

**SYNTHESIS OF 2-(4-ARYL-1E,3E-BUTADIENYL)BENZOXAZOLES
BY THE HORNER-WADSWORTH-EMMONS REACTION**

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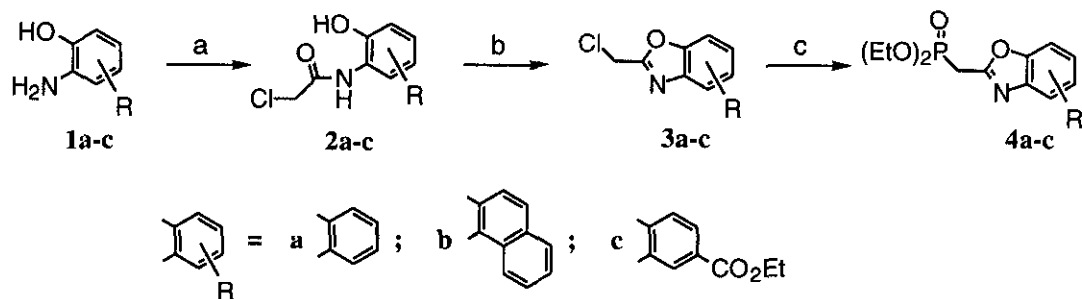
Abstract - 2-(4-Aryl-1E,3E-butadienyl)benzoxazole derivatives were synthesized by the Horner-Wadsworth-Emmons reaction of 2-phosphorylmethylbenzoxazoles with cinnamaldehydes in fair to good yield.

In our antiasthmatic drug research project, we planned to synthesize a variety of 2-(4-aryl-1E,3E-dienyl)benzoxazole derivatives. There are many kinds of 2-substituted benzoxazoles in natural products,¹ synthetic drugs² and fluorescent whiteners.³ However, 2-(4-aryl-1E,3E-dienyl) derivatives have not been reported.

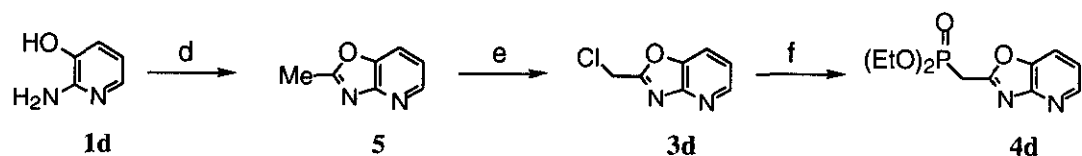
Recently, synthesis of 2-styrylbenzoxazole by means of the Horner-Wadsworth-Emmons (HWE) reaction of 2-phosphorylmethylbenzoxazole with benzaldehyde was reported.⁴ We also investigated this type of reaction for the synthesis of a variety of 2-(4-aryl-1E,3E-dienyl)oxazoles using cinnamaldehyde derivatives with 2-phosphorylmethylbenzoxazoles and 2-phosphorylmethylloxazopyridine.

2-Phosphorylmethylbenzoxazoles (**4a-c**) were prepared in three steps from *o*-aminophenols (**1a-c**) by i) *N*-chloroacetylation with chloroacetyl chloride in the presence of NaHCO₃; ii) oxazole formation by treatment with ethyl polyphosphate,⁵ and iii) the Arbuzov reaction with triethyl phosphite. For the preparation of oxazopyridylmethyl phosphonate (**4d**), the 2-chloromethyl precursor (**3d**)⁶ was obtained by trichloroisocyanuric acid-mediated chlorination⁷ of **5**, which was derived from **1d** by cyclization with triethyl orthoacetate.⁸

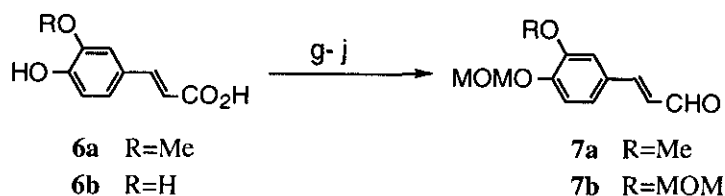
Aldehydes (**7a**)⁹ and (**7b**) were prepared from ferulic acid (**6a**) and caffeic acid (**6b**) by esterification,



Reagents: (a) ClCH_2COCl , NaHCO_3 , acetone, room temperature; (b) ethyl polyphosphate, $\text{ClCH}_2\text{CH}_2\text{Cl}$, reflux; (c) $(\text{EtO})_3\text{P}$, 150°C .



