

Reactions of Nitroso Hetero-Diels–Alder Cycloadducts with Azides: Stereoselective Formation of Triazolines and Aziridines

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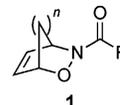
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The addition of azides to acylnitroso hetero-Diels–Alder cycloadducts derived from cyclopentadiene affords *exo*-triazolines in excellent yield. The reaction is greatly affected by the level of alkene strain, while sterically demanding azides do not hinder the reaction. Conversion of the triazolines to aziridines is also described.

The nitroso hetero-Diels–Alder (HDA) reaction provides a useful method for incorporating 1,4-aminoalcohol moieties into a carbon framework in a diastereoselective fashion.¹ Stereoselective nitroso HDA reactions² have also provided access to new classes of synthetically useful molecules. While a variety of nitroso species have been investigated for use in HDA reactions,³ our research has largely focused on acyl- and carboxylnitroso species due to their ease of synthesis and high reactivity. Hydroxamic acids and *N*-hydroxy carbamates, when oxidized in the presence of cyclic dienes, afford hetero-Diels–Alder adducts **1**.^{1a,4} Reduction of the N–O bond of **1**

results in amino alcohols,⁵ which are suitable intermediates for the synthesis of natural products,⁶ carbocyclic nucleosides,⁷ and other important biologically active molecules.⁸ The C–O bond can be cleaved through metal-mediated reactions in the presence of nucleophiles⁹ or electrophiles,¹⁰ yielding 1,4-benzodiazepines¹¹ and other useful synthetic intermediates. The *N*-acyl group can also be cleaved under relatively mild conditions (where R = alkyl or aryl).¹² While extensive chemistry has been developed that capitalizes on the strained nature of **1**, modifications of the olefin have been mainly limited to epoxidation,^{6c} dihydroxylation,¹³ and oxidative cleavage.¹⁴



In an effort to expand upon the versatility of **1**, we were interested in selective functionalization of the olefin to produce new structural features. Encouraged by a recent report highlighting the addition of nitrile oxides to **1**,¹⁵ we wish to report on studies regarding the reactivity of **1** with azides to form triazolines and their subsequent transformation to aziridines.

Intermolecular [3 + 2] cycloaddition reactions of azides to strained bicyclic alkenes are well-documented in the literature.¹⁶ Examples include additions to norbornene, 2-azabicyclo[2.2.1]-hept-5-en-3-one (ABH) **2** to afford 2'-3'-epimino carbocyclic

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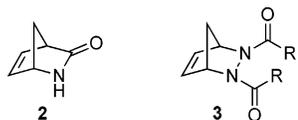
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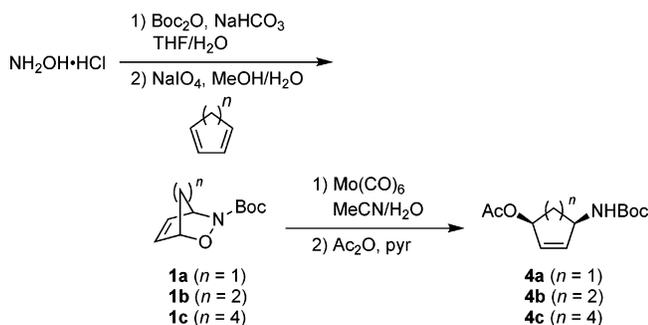
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nucleosides,¹⁷ 2,3-diazabicyclo[2.2.1]hept-5-enes **3** to afford 1,4-dihydropyridines,¹⁸ as well as many other strained systems.^{16h,19} However, the addition of azides to bicyclic oxazines such as **1** has not been disclosed in the literature.

