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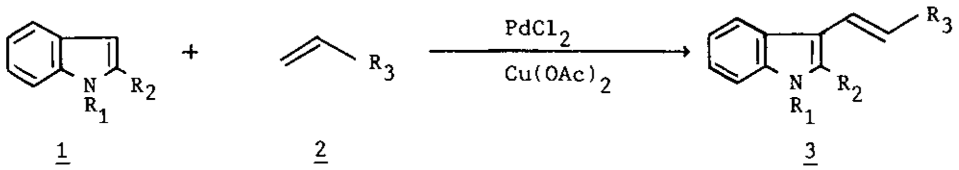
DIRECT REGIOSELECTIVE VINYLATION OF INDOLES USING PALLADIUM (II) CHLORIDE

Yasuoki Murakami,* Yuusaku Yokoyama, and Tsuyoshi Aoki
School of Pharmaceutical Science, Toho University
2-2-1, Miyama, Funabashi, Chiba 274, Japan

Abstract ——Direct regioselective vinylation at C_3-position of ethyl indole-2-carboxylate, its N-benzyl derivative, and N-benzylindole with various conjugated olefins was accomplished in the presence of palladium (II) chloride and acetate salt in good to moderate yields.

Applications of organopalladium chemistry to indoles have been studied extensively in recent years; those involve carbonylation,[1a] arylation,[1b] allylation,[1c,d] and vinylation.[1e,f,2] Among these reactions, the regioselective C_3-vinylation of indoles is especially attractive, because the introduction of functionalized carbon side chain at the C_3-position is very effective for the synthesis of various indole alkaloids. Although such reactions appeared in the literatures,[2] the starting materials were limited to N-acyl derivatives, and the yields were not satisfactory. We wish to report here the regioselective vinylation of ethyl indole-2-carboxylate (1b), its N-benzyl derivative (1c), and N-benzylindole (1d) using palladium (II) (Scheme I).

Various indole derivatives (1b-d) smoothly reacted with ethyl acrylate (2, R_3=OEt) in the presence of palladium (II) chloride and cupric acetate to give the vinylated products (3b-c) having *trans* geometry[3] in good to moderate yields, as is shown in Table I. Since the structure of each product was determined by the alternative synthesis starting from the known 3-formylindoles (4b,[4] 4d[5])(Scheme II), the vinylation was proved to occur at the C_3-position exclusively.[6] In contrast to the successful vinylation of N-unprotected indole derivative (1b), indole itself (1a) was so sensitive under this reaction condition as to give only the unidentified tarry products.[8]



1a: $R_1=R_2=H$, 1b: $R_1=H$, $R_2=CO_2Et$

1c: $R_1=CH_2Ph$, $R_2=CO_2Et$, 1d: $R_1=CH_2Ph$, $R_2=H$

Scheme I

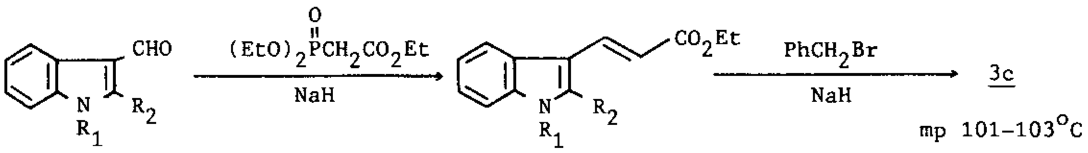
Table I. The Vinylation with Ethyl Acrylate (2, $R_3=CO_2Et$)

Indole (1)	Condition[a,b]		Product (3)[9]		
	Temp. (°C)	Time (h)		Yield (%)	mp (°C)
1b	80	2.2	3b	50	188-191
1c	60	4.0	3c	72	105
1d	40	1.2	3d	60[c)]	107-108

a) indole : olefin : $PdCl_2$: $Cu(OAc)_2$ = 1 : 2 : 1 : 4

b) Acetonitrile was used as a solvent. c) 2 eq. of $Cu(OAc)_2$ was used.

The effect of acetate salts and solvents was investigated on the reaction of 1c with methyl acrylate (2, $R_3=CO_2Me$), as 1c gave the best result among the attempted indole (Table I). The results are shown in Table II. Acetic acid and acetonitrile were the best solvent in the presence of cupric acetate and sodium acetate (runs 1 and 5). The starting material was recovered quantitatively in the absence of acetate salt (run 3), whereas the reaction proceeded smoothly when palladium (II) acetate was used instead of palladium (II) chloride (run 4). These results clearly showed that the acetate anion was essential to carry out this reaction.



