A Cyclopropyl-Homoallyl Rearrangement Accompanying the Borane-Mediated Reduction of Tosylhydrazones

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Dedicated to Professor Nenad Trinajstić on the occasion of his 65th birthday

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The Wolff–Kishner reduction of strained cyclopropyl ketones 9-oxo-2,8-didehydronoradamantane (**1**) and 5-oxo-2,4-didehydrobrendane (**5**) proceeds without rearrangement, while the borane-mediated reduction of the corresponding tosylhydrazones **1a** and **5a** affords the rearranged products tricyclo[4.2.1.0^{3,8}]non-4-ene (**3**) and 4-brendene (**7**), respectively. Rearrangement also occurs during the reduction of the less-strained tosylhydrazones **8a** and **10a** derived from cyclopropyl methyl ketone (**8**) and bicyclo[4.1.0]heptan-2-one (**10**). The results obtained in experiments with deuterated reagents support a concerted mechanism of diazene decomposition/cyclopropyl-homoallyl rearrangement. This rearrangement offers a great possibility for the preparation of new polycyclic molecules and, moreover, is a convenient method for regiospecific isotopic labeling using deuterated reagents.
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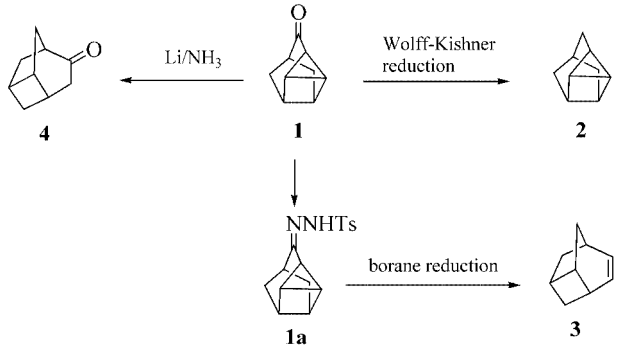
Introduction

The enormous importance of the cyclopropyl group in the various fields of chemistry lies in its versatile reactivity. The propensity of cyclopropane-containing molecules to undergo a variety of ring-opening reactions is well documented.[1] Although the bonding characteristics of the cyclopropane ring would suggest that they should stabilize adjacent carbanions, experiments have shown that cyclopropanes themselves are very poor acceptors.[2] Nevertheless, the cyclopropyl moiety has been used extensively in synthetic chemistry.[3−7]

During the course of our studies on the chemistry of strained polycyclic molecules that contain the cyclopropyl moiety,[4−6] we found that the cyclopropane ring-opening reactions of cyclopropyl ketone **1** are very dependent upon the reaction conditions used.[7] The Wolff−Kishner reduction of **1** gives the nonrearranged product 2,8-didehydronoradamantane (**2**), while the borane-mediated reduction of the tosylhydrazone **1a** and electron-transfer reduction of **1** both give a ring-opening reaction with formation of the tricyclo[4.2.1.0^{3,8}]nonane compounds **3** and **4**, respectively (Scheme 1).



Scheme 1

To the best of our knowledge this is the first example of a cyclopropyl-homoallyl rearrangement accompanying the reduction of cyclopropyl ketone tosylhydrazone derivatives. Nevertheless, because of the similarity between cyclopropyl ketone and enone systems, this reaction could be regarded as an extension of borane-driven transformations of enone hydrazones into transposed alkenes.[8]

To gain more knowledge regarding the ring opening of cyclopropylcarbonyl systems with a negative charge built up on the carbon atom adjacent to the ring, we have also investigated reduction reactions, as these may involve cyclopropylmethyl anions or closely related structures.

Since it is known that the reduction of tosylhydrazones with boron hydrides[9] offers a mild and convenient alternative to the Wolff−Kishner and Clemmensen reduction, in this work we studied the borane-mediated reduction of

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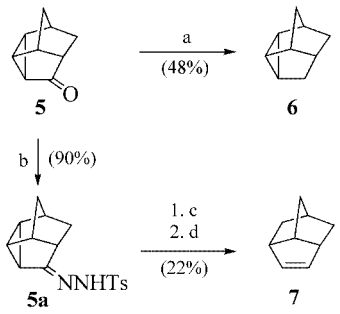
cyclopropyl ketone tosylhydrazones in which the cyclopropyl ring is either incorporated into strained polycyclic molecules (such as **1a** and **5a**) or into less-strained compounds (such as **8a** and **10a**).

