Simple and Mild Method for Preparation of α-Pyridinecarboxylates and α-Pyridyl Ketones *via* Trimethylstannyl Derivatives[1)]

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Alkoxycarbonylation and acylation at the α-position of pyridine, quinoline, and isoquinoline *via* the respective trimethylstannyl derivatives were satisfactorily performed by employing ethyl chloroglyoxylate and acylformyl chloride under mild conditions.

Key words trialkylstannylazine; bis(trimethylstannyl)azine; alkoxycarbonylation; acylation; ethyl chloroglyoxylate; acylformyl chloride

Recently, there has been a great increase in the use of organostannyl compounds for carbon–carbon bond formation.[2)] In the field of electron-deficient *N*-heterocycles, especially, the organostannyl group is a powerful tool for functionalization.[3)] A previous paper[3a)] from our laboratory has described acylation in the pyridine ring system by the reactions of trimethylstannyl (TMSn) derivatives with acyl chlorides, in which the TMSn group at the α-position to the pyridine ring nitrogen was spontaneously replaced, giving the corresponding α-acylated derivatives. Our attention was focused on application of the α-located TMSn group to functionalization of such *N*-heterocycles. This report describes direct introduction of ethoxycarbonyl and acyl groups at the α-position of the pyridine ring by the use of ethyl chloroglyoxylate and acylformyl chloride.

2-TMSn-pyridine (**1a**) was treated with ethyl chloroformate (**2**) at room temperature in a similar manner to that described in a previous paper,[3a)] to give ethyl 2-pyridinecarboxylate (**4a**) in only 25% yield. Analogously, reaction of 1-TMSn-isoquinoline (**1c**) with **2** afforded ethyl 1-isoquinolinecarboxylate (**4c**) in 34% yield.

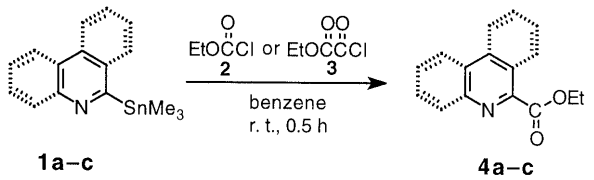

Chart 1

Table 1. Preparation of 2-Pyridine- (**4a**), 2-Quinoline- (**4b**), and 1-Isoquinolinecarboxylate (**4c**)[a)]

Starting material	No.	Electrophile	No.	Product No.	Yield (%)	bp, °C	(Torr)
2-TMSn-Py	**1a**	EtOCOCl	**2**	**4a**	25	85	(5.0)[b)]
2-TMSn-Qu	**1b**	EtOCOCl	**2**	**4b**	0		
1-TMSn-IQ	**1c**	EtOCOCl	**2**	**4c**	34	113	(0.2)[c)]
2-TMSn-Py	**1a**	EtOCOCOCl	**3**	**4a**	85	80—82	(4.0)[b)]
2-TMSn-Qu	**1b**	EtOCOCOCl	**3**	**4b**	82	110	(0.2)[d)]
1-TMSn-IQ	**1c**	EtOCOCOCl	**3**	**4c**	91	108—110	(0.2)[c)]

a) The following abbreviations are used: TMSn = trimethylstannyl, Py = pyridine, Qu = quinoline, IQ = isoquinoline. *b*) Lit.[4)] bp 241—243 °C (760 Torr). *c*) Lit.[5)] bp 197—199 °C (20 Torr). *d*) Lit.[6)] bp 131—136 °C (0.3 Torr).

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In the above reactions, employing ethyl chloroglyoxylate (**3**) instead of **2** dramatically increased the yield of the desired ester; thus, when **1a** was treated with **3** in benzene at room temperature for 0.5 h, **4a** was obtained in 85% yield, accompanied with loss of carbon monoxide. 2-TMSn-quinoline (**1b**) and 1-TMSn-isoquinoline (**1c**) similarly reacted with **3**, affording the corresponding esters **4** in satisfactory yields (Table 1).

The formation of the ester **4** presumably proceeds *via* the following sequence involving the intermediate II, through migration of the ethoxycarbonyl group to the 2-position with loss of carbon monoxide[7)] and chlorotrimethylstannane (pathway B), as shown in Chart 2. The migration would take place more readily than that of the ethoxycarbonyl group in the case of employing **2** (pathway A).

