JOC*Note*

Convenient Access to Bicyclic and Tricyclic Diazenes

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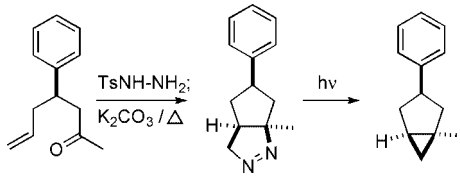
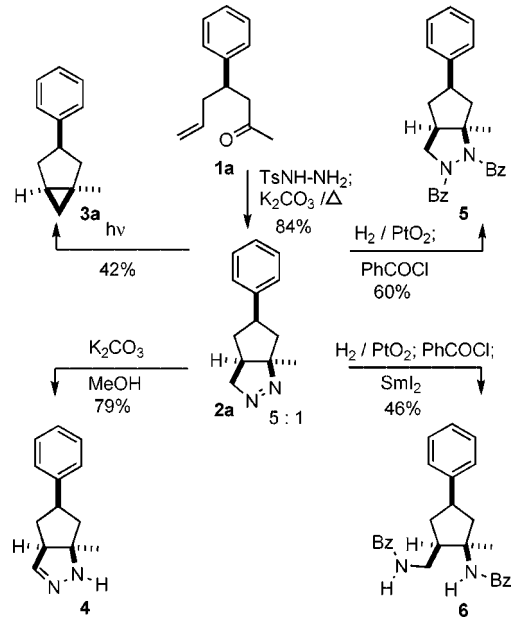


Heating the tosylhydrazone of an ω-alkenyl ketone or aldehyde to reflux in toluene in the presence of K_2CO_3 delivered the bicyclic diazene. Irradiation of the diazene converted it to the cyclopropane. This appears to be a generally useful method for the construction of substituted cyclopentanes and cyclohexanes.

Carbocycle construction by intramolecular 1,3-dipolar cycloaddition has long been a workhorse of organic synthesis.[1,2] 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**), had not been developed as a generally useful synthetic method.[3,4] We have found that simply heating the tosylhydrazone of a ketone such as **1a** to reflux in toluene in the presence of K_2CO_3 delivered the bicyclic diazene **2a**.[5] Irradiation of **2a** converted it to the cyclopropane **3a**,[6,7] while tautomerization[3] of **2a** equilibrated it to the more stable cyclic hydrazone **4**. Hydrogenation of **2a** followed by acylation led to the cyclic hydrazide **5**, reduction[8] 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.

SCHEME 1



There is precedent[3,4] for the conversion of **1a** to **2a**. In 1980, Padwa[3a] reported that heating the sodium salt of an ω-alkenyl tosylhydrazone gave the tautomerized dihydropyrazole 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[3b−e,4] on this approach to carbocyclic construction since that time.

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, cyclization to form the cyclohexane (entry 6) did not. As expected,[3a] ω-alkenyl *aldehydes* (entry 5) also cyclized efficiently, with useful diastereocontrol. It is also noteworthy (entry 7) that *cyclic* ketones participated smoothly. With the

(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-alkenyl diazo alkane to form the cyclic diazene is not mentioned in this thorough review.

(2) For more recent examples of C−C ring construction by intramolecular dipolar cycloaddition, see: (a) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398. (b) Belanger, G.; April, M.; Dauphin, E.; Roy, S. *J. Org. Chem.* **2007**, *72*, 1104. (c) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram., N. *Angew. Chem, Int. Ed.* **2007**, *46*, 6159. (d) Pouilhes, A.; Amado, A. F.; Vidal, A.; Langlois, Y.; Kouklovsky, C. *Org. Biomol. Chem.* **2008**, *6*, 1502.

(3) There have been isolated reports over the years of the cyclization of simple alicyclic ω-alkenyl ketones and aldehydes to the cyclic diazenes. For the most detailed account, see: (a) Padwa, A.; Ku, H. *J. Org. Chem.* **1980**, *45*, 3756. (b) Brinker, U. H.; Schrievers, T.; Xu, L. *J. Am. Chem. Soc.* **1990**, *112*, 8609. (c) Ashby, E. C.; Park, B.; Patil, G.; S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424. (d) Jung, M. E.; Huang, A. *Org. Lett.* **2000**, *2*, 2659. In each of these cases, ready tautomerization has commonly been observed. (e) For alternative methods for converting ketones to the corresponding diazo compounds, see: Miller, P. C.; Gaspar, P. P. *J. Org. Chem.* **1991**, *56*, 5101.

