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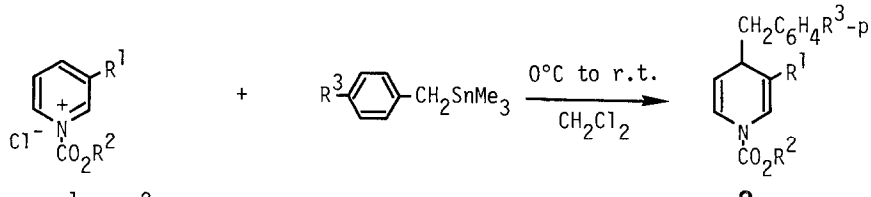
Highly Regio- and Chemo-selective γ-Addition of Benzylic Group to N-Alkoxycarbonylpyridinium Salts by means of Organotin Reagent

Ryohei Yamaguchi,* Masataka Moriyasu, and Mituyosi Kawanisi
Department of Industrial Chemistry, Faculty of Engineering, Kyoto University,
Yoshida, Kyoto 606, Japan

Abstract: Benzyltin reagents undergo highly regio- and chemo-selective γ-addition to a variety of N-acylpyridinium salts to give 4-benzyl-1,4-dihydropyridines exclusively in good yields.

Regioselective addition of a carbon nucleophile to a pyridinium salt is currently studied extensively. A few methods have been developed for the regioselective introduction of a carbon substituent into the 4-position of a pyridine ring; organocopper reagents,[1] silyl enol ethers,[2] and titanium enolates[3] attack regioselectively the γ-position of N-alkoxycarbonylpyridinium salts to give 4-substituted 1,4-dihydropyridines. Meantime, we have found that alkynyl- and alkenyl-Grignard reagents attack exclusively the α-position of N-alkoxycarbonylpyridinium salts to give 2-substituted 1,2-dihydropyridines.[4] More recently, we have revealed that allylic group can be introduced regio- and chemo-selectively into the α-position by the use of organotin reagents to afford a variety of 2-allyl-1,2-dihydropyridines.[5] In order to extend this methodology to the introduction of other organic functionality, we have tried the reaction of pyridinium salts with benzyltin reagents. Surprisingly, an exclusive γ-attack takes place to give 4-benzyl-1,4-dihydropyridine. Since 4-substituted 1,4-dihydropyridines have proved to be biologically important substances as well as useful synthetic intermediates for nitrogen heterocycles,[6] we wish to report here the highly regio- and chemoselective synthesis of 4-benzyl-1,4-dihydropyridines, which are otherwise difficult to be obtained.



1a;R^1=H, R^2=Me

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The reaction of N-methoxycarbonylpyridinium chloride (**1a**), prepared *in situ* from methyl chloroformate and pyridine, with benzyltrimethyltin in dry dichloromethane proceeded smoothly at room temperature to give 4-benzyl-N-methoxycarbonyl-1,4-dihydropyridine (**2a**)[7] exclusively in 68% yield. The use of more electronattracting 2,2,2-trichloroethoxycarbonyl group instead of methoxycarbonyl increased the yield up to 100%.

This high γ-selectivity of benzyltin reagent is also observed in the case of a variety of 3-substituted pyridines as well as substituted benzyltin reagents. The results are summarized in Table 1. The electronattracting groups on the pyridine ring evidently increased the yields, indicating the ionic nature of the reaction. Formyl, cyano and acetoxy groups are intact, demonstrating the high chemoselectivity of the present reactions.

Table 1. Reactions of Pyridinium Salts with Benzyltin Reagents.

