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

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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. © 1998 Elsevier Science Ltd. All rights reserved.

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 compounds⁵; 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.



In addition, the conversion met all the required selectivities. The reaction was regio- and stereoselective, providing the *trans*-2,3-disubstituted products ($J_{H2-3} < 1.4$ 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-dih	ydro-4-pyridones 2

entry ^a	R ¹	R ²	1, yield, % ^b	2	yield, <u>%^{b,d}</u>
a	Ph	Me	74	Aco Me ^{rri} N Co ₂ Ph	80
b	Ph	Ph	72		84
с	Bn	<i>n-</i> Pr	80		92
d	Ph	t-Bu	30	AcO	98
e	Ph	Bn	77		90
f	Bn	CICH ₂ CH ₂ CH ₂	65°		70
g	Ph	Me ₂ PhSiCH ₂	84	Aco	83

^aReactions were generally performed on 1 to 3 mmol scale. ^bYields 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 ¹³C 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, CHCl₃) in 70% yield. We were able to hydrolyze the acetoxy group of **2f** with anhydrous K₂CO₃ in MeOH at 0 °C to give the alcohol **4** (70%, $[\alpha]_D^{25} + 121$ (c 0.05, CHCl₃)), 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 propiolate¹⁰ provided dihydropyridone 6 (mp 117-119 $^{\circ}$ 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, CHCl₃)) 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, CHCl₃)).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, CHCl₃)) 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 $(J_{\rm H2-3} = 1.9 \text{ Hz})$ 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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References and Notes

- (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. J. Am. Chem. Soc. 1994, 116, 4719. (b) Comins, D. L.; Guerra-Weltzien, L. Tetrahedron Lett. 1996, 37, 3807 and references cited therein.
- (a) Comins, D. L.; Joseph, S. P.; Chen, X. Tetrahedron Lett. 1995, 36, 9141. (b) Comins, D. L.; Joseph, S. P.; Peters, D. D. Tetrahedron Lett. 1995, 36, 9449. (c) Comins, D. L.; Joseph, S. P.; Zhang, Y. Tetrahedron Lett. 1996, 37, 793. (d) Comins, D. L.; Zhang, Y. J. Am. Chem. Soc. 1996, 118, 12248. (e) Comins, D. L.; Chen, X.; Joseph, S. P. Tetrahedron Lett. 1996, 37, 9275.
- (a) Comins, D. L.; Joseph, S. P. In Advances in Nitrogen Heterocycles; Moody, C. J., Ed.; JAI Press Inc.: Greenwich, CT, 1996; Vol. 2, pp. 251-294. (b) Comins, D. L.; Joseph, S. P.; Hong, H.; Alawar, R. S.; Foti, C. J.; Zhang, Y.; Chen, X.; LaMunyon, D. H.; Guerra-Weltzien, M. Pure and Applied Chem. 1997, 69, 477. (c) Comins, D. L.; Chen, X.; Morgan, L. A. J. Org. Chem. 1997, 62, 7435. (d) Comins, D. L.; LaMunyon, D. H.; Chen, X. J. Org. Chem. 1997, 62, 8182.
- For leading references, see: (a) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. J. Am. Chem. Soc. 1997, 119, 4856 (b) Nishimura, Y. In Studies in Natural Products Chemistry, Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992, Vol. 10, pp. 495-583.
- 5. (a) Review: Demir, A. S.; Jeganathan, A. Synthesis 1992, 235-247. (b) Davis, F. A.; Chen, B.-C. Chem. Rev. 1992, 92, 919-934.
- 6. Fang, F. G.; Prato, M.; Kim, G.; Danishefsky, S. J. Tetrahedron Lett. 1989, 30, 3625.
- 7. Deslongchamps, P. Stereoelectronic Effects in Organic Chemistry; Pergamon: New York, 1983; Chapter 6.
- 8. Brown, J. D.; Foley, M. A.; Comins, D. L. J. Am. Chem. Soc. 1988, 110, 7445.
- 9. Comins, D. L.; Zeller, E. Tetrahedron Lett. 1991, 32, 5889.
- 10. Midland, M. M.; Tramontano, A.; Cable, J. R. J. Org. Chem. 1980, 45, 28.
- 11. The C-2 stereochemistry of 2-alkyl-2,3-dihydro-4-pyridones of the type 7 can be assigned by the location of the vinylic C-6 proton peak in the ¹H NMR spectrum (300 MHz, CDCl₃). The 2S diastereomer exhibits a singlet at 7.7 ppm, whereas the vinylic proton of the 2*R* isomer is found at 7.3 ppm.
- 12. An asymmetric synthesis of (+)-9 has been reported; however, the absolute configuration was misassigned. Waldmann, H.; Braun, M. J. Org. Chem. 1992, 57, 4444.
- (a) Comins, D. L.; Salvador, J. M. J. Org. Chem. 1993, 58, 4656. (b) (+)- and (-)-TCC alcohols are available from Aldrich Chemical Company.