Lactams as Hetero-Dienophiles in Diels–Alder Chemistry

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Recently, a number of biologically active compounds have been reported which contain the relatively rare spirohemiaminal moiety as part of the structure.[1-3] The most interesting class of these compounds is the guanidine alkaloids, including ptilomycalin A[2] (Figure 1) and the crambescidins,[3] which display antitumor, antifungal, and antiviral activity. Our synthetic efforts toward these compounds have focused on the preparation of highly functionalized spirohemiaminal intermediates. Herein, we wish to report the facile preparation of 7-aza-1-oxospiro[5.5]-2-undecen-4-one and related analogs via novel, highly convergent heteroatom [4 + 2] cycloaddition reactions of lactams.

Heteroatom [4 + 2] cycloaddition reactions, involving aldehydes and ketones as the dienophile, were first reported by Gresham and Steadman in 1949.[4] Several advances have contributed to making these reactions quite useful, including the use of electron-rich oxygen-substituted dienes and Lewis acid catalysts. The use of silyloxy dienes, in particular, 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (Danishefsky's diene, **1**),[5] in cycloaddition reactions of aldehydes catalyzed by mild Lewis acid lanthanide metal complexes (Eu(fod)$_3$ and Eu(hfc)$_3$)[6] has been exploited in the synthesis of oxygen-containing heterocyclic compounds, including carbohydrates.[7] Unactivated amides (lactams) have not previously been reported to show Diels–Alder reactivity. The discoveries of better catalysts and very mild reaction conditions for aldehydes and ketones suggest this methodology can be applied to less reactive carbonyl systems, and we now report the successful use of lactams as heterodienophiles in Diels–Alder cycloaddition reactions.

The reaction of δ-valerolactam with Danishefsky's diene (**1**), with Eu(fod)$_3$ as catalyst, afforded only 7-aza-1-oxospiro[5.5]-2-undecen-4-one (**2**) in 65% yield, characterized by ^{1}H and ^{13}C NMR spectra, as well as combustion analysis (Scheme 1). The product could also be obtained, albeit in a reduced yield of 22%, even in the absence of catalyst. The regiochemistry obtained is consistent with the prediction from frontier molecular orbital (FMO) analysis.[8] The analogous reaction of

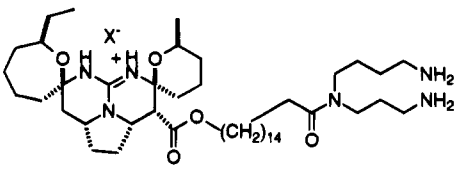
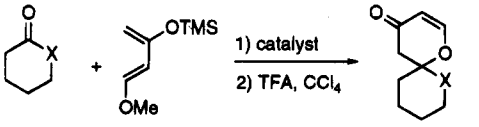


Figure 1. Structure of ptilomycalin A.

Scheme 1. Reaction of δ-Valerolactam with Danishefsky's Diene.



1 **2 (X = NH)**

X	Catalyst	Solvent	Temperature	Yield
NH	BF_3-Et_2O	CH_2Cl_2	23°C - 45°C	none
NH	Eu(fod)$_3$	toluene	110°C	65%
NH	none	toluene	110°C	22%
O	Eu(fod)$_3$	toluene	110°C	none

δ-valerolactone with **1**, to afford the spiroketal product, was unsuccessful.

We have extended our studies to include the use of several lactams, differing in ring size and substitution, as well as simple amides (Table 1).[9] The lactam ring size appears to be a critical factor in this reaction, with the 5- and 6-membered ring lactams providing the highest yields of cycloadducts (**4** and **2**, respectively). The yield is about half as much for the reaction of the larger 7-membered ring ϵ-caprolactam (cycloadduct **5**), but drops to less than 10% for the highly strained 2-azetidinone (cycloadduct **3**). The reaction is slow, requiring 2 days to achieve maximum yield in the case of spirohemiaminal **2**, based on studies of the reaction progress.

Of equal interest was the result of the reactions involving methyl substituents either at the lactam N or at C3 of the lactam. We felt *a priori* that the substituted lactams would have reasonably similar steric environments about the carbonyl group and thus react in a similar fashion. (±)-3-Methyl-2-pyrrolidinone provided the cycloaddition adduct **6** as expected in 70% yield, whereas *N*-methyl-2-pyrrolidinone (NMP) was unreactive under any conditions applied, leading solely to recovery of the lactam starting material and decomposed diene. Preliminary molecular modeling using Chem3DPlus[10] suggests that NMP has a rigid arrangement about the amide bond with the *N*-methyl group in the same plane as the carbonyl group, but provides no compelling evidence for the difference in reactivity of the two substrates based on steric arguments. Further modeling studies based on the transition state of the reaction should be more informative.

The use of simple amides in the cycloaddition reaction with Danishefsky's diene was pursued to probe the generality of this reaction. In all cases studied, however, only unreacted amide and decomposed starting material

(1) (a) Yamashita, T.; Fujimura, N.; Yahara, S.; Nohara, T.; Kawanobu, S.; Fujieda, K. *Chem. Pharm. Bull.* **1990**, *38*, 827. (b) Mimaki, Y.; Sashida, Y. *Chem. Pharm. Bull.* **1990**, *38*, 3055.

(2) Kashman,Y.; Hirsh, S.; McConnell, O.; Ohtani, I.; Kusumi, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1989**, *111*, 8925.

(3) Jares-Erijman, E.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5712.

