# Studies on Organometallic Compounds. VII.[1] Reaction of Di-*tert*-butyl Dicarbonate with α-Trialkylstannyl Derivatives of Pyridine, Quinoline, and Isoquinoline

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**Di-*tert*-butyl dicarbonate was found to be effective for direct introduction of a *tert*-butoxycarbonyl group at the α-position of the pyridine nucleus *via* the trialkylstannyl group; reaction of α-trialkylstannyl derivatives of pyridine, quinoline, and isoquinoline with di-*tert*-butyl dicarbonate gave the corresponding α-*tert*-butoxycarbonyl derivatives in good yields, although small amounts of a variety of by-products were formed except in the case of pyridine.**

**Key words** trialkylstannylazine; alkoxycarbonylation; di-*tert*-butyl dicarbonate; mixed anhydride

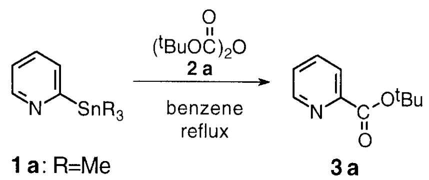
Recently, interest in applications of the organostannyl group in the field of synthetic chemistry has considerably increased.[2] This group is especially valuable for elaboration of electron-deficient *N*-heterocycles,[3] because of the difficulty in their functionalization by electrophilic reagents. We have reported[3a] an effective carbon–carbon bond formation reaction in the pyridine ring *via* the stannyl derivatives with acyl chloride. A trimethylstannyl (TMSn) group at the α-position of the pyridine ring is rather more active than those at other positions in spontaneous reaction with acyl chloride to give the corresponding α-acyl derivatives. This paper deals with an application of the α-trialkylstannyl group to a simple and mild method for introduction of an alkoxycarbonyl group into a pyridine ring by using di-*tert*-butyl dicarbonate,[4] which is a standard reagent for protecting the amino group in peptide synthesis.

2-TMSn-pyridine (**1a**) smoothly reacted with di-*tert*-butyl dicarbonate (**2a**) to give *tert*-butyl 2-pyridinecarboxylate (**3a**) as a sole product in 87% yield. 2-Tributylstannylpyridine (**1b**) also reacted with **2a** to afford the expected **3a** in 87% yield.

Reaction of 2-TMSn-quinoline (**1c**) with **2a** in refluxing benzene gave *tert*-butyl 2-quinolinecarboxylate (**3b**) in 52% yield, together with two types of by-products, the carbonate **4** (31%) and bis(2-quinolyl) ketone (**5**,[5] 14%). Employing xylene as a solvent increased the yield of **3b** to 78% and gave rise to a third type of by-product, *tert*-butyl tris(2-quinolyl)methyl carbonate (**6**) in 2% yield. The reactions of **1b** and **1c** with **2a** occurred very slowly, with decomposition of **2a**. Therefore, an excess of **2a** was employed.

Refluxing a solution of 1-TMSn-isoquinoline (**1d**) and **2a** in dry benzene for 3 h provided *tert*-butyl 1-isoquinolinecarboxylate (**3c**) and 14*H*-imidazo[2,1-*a*:4,3-*a*′]diisoquinolin-14-one (**7**)[6] in 32% and 48% yields, respectively. Reaction of **1d** with **2a** at room temperature raised the yield (73%) of **7**. The results are summarized in Table 1.

In these reactions, a mixed anhydride **8** might be an important intermediate. In order to elucidate the pathway to these products, the reactions of *p*-nitrobenzoic *tert*-butylcarbonic anhydride (**8a**), 2-quinolinecarboxylic *tert*-butylcarbonic anhydride (**8b**), and 1-isoquinolinecarboxylic *tert*-butylcarbonic anhydride (**8c**), which were synthesized according to the literature procedure,[7] with **1** were investigated. The mixed anhydride **8a** was treated




