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Divergent Change of Regioselectivity in Nucleophilic Addition of Electron Deficient Allylic Tin Reagents to 4-Acylpyridinium Salts; Selective Formation of 4,4-Disubstituted 1,4-Dihydropyridines

Ryohei Yamaguchi,*[a] Katsunobu Mochizuki,[b] Sinpei Kozima[a] and Hidemasa Takaya[b]

[a] *Department of Natural Environment Sciences, Faculty of Integrated Human Studies, Kyoto University, Yoshida, Kyoto 606-01, Japan*

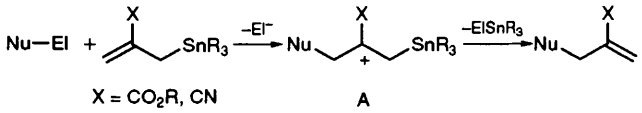
[b] *Department of Material Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606-01, Japan*

Nucleophilic additions of 2-methoxycarbonyl- and 2-cyano-allyltributyltins to 4-methoxycarbonyl-, 4-formyl-, and 4-acetyl-pyridines activated by methyl chloroformate afford 1,4-adducts exclusively or predominantly, while the reactions of 2-methylallyltributyltin with 4-methoxycarbonyl- and 4-acetyl-pyridines activated by methyl chloroformate give the 1,2-adducts exclusively.

Development of effective methodology for introduction of functionalized carbon substituents into nitrogen heterocycles is of great importance in the synthesis of a number of useful nitrogen compounds. We have already reported that several kinds of organotin reagents react regio- and/or chemo-selectively with nitrogen heteroaromatics and cyclic imines activated by a variety of acyl chlorides.[1] Recently, Baldwin and others have reported several radical reactions of 2-alkoxycarbonyl- and 2-cyano-allyltin reagents, which serve as Michael acceptor transfer reagents.[2] It seemed to us that nucleophilic reactions of the tin reagents would be affected by electron-withdrawing groups on the 2-position because a plausible carbocation intermediate (**A**) might be destabilized (Scheme 1).[3] However, no such effect was observed in the Lewis acid-promoted additions of 2-alkoxycarbonylallytin reagents to aldehydes.[4] We now report the first experimental indication of the above effect in nucleophilic additions of the electron-deficient allylic tin reagents to 4-acylpyridines activated with methyl chloroformate, where reversal of the regioselectivity has been found.

We first observed that 2-methoxycarbonylallyltributyltin **2a** does not react with the parent pyridine in the presence of methyl chloroformate, probably owing to the reduced nucleophilicity of **2a** as mentioned above. We have found, however, that pyridines substituted by electron-withdrawing groups readily react with **2a** in the presence of methyl chloroformate. With 3-acetylpyridine activated by methyl chloroformate, a mixture of 1,2- and 1,4-adducts was formed in an essentially non-regioselective manner (26:47:27 by HPLC analysis).

On the other hand, a clear substituent effect on the regioselectivity was observed in the reactions of 4-substituted pyridines **1a–1c** with **2a** and 2-cyanoallyltributyltin **2b** (Scheme 2). The results are summarized in Table 1. When



Scheme 1

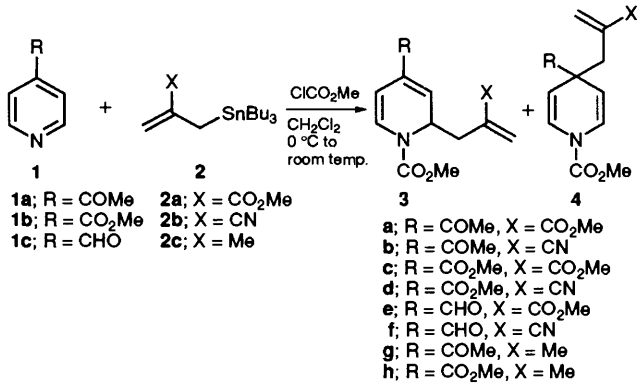
4-acetylpyridine **1a** was allowed to react with **2a** or **2b** in the presence of methyl chloroformate, both 1,2- and 1,4-adducts **3a** and **4a** or **3b** and **4b** were obtained with the 1,4-adduct predominating.† Furthermore, it is significant that the 1,4-adducts, **4c**, **4d**, **4e** or **4f**, are produced exclusively when 4-methoxycarbonylpyridine **1b** or 4-formylpyridine **1c** activated by methyl chloroformate is allowed to react with **2a** or **2b**. Thus, the quaternary carbon centre is formed exclusively in spite of the steric repulsion. The reactions of 2-methylallyltributyltin **2c** with **1a** and **1b** in the presence of methyl chloroformate give only the 1,2-adducts **3g** and **3h**, respectively. Thus, it is apparent that a change of the regioselectivity emerges in the reactions of allylic tin reagents containing electron-withdrawing groups, such as **2a** and **2b**. Furthermore, the selective formation of 4,4-disubstituted 1,4-dihydropyridine derivatives is synthetically valuable,[5] because almost all reactions of carbon nucleophiles,[6] except for benzylic tin reagents,[7] with 4-substituted pyridinium salts have produced 2,4-disubstituted 1,2-dihydropyridine derivatives exclusively.

