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Synthesis and Reactivity of *N*-Acyl-5-(1-hydroxyalkyl)-2,3-dihydro-4-pyridones

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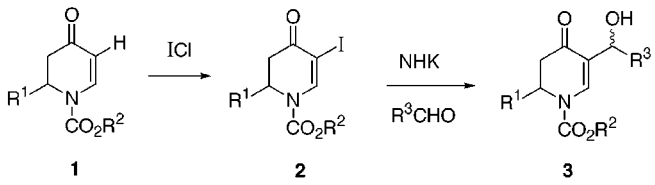
ABSTRACT

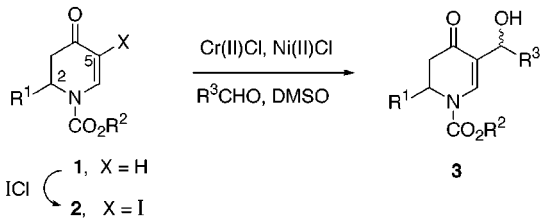


The Nozaki–Hiyama–Kishi reaction was used to prepare the 5-(1-hydroxyalkyl)-2,3-dihydro-4-pyridones 3. Reduction, oxidation, and substitution reactions of 3 were examined.

N-Acyldihydropyridones of type **1** are versatile synthetic intermediates.[1] They can be readily prepared in racemic or enantiopure form by the addition of organometallics to 1-acyl-4-methoxypyridinium salts followed by acidic workup.[2,3] As part of a program directed at expanding the synthetic utility of dihydropyridones as building blocks, we have been investigating methods for their regio- and stereoselective substitution.[4] Reported herein is a regiospecific substitution of **1** at C-5 using a halogenation and Ni(II)/Cr(II)-mediated aldehyde addition reaction sequence (Scheme 1). The resulting 5-(1-hydroxyalkyl)-2,3-dihydro-4-pyridones **3** were subjected to reduction, oxidation, and various substitution reactions.

Several attempts at preparing alcohols **3** from dihydropyridones **1** using various modifications of the Baylis−Hillman reaction[5,6] were unsuccessful. As an alternative approach, we considered a two-step procedure involving C-5 iodination and subsequent hydroxyalkylation using the Nozaki−Hiyama−Kishi (NHK) reaction.[7] The NHK reaction was an attractive alternative for the preparation of alcohols **3** because of its excellent chemoselectivity and its proven utility in natural product synthesis. Although examination of the literature revealed no example of a NHK reaction using an α-iodoenone and an aldehyde, we were encouraged to proceed by a report of an analogous transformation using an α-iodoacrylate.[8] In this case the vinyl iodide was used in large

Scheme 1



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(3) For the synthesis of related dihydropyridones using the aza Diels−Alder reaction, see: Kirschbaum, S.; Waldmann, H. *J. Org. Chem.* **1998**, *63*, 4936 and references therein.

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excess (10 equiv) relative to the aldehyde. Excess halide is often necessary to obtain good yields due to side reactions involving reduction and coupling.[7] In our case the iodide is too valuable to be used in excess, so it was hoped that conditions could be found to allow the NHK reaction to proceed with 1 equiv of halide.

Previously in our laboratories was developed a C-5 iodination of dihydropyridones **1** using NIS/catalytic HTIB.[6] This procedure requires a long reaction time (3 d) and uses an expensive iodine source. To circumvent these drawbacks, ICl (1 M in CH_2Cl_2)[10] was examined as an alternative reagent for the preparation of iodides **2**. Treatment of dihydropyridones **1** with ICl (1.5 equiv) in methylene chloride (0 °C, 1 h) provided high yields of the desired iodides **2** via a convenient procedure. Initial attempts at coupling dihydropyridones **2** with benzaldehyde under standard NHK conditions resulted in poor results with reduction products **1** predominating. Conditions were eventually found, involving DMSO as solvent and adding the iodide last to the reaction mixture, which allowed the iododihydropyridones **2** to couple with various aldehydes (3 equiv) to give the desired alcohols **3** in moderate to good yields as shown in Table 1.

