SYNTHESIS OF 2-SUBSUTITUTED 3-ALKENYLINDOLES BY THE PALLADIUM-CATALYZED CYCLIZATION FOLLOWED BY ALKENYLATION (HECK REACTION)

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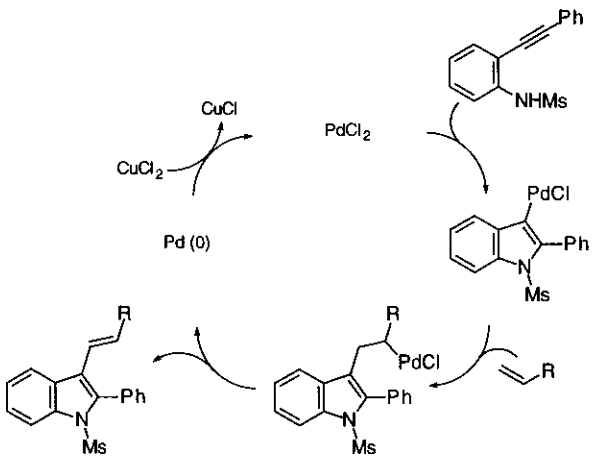
Abstract - The reaction of *N*-protected 2-alkynylanilines with electron-deficient alkenes in the presence of a palladium(II) catalyst and copper dichloride in acetonitrile gave 2-substituted 3-alkenylindoles.

We have reported the synthesis[1,2] of 2-substituted indoles by the basic cyclization of ethyl *N*-(2-alkynylphenyl)carbamates which were produced by the palladium(0)-catalyzed cross-coupling reaction of 2-bromoanilines with terminal alkynes.

On the other hand, the palladium(II)-catalyzed cyclization reaction of 2-alkynylaniline derivatives to 2-substituted indoles has also been reported.[3-6] The palladium(II)-catalyzed indole cyclization reaction is considered to proceed *via* the indolylpalladium species as intermediates. The reaction in the presence of allyl halides and acetate or aryl halides and triflates has been developed into the synthesis of 3-allyl and 3-aryl 2-substituted indoles.[6-8] The reaction was further applied for the synthesis of 2-substituted 3-aroylindoles using aryl halides and carbon monoxide.[9] The palladium(II)-catalyzed 2,3-disubstituted indole cyclization reaction proceeds in the absence of reoxidant of palladium(0) species, because allyl-, aryl-, and aroylpalladium(II) species act as a catalyst of cyclization and as a reagent for introduce the substituents at the 3-position of indoles.

In connection with the above reaction, we have reported the synthesis of methyl 2-substituted indole-3-carboxylates by the reaction of *N*-(2-alkynylphenyl)methanesulfonamides with carbon monoxide in the presence of palladium diacetate and copper dichloride in methanol.[10,11] The reaction essentially proceeds by the catalytic action of palladium(II) species, but the presence of reoxidant (e.g., copper dichloride) is necessary, because there are no palladium(II) species such as allyl- or arylpalladium halides which are reproducible by the oxidative addition reaction of palladium(0) species to ally or aryl halides.

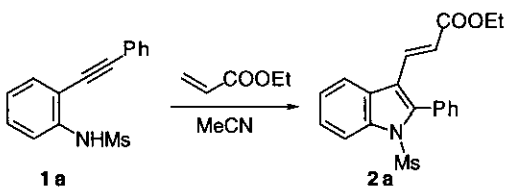
In order to develop the oxidant-necessary palladium-catalyzed indole cyclization reaction and to synthesize of 2-substituted 3-alkenylindoles, we report here the cross-coupling reaction of the intermediary indolylpalladium species with electron-deficient alkenes (Heck reaction) as shown in Scheme 1.



