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Intramolecular Azide Trapping of the Nazarov Intermediate: Formation of Peroxy-Bridged Indolizidinones via a Deep-Seated Rearrangement and Aerobic Oxidation

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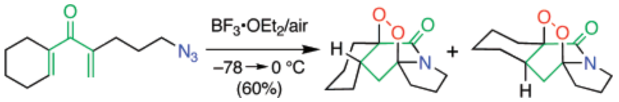
ABSTRACT



Cross-conjugated dienones with pendent azide side chains undergo interrupted Nazarov trapping, leading to peroxy-bridged indolizidinones in good yields. This process is proposed to involve skeletal rearrangement of the initial trapping product, with loss of dinitrogen, to give an intermediate 1,4-betaine, which then undergoes reaction with atmospheric oxygen. The endoperoxide products can be reduced under catalytic hydrogenation conditions to furnish α-hydroxylactams.

Domino processes[1] involving the 2-oxidocyclopentenyl intermediate formed during the Nazarov cyclization[2] (i.e., the "interrupted Nazarov" reaction) furnish a wide range of complex, polycyclic products.[3] With the notable exception of Dhoro and Tius' recent report of interception by simple amines,[3c] all examples of nucleophilic trapping have employed either carbon π nucleophiles or silyl hydride. We are exploring intramolecular trapping by heteronucleophiles as a rapid entry to polycyclic systems containing heterocyclic rings. The initial focus has been cycloaddition processes involving 1,3-dipoles, in analogy to previously reported intramolecular [4 + 3] trapping by pendent 1,3-dienes.[4] Given the expected stability of azides to the Lewis acidic conditions employed to initiate the Nazarov cyclization, we chose to test their suitability as traps.

Two possible reaction pathways were envisioned (Scheme 1): either nucleophilic capture of the allyl carbocation by the internal nitrogen atom (path *a*) to give zwitterions **1** or [3 + 3] cycloaddition (path *b*) to give dihydrotriazines **2**. Nucleophilic trapping of carbocations by pendent azides has considerable precedent[5] and generally involves a subsequent bond migration with concomitant expulsion of dinitrogen. Rearrangement of the zwitterionic intermediate **1** might be expected to occur with migration of the enolate carbon to form the Lewis acid complexed 1,4-dipole **3**, which could then suffer a 1,5-hydrogen shift to give a dihydropyridone.[6]

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(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Tietze, L. F. *Domino Reactions In Organic Synthesis*; John Wiley: New York, 2006.

(2) Reviews: (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React. (N.Y.)* **1994**, *45*, 1−158. (b) Pellisier, H. *Tetrahedron* **2005**, *61*, 6479−6517. (c) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577−7606.

(3) Recent examples: (a) White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629−5632. (b) Giese, S.; Mazzola, R. D., Jr.; Amann, C. M.; Arif, A. M.; West, F. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 6546−6549. (c) Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472−12473. (d) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2006**, *128*, 5312−5313. (e) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348−9349. (f) Review: Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193−2206.

(4) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876−877.

(5) For recent reviews concerning the reaction of azides with electrophiles, see: (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240. (b) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146−156.

