CARBON FUNCTIONALIZATIONS ON PYRIDINE RING *VIA* TRIMETHYLSTANNYL DERIVATIVES-----AN EXAMPLE OF FUSARIC ACID SYNTHESIS-----

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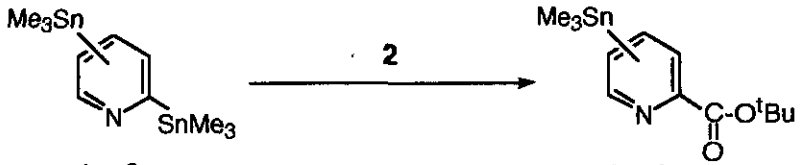
Abstract --- Method for introduction of two types of carbon functional groups, acyl and *tert* - butoxycarbonyl groups, in pyridine ring *via* bis(trimethylstannyl)pyridine (**1**) is explored. Application of this method to the synthesis of fusaric acid (**11**) is also described.

There have been reported many papers[1] concerning with carbon-carbon bond formation on pyridine ring system, because of the difficulty in introduction of carbon functional group into pyridine ring by electrophilic reagents. Especially, interest in organostannyl group has rapidly increased owing to the potential utility[2] for such purpose. An effective method for carbon-carbon bond formation on pyridine ring through the trimethylstannyl (TMSn) derivatives has been reported from our laboratory.[3] Thus, in the reaction of TMSn derivatives with acyl chloride, the TMSn group at the α-position to the ring nitrogen was found replaced in the absence of a catalyst, whereas the reaction of the TMSn groups at β- and γ-positions required palladium compound as a catalyst. We wish to report in this paper the method for introduction of two functional groups of acyl and *tert*-butoxycarbonyl in pyridine ring *via* bis(trimethylstannyl)pyridine (**1**) and an application to synthesis of fusaric acid (**11**).

First, synthesis of *tert*-butyl trimethylstannylpyridine-2-carboxylates (**3**) by reaction of four isomers of bis(trimethylstannyl)pyridine with di-*tert*-butyl dicarbonate[4] (**2**) was simply carried out by regiospe-

cific replacement of 2-TMSn group. For example, a benzene solution of 2,3-bis(trimethylstannyl)-pyridine (**1a**) and **2** was heated under reflux to give *tert*-butyl 3-trimethylstannylpyridine-2-carboxylate (**3a**) in 85% yield. By a similar procedure, the other esters (**3b** - **d**) were prepared in good yields (Scheme 1).

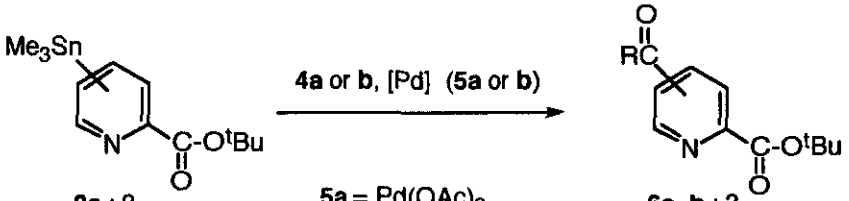


1a : 3-
b : 4-
c : 5-
d : 6-

3a : 3-
b : 4-
c : 5-
d : 6-

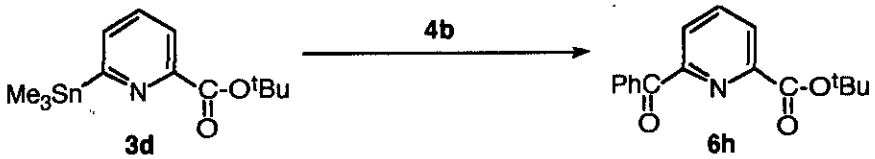
Scheme 1

Next, introduction of the second carbon functional group onto the pyridinecarboxylate (**3a** - **d**) was performed in the presence of a palladium catalyst (**5a**,**b**) using cyclohexanecarbonyl chloride (**4a**) and benzoyl chloride (**4b**) as aliphatic and aromatic acylating agents (Scheme 2).



