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-1*H*-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-1*H*-imidazoles, in 10 - 84 % yields.

We have developed methods for regioselective introduction of carbogenic 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]

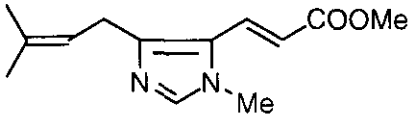


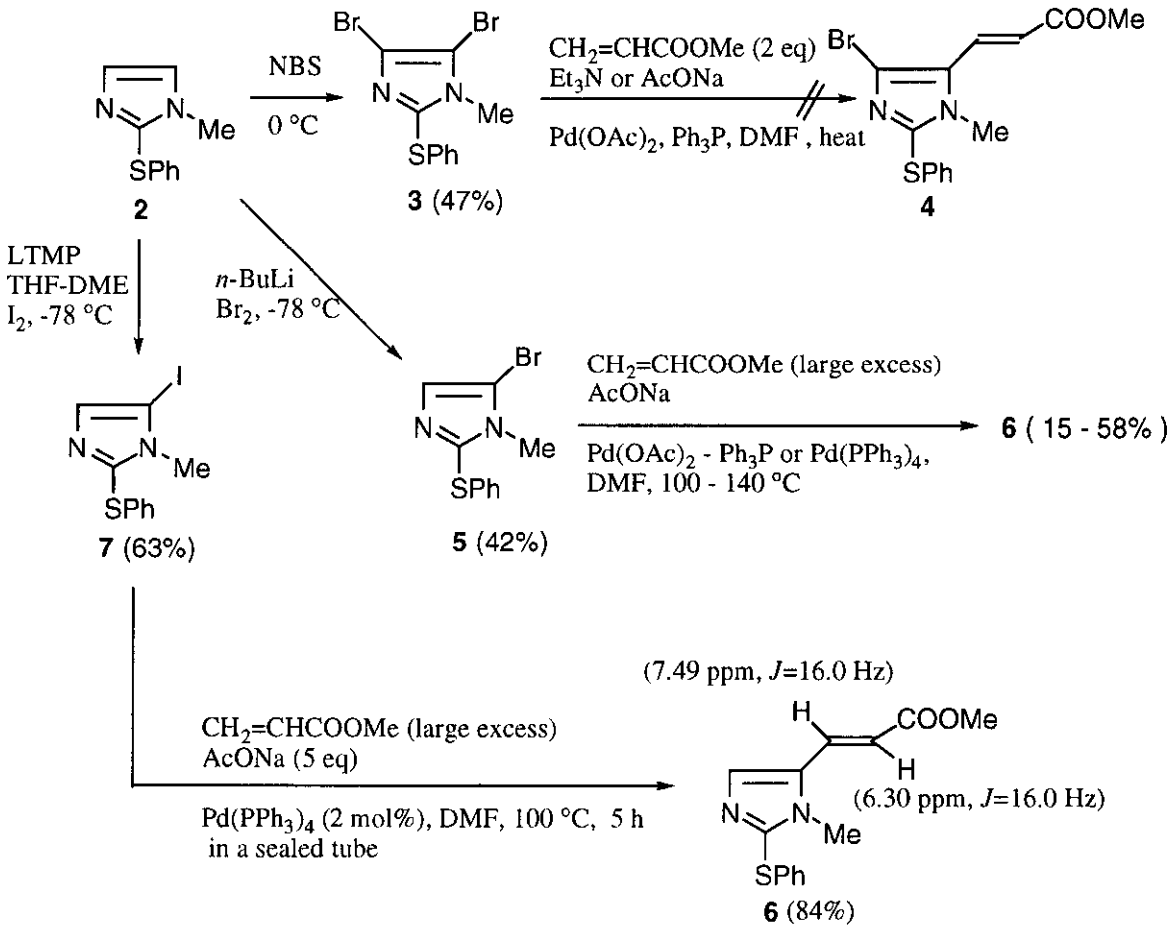
Figure 1. Visoltricin (**1**)

Visoltricin (**1**) is one of the natural products containing imidazole ring, which was isolated in 1989 from *Fusarium tricinetum* 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 reaction[4] between alkenyl compound bearing an electron-withdrawing group (EWG) and 5-haloimidazoles prior to the synthesis of **1**, we would like to report the results in this paper.

