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Studies on the Synthesis and Anti-inflammatory Activity of 2,6-Di-*tert*-butylphenols with a Heterocyclic Group at the 4-Position. V.[1] Elimination Reaction of the Sulfinyl Group of 2,3-Dihydroimidazo[2,1-*b*]thiazole 1-Oxide

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Reaction of 6-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole 1-oxide (**1**) with superoxide anion gave 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-vinylimidazole (**2**). Compound **2** was also obtained by treatment of **1** with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) in the presence of oxygen, while 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-thioxo-1-vinyl-4-imidazoline (**3**) was obtained together with **2** in the absence of oxygen. When the same reaction was carried out in *N*, *N*-dimethyl formamide, **1** gave **2** and **3** in the absence of oxygen, and 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-vinylimidazole-2-sulfonic acid (**4**) in the presence of oxygen. A possible mechanistic explanation for the formation of these products is presented. Oxygenation of 6-phenyl-2,3-dihydroimidazo[2,1-*b*]thiazole 1-oxide (**6**) was also examined.

Keywords—2,6-di-*tert*-butylphenol; 2,3-dihydroimidazo[2,1-*b*]thiazole 1-oxide; sulfinyl group; elimination; superoxide; oxygenation

In the previous paper, we reported that 6-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole 1-oxide (**1**) has potent anti-inflammatory and analgesic activities.[2] 2,6-Di-*tert*-butylphenol derivatives are known to be an antioxidants, and their oxygenation reations have been extensively studied by several workers.[3] However, there is no report on the oxygenation of 2,6-di-*tert*-butylphenols with a heterocyclic group to our knowledge. We found that **1** has a radical scavenging activity through a pharmacological study of **1**. Because of our interest in the chemical behavior of **1** in relation to its pharmacological activities, we studied the reaction of **1** with superoxide anion. The present paper describes an unexpected elimination reaction of the sulfinyl group of **1** encountered in these studies, as well as the base-catalyzed oxygenation of **1**.

When compound **1** was treated with superoxide anion[4] under nitrogen at room temperature, the product isolated was 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-vinylimidazole (**2**). The structure of **2** was determined on the basis of mass and nuclear magnetic resonance (NMR) spectral data as well as elemental analysis. Mass spectral and microanalytical data indicated a molecular formula of $C_{19}H_{26}N_2O$. In the NMR spectra, vinyl group signals were newly observed at 4.84 ppm (d, $J=11$ Hz), 5.32 ppm (d, $J=22$ Hz) and 6.90 ppm (dd, $J=11$, 22 Hz).

Superoxide anion is a mild multifunctional agent[5] which possesses both oxidizing and reducing abilities and also radical or anionic character, and in this reaction superoxide anion seemed to act as a base and oxidizing agent. Oae *et al.*[6] reported that the base-catalyzed oxygenation of organic sulfur compounds is closely similar to the oxidation with superoxide anion. Thus, **1** was next subjected to base-catalyzed oxygenation.

Treatment of **1** with potassium *tert*-butoxide in DMSO gave **2** in the presence of oxygen, and **2** and 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-thioxo-1-vinyl-4-imidazoline (**3**) in the

absence of oxygen. When *N*, *N*-dimethyl formamide (DMF) was used as a solvent, similar oxygenation of **1** gave 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-vinylimidazole-2-sulfonic acid (**4**), while in the absence of oxygen **1** gave **2** and **3**. Formation of **2**, **3** and **4** can be well