(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.

(6) For an early report of the photolysis of cyclic diazenes to make cyclopropanes, see: (a) Rinehart, K. L., Jr.; Van Auken, T. L. *J. Am. Chem. Soc.* **1960**, *82*, 5251. (b) Van Auken, T. L.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3736.

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

(8) For the reduction of hydrazine amides with SmI_2, see: Shirakawa, S.; Lombardi, P. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 9974.

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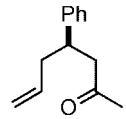
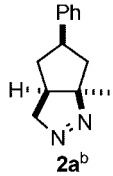
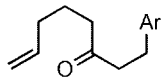
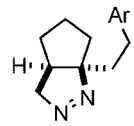
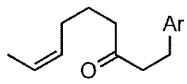
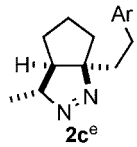
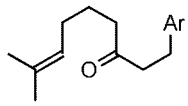
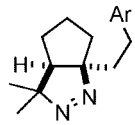
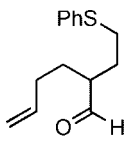
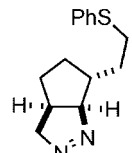
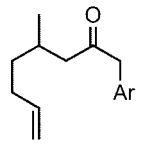
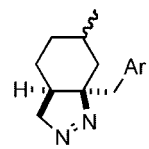
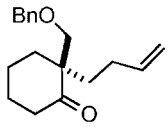
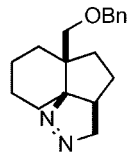
TABLE 1. Bicyclic and Tricylic Diazenes

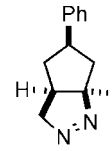
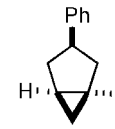
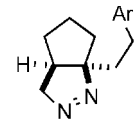
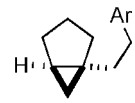
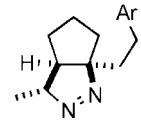
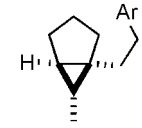
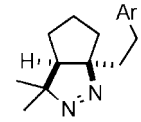
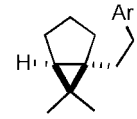
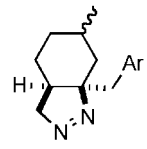
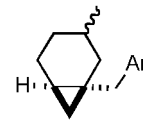
Entry	Ketone	Diazene	Yield (%)[a]
1	 **1a**	 **2a**[b]	84
2	 **1b**[c]	 **2b**	76
3	 **1c**[d]	 **2c**[e]	70
4	 **1d**	 **2d**	68
5	 **1e**	 **2e**[f]	91
6	 **1f**	 **1f**[g]	72
7	 **1g**	 **2g**	68

[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 ^{13}C NMR methine at δ = 100.2. The minor diastereomer ^{13}C NMR methine was at δ = 95.1. [g] The product was an ~1:1 mixture of diastereomers.

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.

TABLE 2. Cyclopropanes from Cyclic Diazenes

Entry	Diazene	Cyclopropane	Yield (%)
1	 **2a**	 **3a**	42
2	 **2b**	 **3b**	89
3	 **2c**	 **3c**	71
4	 **2d**	 **3d**	74
5	 **2f**	 **3f**	80

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 α-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 long-standing goal. Although strategies have been developed for effecting this transformation,[7] the protocol described here appears to be a practical alternative.

(9) Kende, A. S.; Liu, K.; Brands, K. M. J. *J. Am. Chem. Soc.* **1995**, *117*, 10597.

(10) For a representative cyclization of an ω-alkenyl diazo ketone, see: Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699.

