

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

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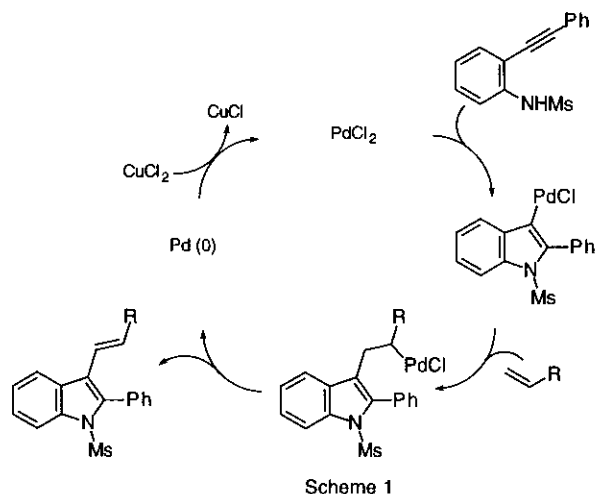
Abstract - The reaction of *N*-protected 2-alkynylanilines with electron-deficient alkenes in the presence of a palladium(II) catalyst and copper dichloride in acetonitrile gave 2-substituted 3-alkenylindoles.

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-aryloxyindoles 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 aryloxy-palladium(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 aryloxy-palladium halides which are reproducible by the oxidative addition reaction of palladium(0) species to allyl 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.



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°C gave the expected product, ethyl 3-[1-phenylsulfonyl-2-phenylindol-3-yl]prop-2-enoate (**2a**) in 74% yield (Entry 1 in Table 1).

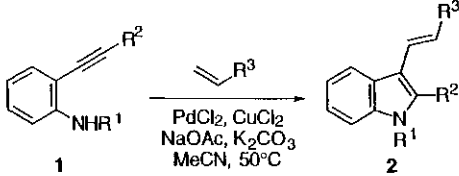
Table I Palladium (II) catalyzed cyclization / Heck reaction of **1a** with ethyl acrylate

Entry	Pd(II)	Oxidant	Base	Time (h)	Yield (%)
1	PdCl ₂	CuCl ₂	K ₂ CO ₃ , NaOAc	16	29
2	PdCl ₂	CuCl ₂	K ₂ CO ₃ , NaOAc	1.5	74
3	PdCl ₂	CuCl ₂	K ₂ CO ₃ , NaOAc	1.5	42
4	Pd(OAc) ₂	CuCl ₂	K ₂ CO ₃ , NaOAc	1.5	50
5	PdCl ₂	Cu(OAc) ₂	K ₂ CO ₃ , NaOAc	2	3
6	PdCl ₂	CuCl ₂	K ₂ CO 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°C to give ethyl 2-substituted 3-(indol-3-yl)propenoate in 32–74% yields.

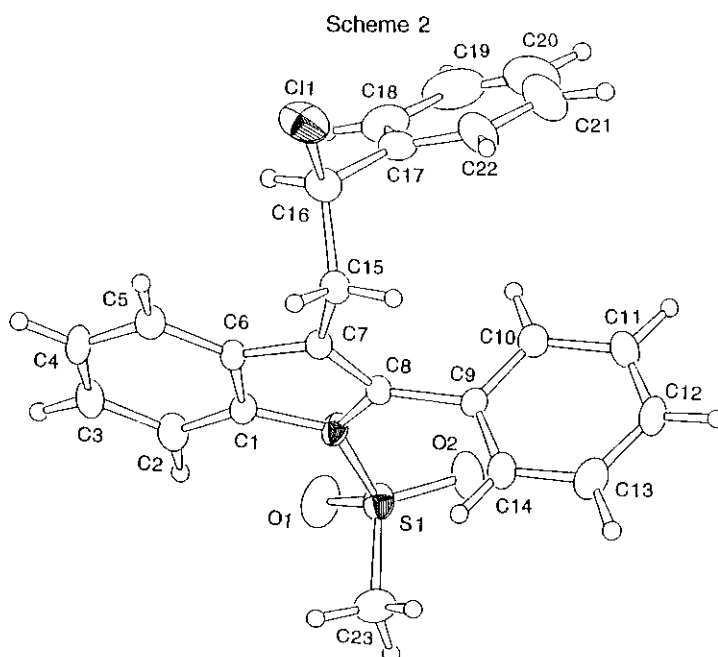
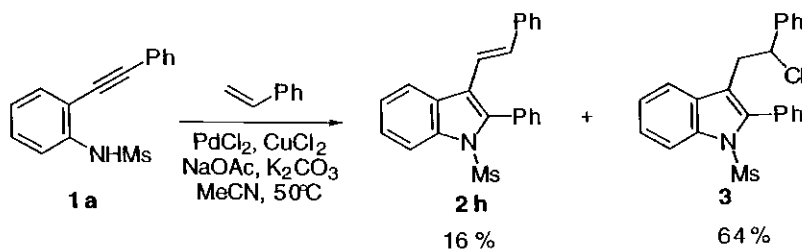
It has been reported that the cyclization reaction of trimethylsilylethynylanilines does not proceed or produce the desilylated indoles instead of the expected 2-silylated derivatives.² But the reaction of the trimethylsilylethynyl derivative (**1e**) with ethyl propenoate gave the 2-trimethylsilylindole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

