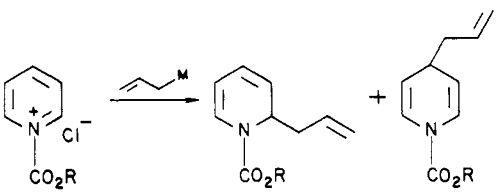
Highly Regioselective α-Allylation of N-(Alkoxycarbonyl)pyridinium Salts by means of Allyltin Reagents

Summary: N-(Alkoxycarbonyl)pyridinium salts are regioselectively allylated in the α-positions by means of allyltributyltin to give α-allyl-1,2-dihydropyridines in moderate to good yields.

Sir: We have recently reported that reactions of N-(methoxycarbonyl)pyridinium salts with alkynyl- and alkenyl-Grignard reagents proceed in a highly regioselective 1,2-addition manner to afford exclusively 2-substituted 1,2-dihydropyridines,[1,2] while, with alkyl-Grignard reagents, 4-alkyl-1,4- as well as 2-alkyl-1,2-dihydropyridines are produced in variable ratios, showing a lack of regioselectivity.[1,3] The recent interest in α-allylation of N-heterocycles[4] and the valuable role of 2-substituted 1,2-dihydropyridines as synthetic intermediates for a variety of N-heterocycles[5,6] prompt us to report here a highly efficient method for regioselective α-allylation of N-(alkoxycarbonyl)pyridinium salts by means of allyltin reagents.

At first we observed that the reaction of N-(methoxycarbonyl)pyridinium chloride (1, R = Me) with allylmagnesium bromide resulted in rather low α-regioselectivity (79%) and chemical yield (57%) (entry a, Table I). Allyltrimethylsilane, which has been widely used as an allylating reagent,[4] does not react with 1 (R = Me) (entry b, Table I). We have found, however, that allyltributyltin readily reacts with 1 (R = Me) to afford 2-allyl-1,2-dihydropyridine (2, R = Me) with 94% regioselectivity in 87% chemical yield (entry c, Table I). To the best of our knowledge, this is the first example of the reaction of allylstannane with pyridinium salt and clearly indicates that an allylstannane is sufficiently nucleophilic to react with pyridinium salt.[7]



1 2 3

Table I. Reactions of N-(Alkoxycarbonyl)pyridinium Chlorides with Allylmetals

entry	M	R	yield,[a] %	α-regioselectivity,[b] %
a	MgBr	Me	56	79
b	$SiMe_3$	Me	0	
c	$SnBu_3$	Me	87	94
d	$SnBu_3$	Et	84	93
e	$SnBu_3$	CH_2CCl_3	84	95
f	$SnBu_3$	$CH_2CH{=}CH_2$	64	91

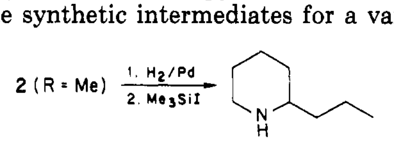
[a] Isolated yield. [b] Determined by VPC.

The similar high α-regioselectivity was observed in the reaction of a variety of N-(alkoxycarbonyl)pyridinium salts with allyltributyltin as well. The results are summarized in Table I (entries d and e). In addition to the higher regioselectivity and chemical yield, a practical advantage of the allyltin reagent over allyl-Grignard reagent is that the former reacts with the pyridinium salt chemoselectivity and, hence, the pyridinium salt need not be preformed.[8] Thus, the reaction can be accomplished by simply adding a chloroformate ester to a solution of pyridine and allyltributyltin in dichloromethane. Furthermore, the resulting tributyltin chloride can be recovered almost quantitatively and recycled to prepare allyltributyltin.

A typical procedure is as follows: To a mixture of pyridine (351 mg, 4.4 mmol) and allyltributyltin (1331 mg, 4.0 mmol) in dry dichloromethane (8 mL) was added methyl chloroformate (0.40 mL, 5.2 mmol) dropwise over 10 min under ice-cooling. The mixture was stirred for 2 h and the solvent was evaporated. The residue was rapidly chromatographed on silica gel. Elution by hexane gave tributyltin chloride (1276 mg, 98%) and the subsequent elution by dichloromethane afforded a mixture of 2 (R = Me) and 3 (R = Me) (628 mg, 87%) in a ratio of 94:6. 2 (R = Me): MS, *m/e* (relative intensity) 179 (M^+, 1), 138 ($M^+ - 41$, 100), 94 (57); IR (neat) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.49–6.84 (br, 1 H), 5.39–6.08 (m, 3 H), 4.57–5.33 (m, 4 H), 3.73 (s, 3 H), 1.99–2.53 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 154.3 (s), 133.5 (d), 125.2 (d), 122.3 (d), 121.7 (d), 117.7 (t), 105.9 (d), 53.0 (q), 52.0 (d), 38.6 (t). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 66.72; H, 7.31. Found: C, 66.98; H, 7.33.[9]

