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Enantioselective Preparation and Hydroboration of Cyclic Enamides: Synthesis of (2*S*)-Pseudoconhydrine

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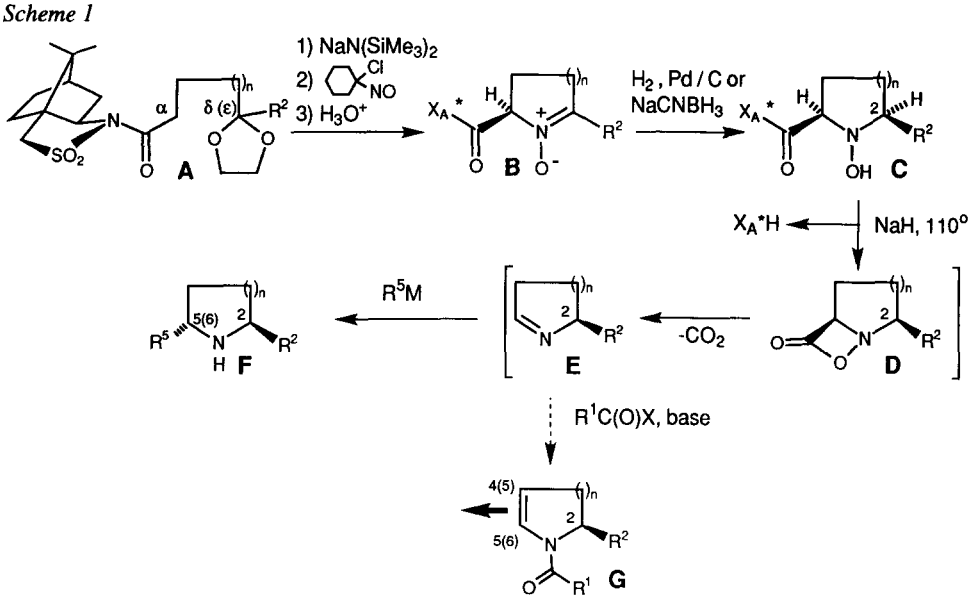
Abstract: Successive treatment of 2-alkyl-1-hydroxy-6-carbonylsultampiperidines **1** with NaH and an acylating agent/pyridine in boiling toluene affords optically pure 1-acyl-2-alkyl-1,2,3,4-tetrahydropyridines **2**. Hydroboration/oxidation of *N*-benzoylenamides **2f** and **2g** furnishes *trans*-2-alkyl-1-benzyl-5-hydroxypiperidines **5f** and **5g**, respectively. Hydrogenolysis of **5f** provides pure (2*S*)-pseudoconhydrine (**7**), in 3 steps from **1**, R^2=*n*-C_3H_7 (31% overall yield).

Recently, we described the 2-step conversion of *N*-acylsultams into carbonylsultam-substituted *N*-hydroxypiperidines and pyrrolidines **A** → **B** → **C**. Deoxygenative decarboxylation of hydroxylamines **C** (NaH, toluene, reflux) and trapping of the non-isolated imines **E** with *i*-Bu_2AlH or $R^5Li/CeCl_3$ provided C(2)-monosubstituted or C(2,6)/C(2,5)-*trans*-disubstituted piperidines/pyrrolidines **F** in 50 to 68% yield from **C** (Scheme 1). [1]

Scheme 1



We then envisaged trapping the *in situ*-produced imines **E** by *N*-acylation to prepare enantiomerically pure cyclic enamides **G**. [2] The latter are promising synthetic intermediates given the potential of substituents R^2 to direct the stereochemistry of addition reactions to the enamide group. [3,5]

Our results are summarized in Scheme 2.