Reagents: (d) $\text{MeC}(\text{OEt})_3$, 100°C ; (e) trichloroisocyanuric acid, CH_2Cl_2 , 40°C ; (f) $(\text{EtO})_3\text{P}$, 150°C .



Reagents: (g) EtOH , H_2SO_4 , reflux; (h) MOMCl , $^i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , room temperature; (i) DIBALH , THF , -78°C ; (j) MnO_2 , CH_2Cl_2 , room temperature.

protection of the ring hydroxyl group as the MOM ether, DIBALH reduction to alcohol, and oxidation by MnO_2 .

Our preliminary investigation of the HWE reaction was carried out with sodium hydride as a base. Typically, 2-phosphorylmethylbenzoxalole (**4a**)⁴ was treated with sodium hydride (1.1 eq.) in tetrahydrofuran at -15°C for 10 min under an argon atmosphere followed by the addition of aldehyde (**7a**) (1 eq.) and stirring at 0°C for 2.5 h to give **8a** in 79% yield (Method A). Similarly, the phosphonates (**4b** and **4c**) afforded **8b**, **8c** and **8d** in good yields (Table). The geometry of the newly produced double bonds was assigned as *E* based on ^1H nmr spectra which exhibits a doublet of $J = 15\text{-}16$ Hz at *ca.* 6.6-6.8 ppm.

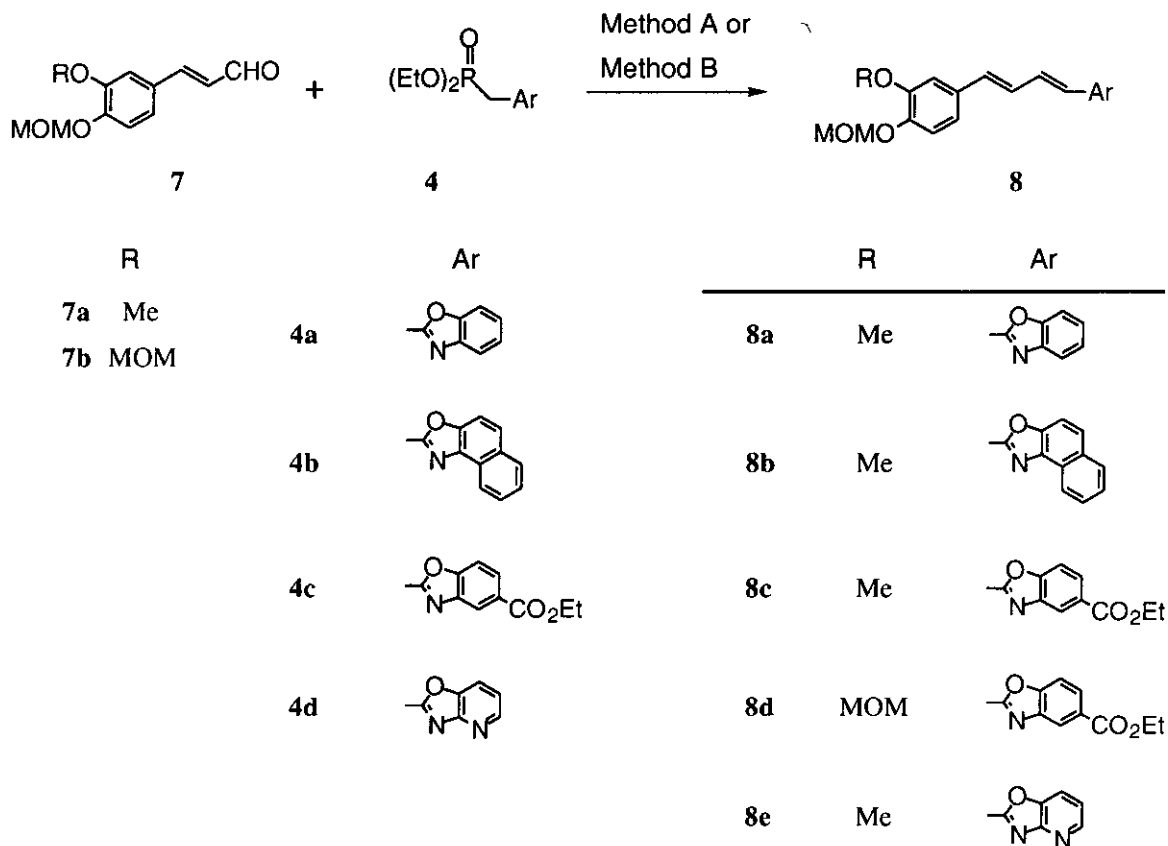


Table. The Horner-Wadsworth-Emmons Reaction of 2-Phosphoryl-methylbenzoxazoles with Cinnamaldehydes