ᵗBu = *tert*-butyl

Chart 1

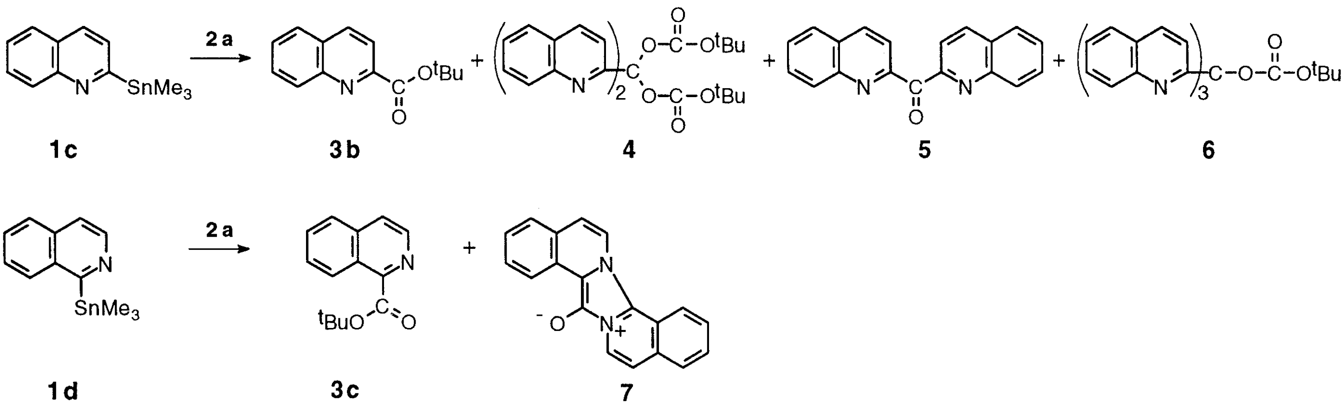



Chart 2

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Table 1. Synthesis of 2-Pyridine- (**3a**), 2-Quinoline- (**3b**), and 1-Isoquinolinecarboxylate (**3c**)

| Starting material | | 2a | Solvent | Temp. | Time (h) | Product | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. | mmol | mmol | | | | No. | Yield (%) | mp, °C | bp, °C (Torr) |
| **1a** | 5 | 6 | Benzene | Reflux | 3 | **3a** | 87 | | 105 (6.0) |
| **1b** | 5 | 12 | Benzene | Reflux | 5 | **3a** | 87 | | |
| **1c** | 5 | 18 | Benzene | Reflux | 20 | **3b** | 52 | 89—91 | |
| | | | | | | **4** | 31 | 180—181 | |
| | | | | | | **5** | 14 | 166—167[a)] | |
| **1c** | 5 | 24 | Xylene | Reflux | 5 | **3b** | 78 | | |
| | | | | | | **5** | 8 | | |
| | | | | | | **6** | 2 | 182—183 | |
| **1d** | 5 | 6 | Benzene | Reflux | 3 | **3c** | 32 | | 100 (0.1) |
| | | | | | | **7** | 48 | 273—277[b)] | |
| **1d** | 5 | 6 | Benzene | r.t. | 48 | **7** | 73 | | |

*a)* Lit.[5)] mp 165—166 °C. *b)* Lit.[6)] mp 280 °C. r.t. = room temperature.

