

CONDENSED HETEROAROMATIC RING SYSTEMS. XIV.¹
 CYCLIZATION OF ORTHO-SUBSTITUTED α -ETHOXYCINNAMATES
 TO SOME HETEROAROMATICS

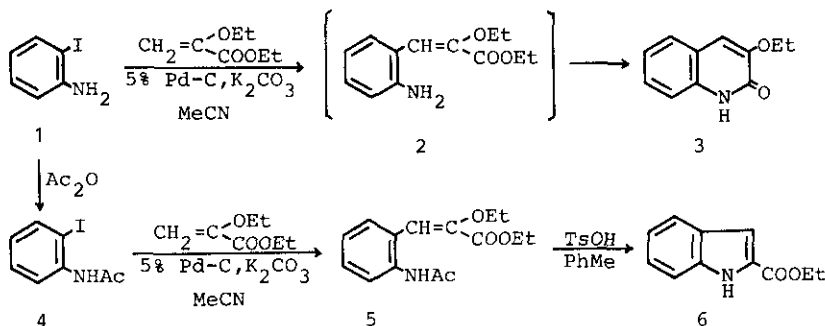
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Abstract—— The reaction of 2-iodoaniline with ethyl 2-ethoxyacrylate in the presence of palladium-charcoal gave 3-ethoxy-2(1H)-quinolinone, and the reaction of 2-iodoacetanilide with the same reagent yielded ethyl 2-acetyl-amino- α -ethoxycinnamate which was cyclized to ethyl indole-2-carboxylate under acidic conditions. On the other hand, the palladium-catalyzed reaction of 2-iodobenzonitrile and ethyl 2-iodobenzoate afforded the corresponding cinnamates which were transformed into isoquinoline and isocoumarin derivatives.

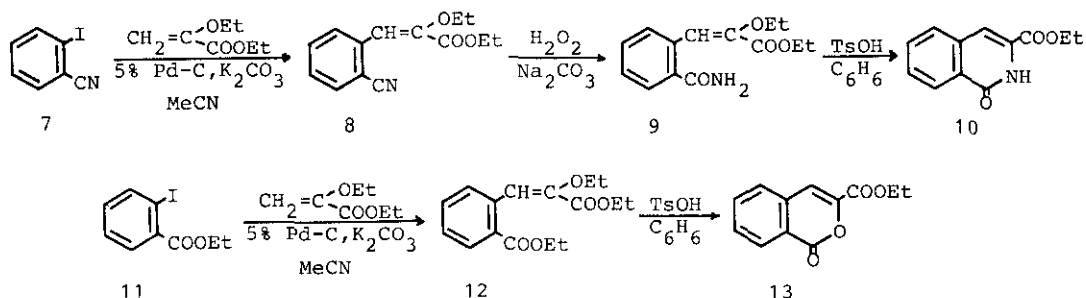
Previously, we have reported the palladium-catalyzed reaction of aromatic iodide with ethyl 2-ethoxyacrylate to afford ethyl α -ethoxyarylacrylates which were considered to be an equivalent synthon to α -ketoesters.² In this paper, we describe the synthesis of quinoline, isoquinoline, isocoumarin, and indole derivatives by the palladium-catalyzed reaction of ortho-substituted iodobenzenes with ethyl α -ethoxyacrylate followed by cyclization.

When 2-iodoaniline (1) was allowed to react with ethyl 2-ethoxyacrylate in the presence of 5 % palladium-charcoal and potassium carbonate in acetonitrile at 120°C for 24 h in a sealed tube, the intermediate, ethyl 2-amino- α -ethoxycinnamate (2) spontaneously cyclized to 3-ethoxy-2(1H)-quinolinone (3) in 63 % yield. On the other hand, the palladium-catalyzed reaction of 2-iodoacetanilide (4) with the same reagent afforded ethyl 2-acetyl-amino- α -ethoxycinnamate (5) in 58 % yield, which on treatment with *p*-toluenesulfonic acid (TsOH) was converted to ethyl indole-2-carboxylate (6) in 73 % yield.



Scheme 1

Furthermore, the reactions of 2-iodobenzonitrile (7) and ethyl 2-iodobenzoate (11) with ethyl 2-ethoxyacrylate under the same conditions provided the ortho-substituted cinnamates (8 and 12). Transformation of 8 to the amide (9) by treatment with hydrogen peroxide in aqueous sodium carbonate followed by cyclization with TsOH gave ethyl 1-oxo-1,2-dihydroisoquinoline-3-carboxylate (10). Similarly, cyclization of 12 to ethyl isocoumarin-3-carboxylate (13) was easily achieved by the action of TsOH.