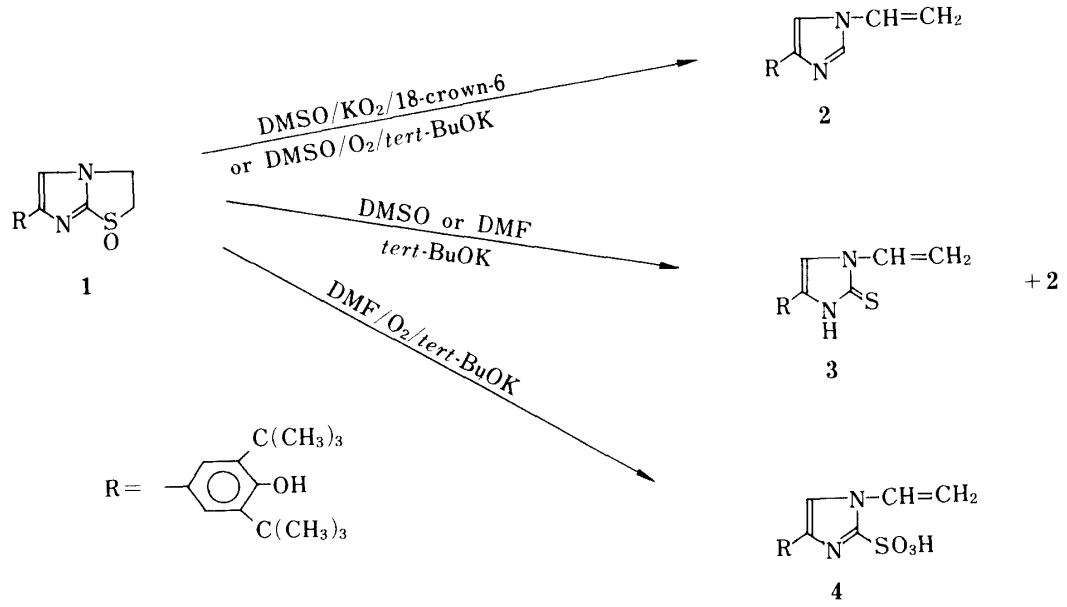

Chart 1

rationalized in terms of involvement of the sulfenate anion (**5a**), which is a proposed intermediate in the base-catalyzed oxygenation.[7] Namely, **1** first reacts with base to form **5a**. Then, in the presence of oxygen, **5a** is oxidized with oxygen to give the sulfinate anion (**5b**) which undergoes elimination of SO_2 to give **2** or further oxidation to give **4**. In the absence of oxygen, **5a** disproportionates to **5b** and **3**. Such disproportionation of a sulfenate anion has

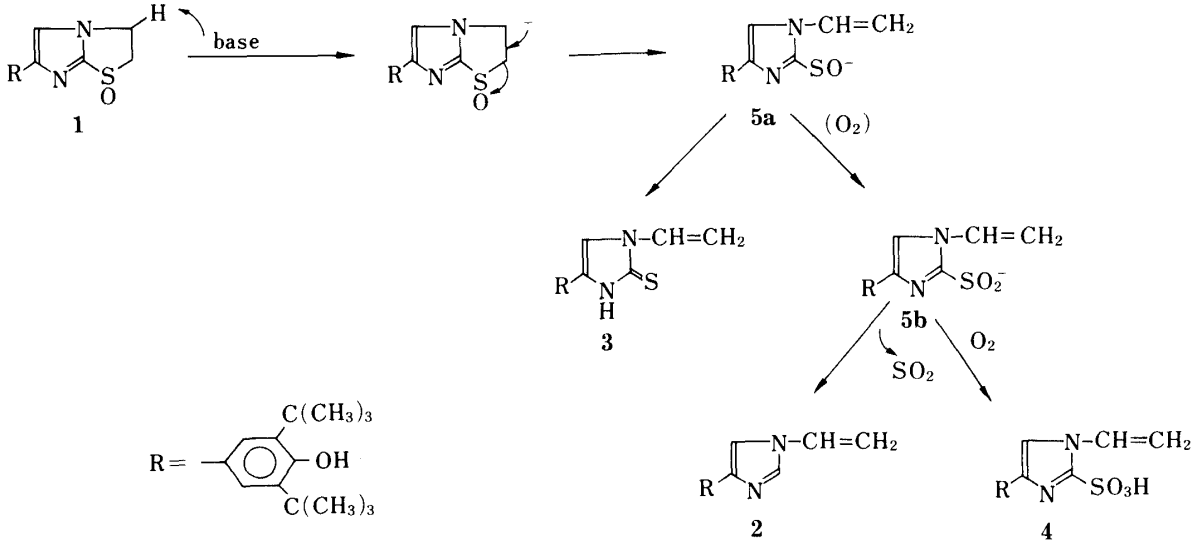

Chart 2

already been proposed.[7] Thus, **2** most probably arises from SO_2 elimination of **5b**. However, one cannot exclude **5a** and the sulfonate anion as potential sources of **2** *via* SO and SO_3 elimination. It is reasonable to consider that the reaction of **1** with superoxide anion also proceeds *via* the above-mentioned mechanism.

