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Studies of Intramolecular Cyclizations of *N*-Acyliminium Ions Derived from Acyclic Ketones: Unanticipated Stereochemical and Structural Results

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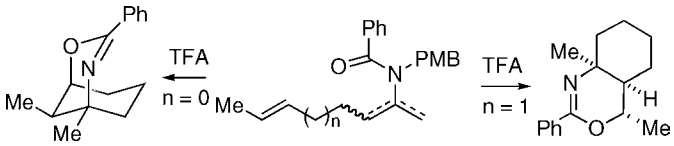
ABSTRACT



Intramolecular cyclizations of a series of (*E*)- and (*Z*)-olefinic acyclic ketone-derived *N*-acyliminium ions have been studied. It has been found that both the course of the reaction and the stereochemistry of the products are critically dependent upon the tether length and olefin geometry of the cyclization substrate.

N-Acylimines and *N*-acyliminium ions have become important synthons in the construction of a wide array of nitrogen-containing molecules, as well as nitrogen heterocycles, due to their susceptibility to nucleophilic attack and their ability to act as partners in several cycloaddition reactions.[1] Much of the early classical work on aromatic amidoalkylation reactions made use of "linear" *N*-acylimines derived from the direct condensation of highly electrophilic nonenolizable aldehydes (e.g., formaldehyde, chloral, glyoxylate, etc.) with amides.[2] These kinds of acyclic *N*-acylimines have also been used in other synthetic processes.[1] However, to date there has been minimal usage of linear *N*-acylimines derived from enolizable aldehydes, perhaps due to a somewhat limited amount of efficient methodologies for generating these species,[3] along with their propensity to hydrolyze readily. Interestingly, even less has been done with acyclic acylimines derived from ketones.

It has been known for a number of years that *N*-acylimines and iminium salts can act as azadienes in hetero Diels−Alder cycloadditions with olefins to produce 5,6-dihydro-1,3-oxazines.[4,5] Several years ago, we described the first examples of intramolecular [4 + 2]-cycloadditions of this type utilizing *N*-acyliminium salts derived from enolizable aldehydes and showed that these reactions are completely stereospecific.[6] Thus, we found that it was possible to generate *N*-acyliminium ions in situ from unsaturated alde-

(1) For extensive reviews of the chemistry of *N*-acylimines and iminium ions, see: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Hiemstra, H.; Speckamp, W. N. In *N-Acyliminium Ions as Intermediates in Alkaloid Synthesis* In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 32, p 271. (c) Hiemstra, H.; Speckamp, W. N. Additions to *N*-Acyl Iminium Ions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1047. (d) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(2) (a) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52. (b) Zaugg, H. E. *Synthesis* **1984**, 85, and 181.

(3) See, for example: (a) Johnson, A. P.; Luke, R. W. A.; Steele, R. W.; Boa, A. N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 883. (b) Johnson, A. P.; Luke, R. W. A.; Boa, A. N. *J. Chem Soc., Perkin Trans. 1* **1996**, 895. (c) Al-Talib, M.; Zaki, M.; Hehl, S.; Stumpf, R.; Fischer, H.; Jochims, J. C. *Synthesis* **1996**, 1115. (d) Hoffman, R. V.; Nayyar, N. K.; Shankweiler, J. M.; Klinekole, B. W., III. *Tetrahedron Lett.* **1994**, *35*, 3231. (e) Chao, W.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 9199.

(4) For reviews of uses of *N*-acylimines as heterodienes, see: (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Chapter 9. (b) Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525.

(5) For more recent examples, see: (a) Gizecki, P.; Dhal, R.; Toupet, L.; Dujardin, G. *Org. Lett.* **2000**, *2*, 585. (b) Shimizu, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **2000**, *41*, 5715. (c) Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J.-I. *Org. Lett.* **2003**, *5*, 945. (d) Gizecki, P.; Dhal, R.; Poulard, C.; Gosselin, P.; Dujardin, G. *J. Org. Chem.* **2003**, *68*, 4338.

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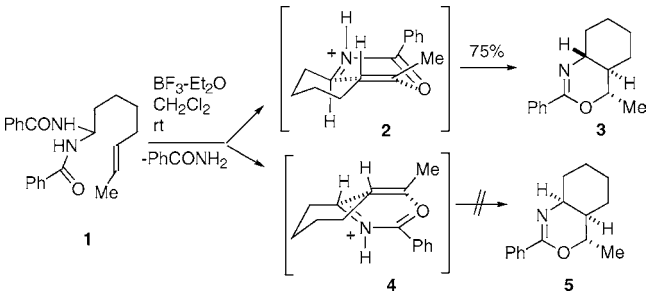
hyde bis-amides such as **1** using boron trifluoride etherate as a Lewis acid catalyst at room temperature. These intermediates then cyclized to afford, with both (*E*)- and (*Z*)-olefinic dienophiles, exclusively trans-fused bicyclic dihydrooxazines such as **3** (Scheme 1). We rationalized this

