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Novel synthesis of sterically hindered N-substituted lactams from imides

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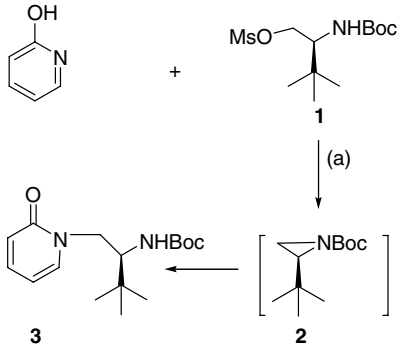
Abstract—An efficient and practical synthesis of sterically hindered N-substituted lactams has been developed starting from simple starting materials. The stereochemistry of the synthetically useful *N*,*N* acetal intermediate has been established.

Pyridones are well known pharmacophores and have emerged as potent antitumor, antiviral, and antimicrobial agents over the last decade.[1] During the course of our chemistry program there was a need to synthesize and incorporate these moieties in our scaffold. Unsubstituted pyridones are generally prepared via nucleophilic displacement of an appropriate bromide or mesylate by hydroxypyridine.[2] In our case we used mesylate **1** as the leaving group but the presence of an adjacent *tert*-butyl group created a rather sterically hindered environment.

The reaction proceeded through intramolecular aziridine formation followed by the opening of aziridine **2**, to give the desired pyridone **3**, albeit in low yields (Scheme 1).



Scheme 1. Reagents and conditions: (a) TBAB, KOH; 30%.

It was envisioned that reduction of pyridone **3** to the corresponding lactam would give us access to another biologically and pharmacologically important class of compounds.[3] Unfortunately this methodology was unsuitable for the synthesis of substituted lactams that were required in our project. Due to the ubiquity of lactams in alkaloids, there are several synthetic routes that have been reported in literature.

Recently, Milewska and co-workers outlined a general method to make lactams starting from a diimide.[4] In this case the diimide, analogous to compound **4**, was treated with Lawesson's reagent to afford the corresponding monothioamide which was subsequently reduced with Raney-Nickel at elevated temperature. Due to the toxic nature of Lawesson's reagent and harsh reaction conditions that were applied we avoided using this protocol.

Oxidation of cyclic amines to amides is another commonly used route to access asymmetrically substituted amides.[5] However, in our case due to the symmetrical nature of our starting amine and the eminent lack of regioselectivity during oxidation made this method unattractive for our synthesis.

Although there was ample precedence in the literature for N-alkylation's of amides through displacement of primary or secondary halides,[6] there have been no reported cases where the halide carries a substitution at the β position. When we tried to alkylate **5** with the β-substituted mesylate **6**; none of **7** was isolated (Scheme 2).

On the other hand, a wide variety of imides are commercially available and can be readily converted to

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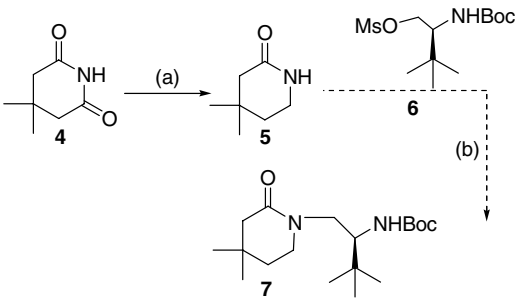


Scheme 2. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2; $NaCNBH_3$, AcOH; (b) K_2CO_3, TBAB, PhMe, H_2O.

N-substituted imides containing the amino acid derivative through Mitsunobu chemistry on the corresponding amino alcohol. Imides such as **9** could also be obtained from condensation of amino acid derived diamines of type **8** with the corresponding anhydride. The ease of synthesis of the starting imide from relatively simple starting materials made this an attractive starting point.

