Convenient Access to Bicyclic and Tricyclic Diazenes
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Convenient Access to Bicyclic and Tricyclic Diazenes

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Heating the tosylhydrazone of an ω-alkenyl ketone or aldehyde to reflux in toluene in the presence of K$_2$CO$_3$ delivered the bicyclic diazene. Irradiation of the diazene converted it to the cyclopropane. This appears to be a generally useful method for the construction of substituted cyclopentanes and cyclohexanes.

Carbocycle construction by intramolecular 1,3-dipolar cycloaddition has long been a workhorse of organic synthesis. Yet one of the simplest of such ring-forming reactions, the generation and intramolecular cycloaddition of an ω-diazo alkene to form the cyclic diazene (Scheme 1, 1a → 2a), has not been developed as a generally useful synthetic method. We have found that simply heating the tosylhydrazone of a ketone such as 1a to reflux in toluene in the presence of K$_2$CO$_3$ delivered the bicyclic diazene 2a. Irradiation of 2a converted it to the cyclopropane 3a. While tautomerization of 2a equilibrated it to the more stable cyclic hydrazone 4. Hydrogenation of 2a followed by acylation led to the cyclic hydrazide 5, reduction of which with SmI$_2$ generated the cyclopentane 6. This appears to be a generally useful method for the construction of substituted cyclopentanes and cyclohexanes.

We have briefly (Table 1; all yields in Tables 1 and 2 are for pure isolated products) examined the scope of this cyclization. Both five-membered and six-membered ring formation proceeded efficiently. The geometry of the starting alkene appeared (entry 3) to be maintained in the product. While the cyclization to form the cyclopentane (Scheme 1, structure established by X-ray analysis) proceeded with significant diastereocontrol, (entry 7) that the cyclohexane (entry 6) did not. As expected, ω-alkenyl aldehydes (entry 5) also cyclized efficiently, with useful diastereoccontrol. It is also noteworthy (entry 7) that cyclic ketones participated smoothly. With the

SCHEME 1

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There is precedent for the conversion of 1a to 2a. In 1980, Padwa reported that heating the sodium salt of an ω-alkenyl tosylhydrazone gave the tautomerized dihydroazirazole analogous to 4. Alternatively, when the diazo intermediate was generated by heating the ω-alkenyl ketone with an N-aminoaziridine, the cyclic diazene was isolated. Curiously, there had been very little further work on this approach to carbocyclic construction since that time.

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(1) For a recent review of the use of intramolecular dipolar cycloaddition in target-directed organic synthesis, see: Nair, V.; Suja, T. D. Tetrahedron 2007, 63, 12247. It should be noted that the intramolecular cycloaddition of an ω-diazo alkene to form the cyclic diazene is not mentioned in this thorough review.


(4) For the single instance of the use of intramolecular addition of a diazo alkane to an alkene in natural product synthesis, see: Schultz, A. G.; Puig, S. J. Org. Chem. 1985, 50, 915. Note that in this case, conversion of the aldehyde to the intermediate diazo alkane by reaction with an N-aminoaziridine also led to the nitrile as a major byproduct.

(5) The structure of 2a was established by X-ray analysis.


(7) For leading references to efforts toward cyclopropane construction by the conversion of ketones into carbene equivalents, see: Motherwell, W. B. J. Org. Chem. 2001, 624, 41.

results reported here, the generation and intramolecular cycloaddition of a (presumed) intermediate diazo alkene to form the cyclic diazene appears to now be a generally applicable synthetic method.

As outlined in Scheme 1, the product cyclic diazenes are versatile intermediates for further transformation. We were pleased to observe that the diazene 2a was readily tautomerized to the dihydropyrazole 4, and was easily reduced to the tetrahydropyrazole, isolated as the bis-benzamide 5. Such bicyclic dihydro and tetrahydro pyrazoles such as 4 and 5 should be useful scaffolds for pharmaceutical discovery. It was equally exciting that the benzamide 5 could be further reduced to the cyclopentane 6. Such aminated cyclopentanes, useful intermediates for alkaloid synthesis,9 are not readily prepared by other means.