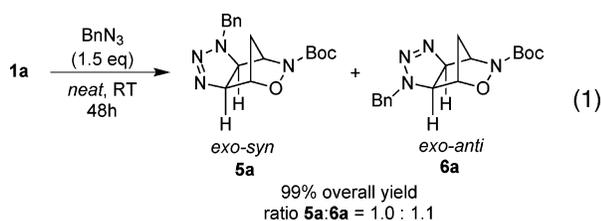


Since we wished to probe the role of olefin strain on reactivity with azides, we chose to subject the olefins of **1a–c** as well as protected amino alcohols **4a–c** to reactions with various azides (Scheme 1). Oxazines **1a–c** can be prepared on a large scale from hydroxylamine hydrochloride in two steps in moderate to high yields.²⁰ N–O bond reduction with Mo(CO)₆²¹ followed by protection of the resulting alcohol yielded monocyclic olefins **4a–c**.²²

SCHEME 1. Synthesis of Cycloadducts and Protected Amino Alcohols



We were very pleased to find that, when **1a** was treated with benzyl azide,²³ the regioisomeric *exo*-triazolines **5a** and **6a** were obtained in quantitative yield after stirring for 2 days neat at room temperature (eq 1). Similar reactions of 2-azabicyclo[2.2.2]-hept-5-en-3-ones reportedly required high pressure for the cycloaddition reaction to occur.^{17c} The *exo*-specificity of the reaction is in agreement with what has been reported in the literature in related reactions of bicyclo[2.2.1]hept-5-ene-2,3-dicarboximides,^{16h} ABH (**2**) and derivatives,²⁴ 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives, and **3**.^{18,25}



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TABLE 1. Reaction of **1a** with Various Azides

entry	R	conditions ^a	products ^b	yield ^c (%)
1	Bn	A	5a/6a	99
2	Bn	B	5a/6a	99
3	Ad ^d	B	5b/6b	95
4	Bn	C	5a/6a	88
5	<i>n</i> -octyl	C	5c/6c	99
6	cyclopentyl	C	5d/6d	97
7	Ph	C	5e/6e	97
8	Bn	D	5a/6a	88
9	<i>n</i> -octyl	D	5c/6c	81
10	cyclopentyl	D	5d/6d	86
11	Ad ^d	D	5b/6b	85
12	Ph	D	5e/6e	99

^a A = neat, rt, 2 days; B = CHCl₃, rt, 4 weeks; C = CHCl₃, reflux, 3 days; D = PhCH₃, reflux, 4 h. ^b Ratio of **5:6** = 1.0:1.1 in all cases as determined by ¹H NMR. ^c Isolated yield. ^d Ad = 1-adamantyl.

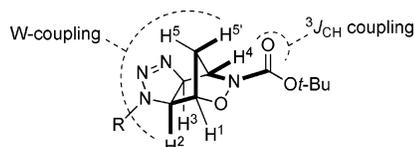


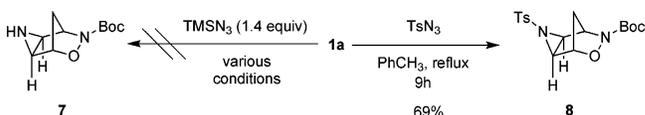
FIGURE 1. Observed W-coupling and ³J_{CH}-coupling of *exo*-triazolines.

In an effort to ascertain the limitations of this chemistry, we treated alkene **1a** with various organic azides under a number of reaction conditions (Table 1). The reaction proceeded equally well refluxing in toluene or chloroform (entries 4 and 8); however, it was sluggish when stirred in solution at room temperature (entry 2). The steric bulk of the azide had little effect on either the regioselectivity or yield of the reaction, with primary, secondary, tertiary, and aryl azides affording triazolines **5** and **6** in excellent yield (entries 8–12).

