Alkenylation of 1-Acylindoles with Olefins Bearing Electron-withdrawing Substituents and Palladium Acetate

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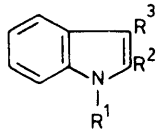
The oxidation of 1-(2,6-dichlorobenzoyl)indole with olefins, such as alkyl acrylates and acrylonitrile, and palladium acetate resulted in selective 3-alkenylation of the indole nucleus. Treatment of 1-acyl-3-methylindoles under similar conditions gave the corresponding 2-alkenyl substituted indoles, while the oxidation of 6-oxo-6*H*-isoindolo[2,1-*a*]indole gave the corresponding 3-alkenyl substituted indoles.

Coupling reactions of arenes and olefins with palladium(II) salts [1] are an effective method for the preparation of aryl substituted olefins. Such reactions have also been applied to heterocyclic molecules by Fujiwara *et al.*[2,3] who reported the alkenylation of furan, 2-methylfuran, benzofuran, thiophen, benzothiophen, and 1-acetylindole (1a) with palladium acetate and olefins such as methyl acrylate and acrylonitrile. In the course of our work on various aspects of the oxidation of 1-acylindoles with palladium acetate, *e.g.*, the intramolecular ring-closure,[4] the arylation with arenes,[5] and the carboxylation with carbon monoxide,[6] we have investigated the coupling reaction of 1-acylindoles and alkyl acrylates with palladium acetate, a potentially effective method for the preparation of indolylacrylic acids and their esters which are important precursors for the synthesis of biologically and physiologically active compounds.

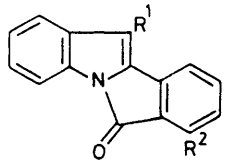
In contrast to the published report [2] describing the reaction of (1a) with methyl acrylate and palladium acetate to give (*E*)-methyl 3-(1-acetyl-1*H*-indol-3-yl)acrylate (2a), (*E*)-methyl 3-(1-acetyl-1*H*-indol-2-yl)acrylate, and other products, we found that oxidation of 1-(2,6-dichlorobenzoyl)indole (1d) with olefins and palladium acetate resulted in selective 3-alkenylation of the indole nucleus. Furthermore, it was found that treatment of 1-acyl-3-methylindoles (10a) and (10d) with olefins and palladium acetate gave the corresponding 2-alkenyl substituted indoles, while the oxidation of 2-substituted 1-acylindoles such as 6-oxo-6*H*-isoindolo[2,1-*a*]-indole (6) gave the corresponding 3-alkenyl substituted indoles.

In an effort to determine the effect of 1-substituents on the alkenylation of indoles with olefins and palladium acetate, the oxidation of 1-methylindole, 1-benzylindole, 1-acetylindole (1a), and 1-benzoylindole (1b) with methyl acrylate and palladium acetate was studied. The treatment of 1-methylindole and 1-benzylindole gave complex reaction mixtures. The oxidation of (1a) gave (2a) in 20% yield together with small amounts of other products. Meanwhile, (1b) was treated with methyl acrylate and palladium acetate under nitrogen to give the ring-closed products (6) [4] (30%) and (8) (2%) and the expected alkenyl substituted compound (2b) (27% yield based on the substrate consumed, conversion 88%).

Previously we reported that the oxidation of 1-(2-chlorobenzoyl)indole (1c) with palladium acetate gave (7) but not (6).[4] Therefore, in an attempt to avoid the ring-closure, the alkenylation of 1-(2,6-dichlorobenzoyl)indole (1d) with olefins and palladium acetate was investigated. The treatment of (1d) with methyl acrylate and palladium acetate gave the expected product (2d) in good yields based on (1d) consumed. The 3-alkenylation of (1d) with both ethyl acrylate and acrylonitrile was also achieved, in satisfactory yields. These results are summarized in Table 1, which compares 3-alkenylations of (1a) and of (1d). Under similar conditions, the oxidation of 1-cinnamoylindole (1e) gave a complex reaction mixture.