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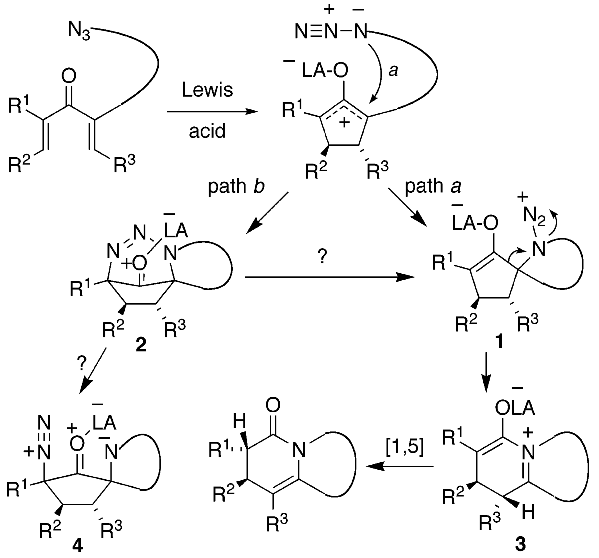
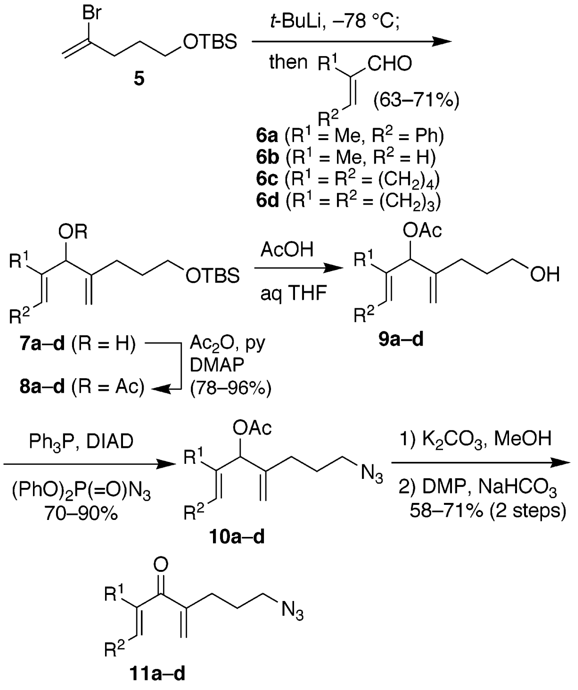
Scheme 1. Possible Azide Trapping Pathways



In the case of allylic cations, Pearson has observed both [3 + 2] and [3 + 3] trapping.[7] Schultz showed that a 2-oxidopentadienyl cation generated photochemically from a cross-conjugated dienone underwent intramolecular [3 + 3] trapping,[8] and more recently, Aubé found that a simple cyclopropanone-derived 2-oxidoallyl cation reacted with benzyl azide in an apparent [3 + 3] process.[9] Although the [3 + 3] adduct **2** could be isolable,[8] the Lewis acidic conditions might be expected to promote either CN fragmentation to give zwitterion **1** or N−N cleavage to diazonium intermediate **4** in analogy to Aubé's result. Here we describe the initial results of this study, including the unexpected formation of a bridged endoperoxide via oxygen trapping of the putative 1,4-dipole **3**.

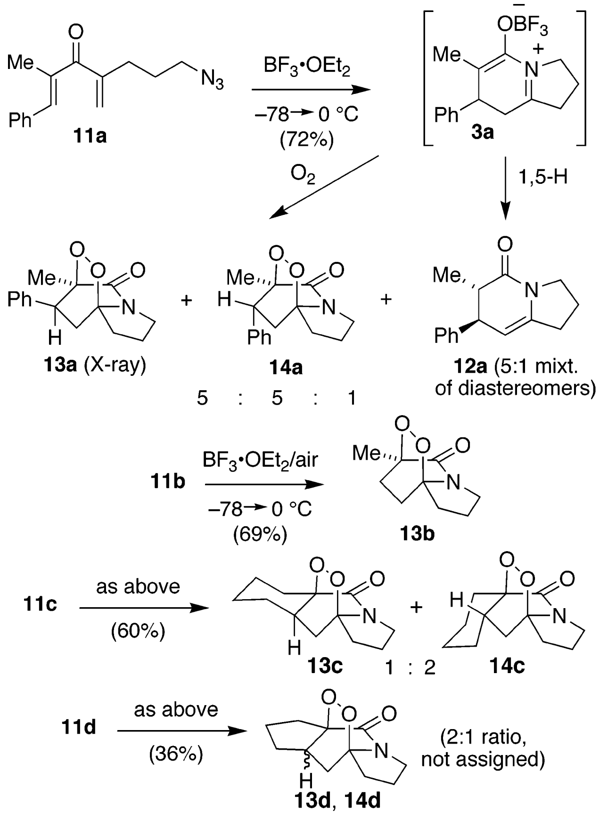
Scheme 2. Preparation of Dienone Substrates with Pendent Azide Groups



The substrates needed to test this process could be prepared by a short reaction sequence (Scheme 2). Alkenyl bromide **5** was subjected to lithium−halogen exchange at low temperature and then was allowed to react with unsaturated aldehydes **6a**−**d**. Protection of the dienol and removal of the primary TBS ether gave alcohols **9a**−**d**, which could be converted to azides **10a**−**d**. Finally, the doubly allylic acetate was cleaved, and the resulting secondary alcohols were subjected to oxidation with the Dess−Martin periodinane to give dienones **11a**−**d**.