entry	Aldehyde	Phosphonate	Method	Product	Yield (%)
1	7a	4a	A	8a	79
2	7a	4a	B	8a	67
3	7a	4b	A	8b	69
4	7a	4c	A	8c	69
5	7b	4c	A	8d	59
6	7a	4d	A	8e	6
7	7a	4d	B	8e	47

On the other hand, the HWE reaction of oxazolopyridylmethyl phosphonate (**4d**) did not proceed smoothly resulting in only a 6% yield of **8e**, but a much higher yield was successfully obtained under phase transfer catalytic conditions.¹⁰

Thus, the reaction of **4d** and **7a** in the presence of tetrabutylammonium bromide (0.2 eq.), under 50% NaOH/CH₂Cl₂ system at room temperature for 1 h (Method B) afforded **8e** in 47% yield. This phase transfer procedure was also applied to **4a** to give **8a** in 67% yield.

The MOM group of aryldienyloxazoles (**8a-e**) were deprotected. The bioassay of the resulting phenolic compounds is undergoing investigation.

In conclusion, this work provides a general synthesis for a variety of 2-(4-arylbutadienyl)benzoxazoles and for 2-(4-arylbutadienyl)oxazolopyridines.

EXPERIMENTAL

All mps are uncorrected. The ¹H nmr spectra were determined on a Varian Gemini 200 spectrometer using tetramethylsilane as an internal standard. The ir spectra were recorded with a JASCO VALOR III Fourier transform spectrophotometer.

N-(2-Hydroxyphenyl)chloroacetoamide (**2a**).

To a stirred suspension of 2-aminophenol (**1a**) (2.05 g, 18.8 mmol) and NaHCO₃ (3.16 g, 37.6 mmol) in acetone (30 ml) under an argon atmosphere was added, dropwise, chloroacetyl chloride (1.57 ml, 19.7 mmol). The reaction mixture was stirred for 2 h at room temperature, then the precipitate was separated by suction and washed with acetone. The combined filtrate was concentrated under vacuum and the residue was recrystallized from ethyl acetate to give **2a** as colorless crystals (2.58 g, 74%), mp 139-140.5 °C; ir (KBr): 1656 cm⁻¹; ¹H nmr (CDCl₃) δ 4.27 (s, 2H), 6.85-7.10 (m, 2H), 7.10-7.35 (m, 2H), 7.85 (br s, 1H), 8.55 (br s, 1H). Anal. Calcd for C₈H₈NO₂Cl: C, 51.76; H, 4.34; N, 7.55. Found: C, 51.46; H, 4.29; N, 7.48.

N-(2-Hydroxy-1-naphthyl)chloroacetoamide (**2b**).

This product was prepared by a method similar to that of **2a**, from 1-amino-2-naphthol hydrochloride (**1b**) (85% purity, 2.51 g, 10.9 mmol) and was washed with acetone-Et₂O (1 : 10) to give **2b** as a red solid (2.21

g, 86%), which was used without further purification for the next step.

Ethyl 3-(*N*-Chloroacetyl)amino-4-hydroxybenzoate (2c).

This product was prepared by a method similar to that of **2a**, from ethyl 3-amino-4-hydroxybenzoate hydrochloride (**1c**) (6.35 g, 29.2 mmol) and was purified by recrystallization from acetone-hexane to afford **2c** as a gray powder (6.58 g, 87%). Recrystallization from MeOH gave colorless prisms, mp 178-179 °C; ir (KBr): 1702, 1665 cm^{-1} ; ^1H nmr (DMSO- d_6) δ 1.29 (t, $J = 7$ Hz, 3H), 4.26 (q, $J = 7$ Hz, 2H), 4.40 (s, 2H), 6.98 (d, $J = 9$ Hz, 1H), 7.64 (dd, $J = 9$ Hz, 2 Hz, 1H), 8.56 (d, $J = 2$ Hz, 1H), 9.57 (s, 1H), 10.97 (s, 1H). Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_4\text{Cl}$: C, 51.27; H, 4.69; N, 5.44. Found: C, 51.31; H, 4.62; N, 5.56.

2-Chloromethylbenzoxazole (3a).

