

A CONCISE SYNTHESIS OF 7-SUBSTITUTED INDOLES

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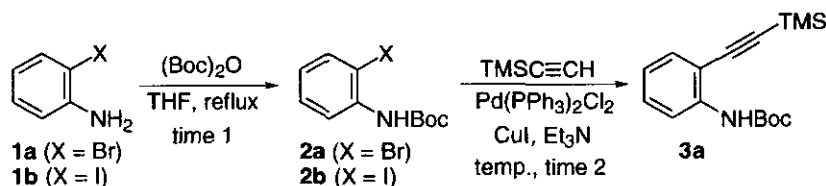
Abstract - 7-Substituted indoles were synthesized by the basic cyclization of 6-substituted *tert*-butyl 2-(trimethylsilylethynyl)phenylcarbamates which were derived by the lithiation of *tert*-butyl 2-(trimethylsilylethynyl)phenylcarbamate and the subsequent reaction with electrophiles.

In our previous work, we discovered a novel cyclization of ethyl 2-ethynylphenylcarbamates to indoles in the presence of sodium ethoxide in ethanol.¹ The indole formation has been used as a key step of synthesis of some natural indole derivatives.²

On the other hand, ortho lithiation of substituted benzenes is a powerful method for the preparation of synthetically useful aryllithium intermediates. Studies to date indicate that some of directing metalation groups such as pivaroilamino³ or *tert*-butoxycarbonylamino group⁴ can be used to achieve metalation of aniline derivatives.

In this paper, we report here a concise synthesis of 7-substituted indoles by combination of the lithiation of *tert*-butyl ethynylphenylcarbamates and our indole cyclization.

tert-Butyl 2-bromo- (**2a**) and 2-iodophenylcarbamate (**2b**) were respectively prepared from the reaction of 2-bromo- (**1a**) and 2-iodoaniline (**1b**) with di-*tert*-butyl dicarbonate in good yields. While palladium-catalyzed cross-coupling of **2a** with trimethylsilylacetylene under relatively severe conditions gave *tert*-butyl 2-(trimethylsilylethynyl)phenylcarbamate (**3a**) in only 50% yield, the same reaction of **2b** under milder conditions afforded **3a** in good yield as shown below.



Compound	X	Time 1 (h)	Yield (%)
1a	Br	91	89
1b	I	114	86

Compound	Temp. (°C)	Time 2 (h)	Yield (%)
2a	100 (sealed tube)	13	50
2b	room temp.	0.25	95

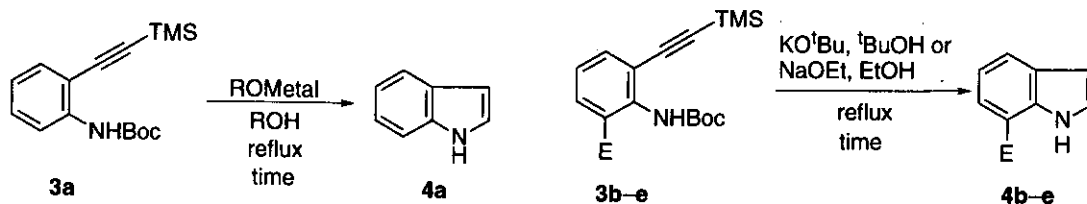
The lithiation of **3a** with *tert*-butyllithium in ether at -20°C followed by the reaction with 1,2-dibromoethane, iodine, and prenyl bromide gave the corresponding *tert*-butyl 6-bromo-, 6-iodo-, and 6-prenyl-2-(trimethylsilylethynyl)phenylcarbamates (**3b-d**) in moderate yields, but the yield of **3e** with *O,N*-dimethylbenzoylhydroxylamine was somewhat low.

