INTRODUCTION OF ALKENYL GROUP BEARING AN ELECTRON-WITHDRAWING GROUP TO THE 5-POSITION OF IMIDAZOLE RING BY HECK REACTION

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Abstract- A DMF solution of 5-iodo-1-methyl-2-phenylthio-1H-imidazole (7) and a large excess of acrylic esters, acrylonitrile, or methyl vinyl ketone was heated in a sealed tube in the presence of Pd(PPh₃)₄ to give the Heck reaction products, 5-alkenyl-1-methyl-2-phenylthio-1H-imidazoles, in 10 - 84 % yields.

We have developed methods for regioselective introduction of carboxylic substituent into the 2-, 4-, and/or 5-positions of imidazole ring and studied on the preparation of various imidazole compounds including natural products.¹

Visoltricin (1) is one of the natural products containing imidazole ring, which was isolated in 1989 from Fusarium tricinctum and found its cytotoxicity to tumor cells, anticholinesterase activity, and toxicity to Artemia salina (Figure 1).² For the synthesis of 1, the construction of methyl acrylate group at the 5-position of imidazole ring is required. In our knowledge, the reports with respect to the introduction of α,β-unsaturated carbonyl group on the imidazole ring are quite few.³ As we investigated the Heck reaction⁴ between alkenyl compound bearing an electron-withdrawing group (EWG) and 5-halimidazoles prior to the synthesis of 1, we would like to report the results in this paper.

1-Methyl-2-phenylthio-1H-imidazole (2)¹ was brominated with two equivalents of NBS to give the dibromide (3). Although the dibromide (3) was heated with methyl acrylate in the presence of palladium(0) catalyst under various conditions, the desired Heck reaction product (4) was not obtained at all. The compound (2) was treated with n-BuLi followed by addition of one equivalent of bromine to give the 5-bromimidazole (5) in 42 % yield.⁵ The monobromide (5) was subjected to the Heck reaction conditions in the presence of Pd(OAc)₂ - Ph₃P or Pd(PPh₃)₄ and a large excess of methyl acrylate in DMF at 1 atm or in a sealed tube to give 6 in the variable yields (15 - 58 %). The stereochemistry of 6 was determined as E on the basis of the ¹H-NMR coupling constants between the olefinic protons on the side-chain (each d, J = 16.0 Hz at 6.30 and 7.49 ppm, respectively) (Scheme 1).⁶
To improve the yield of 6, we prepared the 5-iodoimidazole (7) in 63% yield by treatment of 2 with LTMP followed by addition of one equivalent of iodine. A solution of 7 and a large excess of methyl acrylate (22 equivalents) in DMF was heated in a sealed tube at 100°C in the presence of Pd(PPh3)4 and sodium acetate to give 6 in 84% yield (Scheme 1).

\[
\begin{align*}
NBS & \quad 0 \degree C & \quad \text{Br} & \quad \text{Br} & \quad \text{Br} & \quad \text{Br} & \quad \text{CH}_2=\text{CHCOOMe} & (\text{large excess}) & \quad \text{AcONa} \\
& \quad \text{LTMP} & \quad \text{THF-DME} & \quad \text{I}_2, -78 \degree C & \quad n-\text{BuLi} & \quad \text{Br}_2, -78 \degree C & \quad \text{CH}_2=\text{CHCOOMe} & (2 \text{ eq}) & \quad \text{Et}_3\text{N} \text{ or } \text{AcONa} \\
& \quad 2 & \quad \text{3 (47%)} & \quad \text{3} & \quad \text{4} & \quad \text{6 (15 - 58%)} & \quad \text{Pd(OAc)}_2, \text{Ph}_3\text{P}, \text{DMF}, \text{heat} & \quad \text{Pd(OAc)}_2 - \text{Ph}_3\text{P} \text{ or } \text{Pd(PPh}_3)_4, \text{DMF}, 100 - 140 \degree C
\end{align*}
\]