Scheme 2

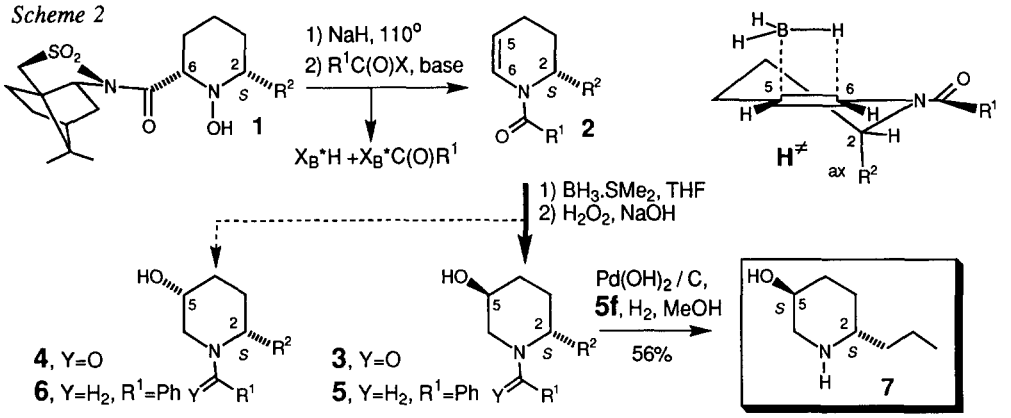


Table 1: Optically Pure Cyclic Enamides by Deoxygenative Decarboxylation/Imine Acylation: **1** → **2**. [4]

Entry	*N*-Hydroxypiperidine	R^2	Acylation Conditions [a]	Cyclic Enamide	R^1	Yield[%]	"Recovered Sultam" X_B*H / X_B*COR¹[%]
1	**1**	*n*-C_3H_7	A	**2a**	OMe	10-34	44/29
2	**1**	*n*-$C_{11}H_{23}$	A	**2b**	OMe	22-49	20/58
3	**ent-1**	*n*-C_3H_7	A	**ent-2c**	OBn	21-56	---- [b]
4	**1**	*n*-$C_{11}H_{23}$	A	**2d**	OBn	33-42	---- [b]
5	**1**	*n*-$C_{11}H_{23}$	A	**2e**	O*t*-Bu	8	---- [b]
6	**1**	*n*-$C_{11}H_{23}$	B	**2e**	O*t*-Bu	56	<10/75
7	**1**	*n*-C_3H_7	B	**2f**	C_6H_5	55	47/53
8	**1**	*n*-$C_{11}H_{23}$	B	**2g**	C_6H_5	59	32/47
9	**1**	*n*-$C_{11}H_{23}$	A	**2h**	$3,5(NO_2)_2C_6H_3$	57	---- [b]

a) i) **1**, NaH, toluene reflux; Method A: ii) R^1COCl or *t*-$Bu(OCO)_2O$ [entry 5], collidine, r.t., 16 h; Method B: ii) R^1COCl or $(t\text{-}BuOCO)_2O$ [entry 6], pyridine, 110°→ r.t.. b) Not determined.

Heating a 0.02 M solution of *N*-hydroxylamines **1** in toluene with NaH (1.5 mol equiv., reflux, 3-17 h), followed by addition of an acyl chloride (3 mol equiv.)/sym-collidine at r.t. and stirring at r.t. for 16 h (Method A) gave the expected enecarbamates **2a** - **2e** in variable yields and the *N*-3,5-dinitrobenzoyl derivative **2h** in a more reproducible yield of 57% (Table 1). Alternatively, enamides **2** were obtained in reproducible yields of 55-59% when the acylating agent/pyridine was added to the boiling imine solution and the mixture allowed to cool to r.t. (Method B, *c.f.* entries 5,6). [4] In most cases, sultam auxiliary X_B*H and its *N*-acyl derivative X_B*C(O)R¹ were efficiently "recovered".

With cyclic enamides **2** in hand, we studied their hydroboration/oxidation as a possible route to *trans*-2-alkyl-5-hydroxypiperidines (Table 2). [3,5]

$BH_3.SMe_2$ (1.2 mol equiv.) was added to a solution of enecarbamate **2a** in THF at -78°C. Warming the mixture to r.t. over 17 h, addition of water (10-20 mol equiv.), oxidation with aq. 20% NaOH/30% H_2O_2 (1:1, 20-50 mol equiv., 1-2 h, r.t.), extraction (CH_2Cl_2) and FC provided a 3:1-mixture of *trans*- and *cis*-hydroxypiperidines **3a** and **4a**, respectively. This modest diastereomer ratio does not match the ratio **3a/4a** = 6:1, previously claimed to result from similar reaction conditions but rather resembles the 2:1-ratio of **3i/4i**

obtained *via* hydroboration of carbamate **2i** at higher temperature (20°, Table 2, entry 20). [5]

Table 2: Diastereoselective Hydroboration/Oxidation of Cyclic Enamides: **2** → **3** + **4** and **2** → **5** + **6**. [4]