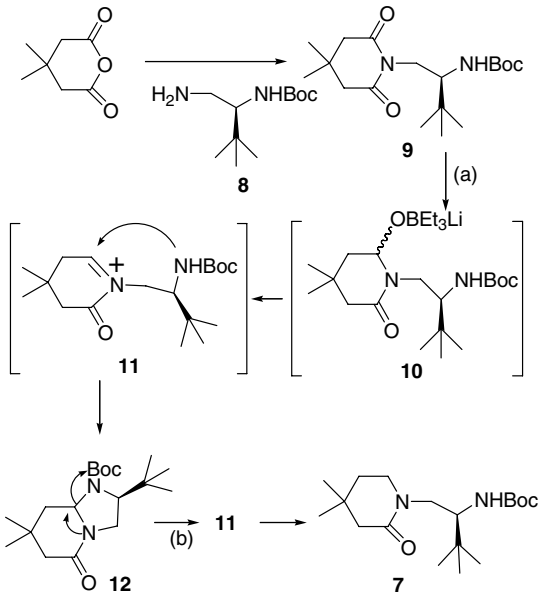
Addition of alkyl magnesium bromides to these N-substituted imides seemed to be a straightforward way of introducing the alkyl units alpha to the tertiary nitrogen. However, attempts to carry out this reaction by treating imide **9** with 2 equiv of methyl magnesium bromide never proceeded beyond the monoaddition of the methyl group to the carbonyl imide. Similar observations have been precedented in the literature.[7]

A more commonly used route involved the reduction of a suitably substituted imide to the corresponding hydroxy lactam using a hydride donating reducing agent, followed by the generation of the *N*-acyliminium ion using boron trifluoroetherate and in situ quenching with triethylsilane.[8]

In an attempt to evaluate this concept, we started out with the imide **9** and treated it with $LiEt_3BH$ with the expectation of generating the required hydroxy lactam intermediate **10** as shown in Scheme 3. To our surprise we isolated a separable mixture of product with a mass difference of 18 units from the expected product **10**. After thorough analysis the products were confirmed to be a diastereomeric mixture of *N*,*N* acetal **12**. Replacing super hydride with DIBAL-H gave identical results. This unexpected outcome prompted us to investigate the generality of this reaction.

We envisioned that **12** being an *N*,*N* acetal, ring opening to generate the acyliminium ion should be feasible using a mild acid, such as, acetic acid, which in the presence of excess $NaCNBH_3$ should give **7**. Indeed, when **12** was treated under refluxing conditions in the presence of the hydride donating agent, as expected, compound **7** was obtained in good yield.

To the best of our knowledge this reaction sequence is unprecedented in literature. However, a related reaction involving reduction of an acyliminium ion generated in situ on treatment of an amido methylol with



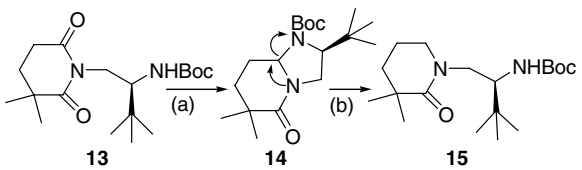
Scheme 3. Reagents and conditions: (a) $LiEt_3BH$, CH_2Cl_2, −78 °C, 15 min; (b) $NaCNBH_3$, CH_3CN; AcOH.

CF_3CO_2H and $NaCNBH_3$ to give the corresponding *N*-methyl amide have been reported in the literature.[9]

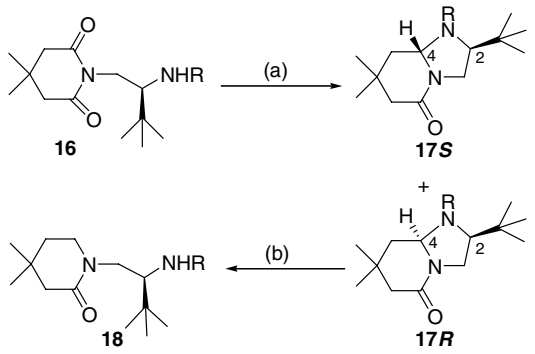
To further explore the generality of our methodology, we applied the same synthetic sequence to the geminally substituted lactam **13** and observed the expected cyclized product **14** obtained through the reduction of the less sterically hindered imide carbonyl. The bicyclic intermediate **14** was efficiently converted to the desired lactam **15** as shown in Scheme 4.

Next, we proceeded to study the effect of the nucleophilicity of the secondary amine **16** on the cyclization reaction leading to **17** (Scheme 5) by varying the electron inducting nature of the N-protecting group. Replacing the *t*-Boc group on the amine with benzoyl, methylsulfonamide, acetamide, and trifluoroacetamide not only served the above purpose but also allowed us to study the steric effect of these groups on the stereoselectivity of the cyclization reaction.

