Studies on Organometallic Compounds. VII.¹⁾ Reaction of Di-*tert*-butyl Dicarboxate with α -Trialkylstannyl Derivatives of Pyridine, Quinoline, and Isoquinoline

Yutaka YAMAMOTO,* Hidekazu OUCHI, and Takuo TANAKA

Tohoku College of Pharmacy, 4-1, Komatsushima 4-chome, Aoba-ku, Sendai 981, Japan.

Received November 16, 1994; accepted January 30, 1995

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; alkoxy-carbonylation; 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 alkoxy-carbonyl 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-pyridine-carboxylate (**3a**) as a sole product in 87% yield. 2-Tri-*n*-butylstannylpyridine (**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

Chart 1

Chart 2

* To whom correspondence should be addressed.

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

Starting material		2a mmol	Solvent	Temp.	Time (h)	Product			
No.	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*-nitrobenzoyl carbonyl 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 A⁸⁾ 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. ^1H - 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} . ^1H -NMR (CDCl_3) δ : 1.63 (9H, s), 7.20–8.10 (3H, m), 8.60–8.80 (1H, m). ^{13}C -NMR (CDCl_3) δ : 28.1, 82.0, 124.7, 126.4, 136.8, 149.5, 149.8, 164.1. MS m/z : 179 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_2$: 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} . ^1H -NMR (CDCl_3) δ : 1.70 (9H, s), 7.50–8.43 (6H, m). ^{13}C -NMR (CDCl_3) δ : 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 $\text{C}_{14}\text{H}_{15}\text{NO}_2$: 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} . ^1H -NMR (CDCl_3) δ : 1.43 (18H, s), 7.20–7.83 (6H, m), 7.93–8.30 (6H, m). ^{13}C -NMR (CDCl_3) δ : 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 $\text{C}_{29}\text{H}_{30}\text{N}_2\text{O}_6$: 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} . ^1H -NMR (CDCl_3) δ : 1.36 (9H, s), 7.20–8.20 (18H, m). ^{13}C -NMR (CDCl_3) δ :

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 $\text{C}_{33}\text{H}_{27}\text{N}_3\text{O}_3$: 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} . ^1H -NMR (CDCl_3) δ : 1.75 (9H, s), 7.30–7.95 (4H, m), 8.40–8.70 (2H, m). ^{13}C -NMR (CDCl_3) δ : 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 $\text{C}_{14}\text{H}_{15}\text{NO}_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.39; H, 6.64; N, 6.05.

1*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 chlorocarbonate¹⁰ (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} . ^1H -NMR (CDCl_3) δ : 1.60 (9H, s), 7.53–8.03 (3H, m), 8.10–8.50 (3H, m). MS m/z : 273 (M^+). Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_4$: 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 chlorocarbonate¹⁰ (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} . ^1H -NMR (CDCl_3) δ : 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 $\text{C}_{15}\text{H}_{15}\text{NO}_4$: 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} . ^1H -NMR

(CDCl₃) δ : 7.53–8.65 (10H, m). MS m/z : 278 (M⁺). Anal. Calcd for C₁₆H₁₀N₂O₃: 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. ¹H-NMR (CDCl₃) δ : 1.43 (9H, s), 7.33–8.50 (16H, m). ¹³C-NMR (CDCl₃) 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 C₃₀H₂₅N₃O₅: 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:Et₂O=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 Na₂CO₃, and extracted with CH₂Cl₂. The CH₂Cl₂ 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:Et₂O:CH₂Cl₂=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 Et₂O) [lit.⁹⁾ 199–200 °C].

Acknowledgement The authors are grateful to Mr. S. Satoh of this College for the measurements of ¹³C-NMR spectra, MS, and elemental analyses.

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