General and Facile Synthesis of Indoles with Oxygen-Bearing Substituents at the Benzene Moiety

Yoshinori Kondo,* Satoshi Kojima, and Takao Sakamoto*

Faculty of Pharmaceutical Sciences, Tohoku University, Aramaki-aza Aoba, Aoba-ku, Sendai 980-77, Japan

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Indoles with oxygen-bearing substituents such as a methoxy or (triisopropylsilyl)oxy group at all of the positions of the benzene moiety were synthesized by cyclization of *tert*-butyl methoxy(or (triisopropylsilyl)oxy)-2-((trimethylsilyl)ethynyl)phenyl)carbamates with potassium *tert*-butoxide in *tert*-butyl alcohol. The (ethynylphenyl)carbamates were synthesized by the palladium-catalyzed reaction of (trimethylsilyl)acetylene and the corresponding (iodophenyl)carbamates, which were selectively synthesized by directed lithiation of the phenylcarbamates and subsequent iodination.

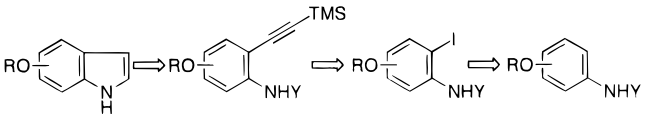
Introduction

Many indole derivatives with oxygen-bearing substituents, such as a hydroxy, alkoxy, or acyloxy group, at the benzene moiety are known to be synthetic medicines (*e.g.*, pindolol), physiologically active substances (*e.g.*, serotonin), and alkaloids (*e.g.*, reserpine). Many methods have been developed to synthesize indoles with oxygen-bearing functional groups at the benzene moiety. Among these methods, synthesis by cyclization is more widely used than the introduction of an oxygen-bearing functional group into indole rings.

However, cyclization reactions to synthesize oxygen-functionalized indoles at all of the positions of the benzene moiety have not been well developed.[1] The most commonly known indole cyclization reactions are limited and inadequate for the synthesis of oxygen-functionalized indoles. For example, Nenitzescu cyclization reactions have only been used to synthesize 5-hydroxyindoles,[2] and Fischer cyclization reactions of alkoxyphenylhydrazones sometimes give indoles with rearranged alkoxy groups.[3] Reissert, Leimgruber−Batcho, and related cyclization reactions have been widely used for the synthesis of oxygen-functionalized indoles;[4] however the synthesis of some of the starting compounds can be difficult.

In a previous report, we described the cyclization of ethyl (2-ethynylphenyl)carbamates into indoles in the presence of sodium ethoxide in ethanol.[5] Recently, the reaction conditions for indole cyclization were improved, and reflux conditions using potassium *tert*-butoxide in *tert*-butyl alcohol were found to be superior to the previously reported conditions.[6] These improved reaction conditions were applied to the synthesis of 7-substituted indoles from *tert*-butyl 6-substituted (2-ethynylphenyl)-carbamates.[6] On the other hand, the directed *ortho*-lithiation of substituted benzene derivatives followed by reaction with various electrophiles has been used as a powerful synthetic method to introduce substituents regioselectively.[7]

Scheme 1



We developed a strategy for synthesizing indole derivatives with an oxygen-bearing substituent at all of the positions of the benzene moiety by combining directed *ortho*-lithiation and our indole cyclization reaction, as shown in Scheme 1.

Results and Discussion

Preparation of *tert*-Butyl (2-Iodophenyl)carbamates. It has been reported that *tert*-butyl phenylcarbamates are *ortho*-lithiated with 2 equiv of *tert*-butyllithium[8,9] and that methoxyanilines are also lithiated at the *ortho*-position to the methoxy group with butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine in diethyl ether at 0 °C.[10] These findings show that (*tert*-butoxycarbonyl)amino and methoxy groups also serve as directed metalation groups for the lithiation of a benzene ring.

The *ortho*-lithiation reaction of benzene derivatives with two directed metalation groups, (*tert*-butoxycarbonyl)amino and methoxy groups, has been reported,[11,12] *i.e.*, *tert*-butyl (4-methoxyphenyl)carbamate was regiose-

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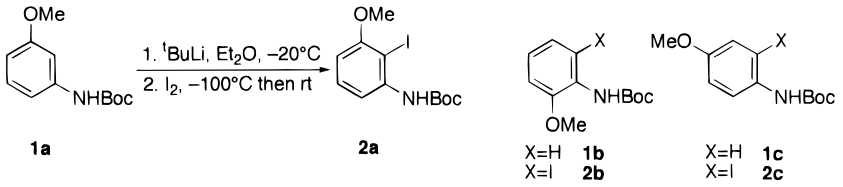
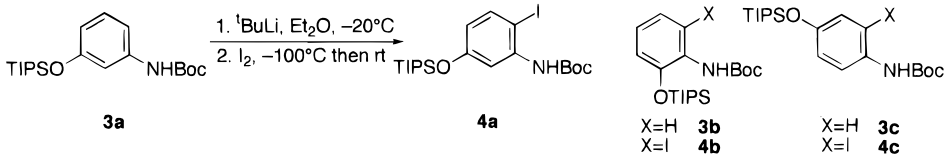
Scheme 2



