

Complex Polycyclic Lactams from Pericyclic Cascade Reactions of Zincke Aldehydes

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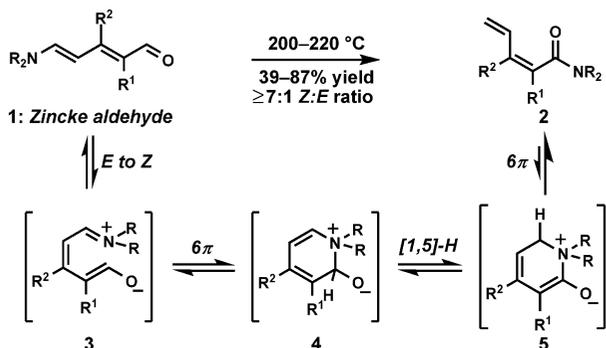
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Functional group-rich polycyclic scaffolds that are readily available from simple starting materials via general reaction sequences offer potential utility for natural product synthesis and medicinal chemistry. In the course of a simple mechanistic investigation of the thermal rearrangement chemistry of Zincke aldehydes (5-amino-2,4-pentadienals), we have discovered a general pericyclic reaction cascade that generates polycyclic lactams in only two steps from pyridinium salts and secondary amines; the alkaloid-like products are rigid yet versatile scaffolds with multiple functional group handles for further elaboration.

We recently described a stereoselective synthesis of Z- $\alpha,\beta,\gamma,\delta$ -unsaturated amides via thermal pericyclic rearrangement of Zincke aldehydes (Scheme 1).^{1,2} These donor–acceptor diene substrates

Scheme 1. Stereoselective Synthesis of Z-Dienes by Thermal Rearrangement of Zincke Aldehydes

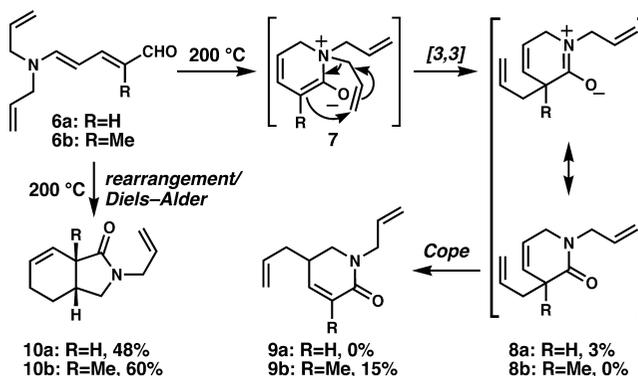


(1) derive from the simple Zincke ring-opening aminolysis of pyridinium salts,^{3,4} and are therefore readily available with substituents on the five-carbon backbone, and with varied groups appended to the amine used for ring-opening.

While the regiochemical results (the position of R¹ in the substrates and products) of the rearrangement (1 → 2) ruled out an alternate mechanism involving pyran intermediates,¹ we sought further support for the pathway shown in Scheme 1. In particular, we wanted to validate the transient existence of zwitterionic dienolate intermediate 5. We posited that a Zincke aldehyde bearing an *N*-allyl group might, upon heating, rearrange to its corresponding zwitterionic dienolate, which could then undergo a [3,3]-sigmatropic rearrangement with neutralization of charges (7 → 8, Scheme 2). A substituted dihydropyridone would result.

