Published in final edited form as:

Org Lett. 2007 February 15; 9(4): 703–706. doi:10.1021/ol070053m.

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

Ali Rostami, Yong Wang, Atta M. Arif[†], Robert McDonald[‡], and F. G. West^{*}

Department of Chemistry, University of Alberta, Edmonton, AB, Canada T6G 2G2

Abstract

Cross-conjugated dienones with pendant 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 processes¹ involving the 2-oxidocyclopentenyl intermediate formed during the Nazarov cyclization² (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 pendant 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 pendant 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 1,5-hydrogen shift to give a dihydropyridone.⁶ 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**.

frederick.west@ualberta.ca.

[†]X-Ray Crystallographic Facility, Dept. of Chemistry, University of Utah, 315 S. 1400 East, Salt Lake City, UT, 84112-0850.

[‡]X-Ray Crystallography Lab, Dept. of Chemistry, University of Alberta.

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, 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 $\text{BF}_3 \cdot \text{OEt}_2$ at low temperature, followed by warming to 0 °C. 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 subsequent 1,5-hydrogen shift, or by 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 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. While 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 $^3\text{O}_2$.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**.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We thank NIH and NSERC for support of this work, and Dr. Patrick H. Dussault (University of Nebraska-Lincoln) for helpful discussions.

References

1. (a) Tietze LF. *Chem. Rev* 1996;96:115–136. [PubMed: 11848746] Tietze, LF. *Domino Reactions In Organic Synthesis*. New York: John Wiley; 2006.
2. Reviews: (a) Habermas KL, Denmark SE, Jones TK. *Org. React. (N.Y.)* 1994;45:1–158. (b) Pellisier H. *Tetrahedron* 2005;61:6479–6517. (c) Frontier AJ, Collison C. *Tetrahedron* 2005;61:7577–7606.
3. Recent examples: (a) White TD, West FG. *Tetrahedron Lett* 2005;46:5629–5632. (b) Giese S, Mazzola RD Jr, Amann CM, Arif AM, West FG. *Angew. Chem., Int. Ed* 2005;44:6546–6549. (c) Dhoro F, Tius MA. *J. Am. Chem. Soc* 2005;127:12472–12473. [PubMed: 16144378] (d) Janka M, He W, Haedicke IE, Fronczek FR, Frontier AJ, Eisenberg R. *J. Am. Chem. Soc* 2006;128:5312–5313. [PubMed: 16620081] (e) Grant TN, West FG. *J. Am. Chem. Soc* 2006;128:9348–9349. [PubMed: 16848467] Review: (f) Tius MA. *Eur. J. Org. Chem* 2005:2193–2206.
4. Wang Y, Arif AM, West FG. *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 JA. *Chem. Soc. Rev* 2006;35:146–156. [PubMed: 16444296]
6. For other examples of formation of transient 1,4-dipoles and their subsequent 1,5-hydrogen shifts, see: (a) Lenz GR. *Synthesis* 1978:489–518. (b) Ninomiya I, Naito T. *Heterocycles* 1981;15:1433–1462. (c) Potts KT, Rochanapruk T, Padwa A, Coats SJ, Hadjiarapoglou L. *J. Org. Chem* 1995;60:3795–3805. (d) Padwa A, Flick AC, Lee HI. *Org. Lett* 2005;7:2925–2928. [PubMed: 15987171]
7. Pearson WH, Fang W, Kampf JW. *J. Org. Chem* 1994;59:2682–2684.
8. Schultz AG, Macielag M, Plummer M. *J. Org. Chem* 1988;53:391–395.
9. Aubé J, Desai P. *Org. Lett* 2000;2:1657–1659. [PubMed: 10880194]
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 BD, Arif AM, West FG. *Org. Lett* 2003;5:2747–2750. [PubMed: 12868905]
13. Review: Chen B-C, Zhou P, Davis FA, Ciganek E. *Org. React. (N.Y.)* 2003;62:1–356.
14. In preliminary studies, we have found that monocyclic betaines analogous to **3** undergo rapid 1,5-hydrogen shift with no detectable peroxide formation: Song D, Rostami A, West FG. unpublished results.
15. Henry-Riyad H, Lee C, Purohit VC, Romo D. *Org. Lett* 2006;8:4363–4366. [PubMed: 16956227]
16. (a) Najjar F, André-Barrès C, Lauricella R, Gorrichos L, Tuccio B. *Tetrahedron Lett* 2005;46:2117–2119. (b) Eichberg MJ, Dorta RL, Grotjahn DB, Lamottke K, Schmidt M, Vollhardt KPC. *J. Am. Chem. Soc* 2001;123:9324–9337. [PubMed: 11562215](c)

17. Barton DHR, Haynes RK, Leclerc G, Magnus PD, Menzies ID. J. Chem. Soc., Perkin Trans. 1 1975:2055–2065.
18. (a) Tang R, Yue HJ, Wolf JF, Mares F. J. Am. Chem. Soc 1978;100:5248–5249. (b) Nelsen SF, Teasley MF, Kapp DL. J. Am. Chem. Soc 1986;108:5503–5509.

Scheme 1.
Possible azide trapping pathways.

Scheme 2.
Preparation of dienone substrates with pendant azide groups.

Scheme 3.
Azide trapping and peroxide formation.

Scheme 4.

Cation radical chain mechanism for peroxide formation.

Scheme 5.
Peroxide hydrogenolysis.