Scheme 2

From the above experiments, it is clear that the palladium-catalyzed reaction of ortho-substituted iodobenzenes with ethyl 2-ethoxyacrylate supplies a method for the synthesis of functionalized heterocyclic compounds.

EXPERIMENTAL

3-Ethoxy-2(1H)-quinolinone (3)—A mixture of 2-iodoaniline (1) (1.10 g, 5 mmol), ethyl 2-ethoxyacrylate (1.08 g, 7.5 mmol), 5 % Pd-C (400 mg), K₂CO₃ (1.03 g, 7.5 mmol), and MeCN (2 ml) was heated at 120°C for 24 h in a sealed tube. The mixture was diluted with H₂O and extracted with CHCl₃. The CHCl₃ extract was purified by silica gel column chromatography using AcOEt as an eluent. The product was recrystallized from C₆H₆ to give colorless scales, mp 202-203°C. Yield 0.60

g (63 %). Ir (CHCl₃) cm⁻¹: 1660. ¹H-Nmr (CF₃COOH) ppm: 1.60 (3H, t, J=7Hz), 4.45 (2H, q, J=7Hz), 7.5-8.1 (5H, m). Anal. Calcd for C₁₁H₁₁NO₂: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.53; H, 5.91; N, 7.37.

Ethyl 2-Acetylamino- α -ethoxycinnamate (5)—— A mixture of 2-iodoacetanilide (4) (1.31 g, 5 mmol), ethyl 2-ethoxyacrylate (1.08 g, 7.5 mmol), 5 % Pd-C (400 mg), K₂CO₃ (1.03 g, 7.5 mmol), and MeCN (2 ml) was heated at 120°C for 24 h in a sealed tube. The mixture was diluted with H₂O and extracted with CHCl₃. The CHCl₃ extract was purified by silica gel column chromatography using CHCl₃ as an eluent. The product was recrystallized from hexane to give colorless needles, mp 99-101°C. Yield 0.80 g (58 %). Ir (CHCl₃) cm⁻¹: 3320, 1720, 1685. ¹H-Nmr (CDCl₃) ppm: 1.20 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 2.13 (3H, s), 3.93 (2H, q, J=7Hz), 4.35 (2H, q, J=7Hz), 7.33 (1H, s), 7.0-7.7 (3H, m), 7.8-8.1 (1H, m), 8.50 (1H, br s). Anal. Calcd for C₁₅H₁₉NO₄: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.13; H, 7.12; N, 4.84.

Ethyl Indole-2-carboxylate (6)—— A mixture of 5 (0.80 g, 2.9 mmol), TsOH (100 mg), and toluene (20 ml) was refluxed for 16 h. The mixture was washed with 1 N NaHCO₃ and dried over K₂CO₃. The product was recrystallized from hexane to give colorless needles, mp 122-123°C (lit.³ mp 122.5-124°C). Yield 0.40 g (73 %). Ir (CHCl₃) cm⁻¹: 3450, 1700. ¹H-Nmr (CCl₄) ppm: 1.43 (3H, t, J=7Hz), 4.40 (2H, q, J=7Hz), 6.9-7.7 (5H, m), 9.85 (1H, br s).

Ethyl α -Ethoxy-2-cyanocinnamate (8)—— A mixture of 2-iodobenzonitrile (7) (1.15 g, 5 mmol), ethyl 2-ethoxyacrylate (1.08 g, 7.5 mmol), 5 % Pd-C (400 mg), K₂CO₃ (1.03 g, 7.5 mmol), and MeCN (2 ml) was heated at 120°C for 24 h in a sealed tube. The mixture was diluted with H₂O and extracted with ether. The ethereal extract was purified by silica gel column chromatography using hexane-Et₃N (9:1 v/v) as an eluent. Distillation of the product gave a colorless liquid, bp 140-150°C/3 mmHg. Yield 0.82 g (67 %). Ir (CHCl₃) cm⁻¹: 2230, 1720. ¹H-Nmr (CDCl₃) ppm: 1.33 (3H, t, J=7Hz), 1.40 (3H, t, J=7Hz), 4.15 (2H, q, J=7Hz), 4.35 (2H, q, J=7Hz), 7.33 (1H, s), 7.4-7.8 (3H, m), 8.3-8.6 (1H, m). Anal. Calcd for C₁₄H₁₅NO₃: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.84; H, 6.06; N, 5.78.