For further mechanistic study, 6-phenyl-2,3-dihydroimidazo[2,1-*b*]thiazole 1-oxide (**6**) was utilized to avoid complications arising from the hydroxy function. Reaction of **6** with potassium *tert*-butoxide in DMSO gave 4-phenyl-1-vinylimidazole (**7**) in the presence of oxygen, and **7** and 4-phenyl-2-thioxo-1-vinyl-4-imidazoline (**8**) in the absence of oxygen. When DMF was used as a solvent, **6** gave **7** and **8** in the absence of oxygen. Evidence for the presence of the sulfenate anion as a key intermediate was provided by the formation of methyl 4-phenyl-1-vinylimidazole-2-sulfenate (**11**). Compound **11** was isolated as a main product in addition to 2-methylthio-4-phenyl-1-vinylimidazole (**9**) and 2-methylsulfonyl-4-phenyl-1-vinylimidazole (**10**) when **6** was treated with potassium *tert*-butoxide in the absence of oxygen, followed by treatment with methyl iodide. In the presence of oxygen, **6** gave **10** and **11**. The identity of **9** was confirmed by comparison with an authentic sample which was prepared from **8** and methyl iodide. The site of methylation in **10** and **11** was established by comparison with the isomers **12** and **13**, which were obtained by oxidizing **9** and **11** with *m*-chloroperbenzoic acid, respectively. Namely, the sulfone **10** and sulfenate **11** markedly differed from the sulfoxide **12** and sulfinate ester **13**, respectively, in the chemical shift of the methyl group in the NMR spectra.