Scheme 1



stereochemical outcome on the basis of the assumption that due to unfavorable nonbonded interactions, the *N*-acyliminium ion transition state conformer **4**, leading to the cis-fused product **5**, is of higher energy than conformer **2**, which would afford the observed trans-fused product **3**. A similar preference for the trans product was also observed in systems leading to 6,5-fused dihydrooxazines.[6] In addition, since synthesis of bis-amides such as **1** from aldehydes often suffers from low yields, we have developed a new and more efficient approach for generation of the *N*-acyliminium ion heterodienes using our radical transposition methodology.[3e]

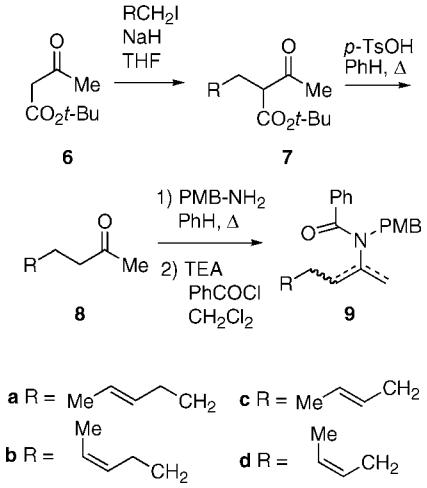
More recently, we considered the possibility of extending this intramolecular hetero Diels−Alder chemistry to ketone-derived *N*-acyliminium ions[7] since the [4 + 2]-cycloadducts from this variation of the methodology would have a quaternary center adjacent to nitrogen (vide infra), and we believed these heterocycles might be attractive intermediates for alkaloid synthesis. It was our expectation a priori that the stereochemistry of the ketone-derived systems should parallel that of the aldehyde *N*-acyliminium ion substrates. However, as described in this communication, we have found that there are significant and unexpected differences in the chemistry of these two types of systems.

The strategy was to generate the requisite ketone-derived *N*-acyliminium salt by protonation of an enamide (cf. **9**, Scheme 2). Since we knew from previous experience that enamides bearing an alkyl group on nitrogen are more stable to hydrolysis by adventitious moisture than unsubstituted (NH) enamides and also more easily prepared, we opted to investigate *N*-*p*-methoxybenzyl (PMB)-substituted cases. In addition, on the basis of observations in our previous work, we anticipated that this substituent would be lost under the conditions of the cycloaddition.[3e]

(6) (a) Scola, P. M.; Weinreb, S. M. *J. Org. Chem.* **1986**, *51*, 3248. (b) Scola, P. M. Ph.D. Thesis, The Pennsylvania State University, University Park, Pennsylvania, 1993.

(7) A few cases exist of intermolecular hetero Diels−Alder cycloadditions involving *N*-acylimines derived from nonenolizable ketones. See for example: (a) Hall, H. K., Jr.; Miniutti, D. L. *Tetrahedron Lett.* **1984**, *25*, 943. (b) Safronova, Z. V.; Simonyan, L. A.; Zeifman, Y. V.; Gambaryan, N. P. *Bull. Acad. Sci USSR, Div. Chem. Sci. (Engl. Transl.)* **1979**, 1688.

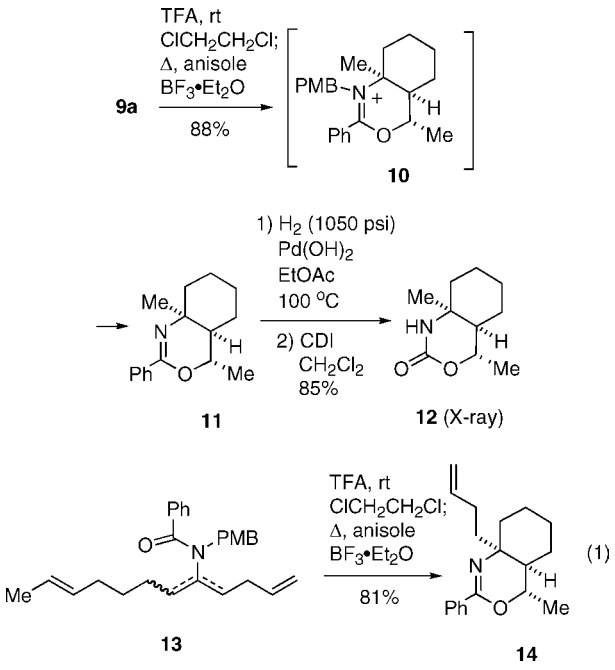
Scheme 2



The substrates for the cycloadditions were readily prepared by the route shown in Scheme 2. Thus, alkylation of *tert*-butyl acetoacetate (**6**) with some (*E*)- and (*Z*)-olefinic primary iodides afforded products **7a**−**d** (see Supporting Information). Decarboxylation of these compounds produced ketones **8a**−**d**, which could be converted in two steps to the desired enamides **9a**−**d** (mixtures of isomers).