Scheme 3



lectively lithiated at the *ortho*-position to the (*tert*-butoxycarbonyl)amino group and *tert*-butoxy (3-methoxyphenyl)carbamate was also lithiated at the *ortho*-position between the (*tert*-butoxycarbonyl)amino group and the methoxy group.[11,12]

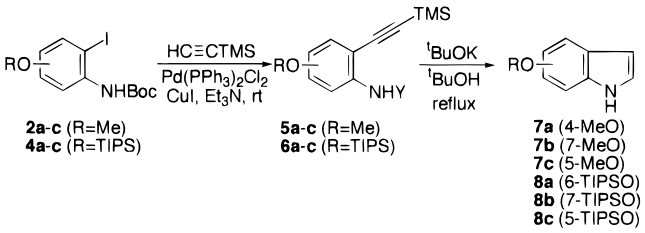
On the basis of these findings, the starting iodobenzene derivatives for the synthesis 4-, 5-, and 7-methoxyindoles were easily prepared. *tert*-Butyl (3-methoxyphenyl)-carbamate (**1a**) was lithiated with 2.2 equiv of *tert*-butyllithium in diethyl ether followed by iodination with molecular iodine to give *tert*-butyl (2-iodo-3-methoxyphenyl)carbamate (**2a**) in 55% yield (Scheme 2). Analogously, *tert*-butyl (2-iodo-6-methoxy- and (2-iodo-4-methoxyphenyl)carbamate (**2b** and **2c**) were prepared from *tert*-butyl (2-methoxy- and 4-methoxyphenyl)carbamate (**1b** and **1c**) in yields of 61 and 55%, respectively.

Using this method, the starting materials for the synthesis of indoles with an oxygen-bearing functional group at the 4-, 5-, and 7-positions were obtained. However, this method is not applicable to the synthesis of *tert*-butyl 2-iodo-5-substituted phenylcarbamates, which could be starting materials for the synthesis of 6-substituted indoles using our method.

This problem was solved by using *tert*-butyl (3-((triisopropylsilyl)oxy)phenyl)carbamate (**3a**) instead of **1a** (Scheme 3). As described above,[11,12] the (*tert*-butoxycarbonyl)amino group is more effective than the methoxy group as a directed metalation group, and the (triisopropylsilyl)oxy group is bulkier than the methoxy group. Based on these two points, we predicted that the lithiation of **3a** would occur at the *ortho*-position to the (*tert*-butoxycarbonyl)amino group and at the *para*-position to the (triisopropylsilyl)oxy group. Thus, the lithiation reaction of **3a** with *tert*-butyllithium in diethyl ether followed by iodination with molecular iodine gave *tert*-butyl (2-iodo-5-((triisopropylsilyl)oxy)phenyl)carbamates (**4a**) in 66% yield. Similarly, directed lithiation and iodination of *tert*-butyl (2-((triisopropylsilyl)oxy)- and (4-((triisopropylsilyl)oxy)phenyl)carbamate (**3b** and **3c**) gave *tert*-butyl (2-iodo-6-((triisopropylsilyl)oxy)- and (2-iodo-4-((triisopropylsilyl)oxy)phenyl)carbamate (**4b** and **4c**) in yields of 47 and 48%, respectively.

Preparation of *tert*-Butyl(2-((Trimethylsilyl)ethynyl)phenyl)carbamates and Their Cyclization to Indoles. According to the reported reaction conditions for the standard palladium-catalyzed cross-coupling of aryl iodides and (trimethylsilyl)acetylene,[5] *tert*-butyl methoxy (**2a**−**c**) and (triisopropylsilyl)oxy (2-iodophenyl)-carbamates (**4a**−**c**) were allowed to react with (trimethylsilyl)acetylene in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide in triethylamine to give the corresponding (trimethylsilyl)ethynyl phenylcarbamates (**5a**−**c** and **6a**−**c**) in yields of 85−100% (Scheme 4).

Scheme 4



Cyclization of the (ethynylphenyl)carbamates (**5a**−**c**) in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol proceeded smoothly to give methoxyindoles (**7a**−**c**) in yields of 70−79%. Analogous cyclization of (((triisopropylsilyl)oxy)phenyl)carbamates (**6a**−**c**) gave ((triisopropylsilyl)oxy)indoles (**8a**,**c**), except for **8b**. The cyclization of **6b** under reflux conditions for 96 h gave a complex mixture, and the desired product was obtained in only 10% yield. This low yield is believed to be due to the prolonged reflux conditions and decomposition of the product (**8b**). With a shorter reaction time (1 h), 1-(*tert*-butoxycarbonyl)-7-((triisopropylsilyl)oxy)indole was obtained in 62% yield. This result suggests that indole cyclization proceeds *via* 1-(*tert*-butoxycarbonyl)indole as an intermediate to give 1-unsubstituted indoles.

