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Highly Chemoselective Reduction of N-Boc Protected Lactams

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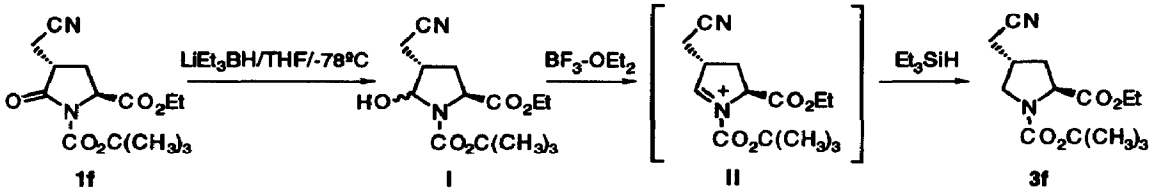
Abstract: N-Boc protected lactams can be reduced chemoselectively in the presence of other groups such as esters, nitriles, carbamates or double bonds by first reducing the amide carbonyl group into the corresponding hemiaminal using lithium triethylborohydride followed by further reduction of the hemiaminal intermediate with triethylsilane/Boron trifluoride etherate. This method preserves the chirality present in the substrate.

Selective reduction of a lactam carbonyl group in the presence of other reducible groups such as esters, has usually been accomplished with diborane.[1] Other reagents like $NaBH_4$-I_2[2] allow the chemoselective reduction of lactams in the presence of a urethane functionality. The use of a large excess of BH_3-SMe_2[3] is reported to do the same lactam selective reduction in the presence of both esters and carbamates. Although these methods achieve the complete reduction of the lactams into the cyclic amines in one single step other chemoselective approaches can be used. Thus, the lactam can be transformed into its thioamide derivative with Lawesson's reagent followed by reduction with nickel boride.[4] More recently it has been shown[5] that good yields can be obtained by partial reduction of the lactam into the corresponding hemiaminal with DIBAL-H and further reduction of this intermediate with $NaBH_3CN$ after the conversion of the hemiaminal into an aminal. We would like to report here that $LiEt_3BH/Et_3SiH$-Et_2O-BF_3 is able to achieve a highly chemoselective lactam reduction, as other groups such as double bonds, esters, nitriles or carbamates are not affected. Furthermore, this method preserves the integrity of stereogenic centres present in the substrate.

In **scheme I** an illustrative example of the method with the proposed mechanism is shown and in **Table I** are collected all the substrates reduced.

The reduction to the hemiaminal of several *N*-urethane protected lactams, has been usually conducted with $NaBH_4/H^+$[6] and more recently with $LiBEt_3H$[7] and DIBAL-H.[5] Only in the latter case has the reduction of the lactam carbonyl group been reported to be chemoselective.

The use of $LiBEt_3H$ in THF at -78°C (**Scheme I**) for the reduction of the highly functionalized pyroglutamate **1f**[8] into the hemiaminal **I** proved to be equally effective in yield and chemoselectivity as in the DIBAL-H case. Without purification, the intermediate **I** was transformed into the ethylprolinate **3f** by treatment with 2 equivalents of Et_3SiH and 2.2 equivalents of $Et_2O{\cdot}BF_3$ in CH_2Cl_2 at -78°C for two hours.[9] The Lewis acid is responsible of the generation of the N-acyliminium intermediate[10] **II** which is effectively reduced by the triethylsilane.



Scheme I

Although $Et_3SiH/Et_2O{\cdot}BF_3$ has been widely used to reduce lactols to ethers,[11] this is the first time it has been applied to reduce directly hemiaminals.[12]

Depending on the experimental conditions the *tert*-butoxycarbonyl group can be removed by the action of an excess of the Lewis acid, it being possible to isolate the corresponding cyclic amine with or without the Boc protecting group.[9]

The method has been applied to several substituted five and six membered ring lactams (**Table I**). Yields are good in all cases (70-85%), expect for **3b** (53%). The isolation of N-deprotected amines **3a**, **3b**, **3d** and **3f** turned out to be difficult due to their high water solubility and the yield dropped during the reaction workup. This problem can be circumvented by isolating the BOC protected derivatives **3** (Table I, entries 1, 2, 4, 6).

As the reaction proceeds through the N-acyliminium intermediate **II** it was necessary to investigate that the sterogenic centres present in the substrates, especially the substituent in the four position, were not affected during the reaction process. This is important since other reduction methods mentioned before[4,5] do not verify whether the chirality is preserved or not. Therefore, compound **4c** was treated with (R)-(-)-methoxy-α-(trifluoromethyl)phenylacetyl chloride[13] in the presence of 4-dimethylaminopyridine, giving an enantiomeric excess (ee) >95% based on careful ^1H-NMR analysis of the corresponding Mosher amide.