	R^1	R^2	R^3	M.p. (°C)
(1a)	MeCO	H	H	Ref. 11
(1b)	PhCO	H	H	Ref. 4
(1c)	2-ClC_6H_4CO	H	H	Ref. 4
(1d)	2,6-$Cl_2C_6H_3CO$	H	H	131—132
(1e)	PhCH=CHCO	H	H	101—102
(2a)	MeCO	H	MeOCOCH=CH	Ref. 2
(2b)	PhCO	H	MeOCOCH=CH	126—127
(2d)	2,6-$Cl_2C_6H_3CO$	H	MeOCOCH=CH	159—160.5
(3a)	MeCO	H	EtOCOCH=CH	132—133
(3d)	2,6-$Cl_2C_6H_3CO$	H	EtOCOCH=CH	143—144
(4a)	MeCO	H	NCCH=CH	169—170
(4d)	2,6-$Cl_2C_6H_3CO$	H	NCCH=CH	195—197
(5)	H	H	HO_2C	Ref. 12
(10a)	MeCO	H	Me	Ref. 11
(10d)	2,6-$Cl_2C_6H_3CO$	H	Me	174—175
(11a)	MeCO	MeOCOCH=CH	Me	88—89
(11d)	2,6-$Cl_2C_6H_3CO$	MeOCOCH=CH	Me	124.5—126
(12a)	MeCO	EtOCOCH=CH	Me	71—72
(12d)	2,6-$Cl_2C_6H_3CO$	EtOCOCH=CH	Me	143—145



	R^1	R^2	M.p. (°C)
(6)	H	H	Ref. 4
(7)	Cl	H	Ref. 4
(8)	H	MeOCOCH=CH	206.5—207
(9)	H	EtOCOCH=CH	188—189

Table 1. Alkenylation of 1-acylindoles with olefins and palladium acetate [a]

Substrates	Olefins	Solvents	Conversion (%)	Products yields (%) [b]
(1a)	CH_2=$CHCO_2Me$	$MeCO_2H$	100	(2a) 20
(1a)	CH_2=$CHCO_2Et$	$MeCO_2H$	100	(3a) 23
(1a)	CH_2=CHCN	$MeCO_2H$	100	(4a) 20 [c]
(1d)	CH_2=$CHCO_2Me$	$MeCO_2H$	33	(2d) 75
(1d)	CH_2=$CHCO_2Et$	$MeCO_2H$	40	(3d) 76
(1d)	CH_2=CHCN	$MeCO_2H$	47	(4d) 52 [c]
(1d)	CH_2=$CHCO_2Me$	$EtCO_2H$	39	(2d) 56
(1d)	CH_2=$CHCO_2Me$	MeCN	33	(2d) 66
(1d)	CH_2=$CHCO_2Me$	$MeNO_2$	22	(2d) 74
(6)	CH_2=$CHCO_2Me$	$MeCO_2H$	76	(8) 48
(6)	CH_2=$CHCO_2Et$	$MeCO_2H$	75	(9) 50
(10a)	CH_2=$CHCO_2Me$	$MeCO_2H$	93	(11a) 67
(10a)	CH_2=$CHCO_2Et$	$MeCO_2H$	92	(12a) 65
(10d)	CH_2=$CHCO_2Me$	$MeCO_2H$	59	(11d) 87
(10d)	CH_2=$CHCO_2Et$	$MeCO_2H$	62	(12d) 83

[a] Conditions used in all experiments; substrate (1 mmol), $Pd(OAc)_2$ (1 mmol), olefin (3 mmol), solvent (50 ml), at reflux temperature, under nitrogen, 16 h reaction. [b] Yields based on substrate consumed. [c] A mixture of (*E*) and (*Z*) isomers (3 : 1).

The structures of the 3-alkenyl substituted compounds (2), (3), and (4) were confirmed on the basis of analytical and spectral data.* Furthermore, a hydrolysis of (3a) with NaOH in EtOH–H_2O gave 3-(1*H*-indol-3-yl)acrylic acid (5), providing additional evidence for the structure of (3a). On the other hand, the n.m.r. spectra confirmed that all the alkenyl substituted products from the reactions with methyl acrylate and with ethyl acrylate have *E* stereochemistry, although the products with acrylonitrile are mixtures of the (*E*) and (*Z*) isomers (*E*/*Z* = 3).

