

Palladium-catalyzed Synthesis of  
Isocoumarin and 1-Isoquinolinone Derivatives

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In the presence of copper(I) chloride, the palladium catalyzed oxidation of methyl 2-ethenylbenzoates and 2-ethenylbenzamides have been studied. This reaction was used to form isocoumarins and 1-isoquinolinones.

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In recent years, organometallic reagents have been used in the synthesis of a variety of heterocyclic ring systems [1]. Isocoumarins **1** are a class of naturally occurring lactones which display a wide range of biological activity [2]. Despite the apparently simple structure, much effort has been expended in developing good synthetic routes to these compounds [3]. Previously, Hegedus *et al.* [3] reported a synthetic method using a  $\pi$ -allylnickel halide complex for the facile palladium-assisted cyclization of 2-allylbenzoic acids to **1** and also for the cyclization of 2-allylbenzamides to form 1-isoquinolinones **2**. We also described that the treatment of 2-alkenylbenzoic acids and 2-alkenylbenzamides with palladium chloride led to the formation of **1** and **2**, respectively [4].

In previous work we reported that in the presence of copper(I) chloride and propane-1,3-diol, various 2-nitrostyrenes could be oxidized with palladium catalysts to form 2-nitrophenylacetaldehyde acetals, and following reductive cyclization, could result in the formation of indoles [5]. We wish to report herein an extension of our previous work: the palladium-catalyzed oxidation of methyl 2-ethenylbenzoates **3** and 2-ethenylbenzamides **4**, which form the oxygen and nitrogen heterocycles **1** and **2**, respectively.

### Results and Discussion.

#### Synthesis of Isocoumarins (1).

The over-all reaction scheme is presented in Figure 1. Literature methods for the synthesis of the starting materials **3** are characterized by low yields and intolerance toward functional groups [6]. Patel *et al.* [7] previously reported that the palladium-catalyzed reaction of methyl *o*-bromobenzoate (**5a**) with methyl acrylate proceeded to form methyl *o*-methoxycarbonylcinnamate. Plevyak and Heck [8] also mentioned that a variety of styrene derivatives were prepared in moderate yields by the palladium-catalyzed reaction of ethylene with aryl bromides. In our case, in the presence of palladium(II) acetate, tri-*o*-tolylphosphine, and triethylamine, the methyl *o*-bromobenzoate derivatives **5** undergo palladium-catalyzed substitution with ethylene to form **3** in moderate yields.

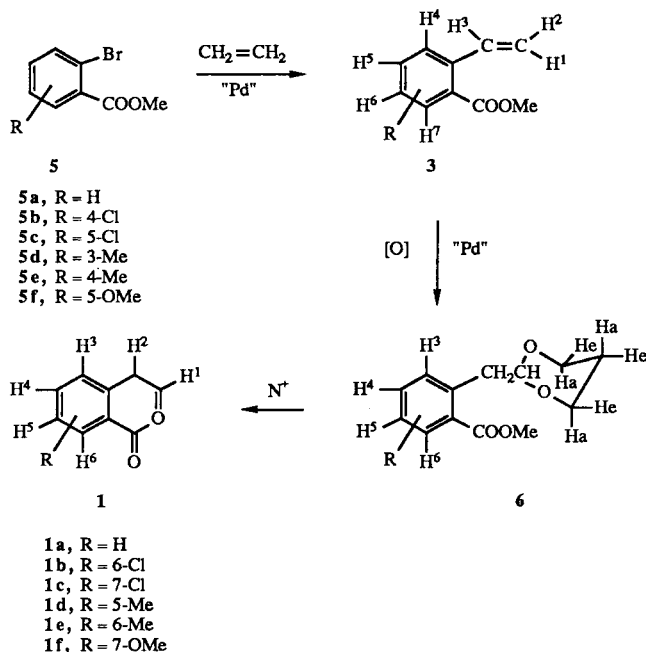
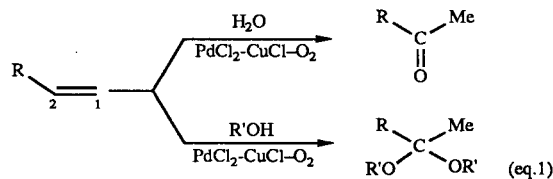
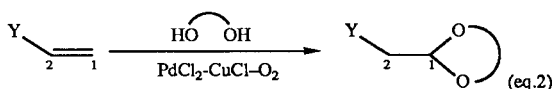


Figure 1. Synthesis of Isocoumarins **1** from Methyl *o*-Benzoates **5**.

The palladium-catalyzed oxidation of terminal olefins in the presence of water, known as the Wacker reaction, usually produce methyl ketones [9]. A similar reaction in the presence of alcohols gives the corresponding ketals (eq 1). These products arise *via* the attack of oxygen nucleophiles at the non-terminal olefinic carbon (C-2). On the other hand, Hosokawa *et al.* [10] recently reported that the treatment of diols such as ethylene glycol with terminal olefins bearing electron-withdrawing groups, in the presence of a palladium(II) catalyst, afforded cyclic acetals *via* attack of the C-1 carbon (eq 2). For example, in the presence of palladium(II) chloride and copper(I) chloride, 2-ethenylnitrobenzene reacted with propane-1,3-diol



under an oxygen atmosphere (1 atm) and led to the formation of 2-[(2-nitrophenyl)methyl]-1,3-dioxane in 90% yield [5].



In our case, in the presence of palladium(II) chloride (0.1 equivalent) and copper(I) chloride (1 equivalent) in dimethoxyethane, the compounds **3** are regioselectively acetalized at the terminal carbon (C-1) by propane-1,3-diol at 50-60° under an oxygen atmosphere (1 atm). This resulted in a fairly good yield of cyclic acetals **6**. Subsequently, the cyclization of the acetals **6** to the corresponding isocoumarins **1** was carried out by treatment with dilute hydrochloric acid.

