Simple and Mild Method for Preparation of α -Pyridinecarboxylates and α -Pyridyl Ketones *via* Trimethylstannyl Derivatives¹⁾

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Alkoxyacylation 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; alkoxyacylation; 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	EtOCOC(=O)Cl	2	4a	25	85 (5.0) ^{b)}
2-TMSn-Qu	1b	EtOCOC(=O)Cl	2	4b	0	
1-TMSn-IQ	1c	EtOCOC(=O)Cl	2	4c	34	113 (0.2) ^{c)}
2-TMSn-Py	1a	EtOCOC(=O)Cl	3	4a	85	80–82 (4.0) ^{b)}
2-TMSn-Qu	1b	EtOCOC(=O)Cl	3	4b	82	110 (0.2) ^{d)}
1-TMSn-IQ	1c	EtOCOC(=O)Cl	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 monoxide⁷⁾ 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.	RCOCOCI		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. ^1H -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-tributylstannylpyridine,¹² 2,6-bis(trimethylstannyl)pyridine,¹¹ pyruvoyl chloride,¹³ and benzoylformyl chloride¹³ 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} . ^1H -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 $\text{C}_9\text{H}_9\text{NO}_3$: 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} . ^1H -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 $\text{C}_{15}\text{H}_{13}\text{NO}_3$: 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} . ^1H -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 $\text{C}_{12}\text{H}_{13}\text{NO}_5$: 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} . ^1H -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 $\text{C}_{16}\text{H}_{13}\text{NO}_4$: 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} . ^1H -NMR (CDCl_3) δ : 0.33 (9H, s), 7.23–8.02 (6H, m), 8.10–8.36 (2H, m). MS m/z : 347 ($\text{M}^+ + 1$), 346 (M^+). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_2\text{Sn}$: 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} . ^1H -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 ($\text{M}^+ + 1$), 314 (M^+). Anal. Calcd for $\text{C}_{11}\text{H}_{17}\text{NO}_2\text{Sn}$: 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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