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Domino Electrocyclization/Azide-Capture/Schmidt Rearrangement of Dienones: One-Step Synthesis of Dihydropyridones from Simple Building Blocks

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Abstract: Simple 1,4-dien-3-ones undergo Lewis acid-catalyzed Nazarov electrocyclization and intermolecular trapping by various azides to furnish 3,4-dihydropyridin-2-ones in moderate to good yields. The reaction is proposed to proceed via nucleophilic trapping of the 2-oxidocyclopentenyl intermediate, followed by Schmidt-type rearrangement to give a transient 1,4-dipole. In unsymmetrical examples, complete regioselectivity in favor of attack on the less substituted side was observed. The 1,4-dipole intermediate then rearranges to the observed dihydropyridone, via either proton transfer or 1,5-hydride shift.

Introduction

The Nazarov cyclization of cross-conjugated dienones provides a convenient method for accessing cyclopentanoid products.¹ As a result of its unique mechanistic features (conrotatory pentadienyl \rightarrow cyclopentenyl electrocyclization), the Nazarov reaction has recently attracted considerable attention as a tool for initiating domino processes² that result in complex, polycyclic products.³ Common trapping modes include [4 + 3] cycloaddition with 1,3-dienes or nucleophilic capture by carbon π -nucleophiles. However, silyl hydride⁴ or simple amines^{3c} have also been shown to efficiently trap the Nazarov intermediate in intermolecular processes.

Organic azides can react as 1,3-dipoles with various π -systems and are also well-known to act as nucleophiles in the presence of carbocations or other electron-deficient species.⁵ With this in mind, we envisioned a possible trapping process involving simple azides and the Nazarov intermediate. Prior work indicated that simple allyl cations,⁶ an acyclic 2-oxidoallyl cation,⁷ or photochemically generated 2-oxidopentadienyl cat-

ions⁸ all could be intercepted with azide groups in either inter- or intramolecular fashion.

Initial studies focused on intramolecular trapping using dienone substrates containing azide-terminated side chains (Scheme 1).⁹ In the event, efficient electrocyclization and reaction of the resulting cyclopentenyl cation with the pendent azide was observed. However, this work revealed an unexpected oxidative pathway leading to peroxy-bridged piperidones as the major or exclusive products. These products were presumed to arise via intermediate cyclic 1,4-dipoles resulting from nucleophilic attack and ring expansion with loss of dinitrogen. Trace amounts of molecular oxygen could then trap the reactive dipole intermediate by an electron-transfer chain process. Carrying the reaction out with rigorous exclusion of air led to the exclusive formation of the corresponding indolizidinone lacking the peroxide bridge, a product which had been observed in only trace quantities under the normal conditions.

Although this process results in a major skeletal reorganization and furnishes a potentially useful bicyclic product, its synthetic appeal was attenuated somewhat by the sensitivity of the products and the multistep route required for the synthesis of the azidodienone substrates. Moreover, although the peroxy group found in the major products provided an additional functionality handle, we were interested in accessing the nonoxygenated dihydropyridone products without resorting to extraordinary efforts at oxygen exclusion. Here we describe the *intermolecular* version of this reaction, offering a surprisingly efficient and general method for the convergent synthesis of dihydropyridones from simple dienone and azide partners.

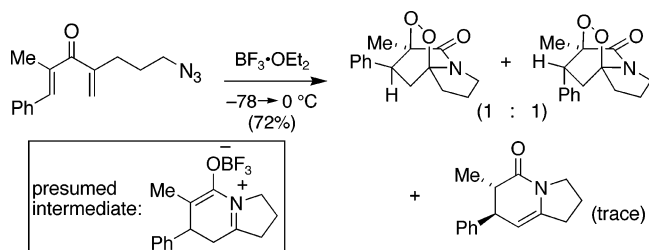
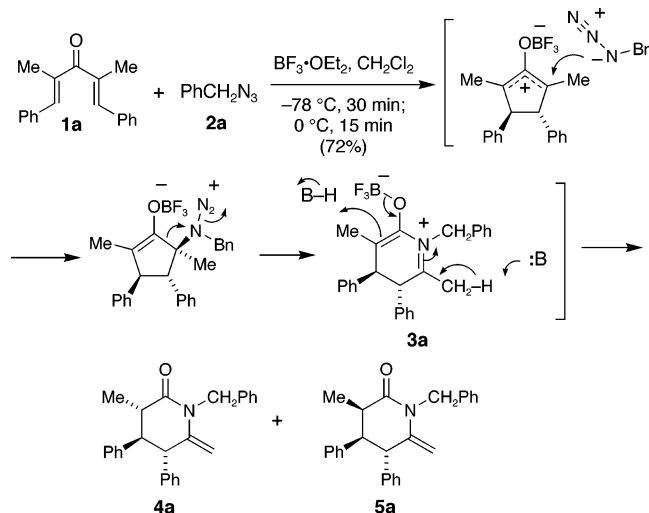
Results and Discussion