Table I. Preparation of *tert*-Butyl 6-Substituted 2-(Trimethylsilylethynyl)phenylcarbamates

Electrophile	Temp. ($^{\circ}\text{C}$)	Time (h)	Product	E	Yield (%)
$\text{BrCH}_2\text{CH}_2\text{Br}$	$-100 \rightarrow \text{room temp.}$	overnight	3b	Br	61
I_2	-100	0.5	3c	I	50
$\text{Me}_2\text{C}=\text{CHCH}_2\text{Br}$	$-100 \rightarrow \text{room temp.}$	overnight	3d	$\text{Me}_2\text{C}=\text{CHCH}_2$	56
$\text{PhCON}(\text{OMe})\text{Me}$	$-100 \rightarrow \text{room temp.}$	overnight	3e	PhCO	24

In order to obtain best cyclization conditions of **3b-e**, *tert*-butyl 2-(trimethylsilylethynyl)phenylcarbamate (**3a**) was treated with some alkali metal alkoxides in the corresponding alcohols. As shown in Table II, cyclization of **3a** with sodium ethoxide in ethanol and with potassium *tert*-butoxide in *tert*-butanol gave good results. Application of the two cyclization conditions to **3b-e** gave generally good results and a concise synthesis of 7-substituted indoles was achieved.

Tables II and III. Cyclization of *tert*-Butyl 2-(Trimethylsilylethynyl)phenylcarbamates to Indoles



R	Metal	Time (h)	Yield (%)
Me	Na	24	10
Et	Na	9	89
^tBu	Na	22	60
^tBu	K	3	87
^tBu	Li	48	19

Product	$\text{KO}^t\text{Bu, } ^t\text{BuOH}$		NaOEt, EtOH	
	Time (h)	Yield (%)	Time (h)	Yield (%)
4b	3	60	2	77
4c	8	70	3	67
4d	8	66	7.5	61
4e	7	78	15	33

EXPERIMENTAL

General Comments

THF and Et₂O were distilled from sodium/benzophenone ketyl before use. MeOH was distilled from sodium, EtOH was distilled from magnesium, and *tert*-BuOH was distilled from CaH₂ before use. *n*-BuLi and *tert*-BuLi was titrated using 2,5-dimethoxybenzyl alcohol before use. All melting points and boiling points are uncorrected. IR spectra were taken on a JASCO ir-810 spectrophotometer. ¹H-Nmr spectra were recorded on a Varian Gemini 2000 (300 M Hz), and a Hitachi R-3000 (300 MHz) spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) as the internal references, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet, dt=double triplet, and br=broad. Mass spectra (ms) and high resolution mass spectra (HRms) were recorded on a JMS-DX303 and a JMS-AX500 instruments.

tert-Butyl 2-Bromophenylcarbamate (2a)

A mixture of 2-bromoaniline (**1a**) (1.720 g, 10 mmol) and di-*tert*-butyl dicarbonate (6.9 ml, 30 mmol) in THF (20 ml) was refluxed for 91 h. The solvent was evaporated under reduced pressure. To the residue, H₂O (20 ml) was added, and the mixture was extracted with Et₂O (40 ml x 3). The ethereal extract was washed with satd. aq. NaCl solution (30 ml) and dried over MgSO₄. The crude product obtained from the ethereal extract was purified by silica gel (200 g) column chromatography using AcOEt-hexane (1:99) to give a pale yellow liquid which was distilled under reduced pressure. Yield 2.424 g (89 %). bp 100°C/4 mmHg. 300 MHz ¹H-nmr (CDCl₃/TMS) δ (ppm): 1.54 (9H, s), 6.90 (1H, dt, *J*=1.4, 7.7 Hz), 7.00 (1H, br), 7.28 (1H, dt, *J*=1.4, 7.7 Hz), 7.50 (1H, dd, *J*=1.6, 8.0 Hz), 8.15 (1H, dd, *J*=1.6, 8.5 Hz). IR ν (CHCl₃) cm⁻¹: 3415, 1730. Ms *m/z*: 271 (M⁺). HRms Calcd for C₁₁H₁₄NO₂Br 271.0208. Found: 271.0193.

tert-Butyl 2-Iodophenylcarbamate (2b)

bp 140°C/4 mmHg. 300 MHz ¹H-nmr (CDCl₃/TMS) δ (ppm): 1.54 (9H, s), 6.76 (1H, t, *J*=7.7 Hz), 6.81 (1H, br), 7.31 (1H, t, *J*=7.9 Hz), 7.74 (1H, d, *J*=8.1 Hz), 8.04 (1H, d, *J*=8.1 Hz). IR ν (CHCl₃) cm⁻¹: 3400, 1730. Ms *m/z*: 319 (M⁺). Anal. Calcd for C₁₁H₁₄NO₂I: C, 41.40; H, 4.42; N, 4.39; I, 39.76. Found: C, 41.63; H, 4.09; N, 4.46; I, 39.76.