Synthesis of 1-Isoquinolinones **2** from 2-Bromobenzamides **7**.

The over-all reaction is presented in Figure 2. Hegedus *et al.* [3] previously reported that 2-(2-propenyl)-*N*-methylbenzamide was converted to 3-methyl-*N*-methylisoquinolinone by treatment with palladium(II) chloride and sodium hydride in tetrahydrofuran. We also report the intramolecular cyclization of 2-styrylbenzamide to 3-phenyl-1-isoquinolinone with palladium(II) chloride in acetonitrile. We have thus developed a synthesis of **2** from **7**, *via* **4**. In the presence of palladium(II) acetate, tri-*o*-tolylphosphine, and triethylamine, **7**, undergoes a palladium-catalyzed substitution with ethylene to form **4** in moderate yields. We found however, that under the similar conditions described for the palladium-catalyzed

acetalation of **3** to **1**, the compounds **4** are regioselectively and intramolecularly cyclized to the corresponding **2** rather than undergoing acetalation at the terminal carbon of the olefinic bond in **4** to form the cyclic acetals **8**.

## EXPERIMENTAL

The ir and <sup>1</sup>H nmr spectra were recorded on Hitachi 260-10 and Hitachi R-90H spectrometers, respectively. Deuteriochloroform was used with tetramethylsilane as an internal standard in the determination of the nmr spectra. The mass spectrum was recorded on a Hitachi RMU-6M spectrometer. Melting points were taken with a Gallenkamp melting point apparatus and are uncorrected.

General Procedure for the Reaction of Methyl 2-Bromobenzoates **5** with Ethylene.

In a 100 ml stainless autoclave, a mixture of 20 mmoles of **5**, 0.045 g (0.20 mmoles) of palladium(II) acetate, 0.122 g (0.40 mmole) of tri-*o*-tolylphosphine, and 2.02 g (20 mmoles) of triethylamine in 30 ml of acetonitrile was stirred at 120° under an atmosphere of ethylene (30 atm) for 24 hours. After cooling and separation of the resulting palladium black, ether and water were added, and the organic layer was separated, washed successively with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water, and dried over anhydrous magnesium sulfate. After removal of the solvents under reduced pressure, the product was isolated by column chromatography on silica gel using benzene-hexane (1:2) as the eluent. The structures of the products were verified by their ir, <sup>1</sup>H nmr, and mass spectra, and by comparison with an authentic sample.

Methyl 2-Ethenylbenzoate (**3a**).

This compound was obtained from **5a** as a colorless oil in 89% yield; ir (neat): 1720 (-COOMe), 990, 920 (-CH=CH<sub>2</sub>), 1600, 1580, 750 cm<sup>-1</sup> (*o*-disub Ar-H); <sup>1</sup>H nmr: δ 3.82 (s, 3H, -COOCH<sub>3</sub>), 5.38 (dd, 1H, J<sub>1,2</sub> = 1.5 Hz, J<sub>2,3</sub> = 10.5 Hz, H-2), 5.68 (dd, 1H, J<sub>1,2</sub> = 1.5 Hz, J<sub>1,3</sub> = 17 Hz, H-1), 7.18 (dd, 1H, J<sub>2,3</sub> = 10.5 Hz, J<sub>1,3</sub> = 17 Hz, H-3), 7.31-7.69 ppm (m, 4H, Ar-H); ms: m/z 162 (M<sup>+</sup>).

Anal. Calcd. for C<sub>10</sub>H<sub>10</sub>O<sub>2</sub>: C, 74.05; H, 6.22. Found: C, 73.95; H, 6.13.

Methyl 2-ethenyl-4-chlorobenzoate (**3b**).

This compound was obtained from methyl 2-bromo-4-chlorobenzoate (**5b**) as a colorless oil in 78% yield; ir (neat): 1720 (-COOMe), 990, 910 (-CH=CH<sub>2</sub>), 1600, 1580, 890, 830 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 3.85 (s, 3H, -COOCH<sub>3</sub>), 5.34 (dd, 1H, J<sub>1,2</sub> = 1.5 Hz, J<sub>2,3</sub> = 11.5 Hz, H-2), 5.61 (dd, 1H, J<sub>1,2</sub> = 1.5 Hz, J<sub>1,3</sub> = 17.5 Hz, H-1), 7.21 (dd, 1H, J<sub>4,6</sub> = 2 Hz, J<sub>6,7</sub> = 8 Hz, H-6), 7.43 (dd, 1H, J<sub>1,3</sub> = 17.5 Hz, J<sub>2,3</sub> = 11.5 Hz, H-3), 7.49 (d, 1H, J<sub>4,6</sub> = 2 Hz, H-4), 7.77 ppm (d, 1H, J<sub>6,7</sub> = 8 Hz, H-7); ms: m/z 196.5 (M<sup>+</sup>).

Anal. Calcd. for C<sub>10</sub>H<sub>9</sub>ClO<sub>2</sub>: C, 61.08; H, 4.61. Found: C, 60.91; H, 4.48.

Methyl 2-Ethenyl-5-chlorobenzoate (**3c**).