Initial Trapping Studies. Dibenzylidenepentan-3-one **1a** was employed for the initial experiments, given its exceptional

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- (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) Mahmoud, B.; West, F. G. *Tetrahedron Lett.* **2007**, *48*, 5091–5094. (g) Review: Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193–2206.
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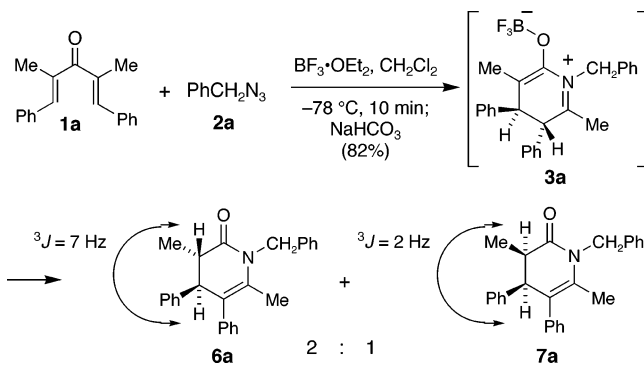
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(9) Rostami, A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703–706.

Scheme 1. Intramolecular Azide Trapping of the Nazarov Intermediate with Oxygen Incorporation**Scheme 2.** Initial Intermolecular Trapping Experiments

reactivity toward electrocyclic closure even at low temperatures.⁴ Treatment of **1a** with $\text{BF}_3 \cdot \text{OEt}_2$ at -78°C in the presence of 2 equiv of benzyl azide **2a**, followed by warming to 0°C and aqueous workup, yielded two new products, **4a** and **5a**, as a 1:1 ratio in 72% yield (Scheme 2). Spectral analysis indicated that these compounds were diastereomeric, containing three adjacent methine centers and an exocyclic methylene group. Product **4a** was assigned as the all-trans isomer on the basis of large vicinal coupling constants for the methine protons, while **5a** was tentatively assigned to be epimeric at C-3. Analogous to earlier work, we presume that both products arise from the 1,4-dipole **3a** resulting from addition of azide followed by Schmidt-type rearrangement. Formation of the exocyclic methylene moiety and both epimers at C-3 may then occur from **3** via proton transfer.

We were surprised to find no evidence of endoperoxide products resulting from oxygen trapping, a process that was extremely efficient in examples involving intramolecular azide trapping.^{8,10} Equally unexpected was the isolation of products possessing an exocyclic alkene resulting from apparent proton-transfer processes, as opposed to the 3,4-dihydropyridone product seen in the earlier intramolecular case when oxygen was scrupulously excluded. Other examples of transiently formed 1,4-dipoles analogous to **3** have typically rearranged to give endocyclic alkenes, a process postulated to occur via a concerted 1,5-hydrogen shift.¹¹ Given the geometrical constraints prohibiting continuous orbital overlap between C-3 and the methyl C–H bond, this mechanism is unlikely to apply in the

Scheme 3. Optimized Intramolecular Trapping To Form Dihydropyridones

formation of **4a** and **5a**. Instead, we propose a proton-transfer process involving an as-yet unidentified base.¹²

The effect of reaction time and temperature on the products was examined. In the event, it was found that longer reaction times at low temperature resulted in an alternative pair of products, **6a** and **7a** (1:1), in 71% yield (Scheme 3), with none of the previously observed **4a** and **5a**. In contrast to the earlier result, these products contained a tetrasubstituted, endocyclic alkene and were assigned as diastereomeric dihydropyridones. Further experimentation revealed optimal conditions for the formation of these products to be relatively short reaction at -78°C , followed by an immediate aqueous quench and workup, giving an 82% yield of **6a** and **7a** in a 2:1 ratio.