Scheme 1

The reaction conditions for the indole cyclization and the succeeding alkenylation reaction of *N*-(2-phenylethynylphenyl)methanesulfonamide (**1a**) were examined using ethyl propenoate in acetonitrile as shown in Table 1. As a result, the reaction using palladium dichloride and copper dichloride as catalysts at 50℃ gave the expected product, ethyl 3-[1-phenylsulfonyl-2-phenylindol-3-yl]prop-2-enoate (**2a**) in 74% yield (Entry 1 in Table 1).

Table I Palladium (II) catalyzed cyclization / Heck reaction of **1a** with ethyl acrylate



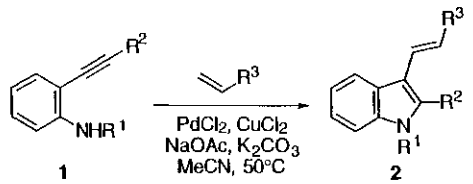
1a **2a**

Entry	Pd(II)	Oxidant	Base	Time (h)	Yield (%)
1	$PdCl_2$	$CuCl_2$	K_2CO_3, NaOAc	16	29
2	$PdCl_2$	$CuCl_2$	K_2CO_3, NaOAc	1.5	74
3	$PdCl_2$	$CuCl_2$	K_2CO_3, NaOAc	1.5	42
4	$Pd(OAc)_2$	$CuCl_2$	K_2CO_3, NaOAc	1.5	50
5	$PdCl_2$	$Cu(OAc)_2$	K_2CO_3, NaOAc	2	3
6	$PdCl_2$	$CuCl_2$	K_2CO_3	2	32

Under the same reaction conditions, the cyclization and alkenylation reactions using various 2-ethynylaniline derivatives and alkenes were investigated. As shown in Table 2, the methylsulfonyl group was effective for protection of the amino group (Entry 1 in Table 2), and the reaction of **1a**, **1d**, and **1e** with ethyl propenoate proceeded for 1 h at 50℃ to give ethyl 2-substituted 3-(indol-3-yl)propenoate in 32-74% yields.

It has been reported that the cyclization reaction of trimethylsilylethynylanilines does not proceed or produce the desilylated indoles instead of the expected 2-silylated derivatives.[2] But the reaction of the trimethylsilylethynyl derivative (**1e**) with ethyl propenoate gave the 2-trimethylsilylindole (**2e**) in 32% yield.

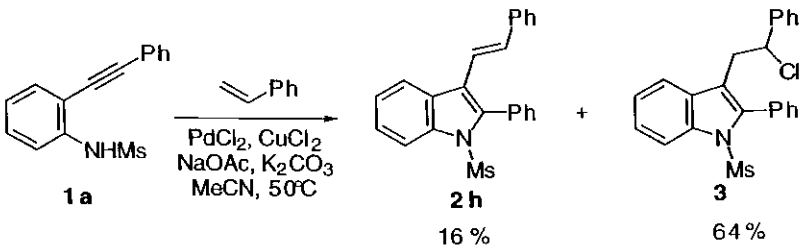
Table 2 Palladium (II) catalyzed synthesis of 2,3-disubstituted indole



1 2

Entry	1	R^1	R^2	R^3	Time (h)	Yield (%)	2
1	a	Ms	Ph	COOEt	1	74	a
2	b	$PhSO_2$	Ph	COOEt	1	51	b
3	c	COOEt	Ph	COOEt	1	34	c
4	d	Ms	Hex	COOEt	1	46	d
5	e	Ms	TMS	COOEt	1	32	e
6	a	Ms	Ph	Ac	1.5	55	f
7	a	Ms	Ph	CHO	1.5	48	g

As shown in Scheme 2, the reaction of **1a** with ethenylbenzene was proceeded for 1.5 h at 50℃ to give 1-methylsulfonyl-2-phenyl-3-(2-chloro-2-phenylethyl)indole (**3a**) in 64 % yield. The structure of **3a** was decided with X-Ray crystallographic analysis (Figure 1).



