H, 4.84; N, 7.09. Found: C, 51.12; H, 4.79; N, 6.87. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, $J=7$ Hz), 3.67 (3H, s), 3.80 (3H, s), 4.20 (2H, s), 4.30 (2H, q, $J=7$ Hz), 5.35 (1H, s), 6.8—7.0 (2H, d like), 7.05—7.25 (1H, t like). **6e**: Syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, $J=7$ Hz), 3.68 (3H, s), 3.84 (3H, s), 4.16 (2H, s), 4.40 (2H, q, $J=7$ Hz), 5.95 (1H, s), 6.8—7.0 (2H, d like), 7.0—7.2 (1H, d like).

Isomerization of 6a to 5a——A mixture of **6a** (0.5 g, 1.5 mmol) in acetic acid (2.5 ml) and 1,2-dichloroethane

(25 ml) was refluxed for 2 h. The mixture was evaporated *in vacuo* to give the residue, which was purified by column chromatography on silica gel (35 g) using $CHCl_3$ as an eluent to afford **5a** (0.39 g, 78% yield), mp 105—106 °C, identical with an authentic sample.

Methyl 3-(4-Ethoxy-2-phenylimidazol-5-yl)acrylate (7a and 8a)——A mixture of **1a** (10.74 g, 57 mmol) and methyl propiolate (4.8 g, 57 mmol) in toluene (50 ml) was heated at 70—90 °C for 16 h. The mixture was concentrated to dryness *in vacuo* to give the residue, which was chromatographed on silica gel (250 g) using $CHCl_3$ as an eluent to afford **7a** (2.76 g, 18% yield) and **8a** (4.6 g, 30% yield). **7a**: Orange-yellow prisms, mp 195—197 °C (from $CHCl_3$). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.19; H, 5.80; N, 10.03. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz), 3.76 (3H, s), 4.34 (2H, q, J=7 Hz), 6.20 (1H, AB type, J=16 Hz), 7.2—7.5 (3H, m), 7.7—8.0 (2H, m), 7.80 (1H, AB type, J=16 Hz). **8a**: Yellow prisms, mp 101 °C (from $CHCl_3$). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.29; H, 5.78; N, 10.13. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 3.72 (3H, s), 4.61 (2H, q, J=7 Hz), 5.30 (1H, AB type, J=12 Hz), 6.73 (1H, AB type, J=12 Hz), 7.2—7.6 (3H, m), 7.7—7.9 (2H, m).

Dimethyl 2-(4-Ethoxy-2-phenylimidazol-5-yl)succinate (9a)——Catalytic hydrogenation of **5a** and **6a** (0.12 g, each) in MeOH (50 ml) with Pd–C (10%, 0.04 g) gave **9a** as a colorless syrup (0.09 g and 0.13 g, respectively). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7 Hz), 2.98 (2H, d, J=6 Hz), 3.66 (6H, s), 4.16 (1H, t, J=6 Hz), 4.25 (2H, q, J=7 Hz), 10.13 (1H, br s). UV λ_{max}^{EtOH} nm: 298.

1-Benzyl-3-(4-ethoxy-2-phenylimidazol-5-yl)maleimide (10a)——A solution of 5% trimethylaluminum in hexane (10 ml) was added to a solution of benzylamine (2.15 g, 20 mmol) in CH_2Cl_2 (150 ml) under a nitrogen atmosphere, and the mixture was stirred for 15 min at room temperature. Then a solution of **5a** (3.0 g, 9 mmol) in CH_2Cl_2 (30 ml) was added and the mixture was refluxed for 48 h. After cooling, the mixture was concentrated *in vacuo* to give the residue, which was purified by column chromatography on silica gel (150 g) using $CHCl_3$ as an eluent to afford **10a** as red crystals (1.68 g, 50% yield). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7 Hz), 4.37 (2H, q, J=7 Hz), 4.52 (2H, s), 6.10 (1H, s), 7.0—7.8 (10H, m). **10a** HCl: Orange powder, mp 131—132 °C (dec.). *Anal.* Calcd for $C_{22}H_{23}ClN_3O_3$: C, 64.47; H, 4.92; N, 10.25. Found: C, 64.60; H, 4.92; N, 10.09.