3a : 3-
b : 4-
c : 5-
d : 6-

6a, **b** : 3-
c, **d** : 4-
e, **f** : 5-
g, **h** : 6-

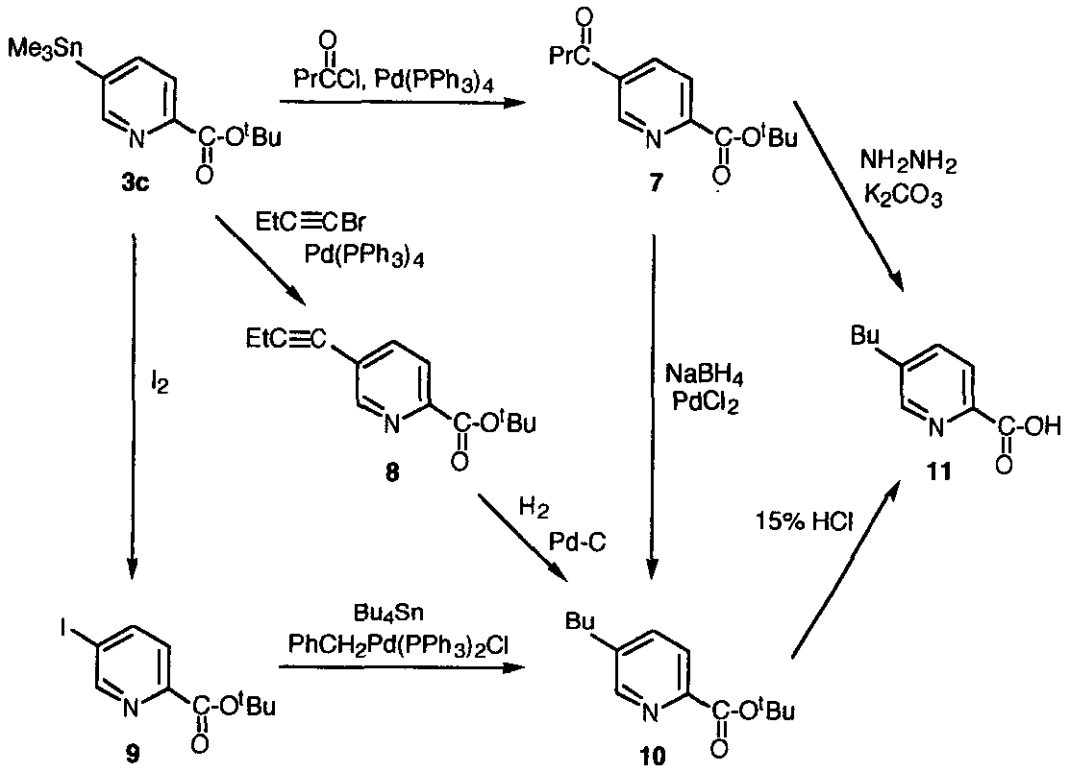


3d **6h**

Scheme 2

Finally, as an extension of the above reactions, preparation of fusaric acid (**11**)[5] was accomplished by the following three pathways (Scheme 3). Route A; 5-butyrylpyridine (**7**) was synthesized from **3c** and butyryl chloride (**4c**), followed by reduction with sodium borohydride leading to ester (**10**). Route B; cross-coupling reaction of **3c** with 1-butynyl bromide led to **8**, followed by hydrogenation

in the presence of palladium-carbon leading to ester (**10**). Route C; quantitative destannylation-iodination of **3c** with iodine, followed by cross-coupling with tetrabutylstannane in the presence of a palladium catalyst afforded **10**. Thus obtained **10** was easily hydrolyzed to give fusaric acid (**11**). Wolff-Kishner reduction of **7** also gave **11** (Scheme 3). These methods have advantages in the following respects in comparison with the reported methods[6] ; a) yield in the each step is satisfactory, b) the reaction conditions are mild, c) the procedure is simple.



Scheme 3

EXPERIMENTAL

Benzene and toluene were distilled from calcium chloride and dried over sodium wire. Ethyl alcohol and methyl alcohol were distilled from magnesium and iodine. Chloroform was distilled from phosphorus pentoxide. Hexamethylphosphoric amide (HMPA) was distilled from calcium hydride. All melting and boiling points are uncorrected. Infrared spectra were taken with a PERKIN ELMER 1600 series FT-IR apparatus. ^{1}H-Nmr spectra were recorded on a JEOL JNM PMX-60Si. Chemical shifts are recorded in δ value (ppm) from tetramethylsilane (internal standard). The following ab-

breviations are used : s=singlet, t=triplet, q=quartet, br=broad, m=multiplet. Ms spectra were measured on a JEOL-DX303. All analytical data were measured on a PERKIN ELMER 2400 CHN Elemental Analyzer.

tert - Butyl Trimethylstannylpyridine-2-carboxylate (3a-d) . General Procedure.