tert-Butyl 2-(Trimethylsilylethynyl)phenylcarbamate (3a)

A mixture of **2b** (1.597 g, 5.0 mmol), trimethylsilylacetylene (1.06 ml, 7.5 mmol), Pd(PPh₃)₂Cl₂ (176 mg, 0.3 mmol), CuI (48 mg, 0.3 mmol), and Et₃N (10 ml) was stirred at room temperature for 15 min. To the reaction mixture, was added H₂O (50 ml), and Et₂O (50 ml) and the whole was filtered through Celite® pad. The filtrate was extracted with Et₂O (50 ml x 2). The ethereal extract was washed with satd. aq. NaCl solution (50 ml), dried over MgSO₄ and evaporated under reduced pressure. The residue was purified by silica gel (70 g) column chromatography using AcOEt-hexane (1:50) to give a pale yellow liquid which was distilled under reduced pressure. Yield 1.373 g (95 %). bp 115°C/2 mmHg. 300 MHz ¹H-nmr (CDCl₃/TMS) δ (ppm): 0.29 (9H, s), 1.53 (9H, s), 6.93 (1H, t, *J*=7.7 Hz), 7.37-7.26 (3H, m), 8.10

(1H, d, $J=8.4$ Hz). Ir v (CHCl_3) cm^{-1} : 3400, 2150, 1725. Ms m/z : 289 (M^+). HRms Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_2\text{Si}$: 289.1497. Found: 289.1497.

***tert*-Butyl 6-Bromo-2-(trimethylsilylethynyl)phenylcarbamate (3b)-Typical Procedure for Directed Lithiation**

Addition of 1.04 M *tert*-butyllithium in pentane (5.1 ml, 5.3 mmol) to a solution of 3a (700 mg, 2.4 mmol) in Et_2O (5 ml) at -20°C under argon atmosphere followed by stirring for 3 h. To the mixture, was added 1,2-dibromoethane (0.25 ml, 2.9 mmol) at -100°C , and the whole was gradually warmed up to room temperature and stirred overnight. After addition of satd. aq. NaCl solution (20 ml), the mixture was extracted with Et_2O (20 ml x 3). The ethereal extract was washed with satd. aq. NaCl solution (10 ml), dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by silica gel (50 g) chromatography using AcOEt-hexane (1:200). The crude product was recrystallized from hexane to give colorless prisms. Yield 543 mg (61%). mp $86 - 88^\circ\text{C}$. 300 MHz ^1H -nmr (CDCl_3/TMS) δ (ppm): 0.25 (9H, s), 1.51 (9H, s), 6.30 (1H, br), 7.03 (1H, t, $J=7.7$ Hz), 7.42 (1H, dd, $J=1.1, 7.7$ Hz), 7.55 (1H, dd, $J=1.5, 8.1$ Hz). Ir v (CHCl_3) cm^{-1} : 3425, 2170, 1735. Ms m/z : 367 (M^+). HRms Calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_2\text{BrSi}$: 367.0602. Found: 367.0650. Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_2\text{BrSi}$: C, 52.17; H, 6.02; N, 3.80; Br, 21.69. Found: C, 52.02; H, 6.05; N, 3.81; Br, 21.48.

***tert*-Butyl 6-Iodo-2-(trimethylsilylethynyl)phenylcarbamate (3c)**

Colorless prisms from hexane. Mp $89 - 91^\circ\text{C}$. 300 MHz ^1H -nmr (CDCl_3/TMS) δ (ppm): 0.25 (9H, s), 1.51 (9H, s), 6.37 (1H, br), 6.89 (1H, t, $J=7.7$ Hz), 7.45 (1H, dd, $J=1.5, 7.9$ Hz), 7.81 (1H, dd, $J=1.5, 7.9$ Hz). Ir v (CHCl_3) cm^{-1} : 3430, 2170, 1735. Ms m/z : 415 (M^+). HRms Calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_2\text{ISi}$: 415.0462. Found: 415.0442. Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_2\text{ISi}$: C, 46.27; H, 5.34; N, 3.37; I, 30.55. Found: C, 46.15; H, 5.25; N, 3.44; I, 30.84.

