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$NaBH_4$–$InCl_3$-Mediated One-Pot Chemo- and Stereoselective Decarboxylative Reduction of α-Aza *gem*-Dicarboxylic Esters to Monoalcohols

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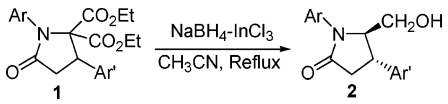
ABSTRACT



The combination of $NaBH_4$ and a catalytic amount of $InCl_3$ provides a one-pot method for chemo- and stereoselective decarboxylative reduction of *gem*-dicarboxylic esters 1 to monoalcohols 2 in the presence of the lactam carbonyl in refluxing acetonitrile under inert atmosphere.

The reduction of carboxylic esters to monoalcohols in the γ-lactam moiety is an important multistep transformation in synthetic organic chemistry.[1] This type of transformation has traditionally been accomplished with lithium borohydride[2] ($LiBH_4$), but the reduction is often accompanied by the cleavage of lactam ring via carbon−nitrogen bond fissions.[3]

Due to the lack of a proper reducing agent, the selective decarboxylative reduction of *gem*-dicarboxylic esters to monoalcohols in a single step is a challenging problem in synthetic organic chemistry.

To the best of our knowledge, to date there is no report of single-step chemo- and stereoselective decarboxylative reduction of *gem*-dicarboxylic esters to monoalcohols in the presence of a lactam, though this one-pot transformation would be very useful for the synthesis of various bioactive compounds.[1,2,4]

Recently, we reported a chemoselective reduction of γ-butyrolactams to tetrahydro pyrroles with $NaBH_4$−I_2 in the presence of geminal dicarboxylic esters.[5] Herein we are eager to report on our study to explore a reagent system that could chemoselectively as well as stereoselectively reduce the *gem*-dicarboxylic esters of various 1,4-diarylpyrrolidin-2-one-5,5-dicarboxylic esters to the corresponding 5-hydroxymethyl derivatives in one step, keeping the lactam carbonyl intact.

A literature survey shows that dichloroindium hydride[6] (Cl_2InH), generated in situ from sodium borohydride and a catalytic amount of indium trichloride, is a very good reagent system for the dehalogenation of alkyl halides,[6] radical cyclization,[6] selective reduction of *vic*-dibromides,[7] reductive cleavage of the C−O bond[8] in 2,3-epoxy bromides, and the selective reduction of carbon−carbon double bonds.[9]

In view of the novel pattern of reactivity of $NaBH_4$−$InCl_3$ reagent system, we became interested in exploring its reactivity toward the reduction of γ-lactam-5,5-dicarboxylic

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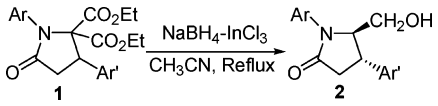
esters, and herein we are gratified to report an exclusively novel and efficient method for the chemo- and stereoselective reduction of gem-diesters to monoalcohols by using the $NaBH_4-InCl_3$ reagent system. The ultimate utility of that system extends to unexpected applications that were not initially envisioned.

The starting materials for this study, 1,4-diarylpyrrolidin-2-one-5,5-dicarboxylic esters **1**, were synthesized following the general method[5,10] developed in our laboratory. Chemoselective and in situ stereoselective decarboxylative reduction of these dicarboxylic esters with sodium borohydride and catalytic indium trichloride in dry acetonitrile at reflux temperature for 8−11 h, furnished exclusively *trans*-1,4-diaryl-5-hydroxymethyl-pyrrolidin-2-ones **2** (Scheme 1) in

Scheme 1. Reduction of γ-Lactam-5,5-dicarboxylic Esters **1** to Alcohols **2**



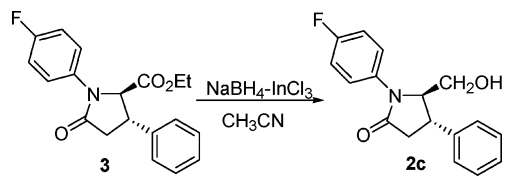
high yields (Table 1). The *trans* geometry of the product has been elucidated by single-crystal-X-ray[11] and also by

Table 1. Synthesis of 5-Hydroxymethyl γ-Lactams **2** from γ-Lactam 5,5-Dicarboxylic Esters **1**

substrate	Ar	Ar′	product	yield (%)
1a	phenyl	phenyl	**2a**	84
1b	4-Cl-C_6H_4	phenyl	**2b**	81
1c	4-F-C_6H_4	phenyl	**2c**	83
1d	4-F-C_6H_4	2- furyl	**2d**	79
1e	4-F-C_6H_4	2-thienyl	**2e**	77
1f	3,5-dichlorophenyl	phenyl	**2f**	79
1g	3,4- difluorophenyl	phenyl	**2g**	82
1h	3-Cl,4-F-C_6H_3	2-thienyl	**2h**	80

matching the NMR spectra of product 2c obtained independently from reductive decarboxylation of 1c (Table 1) and the $NaBH_4-InCl_3$-mediated reduction of *trans*-monoester 3 (Scheme 2). Compound **3** was synthesized from the corre-