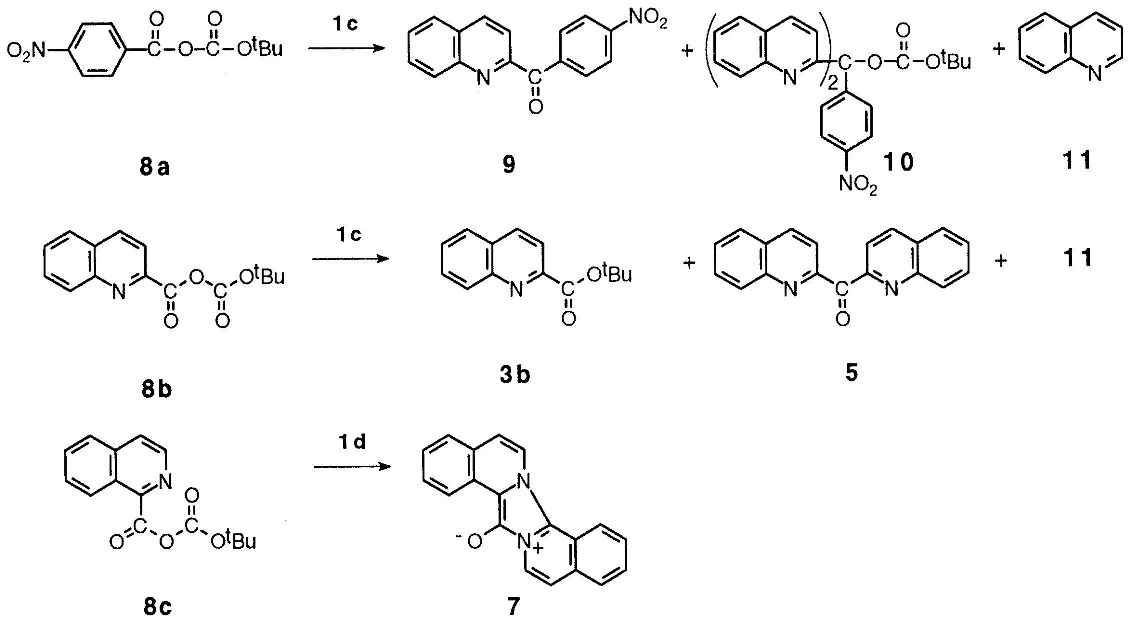


Chart 3

with **1c** as described above for the reaction of **2a** to give rise to 2-(*p*-nitrobenzoyl)quinoline (**9**), *tert*-butyl (*p*-nitrobenzoyl)bis(2-quinolyl)methyl carbonate (**10**), and quinoline (**11**) as a hydrolysis product of **1c**. The formation of the ketone **9** and monocarbonate **10** evidently resulted from the attack of **1c** at the *p*-nitrobenzoylcarbonyl carbon atom. This finding strongly suggested that an intermediate **8b** was formed from **1c** and **2a**, and subsequently underwent the attack of another **1c**, giving **3b**, **5**, and **6**. In fact, the mixed anhydride **8b** was treated with **1c** to provide **5**, besides **3b** and **11**. In addition, compound **4** was considered as a precursor of **5**, because quantitative conversion to **5** occurred on heating in benzene under reflux or on treatment with an acid such as tetrahydrofuran (THF) containing a trace of 10% hydrochloric acid. However, the pathway to **4** cannot be explained at present.

The mixed anhydride **8c** was concluded to be a precursor leading to **7** based on the following evidence; when **8c** was treated with **1d** in benzene at room temperature, **7** was produced in 86% yield. Taking this fact into account, the formation mechanism of **7** may be as follows: **8c** was first generated from **1d** and **2**, followed by the attack of unreacted **1d** with release of *tert*-butyl trimethylstannyl carbonate to give **7**.

Finally, formation of the ester **3** can be explained by pathways A and B; pathway A[8)] includes the migration of the *tert*-butoxycarbonyl group to the α-position, together with loss of carbon dioxide, and pathway B involves decomposition of the mixed anhydride **8**, formed from the intermediate I and **2a**, leading to **3** as shown in Chart 4. Pathway B is supported by the following results: 1) refluxing a xylene solution of **8b** afforded two kinds of products, **3b** and **5**, in 61% and 21% yields, respectively, 2) similar treatment of **8c** yielded **3c** and bis(1-isoquinolyl) ketone (**12**)[9)] in 12% and 76% yields, respectively.

It is of interest to note that use of diethyl dicarbonate (**2b**) resulted only in decomposition of **6b**, and no reaction with diethyl monocarbonate, benzoic anhydride, or acetic anhydride occurred.

The above reaction with di-*tert*-butyl dicarbonate (**2a**) is, to our knowledge, the first such example of carbon–carbon bond formation and appears to be advantageous for functionalization in π-deficient *N*-heterocyclic chemistry.