Methyl (6-Ethoxycarbonyl-3,4-dihydro-4-oxo-2-phenylpyrimidin-5-yl)acetate (12a)——i) A mixture of **5a** (0.25 g) in 1 N HCl (15 ml) and 1,4-dioxane (15 ml) was heated at 60—65 °C for 1.5 h. After removal of the solvent, the residue was treated with water (20 ml) and extracted with $CHCl_3$ (50 ml × 2) to give a pale brown liquid (0.24 g), which was purified by column chromatography on silica gel (35 g) using $CHCl_3$–AcOEt (3 : 1) as an eluent to afford **12a** as pale yellow plates (0.11 g, 46% yield), mp 168—169 °C (from EtOH–ethyl acetate). ^{1}H-NMR (DMSO-d_6) δ: 1.33 (3H, t, J=7 Hz), 3.65 (3H, s), 3.76 (2H, s), 4.35 (2H, q, J=7 Hz), 7.40—7.64 (3H, m), 8.00—8.24 (2H, m). *Anal.* Calcd for $C_{16}H_{16}N_2O_5$: C, 60.76; H, 5.10; N, 8.86. Found: C, 60.90; H, 4.93; N, 8.79. MS m/z: 316 (M^+).

ii) A mixture of **5a** and **6a** (1 : 1, 30 g) in formic acid (400 ml) was stirred at 80—85 °C for 1.5 h. After removal of the solvent, the residue was treated with water (300 ml) and extracted with CH_2Cl_2 (500 ml) to give a crude product (35.5 g), which was recrystallized from EtOH–ethyl ether to afford **12a** (12.2 g) as a brown powder. The mother liquor was purified by column chromatography on silica gel (350 g) to give additional **12a** (2.4 g). Total yield: 51%.

iii) A mixture of **1a** (50.0 g) and DMAD (38.0 g) in $CHCl_3$ (600 ml) was refluxed for 30 min. After cooling, the mixture was concentrated to dryness under reduced pressure to give the residue (90.0 g), which was dissolved in a mixture of 1,4-dioxane (700 ml), formic acid (700 ml) and water (700 ml). The mixture was refluxed for 5 h. After removal of the solvent, the residue was treated with water and extracted with $CHCl_3$ (300 ml × 3) to give a crude product, which was triturated with iso-propyl ether to give **12a** (63.0 g, 75% yield from **1a**), mp 163—164.5 °C (from EtOH–ethyl acetate), identical with an authentic sample on ^{1}H-NMR comparison.

Methyl (2-*p*-Chlorophenyl-, 2-*o*-Methoxyphenyl- and 2-Butyl-6-ethoxycarbonyl-3,4-dihydro-4-oxopyrimidin-5-yl)acetate (12b, c, d)——A mixture of **5** and **6** (**b**, **c**, or **d** series) was heated with formic acid in 50% aqueous 1,4-dioxane at 80—100 °C for 2.5 h. After cooling, the mixture was evaporated *in vacuo* to give a red-yellow liquid, which was chromatographed on silica gel using $CHCl_3$–acetone–formic acid (10 : 1 : 0.1) as an eluent to afford **12b—d**. **12b**: Colorless needles (56% yield), mp 224—225 °C (from AcOEt–isopropyl ether). *Anal.* Calcd for $C_{16}H_{15}ClN_2O_5$: C, 54.79; H, 4.31; Cl, 10.11; N, 7.99. Found: C, 54.84; H, 4.27; Cl, 10.35; N, 8.00. ^{1}H-NMR (DMSO-d_6) δ: 1.33 (3H, t, J=7 Hz), 3.62 (3H, s), 3.73 (2H, s), 4.35 (2H, q, J=7 Hz), 7.57 (2H, d, J=9 Hz), 8.17 (2H, d, J=9 Hz).

12c: Brown plates (34% yield), mp 115 °C (from EtOH–iso-propyl ether). *Anal.* Calcd for $C_{17}H_{18}N_2O_6$: C, 58.95; H, 5.24; N, 8.09. Found: C, 59.16; H, 5.15; N, 7.94. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 3.67 (3H, s), 3.83 (2H, s), 3.98 (3H, s), 4.35 (2H, q, J=7 Hz), 6.80—7.60 (3H, m), 8.20—8.47 (1H, m), 11.3 (1H, br s). **12d**: Colorless needles (41% yield), mp 87—88 °C (from isopropyl ether). *Anal.* Calcd for $C_{14}H_{20}N_2O_5$: C, 56.74; H, 6.80; N, 9.45. Found: C, 56.90; H, 6.93; N, 9.40. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7 Hz), 2.73 (2H, t like, J=8 Hz), 4.37 (2H, q, J=7 Hz), 3.67 (3H, s), 3.83 (2H, s).