Results and Discussion

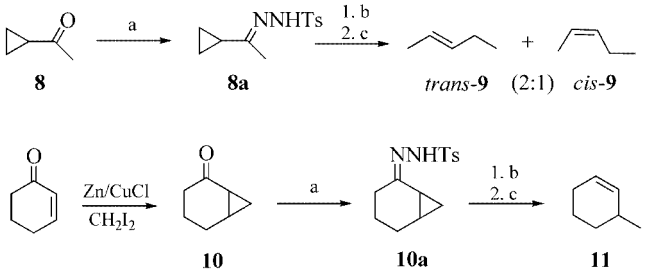
5-Oxo-2,4-didehydrobrendane (**5**) was prepared according to a literature procedure.[10] The corresponding tosylhydrazone **5a** was readily prepared by our usual procedure[11] requiring no acid or base catalysis.[12] Upon the reduction of tosylhydrazone **5a** with an excess of borane in THF and the decomposition of the resulting borane derivative under basic conditions, the cleavage of the cyclopropane ring occurred and 4-brendene (**7**) was obtained as the only product.[13] However, Wolff−Kishner reduction of ketone **5** gave the unrearranged product 2,4-didehydrobrendane (**6**; Scheme 2).



(a) H_2NNH_2, KOH, diethylene glycol
(b) *p*-$TsHNNH_2$, dry ethanol
(c) BH_3·THF
(d) NaOH, H_2O

Scheme 2

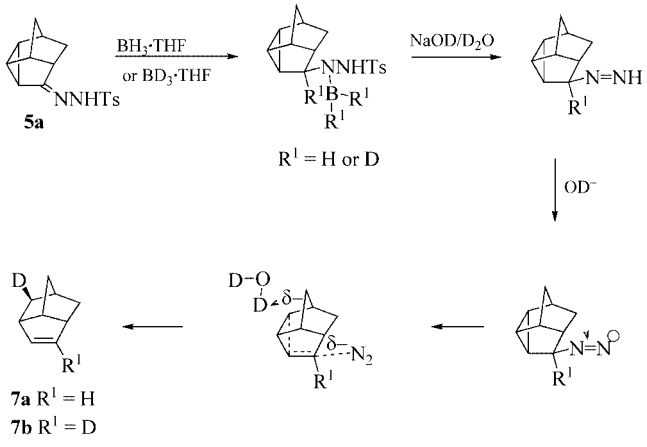
To prove the generality of this rearrangement we also studied the borane-mediated reduction of nonstrained cyclopropyl ketone tosylhydrazones **8a** and **10a** derived from cyclopropyl methyl ketone (**8**) and bicyclo[4.1.0]heptan-2-one (**10**), respectively. Cyclopropyl methyl ketone is commercially available, while bicyclo[4.1.0]heptan-2-one was prepared by a Simmons−Smith cyclopropanation of cyclohex-2-en-1-one. The best yield of the cyclopropanation (58%) was obtained when the ratio of cyclohex-2-en-1-one, $Zn/CuCl_2$ and CH_2I_2 was 1:8:4. The borane-mediated reduction of cyclopropyl ketone tosylhydrazones **8a** and **10a** also proceeded with cyclopropane ring opening, and the corresponding *cis*- and *trans*-2-pentene (**9**) and 3-methylcyclohexene (**11**) were obtained, respectively, as the sole olefinic products (Scheme 3). The Wolff−Kishner reduction of cyclopropyl methyl ketone afforded an unrearranged product.[14]



