

PALLADIUM-CATALYZED CROSS-COUPLING OF ARYL IODIDES WITH ETHYL
2-ETHOXY- AND 3-ETHOXYACRYLATE

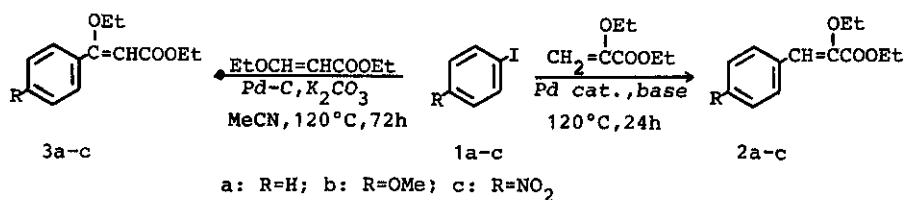
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Abstract—— The cross-coupling of iodobenzenes with ethyl 2-ethoxy- and 3-ethoxyacrylate in the presence of palladium-charcoal gave ethyl α -ethoxy- and β -ethoxycinnamates in moderate yields. The cross-coupling of N-heteroaryl iodides with the same acrylates was also described.

The palladium-catalyzed cross-coupling of aryl and heteroaryl halides with olefins (Heck reaction) is a powerful method to introduce alkenyl side-chains into arenes and heteroarenes.^{1,2} We investigated the palladium-catalyzed cross-coupling of aryl and N-heteroaryl iodides with ethyl 2-ethoxy- and 3-ethoxyacrylate in order to introduce α - and β -ketoester equivalent side-chains into arenes and N-heteroarenes,³ which is subject of the present paper.

When iodobenzene (1a) was allowed to react with ethyl 2-ethoxyacrylate under typical Heck reaction conditions which are to heat the substrate in the presence of palladium (II) acetate at 120°C for 24 h in triethylamine, ethyl α -ethoxycinnamate (2a) was obtained in only 20 % yield (Run 1). Therefore, in order to find more suitable reaction conditions, 1a was treated with ethyl 2-ethoxyacrylate under the conditions shown in Table I. Consequently, it is concluded that the reaction conditions using 5 % palladium-carbon as a catalyst, potassium carbonate as a base, and dimethylformamide (DMF) or acetonitrile as a solvent were more favorable to the cross-coupling (Run 4 and 5).



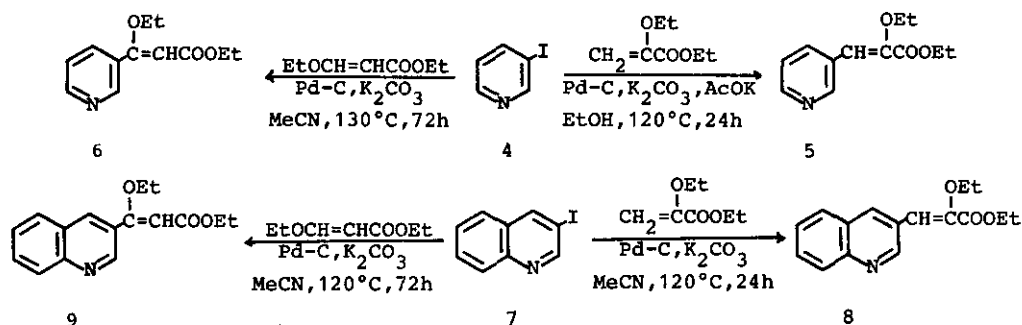
Scheme 1

Table I. Palladium-catalyzed Reaction of Iodobenzene with Ethyl 2-Ethoxyacrylate

Run	Catalyst	Base	Solvent	Yield(%)
1	Pd(OAc) ₂	Et ₃ N	—	20
2	Pd(OAc) ₂	Et ₃ N	DMF	50
3	Pd(OAc) ₂ -Et ₄ NCl	K ₂ CO ₃	DMF	54
4	5% Pd-C	K ₂ CO ₃	DMF	57
5	5% Pd-C	K ₂ CO ₃	MeCN	60
6	5% Pd-C	K ₂ CO ₃	EtOH	24
7	5% Pd-C	K ₂ CO ₃ -AcOK	EtOH	36

