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Efficient Generation and Intramolecular Cyclization Reactions of Acyl Imines

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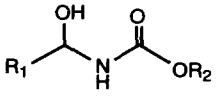
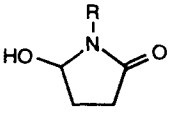
Abstract: Acyl carbamates can be selectively reduced with diisobutyl aluminum hydride to provide high yields of *N*-acyl hemiaminals **1**. With appropriate substitution, these intermediates undergo Lewis acid catalyzed intramolecular exo cyclization reactions to afford 1-amino 1,2,3,4-tetrahydronaphthalene derivatives. © 1997 Elsevier Science Ltd.

N-Acyl imine precursors such as **1** have shown great utility in a number of nucleophilic addition reactions.[1] Unlike the cyclic variants **2**, which can be readily prepared by reduction of the corresponding imide, the synthesis of complex versions of **1** has been limited by a lack of general methods. Newer methods have been reported[2] which expand the scope of achievable targets, however, they still lack wide spread applicability. We wish to describe a simple and direct approach to the preparation of compounds of type **1** and demonstrate their utility in intramolecular *N*-acyl imine cyclization reactions.

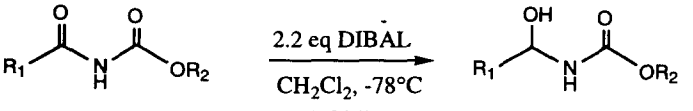


1



2

A straightforward approach to the synthesis of **1** would be from the corresponding *N*-acyl carbamate through a reduction, related to that routinely achieved in the cyclic imide cases.[3] Surprisingly, to the best of our knowledge, such reductions in acyclic systems have not been reported. To avoid regiochemical issues, we chose to examine the reduction of the *N*-acyl carbamates **3**. These compounds can be readily prepared from carboxylic acids.[4] Surveying a number of reducing agents commonly used for the cyclic imides (e.g. $NaBH_4$, $LiEt_3BH$), we found only one which gave satisfactory results. Thus, treatment of **3** with 2.2 eq of DIBAL in dichloromethane at -78 °C, afforded the *N*-acyl hemiaminal products **1** in quantitative recovery and with purity sufficient to use without purification (>90%). Remarkably, these compounds are quite stable, and when crystalline, they can be stored for months at room temperature.

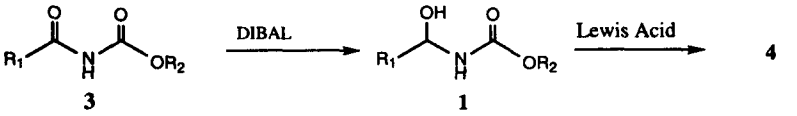


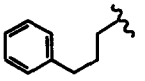
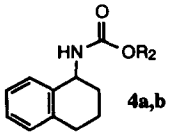
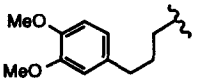
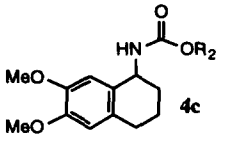
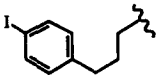
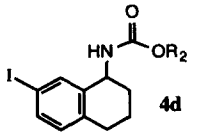
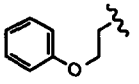
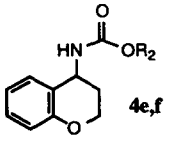
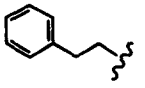
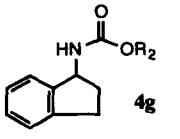
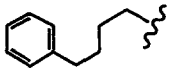
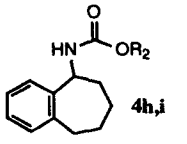
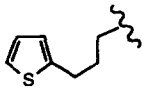
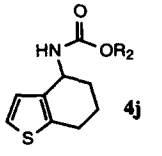
3 (>90%) **1**

Although there are a large number of intermolecular reactions for which **1** could be used, we chose to examine intramolecular exo-cyclization reactions. Such reactions leading to the protected amino compounds **4** have very little precedent.[5] To promote the reaction, we first surveyed a number of protic acids without success, and then turned our attention to Lewis acids. Success was realized using titanium tetrachloride in dichloromethane at -78 °C. In this manner, the yields of cyclized products were 75-85% for six-membered rings starting from **3** (see Table). The reactions generally required an hour or less to go to completion, and both methyl and benzyl carbamates could be prepared.[6] In some cases where solubility became an issue,

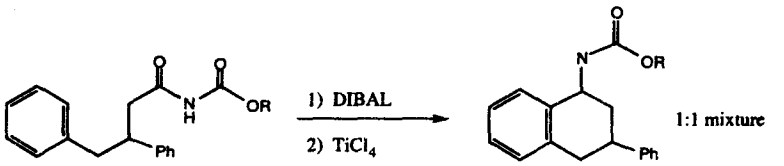
$BF_3\,OEt_2$ proved to be the more effective reagent as it can be used at a higher temperature without causing decomposition of the product. Numerous attempts to prepare the five-membered ring **4g** by varying the Lewis acid, time and temperature were unsuccessful leading only to recovered staring material or the aldehyde hydrolysis product. Seven membered rings could be formed, albeit in modest yield.