Generalization of Optimized Conditions to Other Substrates. The modified conditions were then applied to all combinations of dienones **1a–1d**¹³ and azides **2a–2c** (Table 1), in all cases furnishing dihydropyridone adducts **6** and **7**. Notably, unsymmetrical substrates reacted with complete regioselectivity in favor of initial nucleophilic attack by azide on the less hindered end of the intermediate 2-oxocyclopentenyl cation (entries 4–12). Moreover, substrates **1b** and **1c** furnished the trans isomer exclusively with all azides. Higher temperatures were required to consume dienones **1c** and **1d** (entries 7–12). For **1d**, this may reflect a higher barrier for the initial electrocyclozation due to the fusion of a second ring,¹⁴ whereas the absence of a C-4 alkyl group in **1c** is the probable explanation for its sluggish reactivity.^{1a} Lower yields in the case of **1c** could result from a greater propensity for side reactions by the starting dienone or the 2-oxocyclopentenyl intermediate.

Mechanistic and Stereochemical Considerations. It is notable that, for unsymmetrically substituted dienones **1b–1d**, complete regioselectivity was observed (entries 4–12). The products isolated result from cyclic 1,4-dipoles **3d–3l**, which derive from selective attack by azides **2a–2c** on the less hindered terminus of the cyclopentenyl cation formed during

(10) No peroxy-bridged products were observed even when the reaction was carried out under an atmosphere of O_2 .

(11) For examples of 1,5-hydrogen shifts by cyclic 1,4-dipoles, 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.; Hadjirapoglou, L. *J. Org. Chem.* **1995**, *60*, 3795–3805. (d) Padwa, A.; Flick, A. C.; Lee, H. I. *Org. Lett.* **2005**, *7*, 2925–2928.

(12) Potts and Padwa proposed a 1,5-shift mechanism for enamide products in which the new C=C bond was exocyclic to the original 6-membered ring of the 1,4-dipole (see ref 11c); however, these cases involved highly rigid, tricyclic systems which might permit a concerted suprafacial rearrangement.

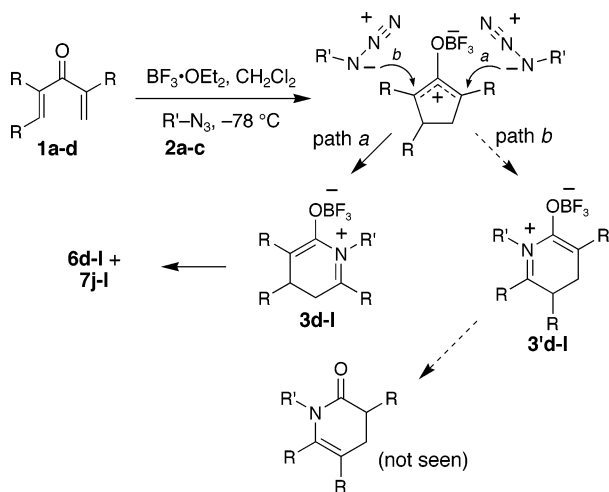
(13) Dienones **1b–1d** were prepared by addition of $\text{CH}_2=\text{C}(\text{Me})\text{MgBr}$ or $\text{CH}_2=\text{CHMgBr}$ to the corresponding unsaturated aldehydes, followed by oxidation of the resulting dienols with BaMnO_4 . See Supporting Information for details.

(14) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747–2750.