This compound was obtained from methyl 2-bromo-5-chlorobenzoate (**5c**) as a colorless oil in 75% yield; ir (neat): 1720 (-COOMe), 990, 910 (-CH=CH<sub>2</sub>), 1600, 1580, 890, 830 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 3.82 (s, 3H, -COOCH<sub>3</sub>), 5.29 (dd, 1H, J<sub>1,2</sub> = 1.0 Hz, J<sub>2,3</sub> = 11 Hz, H-2), 5.55 (dd, 1H, J<sub>1,2</sub> = 1.0 Hz, J<sub>1,3</sub> = 17.5 Hz, H-1), 7.16-7.36 (m, 2H, H-4 + H-5), 7.40 (dd, 1H, J<sub>1,3</sub> = 17.5 Hz, J<sub>2,3</sub> = 11 Hz, H-3), 7.75 ppm (d, 1H, J<sub>5,7</sub> = 1.5 Hz,

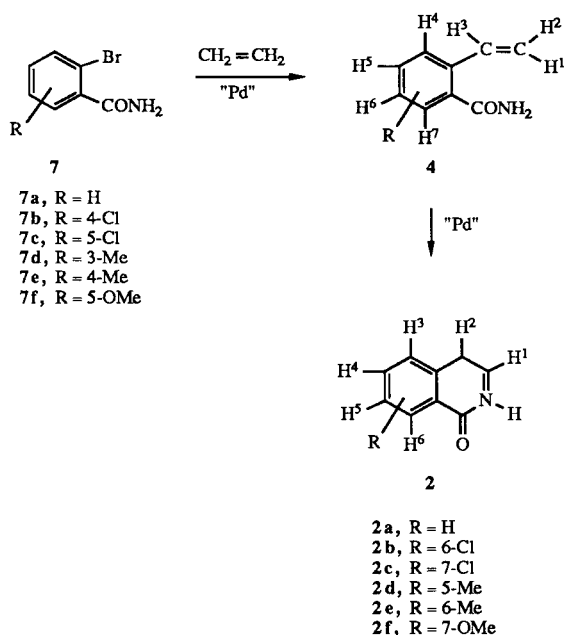


Figure 2. Synthesis of 1-Isoquinolinones **2** from 2-Bromobenzamides **7**.

*H*-7); ms: *m/z* 196.5 ( $M^+$ ).

*Anal.* Calcd. for  $C_{10}H_9ClO_2$ : C, 61.08; H, 4.61. Found: C, 61.01; H, 4.55.

#### Methyl 2-Ethenyl-3-methylbenzoate (**3d**).

This compound was obtained from methyl 2-bromo-3-methylbenzoate (**5d**) as a colorless oil in 53% yield; ir (neat): 1720 ( $-COOMe$ ), 990, 920 ( $-CH=CH_2$ ), 1600, 1580, 770, 730  $cm^{-1}$  (1,2,3-trisub Ar-H);  $^1H$  nmr:  $\delta$  2.32 (s, 3H, Ar- $CH_3$ ), 3.81 (s, 3H,  $-COOCH_3$ ), 5.16 (dd, 1H,  $J_{1,2} = 2$  Hz,  $J_{1,3} = 18$  Hz, *H*-1), 5.42 (dd, 1H,  $J_{1,2} = 2$  Hz,  $J_{2,3} = 11.5$  Hz, *H*-2), 6.92 (dd, 1H,  $J_{1,3} = 18$  Hz,  $J_{2,3} = 11.5$  Hz, *H*-3), 7.13 (t, 1H,  $J_{5,6} = J_{6,7} = 7.5$  Hz, *H*-6), 7.24 (dd, 1H,  $J_{5,6} = 7.5$  Hz,  $J_{5,7} = 2$  Hz, *H*-5), 7.53 ppm (dd, 1H,  $J_{5,7} = 2$  Hz,  $J_{6,7} = 7.5$  Hz, *H*-7); ms: *m/z* 176 ( $M^+$ ).

*Anal.* Calcd. for  $C_{11}H_{12}O_2$ : C, 74.97; H, 6.86. Found: C, 74.88; H, 6.83.

#### Methyl 2-Ethenyl-4-methylbenzoate (**3e**).

This compound was obtained from methyl 2-bromo-4-methylbenzoate (**5e**) as a colorless oil in 67% yield; ir (neat): 1720 ( $-COOMe$ ), 990, 910 ( $-CH=CH_2$ ), 1600, 1580, 890, 790  $cm^{-1}$  (1,2,4-trisub Ar-H);  $^1H$  nmr:  $\delta$  2.38 (s, 3H, Ar- $CH_3$ ), 3.87 (s, 3H,  $-COOCH_3$ ), 5.32 (dd, 1H,  $J_{1,2} = 1.5$  Hz,  $J_{2,3} = 12$  Hz, *H*-2), 5.61 (dd, 1H,  $J_{1,2} = 1.5$  Hz,  $J_{1,3} = 17.5$  Hz, *H*-1), 7.09 (d, 1H,  $J_{6,7} = 7.5$  Hz, *H*-6), 7.34 (br s, 1H, *H*-4), 7.50 (dd, 1H,  $J_{2,3} = 12$  Hz,  $J_{1,3} = 17.5$  Hz, *H*-3), 7.78 ppm (d, 1H,  $J_{6,7} = 7.5$  Hz, *H*-7); ms: *m/z* 176 ( $M^+$ ).

*Anal.* Calcd. for  $C_{11}H_{12}O_2$ : C, 74.97; H, 6.86. Found: C, 74.91; H, 6.75.

#### Methyl 2-Ethenyl-5-methoxybenzoate (**3f**).

This compound was obtained from methyl 2-bromo-5-methoxybenzoate (**5f**) as a colorless oil in 84% yield; ir (neat): 1720 ( $-COOMe$ ), 990, 910 ( $-CH=CH_2$ ), 1600, 1580, 890, 820  $cm^{-1}$  (1,2,4-trisub Ar-H);  $^1H$ -nmr:  $\delta$  3.77 (s, 3H,  $-OCH_3$ ), 3.85 (s, 3H,  $-COOCH_3$ ), 5.22 (dd, 1H,  $J_{1,2} = 2$  Hz,  $J_{2,3} = 11$  Hz, *H*-2), 5.51 (dd, 1H,  $J_{1,2} = 2$  Hz,  $J_{1,3} = 17.5$  Hz, *H*-1), 6.95 (dd, 1H,  $J_{4,5} = 9$  Hz,  $J_{5,7} = 2.5$  Hz, *H*-5), 7.23-7.54 ppm (m, 3H, *H*-3 + *H*-4 + *H*-7); ms: *m/z* 192 ( $M^+$ ).