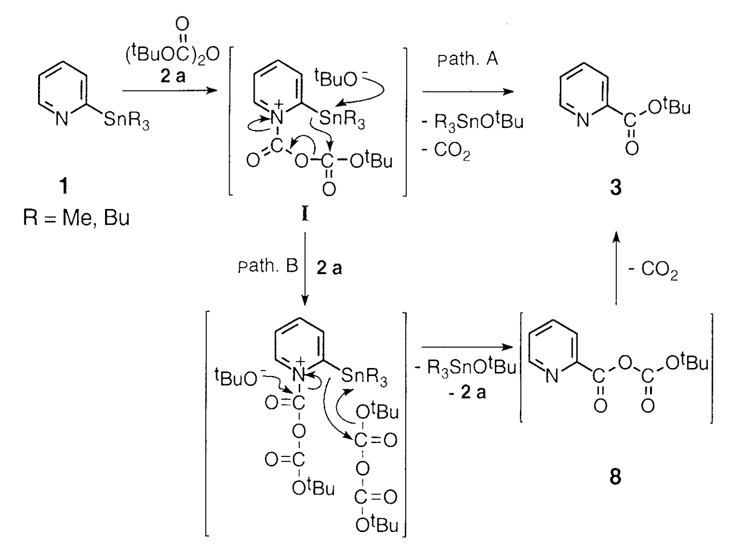


Chart 4

**Experimental**

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 1600 series Fourier transform-IR (FT-IR) spectrometer. Mass spectra (MS) were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. $^1$H- and $^{13}$C-nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-PMX 60si and JEOL JNM-EX 270 spectrometer, using tetramethylsilane as an internal standard. Column chromatography was carried out on Merck Silica gel 60 (230—400 mesh for flash chromatography).

***tert*-Butyl 2-Pyridinecarboxylate (3a)** i) A mixture of **1a** (1.21 g, 5 mmol) and **2a** (1.31 g, 6 mmol) in dry benzene (15 ml) was refluxed for 3 h under an argon atmosphere, then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane : $Et_2O$ = 2 : 1) to give **3a** (0.78 g, 87%) as a colorless liquid, bp 105 °C (6.0 Torr). IR (neat): 1734, 1713 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.63 (9H, s), 7.20—8.10 (3H, m), 8.60—8.80 (1H, m). $^{13}$C-NMR ($CDCl_3$) $\delta$: 28.1, 82.0, 124.7, 126.4, 136.8, 149.5, 149.8, 164.1. MS *m/z*: 179 (M$^+$). *Anal.* Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.85; H, 7.51; N, 7.72.

ii) A mixture of **1b** (1.84 g, 5 mmol) and **2a** (2.62 g, 12 mmol) in dry benzene (15 ml) was heated under reflux for 5 h under an argon atmosphere, then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane : $Et_2O$ = 2 : 1) to give **3a** (0.78 g, 87%) as a colorless liquid.

***tert*-Butyl 2-Quinolinecarboxylate (3b)** i) A mixture of **1c** (1.46 g, 5 mmol) and **2a** (3.93 g, 18 mmol) in dry benzene (15 ml) was refluxed for 20 h under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane : $Et_2O$ : $CH_2Cl_2$ = 3 : 1 : 1) to afford **3b** (0.59 g, 52%) as colorless prisms, **4** (0.39 g, 31%) as a colorless powder, and **5** (0.10 g, 14%) as pale yellow prisms.

**3b**: mp 89—91 °C (from $Et_2O$). IR (KBr): 1716 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.70 (9H, s), 7.50—8.43 (6H, m). $^{13}$C-NMR ($CDCl_3$) $\delta$: 28.2, 82.6, 120.9, 127.4, 128.3, 129.1, 130.0, 131.0, 137.0, 147.7, 149.5, 164.2. MS *m/z*: 229 (M$^+$). *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.32; H, 6.79; N, 5.93.