A solution of **2** (3.45 g, 15 mmol) in benzene (50 ml) was added to a solution of **1** (4.06 g, 10 mmol) in benzene (50 ml). The mixture was refluxed for the period indicated in Table I. The resulting mixture was concentrated *in vacuo*. The oily residue was purified by distillation under reduced pressure to give **3**. The results obtained are summarized in Table I.

Table I. Synthesis of *tert*-Butyl Trimethylstannylpyridine-2-carboxylate (**3a-d**)

Product	Time (h)	Yield (%)	bp(°C/Torr)	Ir (cm^{-1})	^{1}H-Nmr	Formula Cl-Ms (M^+H)	Analysis (%) Calcd (Found)		
3a	48	85	97-100/0.015	1699.0 766.6	0.33 (9H, s),1.66 (9H, s),7.26-7.50 (1H, m), 7.92-8.13 (1H, m), 8.59-8.82 (1H, m)	$C_{13}H_{21}NO_2Sn$ (344)	45.47 (45.41	6.17 6.17	4.08 4.11)
3b	36	75	131-133/3	1735.4 1709 4 781.8	0.33 (9H, s), 1.66 (9H, s), 7.46-7.59 (1H, m), 8.16-8.23 (1H, m), 8.53-8 72 (1H, m)	$C_{13}H_{21}NO_2Sn$ (344)	45.47 (45 78	6.17 6.25	4.08 3.88)
3c	12	92	110-113/3	1725.1 743.8	0.33 (9H, s), 1.66 (9H, s), 7 95-8 10 (2H, m), 8.72-8.82 (1H, m)	$C_{13}H_{21}NO_2Sn$ (344)	45 47 (45.66	6.17 6.23	4.08 4.21)
3d	12	92	115-120/0.02	1734.3 1711.2 758.6	0.33 (9H, s), 1.66 (9H, s), 7.50-8.00 (3H, m)	$C_{13}H_{21}NO_2Sn$ (344)	45.47 (45.52	6.17 6 15	4.08 4.38)

tert - Butyl 3-Cyclohexylcarbonylpyridine-2-carboxylate (6a)

A solution of **4a** (1.75 g, 12 mmol) in benzene (50 ml) was added to a mixture of **3a** (3.44 g, 10 mmol) and **5a** (0.11 g, 0.5 mmol) in benzene (50 ml). The mixture was refluxed for 8 h. The resulting mixture was washed with saturated aqueous solution of Na_2CO_3 (20 ml). The aqueous layer was extracted with benzene (20 ml). The combined organic layer was dried over K_2CO_3, then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ether : hexane = 1 : 5) to give **6a**. Yield: 1.59 g (55%). mp 82-83°C. Ir (KBr):

1664, 1728 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.15-2.15 (19H, br), 2.60-3.15 (1H, br), 7.33-8.00 (2H, m), 8.70-8.81 (1H, m). Ms (m/z): 289 (M^+). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 70.59; H, 7.96; N, 4.84. Found: C, 70.59; H, 7.71; N, 4.86.

tert - Butyl 3-Benzoylpyridine-2-carboxylate (6b)

Following the procedure described for the preparation of **6a**, compound(**6b**) was isolated as a colorless oil. Yield: 1.44 g (51%). Ir (neat): 1673, 1731 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.33 (9H, s), 7.33-8.00 (7H, m), 8.81-9.00 (1H, m). Ms (m/z): 283 (M^+). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.01; N, 4.95. Found: C, 71.97; H, 5.89; N, 4.86.

tert - Butyl 4-Cyclohexylcarbonylpyridine-2-carboxylate (6c)

A solution of **4b** (1.75 g, 12 mmol) in benzene (50 ml) was added to a mixture of **3a** (3.44 g, 10 mmol) and **5b** (0.57 g, 0.5 mmol) in benzene (50 ml). The mixture was refluxed for 8 h. The resulting mixture was washed with saturated aqueous solution of Na_2CO_3 (20 ml). The aqueous layer was extracted with benzene (20 ml). The combined organic layer was dried over anhydrous K_2CO_3, then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ether : hexane = 1 : 5) to give **6c**. Yield: 2.51 g (87%). Ir (KBr): 1664, 1728 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.15-2.33 (19H, br), 3.00-3.50 (1H, br), 7.81-8.00 (1H, m), 8.33-8.66 (1H, m), 8.81-9.15 (1H, m). Ms (m/z): 289 (M^+). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 70.59; H, 7.96; N, 4.84. Found: C, 70.34; H, 8.04; N, 4.80.

tert - Butyl 4-Benzoylpyridine-2-carboxylate (6d)