To effect the desired Diels−Alder reaction, substrate **9a** was exposed to trifluoroacetic acid in 1,2-dichloroethane at room-temperature overnight (Scheme 3).[3e] A single cycloadduct was produced in 65% yield which, to our surprise, proved to be the cis-fused bicyclic dihydro-1,3-oxazine **11**. The structure of adduct **11** was confirmed by its conversion into a crystalline cyclic carbamate **12** by hydrogenolysis of

Scheme 3

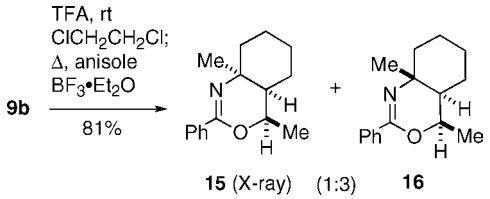


the dihydrooxazine,[8] followed by treatment of the resulting amino alcohol with 1,1′-carbonyldiimidazole and subsequent X-ray analysis.[9] It seems likely that dihydrooxazinium salt **10** is an intermediate in this process but is not observed since it apparently undergoes facile dealkylation in situ. We cannot, however, rule out the possibility that the PMB group comes off prior to the cyclization. Interestingly, it was subsequently found that the isolated yield of cyclization product **11** improves to 88% if, after ~20 h at room temperature, boron trifluoride etherate and anisole are added to the reaction mixture, which was then heated at reflux for approximately 18 additional hours (see Supporting Information). Although we are not sure as to the exact role of these reagents at present, it is possible that they help promote cleavage of the PMB group of any remaining oxazinium salt **10** and/or help in product isolation by destroying PMB-containing byproducts. This same yield improvement was also observed in other cyclizations (vide infra).

Another cycloaddition was conducted with the related enamide substrate **13** using the optimum reaction conditions described in eq 1 (Scheme 3). Once again the cis-fused dihydrooxazine **14** was produced here in good yield as the only isolable product. In this example, the terminal olefin functionality proved to be compatible with the reaction.

We next turned to the substrate **9b** containing a (*Z*)-olefin dienophile (Scheme 4). In this case, exposure of enamide

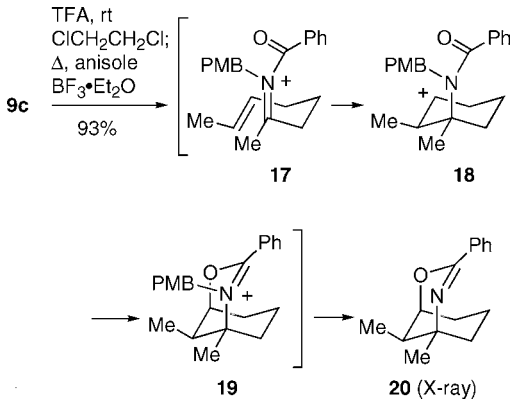
Scheme 4



9b to the identical reaction conditions developed for the (*E*)-olefins now afforded a 1:3 mixture of the cis-fused cycloadduct **15** and the trans-fused system **16** in good overall yield. The structure of the minor isomer **15** was confirmed by X-ray crystallography.[9]

Another system that was investigated was enamide **9c**, bearing an (*E*)-olefinic dienophile, which we anticipated would afford a 6,5-fused dihydro-1,3-oxazine Diels−Alder product. Again to our surprise, exposure of substrate **9c** to the standard cyclization conditions led cleanly and in 93% yield to the bridged dihydrooxazine **20** as a single stereoisomer (Scheme 5). If the boron trifluoride/anisole treatment is omitted, the product is obtained in lower yield and contaminated by an inseparable impurity. The structure of product **20** was again secured by X-ray crystallography.[9] It

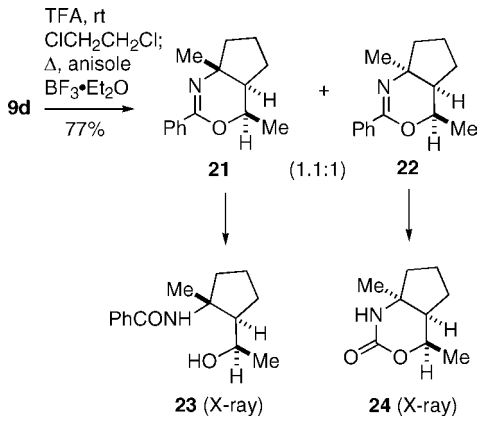
Scheme 5



seems probable that **20** arises by stepwise cyclization of *N*-acyliminium ion **17** via intermediate carbocation **18** to oxazinium salt **19**, which then loses the PMB group.