(a) *p*-$TsHNNH_2$, dry ethanol; (b) BH_3·THF; (c) NaOH, H_2O

Scheme 3

It has been suggested that an alkyl diimide intermediate is formed in both the Wolff−Kishner reduction of ketones[15] and in the reduction of the corresponding tosylhydrazones with boron hydrides.[16] However, the mechanism of the subsequent base-promoted decomposition of diazene derivatives and the possible existence of carbanionic species is still questionable.[17] Our results indicate that the last steps in the borane-mediated reduction of tosylhydrazones and the Wolff−Kishner reduction are rather different. To obtain more insight into the mechanism of the cyclopropyl rearrangement during the borane-mediated reduction of cyclopropyl ketone tosylhydrazones, we performed the experiments with tosylhydrazone **5a** using common and/or deuterated reagents (BD_3·THF and $NaOD/D_2O$). The combination of common BH_3·THF and deuterated $NaOD/D_2O$ gave only *exo*-2-deuterio-4-brendene (**7a**), while the combination of deuterated BD_3·THF and $NaOD/D_2O$ yielded *exo*-2,5-dideuterio-4-brendene (**7b**).[18,19] The formation of only the *exo*-2-deuterio derivative **7a** favors the concerted mechanism of the diazene decomposition/cyclopropyl-homoallyl rearrangement during the borane-mediated reduction of cyclopropyl ketone tosylhydrazones without the formation of free carbanion (Scheme 4).



Scheme 4

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Conclusion

In summary, we have found that a cyclopropyl-homoallyl rearrangement occurs during the borane-mediated reduction of various cyclopropyl ketone tosylhydrazones, while the Wolff−Kishner reduction of the corresponding cyclopropyl ketones gives unrearranged products. The results obtained with deuterated reagents imply that the borane-mediated reduction proceeds through a concerted mechanism of diazene decomposition/cyclopropyl-homoallyl rearrangement. In addition, this cyclopropyl-homoallyl rearrangement offers a great possibility for the preparation of new polycyclic molecules and, moreover, is a convenient method for regiospecific isotopic labeling employing deuterated reagents.

Experimental Section

General Remarks: The purity of all compounds was determined by GLC and/or ^{1}H and ^{13}C NMR spectroscopy. GLC analyses were carried out with a Varian 3300 gas chromatograph fitted with a DB-210 capillary column. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 300 spectrometer. IR spectra were recorded with a Perkin−Elmer M-297 spectrophotometer and high-resolution mass spectra were recorded with an Extrel FTMS 2001 spectrometer. Melting points were determined with a Kofler apparatus.

General Procedure for the Preparation of Tosylhydrazones: A mixture of the corresponding cyclopropyl ketone and *p*-TsHNNH$_2$ (1:1 ratio) in dry ethanol was stirred at 50 °C for 1 h, cooled to room temperature and left in the refrigerator overnight. Water was then added to the resulting suspension and the product was extracted with diethyl ether and dried with anhydrous $MgSO_4$. The solvent was evaporated to give a mixture of two isomers of the corresponding tosylhydrazone as a white solid.

Preparation of Tosylhydrazone 5a: According to the General Procedure, ketone **5** (0.38 g, 2.84 mmol) was mixed with *p*-TsHNNH$_2$ (0.526 g, 2.84 mmol) in dry ethanol (3.5 mL). Dilution with water (30 mL), extraction with diethyl ether (4 × 15 mL), drying and solvent evaporation gave tosylhydrazone **5a** (0.77 g, 90%); m.p. 142−144 °C (ref.[12a] 183−188 °C). IR (KBr): $\tilde{\nu}$ = 3220 (s), 3060 (w), 2980 (s), 2920 (m), 2880 (m), 1670 (m), 1600 (m), 1170 (vs) cm^{-1}. ^{1}H NMR (CD_3OD): δ = 1.23−1.34 (m), 1.58−1.72 (m), 1.88−2.20 (m), 2.42−2.60 (m with distinguishable s at δ = 2.54 ppm, CH_3), 2.74 (br. s), 3.00−3.08 (m), 7.46 (d, *J* = 8 Hz), 7.88 (d, *J* = 8 Hz) ppm. ^{13}C NMR (CD_3OD): δ = 21.7, 31.8, 32.0, 33.7, 36.2, 36.6, 37.2, 37.4, 38.2, 42.1, 42.6, 43.0, 43.6, 43.7, 51.2, 51.3, 129.4, 130.9, 138.0, 145.5, 178.5, 178.7 ppm. $C_{16}H_{18}N_2O_2S$ (302.398): calcd. C 63.55, H 6.00 N, 9.26; found C 63.55, H 6.22, N 9.46.