Following the procedure described for the preparation of **6c**, compound (**6d**) was isolated as a colorless oil. Yield: 2.57 g (91%). Ir (neat): 1669, 1735 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.66 (9H, s), 7.33-8.10 (6H, m), 8.40-8.48 (1H, m), 8.90-9.10 (1H, m). Ms (m/z): 283 (M^+). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.01; N, 4.95. Found: C, 71.97; H, 5.93; N, 4.84.

tert - Butyl 5-Cyclohexylcarbonylpyridine-2-carboxylate (6e)

Following the procedure described for the preparation of **6c**, compound (**6e**) was isolated as a colorless solid. Yield: 2.19 g (76%). mp 95-96°C (hexane). Ir (KBr): 1681, 1728 cm^{-1}. ^{1}H-Nmr

($CDCl_3$) δ: 1.15-2.27 (19H, br), 3.00-3.50 (1H, br), 8.15-8.60 (2H, m), 9.30-9.35 (1H, m), 8.81-9.15 (1H, m). Ms (m/z): 289 (M^+). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 70.59; H, 7.96; N, 4.84. Found: C, 70.48; H, 7.98; N, 4.90.

***tert* - Butyl 5-Benzoylpyridine-2-carboxylate (6f)**

Following the procedure described for the preparation of **6c**, compound (**6f**) was isolated as a colorless solid. Yield: 2.12 g (75%). mp 115-116°C (hexane). Ir (KBr): 1662, 1727 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.66 (9H, s), 7.50-8.10 (5H, m), 8.15-8.33 (2H, m), 9.10-9.15 (1H, m). Ms (m/z): 283 (M^+). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.01; N, 4.95. Found: C, 71.85; H, 5.89; N, 4.86.

***tert* - Butyl 6-Cyclohexylcarbonylpyridine-2-carboxylate (6g)**

Following the procedure described for the preparation of **6c**, compound (**6g**) was isolated as a colorless oil. Yield: 2.54 g (88%). Ir (neat): 1697, 1739 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.15-2.33 (19H, br), 3.66-4.20 (1H, br), 7.95-8.33 (3H, m). Ms (m/z): 289 (M^+). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 70.59; H, 7.96; N, 4.84. Found: C, 70.56; H, 7.99; N, 4.97.

***tert* - Butyl 6-Benzoylpyridine-2-carboxylate (6h)**

Method A

Following the procedure described for the preparation of **6c**, compound (**6h**) was isolated as a colorless solid. Yield: 2.12 g (75%). mp 112-114°C (hexane). Ir (KBr): 1664, 1728 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.66 (9H, s), 7.50-7.73 (3H, m), 8.10-8.56 (5H, m). Ms (m/z): 283 (M^+). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.01; N, 4.95. Found: C, 72.25; H, 6.17; N, 5.00.

Method B

A solution of **4b** (1.75 g, 12 mmol) in toluene (50 ml) was added to a solution of **3d** (3.44 g, 10 mmol) in toluene (50 ml). The mixture was refluxed for 8 h and worked up by the same procedure as described above for **6a** to give **6h**. Yield: 1.83 g (65%).

***tert* - Butyl 5-Butyrylpyridine-2-carboxylate (7)**

A solution of butyryl chloride (0.64 g, 6 mmol) in benzene (30 ml) was added to a mixture of **3c** (1.72 g, 5 mmol) and **5b** (0.28 g, 0.25 mmol) in benzene (30 ml). The mixture was refluxed for 8 h. The resulting mixture was washed with saturated aqueous solution of Na_2CO_3 (20 ml). The aqueous layer was extracted with benzene (20 ml). The combined organic layer was dried over anhydrous K_2CO_3, then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ether : hexane = 1 : 4) to give **7** (77%). mp 80-81°C (hexane). Ir (KBr): 1689, 1728 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.82-2.16 (14H, m), 2.82-3.33 (3H, m), 8.07-8.50 (2H, m), 9.23-9.50 (1H, m). Ms (m/z): 249 (M^+). *Anal.* Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.47; H, 7.94; N, 5.51.

tert - Butyl 5-Butynylpyridine-2-carboxylate (8)

A mixture of **3c** (1.72 g, 5 mmol), 1-butynyl bromide (0.79 g, 6 mmol), and **5b** (0.28 g, 0.25 mmol) in benzene (50 ml) was heated under reflux for 48 h. The resulting mixture was worked up by the same procedure as described above for **7** to give **8** (84%). bp 110-112°C (1.1 torr.). Ir (neat): 1712, 1736 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.33 (3H, t, J =8 Hz), 1.66 (9H, s), 2.50 (2H, q, J =6 Hz), 7.66-8.15 (2H, m), 8.69-8.85 (1H, m). Ms (m/z): 231 (M^+). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 72.43; H, 7.39; N, 5.75. Found: C, 72.69; H, 7.39; N, 5.75.