1-Methyl-2-phenylthio-1*H*-imidazole (**2**)[1a] 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-bromoimidazole (**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 ^{1}H-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]

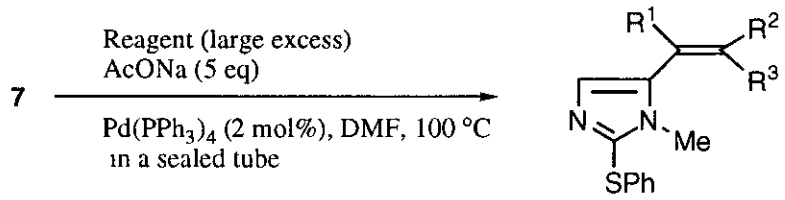
To improve the yield of **6**, we prepared the 5-iodoimidazole (**7**) in 63 % yield by treatment of **2** with LTMP followed by addition of one equivalent of iodine.[1a] A solution of **7** and a large excess of methyl acrylate (22 equivalents) in DMF was heated in a sealed tube at 100°C in the presence of $Pd(PPh_3)_4$ and sodium acetate to give **6** in 84 % yield (Scheme 1).

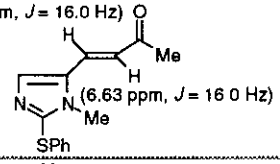
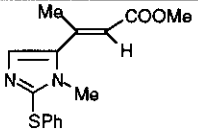
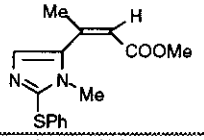
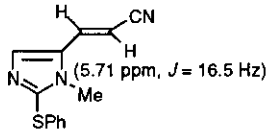
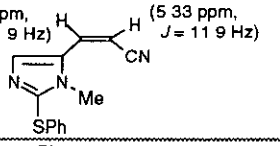
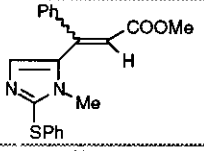
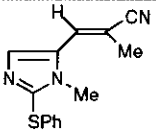
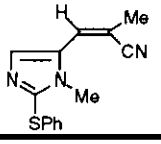


Scheme 1

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 ^{1}H-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.[7] In Entry 4, although the isomers could not be separated by PTLC, the *ratio* of them was found *ca.* 1 : 1 from ^{1}H-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 ^{1}H-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 $Pd(PPh_3)_4$.



Entry	Reagent	Reaction Time (h)	Product	Isolated Yield (%)
1	CH_2=CHCOMe	2	**8** : 	80
2	MeCH=CHCOOMe[a]	6	**9a** : 	21 (less polar)
			9b : 	10 (more polar)
3	CH_2=CHCN	6	**10a** : 	42 (less polar)
			10b : 	47 (more polar)
4	PhCH=CHCOOMe[a,b]	6	**11** : 	13 (1 : 1)
5	CH_2=C(Me)CN	5	**12a** : 	24 (less polar)
			12b : 	30 (more polar)

a. Predominantly *E*-form was used.
b. Two equivalents of methyl cinnamate were used.