Table



Entry	R_1	R_2	Lewis Acid	Time	Overall Yield	Product
a		Me	$TiCl_4$	1 h	83 %	 **4a,b**
b	"	Bn	$TiCl_4$	1 h	80 %	
c		Me	$TiCl_4$	15 min	79 %	 **4c**
d		Bn	$TiCl_4$	2 h	84 %	 **4d**
e		Me	BF_3OEt_2	40 min	76 %	 **4e,f**
f	"	Bn	BF_3OEt_2	40 min	86 %	
g		Me	$TiCl_4$	4 h	0 %	 **4g**
h		Me	$TiCl_4$	2 h	38 %	 **4h,i**
i	"	Bn	$TiCl_4$	2 h	39 %	
j		Bn	$TiCl_4$	1 h	81 %	 **4j**

It was of interest to study the stereoselectivity of this reaction. Toward this end, the phenyl analogs **5** and **6** were prepared and subjected to the standard two-step protocol. The reactions proceeded uneventfully in good yield, however, the products were approximately 1:1 mixtures of stereoisomers. The lack of selectivity was surprising in light of known stereoselective cyclizations in similar systems.[7] This result, coupled with our inability to prepare the five-membered ring **4g**, led us to question the mechanism of the cyclization reaction. Although it is likely that a Lewis acid complexed *N*-acyl imine was an intermediate, a more SN_2-like mechanism in which the aryl group displaces a titanium hydroxide complex could not be ruled out. Because the stereochemical outcome of such a process would be defined by the relative stereochemistry of the hemiaminal, a straightforward experiment was conducted to explore this possibility. Thus, the mixture of hemiaminals from the reduction of **5** were separated, and a single isomer was treated with $TiCl_4$. This reaction gave the same ratio of products as that produced from the mixture of hemiaminals, which supports the *N*-acyl imine mechanistic pathway. The possible formation of spirocyclic intermediates through *ipso* attack on the aromatic ring, while explaining the inability to form a five-membered ring, is not easily tested. We are presently aiming to improve the selectivity of this reaction, as well as examining the selectivity in other systems.



5 R = Me
6 R = Bn

7 R = Me (76%)
8 R = Bn (80%)

General Procedure: Step 1. A solution of diisobutyl aluminum hydride in toluene (2.2 mmol) was added to a stirred solution of compound **3** (1 mmol) in dichloromethane (8 mL) at -78 °C. After 1.5 h, the reaction was quenched with methanol (0.5 mL) and the dry ice bath was removed. Florisil (4 g) was added followed by saturated aqueous NaCl (0.8 mL) and the mixture was diluted with ethyl acetate (10 mL). After stirring for 15 min, $MgSO_4$ was added (4 g) and the mixture was stirred for 15 min. The mixture was filtered through sintered-glass and the solids were washed thoroughly with EtOAc. The filtrate was concentrated *in vacuo* to provide the hemiaminal **1**.

Step 2. The crude hemiaminal from above was dissolved in dichloromethane (8 mL) and cooled to either -78 °C ($TiCl_4$ catalyst) or -50 °C ($BF_3{\cdot}OEt_2$ catalyst). The Lewis acid was added (1.5-2.0 equiv) and the mixture stirred until complete (0.25-2 hours). The cold reaction mixture was poured into a stirred aqueous solution of sodium bicarbonate. The mixture was extracted with EtOAc (2x). The extracts were washed with brine, dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. The product **4** was purified by flash chromatography.

In summary, a simple but unprecedented reduction of acyl carbamates allows for the general and high yielding synthesis of *N*-acyl hemiaminals. These intermediates are precursors to *N*-acyl imines which can undergo a number of nucleophilic addition reactions. In this communication, we chose to examine Lewis-acid mediated exo-cyclization reactions which occur cleanly at low temperature. This two-step method allows for the mild and high yielding synthesis of 1-amino tetrahydronaphthalene derivatives. These useful compounds have previously been prepared from the corresponding ketones which in turn are generated using harsh and strongly acidic intramolecular Freidal-Crafts acylation reactions. We are presently evaluating the extension of this methodology for the synthesis of other ring systems as well as exploring asymmetric variants.

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