The structures of **5** and **6** were assigned based on single-crystal X-ray diffraction for **5a** and **6a** and by 2D NMR experiments for **5b–e** and **6b–e**. The *exo* stereochemistry was confirmed from the observed ⁴J-coupling (“W-coupling”) of H² and H³ with H^{5'}, but not with H⁵. The position of the Boc group relative to the R group was confirmed by HMBC experiments based on the observed ³J-coupling between H⁴ (or H^{1'}) and the carbonyl (Figure 1).²⁶

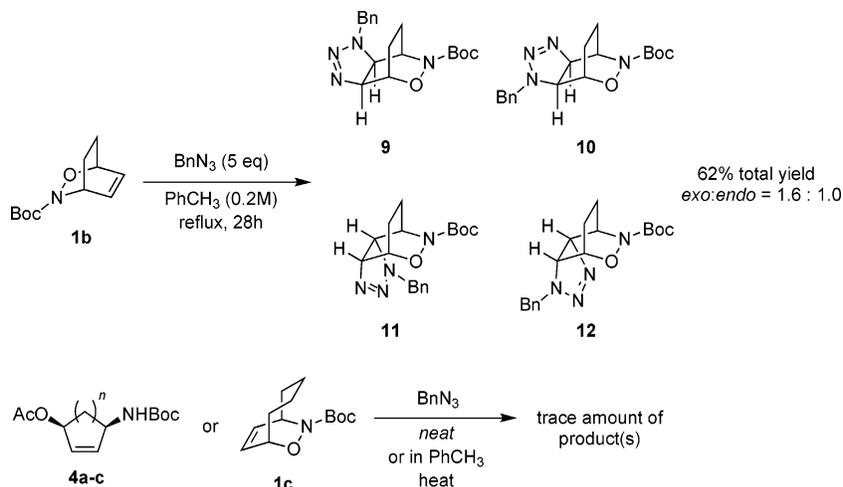
Trimethylsilyl azide has been reported to add to norbornene systems and other bicyclic olefins to yield triazolines and/or aziridines directly.^{18,27} Since we were interested in obtaining the unsubstituted aziridine **7**, **1a** was subjected to azidotrimethylsilane (Scheme 2). Under a variety of reaction conditions

SCHEME 2. Reaction of **1a** to Yield Aziridines Directly



(neat, 25–80 °C; PhCH₃, 25–110 °C), only decomposition of the alkene was observed. Tosyl azide²⁸ has also been reported

SCHEME 3. Reaction of Other Alkenes with Benzyl Azide



to afford aziridines directly,^{17b} and upon treatment of **1a** with tosyl azide, we were able to obtain aziridine **8** in good yield.

Substantial rate increases were reported for [3 + 2] cycloadditions (especially “Click chemistry”²⁹ reactions) when both reactants were “floated” on water compared to reactions that were stirred with or without solvent.³⁰ We found no significant increase in the rate of reaction when **1a** was treated with benzyl azide “on water” or in a concentrated solution of toluene “on water” when compared to stirring the two reagents neat at room temperature.

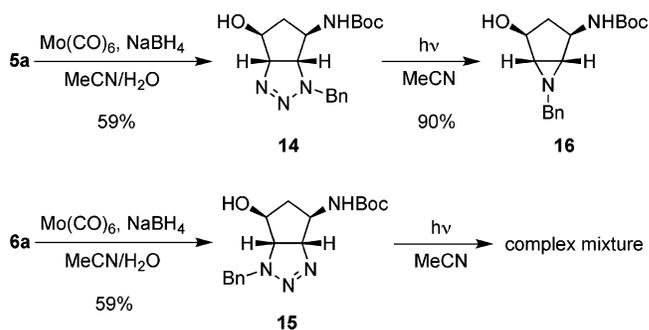
The effect of alkene strain on the formation of triazolines was also studied. When the bicyclo[2.2.2] cycloadduct **1b** was treated with 1.4 equiv of benzyl azide neat at room temperature, no reaction was observed. When **1b** was treated with a large excess of benzyl azide in refluxing toluene, however, a mixture of triazolines **9–12** was obtained in moderate yield (Scheme 3). In contrast to bicyclo[2.2.1] cycloadduct **1a**, *endo*-triazolines **11** and **12** were formed along with the *exo*-triazolines **9** and **10**. The influence of ring strain on reactivity was especially evident when bicyclo[2.2.4] cycloadduct **1c** and monocyclic alkenes **4a–c** were subjected to the same conditions. When heated neat or in toluene, only trace amounts of triazoline products were observed.