1a 2h 16 % 3 64 %

Scheme 2

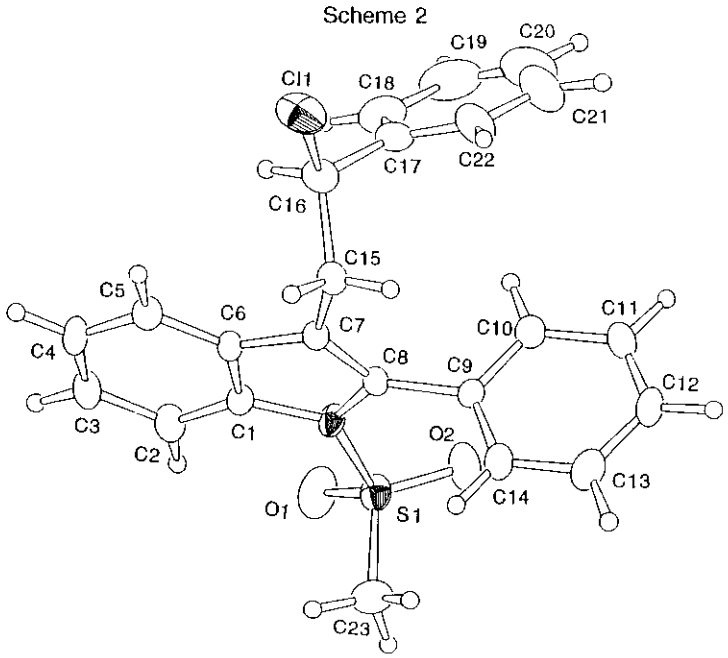
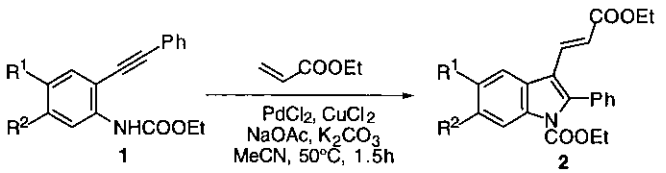


Figure 1. ORTEP View of **3**

When substituted 2-ethynylaniline derivertives (**1i** and **1j**) were used as a starting material, 2,3-substituted indoles (**2i** and **2j**) with substituents at benzene moiety were obtained (scheme 3).



i: R^1 = CN, R^2 = H 26%

j: R^1 = H, R^2 = OMe 20%

Scheme 3

The results of this work show that the cross-coupling reaction of the indolylpalladium complexes generated by the palladium-catalyzed cyclization reaction of 2-alkynylanilines with the alkenes (Heck reaction) proceeds to give the corresponding 2,3-disubstituted indoles. Namely, 2-substituted 3-alkenylated indoles were effectively synthesized in two steps from 2-haloanilines.

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EXPERIMENTAL

All melting points and boiling points are uncorrected. IR spectra were measured on a JASCO IR-810 spectrophotometer. ^{1}H-NMR spectra were recorded on Varian Gemini 2000 (300 MHz). Chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) as the internal reference, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, and dd = doublet of doublet. MS and HRMS were recorded on JMS-DX303 and JMS-AX500 instruments.

General procedure

A mixture of **1** (0.5 mmol), alkene (1.0 mmol), $PdCl_2$ (0.05 mol), $CuCl_2$•$2H_2O$ (1.0 mmol), NaOAc (1.0 mmol), and K_2CO_3 (1.0 mmol) in MeCN (6 mL) was stirred at 50℃. The reaction mixture was evaporated and H_2O (20 mL) was added to the residue. The mixture was extracted with $CHCl_3$ (20 mL). The $CHCl_3$ layer was dried over $MgSO_4$, concentrated, and chromatographed on a silica gel followed by distillation or recrystallization.