To a solution of ethyl polyphosphate (10.0 g) in 1,2-dichloroethane (30 ml) under an argon atmosphere was added, portionwise, **2a** (2.50 g, 13.5 mmol) and the mixture was heated to reflux for 2 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 (50 ml), washed with water, dried over MgSO_4 , and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2 -hexane = 1 : 3) to afford **3a** as a colorless oil (1.47 g, 60%) (lit.,¹¹ oil).

2-Chloromethylnaphth[1,2-*d*]oxazole (3b).

This product was prepared by a method similar to that of **3a**, from **2b** (2.04 g, 8.66 mmol) and was purified by flash column chromatography on silica gel (CH_2Cl_2 -hexane = 1 : 12) to afford **3b** as colorless crystals (1.01 g, 54%), mp 104-105.5 °C (from CH_2Cl_2 -hexane); ^1H nmr (CDCl_3) δ 4.85 (s, 2H), 7.45-7.80 (m, 3H), 7.81 (d, $J = 9$ Hz, 1H), 7.95 (d, $J = 8$ Hz, 1H), 8.46 (d, $J = 8$ Hz, 1H). Anal. Calcd for $\text{C}_{12}\text{H}_8\text{NOCl}$: C, 66.22; H, 3.70; N, 6.44. Found: C, 66.42; H, 3.65; N, 6.37.

Ethyl 2-Chloromethylbenzoxazole-5-carboxylate (3c).

This product was prepared by a method similar to that of **3a**, from **2c** (5.00 g, 19.4 mmol) and was purified by flash column chromatography on silica gel (CH_2Cl_2 -hexane = 1 : 3) to afford **3c** as colorless crystals (3.59 g, 77%), mp 90-90.5 °C (from CH_2Cl_2 -hexane); ir (KBr): 1713, 1623, 1577 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.43 (t, $J = 7$ Hz, 3H), 4.42 (q, $J = 7$ Hz, 2H), 4.78 (s, 2H), 7.60 (d, $J = 9$ Hz, 1H), 8.15 (dd, $J = 9$ Hz, 1.5 Hz, 1H), 8.45 (d, $J = 1.5$ Hz, 1H). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{NO}_3\text{Cl}$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.23;

H, 4.15; N, 5.86.

2-(Diethoxyphosphorylmethyl)benzoxazole (4a).

A stirred mixture of **3a** (987 mg, 5.89 mmol) and triethyl phosphite (1.70 ml, 9.82 mmol) was heated at 150 °C for 3.5 h, and then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (CH₂Cl₂-ethyl acetate = 5 : 1) to give **4a** as a brown oil (1.55 g, 98%) (lit.,⁴ oil).

2-(Diethoxyphosphorylmethyl)naphth[1,2-*d*]oxazole (4b).

This product was prepared by a method similar to that of **4a**, from **3b** (784 mg, 3.60 mmol) and was purified by flash column chromatography on silica gel (CH₂Cl₂-ethyl acetate = 15 : 1) to afford **4b** as a yellow oil (1.15 g, 100%); ir (neat): 1590 cm⁻¹; ¹H nmr (CDCl₃) δ 1.35 (t, J = 7 Hz, 6H), 3.68 (d, J = 22 Hz, 2H), 4.10-4.35 (m, 4H), 7.50-7.70 (m, 3H), 7.80 (d, J = 9 Hz, 1H), 7.97 (d, J = 8 Hz, 1H), 8.48 (d, J = 8 Hz, 1H).

Ethyl 2-(Diethoxyphosphorylmethyl)benzoxazole-5-carboxylate (4c).

This product was prepared by a method similar to that of **4a**, from **3c** (3.40 g, 14.2 mmol) and was purified by flash column chromatography on silica gel (CH₂Cl₂-ethyl acetate = 19 : 1) to afford **4c** as colorless crystals (4.41 g, 91%), mp 71-72 °C (from Et₂O-hexane); ir (KBr): 1700, 1623 cm⁻¹; ¹H nmr (CDCl₃) δ 1.34 (t, J = 7 Hz, 6H), 1.42 (t, J = 7 Hz, 3H), 3.59 (d, J = 22 Hz, 2H), 4.18 (q, J = 7 Hz, 2H), 4.22 (q, J = 7 Hz, 2H), 4.41 (q, J = 7 Hz, 2H), 7.56 (d, J = 9 Hz, 1H), 8.10 (dd, J = 9 Hz, 1.5 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H). Anal. Calcd for C₁₅H₂₀NO₆P: C, 52.79; H, 5.91; N, 4.10. Found: C, 52.88; H, 5.85; N, 4.14.