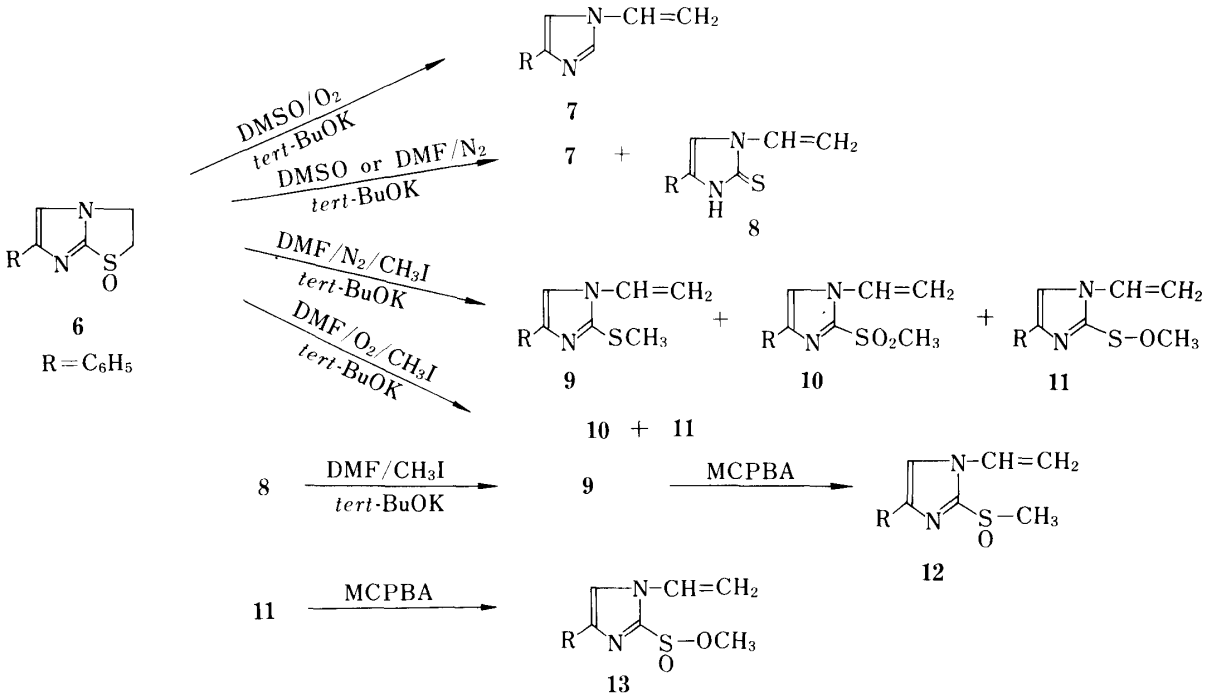

Chart 3

Base-catalyzed elimination reaction of a sulfinyl group has been reported by Wallace *et al.*,[8] who proposed the sulfenate anion as an intermediate. To our knowledge, however, base-catalyzed elimination of a sulfinyl group in a heterocyclic compound has not been reported. In order to rationalize the formation of **2**, we propose a mechanism involving a sulfenate anion intermediate. However, a detailed mechanistic interpretation must await further study.

Experimental

All melting points were determined by using a Yanagimoto micromelting point apparatus, and are uncorrected. IR spectra were obtained with a Hitachi 215 spectrometer. The NMR spectra were obtained with a JEOL-FX 90 or 100 spectrometer using $(CH_3)_4Si$ as an internal standard. Mass spectra (MS) were obtained with an RMU-6MG spectrometer.

4-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1-vinylimidazole (2)——Method a): A solution of 6-(3,5-di-*tert*-butyl-4-

hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole 1-oxide (**1**) (1.70 g, 5 mmol) in DMSO (10 ml) was added dropwise to a solution of 18-crown-6-ether (2.60 g, 10 mmol) and potassium superoxide (0.8 g, 10 mmol) in DMSO (25 ml) at room temperature under nitrogen. After being stirred for 4 h, the reaction mixture was poured into ice-cold dil. HCl solution. The whole was extracted with AcOEt and the extract was dried and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography and eluted with $CHCl_3$ to give **2**, 0.6 g (yield 40.3%). NMR ($CDCl_3$) δ: 1.24 (18H, s, $C(CH_3)_3$), 4.84 (1H, d, J=11 Hz, C=CH_2), 5.26 (1H, s, OH), 5.32 (1H, d, J=22 Hz, C=CH_2), 6.90 (1H, dd, J=11, 22 Hz, CH=C), 7.36 (1H, s, imidazole-H), 7.60 (2H, s, aromatic-H), 7.62 (1H, s, imidazole-H). MS *m/z*: 298 (M^+). IR (KBr): 3650 cm^{-1} (OH). mp 151—152 °C (from iso-octane). *Anal.* Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.24; H, 8.85; N, 9.14.

Method b): A solution of **1** (1.70 g, 5 mmol) and potassium *tert*-butoxide (1.12 g, 10 mmol) in DMSO (20 ml) was stirred under oxygen at below 25 °C. After being stirred for 15—30 min, the reaction mixture was poured into ice-cold dil. HCl solution. The whole was extracted with AcOEt and the extract was dried and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to give **2**, 1.0 g (yield 67%). 6-Phenyl-2,3-dihydroimidazo[2,1-*b*]thiazole 1-oxide (**6**) was treated in similar manner to give 4-phenyl-1-vinylimidazole (**7**) (yield 58.8%). NMR (DMSO-d_6) δ: 5.34 (1H, d, J=9 Hz, C=CH_2), 5.96 (1H, d, J=16 Hz, C=CH_2), 7.28 (1H, dd, J=9, 16 Hz, CH=C), 7.44 (3H, aromatic-H), 7.90 (2H, aromatic-H), 8.50 (1H, s, imidazole-H), 9.40 (1H, s, imidazole-H). MS *m/z*: 170 (M^+). mp 48—49 °C (from C_6H_{12}). *Anal.* Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.62; H, 5.72; N, 16.39.