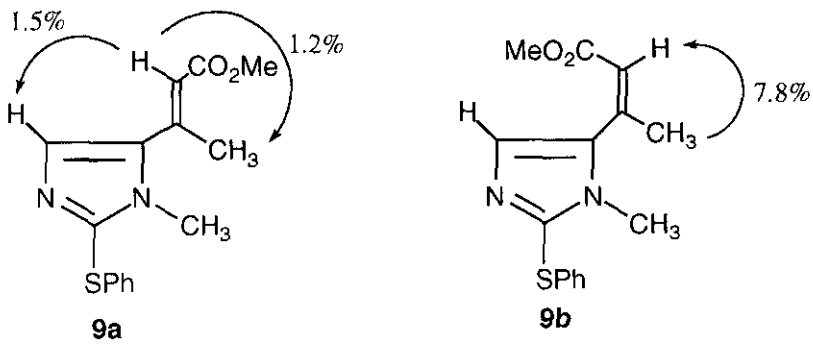


Figure 2. NOE Result of **9**

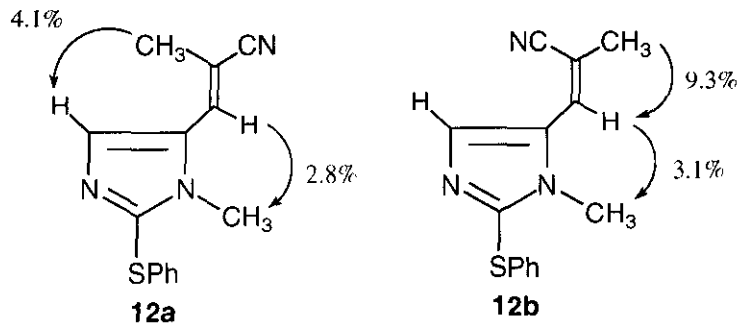


Figure 3. NOE Result of **12**

Now, we are continuously investigating total synthesis of visoltricin (**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*. ^{1}H-NMR *spectra* were measured on a Varian XL-300 (300 MHz) and Hitachi R-90H (90 MHz) with tetramethylsilane 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 PF_{254} (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-1*H*-imidazole (3): NBS (1.07 g, 6.00 mmol) was added portionwise to a solution of 1-methyl-2-phenylthio-1*H*-imidazole (**2**; 576 mg, 3.00 mmol) in THF (6 mL) under an N_2 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. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 3.62 (s, 3H), 7.2 - 7 3 (m, 5H). IR ($CHCl_3$): 3060, 1580 cm^{-1} HR-EIMS (*m/z*) *Calcd* for $C_{10}H_8N_2Br_2S$: 345.8793. Found; 345.8770 (M^+).

5-Bromo-1-methyl-2-phenylthio-1*H*-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 N_2 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 % $Na_2S_2O_3$ 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). ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 3.60 (s, 3H), 7.15 - 7.30 (m, 6H). IR ($CHCl_3$): 3060, 1580 cm^{-1}. HR-EIMS (*m/z*) *Calcd* for $C_{10}H_9N_2BrS$; 267.9687. Found; 267.9664 (M^+). *Anal.* Calcd for $C_{10}H_9N_2BrS$: 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-1*H*-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 N_2 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 oneportion to the mixture and the whole was stirred for 12 h at ambient temperature. After addition of 10 % $Na_2S_2O_3$ 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). ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 3.63 (s, 3H), 7.15 - 7.30 (m, 6H). IR ($CHCl_3$): 3060, 1579 cm^{-1}. HR-EIMS (*m/z*) *Calcd* for $C_{10}H_9N_2IS$; 315.9550. Found; 315.9532 (M^+). *Anal.* Calcd for $C_{10}H_9N_2IS$: 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 N_2 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). ^{1}H-NMR ($CDCl_3$, 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 ($CHCl_3$): 1704, 1636 cm^{-1}. HR-EIMS (*m/z*) *Calcd* for $C_{14}H_{14}N_2O_2S$; 274.0793. Found; 274.0770 (M^+). *Anal.* Calcd for $C_{14}H_{14}N_2O_2S$: 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-yl)-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. ^{1}H-NMR ($CDCl_3$, 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 ($CHCl_3$): 1664, 1641, 1618 cm^{-1}. HR-EIMS (*m/z*) *Calcd* for $C_{14}H_{14}N_2OS$: 258.0844. Found; 258.0851 (M^+).

Methyl (*E*)-3-Methyl-3-(1-methyl-2-phenylthioimidazol-5-yl)-2-propenoate (9a) and Methyl (*Z*)-3-Methyl-3-(1-methyl-2-phenylthioimidazol-5-yl)-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 ($CHCl_3$).

