# A CONCISE SYNTHESIS OF 7-SUBSTITUTED INDOLES

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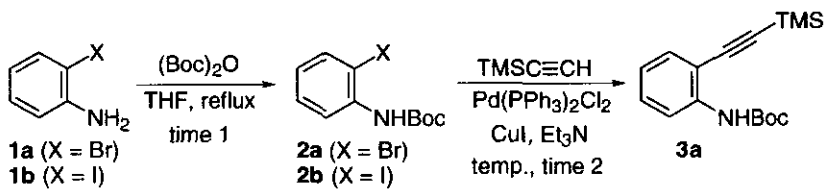
**Abstract** - 7-Substituted indoles were synthesized by the basic cyclization of 6-substituted *tert*-butyl 2-(trimethylsilylethynyl)phenylcarbamates which were derived by the lithiation of *tert*-butyl 2- (trimethylsilylethynyl)phenylcarbamate and the subsequent reaction with electrophiles.

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 pivaroylamino[3] or *tert*-butoxycarbonylamino group[4] 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.




**1a** (X = Br)
**1b** (X = I)

**2a** (X = Br)
**2b** (X = I)

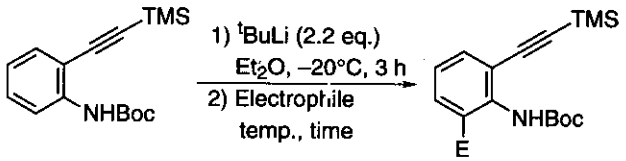
**3a**

| 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℃ 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

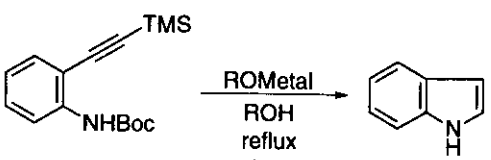



**3a** **3b–e**

| Electrophile | Temp. (°C) | Time (h) | Product | E | Yield (%) |
|---|---|---|---|---|---|
| $BrCH_2CH_2Br$ | –100 → room temp. | overnight | **3b** | Br | 61 |
| $I_2$ | –100 | 0.5 | **3c** | I | 50 |
| $Me_2C{=}CHCH_2Br$ | –100 → room temp. | overnight | **3d** | $Me_2C{=}CHCH_2$ | 56 |
| PhCON(OMe)Me | –100 → room temp. | overnight | **3e** | PhCO | 24 |

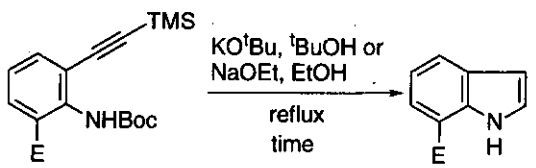
In order to obtain best cyclization conditions of **3b-e**, *tert*-butyl 2-(trimethylsilylethynyl)phenylcarbamate (**3a**) was treated with some alkali metal alkoxides in the corresponding alcohols. As shown in Table II, cyclization of **3a** with sodium ethoxide in ethanol and with potassium *tert*-butoxide 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




**3a** **4a**

| 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 |




**3b–e** **4b–e**

| | KO$^t$Bu, $^t$BuOH | | NaOEt, EtOH | |
|---|---|---|---|---|
| Product | 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 |

## EXPERIMETNAL

### General Comments

THF and $Et_2O$ were distilled from sodium/benzophenone ketyl before use. MeOH was distilled from sodium, EtOH was distilled from magnesium, and *tert*-BuOH was distilled from $CaH_2$ 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. $^1$H-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, $H_2O$ (20 ml) was added, and the mixture was extracted with $Et_2O$ (40 ml x 3). The ethereal extract was washed with satd. aq. NaCl solution (30 ml) and dried over $MgSO_4$. 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 $^1$H-nmr ($CDCl_3$/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 ($CHCl_3$) cm$^{-1}$: 3415, 1730. Ms *m/z*: 271 ($M^+$). HRms Calcd for $C_{11}H_{14}NO_2Br$ 271.0208. Found: 271.0193.

