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An Improved Synthesis of the Strained Pyrrolidine-5,5-Translactam Ring System

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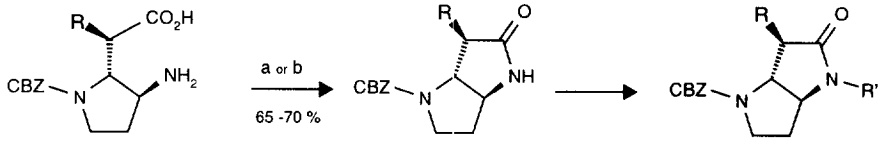
Abstract: An improved synthesis of the 5-Oxo-hexahydro-pyrrolo[3,2-b]pyrrole ring system (Pyrrolidine-5,5-*trans*-lactam ring system) has been achieved using cyclisation of the amino ethyl ester **4** with *t*-butyl magnesium chloride in THF to give the translactam **5** in 78% yield

Keywords: Lactamisation, Strained compounds, Lactams, Pyrrolidines/Pyrrolidinones

The novel pyrrolidine-*5,5*-translactam ring system (5-oxo-hexahydro-pyrrolo[3,2-b]pyrrole) **3** has been shown[1,2] to be an effective serine protease inhibitor mainly due to its inherent ring strain. This strained *5,5*-translactam ring system has been prepared by cyclising the 3-amino and 2-acetic acid substituents that are *trans* to each other on the pyrrolidine ring **1** with the usual reagents for forming amide bonds. However, while the α-substituted acids **1** (R = Alkyl) cyclise to give good yields (65-75%) of the *5,5*-translactam ring **2** with diphenylphosphoryl azide or Mukaiyama reagent this is not the case with the unsubstituted acid **1** (R = H), which gives 15% and 30-40% yields respectively of **2** (R = H), and only at high dilution (0.008M).

Scheme 1



1 **2** **3**

Reagents and conditions: (a) $(PhO)_2PON_3$, Et_3N, DMF, 23hr, RT. (b) 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, RT.

Efforts to improve this cyclisation by variation of solvent, temperature or increasing concentration resulted in a reduction in yield. Using DMF as the solvent in the Mukaiyama reaction gave 48% yield under high dilution, but at higher concentration (0.05M) this decreased to 33%. Other conditions[4] were considered in order to improve this key step. Attempts to cyclise the aminoacid **1** (R = H) with DCC in dioxane or with WSCDI [6] in

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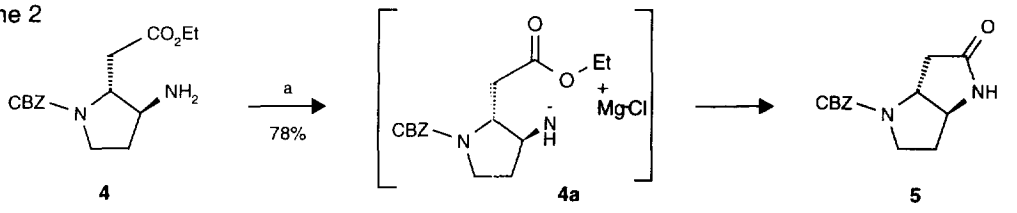
dichloromethane gave only 5- 6% of the required lactam **2** (R = H). Dibutyl tin oxide has been used to cyclise aminoacids to 5,6 and 7-membered lactams, but not to β-lactams[3]. However refluxing **1** (R = H) with dibutyl tin oxide in toluene or xylene failed to give the required lactam **2** (R = H). The low yield in the successful cyclisations using diphenylphosphoryl azide or Mukaiyama reagent (Scheme 1) could be due to the reactive intermediate taking other pathways (dimerisation, retro-Michael reaction, ketene formation and in the case of the acyl azide a Curtius rearrangement) in parallel to the required cyclisation.

One way to overcome this problem is to cyclise an amino ester using a more nucleophilic amine. This can be achieved by using an organometallic reagent to remove a hydrogen from the amine without removing the hydrogen next to the ester which causes a retro-Michael reaction of the pyrrolidine nitrogen. The Grignard reagent, t-butyl magnesium chloride, has been used with success to prepare β-lactams[5] from aminoesters. It is advantageous in our

Scheme 2



4 **4a** **5**

Reagents and conditions: (a) TFA neat, 2hr, RT. (b) ^{t}BuMgCl (3eq) THF, < 1°1hr then , 0°- RT 45mins.

system since Grignard reagents tend not to form enolates, which would avoid intermolecular addition to the carbonyl of the ester and in our case would also avoid any retro-Michael reaction of the pyrrolidine nitrogen occurring. Cyclisation of the amino ethyl ester **4** with *t*-butyl magnesium chloride in THF gave the translactam **5** in 78% yield (Scheme 2). These conditions avoid the use of high dilution (0.13M) and on a multigram scale have given the translactam as a crystalline solid in a very clean reaction. It has been suggested that cyclisation goes *via* the cyclic organometallic intermediate **4a**, which facilitates the intramolecular reaction over the intermolecular reaction by lining up the bonds *via* chelation of the O and N atoms to Mg. This has become the method of choice even with α-substitued esters to give the corresponding substituted 5,5-translactams.

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