



Synthesis of 2,4-Disubstituted *N*-Acyl-5,6-dihydro-2-pyridones

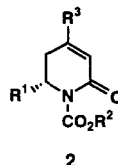
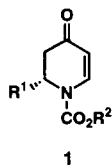
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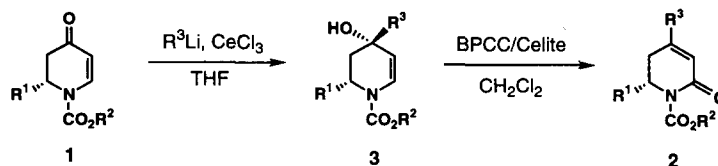
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Abstract: A simple two-step procedure converts 2-substituted *N*-acyl-2,3-dihydro-4-pyridones to 2,4-disubstituted *N*-acyl-5,6-dihydro-2-pyridones. Copyright © 1996 Elsevier Science Ltd

Dihydropyridones of the type **1** are versatile synthetic building blocks due to their facile preparation, the functionality present, their availability in either antipode, good air stability, and the ease of introducing ring substituents in a regio- and stereocontrolled fashion.^{1,2} The isomeric dihydropyridones **2** would be versatile synthetic intermediates as well, if a practical method for their enantioselective preparation were available.³



We now report a synthesis of **2** from dihydropyridones **1** in two steps as shown in Scheme 1. The first step involves a cerium-mediated addition of an alkyl lithium to **1** to give tertiary alcohols **3** in high yield.⁴ The addition is highly stereoselective giving the relative stereochemistry shown (**3**) as determined by NOE experiments on alcohol **3c** (Figure 1). The second step of the synthesis requires an oxidative rearrangement⁵ of γ -hydroxyenecarbamates **3** to provide dihydropyridones **2**. After investigating several chromate oxidants with little success (Table 1), it was found that bipyridinium chlorochromate (BPCC)⁶ gave the best results (Celite, CH₂Cl₂, RT) providing moderate to good yields of **2** as shown in Table 2. To our knowledge these are the first examples of an oxidative rearrangement of allylic tertiary alcohols of the type **3** to lactams.⁷



Scheme 1

Table 1. Oxidative rearrangement of **3a** ($R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R^3 = \text{Me}$)

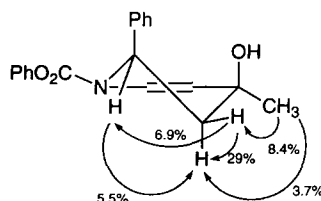
entry ^a	oxidant/additive	solvent ^b	yield, ^c %
1	PCC	pyridine	sm
2	PDC	pyridine	sm
3	PCC/NaHCO ₃ (1:2)	CH ₂ Cl ₂	10
4	CrO ₃ /2 equiv pyridine	CH ₂ Cl ₂	21
5	PDC/NaOAc (1:2)	CH ₂ Cl ₂	16
6	CrO ₃	pyridine	16
7	CrO ₃ /2 equiv DMAP	pyridine	18

^aThe reactions were generally performed on a 1 mmol scale. ^bSolvents were anhydrous. ^cYield obtained from radial PLC (silica gel, EtOAc/hexanes).

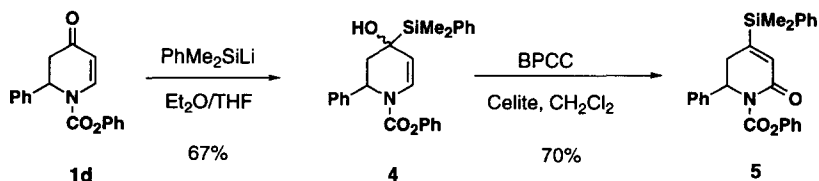
Table 2. Preparation of *N*-Acyl-5,6-dihydro-2-pyridones **2** from **1**

entry ^a	sm 1	R^1	R^2	R^3	yield, ^b % 3	yield, ^c (%) 2
1	1a	Me	Ph	Me	81	68
2	1b	Me	Ph	Bu	92	51
3	1c	Ph	Ph	Me	80	53
4	1d	Ph	Ph	Bu	90	50
5	1e	CH ₂ =CH(CH ₂) ₃	Bn	Me	82	52

^aThe reactions were generally performed on a 1–3 mmol scale. ^bYield of purified product obtained from radial PLC (silica gel, EtOAc/hexanes/1% TEA). ^cYield obtained from radial PLC (silica gel, EtOAc/hexanes).

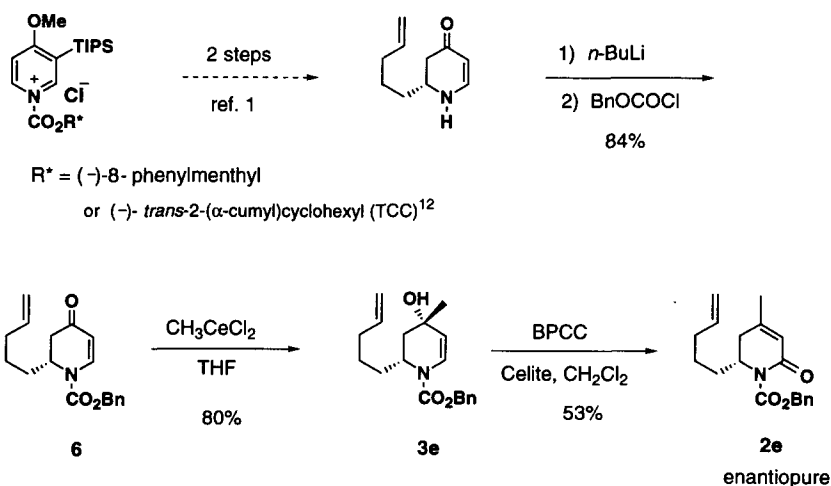
**Fig. 1** Selective NOE correlations for tertiary alcohol **3c**

A silicon variant of this protocol was carried out as shown in Scheme 2. Dimethylphenylsilyllithium⁸ was added to **1d** to give a 67% yield of tertiary alcohol **4**. Although one diastereomer appeared to be formed by NMR and HPLC analysis, the relative stereochemistry could not be determined. Oxidative rearrangement of **4** using BPCC provided dihydropyridone **5** in 70% yield. Since the dimethylsilyl group can be transformed into a hydroxyl function or protodesilylated in certain cases,⁹ this silicon modification broadens the scope of the methodology.



Scheme 2

Although the examples listed in Table 2 are racemic, enantiopure dihydropyridones **1** are readily available^{1,2} and can be converted into non-racemic **2**. An example of this is shown in Scheme 3. Enantiopure dihydropyridone **6**¹ was treated with MeLi/CeCl₃ to provide tertiary alcohol **3e** $[[\alpha]_D^{23} -97$ (*c* 1.06, CHCl₃)] in 80% yield. Oxidative rearrangement with BPCC (CH₂Cl₂ RT, 18 h) gave enantiopure lactam **2e** $[[\alpha]_D^{24} -102$ (*c* 1.11, CHCl₃)] in 53% yield.^{10, 11}



Scheme 3

Regio- and stereoselective introduction of substituents on dihydropyridones **2** and the scope of the synthetic utility of these heterocycles are being studied in our laboratories.

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