Scheme 1

To examine the generality of the Heck reaction, various alkenyl compounds having an EWG were subjected to the same reaction conditions and the results are summarized in Table 1. When methyl vinyl ketone was used, the obtained product (8) was a single isomer and its stereochemistry was determined as E on the basis of the 1H-NMR coupling constants of the olefinic protons. In the cases of Entries 2 - 5, the obtained products (9 - 12) were mixture of E and Z isomers. In Entry 4, although the isomers could not be separated by PTLC, the ratio of them was found ca. 1:1 from 1H-NMR spectrum. In Entries 2, 3 and 5, E and Z isomers could be separated by PTLC (Table 1). The stereochemistry of the less polar compound (10a) was determined as E and that of the more polar compound (10b) as Z on the basis of the 1H-NMR coupling constants of the olefinic protons. On the other hand, stereochemistry of 9 and 12 was determined on the basis of NOE experiments (Figures 2 and 3).
Table 1. Reaction of 7 with Various α,β-Unsaturated Compounds in the Presence of Pd(PPh₃)₄.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Reaction Time (h)</th>
<th>Product</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂=CHCOMe</td>
<td>2</td>
<td>8</td>
<td>80 (7 35 ppm, (J = 16.0) Hz)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9a</td>
<td>21 (less polar)</td>
</tr>
<tr>
<td>2</td>
<td>MeCH=CHCOOMe (^a)</td>
<td>6</td>
<td>9b</td>
<td>10 (more polar)</td>
</tr>
<tr>
<td>3</td>
<td>CH₂=CHCN</td>
<td>6</td>
<td>10a</td>
<td>42 (less polar)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10b</td>
<td>47 (more polar)</td>
</tr>
<tr>
<td>4</td>
<td>PhCH=CHCOOMe (^a,b)</td>
<td>6</td>
<td>11</td>
<td>13 (1 : 1)</td>
</tr>
<tr>
<td>5</td>
<td>CH₂=C(Me)CN</td>
<td>5</td>
<td>12a</td>
<td>24 (less polar)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12b</td>
<td>30 (more polar)</td>
</tr>
</tbody>
</table>

\(^a\) Predominantly \(E\)-form was used.
\(^b\) Two equivalents of methyl cinnamate were used.
Now, we are continuously investigating total synthesis of visoltrin (1).

**EXPERIMENTAL**

Melting points were measured with a Yanaco MP micro-melting point apparatus and are uncorrected. IR spectra were taken with a Shimadzu IR-435 spectrophotometer. ^1H-NMR spectra were measured on a Varian XL-300 (300 MHz) and Hitachi R-90H (90 MHz) with tetramethysilane as an internal standard and chemical shifts are reported in ppm. MS were recorded with a JEOL JMS SX 102A QQ spectrometer for FAB-MS and a JEOL MS BU20 for EI-MS. Silica gel 60 (Merck) for column chromatography and Silica gel 60 PF254 (Nacalai Tesque Inc.) for preparative TLC (PTLC) were used. All extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure.