Heating of Zincke aldehyde **6a** at 200 °C in a microwave reactor generated the anticipated dihydropyridone **8a** in trace amounts; bicyclic lactam **10a** was the major product. Methyl-substituted Zincke aldehyde **6b** similarly generated bicyclic lactam **10b** as the major product; dihydropyridone **9b**, in which a terminal Cope rearrangement has occurred, was isolated in 15% yield. These results clearly support the involvement of intermediates of type 5/7 in the rearrangement reaction, although the generation of dihydropyridones

Scheme 2. *N,N*-Diallyl Zincke Aldehydes Afford Dihydropyridones and Bicyclic Lactams upon Heating

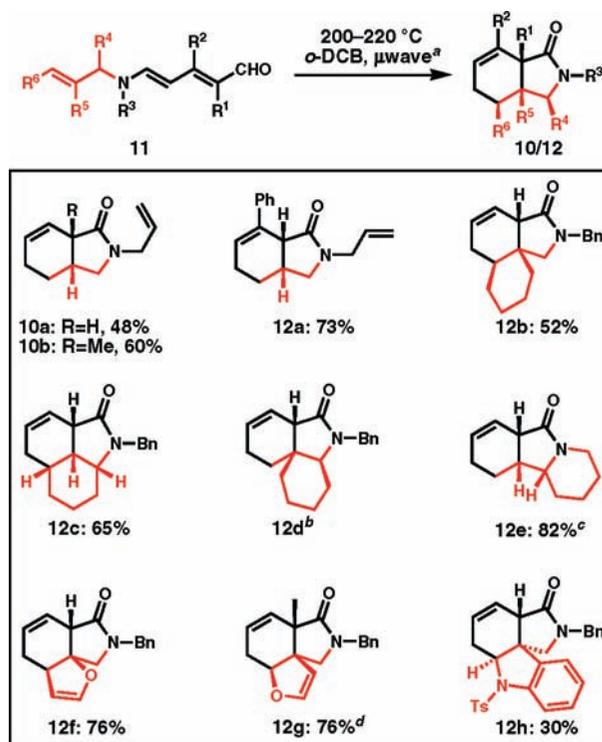


under these conditions is inefficient. The cascade reactions that afford bicyclic lactams **10a** and **10b** were unanticipated, but demonstrated promise for the rapid generation of complex, alkaloid-like scaffolds from simple precursors. Products **10a** and **10b**, formed via a cascade of alkene isomerization, 6 π -electrocyclization, [1,5]-sigmatropic shift of hydrogen, 6 π -electrocyclic ring-opening, and Diels–Alder cycloaddition, are formed as single diastereomers with a *cis* ring junction.

A series of Zincke aldehydes derived from the ring-opening of pyridine or substituted pyridines with various unsaturated secondary amines were synthesized according to established procedures.⁵ When heated, each of these substrates afforded the products of the rearrangement/Diels–Alder cascade (Table 1).⁶ Substitution could be varied at six different positions; when rings were incorporated into the allylic amine portion, four different fused tricyclic scaffolds (**12b–e**) resulted. The polycyclic γ -lactams were all formed as single diastereomers with the exception of **12e**. Notably, furan-bearing Zincke aldehydes led to tricyclic dihydrofurans **12f** and **12g** (gram scale), respectively; the two electronically different alkenes (the vinyl ether can also serve as a protected hydroxyaldehyde) and a lactam provide significant opportunities for post-rearrangement elaboration. In both instances, the furan had served as the 2 π component in the [4 + 2] cycloaddition. Furans are particularly suited to the role of diene in Diels–Alder reactions,⁷ and examples of furans serving as dienophiles are rare, especially when the heterocycle bears no electron-withdrawing substituents.^{8,9} Intrigued, we synthesized an indole-containing substrate and found that it, too, behaved as a dienophile toward the *in situ*-generated diene, affording tetracyclic product **12h**. This product maps well onto the tetracyclic core of many indole monoterpene alkaloids, with translocation of the amine from the usual tryptamine-like position. These products could serve as intermediates in the synthesis of indole alkaloid analogues.