Reaction of 2-tributylstannylpyridine (**1d**) with **3**, meanwhile, gave rise to a small amount of ethyl 2-pyridylglyoxylate (**5**), besides the expected **4a** (Chart 3).

The formation of **5** implies another pathway D; that is, another mole of **3** reacted with the intermediate II before the migration of the ethyl glyoxylate moiety, followed by simultaneous release of chlorotrimethylstannane and **3**,

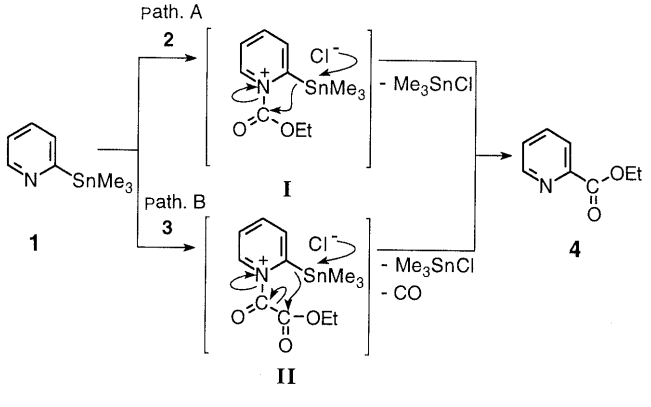

Chart 2

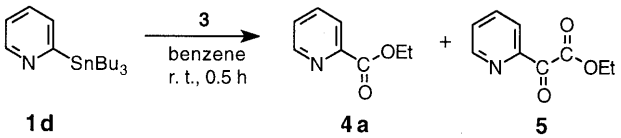

Chart 3

leading to **5**.

Use of pyruvoyl chloride (**6a**) and benzoylformyl chloride (**6b**) brought about a synthesis of pyridyl ketones; 2-TMSn-pyridine (**1a**) reacted with **6a** and **6b** yielded methyl 2-pyridyl ketone (**7a**) and phenyl 2-pyridyl ketone (**7b**) in 83% and 91% yields, respectively. Similar treatment of 2-TMSn-quinoline (**1b**), 1-TMSn-isoquinoline (**1c**), and 2-tributylstannylpyridine (**1d**) with **6a, b** afforded the corresponding ketones. The results obtained are summarized in Table 2.

Diacylation of 2,6-bis(TMSn)-pyridine (**1e**) also took place; thus, the bis(TMSn) derivative **1e** was treated with **6a** and **6b** to give 2,6-diacetylpyridine (**8a**) and 2,6-dibenzoylpyridine (**8b**), respectively. Interestingly, ethyl 6-ethoxycarbonyl-2-pyridylglyoxylate (**9a**) was generated in the reaction with **3**, together with 2,6-diethoxycarbonylpyridine (**8c**). The formation of **9a** can be explained in terms of stepwise diacylation and dialkoxycarbonylation. Thereby, stepwise diacylation was satisfactorily accomplished; monoacylated **10a** was obtained in 94% yield from **1e** and 1 eq of **6b**, followed by treatment with another equivalent of **6b** to yield **8b** quantitatively. The ester **8d** was also formed from **1e** through the same sequential steps *via* **10b**. Similar treatment of **10a** and **10b** with **3** afforded the corresponding **8c, d** and **9a, b**, respectively, which were also generated by direct dialkoxycarbonylation of **1e** with 2 eq of **3**. Accordingly, the first acylation of **1e** with **3** or **6b** took place with loss of carbon monoxide and the second acylation proceeded with or without loss of carbon monoxide. The basicity of the substrate clearly influences the reaction mode of **3**.

