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THE REACTION OF 1-ACYLPYRIDINIUM SALTS WITH GRIGNARD AND ORGANOCADMIUM REAGENTS

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The formation of dihydropyridines from the reaction of organometallic reagents with N-alkyl or N-arylpyridinium salts has been well established.[1] Except for the reaction of 1-alkoxycarbonylpyridinium salts[2] the corresponding reaction of 1-acylpyridinium salts with organometallic reagents has received limited attention. Since 1-acylpyridinium salts are intermediates in acylations using pyridines as catalysts, it would be assumed that reaction with the organometallic reagent might occur at the carbonyl carbon in preference to the heterocyclic ring. The formation of 1-benzoyl-2-phenylethynyl-1,2-dihydropyridine from silver phenylacetylide and 1-benzoylpyridinium chloride[3] and dihydropyridines from organometallic reagents and alkoxycarbonylpyridinium salts led to the investigation summarized in Table 1. These reactions show that phenyl magnesium and phenyl cadmium reagents give reaction by addition at the 2- or 6-position of the heterocyclic ring rather than at the 1-acyl carbonyl. The 1,2-dihydropyridines from the reaction of 1-ethoxycarbonyl pyridinium salts with organometallic reagents are more stable than those with other 1-acyl groups and frequently give better yields. The regioselectivities of the magnesium and cadmium reagents for the 2- and 6-positions in 1-ethoxycarbonylpyridinium ion are very similar; however, the advantage of the organocadmium reagent is evident in the reaction with 1,3-dibenzoylpyridinium chloride. While the Grignard reagent gives addition at the carbonyl carbon at the 3-position as well as on the 6- and 4-ring carbons, the cadmium reagent gives good yields of ring addition only. 3-Benzoylpyridine itself has been reported to give reaction at the 3-acyl carbonyl and the 4-ring carbons.[4] The simple alkyl Grignard reagent studied, methylmagnesium iodide, added at the 2-position of 1-acetyl-4-picolinium chloride to give a 56% yield of 1-acetyl-2,4-dimethyl-1,2-dihydropyridine, which was characterized by oxidation (DDQ) to 2,4-lutidine.

It is interesting to note that the reaction of pyridines with an acid chloride is very rapid. This permits the reaction to form dihydropyridines to be run by the addition of the acid chloride to a mixture of the pyridine and the organometallic reagent without serious competition of the reaction of the organometallic reagent with the acid chloride (see Footnote b, Table 1).

These results show that 1-acyl-dihydropyridines can be prepared from the reaction or organomagnesium and cadmium reagents with 1-acylpyridinium salts. Addition occurs primarily at the ring carbons adjacent to the nitrogen. This method of synthesis offers a convenient and versatile alternative to the synthesis by acylation of the anion formed by the addition of an organolithium reagent to a pyridine derivative.[5]

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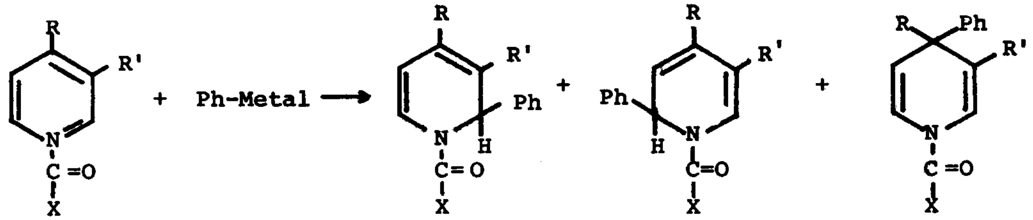
TABLE 1

The Reaction of 1-Acyl-pyridinium Salts with Organometallic Reagents*



I II III IV

R	R'	X	Metal[Source]	Yield	Properties^{a}
H	H	CH_3	Cd[PhLi]	32%(II)	110-120/0.15mm Ref. 5
H	H	C_2H_5O	Cd[PhLi]	38%(II)	115-120/0.15 Ref. 5
CH_3	H	CH_3	Cd[PhLi]	30%(II)	bp 115-118°/0.15mm
CH_3	H	CH_3	Cd[PhMgBr]	49%(II)	
CH_3	H	CH_3	Cd[PhMgBr]^{b}	68%^{c}(II)	
CH_3	H	CH_3	MgBr	83%(II)	
CH_3	H	CH_3	MgBr^{b}	52%(II)	
CH_3	H	CH_3	Li^{d}	<5%(II)	
CH_3	H	C_2H_5O	Cd[PhMgBr]^{b}	71%(II)	bp 107-111°0.5mm
CH_3	H	C_2H_5O	MgBr^{b}	87%(II)	
CH_3	CH_3	C_2H_5O	MgBr	31^{e}II(22%) III(78%)	Ref. 2b
CH_3	CH_3	C_2H_5O	Cd[PhMgBr]	18^{e}II(17%) III(83%)	
H	PhCO	Ph	MgBr	13%(IV)^{f} 49%(III)	mp 152.5-.54.5° mp 132.5-134.5°
H	PhCO	Ph	Cd[PhMgBr]^{b}	19%(IV) 61%(III)	

**The reaction was run by adding a slight molar excess of the organometallic reagent to a suspension of the preformed 1-acyl-pyridinium chloride in THF at 10°. The mixture was decomposed with 20% ammonium chloride solution and the organic layer was washed with cold dil HCl, dil KOH, saturated NaCl solution and dried over K_2CO_3. After removal of the solvent the residue was purified by distillation, recrystallization or chromatography.*

Footnotes

[a] All new compounds gave correct elemental analyses

[b] The acid chloride was added to the mixture of organometallic reagent and pyridine.

[c] Prepared with 0.5 mole of $CdCl_2$/mole of Grignard reagent. Lower yields of 43 and 36% were obtained with ratios of 0.79 and 1.0 moles.

[d] Run at -78°.

[e] The product mixture was oxidized to the pyridine before analysis and the yields are for these compounds.

[f] About 15% of diphenyl-3-pyridylcarbinol (identified by nmr) was also isolated.[4]