### *tert*-Butyl 2-Iodophenylcarbamate (2b)

bp 140°C/4 mmHg. 300 MHz $^1$H-nmr ($CDCl_3$/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 ($CHCl_3$) cm$^{-1}$: 3400, 1730. Ms *m/z*: 319 ($M^+$). *Anal.* Calcd for $C_{11}H_{14}NO_2I$ : 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), $Pd(PPh_3)_2Cl_2$ (176 mg, 0.3 mmol), CuI (48 mg, 0.3 mmol), and $Et_3N$ (10 ml) was stirred at room temperature for 15 min. To the reaction mixture, was added $H_2O$ (50 ml), and $Et_2O$ (50 ml) and the whole was filtered through Celite® pad. The filtrate was extracted with $Et_2O$ (50 ml x 2). The ethereal extract was washed with satd. aq. NaCl solution (50 ml), dried over $MgSO_4$ 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℃/2 mmHg. 300 MHz $^1$H-nmr ($CDCl_3$/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 ν ($CHCl_3$) $cm^{-1}$: 3400, 2150, 1725. Ms *m/z*: 289 ($M^+$). HRms Calcd for $C_{16}H_{23}NO_2Si$: 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℃ 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℃, 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 slica 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℃. 300 MHz $^1$H-nmr ($CDCl_3$/TMS) $\delta$ (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 ν ($CHCl_3$) $cm^{-1}$: 3425, 2170, 1735. Ms *m/z*: 367 ($M^+$). HRms Calcd for $C_{16}H_{22}NO_2BrSi$: 367.0602. Found: 367.0650. *Anal.* Calcd for $C_{16}H_{22}NO_2BrSi$: 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℃. 300 MHz $^1$H-nmr ($CDCl_3$/TMS) $\delta$ (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 ν ($CHCl_3$) $cm^{-1}$: 3430, 2170, 1735. Ms *m/z*: 415 ($M^+$). HRms Calcd for $C_{16}H_{22}NO_2ISi$: 415.0462. Found: 415.0442. *Anal.* Calcd for $C_{16}H_{22}NO_2ISi$: 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℃. 300 MHz $^1$H-nmr ($CDCl_3$/TMS) $\delta$ (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 ν ($CHCl_3$) $cm^{-1}$: 3410, 2155, 1730. Ms *m/z*: 301. *Anal.* Calcd for $C_{21}H_{31}NO_2Si$: 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℃. 300 MHz $^1$H-nmr ($CDCl_3$/TMS) $\delta$ (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 ν ($CHCl_3$) $cm^{-1}$: 3400, 2155, 1730, 1665. Ms *m/z*: 393 ($M^+$). HRms Calcd for $C_{23}H_{27}NO_3Si$: 393.1759. Found: 393.1768. *Anal.* Calcd for $C_{23}H_{27}NO_3Si$: 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, $H_2O$ (10 ml) was added to the residue, and the mixture was extracted with $CHCl_3$ (20 ml x 3). The $CHCl_3$ extract was washed with satd. aq. NaCl solution (20 ml), dried over $MgSO_4$, 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, $H_2O$ (20 ml) was added to the residue, and the mixture was extracted with $CH_2Cl_2$ (30 ml x 3). The residue obtained from the $CH_2Cl_2$ 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, $H_2O$ (20 ml) was added to the residue and the mixture was extracted with $CH_2Cl_2$ (30 ml x 3). The residue obtained from the $CH_2Cl_2$ 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, $H_2O$ (20 ml) was added to the residue, and the mixture was extracted with $CH_2Cl_2$ (30 ml x 3). The residue obtained from the $CH_2Cl_2$ 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, $H_2O$ (20 ml) was added to the residue, and the mixture was extracted with $CHCl_3$ (30 ml x 3). The residue obtained from the $CHCl_3$ 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℃ (lit.,[5] mp 53℃). bp 50℃/3 mmHg

**7-Bromoindole (7a)**

Colorless scales from hexane. Mp 45 - 46℃ (lit.,[5] mp 45.0 - 45.5℃). 300 MHz $^1$H-nmr ($CDCl_3$/TMS) $\delta$ (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 ν ($CHCl_3$) $cm^{-1}$: 3465. Ms *m/z*: 195 ($M^+$). HRms Calcd for $C_8H_6NBr$: 194.9684. Found: 194.9697. *Anal.* Calcd for $C_8H_6NBr$: 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℃ (lit.,[6] mp 55 - 56℃). 300 MHz $^1$H-nmr ($CDCl_3$/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 ν ($CHCl_3$) $cm^{-1}$: 3455. Ms *m/z*: 243 ($M^+$). HRms Calcd for $C_8H_6NI$: 242.9543. Found: 242.9543. *Anal.* Calcd for $C_8H_6NI$: 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℃ (lit.,[5] mp 43 - 44℃). 300 MHz $^1$H-nmr ($CDCl_3$/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 ν ($CHCl_3$) $cm^{-1}$: 3490. Ms *m/z*: 185 ($M^+$). HRms Calcd for $C_{13}H_{15}N$: 185.1204. Found: 185.1198.

**7-Benzoylindole (10d)**

Pale yellow needles from $Et_2O$-hexane. Mp 104 - 105℃ (lit.,[7] mp 103 - 104℃). 300 MHz $^1$H-nmr ($CDCl_3$/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 ν ($CHCl_3$) $cm^{-1}$: 3460, 1635. Ms *m/z*: 221 ($M^+$). HRms Calcd for $C_{15}H_{11}NO$: 221.0840. Found: 221.0810.

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Received, 2nd September, 1996