*Anal.* Calcd. for  $C_{11}H_{12}O_3$ : C, 68.73; H, 5.30; Found: C, 68.66; H, 5.18.

#### General Procedure of Acetalation of **3**.

Into a 50 ml flask fitted with a rubber balloon filled with oxygen and a teflon-coated magnetic stirring bar were placed palladium(II) chloride (0.248 g, 1.4 mmoles) and copper(I) chloride (1.386 g, 14 mmoles). Into the flask was added a solution of the ester **3** (14 mmoles) and 1,3-propanediol (1 ml, 14 mmoles) in 1,2-dimethoxyethane (25 ml), and the resulting suspended solution was stirred for 24 hours at 50-60° under an atmosphere of oxygen. After the reaction mixture was cooled to room temperature, ether (100 ml) was added to the mixture. The resulting insoluble materials were removed by filtration, and the filtrate was concentrated under a reduced pressure. The residue was then purified by column chromatography on silica gel (hexane-benzene (2:1)), followed by recrystallization from ethanol. The structures of the products (**6**) were confirmed by the observation of the ir,  $^1H$  nmr, and mass spectral data.

#### 2-[(2-Methoxycarbonylphenyl)methyl]-1,3-dioxane (**6a**).

This compound was obtained from **3a** as a colorless oil in 82%

yield; ir (neat): 1720 ( $-COOMe$ ), 1600, 1580, 755  $cm^{-1}$  (*o*-disub Ar-H);  $^1H$  nmr:  $\delta$  1.17-1.44 (m, 1H,  $-O-CH^a-C-O^a$ ), 1.79-2.30 (m, 1H,  $-O-C-CH^a-C-O^a$ ), 3.34 (d, 1H, Ar- $CH_2$ ), 3.49-4.19 (m, 4H,  $-CH_2-C-C-O^a$ ), 4.75 (t, 1H, Ar-C- $CH-O^a$ ), 7.25-7.80 ppm (m, 4H, Ar-*H*); ms: *m/z* 236 ( $M^+$ ).

*Anal.* Calcd. for  $C_{13}H_{16}O_4$ : C, 66.08; H, 6.83. Found: C, 65.93; H, 6.68.

#### 2-[(5-Chloro-2-methoxycarbonylphenyl)methyl]-1,3-dioxane (**6b**).

This compound was obtained from **3b** as colorless crystals in 73% yield, mp 77-78°; ir (potassium bromide): 1715 ( $-COOMe$ ) 1600, 1580, 880, 820  $cm^{-1}$  (1,2,4-trisub Ar-H);  $^1H$  nmr:  $\delta$  1.18-1.50 (m, 1H,  $-O-C-CH^a-C-O^a$ ), 1.78-2.36 (m, 1H,  $-O-C-CH^a-C-O^a$ ), 3.26 (d, 2H, Ar- $CH_2$ ), 3.58-3.85 (m, 2H,  $-O-CH^a-C-CH^a-O^a$ ), 3.89 (s, 3H,  $-COOCH_3$ ), 3.97-4.22 (m, 2H,  $-O-CH^a-C-CH^a-O^a$ ), 4.75 (t, 1H, Ar-C- $CH-O^a$ ), 7.11-7.40 (m, 2H, *H*-4 + *H*-6), 7.81 ppm (d, 1H, *H*-3); ms: *m/z* 270.5 ( $M^+$ ).

*Anal.* Calcd. for  $C_{13}H_{15}ClO_4$ : C, 57.68; H, 5.59. Found: C, 57.57; H, 5.54.

#### 2-[(4-Chloro-2-methoxycarbonylphenyl)methyl]-1,3-dioxane (**6c**).

This compound was obtained from **3c** as colorless crystals, mp 72-73°, in 86% yield; ir (potassium bromide): 1720 ( $-COOMe$ ), 1600, 1580, 890, 820  $cm^{-1}$  (1,2,4-trisub Ar-H);  $^1H$  nmr:  $\delta$  1.16-1.42 (m, 1H,  $-O-C-CH^a-C-O^a$ ), 1.79-2.40 (m, 1H,  $-O-C-CH^a-C-O^a$ ), 3.32 (d, 2H, Ar- $CH_2$ ), 3.53-3.83 (m, 2H,  $-O-CH^a-C-CH^a-O^a$ ), 3.88 (s, 3H,  $-COOCH_3$ ), 3.95-4.20 (m, 2H,  $-O-CH^a-C-CH^a-O^a$ ), 4.71 (t, 1H, Ar-C- $CH-O^a$ ), 7.22 (d, 1H, *H*-6), 7.37 (dd, 1H, *H*-4), 7.81 ppm (d, 1H, *H*-3); ms: *m/z* 270.5 ( $M^+$ ).

*Anal.* Calcd. for  $C_{13}H_{15}ClO_4$ : C, 57.68; H, 5.59. Found: C, 57.65; H, 5.44.

#### 2-[(2-Methoxycarbonyl-6-methylphenyl)methyl]-1,3-dioxane (**6d**).

This compound was obtained from **3d** as a colorless oil, in 85% yield; ir (neat): 1720 ( $-COOMe$ ), 1600, 1580, 780, 720  $cm^{-1}$  (1,2,3-trisub Ar-H);  $^1H$  nmr:  $\delta$  1.13-1.48 (m, 1H,  $-O-C-CH^a-C-O^a$ ), 1.76-2.36 (m, 1H,  $-O-C-CH^a-C-O^a$ ), 2.43 (s, 3H, Ar- $CH_3$ ), 3.31 (d, 2H, Ar- $CH_2$ ), 3.49-3.85 (m, 2H,  $-O-CH^a-C-CH^a-O^a$ ), 3.88 (s, 3H,  $-COOCH_3$ ), 3.93-4.20 (m, 2H,  $-O-CH^a-C-CH^a-O^a$ ), 4.75 (t, 1H, Ar-C- $CH-O^a$ ), 7.12 (t, 1H, *H*-4), 7.28 (dd, 1H, *H*-5), 7.61 ppm (dd, 1H, *H*-3); ms: *m/z* 250 ( $M^+$ ).

