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The versatile conversion of lactams to the α-alkylated azacycles via cyclic *N,O*-acetal TMS ether

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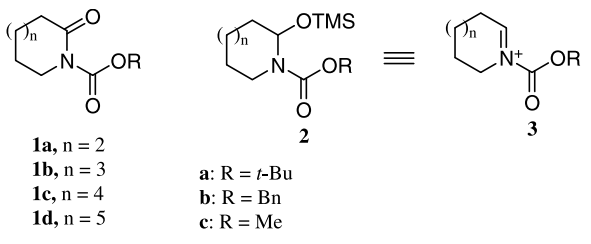
Abstract—The efficient preparation of the cyclic *N,O*-acetals from lactams by DIBAL reduction followed by direct trapping of the resulting *N,O*-hemiacetals using TMSOTf/pyridine system is described. In addition, the facile nucleophilic addition of various carbon nucleophiles at the carbonyl carbons of the lactams through the corresponding *N,O*-acetals is also reported. © 2002 Published by Elsevier Science Ltd.

As a part of our continuing studies directed toward the synthesis of the medium to macrolactam alkaloids, we have been interested in the versatile functionalization of the lactam carbonyl (Fig. 1).[1]

Synthetic routes involving cyclic *N*-acyliminium ions are generally useful strategies that have been applied to a wide variety of synthetic transformations.[2] The use of α-alkoxy azacycles as precursors to cyclic *N*-acyliminium ions has been especially well reviewed.[2] Despite significant progress made in the preparation of these intermediates, most of these methods are limited in that they are only applicable to the five- or six-membered azacycles, and are rarely applicable to the seven-membered azacycle.[3] In fact, unlike the five- and six-membered α-alkoxy azacycles, which can be readily prepared by sequential reduction of the corresponding *N*-acyl lactam or imide and etherification, the synthesis of the medium to large sized α-alkoxy azacycle from the corresponding lactam has not been successful due to the considerable difficulty in manipulation of their lactam functionality and the instability of the reaction intermediate (e.g. imine or enamine, which were readily hydrolyzed to the corresponding amido aldehyde). In light of the result[4,5] that aluminum alkoxide of hemiacetal prepared by DIBAL reduction of esters is more stable than the free hemiacetal, we were able to reduce the medium-sized lactam without lactam ring-opening and trap the resulting *N,O*-hemiacetal.



1a, n = 2
1b, n = 3
1c, n = 4
1d, n = 5

2

a: R = *t*-Bu
b: R = Bn
c: R = Me

3

Figure 1.

We herein report a novel and versatile method for the preparation of the stable *N,O*-acetal TMS ether **2**[6] as an excellent precursor of cyclic acyliminium ions **3**. To the best of our knowledge, such a method in the medium to large-sized lactam systems has not been reported in spite of its significant synthetic utilities. Moreover, the facile nucleophilic additions of various carbon nucleophiles to the resulting *N,O*-acetal TMS ether in the presence of the Lewis acid are also reported.

Our initial studies were carried out by intensive examination of the reaction conditions for the transformation of lactam to *N,O*-acetal alkyl ether. Surveying a number of trapping reagents commonly used, we have found the TMSOTf/pyridine system[4a,b] which only gives satisfactory results as shown in Table 1. Thus, treatment of **1aa** with DIBAL (1.2 equiv.) in CH_2Cl_2 at −78°C followed by sequential addition of pyridine (3 equiv.) and TMSOTf (2.5 equiv.) afforded the *N,O*-acetal **2aa**[7] in excellent yield along with a small amount (<5%) of the remaining amido aldehyde **4**.[8]

The *N,O*-acetal TMS ethers are quite stable, and can be stored for months at room temperature in 1% Et_3N/ether solution. When an MeOTf/pyridine or an Ac_2O/

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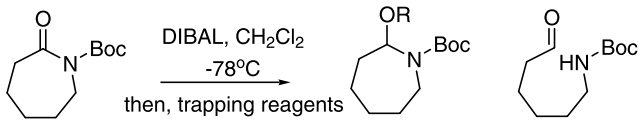
Table 1. Synthesis of α-alkoxy azacycle