Much to our satisfaction, the conversion of imides **16a**–**e** to the corresponding N-substituted cyclic acetals **17a**–**e** proceeded efficiently and the variation in nucleophilicity of the N-protecting group of the imide seemed to have little effect on the yield of the reaction (Table 1). Interestingly these variations did have an impact on the stereochemical outcome of the formation of acetals **17a**–**e**



Scheme 4. Reagents and conditions: (a) $LiEt_3BH$, CH_2Cl_2, −78 °C, 15 min; 80%; (b) $NaCNBH_3$, CH_3CN; AcOH; 82%.



Scheme 5. Reagents and conditions: (a) $LiEt_3BH$, CH_2Cl_2, −78 °C; (b) $NaCNBH_3$, CH_3CN; AcOH.

Table 1. Conversion of imide **16** to lactam **18** via acetal **17**

Imide	R	Ratio **17**(**a**–**e**) 2*S*,4*S*:2*S*,4*R*	**17**(**a**–**e**) *R* + **17**(**a**–**e**) *S* (%)	**18** (%)
16a	*t*-Boc	75:25	77	90
16b	CBz	74:26	75	93
16c	$C(O)CH_3$	61:39	63	81
16d	$C(O)CF_3$	56:44	68	84
16e	SO_2Me	39:61	87	88

as shown in Table 1. In each case, with the exception of **16e**, the secondary nitrogen favored attack on the (Si)-face of the imine **11** (Scheme 3). The stereochemical bias of the reaction was an interplay between the *gem*-dimethyl, the *tert*-leucine unit and the protecting group on the nitrogen of the secondary amine which could be explained on the basis of the possible transition states shown in Figure 1.

The loss of stereoselectivity observed in **17c** or **17d** is presumably due to the increased steric interaction between the *tert*-leucine and the acetamide moiety. For the carbamates **17a** and **17b**, the oxygen atom in N-protecting group R next to the carbonyl occupied the same space as that of the bulky CH_3 and CF_3 of **17c** and **17d**, making the conformer A *relatively* less favorable in the latter case due to the proximity of the adjacent *tert*-leucine group. Although the aforementioned interaction was minimized in conformer B, the interaction between the axial methyl and the *tert*-leucine, which was absent in conformer A, was a key steric interaction here (Fig. 1). In the anomalous case of **17e**, the tetrahedral

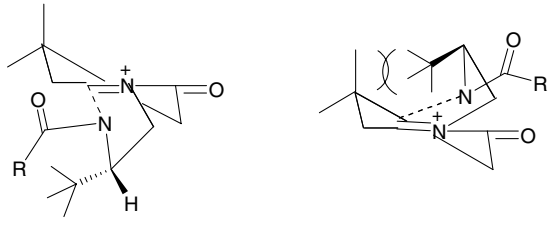
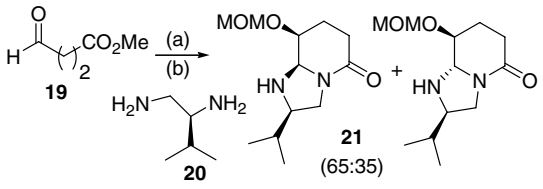


Figure 1. Proposed transition states for cyclization of **16** to **17**.



Scheme 6. Reagents and conditions: (a) (s)-HbHNl, HCN, pH = 4.5; $MeOCH_2OMe$, P_2O_5; (b) H_2, Pd/C, MeOH.

nature of the *N*-methylsulfonamide group had a pronounced effect on the outcome. Using the same arguments as before it was apparent that conformer B, where the steric interaction between the *N*-sulfonamide and the *tert*-leucine was minimized, should be the favored one in this case.

Furthermore, when isomers **17a** (*R*) and **17a** (*S*) were individually subjected to the exact reaction conditions (Scheme 5, step b) no interconversion was observed, leading us to believe that their formation is indeed kinetically controlled.