Using **11a** as a test case, the Lewis acid catalyzed rearrangement was examined (Scheme 3). In the event, the starting dienone was cleanly consumed after treatment with $BF_3{\cdot}OEt_2$ at low temperature, followed by warming to 0 °C.

Scheme 3. Azide Trapping and Peroxide Formation



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(6) For other examples of formation of transient 1,4-dipoles and their subsequent 1,5-hydrogen shifts, see: (a) Lenz, G. R. *Synthesis* **1978**, 489−518. (b) Ninomiya, I.; Naito, T. *Heterocycles* **1981**, *15*, 1433−1462. (c) Potts, K. T.; Rochanapruk, T.; Padwa, A.; Coats, S. J.; Hadjiarapoglou, L. *J. Org. Chem.* **1995**, *60*, 3795−3805. (d) Padwa, A.; Flick, A. C.; Lee, H. I. *Org. Lett.* **2005**, *7*, 2925−2928.

(7) Pearson, W. H.; Fang, W.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682−2684.

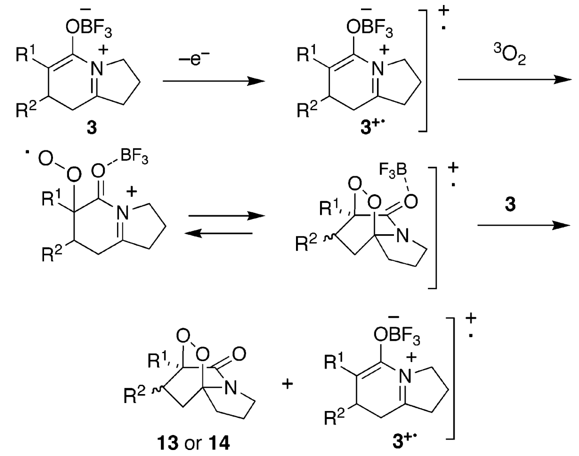
(8) Schultz, A. G.; Macielag, M.; Plummer, M. *J. Org. Chem.* **1988**, *53*, 391−395.

(9) Aubé, J.; Desai, P. *Org. Lett.* **2000**, *2*, 1657−1659.

Careful analysis revealed three products, including a minor amount of dihydropyridone **12a**. The major components were diastereomeric endoperoxides **13a** and **14a**. These compounds were clearly stereoisomeric, and the indicated structures were suggested by HRMS exact mass measurements and ^{13}C chemical shifts. Eventually, X-ray diffraction analysis of **13a** confirmed this assignment. We presume that all three products arise from a common intermediate, Lewis acid complexed betaine **3a**, with **12a** resulting from a subsequent 1,5-hydrogen shift or from proton transfer. Products **13a** and **14a** appear to arise from reaction with adventitious oxygen. Although an example of singlet oxygen trapping of a 1,4-dipole has been reported,[10] efficient scavenging of triplet oxygen appears to be without precedent. When oxygen is rigorously excluded from the reaction, only **12a** is isolated in 70% yield.[11] However, we deemed the additional functionality introduced via the final peroxide-forming step to be advantageous, so the other examples were run in the presence of oxygen. Substrates **11b**,**c** furnished the peroxy products in good yield, but **11d** gave only minor amounts of one of the desired products **13d** or **14d**, together with several other inseparable components.[12] Direct stereochemical assignments for the products of the last two examples were not possible; however, an X-ray crystal structure of a derivative of **13c** (vide infra) permitted assignments as shown.