Ethyl 3-[1-(Methylsulfonyl)-2-phenylindol-3-yl]propenoate (2a)

Accoding to the general procedure, the reaction using **1a** (135 mg) and ethyl propenoate (100 mg) for 1 h gave **2a** (136 mg) in 74% yield as colorless needles (Et_2O - hexane). mp 159-160℃. ^{1}H NMR ($CDCl_3$) δ : 1.29 (3H, t, J = 7.5 Hz), 2.89 (1H, s), 4.21 (2H, q, J = 7.5 Hz), 6.55 (1H, d, J = 17.0), 7.46 (8H, m), 7.95 (1H, t, J = 4.5 Hz), 8.19 (1H, t, J = 4.5 Hz). IR (KBr) ν (cm^{-1}): 1710, 1630, 1360, 1280, 1120. MS *m/z*: 369 (M^+). *Anal.* Calcd for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; S, 8.68. Found: C,

64.90; H, 5.12; N, 3.63; S, 8.58.

Ethyl 3-[1-(Phenylsulfonyl)-2-phenylindol-3-yl]propenoate (2b)

Accoding to the general procedure, the reaction using **1b** (166 mg) and ethyl propenoate (100 mg) for 1 h gave **2b** (109 mg) in 51% yield as colorless needles (Et_2O - hexane). mp 158℃. ^1H NMR ($CDCl_3$) δ : 1.27 (3H, t, J = 7.0 Hz), 4.17 (2H, q, J = 7.0 Hz), 6.47 (1H, d, J = 16.2 Hz), 7.06 - 7.56 (13H, m), 7.87 (1H, d, J = 7.7 Hz), 8.44 (1H, d, J = 8.2 Hz). IR (KBr) ν (cm^{-1}): 1700, 1370, 1170. MS *m/z*: 431 (M^+). HRMS calcd for $C_{25}H_{21}NO_4S$: 431.1190. Found: 431.1165. *Anal.* Calcd for $C_{25}H_{21}NO_4S$(1/3 H_2O): C, 68.63; H, 4.99; N, 3.20; S, 7.33. Found: C, 68.69; H, 4.97; N, 3.23; S, 7.20.

Ethyl 3-[1-(Ethoxycarbonyl)-2-phenylindol-3-yl]propenoate (2c)

Accoding to the general procedure, the reaction using **1c** (133 mg) and ethyl propenoate (100 mg) for 1 h gave **2c** (61 mg) in 34% yield as a pale yellow liquid. bp 113 - 121℃ / 32 mmHg. ^1H NMR ($CDCl_3$) δ : 0.75 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 8.8 Hz), 4.13 - 4.26 (4H, m), 6.56 (1H, d, J = 16.2 Hz), 7.26 - 7.47 (7H, m), 7.55 (1H, d, J = 16.2 Hz), 7.94 (1H, d, J = 8.6 Hz), 8.29 (1H, d, J = 8.6 Hz). IR (KBr) ν (cm^{-1}): 1730, 1710. MS *m/z*: 363 (M^+). HRMS calcd for $C_{22}H_{21}NO_4$: 363.1469. Found: 363.1465.

Ethyl 3-[2-Hexyl-1-(methylsulfonyl)indol-3-yl]propenoate (2d)

Accoding to the general procedure, the reaction using **1d** (140 mg) and ethyl propenoate (100 mg) for 1 h gave **2c** (88 mg) in 46% yield as colorless needles (Et_2O - hexane). mp 90 - 91℃. ^1H NMR ($CDCl_3$)δ : 0.89 - 0.91 (3H, m), 1.31 - 1.39 (9H, m), 1.69 - 1.73 (2H, m), 3.00 (1H, s), 4.30 (2H, q, J = 7.14 Hz), 6.58 (1H, d, J = 16.2 Hz), 7.35 - 7.40 (2H, m), 7.88 (d, 1H, J = 15.9 Hz), 7.86 - 7.89 (1H, m), 8.06 - 8.09 (1H, m). IR (KBr) ν (cm^{-1}): 1700, 1370, 1170. MS *m/z*: 377 (M^+). *Anal.* Calcd for $C_{20}H_{27}NO_4S$: C, 63.63; H, 7.21; N, 3.71; S, 8.49. Found: C, 63.43; H, 7.35; N, 3.80; S, 8.42.