**4**: mp 180—181 °C (dec.) (from $Et_2O$). IR (KBr): 1771 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.43 (18H, s), 7.20—7.83 (6H, m), 7.93—8.30 (6H, m). $^{13}$C-NMR ($CDCl_3$) $\delta$: 22.8, 83.0, 102.0, 119.2, 126.7, 127.4, 127.5, 129.3, 129.5, 136.8, 147.1, 150.3, 157.6. MS *m/z*: 502 (M$^+$). *Anal.* Calcd for $C_{29}H_{30}N_2O_6$: C, 69.31; H, 6.02; N, 5.57. Found: C, 69.31; H, 6.00; N, 5.42.

ii) A mixture of **1c** (1.46 g, 5 mmol) and **2a** (1.31 g, 6 mmol) in dry xylene (15 ml) was refluxed for 5 h under an argon atmosphere followed by addition of **2a** (1.31 g, 6 mmol) every 1.5 h. After concentration *in vacuo*, the residue was purified by silica gel flash column chromatography (hexane : $Et_2O$ : $CH_2Cl_2$ = 3 : 1 : 1) to give **6** (0.02 g, 2%) as colorless prisms, **3b** (0.89 g, 78%) as colorless prisms, and **5** (0.06 g, 8%) as pale yellow prisms.

**6**: mp 178—179 °C (from $Et_2O$). IR (KBr): 1754 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.36 (9H, s), 7.20—8.20 (18H, m). $^{13}$C-NMR ($CDCl_3$) $\delta$: 27.7, 82.2, 90.6, 122.1, 126.5, 127.3, 128.9, 129.9, 135.3, 146.7, 151.6, 159.9. MS *m/z*: 513 (M$^+$). *Anal.* Calcd for $C_{33}H_{27}N_3O_3$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.11; H, 5.27; N, 7.96.

***tert*-Butyl 1-Isoquinolinecarboxylate (3c)** A mixture of **1d** (1.46 g, 5 mmol) and **2a** (1.31 g, 6 mmol) in dry benzene (15 ml) was refluxed for 3 h under an argon atmosphere. The reaction mixture was allowed to cool at room temperature. The insoluble substance that separated from the solution was separated by filtration. Recrystallization from EtOH gave **7** (0.34 g, 48%) as red small needles.

The filtrate was concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane : $Et_2O$ = 2 : 1) to give **3c** (0.37 g, 32%) as a pale yellow liquid.

**3c**: bp 100 °C (0.1 Torr). IR (neat): 1720 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.75 (9H, s), 7.30—7.95 (4H, m), 8.40—8.70 (2H, m). $^{13}$C-NMR ($CDCl_3$) $\delta$: 28.3, 83.2, 123.0, 126.0, 126.2, 127.1, 128.2, 130.4, 136.8, 141.7, 151.4, 165.7. MS *m/z*: 229 (M$^+$). *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.39; H, 6.64; N, 6.05.

**14*H*-Imidazo[2,1-*a*:4,3-*a*′]diisoquinolin-14-one (7)** A mixture of **1d** (1.46 g, 5 mmol) and **2a** (1.31 g, 6 mmol) in dry benzene (15 ml) was stirred for 48 h at room temperature under an argon atmosphere. The insoluble substance that separated from the solution was collected by filtration. Recrystallization from EtOH gave **7** (0.52 g, 73%) as red small needles.

**2-Quinolinecarboxylic *tert*-Butylcarbonic Anhydride (8b)** A solution of $Et_3N$ (3.04 g, 30 mmol) was added dropwise to an ice-salt-cooled mixture of 2-quinolinecarboxylic acid (5.2 g, 30 mmol) and *tert*-butyl chlorocarbonate[10] (4.1 g, 30 mmol) in dry $Et_2O$ (200 ml) with stirring. The reaction mixture was kept at the same temperature for 1 h and then at an ambient temperature for 1 h. The resulting mixture was washed successively with 10% $Na_2CO_3$ solution and water, dried, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography ($Et_2O$) to give **8b** (6.39 g, 78%) as a colorless powder, mp 59—60 °C (from $Et_2O$). IR (KBr): 1792, 1738 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.60 (9H, s), 7.53—8.03 (3H, m), 8.10—8.50 (3H, m). MS *m/z*: 273 (M$^+$). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 65.67; H, 5.43; N, 4.99.