(4) Gresham, T. L.; Steadman, T. R. *J. Am. Chem. Soc.* **1949**, *71*, 737.

(5) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.

(6) fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedianato. hfc = (3-heptafluoropropyl)hydroxymethylenecamphorato.

(7) (a) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269. (b) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. W. *J. Am. Chem. Soc.* **1988**, *110*, 8117. (c) Myles, D. C.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636.

(8) Fleming, I. *Frontier Molecular Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, 1976.

(9) For a typical reaction, a solution of the lactam, Danishefsky's diene (1.1 equiv), and Eu(fod)$_3$ catalyst (0.1 equiv) in toluene is heated at reflux for 2 days. The product mixture is then concentrated and hydrolyzed using trifluoroacetic acid in CCl_4. The reaction mixture is subsequently worked up via aqueous extractions and the product isolated via silica gel chromatography. The spirocyclic products are stable at room temperature, except for the product from the reaction with 2-pyrrolidinone, which decomposes slowly during storage at room temperature.

(10) Chem3DPlus (3.1.2), Cambridge Scientific Computing, Inc.

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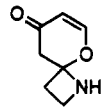
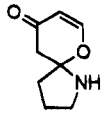
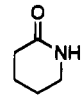
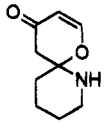
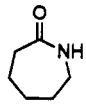
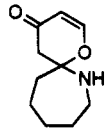
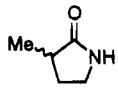
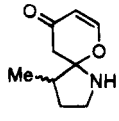
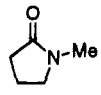
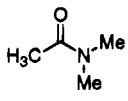
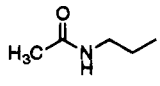
Table 1. Reaction of Lactams and Amides with Danishefsky's Diene

Substrate	Product	% yield
	 3	6
	 4	56
	 2	65
	 5	36
	 6	70
		no reaction
		no reaction
		no reaction

were recovered. One possible explanation for this is the preferred *trans* conformation of the alkyl substituents in simple monosubstituted amides which may inhibit reactivity due to steric interactions. Energy minimization of (*E*)-*N*-methylacetamide and (*Z*)-*N*-methylacetamide by *ab initio* calculations at the 6-31G level indicate the *E* conformation is favored by 2.6 kcal/mol.[11] If the Diels–Alder transition states for the reactions of both the *E* and *Z* amides have similar energies, then the greater ground-state stabilization of the *E* amides may account for their lower reactivity. This may also provide an explanation for the reactivity of lactams with an NH group (H is *cis* to the carbonyl group) versus the NMe derivatives (Me group is *cis* to the carbonyl group).

(11) Sapse, A. M.; Fugler, L. M.; Cowburn, D. *Int. J. Quant. Chem.* **1986**, *29*, 1241.

There are two mechanistic possibilities for this reaction: (1) a Diels–Alder cycloaddition pathway or (2) a two-step Mukaiyama "aldol" process, requiring the loss of the highly labile trimethylsilyl (TMS) group.[12] To probe the mechanistic possibilities, several other dienes have been used, including 2,3-dimethoxy-1,3-butadiene, 1,3-dimethoxy-1-[(trimethylsilyl)oxy]-1,3-butadiene (Brassard's diene),[13] and 1,3-diethoxy-1,3-butadiene.[14] In all of these substrates, no labile (trimethylsilyl)oxy group is present in the 3 position of the diene. In all cases studied to date, no cycloadducts have been recovered from these reactions. The reaction of δ-valerolactam with **1** in the absence of catalyst, which yielded 22% of cycloadduct **2** (Scheme 1), is consistent with both possible mechanisms. The labile TMS group may be removed slowly under the reaction conditions, providing the opportunity for the two-step reaction to occur. Further mechanistic work with other dienes and modified reaction conditions are being pursued to clarify the mechanistic pathway.

The surprising reactivity of lactams as dienophiles provides a highly convergent route to spirolinked nitrogen heterocyclic compounds which are not readily prepared by other synthetic methods. By taking advantage of the high regioselectivity and stereoselectivity available through Diels–Alder chemistry, this methodology may be developed for the formation of highly substituted, optically active intermediates for the synthesis of natural products such as the guanidine alkaloids. Alternately, modification of the cycloadducts and subsequent hydrolysis of the hemiaminal moiety should provide linear fragments for the stereoselective synthesis of complex molecules.[15]

In summary, the novel heteroatom cycloaddition of lactams with activated dienes offers a convergent approach toward the synthesis of the relatively unknown spirohemiaminal moiety which is a potentially useful intermediate in organic synthesis. Our current work is directed at determining the mechanism, stereoselectivity, and synthetic applications of this reaction.

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Supporting Information Available: Experimental details for the preparation of 7-aza-1-oxospiro[5.5]-2-undecen-4-one as well as spectroscopic and analytical data for the cycloaddition adducts from the reaction of 2-azetidinone, 2-pyrrolidinone, ε-caprolactam, and (±)-3-methyl-2-pyrrolidinone with Danishefsky's diene (3 pages).

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(12) Larson, E. R.; Danishefsky, S. *Tetrahedron Lett.* **1982**, 1975.
(13) Savard, J.; Brassard, P. *Tetrahedron Lett.* **1979**, 4911.
(14) Dowd, P.; Weber, W. *J. Org. Chem.* **1982**, *47*, 4774.
(15) Sauve, G.; Schwartz, D. A.; Ruest, L.; Delongchamps, P. *Can. J. Chem.* **1984**, *62*, 2929.