Consequently, the direct introduction of ethoxycarbonyl and acyl groups at the α-position of the pyridine ring by means of ethyl chloroglyoxylate and acylformyl chloride

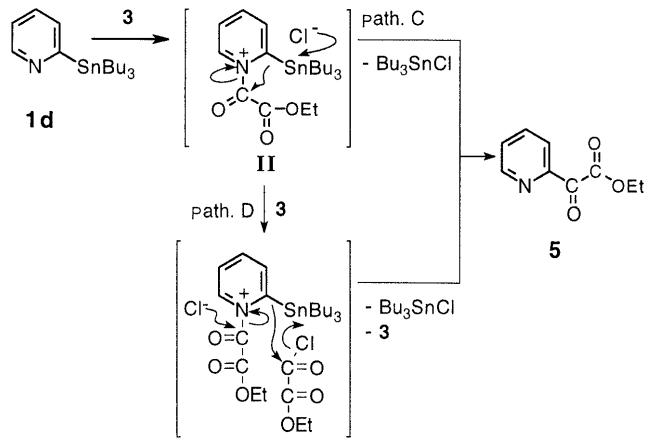

Chart 4

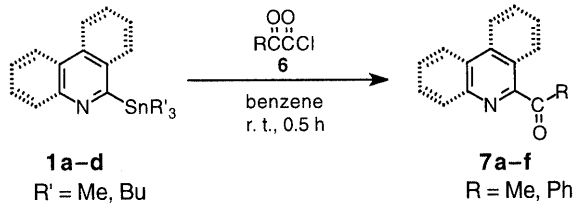

Chart 5

Table 2. Preparation of 2-Pyridyl (**7a, b**), 2-Quinolyl (**7c, d**), and 1-Isoquinolyl Ketones (**7e, f**)[a]

Starting material	No.	RCOCOCl		Product				
		R	No.	No.	Yield (%)	bp, °C	(Torr)	mp, °C
2-TMSn-Py	**1a**	Me	**6a**	**7a**	83	94—95	(40.0)[b]	
		Ph	**6b**	**7b**	91	92—95	(0.2)[c]	
2-TMSn-Qu	**1b**	Me	**6a**	**7c**	88			51—52[d]
		Ph	**6b**	**7d**	93			108—109[e]
1-TMSn-IQ	**1c**	Me	**6a**	**7e**	81	115—117	(3.0)[f]	
		Ph	**6b**	**7f**	92			76—77[g]
2-TBSn-Py	**1d**	Me	**6a**	**7a**	91	83	(25.0)[b]	
		Ph	**6b**	**7b**	87	105	(1.0)[c]	

a) The following abbreviations are used: TMSn = trimethylstannyl, TBSn = tributylstannyl, Py = pyridine, Qu = quinoline, IQ = isoquinoline. *b*) Lit.[8] bp 188—189 °C (760 Torr). *c*) Lit.[9] bp 165 °C (7 Torr). *d*) Lit.[6] mp 47.5—48 °C. *e*) Lit.[9] mp 111 °C. *f*) Lit.[5] bp 145—149 °C (11 Torr). *g*) Lit.[10] mp 74—77 °C.

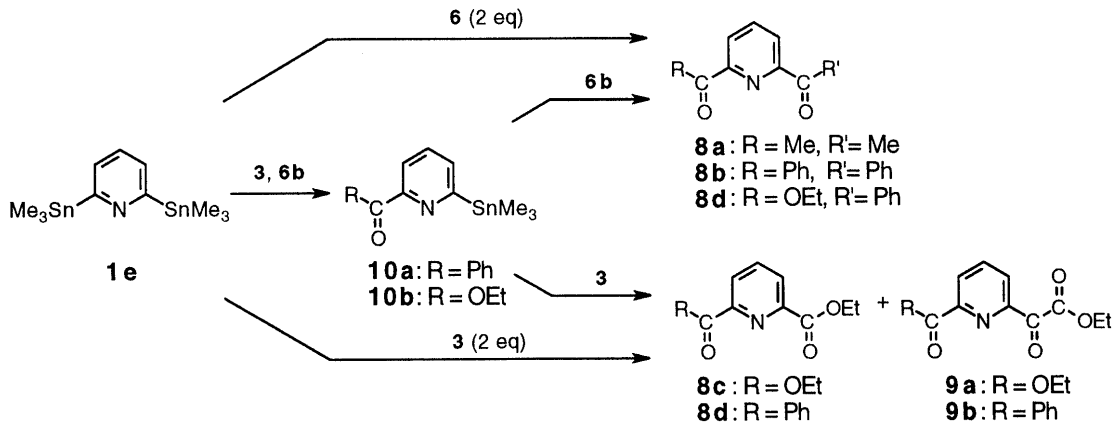

Chart 6

was achieved in sufficient yield under milder conditions than required in the previous acylation with acyl chloride, and this procedure should be advantageous for functionalization of π-deficient *N*-heterocycles.