Conclusion

Three methoxyindoles (**7a**−**c**) and three ((triisopropylsilyl)oxy)indoles (**8a**−**c**) were synthesized easily and in good yields. As a result, the synthesis of indoles with oxygen-bearing substituents at all of the positions of the benzene moiety was achieved. Since alkoxy- and ((triisopropylsilyl)oxy)indoles can be converted to (((trifluoromethyl)sulfonyl)oxy)indoles *via* hydroxyindoles and (((trifluoromethyl)sulfonyl)oxy)indoles can be transformed into various carbon-substituted indoles by a palladium-catalyzed reaction,[13] the present synthesis of methoxyindoles and ((triisopropylsilyl)oxy)indoles can be used for the synthesis of many indole derivatives.

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Experimental Section

General Comments. THF and Et_2O were distilled from sodium/benzophenone ketyl before use. *t*-BuOH was distilled from CaH before use. *n*-BuLi and *t*-BuLi were 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 Varian Gemini 2000 (300M Hz) and Hitachi R-3000 (300 MHz) spectrometers. 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, dd = doublet of doublet, and br = broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on JMS-DX303 and JMS-AX500 instruments.

***tert*-Butyl (3-Methoxyphenyl)carbamate (1a).** A solution of 3-methoxyaniline (2.463 g, 20 mmol) and di-*tert*-butyl dicarbonate (5.1 mL, 22 mmol) in dry THF (30 mL) was refluxed for 5 h. The solvent was evaporated under reduced pressure. To the residue was added H_2O (20 mL), and the mixture was extracted with Et_2O (30 mL × 3). The Et_2O extract was washed with a saturated aqueous NaCl solution (20 mL) and dried over $MgSO_4$. The residue was purified by silica gel (88 g) column chromatography using AcOEt−hexane (1:10) as eluent to give colorless prisms which were recrystallized from Et_2O−hexane: yield 4.049 g (91%); mp 57−58 °C; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.52 (9H, s), 3.80 (3H, s), 6.46 (1H, br), 6.58 (1H, dd, J = 2.6, 8.2 Hz), 6.83 (1H, dd, J = 1.5, 8.1 Hz), 7.10 (1H, s), 7.17 (1H, t, J = 8.1 Hz); IR ν ($CHCl_3$) cm^{-1} 3440, 1725; MS *m*/*z* 223 (M^+); HRMS calcd for $C_{12}H_{17}NO_3$ 223.1207, found 223.1221. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.77; H, 7.69; N, 6.27.

***tert*-Butyl (2-Methoxyphenyl)carbamate (1b).** A solution of 2-methoxyaniline (246 mg, 2 mmol) and di-*tert*-butyl dicarbonate (0.69 mL, 3 mmol) in dry THF (5 mL) was stirred at room temperature for 17 h. The solvent was evaporated under reduced pressure. To the residue was added H_2O (10 mL), and the mixture was extracted with CH_2Cl_2 (30 mL × 3). The CH_2Cl_2 extract was washed with a saturated aqueous NaCl solution (10 mL) and dried over $MgSO_4$. The residue was purified by silica gel (9 g) column chromatography using AcOEt−hexane (1:20) as eluent to give a colorless viscous liquid which was distilled under reduced pressure: yield 444 mg (99%); bp 60 °C/3 mmHg; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.53 (9H, s), 3.86 (3H, s), 6.86−6.83 (1H, m), 6.97−6.93 (2H, m), 7.08 (1H, br), 8.07 (1H, d, J = 6.6 Hz); IR ν ($CHCl_3$) cm^{-1} 3440, 1725; MS *m*/*z* 319 (M^+); HRMS calcd for $C_{12}H_{17}NO_3$ 223.1207, found 223.1210.

***tert*-Butyl (4-Methoxyphenyl)carbamate (1c).** A solution of 4-methoxyaniline (1.847 g, 15 mmol) and di-*tert*-butyl dicarbonate (5.1 mL, 22 mmol) in dry THF (15 mL) was stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure. To the residue was added H_2O (20 mL), and the mixture was extracted with CH_2Cl_2 (30 mL × 3). The CH_2Cl_2 extract was washed with a saturated aqueous NaCl solution (20 mL) and dried over $MgSO_4$. The residue was purified by silica gel (70 g) column chromatography using AcOEt−hexane (1:5) as eluent to give colorless needles which were recrystallized form Et_2O−hexane: yield 3.072 g (92%); mp 92−94 °C; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.51 (9H, s), 3.78 (3H, s), 6.32 (1H, br), 6.83 (2H, d, J = 9.2 Hz), 7.26 (2H, d, J = 8.8 Hz); IR ν ($CHCl_3$) cm^{-1} 3450, 1730; MS *m*/*z* 223 (M^+); HRMS calcd for $C_{12}H_{17}NO_3$ 223.1207, found 223.1200. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.53; H, 7.66; N, 6.32.

