HETEROCYCLES, Vol 27, No 1, 1988

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

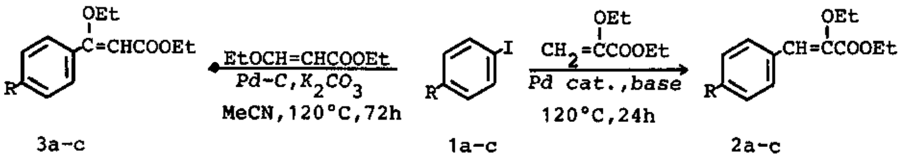
Takao Sakamoto, Yoshinori Kondo, Yoshitomo Kashiwagi,
and Hiroshi Yamanaka*

Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan

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).



a: R=H; b: R=OMe; c: R=NO_2

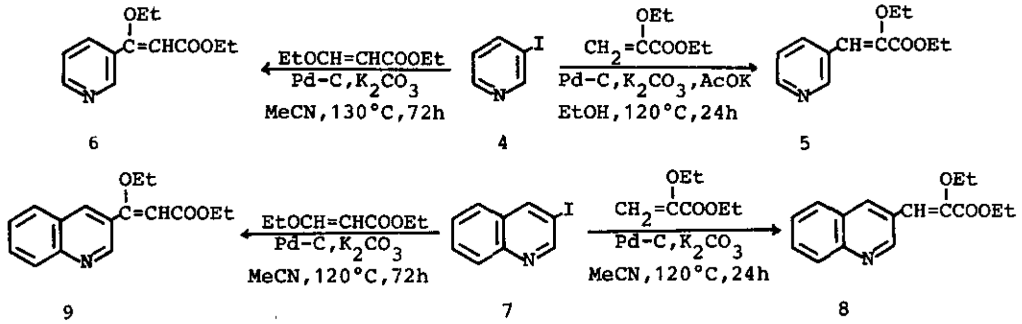
Scheme 1

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

Run	Catalyst	Base	Solvent	Yield(%)
1	$Pd(OAc)_2$	Et_3N	——	20
2	$Pd(OAc)_2$	Et_3N	DMF	50
3	$Pd(OAc)_2$-Et_4NCl	K_2CO_3	DMF	54
4	5% Pd-C	K_2CO_3	DMF	57
5	5% Pd-C	K_2CO_3	MeCN	60
6	5% Pd-C	K_2CO_3	EtOH	24
7	5% Pd-C	K_2CO_3-AcOK	EtOH	36

Although the cross-coupling of **1a** with ethyl 3-ethoxyacrylate under the same reaction conditions to Run 4 gave ethyl β-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-Ethoxyacrylate[5]

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 β-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 pruduct was distilled in vacuo to give colorless liquid.

Table III. Boiling Points and Analytical Data for Ethyl Ethoxyareneacrylates

No.	bp/mmHg (°C)	Formulae	Analysis (%) Calcd C	H	N	Found C	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, Teterahedron 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-ethoxyacryrate 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