Ethyl α -Ethoxy-2-carbamoylcinnamate (9)—— A mixture of 8 (1.23 g, 5 mmol), 3 N Na₂CO₃ (10 ml), 30 % H₂O₂ (3 ml), and EtOH (5 ml) was stirred at room temperature for 12 h. The mixture was diluted with H₂O and extracted with CHCl₃. The product was recrystallized from hexane-ether to give colorless needles, mp 116-117°C. Yield 1.09 g (83 %). Ir (CHCl₃) cm⁻¹: 3520, 3400, 1715, 1675. ¹H-Nmr (CDCl₃) ppm:

1.30 (3H, t, $J=7\text{Hz}$), 1.36 (3H, t, $J=7\text{Hz}$), 4.00 (2H, q, $J=7\text{Hz}$), 4.30 (2H, q, $J=7\text{Hz}$), 5.90 (2H, br s), 7.36 (1H, s), 7.3-7.7 (3H, m), 8.0-8.3 (1H, m). Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 64.02; H, 6.33; N, 5.16.

Ethyl 1-Oxo-1,2-dihydroisoquinoline-3-carboxylate (10)—— A mixture of **9** (0.79 g, 3 mmol), TsOH (100 mg) and C_6H_6 (20 ml) was refluxed for 24 h. After removal of the solvent, the residue was diluted with H_2O and extracted with CHCl_3 . The product was recrystallized from hexane to give colorless needles, mp 142-143°C. Yield 0.51 g (78 %). Ir (CHCl_3) cm^{-1} : 3360, 1720, 1660. $^1\text{H-Nmr}$ (CDCl_3) ppm: 1.45 (3H, t, $J=7\text{Hz}$), 4.46 (2H, q, $J=7\text{Hz}$), 7.36 (1H, s), 7.5-7.7 (3H, m), 8.3-8.6 (1H, m), 9.20 (1H, br s). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{NO}_3$: C, 66.35; H, 5.11; N, 6.45. Found: C, 66.51; H, 5.26; N, 6.31.

Ethyl α -Ethoxy-2-ethoxycarbonylcinnamate (12)—— A mixture of ethyl 2-iodobenzoate (**11**) (1.38 g, 5 mmol), ethyl 2-ethoxyacrylate (1.08 g, 7.5 mmol), 5 % Pd-C (400 mg), K_2CO_3 (1.03 g, 7.5 mmol), and MeCN (2 ml) was heated at 120°C for 24 h in a sealed tube. The mixture was diluted with H_2O and extracted with ether. The ethereal extract was purified by silica gel column chromatography using C_6H_6 as an eluent. Distillation of the product gave a colorless liquid, bp 150-155°C/3 mmHg. Yield 0.90 g (62 %). Ir (CHCl_3) cm^{-1} : 1720. $^1\text{H-Nmr}$ (CDCl_3) ppm: 1.20 (3H, t, $J=7\text{Hz}$), 1.40 (6H, t, $J=7\text{Hz}$), 3.90 (2H, q, $J=7\text{Hz}$), 4.26 (2H, q, $J=7\text{Hz}$), 4.35 (2H, q, $J=7\text{Hz}$), 7.0-7.5 (2H, m), 7.60 (1H, s), 7.7-8.1 (2H, m). Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_5$: C, 65.74; H, 6.90. Found: C, 65.66; H, 6.72.

Ethyl Isocoumarin-3-carboxylate (13)—— A mixture of **12** (0.50 g, 1.7 mmol), TsOH (50 mg), and C_6H_6 (20 ml) was refluxed for 20 h. The mixture was washed with 1 N NaHCO_3 and dried over K_2CO_3 . The product was recrystallized from cyclohexane to give colorless needles, mp 142-143°C. Yield 0.26 g (70 %). Ir (CHCl_3) cm^{-1} : 1735. $^1\text{H-Nmr}$ (CDCl_3) ppm: 1.43 (3H, t, $J=7\text{Hz}$), 4.40 (2H, q, $J=7\text{Hz}$), 7.45 (1H, s), 7.5-7.9 (3H, m), 8.3-8.5 (1H, m). Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{O}_4$: C, 66.05; H, 4.62. Found: C, 65.86; H, 4.38.

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