2-((Triisopropylsilyl)oxy)aniline. Triisopropylsilyl chloride (0.64 mL, 3 mmol) was added to a dichloromethane solution (5 mL) of 2-aminophenol (218 mg, 2 mmol) and imidazole (204 mg, 3 mmol) at room temperature, and the mixture was stirred for 33 h. After addition of H_2O (10 mL), the mixture was extracted with CH_2Cl_2 (30 mL × 3). The CH_2Cl_2 extract was washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel (54 g) column chromatography using AcOEt-hexane (1:200) as eluent to give a colorless liquid which was distilled under reduced pressure: yield 446 mg (84%); bp 110 °C/3 mmHg; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.12 (18H, d, J = 7.3 Hz), 1.38−1.21 (3H, m), 3.86 (2H, br), 6.63−6.57 (1H, m), 6.79−6.69 (3H, m); IR ν ($CHCl_3$) cm^{-1} 3450, 3390; MS *m*/*z* 265 (M^+); HRMS calcd for $C_{15}H_{27}NOSi$ 265.1860, found 265.1887.

3-((Triisopropylsilyl)oxy)aniline. Triisopropylsilyl chloride (0.47 mL, 2.4 mmol) was added to a dichloromethane solution (5 mL) of 3-aminophenol (218 mg, 2 mmol) and imidazole (163 mg, 2.4 mmol) at room temperature, and the mixture was stirred for 26 h. After addition of H_2O (10 mL), the mixture was extracted with CH_2Cl_2 (20 mL × 3). The CH_2Cl_2 extract was washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel (16 g) column chromatography using AcOEt hexane (1:10) as eluent to give a viscous colorless liquid: yield 385 mg (73%); bp 100 °C/3 mmHg; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.09 (18H, d, J = 7.3 Hz), 1.29−1.18 (3H, m), 3.58 (2H, br), 6.30−6.24 (3H, m), 6.97 (1H, t, J = 7.7 Hz); IR ν ($CHCl_3$) cm^{-1} 3455, 3385; MS *m*/*z* 265 (M^+); HRMS calcd for $C_{15}H_{27}NOSi$ 265.1860, found 265.1904.

***tert*-Butyl (3-((Triisopropylsilyl)oxy)phenyl)carbamate (3a).** A solution of 3-((triisopropylsilyl)oxy)aniline (265 mg, 1 mmol) and di-*tert*-butyl dicarbonate (0.35 mL, 1.5 mmol) in dry THF (5 mL) was stirred at room temperature for 4 days. The solvent was evaporated under reduced pressure. To the residue was added H_2O (10 mL), and the mixture was extracted with CH_2Cl_2 (30 mL × 3). The CH_2Cl_2 extract was washed with a saturated aqueous NaCl solution (20 mL) and dried over $MgSO_4$. The residue was purified by silica gel (10 g) column chromatography using AcOEt−hexane (1:20) as eluent to give colorless needles which were recrystallized from hexane: yield 313 mg (86%); mp 124−126 °C; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.09 (18H, d, J = 7.0 Hz), 1.28−1.18 (3H, m), 1.51 (9H, s), 6.37 (1H, br), 6.54 (1H, dd, J = 1.1, 7.7 Hz), 6.88 (1H, s), 6.97 (1H, d, J = 8.1 Hz), 7.10 (1H, t, J = 7.7 Hz); IR ν ($CHCl_3$) cm^{-1} 3455, 1735; MS *m*/*z* 365 (M^+); HRMS calcd for $C_{20}H_{35}NO_3Si$ 365.2384, found 365.2361. Anal. Calcd for $C_{20}H_{35}NO_3Si$: C, 65.71; H, 9.65; N, 3.83. Found: C, 65.59; H, 9.65; N, 3.89.

***tert*-Butyl (2-((Triisopropylsilyl)oxy)phenyl)carbamate (3b).** A solution of 2-((triisopropylsilyl)oxy)aniline (531 mg, 2 mmol) and di-*tert*-butyl dicarbonate (0.7 mL, 3 mmol) in dry THF (5 mL) was stirred at room temperature for 72 h. The solvent was evaporated under reduced pressure. To the residue was added H_2O (10 mL), and the mixture was extracted with CH_2Cl_2 (30 mL × 3). The CH_2Cl_2 extract was washed with a saturated aqueous NaCl solution (10 mL) and dried over $MgSO_4$. The residue was purified by silica gel (15 g) column chromatography using AcOEt−hexane (1:100) as eluent to give a colorless viscous liquid: yield 683 mg (93%); 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.12 (18H, d, J = 7.3 Hz), 1.37−1.26 (3H, m), 1.51 (9H, s), 6.94−6.79 (3H, m), 7.09 (1H, br), 7.97 (1H, d, J = 7.3 Hz); IR ν ($CHCl_3$) cm^{-1} 3440, 1725; MS *m*/*z* 365 (M^+); HRMS calcd for $C_{20}H_{35}NO_3Si$ 365.2384, found 365.2369.