Entry	Product	R^1	R^2	R^3	Yield(%)[a]
a	**2a**	H	CH_3	H	68
b	**2b**	H	CH_2CCl_3	H	100
c	**2c**	Cl	CH_3	H	77
d	**2d**	Br	CH_3	H	70
e	**2e**	CHO	CH_3	H	92
f	**2f**	CN	CH_3	H	90
g	**2g**	OAc	CH_3	H	55
h	**2h**	OAc	CH_2CCl_3	H	63
i	**2i**	H	CH_3	CH_3	56
j	**2j**	CHO	CH_3	CH_3	90
k	**2k**	Cl	CH_3	CH_3	78
l	**2l**	Br	CH_3	CH_3	75
m	**2m**	H	CH_3	OCH_3	56
n	**2n**	CHO	CH_3	OCH_3	91
p	**2p**	Cl	CH_3	OCH_3	69
q	**2q**	Br	CH_3	OCH_3	83

a) Isolated yields.

More interestingly, the high γ-regioselectivity mentioned above is maintained even in the cases of 4-substituted pyridines. The results are summarized in Table 2. Thus, 4,4-disubstituted-1,4-dihydropyridines (**3**) can be obtained exclusively in more than 90% yields. This is a marked contrast to that of the Grignard reagents which add exclusively to the α-position of the 4-substituted N-acylpyridinium salts to give 2,4-disubstituted 1,2-dihydro-

pyridines.[8,9]

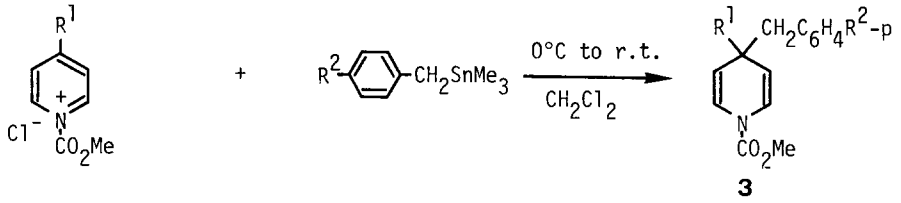

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Table 2. Reactions of 4-Substituted Pyridinium Salts with Benzyltin Reagents.

Entry	Product	R^1	R^2	Yield(%)[a]
a	**3a**	CN	H	98
b	**3b**	CHO	H	90
c	**3c**	CN	CH_3	99
d	**3d**	CHO	CH_3	91
e	**3e**	CN	OCH_3	99
f	**3f**	CHO	OCH_3	93

a) Isolated yields.

Typical experimental procedures are as follows: To a solution of pyridine (207 mg, 2.61 mmol) and $PhCH_2SnMe_3$ (522 mg, 2.05 mmol) in dry CH_2Cl_2 (6 ml) was added $ClCO_2CH_2CCl_3$ (0.34 ml, 2.50 mmol) dropwise under ice-cooling. After 2 h, an ice-bath was removed and the reaction mixture was allowed to stand at room temp. overnight. Additional CH_2Cl_2 (20-30 ml) was added to the mixture, and the whole was washed with water and dried (Na_2SO_4). After the solvent was evaporated, the residue was chromatographed on silica gel. After being eluted by some amount of hexane, subsequent elution by CH_2Cl_2 gave 4-benzyl-*N*-2,2,2-trichloroethoxycarbonyl-1,4-dihydropyridine (**2b**) (707 mg, 100%): MS *m/e* (rel. intensity) 347, 345 (M^+, 2, 2), 260, 258, 256, 254 (M^+-91, 4, 31, 99, 100); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11-7.44 (m, 5H), 6.84 (d, 2H, J=8 Hz), 4.80-5.10 (m, 2H), 4.82 (s, 2H), 3.10-3.60 (m, 1H), 2.76 (d, 2H, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ 149.5 (s), 138.3 (s), 129.1 (d), 128.2 (d), 126.1 (d), 122.4 and 121.8 (d), 111.2 and 110.7 (d), 77.2 (s), 75.3 (t), 44.8 (t), 34.6 (d).

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9) It should be also noted that reactions of benzyl Grignard reagents with 4-substituted pyridinium salts give 2,4-disubstituted 1,2-dihydropyridines exclusively; M. Takeda, A. E. Jacobson, K. Kanematsu, and E. L. May, J. Org. Chem., **1969**, 34, 4154.

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