2-Methyloxazolo[4,5-*b*]pyridine (5).

A stirred mixture of 2-amino-3-hydroxypyridine (**1d**) (4.03 g, 36.6 mmol) and triethyl orthoacetate (22.4 g, 138 mmol) under an argon atmosphere was heated at 100 °C for 7 h. Excess orthoacetate was removed under vacuum, and the residue was recrystallized from hexane to give **5** as slightly brown needles (4.20 g, 86%), mp 66-68 °C (lit.,^{8b} mp 67-69 °C).

2-Chloromethyloxazolo[4,5-*b*]pyridine (3d).

A stirred mixture of **5** (2.27 g, 16.9 mmol) in 1,2-dichloroethane (100 ml) and trichloroisocyanuric acid (4.33 g, 18.0 mmol) was heated to reflux for 3 h. After cooling, the precipitate was separated by suction and

washed with CH_2Cl_2 . The combined filtrate was concentrated under vacuum and the residue was purified by column chromatography on silica gel (CH_2Cl_2). The first fraction gave 2-trichloromethyloxazolo[4,5-*b*]pyridine as a brown solid (2.30 g, 58%), mp 100-103 °C (from CH_2Cl_2 -hexane). The second fraction afforded 2-dichloromethyloxazolo[4,5-*b*]pyridine as a brown solid (320 mg, 9%), mp 63-65 °C (from CH_2Cl_2 -hexane). The third fraction gave **3d** as a brown solid (760 mg, 27%), mp 113 °C (decomp., from CH_2Cl_2 -hexane) (lit.,⁶ mp 115-118 °C).

2-(Diethoxyphosphorylmethyl)oxazolo[4,5-*b*]pyridine (**4d**).

This product was prepared by a method similar to that of **4a**, from **3d** (520 mg, 3.10 mmol) and was purified by column chromatography on silica gel (CH_2Cl_2 -acetone = 15 : 1) to afford **4d** as a brown oil (530 mg, 64%); ^1H nmr (CDCl_3) δ 1.36 (t, $J = 7$ Hz, 6H), 3.64 (d, $J = 22$ Hz, 2H), 4.10-4.35 (m, 4H), 7.32 (dd, $J = 8$ Hz, 5 Hz, 1H), 7.85 (dd, $J = 8$ Hz, 1.5 Hz, 1H), 8.58 (dd, $J = 5$ Hz, 1.5 Hz, 1H).

Method A. The HWE Reaction Under Homogeneous Conditions. 2-[(1*E*,3*E*)-4-(3-Methoxy-4-methoxy-methoxyphenyl)-1,3-butadienyl]benzoxazole (**8a**).

To a stirred suspension of NaH (60% in oil, 34 mg, 0.858 mmol) in tetrahydrofuran (1 ml) under an argon atmosphere at -15 °C was added, dropwise, a solution of phosphonate (**4a**) (210 mg, 0.780 mmol) in tetrahydrofuran (1.5 ml). The mixture was stirred for 8 min, and then aldehyde (**7a**) was added in one portion. The mixture was allowed to warm to 0 °C and stirred for 2.5 h, then quenched by the slow and careful addition of EtOH (0.5 ml). The mixture was diluted with CH_2Cl_2 , passed through a short column of silica gel (CH_2Cl_2 -EtOH = 30 : 1 as an eluent) and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2) to give **8a** as a yellow solid (208 mg, 79 %), mp 123-125 °C (from CH_2Cl_2 -MeOH); ir (KBr): 1630, 1585 cm^{-1} ; ^1H nmr (CDCl_3) δ 3.53 (s, 3H), 3.95 (s, 3H), 5.26 (s, 2H), 6.60 (d, $J = 16$ Hz, 1H), 6.80-7.90 (m, 10H). Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.26; H, 5.67; N, 4.14.

2-[(1*E*,3*E*)-4-(3-Methoxy-4-methoxymethoxyphenyl)-1,3-butadienyl]naphth[1,2-*d*]oxazole (**8b**).

