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REGIOSELECTIVE ADDITION OF NUCLEOPHILES TO 1-(PHENOXYCARBONYL)-3-TRIALKYLSTANNYLPYRIDINIUM SALTS

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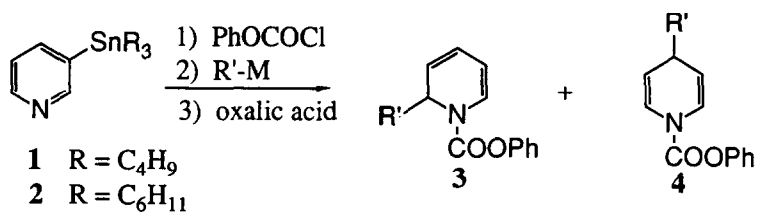
Summary: The regioselectivity of nucleophilic addition to 1-(phenoxycarbonyl)-3-trialkylstannylpyridinium salts was studied.

The reaction of 1-acylpyridinium salts with nucleophiles has proven to be a valuable method for the synthesis of substituted dihydropyridines and pyridines.[1,2] However, the nucleophilic addition is frequently not regiospecific, and a mixture of isomeric dihydropyridines results. A small substituent at the 3-position of a 1-acylpyridinium salt can exert an "ortho"-directing effect, causing nucleophilic attack to occur mainly at the 4- and 2-positions.[3] If the 3-substituent or the nucleophile is sufficiently large, steric congestion will overcome the "ortho" effect and attack will occur mainly at the less sterically hindered α-position. If a large 3-substituent could be used as a handle for subsequent introduction of other groups at that β-position, then a regiospecific synthesis of 2,5-disubstituted 1-acyl-1,2-dihydropyridines could be achieved. It appeared that use of a β-trialkylstannyl group would let us reach this goal, for it is bulky and will undergo a variety of ipso substitution reactions.[4] Towards this end, we initiated an investigation on the regioselectivity of nucleophilic addition to 1-(phenoxycarbonyl)-3-trialkylstannylpyridinium salts.

A study of the reaction of organometallics with 3-trialkylstannylpyridines (1 and 2)[5] and phenyl chloroformate under a variety of reaction conditions was carried out. The intermediate trialkylstannyldihydropyridines[6] were protodestannylated in situ with aqueous oxalic acid to give 1,2- and 1,4-dihydropyridines 3 and 4, which were readily analyzed by GC or ^{1}H NMR. Standards for comparison were prepared by methods previously developed in our laboratories. The 1-acyl-4-alkyl-1,4-dihydropyridines 4 were prepared by the CuI-catalyzed addition of alkyl Grignard reagents



1 R = C_4H_9
2 R = C_6H_{11}

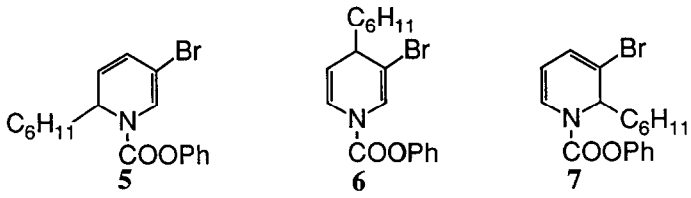
Table. Addition of Nucleophiles to 1-(Phenoxycarbonyl)-3-trialkylstannylpyridinium salts.

Entry	Stannyl-pyridine	RM[a]	Solvent, Temp. (°C)	Ratio[b] 3:4	Yield[c] (%)
a	1	$C_6H_{11}MgCl$	$PhCH_3$, -78	72:28	63
b	1	$C_6H_{11}MgCl$	THF, -78	63:37	68
c	1	$C_6H_{11}MgCl$	THF, -23	56:44[d]	
d	1	$(CH_3)_2CHMgCl$	THF, -78	61:39	67
e	1	PhMgCl	THF, -23	99:1	80
f	1	$C_4H_9CeCl_2$	THF, -78	68:32	58
g	1	5-pentenyl-magnesium chloride	THF, -78	77:23	77
h	2	$C_6H_{11}MgCl$	THF, -23	81:19[d]	
i	2	$C_6H_{11}MgCl$	THF, -78	87:13	62
j	2	$C_6H_{11}MgCl$	$PhCH_3$, -78	95:5[d]	

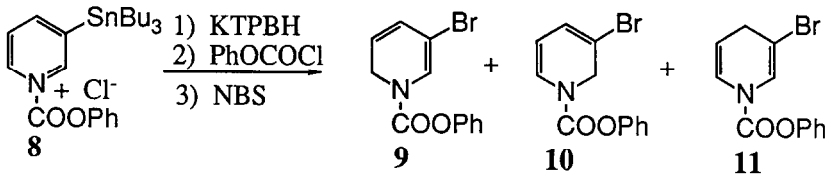
[a]Reactions were performed by dissolving the stannylpyridine in the indicated solvent and cooling to the indicated temperatures. One equiv of the acyl halide was added slowly, and after 20 min the nucleophile was added dropwise. After 10 min the reaction was warmed to RT, water and oxalic acid (4 equiv) were added, and the reaction was stirred overnight. Extraction with ether provided the crude products. [b]Determined by GC. [c]Purified by radial-PLC (SiO_2, hexane-CH_2Cl_2). [d]Products were not purified. GC analysis was performed on the crude material.

