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C-3 Acetoxylation of *N*-Acyl-2,3-dihydro-4-pyridones

Daniel L. Comins*, David A. Stolze, Paresh Thakker and Cheryl L. McArdle

Department of Chemistry

North Carolina State University, Raleigh, NC 27695-8204

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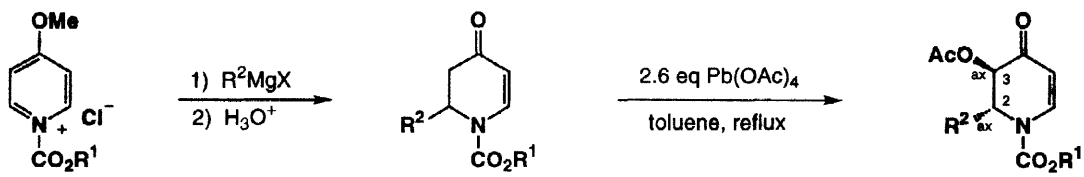
Abstract: *Stereoselective acetoxylation at the C-3 position of N-acyl-2-alkyl-2,3-dihydro-4-pyridones was effected with $Pb(OAc)_4$ in refluxing toluene.*

As part of a program to expand the synthetic utility of *N*-acyl-2,3-dihydro-4-pyridones **1**[1], we have been investigating methods for their regio- and stereoselective substitution.[2] Dihydropyridones of the type **1** are versatile building blocks for piperidine, indolizidine, quinolizidine and other alkaloid ring systems.[3] Given the importance of polyhydroxy-piperidines and -indolizidines as potential anti-viral and anti-cancer agents,[4] the regioselective oxidation of heterocycles **1** seemed worthy of study.

Several methods are available for the direct α-hydroxylation of carbonyl compounds[5]; however, selective oxidation of vinylogous amide derivatives, i.e. **1**, has received little attention.[6] A general procedure was desired, one that would ideally be (1) regioselective, (2) stereoselective, (3) chemoselective, and (4) carried out under mild conditions in the absence of a strong base. The α-acetoxylation of enones using $Pb(OAc)_4$ appeared to have the potential to meet the desired criteria listed above. Several *N*-acyldihydropyridones **1** were prepared using our published procedures[1,2] and subjected to oxidation with $Pb(OAc)_4$ in refluxing toluene. The results of this study are given in Table 1. To our satisfaction, the oxidation proceeded smoothly to give acetates **2** in good to excellent yield.



1 **2**

In addition, the conversion met all the required selectivities. The reaction was regio- and stereoselective, providing the *trans*-2,3-disubstituted products ($J_{H2\text{-}3}$ < 1.4 Hz). The *trans* stereochemistry obtained can be explained by stereoelectronic control.[7] Intramolecular acetate transfer from the enol-lead triacetate intermediate **3** (Figure 1) occurs from the axial direction to maintain a chair-like transition state. The C-2 substituent of **3** is in the axial orientation due to $A^{(1,3)}$ strain with the *N*-acyl group.[8]

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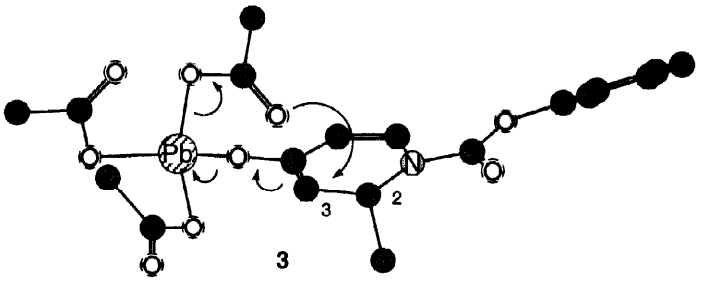
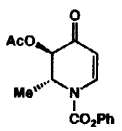
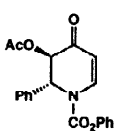
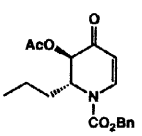
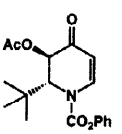
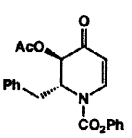
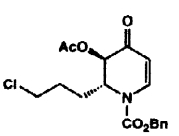
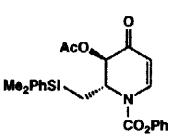


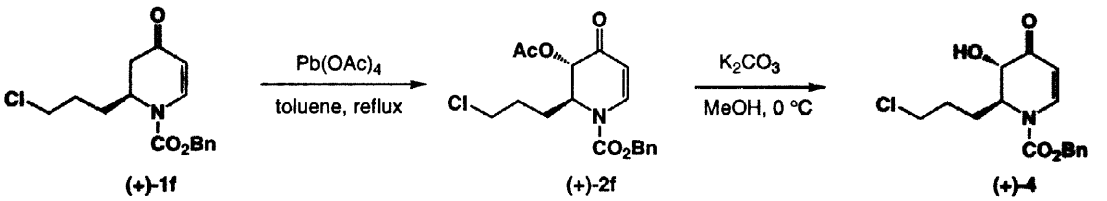
Figure 1. Stereoselective $Pb(OAc)_4$ acetoxylation