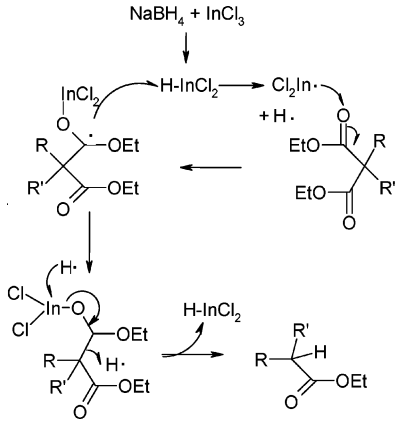
Scheme 2. Reduction of γ-Lactam Monoester **3** to Alcohol **2c**



sponding *trans*-1-(4-fluorophenyl)-4-phenylpyrrolidin-2-one-5-carboxylic acid. The latter was synthesized by hydrolysis of **1c** with $KOH-H_2O$, EtOH, followed by in situ stereoselective decarboxylation.

Though the mechanism of the reaction is still uncertain, but as the γ-lactam diester **1c** and γ-lactam monoester **3** gave the same reduced product **2c**, we speculated that the decarboxylative reduction to alcohols proceeds via an initial stereoselective radical decarboxylation mediated by $HInCl_2$ followed by chemoselective reduction of the ester functionality. A plausible mechanism for the radical decarboxylation is depicted in Scheme 3.

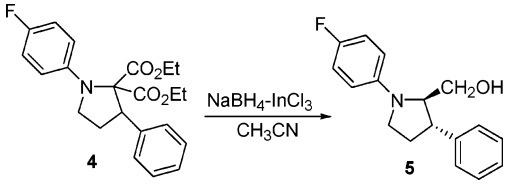
Scheme 3. Plausible Mechanism of Decarboxylation of *gem*-Dicarboxylic Ester by $HinCl_2$



Alternatively the first carbon radical may easily break into carbon monoxide and $EtOInCl_2$.

The pleasing outcome of the above reaction prompted us to extend this method to include other substrates. We selected the amine derivatives diethyl 1-(4-fluorophenyl)-4-phenyl-pyrrolidine-2,2-dicarboxylate **4**[5] (Scheme 4) and diethyl 2-(4-

Scheme 4. Reduction of Pyrrolidine-2,2-dicarboxylic Ester **4** by $NaBH_4-InCl_3$



fluorophenylamino)malonate **6** (Scheme 5) to study the effect of the amide (lactam) carbonyl on the outcome of the reaction. While the reaction was successful, it was much slower than those reported in Table **1**; it took nearly 15 h for the conversion of **4** to provide **5** in 62% yield and **6** to afford **7** in 38% yield.

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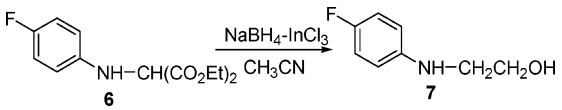
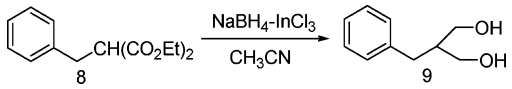
Scheme 5. Reduction of Diethyl Arylaminomalonate **6** by $NaBH_4-InCl_3$



To further test the generality of this reduction, and assess the effect of NH on the reaction, we investigated the reduction of diethyl 2-benzylmalonate **8**[12] as a substrate wherein there is no N-atom α to the dicarboxylic esters. Under the same reaction condition as before, the compound **8** underwent reduction (Scheme 6) in much more slower rate, and

Scheme 6. Reduction of Diethyl 2-Benzylmalonate **8** by $NaBH_4-InCl_3$



after 20 h it was converted to 2-benzylpropane-1,3-diol **9**[13] in 14% yield. Increase in the reaction time up to 42 h increased the yield of the product **9** to 32%. So, it is apparent that a substrate "N" is essential for insitu dealkylative-decarboxylation.

In conclusion, we have developed a novel and simple method for the chemo- and stereoselective decarboxylative reduction of *gem*-diesters to monoalcohols in the presence of lactam carbonyls in one step with good yields. Certainly, this demonstrates the potential of the $NaBH_4-InCl_3$ reagent system as a stereoselective decarboxylative agent under refluxing acetonitrile. To the best of our knowledge, this constitutes the first efficient method of such selective reduction of *gem*-diesters by $NaBH_4-InCl_3$, which is not achievable by any other conventional reducing agents. Furthermore, the reagent system used is safe and easy to handle. The operational simplicity and selectivity of this one-pot process probably opens up new opportunities for the use of this transformation in synthetic industrial procesess by reducing the number of steps in multistep synthetic procedures, and definitely it broadens the preview of further research in this area. Studies on the mechanistic aspects of the reaction, in particular structural requirements of the substrates, are underway.

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Supporting Information Available: Analytical and spectroscopic data of compounds **2a**−**h**, **5**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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