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-NMR spectra were recorded on a JEOL JNM-PMX 60si spectrometer, using tetramethylsilane as an internal standard. Column chromatography was carried out on Merck Silica gel 60 (230—400 mesh for flash chromatography).

2-Trimethylstannylpyridine,[11] 2-trimethylstannylquinoline,[11] 1-trimethylstannylisoquinoline,[11] 2-tributhylstannylpyridine,[12] 2,6-bis(trimethylstannyl)pyridine,[11] pyruvoyl chloride,[13] and benzoylformyl chloride[13] were prepared according to the cited methods. Ethyl chloroformate and ethyl chloroglyoxylate were used as received.

Ethyl 2-Pyridinecarboxylate (4a): General Procedure for the Synthesis of 4a—c and 7a—f A solution of **3** (0.82 g, 6 mmol) was added dropwise to a stirred solution of **1a** (1.21 g, 5 mmol) in dry benzene (15 ml), with stirring under an argon stream for 0.5 h at room temperature. The reaction mixture was washed successively with 10% aqueous NH_3 solution (10 ml) and saturated NaCl solution (10 ml), dried, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane : Et_2O = 3 : 1) to give **4a** (0.64 g, 85%) as a colorless liquid (Tables 1 and 2).

Ethyl 2-Pyridylglyoxylate (5) This compound was prepared from **3** (0.82 g, 6 mmol) and **1d** (1.84 g, 5 mmol) in dry benzene (15 ml) according to the procedure described for **4a**. The oily substance obtained was purified by silica gel flash column chromatography (hexane : Et_2O = 1 : 1) to give **5** (0.17 g, 19%) as a colorless liquid and **4a** (0.46 g, 61%) as a colorless liquid. **5**: bp 85—88 °C (0.5 Torr). IR (neat): 1745, 1708 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J = 7 Hz), 4.50 (2H, q, J = 7 Hz), 7.40—8.23 (3H, m), 8.65—8.86 (1H, m). MS *m/z*: 179 (M^+). *Anal.* Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.54; H, 5.09; N, 7.64.

2,6-Diacetylpyridine (8a) A solution of **6a** (0.64 g, 6 mmol) was added dropwise to a stirred solution of **1e** (1.01 g, 2.5 mmol) in dry benzene (15 ml), with stirring under an argon stream for 0.5 h at room temperature. The reaction mixture was washed successively with 10% aqueous NH_3 solution (10 ml) and saturated NaCl solution (10 ml), dried, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane : Et_2O = 3 : 1) to give **8a** (0.24 g, 59%) as colorless needles, mp 79—80 °C (from hexane) [lit.[14] mp 79 °C].

2,6-Dibenzoylpyridine (8b) i) This compound was prepared from **6b** (1.01 g, 6 mmol) and **1e** (1.01 g, 2.5 mmol) in dry benzene (15 ml) according to the procedure described for the preparation of **8a**. Yield, 0.705 g (98%); mp 107—108 °C (from Et_2O) [lit.[15] mp 108—109 °C].

ii) This compound was prepared from **6b** (0.202 g, 1.2 mmol) and **10a** (0.346 g, 1 mmol) in dry benzene (5 ml) according to the procedure described for the preparation of **8a**. Yield, 0.285 g (99%).

Ethyl 6-Benzoyl-2-pyridinecarboxylate (8d) This compound was prepared from **6b** (0.202 g, 1.2 mmol) and **10b** (0.314 g, 1 mmol) in dry benzene (5 ml) according to the procedure described for the preparation of **8a**. Yield, 0.23 g (90%); mp 107—108 °C (from hexane). IR (KBr): 1723, 1672 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J = 7 Hz), 4.46 (2H, q, J = 7 Hz), 7.26—7.70 (3H, m), 7.83—8.46 (5H, m). MS *m/z*: 255 (M^+). *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.61; H, 5.17; N, 5.30.