*Anal.* Calcd. for  $C_{14}H_{18}O_4$ : C, 67.18; H, 7.25. Found: C, 67.05; H, 7.12.

#### 2-[(2-Methoxycarbonyl-5-methylphenyl)methyl]-1,3-dioxane (**6e**).

This compound was obtained from **3e** as colorless crystals, mp 86-87°, in 86% yield; ir (potassium bromide): 1720 ( $-COOMe$ ), 1600, 1580, 880, 800  $cm^{-1}$  (1,2,4-trisub Ar-H);  $^1H$  nmr:  $\delta$  1.13-1.44 (m, 1H,  $-O-C-CH^a-C-O^a$ ), 1.80-2.25 (m, 1H,  $-O-C-CH^a-C-O^a$ ), 2.35 (s, 3H, Ar- $CH_3$ ), 3.23 (d, 2H, Ar- $CH_2$ ), 3.35-3.91 (m, 2H,  $-O-CH^a-C-CH^a-O^a$ ), 3.87 ( $-COOCH_3$ ), 3.97-4.22 (m, 2H,  $-O-CH^a-C-CH^a-O^a$ ), 4.76 (t, 1H, Ar-C- $CH-O^a$ ), 6.92-7.20 (m, 2H, *H*-4 + *H*-6), 7.77 ppm (d, 1H, *H*-3); ms: *m/z* 250 ( $M^+$ ).

*Anal.* Calcd. for  $C_{14}H_{18}O_4$ : C, 67.18; H, 7.25. Found: C, 67.11; H, 7.19.

#### 2-[(4-Methoxy-2-methoxycarbonylphenyl)methyl]-1,3-dioxane (**6f**).

This compound was obtained from **3f** as colorless crystals, mp 69-70°, in 84% yield; ir (potassium bromide): 1710 ( $-COOMe$ ), 1600, 1580, 890, 815  $cm^{-1}$  (1,2,4-trisub Ar-H);  $^1H$  nmr:  $\delta$  1.03-1.40 (m, 1H,  $-O-C-CH^a-C-O^a$ ), 1.75-2.30 (m, 1H,  $-O-C-CH^a-C-O^a$ ), 3.18 (d,

2H, Ar-CH<sub>2</sub>), 3.36-4.25 (m, 4H, -O-CH<sub>2</sub>-C-CH<sub>2</sub>-O-), 3.77 (s, 3H, Ar-OCH<sub>3</sub>), 3.85 (s, 3H, -COOCH<sub>3</sub>), 4.68 (t, 1H, Ar-C-CH-O-), 6.92 (dd, 1H, H-5), 7.20 (d, 1H, H-6), 7.35 ppm (d, 1H, H-3); ms: m/z 266 (M<sup>+</sup>).

Anal. Calcd. for C<sub>14</sub>H<sub>18</sub>O<sub>5</sub>: C, 63.14; H, 6.81. Found: C, 63.13; H, 6.67.

#### General Procedure for Cyclization of Acetals **6**.

A solution of 5 mmoles of the acetal **6** in ethanol (50 ml) was refluxed with 50 ml of 5% hydrochloric acid for 2 hours with stirring. After cooling and evaporation of the ethanol *in vacuo*, the reaction mixture was extracted with ether. The ether layers were successively washed with saturated sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was then purified by column chromatography (silica gel, benzene-hexane (1:2)), followed by recrystallization from ethanol. The structure of the products **1** was confirmed by a mixed-melting point determinations with authentic samples and from the observation of the ir, <sup>1</sup>H nmr, and mass spectra.

#### Isocoumarin (**1a**).

This compound was obtained from **6a** as colorless crystals, in 82% yield, mp 46-47° (lit [11], mp 46°); ir (potassium bromide): 1725 (-C=O), 1635 (-CH=CH-), 1600, 1580, 775 cm<sup>-1</sup> (*o*-disub Ar-H); <sup>1</sup>H nmr: δ 6.48 (d, 1H, J<sub>1,2</sub> = 5.5 Hz, H-2), 7.24 (d, 1H, J<sub>1,2</sub> = 5.5 Hz, H-1), 7.31-7.81 (m, 3H, H-3 + H-4 + H-5), 8.07-8.34 ppm (m, 1H, H-6); ms: m/z 146 (M<sup>+</sup>).

Anal. Calcd. for C<sub>9</sub>H<sub>8</sub>O<sub>2</sub>: C, 73.96; H, 4.14. Found: C, 73.78; H, 4.05.

#### 6-Chloroisocoumarin (**1b**).

This compound was obtained from **6b** as colorless crystals, mp 192-193°, in 87% yield; ir (potassium bromide): 1720 (-C=O), 1635 (-CH=CH-), 1600, 1580, 890, 800 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 6.41 (d, 1H, J<sub>1,2</sub> = 6 Hz, H-2), 7.27 (d, 1H, J<sub>1,2</sub> = 6 Hz, H-1), 7.33-7.55 (m, 2H, H-3 + H-5), 8.20 ppm (d, 1H, H-6); ms: m/z 180.5 (M<sup>+</sup>).

Anal. Calcd. for C<sub>9</sub>H<sub>7</sub>ClO<sub>2</sub>: C, 60.35; H, 2.79. Found: C, 60.23; H, 2.68.