Ethyl 3-[2-Trimethylsilyl-1-(methylsulfonyl)indol-3-yl]propenoate (2e)

Accoding to the general procedure, the reaction using **1e** (134 mg) and ethyl propenoate (100 mg) for 1 h gave **2c** (58 mg) in 32% yield as colorless needles (hexane). mp 82 - 84℃. ^1H NMR ($CDCl_3$) δ : 0.50 (9H, s), 1.36 (3H, t, J = 7.5 Hz), 2.95 (3H, s), 4.30 (2H, q, J = 7.5 Hz), 6.44 (1H, d, J = 16.2 Hz), 7.26 - 7.42 (2H, m), 7.82 (1H, d, J = 7.1 Hz), 8.04 (1H, d, J = 8.2 Hz), 8.07 (1H, d, J = 16.2 Hz). IR (KBr) ν (cm^{-1}): 1710, 1360, 1170. MS *m/z*: 377 (M^+). *Anal.* Calcd for $C_{17}H_{23}NO_4SSi$: C, 55.86; H, 6.34; N, 3.83. Found: C, 55.90; H, 6.35; N, 3.99.

4-[1-Methylsulfonyl)-2-phenylindol-3-yl]but-3-en-2-one (2f)

Accoding to the general procedure, the reaction using **1a** (135 mg) and 3-buten-1-one (70 mg) for 1.5 h gave **2f** (94 mg) in 55 % colorless needles (MeOH). mp 152 - 156℃. ^1H NMR ($CDCl_3$) δ : 2.21 (3H, s), 2.91 (3H, s), 6.83 (1H, d, J = 16.6 Hz), 7.28 (1H, d, J = 16.6 Hz), 7.37 - 7.54 (7H, m), 7.95 (1H, dd, J = 4.2, 4.7 Hz), 8.18 (1H, dd, J = 4.2, 4.7 Hz). IR (KBr) ν (cm^{-1}): 1710, 1370, 1170. MS *m/z*: 339 (M^+). *Anal.* Calcd for $C_{19}H_{17}NO_3S$: C, 67.24; H, 5.05; N, 4.13; S, 9.45. Found: C, 67.22; H, 5.15; N,

4.11; S, 9.50.

3-[1-Methylsulfonyl)-2-phenylindol-3-yl]propenal (3c)

Accoding to the general procedure, the reaction using **1a** (135 mg) and propenal (56 mg) for 1.5 h gave **3g** (78 mg) in 48 % colorless needles (acetone - hexane). mp 228 - 232℃. ^{1}H NMR ($CDCl_3$) δ : 2.97 (3H, s), 6.83 (1H, dd, J = 7.7, 16.2 Hz), 7.22 (1H, d, J = 16.2 Hz), 7.45 - 7.58 (7H, m), 7.95 (1H, dd, J = 2.4, 5.2 Hz), 8.71 (1H, dd, J = 2.4, 5.2 Hz), 9.48 (1H, d, J = 7.7 Hz). IR (KBr) ν (cm^{-1}): 1680, 1370, 1180. MS *m/z*: 325 (M^+). *Anal.* Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30; S, 9.85. Found: C, 66.10; H, 4.75; N, 4.67; S, 9.90.

Reaction of 1a with Ethenylbenzene

Acooding to the general procedure, the reaction using **1a** (135 mg) and ethenylbenzene (104 mg) for 1.5 h gave **3** in 64 % (130 mg,) as colorless needles and **2h** in 16% (30 mg) as colorless needles.