In the course of this study, we found that triazolines **5a** and **6a** were stable to temperatures up to 120 °C and did not decompose readily in ambient light. When irradiated below ~300 nm, **5a** and **6a** readily underwent photolytic conversion to aziridine **13** in 2–4 h (Table 2). At wavelengths higher than

TABLE 2. Photolysis of Triazolines **5a** and **6a**

entry	isomer	solvent	filter	time ^a (h)	yield ^b (%)
1	5a	CHCl ₃	quartz	1.5	65
2	6a	CHCl ₃	quartz	3.5	78
3	5a	CH ₃ CN	vykor	2	75
4	6a	CH ₃ CN	vykor	3	67
5	5a	CH ₃ CN	pyrex	20	93

^a Reactions were monitored by TLC and/or ¹H NMR. ^b Isolated yield.

SCHEME 4. Structural Elaboration of Triazolines **5a** and **6a**

300 nm, the time required for the reaction to proceed to 100% conversion increased greatly (entry 5).

Surprisingly, N–O bond reduction of triazolines **5a** and **6a** proceeded cleanly to afford triazolines **14** and **15** without decomposition of the triazoline ring (Scheme 4). Triazoline **14** was cleanly transformed to aziridine **16** upon irradiation in acetonitrile; however, a complex mixture of products was observed when triazoline **15** was subjected to the same conditions. The reason for this result is unclear at this time and will be investigated further.

In summary, the addition of azides to cycloadduct **1a** affords a mixture of *exo*-triazolines in good to excellent yield. The steric bulk of the azide does not appear to play a significant role in the course of the reaction; however, the reactivity of the alkene

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was diminished significantly in cycloadducts derived from larger cyclic dienes (**1b** and **1c**) or in monocyclic alkenes (**4a–c**).

Experimental Section

General Procedure for the Synthesis of Triazolines Using Method A. The alkene (1 mmol) and azide (1.5 mmol) were combined and stirred neat at 25 °C in a single-necked round-bottomed flask. The progress of the reaction was monitored by TLC or ¹H NMR for the disappearance of the alkene, and the crude material was chromatographed through silica gel 60 (230–400 mesh).

General Procedure for the Synthesis of Triazolines Using Method B. The alkene (1 mmol) and azide (1.5 mmol) were dissolved in 10 mL of CHCl₃ in a single-necked round-bottomed flask and stirred at 25 °C. The progress of the reaction was monitored by TLC or ¹H NMR for the disappearance of the alkene (typically 4 weeks), and the crude material was chromatographed through silica.

General Procedure for the Synthesis of Triazolines Using Method C. The alkene (1 mmol) and azide (1.5 mmol) were dissolved in 10 mL of CHCl₃ in a single-necked round-bottomed flask fitted with a condenser and heated to reflux in an oil bath (oil temp = 80 °C). The progress of the reaction was monitored by TLC or ¹H NMR for the disappearance of the alkene (typically 3 days), and the crude material was chromatographed through silica.

General Procedure for the Synthesis of Triazolines Using Method D. The alkene (1 mmol) and azide (1.5 mmol) were dissolved in 10 mL of PhCH₃ in a single-necked round-bottomed flask fitted with a condenser and heated to reflux in an oil bath (oil temp = 125 °C). The progress of the reaction was monitored by TLC or ¹H NMR for the disappearance of the alkene (typically 3–4 h), and the crude material was chromatographed through silica.

tert-Butyl (3α,4β,7β,7α)-1-Benzyl-3a,4,7,7a-tetrahydro-4,7-methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(1H)-carboxylate (5a) and tert-Butyl (3α,4β,7β,7α)-3-Benzyl-3a,4,7,7a-tetrahydro-4,7-methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(3H)-carboxylate (6a). Prepared following the general procedure for the synthesis of triazolines using Method A. Cycloadduct **1a** (198 mg, 1.01 mmol) and benzyl azide (211 mg, 1.58 mmol) were reacted for 48 h. The brown crude material was chromatographed through 15 g of silica using a solvent gradient of 100% CH₂Cl₂ to 98% CH₂Cl₂/EtOAc to afford triazoline **6a** (159 mg, 48% yield) as a white solid, then 85% CH₂Cl₂/EtOAc to afford triazoline **5a** (170 mg, 51% yield) as a white solid (99% total combined yield). Analytical and X-ray crystallographic samples of **5a** and **6a** were prepared by recrystallization from EtOAc/hexanes. **5a**: mp = 104–105 °C; λ_{max} = 255 nm; ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.27 (m, 5H), 4.92 (s, 1H), 4.90 (d, *J* = 14.5 Hz, 1H), 4.82 (d, *J* = 9.8 Hz, 1H),