#### 7-Chloroisocoumarin (**1c**).

This compound was obtained from **6c** as colorless crystals, mp 114-115°, in 90% yield; ir (potassium bromide): 1710 (-C=O), 1630 (-CH=CH-), 1600, 1580, 890, 820 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 6.46 (d, 1H, J<sub>1,2</sub> = 6 Hz, H-2), 7.26 (d, 1H, J<sub>1,2</sub> = 6 Hz, H-1), 7.35 (d, 1H, J<sub>3,4</sub> = 8.5 Hz, H-3), 7.65 (dd, 1H, J<sub>3,4</sub> = 8.5 Hz, J<sub>4,6</sub> = 2 Hz, H-4), 8.22 ppm (d, 1H, J<sub>4,6</sub> = 2 Hz, H-6); ms: m/z 180.5 (M<sup>+</sup>).

Anal. Calcd. for C<sub>9</sub>H<sub>7</sub>ClO<sub>2</sub>: C, 60.35; H, 2.79. Found: C, 60.28; H, 2.70.

#### 5-Methylisocoumarin (**1d**).

This compound was obtained from **6d** as colorless crystals, mp 85-87°, in 82% yield; ir (potassium bromide): 1720 (-C=O), 1640 (-CH=CH-) 1600, 1580, 790, 710 cm<sup>-1</sup> (1,2,3-trisub Ar-H); <sup>1</sup>H nmr: δ 2.47 (s, 3H, Ar-CH<sub>3</sub>), 6.59 (d, 1H, J<sub>1,2</sub> = 6 Hz, H-2), 7.26 (d, 1H, J<sub>1,2</sub> = 6 Hz, H-1), 7.36 (t, 1H, J<sub>4,5</sub> = J<sub>5,6</sub> = 7.5 Hz, H-5), 7.54 (dd, 1H, J<sub>4,6</sub> = 1.5 Hz, J<sub>4,5</sub> = 7.5 Hz, H-4), 8.13 ppm (dd, 1H, J<sub>4,6</sub> = 1.5 Hz, J<sub>5,6</sub> = 7.5 Hz, H-6); ms: m/z 160 (M<sup>+</sup>).

Anal. Calcd. for C<sub>10</sub>H<sub>8</sub>O<sub>2</sub>: C, 74.99; H, 5.03. Found: C, 74.85; H, 4.97.

#### 6-Methylisocoumarin (**1e**).

This compound was obtained from **6e** as colorless crystals, mp 93-95°, in 85% yield; ir (potassium bromide): 1710 (-C=O), 1620 (-CH=CH-) 1600, 1580, 890, 810 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 2.40 (s, 3H, Ar-CH<sub>3</sub>), 6.40 (d, 1H, J<sub>1,2</sub> = 6 Hz, H-2), 7.14-7.50 (m, 2H, H-1 + H-3 + H-5), 8.12 ppm (d, 1H, J<sub>5,6</sub> = 7.5 Hz, H-6); ms: m/z 160 (M<sup>+</sup>).

Anal. Calcd. for C<sub>10</sub>H<sub>8</sub>O<sub>2</sub>: C, 74.99; H, 5.03. Found: C, 74.91; H, 4.88.

#### 7-Methoxyisocoumarin (**1f**).

This compound was obtained from **6f** as colorless crystals, mp 108-109° (lit [12] mp 109-110°), in 92% yield; ir (potassium bromide): 1705 (-C=O), 1630 (-CH=CH-), 1600, 1580, 870, 840 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 3.87 (s, 3H, -OCH<sub>3</sub>), 6.43 (d, 1H, J<sub>1,2</sub> = 6 Hz, H-2), 7.15 (d, 1H, J<sub>1,2</sub> = 6 Hz, H-1) 7.20-7.42 (m, 2H, H-3 + H-4), 7.63 ppm (d, 1H, J<sub>4,6</sub> = 2 Hz, H-6); ms: m/z 176 (M<sup>+</sup>).

Anal. Calcd. for C<sub>10</sub>H<sub>8</sub>O<sub>3</sub>: C, 68.18; H, 4.58. Found: C, 68.02; H, 4.49.

#### General procedure for the Heck Reaction of 2-Bromobenzamides **7** with Ethylene.

The procedure was essentially as described for the Heck reaction of **5** with ethylene. The products **4** were purified by column chromatography (silica gel, benzene), followed by recrystallization from ethanol.

#### 2-Ethenylbenzamide (**4a**).

This compound was obtained from **7a**, as colorless crystals, mp 145-146°, in 74% yield; ir (potassium bromide): 3300, 3150 (-NH<sub>2</sub>), 1660, 1620 (-CONH<sub>2</sub>), 990, 910 (-CH=CH<sub>2</sub>), 1600, 1580, 740 cm<sup>-1</sup> (*o*-disub Ar-H); <sup>1</sup>H nmr: δ 5.36 (dd, 1H, J<sub>1,2</sub> = 1.5 Hz, J<sub>1,3</sub> = 17.5 Hz, H-1), 5.71 (dd, 1H, J<sub>1,2</sub> = 1.5 Hz, J<sub>2,3</sub> = Hz, H-2), 6.10 (br s, 2H, -CONH<sub>2</sub>), 7.14 (dd, 1H, J<sub>1,3</sub> = 17.5 Hz, J<sub>2,3</sub> = 11 Hz, H-3), 7.23-7.65 ppm (m, 4H, Ar-H); ms: m/z 147 (M<sup>+</sup>).

Anal. Calcd for C<sub>9</sub>H<sub>9</sub>NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.31; H, 6.04; N, 9.37.