In conclusion, the present method allows the chemoselective reduction of highly functionalized lactams without affecting the stereochemical integrity of the stereogenic centres present in the substrate. Further synthetic applications of this novel reduction system are in progress.

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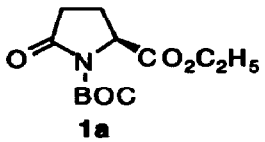
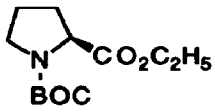
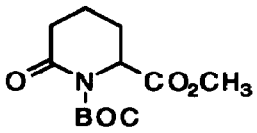
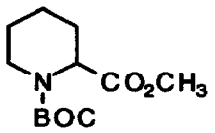
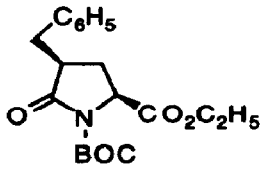
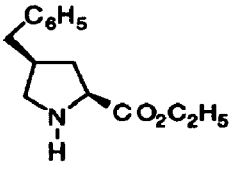
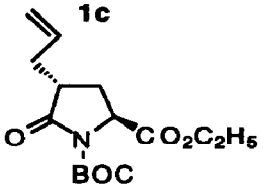
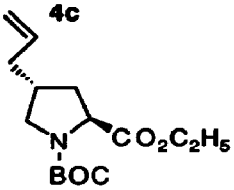
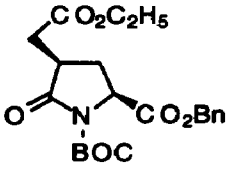
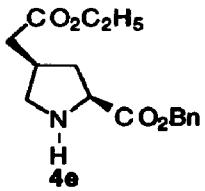
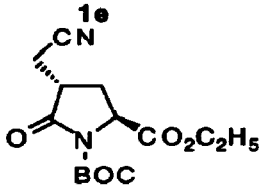
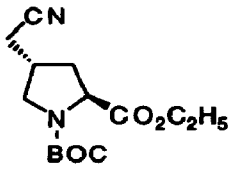
Table I. Chemoselective lactam reduction using $LiEt_3BH/SiEt_3H$, Et_2O-BF_3 system

Entry	Substrate	Product	Yield (%)	$[\alpha]_D$
1[a,d]	 **1a**	 **3a**	85	-47.7° (c= 1.1, $CHCl_3$)
2[b,d]	 **1b**	 **3b**	53	----
3[c]	 **1c**	 **4c**	85	-51.7° (c= 0.53, CH_3OH)
4[c,d]	 **1d**	 **3d**	70	-30.2° (c= 1.1, $CHCl_3$)
5[c]	 **1e**	 **4e**	76	-35.7° (c= 0.45, CH_3OH)
6[c,d]	 **1f**	 **3f**	78	-29.8° (c= 1.19, $CHCl_3$)

[a] Obtained from L-glutamic acid.[14] [b] Obtained by ruthenium oxidation[15] of (±) Methyl N-Boc pipecolate.

[c] Prepared as described in *ref.*9. [d] A mixture of conformers of the N-*tert*-Butoxycarbonyl group in the NMR spectra can be observed.[16]

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9 **General procedure:** A 1.0 M solution of lithium triethylborohydride in THF (1.62 ml, 1.62 mmol) was added to a solution of **1** (1.35 mmol) at -78°C under nitrogen atmosphere. After 30 minutes the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2.5 ml) and warmed to 0°C. 30% H_2O_2 (5 drops) was added and the mixture was stirred at 0°C. After 20 minutes the organic solvent was removed in *vacuo*, and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude products **2** were used without further purification.

A solution of **2** and triethylsilane (0.21 ml, 1.35 mmol) in CH_2Cl_2 (20 ml) was cooled at -78°C and boron trifluoride etherate (0.18 ml, 1.48 mmol) was then added dropwise under nitrogen atmosphere. After 30 minutes, 0.21 ml of triethylsilane and 0.18 ml of boron trifluoride etherate were added. The resulting mixture was stirred 2 hours at -78°C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 ml), extracted with CH_2Cl_2 (3x10 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification by flash chromatography (CH_2Cl_2/MeOH 100/1) yielded **3**. If the temperature is allowed to reach room temperature and stirring for a further 30 minutes, the same workup and flash chromatography purification (CH_2Cl_2/MeOH 18:1), gave compounds **4**.

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