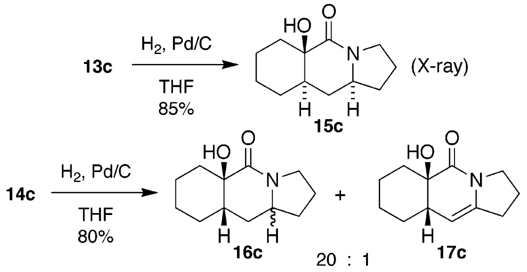
The mechanism by which intermediates **3** are efficiently trapped by ambient oxygen merits some comment. Although a direct electron-transfer process analogous to enolate oxygenation is possible, this seems unlikely. Such reactions are typically run under an atmosphere of oxygen,[13] to permit effective trapping of the enolate; in the present cases, an unexpectedly long lifetime for the betaine intermediates would be required to explain the efficient conversion to peroxides. The lifetime of the putative 1,4-dipole intermediate **3** should be limited due to the availability of a 1,5-H shift pathway. However, the rigidity of the bi- and tricyclic betaines in this study may impede this process.[14] It is notable that apparently no oxygenation was seen for the structurally related pyridinium enolates formed during Romo's NCAL reactions.[15] Critical distinctions include the endocyclic structure of dipoles **3** and the presence of BF_3. There are several examples of surprisingly facile oxidation of electron-rich, cyclic dienes by $^3O_2$.[16] Barton has described the formation of endoperoxides from steroidal cyclohexadienes and triplet oxygen in the presence of catalytic ammoniumyl cation radicals or Lewis acids.[17] Although this was initially explained in terms of facilitation of intersystem crossing by the catalyst, later work has implicated a chain process involving diene cation radicals or their oxygen adducts.[18] A variant of this mechanism (Scheme 4) offers a reasonable rationale for the formation of **13** and **14**.

Scheme 4. Cation Radical Chain Mechanism for Peroxide Formation



Reduction of the peroxy bridge was also investigated, using polycyclic endoperoxides **13c** and **14c** (Scheme 5).

Scheme 5. Peroxide Hydrogenolysis



After examining several conditions, we found that hydrogenolysis furnished the reduced α-hydroxylactams **15c** and **16c**, along with minor amounts of unsaturated product **17c**. Product **15c** was obtained as a crystalline solid, permitting unambiguous structural assignment of both that compound and its precursor, **13c**. Although **16c** was obtained as one predominant diastereomer, rigorous assignment of the relative configuration at the reduced bridgehead carbon was not

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(10) Gotthardt, H.; Schenk, K.-H. *Tetrahedron Lett.* **1983**, *24*, 4669–4670.

(11) See Supporting Information for a discussion of the relative configuration of the major isomer of **12a**.

(12) We have previously observed that dienones incorporating a cyclopentene ring undergo electrocyclization at a much slower rate, presumably due to ring strain in the resulting bicyclo[3.3.0]octenyl cation: Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747–2750.

(13) Review: Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Org. React. (N.Y.)* **2003**, *62*, 1–356.

(14) In preliminary studies, we have found that monocyclic betaines analogous to **3** undergo a rapid 1,5-hydrogen shift with no detectable peroxide formation: Song, D.; Rostami, A.; West, F. G. unpublished results.

(15) Henry-Riyad, H.; Lee, C.; Purohit, V. C.; Romo, D. *Org. Lett.* **2006**, *8*, 4363–4366.

(16) (a) Najjar, F.; André-Barrès, C.; Lauricella, R.; Gorrichos, L.; Tuccio, B. *Tetrahedron Lett.* **2005**, *46*, 2117–2119. (b) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **2001**, *123*, 9324–9337.

(17) Barton, D. H. R.; Haynes, R. K.; Leclerc, G.; Magnus, P. D.; Menzies, I. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2055–2065.

(18) (a) Tang, R.; Yue, H. J.; Wolf, J. F.; Mares, F. *J. Am. Chem. Soc.* **1978**, *100*, 5248–5249. (b) Nelsen, S. F.; Teasley, M. F.; Kapp, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5503–5509.

possible. However, delivery of hydrogen from the convex face seems likely in this case.

This unexpected example of the interrupted Nazarov reaction involves one of the first cases of trapping the oxidocyclopentenyl cation intermediate with a nitrogen-based moiety and entails a significant reorganization of the original dienone framework. In the presence of air, additional oxygenation to form peroxides is efficient, and these intermediates are subject to stereoselective reduction. Further applications of this chemistry are under investigation and will be described in due course.

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Supporting Information Available: Experimental procedures and spectral data for cyclization substrates, precursors, and cyclization products, as well as X-ray data for **13a** and **15c** (cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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