**1-Isoquinolinecarboxylic *tert*-Butylcarbonic Anhydride (8c)** This compound was prepared from 1-isoquinolinecarboxylic acid (5.2 g, 30 mmol), *tert*-butyl chlorocarbonate[10] (4.1 g, 30 mmol), and $Et_3N$ (3.04 g, 30 mmol) by the same procedure as described for **8b**; yield 5.8 g (71%); an orange oil. IR (KBr): 1801, 1758 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.60 (9H, s), 7.53—8.03 (4H, m), 8.66 (1H, d, $J$ = 5.5 Hz), 8.80—9.10 (1H, m). MS *m/z*: 179 (M$^+$). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 66.22; H, 5.56; N, 4.91.

**Reaction of 2-Trimethylstannylquinoline (1c) with *p*-Nitrobenzoic *tert*-Butylcarbonic Anhydride (8a)** A mixture of **1c** (1.46 g, 5 mmol) and **8a** (2.67 g, 10 mmol) in dry benzene (15 ml) was refluxed for 8 h under an argon atmosphere, then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane : $Et_2O$ = 10 : 1) to give **9** (0.603 g, 43%) as colorless prisms, **10** (0.13 g, 10%) as a colorless powder, and **11** (0.10 g, 14%) as a colorless liquid.

**9**: mp 173—174 °C (from benzene). IR (KBr): 1670 cm$^{-1}$. $^1$H-NMR

(CDCl$_3$) δ: 7.53—8.65 (10H, m). MS *m/z*: 278 ($M^+$). *Anal.* Calcd for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 69.15; H, 3.57; N, 9.79.

**10**: mp 106—108 °C (dec.) (from pentane). IR (KBr): 1756 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) δ: 1.43 (9H, s), 7.33—8.50 (16H, m). $^{13}$C-NMR (CDCl$_3$) δ: 27.7, 82.9, 88.8, 121.0, 122.9, 127.0, 127.1, 127.4, 129.5, 129.6, 129.8, 136.1, 146.8, 147.1, 149.4, 151.4, 159.2. MS *m/z*: 507 ($M^+$). *Anal.* Calcd for $C_{30}H_{25}N_3O_5$: C, 70.99; H, 4.96; N, 8.28. Found: C, 70.89; H, 5.02; N, 8.11.

**Reaction of 2-Trimethylstannylquinoline (1c) with 2-Quinolinecarboxylic *tert*-Butylcarbonic Anhydride (8b)** A mixture of **1c** (0.584 g, 2 mmol) and **8b** (1.1 g, 4 mmol) in dry benzene (15 ml) was refluxed for 24 h under an argon atmosphere, followed by addition of **8b** (1.1 g, 4 mmol) every 8 h. After concentration *in vacuo*, the residue was purified by silica gel flash column chromatography (hexane : $Et_2O$ = 3 : 1) to give **3b** (1.13 g, 41%)[11] as colorless prisms, **11** (0.082 g, 32%) as a colorless liquid, and **5** (0.085 g, 15%) as pale yellow prisms.

**Reaction of 1-Trimethylstannylisoquinoline (1d) with 1-Isoquinolinecarboxylic *tert*-Butylcarbonic Anhydride (8c)** A mixture of **1d** (0.73 g, 2.5 mmol) and **8c** (0.69 g, 2.5 mmol) in dry benzene (15 ml) was stirred for 48 h at room temperature under an argon atmosphere. The insoluble substance was separated from the solution by filtration. Recrystallization from EtOH gave **7** (0.61 g, 86%) as red small needles.

**Thermal Decomposition of 4** A solution of **4** (0.10 g, 0.2 mmol) in benzene (5 ml) was refluxed for 55 h, then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane : AcOEt = 2 : 1) to give **5** (0.05 g, 90%) as pale yellow prisms.