***tert*-Butyl (4-((Triisopropylsilyl)oxy)phenyl)carbamate (3c).** Triisopropylsilyl chloride (1.6 mL, 7.5 mmol) was added to a solution of 4-aminophenol (546 mg, 5.0 mmol) and imidazole (510 mg, 7.5 mmol) in dichloromethane (10 mL) at room temperature, and the mixture was stirred for 2 h. After addition of H_2O (10 mL), the mixture was extracted with CH_2Cl_2 (30 mL × 3). The CH_2Cl_2 extract was washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. Di-*tert*-butyl dicarbonate (1.7 mL, 7.5 mmol) was added to a solution of the residue in dry THF (15 mL), and the mixture was stirred at room temperature for 39 h. The solvent was evaporated under reduced pressure. To the residue was added H_2O (20 mL), and the mixture was extracted with CH_2Cl_2 (30 mL × 3). The CH_2Cl_2 extract was washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel (100

g) column chromatography using AcOEt−hexane (1:20) as eluent to give a pale yellow liquid which was distilled at 70 °C under 4 mmHg. The residue was purified by silica gel (100 g) column chromatography using AcOEt−hexane (1:20) as eluent to give a pale yellow solid. Recrystallization from hexane at 0 °C gave colorless prisms: yield 1.494 g (82%); mp 57−58 °C; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.08 (18H, d, J = 7.0 Hz), 1.31−1.16 (3H, m), 1.50 (9H, s), 6.31 (1H, br), 6.80 (2H, d, J = 8.8 Hz), 7.18 (2H, d, J = 8.4 Hz); IR ν ($CHCl_3$) cm^{-1} 3440, 1730; MS m/z 365 (M^+); HRMS calcd for $C_{20}H_{35}NO_3Si$ 365.2384, found 365.2359. Anal. Calcd for $C_{20}H_{35}NO_3Si$: C, 65.71; H, 9.65; N, 3.83. Found: C, 65.58; H, 9.64; N, 3.84.

***tert*-Butyl (2-Iodo-3-methoxyphenyl)carbamate (2a): Representative Procedure.** Addition of 1.34 M *tert*-butyllithium in pentane (8.2 mL, 11 mmol) to a solution of *tert*-butyl (3-methoxyphenyl)carbamate (**1a**) (1.116 g, 5 mmol) in dry Et_2O (6 mL) under an argon atmosphere at −20 °C followed by stirring for 3 h. To the mixture was added iodine (1.523 g, 6 mmol) in dry Et_2O (14 mL) at −100 °C, and the whole was gradually warmed up to room temperature and stirred overnight. After addition of a saturated aqueous $Na_2S_2O_3$ solution (20 mL), the mixture was extracted with Et_2O (30 mL × 3). The Et_2O extract was washed with a saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel (85 g) column chromatography using AcOEt-hexane (1:100) as eluent to give a crude product. Recrystallization from hexane gave colorless prisms: yield 0.954 g (55%); mp 73−75 °C; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.54 (9H, s), 3.88 (3H, s), 6.53 (1H, d, J = 8.4 Hz), 7.04 (1H, br), 7.25 (1H, t, J = 7.7 Hz), 7.73 (1H, d, J = 8.4 Hz); IR ν ($CHCl_3$) cm^{-1} 3395, 1730; MS m/z 349 (M^+); HRMS for calcd $C_{12}H_{16}INO_3$ 349.0173, found 349.0129. Anal. Calcd for $C_{12}H_{16}INO_3$: C, 41.28; H, 4.62; N, 4.01. Found: C, 41.24; H, 4.44; N, 3.97.

***tert*-Butyl (2-iodo-6-methoxyphenyl)carbamate (2b):** colorless scales (61%) from Et_2O; mp 106−108 °C; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.50 (9H, s), 3.82 (3H, s), 6.00 (1H, br), 6.95−6.85 (2H, m), 7.43 (1H, d, J = 7.7 Hz); IR ν ($CHCl_3$) cm^{-1} 3420, 1725; MS m/z 349 (M^+); HRMS calcd for $C_{12}H_{16}INO_3$ 349.0173, found 349.0155. Anal. Calcd for $C_{12}H_{16}INO_3$: C, 41.28; H, 4.62; N, 4.01; I, 36.34. Found: C, 41.05; H, 4.65; N, 3.99; I, 36.26.