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

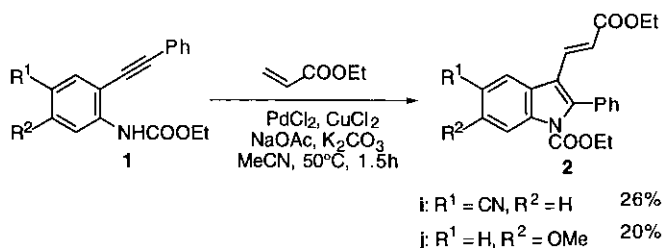


Entry	1	R ¹	R ²	R ³	Time (h)	Yield (%)	2
1	a	Ms	Ph	COOEt	1	74	a
2	b	PhSO ₂	Ph	COOEt	1	51	b
3	c	COOEt	Ph	COOEt	1	34	c
4	d	Ms	Hex	COOEt	1	46	d
5	e	Ms	TMS	COOEt	1	32	e
6	a	Ms	Ph	Ac	1.5	55	f
7	a	Ms	Ph	CHO	1.5	48	g

As shown in Scheme 2, the reaction of **1a** with ethenylbenzene was proceeded for 1.5 h at 50°C 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).

Figure 1. ORTEP View of **3**

When substituted 2-ethynylaniline derivatives (**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).



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.

ACKNOWLEDGEMENT

Our special thanks are due to Prof. H. Oshio for analysis of X-Ray crystallography. This research was supported in part by Fujisawa Pharmaceutical Co., Ltd. Award in Synthetic Organic Chemistry, Japan.

EXPERIMENTAL

All melting points and boiling points are uncorrected. IR spectra were measured on a JASCO IR-810 spectrophotometer. $^1\text{H-NMR}$ 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), $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (1.0 mmol), NaOAc (1.0 mmol), and K_2CO_3 (1.0 mmol) in MeCN (6 mL) was stirred at 50°C . 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**)

According 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 $159\text{--}160^\circ\text{C}$. $^1\text{H NMR}$ (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 $\text{C}_{20}\text{H}_{19}\text{NO}_4\text{S}$: 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)

According 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 (Et₂O - hexane). mp 158°C. ¹H NMR (CDCl₃) 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 C₂₅H₂₁NO₄S: 431.1190. Found: 431.1165. Anal. Calcd for C₂₅H₂₁NO₄S(1/3 H₂O): 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)

According 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°C / 32 mmHg. ¹H NMR (CDCl₃) 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 C₂₂H₂₁NO₄: 363.1469. Found: 363.1465.

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

According 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 (Et₂O - hexane). mp 90 - 91°C. ¹H NMR (CDCl₃) 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 C₂₀H₂₇NO₄S: 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)

According 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°C. ¹H NMR (CDCl₃) 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 C₁₇H₂₃NO₄SSi: 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)

According 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% yield as colorless needles (MeOH). mp 152 - 156°C. ¹H NMR (CDCl₃) 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 C₁₉H₁₇NO₃S: 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)

According 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°C. ¹H NMR (CDCl₃) 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 C₁₈H₁₅NO₃S: 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

According 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°C (Et₂O - hexane). ¹H NMR (CDCl₃) 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 C₂₃H₂₀NO₂ClS: 409.0871. Found: 409.0887. IR (KBr) ν (cm⁻¹): 1360, 1170. Anal. Calcd for C₂₃H₂₀NO₂ClS: 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-Methylsulfonyl-2-phenyl-3-(2-phenyl)ethenylindole (2h)

mp 141 - 142°C (Et₂O - hexane). ¹H NMR (CDCl₃) 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 C₂₃H₁₉NO₂S: 365.1116. Found: 365.1124. Anal. Calcd for C₂₃H₁₉NO₂S: 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)

According 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°C / 32 mmHg. ¹H NMR (CDCl₃) 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 C₂₃H₂₃NO₅: 393.1576. Found: 393.1581.

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

According 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°C / 32 mmHg. ¹H NMR (CDCl₃) 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 C₂₃H₂₃NO₅: 393.1576.

Found: 393.1581.

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Received, 23rd April, 1998