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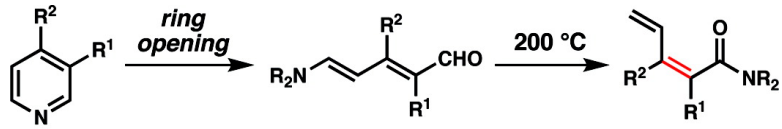

high Z-selectivity for di- and trisubstituted alkenes

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Stereocontrolled Synthesis of *Z*-Dienes via an Unexpected Pericyclic Cascade Rearrangement of 5-Amino-2,4-pentadienals

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Polyene natural products display an impressive array of important biological activities.[1] Polyunsaturated molecules have also demonstrated significant utility in complex molecule synthesis because they can be used in cascade reactions for the rapid buildup of molecular complexity.[2] They are ideally suited for pericyclic, radical, cationic, and transition-metal-mediated polycyclizations. Therefore, new methods for the synthesis of functionalized, stereodefined polyenes are of great value. We report a new method for the stereoselective synthesis of *Z*-α,*β*,*γ*,*δ*-unsaturated amides, based on a pericyclic cascade rearrangement that was discovered serendipitously during our investigations into the chemistry of Zincke aldehydes. This particular polyunsaturated motif is frequently encountered in important, biologically active molecules.[3]

The ring-opening reaction of pyridinium salts dates back over a century to the pioneering work of Zincke and König.[4] Activation of pyridines as their pyridinium salts (**1**, Figure 1), followed by treatment with primary amines, leads to the formation of new pyridinium salts (**2**), while the use of secondary amines cleanly affords the products of ring opening.[5] Frequently, the ring-opened 5-amino-2,4-pentadienal products (**3**), now known as Zincke aldehydes, can be obtained in high yield and purity, and in large quantities, without chromatographic purification. Both the ring-opening process and the products appear ideally suited for manifold applications in synthesis; to date, however, this potential has remained largely unrealized.[6,7]

In the course of a projected alkaloid synthesis, we attempted the intramolecular Diels−Alder reaction of tetrahydro-*β*-carboline-derived Zincke aldehyde **4** (Scheme 1).[8] Warming this polyunsaturated precursor to 160 °C for 16 h did not afford cycloaddition product; rather, clean but partial conversion occurred to yield a product in which the Zincke aldehyde portion had been transformed; the prospective dienophile was unchanged. The product was *Z*-α,*β*,*γ*,*δ*-unsaturated amide **5**, an isomer of the starting material, which appeared to derive from an internal redox process. We next performed this thermal reaction on the simple Zincke aldehyde derived from pyridine and dimethylamine (**6**); *Z*-diene **7** was the sole product.

We reasoned that two different pericyclic cascade reactions could account for our observations with **6**; a substituted Zincke aldehyde substrate would be required to distinguish between them. 3-Picoline-derived substrate **8** served this purpose. A thermally instigated *E* to *Z* isomerization of the C2−C3 double bond of **8** might enable a 6-*π* electrocyclic ring closure of **11** to pyran **12**. A [1,5]-H shift would afford the isomeric pyran **13**, which could undergo an electrocyclic ring-opening reaction to deliver product **9**; the cyclic nature of the pyran intermediates would account for the *Z* geometry of the product. Alternatively, a sequence proceeding via dihydropyridinium intermediates **14**, **15**, and **16** would lead to **10**, an isomer of **9**.[9] Heating of **8** led exclusively to **10**, which bears the methyl group α to the carbonyl carbon; isomeric amide **9** was not observed. Therefore, the reaction appears to involve transposition of the amino group from one end of the carbon chain to the other, rather than oxygen transposition. To the best of our knowledge, in the century since pyridinium salt ring openings to form Zincke aldehydes were discovered, no such rearrangement has been reported.[10,11]

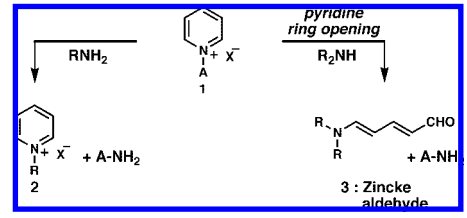
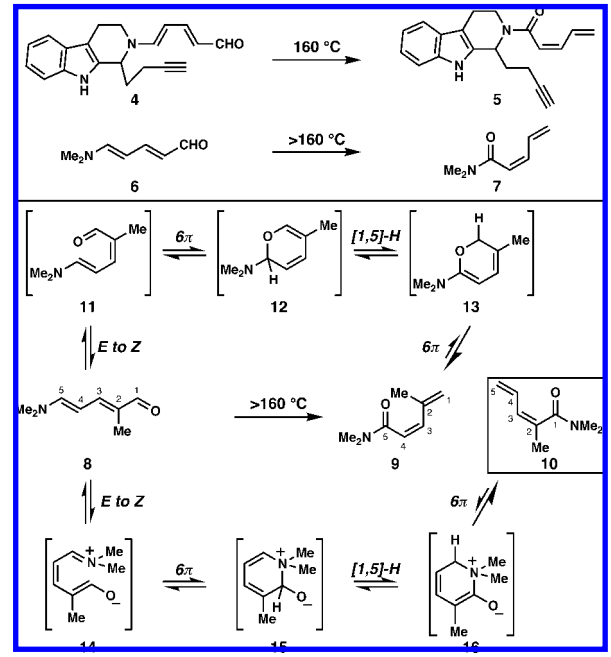


Figure 1. Aminolysis of pyridinium salts. A = activating group.