Methyl (6-Carboxy-3,4-dihydro-4-oxo-2-phenylpyrimidin-5-yl)acetate (13a)——A mixture of **12a** (1.0 g) in MeOH (20 ml) and 0.5 N NaOH (10 ml) was stirred for 24 h at room temperature. The mixture was extracted with $CHCl_3$ (100 ml × 3) to recover **12a** (0.14 g, 14%). The aqueous phase was acidified with 1 N HCl to pH 1—2 and **13a** (0.37 g) precipitated as pale yellow plates (41% yield), mp 202—203 °C (from EtOH). *Anal.* Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 57.98; H, 4.31; N, 9.64. MS m/z: 288 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 3.60 (3H, s),

3.75 (2H, s), 7.2—7.7 (3H, m), 7.9—8.2 (2H, m).

(6-Carboxy-3,4-dihydro-4-oxo-2-phenylpyrimidin-5-yl)acetic Acid (14a)——A mixture of **12a** (1.0 g) in MeOH (20 ml) and 1 N NaOH (20 ml) was stirred for 5 h at room temperature. The mixture was washed with $CHCl_3$ (100 ml × 3). The aqueous phase was acidified with 1 N HCl to pH 1—2 and cooled with ice to give **14a** as a pale pink powder (0.65 g, 75% yield), mp 235 °C (from DMF–MeOH). *Anal.* Calcd for $C_{13}H_{10}N_2O_5$: C, 56.94; H, 3.68; N, 10.22. Found: C, 56.63; H, 3.48; N, 10.22. ^{1}H-NMR (DMSO-d_6) δ: 3.1—3.6 (2H, br s), 7.0—7.3 (3H, m), 7.80 (2H, m). MS *m/z*: 256 ($M^+ - 18$), 238.

6-Carboxy-3,4-dihydro-5-methyl-4-oxo-2-phenylpyrimidine (16a)——A solution of **14a** (0.6 g) in dimethylacetamide (DMA) (10 ml) was heated at 120 °C for 3 h. After cooling, the mixture was concentrated *in vacuo* to dryness. The residue was washed with hexane to give **16a** as a yellow powder (0.43 g, 85% yield). ^{1}H-NMR (DMSO-d_6) δ: 2.10 (3H, s), 7.30—7.60 (3H, m), 7.80—8.20 (2H, m).

3,4-Dihydro-5-methyl-4-oxo-2-phenylpyrimidine (15)——**14a** (0.25 g) was placed in a flask and heated at over 250 °C for 5 min. The residue was extracted with MeOH to give **15** (0.14 g, 82% yield) as pale yellow plates (from EtOH), mp 202—203 °C (lit.[7] 185—186 °C). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.89; H, 5.43; N, 14.84. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 7.93 (1H, s).

2-Butyl-6-ethoxycarbonyl-3,4-dihydro-5-methyl-4-oxo-pyrimidine (17)——i) Pentanamidine hydrochloride (**18**) (15.0 g) and diethyl 2-oxo-3-methylsuccinate (**19**) (22.2 g)[15] were added to a solution of NaOEt (14.8 g) in EtOH (150 ml) at room temperature. The mixture was refluxed for 2 h, then allowed to cool. The precipitate was filtered off, AcOH (7.1 ml) was added to the filtrate and the mixture was evaporated *in vacuo* to give the residue, which was partitioned between $CHCl_3$ (150 ml) and water (150 ml). The organic phase was evaporated *in vacuo* to give a crude product, which was crystallized from 50% EtOH (50 ml) to afford **17** as colorless needles (5.0 g, 19% yield), mp 109—110 °C. *Anal.* Calcd for $C_{12}H_{18}N_2O_3$: C, 60.50; H, 7.62; N, 11.74. Found: C, 60.25; H, 7.67; N, 11.55. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 2.20 (3H, s), 2.75 (2H, t, J=7 Hz), 4.43 (2H, q, J=7 Hz).

ii) A mixture of **12d** (1.50 g) in MeOH (20 ml) and 1 N NaOH (20 ml) was stirred for 1 h at room temperature. The mixture was acidified with 1 N HCl to pH 1—2 and evaporated *in vacuo* to give the residue (**14d**). The residue (**14d**) was dissolved in DMA (100 ml) and heated at 120 °C for 6 h. After cooling, the solution was evaporated under reduced pressure to afford the residue (**16d**, 1.3 g), which was dissolved in EtOH (50 ml) and refluxed for 20 h in the presence of a catalytic amount of H_2SO_4. The mixture was evaporated *in vacuo* to give the residue, which was chromatographed on silica gel (50 g) using $CHCl_3$–acetone–formic acid (10 : 1 : 0.1) as an eluent to afford **17** as pale yellow needles (0.31 g, 26% yield from **12d**), mp 109—111 °C, identical with an authentic sample.

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