Although the cross-coupling of **1a** with ethyl 3-ethoxyacrylate under the same reaction conditions to Run 4 gave ethyl 3-ethoxycinnamate (**3a**) in 28 % yield accompanying with biphenyl, the same palladium-charcoal-catalyzed reaction in acetonitrile at 120°C for 72 h provided **3a** in 70 % yield.

The cross-couplings using ethyl 2-ethoxy- and 3-ethoxyacrylate were applied to 4-substituted iodobenzenes which contain an electron-donating or an electron-withdrawing group. Namely, the reaction of 4-methoxyiodobenzene (**1b**) with the acrylates afforded the corresponding products (**2b** and **3b**), but 4-nitroiodobenzene (**1c**) did not react with the acrylates and was recovered from the reaction mixture. As well as iodobenzene, the reactions of 3-iodopyridine (**4**) and 3-iodoquinoline (**7**) with the acrylates under the same reaction conditions to Run 5 gave the corresponding products in yields as shown in Table II. Exceptionally, coexistence of potassium acetate and use of ethanol as a solvent gave a improved yield (43 %) in the reaction of **4** with ethyl 2-ethoxyacrylate.



Scheme 2

Table II. Yields and Spectral Data for Ethyl Ethoxyareneacrylates

No.	Yield ^{a)} (%)	Ir cm ⁻¹ (CHCl ₃)	¹ H-Nmr δ (ppm) (CCl ₄)
2a	60	1710	1.35 (6H, t, J=7Hz), 4.00 (2H, q, J=7Hz), 4.23 (2H, q, J=7Hz), 6.82 (1H, s), 7.1-7.4 (3H, m), 7.6-7.8 (2H, m)
2b	62	1710	1.33 (6H, t, J=7Hz), 3.80 (3H, s), 4.00 (2H, q, J=7Hz), 4.25 (2H, q, J=7Hz), 6.80 (2H, d, J=9Hz), 6.83 (1H, s), 7.73 (2H, d, J=9Hz)
3a	70	1710	1.0-1.6 (6H, m), 3.8-4.4 (4H, m), 5.10 (0.5H, s), 5.55 (0.5H, s), 7.1-7.7 (5H, m)
3b	52	1710	1.13 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 3.75 (3H, s), 3.93 (2H, q, J=7Hz), 3.97 (2H, q, J=7Hz), 5.02 (0.7H, s), 5.43 (0.3H, s), 6.73 (2H, d, J=8Hz), 7.37 (2H, d, J=8Hz)
5	23	1715	1.35 (6H, t, J=7Hz), 4.07 (2H, q, J=7Hz), 4.28 (2H, q, J=7Hz), 6.78 (1H, s), 7.0-7.4 (1H, m), 8.0-8.6 (2H, m), 8.7-8.9 (1H, m)
6	43 ^{b)}	1715	1.0-1.6 (6H, m), 3.8-4.5 (4H, m), 5.20 (0.6H, s), 5.80 (0.4H, s), 7.0-7.4 (1H, m), 7.5-8.0 (1H, m), 8.3-8.9 (2H, m)
8	62	1710	1.40 (3H, t, J=7Hz), 1.43 (3H, t, J=7Hz), 4.14 (2H, q, J=7Hz), 4.30 (2H, q, J=7Hz), 6.97 (1H, s), 7.3-8.2 (4H, m), 8.55 (1H, d, J=2Hz), 9.06 (1H, d, J=2Hz)
9	52	1710	1.0-1.6 (6H, m), 3.8-4.4 (4H, m), 5.25 (0.7H, s), 5.73 (0.3H, s), 7.2-7.9 (3H, m), 7.9-8.3 (2H, m), 8.77 (0.7H, d, J=2Hz), 9.00 (0.3H, d, J=2Hz)

a) Yields from the 5% palladium-charcoal-catalyzed reactions.

b) Reaction at 130°C.