***tert*-Butyl 6-Prenyl-2-(trimethylsilylethynyl)phenylcarbamate (3d)**

Colorless prisms from hexane. Mp $92 - 95^\circ\text{C}$. 300 MHz ^1H -nmr (CDCl_3/TMS) δ (ppm): 0.25 (9H, s), 1.49 (9H, s), 1.71 (3H, s), 1.73 (3H, s), 3.35 (2H, d, $J=7.0$ Hz), 5.21-5.18 (1H, m), 6.33 (1H, br), 7.09 (1H, t, $J=7.7$ Hz), 7.18 (1H, d, $J=7.3$ Hz), 7.31 (1H, d, $J=7.7$ Hz). Ir v (CHCl_3) cm^{-1} : 3410, 2155, 1730. Ms m/z : 301. Anal. Calcd for $\text{C}_{21}\text{H}_{31}\text{NO}_2\text{Si}$: C, 70.54; H, 8.74; N, 3.92. Found: C, 70.36; H, 8.75; N, 3.75.

***tert*-Butyl 6-Benzoyl-2-(trimethylsilylethynyl)phenylcarbamate (3e)**

Colorless prisms from Et_2O -hexane. Mp $157 - 159^\circ\text{C}$. 300 MHz ^1H -nmr (CDCl_3/TMS) δ (ppm): 0.28 (9H, s), 1.29 (9H, s), 7.23 - 7.13 (2H, m), 7.75 - 7.39 (5H, m), 7.77 (2H, d, $J=7.0$ Hz). Ir v (CHCl_3) cm^{-1} : 3400, 2155, 1730, 1665. Ms m/z : 393 (M^+). HRms Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_3\text{Si}$: 393.1759. Found: 393.1768. Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_3\text{Si}$: C, 70.19; H, 6.91; N, 3.56. Found: C, 70.24; H, 6.88; N, 3.58.

Cyclization of 3a to Indole (4a)**a) With Sodium Methoxide**

A mixture of **3a** (145 mg, 0.5 mmol) and methanolic sodium methoxide prepared from methanol (10 ml) and sodium (57 mg, 2.5 mmol) was refluxed for 24 h under argon atmosphere. After removal of the solvent, H₂O (10 ml) was added to the residue, and the mixture was extracted with CHCl₃ (20 ml x 3). The CHCl₃ extract was washed with satd. aq. NaCl solution (20 ml), dried over MgSO₄, and evaporated under reduced pressure. The residue was purified by silica gel (10 g) column chromatography using AcOEt-hexane (1:40). The crude product was distilled under reduced pressure to give a colorless solid. Yield 6 mg (10 %).

b) With Sodium Ethoxide

A mixture of **3a** (290 mg, 1.0 mmol) and ethanolic sodium ethoxide prepared from ethanol (10 ml) and sodium (115 mg, 5.0 mmol) was refluxed for 9 h under argon atmosphere. After removal of the solvent, H₂O (20 ml) was added to the residue, and the mixture was extracted with CH₂Cl₂ (30 ml x 3). The residue obtained from the CH₂Cl₂ extract was distilled under reduced pressure to give a colorless solid. Yield 107 mg (89 %).

c) With Sodium *tert*-Butoxide

A mixture of **3a** (290 mg, 1.0 mmol) and *tert*-butanolic sodium *tert*-butoxide prepared from *tert*-butanol (17 ml) and sodium (115 mg, 5.0 mmol) was refluxed for 22 h under argon atmosphere. After removal of the solvent, H₂O (20 ml) was added to the residue and the mixture was extracted with CH₂Cl₂ (30 ml x 3). The residue obtained from the CH₂Cl₂ extract was purified by silica gel (12 g) column chromatography using AcOEt-hexane (1:10). The crude product was distilled under reduced pressure to give a colorless solid. Yield 78 mg (60 %).

d) With Potassium *tert*-Butoxide

A mixture of **3a** (145 mg, 0.5 mmol) and potassium *tert*-butoxide (281 mg, 2.5 mmol) in *tert*-butanol (5 ml) was refluxed for 3 h under argon atmosphere. After removal of the solvent, H₂O (20 ml) was added to the residue, and the mixture was extracted with CH₂Cl₂ (30 ml x 3). The residue obtained from the CH₂Cl₂ extract was purified by silica gel (6 g) column chromatography using AcOEt-hexane (1:5). The crude product was distilled under reduced pressure to give a colorless solid. Yield 51 mg (87%).