***tert*-Butyl (2-Iodo-4-methoxyphenyl)carbamate (2c).** 1,2-Diiodoethane was used as an iodinating reagent. **2c**: colorless prisms (55%) from Et_2O−hexane; mp 49−50 °C; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.52 (9H, s), 3.76 (3H, s), 6.53 (1H, br), 6.89 (1H, dd, J = 2.9, 9.0 Hz), 7.29 (1H, d, J = 2.9 Hz), 7.80 (1H, d, J = 9.1 Hz); IR ν ($CHCl_3$) cm^{-1} 3400, 1730; MS m/z 349 (M^+); HRMS calcd for $C_{12}H_{16}INO_3$ 349.0173, found 349.0197. Anal. Calcd for $C_{12}H_{16}INO_3$: C, 41.28; H, 4.62; N, 4.01. Found: C, 41.46; H, 4.69; N, 4.04.

***tert*-Butyl (2-iodo-5-((triisopropylsilyl)oxy)phenyl)-carbamate (4a):** colorless viscous liquid; yield 66%; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) (1.10 (18H, d, J = 7.3 Hz), 1.19−1.35 (3H, m), 1.56 (9H, s), 6.35 (1H, dd, J = 2.9, 8.4 Hz), 6.72 (1H, br), 7.51 (1H, d, J = 8.8 Hz), 7.70 (1H, d, J = 2.6 Hz); IR ν ($CHCl_3$) cm^{-1} 3395, 1735; MS m/z 491 (M^+); HRMS calcd for $C_{20}H_{34}INO_3Si$ 491.1350, found 491.1346.

***tert*-Butyl (2-Iodo-6-((triisopropylsilyl)oxy)phenyl)-carbamate (4b).** 1,2-Diiodoethane was used as an iodinating reagent. **4b**: colorless prisms from Et_2O−hexane; yield 47%; mp 117−118 °C; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.10 (18H, d, J = 6.9 Hz), 1.22−1.34 (3H, m), 1.48 (9H, s), 6.08 (1H, br), 6.85−6.77 (2H, m), 7.43 (1H, dd, J = 2.2, 7.0 Hz); IR ν ($CHCl_3$) cm^{-1} 3430, 1735; MS m/z 392. Anal. Calcd for $C_{20}H_{34}INO_3Si$: C, 48.88; H, 6.97; N, 2.85; I, 25.82. Found: C, 48.75; H, 6.68; N, 2.92; I, 25.58.

***tert*-Butyl (2-iodo-4-((triisopropylsilyl)oxy)phenyl)-carbamate (4c):** pale yellow viscous liquid; yield 58%; 300 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 1.08 (18H, d, J = 7.0 Hz), 1.30−1.12 (3H, m), 1.52 (9H, s), 6.54 (1H, br), 6.84 (1H, dd, J = 2.9, 9.0 Hz), 7.29 (1H, d, J = 2.9 Hz), 7.76 (1H, d, J = 9.2 Hz); IR ν ($CHCl_3$) cm^{-1} 3400, 1725; MS m/z 491 (M^+); HRMS calcd for $C_{20}H_{34}INO_3Si$ 491.1350; found 491.1317.

***tert*-Butyl (3-Methoxy-2-((trimethylsilyl)ethynyl)-phenylcarbamate (5a): Representative Procedure.** A mixture of *tert*-butyl (2-iodo-3-methoxyphenyl)carbamate (**2a**) (105 mg, 0.30 mmol), (trimethylsilyl)acetylene (0.06 mL, 0.45 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 0.02 mmol), CuI (3 mg, 0.02 mmol), and Et_3N (1 mL) in a sealed tube was heated at 80 °C for 24 h. To the reaction mixture were added H_2O (10 mL) and Et_2O (20 mL), and the whole was filtered through a Celite pad. The filtrate was extracted with Et_2O (20 mL × 2). The ethereal extract was washed with a saturated aqueous 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) as eluent to give a colorless viscous liquid: yield 82 mg (85%); 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 0.31 (9H, s), 1.53 (9H, s), 3.87 (3H, s), 6.52 (1H, d, J = 8.4 Hz), 7.23 (1H, t, J = 8.1 Hz), 7.44 (1H, br), 7.75 (1H, d, J = 8.4 Hz); IR ν ($CHCl_3$) cm^{-1} 3395, 2145, 1730; MS m/z 319 (M^+); HRMS calcd for $C_{17}H_{25}NO_3Si$ 319.1602, found 319.1582.