The cyclization of (*Z*)-olefin analogue **9d** was investigated next (Scheme 6). This transformation yielded a 1.1:1 mixture

Scheme 6



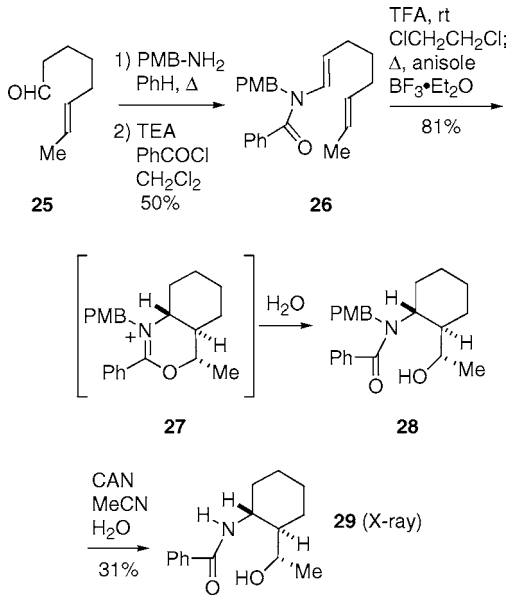
of the trans- and cis-fused [4 + 2]-cycloadducts **21** and **22**. The stereochemistry of these Diels−Alder products was determined by X-ray analysis of the crystalline derivatives **23** and **24**.[9]

Since it seemed possible that these major differences in the reactions of aldehyde- vs ketone-derived systems were due to the method of generation of the *N*-acyliminium salts and/or the presence of the *N*-PMB group, we conducted the experiments shown in Scheme 7 to probe these issues. Thus, (*E*)-olefin aldehyde **25** was converted to *N*-PMB enamide **26** in two steps. When treated under the same conditions as for the ketone-derived cases, substrate **26** afforded a single product **28**, which could be isolated in good yield. Amide alcohol **28** likely derives via an initial hetero Diels−Alder process leading to oxazinium salt **27**, which does not lose the PMB group but rather is hydrolyzed on aqueous workup. The structure and stereochemistry of **28** were confirmed by X-ray analysis of the dealkylated derivative **29**.[9] Signifi-

(8) Cf.: Fulop, F.; Simon, L.; Simon-Talpas, G.; Bernath, G. *Synth. Commun.* **1998**, *28*, 2303.

(9) We thank Dr. Louis Todaro (Hunter College) for the X-ray determination of carbamate **12** and Dr. Hemant Yennawar (Penn State Small Molecule X-ray Crystallographic Facility) for the structures of compounds **15**, **20**, **23**, **24**, and **29**.

Scheme 7



cantly, the trans-stereospecificity of this variation of the cycloaddition is in accord with that shown in Scheme 1, which utilizes a bis-amide precursor **1** for generating the *N*-acyliminium ion.[6]

The work described above has demonstrated that in contrast to aldehyde-derived systems, the course of the intramolecular hetero Diels−Alder cyclizations with ketone-derived *N*-acyliminium ions is highly dependent upon the tether length as well as the geometry of the olefin dienophile. In general, hetero Diels−Alder reactions of electrophilic *N*-acyliminium ions with olefins are considered to be "polar" cycloadditions which proceed via a concerted but nonsynchronous mechanism.[4b,10] Such a mechanistic pathway probably holds for the aldehyde *N*-acyliminium ion cases, but with the keto systems described here there may in fact be a change of mechanism to one that is stepwise (cf. Scheme 5). At this stage, it is difficult to fully rationalize all of the diverse results we have observed. We are, however, continuing to explore this chemistry to better understand the parameters controlling the reactions and also currently utilizing cis-fused cycloadducts such as **11** and **14** in synthesis of some marine alkaloids.

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Supporting Information Available: Experimental procedures for preparation of new compounds, including spectral data, along with X-ray data for compounds **12**, **15**, **20**, **23**, **24**, and **29** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl*. **1973**, *12*, 212. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl*. **1969**, *8*, 602. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl*. **1970**, *9*, 31. (c) Schmidt, R. R. *Chem. Ber*. **1970**, *103*, 3242. Schmidt, R. R.; Hoffmann, A. R. *Chem. Ber*. **1974**, *107*, 78.