Solvent effects on the alkenylation of (1d) with methyl acrylate were further investigated. Although (1d) was unreactive towards palladium acetate and methyl acrylate in methanol or benzene, the oxidation in acetonitrile and in nitromethane gave (2d) (Table 1).

Palladium acetate-catalysed reactions of (1d) with methyl acrylate were carried out using AgOAc,[1] $Cu(OAc)_2$,[1] $Na_2S_2O_8$,[7] and $NaNO_2$ [8] as re-oxidants in air. These results are summarized in Table 2.

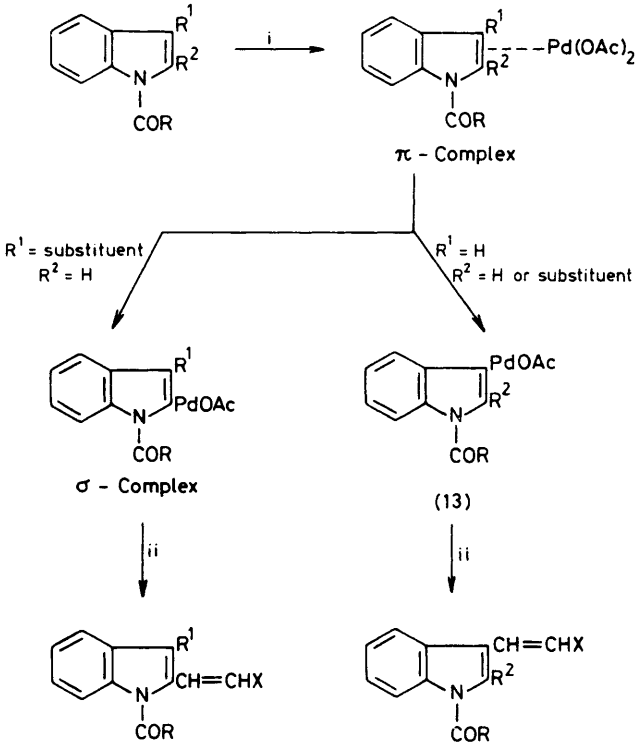
In order to elucidate the scope and the mechanism of the alkenylation of 1-acylindoles with olefins and palladium acetate, the behaviour of 2- and 3-substituted indole nuclei was further investigated. Oxidation of 2-substituted 1-acylindoles such as (6) with palladium acetate and olefins such as

* The spectral and elemental data of the 1-acylindoles are summarized in the Supplementary Publication (see Experimental section).

Table 2. Palladium acetate-catalysed alkenylation of (1d) with methyl acrylate and re-oxidants [a]

Re-oxidants (mmol)	Yields of (2d) Yield [b] (%)	Yield [c] [conversion(%)]
AgOAc (1)	880	77 (23)
$Cu(OAc)_2$ (1)	520	52 (20)
$Na_2S_2O_8$	315	24 (26)
$NaNO_2$ (2)	340	24 (28)

[a] The reaction was performed by heating an acetic acid (50 ml) solution of (1c) (1 mmol), $Pd(OAc)_2$ (0.02 mmol), re-oxidant (1—2 mmol), and methyl acrylate (3 mmol) in air for 16 h. [b] Yields based on $Pd(OAc)_2$ used. [c] Yields based on (1d) consumed.



Scheme. *Reagents:* i, $Pd(OAc)_2$; ii, CH_2=CHX

methyl acrylate and ethyl acrylate gave 3-alkenyl substituted indoles such as (8) and (9), respectively. On the other hand, oxidation of 3-substituted 1-acylindoles under similar conditions resulted in 2-alkenylation of the indole nucleus. Thus, the oxidation of 1-acetyl-3-methylindole (10a) with methyl acrylate and with ethyl acrylate gave (11a) and (12a), respectively, and 1-(2,6-dichlorobenzoyl)-3-methylindole (10d) reacted with palladium acetate and olefins to give (11d) and (12d) in good yields. These results are also shown in Table 1.

