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REGIOSELECTIVE ADDITION OF TITANIUM ENOLATES TO 1-ACYLPYRIDINIUM SALTS. A CONVENIENT SYNTHESIS OF 4-(2-OXOALKYL)PYRIDINES

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Summary: Titanium enolates add to the 4-position of 1-phenoxycarbonylpyridinium salts to give 1,4-dihydropyridines; subsequent aromatization provides 4-(2-oxoalkyl)pyridines.

Development of practical methods for directing nucleophiles to the 4-position of a pyridine ring has been a challenge to synthetic chemists for many years. We and the research groups of Lyle[1], Piers[2], Katritzky[3], and Akiba[4] have made recent contributions in this area. We recently developed a convenient and practical method for the synthesis of various 4-alkyl(aryl)pyridines via the regiospecific 1,4-addition of Grignard reagents to 1-acylpyridinium salts in the presence of a catalytic amount of cuprous iodide.[5] In an effort to expand this approach to the synthesis of 4-(2-oxoalkyl)-pyridines, we have been studying the reaction of metallo enolates with 1-acylpyridinium salts.

The reaction of lithium enolates with pyridine and phenyl chloroformate gave approximately 50/50 mixtures of 1,2- and 1,4-dihydropyridines. In an attempt to improve the selectivity and yield, we prepared various titanium enolates from the corresponding lithium enolates via transmetalation[6], and treated them with pyridine and phenyl chloroformate in a one-pot reaction as shown in Scheme I. The resulting dihydropyridines (1 + 2) were isolated by chromatography and the ratio of 1/2 was determined by ^{1}H NMR. The 1-acyldihydropyridines were treated with 1 equiv of sulfur and 5% Pd/C (10% by weight) in refluxing naphthalene for four hours to give pyridines 3 in good yield (See Table). Interestingly, the minor 1,2-isomer 2 decomposes under these conditions, thus the isolated 4-substituted pyridines 3 are free of their 2-substituted isomers.[7]

Scheme I

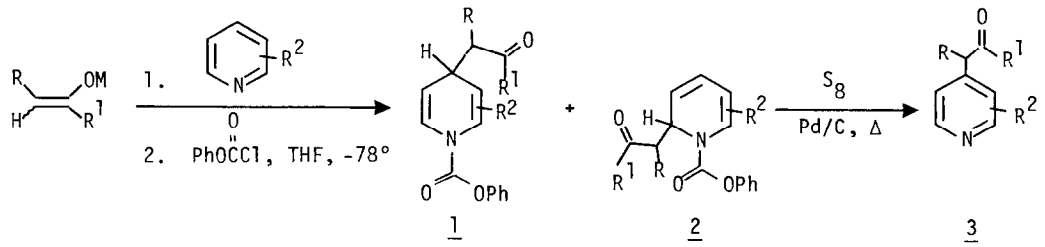


Table. Synthesis of 4-(2-Oxoalkyl)pyridines 3.

