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SYNTHESIS OF 3-ACYLPYRIDINES UTILIZING A FRIEDEL-CRAFTS REACTION

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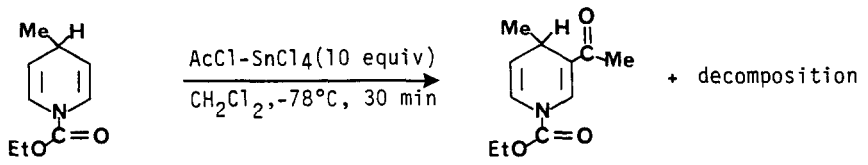
Summary: A synthesis of 3-acylpyridines via a Friedel-Crafts acylation of a dihydropyridine intermediate is described.

The Friedel-Crafts acylation is an important method for the preparation of aryl ketones.[1] The reaction fails in the pyridine series however, and thus substituted 3-acylpyridines are difficult to prepare.[2] The failure of the Friedel-Crafts reaction with pyridines is due to the basicity of the ring nitrogen. Under the Friedel-Crafts conditions the ring nitrogen lone pair coordinates with the Lewis acid catalyst, thus making an electron-deficient ring more electron-deficient and resistant to electrophilic attack. It is clear that the coordinating power of the ring nitrogen must be "neutralized" in order to effect a Friedel-Crafts acylation of a pyridine nucleus.

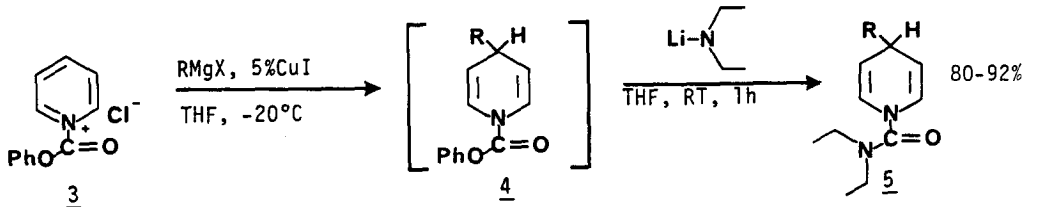
We recently described a convenient synthesis of 1-acyl-4-alkyl(aryl)-1,4-dihydropyridines via addition of Grignard reagents (5% CuI) to 1-acylpyridinium salts.[3] Prompted by the synthetic potential of these pyridine derivatives,[4] we have been developing methodology for introducing substituents on the dihydropyridine ring. For example, we have reported an α-metalation-alkylation of 4-substituted 1-(tert-butoxycarbonyl)-1,4-dihydropyridines; subsequent aromatization gives 2,4-substituted pyridines.[5] It occurred to us that the β-positions of 1-acyl-1,4-dihydropyridines are electron rich and should be susceptible to electrophilic attack. In addition, these pyridine derivatives have no basic nitrogen to coordinate with a Lewis acid catalyst. Since enecarbamates are reported to acylate at the β-position by the Friedel-Crafts reaction,[6] we decided to study the analogous reaction with 1-acyl-1,4-dihydropyridines.

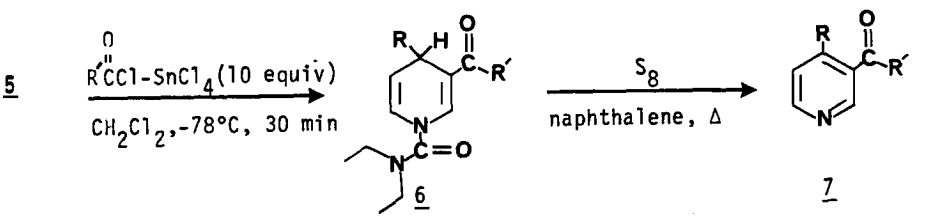
The initial reaction was performed on dihydropyridine 1. The desired product (2) was obtained; however, it was contaminated with other products (50% pure by NMR). This



1 2

contamination was probably due to decomposition of the dihydropyridine 1 in the presence of the Lewis acid. A 1-dialkylcarbamyl-1,4-dihydropyridine should be more stable than the 1-ethoxycarbonyl derivative 1, and therefore a better substrate for the Friedel-Crafts acylation. An attempt to prepare a 1-dialkylcarbamyl-1,4-dihydropyridine (5, R = n-butyl), with diethylcarbamyl chloride, pyridine, 5% CuI, and butylmagnesium chloride, failed to give any of the desired product.[7] An alternative one-pot synthesis of 5 was developed as shown below.