Table 1. Preparation of Hydroxyalkyldihydropyridones **3** from **2**

entry[a]	R^1	R^2	R^3	product	yield,[b] %	(dr)[c]
1	Ph	Bn	$PhCH_2CH_2$	**3a**	64	(1/2.5)
2	Ph	Bn	*n*-C_5H_{11}	**3b**	57	(1/1.7)
3	Ph	Bn	Ph	**3c**	80	(1/7)
4	Ph	Bn	3-furanyl	**3d**	68	(1/2.6)
5	Ph	Bn	C_6H_{11}	**3e**	64	*d*
6	Me	Bn	*n*-C_5H_{11}	**3f**	64	(1/2.6)
7	Me	Bn	Ph	**3g**	57	(1/3.5)

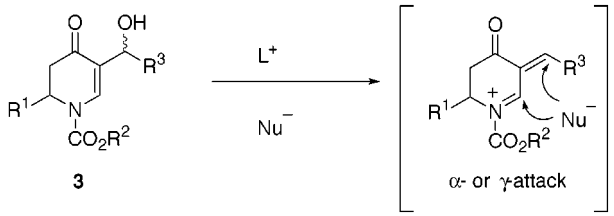
[a] The reactions were generally performed on a 0.5−1.0 mmol scale in 6 mL of DMSO using 3 equiv of aldehyde (R^3CHO). [b] Yield of products obtained from radial preparative-layer chromatography. [c] The ratio of diastereomers (dr) was determined by ^1H NMR. [d] The dr was not determined.

Interestingly, some aldehyde facial selectivity was observed due to chirality transfer from the C-2 center of the dihydropyridone. The selectivity was low in most cases with the exception of entry 3, where the combination of the 2-phenyl derivative **2c** and benzaldehyde resulted in a 7/1 mixture of diastereomers **3c**. Except for alcohols **3e** (entry 5), all diastereomers could be separated by chromatography.[11]

Since the hydroxyl group of **3** is γ to the nitrogen, it was anticipated that the addition of a Lewis acid would effect *N*-acyliminium ion formation.[12] In the presence of a nucleophile, α- or γ-attack could proceed to give substitution products (Scheme 2). In this vein, exploratory reactions were carried out with **3g**, allyltrimethylsilane, and a Lewis acid ($SnCl_4$ or $BF_3{\cdot}Et_2O$) in methylene chloride.

To our satisfaction, the use of 1.5 equiv of $BF_3{\cdot}Et_2O$ and 1.2 equiv of allyltrimethylsilane (−30 °C, 30 min) afforded

Scheme 2



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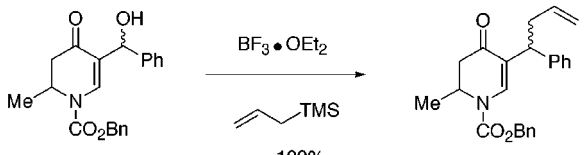
a quantitative yield of allylated dihydropyridone **4** (Scheme 3). Several other nucleophiles (Et_3SiH, methanol, thiophenol,

Scheme 3

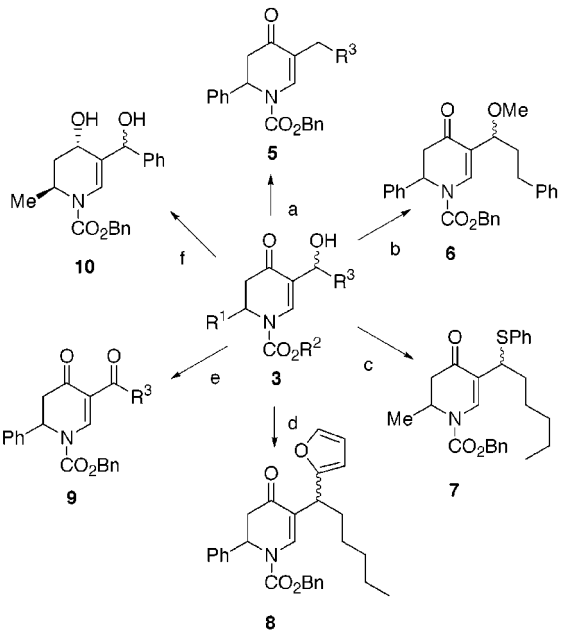


3g 4

and furan) were examined, and the results are depicted in Scheme 4. In all cases γ-attack occurred exclusively to afford the observed products.