The straightforward conversion of 1a to the cyclopropane 3 was particularly interesting. We have made a preliminary investigation (Table 2) of this reaction, which appears to be general. Intramolecular cyclopropanation is usually carried out with ω-diazo ketones or esters.10 The net conversion of an ω-alkenyl ketone or aldehyde to the corresponding carbene with subsequent intramolecular cyclopropanation has been a longstanding goal. Although strategies have been developed for effecting this transformation,7 the protocol described here appears to be a practical alternative.

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<th>TABLE 1. Bicyclic and Tricyclic Diazenes</th>
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a Yields are for pure isolated products. b The product was an ~5:1 mixture of diastereomers. c Ar = 4-methoxyphenyl. d The alkene was an ~5:1 Z/E mixture. e The product was an ~5:1 mixture of diastereomers. f The product was an ~6:1 mixture of diastereomers. The major product had a 13C NMR methine at δ = 100.2. The minor diastereomer 13C NMR methine was at δ = 95.1. g The product was an ~1:1 mixture of diastereomers.

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<th>TABLE 2. Cyclopropanes from Cyclic Diazenes</th>
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The approach delineated here makes cyclic diazenes such as 

2a routinely available. We expect that this approach to car-
bocyclic construction by intramolecular dipolar cycloaddition
will have many applications both in natural product synthesis
and in medicinal chemistry.11,12

Experimental Section

Diazene 2a. Ketone 1a13 (85 mg, 0.45 mmol) and tosylhydrazine
(1.07 equiv, 92 mg, 0.49 mmol) were stirred in MeOH (2 mL) at
room temperature overnight. The MeOH was removed under
reduced pressure, the crude hydrazone was redissolved in toluene
(3 mL), K2CO3 (6 equiv, 385 mg, 2.8 mmol) was added, and the
reaction mixture was partitioned between CH2Cl2 and, sequentially,
water and brine. After cooling to room temperature, the reaction mixture
was concentrated and chromatographed to yield cyclopropane
apparatus (350 nm). The reaction mixture was concentrated and
toluene was photolyzed for 24 h at room temperature in a Rayonet
solution of the recrystallized diazene

3H), 1.05 (m, 1H);13C NMR (major isomer)
3.10 (m, 1H), 2.40 (m, 1H), 2.25 (m 1H), 2.05 (m, 2H), 1.40 (s
3H), 1.05 (m, 1H); 13C NMR (major isomer) δ u 114.2, 142.5, 100.8,
81.0, 44.2, 42.1; d 128.5, 126.9, 126.5, 42.3, 42.0; HRMS calcd for C13H16 (MH+
+) 201.1392, obsd 201.1397. The diazene 2a was recrystallized from hexane as a 20:1 mixture (1H NMR) of isomers,
mp 69 °C.

(1R*,3R*,5S*)-1-Methyl-3-phenylbicyclo[3.1.0]hexane (3a). A
solution of the recrystallized diazene 2a (76 mg, 0.38 mmol) in
toluene was photolyzed for 24 h at room temperature in a Rayonet
apparatus (350 nm). The reaction mixture was concentrated and
chromatographed to yield cyclopropane 3a (28 mg, 42% yield) as
a colorless oil: TLC Rf (5% MTBE/ CH2Cl2) 0.45; IR (cm−1) 3027, 2958, 1442, 1270;1H NMR δ 7.10−7.35 (m, 5H),
4.50 (dd, J = 2.2, 18.0 Hz, 1H), 4.30 (dd, J = 8.0, 18.0 Hz, 1H),
3.10 (m, 1H), 2.40 (m, 1H), 2.25 (m 1H), 2.05 (m, 2H), 1.40 (s
3H), 1.05 (m, 1H); 13C NMR (major isomer) δ u 172.3, 142.5, 131.6, 128.7, 128.5, 128.2, 127.7, 127.6, 127.0, 126.5, 53.3, 45.2, 24.9; HRMS calcd for C27H27N2O2 (MH+
+) 413.2229, obsd 413.2227. The diazene 2a was recrystallized from hexane as a 20:1 mixture (1H NMR) of isomers,
mp 69 °C.