Table 1. Intermolecular Azide Trapping of Dienones **1a–1d**^a

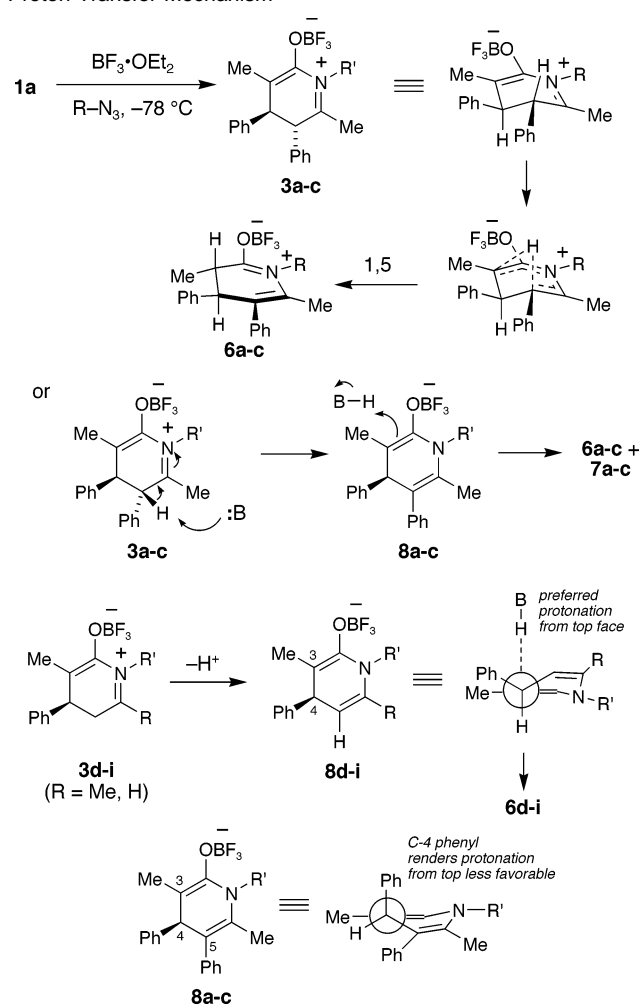
entry	dienone	azide	conditions	products (% yield; ratio) ^b
1	1a	2a	-78 °C/10 min	6a + 7a (82; 2:1)
2	1a	2b	-78 °C/10 min	6b + 7b (78; 2.3:1)
3	1a	2c	-78 °C/10 min	6c + 7c (85; 2:1)
4	1b	2a	-78 °C/0.5 h	6d (75)
5	1b	2b	-78 °C/0.5 h	6e (80)
6	1b	2c	-78 °C/0.5 h	6f (72)
7	1c	2a	0 °C/1 h	6g (62)
8	1c	2b	0 °C/1 h	6h (40)
9	1c	2c	0 °C/1 h	6i (43)
10	1d	2a	0 °C/0.5 h	6j + 7j (80; 2:1)
11	1d	2b	0 °C/0.5 h	6k + 7k (70; 3:1)
12	1d	2c	0 °C/0.5 h	6l + 7l (73; 2.5:1)

^a See Experimental Section for standard procedure. ^b All yields given are based on isolated material after chromatographic purification.

Scheme 4. Regioselective Azide Trapping of Unsymmetrical Cyclopentenyl Cation Intermediates

electrocyclization (Scheme 4, path a). No evidence for the alternative regioisomer **3'** (via path b) was seen in any of these examples. Regioselective attack at the less substituted terminus (as in entries 7–9) was also seen in intermolecular 3 + 2 trapping of the Nazarov intermediate by allyl silanes,¹⁵ and selectivity for nucleophilic trapping adjacent to the less substituted carbon (as in entries 4–12) was recently described for vinyl sulfide trapping processes.^{3f}

Once zwitterions **3** were formed, a rapid rearrangement to dihydropyridones apparently ensued. As noted above, this result stands in contrast to the earlier intermolecular studies. What

Scheme 5. Stereochemical Implications of 1,5-Hydrogen Shift vs Proton-Transfer Mechanism

features lead to these divergent reactivity paths? When taken in sum, it is the facile oxygenation seen in the intramolecular examples that is the most surprising. Conformational restrictions on the bicyclic 1,4-dipoles formed in those cases may diminish the rate of proton transfer or 1,5-hydrogen shift processes as compared with the simpler systems reported in this study. However, it should be noted that bicyclic zwitterions derived from dienone **1d** (entries 10–12) also show no evidence for oxygen incorporation. The relatively short reaction times and modified quenching conditions (vide infra) may also be responsible for the preferred formation of the dihydropyridone products.

In all cases examined, *trans* diastereomer **6** was formed predominantly or exclusively. In the cases employing dienone **1a** (Table 1, entries 1–3), the *trans* relative stereochemistry is consistent with suprafacial 1,5-hydrogen shift by the C-5 hydrogen (Scheme 5); however, this rationale does not account for the significant amounts of *cis* diastereomer **7**. Possible *in situ* epimerization of **6** to **7** was considered, but preliminary control experiments with **6a** indicate that this scenario is unlikely.¹⁶ Instead, proton transfer with diastereoselective enolate protonation seems most likely and is also consistent with the

(15) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1970–1973.

(16) Subjection of pure **6a** to the reaction conditions did not result in any epimerization to **7a**. Extended stirring in the presence of DBU also failed to effect epimerization.

earlier observation of products **4a** and **5a**, whose formation is most readily explained by this mechanism. Moreover, the low-temperature aqueous quench used in the optimized conditions introduces an abundance of proton donors and acceptors to the reaction mixture. The complete trans diastereoselectivity seen using dienones **1b** and **1c**, which lack nonhydrogen substituents at what will become C-5 of the eventual dihydropyridone (entries 4–9), is notable. The conformational preferences of enolates **8** arising from deprotonation of **3d–3i** provide one possible explanation. In these cases, the C-4 phenyl group may well sit in a quasi-equatorial orientation, in which enolate protonation is subject to product development control (avoidance of developing eclipsing interaction between the C-3 methyl and the C-4 phenyl groups by proton delivery syn to the C-4 phenyl). In the cases employing **1a** (entries 1–3), enolates **8a–8c** may adopt conformations in which the C-4 phenyl group assumes a quasi-axial position to avoid allylic strain with the neighboring C-5 phenyl, leading to erosion of the facial selectivity for protonation. The factors leading to lower selectivity in bicyclic examples (entries 10–12) are less clear and merit further study.