4-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-thioxo-1-vinyl-4-imidazoline (3) and 2——A solution of **1** (3.46 g, 10 mmol) and potassium *tert*-butoxide (2.24 g, 20 mmol) in DMSO (40 ml) was stirred for 0.5 h under argon at room temperature. The reaction mixture was poured into ice-cold dil. HCl solution. The whole was extracted with AcOEt and the extract was dried and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography and eluted with $CHCl_3$ to give **2**, 0.70 g (yield 23.5%) and **3**, 1.53 g (yield 46.4%). NMR ($CDCl_3$) δ: 1.24 (18H, s, $C(CH_3)_3$), 4.96 (1H, d, J=11 Hz, C=CH_2), 5.20 (1H, d, J=22 Hz, C=CH_2), 5.40 (1H, s, OH), 7.02 (1H, s, imidazole-H), 7.24 (2H, s, aromatic-H), 7.58 (1H, dd J=11, 22 Hz, CH=C), 11.0 (1H, br). MS *m/z*: 330 (M^+). IR (KBr): 3500 cm^{-1} (OH). mp 275—280 °C (dec.) (from CH_3CN). *Anal.* Calcd for $C_{19}H_{26}N_2OS$: C, 69.05; H, 7.93; N, 8.48. Found: C, 69.30; H, 8.06; N, 8.77. **6** was treated in a similar manner to give **7** (yield, 30.1%) and 4-phenyl-2-thioxo-1-vinyl-4-imidazoline (**8**) (yield 23.0%). NMR ($CDCl_3$) δ: 4.96 (1H, d, J=10 Hz, C=CH_2), 5.20 (1H, d, J=16 Hz, C=CH_2), 7.16 (1H, s, imidazole-H), 7.24—7.60 (6H, m), 11.70 (1H, br). MS *m/z*: 202 (M^+). mp 194—196 °C (from C_6H_6). *Anal.* calcd for $C_{11}H_{10}N_2S$: C, 65.32; H, 4.98; N, 13.85. Found: C, 65.48; H, 4.93; N, 13.80. When DMF was used as a solvent, **1** gave **2** (13.4%) and **3** (yield, 39.4%), and **6** gave **7** (yield, 39.2%) and **8** (yield, 25.7%).

4-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1-vinylimidazole-2-sulfonic Acid (4)——A solution of **1** (3.40 g, 10 mmol) and potassium *tert*-butoxide (2.24 g, 20 mmol) in DMF (40 ml) was stirred for 1—2 h at room temperature under oxygen. The reaction mixture was poured into ice-cold dil. HCl and the whole was extracted with AcOEt. The extract was dried and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography and eluted with $CHCl_3$–MeOH to give **4**, 0.98 g (yield 25.9%). NMR ($CDCl_3$) δ: 1.28 (18H, s, $C(CH_3)_3$), 3.0 (1H, br), 5.40 (1H, d, J=11 Hz, C=CH_2), 5.60 (1H, s, OH), 5.68 (1H, d, J=22 Hz, C=CH_2), 7.40 (2H, s, aromatic-H), 7.48 (1H, s, imidazole-H), 7.84 (1H, dd, J=11, 22 Hz). MS *m/z*: 378 (M^+). IR (KBr): 3600 cm^{-1} (OH). mp >300 °C (from iso-$(CH_3)_2CHOH$). *Anal.* Calcd for $C_{19}H_{26}N_2O_4S$: C, 60.30; H, 6.92; N, 7.40. Found: C, 60.21; H, 7.33; N, 7.18.

Methylation of the Sulfenate Anion——A solution of **6** (2.18 g, 10 mmol) and potassium *tert*-butoxide (1.12 g, 10 mmol) in DMF (40 ml) under nitrogen was stirred for 1—2 h, and then methyl iodide (1.5 g, 10 mmol) was added to it. After being stirred for 1 h under nitrogen, the reaction mixture was poured into cold water. The whole was extracted with AcOEt and the extract was dried and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography and eluted with $CHCl_3$ to give 2-methylthio-4-phenyl-1-vinylimidazole (**9**), 0.34 g (yield, 15.7%). NMR ($CDCl_3$) δ: 2.64 (3H, s, CH_3), 4.92 (1H, d, J=12 Hz), 5.24 (1H, d, J=24 Hz), 7.04 (1H, dd, J=11, 24 Hz), 7.20—7.44 (3H, aromatic-H), 7.52 (1H, s, imidazole-H), 7.76—7.90 (2H, aromatic-H). MS *m/z*: 216 (M^+). mp 149—150 °C (from MeOH–Et_2O). *Anal.* Calcd for $C_{12}H_{12}N_2S \cdot HCl \cdot 2H_2O$: C, 49.91; H, 5.93; N, 9.69. Found: C, 49.98; H, 5.97; N, 9.69.