to 1-(phenoxycarbonyl)pyridinium chloride.[3,7] The 1-acyl-2-alkyl-1,2-dihydropyridines 3 were prepared from 4-trimethylstannylpyridine.[8] As shown in the Table, better regioselectivity was achieved with 3-tricyclohexylstannylpyridine (2) as compared to 3-tributylstannylpyridine (1). This was expected due to steric effects; however, the amount of attack at the 4-position was more than anticipated. This may be due to the long carbon-tin bond (approx. 2.14 Å),[9] which could lower the β-trialkylstannane group's effectiveness at blocking the 4-position. The reaction of phenylmagnesium chloride with 1-(phenoxycarbonyl)-3-tributylstannylpyridinium chloride gave a high ratio (99:1) of α- vs γ-addition (entry e). This was expected as aryl Grignard reagents exhibit a greater preference than their aliphatic counterparts for attack at the α-position of a 1-acylpyridinium salt.[3] The use of n-butylcerium dichloride, which adds selectively in a 1,2 manner to β-enones,[10] did not give a high degree of regioselectivity (entry f).

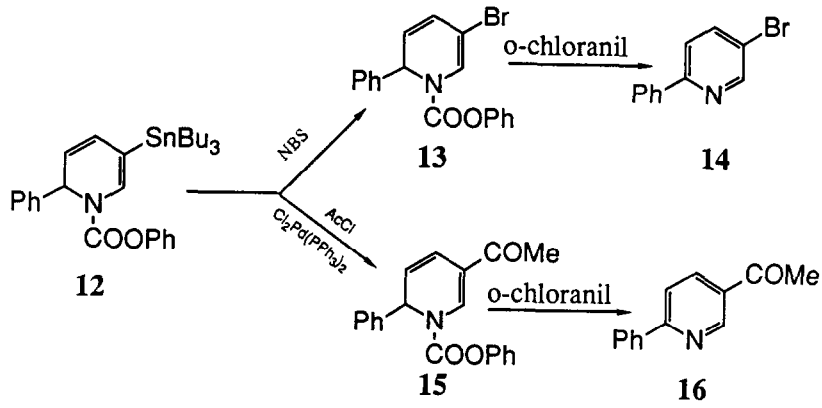
The data given in Table 1 do not indicate how much 2 vs 6 addition occurred. We assume that in most cases less than 5% of α-addition was at the more sterically hindered 2-position, based on the following result. The product mixture from the reaction of 1-(phenoxycarbonyl)-3-tributylstannylpyridinium chloride with $C_6H_{11}MgCl$ was bromodestannylated by treatment with N-bromosuccinimide (CH_2Cl_2, -15°C, 18h) in 71% yield. The ratio of regioisomers 5, 6, and 7 was found to be 64:32:2 as determined by GC and ^1H NMR. In contrast, the reaction of $C_6H_{11}MgCl$ with 3-bromo-1-(phenoxycarbonyl)pyridinium chloride gave these dihydropyridines in a ratio of 14:59:27.



The reaction of 1-(phenoxycarbonyl)-3-tributylstannylpyridinium chloride (8) with the bulky reducing agent potassium triisopropoxyborohydride (KTPBH) was investigated.[11] Without purification, the intermediate tributylstannyldihydropyridines were treated with NBS to afford bromodihydropyridines 9, 10, and 11 in a ratio of 82:16:2. The analogous reaction with 3-bromo-1-(phenoxycarbonyl)pyridinium chloride gave these dihydropyridines in a ratio of 24:61:15.



Two 2,5-disubstituted pyridines were prepared in a regiospecific manner using the above methodology. Bromination of 2-phenyl-5-tributylstannyl-1,2-dihydropyridine 12 with NBS gave 13 in 87% yield. Palladium-catalyzed acylation[12] of dihydropyridine 12 gave the 5-acetyl-1,2-dihydropyridine 15 (45%). Aromatization of dihydropyridines 13 and 15 with o-chloranil gave the desired pyridines 14 and 16 in good yield.



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5. 3-Tributylstannylpyridine (1) was prepared from 3-bromopyridine and tributyltin lithium in THF (59%). 3-Tricyclohexylstannylpyridine (2) was prepared from 3-lithiopyridine and tricyclohexyltin chloride (22%).

6. The intermediate trialkylstannyldihydropyridines could be isolated, but the ratio of isomers could not be determined accurately.

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