Conclusions

The trapping of various 2-oxidocyclopentenyl cation intermediates by added azides has been shown to be efficient and remarkably regioselective. The product dihydropyridones result from a Schmidt-type rearrangement, with the overall process entailing intercalation of the internal azide nitrogen atom between the dienone carbonyl and the neighboring α carbon. The sequence is believed to involve a transient 1,4-dipole which can undergo elimination to form either an exocyclic or an endocyclic alkene. In a number of cases, complete diastereoselectivity for the trans product was observed, consistent with either a highly stereoselective enolate protonation, or a concerted 1,5-hydrogen shift. In all examples employing unsymmetrically substituted dienones, complete regioselectivity in favor of attack on the less hindered end of the cyclopentenyl cation was seen. Future applications of this new domino process will focus on more elaborate reaction partners and selective functionalization of their products, and the application of this chemistry to polycyclic alkaloid targets.

Experimental Section

Representative Procedure: Formation of Dihydropyridones **6a and **7a**. Trapping of **1a** with Benzyl Azide **2a**.** To a solution of dienone (100 mg, 0.38 mmol) and benzyl azide **2a** (101 mg, 0.76 mmol) in dichloromethane (5 mL) was added $\text{BF}_3 \cdot \text{OEt}_2$ (53 μL , 0.42 mmol) in -78°C (dry ice/acetone bath). The reaction mixture was stirred for 10 min. Saturated NaHCO_3 solution (2 mL) was added to quench the reaction and after warming to rt the resulting mixture was extracted with CH_2Cl_2 (20 mL). The organic layer was washed with brine (10 mL) and dried over MgSO_4 . The solvent was then evaporated under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford the trans isomer **6a** (76.7 mg, 55% yield) and cis isomer **7a** (37.6 mg, 27% yield) as colorless oils.

6a. R_f 0.36 (5:1 hexanes/EtOAc); IR (microscope) 1667, 1599, 1494, 1453 cm^{-1} ; ^1H NMR (400 MHz, C_6D_6) δ 7.36–6.84 (m, 15H), 5.08 (d, 1H, $J = 15.4$ Hz), 4.58 (d, 1H, $J = 15.4$ Hz), 3.34 (d, 1H, $J = 7.0$ Hz), 2.94 (app pentet, 1H, $J = 7.0$ Hz), 1.67 (d, 3H, $J = 0.7$ Hz), 1.19 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 171.6, 141.5, 139.3, 138.1, 132.8, 129.5, 129.2, 128.7, 128.6, 128.5, 128.4, 127.4, 127.2, 126.8, 122.5, 50.7, 45.9, 40.7, 16.8, 13.5; HRMS (EI) calcd for $\text{C}_{26}\text{H}_{25}\text{ON}$ 367.1936, found m/z 367.1934. Anal. Calcd for $\text{C}_{26}\text{H}_{25}\text{ON}$: C, 84.98; H, 6.86; N, 3.81. Found: C, 84.67; H, 7.03; N, 3.72.

7a. R_f 0.32 (5:1 hexanes/EtOAc); IR (microscope) 1667, 1599, 1494, 1453 cm^{-1} ; ^1H NMR (400 MHz, C_6D_6) δ 7.18–6.91 (m, 15H), 5.16 (d, 1H, $J = 15.7$ Hz), 4.46 (d, 1H, $J = 15.7$ Hz), 3.33 (s, 1H), 3.02 (dq, 1H, $J = 2.0, 7.3$ Hz), 1.65 (d, 3H, $J = 0.5$ Hz), 1.37 (d, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 172.7, 141.0, 140.5, 138.2, 132.1, 129.1, 128.4, 128.3, 128.1, 127.4, 127.3, 127.0, 126.7, 126.6, 118.1, 50.9, 45.2, 43.9, 17.7, 16.7; HRMS (EI) calcd for $\text{C}_{26}\text{H}_{25}\text{ON}$ 367.1936, found m/z 367.1929.

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Supporting Information Available: Experimental procedures and spectral data for **1b–1d** and spectral data for all azide adducts **4–7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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