1-Methylsulfonyl-2-phenyl-3-(2-chloro-2-phenylethyl)indole (3)

mp 133℃ (Et_2O - hexane). ^{1}H NMR ($CDCl_3$) δ : 2.74 (3H, s), 3.22 (1H, dd, J = 8.3, 14.3 Hz), 3.43 (1H, dd, J = 7.2, 14.3 Hz), 5.14 (1H, t, J = 7.2 Hz), 7.07 - 7.64 (13H, m), 8.13 (1H, t, J = 3.8 Hz). MS *m/z*: 409 (M^+). HRMS calcd for $C_{23}H_{20}NO_2ClS$: 409.0871. Found: 409.0887. IR (KBr) ν (cm^{-1}): 1360, 1170. *Anal.* Calcd for $C_{23}H_{20}NO_2ClS$: C, 67.39; H, 4.92; N, 3.42; S, 7.82. Found: C, 67.42; H, 5.07; N, 3.56; S, 7.89.

N-Methylsufonyl-2-phenyl-3-(2-phenyl)ethenylindole (2h)

mp 141 - 142℃ (Et_2O - hexane). ^{1}H NMR ($CDCl_3$) δ : 2.84 (3H, s), 6.87 (1H, dd, J = 7.7, 16.8 Hz), 7.20 - 7.50 (12H, m), 8.05 (1H, dd, J = 3.0, 4.9 Hz), 8.21 (1H, dd, J = 3.0, 4.9 Hz). MS *m/z*: 365 (M^+). HRMS calcd for $C_{23}H_{19}NO_2S$: 365.1116. Found: 365.1124. *Anal.* Calcd for $C_{23}H_{19}NO_2S$: C, 73.09; H, 5.20; N, 3.71; S, 8.60. Found: C, 73.23; H, 5.30; N, 3.96; S, 8.48.

Ethyl 3-[1-(Ethoxycarbonyl)-5-cyano-2-phenylindol-3-yl]prop-2-enoate (2i)

Acooding to the general procedure, the reaction using **1f** (135 mg) and ethyl propenoate (100 mg) for 1.5 h gave **2f** in 40% (77 mg) as a pale yellow liquid. bp 141 - 142℃ / 32 mmHg. ^{1}H NMR ($CDCl_3$)δ : 0.95 (3H, t, J = 7.1 Hz), 1.31 (3H, t, J = 7.1 Hz), 4.14 - 4.26 (4H, m), 6.48 (1H, d, J = 16.5 Hz), 7.26 - 7.52 (6H, m), 7.67 (1H, dd, J = 1.6, 8.8 Hz), 8.23 (1H, s), 8.38 (1H, d, J = 8.8 Hz). IR (KBr) ν (cm^{-1}): 1710, 1360, 1170. MS *m/z*: 393 (M^+). HRMS calcd for $C_{23}H_{23}NO_5$: 393.1576. Found: 393.1581.

Ethyl 3-[1-(Ethoxycarbonyl)-6-methoxy-2-phenylindol-3-yl]prop-2-enoate (2g)

Acooding to the general procedure, the reaction using **1g** (135 mg) and ethyl propenoate (100 mg) for 1.5 h gave **2g** in 26% (51 mg) as a pale yellow liquid. bp 208 - 215℃ / 32 mmHg. ^{1}H NMR ($CDCl_3$) δ : 0.94 (3H, t, J = 7.1 Hz), 1.28 (3H, t, J = 14.3 Hz), 3.90 (3H, s), 4.10 - 4.24 (4H, m), 6.52 (1H, d, J = 16.2 Hz), 7.00 (1H, dd, J = 2.2, 8.7 Hz), 7.31 - 7.45 (6H, m), 7.80 (1H, d, J = 8.8 Hz), 7.87 (1H, d, J = 2.2 Hz). IR (KBr) ν (cm^{-1}): 1730, 1210. MS *m/z*: 393 (M^+). HRMS calcd for $C_{23}H_{23}NO_5$: 393.1576.

Found: 393.1581.

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