Conclusively, the palladium-catalyzed reaction of aryl and N-heteroaryl iodides with ethyl 2-ethoxy- and 3-ethoxyacrylate may offer a facile method to introduce α-keto- and β-ketoester equivalent side-chains into aromatic nuclei, although the stereochemistry of the products was not determined.

EXPERIMENTAL

Ethyl 2-ethoxyacrylate was prepared according to the literature.⁴

Ethyl 3-Ethoxyacrylate⁵

A mixture of (ethoxycarbonylmethylene)triphenylphosphorane (17.5 g, 50 mmol) and ethyl formate (40 ml) was heated in a sealed tube at 120°C for 24 h. The mixture

was concentrated, and the residue was extracted with hexane. The hexane extract was distilled in vacuo to give a colorless liquid, bp 94-95°C/26 mmHg. Yield 4.29 g (60 %).

Typical Procedure: Ethyl 8-Ethoxycinnamate (3a)

A mixture of iodobenzene (1.02 g, 5 mmol), ethyl 3-ethoxyacrylate (1.08 g, 7.5 mmol), 5 % Pd-C (400 mg), K_2CO_3 (0.83 g, 6 mmol), and MeCN (2 ml) was heated in a sealed tube at 120°C for 72 h. The mixture was diluted with H_2O and extracted with ether. The ethereal extract was dried over $MgSO_4$, and the ether was removed. The residue was purified by silica gel column chromatography using C_6H_6 as an eluent. The crude product was distilled in vacuo to give colorless liquid.

Table III. Boiling Points and Analytical Data for Ethyl Ethoxyareneacrylates

No.	bp/mmHg (°C)	Formulae	Analysis(%)					
			C	Calcd H	N	C	Found H	N
2a	125-130/2	$C_{13}H_{16}O_3$	70.89	7.32		70.93	7.16	
2b	135-140/2	$C_{14}H_{18}O_4$	67.18	7.25		67.32	7.34	
3a	120/4	$C_{13}H_{16}O_3$	70.89	7.32		71.05	7.29	
3b	165/4	$C_{14}H_{18}O_4$	67.18	7.25		67.22	7.22	
5	130-135/3	$C_{12}H_{15}NO_3$	65.14	6.83	6.33	65.27	6.97	6.14
6	130/4	$C_{12}H_{15}NO_3$	65.14	6.83	6.33	64.96	6.98	6.34
8	170-175/3	$C_{16}H_{17}NO_3$	70.82	6.32	5.16	70.95	6.44	5.08
9	160-165/2	$C_{16}H_{17}NO_3$	70.82	6.32	5.16	71.06	6.18	5.45

REFERENCES AND NOTES

1. R. F. Heck, "Palladium Reagents in Organic Syntheses", Academic Press, London, 1985.
2. R. F. Heck, "Organic Reactions", ed. by W. G. Dauben, John Wiley & Sons, New York, 1982, p. 345.
3. Recently, a paper dealing with the palladium-catalyzed cross-coupling of aryl iodides with methyl 2-methoxyacrylate was published [S. Cacchi, P. G. Ciattini, E. Morera, and G. Ortar, Tetrahedron Lett., 1987, **28**, 3039].
4. C. G. Wermuth and H. Marx, Bull. Soc. Chim. France, 1964, 732.
5. We tried the synthesis of ethyl 3-ethoxyacrylate according to the literature [V. Subramanyam, E. H. Silver, and A. H. Soloway, J. Org. Chem., 1976, **41**, 1272], but ethyl 3-ethoxyacrylate was isolated in poor yield.

Received, 25th September, 1987