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

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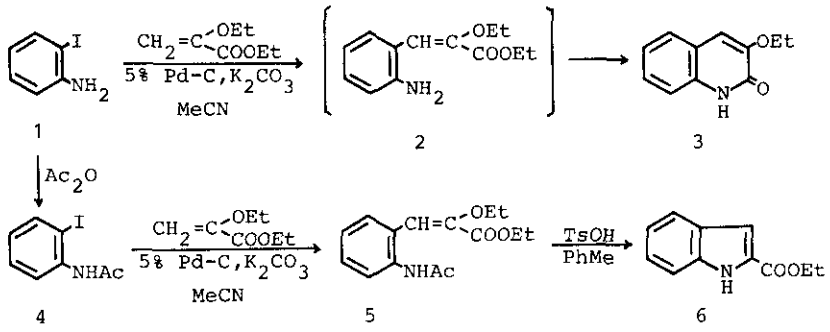
Abstract——— The reaction of 2-iodoaniline with ethyl 2-ethoxyacrylate in the presence of palladium-charcoal gave 3-ethoxy-2(1H)-quinolinone, and the reaction of 2-iodoacetanilide with the same reagent yielded ethyl 2-acetylamino-α-ethoxycinnamate which was cyclized to ethyl indole-2-carboxylate under 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.

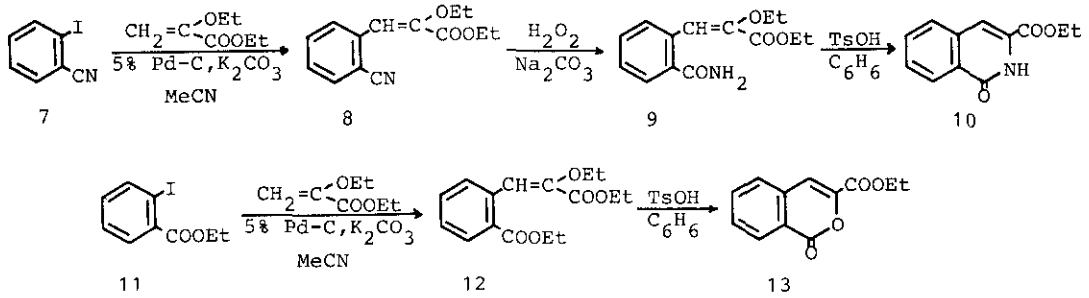
Previously, we have reported the palladium-catalyzed reaction of aromatic iodide with ethyl 2-ethoxyacrylate to afford ethyl α-ethoxyarylacrylates which were considered to be an equivalent synthon to α-ketoesters.[2] In this paper, we describe the synthesis of quinoline, isoquinoline, isocoumarin, and 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-acetylamino-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), 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 $CHCl_3$. The $CHCl_3$ extract was purified by silica gel column chromatography using AcOEt as an eluent. The product was recrystallized from C_6H_6 to give colorless scales, mp 202-203°C. Yield 0.60

g (63 %). Ir ($CHCl_3$) cm^{-1}: 1660. ^{1}H-Nmr (CF_3COOH) ppm: 1.60 (3H, t, J=7Hz), 4.45 (2H, q, J=7Hz), 7.5-8.1 (5H, m). Anal. Calcd for $C_{11}H_{11}NO_2$: 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), 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 $CHCl_3$. The $CHCl_3$ extract was purified by silica gel column chromatography using $CHCl_3$ as an eluent. The product was recrystallized from hexane to give colorless needles, mp 99-101°C. Yield 0.80 g (58 %). Ir ($CHCl_3$) cm^{-1}: 3320, 1720, 1685. ^{1}H-Nmr ($CDCl_3$) 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 $C_{15}H_{19}NO_4$: 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 $NaHCO_3$ and dried over K_2CO_3. 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 ($CHCl_3$) cm^{-1}: 3450, 1700. ^{1}H-Nmr (CCl_4) 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), 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 hexane-Et_3N (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 ($CHCl_3$) cm^{-1}: 2230, 1720. ^{1}H-Nmr ($CDCl_3$) 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 $C_{14}H_{15}NO_3$: 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 Na_2CO_3 (10 ml), 30 % H_2O_2 (3 ml), and EtOH (5 ml) was stirred at room temperature for 12 h. The mixture was diluted with H_2O and extracted with $CHCl_3$. The product was recrystallized from hexane-ether to give colorless needles, mp 116-117°C. Yield 1.09 g (83 %). Ir ($CHCl_3$) cm^{-1}: 3520, 3400, 1715, 1675. ^{1}H-Nmr ($CDCl_3$) ppm:

1.30 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 4.00 (2H, q, J=7Hz), 4.30 (2H, q, J=7Hz), 5.90 (2H, br s), 7.36 (1H, s), 7.3-7.7 (3H, m), 8.0-8.3 (1H, m). Anal. Calcd for $C_{14}H_{17}NO_4$: 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}H-Nmr ($CDCl_3$) ppm: 1.45 (3H, t, J=7Hz), 4.46 (2H, q, J=7Hz), 7.36 (1H, s), 7.5-7.7 (3H, m), 8.3-8.6 (1H, m), 9.20 (1H, br s). Anal. Calcd for $C_{12}H_{11}NO_3$: 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. Distilation 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}H-Nmr ($CDCl_3$) ppm: 1.20 (3H, t, J=7Hz), 1.40 (6H, t, J=7Hz), 3.90 (2H, q, J=7Hz), 4.26 (2H, q, J=7Hz), 4.35 (2H, q, J=7Hz), 7.0-7.5 (2H, m), 7.60 (1H, s), 7.7-8.1 (2H, m). Anal. Calcd for $C_{16}H_{20}O_5$: 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}H-Nmr ($CDCl_3$) ppm: 1.43 (3H, t, J=7Hz), 4.40 (2H, q, J=7Hz), 7.45 (1H, s), 7.5-7.9 (3H, m), 8.3-8.5 (1H, m). Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.86; H, 4.38.

REFERENCES

1. Part XIII: T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano, and H. Yamanaka, Chem. Pharm. Bull., in press.
2. T. Sakamoto, Y. Kondo, Y. Kashiwagi, and H. Yamanaka, Heterocycles, 1988, 27, 257.
3. W. E. Noland and F. J. Baude, 'Organic Syntheses', Coll. Vol. 5, ed. by H. E. Baumgarten, John Wiley and Sons, New York, 1973, p. 567.

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