Table 1. Preparation of 3-acetoxy-2,3-dihydro-4-pyridones **2**

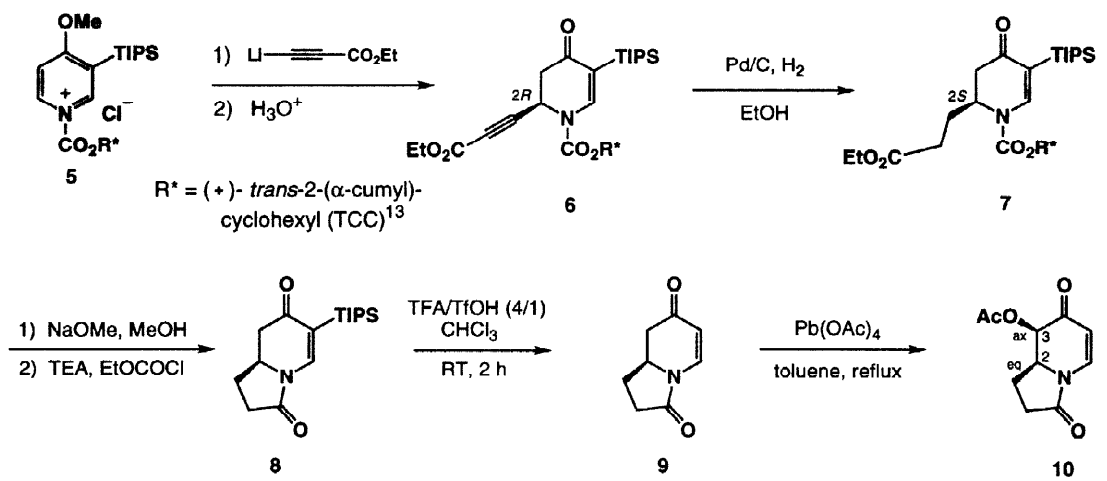
entry[a]	R^1	R^2	**1**, yield, %[b]	**2**	yield, %[b,d]
a	Ph	Me	74		80
b	Ph	Ph	72		84
c	Bn	*n*-Pr	80		92
d	Ph	*t*-Bu	30		98
e	Ph	Bn	77		90
f	Bn	$ClCH_2CH_2CH_2$	65[c]		70
g	Ph	$Me_2PhSiCH_2$	84		83

[a]Reactions were generally performed on 1 to 3 mmol scale. [b]Yields are for isolated products obtained from radical PLC (silica gel, EtOAc/hexanes).[c] Yield from a 2-step synthesis, see reference 9.[d] Satisfactory IR, ^1H and ^{13}C NMR spectra, and HRMS or microanalyses were obtained for all new compounds.

Enantiopure dihydropyridone **1f** has been utilized as a precursor to indolizidine alkaloids.[3d] Treatment of this heterocycle with $Pb(OAc)_4$ gave the *trans* enantiopure acetoxy derivative **2f** ($[\alpha]_D^{23}$+ 130.2 (*c* 0.03, $CHCl_3$) in 70% yield. We were able to hydrolyze the acetoxy group of **2f** with anhydrous K_2CO_3 in MeOH at 0 °C to give the alcohol **4** (70%, $[\alpha]_D^{25}$+ 121 (*c* 0.05, $CHCl_3$)), thus demonstrating a simple, two-step introduction of a hydroxyl group at C-3 of chiral *N*-acyl-2,3-dihydro-4-pyridones.



An acetoxylation of a bicyclic dihydropyridone derivative was investigated as another potential entry into hydroxylated indolizidines. Although this route was successful, the yield of the acetoxylation step was considerably lower than observed in the corresponding monocyclic series (Table 1). Indolizidinone **9** was prepared enantiopure in five steps as described below. Treatment of 1-acylpyridinium salt **5**[1] with lithiated ethyl propiolate[10] provided dihydropyridone **6** (mp 117-119 °C) in 68% yield. The diastereoselectivity of this reaction was determined to be >96% by HPLC and NMR analysis of the crude product. The stereochemistry at C-2 of **6** was tentatively assigned *R* by analogy to similar reactions reported from these laboratories.[1] With the TIPS group protecting the enone system, catalytic hydrogenation of **6** gave the 2-alkyl-2,3-dihydro-4-pyridone **7** in 97% yield. ^1H NMR analysis of **7** confirmed that the assignment of absolute stereochemistry at C-2 is correct as shown.[11] Hydrolysis with sodium methoxide and cyclization via a mixed anhydride converted **7** to indolizidine derivative **8** ($[\alpha]_D^{23}$- 333 (*c* 0.2, $CHCl_3$)) in 82% overall yield . Protodesilylation using TFA/TfOH in chloroform provided enantiopure **9** (83%, mp 96-97 °C, ($[\alpha]_D^{23}$- 509 (*c* 0.25, $CHCl_3$)).[12] Indolizidinone **9** was treated with $Pb(OAc)_4$ in the usual manner. A 19% yield of the desired acetoxylated indolizidine derivative **10** ($[\alpha]_D^{25}$- 85 (*c* 0.05, $CHCl_3$)) was obtained accompanied by starting material (14%) and significant decomposition. Apparently, the vinylogous imides **9** and **10** are not as stable to the reaction conditions as the dihydropyridones **1** and **2**. The conversion was stereoselective (>10:1), however, providing the *cis* product **10** ($J_{H2\text{-}3}$ = 1.9 Hz) via axial acetoxylation at C-3.



In summary, a mild, regio- and stereoselective C-3 acetoxylation of various *N*-acyl-2,3-dihydro-4-

pyridones has been accomplished. Applications of this methodology towards the asymmetric synthesis of biologically interesting alkaloids are under study.

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