e) With Lithium *tert*-Butoxide

A mixture of **3a** (290 mg, 1.0 mmol) and *tert*-butanolic lithium *tert*-butoxide prepared from *tert*-butanol (17 ml) and lithium (35 mg, 5.0 mmol) was refluxed for 48 h under argon atmosphere. After removal of the solvent, H₂O (20 ml) was added to the residue, and the mixture was extracted with CHCl₃ (30 ml x 3). The residue obtained from the CHCl₃ extract was purified by silica gel (12 g) column chromatography using AcOEt-hexane (1:50). The crude product was distilled under reduced pressure to give a colorless solid. Yield 23 mg (19%).

mp 50 - 52°C (lit.,⁵ mp 53°C). bp 50°C/3 mmHg

7-Bromoindole (7a)

Colorless scales from hexane. Mp 45 - 46°C (lit.,⁵ mp 45.0 - 45.5°C). 300 MHz ¹H-nmr (CDCl₃/TMS) δ (ppm): 6.63 (1H, t, *J*=2.9 Hz), 7.00 (1H, t, *J*=7.7 Hz), 7.26 (1H, t, *J*=2.9 Hz), 7.34 (1H, d, *J*=7.7

Hz), 7.57 (1H, d, $J=8.1$ Hz), 8.33 (1H, br). Ir v (CHCl₃) cm⁻¹: 3465. Ms m/z : 195 (M⁺). HRms Calcd for C₈H₆NBr: 194.9684. Found: 194.9697. Anal. Calcd for C₈H₆NBr: C, 49.01; H, 3.08; N, 7.14. Found: C, 49.04; H, 3.20; N, 7.17.

7-Iodoindole (10b)

Colorless scales from hexane. Mp 55 - 56°C (lit.,⁶ mp 55 - 56°C). 300 MHz ¹H-nmr (CDCl₃/TMS) δ (ppm): 6.69 (1H, dd, $J=2.2, 2.9$ Hz), 6.89 (1H, t, $J=7.7$ Hz), 7.26 (1H, t, $J=3.3$ Hz), 7.54 (1H, d, $J=7.3$ Hz), 7.60 (1H, d, $J=8.1$ Hz), 8.25 (1H, br). Ir v (CHCl₃) cm⁻¹: 3455. Ms m/z : 243 (M⁺). HRms Calcd for C₈H₆NI: 242.9543. Found: 242.9543. Anal. Calcd for C₈H₆NI: C, 39.53; H, 2.49; N, 5.76. Found: C, 39.79; H, 2.58; N, 5.70.

7-Prenylindole (10c)

Colorless prisms from hexane. Mp 42 - 44°C (lit.,⁵ mp 43 - 44°C). 300 MHz ¹H-nmr (CDCl₃/TMS) δ (ppm): 1.78 (3H, s), 1.83 (3H, s), 3.58 (2H, d, $J=7.0$ Hz), 5.45-5.39 (1H, m), 6.56 (1H, dd, $J=2.2, 2.9$ Hz), 7.08-6.98 (2H, m), 7.20 (1H, t, $J=2.6$ Hz), 7.51 (1H, d, $J=7.7$ Hz), 8.16 (1H, br). Ir v (CHCl₃) cm⁻¹: 3490. Ms m/z : 185 (M⁺). HRms Calcd for C₁₃H₁₅N: 185.1204. Found: 185.1198.

7-Benzoylindole (10d)

Pale yellow needles from Et₂O-hexane. Mp 104 - 105°C (lit.,⁷ mp 103 - 104°C). 300 MHz ¹H-nmr (CDCl₃/TMS) δ (ppm): 6.66 (1H, t, $J=3.3$ Hz), 7.16 (1H, t, $J=7.7$ Hz), 7.40 (1H, t, $J=2.9$ Hz), 7.62-7.48 (4H, m), 7.77 (2H, dd, $J=1.8, 8.2$ Hz), 7.93 (1H, d, $J=7.7$ Hz), 10.41 (1H, br). Ir v (CHCl₃) cm⁻¹: 3460, 1635. Ms m/z : 221 (M⁺). HRms Calcd for C₁₅H₁₁NO: 221.0840. Found: 221.0810.

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Received, 2nd September, 1996