**4,5-Dibromo-1-methyl-2-phenylthio-1H-imidazole (3):**
NBS (1.07 g, 6.00 mmol) was added portionwise to a solution of 1-methyl-2-phenylthio-1H-imidazole (2; 576 mg, 3.00 mmol) in THF (6 mL) under an N2 atmosphere at rt and the whole was stirred for 1 h. After addition of water, the mixture was extracted with ethyl acetate. The combined extracts were washed with water, dried, and evaporated. The residue was purified with column chromatography (ethyl acetate / n-hexane = 1 / 5) to give 3 (488 mg, 47 %) as a colorless oil. ^1H-NMR (CDCl3, 90 MHz) δ: 3.62 (s, 3H), 7.2 - 7.3 (m, 5H). IR (CHCl3): 3060, 1580 cm⁻¹. HR-EIMS (m/z) Calcd for C10H8N2Br2S: 345.8793. Found: 345.8770 (M⁺).
5-Bromo-1-methyl-2-phenylthio-1H-imidazole (5): n-BuLi (6.3 mL, 10 mmol, 1.6 M solution in n-hexane) was added dropwise to a solution of 2 (1.92 g, 10.0 mmol) in THF (20 mL) under an N2 atmosphere at -78°C and the whole was stirred for 30 min at the same temperature. A solution of bromine (1.60 g, 0.53 mL, 10 mmol) in THF (10 mL) was added dropwise to the mixture and the whole was stirred for 1 h at -78°C. After addition of 10 % Na2S2O3 solution, the mixture was extracted with ethyl acetate. The combined extracts were washed with water, dried, and evaporated. The residue was purified with column chromatography (ethyl acetate / n-hexane = 1 / 5) to give 5 (1.13 g, 42 %) as colorless prisms. mp 92 - 93°C (from ethyl acetate). 1H-NMR (CDCl3, 90 MHz) δ: 3.60 (s, 3H), 7.15 - 7.30 (m, 6H). IR (CHC13): 3060, 1580 cm⁻¹. HR-EIMS (m/z) Calcd for C10H9N2BrS; 267.9687. Found: 267.9664 (M⁺). Anal. Calcd for C10H9N2BrS: C, 44.62; H, 3.37; N, 10.41. Found: C, 44.70; H, 3.41; N, 10.34.

5-Iodo-1-methyl-2-phenylthio-1H-imidazole (7): n-BuLi (1.88 mL, 3.00 mmol, 1.6 M solution in n-hexane) was added dropwise to a solution of 2,2,6,6-tetramethylpiperidine (466 mg, 0.56 mL, 3.3 mmol) in DME (6 mL) and THF (12 mL) under an N2 atmosphere at -78°C and the whole was stirred for 15 min at the same temperature. A solution of 2 (570 mg, 3.00 mmol) in THF (3 mL) was added dropwise to the mixture at -78°C and the whole was stirred for additional 1 h. Iodine (762 mg, 3.00 mmol) was added one portion to the mixture and the whole was stirred for 12 h at ambient temperature. After addition of 10 % Na2S2O3 solution, the mixture was extracted with ethyl acetate. The combined extracts were washed with water, dried, and evaporated. The solid residue was recrystallized from ethyl acetate to give 7 (600 mg, 63 %) as colorless plates. mp 179 - 180°C (from ethyl acetate). 1H-NMR (CDCl3, 90 MHz) δ: 3.63 (s, 3H), 7.15 - 7.30 (m, 6H). IR (CHC13): 3060, 1579 cm⁻¹. HR-EIMS (m/z) Calcd for C10H9N2I; 315.9550. Found: 315.9532 (M⁺). Anal. Calcd for C10H9N2I: C, 37.99; H, 2.87; N, 8.86. Found: C, 38.19; H, 2.87; N, 8.75.

Methyl (E)-3-(1-Methyl-2-phenylthioimidazol-5-yl)-2-propenoate (6): A mixture of 7 (158 mg, 0.50 mmol), sodium acetate (205 mg, 2.5 mmol), tetrakis(triphenylphosphine)palladium (10 mg), methyl acrylate (956 mg, 1.00 mL, 11.1 mmol), and DMF (3 mL) was put in a sealed tube and replaced air with N2 gas. The sealed tube was heated at 100°C for 5 h. After cooling followed by addition of water, the mixture was extracted with ether. The combined extracts were washed with water, dried, and evaporated. The residue was purified with column chromatography (ethyl acetate / n-hexane = 1 / 1) to give 6 (115 mg, 84 %) as pale yellow prisms. mp 89 - 91°C (from ethyl acetate - n-hexane). 1H-NMR (CDCl3, 90 MHz) δ: 3.68 (s, 3H), 3.79 (s, 3H), 6.30 (d, 1H, J = 16.0 Hz), 7.2 - 7.3 (m, 5H), 7.49 (d, 1H, J = 16.0 Hz), 7.58 (s, 1H). IR (CHC13): 1704, 1636 cm⁻¹. HR-EIMS (m/z) Calcd for C14H14N2O2S; 274.0793. Found: 274.0770 (M⁺). Anal. Calcd for C14H14N2O2S: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.33; H, 5.19; N, 9.99.
(E)-4-(1-Methyl-2-phenylthioimidazol-5-y1)-3-buten-2-one (8): According to the procedure described above for the synthesis of 6, the reaction using 7 (158 mg, 0.50 mmol) and methyl vinyl ketone (842 mg, 1.00 mL, 12.0 mmol) gave 8 (104 mg, 80%), which was purified with PTLC (ethyl acetate / n-hexane = 1 / 1). Pale brown oil. 1H-NMR (CDCl3, 90 MHz) δ: 2.33 (s, 3H), 3.69 (s, 3H), 6.63 (d, 1H, J = 16.0 Hz), 7.2 - 7.3 (m, 5H), 7.35 (d, 1H, J = 16.0 Hz), 7.61 (s, 1H). IR (CHCl3): 1664, 1641, 1618 cm⁻¹. HR-EIMS (m/z) Calcd for C13H14N2O2S: 258.0844. Found: 258.0851 (M⁺).