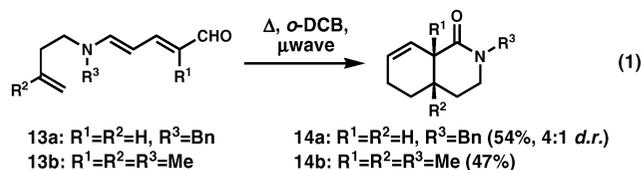
Homoallylic amine-derived Zincke aldehydes **13a** and **13b** also undergo this reaction cascade to generate hexahydroisoquinolone

Table 1. Polycyclic Lactam Cascade Products

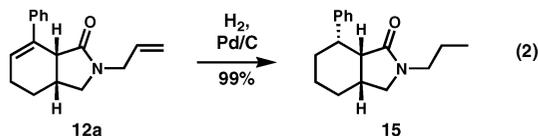


^a Please refer to the Supporting Information for specific reaction times and temperatures. ^b The combined yield of **12d** and the [3,3]-rearranged product corresponding to **8a** was 61% (2:1 mixture, inseparable). ^c Approximate 4:2:1 mixture of diastereomers, stereochemistry of major isomer tentatively assigned as shown. ^d Greater than 1 g scale.

scaffolds **14a** and **14b**, respectively (eq 1); the yields are moderate and in the case of **14a**, the stereochemical control is slightly attenuated.

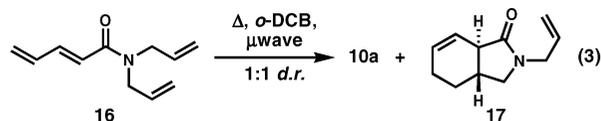


Cis-fused bicycles are effective stereocontrol elements;¹⁰ to demonstrate the ability to perform stereoselective reactions on these scaffolds, the trisubstituted alkene of **12a** was reduced with complete stereoselectivity to afford **15** (eq 2).



We synthesized *E*-dienamide **16** to determine if the cycloaddition diastereoselectivity was dependent upon the configuration of the diene. The product lactam derived from **16** was formed as a nearly equimolar mixture of diastereomers (**10a** and **17**, eq 3);^{5,11} therefore, there is substantial benefit to the *in situ*-formation of the *Z*-diene

via the thermal rearrangement of Zincke aldehydes, which enables a diastereoselective cycloaddition reaction.¹²



The pericyclic reaction cascade that results from heating Zincke aldehydes derived from unsaturated amines delivers rigid polycyclic lactam scaffolds of diverse structure with potential utility for natural product synthesis and medicinal chemistry. In this way, substantial complexity is obtained in only two steps from pyridinium salts and unsaturated amines. Applications to complex natural product synthesis are currently being evaluated.

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Supporting Information Available: Complete experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (5) Please see Supporting Information for details.
- (6) Except for **12e**, the crude cycloadducts were formed in $\geq 10:1$ dr.
- (7) For a review of the extensive use of furans as Diels–Alder dienes, see: Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179–14233.
- (8) For examples of furans serving as dienophiles, see: Chen, C.-H.; Rao, P. D.; Liao, C.-C. *J. Am. Chem. Soc.* **1998**, *120*, 13254–13255, and references therein.
- (9) It is probable that the normal electron demand cycloaddition with furan serving as diene is operative here, but that the reversible nature of furan Diels–Alder reactions enables eventual formation of thermodynamic products **12f** and **12g**. Preliminary calculations that support this hypothesis can be found in the Supporting Information. It appears unlikely that a cycloaddition with furan serving as the diene followed by a [3,3]-sigmatropic rearrangement could account for the observed product; the stereospecificity of the Diels–Alder reaction of a *Z*-diene with the furan precludes formation of the stereoisomer of product that could undergo such a sigmatropic rearrangement.
- (10) For an important early discussion of this general mode of stereocontrol, see: Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1–57.
- (11) For a related study that demonstrates an interesting solvent dependence on stereochemical outcome, see: Guy, A.; Lemaire, M.; Negre, M.; Guette, J. P. *Tetrahedron Lett.* **1985**, *26*, 3575–3578.
- (12) Another advantage of this method for *in situ* *Z*-diene synthesis is that the α - and β -substituted $\alpha,\beta,\gamma,\delta$ -unsaturated amides generated in this way would be difficult to access so efficiently by other means.

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