#### 4-Chloro-2-ethenylbenzamide (**4b**).

This compound was obtained from **7b** as colorless crystals, mp 148-149°, in 86% yield; ir (potassium bromide): 3320, 3150 (-NH<sub>2</sub>), 1660, 1610 (-CONH<sub>2</sub>), 990, 920 (-CH=CH<sub>2</sub>), 1600, 1580, 880, 830 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 5.44 (d, 1H, J<sub>2,3</sub> = 11 Hz, H-2), 5.74 (d, 1H, J<sub>1,3</sub> = 18 Hz, H-1), 5.56-6.19 (br s, 2H, -CONH<sub>2</sub>), 7.11 (dd, 1H, J<sub>1,3</sub> = 18 Hz, J<sub>2,3</sub> = 11 Hz, H-3), 7.27 (dd, 1H, J<sub>4,6</sub> = 2 Hz, J<sub>6,7</sub> = 8 Hz, H-6), 7.49 (d, 1H, J<sub>6,7</sub> = 8 Hz, H-7), 7.53 ppm (d, 1H, J<sub>4,6</sub> = 2 Hz, H-4); ms: m/z 181.5 (M<sup>+</sup>).

Anal. Calcd. for C<sub>9</sub>H<sub>8</sub>ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.44; H, 4.27; N, 7.58.

#### 5-Chloro-2-ethenylbenzamide (**4c**).

This compound was obtained from **7c** as colorless crystals, mp 167-168°, in 79% yield; ir (potassium bromide): 3380, 3190 (-NH<sub>2</sub>), 1640, 1620 (-CONH<sub>2</sub>), 980, 920 (-CH=CH<sub>2</sub>), 1600, 1580, 890, 840 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 5.35 (d, 1H, J<sub>2,3</sub> = 11 Hz, H-2), 5.80 (d, 1H, J<sub>1,3</sub> = 18 Hz, H-1), 6.94 (dd, 1H, J<sub>1,3</sub> = 18 Hz, J<sub>2,3</sub> = 11 Hz, H-3), 7.36-7.60 (m, 2H, H-5 + H-7), 7.68 ppm (d, 1H, J<sub>4,5</sub> = 7.5 Hz, H-4); ms: m/z 181.5 (M<sup>+</sup>).

Anal. Calcd. for C<sub>9</sub>H<sub>8</sub>ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.38; H, 4.35; N, 7.64.

2-Ethenyl-3-methylbenzamide (**4d**).

This compound was obtained from **7d** as colorless crystals, mp 148-149°, in 75% yield; ir (potassium bromide): 3360, 3170 (-NH<sub>2</sub>), 1640, 1620 (-CONH<sub>2</sub>), 990, 910 (-CH=CH<sub>2</sub>), 1600, 1580, 790, 730 cm<sup>-1</sup> (1,2,3-trisub Ar-H); <sup>1</sup>H nmr: δ 2.28 (s, 3H, Ar-CH<sub>3</sub>), 5.36 (dd, 1H, J<sub>1,2</sub> = 2 Hz, J<sub>1,3</sub> = 17.5 Hz, H-1), 5.44 (dd, 1H, J<sub>1,2</sub> = 2 Hz, J<sub>2,3</sub> = 12 Hz, H-2), 5.82-6.45 (br s, 2H, -CONH<sub>2</sub>), 6.82 (dd, 1H, J<sub>1,3</sub> = 17.5 Hz, J<sub>2,3</sub> = 12 Hz, H-3), 7.07-7.25 (m, 2H, H-5 + H-6), 7.31 ppm (dd, 1H, J<sub>6,7</sub> = 7.5 Hz, J<sub>5,6</sub> = 2 Hz, H-7); ms: m/z 161 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>NO: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.38; H, 6.72; N, 8.55.

2-Ethenyl-4-methylbenzamide (**4e**).

This compound was obtained from **7e** as colorless crystals, mp 152-154°, in 75% yield; ir (potassium bromide): 3360, 3170 (-NH<sub>2</sub>), 1630, 1610 (-CONH<sub>2</sub>), 980, 910 (-CH=CH<sub>2</sub>), 1600, 1580, 880, 810 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 2.36 (s, 3H, Ar-CH<sub>3</sub>), 5.32 (dd, 1H, J<sub>1,2</sub> = 1.5 Hz, J<sub>2,3</sub> = 11 Hz, H-2), 5.68 (dd, 1H, J<sub>1,2</sub> = 1.5 Hz, J<sub>1,3</sub> = 17 Hz, H-1), 5.83-6.55 (br s, 2H, -CONH<sub>2</sub>), 6.98-7.28 (m, 2H, H-3 + H-6), 7.34 (s, 1H, H-4), 7.42 ppm (d, 1H, J<sub>6,7</sub> = 7.5 Hz, H-7); mass: m/z 161 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>NO: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.45; H, 6.80; N, 8.78.

2-Ethenyl-5-methoxybenzamide (**4f**).

This compound was obtained from **7f** as colorless crystals, mp 160-161°, in 89% yield; ir (potassium bromide): 3350, 3160 (-NH<sub>2</sub>), 1640, 1610 (-CONH<sub>2</sub>), 990, 900 (-CH=CH<sub>2</sub>), 1600, 1580, 865, 810 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 3.82 (s, 3H, Ar-OCH<sub>3</sub>), 5.21 (dd, 1H, J<sub>1,2</sub> = 2 Hz, J<sub>2,3</sub> = 11 Hz, H-2), 5.60 (dd, 1H, J<sub>1,2</sub> = 2 Hz, J<sub>1,3</sub> = 17.5 Hz, H-1), 6.48-6.89 (br s, 2H, -CONH<sub>2</sub>), 6.82 (m, 1H, H-5), 7.03 (dd, 1H, J<sub>2,3</sub> = 11 Hz, J<sub>1,3</sub> = 17.5 Hz, H-3), 7.06 (m, 1H, H-7), 7.51 ppm (d, 1H, J<sub>4,5</sub> = 9 Hz, H-4); ms: m/z 177 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub>: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.74; H, 6.15; N, 7.81.

General Procedure of Palladium-catalyzed Cyclization of **7** to 1-Isoquinolinones **2**.

The procedure was essentially the one described for the palladium-catalyzed acetalization of **3** to **6**.

1-Isoquinolinone (**2a**).