The present allylation method is also applicable to substituted pyridines as well as other N-heteroaromatics. The results are summarized in Table II. In most of the cases, α-regioselectivity exceeded 90%. The reactions of pyridinium salts derived from 2- and 4-methylpyridines gave the rather low yields of products probably because of the reduced electrophilicity, though the yields could be improved by making use of allyltrimethyltin (entries a and b). It is interesting that the sterically crowded products are obtained with more than 90% selectivity in the cases of 3-halo- and 3-acetoxypyridines (entries d–f). It should be noted that the reaction of 3-bromopyridinium salt with allyl-Grignard reagent gave only a trace of the allylated product but a lrage amount of triallylcarbinol (81%) via the attack on the carbonyl carbon, demonstrating the superiority of the allyltin reagent. Quinoline and isoquinoline can also be α-allylated very well (entries h and i).

The α-allylated 1,2-dihydropyridines thus obtained may be valuable synthetic intermediates for a variety of N-heterocycles such as alkaloids. For instance, catalytic hydrogenation of 2 (R = Me) followed by demethoxy-



(±)-coniine

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(1) Yamaguchi, R.; Nakazono, Y.; Kawanisi, M. *Tetrahedron Lett.* **1983**, *24*, 1801.

(2) For the synthesis of (±)-solenopsine A by this methodology, see: Nakazono, Y.; Yamaguchi, R.; Kawanisi, M. *Chem. Lett.* **1984**, 1129.

(3) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315.

(4) (a) Hart, D. J.; Tsai, Y.-H. *Tetrahedron Lett.* **1981**, *22*, 1567. (b) Kraus, G. A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134. (c) Kozikowski, A. P.; Park, P.-u. *J. Org. Chem.* **1984**, *49*, 1674. (d) Shono, T.; Matsumura, Y.; Onomura, O.; Kanazawa, T.; Habuka, M. *Chem. Lett.* **1984**, 1101. All of these reactions make use of allyltrimethylsilane as a carbon nucleophile in the presence of Lewis acid.

(5) For pertinent references of dihydropyridine chemistry: (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1. (b) Stout, D. M.; Meyers, A. I. *Ibid.* **1982**, *82*, 223.

(6) For synthesis of some piperidine alkaloids starting from 2-substituted 1,2-dihydropyridines: Ogawa, M.; Kuriya, N.; Natsume, M. *Tetrahedron Lett.* **1984**, *25*, 969 and references cited therein.

(7) It has been suggested that allylstannanes are more nucleophilic than allylsilanes: Hosomi, A.; Iguchi, H.; Endo, M.; Sakurai, H. *Chem. Lett.* **1979**, 977.

(8) In the case of allyl-Grignard reagent, the pyridinium salts must be preformed and the reaction should be conducted at −78 °C.

(9) All new compounds gave consistent spectral data (MS, IR, ^1H and ^{13}C NMR) with the proposed structures.

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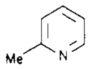
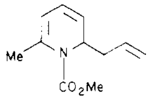
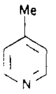
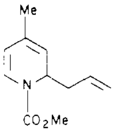
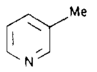
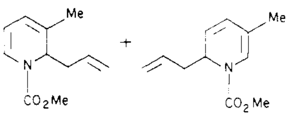
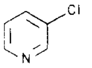
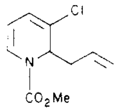
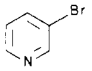
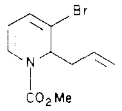
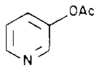
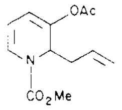
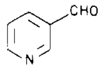
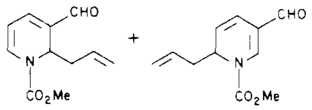
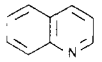
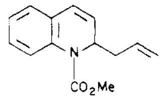
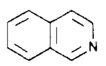
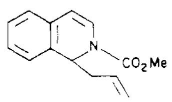
Table II. Allylation of Substituted Pyridines and N-Heteroaromatics by means of the Allyltin Reagent

entry	reactant	temp, °C	product	yield,[a] %	α-selectivity,[b] %
a		r.t.[e]	 4	65,[c] 28	95
b		r.t.	 5	66,[c] 38	99
c		0	 6a (75:25)[d] 6b	74	89
d		-78	 7	87	93
e		-78	 8	87	94
f		-78	 9	96	91
g		-78	 10a (76:24)[d] 10b	88	86
h		0	 11	92	93
i		0	 12	93	98

[a] Isolated yield. [b] Determined by VPC and/or ^1H NMR. [c] Allyltrimethyltin is used. [d] Determined by ^1H NMR. [e] r.t. = room temperature.

carbonylation with iodotrimethylsilane[10] gave (±)-coniine, the major component of the hemlock alkaloids.[11] Further study along this line is in progress.

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Supplementary Material Available: Spectral data for new compounds (4 pages). Ordering information is given on any current masthead page.

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