Methyl (E)-3-Methyl-3-(1-methyl-2-phenylthioimidazol-5-y1)-2-propenoate (9a) and Methyl (Z)-3-Methyl-3-(1-methyl-2-phenylthioimidazol-5-y1)-2-propenoate (9b): According to the procedure described above for the synthesis of 6, the reaction using 7 (158 mg, 0.50 mmol) and methyl crotonate (944 mg, 1.00 mL, 9.44 mmol) gave 9a (30 mg, 21%) and 9b (14 mg, 10%), which was purified with PTLC (CHCl3). 9a: Less polar. Colorless oil. 1H-NMR (CDCl3, 300 MHz) δ: 2.51 (d, 3H, J = 1.3 Hz), 3.67 (s, 3H), 3.74 (s, 3H), 5.91 (q, 1H, J = 1.3 Hz), 7.2 - 7.3 (m, 5H), 7.31 (s, 1H). IR (CHCl3): 1709, 1623 cm⁻¹. HR-EIMS (m/z) Calcd for C15H16N2O2S: 288.0932. Found: 288.0913 (M⁺).

9b: More polar. Colorless oil. 1H-NMR (CDCl3, 300 MHz) δ: 2.17 (d, 3H, J = 1.5 Hz), 3.42 (s, 3H), 3.57 (s, 3H), 6.07 (q, 1H, J = 1.5 Hz), 7.2 - 7.3 (m, 6H). IR (CHCl3): 1709, 1623 cm⁻¹. HR-EIMS (m/z) Calcd for C15H16N2O2S: 288.0932. Found: 288.0925 (M⁺).

(E)-3-(1-Methyl-2-phenylthioimidazol-5-y1)acrylonitrile (10a) and (Z)-3-(1-Methyl-2-phenylthioimidazol-5-y1)acrylonitrile (10b): According to the procedure described above for the synthesis of 6, the reaction using 7 (158 mg, 0.50 mmol) and acrylonitrile (806 mg, 1.00 mL, 15.2 mmol) gave 10a (51 mg, 42%) and 10b (57 mg, 47%), which was purified with column chromatography (ethyl acetate / n-hexane = 1 / 2).

10a: Less polar. Colorless plates. mp 130 - 132°C (from ethyl acetate - n-hexane). 1H-NMR (CDCl3, 90 MHz) δ: 3.65 (s, 3H), 5.71 (d, 1H, J = 16.5 Hz), 7.15 (d, 1H, J = 16.5 Hz), 7.2 - 7.3 (m, 5H), 7.56 (s, 1H). IR (CHCl3): 2207, 1618 cm⁻¹. HR-EIMS (m/z) Calcd for C13H11N3S: 241.0674. Found: 241.0674 (M⁺). Anal. Calcd for C13H11N3S: C, 64.71; H, 4.59; N, 17.41. Found: C, 64.47; H, 4.63; N, 17.42.