In view of the known results on alkenylation of arenes [1] and of furan [2] and our present results, the alkenylations of 1-acylindoles are reasonably explained in terms of formation of indolyl-palladium intermediates (Scheme). Several reports [9] describe the regioselective metallation of 1-substituted indoles at the 2-position by alkyl-lithium. It is therefore interesting that palladium acetate preferentially attacks the 3-position of the indole nucleus to yield a 3-indolyl-palladium complex (13) when the substrate is a 2- and 3-unsubstituted 1-acylindole, particularly in the case of (1d). The earlier paper [10] which

describes the mercuriation of indole with mercuric acetate to yield 1,3-diacetoxymercuriated indole provides further support for the mechanistic pathway *via* (13) in the oxidation of (1d) with palladium acetate.

Experimental

All m.p.s are uncorrected. Elemental analyses were performed by the Analytical Centre of Kyoto University. I.r. spectra were recorded with a JASCO IRA-1 spectrometer. ^{1}H N.m.r. were recorded with a JEOL JNM-60 spectrometer using Me_4Si as the internal reference. 1-Acetylindole (1a) and 1-acetyl-3-methylindole (10a) were prepared according to the method described by Gribble *et al.*[11] 1-Benzoylindole (1b) and 6-oxo-6*H*-isoindolo[2,1-*a*]indole (6) were prepared according to the method described before.[4] Spectral and elemental data for the 1-acylindoles (1d), (1g), (2b), (2d), (3a), (3d), (4a), (4d), (8), (9), (10d), (11a), (11d), (12a), and (12d) are available as a Supplementary Publication * (SUP No. 23571, 5 pages).

1-*Acylindoles* (1d), (1g), *and* (10d).—To a stirred solution of indole (50 mmol) and sodium hydride (50 mmol) in dimethylformamide (150 ml), 2,6-dichlorobenzoyl chloride (47 mmol) in dimethylformamide (50 ml) was added dropwise under nitrogen and the solution was heated at 80 °C for 8 h. The reaction mixture was poured into an excess of ice-cooled water to give 1-(2,6-dichlorobenzoyl)indole (1d) (40 mmol, 84%), as a crystalline product, which was collected by suction and recrystallized from ether–hexane as colourless prisms.

1-Cinnamoylindole (1g) (76% yield) and 1-(2,6-dichlorobenzoyl)-3-methylindole (10d) (78% yield) were prepared according to the method described above by treatment of indole with cinnamoyl chloride and 3-methylindole with 2,6-dichlorobenzoyl chloride, respectively.

General Procedure for the Stoicheiometric Alkenylation of 1-*Acylindoles with Olefins and Palladium Acetate.*—A solution of 1-acylindoles (1 mmol), olefins (3 mmol), and palladium acetate (1 mmol) in acetic acid (50 ml) was heated at reflux temperature under nitrogen for 16 h. The reaction mixture was evaporated to give a brown residue which was then chromatographed on a silica-gel plate, developed by chloroform, to give alkenyl substituted 1-acylindoles. The results are summarized in Table 1.

* For details of the Supplementary Publications Scheme see Instructions to Authors (1983) in *J. Chem. Soc., Perkin Trans. 1*, 1983, Issue 1.

Palladium Acetate-catalysed Alkenylation of 1-(2,6-*Dichlorobenzoyl*)*indole* (1d) *with Methyl Acrylate.*—A solution of (1d) (1 mmol), methyl acrylate (3 mmol), re-oxidants (listed in Table 2) and palladium acetate (0.02 mmol) in acetic acid (50 ml) was heated at reflux temperature under nitrogen for 16 h. The reaction mixture was evaporated to give a brown residue which was chromatographed on a silica-gel plate, developed by chloroform, to give (2d). The results are summarized in Table 2.

Hydrolysis of (E)-*Methyl* 3-(1-*Acetyl*-1H-*indol*-3-*yl*)*acrylate* (2a).—A solution of (2a) (0.123 mmol) and NaOH (100 mmol) in a mixture of EtOH (50 ml) and H_2O (50 ml) was heated at 70 °C for 8 h. The reaction mixture was poured into water and extracted with chloroform. The chloroform extract was evaporated to give (5) (0.105 mmol, 86%); m.p. 192—195 °C (lit.,[12] 195 °C).

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