Preparation of Tosylhydrazone 8a: According to the General Procedure, ketone **8** (2.94 mL, 30.0 mmol) was mixed with *p*-TsHNNH$_2$ (5.81 g, 30.0 mmol) in dry ethanol (50 mL). Dilution with water (200 mL), extraction with diethyl ether (4 × 75 mL), drying and solvent evaporation gave tosylhydrazone **8a** (7.09 g, 94%); m.p. 127−129 °C (ref.[20] 123 °C). IR (KBr): $\tilde{\nu}$ = 3210 (s), 3020 (w), 2990 (w), 2925 (w), 1625 (m), 1325 (s), 1165 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.63−0.69 (m), 0.84−0.90 (m), 1.50−1.65 (m with 2 distinguishable s at δ = 1.64 and 1.65 ppm, CH_3), 2.41 (s), 7.29 (d, *J* = 8.2 Hz), 7.83 (d, *J* = 8.2 Hz). ^{13}C NMR ($CDCl_3$): δ = 5.3, 6.0, 10.5, 13.5, 17.5, 19.1, 21.3, 128.0, 129.3, 135.3, 143.8, 160.1 ppm.

Preparation of Tosylhydrazone 10a: According to the General Procedure, ketone **10** (4.47 g, 40.0 mmol) was mixed with *p*-TsHNNH$_2$ (7.93 g, 40.0 mmol) in dry ethanol (70 mL). Dilution with water (200 mL), extraction with diethyl ether (4 × 70 mL), drying and solvent evaporation gave a yellowish product. Recrystallization from ethanol gave tosylhydrazone **10a** (2.19 g, 20%); m.p. 154−156 °C. IR (KBr): $\tilde{\nu}$ = 3230 (s), 3020 (w), 2940 (m), 2860 (w), 1600 (m), 1395 (m), 1330 (s), 1165 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.26−0.34 (m), 0.75−0.81 (m), 0.97−2.05 (m), 2.15−2.25 (m), 2.42 (s, CH_3), 2.44 (s, CH_3), 7.30 (d, *J* = 8.0 Hz), 7.84 (d, *J* = 8.0 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 7.9, 8.7, 10.8, 11.6, 13.3, 15.4, 17.7, 18.5, 20.6, 21.3, 22.0, 23.8, 31.1, 127.8, 129.4, 135.6, 143.7, 160.1 ppm. HRMS: calcd. for $C_{14}H_{18}N_2O_2S$ 278.10835; found 278.10871.

General Procedure for the Reduction of Tosylhydrazones with Borane: A 1 M solution of BH_3 in THF was added under nitrogen to an ice-cold solution of the corresponding tosylhydrazone in dry THF. After stirring for 15 min, the ice/water bath was removed and the reaction mixture was stirred for a further 1 h. The excess of BH_3·THF was destroyed by careful addition of water until no reaction was observed. Then a 5 M aqueous NaOH solution was added and stirring was continued at room temperature for 1 h. The reaction mixture was diluted with water and the product was extracted with pentane and dried with anhydrous $MgSO_4$. After filtration, the solution was concentrated under reduced pressure and the residue was filtered through a short column of alumina (activity I), with pentane as eluent, to give the olefinic products as highly volatile substances.

Reduction of Tosylhydrazone 5a with BH_3·THF: According to the General Procedure, tosylhydrazone **5a** (0.453 g, 1.5 mmol) was reduced with a 1 M solution of BH_3·THF (2 mL, approx. 2 mmol) in dry THF (8 mL). After addition of a 5 M NaOH aq. solution (2 mL) and stirring for 1 h, the mixture was diluted with water (20 mL). Extraction with pentane (4 × 15 mL), followed by drying, concentrating, and purification gave 4-brendene (**7**)[13,19] (0.040 g, 22%). ^{1}H NMR ($CDCl_3$): δ = 1.16 (d, *J* = 11.7 Hz, 2 H, 2-H$_{endo}$ and 9-H$_{endo}$), 1.37−1.47 (m, 2 H, 2-H$_{exo}$ and 9-H$_{exo}$), 1.59 (s, 2 H, 8-H), 2.32−2.38 (m, 3 H, 3-H, 6-H and 1-H), 2.91−2.96 (m, 1 H, 7-H), 6.01 (br. s, 2 H, 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 36.1 (t, 2 C, C-2 and C-9), 39.3 (t, 1 C, C-8), 42.1 (d, 1 C, C-1), 42.9 (d, 2 C, C-3 and C-6), 54.0 (d, 1 C, C-7), 139.4 (d, 2 C, C-4 and C-5).