***tert*-Butyl (6-Methoxy-2-((trimethylsilyl)ethynyl)phenyl)carbamate (5b).** Reaction was carried out at room temperature for 24 h. **5b**: colorless prisms from Et_2O−hexane: yield 87%; mp 116−118 °C; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 0.24 (9H, s), 1.50 (9H, s), 3.84 (3H, s), 6.18 (1H, br), 6.88 (1H, dd, J = 3.0, 6.5 Hz), 7.13−7.07 (2H, m); IR ν ($CHCl_3$) cm^{-1} 3420, 1730; MS m/z 319 (M^+); HRMS calcd for $C_{17}H_{25N}O_3$ 319.1602, found 319.1601. *Anal.* Calcd for $C_{17}H_{25}NO_3Si$: C, 63.91; H, 7.89; N, 4.38. Found: C, 63.75; H, 7.73; N, 4.37.

***tert*-Butyl (4-Methoxy-2-((trimethylsilyl)ethynyl)phenyl)carbamate (5c).** Reaction was carried out at room temperature for 24 h. **5c**: colorless prisms from hexane; yield 93%; mp 70−72 °C; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 0.29 (9H, s), 1.52 (9H, s), 3.76 (3H, s), 6.89−6.85 (2H, m), 7.15 (1H, br), 7.98 (1H, d, J = 8.8 Hz); IR ν ($CHCl_3$) cm^{-1} 3410, 2150, 1725; MS m/z 319 (M^+); HRMS calcd for $C_{17}H_{25}NO_3Si$ 319.1602, found 319.1618. Anal. Calcd for $C_{17}H_{25}NO_3Si$: C, 63.91; H, 7.89; N, 4.38. Found: C, 63.93; H, 7.81; N, 4.37.

***tert*-Butyl (5-((Triisopropylsilyl)oxy)-2-((trimethylsilyl)ethynyl)phenyl)carbamate (6a).** Reaction was carried out at room temperature for 47 h. **6a**: pale yellow viscous liquid; yield 95%; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 0.25 (9H, s), 1.07 (18H, d, J = 7.1 Hz), 1.28−1.20 (3H, m), 1.50 (9H, s), 6.42 (1H, dd, J = 2.2, 8.4 Hz), 7.20 (1H, d, J = 8.5 Hz), 7.30 (1H, br), 7.69 (1H, d, J = 2.2 Hz); IR ν ($CHCl_3$) cm^{-1} 3405, 2160, 1735; MS m/z 461 (M^+); HRMS calcd for $C_{25}H_{43}NO_3Si_2$ 461.2779, found 461.2782.

***tert*-Butyl (6-((Triisopropylsilyl)oxy)-2-((trimethylsilyl)ethynyl)phenyl)carbamate (6b).** Reaction was carried out at room temperature for 24 h. **6b**: pale yellow viscous liquid; yield 99%; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 0.23 (9H, s), 1.09 (18H, d, J = 7.0 Hz), 1.33−1.19 (3H, m), 1.48 (9H, s), 6.19 (1H, br), 6.83 (1H, dd, J = 1.1, 8.2 Hz), 6.97 (1H, t, J = 8.1 Hz), 7.08 (1H, dd, J = 1.1, 7.7 Hz); IR ν ($CHCl_3$) cm^{-1} 3430, 2160, 1730; MS m/z 461 (M^+); HRMS calcd for $C_{25}H_{43}NO_3Si_2$: 461.2779, found 461.2780.

***tert*-Butyl (4-((Triisopropylsilyl)oxy)-2-((trimethylsilyl)ethynyl)phenyl)carbamate (6c).** Reaction was carried out at room temperature for 24 h. **6c**: pale yellow viscous liquid; yield 100%; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 0.29 (9H, s), 1.08 (18H, d, J = 6.6 Hz), 1.30−1.18 (3H, m), 1.51 (9H, s), 6.87−6.81 (2H, m), 7.16 (1H, br), 7.91 (1H, d, J = 8.8 Hz); IR ν ($CHCl_3$) cm^{-1} 3400, 2150, 1725; MS m/z 461 (M^+); HRMS calcd for $C_{25}H_{43}NO_3Si_2$ 461.2779, found 461.2769.

4-Methoxyindole (7a): Representative Procedure. *tert*-Butyl (3-methoxy-2-((trimethylsilyl)ethynyl)phenyl)carbamate (**5a**) (432 mg, 1.4 mmol) in dry *t*-BuOH (3 mL) was added to a dry *t*-BuOH solution (3 mL) of potassium *tert*-butoxide (561 mg, 6.8 mmol) under an argon atmosphere, and the mixture was refluxed for 5 h. After evaporation of the solvent, H_2O (10 mL) was added to the residue, and the whole was extracted with CH_2Cl_2 (20 mL × 3). The CH_2Cl_2 extract was washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel (6 g) column chromatography using AcOEt−hexane (1:20) as eluent to give a crude product.