Ethyl 6-Ethoxycarbonyl-2-pyridylglyoxylate (9a) i) This compound was prepared from **3** (0.82 g, 6 mmol) and **1e** (1.01 g, 2.5 mmol) in dry benzene (15 ml) according to the procedure described for the preparation of **8a**. The residue was purified by silica gel flash column chromatography (hexane : Et_2O = 1 : 1) to give **9a** (0.22 g, 35%) as colorless needles and **8c** (0.06 g, 11%) as colorless needles. **9a**: mp 52—53 °C (from hexane). IR (KBr): 1748, 1724, 1709 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J = 7 Hz), 1.47 (3H, t, J = 7 Hz), 4.43 (2H, q, J = 7 Hz), 4.56 (2H, q, J = 7 Hz), 7.90—8.50 (3H, m). MS *m/z*: 251 (M^+). *Anal.* Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.30; H, 5.31; N, 5.53. **8c**: mp 39—40 °C (from pentane) [lit.[16] mp 42—43 °C].

ii) This compound was prepared from **3** (0.164 g, 1.2 mmol) and **10b** (0.314 g, 1 mmol) in dry benzene (5 ml) according to the procedure described for the preparation of **8a**. The residue was purified by silica gel flash column chromatography (hexane : Et_2O = 1 : 1) to give **9a** (0.123 g, 49%) as colorless needles and **8c** (0.022 g, 10%) as colorless needles.

Ethyl 6-Benzoyl-2-pyridylglyoxylate (9b) This compound was prepared from **3** (0.164 g, 1.2 mmol) and **10a** (0.346 g, 1 mmol) in dry benzene (5 ml) according to the procedure described for the preparation of **8a**. The residue was purified by silica gel flash column chromatography (hexane : Et_2O = 3 : 1) to give **8d** (0.06 g, 24%) as colorless needles and **9b** (0.156 g, 55%) as colorless prisms. **9b**: mp 52—53 °C (from hexane). IR (KBr): 1746, 1711, 1668 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J = 7 Hz), 4.30 (2H, q, J = 7 Hz), 7.23—7.70 (3H, m), 7.93—8.50 (5H, m). MS *m/z*: 283 (M^+). *Anal.* Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.75; H, 4.76; N, 4.86.

Phenyl 6-Trimethylstannyl-2-pyridyl Ketone (10a) A solution of **6b** (0.84 g, 5 mmol) was added dropwise to a stirred solution of **1e** (2.02 g, 5 mmol) in dry benzene (15 ml), with stirring under an argon stream for 0.5 h at room temperature. The reaction mixture was washed successively with saturated Na_2CO_3 solution (10 ml), dried, and concentrated *in vacuo*. The residue was purified by distillation under reduced pressure to give **10a** (1.63 g, 94%) as pale yellow crystals, bp 158—163 °C (0.2 Torr), mp 66—67 °C (from pentane). IR (KBr): 1656, 762 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.33 (9H, s), 7.23—8.02 (6H, m), 8.10—8.36 (2H, m). MS *m/z*: 347 (M^+ + 1), 346 (M^+). *Anal.* Calcd for $C_{15}H_{17}NOSn$: C, 52.02; H, 4.19; N, 4.05. Found: C, 51.74; H, 4.95; N, 3.88.

Ethyl 6-Trimethylstannyl-2-pyridinecarboxylate (10b) This compound was prepared from **3** (0.683 g, 5 mmol) and **1e** (2.02 g, 5 mmol) in dry benzene (15 ml) according to the procedure described for the preparation of **10a**. The residue was purified by distillation under reduced pressure to give **10b** (1.19 g, 76%) as a colorless liquid, bp 105—109 °C (0.5 Torr). IR (neat): 1741, 1716, 759 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.38 (9H, s), 1.43 (3H, t, J = 7 Hz), 4.43 (2H, q, J = 7 Hz), 7.43—8.10 (3H, m). MS *m/z*: 315 (M^+ + 1), 314 (M^+). *Anal.* Calcd for $C_{11}H_{17}NO_2Sn$: C, 42.08; H, 5.46; N, 4.46. Found: C, 41.88; H, 5.21; N, 4.25.

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References and Notes

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