† A typical experimental procedure is as follows: to a solution of **1a** (239 mg, 1.97 mmol) and **2a** (774 mg, 1.99 mmol) in dry CH_2Cl_2 (8 ml) was added methyl chloroformate (0.2 ml, 2.6 mmol) with ice-cooling. The ice-cold mixture was stirred for 1 h and then for 5 h at room temp. Evaporation and chromatography of the residue on silica gel afforded **3a** (130 mg), a mixture of **3a** and **4a** (40 mg), and **4a** (215 mg). The combined yield was 70% and the ratio of **3a** to **4a** was determined to be 36:64 by ^1H NMR spectroscopy. NMR spectra of the 1,2-adduct **3a** indicated the presence of two amide rotamers. The 1,4-adduct **4a** showed characteristic NMR spectra owing to its symmetry. The ratio of **3a** to **4a** did not change after 48 h under the reaction conditions. **3a**: IR (neat) 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.82, 6.67 (d, 1H, *J* 7.3 Hz), 6.40 (d, 1H, *J* 7.3 Hz), 6.12 (s, 1H), 5.88, 5.77 (d, 1H, *J* 7.6 Hz), 5.43 (s, 1H), 5.00–5.27 (m, 1H), 3.72 (s, 3H), 3.69, 3.66 (s, 3H), 2.30–2.60 (m, 2H) and 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 195.6 (s), 171.1 (s), 166.9 (s), 135.4, 134.9 (s), 134.3, 133.9 (s), 130.1, 129.6 (d), 128.5, 128.3 (t), 126.0, 125.5 (d), 102.7, 102.2 (d), 53.4, 52.8 (d), 52.0, 51.9 (q), 50.9, 50.8 (q), 35.2, 35.0 (t) and 25.3, 25.2 (q). **4a**: IR (neat) 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88 (d, 1H, *J* 7.3 Hz), 6.78 (d, 1H, *J* 7.3 Hz), 6.18 (s, 1H), 5.43 (s, 1H), 4.76–4.71 (m, 2H), 3.75 (s, 3H), 3.64 (s, 3H), 2.57 (s, 2H) and 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.2 (s), 167.5 (s), 151.3 (s), 136.0 (s), 128.8 (t), 124.0 (d), 123.7 (d), 107.6 (d), 107.3 (d), 53.5 (q), 52.7 (s), 51.7 (q), 39.4 (t) and 26.6 (q). Elemental analyses were satisfactory.

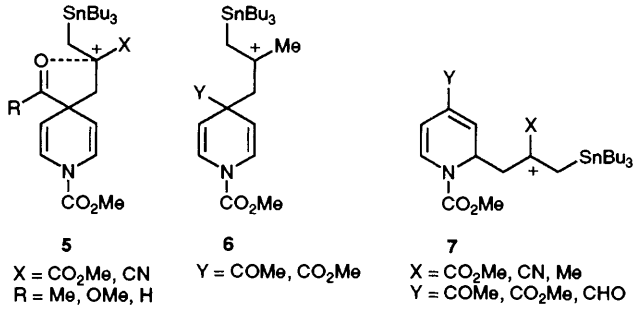
Table 1 Reactions of various 2-substituted allylic tin reagents with 4-substituted pyridines activated by methyl chloroformate

Entry	Reactants	R	X	Product(s)	Yield (%)[a]	Ratio[b] **3**:**4**
1	**1a** + **2a**	COMe	CO_2Me	**3a**, **4a**	70	36:64
2	**1a** + **2b**	COMe	CN	**3b**, **4b**	76	20:80
3	**1b** + **2a**	CO_2Me	CO_2Me	**4c**	91	<5:>95
4	**1b** + **2b**	CO_2Me	CN	**4d**	68	<5:>95
5	**1c** + **2a**	CHO	CO_2Me	**4e**[c]	64	<5:>95
6	**1c** + **2b**	CHO	CN	**4f**	72	<5:>95
7	**1a** + **2c**	COMe	Me	**3g**[d]	69	>95:<5
8	**1b** + **2c**	CO_2Me	Me	**3h**[d]	89	>95:<5

[a] Combined, isolated yield after chromatographic separation on silica gel. [b] Determined by ^1H NMR spectroscopy. [c] A small amount of an unidentified product was obtained. [d] The products are not stable, especially in the condensed state, probably owing to polymerization.



Scheme 2



Scheme 3

The above regiochemical outcome might be explained by the relative stability of the carbocation intermediates **5** and **6** which form the 1,4-adducts, compared to **7** that produces the 1,2-adducts. In view of steric repulsion, **7** would be more stable than **5** and **6**. However, **5** could be favourably stabilized by coordination of the carbonyl groups at the 4-position in a geometrically suitable 5-membered cyclic mode, because the carbocation centres are destabilized by the adjacent electron-withdrawing groups.[8] Thus, the 1,4-adducts could be produced exclusively or predominantly *via* the intermediates **5**. On the other hand, neighbouring group participation would not occur in the intermediates **6**, because the carbocation centre is stabilized rather than destabilized by the methyl group, and so the 1,2-adducts would be formed exclusively *via* **7** owing to the steric repulsion.

It has been reported that the regioselectivity in reactions of pyridinium salts with nucleophiles may be rationalized by hard and soft acids and bases principles.[9] Thus, hard carbon nucleophiles such as alkynyl Grignard reagents afford the 1,2-adducts exclusively,[10] while soft nucleophiles such as copper reagents produce the 1,4-adducts predominantly.[11] The present results have demonstrated for the first time a striking characteristic of electron deficient allylic tin reagents in nucleophilic reactions. In addition, the 4,4-disubstituted 1,4-dihydropyridines thus obtained contain a Michael acceptor and an acyl group at the 4-position and may be valuable synthetic intermediates for a variety of 1,4-dihydropyridine derivatives which are of biological interest.[5]

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