Dihydropyrazole 4. To a stirred solution of the recrystallized diazene 2a (47 mg, 0.24 mmol) in MeOH (2 mL) was added K2CO3
(200 mg, 1.5 mmol) at rt. The reaction mixture was stirred in the
dark at rt for 20 h, then concentrated. The residue was chromatographed
to yield 4 (37 mg, 79% yield) as a colorless oil: TLC Rf
(MTBE) 0.42; IR (cm−1) 3309, 2956, 1649, 1451; 1H NMR
(MeOD) δ 7.00−7.20 (m, 5H), 6.65 (s, 1H), 3.20 (s, 1H), 2.90−3.10
(m, 2H), 2.40 (m, 1H), 2.05 (m, 1H), 1.80 (t, J = 12 Hz,1H), 1.50
(q, 1H), 1.35 (3H); 13C NMR (MeOD) δ u 144.6, 71.9, 50.0,
40.0; 13C NMR (MeOD) δ d 149.4, 129.5, 127.8, 127.3, 59.6, 45.4,
23.6; HRMS calcd for C16H14N2O2 (M+) 200.1313, obsd 200.1314.

Bis-benzamide 5. A suspension of the recrystallized diazene 2a
(85 mg, 0.43 mmol) and PtO2 (10 mg) in MeOH (3 mL) was stirred
at rt under H2 atmosphere for 3 h. The reaction mixture was filtered
and concentrated to give the crude diamine (84 mg). To a stirred
solution of the crude diamine and Et3N (182 mg, 1.8 mmol) in
toluene (3 mL) was added benzoyl chloride (250 mg, 1.78 mmol)
at 0 °C. After stirring at rt overnight, the reaction mixture was
concentrated and chromatographed to yield pyrazolidine 5 (105 mg,
60% yield) as a pale yellow solid: mp 168 °C; TLC Rf (5% MTBE/
CH2Cl2) 0.62; IR (cm−1) 3054, 2955, 1667, 1396, 1234; 1H NMR
δ 7.00−7.70 (m, 15H), 3.00−4.10 (m, 3H), 2.50−2.80 (m, 2H),
2.10−2.40 (m, 1H), 1.80 (s, 3H), 1.60−1.75 (m, 1H), 1.20 (m,
1H); 13C NMR δ u 172.3, 167.3, 142.5, 134.6, 133.7, 72.1, 54.0,
47.0, 40.2; 13C NMR δ d 131.6, 130.4, 128.7, 128.5, 128.2, 127.7,
127.6, 127.0, 126.5, 53.3, 45.2, 24.9; HRMS calcd for C27H29N2O2
(MH+) 411.2072, obsd 411.2067.

Bis-benzamide 6. To a stirred solution of pyrazolidine 5 (25 mg,
0.06 mmol) in MeOH (0.5 mL) was added SnCl2 (3 mL, 0.3
mmol, 0.1 M in THF) at rt. After stirring for 30 min at rt, the
reaction mixture was concentrated and chromatographed to yield
6 (19 mg, 76% yield) as a pale yellow solid: mp 155 °C; TLC Rf
(5% MTBE/PE) 0.31; IR (cm−1) 3312, 2918, 1638, 1530, 1299;
1H NMR δ 7.00−7.90 (m, 15H), 6.30 (s, 1H), 3.75 (m, 1H), 3.20
(m, 2H), 2.10−2.40 (m, 3H), 1.60 (s, 1H), 1.70−1.80 (m, 1H),
1.10−1.30 (m, 2H); 13C NMR δ u 167.6, 166.0, 143.2, 133.9, 133.4,
61.8, 48.9, 40.2, 37.2; 13C NMR δ d 130.6, 130.2, 127.7, 127.6,
127.5, 126.0, 125.9, 125.8, 48.8, 39.8, 26.0; HRMS calcd for C27H29N2O2
(MH+) 413.2229, obsd 413.2227.

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spectrometric measurements, supported by the NSF (0541775),
Dr. Glenn Yap for the X-ray analysis, and the NIH (GM60287)
for financial support.

Supporting Information Available: Experimental proce-
dures, details of the X-ray analysis, and 1H and 13C NMR spectra
for all new compounds. This material is available free of charge
via the Internet at http://pubs.acs.org.

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