9a; Less polar. Colorless oil. ^{1}H-NMR ($CDCl_3$, 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 ($CHCl_3$): 1709, 1623 cm^{-1} HR-EIMS (*m/z*) *Calcd* for $C_{15}H_{16}N_2O_2S$: 288.0932. Found; 288.0913 (M^+).

9b; More polar. Colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.17 (d, 3H, *J* = 1.5 Hz), 3.42 (s, 3H), 3.57 (s, 3H), 6.09 (q, 1H, *J* = 1.5 Hz), 7.2 - 7.3 (m, 6H). IR ($CHCl_3$): 1709, 1623 cm^{-1}. HR-EIMS (*m/z*) *Calcd* for $C_{15}H_{16}N_2O_2S$: 288.0932. Found; 288.0925 (M^+).

(*E*)-3-(1-Methyl-2-phenylthioimidazol-5-yl)acrylonitrile (10a) and (*Z*)-3-(1-Methyl-2-phenylthioimidazol-5-yl)acrylonitrile (10b): According to the procedure described above for the synthesis of **6**, the reaction using **7** (158 mg, 0.50 mmol) and acryronitrile (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). ^{1}H-NMR ($CDCl_3$, 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 ($CHCl_3$): 2207, 1618 cm^{-1}. HR-EIMS (*m/z*) *Calcd* for $C_{13}H_{11}N_3S$; 241.0674. Found; 241.0647 (M^+). *Anal.* Calcd for $C_{13}H_{11}N_3S$: 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). ^{1}H-NMR ($CDCl_3$, 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 ($CHCl_3$): 2206, 1602, 1580 cm^{-1}. HR-EIMS (*m/z*) *Calcd* for $C_{13}H_{11}N_3S$; 241.0674. Found; 241.0674 (M^+). *Anal.* Calcd for $C_{13}H_{11}N_3S$: 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-yl)-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. ^{1}H-NMR ($CDCl_3$, 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 ($CHCl_3$): 17, 1605, 1589 cm^{-1}. HR-EIMS (*m/z*) *Calcd* for $C_{20}H_{18}N_2O_2S$: 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 ($CHCl_3$).

12a; Less polar. Colorless needles. mp 119 - 121°C (from ethyl acetate - *n*-hexane). ^{1}H-NMR ($CDCl_3$, 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 ($CHCl_3$): 2203, 1674, 1621, 1581 cm^{-1}. HR-FABMS (*m/z*) *Calcd* for $C_{14}H_{14}N_3S$; 256.0908. Found; 256.0926 $(M+H)^+$. *Anal* Calcd for $C_{14}H_{13}N_3S$: 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). ^{1}H-NMR ($CDCl_3$, 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 ($CHCl_3$): 2204, 1618, 1580 cm^{-1}. HR-FABMS (*m/z*) *Calcd* for $C_{14}H_{14}N_3S$; 256.0908. Found; 256.0918 $(M+H)^+$. *Anal.* Calcd for $C_{14}H_{13}N_3S$: C, 65.86; H, 5.13; N, 16.46. Found: C, 65.90: H, 5.19: N, 16.35.

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6. In the coupling reaction with iodobenzene and methyl acrylate, Heck reported the predominate formation of (*E*)-$C_6H_5CH{=}CHCO_2Me$ in Ref. 4a
7. In the coupling reaction with holobenzene derivatives and alkenyl groups bearing an electron-withdrawing group, most of the obtained products were (*E*)-form. However, in some cases, mixtures

of (*E*)- and (*Z*)-isomers were obtained. J. B. Melpolder and R. F. Heck, *J. Org. Chem.*, **1976**, *41*, 265; N. A. Cortese, C. B. Ziegler, Jr., B. J. Hrnjez, and R. F. Heck, *J. Org. Chem.*, **1978**, *43*, 2953; A. Spencer, *J. Organometal. Chem.*, **1983**, *258*, 101.

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