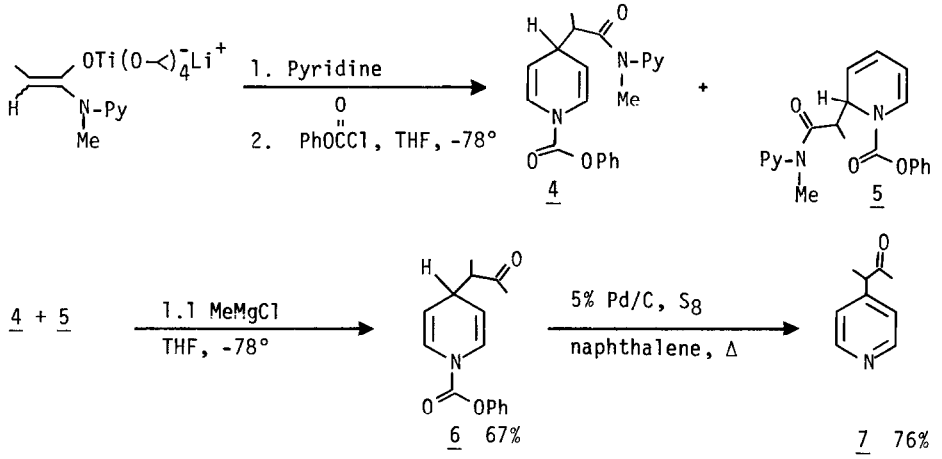
Entry	R	R^1	M	R^2	Yield of 1 and 2, %[a] (ratio)[b]	Yield of 3 %[c]	mp of picrates, °C (lit. mp)
1	H	Me	Li	H	71 (52/48)	32	154-155 (156-157.5)[3d]
2	H	Me	$Ti(O-\langle)_3$	H	81 (74/26)	62	154-155
3	H	Me	$Ti(O-\langle)_4^-Li^+$	H	90 (87/13)	71	154-155
4	Me	Et	$Ti(O-\langle)_3$	H	78 (93/7)	65	116-117 (116-117)[3d]
5	$-(CH_2)_5-$		$Ti(O-\langle)_3$	H	91 (87/13)	57	137-138 (138-139)[3d]
6	$-(CH_2)_5-$		$Ti(O-\langle)_4^-Li^+$	H	93 (92/8)	62	137-138
7	Me	Ph	$Ti(O-\langle)_3$	H	74 (98/2)	59	152-153 (152-153)[3d]
8	H	Ph	$Ti(O-\langle)_3$	H	73 (92/8)	52	169-170 (170-170.5)[9]
9	H	OEt	Li	H	55 (46/54)	--	
10	H	OEt	$Ti(O-\langle)_3$	H	68 (30/70)	--	
11	H	OEt	$Ti(O-\langle)_4^-Li^+$	H	72 (42/58)	--	
12	Me	OEt	$Ti(O-\langle)_3$	H	64 (73/27)	59[d]	118-119
13	Me	OEt	$Ti(O-\langle)_4^-Li^+$	H	71 (88/12)	63	118-119
14	H	Ph	$Ti(O-\langle)_4^-Li^+$	α-Me	52 (92/8)	67	135-136 (135-135.5)[3d]
15	H	Ph	$Ti(O-\langle)_4^-Li^+$	β-Me	86 (88/12)	53	168-169 (168-169)[3d]

[a]Reactions were performed on a 3 mmol scale and the products were purified by radial preparative layer chromatography (SiO_2, EtOAc-hexanes). [b]The ratio was determined by ^1H NMR (90 MHz). [c]This is the yield of the aromatization step. The products were purified by radial preparative layer chromatography (SiO_2, MeOH-CH_2Cl_2) and were >95% pure by GC or NMR. [d]Satisfactory analytical data (0.4% for C,H,N) were obtained for this compound.

The use of titanium "ate" complexes[6], generated from the addition of titanium (IV)isopropoxide to the lithium enolates (-78°, 1h), increased the ratio of 1,4-isomer and the overall yield in most cases. 2-Picoline and 3-picoline were also substituted at the 4-position using this procedure (entries 14-15).

The products obtained by this methodology result from the addition of "kinetic" enolates to the pyridine ring. To circumvent this limitation and provide a route equivalent to the addition of "thermodynamic" enolates, we performed the following (see Scheme II). The propionamide of 2-(methylamino)pyridine[8] was treated sequentially with LDA, titanium(IV) isopropoxide, pyridine, and phenyl chloroformate to give dihydropyridines 4 and 5. The crude dihydropyridine mixture was treated with 1.1 equiv of methylmagnesium chloride in THF (-78°, 1h).[8] Under these conditions 1,2-dihydropyridine 5 did not react, and after workup 5 was easily separated from the desired ketone 6 via chromatography (SiO_2, EtOAc-hexanes). Aromatization of 6 gave pyridine 7 in good yield. This sequence is tantamount to a pyridine synthesis via an addition of the "thermodynamic" enolate of 2-butanone to the 4-position of pyridine.

Scheme II.



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