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

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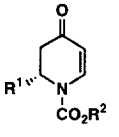
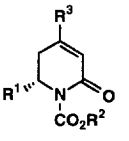
Abstract: *A simple two-step procedure converts 2-substituted N-acyl-2,3-dihydro-4-pyridones to 2,4-disubstituted N-acyl-5,6-dihydro-2-pyridones.* Copyright © 1996 Elsevier Science Ltd

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]

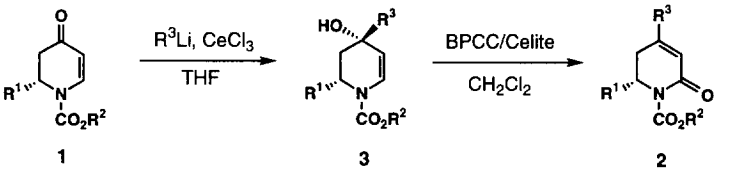


1



2

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 alkyllithium 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 rearrangement[5] 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, CH_2Cl_2, 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]



1 **3** **2**

Scheme 1

Table 1. Oxidative rearrangement of **3a** (R^1 = Me, R^2 = Ph, R^3 = Me)

entry[a]	oxidant/additive	solvent[b]	yield,[c] %
1	PCC	pyridine	sm
2	PDC	pyridine	sm
3	PCC/$NaHCO_3$ (1:2)	CH_2Cl_2	10
4	CrO_3/2 equiv pyridine	CH_2Cl_2	21
5	PDC/NaOAc (1:2)	CH_2Cl_2	16
6	CrO_3	pyridine	16
7	CrO_3/2 equiv DMAP	pyridine	18

[a]The reactions were generally performed on a 1 mmol scale. [b]Solvents were anhydrous. [c]Yield 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

[a]The reactions were generally performed on a 1-3 mmol scale. [b]Yield of purified product obtained from radial PLC (silica gel, EtOAc/hexanes/1% TEA). [c]Yield obtained from radial PLC (silica gel, EtOAc/hexanes).

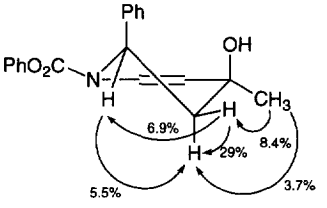
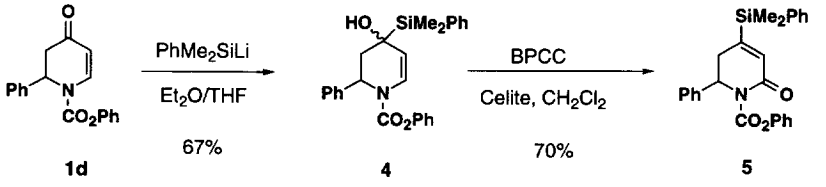


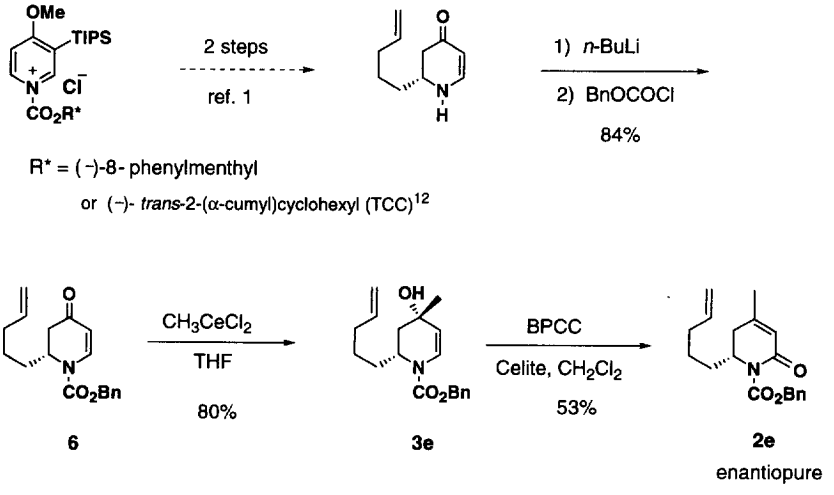
Fig. 1 Selective NOE correlations for tertiary alcohol **3c**

A silicon variant of this protocol was carried out as shown in Scheme 2. Dimethylphenylsilyllithium[8] was added to **1d** to give a 67% yield of tertiary alcohol **4.** Although one diastereometer 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/$CeCl_3$ to provide tertiary alcohol **3e** $[[\alpha]_D^{23}$-97 (*c* 1.06, $CHCl_3$)] in 80% yield. Oxidative rearrangement with BPCC (CH_2Cl_2, RT, 18 h) gave enantiopure lactam **2e** $[[\alpha]_D^{24}$ -102 (*c* 1.11, $CHCl_3$)] 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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