This compound was obtained from **4a**, as colorless, crystals, mp 209-210° (lit [13] mp 208°), in 73% yield; ir (potassium bromide): 3150 (-NH), 1660 (-CONH), 1600, 1580, 745 cm<sup>-1</sup> (o-disub Ar-H); <sup>1</sup>H-nmr (deuteriomethanol-d<sub>4</sub>): δ 6.61 (d, 1H, J<sub>1,2</sub> = 7 Hz, H-2), 7.14 (d, 1H, J<sub>1,2</sub> = 7 Hz, H-1), 7.32-7.78 (m, 4H, H-3 + H-4 + H-5), 8.34 (d, 1H, J<sub>5,6</sub> = 8 Hz, H-6) 10.85 ppm (br s, 1H, -NH); ms: m/z 145 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>9</sub>H<sub>7</sub>NO: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.33; H, 4.72; N, 9.58.

6-Chloro-1-isoquinolinone (**2b**).

This compound was obtained from **4b**, as colorless crystals, mp 272° dec in 75% yield, ir (potassium bromide): 3150 (-NH), 1680 (-CONH), 1630 (-CH=CH-), 1600, 1580, 870, 800 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr (deuteriodimethyl sulfoxide): δ 6.58 (d, 1H, J<sub>1,2</sub> = 7 Hz, H-2), 7.22 (d, 1H, J<sub>1,2</sub> = 7 Hz, H-1), 7.47 (dd, 1H, J<sub>3,4</sub> = 1.5 Hz, J<sub>5,6</sub> = 8.5 Hz, H-5), 7.69 (d, 1H, J<sub>3,5</sub> = 1.5 Hz, H-3), 8.23 (d, 1H, J<sub>5,6</sub> = 8.5 Hz, H-6) 11.51 ppm (br s, 1H, -NH); ms: m/z

179.5 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>9</sub>H<sub>6</sub>ClNO: C, 60.18; H, 3.37; N, 7.80. Found: C, 60.07; H, 3.31; N, 7.68.

7-Chloro-1-isoquinolinone (**2c**).

This compound was obtained from **4c**, as colorless crystals, mp 243° dec (lit [14] mp 243°), in 85% yield; ir (potassium bromide): 3150 (-NH), 1660 (-CONH), 1620 (-CH=CH-), 1600, 1580, 900, 830 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr (deuteriodimethyl sulfoxide): δ 6.54 (d, 1H, J<sub>1,2</sub> = 6.5 Hz, H-2), 7.13 (d, 1H, J<sub>1,2</sub> = 6.5 Hz, H-1), 7.56-7.68 (m, 2H, H-3 + H-4), 8.21 (s, 1H, H-6), 11.46 ppm (br s, 1H, -NH); ms: m/z 179.5 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>9</sub>H<sub>6</sub>ClNO: C, 60.18; H, 3.37; N, 7.80. Found: C, 60.06; H, 3.25; N, 7.73.

5-Methyl-1-isoquinolinone (**2d**).

This compound was obtained from **4d**, as colorless crystals, mp 182-183° (lit [14] mp 184-185°), in 84% yield; ir (potassium bromide): 3150(-NH), 1650 (-CONH), 1630 (-CH=CH-), 1600, 1580, 990, 700 cm<sup>-1</sup> (1,2,3-trisub Ar-H); <sup>1</sup>H-nmr: δ 2.53 (Ar-CH<sub>3</sub>), 6.68 (d, 1H, J<sub>1,2</sub> = 8.5 Hz, H-2), 7.24 (d, 1H, J<sub>1,2</sub> = 8.5 Hz, H-1), 7.32-7.57 (m, 2H, H-4 + H-5), 8.31 (dd, 1H, J<sub>4,5</sub> = 2 Hz, J<sub>5,6</sub> = 8.5, H-6), 11.45 ppm (br s, 1H, -NH); ms: m/z 159 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>10</sub>H<sub>9</sub>NO: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.38; H, 5.59; N, 8.67.

6-Methyl-1-isoquinolinone (**2e**).

This compound was obtained from **4e**, as colorless crystals, mp 191-193°, in 90% yield; ir (potassium bromide): 3150 (-NH), 1650 (-CONH), 1630(-CH=CH-), 1600, 1580, 900, 820 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 2.48 (s, 3H, Ar-CH<sub>3</sub>), 6.48 (d, 1H, J<sub>1,2</sub> = 7 Hz, H-2), 7.18 (d, 1H, J<sub>1,2</sub> = 7 Hz, H-1), 7.25-7.41 (m, 2H, H-3 + H-5), 8.32 (d, 1H, J<sub>5,6</sub> = 8.5 Hz, H-6), 11.28 ppm (br s, 1H, -NH); ms: m/z 159 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>10</sub>H<sub>9</sub>NO: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.40; H, 5.61; N, 8.75.

7-Methoxy-1-isocoumarin (**2f**).

This compound was obtained from **4f**, as colorless crystals, mp 201-202°, in 74% yield; ir (potassium bromide): 3200(-NH), 1650 (-CONH), 1630 (-CH=CH-), 1600, 1580, 870, 830 cm<sup>-1</sup> (1,2,4-trisub Ar-H); <sup>1</sup>H nmr: δ 3.94 (s, 3H, Ar-OCH<sub>3</sub>), 6.52 (d, 1H, J<sub>1,2</sub> = 6.5 Hz, H-2), 7.06 (d, 1H, J<sub>1,2</sub> = 6.5 Hz, H-1), 7.27 (dd, 1H, J<sub>3,4</sub> = 9 Hz, J<sub>4,6</sub> = 3 Hz, H-4), 7.47 (d, 1H, J<sub>3,4</sub> = 9 Hz, H-3), 7.81 (d, 1H, J<sub>4,6</sub> = 3 Hz, H-6), 11.47 ppm (br s, 1H -NH); ms: m/z 175 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>10</sub>H<sub>9</sub>NO<sub>2</sub>: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.45; H, 5.04; N, 7.89.

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