4.72 (d, *J* = 14.5 Hz, 1H), 4.09 (s, 1H), 3.55 (d, *J* = 9.8 Hz, 1H), 1.70 (dt, *J* = 11.4, 1.5 Hz, 1H), 1.45 (d, *J* = 11.5 Hz, 1H), 1.39 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 156.4, 135.6, 128.8, 128.24, 128.17, 84.6, 82.6, 79.9, 61.2, 59.3, 53.4, 32.4, 27.9 ppm; HRMS (FAB), *m/z* (M + H) calcd for C₁₇H₂₃N₄O₃⁺, 331.1770; obsd, 331.1745. **6a**: mp = 100–101 °C; λ_{max} = 255 nm; ¹H NMR (500 MHz, CDCl₃) δ 7.35–7.24 (m, 5H), 4.92 (d, *J* = 14.7 Hz, 1H), 4.85 (s, 1H), 4.84 (d, *J* = 9.9 Hz, 1H), 4.61 (d, *J* = 14.7 Hz, 1H), 4.09 (s, 1H), 3.50 (d, *J* = 9.9 Hz, 1H), 1.68 (d, *J* = 11.5 Hz, 1H), 1.45–1.43 (m, 10H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 156.4, 135.6, 128.8, 128.3, 128.2, 83.7, 82.7, 79.6, 61.5, 59.9, 53.6, 32.3, 27.9 ppm; HRMS (FAB), *m/z* (M + H) calcd for C₁₇H₂₃N₄O₃⁺, 331.1770; obsd, 331.1753.

General Procedure for Photolysis of Triazolines. tert-Butyl (1α,2β,4β,5α)-3-Benzyl-6-oxa-3,7-diazatricyclo[3.2.1.0^{2,4}]octane-7-carboxylate (13). **5a** (333 mg, 1.01 mmol) was dissolved in 300 mL of degassed CH₃CN and transferred to a 450 mL photochemical reaction vessel. The solution was irradiated in an immersion-well reactor under a stream of Ar with a Hanovia 450 W mercury lamp equipped with a Vycor filter sleeve. Reaction progress was monitored by TLC and ¹H NMR for the disappearance of **5a**. After 3 h, the reaction was concentrated, and the crude material was chromatographed through 30 g of silica using a gradient consisting of 100% CH₂Cl₂ to 95% CH₂Cl₂/EtOAc to afford **13** as a colorless oil (205 mg, 67% yield): ¹H NMR (500 MHz, CDCl₃) δ 7.35–7.27 (m, 5H), 4.79 (m, 1H), 4.62 (m, 1H), 3.40 (d, *J* = 13.5 Hz, 1H), 3.35 (d, *J* = 14.0 Hz, 1H), 2.29–2.22 (m, 3H), 1.50 (s, 9H), 1.39 (d, *J* = 10.5 Hz, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 157.5, 138.6, 128.4, 127.7, 127.3, 82.3, 79.9, 60.7, 59.1, 37.1, 36.7, 29.4, 28.2 ppm; MS (FAB) *m/z* 303 (M + H), 247, 203, 171 (100%); HRMS (FAB) *m/z* (M + H) calcd for C₁₇H₂₃N₂O₃⁺, 303.1709; obsd, 303.1712.

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Supporting Information Available: Experimental details and characterization data for triazolines **5a–e**, **6a–e**, **9–12**, and **14–16**, including 1D and 2D NMR spectra and X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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