The diastereomers of acetal **17** (2*S*, 4*R* and 2*S*, 4*S*) were easily separable by column chromatography thereby facilitating in the characterization. Thus, 2D NMR analysis (HSQC, HSQCTOXY, HMBC, and COSY) was used to establish the connectivity of proton and carbon nuclei. NOE experiments unambiguously established the trans relationship between the protons H-2 and H-4 for the major product of entry **17a**–**d** and a cis-relationship for the minor isomer.

Cores similar to **17**, had been previously observed during the hydrogenation of cyanogroups in the presence of (*R*)-valine derived diamine **20** by Vink et al. (Scheme 6).[10] However, the stereochemical outcome of the acetals **21** was dependent on the stereochemistry of the protected hydroxyl group of the starting cyanohydrin, which was introduced by enzymatic asymmetric addition of HCN to the corresponding aldehyde, making the route undesirable.

Our present methodology provides ready access to either diastereoisomer of the pyridone *N*,*N*, acetal which can be further functionalized to provide important intermediates for medicinal chemistry. Importantly, a practical and efficient route to synthesize functionalized lactams where the nitrogen is attached to a sterically hindered unit, which was not accessible through any other known approaches, has been developed.[11] It is reasonable to assume that this methodology could be extended to other ring sizes although with a possibility of different stereochemical outcome. The practicality of this route has been established by applying the sequence to multigram (100 g) scale synthesis of compound **18a** successfully.

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11. Representative procedure to obtain **18**: Superhydride (2.2 mmol, 1 M soln in THF) was added to a cooled (−78 °C) solution of the imide **16a** (1.0 mmol) in anhydrous CH_3CN (5.0 mL) and the reaction mixture was stirred for 1.5 h. Satd NH_4Cl (3.5 mL) was added at (−78 °C) and the reaction mixture allowed to warm up to room temperature. The reaction mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, concentrated and purified over silica gel using 0–20% ethyl acetate in CH_2Cl_2 to yield **17a** (*R*) and **17a** (*S*). Either the crude diastereomeric mixture of **17** or the separated isomers **17a** (*R*) or **17a** (*S*) could be used in the next step. To a solution of **17a** (1.0 mmol) in CH_3CN (9.0 mL) and glacial acetic acid (3 mL) was added $NaCNBH_3$ (3.0 mmol) and the reaction mixture was heated at 55 °C for 12 h, cooled to RT, evaporated to dryness and redissolved in CH_2Cl_2. The organic layer was washed with 1N NaOH, brine and filtered through Na_2SO_4, concentrated and purified over silica gel using 50% EtOAc in hexanes to yield **18a**. Spectral data were obtained for all new compounds. Analytical and 1H NMR data for some representative compounds are included below. Compound **17a** (*S*) (major isomer): mp 147–150 °C. MS (ES) calcd for $C_{18}H_{32}N_2O_3$ $(M+H)^+$ 324.2, found 324.2; 1H NMR (400 MHz, CD_3OD): δ ppm: 0.94 (s, 9H); 0.95 (s, 3H); 0.96 (s, 3H); 1.04 (s, 9H); 1.58 (m, 1H); 1.98 (m, 1H); 2.19 (m, 2H); 3.25 (m, 2H); 3.78 (m, 1H); 5.02 (m, 1H). Compound **17a** (*R*) (minor isomer): mp 132–136 °C. MS (ES) calcd for $C_{18}H_{32}N_2O_3$ $(M+H)^+$ 324.2, found 324.2; 1H NMR (400 MHz, CD_3OD): δ ppm: 0.95 (s, 12H); 1.04 (s, 3H); 1.38 (s, 9H); 1.6 (m, 1H); 1.98 (m, 1H); 2.20 (m, 2H); 3.39 (m, 1H); 3.70 (m, 1H); 4.05 (m, 1H); 5.02 (m, 1H). Compound **18a**: mp 116–118 °C. MS (ES) calcd for $C_{18}H_{34}N_2O_3$ $(M+H)^+$ 327.2, found 327.2; 1H NMR (400 MHz, $CDCl_3$): δ ppm: 0.97 (s, 12H); 1.38 (s, 9H); 1.57 (s, 3H); 2.14 (s, 2H); 2.62 (m, 1H); 3.15 (m, 1H); 3.51 (m, 1H); 3.71 (9m, 1H); 4.30 (t, 1H, $J = 12.8$ Hz); 4.71 (d, 1H, $J = 10.2$ Hz).