Dihydropyridines 5 underwent Friedel-Crafts acylation in good yield with most acid chlorides studied. The crude products (6) were aromatized with sulfur (1 equiv) in refluxing naphthalene (4-5 h) to provide 3-acyl-4-substituted pyridines (7) as shown in the table. Although the overall yields are not high, this three-step synthesis is convenient and represents an indirect Friedel-Crafts acylation of the pyridine nucleus.

The Friedel-Crafts acylation of 2-substituted 1,2-dihydropyridines could provide access to 2-substituted 5-acylpyridines. However, synthesis of the starting material via the addition of Grignard reagents to 4-unsubstituted 1-acylpyridinium salts is not very regioselective, and a mixture of 2- and 4- substituted dihydropyridines result.[3,8] In addition, one would anticipate the 1,2-dihydropyridines to be less stable than 1,4-dihydropyridines in the presence of Lewis acids.[9] In an attempt to circumvent these problems, dihydropyridine 9 was prepared as shown below.

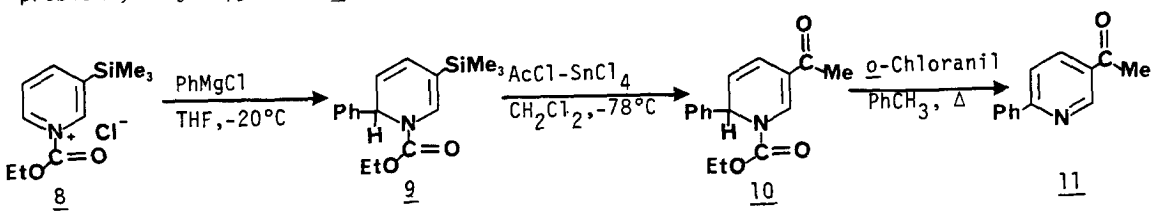


Table. Synthesis of 3-Acylpyridines 7 from Dihydropyridines 5

R(5)	R-C(=O)-Cl (acyl chlorides)	Product[a] (7)	Overall yield,[b] %
n-butyl	acetyl	4-butyl-3-acetylpyridine	38
n-butyl	propionyl	4-butyl-3-propionylpyridine	46
n-butyl	butyryl	4-butyl-3-butyrylpyridine	42
n-butyl	isobutyryl	4-butyl-3-isobutyrylpyridine	30
n-butyl	benzoyl	———[c]	—
n-butyl	methyl chloroformate	———[c]	—
cyclohexyl	acetyl	4-cyclohexyl-3-acetylpyridine	49
cyclohexyl	propionyl	4-cyclohexyl-3-propionylpyridine	37
cyclohexyl	butryl	4-cyclohexyl-3-butyrylpyridine	43
cyclohexyl	isobutyryl	4-cyclohexyl-3-isobutyrylpyridine	28
phenyl	acetyl	4-phenyl-3-acetylpyridine	28
methyl	propionyl	4-methyl-3-propionylpyridine	36

[a]All products gave the expected IR and ^{1}H NMR spectra. New compounds gave satisfactory analytical data.

[b]Reactions were performed on a 3 mmol scale and the products were purified by preparative layer chromatography (silica gel, acetone-hexanes).

[c]None of the desired product was isolated.

Due to the trimethylsilyl blocking-group at the 3-position of the pyridine ring, the addition of phenylmagnesium chloride to 8 was regiospecific for the 6-position. Dihydropyridine 9, which is activated toward electrophilic substitution at the site of the silicon atom,[10] was acylated-desilylated to give 10 in 35% yield after purification (SiO_2, acetone-hexanes). Aromatization with o-chloranil in refluxing toluene gave 5-acetyl-2-phenylpyridine (11) (67%). This synthetic sequence is tantamount to the regiospecific Friedel-Crafts acylation of 2-phenylpyridine.

Further investigations of the synthetic utility of dihydropyridines 5, 6, 9, and 10 are currently in progress.

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