Reduction of Tosylhydrazone 8a with BH_3·THF: According to the General Procedure, tosylhydrazone **8a** (3.12 g, 12.0 mmol) was reduced with a 1 M solution of BH_3·THF (17 mL, approx. 17 mmol) in dry THF (65 mL). After addition of a 5 M NaOH aq. solution (16 mL) and stirring for 1 h, the product was distilled off (36 °C) at atmospheric pressure through a Vigreux column with a dry ice/acetone cooling condenser to yield a mixture (0.126 g, 15%) of *cis*- and *trans*-2-pentene[20] (1:2 ratio).

Reduction of Tosylhydrazone 10a with BH_3·THF: According to the General Procedure, tosylhydrazone **10a** (1.0 g, 3.6 mmol) was reduced with a 1 M solution of BH_3·THF (5 mL, ca. 5 mmol) in dry THF (20 mL). After addition of a 5 M NaOH aq. solution (5 mL) and stirring for 1 h, the mixture was diluted with water (30 mL) and extracted with pentane (3 × 30 mL). Most of the solvent was distilled off at atmospheric pressure and then the residue was transferred in vacuo to afford 3-methylcyclohexene (**11**), traces of pentane and THF. The yield of the reaction was calculated to be 12.5%

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by a gas chromatographic method with internal standard. The NMR spectroscopic data of the product are identical with the literature data.[21]

Wolff−Kishner Reduction of 5-Oxo-2,4-didehydrobrendane (5): A solution of ketone **5** (0.27 g, 2.0 mmol), diethylene glycol (10 mL), 98−100% hydrazine hydrate (0.5 mL, 10.0 mmol) and KOH (0.37 g, 6.6 mmol) was heated at 100 °C for 2 h and then at 210 °C for 5 h, during which time the product sublimed. The sublimate was washed with pentane (20 mL) and dried with anhydrous $MgSO_4$. The pentane was evaporated to give 0.115 g (48%) of 2,4-didehydrobrendane (**6**). IR (KBr): $\tilde{\nu}$ = 3040 (w), 2960 (s), 2930 (s), 2870 (m), 2850 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.89 (d, J = 9.6 Hz, 1 H, 5-H_{endo}), 1.15 (dd, J = 13.1, 5.8 Hz, 1 H, 2-H), 1.27 (dd, J = 9.6, 9.3 Hz, 1 H, 5-H_{exo}), 1.51−1.56 (m, 2 H, 4-H and 9-H_{endo}), 1.70−2.00 (m, 4 H, 3-H, 8-H and 9-H_{exo}), 2.02−2.09 (m, 1 H, 6-H), 2.33 (br. s, 1 H, 1-H), 2.55 (br. s, 1 H, 7-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.0 (d, C-3), 30.4 (d, C-4), 30.6 (d, C-2), 35.0 (d, C-6), 37.6 (d, C-1), 39.5 (t, C-9), 39.8 (t, C-5), 44.2 (d, C-7), 51.7 (t, C-8) ppm. HRMS: calcd. for C_9H_{12} 120.09390; found 120.09362.

Preparation of Ketone 10: Cyclohex-2-en-1-one (5 mL, 0.05 mol) and CH_2I_2 (16.63 mL, 0.2 mol) were added under nitrogen to a freshly prepared suspension of Zn/Cu dust, obtained by the ultrasound-promoted reaction of zinc (26.15 g, 0.4 mol) and CuCl (39.60 g, 0.4 mol) in dry diethyl ether (125 mL). The reaction mixture was stirred at 40−50 °C for 48 h and the excess of Zn/Cu dust was then destroyed by addition of a saturated aqueous NH_4Cl solution until no reaction was observed. The suspension was diluted with water (200 mL), filtered, and the filtrate was extracted with diethyl ether (4 × 60 mL). The extracts were combined, dried with anhydrous $MgSO_4$ and the solvents evaporated under reduced pressure to afford a heavy yellow oil. The pure ketone **10** (3.34 g, 59%) was obtained by distillation under reduced pressure as a clear yellowish oil; b.p. (10 Torr) 85 °C. The NMR spectra are in agreement with the literature data.[22]

Acknowledgments

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