Recrystallization from Et_2O−hexane gave colorless prisms. **7a**: yield 139 mg (70%); mp 69−70 °C (lit.[4c] mp 67−68 °C; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 3.97 (3H, s), 6.54 (1H, d, J = 7.7 Hz), 6.68−6.65 (1H, m), 7.03 (1H, dd, J = 0.8, 8.2 Hz), 7.15−7.10 (2H, m), 8.16 (1H, br); IR ν ($CHCl_3$) cm^{-1} 3485; MS m/z 147 (M^+); HRMS calcd for C_9H_9NO 147.0684, found 147.0694. Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.54; H, 6.16; N, 9.40.

7-Methoxyindole (7b). Reaction time was 3 h. **7b**: colorless viscous liquid; yield 70%; bp 130 °C/3.5 mmHg (lit.[4c] bp 138−139 °C/5 Torr); 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 3.96 (3H, s), 6.53 (1H, t, J = 2.6 Hz), 6.64 (1H, d, J = 7.7 Hz), 7.03 (1H, t, J = 8.1 Hz), 7.18 (1H, t, J = 2.6 Hz), 7.25 (1H, d, J = 8.1 Hz), 8.36 (1H, br); IR ν ($CHCl_3$) cm^{-1} 3495; MS m/z 147 (M^+); HRMS calcd for C_9H_9NO 147.0684, found 147.0666.

5-Methoxyindole (7c). Reaction time was 3 h. **7c**: colorless solid; yield 79%; mp 55−56 °C (lit.[4c] mp 55−56 °C), bp 160 °C/4 mmHg); 300 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 3.86 (3H, s), 6.50−6.48 (1H, m), 6.87 (1H, dd, J = 2.5, 8.8 Hz), 7.11 (1H, d, J = 2.5 Hz), 7.19 (1H, t, J = 2.5 Hz), 7.29 (1H, d, J = 8.8 Hz), 8.05 (1H, br); IR ν ($CHCl_3$) cm^{-1} 3485; MS m/z 147 (M^+); HRMS calcd for C_9H_9NO: 147.0684, found 147.0660. Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.33; H, 6.20; N, 9.48.

6-((Triisopropylsilyl)oxy)indole (8a). Reaction time was 17 h. **8a**: pale yellow viscous liquid; yield 67%; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.11 (18H, d, J = 7.0 Hz), 1.33−1.21 (3H, m), 6.46 (1H, s), 6.74 (1H, dd, J = 1.8, 8.4 Hz), 6.88 (1H, s), 7.08 (1H, t, J = 2.6 Hz), 7.43 (1H, d, J = 8.4 Hz), 7.93 (1H, br); IR ν ($CHCl_3$) cm^{-1} 3490; MS m/z 289 (M^+); HRMS calcd for $C_{17}H_{27}NOSi$ 289.1860, found 289.1835.

7-((Triisopropylsilyl)oxy)indole (8b). Reaction time was 96 h. **8b**: colorless viscous liquid; yield 10%; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.14 (18H, d, J = 7.1 Hz), 1.41−1.30 (3H, m), 6.52 (1H, t, J = 3.0 Hz), 6.65 (1H, d, J = 7.7 Hz), 6.93 (1H, t, J = 7.7 Hz), 7.18 (1H, t, J = 3.0 Hz), 7.24 (1H, d, J = 7.7 Hz), 8.20 (1H, br); IR ν ($CHCl_3$) cm^{-1} 3500; MS m/z 289 (M^+); HRMS calcd for $C_{17}H_{27}NOSi$ 289.1860, found 289.1890.

1-(*tert*-Butoxycarbonyl)-7-((triisopropylsilyl)oxy)indole. Reaction time was 1 h. Colorless viscous liquid: yield 62%. 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.11 (18H, d, J = 7.3 Hz), 1.50−1.16 (3H, m), 1.60 (9H, s), 6.47 (1H, d, J = 3.7 Hz), 6.76 (1H, d, J = 7.3 Hz), 7.13−7.03 (2H, m), 7.42 (1H, d, J = 3.7 Hz); IR ν ($CHCl_3$) cm^{-1} 1755; MS m/z 389 (M^+); HRMS calcd for $C_{22}H_{35}NO_3Si$ 389.1780, found 389.2376.

5-((Triisopropylsilyl)oxy)indole (8c). Reaction time was 18 h. **8c**: pale yellow viscous liquid; yield 70%; 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.12 (18H, d, J = 7.0 Hz), 1.33−1.19 (3H, m), 6.42 (1H, t, J = 2.2 Hz), 6.81 (1H, dd, J = 2.6, 8.6 Hz), 7.10 (1H, d, J = 2.2 Hz), 7.15 (1H, t, J = 2.6 Hz), 7.20 (1H, d, J = 8.8 Hz), 7.98 (1H, br); IR ν ($CHCl_3$) cm^{-1} 3490; MS m/z 289 (M^+); HRMS calcd for $C_{17}H_{27}NOSi$ 289.1860, found 289.1859.

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