10b: More polar. Colorless plates. mp 135 - 137°C (from ethyl acetate - n-hexane). 1H-NMR (CDCl3, 90 MHz) δ: 3.63 (s, 3H), 5.33 (d, 1H, J = 11.9 Hz), 6.89 (d, 1H, J = 11.9 Hz), 7.1 - 7.3 (m, 5H), 8.21 (s, 1H). IR (CHCl3): 2206, 1602, 1580 cm⁻¹. HR-EIMS (m/z) Calcd for C13H11N3S: 241.0674. Found: 241.0674 (M⁺). Anal. Calcd for C13H11N3S: C, 64.71: H, 4.59; N, 17.41. Found: C, 64.90: H, 4.61; N, 17.49.

Methyl 3-(1-Methyl-2-phenylthioimidazol-5-y1)-3-phenyl-2-propenoate (11): According to the procedure described above for the synthesis of 6, the reaction using 7 (316 mg, 1.00 mmol) and methyl cinnamate (324 mg, 2.00 mmol) gave 11 (46 mg, 13%), which was purified with PTLC (ethyl acetate / n-hexane = 1 / 1). Pale brown oil. 1H-NMR (CDCl3, 90 MHz) δ: 3.21 and 3.29 (each s, total 3H), 3.62
and 3.65 (each s, total 3H), 6.18 and 6.53 (each s, total 1H), 7.1 - 7.4 (m, 11H). IR (CHCl₃): 17, 1605, 1589 cm⁻¹. HR-EIMS (m/z) Calcd for C₂₀H₁₈N₂O₂S: 350.1089. Found; 350.1086 (M⁺).

(E)-2-Methyl-3-(1-methyl-2-phenylthioimidazol-5-yl)acrylonitrile (12a) and (Z)-2-methyl-3-(1-Methyl-2-phenylthioimidazol-5-yl)acrylonitrile (12b): According to the procedure described above for the synthesis of 6, the reaction using 7 (158 mg, 0.50 mmol) and 2-methylacrylonitrile (800 mg, 1.00 mL, 11.9 mmol) gave 12a (31 mg, 24 %) and 12b (38 mg, 30 %), which was purified with PTLC (CHCl₃).

12a; Less polar. Colorless needles. mp 119 - 121°C (from ethyl acetate - n-hexane). ¹H-NMR (CDCl₃, 300 MHz) δ: 2.16 (d, 3H, J = 1.4 Hz), 3.63 (s, 3H), 6.92 (s, 1H), 7.2 - 7.3 (m, 5H), 7.42 (s, 1H). IR (CHCl₃): 2203, 1674, 1621, 1581 cm⁻¹. HR-FABMS (m/z) Calcd for C₁₄H₁₄N₃S; 256.0908. Found; 256.0926 (M+H)+. Anal Calcd for C₁₄H₁₃N₃S: C, 65.86; H, 5.13; N, 16.46. Found: C, 65.84; H, 5.18; N, 16.51.

12b; More polar. Colorless plates. mp 109 - 111°C (from ethyl acetate - n-hexane). ¹H-NMR (CDCl₃, 300 MHz) δ: 2.15 (d, 3H, J = 1.6 Hz), 3.60 (s, 3H), 6.67 (s, 1H), 7.15 - 7.3 (m, 5H), 8.07 (s, 1H). IR (CHCl₃): 2204, 1618, 1580 cm⁻¹. HR-FABMS (m/z) Calcd for C₁₄H₁₄N₃S; 256.0908. Found; 256.0918 (M+H)+. Anal. Calcd for C₁₄H₁₃N₃S: C, 65.86; H, 5.13; N, 16.46. Found: C, 65.90; H, 5.19; N, 16.35.

REFERENCES and NOTES
6. In the coupling reaction with iodobenzene and methyl acrylate, Heck reported the predominat formation of (E)-C₆H₅CH=CHCO₂Me in Ref. 4a.
7. In the coupling reaction with halobenzene derivatives and alkenyl groups bearing an electron-withdrawing group, most of the obtained products were (E)-form. However, in some cases, mixtures

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