tert - Butyl 5-Iodopyridine-2-carboxylate (9)

A solution of iodine (0.88 g, 6 mmol) in $CHCl_3$ (30 ml) was added to a solution of **3c** (1.72 g, 5 mmol) in $CHCl_3$ (30 ml). The reaction mixture was stirred for 3 h at room temperature and washed with saturated aqueous solution of $Na_2S_2O_4$ (20 ml). The aqueous layer was extracted with $CHCl_3$ (20 ml). The combined organic layer was dried over anhydrous K_2CO_3, then filtered. The filtrate was concentrated *in vacuo*. The black oily residue was purified by column chromatography on alumina (ether) to give **9** (91%). mp 112-113°C (hexane). Ir (KBr): 1725 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.66 (9H, s), 7.66-7.86 (1H, m), 8.00-8.23 (1H, m), 8.92-9.00 (1H, m). Ms (m/z): 305 (M^+). *Anal.* Calcd for $C_{10}H_{12}INO_2$: C, 39.35; H, 3.97; N, 4.59. Found: C, 39.60; H, 3.88; N, 4.37.

tert - Butyl 5-Butyrylpyridine-2-carboxylate (10)

Method A: A mixture of **7** (0.51 g, 2 mmol), $NaBH_4$ (0.37 g, 10 mmol) and $PdCl_2$ (1.77 g, 10 mmol) in MeOH (50 ml) was stirred for 0.5 h at room temperature. The resulting mixture was acidified with 15% HCl and filtered. The filtrate was concentrated under reduced pressure, followed by extraction with $CHCl_3$ (20 ml × 3). The organic layer was dried over anhydrous K_2CO_3 then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ether : hexane = 1 : 10) to give **10** (88%). bp 122-123 °C (3 torr.). Ir (neat): 1709, 1734 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 0.81-2.00 (16H, m), 2.45-2.66 (2H, m), 7.50-7.73 (1H, m), 7.83-8.10 (1H, m), 8.50-8.66 (1H, m). Ms (m/z): 235 (M^+). *Anal.* Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.9; N, 5.95. Found: C, 71.27; H, 8.78; N, 5.97.

Method B: A mixture of **8** (0.46 g, 2 mmol) and 5% Pd-C (0.10 g) in EtOH (50 ml) was stirred for 3 h under hydrogen at room temperature. After filtration of the catalyst, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ether : hexane = 1 : 10) to give **10** (96%). The ir spectrum of **10** was identical with that a sample prepared by the method A.

Method C: A mixture of **9** (1.15 g, 3 mmol), tetrabutylstannane (1.25 g, 3.6 mmol) and $PhCH_2Pd(PPh_3)_2Cl$ (0.15 g, 0.2 mmol) in HMPA (10 ml) was heated at 70°C for 8 h. The reaction mixture was poured into water and extracted with hexane. After concentration of the hexane layer *in vacuo*, the crude product was purified by column chromatography on silica gel (ether : hexane = 1 : 100) to give **10**. Yield: 0.97 g (84%). The ir spectrum of **10** was identical with that a sample prepared by the method A.

Fusaric Acid (11)

A solution of **10** (0.23 g, 1 mmol) in THF (50 ml) was added to 15% HCl (50 ml) at room temperature and stirred for 3 h. The reaction mixture was concentrated *in vacuo*. The pH of the residue was adjusted to 3.5 with saturated Na_2CO_3 and extracted with ether (30 ml × 3). The ether layer was dried over $MgSO_4$, then filtered. The filtrate was concentrated *in vacuo*. The residue was recrystallized from hexane to give **11**. Yield ; 0.17 g (93%). This compound was identical in all respects with an authentic sample prepared by the reported procedure. [6i]

Wolff-Kishner Reduction of 7

A mixture of **7** (1.06 g, 4.3 mmol), 80% hydrazine monohydrate (0.46 g, 14.6 mmol), and KOH (0.48 g, 8.6 mmol) in triethylene glycol (10 ml) was heated with stirring at 110°C for 3 h. The reaction mixture was dissolved into water (50 ml), and pH was adjusted to 3.5 by using H_3PO_4. The solution was extracted with ether (30 ml × 3). The ether layer was dried over anhydrous $MgSO_4$, then filtered. The filtrate was concentrated *in vacuo*. The residue was recrystallized from hexane to give **11**. Yield: 0.45 g (55%).

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