The approach delineated here makes cyclic diazenes such as **2a** routinely available. We expect that this approach to carbocyclic 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 **1a**[13] (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), K_2CO_3 (6 equiv, 385 mg, 2.8 mmol) was added, and the reaction mixture was heated in a sealed vial at 120 °C (oil bath) for 18 h. After cooling to room temperature, the reaction mixture was partitioned between CH_2Cl_2 and, sequentially, water and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield diazene **2a** (76 mg, 84% yield, 5:1 mixture of two isomers based on ^{1}H NMR) as a pale yellow solid: mp 64 °C; TLC R_f (5% MTBE/ CH_2Cl_2) 0.45; IR (cm^{-1}) 3027, 2958, 1442, 1270; ^{1}H 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); ^{13}C NMR (major isomer) δ u[14] 142.5, 100.8, 81.0, 44.2, 42.1; d 128.5, 126.9, 126.5, 42.3, 42.0; HRMS calcd for $C_{13}H_{17}N_2$ (MH^+) 201.1392, obsd 201.1397. The diazene **2a** was recrystallized from hexane as a 20:1 mixture (^{1}H NMR) of isomers, mp 69 °C.

(1*R,3*R**,5*S**)-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 R_f (2% MTBE/PE) 0.54; IR (cm^{-1}) 3011, 2932, 1449, 1021; ^{1}H NMR δ 7.05−7.30 (m, 5H), 3.55 (m, 1H), 2.45 (m, 1H), 2.15 (m, 1H), 1.90 (dd, J = 6.4, 13.2 Hz, 1H), 1.80 (m, 1H), 1.20 (s, 3H), 1.05 (m, 1H), 0.45 (m, 1H), 0.35 (m, 1H); ^{13}C NMR (major isomer) δ u 146.2, 42.5, 37.2, 26.3, 22.5; ^{13}C NMR (major isomer) δ d 128.1, 127.2, 125.5, 47.2, 26.0, 22.6; HRMS calcd for $C_{13}H_{16}$ (MH^+) 172.1252, obsd 172.1250.

Dihydropyrazole 4. To a stirred solution of the recrystallized diazene **2a** (47 mg, 0.24 mmol) in MeOH (2 mL) was added K_2CO_3 (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 R_f (MTBE) 0.42; IR (cm^{-1}) 3309, 2956, 1649, 1451; ^{1}H 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 (s, 3H); ^{13}C NMR (MeOD) δ u 144.6, 71.9, 50.0, 40.0; ^{13}C NMR (MeOD) δ d 149.4, 129.5, 127.8, 127.3, 59.6, 45.4, 23.6; HRMS calcd for $C_{13}H_{16}N_2$ (M^+) 200.1313, obsd 200.1314.

Bis-benzamide 5. A suspension of the recrystallized diazene **2a** (85 mg, 0.43 mmol) and PtO_2 (10 mg) in MeOH (3 mL) was stirred at rt under H_2 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 Et_3N (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 R_f (5% MTBE/ CH_2Cl_2) 0.62; IR (cm^{-1}) 3054, 2955, 1667, 1396, 1234; ^{1}H 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); ^{13}C NMR δ u 172.3, 167.3, 142.5, 136.4, 133.7, 72.1, 54.0, 47.0, 40.2; ^{13}C 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 $C_{27}H_{27}N_2O_2$ (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 SmI_2 (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 R_f (5% MTBE/PE) 0.31; IR (cm^{-1}) 3312, 2918, 1638, 1530, 1299; ^{1}H 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, 3H), 1.70−1.80 (m, 1H), 1.10−1.30 (m, 2H); ^{13}C NMR δ u 167.6, 166.0, 143.2, 133.9, 133.4, 61.8, 48.9, 40.2, 37.2; ^{13}C NMR δ d 130.6, 130.2, 127.7, 127.6, 127.5, 126.0, 125.9, 125.8, 125.3, 48.8, 39.8, 26.0; HRMS calcd for $C_{27}H_{29}N_2O_2$ (MH^+) 413.2229, obsd 413.2227.

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Supporting Information Available: Experimental procedures, details of the X-ray analysis, and ^{1}H and ^{13}C 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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(11) de los Santos, J. M.; López, Y.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2008**, *73*, 550.

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