1aa **2aa** **4**

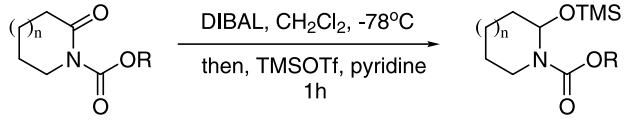
Entry	Conditions	R	Yields[a] (%)
1	TMSOTf (2.5 equiv.)/pyridine (3 equiv.)	TMS	87[b]
2	MeOTf (2.5 equiv.)/pyridine (3 equiv.)	Me	–[c]
3	Ac_2O (4 equiv.)/pyridine (3 equiv.)/DMAP (2 equiv.)[d]	Ac	–[c]

[a] Isolated yields after chromatography.
[b] Compound **4** was isolated in about 5% yield.
[c] Trace amounts of the corresponding products were detected.
[d] Variation of the reagent equivalents gave similar results.

pyridine/4-DMAP system[5] was employed, only a trace amount of the corresponding product was formed.

The DIBAL reduction of a variety of medium-sized lactams (**1a**–**c**)[9] and subsequent etherification of the resulting *N*,*O*-hemiacetal with TMSOTf is illustrated in Table 2. All reactions were completed in 1 h. After an aqueous work-up, the *N*,*O*-acetal TMS ether was isolated by flash column chromatography using 1% Et_3N eluents in excellent yield. The benzyl and *tert*-butyl carbamate were superior to the methyl carbamate in terms of yield due to the decomposition of the methyl carbamate upon DIBAL reduction.

Table 2. Formation of the cyclic *N*,*O*-acetals[a]



1a, n = 2
1b, n = 3
1c, n = 4

2

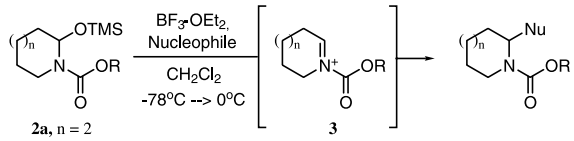
a: R = *t*Bu, **b**: R = Bn, **c**: R = Me

Entry	Lactams	Products	Yields[b] (%)
1	**1aa**	**2aa**	87
2	**1ab**	**2ab**	85
3	**1ac**	**2ac**	71
4	**1ba**	**2ba**	82
5	**1ca**	**2ca**	89

[a] Reaction conditions, see the representative procedure in text.
[b] Isolated yields after chromatography

With the desired *N*,*O*-acetal TMS ether **2** in hand, a survey of the nucleophilic addition of the various carbon nucleophiles was carried out in the presence of Lewis acid as shown in Table 3. Boron trifluoride etherate turned out to be the most effective Lewis acid. As expected, TMSCN underwent facile addition to afford the α-cyano azacycle **5** in quantitative yield (entries 1–5). In the case of allylsilane,[10] the homoallylic amine **6** was obtained in excellent yield although this reaction generally required the higher temperature

Table 3. Nucleophilic additions of the carbon nucleophile to the cyclic *N*,*O*-acetal TMS ethers



2a, n = 2
2b, n = 3
2c, n = 4

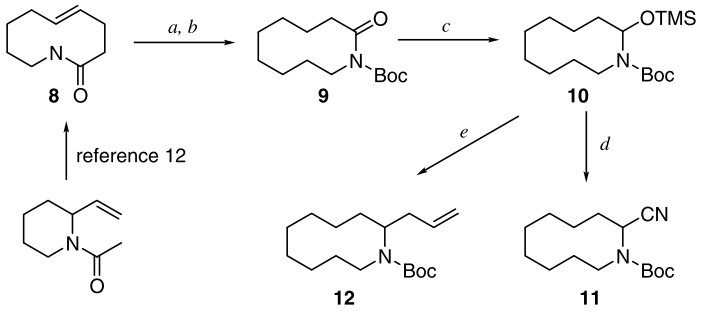
3

a: R = *t*Bu, **b**: R = Bn, **c**: R = Me

Entry	Nucleophile	Cyclic *N*,*O*-acetal	Yields(%)[a]	Products
1		**2aa**	97	
2		**2ab**	97	
3	TMSCN	**2ac**	98	
4		**2ba**	94	**5**
5		**2ca**	91	
6		**2aa**	93	
7		**2ab**	96	
8	TMS	**2ac**	94	
9		**2ba**	90	**6**
10		**2ca**	92	
11		**2aa**	86[b]	
12	OTMS	**2ba**	89[c]	
13		**2ca**	91[d]	**7**

a: Isolated yields after chromatography. b: Diastereomeric ratio 11 : 1. c: Diastereomeric ratio 5 : 1. d: Diastereomeric ratio 2 : 1

