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ADDITION OF GRIGNARD REAGENTS TO 1-ACYL-4-METHOXYPYRIDINIUM SALTS. AN APPROACH TO THE SYNTHESIS OF QUINOLIZIDINONES.

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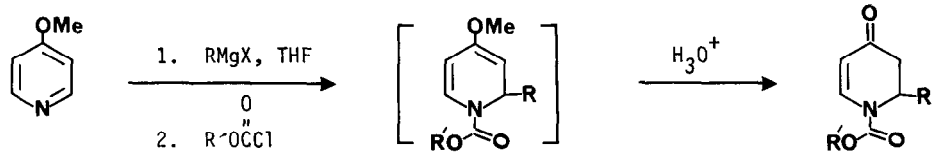
Summary: The addition of Grignard reagents to 1-acyl-4-methoxypyridinium salts gives 2-substituted 1-acyl-2,3-dihydropyridones. This reaction was utilized to synthesize (±)-epi-myrtine and trans-4-phenylquinolizidin-2-one.

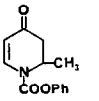
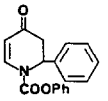
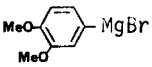
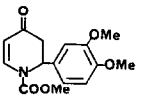
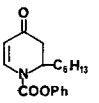
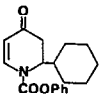
The reaction of 1-acylpyridinium salts with nucleophiles has proven to be a valuable method for the synthesis of substituted dihydropyridines and pyridines.[1,2] We have been studying this reaction using pyridines containing various substituents. A small alkyl substituent at the 2-position can be tolerated, but frequently the 2-substituent will inhibit acyl salt formation and the reaction will fail. The 1-acylpyridinium salts are so reactive toward nucleophiles that many substituents at the 3- or 4-positions of the pyridine ring can be tolerated (e.g., halogens, esters, ketones).[2] We recently reported that 4-alkyl-3-pyridinols can be prepared from 3-benzyloxypyridine and Grignard reagents (5% CuI) via a 1-acylpyridinium salt intermediate.[2p] Because of its potential for the synthesis of 2-alkyl-4-pyridones and the corresponding 2,3-dihydropyridones, we explored the reaction of Grignard reagents with 1-acylpyridinium salts of 4-methoxypyridine (1).[3]



1 2 3

The intermediate 1-acyl-4-methoxy-1,2-dihydropyridines 2 are very sensitive to hydrolysis[4] and were not isolated; workup with aqueous 10% hydrochloric acid gave good yields of the desired dihydropyridones 3 as shown in the Table.

TABLE. Synthesis of 2,3-Dihydropyridones 3 from 4-Methoxypyridine

RMgX[a]	Chloroformate	Product 3	Yield[b] %
CH_3MgCl	phenyl		74
	phenyl		72
	methyl		56
$n\text{-}C_6H_{13}\text{-}MgBr$	phenyl		91
	phenyl		88

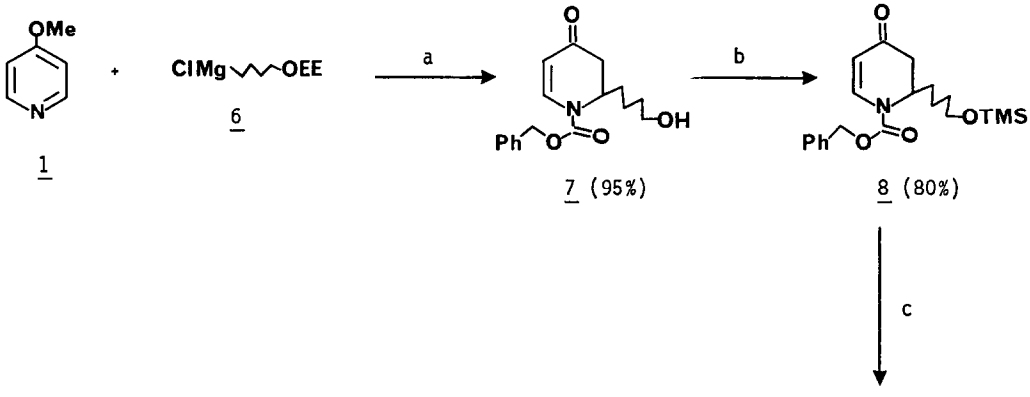
[a]Reactions were performed on a 3 mmol scale. The chloroformate (3.0 mmol) was added dropwise to 4-methoxypyridine[5] (3.0 mmol) and Grignard reagent (3.0 mmol) in THF (-23°C). The mixture was stirred at -23°C for 20 min, then poured into stirred 10% HCl. After stirring at RT for 10 min, extraction with ether provided the crude dihydropyridones 3. [b]Yields are for isolated, pure material obtained from radial preparative layer chromatography (silica gel, EtOAc/hexanes). All products gave the expected IR and ^1H NMR spectra and elemental analysis.

This simple synthesis of 2-substituted 2,3-dihydropyridones has considerable potential for the synthesis of quinolizidine alkaloids. We have utilized this methodology to synthesize (±)-epi-myrtine (4) and trans-4-phenylquinolizidin-2-one (5).

The addition of benzyl chloroformate to Grignard reagent 6 and 4-methoxypyridine[5] in THF at -23°C gave upon acidic workup the dihydropyridone 7, which was treated with chlorotrimethylsilane and triethylamine to give the TMS-ether 8. The addition of methyl Grignard (5% CuI, THF, -23°C) to 8 gave on acidic workup the cis-2,6-disubstituted piperidone 9a in 85% yield.[6] The alcohol 9a was converted to the tosylate 10a with p-toluenesulfonyl chloride and pyridine in 86% yield. This

material was cyclized in a one-pot procedure via catalytic hydrogenolysis of the benzyl carbamate group in the presence of lithium carbonate to give a 61% yield of trans-4-methylquinolizidin-2-one ((±)-epi-myrtine (4)) as the sole product isolated. This product was identical to an authentic sample prepared from pelletierine and acetaldehyde using a literature procedure.[7]

Following the procedure outlined above, and using phenylmagnesium chloride in the copper-catalyzed conjugate addition step to give 9b, trans-4-phenylquinolizidin-2-one (5) was prepared. The diastereoselectivity of the copper-catalyzed Grignard reaction was determined by ^{1}H NMR to be greater than 8 to 1 in favor of the cis-2,6-disubstituted piperidone 9b. The quinolizidinone 5 was identical to an authentic sample prepared using a known procedure.[8]



a) benzyl chloroformate, THF, -23°C; H_3O^+ b) TMSCl, TEA, THF
c) RMgX (R = Me, Ph), 5% CuI, THF, -23°C; oxalic acid, THF, H_2O
d) TsCl, pyridine e) H_2, 10% Pd/C, $LiCO_3$, EtOAc

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5. The 4-methoxypyridine was prepared from 4-methoxypyridine-N-oxide (Aldrich) by catalytic hydrogenation (5% Pd/C, H_2, EtOH).

6. Although the diastereoselectivity of this reaction appears to be high, the exact ratio of cis to trans diastereomers formed was not determined.

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