Yield 69%. Yellow solid, mp 137.5-138 °C (from CH_2Cl_2 -MeOH); ir (KBr): 3447, 1592 cm^{-1} ; ^1H nmr (CDCl_3) δ 3.53 (s, 3H), 3.97 (s, 3H), 5.27 (s, 2H), 6.72 (d, $J = 16$ Hz, 1H), 6.85-7.20 (m, 5H), 7.50-7.70 (m, 4H), 7.79 (d, $J = 9$ Hz, 1H), 7.96 (d, $J = 8$ Hz, 1H), 8.51 (d, $J = 8$ Hz, 1H). Anal. Calcd for $\text{C}_{24}\text{H}_{21}\text{NO}_4$: C,

74.40; H, 5.46; N, 3.62. Found: C, 74.52; H, 5.46; N, 3.64.

Ethyl 2-[(1*E*,3*E*)-4-(3-Methoxy-4-methoxymethoxyphenyl)-1,3-butadienyl]benzoxazole-5-carboxylate (8c).

Yield 69%. Yellow solid, mp 127-128 °C (from CH₂Cl₂-MeOH); ir (KBr): 1712, 1634, 1591 cm⁻¹; ¹H nmr (CDCl₃) δ 1.43 (t, J = 7 Hz, 3H), 3.53 (s, 3H), 3.95 (s, 3H), 4.41 (q, J = 7 Hz, 2H), 5.27 (s, 2H), 6.61 (d, J = 15 Hz, 1H), 6.80-7.00 (m, 2H), 7.03 (d, J = 9 Hz, 1H), 7.05 (s, 1H), 7.15 (d, J = 9 Hz, 1H), 7.53 (d, J = 9 Hz, 1H), 7.50-7.67 (m, 1H), 8.07 (d, J = 9 Hz, 1H), 8.37 (s, 1H). Anal. Calcd for C₂₃H₂₃NO₆: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.39; H, 5.56; N, 3.41.

Ethyl 2-[(1*E*,3*E*)-4-[3,4-Bis(methoxymethoxy)phenyl]-1,3-butadienyl]benzoxazole-5-carboxylate (8d).

Yield 59%. Yellow solid, mp 135-136 °C (from CH₂Cl₂-MeOH); ir (KBr): 1720, 1630, 1592 cm⁻¹; ¹H nmr (CDCl₃) δ 1.42 (t, J = 7 Hz, 3H), 3.53 (s, 3H), 3.56 (s, 3H), 4.42 (q, J = 7 Hz, 2H), 5.27 (s, 2H), 5.29 (s, 2H), 6.60 (d, J = 16 Hz, 1H), 6.80-7.00 (m, 2H), 7.05-7.35 (m, 3H), 7.52 (d, J = 8.5 Hz, 1H), 7.50-7.67 (m, 1H), 8.07 (dd, J = 8.5 Hz, 1.5 Hz, 1H), 8.38 (d, J = 1.5 Hz, 1H). Anal. Calcd for C₂₄H₂₅NO₇: C, 65.59; H, 5.73; N, 3.18. Found: C, 65.40; H, 5.64; N, 3.20.

Method B. The HWE Reaction under Heterogeneous Conditions. 2-[(1*E*,3*E*)-4-(3-Methoxy-4-methoxymethoxyphenyl)-1,3-butadienyl]oxazolo[4,5-*b*]pyridine (8e).

To a vigorously stirred mixture of tetrabutylammonium bromide (16 mg, 0.050 mmol) in 50 % aqueous sodium hydroxide solution (0.3 ml) and CH₂Cl₂ (0.5 ml) was added, dropwise, a solution of 4d (68 mg, 0.25 mmol) and 7a (56 mg, 0.25 mmol) in CH₂Cl₂ (2 ml). After stirring at room temperature for 30 min, the organic layer was separated and washed with brine, dried over MgSO₄, and concentrated under vacuum. The residue was purified by column chromatography (CH₂Cl₂-acetone = 20 : 1) to afford 8e as a yellow solid (40 mg, 47 %), mp 118-119.5 °C (from CH₂Cl₂-Et₂O); ir (KBr): 1618, 1593 cm⁻¹; ¹H nmr (CDCl₃) δ 3.53 (s, 3H), 3.95 (s, 3H), 5.27 (s, 2H), 6.65 (d, J = 15.5 Hz, 1H), 6.90-7.30 (m, 6H), 7.62-7.80 (m, 1H), 7.77 (d, J = 8 Hz, 1 Hz, 1H), 8.53 (dd, J = 5 Hz, 1.5 Hz, 1H). Anal. Calcd for C₁₉H₁₈N₂O₄: C, 67.45; H, 5.36; N, 8.28. Found: C, 67.30; H, 5.29; N, 8.21.

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