Using this procedure, the hydroxyl group of **3** can be

Scheme 4[a]



[a] Reagents and conditions: (a) Et_3SiH, TFA, CH_2Cl_2, −20 °C, R^3 = Ph (77%), R^3 = $PhCH_2CH_2$ (72%); (b) MeOH, catalytic PPTS, rt (100%); (c) PhSH, CH_2Cl_2, catalytic TMSOTf, rt (73%); (d) toluene $BF_3{\cdot}OEt_2$, furan, −78 °C (80%); (e) MnO_2, CH_2Cl_2, rt, R^3 = Ph (62%), R^3 = cyclohexyl (50%), R^3 = 3-furanyl (50%); (f) $NaBH_4$, $CeCl_3$, MeOH, −40 °C (77%).

(8) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647.
(9) Comins, D. L.; Joseph, S. P.; Chen, X. *Tetrahedron Lett.* **1995**, *36*, 9141.

replaced with allyl, hydrogen, alkoxy, alkylsulfanyl, and furanyl groups. It is likely other common nucleophiles that have been found to add to various acyliminium ions will also be effective in this system. Alcohols **3** can also be oxidized with MnO_2 to provide the corresponding keto derivatives **9** in good yield, or reduced with $NaBH_4/CeCl_3$ to afford diol **10**.[13]

In summary, a new and convenient procedure using ICl was developed to prepare 5-iododihydropyridones **2** which were subjected to the Nozaki−Hiyama−Kishi reaction to afford *N*-acyl-5-(1-hydroxyalkyl)-2,3-dihydro-4-pyridones **3**. These heterocycles proved to be useful intermediates for the synthesis of various C-5 substituted 2,3-dihydro-4-pyridones.[14]

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Supporting Information Available: Characterization data for compounds **2a**, **3a**−**g**, and **4**−**10**. ^1H and ^{13}C NMR spectra of **2a**, **3f**−**g**, **4**, **5**, and **6**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) ICl was purchased from Aldrich Chemical Co. as a 1 M solution in CH_2Cl_2. (b) For the synthesis of α-iodo enones from the corresponding α-silyl precursors using ICl, see: Alimardanov, A.; Negishi, E. *Tetrahedron Lett.* **1999**, *40*, 3839.

(11) The relative stereochemistry of the diastereomers **3** was not determined.

(12) For examples of γ-hydroxyenecarbamates as unsaturated *N*-acyliminium ion precursors, see: (a) Kozikowski, A. P.; Park, P.-u. *J. Org. Chem.* **1984**, *49*, 1674. (b) Comins, D. L.; Abdullah, A. H. *Tetrahedron Lett.* **1985**, *26*, 43. (c) Comins, D. L.; Stroud, E. D. *Tetrahedron Lett.* **1986**, *27*, 1869. (d) Kozikowski, A. P.; Park, P.-u *J. Org. Chem.* **1990**, *55*, 4668. (e) Comins, D. L.; Killpack, M. O. *J. Am. Chem. Soc.* **1992**, *114*, 10972.

(13) Luche reduction of dihydropyridones of type **1** generally gives equatorial alcohols, see: Comins, D. L.; Chung, G.; Foley, M. A. *Heterocycles* **1994**, *37*, 1121.

(14) The structure assigned to each new compound is in accordance with its IR, ^1H NMR, and ^{13}C NMR spectra and elemental analysis or high-resolution mass spectra.