(0°C) for completion of the reaction (entries 6–10). It was of interest to study the diastereoselectivity of this addition reaction. To this end, the diastereoselective addition of siloxyfurans to the cyclic *N*-acyliminium ions prepared by a different route was investigated, although the intermolecular nucleophilic addition of 2-trialkylsiloxyfurans to the five- to seven-membered *N*-acyliminium ions has been reported.[3] In the seven-membered ring systems, the results were similar to that reported by Pilli et al.[3] to show good diastereoselectivity (entry 11). The addition of siloxyfurans to the eight and nine-membered ring systems also afforded the corresponding α-alkylated products **7** in 89 and 91% yields, respectively. However, the diastereoselectivities for the eight- and nine-membered ring systems were lower than that of seven-membered ring system (entries 12, 13).[11]



Scheme 1. *Reagents and conditions*: (a) H_2, Pd/C, MeOH; (b) *n*-BuLi, Boc anhydride, THF, −78°C, 91% from **8**; (c) DIBAL, CH_2Cl_2, −78°C, then, TMSOTf, pyridine, 87%; (d) BF_3–OEt_2, TMSCN, CH_2Cl_2, −78°C, 95%; (e) BF_3–OEt_2, allyltrimethylsilane, CH_2Cl_2, −78°C to 0°C, 88%.

Based on the above results, we next attempted to expand the same reaction on the 10-membered lactam as shown in Scheme 1. DIBAL reduction of Boc-protected lactam **9**, derived from the lactam **8**,[12] followed by TMSOTf/pyridine treatment afforded the desired 10-membered *N*,*O*-acetal TMS ether **10** in 87% yield. Finally, on treatment with TMSCN or allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$, the *N*,*O*-acetal **10** gave the α-cyano azacycle **11** or α-allyl azacycle **12** in good yields, respectively.

Representative procedure: The lactam **1aa** (213 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (5 mL). Upon cooling to −78°C, DIBAL (1.0 M solution in CH_2Cl_2, 1.2 mL, 1.2 mmol, 1.2 equiv.) was added dropwise via syringe. After 15 min, the reaction mixture was treated with pyridine (243 μL, 3.0 mmol, 3.0 equiv.) and then TMSOTf (452 μL, 2.5 mmol, 2.5 equiv.). The mixture was stirred at −78°C for 30 min, quenched with 15% aqueous sodium potassium tartrate (5 mL), and diluted with Et_2O (20 mL). The resultant mixture was warmed to room temperature and stirred vigorously until two layers were completely separated. The mixture was extracted with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc/hexanes with 1% Et_3N) to afford 250 mg (87%) of the *N*,*O*-acetal TMS ether **2aa** as a colorless oil.

In summary, an unprecedented simple preparation of the cyclic *N*,*O*-acetal silyl ether from the medium to large-sized lactams as an important precursor for the corresponding *N*-acyliminium ions has been developed. Particularly, these useful intermediates undergo a facile nucleophilic addition reaction by a variety of nucleophiles in the presence of Lewis acid. We are currently evaluating the extension of this methodology to the acyclic system as well as the asymmetric variants. Moreover, this methodology will be extended to the second-generation synthesis of the macrolactam antibiotic alkaloids such as fluvirucins.

Acknowledgements

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7. Satisfactory spectral and analytical data were obtained for all new compounds.
8. These compounds always remained irrespective of amount of reagent, reaction time and reaction temperature.
9. Compounds **1a**–**c** were synthesized by simple protection of the commercially available lactams.
10. The use of allyltributyltin gave a similar result.
11. The relative stereochemistry of **7** was not determined since **7** was obtained as an inseparable mixture, see Ref. 3.
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