**Acidolysis of 4** A 10% HCl solution (2 ml) was added to a solution of **4** (0.10 g, 0.2 mmol) in THF (10 ml), and the mixture was heated under reflux for 1 h, then concentrated under reduced pressure. The resulting mixture was made alkaline with $Na_2CO_3$, and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ layer was dried and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane : AcOEt = 2 : 1) to give **5** (0.052 g, 92%) as pale yellow prisms.

**Thermal Decomposition of 8b** A solution of **8b** (0.273 g, 1 mmol) in xylene (10 ml) was refluxed for 5 h, then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane : $Et_2O$ : $CH_2Cl_2$ = 3 : 1 : 1) to give **3b** (0.14 g, 61%) as colorless prisms and **5** (0.03 g, 21%) as pale yellow prisms.

**Thermal Decomposition of 8c** A solution of **8c** (0.10 g, 0.37 mmol) in benzene (10 ml) was refluxed for 5 h, then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane : AcOEt = 2 : 1) to give **3c** (0.01 g, 12%) as a colorless liquid and **12** (0.04 g, 76%) as colorless prisms.

**12**: mp 194—195 °C (from $Et_2O$) [lit.[9] 199—200 °C].

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**References and Notes**


1) Part VI: Yamamoto Y., Ouchi H., Tanaka T., *Chem. Pharm. Bull.*, **43**, 1028 (1995).
2) *a*) Pereyre M., Quintard J.-P., Rahm A., "Tin in Organic Synthesis," Butterworths, London, 1987; *b*) Wardell J. L., "The Use of Organotin Compounds in Organic Synthesis" in "Chemistry of Tin," ed. by Harrison P. G., Chapman and Hall, New York, 1989, pp. 315—358.
3) *a*) Yamamoto Y., Yanagi A., *Chem. Pharm. Bull.*, **30**, 2003 (1982); *b*) Yamamoto Y., Azuma Y., Mitoh H., *Synthesis*, **1986**, 564; *c*) Bailey T. R., *Tetrahedron Lett.*, **27**, 4407 (1986); *d*) Sandosham J., Benneche T., Moller B. S., Undheim K., *Acta Chem. Scand.*, **B42**, 455 (1988); *e*) Sandosham J., Undheim K., *Acta Chem. Scand.*, **B43**, 684 (1989); *f*) Arukwe J., Benneche T., Undheim K., *J. Chem. Soc., Perkin Trans. 1*, **1989**, 255; *g*) Majeed A. J., Antonsen O., Benneche T., Undheim K., *Tetrahedron*, **45**, 993 (1989); *h*) Godard A., Rovera J.-C., Marsais F., Ple N., Queguiner G., *Tetrahedron*, **48**, 4123 (1992); *i*) Kelly T. R., Kim M. H., *J. Org. Chem.*, **57**, 1593 (1992).
4) *a*) Dean C. S., Tarbell D. S., Friederang A. W., *J. Org. Chem.*, **35**, 3393 (1970); *b*) Pope B. M., Yamamoto Y., Tarbell D. S., *Org. Syn.*, **57**, 45 (1977).
5) Hamana M., Yamazaki M., *Chem. Pharm. Bull.*, **11**, 415 (1963).
6) Krollpfeiffer F., Schneider K., *Justus Liebigs Ann. Chem.*, **530**, 34 (1937).
7) Michejda C. J., Tarbell D. S., *J. Org. Chem.*, **29**, 1168 (1964).
8) Pathway A was suggested from the migration of the ethoxycarbonyl group to the α-position of the pyridine ring, along with loss of carbon monoxide, in the reaction of 2-trimethylstannylpyridine with ethyl chloroglyoxylate, as shown in the preceding paper.[1]
9) Engl R. B., Ingraham L. L., *J. Org. Chem.*, **26**, 4933 (1961).
10) Choppin A. R., Rogers J. W., *J. Am. Chem. Soc.*, **70**, 2967 (1948).
11) The theoretical amount of **3b** is based on the total amount of **8b** and **1c**, because **3b** is formed both by decomposition of **8b** and reaction of **1c** with **8b**.