4b,d

3b: mp 188-190°C

3d: mp 107-108°C

b: $R_1=H$, $R_2=CO_2Et$, c: $R_1=CH_2Ph$, $R_2=CO_2Et$, d: $R_1=CH_2Ph$, $R_2=H$

Scheme II

Table II. The Vinylation of 1c with Methyl Acrylate (2, $R_3=CO_2Me$)

Run	Solvent	$M(OAc)_n$	Condition$^{a)}$ Temp. (°C)	Time (h)	Product $(3)^{b),9}$ Yield (%)	SM. (1c) Recov. (%)
1	MeCN	$Cu(OAc)_2$	60	4.0	84	7
2	MeCN	NaOAc	60	4.0	60	24
3	MeCN	None	60	4.0	2	94
4	MeCN	None$^{c)}$	60	3.0	77	10
5	AcOH	NaOAc	100	2.5	80	11
6	MeOH	$Cu(OAc)_2$	60	4.5	7	75
7	DMF	$Cu(OAc)_2$	60	3.5	50	44

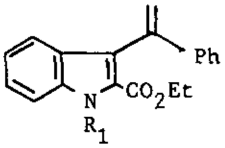
a) 1c : olefin : $PdCl_2$: $M(OAc)_2$ =1 : 2 : 1 : 4 b) mp 109-111°C
c) $Pd(OAc)_2$ was used.

The reaction of the various conjugated olefins other than acrylic acid ester with indoles (1b-d) was also investigated. Only C_3-vinylated indoles (3) were obtained in all cases, in more than 50% yield, as is shown in Table III. Most of the olefins (2) were substituted at their β-position with *trans* geometry; however, the reaction with styrene (2, R_3=Ph) gave the α-substituted styrene derivatives (5b and 5c) as minor components (runs 2 and 4), and the reaction with acrylo-

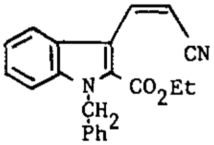
Table III. The Vinylation with Various Conjugated Olefins (2) in Acetonitrile

Run	Indole	Olefin (2) R_3	Condition$^{a)}$ Temp. (°C)	Time (h)	Product $(3)^{9}$ Yield (%)	mp (°C)
1	1b	COMe	40	4.0$^{e)}$	53	244-248
2		Ph	40	2.0$^{e)}$	63$^{b)}$	166-168
3	1c	COMe	60	5.0	69	97-99
4		Ph	80	7.0	74$^{c)}$	124-127
5		CN	60	7.5	73$^{d)}$	89-92
6	1d	COMe	40	1.0$^{e)}$	56	137-140

a) indole : olefin : $PdCl_2$: $Cu(OAc)_2$ = 1 : 2 : 1 : 4 b) including 19% of 5b
c) including 5% of 5c d) including 31% of 6 e) 2 eq. of $Cu(OAc)_2$ was used.



5b: R_1=H, mp 153-155°C
5c: $R_1=CH_2Ph$, oil



6: mp 125-129°C

nitrile (2, R_3=CN) gave the products as a mixture of *trans* and *cis* isomers (run 5).

The present study indicates that the substrates can be extended to N-alkyl[10] and N-unprotected indole derivatives which give the C_3-vinylated products in good yields, and this fact increases the synthetic applicability of this reaction. The application to the syntheses of more useful indole derivatives is now under investigation.

REFERENCES AND NOTES

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3) The *trans* geometry of the products was determined by the coupling constant (17 Hz) of the vinylic protons in the ^{1}H-NMR spectrum.
4) W.C. Shabica, E.E. Howe, J.B. Ziegler, and M. Tishler, J. Am. Chem. Soc. 1946, 68, 1156.
5) J.D. Lambert and Q.N. Porter, Aust. J. Chem., 1981, 34, 1483.
6) It is interesting that the arylation of N-acylindole was reported to occur at the C_2-position.[1b]
7) It was exemplified that 1b was a stable synthetic equivalent of indole itself. Y. Murakami, M. Tani, K. Tanaka, and Y. Yokoyama, Heterocycles, 1982, 14, 1939, and Heterocycles, 1984, 22, 241.
8) It has also been reported[2a] that 3-bromoindole gave the tarry products under the vinylation condition, whereas its N-acylated derivative reacted smoothly.
9) All new compounds gave satisfactory elemental analyses and spectral data.
10) It has been reported[2c] that the vinylation of N-alkylindoles was unsuccessful under the similar condition.

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