2-Methylsulfonyl-4-phenyl-1-vinylimidazole (10): 0.31 g (yield, 12.4%). NMR ($CDCl_3$) δ: 3.44 (3H, s, CH_3), 5.14 (1H, d, J=12 Hz), 5.44 (1H, d, J=24 Hz), 7.24—7.52 (3H, aromatic-H), 7.58 (1H, dd, J=12, 24 Hz), 7.60 (1H, s, imidazole-H), 7.76—7.88 (2H, aromatic-H). MS *m/z*: 248 (M^+). mp 77—78 °C (from C_6H_{12}). *Anal.* Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.18; H, 4.73; N, 11.23.

Methyl 4-Phenyl-1-vinylimidazole-2-sulfenate (11): 0.84 g (yield 36.2%). NMR ($CDCl_3$) δ: 3.88 (3H, s, CH_3), 6.08 (1H, d, J=12 Hz), 6.28 (1H, d, J=24 Hz), 6.92 (1H, dd, J=12, 24 Hz), 7.20—7.74 (6H). MS *m/z*: 232 (M^+). mp 74—75 °C (from toluene–*n*-C_6H_{14}). *Anal.* Calcd for $C_{12}H_{12}N_2OS$: C, 62.05; H, 5.21; N, 12.06. Found: C, 61.87; H, 5.10; N, 11.80. **6** was treated in similar manner under oxygen to give **10**, 0.74 g (yield, 29.8%) and **11**, 0.5 g (yield, 21.6%).

2-Methylthio-4-phenyl-1-vinylimidazole (9)——A solution of **8** (0.40 g, 2 mmol) and potassium *tert*-butoxide (0.23 g, 2 mmol) in MDF (5 ml) under nitrogen was stirred for 15 min, then methyl iodide (0.35 g, 2.5 mmol) in DMF (2 ml) was added. After being stirred for 1 h, the reaction mixture was poured into water and the whole was extracted

with AcOEt. The extract was dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **9**, 0.38 g (yield 88%).

2-Methylsulfinyl-4-phenyl-1-vinylimidazole (12)——*m*-Chloroperoxybenzoic acid (0.35 g, 2 mmol) was added portionwise to a solution of **9** (0.35 g, 1.6 mmol) in $CHCl_3$ (10 ml) below 10 °C. After being stirred for 1 h, the whole was washed with 1 N NaOH, dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **12**, 0.26 g (yield 69.1%). NMR ($CDCl_3$) δ: 3.20 (3H, s, CH_3), 5.12 (1H, d, $J=11$ Hz), 5.26 (1H, d, $J=24$ Hz), 7.24—7.48 (3H, aromatic-H), 7.52 (1H, dd, $J=12$, 24 Hz), 7.62 (1H, s, imidazole-H), 7.76—7.88 (2H, aromatic-H). MS *m/z*: 232 (M^+). mp 80—81 °C (from C_6H_6–*n*-C_6H_{14}). *Anal.* Calcd for $C_{12}H_{12}N_2OS$: C, 62.05; H, 5.21; N, 12.06. Found: C, 62.24; H, 5.11; N, 12.16.

Methyl 4-Phenyl-1-vinylimidazole-2-sulfinate (13)——*m*-Chloroperoxybenzoic acid (0.23 g, 1.3 mmol) was added to a solution of **11** (0.25 g, 1.1 mmol) in $CHCl_3$ (10 ml) below 10 °C. After being stirred overnight, the reaction mixture was washed with dil. $NaHCO_3$, dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **13**, 0.2 g (yield 74.9%). NMR ($CDCl_3$) δ: 4.00 (3H, s, CH_3), 6.20 (1H, d, $J=12$ Hz), 6.56 (1H, d, $J=24$ Hz), 7.04 (1H, dd, $J=12$, 24 Hz), 7.28—7.80 (6H). MS *m/z*: 248 (M^+). mp 104—105 °C (from C_6H_6–*n*-C_6H_{14}). *Anal.* Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.19; H, 4.73; N, 11.14.

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References and Notes

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