Scheme 1. Attempted Intramolecular Diels−Alder Cycloaddition of **4** Yielded Unexpected Rearrangement Product **5**. Two Reasonable Pericyclic Cascade Mechanisms Were Evaluated.



The results shown in Table 1 demonstrate that this rearrangement is general with respect to the amine and the substitution patterns on the Zincke aldehyde substrates.[12] Heating the substrates at 200−220 °C in *o*-dichlorobenzene under microwave irradiation cleanly converted each into α,*β*,*γ*,*δ*-unsaturated amides. Excellent *Z*-selectivity is observed in all cases except with some Zincke aldehydes derived from unsubstituted pyridines; in these cases (see **7** and **17**), the formation of the *E* isomer increases with prolonged heating.[13] The depressed yield of **7** reflects loss of this relatively volatile compound during the removal of the high boiling reaction solvent. The formation of trisubstituted alkenes (**10** and **19**−**22**)

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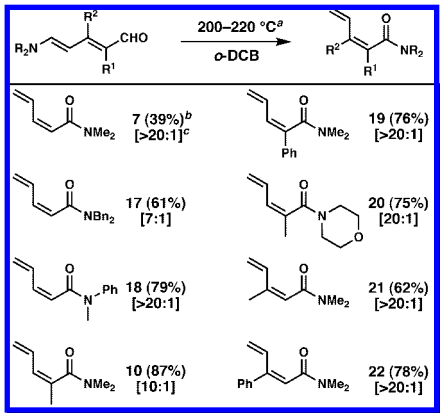
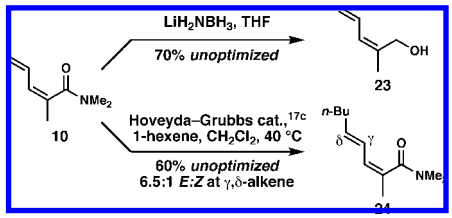
Table 1. Synthesis of *Z*-α,*β*,*γ*,*δ*-Unsaturated Amides by Thermal Rearrangement of Zincke Aldehydes



[a] See Supporting Information for reaction times and temperatures. [b] A 9:1 crude mixture of *Z*:*E* isomers, yield refers to purified *Z* isomer. [c] *Z*:*E* isomer ratio; except for **7**, ratio is unchanged after purification.

Scheme 2. Selective Manipulation of Amide **10**



proceeds smoothly and with excellent stereocontrol. With C3-substituted Zincke aldehydes ($R^2 \neq H$), an interesting case of stereoconvergence occurs; these aminodienal substrates are generated as thermodynamic mixtures of geometrical isomers about their trisubstituted alkenes (ca. 3:1), and this mixture is rearranged to the *Z*-products with selectivities of ≥10:1.[14] The smooth formation of morpholino amide **20** is noteworthy due to the known ability of these amides to serve as effective acyl transfer substrates.[15] Although more studies are needed, preliminary experiments have shown that rearrangement rates are increased with the addition of small amounts of camphorsulfonic acid, suggesting that catalysis might result in milder conditions for this novel reaction.

The utility of the products can be demonstrated by selective manipulation of either terminus of representative product **10**. Preliminary results include the reduction of the amide to alcohol **23**[16] and selective alkene cross-metathesis[17] to afford *Z*,*E*-diene **24** (Scheme 2) in moderate, but unoptimized yields.

We have uncovered a new rearrangement of donor−acceptor dienes known as Zincke aldehydes, which originate in two simple steps from inexpensive pyridines. While we have not yet studied the mechanism of the reaction in detail, it is consistent with a multistep pericyclic process; this reaction might serve as the prototype of a new type of rearrangement process of donor−acceptor dienes. The high kinetic selectivity for *Z*-dienamides is a consequence of the presumed mechanism of the rearrangement and engenders great potential utility to this interesting transformation. Facile and stereoselective access to *Z*-trisubstituted alkenes with two different substitution patterns demonstrates the versatility of the method. Further studies on the scope and mechanism, as well as applications in natural product synthesis, will be reported in due course.

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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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(12) On the basis of literature precedent and our own exploratory experiments, Zincke aldehydes with any substitution at C1 or C5 (derived from pyridine C2 and C6) are not accessible from the pyridine ring-opening process. Due to the regioselectivity of the ring-opening aminolysis/iminium hydrolysis process, monosubstitution at C4 is also not possible using this route. Studies to access substituted Zincke aldehydes by other means are underway.
(13) Presumably, the *Z* to *E* isomerization is not purely thermal but is instigated by an impurity in the reaction medium. To date, we have been unable to fully suppress the isomerization. Fortunately, those products that are most difficult to access with high *Z*-selectivity (**7** and **17**) are those that might be readily obtained by alkyne semi-hydrogenation.
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