Entry	Enamide			Mol equiv.	Hydroboration	2-Alkyl-5-hydroxypiperidines		
		R^1	R^2	BH_3	Temp. [°C]	*trans* + *cis*	Ratio *trans/cis*	Yield [%]
10	**2a**	OMe	n-C_3H_7	1.2	-78 → r.t.	**3a/4a**	76:24 (GC)	68 [a]
11	**2b**	OMe	n-$C_{11}H_{23}$	1.2	-78 → r.t.	**3b/4b**	75:25 (GC)	84 [a]
12	**ent-2c**	OBn	n-C_3H_7	1.2	-78 → r.t.	**ent-(3c/4c)**	77:23 (HPLC)	46 [b]
13	**2d**	OBn	n-$C_{11}H_{23}$	1.2	-78 → r.t.	**3d/4d**	77:23 (HPLC)	56 [b]
14	**2e**	O-*t*-Bu	n-$C_{11}H_{23}$	1.2	-78 → r.t.	**3e/4e**	74:26 (GC)	55 [a]
15	**2e**	O-*t*-Bu	n-$C_{11}H_{23}$	10	-78 → r.t.	**3e/4e**	76:24 (GC)	54 [a]
16	**2e**	O-*t*-Bu	n-$C_{11}H_{23}$	1.2	20	**3e/4e**	85:15 (GC)	77 [a]
17	**2e**	O-*t*-Bu	n-$C_{11}H_{23}$	1.2	55	**3e/4e**	86:14 (GC)	77 [a]
18	**2f**	C_6H_5	n-C_3H_7	10	-78 → r.t.	**5f/6f**	>90:10 (^{1}H-NMR)	98 [b]
19	**2g**	C_6H_5	n-$C_{11}H_{23}$	10	-78 → r.t.	**5g/6g**	>90:10 (^{1}H-NMR)	55 [b]
20	**2i**	OMe	CH_3	1.0	20	**3i/4i**	66:34 (FC) lit. [5]	79 [b]

a) by GC; b) isolated sum of isomers.

Applying our low temperature hydroboration protocol to **2**, and varying the C(2)- and carbamate substituents R^2 and R^1, gave products **3/4** in unchanged 3:1-ratios from the *O*-methyl-, *O*-benzyl- and *O*-*t*-butyl carbamates **2b** - **2e**. The product ratio **3e/4e** was virtually independent of borane molarity but improved slightly at higher reaction temperatures (entries 14-17).

It was plausible to expect improved stereoselectivities in the hydroboration of cyclic en**amides** relative to that of enecarbamates owing to the increased double bond character of the amide group. Hence, $A^{(1,3)}$ strain should become more effective in imposing the axial position (and the face-shielding) of the C(2)-substituent R^2 (*c.f.* transition state $\mathbf{H}^{\neq}$). [6] Indeed, successive treatment of *N*-benzoylenamides **2f** and **2g** with $BH_3.SMe_2$ (10 mol equiv., -78° → r.t.) and H_2O_2/NaOH furnished *trans*-*N*-benzyl-2-alkyl-5-hydroxypiperidines **5f** and **5g**, respectively, with over 90% diastereoselectivity (^{1}H-NMR). [4] These conditions effected the concomitant reduction of the *N*-benzoyl to the *N*-benzyl group which can be conveniently removed by catalytic hydrogenolysis. For example, stirring crude *N*-benzylpiperidine **5f** with $Pd(OH)_2$/C under H_2 (1 atm, MeOH, 15 h), addition of dry HCl and crystallization (Et_2O/*i*-PrOH) furnished the hydrochloride salt of the hemlock alkaloid pseudoconhydrine (**7**.HCl, m.p. 205-207°) [7] in 56% yield from enamide **2f**. A sample, crystallized from $CDCl_3$, m.p. 213-215°, {lit.: 212-213° [8b]; 208-209° [9a]; 220° [9b]; 214-215° [10a]}; $[\alpha]_D$= +3.56, (c=0.4, MeOH, 21°), {lit.[9b]: $[\alpha]_D$= +3.06, (MeOH, 25°)}, showed the same IR, ^{1}H-NMR and ^{13}C-NMR data as those previously reported. [9a,10c] Synthetic **7** was converted into its *N*-benzoyl derivative: m.p. 132-133° (Et_2O, pentane), {lit.[9a]: 130-131°}; $[\alpha]_D$= +28.5, (c=0.2, $CHCl_3$, 26°), {lit.[9a]: $[\alpha]_D$= +21.3 (c=0.75, $CHCl_3$, 26°)}.

In summary, optically pure cyclic enamides, accessible *via* a three-step sequence starting from *N*-acylsultams **A** and their antipodes, undergo *trans*-selective hydroborations. This extends the preparative versatility of the deoxygenative decarboxylation/imine trapping concept as illustrated by a synthesis of (2*S*)-pseudoconhydrine.

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